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Research Article

MICROWAVE ASSISTED SYNTHESIS AND EVALUATION OF FLUORO, CHLORO, 2-(α- SUBSTITUTED ARYL AMINO ACETAMIDO) BENZOTHIAZOLES DERIVATIVES FOR ANTIMICROBIAL ACTIVITY

Hipparagi S. M[1]*, Ranjeeta V[1], Muttu C. T[2], Tikare V.P[3], Bhanushali M. D[4]
[1]Department of pharmaceutical Chemistry, K.L.E.S's College of Pharmacy, Rajajinagar, Bangalore, Karnataka, India
[2]Department of pharmacology, RIMS, Raichur, Karnataka, India
[3]Department of Pharmacology, MM College of Pharmacy, Belgaum, Karnataka, India
[4]Department of Pharmaceutical Chemistry, MM College of Pharmacy, Belgaum, Karnataka, India

*Dr S.M.Hipparagi, Professor, Department of Pharmaceutical Chemistry, K.L.E.S's College of Pharmacy, 4th T Block Rajajinagar, Bangalore-40 Email: chemsmh@yahoo.co.in
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ABSTRACT
A series of various substituted benzothiazole derivatives containing 7- chloro-6-fluoro-2-chloroacetamidobenzothiazole derivatives were synthesized and their structures were established by means of spectroscopic techniques Structures of compounds have been established by means of IR, ^{1}H-NMR and elemental analysis.
All the compounds were evaluated for antibacterial and antifungal activities. Most of the compounds have shown significant antibacterial and antifungal activity when compared with the standard drug.

KEYWORDS: Antimicrobial activity, Benzothiazole, Microwave synthesis.

INTRODUCTION
Synthesis of benzothiazole derivatives was aimed because it plays a vital role in the field of medicinal chemistry and exhibits outstanding biological activities. Heterocycles bearing benzothiazole ring residue are reported to shows anti-inflammatory[1], antimicrobial[2, 3] anthelmintics[4] and antidiabeticactivities[5].
Microwave–assisted organic synthesis (MAOS) was employed, which not only reduced reaction times, but also provided higher yields of the desired products as compared to traditional heating methods[6].
The compound 7-chloro-6-fluorobenzothiazole-2-yl amine (P) was synthesized by traditional heating method according to the literature. Then the further different derivatives were synthesized by microwave method (R_1-R_8).

MATERIAL AND METHODS
Antimicrobial Activity
The antimicrobial activity of the synthesized compounds was determined by cup-plate method. The organisms selected for antibacterial activity were Staphylococcus aureus (NTCC 6571) and Escherichia coli (NTCC 10418). Similarly the antifungal activity was carried out by using Aspergillus niger (ATCC 16404) and Candida albicans (ATCC 10231). The concentration of sample compounds was 100mcg/ml. Norfloxacin, Ampicillin and Griseofulvin were used as standard drugs for antibacterial and antifungal activity respectively. Control test with Dimethyl formamide was formed for every assay but showed no inhibition of the microbial growth[7, 8, 9].
Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Jasco FT\ IR-460 spectrophotometer using KBr disc method.. ^{1}H NMR spectra were scanned on a

bruker ultraspec 500MHZ/ AMX400MHZ spectrometer using Dimethyl Sulfoxide d_6 as solvent and tetramethylsilane as internal standard. The reactions were carried in domestic microwave oven.

A] Synthesis of 7-chloro-6-fluorobenzothiaozol-2-yl-amine. (P)

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. 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 (P) was obtained as colorless powder (92%); m.p. 188-191°C.

B] Synthesis of 7- chloro-6-fluoro-2-chloroacetamidobenzothiazole (P_1)

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.

C] General procedure for the microwave assisted synthesis of substituted aryl amino acetamido benzothiazoles (R_1-R_8)

7-chloro-6-fluoro-2-chloroacetamidobezothiazole was treated with equimolar quantities of various substituted aniline in microwave for 7 minutes with 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).

D] General procedure for the conventional synthesis of substituted aryl amino acetamido benzothiazoles

7-chloro-6-fluoro-2-chloroacetamidobezothiazole was treated with equimolar quantities of various substituted aniline and refluxed 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).

RESULT AND DISCUSSION

In the present research work a series of various substituted benzothiazole derivatives containing 7-chloro-6-fluoro-2(α- substituted aryl amino acetamido) benzothiazole were synthesized as mentioned in the scheme and experimental work.

