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Synthesis and Biological Evaluation of N-Heterocyclic Substituted Fluoro-Benzothiazole Sulphonamido Analogs as a Potential Therapeutic Agents

Sri Ranga.T*, Neelesh Chaubey

College of Pharmacy, Sri Satya Sai University of Technology and Medical sciences, Sehore (M.P)

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Address for Correspondence: Sri Ranga.T*
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Abstract:
The present investigation is aimed to synthesize fluorobenzothiazole comprising sulphonamido pyrazole analogs starting from fluoro-chloroaniline to get 2-amino-6-fluoro-7-chloro (1,3) benzothiazole (I), this was treated with anilino-s-methyl ethylene cyanoacetamide in the presence of ethanol to get desired molecules. The synthesized targeted molecules are characterized, docked and screened for their invitro antidiabetic properties.
Keywords: Fluorobenzothiazole, Docking, antidiabetic

Introduction

Fluorobenzothiazole[1] comprising sulfonamide pyrazole derivatives have been synthesized and evaluated for their various activities.

The sulfonamide[2-5] 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 sulphamethoxazole has resulted in increased use of sulfonamide for the treatment of specific microbial infection. Benzothiazoles with sulphonyl group and pyrazole etc were reported to posses various pharmacological activity of clinical importance.

The chemistry and pharmacology of pyrazole[6-10] have been of great interest because pyrazole derivatives possess various biological activities. Therefore in present work we have prepared sulphonamido-pyrazole analogs incorporate with substituted benzothiazole.

Molecular docking studies[11-13] are used to determine the interaction of two molecules and to find the best orientation of ligand which would form a complex with overall minimum energy. The small molecule, known as ligand usually fits within protein's cavity which is predicted by the search algorithm. These protein cavities become active when they come in contact with any external compounds and are thus called as active sites.

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational drug design.

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 n-butyl alcohol, ethyl acetate and carbontertachloride (1:2:1) as developing solvent for the purity of the compounds. I.R. Spectra were recorded on Shimadzu FTIR Spectrophotometer by using KBr pellet technique.

Experimental:

Synthesis of 6-fluoro-7-substituted-2-[(3'-amino-4'-carboxamido-5'-s-methyl-pyrazolidin-1'-yl)-*p*-benzene sulphonamido] (1,3)- benzothiazole.

A mixture of 6-fluoro-7-substituted-2-(*p*-hydrazino benzene sulphonamido)-(1,3)-benzothiazole and anilino-s-methyl ethylene cyanoacetamide were refluxed in ethanol for 2 hrs. and later excess of ethanol was distilled off and poured onto crushed ice. The obtained was filtered and was recrystallised from ethanol.

6-fluoro-7-substituted-2-(3'-amino-4'-carboxamido-5'-anilino-pyrazolidin-1'-yl-phenyl-*p*-sulphonamido) (1,3)- benzothiazole was taken with 0.015 mol solution of aldehydes (p-dimethylaminobenzaldehyde) in round bottom flask, then added 20 ml of ethanol and 3-4 drops of HCl and refluxed for 2 – 3 hours, then the mixture in concentrated to remove ethanol. The remaining solution is cooled and poured in to crushed ice in small portions to get targeted molecules.

Results and Discussion:

1) INSILICO ANTIDIABETIC activity for SRT Compounds:

The synthesized compounds **of SRT 1-12 were submitted to in-silico evaluation by using molecular docking approach.** Insilico screening for antidiabetic activity was done by using Autodock. The selected target is Insulin Receptor Tyrosine Kinase enzyme, with **PDB ID-2B4S**, consisting of resolution **2.30** Angstroms.

Table 1: DOCKING RESULTS for SRT 1-12 Compounds.

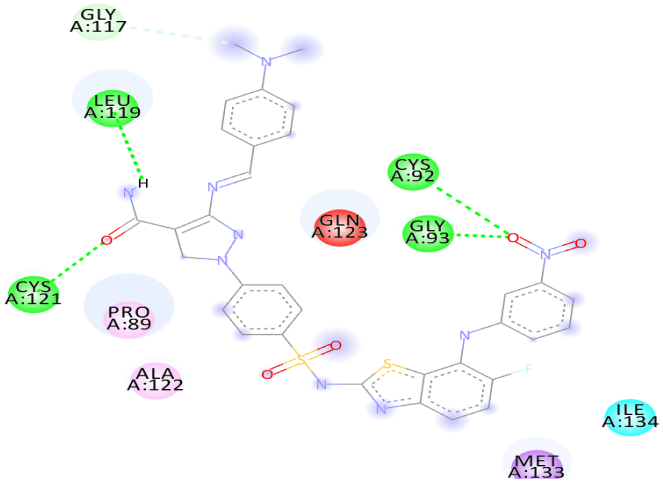
Sl No	Compound name	Docking score
1.	SRT1	-7.6
2.	SRT2	-7.3
3.	SRT3	-7.9
4.	SRT4	-8.2
5.	**SRT5**	**-8.6**
6.	SRT6	-8.4
7.	SRT7	-7.8
8.	SRT8	-8.3
9.	SRT9	-8.0
10.	SRT10	-7.6
11.	SRT11	-8.3
12.	SRT12	-6.9
13.	METFORMINE	-5.6
14.	GLIMEPIRIDE	-7.4

