Design and synthesis of novel diamide derivatives of glycine as antihyperglycemic agents

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ABSTRACT
DPP-4 inhibition is one of the most extensively explored approaches for the management of type 2 diabetes (T2D). Most DPP-4 inhibitors in the market contain a proline mimetic active pharmacophore. Herein, we report the design, synthesis, and preliminary evaluation of a series of novel diamide derivatives of glycine, devoid of the proline mimic, for the treatment of T2D. As predicted from in silico studies, the diamide derivatives of glycine exhibited comparable DPP-4 inhibition with the standard as confirmed by the preliminary in vitro studies. Compound 6b was found to be the most potent (IC_{50} 94.82 nM) DPP-4 inhibitor among all the molecules synthesized in the series.

GRAPHICAL ABSTRACT

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Introduction
Diabetes mellitus is a chronic metabolic disorder symptomatically characterized by hyperglycemia or high blood sugar.\(^1\) The onset of hyperglycemic events can occur because of either absence of insulin secretion (type 1 diabetes) or lack of insulin secretion and insulin resistance both (T2D). In recent years, diabetes has become a severe and increasingly prevalent disease due to urbanization and lifestyle changes.\(^2\) About 415 million people worldwide suffer from diabetes and this is projected to increase to 642 million by 2040.\(^3\) Type 2 diabetes (T2D) is the major contributor to the overall diabetic population. T2D is linked to aging, hypertension, and obesity and often remains undetected until the microvascular or macrovascular complications begin to show.\(^4\) Long-term hyperglycemia is associated with adverse cardiovascular complications, leading to high mortality rates.\(^5\) Most of the modern therapeutic interventions are directed toward decreasing the hyperglycemic events within the patients. A major drawback of this first-line therapy is the induction
of hypoglycemia and weight gain. To overcome these side effects, targets involving glucose-dependent insulin secretion (GDIS) have gained importance. Glucagon-like peptide-1 (GLP-1), an incretin hormone, plays an important role in GDIS. GLP-1 acts as a stimulator of endogenous insulin release, while inhibiting the glucagon secretion in glucose-dependent manner, thereby reducing the risk of hypoglycemia. However, the GLP-1(7-36)amide is rapidly degraded, by a serine protease, dipeptidyl aminopeptidase-4 (DPP-4, EC 3.4.14.5), into its inactive form, GLP-1(9-36)amide, with no therapeutic effects. Hence DPP-4 is involved in pathogenesis of T2D and is an attractive target for therapeutic intervention. Thus, inhibition of DPP-4 has gained importance, as it results in increased half-life of endogenous GLP-1, thereby improving glucose exclusion in diabetics. The DPP-4 inhibitors tested in animal models and in clinical trials have clearly demonstrated therapeutic potential for treatment of T2D (Fig. 1).

The DPP-4 acts by cleaving the N-terminal dipeptides with L-proline or L-alanine at the penultimate position. Several classes of DPP-4 inhibitors have been reported from many laboratories and most of them are derived from α- or β-amino acids mimicking the N-terminal dipeptide residues of the incretin hormones. In view of all these studies and with the aim of identifying it for DPP-4 inhibition, studies were carried out in our laboratory by preparing diamide derivatives of glycine (Fig. 2).

Figure 1. Some DPP-4 inhibitors.

Figure 2. General structure of glycine derivatives.
Results and discussion

A series of novel, non-proline mimetic, diamide derivatives of glycine 6a–k were designed by substituting 1-(phenylsulfonyl)piperidine-3-carboxamide at the P2 site and various secondary or tertiary amides at the P1 site. From the in silico studies it was predicted that the binding affinity of the diamide derivatives of glycine (6b = −8.5 kcal/mol) for the DPP-4 enzyme was comparable with that of the marketed drug (Vildagliptin = −6.7 kcal/mol) and hence was expected to show comparable potency. To synthesize diamide derivatives of glycine, commercially available boc-protected glycine 1 was at first reacted with amine in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBT), and 4-dimethylaminopyridine (DMAP) to yield various C-substituted amide derivatives of glycine 2a–k as shown in Scheme I.

