Synthesis, Spectral Studies And Screening Of 1-Phenyl-3-(2)-Hydrazino-1,3 -Substituted Benzothiozolyl Thiocarbamides

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Abstract:-

Benzothiazole is one of the most important heterocyclic compound, a weak base, having varied biological activities and still of great scientific interest nowadays. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole is a privileged bicyclic ring system. Due to its potent and significant biological activities, it has great pharmaceutical importance; hence, synthesis of this compound is of considerable interest. The small and simple benzothiazole nucleus if present in compounds involved in research aimed at evaluating new products that possess interesting biological activities. Keeping in this view, when one biological active molecule is linked to another, the resultant molecule generally has increased potency.

Hence for the first time, in present work, we have interacted two pharmocophores, phenyl isothiocynate and substituted 2-hydrazino-1,3-benzothiazoles in acetone medium to yield 1-Phenyl-3-(2)-Hydrazino-1,3-Substituted Benzothiozolyl thiocarbamides. 1-Phenyl-3-(2)-Hydrazino-1,3-Substituted Benzothiozolyl thiocarbamides have been established on the basis of usual chemical transformations and IR , ^{1}H NMR and Mass spectral studies. The antibacterial activities of also reported. Some of these derivatives exhibit significant antimicrobial activity.

Keyword: *2-hydrazino-1,3 benzothiozole , substituted benzothiozolyl thiocarbamide, phenyl isothiocyanate, Biological studies.*

Introduction:

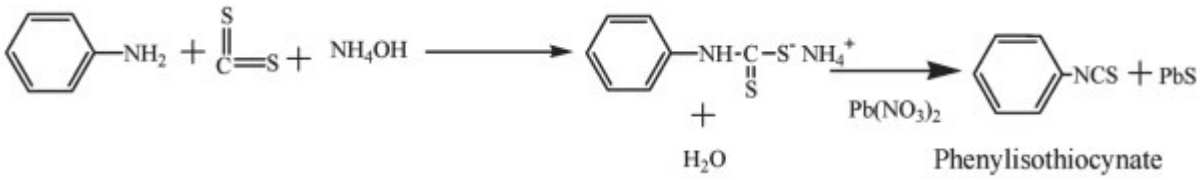
Benzothiazoles are bicyclic ring system with multiple applications.A number of 2-aminobenzothiazoles were intensively studied, as in medicinal chemistry[1,2]and reported cytotoxic on cancer cells[3]. Benzothiazole moieties are part of compounds showing numerous biological activities such as antimicrobial [4-8], anticancer [9-13], anthelmintic [14], and anti-diabetic[15] activities. They have also found application in industry as antioxidants, vulcanization accelerators. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to the unique structure and its uses as radioactive amyloid imagining agents and anticancer agents. In this review, we have discussed in brief about some commonly developed benzothiazole derivatives and various structural alterations conducted on benzothiazole ring and preferential specificities imparted in their biological responses. Hydrazino benzothiazole and isatin derivatives are an important class of organic heterocycles because of their potential activities are reported to be effectivein CNS disorders such as convulsion and depressions Indole and benzothiazoles its analogs constitute the active class of the compounds possessing wide spectrum of antimicrobial, anthelmintic, analgesic, anti-inflammatory, and tuberculosis activities

Results and discussion

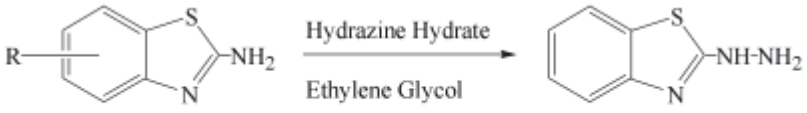
Herein, we report the synthesis of various 1-Phenyl-3-(2)-Hydrazino-1,3-Substituted Benzothiozolyl thiocarbamides **III(a-g)** by interaction of Phenyl isothiocyanate **(I)** and substituted 2-hydrazino-1,3-benzothiazole **II(a-g)** in acetone medium. All products were crystallized from ethanol before recording the physical data (Table-1). The purity of compounds was checked by TLC. The spectral analysis[15-17] IR, 1H NMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded**. III (a-g)**

Scheme for synthesis shown as follows:

