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Synthesis, characterization and biological evaluation of some novel 6-fluoro benzothiazole substituted thiazolidinones as anthelmintic activity

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ABSTRACT

Some 3-(7-Chloro-6-fluoro benzo [d] thiazol-2-yl)-2-(4-Chlorophenyl) thiazol 1,3 lidin-4-one have been synthesized by the reaction of substituted -2-aminobenzothiazole with aromatic amines (para amino benzoicacid, diphenylamine, morpholine, dimethylamine and diethylamine) followed by condensation with mercaptoacetic acid. All the synthesized compounds were characterized by elemental analysis, IR Spectra, ^{1}H NMR and Mass Spectral studies. These were screened for anthelmintic activity.

Key words: Benzothiazole, thiazolidinones, anthelmintic activity.

INTRODUCTION

Nitogen and sulfur containing heterocycles play an important role, not only for life sciences, but also in many other industrial fields related to special and fine chemistry. The survey of literature related to benzothiazole and thiazolidinone derivatives show that compounds with these nuclei have vast medicinal importance in the fiels of pharmaceutical chemistry. Benzothiazole derivatives possess a wide spectram of biological activitiers such as antimicrobial[1], anti-inflammatory[2], antitubercular[3,4], anticancer[5] etc. the chemistry of thiazolidin-4-one ring systems is of considerable interest as it is a a core structure in various synthetic pharmaceuticals diaplaying broad spectram of biological acivities[6]. Thiazolidin-4-one a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus)which possess almost all types of biological activities such as anti-HIV agent[7], anti-diarrhoeal[8], anti-convulsant[9], anti-diabetic[10].

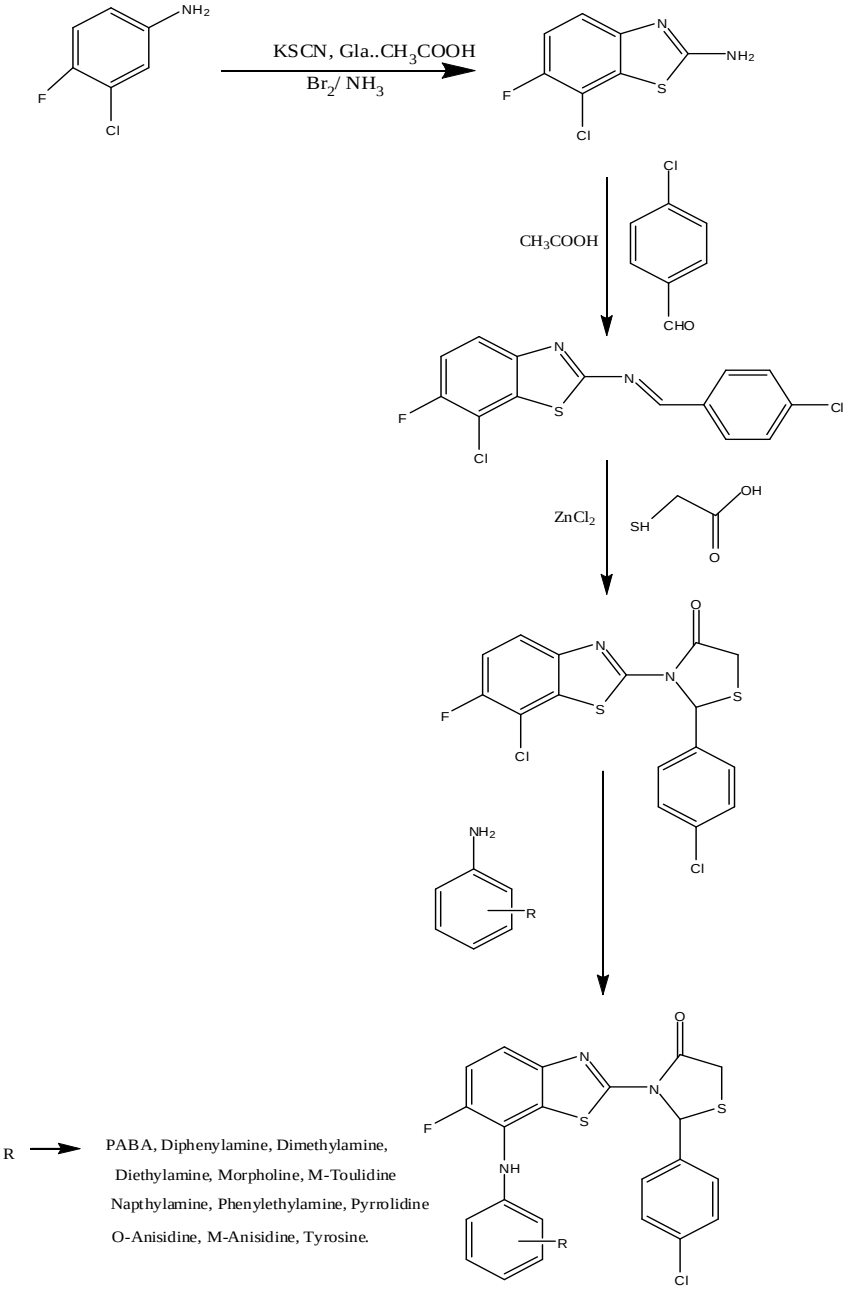
Looking at the importance of these heterocyclic nuclei, it is thought of interest to accommodate thiazolidin-4-one and 2-aminobenzthiazole moieties in single molecular frame work and screen them for there various biological activities. In continuation to our research work on benzothiazole derivatives we are reporting the synthesis and antibacterial activities of substitutes 3-(7-Chloro-6-Fluoro benzo [d] thiazol-2-yl)-2-(4-Chlorophenyl) thiazol 1,3 lidin-4-one. 2-amino-5-substituted benzothiazoles on reaction with substituted aromatic aldehyde give 7-Chloro-N-(4-Chloro benzylidine)-6-Fluoro benzo [d] thiazole-2-amine. Which on reaction with Mercaptoacetic acid gives 3-(7-Chloro-6-Fluoro benzo [d] thiazol-2-yl)-2-(4-Chlorophenyl) thiazol 1,3 lidin-4-one. The structures of all the synthesized compounds established on the basis of spectroscopic and analytical data.

