Strategy for Synthesis of Structural Analogues of Artemisinin

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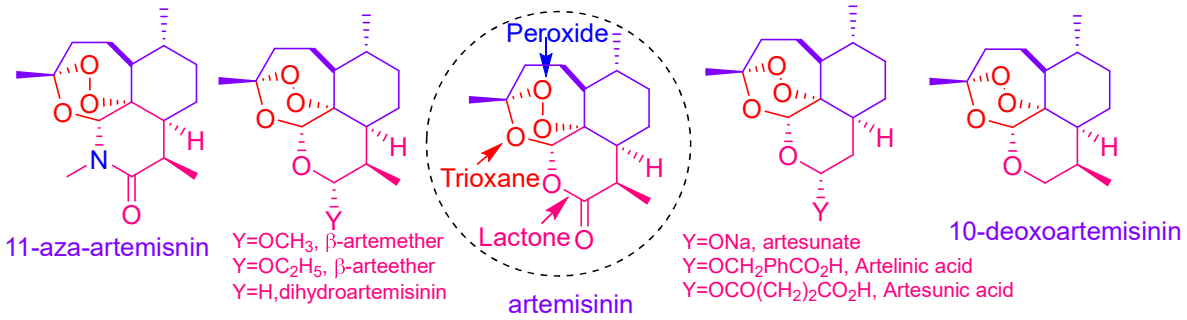
(66th birth anniversary of **Professor Satyaban Jena** and 80th birth anniversary of **Professor Anandi Charan Dash**)

Abstract:
The *endo* peroxide present in artemisinin produces potent carbon radical to kill malaria parasite. However the lower solubility of artemisinin in protic solvent and multidrug resistance of parasite forcing the synthetic chemist to design copious analogous of it that is more effective against falciparum. Moreover these compounds also show promising result in cytotoxicity effect to malaria parasite. This review summarizes structure activity relationships (SAR) of artemisinin intact with trioxane molecule.



Keywords: Artemisinin, antimalaria, endoperoxide, trioxane

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1.1. Introduction

Malaria is a brutal disease that devastate the lives of many patients including children and parturient mothers. Artemisinin is used as an anti-malarial drug that capable of killing the parasite Plasmodium falciparum. Most of the medicine should be water soluble for easy uptake to Human body. For example articulate reaches peak levels within minutes but at same tome artemether takes 2–6 h to reach intracellular site. But low solubility of artemisinin in water, miniature half-life in vivo and impecunious pharmacokinetics forcing the organic chemist to redesign the drugs for making it water soluble. Synthetic organic chemist has designed variety of artemisinin analogues to provide better consequence of former compound. Artemisinin-based combination therapy (ACT) and their derivatives are proved as first-line treatment of malaria. Later on artemether-lumefantrine is the fixed-dose for uncomplicated malaria parasite recommended by World Health Organization (WHO).[1] Moreover artemisinin and its analog impede cell proliferation and specific cancer cell.[2] The current review will summarize the strategy developed so far for synthesis of artemisinin analog modifying lactone ring and retaining trioxane moiety (Figure 1).

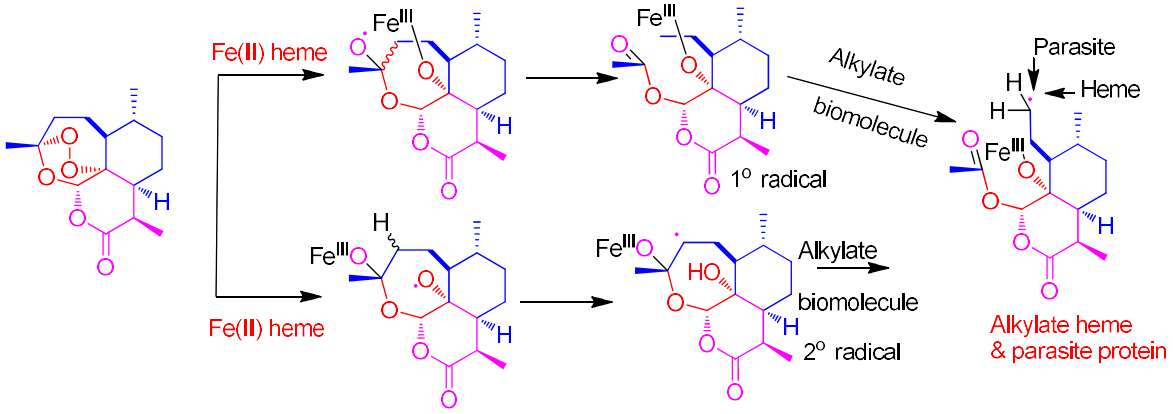


Figure 1: Biochemistry of peroxide moiety with hemoglobin in the human body

1.2. Artemisinin

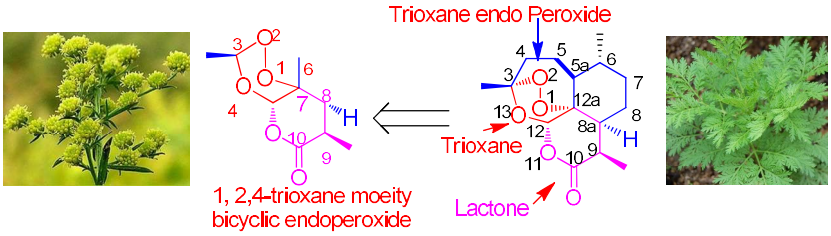


Figure 2: Structure of artemisinin showing endo trioxolane moiety

Artemisinin is a flavonoid compound was isolated from the aerial parts of Artemisia annua L (Asteraceae).[3] It has sesquiterpene lactone[4] squeezed with 1,2,4- endo trioxolane moiety (Figure **2**).[5-6] It has endoperoxide framework which is leading to development of well known anti-malaria properties. However the lactone

opening of artemisinin by protic solvent causes decline its solubility as well as diminished therapeutic potential in vitro.[7]

