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Synthesis and antidiabetic performance of β-amino ketone containing nabumetone moiety

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ABSTRACT

We wish to report the further design and improved synthesis that resulted in two series of target molecules, **TM-1** and **TM-2**, with remarkably simplified structures containing β-amino ketone of discrete nabumetone moiety. These were obtained via a 'one-pot, two-step, three-component' protocol of Mannich reaction with yield up to 97%. A total of 28 out of 31 new compounds were characterized using ^{1}H NMR, ^{13}C NMR, ESI MS and HRMS techniques. Studies on their antidiabetic activities, screened in vitro at 10 μg mL^{-1} level, indicate that **TM-2** possesses peroxisome proliferator-activated receptor activation and α-glucosidase inhibition activity significantly stronger than that of **TM-1**, and also that of the series **B** compounds that were previously synthesized by the group. Analysis of the structure–activity relationship points to the sulfanilamide unit as the most probable potent group of β-amino ketone and, on the basis of which, a tangible strategy is presented for the development of new antidiabetic drugs.

1. Introduction

Diabetes mellitus is a metabolic disorder caused by a variety of factors including genetic defects, endocrinopathy, exocrine pancreatitis and infection. Among the various forms, type 2 diabetes mellitus (T2DM) takes account of over 90% of the total occurrence. According to their mechanism of action, T2DM drugs can be categorized into the following seven groups: insulin secretagogues (including sulfonylureas, phenylalanine derivatives and glucagon-like peptides), insulin sensitizers (including metformin, thiazolidinediones (TZDs) and β-receptor agonists), α-glucosidase inhibitors (such as acarbose, miglitol and voglibose), aldose reductase (AR) inhibitors (such as tolrestat and epalrestat), simulation insulin sensitizers (including insulin-like growth factors and vanadate compounds), insulin medication (oral, injection and inhaled insulin preparations) and traditional Chinese hypoglycemic medicine (including single herbal medicine or composite formulation).[1] Despite a great number of drugs available on the market, none of them fully addresses the need for T2DM treatment. Therefore it remains highly critical to develop target molecules of higher efficacy and lower toxicity.

β-Amino ketones are well accepted as key synthetic intermediates of numerous drugs and natural products such as β-amino alcohols, β-amino acids, β-lactam, etc.[2,3] As important bioactive substances, they are widely used with functionalities spanning from anti-inflammatory,[4] anticancer,[5–8] antibacterial,[9] analgesia,[10] anti-tuberculosis,[11,12] antiandrogen[13,14] and so on. As shown in Figure 1 below, some marketed drugs also contain the structural moiety of β-amino alcohol (Artane) or β-amino ketones (Dyclonine, Ondansetron).

Benzenesulfonamide structural module has been widely incorporated into drugs such as antibacterial,[15] diuretics,[16] hypoglycemic agents,[17] α-adrenergic receptor antagonist[18] and precursor molecules, as well as sulfonylurea drugs for insulin secretion, including diabetoplex, gliclazide and glimepiride.[19] Certain benzenesulfonamide containing compounds also display HIV-1 protease inhibition effect.[20] It was also revealed by the group that certain molecules containing a sulfamethoxazole (SMZ) structural

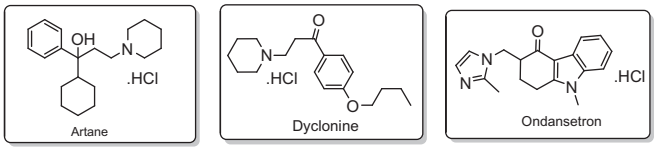

Figure 1. Examples of drugs containing structural moiety of β-amino alcohol or β-amino ketones.

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moiety exhibit remarkable peroxisome proliferator-activated receptor (PPAR) activities[21,22] (Fig. 2). All the evidence implies that it is most likely the benzenesulfonamide structural module be an important part of a new class of antidiabetic agents.

It was reported that naphthalene-containing compounds exhibited more effective PPAR activation activities than benzene-containing analogues.[23] We subsequently designed new β-amino ketones containing both nabumetone and SMZ moieties, anticipating enhanced performance due to the combined functionalities. Some of the compounds showed significant antidiabetic activities. For example, the α-glucosidase inhibition (α-GI) of compound **B-m** reached a remarkable level of 70.5% (IC_{50} = 3.24 μg mL^{-1}), closely resemble that of Acarbose whose effective concentration is 10 times higher. The PPAR relative activity of compounds **B-n**, **B-b** and **B-j** approached 83.30%, 81.78% and 78.17%, respectively (see Fig. 3).[24,25] These data represent a new class of antidiabetic agents of high performances.

It is unfortunate, though, such potent compounds have fairly large molecular weights (over 500) and exert only limited solubility in water. In order to develop target molecules of higher efficacy, from the Lipinski's Rule of Five,[26] it is favorable to enhance the solubility in water and reduce the molecular weight. One of practical optimizations, for this purpose, is to disconnect the mother molecule into relative small chemical entity. We took a strategy to retaining the nabumetone fragment (for building the β-amino ketone) and dividing SMZ into sulfanilamide and isoxazole fragment, both are potent and contain the amino group to participate in the Mannich reaction. As such the two series of target molecules **TM-1** and **TM-2** were designed (Scheme 1). The new class of β-amino ketones consists of hydrophobic nabumetone, sulfanilamide or 5-methylisoxazole, the latter two being known potent agents, bridged via an aldehyde component. This strategy has proven effective in achieving the dual objectives of reducing molecular weight and enhancing solubility in water. In addition, it allows the pharmacological effects of SMZ, sulfanilamide and 5-methylisoxazole be probed within different molecular entities.

2. Chemistry

The Mannich reaction is one of the most important basic reactions in organic chemistry commonly used in the synthesis of numerous pharmaceuticals and natural products.[27–30] Recent developments also show stringent chemoselectivity, stereoselectivity, diastereoselectivity of the products,[31] greatly expands the validity of this classic reaction.

It is common to adopt either a two-step, or 'one-pot', protocol for direct Mannich reaction.[32] The former approach allows aldehyde reacting with amine first to form Schiff base, which then in turn reacts with ketone to yield the final product.[33] On the other hand, the latter method mixes all the three components, namely, aldehyde, ketone and amine, plus catalyst, in the same reaction vessel from beginning to the end.[34] This method is very simple to set up, but it is difficult to monitoring the reaction process and determining the endpoint. Subsequent to years of research and successive modifications, the authors established a 'one-pot, two-step, three-component' protocol (Scheme 2), that is, first allow the reaction between aldehyde and amine; but instead of separating, and purifying, the resultant Schiff base as would normally ensue, ketone and catalyst are added to the same reaction vessel to continue the reaction till the end.[35–37] In essence, this protocol inherits the simplicity of the 'one-pot' analogue but with a bonus of clearly defined endpoint. In the present article, we synthesized a total of thirty one β-amino ketone target molecules using the aforementioned protocol with yield up to an outstanding 97%. Up to 28 target compounds were comprehensively characterized using ^1H NMR, ^{13}C NMR, ESI MS and HRMS techniques. In addition, their antidiabetic performances were screened in vitro.

3. Results and discussion

It is fairly easy to produce β-amino ketone target molecules in the presence of the three starting materials plus catalyst. However, to achieve high purity product requires delicate optimization of the experimental parameters.

3.1. Optimal temperatures

It was observed that for both **TM-1** and **TM-2** series the reactions were able to proceed in the temperature range of 25–30 °C. The same applies at expanded range of aldehydes when most of the reactions complete within 22–47 h. On the other hand, change of temperature did not show any apparent improvement for those relatively low yield reactions such as **TM-1a**(4-NO_2). In addition, change of temperatures in the range of 5–45 °C could not activate those reactions did not occur under normal conditions, such as those involving isonicotinaldehyde, 2-chlorobenzaldehyde, 3-hydroxylbenzaldehyde, 3-hydroxy-4-methoxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde. Therefore it can be concluded that temperature is not a key governing parameter.

3.2. Selection of solvent

Small alcohol in particular ethanol is often the primary choice due to its high solubility differential from reactant against product, and ready availability. But ethanol solvent resulted in fairly limited yield involving 4-methylbenzaldehyde starting material. Further attempts covered methanol, benzene, dichloromethane (DCM), chloroform, and binary mixtures of ethanol–DCM, ethanol–chloroform, etc. It was found that the reactions tended to be stopped at the Schiff base stage without proceeding further in methanol or benzene solvent, but finished with the highest yield of β-amino ketones as the final product in ethanol–chloroform mixed solvent. In addition, it was also found advantageous of using different solvents at different stages of the reaction. For example, mixed aldehyde and amine in the single solvent of ethanol to form Schiff base; and then added the solution of nabumetone in chloroform to continue the reaction in ethanol–chloroform mixed solvents till the final product of β-amino ketone was formed. These combinations were also applicable for the Mannich reactions involving other aldehydes, sulfanilamide or 5-methylisoxazole and nabumetone.

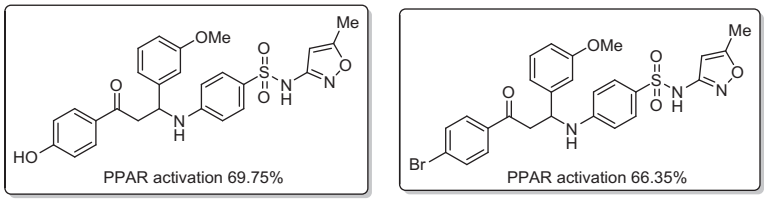


Figure 2. Two representative compounds with strong PPAR activation activities.

