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MICROWAVE ASSISTED SYNTHESIS OF FLUORO, CHLORO, 2-N (SUBSTITUTED SCHIFF'S BASES) AMINO BENZOTHIAZOLES AS POTENTIAL ANTIMICROBIAL AND ANTITUBERCULAR AGENTS

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ABSTRACT

A series of various substituted benzothiazole derivatives containing 6-fluoro-7-chloro-N (substituted hydrozones) - benzothiazole was synthesized and their structures were identified by spectroscopic techniques.

Keywords: benzothiazole, hydrozones

1. INTRODUCTION

Benzothiazoles play a vital role in the field of medicinal chemistry. Benzothiazole moiety is an important pharmacophore and exhibits outstanding biological activities[1-5]. Day by day Schiff bases are more frequently applied for the treatment of human welfare. Though extensive research work has been reported on benzothiazole with Schiff base, but relatively very little is known so far about substituted benzothiazole with Schiff's base.

Microwave–assisted organic synthesis (MAOS) has been widely employed to enable and expedite the synthesis of diverse heterocycles[6].

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Microwave irradiation has been shown not only to reduce reaction times, but also often to provide higher yields of the desired products as compared to traditional heating methods.

The compound 2-aminobenzothiazole is a versatile material for a number of syntheses. 7-chloro-6-fluorobenzothiazole-2-yl amine (MI) was synthesized from 3-chloro-4-fluoro phenylamine by reacting with potassium thiocynate and bromine solution in glacial acetic acid according to the literature. 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 (MII). Different derivatives were synthesized by reacting various substituted aromatic aldehydes, and forming the Schiff's base MIII (a-j).

2. Experiment

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Jasco FT\ IR-460 plus Fourier transform Infrared spectrometer. ^{1}H NMR spectra were scanned on a bruker ultraspec 500MHZ/ AMX400MHZ spectrometer using DMSO as solvent (chemical shift in δppm). Mass spectra were recorded on JEOL SX 102/DA-6000 mass spectrophotometer using Argon/Xenon (6KV, 10 mA) as the FAB gas with m-nitrobenzyl alcohol as the matrix.

Synthesis of 7-chloro-6-fluorobenzothiaozol-2-yl-amine. (M1)

To glacial acetic acid (40 ml) precooled to 5°C were added 40 g (0.416 mol) of potassium thiocyanate and 7.25g (.05 mol) of 3-chloro-4-fluoroaniline. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while 6 ml of bromine in 24 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature does not rise beyond 0°C. After all the bromine has been added (105min), the solution was stirred for an additional 2 hour at 0°C 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 85°C 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 85°C 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 (MI) was obtained as colorless powder (85%); m.p. 189-191°C. IR (KBr) bands: 3477, 3290 (Ar-NH_2 symm, asymm), 3089 (Ar-CH), 1648 (C=N), 1216 (C-F), 686(C-Cl) and ^{1}H NMR($CDCl_3$) showed 7.54 δ (d, 1H, Ar-H), 7.35 δ (d, 1H, Ar-H), 5.32 δ (s, 2H, NH_2).

Synthesis of 7-chloro-6-fluorobenzothiaozol-2-yl-hydrazine. (MII)

Concentrated HCl (10 ml) was added dropwise with stirring to hydrazine hydrate (10 ml) at 5-10°C; 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 (MII) was obtained as colorless crystals (65%); m.p. 218-220°C. IR (KBr) bands: 3317 (-NH_2), 3200 (-NH), 3067 (Ar-CH), 1202 (C-F), 687 (C-Cl) and ^{1}H NMR(DMSO) showed 7.40 δ (d, 2H, Ar-H), 5.05 δ (s, 2H, NH_2), 9.19 δ (s, H, NH).

General procedure for the microwave assisted synthesis of 6-fluoro-7-chloro-N(substituted hydrozones)-benzothiazole.MIII (a-j)

Substituted benzaldehyde (0.002 Mol) and 7-chloro- 6- Fluoro- benzothiazol- 2-yl hydrazine (0.002 Mol) were added with suitable solvent (DMF, DMSO, Ethanol) and charged in microwave for 5 minutes, on cooling solid separated out, which was filtered and re-crystallized with ethanol.

General procedure for the conventional synthesis of 6-fluoro-7-chloro-N(substituted hydrozones)-benzothiazole. MIV (a-j)

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.

