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Synthesis and Biological, Pharmacolgical Activites of Bioactive Benzothiazole Deravatives.

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Research Article

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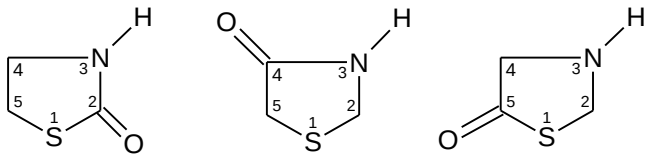
ABSTRACT

2-amino-6-fluoro-7-chloro (1,3) benzothiazoles are treated with aldehydes to get Schiff's base (Azomethine) in presence of ethanol and HCl, then all the Schiff's bases are separately refluxed with thioglycolic acid in presence of the solvent 1,4-dioxane and triturated with $NaHCO_3$ solution results to give parent oxothiazolidine.The resulted azomethine (Schiff's base) are treated with chloro acetyl chloride, triethylamine in presence of dioxane results gives the parent compounds of azetidinone. The identities of compounds were confirmed on the basis of their spectral (IR, ^{1}HNMR and MASS) data further, they have been screened for their antifungal and anti-inflammatory activities.

INTRODUCTION

The rapid progress of organic Fluorine chemistry [1,2,3,4,5] since 1950 has been translated as a pathfinder to invent useful biodynamic agents in Medicinal and Biochemistry.The new generation antibiotics like Norfloxacin, Ciproflaxacin, Flufloxacin, Sporfloxacin and Ofloxacin which were incorporated with fluorobenzene moiety proved their efficacy as potent bio active molecules.

Thiazolidinones [6,7,8] are the derivatives of thiazolidine, which belongs to an important group of heterocyclic compounds. Thiazolidinones, with carbonyl group at 2, 4 or 5 have been subjected to extensive study in the recent past.



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Numerous reports have appeared in the literature, which highlight their chemistry and use. Diverse biological activities such as bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, anti-tuberculosis, anti-inflammatory, antithyroidal, potentiation of pentobarbital induced of sleeping time, etc., have been found to be associated with thiazolidinone derivatives. In recent years several new methods for the preparation of thiazolidinone derivatives and reactions have been reported in the literature. Thiazolidinones, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds, e.g., thiazole, benzothiophenes, triazinones etc. These advances warrant reviewing the chemistry and biological properties of various 4-thiazolidinones

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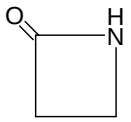
Azetidinone [9,10,11] is a 4 membered cyclic amide, which is present in the clinically useful penicillins and cephalosporins.



2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among the organic and medicinal chemists.The activity of the famous antibiotics such as penicillins, cephalosporins, monobactams and carbapenems are attributed to the presence of 2-azetidinone ring in them. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring. Such biological activities include antimicrobial, anti-tubercular, carbonic anhydrase inhibitors, local anesthetics, anti inflammatory, anthelmintic, anticonvulsant, hypoglycemic activity.

Based on the above observations we have synthesized some Fluoro-Benzothiazole incorporated with Thiazolidinones and Azetidinone derivatives starting with fluoro-chloro-aniline, in hope of getting pharmacological agents with broad spectrum of clinical activity.

MATERIALS AND METHODS

Melting points were determined by open capillary tube method and are uncorrected. T.L.C. was run on silica gel G plates using butanol, ethyl acetate and chloroform (1:2:1) as developing solvent for the purity of the compounds. I.R. Spectra were recorded on Shimadzu FTIR Spectrophotometer by using NUJOL MULL technique.

Synthesis of 2[(7-chloro-6-fluoro-1,3-benzothiazol-2yl)amino]-N[arylidene] acetohydrazides (VIII)

An equimolar (0.01 mole) each mixture of 2-[(7-chloro-6-fluoro-1,3 benzothiazole-2-yl) amino] aceto hydrazide (VI) and appropriate aromatic aldehyde (VII) in ethanol (25 ml) containing 2-3 drops of acetic acid was heated under reflux on a water bath for 3 – 4 hrs. The solvent was distilled off under reduced pressure to a possible extent and residue was poured into ice cold water to get the product. It was filtered, washed with portion of a cold water and dried. The crude product was purified by recrystallisation from ethanol.

