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Design, ADME Evaluation, Lewis Acid Catalysed Synthesis and Biological Evaluation of 1,4 Naphthoquinone Derivatives as Antimalarial Agents

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ABSTRACT

In an effort to develop new antimalarials, some 1,4 naphthoquinone derivatives were designed on the basis of results of computational studies reported in previous paper, which showed that 2^{nd} or 3^{rd} or both position of 1,4 naphthoquinone is most suitable for better antimalarial activity. When the reaction of 1,4 naphthoquinone was performed without a catalyst several secondary products were formed, but when performed in presence of lewis acid like $CeCl_3.7H_2O$,Ce^{4+} provides a unique catalytic effect promoted by redox properties with formation of the desired products in very good yields. Therefore compounds have been synthesized using Lewis acid as catalyst, which reduces reaction time and gives better yield. Characterisation of compounds was done using IR, 1H NMR, 13CNMR and mass spectroscopy. All the compounds were screened for intra erythrocytic *in vitro* antimalarial evaluation against Chloroquine-sensitive ($3D_7$) strain of *Plasmodium falciparum* using the SYBR Green I fluorescence assay. The results revealed that 2-(2,4-dimethylphenylamino)naphthalene-1,4-dione (P_2) as most potent compound with IC_{50} of 1.8 µM.

INTRODUCTION

There is an urgent need for new antimalarial drugs with novel mechanisms of action for implicit control and eradication of malaria. Parasite resistance to almost all existing antimalarial classes, including the artemisinins, have been reported during their clinical use. A failure to generate new antimalarials with novel mechanisms of action that circumvent the current resistance challenges will contribute to resurgence in the disease which would represent a global health emergency [1,2]. Naphthoquinone pharmacophore impart pronounced biological effects, such as antitumor [3-10], antimycobacterial [11], anti-inflammatory, anti-allergic [12], antimalarial [13,14,15] and antileishmanial [16]. The antimalarial mode of action of 1,4 naphthoquinone involves a cascade of redox reactions in the parasite. The postulated bioactivation of the antimalarial 3-benzyl-menadione (a naphthoquinone derivative) is thought to generate redox-active metabolites which, in their oxidized form, are reduced by NADPH in glutathione reductase-catalyzed reactions within the cytosol of infected red blood cells and in their reduced forms, can convert methaemoglobin (Fe III), the major nutrient of the parasite, into the very slowly digestible haemoglobin (Fe II). Consequently, the antimalarial naphthoquinones are suggested to perturb nutrient acquisition and the major redox equilibrium of the targeted infected red blood cells, ultimately results in arrest and death of the malaria parasite at the trophozoite stage [17]. A number of naphthoquinone derivatives (Figure-1) have shown potential antimalarial activity.

1,4-napthoquinones acts by a non-*bc*1-dependent mechanism and remain potent against atovaquone and chloroquine resistant parasites. The variable capacity of naphthoquinones to accept electrons is due to the electron-attracting or -donating substituents at the quinone moiety which modulate the redox properties responsible for the resulting oxidative stress.

The ease and low cost of synthesis of these inhibitors fulfill the target product profile for the generation of a potent, safe, and inexpensive drug with the potential for eventual clinical deployment in the control and eradication of falciparum malaria.

