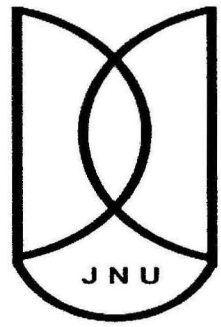
SYNTHESIS, BIOLOGY AND CHEMISTRY OF NOVEL SYNTHETIC 1, 2, 4-TRIOXANES

THESIS
SUBMITTED TO

JAWAHAR LAL NEHRU UNIVERSITY
NEW DELHI



IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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"Hey man! Rise, rise above all extents,
Where God can be felt, neither debts nor rents,
Where deeds are your real medal, what for you are mend."

Dedicated to My Loving Parents

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CERTIFICATE

This is to certify that the dissertation entitled **"Synthesis, Biology and Chemistry of Novel Synthetic 1,2,4-Trioxanes"** being submitted to the Jawaharlal Nehru University, New Delhi in partial fulfillment of the requirements for the award of the degree of Doctor of Philosophy, embodies the research work done by **Mr. Ajit Shankar Singh** under my supervision at Central Drug Research Institute, Lucknow. The work presented here is original and has not been submitted so far, in part or full, for any degree or diploma of any other university/institute.

Chandan Singh

(Chandan Singh)
Supervisor

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Date: 15|05|08

Ajit Shankar Singh

(Ajit Shankar Singh)

Contents

°C	:	degree Celsius
Anal.	:	Microanalysis
Anhyd.	:	anhydrous
aq	:	aqueous
ATP	:	adenosine triphosphate
bm	:	broad multiplet
bs	:	broad singlet
bdd	:	broad double doublet
$BF_3.Et_2O$	:	Boron trifluoride diethyl etherate
cat	:	catalytic amount
$CDCl_3$	:	deuterated chloroform
concd	:	concentrated
CQ	:	chloroquin
d	:	doublet
ddd	:	doublet of doublet of doublet
DCC	:	dicyclohexyl carbodiimide
dd	:	double doublet
DHA	:	Dihydroartemisinin
DMAP	:	N,N-dimethyl amino pyridine
dt	:	doublet of triplet
ED_{50}	:	effective dose for 50% inhibition
ED_{90}	:	effective dose for 90% inhibition
EI-MS	:	Electron ionization mass spectrometry
ES-MS	:	Electron spray mass spectroscopy
EtOAc	:	Ethyl Acetate
FT-IR	:	Fourier transform infrared spectroscopy
FAB-MS	:	Fast atom bombardment mass spectroscopy
g	:	gram
h	:	hour(s)

HR-EIMS	:	High resolution electron ionization mass spectrometry
hν	:	quantum of light/photon
Hz	:	hertz
im	:	intramuscular
ip	:	intraparetoneal
iv	:	intravenous
J	:	coupling constant
L	:	litre
m	:	multiplet
m-CPBA	:	*m*-chloroperbenzoic acid
MDR	:	multidrug-resistant
MHz	:	mega hertz
MIC	:	minimum inhibitory concentration
min	:	minute(s)
mL	:	millilitre
mp	:	melting point
m/z	:	mass per unit (+ve) charge
μg	:	microgram
mmol	:	millimole
NMR	:	nuclear magnetic resonance
p-TsOH	:	*p*-toluenesulphonic acid
QHS	:	Qinghaosu
q	:	quartet
quin	:	quintet
rt	:	room temperature
s	:	singlet
t	:	triplet
td	:	triplet of doublet
THF	:	tetrahydrofuran
TLC	:	Thin layer chromatography
TMSOTf	:	Trimethylsilyl trifluoromethanesulphonate

Preface

The burgeoning global problem of malaria is largely due to the emergence of parasite resistance to our limited armamentarium of antimalarial drugs. The prevalence of resistance to known antimalarial drugs has resulted in the expansion of antimalarial drug discovery efforts. The isolation in 1972 of artemisinin by Chinese scientists, and their development of all the derivatives now used in the treatment of malaria today, were of outstanding importance. The results which have accumulated both from the Chinese work and from that subsequently conducted on a worldwide basis provide for a relatively comprehensive understanding of the chemistry, pharmacological profiles, toxicology, metabolism, and effects on the malaria parasite. The optimal regimens for use in the field are also apparent, particularly in combinations with longer half-life quinoline antimalarials. Thus the future use of the artemisinin class of drug appears assured. However, the mechanism of action needs to be clarified. More importantly from a clinical viewpoint, problems inherent in the current derivatives must be addressed, particularly that of neurotoxicity, if new artemisinin derivatives are to be introduced in a normal drug regulatory environment.

The most important artemisinin derivatives like artesunate, artemether, arteether and dihydroartemisinin are fast acting drugs but they are eliminated quickly as they have short plasma half life. Their rapid onset makes them especially effective against severe malaria. Their rapid disappearance may be a key reason why artemisinin resistance has been so slow to develop, and may also explain reason of recrudescence when used in monotherapy, so WHO has now recommended use of artemisinin derivatives in combination which classical drugs that have long plasma half life.

Efforts have been made to understand the mechanism of action and pharmacokinetics of artemisinin derivatives so as to synthesize compounds that have reduced neurotoxicity, better bioavailability, good solubility and large plasma half life.

Although artemisinin and its derivatives are still the best known antimalarials but it suffers real problem of poor natural abundance, high cost, poor bioavailability and high rate of recrudescence.

The identification of 1,2,4-trioxane moiety as principal pharmacophore of artemisinin has led to the development of several synthetic peroxides that have shown potential antimalarial activity and have gone up to clinical stages.

Central Drug Research Institute (CDRI), Lucknow is also one of the leading institutions in the World that have given huge contribution towards the development of artemisinin based antimalarials together with synthetic peroxides. The main objective of **CDRI** malaria research programme is to develop antimalarials that are effective against multi-drug resistant malaria and are commercially viable.

As a part of this programme in search for better antimalarials, an attempt has been made to synthesize synthetic as well as semisynthetic analogues of artemisinin that have high antimalarial potency. In this thesis synthesis of structurally diverse synthetic 1,2,4-trioxanes, their antimalarial activity and chemistry have been reported. The present thesis also covers the synthesis and antimalarial assessment of several semisynthetic derivatives of artemisinin as well. The results of these studies are discussed in five chapters as summarized below:

The **first chapter** includes a brief review on malaria, historical perspectives in development of malarial chemotherapy especially in the field of artemisinin and its related peroxides and a brief note of their mode of action.

The **second chapter** describes the details of synthesis and antimalarial assessment of new class of synthetic 1,2,4-trioxanes in search for better substitutes for artemisinin analogues.

The **third chapter** covers the synthesis and antimalarial activity of novel hydroxy-functionalized 1,2,4-trioxanes that have enhanced oil and water solubility.

The **fourth chapter** describes the chemistry of 1,2,4-trioxanes, which involves a novel and unprecedented acid catalyzed rearrangement.

The **fifth chapter** covers the details of synthesis and antimalarial assessment of a new class of artemisinin derivatives having free amino functionality.

Chapter 1

Role of Peroxides in Malaria Chemotherapy: A Voyage from Artemisinin to Synthetic Peroxides

1.1 Introduction

Since ancient times, humankind has had to struggle against the persistent onslaught of pathogenic microorganisms. Malaria is still one of the world's most deadly disease that threatens nearly 40% of the world's population putting 3.2 billion people at risk in 107 countries and infects approximately 300 to 500 million people annually world wide mainly in tropical and subtropical areas.[1] It is estimated that there are between 1 million to 3 million deaths every year due to malaria. In Africa alone, more than 1 million people die because of malaria and most of them are children under 5 years of age.[2] The economic toll of malaria is tremendous. It has been estimated that the African continent has forgone almost $100 billion in lost GDP over the last 35 years due to malaria alone.[3] Malaria ranks third among the major infectious diseases in causing deaths after pneumococcal acute respiratory infections and tuberculosis, and accounts for approximately 2.6% of the total disease burden of the world.[4]

This review chapter includes a short description of the malaria disease, its cause, a short address to the history of antimalarial drug development and a focus on the development of peroxides that can be used for malaria chemotherapy together with a brief description about their mode of action.

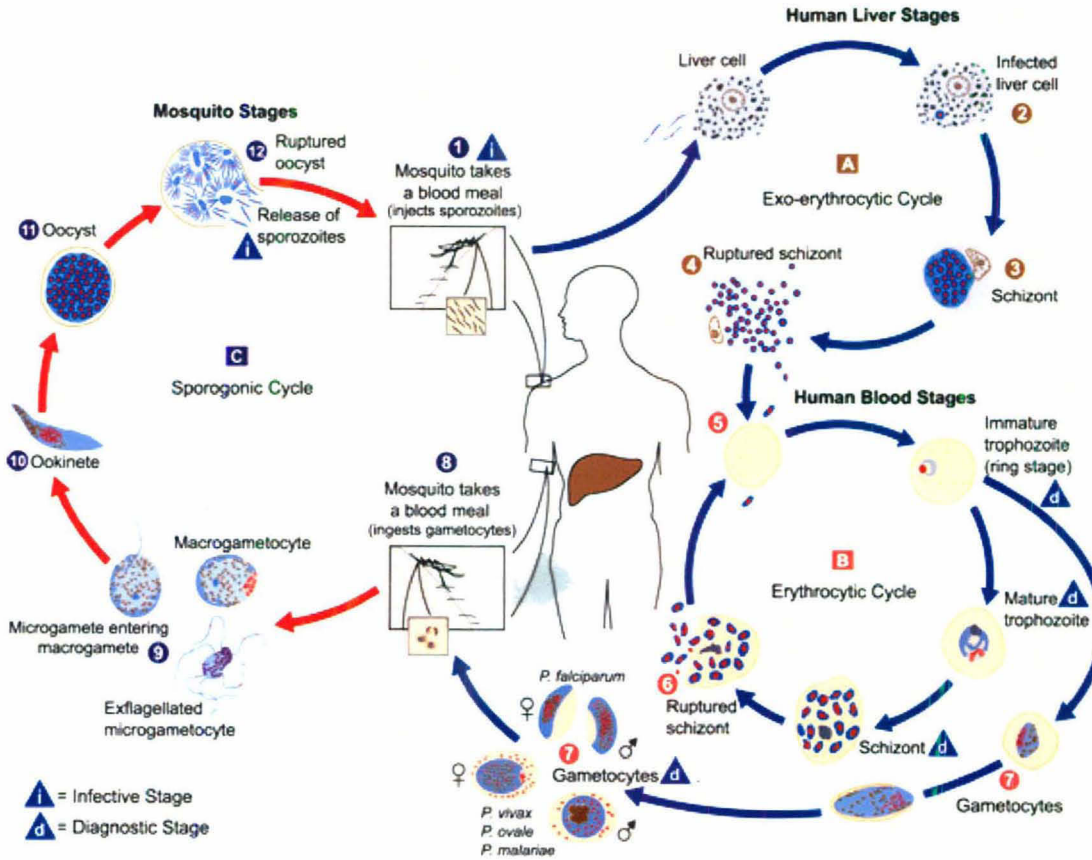
1.2 Life Cycle of Malarial Parasite

Malaria is caused by a protozoal parasite of genus *Plasmodium*, and out of 100s of species so far known only four is found to be infective to human beings which include *P. falciparum* (causes tropical malaria), *P. vivax, P. ovale* (both causes tertian malaria), and *P. malariae* (causes quartan malaria). *P. falciparum* and *P. vivax* account for 95% of all malaria infections. Nearly all severe and fatal cases are caused by *P. falciparum* which is the most wide spread geographically, out of the four known species, and the most pernicious one, causing the majority of the malaria related morbidity and mortality, while *P. vivax* and *P. ovale* causes true relapsing malaria. Malaria is found chiefly in tropical regions that includes sub-Saharan Africa, Southeast Asia, Pacific Islands, India, and Central & South America. *P. falciparum* is found throughout tropical Africa, Asia, and Latin America. It is the predominant species in most areas. *P. vivax* is more common in India and South America, but is also found worldwide in tropical and some temperate zones. *P. ovale* is mainly confined to tropical West Africa, while the occurrence of *P. malariae* is worldwide, although its distribution is patchy.[5]

The infectious stages of the malaria parasite reside in the salivary glands of female *Anopheles* mosquitoes that bite humans for a blood meal. During blood extraction, the mosquito injects its saliva into the wound, thereby transferring approximately 15-20 so-called sporozoites into the blood stream. In a matter of minutes, these sporozoites are able to conceal themselves from the host's immune system by entering into the liver cells. Each sporozoite develops into a tissue schizont, containing 10000-30000 merozoites.[6] The schizont ruptures after one to two weeks and releases the merozoites into the blood stream, starting the erythrocytic phase of the parasite's life cycle. In the cases of *P. vivax* and *P. ovale*, some sporozoites turn into hypnozoites, a form that can remain dormant in the liver cells, causing relapses months or even years after the initial infection. *P. falciparum* and *P. malariae* lack this liver persistent phase, but *P. malariae* can persist in the blood for many years if inadequately treated.[6] Merozoites released into the bloodstream hide again from the host's immune system by invading erythrocytes. In the erythrocyte, the parasite develops from a ring stage via a trophozoite stage into a blood schizont. After a time characteristic for each specific *Plasmodium* species, the erythrocyte ruptures and releases 16-32 new merozoites into the blood stream which in turn again invade erythrocytes, thereby starting a new erythrocytic cycle. This asexual life cycle, from invasion of the erythrocytes until the schizont ruptures, spans 48 h for *P. falciparum*, *P. vivax*, and *P. ovale*, and 72 h for *P. malariae*. After a number of asexual life cycles, some merozoites develop into sexual forms, the gametocytes, which are transferred to a mosquito during another blood meal.

These gametocytes undergo sexual reproduction within the mosquito mid-gut producing thousands of infective sporozoites, which migrate to the salivary gland where they are ready for a new infection. With the rupture of the erythrocyte, the parasite's waste and cell debris is released into the blood stream, causing some of the clinical symptoms of malaria. The main symptom is fever, but rarely in the classical tertian (every 48 h) or quartan (every 72 h) patterns. Further symptoms include chill, headache, abdominal and back pain, nausea, and sometimes vomiting. Thus, the early stages of malaria often resemble the onset of an influenza infection. *P. vivax*, *P. ovale*, and *P. malariae* show distinct selectivity towards the age of the infected erythrocytes. For that reason, the degree of total parasitaemia is limited. In contrast, *P. falciparum* infects erythrocytes of all ages, leading to high parasitaemia. Although the symptoms of *P. vivax*, *P. ovale*, and *P. malariae* infections can be severe in non-immune persons, these parasites seldom cause fatal disease. Nevertheless, chronic infection with *P. malariae* can result in an (eventually fatal) nephrotic syndrome.[7] Malaria caused by these three parasites is often called benign malaria. In contrast, *P. falciparum* malaria (also known as tropical malaria) can progress within a few

days from uncomplicated to severe malaria with a fatal outcome in 10–40% of all cases of severe malaria, depending on the time lag between the onset of the symptoms and effective treatment, as well as on the hospital facilities for the management of complications.[8] Observed complications can include coma (cerebral malaria), respiratory distress, renal failure, hypoglycemia, circulatory collapse, acidosis, and coagulation failure.[9]



Life Cycle of Malaria Parasite

1.3 Classification of Antimalarial Drugs

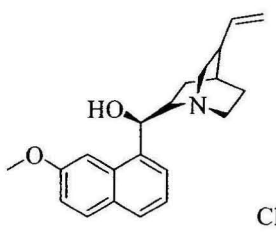
Traditionally, antimalarial agents are classified by the stages of the malaria life cycle that are targeted by the drug.

Blood schizonticides: They act on the asexual intraerythrocytic stages of the parasites; there by terminate clinical attacks of malaria. The drugs belonging to this class include quinine **1**, chloroquine **2**, mefloquine **3**, halofantrine **4**, pyrimethamine **5**, sulfadoxine **6**, sulfones and tetracycline derivatives.

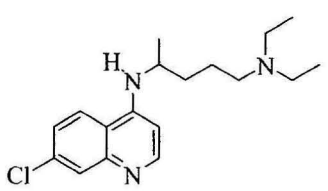
Tissue schizonticides: These kill hepatic schizonts, and thus prevent the invasion of erythrocytes, acting in a causally prophylactic manner. Primaquine and pyrimethamine (to a lesser extent) have activity against this stage. However, since it is impossible to predict the infection before clinical symptoms begin; this mode of therapy is more theoretical than practical.

Hypnozoiticides: They kill the persistent intrahepatic stages of *P. vivax* and *P. ovale*, thus preventing relapses from these dormant stages. Primaquine **7** is the only prototype drug available for this stage.

Gametocytocides: They destroy the intraerythrocytic sexual forms of the parasites and prevent transmission from human to mosquito. As there are no dormant liver stages in *P. falciparum* malaria (tropical malaria), blood schizonticidal drugs are sufficient to cure the infection. In cases of *P. vivax* and *P. ovale*, a combination of blood schizonticides and tissue schizonticides is required. Chloroquine and quinine have gametocytocidal activity against *P. vivax* and *P. malariae*, but not against *P. falciparum*. However, primaquine has gametocytocidal activity against all human malarial parasite species including that against *P. falciparum*.

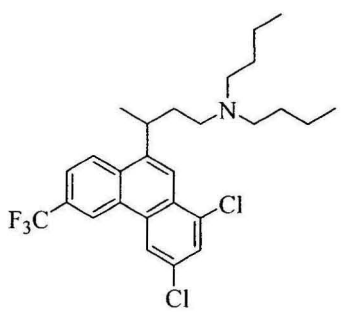


Quinine 1



Chloroquine 2

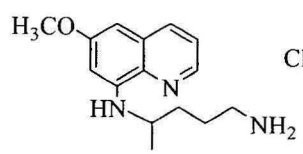
Mefloquine 3



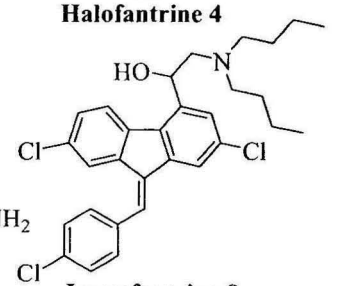
Halofantrine 4

Pyrimethamine 5

Sulphadoxine 6



Primaquine 7



Lumefantrine 8

1.4 Drug Resistance in Malaria Chemotherapy

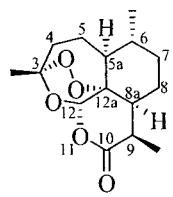
Considerable success in gaining control over malaria was achieved in the 1950s and 60s through landscaping measures, vector control with the insecticide DDT, and the widespread administration of chloroquine, the most important and cheapest antimalarial agent so far discovered. In the late 1960s, the final victory over malaria was believed to be within reach,

however, the parasites could not be eradicated because they developed resistance against the most widely used and affordable drugs of that time. Since then the cases of malaria infections were on the rise and has now reached up in record numbers. With due course of time the parasite developed resistance against most of the conventionally used drugs due to their indiscriminate use, incomplete dose regimen, lack of proper antimalarial campaigns. One of the major factors for rise in malaria cases was the development of resistant varieties of vectors against commonly used insecticides. There are numerous reports of resistance of malaria parasite against chloroquine and sulfadoxine-pyrimethamine. This growing emergence of drug-resistance against chloroquine, the cheapest drug so far discovered then led to the use of several other relatively costlier drugs both as single (mono therapy) and in combinations (combination therapy) which include primaquine, mefloquine, halofantrine and lumifantrine **8** but the reports of development of resistance against them as well in several areas enforced to develop new fast acting drugs which are different both in terms of pharmacophore and mode of action.

1.5 Artemisinin: A Lead in Malaria Chemotherapy

Extracts of the herb known as sweet wormwood have been used in China for the treatment of fever for as long as 2000 years. Its earliest mention occurs in the ***Recipes for 52 Kinds of Diseases*** found in the Mawangdui Han dynasty tomb dating from 168 B.C. In that work, the herb is recommended for use in hemorrhoids. This plant is mentioned further in the ***Zhou Hou Bei Ji Fang*** (Handbook of Prescriptions for Emergency Treatments) written in 340 A.D. Li Shizhen, the famous herbalist, wrote in his ***Ben Cao Gang Mu*** (Compendium of Materia Medica) of 1596, that chills and fever of malaria can be combated by ***qing hao*** (*Artemisia annua* L., sweet wormwood) preparations. It was actually in1971 that Chinese chemists were able to isolate the substance responsible for its reputed medicinal action from the leafy portions of the plant. This compound, which they called *qinghaosu* (QHS, artemisinin **9**), is a sesquiterpene lactone that bears a peroxide grouping and, unlike most other antimalarials, lacks a nitrogen-containing heterocyclic ring system.[10] Artemisinin **9** is very effective and safe against chloroquine (CQ) sensitive and chloroquine (CQ) resistant strains of *P. falciparum*[11] but has certain limitations like poor oil and water solubility, and high rate of recrudescence. The limited availability of artemisinin and that too from natural source was another lagging factor that led to the development of various synthetic methodologies for the synthesis of artemisinin but none of

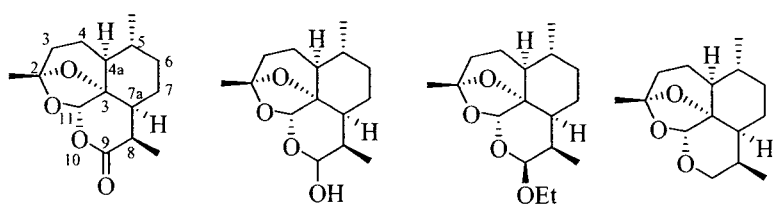
them was commercially viable.[12] Hence a lot of efforts have been put only to develop semi synthetic derivatives of artemisinin.



Artemisinin 9

1.6 Identification of the Pharmacophore

Structure activity relationship studies of artemisinin and its deoxy derivative have revealed that it is actually the endoperoxide linkage of artemisinin in the form of 1,2,4-trioxane is responsible for its activity.[13] Deoxyartemisinin **10** a major metabolite was isolated in the urine of the patients treated with artemisinin[14] which was later on obtained by total synthesis.[15] Deoxyartemisinin was found 300 times less active in comparison to artemisinin when tested in *P.falciparum* (D-6 Sierra Leone Clone).[16] The role of peroxide linkage in antimalarial activity was also confirmed by certain other deoxy derivatives,[17] deoxy dihydroartemisinin **11**, deoxyarteether **12**[1] and deoxydeoxoartemisinin **13**.



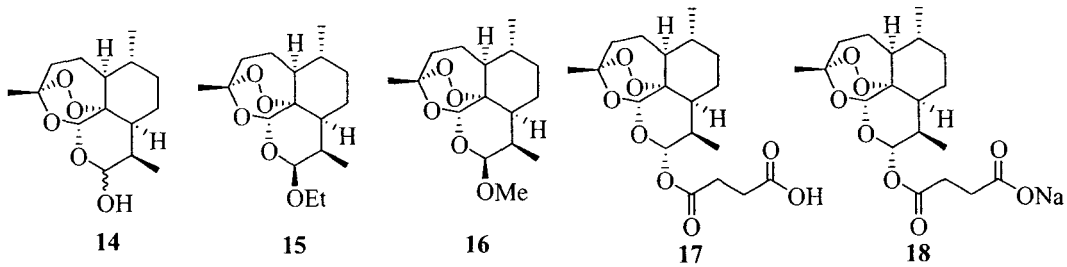
10 **11** **12** **13**

1.7 Semisynthetic Derivatives of Artemisinin as Potent Antimalarials

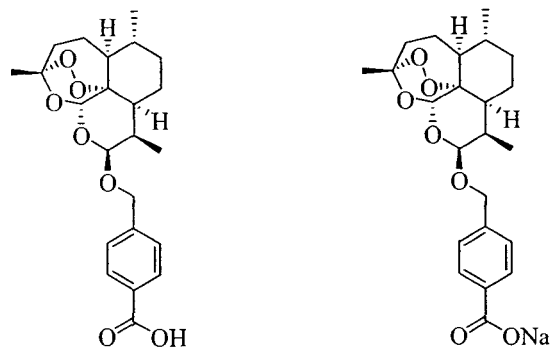
1.7.1 First generation artemisinin derivatives, their scope and limitations

Artemisinin **9** has been used in China for the treatment of malaria, but poor oil and water solubility as well as poor absorption via gastrointestinal tract were its limiting factor. A lot of attention has been put so far to synthesize better analogs of artemisinin that can have enhanced bioavailability. To overcome this problem Chinese workers made several derivatives of artemisinin and assessed them for their antimalarial efficacy They reduced the lactone moiety of parent molecule to hemiacetal to synthesize dihydroartemisinin **14**.[19] This compound was although having better oil and water solubility, but suffered the problem of neurotoxicity and

relative instability under acidic conditions. In order to reduce its toxicity and increase its stability it was converted into its corresponding ethyl and methyl ether derivatives arteether **15**[20] and artemether **16**[21] respectively, the first generation analogues of artemisinin.[18] Both of these compounds were found several times more active both *in vitro* and *in vivo* against multi-drug resistant malaria in comparison to artemisinin and are at present the drugs of choice for treatment of complicated malaria. Arteether is chiefly used in India and in Netherlands (Artemotil, Emal) but the more prevalent substance is artemether (Paluther, Artenam, Artemos).[22] Currently, the application of artemether **16** with lumefantrine (**8**) (Coartem or Riamet) is the only artemisinin-based combination therapy available manufactured under Good Manufacturing Practice (GMP) standards. In addition, a formulation for small children (Pediatric Coartem) is in clinical development.[23] Although expensive and for most malaria patients unaffordable, this combination is generally thought to be effective and well tolerated.[24-26]



14 **15** **16** **17** **18**



19 **20**

Another modification of dihydroartemisinin which was developed by Chinese workers was artesunic acid **17** which is another first generation artemisinin derivative, in which the hemiacetal OH group is acetylated with succinic acid.[27] Artesunate **18**, its sodium salt is an unstable drug as the succinic ester linkage gets rapidly cleaved, releasing dihydroartemisinin as the active agent. Because of the free carboxylate, artesunate is a water-soluble drug that can be administered via iv route. This is of particular importance for the treatment of severe malaria tropica in which the condition of the patients prohibits any other route of administration. A study on 80 children with

complicated malaria conducted in India showed the superiority of artesunate over quinine.[28] In a recent study conducted in various regions of Asia, intravenous artesunate was significantly superior to the standard iv regime with quinine in the treatment of adult severe malaria.[29]

Currently available artesunate preparations for parenteral application originate from China or Vietnam and are unable to meet western quality standards. Phase II and III studies were to commence in 2006 in a joint project by the University of Tubingen in Germany (P. G. Kremsner), an industrial partner, and the Walter Reed Army Institute of Research, with the aim of bringing an intravenous artesunate preparation to the market by 2009, to be manufactured according to western drug regulations.[30] In addition to iv application, artesunate can also be administered via the im, rectal, or oral routes. In a recent study of severe malaria in children, rectally administered artesunate **18** was at least as effective as im applied artemether **16** and thus may be useful in settings in which parenteral therapy cannot be given.[31] Artesunate is the main artemisinin combination partner in artemisinin-based combination therapy (ACT), which is now used as the standard therapy in many countries. Combinations with numerous antimalarials are used, most of which are questionable because of unmatched pharmacokinetic profiles or widespread resistance against the non-artemisinin component of the combination. In particular, the combination of artesunate **18** with mefloquine **3** is widely used in Asia.[32-34]

The utility of sodium artesunate, however, is impaired by its poor stability in aqueous solution due to the facile hydrolysis of the ester linkage and short plasma half-life (20-30 min).[35] Lin *et al* have reported a new series of water-soluble derivatives in which the solubilizing group, carboxylate, is on a moiety that is joined to dihydroartemisinin by ether, rather than an ester, linkage. One of these derivatives, artelinic acid **19**, is not only considerably more stable than artesunic acid in weakly alkaline solution but is also more active against *P. berghei* in mice. Its sodium salt, sodium artelinate **20** possesses comparable antimalarial activity both *in vivo* as well as *in vitro* to artemether or arteether. Sodium artelinate was not only found stable in aqueous solution but also has a much longer plasma half-life (1.5-3 h).[36] Because of its encouraging chemical and biological properties, sodium artelinate was subjected to preclinical testing. In an animal model, intravenous sodium artelinate was shown to be superior to artesunate.[37] However further development of sodium artelinate has been discontinued in favor of sodium artesunate[22] because of the higher neurotoxicity of sodium artelinate.[38, 39]

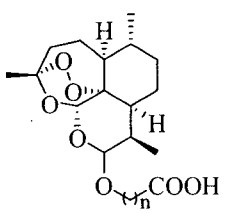
1.7.2 Second generation artemisinin derivatives, a need for better antimalarials

Neurotoxicity[40] was the major concern with all the first generation artemisinin derivatives owing to their short plasma half-life and biotransformation to neurotoxic dihydroartemisinin **14**, hence lot of work has been made for the development of second generation artemisinins that can have reduced toxicity and increased bioavailability. Methyl and ethyl residues of the first-generation semisynthetic artemisinins, artemether **16** and arteether **15** have been replaced by numerous other residues. Most variations have been carried out at position 10, where the exocyclic oxygen atom is replaced by carbon substituents to remove the metabolically sensitive acetal substructure. Alkyl, aryl, hetroalkyl and heteroaryl residues have been placed at this position. Some substituents have even been used for the formation of dimers that carry two dihydroartemisinin substructures.

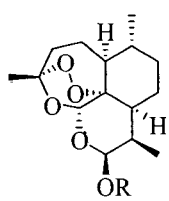
1.7.2.1 Artemisinin based monomers

C-10 acetal analogues of artemisinin

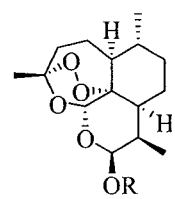
Lin *et al.*[41] **(1987)** carried out structure activity relationship various water soluble derivatives of DHA **21a-c**) by joining various alkyl groups containing free carboxylate group via ether linkage rather than ester linkage as in case of artesunic acid **19** to insure better stability in aqueous solution.



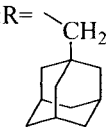
21a: n=1
21b: n=2
21c: n=3



22a: R=(*R*)-$CH_2CH(CH_3)COOH$
22b: R=(*S*)-$CH_2CH(CH_3)COOH$
22c: R=(*S*)-$CH(CH_3)CH_2COOH$
22d: R=(*R*)-$CH(CH_3)CH_2COOH$



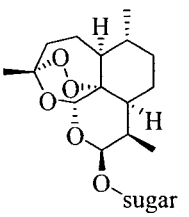
23a: R=(*R*)-$CH_2CH(CH_3)COOMe$
23b: R=(*S*)-$CH_2CH(CH_3)COOMe$
23c: R=(*S*)-$CH(CH_3)CH_2COOMe$
23d: R=(*R*)-$CH(CH_3)CH_2COOMe$
23e :R=

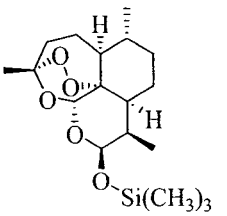


Lin *et al.*[42] **(1989)** have synthesized various optically active ether derivatives of artemisinin in order to search for new hydrolytically stable and less toxic analogs. He made both water soluble **22a-d** and oil soluble derivatives **23a-e**, out of which compound **23a-d** showed very promising *in vitro* antimalarial activity against *P. falciparum* both in Sierra Leone (IC_{50} = 0.44 to 2.15 ng/mL)

and Indochina strains (IC_{50} = 0.015 to 0.480 ng/mL). Compound **23c** also showed very good *in vivo* activity against *P. berghei* in mice.

Lin *et al.*[43] **(1992)** in search for more and more hydrophilic derivatives of dihydroartemisinin prepared various sugar analogs **24a-d**, together with a trimethylsilylated analog **25** which showed much better activity compared to artemisinin.

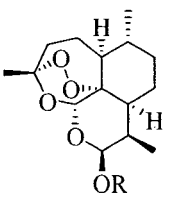




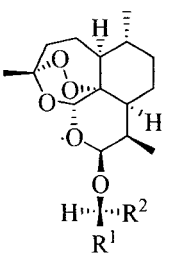
25

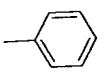
24a: D-glucose
24b: D-galactose
24c: 5,6-isopropylidene-D-glucose
24d: D-cellobiose

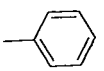
Venugopalan *et al.*[44] **(1995)** prepared several ether derivatives in a search for compounds having better therapeutic index, good solubility and bioavailability. Compound **26, 27** and **28** were found most active derivatives of the series when tested against multidrug resistant *P. yoelii nigeriensis.*

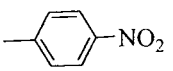


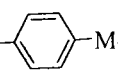
26: R=$OCH(CH_3)C{\equiv}CH$
27: R=$OC(CH_3)_2C{\equiv}CH$
28: R=(4-$OCH_2C{=}CHC_6H_5$)-O-



29a: (*R*) R^1=-$CH_2COOCH_2CH_3$ R^2= 

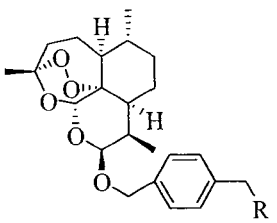
29b: (*S*) R^1=  R^2=-$CH_2COOCH_2CH_3$

29c: (*R*) R^1=-$CH_2COOCH_2CH_3$ R^2= 

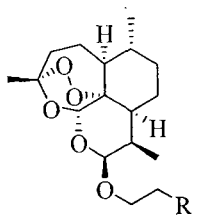
29d: (*S*) R^1=  Me R^2=-$CH_2COOCH_2CH_3$

Lin *et al.*[45] **(1995)** showed that α-alkylbenzylic ethers of dihydroartemisinin **29a-d** have much better activity *in vitro* in comparison to artemether, arteether and artesunate against two clones of

human malaria, P. *falciparum* D-6 (Sierra Leone I clone) and W-2 (Indochina clone). In this study he demonstrated the role of steric factors and lipophilicity in antimalarial activity.

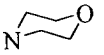


30a: R=OH
30b: R=NH_2



31a: R=NHMe
31b: R=NHEt

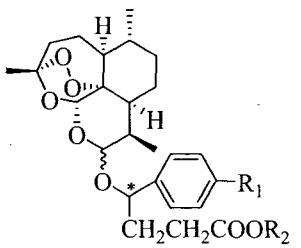
30c: R= 

30d: R= 

30e: R= 

P. M. O'Neill *et al.*[46] **(1996)**, synthesized several mechanism based benzamino **30a-e** and alkylamino **31a-b** ethers of artemisinin by taking account of this fact, that the food vacuole has a slightly acidic *p*H, so the introduction of a basic alkyl chain would assist in accumulation of drug inside the parasite.

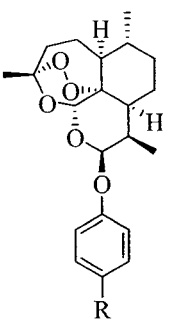
Lin *et al.*[47] **(1997)** synthesized several analogs of DHA **32a-e** that showed higher efficacy and longer half-life than artelinic acid. Compound **32d** was the most active compound of the series.



Compound	*	R_1	R_2
32a:	*S*(β)	Cl	Me
32b:	*R*(β)	Cl	Me
32c:	*R*(α)	Cl	Me
32d:	*R*(β)	F	Me
32e:	*S*(β)	F	Me

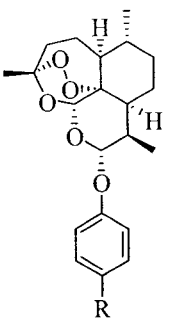
P. M. O'Neill *et al.*[48] **(2001)** have synthesized C-10 phenoxy derivatives of artemisinin **33a-g** and **34a-g** in both α and β series respectively. The C-10-phenoxy derivatives were tested *in vitro* against the K-1 chloroquine-resistant strain of *P. falciparum.* The phenoxy derivatives were also tested against the chloroquine sensitive HB3 strain. The most potent *β*-isomers, the phenyl **33a**,

and 4-fluorophenyl **33c** were also tested *in vivo* against *P berghei* and were found more active than arteether.



Beta (β) series

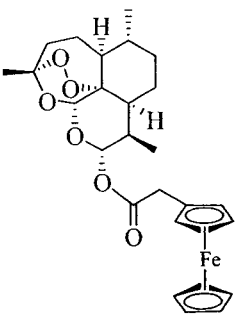
33a: R=H
33b: R=Me
33c: R=CF_3
33d: R=OMe
33e: R=F
33f: R=Cl
33g: R=Napthyl



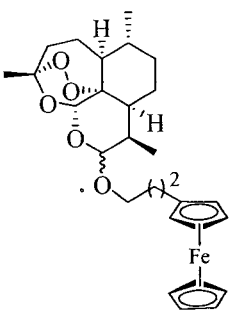
Alpha (α) series

34a: R=H
34b: R=Me
34c: R=CF_3
34d: R=OMe
34e: R=F
34f: R=Cl
34g: R=Napthyl

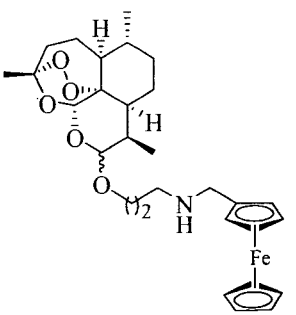
Delhaes *et al.*[49] **(2000)** reported a new series of dihydroartemisinin derivatives **35a-c** containing a ferrocene nucleus. These compounds showed *in vitro* activity comparable to that of artemisinin against *P. falciparum.*



35a



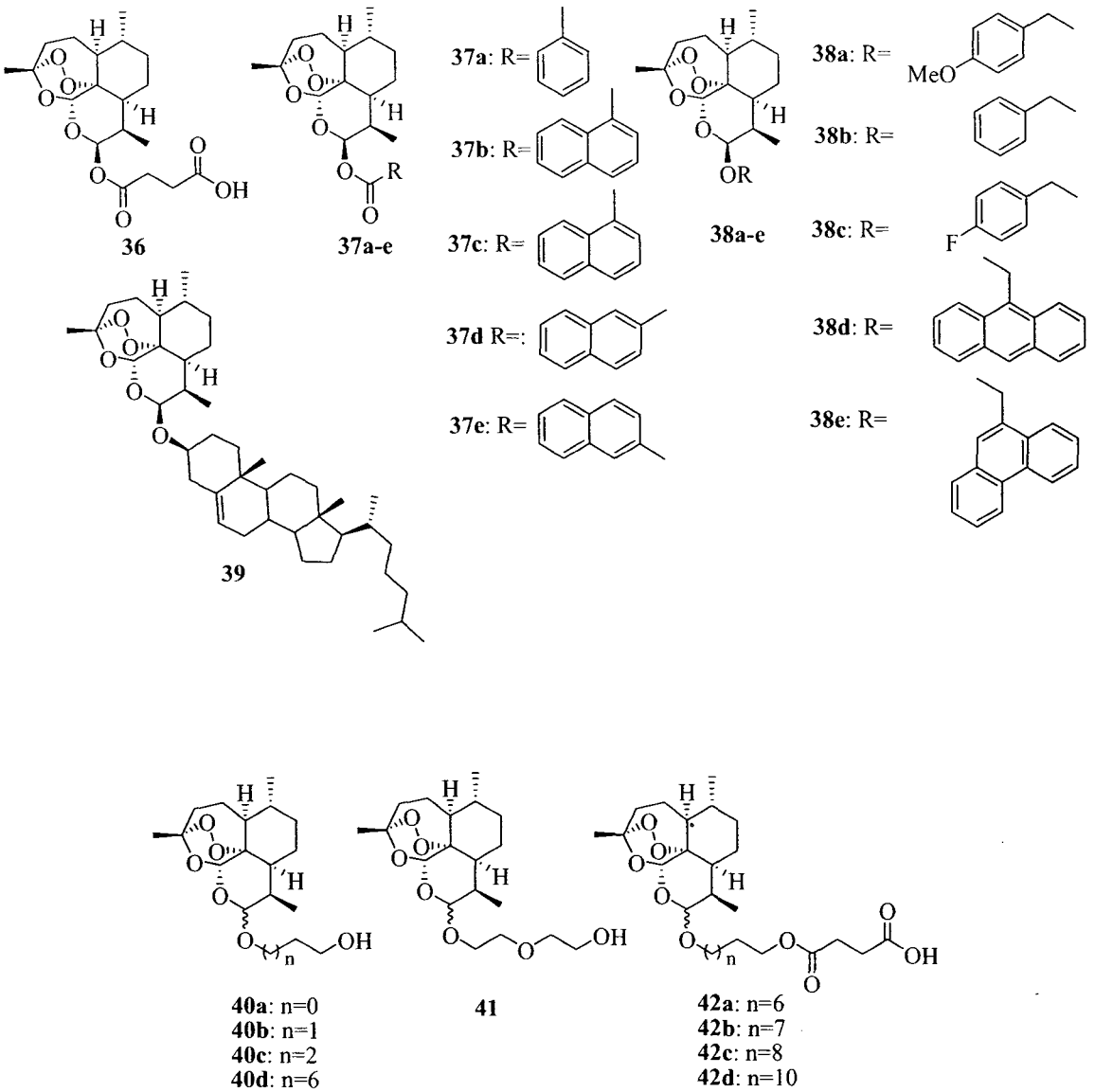
35b



35c

Haynes *et al.*[50] **(2002)** reported various C-10 ether and ester derivatives of DHA. They also first of all reported a convenient synthesis of β-artesunate **36** via base catalyzed esterification. Novel esters derivatives **37a-e** were prepared using Mitsunobu and Schmidt reaction procedures. Coupling reaction using DCC or normal acylation conditions were also reported for the synthesis of various esters. Synthesis of various lipophilic ethers **38a-e** was reported using either $BF_3.Et_2O$ or TMSOTf as acid catalyst, out of which steroidal ester **39** not only showed good antimalarial activity but also very good antiparasitic activity. Mitsunobu and Schmidt reactions were also utilized for the synthesis of ethers as well.

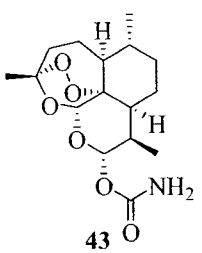
Singh et al.[51] have also reported the synthesis of hydrolytically stable derivatives of artemisinin **40a-d** and **41** by the incorporation of various alkyl chains. Among these compounds **40a-d** and **41** were found to have activity comparable to *β*-arteether. Hemisuccinates **42a-d** showed activity comparable to that of artesunic acid.



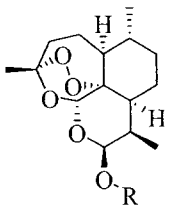
Several workers synthesized various nitrogen containing ethers of DHA that have shown potential antimalarial activity.[48]

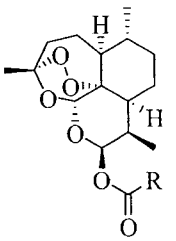
Liu *et al.*[52] synthesized carbamate derivative **43** and assessed its cytotoxicity.

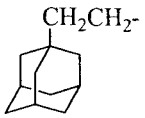
Singh *et al.*[53] (**2006**) recently reported synthesis and *in vivo* antimalarial assessment of highly lipophilic ether derivatives **44a-e** of dihydroartemisinin. He showed that in contrary to arteether where beta isomer is more active α isomers were far more active than β isomers. They also synthesized various ester derivatives of DHA, **45a-f**. Several of these derivatives showed better activity profile in comparison to β-arteether.

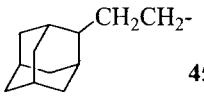


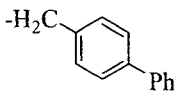
43

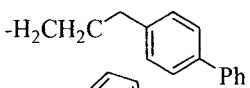


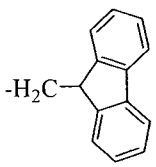


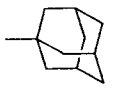
44a: R= 

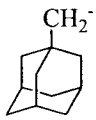
44b: R= 

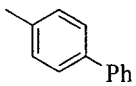
44c: R= 

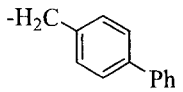
44d: R= 

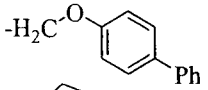
44e: R= 

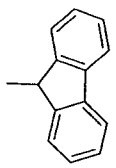
45a: R= 

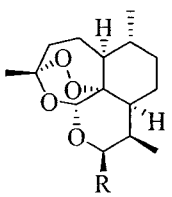
45b: R= 

45c: R= 

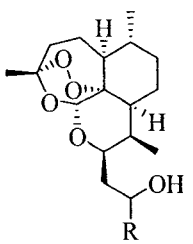
45d: R= 

45e: R= 

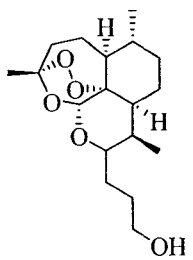
45f: R= 



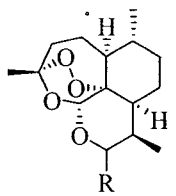
46: R=H
47: R=C_4H_9
48a: R=$CH_2CH{=}CH_2$
48b: R=$CH_2CH_2CH_3$
48c: R=CH_2CH_3
48c: R=CH_2CH_2OH



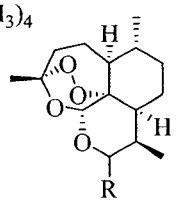
49a: R=CH_3
49b: R=CH_2CH_3
49c: R=$CH(CH_3)_3$
49c: R=$C(CH_3)_4$



50: 10*S*
51: 10*R*



52a: R=cycloalkyl
52b: R=hydroxyalkyl
52c: R=aryl



53a: R=n-C_4H_9
53b: R=$CH_2CH_2C_6H_5$

C-10 carba analogues of artemisinin

Several analogs of artemisinin have been prepared by the replacement of oxygen at C-10 with carbon substituted alkyl or aryl residues. These deoxoartemisinin[54] **46** analogs were being designed to be more chemically robust towards acidic hydrolysis due to lack of C-10 acetal

functionality together with the fact that these compounds on oxidative dealkylation would not lead to neurotoxic dihydroartemisinin.

Several approaches have been made in made in this regard; Jung *et al.*[55] (**1990**) first time reported the synthesis and antimalarial activity of 10β-n-butyldeoxoartemisinin **47**. It was found to have *in vivo* antimalarial activity comparable to that of artemisinin. Haynes *et al.*[56] (**1992**) also reported the synthesis of 12α and 12β alkyldeoxoartemisnins using artemisinic acid as starting material. Ziffer *et al.*[57] (**1995**) have reported synthesis of various 10β-alkyldeoxoartemisinin **48a-c**. 10β-allyldeoxoartemisinin **48a** was converted into several promising derivatives, of which 10β-n-propyldeoxoartemisinin **48b** was having *in vitro* antimalarial activity approx. equal to that of arteether against W-2 and D-6 clones of *P. falciparum*. Ma *et al.*[58] (**2000**) utilized 10β-allyldeoxoartemisinin for the synthesis of various potent carba analogs **49a-c**. Several of these compounds showed better activity than artemisinin.

Jung *et al.*[59] reported the synthesis of 12-(3'-hydroxy-n-propyl) deoxoartemisinin **50** and **51** from artemisinic acid. Compound **50** showed 5 times more activity than artemisinin *in vitro* against chloroquine-resistant *P. falciparum*.

McChesney *et al.*[60] reported the synthesis of another series of deoxo-artemisinin analogues having prototype **52a-c** from artemisinic acid.

Vroman *et al.*[61] (**1997**) gave a new synthetic method for the synthesis of 9-alkyl-12-deoxoartemisinin. Compounds **53a** and **53b** prepared by this method were reported to be highly potent antimalarials.

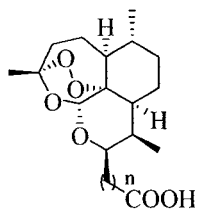
Jung *et al.*[62] (**1998**) also reported the synthesis and stability of various water soluble carba anlogs **54a-c** of artemisinin.

Posner and coworkers.[63] **(1998)** reported various aromatic analogs of 10-deoxoartemisinin Posner and coworkers [64] **(1999)** also reported the chemo selective synthesis of 10-deoxoartemisinin analogues **55a-c** which showed good *in vitro* antimalarial activity. He also reported the synthesis and antimalarial assessment of several orally active derivatives of artemisinin family in this report.

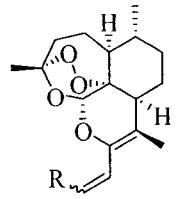
P. M. O'Neill *et al.*[65] (**1999**) reported the synthesis of carba analogs of first generation 1,2,4-trioxane artemether **56a-e** and **57a-e** which showed potent antimalarial activity.

Hindley *et al.*[66] (**2002**) reported the synthesis of carba amino derivatives of artemisinin **58a-e** out of which compound **58b** showed ED_{90} less than 10 mg/kg against *P. yoelii* in mice.

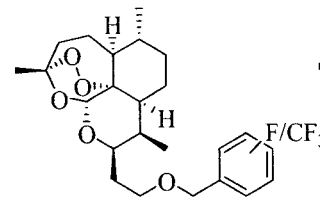
Wang *et al.*[67] reported the synthesis of 2-hydroxy-naphthyl carba analogs of artemisinin. The C-10 naphthyl substituted derivative **59a** and **59b** exhibited antimalarial activities similar to that of artemisinin *in vivo*.



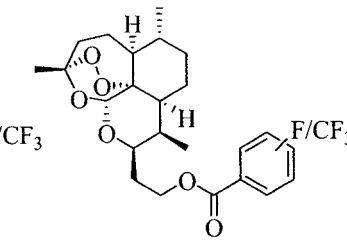
54a: n=1
54b: n=3
54c: n=4



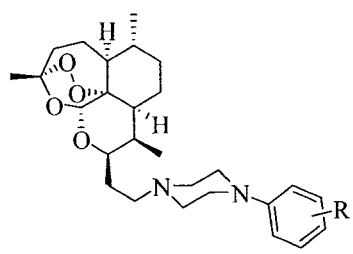
55a: R=H
55b: R=Me
55c: R=Ph



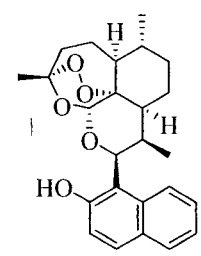
56a: 2-fluoro phenyl
56b: 3-fluoro phenyl
56c: 4-fluoro phenyl
56d: 2-trifluoromethylphenyl
56e: 4-trifluoromethylphenyl



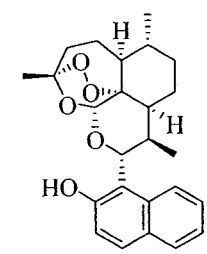
57a: 2-fluoro phenyl
57b: 3-fluoro phenyl
57c: 4-fluoro phenyl
57d: 3-trifluoromethylphenyl
57e: 4-trifluoromethylphenyl



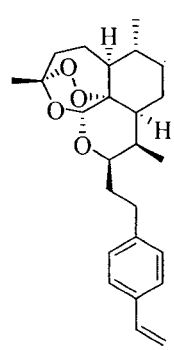
58a: R=*p*-Cl
58b: R=*m*-CF_3
58c: R=*p*-H
58d: R=*p*-NO_2
58e: R=*p*-F



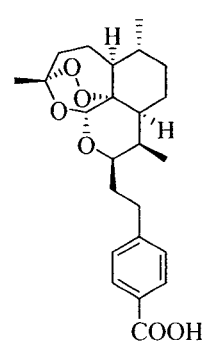
59a



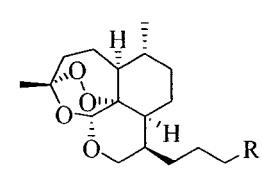
59b



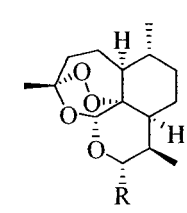
60



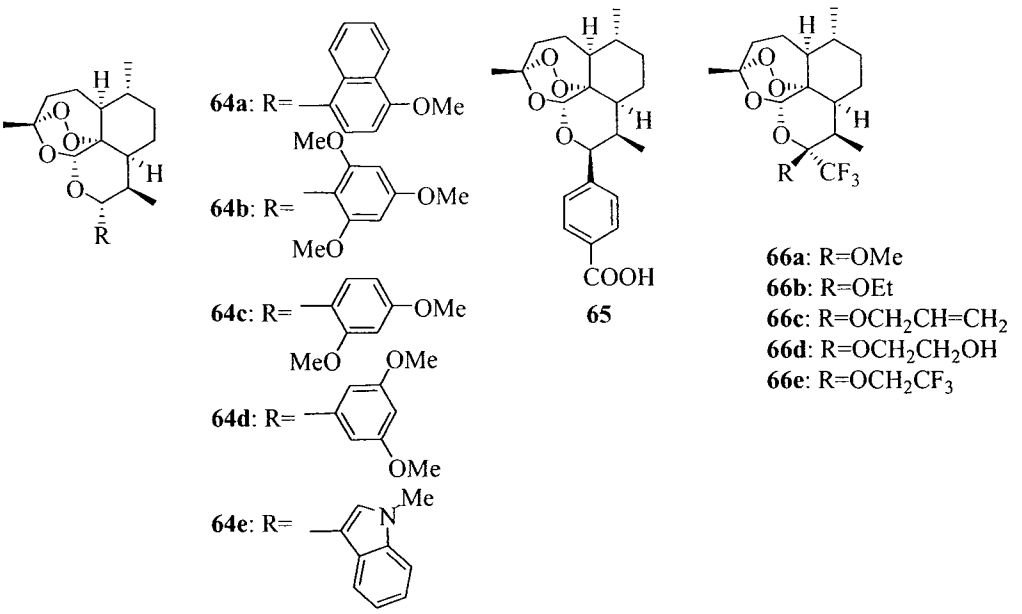
61



62a: R=H
62b: R=C_6H_5
62c: R=*p*-FC_6H_4
62d: R=*p*-$MeOC_6H_4$
62e: R=*p*-3,4-$Cl_2C_6H_3$



63a: R=CF_3
63b: R=C_4H_9



Jung *et al.*[68] (**2002**) reported water soluble, hydrolytically stable (+) deoxoartelinic acid **61** from **60** and assessed its antimalarial activity.

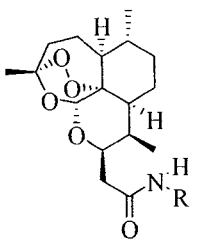
Avery *et al.*[69] reported the synthesis and antimalarial activity of novel substituted deoxo artemisinins **62a-e**.

Chorki *et al.*[70] (**2002**) for the first time reported synthesis of C-10α trifluoromethyl deoxoartemisinins **63a** and **63b**.

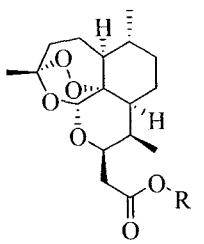
Haynes *et al.*[71] reported stereo selective preparation of 10α and 10β aryl derivatives of artemisinin of prototypes like **64a-e** and **65**.

Bonnet-Delphon and co-workers[72] (**2004**) tried to increase the metabolic and chemical stability of arteether and DHA by the incorporation of C-10 CF_3 group, thereby, making CF_3 analogues of arteether **66a-e** 45 times more stable than arteether itself under "simulated stomach acid conditions".

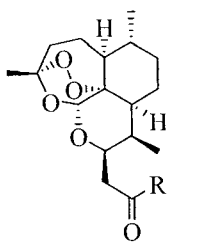
Liu *et al* [73] reported synthesis and cytotoxicity of various carba analogs **67a-c**, **68a-c** and **69a-c**.



67a: R=C_2H_5
67b: R=C_4H_9
67c: R=C_6H_{13}



68a: R=C_2H_5
68b: R=$C_{12}H_{25}$
68c: R=$C_{18}H_{37}$



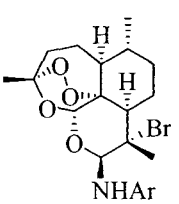
69a: R=C_2H_5
69b: R=$C_{12}H_{25}$
69c: R=$C_{18}H_{37}$

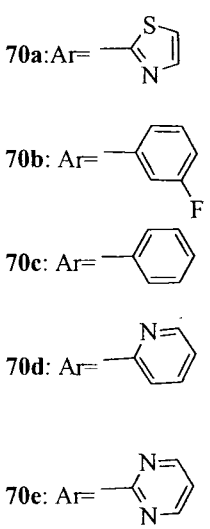
C-10 aza analogues of artemisinin

Lin *et al.*[74] first time reported the synthesis and antimalarial activity of C-10 aza analogs of artemisinin **70a-e**. These compounds showed very good *in vitro* antimalarial activity but poor *in vivo* antimalarial activity

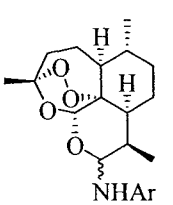
Yang *et al.*[75] then reported synthesis and antimalarial assessment of aniline substituted aza analogs of artemisinin **71a-j**.

Haynes *et al.*[76] (**2005**) carried out detailed structure activity relationship of C-10 aza analogs of artemisinin **72a-e**, **73a-f** and **74a-e**. Out of these compound **73f** (artemisone) was chosen for clinical trials on account of its better pharmacokinetic and activity profile.

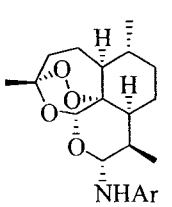




70a:Ar=
70b: Ar=
70c: Ar=
70d: Ar=
70e: Ar=



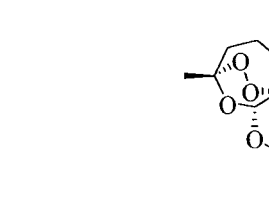
71a: Ar=C_6H_5
71b:Ar=*m*-ClC_6H_4
71c: Ar=*p*-ClC_6H_4
71d:Ar=*m*-BrC_6H_4
71e: Ar=*p*-BrC_6H_4
71f: Ar=*p*-IC_6H_4
71g: Ar=*p*-$CH_3C_6H_4$
71h: Ar=*p*-$CH_3OC_6H_4$
71i:Ar=*p*-$COOHC_6H_4$
71j: Ar=*p*-$COOHC_6H_4$

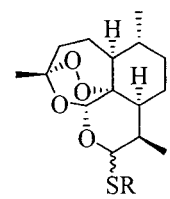


72a:Ar=*p*-PhC_6H_4
72b: Ar=*p*-FC_6H_4
72c:Ar=*m*-$CH_3SO_2C_6H_4$
72d: Ar=*p*-$CH_3SO_2C_6H_4$
72e:Ar=*p*-$COOCH_3C_6H_4$

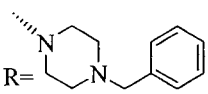
C-10 thio analogues of artemisinin

Venogopalan *et al.*[44] **(1995)** have synthesized several C-10 thioether analogs of prototype **75** of artemisinin by treating DHA with various thiols in the presence of $BF_3.Et_2O$ to furnish α and β isomers which were separated. These thioethers were found active both in *P. berghei* (K-173) infected mice and in *P. yoelii nigeriensis* (NS) infected mice via subcutaneous and oral route.

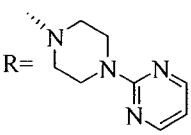




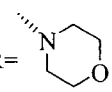
73a: R=



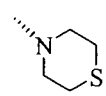
73b: R=



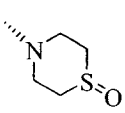
73c: R=



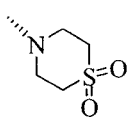
73d: R=



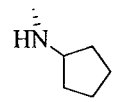
73e: R=



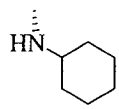
73f: R=



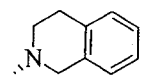
74a: R=



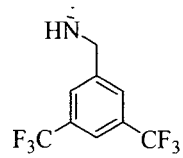
74b: R=



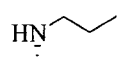
74c: Rr=



74d: R=



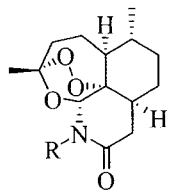
74e: R=



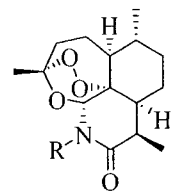
75a: R=C_2H_5
75b: R=C_6H_5
75c: R=cyclohexyl
75d: R=CH_2COOH
75e: R=CH_2CH_2COOH
75f: R=CH_2CH_2OH

Azaartemisnins

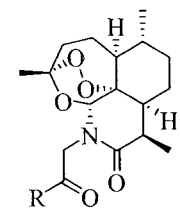
Avery *et al.*[77] **(1995)** gave a synthetic methodology for the synthesis of 11-aza-9-desmethylartemisins **76a-f** and assessed their antimalarial activity Torok *et al.*[78] **(1995)** developed semisynthetic method for preparation *N*-alkyl -11-azaartemisinins **77a-f** and screened them for antimalarial activity. One of the compounds in them showed much better activity than artemisinin *in vivo*. Mekonnen *et al.*[79] have also synthesized several analogs of artemisinin of prototype **78**. Haynes *et al.*[80] **(2007)** carried out detailed thermal stability and *in vitro* efficacy study of various *N*-sulfonyl derivatives of 11-azaartemisinin of prototype **79**.



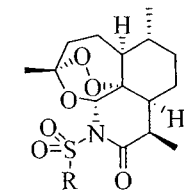
76a: R=CH_3
76b: R=$CH_2CH_2CH_3$
76c: R=CH_2COOH
76d: R=$CH_2C_6H_5$
76e: R=$CH_2CH_2C_6H_5$
76f: R=$CH_2CH_2CH_2C_6H_5$



77a: R=H
77b: R=$CH_2CH=CH_2$
77c: R=$CH_2CH(CH_3)_2$
77d: R=CH_3
77e: R=$CH_2C_6H_5$
77f: R=CH_2CHO

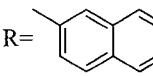


78a: R=CH_3
78b: R=C_6H_5

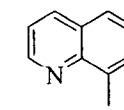


79a: R=CH_3

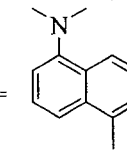
79b: R=



79c:R=



79d: R=



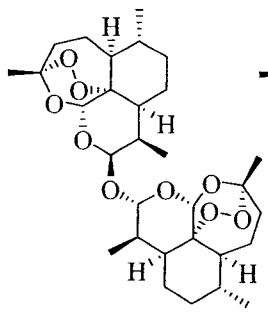
1.7.2.2 Artemisinin based dimers

The first report of artemisinin based dimer and it antimalarial activity comes from Chinese group, who isolated the compound **80** as self dimer of dihydroartemisinin formed during the course of acetal formation reaction under acidic conditions. This compound has been mentioned in literature by various other workers as well.[81]

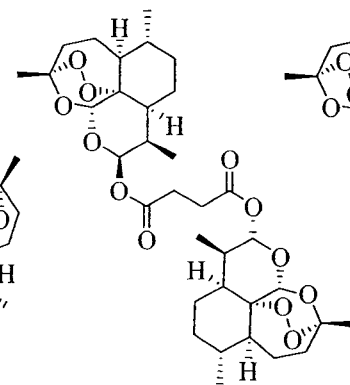
Physical properties and antimalarial activity of dimers of dihydroartemisinin **81-83** with intercalating succinyl group have also been reported by several groups.[82]

Venugopalan *et al.*[83] **(1995)** synthesized various ring contracted dimers of artemisinin **84** and **85** and assessed them for antimalarial activity.

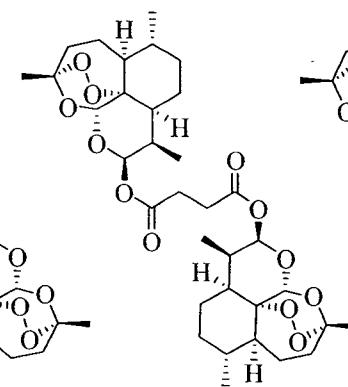
Posner *et al.*[84] **(1997)** reported the antimalarial and antiproliferative activity of various artemisinin based dimers **86**.



80



81



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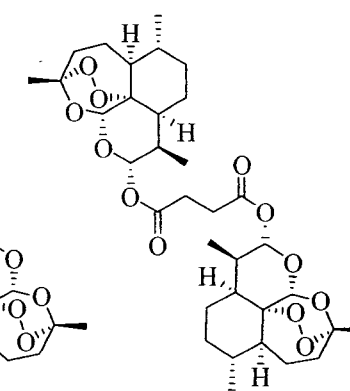

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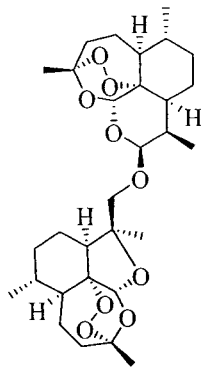

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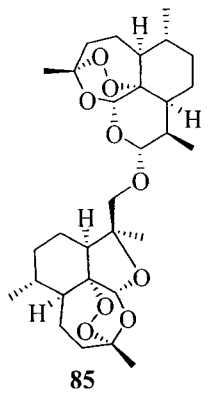

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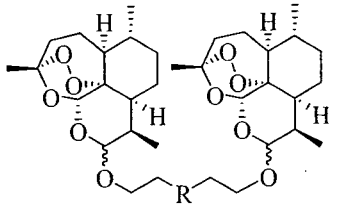
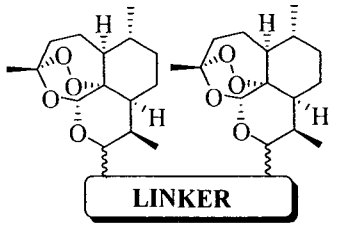
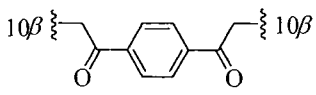


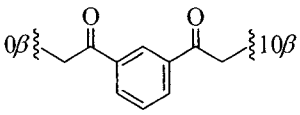
86a: R=OCH_3CH_2O
86b: R=$(CH_2)_4$
86c: R=S-S



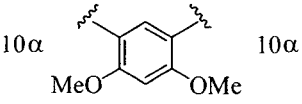
87a:



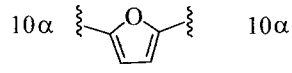
87b:



87c:

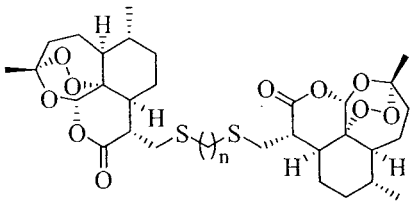


87d:

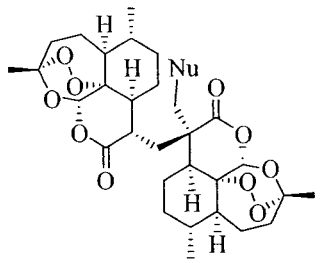


Posner *et al.*[85] **(1999)** reported the antimalarial, antiproliferative and antitumor activity of artemisinin derived chemically robust trioxane dimers **87**. He in his ongoing research developed varieties of artemisnins derived dimers **87a-d** and assessed them for their antimalarial and anticancer activity.

Ekthawatchai *et al.*[86] reported the antimalarial activity of various prototype dimers **88** and **89** of artemisinin formed upon nucleophilic addition to artemisitene.

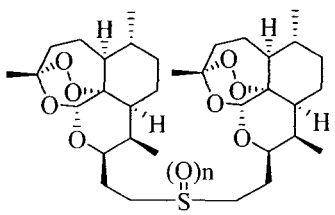


88a: n=1
88b: n=2
88c: n=3
88d: n=4
88e: n=5

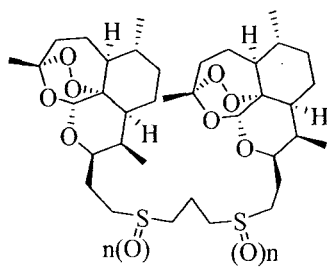


89a: Nu=CH_2CH_3
89b: Nu=$CH_2CH_2CH_3$
89c: Nu=$(CH_2)_2CH_2CH_3$
89c: Nu=$CH_2(CH_2)_2CH_2CH_3$

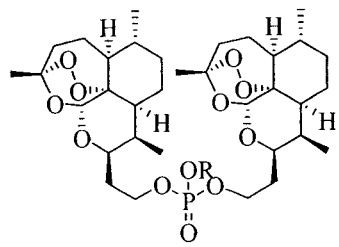
Jung *et al.*[87] also synthesized various artemisinin based dimers **90** and **91**. Jeyadevan *et al.*[88] carried out synthesis and antimalarial assessment of C-10 non acetal dimers of artemisinin **92**.



90a: n=0
90b: n=2

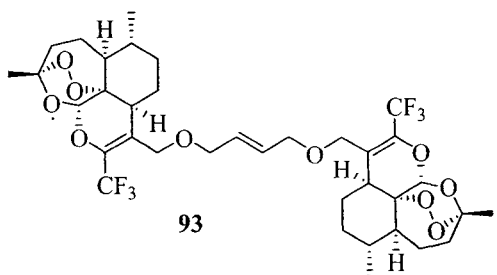


91a: n=0
91b: n=2



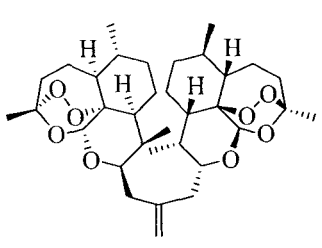
92a: R=Me
92b: R=Ph

Grellepois *et al.*[89] synthesized various artemisinin based dimers having prototype **93** via self cross metathesis reaction using Grubbs catalyst.[90]



93

Posner *et al.* published several papers regarding the synthesis and bio evaluation of artemisinin based dimers **94-105**.[91]



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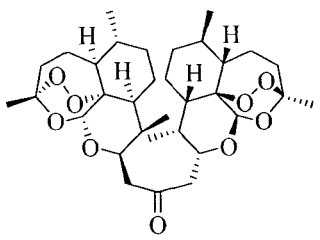

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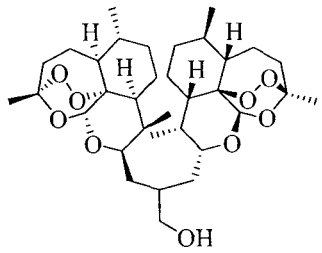

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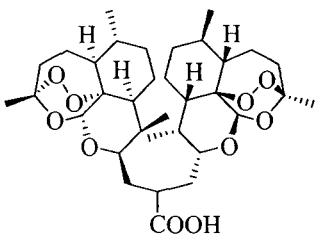

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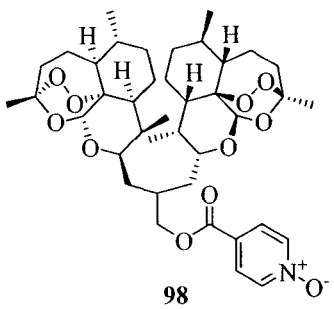

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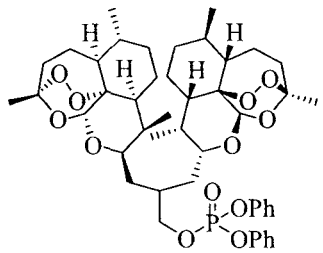

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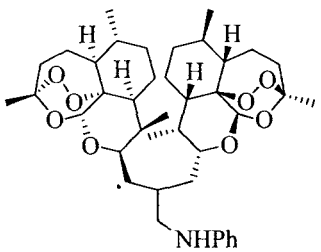

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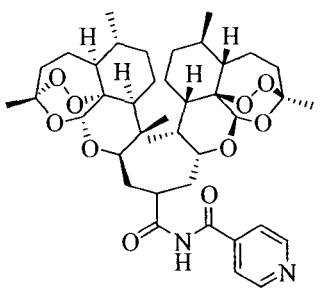

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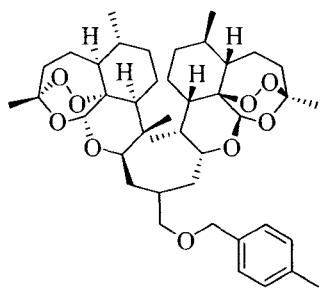

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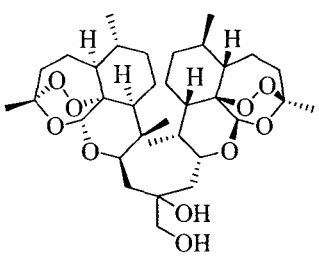

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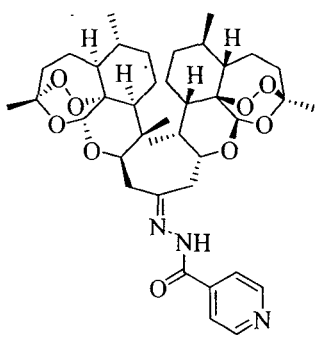
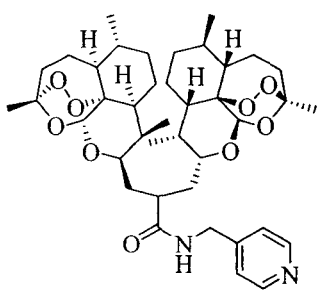


104



105

1.7.2.3 Non privileged analogs of artemisinin

Together with these privileged analogs of artemisinin there are various non privileged analogs as well which have been synthesized by various workers. Jung *et al.*[92] **(2001)** reported the synthesis of (+)-deoxoartemisnin and its novel C-11 derivatives. Avery *et al.*[93] reported the synthesis and activity of various C-13 analogs of artemisinin. They also synthesized design based C-9β substituted analogs of artemisinin and assessed their structure activity relationship.

1.8 Drawbacks and problems associated with artemisinins

Although artemisinin and its derivatives are still the best known antimalarials, they are often associated with several serious problems such as high cost, limited availability from natural sources, sometimes poor oil and water solubility as in case of artemisinin itself and in some cases high rate of recrudescence, short plasma half life, toxicity and poor bioavailability as well.[94] These factors limit the use of artemisinin as continuous source of drug for the treatment of malaria. The extensive use of artemisinin during clinical trials early in china, without report of serious human toxicity, animal studies have yielded some cautionary findings. Arteether and artemether have short plasma half-lives and produce fatal central nervous system (CNS) toxicity in chronically dosed rats and dogs.[95] Rats dosed with artemether and arteether at 2.5 mg/kg/day showed cardiac abnormalities and neurotoxicity within 2 weeks, and dogs dosed at 20 mg/kg/day with these artemisinin analogs developed progressive neurological defects, leading to death in approximately 1 week.[96] These daily doses are an order of magnitude more than necessary to clear both chloroquine-sensitive and chloroquine-resistant *P. berghei* (various strains) in mice in 4 days or less.[97] Given the neurotoxic effects of artemisinin and its analogs in these animal studies, researchers investigated the effects of these antimalarials on neuronal cells *in vitro*.[98] The drugs inhibited both neuronal cell proliferation and formation of neurite outgrowths at concentrations as low as 10 nM,[99] which is comparable to the effective level of these drugs *in vitro* against many strains of *P. falciparum*. As far as potential neurotoxicity is concerned, any analogue with a log *P* higher than that of artemether (3.3-3.5) can cross the blood-brain barrier. By use of the ADME (absorption, distribution, metabolism, and excretion) paradigm for enhancing efficacy through increased absorption, the application of *Lipinski's Rule of Five*[100] to the design of new semisynthetic analogues have been employed.[101]

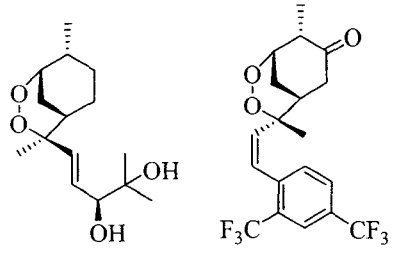
The discovery of 1,2,4 trioxane, a peroxide moiety as the pharmacophore for the antimalarial activity of artemisinin, several efforts have been made in past few decades towards the preparation of simpler synthetic peroxides in order to meet the growing demand of new and cheaper antimalarials

1.9 Synthetic Peroxides as Potential Antimalarial Agents

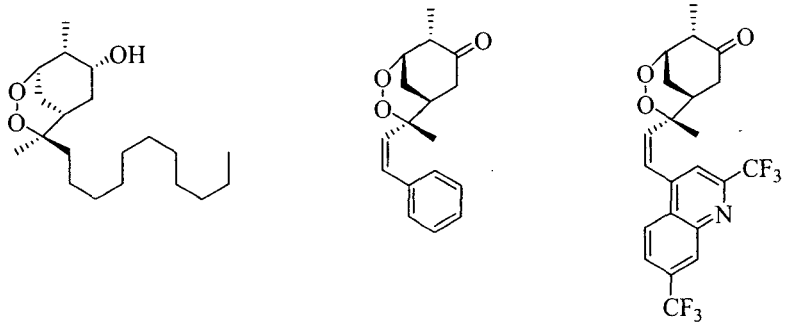
1,2 Dioxanes

Yingzhaosu A **106**, a natural product endoperoxide with antimalarial properties was isolated from Chinese herb, Yingzhao, *Artabotrys uncinatus*,[102] but its scarcity in nature and difficult total synthesis[103] had led to the development of its various structurally simpler synthetic analogs.

Roche,s group[104] reported variety of analogs of **106** containing its 2,3 dioxabicyclo[3.3.1]nonane core were prepared from the enantiomers of carvone. Endoperoxide **107b**, the core structure of **106**, has weak antimalarial activity *in vivo*. Replacement of the methyl group at position 4 with n-alkyl chains of 9-11 carbon atoms **107c** led to a nearly order of magnitude increase in *in vivo* activity; analogs with shorter or longer chains were less active. As illustrated by **107d**, compounds containing polar functional groups such as alcohols, acids esters, or amines at position 4 showed little or no activity, although reduction of the ketone group at position 7 to the more polar alcohol **107e** did not affect activity significantly. As shown by **107f**, replacement of the undecyl chain in **107c** with a styryl group abolished antimalarial activity. However, analogs of **107f**, including quinoline **107g**, and especially **107a**, the 2,4-di(trifluoromethyl)styryl derivative, had very good antimalarial profiles.



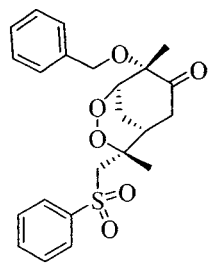
106 **107a** **107b** **107c** **107d**



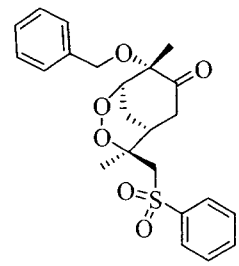
107e **107f** **107g**

Although **107a** is an order of magnitude less potent than the semisynthetic artemisinins *in vitro*, it is only 3-fold less active than artemether *in vivo*.[104a] Other attractive properties of **107a** include a chemically more stable 1,2-dioxane (endoperoxide) versus the 1,2,4-trioxane in artemisinin, and a lower rate of recrudescence and a longer plasma half-life than either artemether or arteether. From these data, **107a** (arteflene) was selected as the clinical candidate, and it progressed to Phase II clinical trials in semi-immune African patients with mild *P. falciparum* malaria. In these trials, the drug was given orally as a lipid suspension, but the results were inconsistent and the compound was abandoned.[105]

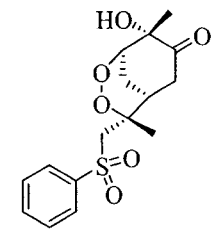
A short and efficient synthesis of 4,8-dimethyl-4-phenylsulfonylmethyl-2,3 dioxabicyclo[3.3.1]nonanes from the enantiomers of limonene or *R*-(-)-carveol afforded a new series **108** of analogs of yingzhaosu **106** with a variety of substituents at C-8.[106] Relative to benzyl ether **108a**, activity declined substantially for the more polar carbinol **108c**, a trend that was partially reversed by acetylation to form **108d**. In contrast, the less polar olefin, a dehydration product of **108c**, and its fully saturated hydrogenation product, were less active than **108c**. Although **108b** was marginally less potent than its diastereomer **108a** *in vitro*, it was significantly more active than **108a** and only slightly less active than artemisinin when it was administered orally.



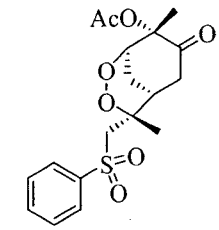
108a



108b



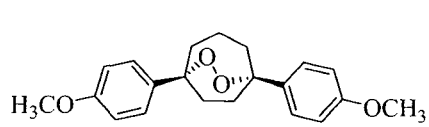
108c



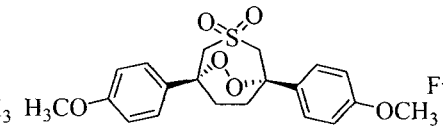
108d

Posner's group reported the mechanism-based design of a series of easily prepared symmetrical bicyclo[3.2.2]nonane **109** and bicyclo[2.2.2]octane **110** endoperoxides. As illustrated by sulfone **109b**, seven heterocyclic analogs of **109a** containing sulfur, oxygen or nitrogen atoms were synthesized; however, these were all an order of magnitude less potent than their carbocyclic analog **109a** even though they are reduced by ferrous iron to form reactive carbon centered radicals and epoxides.[107]

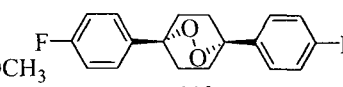
Varieties of dioxanes have been prepared so far and have been assessed for their antimalarial activity but none of them have shown potent antimalarial activity.



109a



109b



110

1,2,4-Trioxanes

This class of compounds have been known in literature since 1957, when Payne and Smith first of all synthesized first synthetic trioxane.[108] Later on several researchers developed various methodologies for the synthesis of different types of trioxanes only from synthetic point of view.[109] It was only after the disclosure of the fact that it is actually the endoperoxide linkage of artemisinin in form of 1,2,4-trioxane, which is responsible for its antimalarial activity large emphasis has been made towards the synthesis and bio-evaluation of various types of synthetic trioxanes.

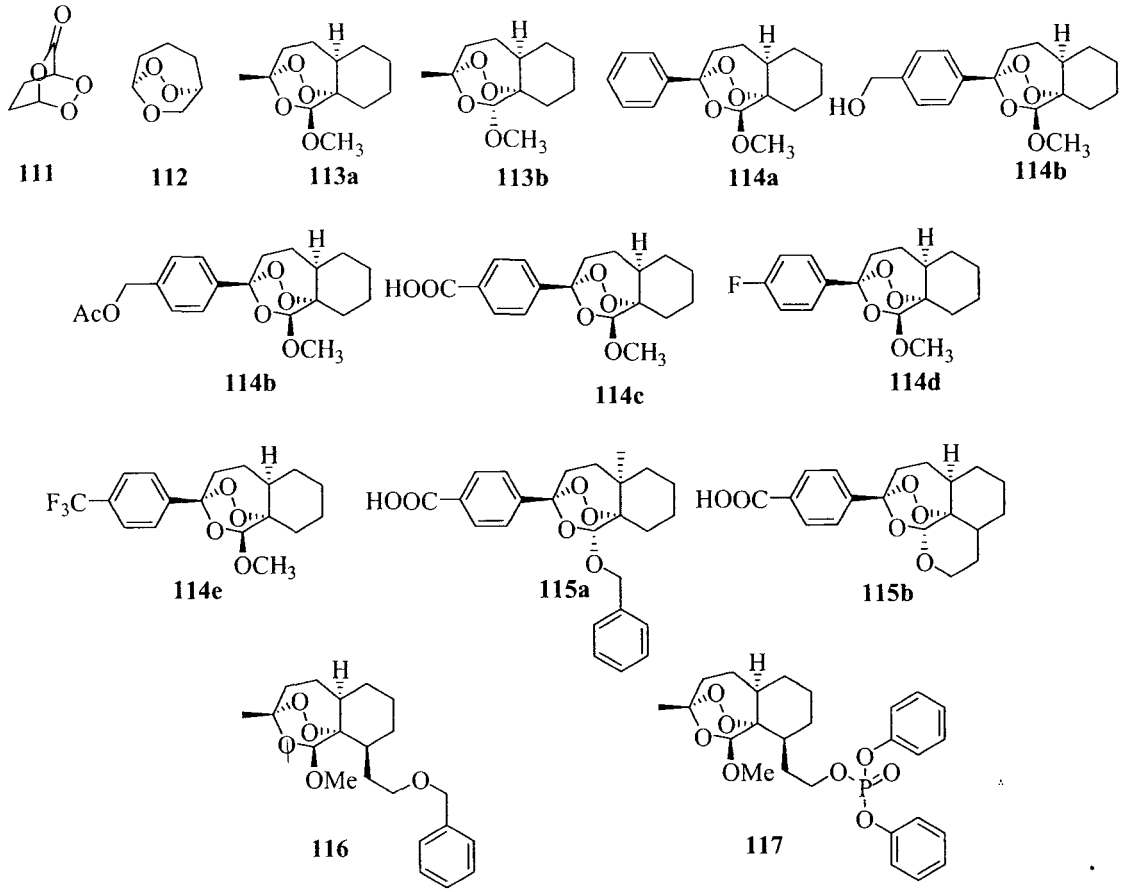
The bicyclic trioxanone[109e] **111** was prepared from 2-methyl-2-cyclopenten-1-ol as in six steps. Bicyclic trioxane[110] **112** (2,3,5-trioxabicyclo[2.2.3]nonane), easily recognizable as the pharmacophoric core of artemisinin, was prepared from 6-tetrahydrooxepanol as starting material. However, these bicyclic trioxanes had only marginal antimalarial activity.

The epimeric 1,2,4-trioxanes **113a** and **113b** were synthesized by the photooxygenation reaction. Compound **113a** was just an order of magnitude less potent than artemisinin, whereas **113b** was quite less potent than artemisinin. Jefford *et al.* showed that replacement of the bridgehead C-3 methyl group by C-3 phenyl group in **113a** improved 6-fold antimalarial potency.[111] Based on these facts Posner[112] *et al.* synthesized various substituted C-3 phenyl analogs of prototype **114.** Some of these compounds **114a-e** have shown promising *in vivo* activity. Trioxane alcohol **114b**, acetate trioxane **114c** were more potent to artemisinin whereas water soluble carboxylic acid derivative **114d** was less active than artemisinin.

In continuation of their work, Posner *et al.*[113] prepared carboxyphenyl trioxanes **115a** and **115b** which were more soluble in water at pH 7.4 than artesunate. These compounds were less effective than their less lipophilic and more easily prepared parent compound **114**.

A large number of derivatives of artemisinin like 1,2,4-trioxanes, including ethers, carboxylate esters, phosphate esters, carbamates and sulfonates have been prepared by Posner and coworkers. Some of the compounds found active *in vitro* were also tested *in vivo* in mice model. Based on their antimalarial potency in mice, two trioxanes **116** and **117** were selected for biological evaluation in Aotus monkeys infected with multidrug-resistant (MDR) *P. falciparum.* The activity data revealed that both **116** and **117** are as effective as arteether against MDR *P. falciparum* in Aotus monkeys.[114]

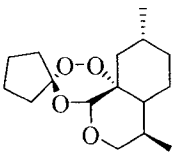
Spiro ring-fused trioxane **118** was synthesized starting with (-)-isopulegol. This trioxane was only slightly less potent than artemisinin. The analog in which the spirocyclopentane ring was replaced with geminal methyl substituents was 9-fold less potent than **118**.[111, 115]



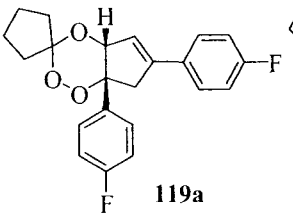
1,4-Endoperoxides, formed from photooxygenation of 1,4-diaryl-1,3-cyclopentadienes, reacted with aldehydes or ketones in reactions catalyzed by Me_3SiOTf to produce a large series of cis-fused cyclopenteno-1,2,4-trioxanes, examplified by **119a** (Fenozan B07).[116] Several such analogs **119b-f** were synthesized and assessed for antimalarial activity.[117]

Among these cis-fused cyclopenteno-1,2,4-trioxanes, **119a** (Fenozan B07) had the most promising activity profile and was chosen for further development.[118]

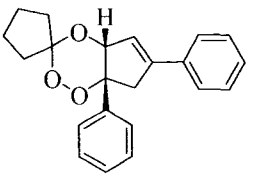
Spiro trioxanes **120** and **121** and their analogs were prepared by photooxygenation of the corresponding allylic alcohols followed by peroxyacetalization reactions with aldehydes or ketones. Griesbeck *et al.*[119] (**2002**) reported synthesis of antimalarial 1,2,4-trioxanes via photooxygenation of chiral allylic alcohol 4-methyl-3-penten-2-ol followed by subsequent BF_3 catalyzed peroxyacetalization with aldehydes or ketones afforded four monocyclic and spirobicyclic 1,2,4-trioxanes, of which **120** was the most potent. O'Neill *et al.*[120] (**2001**) reported Co(II)-mediated regioselective Mukaiyama hydroperoxysilylation of 2-alkyl- or 2-aryl-prop-2-en-1-ols furnished peroxysilyl alcohols which were treated with aldehydes or ketones to provide various spiro trioxanes. Trioxane **121**, the best of these, was only an order of magnitude less potent than artemisinin.



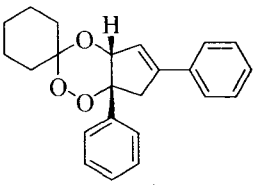
118



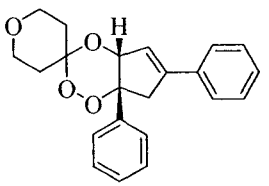
119a



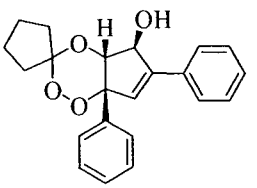
119b



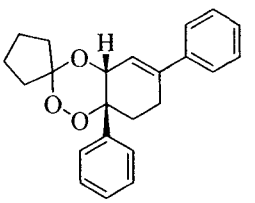
119c



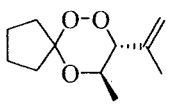
119d



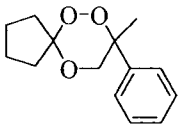
119e



119f

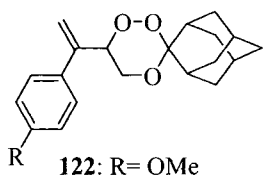


120

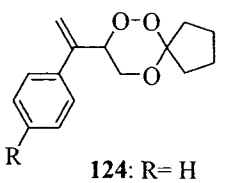


121

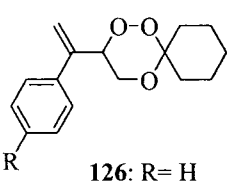
Singh (**1990**) reported a new and convenient $^1O_2$-mediated synthesis of 6-arylvinyl-1,2,4-trioxanes.[121] The key steps of this method are the preparation of β-hydroxyhydroperoxides by photooxygenation of suitably substituted allylic alcohols and then elaboration of these β-hydroxyhydroperoxides into 1, 2, 4-trioxanes by acid catalyzed condensation with various ketones or aldehydes. This method is safe and has been used for the preparation of trioxanes on multigram scale.



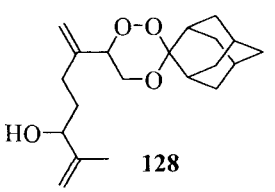
122: R= OMe
123: R= Cl



124: R= H
125: R= Cl



126: R= H
127: R= Cl

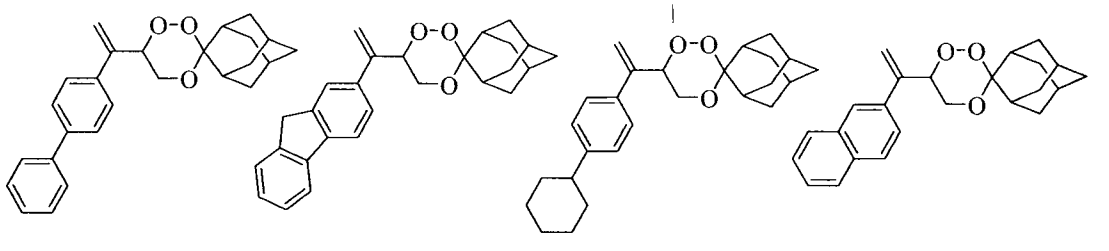


128

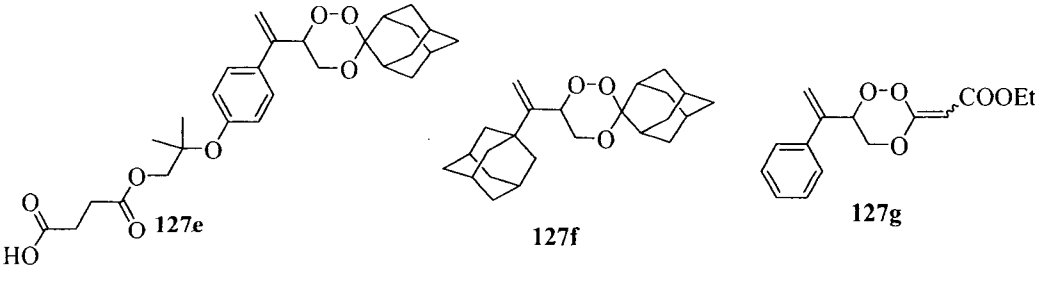
Singh *et al.*[122] have prepared several *in vivo* potent spiro 1, 2, 4-trioxanes of different prototypes and were the first to report antimalarial potency of synthetic 1, 2, 4- trioxanes *in vivo*. In the preliminary study on 6-arylvinyl-1,2,4-trioxanes, compounds **122-128** showed promising activity by intra peritoneal (ip) route against chloroquine-sensitive *P. berghei* in mice but these compounds were poorly active against chloroquine-resistant *P. yoelii* in mice. Among geraniol

derived 6-arylalkylvinyl trioxanes, compound **126** showed 100% survival rate at 96 mg/kg against MDR *P. yoelii* in mice by oral and im routes. Although no *in vitro* data was presented for these trioxanes, the *in vivo* data showed that the order of efficacy was spiroadamantane > spirocyclopentane > spirocyclohexane. Introduction of a methyl group at the carbon atom bearing the α-arylvinyl group abolished activity.

Singh *et al.* in continuation of their SAR have prepared several highly lipophilic synthetic trioxanes **127a-g** and amino functionalized trioxanes **128a-d** and trioxane quinoline hybrids (trioxaquines) **129a-f**. Compound **127a** and **127b** showed 100% survival at 12 mg/kg and 24 mg/kg dose respectively, by oral route against multidrug resistant *P. falciparum* in swiss mice. Water soluble trioxanes **127e** is active by both oral and i.m. route at 72 mg/kg dose and has been selected for clinical trials on account of its better pharmacokinetic profile. Among amino derivatives compound **128d** showed 80% survival rate at 24mg/kg dose by oral route against MDR *P. yoelii* in mice. The trioxaquines **129a-e** were found to have poor activity.

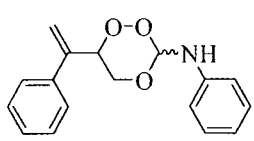


127a **127b** **127c** **127d**

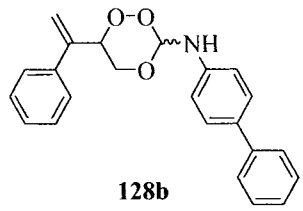


127e **127f** **127g**

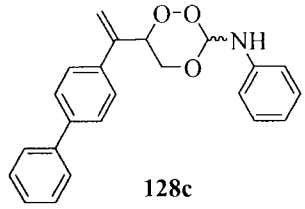
Meunier *et al.*[123] have also synthesized several trioxane quinoline hybrids (trioxaquines), some of which have shown promising activity profile *in vitro* and *in vivo*. Ascaridole-derived, trioxaquine **130** was the best compound of the series. It exhibited ED_{50} values of 5 mg/kg/day and 18 mg/kg/day by i.p. and p.o. routes respectively against *P. vinckei* in mice. This compound completely cleared parasitaemia in *P. vinckei* infected mice, without recrudescence, at an i.p. dose of 20 mg/kg /day.



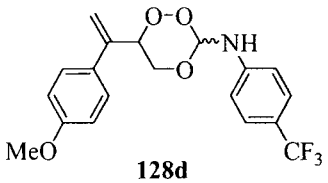
128a



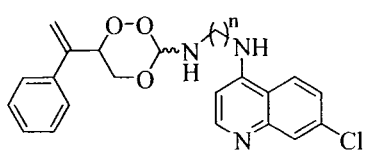
128b



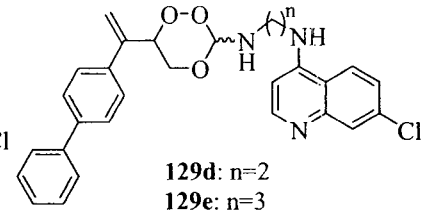
128c



128d

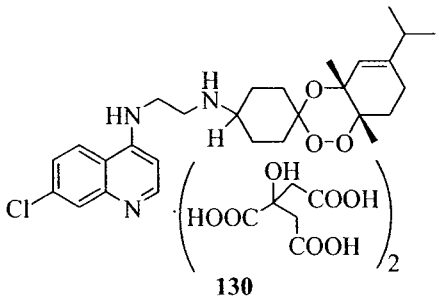


129a: n=2
129b: n=3
129c: n=4

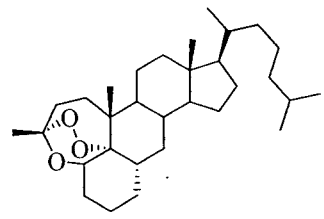


129d: n=2
129e: n=3
129f: n=4

Rong and Wu[124] melded most of the structural elements of artemisinin in a cholestane-type steroid trioxane hybrid structure. Compound **131** has been prepared in five steps from methyl 3-oxocholest-4-en-6b-yl acetate using photooxygenation reaction as key step. Both **131** and its diastereomer were more effective than artemisinin *in vivo*.



130



131

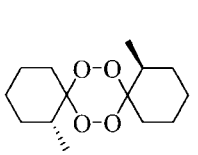
1,2,4,5-Tetraoxanes

Symmetrical meso dispiro 1, 2, 4, 5-tetraoxane **132a**, readily obtained by reaction of 2-methylcyclohexanone with acidified hydrogen peroxide, was found to be only 6-fold less active than artemisinin. Tetraoxane **132a** is synergistic with chloroquine, quinine, mefloquine, and artemisinin against *P. falciparum*.[125]

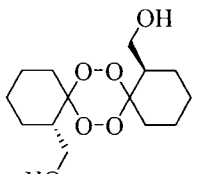
Sixteen dispiro tetraoxane analogs of **132a** with various alkyl substitutions were synthesized and found to be inactive or weakly active because of steric effects preventing or hindering peroxide bond access to parasite heme. For these tetraoxanes, there was no apparent relationship between tetraoxane structure and *in vitro* neurotoxicity, nor there was any correlation between antimalarial activity and neurotoxicity. Dispiro tetraoxanes **132b** and **132c** bearing unsaturated and polar

functional groups were prepared to improve antimalarial activity of prototype tetraoxane **132a** by oral route. But both **132b** and **132c** were found to be inactive. However, the more lipophilic ethyl ester of **132c** (IC_{50} 6.4 nM) and methyl ether of **132b** (IC_{50} 15 nM) showed significant *in vitro* antimalarial potency. These tetraoxanes possessed poor activity *in vivo*.

