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SYNTHESES AND EXPLORATION OF NEW BIOLOGICAL ACTIVITIES IN ETHYL 6/7-SUBSTITUTED AND 6, 7-DISUBSTITUTED QUINOLIN-4-ONE-3-CARBOXYLATES

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Abstract : Syntheses of a number of ethyl 1H, 4H-quinolin-4-one-3-carboxylates carrying substituted piperidinedione ring at position 6 (**25 & 31-35**), tetrahydrofuranone (**37**) or tetrahydropyridazinone ring (**39**) at position 7 and hydroxy and hydroxymethyl substituents at positions **6** and **7** respectively (**41**) of the quinolone ring, are reported here. Effect of these compounds on the in vitro heme polymerase activity of Plasmodia and on the in vitro fungal growth are described.

A large number of quinolones as broad spectrum antibacterials are on the market. Since quinolones are implicated to form ternary complexes with DNA gyrase resulting in the breakage of the DNA strand, this class of compounds has been evaluated for their ability to combat Mycobacterium avium infection[1]. The possibility of 6, 7-disubstituted quinolones as radical curative antimalarials has also been suggested[2]. There is, therefore, a growing consciousness that structural modifications of quinolones may help in discovering new biological activities. In the present study the exploration is aimed at discovering antiheme polymerase activity in drug resistant Plasmodia. Yet another area of present exploration is aimed at discovering antifungal activity if any. An extensive structure to activity relationship studies on quinolones have been carried out earlier[1,3] and the need for fluorinated quinolones for the antibacterial activity has been established. It is therefore, essential to ascertain whether non-fluoroquinolones themselves represent a pharmacophore which are associated with new biological properties. This led to the synthesis of quinolones with substituents representing oxygen and nitrogen heterocycles at positions 6- or 7- and hydroxy and hydroxymethyl group at positions 6- and 7- respectively. The details of this study are presented here.

Chemistry

The synthetic strategy for building the molecular framework of

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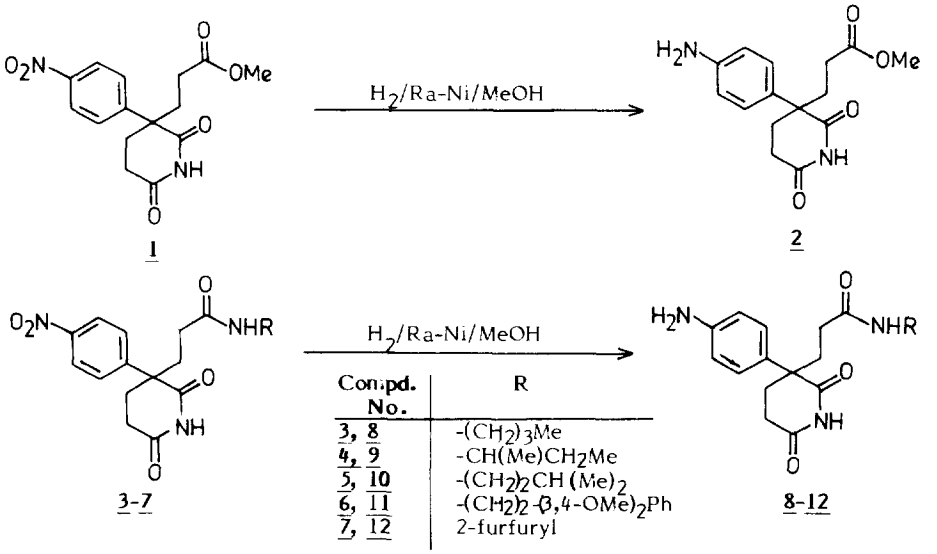
the quinolone ring relates to two reactions[4]. The first one is concerned with the reaction of diethyl ethoxymethylenemalonate with the candidate amino compound (**2**, **8-12**, **18**, **20**, **23**) to yield the corresponding enamine diesters (**24**, **26-30**, **36**, **38**, **40**). These are then thermally cyclised to the desired quinolones[5] (Scheme 4). The synthesis of the different aromatic amines required for the present study are summarized in Schemes 1-3.

