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Original article

Synthesis and evaluation of monoamidoxime derivatives: Toward new antileishmanial compounds

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ABSTRACT

A new series of monoamidoxime derivatives was synthesized using manganese(III) acetate by microwave irradiation. Several amidoximes (**27**–**31**, **33**, **38**) showed valuable *in vitro* activities toward *Leishmania donovani* promastigotes, exhibiting IC_{50} values between 5.21 and 7.89 μM. In parallel, the cytotoxicity of these compounds was evaluated on murine J774A.1 cells, revealing the corresponding selectivity index (SI). Among the 13 tested compounds, 4 monoamidoximes (**27**–**30**) exhibited an SI more than 20 times better than pentamidine. Moreover, monoamidoxime **28** (4-[5-Benzyl-3-(4-fluorophenylsulfonyl)-5-methyl-4,5-dihydrofuran-2-yl]-N′-hydroxybenzimidamide) is 40 times more selective than pentamidine, and 1.6 times more than amphotericin B, used as reference drug compounds.

1. Introduction

Leishmaniasis is one of the most widespread parasitic diseases. It is transmitted by the bite of a sand-fly contaminated by a flagellate protozoan belonging to the genus *Leishmania*. The disease is endemic in 89 countries and its visceral form, caused by *Leishmania donovani*, leads to 5,00,000 new cases and 50,000 deaths per year [1].

1,5-Bis(4-amidinophenoxy)pentane (pentamidine, Scheme 1) is a well-known antiprotozoan aromatic diamidine [2]. It is commonly used against various infections such as leishmaniasis [3,4], trypanosomiasis [3,5] and HIV-related *Pneumocystis jirovecii* opportunistic pneumonia [6]. In spite of its wide antiparasitic spectrum, the use of pentamidine remains limited by its high toxicity, in particular nephro-, cardio- and neurological toxicities [2,7]. Furthermore, at physiological pH, amidine groups are salified, decreasing membrane permeability and thus necessitating parenteral administration [8].

Arylamidines are known to bind to the minor groove of AT DNA sequences along the phosphodiester backbone [9,10]. Two amidinium end groups appear to be necessary for this interaction [11] while the central part of the drug inserts into the minor groove. Among the series of synthetic arylamidines, pafuramidine (Scheme 1) has shown interesting therapeutic activities against *L. donovani* and offers good oral bioavailability due to the replacement of amidines by methoxyamidoximes [12].

In the course of our ongoing work on the preparation of antiparasitic compounds [13], we have previously reported the synthesis of diarylamidoxime derivatives, yielding a 2,3-dihydrofuran instead of the furan scaffold of pafuramidine [14]. Several of these diamidoxime derivatives exhibited good activity against *L. donovani*. Surprisingly, monoamidoxime derivatives also had good activity, whereas with amidoxime, two scaffolds appeared to be necessary for antiparasitic potential. We present herein a complementary study in which we synthesized various substituted monoamidoximes, in order to confirm and further characterize this newly-observed activity.

2. Results and discussion

2.1. Chemistry

Several β-ketosulfones (**1**–**13**) were synthesized using a previously reported microwave-irradiated method [15].

Sodium sulfite, sodium bicarbonate and sulfonyl chlorides in water were irradiated at 500 W for 20 min in a microwave oven. An ethanolic solution of the corresponding acetophenone was then

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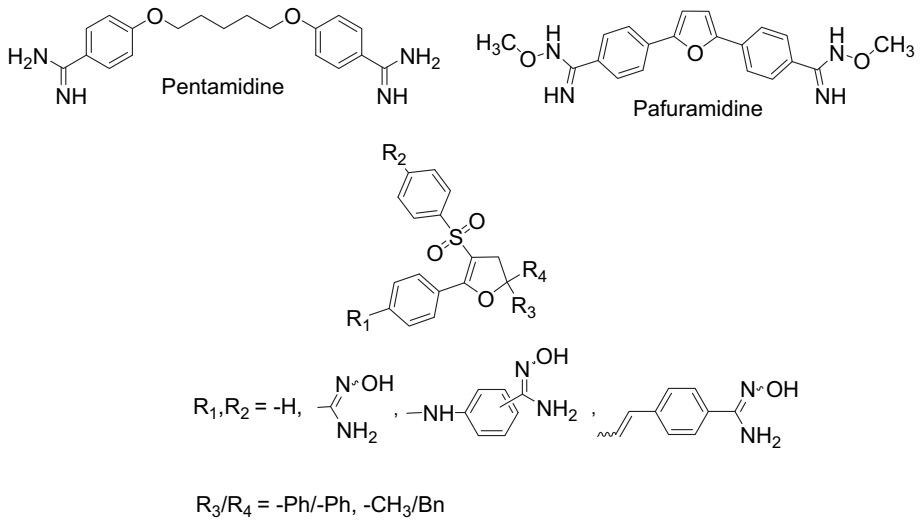


Scheme 1.

added to sodium sulfinate and the reaction mixture was irradiated for 10 min to produce sulfones in good yields (**1**–**13**) (Scheme 2).