2. Bioavailability of Artemisinin Analog

The trioxane structure of artemisinin is responsible for anti-malarial activity. The peroxide linkage is activated by Fe(II) leading to a reactive intermediate to produce alkoxy radical radicals which inturn produce primary and secondary radicals. This radical alkylated the hame group of parasite leading to death.[8] As cancer cells possess a high number of transferring receptors on their cell surface before cell division. The peroxide of artemisinin is covalently attached to the receptors and build up the cytotoxic potency on cancer cells by entering into it. [9]

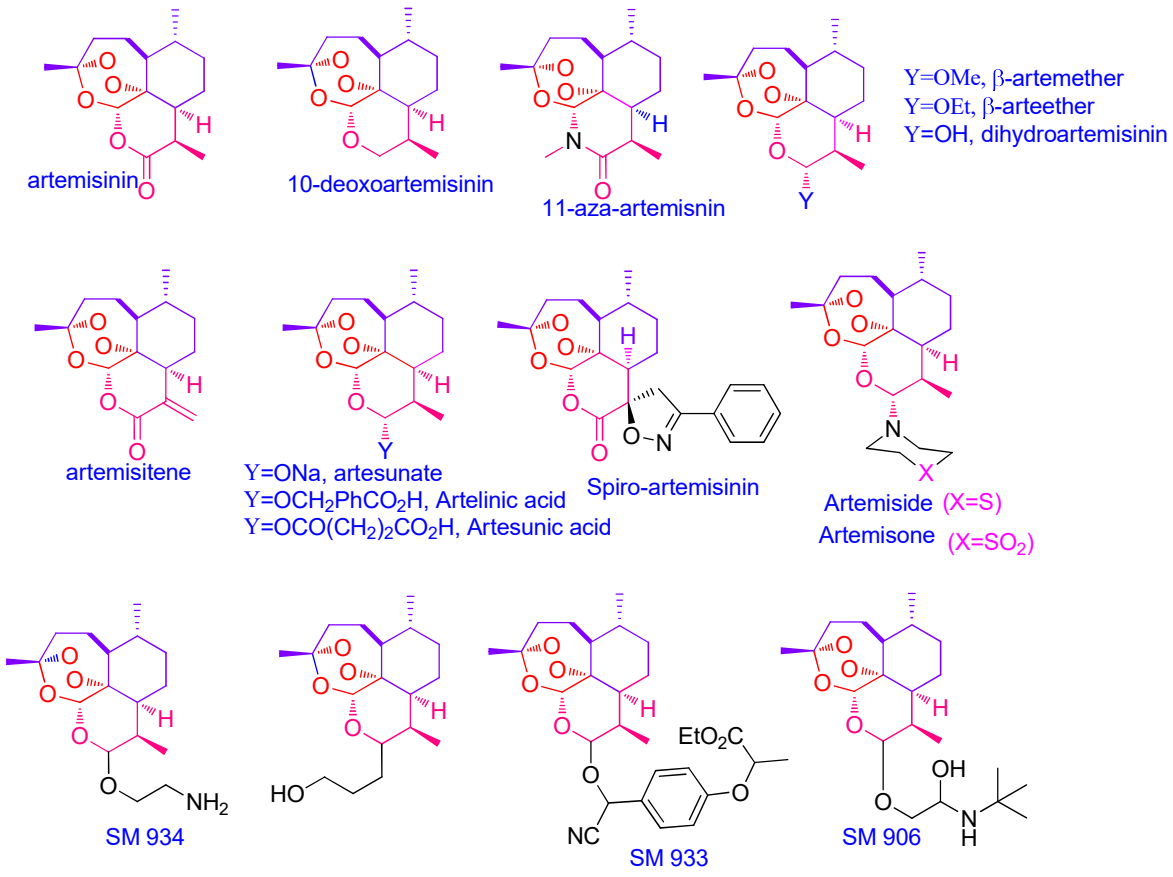


Figure 3: Bioactive analogues of artemisinin with trioxane moiety

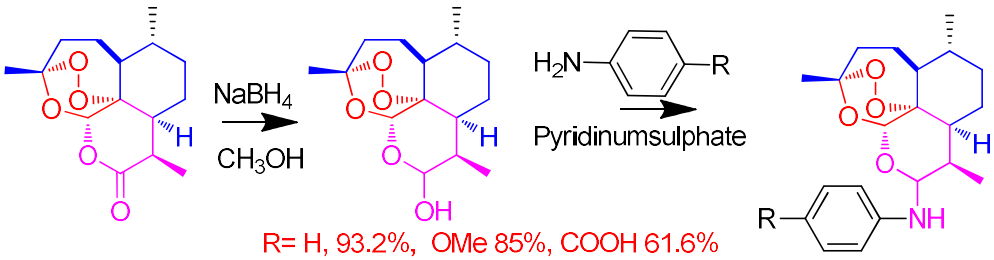
Chemists need to design a variety of artemisinin analog containing trioxane moiety which is responsible for generation of highly potent alkylating agents. The lactone ring of artemisinin is modified to dihydro artemisinin, artemether and artesunate; among them the most potent antimalaria properties shown by