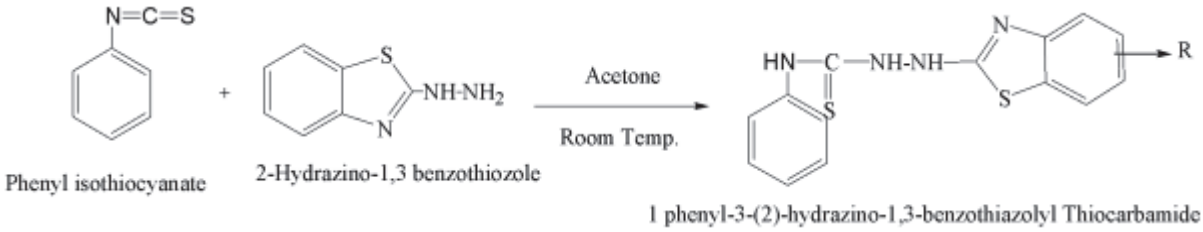
Scheme 1



Scheme 2



Scheme 3



Phenyl isothiocyanate 2-Hydrazino-1,3 benzothiozole 1 phenyl-3-(2)-hydrazino-1,3-benzothiazolyl Thiocarbamide

Where, R= (a) Phenyl, (b) *o*-tolyl, (c) *m*-tolyl , (d) *p*-tolyl, (e) o-Cl-Phenyl, (f) m-Cl-Phenyl, (g) p-Cl-Phenyl

Experimental

Material and Methods

All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450cm^{-1}) spectrophotometer. ^{1}H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Thin layer chromatography (TLC) was performed on silica Gel G and spots were visualized by iodine vapour. The compounds were screened for their antibacterial and antifungal activities by the disc diffusion assay method [18]. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.

1] Preparation of Phenyl isothiocyanate:

Equip a 500 ml three-necked flask with a powerful mechanical stirrer and separatory funnel leave the third neck open or loosely stopper. Introduce, while the flask is cooled in a freezing mixture ice and salt, 30ml of concentrated ammonia solution (d.0.88) and 15ml of pure carbon disulphide. Stir the mixture and run in 18ml of aniline from the separatory funnel during about 20 minute. Stir for the further 30 minutes and allow standing for another 30 minutes. A heavy precipitate of ammonium phenyl dithiocarbamate separate. Transfer the salt to 2-litre RBF by four extractions with 100ml portion of water. Add to the resulting solution with constant stirring a solution of 65gm of Lead Nitrate in 150ml of distilled water Lead Sulphide precipitate. Steam distils the mixture into a receiver containing 10ml of 0.5m H_2SO_4 as long as organic material possess over. Separate the oil dry it over anhydrous Calcium Chloride or Magnesium sulphide and distilled under diminished pressure. Scheme 1

2] Preparation of 2- hydrazino-1,3-benzothiozole

Concentrated HCl (1mL) was added drop wise to hydrazine hydrate (0.2 M, 1mL 80%) at 5-10^{o}C followed by ethylene glycol (20mL). To the above solution 2-aminobenzothiazole (0.01 M, 1.85g) was added in portions. It was then refluxed for 3 h, cooled and poured onto crushed ice. The separated solid was filtered, dried and recrystalized from ethanol. **II(a-g). Sceme 2:**

3] Preparation of 1-Phenyl-3-(2)-Hydrazino-1,3-Substituted Benzothiozolyl thiocarbamides

A acetone solution of Phenyl isothiocyanate (0.025M, 2.5g in 20mL) was mixed with acetone solution of 2-hydrazino-1,3-benzothiazole (0.025M, 0.37g in 10mL), and mixture after shaking for sometime was kept at room temperature for 24 h. Acetone was distilled off to obtained sticky residue. This residue was triturated several times with petroleum ether to afford a light coloured solid. **III(a-g). (Scheme-III).**

3a: IR (KBr):υ 3363 (N-H), 3201 (Ar-H), 1523 (C=N), 1159 (C=S), 939. 694 (C-S), ^{1}H NMR (δ in ppm, $CDCl_3$): δ 5.58-5.21 (4H, s, N-H), δ8.07-7.04 (9H, m, Ar-protons) Mass (m/z): 300 (M^+), 223, 165, 77; Anal. Calcd for $C_{14}H_{12}N_4S_2$: C, 56; H, 4; N, 18.66; S, 21.33; Found: C, 55.25; H, 3.8; N, 18.70; S, 21.45.

On the basis of all above facts the product with m. p. 145^{o}C was assigned the structure 1-Phenyl-3-(2)-Hydrazino-1,3-Substituted Phenyl Benzothiozolyl thiocarbamides When the reaction of Phenyl isothiocyanate was extended to several other 2- hydrazino-1,3-benzothiozole corresponding 1-Phenyl-3-(2)-Hydrazino-1,3-Substituted Benzothiozolyl thiocarbamides has been synthesized.

3b: IR (KBr):υ 3360 (N-H), 3021 (Ar-H), 1523 (C=N), 1159 (C=S), 939. 694 (C-S), ^{1}H NMR (δ in ppm, $CDCl_3$): δ 5.58-5.21 (4H, s, N-H), δ8.07-7.04 (9H, m, Ar-protons) Mass (m/z): 334 (M^+), 300, 166, 77; Anal. Calcd for $C_{14}H_{11}N_4S_2Cl$: C, 50.29; H, 3.29; N, 16.76; S, 19.16; Found: C, 50.25; H, 3.33; N, 16.80; S, 19.20.

