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Synthesis, Molecular Properties Prediction and Biological Evaluation of Benzothiazole Trithiocarbamate Derivatives

Akula Naga Venkata Sunitha[1], Seeta Sharada[1], Gambiraopet Alekya[1], Oleti Navneetha[1], Sandala Anuradha Bai[1], Tangeda Saritha Jyostna[1]*

1. Medicinal Chemistry Division, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Hyderabad-500017, India.

ABSTRACT

In the present investigation, a series of novel benzothiazole trithiocarbamates have been synthesized. It deals with the design and calculation of Molecular Properties, Drug likeness, Lipophilicity and solubility parameters using Molinspiration, Molsoft softwares. Toxicity parameters were calculated using Osiris software. All the compounds are non-toxic, fulfill the solubility requirements and passing oral bioavailiability criteria. The compounds were synthesized and characterized by IR, ^{1}HNMR, Mass spectral analysis followed by antimicrobial screening. Most of the synthesised compounds (4a-4g) were found to be on conformity with Lipinski's "Rule of Five" and other parameters, for their onward screening for antimicrobial activity as oral active drugs.

Keywords: Benzothiazole, Trithiocarbamates, Molinspiration, Molsoft, Osiris, Antimicrobial activities.

*Corresponding Author Email: saritha_tangeda@yahoo.co.in

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INTRODUCTION

Benzothiazole derivatives are one of the most extensively studied classes of heterocyclic compounds[1]. Benzothiazole is a privileged bicyclic ring system and it constitutes an important scaffold of drugs, possessing several pharmacological functions, rendering this molecule and its derivatives powerful chemotherapeutic agents[2], neurotransmission blocker[3], calmodulin (CaM) antagonists[4], neuroprotective agent[5] and exhibiting other interesting biological activities[6-10]. Beside this trithiocarbonates[11] have industrial, synthetic and medicinal properties. They have been used extensively as pharmaceuticals, organic chemicals and as intermediates in organic synthesis for the protection of thiol functional group. Besides that organic trithiocarbamates have numerous synthetic applications. Moreover Dithiocarbamateshave various biological activities which are capable of forming mono and bidentate co-ordination complexes to transition metal centres. Transistion metal complexes of dithiocarbamates present a wide range of biological activities. Drugs which possessing dithiocarbamates are oxaramate, sulfaramate and natural products like brassinin and isobrassinin found to have chemotherapeutic activity. There is structural similarity between dithiocarbamates and trithiocarbamates.In the course of our search for new antimicrobial agents, we recently published the trithiocarbamate possessing benzimidazole moiety as possible antimicrobial activity. Based on the encouraging results obtained in regard to the antimicrobial activity, we propose to extend the studies by replacing isosterically benzimidazole with benzothiazole and to find its biological activity.

MATERIALS AND METHODS

All reagents were purchased from commercial suppliers like Sigma Aldrich, Merck India Ltd., Sd chemicals. All reagents were of AR grade and were used without purification. Melting points of the synthesized compounds were determined using MELTER FD-51 apparatus and were found uncorrected. The IR spectra of the synthesized compounds were recorded on Perkin Elmer Model 2833 and Nicolet-740 FT-IR instruments and frequencies were recorded in wave numbers were expressed as δ values in ppm, downfield from internal standard TMS. The mass spectrum was recorded on VG Micromass 7070H (ESI and EI) and were given in mass units (m/z). Purity of the compounds were checked by TLC on silica gel 60-254 (Merck) in an appropriate solvent.

Synthetic Procedures

Procedure for the synthesis of 1, 3-benzothiazole-2-thiol

A mixture of 2-Aminothiophenol (0.01 mol) was dissolved in Alc.KOH (50 ml) and to the mixture carbon disulphide (0.015 mol) was added and refluxed for 3 hrs at 45-50 °C , then cooled and

poured into ice cold water and neutralized with 10N HCl. The resulting solid was filtered, dried and purified by the recrystallization from methanol to yield 2- Mercaptobenzothiazole[12] (1, 3-benzothiazole-2-thiol).

