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Research Article

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Synthesis and antimicrobial activity of benzothiazine containing thiosemicarbazides and 1,3,4-thiadiazole derivatives

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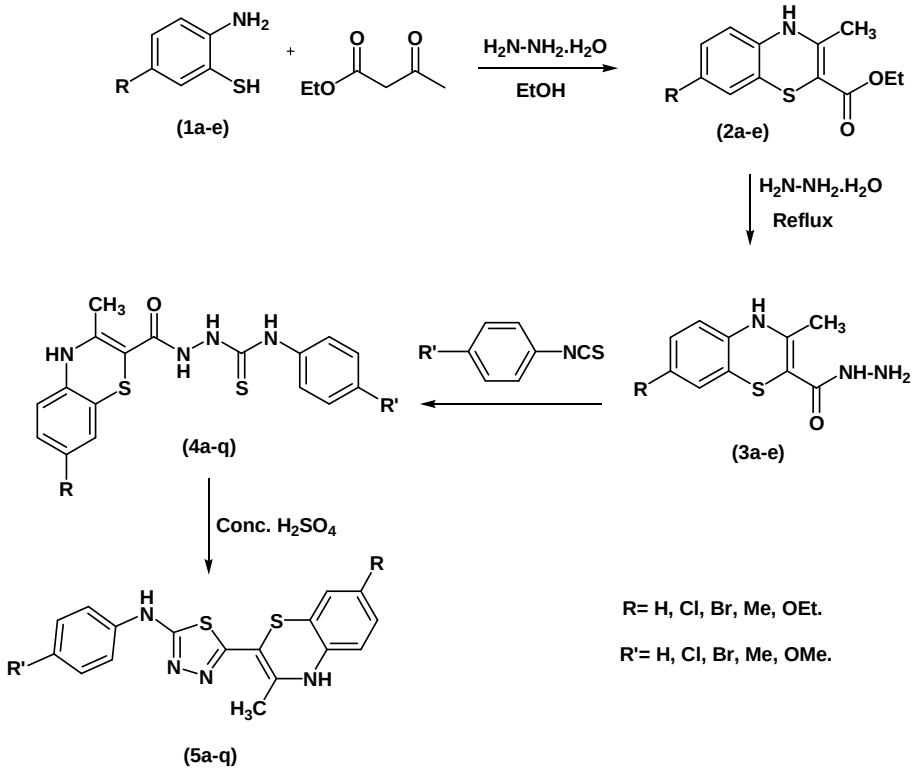
ABSTRACT

*A series of novel 3-methyl-7-substituted-4H-1,4-benzothiazine-2-carbohydrazide (**3a-e**) and corresponding thiosemicarbazides (**4a-q**); 2-[3-methyl-7-substituted-4H-1,4-benzothiazine-2-yl]-N-(aryl)hydrazine carbothiamide have been synthesized. By the intramolecular cyclization of thiosemicarbazide compounds 4a–q in concentrated H_2SO_4, thiadiazoles were obtained in high yields and the compounds were tested for antibacterial and antifungal activities against different microorganisms.*

Keywords: 1,4-Benzothiazine, 1,3,4-Thiadiazole, Thiosemicarbazide, Intramolecular cyclisation, Antimicrobial activity.

