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Synthesis, molecular docking and molecular dynamic simulation studies of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(alkyl/aryl)-4-nitrobenzamide derivatives as antidiabetic agents

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Abstract

A series of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(alkyl/aryl)-4-nitrobenzamide derivatives (**5a–5v**) has been synthesized and confirmed by physicochemical (R_f , melting point) and spectral means (IR, ^1H NMR, ^{13}C NMR). The results of in vitro antidiabetic study against α -glucosidase indicated that compound **5o** bearing 2- CH_3 -5- NO_2 substituent on phenyl ring was found to be the most active compound against both enzymes. The electron donating (CH_3) group and electron withdrawing (NO_2) group on a phenyl ring highly favoured the inhibitory activity against these enzymes. The docking simulations study revealed that these synthesized compounds displayed hydrogen bonding, electrostatic and hydrophobic interactions with active site residues. The structure activity relationship studies of these compounds were also corroborated with the help of molecular modeling studies. Molecular dynamic simulations have been done for top most active compound for validating its α -glucosidase and α -amylase inhibitory potential, RMSD analysis of ligand protein complex suggested the stability of top most active compound **5o** in binding site of target proteins. In silico ADMET results showed that synthesized compounds were found to have negligible toxicity, good solubility and absorption profile as the synthesized compounds fulfilled Lipinski's rule of 5 and Veber's rule.

Keywords: α -Glucosidase, α -Amylase, Molecular docking, Molecular dynamic simulations, ADMET

Introduction

Diabetes mellitus (DM) is a complex metabolic disorder resulting either due to relative or absolute deficiency of pancreatic insulin secretion or insensitivity to insulin action, ensuing in postprandial hyperglycemia and assorted diabetic complications [1, 2]. According to World Health Organization reports, at present around 250 million peoples are living with diabetes and this

number is expected to be more than 366 million by 2030 [3] and these statistics are predicted to reach 592 million by 2035 of which 46% may still remain undiagnosed. The reduction of postprandial hyperglycemia by inhibiting carbohydrate hydrolyzing enzymes in gastrointestinal tract is one of the promising approaches for management of diabetes [4, 5]. α -Amylase is involved in hydrolyzing long chain of starch and α -glucosidase release glucose into the small intestine by breaking down oligo-saccharides and disaccharides [2, 6]. α -Glucosidase and α -amylase inhibitors reduced postprandial blood glucose level by delaying the hydrolysis of carbohydrate by inhibiting the digestive enzymes [7]. Acarbose, Miglitol

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and Voglibose are currently available drugs used as α -glucosidase and α -amylase inhibitors, but due to their deleterious side effects such as abdominal distention, diarrhoea and bloating, flatulence [8–10] there is need to explore and synthesize new drug candidates for the management of type-II diabetes mellitus with no or low risk of side effects.

The sulphonamide moiety ($-\text{SO}_2\text{NH}_2$) is an effective pharmacophore revealing the clinical and medicinal importance of sulphonamide drugs in the field of drug discovery [11]. The lead molecules bearing sulphonamide structure exhibited diverse biological properties viz. antibacterial [12, 13], diuretics, carbonic anhydrase (CA) inhibitors [14], antithyroid, antidiabetic [11, 15, 16], anticancer [17], antitubercular [18], selective Cox II inhibitors [19], anti-inflammatory [20], aldose reductase inhibitor [21], anti-oxidant [22], and anticancer [20] etc. Benzamides are the carbonic acid amide of benzoic acid and have also been described for exhibiting various biological activities i.e. antimicrobial [23, 24], anti-inflammatory [25], anticancer [26, 27], antidiabetic [28], antidepressant, antitubercular [29], anticonvulsant [30] and analgesic [31] etc. 2,4-Dichlorobenzoic acid derivatives have also been reported for their antidiabetic potential exhibiting α -glucosidase and α -amylase inhibitory activity, as described in our previous studies [32, 33]. Singh et al., reported the benzamides as glucokinase activators possessing hypoglycaemic activity [34]. Thiazole-2-yl and *N*-pyridin-2-yl benzamides from benzoic acids showed glucokinase activation and possessed good antidiabetic potential in animal rat model [35, 36]. A series of sulfamoyl benzamide derivatives have also been reported by Grewal et al., having glucokinase activation potential for the treatment of type 2 diabetes [37]. In view of the vital importance of benzamides in management of type 2 diabetes, we have synthesized a series of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(alkyl/aryl)-4-nitrobenzamides and evaluated its antidiabetic potential in the current report.

