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Thiosemicarbazone fragment embedded within 1,2,4-triazole ring as inhibitors of *Entamoeba histolytica*

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ABSTRACT

A series of 1,2,4-triazole derivatives containing thiosemicarbazone linkage was synthesized and evaluated for their in vitro antiamoebic activity against HM1:IMSS strain of *Entamoeba histolytica*. All the compounds were capable of inhibiting the growth of *E. histolytica* out of which four compounds (IC_{50} = 0.28–1.38 μM) were found to have better efficacy than the standard drug Metronidazole (IC_{50} = 1.8 μM). Cytotoxicity of the active compounds was assessed by MTT assay using human breast cancer MCF-7 cell line, which revealed that all the compounds were low cytotoxic in the concentration range of 2.5–250 μM.

Invasive amoebiasis is an emerging parasitic disease in HIV-infected patients in an area endemic for amoebic infection.[1] This awful gastrointestinal infection is caused by an anaerobic parasitic protozoa *Entamoeba histolytica*,[2] which lyses host cells by direct contact using surface lectins and releases cysteinase proteinases.[3] It is more virulent than other pathogens as it can cause severe infections, both in immunocomponent and immunodeficient hosts. Infection from this parasite occurs in a number of countries of the world, resulting in 50 million cases of invasive disease and up to 100,000 fatalities per year.[4–7] Nitroimidazoles such as metronidazole, ornidazole, and tinidazole are main drugs used for the treatment of this protozoan disease. Cross resistance exists among the nitroimidazoles[8] and long-term use of these medicaments produces plenty of perilous side effects in patients.[9] Furthermore, Metronidazole, the first-line medication for amoebiasis chemotherapy, is potentially carcinogenic to humans because it is genotoxic to human cells.[10] Therefore, the treatment of this dangerous disease is demanding and attracting scientists to develop novel antiamoebic agents.

Thiosemicarbazones, a very promising class of compounds show a broad spectrum of therapeutic properties.[11–21] These compounds exhibit thione-thiol tautomerism (Fig. 1). It has been observed that the drugs containing a thiosemicarbazone fragment (e.g. Thioacetazone) is often the source of acute toxicity such as Stevens–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) caused through allergic drug reaction.[22] Over the years, we have synthesized a range of thiosemicarbazone derivatives that have exhibited potent in vitro antiamoebic activity[23] comparable or superior to metronidazole, the reference drug.

Figure 1. Thione-thiol tautomerism in thiosemicarbazones.

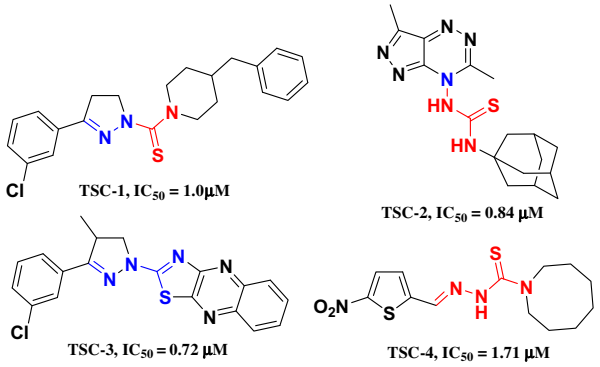

Figure 2. Antiamoebic compounds containing TSC fragment embedded in various heterocycles.

Pyrazoline compounds[24] (TSC-1) containing hydrazine (N–N) part (in blue) of TSC-Fragment embedded within the pyrazoline ring and 3,7-dimethyl-4*H*-pyrazolo[3,4-*e*][1,2,4]triazine derivative

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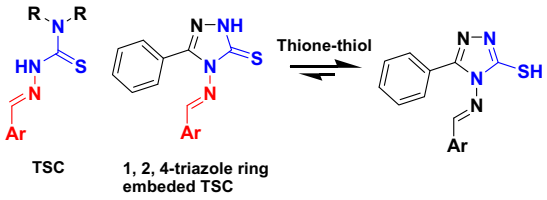
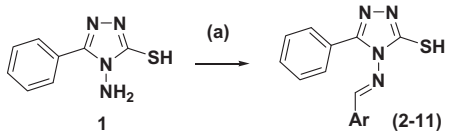


Figure 3. Thiourea (blue) part of thiosemicarbazone fragment embedded in 1,2,4-triazole ring and tautomerism.



