iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 6 **Issue:** III **Month of publication:** March 2018

DOI: http://doi.org/10.22214/ijraset.2018.3324

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 6.887
Volume 6 Issue III, March 2018- Available at www.ijraset.com

Synthesis of 1, 2, 4-Dioxazinane, Bis-1,2,4-Dioxazinane, 1,2,4-Trioxanes and their Sugar Analogues as an Antimalarial drugs

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Abstract: ***Currently the focus is on synthesis of easily accessible, structurally simple 1, 2, 4-trioxane which can substitute artemisinin as second line of antimalarials. The 1, 2, 4- trioxanes ring system in artemisinin skeleton is the main pharmacophore which is responsible for the antimalarial activity. Several semisynthetic derivatives of artemisinin e.g. artemether, arteether and artesunic acid are more active than artemisinin and are currently available drugs of choice for the treatment of multidrug resistant malaria. The present study is an extension of our on-going efforts in this area with the express objectives to produce therapeutically more acceptable and cheaper 1, 2, 4-trioxanes, 1,2,4-Dioxazinane, Bis-1,2,4-Dioxazinane.***
Key Words: Artemisinin; Anti-malarial; 1, 2, 4-trioxanes; 1,2,4-Dioxazinane; Bis-1,2,4-Dioxazinane

I. INTRODUCTION

Malaria is endemic in most part of the world especially in tropical & subtropical region. Natural products as lead for malaria chemotherapy dates back to the early 18th century when bark of Cinchona tree was used in the treatment of fever by the natives of South America. It was in 1820 that quinine was isolated as active principle of the bark. Unfortunately due to indiscriminate use of chloroquine and its analogues the parasite developed resistance towards these drugs. Therefore is a need to develop new drugs which are novel both in terms of mechanism of action and pharmacophore. Despite comprehensive global efforts for eradication of malaria, about 40% of world population is still at risk of the disease. Of these 2.5 billion people are at risk, more than 500 million become ill and more than 1 million, mostly children, die of malaria every year.[1] Against this background, the isolation of artemisinin **1**, as the active principle of the Chinese traditional drug against malaria, Artemisia annua, is a major breakthrough in malarial chemotherapy. Artemisinin and its derivatives e.g. artemether **2a**, arteether **2b** and artesunic acid **3** (Figure 1) are effective against both chloroquine-sensitive and chloroquine-resistant malaria.[2] The peroxide group present in the form of 1,2,4-trioxane (Figure 2), is essential for the antimalarial activity of these compounds and currently the focus of literature is on structurally simple synthetic 1,2,4-trioxanes.[3] The mode of action of these compounds appears to involve the heme-mediated decomposition of the endoperoxide bridge to produce carbon-centred free radicals. The involvement of heme explains why the drugs are selectively toxic to malarial parasites. The resulting carbon-centred free radicals are alkylate heme and proteins, one of which is the translationally controlled tumour protein (Figure 3).[4]

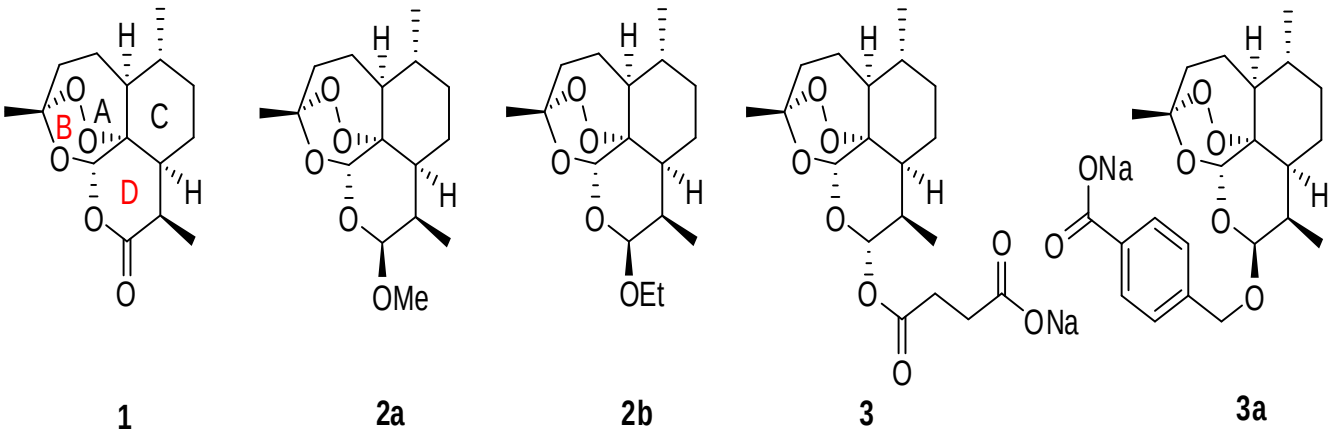


Figure 1. Artemisinin and its derivatives.

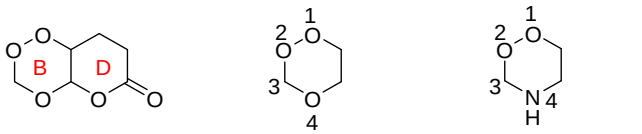


Figure 2. 1,2,4-trioxane and 1,2,4-dioxazinane.

