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Synthesis, Structural S tudy and Biological Evaluation of Pharmacologically Important -1, 3-Substituted Benzothiozolyl Thiocarbamide

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Abstract

Heterocyclic compounds are widely distributed in nature and are essential to life in various ways. Benzothiazole is a heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiozoles constitute an importance's class of compounds. In recent year heterocyclic compound analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. They have also found application in industry as an antioxidant, vulcanization accelerators. Benzothiozole are bicyclic ring system with multiple applications. In the 1950s various benzothiazole such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloidal imagining agent and anticancer agent. A number of 2-aminobenzothiazole were intensively studied in medicinal chemistry and reported cytotoxic on cancer cells.

Serial of 1 phenyl- 3(2)hydrazine -1,3 substituted benzothiozolyl thiocarbamide has been synthesized by the interaction of phenyl isothiocynate and 2-hydrazino-1,3-benzothiozole in acetone medium. The reaction mixture was kept at room temp for 24 hrs. Acetone is evaporated then product is recrystallised by petroleum ether (60-80%). Synthesized compound have been delineated on the basis of chemical transformation, IR, NMR and mass spectral studies. These compounds were screened for their antibacterial and antifungal activities against–Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium, Aspergillus Niger and Candida albicance. These compounds show appreciable activity towards these microorganisms.

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

Introduction:

Benzothiazole is a heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. They have also found application in industry as anti-oxidants, vulcanization accelerators. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agents[1], and anticancer agents[2]. Benzothiazoles are bicyclic ring system with multiple applications. A number of 2-aminobenzothiazoles were intensively studied, as in medicinal chemistry[3,4] and reported cytotoxic on cancer cells[5]. 2-aminobenzothiazoles, substituted benzothiazoles have found applications in several areas of chemistry. 2-aminobenzothiazoles are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development of the treatment of diabetes[6], epilepsy[7-8], thrombin inhibitors[9] inflammation[10] amyotropic lateral sclerosis[11], analgesic[12], tuberculosis[13-14], and viral infection[15]. Also 2-(4-aminophenyl) benzothiazoles comprise a novel mechanistic class of antitumor agents[16-17]. 2-

Aminobenzothiazoles have received much attention due to their unique structures and interesting biological properties that lead to their use as anticonvulsant[18], antibacterial[19-20], and muscle relaxant agents[21].Hence, in present work, different benzothiazoles react with hydrazine hydrate and this hydrazino benzothiazoles then focused to fuse with Phenyl isothiocyanate.

Experimental

Material and Methods

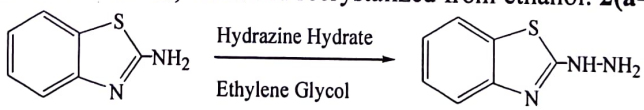
All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450cm^{-1}) spectrophotometer. ^{1}H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as internal 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 describe in this paper were first time synthesized by the multistep reaction protocol.

Preparation of Phenyl isothiocynate

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. Collect the Phenyl isothiocynate.

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°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 hr, cooled and poured onto crushed ice. The separated solid was filtered, dried and recrystalized from ethanol. **2(a-d).**

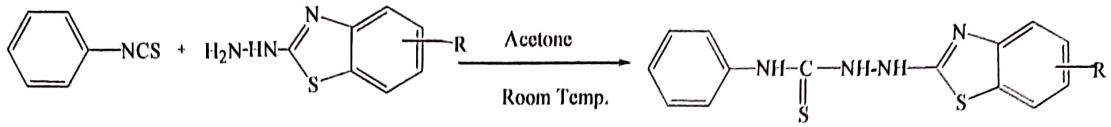


2 amion-1,3 benzothiozole — 2-Hydrazino-1,3 benzothiozole

(2)

Preparation of 1- phenyl- 3(2)-hydrazino-1,3- substituted benzothiozolyl thiocarbamide

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 hrs. Acetone was distilled off to obtained sticky residue. This residue was triturated several times with petroleum ether to afford a light coloured solid. **(1-4).**



