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Novel benzenesulfonylureas containing thiophenylpyrazoline moiety as potential antidiabetic and anticancer agents

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ABSTRACT

In the present study a library of twenty six benzenesulfonylureas containing thiophenylpyrazoline moiety has been synthesized. All the compounds were docked against PPAR-γ target. Most of the compounds displayed higher dock score than standard drugs, glibenclamide and rosiglitazone. All the synthesized compounds were primarily evaluated for their antidiabetic effect by oral glucose tolerance test. Further assessment of antidiabetic potential of sixteen active compounds was then done on STZ induced diabetic model. The results of in vivo activity by both the methods were found to be consistent with each other as well as with docking studies. Change in body weight of STZ induced animals post treatment was also assessed at the end of study. In vitro PPAR-γ transactivation assay was performed on active compounds in order to validate docking results and the most active compound **3k** was also shown to elevate gene expression of PPAR-γ. Furthermore, the compounds were screened by National Cancer Institute, Bethesda for anticancer effect and two compounds **3h** and **3i** were selected at one dose level since they exhibited sensitivity towards tumor cell lines (mainly melanoma).

The peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors which are involved in the regulation of lipid and glucose metabolism.[1] PPARs are classified into three subclasses-α, β and γ which are coded by different genes and associated with activation of different target genes by binding to their regulatory region. One of these, PPAR-γ regulates gene expression in response to lipophilic ligands since its ligand binding pocket is quite spacious.[2] PPAR-γ increases fatty acid flux in adipocytes which on contrary alleviates insulin resistance.[3] In addition, many reports contemplated that during adipocyte differentiation, PPAR-γ exerts antimitotic action, thereby reduces the risk of cell proliferation. The activation of PPAR-γ in fibroblasts leads to retraction of cell cycle in tumor cells which have exponential growth rate. It has also been reported that the mutations in PPAR-γ resulting in loss of function were found to be associated with risk of cancer.[4] Therefore, it is evident that there is close relation between PPAR-γ and cancer.

The utility of sulfonylureas have been proved as effective oral antidiabetic agents till date.[5] Consequently, the research is still being pursued by scientists to synthesize new sulfonylurea derivatives with lesser side effects. The mode of action of sulfonylureas is mainly to stimulate insulin secretion by binding to sulfonylurea receptors (SURs) of ATP assisted potassium ion (K_{ATP}) channels present in pancreatic β-cells.[6] Their mechanistic action on molecular level has not yet been too intensively studied. The activation of PPAR-γ is the general known mechanism of thiazolidinediones for improving a glycemic condition.[7,8] But in some recent studies it has been reported that several marketed sulfonylureas also induce PPAR-γ transcriptional activity. Sulfonylureas like glibenclamide, glimepiride, gliquidone and glipizide has been reported to stimulate pancreatic insulin secretion by acting as PPAR-γ agonist in addition to binding with sulfonylurea receptor (SUR) on the plasma membrane of pancreatic β-cells.[9] It has also been studied that glibenclamide binds to PPAR-γ receptor site in a competitive manner with respect to marketed PPAR-γ agonists like pioglitazone and rosiglitazone. Therefore, in the present study we are presenting a library of twenty six sulfonylurea derivatives which have been showing significant antidiabetic activity by acting as PPAR-γ agonists. Increase in body weight which is one of the major side effects

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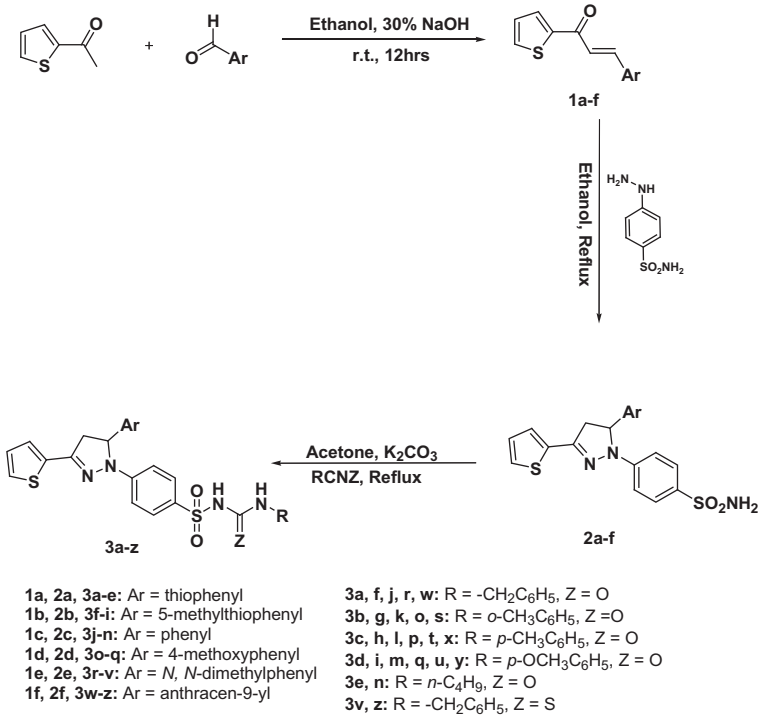

Scheme 1.

of sulfonylurea agent has also been evaluated for their effect on body weight.