Synthesis of 2-[(7-chloro-6-fluorobenzothiazol-2yl)amino]-N(2-aryl-4-oxothiazolidine-3-yl) acetamide (IX)

A mixture of 2[(7-chloro-6-fluoro-1,3-benzothiazol-2yl)amino]-N-[arylidine] acetohydrazides (VIII; 0.001 mole) and mercaptoacetic acid (0.001 mole) was dissolved in dioxane (20 ml) and pinch of anhydrous zinc chloride was added. The reaction mixture was heated under reflux for 12 hrs. and the solvent was removed as far as possible. The residue was cooled triturated with crushed ice (50 gm). The solid separated was filtered, washed with 5% sodium bicarbonate solution until no effervescence were observed and than with portion of a cold water. The crude product was purified by recrystallisation from ethanol to get a crystalline compound

Synthesis of 2[(7-chloro-6fluorobenzothiazole-2-yl)amino]-N (4-aryl-3-chloro-2-oxoazetidin-1-yl) acetamide (X)

To a mixture of 2[(7-chloro-6-fluoro-benzothiazol-2yl)amino]-N-[arylidene] acetohydrazides (VIII; 0.001 mole), triethylamine (0.003 mole) dissolved in dioxane (25 ml) and chloroacetylchloride (0.0012 mole) was added drop wise while cooling and stirring. The reaction mixture was stirred for 14 hrs. at room temperature and solvent was removed under reduced pressure. The residue was cooled and triturated with crushed ice (50 gm). The solid separated was filtered, washed with small portion of cold water and dried. The product was purified by recrystallisation from aqueous ethanol to get a pure crystalline compound.

Biological Activities

Anti-fungal Activity

The synthesized compounds are screened against fungi like *Candida albicans* and *Aspergillus niger* to know their antimicrobial activity (by cup plate method) [12,13,14,15,16,17,18].

Anti-inflammatory activity (*in-vitro)*

The synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique which was studied according to Jayachandran E. and G.M. sreenivasa with slight modification.

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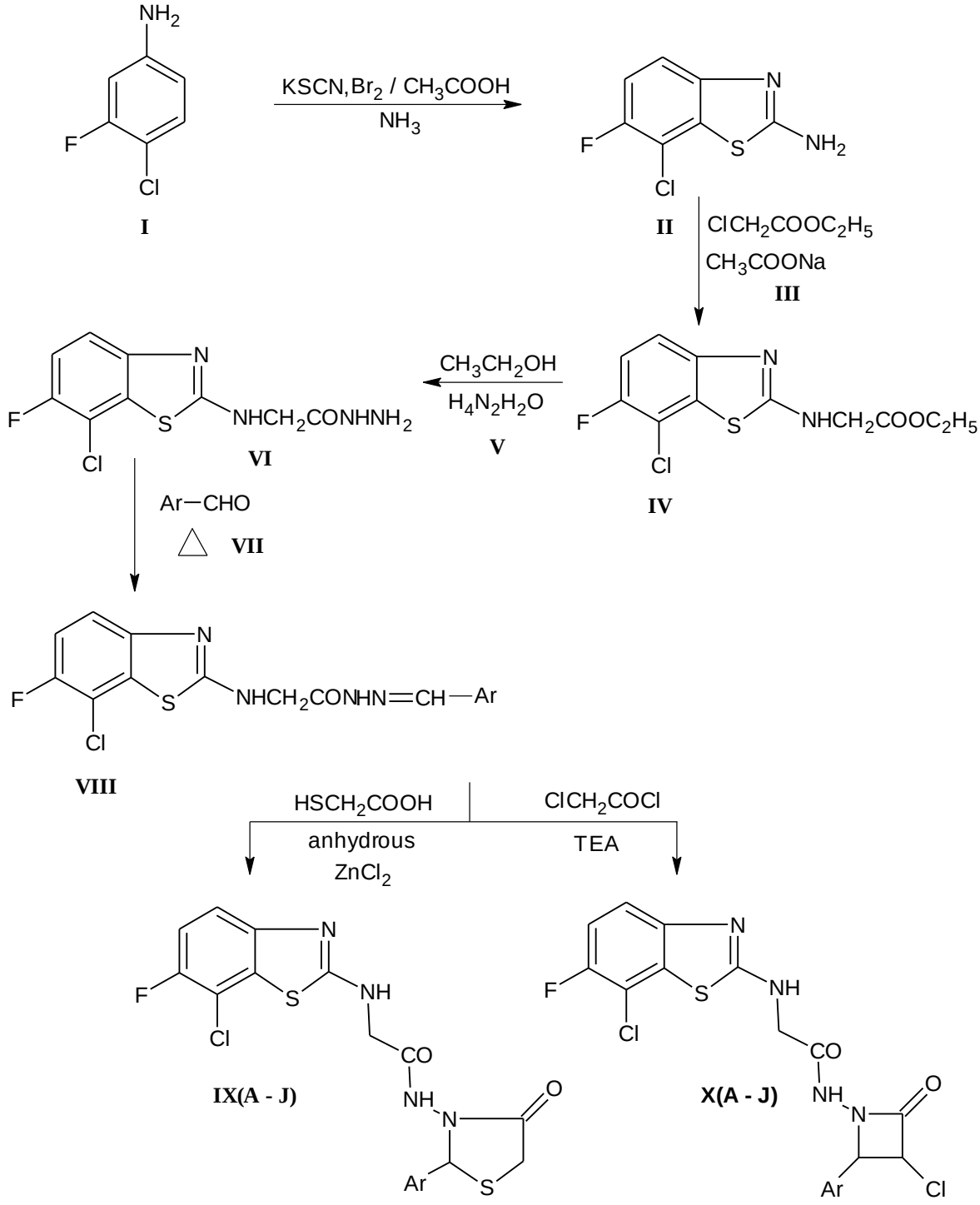
The standard drug and test compounds were dissolved in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0%. Test solution (1 ml) containing different concentrations of drug was mixed with 1 ml of 1% mM Bovine albumin solution in phosphate buffer and incubated at $27^0 \pm 1^0$C in incubator for 15 min. Denaturation was induced by keeping the reaction mixture at $60^0 \pm 1^0$C in water bath for 10 min. After cooling the turbidity was measured at 660 nm (UV-Visible Spectrophotometer SL-159, Elico India Ltd.). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken. The Ibuprofen was used as standard drug [19,20,21,22,23].