However, when dicyclohexyl carbodiimide (DCC) was used in place of EDCI and HOBT for the reaction, a very strong ester bond was formed between the carboxylate of glycine and carbodiimide carbon, which rendered it unreactive for further reaction with the amines, and it was isolated by column chromatography as a nonpolar compound. Also, EDCI, in itself, could not sufficiently activate the carboxylic acid group of glycine and thus addition of HOBT was necessary for this coupling reaction. On the other hand, reaction of piperidine-3-carboxylic acid with benzene sulfonyl chloride, in the presence of sodium carbonate as a base, in a mixture of dichloromethane (DCM)/water (1:1) yielded 1-(phenylsulfonyl)piperidine-3-carboxylic acid 5 on acidification. Infrared (IR) spectrum of 5 showed bands at 1693 and 1352 cm\(^{-1}\) for the carbonyl group of carboxylic acid and sulfonamide group respectively while the \(^1\)H NMR showed a multiplet from \(\delta\) 7.56 to 7.79 for the five aromatic protons and a broad singlet at \(\delta\) 8.98, indicating the proton of the carboxylic acid group and thereby confirming the formation of 5. Compounds 2a–k were converted into their salts 3a–k by addition of 10% trifluoroacetic acid (TFA) in DCM. The salts 3a–k, on further

![Scheme 1](image_url)

**Scheme 1.** Synthesis of diamide derivatives of glycine, reagents and conditions: (i) EDCI, HOBT, DMAP, amine, DCM, 25°C, 16h; (ii) 10% TFA in DCM; (iii) PhSO\(_2\)Cl, Na\(_2\)CO\(_3\), DCM/H\(_2\)O (1:1), 25°C, 16h, (iv) HCl, pH 2; (v) EDCI, HOBT, DMAP, 3a–k, DCM, 25°C, 10 h.
reaction with acid 5 in the presence of peptide coupling agents EDCI, HOBr, and DMAP, gave the desired diamide derivatives of glycine 6a–k as shown in Scheme 1. The structures of 6a–k were confirmed by their IR, $^1$H NMR, $^{13}$C NMR, and ESI-MS analyses. While the IR spectra of compounds 6a–k exhibited one strong band at $\sim$3300 cm$^{-1}$ for the –NH (amide), two strong bands between 1730 and 1600 cm$^{-1}$ for amide carboxyls and a strong band $\sim$1350 cm$^{-1}$ for the sulfonamide group were found. In the $^1$H NMR of 6a–k, a multiplet at $\delta$~4.00 for the methylene group of glycine is observed due to the interactions with the neighboring amide group protons. The IR spectrum of compound 6b exhibited five strong bands: two bands at 3329, 3303 cm$^{-1}$ for the two –NH (amide), another two bands 1679 and 1644 cm$^{-1}$ for amide carboxyls, and a band at 1355 cm$^{-1}$ for the sulfonamide group. In the $^1$H NMR spectrum of 6b, the methylene group of glycine exhibited a multiplet at $\delta$ 3.84–3.86 due to the interactions with the neighboring amide group protons and a multiplet from $\delta$ 7.36 to 7.74 representing the aromatic protons. In the $^{13}$C NMR spectrum two peaks at 168.26 and 173.16 for the carbonyl carbons of the amide groups, six peaks from 24.14 to 48.63 for the piperidyl and glycyl carbons, and eight peaks ranging from 121.10 to 138.25 for the aromatic carbons confirmed the formation of 6b, which was also supported by its ESI-MS spectrum with a peak at m/z 435.9 for [M + H]$^+$.

The molecular docking studies were performed by selecting binding site residues of the A chain of DPP-4 (PDB ID: 3W2T) at a distance of 4.5 Å from NVP-LAF237. To carry out the docking studies, chain

Figure 3. Binding of 6b at the active site of DPP-4. All the images have been generated using PyMOL.
A of 3W2T was considered for analysis. The molecular docking was carried out using AutoDock (version 4.2) for predicting the mode of binding.\cite{19} The binding affinity of the most potent compound in the series, 6b, for DPP-4 enzyme was calculated to be $-8.5$ kcal/mol. The list of residues interacting with the ligand were also obtained from AutoDock Tools.\cite{19} Pymol\cite{20} was used to visualize the structures (the protein and the docked compound 6b) and align the ligands to highlight the interactions as seen in Fig. 3.