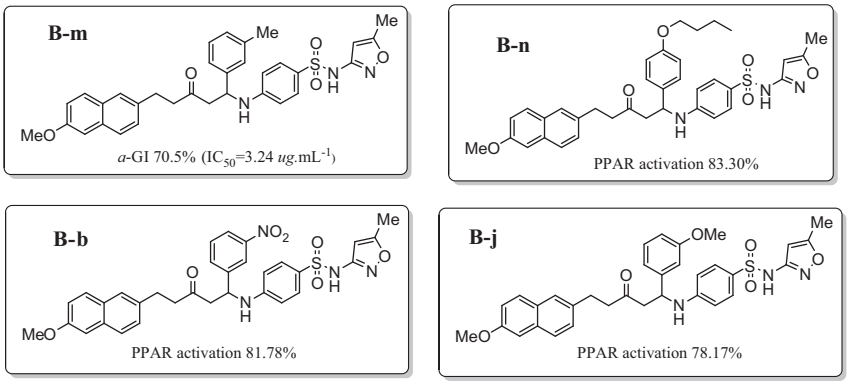
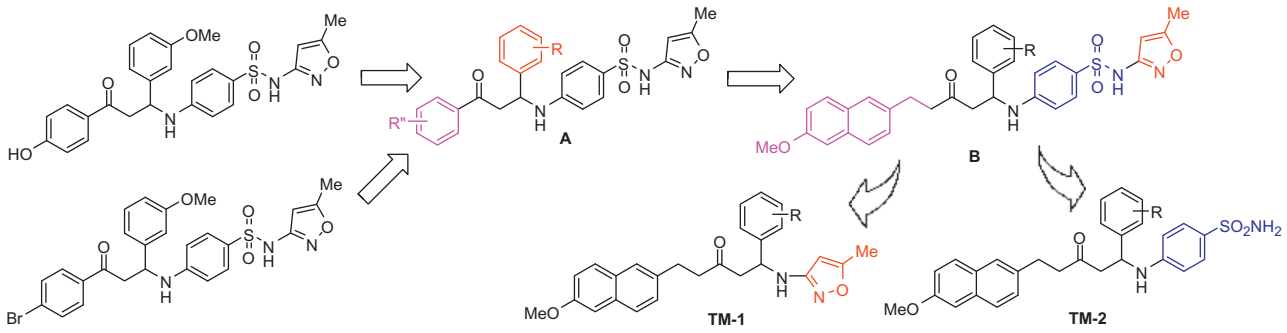
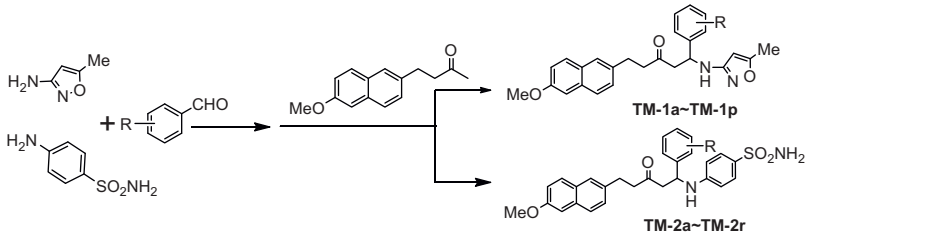


Figure 3. Structures and biological activities of compound **B-m**, **B-n, B-b** and **B-j.**



Scheme 1. Design of target molecules.



Scheme 2. Synthetic routes to the target molecules.

3.3. Selection of catalyst

There are numerous species that may be used as catalysts for the Mannich reaction, including Lewis[38–40] or Brönsted[41,42] acids, and transitional metal salts.[43] In a model reaction system involving furaldehyde, sulfanilamide and nabumetone starting materials, a number of potential catalysts were screened including concentrated hydrochloric acid, phosphoric acid, nitric acid, acetic acid, ironic chloride and aluminum chloride. It was observed that concentrated hydrochloric acid exerted the best catalytic performance among the candidates examined, while nitric acid showed literally no enhancement in reaction rate at all. In addition, the effect of pH was also investigated. While most of the reactions proceeded as expected in the domain of pH 4–5, a few of the **TM-1** series molecules, such as **TM-1a**(4-NO_2), **TM-1b**(3-NO_2), **TM-1d**(2,4-diCl) and **TM-1f**(4-Cl), required a lower pH range of 3–4 in order to obtain the final products.

3.4. Yield-substituent relationship

In the **TM-1** series, reactions using 3,4-dichlorobenzaldehyde, 4-chlorobenzaldehyde as starting materials reached yields over 85%, while that using 3-chlorobenzaldehyde only had a yield of 48.8%, indicating the impact of the number and location of chloro atom on the yield. Specifically, substitution at the 4-position appeared to be able to significantly enhance the yield. However, both 3- and 4-nitrobenzaldehydes only led to yields (**1b**) below the 50% mark, showing a moderate effect of strong electron-withdrawing group on the yield. On the other hand, strong electron-donating groups such as 3,4-OCH_2O led to an excellent yield (**1o**) of 96.3%.

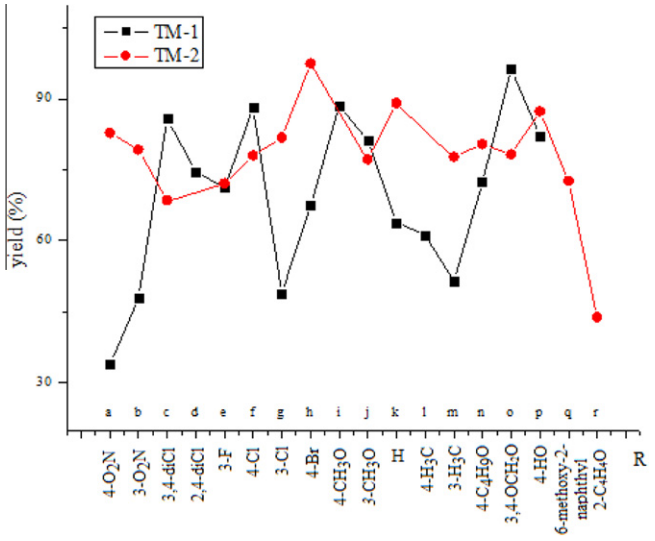


Figure 4. Yield–substituent relationships.

For **TM-2** series, the yield of reactions involving double substituted benzaldehyde by chloro atom tend to be lower than the single substituted counterpart, for example, **2c**(3,4-diCl) < **2f**(4-Cl). For different substitution groups at the identical location of benzaldehyde, the yield is in line with the trend of the electron-donating ability of the substituent, for example, **2b**(3-NO_2) ≈ **2e** (3-F) < **2g**(3-Cl). These results highlight the remarkable impact on the final yield by the electron density distribution and the number of substituent on the benzaldehyde ring (Fig. 4).

In addition, the modifications made on **TM-1** and **TM-2** series rendered considerably higher solubilities in both aqueous and organic solvents, compared to previously reported **B** series. This presents a significant advantage in the subsequent characterization and investigation in their antidiabetic performances.

3.5. Biological activities

Among the numerous antidiabetic targets being investigated, most of the on-going efforts focus on dipeptidyl peptidase-IV (DPP-4), protein tyrosine phosphatase 1B (PTP1B) and PPARs, while works on α-glucosidase inhibitor lack of appreciable progress. At present, the traditional Chinese hypoglycemic medicines, and carbohydrate-analogous, are the main clinical drugs. While there are reports about PTP1B research, no chemical entity has reached the clinical stage.[21,22] DPP-4 family drugs have been outstanding in recent years with a few new products, for example of the Saxagliptin (Onglyza®, marketed in 2009),[44] Alogliptin (approved in Japan in 2010),[45] and Linagliptin (approved by US FDA in 2011)[46] (Fig. 5), perhaps due to their relatively low acute toxicities, but their chronic toxicities remain to be determined. As a member of the nuclear receptor superfamily, PPAR targets received considerable attention for their involvement in a wide range of gene expression affecting lipid and carbohydrate metabolisms. Among the three subtypes, PPARα, PPARγ and PPARδ, PPARγ takes part in the tuning of insulin sensitivity and lipid concentration, as well as the gene expressions of multiple metabolisms.[47] Glycosidase exerts a number of critical activities such as promoting hydrolysis of glycosides in a wide range of substrates including microorganisms, plants and animals. Both α- and β-glucosidases are associated with a variety of biochemical processes relevant to diabetes, viral and/or bacterial infection, and cancer. Studies of their inhibitors are of great importance to the in-depth understanding of the physiochemical processes and in turn guide the development of new medications.[48]

The present work probes the target molecules' antidiabetic performances by measuring their PPAR activation and α-glucosidase inhibition in vitro. Table 1 depicts the bioactivity of all the target molecules. Among them, **TM-2p**(4-OH) reaches a remarkable level of PPAR in 73.37%, and **TM-2h**(4-Br)'s α-GI goes up to 79.70%. Table 2 presents the EC_{50} and IC_{50} values of a few selected target molecules.

3.5.1. PPAR agonist activity

As presented in Table 1 and Fig. 6a, there is only 1 molecule(**TM-1j**), out of 16, in **TM-1** whose PPAR relative activation is greater than 40%; for **TM-2**, that ratio is 9 out of 14, while for previously made series **B,** the ratio is 8 out of 14. Therefore the PPAR relative activation takes an order as: **TM-2** > **B** > **TM-**1. However, 3 molecules in the **B** series show even stronger PPAR relative activation, culminated by **B-b** and **B-n**. In addition, most of the active target molecules are 4-substituted; least active counterparts are either 3-substituted or 4-substituted with bulky functional group, for example OC_4H_9(**TM-2n**), or other aldehydes such as 6-methoxy-2-naphthaldehyde(**TM-2q**) or furan-2-carbaldehyde(**TM-2r**). For identical substituent at identical location, **TM-2** is almost invariably more active than their **TM-1** counterparts. Further analysis of the structural features also transpires that both **TM-2** and **B** series contain the benzenesulfonamide moiety, which is categorically absent from **TM-1**. It naturally prompts a plausible hypothesis of benzenesulfonamide being the potent pharmacophore. In general, the molecular weight of **TM-2** is smaller than its **B** counterpart, which in turn led the benzenesulfonamide moiety more accessible from the external environment. This could well be the key to its superior bioactivity. Also, for the weaker molecules, they tend to carry small 4-substituent, for example Cl (**B-f**), H (**B-k**) and HO (**B-p**). In comparison, those weak **TM-2** counterparts carry more bulky 4-substituent, for example OC_4H_9 (**TM-2n**). Thus, it can be reasonably speculated that the spatial hindrance of the SMZ moiety in **B** series is significantly greater than that of the sulfonamide moiety in **TM-2** series because of the presence of methylisoxazole fragment. The bulky substituent might have squeezed the SMZ fragment in order to achieve effective integration with its ligand(s). But for **TM-2** series, the molecules contained bulky substituent cannot achieve a reasonable three dimensional conformation to integrate with ligand. It is exactly such a spatial effect dictates that the sulfonamide structure cannot be abnormally bulky (Fig. 7).

3.5.2. α-Glucosidase inhibition activity

It is apparent from Table 1 and Fig. 6b that **TM-1** only possesses very weak α-GI activities, and there is hardly any appreciable disparity in α-GI activities among individual **TM-1** series molecules.

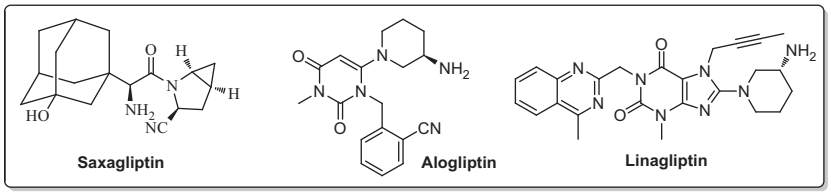


Figure 5. DPP-4 family drugs marketed in recent years.