DHA.[10] The ether derivatives of artemisinin was synthesised by joining alkyl group at C-10 that are optically active and effective against P.falciparum in vitro.[11] By removing oxygen atom at C-10 leading to carba analogs showed more activity against chloroquine-resistant P. falciparum.[12] Nevertheless the dimer, trimer and tetramer of artemisinin are more potent and bioavailable as well as hydrolytically stable.[13] More over SAR of artemisinin leading to dihydroartenisinic acid, artesunic acid and artesunate shows anticancer activity against different types of cancer cell lines (leukemia melanoma, lung, colon, renal, ovarian, prostate, and breast) and anti-schistosomiasi (Figure 3).[14-19]

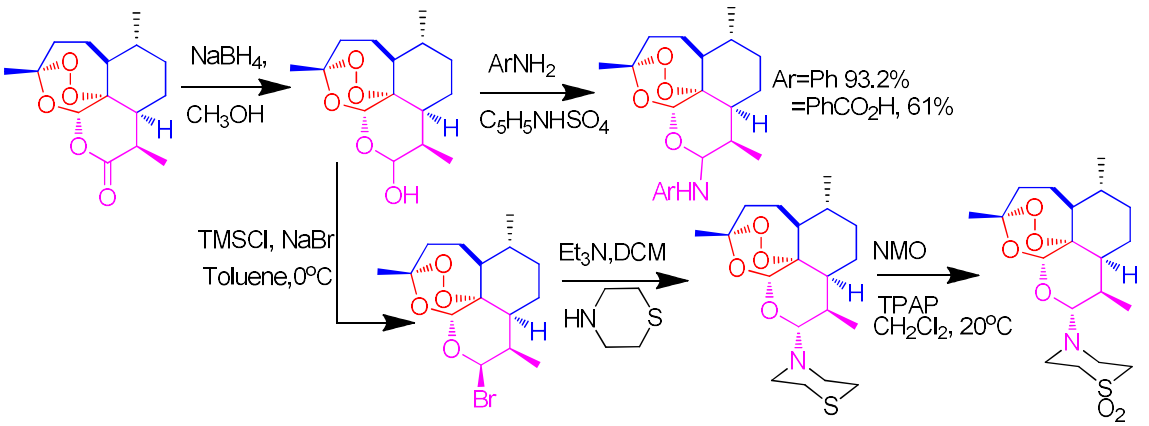
3. Structural Modification Strategy of Artemisinin

3.1 C-N coupling at C_{10} of Lactone ring:

Dihydroartemisininic acid has been synthesized by reduction of artemisinin with sodium borohydride in methanol. The DHAA was further reacted with aromatic amines in the presence of pyridinium sulphate to afford amine derivatives (Scheme **1**).[20]



Scheme 1: C-N coupling at C_{10} of Lactone ring of artemisinin



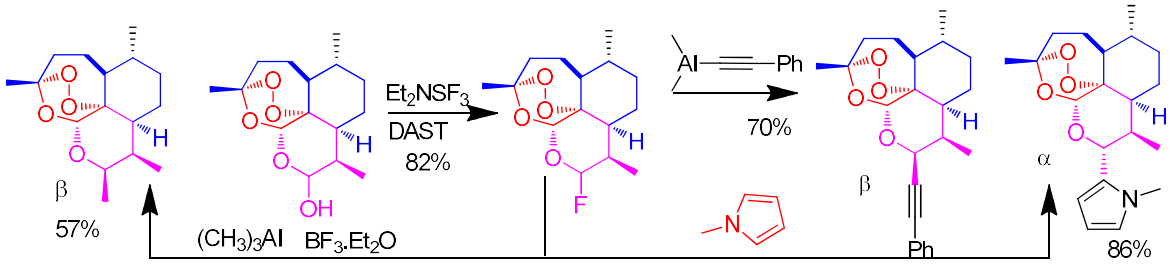
Scheme 2: Synthesis of thiomophine analogues of artemisinin by C-N coupling

Hayne group reported highly active antimalarial drugs thiomorphine artemisones has been synthesized from 10-alkylamino artemisinin by oxidation.[21] Dihydroartemisinin was treated with a mixture of NaBr

and TMSCl in toluene to form an bromide intermediate. Subsequently amino nucleophile reacts to afford alkyl amino compounds which upon oxidation provides artemisone (Scheme **2**).

