ABSTRACT

Objective

The diabetes is a global health issue of every age group and is progressively increase day by day. The medicines used for treatment were developed resistance in the genes as well as exerting side effect to the patients. Some patient treated with insulin suffered from the problem of insulin resistance was made a more problematic condition for treatment. To overcome the problems like the side effect of existing antidiabetic drug, gene resistance and insulin resistance in diabetic patient need to develop some new antidiabetic compounds for the treatment. Our aim is to develop some new antidiabetic compound with devoid of an existing problem with minimum toxic effect.

This dissertation included the synthetic procedure of newer series sulfonylurea derivative with effective substitution and convenient route of their synthesis. The lead molecule is associated with different heterocyclic rings viz. thiazine, thiazolidine-2,4-dione, pyrazole and pyridine. The primary objectives of the study explore the alternative site of substitution in sulfonylurea to avoid early ionization with the potent antidiabetic profile. Another study for anticonvulsant activity is included in the search of an alternative class of drug for the treatment of seizure attack. The in silico study of active compounds was also performed to find the molecular mechanism of action of compounds.

Methods

The structural characterization of synthesized compounds was done by the spectral obtained from FT/IR, 1H NMR, GC-MS, UV-Visible spectroscopy and Elemental analysis.

The toxicity profile was evaluated by acute oral toxicity study as per OECD guideline No.420 (2000).

The evaluation of antidiabetic activity was performed in rats by using alloxan induced diabetes model along with the oral glucose tolerance test (OGTT) in normal rats in the excess of oral glucose feed. The dose of test compounds was 50 mg/kg body weight was used for oral administration of the compound in the form of suspension with tween 20 and water against the standard compound gliclazide in a similar dose.
The neurotoxicity study was performed by intraperitoneal administration of test compounds using rotarod method.

Anticonvulsant effect of compounds was evaluated by maximal electroshock method (MES) and subcutaneous pentylentetrazole (scPTZ) induced seizure model in different dose level of 30, 100 and 300 mg/kg body weight by using phenytoin as standard drug.

The in silico study was performed by using Argus Lab 4.0 docking software against targeted proteins retrieved from Protein Data Bank (PDB). Pymol 1.3 was also used to find the mode of corresponding interactions of the test compound with the target to find protein–ligand interaction.

Results

Among all the synthesized compounds thiazine and pyridyl containing trisubstituted sulfonylurea derivative 1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-phenyl-1-(pyridin-2-yl) urea (5k) was found to be the most active antidiabetic compound which was shown better activity than the standard drug gliclazide at same dose level. The trisubstituted sulfonylureas were more active than the bisubstituted sulfonylureas. However the hydroxyl derivatives were also very significant for reduction of blood glucose level, other electronegative group containing compounds were also found to exert better antidiabetic activity than the compounds containing electron withdrawing group. The sulfonylurea derivatives were better than the sulfonylthiourea derivatives to impart blood glucose lowering effect. The oral glucose tolerance test of most active compound was performed at two different dose level 10 mg/kg and 50 mg/kg body weight. The dose of 50 mg/kg body weight was showed the faster glucose clearance rate that was concluded by the area under curve of blood glucose level. The in silico study shows the satisfactory result with good docking energy -12.49 kcal/mol of compound 5k to support the predicted mechanism for reducing blood glucose level.

The nitro containing derivatives were found toxic on intraperitoneal administration were discarded from the further studies. The rest of derivatives were evaluated for the anticonvulsant study. The bisubstituted thiazine containing sulfonylurea compounds 1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-(4-hydroxyphenyl)urea (6c) was found most active anticonvulsant compound. The trisubstituted sulfonylureas were given less
activity than the bisubstituted sulfonyleurea compounds against induced convolution model used. Electronegative groups were enhanced more the anticonvulsant effect of sulfonyleurea than the electron donating nonpolar methyl derivatives. The hydroxyl derivatives 1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-(4-hydroxyphenyl)urea (6c), 1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylsulfonyl)-3-(4-hydroxyphenyl)-1-(pyridin-2-yl)-urea (6iii), 4-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(4-hydroxyphenylcarbamoyl) benzene-sulfonamide (3iv) were showed considerable anticonvulsant effect. The order of electron withdrawing substituent found for anticonvulsant activity was –OH > -Cl > -OCH₃. The sulfonylethiourea were less active as anticonvulsant than sulfonyleurea this interpretation was supported after the considering the activity of sulfonylethiourea structural analog compound 6i of most active compound (6c) was not given any significant anticonvulsant activity as sulfonyleurea analogs were given. The predicted mechanism of action was supported by in silico study where the efficient docking of active was occurred with open sodium channel pore as targeted protein along with effective docking scores.