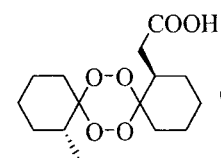
Mixed tetraoxanes possessing spirocycloalkane and spirocholic acid-derived steroid substructures were prepared **133** and found to be 6-fold more potent than artemisinin. Mixed tetraoxanes with a spirocyclohexane were more potent than the corresponding spirocyclopentane and spirocyclooctane analogs.[126] Several diester and diamide cholic acid-derived tetraoxanes were synthesized, best one of these, cis diamide tetraoxane **134**, was only 4-fold less potent than artemisinin.[127] Cholestane-type steroid tetraoxane hybrid **135** was found to be less active than artemisinin.[128] Solaja and his coworkers have developed several bile acid derived highly potent tetraoxanes in past few years.[129]



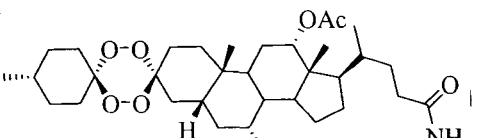
132a



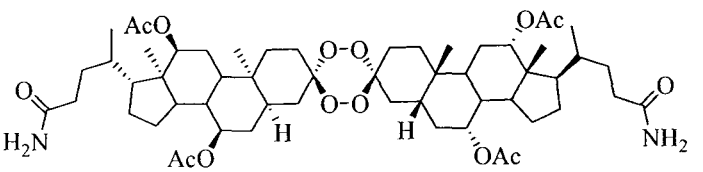
132b



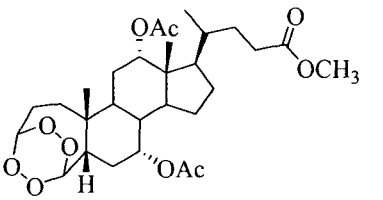
132c



133



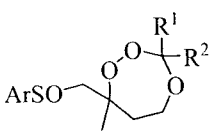
134



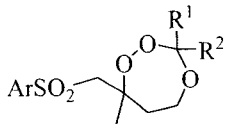
135

1,2,4-Trioxepanes

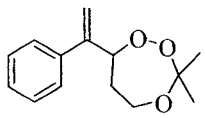
There are only few methods[130] reported in literature for the synthesis of 1,2,4-trioxepanes, the next higher homolog of 1,2,4-trioxanes and only two reports of their antimalarial activity. O'Neill[131] and his coworkers first of all reported *in vitro* activity of 1,2,4-trioxepanes having prototype **136** and **137**. Singh[132] *et al.* have also reported *in vivo* assessment of new class of aryl vinyl 1,2,4-trioxepanes **138a-c**.



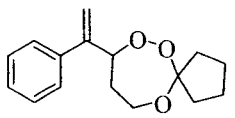
136a: R_1 and R_2=$(CH_2)_4$
Ar=*p*-Cl-C_6H_4
136b: R_1 and R_2=$(CH_2)_5$
Ar=*p*-Cl-C_6H_4



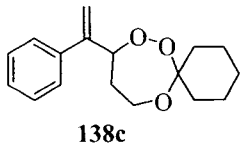
137a: R_1 and R_2=$(CH_2)_4$
Ar=*p*-Cl-C_6H_4
137b: R_1 and R_2=$(CH_2)_5$
Ar=*p*-Cl-C_6H_4



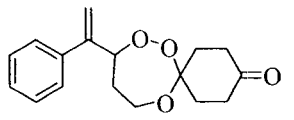
138a



138b



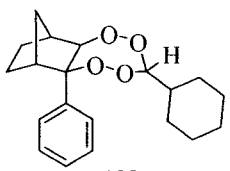
138c



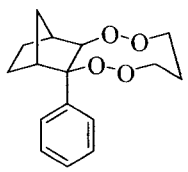
138d

1,2,4,5-Tetraoxepanes, 1,2,4,5-Tetraoxocanes & 1,2,5,6-Tetraoxonanes

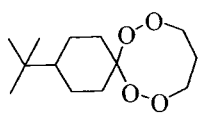
Tricyclic 1,2,4,5-tetraoxepane **139** and 1,2,5,6-tetraoxonane **140** were 35 to 40-fold less potent than artemisinin, but **140** had notably better *in vivo* activity (ip). Both **139** and **140** however, were completely inactive when they were administered orally.[133] 1,2,4,5-tetraoxocanes **141a** and **141b** exhibited excellent *in vitro* potency, however, both were less effective than artemisinin *in vivo*.[134]



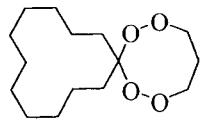
139



140



141a



141b

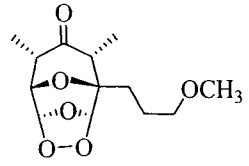
1.2.4-Trioxolanes

The 1,2,4-trioxolane system is well known to organic chemists as secondary ozonide, a highly reactive intermediate of the ozonolysis reaction.

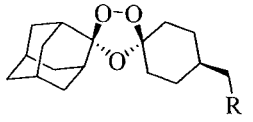
De Almeida Barbosa *et al.*[135] firstly reported antimalarial activity of a new series of tricyclic trioxolanes (8,9,10,11-tetraoxatricyclo [5.2.1.12.6] undecan-4-ones) which were synthesized from various 8-oxabicyclo [3.2.1] oct-6-en-3-ones by ozonolysis. Trioxolane **142** was prepared in five steps from 3-(2-furyl) propan-1-ol in a sequence of hydroxy group protection, cycloaddition, deprotection, methoxylation, and ozonolysis. With their low potencies ranging from 7,300 to 90,000 nM, these tricyclic trioxolanes were found to be inactive. **142**, the best of these, had an IC_{50} of 7,300 nM which was three orders of magnitude less potent than artemisinin.

Research efforts made by Vennerstrom *et al.*[136] led to the discovery of various novel antimalarial 1,2,4-trioxolanes **143**. Out of which trioxolane **143c** displayed *in vitro* IC_{50} values of 0.39 ng/mL and 0.42 ng/mL versus chloroquine-resistant *P. falciparum* K1 and chloroquine sensitive NF-54

strains, and was found to be more active than chloroquine, and mefloquine *in vivo* after a single 3 mg/kg dose administration against *P. berghei* infected mice. Compound **143c** OZ-277 displayed high activity against field isolates from Gabon (median IC_{50} 0.47 nm; range: 0.13–2.23 nm).[137] Its stage specificity is similar to that of artemisinins.[138] The activity against *P. vivax* is in the same range as the activity against *P. falciparum.*[139] This compound had been taken upto clinical trials but the clinical development of OZ-277 has been discontinued because areas under the curve (AUC) in malaria patients were less than 50% of those recorded in healthy volunteers (W. Gutteridge, personal communication).



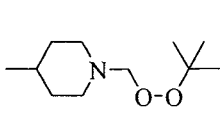
142



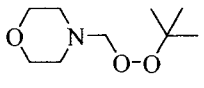
143a: R=COOH
143b: R=NH_2
143c: R=$CONHCH_2C(CH_3)_3NH_2$

Amine Peroxides

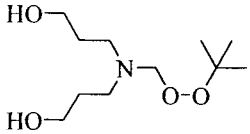
Amine peroxides **144** were synthesized from the corresponding secondary amines by treatment with formaldehyde and t-butyl hydroperoxide.[140] Morpholine peroxide **144b**, the most potent member of this class, was only 20-fold less potent than artemisinin, but with the exception of the weakly active **144c**, each was inactive *in vivo*. 4-Aminoquinoline peroxide **144d** was only weakly potent and at dose of 640 mg/kg was toxic (Vennerstrom, unpublished results).



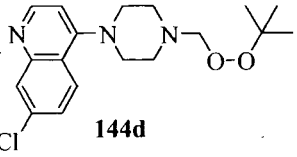
144a



144b



144c



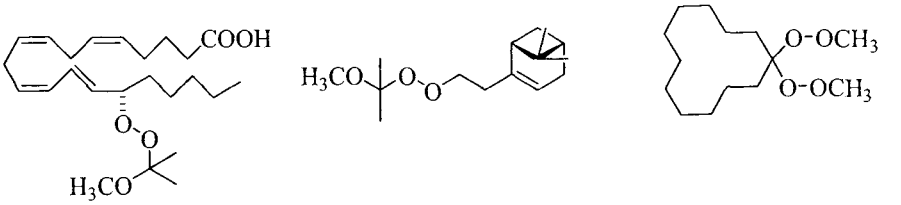
144d

Miscellaneous Peroxides

Together with above reported various class peroxides, different other structurally modified peroxides have also been synthesized and assessed for their antimalarial activity.

Perketal derivatives of unsaturated fatty acid hydroperoxide such as **145** was found inactive[141] although terpene derived perketal **146** is considerably more potent than **145**, it is still some two orders of magnitude less potent than artemisinin.[142] Compound **147** was one of the most potent

molecule with an IC_{50} value of 86 nM. More importantly, **147** is the first acyclic peroxide with demonstrable *in vivo* efficacy.[143]

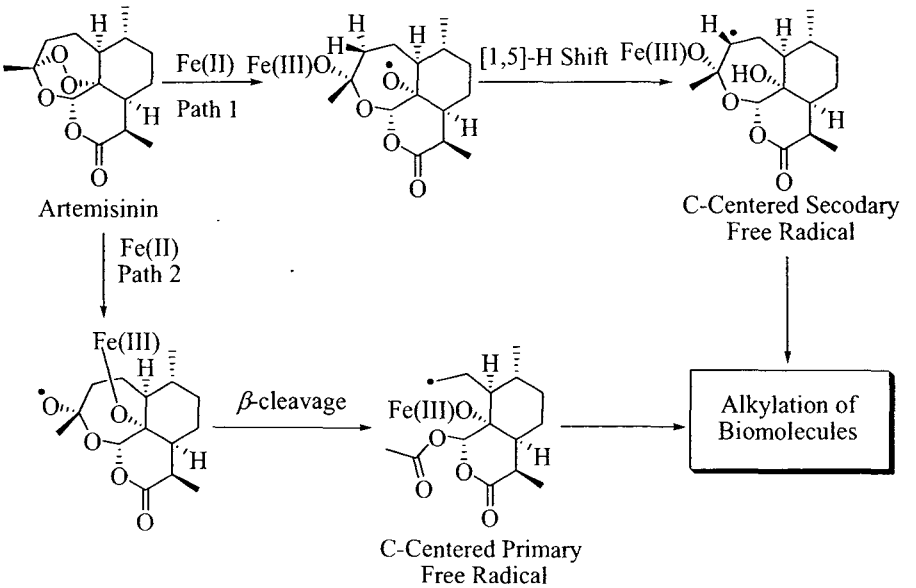


145 **146** **147**

Various other acyclic peroxides have been synthesized and assessed for their antimalarial efficacy but none of them was found to have activity comparable to that of artemisinin.

1.10 Mechanism of Artemisinin and Related Peroxides

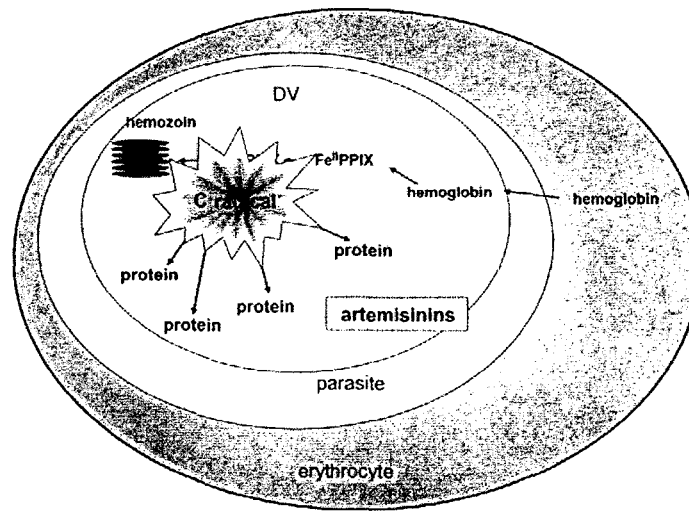
Efforts to elucidate the antimalarial action of artemisinin started in the 1970s, and last three decades large no of papers have been published by various workers regarding the mode of action of artemisinin and related peroxides.[144-151]



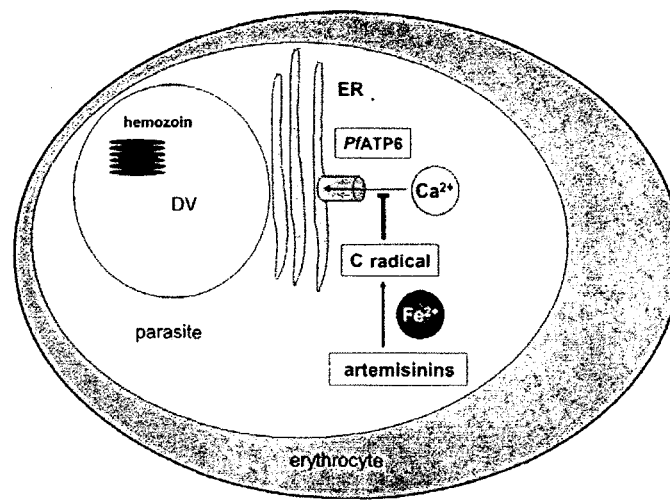
Mechanism of formation of carbon centered free radicals

Despite the growing importance of artemisinins, their exact mechanism of action is still unresolved and remains a matter of intense debate. It has been proposed that Fe^{2+} mediated cleavage of the endoperoxide leads to the formation of different C-centered radicals which may

be primary or secondary in nature. Which, if not possibly both, of these radicals is the active species is unclear. For a long time it was thought that the formation of C-centered radicals takes place in the digestive vacuole and that ferrousprotoporphyrin IX is the activating species. The reactive C-centered radicals are thought to subsequently react more or less indiscriminately with different protein targets as well as with ferriprotoporphyrin IX itself, thus preventing heme detoxification and inhibiting a multitude of enzymes.[152-155] O'Neill and Posner formulated the mechanism of artemisinins as "iron-triggered cluster bombs".[156]



The "iron-triggered cluster bomb"



Radical mediated inhibition of Ca^{2+} ATPase (SERCA) called as *Pf*ATP6

Although very attractive, the development of resistance against a drug that acts nonspecifically against multiple targets is unlikely, so this concept has been questioned owing to some

contradictory findings: Artemisinins act against all developmental parasite stages, including those which do not produce hemozoin. Several experiments detected labeled artemisinin derivatives localized not within but only outside the digestive vacuole, and there are some highly active artemisinin derivatives that are more or less insensitive to Fe^{2+} mediated cleavage.[157]

Recently, Krishna and co-workers put forward another theory which says that the endoperoxide cleavage should take place in the cytoplasm catalyzed by a cytoplasmic Fe^{2+} source. The resulting reactive species then very specifically inhibits an ATP-dependent Ca^{2+} pump located on the endoplasmic reticulum. The pump, called *Pf*ATP6, is a homologue of a mammalian sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA).[158]

1.11 Discussion

In the last few decades none of the peroxide based compounds other than clinically used arteether, artemether and artesunate, both semisynthetic and synthetic has come up to the task of becoming drug of future although a lot of effort in this regard has been made. Artelinate **20** was one such compound which was thought to replace artesunate **17** as it was more stable and water soluble and has better activity profile; however, further development of artelinate has been discontinued in favor of artesunate because of the higher neurotoxicity of artelinate. Artemisone **73f**, have been found as lead candidate for clinical studies. This compound was designed on the basis of ADME parameters by the application of *Lipinski's Rule of Five,* and incorporating suitable polar residues and their isosteres. It was found to have considerably reduced neurotoxicity and have much improved properties over the first-generation analogues and represents the success of the ADME approach to drug design. Artemisone had been in clinical studies, but at present, further development of this promising drug is allegedly uncertain.

None of the synthetic peroxides identified so far has an antimalarial profile superior to that of arteether **16**, the best semisynthetic artemisinin, although available data indicates that 1,2,4-trioxanes **114a** and **119a** (Fenozan B07) are only marginally less effective than **16**. Recently a compound **127e**, from Singh's group has been chosen for Phase I clinical studies.

In case of synthetic peroxides other than 1,2,4-trioxanes, compound **143c** (OZ-277) was taken up to clinical trials but withdrawn because of poor performance in malaria affected patients.

Of course, the very instability of the peroxide bond that endows these compounds with their unique antimalarial specificities also precludes a number of synthetic transformations and reaction conditions that could normally be considered for nonperoxidic compounds. However,

like the semisynthetic artemisinins, within a given peroxide chemical family, the more lipophilic members are more potent and possess better oral antimalarial activity in animal models than their more polar counterparts. This poses a challenge to identify peroxide structures with suitable ''drug-like'' physicochemical properties. Synthesis complexity, source of peroxide oxygen atoms (hydrogen peroxide, singlet or triplet oxygen, ozone), reduced stability of unsaturated versus saturated peroxide heterocycles, and stereochemistry, are other chemical parameters that must be considered in synthetic peroxide design and development.

1.12 Conclusion

The growing emergence of resistant varieties of malaria parasites against conventional therapies have enforced medicinal chemists to search for new antimalarial drugs. The real problem in developing an antimalarial drug is of course its cost and toxicity. The major problem in research and development for antimalarial drugs is that, this disease is considered to be as a disease of poor and developing countries where patients can't afford to buy expensive drugs, consequently pharmaceutical industries have not paid lot of emphasis in this regard as they do not see it as a profitable business. The partnership between research institutions, academia, private industries and international agencies can prove as mile stone in the development of new antimalarial drugs. Growing emergence of resistance against artemisinin derivatives in some areas have made researchers to think about combination therapies. Various artemisinin based combination therapies are now being used in areas where parasite has become resistant against conventional monotherapy.

Although no alternatives to artemisinin based therapies is currently available for the treatment of complicated malaria, efforts are now being made to develop synthetic peroxides as possible alternative to artemisinin based therapies in order to search for a cost effective remedy. Most of the peroxide based compounds other than conventionally used artemisinin derivatives that have come up to clinical stages have been withdrawn because of their toxicity. Various synthetic peroxides like **107a** (arteflene), **143c** (OZ-277), **119a** (Fenozan B07) come up to clinical trials, but failed due to toxicity. Recently compound **127e** (CDRI-97/78) which have shown very good preclinical results have been taken up for Phase I clinical testing.

The analysis of the genome sequence can provide some valuable information regarding the development of new leads for vaccine development, but such efforts are still at laboratory stages. A number of new potential target pathways have already been identified so far and efforts are

now being made to develop lead compounds for these putative targets which will allow treating the malaria infections in a uniform and sustained way.

In conclusion, in order to combat the growing resistance of malarial parasite against various conventionally used artemisinin based drugs, efforts are now being made to develop new synthetic peroxides as potential antimalarial agents on account of their relative cheapness and versatility of structural modification, enabling them to tailored to fit a drug profile characterized by potency superior to that of natural product artemisinin, by enhanced bioavailability and minimal toxicity.

1.12 Summary

In the last few decades lot of effort has been put to develop new antimalarial drugs that have better activity profile and reduced neurotoxicity. Knowledge of mechanism of artemisinin based therapies has allowed to researchers to develop compounds that have reduced neurotoxicity. Compounds based upon ADME parameters have been developed to insure optimum activity and reduced toxicity. Various scientific tools are now being used to design and develop new structurally modified synthetic peroxides in order to search for new leads for malaria chemotherapy. As the mode of action of artemisinin based compounds and various other antimalarial synthetic peroxides is fully known scientists are now trying to develop mechanism based compounds in order to combat the malaria, but the search is still going on.

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Chapter 2

Synthesis, Biology and Chemistry of 6-Arylethyl-1,2,4-Trioxanes: An Approach Towards Diimide Reduction

2.1 Introduction

Malaria is still one of the world's most deadly diseases that threatens nearly 40% of the world's population and infects approximately 300 to 500 million people annually world wide mainly in tropical and subtropical areas. It is estimated that there are about 1 to 3 million deaths every year due to malaria.[1] In Africa alone, more than 1 million children under the age of 5 die from malaria each year.[2]

The emergence of the malaria as a global epidemic can largely be attributed to the indiscriminate use of conventional drugs due to which there has been rapid development of resistant parasites towards these drugs. In this regard discovery of artemisinin[3] **1**, a sesquiterpene lactone endoperoxide isolated from Chinese traditional medicinal herb *Artemisia annua*, has proven a milestone in malaria chemotherapy. Artemisinin is active against both chloroquine-sensitive and chloroquine-resistant malaria. Its semisynthetic derivatives like artemether **2**, arteether **3** and artesunic acid **4** (Fig. 2.1) have shown tremendous potential and are presently the drugs of choice for the treatment of malaria caused by multidrug resistant *Plasmodium falciparum.*

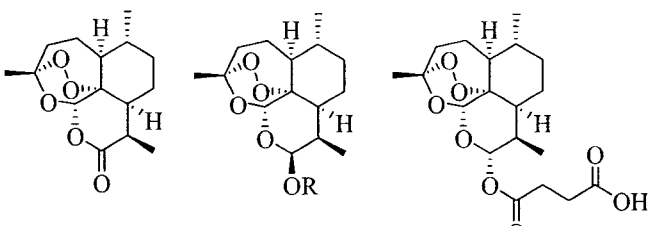
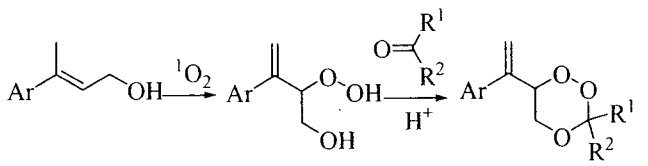


Figure 2.1 Artemisinin and its semisynthetic derivatives.

The fact that it is actually the endoperoxide linkage present in the form of 1,2,4-trioxane in artemisinin and its semisynthetic analogs is responsible for their antimalarial activity has led to the synthesis and antimalarial assessment of large number of trioxanes.[4-9]

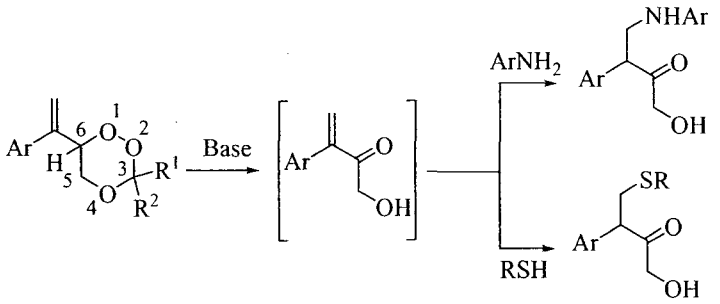
As a part of our endeavor to develop synthetic substitutes for artemisinin and its derivatives our group had earlier reported a photooxygenation route for the preparation of 6-arylvinyl-1,2,4-trioxanes.[10, 11] Preparation of β-hydroxy-hydroperoxides by the photooxygenation of allylic alcohols and their acid-catalyzed condensation with ketones are the key steps of this method (Scheme 2.1).



Scheme 2.1 General method for preparation of 6-Arylvinyl-1,2,4-trioxanes.

Several 6-arylvinyl-1,2,4-trioxanes prepared via this route have shown promising antimalarial activity against multi-drug resistant *Plasmodium yoelii nigeriensis* in Swiss mice.[12]

A very unique feature of these 6-arylvinyl substituted 1,2,4-trioxanes is the presence of an acidic proton at C-6 position of the trioxane ring system, due to which they undergo a highly facile fragmentation under basic conditions to furnish α,β-unsaturated ketoalcohols which react very efficiently with various amines and thiols to furnish corresponding Michael adducts (Scheme 2.2).[13]



Scheme 2.2. Base catalyzed cleavage of 6-Arylvinyl-1,2,4-trioxanes.

Based on these results we had earlier suggested that this facile formation of α,β-unsaturated keto systems under mild basic conditions and their equally facile reaction with amines and thiols might have relevance to their mechanism of action as antimalarials.[9] This suggestion naturally brings the role of the double bond as the key group for the activity of these group of 1,2,4-trioxanes and calls for the preparation and antimalarial assessment of corresponding saturated analogs as a proof for this mechanism of action. Towards this end we have prepared several saturated analogs (6-Arylethyl-1,2,4-trioxanes) and assessed them for their antimalarial efficacy. In this chapter we describe the details of this study

2.2 Preparation of 6-Arylethyl-1,2,4-Trioxanes

6-Arylvinyl substituted 1,2,4-trioxanes **5-30** (Fig. 2.2) prepared by the published procedure, were subjected to different conditions for the reduction of the double bond. We first attempted diimide

(NH.NH)[14] reduction using $N_2H_4.H_2O$ and 30% H_2O_2.[15] Thus, the reaction of trioxane **5** with $N_2H_4.H_2O/30\%H_2O_2$ in a 1:1 mixture of THF/EtOH furnished corresponding saturated trioxanes as a mixture of diastereomers **5a** (Higher *Rf*) and **5b** (Lower *Rf*) in a ratio of 2:3 in 44% yield. Reaction of trioxane **6** under similar conditions furnished a mixture of trioxanes **6a** (Higher *Rf*) and **6b** (Lower *Rf*) in 36% yield in same the ratio (Scheme 2.3).

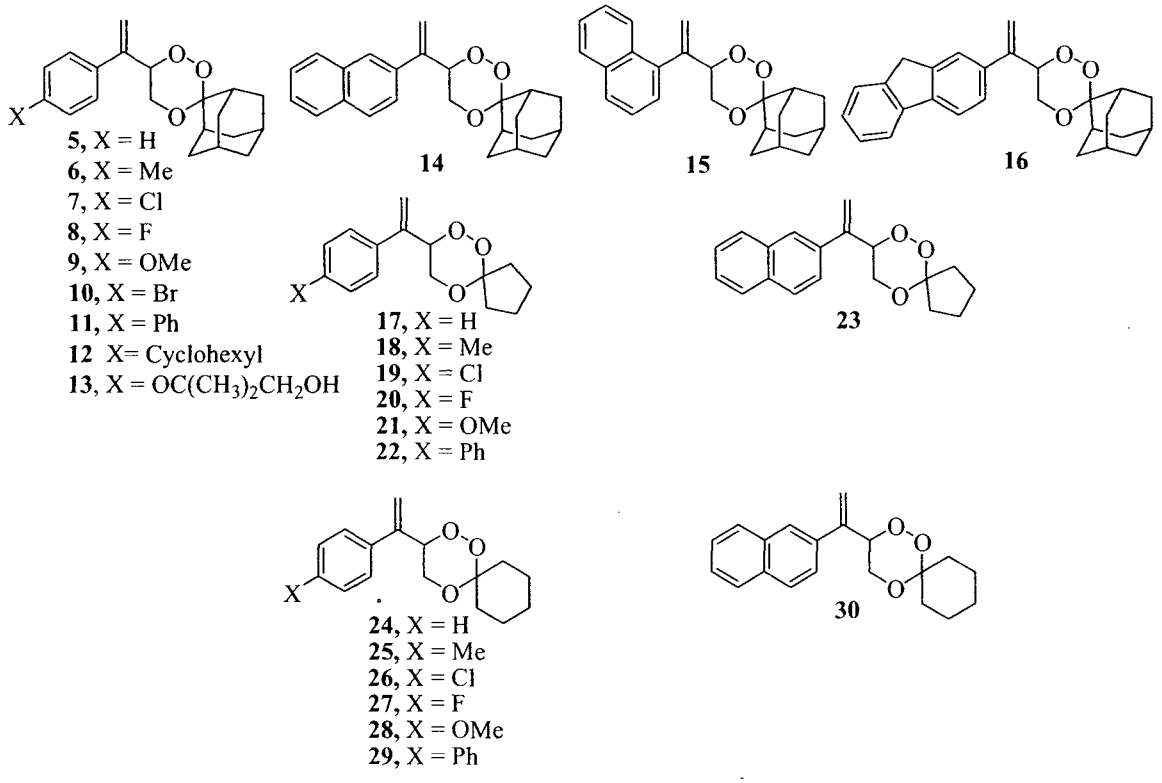
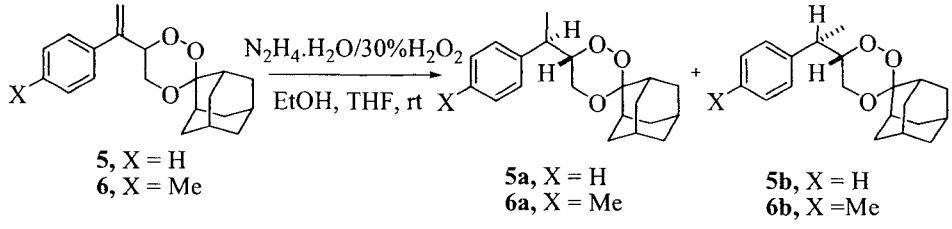


Figure 2.2 6-Arylvinyl-1,2,4-trioxanes used in diimide reduction.



Scheme 2.3 Diimide reduction of trioxanes **5** and **6** using $N_2H_4.H_2O/30\%H_2O_2$.

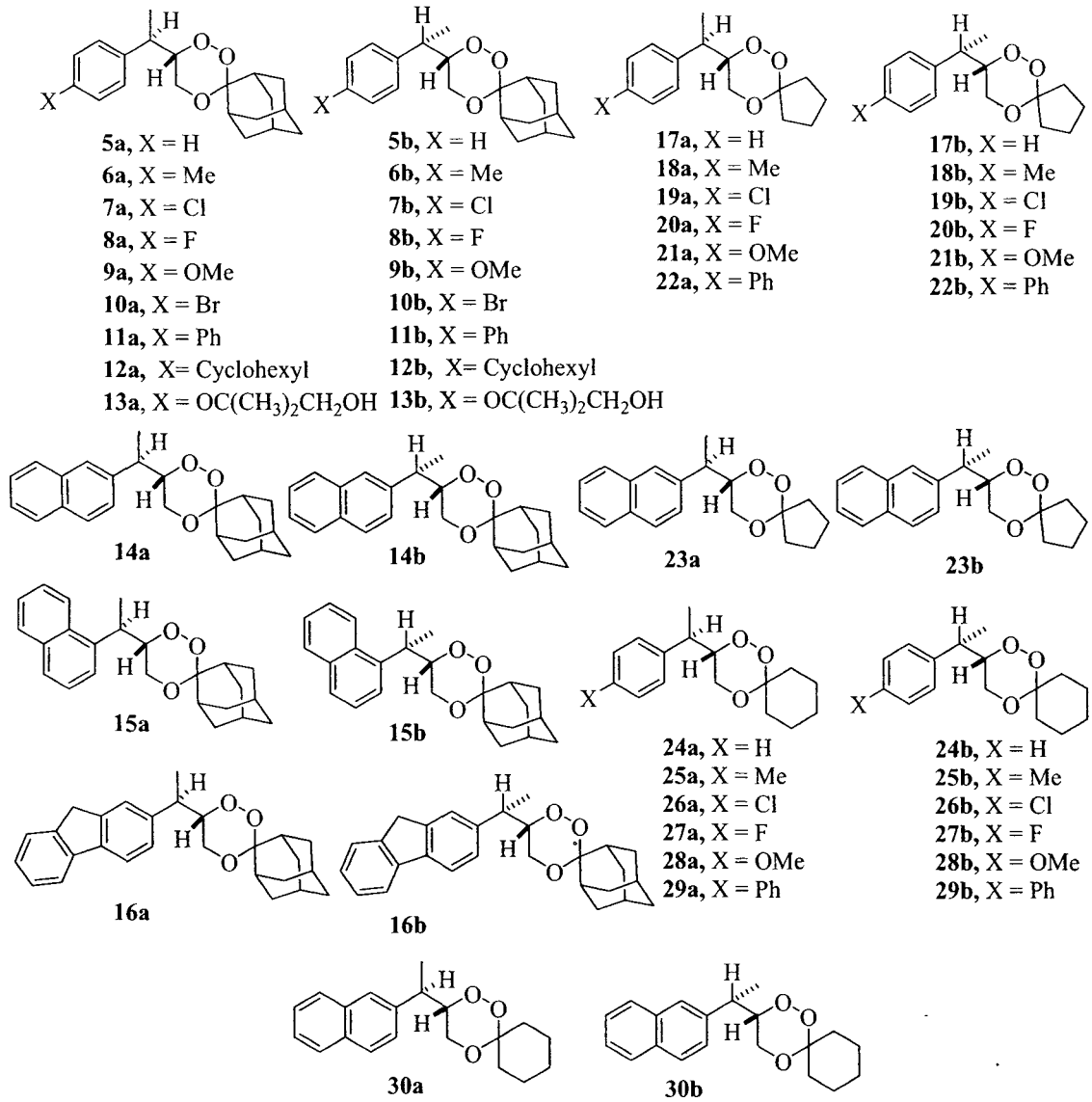
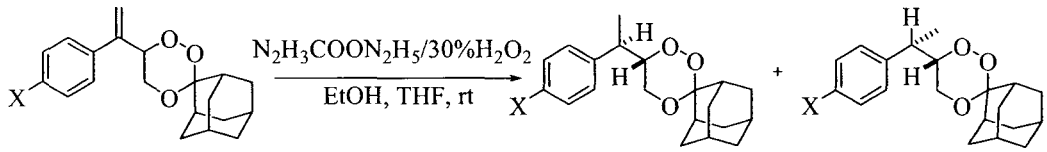


Figure 2.3 Products formed on diimide reduction of 6-Arylvinyl-1,2,4-trioxanes.

We believed that the low yields in diimide reduction of these trioxanes were due to the high basicity of $N_2H_4.H_2O$ which could lead to the fragmentation of the trioxane moiety by a mechanism similar to that as shown in Scheme 2.2. Thus there was a need for a reagent with less basic character. Hydrazine hydrate ($N_2H_4.H_2O$) is known to react with CO_2 to form hydrazinium carbazate ($N_2H_3COON_2H_5$), a 2:1 adduct of hydrazine and CO_2.[16, 17]A comparison of the *p*H values of aqueous solutions of hydrazine hydrate ($N_2H_4.H_2O$) and hydrazinium carbazate ($N_2H_3COON_2H_5$) prepared in our laboratory showed that the later was much less basic and therefore more suitable for our work.

In fact the reaction of trioxane **5** with hydrazinium carbazate and 30% H_2O_2, though took more time to complete, gave a mixture of trioxanes **5a** and **5b** as a diastereomeric mixture in 2:3 ratio in 97% yield. Reaction of trioxane **6** under similar conditions furnished corresponding saturated analogs **6a** and **6b** as a mixture of diastereomers in 93% yield (Scheme 2.4).



5, X = H
6, X = Me

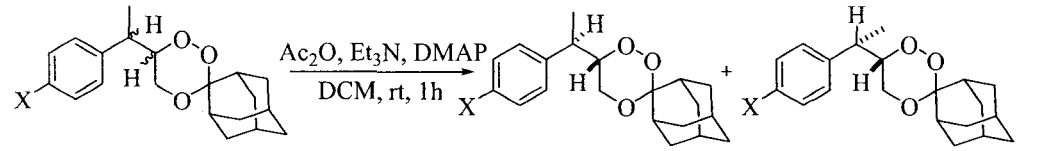
5a, X = H
6a, X = Me

5b, X = H
6b, X =Me

Scheme 2.4 Diimide reduction of trioxanes **5** and **6** using $N_2H_3COON_2H_5$/30% H_2O_2.

Several related trioxanes for example **7-30** were subjected to similar reduction conditions and the corresponding saturated trioxanes were isolated as mixture of diastereomers in 87-95% yields (Table 2.1 and Figure.2.3). The comparative yields of the diimide reduction of 6-Arylvinyl-1,2,4-trioxanes under above mentioned two conditions have been shown in Table 2.1.

The relative ratio of the two diastereomers[18] as assessed by ^{1}H NMR was found to be 2:3 and was independent of the reagent used. The diastereomers formed in all these cases were separated by column chromatography and were characterized separately. The diastereomeric mixture of compounds **13a** (Higher *Rf*) and **13b** (Lower *Rf*) was inseparable by column chromatography, so it was subjected to acetylation to furnish corresponding mixture of acetates **13c** (Higher *Rf*) and **13d** (Lower *Rf*) in 98% yield, which was separated by column chromatography (Scheme 2.5).



13a+13b
X = $OC(CH_3)_2CH_2OH$

13c
X = $OC(CH_3)_2CH_2OCOCH_3$

13d
X = $OC(CH_3)_2CH_2OCOCH_3$

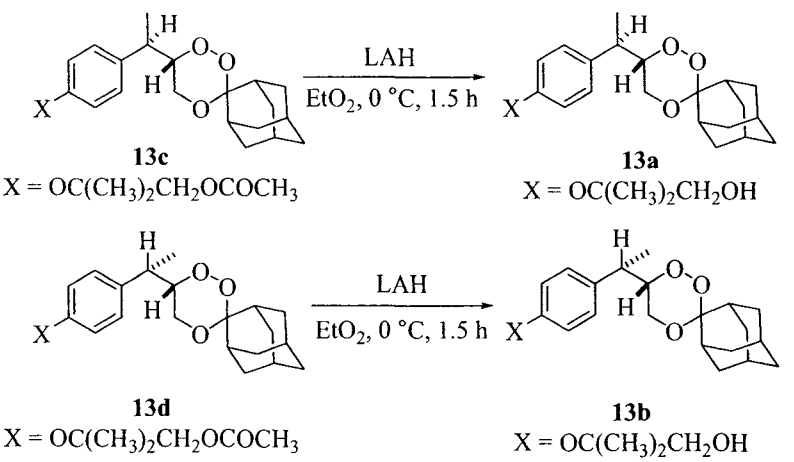
Scheme 2.5 Acetylation of **13a+13b**

Table 2.1 Diimide reduction of 1,2,4-trioxanes using $N_2H_4.H_2O$ and 30% H_2O_2 and $N_2H_3COON_2H_5$ and 30% H_2O_2.

Unsaturated trioxanes	Reaction Conditions	Time	Products	Yields (%)
5	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	3 days	**1a** + **1b**	44
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	9 days	**1a** + **1b**	97
6	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	3 days	**6a** + **6b**	36
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	14 days	**6a** + **6b**	93
7	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	2 days	**7a** + **7b**	36
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	14 days	**7a** + **7b**	95
8	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	2 days	**8a** + **8b**	37
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	10 days	**8a** + **8b**	92
9	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	3 days	**9a** + **9b**	37
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	16 days	**9a** + **9b**	94
10	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	3 days	**10a** + **10b**	44
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	10 days	**10a** + **10b**	95
11	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	4 days	**11a** + **11b**	59
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	8 days	**11a** + **11b**	97
12	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	11 days	**12a** + **12b**	91
13	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	10 days	**13a** + **13b**	94
14	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	6 days	**14a** + **14b**	68
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	20 days	**14a** + **14b**	91
15	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	29 days	**15a** + **15b**	35
16	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	10 days	**16a** + **16b**	90
17	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	2 days	**17a** + **17b**	37
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	12 days	**17a** + **17b**	89
18	$N_2H_4.H_2O$/30%H_2O_2, EtOH, THF, rt	3 days	**18a** + **18b**	32
	$N_2H_3COON_2H_5$/30%H_2O_2, EtOH, THF, rt	11 days	**18a** +**18b**	89

Unsaturated trioxanes	Reaction Conditions	Time	Products	Yields (%)
19	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	3 days	**19a + 19b**	52
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	11 days	**19a + 19b**	91
20	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	9 days	**20a + 20b**	66
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	9 days	**20a + 20b**	91
21	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	4 days	**21a + 21b**	64
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	18 days	**21a + 21b**	90
22	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	2 days	**22a + 22b**	43
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	12 days	**22a + 22b**	92
23	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	4 days	**23a + 23b**	65
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	15 days	**23a + 23b**	91
24	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	4 days	**24a + 24b**	58
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	16 days	**24a + 24b**	91
25	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	5 days	**25a + 25b**	58
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	15 days	**25a + 25b**	89
26	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	4 days	**26a + 26b**	60
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	14 days	**26a + 26b**	91
27	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	6 days	**27a + 27b**	68
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	16 days	**27a + 27b**	96
28	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	4 days	**28a + 28b**	56
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	10 days	**28a + 28b**	90
29	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	4 days	**29a + 29b**	59
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	17 days	**29a + 29b**	94
30	$N_2H_4.H_2O/30\%H_2O_2$, EtOH, THF, rt	5 days	**30a + 30b**	51
	$N_2H_3COON_2H_5/30\%H_2O_2$, EtOH, THF, rt	17 days	**30a + 30b**	87

Compounds **13c** and **13d** were then separately subjected to LAH reduction to furnish the corresponding alcohols **13a** and **13b** in 80% and 84% yields respectively (Scheme 2.6).

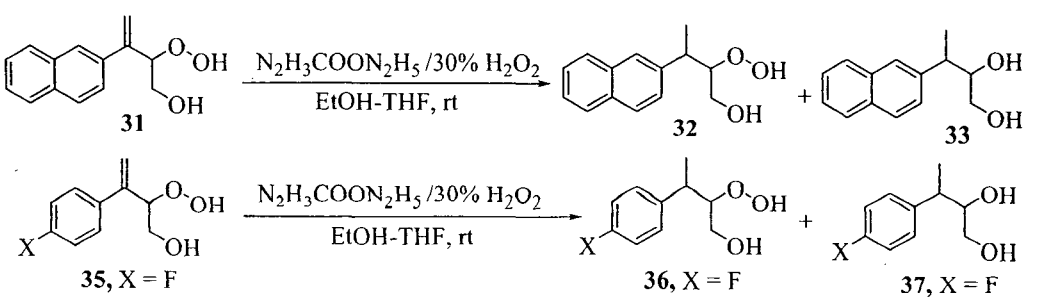


13c X = $OC(CH_3)_2CH_2OCOCH_3$ **13a** X = $OC(CH_3)_2CH_2OH$

13d X = $OC(CH_3)_2CH_2OCOCH_3$ **13b** X = $OC(CH_3)_2CH_2OH$

Scheme 2.6 LAH reduction of **13c** and **13d**.

The difference in diimide reduction using and $N_2H_3COON_2H_5/H_2O_2$ was found to be even more dramatic in the case of reduction of unsaturated β-hydroxyhydroperoxides, the precursors of 6-arylvinyl-1,2,4-trioxanes. The diimide reduction of β-hydroxyhydroperoxides **31** and **35** with $N_2H_3COON_2H_5/H_2O_2$ furnished the saturated β-hydroxyhydroperoxides **32** and **36** in 50% and 51% yields, together with the corresponding saturated diols **33** and **37** in 17% and 28% yields, respectively, (Scheme 2.7).



31 **32** **33**

35, X = F **36**, X = F **37**, X = F

Scheme 2.7

For confirmation of the structures, β-hydroxyhydroperoxides **32** and **36** were reduced with $NaBH_4$ to furnish saturated diols **33** and **37** which on acetylation furnished the corresponding diacetates **34** and **38** in 91% and 93% yields, respectively (Figure 2.3).

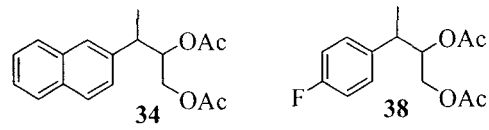
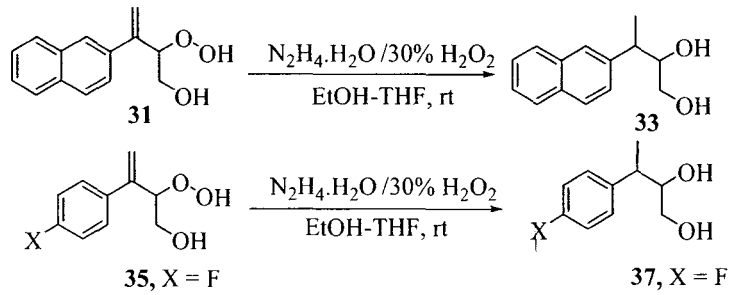


Figure 2.3 Saturated diacetates

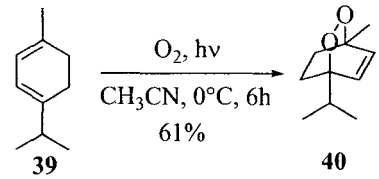
To the best of our knowledge, this is the first report on reduction of the allylic hydroperoxides to the saturated hydroperoxides.

Reduction of the allylic hydroxyhydroperoxides **31** and **35** using $N_2H_4.H_2O$/30% H_2O_2, on the other hand, furnished only the corresponding diols **33** and **37** in 78% and 81% yields, respectively (Scheme 2.8).



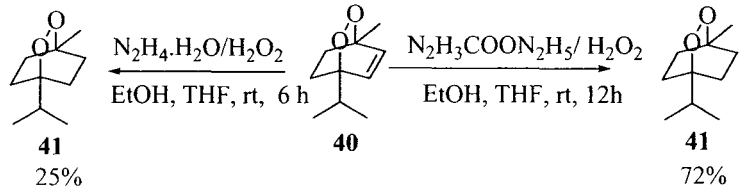
Scheme 2.8 Diimide reduction of β-hydroxyhydroperoxides **32** and **36** with .H_2O/30% H_2O_2.

In order to test the comparative superiority of $N_2H_3COON_2H_5/H_2O_2$ over $N_2H_4.H_2O/H_2O_2$ in some other peroxy substrates, we synthesized ascaridole **40** from α-terpene **39** (Scheme 2.9) and subjected it to diimide reduction under both the conditions.



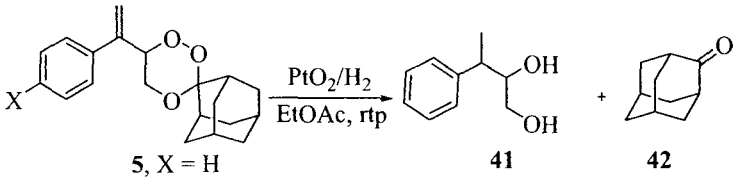
Scheme 2.9 Photooxygenation of α-terpene **39.**

While the reduction with $N_2H_4.H_2O/H_2O_2$ furnished dihydroascaridole **41** in only 25% yield, the reaction with $N_2H_3COON_2H_5/H_2O_2$ furnished the same compound in 72% yield (Scheme 2.10).



Scheme 2.10 Diimide reduction of ascaridole **40**.

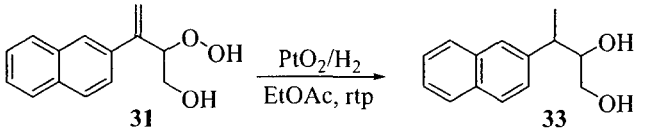
Catalytic hydrogenation using Adams catalyst (PtO_2/H_2) has earlier been reported for the double bond reduction of endoperoxides.[19] We subjected trioxane **5**, hydroperoxide **31** and endoperoxide **40** to PtO_2/H_2 hydrogenation at room temperature and pressure (rtp). While the catalytic reduction of **40** furnished the saturated endoperoxide **41** in 78% yields, trioxane **5** on the other hand furnished diol **42** and 2-adamantanone **43** in 64% and 89% yields, respectively (Scheme 2.110).



5, X = H **41** **42**

Scheme 2.11 Catalytic hydrogenation of trioxane **5**.

The reduction of unsaturated hydroperoxide **31** under similar conditions furnished only corresponding saturated diol **43** in 97% yield and no saturated hydroperoxide **32** was obtained (Scheme 2.12).



31 **33**

Scheme 2.12 Catalytic hydrogenation of hydroperoxide **31**.

Thus hydrazinium carbazate and hydrogen peroxide is a convenient reagent for the reduction of double bond in cyclic peroxides and hydroperoxides and is superior to other existing methods.

2.3 Antimalarial Assessment

Saturated trioxanes **5a-30a** and **5b-30b** were initially screened at 96 mg/kg × 4 days via oral as well as intramuscular routes using Peter's procedure. Trioxanes which showed 100% protection at 96 mg/kg × 4 days were further screened at 48-6 mg/kg × 4 days dose by corresponding routes. In this model β-arteether shows 100% clearance of parasitaemia at 48 mg/kg × 4 days and all the treated mice survive beyond day 28. At 24 mg/kg × 4 days β-arteether provides only 20% protection to the treated mice. To evaluate the effect of double bond reduction on antimalarial activity we also assessed the antimalarial activity of unsaturated trioxanes **5-10**. The results are summarized in Table 2.3.

2.4 SAR Studies of 1,2,4-Trioxanes

As it can be seen from Table 2.3, that none of the adamantane based 6-arylvinyl 1,2,4-trioxanes **5-10** show significant antimalarial activity. Trioxanes **7**, **9** and **10** the most active compound of the series though showed 100% suppression of the parasitaemia on day 4 at 96 mg/kg × 4 days dose but none of the treated mice survive till day 28. On the other hand one of the isomers of corresponding reduced products, **5a-16a** (higher R_f) showed high order of antimalarial activity. The interesting feature about their activity was that, the more polar isomer (lower R_f) showed only moderate activity. Adamantane based 6-arylethyl 1,2,4-trioxanes compounds **11a**, **12a** and **16a** were found to be most active compounds of the series as they provided 100% clearance of parasitaemia when administered at 24 mg/kg × 4 days and 12 mg/kg × 4 days dose via oral route. Compound **11a** also provided 60% protection at 6 mg/kg × 4 days dose while compounds **12a** and **16a** provided 20% and 25% protection, respectively at the dose of 6 mg/kg × 4 days. The corresponding lower isomers **11b**, **12b** and **16b** also provided 100% protection at 48 mg/kg × 4 days when administered orally. Although compounds **12b** and **16b** showed 100% suppression of parasitaemia on day 4, but none of the mice survived in either case till day 28 at 24 mg/kg × 4 days dose. While compound **11b** provided 100% clearance of parasitaemia at 24 mg/kg × 4 days dose, it was found to be ineffective when administered at 12 mg/kg × 4 days dose.

The saturated trioxanes **7a**, **10a**, **14a** and **15a** the next most active compounds of the series provided 100% clearance of parasitaemia at 48 mg/kg × 4 days and 24 mg/kg × 4 days dose when administered orally. While compounds **7a** and **14a** provided 60% protection at 12mg/kg × 4 days dose compounds **10a** and **15a** showed no protection. The corresponding polar isomers of these compounds **7b**, **10b**, **14b** and **15b** were found to be ineffective even at 48 mg/kg × 4 days dose orally as none of the mice survived till day 28.

Compound **5a** when tested at 96 mg/kg × 4 days via oral route was found curative while it was ineffective via im route. Compounds **5a**, **6a**, **8a** and **9a** were found active at 48 mg/kg × 4 days dose as all of them provided 100% protection, when given orally. While compound **5a** also provided 60% protection at 24mg/kg × 4 days dose other three compounds were found ineffective at this dose. The corresponding polar isomers of these compounds **5b**, **6b**, **8b** and **9b** were found ineffective at a dose level of 48 mg/kg × 4 days via oral route. Compound **5b** was not even effective at 96 mg/kg × 4 days both via oral and im routes.

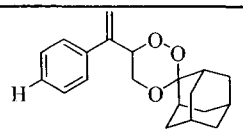
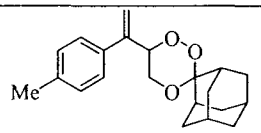
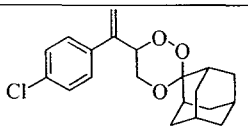
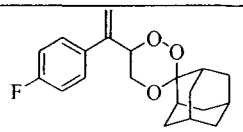
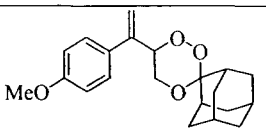
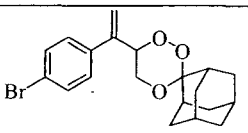
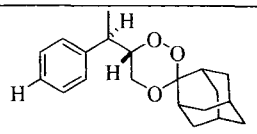
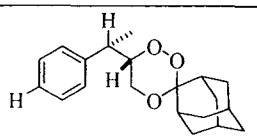
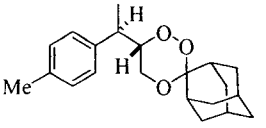
Trioxanes **13a** and its polar isomer **13b** were found active both via oral as well as im routes. Compound **13a** provided 100% clearance of parasitaemia both via oral and im routes when

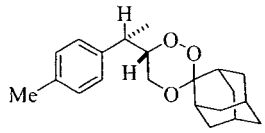
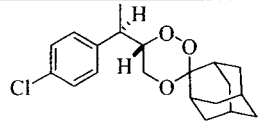
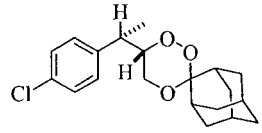
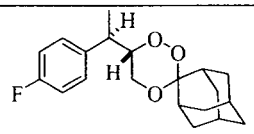
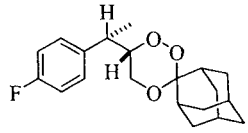
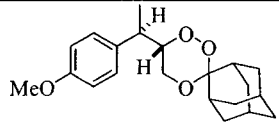
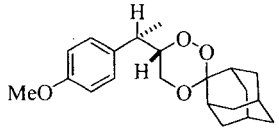
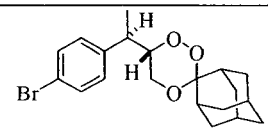
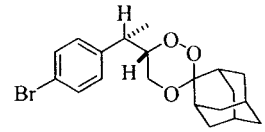
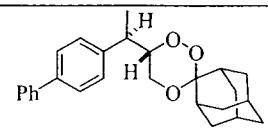
administered at 48 mg/kg × 4 days dose. Compound **13a** also provided 40% protection orally and 60% protection intramuscularly at 24 mg/kg × 4 days dose. The polar isomer **13b** also provided 100% protection both via oral and im routes when administered at 96 mg/kg × 4 days dose, while at 48 mg/kg × 4 days dose 20% and 60% protection was observed via oral and im routes, respectively.

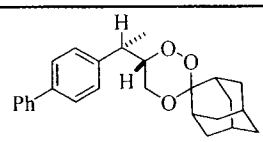
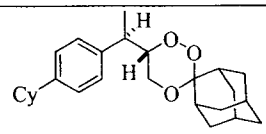
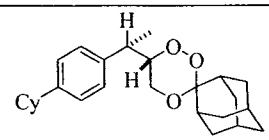
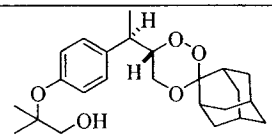
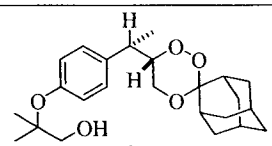
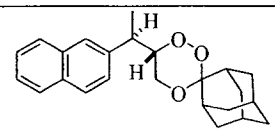
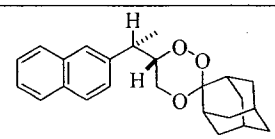
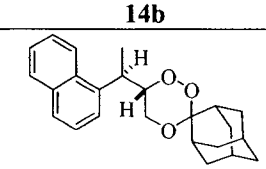
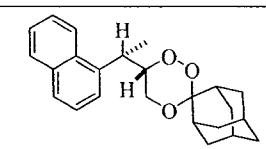
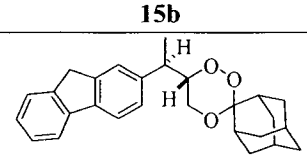
The cyclopentane based trioxanes were found to be relatively less active in comparison to adamantyl derivatives as only compound **22a** provided 100% protection at 96mg/kg × 4 days dose and 80% protection at 24 mg/kg × 4 days dose when administered orally. Its polar isomer **22b** was found inactive even at 96 mg/kg × 4 days dose via oral route. Compound **23a** also provided 60% and 80% clearance of parasitaemia when administered at 96mg/kg × 4 days dose via oral and im routes, respectively, while its polar isomer **23b** didn't show any activity. Among other cyclopentane based trioxanes compound **17a** showed 20% protection, while compound **19a** was 60% curative via im route when given at 96mg/kg × 4 days dose, their polar isomers were inactive at this dose. Rest of the cyclopentyl derivatives **18a**, **18b**, **20a**, **20b**, **21a** and **21b** showed only partial suppression at 96mg/kg × 4 days dose and none of them was found to be curative at this dose.

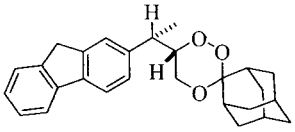
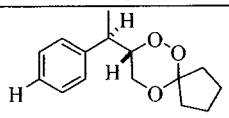
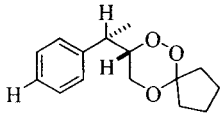
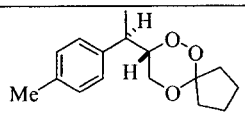
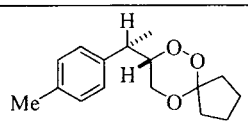
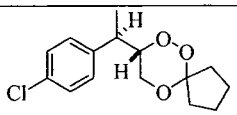
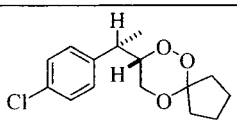
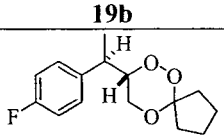
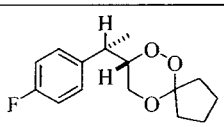
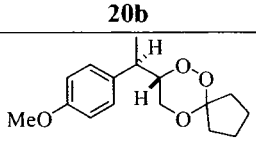
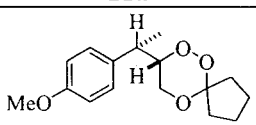
The cyclohexane based trioxanes were found to be relatively much less active in comparison to adamantyl substituted compounds as only compound **29a** provided 80% protection at 96 mg/kg × 4 days dose when administered orally, while its corresponding polar isomer **29b** was only suppressive. Trioxane **30a** was also found to be 20% curative at 96 mg/kg × 4 days dose when administered orally, while its polar isomer **30b** was only partially suppressive. Rest of the compounds **24a-28a**, **24b-28b**, were found to be only suppressive both via oral and im routes when administered at 96 mg/kg × 4 days dose.[20, 21] A careful analysis of Table 2.3 also shows that there is a direct co-relation between *in vivo* antimalarial activity and log *P* values and in this present series the compounds having best antimalarial activity were having the log *P* values in the range of 4.90 to 6.74. The compounds having log *P* value less than 4.90 showed poor antimalarial activity. Although in artemisinin based compounds, even compounds having log *P* values much lower than 4.90 show potent antimalarial activity. For example, arteether, a clinically useful drug with very powerful antimalarial activity has log *P* value of 3.84. Recent reports of *in vivo* antimalarial activity both in case of artemisinin and in trioxanes have also revealed the effect of log *P* on *in vivo* antimalarial activity.[3h, 5, 12e]

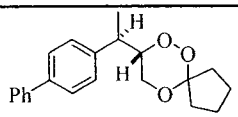
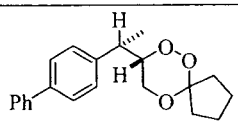
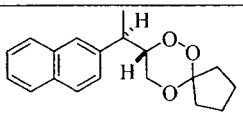
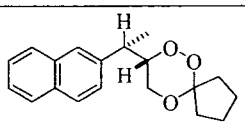
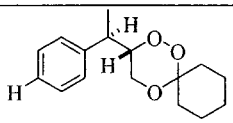
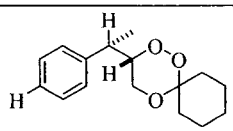
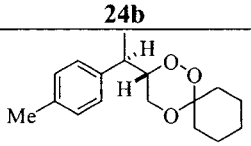
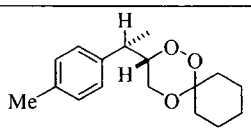
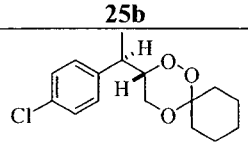
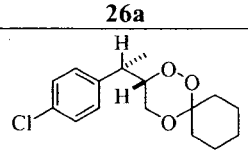
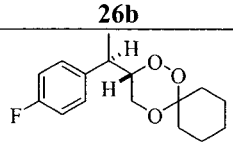
Table 1. *In vivo* antimalarial activity of compounds **5-10**, **5a-30a** and **5b-30b** against multi-drug resistant *Plasmodium yoelii nigeriensis* in Swiss mice.by oral and im routes.

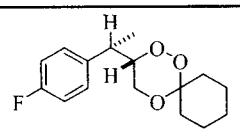
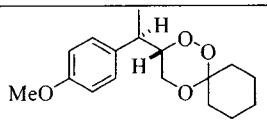
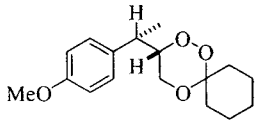
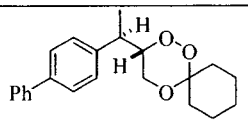
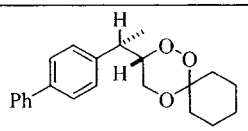
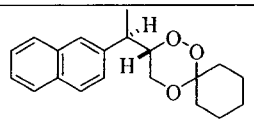
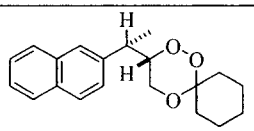
Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
 **5**	4.65	Oral Im	96 96	96 87	0/5 0/5
 **6**	5.14	Oral Im	96 96	95 53	0/5 0/5
 **7**	5.21	Oral Im	96 96	100 98	0/5 0/5
 **8**	4.81	Oral Im	96 96	99 83	0/5 0/5
 **9**	4.53	Oral Im	96 96	100 83	0/5 0/5
 **10**	5.48	Oral Im	96 96	100 83	0/5 0/5
 **5a**	5.01	Oral Im	96 48 24 12 96	100 100 100 100 85	10/10 10/10 6/10 0/5 0/5
 **5b**	5.01	Oral Im	96 48 96	40 32 24	0/5 0/5 0/5
 **6a**	5.49	Oral	48 24	100 96	10/10 0/5

Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
 **6b**	5.49	Oral	96	32	0/5
 **7a**	5.56	Oral	48 24 12	100 100 100	10/10 15/15 3/5
 **7b**	5.56	Oral	96	99	0/5
 **8a**	5.16	Oral	48 24 12	100 100 100	10/10 0/5 0/5
 **8b**	5.16	Oral	96	33	0/5
 **9a**	4.88	Oral	48 24 12	100 100 82	10/10 0/5 0/5
 **9b**	4.88	Oral	96	11	0/5
 **10a**	5.84	Oral	48 24 12	100 100 100	5/5 10/10 0/5
 **10b**	5.84	Oral	48	100	0/5
 **11a**	6.68	Oral	48 24 12 6	100 100 100 100	5/5 10/10 10/10 3/5

Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
 **11b**	6.68	Oral	48 24 12	100 100 33	5/10 5/5 0/5
 **12a**	6.99	Oral	48 24 12 6	100 100 100 100	5/5 5/5 10/10 1/5
 **12b**	6.99	Oral	48 24	100 100	5/5 0/5
 **13a**	4.90	Oral Im	48 24 48 24	100 100 100 100	5/5 2/5 5/5 3/5
 **13b**	4.90	Oral Im	96 48 96 48	100 100 100 100	5/5 1/5 5/5 3/5
 **14a**	6.00	Oral	48 24 12	100 100 100	5/5 10/10 3/5
 **14b**	6.00	Oral	48	99	0/5
 **15a**	6.00	Oral	48 24 12	100 100 100	5/5 10/10 0/5
 **15b**	6.00	Oral	48	100	0/5
 **16a**	6.74	Oral	48 24 12 6	100 100 100 100	5/5 10/10 10/10 1/4

Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
 **16b**	6.74	Oral	48 24	100 100	5/5 0/5
 **17a**	3.95	Oral Im	96 96	51 100	0/5 1/5
 **17b**	3.95	Oral Im	96 96	28 51	0/5 0/5
 **18a**	4.44	Oral Im	96 96	43 100	0/5 0/5
 **18b**	4.44	Oral Im	96 96	19 52	0/5 0/5
 **19a**	4.51	Oral Im	96 96	38 100	0/5 3/5
 **19b**	4.51	Oral Im	96 96	25 77	0/5 0/5
 **20a**	4.11	Oral Im	96 96	22 100	0/5 0/5
 **20b**	4.11	Oral	96 96	20 60	0/5 0/5
 **21a**	3.83	Oral Im	96 96	17 100	0/5 0/5
 **21b**	3.83	Oral Im	96 96	6 40	0/5 0/5

Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
 **22a**	5.63	Oral Im	96 48 96	100 100 45	5/5 4/5 0/5
 **22b**	5.63	Oral Im	96 96	57 33	0/5 0/5
 **23a**	4.95	Oral Im	96 96	100 100	3/5 4/5
 **23b**	4.95	Oral Im	96 96	19 60	0/5 0/5
 **24a**	4.37	Oral Im	96 96	22 68	0/5 0/5
 **24b**	4.37	Oral Im	96 96	20 14	0/5 0/5
 **25a**	4.86	Oral Im	96 96	43 40	0/5 0/5
 **25b**	4.86	Oral Im	96 96	24 30	0/5 0/5
 **26a**	4.93	Oral Im	96 96	94 65	0/5 0/5
 **26b**	4.93	Oral Im	96 96	13 27	0/5 0/5
 **27a**	4.53	Oral Im	96 96	46 88	0/5 0/5

Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
 **27b**	5.63	Oral Im	96 96	11 38	0/5 0/5
 **28a**	4.25	Oral Im	96 96	25 18	0/5 0/5
 **28b**	4.25	Oral Im	96 96	02 00	0/5 0/5
 **29a**	6.05	Oral Im	96 96	100 51	4/5 0/5
 **29b**	6.05	Oral Im	96 96	74 03	0/5 0/5
 **30a**	5.37	Oral Im	96 96	100 78	1/5 0/5
 **30b**	5.37	Oral Im	96 96	95 11	0/5 0/5
β-Arteether **2**	3.84	Oral	48 24	100 100	5/5 1/5
Vehicle control	- -	Oral Im	- -	- -	0/15 0/15

[a]Percent suppression = [(C-T)/C] × 100; where C = parasitaemia in control group and T = parasitaemia in treated group of mice.

2.5 Conclusion

In conclusion, in our efforts to assess the role of double bond of 6-arylvinyl-1,2,4-trioxanes in antimalarial activity we have discovered hydrazinium carbazate ($N_2H_3COON_2H_5$) and 30% H_2O_2 as suitable combination for the generation of diimide used for the double bond reduction of base sensitive 6-arylvinyl-1,2,4-trioxanes, their precursors, β- hydroxyhydroperoxides and

endoperoxide such as ascaridole. While doing so we have prepared a new series of 6-arylethyl-1,2,4-trioxanes **5a-30a** and **5b-30b** and assessed their structure activity relationship. Several of these novel trioxanes have shown better activity profile than the parent trioxanes. The activity profile of some of the trioxanes prepared in this series, was found even better than that of the clinically used drug, *β*-arteether. The results of this study clearly show that the presence of the double bond is not essential for the antimalarial activity of 6-arylvinyl-1,2,4-trioxanes and our hypothesis on the possible role of double bond in the mechanism of action is not true. The study also shows the role of stereochemistry in activity, as one of isomer in the present series was far more active in comparison to the other isomer.

2.6 Experimental Section

General details and instrumentation: All glass apparatus were oven dried prior to use. Melting points were taken in open capillaries on Complab melting point apparatus and are presented[1] uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 MHz and 300 MHz respectively for 1H; 50 MHz and 75 MHz respectively for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quintet (quin), multiplet (m), and broad (br). Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (EI-HRMS) were obtained on JEOL MS route 600H instrument. Elemental analyses were performed on Vario EL-III C H N S analyzer (Germany), and values were within (0.4% of the calculated values). Column chromatography was performed over Merck silica gel (particle size: 60-120 Mesh) procured from Qualigens (India), or flash silica gel (particle size: 230-400 Mesh). All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used

without further purification. Nomenclature and Log *p* values of the compounds were assigned using Chem Draw Ultra 7.0 software.

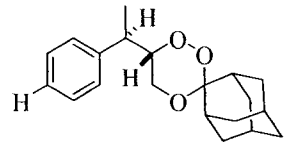
Procedure for preparation of hydrazinium carbazate solution: In an ice cooled solution of hydrazine hydrate ($N_2H_4.H_2O$, 103 g, 2.06 mol), a slow stream of CO_2 gas was bubbled till the weight of reaction mixture became constant (150 g, which corresponds to a 2:1 adduct of $N_2H_4.H_2O$ and CO_2). 1g of this highly viscous material (density 1.45) was dissolved in 100 mL of water for the measurement of pH which was found to be 7.51, while the *p*H value of 1% aqueous solution of $N_2H_4.H_2O$ was found to be 9.79.

General procedure for diimide reduction of 1,2,4-trioxanes using hydrazine hydrate ($N_2H_4.H_2O$) and 30% H_2O_2, (Reduction of 1,2,4-trioxane **5** as representative): To a stirred and ice cooled solution of trioxane **5** (1.00 gm, 3.205 mmol) and hydrazine hydrate (3.2 ml, 20 equiv) in 1:1 mixture of EtOH-THF (50 mL) was added 30% H_2O_2 (10.89 mL, 30 equiv) dropwise over 30 min and the reaction mixture was allowed to stir at rt for 3 days. The reaction mixture was evaporated on a rotavapor, diluted with water (20 mL) and extracted with ether (2 × 50 mL). The combined organic extract was washed successively with 10% HCl (10 mL), water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), concentrated and the crude product was purified by column chromatography over silica gel to furnish saturated trioxanes **5a** and **5b** (0.440 g, 43% yield) as a mixture of diastereomers in approximately 2:3 ratio which on flash chromatography furnished the pure isomers **5a** (higher R_f, oil) and **5b** (lower R_f, white solid, mp 84-85°C).

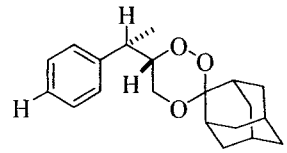
The unsaturated trioxanes **6-11**, **14**, **17-30** were also reduced by the same procedure.

General procedure for diimide reduction of 1,2,4-trioxanes using hydrazinium carbazate ($N_2H_3COON_2H_5$) and 30% H_2O_2, (Reduction of 1,2,4-trioxane **5** as representative): To a stirred and ice cooled solution of trioxane **5** (3.00 g, 9.62 mmol) and hydrazinium carbazate (9.55 ml, 10 equiv) in 1:1 mixture of EtOH-THF (150 mL) was added 30% H_2O_2 (32.69 mL, 30 equiv) drop wise over 30 min and the reaction mixture was allowed to stir at rt for 9 days. The reaction mixture was worked up and chromatographed as above to furnish **5a** and **5b** (2.92 g, 97% yield).

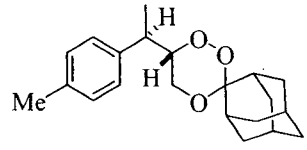
The unsaturated trioxanes **6-30** were also reduced by the same procedure.



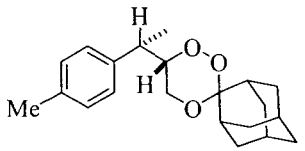
Trioxane 5a: oil; FT-IR (neat cm^{-1}) 763, 1025, 1117, 1223, 1602, 2914; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, 3H, J=6.9 Hz), 1.59-2.05 (m, 14H), 2.76 (quin, 1H, J = 6.9 Hz), 2.81 (s, 1H), 3.34 (dd, 1H, J = 11.8, 2.6 Hz), 3.62 (dd,1H, J = 11.8, 9.6 Hz), 4.35 (dt, 1H, J=9.6, 2.6 Hz) 7.18-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.63 (CH_3), 27.38 (2 × CH), 30.10 (CH), 33.24 (CH_2), 33.48 (CH_2), 33.66 (2 × CH_2), 35.72 (CH), 37.44 (CH_2), 40.96 (CH), 61.22 (CH_2), 83.30 (CH), 104.52 (C), 127.25 (CH), 127.80 (2 × CH), 128.93 (2 × CH), 142.03 (C); FAB-MS (*m/z*) 315 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{26}O_3$: %C 76.40, %H 8.33. Found: %C 76.10, %H 8.40.



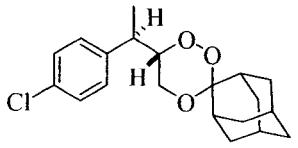
Trioxane 5b: mp 84-85 °C; FT-IR, (KBr cm^{-1}) 759, 1029, 1086, 1113, 1219, 1604, 2914; ^1H NMR (300 MHz, CDCl3) δ 1.29 (d, 3H, J = 7.2 Hz), 1.55-2.08 (m, 14H), 2.77 (s, 1H), 2.87 (quin, 1H, J = 7.2 Hz), 3.77 (dd, 1H, J =11.6, 3.4 Hz), 3.83 (dd, 1H, J = 11.6, 9.6 Hz), 4.35 (ddd, 1H, J = 9.6, 7.6, 3.4 Hz) 7.23-7.35 (m,5H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 17.53 (CH_3), 27.29 (CH), 27.33 (CH), 29.69 (CH), 33.19 (CH_2), 33.34 (CH_2), 33.56 (CH_2), 33.67 (CH_2), 36.10 (CH), 37.39 (CH_2), 40.74 (CH), 60.88 (CH_2), 82.55 (CH), 104.60 (C), 126.92 (CH), 127.82 (2 × CH), 128.66 (2 × CH), 142.45 (C); FAB-MS (*m/z*) 315 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{26}O_3$: %C 76.40, %H 8.33. Found: %C 76.37, %H 7.96.



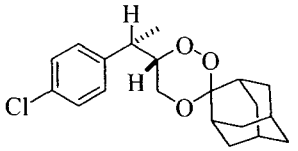
Trioxane 6a: oil; FT-IR (neat cm^{-1}) 766, 1003, 1028, 1602, 2914; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 3H, J = 6.9 Hz), 1.54-1.97 (m, 14H), 2.29 (s, 3H), 2.70 (quin, 1H, J = 6.9 Hz), 2.76 (s, 1H), 3.30 (dd, 1H, J = 11.8, 2.8 Hz), 3.56 (dd, 1H, J = 11.8, 9.5 Hz), 4.28 (dt, 1H, J = 9.5, 2.8 Hz), 7.02 (dd, 2H, J = 8.1 Hz), 7.08 (dd, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.82 (CH_3), 21.23 (CH_3), 27.35 (2 × CH), 29.99 (CH), 33.22 (CH_2), 33.46 (CH_2), 33.65 (2 × CH_2), 35.77 (CH),37.41 (CH_2), 40.54 (CH), 61.29 (CH_2), 83.37 (CH), 104.47 (C), 127.64 (2 × CH), 129.60 (2 × CH), 136.83 (C), 138.92 (C); FAB-MS (*m/z*) 329 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{28}O_3$ [M$^+$]: 328.2039. Found: 328.2039; Anal. Calcd. for $C_{21}H_{28}O_3$: %C 76.79, %H 8.59. Found: %C 76.78, %H 8.81.



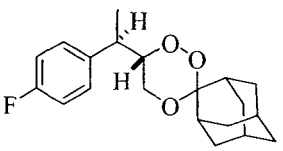
Trioxane 6b: mp 74-76 °C; FT-IR, (KBr cm^{-1}) 767, 1041, 1216, 1636, 2926; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 3H, J =7.3 Hz), 1.55-2.08 (m, 14H), 2.35 (s, 3H) 2.78 (s, 1H), 2.84 (quin, 1H, J=7.3 Hz), 3.76 (dd, 1H, J =11.6, 3.4 Hz), 3.83 (dd, 1H, J =11.6, 9.6 Hz), 4.47 (ddd, 1H, 9.6, 7.7, 3.4 Hz) 7.13 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.62 (CH_3), 21.23 (CH_3), 27.38 (CH), 27.42 (CH), 29.80 (CH), 33.27 (CH_2), 33.40 (CH_2), 33.62 (CH_2), 33.74 (CH), 36.17 (CH), 37.48 (CH_2), 40.41 (CH), 80.95 (CH_2), 82.69 (CH), 104.59 (C), 127.71 (2 × CH), 129.40 (2 × CH), 136.42 (C), 139.47 (C); FAB-MS (*m/z*) 329 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{28}O_3$ [M$^+$]: 328.2039. Found: 328.2018; Anal. Calcd. for $C_{21}H_{28}O_3$: %C 76.79, %H 8.59. Found: %C 76.79, %H, 8.59.



Trioxane 7a: mp 92-94 °C; FT-IR (KBr cm^{-1}) 768, 1091, 1112, 1217, 1655, 29117; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, 3H, J=6.9 Hz), 1.59-2.03 (m, 14H), 2.75 (s, 1H), 2.81 (quin, 1H, J = 6.9 Hz), 3.36 (dd, 1H, J = 11.8, 2.5 Hz), 3.59 (dd,1H, J = 11.7, 9.4 Hz), 4.28 (dt, 1H, J = 9.1, 2.3 Hz), 7.13 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.49 (CH_3), 27.31 (2 × CH), 30.19 (CH), 33.20 (CH_2), 33.42 (CH_2), 33.60 (2 × CH_2), 35.52 (CH), 37.36 (CH_2), 40.28 (CH), 60.90 (CH_2), 82.96 (CH), 104.62 (C), 129.08 (2 × CH), 129.14 (2 × CH), 132.95 (C), 140.56 (C); FAB-MS (*m/z*) 349 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{25}ClO_3$: %C 68.69, %H 7.22. Found: %C 68.69, %H 6.99.

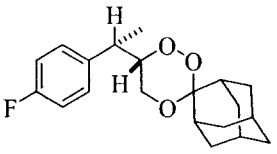


Trioxane 7b: mp 114-115 °C; FT-IR, (KBr cm^{-1}) 772, 1089, 1113, 1220, 1636, 2918; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.2 Hz), 1.55-2.06 (m, 14H), 2.71 (s, 3H), 2.84 (quin, 1H, J = 7.2 Hz), 3.78-3.80 (m, 2H), 4.41 (brddd, 1H), 7.16 (d, 2H, J = 8.3 Hz), 7.29 (d, 2H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.68 (CH_3), 27.31 (CH), 27.35 (CH), 29.90 (CH), 33.23 (CH_2), 33.35 (CH_2), 33.56 (CH_2), 33.68 (CH), 35.94 (CH), 37.40 (CH_2), 40.18 (CH), 60.87 (CH_2), 82.45 (CH), 104.72 (C), 128.81 (2 × CH), 129.22 (2 × CH), 132.66 (C), 141.06 (C); FAB-MS (*m/z*) 349 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{25}ClO_3$: %C 68.69, %H 7.22. Found: %C 68.78, %H 6.88.

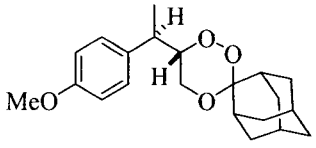


Trioxane 8a: oil; FT-IR (neat cm^{-1}) 772, 1111, 1653, 2925; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 3H, J = 6.9 Hz), 1.57-2.02 (m, 14H), 2.75 (s, 1H), 2.78 (brquin, 1H), 3.32 (dd, 1H, J = 11.8, 2.6 Hz), 3.58 (dd,1H,

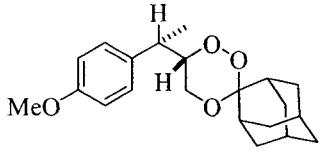
J = 11.8, 9.3 Hz), 4.26 (dt, 1H, J = 9.3, 2.6 Hz) 6.95-7.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.63 (CH_3), 27.36 (2 × CH), 30.15 (CH), 33.24 (CH_2), 33.47 (CH_2), 33.65 (2 × CH_2), 35.62 (CH), 37.41 (CH_2), 40.17 (CH), 61.01 (CH_2), 83.19 (CH), 104.62 (C), 115.76 (d, 2 × CH, $J_{C\text{-}F}$ = 21 Hz), 129.24 (d, 2 × CH, $J_{C\text{-}F}$ = 7.5 Hz), 137.79 (C), 162.04 (d, C, $J_{C\text{-}F}$ = 244 Hz); FAB-MS (*m/z*) 333 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{27}O_3F$ [M$^+$]: 332.1788. Found: 332.1786.



Trioxane 8b: mp 80-81 °C; FT-IR, (KBr cm^{-1}) 767, 1113, 1637, 2923; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.2 Hz), 1.54-2.06 (m, 14H), 2.73 (s, 1H), 2.86 (quin, 1H, J = 7.2 Hz) 3.73-3.85 (m, 2H,), 4.41 (brddd,1H), 6.98-7.21 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.73 (CH_3), 27.26 (CH), 27.30 (CH), 29.76 (CH), 33.16 (CH_2), 33.30 (CH_2), 33.53 (CH_2), 33.64 (CH_2), 35.97 (CH), 37.35 (CH_2), 39.97 (CH), 60.85 (CH_2), 82.53 (CH), 104.64 (C), 115.42 (2 × CH, d, $J_{C\text{-}F}$ = 21 Hz), 129.24 (d, 2 × CH, $J_{C\text{-}F}$ = 7.5 Hz), 138.16 (d, C, $J_{C\text{-}F}$ = 3 Hz), 161.84 (d, C, $J_{C\text{-}F}$ = 242 Hz); FAB-MS (*m/z*) 333 [M+H]$^+$; EI-HRMS Calcd. for $C_{21}H_{27}O_3F$ [M$^+$]: 332.1788. Found: 332.1781.

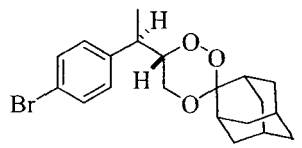


Trioxane 9a: oil; FT-IR (neat cm^{-1}) 772, 1115, 1635, 1602, 2928; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, J = 6.9 Hz), 1.53-2.03 (m, 14H), 2.72 (quin, 1H, J = 6.9 Hz), 2.76 (s,1H), 3.32 (dd, 1H, J = 11.8, 2.9 Hz), 3.58 (dd, 1H, J = 11.8, 9.5 Hz), 3.78 (s, 3H), 4.26 (dt, 1H, J = 9.5, 2.9 Hz), 6.83 (d, 2H, J = 8.6 Hz), 7.08 (d, 2H, J = 8.6 Hz); ^{13}C NMR (75 MHz,$CDCl_3$) δ 18.82 (CH_3), 27.34 (2 × CH), 29.91 (CH), 33.21 (CH_2), 33.45 (CH_2), 33.64 (2 × CH_2), 35.82 (CH), 37.40 (CH_2), 40.08 (CH), 55.46 (CH_3), 61.26 (CH_2), 83.44 (CH), 104.45 (C), 114.28 (2 × CH), 128.70 (2 × CH), 133.97 (C), 158.75 (C); FAB-MS (*m/z*) 345 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{28}O_4$ [M$^+$]: 344.1988. Found: 344.1988; Anal. Calcd. for $C_{21}H_{28}O_4$: %C 73.23, %H 8.19. Found: % C 73.00, %H 8.40.

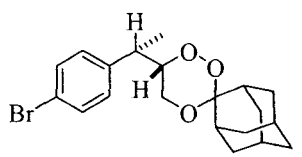


Trioxane 9b: mp 60-62 °C; FT-IR, (KBr cm^{-1}) 757, 1033, 1113, 1612, 2913; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, 3H, J = 7.2 Hz), 1.52-2.04 (m, 14H), 2.73 (s, 1H), 2.80 (quin, 1H, J = 7.2 Hz) 3.71 (dd, 1H, J = 11.6, 3.4 Hz),3.78 (dd merged, 1H), 3.78 (s, 3H), 4.41 (ddd, 1H, J = 10.6, 7.6, 3.4 Hz), 6.84 (d, 2H, J = 8.7 Hz) 7.12 (d, 2H, J = 8.7 Hz);^{13}C NMR (75 MHz, $CDCl_3$) δ 17.68 (CH_3), 27.34 (CH), 27.37 (CH), 29.73 (CH), 33.23 (CH_2), 33.37 (CH_2), 33.59 (CH_2), 33.71 (CH_2),

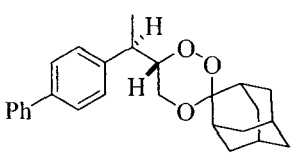
36.15 (CH), 37.44 (CH_2), 39.96 (CH), 55.43 (CH_3), 60.91 (CH_2), 82.72 (CH), 104.57 (C), 114.10 (2 × CH), 128.78 (2 × CH), 134.51 (C), 158.55 (C); FAB-MS (*m/z*) 345 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{28}O_4$ [M$^+$]: 344.1988. Found: 344.1988; Anal. Calcd. for $C_{21}H_{28}O_4$: %C 73.23, %H 8.19. Found: % C 73.40, %H 8.52.



Trioxane 10a: mp 115-116 °C; FT-IR (KBr cm^{-1}) 772, 1115, 1635, 1602, 2928; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, 3H, J = 6.7 Hz), 1.58-2.02 (m, 14H), 2.75 (brm, 2H), 3.35 (dd, 1H, J = 11.7, 1.9 Hz), 3.59 (dd, 1H, J = 11.7, 9.3 Hz), 4.28 (dt, 1H, J = 9.3, 1.9 Hz), 7.07 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.43 (CH_3), 27.30 (2 × CH), 30.16 (CH), 33.20 (CH_2), 33.41 (CH_2), 33.59 (2 × CH_2), 35.55 (CH), 37.35 (CH_2), 40.33 (CH), 60.88 (CH_2), 82.87 (CH), 104.61 (C), 120.99 (C), 129.52 (2 × CH), 132.02 (2 × CH), 141.08 (C); ES-MS (*m/z*) 392.9 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{25}O_3Br$ [M$^+$]: 392.0987. Found: 392.1027; Anal. Calcd. for $C_{21}H_{25}O_3Br$: % C 61.07, %H 6.41. Found: %C 60.93, %H 6.61.

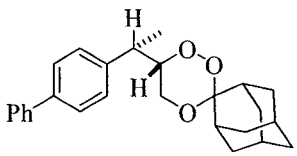


Trioxane 10b: mp 130-131 °C; FT-IR (KBr cm^{-1}) 782, 1074, 1112, 1594, 2930; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 7.2 Hz), 1.45-2.07 (m, 14H), 2.75 (quin, 1H, J = 7.2 Hz), 2.72(s, 1H) 3.74-3.84 (m, 2H), 4.41 (brddd, 1H), 7.44 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.57 (CH_3), 27.28 (CH), 27.33 (CH), 29.91 (CH), 33.20 (CH_2), 33.32 (CH_2), 33.53 (CH_2), 33.64 (CH_2) 35.88 (CH), 37.37 (CH_2), 40.19 (CH), 60.79 (CH_2), 82.35 (CH), 104.65 (C), 120.70 (C), 129.58 (2 × CH), 131.70 (2 × CH), 141.58 (C); ES-MS (*m/z*) 392.9 [M+H]$^+$; EI-HRMS Calcd. for $C_{21}H_{25}O_3Br$ [M$^+$]: 392.0987. Found: 392.0987; Anal. Calcd. for $C_{21}H_{25}O_3Br$: % C 61.07, %H 6.41. Found: %C 60.90, %H 6.42.

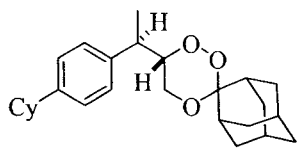


Trioxane 11a: mp 138-140°C; FT-IR (KBr cm^{-1}) 765, 1061, 1115, 1596, 2908; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (d, 3H, J = 6.9 Hz), 1.58-1.99 (m, 14H), 2.81 (brm 2H), 3.38 (dd, 1H, J = 11.8, 2.6 Hz), 3.64 (dd, 1H, J = 11.8, 9.8 Hz), 4.36 (dt, 1H, J = 9.4, 2.5 Hz), 7.25-7.58 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.63 (CH_3), 27.42 (2 × CH), 30.22 (CH), 33.30 (CH_2), 33.52 (CH_2), 33.70 (2 × CH_2), 35.74 (CH), 37.47 (CH_2), 40.64 (CH), 60.22 (CH_2), 83.30 (CH), 104.60 (C), 127.23 (2 × CH), 127.48 (CH), 127.66 (2 × CH), 128.25 (2 × CH), 129.00 (2 × CH), 140.25 (C), 140.98 (C),

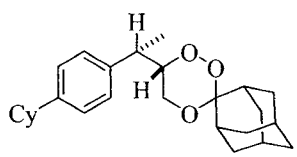
141.17 (C); FAB-MS (*m/z*) 391 [M+H$^+$]; EI-HRMS Calcd. for $C_{26}H_{30}O_3$ [M$^+$]: 390.2195. Found: 390.2189; Anal. Calcd. for $C_{26}H_{30}O_3$: % C 79.97, %H 7.74. Found: %C 79.85, %H 7.50.



Trioxane 11b: mp 145-147 °C; FT-IR (KBr cm^{-1}) 835, 1091, 1118, 1609, 2936; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, 3H, J = 7.2 Hz), 1.43-2.07 (m, 14H), 2.77 (s, 1H), 2.89 (quin, 1H, J = 6.9 Hz) 3.81 (m, 2H), 4.50 (brddd, 1H), 7.26-7.59 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.67 (CH_3), 27.28 (CH), 27.32 (CH), 29.71 (CH), 33.21 (CH_2), 33.34 (CH_2), 33.55 (CH_2), 33.68 (CH_2), 36.08 (CH), 37.38 (CH_2), 40.41 (CH), 60.99 (CH_2), 82.61 (CH), 104.66 (C), 127.24 (2 × CH), 127.30 (CH), 127.44 (2 × CH), 128.21 (2 × CH), 129.91 (2 × CH), 139.81 (C), 141.15 (C), 141.63 (C); FAB-MS (*m/z*) 391 [M+H$^+$]; EI-HRMS Calcd. for $C_{26}H_{30}O_3$ [M$^+$]: 390.2195. Found: 390.2191; Anal. Calcd. for $C_{26}H_{30}O_3$: % C 79.97, %H 7.74. Found: %C 80.25, %H 8.05.

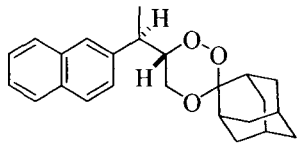


Trioxane 12a: mp 117-118 °C; FT-IR (KBr cm^{-1}) 770, 1059, 1115, 1597, 2921; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, 3H, J = 6.7 Hz), 1.37-2.06 (m, 24H), 2.45 (m 1H), 2.74 (quin, 1H, J = 6.9 Hz), 2.81 (s, 1H) 3.33 (dd, 1H, J = 11.9, 2.8 Hz), 3.61 (dd, 1H, J = 11.9, 9.6 Hz), 4.31 (dt, 1H, J = 9.6, 2.8 Hz), 7.09 (d, 2H, J = 8.2 Hz), 7.37 (d, 2H, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.57 (CH_3), 26.39 (CH_2), 27.13 (2 × CH_2), 27.42 (2 × CH), 30.09 (CH), 33.28 (CH_2), 33.51 (CH_2), 33.70 (2 × CH_2), 34.68 (2 × CH_2), 35.81 (CH), 37.48 (CH_2), 40.58 (CH), 44.39 (CH), 61.36 (CH_2), 83.50 (CH), 104.48 (C), 127.31 (2 × CH), 127.66 (2 × CH), 139.27 (C), 147.10 (C); ESI-MS (*m/z*) 397 [M+H$^+$]; EI-HRMS Calcd. for $C_{26}H_{36}O_3$ [M$^+$]: 396.2665. Found: 396.2664; Anal. Calcd. for $C_{26}H_{36}O_3$: % C 78.75, %H 9.15. Found: %C 79.10, %H 9.51.

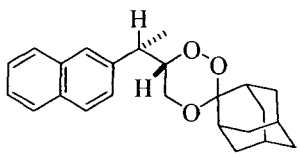


Trioxane 12b mp 141-143 °C; FT-IR (KBr cm^{-1}) 771, 1086, 1119, 1596, 2927; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.2 Hz), 1.39-2.09 (m, 24H), 2.50 (m, 1H),2.80 (s, 1H), 2.85 (quin, 1H, J = 7.2 Hz), 3.75 (dd, 1H, J = 11.6, 3.2 Hz), 3.85 (dd,1H, J = 11.6, 10.0 Hz), 4.48 (ddd, 1H, J = 10.0, 7.3, 3.2 Hz), 7.16 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.29 (CH_3), 27.41 (CH_2), 27.16 (2 × CH_2), 29.73 (CH), 33.25 (CH_2), 33.40 (CH_2), 33.61 (CH_2), 33.74 (CH_2), 34.67 (2 × CH_2), 36.20 (CH), 37.47 (CH_2), 40.29 (CH), 44.36 (CH), 60.85 (CH_2), 82.68 (CH), 104.55 (C), 127.08 (2 × CH), 127.63 (2 × CH), 139.76 (C), 146.55 (C); ESI-MS (*m/z*) 397 [M+H$^+$]; EI-HRMS Calcd. for

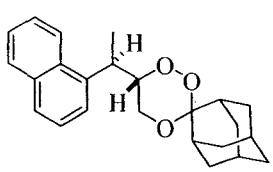
$C_{26}H_{37}O_3$ [M+H$^+$]: 397.2743. Found: 397.2741; Anal. Calcd. for $C_{26}H_{36}O_3$: % C 78.75, %H 9.15. Found: %C 78.40, %H 9.25.



Trioxane 14a: mp 120-121 °C; FT-IR (KBr cm^{-1}) 761, 1109, 1624, 2921; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, 3H, J = 6.9 Hz), 1.61-2.08 (m, 14H), 2.83 (s, 1H), 2.83 (brquin, 1H), 3.36 (dd, 1H, J = 11.8, 2.5 Hz), 3.66 (dd,1H, J = 11.8, 9.4 Hz), 4.47 (dt, 1H, J = 9.4, 2.5 Hz) 7.33-7.84 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.73 (CH_3), 27.37 (2 × CH), 30.18 (CH), 33.25 (CH_2), 33.49 (CH_2), 33.65 (2 × CH_2), 35.66 (CH), 37.42 (CH_2), 41.07 (CH), 61.22 (CH_2), 83.21 (CH), 104.58 (C), 125.75 (CH), 125.92 (CH), 126.41 (CH), 126.58 (CH), 127.80 (CH), 127.84 (CH), 128.73 (CH), 132.80 (C), 133.73 (C), 139.50 (C); FAB-MS (*m/z*) 365 [M+H$^+$]; EI-HRMS Calcd. for $C_{24}H_{28}O_3$ [M$^+$]: 364.2039. Found: 364.2007; Anal. Calcd. for $C_{24}H_{28}O_3$: %C 79.09, %H 7.74. Found: %C 79.01 , %H 7.51.

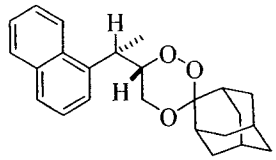


Trioxane 14b: mp 130-131 °C; FT-IR, (KBr cm^{-1}) 750, 1113, 1636, 2914; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, 3H, J = 7.2 Hz), 1.54-2.07 (m, 14H), 2.77 (s, 1H), 3.05 (quin, 1H, J = 7.2 Hz), 3.80 (dd, 1H, J = 11.7, 3.6 Hz), 3.87 (dd, 1H, J = 11.7, 9.5 Hz), 4.60 (ddd, 1H, J = 9.5, 7.6, 3.6 Hz) 7.23-7.35 (m, 7H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 17.80 (CH_3), 27.32 (2 × CH), 29.70 (CH), 33.22 (CH_2), 33.34 (CH_2), 33.57 (CH_2), 33.69 (CH_2), 36.13 (CH), 37.38 (CH_2), 41.00 (CH), 61.04 (CH_2), 82.60 (CH), 104.68 (C), 125.70 (CH), 126.12 (CH), 126.16 (CH), 126.50 (CH), 127.80 (CH), 127.90 (CH), 128.40 (CH),132.72 (C),133.67 (C), 139.97 (C); FAB-MS (*m/z*) 365 [M+H$^+$]; EI-HRMS Calcd. for $C_{24}H_{28}O_3$ [M$^+$]: 364.2039. Found: 364.2046; Anal. Calcd. for $C_{24}H_{28}O_3$: %C 79.09, %H 7.74. Found: %C 78.89, %H 7.87.

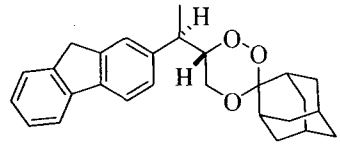


Trioxane 15a: oil; FT-IR (neat cm^{-1}) 776, 1122, 1655, 2917; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 3H, J = 6.8 Hz), 1.61-2.12 (m, 14H), 2.87 (s, 1H), 3.42 (brdd, 1H), 3.62 (dd,1H, J = 11.8, 9.8 Hz), 3.76 (brquin, 1H) 4.63 (brdt, 1H) 7.46-8.15 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.98 (CH_3), 27.30 (CH),27.35, (CH), 30.29 (CH), 33.21 (CH_2), 33.46 (CH_2), 33.59 (CH_2), 33.62 (CH_2), 33.62 (CH), 35.49 (CH), 37.38 (CH_2), 60.92 (CH_2), 83.91 (CH), 104.61 (C), 122.96 (CH), 124.46 (CH), 125.78 (2 × CH), 126.39 (CH), 127.52 (CH), 129.27 (CH), 131.75 (C), 134.20 (C), 138.66 (C);

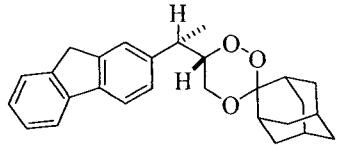
ESI-MS (*m/z*) 365 [M+H$^+$]; EI-HRMS Calcd. for $C_{24}H_{28}O_3$ [M$^+$]: 364.2039. Found: 364.2038; Anal. Calcd. for $C_{24}H_{28}O_3$: %C 79.09, %H 7.74. Found: %C 78.88 , %H 7.77.



Trioxane 15b: mp 120-122 °C; FT-IR, (KBr cm^{-1}) 776, 1029,1113, 1597, 2915; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, 3H, J = 7.2 Hz), 1.56-2.08 (m, 14H), 2.85 (s, 1H),), 3.75 (dd, 1H, J =11.6, 2.9 Hz), 3.88 (quin, 1H, J = 7.2 Hz) 3.98 (dd, 1H, J =11.6, 10.1 Hz), 4.77 (ddd, 1H, J =10.1, 7.3, 2.9 Hz) 7.46-8.11 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.87 (CH_3), 27.33 (CH),27.38, (CH), 29.83 (CH), 33.25 (CH_2), 33.39 (CH_2), 33.60 (CH_2), 33.72 (CH_2), 33.70 (CH), 36.15 (CH), 37.43 (CH_2), 60.53 (CH_2), 81.90 (CH), 104.66 (C) , 123.06 (CH), 124.05 (CH), 125.62 (CH), 125.68(CH), 126.25 (CH), 127.47 (CH), 129.23 (CH), 131.90 (C), 134.23 (C), 138.11 (C); ESI-MS (*m/z*) 365 [M+H$^+$]; EI-HRMS Calcd. for $C_{24}H_{28}O_3$ [M$^+$]: 364.2039. Found: 364.2042; Anal. Calcd. for $C_{24}H_{28}O_3$: %C 79.09, %H 7.74. Found: %C 79.30, %H 7.55.

