European Journal of Medicinal Chemistry 87 (2014) 79–88

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel nitro(triazole/imidazole)-based heteroarylamides/sulfonamides as potential antitrypanosomal agents

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ARTICLE INFO

Article history:
Received 18 August 2014
Received in revised form
9 September 2014
Accepted 12 September 2014
Available online 16 September 2014

Keywords:
Nitrotriazoles
Nitroimidazoles
Heteroarylamides
Heteroarylsulfonamides
Chagas disease
Antitrypanosomal agents

ABSTRACT

We have previously shown that 3-nitro-1*H*-1,2,4-triazole-based arylamides and arylsulfonamides demonstrate significant activity *in vitro* against *Trypanosoma cruzi*, the causative parasite of Chagas disease. More importantly, several such analogs displayed significant antichagasic activity *in vivo*, superior to that of benznidazole, the current clinical standard. We now report the synthesis and *in vitro* evaluation of a small series of novel nitro(triazole/imidazole)-based heteroarylamides/sulfonamides (including 3-nitrotriazole-, 2- and 4-nitroimidazole-based compounds) as potential antitrypanosomal agents. All nitrotriazoles displayed significant growth inhibitory properties against *T. cruzi* with the most potent generating IC_{50} values of <1 μM and up to >1400-fold selectivity toward the parasite. The 2-nitroimidazole-based derivatives were moderately active against *T. cruzi* and displayed selectivity <50, while the 4-nitroimidazoles were mostly inactive. Several 3-nitrotriazole-based analogs showed activity against *Trypanosoma brucei rhodesiense* but none of the tested compounds displayed activity toward *Leishmania donovani*. From the detailed SARs presented here, we identified the 3-nitrotriazole-based chlorinated thiophene/benzothiophene sulfonamides/amides as being the most active antichagasic compounds, displaying up to 14-fold higher potency against *T. cruzi* than the reference compound benznidazole.

1. Introduction

Neglected tropical diseases (NTD) represent a group of bacterial, viral and parasitic infections that cause substantial illness to more than 1 billion people globally [1]. Parasitic trypanosomatids cause a variety of NTDs. *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense* cause human African Trypanosomiasis (HAT), also known as African sleeping sickness, which is endemic in 36 African countries; *Trypanosoma cruzi* (*T. cruzi*) causes American Trypanosomiasis or Chagas Disease, which is endemic in 21 countries across Latin America; *Leishmania* species are the causative agents of various forms of leishmaniasis, a poverty-associated disease occurring in 98 countries. Over 20 million people are infected by these parasites and 100,000 die per year [2]. Besides causing deaths, NTDs often impair the physical and cognitive development of children and can lead to pathologies resulting in social stigma.

Chagas disease, the most important NTD, is transmitted by blood-sucking triatomine bugs and occurs in two phases: acute and chronic. During the initial 'acute' stage, patients are often asymptomatic with most infections normally going undiagnosed. The most important clinical manifestations of the chronic form are cardiac insufficiency (Chagasic cardiomyopathy and arrhythmias in about 90% of cases) and gastrointestinal syndromes (megaoesophagus and megacolon). It is estimated that about 7–8 million people will be infected with *T. cruzi* worldwide, mostly in Latin America [3]. Although the number of incidences has significantly

Abbreviations: NTD, neglected tropical diseases; *T. cruzi*, *Trypanosoma cruzi*; *T. brucei*, *Trypanosoma brucei*; HAT, human African trypanosomiasis; Nfx, nifurtimox (4-(5-nitrofurfurylindenamino)-3-methylthio-morpholine-1,1-dioxide); Bnz, benznidazole (*N*-benzyl-2-(2-nitro-1*H*-imidazol-1-yl)acetamide); NTR, type I nitroreductase; TbNTR, *T. brucei* NTR; IC_{50}, concentration for 50% growth inhibition; SI, selectivity index; SARs, structure–activity relationships; TDR, Tropical Diseases Research (http://www.who.int/tdr/research/ntd/en/).

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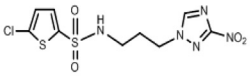
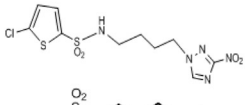
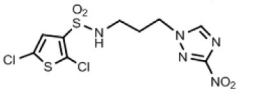
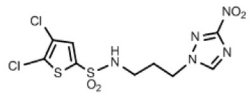
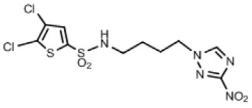
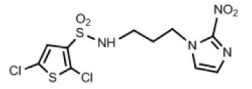
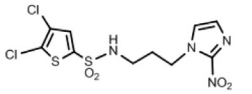
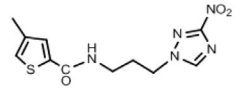
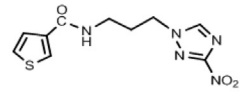
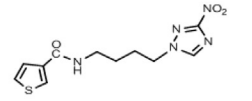
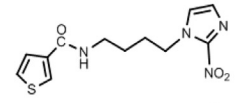
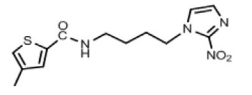
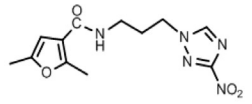
http://dx.doi.org/10.1016/j.ejmech.2014.09.045
0223-5234/

Table 1
In vitro antiparasitic activity and physical properties of 3-nitrotriazole-based heteroaryl-amides/sulfonamides.

ID No	*T.b.rhod.* [a] IC-50 μM	SI	*T. cruzi* [b] IC-50 μM	SI	*L.don. axen.* [c] IC-50 μM	SI [d]	Cytotox. L6 [e] IC-50 μM	Chemical Structure	Bnz/comp	clogP	PSA (Å^2)
Melars.	0.006 ± 0.002										
Bnz			2.13 ± 0.11								
Miltef.					0.390 ± 0.017						
1	1.99	122	0.438	556	33	7	244		3.60	1.74	122.7
2	0.52	247	0.462	278	20.0	6	128		4.42	2.26	122.7
3	1.59	75	0.552	216	17.8	7	119		3.70	2.35	122.7
4	0.505	200	0.158	639	13.2	8	101		14.31	2.35	122.7
5	0.218	447	0.373	261	10.6	9	97		6.07	2.86	122.7
6	40.3	3	6.99	15	13.1	8	108		0.32	2.71	109.8
7	32.7	2	4.75	16	7.35	10	75		0.48	2.71	109.8
8	0.980	176	2.55	68	46.1	4	173		0.80	1.7	105.6
9	0.915	>389	3.99	>89	71.2	>5	>356		0.57	1.05	105.6
10	0.810	> 418	1.75	>194	27.7	>12	>339		1.30	1.57	105.6
11	nd		nd		nd		nd			1.94	92.7
12	nd		nd		nd		nd			2.58	92.7
13	4.71	>73	8.87	>39	131.7	>3	>341		0.25	0.81	118.8