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ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY LETTERS · OCTOBER 2009

Impact Factor: 2.42 · DOI: 10.1016/j.bmcl.2009.08.013 · Source: PubMed

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Bioorganic & Medicinal Chemistry Letters 19 (2009) 5962–5964

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Synthesis and biological evaluation of new heterocyclic quinolinones as anti-parasite and anti-HIV drug candidates

Albert Darque [a], Aurélien Dumètre [a], Sébastien Hutter [a], Gilles Casano [b], Maxime Robin [b], Christophe Pannecouque [c], Nadine Azas [a,*]

[a] UMR-MD3—Relations Hôte-Parasites, Pharmacologie et Thérapeutique, Faculté de Pharmacie, Université de la Méditerranée, Marseille Cedex 05, France
[b] Institut des Sciences Moléculaire de Marseille, iSm2 CNRS UMR 6263, Aix-Marseille Universités, Centre de St. Jérôme, Service 552, 13397 Marseille Cedex 20, France
[c] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 5 June 2009
Revised 31 July 2009
Accepted 1 August 2009
Available online 7 August 2009

ABSTRACT

We have synthesized quinolinones with potential antiparasitic and anti-HIV activities by an original two-step method involving microwave irradiation and have evaluated their activities against *Plasmodium falciparum*, *Leishmania donovani*, *Trichomonas vaginalis*, and HIV. None of the tested compounds had been previously described using this method of synthesis. One of the compounds had interesting antiparasitic and anti-HIV activity, which could be improved by substitution with different radicals.

Treatment of prominent parasitic diseases remains challenging due to parasite's resistance to available drugs. Malaria has been known since antiquity, but it is still responsible for the death of more than one million people every year, mostly in Africa.[1] Parasite's resistance to drugs continues to undermine efforts for malaria control. During the past decade, antileishmanial therapy has become a bewildering subject due to the complexity of the disease[2] and the continuous appearance of glucantime-resistant *Leishmania* strains responsible for therapeutic failures in immuno-competent patients. Another parasitic disease such as urogenital trichomonosis, previously considered as a benign sexually transmitted disease (STD), has received more attention following the spread of the AIDS epidemic given that STDs are favouring factors for the transmission of human immunodeficiency virus (HIV).[3] Infection by HIV is still a major worldwide concern. Despite availability of effective drugs, HIV becomes resistant to medications over time, thus allowing the virus to replicate. Moreover, co-infections with parasites and HIV are frequently occurring, making their treatment even more challenging. Increasing drug resistance or sparse therapeutic options urge the need for developing new and efficient molecules to complete the therapeutic armamentarium.

Acridine derivatives and heterocyclic compounds such as benzothiazoles have anti-parasite activity but most of them are toxic.[4] The quinolone scaffold and its different substituted arylquinolinone derivatives have anticancer (Fig. 1A and B),[5–9] antimicrobial (Fig. 1C),[10] or neuroprotective (Fig. 1D)[11] properties. We have synthesized quinolinone with antiparasitic and anti-HIV activities by an original two-step method involving microwave irradiation (MWI). Then, we have evaluated biological activities of both intermediates and corresponding quinolinones against *Plasmodium falciparum*, *Leishmania donovani*, *Trichomonas vaginalis*, and HIV.

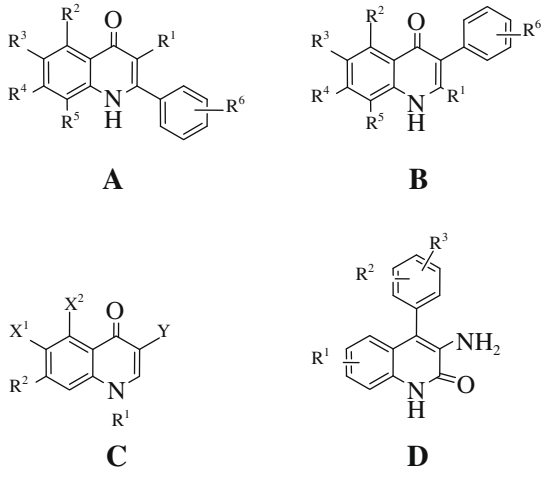

Figure 1. Chemical structures of quinolinones with anticancer (A, B), antimicrobial (C), or neuroprotective (D) properties.

Descriptions of quinolinone synthesis using microwave irradiation (MWI) in various media[12] are numerous. We prepared our tricyclic compounds by condensation of the appropriate aminoheterocycle with Meldrum's acid derivatives (Scheme 1), followed by thermal cyclization of the resulting synthetic intermediate.

The conventional heating methodology involves a 5 h reflux step for the Meldrum acid intermediate's **1a** (Scheme 1), using *p*-

* Corresponding author.
E-mail address: nadine.azas@pharmacie.univ-mrs.fr (N. Azas).