Results and discussion

Chemistry

The 2-chloro-5-(chlorosulfonyl)-4-nitrobenzoic acid (**2**) was prepared from 2-chloro-4-nitro benzoic acid according to our previously reported procedure [32]. The reaction of commercially available *para* chloro substituted aniline with compound **2** in DMF yielded 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzoic acid in appropriate amount. The treatment of compound **3** with excess of thionyl chloride in presence of DMF as a catalyst afforded intermediate **4**, which was further refluxed with aromatic/aliphatic/heterocyclic amines in DMF to provide the target compounds **5a–5v** (Table 1, Scheme 1).

The structure of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(alkyl/aryl)-4-nitrobenzamide compounds was elucidated by IR, ^1H NMR and ^{13}C NMR spectral analysis. The stretching frequency due to NH and carbonyl of amide bond were obtained at $3294\text{--}3524\text{ cm}^{-1}$ and $1614\text{--}1692\text{ cm}^{-1}$ respectively. The bands around $1302\text{--}1398\text{ cm}^{-1}$ and $1127\text{--}1183\text{ cm}^{-1}$ were assigned to asymmetric and symmetric stretching of SO_2 of sulfonamide group respectively. The IR spectrum of synthesized compounds exhibits a band around $1506\text{--}1587\text{ cm}^{-1}$ to $1302\text{--}1378\text{ cm}^{-1}$ assignable to asymmetric and symmetric stretching of NO_2 . In the ^1H NMR spectra of compound, singlet for NH protons of SO_2NH and CONH appeared at δ 3.37–4.08 ppm and δ 10.19–10.81 ppm, respectively. The two aromatic protons of 2-chloro-4-nitro benzoic acid appeared around at δ 8.50 ppm and δ 7.50 ppm. The aromatic protons showed the chemical shift values in region of δ 6.58–8.58 ppm based on their chemical structure. In ^{13}C NMR, signals for various carbons appeared in the region of δ 17.72 to 168.51 ppm.

In vitro antidiabetic evaluation

α -Glucosidase inhibitory activity

All the synthesized compounds were tested for their in vitro α -glucosidase inhibitory activity and revealed their varying degree of inhibitory potential with IC_{50} values of 10.75 ± 0.52 to $130.90 \pm 2.42\ \mu\text{M}$ (Table 2) as compared to reference acarbose ($\text{IC}_{50} = 39.48 \pm 0.80\ \mu\text{M}$). The compound **5o** ($\text{R} = 2\text{-CH}_3\text{-5-NO}_2$) was found to be most active among this series of synthesized compounds. Most of the compounds exhibited good inhibitory potential with significant IC_{50} as compared to positive reference.

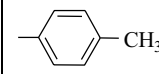
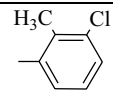
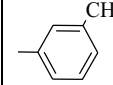
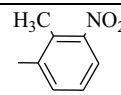
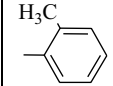
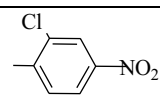
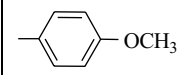
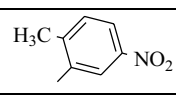
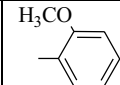
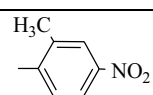
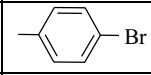
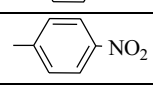
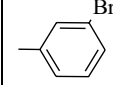
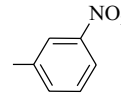
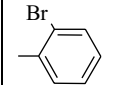