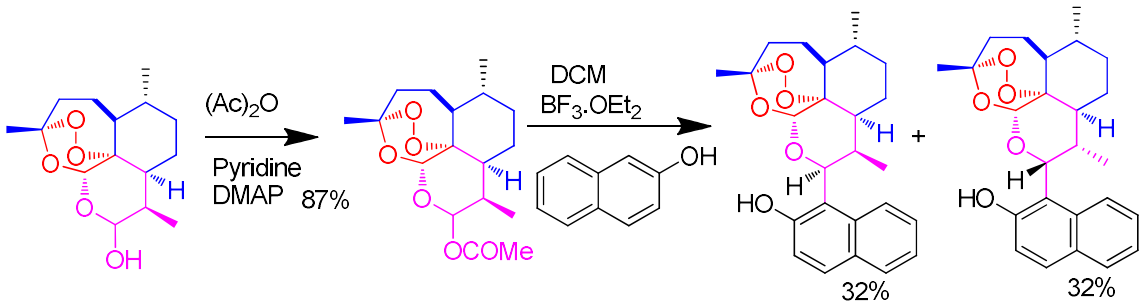
3.2 C-C coupling at C-10 of lactone ring:

Dihydroartemisinin lactol with a free anomeric hydroxyl group directly underwent fluorination and replaced by alkyl, alkynyl, aryl and heteroaryl carbon nucleophiles in the presence of boron trifluoride to form C_{10} substituted α- (down) and β- (top) deoxo artemisinins.[22] Among heteroaryl compound, thiophene does not react in this condition (Scheme **3**)



Scheme 3: C-10 substituted α- (down) and β- (top) deoxoartemisinins

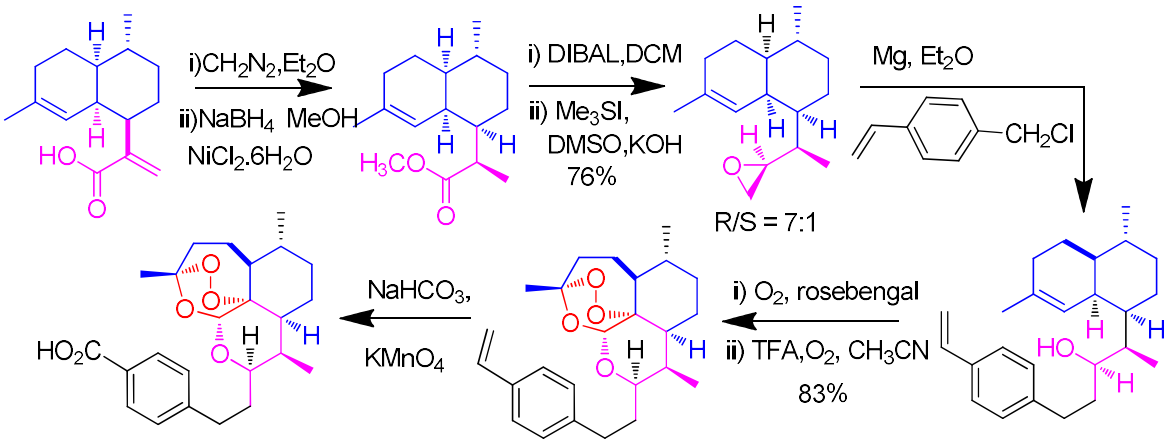
The synthesis of 10-(2-hydroxy-1-naphthyl)-deoxoartemisinin was achieved from DHA in (Scheme **4**). The later compound was synthesized from acetylation of DHA with acetic anhydride and DMAP [4-(dimethylamino)- pyridine] in 87% yield. Friedel–Crafts alkylation was carried out at C_1 of the 2-naphthol with activated acetal under the catalysis of $BF_3.OEt_2$, giving 1:1 mixture of napthyl epimers product in 68% yield. [23]



Scheme 4: C_{10} substituted synthesis of 10-(2-hydroxy-1-naphthyl)-deoxoartemisinin

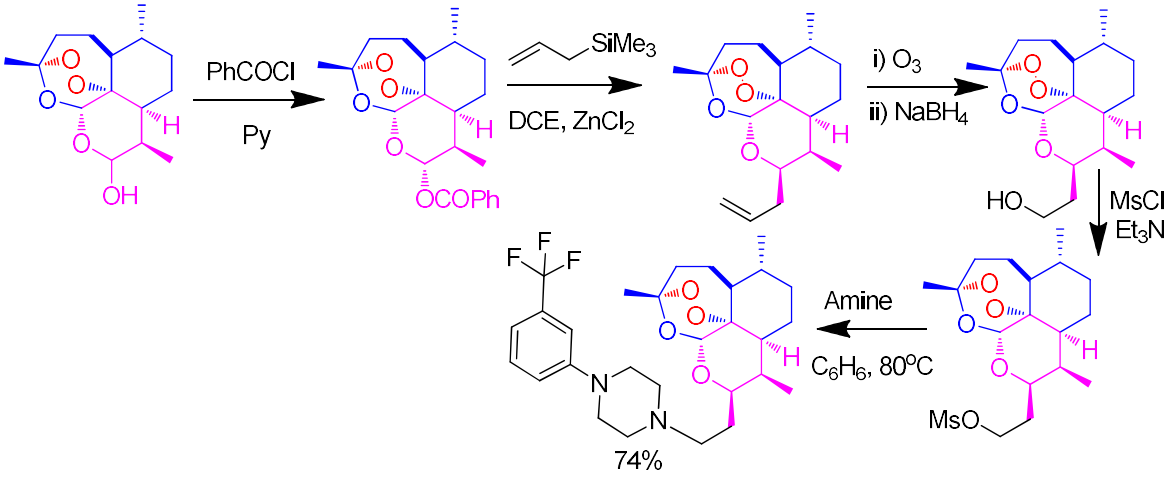
Highly water soluble deoxoartelinic acid was prepared by Jung[24] from artemisinic acid (Scheme **5**). The later compound was converted into dihydroartemisinyl ester by methylation and reduction by $NaBH_4$. Epoxide with 76% was yielded by using trimethylsulfur iodide. The ring opening of epoxide with 4-vinylbenzylmagnesium chloride afforded an alcohol. 4- vinylhomobenzyl deoxoartemisinin with natural β-

configuration was produced from alcohol via photooxygenative cyclization process. Finally, deoxoartelinic acid (83%) was isolated by oxidation of the above product with $KMnO_4$.