INTRODUCTION

The chemistry of nitrogen containing heterocyclic compounds has been an interesting field of study for a long time. 4*H*-1,4-Benzothiazines possess the wide range of biological and pharmacological activities due to presence of fold along the nitrogen and sulphur axis, which is considered to be responsible as one of the structural features to impart their activities. The synthesis of novel 1,4-benzothiazine derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades for medicinal and agricultural reasons. In some cases 1,4-benzothiazine are also known for their utility as dyes[1], photographic developers [2], ultraviolet light absorbers and antioxidants [3]. The multifarious applications of 1,4-benzothiazine have directed organic chemists to synthesize new 1,4-benzothiazine bearing heteryl pharmacophores. The literature survey revealed that some thiosemicarbazides had been used as plant growth regulators. Moreover, aroylthiosemicarbazide is also valuable as a synthetic intermediate for the preparation of some thiadiazole derivatives [4].Naturally occurring heterocyclic compounds containing 1,3,4-thiadiazole core are one of the most active classes of compounds possessing a wide spectrum of biological activity. It is well established that various substituted 1,3,4-thiadiazoles have become very useful compounds in medicine, agriculture, and many fields of technology. Some of these compounds exhibit interesting biological activities, like anti-inflammatory and analgesic [4,5,6], anticancer [4,7] and Antioxidant Activity [4].A large number of 1,3,4-thiadiazoles have been patented in the agricultural field as herbicides [4,8],fungicides [4,9], bactericides [4] and plant-growth-regulating activity [4,10].These observations prompted us to synthesize some new compounds wherein biologically active moieties are present. In addition, in order to improve the biological ability of compounds, much attention has been paid to the development of the functional group in the ring. In view of this, we are working on the synthesis of new 1,4, benzothiazine containing 1,3,4-thiadiazole derivatives, because it is common observation that combination of two or more biologically active heterocyclic rings in some compounds results in enhancement of biological profiles of such compounds by many folds. It is significant that the combined effect of all the entities will result in increased biological activity. In view of these and in continuation of our earlier work on the synthesis of 1,4-benzothiazine containing thiosemicarbazide and its intramolecular cyclized azole derivatives [11,12], we report some new compounds containing Thiosemicarbazides and thiadiazole rings. All of these compounds have never been reported before.



Reaction Scheme

EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial suppliers. The purity of compounds and the progress of the reaction were checked by TLC. Melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. Infrared spectra were recorded in the region of 4000 $cm^{-1}$to 400 cm^{-1}on an FT-IR-Alpha Bruker IR spectrometer in KBr pellets. The ^{1}HNMR spectra in DMSO-d_6 using TMS as internal standard.

*Step I: Preparation of 2-carboethoxy-3-methyl-7-substituted-1,4-benzothiazine (**2a-e**)*
A mixture of 2-amino-5-substituted-thiophenol (**1a-e**) (0.1 mol) and hydrazine hydrate (0.01 mol) was heated at 100 °C for 2-3 min before introducing the ethyl acetoacetate (0.1 mol) and warming the reaction mixture to 100°C for further 10 min. After cooling to room temperature, 4-5 mL of ethyl alcohol was added. The solid was separated by filtration and recrystallized from ethyl alcohol. The other compounds (**2a-e**) were prepared in same fashion and their physical constants are given in Table 1.

*Step II: Preparation of 3-methyl-7-substituted-4H-1, 4-benzothiazine-2-carbohydrazide(**3a-e**)*
To the (**2a-e**)(0.1mol) in ethanol (20mL), hydrazine hydrate (0.1mol, 99%) was added, followed by the addition of a catalytic amount of conc.H_2SO_4 (2-3drops). The mixture was refluxed for 2h. Excess solvent was removed and on cooling a solid was formed. The obtained solid was recrystallized by ethanol. The compounds (**3a-e**) were prepared in the same method and their physical constants are given in Table 1.

Table 1.Characterization data of synthesized compounds (2a-e) and (3a-e)

Compound No.	-R	Compound 2		Compound 3	
		Yield(%)	M.P. (°C)	Yield(%)	M.P. (°C)
a	H	92	145	60	92
b	Cl	88	166	65	190
c	Br	84	160	65	198
d	CH_3	90	174	70	217
e	OC_2H_5	86	196	56	240

*Step III: Preparation of 2-[3-methyl-7-substituted- 4H -1, 4-benzothiazine-2-yl]-N-(aryl) hydrazine carbothiamide (**4a-q**).*
The acid hydrazide (**3a-e**) (0.1 mol) was treated with 4-substitued phenyl isothiocyanate (0.2 mol) in the presence of ethyl alcohol. The reaction mixture was refluxed for 2 h, cooled, solid obtained was filtered, wash with aq. ethanol

and recrystallized from ethyl alcohol. The compounds (**4a-q**) were prepared in the same fashion and their physical constants are given in Table 2.