On the basis of all above facts the product with m. p. 135°C was assigned the structure 1-Phenyl-3-(2)-Hydrazino-1, 3-Substituted o-Cl-Phenyl Benzothiozolyl thiocarbamides

3c: IR (KBr):υ 3358 (N-H), 3100 (Ar-H), 1525 (C=N), 1168 (C=S), 700 (C-S), ^{1}H NMR (δ in ppm, $CDCl_3$): δ 5.58-5.21 (4H, s, N-H), δ8.07-7.04 (9H, m, Ar-protons) Mass (m/z): 314 (M^+), 300, 165, 77; Anal. Calcd for $C_{15}H_{14}N_4S_2$: C, 57.32; H, 4.45; N, 17.83; S, 20.38; Found: C, 57.28; H, 4.52; N, 17.90; S, 20.44.

On the basis of all above facts the product with m. p. 110°C was assigned the structure 1-Phenyl-3-(2)-Hydrazino-1,3-Substituted o-tolyl Benzothiozolyl thiocarbamides

Table -1: Physical data for characterization of compounds (3a-g)

Compd	Yield %	R_f	M.P. ^{0}C	Analysis (%): Found (calcd)	
				N	S
3a	45.00	0.52	145	18.70 (18.66)	7.50(21.33)
3b	50.00	0.65	135	16.80 (16.76)	7.40(19.16)
3c	78.00	0.53	120	16.70 (16.76)	7.42(19.16)
3d	65.00	0.48	140	16.72 (16.76)	7.48(19.16)
3e	75.00	0.59	110	17.90 (17.83)	7.30(20.38)
3f	69.00	0.62	130	17.85 (17.83)	7.35(20.38)
3g	53.00	0.40	148	17.80 (17.83)	7.32(20.38)

C and H analysis was found satisfactory in all cases.

Antimicrobial Studies

All the compounds have been screen for both antimicrobial and antifungal activity using cup plate agar diffusion method18-20 by measuring the inhibition zone in mm. the compounds were taken at a concentration of 1 mg/mL using Dimethyl Sulphoxide (DMSO) as solvent. Amikacin (100 µg/mL) was used as standard for antibacterial activity and Fluconazole (100 µg/mL) as standard for antifungal activity. The compounds were screen for antibacterial activity against *Escherichia coli, Staphylococcus aureus, Proteus vulgaris, Pseudomonas aeruginosa* and *Klebsiyella species* by using Nutrient Agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized cotton swab. After inoculation the well was punched by using sterile stainless steel cork borer of 6mm diameter. In to these wells were added 0.1 mL portion of the test compounds in solvent. The drug solution was allowed to diffuse for an hour into the medium. The plate was incubated at 37°C for 24 h and 30°C for antibacterial activitiesThe zone of inhibition observed around the cups after respective incubation was measured. The results are presented in Table 2. Antibacterial studies of these compounds indicated that compounds exhibited most significant activity against All the other compounds exihibited low to moderate activity. (Table2)

Sr. no	*E. c.*	S. *a.*	*P.v*	*P.a*	*S.t*	*K.p*
1(3a)	17	20	20	19	18	21
2(3b)	10	19	15	12	20	19
3(3c)	18	14	19	17	15	18
4(3d)	14	20	18	18	19	20
5(3e)	16	--	16	--	12	--
6(3f)	10	10	20	10	10	12
7(3g)	--	12	18	14	08	17
Amikacin	18	21	23	19	20	21

Sample	**Disc content**	**Resistant**	**Intermediate**	**Sensitive**
Amikacin	100ug/ml	≤ 15 mm	16-20 mm	≥ 21 mm

Conclusion

Derivatives were synthesized and characterized for their structure elucidation. As outline in synthesis process, important novel -1,3- substituted benzothiozolyl thiocarbamide has been synthesized. All the structure of the above compounds was in good agreement with Spectral and Analytical data. Various chemical and spectral data supported the structures. Some of the compounds synthesized showed promising antimicrobial activities. The newly synthesized thiocarbamides exhibits comparable antibacterial and antifungal activities

against the organisms tested. The method adopted in this investigation is simple, efficient and inexpensive and is useful in synthesizing pharmacologically important molecules.

Acknowledgement

Authors are thankful to SAIF, CDRI Chandigarh for providing the spectral data. Authors are also thankful to Dr. Rupali Mantri (M. D. Microbiology), Assistant Professor, G. M. C., Akola for her help in doing antimicrobial activity and also Dr. V. D. Nanoty for encouragement and necessary facilities.

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