Table 1
Antidiabetic activity of target molecules

TM	α-Glucosidase inhibition (%)	PPAR relative activation (%)	TM	α-Glucosidase inhibition (%)	PPAR relative activation (%)	B	α-Glucosidase inhibition (%)	PPAR relative activation (%)
1a	24.57	4.18	**2a**	31.65	46.75	**B-b**	41.57	81.78
1b	24.40	9.11	**2b**	32.66	14.75	**B-c**	53.71	22.38
1c	22.30	5.37	**2c**	34.75	45.77	**B-d**	20.31	64.52
1d	13.00	11.48	**2f**	66.26	71.87	**B-e**	24.71	36.67
1e	13.27	30.08	**2g**	40.77	58.68	**B-f**	44.23	3.92
1f	26.30	6.32	**2h**	79.70	67.32	**B-g**	47.08	19.55
1g	26.27	4.86	**2j**	15.68	60.31	**B-i**	50.75	48.38
1h	1.42	2.87	**2k**	41.73	60.98	**B-j**	12.67	78.17
1i	10.76	3.13	**2m**	14.09	57.32	**B-k**	14.95	17.83
1j	15.75	41.56	**2n**	−4.69	17.98	**B-l**	15.83	58.52
1k	7.36	5.83	**2o**	-4.32	9.87	**B-m**	70.51	68.41
1l	7.23	11.52	**2p**	52.81	73.37	**B-n**	14.33	83.30
1m	10.25	12.65	**2q**	6.39	19.05	**B-o**	19.18	43.05
1n	10.97	6.33	**2r**	−9.77	6.64	**B-p**	7.07	13.77
1o	0.35	12.64						
1p	21.38	5.30						

Note: PPAR relative activation is the average of four measurements at a constant concentration of 10 $\mu g \cdot mL^{-1}$; positive controls of α-GI and PPAR were acarbose and rosiglitazone, respectively.

Table 2
EC_{50} and IC_{50} of some active compounds

Entry	R	Object ID	Max Concn (μg/mL)	IC_{50} (μg/mL)	EC_{50} (μg/mL)
TM-2f	4-Cl	DIAO-000003638	10	4.07	6.74
TM-2h	4-Br	DIAO-000003633	10	2.92	8.21
TM-2p	4-OH	DIAO-000003636	10	4.14	5.56
Rosiglitazone			0.974		0.043
Acarbose			100	/	

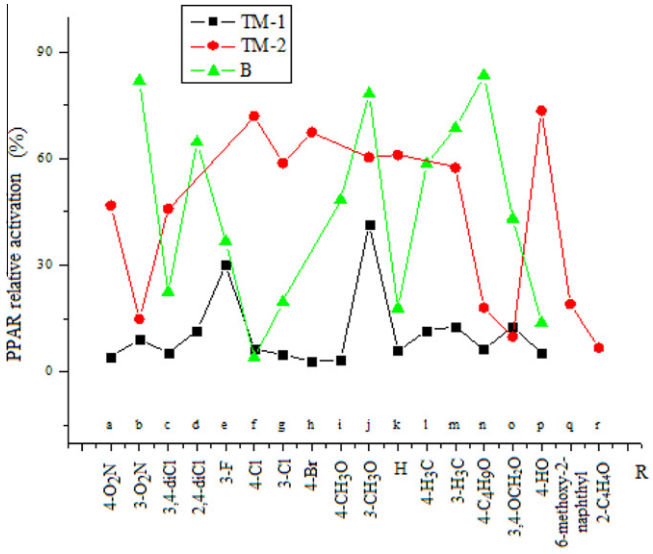


Figure 6a. PPAR relative activation-substituent diagram.

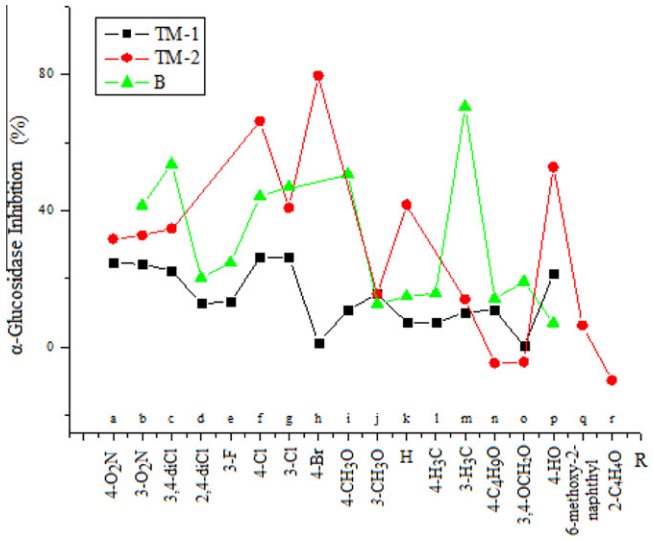


Figure 6b. α-GI-substituent diagram

The fact that **TM-1** does not show any significant α-GI activity corroborates well with the notion of sulfonamide being the likely potent pharmcophore. For **TM-2** whose α-GI activities are greater than 40%, their activities follow this order: **TM-2h**(4-Br) > **TM-2f**(4-Cl) > **TM-2p**(4-OH) > **TM-2k**(H) > **TM-2g**(3-Cl). Again, 4-substitution results in stronger α-GI activity. In comparison, **B** series follow a different order of activity: **B-m**(3-Me) > **B-c** (3,4-diCl) > **B-i**(4-OMe) > **B-g**(3-Cl) > **B-f**(4-Cl) > **B-b**(3-NO_2). The disparity in α-GI activities among **B** series is not as great as those in the **TM-2** series. The fact that **TM-2** and **B** series show clear distinction in their α-GI activities, despite of the common feature of sulfonamide moiety, implies the multiple factors involved in the competitive inhibition of α-GI activity, including perhaps spatial hindrance, charge density distribution, solubility and other functional groups. Both **TM-2f**(4-Cl) and **TM-2p**(4-HO) show significant α-GI activities, the former maybe due to the optimal size of chloro atom, and in turn electron density distribution, plus a fair lipo-hydro distribution coefficient (see Fig. 12); the latter maybe

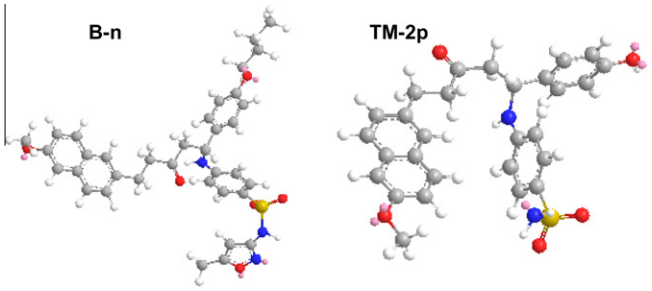


Figure 7. Three dimensional structures of **B-n** and **TM-2p**.

attributed to its hydrophilicity. **TM-2h**(4-Br) and **B-m**(3-CH_3) are most active in α-GI in the three series, their three dimensional structures show that the naphthalene ring does not share its plane with any other ring moieties. Despite drastically different three dimensional structures (Fig. 8), the two molecules show little disparity in their activities. This may point to the three dimensional conformation not being the decisive factor of its activity.

Comparison of the overall antidiabetic activities, as outlined in Figures 9, 10 and 11, shows considerable fluctuations in PPAR among **TM-1,** but their overall levels of α-GI are fairly moderate and constant; on the other hand, **TM-2** displays the common feature of high PPAR and α-GI performances, an invaluable pattern of multiple target activities. It is also noteworthy that the **B**-series exhibits diverse trends of PPAR and α-GI, indicating an intriguing structure–activity relationship.

It is interesting to note, as shown in Figure 12, that the lipo-hydro distribution coefficients (calculated by Chemdraw Ultra 12.0) for **TM-1**, **TM-2** and **B** series against individual substituent show to a great extent similar trend, which once again corroborates from

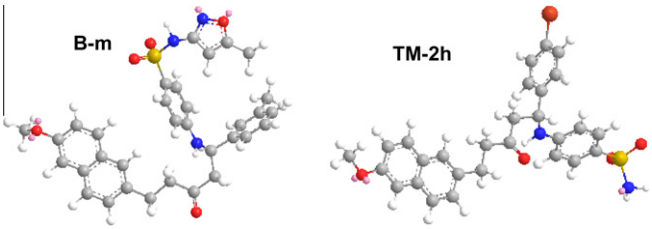


Figure 8. Threedimensional structures of **B-m** and **TM-2h**.

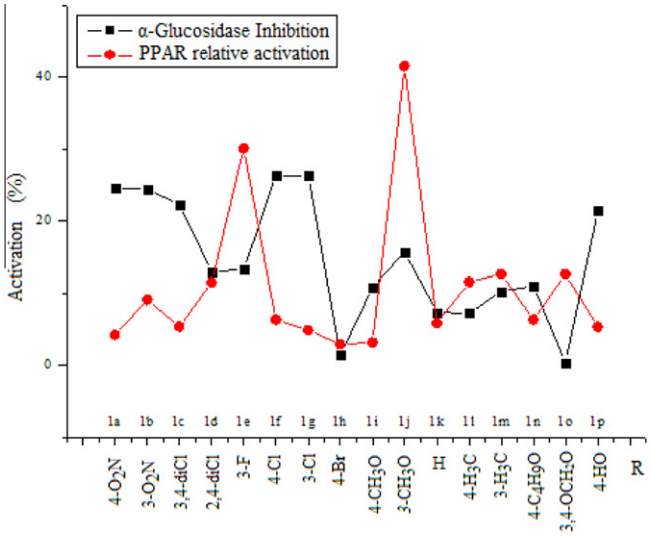


Figure 9. PPAR and α-GI of **TM-1**.

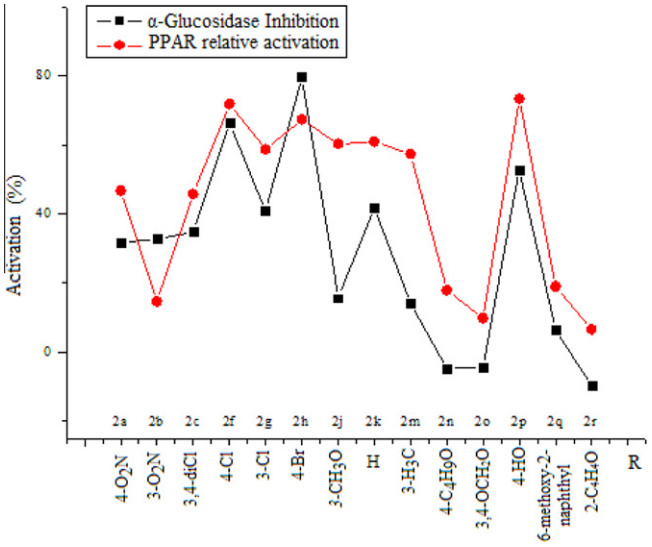


Figure 10. PPAR and α-GI of **TM-2**.

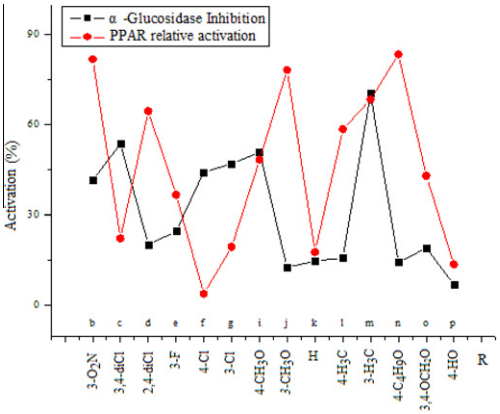


Figure 11. PPAR and α-GI of **B** series.

