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Synthesis of 1-Aryloxy-2-hydroxy-3-substituted Aminocyclohexane and its Analogues for Possible Antimalarial Activity

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ABSTRACT

Malaria remains one of the most important diseases of man with over half of the world's population at a risk of infection and 1-2 million deaths annually. The emergence and rapid spread of Chloroquine-resistant strains of Plasmodium *falciparum* has dramatically reduced the Chemotherapeutic options. It is important to recognize that antiparasitic drug discovery differs in many ways from drug discovery for the chronic conditions that have become a primary focus of the pharmaceutical industry today. A short review of the antimalarial drugs currently used in human clinics reported. Amodiaquine (AQ) (2) is a 4-Aminoquinoline antimalarial that can cause adverse effects including agranulocytosis and liver damage. This study describes the synthesis of new 4-Aminoquinoline derivatives and evaluation of their activity against Chloroquine-sensitive strain of Plasmodium *falciparum* invitro and Chloroquine-resistant N-67 strain of Plasmodium *yoelli* invivo. It is clear that Chloroquine resistant parasites accumulate fewer drugs than sensitive strains. It has been synthesized a new series of Chloroquine analogues where the diethylamino isopentyl function of the side chain has been replaced by shorter side chains, containing metabolically more resilient terminal secondary and tertiary alkyl amino group. In our present studies in search for more effective drug as antimalarials, we took the lead compound Amodiaquine and replace Aminoquinoline and place them in spatial disposition in bio-phase and their likely geometry responsible for drug-receptor interaction.

KEYWORDS: Malaria, Chloroquine, chemotherapeutic, antiparasitic drug discovery, chloroquine-resistant, Amodiaquine, Aminoquinoline, drug-receptor interaction.

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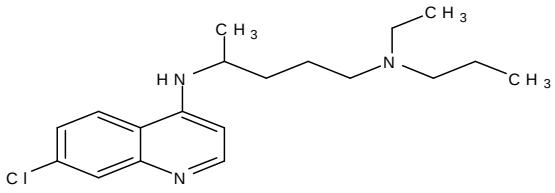
INTRODUCTION

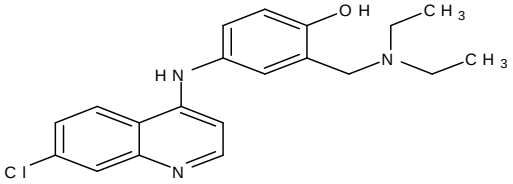
Malaria remains one of the most important diseases of man with over half of the world's population at risk of infection. Approximately 40% of the world population lives in malaria endemic areas. Every year, 300-500 million people suffer from acute malaria and 0.5 -2.5 million die from this disease.[1] Although much of the current efforts are directed towards the identification of novel chemotherapeutic targets, we still don't fully understand the mode of action and the mechanism of resistance to the Quinoline compounds, knowledge that would greatly assist the design of novel, potent and inexpensive Quinoline antimalarials. Chloroquine (CQ) and other Quinoline antimalarials have been mainstays of malaria chemotherapy for much of the past 40 years. The success of these drugs was based on excellent clinical efficacy, limited host toxicity, ease of use and simple, cost effective synthesis. However, these drugs have been seriously eroded in recent years mainly as a result of the development and spread of parasite resistance to CQ and related compounds.[2]

A BRIEF REVIEW

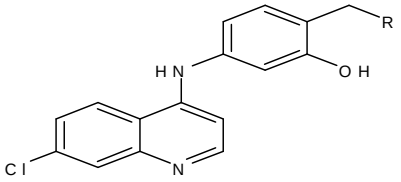
Amodiaquine (AQ) is a 4-aminoquinoline antimalarial which is effective against many Chloroquine-resistant strains of P. *falciparum*. However, clinical use of AQ has been severely restricted because of associations with hepatotoxicity and agranulocytosis.[3,4]



Chloroquine (1)

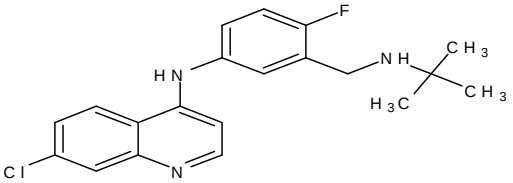


Amodiaquine (2)



