Research Article

Synthesis of Bioactive Molecules Fluoro Substituted Benzothiazole Comprising Potent Heterocyclic Moieties for Biological and Pharmacological Screening

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ABSTRACT

Various substituted 2-benzene sulphonamido-N-(2'-benzothiazolyl 6'-fluoro-7'-substituted) benzamide or 2-(2-phenyl-4-benzylidenyl-5-oxo-imidazolin-1-yl) N-(2'-amino(1',3') benzothiazolyl 6'-fluoro 7'- substituted) benzamide have been synthesized by condensing the compound **1** with anthranilic acids in dry pyridine (Scheme-I) or with oxazolone refluxed in pyridine (Scheme-II). The identities of compounds were confirmed on the basis of their spectral UV-Visible, IR, ^{1}HNMR and Mass spectral data. Further, they have been screened for their antibacterial, antifungal, anti-inflammatory (in vivo & in vitro) and anticonvulsant activities.

Keywords: Fluorine, Benzothiazole, Sulphonamide, Oxazolone.

INTRODUCTION

The rapid progress of organic Fluorine chemistry[1-2] 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, which were incorporated with fluorobenzene moiety proved their efficacy as potent bio active molecules.

Now a days vast number of compounds with Fluorobenzene[3-5] moiety features in diverse areas like antibacterial, antifungal, anti-inflammatory, psychoactive agents, pesticides, herbicides etc.

Based on the above observations we have synthesized some Fluoro-Benzothiazolo-sulfonamido imidazole derivatives starting with fluoro-chloro-aniline, in hope of getting pharmacological agents with broad spectrum of clinical activity.

The reasons forever increasing importance of Fluorine incorporated bio active molecules may be listed below.

a) Fluorine being the second smallest substituent next to Hydrogen, closely mimics Hydrogen in Enzyme-receptor interactions.

b) The substitution of fluorine by hydrogen increases lipid solubility which in turn increases the transport and absorption of drug in-vivo.

c) The strong electron withdrawing, inductive effect (-I effect) of Fluorine influences stability and reactivity of functional groups which may in turn influence the reactivity of neighbouring reaction centers.

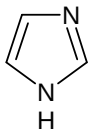
d) The replacement of 'Hydrogen' by 'Fluorine' at or near reactive sites causes inhibition of metabolism due to high C-F bond energy.

The sulfonamide[6-10] drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infection in human beings. The introduction of trimethaprim and sulphamethazole has resulted in increased use of sulfonamide for the treatment of specific microbial infection. Benzothiazoles with sulphonyl group, imidazolone etc were reported to posses various pharmacological activity of clinical importance.

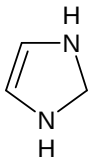
Imidazole[11-15] exhibit diverse biological properties. Hence synthesis of new imidazolinones is of considerable interest. In the recent years the chemistry of sulphonamides imidazolinones has received much attention due to their use

as intermediates for the synthesis of some heterocyclic systems

However, little is known about substituted benzothiazoles having sulphonamido moiety and imidazole with sulphonamido group. Therefore in present work we have sulphonamido group link with benzothiazole ring and imidazolone group to get good biodynamic leads.



Imidazole



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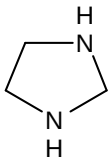
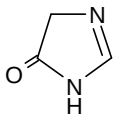
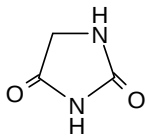


Imidazolidine



Imidazolinone



Imidazolidinedione

Imidazole[11-15] exhibit diverse biological properties. Hence synthesis of new imidazolinones is of considerable interest. In the recent years the chemistry of sulphonamides imidazolinones has received much attention due to their use as intermediates for the synthesis of some heterocyclic systems.

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 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.

ANTI-MICROBIAL ACTIVITY[16-22]

All the compounds synthesized were screened for antibacterial and antifungal activities at two different concentrations (50µg/ml, 100µg/ml) against *Staphylococcus aureus*, (MTCC-737),*Escherchia coli,*(MTCC-1687) *B. subtilis,*(MTCC-441) *Pseudomonas aeruginosa* (MTCC-1035) and *Candida albicans*, (MTCC-3018) *Aspergillus niger* (MTCC-2638) by cup plate method using Procaine Penicillin, Streptomycin and Griseoflavin respectively as standards. The compounds showed considerable activity against all species tested at 50µg/ml, 100µg/ml. Fluoro substituted benzothiazoles series was tested for antibacterial activity.