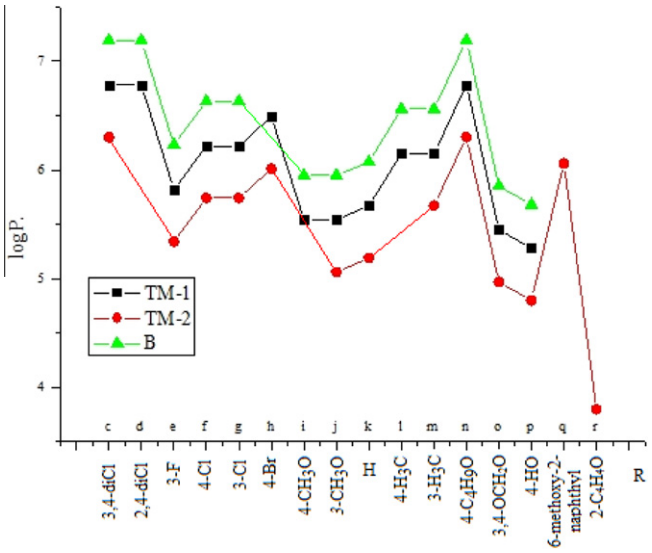


Figure 12. Relationship of lipo-hydro distribution coefficient-substituent.

a unique aspect the critical roles played by the substituent. Under the condition of identical substituent, the magnitude of the lipo-hydro distribution coefficient takes the following order: **TM-2** < **TM-1** < **B**, which indicates improved hydrophilicity for the new target molecules as reported in the present study. This also endorsed our approach to enhance the hydrophilicity by simple mass reduction without touching the key functional groups. Furthermore, the coincidence of trends of lipo-hydro distribution coefficient and biological activities against individual substituent shows a close correlation between the two parameters. Therefore the impact of the lipo-hydro distribution coefficient should be rightly taken into consideration in any further optimization of the target molecules.

In conclusion, implementation of our strategy to systematically tuning the size of the SMZ fragment has successfully led to novel β-amino ketone target molecules with significantly enhanced antidiabetic activities than their predecessors. In particular, novel target molecules **TM-2f**, **-2h** and **-2p** have demonstrated outstanding antidiabetic performances in all the tests conducted. The current results unambiguously pinpoint to the benzenesulfonamide moiety as the potent pharmacophore in the target molecules. This overall approach should have set important guidelines to the further development of antidiabetic drugs.

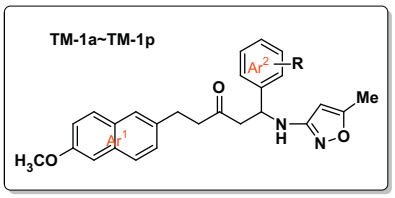
4. Experimental section

4.1. Reagents and instrumentation

Melting points were determined by an electrothermal X-6 apparatus. FT-IR spectra were carried out on Perkin-Elmer, Spectrum GX, USA, using KBr pellets in the 400–4000 cm^{-1} range. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 300 spectrometer using TMS as an internal standard. The chemical shifts were reported in parts per million (ppm), the coupling constants (*J*) are expressed in hertz (Hz) and signals were described as singlet (s), doublet (d), triplet (t), quartet (q), as well as multiplet (m). ESI-MS were obtained on an Agilent 1946B instrument. High resolution mass spectra (HRMS) analyse were conducted on a Daltonics Data Analysis 3.2 (Bruker) using ESI (electrospray ionization) techniques. The purity of the compounds was examined by thin-layer chromatography (TLC) on silica gel plate using petroleum ether and ethyl acetate. All chemical reagents and solvents were commercially available, and were used without further purification.

4.2. Chemistry

General procedure for synthesis of the target molecules: Aromatic aldehyde (2 mmol) and aromatic amine were added to the mixed solvent of anhydrous ethanol–chloroform (5–10 mL, v/v = 3:1). This mixture was stirred vigorously until the appearance of the precipitate, and then ketone (2 mmol) was added followed by a few droplets (0.1–0.2 mL) of concentrated hydrochloric acid as catalyst. Stirred continuously at 20–32 °C, and if necessary, additional amount of anhydrous ethanol was added. The reaction progress was monitored by TLC. Upon completion, the suspension was cooled in the refrigerator for about 2–5 h. The solid was subsequently collected by filtration. The filter cake was dispersed in 95% ethanol (4–10 mL), adjusting to pH 7–8 with 10% K_2CO_3 and stirring for approximately 2 h. Subsequently, the suspension was filtered with suction on a sintered glass funnel, the filter cake obtained was washed thoroughly with water (2 × 5 mL) and cool absolute ethanol (2 × 1.5 mL), and then dried in vacuo overnight to afforded the crude product. Recrystallising from ethanol, methanol, chloroform, or ethanol–acetone affords analytically pure product. Melting point was determined, and the structure was confirmed by ^1H NMR, ^{13}C NMR, ESI MS and HRMS techniques.



4.2.1. TM-1a 5-(6-Methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)-1-(4-nitrophenyl)pentan-3-one

Yield: 33.9%, mp: 166–168 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 2.23 (3H, s, CH_3), 2.77 (2H, q, *J* = 7.8 Hz, CH_2), 2.93–3.02 (4H, m, 2×CH_2), 3.92 (3H, s, OCH_3), 4.95–5.01 (1H, m, *CH), 4.99 (1H, s, NH), 5.41 (1H, s, O–C(Me)=C*H*), 7.09 (1H, s, Ar^1-H), 7.12 (1H, d, *J* = 9.0 Hz, Ar^1-H), 7.17 (1H, d, *J* = 8.8 Hz, Ar^1-H), 7.39 (2H, d, *J* = 8.6 Hz, Ar^2-H), 7.44 (1H, s, Ar^1-H), 7.61 (2H, d, *J* = 8.5 Hz, Ar^1-H), 8.03 (2H, d, *J* = 8.5 Hz, Ar^2-H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 12.5, 29.5, 44.9, 48.6, 53.7, 55.4, 93.5, 105.8, 119.1, 123.9 (2×C), 126.4, 127.1, 127.3 (2×C), 128.1, 128.9, 129.0, 133.2, 135.4, 147.2, 149.4, 157.6, 163.4, 169.1, 208.1. MS (*m*/*z*, %): 460 ($[M+H]^+$,100), 482 ($[M+Na]^+$, 10). HRMS: formula: $C_{26}H_{25}N_3NaO_5$, calcd: 482.1686, found: 482.1671.

4.2.2. TM-1b 5-(6-Methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)-1-(3-nitrophenyl)pentan-3-one

Yield: 47.8%, mp: 173–174 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 2.16 (3H, s, CH_3), 2.72 (2H, dd, *J* = 7.4, 15.4 Hz, CH_2), 2.86–2.91 (3H, m, CH_2 and CH_2*CH), 2.99 (1H, dd, *J* = 6.2, 16.9 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.92–4.97 (1H, m, *CH), 5.36 (1H, s, O–C(Me)=C*H*), 7.02 (1H, s, Ar^1-H), 7.04 (1H, d, *J* = 8.9 Hz, Ar^1-H), 7.12 (1H, d, *J* = 8.3 Hz, Ar^1-H), 7.29–7.32 (1H, m, Ar^2-H), 7.38 (1H, s, Ar^1-H), 7.50–7.57 (3H, m, Ar^2-H and 2Ar^1-H), 7.95 (1H, d, *J* = 8.4 Hz, Ar^2-H), 8.10 (1H, s, Ar^2-H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) *δ*: 12.6, 29.5, 44.9, 48.7, 53.5, 55.4, 93.6, 105.7, 119.0, 121.3, 122.5, 126.4, 127.1, 127.3, 127.4, 129.0, 129.6, 133.0, 133.3, 135.5, 144.3, 148.5, 157.5, 163.4, 169.1, 208.2. MS (*m*/*z*, %): 460 ($[M+H]^+$, 100), 482 ($[M+Na]^+$, 8). HRMS formula $C_{26}H_{25}N_3NaO_5$, calcd 482.1686, found 482.1693.

4.2.3. TM-1c 1-(3,4-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 85.7%, mp: 179–181 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 2.23 (3H, s, CH_3), 2.75 (2H, t, *J* = 7.9 Hz, CH_2), 2.92–2.98 (4H, m, 2×CH_2), 3.91 (3H, s, OCH_3), 4.85 (1H, s, NH), 4.86–4.89 (1H, m, *CH), 5.48 (1H, s, O–C(Me)=C*H*), 7.09–7.12 (2H, m, Ar^1-H), 7.16–7.29 (3H, m, 2 Ar^2-H and 1Ar^1-H), 7.40 (1H, s, Ar^2-H), 7.46 (1H, s, Ar^1-H), 7.63 (2H, d, *J* = 8.6 Hz, Ar^1-H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) *δ*: 12.7, 29.5, 45.8, 49.8, 53.2, 55.7, 105.4, 118.6, 126.5, 126.8, 127.1, 128.0, 128.7, 129.0, 129.5, 129.8, 131.1, 132.5, 133.9, 136.0, 136.9, 144.8, 157.4, 158.4, 163.8, 208.7. MS (*m*/*z*, %): 483 ($[M+H]^+$, 100), 505 ($[M+Na]^+$, 10). HRMS formula $C_{26}H_{24}Cl_2N_2NaO_3$, calcd 505.1056, found 505.1055.

4.2.4. TM-1d 1-(2,4-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 74.6%, mp: 161–163 °C. ^1H NMR (300 MHz, DMSO-d_6, ppm) *δ*: 2.17 (3H, s, CH_3), 2.70–2.90 (6H, m, CH_2CH_2, *$CHCH_2$), 3.85 (3H, s, OCH_3), 5.19 (1H, dd, *J* = 6.8, 13.9 Hz, *CH), 5.99 (1H, s, O–C(Me)=C*H*), 6.75 (1H, d, *J* = 6.6 Hz, Ar^1-H), 7.12 (1H, d, *J* = 8.5 Hz, Ar^1-H), 7.26 (1H, s, Ar^2-H), 7.31 (1H, d, *J* = 7.8 Hz, Ar^1-

H), 7.38 (1H, d, J = 7.5 Hz, Ar^2-H), 7.46 (1H, d, J = 7.7 Hz, Ar^2-H), 7.55–7.58 (2H, m, NH, Ar^1-H), 7.69–7.72 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 12.0, 28.8, 43.6, 47.6, 49.8, 55.1, 93.5, 105.8, 118.5 (2×C), 125.9, 126.7, 127.5, 127.6, 128.6, 128.7, 128.8, 132.1, 132.8, 136.2, 139.8, 156.8 (2×C), 163.0, 167.8, 206.5. MS (m/z, %): 483 ($[M+H]^+$, 100), 484 ($[M+2]^+$, 27), 485 ($[M+3]^+$, 67), 505 ($[M+Na]^+$, 5). HRMS formula $C_{26}H_{24}Cl_2N_2NaO_3$, calcd 505.1056, found 505.1042.

