

Synthesis and Antimicrobial Activity of Novel Benzothiazole-Hydrazone Derivatives

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ABSTRACT

Benzothiazole consists of thiazole ring fused with benzene ring and possess multiple applications. The survey of literature related to benzothiazoles reveals the presence of the bicyclic ring system in various amine or terrestrial natural compounds, which have useful biological properties. Benzothiazole derivatives possess a wide spectrum of biological applications such as antitumor, antimicrobial, anti-inflammatory, anticonvulsants, antifungal activity. The present work explains the synthesis of derivatives of 7-chloro-6-fluorobenzothiazole-2-yl-hydrazones.

Keywords :-- hydrazones, benzothiazole, antimicrobial activity, gram positive bacteria, gram negative bacteria.

Introduction

Hydrazones and their derivatives represent a resourceful class of compounds in organic chemistry. Benzothiazoles are an interesting group of compounds and biological activities of this class of compounds that are reported in literature are anti-cancer [1], antitumor[2], antimicrobial[4], anticonvulsant [5], anti-fungal[7], anti-tubercular , antibacterial activity [9]. The azomethine group $-NHN=CH-$ in hydrazones is highly reactive, in this two nitrogens have nucleophilic nature and carbon atom has both electrophilic and nucleophilic nature .Due to the ability to react with electrophiles and nucleophiles hydrazones are widely used in synthesis of heterocyclic compounds. The present work explains the synthesis of derivatives of 7-chloro-6-fluorobenzothiazole-2-yl-hydrazones from 3- chloro-4-fluoro-phenylamine.

MATERIALS AND METHODS

Chemicals and solvents used were of analytical grade. The newly synthesized compounds are characterized by $^1\text{H-NMR}$, mass and IR spectral data. The IR spectra (max, cm^{-1}) were recorded in solid state KBr dispersion using Perkin Elmer FT-IR spectrometer. The $^1\text{H-NMR}$ spectra were recorded on Bruker-Avance 300 MHz spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The mass spectra were recorded on API 2000 Perkin Elmer PE-Sciex mass spectrometer. The reactions were monitored by Thin-layer chromatography (TLC). Melting points were determined on plowman melting point apparatus (Model No MP96) by open capillary method. The present paper explains the synthesis of 7-chloro-6-fluorobenzothiazole-2-yl-hydrazones (**AIII**)(a-g) from 3-chloro-4-fluoro-phenylamine. The anti-bacterial studies were effectively done for newly synthesized hydrazones by standard disc diffusion method [10].

Synthesis of 7-chloro-6-fluorobenzothiazol-2-yl-amine(AI) :-

To glacial acetic acid (40 ml) add 40 g (0.416 mol) of potassium thiocyanate and 7.25g (.05 mol) of 3-chloro-4-fluoro aniline. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while 6 ml of bromine in 24ml of glacial acetic acid was added from a dropping funnel. After all the bromine has been added (105min), the solution was stirred for an additional 2 hour at 0C and at room temperature for 10 hours. It was allowed to stand overnight, during which an orange precipitate settled at the bottom, water (30 ml) was added quickly and slurry was heated at 85C on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10 ml of glacial acetic acid, heated again to 85C and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to pH 6 when a dark yellow precipitate was collected. Recrystallization from ethanol and water mixture. Compound (AI) was obtained as colorless powder (85%). m.p. 189-191C, IR (KBr) bands: 3477, 3290 (Ar-NH₂ symm, asymm), 3089 (Ar-CH), 1648 (C=N), 1216 (C-F), 686(C-Cl) and $^1\text{H NMR}(\text{CDCl}_3)$ showed 7.54 (d, 1H, Ar-H), 7.35 (d, 1H, Ar-H), 5.32 (s, 2H, NH₂).