A series of various substituted benzothiazole derivatives containing 7-chloro-6-fluoro-2(α-substituted aryl amino acetamido) benzothiazole were synthesized by microwave as well as with conventional method and only time factor and percentage yield were compared.

All these compounds were tested for their purity by TLC and melting point. The structures of these compounds were confirmed by IR, NMR and CNH analysis. All these were found to be satisfactory.

The compounds synthesized were screened for antibacterial and antifungal activities by cup-plate method. Compounds R_2, R_4 and R_5 have shown significant antibacterial activity. Remaining compounds have also shown moderate to weak antibacterial activity. Compounds R_2 and R_4 have shown significant antifungal activity. Remaining compounds have also shown weak antifungal activity.

With the suitable molecular modification of these compounds can prove as potent antimicrobial agents in future.

The microwave assisted organic synthesis required less time and also percentage yield was more compared with conventional method.

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Table-1: Analytical data of the synthesized compounds

Comp	Mol. Formula	Mol. Wt	M.P° C	Yield%	Elemental analysis Calculated		
					C	H	N
P	$C_7H_4ClFN_2S$	203	188-191	92	41.37	1.97	13.79
P_1	$C_9H_5C_{l2}FN_2OS$	279	197-198	84	38.70	1.79	10.03
R_1	$C_{15}H_{11}ClFN_3S$	320	205-207	65	56.25	3.43	13.12
R_2	$C_{15}H_{10}ClFN_3SBr$	389	238-240	60	46.27	2.57	10.79
R_3	$C_{15}H_{10}Cl_2FN_3S$	354	228-230	70	50.84	2.82	11.86
R_4	$C_{16}H_{13}ClFN_3S$	334	234-235	69	57.48	3.89	12.57
R_5	$C_{15}H_{10}ClFN_4O_2S$	365	238-240	75	49.31	2.73	15.34
R_6	$C_{15}H_{17}ClFN_3S$	326	223-225	70	55.21	5.21	12.88
R_7	$C_{15}H_{10}ClFN_4O_2S$	365	248-250	80	49.31	2.73	15.34
R_8	$C_{15}H_{10}ClFN_4O_2S$	365	218-220	70	49.31	2.73	15.34

Table-2 Physical properties of various compounds and derivatives

COMPOUND	Solubility	MOBILE PHASE	Rf value for TLC
R1	DMSO	C:M; (9:1)	0.4564
R2	DMSO	B:E; (8:2)	0.2345
R3	DMSO	C:E; (9:1)	0.2131
R4	DMSO	E:EA; (8:2)	0.2140
R5	DMSO	C:E; (9:1)	0.1268
R6	DMSO	C:M; (9:1)	0.2310
R7	DMSO	C:M; (9:1)	0.3210
R8	DMSO	C:M; (9:1)	0.4312

C = Chloroform, M = Methanol, B = Benzene, E = Ethanol, EA= Ethylacetoacetate

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

Drug Code	Time Taken		Percentage Yield	
	Conventional Method	Microwave Method	Conventional Method	Microwave Method
R_1	2hr	7min 30 sec	50	65
R_2	4hr	10min 50sec	40	60
R_3	4hr	7min 30 sec	50	70
R_4	4 hr	6min 20sec	55	69
R_5	4 hr	5min 50 sec	60	75
R_6	3 hr 35min	8min 10sec	59	70
R_7	4 hr 10min	4min 30 sec	69	80
R_8	4 hr 10min	4min 45 sec	65	70