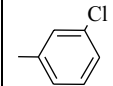

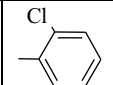

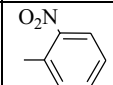
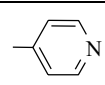
α -Amylase inhibitory activity

All the compounds were also evaluated for α -amylase inhibitory activity and the inhibition potential with IC_{50} values were found in range of $0.90 \pm 0.31\ \mu\text{M}$ to $55.14 \pm 0.71\ \mu\text{M}$ (Table 2). The compound **5o** showed excellent inhibitory potential against α -amylase with IC_{50} value of $0.90 \pm 0.31\ \mu\text{M}$. Compounds **5b**, **5m**, **5p** showed most significant inhibitory potential against α -amylase with IC_{50} values of 5.30 ± 1.23 , 1.52 ± 0.84 and $2.10 \pm 0.52\ \mu\text{M}$, respectively, when compared to acarbose, used as reference compound ($\text{IC}_{50} = 5.60 \pm 0.30\ \mu\text{M}$).

Structure activity relationship

The compound **5o** ($\text{R} = 2\text{-CH}_3\text{-5-NO}_2$) was the most active compound ($\text{IC}_{50} = 10.75 \pm 0.52\ \mu\text{M}$; $0.90 \pm 0.31\ \mu\text{M}$) which may be due to the presence of electron withdrawing and electron donating group which generate a uniform electron flow, leading the compound to be more active and potent inhibitor against both enzymes. This fact is supported by the similar results

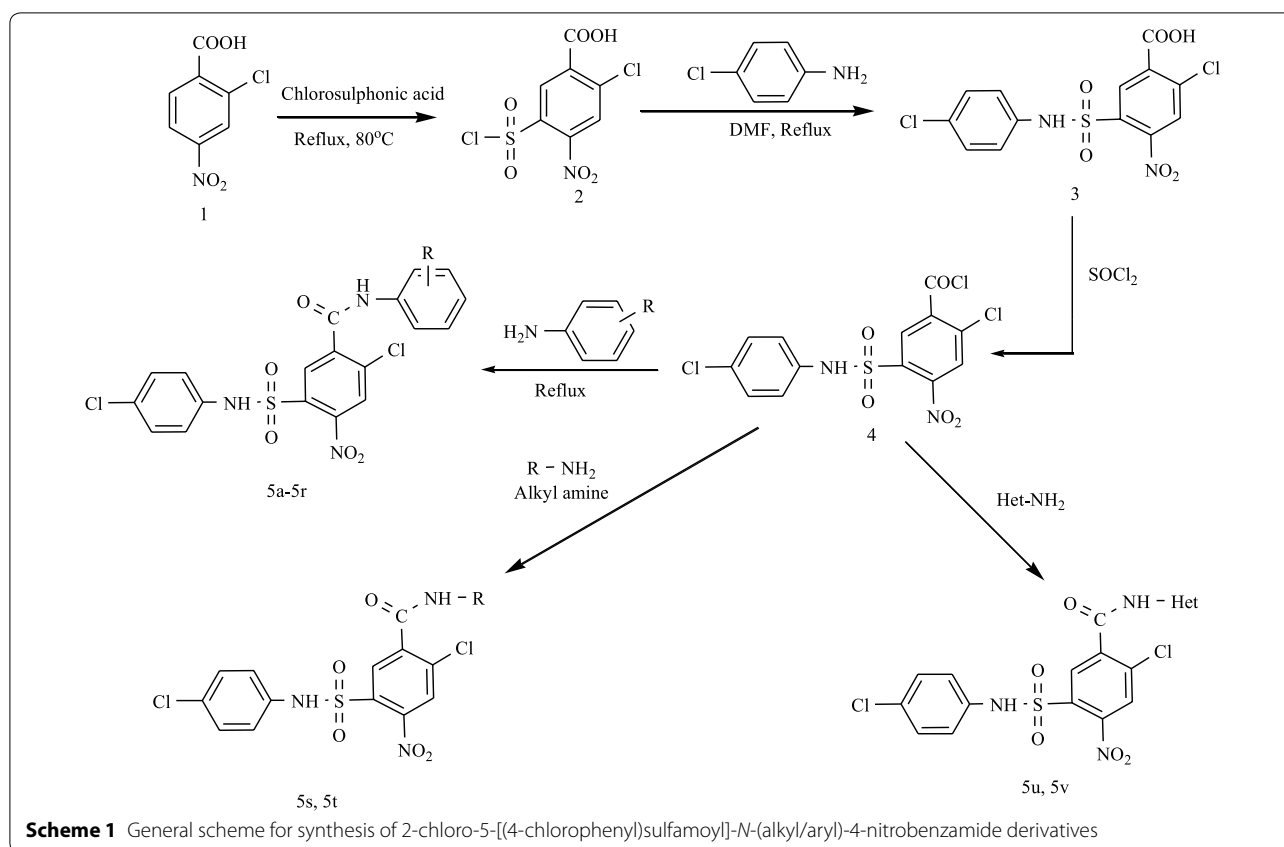
Table 1 List of synthesized 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(alkyl/aryl)-4-nitrobenzamide compounds