Table 2: Characterization data for the synthesized compounds (4.a-q)

Compound	-R	-R'	Yield (%)	M.P.(°C)
4a	H	H	56	138
4b	H	Cl	66	216
4c	H	Br	62	232
4d	H	CH_3	67	170
4e	H	OCH_3	54	210
4f	Cl	H	58	173
4g	Cl	Cl	64	225
4h	Cl	Br	68	177
4i	Cl	CH_3	63	221
4j	Cl	OCH_3	58	232
4k	CH_3	H	56	198
4l	CH_3	Cl	61	187
4m	CH_3	Br	64	176
4n	CH_3	CH_3	65	153
4o	CH_3	OCH_3	62	194
4p	Br	Cl	56	102
4q	OC_2H_5	Cl	54	272

Step IV: Preparation of *5-(3-methyl-7-substitued-4H- 1,4-benzothiazin-2-yl)- N-aryl-1,3,4- thiadiazol-2-amine*(**5a-q**).

A mixture of thiosemicarbazide (**4a-q**) (0.1 mol) and concentrated sulphuric acid (10 ml) was refluxed for half an hour and kept at room temperature for 24 h. After completion of reaction, reaction mixture was extracted with dichloromethane. Organic layer was dried over sodiumsulfate and distilled off to get crude product. Further purification was accomplished by column chromatography (Mobile Phase: Hexane: Ethylacetate – 4:5).

Table 3.Characterization data for the synthesized compounds (5a-q)

Compound	-R	-R'	Yield (%)	M.P.(°C)
5a	H	H	62	207
5b	H	Cl	66	90
5c	H	Br	64	175
5d	H	CH_3	60	140
5e	H	OCH_3	58	112
5f	Cl	H	62	140
5g	Cl	Cl	66	91
5h	Cl	Br	62	255
5i	Cl	CH_3	64	152
5j	Cl	OCH_3	56	167
5k	CH_3	H	62	94
5l	CH_3	Cl	68	198
5m	CH_3	Br	64	87
5n	CH_3	CH_3	60	82
5o	CH_3	OCH_3	58	103
5p	Br	Cl	60	94
5q	OC_2H_5	Cl	54	134

Antimicrobial screening

All the newly synthesized compounds (**5a-q**) were evaluated for *in vitro* antibacterial activity against gram positive and gram negative bacterial strains such as *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *pseudomonas aureginosa* at concentration 100 µg/mL by disc diffusion method by using DMSO as solvent control and nutrient agar was employed as culture media [13]. After 24 h of incubation at 37°C, the zone of inhibition were measured in mm. The activity was compared with known antibiotic ciprofloxacin. All these compounds were also screened (doses of 100 µg) for their antifungal activity against *Aspergillus niger* using Greseofulvin as a standard. The results of antibacterial to antifungal screening studies are reported in Table 4.

Table 4.Antimicrobial activity of compounds (5a-q)

Compound	*Inhibition of zone diameter in mm*				
	B. subtilis	*B.Pulmilis*	*E. coli*	*P.aeruginosa*	*A.niger*
	100 µg	100 µg	100 µg	100 µg	100 µg
5a	11	12	08	08	4
5b	09	11	13	08	6
5c	12	10	11	10	7
5d	08	11	12	09	5
5e	08	09	13	11	5
5f	14	14	12	14	6
5g	13	13	14	13	8
5h	11	12	12	16	9
5i	09	12	13	10	6
5j	13	11	14	14	7
5k	10	09	12	08	5
5l	11	14	13	11	6
5m	10	11	12	10	5
5n	09	11	13	08	5
5o	10	13	11	10	4
5p	13	13	12	12	7
5q	11	14	13	10	6
Ciprofloxacin	22	23	20	22	NT
Griseofulvin	NT	NT	NT	NT	14
DMSO	0	0	0	0	0

RESULTS AND DISCUSSION

All the 17 newly synthesized compounds were screened for antibacterial and antifungal studies. The data in the table indicates that among the synthesized compounds **5f, 5g, 5j, 5p and 5q** has found to broad spectrum of activity. However, the activities of tested compounds are much less than those of standard antibacterial and antifungal agents used.

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