Several potent diamide and sulfonamide derivatives with peptidomimetics pharmacophore (proline mimic) as DPP-4 inhibitors have been reported but the aim of this study was to recognize the DPP-4 inhibition potential of this new series of nonproline mimetic, diamide derivatives of glycine.\cite{21,22} Preliminary \textit{in vitro} DPP-4 inhibition assay was performed to screen test compounds 6a–k and to study the effect of different amides at the P1 site, for the DPP-4 enzyme inhibition potential. The IC$_{50}$ values were then determined for those compounds that exhibited greater than 50% enzyme inhibition at 3 µM concentration, as shown in Table 1.

Among the substituted secondary amide analogs 6a–f (at the P1 site), the effect of fluoro, chloro, and methyl substituents on the benzamide was studied and it was observed that the $p$-chloro benzamide derivative 6b (IC$_{50}$ 94.82 nM) was six-fold more potent than $p$-fluoro benzamide derivative 6a (IC$_{50}$ 573.74 nM) and about three-fold more potent than $m$-fluoro benzamide derivative 6d (IC$_{50}$ 205.40 nM), but $p$-methyl benzamide derivative 6c was relatively inactive. Also, 6d was found to be twice as potent as 6a but a similar trend was not observed in 6e, 6f, and 6b. While among the substituted tertiary amide analogs (at the P1 site) 6g–k, the simplest tertiary amide, N,N-dimethyl amide derivative 6g (IC$_{50}$ 188.97 nM), was three times more potent than N-methyl benzamide derivative 6k (IC$_{50}$ 592.56 nM) and twice as potent as the tetrahydroisoquinoline amide derivative 6j (IC$_{50}$ 444.60 nM). Cyclic aliphatic amide derivatives 6h and 6i were reported inactive. Thus the calculated IC$_{50}$ values, obtained from the \textit{in vitro} analysis of the diamide derivatives of glycine 6a–k, clearly demonstrated 6b (IC$_{50}$ 94.82) as the most potent DPP-4 inhibitor.

\begin{table}[h]
\centering
\begin{tabular}{lll}
\hline
\textbf{Compound} & \textbf{Inhibition of DPP-4 (%)} & \textbf{IC$_{50}$ (nM)} \\
\hline
6a & 55.0 & 573.74 \\
6b & 69.5 & 94.82 \\
6c & 14.4 & ND \\
6d & 58.5 & 205.40 \\
6e & 14.1 & ND \\
6f & 14.4 & ND \\
6g & 51.3 & 188.97 \\
6h & 12.4 & ND \\
6i & 10.1 & ND \\
6j & 51.6 & 444.60 \\
6k & 50.5 & 592.56 \\
Sitagliptin phosphate & 91.7 & 5.37 \\
\hline
\end{tabular}
\caption{\textit{In vitro} DPP-4 inhibition by diamide derivatives of glycine.}
\end{table}

\textsuperscript{a}The DPP-4 inhibitory activity determined by fluorescence-based assay was measured using Spectra Max fluorometer (Molecular Devices, CA). Values of inhibition are mean of three independent determinations at 3 µM concentration of the test samples.

\textsuperscript{b}IC$_{50}$ values were determined using Graph Pad Prism software. Values of DPP-4 inhibition (expressed as IC$_{50}$) are mean of the three independent determinations.

\textit{Note.} ND, not determined.
Conclusion

A novel series of diamide derivatives of glycine devoid of a proline mimic has been designed and synthesized, and its application as DPP-4 enzyme inhibitor for treatment of T2D has been evaluated. Compound 6b (IC$_{50}$ = 94.82 nM) was found to be the most potent compound in the series, which is in agreement with the molecular docking studies. An extension of this approach to other scaffolds is in progress in our laboratory.

Experimental

Chemistry

Reagent-grade chemicals and solvents were purchased from commercial supplier and used after purification. Thin-layer chromatography (TLC) was performed on silica-gel F254 plates (Merck). Merck silica gel (60–120 mesh) was used for column chromatographic purification. All reactions were carried out in a nitrogen atmosphere. Melting points are uncorrected and were measured in open capillary tubes, using a Rolex melting-point apparatus. IR spectra were recorded as KBr pellets on a Perkin-Elmer RX 1 spectrometer and the wave numbers are reported in cm$^{-1}$. $^1$H NMR and $^{13}$C NMR spectral data were recorded on Advance Bruker 400 spectrometer ($^1$H 400 MHz/$^{13}$C 100 MHz) with CDCl$_3$ or DMSO-$d_6$ as solvent and tetramethylsilane (TMS) as internal standard and reported in $\delta$ (ppm). $J$ values are in hertz (Hz). Mass spectra were determined by ESI-MS, using a Shimadzu LCMS 2020 apparatus. Elemental analyses were recorded on ThermoFinnigan Flash 11-12 series EA. All reactions were carried out under a nitrogen atmosphere. Purity of all the tested compounds was greater than 97%.