4.2.5. TM-1e 1-(3-Fluorophenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 71.2%, mp: 150–153 °C. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.17 (3H, s, CH_3), 2.81 (1H, dd, J = 6.7, 15.7 Hz, *CHCH_2), 2.86 (4H, m, CH_2), 2.99 (1H, dd, J = 7.0, 15.8 Hz, *CHCH_2), 3.85 (3H, s, OCH_3), 4.88 (1H, dd, J = 6.8, 13.9 Hz, *CH), 5.65 (1H, s, O–C(Me)=CH), 6.65 (1H, d, J = 7.7 Hz, Ar^1-H), 7.03 (1H, d, J = 7.5 Hz, Ar^2-H), 7.11–7.19 (2H, m, Ar^2-H), 7.26–7.31 (4H, m, Ar^1-H), 7.56 (1H, s, NH), 7.70 (2H, d, J = 7.5 Hz, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 12.0, 28.8, 43.5, 49.4, 52.7, 55.1, 93.7, 105.7, 118.5, 122.7, 125.9, 126.7, 127.7, 128.6, 128.8, 130.1, 130.2, 132.8, 136.2, 146.6, 156.8, 160.6, 163.4, 163.7, 167.6, 207.1. HRMS formula $C_{26}H_{25}FN_2NaO_3$, calcd 455.1741, found 455.1731.

4.2.6. TM-1f 1-(4-Chlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 88.1%, mp: 169–171 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.22 (3H, s, CH_3), 2.74 (2H, dd, J = 6.8, 14.1 Hz, CH_2), 2.93 (3H, d, J = 7.4 Hz, CH_2, CH_2*CH), 3.10 (1H, dd, J = 6.7, 16.5 Hz, CH_2*CH), 3.91 (3H, s, OCH_3), 4.85 (1H, s, NH), 4.89–4.92 (1H, m, *CH), 5.39 (1H, s, O–C(Me)=CH), 7.12–7.16 (2H, m, Ar^1-H), 7.19–7.23 (5H, m, 4Ar^2-H and Ar^1-H), 7.45 (1H, s, Ar^1-H), 7.63 (2H, d, J = 8.5 Hz, Ar^1-H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 12.8, 29.8, 45.2, 49.7, 53.2, 55.3, 93.6, 105.6, 118.9, 127.2, 127.4, 128.0, 128.7 (2×C), 129.0 (2×C), 129.2, 129.5, 132.5, 133.8, 136.1, 144.6, 157.2, 158.3, 163.8, 208.6. MS (m/z, %): 449 ($[M+H]^+$, 100), 471 ($[M+Na]^+$, 4). HRMS formula $C_{26}H_{25}ClN_2NaO_3$, calcd 471.1446, found 471.1434.

4.2.7. TM-1g 1-(3-Chlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 48.8%, mp: 154–156 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.23 (3H, s, CH_3), 2.75 (2H, t, J = 7.9 Hz, CH_2), 2.92–2.97 (3H, m, CH_2 and CH_2*CH), 3.00 (1H, dd, J = 6.5, 16.6 Hz, CH_2*CH), 3.91 (3H, s, OCH_3), 4.79 (1H, d, J = 7.1 Hz, NH), 4.87–4.91 (1H, m, *CH), 5.40 (1H, s, O–C(Me)=CH), 6.91 (1H, s, Ar^1-H), 7.15–7.23 (5H, m, 3Ar^2-H and 2Ar^1-H), 7.30 (1H, s, Ar^2-H), 7.47 (1H, s, Ar^1-H), 7.63 (2H, d, J = 8.5 Hz, Ar^3-H). ^{13}C NMR (75 MHz,$CDCl_3$,ppm) δ: 12.8, 29.8, 45.2, 49.8, 53.8, 55.4, 93.5, 105.4, 118.7, 126.4, 126.8, 127.1, 127.4, 127.5, 128.6, 129.3, 129.5, 131.6, 132.8, 133.8, 136.1, 145.2, 157.3, 158.3, 163.9, 208.6. MS (m/z, %): 449 ($[M+H]^+$, 100), 471 ($[M+Na]^+$, 5). HRMS formula $C_{26}H_{25}ClN_2NaO_3$, calcd 471.1446, found 471.1431.

4.2.8. TM-1h 1-(4-Bromophenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 67.5%, mp: 188–190 °C. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.17 (3H, s, CH_3), 2.76–2.81 (1H, m, *CHCH_2), 2.84–2.89 (4H, m, 2×CH_2), 2.99 (1H, dd, J = 8.5, 16.3 Hz, *CHCH_2), 3.85 (3H, s, OCH_3), 4.82 (1H, dd, J = 8.0, 13.9 Hz, *CH), 5.62 (1H, s, O–C(Me)=CH), 6.65 (1H, d, J = 7.9 Hz, Ar^1-H), 7.12 (1H, d, J = 8.4 Hz, Ar^1-H), 7.26–7.30 (4H, m, NH, Ar^1-H and 2 Ar^1-H), 7.45 (2H, d, J = 8.2 Hz, Ar^2-H), 7.55 (1H, s, Ar^1-H), 7.68–7.72 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz,$CDCl_3$, ppm) δ: 12.0, 28.8, 43.5, 49.3, 52.6, 55.1, 93.7, 105.7, 118.5, 119.8, 125.9, 126.7, 127.7, 128.6(2×C), 128.7 128.8, 131.0(2×C), 132.8, 136.2, 142.9, 156.8, 163.4, 167.5, 207.1. MS (m/z, %): 493 ($[M+H]^+$, 100), 515 ($[M+Na]^+$, 5). HRMS formula $C_{26}H_{25}BrN_2NaO_3$, calcd 515.0941, found 515.0923.

4.2.9. TM-1i 5-(6-Methoxynaphthalen-2-yl)-1-(4-methoxyphenyl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 88.5%, mp: 163–165 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.15 (3H, s, CH_3), 2.67–2.69 (2H, m, CH_2), 2.84–2.89 (3H, m, CH_2, CH_2*CH), 2.98 (1H, dd, J = 6.7, 16.0 Hz, CH_2*CH), 3.69 (3H, s, Ar^2-OCH_3), 3.84 (3H, s, OCH_3), 4.79–4.82 (1H, m, *CH), 5.33 (1H, s, O–C(Me)=CH), 6.73 (2H, d, J = 8.5 Hz, Ar^1-H), 7.04 (2H, d, J = 9.8 Hz, Ar^2-H), 7.10–7.14 (3H, m, 2Ar^2-H and 1Ar^1-H), 7.39 (1H, s, Ar^1-H), 7.58 (2H, d, J = 8.5 Hz, Ar^1-H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 12.5, 29.4, 45.2, 49.3, 54.0, 55.3, 55.4, 93.6, 105.7, 114.1 (2×C), 118.9, 126.3, 127.0, 127.6, 128.9 (2×C), 129.0, 130.1, 133.2, 133.9, 136.0, 157.4, 159.0, 164.0, 168.7, 208.6. MS (m/z, %): 445 ($[M+H]^+$, 51), 467 ($[M+Na]^+$, 8). HRMS formula $C_{27}H_{28}N_2NaO_4$, calcd 467.1941, found 467.1959.

4.2.10. TM-1j 5-(6-Methoxynaphthalen-2-yl)-1-(3-methoxyphenyl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 81.3%, mp: 185–187 °C. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.17 (3H, s, CH_3), 2.80 (1H, dd, J = 5.7, 16.7 Hz, *CHCH_2), 2.83–2.88 (4H, m, 2×CH_2), 3.05 (1H, dd, J = 5.9, 16.5 Hz, *CHCH_2), 3.71 (3H, s, Ar^2-OCH_3), 3.85 (3H, s, OCH_3), 4.83 (1H, dd, J = 6.8, 13.9 Hz, *CH), 5.63 (1H, s, O–C(Me)=CH), 6.59 (1H, d, J = 7.9 Hz, Ar^1-H), 6.77 (1H, d, J = 7.3 Hz, Ar^1-H), 6.92 (1H, s, Ar^2-H), 6.93 (1H, d, J = 8.0 Hz, Ar^2-H), 7.10–7.30 (4H, m, NH, Ar^1-H and 2Ar^2-H), 7.56 (1H, s, Ar^1-H), 7.70 (2H, d, J = 8.0 Hz, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 12.0, 28.8, 43.6, 49.8, 53.2, 55.0, 55.1, 93.7, 105.7, 112.0, 112.3, 118.5, 118.7, 125.9, 126.7, 128.6, 128.8, 129.3, 132.8, 136.2, 145.2, 156.8, 159.2, 163.6, 163.7, 167.5, 207.3. MS (m/z, %): 445 ($[M+H]^+$, 100), 446 ($[M+Na]^+$, 23). HRMS formula $C_{27}H_{28}N_2NaO_4$, calcd 467.1941, found 467.1923.

4.2.11. TM-1k 5-(6-Methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)-1-phenylpentan-3-one

Yield: 63.8%, mp: 177–179 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.22 (3H, s, CH_3), 2.68–2.72 (2H, m, CH_2), 2.88–2.95 (3H, m, CH_2, CH_2*CH), 3.06 (1H, dd, J = 6.7, 16.0 Hz, CH_2*CH), 3.91 (3H, s, OCH_3), 4.91–4.95 (1H, m, *CH), 5.41 (1H, s, O–C(Me)=CH), 7.08–7.10 (2H, m, Ar^1-H), 7.14–7.16 (1H, m, Ar^1-H), 7.22–7.29 (5H, m, Ar^2-H), 7.45 (1H, s, Ar^1-H), 7.63 (2H, d, J = 8.5 Hz, Ar^1-H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 12.5, 29.6, 45.7, 49.2, 53.7, 55.2, 93.6, 105.8, 118.9, 126.7, 126.8, 127.0, 127.4 (2×C), 128.7, 129.0 (2×C), 129.9, 130.1, 133.0, 133.8, 141.2, 157.1, 158.4, 163.8, 208.5. MS (m/z, %): 415 ($[M+H]^+$, 100), 437 ($[M+Na]^+$, 5). HRMS formula $C_{26}H_{26}N_2NaO_3$, calcd 437.1836, found 437.1833.

4.2.12. TM-1l 5-(6-Methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)-1-p-tolylpentan-3-one

Yield: 61.2%, mp: 144–147 °C. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.16 (3H, s, Ar^3-CH_3), 2.24 (3H, s, Ar^2-CH_3), 2.74 (1H, dd, J = 9.3, 15.1 Hz, *CHCH_2), 2.84 (4H, m, 2×CH_2), 2.97 (1H, dd, J = 8.0, 15.4 Hz, *CHCH_2), 3.85 (3H, s, OCH_3), 4.79 (1H, dd, J = 6.8 Hz, 13.9 Hz, *CH), 5.61 (1H, s, O–C(Me)=CH), 6.55 (1H, d, J = 7.8 Hz, Ar^1-H), 7.07 (2H, d, J = 6.6 Hz, Ar^2-H), 7.11 (1H, d, J = 7.7 Hz, Ar^1-H), 7.21 (2H, d, J = 6.6 Hz, Ar^2-H), 7.23–7.26 (2H, m, Ar^1-H), 7.54 (1H, s, NH), 7.69 (2H, d, J = 7.0 Hz, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 12.0, 20.7, 28.8, 43.6, 49.7, 53.0, 55.1, 93.8, 105.7, 118.5, 125.9, 126.4 (2×C), 126.7, 127.7, 128.6, 128.8 (2×C), 132.8, 135.9, 136.2, 136.3, 140.4, 156.8, 163.6, 167.4, 207.4. MS (m/z, %): 429 ($[M+H]^+$, 100), 451 ($[M+Na]^+$, 7). HRMS formula $C_{27}H_{28}N_2NaO_3$, calcd 451.1992, found 451.1993.

