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Synthesis, Characterization and Antibacterial activity of 3-(6,7 substituted-1,3-benzothiazol-2-yl)-4-(4-substituted phenyl)-1,3-thiazolidin-2-one derivatives

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Abstract : Disubstituted 2-aminobenzothiazole derivatives **(2)** have been prepared from disubstituted aniline **(1)** in presence of potassium thiocynate, bromine, glacial acetic acid and ammonia solution. It has been reacted with various aromatic aldehydes **(3a-g)** to afford Schiffs base derivatives **(4a-g)**. Further , these schiff's bases are refluxed with thioglycolic acid in presence of DMF to afford 3-(6, 7-substituted-1,3-benzothiazol-2-yl)-4-(4-substituted phenyl)-1,3-thiazolidin-2-one derivatives **(5a-g, 6a-g, 7a-g, 8a-g, 9a-g, 10a-g)**. The title compounds and their derivatives have been characterized by their spectral data. The synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Bacillus substilis Escherichia coli* and *Pseudomonas aeruginosa*.

Keywords: Benzothiazole, Schiff's Base, Antibacterial Activity .

INTRODUCTION

Literature survey reveals that 2-aminobenzothiazole possess various pharmacological activities like diuretic, anti-ulcer, anti-histaminic, anticancer, anticonvulsant, antileishmanial, antidiabetic, antituberculosis.[1-8] Based on the importance of 2-aminobenzothiazole and their biological activities. The synthetic approach to the title compounds is outlined in scheme.

EXPERIMENTAL

Melting points were determined in open capillaries in liquid paraffin and are uncorrected. Purity of the compounds was checked by percolated TLC using Silica gel G as stationary phase and benzene : ethanol (9:1) as mobile phase. IR-spectra (KBr) were recorded on Shimadzu-IR 400 spectrophotometer and ^{1}H-NMR spectra in DMSO-d_6 on Brucker Avance II-400MHz using TMS as internal standard. Yields, melting points, R_f values, and molcular formulas are mentioned in Table I. The compounds were screened for antibacterial activity against *Staphylococcus aureus*, *Bacillus substilis Escherichia coli* and *Pseudomonas aeruginosa* by Cup-plate method.[9] All the observations are given in Table II.

SYNTHESIS OF 7-CHLORO -6-FLUORO-2-AMINO –BENZOTHIAZOLE (2)[8]

To glacial acetic acid (20 ml) cooled below room temperature were added 8 g (0.08 mol) of potassium thiocyanate and 1.45 g (0.01) of 3- chloro- 4-fluoro-aniline **(1)**. The mixture was placed in freezing mixture of ice and salt and mechanically stirred. While, 1.6 ml of bromine in 6 ml of glacial acetic acid was added, from a dropping funnel at such a rate that the temperature never rose beyond 0^{o}C. After all the bromine was added (105 min.), the solution was stirred

for 3 hours below room temperature for 10 hours. It was then allowed to stand overnight, during which period an orange precipitate settled at the bottom. Water (6 ml) was added quickly and slurry was heated at 85°C on a steam bath and filtered hot. The orange residue was pleased in a reaction flask and treated with 10 ml of glacial acetic acid, heated again to 85°C and filtered. The combined filtrate was cooled and the pH was adjusted to 6 by using ammonia. The yellow precipitate was collected after filtration and re-crystallized with benzene:ethanol (1:1) after treatment with charcoal which gave yellow plates of 7-chloro-6-fluoro-2-aminobenzothiazole **(2)**.

M.p 170^{0}C; IR (KBr, cm^{-1}): 3425 (1^0 -NH), 1530 (aromatic C=C), 1632 (C=N), 1442 (thiazole), 1320 (C-N), 1195 (C-F), 716 (C-Cl); ^{1}H-NMR (DMSO-d_6, ppm): 6.8 (s, 2H, NH_2), 7.1-7.5 (m, 2H, Ar-H).

SYNTHESIS OF 7-CHLORO-6-FLUORO-N-[(1E)-(4-SUBSTITUTED PHENYL) METHYLIDENE] 6-FLUORO-1, 3-BENZOTHIAZOL-2-AMINE (4a-g)