Scheme 1. The synthetic route for obtaining the TSC–embedded 1,2,4-triazoles. Reagents: (a) Ar–CHO, EtOH Reflux.

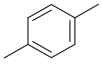
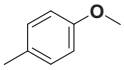
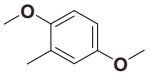
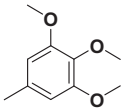
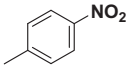
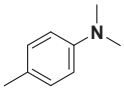
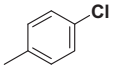
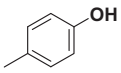
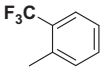
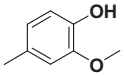
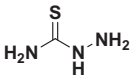
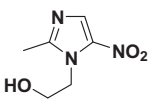
(TSC-2) having only one terminal nitrogen (in blue) of the hydrazine part embedded in the triazine ring[25] displayed appreciable activity. 2-(3-(3-chlorophenyl)-4,5-dihydro-4-methylpyrazol-1-yl)thiazolo-[5,4-*b*]quinoxaline derivatives (TSC-3) having full thiosemicarbazone fragment (in blue) present within the heterocyclic ring system were found as most effective inhibitor of *E. histolytica*.[26] Linear TSC-fragment containing compounds such as nitrothiophene derivative (in red) (TSC-4) also showed good antiamoebic activities[27] (Fig.2).

In view of the number of pharmacological significances of 1,2,4-triazole derivatives[28–33] and to confirm the importance of thiosemicarbazone fragment for the display of antiamoebic activity, we designed compounds containing this fragment by using thiourea (in blue) part embedded within the 1,2,4-triazole ring (Fig. 3).

The combination of these two biologically important structural features is expected to exhibit synergistic effects to display antiamoebic activity. To the best of our knowledge, this is the first report of 1,2,4-triazole derivatives showing promising in vitro activity against *E. histolytica*.

The route employed for synthesis of target compounds is shown in Scheme 1. 4-Amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**1**), the key intermediate for the synthesis of desired compounds, was obtained by the reported method.[34] Finally, condensation of compound **(1)** with various substituted aromatic aldehydes in the presence of catalytic amount of conc. hydrochloric acid, under reflux in ethanol for 2 h furnished the title compounds (**2–11**) in reasonable yields (62–70%).

Table 1
In vitro antiamoebic activity of 1,2,4-Triazole derivatives (**2–11**) against HM1: IMSS strain of *E. histolytica* and cytotoxicity profile of compounds **2**, **3**, **6**, **7** and metronidazole

Compound no.	Ar	Antiamoebic activity		Cytotoxicity profile	
		IC_{50} (μM)	SD[a]	IC_{50} (μM)	SD[a]
1	NH	10.81	0.022	ND	ND
2		**1.38**	**0.018**	**>250**	**0.21**
3		**0.322**	**0.016**	**>250**	**0.27**
4		8.79	0.008	N.D.	N.D.
5		2.70	0.006	N.D.	N.D.
6		**0.280**	**0.007**	**>250**	**0.23**
7		**0.309**	**0.008**	**>250**	**0.25**
8		9.55	0.006	N.D.	N.D.
9		10.16	0.014	N.D.	N.D.
10		4.68	0.013	N.D.	N.D.
11		3.05	0.007	N.D.	N.D
12		**2.29**	**0.031**	**ND**	**ND**
MNZ		1.80	0.029	>250	0.22

Bold values indicates the activity of the compounds is better than the standard drug metronidazole.
[a] Standard Deviation, N.D. Not determined.