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"2-Amino-N-(7-substituted Benzo [d] thiazol-2yl) benzamide: Synthesis and characterization of novel antibacterial compounds"

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ABSTRACT

Various 2-Amino-N-(7-subtituted Benzo [d] thiazol-2yl) benzamide containing different secondary amines have been synthesized by treating aniline with KSCN in presence of bromine in glacial acetic acid and ammonia to get to get 2-aminobenzothiazole which was treated with anthranillic acid in presence of dry pyridine to get N- (Benzo [d] thiazol-2-yl) benzamide. To the above appropriate amine in equimolar Quantities were refluxed for 2-6 hrs in an oil bath in the Presence of DMF to get colorless crystalline Derivatives 3 A-E. The derivatives were characterized by melting point, IR, [1]HNMR, and mass spectral studies. The compounds were tested for antimicrobial activity against Staphylococcus aureus (MTCC 83), Streptococcus pyogen (MTCC 442), Escherichia coli (MTCC443), Pseudomonas aeruginosa (MTCC 741), Aspergillus niger (MTCC 134), Candida albicans (MTCC 183) taking Ceftizoxime, Ampilicilline, Gentamicin and Fluconazole as standard drugs and showed significant activity.

Key Words: Benzothiazole, 2-Amino-N-(7-subtituted Benzo [d] thiazol-2yl) benzamide, Antimicrobial activity.

INTRODUCTION

Heterocyclic compounds containing nitrogen and sulphur possess potential pharmacological activities. Benzothiazoles are bicyclic ring systems which have been the subject of great interest because of their biological activities. Benzothiazole moiety possesses diverse type of biological activities viz. antifungal [1], antibacterial [2], antihelminthic [3], antimalarial [4], analgesic [5], anti-inflammatory [6], anticancer [7] and various CNS activities. Benzothiazoles when combined with biologically active heterocycles such as pyrimidine have exhibited potentbpharmacological

activities with improved pharmacokinetic properties [8-11]. The above observation led to the synthesis and biological evaluation of some new benzothiazole derivatives.

MATERIALS AND METHODS

Melting points were determined by open capillary method and are uncorrected. Infrared spectra of the synthesized compounds were recorded as KBr pellet for solid samples on Perkin Elmer spectrum BX FT-IR spectrophotometer. The proton Nuclear Magnetic Resonance spectra were recorded on Bruker Avance (400MHz) NMR spectrometer in $CDCl_3$ using Tetramethylsilane (TMS) as internal reference. Chemical shift is reported in δ (ppm) on Bruker Avance (400MHz) NMR spectrometer

Synthesis of 2- aminobenzothiazoles (1)

A mixture of aniline (0.01 mol, 1.45 g) and potassium thiocyanate (8 g) were added to glacial acetic acid (20 ml), precooled to 0°C. A solution of bromine (1.6 ml) in acetic acid was added slowly with constant stirring. The temperature was maintained at 0°C throughout the addition. After all the bromine has been added, the solution was stirred at additional 2 hr at 0°C and at room temperature for 10 hr. it was allowed to stand overnight, the water (6 ml) was added quickly and the slurry was heated to 85°C on a steam bath and filtered hot. The residue was placed in a reaction flask and treated with glacial acetic acid (10 ml) heated again to 85°C and filtered hot. The filtrates were combined, cooled and neutralized with conc. Ammonia solution to pH 6. The precipitate was collected, recrystallized (twice) from benzene. After treating with activated charcoal, it gave colorless plaques of 2- Aminobenzothiazoles . The dry material (yield 59%) melted at 200 to 202 °C

Synthesis of N- (benzo [d] thiazol-2-yl) benzamide (2)

2-amino-benzothiazole (5.22g, 0.026 mol), and Anthranilic Acid (4.0g, 0.029 mol) were dissolved in Dry pyridine (20 ml, 0.25 mol). The solution was refluxed for 8-10 hrs. The Solution was cooled and poured in water. The separated Mass was filtered, washed with water and dried. The Product was recrystallized using ethanol. (yield 85%), melted at 248°C