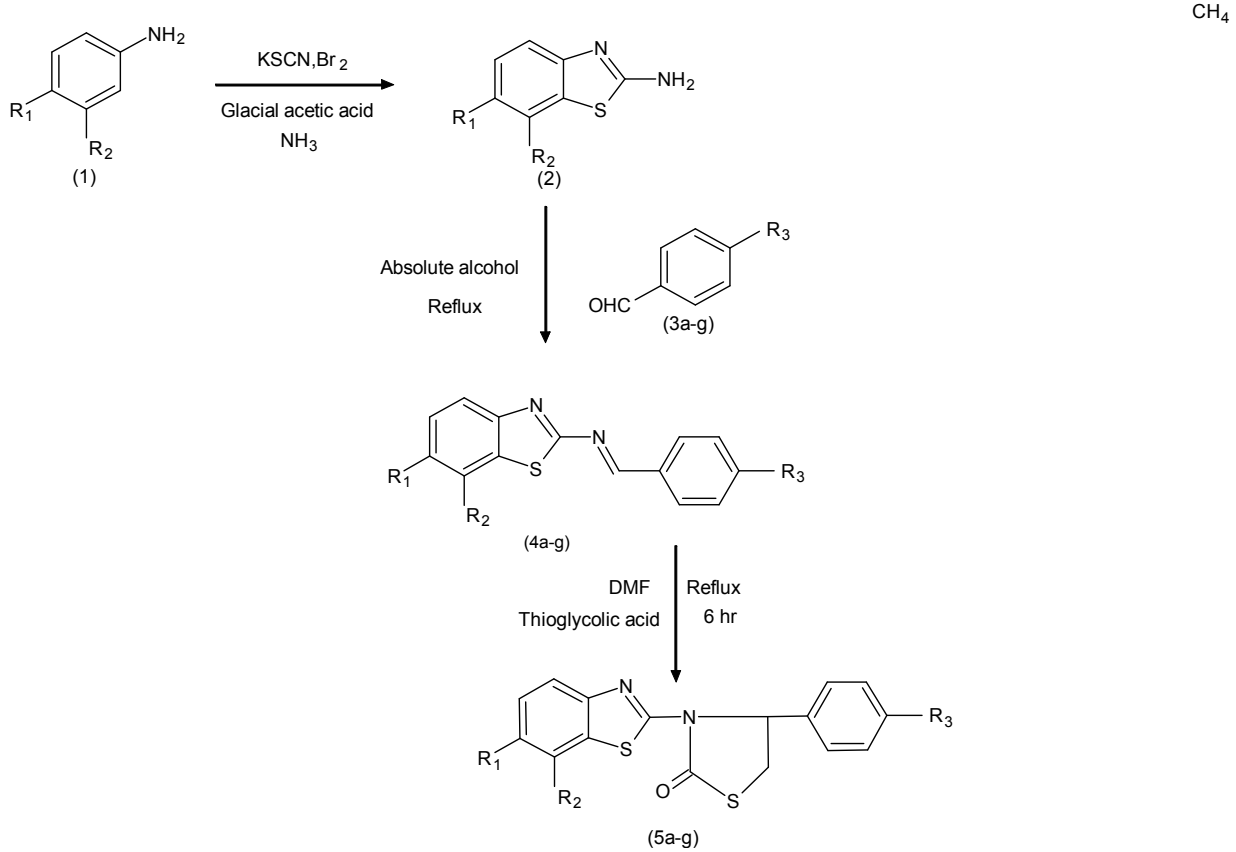
7-chloro-6-fluoro-2-aminobenzothiazole **(2**, 0.01 mol) and 4-subsituted aromatic aldehyde (**3a-h**, 0.01mol) were dissolved in 50 ml absolute alcohol. To this solution a pinch of anhydrous zinc chloride was added. The reaction mixture was refluxed for 10-12 hours on a water bath. It was cooled and poured into crushed ice. The solid thus obtained was filtered & washed with water and recrystallized from ethanol.

M.p 140-165°C; IR (KBr): 685 (C-Cl), 1193 (C-F), 1449 (C=C aromatic), 1257 (C-N), 1647 (C=N); ^{1}H-NMR (DMSO-d_6, ppm): 8.5-9.2 (1H, s, N=CH), 7.1-8.2 (6H, m, Ar-H).

SYNTHESIS 3-(6, 7 SUBSTITUTED-1,3-BENZO THIAZOL-2-YL)-4-(4-SUBSTITUTED PHENYL)-1,3-THIAZOLIDIN-2-ONE (5a-g, 6 a-g, 7 a-g, 8 a-g, 9 a-g, 10 a-g)

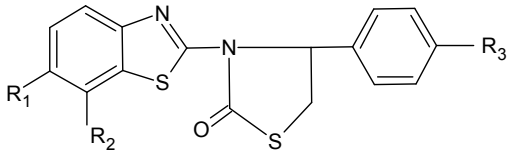
Schiff's bases (0.1 mol) were dissolved individually in 50 ml DMF in a 100 ml of round bottom flask fitted with a double surface reflux condenser. Thioglycolic acid (0.1 mol) was added carefully to it and the reaction contents were subjected to gentle reflux over water bath for 6 hrs. The reaction was continuously monitored for its completeness using TLC techniques. After 6 hrs the reaction contents were cool down, the resultant product was separated and subjected to re crystallization with alcohol.