Phenyl isothiocyanate 2-Hydrazino-1,3 benzothiozole 1- phenyl- 3(2)-hydrazino-1,3- substituted benzothiozolyl thiocarbamide

Where, R= (a) Phenyl, (b) o-nitro-aniline, (c) m- nitro-aniline, (d) p- nitro-aniline,

Results and discussion

Herein, we report the synthesis of various 1- phenyl- 3(2)-hydrazino-1,3- substituted benzothiozolyl thiocarbamide **(1-4)** by interaction of Phenyl isothiocyanate **(1)** and substituted 2-hydrazino-1,3-benzothiazole 2 **(1-4)** 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[19-21]] IR, 1H NMR and Mass spectra of the product were observed.

1: IR (KBr):υ 3363 (N-H), 3201 (Ar-H), 1523 (C=N), 1154 (C=S), 783.10 (C-S), H NMR (δ in ppm, $CDCl_3$): δ 6.92-6.41 (3H, s, N-H), δ 8.22-7.00(9H, m, aromatic protons), Mass (m/z): 300 (M^+), 223, 166,77,; Anal. Calcd for $C_{14}H_{12}N_4S_2$: C, 56.00; H, 4.00; N,18.66; S, 21.33; Found: C, 56.32; H, 4.05; N, 18.60.; S, 21.50.

On the basis of all above facts the product with m. p. 145°C was assigned the structure 1-phenyl- 3(2)-hydrazino-1,3- Phenyl substituted benzothiozolyl thiocarbamide . 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 thiocarbamide has been synthesized.

2: IR (KBr):υ 3358 (N-H), 3062 (Ar-H), 1620 (C=N), 1127 (C=S), 785.10 (C-S), H NMR (δ in ppm, $CDCl_3$): δ 6.82-6.43 (3H, s, N-H), δ 8.20-7.00 (8H, m, aromatic protons), Mass (m/z): 334 (M^+), 300, 223, 166, 77; Anal. Calcd for $C_{14}H_{11}N_5S_2O_2$: C, 51.69; H, 3.38; N, 21.53; S, 19.69; O, 9.84 Found: C, 51.65; H, 3.35; N, 21.50; S, 19.63; O, 9.80.

On the basis of all above facts the product with m. p. 130°C was assigned the structure 1- phenyl-3(2)-hydrazino-1,3-o-nitro-aniline substituted benzothiozolyl thiocarbamide.

Table -1: Physical data for characterization of compounds (1-4)

Compd	Yield %	R_f	M.P. °C	Analysis (%): Found (calcd)	
				N	S
1	69.00	0.50	145	18.60(18.66)	21.50(21.33)
2	60.00	0.46	130	21.50 (21.53)	19.63(19.69)
3	75.00	0.50	115	21.56 (21.53)	19.60(19.69)
4	62.00	0.65	140	21.60 (21.53)	19.73(19.69)

C and H analysis was found satisfactory in all cases.

Antimicrobial activity:

All the compounds have been screened for both; antimicrobial and antifungal activity by using disc diffusion assay. For this, sterial filter paper disc (6 mm) impregnated with fixed doses of compounds was placed on pre-innoculated surface. The disc bearing plates were incubated at 37°C for 24 h. After incubation, zone diameters were measured. The compounds were taken at a concentration or 1 mg/mL using dimethyl sulphoxide as a solvent. Amikacin (100 µg/mL) was used as standard for antibacterial and fluconazole (100µg/mL) as a standard for antifungal activity. The compound were screened for antibacterial activity against Eschrichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhi, in nutrient agar medium and for, antifungal

activity against Aspergillus niger and Candida albicance in potato dextrose agar medium. It has been observed that all the compounds showed good activity against both; bacteria and fungi.

Compound	E. coli	S. aureus	P. vulgaris	S. typhi	A. niger	C. albicance
1(3a)	17	16	20	18	19	20
2(3b)	10	15	15	20	20	21
3(3c)	18	14	19	15	17	19
4(3d)	14	19	18	19	20	19
Amikacin	18	21	23	20		
Fluconazole					24	24

Zone of inhibition in mm. (15 or less) resistance, (16-20 mm) moderate and more than

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.

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