4.2.13. TM-1m 5-(6-Methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)-1-m-tolylpentan-3-one

Yield: 51.3%, mp: 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.22 (3H, s, CH_3), 2.30 (3H, s, Ar^2-CH_3), 2.72 (2H, t, J = 7.3 Hz, CH_2), 2.89–2.95 (3H, m, CH_2 and *$CHCH_2$), 3.03 (1H, dd, J = 6.8, 15.9 Hz, CH_2*CH), 3.90 (3H, s, OCH_3), 4.68–4.72 (1H, m, *CH), 4.89 (1H, d, J = 5.9 Hz, NH), 5.41 (1H, s, O–C(Me)=CH), 7.09 (5H, m, 4Ar^2-H and 1Ar^1-H), 7.19 (2H, d, J = 8.4 Hz, Ar^1-H), 7.46 (1H, s, Ar^1-H), 7.62 (2H, d, J = 8.4 Hz, Ar^1-H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 12.4, 21.4, 28.3, 45.1, 49.4, 53.9, 55.3, 93.4, 105.7, 119.0, 124.5, 127.3, 127.4, 127.9, 128.2, 128.5, 128.8, 129.0, 129.1, 133.0, 133.9, 137.0, 142.3, 157.1, 158.7, 163.9, 208.4. MS (m/z, %): 429 ([M+H]$^+$, 100), 451 ([M+Na]$^+$, 7). HRMS formula $C_{27}H_{28}N_2NaO_3$, calcd 451.1992, found 451.1993.

4.2.14. TM-1n 1-(4-Butoxyphenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

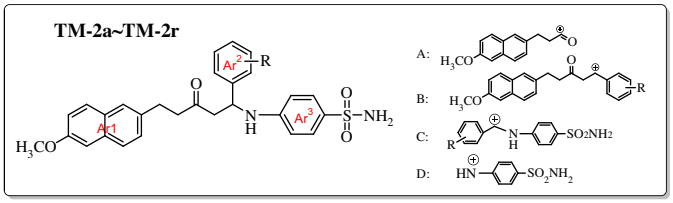
Yield: 72.3%, mp: 120–123 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 0.92 (3H, t, J = 7.3 Hz, CH_2CH_3), 1.37–1.44 (2H, m, CH_2CH_3), 1.63–1.68 (2H, m, $CH_2CH_2CH_3$), 2.16 (3H, s, CH_3), 2.75–3.01 (6H, m, $COCH_2CH_2$, *$CHCH_2$), 3.85 (3H, s, OCH_3), 3.90 (2H, d, J = 6.3 Hz, OCH_2), 4.77 (1H, dd, J = 6.8, 13.9 Hz, *CH), 5.60 (1H, s, O–C(Me)=CH), 6.50 (1H, d, J = 7.5 Hz, Ar^1-H), 6.80 (2H, d, J = 6.3 Hz, Ar^2-H), 7.11 (1H, d, J = 8.3 Hz, Ar^1-H), 7.21–7.25 (4H, m, 2Ar^1-H, 2Ar^2-H), 7.53 (1H, s, NH), 7.69 (2H, d, J = 8.4 Hz, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 12.0, 13.7, 18.8, 28.8, 30.8, 43.6, 49.7, 52.8, 55.1, 67.0, 93.8, 105.7, 114.0 (2×C), 118.5, 125.9, 126.7, 127.5, 127.6 (2×C), 128.6, 128.8, 132.7, 135.1, 136.2, 156.8, 157.6, 163.6, 167.4, 207.5. MS (m/z, %): 487 ([M+H]$^+$, 91). HRMS formula $C_{30}H_{34}N_2NaO_4$, calcd 509.2411, found 509.2394.

4.2.15. TM-1o 1-(Benzo[*d*][1,3]dioxol-5-yl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 96.3%, mp: 187–189 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.17 (3H, s, CH_3), 2.76 (1H, dd, J = 5.4, 15.9 Hz, CH_2*CH), 2.80–2.86 (4H, m, 2×CH_2), 2.96 (1H, dd, J = 8.6, 15.7 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.74–4.79 (1H, m, *CH), 5.63 (1H, s, O–C(Me)=CH), 5.95 (2H, s, OCH_2O), 6.53 (1H, d, J = 8.6 Hz, Ar^1-H), 6.78–6.80 (2H, m, 2Ar^2-H), 6.93 (1H, s, NH), 7.10–7.14 (1H, m, Ar^1-H), 7.25–7.30 (2H, m, Ar^1-H and Ar^2-H), 7.55 (1H, s, Ar^1-H), 7.69–7.72(2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 12.0, 28.8, 43.6, 53.1, 55.1, 56.1, 93.7, 105.7, 107.9, 112.1, 118.5, 119.8, 126.1, 126.7, 127.7, 128.6, 128.8, 129.5, 132.8, 136.2, 144.7, 146.0, 156.8, 157.5, 167.4, 207.1. MS (m/z, %):459 ([M+H]$^+$, 100), 481 ([M+Na]$^+$, 43). HRMS formula $C_{27}H_{26}N_2NaO_5$, calcd 481.1734, found 481.1741.

4.2.16. TM-1p 1-(4-Hydroxyphenyl)-5-(6-methoxynaphthalen-2-yl)-1-(5-methylisoxazol-3-ylamino)pentan-3-one

Yield: 82.2%, mp: 174–176 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.16 (3H, s, CH_3), 2.74 (1H, dd, J = 5.4, 15.5 Hz, CH_2*CH), 2.80–2.86 (4H, m, 2×CH_2), 2.96 (1H, dd, J = 8.5, 15.7 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.73 (1H, q, J = 6.3 Hz, *CH), 5.60 (1H, s, O–C(Me)=CH), 6.48 (2H, d, J = 8.4 Hz, Ar^1-H), 6.66 (2H, d, J = 8.2 Hz, Ar^2-H), 7.10–7.14 (2H, m, Ar^1-H), 7.27 (2H, d, J = 8.6 Hz, Ar^2-H), 7.54 (1H, s, NH), 7.70 (2H, d, J = 8.9 Hz, Ar^1-H), 9.28 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 11.9, 28.7, 43.6, 49.7, 52.8, 55.1, 93.7, 105.7, 114.8 (2×C), 118.4, 125.8, 126.5, 126.6, 127.5 (2×C), 128.5, 128.7, 132.7, 133.5, 136.2, 156.2, 156.7, 163.6, 167.2, 207.5. MS (m/z, %): 431 ([M+H]$^+$, 67), 453 ([M+Na]$^+$, 37). HRMS formula $C_{26}H_{26}N_2NaO_4$, calcd 453.1785, found 453.1770.



4.2.17. TM-2a 4-(5-(6-Methoxynaphthalen-2-yl)-1-(4-nitrophenyl)-3-oxopentylamino)benzenesulfonamide

Yield: 82.8%, mp: 167.2–169.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.84–2.95 (5H, m, CH_2CH_2, CH_2*CH), 3.01 (1H, dd, J = 8.8, 16.7 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 5.12 (1H, dd, J = 8.1, 12.5 Hz, *CH), 6.60 (2H, d, J = 8.5 Hz, Ar^3-H), 6.91 (2H, s, NH_2), 7.05 (1H, d, J = 7.7 Hz, Ar^1-H), 7.11 (1H, dd, J = 2.1, 8.9 Hz, Ar^1-H), 7.25 (1H, s, Ar^1-H), 7.30 (2H, d, J = 8.5 Hz, Ar^2-H), 7.44 (2H, d, J = 8.5 Hz, Ar^3-H), 7.56 (1H, s, Ar^1-H), 7.64–7.70 (3H, m, Ar^1-H), 8.14 (2H, d, J = 8.5 Hz, Ar^2-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.4, 49.5, 51.9, 55.2, 105.8, 111.9(2×C), 118.6, 123.7, 125.9, 126.8, 127.3, 127.7, 127.9, 128.6, 128.8(2×C), 131.2, 132.8, 136.1, 146.6, 150.0, 151.3, 156.8, 206.5. ESI MS (m/z, %): 213 (A, 63), 361 (B, 17), 305 (C, 8), 171 (D, 36), 534 ([M+H]$^+$, 9), 556 ([M+Na]$^+$, 72). HRMS calcd for $C_{28}H_{27}N_3NaO_6S$ 556.1518, found [M+Na]$^+$ 556.1507, [M+K]$^+$ 572.1240.

4.2.18. TM-2b 4-(5-(6-Methoxynaphthalen-2-yl)-1-(3-nitrophenyl)-3-oxopentylamino)benzenesulfonamide

Yield: 79.2%, mp: 121.2–124.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.90–2.99 (5H, m, CH_2CH_2, CH_2*CH), 3.09 (1H, dd, J = 8.6, 16.2 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 5.08 (1H, m, *CH), 6.64 (2H, d, J = 8.6 Hz, Ar^3-H), 6.91 (2H, s, NH_2), 7.06–7.13 (2H, m, NH and Ar^1-H), 7.25–7.31 (2H, m, Ar^2-H), 7.45 (2H, d, J = 8.6 Hz, Ar^3-H), 7.54–7.62 (2H, m, Ar^1-H), 7.66–7.71 (2H, m, Ar^1-H), 7.88 (1H, d, J = 7.6 Hz, Ar^1-H), 8.05 (1H, d, J = 8.0 Hz, Ar^2-H), 8.31 (1H, s, Ar^2-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.6, 43.6, 49.3, 51.4, 55.2, 105.8, 111.6 (2×C), 118.4, 119.9 (2×C), 125.8, 126.8, 127.2 (2×C), 127.6, 128.5, 128.7 (3×C), 130.8, 132.7, 134.5, 145.8, 147.5, 150.1, 156.7, 207.0. ESI MS (m/z, %): 213 (A, 54), 361 (B, 23), 305 (C, 9), 171 (D, 38), 534 ([M+H]$^+$,4), 556 ([M+Na]$^+$, 68). HRMS calcd for $C_{28}H_{27}N_3NaO_6S$ 556.1518, found [M+Na]$^+$ 556.1528, [M+K]$^+$ 572.1289.

4.2.19. TM-2c 4-(1-(3,4-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 68.5%, mp: 164.0–-166.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 3.00 (2H, t, CH_2CO, J = 7.1 Hz), 3.12 (2H, t, J = 7.1 Hz, CH_2), 3.29–3.35 (2H, m, J = 6.9 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.96 (1H, dd, J = 7.9, 13.7 Hz, *CH), 6.78–6.83 (2H, m, Ar^3-H), 7.05 (1H, s, Ar^1-H), 7.13 (2H, d, J = 8.4 Hz, Ar-H), 7.20–7.27 (3H, m, Ar-H), 7.40 (1H, d, J = 8.2 Hz, Ar^1-H), 7.33–7.59 (1H, m, Ar^1-H), 7.67 (1H, s, Ar^1-H), 7.74 (2H, d, J = 8.6 Hz, Ar^3-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.5, 50.1, 51.9, 55.1, 105.8, 111.8 (2×C), 111.9, 118.5, 125.6, 126.8, 127.3 (3×C), 127.8, 128.8, 129.1, 130.7, 130.5, 131.2, 131.8, 132.6, 136.2, 144.6, 150.1, 156.8, 207.3. ESI MS (m/z, %): 213 (A, 100), 385 (B, 33), 329 (C, 4), 171 (D, 10), 557 ([M+H]$^+$, 68), 579 ([M+Na]$^+$, 4). HRMS calcd for $C_{28}H_{26}Cl_2N_2NaO_4S$ 579.0883, found [M+Na]$^+$ 579.0863, [M+K]$^+$ 595.0619.