ANTI-INFLAMMATORY ACTIVITY (*in-vivo* model)[23-25]:

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. Mean difference in paw volume was measured and percentage inhibition was calculated.

ANTI-INFLAMMATORY ACTIVITY (*in-vitro* models) [26-30]

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 albumin solution in phosphate buffer and incubated at $27^0 \pm 1^0$C in BOD 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 **Diclofenac sodium** was used as standard drug.

ANTICONVULSANT ACTIVITY [31-33]

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.

EXPERIMENTAL

Synthesis of 6-fluoro-7-chloro-2-(*p*-acetamido benzene sulphonamido) (1,3)- benzothiazole.

2-amino-6-fluoro-7-chloro (1,3) benzothiazole (0.013 mol) pyridine (4 ml) and acetic anhydride (20 ml), has been added with *p*-acetamido benzene sulphonyl chloride (0.01 mol), the mixture were refluxed in water bath for 2 hrs. then reaction mixture poured into 20 ml of ice cold water. The solid obtained was filtered and recrystallized from dil ethanol (80%) to get titled compound 6-fluoro-7-chloro-2-(*p*-acetamido benzene sulphonamido) (1,3)- benzothiazole

Synthesis of 2-benzene sulphonamido-N-(2'-benzothiazolyl 6'-fluoro-7'-substituted) benzamide.:

The 0.0075 mol (2.7 gm) of 6-fluoro-7-chloro-2-(*p*-acetamido benzene sulphonamido) (1,3)- benzothiazole was treated with 0.008 mol of various substituted aromatic amines, PABA, morpholine, piperazine, diphenylamine o-toluidine, N-methyl piperazine and refluxed for 2 hrs in presence of DMF (dimethyl formamide) then the mixture was cooled and poured into crushed ice.

The solid separated was filtered, dried and recrystallized from super dry alcohol.

Synthesis of 2-(2-phenyl-4-benzylidenyl-5-oxo-imidazolin-1-yl) N-(2'-amino(1',3') benzothiazolyl 6'-fluoro 7'-chloro) benzamide

2-Amino N-(2'-amino(1,3) benzothiazolyl 6'-fluoro 7'-chloro) benzamide. and oxazolone refluxed in pyridine for 6-8 hours. excess of pyridine was distilled off and resulting mass was poured on to crushed ice and neutralised with dil HCl, filtered and product was recrystallised from ethanol gave 2-(2-phenyl-4-benzylidenyl-5-oxo-imidazolin-1-yl) N-(2'-amino(1',3') benzothiazolyl 6'-fluoro 7'-chloro) benzamide

Synthesis of 2-(2-phenyl-4-benzylidenyl-5-oxo-imidazolin-1-yl) N-(2'-amino(1',3') benzothiazolyl 6'-fluoro 7'-substituted) benzamide:

The 0.007 mol 2-(2-phenyl-4-benzylidenyl-5-oxo-imidazolin-1-yl) N-(2'-amino(1',3') benzothiazolyl 6'-fluoro 7'-chloro) benzamide was treated with equimolar quantity (0.0075 mol) of various substituted aromatic primary and secondary amines were refluxed for 2 hrs. in presence of DMF (dimethyl formamide) then the mixture was cooled and poured into crushed ice.

The solid separated was filtered, dried and recrystallised from benzene and super dry alcohol (1:1).

RESULTS AND DISCUSSION

1) Anti-bacterial activity

2-benzene sulphonamido-N-(2'-benzothiazolyl 6'-fluoro-7'-substituted) benzamide and 2-(2-phenyl-4-benzylidenyl-5-oxo-imidazolin-1-yl) N-(2'-amino(1',3') benzothiazolyl 6'-fluoro 7'-substituted) benzamide were tested for the antibacterial activity against following bacteria;

i) *Staphylococcus aureus*
ii) ii) *Bacillus substillis (gram +ve)* and
iii) iii) *Escherichia coli*
iv) *Pseudomonas aeruginosa (gram –ve)*.

The compounds S_1, S_4, S_{10}, S_{11}, S_{12}, R_2, R_3, R_4, and R_8, showed better antibacterial activity against *Staphylococcus aureus* (gm +ve) at lower and higher concentration the compounds S_2, S_4, S_5, S_6, S_{11}, S_{12}, R_1, R_2, R_6, and R_{11}, showed better antibacterial activity against *Bacillus substillis* (gm +ve) at lower and higher concentration. **Procaine penicillin** used as standard for *Staphylococcus aureus* and *Bacillus substillis.*

The compounds S_3, S_5, S_6, S_{12}, S_{14}, R_2, R_4, R_7, R_8, and R_{12}, showed better antibacterial activity against *Escherichia coli* gm –ve, **Streptomycin** used as standard.