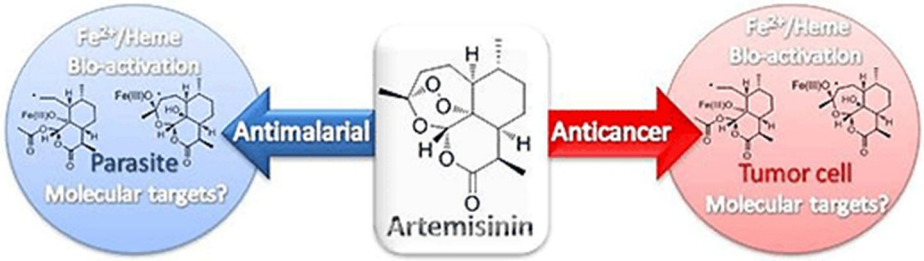
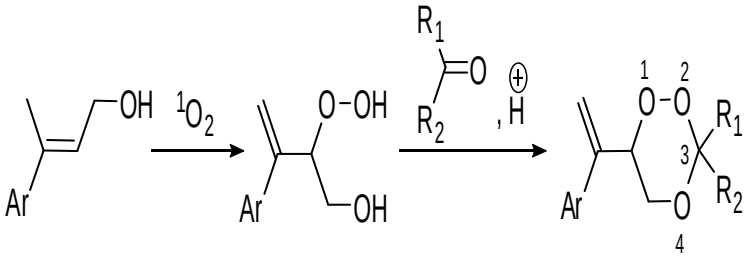


Figure 3. (Excerpted from reference [4]).

II. REVIEW OF LITERATURE

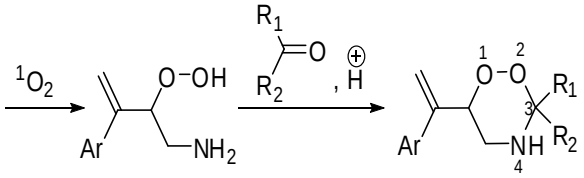
Singh et al. have earlier reported a photooxygenation route for the preparation of 1,2,4-trioxanes. The key steps of this method are (i) preparation of β-hydroxyhydroperoxides by photooxygenation of allylic alcohols and (ii) elaboration of these β-hydroperoxides into 1,2,4-trioxanes (Scheme 1). [5] Several trioxanes prepared by this method have shown promising antimalarial activity.[6]

A. *Scheme 1*

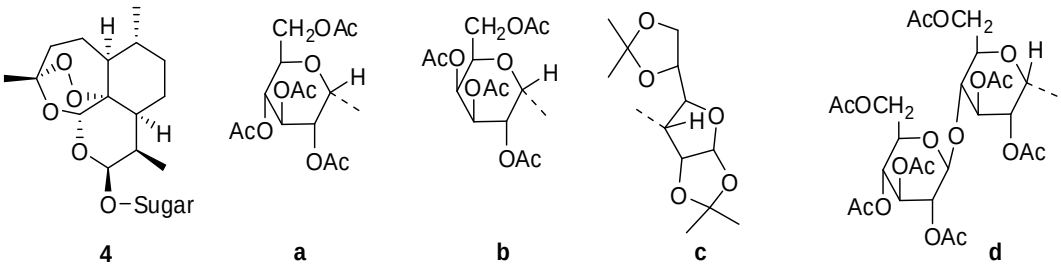


Since the rapid emergence of multidrug-resistant P. falciparum has further complicated the problem, the development of new drug candidates showing better antimalarial activity is in an urgent need. Therefore we extend this strategy for the preparation of nitrogen containing peroxides of 1,2,4-dioxazinane (Scheme 2) and propose herein, the synthesis of 1,2,4-dioxazinane in which O4 of the 1,2,4-trioxane is replaced with nitrogen.

B. *Scheme 2*



In 1992 Lin et al. has prepared a series, of dihydroartemisinin derivatives containing a sugar moiety in the search for analogue with good water solubility and high antimalarial activity.[7] These derivatives 4a-d (Figure 4), tested in vitro against Plasmodium falciparum, were found to be more effective against W-2 than D-6 clones and were not cross-resistant with existing antimalarials.

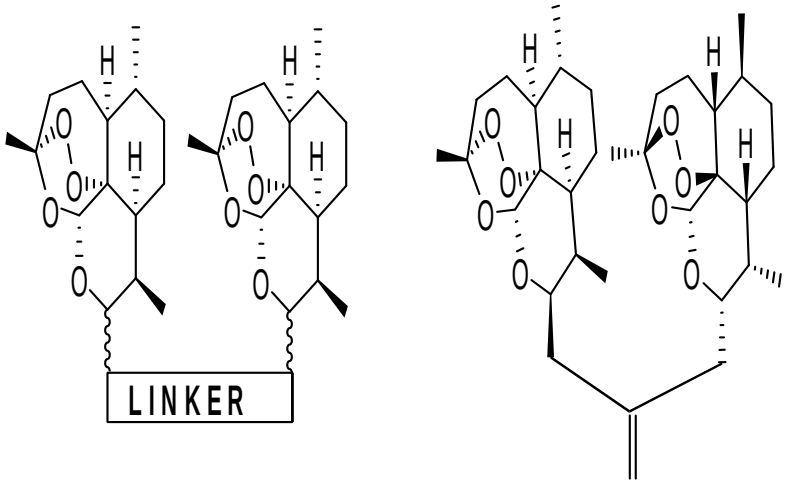


Acylated Sugar
4a D-glucose
4b D-galactose
4c D-5,6-isopropyidene-D-glucose
4d D-cellobiose

Sugar
5a D-glucose
5b D-galactose
5c D-5,6-isopropyidene-D-glucose
5d D-cellobiose

Figure 4. Sugar analogues of artemisinin.

