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Microwave Assisted Synthesis of Fluoro, Chloro2-(α-Substituted aryl amino acetamido) Benzothiazole and screening for antimicrobial activities

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ABSTRACT

A series of various substituted benzothiazole derivatives containing 7-chloro-6-fluoro-2-chloroacetamidobenzothiazole derivatives was synthesized and their structures were identified by spectroscopic techniques.

Keywords: benzothiazole, chloroacetamidobenzothiazole

1. INTRODUCTION

Benzothiazoles play a vital role in the field of medicinal chemistry. Benzothiazole moiety is an important pharmacophore and exhibits outstanding biological activities. Microwave–assisted organic synthesis (MAOS) has been widely employed to enable and expedite the synthesis of diverse heterocycles. 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. Heterocycles bearing benzothiazole ring residue are reported to shows anti-inflammatory[1], antimicrobial[2,4] anthelmintics [3] and antidiabetic[5] activities.

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The compound 2-aminobenzothiazole is a versatile material for a number of synthesis. 7-chloro-6-fluorobenzothiazole-2-yl amine **(P)** 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 chloroacetyl chloride in the presence ethanol to give 7- chloro-6-fluoro-2-chloroacetamidobenzothiazole.
Different derivatives were synthesized by reacting various substituted aromatic amines, and forming the different derivatives (**R1**-**R9**).

2. Experiment

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Jasco FTIR-460 plus Fourier transform Infrared spectrometer. ^{1}H NMR spectra were scanned on a Bruker ultraspec 500MHZ/ AMX400MHZ spectrometer using $CDCl_3$ as solvent (chemical shift in δppm). FAB 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 .

3. Synthesis of 7-chloro-6-fluorobenzothiaozol-2-yl-amine[5]

To glacial acetic acid (40 ml) precooled to 5°C were added 40 g (0.416 mol) of potassium thiocyanate and 7.25g (0.05 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. When, 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 Ar-NH_2 symm)3089 (Ar-CH), 1648 (C=N), 1216 (C-F), 686(C-Cl cm^{-1}) and ^1H 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) ppm.

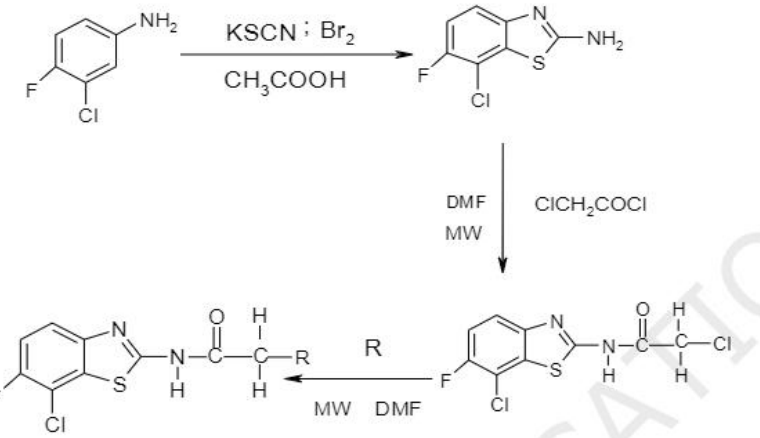
4. Synthesis of 7- chloro-6-fluoro-2-chloroacetamidobenzothiazole[4]

To a cooled solution obtained from previous step (0.05mol) in ethanol (250ml) ,chloroacetylchloride (5.65g,0.05mol) was added drop wise for 1 hr.It was stirred for 2 hr and refluxed for 1hr by microwave method . The reaction mixture was cooled and poured into crushed ice. The separated solid was filtered, washed with water and recrystallized from methanol. IR (KBr) bands: 3451 Ar-NH_2 symm, asymm), 3089 (Ar-CH),2915(CH2),1706(C=O) and ^1H NMR ($CDCl_3$) showed at 7.54 δ (d, 1H, Ar-H), 6.35 δ (d, 1H, Ar-H), 5.32 δ (s, 2H, NH_2) ppm.

