SYNTHETIC APPROACH TOWARDS SOME SUBSTITUTED SULPHONYLUREAS AND GUANIDINE DERIVATIVES AS HYPOGLYCEMIC AGENTS

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ABSTRACT
Diabetes mellitus (DM) is a major degenerative disease associated with a group of disorders of carbohydrate metabolism results from body's failure to produce insulin in type 1 and insulin resistance in type 2 diabetes mellitus through altered secretion, decreased insulin activity known as hyperglycaemia. There is direct relationship between hyperglycaemia and long-term complications such as retinopathy, nephropathy and neuropathy like micro and macrovascular concerns. Existing oral treatment options for T2DM include metformin, sulfonylurea, thiazolidinedione derivatives, glycosidase inhibitors and the recently Dipeptidyl peptidase IV inhibitors which have been introduced successfully. There remains avital need to improve new antidiabetic agents with higher efficacy and lower toxicity for the long term treatment of T2DM. Search for new innocent anti-diabetic agents is still a challenge for medicinal chemists. The detailed study of literature reviewand study we have decided to design and synthesis of novel antidiabetic agents. In order to reduce the space volume of this kind of molecule, we have designed and synthesized a series of cyclohexane, p-Nitro benzoic acid, p-Cl benzoic acid, Cinnamic acid derivatives of sulphonylureas and guanidine. All the synthesize compounds were characterized by melting points, TLC, IR spectroscopy, 1H-NMR and 13C-NMR. The synthesized compounds will proposed for biological evaluation by most relevant animal models like alloxan induced diabetic animal model for in-vivo studies.

KEYWORDS: Diabetes mellitus, sulphonylureas, DPP-IV inhibitors, IR, NMR, Mass.

INTRODUCTION
Diabetes mellitus (DM) is a major degenerative disease in the world today. It is a group of disorders of carbohydrate metabolism results from body's failure to produce insulin in Type 1 and insulin resistance in Type 2 diabetes mellitus through altered secretion, decreased insulin activity, or a combination of both factors and characterized by hyperglycaemia.[1] Several epidemiological and clinical studies indicate a direct relationship between hyperglycaemia and long-term complications such as retinopathy, nephropathy, neuropathy like micro and macrovascular complications. This disease is associated with reduced life expectancy significant morbidity due to specific diabetes related micro vascular complications that diminish the quality of life. India has today become the diabetic capital of the world with over 20 million diabetics and this number is set to increase to 57 million by 2025.[2,3]

Numerous drugs such as sulfonylureas and Biguanides are presently available to reduce hyperglycaemia in diabetes mellitus. These drugs have side effects and thus searching for a new class of compounds is essential to overcome this problems.[4] The onset of insulin in body, which causes an abnormal effect on glucose metabolism, is related not only to the development of Type II diabetes but also to cardiovascular disease.[5] Sulfonylureas are the mainstay of antidiabetic therapy for many years. Several structurally modified agents, which have been added in Sulfonylurea class, still there is need of efficacious agents, which are sufficiently nontoxic for chronic use.[6]

The generally agreed treatment goal in T2DM is to maintain near-normal levels of glycemic control in both the fast inpost prandial states. Although diet and exercise are the first steps toward achieving this goal, oral antidiabetic pharmacotherapy also plays an important
role. Type 2 diabetes mellitus (T2DM) presents a major challenge to healthcare system around the world. The current oral treatment options for T2DM include metformin, sulfonylurea or thiazolidinedione derivatives, glycosidase inhibitors and the recently Dipeptidyl Peptidase IV inhibitors which have been introduced. Antioxidants are used as supportive therapy in the treatment of DM and hypoglycemic plants have been shown to regulate the oxidative complications of DM.\(^\text{[7]}\)

Sulfonylureas, the first generation of antidiabetic agents such as Chlorpropamide, Tolbutamide and tolanazide are still in use but are less potent than the second generation drugs like glibenclamide, glipizide and glimepiride. Sulfonylureas are mostly subjected to hepatic metabolism, yielding less active or inactive metabolites that are then eliminated through the kidneys. Patients with impaired hepatic or renal function risk severe hypoglycemia because of accumulation of active drug in circulation. Although these drugs are useful in the treatment of T2DM, their long-term use may lead to a variety of adverse effects including hepatotoxicity, weight gain, edema and indigestion. Thus there remains an urgent need to develop new antidiabetic agents with higher efficacy and lower toxicity for the long term treatment of T2DM.\(^\text{[8]}\)