Inhibitory activity

In vitro enzyme (DPP-4) inhibitory activity was determined using fluorescence based assay. Gly-ProAminomethylcoumarin (AMC) was used as a substrate to measure DPP-4 activity. Cleavage of the peptide bond by DPP-4 releases the free AMC group, resulting in fluorescence that is analysed using an excitation wavelength of 350–360 nm and emission wavelength of 450–465 nm. Human recombinant DPP-4 enzyme was procured from Enzo Life Science (batch no. BML-SE434-9091), substrate H-Gly-Pro-AMC was procured from Enzo Life Science (batch no. BML-P189-9091), and assay buffer of pH 7.8 was used in the assay. DPP-4 activity was measured by mixing reagents in a 96-well plate (order of addition of reagents: assay buffer, enzyme, solvent/inhibitor, and finally substrate). Both the enzyme and 96-well plate were incubated for 30 min and the resulting fluorescence was measured using Spectra Max Fluorometer (Molecular Devices, Sunnyvale CA) by exciting at 360 nm and emission at 460 nm with the excitation filter at 360 nm and emission filter at 460 nm at sensitivity of 45.

General procedure for the preparation of compounds 2a–k

A mixture of boc-glycine 1 (1.11 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (1.67 mmol), 1-hydroxybenzotriazole (HOBT) (1.11 mmol), 4-dimethylaminopyridine (DMAP) (1.34 mmol), and amine ($^1$H and $^2$H) (1.22 mmol) in dichloromethane (DCM) (50 mL) was stirred at room temperature for 16 h. The reaction
was monitored using TLC. On completion of the reaction, it was washed with water (2 × 20 mL) and brine (1 × 10 mL), dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to give the crude product, which was then purified by column chromatography using silica gel as stationary phase and methanol/dichloromethane (5:95) as eluent to yield desired N-boc glycine amide 2a–k, as a white solid.

1-(Phenylsulfonyl)piperidine-3-carboxylic acid (5)

Benzene sulfonyl chloride (1.1 mmol) was added to a mixture of piperidine-3-carboxylic acid 4 (1.0 mmol) and sodium carbonate (3.0 mmol) in 25 mL DCM/water (1:1), and the reaction mixture stirred at room temperature for 16 h or until the completion of reaction, as monitored by TLC. On completion of reaction, the reaction mixture was washed with petroleum ether (20 mL) and then acidified with concentrated HCl, to pH 2. The white solid thus separated was filtered, washed with water several times, and then dried to yield the desired product as white solid.

Yield: 91%; white solid; mp: 115–117°C; IR (KBr): 2940, 1693, 1352 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.41–1.50 (m, 1H), 1.65–1.73 (m, 1H), 1.80–1.85 (m, 1H), 1.99–2.04 (m, 1H), 2.41 (dt, 1H, J₁ = 2.8 Hz, J₂ = 11.2 Hz), 2.57 (t, 1H, J = 10.8 Hz), 2.65–2.71 (m, 1H), 3.59 (br d, 1H, J = 11.6 Hz), 3.83 (dd, 1H, J₁ = 3.2 Hz, J₂ = 7.2 Hz), 7.54–7.58 (m, 2H), 7.61–7.63 (m, 1H), 7.77–7.79 (m, 2H), 8.98 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 23.88, 26.21, 40.73, 46.26, 47.35, 127.62, 129.18, 132.94, 135.96, 178.63.

General procedure for the preparation of compounds 6a–k

Compounds 2a–k were deprotected by stirring in 10% trifluoroacetic acid (TFA) in DCM. On completion of the reaction after an hour or as monitored by TLC, the solvent was evaporated under reduced pressure and once again the product was dissolved in DCM to give a solution of compounds 3a–k. To a solution of compound 5 (1.0 mmol) in DCM (20 mL), EDCI (1.5 mmol), HOBt (1.0 mmol), and DMAP (1.0 mmol) were added at 0–5°C, followed by the solution of compound 3a–k in DCM (5 mL), and the reaction mixture was then stirred at room temperature for 10 h or until the completion of the reaction as detected by TLC. After completion of the reaction, it was washed with water (2 × 20 mL) and brine (1 × 10 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the crude product, which was then purified by column chromatography using silica gel, employing ethylacetate/petroleum ether (70:30) as eluent to give pure product 6a–k as a white solid.