General procedure for the microwave assisted synthesis of substituted aryl amino acetamido benzothiazoles(R1-R9)[5]

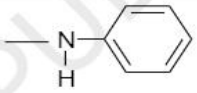
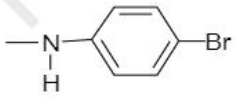
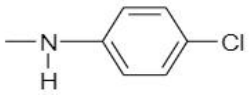
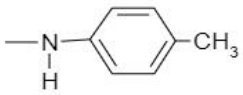
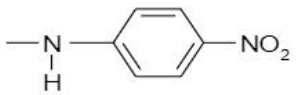
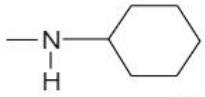
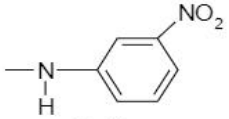
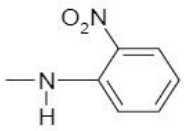
7-chloro-6-fluoro-2-chloroacetamido bezothiazole was treated with equimolar quantities of various substituted aniline like p- chloroaniline ,p- bromoaniline, cyclohexyl amine, ortho nitroaniline, p-nitroaniline and p-toluidine(-4-methyl aniline) and in each case refuxed for 2hr, in presence of DMF . The mixture was cooled and poured in to crushed ice. The solid separated was filtered, washed with water and dried.

It was purified by recrystallisation from ethanol- benzene mixture (1:1).R1:FT-IR(KBr disc):3450(N-H amide str),3303(N-Hstr), 1692 (C=O), 2918(CH_2-str) ,3092(C-H aromatic) and ^1H NMR($CDCl_3$) showed at7.54 δ (d, 1H, Ar-H), 6.35 δ (d, 1H, Ar-H), 12.3δ (s, 1H, NH)., 1.5 δ (CH2) ppm.



[Where R=Substituted amines]

Table-1 The Code and corresponding R of different derivatives:-

CODE	R
R1	
R2	
R3	
R4	
R5	
R6	
R7	
R8	

5.

Table-2 Physical properties of various compounds and derivatives

Code No.	Solubility	Rf value	Melting point (^{o}C)
R1	DMSO	0.4564	205-207
R2	DMSO	0.2345	238-240
R3	DMSO	0.2131	228-230
R4	DMSO	0.2140	234-235
R5	DMSO	0.1268	238-240
R6	DMSO	0.2310	223-225
R7	DMSO	0.3210	248-250
R8	DMSO	0.4312	218-220

Mobile phase TLC: - Chloroform:Methanol 9:1(R1), Benzene:ethanol 4:1(R2),Chloroform: ethano 9:1(R3), Benzene:ethylacetoacetate 9:2(R4), Chloroform:ethanol 9:1 (R5), Chloroform: methanol 9:1(R6,R7,R8,R9).

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

Drug Code (R1-R9)	Time Taken		Percentage Yield	
	Conventional Method	Microwave Method	Conventional Method	Microwave Method
R1	2 hr	450sec	50	65
R2	4 hr	650 sec	40	60
R3	4 hr	450 sec	50	70
R4	4 hr	380 sec	55	69
R5	4 hr	350 sec	60	75
R6	3 hr 35min	490 sec	59	70
R7	4 hr 10min	270 sec	69	80
R8	4 hr 10min	285 sec	65	70

Result and Discussion

7-chloro-6-fluorobenzothiaozol-2-yl-amine(1) , required in this work , was synthesized from 3-chloro-4-fluoroaniline via bromination , according to published procedures [3,5] 7- chloro-6-fluoro-2-chloroacetamidobenzothiazole (2) was synthesized from chloroacetylchloride by removal of HCL molecules in presence of DMF by microwave method. Substituted aryl amino acetamido benzothiazoles was synthesized from treated with equimolar quantities of various substituted aniline like p-chloroaniline ,p- bromoaniline, cyclohexyl amine, ortho nitroaniline, p-nitroaniline and p-toluidine(-4-methyl aniline) and in each case refuxed for 2hr, in presence of DMF . The mixture was cooled and poured in to crushed ice. The solid separated was filtered, washed with water and dried. It was purified by recrystallisation from ethanol- benzene mixture (1:1).R1:FT-IR(KBr disc). The structures ,melting points ,yields,purification methods used and spectroscopic data are given in the Table.