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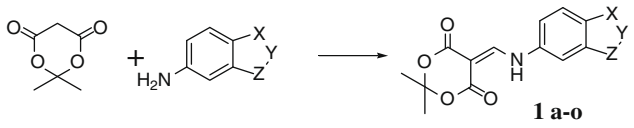


Scheme 1. Synthesis of Meldrum's acid derivatives **1**. Reagents and conditions: trimethylorthoformate 5 mL, MWI, 100 °C, 2 min.

nitroaniline as starting material.[13] We optimized the protocol on a milligram scale, and performed a successful MWI-scale-up to gram quantities with comparable yields. We have applied this method to various heterocycles (Table 1) successfully (compounds **1a**–**o**) with good yields (39–92%). None of our compounds has been previously described using this method of synthesis.

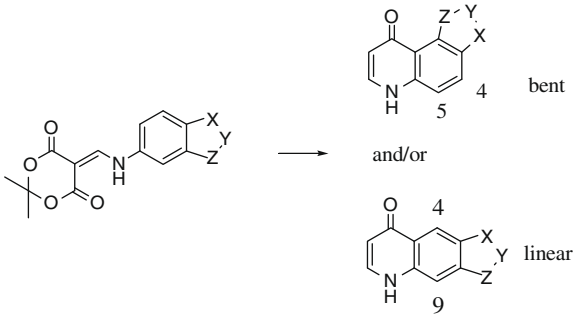
The second step was a thermal cyclization usually done in diphenyl ether at 240 °C for 20 min. Using MWI requires a solvent with a high dielectric constant to take advantage of MW heating. Diphenyl ether can rise without degradation to 200 °C in 30 min at full power MWI (300 W). Ionic liquids enhance MW heating,[14] thus we added bmimPF6 (50 mg) into diphenyl ether (**2g**). It allowed reaching 220 °C in 3 min with full power MWI (300 W) (Scheme 2). The cyclization of our compounds occurred by precipitating the product in a mixture of diethyl ether/acetonitrile and removing ionic liquid and diphenyl ether.

Products obtained were bent or linear tricyclic quinolinones, depending on the starting heterocycle. Structures and isomeric ratio of bent and linear derivatives (Table 2) were determined without ambiguity by ^{1}H and ^{13}C NMR spectroscopy. There was an AB system for protons H4 and H5 (J_{AB} = 9 Hz) for the bent structure. For the linear one, two singlets appeared, that corresponded to protons H4 and H9 of the structure. In our case, MWI was a clean, simple and faster protocol compared to the conventional heating method. We have obtained nine new quinolinone (**2a**–**j**) within 5 min. of reaction time.

Table 1
MWI Meldrum acids preparation

Name	X	Y	Z	Yield (%)	1
p-Nitroaniline	NO_2			92	**a**
m-Nitroaniline			NO_2	66	**b**
o-Nitroaniline				90	**c**
Benzodioxane	O	CH_2–CH_2	O	71	**d**
Benzothiazole	N	C–CH3	S	83	**e**
Benzotriazole	N–H	N	N	79	**f**
Indazole	NH	N	C–H	83	**g**
Benzoxazole	N	C–N–Me_2	O	39	**h**
Benzothiazole	N	C–H	S	83	**i**
2-(phenyl-2-amino)benzothiazole				81	**j**
Benzodioxol	O	CH_2	O	39	**k**
Indane	CH_2	CH_2	CH_2	41	**l**
p-Nitroaniline	NO_2			96	**m**
2-(Phenyl-3-amino)benzothiazole				67	**n**
Benzimidazolone	N–H	C=O	N–H	67	**o**

Yield (%): Average of three different experiments with 1, 10 and 20 mmol of amino compounds.



Scheme 2. Thermal cyclization with MWI in full power irradiation.

Table 2
Ratio of various quinolinones

1	Linear ratio	Bent ratio	Compounds **2**	Yield (%)
a	One possibility		**2a**	53
b	50	50	No separation	79
c	One possibility		**2c**	88
d	50 (**2d**)	50	**2d** (10%)	95
e		100	**2e**	52
f		100	**2f**	76
g		100	**2g**	90
h	100		**2h**	35
i		100	**2i**	88
j	One possibility		**2j**	76
k	50	50	No separation	82
l	50	50	No separation	35
m	One possibility		No cyclization	
n			No cyclization	
o			No cyclization	

Human therapies already use benzothiazole derivatives although they have a potential toxicity due to the presence of a benzyl moiety in their structure. Our goal was to synthesize similar products with less toxicity, by suppressing an aromatic nucleus while maintaining the antiparasitic activity. This synthesis was already effective with quinolones.[15]

Most of our products (Table 3) were not cytotoxic (IC_{50} THP1 >250 μM), and only five had low to moderate cytotoxicity. Compounds **1a** and **1d** were even less toxic than their respective cyclized derivatives, compounds **2a** and **2d**.