SCHEME

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RESULTS AND DISCUSSION

Synthesized compounds of 2-[(7-chloro-6-fluoro-benzothiazol-2-yl)amino]-N-[2-aryl-4-oxothiazolidin-3-yl] acetamide and 2-[(7-chloro-6-fluoro-benzothiazol-2-yl)amino]-N-[4-aryl-3-chloro-2-oxoazetidene-1-yl) acetamide have been screened for following.

Antifungal Activity

The same types of compounds were subjected to antifungal activity. For these activities *Candida albicans* and *Aspergillus flavus* fungal organisms were used. The Griseofulvin were used as a standard. Standard and synthesized compound were tested at two conc. viz., 50 μg/ml and 100 μg/ml.

The compounds have shown activity but non of them have shown better activity than the standard. Some of the compounds like XB, XH and XJ have shown activity almost equal to standard against *Aspergillus flavus* organism at 100 μg/ml conc. and XB, XH, XJ have shown activity near to standard at 50 μg/ml conc. And the compounds IXI, XA, XB have shown activity near to standard against *Candida albicans* organisms at 100 μg/ml conc. and at 50 μg/ml conc. The remaining compounds have shown very low activity.
From this it is concluded that the synthesized compounds have shown better activity against *Aspergillus flavus* than *Candida albicans*.

Anti-Inflammatory Activity

Synthesized compounds of 2-[(7-chloro-6-fluoro-benzothiazol-2-yl)amino]-N-[2-aryl-4-oxathiazolidin-3-yl] acetamide and 2-[(7-chloro-6-fluoro-benzothiazol-2-yl)amino]-N-[4-aryl-3-chloro-2-oxoazetidene-1-yl) acetamide have been evaluated for anti-inflammatory activity *(in-vitro*). The results are presented in table reveals that some of compound promisingly inhibit albumin denaturation in comparison with standard drugs, ibuprofen exhibited 80% and diclofenac sodium exhibited 88% inhibition of albumin denaturation.

Azetidinone series showed 5 compounds and thiazolidinone series 5 compounds having more than 25% inhibition of albumin denaturation. Out of that IXJ and XD showed 53% and 45% inhibition of albumin denaturation.