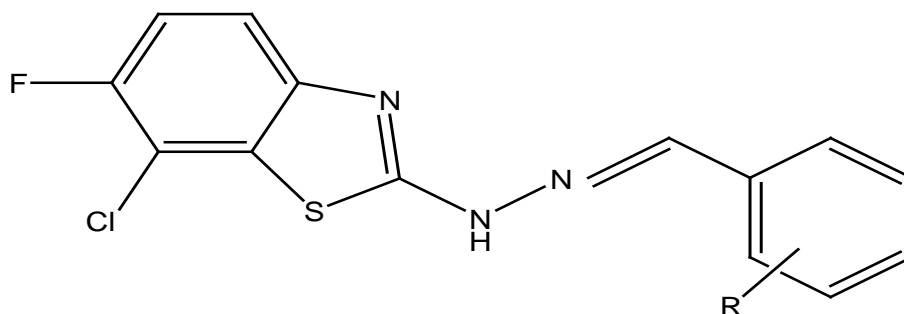
Synthesis of 7-chloro-6-fluorobenzothiazol-2-yl-hydrazine (AII) :-

Concentrated HCl (10 ml) was added dropwise with stirring to hydrazine hydrate (10 ml) at 5-10C; to it ethylene glycol (22 ml) and 7-chloro-6-fluoro-benzothiazol-

2-ylamine (0.01 mol) were added and charged in a modified microwave for 6 minutes. On cooling solid separated out, which was filtered and washed with water and recrystallized from ethanol and water mixture. By conventional method the time required for the synthesis is 3-4 hrs. Compound (AII) was obtained as colorless crystals (65%); m.p. 218-220C. IR (KBr) bands: 3317 (-NH₂), 3200 (-NH), 3067 (Ar-CH), 1202 (C-F), 687 (C-Cl) and ¹H NMR(DMSO) showed 7.40 (d, 2H, Ar-H), 5.05 (s, 2H, NH₂), 9.19 (s, H, NH).

synthesis of 6-fluoro-7-chloro-N(substituted hydrozones) benzothiazole(AIII)

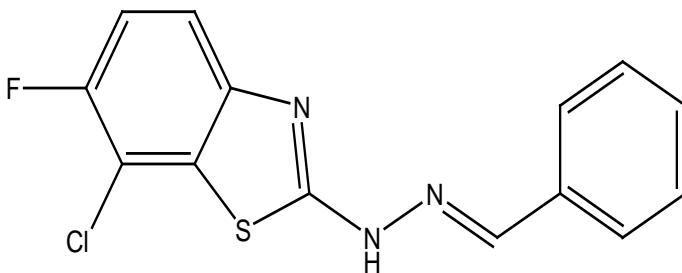
(a-g);-- Substituted benzaldehyde (2.44 gm. 0.02 Mol) added 100ml of absolute alcohol in three necked round bottom flask and shake well, add 7-chloro-6- Fluoro- benzothiazol- 2- yl hydrazine (0.460 gm. 0.002 Mol) as the reactants. The reaction mixture was stirred until (3- 4 hours) yellow or Jacinth crystals precipitated out, if no crystals were formed, the reaction mixture was concentrated to remove the alcohol until the crystal precipitated. The powder was filtered washed and re-crystallized with alcohol.



6-fluoro-7-chloro-N(substituted hydrozones)- benzothiazole

Benzaldehyde(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) hydrazone(AI II) (a)

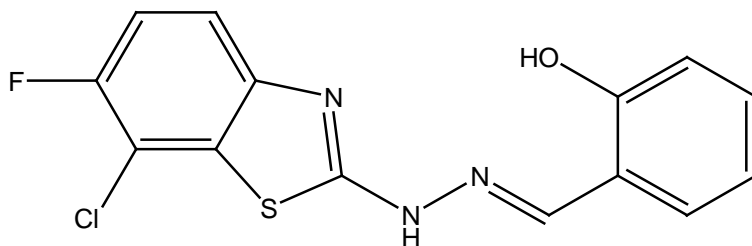
;-- Yield (60%), m.p. 258-260 C. IR (KBr) bands: 3084 (Ar-CH), 3200 (-NH), 1448(-C=N) and ¹H NMR (DMSO) showed 11.92 (s, 1H, -NH), 8.03 (s, 1H, -C-H), 7.69 (7H, ArH) .



