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Synthesis and Characterization of Novel Heterocyclic Compounds

K.M. Shailaja[1], B. Shivakumar*[2] E. Jayachandran[1],G.M. Sreenivasa[1] and Sriranga T[1]
1 S.C.S College of pharmacy, Harapanahalli. Karnataka, India
2. B.L.D.E.A's College of pharmacy, B.L.D.E. University Campus, Bijapur Dist. Karnataka, India

ABSTRACT

2-amino-6-fluoro-7-chloro (1,3) benzothiazoles is treated with six different aldehydes to get six different 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 dioxane and triturated with $NaHCO_3$ solution, as six different parent compounds. The resulted six azomethine (Schiff's base) are treated with chloro acetyl chloride, triethylamine in presence of dioxane results gives six different, the parent compounds were treated with various aromatic primary and secondary amines in presence of Dimethyl formamide (DMF) gives various derivatives. Further, they have been screened for their antimicrobial, antiinflammatory *(in-vitro* and *in-vivo*) anticonvulsant and anthelmintic activity by standard method.

Keywords; Fluorine, Schiff's base, Thiazolidinone and Azetidinone

*Corresponding Author Email: drbsk_2007@yahoo.com
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INTRODUCTION

The rapid progress of organic Fluorine chemistry[1-5] 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[6-8] 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 subject to extensive study in the recent past. 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.

Azetidinone[9-11] 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 point was determined by open capillary tube method and are uncorrected. T.L.C was run on silica gel G plates using Petrolium ether : Ethyl acetate [5:1] as developing solvent for the

purity of the compounds. I.R. Spectra were recorded on Shimadzu FTIR Spectrophotometer by using NUJOL MULL technique.

A mixture of Schiff's base (0.01 mol) and 2-mercaptoacetic acid (Thioglycollic acid) of 0.025mol was heated on an oil bath at 115 – 116^{o} C for 12 hours. The reaction mixture was cooled and triturated with 10% sodium bicarbonate solution. The separated solid was filtered and washed with excess of water and then recrystallized from alcohol.

Thiazolidine was treated with equimolar quantities of various substituted aniline, morpholine, piperazine, diphenylamine, refluxed for 2 hours in presence of N-N', dimethyl formamide (DMF). The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and recrystallized from alcohol and benzene.

A solution of Schiff's base (0.01 mol) in 1,4- dioxone (50 ml) was added to well stirred mixture of chloroacetyl chloride (.95 ml, 0.012 mol) and triethyl amine (1.08 ml, 0.02 mol) at 0^{o} C. the reaction mixture was then stirred for 18-20 hours and kept aside for three days at room temperature. The product was poured in to the ice water, filter it and recrystallized from N,N'-dimethy formamide (DMF).