Comp.	R	Comp.	R
5a		5l	
5b		5m	
5c		5n	
5d		5o	
5e		5p	
5f		5q	
5g		5r	
5h		5s	
5i		5t	
5j		5u	
5k		5v	

of Adegboye et al. [38]. In compounds **5m** (R=2-CH₃-3-NO₂) and **5p** (R=2-CH₃-4-NO₂) difference in inhibitory potential was mainly affected by position of NO₂ substituent.

However the inhibitory activity increased when the phenyl ring was substituted with CH₃ at *meta* position, as observed in compound **5b** (IC₅₀=24.78±2.69 μM; 5.30±1.23 μM) in comparison to compounds **5a** and **5c** having CH₃ substitution at *para* and *ortho* positions. Further a decrease in inhibitory activity was observed for compounds **5d** (IC₅₀=38.57±0.01 μM; 38.00±0.51 μM) and **5e** (IC₅₀=41.75±1.08 μM; 50.30±0.21 μM) bearing OCH₃ substituted phenyl ring instead of compounds having CH₃ substituted phenyl ring. The compounds **5f–5k**, **5q** and **5r** bearing electron withdrawing groups were found to have considerable inhibitory potential.

The results illustrated that compounds **5g** (R=3-Br), **5i** (R=3-Cl), **5r** (R=3-NO₂), substitution at *meta* position of phenyl ring was found to be most favored for the α-glucosidase inhibitory activity while compounds **5f** and **5q** bearing electron withdrawing groups at *para* position were found to be most favorable for α-amylase inhibitory activity. This fact is supported by Taha et al. [39]. The compounds **5u** (IC₅₀=89.04±1.76 μM, 38.20±0.34 μM) and **5v** (IC₅₀=52.37±1.92 μM, 40.40±0.87 μM) substituted with heterocyclic amine displayed reduced inhibitory activities compared to aryl amines. This fact is supported by similar results of Kumar et al. [40] and Charaya et al. [35]. Substituting the compounds with *n*-propyl amine and butyl amine resulted in diminished activity as in compounds **5s** (IC₅₀=106.23±0.61 μM, 48.05±0.23 μM) and **5t** (IC₅₀=130.90±2.42 μM,



55.14 ± 0.71 μM). This fact is supported by the similar study on benzamide derivatives by Charaya et al. [35].

Molecular docking

In silico molecular docking study was performed to investigate binding interactions and to explore binding modes of synthesized compounds with their respective targets. The binding affinities of all the synthesized compounds are reported in Table 2.