Posner et al. have shown strong interest the dual medicinal value of 1,2,4-trioxanes and trioxane dimers as both antimalarial and especially anticancer agents.[8] They reported orally active, antimalarial, anticancer, artemisinin-derived trioxane dimers with high stability and efficacy. Two of these new chemical entities were shown in rodents to be more orally efficacious as antimalarials than either artelinic acid 3a or clinically used sodium artesunate 3. On the basis of above observations and results, here we plan to synthesize and screen new prototypes of peroxides shown in Figure 5, in the search for analogues with good water solubility and high antimalarial activity as well as anticancer. The design will be described in detail in this proposal.



C. Research Design

A careful survey of literature reveals that nitrogen containing peroxide 1,2,4-dioxazinane, bis-1,2,4-dioxazinane and sugar analogue of synthetic 1,2,4-trioxanes and 1,2,4-dioxazinane have not yet been synthesized in laboratory. To find new drug candidates and to study Structure-Based Activity Relationship (SAR as listed Figure 5). Here we have designed five prototypes to synthesize and to investigate in future.

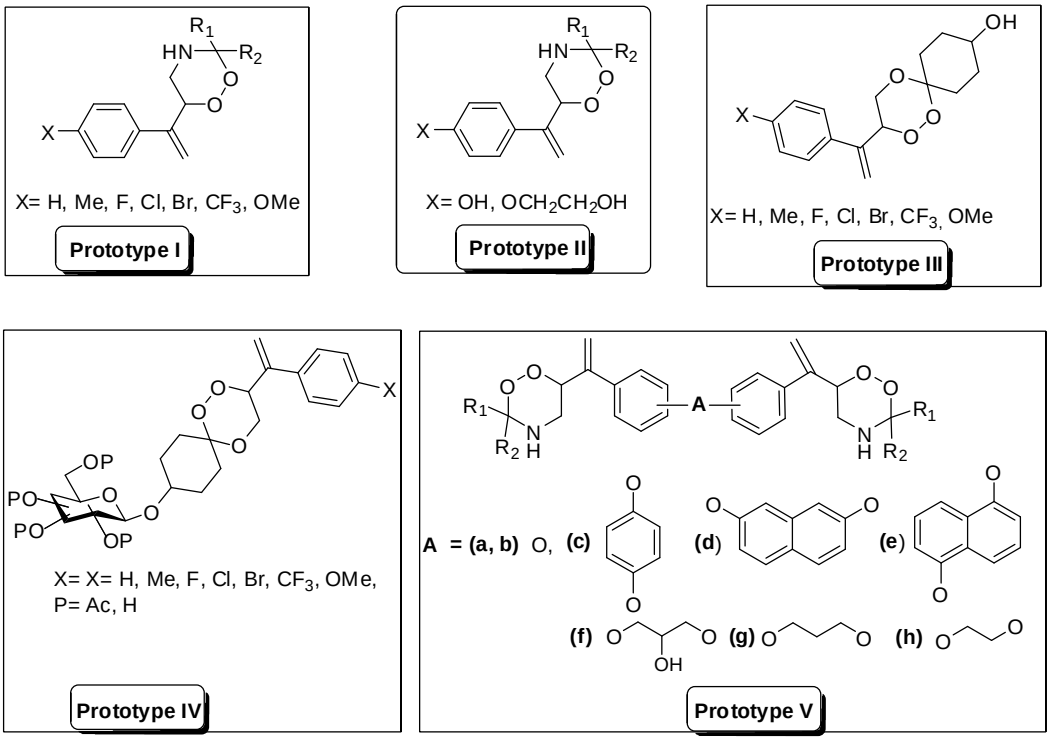
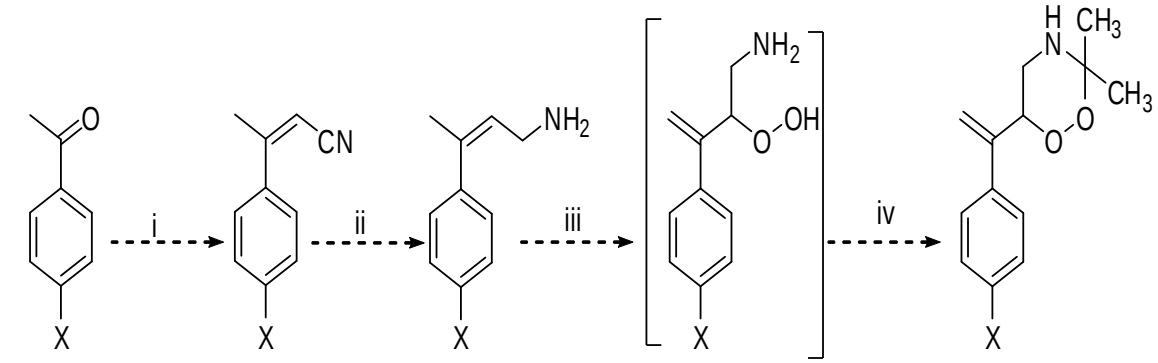


Figure 5. Prototypes I-V

D. Synthesis plan of prototype I:

1) Synthesis of 1,2,4-dioxazinanes 11a-g, 12a-g, 13a-g and 14a-g.: 1,2,4-dioxazinanes is prepared by the procedures given in Scheme 3. Wittig reaction of acetophenone derivatives 7a-g with diethyl cyanomethylphosphonate/NaH has given α,β-unsaturated nitriles 8a-g. Allylic amines 9a-g was produced via reduction of 8a-g with $LiAlH_4$.