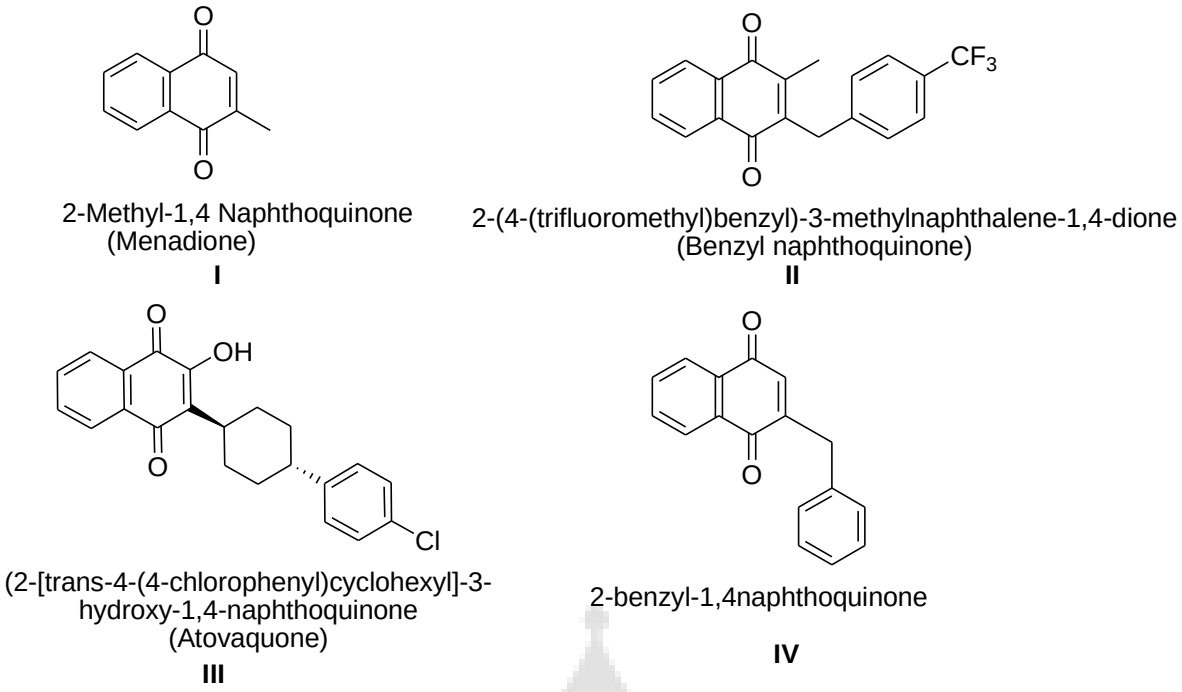


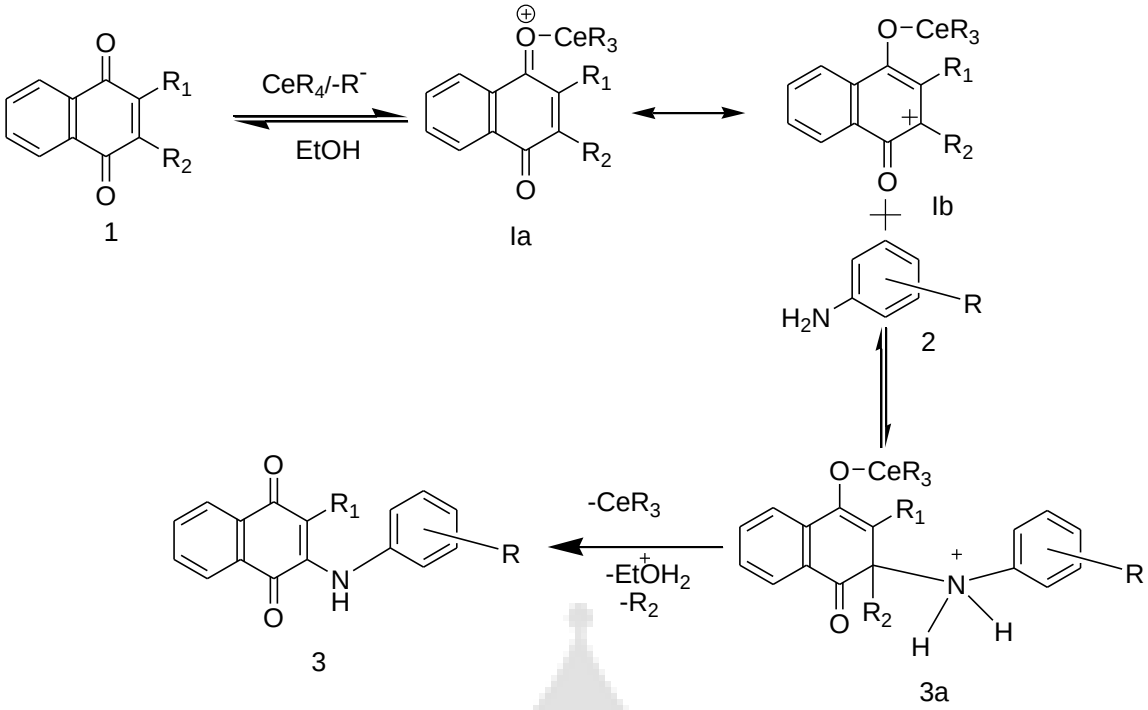
Figure-1 Structures of Naphthoquinone derivatives with potent antimalarial activity