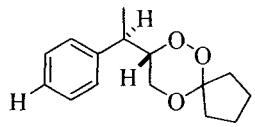


Trioxane 16a: mp 133-135 °C; FT-IR (KBr cm^{-1}) 768, 1091,1115, 1599, 2910; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 3H, J = 6.9 Hz), 1.61-2.09 (m, 14H), 2.84 (s, 1H), 2.87 (brquin, 1H), 3.40 (dd, 1H, J = 11.9, 2.7 Hz), 3.66 (dd,1H, J = 11.9, 9.5 Hz), 3.89 (s, 2H) 4.41 (dt, 1H, J = 9.5, 2.7 Hz) 7.19-7.79 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.94 (CH_3), 27.41 (2 × CH), 30.15 (CH), 33.28 (CH_2), 33.52 (CH_2), 33.69 (2 × CH_2), 35.77 (CH), 37.07 (CH_2), 37.46 (CH_2) 41.09 (CH), 61.29 (CH_2), 83.45 (CH), 104.56 (C), 119.99 (CH), 120.24 (CH), 120.36 (CH), 125.25 (CH), 126.55 (CH), 126.87 (CH), 126.99 (CH), 140.74 (C), 140.98 (C), 141.61 (C), 143.41 (C), 144.06 (C); ESI-MS (*m/z*) 425 [M+Na$^+$]; EI-HRMS Calcd. for $C_{27}H_{30}O_3$ [M$^+$]: 402.2195. Found: 402.2194; Anal. Calcd. for $C_{27}H_{30}O_3$: %C 80.56, %H 7.51. Found: %C 80.76, %H 7.90.

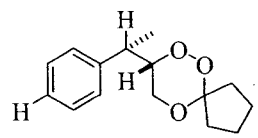


Trioxane 16b mp 136-138 °C; FT-IR (KBr cm^{-1}) 739, 1086, 1113, 1596, 2912; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, J = 7.3 Hz), 1.59-2.03 (m, 14H), 2.77 (s, 1H), 2.95 (quin, 1H, J = 7.3 Hz), 3.79 (dd, 1H, J = 11.7, 3.6 Hz), 3.85 (dd merged,1H), 3.89 (s, 2H) 4.54 (ddd, 1H, J = 9.4, 7.7, 3.6 Hz) 7.23-7.78 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.94 (CH_3), 27.41 (2 × CH), 30.15 (CH), 33.28 (CH_2), 33.52 (CH_2), 33.69 (2 × CH_2), 35.77 (CH), 37.07 (CH_2), 37.46 (CH_2) 41.09 (CH), 61.29 (CH_2), 83.45 (CH), 104.56 (C), 119.99 (CH), 120.24 (CH), 120.36 (CH), 125.25 (CH), 126.55 (CH), 126.87 (CH), 126.99 (CH), 140.74 (C), 140.98 (C), 141.61 (C), 143.41 (C), 144.06

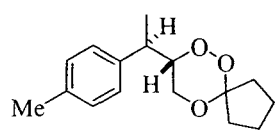
(C); ESI-MS (*m/z*) 403 [M+H$^+$]; EI-HRMS Calcd. for $C_{27}H_{30}O_3$ [M$^+$]: 402.2195. Found: 402.2196; Anal. Calcd. for $C_{27}H_{30}O_3$: %C 80.56, %H 7.51. Found: %C 80.92, %H 7.81.



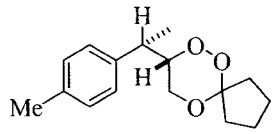
8-(1-Phenyl-ethyl)-6,7,10-trioxa-spiro[4.5]decane (17a): oil; FT-IR (neat cm^{-1}) 760, 1063, 1118, 1604, 2970; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.36 (d, 3H, J = 6.9 Hz), 1.63-1.87 (m, 7H), 2.35 (m, 1H), 2.80 (quin, 1H, J = 6.9 Hz), 3.41 (dd, 1H, J =11.8, 2.9 Hz), 3.52 (dd, 1H, J = 11.8, 9.0 Hz), 4.34 (dt, 1H, J = 9.0, 2.9 Hz), 7.16-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.86 (CH_3), 23.64 (CH_2), 24.69 (CH_2), 33.40 (CH_2), 36.61 (CH_2), 40.69 (CH), 63.87 (CH_2), 83.23 (CH), 114.44 (C), 127.22 (CH), 127.78 (2 × CH), 128.92 (2 × CH), 142.05 (C); FAB-MS (*m/z*) 249 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{20}O_3$ [M$^+$]: 248.14125. Found: 248.13959; Anal. Calcd. for $C_{15}H_{20}O_3$: %C 72.55, %H 8.12. Found: %C 72.32, %H 7.95.



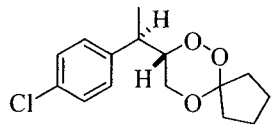
8-(1-Phenyl-ethyl)-6,7,10-trioxa-spiro[4.5]decane (17b): oil; FT-IR (neat cm^{-1}) 701, 1031, 1110, 1603, 2966; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.27 (d, 3H, J = 7.2 Hz), 1.60-1.78 (m, 7H), 2.32 (m, 1H), 2.86 (quin, 1H, J = 7.2 Hz), 3.69 (dd, 1H, J = 11.5, 9.8 Hz), 3.82 (dd, 1H, J = 11.5, 2.8 Hz), 4.48 (ddd, 1H, J = 9.8, 7.6, 2.8 Hz), 7.20-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.36 (CH_3), 23.46 (CH_2), 24.69 (CH_2), 32.95 (CH_2), 36.87 (CH_2), 40.52 (CH), 63.58 (CH_2), 82.53 (CH), 114.39 (C), 126.83 (CH), 127.80 (2 × CH), 128.52 (2 × CH), 142.19 (C); FAB-MS (*m/z*) 249 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{20}O_3$ [M$^+$]: 248.1413. Found: 248.1413; Anal. Calcd. for $C_{15}H_{20}O_3$: %C 72.55, %H 8.12. Found: %C 72.90, %H 8.50.



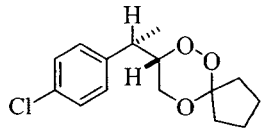
8-(1-Tolyl-ethyl)-6,7,10-trioxa-spiro[4,5]decane (18a): oil; FT-IR (neat cm^{-1}) 818, 1062, 1116, 1597, 2967; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.36 (d, 3H, J = 6.9 Hz), 1.63-1.89 (m, 7H), 2.35 (s, 3H), 2.39 (m, 1H), 2.78 (quin, 1H, J = 6.9 Hz), 3.44 (dd, 1H, J =11.8, 2.9 Hz), 3.54 (dd, 1H, J = 11.8, 9.1 Hz), 4.34 (dt, 1H, J = 9.1, 2.9 Hz), 7.08 (d, 2H, J =8.0 Hz), 7.14 (d, 2H, J =8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.54 (CH_3), 21.22 (CH_3), 23.67 (CH_2), 24.74 (CH_2), 33.39 (CH_2), 36.68 (CH_2), 40.31 (CH), 63.99 (CH_2), 83.33 (CH), 114.44 (C), 127.65 (2 × CH), 129.62 (2 × CH), 136.82 (C), 138.98 (C); FAB-MS (*m/z*) 263 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{22}O_3$ [M$^+$]: 262.1569. Found: 262.1584; Anal. Calcd. for $C_{16}H_{22}O_3$: %C 73.25, %H 8.45. Found: %C 72.10, %H 8.25.



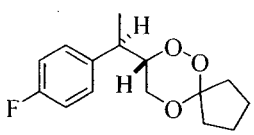
8-(1-Tolyl-ethyl)-6,7,10-trioxa-spiro[4,5]decane (18b): oil; FT-IR (neat cm^{-1}) 817, 1033, 1108, 1597, 2968; ^1H NMR (200 MHz, $CDCl_3$); δ 1.26 (d, 3H, J = 7.2 Hz), 1.60-1.79 (m, 7H), 2.31 (m, 4H), 2.83 (quin, 1H, J = 7.2 Hz), 3.69 (dd, 1H, J =11.6, 9.6 Hz), 3.81 (dd, 1H, J = 11.6, 2.9 Hz), 4.45 (dt, 1H, J = 9.2, 7.5, 3.0 Hz), 7.10 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.77 (CH_3), 21.41 (CH_3), 23.75 (CH_2), 24.99 (CH_2), 33.25 (CH_2), 37.19 (CH_2), 40.43 (CH), 63.97 (CH_2), 82.94 (CH), 114.72 (C), 127.94 (2 × CH), 129.54 (2 × CH), 136.65 (C), 139.39 (C); FAB-MS (*m/z*) 263 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{22}O_3$ [M$^+$]: 262.1569. Found: 262.1569.



8-[1-(4-Chloro-phenyl)-ethyl]-6,7,10-trioxa-spiro[4,5]decane (19a): oil; FT-IR (neat cm^{-1}) 722, 1017, 1101, 1596, 2968; ^1H NMR (200 MHz, $CDCl_3$); δ 1.34 (d, 3H, J = 7.0 Hz), 1.63-1.83 (m, 7H), 2.28-2.31 (m, 1H), 2.83 (quin, 1H, J = 7.0 Hz), 3.43 (dd, 1H, J =11.7, 3.6 Hz), 3.52 (dd, 1H, J = 11.7, 8.2 Hz), 4.29 (dt, 1H, J = 8.6, 3.6 Hz), 7.11 (d, 2H, J = 8.4 Hz), 7.28 (d, 2H, J = 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.42 (CH_3), 23.89 (CH_2), 24.88 (CH_2), 33.70 (CH_2), 36.72 (CH_2), 40.24 (CH), 63.79 (CH_2), 83.14 (CH), 114.79 (C), 129.30 (2 × CH), 129.36 (2 × CH), 133.19 (C), 140.80 (C); FAB-MS (*m/z*) 283 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{19}ClO_3$ [M$^+$]: 282.1023. Found: 282.1037; Anal. Calcd. for $C_{15}H_{19}ClO_3$: %C 63.71, %H 6.77. Found: %C 63.95, %H 6.99.

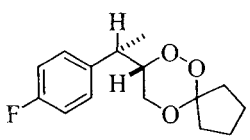


8-[1-(4-Chloro-phenyl)-ethyl]-6,7,10-trioxa-spiro[4,5]decane (19b): oil; FT-IR (neat cm^{-1}) 828, 1014, 1097, 1596, 2969; ^1H NMR (200 MHz, $CDCl_3$); δ 1.26 (d, 3H, J = 7.2 Hz), 1.64-1.77 (m, 7H), 2.25-2.29 (m, 1H), 2.85 (quin, 1H, J = 7.3 Hz), 3.67 (dd, 1H, J =11.5, 9.6 Hz), 3.84 (dd, 1H, J = 11.5, 2.8 Hz), 4.41 (brddd, 1H), 7.15 (d, 2H, J = 8.4 Hz), 7.28 (d, 2H, J = 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.87 (CH_3), 23.81 (CH_2), 24.98 (CH_2), 33.38 (CH_2), 37.08 (CH_2), 40.23 (CH), 63.91 (CH_2), 82.73 (CH), 114.86 (C), 129.99 (2 × CH), 129.49 (2 × CH), 132.90 (C), 141.04 (C); FAB-MS (*m/z*) 283 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{19}ClO_3$ [M$^+$]: 282.1023. Found: 282.1022.

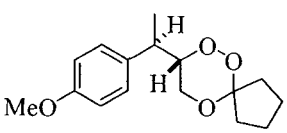


8-[1-(4-Fluoro-phenyl)-ethyl]-6,7,10-trioxa-spiro[4,5]decane (20a): oil; FT-IR (neat cm^{-1}) 820, 1072, 1117, 1598, 2969; ^1H NMR (200 MHz,

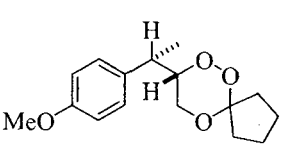
$CDCl_3$); δ 1.34 (d, 3H, J = 6.9 Hz), 1.61-1.86 (m, 7H), 2.29-2.33 (m, 1H), 2.83 (quin, 1H, J = 7.0 Hz), 3.42 (dd, 1H, J =11.8, 3.2 Hz), 3.52 (dd, 1H, J = 11.8, 8.8 Hz), 4.29 (dt, 1H, J = 8.8, 3.2 Hz), 6.95-7.04 (m, 2H), 7.12-7.27 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.57 (CH_3), 23.87 (CH_2), 24.89 (CH_2), 33.64 (CH_2), 36.77 (CH_2), 40.10 (CH_2), 63.88 (CH_2), 83.33 (CH), 114.74 (C), 115.96 (d, 2 × CH, $J_{C\text{-}F}$ = 21 Hz), 129.43 (d, 2 × CH, $J_{C\text{-}F}$ = 8 Hz), 137.93 (C), 162.21 (d, 2 × CH, $J_{C\text{-}F}$ = 244 Hz); FAB-MS (*m/z*) 266 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{19}FO_3$ [M$^+$]: 266.1318. Found: 266.1324.



8-[1-(4-Fluoro-phenyl)-ethyl]-6,7,10-trioxa-spiro[4,5]decane (20b): oil; FT-IR (neat cm^{-1}) 825, 1077, 1118, 1596, 2970; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.26 (d, 3H, J = 7.2 Hz), 1.57-1,77 (m, 7H), 2.27-2.23 (m, 1H), 2.86 (quin, 1H, J = 7.3 Hz), 3.68 (dd, 1H, J =11.5, 9.7 Hz), 3.83 (dd, 1H, J = 11.5, 2.7 Hz), 4.41 (brddd, 1H), 6.95-7.03 (m, 2H), 7.14-7.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.69 (CH_3), 23.55 (CH_2), 24.74 (CH_2), 30.09 (CH_2), 36.87 (CH_2), 39.84 (CH_2), 63.66 (CH_2), 82.61 (CH), 114.57 (C), 115.38 (d, 2 × CH, $J_{C\text{-}F}$ = 21 Hz), 129.31 (d, 2 × CH, $J_{C\text{-}F}$ = 8 Hz), 138.00 (C), 161.88 (d, C, $J_{C\text{-}F}$ = 243 Hz); FAB-MS (*m/z*) 266 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{19}FO_3$ [M$^+$]: 266.1318. Found: 266.1321.

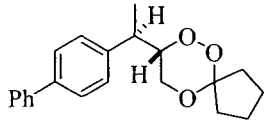


8-[1-(4-Methoxy-phenyl)-ethyl]-6,7,10-trioxa-spiro[4,5] decane (21a): white solid, mp 84-86 °C; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.33 (d, 3H, J = 6.9 Hz), 1.69-1.83 (m, 7H), 2.31-2.34 (m, 1H), 2.74 (quin, 1H, J = 6.9 Hz), 3.40 (dd, 1H, J =11.7, 3.6 Hz), 3.51 (dd, 1H, J = 11.7, 9.1 Hz), 3.79 (s, 1H) 4.29 (dt, 1H, J = 9.2, 3.2 Hz), 6.84 (d, 2H, J = 8.6 Hz), 7.08 (d, 2H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.54 (CH_3), 23.66 (CH_2), 24.73 (CH_2), 33.38 (CH_2), 36.67 (CH_2), 39.88 (CH), 55.45 (CH_3), 63.95 (CH_2), 83.43 (CH), 114.35 (2 × CH), 114.43 (C), 128.72 (2 × CH), 134.08 (C), 158.82 (C); FAB-MS (*m/z*) 278 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{22}O_4$ [M$^+$]: 278.1518. Found: 278.1519.

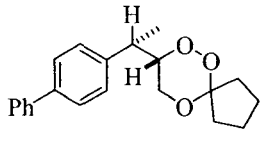


8-[1-(4-Methoxy-phenyl)-ethyl]-6,7,10-trioxa-spiro[4,5] decane (21b): oil; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.26 (d, 3H, J = 7.2 Hz), 1.56-1.79 (m, 7H), 2.28-2.35 (m, 1H), 2.78 (quin, 1H, J = 5.3 Hz), 3.62-3.84 (m, 2H), 3.79 (s, 3H) 4.43 (ddd, 1H, J = 9.9, 7.4, 2.9 Hz), 6.84 (d, 2H, J = 8.7 Hz), 7.13 (d, 2H, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.61 (CH_3), 23.54 (CH_2), 24.77 (CH_2), 33.03

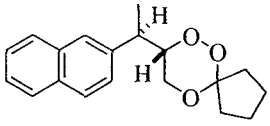
(CH_2), 36.98 (CH_2), 39.81 (CH), 55.41 (CH_3), 63.72 (CH_2), 82.78 (CH), 114.06 (2 × CH), 114.48 (C), 128.82 (2 × CH), 134.29 (C), 158.59 (C); FAB-MS (*m/z*) 278 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{22}O_4$ [M$^+$]: 278.1518. Found: 278.1522.



8-(1-Biphenyl-4-yl-ethyl)-6,7,10-trioxa-spiro[4,5]decane (22a) white solid, 74-76 °C; FT-IR (KBr cm^{-1}) 785, 1062, 1119, 1599, 2964; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.32 (d, 3H, J = 6.9 Hz), 1.62-1.76 (m, 7H), 2.31 (m, 1H), 2.79 (quin, 1H, J = 7.0 Hz), 3.40 (dd, 1H, J =11.7, 3.3 Hz), 3.50 (dd, 1H, J = 11.7, 8.8 Hz), 4.30 (dt, 1H, J = 8.9, 3.3 Hz), 7.16-7.52 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.61 (CH_3), 23.91 (CH_2), 24.95 (CH_2), 33.67 (CH_2), 36.85 (CH_2), 40.55 (CH), 64.12 (CH_2), 83.44 (CH), 114.75 (C), 127.42 (2 × CH), 127.70 (CH), 127.85 (2 × CH), 128.44 (2 × CH), 129.20 (2 × CH), 140.39 (C), 141.08 (C), 141.31 (C); FAB-MS (*m/z*) 325 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{24}O_3$ [M$^+$]: 324.1726. Found: 324.1726; Anal. Calcd. for $C_{21}H_{24}O_3$: %C 77.45, %H 7.46. Found: %C 77.85, %H 7.53.

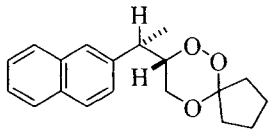


8-(1-Biphenyl-4-yl-ethyl)-6,7,10-trioxa-spiro[4,5]decane (22b) white solid, white solid, 82-84 °C; FT-IR (KBr cm^{-1}) 786, 1065, 1098, 1595, 2968; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.24 (d, 3H, J = 7.2 Hz), 1.57-1.74 (m, 7H), 2.23-2.27 (m, 1H), 2.84 (quin, 1H, J = 7.1 Hz), 3.68 (dd, 1H, J =11.6, 9.6 Hz), 3.80 (dd, 1H, J = 11.6, 3.0 Hz), 4.42 (ddd, 1H, J = 9.6, 7.9, 2.9 Hz), 7.18-7.52 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.61 (CH_3), 23.59 (CH_2), 24.81 (CH_2), 33.13 (CH_2), 36.98 (CH_2), 40.31 (CH), 63.83 (CH_2), 82.73 (CH), 114.62 (C), 127.26 (2 × CH), 127.34 (CH), 127.42 (2 × CH), 128.30 (2 × CH), 128.93 (2 × CH), 139.91 (C), 141.19 (C), 141.43 (C); FAB-MS (*m/z*) 325 [M+H$^+$]; EI-HRMS Calcd. for $C_{21}H_{24}O_3$ [M$^+$]: 324.1726. Found: 324.1718; Anal. Calcd. for $C_{21}H_{24}O_3$: %C 77.45, %H 7.46. Found: %C 77.10, %H 7.30.

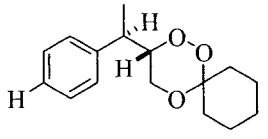


8-(1-Napthalen-2-yl-ethyl)-6,7,10-trioxa-spiro[4,5]decane (23a) white solid, 70-72 °C; FT-IR (KBr cm^{-1}) 780, 1053, 1118, 1591, 2965; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.44 (d, 3H, J = 6.9 Hz), 1.67-1.87 (m, 7H), 2.33 (m, 1H), 2.99 (quin, 1H, J = 6.8 Hz), 3.43 (dd, 1H, J =11.8, 3.0 Hz), 3.57 (dd, 1H, J = 11.8, 8.8 Hz), 4.46 (dt, 1H, J = 9.0, 3.0 Hz), 7.30-7.82 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.28 (CH_3), 23.46 (CH_2), 24.48 (CH_2), 33.28 (CH_2), 36.36 (CH_2), 40.60 (CH), 63.68 (CH_2), 82.97 (CH), 114.32 (C), 125.59 (CH), 127.71 (CH), 126.19 (CH), 126.35 (CH), 127.62 (2 × CH),

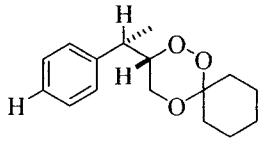
128.50 (CH), 132.59 (C), 133.53 (C), 139.34 (C); FAB-MS (*m/z*) 299 [M+H$^+$]; EI-HRMS Calcd. for $C_{19}H_{22}O_3$ [M$^+$]: 298.1569. Found: 298.1569; Anal. Calcd. for $C_{19}H_{22}O_3$: %C 76.48, %H 7.43. Found: %C 76.85, %H 7.73.



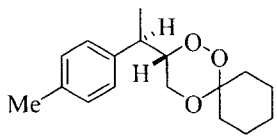
8-(1-Naphthalen-2-yl-ethyl)-6,7,10-trioxa-spiro[4,5]decane (23b) oil; FT-IR (neat cm^{-1}) 779, 1056, 1120, 1596, 2963; ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.44 (d, 3H, J = 6.9 Hz), 1.63-1.80 (m, 7H), 2.29-2.33 (m, 1H), 3.03 (quin, 1H, J = 7.2 Hz), 3.72 (dd, 1H, J =11.4, 9.6 Hz), 3.86 (dd, 1H, J = 11.4, 3.0 Hz), 4.59 (ddd, 1H, J = 9.4, 7.4, 3.0 Hz), 7.36-7.82 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.67 (CH_3), 23.57 (CH_2), 24.80 (CH_2), 33.10 (CH_2), 37.01 (CH_2), 40.88 (CH), 63.83 (CH_2), 82.69 (CH), 114.62 (C), 125.74 (CH), 126.18 (CH), 126.22 (CH), 126.56 (CH), 127.80 (CH), 127.93(CH), 128.33 (CH), 132.77 (C), 133.70 (C), 139.79 (C); FAB-MS (*m/z*) 299 [M+H$^+$]; EI-HRMS Calcd. for $C_{19}H_{22}O_3$ [M$^+$]: 298.1569. Found: 298.1569.



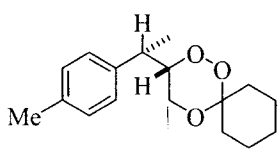
3-(1-Phenyl-ethyl)-1,2,5-trioxa-spiro[5.5]undecane (24a): oil; FT-IR (neat cm^{-1}) 764, 1023, 1097, 1602, 2935; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.37 (d, 3H, J = 6.7 Hz), 1.44-1.64 (m, 8H), 1.84-1.92 (m, 1H), 2.07-2.13 (m, 1H), 2.79 (brquin, 1H), 3.33 (dd, 1H, J = 11.8, 2.1 Hz), 3.62 (dd, 1H, J = 11.8, 9.2 Hz), 4.30 (dt, 1H, J = 9.2, 2.1 Hz) 7.16-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.50 (CH_3), 22.47 (CH_2), 22.51 (CH_2), 25.74 (CH_2), 29.70 (CH_2), 34.17 (CH_2), 40.85 (CH), 61.59 (CH_2), 83.33 (CH), 102.49 (C), 127.25 (CH), 127.80 (2 × CH), 128.94 (2 × CH), 141.97 (C); FAB-MS (*m/z*) 263 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{22}O_3$ [M$^+$]: 262.1569. Found: 262.1569; Anal. Calcd. for $C_{16}H_{22}O_3$: %C 73.25, %H 8.45. Found: %C 73.35, %H 8.50.



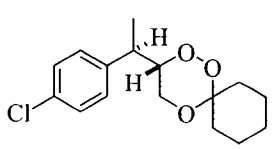
3-(1-Phenyl-ethyl)-1,2,5-trioxa-spiro[5.5]undecane (24b): oil; FT-IR (neat cm^{-1}) 765, 1030, 1091, 1602, 2940; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.27 (d, 3H, J = 7.3 Hz), 1.38-1.61 (m, 8H), 1.79-1.87 (m, 1H), 2.02-2.11 (m, 1H), 2.86 (quin, 1H. J = 7.3Hz), 3.73 (dd, 1H, J = 11.7, 3.2 Hz), 3.82 (dd, 1H, J = 11.7, 9.9 Hz), 4.44 (ddd, 1H, J = 9.9, 7.8, 3.2 Hz) 7.19-7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.48 (CH_3), 22.42 (CH_2), 22.46 (CH_2), 25.71 (CH_2), 29.35 (CH_2), 34.59 (CH_2), 40.73 (CH), 61.37 (CH_2), 82.68 (CH), 102 56 (C), 126.94 (CH), 127.87 (2 × CH), 128.65 (2 × CH), 142.31 (C); FAB-MS (*m/z*) 263 [M+H$^+$]; HRMS Calcd. for $C_{16}H_{22}O_3$ [M$^+$]: 262.1569. Found: 262.1534; Anal. Calcd. for $C_{16}H_{22}O_3$: %C 73.25, %H 8.45. Found: %C 73.10, %H 8.70.



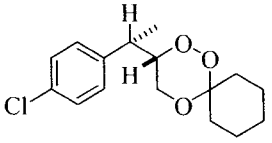
3-(1-*p*-Tolyl-ethyl)-1,2,5-trioxa-spiro[5,5]undecane (25a): oil; FT-IR (neat cm^{-1}) 765, 1011, 1597, 2935; ^1H NMR (300 MHz, $CDCl_3$); δ 1.36 (d, 3H, J = 6.9 Hz), 1.55-1.61 (m, 8H),1.91 (m, 1H), 2.11 (m, 1H), 2.34 (s, 3H), 2.77 (quin, 1H, J = 6.9 Hz), 3.36 (dd, 1H, J = 11.9, 2.5 Hz), 3.63 (dd, 1H, J = 11.8, 9.3 Hz), 4.30 (dt, 1H, J = 9.3, 2.5 Hz), 7.07 (d, 2H, J = 8.1 Hz), 7.13 (d, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.65 (CH_3), 21.22 (CH_3), 22.50 (CH_2), 22.55 (CH_2), 25.78 (CH_2), 29.74 (CH_2), 34.25 (CH_2), 40.47 (CH), 61.64 (CH_2), 83.42 (CH), 102.45 (C), 127.66 (2 × CH), 129.61 (2 × CH), 136.82 (C), 138.96 (C); FAB-MS (*m/z*) 277 [M+H$^+$]; EI-HRMS Calcd. for $C_{17}H_{24}O_3$ [M$^+$]: 276.1726. Found: 276.1724.



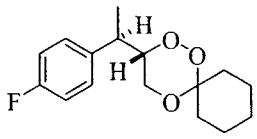
3-(1-*p*-Tolyl-ethyl)-1,2,5-trioxa-spiro[5,5]undecane (25b): oil; FT-IR (neat cm^{-1}) 740, 1012, 1596, 2921; ^1H NMR (300 MHz, $CDCl_3$); δ 1.28 (d, 3H, J = 7.3 Hz), 1.44-1.59 (m, 8H),1.80-1.89 (m, 1H), 2.06-2.14 (m, 1H), 2.34 (s, 3H), 2.85 (quin, 1H, J = 7.3 Hz), 3.76 (dd, 1H, J = 11.7, 3.2 Hz), 3.84 (dd, 1H, J = 11.7, 9.9 Hz), 4.44 (ddd, 1H, J = 9.9, 7.6, 3.2 Hz), 7.13 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.60 (CH_3), 21.23 (CH_3), 22.50 (2 × CH_2), 25.76 (CH_2), 29.43 (CH_2), 34.65 (CH_2), 40.39 (CH), 61.44 (CH_2), 82.81 (CH), 102.55 (C), 127.76 (2 × CH), 129.37 (2 × CH), 136.45 (C), 139.30 (C); FAB-MS (*m/z*) 277 [M+H$^+$]; EI-HRMS Calcd. for $C_{17}H_{24}O_3$ [M$^+$]: 276.1726. Found: 276.1741.



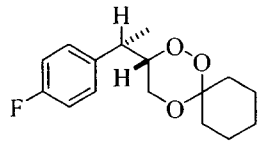
3-[1-(4-Chloro-phenyl)-1,2,5-trioxa-spiro[5,5]undecane (26a): oil; FT-IR (neat cm^{-1}) 790, 1097, 1592, 2973; ^1H NMR (200 MHz, $CDCl_3$); δ 1.34 (d, 3H, J = 6.9 Hz), 1.40-1.60 (m, 8H),1.82-1.89 (m, 1H), 2.05-2.08 (m, 1H), 2.82 (quin, 1H, J = 6.9 Hz), 3.35 (dd, 1H, J = 11.7, 3.1 Hz), 3.60 (dd, 1H, J = 11.7, 9.4 Hz), 4.25 (dt, 1H, J = 9.4, 3.1 Hz), 7.11 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.52 (CH_3), 22.68 (2 × CH_2), 25.92 (CH_2), 30.05 (CH_2), 34.20 (CH_2), 40.39 (CH), 61.44 (CH_2), 83.20 (CH), 102.79 (C), 129.28 (2 × CH), 129.36 (2 × CH), 133.17 (C), 140.79 (C); FAB-MS (*m/z*) 297 [M+H$^+$]; FAB-MS (*m/z*) 297 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{21}ClO_3$ [M$^+$]: 296.1179. Found: 296.1192.



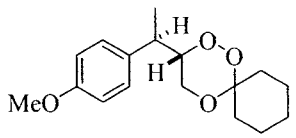
3-[1-(4-Chloro-phenyl)-1,2,5-trioxa-spiro[5,5]undecane (26b): oil; FT-IR (neat cm^{-1}) 746, 1106, 1600, 2938; ^1H NMR (200 MHz, $CDCl_3$); δ 1.25 (d, 3H, J = 7.2 Hz), 1.35-1.60 (m, 8H),1.75-1.84 (m, 1H), 1.99-2.08 (m, 1H), 2.84 (quin, 1H, J = 7.2 Hz), 3.72-3.85 (m, 2H), 4.37 (brddd, 1H), 7.14 (d, 2H, J = 8.5 Hz), 7.27 (d, 2H, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.84 (CH_3), 22.64 (2 × CH_2), 25.90 (CH_2), 29.70 (CH_2), 34.64 (CH_2), 40.36 (CH), 61.54 (CH_2), 82.77 (CH), 102.88 (C), 129.99 (2 × CH), 129.47 (2 × CH), 132.88 (C), 141.12 (C); FAB-MS (*m/z*) 297 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{21}ClO_3$ [M$^+$]: 296.1179. Found: 296.1155.



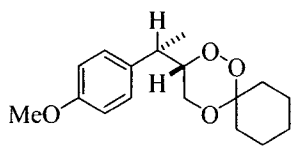
3-[1-(4-Fluoro-phenyl)-1,2,5-trioxa-spiro[5,5]undecane (27a): white solid, mp 56-58 °C; FT-IR (KBr cm^{-1}) 748, 1097, 1592, 2973; ^1H NMR (300 MHz, $CDCl_3$); δ 1.36 (d, 3H, J = 7.0 Hz), 1.45-1.66 (m, 8H),1.86-1.91 (m, 1H), 2.06-2.12 (m, 1H), 2.84 (quin, 1H, J = 7.0 Hz), 3.37 (dd, 1H, J = 11.8, 2.5 Hz), 3.62 (dd, 1H, J = 11.8, 9.2 Hz), 4.26 (dt, 1H, J = 9.2, 2.5 Hz), 6.97-7.03 (m, 2H), 7.13-7.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.45 (CH_3), 22.47 (CH_2), 22.51 (CH_2), 25.73 (CH_2), 29.83 (CH_2), 34.08 (CH_2), 40.08 (CH), 61.33 (CH_2), 83.21 (CH), 102.55 (C), 115.75 (d, 2 × CH, $J_{C\text{-}F}$ = 22 Hz), 129.24 (d, 2 × CH, $J_{C\text{-}F}$ = 7.5 Hz), 137.81 (C), 162.03 (d, C, $J_{C\text{-}F}$ = 236 Hz); FAB-MS (*m/z*) 297 [M+H$^+$]; FAB-MS (*m/z*) 281 [M+H$^+$]; EI-HRMS Calcd. for $C_{16}H_{21}FO_3$ [M$^+$]: 280.1475. Found: 280.1465.



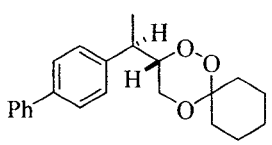
3-[1-(4-Fluoro-phenyl)-1,2,5-trioxa-spiro[5,5]undecane (27b): oil; FT-IR (neat cm^{-1}) 746, 1105, 1601, 2939; ^1H NMR (300 MHz, $CDCl_3$); δ 1.28 (d, 3H, J = 7.2 Hz), 1.44-1.59 (m, 8H),1.80-1.88 (m, 1H), 2.03-2.11 (m, 1H), 2.88 (quin, 1H, J = 7.2 Hz), 3.76 (dd, 1H, J = 11.7, 3.8 Hz), 3.32 (dd, 1H, J = 11.7, 8.7 Hz), 4.39 (dt, 1H, J = 8.7, 3.8 Hz), 6.98-7.04 (m, 2H), 7.17-7.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.74 (CH_3), 22.43 (CH_2), 22.48 (CH_2), 25.72 (CH_2), 29.46 (CH_2), 34.51 (CH_2), 40.02 (CH), 61.37 (CH_2), 83.70 (CH), 102.66 (C), 115.45 (d, 2 × CH, $J_{C\text{-}F}$ = 21 Hz), 129.33 (d, 2 × CH, $J_{C\text{-}F}$ = 7.5 Hz), 138.04 (C), 161.92 (d, C, $J_{C\text{-}F}$ = 243 Hz); FAB-MS (*m/z*) 297 [M+H$^+$].



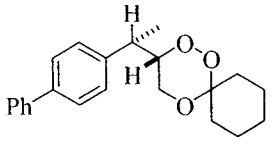
3-[1-(4-Methoxy-phenyl)-1,2,5-trioxa-spiro[5,5]undecane (28a): white solid, mp 65-67 °C; FT-IR (KBr cm^{-1}) 765, 1093, 1557, 2938; ^1H NMR (200 MHz, $CDCl_3$); δ 1.33 (d, 3H, J = 6.8 Hz), 1.43-1.64 (m, 8H),1.84-1.91 (m, 1H), 2.05-2.14 (m, 1H), 2.74 (quin, 1H, J = 6.8 Hz), 3.33 (dd, 1H, J = 11.8, 2.7 Hz), 3.61 (dd, 1H, J = 11.8, 9.5, Hz), 3.78 (s, 3H), 4.25 (dt, 1H, J = 9.3, 2.7 Hz), 6.83 (d, 2H, J = 8.6 Hz), 7.08 (d, 2H, J = 8.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.83 (CH_3), 22.68 (2 × CH_2), 25.94 (CH_2), 29.88 (CH_2), 34.41 (CH_2), 40.20 (CH), 55.64 (CH_3), 61.79 (CH_2), 83.68 (CH), 102.62 (C), 114.51 (2 × CH), 128.91 (2 × CH), 134.20 (C), 158.97 (C); FAB-MS (*m/z*) 297 [M+H$^+$]; EI-HRMS Calcd. for $C_{17}H_{24}O_4$ [M$^+$]: 296.1675 Found: 296.1670.



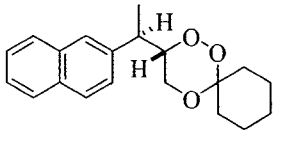
3-[1-(4-Methoxy-phenyl)-1,2,5-trioxa-spiro[5,5]undecane (28b): oil; FT-IR (neat cm^{-1}) 764, 1094, 1584, 2935; ^1H NMR (200 MHz, $CDCl_3$); δ 1.25 (d, 3H, J = 7.2 Hz), 1.31-1.60 (m, 8H),1.75-1.85 (m, 1H), 2.01-2.10 (m, 1H), 2.77 (quin, 1H, J = 7.2 Hz), 3.70 (dd, 1H, J = 11.6, 3.5 Hz), 3.75-3.86 (dd merged, 1H,), 3.78 (s, 3H), 4.39 (ddd, 1H, J = 10.7, 7.5, 3.5 Hz), 6.84 (d, 2H, J = 8.7 Hz), 7.13 (d, 2H, J = 8.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.84 (CH_3), 22.64 (2 × CH_2), 25.93 (CH_2), 29.58 (CH_2), 34.82 (CH_2), 40.15 (CH), 55.64 (CH_3), 61.60 (CH_2), 83.04 (CH), 102.74 (C), 114.27 (2 × CH), 129.03 (2 × CH), 134.57 (C), 158.76 (C); FAB-MS (*m/z*) 297 [M+H$^+$]; EI-HRMS Calcd. for $C_{17}H_{24}O_3$ [M$^+$]: 296.1675. Found: 296.1670.



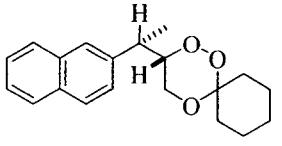
3-(1-Biphenyl-4-yl-ethyl)-1,2,5-trioxa-spiro[5,5]undecane (29a): white solid, mp 80-81 °C; FT-IR (KBr cm^{-1}) 801, 1027, 1605, 2953; ^1H NMR (200 MHz, $CDCl_3$); δ 1.40 (d, 3H, J = 6.9 Hz), 1.44-1.61 (m, 8H),1.89-1.93 (m, 1H), 2.06-2.11 (m, 1H), 2.86 (quin, 1H, J = 7.5 Hz), 3.41 (dd, 1H, J = 11.8, 2.7 Hz), 3.66 (dd, 1H, J = 11.8, 9.4, Hz), 4.33 (dt, 1H, J = 9.1, 2.5 Hz), 7.22-7.59 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.70 (CH_3), 22.73 (CH_2), 22.97 (CH_2), 25.74 (CH_2), 30.06 (CH_2), 34.36 (CH_2), 40.72 (CH), 61.77 (CH_2), 83.53 (CH), 102.77 (C), 127.43 (CH), 127.85 (3 × CH), 128.45 (2 × CH), 129.20 (2 × CH), 140.42 (C), 141.31 (2 × C), 139.48 (C); FAB-MS (*m/z*) 339 [M+H$^+$]; EI-HRMS Calcd. for $C_{22}H_{26}O_3$ [M$^+$]: 338.1882 Found; 338.1882; Anal. Calcd. for $C_{20}H_{24}O_3$: %C 78.07, %H 7.74. Found: %C 78.48, %H 7.45.



3-(1-Biphenyl-4-yl-ethyl)-1,2,5-trioxa-spiro[5,5]undecane (29b): white solid, mp 85-86 °C; FT-IR (KBr cm^{-1}) 770, 1113, 1598, 2915; ^1H NMR (200 MHz, $CDCl_3$); δ 1.30 (d, 3H, J = 7.2 Hz), 1.36-1.58 (m, 8H),1.81-1.88 (m, 1H), 2.04-2.09 (m, 1H), 2.91 (quin, 1H, J = 7.0 Hz), 3.77 (dd, 1H, J = 11.7, 3.8 Hz), 3.86 (dd, 1H, J = 11.7, 9.3, Hz), 4.47 (brddd, 1H), 7.25-7.59 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.69 (CH_3), 22.73 (2 ×CH_2), 25.96 (CH_2), 30.09 (CH_2), 34.34 (CH_2), 40.71 (CH), 61.76 (CH_2), 83.52 (CH), 102.75 (C), 127.41 (CH), 127.68 (2 × CH), 127.84 (CH), 128.43 (2 × CH), 129.18 (2 × CH) 140.40 (C), 141.1 (2 × C), 141.30 (C); FAB-MS (*m/z*) 339 [M+H^+]; EI-HRMS Calcd. for $C_{22}H_{26}O_3$ [M^+]: 338.1882 Found; 338.1882; Anal. Calcd. for $C_{20}H_{24}O_3$: %C 78.07, %H 7.74. Found: %C 78.20, %H 7.99.

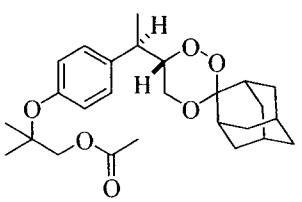


3-(1-Naphthalen-2-yl-ethyl)-1,2,5-trioxa-spiro[5, 5] undecane (30a): white solid, mp 85-87 °C; FT-IR (KBr cm^{-1}) 774, 1113, 1598, 2913; ^1H NMR (200 MHz, $CDCl_3$); δ 1.45 (d, 3H, J = 6.9 Hz), 1.52-1.65 (m, 8H),1.89-1.92 (m, 1H), 2.09-2.12 (m, 1H), 2.95 (quin, 1H, J = 7.5 Hz), 3.36 (dd, 1H, J = 11.8, 2.7 Hz), 3.66 (dd, 1H, J = 11.8, 9.3, Hz), 4.42 (dt, 1H, J = 9.2, 2.6 Hz), 7.29-7.81 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.61 (CH_3), 22.47 (CH_2), 22.52 (CH_2), 25.74 (CH_2), 29.82 (CH_2), 34.11 (CH_2), 40.96 (CH), 61.55 (CH_2), 83.24 (CH), 102.54 (C), 125.77 (CH), 125.91 (CH), 126.40 (CH), 126.57 (CH), 127.81 (2 × CH), 128.72 (CH), 132.78 (C), 133.71(C), 139.48 (C); FAB-MS (*m/z*)313 [M+H^+]; EI-HRMS Calcd. for $C_{20}H_{24}O_3$ [M^+]: 312.1726 Found; 312.1726; Anal. Calcd. for $C_{20}H_{24}O_3$: %C 76.89, %H 7.74. Found: %C 76.50, %H 7.66.

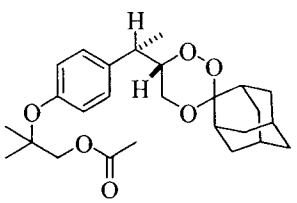


3-(1-Naphthalen-2-yl-ethyl)-1,2,5-trioxa-spiro[5, 5] undecane (30b): white solid, mp 92-94 °C; FT-IR (KBr cm^{-1}) 744, 1184, 1606, 2964; ^1H NMR (200 MHz, $CDCl_3$); δ 1.36 (d, 3H, J = 6.9 Hz), 1.42-1.57 (m, 8H),1.79-1.86 (m, 1H), 2.01-2.07 (m, 1H), 3.03 (quin, 1H, J = 7.2 Hz), 3.76 (dd, 1H, J = 11.7, 3.7 Hz), 3.84 (dd, 1H, J = 11.7, 9.6, Hz), 4.54 (ddd, 1H, J = 9.6, 7.6, 3.7 Hz), 7.35-7.81 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.91 (CH_3), 22.66 (2 × CH_2), 25.93 (CH_2), 29.61 (CH_2), 34.82 (CH_2), 41.20 (CH), 61.70 (CH_2), 82.93 (CH), 102.85 (C), 125.93 (CH), 126.39 (2 × CH), 126.76 (CH), 128.00 (CH), 128.11 (2 × CH), 128.57 (CH), 132.94 (C), 133.88(C), 140.05 (C); FAB-MS (*m/z*) 313 [M+H^+]; EI-HRMS Calcd. for $C_{20}H_{24}O_3$ [M^+]: 312.1726 Found; 312.1724; Anal. Calcd. for $C_{20}H_{24}O_3$: %C 76.89, %H 7.74. Found: %C 76.79, %H 7.95.

General procedure for acetylation of trioxanes 13a+13b: To a stirred solution of diastereomeric mixture of trioxanes **13a** and **13b** (1.80 g, 4.478 mmol) in dichloromethane (20ml), acetic anhydride (2.28 mL, 5 equiv), triethyl amine (2.26 mL, 5 equiv) and catalytic amount of DMAP (5 mg) was added in succession and the reaction mixture was allowed to stir at rt for 2 hours. The reaction mixture was evaporated, and the crude product was purified by column chromatography over silica gel to furnish diacetate **13c** and **13d** as a mixture of diastereomers (1.95 g, 98% yield) which on flash chromatography furnished the pure isomers **13c** (higher R_f, oil) and **13b** (lower R_f, oil).



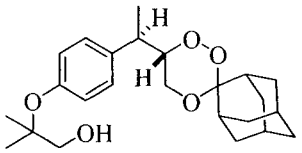
Compound 13c: oil; FT-IR (KBr cm^{-1}) 778, 1115, 1617, 1735, 2935, 3420; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 6H), 1.35 (d, 3H, J = 6.9 Hz), 1.57-2.02 (m, 14H), 2.73 (s, 3H), 2.73 (brquin, 1H), 2.77 (s, 1H), 3.28 (dd, 1H, J = 11.8, 2.5 Hz), 3.58 (dd, 1H, J = 11.8, 9.8 Hz),4.09 (s, 2H), 4.28 (dt, 1H, J = 9.4, 2.4 Hz), 6.92 (d, 2H, J = 8.5 Hz), 7.07 (d, 2H, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.72 (CH_3), 21.36 (CH_3), 24.35 (2 × CH_3), 27.53 (2 × CH), 30.15 (CH), 33.40 (CH_2), 33.64 (CH_2), 33.84 (2 × CH_2), 35.99 (CH), 37.59 (CH_2), 40.47 (CH), 61.42 (CH_2), 70.00 (CH_2), 78.96 (C), 83.50 (CH), 104.73 (C), 124.91 (2 × CH), 128.53 (2 × CH), 137.64 (C), 153.76 (C), 171.33 (C); ESI-MS (*m/z*) 467 [M+Na^+].



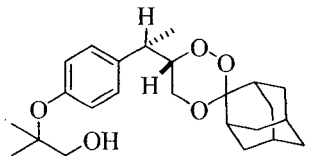
Compound 13d: oil; FT-IR (KBr cm^{-1}) 775, 1119, 1618, 1733, 2930, 3421; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 3H, J = 7.2 Hz), 1.32 (s, 6H), 1.54-2.06 (m, 14H), 2.15 (s, 3H), 2.70 (s, 1H), 2.84 (quin, 1H, J = 7.2 Hz), 3.67 (dd, 1H, J = 11.6, 3.3 Hz), 3.78 (dd, 1H, J = 11.6, 10.0 Hz),4.11 (s, 2H), 4.45 (ddd, 1H, J = 10.0, 7.2, 3.3 Hz), 6.94 (d, 2H, J = 8.5 Hz), 7.12 (d, 2H, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.65 (CH_3), 21.34 (CH_3), 24.37 (2 × CH_3), 27.49 (2 × CH), 29.83 (CH), 33.35 (CH_2), 33.55 (CH_2), 33.79 (CH_2), 33.88 (CH_2), 36.38 (CH), 37.58 (CH_2), 40.30 (CH), 60.93 (CH_2), 70.06 (CH_2), 78.85 (C), 82.63 (CH), 104.82 (C), 124.55 (2 × CH), 128.70 (2 × CH), 138.02 (C), 153.48 (C), 171.39 (C); ESI-MS (*m/z*) 467 [M+Na^+].

General procedure for LAH reduction of trioxane acetates 13c and **13d,** (Reduction of trioxane **13c** as representative): To a stirred and ice cooled slurry of LAH (0.10 gm, 3 equivalents) in dry Et_2O (20 ml), under N_2 atmosphere, was added compound **13c** (0.4 g, 0.905 mmol), dissolved in dry Et_2O (5 mL) via dropping funnel for 10 min and the reaction mixture was allowed to stir at same temperature for 1.5 h. The reaction mixture was quenched by the gradual addition of water (2 mL), and then finally with 10% NaOH (2mL), till a thick sludge settled at the bottom. The ethereal layer was decanted and the sludge was washed with ether (3 × 10 mL). The combined organic layer was dried over anhyd. Na_2SO_4, concentrated, and purified by column chromatography over silica gel to furnish compound **13a** (0.290 g, 80% yield) as an oil.

Compound **13d** was also reduced by same procedure to furnish trioxane **13b**.



Compound 13a: oil; FT-IR (KBr cm^{-1}) 772, 1110, 1596, 2928, 3420; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6H), 1.37 (d, 3H, J = 6.9 Hz), 1.59-2.04 (m, 14H), 2.75 (brs, 1H, OH), 2.75 (brquin, 1H), 2.79 (s, 1H), 3.31 (dd, 1H, J = 11.8, 2.5 Hz), 3.57-3.64 (brm, 3H), 4.29 (dt, 1H, J = 9.4, 2.5 Hz), 6.93 (d, 2H, J = 8.5 Hz), 7.09 (d, 2H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.50 (CH_3), 23.30 (2 × CH_3), 27.34 (CH), 27.35 (CH), 29.99 (CH), 33.22 (CH_2), 33.46 (CH_2), 33.66 (2 × CH_2), 35.84 (CH), 37.41 (CH_2), 40.27 (CH), 61.23 (CH_2), 70.46 (CH_2), 80.86 (C), 83.31 (CH), 104.54 (C), 124.29 (2 × CH), 128.39 (2 × CH), 137.29 (C), 153.71 (C); ESI-MS (*m/z*) 403 [M+H$^+$]; EI-HRMS Calcd. for $C_{24}H_{34}O_5$ [M$^+$]: 402.2406. Found: 402.2419; Anal. Calcd. for $C_{24}H_{34}O_5$: % C 71.61, %H 8.51. Found: %C 71.50, %H 8.23.

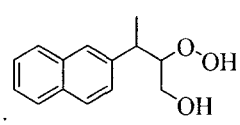


Compound 13b: mp 110-112 °C ; FT-IR (KBr cm^{-1}) 749, 1115, 1602, 2911, 3449; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d merged, 3H,), 1.26 (s, 6H), 1.53-2.04 (m, 14H), 2.25 (brt, 1H, OH), 2.83 (quin, 1H, 7.1 Hz), 3.58 (d, 2H, J = 4.9 Hz), 3.69 (dd, 1H, J = 11.6, 3.2 Hz), 3.78 (dd, 3H, J = 11.6, 10.0 Hz), 4.43 (ddd, 1H, J = 10.0, 6.9, 3.2 Hz), 6.91 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.42 (CH_3), 23.31 (2 × CH_3), 27.30 (CH), 27.34 (CH), 29.68 (CH), 33.18 (CH_2), 33.37 (CH_2), 33.59 (CH_2), 33.69 (CH_2), 36.17 (CH), 37.40 (CH_2), 40.07 (CH), 60.73 (CH_2), 70.48 (CH_2), 80.73 (C), 82.45 (CH), 104.62 (C), 123.93 (2 × CH), 128.53 (2 × CH), 137.69 (C), 153.42 (C); ESI-MS (*m/z*) 403 [M+H$^+$]; EI-HRMS Calcd.

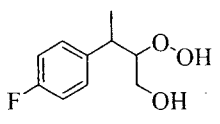
for $C_{24}H_{34}O_5$ [M^+]: 402.2406. Found: 402.2397; Anal. Calcd. for $C_{24}H_{34}O_5$: % C 71.61, %H 8.51. Found: %C 71.95, %H 8.80.

General procedure for diimide reduction of *β*-hydroxyhydroperoxides using hydrazinium carbazate ($N_2H_3COON_2H_5$) and 30% H_2O_2. (Reduction of β-hydroxyhydroperoxide **31** as representative): To a stirred and ice cooled solution of compound **31** (0.500 g, 2.155 mmol) and hydrazinium carbazate (2.16 mL, 10 equiv) in 1:1 mixture of EtOH-THF (25 mL) was added 30% H_2O_2 (7.39 mL, 30 equiv) drop wise over 10 min and the reaction mixture was allowed to stir at rt for 4 days. The reaction mixture was evaporated on a rotavapor, diluted with water (10 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extract was washed with brine solution (10 mL), concentrated and the crude product was purified by column chromatography over silica gel to furnish saturated β-hydroxyhydroperoxide **32** (0.250 g, 50% yield) as an inseparable mixture of diastereomers together with saturated diol **33** (0.080 g, 17% yield), again as an inseparable mixture of diastereomers.

Similarly unsaturated β-hydroxyhydroperoxide **35** was also reduced by the same procedure to furnish saturated β-hydroxyhydroperoxide **36** and saturated diol **37** as inseparable diastereomeric mixtures.



2-Hydroperoxy-3-naphthalen-2-yl-butan-1-ol (32): oil; FT-IR (neat cm^{-1}) 750, 820, 1063, 1599, 2928, 3405; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 and 1.40 (2 × d, J = 7.2 and 7.0 Hz respectively together integrating for 3H), 2.20 and 3.09 (brquin, and quin, J = 7.2 Hz together integrating for 1H), 3.42 and 3.66 (2 × dd, J = 12.2, 6.4 and 12.3, 6.2 Hz respectively together integrating for 1H), 3.50 and 3.74 (2 × dd, J = 12.2, 2.9 and 12.3, 2.3 Hz respectively together integrating for 1H), 4.02-4.15 (m, 1H), 7.21-7.77 (m, 7H), 9.72 (brm, 1H, OOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.76 (CH_3), 18.80 (CH_3), 40.98 (CH), 41.04 (CH), 61.01 (CH_2), 61.23 (CH_2), 82.58 (CH), 83.19 (CH), 125.69 (CH), 125.92 (CH), 126.11 (CH), 126.14 (CH), 126.41 (CH), 126.48 (CH), 126.57 (CH), 127.78 (CH), 127.83 (CH), 127.88 (CH), 128.38 (CH), 128.73 (CH), 132.71 (C), 132.76 (C), 133.67 (C), 139.44 (C), 139.96 (C); ESI-MS (*m/z*) 255 [$M+Na^+$].

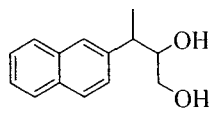


3-(4-Fluoro-phenyl)-2-hydroperoxy-butan-1-ol (36): oil; FT-IR (neat cm^{-1}) 841, 1045, 1603, 2932, 3405; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 and 1.34 (2 × d, J = 7.2 and 7.0 Hz respectively together integrating for 3H), 3.03 and 3.09 (2 × quin, J = 7.0 and 7.2 Hz respectively together integrating for 1H), 3.44 and 3.70 (2 × dd, J = 12.2, 6.6 and 12.3, 6.6 Hz respectively together integrating for 1H), 3.56 and 3.89 (2 × dd, J = 12.2, 2.8 and 12.3, 2.6 Hz respectively together integrating for 1H), 3.96 and 4.05 (m, together integrating for 1H), 6.98-7.21 (m, 4H), 9.73 (brm, 1H, OOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.73 (CH_3), 18.48 (CH_3), 39.99 (CH), 40.05 (CH), 61.37(CH_2), 61.44 (CH_2), 82.68 (CH), 83.21 (CH), 115.44 (d, CH, $J_{C\text{-}F}$ = 21 Hz), 115.76 (d, CH, $J_{C\text{-}F}$ = 22 Hz), 129.23 (d, CH, $J_{C\text{-}F}$ = 7.5 Hz), 129.31 (d, CH, $J_{C\text{-}F}$ = 7.5 Hz), 137.71 (d, C, $J_{C\text{-}F}$ = 3.0 Hz), 138.04 (d, C, $J_{C\text{-}F}$ = 3.0 Hz), 161.89 (d, C, $J_{C\text{-}F}$ = 243 Hz), 162.00 (d, C, $J_{C\text{-}F}$ = 244 Hz); ESI-MS (*m/z*) 223 [$M+H^+$].

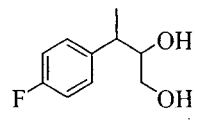
General procedure for sodium borohydride reduction of saturated β-hydroxyhydroperoxides and γ-hydroxyhydroperoxides, (Reduction of saturated β-hydroxyhydroperoxide **32** as representative): To a stirred and ice cooled solution of β-hydroxyhydroperoxide **32** (0.100 g, 0.431 mmol) in methanol (5mL), was added sodium borohydride (0.033 g, 2 equiv) and the reaction mixture was allowed to stir for 5 min. The reaction mixture was quenched with glacial acetic acid (0.5 mL), evaporated, diluted with water (5mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with brine (5 mL), concentrated and the crude product was purified by column chromatography over silica gel to furnish saturated diol **33** (0.090 g, 97% yield) as a colorless oil.

Hydroperoxide **36** was also reduced by the same procedure to furnish diol **37** as an inseparable mixture of diastereomers.

Catalytic hydrogenation of *β*-hydroxyhydroperoxide 31: A solution of β-hydroxyhydroperoxide **31** (0.200 g, 0.869 mmol) in EtOAc (15 mL) was hydrogenated in presence of Adam's catalyst (PtO_2) (0.003 g) using Parr shaker assembly at room temperature and pressure for 1 h. The reaction mixture was filtered over celite, concentrated and the crude product was purified by column chromatography over silica gel to furnish saturated diol **33** (96% yield) as a colorless oil.



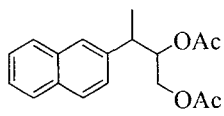
3-Naphthalen-2-yl-butane-1,2-diol (33): oil; FT-IR (neat cm^{-1}) 751, 1068, 1109, 1623, 2929, 3282; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 and 1.41 (2 × d, J = 7.0, together integrating for 3H), 2.84-3.02 (brm, 2H, 2OH) 2.89 and 2.98 (2 × quin, J = 7.0 Hz together integrating for 1H), 3.29 and 3.49 (2 × dd, J = 11.3, 7.5 and 11.4, 7.2 Hz respectively together integrating for 1H , 3.39 and 3.73 (2 × dd, J = 11.3, 2.9 and 11.4, 2.8 Hz respectively together integrating for 1H), 3.81 (dt, J = 7.4, 2.6, 1H), 7.29-7.67 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.71 (CH_3), 18.03 (CH_3), 42.99 (CH), 43.11 (CH), 64.75 (CH_2), 65.23 (CH_2), 76.33 (CH), 76.70 (CH), 125.64 (CH), 125.73 (CH), 126.10 (CH), 126.17 (CH), 126.21 (CH), 126.27 (CH), 126.30 (CH), 126.80 (CH), 127.76 (CH), 127.79 (CH), 128.33 (CH), 128.38 (CH), 132.54 (C), 132.63 (C), 133.64 (C), 133.69 (C), 140.95 (C); ESI-MS (*m/z*) 239 [M+Na^+]; EI-HRMS Calcd. for $C_{14}H_{16}O_2$ [M^+]: 216.1150. Found: 216.1148.



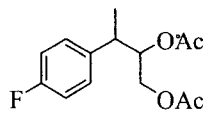
3-(4-Fluoro-phenyl)-butane-1,2-diol (37): oil; FT-IR (neat cm^{-1}) 1035, 1066, 1605, 2929, 3322; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 and 1.30 (2 × d, J=7.1 and 7.0 Hz respectively together integrating for 3H), 2.70-2.86 (bm, 2H, 2OH), 2.75 and 2.82 (2 × quin, J = 7.1 and 7.0 Hz respectively together integrating for 1H), 3.27 and 3.45 (2 × dd, J=11.1, 7.6 and 11.8, 7.7 Hz respectively together integrating for 1H), 3.38-3.72 (m, 2H), 6.94-7.20 (m, together integrating for 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.71 (CH_3), 18.20 (CH_3), 42.17 (CH), 42.26 (CH), 64.77 (CH_2), 65.11 (CH_2), 76.42 (CH), 76.80 (CH), 115.52 (d, CH, $J_{C\text{-}F}$ = 21 Hz), 129.11 (d, CH, $J_{C\text{-}F}$ = 7.5 Hz), 129.58 (CH, d, $J_{C\text{-}F}$ = 8.0 Hz), 139.05 (C, d, $J_{C\text{-}F}$ = 3.0 Hz), 139.61 (C, d, $J_{C\text{-}F}$ = 3.0 Hz), 161.76 (C, d, $J_{C\text{-}F}$ = 244 Hz), 161.87 (C, d, $J_{C\text{-}F}$ = 243 Hz); ES-MS (*m/z*) 227 [M+H^+].

General procedure for acetylation of saturated diols, (Acetylation of saturated diol **33** as representative): To a stirred solution of diol **33** (0.100 g, 0.463 mmol) in dichloromethane (5ml), acetic anhydride (0.23 mL, 5 equiv), triethyl amine (0.23 mL 5 equiv) and catalytic amount of DMAP (2 mg) was added in succession and reaction mixture was allowed to stir for 2 hours. The reaction mixture was evaporated, and the crude product was purified by column chromatography over silica gel to furnish diacetate **34** (0.125 g, 91% yield) as an oil.

Saturated diol **37** was also acetylated by the same procedure to furnish diacetate **38**.



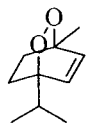
Acetic acid 1-acetoxymethyl-2-naphthalen-2-yl-propyl ester (34): oil; FT-IR neat cm^{-1}) 1047, 1650, 1744, 2971; ^1H, NMR (300 MHz, $CDCl_3$) δ 1.40 and 1.42 (d merged and d, J = 7.1 Hz respectively, together integrating for 3H), 1.95 and 2.03 (2 × s, together integrating for 3H), 2.06 and 2.15 (2 × s, together integrating for 3H), 3.22 and 3.30 (bquin and quin, J = 7.1 Hz together integrating for 1H), 3.85 and 4.08 (2 × dd, J = 12.0, 6.6 and 12.0, 7.1 Hz respectively, together integrating for 1H), 4.17 and 4.32 (2 × dd, J = 12.0, 2.8 and 12.0, 3.0 Hz respectively, together integrating for 1H), 5.44-5.37 (m, 1H , 7.38-7.85 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.48 (CH_3), 18.19 (CH_3), 20.88 (CH_3), 20.93 (CH_3) 21.01 (CH_3), 21.18 (CH_3) 41.06 (CH), 41.36 (CH), 64.07 (CH_2), 64.26 (CH_2), 74.88 (CH), 75.37 (CH), 125.81 (CH), 125.95 (CH), 126.25 (CH), 126.40 (CH), 126.50 (CH), 126.71 (CH), 127.78 (CH), 127.83 (CH), 127.88 (CH), 128.24 (CH), 128.72 (CH), 132.69 (C), 132.63 (C), 132.81 (C), 133.57 (C), 133.75 (C), 139.61 (C), 139.82 (C), 170.50 (C), 170.78 (C), 170.82 (C), 170.92 (C); FAB-MS (*m/z*) 301 [$M+H^+$]; EI-HRMS Calcd. for $C_{18}H_{20}O_4$ [M^+]: 300.1362. Found: 300.1360; Anal. Calcd. for $C_{18}H_{20}O_4$: %C 71.98, %H 6.71. Found: %C 72.25, %H 6.50.



Acetic acid 1-acetoxymethyl-2-(4-fluoro-phenyl)-propyl ester (38): oil; FT-IR (neat cm^{-1}) 1049, 1604, 1743, 2973; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 and 1.30 (2 × d, J = 6.8 and 7.1 Hz respectively together integrating for 3H), 1.94 and 2.01 (2 × s, together integrating for 3H), 2.04 and 2.09 (2 × s, together integrating for 3H), 3.04 and 3.08 (2 × quin, J = 6.8 and 7.1 Hz respectively together integrating for 1H), 3.78 and 4.00 (2 × dd, J = 12.0, 6.5 and 12.0, 6.8 Hz respectively together integrating for 1H), 4.13 and 4.24 (2 × dd, J = 12.0, 2.9 and 12.0, 3.3 Hz respectively together integrating for 1H), 5.20-5.27 (m, 1H), 6.95-7.22 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.64 (CH_3), 17.95 (CH_3), 20.87 (2 × CH_3), 21.06 (2 × CH_3) 40.21 (CH), 40.38 (CH), 63.91 (CH_2), 63.96 (CH_2), 74.75 (CH), 75.26 (CH), 115.31 (d, CH, $J_{C\text{-}F}$ = 21 Hz), 115.74 (d, CH, $J_{C\text{-}F}$ = 22 Hz), 129.19 (d, CH, $J_{C\text{-}F}$ = 8.0 Hz), 129.49 (d, CH, $J_{C\text{-}F}$ = 8.0 Hz), 137.76 (d, C, $J_{C\text{-}F}$ = 3.0 Hz), 138.04 (d, C, $J_{C\text{-}F}$ = 3.0 Hz), 161.89 (d, C, $J_{C\text{-}F}$ = 243 Hz), 162.00 (d, C, $J_{C\text{-}F}$ = 244 Hz), 170.35 (CH_3) 170.65 (CH_3) 170.71 (CH_3); 170.82 (CH_3); ESI-MS (*m/z*) 286 [$M+NH_4^+$].

Photooxygenation of α-terpene 39: A solution of α-terpene **39** (5.0 g, 36.765 mmol), methylene blue (5 mg) in CH_3CN maintained at 0 °C was irradiated with tungsten-halogen lamp (500 W), with continuous influx of O_2 for 6h. The reaction mixture was concentrated and

purified by column chromatography over silica gel to furnish ascaridole **40** (3.70 g, 61%) as an oil.



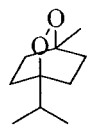
1-Isopropyl-4-methyl-2,3-dioxa-bicyclo[2,2,2]oct-7-ene (Ascaridole, 40): oil; FT-IR (neat cm^{-1}) 750, 1040, 1120, 1590, 2960; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, 6H, J = 6.9 Hz), 1.38 (s, 3H), 1.53 (brm, 2H), 1.93 (sept, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.34 (CH_3), 17.42 (CH_3), 21.58 (CH_3), 25.79 (CH_2), 29.72 (CH_2), 32.32 (CH), 74.54 (C), 79.98 (C), 133.25 (CH), 136.59 (CH); ESI-MS (*m/z*) 169 [$M+H^+$], 186 [$M+NH_4^+$].

Diimide reduction of ascaridole 39 with hydrazine hydrate ($N_2H_4.H_2O$) and 30% H_2O_2: To a stirred and ice cooled solution of ascaridole **40** (1.00 gm, 5.950 mmol) and hydrazine hydrate (5.95 mL, 20 equiv) in 1:1 mixture of EtOH-THF (25 mL) was added 30% H_2O_2 (20.24 mL, 30 equiv) drop wise over 20 min and the reaction mixture was allowed to stir at rt for 6 hours. The reaction mixture was evaporated on a rotavapor, diluted with water (20 mL) and extracted with ether (3 × 50 mL). The organic layer was washed successively with 10% HCl (10 mL), water (10 mL) and saturated $NaHCO_3$ solution (10 mL), concentrated and the crude product was purified by column chromatography over silica gel to furnish dihydroascaridole **41** (0.252 g, 25% yield) as a colorless oil.

Diimide reduction of ascaridole 40 with hydrazinium carbazate ($N_2H_3COON_2H_5$) and 30% H_2O_2: To a stirred and ice cooled solution of ascaridole **39** (1.00 gm, 5.950 mmol) and hydrazinium carbazate (5.91 mL, 10 equiv) in 1:1 mixture of EtOH-THF (25 mL) was added 30% H_2O_2 (20.24 mL, 30 equiv) drop wise over 20 min and the reaction mixture was allowed to stir at rt for 12 hours. The reaction mixture was evaporated on a rotavapor, diluted with water (20 mL) and extracted with ether (3 × 50 mL). The organic layer was washed successively with 10% HCl (10 mL), water (10 mL) and saturated $NaHCO_3$ solution (10 mL), concentrated and the crude product was purified by column chromatography over silica gel to furnish dihydroascaridole **41** (0.725 g, 72% yield) as a colorless oil.

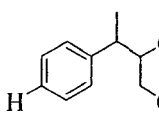
Catalytic hydrogenation of ascaridole 40: A solution of ascaridole **40** (0.500 g, 2.976 mmol) in EtOAc (20 mL) was hydrogenated in presence of Adam's catalyst (PtO_2) (0.003 g) using Parr shaker assembly at room temperature and pressure for 1.5 hours. The reaction mixture was

filtered over celite, concentrated and the crude product was purified by column chromatography over silica gel to furnish dihydroascaridole **41** (0.395 g 78% yield) as an oil.

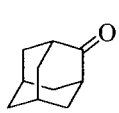


1-Isopropyl-4-methyl-2,3-dioxa-bicyclo[2,2,2]octane (Dihydroascaridole, 41): oil; FT-IR (neat cm^{-1}) 1039, 1116, 2965; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H, J = 7.1 Hz), 1.11 (s, 3H), 1.63-1.75 (brm, 5H), 1.81-1.97 (brm, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.98 (2 × CH_3), 24.14 (CH_3), 26.06 (2 × CH_2), 30.82 (2 × CH_2), 34.37 (CH), 74.40 (C), 79.06 (C); ESI-MS (*m/z*) 171 [M+H$^+$]; EI-HRMS Calcd. for $C_{10}H_{18}O_2$ [M$^+$]: 170.1307. Found: 170.1284.

Catalytic hydrogenation of trioxane 5: A solution of 6-arylvinyl-1,2,4-trioxane **5** (0.200 g, 0.64 mmol) in EtOAc (15 mL) was hydrogenated in presence of Adam's catalyst (PtO_2) (0.003 g) using Parr shaker assembly at room temperature and pressure for 1.5 hours. The reaction mixture was filtered over celite, concentrated and the crude product was purified by column chromatography over silica gel to furnish saturated diol **42** (0.060 g, 64% yield) as a colorless oil together with 2-adamantanone **43** (0.080 g, 89% yield) as white solid.



3-Phenyl-butane-1,2-diol (42): oil; FT-IR (neat cm^{-1}) 1057, 1593, 2923, 3403; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 and 1.35 (2 × d, J = 7.1 and 7.0 Hz respectively, together integrating for 3H), 2.03-2.13 (brm, 2H, 2OH) 2.81 and 2.88 (2 × quin, J = 7.2 Hz together integrating for 1H), 3.35 -3.58 (brm, together integrating for 1H), 3.75-3.79 (brm, together integrating for 1H), 7.17-7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.08 (CH_3), 16.54 (CH_3), 41.54 (CH), 41.68 (CH), 63.27 (CH_2), 63.20 (CH_2), 75.03 (CH), 76.38 (CH), 125.38 (CH), 125.63 (CH), 126.27 (CH), 126.70 (CH), 127.34 (CH), 127.45 (CH), 141.80 (C), 142.36 (C); ESI-MS (*m/z*) 167 [M+H$^+$]; EI-HRMS Calcd. for $C_{10}H_{14}O_2$ [M$^+$]: 166.0994. Found: 166.0990.



2-Adamantanone (43): white solid; mp 256-259 °C; FT-IR, (KBr cm^{-1}) 1717, 2920; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95-2.12 (m, 12H), 2.53 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.23 (CH_2), 36.03 (CH), 38.98(CH), 46.73 (CH_2), 217.67 (C); FAB-MS (*m/z*) 151 [M+H$^+$].

***In vivo* antimalarial efficacy test**

Random bred Swiss mice of either sex (25 ± 1 g) were inoculated intraperitoneally with 1×10^6 *Plasmodium yoelii nigeriensis* (MDR) parasites on day zero. The treatments with test compounds were administered to a group of 5 mice each at different dose levels ranging between 6-96 mg/kg × 4days. The compounds were administered as solutions in oil via oral route for 4 consecutive days i.e. from day 0 to day 3 in two divided dose daily. The drug dilutions were prepared in groundnut oil to contain the required amount of drug (1.2 mg for a dose of 96 mg/kg, 0.6 mg for a dose of 48 mg/kg, 0.3 mg for a dose of 24 mg/kg, 0.15 mg for a dose of 12 mg/kg and 0.075 mg for a dose of 6 mg/kg) in 0.1 mL of oil and administered either orally or intramuscularly for each dose. Mice treated with β-arteether was used as positive control.

Blood smears from experimental mice were observed on day 4, day 7, and day 10 and thereafter at regular interval till day 28 or death of the animal. The parasitaemia level on day 4 was compared with the vehicle control group and the percent suppression of parasitaemia in treated groups was calculated. The compounds which showed more than 100% clearance of parasitaemia were identified for further screening.

2.7 References and Notes

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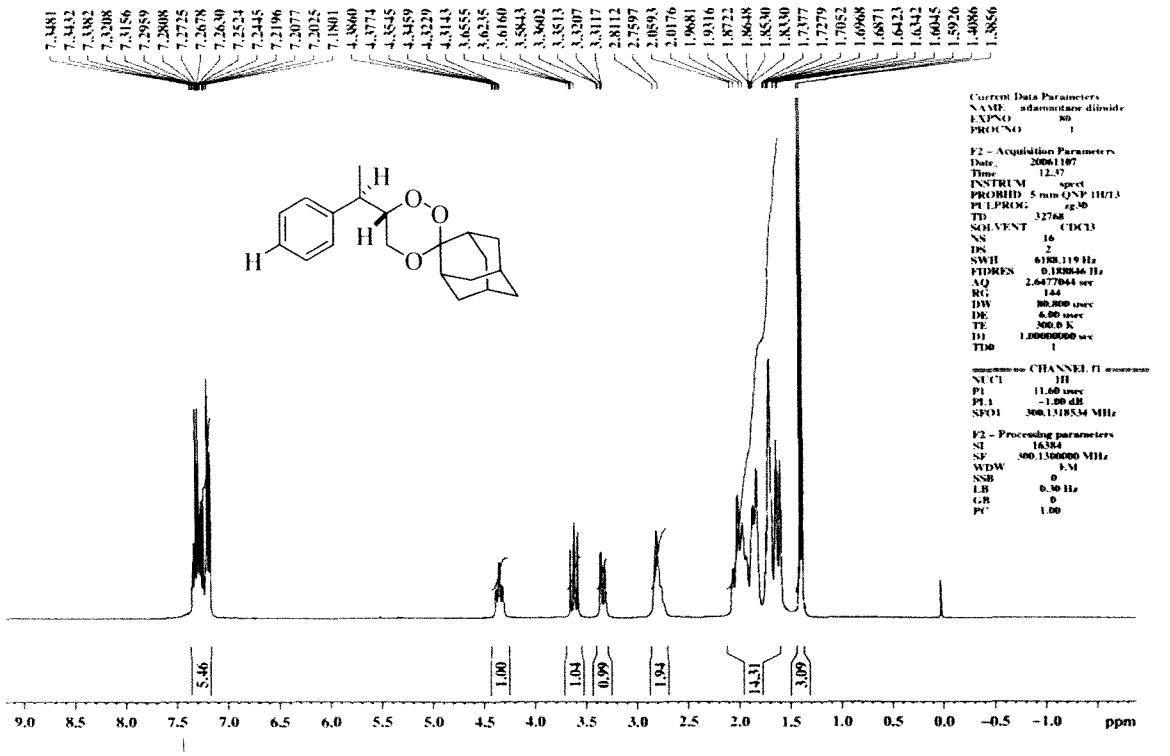
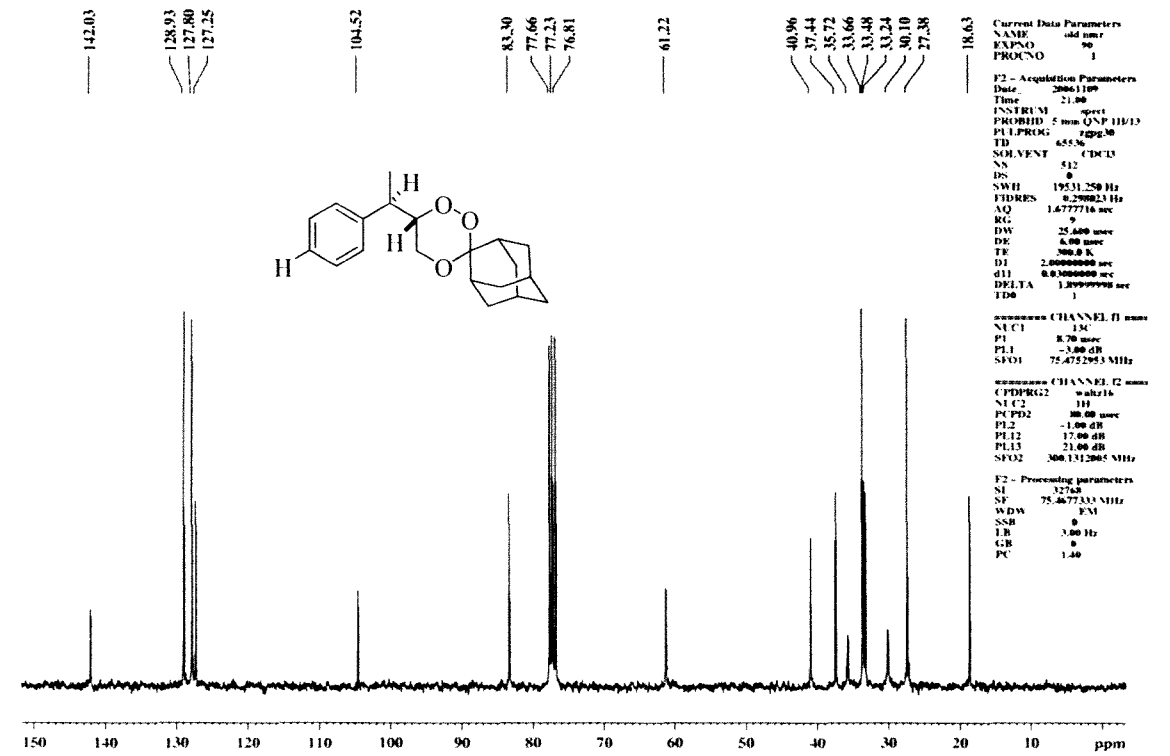


^{1}H NMR Spectra of **5a** (300 MHz, $CDCl_3$)



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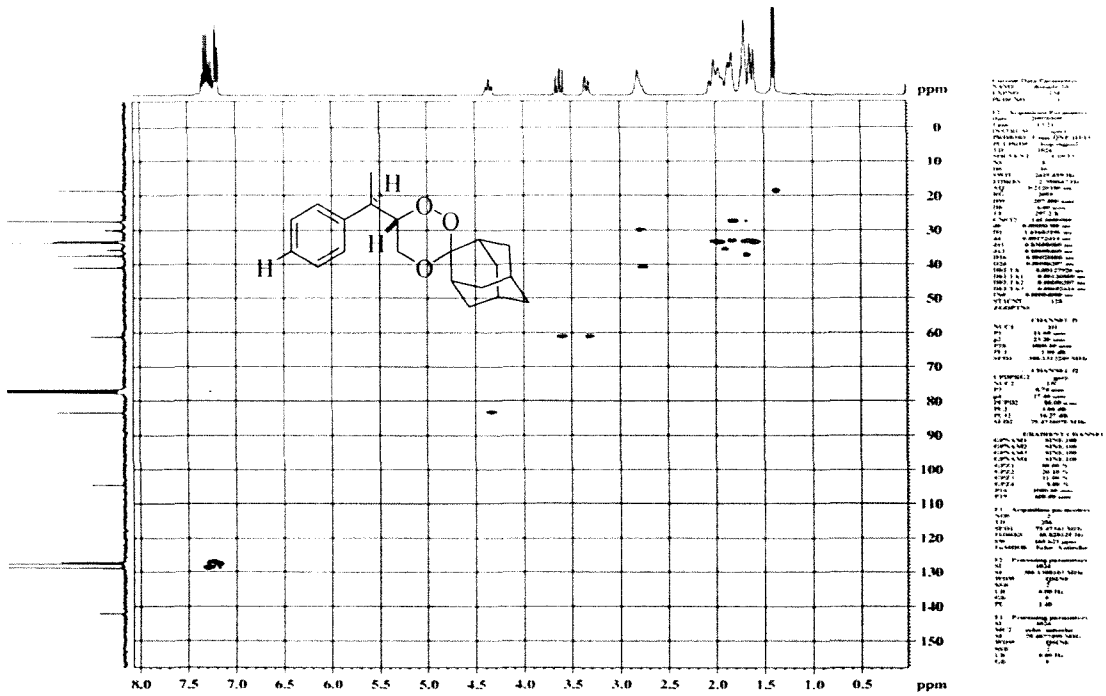

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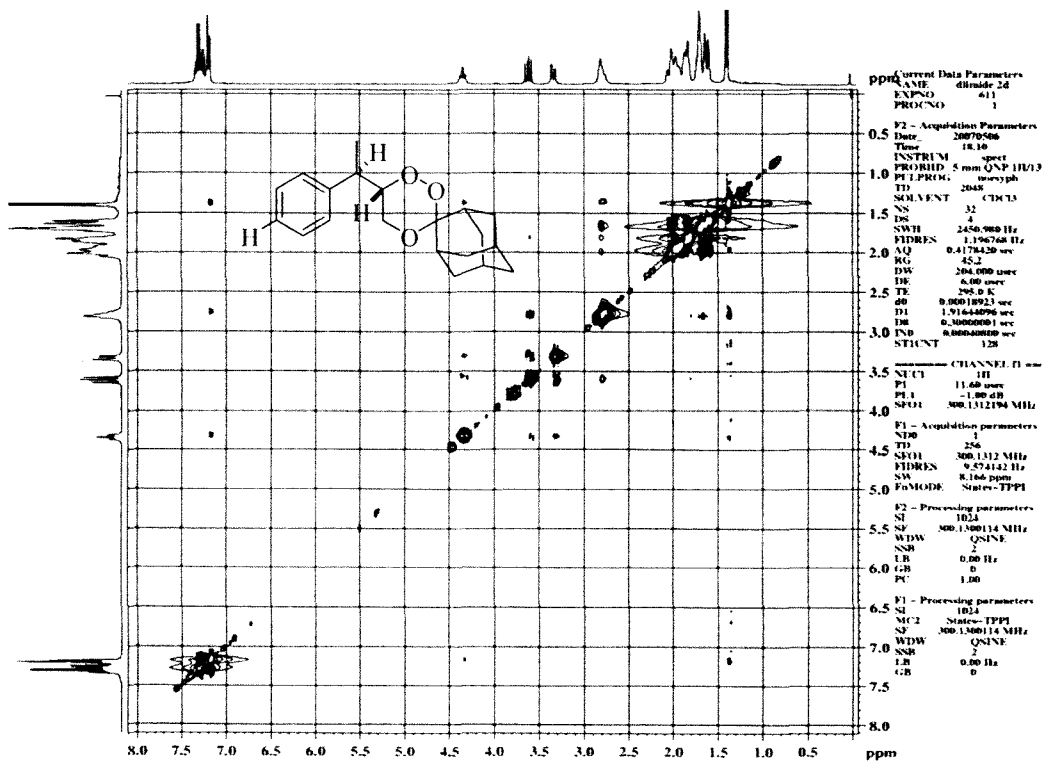

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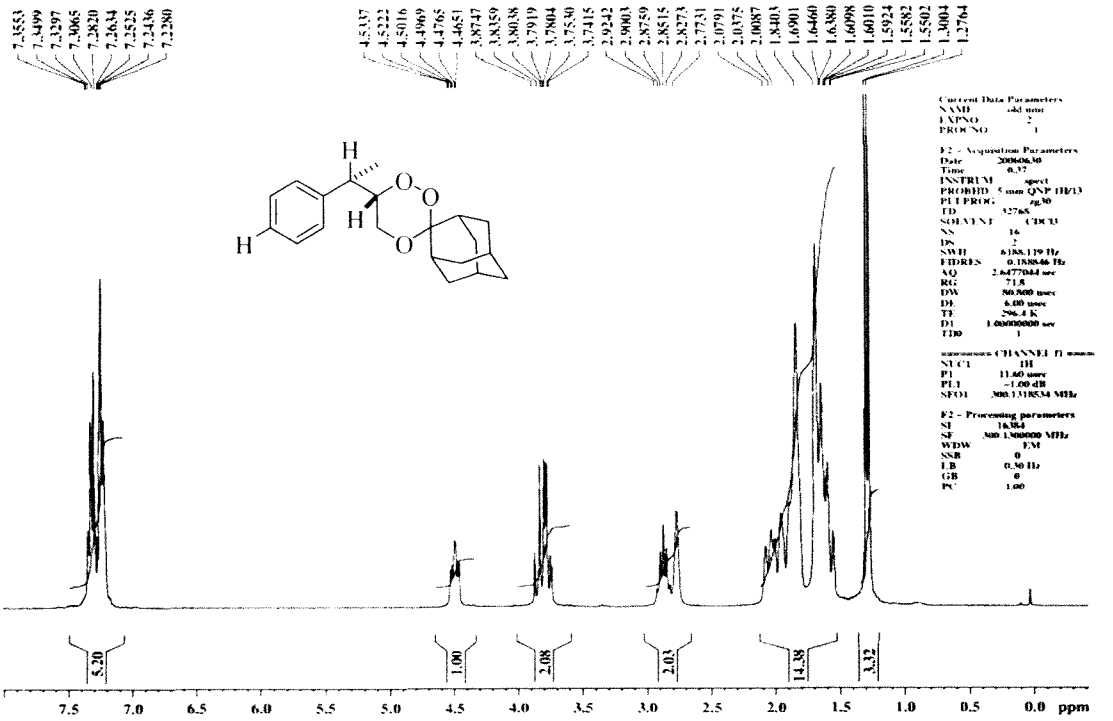

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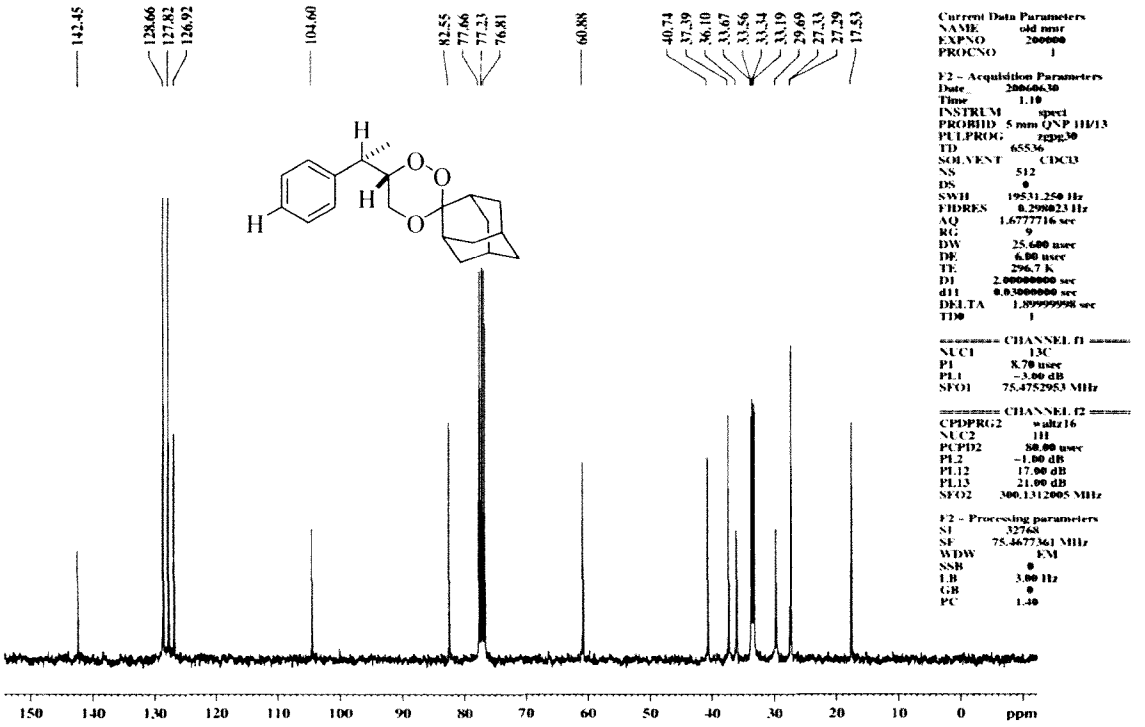

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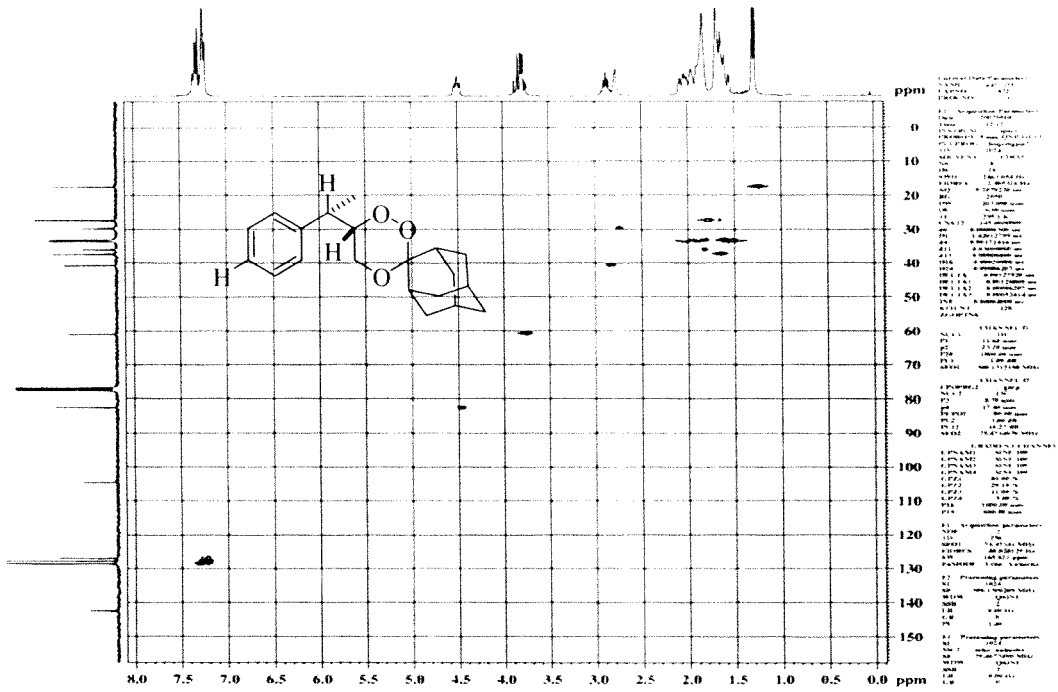

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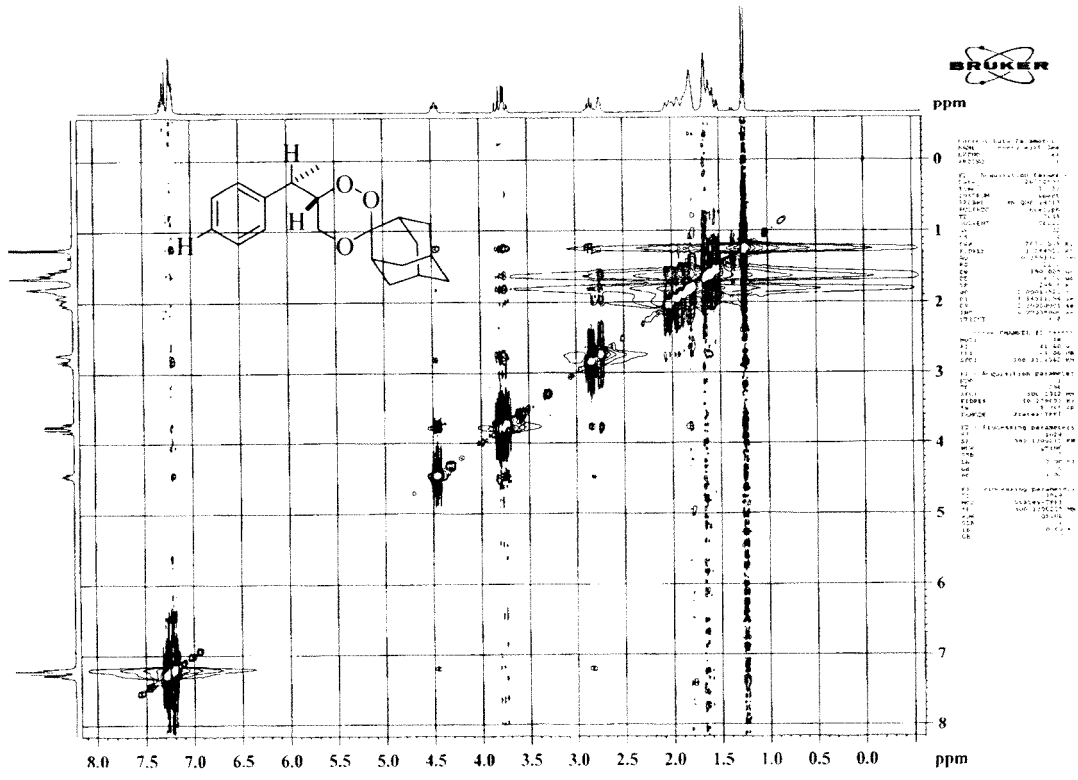

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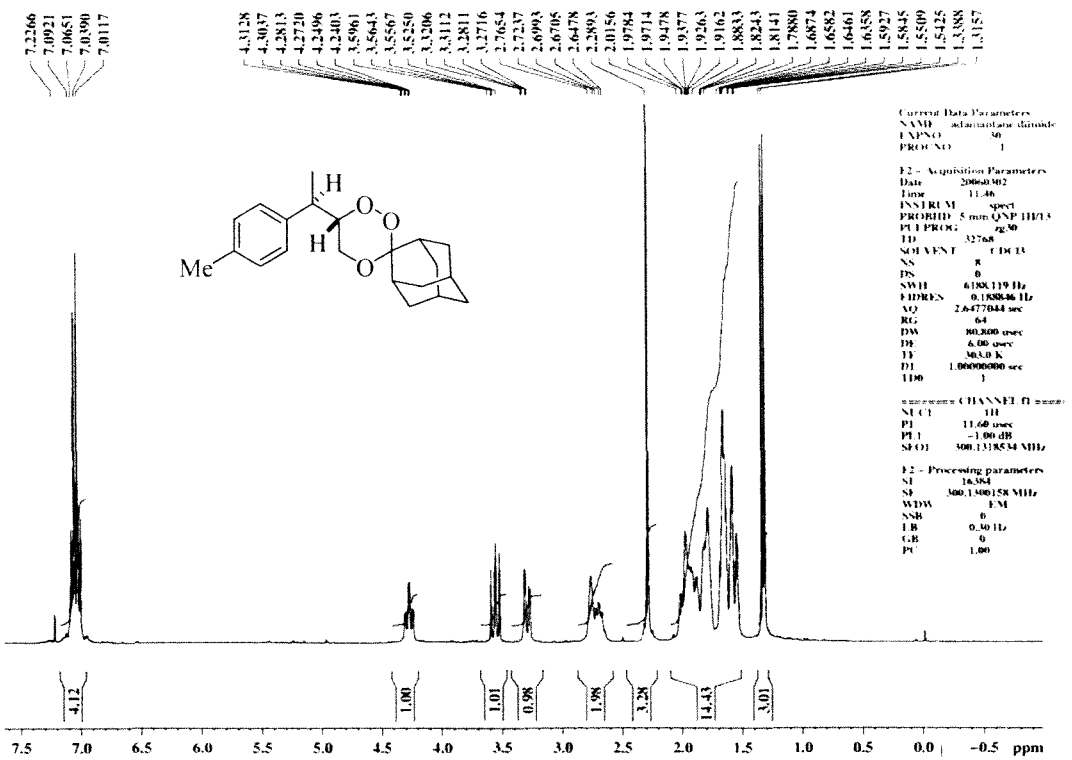

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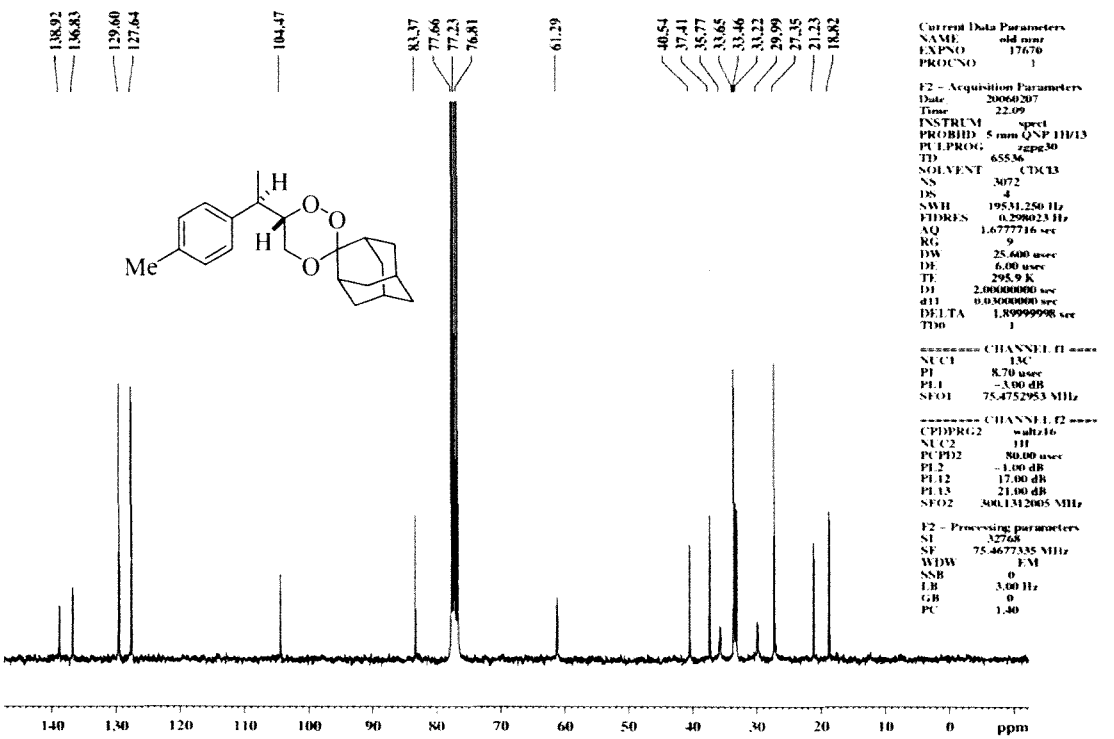