7a, X=H,
7b, X=Me,
7c, X=F,
7d, X=Cl,
7e, X=Br,
7f, X=CF_3,
7g, X=OMe

8a, X=H,
8b, X=Me,
8c, X=F,
8d, X=Cl,
8e, X=Br,
8f, X=CF_3,
8g, X=OMe

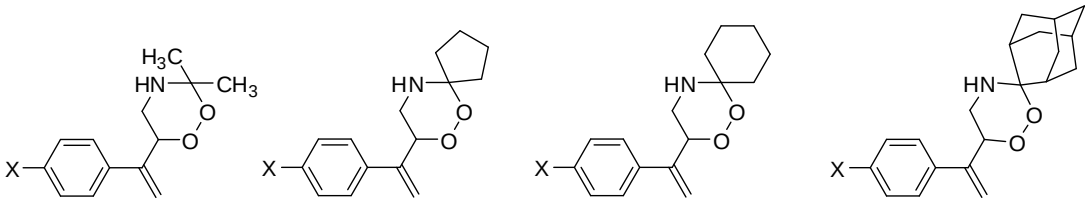
9a, X=H,
9b, X=Me,
9c, X=F,
9d, X=Cl,
9e, X=Br,
9f, X=CF_3,
9g, X=OMe

10a, X=H,
10b, X=Me,
10c, X=F,
10d, X=Cl,
10e, X=Br,
10f, X=CF_3,
10g, X=OMe

11a, X=H,
11b, X=Me,
11c, X=F,
11d, X=Cl,
11e, X=Br,
11f, X=CF_3,
11g, X=OMe

E. Scheme 3

Reagents and conditions: (i) $(OEt)_2P(O)CH_2CN$/NaH, THF; (ii) $LiAlH_4$/THF, 0°C; (iii) $^1O_2$/Organic Solvent, -10 to 0°C; (iv) Acetone/CH_3CN, conc. HCl, rt.



11a, X=H, **11b,** X=Me, **11c**, X=F, **11d**, X=Cl, **11e**, X=Br,**11f**, X=CF_3, **11g**, X=OMe

12a, X=H, **12b**, X=Me, **12c**, X=F, **12d**, X=Cl, **12e**, X=Br,**12f**, X=CF_3, **12g**, X=OMe

13a, X=H, **13b**, X=Me, **13c**, X=F, **13d**, X=Cl, **13e**, X=Br, **13f,** X=CF_3, **13g,** X=OMe

14a, X=H, **14b**, X=Me, **14c**, X=F,**14d**, X=Cl, **14e**, X=Br,**14f**, X=CF_3, **14g,** X=OMe

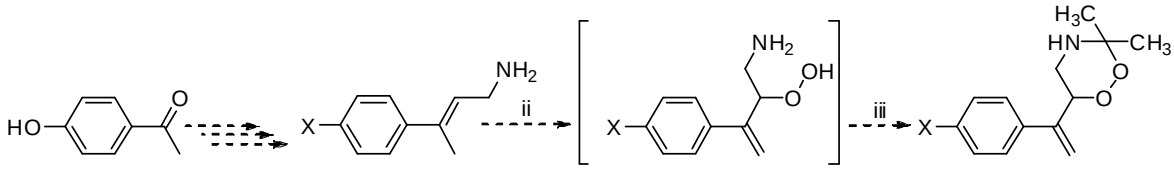
Scheme 4. 1,2,4-dioxazinanes 11a-g, 12a-g, 13a-g and 14a-g.

allylic amines 9a-g have been furnished β-aminohydroperoxides 10a-g which is reacted *in situ* with acetone, cyclopentanone, cyclohexanone, and 2-adamantanone in the presence of an acid catalyst to give 1,2,4-dioxazinanes 11a-g, 12a-g, 13a-g and 14a-g, respectively (Scheme 4).

F. Synthesis plan of prototype II

Synthesis of hydroxyl functionalized 1,2,4-dioxazinanes 18a-b, 19a-b, 20a-b and 21a-b.

Hydroxyl functionalized 1,2,4-dioxazinanes are prepared by the procedures given in Scheme 5. Allyic amines 16a and 16b are prepared from *p*-hydroxyacetophenone 15. Photooxygenation of allylic amines 16a and 16b are afforded β-aminohydroperoxides 17a and 17b which are reacted *in situ* with acetone, cyclopentanone, cyclohexanone and 2-adamantanone in the presence of an acid catalyst to furnish 1,2,4-dioxazinanes 18a-b, 19a-b, 20a-b and 21a-b, respectively (Scheme 6).