Table-4 Spectral data of synthesized compounds

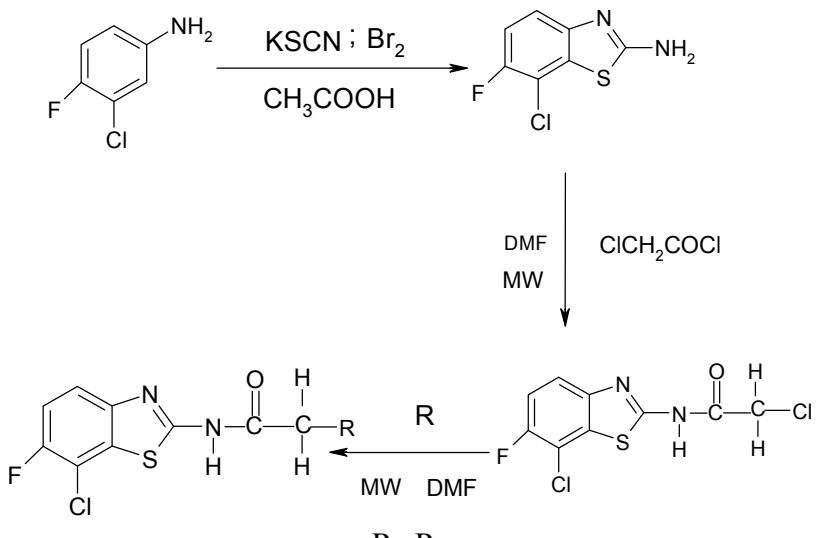
Compounds	IR Bands (cm^{-1})	Types of Vibration	ppm	Proton nature
p	3477,3290,3089, 1648,1216,686	Ar-NH_2 Sym, asym, -C-H Ar str C=N str, C-F str, C-Cl str	5.32 7.35 7.45	2H-NH_2 1H, Ar-H 1H, Ar-H
P_1	3451,3089,1706, 1216,687	Ar-NH_2 , -C-H Ar str, C=O str, C-F str, C-Cl str	5.32 6.35 7.54	2H-NH_2 1H, Ar-H 1H, -Ar-H
R_1	3303,3092,2918, 1692,1215,686	N-H str, -C-H Ar str, CH_2 str' C=O str, C-F str, C-Cl str	1.5 6.35 7.54 12.3	2H- CH_2 1H –Ar-H 1H, Ar-H 1H -NH
R_2	3316,3092, 2915, 1690	N-H str, -C-H Ar str, CH_2 str, C=O str	6.32 7.54 12.3	1H, Ar-H 1H, Ar-H 1H-NH

R_3	3300,3090,2918, 685	N-H str, -C-H Ar str, CH_2 str, C-Cl str.	_	_
R_4	3348,3089,2918, 1690.	N-H str, -C-H Ar CH_2 str, C=O str	_	_
R_5	3318,3092,2915, 1692	N-H str, -C-H Ar str, CH_2 str, C=O str	6.35 7.53 12.3	1H, Ar-H 1H , Ar-H 1H, Ar-H
R_6	3303,3092,2915, 1691,1215,685.	Ar-NH_2 , -C-H Ar str, CH_2 str, C=O str, C-F str, C-Cl str	_	_
R_7	3313,3095,2918, 1690.	N-H str, -C-H Ar str, CH_2 str, C=O str	_	_
R_8	3313,3095,2918, 1690.	N-H str, -C-H Ar str, CH_2 str, C=O str	_	_

Table-5: Antibacterial and Antifungal activity of synthesized compounds

Compounds	**Zone of inhibition at 100 mcg/ml (in mm)**			
	E. coli	**S.aureus**	**A. niger**	**C. albican**
R_1	08	09	10	11
R_2	23	24	24	25
R_3	04	05	07	08
R_4	20	22	22	24
R_5	21	22	18	17
R_6	18	19	17	18
R_7	18	18	19	20
R_8	16	17	18	19
Norfloxacin	24	24	_	_
Ampicillin	28	27	_	_
Greseofulvin	_	_	24	26

SCHEME



R_1-R_8

The Code and corresponding R of different derivatives:-

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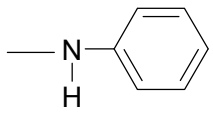
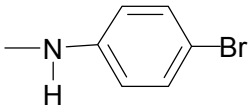
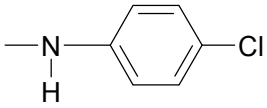
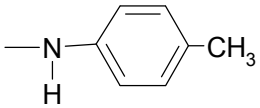
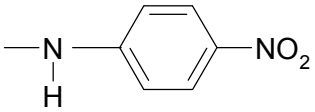
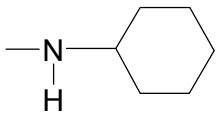
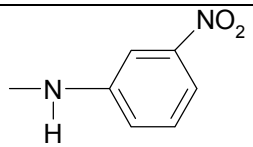
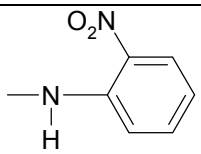
R1	
R2	
R3	
R4	
R5	
R6	
R7	
R8	

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