M.p 165-185°C; IR (KBr): 685 (C-Cl), 1193 (C-F), 1449 (C=C aromatic), 1257 (C-N), 1647 (C=N), 1744 (C=O), 782 (C-S); ^{1}H-NMR (DMSO-d_6,ppm) 8.5-9.2 (1H, s, N-CH), 7.1-8.2 (6H, m, Ar-H).



Schematic representation of benzothiazole derivatives

TABLE: I - PHYSICAL DATA OF BENZOTHIAZOLE DERIVATIVES



Compd	R_1	R_3	R_3	M.pt (^{0}C)	Yield (%)	*R_f	MOLCULAR FORMULAS
5a	F	Cl	Dimethyl amine	180	54	0.52	$C_{18}H_{15}ClFN_3OS_2$
5b	F	Cl	4-chloro	162	58	0.56	$C_{16}H_9C_{12}FN_2OS_2$
5c	F	Cl	4-Hydrogen	174	60	0.49	$C_{16}H_{10}ClFN_2OS_2$
5d	F	Cl	4-Hydroxy	169	62	0.53	$C_{16}H_{10}ClFN_2O_2S_2$
5e	F	Cl	4-Nitro	175	75	0.48	$C_{16}H_9ClFN_3O_3S_2$
5f	F	Cl	4-Methoxy	173	56	0.43	$C_{17}H_{12}ClFN_2O_2S_2$
5g	F	Cl	2-Hydroxy	152	53	0.49	$C_{16}H_{10}ClFN_2O_2S_2$
6a	Cl	Cl	Dimethyl amine	178	53	0.45	$C_{18}H_{15}Cl_2N_3OS_2$
6b	Cl	Cl	4-chloro	163	57	0.51	$C_{16}H_9Cl_3N_2OS_2$
6c	Cl	Cl	4-Hydrogen	159	52	0.53	$C_{16}H_{10}Cl_2N_2OS_2$
6d	Cl	Cl	4-Hydroxy	168	48	0.43	$C_{16}H_{10}Cl_2N_2O_2S_2$
6e	Cl	Cl	4-Nitro	162	59	0.41	$C_{16}H_9Cl_2N_3O_3S_2$
6f	Cl	Cl	4-Methoxy	158	56	0.43	$C_{17}H_{12}Cl_2N_2O_2S_2$
6g	Cl	Cl	2-Hydroxy	153	52	0.53	$C_{16}H_{10}Cl_2N_2O_2S_2$
7a	H	Cl	Dimethyl amine	176	52	0.56	$C_{18}H_{16}ClN_3OS_2$
7b	H	Cl	4-chloro	169	45	0.51	$C_{16}H_{10}Cl_2N_2OS_2$
7c	H	Cl	4-Hydrogen	158	65	0.58	$C_{16}H_{11}ClN_2OS_2$
7d	H	Cl	4-Hydroxy	162	56	0.32	$C_{16}H_{11}ClN_2O_2S_2$
7e	H	Cl	4-Nitro	156	67	0.43	$C_{16}H_{10}ClN_3O_3S_2$
7f	H	Cl	4-Methoxy	164	51	0.48	$C_{17}H_{13}ClN_2O_2S_2$
7g	H	Cl	2-Hydroxy	151	54	0.62	$C_{16}H_{11}ClN_2O_2S_2$
8a	H	Br	Dimethyl amine	173	57	0.57	$C_{18}H_{16}BrN_3OS_2$
8b	H	Br	4-chloro	169	50	0.46	$C_{16}H_{10}BrClN_2OS_2$
8c	H	Br	4-Hydrogen	158	54	0.65	$C_{16}H_{11}BrN_2OS_2$
8d	H	Br	4-Hydroxy	165	62	0.53	$C_{16}H_{11}BrN_2O_2S_2$
8e	H	Br	4-Nitro	157	58	0.46	$C_{16}H_{10}BrN_3O_3S_2$
8f	H	Br	4-Methoxy	154	63	0.38	$C_{17}H_{13}BrN_2O_2S_2$
8g	H	Br	2-Hydroxy	150	64	0.58	$C_{16}H_{11}BrN_2O_2S_2$
9a	H	CH^3	Dimethyl amine	176	56	0.48	$C_{19}H_{19}N_3OS_2$
9b	H	CH^3	4-chloro	171	57	0.68	$C_{17}H_{13}ClN_2OS_2$
9c	H	CH^3	4-Hydrogen	176	64	0.57	$C_{17}H_{14}N_2OS_2$
9d	H	CH^3	4-Hydroxy	154	60	0.62	$C_{17}H_{14}N_2O_2S_2$
9e	H	CH^3	4-Nitro	168	65	0.62	$C_{17}H_{13}N_3O_3S_2$
9f	H	CH^3	4-Methoxy	156	54	0.54	$C_{18}H_{16}N_2O_2S_2$
9g	H	CH^3	2-OH	154	54	0.46	$C_{17}H_{14}N_2O_2S_2$
10a	H	OCH^3	Dimethyl amine	173	53	0.38	$C_{19}H_{19}N_3O_2S_2$
10b	H	OCH^3	4-chloro	167	59	0.35	$C_{17}H_{13}ClN_2O_2S_2$
10c	H	OCH^3	4-Hydrogen	173	57	0.65	$C_{17}H_{14}N_2O_2S_2$
10d	H	OCH^3	4-Hydroxy	158	60	0.54	$C_{17}H_{14}N_2O_3S_2$
10e	H	OCH^3	4-Nitro	156	50	0.47	$C_{17}H_{13}N_3O_4S_2$
10f	H	OCH^3	4-Methoxy	167	59	0.58	$C_{18}H_{16}N_2O_3S_2$
10g	H	OCH^3	2-OH	165	65	0.48	$C_{17}H_{14}N_2O_3S_2$