Search for new safer anti-diabetic agents is still a challenge for medicinal chemists. From the detailed study of literature review and study we have decided to design and synthesis of novel antidiabetic agents.\(^\text{[19,28]}\) In the course of our previous work, we observed that various derivatives of sulfonylurea and guanidine possess remarkable antidiabetic activity.\(^\text{[29]}\) One issue with the synthesis of such molecules containing multiple aromatic rings is the bulky space volume. In order to reduce the space volume of this kind of molecule, we have designed and synthesized a series of cyclohexane, p-Nitro benzoic acid, p-Cl benzoic acid derivatives of urea and guanidine.

### MATERIALS AND METHOD

#### Experimental section

All the recorded melting points were determined in open capillary and were uncorrected. IR spectra were recorded on FTIR spectrophotometer in KBr disc. \(^1\)H-NMR and \(^13\)C-NMR spectra were recorded on 400 MHz spectrophotometer in DMSO-d6 as a solvent and TMS as an internal standard. Peak positions are shown in ppm values. Mass spectra were obtained by mass spectrometer. Thin layer chromatography (TLC) was performed on silica gel coated on glass plate.

#### Procedures for synthesis with spectral discussion

##### General procedure for synthesis of 1-(Phenylsulfonyl) urea

Reflux between urea (1m) and benzene sulfonyl chloride (0.1m) was done for 5hrs in the presence of triethylamine and absolute alcohol (50ml) as solvent. Reaction mixture was cooled and liquid 1-(Phenylsulfonyl) urea was isolated with help of ether solution. 1-(Phenylsulfonyl) urea was obtained in a yield of 50% clear colorless liquid with boiling point: 8220°C. Analysis calculated for C\(_9\)H\(_8\)N\(_2\)O\(_2\)S: C, 41.99; H, 4.03; N, 13.99; O, 23.97; S, 16.02 IR (KBr): 3152 (NH), 1660 (C=O).

##### General procedure for synthesis of 1-(Phenylsulfonyl) guanidine

Reflux between guanidine (1mole) and benzene sulfonyl chloride (0.1m) was done for 5hrs in the presence of triethylamine and absolute alcohol (50ml) as solvent. Reaction mixture was cooled and solid white crystals of 1-(Phenylsulfonil) guanidine was isolated. Product was obtained in a yield of 70% in the form of solid white crystals with melting point: 136-140°C. Analysis calculated for C\(_{10}\)H\(_9\)N\(_2\)O\(_2\)S: C, 42.20; H, 4.55; N, 21.09; O, 16.06; S, 16.09. IR (KBr): 3261 (NH), 1672 (C=NH), 1069 (S=O) Str, 1581 (C-C) Str, 3189 (C-H) Str Ar.

##### General procedure for synthesis 1-cyclohexanecarbonyl-3-(phenylsulfonyl) urea

Reflux between 1-(Phenylsulfonyl) urea (0.1m) and cyclohexane carbonyl chloride (0.1m) was done for 1hr in the presence of triethylamine and absolute alcohol (50ml) as solvent. Reaction mixture was cooled and liquid of 1-cyclohexanecarbonyl-3-(phenylsulfonyl) urea was isolated. Compound was obtained in a yield of 50% with boiling point: 72-74°C. Analysis calculated for C\(_{16}\)H\(_{13}\)N\(_2\)O\(_2\)S: C, 54.18; H, 5.85; N, 9.03; O, 20.62; S, 10.33. IR (KBr): 1738 (C=O), 3448 (NH), 2945 (C-H) Str Ar, 2857 (C-H), 1451 (C-H), 1310 (SO).

##### Synthesis of 1-cyclohexanecarbonyl-3-(Phenylsulfonyl) guanidine

Reflux between 1-(Phenylsulfonil) guanidine (0.1m) and cyclohexane carbonyl chloride (0.1m) was done for 1hr in the presence of triethylamine and absolute alcohol (50ml) as solvent. Reaction mixture was cooled and liquid of 1-cyclohexanecarbonyl-3-(Phenylsulfonyl) guanidine was isolated. 1-cyclohexanecarbonyl-3-(Phenylsulfonyl) guanidine was obtained in a yield of 60% with boiling point: 92-96°C. Analysis calculated for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_2\)S: C, 54.35; H, 6.19; N, 13.58; O, 15.51; S, 10.36. IR (KBr): 1733 (C=O), 3444(NH), 2933 (C-H) Str Ar, 2857 (C-H), 1451 (C-H), 1311 (SO).
Analysis calculated for C_{16}H_{12}N_{2}O_{3}: C, 54.52; H, 6.86; N, 15.90; O, 22.77; S: C, 54.52; H, 6.86; N, 15.90; O, 22.77; S: C, 48.27; H, 3.47; N, 15.90; O, 22.77; S: C, 48.14; H, 3.17; N, 12.03; O, 27.48; S, 9.23. IR (KBr): 3410 (NH), 1663 (CO), 1474 (C-H), 2973 (C-H) Str Ar, 1291 (SO₂).