Synthesis of Benzothiazole Trithiocarbamates

1, 3-benzothiazole-2-thiol and triethylamine were stirred at room temperature for 30 minutes and then carbon disulphide and distilled water was added drop-wise. The reaction mixture stirred for 50 minutes then alkyl halides were added to this solution and allowed to stir and monitored by TLC. The mixture was extracted with ethyl acetate and dried over sodium sulfate and later was subjected to purification by passing through silica gel using mixture of n-hexane and ethyl acetate as eluent.

Molecular Property Prediction

A molecular property[13] is a complex balance of various structutal features which determine whether a particular molecule is similar to the known drugs. It generally means "molecules which contain functional groups and/or have physical properties consistent with most of the known drugs". These properties mainly, hydrophobicity, molecular size, flexibility and presence of various pharmacophoric features, influence the behaviour of molecules in a living organisum, including bioavailability[14-17]. The bioavailability related properties such as solubility, lipophilicity are important before actual synthesis to reduce the chemical expenses and valuable time. Computational chemists have a wide array of tools and approaches available for the assessment of molecular diversity[18-22]. Diversity analysis has been shown to be an important ingredient in designing drugs. So, computational sensitivity analysis and structural analysis have been used to study the drug likeness of the candidate molecule[23-27]. The molecular properties were predicted and presented.

Biological Activity

Antibacterial Activity: The synthesized compounds were screened for their antibacterial activity against *E.Coli*, a gram negative bacteria and *B.Subtilis*, a gram positive bacteria by agar cup plate method[28]. The test compounds were dissolved in methanol to prepare stock solutions. The concentrations of test compounds were 50 and 100 µg/ml in comparision to the standard drug *streptomycin.* Nutrient media was prepared and sterilized by autoclaving at 121ºC for 15 min to which loop full bacteria from 24 hours culture was added, and gently shaken for uniform distribution of organism. The media was poured in petri plates, allowed to solidify, bore wells of 10mm diameter at equal distance were made and a drop of test and standard compound was placed in the plates, evenly distributed with bacteria and incubated at 37ºC for 24-48 hours, for the

inhibition of bacteria. Zone of inhibition of compounds were compared with zone of inhibition of standard drug *Streptomycin.*

Antifungal Activity: The antifungal activity of the synthesized compounds was tested against the fungus *Pencillium Chrysogenum*, by agar cup plate method[29] at a concentrations of 50, and 100µg/ml. Nutrient agar media was prepared and sterilized and incubated with fungi for 2 days. A drop of test and standard compounds was placed in the bore wells made in the plates, and allowed to incubate for 48 hours, for the inhibition of fungi, the zone of inhibition of test compounds was compared with the standard drug *Griseofulvin*.

RESULTS AND DISCUSSIONS

Spectral Data of the Synthesized Compounds

1, 3-benzothiazol-2-yl methyl carbonotrithioate

IR (KBr) v cm^{-1} spectrum aliphatic (C-H) 2838, aromatic (C=C) 1426, amine (C-N) 1237. H^1NMR [$CDCl_3$, 300 MHz] δ 2.8 ppm (s, 3H, CH_3), δ 7.26-7.31 ppm (t, 1H, Ar-H), δ 7.39-7.44 ppm (t, 1H, Ar-H), δ 7.75-7.77 ppm (d, 2H, Ar-H), δ 7.86-7.88 ppm (d, 2H, Ar-H). ESI-MS m/z [M+23] 280.

1, 3-benzothiazol-2-yl ethyl carbonotrithioate

IR (KBr) v cm^{-1} aliphatic (C-H) 2927, aromatic (C=C) 1423, amine (C-N) 1308. H^1NMR [$CDCl_3$, 300 MHz] δ 1.47-1.50 ppm (t, 3H, CH_3, δ 3.32-3.38 ppm (q, 2H, CH_2),δ 7.25-7.30 ppm (t, 1H, Ar-H, a triplet at δ 7.38-7.42 ppm (t, 1H, Ar-H), δ 7.73-7.75 ppm (d, 1H, Ar-H), a doublet **δ** 7.86-7.88 ppm (d,1H, Ar-H). ESI-MS m/z [M+23] 294.