N-(2-(4-Fluorophenylamino)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6a)

Yield: 70%; white solid; mp 196–198°C; IR (KBr): 3324, 3298, 2967, 2934, 2843, 2865, 1677, 1654, 1643, 1355 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 1.23–1.27 (m, 1H), 1.46–1.49 (m, 1H), 1.72–1.79 (m, 2H), 2.10–2.20 (m, 2H), 2.50–2.51 (m, 1H), 3.58–3.63 (m, 1H), 3.66–3.72 (m, 1H), 3.82–3.85 (m, 2H), 7.15 (t, 2H, J = 8.8 Hz), 7.56–7.60 (m, 2H), 7.66 (t, 2H, J = 8.4 Hz), 7.72–7.74 (m, 3H), 8.39 (br s, 1H), 10.05 (s, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 24.14, 27.00, 41.93, 42.85, 46.52, 48.62, 115.68, 115.90, 121.31, 121.39, 127.85, 129.94.
N-(2-(4-Chlorophenylamino)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6b)

Yield: 55%; white solid; mp 178–180°C; IR (KBr): 3329, 3303, 2931, 2863, 2843, 1679, 1644, 1614, 1355, 1334 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.22–1.27 (m, 1H), 1.46–1.49 (m, 1H), 1.75 (t, 2H, \(J = 15\) Hz), 2.10–2.20 (m, 2H), 2.50–2.54 (m, 1H), 3.60–3.69 (m, 2H), 3.84–3.86 (m, 2H), 7.36 (d, 2H, \(J = 8.8\) Hz), 7.59–7.67 (m, 4H), 7.72–7.74 (m, 3H), 8.41 (t, 1H, \(J = 8.0\) Hz), 10.14 (s, 1H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 24.14, 27.01, 41.93, 42.95, 46.52, 48.63, 119.58, 127.86, 129.13, 129.93, 133.68, 135.62, 138.25, 168.26, 173.16. Anal. calc. for C\(_{20}\)H\(_{22}\)ClN\(_3\)O\(_4\)S: C, 55.11; H, 5.09; N, 9.64; found: C, 55.22; H, 5.01; N, 9.58%. ESI-MS: \(m/z\) 435.9 [M + H]^+.

N-(2-Oxo-2-(p-tolylamino)ethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6c)

Yield: 85%; white solid; mp 194–196°C; IR (KBr): 3331, 3327, 2956, 2929, 2846, 1678, 1657, 1644, 1358, 1332 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.23–1.27 (m, 1H), 1.46–1.49 (m, 1H), 1.72–1.79 (m, 2H), 2.10–2.20 (m, 2H), 2.24 (s, 3H), 2.50–2.56 (m, 1H), 3.66–3.69 (m, 2H), 3.77–3.85 (m, 2H), 7.10 (d, 2H, \(J = 8.0\) Hz), 7.45 (d, 2H, \(J = 8.0\) Hz), 7.64–7.68 (m, 2H), 7.72–7.75 (m, 3H), 8.36 (s, 1H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 20.89, 24.15, 27.01, 41.94, 42.87, 46.53, 48.64, 119.58, 127.86, 129.59, 129.94, 132.64, 133.69, 135.60, 136.76, 167.80, 173.10. Anal. calc. for C\(_{21}\)H\(_{25}\)N\(_3\)O\(_4\)S: C, 60.70; H, 6.06; N, 10.11; found: C, 60.78; H, 6.18; N, 9.90%. ESI-MS: \(m/z\) 416.1 [M + H]^+.