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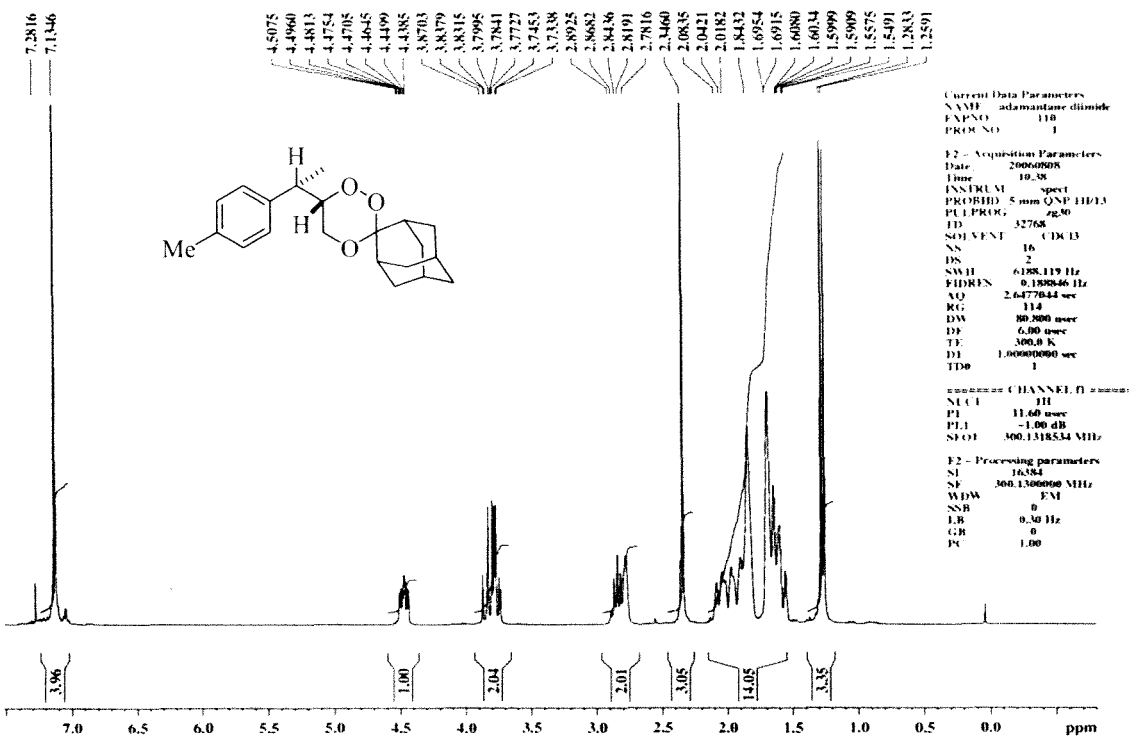

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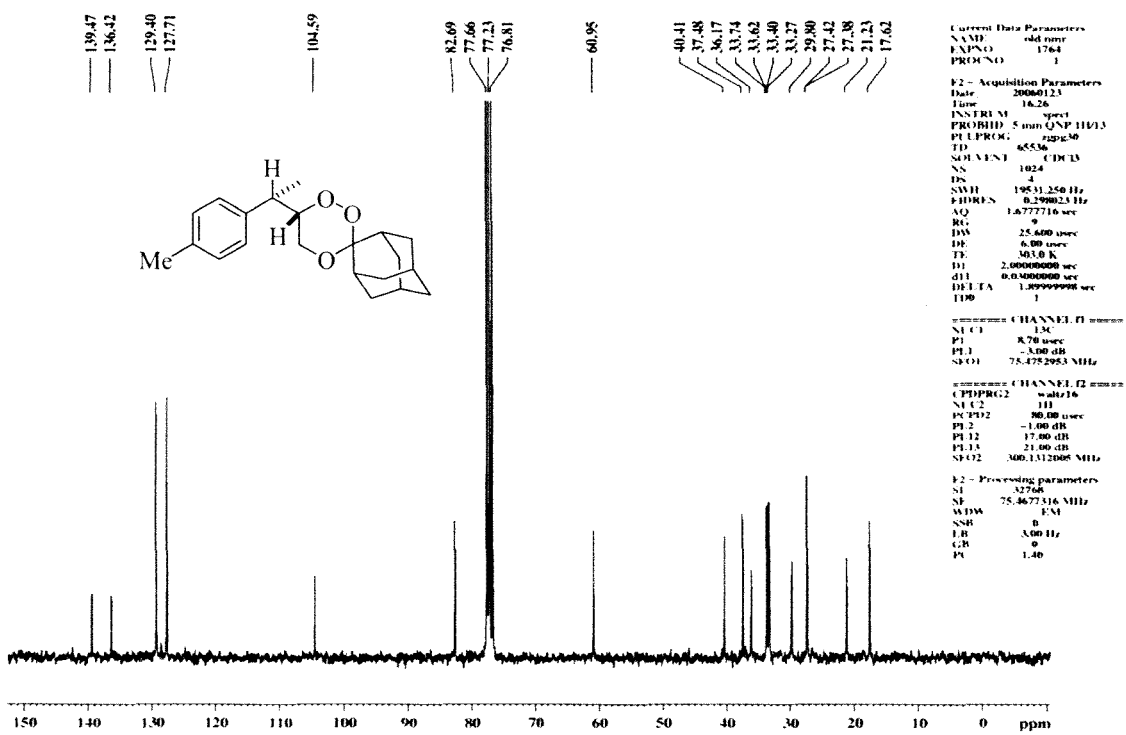

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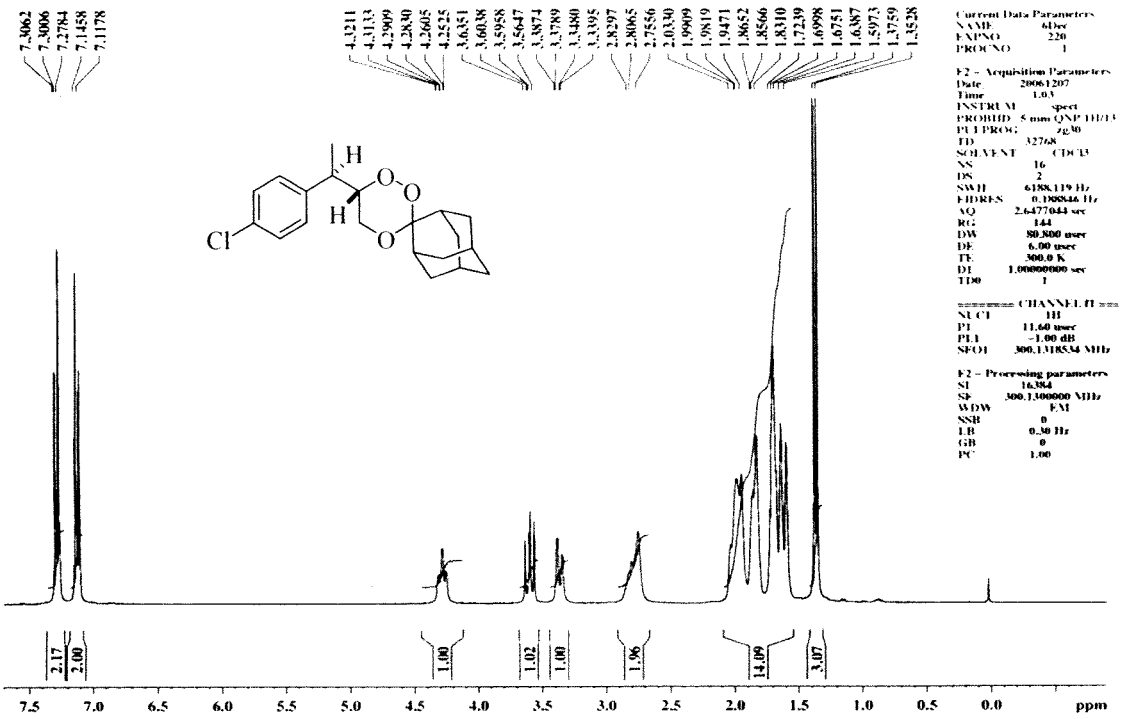

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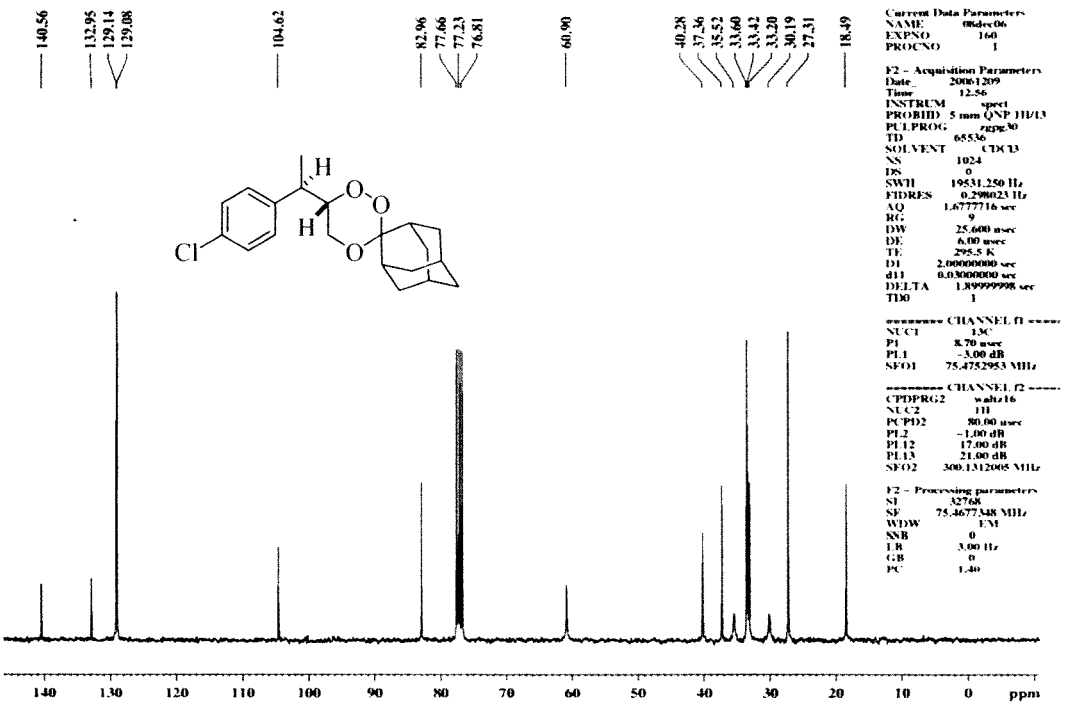

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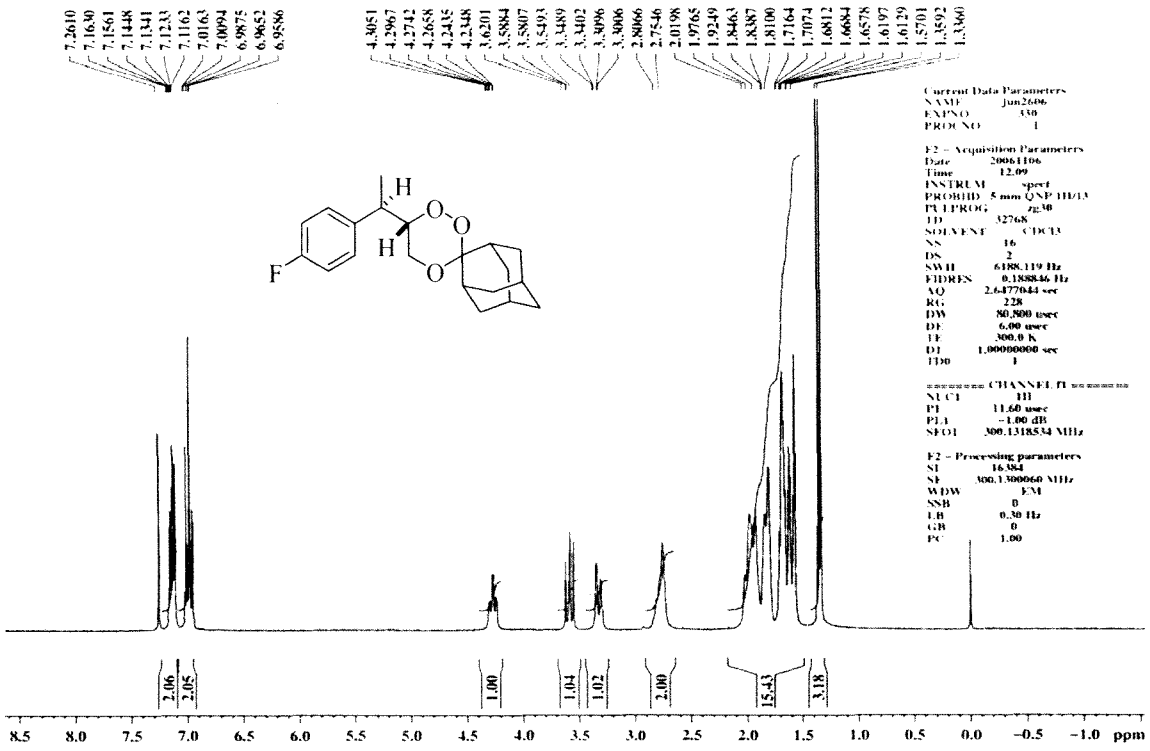

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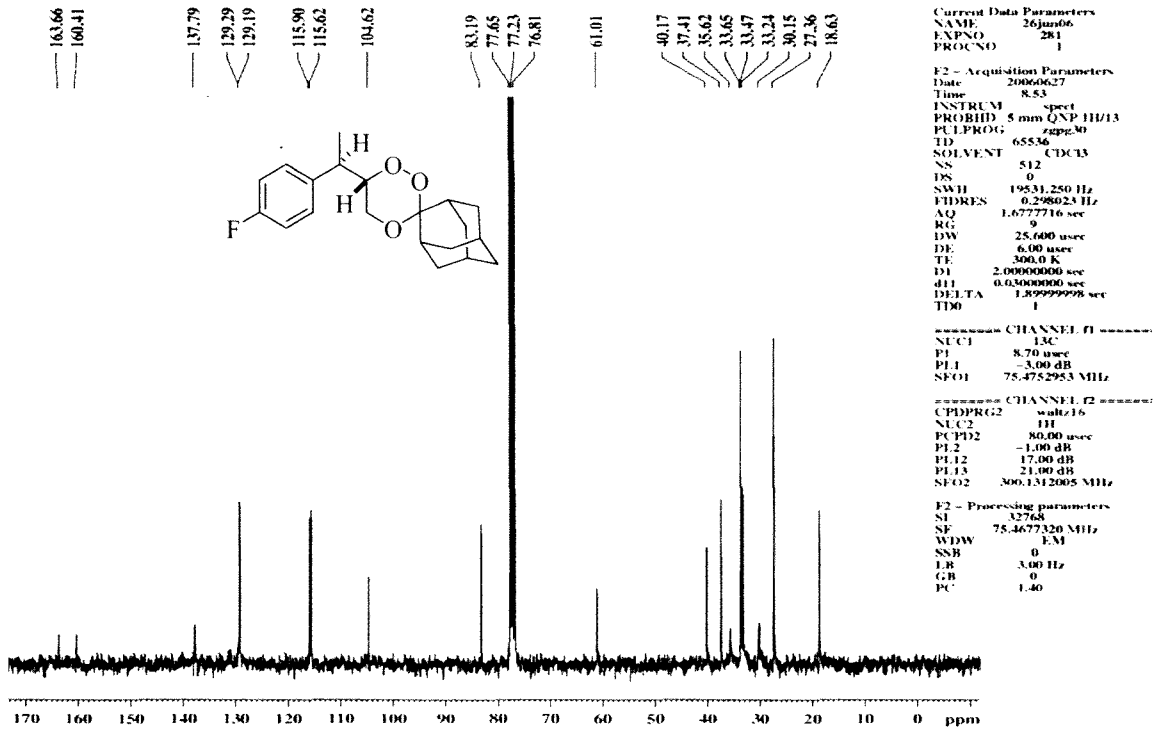

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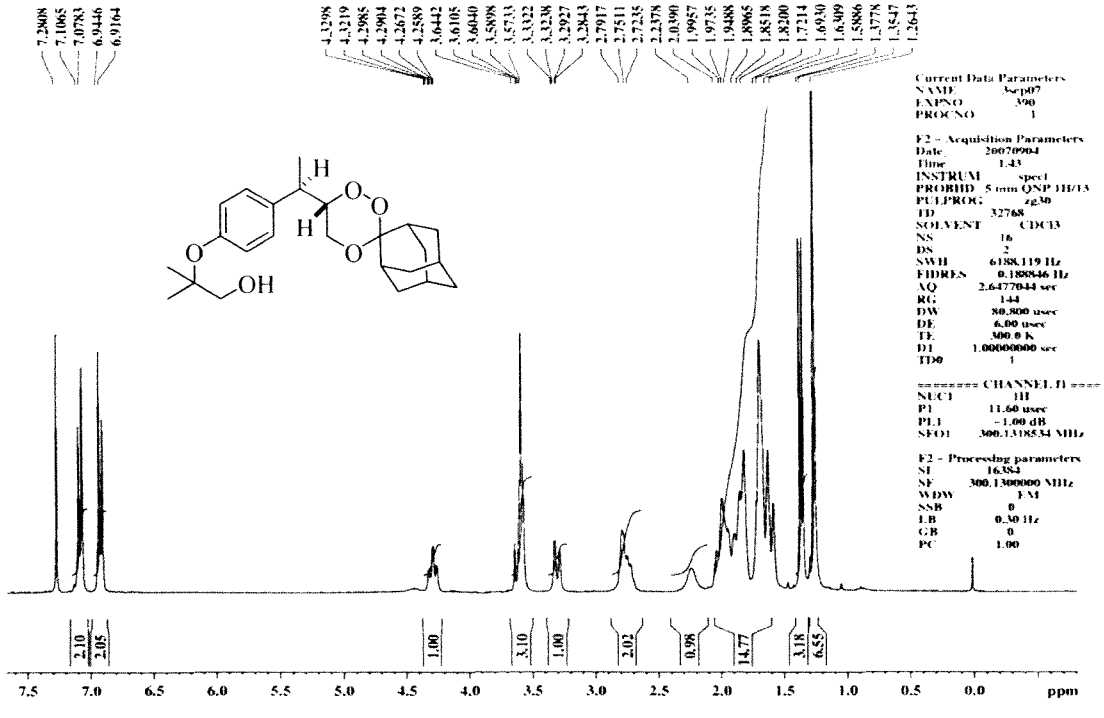

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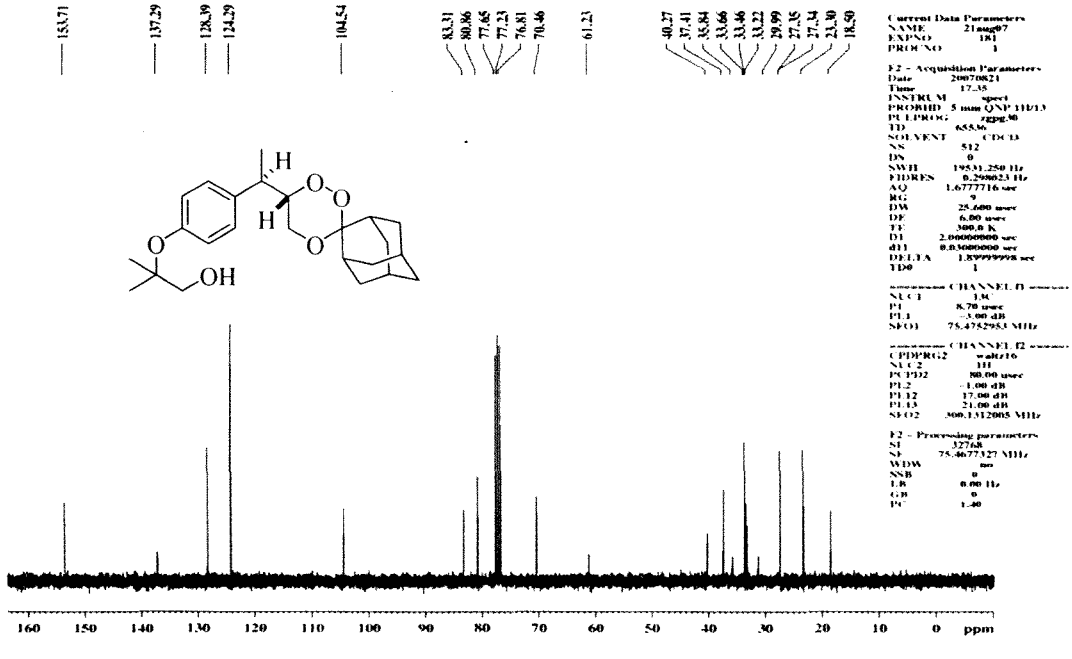

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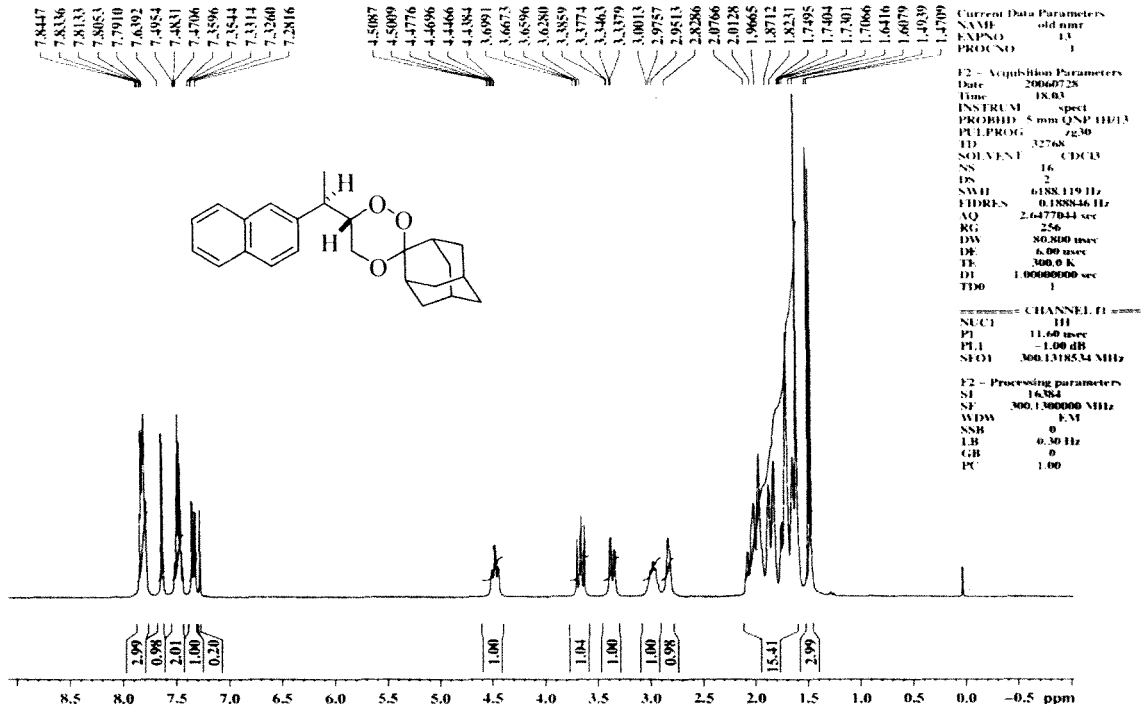

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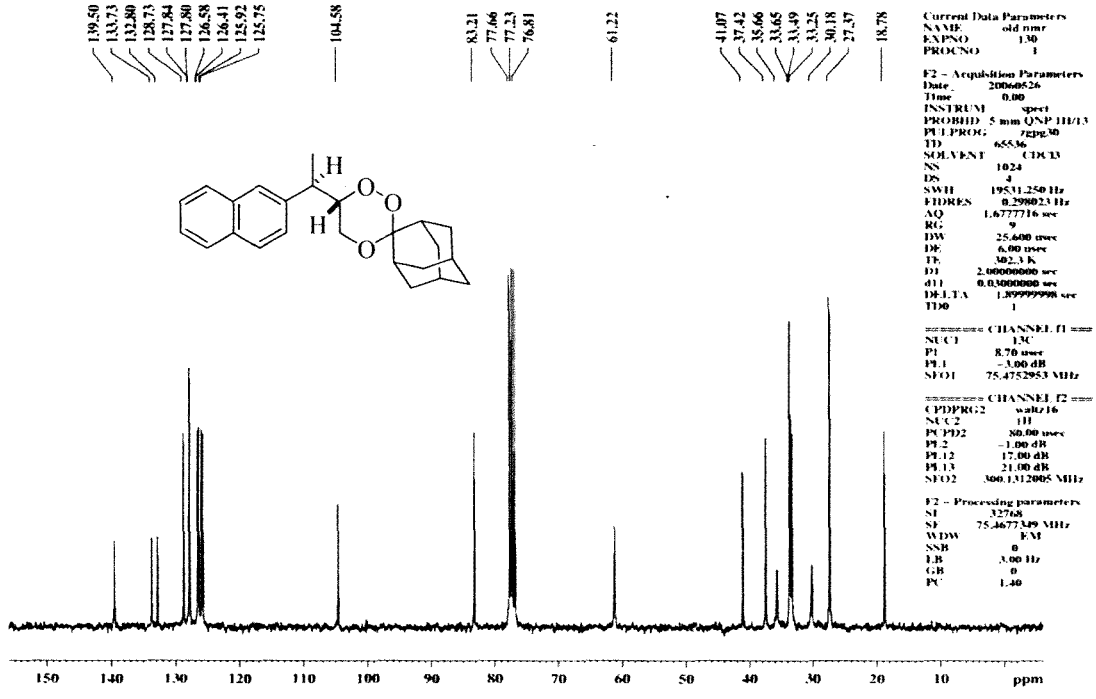

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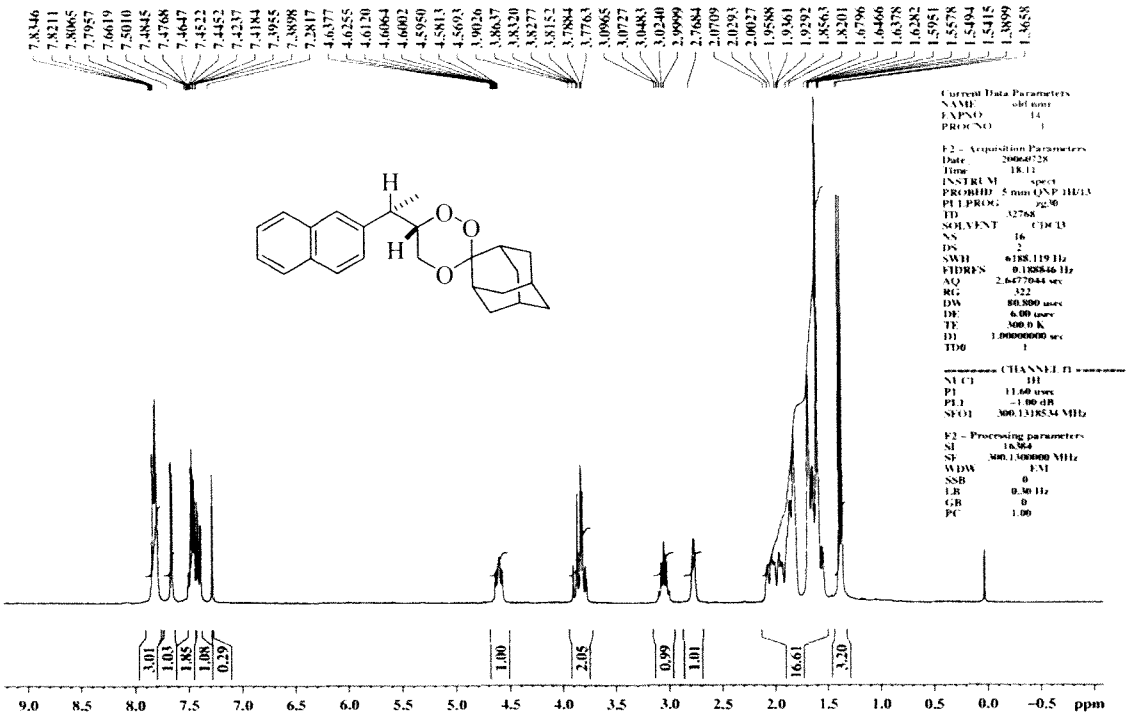

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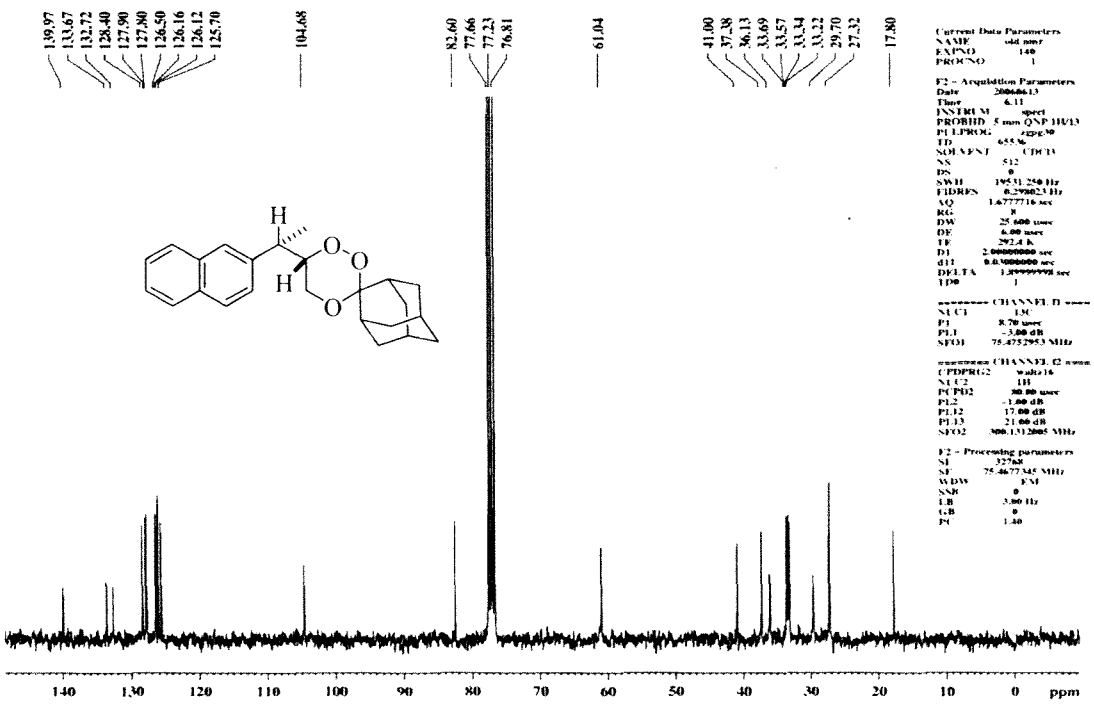

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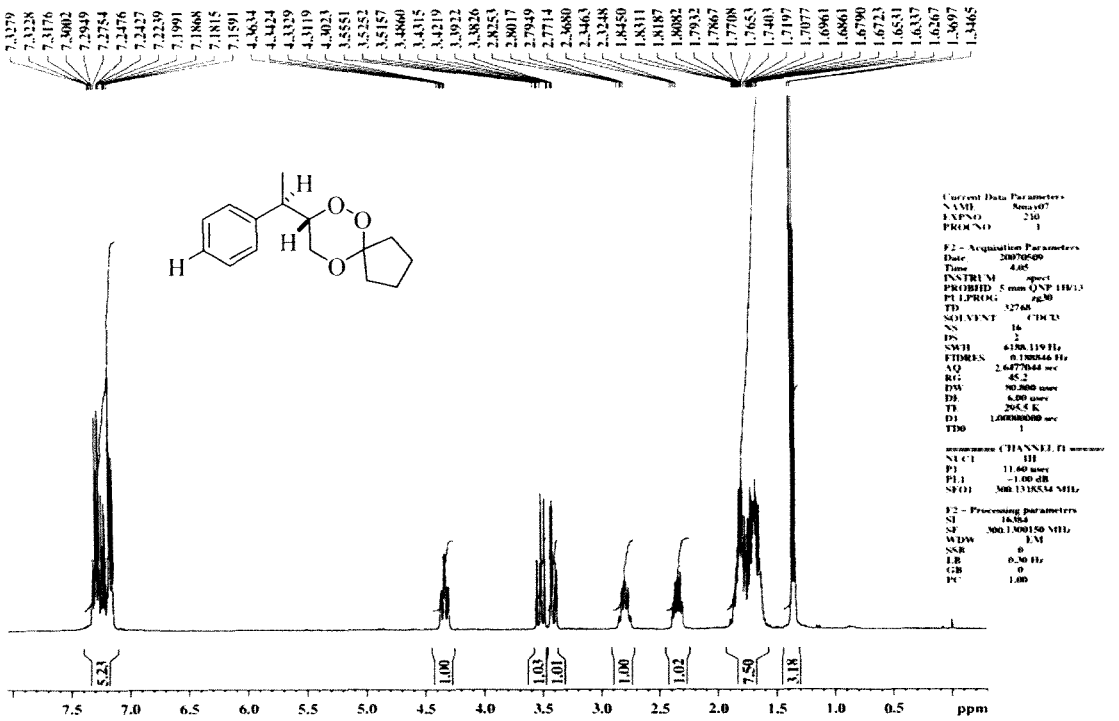

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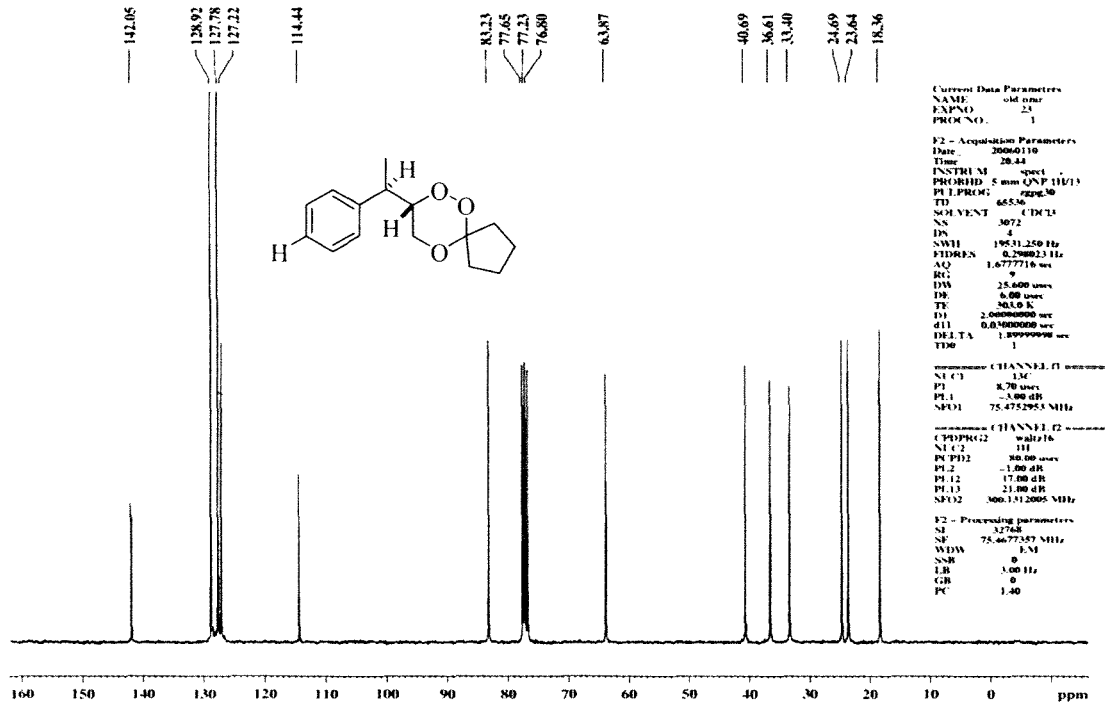

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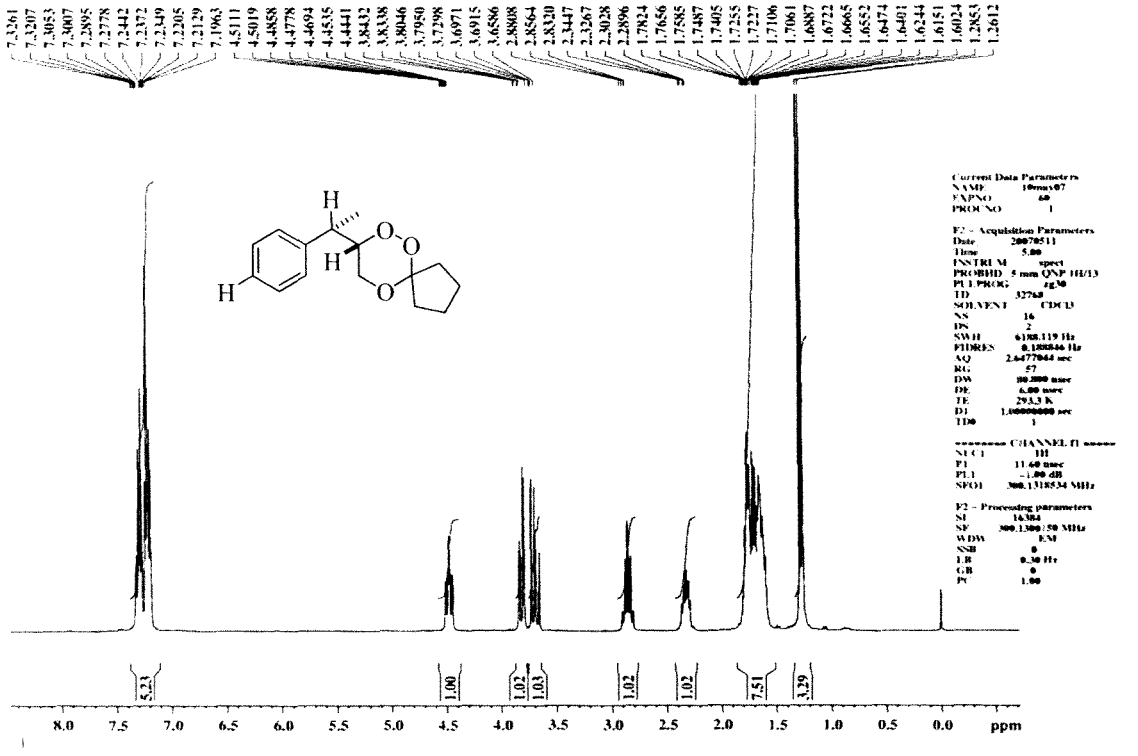

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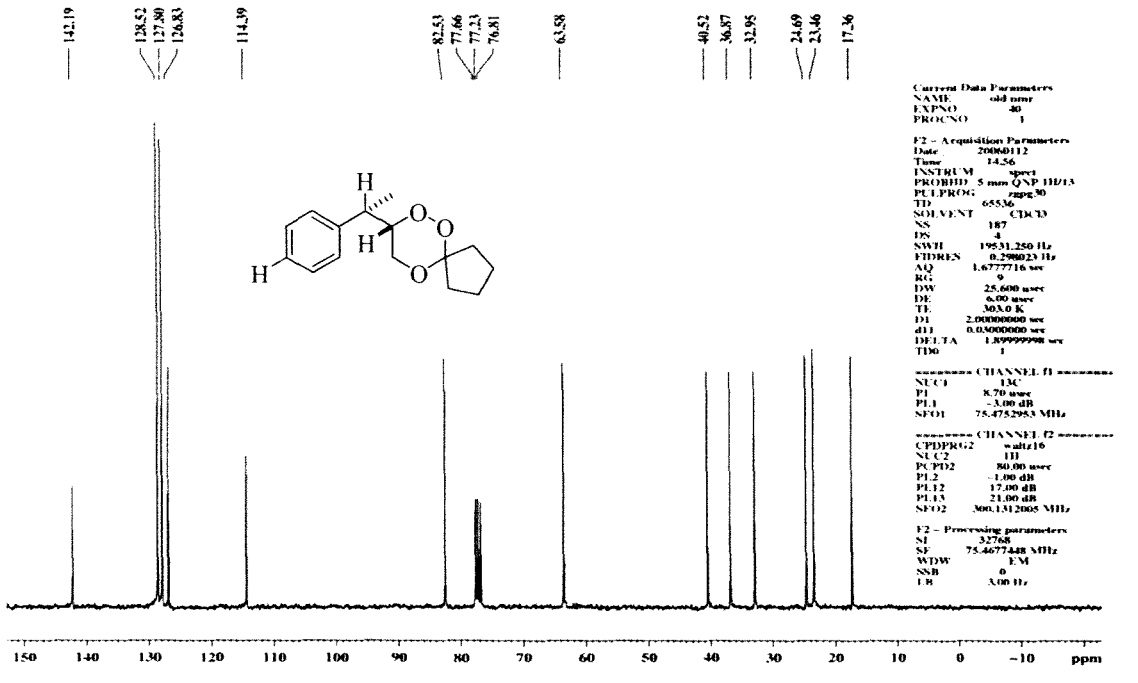
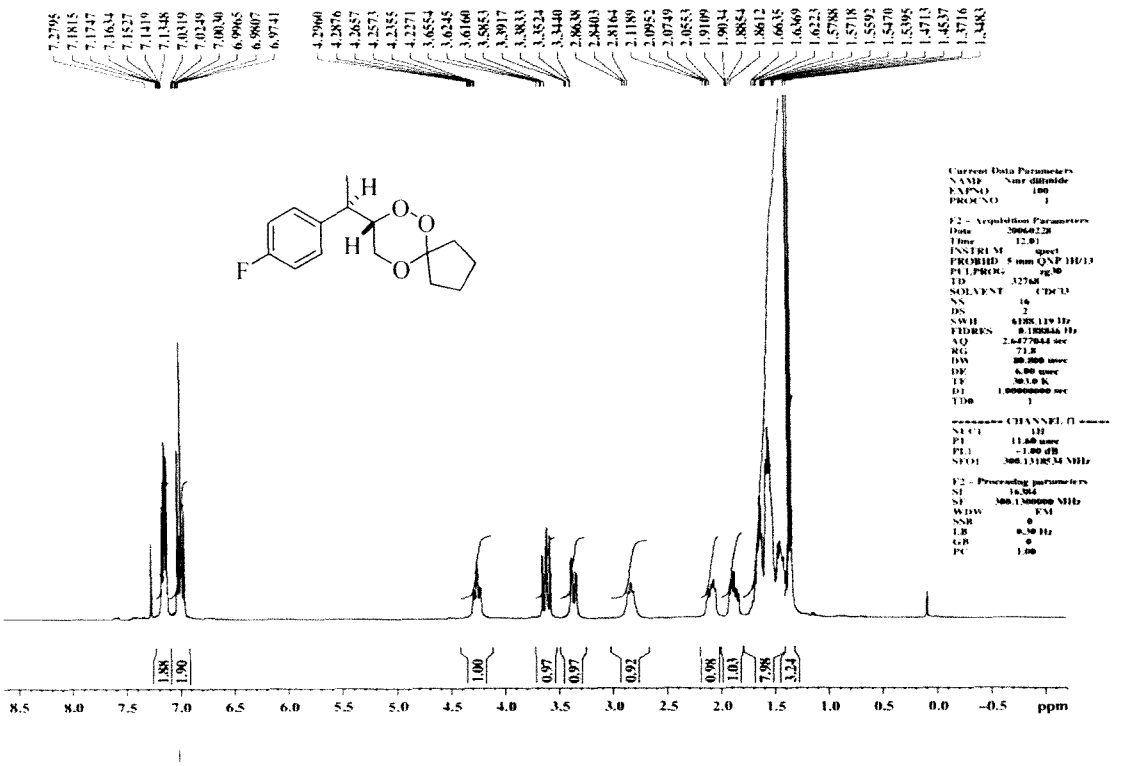
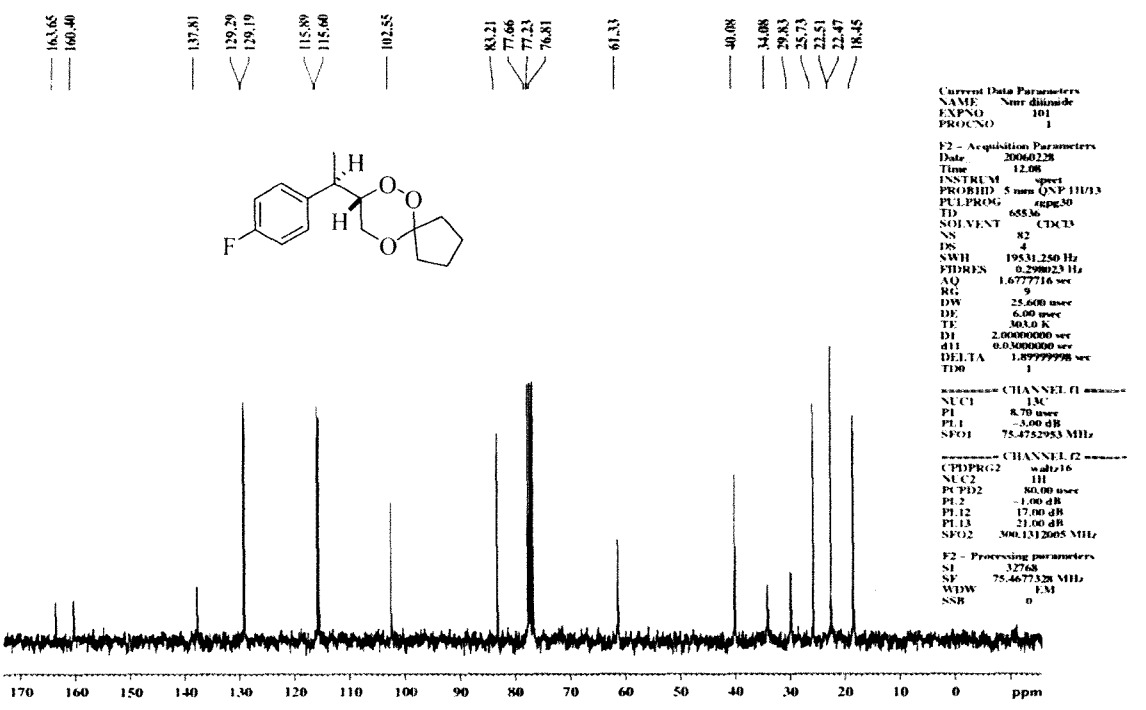


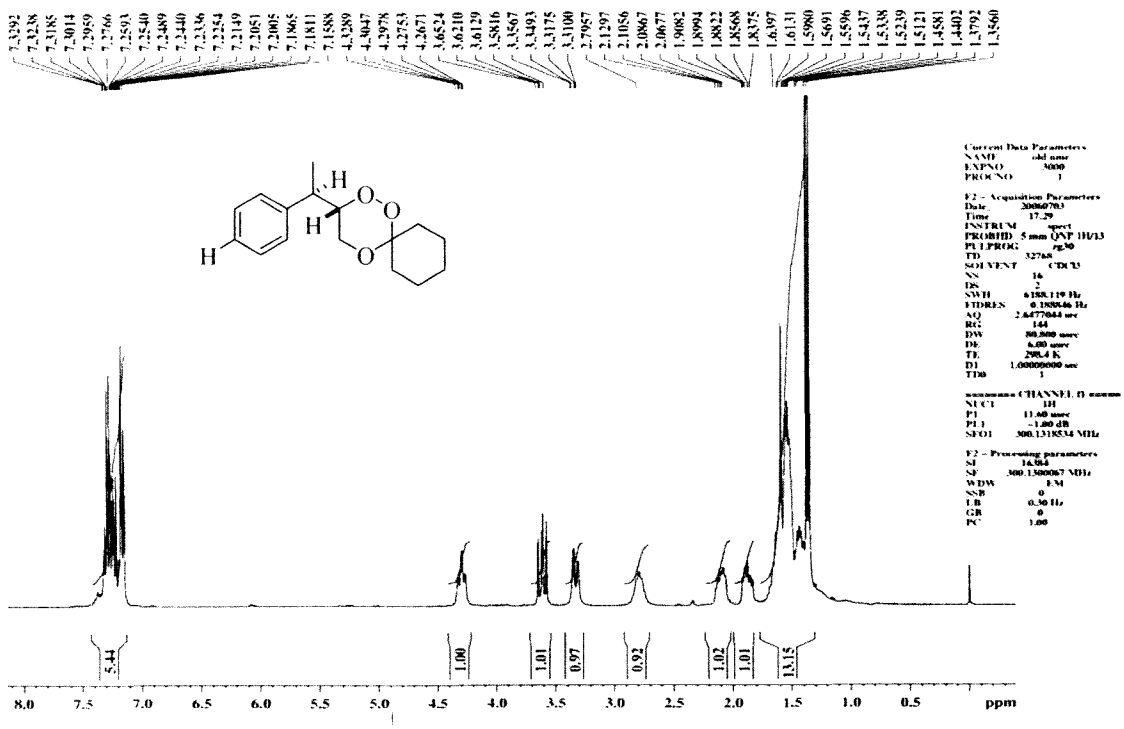
^{13}C NMR Spectra of **17b** (75 MHz, $CDCl_3$)



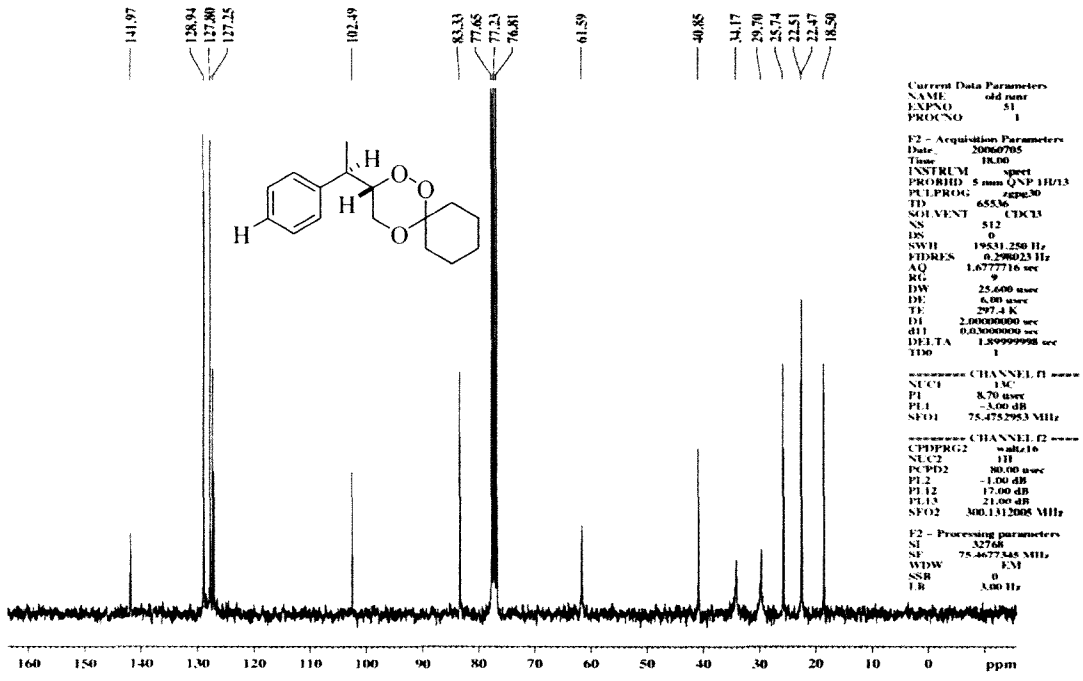
^{1}H NMR Spectra of **20a** (300 MHz, $CDCl_3$)



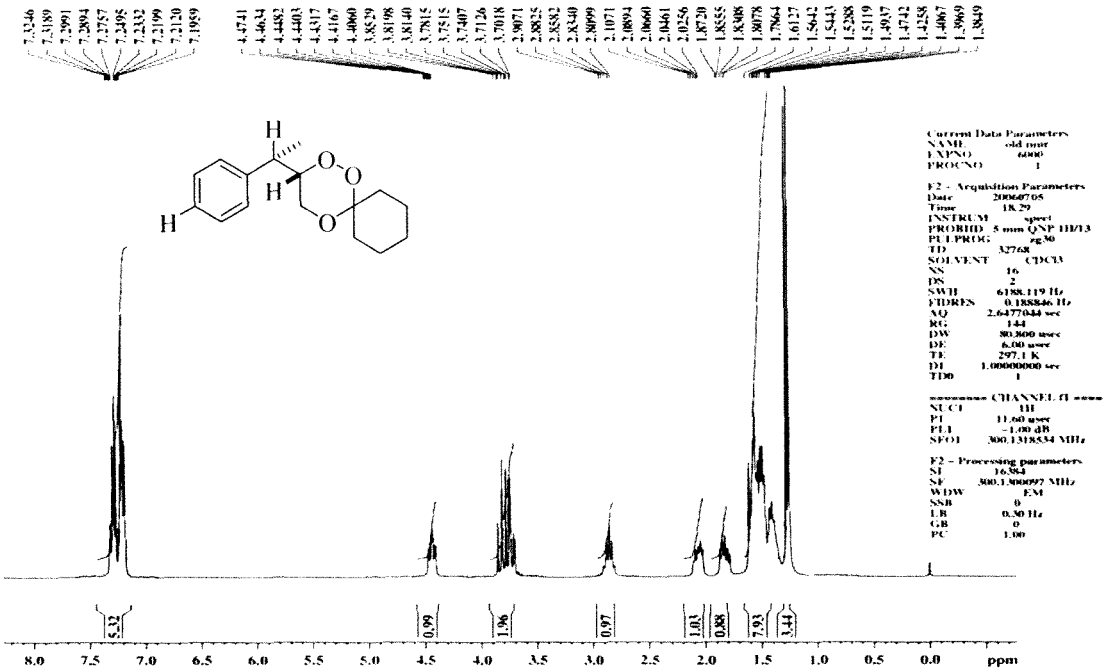
^{13}C NMR Spectra of **20a** (75 MHz, $CDCl_3$)



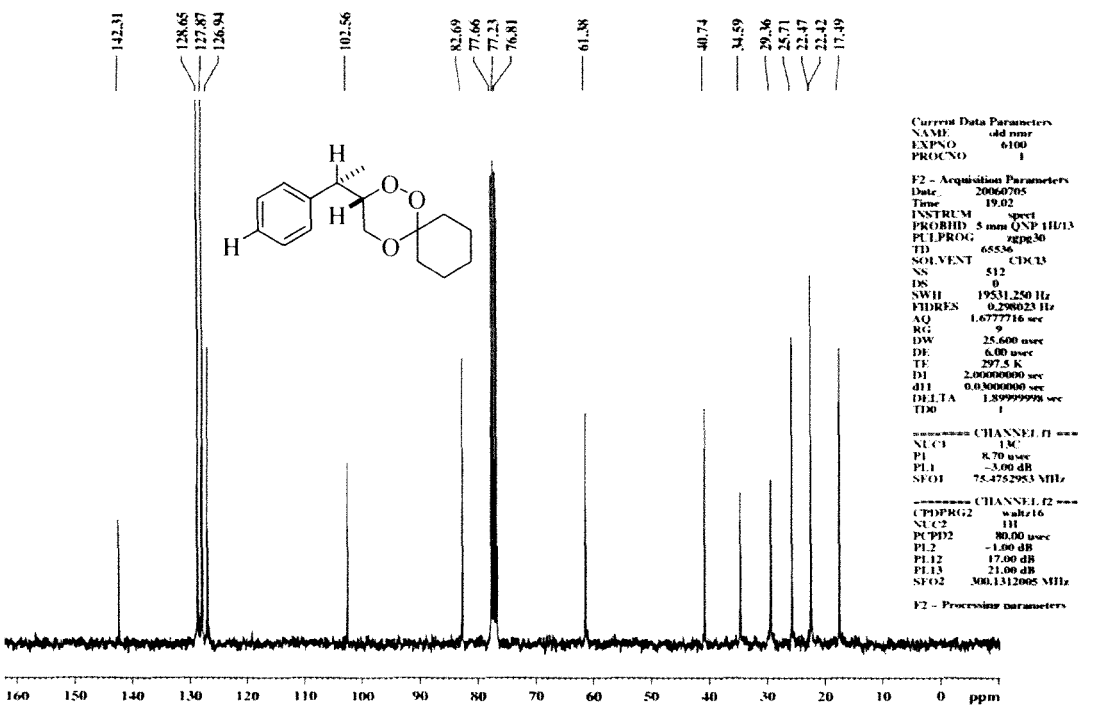
^{1}H NMR Spectra of **24a** (300 MHz, $CDCl_3$)



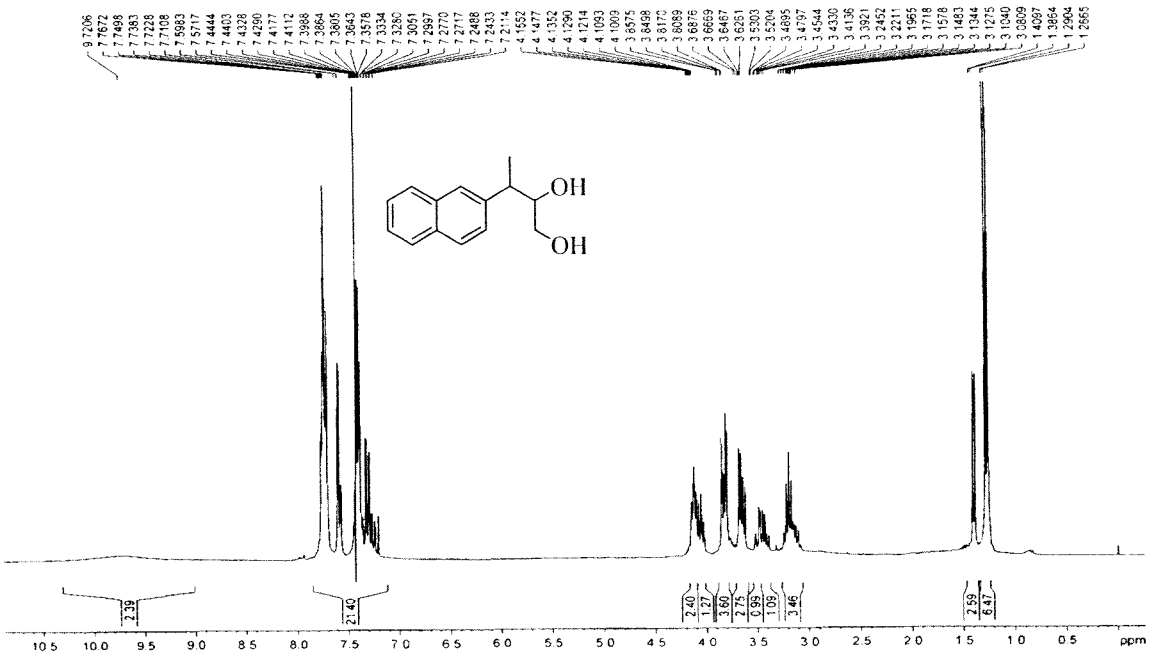
^{13}C NMR Spectra of **24a** (75 MHz, $CDCl_3$)



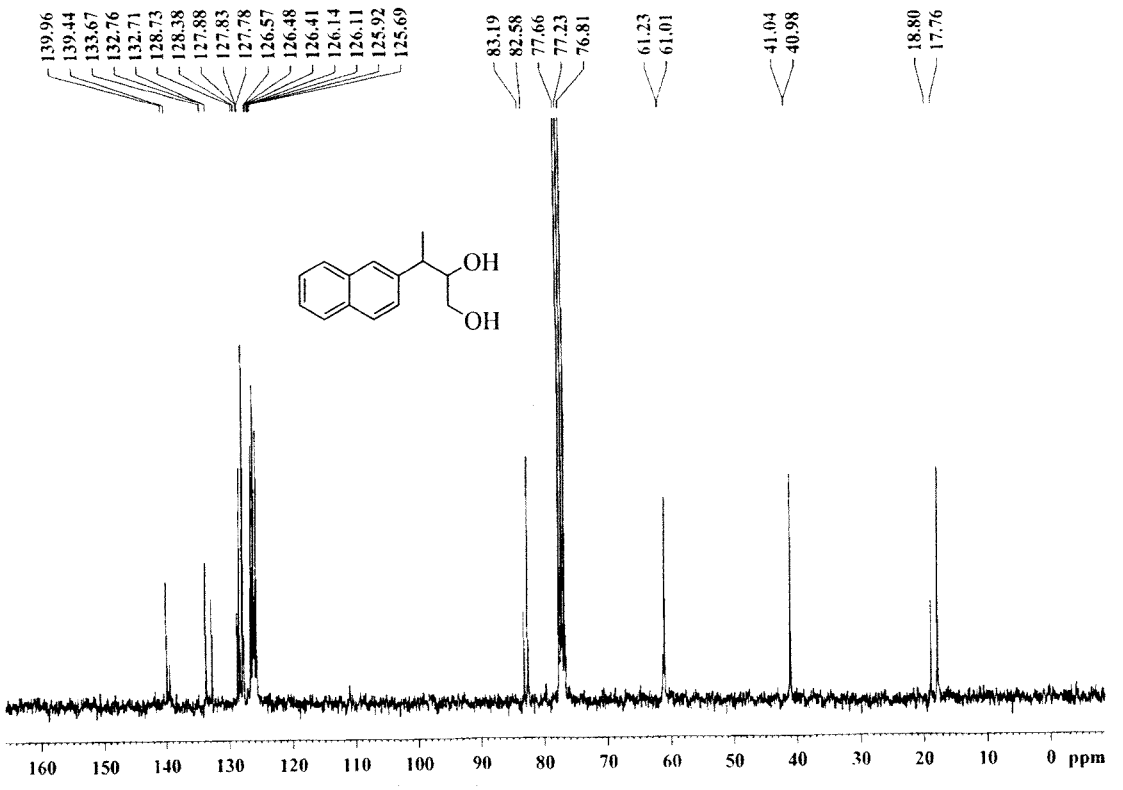
^{1}H NMR Spectra of **24b** (300 MHz, $CDCl_3$)



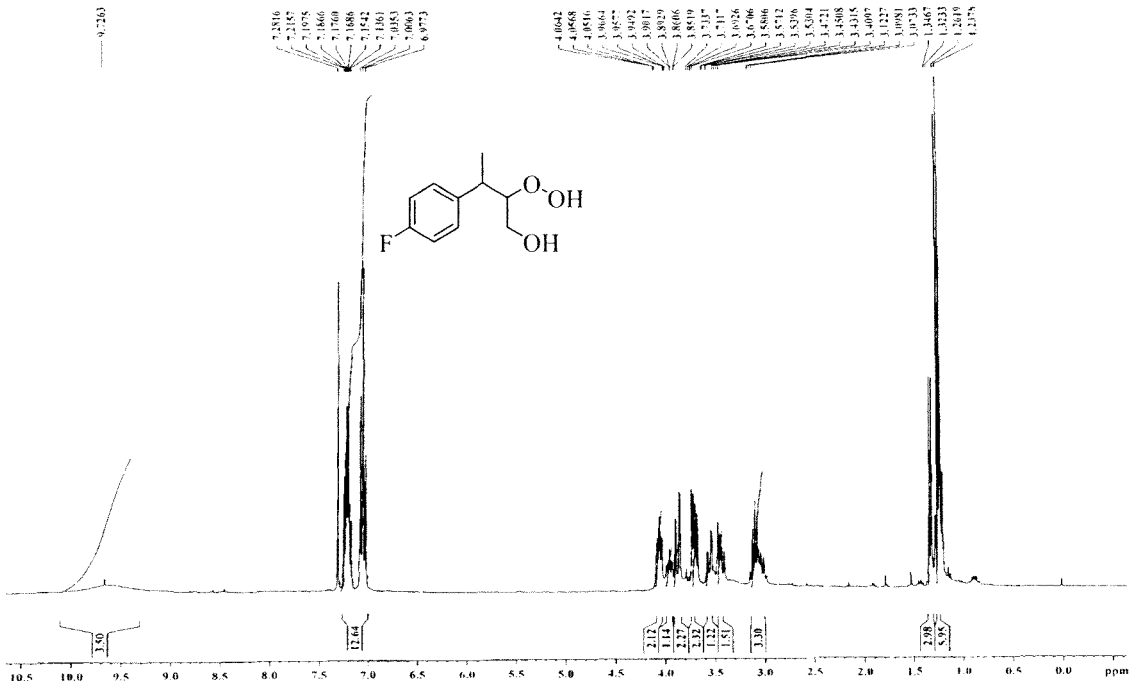
^{13}C NMR Spectra of **24b** (75 MHz, $CDCl_3$)



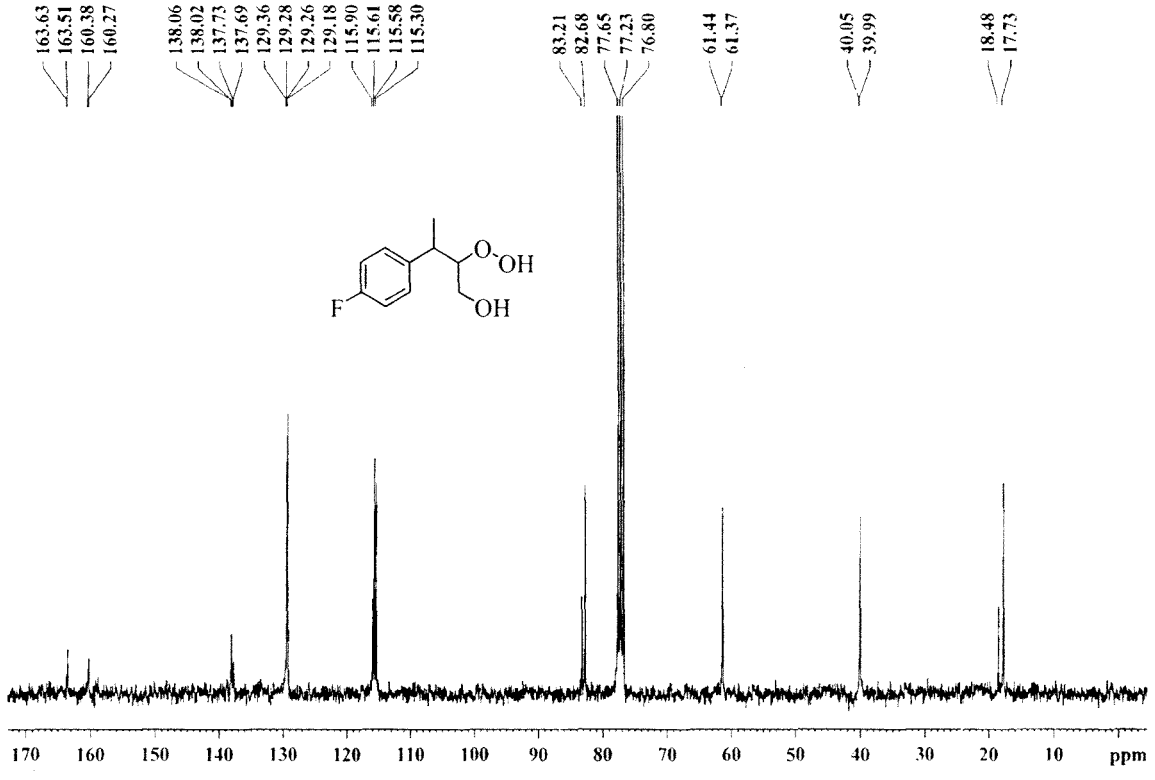
^{1}H NMR Spectra of **32** (300 MHz, $CDCl_3$)



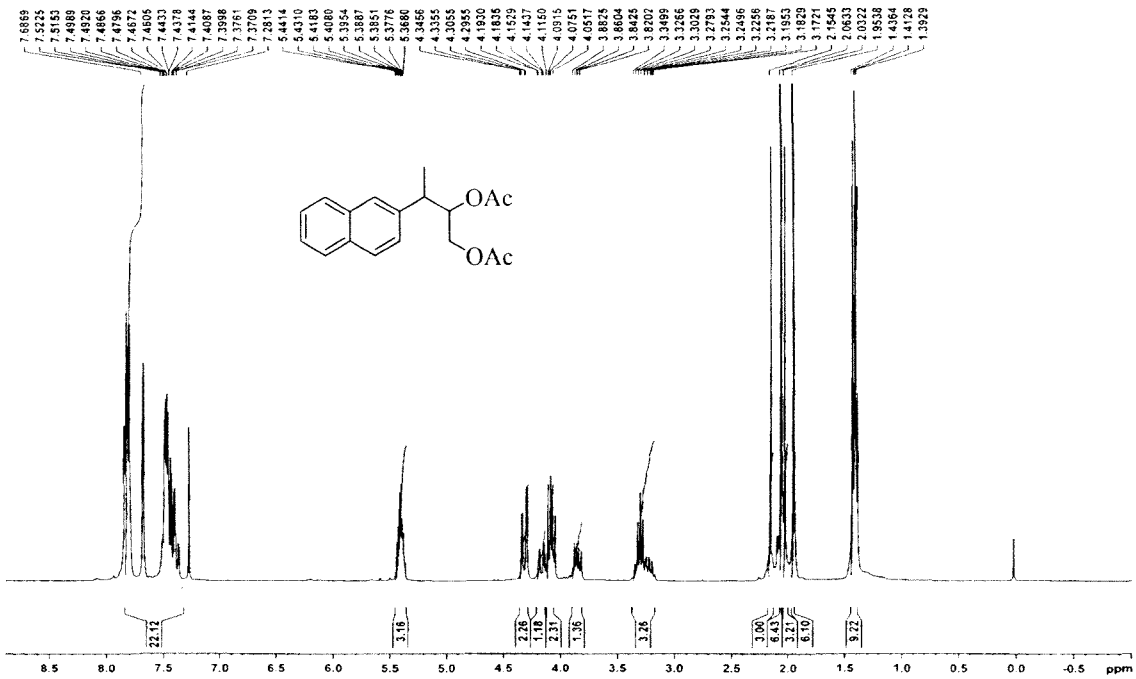
^{13}C NMR Spectra of **32** (75 MHz, $CDCl_3$)



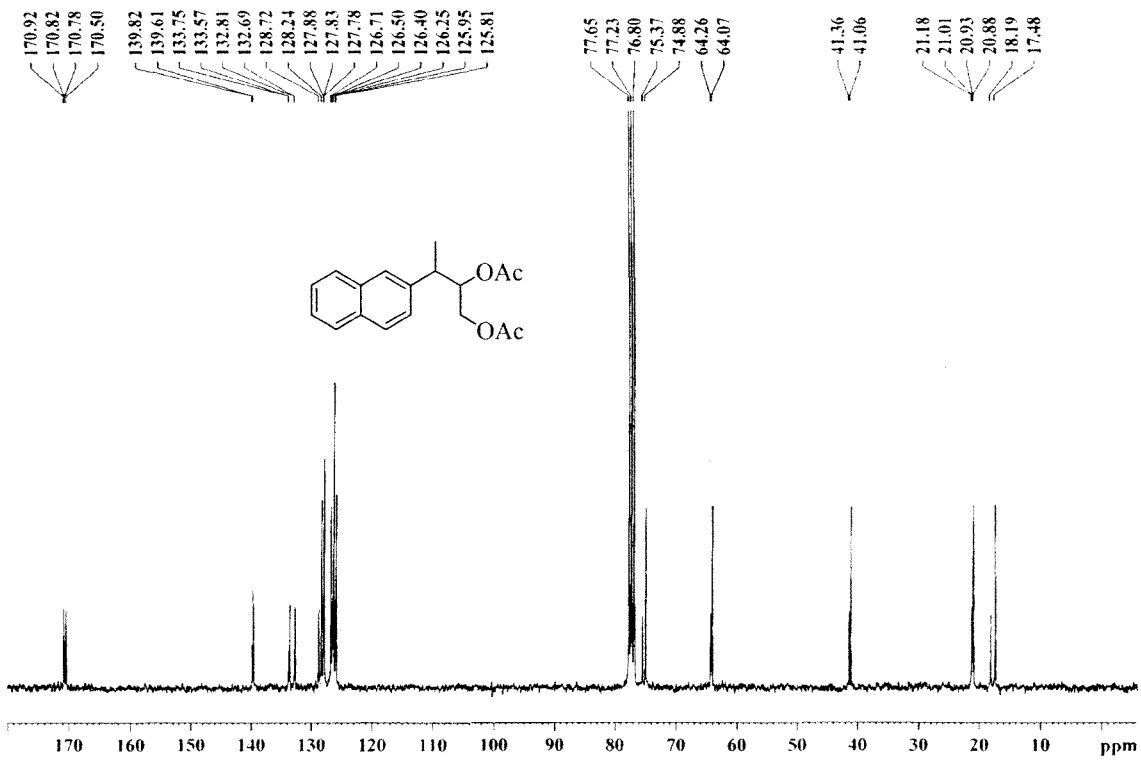
^{1}H NMR Spectra of **36** (300 MHz, $CDCl_3$)



^{13}C NMR Spectra of **36** (75 MHz, $CDCl_3$)



^{1}H NMR Spectra of **34** (300 MHz, $CDCl_3$)



^{13}C NMR Spectra of **34** (75 MHz, $CDCl_3$)

Chapter 3

Synthesis and Biology of Novel Hydroxy-functionalized 1,2,4-Trioxanes

3.1 Introduction

As discussed in chapter 1 artemisinin **1** and its derivatives artemether[1] **2**, arteether **3**, artesunic acid **4**, artelinic acid **3**, and artemisone[2] **4**, have high antimalarial activity (Fig. 3.1). The limited availability of artemisinin from natural resources has prompted us to synthesize synthetic analogs of artemisinin.

Several synthetic peroxides have been synthesized by various groups that have shown promising antimalarial activity.[3-8]

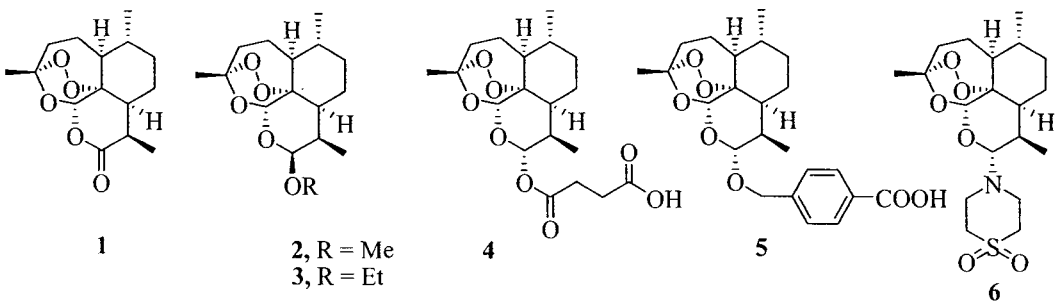


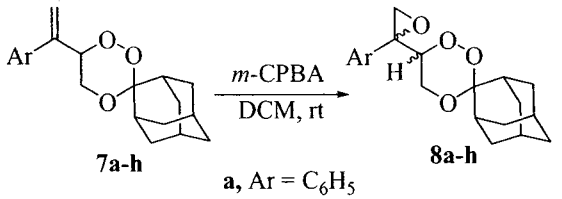
Figure 3.1

In chapter 2 of the thesis we have shown that the reduction of the double bond of the 6-arylvinyl substituted 1,2,4-trioxanes[9, 10, 11] leads to a major improvement in the antimalarial activity. Several of these novel trioxanes obtained by the reduction of the double bond show activity profile better than artemisinin derivatives by the oral route. However, these trioxanes, presumably because of their high hydrophobicity show poor activity by intramuscular route. We reassumed that the introduction of the polar group in this class may improve the activity by intramuscular route

Towards this end we have converted 6-arylvinyl substituted 1,2,4-trioxanes to hydroxy functionalized 1,2,4-trioxanes using the chemistry of double bond. Several of these new trioxanes show high order of activity both by oral and intramuscular routes. In this chapter we describe results of this study.

3.2 Preparation Of Hydroxy-Functionalized 1,2,4-Trioxanes

6-Arylvinyl-1,2,4-trioxanes **7a-h,** prepared according to the reported procedure on epoxidation with *m*-CPBA in DCM furnished corresponding epoxides **8a-h** as an inseparable mixture of two diastereomers in 57-68% yields (Scheme 3.1).

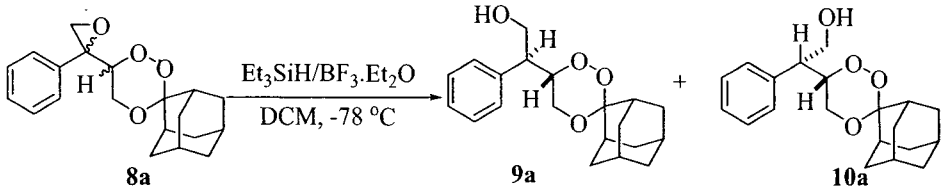


7a-h **8a-h**

a, Ar = C_6H_5
b, Ar = 4-MeC_6H_4
c, Ar = 4-ClC_6H_4
d, Ar = 4-FC_6H_4
e, Ar = 4-BrC_6H_4
f, Ar = 2-Naphthyl
g, Ar = 4-PhC_6H_4
h, Ar = 4-CyC_6H_4

Scheme 3.1 Synthesis of trioxane epoxides **8a-h**.

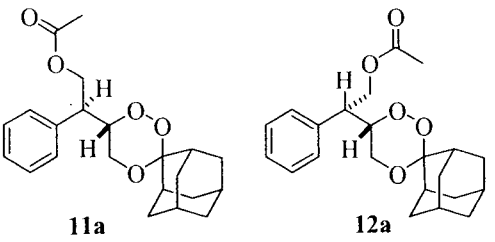
Epoxide **8a** on $Et_3SiH/BF_3.Et_2O$ reduction in dry DCM under inert atmosphere at -78°C furnished corresponding diastereomeric trioxane alcohols **9a** (Higher R_f) and **10a** (Lower R_f) in 11% and 37% yields, respectively (Scheme 3.2).[12] Compounds **9a** and **10a** were converted to their corresponding acetates **11a** and **12a** (93% and 95% yields), respectively and were characterized fully by NMR and mass spectra (Fig 3.1).



8a **9a** **10a**

Scheme 3.2 Synthesis of trioxane alcohols **9a** and **10a**.

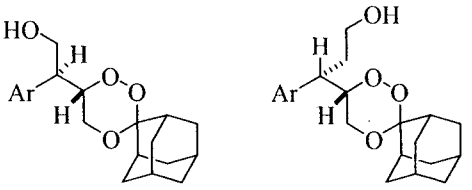
Similarly epoxides **8b-h** were reduced using the same procedure to furnish the corresponding alcohols **9b-h** (Higher R_f in 5-9% yields) and **10b-h** (Lower R_f in 28-30% yields), respectively (Fig 3.2).



11a **12a**

Figure 3.1 Acetates of trioxane alcohols **9a** and **10a**.

The structures and the relative stereochemistry of the two isomers were assigned on the basis of coupling constants and NOESY correlations.



7b-h **10b-h**

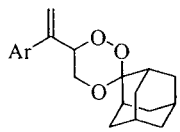
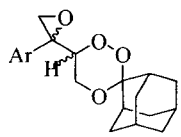
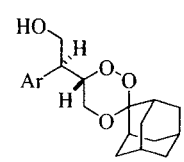
b, Ar = 4-MeC_6H_4
c, Ar = 4-ClC_6H_4
d, Ar = 4-FC_6H_4
e, Ar = 4-BrC_6H_4
f, Ar = 2-Naphthyl
g, Ar = 4-PhC_6H_4
h, Ar = 4-CyC_6H_4

Figure 3.2 Trioxane alcohols.

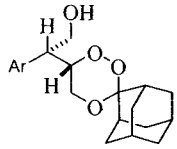
3.3 Antimalarial Activity

Trioxane alcohols **9a-h** and **10a-h** were initially tested against multi-drug resistant *P. yoelii* in Swiss mice at 96 mg/kg × 4 days via oral as well as intramuscular routes. Trioxanes which showed 100% protection at 96 mg/kg × 4 days were further screened at 48-24 mg/kg × 4 days dose. In this model artemisinin provides 100% protection at 48 mg/kg × 4 days via im route while β-arteether shows 100% protection at 48 mg/kg × 4 days and at 24 mg/kg × 4 days it provides only 20% protection to the treated mice.[13, 14] The results of antimalarial activity of these trioxanes **9a-h** and **10a-h** along 6-arylvinyl-trioxnes **7a-e** and their epoxides **8a-f** are shown in Table 3.1.

Table 3.1. *In vivo* antimalarial activity of compounds **7a-e**, **8a-f**, **9a-h** and **10a-h** against multi-drug resistant *P. yoelii* in Swiss mice by oral and im route.

General Structure	Ar	Compound	Route	Dose (mg/kg × 4 days)	% Suppression on day 4[a]	Mice alive on day 28
	C_6H_5	**7a**	Oral	96	96.00	0/5
			Im	96	86.67	0/5
	4-MeC_6H_4	**7b**	Oral	96	95.20	0/5
			Im	96	53.07	0/5
	4-ClC_6H_4	**7c**	Oral	96	100.00	0/5
			Im	96	98.93	0/5
	4-FC_6H_4	**7d**	Oral	96	99.33	0/5
			Im	96	83.20	0/5
	4-BrC_6H_4	**7e**	Oral	96	100.00	0/5
			Im	96	54.40	0/5
	C_6H_5	**8a**	Oral	96	31.79	0/5
			Im	96	84.71	0/5
	4-MeC_6H_4	**8b**	Oral	96	26.07	0/5
			Im	96	18.57	0/5
	4-ClC_6H_4	**8c**	Oral	96	25.00	0/5
			Im	96	32.14	0/5
	4-FC_6H_4	**8d**	Oral	96	55.36	0/5
			Im	96	24.64	0/5
	4-BrC_6H_4	**8e**	Oral	96	30.20	0/5
			Im	96	50.32	0/5
	2-Naphthyl	**8f**	Oral	96	06.50	0/5
			Im	96	13.21	0/5
	C_6H_5	**9a**	Oral	96	100.00	0/5
			Im	96	100.00	3/5
	4-MeC_6H_4	**9b**	Oral	96	100.00	0/5
			Im	96	100.00	4/5
	4-ClC_6H_4	**9c**	Oral	96	100.00	3/5
			Im	96	100.00	5/5
				48	100.00	3/5
				24	71.66	0/5
	4-FC_6H_4	**9d**	Oral	96	100.00	2/5
			Im	96	100.00	5/5
				48	100.00	5/5
				24	100.00	3/5
	4-BrC_6H_4	**9e**	Oral	96	100.00	1/5
			Im	96	100.00	3/5
	2-Naphthyl	**9f**	Oral	96	100.00	5/5
				48	100.00	3/5
			Im	96	100.00	5/5
				48	100.00	4/5
	4-PhC_6H_4	**9g**	Oral	96	100.00	5/5
				48	100.00	3/5
			Im	96	100.00	2/5
	4-CyC_6H_4	**9h**	Oral	96	100.00	5/5
				48	100.00	5/5
				24	80.90	0/5
			Im	96	100.00	1/5

[a]Percent suppression = [(C-T)/C] × 100; where C = parasitaemia in control group and T = parasitaemia in treated group of mice.

General Structure	Ar	Compound	Route	Dose (mg/kg × 4 days)	% Suppression on day 4[a]	Mice alive on day 28
	C_6H_5	**10a**	Oral	96	54.39	0/5
			Im	96	92.89	0/5
	4-MeC_6H_4	**10b**	Oral	96	49.20	0/5
			Im	96	100.00	0/5
	4-ClC_6H_4	**10c**	Oral	96	36.50	0/5
			Im	96	100.00	1/5
	4-FC_6H_4	**10d**	Oral	96	50.20	0/5
			Im	96	100.00	1/5
	4-BrC_6H_4	**10e**	Oral	96	50.21	0/5
			Im	96	93.72	0/5
	2-Naphthyl	**10f**	Oral	96	100.00	1/5
			Im	96	100.00	3/5
	4-PhC_6H_4	**10g**	Oral	96	29.20	0/5
			Im	96	100.00	3/5
	4-CyC_6H_4	**10h**	Oral	96	46.64	0/5
			Im	96	34.27	0/5
β-Arteether	-	**2**	Oral	48	100.00	5/5
				24	100.00	1/5
Artemisinin	-	**1**	Im	48	100.00	5/5
				24	100.00	3/5
Vehicle control	-	-	Oral	-	-	0/15
			Im			0/15

[a]Percent suppression = [(C-T)/C] × 100; where C = parasitaemia in control group and T = parasitaemia in treated group of mice.

3.4 Results and Discussion

As it can be seen from Table 3.1, that the parent 6-arylvinyl-1,2,4-trioxanes **7a-e**, epoxides **8a-f** did not show appreciable activity, trioxane alcohols **9a-f** (higher R_f) showed 50-100% suppression of parasitaemia via oral route and 100% suppression via intramuscular route respectively, while trioxane alcohols **10a-f** (lower R_f) showed 37-100% suppression of parasitaemia via oral route and 93-100% suppression via intramuscular route to the treated mice when administered at 96 mg/kg × 4 days. Trioxane **9d** the most active compound of the series showed 100% suppression of parasitaemia at 96 mg/kg × 4 days both via oral and im routes on day 4 with 40% protection to the treated mice via oral and 100% protection via im route at 96 mg/kg × 4 days dose. Trioxane **9d** also provided 100% clearance of parasitaemia at 48 mg/kg × 4 days dose and 60% clearance at 24 mg/kg × 4 days dose. Trioxane **9f** the next most active compound of the series also provided 100% clearance of parasitaemia via both the routes at 96 mg/kg × 4 days dose. Trioxane **9f** also provided 60% protection via oral and 80% protection via im routes at 48 mg/kg × 4 days dose. Trioxane **9h** the other active compound of the series exhibited 100% protection against parasitaemia via oral route and 20% protection via im route at

96 mg/kg × 4 days. At 48 mg/kg × 4 days dose trioxane **9h** showed 100% protection only via oral route. Compound **9g**, the another active compound of the series showed 100% clearance of parasitaemia via oral route and 40% clearance via im route at 96 mg/kg × 4 days dose. Compound **9g** also showed 60% clearance of parasitaemia via oral route at a dose of 48 mg/kg × 4 days. Compound **9c** also showed 60% clearance of parasitaemia via oral route and 100% clearance by the im route at 96 mg/kg × 4 days dose. It also showed clearance of parasitaemia in 60% of the treated mice. Compound **9e** was found relatively less active as it showed only 20% of the treated mice survived via oral route and 60% of the treated mice survived by the im route when administered at 96 mg/kg × 4 days dose. Compounds **9a** and **9b** although 100% suppression of parasitaemia on day 4 both via oral and im routes but only 60% and 80% of the respective treated mice survived in either case only via im route at 96 mg/kg × 4 days dose.

Among the compounds having lower R_f compound **10f** was found most active as it showed 100% suppression of parasitaemia via both oral and im routes at 96 mg/kg × 4 days dose together with 20% and 60% survival, respectively via either route at 96 mg/kg × 4 days dose. Compound **10g** the next best compound of this class provided 60% protection from parasitaemia only via im route while it showed only moderate suppression via oral route. Compounds **10b**, **10c** and **10d** also showed 100% suppression of parasitaemia on day 4 via im route at 96 mg/kg × 4 days dose but only 20% clearance of parasitaemia was observed in compounds **10c** and **10d** at this dose. These compounds showed only moderate level of suppression via oral route at this dose. Rest two compounds **10a** and **10b** exhibited only moderate level of suppression via either route at 96 mg/kg × 4 days dose.

3.5 Conclusion

In conclusion, in our efforts to improve the antimalarial activity of the 6-arylvinyl-1,2,4-trioxanes by im route we have prepared a new series of hydroxy-functionalized 1,2,4-trioxanes **9a-h** and **10a-h** using the chemistry of double bond and assessed their structure activity relationship. Several of these trioxanes have shown better activity profile than the parent trioxanes. Trioxane **9d** was found to be the most active compound of the series.

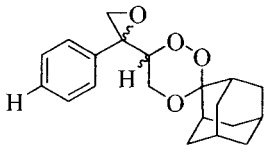
3.6 Experimental Section

General details and instrumentation: All glass apparatus were oven dried prior to use. Melting points were taken in open capillaries on Complab melting point apparatus and are presented

uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 MHz and 300 MHz respectively for 1H; 50 MHz and 75 MHz respectively for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quintet (quin), multiplet (m), and broad (br). Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (EI-HRMS) were obtained on JEOL MS route 600H instrument. Elemental analyses were performed on Vario EL-III C H N S analyzer (Germany), and values were within (0.4% of the calculated values). Column chromatography was performed over Merck silica gel (particle size: 60-120 Mesh) procured from Qualigens (India), or flash silica gel (particle size: 230-400 Mesh). All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used without further purification. Nomenclature and Log *p* values of the compounds were assigned using Chem Draw Ultra 7.0 software.

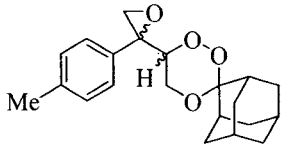
General procedure for preparation of trioxane epoxides 8a-h: (Preparation of trioxane epoxide **8a** as representative). To a stirred solution of trioxane **7a** (5g, 16.025 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added *m*-CPBA (70% slurry in H_2O, 9.84 g, 2.5 equiv.) and reaction was allowed to stir at rt for 6 h. Reaction mixture was quenched with 10% $NaHCO_3$ solution (50 mL), organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). Combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography over silica gel to furnish trioxane epoxide **8a** (3.15 g, 60% yield) as an inseparable mixture of diastereomers in form of an oil.

Compounds **7b-h** were also epoxidated by same procedure to furnish epoxides **8b-h**.

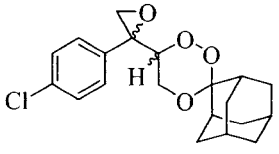


Trioxane 8a: It was isolated in 60% yield as diastereomeric mixture; oil; FT-IR (neat cm^{-1}) 757, 838, 1112, 1165, 1228, 1601, 2922; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-2.06 (m, 14H), 2.74 (m, 2H), 3.11 and 3.34 (2 × d, J = 5.3 and 5.5 Hz respectively, together integrating for 1H), 3.69 and 3.72 (2 × dd, J = 11.6,

3.3 and 12.0, 3.0 Hz respectively, together integrating for 1H), 2.86 and 2.91 (2 × dd, J = 11.6, 10.3 and 12.0, 9.3 Hz respectively, together integrating for 1H), 4.63 and 4.92 (2 × dd, J = 10.3, 3.3 and 9.3, 3.0 Hz respectively, together integrating for 1H), 7.33-7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.28 (CH), 27.31(CH), 29.71 (CH), 33.17 (CH_2), 33.35 (CH_2), 33.45 (CH_2), 33.61 (CH_2), 33.63 (CH_2), 33.66 (CH_2), 33.68 (CH_2), 36.18 (CH), 37.34 (CH_2), 37.35 (CH_2), 52.36 (CH_2), 52.96 (CH_2), 58.28 (C), 58.56 (CH_2), 79.92 (CH), 81.17 (CH), 105.09 (C), 126.15 (CH), 126.61 (CH), 128.43 (CH), 128.47 (CH), 128.61 (CH), 128.71 (CH), 135.26 (C); ESI-MS (*m/z*) 329 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{24}O_4$: %C 73.15, %H 7.37. Found: %C 72.98, %H 7.15.

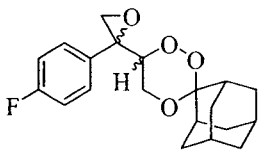


Trioxane 8b: It was isolated in 62% yield as diastereomeric mixture; white solid, 73-77 °C, FT-IR (KBr cm^{-1}) 758, 999, 1116, 1217, 1608, 2860, 2918, 3019; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53-2.03 (m, 14H), 2.34 (s, 3H), 2.69 (m, 2H) 3.06 and 3.29 (2 × d, J = 5.3 and 5.5 Hz respectively, together integrating for 1H), 3.65 and 3.54 (2 × dd, J = 11.6, 3.3 and 12.0, 3.0 Hz respectively, together integrating for 1H), 3.83 and 3.87 (2 × dd, J = 11.8, 10.4 and 12.0, 9.3 Hz respectively, together integrating for 1H), 4.61 and 4.87 (2 × dd, J = 10.4, 3.2 and 9.3, 3.0 Hz respectively, together integrating for 1H), 7.14-7.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.32 (CH), 27.35 (CH), 27.28 (CH_3), 27.31 (CH_3), 29.68 (CH), 33.15 (CH_2), 33.18 (CH_2), 33.34 (CH_2), 33.44 (CH_2), 33.60 (CH_2), 33.62 (CH_2), 33.66 (CH_2), 33.67 (CH_2), 36.19 (CH), 37.34 (CH_2), 37.35 (CH_2), 52.36 (CH_2), 52.98 (CH_2), 57.99 (C), 58.19 (C), 58.50 (CH_2), 58.65 (CH_2), 78.92 (CH), 81.17 (CH), 105.03 (C), 105.06 (C), 126.06 (CH), 126.49 (CH), 129.30 (CH), 129.37 (CH), 133.25 (C), 134.68 (C), 138.20 (C), 138.22 (C); ESI-MS (*m/z*) 329 [M+H$^+$]; Anal. Calcd. for $C_{21}H_{26}O_4$: %C 73.66, %H 7.65. Found: %C 73.98, %H 7.77.

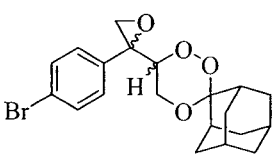


Trioxane 8c: It was isolated in 58% yield as diastereomeric mixture; white solid, 80-84 °C, FT-IR (KBr cm^{-1}) 762, 829, 922, 1001, 1092, 1116, 1224, 1655, 2857, 2918; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-2.05 (m, 14H), 2.72 (m, 2H) 3.10 and 3.36 (2 × d, J = 5.2 and 5.1 Hz respectively, together integrating for 1H), 3.70 and 3.74 (dd and brdd, J = 11.6, 3.3 together integrating for 1H), 3.75 and 3.87 (dd and brdd, J = 11.8, 10.4 together integrating for 1H), 4.60 and 4.63 (dd and brdd, J = 10.2, 3.3 together integrating for 1H), 7.34-7.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.23 (CH), 29.72 (CH), 33.15 (CH_2), 33.32 (CH_2), 33.43 (CH_2), 33.18 (CH_2), 33.59 (CH_2), 36.13 (CH), 37.30 (CH_2), 52.64 (CH_2), 53.27 (CH_2), 57.58 (C), 57.77 (C), 57.99 (CH_2), 58.36 (CH_2),

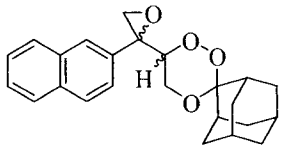
78.93 (CH), 81.09 (CH), 105.22 (C), 127.63 (CH), 128.00 (CH), 128.87 (CH), 128.91 (CH), 134.40 (C), 134.81 (C), 136.41 (C); ESI-MS (*m/z*) 362 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{23}O_4Cl$: %C 66.20, %H 6.39. Found: %C 66.50, %H 6.55.



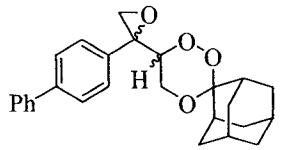
Trioxane 8d: It was isolated in 61% yield as diastereomeric mixture; white solid, 85-88 °C, FT-IR (KBr cm^{-1}) 760, 837, 921, 1000, 1115, , 1226, 1604, 2858, 2919; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-2.02 (m, 14H), 2.69 (m, 2H) 3.07 and 3.32 (2 × d, J = 5.2 and 5.6 Hz respectively, together integrating for 1H), 3.67 and 3.74 (2 × dd, J = 11.7, 3.2 and 12.1, 2.3 Hz respectively, together integrating for 1H), 3.82 and 3.85 (2 × dd, J = 11.7, 10.2 and 12.0, 8.2 Hz respectively, together integrating for 1H), 4.59 and 4.80 (dd and brdd, J = 10.2, 3.2 together integrating for 1H), 7.01-7.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.17 (CH), 27.21 (CH), 29.64 (CH), 33.06 (CH_2), 33.36 (CH_2), 33.51 (CH_2), 33.53 (CH_2), 33.58 (CH_2), 36.04 (CH), 37.22 (CH_2), 37.24 (CH_2), 52.47 (CH_2), 53.04 (CH_2), 57.53 (C), 57.79 (C), 58.01 (CH_2), 58.33 (CH_2), 79.02 (CH), 80.96 (CH), 105.09 (C), 115.54 (d, CH, $J_{C\text{-}F}$ = 21 Hz), 115.57 (d, CH, $J_{C\text{-}F}$ = 21.5 Hz), 128.07 (d, CH, $J_{C\text{-}F}$ = 8.0 Hz), 128.39 (d, CH, $J_{C\text{-}F}$ = 8.0 Hz), 133.56 (C), 133.61 (C), 162.68 (d, C, $J_{C\text{-}F}$ = 246 Hz), 162.70 (d, C, $J_{C\text{-}F}$ = 245 Hz); ESI-MS (*m/z*) 347 [M+H$^+$].



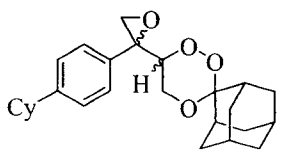
Trioxane 8e: It was isolated in 58% yield as diastereomeric mixture; white solid, 93-95 °C, FT-IR (KBr cm^{-1}) 761, 825, 921, 1003, 1088, 1115, 1221, 1648, 2857, 2917; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56-2.03 (m, 14H), 2.66 (m, 2H) 3.08 and 3.34 (2 × d, J = 5.2 and 4.5 Hz respectively, together integrating for 1H), 3.68 and 3.72 (dd and brdd, J = 11.7, 3.2 Hz together integrating for 1H), 3.81 and 3.86 (2 × dd, J = 10.2, 6.8 and 8.7, 5.7 Hz respectively, together integrating for 1H), 4.58 and 4.80 (dd and brdd, J = 10.2, 3.2 Hz together integrating for 1H), 7.28-7.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.75 (CH), 27.78 (CH), 28.23 (CH), 31.67 (CH_2), 31.84 (CH_2), 31.94 (CH_2), 32.09 (CH_2), 32.11 (CH_2), 32.17 (CH_2), 34.64 (CH), 35.80 (CH_2), 35.82 (CH_2), 51.14 (CH_2), 51.75 (CH_2), 56.03 (C), 56.31 (C), 56.52 (CH_2), 56.85 (CH_2), 79.39 (CH), 79.55 (CH), 103.70 (C), 103.72 (C), 121.05 (CH), 121.11 (CH), 126.50 (CH), 126.80 (CH), 130.32 (CH), 130.36 (CH), 133.88 (C), 135.19 (C); ESI-MS (*m/z*) 362 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{23}O_4Br$: %C 58.98, %H 5.69. Found: %C 60.25, %H 5.88.



Trioxane 8f: It was isolated in 57% yield as diastereomeric mixture; viscous solid, FT-IR (neat cm^{-1}) 764, 837, 917, 998, 1115, 1657, 2857, 2917; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-2.09 (m, 14H), 2.78 (m, 2H) 3.15 and 3.42 (2 × d, J = 5.3 and 5.2 Hz respectively, together integrating for 1H), 3.73 and 3.77 (2 × dd, J = 11.6, 3.1 and 11.9, 2.7 Hz respectively, together integrating for 1H), 3.89 and 3.97 (2 × dd, J = 11.6, 10.5 and 11.9, 9.5 Hz respectively, together integrating for 1H), 5.05 and 5.20 (dd and brdd, J = 10.5, 3.1 Hz together integrating for 1H), 7.49-7.59 (m, 3H), 7.83-7.95 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.24 (CH), 27.99 (CH), 27.30 (CH), 29.67 (CH), 29.90 (CH), 33.13 (CH_2), 33.16 (CH_2), 33.40 (CH_2), 33.44 (CH_2), 33.61 (CH_2), 36.10 (CH), 37.34 (CH_2), 37.38 (CH_2), 52.47 (CH_2), 53.20 (CH_2), 57.87 (C), 58.26 (C), 58.54 (CH_2), 58.56 (CH_2), 78.34 (CH), 81.37 (CH), 104.89 (C), 104.92 (C), 123.62 (CH), 124.14 (CH), 125.64 (CH), 126.43 (CH), 126.47 (CH), 126.52 (CH), 128.30 (CH), 128.49 (CH), 133.22 (C), 133.23 (C),133.27 (C), 133.77 (C); ESI-MS (*m/z*) 379 [M+H$^+$]; Anal. Calcd. for $C_{24}H_{26}O_4$: %C 76.17, %H 6.92. Found: %C 76.35, %H 7.08.