Although a large number of quinones have been synthesized and tested but due to problem of resistance, this has rekindled the interest in naphthoquinones as antimalarials and has provided the stimulus for the present study.

Pharmacophore model generation study was carried out on 1,4 Naphthoquinone derivatives which suggest that position 2^{nd} or 3^{rd} or both are important for antimalarial activity as reported previously[18]. Therefore in present study, we have designed, synthesized and done antimalarial evaluation of six 1,4- naphthoquinone derivatives(Table-1).

Chemistry

Several physicochemical properties and the electron-accepting capacity of a given quinone can be modified by directly adding substituted aniline to the naphthoquinone [19]. In this type of compounds, the electron-attracting and donor properties of the substituents on the aniline modify their redox properties either by facilitating or interfering in the charge transfer process from the substituent to the naphthoquinone [20].



Scheme-1 Mechanism of Ce^{4+} assisted nucleophilic substitution (where $R_1$and R_2=H or Cl)

It has been reported in the literature that when the reaction of 1,4-naphthoquinone derivative 1 is performed with aniline 2 without a catalyst low yields of the 2-(anilino)-1,4-naphthoquinone 3 are obtained (0–50%) and several secondary products are formed [21]. Furthermore, if this reaction is performed under reflux condition then leads to even lower yields (0–30%). few reports exist on the use of Lewis acids to catalyze the reaction of anilines with 1,4-naphthoquinone [22]. When reaction was carried out in the presence of $CeCl_3.7H_2O$, there was a high conversion of reactant species and the naphthoquinone derivatives were reported to obtain in very good yields (70–91%) [23].

$CeCl_3.7H_2O$ (Ce^{4+}) assisted synthesis proceeds via a four steps mechanism (Scheme 1). First of all, the quinone 1 is activated by its reaction with the Lewis acid catalyst to form an organic complex Ia. Secondly, due to resonance electronic interactions, there is a charge transfer in the activated complex with the 2-position of the quinone ring so quinone ring becomes positively charged Ib.

In Third step, the activated complex undergoes a selective nucleophilic attack, by the aniline 2 to give intermediate 3a. In Fourth step, under ethanolic conditions, it easily loses a proton

and decomposes to produce a reduced ion Ce^{3+} and an oxidized compound or 2-(R-anilino)-1,4-naphthoquinone 3. [24]

In the case of cerium, due to the low redox potential between the two ions ($Ce^{3+/}Ce^{4+}$, 1.7 V) in solution, the strong oxidant Ce^{4+} predominates in an oxidative atmosphere. Therefore, in this particular reaction the high yield observed is most likely due to the presence of a strong Lewis acid and a strong oxidizing agent[25].

