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Synthesis and Characterisation of azetidin-2-ones and thiazolidin-4-ones encompassing benzothiazole

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Abstract
Various 7-chloro-6-fluoro-2-arylidenylaminobenzo(1,3)thiazole (2a-h) have been synthesized by the condensation of 7-chloro-6-fluoro-2-aminobenzo(1,3)thiazole (1) with different aromatic aldehydes. The Schiff's bases on reaction with acetyl chloride, chloroacetyl chloride and phenyl acetyl chloride yielded 1-(7-chloro-6-fluorobenzothiazol-2-yl)-3,4-substituted-aryl-azetidin-2-ones (3a-x). Similarly, cyclization of Schiff's base with thioglycolic acid furnished 3-(7-chloro-6-fluoro-benzothiazol-2-yl)-2-substituted-arylthiazolidin-4-ones (4a-h). The structures of the newly synthesized compounds have been established on the basis of their spectral data and elemental analysis.

Keywords: Benzothiazole, azetidinones, thiazolidinones.

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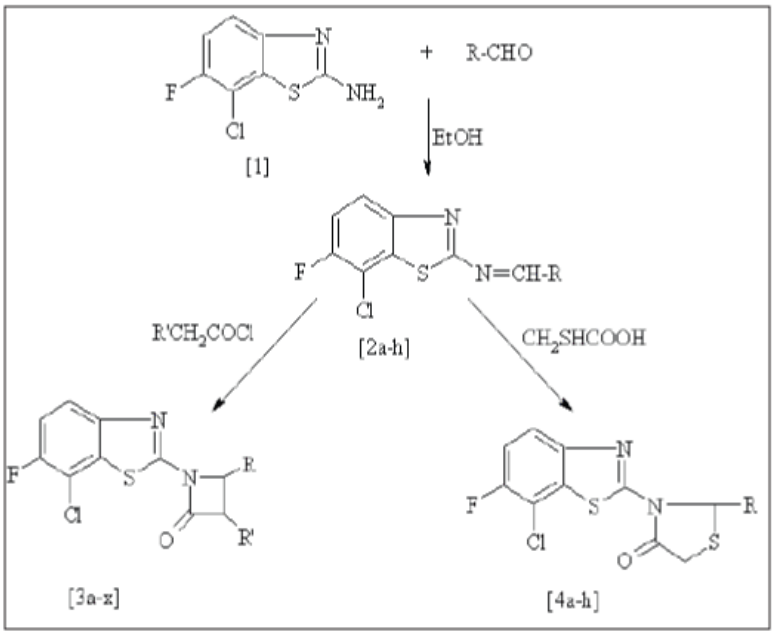
I. Introduction

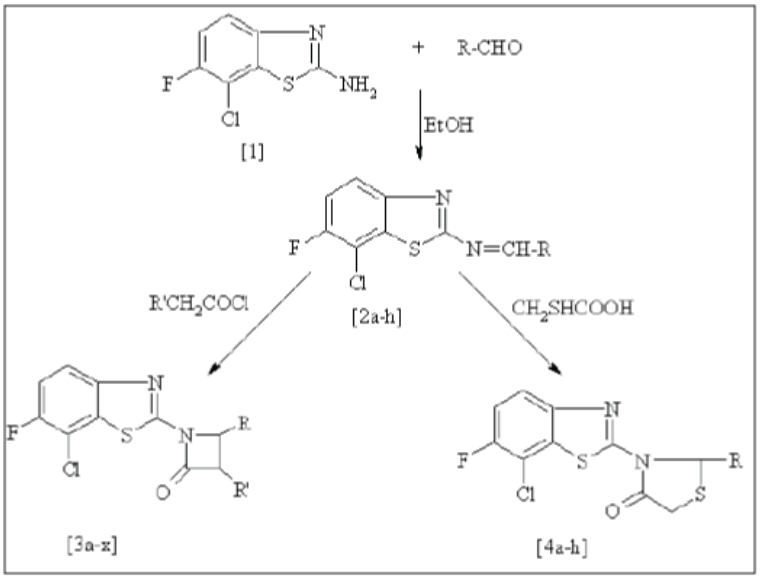
The β-lactam antibiotics are extensively used for bacterial infections. The cephalosporins [1] have withstood the onslaught of microorganisms and have come to be physician's arsenal in combating a wide range of microbial infections. Moreover various β-lactams are associated with antitumor [2], antitubercular [3], antiinfl ammatory [4] activities. Similarly, thiazolidinones have attracted considerable attention as they are also enrolled with wide range of pharmacological activities like anticonvulsant [5], analgesic [6] and antiinfl ammatory [7] activities. In continuation of our studies on benzothiazole [8,9], we have synthesized benzothiazole moiety linked to bioactive β-lactam and thiazolidinone rings, to analyse their biological profile.