Synthesis of 1-(4-(2-Aminomethyl)phenylsulfonyl)-3-(cyclohexanecarbonyl) guanidine
Reflux between 1-cyclohexanecarbonyl-3-(phenylsulfonyl) guanidine (0.1 m) and 2-chloroethanamine (1 m) was done for 4 hrs in the presence of triethylamine and absolute alcohol (50 ml) as solvent. Reaction mixture was cooled and liquid of 1-cyclohexanecarbonyl-3-(Phenylsulfonyl) guanidine was isolated. Yield of 60% with boiling point of 80-84°C was collected.

Analysis calculated for C_{16}H_{12}N_{2}O_{3}: C, 54.52; H, 6.86; N, 15.90; O, 22.77; S: C, 54.52; H, 6.86; N, 15.90; O, 22.77; S: C, 48.27; H, 3.47; N, 15.90; O, 22.77; S: C, 48.14; H, 3.17; N, 12.03; O, 27.48; S, 9.23. IR (KBr): 3410 (NH), 1663 (CO), 1474 (C-H), 2973 (C-H) Str Ar, 1291 (SO₂). Mass (m/z): 353 [M+1].

1-(4-(2-aminoethyl)phenylsulfonyl)-3-cinnamoylguanidine
Reflux between 1-cinnamoyl-3-(phenylsulfonyl) guanidine (0.1 m) and 2-chloroethanamine (1 m) was performed during 5 hrs. triethyl amine is used as catalyst and absolute alcohol as solvent. Reaction mixture was cooled and liquid of 1-(4-(2-aminoethyl)phenylsulfonyl)-3-cinnamoylguanidine was isolated. Solid product was obtained in a yield of 60% with melting point was more than 220°C. Analysis calculated for C_{16}H_{12}N_{2}O_{3}: C, 58.05; H, 5.41; N, 15.04; O, 12.89; S, 8.61. IR (KBr): 3400 (NH), 1713 (CO), 1476 (C-H), 3064 (C-H) Str Ar, 1171 (SO₂).
Synthesis of 1-Cyclohexanecarbonyl-3-(4-(2-(pyrazine-2-carboxamido)ethyl)phenylsulfonyl)guanidine
Reflux between 1-(4-(2-Aminoethyl)phenylsulfonyl)-3-(cyclohexanecarbonyl)guanidine (0.1 mole) and pyrazine-2-carbonyl chloride (1 moles) is done for 1 hrs in the presence of triethylamine and absolute alcohol (50 ml) as solvent. Reaction mixture was cooled and liquid of 1-cyclohexanecarbonyl-3-(Phenylsulfonyl) guanidine was isolated. Final product was obtained in a yield of 50%. Analysis calculated for C_{30}H_{33}N_{3}O_{2}S: C, 55.75; H, 4.27; N, 13.96; S, 6.99. IR (KBr): 1727 (CO), 3416 (NH), 1660 (CO), 2988 (C-H) Str Ar, 1292 (SO_{2}), 2788 (C-H). Mass (m/z): 459 [M+1], 13C NMR (δppm), 39.54 (CH_{2}CH_{2}Ar), 38.28 (CH_{2}CH_{2}Ar), 145.05 (CH, 2nd C pyrazine), 141.26 (CH, 3rd C pyrazine), 141.87 (CH, 3rd C pyrazine), 141.12 (CH, 3rd C pyrazine).