Scheme 5: Synthesis of deoxoartelinic acid from artemisinic acid by C-C coupling

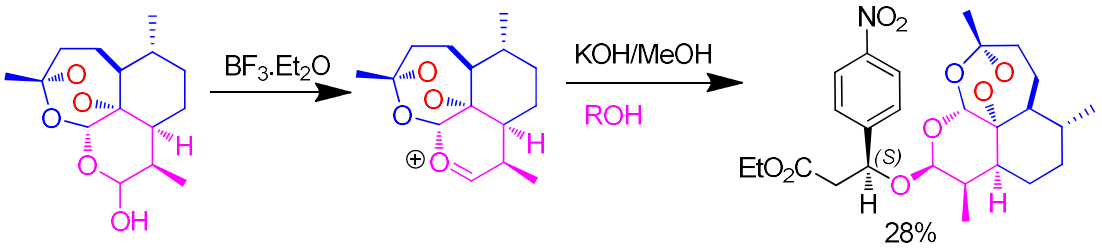
Allyl deoxoartemisinin a key intermediate for synthesis of C_{10} carba linked amino analogues was developed by Hindley and coworker.[25] The C_{10} benzoates were treated with allyltrimethylsilane and anhydrous $ZnCl_2$ in dichloroethane to provide vinyl analouge. Further treatment with ozone and reduction with $NaBH_4$ afforded an alcohol, which underwent mesylation and reacted with an 1-[(3-trifluoromethyl) phenyl]piperazine (an active antimalaria drug) with 74% yield (Scheme **6**).



Scheme 6: C_{10} carba linked amino functionalized artemisinin by C-C coupling

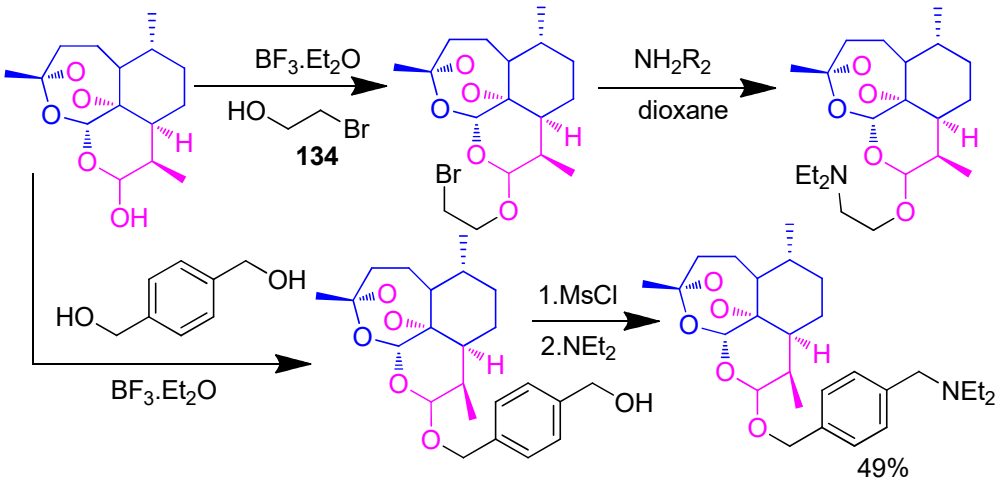
3.3 Retention of oxygen atom in lactone ring

New diastereomeric α-alkylbenzylic ether derivatives of dihydroartemisinin has been synthesized by Lin and coworker.[26] The treatment of dihydroartemisinin with different alcohols at room temperature in presence of boron trifluoride etherate (Scheme **7**). Compounds with electron-withdrawing function (NO_2) substantially increase the antimalarial activity. The (*S*)-diastereomers, in are several fold more potent antimalaria drugs than the corresponding (*R*)-isomer.



Scheme 7: Synthesis of α-alkylbenzylic ether of artemisinin

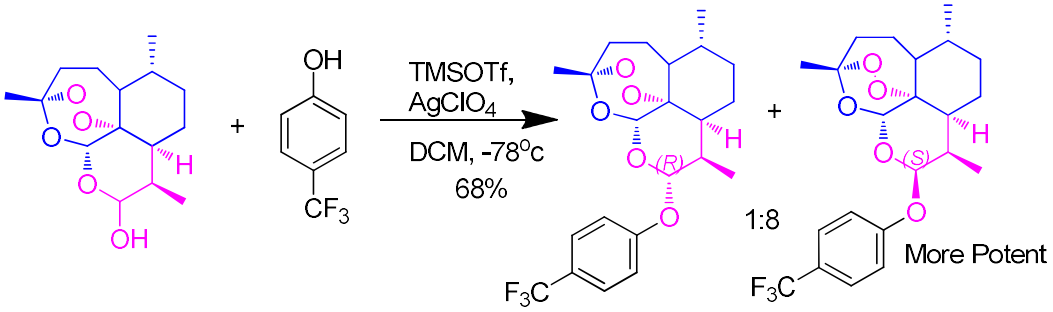
The preparation of benzyl amino ether derivatives of artemisinin from DHA was reported by O'Neill and coworker.[27] DHA was treated with 4-(hydroxymethyl) benzyl alcohol to afford benzyl ether artemisinin with 80% yield in presence of BF_3.OEt. Treatment of this benzylic alcohol in $CH_2Cl_2$with mesyl chloride and triethylamine at low temperature affords the mesylate product which allowed to react with 2 equiv of diethylamine to form amino ether derivatives. Several artemisinin derivatives linked to benzylamino and alkylamino groups were synthesized in order to enhance accumulation within the malaria parasite (Scheme **8**).