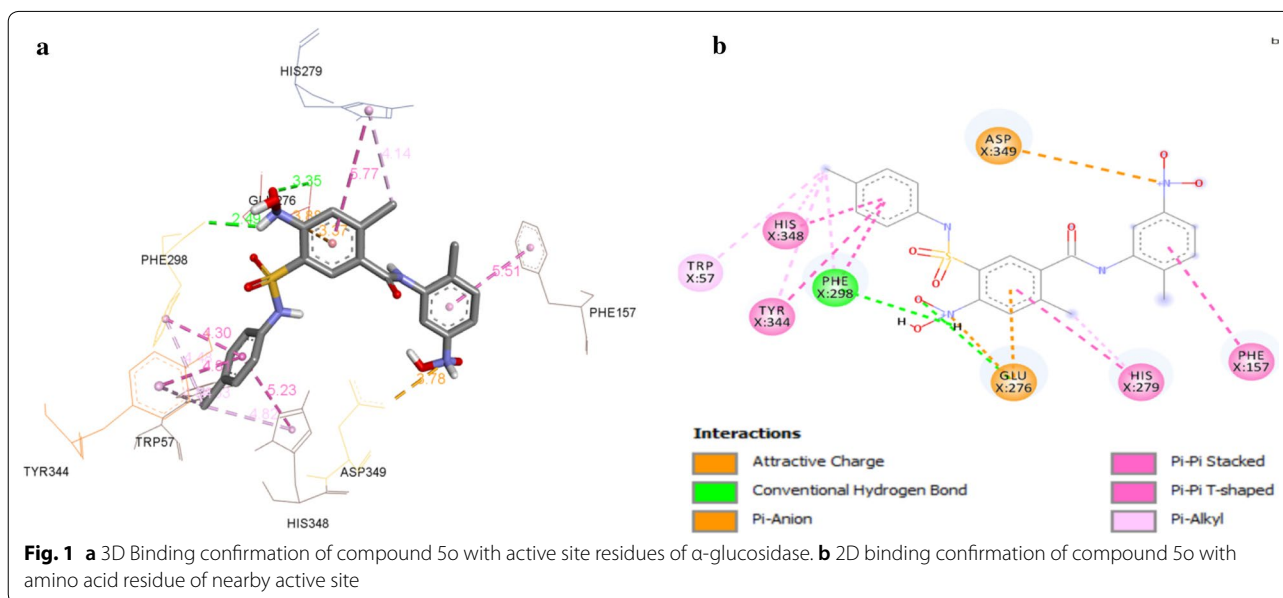
α-Glucosidase enzyme

The docking results revealed that all the synthesized compounds displayed binding energy ranging from −9.7 to −8.0 kcal/mol and depicted various types of significant binding interactions like hydrogen bonding, electrostatic and hydrophobic interactions with the amino acid residues of active site of enzyme. The binding mode of most active compound **5o** and modeled protein is presented in Fig. 1. The oxygen of 2-Cl-4-NO₂ established hydrogen bonding interaction with Glu:276 amino acid residue at a distance of 3.35 Å whereas Phe:298 amino acid was found to engage in hydrogen bond interactions with both protonated nitrogen of NO₂ of same with bond lengths of 2.49 Å. The nitrogen of 2-CH₃-5-NO₂ substituted compound displayed charge–charge interaction

with Asp:349 amino acid residue (3.78 Å) while the nitrogen of 2-Cl-4-NO₂ presented charge–charge interaction with Glu:276 amino acid residue (3.80 Å). The 2-Cl-4-NO₂ substituted phenyl ring created pi-anion interaction with residue Glu:276 of modeled protein at a distance of 3.37 Å. It was noticed that Phe:157 residue (5.51 Å) formed pi–pi T shaped interaction with 2-CH₃-5-NO₂ substituted phenyl ring and *para* chloro substituted phenyl ring displayed two pi–pi T shaped and one pi–pi stacked interaction with His:348, Tyr:344 and Phe:298 amino acid residues. In addition 2-Cl-4-NO₂ substituted phenyl ring created pi–pi stacked and pi–pi T shaped interaction with His:279 amino acid residues with bond length of 5.77 Å. Pi-alkyl interactions were established by chlorine of 2-Cl-4-NO₂ substituted phenyl ring with His:279 residues at a distance of 4.14 Å. The chlorine of *para* chlorosubstituted phenyl ring was found to engage in forming pi–alkyl interactions with Tyr:344, His:348, Phe:298, Trp:57 amino acid residues of modeled protein. The involvement of 2-CH₃-5-NO₂ substituted phenyl ring in forming more hydrophobic interactions i.e. pi–pi interactions may be contributing to better activity of compound **5o** as compared to compounds **5n** (R=2-CH₃-3-NO₂) and **5p** (2-CH₃-4-NO₂). Comparison of compound **5c** (R=2-CH₃) with