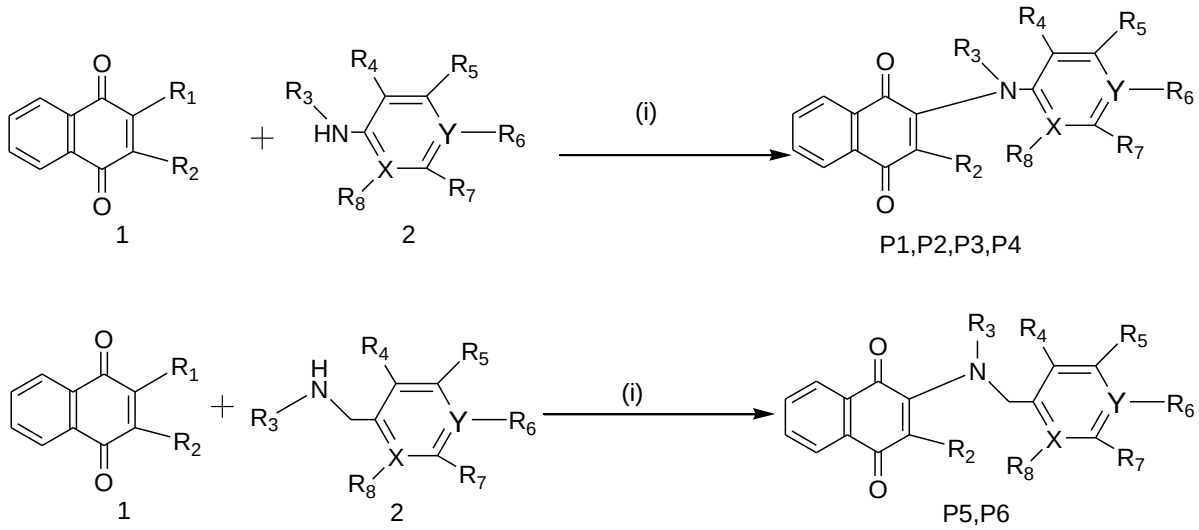
MATERIALS AND METHODS

Materials

All reagents were of commercially available reagent grades and were used without further purification. Melting points were determined by open capillary method and are uncorrected. Infrared spectra were determined as KBr pellets on a Shimadzu model 470 spectro-photometer.1H NMR spectra were recorded in DMSO on an AV- 300 instrument. 13C NMR spectra were obtained in DMSO at 400 MHz. Chemical shifts are expressed in ppm downfield relative to tetramethylsilane (TMS, ∂ scale). Silica gel Merck 60(70-230mesh) was used for preparative column chromatography and thin layer chromatography (TLC) aluminum foil 60F254 for analytical TLC.

Methods

Substitution at both the acceptor quinone nucleus and the donor phenylamino group is designed to study the reactivity of 1,4- naphtoquinone derivatives. To this end, the synthesis of the required phenylaminonaphthoquinone series was achieved by amination of 1,4-naphthoquinone or 2,3-dichloro-1,4-naphthoquinone 1 with a variety of aryl- and arylalkylamines 2, using $CeCl_3$.7H2O as the Lewis acid catalyst (Scheme-2).



Scheme 2: Reagents and conditions: (i) EtOH/MeOH, Base, $CeCl_3.7H2O$, 60°C

General procedure for the synthesis of phenylaminonaphthoquinones

A suspension of quinone 1 (500 mg, 3.16 mmol) or 2 (500 mg, 2.20 mmol), the required amine (2 equiv.), $CeCl_3.7H_2O$ (5% mmol in respect to 1 or 2), and ethanol (15 mL) was left at room temperature with stirring until completion of the reaction as indicated by TLC. The reaction mixture was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using chloroform:methanol (2:1) to yield the corresponding aminoquinone (Table 1).

2-chloro-3-(2,4-dimethylphenylamino)naphthalene-1,4-dione (P1). Prepared from quinone 2 and 2,4 dimethylaniline (3 h, 72%):dark Red solid, mp 371.80°C; λ max (Å**):**279.40; IR(ν in cm^{-1}):3212(-NH-),3001(C-H str),1667(C=O),705(C-Cl);^{1}HNMR(400MHz,DMSO-d6):δ in ppm:8.52(s,1H,NH),8.13(d,2H,Ar-H),7.78(t,2H,Ar-H),7.21(d,1H,Ar-H),6.74(s,1H,Ar-H), 6.43(d,1H,ArH),2.83(s,3H,CH_3);13CNMR:181.53,178.07,143.26,142.72,135.81,135.40, 134.18,131.35,130.80,126.98,126.70,126.55,126.50,122.78,117.44,112.67,20.82,17.70;*m/z* 311 (M^++1).