Synthesis of 1-(4-(4-(phenyl)-1-carboxamido ethyl)phenylsulfonyl)-3-(4-nitrobenzoyl)guanidine
Reflux between 1-(4-(2-aminoethyl)phenylsulfonyl)-3-(4-nitrobenzoyl)guanidine (0.1m) and benzoyl chloride (1m) is done for 1hr in the presence of triethylamine and absolute alcohol (50ml) as solvent. Reaction mixture was cooled and liquid 1-(4-(4-(phenyl)-1-carboxamido ethyl)phenylsulfonyl)-3-(4-nitrobenzoyl)guanidine was isolated with yield of 50%. Boiling point: 208-212°C. Analysis calculated for C_{32}H_{29}N_{3}O_{3}S: C, 55.75; H, 4.27; N, 14.13; O, 19.37; S, 6.47. IR (KBr): 3418 (NH), 1720 (CO), 1602 (C-H), 3064 (C-H) Str Ar, 1528 (NO) Str, 3033 (C-H), 1276 (SO_{2}). Mass (m/z): 105, 1H NMR (δppm) 2.51 (s, 2H, CH_{2}), 4.26 (t, 2H, CH_{2}), 8.0019 (s, 1H, NH), 7.61 (s, 6H, ArH).

Synthesis of 1-(4-(2-benzamidoethyl)phenylsulfonyl)-3-(4-nitrobenzoyl) urea
Reaction between 1-(4-(2-aminoethyl) Phenylsulfonyl)-3-(4-nitrobenzoyl) urea (0.1m) and benzoyl chloride (1m) was done for 1hr in the presence of triethylamine and absolute alcohol (50ml) as solvent. Reaction mixture was cooled and product was isolated with yield of 50%. Analysis calculated for C_{32}H_{29}N_{3}O_{3}S: C, 55.75; H, 4.27; N, 14.13; O, 19.37; S, 6.47. IR (KBr): 3418 (NH), 1720 (CO), 1602 (C-H), 3064 (C-H) Str Ar, 1528 (NO) Str, 3033 (C-H), 1276 (SO_{2}). Mass (m/z): 105, 1H NMR (δppm) 2.51 (s, 2H, CH_{2}), 3.40 (s, 2H, CH_{2}), 5.24 (s, 1H, NH), 7.92 (s, 1H, NH), 7.47 (s, 6H, ArH).

Synthesis of 1-Benzyl-3-(4-(2-(pyrazine-2-carboxamido)ethyl)phenylsulfonyl) urea
Reflux between 1-(4-(2-aminoethyl)phenylsulfonyl)-3-benzylourea (0.1m) and pyrazine-2-carbonyl chloride (1m) was performed in round bottom at under reflux condition for 1hr. Triethylamine was used as catalyst and absolute alcohol (50ml) as solvent. Reaction mixture was cooled and product was isolated with yield of 50%. Analysis calculated for C_{32}H_{29}N_{3}O_{3}S: C, 55.75; H, 4.27; N, 14.13; O, 19.37; S, 6.47. IR (KBr): 3418 (NH), 1720 (CO), 1602 (C-H), 3064 (C-H) Str Ar, 1528 (NO) Str, 3033 (C-H), 1276 (SO_{2}). Mass (m/z): 105, 1H NMR (δppm) 2.51 (s, 2H, CH_{2}), 4.26 (t, 2H, CH_{2}), 8.0019 (s, 1H, NH), 7.61 (s, 6H, ArH).
Synthesis of 1-(4-(2-benzamidoethyl) Phenylsulfonyl)-3-(cyclohexane carbonyl) urea

Reaction between 1-(4-(2-aminoethyl)phenylsulfonyl)-3-(cyclohexanecarbonyl)urea (0.1m) and benzoyle chloride was performed under reflux condition for 1hr. Absolute alcohol is used as solvent and triethylamine as catalyst. Reaction mixture was cooled and solid white crystals were isolated with yield of 75%. Melting point: >220°C. Analysis calculated for C_{60}H_{57}N_{10}O_{10}S: C, 60.38; H, 5.95; N, 13.96; S, 6.38. Mass (m/z): 503.6 [M+1]. ^1H NMR (δ ppm): 1.32 (s, 2H, CH₂ cyclohexane), 1.34 (s, 2H, CH₂ cyclohexane), 1.35 (s, 2H, CH₂ cyclohexane), 2.51 (s, 2H, CH₃), 3.48 (s, 2H, CH₂), 5.24 (s, 1H, NH), 7.62 (s, 1H, NH), 7.47 (s, 6H, ArH).