N-(2-(3-Fluorophenylamino)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6d)

Yield: 62%; white solid; mp 186–188°C; IR (KBr): 3308, 3104, 2930, 2851, 1709, 1670, 1616, 1351, 1317 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.23–1.27 (m, 1H), 1.46–1.49 (m, 1H), 1.72–1.79 (m, 2H), 2.10–2.20 (m, 2H), 2.50–2.51 (m, 1H), 3.61 (d, 1H, \(J = 10.8\) Hz), 3.68 (d, 1H, \(J = 10.8\) Hz), 3.84–3.87 (m, 2H), 6.88–6.90 (m, 1H), 7.26–7.36 (m, 2H), 7.55–7.75 (m, 6H), 8.41 (br s, 1H), 10.22 (s, 1H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 24.14, 27.00, 41.92, 42.97, 46.52, 48.62, 106.18, 106.44, 110.08, 110.29, 115.27, 127.86, 129.93, 130.85, 130.95, 133.69, 135.61, 140.95, 141.06, 161.38, 163.78, 168.49, 173.17. Anal. calc. for C\(_{20}\)H\(_{22}\)FN\(_3\)O\(_4\)S: C, 57.27; H, 5.29; N, 10.02; found: C, 57.42; H, 4.90; N, 9.97%. ESI-MS: \(m/z\) 420.2 [M + H]^+.

N-(2-(3-Chlorophenylamino)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6e)

Yield: 59%; white solid; mp 140–142°C; IR (KBr): 3412, 3303, 2948, 2843, 1692, 1666, 1650, 1350, 1333 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.67–1.71 (m, 1H), 1.75 (s, 1H), 1.82–1.91 (m, 2H), 2.45–2.55 (m, 1H), 2.64–2.74 (m, 2H), 3.57 (d, 1H, \(J = 11.6\) Hz), 3.74 (d, 1H, \(J = 9.2\) Hz), 4.14 (d, 2H, \(J = 5.2\) Hz), 7.01–7.10 (m, 1H), 7.16–7.24 (m, 2H), 7.40–7.42 (m, 1H), 7.52–7.56 (m, 2H), 7.60–7.64 (m, 2H), 7.75–7.77 (m, 2H), 8.82 (s, 1H); \(^{13}\)C NMR
(100 MHz, CDCl3): δ 23.76, 26.90, 42.39, 44.34, 46.35, 48.22, 117.84, 119.92, 124.44, 127.56, 129.25, 130.03, 134.51, 135.59, 138.78, 167.04, 173.90. Anal. calc. for C20H22ClN3O4S: C, 55.11; H, 5.09; N, 9.64; found: C, 55.26; H, 4.98; N, 9.52%. ESI-MS: m/z 436.00 [M + H]+.

**N-(2-(2-Chlorophenylamino)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6f)**

Yield: 48%; white solid; mp 162–164°C; IR (KBr): 3373, 3257, 2953, 2936, 2863, 1707, 1649, 1583, 1386, 1323 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.58–1.76 (m, 2H), 1.80–1.93 (m, 2H), 2.41–2.48 (m, 1H), 2.63–2.70 (m, 2H), 3.61–3.64 (m, 1H), 3.75–3.82 (m, 1H), 4.13–4.14 (m, 2H), 7.01–7.10 (m, 2H), 7.26–7.30 (m, 1H), 7.36–7.39 (m, 1H), 7.53–7.57 (m, 2H), 7.61–7.65 (m, 1H), 7.76–7.78 (m, 2H), 8.30–8.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 23.84, 26.93, 42.59, 44.53, 46.33, 48.21, 121.86, 123.18, 125.16, 127.61, 127.75, 129.17, 129.25, 133.07, 134.06, 135.54, 167.23, 173.79. Anal. calc. for C20H22ClN3O4S: C, 55.11; H, 5.09; N, 9.64; found: C, 55.25; H, 5.12; N, 9.58%. ESI-MS: m/z 436.05 [M + H]+.

**N-(2-(Dimethylamino)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6g)**

Yield: 80%; white solid; mp 128–130°C; IR (KBr): 3351, 3274, 2978, 2940, 1720, 1677, 1635, 1365, 1338 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.46–1.50 (m, 1H), 1.65–1.85 (m, 2H), 1.89–1.93 (m, 1H), 2.28–2.35 (m, 1H), 2.48–2.60 (m, 2H), 3.02 (d, 6H, J = 9.6 Hz), 3.73 (d, 1H, J = 11.6 Hz), 3.85 (d, 1H, J = 9.6 Hz), 4.03 (d, 2H, J = 8.4 Hz), 6.82 (br s, 1H), 7.53–7.57 (m, 2H), 7.60–7.64 (m, 1H), 7.77 (d, 2H, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 24.02, 27.16, 35.68, 35.95, 41.22, 42.84, 46.26, 48.24, 127.66, 129.13, 132.85, 135.92, 167.65, 172.54; C16H23N3O4S; ESI-MS: m/z 354.0 [M + H]+.