Isoquine (3), R = NEt

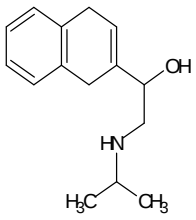
(4) R = NHEtBu, Desethyl Isoquine (5), R = NHEt



4'-Fluoro-N-tertbutyl analog (6) [FAQ-4,6]

The incorporation of fluorine atoms into the 4-Hydroxyanilino side chain of Amodiaquine produces compounds with greater oxidative and metabolic stability. From the previous work, it was noted that in Amodiaquine and Tebuquine series of 4-Aminoquinoline analogues, the presence of 4'-Hydroxyl group within aromatic ring imparts greater inherent antimalarial activity against Chloroquine resistant parasites than the corresponding deoxo analogues. In this, it has been described the synthesis, antimalarial activity and metabolism of the prototype Isoquine (3 ISQ 1), an Amodiaquine regioisomer that cannot form toxic metabolites by simple oxidation and which is potent against Chloroquine-resistant parasites in vitro.

The classical studies of Bovet and coworkers[5]on adrenergic structure established the bio-isosterism of norepinephrine (5) and 2-phenoxyethylamines (6).[6]The bio-isosteric relationship in phenethanolamines and phenoxy propanolamines was indicated from the work of Petrow and Stephenson (1953)[7], who prepared aryloxypropanolamines (7) possessing sympathomimetic and sympatholytic activities, and from a study of molecular models in which it was found that they assume a conformation where ph→O→N distances are almost equal. The insertion of an oxymethylene bridge in pronethalol (8)[8], a potent beta-adrenergic receptor blocker, resulted in the discovery of propranolol (9)[9,10] a clinically useful drug. This established the bio-isosterism in phenethanolamines and phenoxypropanolamines. Since then a large belonging to aryloxypropanolamine (10) have emerged such as Alprenolol (11a)[11], Propranolol (9)[9,10], and Practolol (11b)[12].



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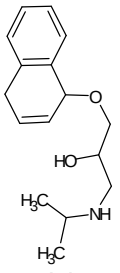

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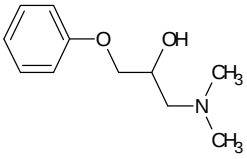

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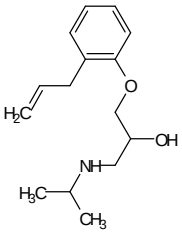
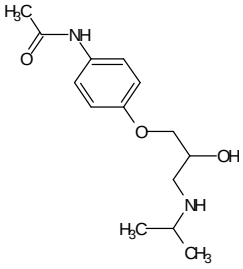


(11 a)

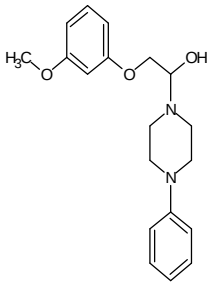


(11 b)

These studies showed the scope of exploration of aryloxypropanolamines as pharmacodynamic agents. A variety of compounds of type (10) incorporating arylpiperazines as the amino component. A variety of compounds was therefore, synthesized in this lab and structures exhibit a variety of interesting biological activites. It was found that substitution in the aryloxy part; in

general, the length of propanol chain and substitution in the amino component in particular, had a marked effect on the pattern of biological activity.

The promising candidates uncovered from this study were (1-Methoxyphenoxy)-2-hydroxy-3-{N'-(N^4-phenyl-piperazinyl)}propane (12)[14] as hypotensive by ganglion block,1-(p-chlorophenoxy)-2-hydroxy-3-{N'-(N^4-3,4-dimethoxyphenyl)piperazinyl}propane (13)[14] as anticonvulsant.