2-(2,4-dimethylphenylamino)naphthalene-1,4-dione (P2). Prepared from quinone 1 and 2,4 dimethylaniline (6 h, 73%) red solid, mp 328.40°C; λ max (Å**):**282.10; IR (KBr, cm^{-1}) IR(ν in cm^{-1}):3286(-NH-),3011(C-Hstr),1679(C=O),1615(C=C).^{1}HNMR(400MHz,DMSO-d6):δ in ppm :8.86(s,1H,NH),8.13(d,2H,Ar-H),7.78(t,2H,Ar-H),7.21(d,1H,Ar-H),6.74(s,1H,Ar-H),6.56(d,1H,Ar-H),6.44(s,1H,Ar-H),2.22(s,3H,CH_3).

13CNMR:182.55,182.21,142.70,140.79,136.46,134.27,132.90,132.18,130.98,126.70,126.60, 126.55,125.82,125.56,119.96,110.59, 20.82,19.44. *m/z* 278 (M^++1).

2-(pyridin-2-ylamino)naphthalene-1,4-dione(P3). Prepared from quinone 1 and 2-aminopyridine (6 h, 70%):dark green solid, mp 341.0 °C; λ max (Å**):** 283.40; IR(*ν* in cm^{-1}): 3321(-NH-),3003(C-Hstr),1771(C=O),1671(C=C).^{1}HNMR(400MHz,DMSO-d6): δ in ppm 8.17(d,2H,Ar-H),8.01(d,2H,Ar-H),7.83(t,2H,Ar-H),7.59(t,1H,Ar-H),6.99(d,2H,Ar-H),7.06(s,1H,Ar-H),6.02(s,1H,Ar-H),5.48(s,1H,NH).
13CNMR:181.39,180.98,154.94,148.45,142.34,138.65,136.46,134.27,132.90,132.18,126.70, 126.60,118.19,112.61,111.04. *m/z* 250 (M^+).

2-chloro-3-(pyridin-2-ylamino)naphthalene-1,4-dione (P4).Prepared from quinone 2 and 2-aminopyridine (4hr, 68%):green solid, mp 383.55°C; λ max (Å**):** 302.10; IR (KBr, cm^{-1})IR(*ν* incm^{-1}):3326(-NH-),3002(C-Hstr),1774(C=O),1673(C=C),708(C-Cl).^{1}HNMR(400MHz,DMSO-d6): δ in ppm: 8.17(d,2H,Ar-H), 8.01(d,2H, Ar-H), 7.83 (t,2H, Ar-H), 7.59(t,1H, Ar-H), 6.99(d,2H, Ar-H), 5.48(s,1H,NH).
13CNMR: 180.75, 176.14, 154.46, 148.56, 142.46, 138.56, 135.81, 135.40, 134.18, 131.35, 126.98, 126.50, 118.83, 118.19, 111.41. *m/z* 284 (M^+),286(M^++2),

2-(benzylamino)naphthalene-1,4-dione(P5).Prepared from quinone 1 and benzylamine (2 h, 78%): brown solid, mp 291.50°C; λ max (Å**):**271.6; IR(*ν* in cm^{-1}):3334(-NH-),2915(-CH_2-)3003(C-H str),1801(C=O), 1680 (C=C); ^{1}H NMR DMSO-d6 (δ in PPM): 8.35(s,1H,NH),8.01(d,2H,Ar-H),7.83(t,2H,Ar-H),7.47(d,2H,Ar-H),7.17(t,1H,Ar-H), 5.65(s,1H,Ar-H), 4.5(s,2H,CH_2).
13CNMR: 183.99, 181.79, 149.96, 138.09, 136.46, 134.27, 132.90, 132.18, 128.29, 127.67, 126.70, 126.60, 102.42, 47.11. *m/z* 263(M^+).

2-(benzylamino)-3-chloronaphthalene-1,4-dione (P6). Prepared from quinone 2 and benzylamine (1.5 h, 72%): red solid, mp 330.40 °C; λ max (Å**):**275.3; IR(*ν* in cm^{-1}):3318(-NH-),2924(-CH_2-)3014(C-H str),1672(C=O), 1641 (C=C),721(C-Cl). ^{1}H NMR DMSO-d6 (δ in PPM): 8.35(s,1H, NH), 8.01(d,2H,Ar-H), 7.83 (t,2H, Ar-H), 7.47(d,2H, Ar-H), 7.17(t,1H, Ar-H), 4.5(s,2H,CH_2).