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

Yield (60%), m.p. 258-260 °C. IR (KBr) bands: 3084 (Ar-CH), 3200 (-NH), 1448(-C=N) and ^{1}H NMR (DMSO) showed 11.92 δ (s, 1H, -NH), 8.03 δ (s, 1H, -C-H), 7.69- 7.38 δ (7H, Ar-H).

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

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

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

Yield (60%), m.p. 180-182 °C. IR(KBr) bands:3068 (Ar-CH), 3366 (-NH), 1434(-C=N), 2850
(-OCH_3) and ^{1}H NMR (DMSO) showed 9.60 δ (s, 1H, -NH), 8.76 δ (s, 1H, -C-H), 7.99- 6.75 δ (5H, Ar-H), 12.68 δ (1H, -OH), 3.87 (s, 3H, -OCH_3).

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

Yield (72%), m.p. 240- 242°C. IR(KBr) bands:3087(Ar-CH), 3366 (-NH), 1454(-C=N).

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

Yield (65%), m.p. 250- 252°C. IR(KBr) bands:2917(Ar-CH), 3071 (-NH), 1454(-C=N), and ^{1}H NMR (DMSO) showed 12.74 δ (s, 1H, -NH), 8.98 δ (s, 1H, -C-H), 7.39- 8.48 δ (6H, Ar-H).

3-nitro benzaldehyde (7-chloro-6-fluoro-1,3-benzothiazol-2-yl) hydrazone MIII(f)

Yield (65%), m.p. 219- 221°C. IR(KBr) bands:2958(Ar-CH), 3235 (-NH), 1456(-C=N),1514(-NO_2). ^{1}H NMR (DMSO) showed 12.47 δ (s, 1H, -NH), 9.01 δ (s, 1H, -C-H), 7.34- 6.88 δ (6H, Ar-H).

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

Yield (80%), m.p. 185-187°C. IR(KBr) bands:3063(Ar-CH), 3200 (-NH), 1455(-C=N), 3250(-OH). Mass (m/z): 322 (M+).

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

Yield(75%), m.p. 245-247°C. IR(KBr) bands:3087(Ar-CH), 3102 (-NH), 1456(-C=N), 1550(-NO_2).

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

Yield (80%), m.p. 256-257°C. IR(KBr) bands:2927(Ar-CH), 3300 (-NH), 1452(-C=N).

3,4,5- trimethoxybenzaldehyde (7-chloro-6-fluoro-1,3-benzothiazol-2-yl) hydrazone MIII(j)

Yield (75%), m.p. 205-207°C. IR(KBr) bands:3088(Ar-CH), 3328 (-NH), 1446(-C=N), 2835
(-OCH_3).

