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Research Article

SYNTHESIS AND BIOLOGICAL SCREENING OF VARIOUS DIFFERENT DERIVATIVES OF FLUOROBENZOTHIAZOLE INCORPORATED AZETIDINONES

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ABST RACT
Various 1-[-6-fluoro-7-substituted (1, 3)-benzothiazol-2-yl]-2-(4-nitrophenyl) 3-chloro-azetidin-2-one containing different functional groups have been synthesized by condensing aromatic aldehyde with 2-aminobenzothiazole in presence of ethanol , acetic acid ,Hcl .Further it is treated with1,4 dioxan ,chloracetylchloride and triethylamine. The obtained product was then refluxed with various aromatic amines in presence of organic solvent to yield above cited compound. The identities of compounds were confirmed on the basis of their spectral (UV-Vis, IR, [1]HNMR and MASS) data. Further, they have been screened for their antimicrobial, anthelmintic and anti-inflammatory (*in vitro*) activities
KEY WORDS: Benzothiazole, Azetidinone,Antibacterial Activity.

INTRODUCTION

The azetidin-2-one is a hydrolytically sensitive, colourless solid, four membered cyclic amide, which is present in clinically useful penicillin's and cephalosporins. The N-CO distance of 1.38 A^{o} this has been attributed to ring strain and to inhibition of normal amide interaction. They are commonly known as β-lactams, are well known heterocyclic compounds among the organic and medicinal chemists. In present study attempt was made to incorporate azetidinone ring with help of aromatic aldehyde to get potent pharmacological active derivatives. The identities of compounds were confirmed on the basis of their spectral (UV-Vis, IR, [1]HNMR and MASS) data.

A large number of azetidinones possess powerful antibacterial[1], anti-inflammatory[2], anti-microbial[3], anticonvulsant[4], and antitubercular[5] anticancer[6] activities.

MATERIAL AND METHODS

Purity of compounds was checked by TLC. Melting points were determined by open capillaries method and uncorrect. IR spectra (NaCl) are recorded on FTIR (Schimadzu-84005)[7] spectrophotometer using nujol mull technique,[1] HNMR[8], Mass spectrophotometer[9], Analytical studies.

First Step

Synthesis of 6-fluoro-7-chloro-2-amino (1, 3) benzothiazole [10]

20ml glacial acetic acid cooled below the room temperature, were added with 8gm of (0.08mols) of potassium thiocyanate and 1.45g (0.01 mol) of 3-chloro-4-fluoroaniline.The mixture was placed in water bath and stirred in magnetic stirrer while 1.6ml of bromine in 6ml of glacial acetic acid was added. The solution was stirred for 12 hrs. at room temperature and slurry was heated at 85^{0}c on hot plate then it was allowed to stand overnight, during which period an orange precipitate settles at the bottom. The orange residue was extracted with 6ml water and 10ml glacial acetic acid separately then the combined and alkalized with ammonia solution. A dark yellow precipitate was filtered and crystallized from benzene and alcohol gave yellow plates of aminobenzothiazole. UV 307.4, 269nm, IR 1542cm^{-1}(aromatic C=C) and 3475cm^{-1} (NH_2); 1456 cm^{-1}(thiazole), 1215 cm^{-1}(aromatic-F), 712 cm^{-1}(aromatic-Cl).

Second Step

0.01 mole of 2-aminobenzothiazole with aromatic aldehyde in refluxing flask and add 20ml of ethanol and 3-4 drops of hydrochloric acid / acetic acid refluxed for 3 hrs. The mixture was cooled and poured into cold water filtered off, dried and recrystallized with suitable organic solvent.

Third Step

The above obtained product (0.01mol) in 1,4 dioxan (50ml) was added to well stirred mixture of chloroacetyl chloride (0.012 mol) and triethyl amine (0.02mol) at freezing mixture .The reaction mixture then stirred in magnetic stirrer for 18-20hours at room temperature for 3 days. The pure product was isolated and dried.

Fourth Step[11]

General procedure for targeted molecules

1[6-fluoro-7chloro-(1,3)benzothiazolo-2-yl]-2-(4-nitrophenyl)-3-chloro-azetidin-2-one were treated with equimolar concentrations of various substituted anilines, like primary and secondary, refluxed for 2 hours in the presence of organic solvent. The mixture was cooled and poured into pure water in cold condition. The residue was filtered off and dried.