13CNMR: 180.42, 178.94, 147.58, 136.75, 135.40, 134.18, 133.78, 129.90, 128.29, 128.24, 127.66, 126.60, 126.50, 111.62, 48.02. *m/z* 297(M^+).

Table-1 Compound code and substitution at 1,4 Naphthoquinone derivatives

Compound code	R1	R2	R3	R4	R5	R6	R7	R8	X	Y
P1	-Cl	-Cl	-H	$-CH_3$	-H	$-CH_3$	-H	-H	-C	-C
P2	-H	-H	-H	$-CH_3$	-H	$-CH_3$	-H	-H	-C	-C
P3	-H	-H	-H	-H	-H	-H	-H	-H	-N	-C
P4	-Cl	-Cl	-H	-H	-H	-H	-H	-H	-N	-C
P5	-H	-H	-H	-H	-H	-H	-H	-H	-C	-C
P6	-Cl	-Cl	-H	-H	-H	-H	-H	-H	-C	-C

Antimalarial Evaluation

In vitro antimalarial evaluation was done by Syber green-1 based assay method. [26,27] Results of antimalarial evaluation are given in table-2

Qikprop Evaluation

The QikProp module of Schrodinger is a quick, accurate, easy-to-use absorption, distribution, metabolism and excretion (ADME) prediction program designed to produce certain descriptors related to pharmacokinetics of drugs. All compounds showed significant values for the properties analyzed (table-3) and showed drug-like characteristics based on Lipinski's rule of 5 and Jorgensen's rule of three. The selected ADME properties that are known to influence metabolism, cell permeation and bioavailability are presented in table-3.

Table-2 *In vitro* antimalarial evaluation of naphthoquinone derivatives

Compound code	%growth at 10 µM concentration	%growth at 50 µM concentration	IC50(µM) 3D7 strain
P1	3.48	0.15	3.6
P2	-1.65	-2.19	1.8
P3	36.72	-0.22	7.6
P4	3.79	-2.39	5.7
P5	2.76	2.81	7.1
P6	-0.467	-3.34	2.5
Chloroquine	-2.65	-3.89	0.04

Table-3 Properties of tested compounds calculated by qikprop

Compound code	QPlogS	QPlogBB	QPlogPo/w	Rule of Five	Rule of Three
P1	-4.037	-0.322	3.024	0	0
P2	-3.736	-0.481	2.62	0	0
P3	-2.033	-0.717	1.22	0	0
P4	-2.495	-0.519	1.674	0	0
P5	-3.222	-0.596	2.432	0	0
P6	-3.771	-0.415	2.909	0	0

QPlogPo/w=Predicted log of the octanol/water partition coefficient, range 95% of drugs (-2-6.5), QPlogS=Predicted log of aqueous solubility S (mol/L), range 95 % of drugs (-6.5-0.5), Rule of five=Number of violations of Lipinski's rule of five, jogerson Rule of three= Number of violations of Jorgensen's rule of three.

RESULTS AND DISCUSSION

Prediction of absorption, distribution, metabolism and excretion properties**:** The expected ADME properties of the designed compounds were evaluated with QikProp module of Schrodinger (Table 3). The selected properties are known to influence metabolism, cell permeation and bioavailability. Almost all the predicted properties of the tested compounds

were in the ranges as predicted by QikProp for 95% of known oral drugs and also satisfy the Lipinski's rule of five and Jorgensen's rule of three to be considered as drug like potential.