Table 2 α -Glucosidase and α -amylase inhibitory activity (IC_{50}) of synthesized derivatives (5a–5v) and their docking affinity with α -glucosidase (modeled protein) and α -amylase (PDB-1qho)

Comp.	IC_{50} α -glucosidase (μ M)	Binding score (α -glucosidase: modeled protein)	IC_{50} α -amylase (μ M)	Binding score (α -amylase: 1qho)
5a	31.39 \pm 1.66	−9.4	7.40 \pm 0.15	−8.9
5b	24.78 \pm 2.69	−9.7	5.30 \pm 1.23	−9.0
5c	26.77 \pm 1.13	−9.3	8.00 \pm 0.71	−9.8
5d	38.57 \pm 0.01	−9.2	38.00 \pm 0.51	−9.1
5e	41.75 \pm 1.08	−9.3	50.30 \pm 0.21	−8.7
5f	50.24 \pm 0.89	−9.4	16.00 \pm 0.33	−9.7
5g	35.92 \pm 0.60	−9.6	16.70 \pm 0.41	−9.8
5h	40.64 \pm 1.49	−9.6	19.30 \pm 0.63	−9.7
5i	14.02 \pm 0.93	−9.5	27.12 \pm 0.51	−8.5
5j	15.75 \pm 0.90	−9.6	20.90 \pm 1.24	−9.5
5k	36.93 \pm 1.30	−9.7	12.50 \pm 0.91	−8.8
5l	29.01 \pm 0.86	−9.3	6.30 \pm 0.42	−9.3
5m	24.47 \pm 1.23	−9.4	1.52 \pm 0.84	−9.7
5n	29.54 \pm 1.53	−9.4	35.30 \pm 0.45	−9.6
5o	10.75 \pm 0.52	−9.3	00.90 \pm 0.31	−9.2
5p	19.51 \pm 0.43	−9.4	02.10 \pm 0.52	−9.1
5q	43.88 \pm 1.18	−9.4	11.20 \pm 0.67	−9.0
5r	34.36 \pm 0.62	−9.7	15.30 \pm 1.24	−9.4
5s	106.23 \pm 0.61	−8.2	48.05 \pm 0.23	−7.9
5t	130.90 \pm 2.42	−8.6	55.14 \pm 0.71	−8.3
5u	89.04 \pm 1.76	−8.9	38.20 \pm 0.34	−8.6
5v	52.37 \pm 1.92	−9.0	40.40 \pm 0.87	−8.9
Acarbose	39.48 \pm 0.88	−8.0	5.60 \pm 0.30	−8.4