Scheme 8: Synthesis of benzyl amino ether and alkyl amino ether of artemisinin

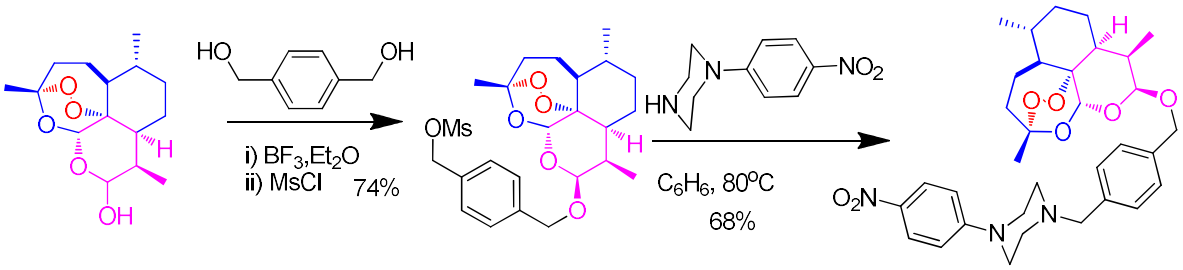
A new series of C_{10}-phenoxy derivatives were synthesized from dihydroartemisinin with excellent stereo selectivity by the combination of TMSOTf and $AgClO_4$ (Scheme **9**). This protocol underwent no O- to C-

aryl glycoside rearrangement but minor quantities of AHA were observed with predominat β-isomer. [28] All of the new phenoxy derivatives have potent in vitro antimalarial activity. *p*-trifluoro methylphenyl derivative is demonstrated wonderful in-vivo antimalaria potency recently.



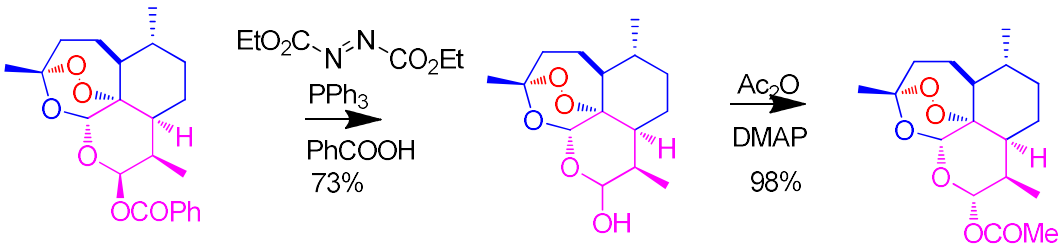
Scheme 9: C_{10}-phenoxy analogues of artemisinin

The preparation of C_{10} ether piperazine linked analogues was developed by Hindley (Scheme **10**). Dihydroartemisinin was coupled with 1,4-dibenzene methanol to afford the corresponding alcohol with β:α 5:1 diastereo selectivity. [29] The alcohol was then mesylated and subsequently reacted with *N*(4-nitrophemyl) piperazine to provide C_{10} ether piperazine in 68% yield.



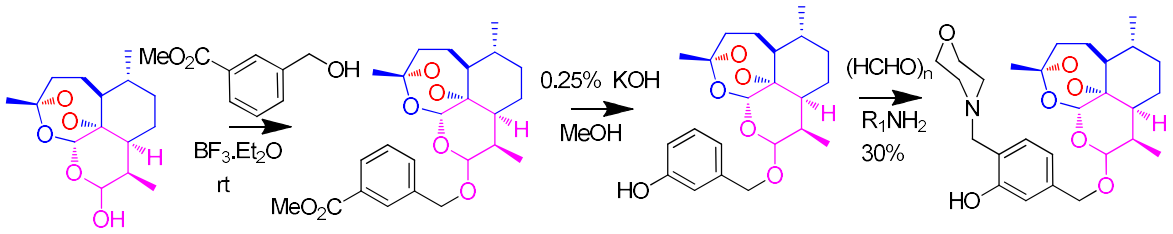
Scheme 10: C_{10} ether piperazine of artemisinin

The conversion of DHA into esters and ethers with stereochemistry was studied by Haynes and coworker (Scheme **11**). α-Esters are exclusively obtained when the hydroxy group of DHA acts as nucleophile with dimethyl aminopyridine with acetic anhydride. Similarly benzoyl esters are synthesized in presence of diethyl azodicarboxylate where as the other isomer obtained when it is activated for displacement.[30]