*Benzene (9) : Ethanol (1)

TABLE II ANTIBACTERIAL ACTIVITIES OF THE COMPOUNDS

Compounds	Antibacterial Activity (Zone of Inhibition in mm)			
	E.coli	*P. aeruginosa*	*S.aureus*	*B.substilis*
	Conc.100 mcg/ml	Conc.100 mcg/ml	Conc.100 mcg/ml	Conc.100 mcg/ml
5a	20	18	21	22
5b	18	17	18	20
5c	16	20	17	18
5d	18	19	20	16
5e	19	18	23	23
5f	22	20	18	20
5g	21	19	16	25
6a	23	21	22	24
6b	21	19	19	18
6c	22	20	22	22
6d	21	23	18	20
6e	18	23	21	19
6f	23	21	16	18
6g	20	17	24	17
7a	18	24	17	24
7b	21	25	21	24
7c	17	19	16	18
7d	22	23	21	17
7e	18	17	17	16
7f	21	23	21	19
7g	24	23	21	20
8a	20	22	21	23
8b	21	24	21	22
8c	17	18	17	19
8d	24	21	23	21
8e	20	19	18	23
8f	21	24	21	22
8g	18	19	20	23
9a	21	22	23	21
9b	22	21	24	26
9c	21	23	18	16
9d	19	15	18	19
9e	18	19	21	22
9f	22	26	21	24
9g	21	25	21	23
10a	19	18	16	15
10b	21	17	18	21
10c	21	24	22	21
10d	20	21	18	23
10e	22	20	19	22
10f	21	20	19	23
10g	21	22	23	26
Standard (ciprofloxacin)	26	31	28	30

RESULT AND DISCUSSION

All synthesized compounds **(5a-g, 6a-g, 7a-g, 8a-g, 9a-g, 10a-g)** were characterized on the basis of IR-spectra and ^{1}H-NMR spectra. All synthesized compounds showed antibacterial activity against *E.coli, P. aeruginosa, S.aureus and B.substilis*. The synthesized compounds 5a, 5f, 5g, 6a, 6b, 6f, 6g, 7b, 7d, 7f, 7g, 8b, 8d, 8f, 9a, 9b, 9c, 9f, 9g, 10b, 10e, 10f &10g have shown good activity against *E. coli* and the synthesized compounds 6d, 6e, 6f, 7a, 7b, 7d, 7f, 7g, 8a, 8b, 8d, 8f, 9a, 9b, 9c, 9f , 9g, 10c,10d &10g showed good activity against *P. aeruginosa* and the synthesized compounds 5a, 5e, 6a, 6c, 6e, 6g, 7b, 7d, 7f, 7g, 8a, 8d, 8f, 9b, 10c & 10g showed good activity against *S. aureus*. Synthesized compounds 5a, 5c, 5g, 6a, 6c, 7a, 7b, 8a, 8b, 8d, 8e, 8f, 8g, 9b, 9f, 9g, 10d, 10f & 10g showed good activity against *B. substilis* when compared with standard drug ciprofloxacin.

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