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Short communication

Design, synthesis and biological evaluation of 3-[4-(7-chloro-quinolin-4-yl)-piperazin-1-yl]-propionic acid hydrazones as antiprotozoal agents

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ABSTRACT

N-Acylhydrazones derived from 7-chloro-4-piperazin-1-yl-quinoline were synthesized and biologically evaluated for blood-stage of *Plasmodium falciparum* and *Entamoeba histolytica* trophozoites. *N*-Acylhydrazone **F12** was found to inhibit the *P. falciparum* growth as well as its life cycle with good selectivity, which was achieved by inhibiting hematin formation. Compound **F24** showed better IC_{50} value than the amoebicidal drug metronidazole.

1. Introduction

Entamoeba histolytica and *Plasmodium falciparum* represent major threats to the human health worldwide, with over one billion clinical cases and between four million deaths annually [1]. The protozoan parasites have now become resistant to some of the antiprotozoal medicaments, thereby pressurizing the control measures in place to treat patients infected with malaria and amoebiasis. This scenario has necessitated the search for novel drugs to contribute to the global chemotherapeutic regimens [2,3].

Quinolines are useful source for drug development of antiprotozoal agents [4–6]. The most notable is chloroquine, which is not only an antimalarial, but also a broad-spectrum antiparasitic agent, including antiamoebic activity [7]. Indeed, a large number of naturally and synthetically-derived quinolines are antiprotozoal agents, such as iodoquinol, mefloquine, and amodiaquine [8–10].

In our previous works, chalcones and hydrazones derived from chloroquinoline exhibited antiamoebic activity of higher potency than the parent quinoline [11,12]. However, no substantial antimalarial activities were observed. The *N*-acylhydrazones have reactivity as Michael-acceptors and are classically employed as warheads during drug design [13]. The attachment of *N*-acylhydrazones has been employed both in the design of ligands for further complexation with transition metals [14] and during the processes of hit-to-lead conversion [15]. *N*-Acylhydrazone is a well-known group of antiparasitic agents, which includes antimalarial and antiamoebic properties [16]. Besides, the synthetic redesign of antiparasitics in *N*-acylhydrazones is a cost-efficient and timely manner for developing chemical libraries [17].

In view of these functional properties, it was envisaged to conjugate aminoquinoline with *N*-acylhydrazone. However, recent literature survey revealed that the most likely way of optimizing antimalarial quinolines is by using a chemical linker between the quinoline ring and a second pharmacophoric group [18,19]. In the present study piperazine was used as a linker between the aminoquinoline and *N*-acylhydrazone because of the potent

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antimalarial activities observed for trioxaquines [20]. Considering this perspective, we designed, synthesized and pharmacologically evaluated a chemical library of *N*-acylhydrazones (**F1**–**F33**) derived from 7-chloro-4-piperazin-1-yl-quinoline.

2. Results and discussion

2.1. Chemistry

The synthesis of *N*-acylhydrazones (**F1**–**F33**) was accomplished in four steps as outlined in Scheme 1. The nucleophilic substitution of 4,7-dichloroquinoline (1) with piperazine afforded 7-chloro-4-piperazin-1-yl-quinoline (2). Synthesized quinoline (2) was then reacted under neat conditions with methyl acrylate, forming 3-[4-(7-chloro-quinolin-4-yl)piperazin-1-yl]propionic acid methyl ester (3). The reaction of compound (3) with hydrazine hydrate furnished hydrazide (4) which was further reacted with commercially available aldehydes to give *N*-acylhydrazones (**F1**–**F33**).

2.2. Biology

2.2.1. Antiamoebic activity

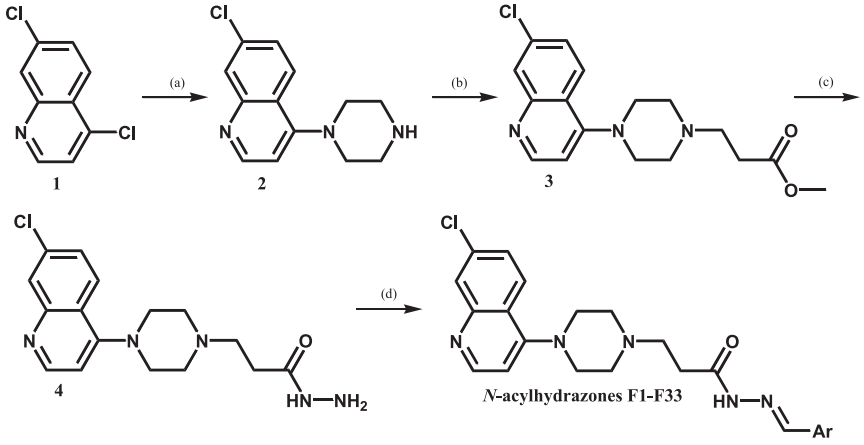
All the desired compounds were screened for antiamoebic activity against HM1:IMSS strain of *E. histolytica* and metronidazole (Mtz) was used as reference amoebicidal drug. Table 1 displays the antiamoebic activity of *N*-acylhydrazone (**F1**–**F20**). The IC_{50} of compound **F1** was 6.6 ± 0.2 μM, which was fourfold higher than the IC_{50} observed for Mtz (1.5 ± 0.1 μM). Incorporation of an alkyl substituent at *para*-position decreased the antiamoebic activity in following order: methyl (**F2**) > ethyl (**F3**) > isopropyl groups (F4). Replacing a phenyl by 2-pyridinyl (**F18**) was deleterious for activity. Electron-donating substituents attached at *para*-position, such as *N*,*N*-dimethylamino (**F5**), hydroxy (**F12**, **F13**) and alkoxy (**F14**, **F15**, **F16**, **F20**) produced weaker amoebicidal than the compound having phenyl group (**F1**). Attaching a chloro atom at *ortho* (**F9**) and *meta* (**F10**) produced active amoebicidal compounds, albeit less potent than the observed for the compound incorporating phenyl group (**F1**). However, attaching a chloro at *para*-position (**F11**) was deleterious for the amoebicidal activity. Furthermore, it was observed that a trifluoromethyl group when attached to the *ortho*-position (**F19**) led to a compound as potent as the compound bearing phenyl group (**F1**) in inhibiting the *E. histolytica* growth. Interestingly, the 4-nitro compound (**F8**) is a potent amoebicidal agent (IC_{50} = 0.95 ± 0.11 μM) without affecting mouse splenocyte viability (IC_{50} = 12.1 ± 2.4 μM). The compounds containing a nitro group at *ortho* (**F6**) and *meta* (**F7**) were less active than compound (**F8**).