Antimirobial activity[6]

Antimicrobial activity of the synthesized compounds have been determined of Bacteria against *B. Subtilis ,S. typhi ,E. coli* and *S. aureus* at 100µg/ml conc by agar diffusion method . The Zone of inhibition was recorded for different test samples and compared to the standard drug norfloxacin and Ampicillin .Standard antibiotic, **Ampicillin** has shown maximum activity against *E.coli* and *S.aureus* (31 mm). It has shown a good activity against *B.subtilis* and *S.typhi* with 25mm and 21mm of respectively zone of inhibition, while Norfloxacin has shown activity less than Ampicillin against *B.subtilis*, *S.typhi, E.coli* and *S.aureus* with a zone of inhibition of 14mm, 15 mm 15 mm and 15 mm respectively.

R1 has shown a weak activity against *S.typhi* and *E.coli,* where as it has no activity against *S.aureus and B.subtilis* compared *to* Norfloxacin and Ampicillin

R2 as shown activity against all the organisms similar to that of Norfloxacin but less to that of Ampicillin.

R3 has shown a weak activity against *E.coli* and *S.aureus* with a zone of inhibition of 4 mm and has no activity against *S.typhi,* but half in its activity towards *B.subtilis* in comparision to that of Norfoxacin while less or no activiy against microbes compared to that of Ampicillin .

R4 has shown a significant activity against E.coli with a zone of inhibition of 20 mm and it has shown to be equivalent in its antibacterial activity against *B.subtilis, S.typhi* and *S.aureus* similar to Norfoxacin but less than Ampicillin

R5 has found to be better in its activity to Norfoxacin towards *E.coli, S.aureus* and *B.subtilis* but slightly weaker towards *S.typhi* compared to Norfoxacin and less active active against all microbes than Ampicillin

R6 has no activity against *B.subtil*s shown a weak activity against *S.typhi E.coli* and *S.aureusn* compared to Norfoxacin and Ampicillin. R2, R4 and R5 have shown better anti-microbial activity similar to the standard Norfloxacilin but less to that of Ampicillin

References

1. Wada J, Suzuki T, Iwasaki M, Miyamatsu H, Ueno S, Shimizu M. A new non steroidal antiinflammatory agents. 2-substituted 5-or 6-benzothiazole acetic acids and their derivatives. *J Med Chem* 1973; 16:930-934.
2. Bhawsar SB, Mane DV, Shinde DB, Shingare MS, Deokate AS, Gangawane LV. Synthesis of 8-[(6'-substituted-1'-benzothiazole-2'-yl)aminomethyl]- substituted hydroxycoumarins and their antimicrobial activity. *Ind J of Heterocyclic Chemistry* 1996;**6:**135-138.
3. Bhusari KP, Khedekar PB, Umathe SN, Bahekar RH, Raghu Ram Rao A. Synthesis of 8- bromo-9-substituted –1,3-benzothiazolo –[5,1-b]-1,3,4-triazoles and their anthelmintics activity *Ind J of Heterocyclic Chemistry* 2000 ,**9**,275-278.
4. Bhusari KP, Khedekar PB, Umathe SN, Bahekar RH, Raghu Ram Rao A. Synthesis and antimicrobial activity of some 2-substituted aminobenzothiazoles. *Ind J of Heterocyclic Chemistry* 2001,**10**,231-232.
5. Pattan SR, Suresh Ch, Pooja VD, Reddy VVK, Rasal VP, Koti BC. Synthesis and antidiabetic activity of 2-amino[5'(4-sulfonylbenzylidine)-2,4-thiazolidindione]-7-chloro-6-fluorobenzothiazole. *Indian J of Chemistry* 2005; 44B:2404-2408.
6. Prescott LM, Harley JP, Klein DA. Microbial Growth and Metabolism. In: Kelvin K, Editor.
7. Microbiology, 2nd edition, England, Wm.C Brown Publisher. 104.

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