Trioxane 8g: It was isolated in 61% yield as diastereomeric mixture; white solid; 105-108 °C, FT-IR (KBr cm^{-1}) 769, 859, 920, 1001, 1116, 1659, 2856, 2920; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63-2.05 (m, 14H), 2.79 (m, 2H) 3.15 and 3.39 (2 × d, J = 5.2 and 5.4 Hz respectively, together integrating for 1H), 3.75 and 3.79 (dd and brdd, J = 11.7, 3.2 Hz together integrating for 1H), 3.89-3.97 (m, 1H), 4.72 and 4.96 (dd and brdd, J = 10.4, 3.2 Hz together integrating for 1H), 7.29-7.64 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.26 (CH), 29.69 (CH), 33.18 (CH_2), 33.36 (CH_2), 33.46 (CH_2), 33.62 (CH_2), 36.20 (CH), 37.33 (CH_2), 52.55 (CH_2), 53.16 (CH_2), 57.91 (C), 58.12 (C), 58.42 (CH_2), 58.57 (CH_2), 78.91 (CH), 81.15 (CH), 105.16 (C), 126.61 (CH), 126.97 (CH), 127.31 (CH), 127.38 (CH), 127.45 (CH), 127.70 (CH), 129.03 (CH), 135.27 (C), 136.72 (C), 140.71 (C), 141.35 (C); ESI-MS (*m/z*) 405 [M+H$^+$]; Anal. Calcd. for $C_{26}H_{28}O_4$: %C 77.20, %H 6.98. Found: %C 77.55, %H 7.10.

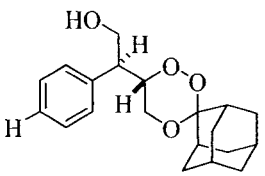


Trioxane 8h: It was isolated in 68% yield as diastereomeric mixture; white solid; 121-123 °C, FT-IR (KBr cm^{-1}) 790, 879, 995, 1009, 1115, 1645, 2859, 2901; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24-2.06 (m, 24H), 2.53 (brm, 1H), 2.69 and 2.70 (2 × d, J = 5.5 and 5.2 Hz respectively, together integrating for 1H), 2.77 (s, 1H), 3.06 and 3.29 (2 × d, J = 5.2 and 5.5 Hz respectively, together integrating for

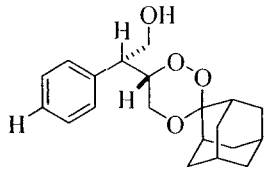
1H), 3.66 and 3.71 (2 × dd, J = 11.6, 3.1 and 12.3, 2.9 Hz respectively, together integrating for 1H), 3.86 and 3.90 (2 × dd, J = 11.6, 10.4 and 9.5, 8.8 Hz respectively, together integrating for 1H), 4.68 and 4.91 (2 × dd, J = 10.4, 3.1 and 8.8, 2.9 Hz respectively, together integrating for 1H), 7.18-7.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.23 (CH_2), 26.96 (CH_2), 27.21 (CH), 29.57 (CH), 30.18 (CH), 33.07 (CH_2), 33.25 (CH_2), 33.34 (CH_2), 33.52 (CH_2), 34.47 (CH_2), 35.32 (CH), 36.08 (CH), 37.26 (CH_2), 44.36 (CH), 52.19 (CH_2), 52.62 (CH_2), 57.86 (C), 58.09 (C), 58.33 (CH_2), 58.51 (CH_2), 78.82 (CH), 80.73 (CH), 104.86 (C), 125.97 (CH), 126.38 (CH), 126.94 (CH), 127.01 (CH), 133.57 (C), 134.98 (CH), 148.18 (C); ESI-MS (*m/z*) 411 [M+H$^+$].

General procedure for $Et_3SiH/BF_3.Et_2O$ reduction of trioxane epoxides: (Preparation of trioxane alcohols **9a** and **10a** as representative). To a stirred solution of trioxane epoxide **8a** (3.00 g, 9.146 mmol) in dry CH_2Cl_2, kept at -78 °C under inert atmosphere, was added $BF_3.Et_2O$ (2.5 mL, 2.5 equiv) followed by gradual addition of Et_3SiH (3.79 mL, 2.5 equiv) via syringe and reaction was allowed to stir at same temperature for 2h. Reaction mixture was quenched with Et_3N (10 mL) and allowed to come at rt, which was then diluted with water (20 ml), organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography over silica gel to furnish trioxane alcohols **9a** (0.33 g, 11% yield, Higher R_f) and **10a** (1.12 g, 37% yield, Lower R_f).

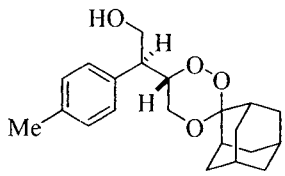
Trioxane epoxides **8b-h** were also reduced via same procedure to furnish compounds **9b-h** (Higher R_f) and **10b-h** (Lower R_f).



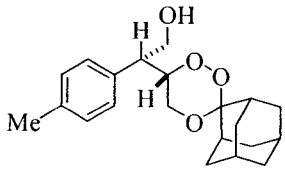
Trioxane 9a: It was isolated in 11% yield; oil; FT-IR (neat cm^{-1}) 758, 1087, 1113, 1645, 2922, 3432; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60-1.99 (m, 14H+OH), 2.77 (s, 1H), 2.98 (brq, 1H), 3.40 (brdd, 1H), 3.64 (dd, 1H, J = 11.8, 9.2 Hz), 3.88 (dd, 1H, J = 11.1, 6.3 Hz), 4.07 (dd, J = 11.1, 5.6 Hz), 4.60 (brdt, 1H), 7.23-7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.31 (2 × CH), 30.45 (CH), 33.22 (CH_2), 33.42 (CH_2), 33.55 (CH_2), 33.61 (CH_2), 35.34 (CH), 37.35 (CH_2), 49.11 (CH), 60.87 (CH_2), 65.12 (CH_2), 81.22 (CH), 105.00 (C) , 127.90 (CH), 128.62 (2 × CH), 128.21 (2 × CH), 137.51 (C); FAB-MS (*m/z*) 331 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{26}O_4$: %C 72.70, %H 7.93. Found: %C 72.35, %H 7.60; EI-HRMS Calcd. for $C_{20}H_{26}O_4$ [M$^+$]: 330.1831. Found: 330.1825.



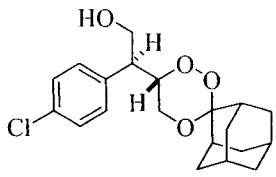
Trioxane 10a: It was isolated in 37% yield; white solid, mp 86-88 °C; FT-IR (KBr cm^{-1}) 703, 1073, 1107, 1638, 2902, 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-2.05 (m, 14H+OH), 2.64 (s, 1H), 2.98 (q, J = 6.5 Hz, 1H), 3.73 (dd, 1H, J = 11.8, 3.5 Hz), 3.80 (dd, 1H, J = 11.8, 9.6 Hz), 3.86 (dd, 1H, J = 10.7, 6.8 Hz), 3.95 (dd, 1H, J = 10.7, 6.6 Hz), 4.78 (ddd, 1H, J =9.6, 6.2, 3.5 Hz) 7.25-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.25 (2 × CH), 29.87 (CH), 33.12 (CH_2), 33.28 (CH_2), 33.53 (CH_2), 33.61 (CH_2) 36.03 (CH), 37.33 (CH_2), 49.60 (CH), 60.84 (CH_2), 63.68 (CH_2), 79.40 (CH), 104.95 (C), 127.54 (CH), 128.05 (2 × CH), 129.02 (2 × CH), 137.75 (C); ESI-MS (*m/z*) 331 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{26}O_4$: %C 72.70, %H 7.93. Found: %C 72.95 , %H 8.25; EI-HRMS Calcd. for $C_{20}H_{26}O_4$ [M$^+$]: 330.1831. Found: 330.1818.



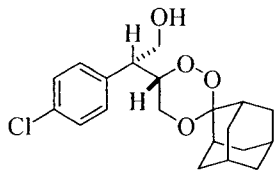
Trioxane 9b: It was isolated in 7% yield; oil; FT-IR (neat cm^{-1}) 754, 1114, 1607, 2918, 3411; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-1.96 (m, 14H+OH), 2.34 (s, 3H), 2.78 (s, 1H) 2.99 (brq, 1H), 3.40 (brdd, 1H), 3.63 (dd, 1H, J = 11.8, 9.2 Hz), 3.86 (dd, 1H, J = 10.6, 6.1 Hz), 4.05 (dd, 1H, J = 10.6, 5.9 Hz), 4.58 (brdt, 1H) 7.10 (d, 2H, J = 8.1 Hz), 7.15 (d, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.23 (CH_3), 27.29 (2 × CH), 30.35 (CH), 33.20 (CH_2), 33.40 (CH_2), 33.54 (CH_2), 33.60 (CH_2) 35.31 (CH), 37.34 (CH_2), 48.71 (CH), 60.92 (CH_2), 65.28 (CH_2), 81.32 (CH), 104.94 (C) , 129.46 (2 ×CH), 129.90 (2 × CH), 134.20 (C), 137.60 (C); FAB-MS (*m/z*) 331 [M+H$^+$]; Anal. Calcd. for $C_{21}H_{28}O_4$: %C 73.23, %H 8.19. Found: %C 73.55 , %H 8.50; EI-HRMS Calcd. for $C_{21}H_{29}O_4$ [M+H$^+$]: 345.2066. Found: 345.2078.



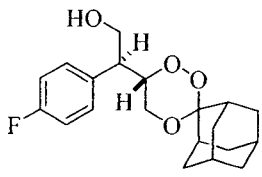
Trioxane 10b: It was isolated in 28% yield; white solid, mp 66-68 °C; FT-IR (KBr cm^{-1}) 745, 1089, 1112, 1658, 2913, 3408; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-2.01 (m, 14H+OH), 2.35 (s, 3H), 2.67 (s, 1H) 2.94 (q, 1H, J = 6.6 Hz), 3.72 (dd, 1H, J = 11.8, 3.3 Hz), 3.80 (dd, 1H, J = 11.8, 9.6 Hz), 3.84 (dd, 1H, J = 10.9, 6.0 Hz), 3.92 (dd, 1H, J = 10.9, 6.7 Hz), 4.75 (ddd, 1H, J = 9.6, 6.0, 3.3 Hz) 7.15 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.27 (CH_3), 27.32 (2 × CH), 29.93 (CH), 33.22 (CH_2), 33.34 (CH_2), 33.59 (CH_2), 33.67 (CH_2) 36.12 (CH), 37.40 (CH_2), 49.30 (CH), 60.92 (CH_2), 63.90 (CH_2), 79.60 (CH), 104.98 (C) , 128.93 (2 ×CH), 129.69 (2 × CH), 134.52 (C), 137.24 (C); FAB-MS (*m/z*) 331 [M+H$^+$]; Anal. Calcd. for $C_{21}H_{28}O_4$: %C 73.23, %H 8.19. Found: %C 72.91 , %H 7.95; EI-HRMS Calcd. for $C_{21}H_{29}O_4$, [M+H$^+$]: 345.2066. Found: 345.2043.



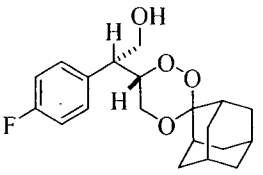
Trioxane 9c: It was isolated in 8% yield; oil; FT-IR (neat cm^{-1}) 758, 1092, 1596, 2921, 3409; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-2.13 (m, 14H+OH), 2.71 (s, 1H) 2.97 (brq, 1H), 3.44 (brdd, 1H), 3.60 (dd, 1H, J = 11.3, 8.9 Hz), 3.86 (dd, 1H, J = 10.8, 6.0 Hz), 3.99 (dd, 1H, J = 10.8, 5.3 Hz), 4.53 (brdt, 1H) 7.16-7.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.23 (2 × CH), 30.58 (CH), 33.17 (CH_2), 33.36 (CH_2), 33.47 (CH_2), 33.54 (CH_2) 34.84 (CH), 37.27 (CH_2), 48.21 (CH), 60.56 (CH_2), 64.52 (CH_2), 80.53 (CH), 105.04 (C), 129.26 (2 ×CH), 129.97 (2 × CH), 133.63 (C), 136.35 (C); FAB-MS (*m/z*) 365 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{25}ClO_4$: %C 65.84, %H 6.91. Found: %C 66.01, %H 6.55; EI-HRMS Calcd. for $C_{20}H_{25}ClO_4$, [M$^+$]: 364.1441. Found: 364.1442.



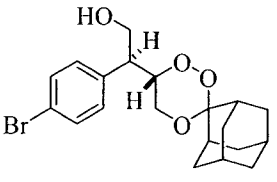
Trioxane 10c: It was isolated in 30% yield; white solid, mp 120-122 °C; FT-IR (KBr cm^{-1}) 758, 1092, 1596, 2920, 3410; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-2.05 (m, 14H+OH), 2.59 (s, 1H) 2.93 (q, 1H, , J = 6.3 Hz), 3.71-3.76 (brm, 2H), 3.80 (dd, 1H, J = 11.0, 6.7 Hz), 3.89 (dd, 1H, J = 11.0, 6.8 Hz), 4.72 (brddd, 1H) 7.19 (d, 2H, J = 8.4Hz), 7.31 (d, 2H, J = 8.4Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.25 (2 × CH), 30.05 (CH), 33.16 (CH_2), 33.29 (CH_2), 33.53 (CH_2), 33.62 (CH_2) 35.92 (CH), 37.32 (CH_2), 48.91 (CH), 60.72 (CH_2), 63.65 (CH_2), 79.20 (CH), 105.08 (C) , 129.03 (2 ×CH), 130.41 (2 × CH), 133.43 (C), 136.42 (C); ESI-MS (*m/z*) 404 [M+K$^+$]; Anal. Calcd. for $C_{20}H_{25}ClO_4$: %C 65.84, %H 6.91. Found: %C 65.70 , %H 7.25; EI-HRMS Calcd. for $C_{20}H_{25}ClO_4$ [M$^+$]: 364.1441. Found: 364.1446.



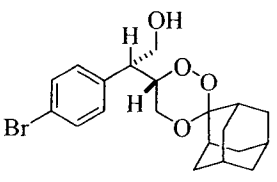
Trioxane 9d: It was isolated in 9% yield; oil; FT-IR (neat cm^{-1}) 832, 1001, 1086, 1106, 1234, 1609, 2908, 3160; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-2.15 (m, 14H+OH), 2.72 (s, 1H) 2.96 (brq, 1H), 3.33 (brdd, 1H), 3.61 (dd, 1H, J = 11.6, 8.9 Hz), 3.85 (dd, 1H, J = 11.1, 6.2 Hz), 3.99 (dd, 1H, J = 11.0, 5.3 Hz), 4.53 (brdt, 1H), 6.99-7.21 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.25 (2 × CH), 30.59 (CH), 33.17 (CH_2), 33.36 (CH_2), 33.49 (CH_2), 33.55 (CH_2) 35.04 (CH), 37.28 (CH_2), 48.11 (CH), 60.63 (CH_2), 64.64 (CH_2), 80.74 (CH), 104.99 (C), 115.98 (d, 2 ×CH, $J_{C\text{-}F}$ = 21 Hz), 130.13 (d, 2 × CH, $J_{C\text{-}F}$ = 8.0 Hz), 133.59 (C), 162.33 (d, C, $J_{C\text{-}F}$ = 245 Hz); ESI-MS (*m/z*) 349 [M+H$^+$]; EI-HRMS Calcd. for $C_{20}H_{25}FO_4$ [M$^+$]: 348.1737. Found: 348.1740.



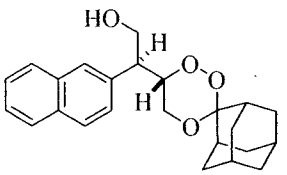
Trioxane 10d: It was isolated in 30% yield; white solid, mp 120-122 °C; FT-IR (KBr cm^{-1}) 840, 1089, 1108, 1239, 1620, 2911, 3456; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-2.04 (m, 14H+OH), 2.61 (s, 1H) 2.95 (q, 1H, J = 6.2 Hz), 3.74 (m, 2H), 3.82 (dd, 1H, J = 11.0, 6.7 Hz), 3.92 (dd, 1H, J = 10.9, 6.6 Hz), 4.72 (brddd, 1H), 7.01-7.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.26 (2 × CH), 29.99 (CH), 33.16 (CH_2), 33.31 (CH_2), 33.55 (CH_2), 33.63 (CH_2) 35.99 (CH), 37.33 (CH_2), 48.79 (CH), 60.78 (CH_2), 63.83 (CH_2), 79.31 (CH), 105.06 (C), 115.80 (d, 2 ×CH, $J_{C\text{-}F}$ = 21 Hz), 130.59 (d, 2 × CH, $J_{C\text{-}F}$ = 7.5 Hz), 133.51 (C), 162.33 (d, C, $J_{C\text{-}F}$ = 245 Hz); ESI-MS (*m/z*) 349 [M+H$^+$]; EI-HRMS Calcd. for $C_{20}H_{25}FO_4$ [M$^+$]: 348.1737. Found: 348.1728.



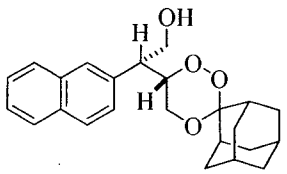
Trioxane 9e: It was isolated in 8% yield; oil; FT-IR (neat cm^{-1}) 690, 761, 829, 1006, 1076, 1106, 1162, 1123, 1654, 2951, 3447; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61-2.96 (m, 14H+OH), 2.71 (s, 1H) 2.99 (brq, 1H), 3.45 (brdd, 1H), 3.62 (dd, 1H, J = 11.6, 8.6 Hz), 3.89 (dd, 1H, J = 11.1, 6.1 Hz), 4.03 (dd, 1H, J = 11.1, 5.4 Hz), 4.54 (brdt, 1H), 7.13 (d, 2H, J = 8.4 Hz), 7.47 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.29 (2 × CH), 30.81 (CH), 33.24 (CH_2), 33.43 (CH_2), 33.53 (CH_2), 33.60 (CH_2) 34.92 (CH), 37.33 (CH_2), 48.39 (CH), 60.58 (CH_2), 64.73 (CH_2), 80.68 (CH), 105.16 (C), 121.83 (C), 130.36 (2 × CH), 132.32 (2 × CH), 136.99 (C); ESI-MS (*m/z*) 409 [M+H$^+$]; EI-HRMS Calcd. for $C_{20}H_{26}BrO_4$ [M+H$^+$]: 409.1014. Found: 409.1016; Anal. Calcd. for $C_{20}H_{25}BrO_4$: %C 58.69, %H 6.16. Found: %C 58.99 , %H 6.54.



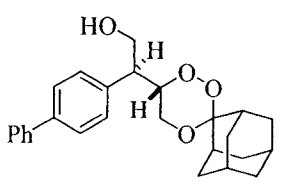
Trioxane 10e: It was isolated in 30% yield; white solid, mp 98-100 °C; FT-IR (KBr cm^{-1}) 699, 758, 921, 1001, 1091, 1216, 1597, 2920, 3433; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-2.01 (m, 14H+OH), 2.57 (s, 1H), 2.89 (q, 1H, J = 8.7 Hz), 3.71 (m, 2H), 3.78 (dd, 1H, J = 11.0, 6.6 Hz), 3.87 (dd, 1H, J = 11.0, 6.6 Hz), 4.69 (brddd, 1H), 7.11 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.23 (CH), 27.25 (CH), 30.04 (CH), 33.16 (CH_2), 33.28 (CH_2), 33.53 (CH_2), 31.61 (CH_2) 35.91 (CH), 37.31 (CH_2), 48.97 (CH), 60.76 (CH_2), 63.60 (CH_2), 79.16 (CH), 105.09 (C), 121.57 (C); 130.78 (2 × CH), 131.98 (2 × CH), 136.96 (C); ESI-MS (*m/z*) 409 [M+H$^+$]; Anal. Calcd. for $C_{20}H_{25}BrO_4$: %C 58.69, %H 6.16. Found: %C 58.95 , %H 6.34.



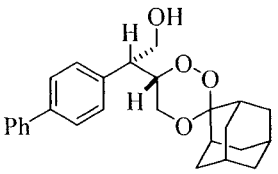
Trioxane 9f: It was isolated in 5% yield; oil; FT-IR (neat cm^{-1}) 669, 749, 818, 1002, 1115, 1106, 1602, 2911, 3449; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-2.02 (m, 14H+OH), 2.78 (s, 1H) 3.15 (brq, 1H), 3.41 (brdd, 1H), 3.66 (dd, 1H, J = 11.7, 9.1 Hz), 3.96 (dd, 1H, J = 11.2, 6.4 Hz), 4.14 (dd, 1H, J = 11.2, 5.6 Hz), 4.71 (brdt, 1H), 7.32 -7.84 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.30 (2 × CH), 30.58 (CH), 33.25 (CH_2), 33.44 (CH_2), 33.54 (CH_2), 33.62 (CH_2) 35.16 (CH), 37.35 (CH_2), 49.18 (CH), 60.89 (CH_2), 65.07 (CH_2), 81.06 (CH), 105.06 (C), 126.12 (CH), 126.28 (CH), 126.63 (CH), 127.87 (3 × CH), 129.08 (CH), 133.03 (C), 133.67 (C), 134.94 (C); ESI-MS (*m/z*) 381 [M+H$^+$]; EI-HRMS Calcd. for $C_{24}H_{28}O_4$ [M$^+$]: 380.1988. Found: 380.1975; Anal. Calcd. for $C_{24}H_{28}O_4$: %C 75.76, %H 7.42. Found: %C 76.01 , %H 7.77.



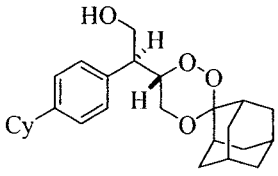
Trioxane 10f: It was isolated in 28% yield; white solid, mp 112-114 °C; FT-IR (KBr cm^{-1}) 675, 754, 860, 1010, 1118, 1601, 2920, 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51-2.04 (m, 14H+OH), 2.63 (s, 1H) 3.16 (q, 1H, J = 6.4 Hz), 3.74 (dd, 1H, J = 11.8, 3.9 Hz), 3.78 (dd, 1H, J = 11.8, 9.2 Hz), 3.91 (dd, 1H, J = 10.7, 7.0 Hz), 4.00 (brdd, 1H), 4.85 (ddd, 1H, J = 9.2, 5.9, 3.9 Hz), 7.38 -7.79 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.24 (2 × CH), 29.89 (CH), 33.16 (CH_2), 33.28 (CH_2), 33.56 (CH_2), 33.62 (CH_2) 36.07 (CH), 37.32 (CH_2), 49.84 (CH), 60.96 (CH_2), 63.82 (CH_2), 79.50 (CH), 105.07 (C), 126.14 (CH), 126.73 (CH), 127.83 (CH), 127.97 (2 × CH), 128.29 (CH), 128.74 (CH), 132.93 (C), 133.60 (C), 135.17 (C); ESI-MS (*m/z*) 381 [M+H$^+$]; EI-HRMS Calcd. for $C_{24}H_{28}O_4$ [M$^+$]: 380.1988. Found: 380.1950.



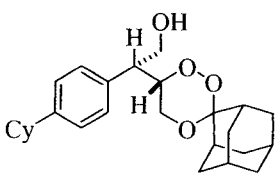
Trioxane 9g: It was isolated in 5% yield; oil; FT-IR (neat cm^{-1}) 670, 780, 890, 1010, 1125, 1595, 1601, 2915, 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62-2.04 (m, 14H+OH), 2.79 (s, 1H) 3.06 (brq, 1H), 3.49 (brdd, 1H), 3.69 (dd, 1H, J = 11.7, 8.9 Hz), 3.94 (dd, 1H, J = 11.2, 6.3 Hz), 4.18 (dd, 1H, J = 11.1, 5.6 Hz), 4.64 (brdt, 1H), 7.28 -7.57 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.34 (2 × CH), 30.56 (CH), 33.26 (CH_2), 33.45 (CH_2), 33.58 (CH_2), 33.63 (CH_2) 35.18 (CH), 37.37 (CH_2), 48.77 (CH), 60.87 (CH_2), 65.14 (CH_2), 81.19 (CH), 105.06 (C), 127.23 (2 × CH), 127.63 (CH), 127.91 (CH), 129.03 (3×CH), 136.57 (CH), 136.57 (C), 140.73 (C), 140.87 (C); ESI-MS (*m/z*) 407 [M+H$^+$]; EI-HRMS Calcd. for $C_{26}H_{30}O_4$ [M$^+$]: 406.2144. Found: 406.2094; Anal. Calcd. for $C_{24}H_{28}O_4$: %C 76.82, %H 7.44. Found: %C 76.91 , %H 7.56.



Trioxane 10g: It was isolated in 30% yield; white solid, mp 146-148 °C; FT-IR (KBr cm^{-1}) 679, 780, 865, 1098, 1119, 1595, 1623, 2926, 3433; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54-2.04 (m, 14H+OH), 2.67 (s, 1H), 2.99 (q, 1H, J = 6.4 Hz), 3.75 (dd, 1H, J = 11.8, 3.4 Hz), 3.82 (dd, 1H, J = 11.8, 9.6 Hz), 3.86-3.95 (m, 2H), 4.78 (ddd, 1H, J = 9.6, 6.4, 3.4 Hz), 7.30 -7.59 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.28 (2 × CH), 29.96 (CH), 33.20 (CH_2), 33.33 (CH_2), 33.56 (CH_2), 33.66 (CH_2) 36.05 (CH), 37.36 (CH_2), 49.27 (CH), 60.93 (CH_2), 63.84 (CH_2), 79.53 (CH), 105.05 (C), 127.22 (2 × CH), 127.52 (CH), 127.63 (CH), 128.99 (2 × CH), 129.45 (2 × CH), 136.81 (C), 140.44 (C), 140.85 (C); ESI-MS (*m/z*) 381 [M+H$^+$]; EI-HRMS Calcd. for $C_{26}H_{30}O_4$ [M$^+$]: 406.2144. Found: 406.2179.



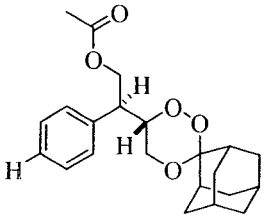
Trioxane 9h: It was isolated in 7% yield; white solid, mp 118-120 °C; FT-IR (KBr cm^{-1}) 675, 777, 839, 895, 1010, 1175, 1245, 1596, 1623, 2915, 3451; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36-1.98 (m, 24H+OH), 2.48 (brm, 1H), 2.78 (s, 1H), 2.94 (brq, 1H), 3.39 (brdd, 1H), 3.63 (dd, 1H, J = 11.9, 3.2 Hz), 3.86 (dd, 1H, J = 11.1, 6.4 Hz), 4.06 (dd, 1H, J = 11.1, 5.8 Hz), 4.57 (brdt, 1H), 7.12 (d, 2H, 8.3 Hz), 7.17 (d, 2H, 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.32 (CH_2), 27.06 (2 × CH_2), 27.32 (2 × CH), 30.41 (CH), 33.22 (CH_2), 33.43 (CH_2), 33.58 (CH_2), 33.62 (CH_2) 34.60 (2 × CH_2), 35.31 (CH), 37.37 (CH_2), 44.37 (CH), 48.77 (CH), 60.98 (CH_2), 65.22 (CH_2), 81.43 (CH), 104.93 (C), 127.63 (2 × CH), 128.47 (2 × CH), 134.52 (C), 147.79 (C); ESI-MS (*m/z*) 407 [M+H$^+$]; Anal. Calcd. for $C_{28}H_{42}O_4$: %C 75.69, %H 8.80. Found: %C 76.91, %H 9.18.



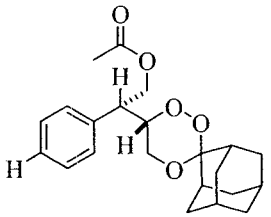
Trioxane 10h: It was isolated in 27% yield; white solid, mp 155-157 °C; FT-IR (KBr cm^{-1}) 690, 786, 895, 1099, 1117, 1598, 1613, 2925, 3443; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38-2.06 (m, 24H+OH), 2.49 (brm, 1H),2.68 (s, 1H), 2.93 (q, 1H, J = 6.5 Hz), 3.73 (dd, 1H, J = 11.8, 3.2 Hz), 3.82 (m, 2H), 3.90 (dd, 1H, J = 11.0, 6.5 Hz), 4.75 (ddd, 1H, J = 9.7, 6.5, 3.2 Hz), 7.11 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.36 (CH_2), 27.10 (2 × CH_2), 27.29 (CH), 27.31 (CH), 29.89 (CH), 33.18 (CH_2), 33.57 (CH_2), 33.67 (2 × CH_2), 34.58 (CH_2) 34.62 (CH_2), 36.10 (CH), 37.39 (CH_2), 44.34 (CH), 49.19 (CH), 60.19 (CH_2), 63.78 (CH_2), 79.69 (CH), 104.97 (C), 127.38 (2 × CH), 128.83 (2 × CH), 134.87 (C), 147.33 (C); ESI-MS (*m/z*) 407 [M+H$^+$]; EI-HRMS Calcd. for $C_{26}H_{36}O_4$ [M$^+$]: 412.2614. Found: 412.2612.

General procedure for acetylation of compounds 9a and 10a, (Acetylation of compound **9a** as representative): To a stirred solution of trioxane **9a** (0.100 g, 0.303 mmol) in dichloromethane (5ml), acetic anhydride (0.15 mL, 5 equiv), triethyl amine (0.15 mL 5 equiv) and catalytic amount of DMAP (2 mg) was added in succession and reaction mixture was allowed to stir for 1 hours. The reaction mixture was evaporated, and the crude product was purified by column chromatography over silica gel to furnish acetate **11a** (0.105 g, 93% yield) as an oil.

Compound **10a** was also acetylated by the same procedure to furnish acetate **12a**.



Trioxane 11a: It was isolated in 93% yield; oil; FT-IR (neat, cm^{-1}) 758, 1113, 1736, 2920; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-1.94 (m, 14H+OH), 1.96 (s, 3H), 2.71 (s, 1H) 3.13 (brq, 1H), 3.44 (brdd, 1H), 3.59 (dd, 1H, J = 11.6, 8.6 Hz), 4.41 (dd, 1H, J = 10.9, 7.8 Hz), 4.48 (dd, 1H, J = 10.9, 4.5 Hz), 4.56 (brdt, 1H) 7.21-7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.98 (CH_3), 27.25 (2 × CH), 29.85 (CH), 33.17 (CH_2), 33.36 (CH_2), 33.50 (CH_2), 33.54 (CH_2) 34.82 (CH), 37.30 (CH_2), 45.40 (CH), 60.55 (CH_2), 64.94 (CH_2), 79.28 (CH), 104.81 (C), 127.83 (CH), 128.63 (2 × CH), 128.95 (2 × CH) 137.26 (C), 170.87 (C); FAB-MS (*m/z*) 373 [M+H$^+$]; EI-HRMS Calcd. for $C_{22}H_{28}O_5$ [M$^+$]: 372.1937. Found: 372.1935.



Trioxane 12a: It was isolated in 95% yield; oil; FT-IR (neat cm^{-1}); 758, 1087, 1111, 1738, 2918; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-1.94 (m, 14H+OH), 2.03 (s, 3H), 2.61 (s, 1H), 3.10 (q, 1H, J = 6.6 Hz), 3.69 (dd, 1H, J = 11.7, 3.5 Hz), 3.77 (dd, 1H, J = 11.7, 9.6 Hz), 4.30 (dd, 1H, J = 11.2, 6.7 Hz), 4.36 (dd, 1H, J = 11.2, 7.4 Hz), 4.73 (ddd, 1H, J = 9.6, 5.9, 3.5 Hz) 7.22-7.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.01 (CH_3), 27.23 (CH), 27.25 (CH), 29.80 (CH), 33.12 (CH_2), 33.25 (CH_2), 33.53 (CH_2), 33.62 (CH_2) 36.09 (CH), 37.32 (CH_2), 46.12 (CH), 60.66 (CH_2), 64.49 (CH_2), 79.02 (CH), 104.97 (C) , 127.69 (CH), 128.79 (2 × CH), 128.88 (2 × CH), 136.95 (C), 170.88 (C); ESI-MS (*m/z*) 373 [M+H$^+$]; Anal. Calcd. for $C_{22}H_{28}O_5$: %C 70.94, %H 7.58. Found: %C 70.56, %H 7.20.

***In vivo* antimalarial efficacy test**

Random bred Swiss mice of either sex (25 ± 1 g) were inoculated intraperitoneally with 1×10^6 *Plasmodium yoelii nigeriensis* (MDR) parasites on day zero. The treatments with test compounds were administered to a group of 5 mice each at different dose levels ranging between 24-96 mg/kg × 4days. The compounds were administered as solutions in oil via oral route for 4 consecutive days i.e. from day 0 to day 3 in two divided dose daily. The drug dilutions were prepared in groundnut oil to contain the required amount of drug (1.2 mg for a dose of 96 mg/kg, 0.6 mg for a dose of 48 mg/kg and 3 mg for a dose of 24 mg/kg) in 0.2 mL of oil and administered either orally or intramuscularly for each dose. Mice treated with β-arteether was used as positive control.

Blood smears from experimental mice were observed on day 4, day 7, and day 10 and thereafter at regular interval till day 28 or death of the animal. The parasitaemia level on day 4 was compared with the vehicle control group and the percent suppression of parasitaemia in treated groups was calculated. The compounds which showed more than 100% clearance of parasitaemia were identified for further screening.

3.7 References and Notes

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12. The relative ratios of the two diastereomers were assigned on the basis of ^{1}H NMR and the compounds were characterized separately by FT-IR, 1D & 2D NMR, Low Resolution & High Resolution Mass and further by Analytical experiments. The stereochemistry assigned to the two diastereomers is only relative and is based upon coupling constants and NOESY experiments.
13. (a) One hundred percent suppression of parasitaemia means, the number of parasites are below the detection limit; (b) One hundred percent protection or 100% clearance of parasitaemia means all the treated mice survive until day 28. Similarly 60% and 20% protection mean only 60% and 20% of the treated mice survived until day 28.
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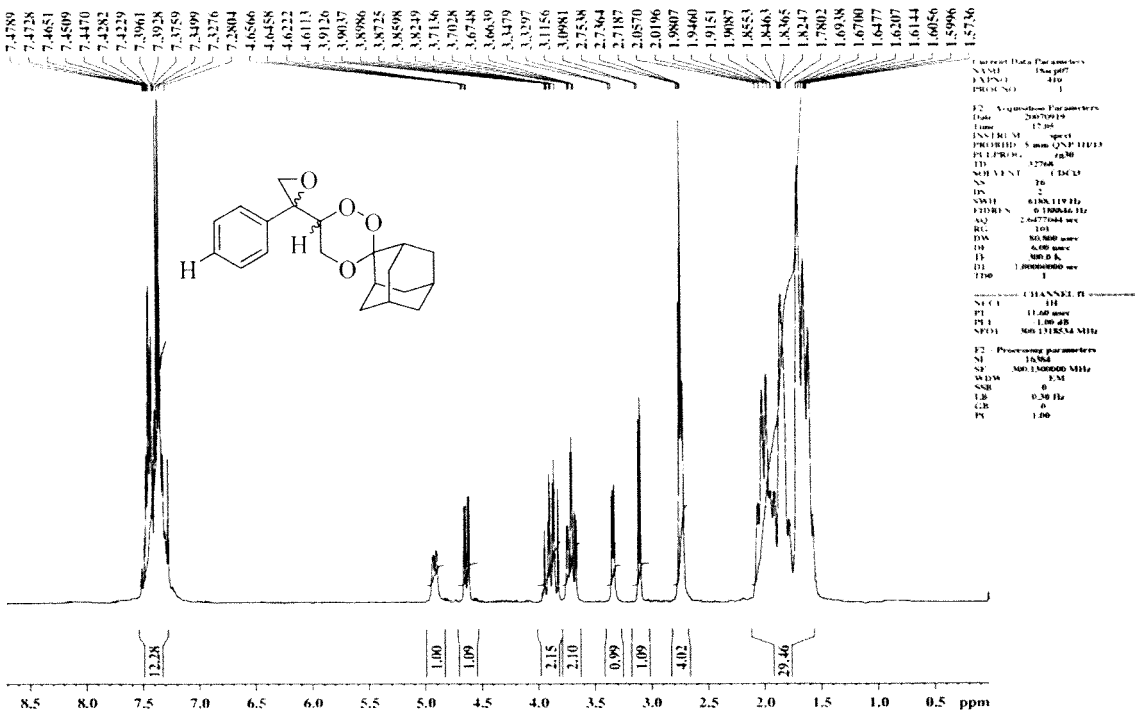
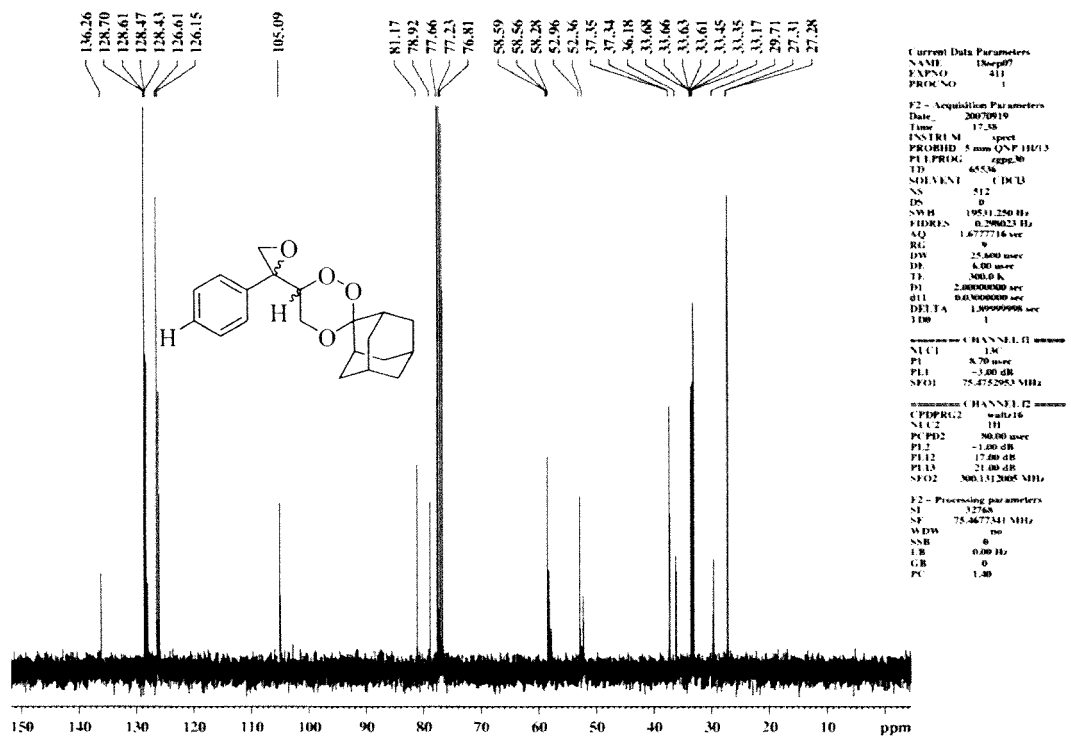
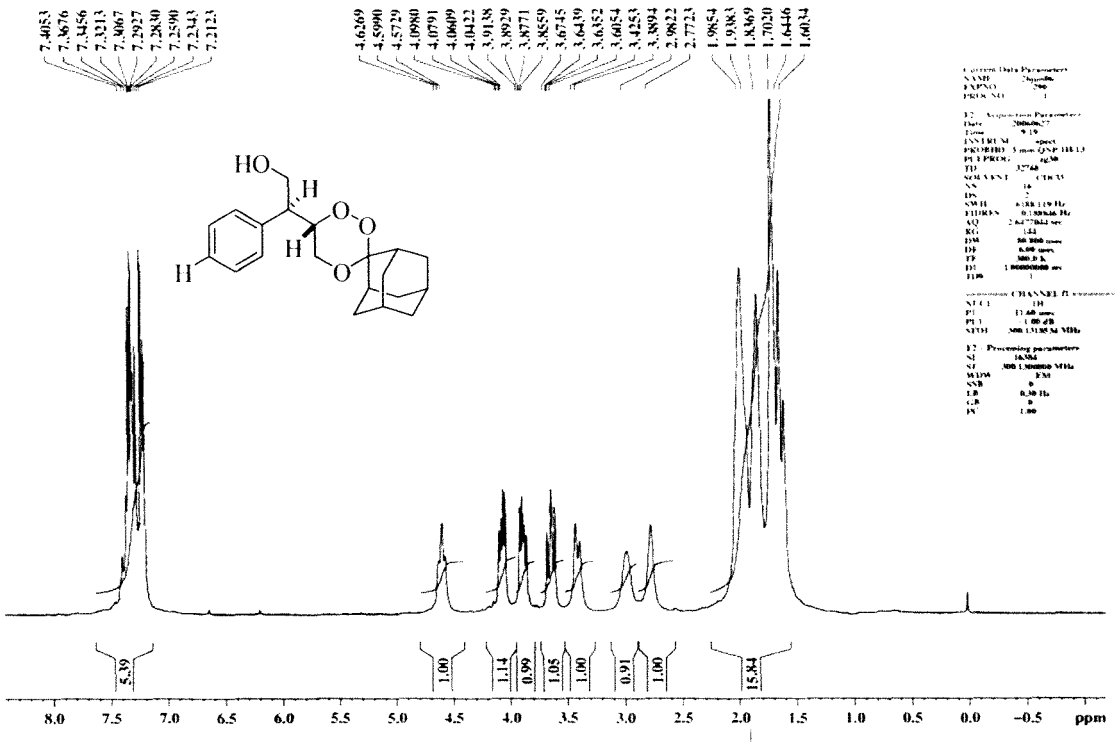


^{1}H NMR Spectra of **8a** (300 MHz, $CDCl_3$)



^{13}C NMR Spectra of **8a** (75 MHz, $CDCl_3$)



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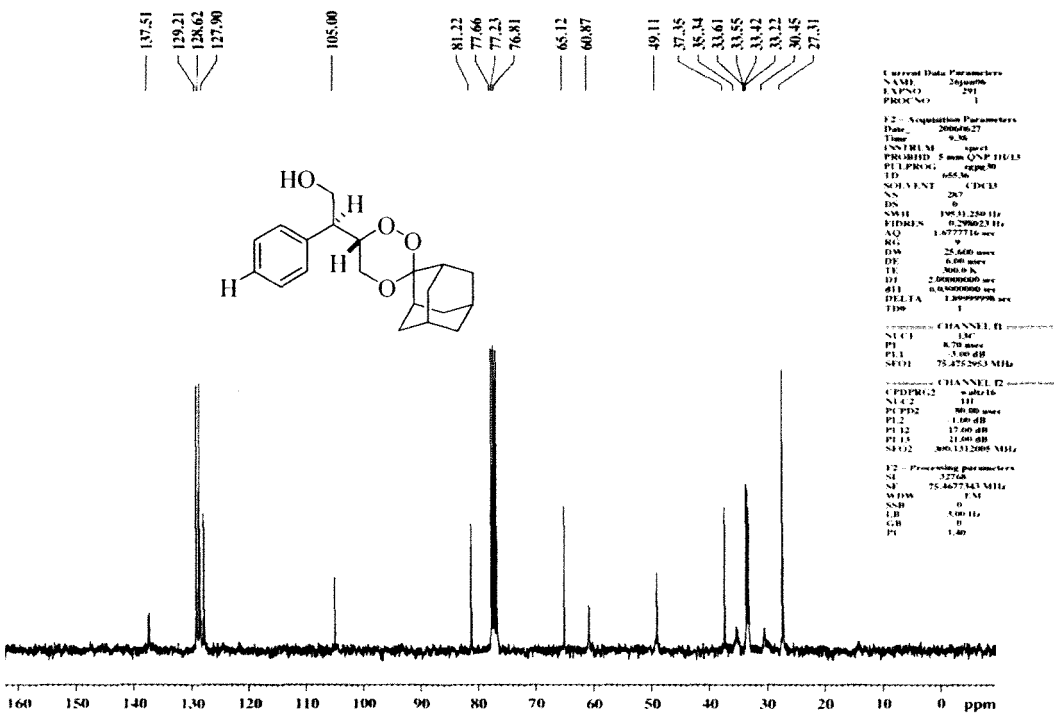

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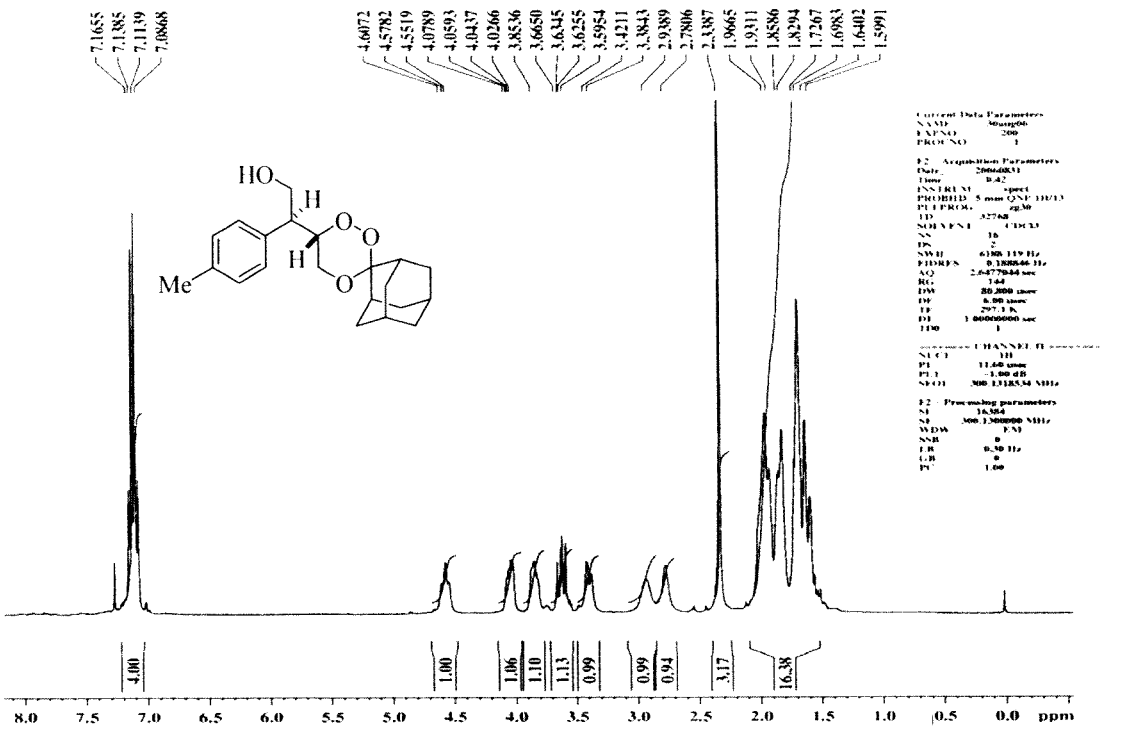

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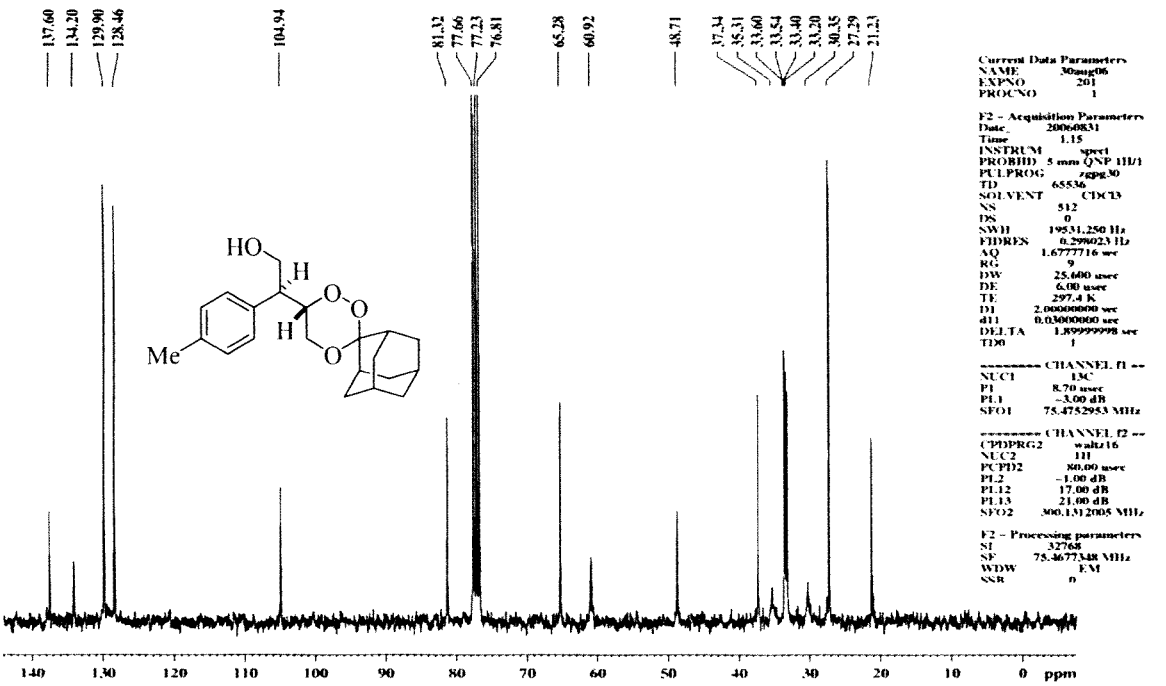

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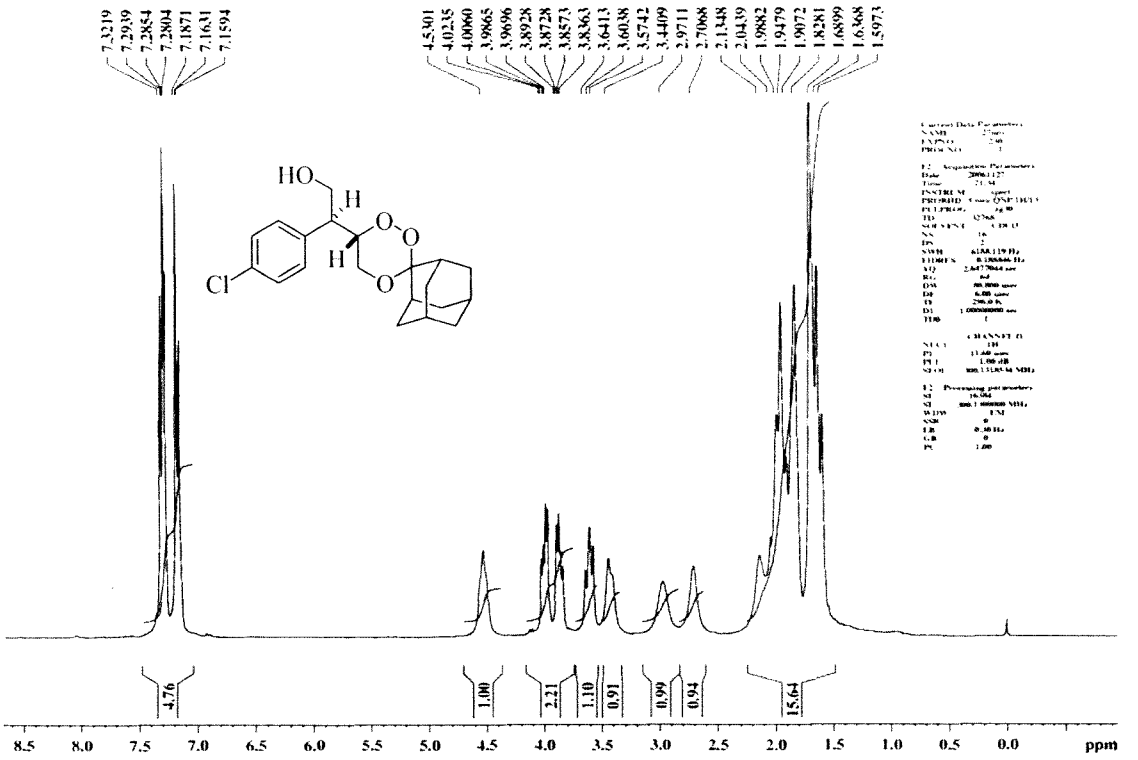

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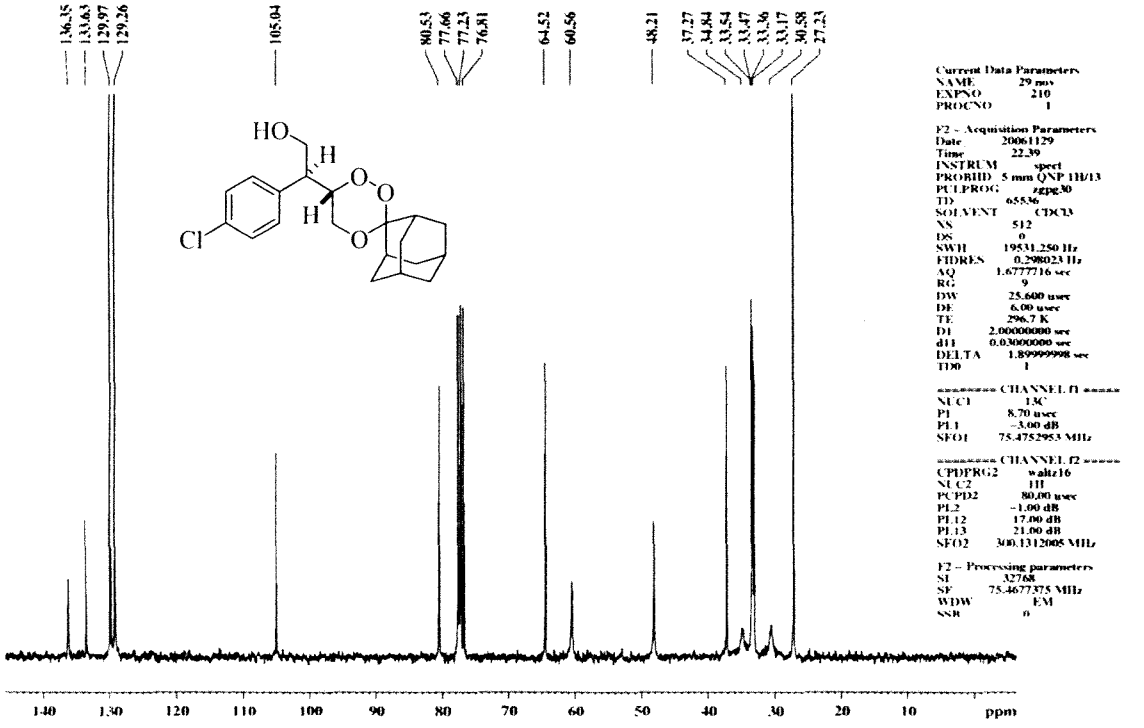

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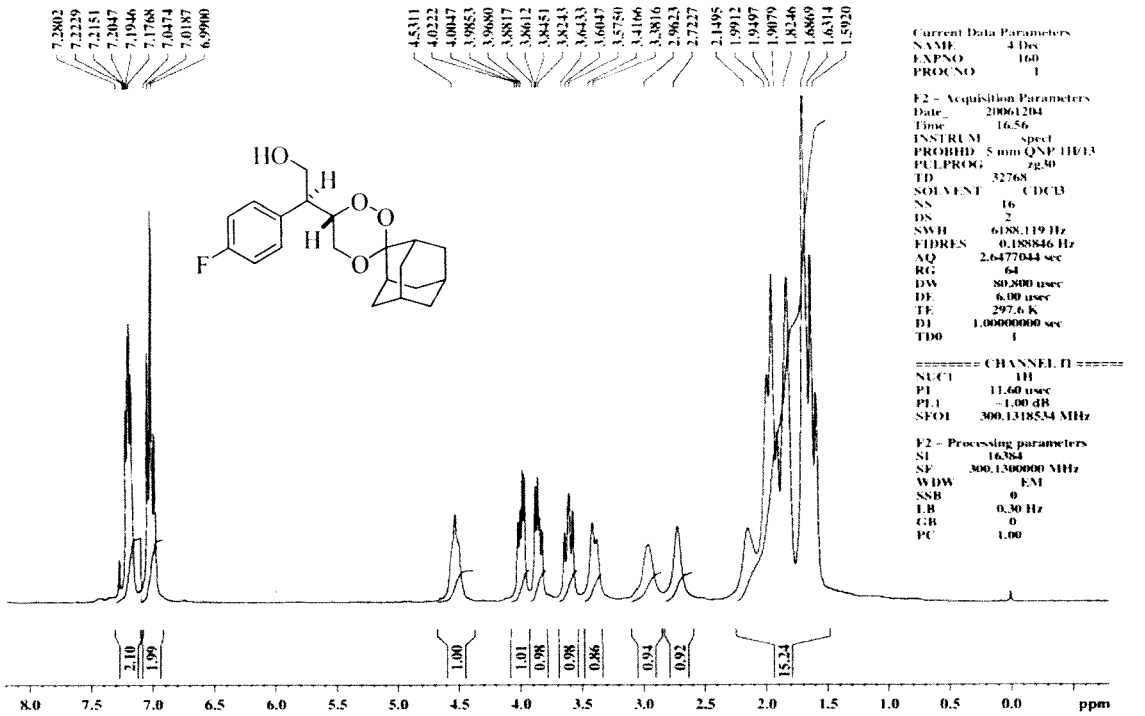

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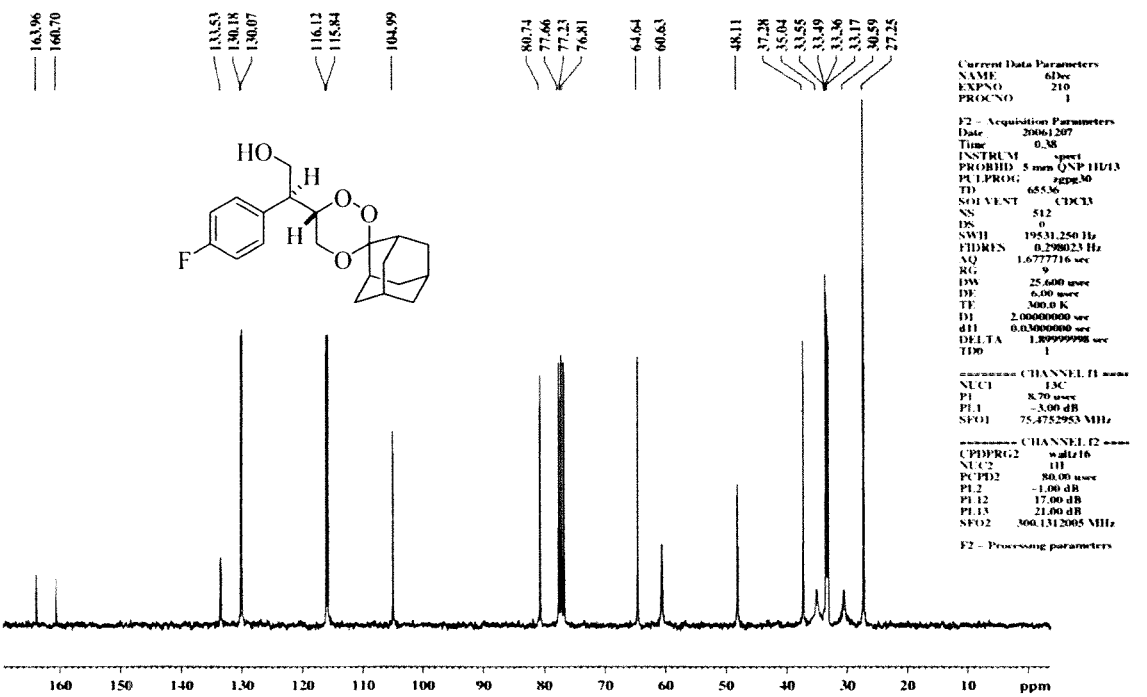

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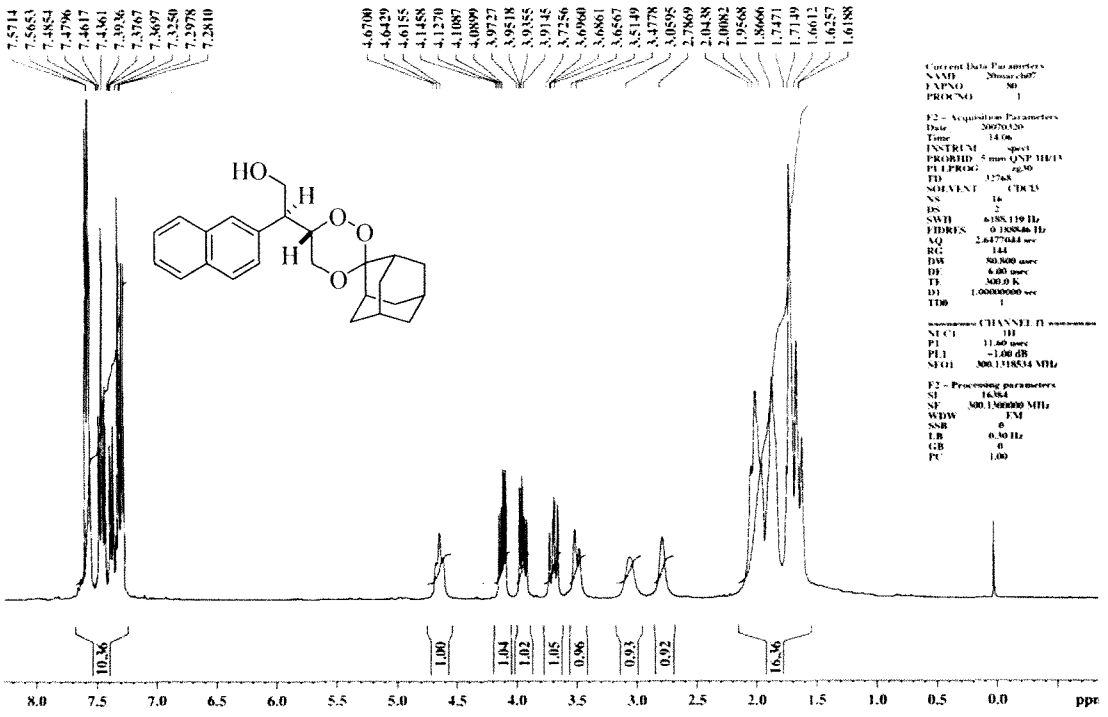

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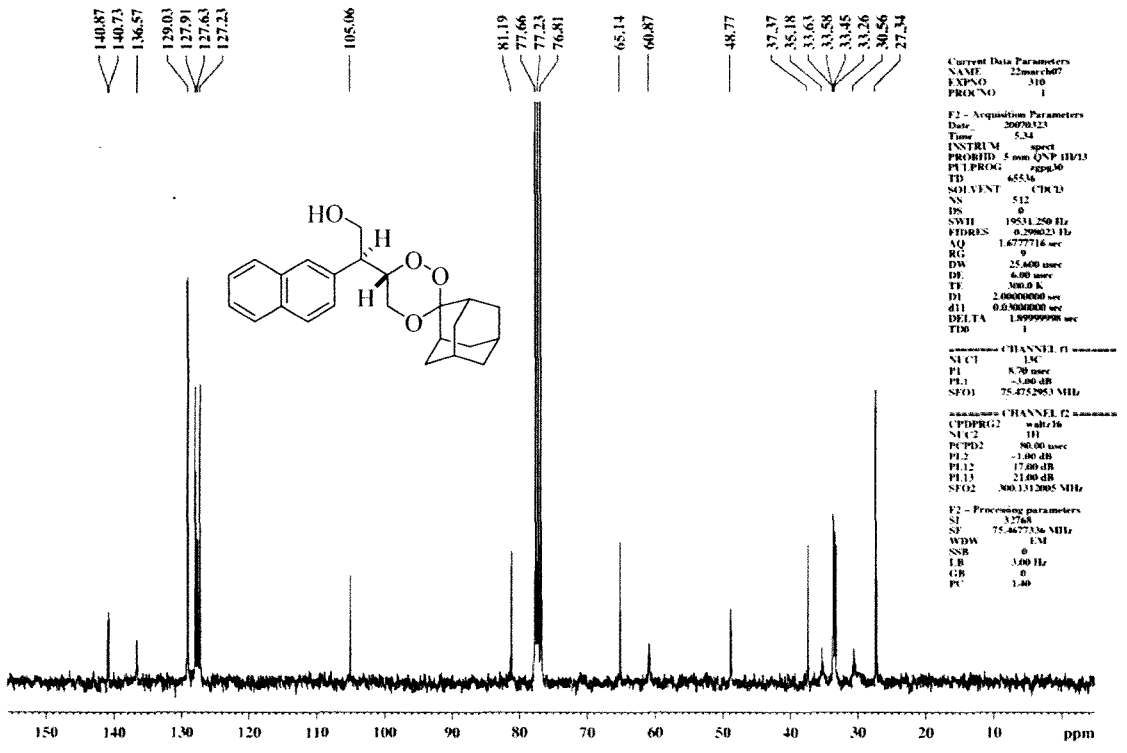

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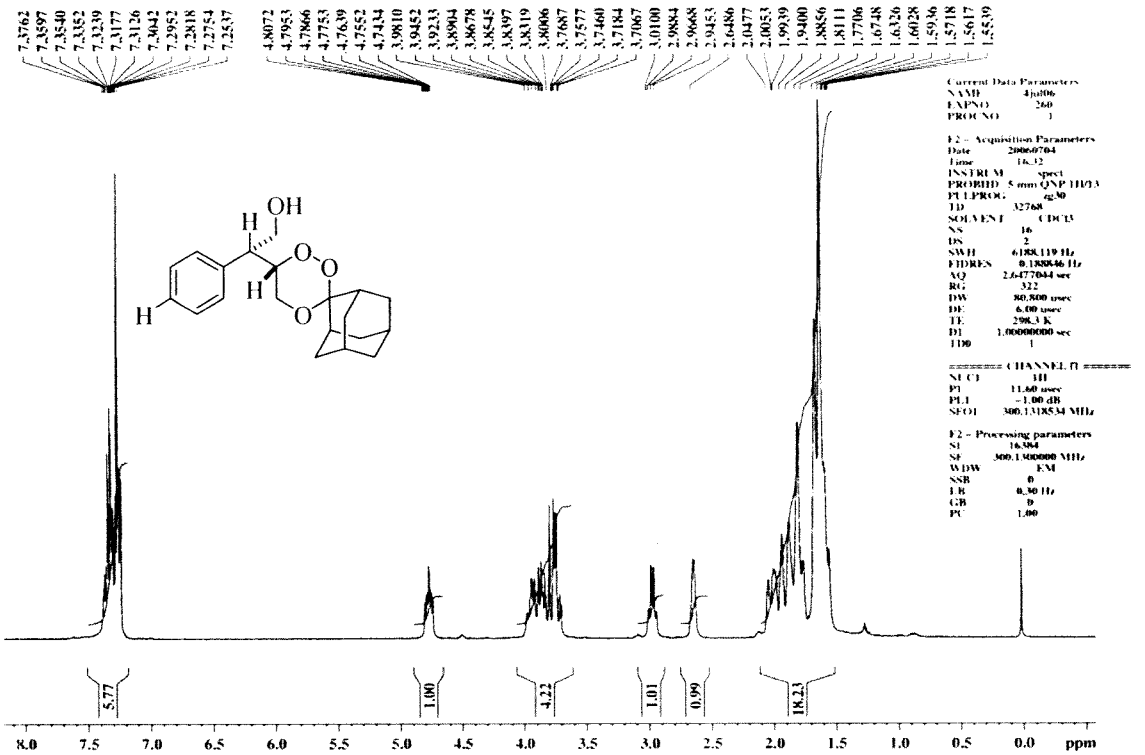

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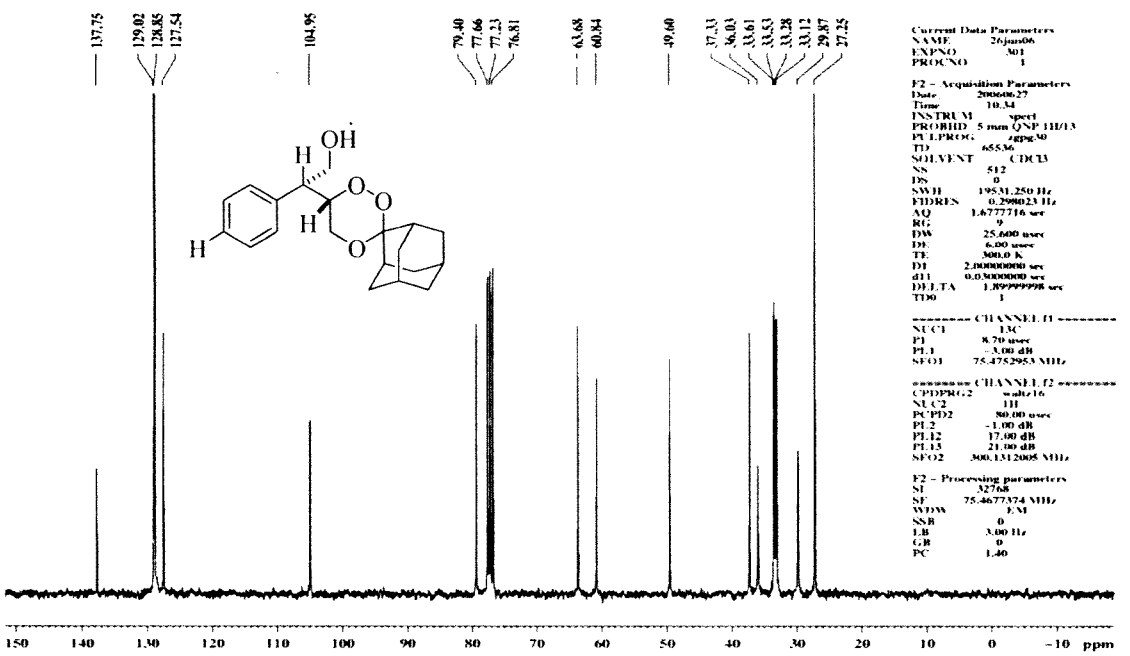

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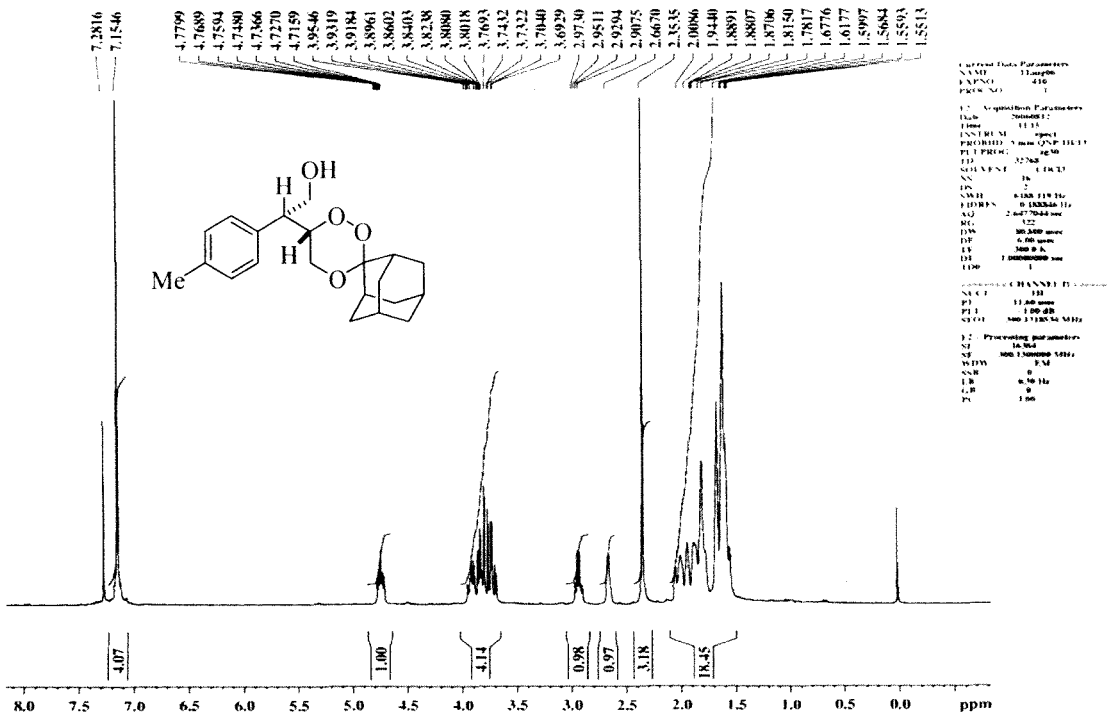

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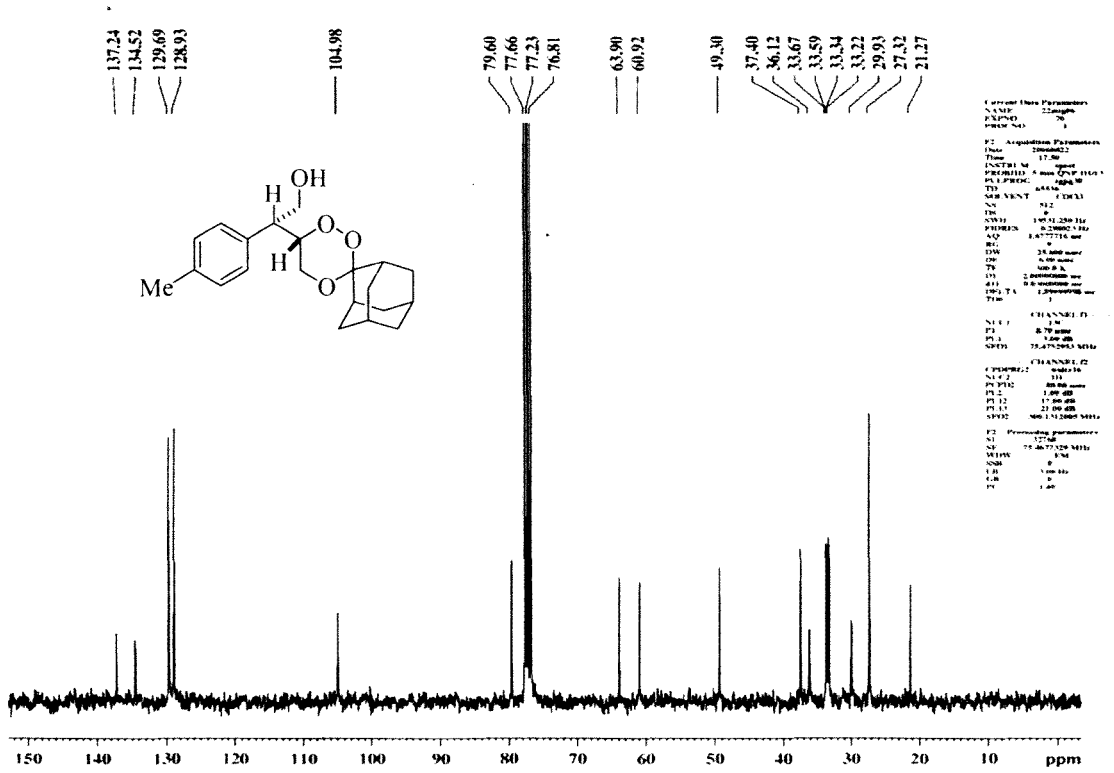

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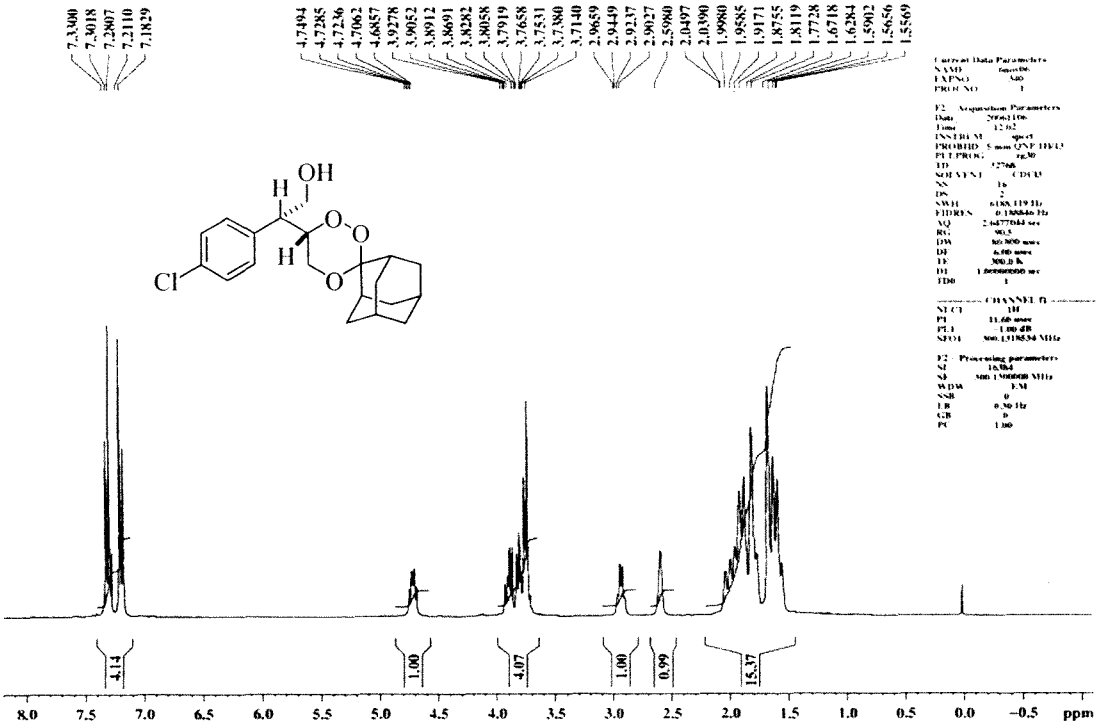

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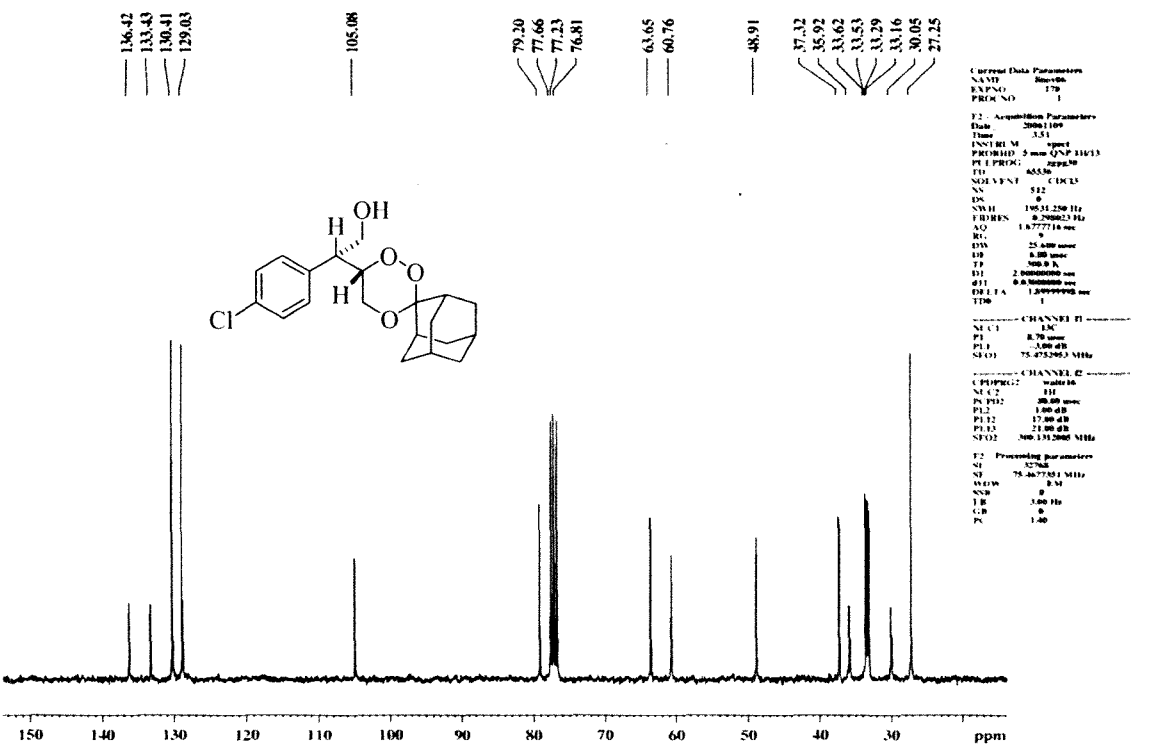

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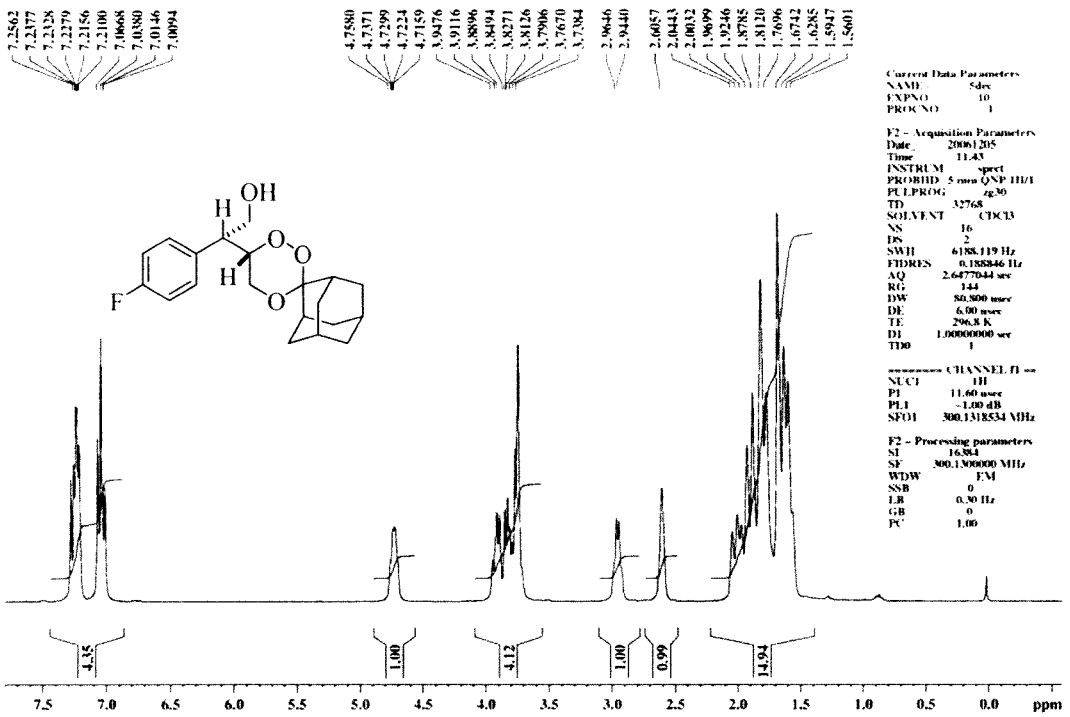

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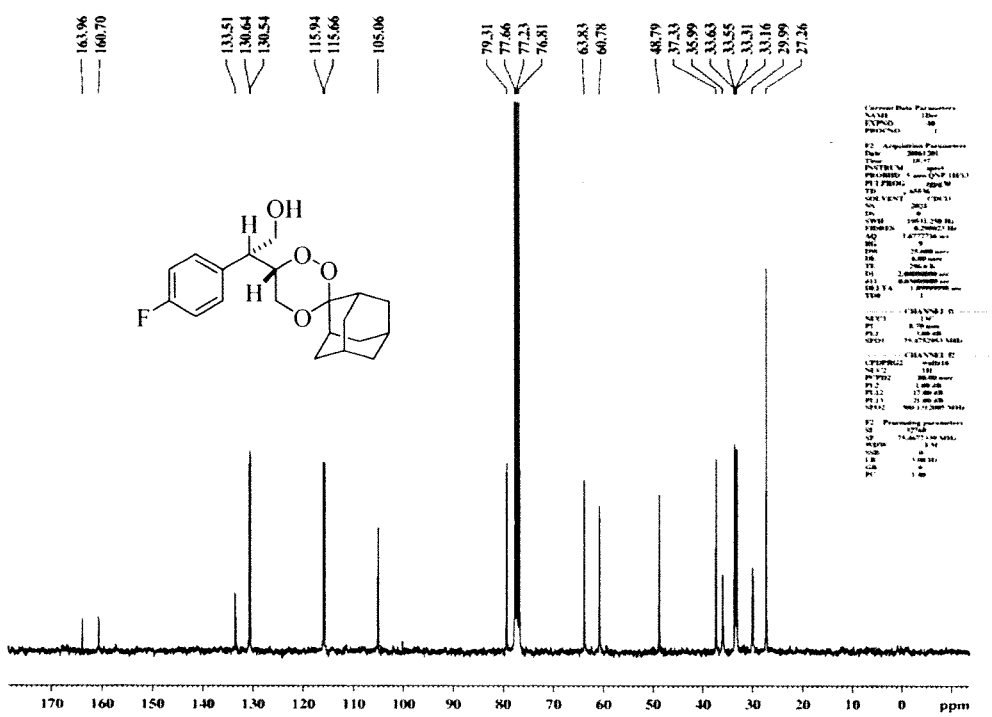

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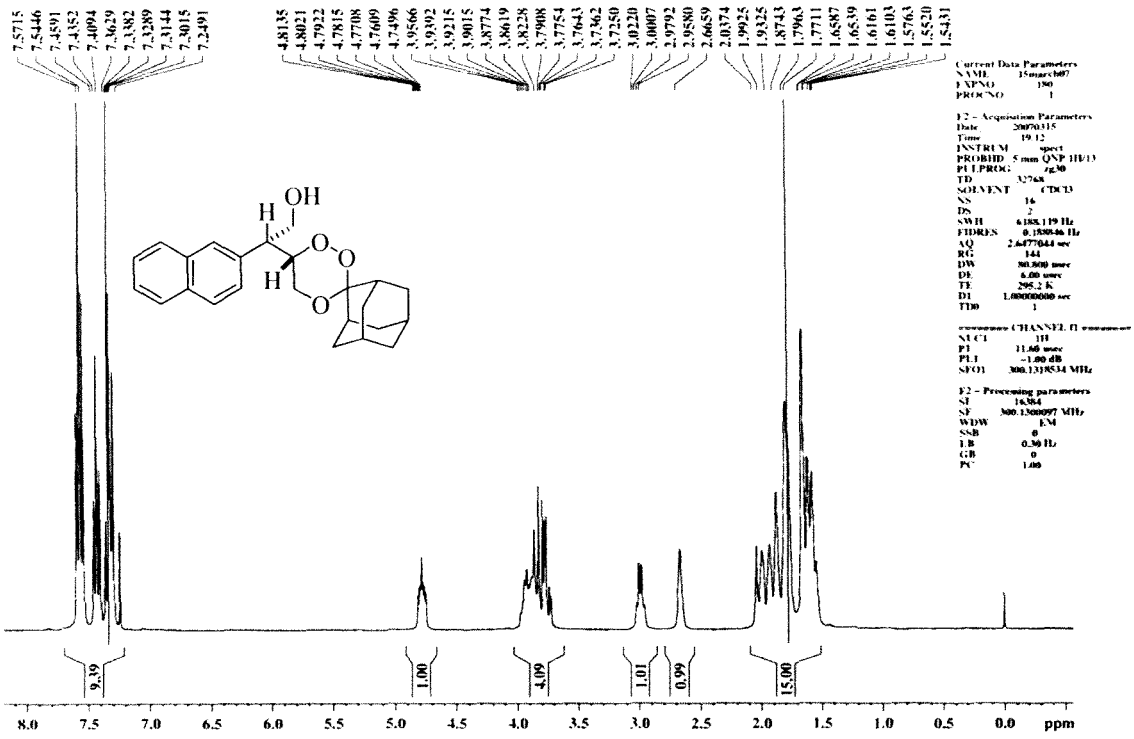

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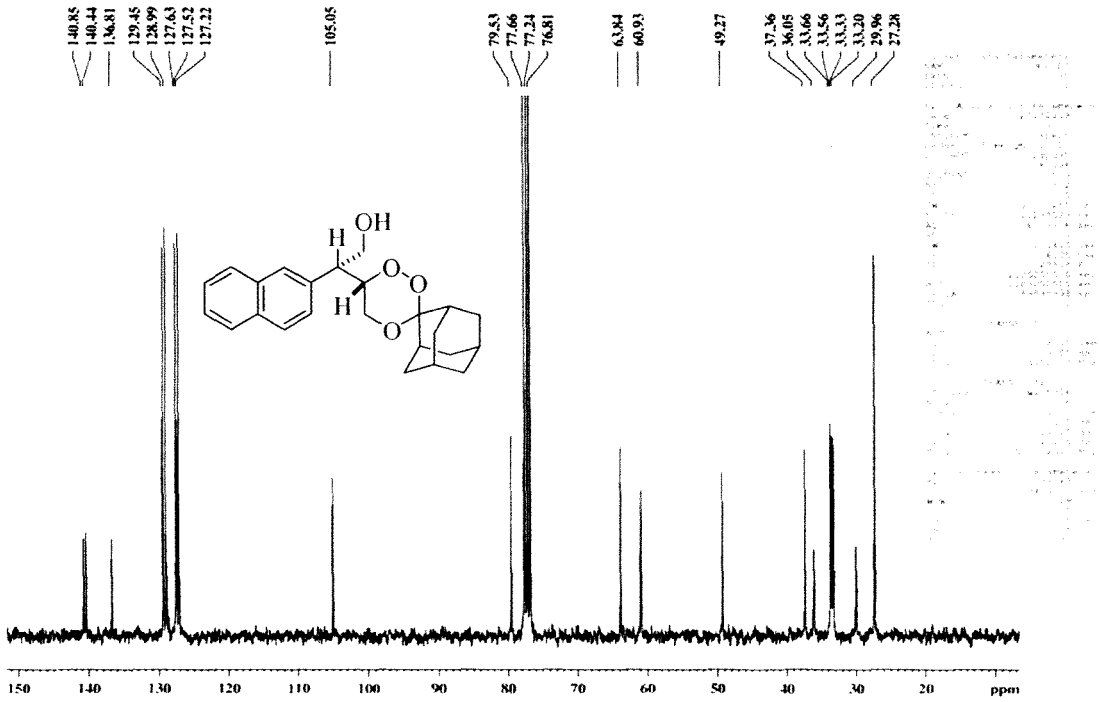

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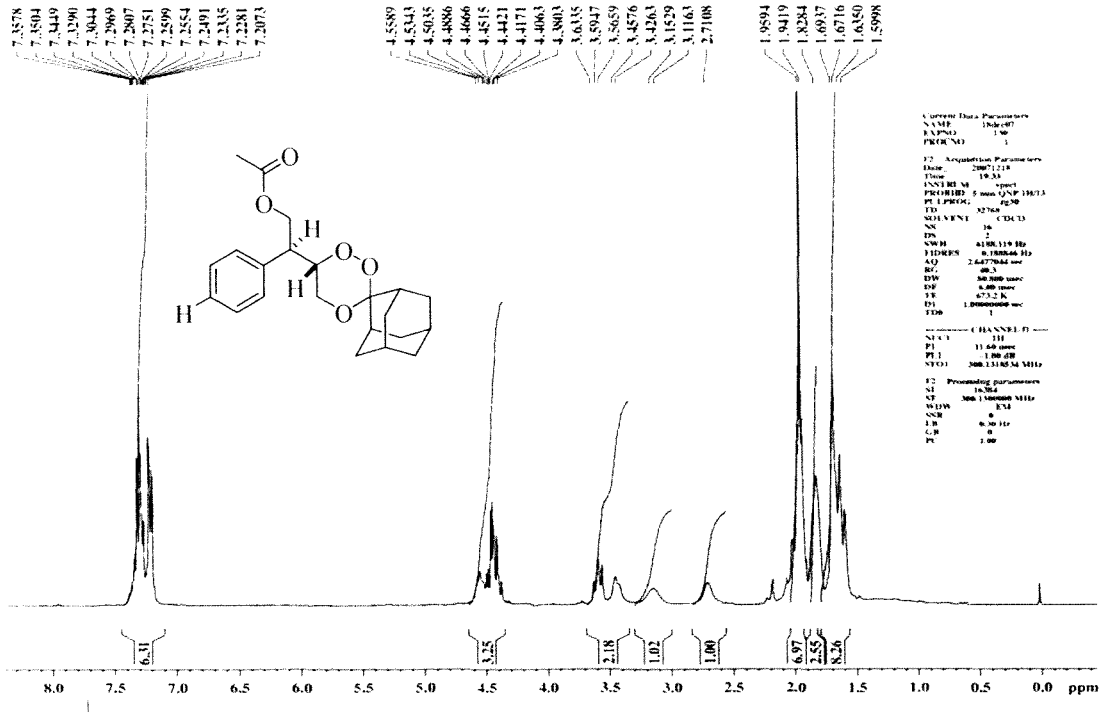

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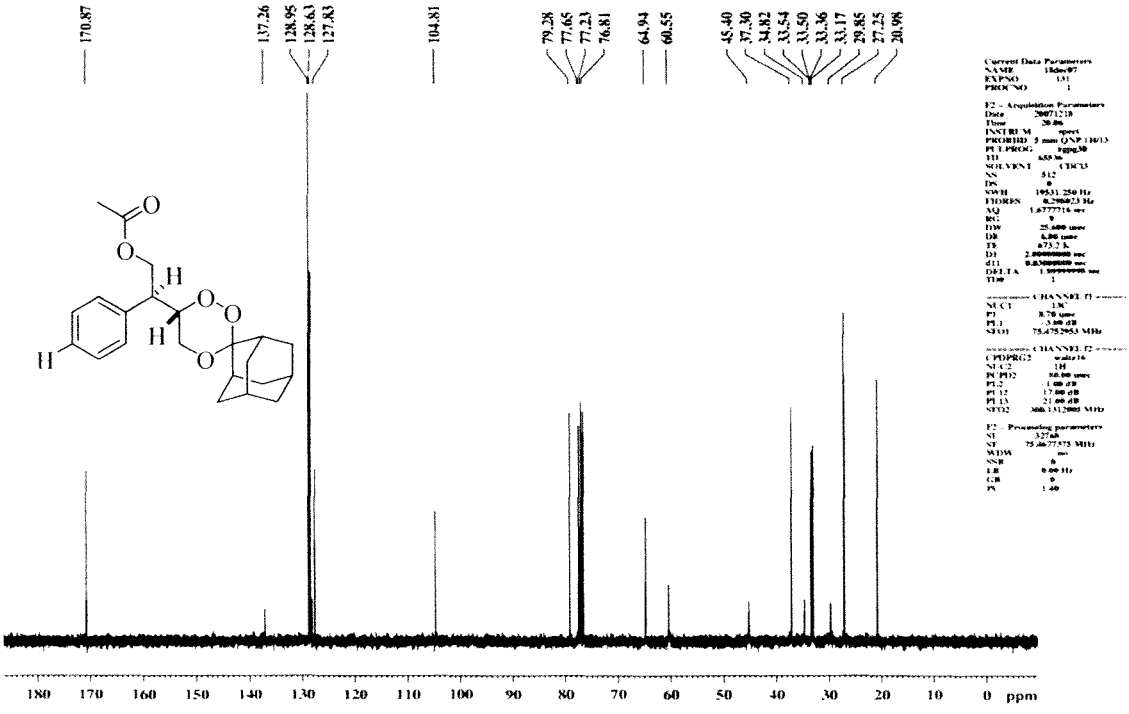
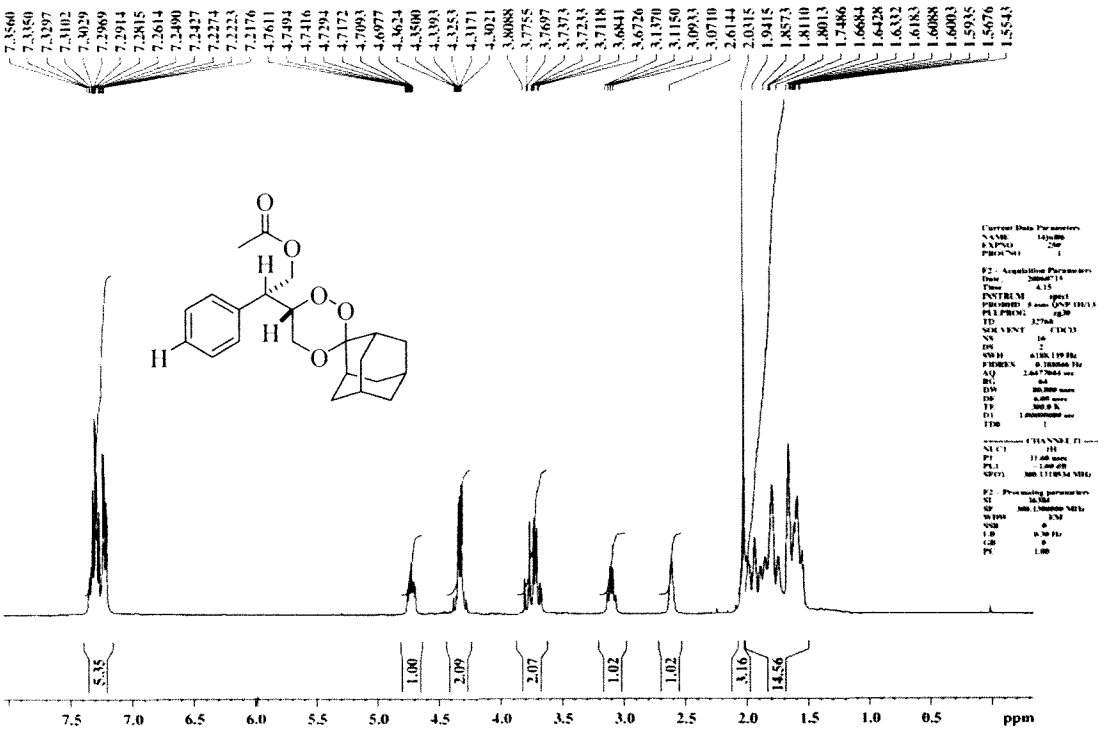


^{13}C NMR Spectra of **11a** (75 MHz, $CDCl_3$)



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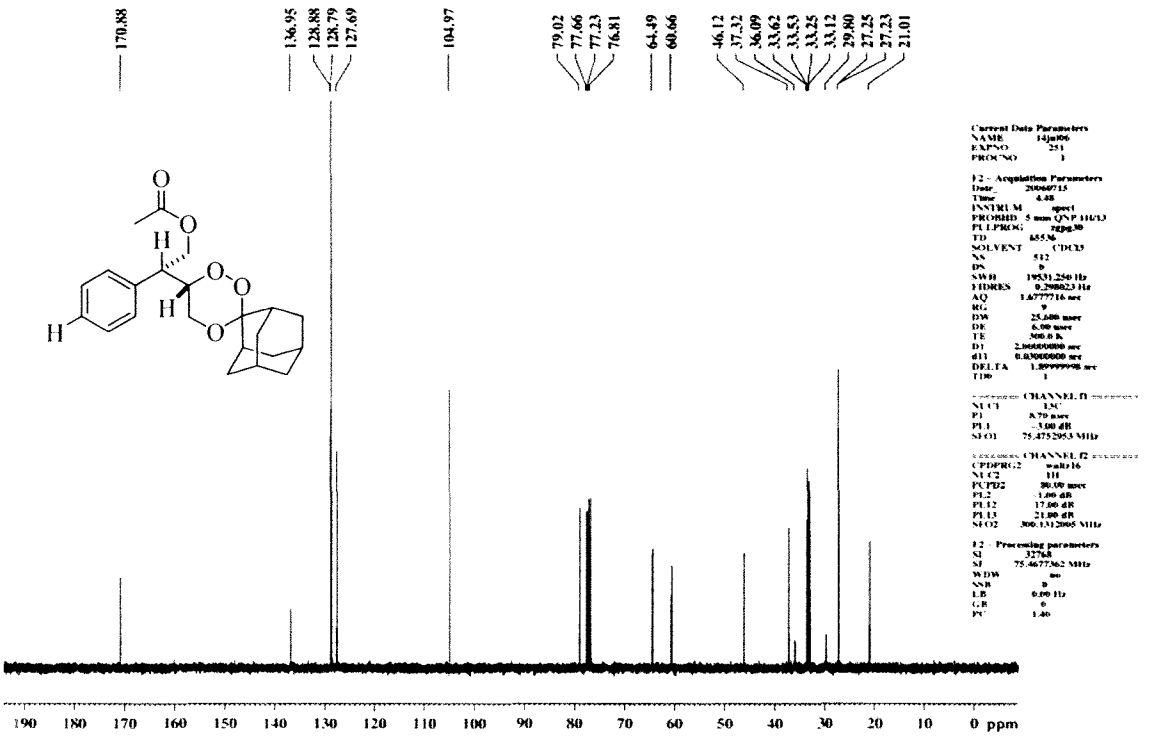


^{13}C NMR Spectra of **12a** (75 MHz, $CDCl_3$)

Chapter 4

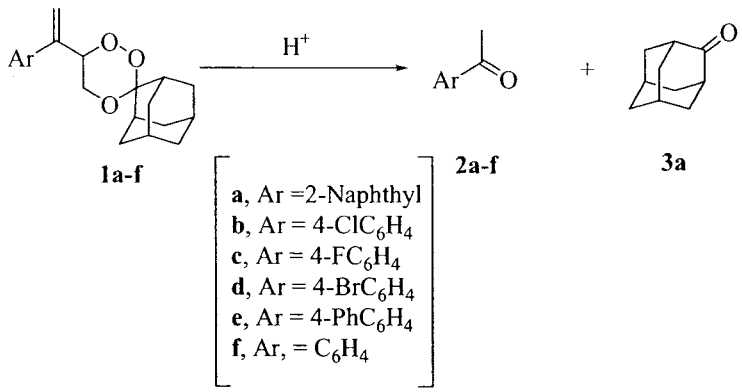
Acid Catalyzed Rearrangement of 6-Arylvinyl-1,2,4-Trioxanes

4.1 Introduction

1,2,4-Trioxanes[1] are relatively new class of peroxides and not much of efforts have gone into the chemistry of these compounds.[2] With the easy availability of 6-arylvinyl-1,2,4-trioxanes[3] by our photooxygenation route, we have undertaken a systematic study on the chemistry of these compounds. Earlier our laboratory have reported the base-catalyzed reaction of these 6-arylvinyl-1,2,4-trioxanes. In that context we have shown that 1,2,4-trioxane is a good protecting group for keto function, which can be deprotected under mild basic conditions.[4] We have taken a similar study on the behavior of these trioxanes under acidic conditions. In this chapter we report a novel acid catalyzed cleavage of 6-arylvinyl-1,2,4-trioxanes.