The screening of *N*-acylhydrazones **F21**–**F33** (Table 2) revealed two other promising antiamoebic compounds **F24** and **F33**. Compound (**F24**) (IC_{50} = 0.13 ± 0.02 μM) was more potent against *E. histolytica* than metronidazole. Indeed, compound (**F24**) was the most potent antiamoebic agent among the studied compounds. It has low cytotoxicity to mouse splenocytes (IC_{50} = 15.8 ± 2.0 μM).

Table 1
Antiparasitic activity of *N*-acylhydrazones **F1**–**F20**.

Cpd	Ar	*P. falciparum* inhibition[a,c]	IC_{50} ± SD (μM)		
			P. falciparum[b,c]	*E. histolytica*[d]	Splenocytes[e]
4	–	74.1	41.7 ± 2.5	–	>100
F1	Ph	93.3	0.2 ± 0.05	6.6 ± 0.2	0.3 ± 0.2
F2	4-CH_3Ph	81.4	–	8.1 ± 0.15	–
F3	4-C_2H_5Ph	97.8	–	11.1 ± 0.11	–
F4	4-^{i}PrPh	97.5	1.7 ± 0.31	17.1 ± 0.15	7.9 ± 1.5
F5	4-$(CH_3)_2$NPh	98.0	1.3 ± 0.45	15.2 ± 0.2	>100
F6	2-NO_2Ph	73.1	–	11.3 ± 0.12	–
F7	3-NO_2Ph	19.9	–	12.6 ± 0.22	–
F8	4-NO_2Ph	38.4	–	0.95 ± 0.11	12.1 ± 2.4
F9	2-ClPh	97.9	0.78 ± 0.05	12.3 ± 0.13	10.8 ± 0.46
F10	3-ClPh	97.3	–	7.7 ± 0.23	>100
F11	4-ClPh	98.4	1.4 ± 0.3	87.2 ± 0.2	0.2 ± 0.04
F12	2-OHPh	98.9	0.33 ± 0.095	25.6 ± 0.15	11.5 ± 0.4
F13	4-OHPh	80.6	–	>100	–
F14	2-OC_2H_5Ph	28.1	–	>100	–
F15	4-OCH_3Ph	43.0	–	19.7 ± 0.32	–
F16	4-OC_2H_5Ph	14.9	–	12.0 ± 0.24	–
F17	4-O^{i}PrPh	98.0	0.8 ± 0.5	5.3 ± 0.22	3.6 ± 2.2
F18	2-Py	0	–	>100	–
F19	2-CF_3Ph	59.6	–	8.1 ± 0.31	–
F20	4-$(OEt)_2$CHPh	71.7	–	>100	–
Mtz	–	–	–	1.5 ± 0.1	5.4 ± 1.6
Mfq	–		0.04 ± 0.01	–	9.5 ± 0.46

[a] % Of parasite inhibition using the concentration of 1.0 μg/mL for each compound.
[b] IC_{50}s were calculated using at least five compound concentrations.
[c] Determined 24 h after incubation of W2 strain *P. falciparum* (erythrocytic stage) with the respective compounds.
[d] Determined 72 h after incubation of HM1:IMSS strain trophozoites with the compounds. IC_{50} was calculated from at least five concentrations using concentrations in triplicate.
[e] IC_{50} values for mouse splenocytes after 24 h of incubation in the presence of the compounds. SD means standard deviation. Mtz is metronidazole; Mfq is mefloquine.



Reagents and conditions: (a) Piperazine, EtOH, reflux, 12 h (b) Methyl acrylate, r.t., 12 h (c) Hydrazine hydrate, EtOH, Reflux, 12 h (d) Aldehydes, EtOH, r.t., 12 h.

Scheme 1. Synthesis of *N*-acylhydrazones (**F1**–**F33**).