Order of showing potent antidiabetic activity:

SRT5> SRT6> SRT11=SRT8> SRT4>SRT9> SRT3> SRT7> SRT1=SRT10>SRT2>SRT>12> GLIMIPRIDE>METFORMIN.

Glimipride and Metfromin are the standard Drugs.Among the all synthesized SRT compounds **SRT5** exhibited more potent antidiabetic activity than other compounds. The SRT5 exhibited binding energy with **-8.6Kcal.** Remaining all the synthesized compounds also exhibit moderate activity when compared with Standard drug Glimipride and Metfromin. The Standard drugs Glimipride and Metfromin Binding energy is -7.4 and -5.6

Docking Results:



2D Structure of SRT-5:

By analyzing of the 2D results of SRT-5 it involved mainly Hydrogen Bonding . The ligand interacts mainly Hydrogen bonding with aminoacid Leucine A119, CYSA121, 92 and Glycine A93. Remaining all SRT Compounds involved mainly Hydrogen Bonding and Hydrophobic interactions with Ligand

In-vitro Antidiabetic Activity:[14-17]

Procedure:

3T3-L1 adipocytes, were seeded at a density of ~1500 cells per well in a 96-well plate, differentiated and maintained for another 10 days prior to use. To assay glucose uptake, adipocytes were starved in 100 µl serum free adipocyte medium overnight (to enhance glucose uptake) then washed with PBS, followed by a incubation (40 min) in an glucose free medium (100 µl Krebs-Ringer-Phosphate-HEPES (KRPH) buffer with 2 % BSA) then stimulated either with insulin (PGZ) (10 µM), compounds (10 µg/ml) or PBS. 10 µl of 10mM 2-Deoxy glucose (DG) was added and the cells incubated for 20 min. The amount of glucose uptake was determined as per manufactures protocol using the Glucose uptake kit from Biovision (glucose uptake colorimetric assay kit, the 2-DG6P is oxidized to generate NADPH, which can be determined by an enzymatic recycling amplification reaction, color generated can be quantified colorimetrically at 412 nm.). The calculation was carried out keeping 100% glucose uptake for Pioglitazones (PGZ) was used as a standard drug.

- ✓ 2-DG uptake = Sa/Sv (pmol/µl or nmol/ml or µM)
- ✓ Where: Sa is the amount of 2-DG6P (in pmol) in sample well calculated from Standard Curve.
- ✓ Sv is sample volume (in 20 µl) added into the sample well. antidiabetic activity of the synthesized derivatives was performed by the Glucose uptake assay and the results were tabulated below.

In-vitro Antidiabetic Activity:

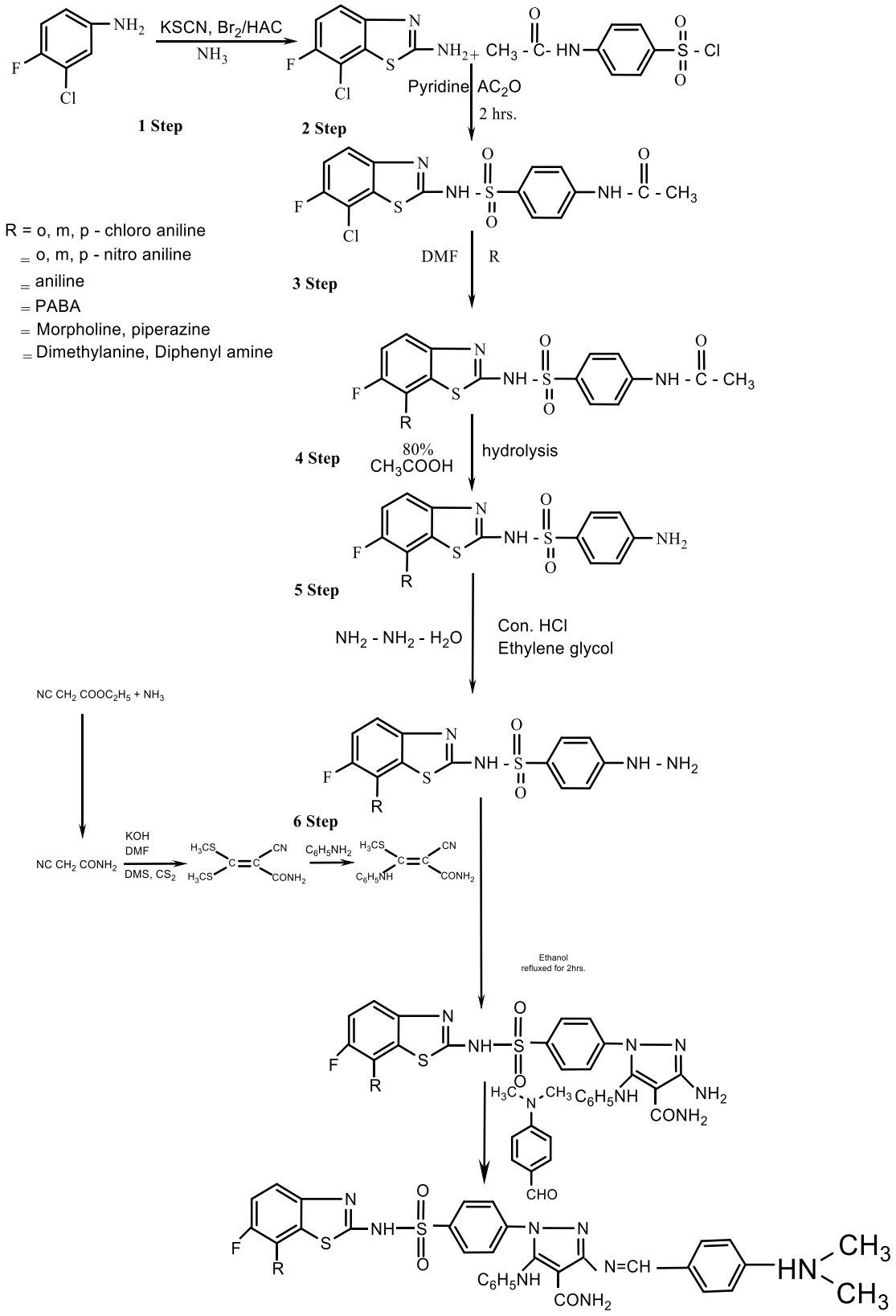
Table 2: Effect of compounds (SRT) on 2-DG uptake in 3T3-L1 presence and absence of insulin:

S.No	Compound	OD (412)	2DG6P(pmol)	2-DGuptak(Pmol/µl)
1	Insulin (1 micro Mol)	3.04	174	11.5
2	SRT 1	4.5	70	5.0
3	SR +Insulin	6.0	90	7.5
4	SRT 2	5.5	80	6.0
5	SR +Insulin	7.0	115	8.5
6	SRT 3	3.5	60	4.0
7	SR +Insulin	5.0	80	6.5
8	SRT 4	2.5	40	3.0
9	SR +Insulin	4.0	70	5.5
10	SRT 5	0.6	10	1.0
11	SR + Insulin	1.5	30	2.5
12	SRT 6	1.0	15	1.5
13	SR+ Insulin	2.6	50	3.5
14	SRT 7	4.0	65	4.5
15	SR + Insulin	5.5	85	7.0
16	SRT 8	1.5	30	2.0
17	SR +Insulin	3.0	60	4.0
18	SRT 9	3.0	50	3.5
19	SR + Insulin	4.5	75	6.0
20	SRT 10	5.0	75	5.5
21	SR + Insulin	6.5	110	8.0
22	SRT 11	2.0	35	2.5
23	SR + Insulin	3.5	65	4.5
24	SRT 12	6.0	90	6.5
23	SR + Insulin	7.0	120	9.0
10	Pioglitazone(10Micro.Mol) +Insulin (1 Micro.Mol)	10.4	450	22.5
11	Pioglitazone (10 Micro.Mol)	3.1	210	10.5

Summary and Conclusion:

In the present research studies, based on the huge literature survey, we designed novel derivatives and screened for their insilico and Invitro methods. We performed Docking for Anti diabetric activities by comparing with Standard Drugs. All the results obtained by insilico and Invitro are in satisfactory manner, containing very near to each other. Based on this promising *in-vitro* anti-diabetic results, also give scope for further studies. Further research need to be carried out to know the relationship between structure and biological activity

SCHEME


KSCN, Br2/HAC
NH3
1 Step
2 Step
Pyridine AC2O
2 hrs.
R = o, m, p - chloro aniline
= o, m, p - nitro aniline
= aniline
= PABA
= Morpholine, piperazine
= Dimethylanine, Diphenyl amine
DMF
R
3 Step
4 Step
80%
CH3COOH
hydrolysis
5 Step
NH2 - NH2 - H2O
Con. HCl
Ethylene glycol
NC CH2 COOC2H5 + NH3
NC CH2 CONH2
KOH
DMF
DMS, CS2
6 Step
Ethanol
refluxed for 2hrs.
CHO

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