Benzaldehyde(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) hydrazone

2-hydroxy benzaldehyde (7-chloro-6-fluoro-1, 3-benzothiazol-2-yl) hydrazone

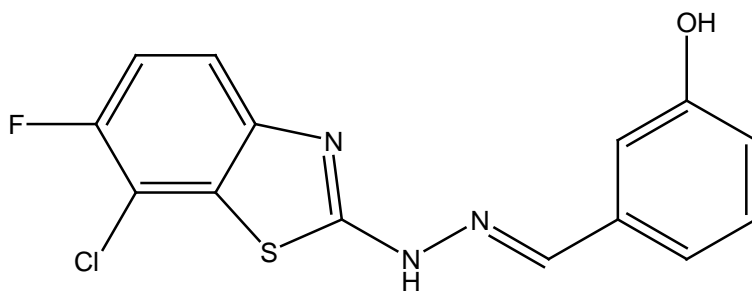
(AIII) (b) ;-- Yield (70%), m.p. 190-192 C. IR (KBr) bands: 3072 (Ar-CH), 3216 (-NH), 1455(-C=N), 3250(-OH) and 1H NMR (DMSO) showed 12.98 (1H, -OH), 10.10 (s, 1H, -NH), 8.65- 7.67 (6H, Ar-H).



2-hydroxy benzaldehyde (7-chloro-6-fluoro-1, 3-benzothiazol-2-yl) hydrazone

3-hydroxy benzaldehyde (7-chloro-6-fluoro-1, 3-benzothiazol-2-yl) hydrazone

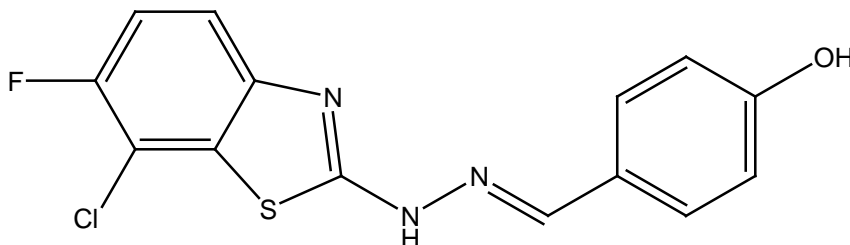
(AIII) (c) ; -- yield (60%), IR (KBr) bands: 2950 (Ar-CH), 3071 (-NH), 1450(-C=N) and 1H NMR (DMSO) showed 12.72 (s, 1H, -NH), 9.02 (s, 1H, -C-H), 7.69- 7.28 (7H, Ar-H).



3-hydroxy benzaldehyde (7-chloro-6-fluoro-1,3-benzothiazol-2-yl) hydrazone

4-hydroxy benzaldehyde (7-chloro-6-fluoro-1,3-benzothiazol-2-yl)

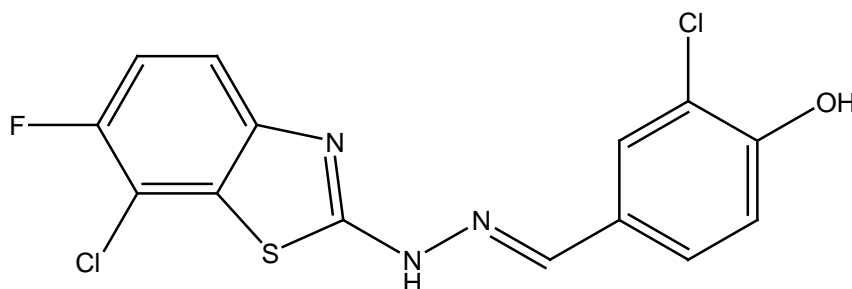
hydrazone (AIII) (d) ;-- Yield (60%), m.p. 180-182 C. IR(KBr) bands:3068 (Ar-CH), 3366 (-NH), 1434(-C=N), 2850 (-OCH₃) and ¹H NMR (DMSO) showed 9.60 (s, 1H, -NH), 8.76 (s, 1H, -C-H), 7.99- 6.75 (5H, Ar-H), 12.68 (1H, -OH), 3.87 (s, 3H, -OCH₃).



4-hydroxy benzaldehyde (7-chloro-6-fluoro-1,3-benzothiazol-2-yl) hydrazone

3chloro,4-hydroxy benzaldehyde (7-chloro-6-fluoro-1, 3-benzothiazol-2-yl)

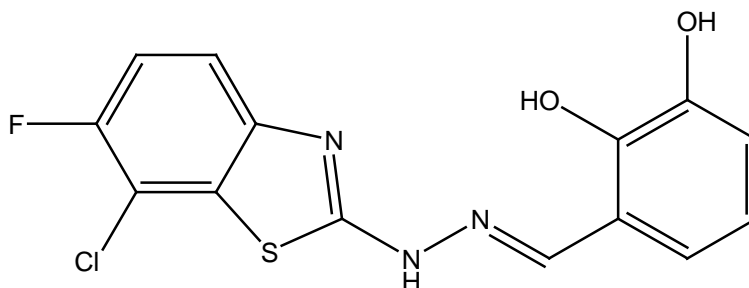
hydrazone (AIII) (e) ;--Yield (80%),. IR(KBr) bands:3082(Ar-CH), 3335 (-NH), 1458(-C=N), and ¹H (DMSO) showed 12.74 (s, 1H, -NH), 8.98 (s, 1H, -C-H).