The first set of required amino compounds (**2** & **8-12**) are synthesized by Hydrogenations of methyl 3-[3-(4-nitrophenyl)-2, 6-dioxo-piperidin-3-yl]-propionate (**1**) and N-substituted 3-[3-(4-nitrophenyl)-2,6-dioxo-piperidin-3-yl]-propionamides (**3-7**)[6] respectively (Scheme 1).

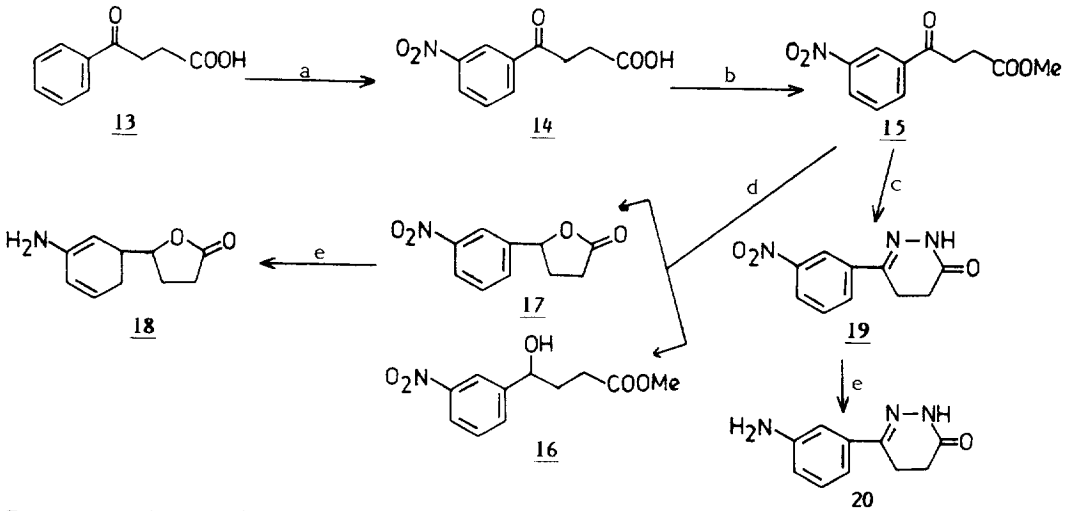
Scheme 1



These nitro derivatives (**1** & **3-7**) are prepared from 3-[(3-phenyl)-2, 6-dioxo-piperidin-3-yl]-propionic acid and the latter in turn is made by following the methods reported in the literature[7,8]. The second set of aromatic amines (**18** & **20**) have been synthesized from β-benzoylpropinonic acid (**13**)[9]. Nitration of compound **13** followed by esterification of the resulting nitro derivative **14** gives the desired methyl ester **15**. Sodium borohydride reduction[10] of this compound yields a mixture of the secondary alcohol **16** and the lactone **17** in almost 1:1 ratio. Compound **16** can also easily be thermally cyclised to compound **17**. Hydrogenation of compound 17

over Raney-nickel furnishes the required amine **18**. Ring closure of compound **15** with hydrazine hydrate yields the tetrahydropyridazinone **19** which after usual Hydrogenation over Raney-nickel furnishes the required amine **20** (Scheme 2).

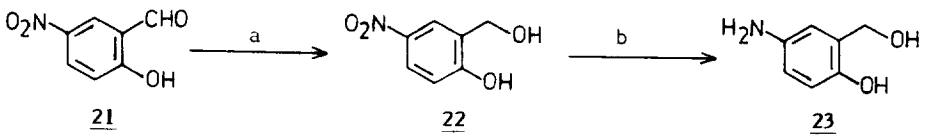
Scheme 2



Reagents : a) HNO_3 (fuming); b) $BF_3.ET_2O$,MeOH; c) $NH_2NH_2.H_2O$,MeOH; d) $NaBH_4$, MeOH; e) H_2, Ra-Ni, MeOH.