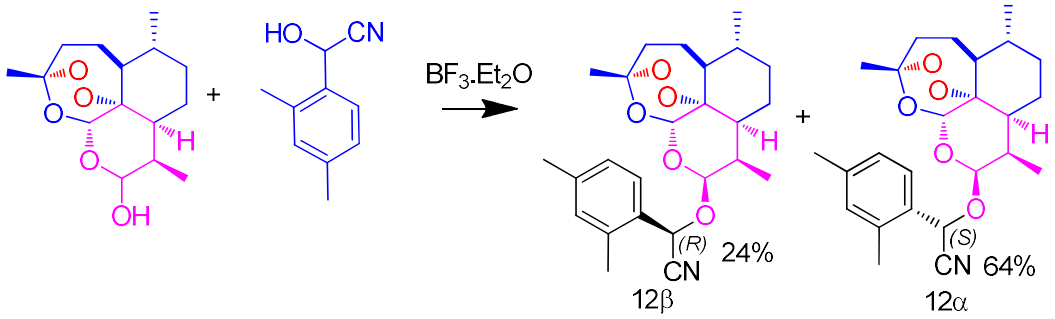
Scheme 11: Synthesis of esters and ethers of artemisinin

The synthesis of artemisinin containing Mannich base is described in Li and co-worker. [31] Herein DHA was reacted with corresponding acetoxy benzyl alcohol in presence of $BF_3.Et_2O$ to afford ether, followed by basic hydrolysis with 0.25% KOH/EtOH. Subsequent reaction with paraformaldehyde and various amines affords the product (Scheme **12**).



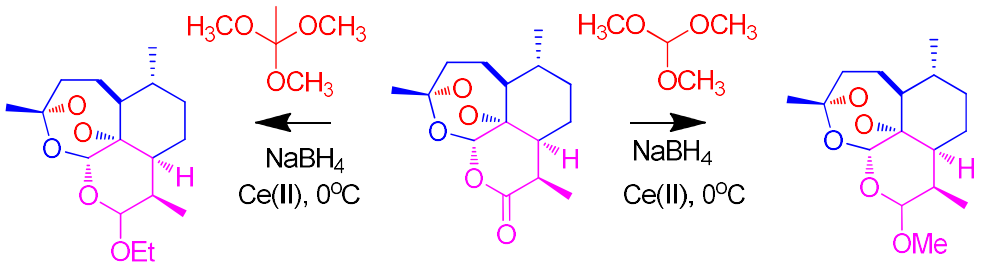
Scheme 12: Synthesis of Mannich base with artemisinin

A new type of ether of dihydroartemisinin containing cyano and aryl groups has been synthesized and tested for cytotoxicity. Cyano artemalogues are condensation product of dihydroartemisinin with corresponding cyanohydrins which is catalysed by $BF_3.Et_2O$ (Scheme **13**). 2-(2,4-dimethylphenyl)-2-hydroxyacetonitril afforded 24% (*R*)-isomer and 64% (*R*)-isomer. [32]



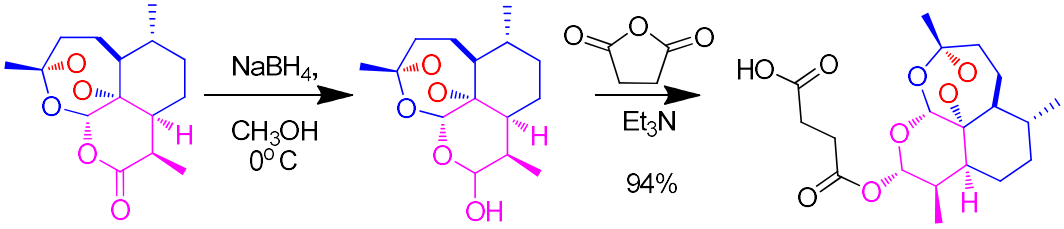
Scheme 13: Synthesis of cyano artemalogues

The synthesis of β-artemether and artemether with diastereoselectivity (β/α-5: 1) from artemisinin has been synthesized by Bishnoi and coworker (Scheme **14**). $NaBH_4$-cellulose sulfuric acid (CellSA) is used as catalyst system. β-artemether/ arteether from artemisinin has been developed using methylorthoformate and trimethyl orthoacetate respectively.[33]



Scheme 14: Synthesis of artemether and arteether from $NaBH_4$- Ce(II)

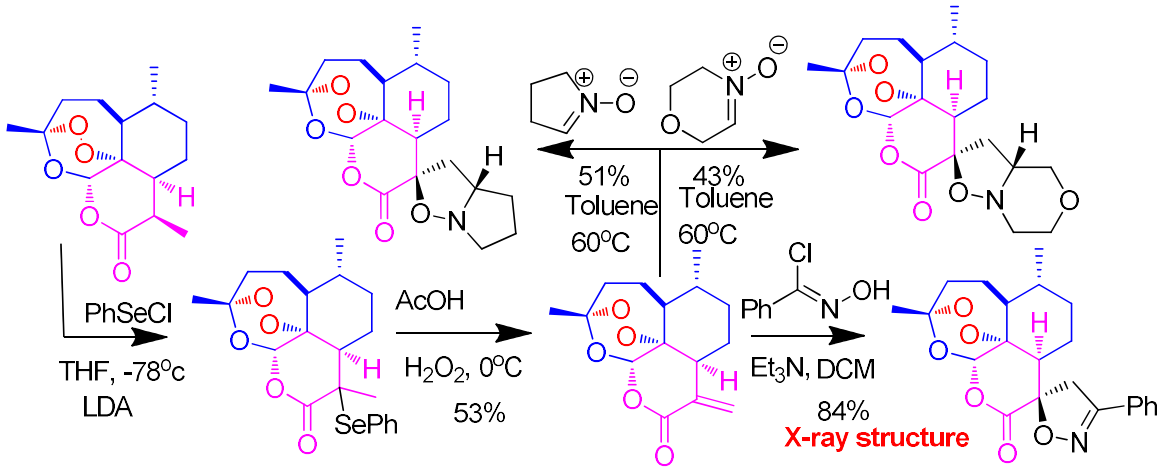
Recently, the large-scale conversion of artemisinin to artesunate was developed by Presser and coworker (Scheme **15**). This synthesis proceeds with reduction by $NaBH_4$, followed by an esterification with succinic anhydride under basic conditions.[34]