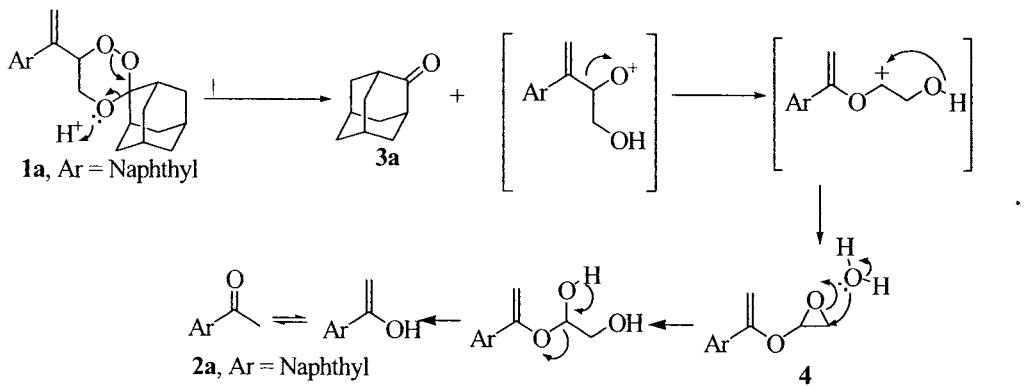
4.2 Chemistry

The acid catalyzed reaction was studied with various substituted 6-arylvinyl-1,2,4-trioxanes, which included adamantane based trioxanes **1a-f**, cyclohexane derived trioxanes **1g-h** and cyclopentane based trioxane **1i**. Trioxane **1a** was subjected to acid catalyzed reactions with different acid catalysts. Trioxane **1a** was found to be stable in 9N HCl at rt as only nominal decomposition was observed after 48 h. However when trioxane **1a** was refluxed in benzene in presence of catalytic amount of *p*-TSA for 15 min, it furnished compounds **2a** and **3a** in 32% and 69% yields, respectively. This acid catalyzed cleavage of trioxane **1a** was less facile when *p*-TSA was replaced with Amberlyst-15 under refluxing benzene, as it took 7 h for the reaction to complete and same products **2a** and **3a** were isolated in 32% and 78% yields, respectively. It took 8.5 h for reaction to complete when trioxane **1a** was stirred in benzene in presence of catalytic amount of $BF_3.Et_2O$ to furnish **2a** and **3a** in 38% and 72% yields. The acid catalyzed decomposition of trioxane **1a** with TMSOTf as acid catalyst was complete within 5 hr and furnished products **2a** and **3a** in 46% and 88% yields, respectively. The acid catalyzed decomposition of trioxane **1a** with other acid catalysts like 70% $HClO_4$, $TiCl_4$ and $AlCl_3$ also gave similar results. Trioxanes **1b-f** also behaved similarly (Scheme 4.1 and Table 4.1).



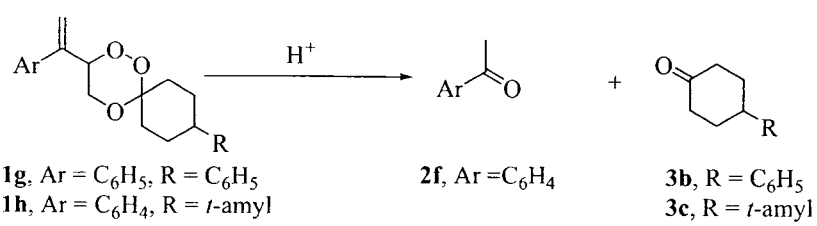
Scheme 4.1.

The proposed mechanism for this acid catalyzed rearrangement of substituted 6-arylvinyl-1,2,4-trioxanes has been shown in Scheme 4.2 taking trioxane **1a** as representative.



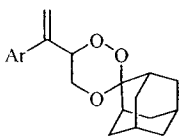
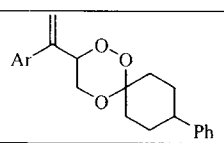
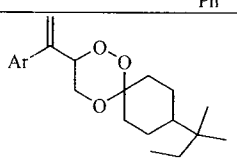
Scheme 4.2 Mechanism of acid-catalyzed rearrangement of 6-arylvinyl-1,2,4-trioxanes.

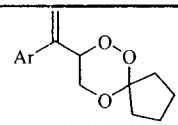
Among cyclohexyl derived trioxanes, compound **1g** when refluxed in benzene with catalytic amount of *p*-TSA furnished products **2f** and **3b** in 14% and 81% yields, respectively. Compound **1h** also behaved similarly and furnished compounds **2f** and **3c** in 11% and 51% yields, respectively. (Scheme 4.3)



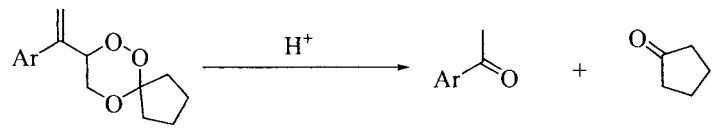
Scheme 4.3

Table 4.1. Reaction conditions and products formed upon acid catalyzed degradation of various substituted 6-arylvinyl-1,2,4-trioxanes.

Reactants			Reaction conditions	Products	
General Structure	**Compound No.**	**Ar**		**Aromatic ketones, (%yield)**	**Aliphatic ketones, (%yield)**
	**1a**	2-Naphthyl	*p*-TSA, PhH, 80 °C, 15 min	**2a** (32)	**3a** (69)
	1a	2-Naphthyl	Amberlyst -15, PhH, 80 °C, 7 h	**2a** (32)	**3a** (78)
	1a	2-Naphthyl	$BF_3.Et_2O$, PhH, rt, 8.5 h	**2a** (38)	**3a** (72)
	1a	2-Naphthyl	70% $HClO_4$, CH_3CN, rt, 12 h	**2a** (36)	**3a** (70)
	1a	2-Naphthyl	$TiCl_4$, THF, rt, 8 h	**2a** (45)	**3a** (87)
	1a	2-Naphthyl	$AlCl_3$, THF, rt, 14 h	**2a** (46)	**3a** (89)
	1a	2-Naphthyl	TMSOTf, THF, rt, 5 h	**2a** (46)	**3a** (88)
	1a	2-Naphthyl	9N HCl, CH_3CN, rt, 48 h	**2a** (4)	**3a** (7)
	1b	4-ClC_6H_4	*p*-TSA, PhH, 80 °C, 20 min	**2b** (22)	**3a** (81)
	1b	4-ClC_6H_4	*p*-TSA, PhH, rt, 48 h	-	-
	1c	4-FC_6H_4	*p*-TSA, PhH, 80 °C, 15 min	**2c** (14)	**3a** (81)
	1d	4-BrC_6H_4	*p*-TSA, PhH, 80 °C, 20 min	**2d** (30)	**3a** (83)
	1e	4-PhC_6H_4	*p*-TSA, PhH, 80 °C, 15 min	**2e** (31)	**3a** (74)
	1e	4-PhC_6H_4	Amberlyst -15, DCM, 38 °C, 30 h	**2e** (14)	**3a** (81)
	1e	4-PhC_6H_4	Amberlyst -15, PhH, 80 °C, 6 h	**2e** (36)	**3a** (62)
	1e	4-PhC_6H_4	$BF_3.Et_2O$, PhH, rt, 7.5 h	**2e** (51)	**3a** (82)
	1e	4-PhC_6H_4	9N HCl, CH_3CN, rt, 48 h	**2e** (4)	**3a** (6)
	1f	C_6H_5	*p*-TSA, PhH, 80 °C, 15 min	**2f** (13)	**3a** (63)
	**1g**	C_6H_5	*p*-TSA, PhH, 80 °C, 15 min	**2f** (14)	**3b** (81)
	**1h**	C_6H_5	*p*-TSA, PhH, 80 °C, 15 min	**2f** (11)	**3c** (51)

Reactants			Reaction conditions	Products	
General Structure	Compound No.	Ar		Aromatic ketones, (%yield)	Aliphatic ketones, (%yield)
	**1i**	4-PhC_6H_4	*p*-TSA, PhH, 80 °C, 15 min	**2e** (36)	**3d** (15)

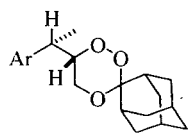
In cyclopentyl derived trioxanes only one compound **1i** was studied. The compound **1i** when refluxed in benzene using catalytic *p*-TSA furnished products **2e** and **3d** in 36% and 15% yields, respectively. (Scheme 4.4)



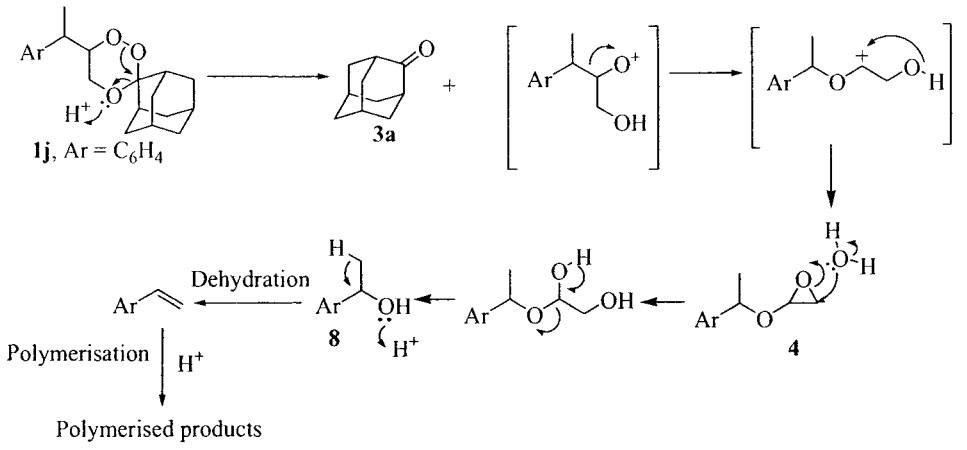
1i, Ar = 4-PhC_6H_4 **2e**, Ar = 4-PhC_6H_4 **3d**

Scheme 4.4.

Table 4.2 Reaction conditions and products formed upon acid catalyzed degradation of various substituted 6-arylethyl-1,2,4-trioxanes.

Reactants			Reaction conditions	Products	
General Structure	Compound No.	Ar		Aromatic ketones, (%yield)	Aliphatic ketones, (%yield)
	**1j**	C_6H_5	*p*-TSA, PhH, 80 °C, 30 min	-	**3a** (76)
	1k	4-ClC_6H_4	*p*-TSA, PhH, 80 °C, 30 min	-	**3a** (80)
	1l	4-PhC_6H_4	*p*-TSA, PhH, 80 °C, 35 min	-	**3a** (79)
	1m	2-Naphthyl	*p*-TSA, PhH, 80 °C, 30 min	-	**3a** (79)

This acid catalyzed decomposition was also studied with saturated (arylethyl) analogues, **1j 1k**, **1l** and **1m** under similar reaction conditions but in all the cases 2-adamantanone **3a** was the only isolable product and in no case corresponding acetophenones **2f, 2b, 2e** and **2a** were obtained (Table 4.2). The possible mechanism has been shown in Scheme 4.5.



Scheme 4.5 Mechanism of acid-catalyzed rearrangement of 6-arylethyl-1,2,4-trioxanes.

4.3 Conclusion

A novel acid-catalyzed rearrangement of 1,2,4-trioxanes is reported. This reaction provides an interesting example of migration of aryl-vinyl group similar to that observed in Baeyer-Villiger oxidation.[5]

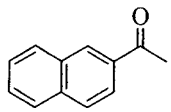
4.4 Experimental Section

General details and instrumentation: All glass apparatus were oven dried prior to use. Melting points were taken in open capillaries on Complab melting point apparatus and are presented uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 MHz and 300 MHz respectively for 1H; 50 MHz and 75 MHz respectively for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quintet (quin), multiplet (m), and broad (br). Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (EI-HRMS) were obtained on JEOL MS route 600H instrument.

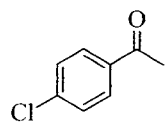
Elemental analyses were performed on Vario EL-III C H N S analyzer (Germany), and values were within (0.4% of the calculated values). Column chromatography was performed over Merck silica gel (particle size: 60-120 Mesh) procured from Qualigens (India), or flash silica gel (particle size: 230-400 Mesh). All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used without further purification. Nomenclature and Log *p* values of the compounds were assigned using Chem Draw Ultra 7.0 software.

General procedure for acid catalyzed cleavage of 1,2,4-trioxanes, (Cleavage of trioxane **1a** as representative using *p*-TSA): A solution of trioxane **1a** (800 mg, 2.210 mmol) and *p*-TSA (80 mg) in benzene (8mL) was refluxed for 15 min. The reaction mixture was cooled to rt, quenched with water (10 mL) and extracted with ether (3 × 15 mL). The combined organic layer was concentrated and purified by column chromatography to furnish acetophenone **2a** (120 mg, 32% yield) and 2-adamantanone **3a** (230 mg, 69% yield).

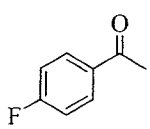
Other trioxanes **1b-m** were also cleaved by the above reported procedure by varying acid catalyst, temperature and solvent.



2-Acetylnaphthalene (2a): white solid, mp 52-55 °C; FT-IR (KBr cm^{-1}) 1625, 1673, 3432; ^1H NMR (300 MHz, $CDCl_3$); δ 2.63 (s, 3H), 7.44-8.36 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.58 (CH_3), 123.81 (CH), 126.72 (CH), 127.72 (CH), 128.33 (CH), 128.41 (CH), 129.51 (CH), 130.13 (CH), 132.44 (C), 134.39 (C), 135.50 (C), 197.94 (C) ; ESI-MS (*m/z*) 171 [M+H$^+$].

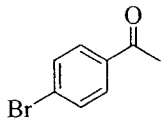


4-Chloroacetophenone (2b): oil; FT-IR (neat cm^{-1})1589, 1687, 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 7.39 (d, 2H, *J*=8.6 Hz), 7.86 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.35 (CH_3), 128.72 (2 × CH), 129.62 (2 × CH), 135.35 (C), 139.32 (C), 196.53 (C); ESI-MS (*m/z*) 121 [M+H$^+$].

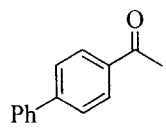


4-Fluoroacetophenone (2c): oil; FT-IR (neat cm^{-1}) 1598, 1685, 3430; ^1H NMR (300 MHz, $CDCl_3$); δ 2.58 (s, 3H), 7.07-7.15 (m, 2H), 7.94-8.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.41 (CH_3), 115.56 (d, 2 × CH, $J_{C\text{-}F}$ = 22 Hz),

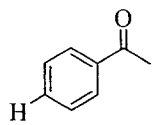
130.19 (d, 2 × CH, $J_{C\text{-}F}$ = 9.0 Hz), 133.56 (d, C, $J_{C\text{-}F}$ = 2.3 Hz), 165.68 (d, 2 × CH, $J_{C\text{-}F}$ = 253 Hz), 196.38 (C); ESI-MS (*m/z*) 178 [M+K$^+$].



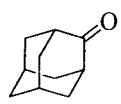
4-Bromoacetophenone (2d): oil; FT-IR (neat cm^{-1})1581, 1672, 3450; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 7.55 (d, 2H, J = 8.6 Hz), 7.78 (d, 2H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.41 (CH_3), 128.11 (C), 129.74 (2 × CH), 131.73 (2 × CH), 135.70 (C), 196.71 (C); ESI-MS (*m/z*) 221 [M+Na]$^+$, 223 [M+Na+2$^+$].



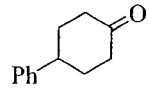
4-Acetylbiphenyl (2e): white solid, mp 116-118 °C; FT-IR (KBr cm^{-1}) 1599, 1679, 3344; ^{1}H NMR (300 MHz, $CDCl_3$); δ 2.61 (s, 3H), 7.24-8.02 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.76 (CH_3), 127.32 (2 × CH), 127.38 (2 × CH), 128.37 (CH), 129.04 (2 × CH), 129.09 (2 × CH), 135.97 (C), 139.96 (C), 145.86 (C), 197.84 (C) ; ESI-MS (*m/z*) 197 [M+H$^+$].



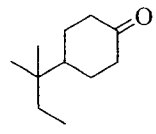
Acetophenone (2f): oil; FT-IR (neat cm^{-1})1600, 1685, 3445; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 7.39-7.94 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.38 (CH_3), 128.12 (2 × CH), 128.40 (2 × CH), 132.94 (CH), 136.89 (C), 197.87 (C); FAB-MS (*m/z*) 121 [M+H$^+$].



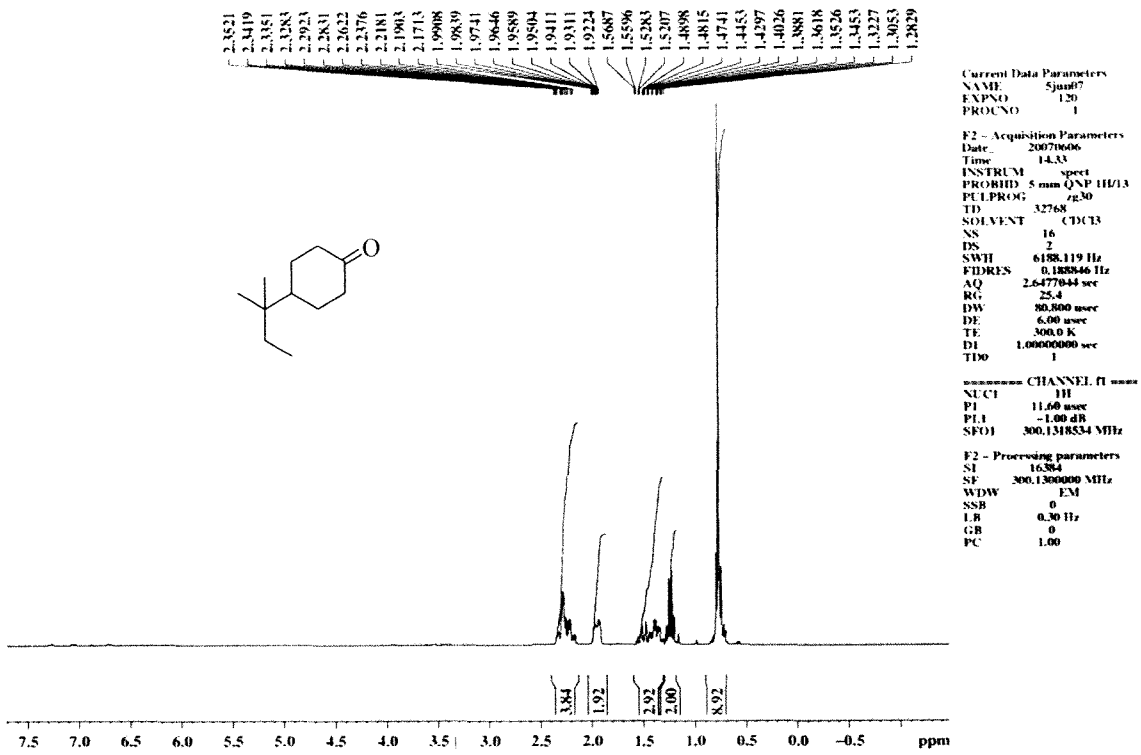
2-Adamantanone (3a): white solid; mp 256-259 °C; FT-IR, (KBr cm^{-1}) 1717, 2920; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95-2.12 (m, 12H), 2.53 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.23 (CH_2), 36.03 (CH), 38.98(CH), 46.73 (CH_2), 217.67 (C); FAB-MS (*m/z*) 151 [M+H$^+$].



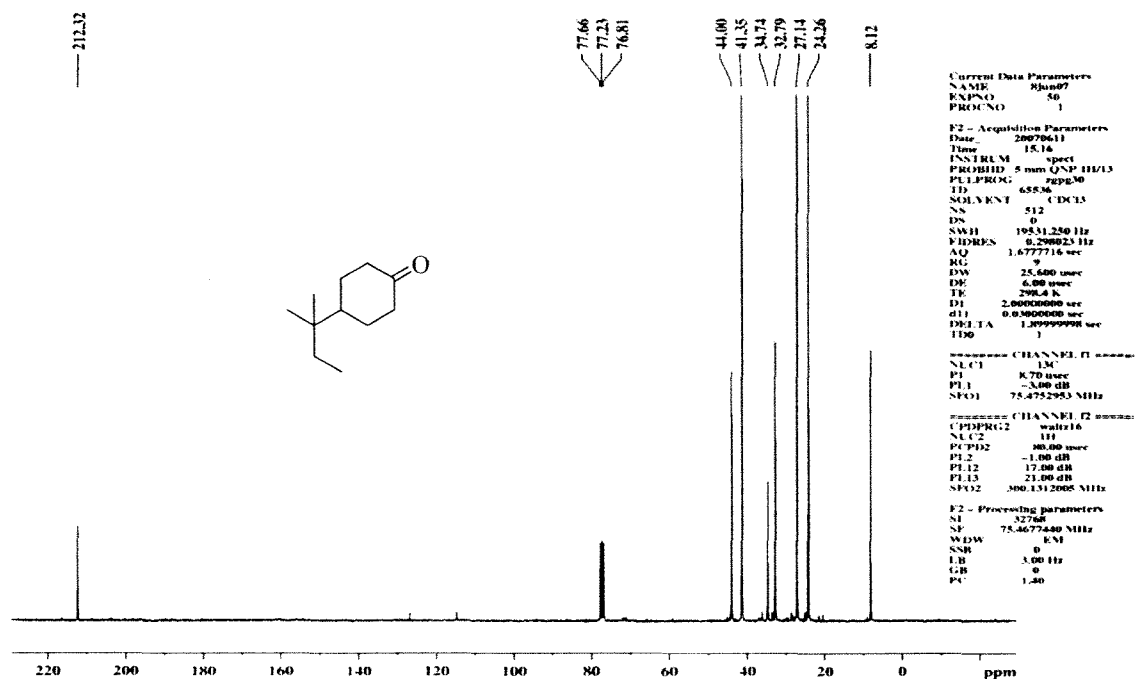
4-Phenylcyclohexanone (3b): white solid, mp 73-77 °C; FT-IR (KBr cm^{-1}) 1599, 1704, 2940 3388; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.89-2.56 (m, 8H), 3.04 (tt, 1H, J = 12.0, 3.3 Hz) 7.23-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.11 (2 × CH_2), 41.52 (2 × CH_2), 42.89 (CH), 126.73 (CH), 126.83 (2 × CH_2), 128.75 (2 × CH_2), 144.93 (C), 211.36 (C); FAB-MS (*m/z*) 175 [M+H$^+$].



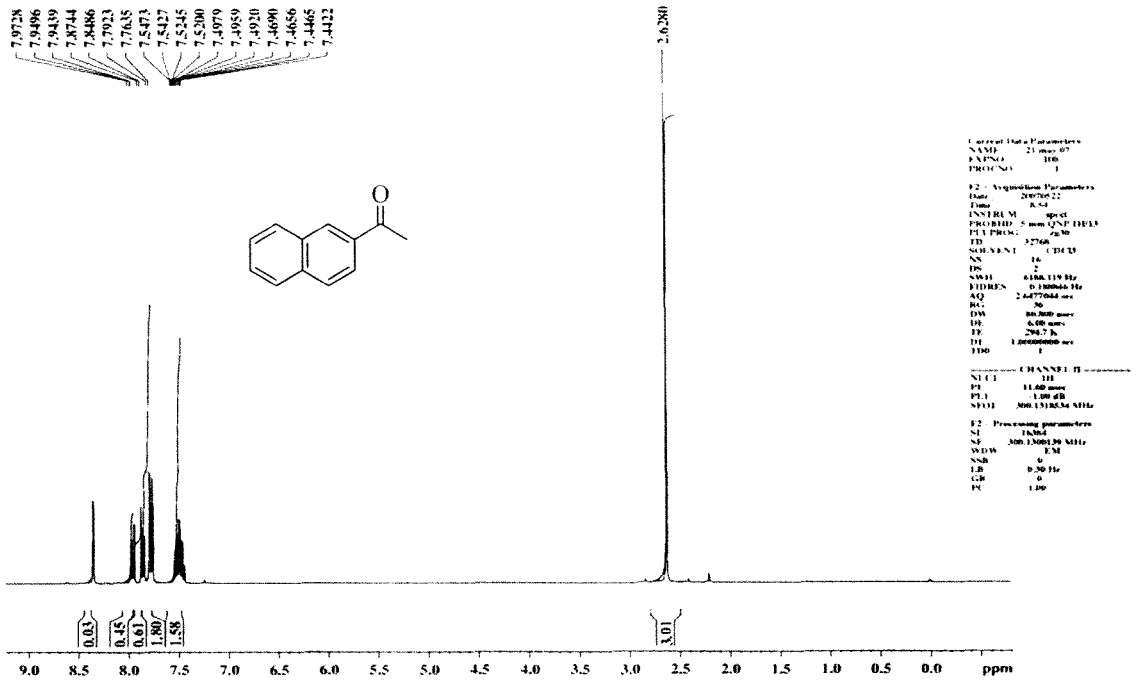
4-*tert*-Amylcyclohexanone (3c): oil; FT-IR (neat cm^{-1}); FT-IR (KBr cm^{-1}) 1719, 2963; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.76 (t, 3H, J= 7.4 Hz), 0.78 (s, 6H),



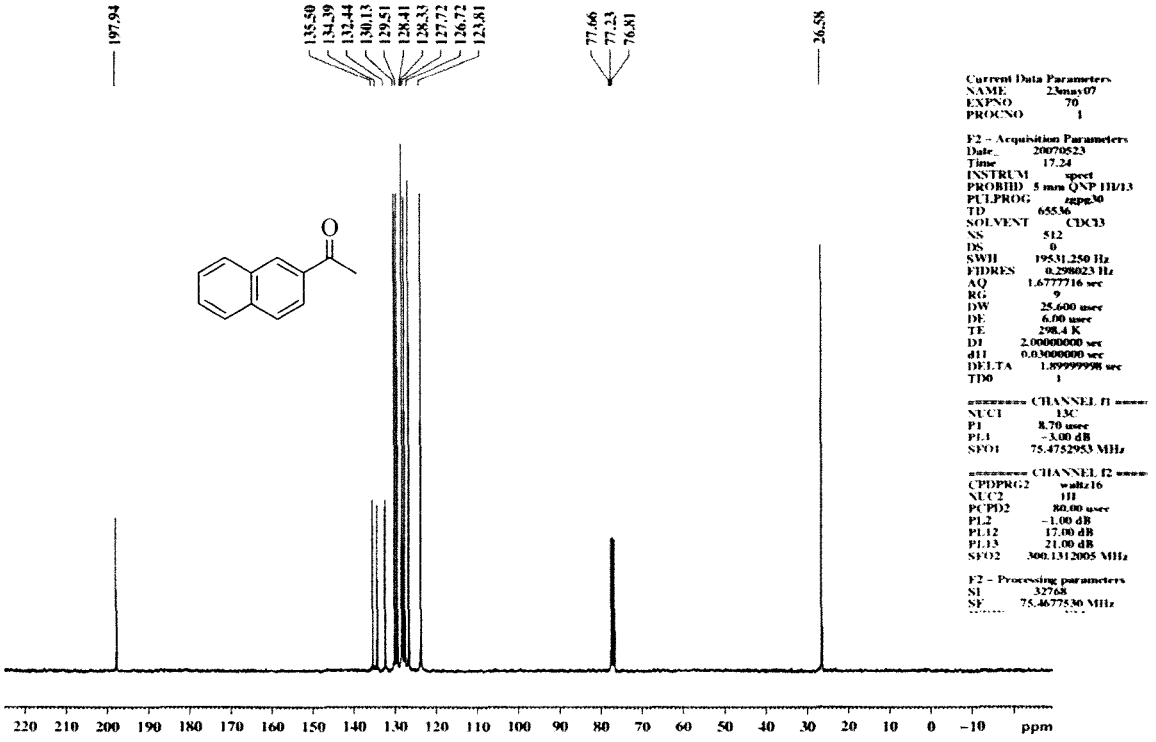
^{1}H NMR Spectra of **3c** (300 MHz, $CDCl_3$)



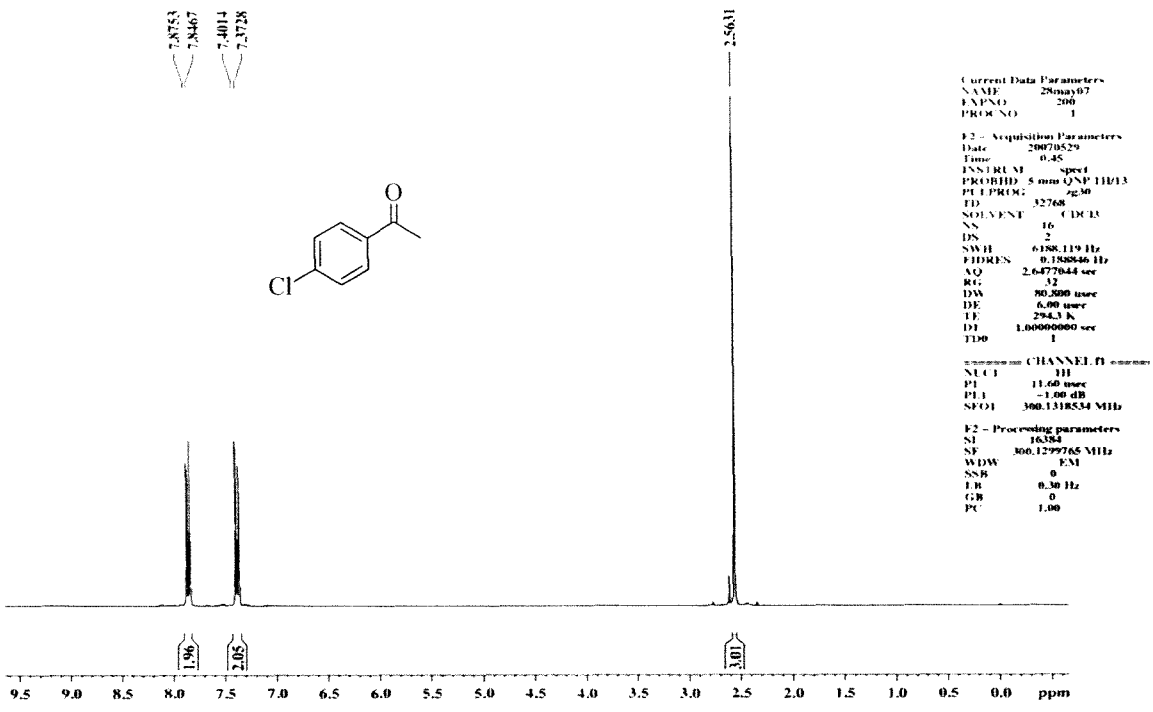
^{13}C NMR Spectra of **3c** (300 MHz, $CDCl_3$)



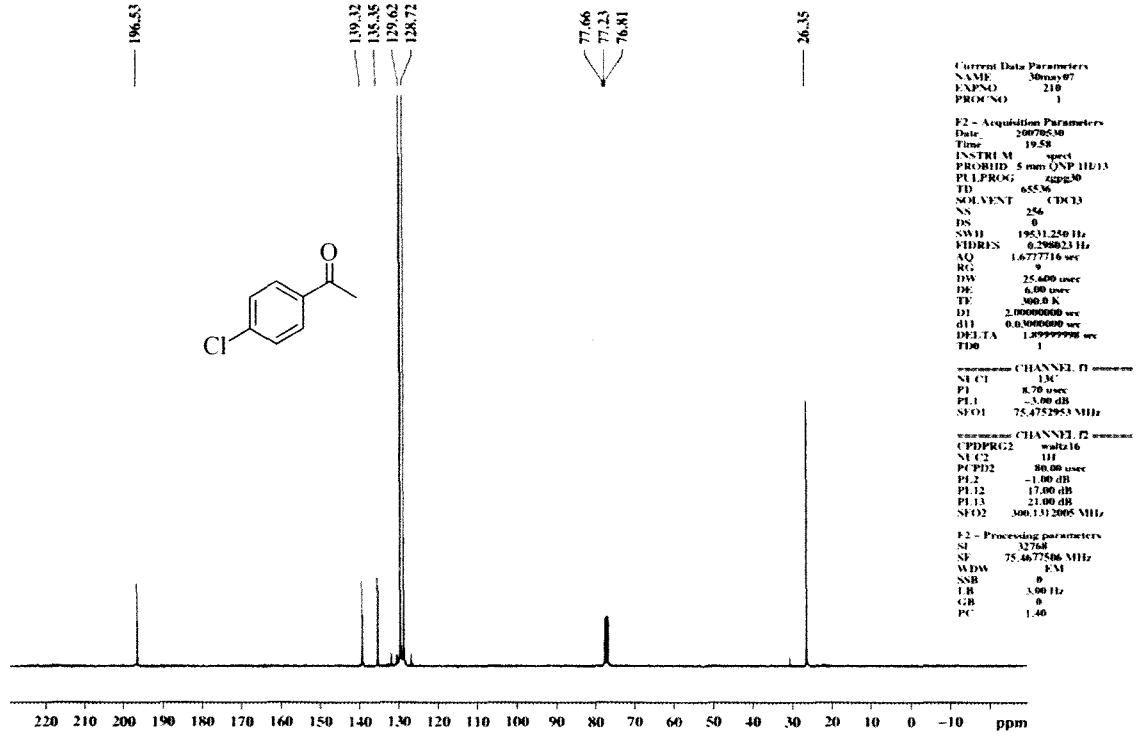
^{1}H NMR Spectra of **2a** (300 MHz, $CDCl_3$)



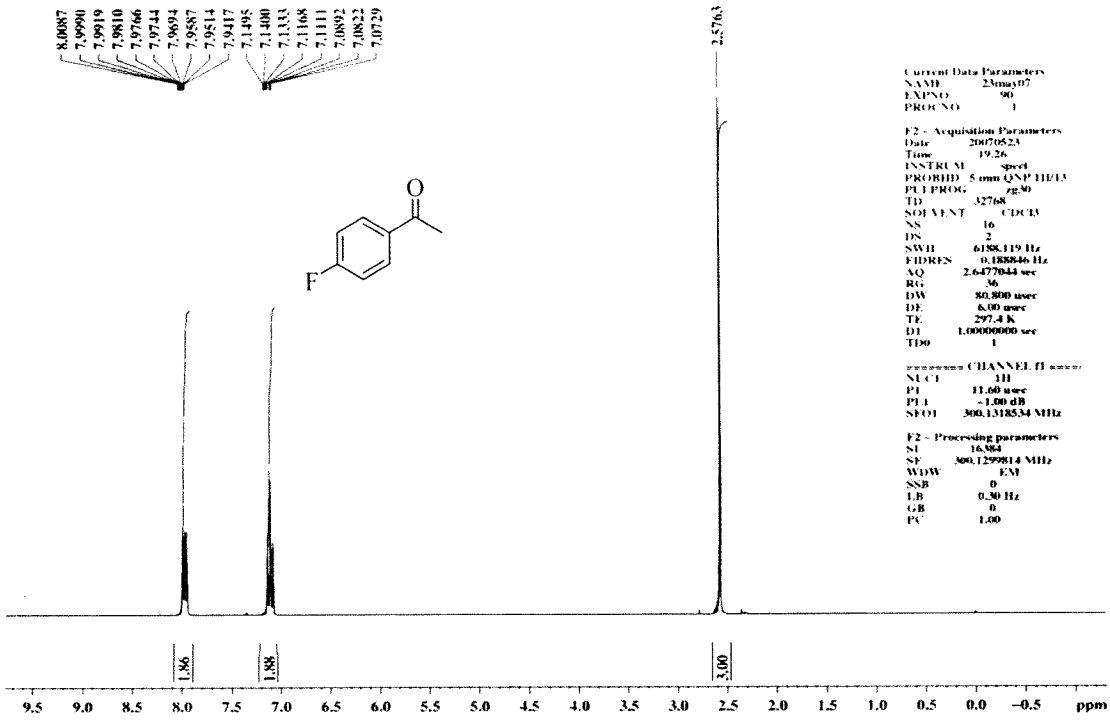
^{13}C NMR Spectra of **2a** (75 MHz, $CDCl_3$)



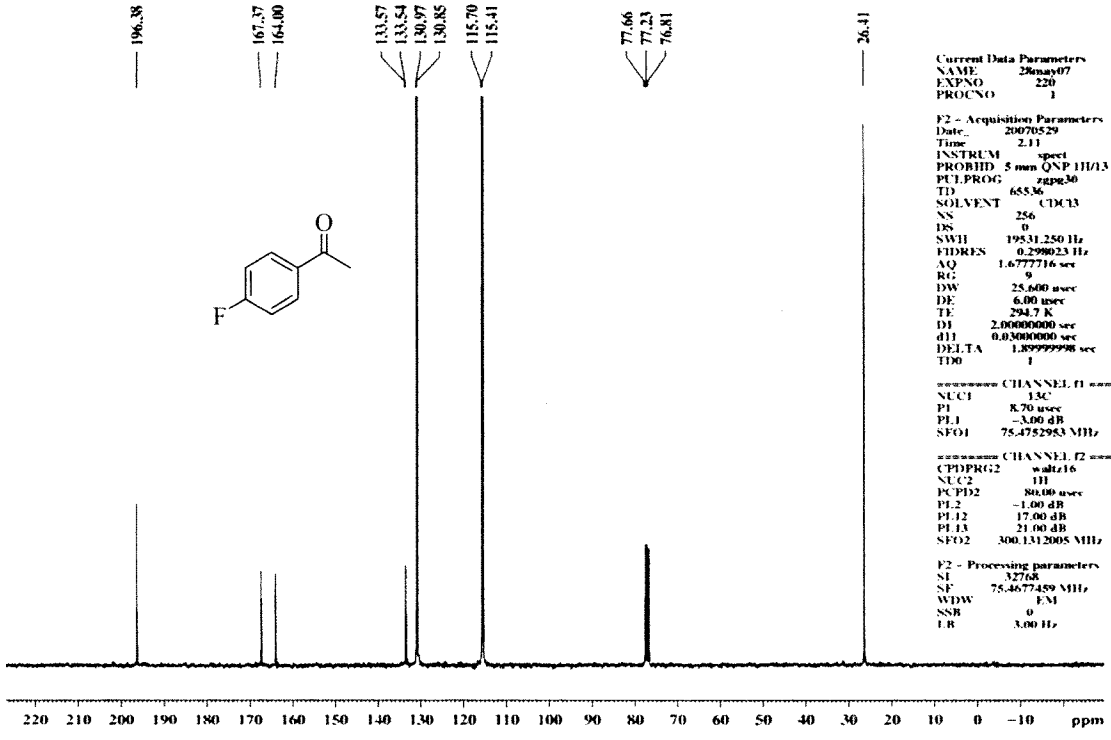
^{1}H NMR Spectra of **2b** (300 MHz, $CDCl_3$)



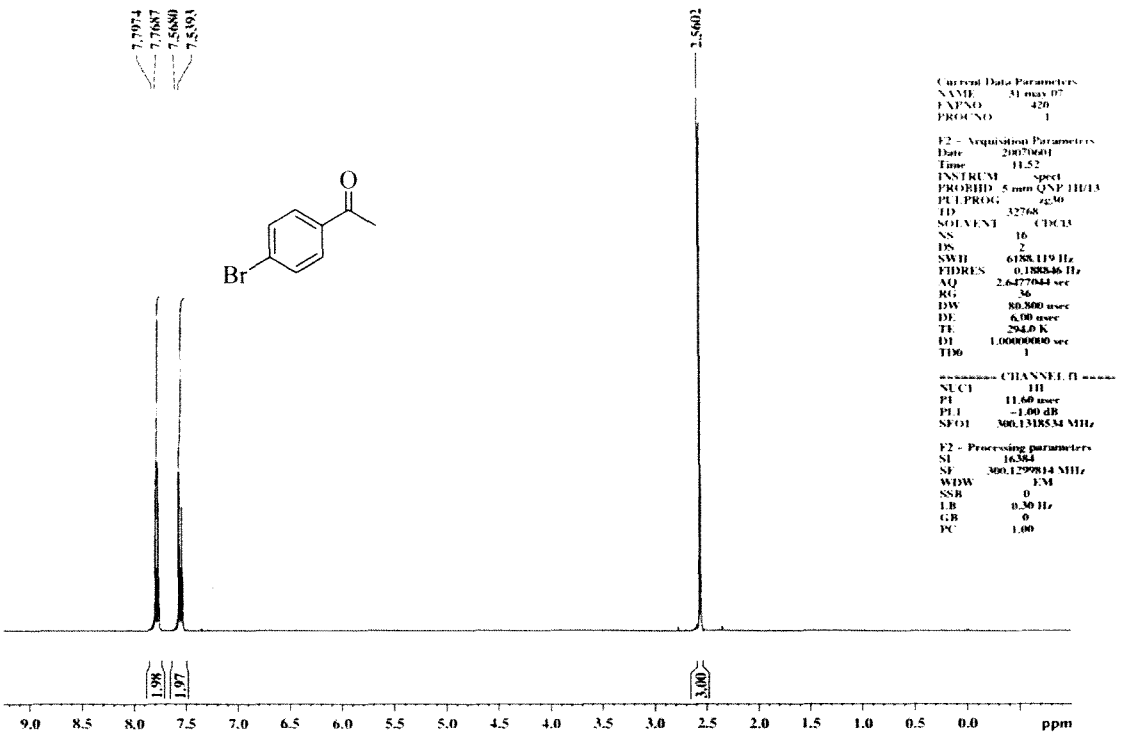
^{13}C NMR Spectra of **2b** (75 MHz, $CDCl_3$)



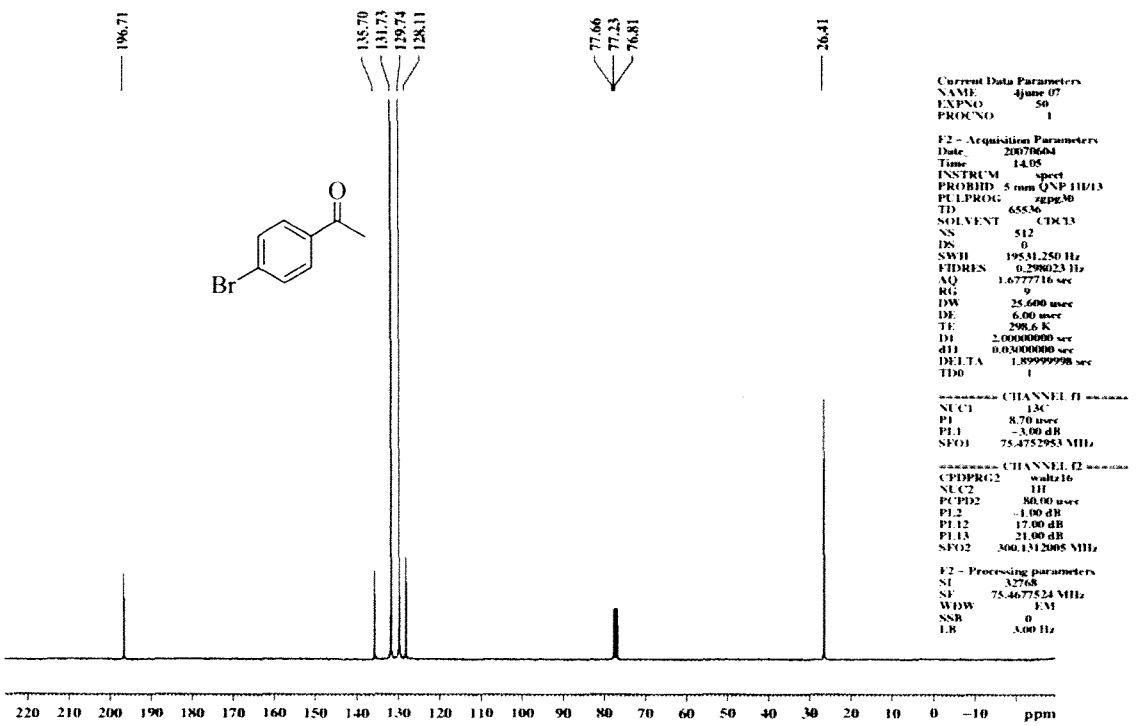
^{1}H NMR Spectra of **2c** (300 MHz, $CDCl_3$)



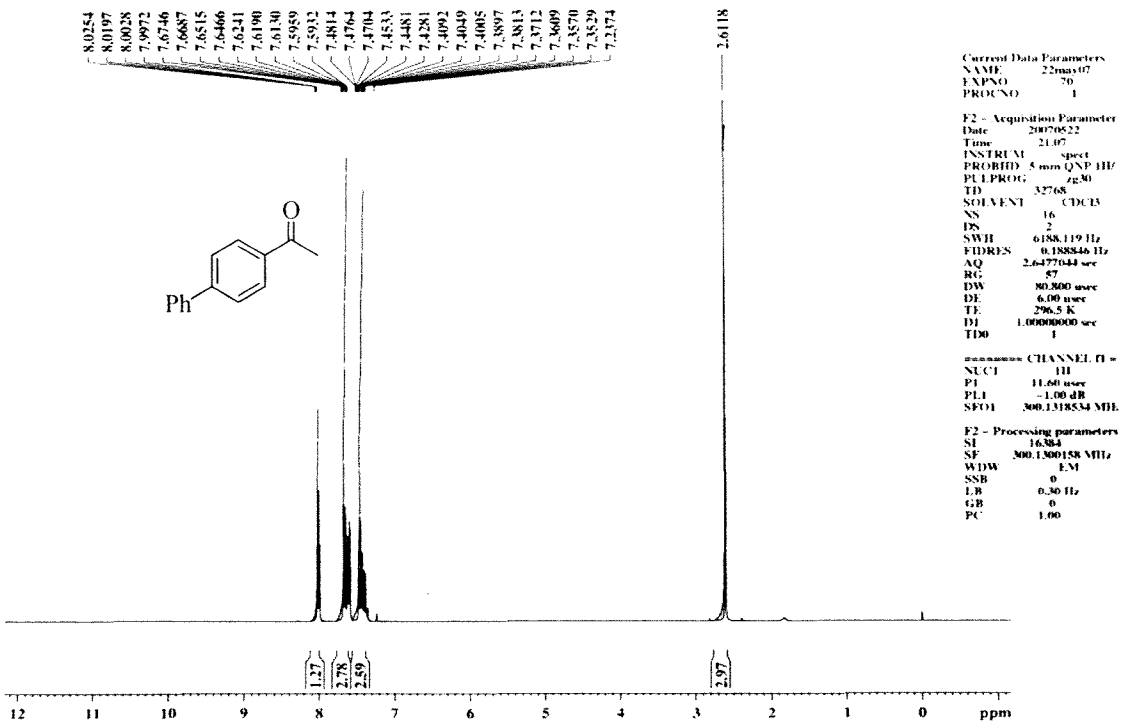
^{13}C NMR Spectra of **2c** (300 MHz, $CDCl_3$)



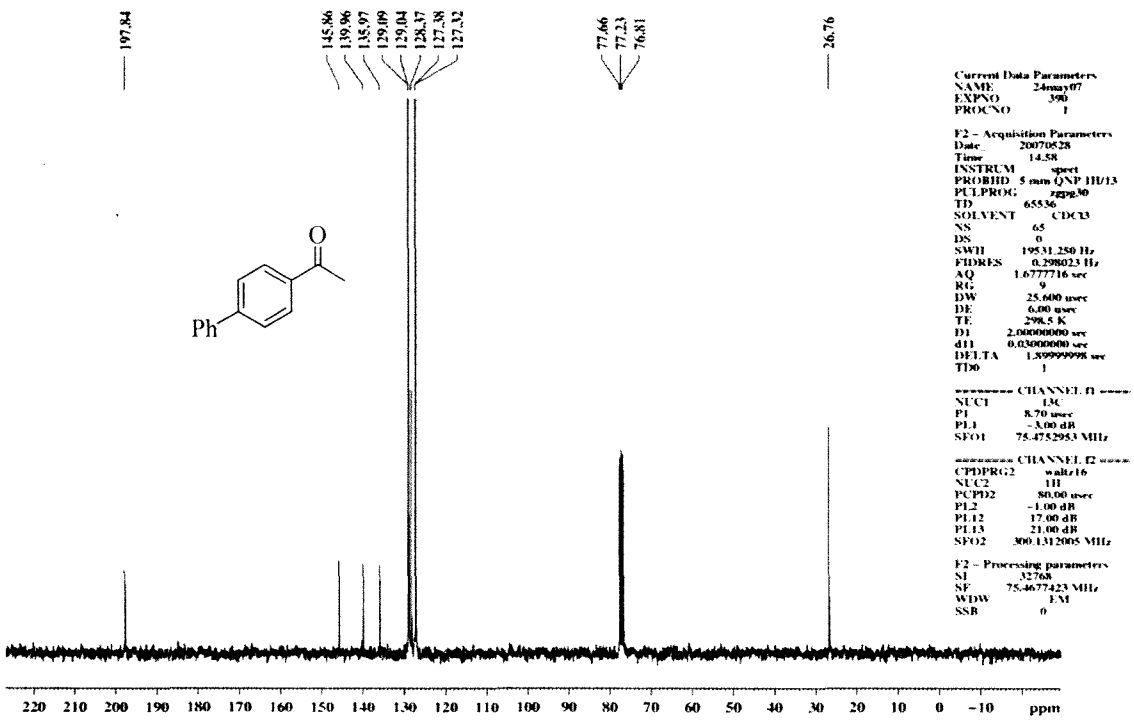
^{1}H NMR Spectra of **2d** (300 MHz, $CDCl_3$)



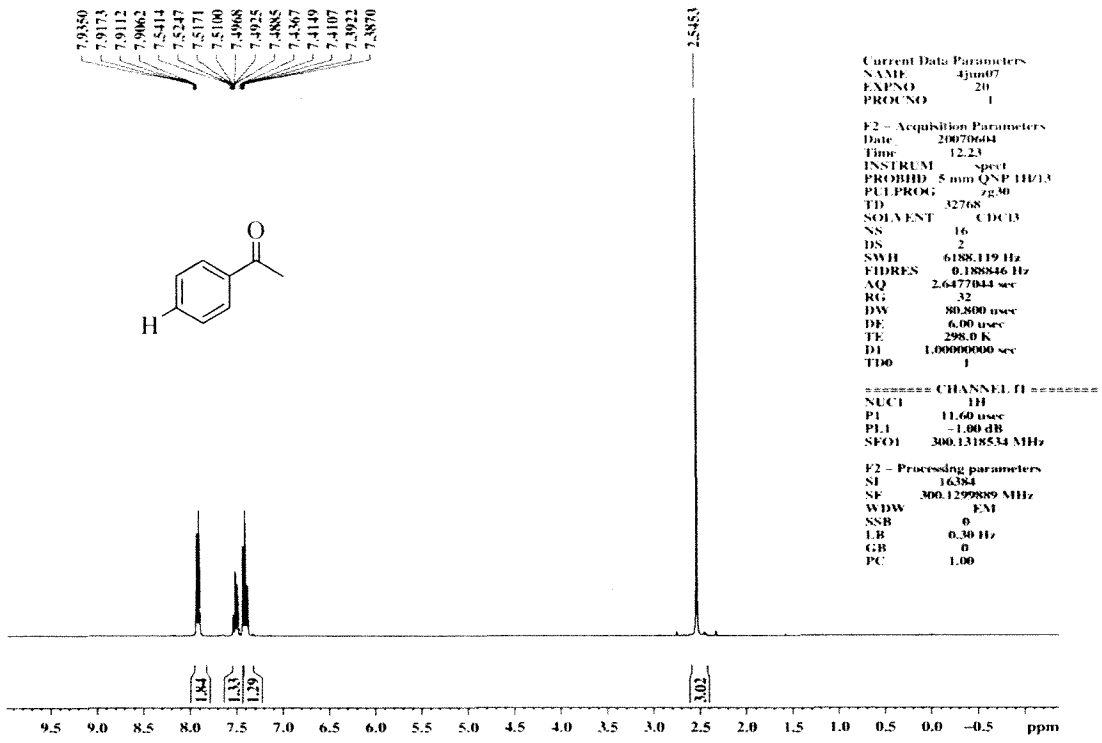
^{13}C NMR Spectra of **2d**(300 MHz, $CDCl_3$)



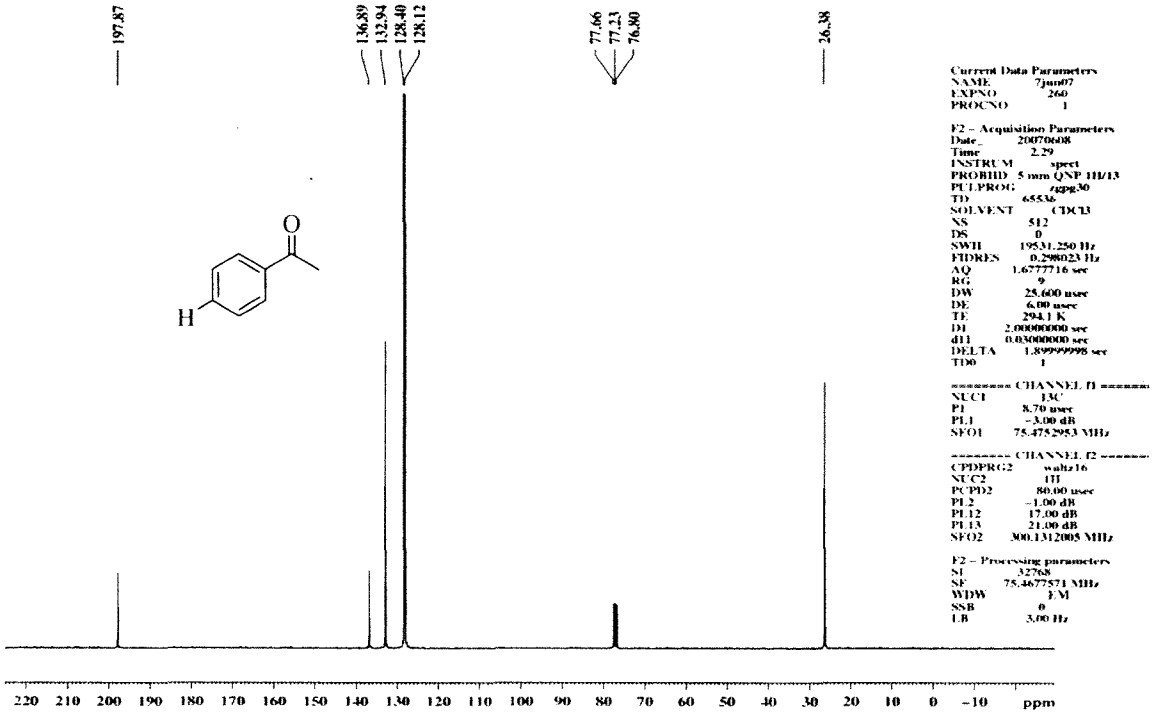
^{1}H NMR Spectra of **2e** (300 MHz, $CDCl_3$)



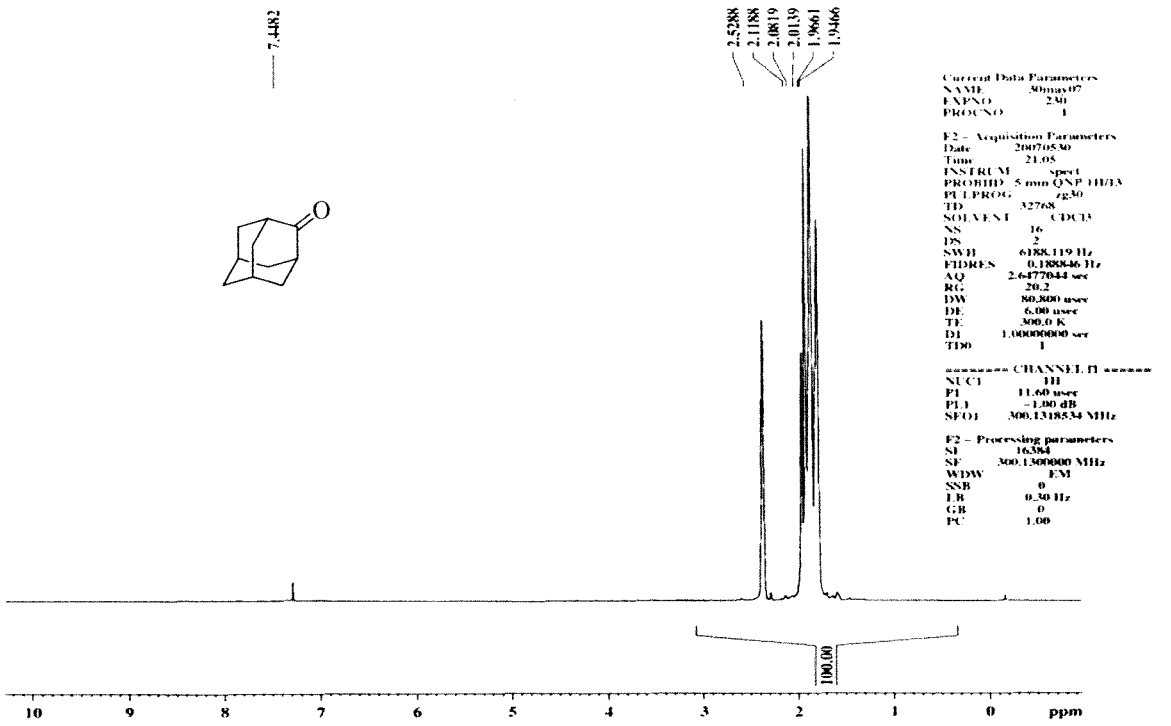
^{13}C NMR Spectra of **2e** (300 MHz, $CDCl_3$)



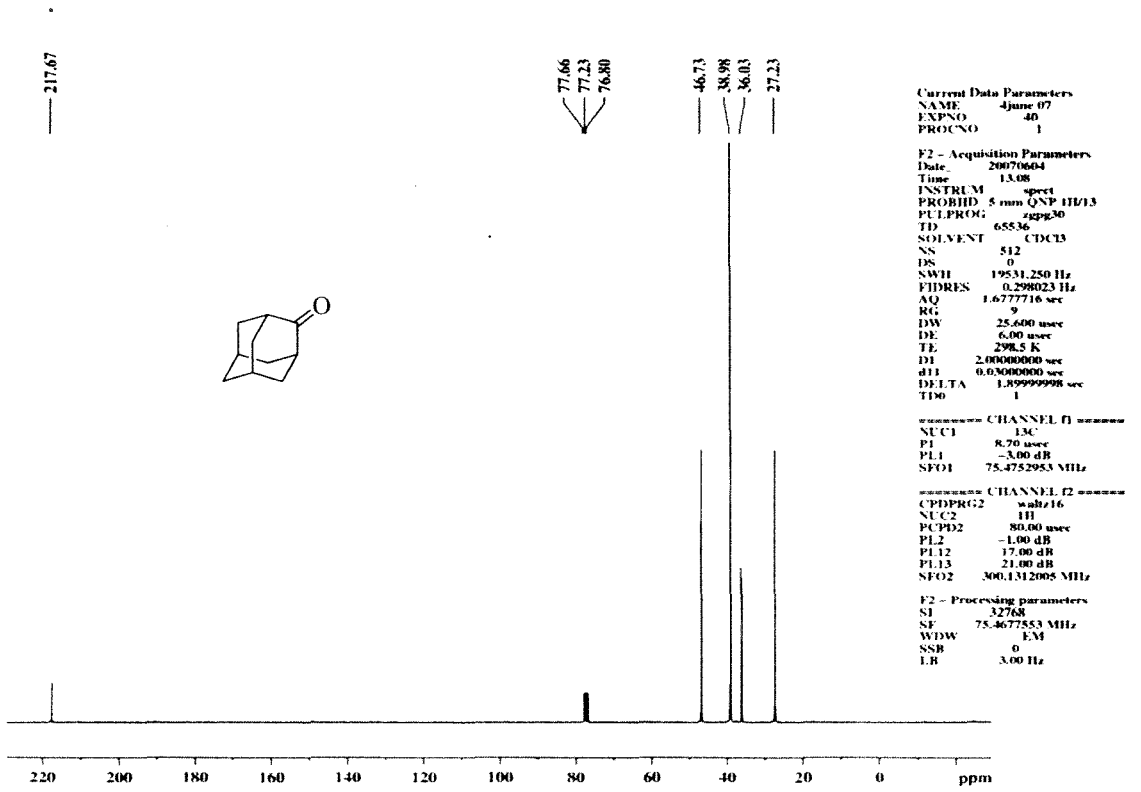
^{1}H NMR Spectra of **2f** (300 MHz, $CDCl_3$)



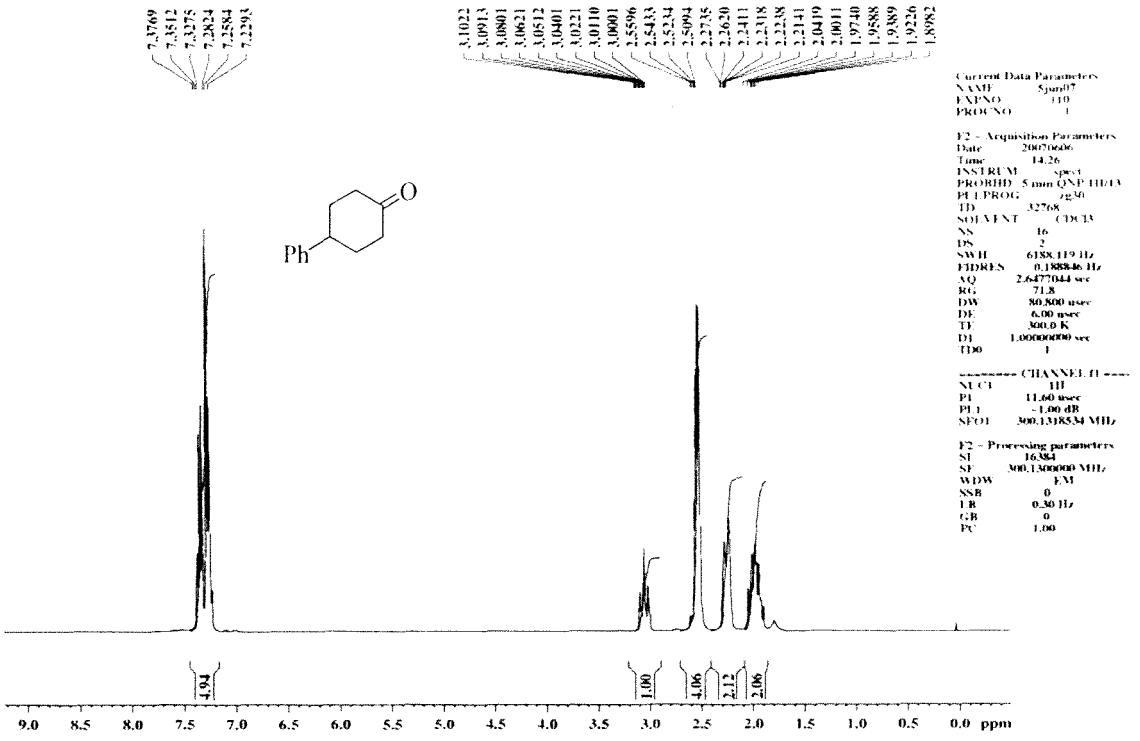
^{13}C NMR Spectra of **2f** (300 MHz, $CDCl_3$)



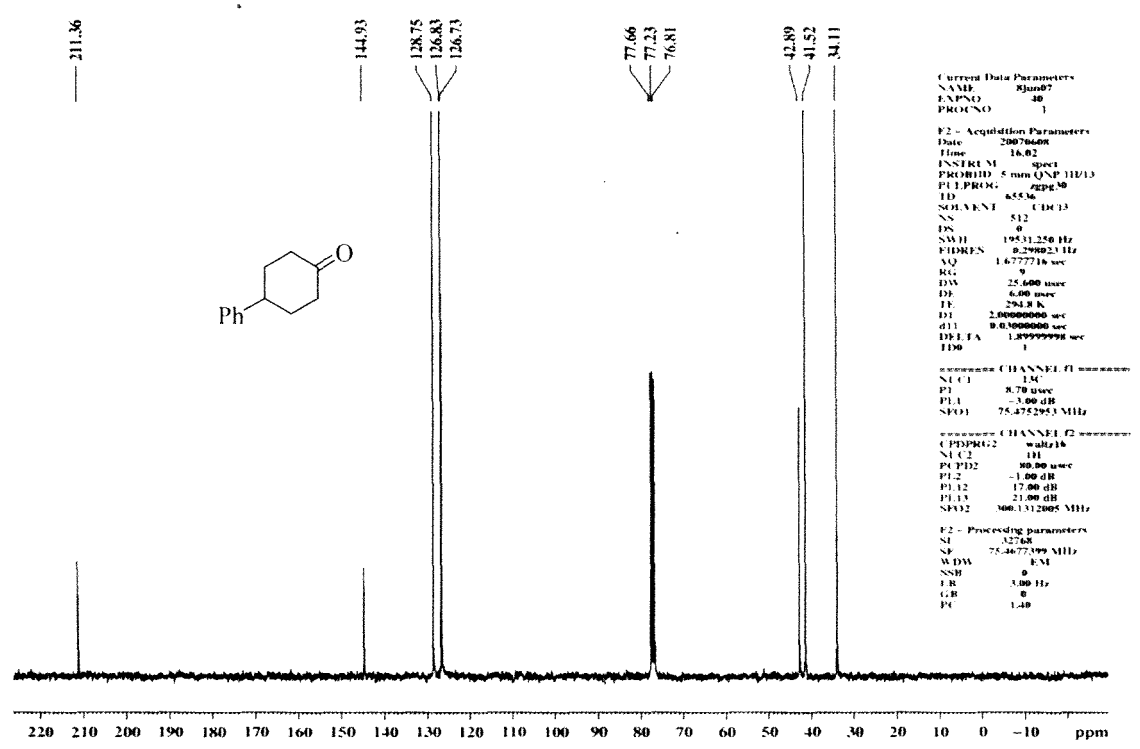
^{1}H NMR Spectra of **3a** (300 MHz, $CDCl_3$)



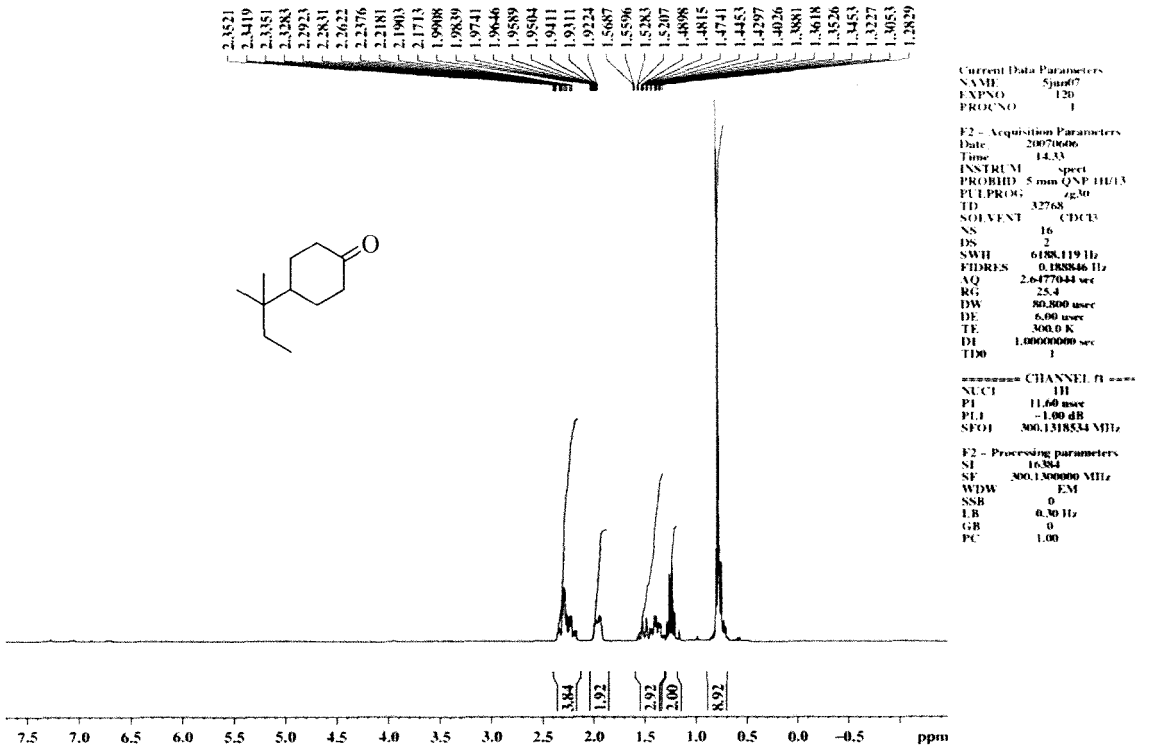
^{13}C NMR Spectra of **3a** (300 MHz, $CDCl_3$)



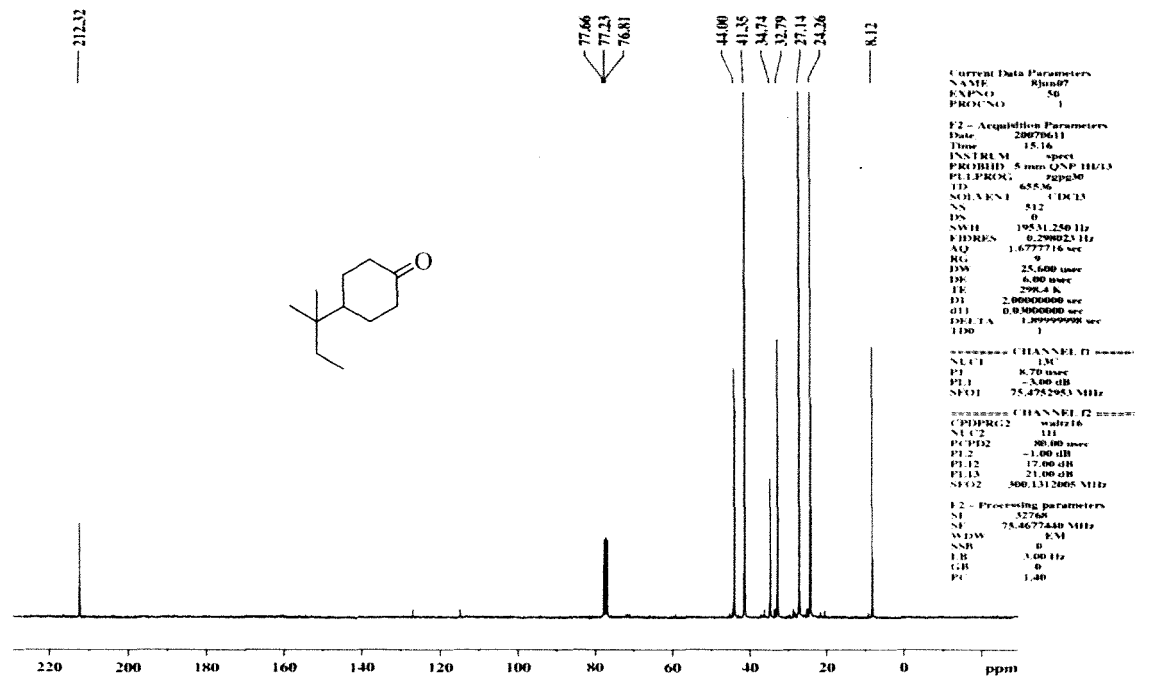
^{1}H NMR Spectra of **3b** (300 MHz, $CDCl_3$)



^{13}C NMR Spectra of **3b** (300 MHz, $CDCl_3$)

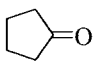


^{1}H NMR Spectra of **3c** (300 MHz, $CDCl_3$)



^{13}C NMR Spectra of **3c** (300 MHz, $CDCl_3$)

1.24 (q, 2H, J= 7.4 Hz) 1.30-2.35 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.12 (CH_3), 24.26 (2 × CH_3), 27.14 (2 × CH_2), 32.79 (CH_2), 34.74 (C), 41.35 (2 × CH_2), 44.00 (CH), 212.32 (C); FAB-MS (*m/z*) 169 [M+H$^+$].



Cyclopentanone (3d): oil; FT-IR (neat cm^{-1}); FT-IR (KBr cm^{-1}) 756, 1743, 2968; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.94-2.17 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.90 (2 × CH_2), 37.93 (2 × CH_2), 219.89 (C); ESI-MS (*m/z*) 85 [M+H$^+$].

4.5 References

1. O'Neill, P. M.; Mukhtar, A.; Ward, S. A.; Bickley, J. F.; Davies, J.; Bachi, M. D.; Stocks, P. A. *Org. Lett.* **2004**, *6*, 3035. (b) O'Neill, P. M.; Pugh, M.; Davies, J.; Ward, S. A.; Park, B. K. *Tetrahedron Lett.* **2001**, *42*, 4569. (c) Bloodworth, A. J.; Johnson, K. A. *Tetrahedron Lett.* **1994**, *35*, 8057. (d) Bloodworth, A. J.; Shah, A. *J. Chem. Soc. Chem. Commun.* **1991**, 947. (e) Posner, G. H.; Oh, C. H.; Milhous, W. K. *Tetrahedron Lett.* **1991**, *32*, 4235. (f) Bunnelle, W. H.; Isbell, T. A.; Barnes, C. L.; Qualls, S. *J. Am. Chem. Soc.* **1991**, *113*, 8168. (g) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *J. Org. Chem.* **1989**, *54*, 1792. (h) Kepler, J. A.; Philip, A.; Lee, Y. W.; Morey, M. C.; Caroll, F. I. *J. Med. Chem.* **1988**, *31*, 713. (i) Jefford, C. W.; Jaggi, D.; Boukouvalas, J.; Kohmoto, S. *J. Am. Chem. Soc.* **1983**, *105*, 6498.
2. Jefford, C. W.; Rossier, J.-C.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1987**, *10*, 713. Yamamato, H.; Akutagawa, M.; Aoyama, H.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1,* **1980**, 2300. Fujisaka, T.; Miura, M.; Nojima, M.; Kusabayashi, S. *J. Chem. Soc., Perkin Trans. 1,* **1989**, 1031. Pu, Y.-M.; Yeh, H. J. C.; Ziffer, H. *Hetrocycles*, **1993**, *36*, 2099.
3. (a) Singh, C. *Tetrahedron Lett.* **1990**, *31*, 6901. (b) Singh. C.; Gupta, N.; Puri, S. K.; *Tetrahedron Lett.* **2005**, *46*, 205-207.
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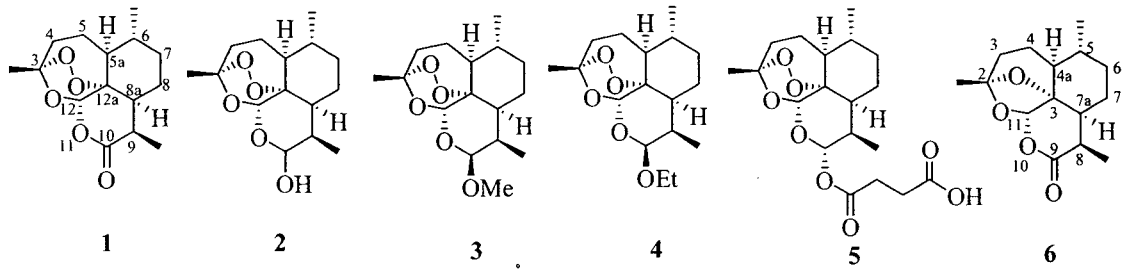
5. For review on Bayer-Villiger Oxidation see: Krow, G. R. *Organic Reactions*. **1993**, *43*, 25.

Chapter 5

Synthesis and Antimalarial Assessment of Novel 11-Hydrazaartemisinins

5.1 Introduction

Following isolation of artemisinin[1] **1** as the active principle of the Chinese traditional drug *Artemisia annua* against malaria, there has been extensive global efforts to build on this important lead. Dihydroartemisinin (DHA) **2,** easily accessible from artemisinin has been converted into ethers, esters, carbamates, urethanes, amines and amides.[2] Most of the derivatives for e.g. artemether **3**, arteether **4** and artesunic acid **5** (Fig. 5.1) show better activity profile than artemisinin and currently are the drugs of choice for the treatment of malaria caused by multidrug resistant *P. falciparum*. These drugs owe their activity to the peroxide group present in the form of 1,2,4-trioxane. Deoxyartemisinin **6** which is structurally very similar to artemisinin but lacks peroxide group is devoid of antimalarial activity.



1 2 3 4 5 6

Figure 5.1 Artemisinin and its analogs.

Notwithstanding these great achievements, artemisinin still remains a molecule of choice to work for scientists working in malaria chemotherapy. Recently a series of aza derivatives of artemisinin (Fig. 5.2) with promising antimalarial activity have been reported.[3-6]

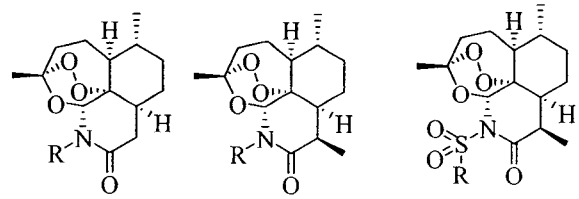


Figure 5.2 Aza analogs of artemisinin.

In these aza derivative nitrogen is present as part of amide bond and therefore is not basic in character. It appeared of interest to us to prepare aza derivatives of artemisinin in which basicity of nitrogen is retained.[7] With this objective in mind we reacted artemisinin with hydrazine. The reaction was very fast and the crude product after treatment with SiO_2/20% H_2SO_4 furnished aza

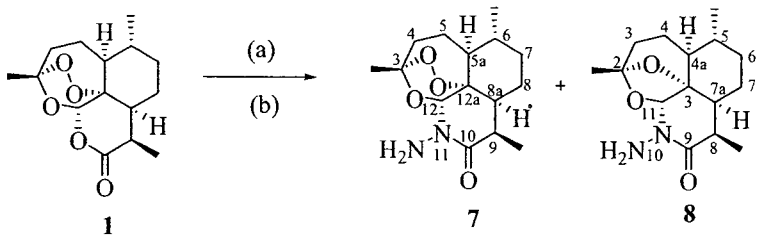
derivative **7** in 64% yield. Compound **7** was further converted to various amide, imine and amino derivatives. (Prototype **14a-h, 15a-h, 16a-h, 17, 18, 19** and **20**). Several of these compounds showed very high order of antimalarial activity against multi-drug resistant *P. yoelii* in mice both via oral and im routes In this chapter we describe the details of this study.

5.2 Preparation of aza derivatives of artemisinin

5.2.1 Preparation of 7 and 8

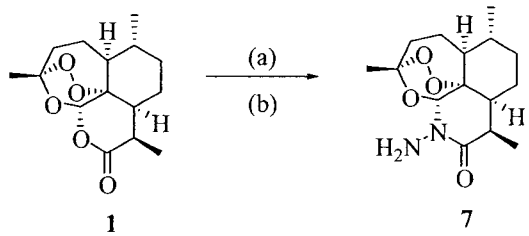
The reaction of artemisinin **1** with methanolic hydrazine hydrate at rt for 1 h furnished a complex mixture of products as observed by TLC. The reaction mixture was concentrated and stirred with silica gel and 20% H_2SO_4 for overnight at rt to furnish an inseparable mixture of 11-hydrazaartemisinin **7** and its deoxy analog 10-hydrazadeoxyartemisinin **8** in a combined yield of 59% and in ratio of 3:7 as determined by ^1H NMR (Scheme 5.1).

Prolonged reaction of artemisinin and $N_2H_4.H_2O$ in methanol at rt for 12 h followed treatment with SiO_2/20% H_2SO_4 furnished only 10-hydrazadeoxyartemisinin **8** in 69% yield.



Scheme 5.1 *Reagents and conditions:* (a) $N_2H_4.H_2O$, MeOH, rt, 1h; (b) SiO_2/20% H_2SO_4, 2,6-di-*tert*-butyl-phenol, DCM, 0°C to rt, 12h.

The yield of 7 improved to 64% when the reaction with hydrazine was conducted in MeOH-$CHCl_3$ at 0 °C. (Scheme 5.2).



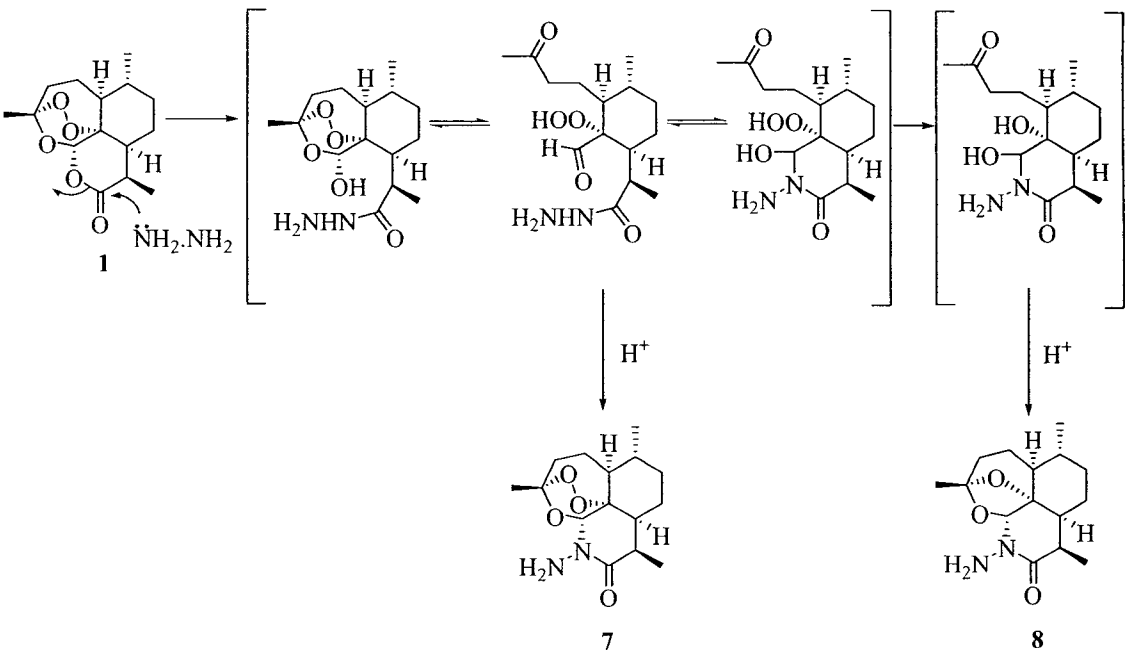
Scheme 5.2 *Reagents and conditions:* (a) $N_2H_4.H_2O$, 70% MeOH/$CHCl_3$, 0°C, 30 min; (b) SiO_2/20% H_2SO_4, 2,6-di-*tert*-butyl-phenol, $CHCl_3$, 0°C to rt, 12h.

The two compounds were characterized on the basis of ^{1}H NMR and mass spectra. While the nmr spectra of compound 11-hydrazaartemisinin **7** was very much similar to that of artemisinin **1,** the nmr spectra of 10-hydrazadeoxyatremisinin **8** was found similar to that of deoxy artemisinin **6.** The C-5a proton of 11-hydrazaartemisinin **7** comes at δ 2.42 and in artemisinin C-5a proton comes at δ 2.36, while in case of 10-hydrazadeoxyartemisinin **8** the C-4a proton which corresponds to C-5a proton in 11-hydrazaartemisinin **7** comes at δ 1.97 which is similar to that of deoxy artemisinin **6** in which it comes at δ 2.01.

The ESI mass spectra of compound **7** gave peak *m/z* at 297 [M+H$^+$] which corresponds to a molecular formula $C_{15}H_{23}N_2O_4$, while the compound **8** gave peak *m/z* at 281 [M+H$^+$] which corresponds to a molecular formula $C_{15}H_{23}N_2O_3$, thus containing one oxygen less in comparison to compound **7.**

Compound **7** was found stable at 65 °C in THF for > 48 h. It was stable under basic conditions as there was no degradation when it was refluxed with K_2CO_3 for >48 h in THF.

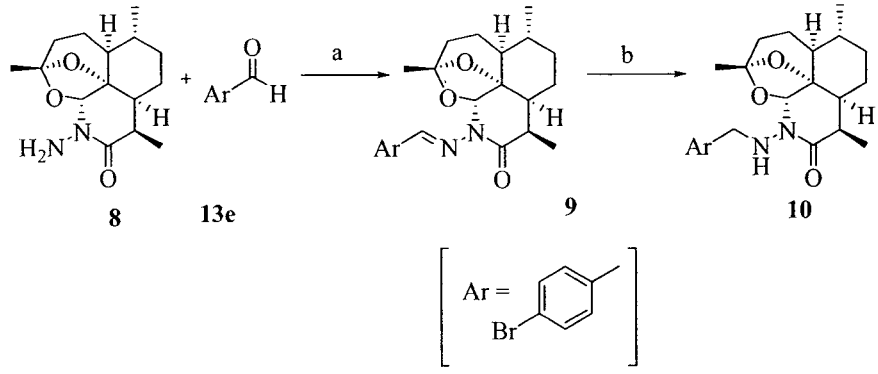
The mechanism of conversation of artemisinin **1** to 11-hydrazaartemisinin **7** and 10-hydrazadeoxyartemisinin **8** is shown in Scheme 5.3.



Scheme 5.3 Mechanism of the formation of compounds **7** and **8**.

5.2.2 Conversion of 7 and 8 to amide, imine and amine derivatives

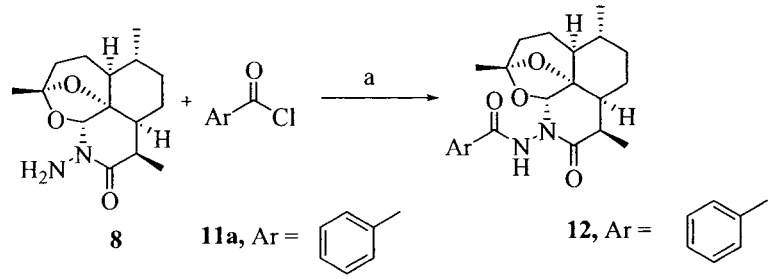
Reaction of compound **8** with 4-Bromobenzaldehyde **13e** in presence of Amberlyst-15 at rt in dry benzene for 2h furnished compound **9** in 95% yield. Compound **9** when subjected to $NaBH_4$ reduction at 0 °C for 4h, furnished compound **10** in 83% yield (Scheme 5.4).



8 **13e** **9** **10**

Scheme 5.4 *Reagents and conditions*: (a) Amberlyst-15, molecular sieves, dry benzene, rt, 2h; (b) $NaBH_4$, dry benzene, 0 °C, 4 h.

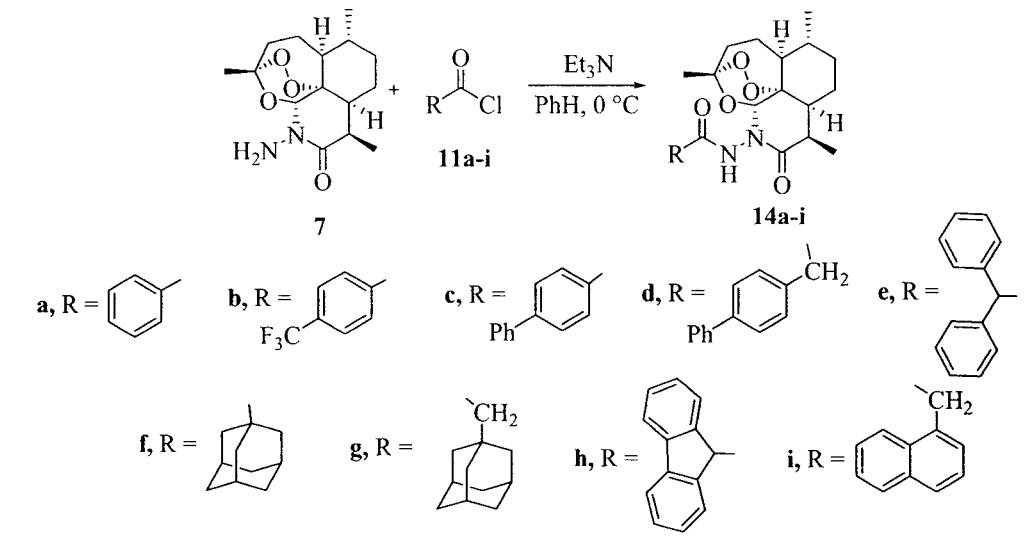
The reaction of compound **8** with benzoyl chloride **11a** at 0 °C in presence of Et_3N furnished corresponding benzamide **12** in 95% yield (Scheme 5.5).



8 **11a**, Ar = **12**, Ar =

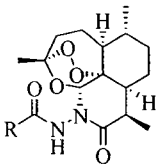
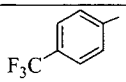
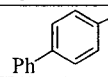
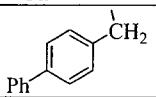
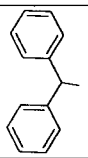
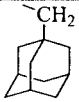
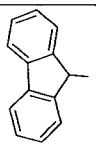
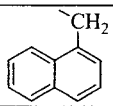
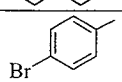
Scheme 5.5 *Reagents and conditions*: (a) Benzoyl chloride, Et_3N, dry benzene, 0 °C, 2h.

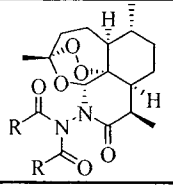
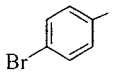
The reaction of compound **7** with benzoyl chloride **11a** under similar conditions furnished compound **14a** in 93% yield. The reaction of various acid chlorides **11b-i** with 11-hydrazaartemisinin **7** furnished corresponding amides **14b-i** in 85-93% yields (Scheme 5.6 and Table 5.1).



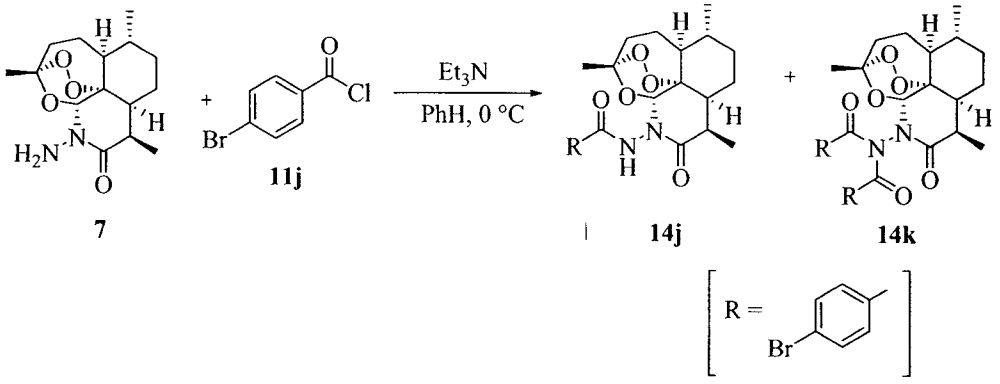
Scheme 5.6 Various amides of 11- hydrazaartemisinin **7**

Table 5.1

General Structure	Compound No.	Substituent (R)	Yields %
	**14a**		93
	14b		85
	14c		93
	14d		91
	14e		93
	14f		89
	14g		88
	14h		91
	14i		89
	14j		38

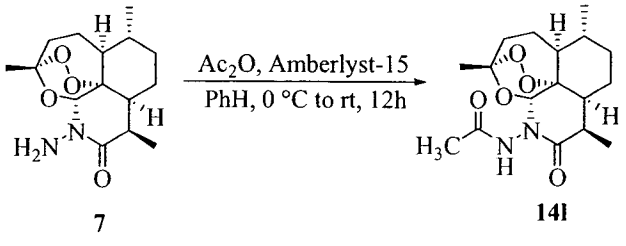
General Structure	Compound No.	Substituent (R)	Yields %
	**14k**		32

However the reaction of compound **7** with 4-Bromobenzoyl chloride **11j** furnished two products, **14j** and **14k** in 38% and 32% yields, respectively (Scheme 5.7).



Scheme 5.7

The reaction of compound **7** with Ac_2O in presence of Amberlyst-15 furnished corresponding acetamide **14l** in 72% yield (Scheme 5.8).

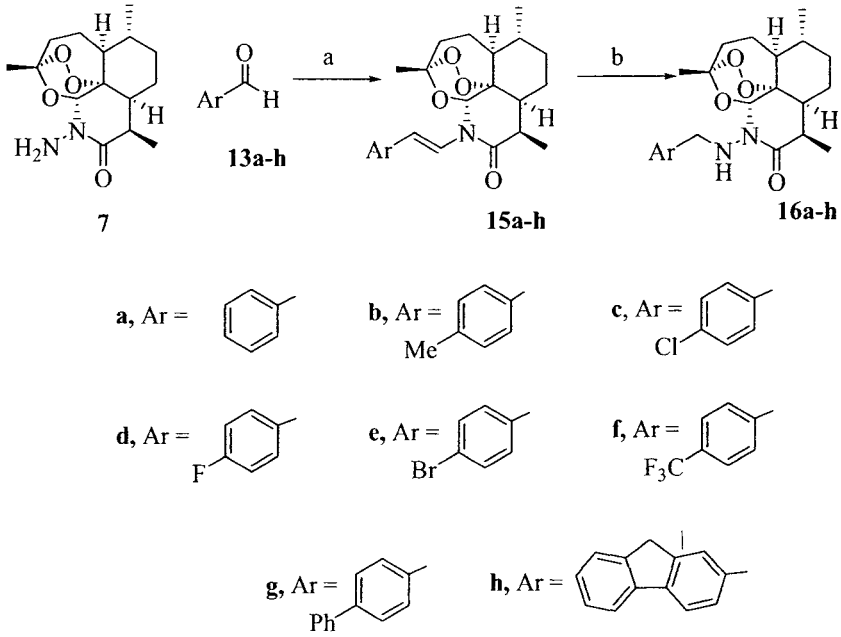


Scheme 5.8 Acetylation of compound **7**

In order to synthesize imine derivatives of 11-hydrazaartemisinin, benzaldehyde **13a** was allowed to react with compound **7** in presence of Amberlyst-15 in dry benzene at 0 °C to furnish corresponding benzylidene derivative **15a** in 94% yield. The reaction of compound **7** with

aldehydes **13b-h** under similar conditions furnished its corresponding imine derivatives **15b-h** in 82-96% yields (Scheme 5.9 and Table 5.2).