MATERIALS AND METHODS

All the chemicals and solvents used, were dried and purifie d by standard methods, and moisture was excluded from the glass apparatus using $CaCl_2$ drying tubes. The melting points were determined open capillary tubes with electronic melting point apparatus. Melting points were determined open capillary tube and are uncorrected. FT-IR(KBr) spectra were recorded on SHIMADZU FTIR-8400 S spectrophotometer. ^{1}H NMR spectra of synthesized

compounds were recaoded on Brukers spectrophotometer at 300 MHz frequency in deuterated chloride($CDCl_3$) as well as Dimethyl sulfoxide (DMSO) using tetramethylsilane(TMS) as internal standared (chemical shift δ in ppm). All the compounds were prepared by conventional method.

Synthetic Scheme



Synthesis of 2-amino-6-fluoro-7-chloro(1,3)benzothiazole:
To glacial acetic acid (20ml) cooled below room temperature were added 8gm(0.08mol) of potassium thiocyanate and 1.45gm (0.01mol) of fluorochloro aniline. The mixture was placed in a water bath and stirred with magnetic stirrer while 1.6ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rises beyond the room temperature. After all the bromine was added(105min) the solution was stirred for 2hrs below room temperature for 10hrs, it was than allow to stand over night, during which period an orange precipitate settled at bottom, water (6ml) was added quickly and slurry was heated at 85^{0}C and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml glacial acetic acid and heat again to 85^{o}c and filter hot. The combined filterate was cooled and neutralized with ammonia solution to the p^H range 6.0. A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) ratio after treatment with animal charcoal at 80^{o}c.

Synthesis of 7-chloro-N-(4-chlorobenzylidene)-6-fluoro benzo[d]thiazol-2-amine:
A Mixture of compound (1)(0.01mol) and substituted chloro banzaldehyde (0.02mol) and 2-3 drops of glacial acetic acid in methanol(20ml) was refluxed on a water bath for about 5hrs. the solid was separated and recrystalised from ethanol.

Synthesis of 3-(7-chloro-6-fluoro benzo[d]thiazol-2-yl)-2-(4-chloro phenyl)thiazo 1,3-lidin-4-one:
A Mixture of compound(2) (0.01mol)in ethanol (50ml) and mercaptoacetic acid (0.01mol) with pinch of Zinc chloride was refluxed on water bath for 8hrs. The solid from recrystalised from methanol and chloroform(1:1) mixture to give compound (3).

Synthesis of title compounds BT (1-5):
It was treated with equimolar quantities of various substituted P-amino benzoic acid, Diphenylamine, Dimethylamine, Diethylamine, Morpholine, m-toulidine, napthalamine, phenylethylamine, pyrrolidine, o-anisidine, m-anisidine, and tyrosine. Compounds were refluxed for 2hrs in oil bath in presence of 30ml, N,N-dimethylformide(DMF). the mixture was cooled and poured in to crushed ice. the solid separated and filtered off, dried and recrystalised from alcohol and benzene.