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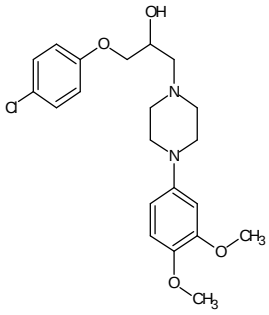

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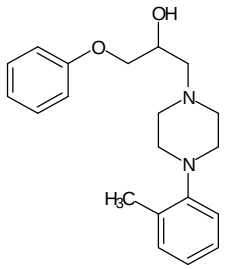

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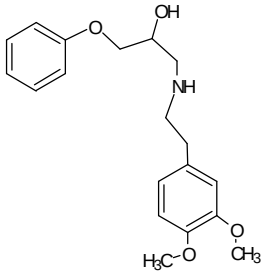
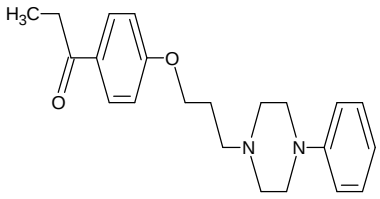


(15)

1-phenoxy-2-hydroxy-3-{N'-(N^4-o-methylphenyl)-piperazinyl}propane (14)[14] as adrenergic receptor blocker and 1-phenoxy-2-hydroxy-3-{β-(3,4-dimethoxyphenyl)ethyl-amino}propane (15)[14] as hypotensive by neuronal block.

The study further indicated that electron withdrawing and electron donating substituents in general had different effects on biological activity. In view of the known marked pharmacodynamic contribution of alkanone residue, 1-(alkanoylphenoxy)-2-hydroxy-3-{N'-(N4-arylpiperazinyl)} propanes (16) were also studied. Quite early in this work it was noted that these alkanoyl compounds possess more marked activity than the other substituted compounds.



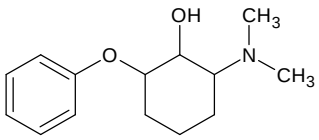
(16)

Although, a large numbers of pharmacologically active agents of this series have been discovered, yet their spatial disposition in bio-phase and their likely geometry responsible for drug-receptor interaction is a matter of speculization only. To shed light on this aspect and to

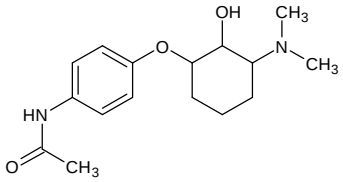
reduce possible biochemical response in biosystem, a promising approach could be to have these acyclic compounds incorporated in a rigid framework. For this purpose, it was decided to study cyclic analogs of some of active compounds described above. Thus, the synthesis and bioevaluation of 1-Aryloxy-2-hydroxy-3-substituted aminocyclohexane of types (17), (18), (19) and (20) were designed for the study of parameters responsible for the activity possessing structural selectivity.

RESEARCH WORK

In our present studies in search for more effective drug as antimalarials, we took the lead compound Amodiaquine and replace Aminoquinoline (A) by phenoxypropanol amines for promising antimalarials activity. Thus we synthesized the following compound:



(17)



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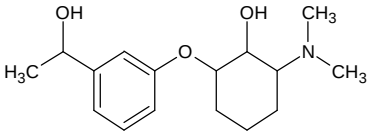

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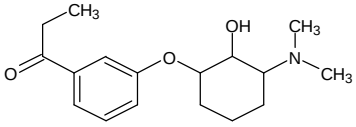


(20)