3chloro,4-hydroxy benzaldehyde (7-chloro-6-fluoro-1, 3-benzothiazol-2-yl) hydrazone

2, 3-dihydroxy benzaldehyde (7-chloro-6-fluoro-1, 3-benzothiazol-2-yl) hydrazone (AIII) (f) :- Yield (60%), m.p. 180-182 C. IR(KBr)

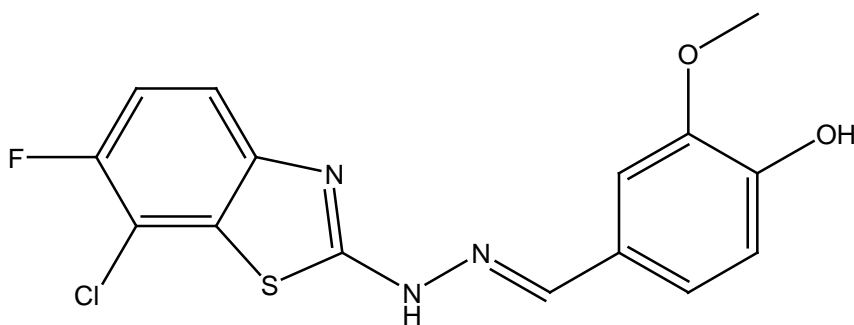
bands:3068 (Ar-CH), 3366 (-NH), 1434(-C=N), 2850 (-OCH₃) and ¹H NMR (DMSO) showed 9.60 (s, 1H, -NH), 8.76 (s, 1H, -C-H), 7.99- 6.75 (5H, Ar-H), 12.68 (1H, -OH), 3.87 (s, 3H, -OCH₃).



2, 3-dihydroxy benzaldehyde (7-chloro-6-fluoro-1, 3-benzothiazol-2-yl) hydrazone

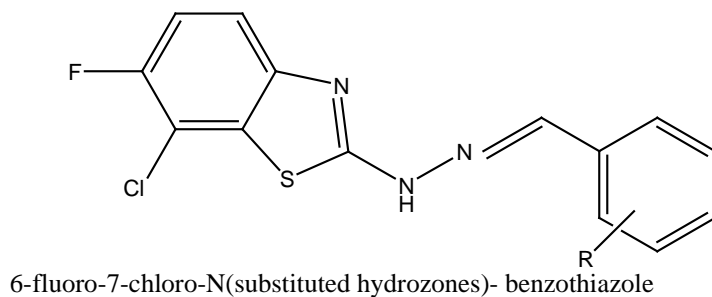
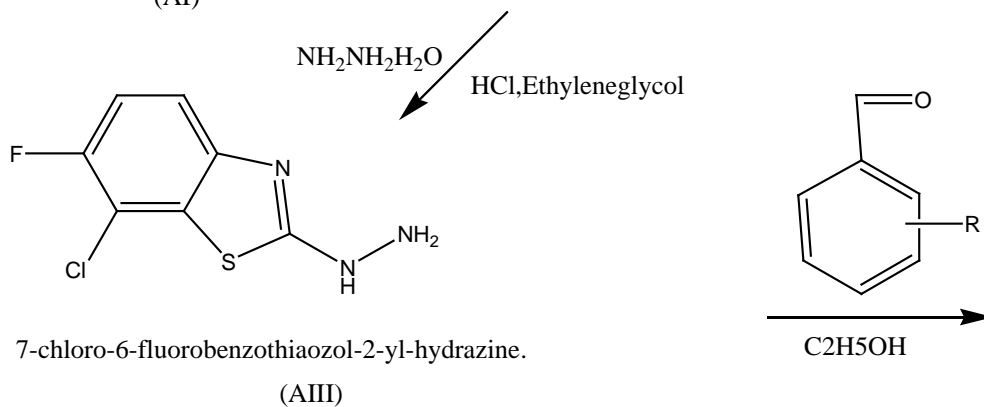
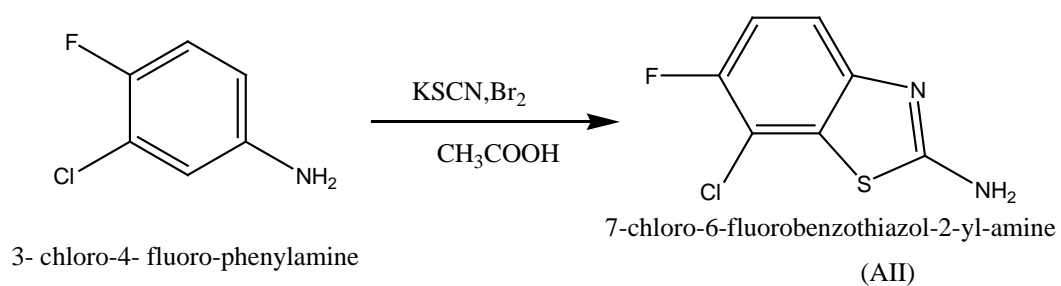
4-hydroxy-3-methoxy benzaldehyde(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)