Scheme 15: Synthesis of artesunate from succinic anhydride

3.4 Diversification of Lactone ring at C-9

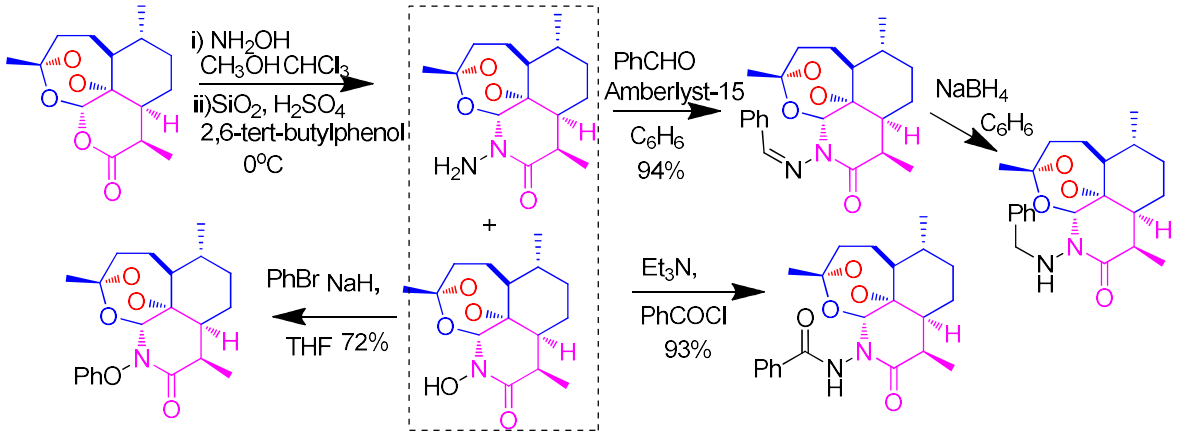
Isoxazoline and Isoxazolidine-containing spirocyclic artemalogues were prepared by Liu and coworker in 2015 through 1,3-dipolar cycloaddition of artemisitene with nitrile oxides or nitrones.[35] Artemisitene containing C_9-exocyclic vinyl moiety was prepared from artemisinin by selenoxide elimination methods. Then it was treated with aldoxime chlorides with Et_3N generated the corresponding nitrile oxides and then underwent 1,3-dipolar addition with DCM at room temperature to form isoxazoline artemalogues in 68-86% yields (Scheme **16**). The product structure has been confirmed by single X-ray spectroscopy.



Scheme 16: Isoxazoline and Isoxazolidine- spirocyclic analogues of Artemisitene

3.5 Synthesis of lactam from artemisinin

N-amino-11-aza-artemisinin and *N*-hydroxy-11-aza artemisinin with its derivatives were prepared from artemisinin (Scheme **17**). Artemisinin with hydrazine hydrate afford *N*-amino-11-aza-artemisinin with 70% yield in MeOH and $CHCl_3$.[36] However, when artemisinin is treated with hydroxylamine in MeOH and $CHCl_3$, followed by treatment with SiO_2 and H_2SO_4 in presence of 2,6-di-tert-butylphenol, afforded *N*-hydroxy-11-azaartemisinin in 45% yield. The amino- and hydroxy-functionalized 11-aza-artemisinin and their derivatives with good antimalarial activity against multidrug-resistant plasmodium yoelii in Swiss mice.



Scheme 17: Synthesis of N-Amino and hydoxy11-aza-artemisinin

4. Conclusion:

Artemisinin and its derivatives have been used for the treatment of malarial infections. They have the advantage over other drugs with an ability to kill faster and kill all the life cycle stages of the parasites. But

low bioavailability due to low solubility in water, poor pharmacokinetic properties and high cost of the drugs are major drawbacks of their use. Malarial parasites has already developed resistance to the artemisinin drug. Therapies that combine artemisinin or its derivatives with some other anti-malarial drug are the preferred treatment for malaria. Most of the medicine should be water soluble for easy uptake to Human body; But low solubility of artemisinin in water, miniature half-life in vivo and impecunious pharmacokinetics forcing the organic chemist to redesign the drugs for making it water soluble. The current review will give a focus on different derivative of artemisinin to increase the bioavailability for quick and easy reaching of molecules in the human body. The different analogue will have good resistance towards parasites.

5.Conflicts of interest

There are no conflicts to declare.

6. Acknowledgements

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