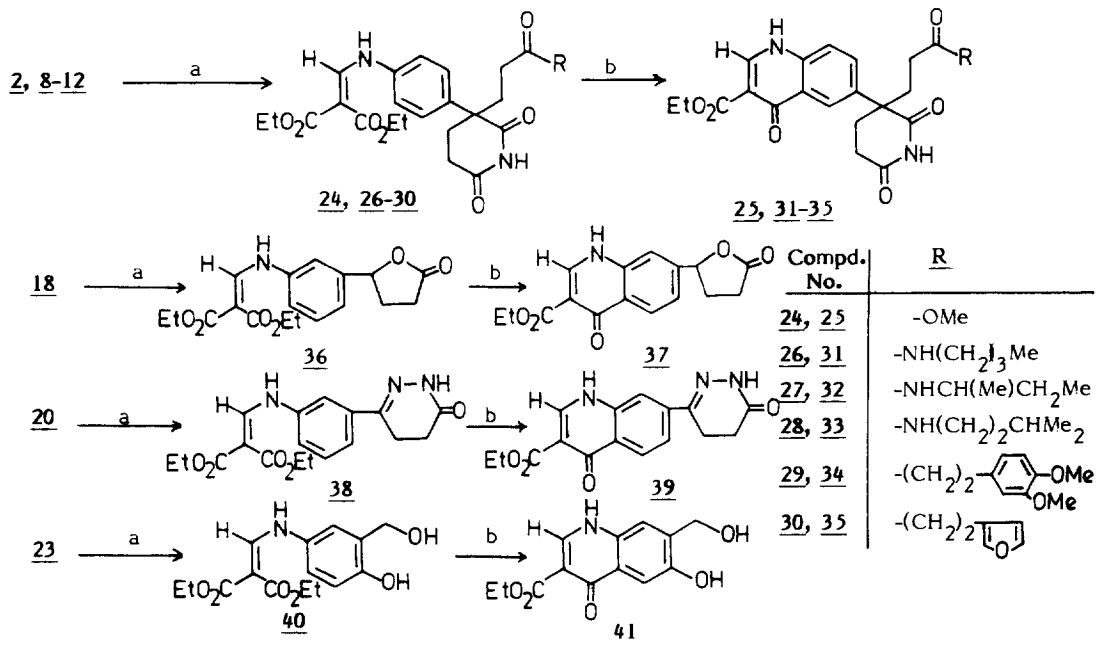
The aromatic amine **23**, required for the synthesis of 6,7-disubstituted quinolone, is obtained by Hydrogenating 5-nitrosalicylalcohol **(22)** (Scheme 3) which in turn is prepared by the sodium borohydride reduction of 5-nitrosalicylaldehyde **(21)**[11].

Scheme 3



Reagents : a) $NaBH_4$, MeOH; b) H_2, Pd-C, MeOH

Scheme 4



Biological Evaluation

Effect of the synthesized quinolones on heme polymerase activity of malaria parasites.

Method : The cell free extract of malaria parasite Plasmodium yoelii is incubated in acetate buffer (pH 5.0) containing 100 uM hemin and the formation of hemozoin is followed [12]. For the evaluation of the inhibitory effects of the synthesized compounds, the enzyme extract is preincubated with the test compound for at least 30 minutes. The results are described in Tables 1 & 2.

Evaluation of in vitro antifungal activity of the synthesized compounds (24-41)

Method : In vitro antifungal screening of the compounds is done by two fold serial diluation method[13] against five fungi namely, Candida albicans, Cryptococcus neoformans, Sporotrichum schenckii, Trichophyton mentagrophytes and Aspergillus fumigatus.