SCHEME:

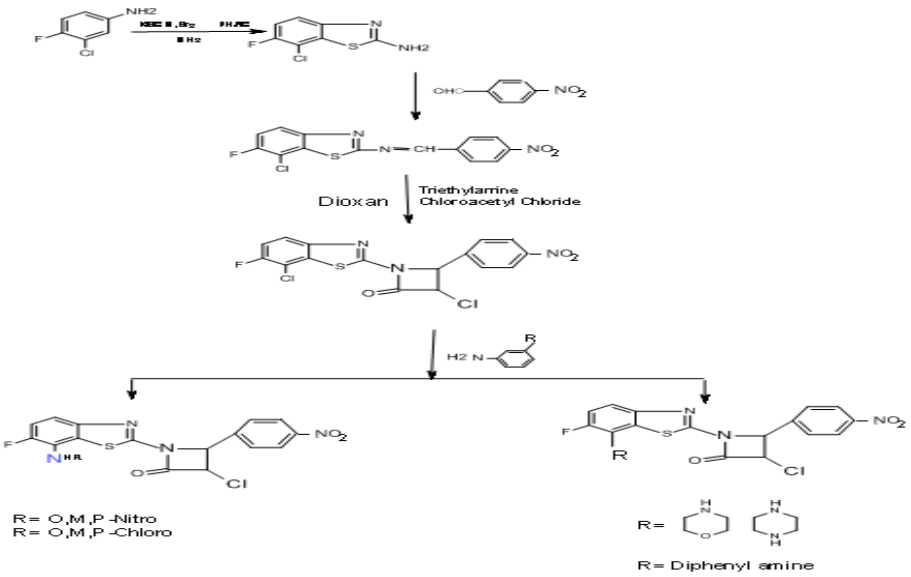

Table No.1: Analytical data of synthesized compounds

Compds	M.P (ºC)	Yield (%)	Molecular Formula	Molecular Wt.	Elemental Analysis Data (Calculated in %)		
					C	H	N
K1	164	65	$C_{22}H_{12}ClFO_5SN_5$	513	51.46	2.33	13.64
K2	172	72	$C_{22}H_{12}ClFO_5SN_5$	513	51.46	2.33	13.64
K3	153	74	$C_{22}H_{12}ClFO_5SN_5$	513	51.46	2.33	13.64
K4	162	69	$C_{22}H_{12}Cl_2FO_3SN_4$	503	52.48	2.38	11.13
K5	152	78	$C_{22}H_{12}Cl_2FO_3SN_4$	503	52.48	2.38	11.13
K6	164	76	$C_{23}H_{13}ClFO_2SN_4$	448	61.60	2.90	12.5
K7	178	67	$C_{20}H_{15}ClFO_4SN_4$	462	51.94	3.24	12.12
K8	182	64	$C_{20}H_{16}ClFO_3SN_5$	461	52.06	3.47	15.18
K9	195	78	$C_{28}H_{17}ClFO_3SN_4$	544	61.76	3.12	10.29
K10	142	62	$C_{22}H_{13}ClFO_3SN_4$	468	56.14	2.77	10.25

Table.No.2. FTIR peak assignments of synthesized compounds

Compounds	IR Absorption bands.(cm^{-1})						
	C=N Str.	Aro.C=C Str.	C-F Str.	NO_2	C-Cl	2^0 Nitrogen	β C-Cl
K1	1620	1455	1200	798	---	1360	760
K2	1640	1460	1235	795	---	1350	735
K3	1630	1450	1230	830	---	1340	740
K4	1625	1452	1220	---	1150	1345	745
K5	1610	1460	1240	---	1160	1370	755
K6	1604	1490	1247	---	---	1350	754
K7	1650	1475	1175	---	---	1375	780
K8	1645	1470	1170	---	---	1400	760
K9	1660	1480	1180	---	---	1380	750
K10	1630	1465	1200	---	---	1375	740

[1]HNMR data of synthesized compounds:

1)2-amino-6-fluoro-7-chloro(1,3)benzothiazole

Protons of aromatic-NH2 groups appeared as a hump at 4.6δ
Aromatic protons appeared as a cluster at 7.2-7.9 δ

2)1[6-fluoro-7-chloro(1,3)benzothiazol-2-yl]-2-(4-nitrophenyl)-3-chloro-azetidin-2-one.

at 7.9 δ Proton CH appeared at 2.5 δ
Proton CH –Cl appeared at 3.0 δ
Aromatic protons appeared at7.5 δ
Aromatic NO2 protons appeared

MASS Spectro]hotometer data of synthesized compounds:

1)2-amino-6-fluoro-7-chloro (1, 3) benzothiazole

Calculated molecular weight =202.

M^+ ion peak=m/zpeak=202,204
(M^+HCN)-m/z=175,177.
[(M^+-HCN)-cl]-m/z=140
[(M^+-HCN)-CHCN]-m/z=148,150

2) Compound B,

1[6-fluoro-7-chloro (1, 3) benzothiazol-2-yl]-2-(4-nitro phenyl)-3-chloro-azetidin-2-one.

Calculated molecular weight =381.

M+1 = 382.5
M+ -F= 382
M+ -O=C-CH-Cl= 305
M+-NHC6H5(Common for all spectra)= 168
M+-F(Common for all spectra)= 148
M+ -HN(Common for all spectra)= 134

Compound K6;

1[6-fluoro-7-p-carboxyl anilino (1, 3) benzothiazol-2-yl]-2-(4-nitrophenyl)-3-chloro-azetidin-2-one.

M+1 = 508.1
M+ -F(508-19=489)= 490.3
M+ -O=C-CH-Cl= 430
M+-=CH-C6H5-NO2 = 302
M+ -COOH= 258
M+- -NHC6H5= 168(Common for all spectra)
M+-F(Common for all spectra)= 148
M+ -HN(Common for all spectra)= 134.

Table No.3.Antibacterial activity

Comp. Code	Mean Zone of Inhibition (in mm)											
	S.aureus		S.faecalis		B.subtilis		E.coli		P.aeruginosa		S.typhi	
	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
Procaine penicillin	**20**	**25**	---	---	**17**	**20**	---	---	**15**	**18**	**10**	**12.5**
Streptomycin	---	---	**18**	**22**	---	---	**17**	**23**	---	---	---	---
K1	11	16	12	17	14	17	14	18	12	16	7	10
K2	15	20	15	21	15	18	15	21	13	16	6.5	10
K3	14	21	16	18	14	19	17	22	14	18	8	11
K4	13	18	14	19	16	20	13	19	13	16	7	9.5
K5	17	22	16	20	13	16	12	20	12	15	6	9
K6	18	23	17	22	12	15	16	22	14	16	7	11
K7	16	21	16	21	15	20	14	19	12	17	7.5	11
K8	19	22	14	20	14	18	11	21	13	15	8	10
K9	12	14	18	21	13	16	10	15	14	17	7	10
K10	19	24	15	17	11	14	16	22	10	12	6	9

RESULTS AND DISCUSSION

1[6-fluoro-7substituted-(1, 3) benzothiazolo-2-yl]-2-(4-nitrophenyl) -3-chloro azetidin-2-one known for their good antimicrobial properties. Antimicrobial studies were carried out and the result obtained is discussed below.

Antimicrobial activity of various substituted benzothiazole azetidinone (100 mg/ml). Among the derivatives screened the following observations were made in comparison with the standard Procaine penicillin, Streptomycin and Griseofulvin (50/100 mg/ml).

Of the derivatives synthesized, K1,K2, K3, K4, K5, K6,K7, K8, K10 showed good degree of antibacterial activity against the strains of *S.aureus, S.faecalis, B.subtilis* (G+ve) and *E.coli, P.aeruginosa, S.typhi* (G-ve) and anti-fungal activity against *C.albicans, A.flavus, and A.niger* as compared to the standard drugs respectively .

CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the antimicrobial activity of novel derivatives. The yields of different synthesized compounds were found to be in the range of 58-78% and the characterization was done by melting point, and TLC. Characteristic IR bands show several functional vibrational modes which confirm the completion of reaction. All the test compounds showed good, moderate and poor biological activity.

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