Table 1 list of synthesized derivatives with their molecular weight

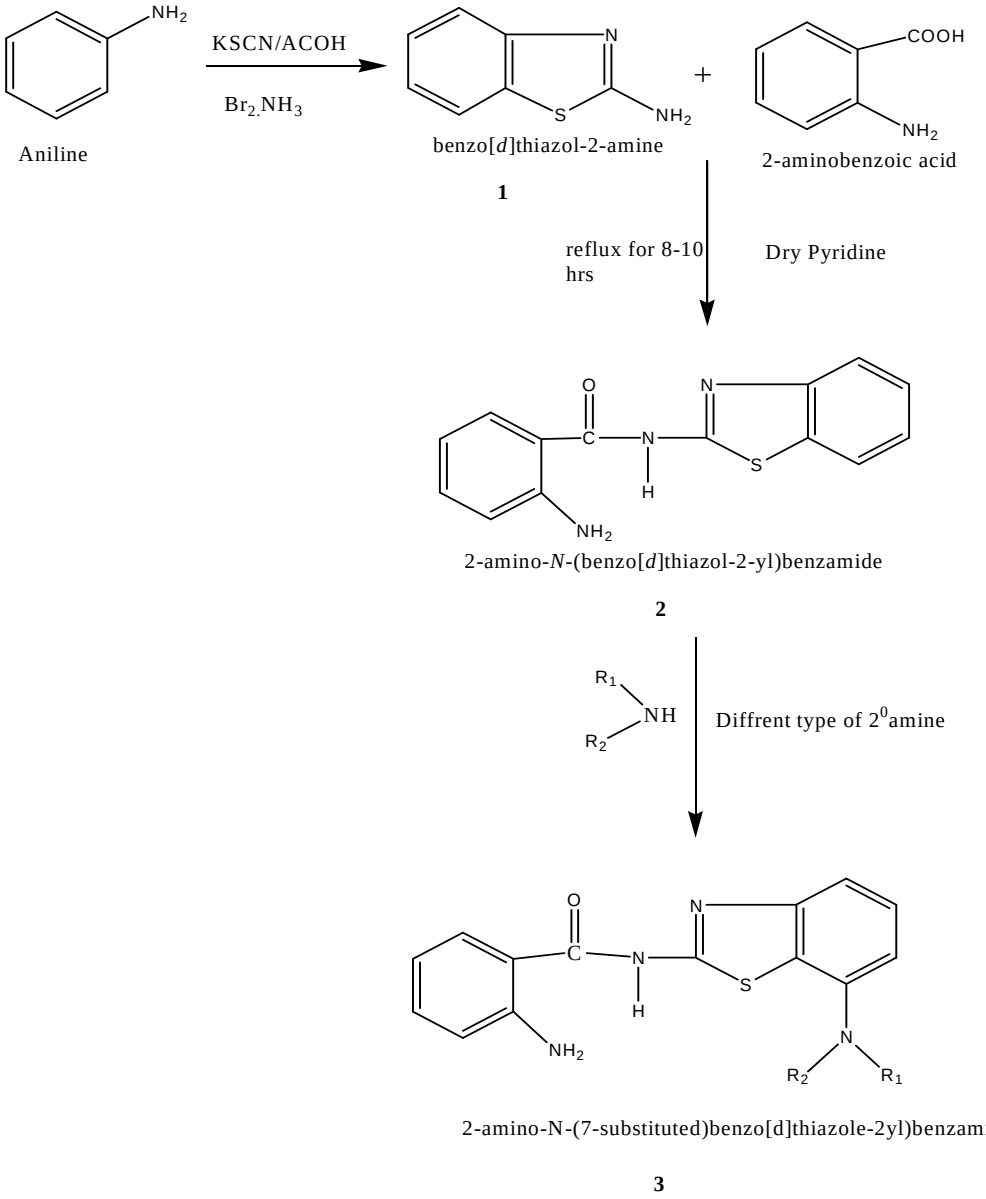
S. No.	Derivatives Code	IUPAC Name of the Derivatives	R	R'	Molecular Formula
1.	A	(E)-2-amino-N-(5-(1-(dimethylamino)prop-1-enyl)thiazol-2-yl)benzamide	CH_3	CH_3	$C_{15}H_{18}N_4OS$
2.	B	(E)-2-amino-N-(5-(1-(diethyalamino)prop-1-enyl)thiazol-2-yl)benzamide	C_2H_5	C_2H_5	$C_{17}H_{22}N_4OS$
3.	C	2-amino-N-(7-(ethyal(methyl)amino)benzo[d]thiazol-2-yl)benzamide	CH_3	C_2H_5	$C_{17}H_{18}N_4OS$
4.	D	2-amino-N-(7-(dipropylamino)benzo[d]thiazol-2-yl)benzamide	C_3H_7	C_3H_7	$C_{20}H_{24}N_4OS$
6.	E	2-amino-N-(7-(methyl(piprazin-1-yl)amino)benzo[d]thiazol-2-yl)benzamide	CH_3	$C_4H_{10}N_2$	$C_{19}H_{22}N_6OS$