BIOLOGICAL ACTIVITIES

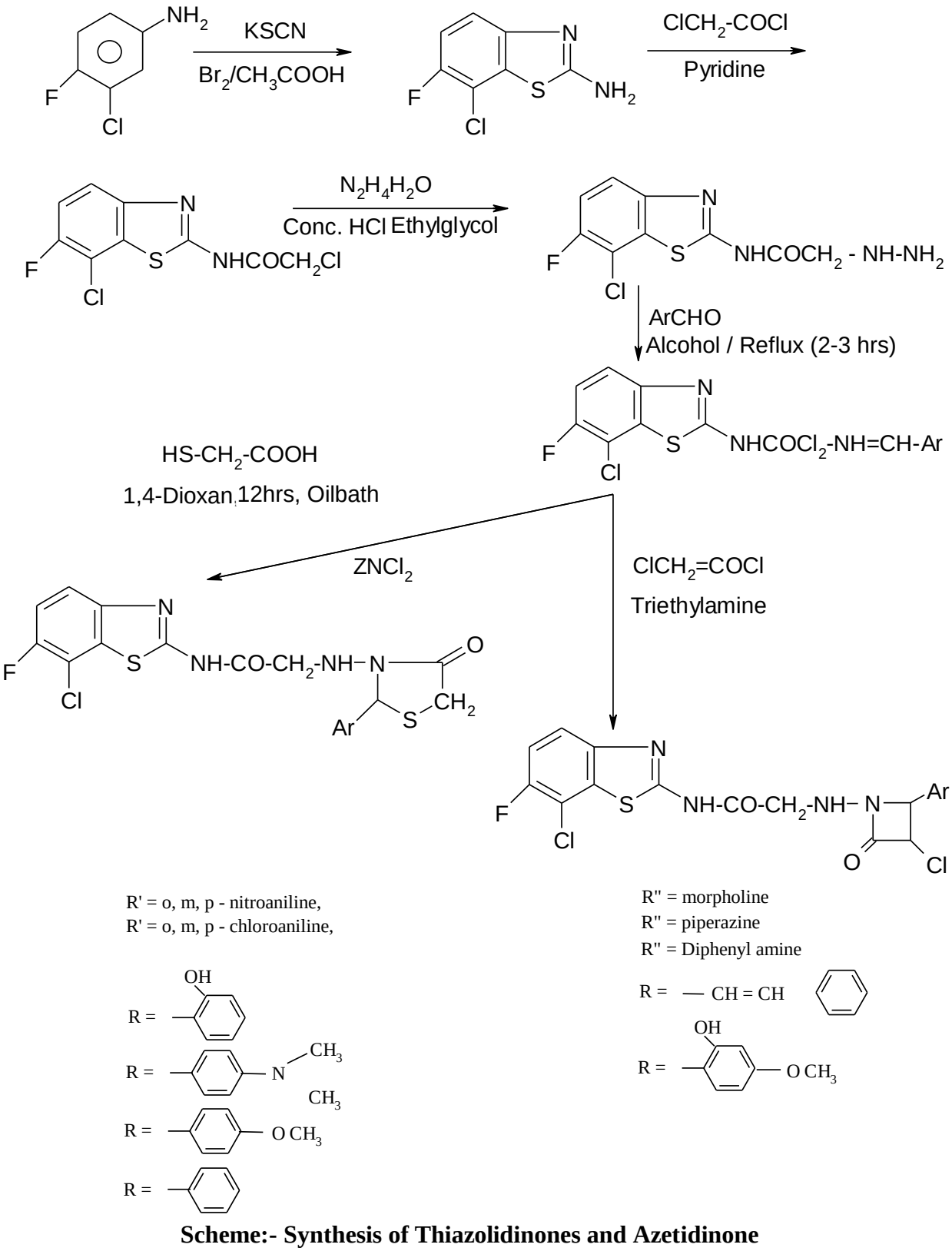
Anti-microbial Activity [12-18]

All the synthesized compounds are screened against bacteria and fungi to know their antimicrobial activity. The screened these compounds for antibacterial activity bacterias like *staphylococcus aureus (Gram +ve)* and *Escherichia coli (Gram -ve)* and *Bacillus subtillis (Gram +ve)* and *Pseudomonas aureus (Gram -ve)* for antifungal activity fungi like *Candida albicans* and *Aspergillus niger* are used.

Anthelmintic activity [19-21]

The synthesized compounds are screened for anthelmintic activity by using earthworms. Six earthworms of nearly equal size were placed in standard drug solution and test compound's solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.1 % w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of the motionless worms were

frequently applied with external stimuli, which stimulates and induces movement in the worms, if alive.



Scheme:- Synthesis of Thiazolidinones and Azetidinone

Anti-inflammatory activity (*in-vitro* models) [22-24]

The synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique which was studied according to Muzushima and Kabayashi with slight modification. 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.

Anti-inflammatory activity (*in-vivo* model)[25-26]

Anti-inflammatory activity by carrageenin induced rat hind paw edema method:

Animals were divided into control, standard, different test groups comprising of five animals in each group. They were fasted overnight with free access to water before experiment. In all groups, acute inflammation was produced by subplanter injection of 0.1 ml of freshly prepared 1% suspension of carrageenin in the right hind paw of the rats and paw of the rats and paw volume was measured plethysmometrically at 0 hr and 3 hrs after carrageenin injection. The test compounds (50 mg/kg) was administered orally, standard group was treated with diclofenac (50 mg/kg) orally 1 hr. before by injection and control group received only vehicle.