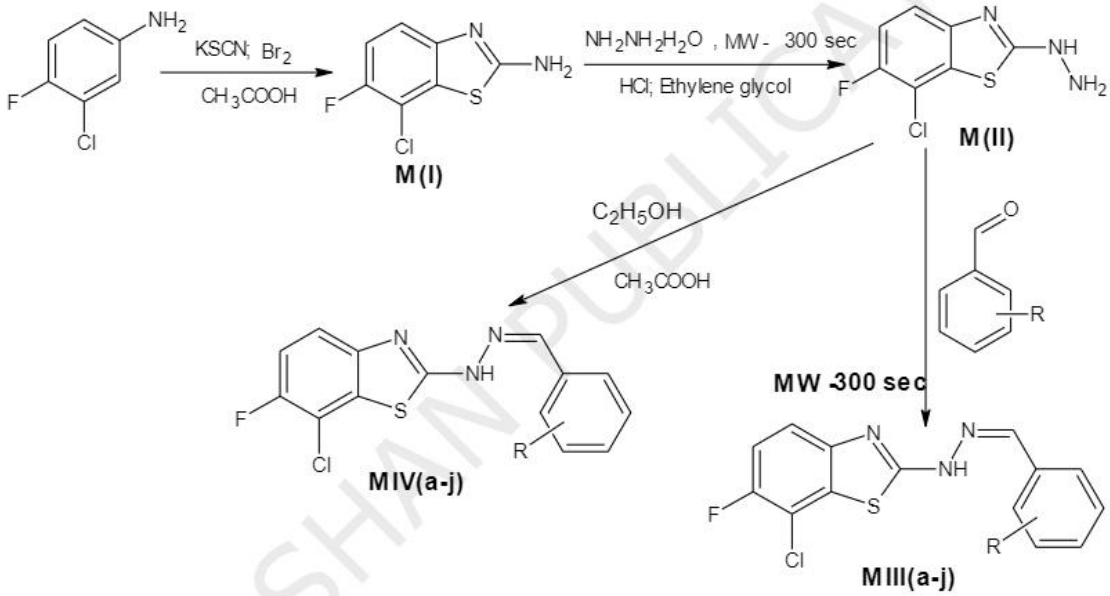

Table-1: Codes and corresponding R of different derivatives

CODE	ORTHO	META	PARA
MIII(a)	H	H	H
MIII(b)	OH	H	H
MIII(c)	H	OCH_3	OH
MIII(d)	H	H	OH
MIII(e)	Cl	H	H
MIII(f)	H	NO_2	H
MIII(g)	H	OH	H
MIII(h)	H	H	NO_2
MIII(i)	Cl	H	Cl
MIII(j)	OCH_3	OCH_3	OCH_3

Table-2: Characterization data of the compounds prepared

Compound	Melting Point (°C)	% yield
M(I)	189-191	95
M(II)	218-220	90
MIII(a)	258-260	60
MIII(b)	190-192	70
MIII(c)	180-182	60
MIII(d)	240-242	72
MIII(e)	250-252	65
MIII(f)	219-221	70
MIII(g)	185-187	80
MIII(h)	245-247	75
MIII(i)	256-257	80
MIII(j)	205-207	75

Table-3: Comparison of the synthesized derivatives by conventional and microwave method.

Drug Code (a-j)	Time Taken		Percentage Yield	
	Conventional Method M(IV)	Microwave Method M(III)	Conventional Method M(IV)	Microwave Method M(III)
a	4 hr	290 sec	50	60
b	3 hr 30min	350 sec	55	70
c	3 hr 50 min	250 sec	45	60
d	4 hr	280 sec	65	72
e	4 hr	350 sec	50	65
f	3 hr 35min	290 sec	60	70
g	4 hr 10min	270 sec	60	80
h	4 hr 10min	285 sec	55	75
i	3 hr 50min	395 sec	60	80
j	4 hr	270 sec	55	75

Results and Discussion

7-Chloro-6-fluoro-benzothiazol-2-ylamine (MI) was synthesized from 3-Chloro-4-fluoro phenylamine. Further using microwave assisted synthesis, 7-chloro-6-fluoro- benzothiazol-2-yl-hydrazine (MII) was synthesized from 7- Chloro-6-fluoro-benzothiazol-2-ylamine (MI). By adding different aldehydes to (MII), various Schiff's base derivative MIII (a-j) were obtained. Various compounds and their derivatives prepared were confirmed by

IR, ^{1}HNMR and FAB MASS Spectroscopy. The structures, melting points, yields, purification methods used and spectroscopic data are given in the Table. The compounds were found to have moderate antimicrobial, and anti-tubercular activity.

Antimicrobial activity

Antimicrobial activity of the synthesized compounds has been determined against three different strain, two gram positive bacteria (bacillus subtilis and staphylococcus aureus) and gram negative bacteriae (proteus vulgaris) at conc 100µg/ml by agar diffusion method[7]. The Zone of inhibition was recorded for different test samples and compared to the standard drug norfloxacin. The compounds were tested for their antifungal activity against Candida albicans with standard drug as griseofulvin by agar diffusion method at a conc. of 100µg/ml. Among the compounds tested MIII (e) and MIII (j) showed good activity against both types of bacteria, where as the compound MIII (f) showed good antifungal activity while rest of the compounds showed moderate activity.

Antitubercular activity

The antitubercular screening was carried out by Lowenstain-Jensen egg medium (L J Medium) as described by Watt against $H_{37}Rv$ Strain. L J Medium containing standard drug as well as control L J Medium was also inoculated with Mycobacterium tuberculosis of $H_{37}Rv$ Strain. The medium inoculated was incubated for 37° C for six weeks. At the end of six weeks reading were taken. Among the compounds tested MIII (d) and MIII (f) and MIII (i) have shown significant anti tubercular activity against $H_{37}Rv$ Strain, in both 50 mcg and 100 mcg/ml dilution. The compounds MIII (b), MIII(c), MIII (e) and MIII (j) were shown resistant in both 50 and 100 mcg/ml dilution.

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