15

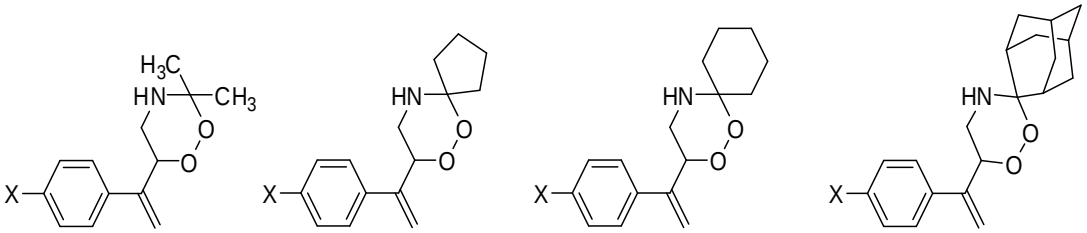
16a, X= OH, **16b,** X= OCH_2CH_2OH

17a, X= OH, **17b,** X= OCH_2CH_2OH

18a, X= OH, **18b,** X= OCH_2CH_2OH

G. Scheme 5

1) Reagents and conditions: (i) $^1O_2$/Organic Solvent, -10 to 0°C, 5-7 h; (ii) Acetone/CH_3CN, conc. HCl, rt, 1 h.



18a, X= OH, **18b,** X= OCH_2CH_2OH

19a, X= OH, **19b,** X= OCH_2CH_2OH

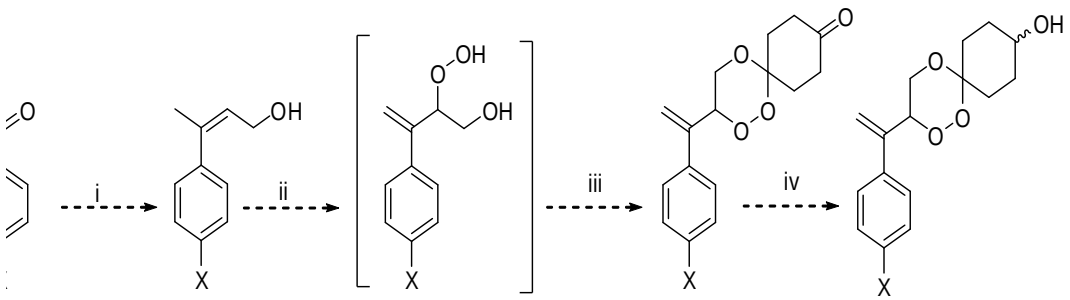
20a, X= OH, **20b,** X= OCH_2CH_2OH

21a, X= OH, **21b,** X= OCH_2CH_2OH

Scheme 6. Hydroxy functionalized 1,2,4-dioxazinanes 18a-b, 19a-b, 20a-b and 21a-b.

H. Synthesis plan of prototype III

1) Synthesis of hydroxyl functionalized 1,2,4-trioxanes 24a-g: Hydroxyl functionalized 1,2,4-trioxanes are prepared by the procedures given in Scheme 7. Allylic alcohols 22a-g is prepared from acetophenone derivatives 7a-g. Photooxygenation of allylic alcohols 22a-g form β-hydroxyhydroperoxides 23a-g which are reacted *in situ* with cyclohexane-1,4-dione, in the presence of an acid catalyst and furnish 1,2,4-trioxanes 24a-g which is reduced further into 25a-g, respectively with $NaBH_4$ (Scheme 7).



=H, =Me, =F, =Cl, =Br, :CF_3, =OMe

22a, X=H, **22b**, X=Me, **22c**, X=F, **22d**, X=Cl, **22e**, X=Br, **22f**, X=CF_3, **22g**, X=OMe

23a, X=H, **23b**, X=Me, **23c**, X=F, **23d**, X=Cl, **23e**, X=Br, **23f**, X=CF_3, **23g**, X=OMe

24a, X=H, **24b**, X=Me, **24c**, X=F, **24d**, X=Cl, **24e**, X=Br, **24f**, X=CF_3, **24g**, X=OMe

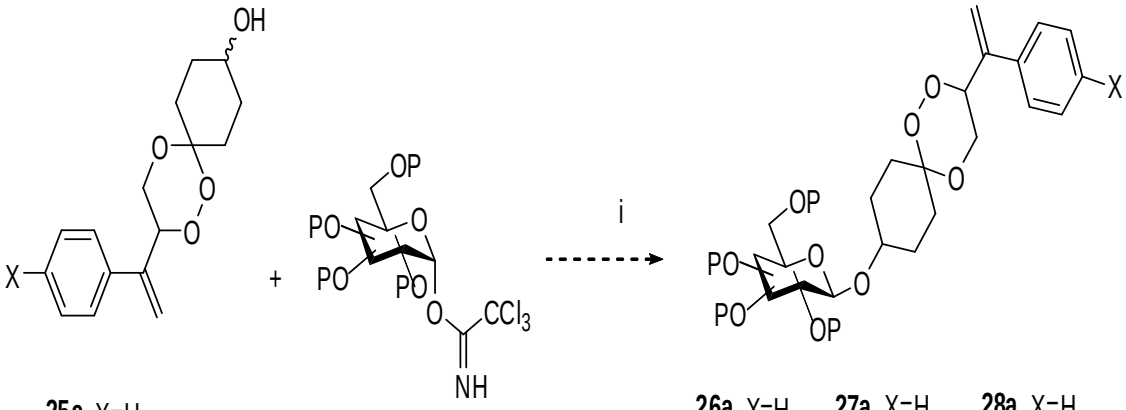
25a, X=H, **25b**, X=Me, **25c**, X=F, **25d**, X=Cl, **25e**, X=Br, **25f**, X=CF_3, **25g**, X=OMe

I. *Scheme 7*

1) *Reagents and conditions*: (i) $^1O_2$/Organic Solvent, -10 to 0°C; (ii) cyclohexane-1,4-dione /CH_3CN, conc. HCl, rt, (iii) $NaBH_4$, MeOH/DCM, 0°C.