Synthesis of 2-amino-N-(7-subtituted benzo [d] thiazol-2yl) benzamide (3 a-e)

Compound (2nd) and appropriate amine in equimolar Quantities were refluxed for 2-6 hrs in an oil bath in the Presence of DMF. Then the reaction mixture was cooled and poured on crushed ice. The solid separated out was filtered and Crystallized from ethanol to get colorless crystalline Derivatives.

The sequence of reactions is depicted in the scheme and list of synthesized derivatives with their molecular weight is shown in Table 1.

Scheme



Analytical data of all the synthesized compounds has been summarized in Table 2, 3 and 4.

Table 2 physiochemical data of final derivatives

S. No.	Derivatives Code	Yield (%)	m.p. (˚C)	Rf-value	Colour
1.	A	55	168	0.72	Cream
2.	B	72	135	0.56	Yellowish Brown
3.	C	38	210	0.69	Light Brown
4.	D	45	156	0.79	Light Green
5.	E	71	191	0.54	Yellow

Table 3 characteristic IR absorbtion bands of final derivatives

S.NO.	COMPOUND CODE	WAVE NUMBER (cm^{-1})	FUNCTIONAL GROUP
1.	A	1237.73 1542.04 3200.00	C=S Streching C=N Streching N-H Streching
2.	B	1542.23 3124.37 1146.76	C=N Streching N-H Streching C-O-C Streching
3.	C	1564.32 1622.97 2863.51 3208.80	C=N Streching C=O Streching C-H Streching. Ar.C-H Streching.
4.	D	1245.85 1540.50 3237.85	C=S Streching C=N Streching N-H Streching
5.	E	1541.44 3299.99 1166.15 2858.87	C=N Streching N-H Streching C-O-C Streching C-H Streching.

Table 4 ^{1}HNMR spectral data of final derivatives

S.NO.	COMPOUND NO.	SHIFT VALUE δ (PPM)
1.	A	2.032-2.489(s, 2H, –NH) 4.734 (s, 2H, Ar-H) 6.393-7.624 (d, 4H, Ar-H) 12.334 (s, 1H, Ar-H)
2.	B	2.153-2.530 (d, 3H, -CH_3) 5.037-5.384 (s, 3H, Ar-H) 6.863 (s, 1H, -NH_2) 7.163-7.189 (s, 1H, Ar-H) 7.737 (s, 1H, Ar-H)
3.	C	.079-2.310 (d, 3H, -CH_3) 5.353- (s, 3H, Ar-H) 6.993 (s, 2H, -NH_2) 7.321-7.624 (s, 4H, Ar-H)
4.	D	0.479-0.524 (d, 2H, -CH_3) 2.091-2.582 (d, 3H, -CH_3) 5.037-5.384 (s, 3H, Ar-H) 6.561-5.384 (s, 2H, -NH_2) 8.247-8.298 (s, 3H, Ar-H) 12.321 (s, 1H, Ar-H)
5.	E	2.032-2.446 (d, 4H, -CH_3) 5.886(s, 3H, Ar-H) 6.993 (s, 2H, -NH_2) 7.321-7.624 (s, 5H, Ar-H) 12.334 (s, 1H, Ar-H)