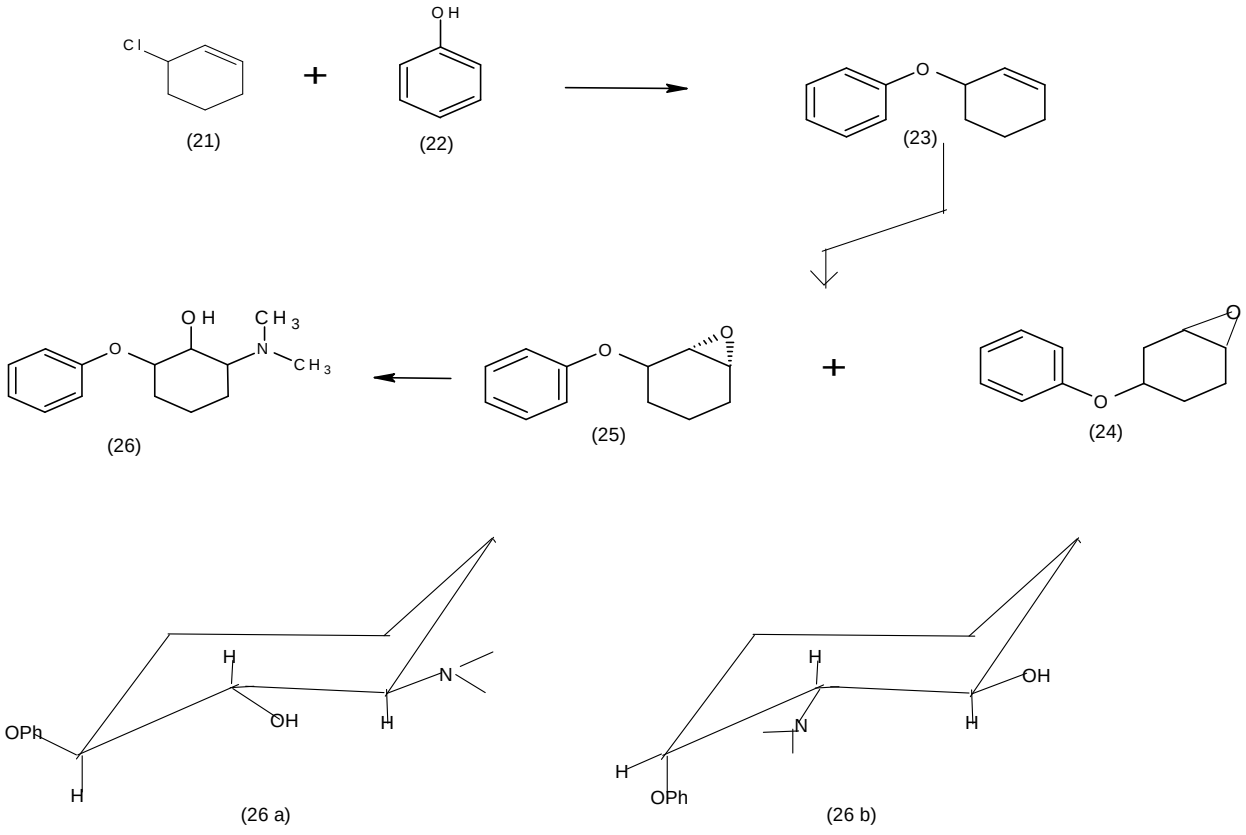
These systems incorporate the corresponding acyclic analogs in a particular spatial manner and thus have the possibility of an improvement of pharmacological activity over the acyclic congeners and are also useful in understanding the geometry of acyclic analogs required for receptor interaction.

1-phenoxy-2-cyclohexane (23) was prepared by treatment of 1-chloro-2-cyclohexene (21) with phenol (22) in aq. NaOH-DMF and (23) thus obtained was epoxidised with m-chloroperbenzopic acid in CH_2Cl_2 to give cis- and trans- epoxide (24) and (25). The trans-epoxide (25) on condensation with various amines in methanol furnished the required 1-phenoxy-2-hydroxy-3-substituted amino-cyclohexane (26). In the NMR of compounds of the type (23), the C_2-H showed a triplet with J= 8.5 Hz (approx.) which suggests a trans-diaxial

opening of the epoxy ring with hydroxyl at 2-position (26a). In the absence of the GLC data of these products the possibility of ring cleavage to give other product such as (26b) cannot be excluded.

Melting points were determined in an electrically heated apparatus (Townson and Mercer Ltd, Croydon, England) and are uncorrected. The NMR spectra were recorded on a Varian A-60D instrument using TMS as internal reference. The chemical shift values are expressed in delta units. Mass spectra were determined on a Hitachi RMU-6E Mass spectrometer recorded on Perkin-Elmer 137 infracord, Perkin Elmer 337 grating or Perkin-Elmer 177 grating instruments and the frequencies are expressed in cm^{-1}. The UV spectra were recorded on Perkin-Elmer 202 automatic recording spectrophotometer. Homogeneity of the compounds was checked by TLC either on silica gel or on alumina plates and by GLC on Varian aerograph 1800 instrument. Analyses of the element were within 0.4% of the calculated values.