The imines **15a-h** were then subjected to $NaBH_4$ reduction in dry benzene at 0 °C to furnish their corresponding amines **16a-h** in 62-74% yields(Scheme 5.9 and Table 5.3).



Scheme 5.9 *Reagents and conditions*: (a) Amberlyst-15, molecular sieves, dry benzene, rt, 2-3 h; (b) $NaBH_4$, dry benzene, 0 °C, 4-6 h.

Table 5.2

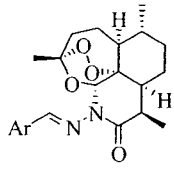
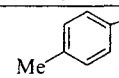
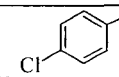
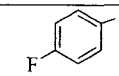
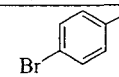
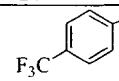
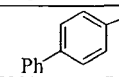
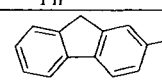
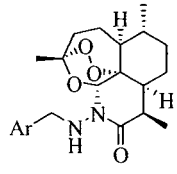
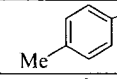
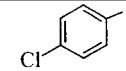
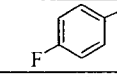
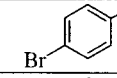
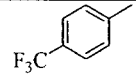
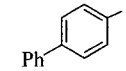
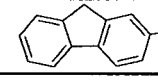
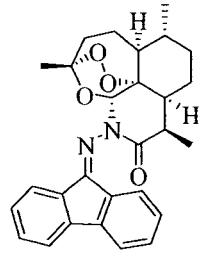
General Structure	Compound No.	Substituent (Ar)	Yields %
	**15a**		94
	15b		87
	15c		96
	15d		88
	15e		96
	15f		82
	15g		94
	15h		92

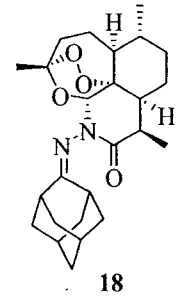
Table 5.3

General Structure	Compound No.	Substituent (Ar)	Yields %
	**16a**		67
	16b		73
	16c		68
	16d		69
	16e		72
	16f		68
	16g		62
	16h		74

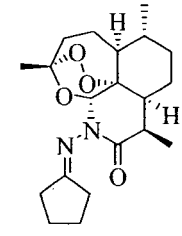
The reaction of **7** with 9-flurenone took 7 days to complete to furnish corresponding imine **18** in 52% yield. The reaction of compound **7** with 2-adamantanone was relatively fast as it took only 24 h for reaction to complete to furnish corresponding imine **20** in 84% yield. The reaction of compound **7** with cyclopentanone was completed in 10 h and furnished compound **22** in 92% yield (Figure 5.3).



17



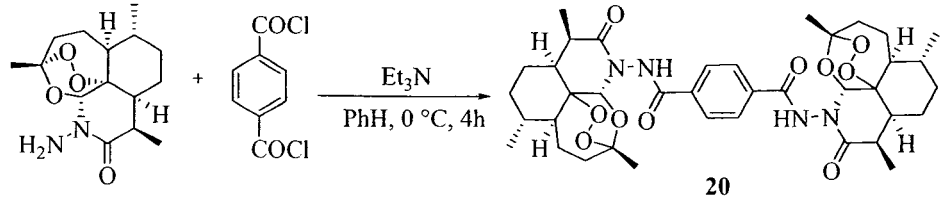
18



19

Figure 5.3

Dimer **20** was prepared by the reaction of compound **7** with acid chloride of terepthalic acid in 12% yield (Scheme 5.10).



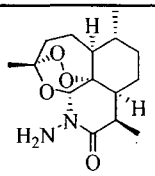
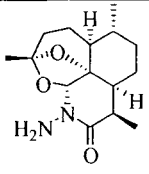
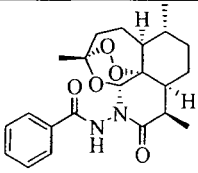
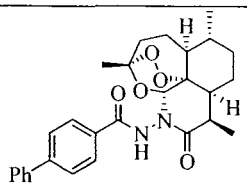
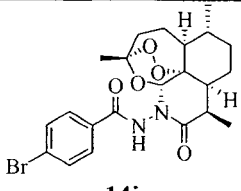
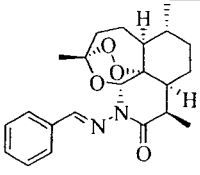
20

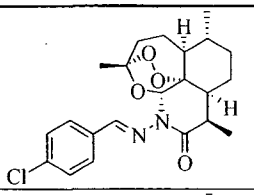
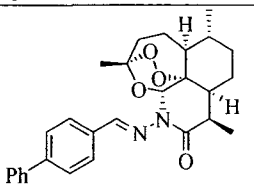
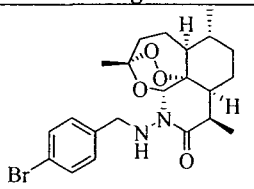
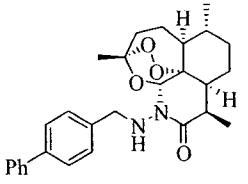
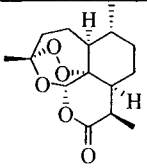
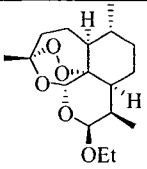
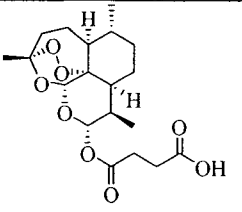
Scheme 5.10

5.3 Antimalarial Assessment

Amino functionalized artemisinin derivatives **7**, **8**, **14a**, **14c**, **14j**, **15a**, **15c**, **15g**, **16e** and **16g** were assessed for antimalarial activity against multi-drug resistant *P. yoelii nigeriensis* in Swiss mice at various dose levels ranging from 6 to 24 mg/kg × 4 days dose both via oral and im routes. The results are summarized in Table 5.4.

Table 5.4. *In vivo* antimalarial activity of hydrazaartemisinins against multi-drug resistant *Plasmodium yoelii nigeriensis* in Swiss mice.by oral and im routes.

Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
 **7**	2.25	Oral Im	12 6	99 94	0/5 0/5
 **8**	1.90	Oral Im	12 6	22 25	0/5 0/5
 **14a**	3.85	Oral Im	12 6	62 85	0/5 0/5
 **14c**	5.53	Oral Im	24 12 12 6	100 100 100 100	5/5 4/5 5/5 3/5
 **14j**	4.68	Oral Im	12 6	80 100	0/5 2/5
 **15a**	4.92	Oral Im	12 6 6	100 36 100	1/5 0/5 5/5

Compound	Log *p*	Route	Dose (mg/kg/day)	% Suppression on day 4[a]	Mice alive on day 28
	5.48	Oral Im	12 6	100 100	2/5 1/5
 **15g**	6.59	Oral Im	12 6 6	100 100 49	5/5 3/5 0/5
 **16e**	5.04	Oral Im	24 12 12	100 100 100	5/5 3/5 5/5
 **16g**	5.89	Oral Im	24 12 6 12 6	100 100 100 100 90	5/5 5/5 1/5 5/5 0/5
 Artemisinin **1**	3.17	Im	48 24	100 100	5/5 3/5
 *β*-Arteether **4**	3.84	Oral Im	48 24 12 6	100 100 100 100	5/5 1/5 5/5 5/5
 Artesunic acid **5**	3.04	Oral Im	48 24 48 24	100 100 100 100	5/5 0/5 5/5 0/5
Vehicle control	-	Oral Im	- -	- -	0/5 0/5

[a]Percent suppression = [(C-T)/C] × 100; where C = parasitaemia in control group and T = parasitaemia in treated group of mice.

5.4 Results and discussion

As it can be seen from the Table 5.4 that out of several 11-Hydrazaartemisinins that were screened against multidrug resistant *P. yoelii* compounds **14c** and **16g** were found to be most active as they showed very good activity both via oral and im routes.

Compound **14c** provided 100% clearance of parasitaemia at 24 mg/kg × 4 days dose via oral route. It also provided 80% protection at 12 mg/kg × 4 days dose via same route. Compound **14c** also showed 100% protection to the treated mice at 12 mg/kg × 4 days dose and 60% protection via im route. Compound **16g** was also found equally effective as it provided 100% protection against parasitaemia both at 24 mg/kg × 4 days and 12 mg/kg × 4 days dose via oral route respectively. It also provided 20% protection at 6 mg/kg × 4 days dose via same route. Compound **16g** exhibited 100% clearance of parasitaemia at 12 mg/kg × 4 days dose im route as well. Compound **16e** the next best active compound of the series provided 100% protection to the parasitaemia at 24 mg/kg × 4 days dose and 60% protection at 12 mg/kg × 4 days dose via oral route. Compound **16g** also provided 100% protection to the treated mice at 12 mg/kg × 4 days dose via im route. Compound **15g** the next active compound of the series provided 100% protection to the treated mice at 12 mg/kg × 4 days dose and 60% protection at 6 mg/kg × 4 days dose via oral route. It did not provide any protection to the mice at 6 mg/kg × 4 days dose via im route. Compound **15c** provided 40% protection to the treated mice at 12 mg/kg × 4 days dose via oral route and 20% protection via im route. While compound **15a** provided only 20% protection to the treated mice at 12 mg/kg × 4 days dose via oral route, it provided 100% protection to the treated mice via im route at 6 mg/kg × 4 days dose. While compound **14j** provide no protection to the treated mice at 12 mg/kg × 4 days dose via route, it showed 40% clearance of parasitaemia at 6 mg/kg × 4 days dose via im route. Although the parent compound **7** provided no protection to the treated mice both via oral and im routes at 12 mg/kg × 4 days dose and 6 mg/kg × 4 days dose respectively, it did provide 99% and 94% suppression of parasitaemia at day 4 via oral and im routes respectively. The deoxy derivative, compound **6** was also found ineffective at 12 mg/kg × 4 days dose and 6 mg/kg × 4 days dose via oral and im routes respectively. It provided only 22% and 25% suppression to the parasitaemia on day 4 via respective routes.[10, 11]

The activity data of these compounds exhibit the role of presence of peroxide group in antimalarial activity and a direct correlation of activity and log *p* of the compounds. While the peroxy compound **7** provided 99% and 94% suppression of parasitaemia at day 4, the deoxy compound **8** showed only 22% and 25% suppression of parasitaemia at day 4 via oral and im

routes respectively. This observation indicated the crucial role of peroxy linkage in antimalarial activity. The role of lipophilicity in activity was also evident from log *p* and activity data of the compounds. The compounds which have log *p* valves ranging from 4.92-6.59 were active via oral route, while the compound having log *p* value ranging from 1.9- 3.85 were less active vial oral route.

5.5 Conclusion

In conclusion we have prepared new analogs of azaartemisinin and assessed them for their antimalarial efficacy. Several of these compounds have shown very high order of activity both via oral and im routes. The activity profile of some of the compounds prepared in this series, was found even better than that of the clinically used drugs, artemisinin, β-arteether and artesunic acid. The compounds **15g** and **16g** are more than 4 times active than β-arteether via oral route.

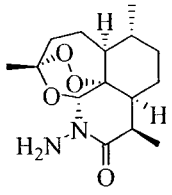
5.6 Experimental Section

General details and instrumentation: All glass apparatus were oven dried prior to use. Melting points were taken in open capillaries on Complab melting point apparatus and are presented uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 MHz and 300 MHz respectively for 1H; 50 MHz and 75 MHz respectively for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quintet (quin), multiplet (m), and broad (br). Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (EI-HRMS) were obtained on JEOL MS route 600H instrument. Elemental analyses were performed on Vario EL-III C H N S analyzer (Germany), and values were within (0.4% of the calculated values). Column chromatography was performed over Merck silica gel (particle size: 60-120 Mesh) procured from Qualigens (India), or flash silica gel (particle size: 230-400 Mesh). All chemicals and reagents were obtained from Aldrich

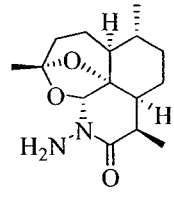
(Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used without further purification. Nomenclature and Log *p* values of the compounds were assigned using Chem Draw Ultra 7.0 software.

Preparation of 11-hydrazaartemisnin and 10-hydrazadeoxyartemisinin (mixture): To a stirred solution of $N_2H_4.H_2O$ (5.32 mL, 20 equiv., 106.38 mmol) in MeOH (30 mL) at rt was added artemisinin **1** (1.5 g, 5.32 mmol) and the reaction mixture was allowed to stir for 1h at the same temperature. The reaction mixture was concentrated, diluted with water (20 mL), extracted with DCM (3 × 25 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure to furnish a viscous solid. The viscous compound was dissolved in DCM (150 mL) and 2,6-di-*tert*-butyl phenol (100 mg) and 20% H_2SO_4 (10 mL) and silica gel (10 g) was added in succession. After stirring overnight at rt the reaction mixture was filtered and silica gel was washed well with DCM. The combined organic layer was washed with water (2 × 25 mL), dried over anhyd Na_2SO_4, concentrated and purified by column chromatography over silica gel using 50% EtOAc/Hexane as eluent to furnish an inseparable mixture of 11-hydrazaartemisnin **7** and 10-hydrazadeoxyartemisinin **8** (900 mg, combined yield 59%) as white solid.

Preparation of 11-hydrazaartemisnin 7: To a stirred solution of $N_2H_4.H_2O$ (21.28 mL, 20 equiv., 425.53 mmol) in 70% MeOH/$CHCl_3$ (120 mL) at rt was added artemisinin **1** (6.0 g, 21.28 mmol) dissolved in 70% MeOH/$CHCl_3$ (30 mL) gradually for five min and the reaction mixture was allowed to stir for 30 min at the same temperature. The reaction mixture was diluted with water (300 mL), extracted with $CHCl_3$ (3× 100 mL). The combined organic layer was dried over anhyd Na_2SO_4 and put to stirring at 0 °C without concentration. To this reaction mixture 2,6-di-*tert*-butyl phenol (400 mg) and 20% H_2SO_4 (40 mL) and silica gel (40 g) was added in succession. After stirring overnight at rt the reaction mixture was filtered and silica gel was washed well with $CHCl_3$. The combined organic layer was washed with water (2 × 75 mL), dried over anhyd Na_2SO_4, concentrated and purified by column chromatography over silica gel using 50% EtOAc/Hexane as eluent to furnish pure 11-hydrazaartemisnin **7** (4.08 g, yield 64%) as white solid.



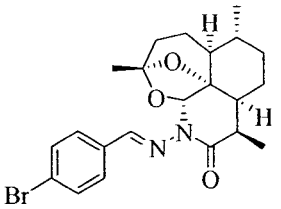
11-Hydrazaartemisinin (7): white solid, mp 122-125 °C; FT-IR (KBr cm^{-1}) 814, 835, 1031, 1142, 1271, 1595, 1653, 2874, 2941, 3315; ^1H NMR (300 MHz, $CDCl_3$); δ 0.86-1.00 (m, 2H), 0.94 (d, 3H, J = 6.2 Hz), 1.10 (d, 3H, J = 7.3 Hz), 1.29-1.44 (m, 3H), 1.33 (s, 3H), 1.59-1.75 (m, 3H), 1.92-2.03 (m, 2H), 2.36 (m, 1H), 3.24-3.33 (m, 1H), 4.63 (brs, 2H, NH_2), 5.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.64 (CH_3), 19.80 (CH_3), 22.77 (CH_2), 25.06 (CH_2), 25.51 (CH_3), 32.85 (CH), 33.65 (CH_2), 36.56 (CH_2), 37.38 (CH), 46.01 (CH), 51.35 (CH), 80.66 (C), 80.99 (CH), 104.92 (C), 169.68 (C); ESI-MS (*m/z*) 297 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{24}N_2O_4$ [M$^+$]: 296.1736. Found: 296.1742; Anal. Calcd. for $C_{15}H_{24}N_2O_4$: %C 60.79, %H 8.16, %N 9.45. Found: %C 60.92, %H 8.65, %N 9.75.



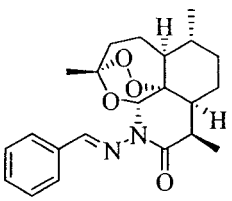
10-Hydrazadeoxyartemisinin (8): white solid, mp 147-150 °C; FT-IR (KBr cm^{-1}) 820, 878, 989, 1270, 1624, 1655, 2942, 3454; ^1H NMR (300 MHz, $CDCl_3$); δ 0.85-1.08 (m, 1H), 0.93 (d, 3H, J = 5.7 Hz), 1.16 (d, 3H, J = 7.3 Hz), 1.24-1.37 (m, 3H), 1.44 (s, 3H), 1.58-1.88 (m, 6H), 1.97 (td, 1H, J = 13.0, 4.3 Hz), 3.08 (dq, 1H, J = 7.3, 4.6 Hz), 4.44 (brs, 2H, NH_2), 5.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.54 (CH_3), 18.70 (CH_3), 22.29 (CH_2), 23.01 (CH_2), 24.45 (CH_3), 33.25 (CH), 33.66 (CH_2), 34.78 (CH_2), 35.31 (CH), 43.01 (CH), 45.90 (CH), 82.87 (C), 88.06 (CH), 107.74 (C), 170.56 (C); ESI-MS (*m/z*) 281 [M+H$^+$]; EI-HRMS Calcd. for $C_{15}H_{24}N_2O_3$ [M$^+$]: 280.1787. Found: 280.1785; Anal. Calcd. for $C_{15}H_{24}N_2O_3$: %C 64.26, %H 8.63, %N 9.99. Found: %C 64.35, %H 8.93, %N 9.88.

General procedure for preparation of imine derivatives of 11-hydrazaartemisnin and 10-hydrazadeoxyartemisinin, (Preparation of compound 9): To a stirred solution of 10-hydrazadeoxyartemisinin **8** (500 mg, 1.786 mmol) in benzene (5 mL) at rt was added 4-bromobenzaldehyde **11a** (660 mg, 3.568 mmol, 2 equiv), amberlyst-15 (50 mg) and molecular sieves (500 mg) in succession and the reaction mixture was allowed to stir for 2 h. The reaction mixture was filtered and residue was washed well with ether. The combined organic layer was concentrated on rotavapor, purified by column chromatography over silica gel using 5% EtOAc/Hexane as eluent to furnish compound **9** (755 mg, 95% yield) as white solid.

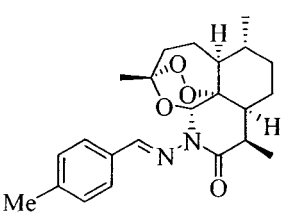
Compounds **15a-h**, **17**, **18** and **19** were also prepared by the same procedure.



(*E*)-*N*-(4-Bromobenzylidene)-10-Hydrazadeoxyartemisinin (9): white solid, mp 218-220 °C; FT-IR (KBr cm^{-1}) 821, 880, 955, 1005 1228, 1657, 2921, 3454; ^1H NMR (300 MHz, $CDCl_3$); δ 0.95 (d, 3H, J = 5.9 Hz), 1.00-1.17 (m, 2H), 1.21 (d, 3H, J = 7.2 Hz), 1.25-1.44 (m, 3H), 1.48 (s, 3H), 1.66-1.98 (m, 5H), 2.02 (td, 1H, J = 13.0, 4.3 Hz), 4.28 (dq, 1H, J = 7.2, 4.3 Hz), 5.48 (s, 1H), 7.51 (d, 2H, J = 8.5 Hz), 7.65 (d, 2H, J = 8.5 Hz), 8.69 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.52 (CH_3), 18.63 (CH_3), 22.35 (CH_2), 23.11 (CH_2), 24.44 (CH_3), 33.58 (CH_2), 34.63 (CH), 34.77 (CH_2), 35.33 (CH), 43.07 (CH), 46.09 (CH), 83.18 (C), 87.62 (CH), 108.24 (C), 124.81 (C), 129.50 (C), 129.50 (2 × CH), 133.79 (C), 152.02 (2 × CH), 169.39 (C); ESI-MS (*m/z*) 447 [$M+H^+$], 449 [$M+2+H^+$]; Anal. Calcd. for $C_{22}H_{27}N_2O_3Br$: %C 59.06, %H 6.08, %N 6.26. Found: %C 58.88, %H 5.95, %N 6.46.

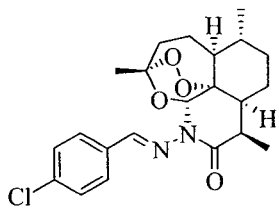


(*E*)-*N*-Benzylidene-11-Hydrazaartemisinin (15a): white solid, mp 178-181 °C; FT-IR (KBr cm^{-1}) 754, 1031, 1067, 1140, 1160, 1218, 1662, 2877, 2930, 3014; ^1H NMR (300 MHz, $CDCl_3$); δ 1.04 (d, 3H, J = 6.3 Hz), 1.09-1.16 (m, 2H), 1.20 (d, 3H, J = 7.2 Hz), 1.34 (s, 3H), 1.41-2.07 (m, 8H), 2.45 (m, 1H), 3.55 (dq, 1H, J = 7.2, 4.5 Hz), 5.77 (s, 1H), 7.39-7.83 (m, 5H), 8.61 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.67 (CH_3), 19.99 (CH_3), 22.02 (CH_2), 25.23 (CH_2), 25.66 (CH_3), 33.91 (CH_2), 34.36 (CH), 36.74 (CH_2), 37.59 (CH), 46.59 (CH), 51.72 (CH), 81.24 (C), 81.80 (CH), 105.20 (C), 128.48 (2 × CH), 128.78 (2 × CH), 131.30 (C), 133.96 (C), 164.67 (CH), 169.12 (C); ESI-MS (*m/z*) 385 [$M+H^+$]; EI-HRMS Calcd. for $C_{22}H_{28}N_2O_4$ [M^+]: 384.2049. Found: 384.2024; Anal. Calcd. for $C_{22}H_{28}N_2O_4$: %C 68.73, %H 7.34, %N 7.29. Found: %C 68.80, %H 7.16, %N 7.25.

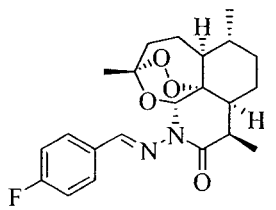


(*E*)-*N*-(4-Methylbenzylidene)-11-Hydrazaartemisinin (15b): white solid, mp 138-140 °C; FT-IR (KBr cm^{-1}) 817, 835, 1026, 1141, 1160, 1234, 1667, 2864, 2936; ^1H NMR (300 MHz, $CDCl_3$); δ 1.03 (d, 3H, J = 6.0 Hz), 1.08-1.11 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.40-2.04 (m, 8H), 2.39 (s, 3H), 2.39-2.45 (m, 1H), 3.54 (brdq, 1H), 5.75 (s, 1H), 7.23 (d, 2H, J = 7.8 Hz), 7.70 (d, 2H, J = 7.8 Hz), 8.54 (s, 1H, Imine H); ^{13}C NMR

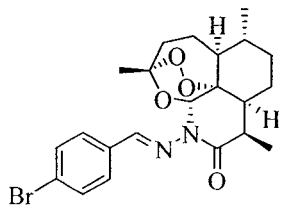
(75 MHz, $CDCl_3$) δ 12.64 (CH_3), 19.96 (CH_3), 21.77 (CH_3), 22.99 (CH_2), 25.20 (CH_2), 25.62 (CH_3), 33.90 (CH_2), 34.29 (CH), 36.72 (CH_2), 36.56 (CH), 46.57 (CH), 51.72 (CH), 81.22 (C), 81.65 (CH), 105.14 (C), 128.47 (2 × CH), 129.49 (2 × CH), 131.19 (C), 141.72 (C), 165.18 (C), 169.02 (C); ESI-MS (*m/z*) 399 [M+H$^+$]; Anal. Calcd. for $C_{23}H_{30}N_2O_4$: %C 69.32, %H 7.59, %N 7.03. Found: %C 69.55, %H 7.77, %N 7.08.



(*E*)-*N*-(4-Chlorobenzylidene)-11-Hydrazaartemisinin (15c): white solid, mp 170-172 °C; FT-IR (KBr cm^{-1}) 670, 760, 932, 1032 1216, 1654, 2931, 3020; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.04 (d, 3H, J = 6.2 Hz), 1.09-1.13 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.41-2.07 (m, 8H), 2.45 (m, 1H), 3.54 (dq, 1H, J = 7.2, 4.4 Hz), 5.76 (s, 1H), 7.40 (d, 2H, J = 8.5 Hz), 7.75 (d, 2H, J = 8.5 Hz), 8.61 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.64 (CH_3), 19.96 (CH_3), 23.01 (CH_2), 25.22 (CH_2), 25.64 (CH_3), 33.88 (CH_2), 34.41 (CH), 36.71 (CH_2), 37.61 (CH), 46.53 (CH), 51.68 (CH), 81.20 (C), 81.91 (CH), 105.25 (C), 129.09 (2 × CH), 129.58 (2 × CH), 132.56 (C), 132.21 (C), 162.48 (CH), 169.26 (C); ESI-MS (*m/z*) 419 [M+H$^+$]; Anal. Calcd. for $C_{22}H_{27}N_2O_4Cl$: %C 63.08, %H 6.50, %N 8.46. Found: %C 62.95, %H 6.66, %N 8.50.

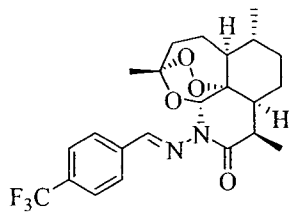


(*E*)-*N*-(4-Fluorobenzylidene)-11-Hydrazaartemisinin (15d): white solid, mp 115-120 °C; FT-IR (KBr cm^{-1}) 702, 759, 1032, 1062, 1216, 1245, 1652, 2877, 2931, 3017; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.03 (d, 3H, J = 6.2 Hz), 1.07-1.14 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H); 1.40-2.06 (m, 8H), 2.40-2.49 (m, 1H), 3.54 (dq, 1H, J = 7.1, 4.5 Hz), 5.75 (s, 1H), 7.07-7.13 (m, 2H), 7.78-7.83 (m, 2H), 8.58 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.61 (CH_3), 19.94 (CH_3), 22.98 (CH_2), 25.19 (CH_2), 25.62 (CH_3), 33.86 (CH_2), 34.32 (CH), 36.69 (CH_2), 37.58 (CH), 46.54 (CH), 51.66 (CH), 81.18 (C), 81.80 (CH), 105.21 (C), 115.93 (d, 2 × CH, $J_{C\text{-}F}$ = 22 Hz), 130.19 (d, C, $J_{C\text{-}F}$ = 3.0 Hz), 130.42 (d, 2 × CH, $J_{C\text{-}F}$ = 9.0 Hz), 163.26 (CH), 164.77 (d, 2 × CH, $J_{C\text{-}F}$ = 250 Hz), 169.20 (C); ESI-MS (*m/z*) 403 [M+H$^+$], 425 [M+Na$^+$]; EI-HRMS Calcd. for $C_{22}H_{27}N_2O_4F$ [M$^+$]: 402.1955. Found: 409.1982.

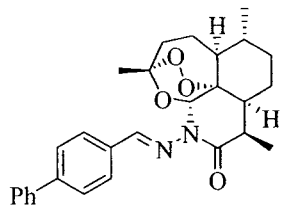


(*E*)-*N*-(4-Bromobenzylidene)-11-Hydrazaartemisinin (15e): white solid, mp 176-178 °C; FT-IR (KBr cm^{-1}) 669, 760, 944, 1031, 1067, 1217, 1659, 2930, 3019; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.04 (d, 3H, J = 6.3 Hz), 1.09 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.41-2.06 (m, 8H), 2.45 (m, 1H),

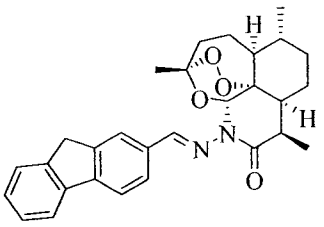
3.54 (dq, 1H, J = 7.2, 4.6 Hz), 5.76 (s, 1H), 7.55 (d, 2H, J = 8.5 Hz), 7.67 (d, 2H, J = 8.5 Hz), 8.60 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.64 (CH_3), 19.96 (CH_3), 23.00 (CH_2), 25.21 (CH_2), 25.64 (CH_3), 33.67 (CH_2), 34.22 (CH), 36.51 (CH_2), 37.40 (CH), 46.33 (CH), 51.48 (CH), 81.18 (C), 81.92 (CH), 105.23 (C), 125.63 (C), 129.76 (2 × CH), 132.04 (2 × CH), 133.01 (C), 162.36 (CH), 169.24 (C); ESI-MS (*m/z*) 363 [M+H$^+$], 465 [M+2+H$^+$]; EI-HRMS Calcd. for $C_{22}H_{27}N_2O_4Br$ [M$^+$]: 462.1154. Found: 462.1152; Anal. Calcd. for $C_{22}H_{27}N_2O_4Br$: %C 56.88, %H 6.28, %N 6.02. Found: %C 57.02, %H 6.28, %N 6.08.



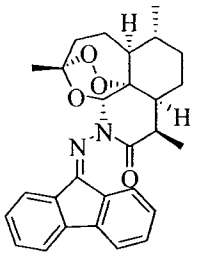
(*E*)-*N*-(4-Trifluoromethylbenzylidene)-11-Hydrazaartemisinin (15f): white solid, mp 170-173 °C; FT-IR (KBr cm^{-1}) 838, 943, 1023, 1063, 1134, 1164, 1232, 1672, 2878, 2932; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.04 (d, 3H, J = 6.2 Hz), 1.09-1.13 (m, 2H), 1.21 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.41-2.06 (m, 8H), 2.40-2.51 (m, 1H), 3.55 (dq, 1H, J = 7.1, 4.5 Hz), 5.79 (s, 1H), 7.67 (d, 2H, J = 8.1 Hz), 8.74 (d, 2H, J = 8.1Hz), 8.74 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.62 (CH_3), 19.92 (CH_3), 22.99 (CH_2), 25.19 (CH_2), 25.60 (CH_3), 33.83 (CH_2), 34.51 (CH), 36.67 (CH_2), 37.59 (CH), 46.46 (CH), 51.64 (CH), 81.15 (C), 82.05 (CH), 105.27 (C), 125.71 (q, C, $J_{C\text{-}F}$ = 4.0 Hz, CF_3), 128.45 (4 × CH), 137.56 (2 × C), 160.75 (CH), 169.38 (C); ESI-MS (*m/z*) 453 [M+H$^+$]; EI-HRMS Calcd. for $C_{23}H_{27}N_2O_4F_3$ [M$^+$]: 452.1923. Found: 452.1922.



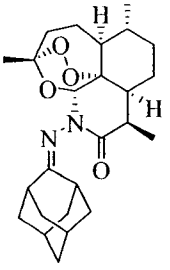
***N*-(4-Biphenyl-1-ylmethylene)-11-Hydrazaartemisinin (15g):** white solid, mp 118-120 °C; FT-IR (KBr cm^{-1}) 669, 760, 930, 1037, 1160, 1217, 1601, 1687, 2940, 3021; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.85-1.13 (m, 2H), 1.05 (d, 3H, J = 6.3 Hz), 1.22 (d, 3H, J = 7.3 Hz), 1.35 (s, 3H), 1.42-1.81 (m, 6H), 2.02-2.08 (m, 2H), 2.41-2.52 (m,1H), 3.57 (dq, 1H, J = 7.2, 4.5 Hz), 5.80 (s, 1H), 7.36-7.91 (m, 9H), 8.66 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.67 (CH_3), 19.97 (CH_3), 23.01 (CH_2), 25.22 (CH_2), 25.66 (CH_3), 33.90 (CH_2), 34.38 (CH), 36.73 (CH_2), 37.58 (CH), 46.58 (CH), 51.72 (CH), 81.23 (C), 81.81 (CH), 105.20 (C), 127.33 (2 × CH), 127.46 (2 × CH), 127.99 (CH), 128.91 (2 × CH), 129.05 (2 × CH), 132.92 (C), 140.55 (C), 143.99 (C), 164.10 (CH), 169.14 (C); ESI-MS (*m/z*) 461 [M+H$^+$]; Anal. Calcd. for $C_{28}H_{32}N_2O_4$: %C 73.02, %H 7.00, %N 6.08. Found: %C 72.95, %H 6.91, %N 6.00.



***N*-(9*H*-Fluoren-2-ylmethylene)-11-Hydrazaartemisinin (15h):** white solid, mp 205-207 °C; FT-IR (KBr cm^{-1}) 734, 947, 1032, 1063, 1142, 1227, 1659, 2930; ^1H NMR (300 MHz, $CDCl_3$); δ 0.88-1.36 (m, 2H), 1.05 (d, 3H, J = 6.2 Hz), 1.21 (d, 3H, J = 7.2 Hz), 1.36 (s, 3H), 1.44-1.88 (m, 6H), 2.02-2.07 (m, 2H), 2.41-2.51 (m, 1H), 3.57 (dq, 1H, J = 7.2, 4.5 Hz), 3.94 (s, 2H), 5.80 (s, 1H), 7.33-7.84 (m, 6H), 8.09 (s, 1H), 8.66 (s, 1H, Imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.68 (CH_3), 19.99 (CH_3), 23.02 (CH_2), 25.23 (CH_2), 25.68 (CH_3), 33.92 (CH_2), 34.34 (CH), 36.72 (CH_2), 36.99 (CH_2), 37.61 (CH), 46.60 (CH), 51.73 (CH), 81.25 (C), 81.77 (CH), 105.22 (C), 120.07 (CH), 120.67 (CH), 124.39 (CH), 125.36 (CH), 127.13 (CH), 124.68 (CH), 128.31 (CH), 132.37 (C), 141.21 (C), 143.68 (C), 144.27 (C), 144.97 (C), 165.31 (CH), 169.14 (C); ESI-MS (*m/z*) 473 [M+H^+]; Anal. Calcd. for $C_{29}H_{32}N_2O_4$: %C 73.70, %H 6.83, %N 5.93. Found: %C 73.99, %H 6.95, %N 5.89.

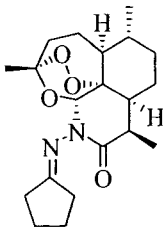


***N*-(Fluoren-9-ylidene)-11-Hydrazaartemisinin (17):** yellow solid, mp 210-213 °C; FT-IR (KBr cm^{-1}) 670, 761, 931, 1033, 1157, 1216, 1661, 2932, 3020; ^1H NMR (300 MHz, $CDCl_3$); δ 1.06 (d, 3H merged), 1.07 (s, 3H), 1.14-2.06 (m, 10H), 1.21 (d, 3H, J = 7.2 Hz), 2.41-2.52 (m, 1H), 3.59 (dq, 1H, J = 7.1, 4.2 Hz), 5.90 (s, 1H), 7.24-8.07 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.50 (CH_3), 20.01 (CH_3), 23.24 (CH_2), 25.24 (CH_2), 25.48 (CH_3), 33.99 (CH_2), 34.34 (CH), 36.78 (CH_2), 37.61 (CH), 46.94 (CH), 51.74 (CH), 81.58 (C), 82.08 (CH), 105.10 (C), 119.78 (CH), 119.96 (CH), 123.93 (CH), 128.23 (CH), 128.27 (CH), 128.97 (CH), 131.92 (CH), 132.02 (C), 132.42 (CH), 136.57 (C), 141.83 (C), 143.01 (C), 167.36 (CH), 169.05 (C); ESI-MS (*m/z*) 459 [M+H^+]; Anal. Calcd. for $C_{28}H_{30}N_2O_4$: %C 73.34, %H 6.59, %N 6.11. Found: %C 73.65, %H 6.88, %N 5.86.



***N*-(2-Adamantylidene)-11-Hydrazaartemisinin (18):** white solid, mp 168-170 °C; FT-IR (KBr cm^{-1}) 669, 759, 944, 1030, 1216, 1654, 2810, 2932, 3018; ^1H NMR (300 MHz, $CDCl_3$); δ 0.99 (d, 3H, J = 6.2 Hz), 1.03-1.07(m, 2H), 1.14 (d, 3H, J = 7.3 Hz), 1.34 (s, 3H), 1.37-2.47 (m, 21H), 2.87 (m, 2H), 3.43 (dq, 1H, J = 7.3, 4.2 Hz), 5.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.59 (CH_3), 19.97 (CH_3), 22.84 (CH_2), 25.09 (CH_2), 26.07 (CH_3), 27.92 (CH), 28.03 (CH), 33.45 (CH), 33.84 (CH_2), 35.19 (CH), 36.60 (CH_2), 36.95 (CH_2), 37.36 (CH_2), 37.45 (CH), 38.85

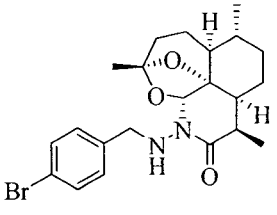
(CH_2), 39.49 (CH_2), 39.64 (CH_2), 40.03 (CH), 47.20 (CH), 51.82 (CH), 81.24 (C), 81.45 (CH), 105.03 (C), 167.95 (C), 187.62 (C); ESI-MS (*m/z*) 429 [M+H$^+$]; Anal. Calcd. for $C_{25}H_{36}N_2O_4$: %C 70.06, %H 8.47, %N 6.54. Found: %C 70.44, %H 8.76, %N 6.49.



***N*-Cyclopentylidene-11-Hydrazaartemisinin (19):** white solid, mp 210-212 °C; FT-IR (KBr cm^{-1}) 670, 761, 929, 1042, 1216, 1652, 3021; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.98 (d, 3H, J = 6.1 Hz), 1.02-1.05 (m, 1H), 1.11 (d, 3H, J = 7.3 Hz), 1.27 (s, 3H), 1.37-2.60 (m, 17H), 3.37 (brdq, 1H), 5.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.48 (CH_3), 19.94 (CH_3), 22.85 (CH_2), 24.57 (CH_2), 24.77 (CH_2), 25.15 (CH_2), 25.66 (CH_2), 32.51 (CH_2), 33.22 (CH_2), 33.48 (CH_3), 33.81 (CH_2), 36.70 (CH_2), 37.51 (CH), 46.67 (CH), 51.62 (CH), 80.75 (C), 81.18 (C), 104.73 (C), 166.14 (C), 189.08 (C); ESI-MS (*m/z*) 362 [M+H$^+$].

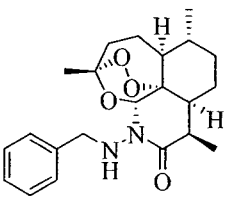
General procedure for preparation of amine derivatives of 11-hydrazaartemisnin and 10-hydrazadeoxyartemisinin, (Preparation of compound 10): To a stirred solution of compound **9** (500 mg, 1.121 mmol) in benzene (15 mL) at 0 °C was added $NaBH_4$ (213mg, 5 equiv) and the reaction mixture was allowed to stir at same temperature for 4 h. The reaction mixture was quenched with glacial AcOH (3 mL), neutralized with saturated $NaHCO_3$ (10 mL), and extracted with ether (3 × 25 mL). The combined organic layer was concentrated on rotavapor, purified by column chromatography over silica gel using 10% EtOAc/Hexane as eluent to furnish compound **9** (410 mg, 83% yield) as white solid.

Compounds **16a-h,** were also prepared by the same procedure.

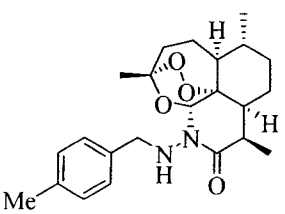


***N*-(4-Bromobenzyl)-10-Hydrazadeoxyartemisinin (10)** white solid, mp 140-142 °C; FT-IR (KBr cm^{-1}) 790, 880, 1006 1268, 1592, 1653, 2935, 3447; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.68-1.06 (m, 2H), 0.88 (d, 3H, J = 5.6 Hz), 1.17 (d, 3H, J = 7.3 Hz), 1.20-1.28 (m, 2H), 1.46 (s, 3H), 1.56-1.85 (m, 5H), 1.91 (td, 1H, J = 13.2, 4.4 Hz), 3.10 (dq, 1H, J = 7.3, 4.4 Hz), 4.04 (s, 2H, Benzylic Hs), 5.01 (s, 1H), 5.22 (brs, 1H, NH), 7.35 (d, 2H, J = 8.3 Hz), 7.46 (d, 2H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.48 (CH_3), 18.61 (CH_3), 22.32 (CH_2), 22.85 (CH_2), 24.46 (CH_3), 33.54 (CH), 33.76 (CH_2), 34.79 (CH_2), 35.17 (CH), 43.02

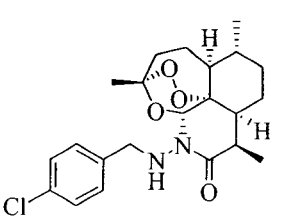
(CH), 45.80 (CH), 54.38 (CH_2), 82.89 (C), 88.79 (CH), 107.57 (C), 121.74 (C), 131.43 (2 × CH), 131.62 (2 × CH), 131.87 (C), 171.70 (C); ESI-MS (*m/z*) 449 [M+H$^+$], 451 [M+2+H$^+$]; Anal. Calcd. for $C_{22}H_{29}N_2O_3Br$: %C 58.80, %H 6.50, %N 6.23. Found: %C 58.79, %H 5.89, %N 6.36.



***N*-Benzyl-11-Hydrazaartemisinin (16a):** oil; FT-IR (neat cm^{-1}) 670, 761, 930, 1034, 1216, 1419, 1659, 2931, 3020; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.77-1.00 (m, 2H), 0.99 (d, 3H, J = 5.7 Hz), 1.17 (d, 3H, J = 7.3 Hz), 1.27-2.11 (m, 9H), 1.49 (s, 3H), 3.45 (dq, 1H, J = 7.1, 4.6 Hz), 4.04 (d, 1H, J = 10.9 Hz, Benzylic H), 4.15 (d, 1H, J = 10.9 Hz, Benzylic H) 5.28 (brs, 1H, NH), 5.36 (s, 1H), 7.28-7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.59 (CH_3), 19.93 (CH_3), 22.88 (CH_2), 22.12 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.78 (CH_2), 36.95 (CH_2), 37.48 (CH), 46.63 (CH), 51.61 (CH), 56.81 (CH_2), 81.11 (C), 82.50 (CH), 105.13 (C), 127.76 (C), 128.67 (2 × CH), 129.43 (2 × CH), 137.69 (C), 172.18 (C); ESI-MS (*m/z*) 387 [M+H$^+$], 409 [M+Na$^+$]; Anal. Calcd. for $C_{22}H_{30}N_2O_4$: %C 68.37, %H 7.82, %N 7.25. Found: %C 68.59, %H 7.96, %N 7.24.

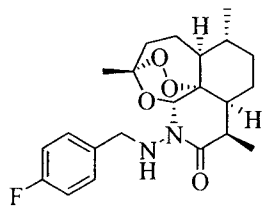


***N*-(4-Methylbenzyl)-11-Hydrazartemisinin (16b):** white solid, mp 125-127 °C; FT-IR (KBr cm^{-1}) 669, 759, 944, 1031, 1216, 1423, 1652, 2928, 3016, 3398; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.77-1.04 (m, 2H), 0.99 (d, 3H, J = 5.8 Hz), 1.17 (d, 3H, J = 7.2 Hz), 1.28-2.12 (m, 8H), 1.49 (s, 3H), 2.34 (s, 3H), 2.40-2.51 (m, 1H), 3.45 (brdq, 1H), 4.03 (d, 1H, J = 10.7 Hz, Benzylic H), 4.10 (d, 1H, J = 10.7 Hz, Benzylic H), 5.01 (s, 1H), 5.23 (brs, 1H, NH), 7.15 (d, 2H, J = 7.8 Hz), 7.37 (d, 2H, J = 7.8Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.61 (CH_3), 19.94 (CH_3), 21.34 (CH_3), 22.89 (CH_2), 25.14 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.80 (CH_2), 36.96 (CH_2), 37.49 (CH), 46.64 (CH), 51.63 (CH), 56.55 (CH_2), 81.12 (C), 82.48 (CH), 105.12 (C), 129.34 (2 × CH), 129.39 (2 × CH), 134.66 (C), 137.38 (C), 172.12 (C); ESI-MS (*m/z*) 401 [M+H$^+$]; Anal. Calcd. for $C_{23}H_{32}N_2O_4$: %C 68.97, %H 8.05, %N 6.99. Found: %C 69.15, %H 8.39, %N 6.77.

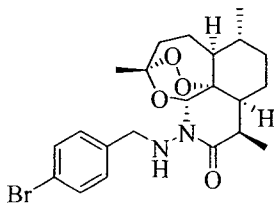


***N*-(4-Chlorobenzyl)-11-Hydrazaartemisinin (16c)**: white solid, mp 118-120 °C; FT-IR (KBr cm^{-1}) 669, 759, 1003, 1007 1217, 1452, 1667, 2860, 2923, 3402; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.77-1.07 (m, 2H), 1.00 (d, 3H, J = 5.9 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.28-1.80 (m, 6H), 1.47 (s, 3H), 1.98-2.12 (m, 2H), 2.41-2.51 (m, 1H), 3.44 (dq, 1H, J = 7.2, 4.6 Hz), 4.01 (m, 1H,

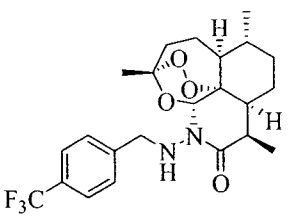
Benzylic H, coupled with NH proton), 4.11 (d, 1H, J = 10.8 Hz, Benzylic H), 5.22 (d, 1H, J = 5.4 Hz, NH coupled with one of the benzylic proton), 5.35 (s, 1H), 7.31 (d, 2H, J = 8.4 Hz), 7.47 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.57 (CH_3), 19.94 (CH_3), 22.92 (CH_2), 25.13 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.76 (CH_2), 36.93 (CH_2), 37.53 (CH), 46.63 (CH), 51.59 (CH), 56.07 (CH_2), 81.12 (C), 82.58 (CH), 105.06 (C), 128.81 (2 × CH), 130.79 (2 × CH), 133.60 (C), 136.24 (C), 172.30 (C); ESI-MS (*m/z*) 421 [M+H$^+$]; Anal. Calcd. for $C_{22}H_{29}N_2O_4Cl$: %C 62.77, %H 6.94, %N 6.66. Found: %C 62.80, %H 6.59, %N 6.60.



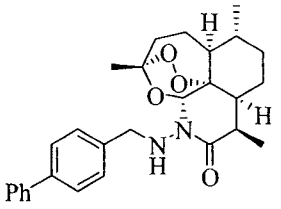
***N*-(4-Fluorobenzyl)-11-Hydrazartemisinin (16d):** oil; FT-IR (neat cm^{-1}) 696, 736, 831, 1031, 1138, 1265, 1457, 1655, 2871, 2926, 3271; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.77-1.07 (m, 2H), 0.99 (d, 3H, J = 5.9 Hz), 1.16 (d, 3H, J = 7.3 Hz), 1.27-2.12 (m, 8H), 1.48 (s, 3H), 2.41-2.51 (m, 1H), 3.45 (dq, 1H, J = 7.2, 4.5 Hz), 4.02 (d, 1H, J = 11.0 Hz, Benzylic H), 4.11 (d, 1H, J = 11.0 Hz, Benzylic H),5.28 (s, 1H, NH) 5.36 (s, 1H), 6.99-7.05 (m, 2H), 7.42-7.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.57 (CH_3), 19.94 (CH_3), 22.91 (CH_2), 25.13 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.77 (CH_2), 36.93 (CH_2), 37.52 (CH), 46.63 (CH), 51.59 (CH), 56.06 (CH_2), 81.13 (C), 82.55 (CH), 105.17 (C), 115.51 (d, 2 × CH, $J_{C\text{-}F}$ = 22 Hz), 131.11 (d, 2 × CH, $J_{C\text{-}F}$ = 8.0 Hz), 133.48 (d, 2 × C, $J_{C\text{-}F}$ = 3.0 Hz), 162.56 (d, 2 × CH, $J_{C\text{-}F}$ = 245 Hz), 172.28 (C); ESI-MS (*m/z*) 405 [M+H$^+$], 427 [M+Na$^+$]; EI-HRMS Calcd. for $C_{22}H_{29}N_2O_4F$ [M$^+$]: 404.2111. Found: 404.2117.



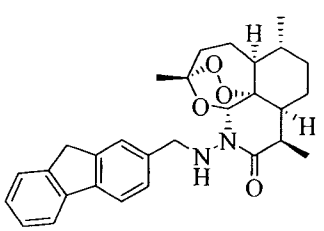
***N*-(4-Bromobenzyl)-11-Hydrazaartemisinin (16e):** white solid, mp 152-154 °C; FT-IR (KBr cm^{-1}) 670, 761, 930, 1033, 1216, 1425, 1650, 2930, 3021, 3401; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.81-1.81 (m, 2H), 1.00 (d, 3H, J = 5.8 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.32-2.12 (m, 8H), 1.47 (s, 3H), 2.46 (m,1H), 3.44 (dq, 1H, J = 7.2, 4.6 Hz), 4.00 (d, 1H, J = 11.1 Hz, Benzylic H), 4.15 (d, 1H, J = 11.1 Hz, Benzylic H) 5.24 (brs, 1H, NH), 5.35 (s, 1H), 7.36 (d, 2H, J = 8.3 Hz), 7.47 (d, 2H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.59 (CH_3), 19.96 (CH_3), 22.93 (CH_2), 25.13 (CH_2), 25.73 (CH_3), 33.61 (CH), 33.76 (CH_2), 36.93 (CH_2), 37.54 (CH), 46.63 (CH), 51.59 (CH), 56.12 (CH_2), 81.14 (C), 82.58 (CH), 105.18 (C), 121.76 (C), 131.15 (2 × CH), 131.79 (2 × CH), 136.72 (C), 172.32 (C); ESI-MS (*m/z*) 465 [M+H$^+$], 467 [M+2+H$^+$]; Anal. Calcd. for $C_{22}H_{29}N_2O_4Br$: %C 56.78, %H 6.28, %N 6.02. Found: %C 56.66, %H 6.54, %N 6.10.



***N*-(4-Trifluoromethylbenzyl)-11-Hydrazartemisinin (16f):** white solid, mp 137-140 °C; FT-IR (KBr cm^{-1}) 819, 1027, 1123, 1252, 1421, 1660, 2878, 2943, 3429; ^1H NMR (300 MHz, $CDCl_3$); δ 0.80-1.03 (m, 2H), 1.00 (d, 3H, J = 5.7 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.32-2.11 (m, 8H), 1.46 (s, 3H), 2.41-2.51 (m, 1H), 3.45 (dq, 1H, J = 7.1, 4.6 Hz), 4.06-4.25 (m, 2H, Benzylic Hs), 5.29 (brs, 1H, NH), 5.35 (s, 1H), 7.59 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.55 (CH_3), 19.90 (CH_3), 22.93 (CH_2), 25.13 (CH_2), 25.69 (CH_3), 33.62 (CH), 33.75 (CH_2), 36.92 (CH_2), 37.54 (CH), 46.63 (CH), 51.59 (CH), 56.17 (CH_2), 81.13 (C), 82.64 (CH), 105.18 (C), 125.58 (q, C, $J_{C\text{-}F}$ = 3.8 Hz, CF_3), 129.63 (4 × CH), 141.83 (C), 141.85 (C), 172.42 (C); ESI-MS (*m/z*) 455 [M+H$^+$]; EI-HRMS Calcd. for $C_{23}H_{29}N_2O_4F_3$ [M$^+$]: 454.2079. Found: 454.2078.



***N*-(4-Biphenyl-1-ylmethyl)-11-Hydrazaartemisinin (16g)**: white solid, mp 68-70 °C; FT-IR (KBr cm^{-1}) 668, 759, 1032, 1216, 1006 1421, 1652, 2877, 2931, 3278; ^1H NMR (300 MHz, $CDCl_3$); δ 0.82-1.04 (m, 2H), 1.00 (d, 3H, J = 5.8 Hz), 1.19 (d, 3H, J = 7.3 Hz), 1.28-1.75 (m, 6H), 1.51 (s, 3H), 1.99-2.14 (m, 2H), 2.42-2.53 (m, 1H), 3.47 (dq, 1H, J = 7.2, 4.5 Hz), 4.12 (d, 1H, J = 11.1 Hz, Benzylic H), 4.21 (d, 1H, J = 11.1 Hz, Benzylic H), 5.32 (d, 1H, NH), 5.38 (s, 1H), 7.33-7.62 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.61 (CH_3), 19.94 (CH_3), 22.89 (CH_2), 25.13 (CH_2), 25.73 (CH_3), 33.61 (CH), 33.77 (CH_2), 36.94 (CH_2), 37.49 (CH), 46.61 (CH), 51.60 (CH), 56.41 (CH_2), 81.12 (C), 82.51 (CH), 105.14 (C), 127.27 (2 × CH), 127.43 (3 × CH), 128.91 (2 × CH), 129.87 (2 × CH), 136.77 (C), 140.71 (C), 141.14 (C), 172.22 (C); ESI-MS (*m/z*) 463 [M+H$^+$]; EI-HRMS Calcd. for $C_{28}H_{34}N_2O_4$ [M$^+$]: 462.2519. Found: 462.2511; Anal. Calcd. for $C_{28}H_{32}N_2O_4$: %C 72.70, %H 7.41, %N 6.06. Found: %C 72.99, %H 7.02, %N 5.95.

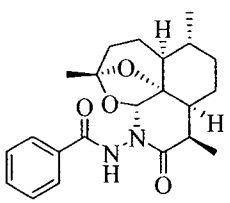


***N*-(9*H*-Fluoren-2-ylmethyl)-11-Hydrazaartemisinin (16h):** white solid, mp 78-80 °C; FT-IR (KBr cm^{-1}) 734, 1031, 1229, 1268, 1458, 592, 1659, 2844, 2930, 3456; ^1H NMR (300 MHz, $CDCl_3$); δ 0.87-1.05 (m, 2H), 0.98 (d, 3H, J = 5.7 Hz), 1.19 (d, 3H, J = 7.3 Hz), 1.28-1.74 (m, 6H), 1.53 (s, 3H), 1.99-2.13 (m, 2H), 2.42-2.53 (m, 1H), 3.57 (dq, 1H, J = 7.2, 4.6 Hz), 3.91 (s, 2H), 4.15 (d, 1H, J = 10.9 Hz, Benzylic H), 4.21 (d,1H, J = 10.7 Hz, Benzylic H), 5.31 (s, 1H, NH), 5.39 (s, 1H), 7.28-7.80 (m, 7H); ^{13}C NMR (75

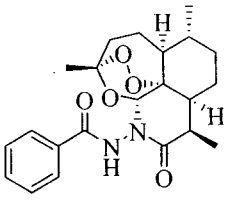
MHz, $CDCl_3$) δ 12.61 (CH_3), 19.92 (CH_3), 22.89 (CH_2), 25.13 (CH_2), 25.76 (CH_3), 33.62 (CH), 33.77 (CH_2), 36.96 (CH_2), 37.00 (CH_2), 37.49 (CH), 46.63 (CH), 51.60 (CH), 57.06 (CH), 81.13 (C), 82.50 (CH), 105.16 (C), 120.04 (CH), 120.06 (CH), 125.21 (CH), 126.21 (CH), 126.81 (CH), 126.88 (CH), 128.21 (CH), 136.17 (C), 141.40 (C), 141.69 (C), 143.59 (C), 143.78 (C), 172.21 (C); ESI-MS (*m/z*) 475 [M+H$^+$], 497 [M+Na$^+$]; Anal. Calcd. for $C_{29}H_{34}N_2O_4$: %C 73.39, %H 7.22, %N 5.90. Found: %C 73.55, %H 6.99, %N 5.95.

General procedure for preparation of amide derivatives of 11-hydrazaartemisnin and 10-hydrazadeoxyartemisinin, (Preparation of compound **12**): To a stirred solution of compound **7** (500mg, 1.786 mmol) and Et_3N (0.9 mL, 8.911 mmol, 5 equiv) in dry benzene (5mL) kept at 0 °C was added benzoyl chloride (1.25 mL, 6.757 mmol, 5 equiv) dissolved in benzene (5 mL) and the reaction mixture was allowed to stir at same temperature for 2 h. The reaction mixture was quenched with water (10 mL), extracted with ether (3 × 25 mL) and the combined organic layer was washed well with saturated $NaHCO_3$ (3 × 10 mL). Concentration and purification by column chromatography over silica gel using 20% EtOAc/Hexane as eluent furnished compound 12 (650 mg, 95% yield) as white solid.

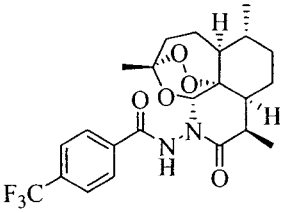
Compounds **14a-k** and **20** were prepared by the same procedure.



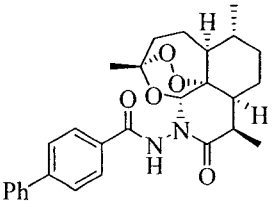
***N*-Benzoyl-10-Hydrazadeoxyartemisinin (12)** white solid, mp 178-180 °C; FT-IR (KBr cm^{-1}) 752, 822, 1100, 1138 1224, 1592, 1669, 1709 2900, 3463; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.91 (d, 3H, J = 6.1 Hz), 1.06-1.10 (m, 2H), 1.22 (d, 3H, J = 7.2 Hz), 1.26-1.39 (m, 3H), 1.50 (s, 3H), 1.61-1.91 (m, 6H), 2.03 (td, 1H, J = 12.9, 4.2 Hz), 3.18 (dq, 1H, J = 7.2, 4.2 Hz), 5.34 (s, 1H), 7.23-7.81 (m, 5H), 9.45 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.36 (CH_3), 18.66 (CH_3), 22.30 (CH_2), 22.71 (CH_2), 24.44 (CH_3), 33.88 (CH), 33.94 (CH_2), 34.72 (CH_2), 35.22 (CH), 43.57 (CH), 45.98 (CH), 83.65 (C), 88.43 (CH), 108.07 (C), 127.65 (2 × CH), 128.47 (2 × CH), 131.47 (C), 132.15 (CH), 166.56 (C), 171.73 (C); ESI-MS (*m/z*) 385 [M+H$^+$]; Anal. Calcd. for $C_{22}H_{28}N_2O_4$: %C 68.73, %H 7.34, %N 7.29. Found: %C 68.50, %H 7.77, %N 7.28.



***N*-Benzoyl-11-Hydrazaartemisinin (14a)** white solid, mp 218-220 °C; FT-IR (KBr cm^{-1}) 670, 761, 930, 1037, 1216, 1523, 1654, 1701, 2936, 3019, 3246; ^1H NMR (300 MHz, $CDCl_3$); δ 1.04 (d, 3H, J = 6.3 Hz), 1.05-1.09 (m, 1H), 1.22 (d, 3H, J = 7.3 Hz), 1.32-1.52 (m, 3H), 1.47 (s, 3H), 1.70-2.05 (m, 6H), 2.39-2.50 (m, 1H), 3.44 (dq, 1H, J = 6.9, 3.5 Hz), 5.62 (s, 1H), 7.24-7.76 (m, 5H), 9.33 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.73 (CH_3), 19.88 (CH_3), 22.74 (CH_2), 25.26 (CH_2), 25.49 (CH_3), 33.71 (CH), 34.05 (CH_2), 36.72 (CH_2), 37.58 (CH), 46.28 (CH), 51.51 (CH), 80.25 (C), 81.29 (CH), 105.19 (C), 127.68 (2 × CH), 128.50 (2 × CH), 131.66 (C), 132.04 (CH), 165.94 (C), 172.51 (C); ESI-MS (*m/z*) 401 [M+H^+]; Anal. Calcd. for $C_{22}H_{28}N_2O_5$: %C 65.98, %H 7.05, %N 7.00. Found: %C 66.06, %H 7.39, %N 7.01.

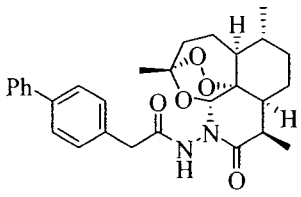


***N*-(4-Trifluoromethylbenzoyl)-11-Hydrazaartemisinin (14b)** white solid, mp 217-220 °C; FT-IR (KBr cm^{-1}) 670, 761, 929, 1039, 1069, 1216, 1534, 1653, 1702 2934, 3020, 3422; ^1H NMR (300 MHz, $CDCl_3$); δ 0.99 (d, 3H, J = 6.1 Hz), 1.03-1.12 (1H), 1.23 (d, 3H, J = 7.3 Hz), 1.37-2.05 (m, 9H), 1.50 (s, 3H), 2.40-2.49 (m, 1H), 3.46 (dq, 1H, J = 7.0, 4.3 Hz), 5.60 (s, 1H), 7.93 (d, 2H, J = 8.2 Hz), 7.84 (d, 2H, J = 8.2 Hz), 10.35 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.83 (CH_3), 19.90 (CH_3), 22.95 (CH_2), 25.28 (CH_2), 25.40 (CH_3), 33.71 (CH), 34.05 (CH_2), 36.64 (CH_2), 37.66 (CH), 46.02 (CH), 51.42 (CH), 79.87 (C), 81.23 (CH), 105.29 (C), 125.48 (q, C, $J_{C\text{-}F}$ = 3.8 Hz), 128.09 (4 × CH), 133.14 (C), 134.34 (CH), 163.81 (C), 173.26 (C); ESI-MS (*m/z*) 469 [M+H^+]; EI-HRMS Calcd. for $C_{23}H_{27}N_2O_5F_3$ [M^+]: 468.1872. Found: 468.1843.

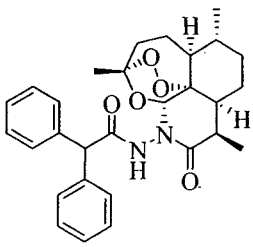


***N*-(4-Biphenylcarbonyl)-11-Hydrazaartemisinin (14c)** white solid, mp 205-207 °C; FT-IR (KBr cm^{-1}) 669, 790, 763, 1035, 1154, 1500, 1614, 1675, 2859, 2930, 3396; ^1H NMR (300 MHz, $CDCl_3$); δ 0.99 (d, 3H, J = 6.1 Hz)), 1.07 (m, 1H), 1.25 (d, 3H, J = 7.3 Hz), 1.38-2.06 (m, 7H), 1.51 (s, 3H), 1.76-2.06 (m, 2H), 2.41-2.51 (m, 1H), 3.47-3.50 (brdq, 1H), 5.66 (s, 1H), 7.37-7.88 (m, 9H), 9.59 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.81 (CH_3), 19.91 (CH_3), 22.85 (CH_2), 25.29 (CH_2), 25.55 (CH_3), 33.74 (CH), 34.09 (CH_2), 36.74 (CH_2), 37.61 (CH), 46.26 (CH), 51.52 (CH), 80.22 (CH), 81.32 (C), 105.20 (C), 127.03 (2 × CH), 127.30 (2 × CH), 128.07 (CH),

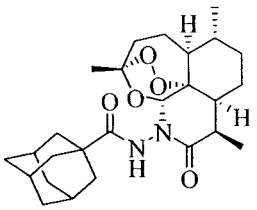
128.20 (2 × CH), 130.23 (C), 140.16 (C), 144.55 (C), 165.56 (C), 172.78 (C); ESI-MS (*m/z*) 477 [M+H$^+$]; EI-HRMS Calcd. for $C_{28}H_{32}N_2O_5$ [M$^+$]: 476.2310. Found: 476.2311; Anal. Calcd. for $C_{28}H_{32}N_2O_5$: %C 70.57, %H 6.77, %N 5.88. Found: %C 70.89, %H 7.00, %N 6.15.



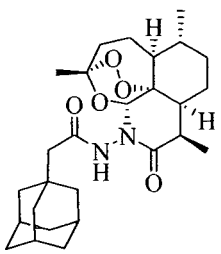
***N*-(4-Biphenylacetyl)-11-Hydrazaartemisinin (14d)** white solid, mp 192-195 °C; FT-IR (KBr cm^{-1}) 669, 887, 1039, 1069, 1144, 1245, 1541, 1645, 1702, 2849, 2905, 3199; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.97-1.03 (m, 1H), 0.98 (d, 3H, J = 6.1 Hz)), 1.19 (d, 3H, J = 7.3 Hz), 1.36 (s, 3H), 1.36-2.05 (m, 9H), 2.38-2.48 (m, 1H), 3.40 (dq, 1H, J = 7.1, 4.3 Hz), 3.75 (s, 2H) 5.53 (s, 1H), 7.36-7.60 (m, 9H), 7.70 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.57 (CH_3), 19.84 (CH_3), 22.58 (CH_2), 25.19 (CH_2), 25.56 (CH_3), 33.74 (CH), 33.93 (CH_2), 36.69 (CH_2), 37.47 (CH), 41.01 (CH_2), 46.30 (CH), 51.42 (CH), 80.51 (CH), 81.24 (C), 105.07 (C), 127.22 (2 × CH), 127.45 (CH), 127.72 (2 × CH), 128.93 (2 × CH), 130.19 (2 × CH), 133.01 (C), 140.38 (C), 140.93 (C), 170.18 (C), 171.91 (C); ESI-MS (*m/z*) 491 [M+H$^+$]; Anal. Calcd. for $C_{28}H_{34}N_2O_5$: %C 71.00, %H 6.99, %N 5.71. Found: %C 71.35, %H 7.25, %N 5.95.



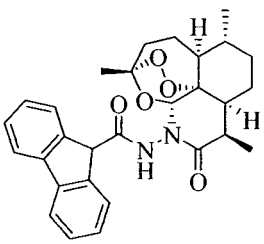
***N*-(2,2-Diphenylacetyl)-11-Hydrazaartemisinin (14e)** white solid, mp 195-197 °C; FT-IR (KBr cm^{-1}) 700, 753, 1036, 1071, 1205, 1493, 1669, 1701, 2933, 3268; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.98 (d, 3H, J = 6.1 Hz)), 1.01-1.07 (m, 1H), 1.19 (d, 3H, J = 7.3 Hz), 1.27 (s, 3H), 1.34-1.84 (m, 7H), 1.96-2.05 (m, 2H), 2.37-2.47 (m, 1H), 3.38 (dq, 1H, J = 7.1, 4.5 Hz), 5.08 (s, 1H), 5.55 (s, 1H), 7.26-7.42 (m, 11H including NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.58 (CH_3), 19.85 (CH_3), 22.70 (CH_2), 25.22 (CH_2), 25.51 (CH_3), 33.79 (CH), 33.93 (CH_2), 36.70 (CH_2), 37.48 (CH), 46.37 (CH), 51.43 (CH), 57.62 (CH), 80.40 (CH), 81.27 (C), 104.98 (C), 127.56 (CH), 127.67 (CH), 128.97 (2 × CH), 129.04 (2 × CH),129.32 (2 × CH), 129.44 (2 × CH), 12.66 (2 × C), 171.01 (C), 171.52 (C); ESI-MS (*m/z*) 491 [M+H$^+$]; EI-HRMS Calcd. for $C_{29}H_{34}N_2O_5$ [M$^+$]: 490.2468. Found: 490.2466; Anal. Calcd. for $C_{29}H_{34}N_2O_5$: %C 71.00, %H 6.99, %N 5.71. Found: %C 70.69, %H 7.35, %N 6.06.



***N*-(1-Adamantanecarbonyl)-11-Hydrazaartemisinin (14f):** white solid, mp 168-170 °C; FT-IR (KBr cm^{-1}) 669, 760, 943, 1036, 1142, 1216, 1448, 1672, 1702, 2851, 2908, 3018, 3334; ^1H NMR (300 MHz, $CDCl_3$); δ 0.63-0.68 (m, 3H), 0.77 (d, 3H, J = 6.3 Hz), 0.97 (d, 3H, J = 7.3 Hz), 1.32-1.87 (m, 21H), 1.19 (s, 3H), 2.18-2.28 (m, 1H), 3.19 (dq, 1H, J = 7.1, 4.0 Hz), 5.26 (s, 1H), 7.16 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.55 (CH_3), 19.86 (CH_3), 22.58 (CH_2), 25.20 (CH_2), 25.73 (CH_3), 28.16 (3 × CH), 33.72 (CH), 36.99 (CH_2), 36.61 (3 × CH_2), 36.76 (CH_2), 37.48 (CH), 39.03 (3 × CH_2), 40.69 (C), 46.48 (CH), 51.51 (CH), 80.76 (CH), 81.35 (C), 104.98 (C), 171.68 (C), 177.23 (C); ESI-MS (*m/z*) 459 [M+H^+]; EI-HRMS Calcd. for $C_{26}H_{39}N_2O_5$ [M+H^+]: 459.2859. Found: 459.2843; Anal. Calcd. for $C_{26}H_{38}N_2O_5$: %C 68.10, %H 8.35, %N 6.11. Found: %C 68.45, %H 8.70, %N 5.88.

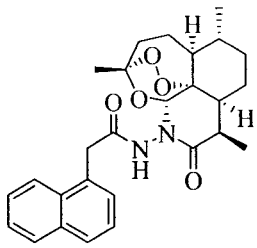


***N*-(2-Adamantan-1yl-acetyl)-11-Hydrazaartemisinin (14g):** white solid, mp 168-170 °C; FT-IR (KBr cm^{-1}) 668, 836, 1039, 1143, 1246, 1537, 1646, 1702, 2849, 2905, 3201; ^1H NMR (300 MHz, $CDCl_3$); δ 0.97-1.05 (m, 1H), 0.98 (d, 3H, J = 6.1 Hz), 1.17 (d, 3H, J = 7.2 Hz), 1.30-2.07 (m, 26H), 1.38 (s, 3H), 2.37-2.48 (m, 1H), 3.37 (dq, 1H, J = 7.1, 4.0 Hz), 5.49 (s, 1H), 7.43 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.65 (CH_3), 19.87 (CH_3), 22.65 (CH_2), 25.28 (CH_2), 25.59 (CH_3), 28.84 (3 × CH), 33.15 (CH), 33.71 (C), 33.98 (CH_2), 36.75 (CH_2), 36.91 (3 × CH_2), 37.59 (CH), 42.55 (3 × CH_2), 46.44 (CH), 49.35 (CH_2), 51.48 (CH), 80.47 (CH), 81.25 (C), 105.08 (C), 169.75 (C), 171.60 (C); ESI-MS (*m/z*) 473 [M+H^+]; Anal. Calcd. for $C_{27}H_{40}N_2O_5$: %C 68.62, %H 8.53, %N 5.93. Found: %C 68.99, %H 8.66, %N 5.67.

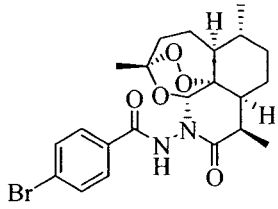


***N*-(9*H*-Fluoren-9-carbonyl)-11-Hydrazaartemisinin (14h)** white solid, mp 181-183 °C; FT-IR (KBr cm^{-1}) 668, 744, 880, 1033, 1152, 1274, 1522, 1664, 1706, 2875, 2934, 3264; ^1H NMR (300 MHz, $CDCl_3$); δ 0.87-1.03 (m, 2H), 0.97 (d, 3H, J = 6.2 Hz), 1.16 (d, 3H, J = 7.3 Hz), 1.25 (s, 3H), 1.28-2.01 (m, 8H), 2.35-2.44 (m, 1H), 3.35 (dq, 1H, J = 7.2, 4.5 Hz), 4.88 (s, 1H), 5.49 (s, 1H), 7.34-7.85 (m, 9H including NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.54 (CH_3), 19.86 (CH_3), 22.70 (CH_2), 25.17 (CH_2), 25.47 (CH_3), 33.75 (CH), 33.96 (CH_2), 36.69 (CH_2), 37.52 (CH), 46.34 (CH), 51.45 (CH), 54.46 (CH), 80.35 (CH), 81.20 (C), 104.97 (C), 120.46 (2 × CH), 125.63 (CH), 125.68 (CH), 127.80 (CH), 128.10 (CH), 128.59 (CH), 128.64 (CH), 140.78 (C), 140.88 (C), 141.63 (C), 141.82 (C), 169.71 (C), 171.43 (C); ESI-MS

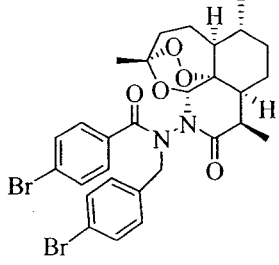
(*m/z*) 489 [M+H$^+$], EI-HRMS Calcd. for $C_{29}H_{32}N_2O_5$ [M$^+$]: 488.2311. Found: 488.2312;; Anal. Calcd. for $C_{29}H_{32}N_2O_5$: %C 71.29, %H 6.60, %N 5.73. Found: %C 71.49, %H 6.34, %N 5.96.



***N*-(1-Naphthylacetyl)-11-Hydrazaartemisinin (14i)** yellow solid, mp 112-115 °C; FT-IR (KBr cm^{-1}) 669, 758, 880, 1035 1216, 1512, 1670, 1703, 2934, 3018, 3272; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.86-1.00 (m, 2H), 0.96 (d, 3H, J = 6.1 Hz),1.12 (s, 3H), 1.16 (d, 3H, J = 7.2 Hz), 1.29-1.96 (m, 8H), 2.341-2.41 (m, 1H), 3.32 (dq, 1H, J = 7.2, 4.4 Hz), 4.15 (s, 2H), 5.46 (s, 1H), 7.42 (s, 1H, NH), 7.44-8.09 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.55 (CH_3), 19.85 (CH_3), 22.64 (CH_2), 25.18 (CH_2), 25.31 (CH_3), 33.77 (CH), 34.95 (CH_2), 36.67 (CH_2), 37.51 (CH), 39.60 (CH_2), 46.31 (CH), 51.44 (CH), 81.37 (CH), 81.19 (C), 104.87 (C), 124.22 (CH), 125.80 (CH), 126.21 (CH), 126.83 (CH), 128.58 (CH), 128.64 (CH), 128.87 (CH), 130.25 (C), 132.32 (CH), 134.15 (C), 169.89 (C), 171.80 (C); ESI-MS (*m/z*) 459 [M+H$^+$]; EI-HRMS Calcd. for $C_{27}H_{32}N_2O_5$ [M$^+$]: 464.2311. Found: 464.2314.

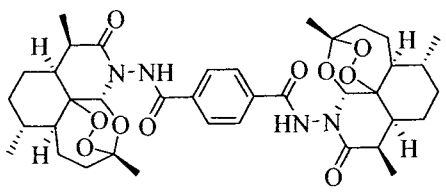


***N*-(4-Bromo-benzoyl)-11-Hydrazaartemisinin (14j)** white solid, mp 230-232 °C; FT-IR (KBr cm^{-1}) 685, 837, 1034, 1069, 1244, 1589, 1692, 1727, 2870, 2937, 3450; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.97-1.01 (m, 1H), 0.98 (d, 3H, J = 6.0 Hz), 1.21 (d, 3H, J = 7.3 Hz), 1.39-2.04 (m, 8H), 1.48 (s, 3H), 2.39-2.49 (m, 1H), 3.44 (brdq, 1H), 5.59 (s, 1H), 7.38 (d, 2H, J = 8.4 Hz), 7.62 (d, 2H, J = 8.4 Hz), 9.87 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.79 (CH_3), 19.90 (CH_3), 22.87 (CH_2), 25.29 (CH_2), 25.47 (CH_3), 33.71 (CH), 34.07 (CH_2), 36.70 (CH_2), 37.64 (CH), 46.14 (CH), 51.48 (CH), 80.03 (C), 81.26 (CH), 105.24 (C), 127.09 (C), 129.27 (2 × CH), 130.22 (C), 131.68 (2 × CH), 164.66 (C), 172.99 (C); ESI-MS (*m/z*) 479 [M+H$^+$]; Anal. Calcd. for $C_{22}H_{27}N_2O_5Br$: %C 55.12, %H 5.68, %N 5.84. Found: %C 54.80, %H 6.06, %N 5.80.



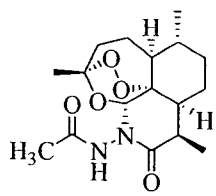
***NN*-Bis-(4-Bromo-benzoyl)-11-Hydrazaartemisinin (14k)** white solid, mp 195-198°C; FT-IR (KBr cm^{-1}) 670, 759, 1033, 1069, 1250, 1587, 1687, 2928, 3021, 3401; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.90 (s, 3H), 1.01-1.12 (m, 2H), 1.03 (d, 3H, J = 6.2 Hz), 1.23 (d, 3H, J = 7.2 Hz), 1.38-2.01 (m, 8H), 2.32-2.41 (m, 1H), 3.59 (dq, 1H, J = 7.2, 4.1 Hz), 5.92 (s, 1H), 7.43 (d, 2H, J = 8.5 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.28 (CH_3), 19.89 (CH_3), 22.54 (CH_2), 24.56

(CH_3), 25.02 (CH_2), 33.98 (CH_2), 34.19 (CH), 36.99 (CH_2), 37.56 (CH), 47.05 (CH), 51.64 (CH), 81.40 (C), 83.44 (CH), 105.50 (C), 127.20 (C), 128.31 (C), 130.14 (2 × CH), 131.26 (2 × CH), 131.97 (4 × CH), 132.63 (C), 134.23 (C), 170.73 (C), 172.17 (C), 172.58 (C); ESI-MS (*m/z*) 661 [M+H$^+$], 663 [M+2+H$^+$], 665 [M+4+H$^+$]; Anal. Calcd. for $C_{29}H_{30}N_2O_6Br_2$: %C 52.59, %H 4.57, %N 4.23. Found: %C 52.80, %H 4.66, %N 4.00.



(Compound 20) white solid, mp 230-233 °C; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.90-1.06 (m, 4H), 0.98 (d, 6H, J = 6.0 Hz), 1.23 (d, 6H, J = 7.3 Hz), 1.39-2.04 (m, 16H), 1.55 (s, 6H), 2.41-2.49 (m, 2H), 3.44 (brdq, 2H), 5.66 (s, 2H), 7.81 (s, 4H), 10.33 (brs, 2H, 2NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.97 (2 × CH_3), 19.94 (2 × CH_3), 22.88 (2 × CH_2), 25.33 (2 × CH_2), 25.60 (2 × CH_3), 33.60 (2 × CH), 34.16 (2 ×CH_2), 36.73 (2 × CH_2), 37.59 (2 × CH), 46.12 (2 × CH), 51.54 (2 × CH), 79.92 (2 × CH), 81.37 (2 × C), 105.26 (2 × C), 128.03 (4 × CH), 134.06 (2 × C), 163.85 (2 × C), 173.31 (C); ESI-MS (*m/z*) 723 [M+H$^+$]; Anal. Calcd. for $C_{38}H_{50}N_4O_{10}$: %C 63.14, %H 6.97, %N 7.75. Found: %C 63.04, %H 6.56, %N 8.00.

Procedure for preparation of acetyl derivative of 11-Hydrazaartemisinin (14l): To a stirred solution of 11-Hydrazaartemisinin **7** (500 mg, 1.689 mmol) in dry DCM (15 mL) kept at 0 °C was added Ac_2O (1.70 mL, 16.891 mmol, 10 equiv) and amberlyst-15 (50 mg) in succession and the reaction mixture was allowed to stir at rt for 14 h. The reaction mixture was filtered, diluted with water (20 mL) and extracted with DCM (3 × 25 mL). The combined organic layer was neutralized with saturated $NaHCO_3$ (3 × 10 mL), dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography over silica gel using 30% EtOAc/Hexane to furnish compound **17** (410 mg, 72% yield) as white solid.



***N*-Acetyl-11-Hydrazaartemisinin (14l):** white solid, mp 122-125 °C; FT-IR (KBr cm^{-1}) 670, 761, 1036, 1216, 1664, 1703, 3020, 3261; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.95-1.01 (m, 2H), 0.96 (d, 3H, J = 6.1 Hz), 1.13 (d, 3H, J = 7.3 Hz), 1.31-2.03 (m, 9H), 1.37 (s, 3H), 2.07 (s, 3H), 2.35-2.45 (m, 1H), 3.34 (dq, 1H, J = 7.1, 3.8 Hz), 5.46 (s, 1H), 8.53 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.52 (CH_3), 19.81 (CH_3), 21.04 (CH_3), 22.42 (CH_2), 25.19 (CH_2), 25.45 (CH_3), 33.65 (CH), 33.94

(CH_2), 36.66 (CH_2), 37.49 (CH), 46.22 (CH), 51.41 (CH), 80.46 (C), 81.14 (CH), 105.08 (C), 169.36 (C), 172.38 (C); ESI-MS (*m/z*) 338 [$M+H^+$]; Anal. Calcd. for $C_{17}H_{26}N_2O_5$: %C 60.34, %H 7.74, %N 8.28. Found: %C 60.55, %H 7.65, %N 8.46.

***In vivo* antimalarial efficacy test**

Random bred Swiss mice of either sex (25 ± 1 g) were inoculated intraperitoneally with 1×10^6 *Plasmodium yoelii nigeriensis* (MDR) parasites on day zero. The treatments with test compounds were administered to a group of 5 mice each at different dose levels ranging between 6-96 mg/kg × 4days. The compounds were administered as solutions in oil via oral or im routes for 4 consecutive days i.e. from day 0 to day 3 in single dose daily. The drug dilutions were prepared in groundnut oil to contain the required amount of drug (0.3 mg for a dose of 24 mg/kg, 0.15 mg for a dose of 12 mg/kg and 0.075 mg for a dose of 6 mg/kg) in 0.1 mL of oil and administered either orally or intramuscularly for each dose. Mice treated with β-arteether and artesunic acid were used as positive control.

Blood smears from experimental mice were observed on day 4, day 7, and day 10 and thereafter at regular interval till day 28 or death of the animal.[8,9] The parasitaemia level on day 4 was compared with the vehicle control group and the percent suppression of parasitaemia in treated groups was calculated. The compounds which showed more than 100% clearance of parasitaemia were identified for further screening.

5.7 References and Notes

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8. (a) One hundred percent suppression of parasitaemia means, the number of parasites are below the detection limit; (b) One hundred percent protection or 100% clearance of

parasitaemia means all the treated mice survive until day 28. Similarly 60% and 20% protection mean only 60% and 20% of the treated mice survived until day 28.

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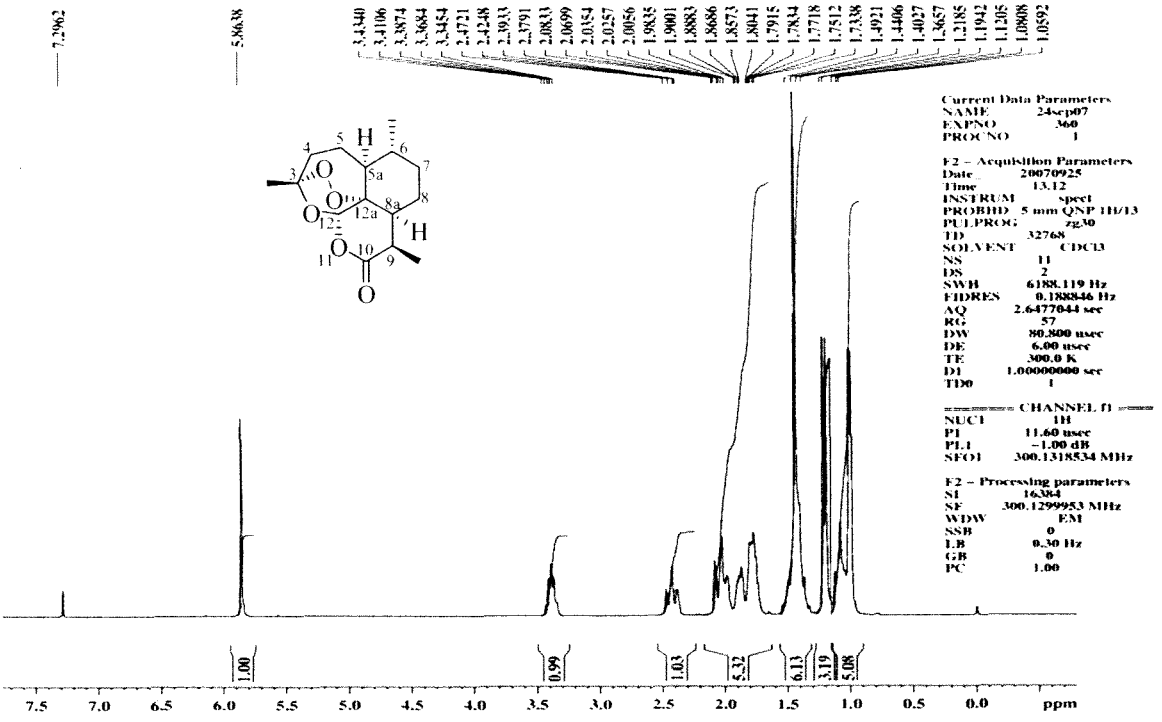
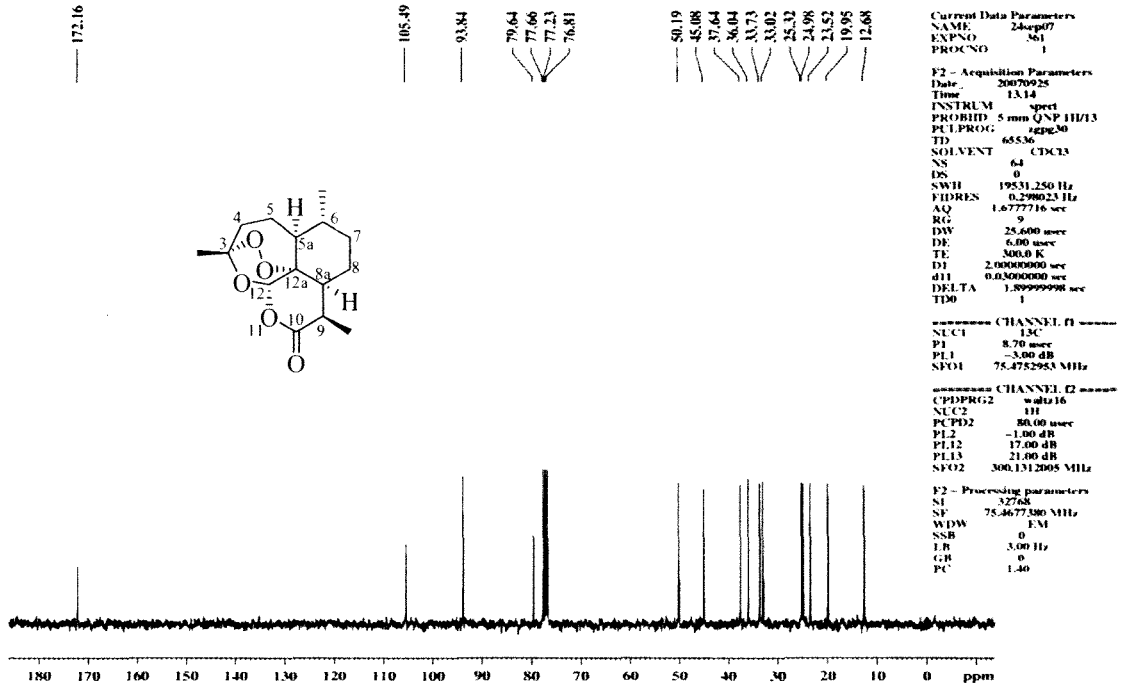
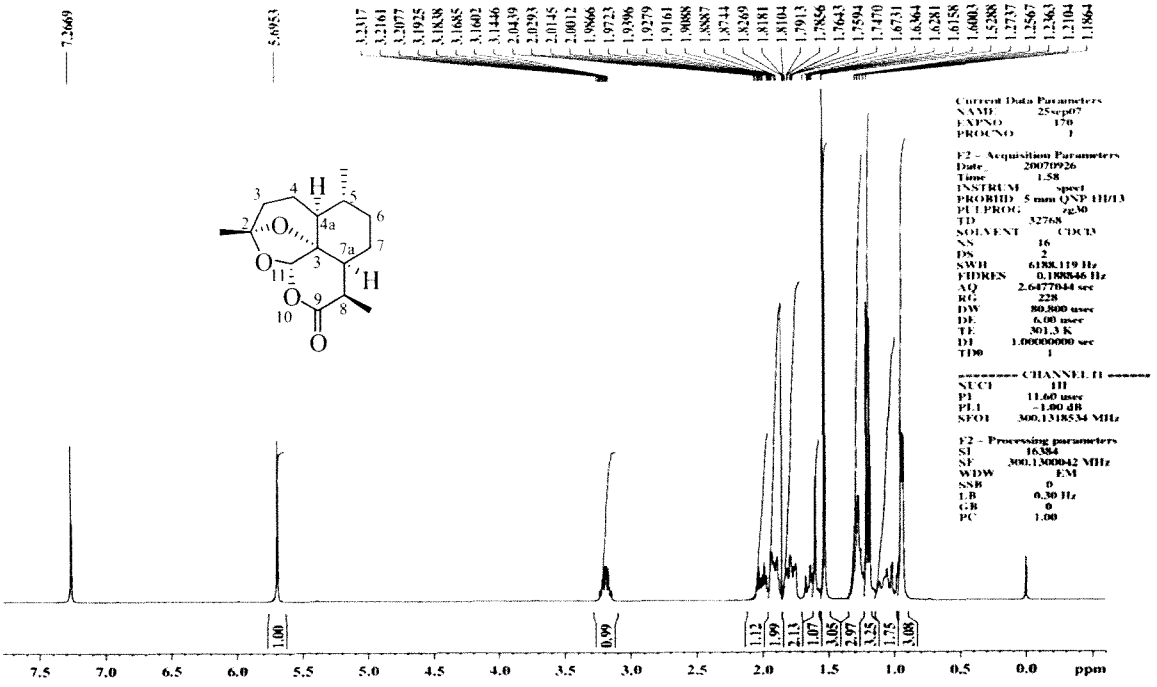


^{1}H NMR Spectra of **1** (300 MHz, $CDCl_3$)



^{13}C NMR Spectra of **1** (75 MHz, $CDCl_3$)



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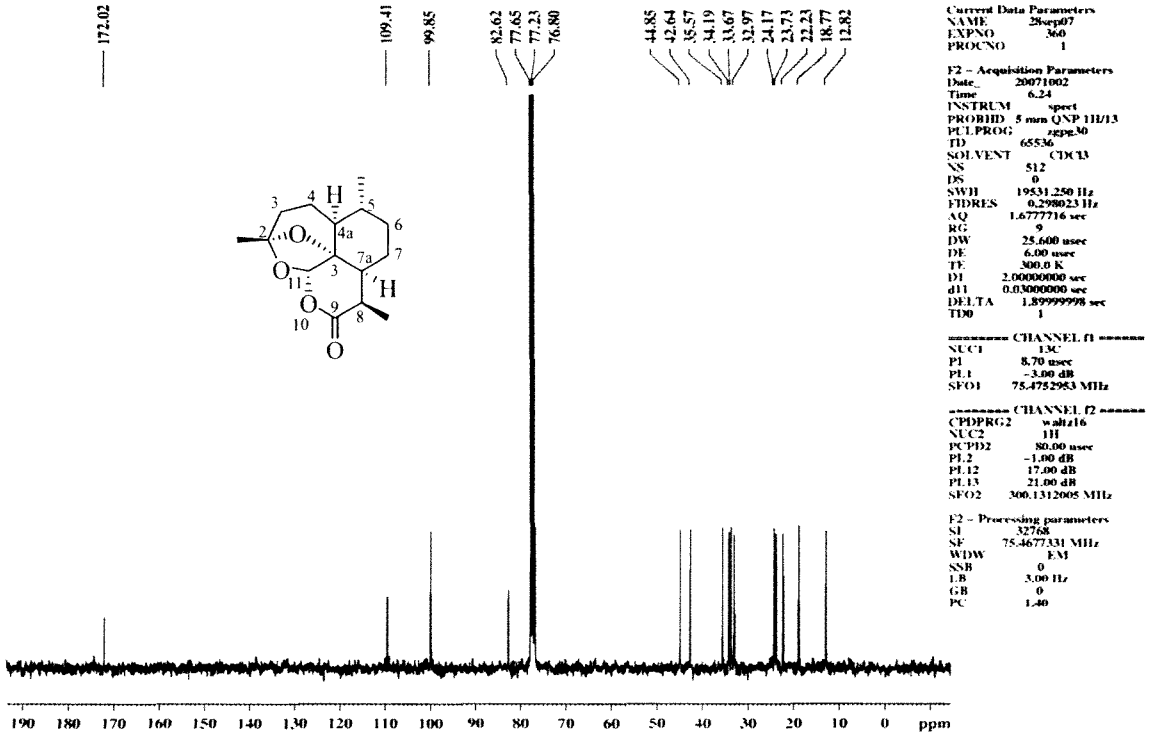
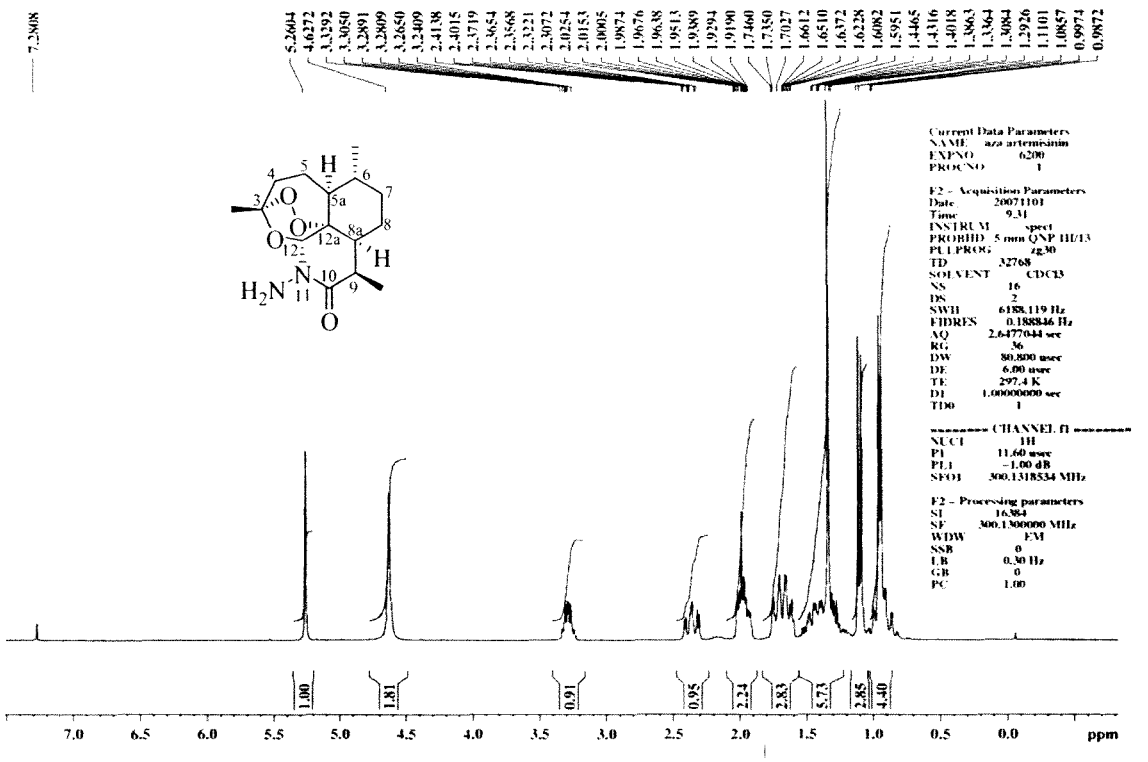


^{13}C NMR Spectra of **6** (75 MHz, $CDCl_3$)



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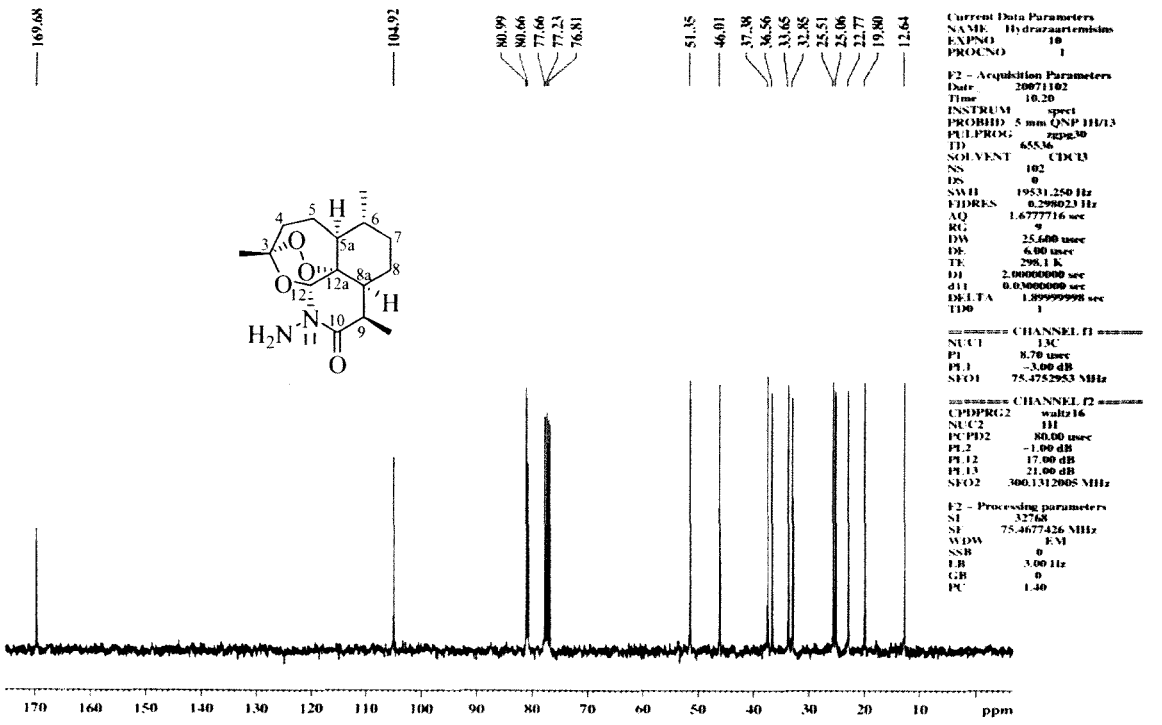