Anthelmintic activity:
Test samples of thw drugs was prepared at the concentrations 50, 100 and 150 µg/ml in DMSO and six earthworms of approximately equal size (samw type) were placed in each 9cm petridish containing 25ml of above test solution of prepared compounds. Albendazole was used as a reference standard and DMSO as a control. All the test and standared drug solutions were prepared freshly before starting the experiment. Observations were made for the time taken for paralysis was noted when no movement of any sort could be observed expect when the worms were shaken vigorously. Time for death of forms were recorded after ascertaining that warm neither moved when shaken vigorously nor when dipped in warm water(50^{o}c). all the results were shown in table and expressed as a mean ± SEM of six worms in each group.

RESULTS AND DISCUSSION

3-(2-(4-chlorophenyl)-4-oxothiazolidine-3-yl)-6-fluorobenzo[d]thiazol-7-yl amine)benzoic acid:
Yield 32%; mp 96^{o}c; IR(KBr/cm^{-1})absorption band at 1544(c=c),1570(C=N),1067(C-F),743(C-Cl),1644(C=O of thiazolidinone ring), 1192(C-S); ^{1}H NMR (300MHz,DMSO) 6.43-7.41(Ar-OH), 3.82CH_2, 12.21(OH)

2-(4-chlorophenyl)-3-(7-(dimethylamino)-6-fluorobenzo[d]thiazol-2-yl)thiazolidin-4-one:
Yield 34.6%; mp 69^{o}c; IR (KBr/cm^{-1}) absorption band at 1500(C=C), 1601(C=N), 1083(C-F), 1665(C=O of thiazolidinone ring)1186(C-S); ^{1}H NMR (300MHz,DMSO)6.82-7.39(Ar-H), 3.09(CH_3), 8.98(CH_2),

2-(4-chlorophenyl)-3-(7-(diethylamino)-6-fluorobenzo[d]thiazol-2-yl)thiazolidin-4-one:
Yield 37%; mp 88^{o}c; IR (KBr/cm^{-1}) absorption band at 1583(C=C), 1589(C=N), 1058(C-F),1733(C-Cl), 1652(C=O of thiazolidinone ring)1135(C-S); ^{1}H NMR (300MHz,DMSO)6.76-7.13(Ar-H), 3.71(CH_2), 2.63(CH).

2-(4-chlorophenyl)-3-(6-fluoro-7-morpholinobenzo[d]thiazol-2-yl)thiazolidin-4-one:
Yield 39%; mp 101^{o}c; IR (KBr/cm^{-1})absorption band at 1446(C=C), 1543(C=N), 1066(C-F), 756(C-Cl), 1644(C=O of thiazolidinone ring)1190(C-S); ^{1}H NMR (300MHz,DMSO) 6.85-7.29(Ar- H), 4.28(CH_2), 3.48(CH_2).

2-(4-chlorophenyl)-3-(6-fluoro-7-(O-tolylamino)benzo[d]thiazol-2-yl)thiazolidin-4-one:
Yield 40%; mp 131^{o}c; IR (KBr/cm^{-1})absorption band at 1501(C=C), 1621(C=N), 1107(C-F), 777(C-Cl), 1621(C=O of thiazolidinone ring)1180(C-S); ^{1}H NMR (300MHz,DMSO) 6.41-7.09(Ar-H), 3.29(CH_2), 9.49(NH).

Table 1. Anthelmintic activity of synthesized compounds

S.No	Name	Time in seconds					
		For paralysis concentration			For death concentration		
		50µg/ml	100µg/ml	150µg/ml	50µg/ml	100µg/ml	150µg/ml
1	Control	2-8			10		
2	Albendazole	1-4			5		
3	BT 1	3-4	2-6	2-3	10	8	6
4	BT 2	2-5	2-4	2-2	9	7	5
5	BT 3	2-8	2-5	2-4	10	8	6
6	BT 4	2-6	2-8	1-7	9	7	6
7	BT5	3-5	2-3	2-2	8	7	6
8	BT 6	3-9	1-8	1-4	14	11	9
9	BT 7	2-6	2-5	1-3	12	11	8
10	BT 8	2-6	2-4	1-2	13	11	9
11	BT 9	3-5	1-5	1-2	10	8	6
12	BT 10	2-8	2-7	2-1	11	9	8
13	BT 11	2-5	1-4	1-2	10	9	7
14	BT 12	2-9	1-8	1-6	11	9	6

CONCLUSION

All the newly synthesized compounds were screened for anthelmintic activity at a concentration of 50, 100, 150 µg/ml using Albendnazole as a standard and DMSO to a control. The data in the table indicate that among the synthesized compounds BT 6 and BT 7 possessed good activity. However, the activities of the tested compounds much less than those of standard anthelmintic agents used. From the results of various biological activity it is clear that these compounds would be of better use in drug development.

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