Scheme 1: Synthetic scheme of Schiff's bases, azetidine-2-ones and thiazolidin-4-ones
R= C_6H_5, C_6H_4-4-OCH_3, C_6H_4-2-OH, C_6H_4-3-OCH_3, C_6H_4-4-$N(CH_3)_2$, C_6H_4-2-NO_2, C_6H_4-3Cl and C_4H_3O (2-furyl). R′ = H, Cl and C_6H_5.

The starting material for the synthesis of desired compounds is 7-chloro-6-fluoro-2-aminobenzo(1,3) thiazole [10] (1), which on treatment with different aromatic aldehydes in concentrated sulphuric acid yields the respective Schiff bases (2a-h). The Schiff bases were separately reacted with substituted acetyl chloride and mercaptoacetic acid produced 1-(7-chloro-6-fluorobenzothiazol-2-yl)-3,4-substitutedarylazetidin-2-ones (3a-x) and 3-(7-chloro-6-fl uorobenzothiazol- 2-yl)-2-substituted–arylthiazolidin-4-ones (4a-h) respectively **(Scheme 1)**. The newly synthesized compounds were characterized by spectroscopic data and elemental analysis .

II. Materials and Methods



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Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on FTIR Shimadzu 1400S and NMR spectra were recorded on AMX-400 in CDCl3/DMSO-d6 using TMS as internal standard (chemical shifts in δ ppm). Satisfactory elemental analyses were obtained for all the compounds and were within ±0.4% of the theoretical values. The reactions were monitored on TLC with solvents of varying polarity and the spots were located by iodine vapors.

To a mixture of 7-chloro-6-fl uoro-2-aminobenzo(1,3) thiazole (1) (0.1 mol) and benzaldehyde (0.1 mol), was added two drops of concentrated sulphuric acid and the reaction mixture was refluxed in ethanol (25 ml) for 3 h. The contents were poured into cold water. The Schiff's base (2a) thus formed was fi ltered off and recrystallised from hot ethanol to give 7-chloro-6-fl uoro-(2-hydroxy-benzylidine)-benzo(1,3) thiazole. IR (vmax): 1650(C=N) and 3480 (Ar-OH). 1H NMR(CDCl3): 9.25 (s, 1H, -N=CH), 12.1 (s, 1H, Ar-OH), 7.0-8.0 (m, 6H, Ar-H). Similarly, the other Schiff's bases (2b-h) were prepared.

The mixture of Schiff's base (2a) (2.90 g, 0.01 mol) and triethylamine (1.02 ml, 0.01 mol) was dissolved in dioxane (40 ml) and kept in an ice bath. To this, cold solution of acetyl chloride (0.72 ml, 0.01 mol) was added slowly at 00, stirred for 10-12 h and left over night. The precipitated triethylammonium chloride was fi ltered off and dioxane was removed by distillation. Residue was poured into cold water; the resulting solid was dried and crystallized from ethanol to give 3a. The Schiff's bases (2b-h) were treated separately with acetyl chloride to get 3b-h. Similarly, 3i-p and 3q-x were prepared by treating 2a-h with chloroacetyl chloride and phenyl acetyl chloride separately. 3i IR (vmax): 1650(C=O). 1H NMR(CDCl3): 3.7(d, 1H, -NCH), 3.9 (d, 1H, CHCl), 7.2-7.9 (m, 6H, Ar-H); 3q IR(vmax): 1660 (C=O stretch) azetidinone ring, 1H NMR(CDCl3): 3.1 (d, 1H, -NCH), 3.7 (d, 1H, CH-Ar), 7.0-7.8 (m, 12H, Ar-H).