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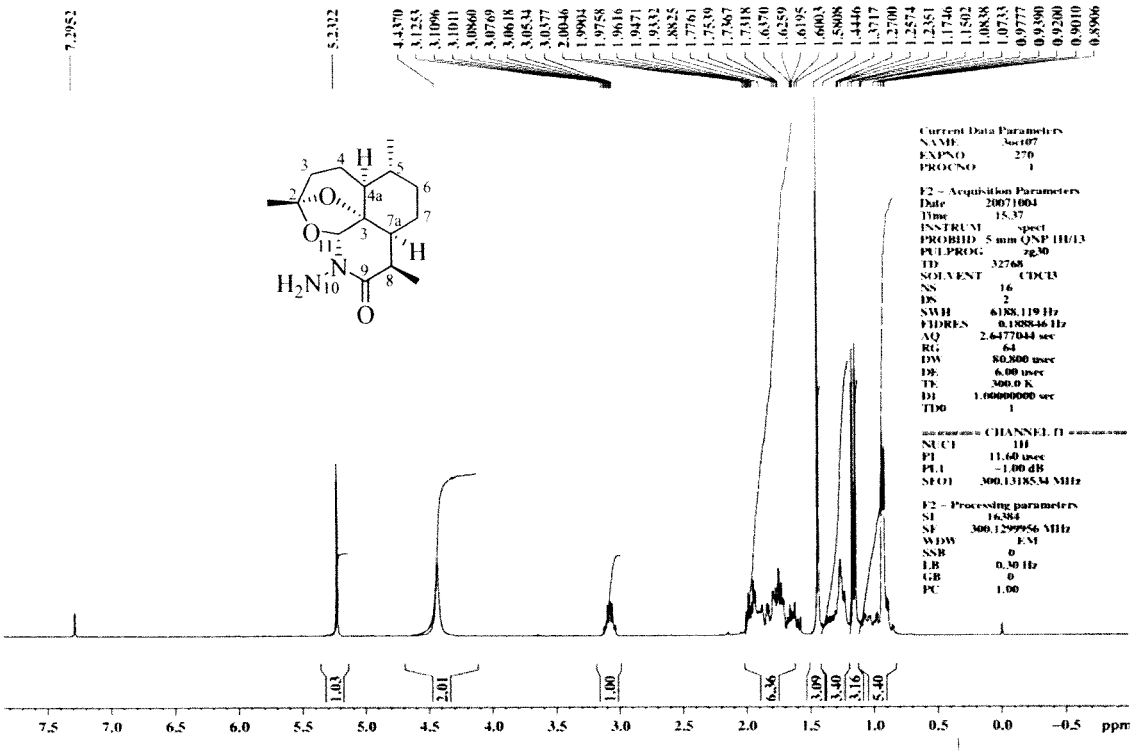
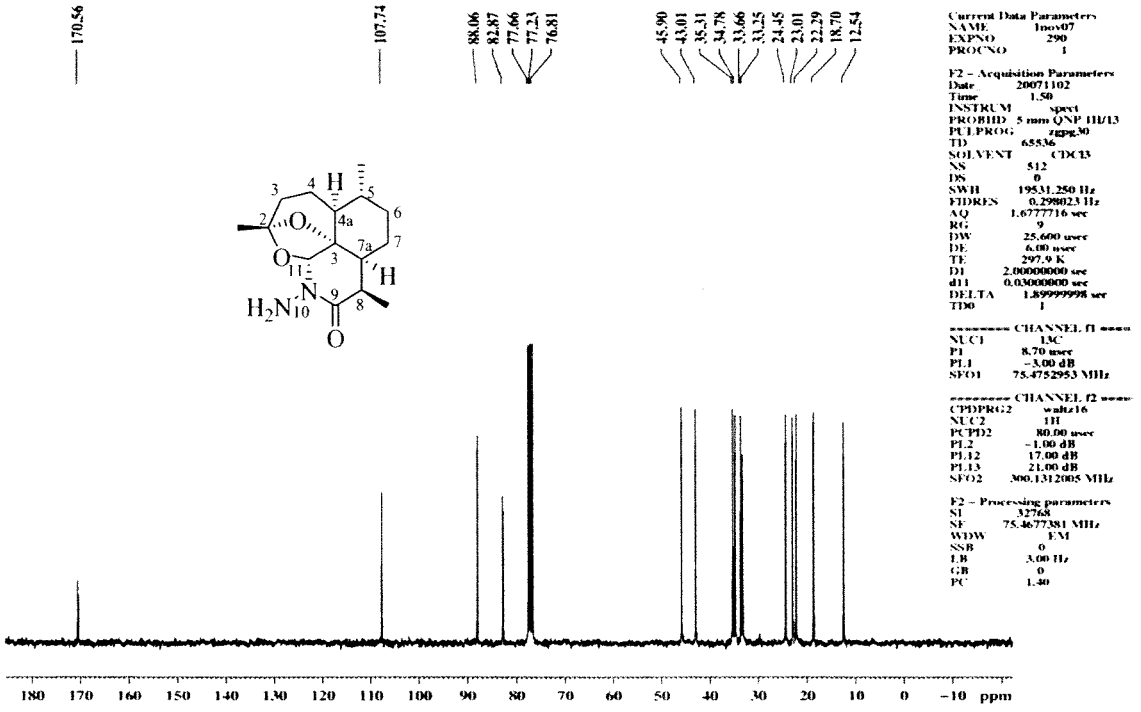


^{1}H NMR Spectra of **8** (300 MHz, $CDCl_3$)



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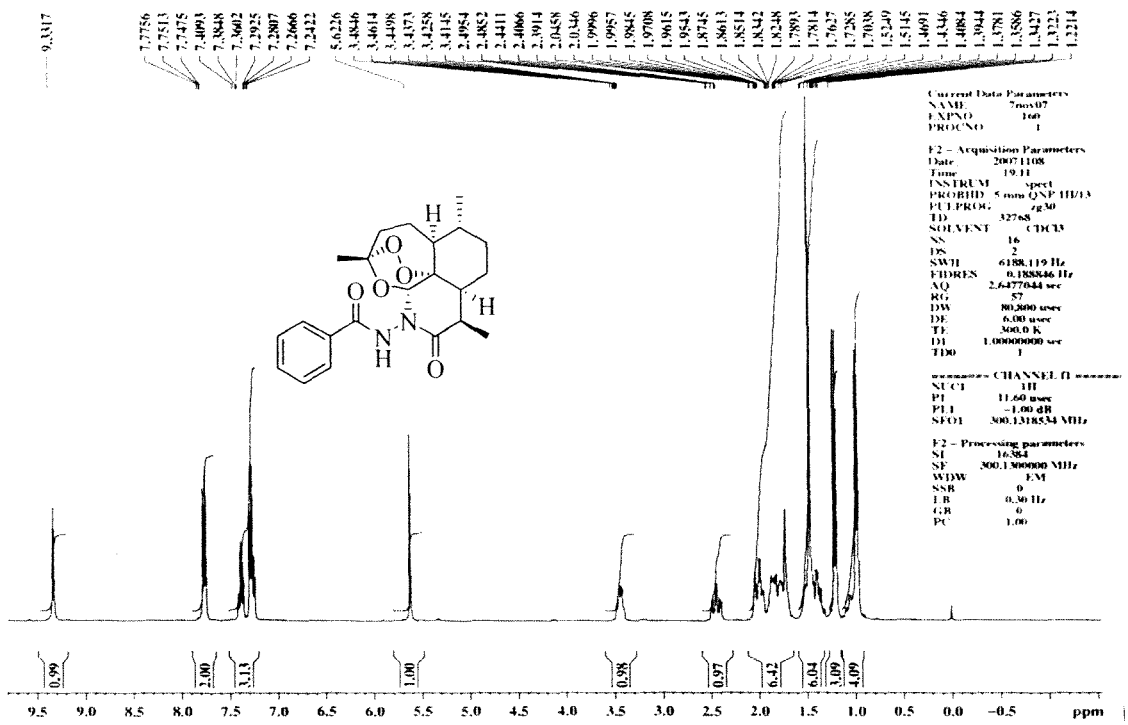
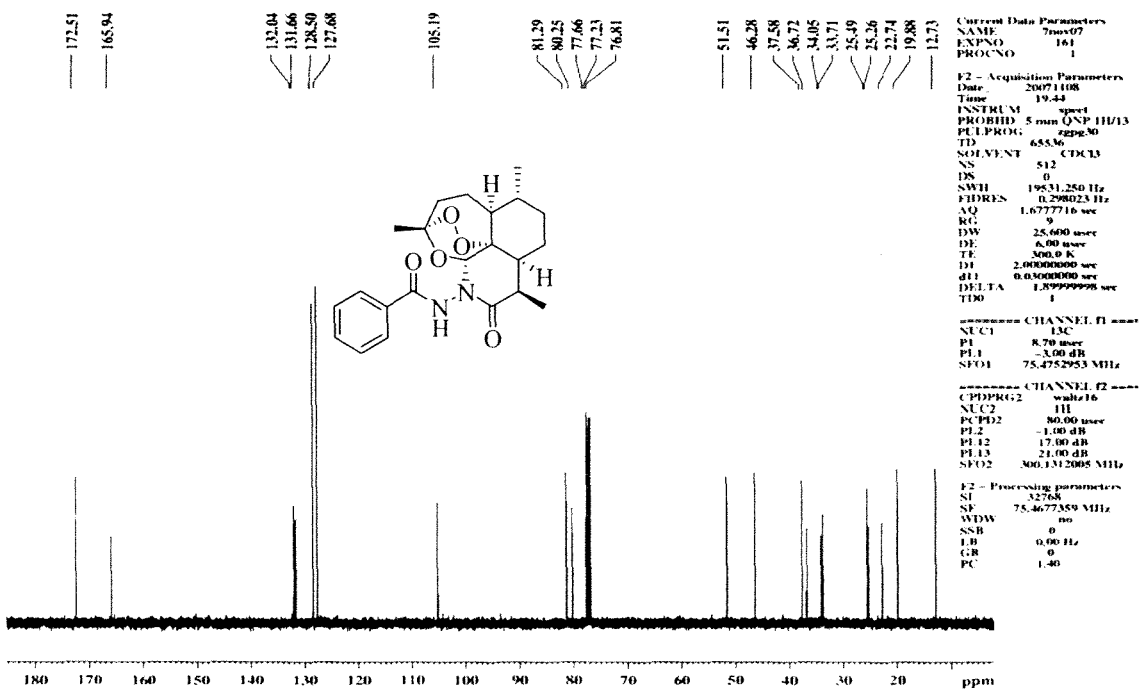
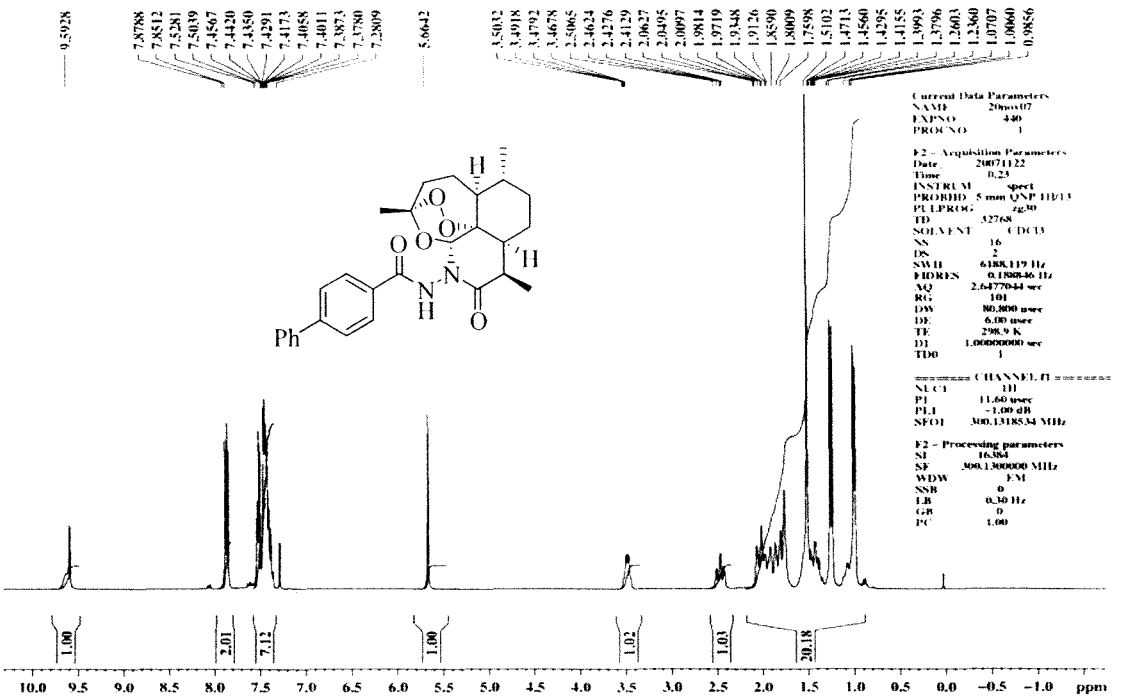


^{1}H NMR Spectra of **14a** (75 MHz, $CDCl_3$)



^{13}C NMR Spectra of **14a** (75 MHz, $CDCl_3$)



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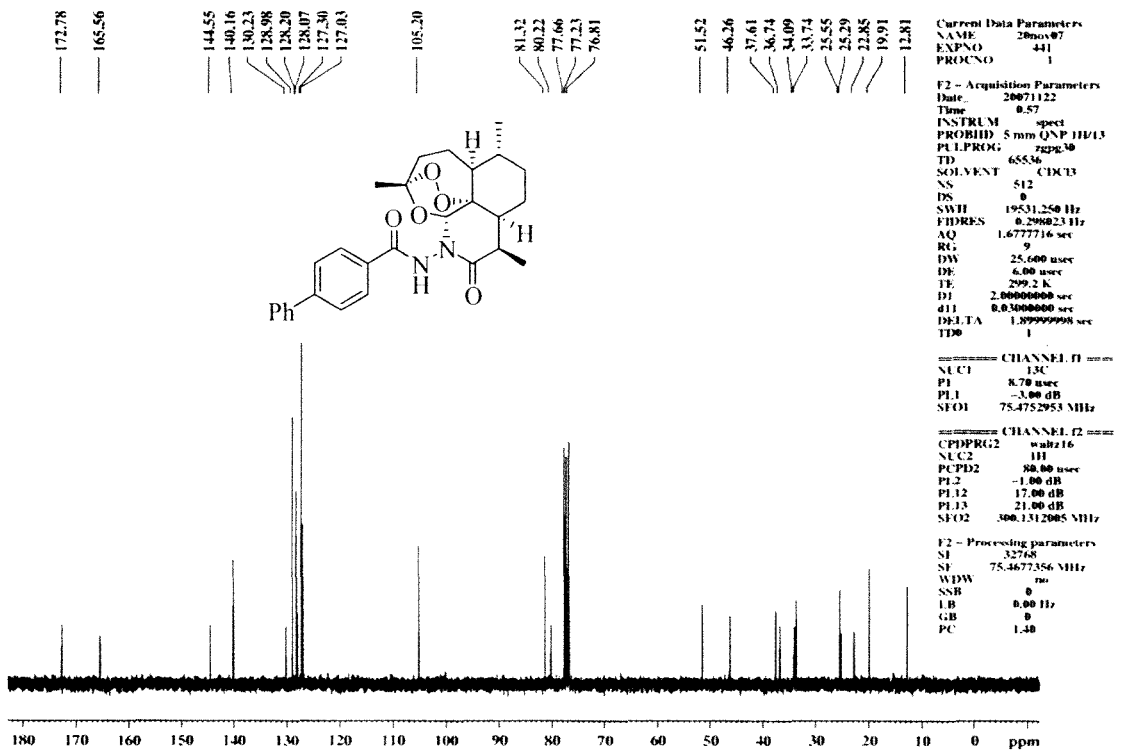

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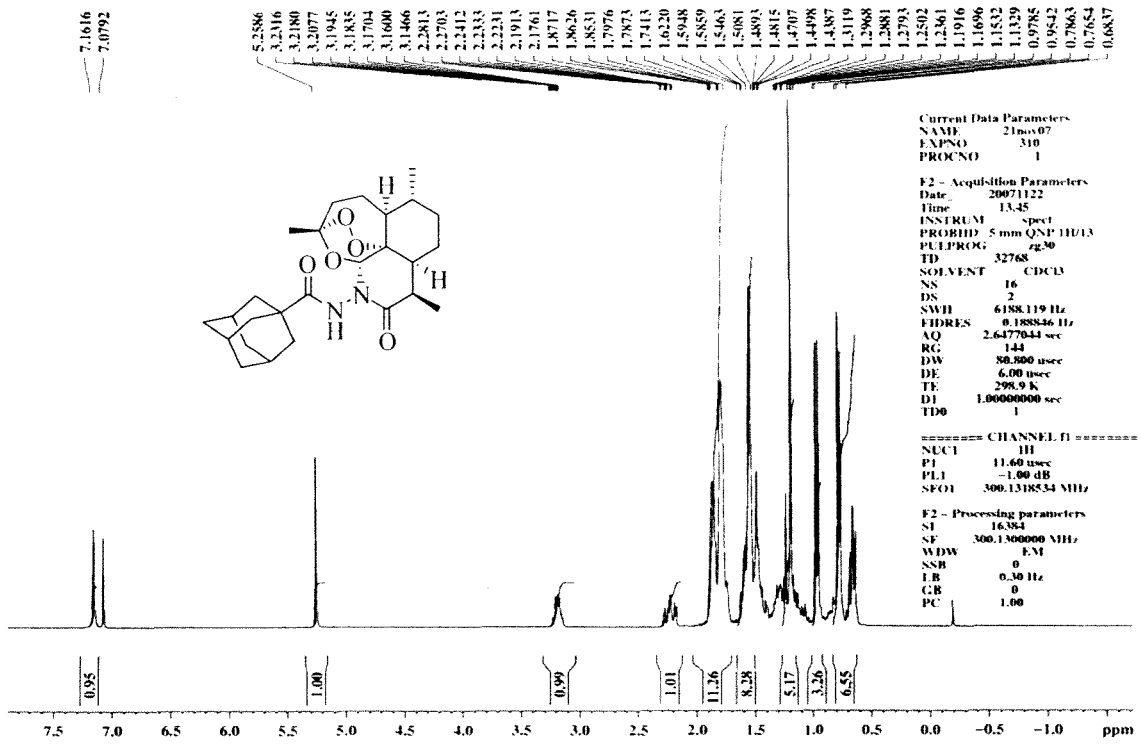

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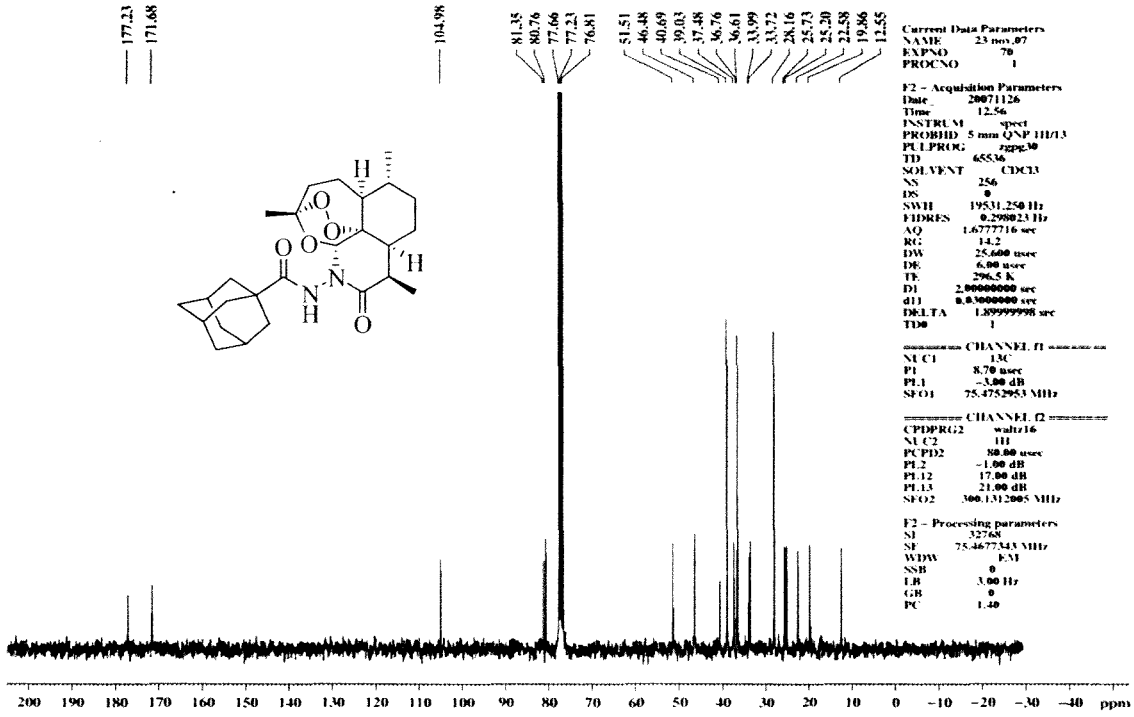

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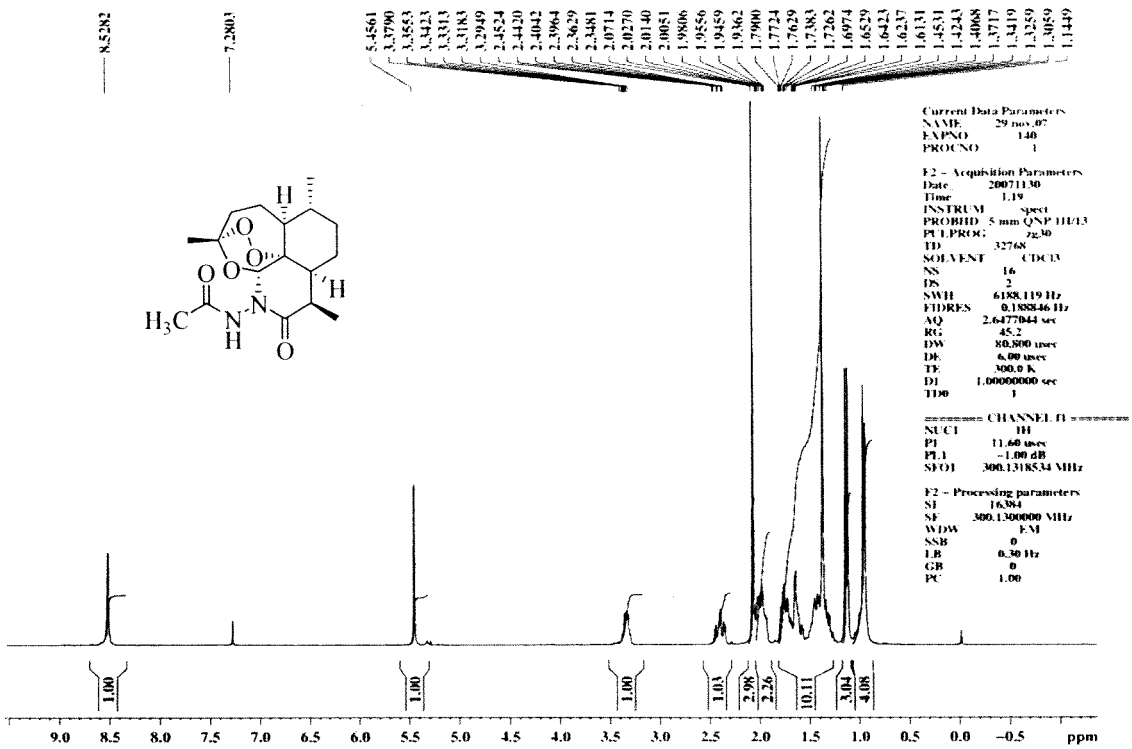
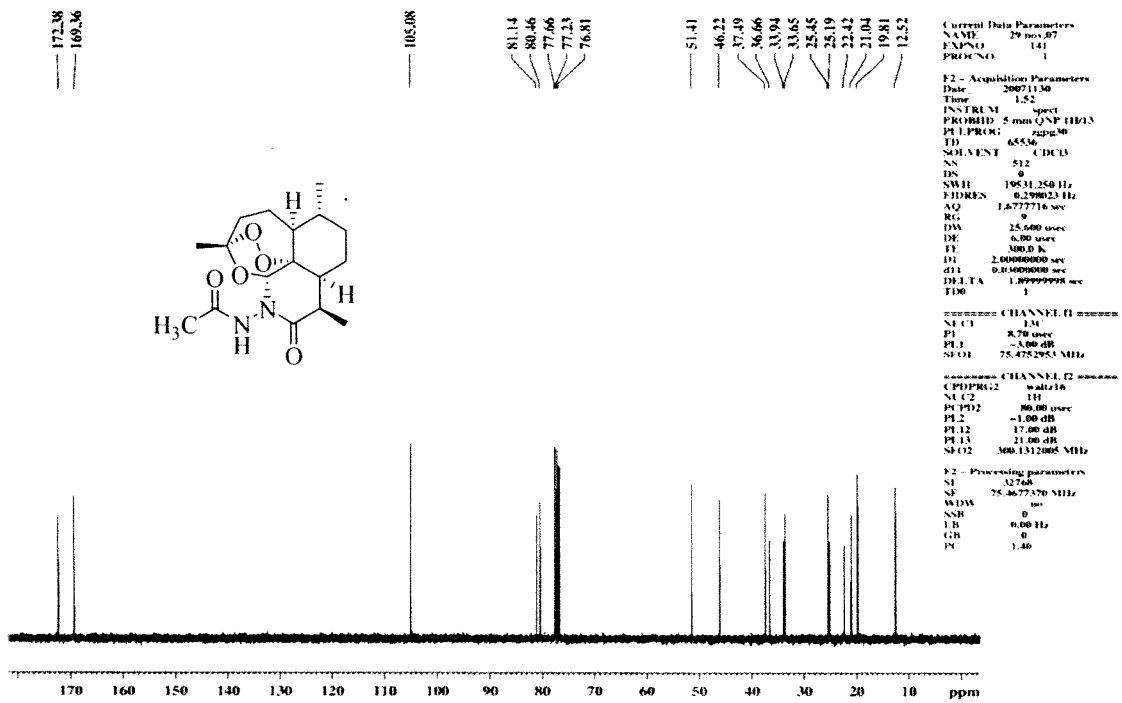


^{1}H NMR Spectra of **14l** (75 MHz, $CDCl_3$)



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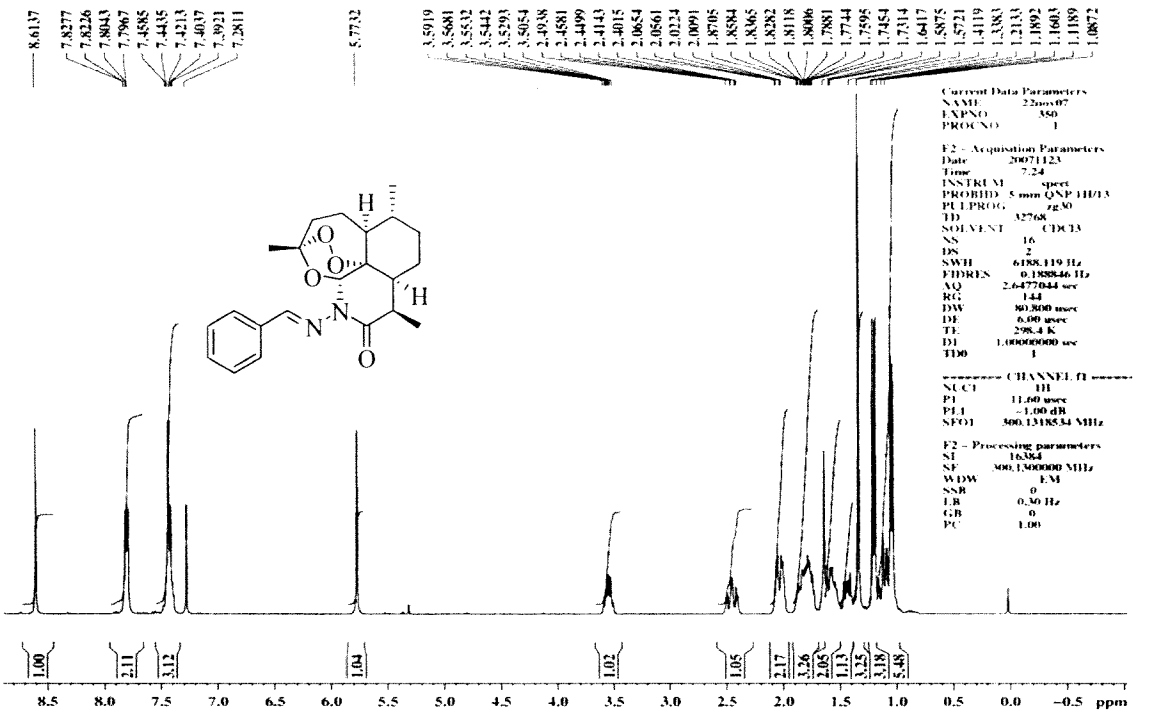
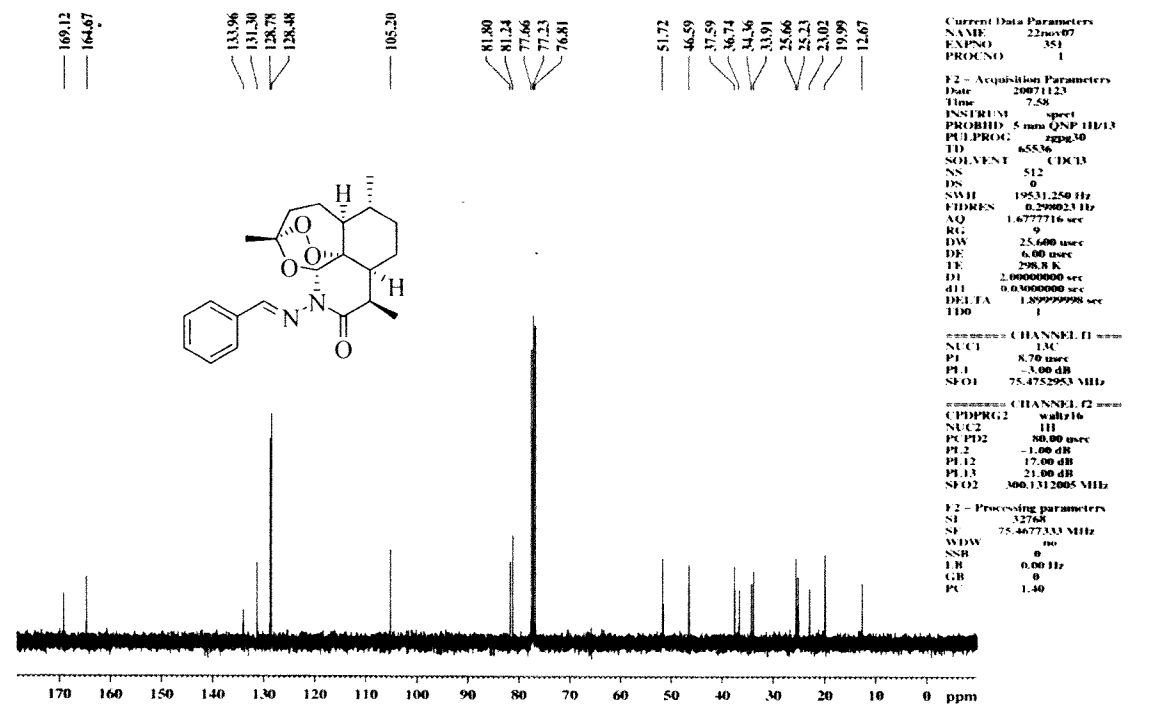
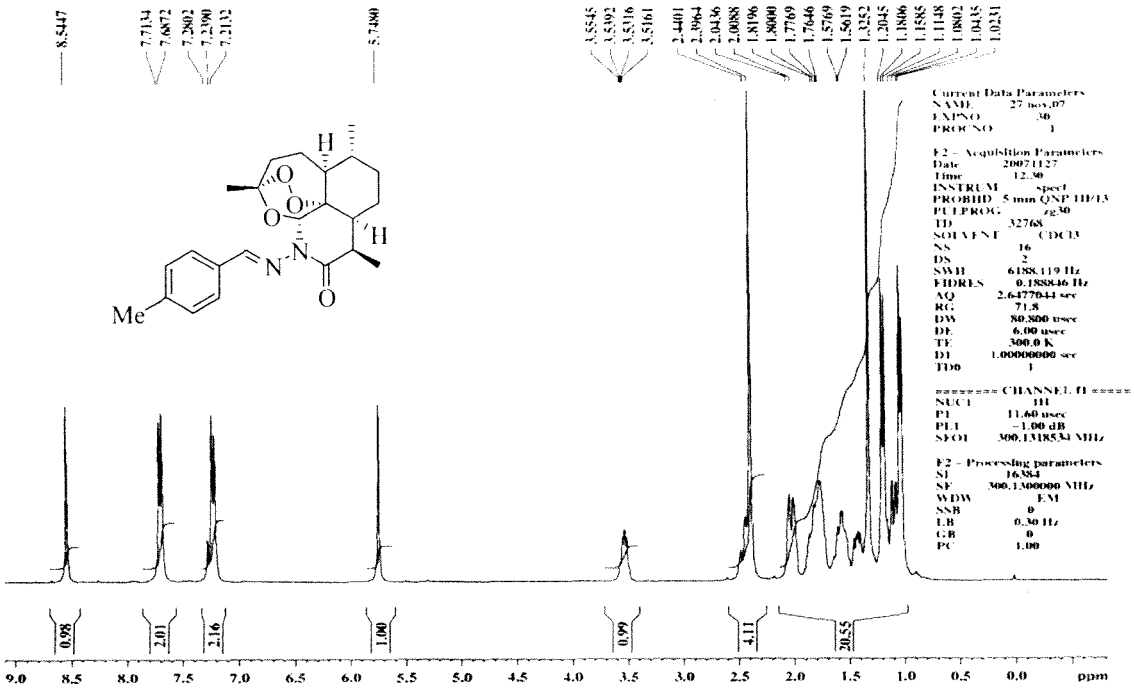


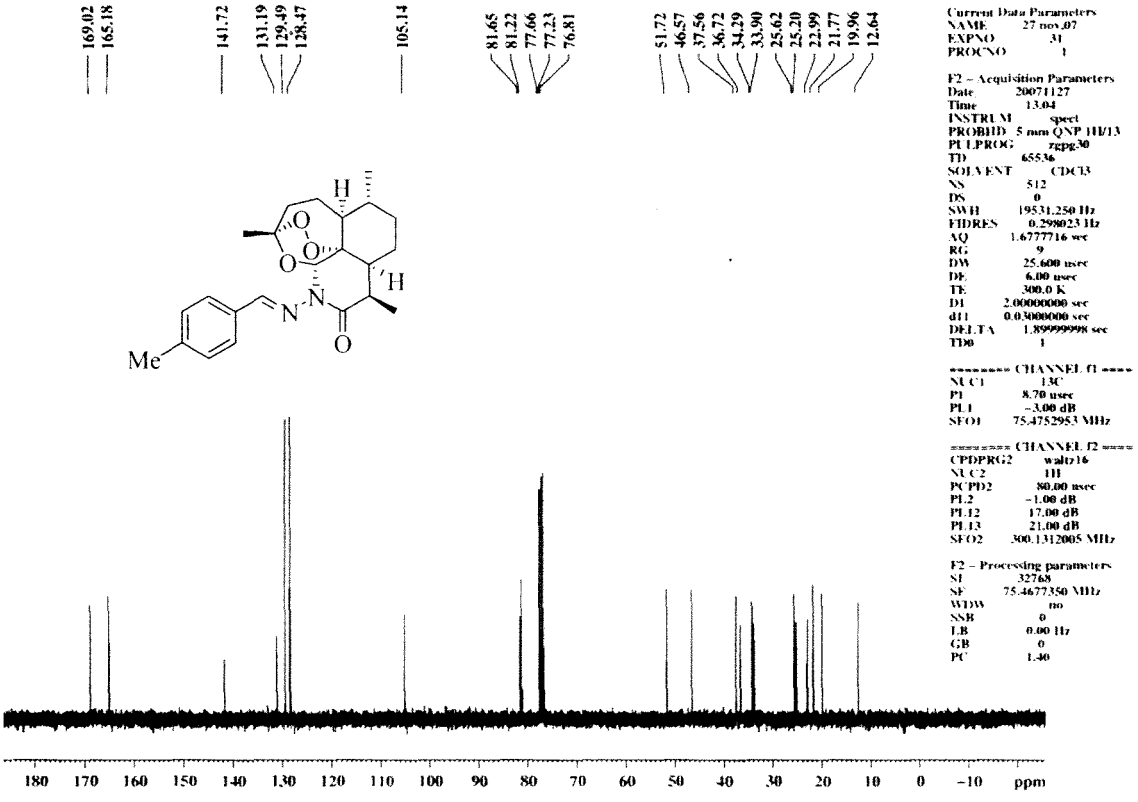
^{1}H NMR Spectra of **15a** (300 MHz, $CDCl_3$)



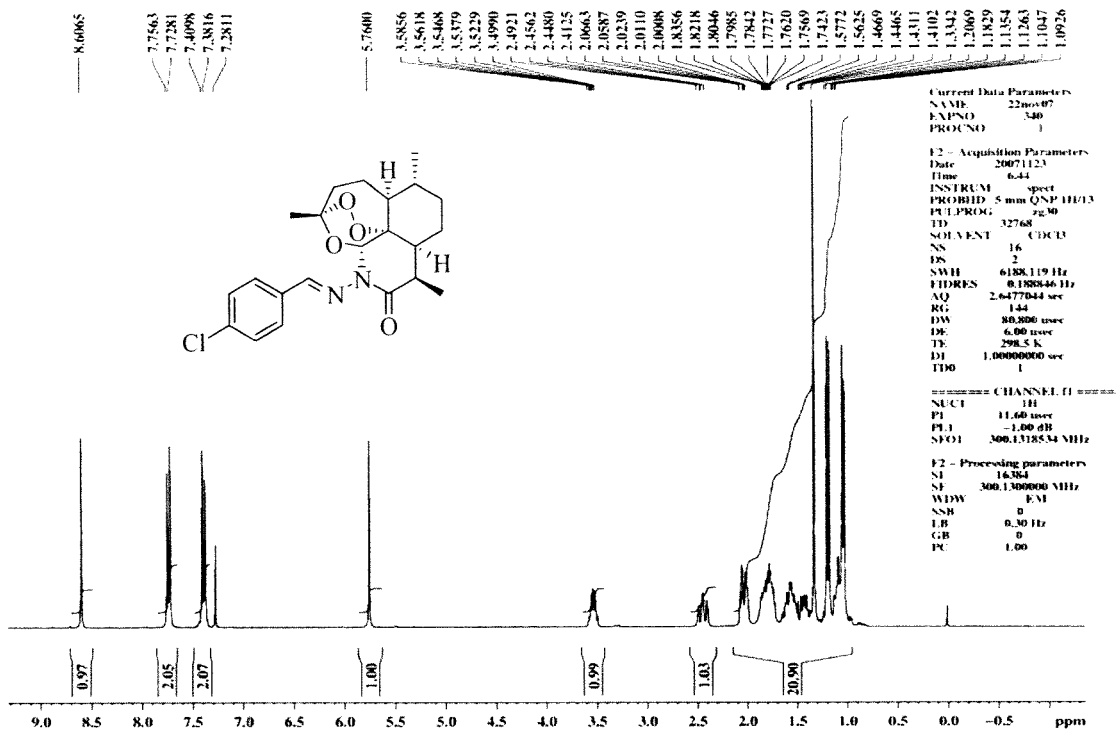
^{13}C NMR Spectra of **15a** (75 MHz, $CDCl_3$)



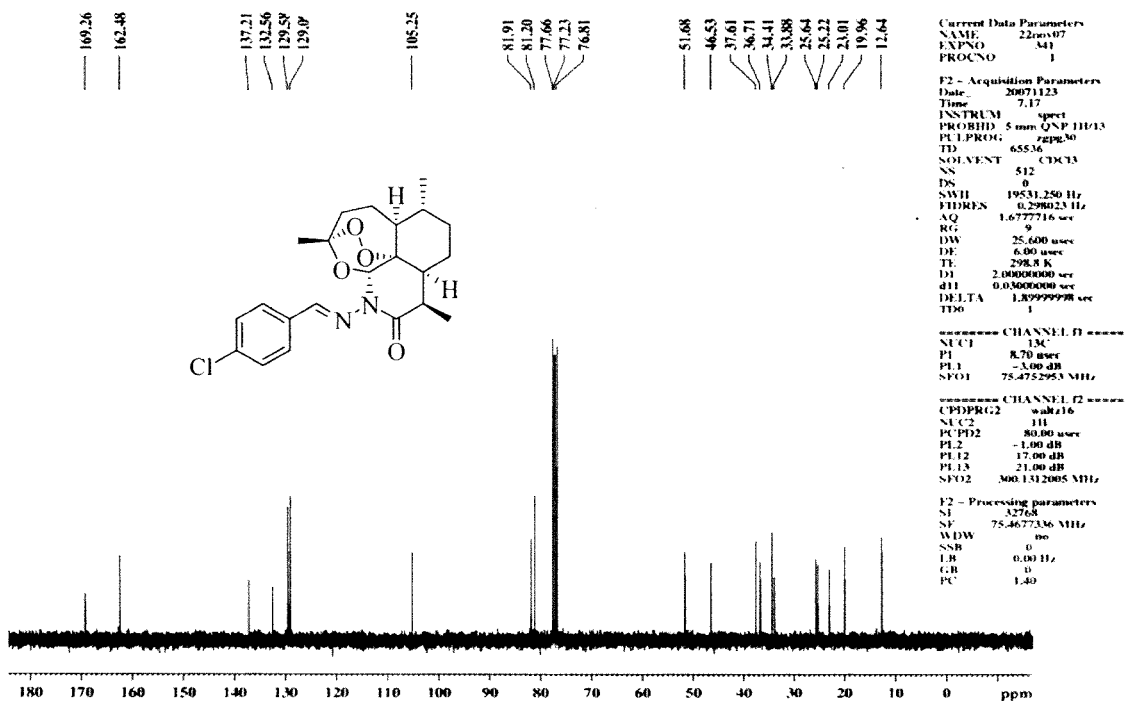
^{1}H NMR Spectra of **15b** (300 MHz, $CDCl_3$)



^{13}C NMR Spectra of **15b** (75 MHz, $CDCl_3$)



^{1}H NMR Spectra of **15c** (75 MHz, $CDCl_3$)



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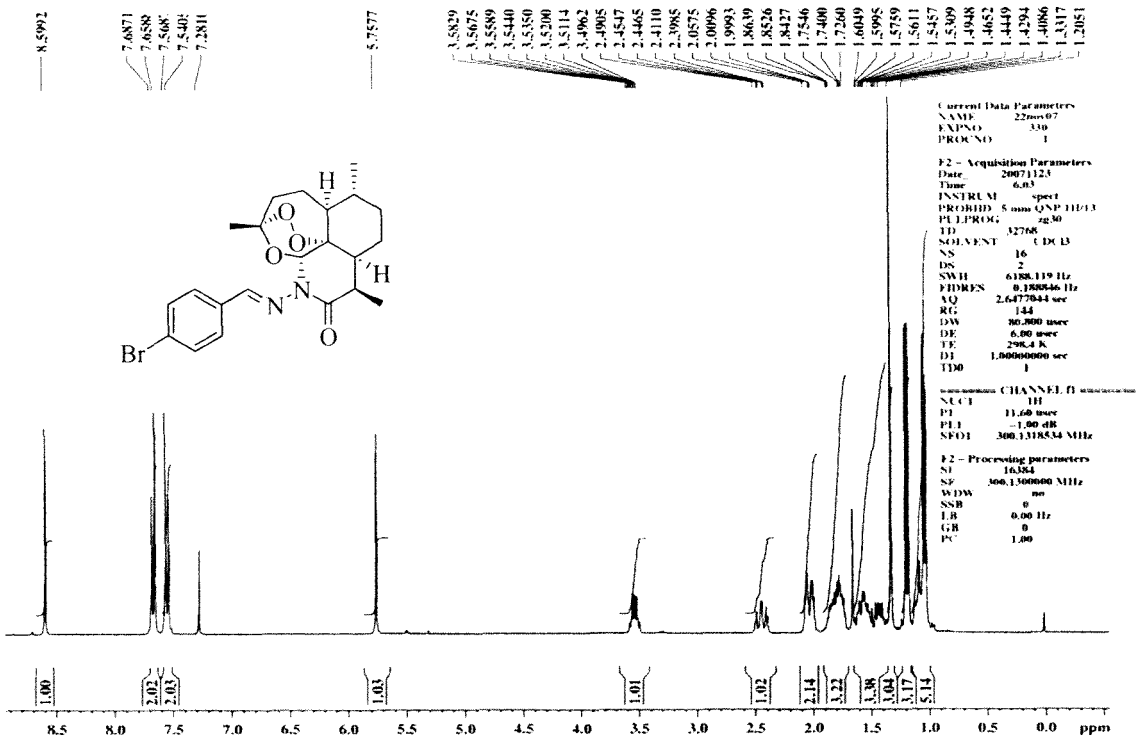
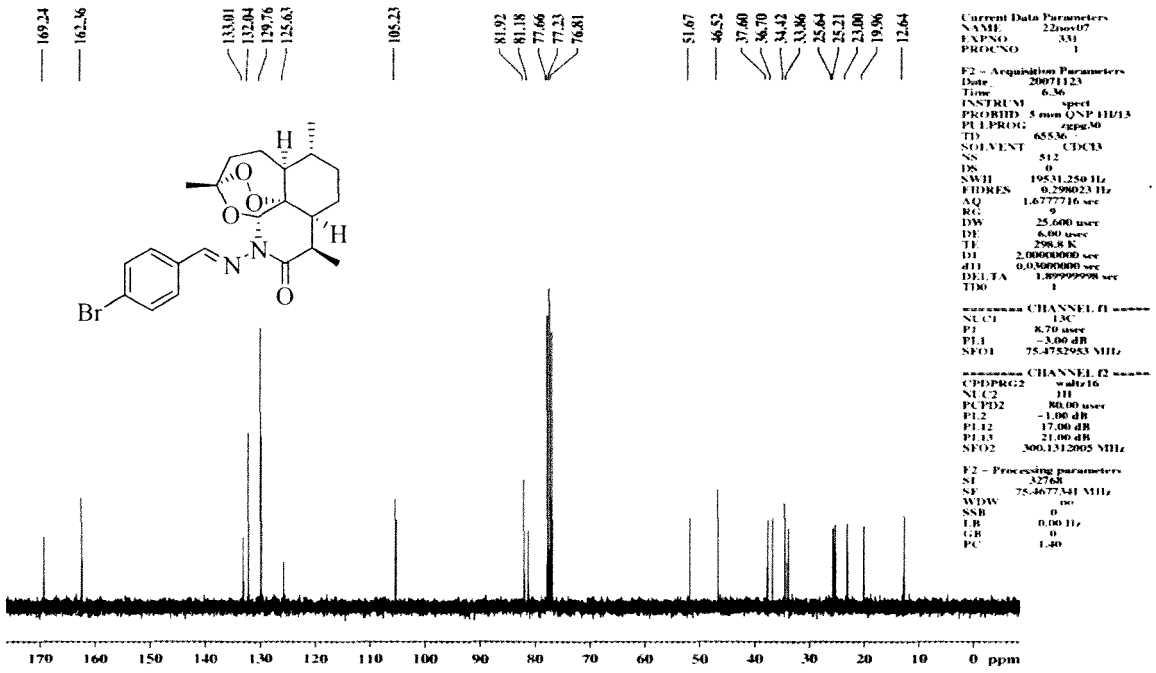
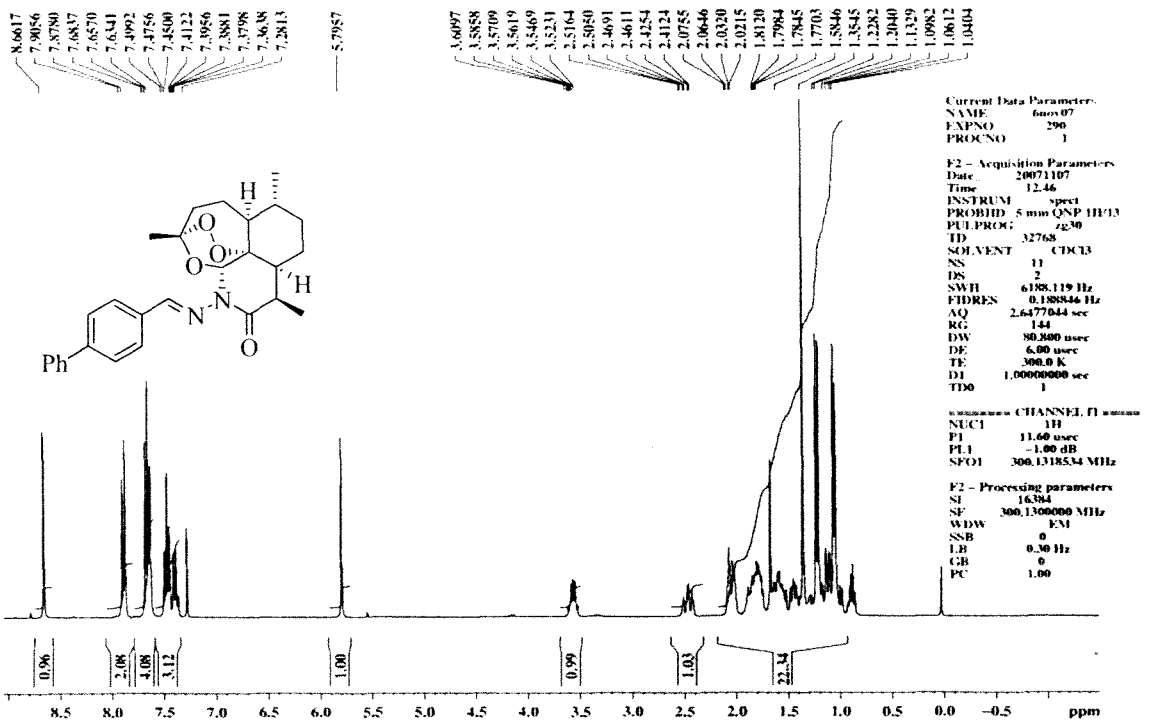


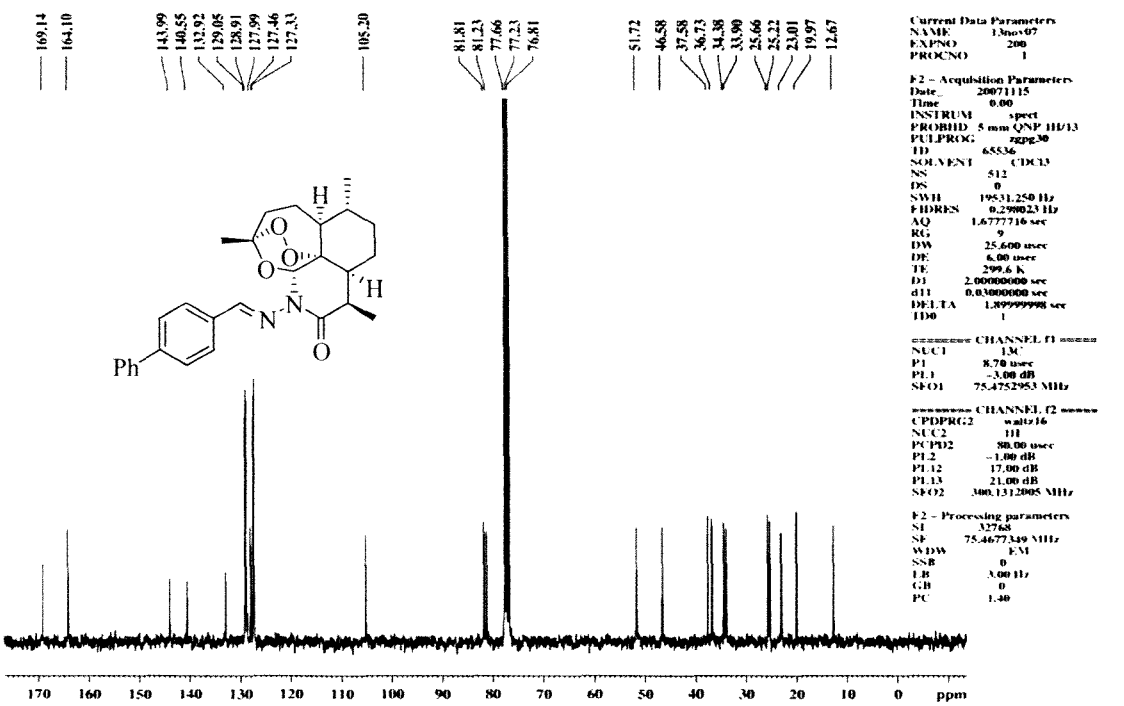
^{1}H NMR Spectra of **15e** (75 MHz, $CDCl_3$)



^{13}C NMR Spectra of **15e** (75 MHz, $CDCl_3$)



^{1}H NMR Spectra of **15g** (75 MHz, $CDCl_3$)



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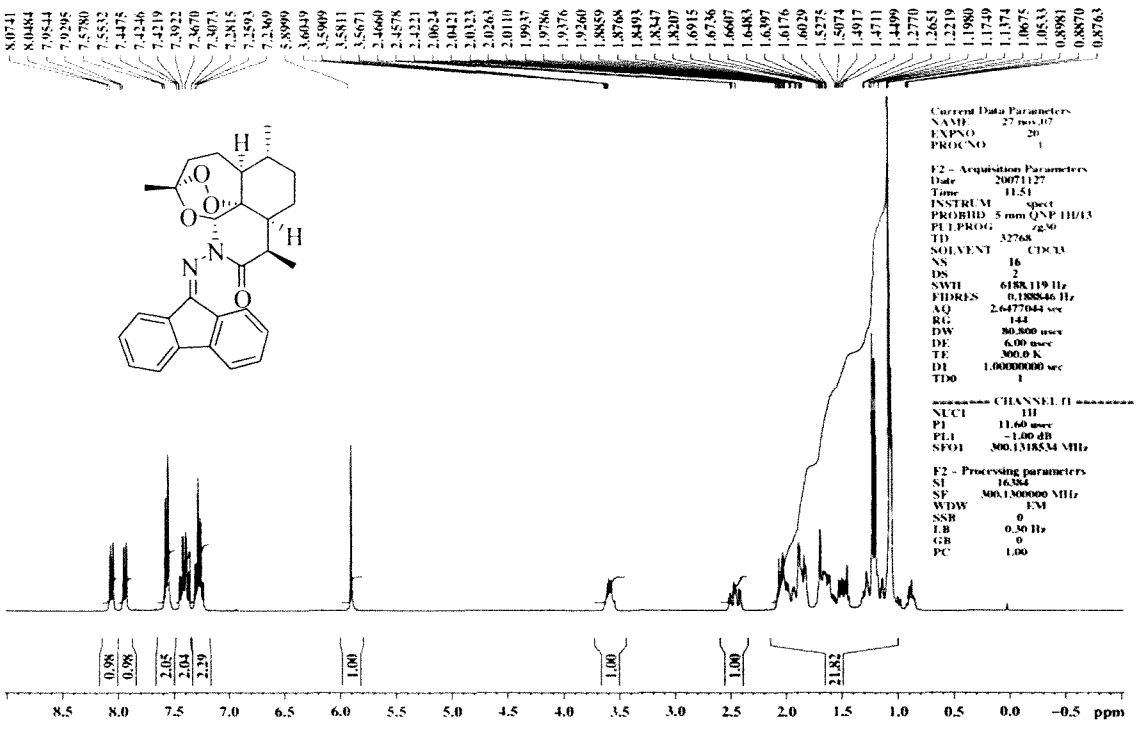
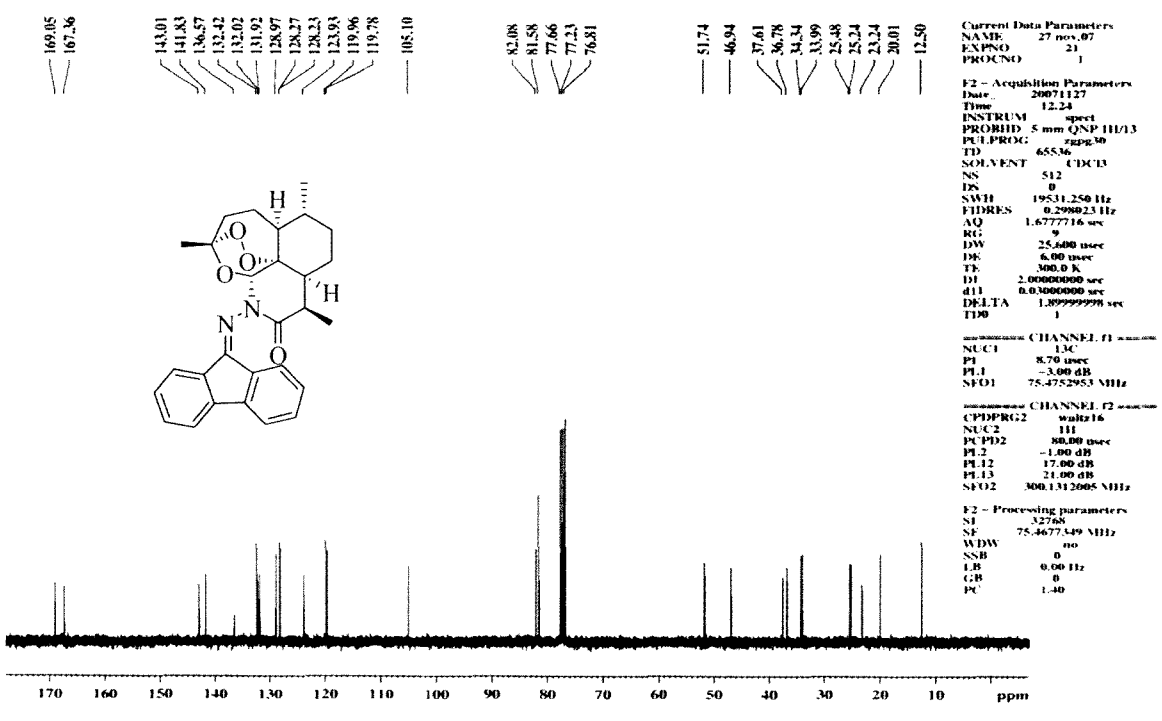


^{1}H NMR Spectra of **17** (75 MHz, $CDCl_3$)



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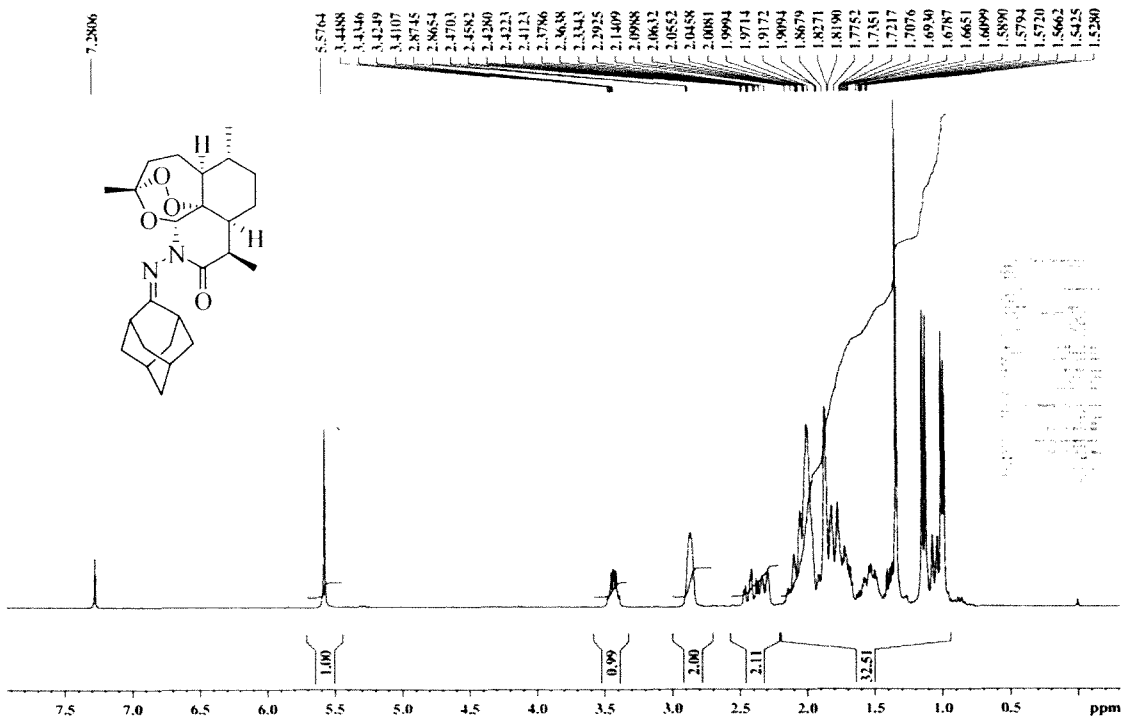

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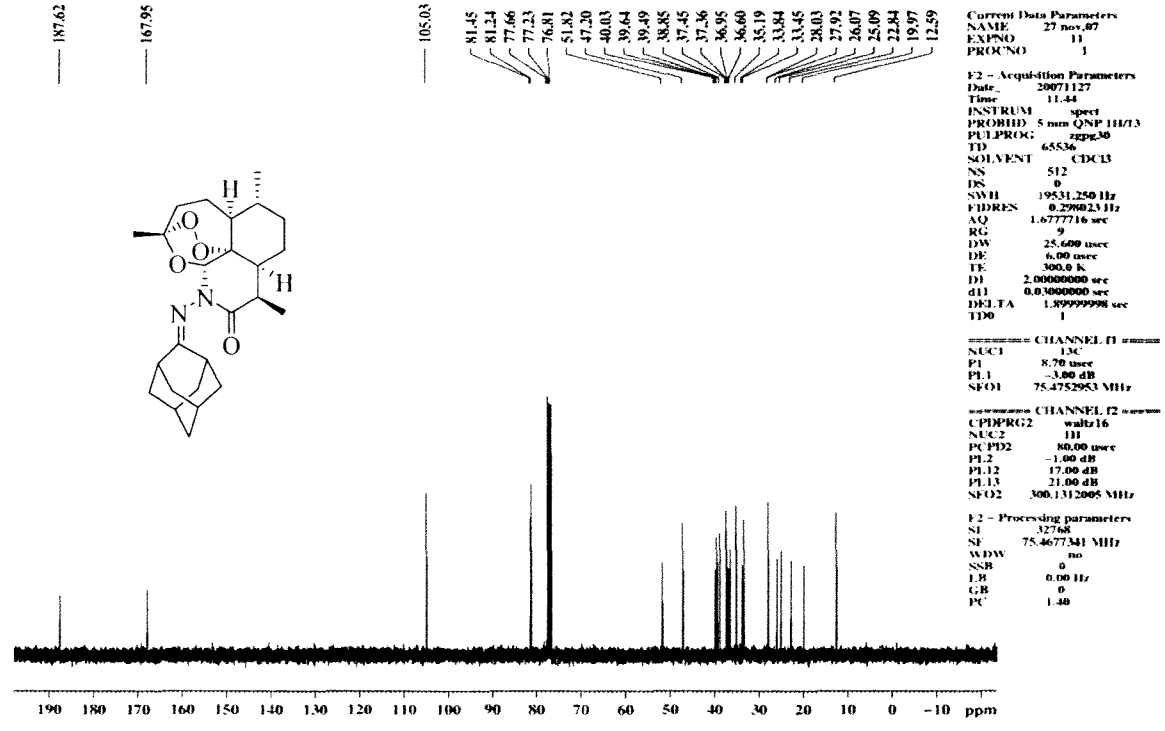
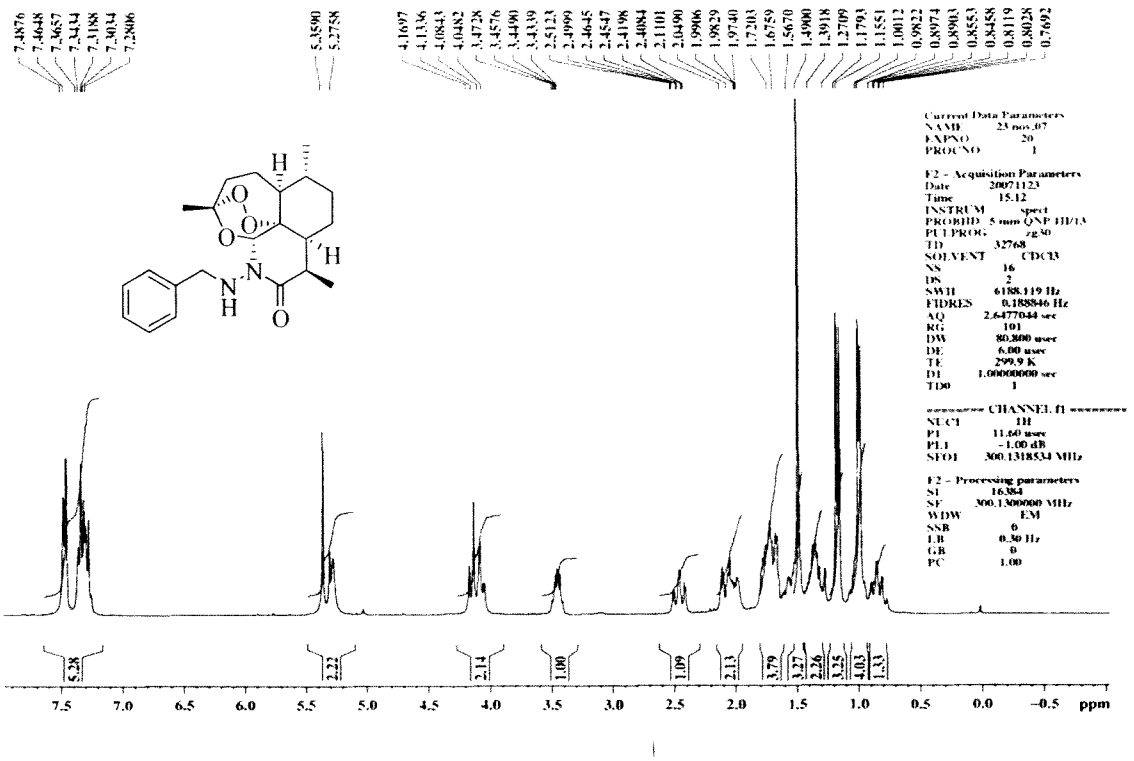
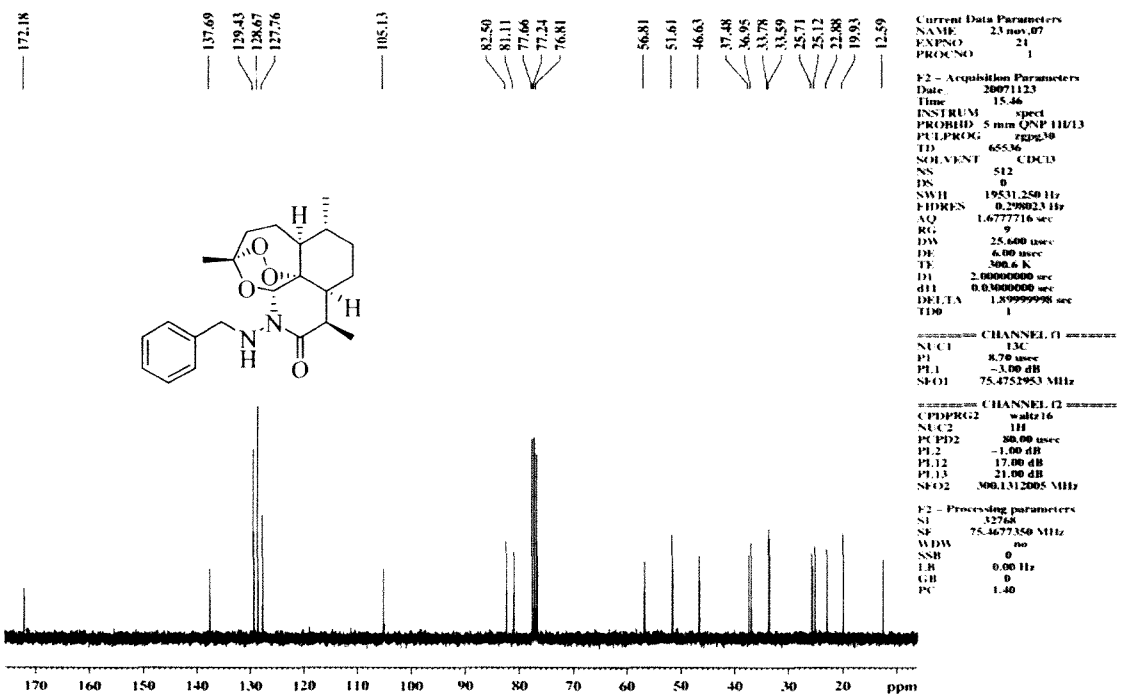


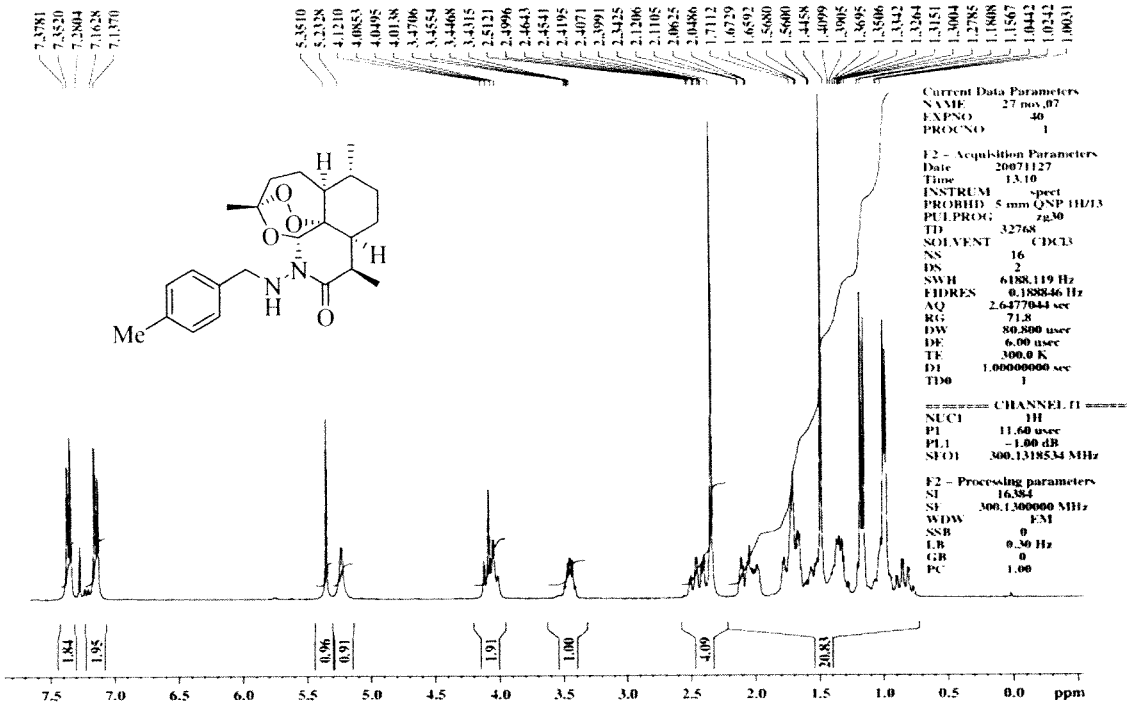
^{13}C NMR Spectra of **18** (75 MHz, $CDCl_3$)



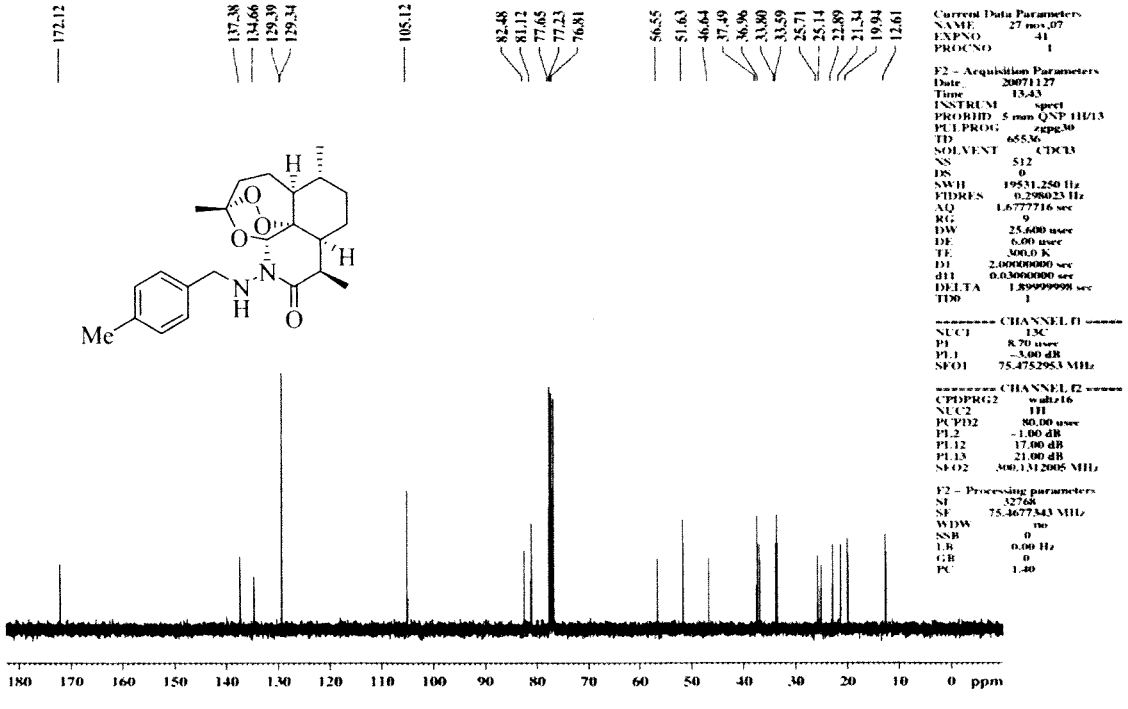
^{1}H NMR Spectra of **16a** (75 MHz, $CDCl_3$)



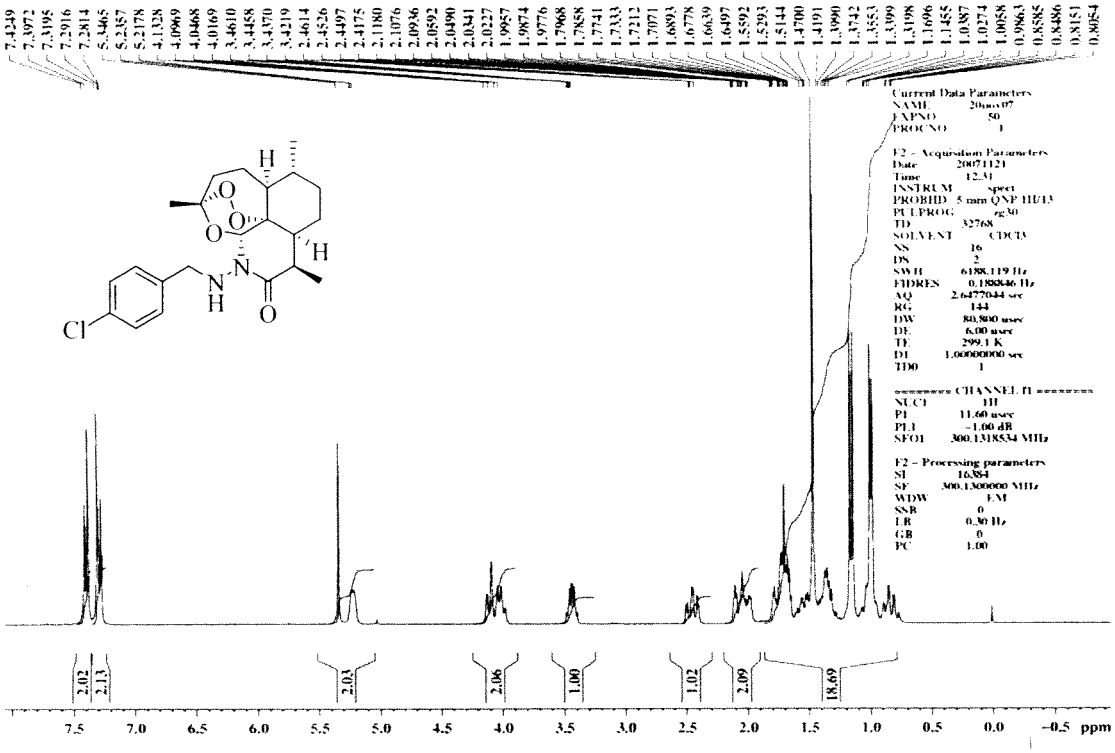
^{13}C NMR Spectra of **16a** (75 MHz, $CDCl_3$)



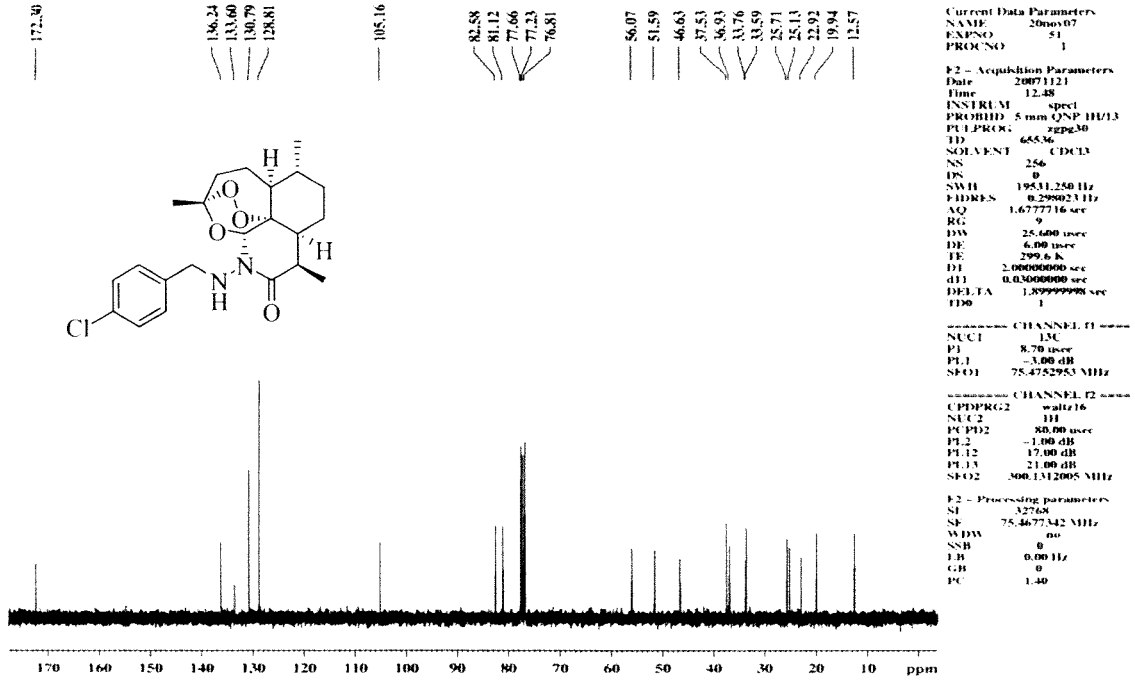
^{1}H NMR Spectra of **16b** (75 MHz, $CDCl_3$)



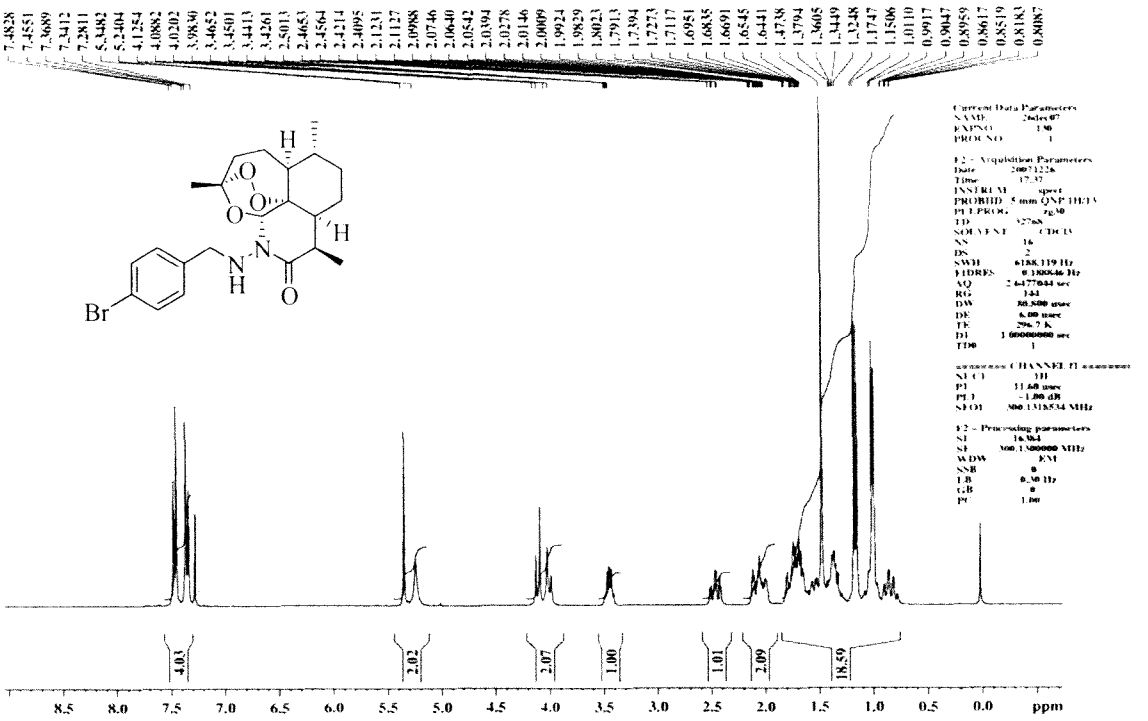
^{13}C NMR Spectra of **16b** (75 MHz, $CDCl_3$)



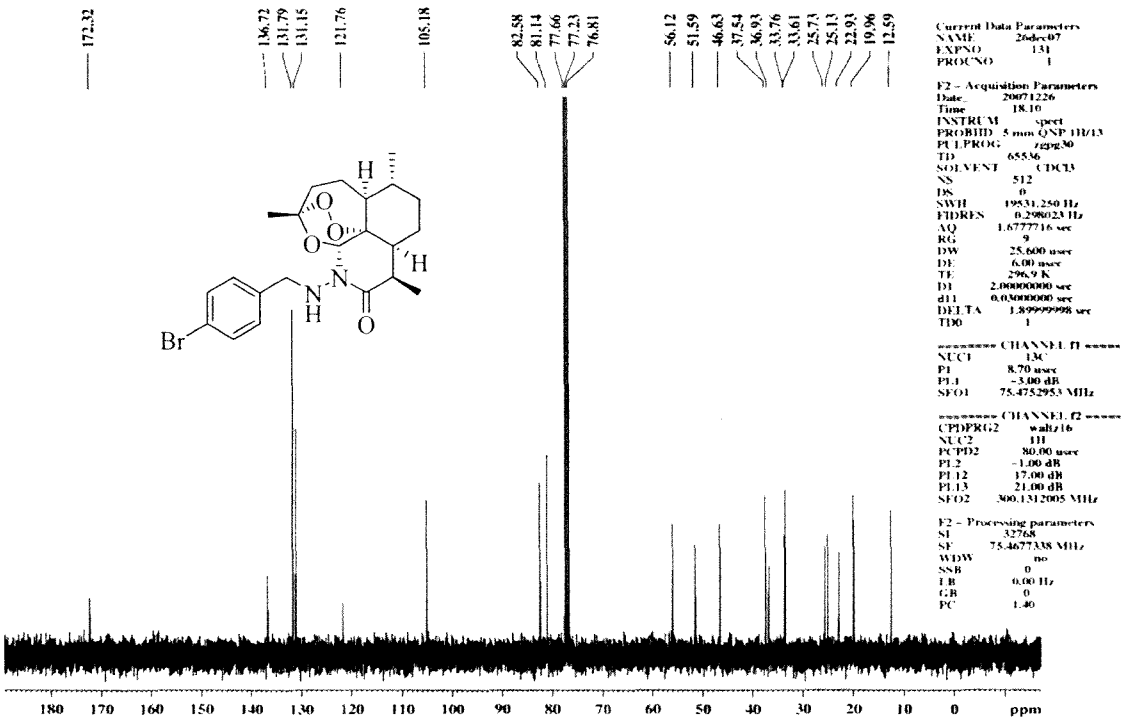
^{1}H NMR Spectra of **16c** (75 MHz, $CDCl_3$)



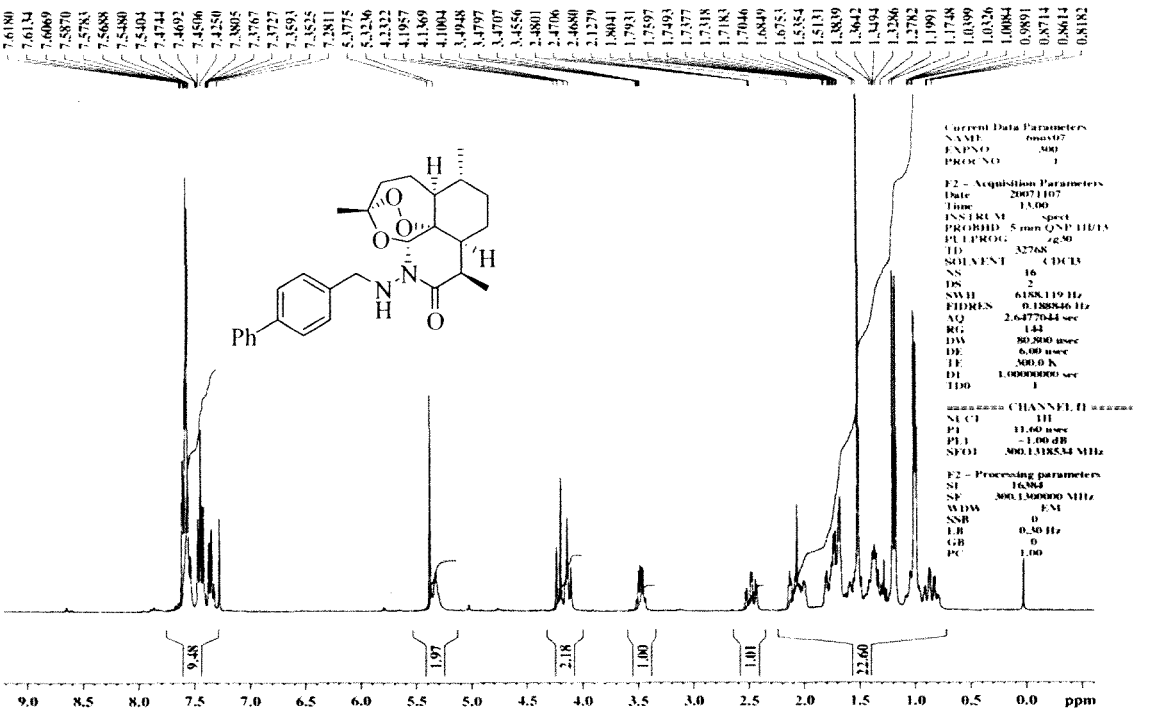
^{13}C NMR Spectra of **16c** (75 MHz, $CDCl_3$)



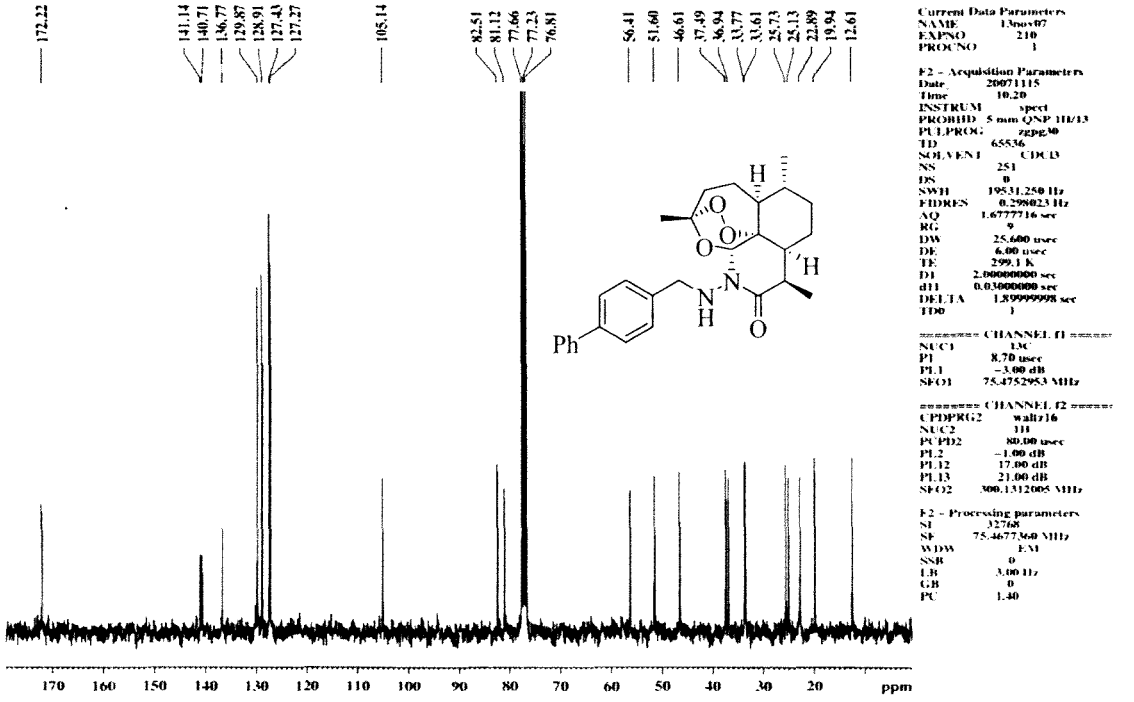
^{1}H NMR Spectra of **16e** (75 MHz, $CDCl_3$)



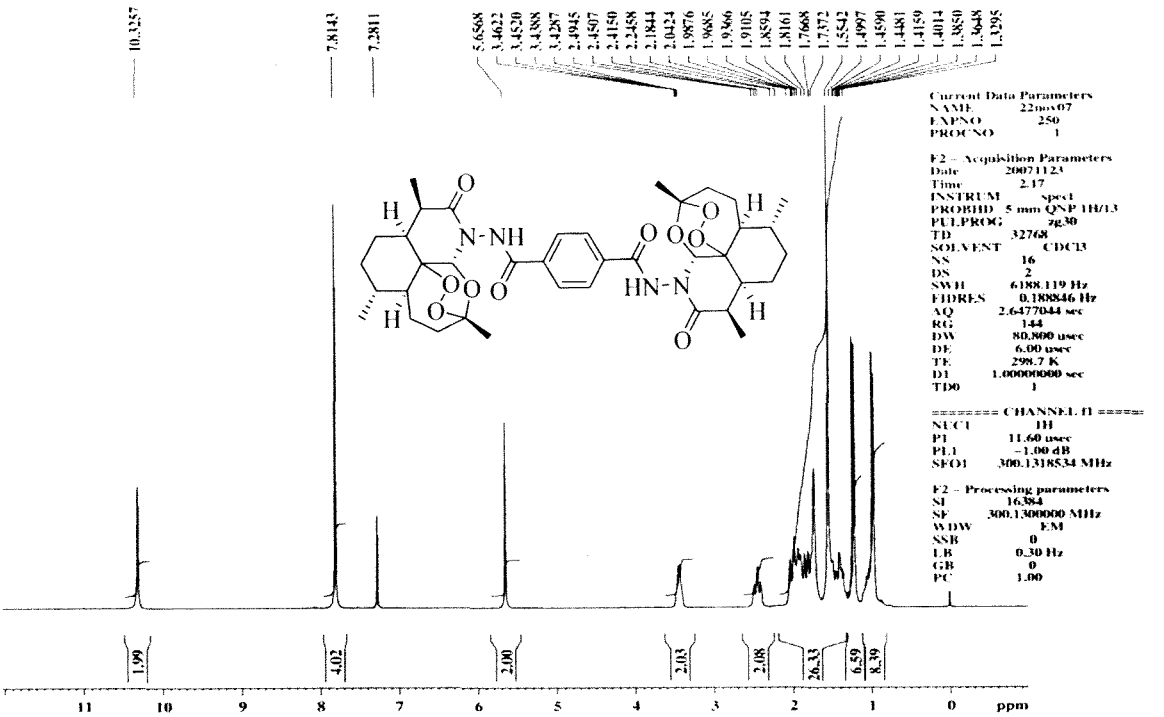
^{13}C NMR Spectra of **16e** (75 MHz, $CDCl_3$)



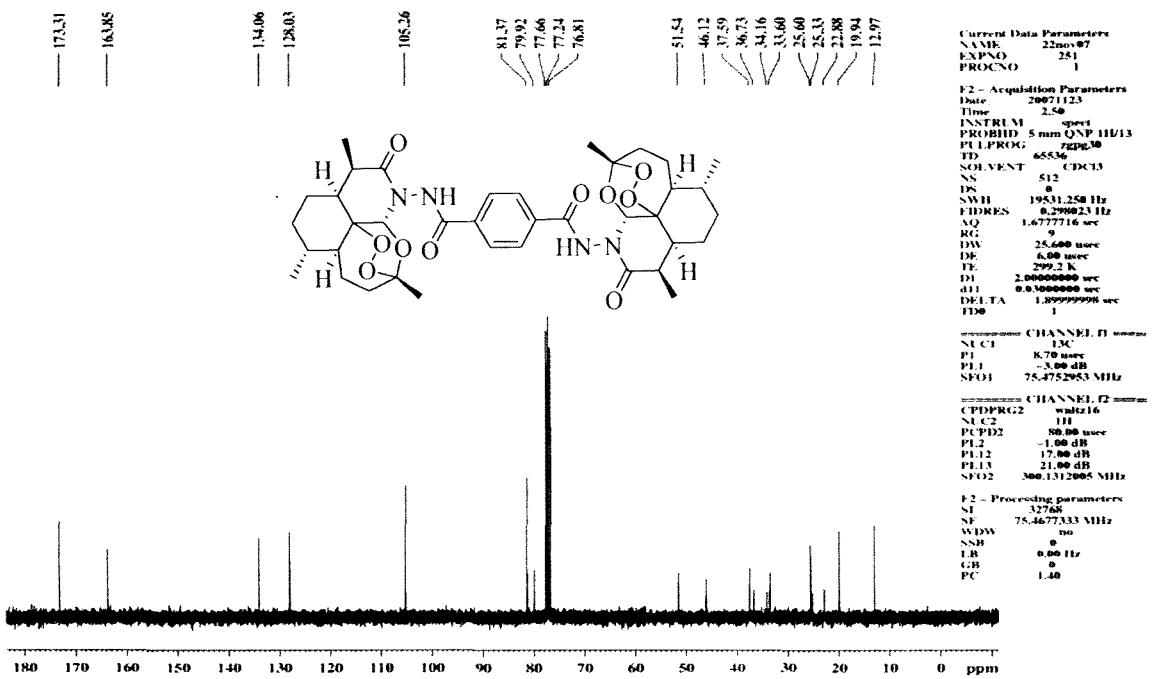
^{1}H NMR Spectra of **16g** (75 MHz, $CDCl_3$)



^{13}C NMR Spectra of **16g** (75 MHz, $CDCl_3$)



^{1}H NMR Spectra of **20** (75 MHz, $CDCl_3$)



^{13}C NMR Spectra of **20** (75 MHz, $CDCl_3$)

Patents Filed

1. "Novel 6-(1-arylethyl)-1,2,4-trioxanes, useful as antimalarial agents and a process for the preparation thereof" Chandan Singh, **Ajit Shankar Singh** and Sunil Kumar Puri, *Indian Patent Ref. No. 2158 DEL 2006, Filing Date:* ***26-09-2006.***
2. "Novel 6-(1-arylethyl)-1,2,4-trioxanes, useful as antimalarial agents and a process for the preparation thereof" Chandan Singh, **Ajit Shankar Singh** and Sunil Kumar Puri, *PCT Patent Ref. No. PCT/IN07/00375, Filing Date:* ***30-08-2007.***

Manuscripts

1. "Hydrazinium Carbazate-H_2O_2: A New Combination for Diimide Reduction of Base Sensitive Unsaturated Peroxides" Chandan Singh, **Ajit Shankar Singh**, Shilpi Pandey and Nitin Gupta. (To be communicated in *JOC*)
2. "Synthesis and Antimalarial Assessment of 6-(1-Arylethyl)-1,2,4-trioxanes" Chandan Singh, **Ajit Shankar Singh**, Nitin Gupta and Sunil K. Puri. (To be communicated in *J. Med. Chem.*)
3. "Unprecedented Acid Catalyzed Rearrangement of Arylvinyl-1,2,4-trioxanes and trioxepanes" Chandan Singh, **Ajit Shankar Singh**, and Shilpi Pandey (To be communicated in *JOC*)
4. "Synthesis and Antimalarial Assessment of Hydroxy-functionalized 1,2,4-trioxanes." Chandan Singh and **Ajit Shankar Singh** and Sunil K. Puri." (To be communicated in *Bioorg. Med. Chem. Lett.*)
5. "Synthesis and Antimalarial Assessment of Novel Azaartemisinins" Chandan Singh, **Ajit Shankar Singh**, Ved P. Verma, Mohd. Hassam and Sunil K. Puri. (To be communicated in *Organic Lett.*)
6. "Synthesis and Antimalarial Assessment of Novel 11-Hydrazaartemisinins" Chandan Singh, **Ajit Shankar Singh**, Ved P. Verma and Sunil K. Puri. (To be communicated in *J. Med. Chem.*)
7. "Synthesis and Antimalarial Assessment of Orally active 1,2,4-trioxanes" Chandan Singh, Pallavi Tiwari, **Ajit Shankar Singh**, and Sunil K. Puri. (To be communicated in *J. Med. Chem.*)

8. "Synthesis and Antimalarial Assessment of Water Soluble 1,2,4-trioxanes" Chandan Singh, Neeraj K. Naikde, **Ajit Shankar Singh**, and Sunil K. Puri. (To be communicated in *J. Med. Chem.*)

Presentation in Scientific Seminars

1. **Ajit Shankar Singh** & Chandan Singh (2007) "A Novel Acid Catalyzed Rearrangement of 6-(1-Arylvinyl)-1,2,4-Trioxanes" (Poster No. 2). Poster presentation at the 3rd *International Symposium on Current Trends in Drug Discovery Research* (***CTDDR-2007***), 17-21st February 2007, CDRI, Lucknow (U.P), India.
   Abstract published in special issue of *Medicinal Chemistry Research*, **2007**, *Vol. 15* (No. 1/6), page 99.