The chalcones (**1a–f**) obtained by reacting 2-acetyl thiophene with appropriate aldehyde resulted in the synthesis of key intermediates, that is, pyrazolines (**2a–f**). The pyrazolines so obtained were made to react with appropriate aryl isocyanate and aryl isothiocyanate in the presence of anhydrous potassium carbonate and acetone by conventional reactions.[10,11] The resulting solid was filtered, washed with water, dried, and crystallized from acetone (Scheme 1). All reagents were procured from commercial source and used without further purification unless indicated. The progress of reaction was monitored by using silica gel GF245 plates (Merck Pvt. Ltd, Germany). The purification of compounds was carried out by recrystallization from ethanol. ^{1}H NMR, IR, Mass spectra and CHNS data was also presented to confirm the synthesis of desired product. ^{1}H NMR spectra of all the synthesized compounds was recorded in parts per million (ppm) using TMS as the standard and at 300–400 MHz frequency. The appearance of three double doublets in the range of δ 3.00–6.00 ppm confirmed the formation of pyrazoline ring. The coupling with isocyanate/isothiocyanate was verified by increase in aromatic protons depending on the substituent. ^{1}H NMR of the compound **3k** at 400 MHz showed singlet at chemical shift 2.09 ppm corresponding to three methyl protons present on tolyl group attached to sulfonylurea linkage. The formation of pyrazoline ring was confirmed by the presence of three double doublets at 3.13 (J = 5.6 Hz, 17.2 Hz), 3.94 (J = 12.0 Hz, 17.2 Hz) and 5.54 ppm (J = 5.6 Hz, 12.0 Hz). Remaining aromatic protons appeared as multiplet in the region 6.69–7.84 ppm. Mass spectra showing peaks at $[M+H]^+$ or $[M-H]^+$ further confirmed the syntheses of desired products.

As discussed earlier, the mode of action of action of sulfonylureas can also be through the activation of PPAR-γ. Such reports on sulfonylureas prompted us to carry out molecular docking studies of synthesized compounds. In order to get better insight of ligand–protein interaction, all the synthesized compounds were docked and their dock scores were compared to that of standard drugs glibenclamide and rosiglitazone. It has been found that glibenclamide (−7.42) exhibited higher docking score than rosiglitazone (−5.72). Captivatingly, docking score of nineteen compounds (**3a–n**, **3p**, **3r**, **3t**, **3v**, **3w**) was found to be higher than rosiglitazone and sixteen compounds (**3a**, **3c–f**, **3h**, **3i–n**, **3p**, **3r**, **3t**, **3w**) showed higher docking score than glibenclamide. On careful examination of different substitutions, it could be inferred that most of the compounds containing unsubstituted benzyl ring exhibited higher docking score than both the standards. The alignment of compounds in active PPAR-γ site was such that the most of the compounds formed H-bond with different amino acid residues. In some cases, more than one H-bond formation or π–π stacking was also found. The images of the compounds displaying high docking score have been shown in Figure 1 and dock scores were given in Table S1 (Supplementary material).

The efficacy of administration of all the synthesized compounds as oral antidiabetic agents has been assessed primarily by loading glucose on normal rats. It has been observed that in comparison to standard drug glibenclamide, seven compounds (**3d**, **3i–n**) significantly controlled increase in plasma glucose level. However, sixteen compounds (**3a**, **3c–f**, **3h**, **3i–n**, **3p**, **3r**, **3t**, **3v**) exhibited significant lowering in plasma glucose level than PPAR-γ agonist, rosiglitazone. The change in plasma glucose level was illustrated graphically in Figure 2. The result of Glucose Tolerance Test on in vivo model was consistent with docking studies. Few exceptions from docking results were related to the compounds with bulky aryl substitution. For instance for compound **3w** docking score was as high as −11.54 but in vivo antidiabetic activity was less significant to standard drug glibenclamide which showed docking score of −7.42.

The compounds which showed significant glucose tolerance were further evaluated for their effect in STZ induced diabetic model.[12] It was found that the results of both the studies are in concurrence. The change in plasma glucose level on 7th and 15th day of study was assessed and given in Figure 3. The supplementation of diabetic rats with glibenclamide as well as rosiglitazone