1, 3-benzothiazol-2-yl propan-2-yl carbonotrithioate

IR (KBr) v cm^{-1} aliphatic (C-H) 2962, aromatic (C=C) 1424 amine (C-N) 1237. H^1NMR [$CDCl_3$, 300 MHz] δ 1.49-1.51ppm (d, 6H, $2CH_3$), δ 4.04-4.11ppm (m, 2H, CH_2), a triplet at δ 7.25-7.31 ppm (t, 1H, Ar-H), a triplet at δ 7.38-7.48 ppm (t,1H, Ar-H), δ 7.74-7.76 ppm (d, 1H, Ar-H), a doublet δ 7.87-7.89 ppm (d, 1H, Ar-H). ESI-MS m/z [M+23] 308.

1,3-benzothiazol-2-yl butyl carbonotrithioate

IR (KBr) v cm^{-1} aliphatic (C-H) 2956, aromatic (C=C) 1424 amine (C-N) 1237. H^1NMR [$CDCl_3$, 300 MHz] δ 1.04-1.08 ppm (t, 3H, CH_3), δ 1.78-1.88 ppm (m, 2H, CH_2), δ 3.28-3.31 ppm (t, 2H, CH_2), a triplet at δ 7.22-7.27 ppm (t,. 1H, Ar-H, a triplet at δ 7.35-7.40 ppm (t, 1H, Ar-H), **δ** 7.69-7.72 ppm (d, 1H, Ar-H), a doublet **δ** 7.84-7.87 ppm (d, 1H, Ar-H). ESI-MS m/z [M+1] 300.

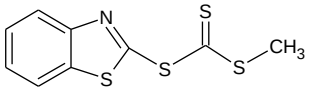
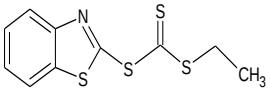
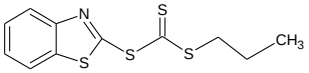
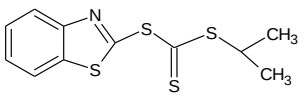
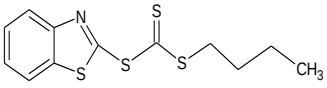
1,3-benzothiazol-2-yl benzyl carbonotrithioate

IR (KBr) v cm^{-1} aromatic (C-H) 3056, aliphatic (C-H) 2926, aromatic (C=C) 1455, amine (C-N)

1309. H^1NMR [$CDCl_3$, 300 MHz] multiplet at δ 4.04-4.11 ppm (m, 2H, SCH_2), a multiplet at δ 7.25-7.43 ppm (m, 4H, Ar-H), δ 7.38-7.43 ppm (t, 2H, Ar-H), δ 7.74-7.89 ppm (d, 5H, Ar-H). ESI-MS m/z [M+1] 334.

Physical data of the synthesized compounds were presented in Table 1. All the synthesized compounds (4a-4g) were evaluated for anti-bacterial and anti fungal activities and results were present in Table 2. The zone of inhibition (in mm) value was taken as a parameter for activity. The zone of inhibition of test compounds were compared to that of the standard drugs i.e., *Streptomycin* for anti bacterial and *Griseofulvin* for anti fungal activity. In the series homologation of side chain from methyl (4mm at 100µg/ml), ethyl (4mm at 50µg/ml, 7mm at 100µg/ml), propyl (8mm at 50µg/ml, 11mm at 100µg/ml), to isobutyl (15 mm at 50µg/ml, 18mm at 100µg/ml), there is increase in antibacterial activity and by the introduction of aromatic substituent-benzyl (16mm at 50µg/ml, 19mm at 100µg/ml),), there is further increase in activity observed when compared to standard *Streptomycin* (20mm at 50µg/ml, 22mm at 100µg/ml), against *E.Coli*. All the compounds exhibited mild activity against gram positive bacteria *B.Subtilis*, when compared to standard. In a series, the compounds trithiocarbamate with methyl and ethyl derivatives showed no activity against fungus *Pencillium Chrsysogenum*. With the increase in carbon atoms, from propyl to benzyl, antifungal activity is observed. The results indicating that the introduction of branched chain (isopropyl, isobutyl) and aromatic substituent (benzyl), is required for antimicrobial activity. The molecular properties were predicted and presented in Table 3. All the compounds followed oral bioavailability criteria. The pharmacokinetic parameters and molecular bioactivity scores were good, all the compounds showed good drug score. Toxicity prediction data showed that all the compounds are non toxic.