J. *Synthesis plan of prototype IV*

1) *Synthesis of sugar analogues 1,2,4-trioxanes:* Sugar analogues of 1,2,4-trioxanes are prepared by the procedures given in Scheme 8. The reaction of compounds 25a-g with glucose trichloroacetimidate (h) in the presence of TMSOTf at -78°C has given compounds 26a-g. Similar reaction of compounds 25a-g with galactose trichloroacetimidate (i) to give compounds 27a-g, and with mannose trichloroacetimidate (j) to give compounds 28a-g. Deprotection of compounds 26a-g, 27a-g, and 28a-g with BaO/MeOH (Scheme 9) has given compounds 29a-g, 30a-g, and 31a-g, respectively.



25a, X=H, **25b**, X=Me, **25c**, X=F, **25d**, X=Cl, **25e**, X=Br, **25f**, X=CF_3, **25g**, X=OMe

h = glucose trichloroacetimidate
i = galactose trichloroacetimidate
j = mannose trichloroacetimidate

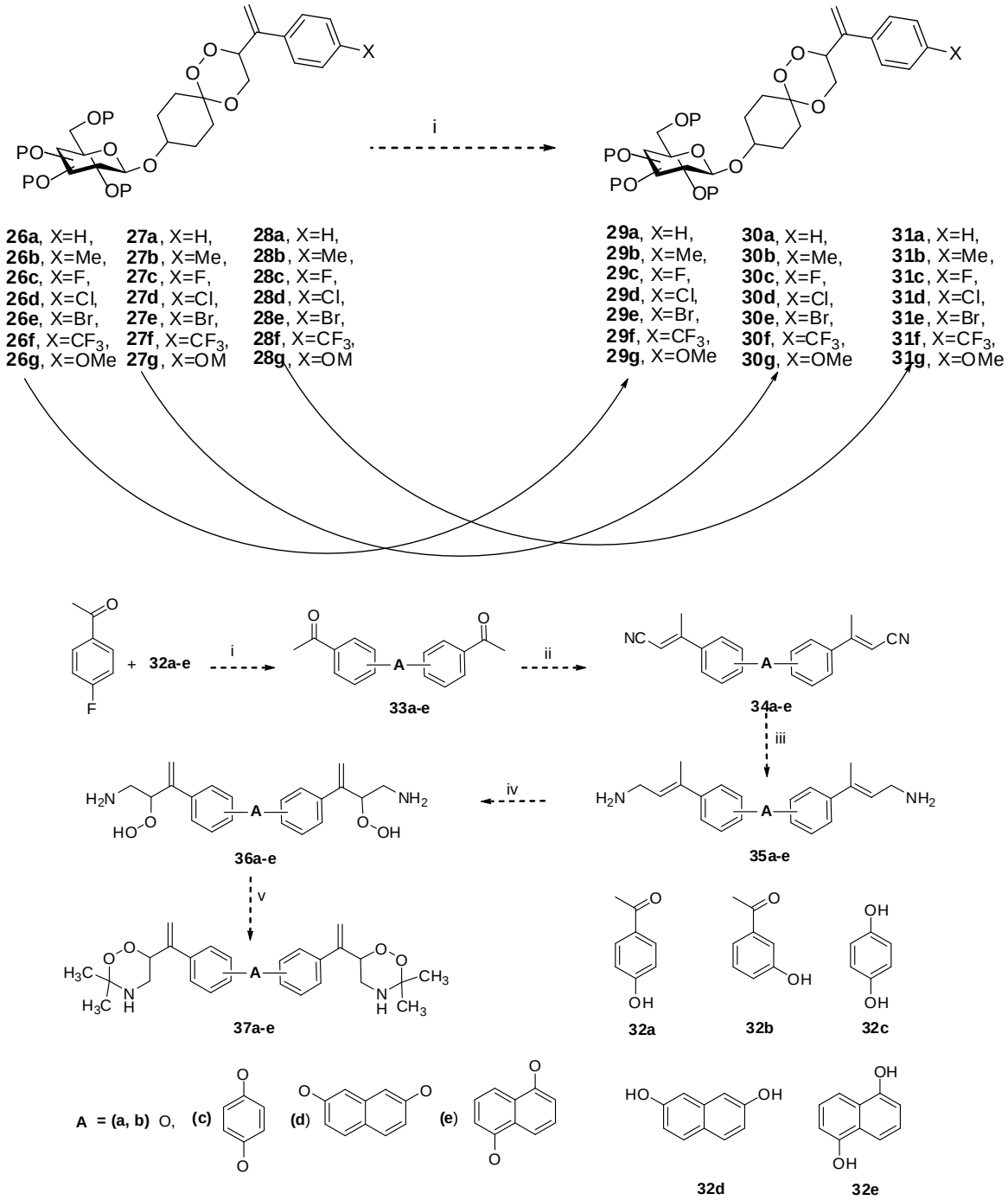
26a, X=H, **26b**, X=Me, **26c**, X=F, **26d**, X=Cl, **26e**, X=Br, **26f**, X=CF_3, **26g**, X=OMe