**N-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6h)**

Yield: 66%; white solid; mp 138–140°C; IR (KBr): 3383, 3304, 2949, 2870, 1681, 1651, 1398 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.43–1.53 (m, 1H), 1.66–1.73 (m, 1H), 1.79–1.84 (m, 2H), 1.90–1.94 (m, 2H), 1.98–2.03 (m, 2H), 2.27–2.33 (m, 1H), 2.49 (t, 1H, J = 10.4 Hz), 2.55–2.60 (m, 1H), 3.39 (t, 2H, J = 6.8 Hz), 3.53 (t, 2H, J = 6.8 Hz), 3.84–3.85 (m, 1H), 3.86–3.87 (m, 1H), 3.95–3.99 (m, 2H), 6.86 (br s, 1H), 7.52–7.56 (m, 2H), 7.59–7.63 (m, 1H), 7.75–7.78 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 24.07, 24.14, 25.89, 27.04, 41.96, 42.66, 45.53, 46.13, 46.26, 48.36, 127.62, 129.11, 132.82, 135.88, 166.33, 172.73. Anal. calc. for C18H25N3O4S: C, 56.97; H, 6.64; N, 11.07; found: C, 57.00; H, 6.82; N, 11.30%. ESI-MS: m/z 380.1 [M + H]+.

**N-(2-Morpholino-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6i)**

Yield: 79%; white solid; mp 178–180°C; IR (KBr): 3311, 2963, 2922, 2856, 1670, 1655, 1640, 1351, 1332 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.49–1.56 (m, 1H), 1.66–1.74 (m, 1H), 1.80–1.91 (m, 2H), 2.33–2.39 (m, 1H), 2.52–2.58 (m, 2H), 3.41–3.44 (m, 2H), 3.66–3.74 (m, 7H), 3.81 (d, 1H, J = 8.0 Hz), 4.03–4.10 (m, 2H), 6.81 (br s, 1H), 7.53–7.57 (m, 2H),
7.60–7.64 (m, 1H), 7.76–7.78 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 23.95, 27.11, 41.04, 42.34, 42.77, 44.78, 46.28, 48.19, 66.31, 66.69, 127.65, 129.14, 132.87, 135.89, 166.39, 172.62. Anal. calc. for C$_{18}$H$_{25}$N$_3$O$_5$S: C, 54.67; H, 6.37; N, 10.63; found: C, 54.75; H, 5.86; N, 10.32%. ESI-MS: m/z 396.1 [M + H]$^+$. 

**N-(2-(1,2,3,4-Tetrahydroisoquinolin-2(1H)-yl)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6j)**

Yield: 62%; white solid; mp 142–144°C; IR (KBr): 3322, 2948, 2913, 2849, 1664, 1650, 1635, 1351, 1343 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.48–1.51 (m, 1H), 1.67–1.70 (m, 1H), 1.80–1.85 (m, 1H), 1.90–1.93 (m, 1H), 2.30–2.36 (m, 1H), 2.50–2.60 (m, 2H), 2.90–2.96 (m, 2H), 3.64 (t, 1H, $J = 6.0$ Hz), 3.72 (d, 1H, $J = 11.2$ Hz), 3.83–3.89 (m, 2H), 4.11–4.16 (m, 2H), 4.57 (s, 1H), 4.78 (s, 1H), 7.16–7.20 (m, 2H), 7.22–7.25 (m, 2H), 7.53–7.57 (m, 2H), 7.60–7.64 (m, 1H), 7.76–7.78 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 24.01, 27.14, 28.28, 29.07, 40.24, 41.42, 41.57, 42.13, 42.81, 44.51, 46.01, 46.27, 48.23, 126.16, 126.62, 126.66, 126.85, 126.91, 127.28, 127.66, 128.39, 128.95, 129.13, 131.47, 132.64, 132.85, 133.70, 134.64, 135.90, 166.22, 166.64, 172.56, 172.62. Anal. calc. for C$_{23}$H$_{27}$N$_3$O$_4$S: C, 62.56; H, 6.16; N, 9.52; found: C, 62.46; H, 6.07; N, 9.49%. ESI-MS: m/z 442.2 [M + H]$^+$. 