Antimalarial activity comparison

On comparison of activity of synthesized 1,4 naphthoquinone derivatives figure 2 (we found that when R_2 is disubstituted aryl amine then compound will be more potent, if R_3=H and less potent if R_3=Cl. For example P2 (1.8µM) is two times more potent than P1 (3.6µM) while When at R_2 position substituted aryl amine is replaced with substituted pyridine then compound will be more potent, if R_3= Cl and less potent if R_3=H. For example P4 (5.7µM) is more potent than P3 (7.6µM). When two compounds contain benzylamine at R_2 position then compound containing -Cl group at R_3 position (P6, IC50=2.5µM) is about 2.8 times more potent than compound containing –H at that position (P5, IC50= 7.1µM). Thus from above it is clear that at position 2 of 1,4 naphthoquinone, if disubstituted aryl amine is present then compound containing –H group at R_3 position is more potent than compound containing –Cl group while in case of compounds containing pyridine or benzylamine at second position if –Cl is present at third position then compound will be more potent than if -H is present at that position.

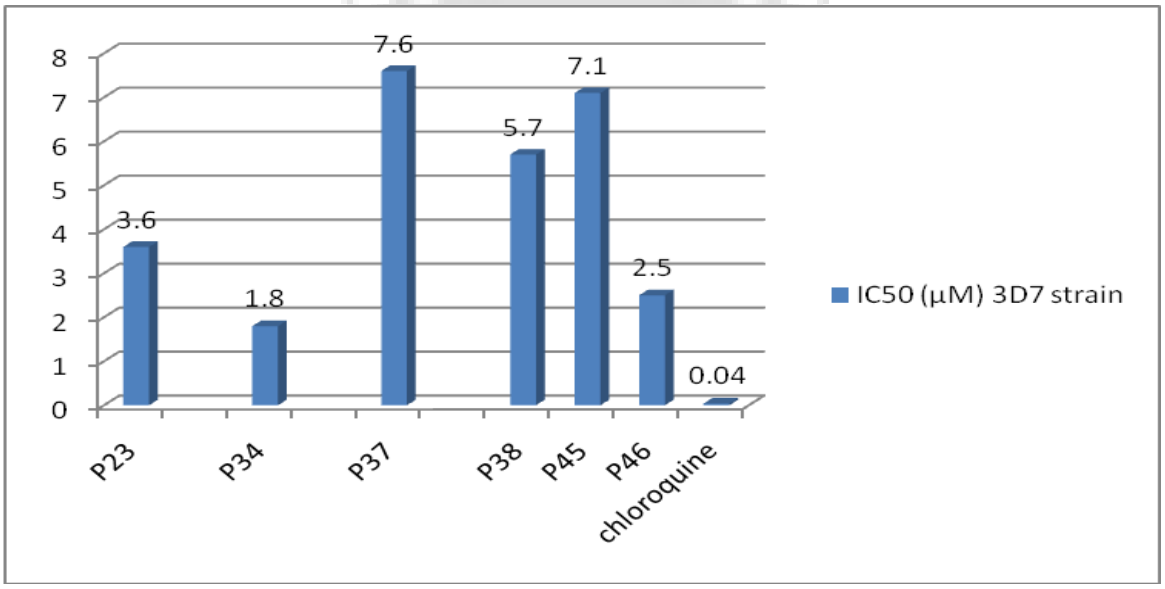


Figure-2 Activity comparison of synthesized 1,4 naphthoquinone derivatives

CONCLUSION

Malaria is a multifaceted disease thus requiring a multi-pronged approach for the treatment. Given the challenges outlined, we can only deem the number of available antimalarials to be

enough once the malaria parasite is finally eradicated. Until this time, innovative and effective medicines will continue to be needed. Currently, we have a small range of good tools with high-quality of ACTs approved by the WHO and some others in the pipeline. The issue of drug resistance in particular is exacerbated with an estimated 300 million patients requiring treatment every year in addition to issues of inappropriate and irrational treatment practices on the ground in many disease-endemic countries. But at the same time, malaria research has entered a new phase the emergence of new approaches that will not simply control the disease but target its eventual eradication. With this view, we have designed and synthesized some 1,4 naphthoquinone derivatives which have significant antimalarial activity. 2-(2,4-dimethylphenylamino)naphthalene-1,4-dione (P2) is most potent compound with IC50 of 1.8 µM. Thus from the present study, results may be helpful in further development of effective, safe and cheap drugs for malaria treatment.

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