Synthesis of 1-Cyclohexanecarbonyl-3-(4-(3-(4-nitrobenzamido)ethyl)phenylsulfonyl) guanidine

Reaction between 1-(4-(2-aminoethyl)phenylsulfonyl)-3-(cyclohexanecarbonyl)guanidine and m-nitrobenzoyl chloride is performed under reflux condition for 1 hr. Absolute alcohol is used as solvent and triethylamine as catalyst. Reaction mixture was cooled and liquid product was isolated with yield of 70%. Boiling point: 40-44°C. Analysis calculated for C_{60}H_{57}N_{10}O_{10}S: C, 55.08; H, 5.43; N, 13.96; O, 6.39. IR (KBr): 3417 (NH), 1726 (CO), 1608 (C-H), 3082 (C-H) Str Ar, 1529 (NO) Str, 2857 (C-H), 1317 (SO₂). Mass (m/z): 503.6 [M+1], 13C NMR (δ ppm).

1-(4-(2-Benzamidoethyl)phenylsulfonyl)-3-cinnamoyl guanidine

Reaction between 1-(4-(2-aminoethyl)phenylsulfonyl)-3-cinnamoyl guanidine (0.1m) and benzoyl chloride (0.1m) was performed under reflux condition for 1hr. Absolute alcohol is used as solvent and triethylamine as catalyst. Reaction mixture was cooled and liquid product was isolated with yield of 70%. Boiling point: 190-194°C. Analysis calculated for C_{60}H_{57}N_{10}O_{10}S: C, 63.01; H, 5.08; N, 11.76; O, 13.43; S, 6.73. IR (KBr): 3417 (NH), 1720 (CO), 1583 (C-H), 3064 (C-H) Str Ar, 1276 (SO₂). Mass (m/z): 503.6 [M+1], ^1H NMR (δ ppm): 2.60 (s, 4H, CH₂), 4.28 (s, 1H, NH), 7.62 (s, 1H, NH), 7.60 (s, 9H, ArH).
(4j)

(4k)

(4l)

(4m)

(4n)

(5a)

(5b)
RESULT AND DISCUSSION

All the recorded melting points were determined in open capillary and are uncorrected. IR spectrawere recorded on FTIR spectrophotometer in KBr disc. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on 400 MHz spectrophotometer in DMSO-d6 as a solvent and TMS as an internal standard. Peak positions are shown in ppm values. Mass spectra were obtained by mass spectrometer. Thin layer chromatography (TLC) was performed on silica gel coated on glass plate. Mobile phase was ethyl acetate, methanol and formic acid. Physical and chemical properties are mention in Table no 2. All novel synthesized compounds structure has been given in Table no 1.

Future plan of work

The synthesized compounds will be proposed for biological evaluation by most relevant animal models like alloxan induced diabetic animal model for in-vivo studies.

Adverse effects

Sulfonylureas can induce weight gain, mainly as a result their effect to increase insulin levels and thus utilization of glucose and other metabolic fuels, abdominal upset, headache. Sulfonylureas are cannot be used in pregnancy or in patients who may become pregnant. Impairment of liver or kidney function increases the risk of hypoglycemia and is contraindications. As other anti-diabetic drugs cannot be used either under these circumstances, insulin therapy is typically recommended during pregnancy and in hepatic and renal failure, although some of the newer agents offer potentially better options. Second-generation sulfonylureas have increased potency by weight, compared to first-generation sulfonylureas. All sulfonylureas carry an FDA required warning about increased risk of cardiovascular death.

TABLE NO 2: PHYSICAL PROPERTIES

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<th>Rf value</th>
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<td>C_{21}H_{23}Cl N_{5}O_{3}S</td>
<td>492</td>
<td>3.8</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>4n</td>
<td>1-(4-(2-Benzamidoethyl)phenyl sulfonyl)-3-cinnamoyl guanidine</td>
<td>C_{25}H_{23}N_{5}O_{3}S</td>
<td>477</td>
<td>3.96</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>5a</td>
<td>1-Cyclohexanecarbonyl-3-(4-(2-(pyrazine-2-carboxamido) ethyl)phenylsulfonyl) urea</td>
<td>C_{21}H_{23}N_{5}O_{3}S</td>
<td>460</td>
<td>0.99</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>5b</td>
<td>1-Cyclohexanecarbonyl-3-(4-(2-(pyrazine-2-carboxamido)ethyl) phenylsulfonyl) guanidine</td>
<td>C_{21}H_{23}N_{5}O_{3}S</td>
<td>458</td>
<td>1.45</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Mobile phase: Methanol:Ethyl acetate/Formic acid=1:0.8:0.1

REFERENCES