Results & Discussions

In the cell free extract of P. yoelii, all the quinolones tested exhibit less antiheme polymerase activity than chloroquine (Table 1). Of these, the two representative compounds (25 & 32), selected for the evaluation of their anti heme polymerase activity in intact erythrocytes infected with drug resistant P. yoelii,

Table : 1 : **Effect of the synthesized quinolones on heme polymerase activity of drug resistant P. yoelii (cell free extract). Observations are recorded as the mean of the duplicates**

Compound No.	Concentration (mμ)	% of Inhibition
Chloroquine	0.10	46
25	1.0	66
31	1.0	85
32	1.0	71
33	1.0	88
34	1.0	86
35	1.0	82
37	1.0	46
39	1.0	69
41	1.0	No effect

Table : 2 : **Effect of the synthesized quinolones on heme polymerase activity of P. yoelii (with intact infected erythrocytes)**

Compound No.	Concentration (mμ)	% of Inhibition
Chloroquine (control)	0.10	47
25	0.01	11
	0.10	40
	1.0	62
32	0.01	17
	0.10	42
	1.0	68

exhibit almost equipotent activity to chloroquine. This suggests that interference with the intraerythrocytic heme catabolism is possible with these quinolones. It is likely that these quinolones may exhibit additive value as an antimalarial agent if administered with chloroquine. Since these quinolones are non-fluorinated it may be concluded that this class of quinolones deserve to be explored for understanding the biological properties associated with them. In the present study this concept is further supported by the fact that all non-fluorinated quinolones subjected for antifungal screening exhibit in vitro activity against Trichophyton mentagrophytes alone at 50 μg/ml minimum inhibitory concentration. The selectivity towards this fungus is somewhat surprising and interesting because this provides an unusual structural lead for antifungal activity.

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5. Characteristic spectral and analytical data for synthesized quinolones are given below as follows : Compound no., Yield (%), mp(°C), IR (KBr, Cm^{-1}), MS : m/z, ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6, δ, ppm).

   25; 33; 135-6; 1730(C=0) ; 414(M^+); 8.58 (brs, 1H, NH), 8.20 (d, J= 12Hz, 1H, =CH), 4.27 (q, J=8Hz, 2H, OCH_2), 3.53 (s, 3H, OCH_3); (Found : C, 60.67; H, 5.27; N, 7.06. Calc. for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.31; N, 6.76%). **34** (one representative compound); 66; 110-11; 1700 (C=0); 563 (M^+); 8.41 (d, J=12Hz, 1H = CH), 4.27 (q, J=9Hz, 2H, OCH_2), 3.74 (s, 6H, 2 x OCH_3), 3.29 (m, 2H, NCH_2), 2.61 (t, J=9Hz, 2H, $ArCH_2$); (Found : C 63.76; H, 6.01; N, 7.56. Calc. for $C_{30}H_{33}N_3O_8$: C, 63.94; H, 5.86; N, 7.46%). **37**; 63; 230-1; 3420 (NH), 1760 (C=0); 301(M^+); 8.57 (brs, 1H, NH), 8.15 (d,J=9Hz, 1H, =CH), 5.55 (t, J=8Hz, 1H, ArCH), 4.30 (q, J=8Hz, 2H, OCH_2); (Found : C, 64.05; H, 4.86; N, 4.75. Calc. for $C_{16}H_{15}NO_5$: C, 63.78; H, 4.98; N, 4.65%). **39** ; 34; 175-6; 3260(NH), 1720(C=0); 313 (M^+); 858 (brs, 2H, 2 x NH), 8.20 (d, J=11Hz, 1H, =CH), 4.10(q, J=8Hz, 2H, OCH_2) : (Found C, 61.03 ; H, 4.70, N, 13.61. Calc. for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.79; N, 13.41%). **41** ; 70; 166-7; 3380(NH) ; 263 (M^+) ; 8.22 (d, J=12Hz, 1H, = CH), 4.58 (s, 2H, CH_2OH), 4.21 (q, J=8Hz, 2H, OCH_2); (Found : C, 59.01; H, 4.88 ; N, 5.21. Calc. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.94 ; N, 5.32%).
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