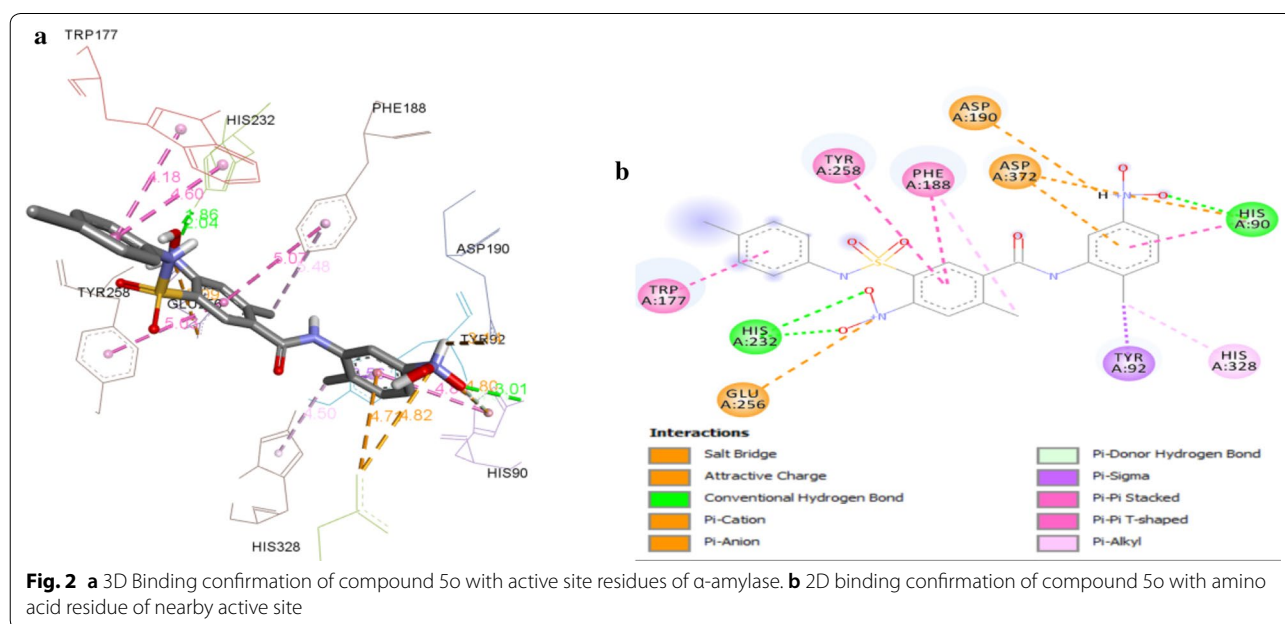
5n (R=2-CH₃-3-NO₂), **5o** (R=2-CH₃-5-NO₂), **5p** (R=2-CH₃-4-NO₂), **5n**, **5o**, **5p** displayed more hydrophobic interactions with Phe:177, Arg:312, Val:108, His:279, Phe:157, His:348, Tyr:344, Phe:298 amino acid residues of modeled protein which may have resulted in their higher inhibitory potential. The binding interaction between compounds **5c** (R=2-CH₃) and residues of modeled protein was nearly same as **5a** (R=4-CH₃) and **5b** (R=3-CH₃). The difference was that *ortho* methyl substituted phenyl ring maintained pi–pi stacked, pi–alkyl and pi–pi T interactions (hydrophobic interactions) with Try:344, His:348, Phe:298, Phe:177, Phe:158, Tyr:344 amino acid residue that made **5c** more active than **5a** and **5b**.

The compound **5e** (R=2-OCH₃) formed less number of hydrogen bonding, electrostatic and hydrophobic interactions as compared to compound **5d** (R=4-OCH₃), resulting in decreased inhibitory potential of compound **5e**. The binding of compound **5i** (R=3-Cl) facilitated one more pi–alkyl interaction with other hydrogen bonding, hydrophobic and electrostatic interactions same as that of compound **5j** (R=2-Cl), which may be contributing to better potential of compound **5i**. Considering the moderately active compound **5r** (R=3-NO₂), additional hydrophobic interaction such as pi–pi interactions with amino acid residues were observed as compared to compounds **5k** (R=2-NO₂) and **5q** (R=4-NO₂). In comparison to compounds bearing aromatic anilines, a decrease in inhibitory potential was observed in compounds **5s** (R=*n*-propyl), and **5t** (R=*n*-butyl), due to less pi–pi interactions between the inhibitory compounds and

amino acid residues. The binding interactions of compound **5u** (R=C₄H₃O-CH₂ (2-furfuryl)) with residues of modeled protein were nearly same as that of **5v** (R=C₅H₅N-(pyridine-2-yl)) but the difference was that 2-furfuryl ring exhibited pi–pi T shaped interaction with Trp:177 residue and four hydrogen bond interaction with Asp:329, Arg:376, His:90, Trp:93 residues of α -glucosidase with other interactions while compound **5v** formed three hydrogen bond interactions, which made **5u** more active than **5v** against α -glucosidase enzyme.