27a, X=H, **27b**, X=Me, **27c**, X=F, **27d**, X=Cl, **27e**, X=Br, **27f**, X=CF_3, **27g**, X=OM

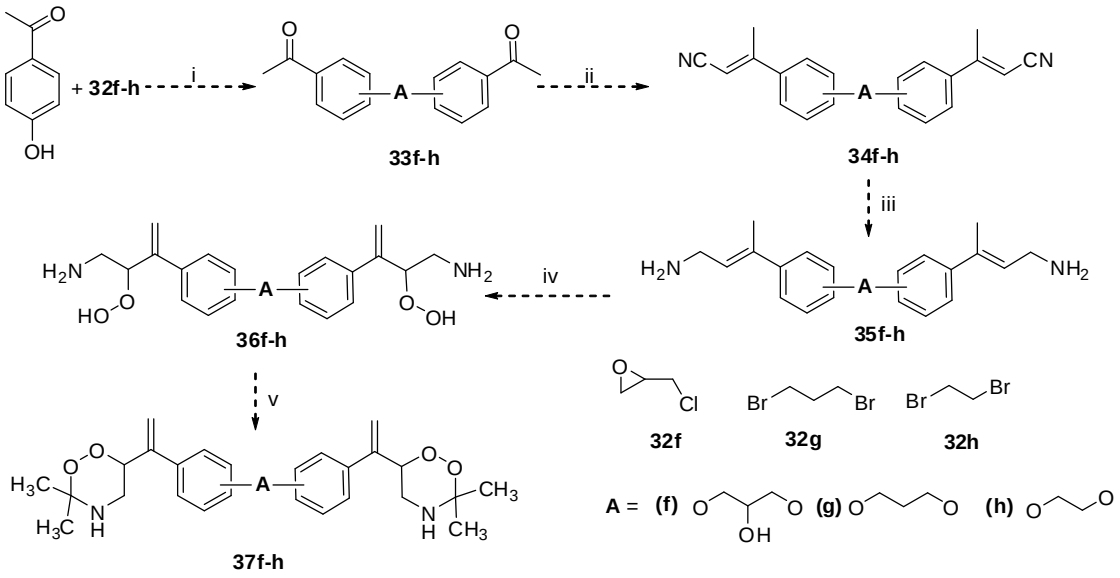
28a, X=H, **28b**, X=Me, **28c**, X=F, **28d**, X=Cl, **28e**, X=Br, **28f**, X=CF_3, **28g**, X=OM

K. *Scheme 8*

Reagents and conditions: (i) TMSOTf/DCM, MS 4A°, -78°C.

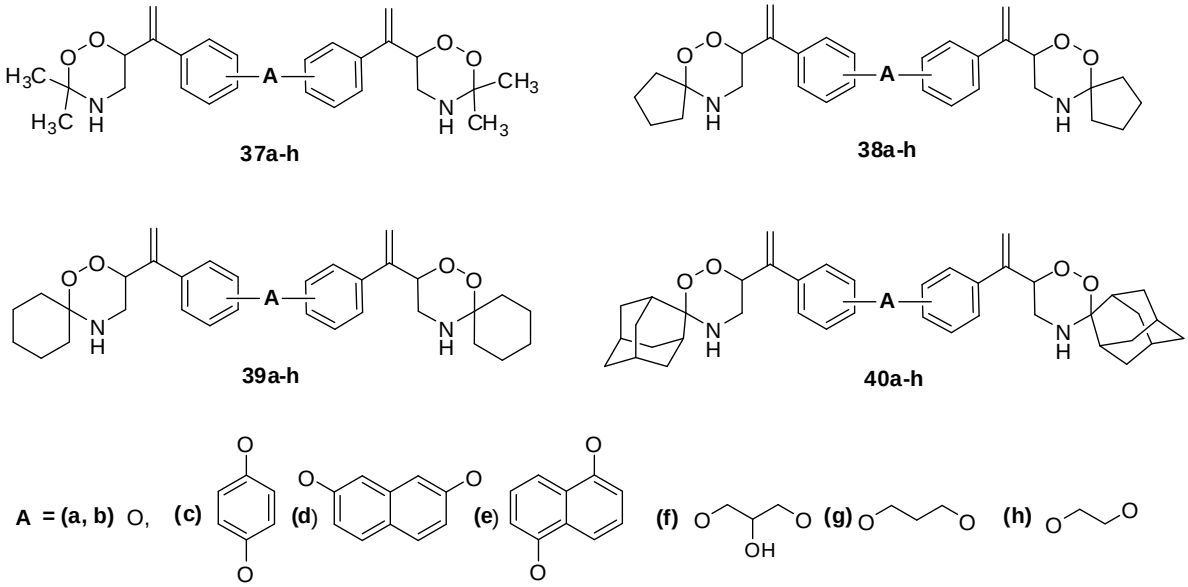


Bis-1,2,4-dioxazinane is prepared by the procedures listed in Scheme 11. The reaction of *p*-hydroxyacetophenone with epichlorohydrin 32f, 1,3-dibromopropane 32g, 1,2-dibromoethane 32h, at 115-130^{o}C is furnished diketones 33f-h. Similarly, Wittig reaction of diketones 33f-h with diethyl cyanomethylphosphonate/NaH is given α,β-unsaturated nitriles 34f-h, which are reduced with $LiAlH_4$ to give allylic amines 35f-h. Photooxygenation of allylic amine 35f-h was afforded β-aminohydroperoxides 36f-h which was reacted *in situ* with acetone, cyclopentanone, cyclohexanone and 2-adamantanone in the presence of an acid catalyst to furnish bis-1,2,4-dioxazinane 37f-h, 38f-h, 39f-h and 40f-h, respectively (Scheme 12).