Following a previously described procedure [16], manganese(III) acetate was added to glacial acetic acid, and the suspension was irradiated in a microwave oven at 80 °C for 15 min until solubilization. To this solution, β-ketosulfone **1**–**13** and (2-methylallyl)benzene were added and the mixture was irradiated (200 W) for 60 min.

The desired 2,3-dihydrofuran derivatives (**14**–**26**) were obtained (Scheme 3) in low to good yields. Yields highly depend on the R_1 substituent on the acetophenone moiety.

Finally, 10 equivalents of hydroxylamine hydrochloride and potassium *tert*-butoxide were added to previously synthesized nitrile derivative (**14**–**26**) in DMSO (Scheme 4) [17]. Corresponding monoamidoximes (**27**–**39**) were obtained in good yields (Table 1.).

2.2. Biology

Synthesized amidoximes **27**–**39** were evaluated *in vitro* for their activity against promastigotes of *L. donovani* strain MHOM/IN/00/DEVI and for their cytotoxicity toward mouse J774A.1 macrophages that serve as an *in vitro* host cell model for screening antileishmanial drugs [18]. The results of the evaluation are summarized in Table 2.

2.2.1. Antiparasitic activity

All monoamidoxime derivatives tested exhibited antileishmanial activity. One of them, monoamidoxime **30**, showed better antileishmanial activity than that of pentamidine (IC_{50} = 5.21 μM *versus* 6.29 μM). Moreover, 6 other monoamidoximes **27**–**29**, **31**, **33**, **38** (Scheme 5) had antileishmanial activities close to that of pentamidine (IC_{50} between 6.29 and 7.89 μM).

Substituents such as halogen, trifluoromethyl or methoxy groups improved antileishmanial activity on monoamidoximes. The best activities were obtained for substituents carried on the sulfone moiety with amidoxime carried on the other benzenic moiety. Given the IC_{50} of monoamidoximes **32** and **39**, nitro groups seem to decrease antileishmanial activities.

2.2.2. Cytotoxicity

Compared to the cytotoxicity of pentamidine (IC_{50} = 1.03 μM) and amphotericin B (IC_{50} = 3.14 μM), the cytotoxicity of monoamidoximes ranged from low to moderate (50.65–7.05 μM).

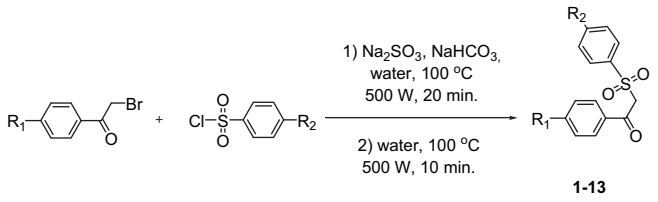
For the most active compounds, cytotoxicity values of monoamidoximes **27**–**30** were low (20.07–45.53 μM). Cytotoxicity seems to be increased by iodo and methoxy substituents when amidoxime is carried on the sulfone moiety.

By comparing antileishmanial activity and cytotoxicity we determined a selectivity index. This SI is better than that of pentamidine (0.16) for all of our molecules. 4 monoamidoximes (**27**–**30**) are over 20 times more selective than pentamidine (3.71–6.37), and the most interesting monoamidoxime, **28**, which bears a fluoro-substituent on the sulfone moiety (Scheme 6), is 40 times more selective than pentamidine and 1.6 times more than amphotericin B.

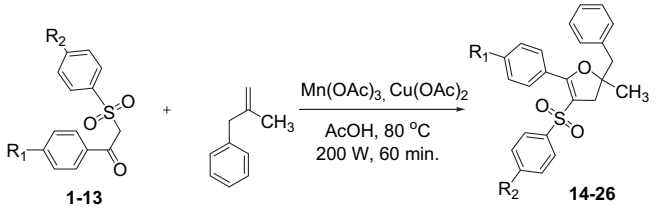
3. Conclusion

In conclusion, manganese(III)-assisted reactions allowed the synthesis of a new series of monoamidoximes. Thirteen tested products exhibited antileishmanial activity and moderate cytotoxicity with a better selectivity index compared to pentamidine, used as reference.

Moreover, molecule **30**, a bromo derivative, has the lowest IC_{50} against *L. donovani* promastigote (5.21 μM *versus* 6.29 μM for pentamidine), and molecule **28**, a fluoro derivative, has an interesting activity coupled with low cytotoxicity, making it 40 times



Scheme 2.



Scheme 3.