Although some had a structural analogy with chloroquine, 16 compounds had no antimalarial activity while the others had a moderate activity. Cyclization did not increase activity seeing that intermediate compounds had antimalarial activities similar to those of their respective cyclized derivatives. Cyclized compounds are usually more active than their corresponding intermediate structures. It was not the case with these series, moreover, intermediate compounds were less toxic than their cyclized derivatives.

Therefore, it is relevant to measure activity of both intermediate and cyclized compounds, rather than that of only the cyclized compounds.

None of the products had a significant antileishmanial activity on either promastigote or amastigote forms, from low to moderate concentrations. None had any antitrichomonal activity either. Compounds **1m** and **1k** were active on HIV-1, while compounds **1c**, **2j**, and **3a** were active on HIV-2. Globally, non-cyclized compounds seemed more active than their respective cyclized derivatives on HIV. Within our products, **1k** was the only one combining activity against both malaria and HIV, having also a low cytotoxicity and the highest specificity index (see 'Supplementary data' for detailed results on HIV strains).[16,17] Although higher than that of chloroquine, IC_{50} of compound **1k** was close to that of doxycycline, another antimalarial drug of reference, both experimentally (6.5 μM) (Table 3) and as reported (8.5 μM).[19] Moreover, compound **1k** was less toxic than doxycycline and had a better specificity index on THP1 (Table 3).[18,19] We are studying structures differing by a single moiety to explain the differences of activity between a compound and its cyclized derivative. A concomitant goal is to improve the structure of our most interesting drug candidate. All of our compounds are new chemical structures deriving from acridine and heterocyclic structures. Suppressing an aromatic nucleus from the acridine nucleus only reduced toxicity. Considering that this third aromatic nucleus is required for biological activity, we are trying to synthesize new products with a third benzyl nucleus that would not be adjacent to the quinolinone structure.

Table 3
Toxicity on human monocytes (THP1) and biological activities of compounds and reference drugs against *L. donovani*, *T. vaginalis*, and *P. falciparum*

Compound	IC_{50}[a] (μM)					SI[b]
	THP1[c]	*L. donovani* promastigote[d]	*L. donovani* amastigote[d]	*T. vaginalis*[d] (TVR79)	*P. falciparum*[c] (W2)	(THP1)
1a	>250	>100	>100	>100	40	6.2
1b	>250	>100	>100	>100	60	4.1
1c	>500	>200	>200	>200	>500	NA
1d	>500	>200	>200	>200	>500	NA
1e	>250	>250	>200	>100	60	4.1
1f	>500	>200	>200	>200	>500	NA
1g	>250	>100	>100	>100	>250	NA
1h	>250	>100	>100	>100	40	6.25
1i	>500	>200	40	>200	60	>8.3
1j	>250	>250	>100	>250	>250	NA
1k	250	>100	20	>100	10	25
1l	>500	>200	>200	>200	>500	NA
1m	>125	>250	>100	>125	>250	NA
1n	115	>200	>200	>200	30	4
1o	>500	>200	>200	>200	>500	NA
2a	130	>200	>200	>200	52	2.5
2c	>500	>200	>200	>200	>500	NA
2d	115	>200	>200	>200	50	2.3
2e	>500	>200	>200	>200	230	>2.1
2f	NS	NS	NS	NS	NS	NS
2g	NS	NS	NS	NS	NS	NS
2h	>125	>250	>100	>125	40	>3.1
2i	NS	NS	NS	NS	NS	NS
2j	>500	>200	>200	>200	>500	NA
3a	>500	>200	>200	>200	90	>5.5
3e	115	>100	>100	>100	>250	NA
Chloroquin	40	—	—	—	0.7	57
Doxycycline	20				6.5	3.1
Amphotericin B	14	0.38	0.10	—	—	
Metronidazole	>500	—	—	2.7	—	
Doxorubicine	0.05	—	—	—	—	

Values are means of [c]three experiments or [d]two experiments, NS = not soluble in DMSO, NA = not active.
[a] IC_{50}, concentration required for reducing viability of monocytes (THP1) or parasite's growth by 50%.
[b] In vitro specificity index ($IC_{50\ THP1}/IC_{50\ P.\ falciparum}$).

We have validated an innovative method for chemical synthesis based on microwave irradiation and allowing the preparation of new chemical structures with potential antiparasitic activity.

Acknowledgment

G.C. acknowledges the Conseil Regional PACA and Syncrosome for finanical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.08.013.

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