L. Scheme 11

Reagents and conditions: (i) K_2CO_3, heated at 115-130°C; (ii) $(OEt)_2P(O)CH_2CN$/NaH, THF, rt; (iii) $LiAlH_4$/THF, 0°C; (iv) $^1O_2$/Organic Solvent, -10 to 0°C; (v) Acetone/CH_3CN, conc. HCl, rt.



Scheme 12. Bis-1,2,4-dioxazinanes 37a-h, 38a-h,39a-h and 40a-h.

III. CONCLUSION

In this research we have prepared nitrogen containing peroxide 1,2,4-dioxazinanes, bis-1,2,4-dioxazinanes and sugar analogue of synthetic 1,2,4-trioxanes and 1,2,4-dioxazinanes. We believe that the results acquired in this research help us to develop potential drug candidates for effective chemotherapy for both malaria and cancer.

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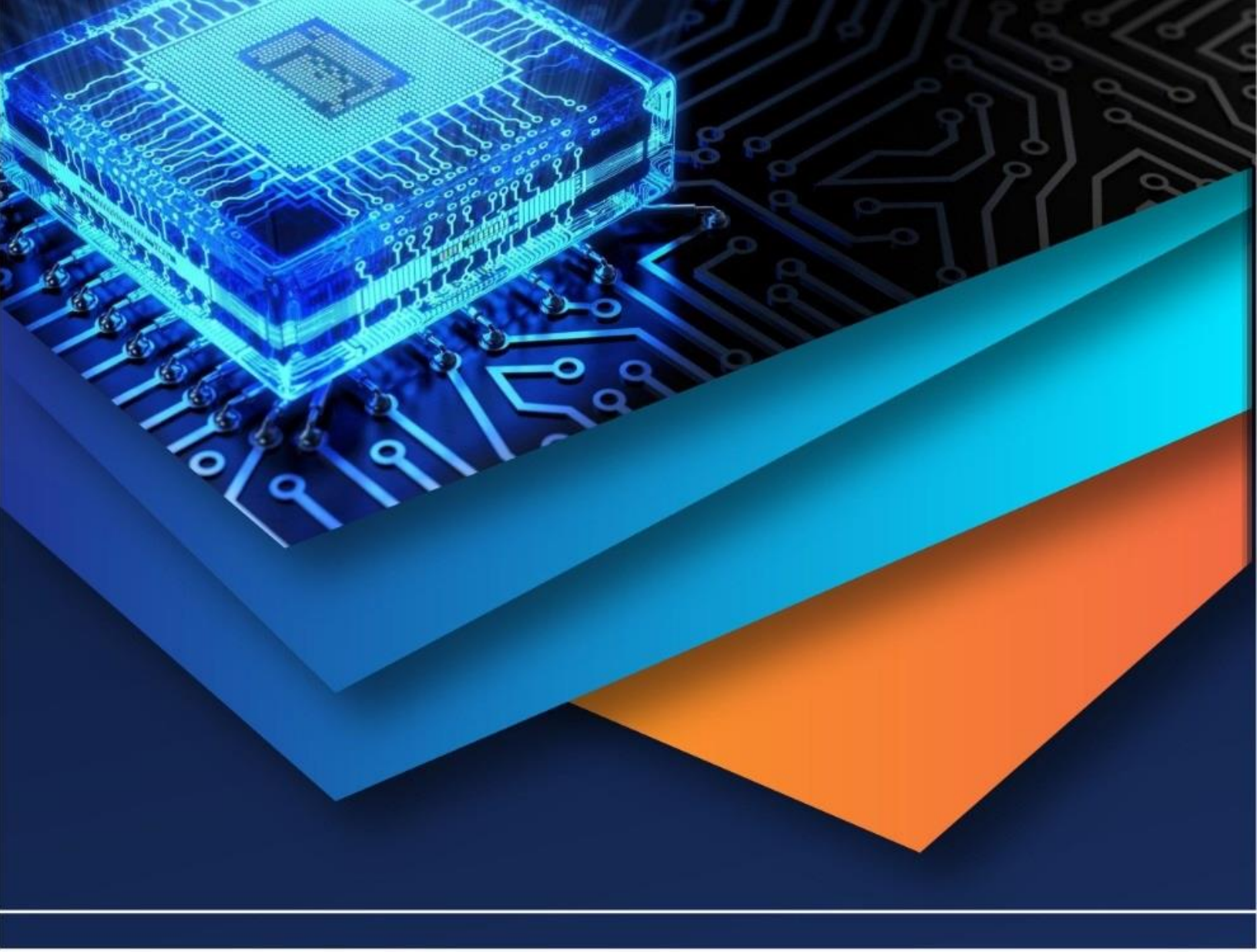

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