**N-(2-(Methyl(Phenyl)amino)-2-oxoethyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (6k)**

Yield: 65%; white solid; mp 156–158°C; IR (KBr): 3222, 2944, 1673, 1635, 1347, 1333 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.44–1.50 (m, 1H), 1.66–1.89 (m, 3H), 2.29–2.35 (m, 1H), 2.44–2.56 (m, 2H), 3.31 (s, 3H), 3.66–3.78 (m, 4H), 6.69 (br s, 1H), 7.20–7.23 (m, 2H), 7.38–7.48 (m, 3H), 7.51–7.55 (m, 3H), 7.59–7.63 (m, 1H), 7.73–7.76 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 23.94, 27.00, 37.60, 42.04, 42.72, 46.26, 48.26, 127.18, 127.64, 128.77, 129.12, 130.27, 132.86, 135.78, 141.68, 168.06, 172.47. Anal. calc. for C$_{21}$H$_{25}$N$_3$O$_4$S: C, 60.70; H, 6.06; N, 10.11; found: C, 60.71; H, 5.85; N, 10.12%. ESI-MS: m/z 416.1 [M + H]$^+$. 

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**References**

[1] American Diabetes Association. *Diabetes Care* 2014, 37, S81–S90.

[2] *Diabetes Atlas*, 7th ed. (International Diabetes Federation, 2015), p. 11. Available at [http://www.diabetesatlas.org/resources/2015-atlas.html](http://www.diabetesatlas.org/resources/2015-atlas.html)
[3] Diabetes Atlas, 7th ed. (International Diabetes Federation, 2015), p. 50. Available at http://www.diabetesatlas.org/resources/2015-atlas.html
[4] Fowler, M. J. Clin. Diabetes 2008, 26, 77–82.
[5] Ceriello, A.; Sportiello, L.; Rafaniello, C.; Rossi, F. Expert Opin. Drug Saf. 2014, 13, S57–S68.
[6] Drucker, D. J. Endocrinology 2001, 142, 521–527.
[7] Drucker, D. J. Nat. Clin. Pract. Endocrinol. Metab. 2005, 1, 22–31.
[8] Drucker, D. J. Gastroenterology 2002, 122, 531–544.
[9] Hui, H.; Zhao, X.; Perfetti, R. Diabetes Metab. Res. Rev. 2005, 21, 313–331.
[10] Deacon, C. F. Horm. Metab. Res. 2004, 36, 761–765.
[11] Baggio, L. L.; Drucker, D. J. Gastroenterology 2007, 132, 2131–2157.
[12] Zander, M.; Madsbad, S.; Madsen, J. L.; Holst, J. J. Lancet 2002, 359, 824–830.
[13] Drucker, D. J. Diabetes Care 2007, 30, 1335–1343.
[14] Kirby, M.; Yu, D. M. T.; O’Connor, S.; Gorrell, M. D. Clin. Sci. 2010, 118, 31–41.
[15] Omar, B.; Ahrén, B. Diabetes 2014, 63, 2196–2202.
[16] Vella, A. J. Clin. Endocrinol. Metab. 2012, 97, 2626–2628.
[17] Duez, H.; Cariou, B.; Staels, B. Biochem. Pharmacol. 2012, 83, 823–832.
[18] Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. Nucl. Acids Res. 2000, 28, 235–242.
[19] Morris, G. M.; Huey, R.; Lindstrom, W.; Sanner, M. F.; Belew, R. K.; Goodsell, D. S.; Olson, A. J. J. Comput. Chem. 2009, 30, 2785–2791.
[20] DeLano, W. L. The PyMOL Molecular Graphics System, vers. 1.5.0.4; Schrodinger, LLC: San Carlos, CA, 2002.
[21] Tsai, T. Y.; Yeh, T. K.; Chen, X.; Hsu, T.; Jao, Y. C.; Huang, C. H.; Song, J. S.; Huang, Y. C.; Chien, C. H.; Chiu, J. H.; Yen, S. C.; Tang, H. K.; Chao, Y. S.; Jiaang, W. T. J. Med. Chem. 2010, 53, 6572–6583.
[22] Zhao, G.; Kwon, C.; Wang, A.; Robertson, J. G.; Marcinkeviciene, J.; Parker, R. A.; Kirby, M. S.; Hamann, L. G. Bioorg. Med. Chem. Lett. 2013, 23, 1622–1625.