The compounds S_5, S_6, S_8, S_9, S_{10}, R_2, R_3 R_4 R_9 and R_{10}, showed better antibacterial activity against *Pseudomonas aeruginosa* gm –ve, **Streptomycin** used as standard.

2) Anti-fungal activity

The above synthesized compounds were tested for antifungal activity against *Candida albicans* and *Aspergillus niger,* using **Griseofulvin** as standard.

The compounds S_9, S_{13}, S_{14}, R_1, R_2, R_3, R_5, R_6, R_7, R_9 and R_{12}, showed significant anti-fungal activity (*Candida albicans*) when compare to standard drug.

The compounds S_4, S_5, S_9, S_{10}, S_{11}, R_4, R_5, R_6, R_7, R_8 and R_{11}, showed significant anti-fungal activity (*Aspergillus niger*) when compare to standard drug.

3) Anti-inflammatory activity (in vivo models)

The above synthesized compounds were tested for anti-inflammatory activity by in vivo method using Diclofenac Sodium (80.00%) as standard drug.

The compounds S_2, S_3, S_4, S_{14}, R_1, R_2, R_4, R_6, and R_7, showed significant anti-inflammatory activity.

4) Anti-inflammatory activity (in vitro models)

The above synthesized compounds were tested for anti-inflammatory activity by in vitro method using Diclofenac Sodium (83.30%) as standard drug.

The compounds S_1, S_3, S_4, S_5, S_7, S_9, S_{12}, S_{14} R_2, and R_4, showed significant anti-inflammatory activity.

5) Anti-convulsant activity

The above synthesized compounds were tested for anticonvulsant activity by PTZ (pentylene tetrazole) induced method, used **Diazepam** as standard.

The anticonvulsant activity conform these compounds S_1, S_6, S_8, S_9, S_{12}, S_{13}, R_4, R_6 R_7 R_9, R_{10} and R_{12}, shown significant anti-convulsant activity compare to standard. The other compounds S_2, S_3, S_4, S_5, S_{10}, S_{11}, R_2,

R_3, R_5, R_8, and R_{11}, showed mild anticonvulsant activity.