Scheme 1: Synthesis of 1-phenoxy-2-hydroxy-3-substituted cyclohexane



cis- and trans- epoxide of 1-phenoxy-2-hydroxy-3-substituted aminocyclohexane

EXPERIMENTAL PROCEDURE

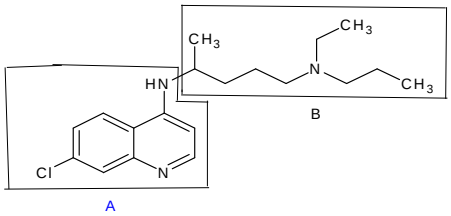
The following experimental procedures are illustrative of the general methods employed to prepare various compounds described in table 1.

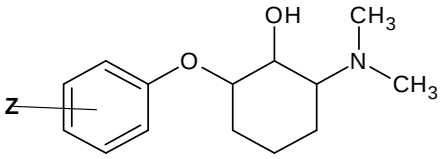
1-Phenoxy-2-hydroxy-3-{N'-(N^4–phenylpiperazinyl)}cyclohexane(26a)

A solution of 1-phenoxy-trans-2,3-epoxycyclohexane (0.3 g, 1.6 mole) and N-phenylpiperazine (0.16 g, 1.6 mole) in ethanol was refluxed for 3 hr on steam bath. It was then concentrated, and residue triturated to get 0.3 g (75%) of the required product XXVIa, m.p. 105^0 (C_6H_6-hexane), hydrochloride 228^0 (MeOH-Et_2O). IR : 3348(OH); NMR: 1.0-2.4 (bm, 6, -$(CH_2)_3$-), 2.4-3.04 (m, 5, CHN$(CH_2)_2$), 3.0-3.42 (m, 4, PhN$(CH_2)_2$), 3.64 (t, 1, CH-OH, J= 9Hz, D2O exchangeable), 4.58-5.05 (bh, 1, CH-OPh), 6. 7-7.5 (m, 10, Ar-H).

RESULT

Table 1: Different substituent modifications and possible activity





1-Aryloxy-2-hydroxy-3-substituted aminocyclohexane

S.No.	Z	M.p./B.p. (^{0}C)	N.M.R. (delta units)	Possible Activity
1.	p-$NHCOCH_3$	100	1.0-2.2 (bm, 6, -$(CH_2)_3$-), 1.95 (s, 3,-$COCH_3$), 4.52 (h,1,Ar-OH, W/2=9Hz), 5.7 (bs, 2, -CH=CH), 6.62 (dd, 2, Ar-H, J=2 and 8.5 Hz), 8.5 (s, 1, -NH, D_2O exchangeable).	Antimalarial activity/β-blocker activity
2.	m-$CH(OH)CH_3$	89	---	Antimalarial activity/ β-blocker activity
3.	m-$COCH_2CH_3$	55	---	Antimalarial activity/β-blocker activity

Following compounds are under analysis and investigation for possible antimalarial activity.

CONCLUSION

In the battle against malaria, we are currently at a stalemate at best. If and when the resistance to artemisinin drugs further develops and spreads, we will be caught unarmed, without any effective weapon against this deadly parasite. Looking at the antimalarial drug development pipeline, new classes of agents, and, in the meantime, a re-optimization of existing drugs using new creative strategies are needed.

Re-optimization of existing drugs through replacement/rotation and combination approaches may prolong their life spans for effective treatment and prophylaxis, until new treatments are found. The future of antimalarial drug discovery lies in innovative thinking and novel areas, some currently under exploration and some yet to explored.

We do not have any choice but explore many or all of these approaches in parallel, until existing drugs with renewed potential, as well as entirely new series of compounds are available for deployment in the field. The discovery of new treatment for malaria, along with their proper execution in the field, will contribute to an important achievement of controlling, and eventually eradicating, this global infectious disease.

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