4.2.20. TM-2e 4-(1-(3-Fluorophenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 72.1%, mp: 183.9–186.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.73–3.07 (6H, m, $CH_2CH_2COCH_2$), 3.85 (3H, s, OCH_3), 4.99–5.02 (1H, m, *CH), 6.61 (2H, d, J = 8.0 Hz, Ar^3-H), 6.90–6.94 (3H, m, NH_2 and NH), 7.03 (1H, t, J = 8.0 Hz, Ar^2-H), 7.12 (1H, d, J = 8.8 Hz, Ar^2-H), 7.22–7.28 (3H, m, Ar^1-H), 7.32 (2H, d, J = 8.2 Hz, Ar^1-H), 7.45 (2H, d, J = 8.0 Hz, Ar^3-H), 7.57 (1H, s, Ar^1-H), 7.66–7.72 (2H, m, Ar^2-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.4, 49.9, 51.8, 55.1, 105.7, 111.9 (2×C), 118.5, 122.6, 125.9, 126.7, 127.3, 127.7, 128.6, 128.8 (2×C), 130.3, 130.4, 130.9, 132.8, 136.2, 148.3, 146.4, 150.2, 156.8, 160.7, 206.8. ESI MS (m/z, %): 213 (A, 61), 351 (B, 18), 295 (C, 17), 171 (D, 12), 507 ([M+H]$^+$, 100), 529 ([M+Na]$^+$, 14). HRMS calcd for $C_{28}H_{27}FN_2NaO_4S$ 528.9173, found [M+Na]$^+$528.9192.

4.2.21. TM-2f 4-(1-(4-Chlorophenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 78.0%, mp: 178.8–181.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.84 (1H, dd, J = 4.5, 16.5 Hz, CH_2*CH), 2.87–2.93 (4H, m, CH_2CH_2), 3.01 (1H, dd, J = 8.9, 16.5 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.96 (1H, dd, J = 8.1,14.2 Hz, *CH), 6.58 (2H, d, J = 8.6 Hz, Ar^3-H), 6.89 (2H, s, NH_2), 6.93 (1H, d, J = 8.6 Hz, NH), 7.14 (1H, d, J = 8.9 Hz, Ar^1-H), 7.25–7.38 (6H, m, Ar-H), 7.43 (2H, d, J = 8.9 Hz, Ar^3-H), 7.56 (1H, s, Ar^1-H), 7.66–7.71 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.5, 49.9, 51.7, 55.1, 105.7, 111.8 (2×C), 118.5, 125.8, 126.7, 127.2 (3×C), 127.6 (2×C), 128.4, 128.5 (2×C), 128.8, 130.8, 131.2, 132.7, 136.1, 142.1, 150.2, 156.8, 206.8. ESI MS (m/z, %): 213 (A, 100), 351 (B, 43), 295 (C, 5), 171 (D, 12), 523 ([M+H]$^+$, 23), 545 ([M+Na]$^+$, 5). HRMS calcd for $C_{28}H_{27}ClN_2NaO_4S$ 545.1272, found [M+Na]$^+$ 545.1260, [M+K]$^+$ 561.1031.

4.2.22. TM-2g 4-(1-(3-Chlorophenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 81.8%, mp: 127.9–130.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.88–2.96 (5H, m, CH_2CH_2CO CH_2*CH), 3.03 (1H, dd, J = 9.1, 16.5 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.99 (1H, dd, *CH, J = 8.4, 12.7 Hz), 6.61 (2H, d, J = 8.7 Hz, Ar^3-H), 6.90 (2H, s, NH_2), 6.93 (1H, d, J = 8.7 Hz, NH), 7.09 (1H, d, J = 7.3 Hz, Ar-H), 7.25–7.35 (5H, m, Ar-H), 7.43–7.46 (3H, m, Ar-H), 7.57 (1H, s, Ar^1-H), 7.66–7.72 (2H, m, Ar^3-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.4, 49.9, 51.8, 55.1, 105.7, 111.8 (2×C), 118.5, 125.3, 125.9, 126.4, 126.7, 127.0, 127.3, 127.6 (2×C), 128.6, 128.8, 130.3, 130.9, 132.7, 133.2, 136.2, 145.9, 150.1, 156.8, 206.8. ESI MS (m/z, %): 213 (A, 78), 351 (B, 18), 295 (C, 9), 171 (D, 6), 523 ([M+H]$^+$, 100), 545 ([M+Na]$^+$, 14). HRMS calcd for $C_{28}H_{27}ClN_2NaO_4S$ 545.1272, found [M+Na]$^+$ 545.1286, [M+K]$^+$ 561.1022.

4.2.23. TM-2h 4-(1-(4-Bromophenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 97.5%, mp: 170.4–172.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.84 (1H, dd, J = 4.5, 16.5 Hz, CH_2*CH), 2.88–2.95 (4H, m, CH_2CH_2), 3.01 (1H, dd, J = 8.8, 16.4 Hz CH_2**CH), 3.85 (3H, s, OCH_3), 4.95 (1H, dd, J = 7.8, 12.8 Hz, *CH), 6.57 (2H, d, J = 8.4 Hz, Ar^3-H), 6.89 (2H, s, NH_2), 6.93 (1H, d, J = 8.7 Hz, NH), 7.12 (1H, d, J = 8.7 Hz, Ar^1-H), 7.25–7.32 (3H, m, Ar^1-H), 7.35 (1H, s, Ar^1-H), 7.43 (2H, d, J = 8.8 Hz, Ar^3-H), 7.47 (2H, d, J = 8.4 Hz, Ar^2-H), 7.56 (1H, s, Ar^1-H), 7.66–7.71 (2H, m, Ar^2-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.7, 43.5), 49.8, 51.7, 55.1, 105.8, 111.8 (2×C), 118.5, 119.9, 125.8, 126.7, 127.2 (2×C), 127.6, 128.5, 128.7 (3×C), 130.8, 131.2 (2×C), 132.7, 136.1, 142.5, 150.1, 156.8, 206.5. ESI MS (m/z, %): 213 (A, 100), 395 (B, 30), 341 (C, 2), 171 (D, 12), 567 ([M+H]$^+$, 12), 589 ([M+Na]$^+$, 8). HRMS calcd for $C_{28}H_{27}BrN_2NaO_4S$ 589.0767, found [M+Na]$^+$ 589.0745, [M+K]$^+$ 605.0556.

4.2.24. TM-2j 4-(5-(6-Methoxynaphthalen-2-yl)-1-(3-methoxyphenyl)-3-oxopentylamino)benzenesulfonamide

Yield: 77.2%, mp: 121.6–124.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.84 (1H, dd, J = 4.3, 16.3 Hz CH_2*CH), 2.88–2.93 (4H, m, CH_2CH_2), 3.01 (1H, dd, J = 9.3, 16.3 Hz, CH_2*CH), 3.70 (3H, s, Ar^2-OCH_3), 3.85 (3H, s, OCH_3), 4.99 (1H, m, *CH), 6.59 (2H, d, J = 8.8 Hz, Ar^3-H), 6.78 (1H, d, J = 8.8 Hz, Ar^2-H), 6.88 (2H, s, NH_2), 6.91–6.96 (2H, m, NH and Ar-H), 6.96 (1H, s, Ar^1-H), 7.12–7.31 (4H, m, Ar-H), 7.43 (2H, d, J = 8.4 Hz, Ar^3-H), 7.56 (1H, s, Ar^1-H), 7.66–7.71 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 27.8, 43.5, 50.3, 52.2, 55.1, 60.2, 105.7, 111.3, 116.4, 119.3 (2×C), 125.7, 126.2, 126.3, 127.2, 127.6 (2×C), 128.2 (2×C), 128.6, 128.8, 131.0, 132.3, 133.2, 143.6, 149.3, 157.8, 159.8, 207.1. ESI MS (m/z, %): 213 (A, 100), 347 (B, 39), 291 (C, 4), 171 (D, 7), 519 ([M+H]$^+$, 63), 541 ([M+Na]$^+$, 18). HRMS calcd for $C_{29}H_{30}N_2NaO_5S$ 541.1768, found [M+Na]$^+$ 541.1794, [M+K]$^+$ 557.1583.

4.2.25. TM-2k 4-(5-(6-Methoxynaphthalen-2-yl)-3-oxo-1-phenylpentylamino)benzenesulfonamide

Yield: 89.1%, mp: 181.5–183.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.83 (1H, dd, J = 4.4, 16.3 Hz, CH_2*CH), 2.88–2.93 (4H, m, CH_2CH_2), 3.02 (1H, dd, J = 9.1, 16.2 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.95 (1H, dd, J = 8.1, 12.4 Hz, *CH), 6.58 (2H, d, J = 8.6 Hz, Ar^3-H), 6.88 (2H, s, NH_2), 6.93 (1H, d, J = 8.5 Hz, NH), 7.20 (1H, d, J = 7.1 Hz, Ar-H), 7.29 (1H, d, J = 7.1 Hz, Ar-H), 7.26–7.31 (4H, m, Ar-H), 7.36–7.44 (4H, m, Ar-H), 7.56 (1H, s, Ar^1-H), 7.66–7.71 (2H, m, Ar^3-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.5, 50.2, 52.3, 55.1, 105.7, 111.8 (2×C), 118.5, 125.9, 126.4, 126.7, 126.9 (2×C), 127.2 (2×C), 127.7, 128.5, 128.6, 128.8 (2×C), 130.6, 132.8, 136.2, 143.1, 150.4, 156.8, 207.0. ESI MS (m/z, %): 213 (A, 100), 317 (B, 30), 261 (C, 7), 171 (D, 7), 489 ([M+H]$^+$, 46), 511 ([M+Na]$^+$, 17). HRMS calcd for $C_{28}H_{28}N_2NaO_4S$ 511.1667, found [M+Na]$^+$ 511.1745, [M+K]$^+$ 527.1414.