A mixture of Schiff's base 2a (2.90 g, 0.01 mol) and mercaptoaceticacid (1.19 ml, 0.01 mol) was dissolved in dioxane (20 ml). A pinch of anhydrous zinc chloride was added and then refluxed for 8 h. Separated solid was filtered, washed with sodium bicarbonate solution and then recrystallised from ethanol. Similarly, the other compounds (4b-h) were prepared. 4a IR (vmax): 1660 (C=O) thiazolidine ring. 1H NMR(CDCl3): 3.8 (s, 2H, CH2), 3.6 (s, 1H, -NCH), 7.2-7.6 (m, 7H, Ar-H). Physical data of newly synthesised compounds is given in **Table 1**.

Table 1: Physical data of the synthesised compounds

Compd No	R	R1	Mp (O)	Yield (%)	Mol. formula*
2a	-	-	165	78	C14H8ClFN2S
2b	-	-	160	76	C15H10ClFN2OS
2c	-	-	175	81	C14H7ClFN2OS
2d	-	-	155	69	C15H10ClFN2O2S
2e	-	-	180	75	C16H13ClFN3S
2f	-	-	168	72	C14H7ClFN3O2S
2g	-	-	170	68	C14H7Cl2FN2S
2h	-		198	70	C12H6ClFN2OS
3a	C6H5	H	188	50	C16H10ClFN2OS
3b	C6H4 -4-OCH3	H	185	63	C17 H12ClFN2O2S
3c	C6H4-2-OH	H	190	58	C16H10ClFN2O2S
3d	C6H3-4-OH, 3-OCH3	H	170	63	C17H12ClFN2O3S
3e	C6H4-4-N(CH3)2	H	195	70	C18H15ClFN3OS
3f	C6H4-2-NO2	H	179	80	C16H9ClFN3O3S
3g	C6H4-3-Cl	H	180	73	C16H9Cl2FN2OS
3h	C4H3O (2-furyl)	H	205	68	C15H8ClFN2O2S
3i	C6H5	Cl	150	72	C15H9ClFN2OS
3j	C6H4-4-OCH3	Cl	200	69	C15H11Cl2FN2OS
3k	C6H4-2-OH	Cl	194	55	C16H9Cl2FN2O2S
3l	C6H3-4-OH, 3-OCH3	Cl	187	62	C17H11Cl2FN2O3S
3m	C6H4-4-N(CH3)2	Cl	198	65	C18H14Cl2FN3OS
3n	C6H4-2-NO2	Cl	202	71	C16H8Cl2FN3OS
3o	C6H4-3-Cl	Cl	170	82	C16H8Cl3FN2OS
3p	C4H3O (2-furyl)	Cl	210	72	C14H7Cl2FN2O2S
3q	C6H5	C6H5	215	82	C22H14ClFN2O2S
3r	C6H4-4-OCH3	C6H5	216	73	C23H16Cl2FN2O2S
3s	C6H4-2-OH	C6H5	210	54	C22H16ClFN2O3S
3t	C6H3-4-OH, 3-OCH3	C6H5	235	63	C22H16ClFN2O3 S

3u	C6H4-4-N(CH3)2	C6H5	208	68	C24H19ClFN3O3S
3v	C6H4-2-NO2	C6H5	193	75	C22H13ClFN3O3S
3w	C6H4-3-Cl	C6H5	218	70	C22H13Cl2FN2OS
3x	C4H3O (2-furyl)	C6H5	219	73	C20H12ClFN2O2S
4a	C6H5	-	191	82	C16H10ClFN2OS2
4b	C6H4-4-OCH3	-	118	85	C17H12ClFN2O2S2
4c	C6H4-2-OH	-	180	80	C16H9ClFN2O2S2
4d	C6H3-4-OH, 3-OCH3	-	157	84	C17H12ClFN2O3S2
4e	C6H4-4-N(CH4)2	-	142	78	C18H15ClFN3OS2
4f	C6H4-2-NO2	-	175	74	C16H9ClFN3OS2
4g	C6H4-3-Cl	-	170	70	C16H9Cl2FN2OS2
4h	C4H3O (2-furyl)	-	186	65	C14H8ClFN2O2S2

III. Results and Discussion

Two new series of compounds namely substituted azetidinones (3a-x) and thiazolidinones (4a-h) possessing fluoro-benzothiazoles have been synthesized by using experimental protocol as shown in **Scheme 1**. All the derivatives were supported by spectral data. The IR and 1H-NMR are in agreement with the proposed structures.

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