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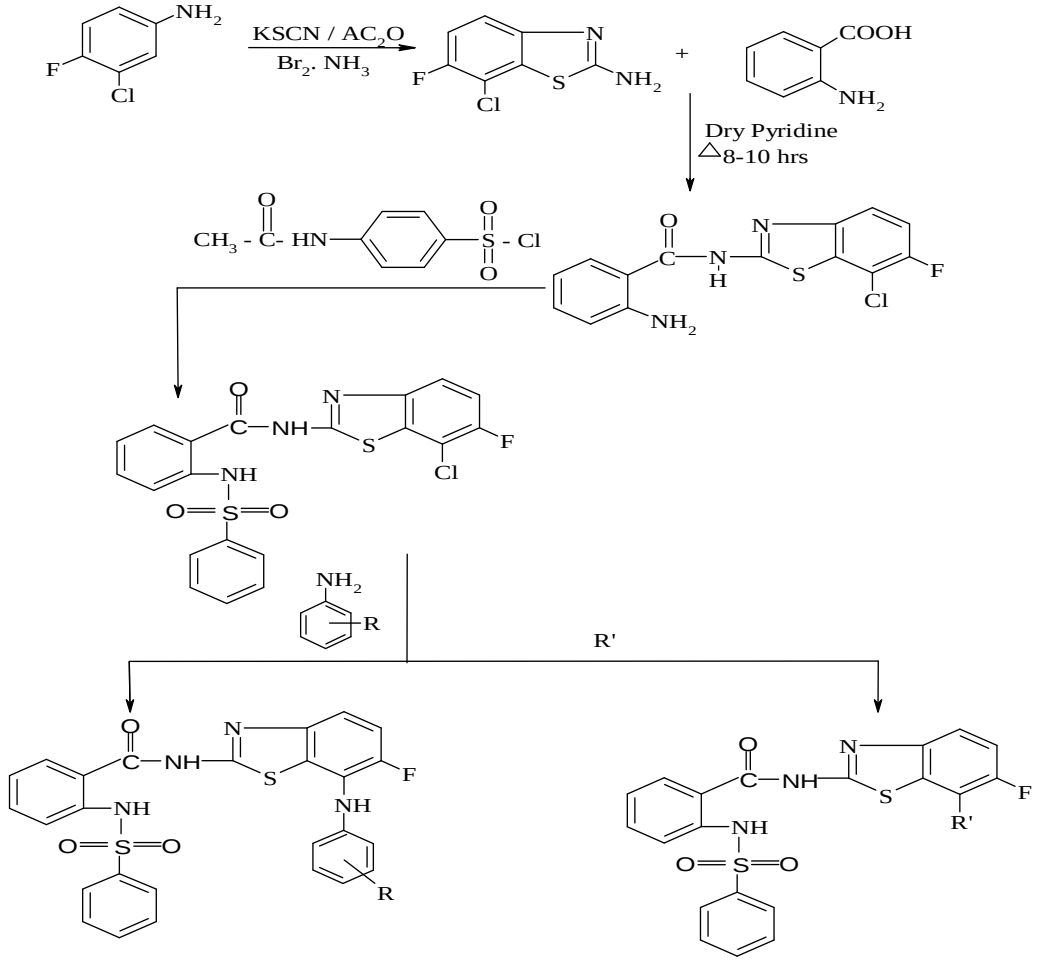
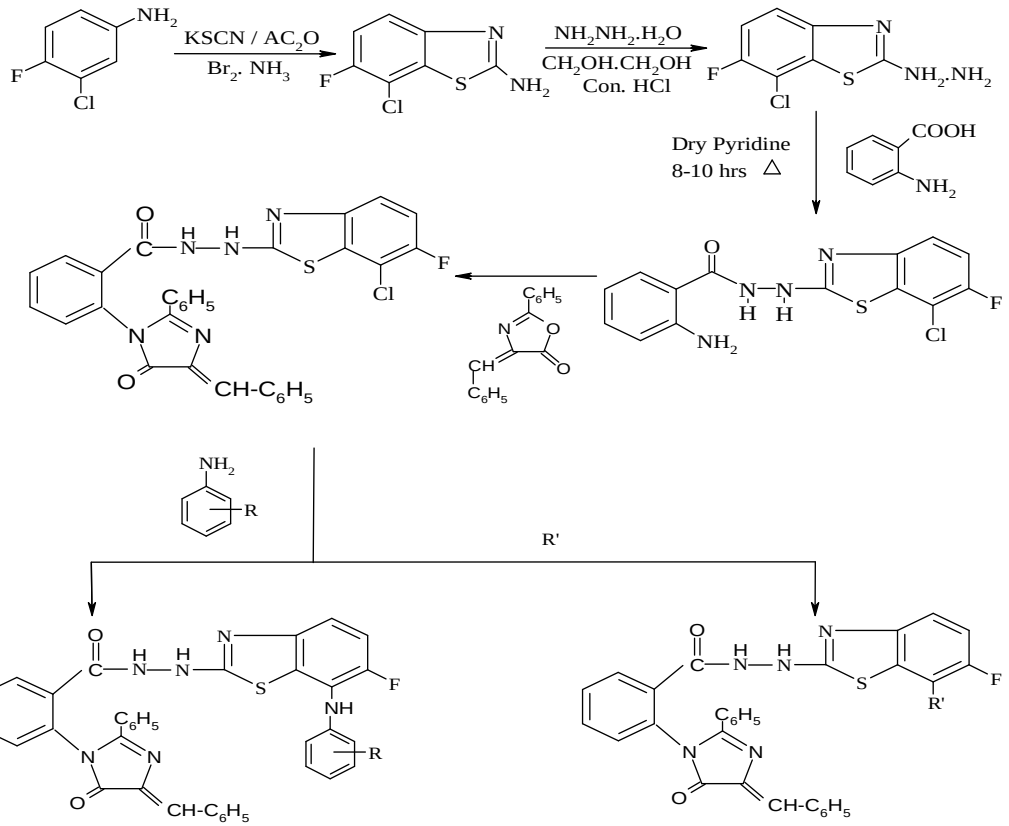
SCHEME-I



R = o, m, p- nitro aniline
R' = morpholine, piperazine
= o, m, p- chloro aniline
= N-methyl piperazine
= N- phenyl
= o-methyl, p-carboxyl

SCHEME-II



R = o, m, p- nitro aniline
R' = morpholine, piperazine
= o, m, p- chloro aniline
= N-methyl piperazine
= p-toluidine
= PABA, diphenyl amine

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