4.2.26. TM-2m 4-(5-(6-Methoxynaphthalen-2-yl)-3-oxo-1-m-tolylpentylamino)benzenesulfonamide

Yield: 77.7%, mp: 139.8–142.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.25 (3H, s, CH_3), 2.78 (1H, dd, J = 4.2, 16.3 Hz, CH_2**CH), 2.82–2.89 (4H, m, CH_2CH_2), 3.00 (1H, dd, J = 9.2, 16.3 Hz CH_2*CH), 3.85 (3H, s, OCH_3), 4.90 (1H, dd, J = 8.2, 12.6 Hz, *CH), 6.58 (2H, d, J = 8.6 Hz, Ar^3-H), 6.89 (2H, s, NH_2), 6.93 (1H, d, J = 8.5 Hz, NH), 7.02 (1H, s, Ar^2-H), 7.10–7.19 (4H, m, Ar-H), 7.29 (2H, d, J = 8.5 Hz, Ar^1-H), 7.43 (2H, d, J = 8.5 Hz, Ar^3-H), 7.56 (1H, s, Ar^1-H), 7.66–7.71 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 21.1, 28.8, 43.5, 50.3, 52.3, 55.1, 105.7, 111.7 (2×C), 118.5, 123.5, 125.8, 126.7, 126.9, 127.2, 127.6 (2×C), 128.3 (2×C), 128.5, 128.8, 130.5, 132.7, 133.2, 137.5, 143.1, 150.4, 156.8, 207.0. ESI MS (m/z, %): 213 (A, 100), 331 (B, 48), 275 (C, 4), 171 (D, 11), 503 ([M+H]$^+$, 36), 525 ([M+Na]$^+$, 8). HRMS calcd for $C_{29}H_{30}N_2NaO_4S$ 525.1818, found [M+Na]$^+$ 525.1804, [M+K]$^+$ 541.1527.

4.2.27. TM-2n 4-(1-(4-Butoxyphenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 80.4%, mp: 173.5–175.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 0.90 (3H, t, J = 7.1 Hz, CH_3), 1.36–1.43 (2H, m, CH_2CH$_3$), 1.62–1.67 (2H, m, CH_2CH$_2$CH$_3$), 2.76–3.03 (6H, m, $CH_2CH_2COCH_2$), 3.85 (3H, s, OCH_3), 3.87–3.90 (2H, m, Ar^2-OCH_2), 4.88–4.91 (1H, m, *CH), 6.59 (2H, d, J = 8.1 Hz, Ar^3-H), 6.80–6.86 (3H, m, Ar-H), 6.89 (2H, s, NH_2), 7.12 (1H, d, J = 8.7 Hz, NH), 7.25–7.28 (4H, m, Ar-H), 7.44 (2H, d, J = 8.2 Hz, Ar^3-H), 7.55 (1H, s, Ar^1-H), 7.66–7.71 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 13.7, 18.8, 28.8, 30.8, 43.6, 50.4, 51.8, 55.1, 67.0, 105.7, 111.8(2×C), 114.3, 118.5, 125.9, 126.7, 127.2, 127.6(2×C), 127.7(2×C), 128.6, 128.8, 130.5, 132.8, 134.6, 136.2, 150.4, 156.8, 157.7, 207.2. ESI MS (m/z, %): 213 (A, 100), 389 (B, 23), 583 ([M+Na]$^+$, 8). HRMS calcd for

$C_{32}H_{36}N_2NaO_5S$ 583.2237, found $[M+Na]^+$ 583.2213, $[M+K]^+$ 599.1937.

4.2.28. TM-2o 4-(1-(Benzo[*d*][1,3]dioxol-5-yl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 78.2%, mp: 168.8–169.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.81 (1H, dd, J = 4.7, 16.1 Hz, CH_2*CH), 2.83–3.02 (5H, m, $CH_2CH_2COCH_2$), 3.85 (3H, s, OCH_3), 4.87–4.90 (1H, m, *CH), 5.95 (2H, s, OCH_2O), 6.60 (2H, d, J = 8.7 Hz, Ar^3-H), 6.78–6.88 (3H, m, Ar-H), 6.90 (2H, s, NH_2), 6.96 (1H, s, Ar^2-H), 7.12 (1H, d, J = 8.9 Hz, Ar-H), 7.25–7.30 (2H, m, Ar-H), 7.44 (2H, d, J = 8.6 Hz, Ar^3-H), 7.56 (1H, s, Ar^1-H), 7.66–7.71 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.5, 50.4, 52.2, 55.1, 100.9, 105.8, 106.8, 108.1, 111.9(2×C), 118.5, 119.7, 125.9, 126.7, 127.2(2×C), 127.7, 128.6, 128.8, 130.7, 132.8, 136.2, 137.1, 146.1, 147.4, 150.4, 156.8, 207.1. ESI MS (m/z, %): 213 (A, 3), 215 (A, 98), 361 (B, 22), 171 (D, 38), 555 ([M+Na]$^+$, 68). HRMS calcd for $C_{29}H_{28}N_2NaO_6S$ 555.1560, found $[M+Na]^+$ 555.1551, $[M+K]^+$ 571.1297.

4.2.29. TM-2p 4-(1-(4-Hydroxyphenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 87.3%, mp: 182.4–184.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.75 (1H, dd, J = 4.7, 15.9 Hz, CH_2*CH), 2.86–2.91 (4H, m, CH_2CH_2), 3.01 (1H, dd, J = 8.9, 16.1 Hz, CH_2*CH), 3.85 (3H, s, OCH_3), 4.95 (1H, dd, J = 7.9, 12.8 Hz, *CH), 6.57 (2H, d, J = 8.7 Hz, Ar^2-H), 6.66 (2H, d, J = 8.4 Hz, Ar^3-H), 6.73 (1H, d, J = 8.7 Hz, NH), 6.87 (2H, s, NH_2), 7.12–7.17 (3H, m, Ar^1-H), 7.25–7.26 (2H, m, Ar^1-H), 7.43 (2H, d, J = 8.6 Hz, Ar^2-H), 7.55 (1H, s, Ar^1-H), 7.66–7.69 (2H, m, Ar^3-H), 9.28 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.6, 50.4, 51.9, 55.1, 105.7, 111.8 (2×C), 115.2 (2×C), 118.5, 125.8, 126.7, 127.2, 127.5 (2×C), 127.7 (2×C), 128.6, 128.8, 130.4, 132.8, 133.0, 136.2, 150.5, 156.3, 156.8, 207.3. ESI MS (m/z, %): 213 (A, 91), 333 (B, 36), 277 (C, 3), 171 (D, 100), 527 ([M+Na]$^+$, 10). HRMS calcd for $C_{28}H_{28}N_2NaO_5S$ 527.1611, found $[M+Na]^+$ 527.1610, $[M+K]^+$ 543.1347.

4.2.30. TM-2q 4-(1,5-Bis(6-methoxynaphthalen-2-yl)-3-oxopentylamino)benzenesulfonamide

Yield: 72.6%, mp: 171.5–173.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.83–2.94 (4H, m, CH_2CH_2), 3.07–3.16 (2H, m, *CHCH_2), 3.85 (6H, s, 2×OCH_3), 5.05–5.08 (1H, m, *CH), 6.64 (2H, d, J = 8.3 Hz, Ar^3-H), 6.89 (2H, s, NH_2), 7.02 (1H, d, J = 8.5 Hz, NH), 7.10–7.15 (2H, m, Ar-H), 7.27 (2H, d, J = 8.6 Hz, Ar-H), 7.43 (2H, d, J = 8.3 Hz, Ar^3-H), 7.48–7.51 (2H, m, Ar-H), 7.62–7.69 (2H, m, Ar-H), 7.72–7.76 (2H, m, Ar-H), 7.80 (2H, s, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.7, 50.1, 52.6, 55.1, 55.2, 105.8, 105.9, 111.8(2×C), 118.5, 118.7, 124.9, 125.2, 125.8, 126.7, 127.2(2×C), 127.6(2×C), 128.3, 128.6, 128.8, 129.2, 130.6, 132.8, 133.5, 136.2, 138.1, 150.5, 156.8, 157.2, 207.1. ESI MS (m/z, %): 213 (A, 100), 397 (B, 12), 171 (D, 20), 591 ([M+Na]$^+$, 41). HRMS calcd for $C_{33}H_{32}N_2NaO_5S$ 591.1924, found $[M+Na]^+$591.1902, $[M+K]^+$ 607.1631.

4.2.31. TM-2r 4-(1-(Furan-2-yl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentylamino) benzenesulfonamide

Yield: 43.9%, mp: 149.1–150.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 2.90–3.13 (6H, m, $CH_2CH_2COCH_2$), 3.85 (3H, s, OCH_3), 5.06–5.09 (1H, m, *CH), 6.27–6.34 (2H, m, Ar^3-H), 6.89–6.75 (3H, m, Ar^2-H), 6.95 (2H, s, NH_2), 7.12 (1H, d, J = 8.8 Hz, NH), 7.26 (1H, s, Ar^1-H), 7.31 (1H, d, J = 8.4 Hz, Ar^1-H), 7.50 (2H, d, J = 7.5 Hz, Ar^3-H), 7.56 (2H, d, J = 9.2 Hz, Ar^1-H), 7.66–7.71 (2H, m, Ar^1-H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 28.8, 43.6, 46.2, 46.4, 55.2, 105.8, 106.4, 110.3, 111.6(2×C), 118.6, 125.9, 126.8, 127.3(2×C), 127.7, 128.6, 128.8, 130.9, 132.8, 136.2, 142.1, 150.3, 154.9, 156.8, 206.9. ESI MS (m/z, %): 478 ([M+H]$^+$, 100), 501 ([M+Na]$^+$, 28). HRMS calcd for $C_{26}H_{26}N_2NaO_5S$ 501.1455, found $[M+Na]^+$ 501.1438, $[M+K]^+$ 517.1197.

4.3. Biology

4.3.1. The determination of α-glucosidase inhibition[21,22,24]

α-Glucosidase activity was determined in a 100 μL reaction mixer containing optimal rat-α-glucosidase (extracted from the rat small intestine), 67 mmol L^{-1} pH 6.8 sodium phosphate buffer and different samples. Blank control (without enzyme and samples) or negative control (without sample) was set as above. After incubation at 37 °C for 10 min, 0.1 mol L^{-1} maltose was added and incubated for another 10 min at room temperature. The reaction was stopped with 200 μL of glucose and the OD values at 490 nm recorded. The inhibition rate was calculated according to the following equation: $I\% = [1-(OD_{Sample}-OD_{Blank})/(OD_{Negative}-OD_{Blank})] \times 100\%$. Based on the inhibition value, IC_{50} was calculated using 4 Parameter Logistic Model in Xlfit.

4.3.2. Inspection and test of PPAR activation[21,22,24,25]

HepG2 cells were cultured in low glucose DMEM supplement with 100 U mL^{-1} streptomycin and penicillin. One day prior to transfection, the cells were plated in 96-well plates with 1.5×10^4 cells per well. When the cells grew at confluence of 70%, plasmid pPPRE-Luc with firefly luciferase reporter gene and the control plasmid phRL-TK with renilla luciferase reporter gene were transfected into the cells. Twenty four hours after the transfection, the medium was replaced with fresh medium containing either different samples, rosiglitazone (positive control) or without sample (negative control). The cells without transfection were used as blank control. After a further 24 h incubation, the expression of luciferases was measured with Dual-Luciferase Reporter Gene Assay Kit (Promega). The sample activation time (T%) was calculated using the following equation: $T = [(L_{1\ Sample}-L_{1\ Blank})/(L_{1\ Negative}-L_{1\ Blank})]/[(L_{2\ Sample}-L_{2\ Blank})/(L_{2\ Negative}-L_{2\ Blank})] \times 100\%$. Where, L_1 represents the values of firefly luciferase and L_2 the values of Renilla luciferase.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2012.01.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

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