Table 1: Physical Data of the Synthesized Compounds

S.no	Molecular structure	Molecular formula	state	colour	Melting point (^{0}C)	Yield
4a		$C_9H_7NS_4$	Solid	colourless	172-174	85%
4b		$C_{10}H_9NS_4$	liquid	colourless	---	86%
4c		$C_{11}H_{11}NS_4$	liquid	colourless	---	82%
4d		$C_{11}H_{11}NS_4$	liquid	colourless	---	86%
4e		$C_{12}H_{13}NS_4$	liquid	colourless	---	84%

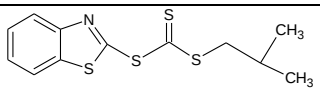
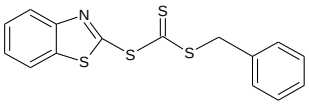
4f		$C_{12}H_{13}NS_4$	liquid	Light yellow	---	86%
4g		$C_{15}H_{11}NS_4$	Solid	White crystalline	182 -184	82%

Table 2: Antimicrobial Data of Title Compounds

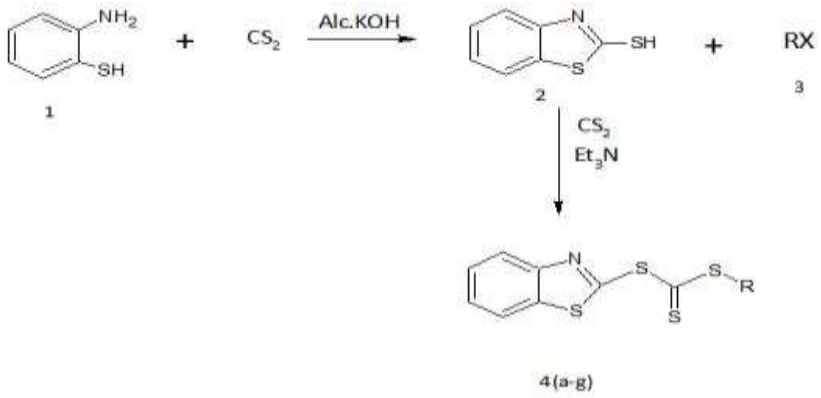
S.No	Compound	Zone of inhibition (in mm)					
		Antibacterial				Antifungal	
		E. Coli		Bacillus subtilis		Pencillium chrysogenum	
		50µg	100µg	50µg	100µg	50µg	100µg
1.	4a	-	4	-	-	-	-
2.	4b	4	7	-	-	-	4
3.	4c	8	11	-	-	4	6
4.	4d	10	12	4	6	8	10
5.	4e	9	11	3	6	6	8
6.	4f	15	18	7	10	10	13
7	4g	16	19	9	12	12	16
8.	Streptomycin	20	22	20	24	-	-
9.	Griseofulvin	-	-	-	-	19	21

Table 3: Toxicity Studies of Benzothiazole Trithiocarbamate

Compound	MUT	TUM	IRR	RE	Clog P	Solubility	Mol.wt	DS
4a	+	+	+	+	4.06	-5.39	237	0.6
4b	+	+	+	+	4.39	-5.11	271	0.54
4c	+	+	+	+	4.88	-5.33	285	0.49
4d	+	+	+	+	4.78	-5.20	285	0.56
4e	+	+	+	+	5.30	-5.87	299	0.32
4f	+	+	+	+	5.20	-5.84	299	0.46
4g	+	+	+	+	5.47	-6.19	333	0.26

MUT: mutagenic, TUM: tumorigenic, IRR: irritant, RE: reproductive effect, DS:drug score.

Scheme



-R	-R		-R
4a:Methyl	4d :Isopropyl	4e :Butyl	4g :Benzyl
4b :Ethyl	4e :Butyl		
4c :Propyl	4f :Isobutyl		

CONCLUSION

In conclusion, a series of benzothiazole trithiocarbamate derivatives have been synthesised and screened for their antimicrobial activities. The biological activity indicating that the introduction of branched chain (isopropyl, isobutyl) and aromatic substituent (benzyl) is important for antimicrobial activity. All the compounds (4a-4g) were found to be on conformity with Lipinski's "Rule of Five" and other parameters,

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