Anticonvulsant activity [27-29]

In the present study the mice of either sex, weighing between 20-25 g were selected and divided into control, test and standard. Before experiment the animal were fasted for 24 hrs with only water *ad-libitum.* Control group received only 0.5 ml DMF as vehicle. Standard group animals were received diazepam (4 mg/kg b.w.) oral test group animals were received the synthesized derivatives at 4 mg/kg b.w. oral in DMF. Now for the animals of control group pentylene tetrazole (PTZ) 1ml/100 g b.w. was administered and actions like stratubs tail, jerky movements of whole body and convulsions were observed. For animals of standard test group PTZ was injected (1 ml/100 g body weight). After 30 min animals of standard and test received diazepam and synthesized derivatives respectively.

RESULTS AND DISCUSSION

Anti-bacterial activity

All synthesized compounds were tested for the antibacterial activity against following bacteria;

i) *Staphylococcus. aureus* ii) *Bacillus substillis (gram +ve)* and

iii) *Escherichia. coli* iv) *Pseudomonas aureus (gram –ve).*

The compounds IVa_1, IVa_2, IVa_4, showed better antibacterial activity against *Staphylococcus aureus* (gram +ve) at lower and higher concentration, the compounds IVa_1, IVa_4, IVa_7, IVa_9, IVb_2, IVb_6, IVc_2, IVd_3, IVf_4, showed better antibacterial activity against *Bacillus substillis* (gram + ve) at lower and higher concentration. (*Staphylococcus. aureus* used as standard drug Procaine penicillin and *Bacillus substillis* used as standard drug Cefazolin sodium. The compounds IVa_1, IVa_4, IVa_7, IVb_4, IVb_5, IVd_3, IVd_4, IVf_5, showed better antibacterial activity against *Escherichia coli* gram – ve Streptomycin used as standard.

The compounds IVa_3, IVa_7, IVb_4, IVb_5, IVc_2, IVd_2, showed better antibacterial activity against *Pseudomonas aureus* gram – ve Sporafloxin used as standard.

Anti-fungal activity :

The above synthesized compounds were tested for antifungal activity against *Candida albicans* and *Aspergillus flavus*. The compounds IVa_1, IVa_3, IVa_4, IVa_5, IVa_8, IVa_9, IVb_5, IVb_6, IVc_1, IVc_2, IVd_3, IVf_3, IVf_4, showed comparatively better antifungal activity against *Candida albicans* at both concentration compare to standard Griseofulvin. The compounds IVa_1, IVa_2, IVa_3, IVa_4, IVa_9, IVb_1, IVb_4, IVb_5, IVb_6, IVc_4, IVd_3, IVd_4, and IVf_5, showed comparatively better antifungal activity against *Aspergillus flavus* at both concentration compare to standard Griseofulvin.

Anthelmintic activity :

The above synthesized compounds were tested for anthelmintic activity. The compounds IVa_2, IVa_3, IVa_9, IVb_7, IVc_1, IVc_2, IVc_3, IVd_1, IVf_1, IVf_3, and IVf_5, showed significant paralytic time of earthworms compared to standard Albendazole of 0.1, 0.2, 0.5% concentrations of compounds, showed comparatively better death time of earthworms with that of standard drug. After all, the synthesized compounds in overall estimation confirms the better activity against (perituma posthuma).

Anti-inflammatory activity (*in-vitro*):

The compounds IVa_1, IVa_7, IVa_9, IVb_6, IVc_2, IVd_3, and IVf_3, showed significant anti-inflammatory activity compare to standard Ibuprofen (93.87%).

Anti-inflammatory activity (*In-vivo* models) :

The above synthesized compounds were tested for anti-inflammatory activity by in-vivo method compared to standard Diclofenac Sodium. The compounds IVa_1, IVa_3, IVa_4, IVa_5, IVa_9, IVb_2, IVb_3, IVb_4, IVc_1, IVc_3, IVd_1, IVd_2 IVf_3, and IVf_4, showed significant anti-inflammatory activity compare to standard drug Diclofenac Sodium (79.60%).

Anticonvulsant activity :

Synthesized compounds were tested for anticonvulsant activity by PTZ (pentylene tetrazole) induced method and the compounds IVa_1, IVa_3, IVa_4, IVa_5, IVa_9, IVb_2, IVb_3, IVb_4, IVc_1, IVc_3, IVd_1, IVd_2 IVf_3, and IVf_4, have shown significant anti- anticonvulsant activity.

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