hydrazone (AIII) (g) :- Yield (60%), m.p. 180-182 C. IR(KBr) bands:3068 (Ar-CH), 3366 (-NH), 1434(-C=N), 2850 (-OCH₃) and ¹H NMR (DMSO) showed 9.60 (s, 1H, -NH), 8.76 (s, 1H, -C-H), 7.99- 6.75 (5H, Ar-H), 12.68 (1H, -OH), 3.87 (s, 3H, -OCH₃).



4-hydroxy-3-methoxy benzaldehyde(7-chloro-6-fluoro-1,3-benzothiazol-2-yl) hydrazone

Mechanism for the Synthesis of hydrazone derivatives



Results and discussion ;--

7-chloro-6-fluorobenzothiazole-2-yl amine was synthesized from 3-chloro-4-fluoro phenylamine by reacting with potassium thiocyanate and bromine solution in glacial acetic acid. The obtained 7-chloro-6-fluoro benzothiazole-2-yl amine was made to react with hydrazine hydrate in the presence of concentrated HCl to give 7-chloro-6-fluoro-benzothiazole-2-yl hydrazine . Different derivatives were synthesized by reacting various substituted aromatic aldehydes, and forming the Schiff's base. The newly synthesized compounds are characterized by H^1 NMR, mass and IR spectral data.

Antibacterial activity of bezothiazole hydrazides ;-- The synthesized compounds were tested for their *in vitro* antibacterial activity against *Bacillus cereus*, *Staphylococcus aureus* (gram positive) and *Pseudomonas aeruginosa*, *Klebsiella pneumonia* (gram negative) and the antifungal activity was screened against *Candida albicans* and *Aspergillus fumigatus* at the concentrations of 50, 100 and 150 μ g/ml by disc diffusion method.

Ciprofloxacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activity respectively. Dimethyl sulfoxide was used as a control and the zone of inhibition of the compounds are presented in the table. Sterile disc of 5 mm in diameter made from Whatmann filter paper which is previously sterilized in U.V. lamp was dipped in solution of different concentrations of synthesized compounds, standard and blank and placed the disc on the surface of agar plates. Allowed the plates to stand for 1 h at room temperature as a period of pre-incubation to minimize the effects of variation in time between the applications of different solutions. Then the plates were incubated for 24 h at 37 \pm 1 \circ C for bacteria and 72 h at 25 \pm 1 \circ C for fungi. The diameter of zone of inhibition was measured. The results of antibacterial activity evaluation are presented in Table -1.

Table 1-Antibacterial activity

CODE	ZONE OF INHIBITION (in mm)					
	gram positive <i>Staphylococcus aureus</i> ($\mu\text{g/ml}$)			Gram negative <i>Pseudomonas aeruginosa</i> ($\mu\text{g/ml}$)		
	50	100	150	50	100	150
(AI II) (a)	12	14	19	14	16	20
(AI II) (b)	13	15	19	12	15	19
(AI II) (c)	15	14	20	16	18	22
(AI II) (d)	11	18	22	13	19	24
(AI II) (e)	15	19	20	15	18	25
(AI II) (f)	14	17	21	13	15	18
(AI II) (g)	15	17	18	15	18	21

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