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REFERENCES

1. Feller. R Biologically active fluoro chemicals. J Fluorine Chem 1986; 33: 361-375
2. Greco Micheal N, Hangman William E. Synthesis of benzothiazole hydroxyl ureas as hibitors of 5-lipoxygenase enzymes; Chem Abstr. 1992; 117; 131109 z.
3. Sutoris V. Synthesis of 3-(2-alkoxy carbomyl-ethyl) 2-benzothiazolinones and their regulating activity on the growth of Triticum Oestivum. Chem Abstr. 1991;106:83584f
4. Woltersdrof OW Jr, Schwam H, Bicking JB, Brown SL, DeSolms SJ, Fishman DR, et al. Topically active carbonic anhydrase inhibitors1-o-acyl derivatives of 6-hydroxy benzothiazol 2-Sulfonamide. Chem Abstr. 1989; 111:194656x
5. Scholewald, Ronald D. Sulfonamido benzothiazole derivatives as topical carbonic anhydrase inhibitors. Chem Abstr. 1984; 100:2069678c
6. Patel KH, Mehta AG. Synthesis of novel azetidinone and thiazolidinones derivatives and evaluation of their antimicrobial efficacy. E-J Chem. 2006;3:103-109.
7. Mistry KM, Desai KR. Synthesis of novel heterocyclic 4-thiazolidinone derivatives and their antibacterial activity. E-J Chem. 2004; 1(4):189-193.
8. Zuhal Turgut , Cigdem Yolacan, Feray Aydogan, Emine Bagdatli and Nuket Ocal; Synthesis of new pyrazolothiazole derivatives from 4-thiazolidinones; Molecules. 2007;12:2151-2159.
9. Vijay Kumar MMJ, et al. Synthesis and characterization of novel N-substituted-3-chloro-2- azetidinones as potential anticonvulsant agents. J Biomed Sci Res. 2009;1(1):1-10.
10. Ameya A. Chavan and Nandini R. Pai ; Synthesis and biological activity of N-substituted- 3-chloro-2-azetidinones; Molecules; 2007;(12): 2467-2477.
11. Ujjwal Sahoo, Seth AK, Sen A, Dhanya, Patel J, Chawla R. Synthesis and characterization of certain novel azetidinone derivatives as antibacterial and antifungal agents. Res J Pharm Biol Chem Sci. 2010;1(2) : 102-107.

12. Gurupadaiah BM, Jayachandran E, Shivakumar B, Nagappa AN, Nargund LVG. Synthesis of Fluorobenzothaizolo sulphonamides and their Anti-bacterial activity. Ind J Heterocyclic Chem. 1998; 7: 213-216.
13. Peclzar, Reid, Cohn. Antibiotics and other chemotherapeutic agents Microbiology, TMH ed, TATA-Mcgraw-Hill Publishing House 1989; 466-93.
14. Basavaraja HS, Sreenivasa GM, Jayachandran E, Nargund LVG and Sreenivasa Rao D. Syntheisis of substituted pyrimidino imidazolinones as Antimicrobial agents. Ind J Hetro Chem. 2005; 15: 69-70.
15. Nagendra Rao R, Jayachandran E, Sreenivasa GM and Jyothi TM. Syntheisis of substituted pyrimidino imidazolinones as Antimicrobial agents, Ori J Chem. 2005; 21(2): 327-330.
16. Perumal R, Jayachandran E, Nargund LVG, Shivakumar B, Sreenivasa GM and Shankariah MM. Synthesis of 3-substituted, 1N-substituted phenyl pyrazolo-5-amino-4-carboxamido derivatives for pharmacological activity, Ori J Chem. 2005; 21(2): 377-378.
17. Indian Pharmacopia. 1995.
18. Sreenivasa GM, Jayachandra E and Shivakumar B. Synthesis of 8-fluoro-9- substituted (1,3) benzothaizolo (5,1-b)-3- substituted 1,2,4, Triazoloes. Ind J Hetro Chem. 2004; 14: 89-90.
19. Paul A Insel. Analgesic, antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout, Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. International edition. McGraw-Hill health professions division New York; 1995; pp617-57.
20. Rang HP, Dale MM, Ritter JM. Anti-inflammatory and immuno-supressant drugs, pharmacology, Third Edition, International Student Edition, Churchill Livingstone Edinuburgh 1995; pp246-66.
21. Srinivasa GM, Jayachandran E, Shivakumar B, Sreenivasa Rao D. Synthesis and pharmacological screening of 2-[3-amino,5-s-met carboxamido pyrazol-1-yl]6-fluoro,7-substituted (1,3)benzothiazole. Oriental J Chem. 2004; 20(1); pp103-110.
22. Sreenivasa Rao D, Jayachandran E., Sreenivasa G.M. and Shivakumar B. Inhibition of albumin denaturation and anti-inflammatory activity of 2-[N-*p*-Tolyl sulphonhydrazino]-6-fluoro-7-substituted (1, 3) benzothiazoles. Oriental J Chem. 2005;21(1), pp113-116.
23. Gelios, Rao MNA. Ind J Exp Biol. 1998; 26.