Biological Activity

In Vitro antibacterial activity was determined by agar well diffusion method [12] against 24 hr old cultures of *Staphylococcus aureus, Staphylococcus pyogen, Eshcerichia coli, Pseudomonas aerugenosa* using 50 µg/ml of Ceftizoxime and Ampilicilline as standard. The test sample was prepared in DMSO, having the concentration 50µg/ml. the zone of inhibition was compared with the standard drugs after 24 hr incubation at 37°C.

Similarly, antifungal activity was also determined by agar well diffusion method [13] against Aspergillus niger and candida albicans using 50 µg/ml of Gentamicin and Fluconazole as standard. The test sample was prepared in DMSO having the concentration 50µg/ml. the zone of inhibition was compared with the standard drugs after 72 hr incubation at 25°C. The result of antimicrobial activity is presented in Table 5.

Table 5 antimicrobial activities of final derivatives

S.No.	Compounds	Bacteria				Fungus	
		Gram-Positive		Gram-Negative			
		S.aureus	***S.pyogen***	***E. Coli***	***P.aeruginosa***	***A.niger***	***C.albicans***
1.	A	+ +	+ +	+	+	-	+
2.	B	+	-	+ + +	+ +	+	+
3.	C	+ +	-	+ +	-	+ + +	-
4.	D	-	+ +	-	-	+	+ +
5.	E	+ +	+	+++	+	-	+
6.	Standard	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
7.	N.S.	-	-	-	-	-	-

Excellent:- + + + , Very Good:- + + , Good:- + , No Activity:- - N.S.:- DMSO

RESULTS AND DISCUSSION

In the present work, five compounds were synthesized and evaluated for their antimicrobial activity. The IR spectra of all synthesized Benzamide derivatives exhibit the absorption bands for C=S, C=N, N-H, C=O, Aliphatic C-H, C-O-C, and C-OH stretching in the region of 1237.73, 1542.04, 3200, 1662.96, 2814.86, 1146.76 and 3500 respectively. The molecular weight of all five synthesized derivatives was 302, 330,326, 368 and 382 of the A, B, C, D and E respectively on the basis of Mass spectral data. The presence of proton in all of five synthesized derivatives has been confirmation the basis of ^{1}HNMR.

In the Antimicrobial activity, both of the antibacterial and antifungal activities were evaluated. In antibacterial activity the following strains were used *Staphylococcus aureus* (MTCC 83), *Streptococcus pyogen* (MTCC 442), *Escherichia coli* (MTCC443), *Pseudomonas aeruginosa* (MTCC 741). In anti fungal activities the following funguses were used *Aspergillus niger* (MTCC 134), *Candida albicans* (MTCC 183).

All the synthesized compounds were found to be have antibacterial activity. In antibacterial activity the compound A and D were found least active. The compound E was having the best antibacterial activity. Compound A exhibit high activity against *S.aureus.* Compound D showed very good activity against *S.pyogen.* Compound E was found to have excellent activity against *E.coli* also it showed potent activity against *P.aeruginosa.*

In fungicidal studies undertaken it was found that most the compounds were active against *Candida albicans*. Out of the five synthesized compounds studies against *A.niger*, C showed best activity compared with standard compounds and D Showed best activity against *C albicans* compared with standard compounds. In the present study, it was observed that the compounds B and C were having both antibacterial and antifungal activities.

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