α -Amylase enzyme

The docking results revealed that all the synthesized compounds displayed binding energy ranging from -9.8 to -7.9 kcal/mol. The binding mode of most active compound **5o** and 1qho is presented in Fig. 2. The oxygen of 2-CH₃-5-NO₂ established hydrogen bonding interaction with His:90 amino acid residue at a distance of 3.01 Å whereas His:232 amino acid was found to engage in hydrogen bond interactions with both oxygen of NO₂ of 2-Cl-4-NO₂ substituted phenyl ring with bond lengths of 2.04 Å and 1.86 Å. The nitrogen of 2-CH₃-5-NO₂ displayed charge–charge interaction with Asp:372 amino acid residue (4.82 Å) while the protonated nitrogen of 2-CH₃-5-NO₂ presented salt bridge charge–charge interaction with Asp:190 amino acid residue (3.14 Å). The charge–charge interaction was also found between the nitrogen of 2-Cl-4-NO₂ substituted phenyl ring and Glu:256 amino acid residue with bond length of 5.09 Å. The 2-CH₃-5-NO₂ substituted phenyl ring created pi-anion interaction with residue Asp:372 of α -amylase



while nitrogen of 2-CH₃-5-NO₂ substituted phenyl ring formed pi-cation interaction with His:90 residue. It was shown that His:90 residue (4.88 Å) formed pi-pi T shaped interaction with 2-CH₃-5-NO₂ substituted phenyl ring and *para* chloro substituted phenyl ring displayed pi-pi stacked interaction with Trp:177 residue (4.60 Å). In addition 2-Cl-4-NO₂ substituted phenyl ring created pi-pi stacked and pi-pi T shaped interaction with Tyr:258, Phe:188 amino acid residues with bond lengths of 5.3 Å and 5.07 Å, respectively. The pi-alkyl interactions were established by chlorine of 2-Cl-4-NO₂ substituted phenyl ring and methyl of 2-CH₃-5-NO₂ substituted phenyl ring with Phe:188 and His:328 residues at a distance of 5.48 Å and 4.50 Å, respectively. The CH₃ of 2-CH₃-5-NO₂ substituted phenyl ring was found to engage in forming pi-sigma interaction with Tyr:92 residue (3.56 Å) while oxygen of NO₂ created pi-donor hydrogen bond with His:90 residue at a distance of 4.01 Å.

The involvement of 2-CH₃-5-NO₂ substituted phenyl ring in forming more hydrophobic interactions may be contributing to better activity of compound **5o** as compared to compounds **5n** (R=2-CH₃-3-NO₂) and **5p** (2-CH₃-4-NO₂). The comparison of compound **5c** (R=CH₃) with **5n** (R=2-CH₃-3-NO₂), **5o** (R=2-CH₃-5-NO₂) and **5p** (R=2-CH₃-4-NO₂), **5n**, **5o**, **5p** displayed more electrostatic and hydrophobic interactions with Asp:372, Asp:190, Glu:256, His:90, Trp:177, Tyr:258, Phe:188, His:328 and Tyr:92 residues of α -amylase enzyme, which may have resulted in increase in inhibitory potential. The binding interactions between compound **5b** (R=3-CH₃) and residues of α -amylase were nearly same as **5a** (R=4-CH₃) and **5c** (R=2-CH₃). The difference was that *meta* methyl substituted phenyl ring and methyl group maintained pi-pi stacked, pi-alkyl and pi-sigma interactions (hydrophobic interactions) with Trp:177 amino acid residue which made **5b** more active than **5a** and **5c**. The compound **5e** (R=2-OCH₃) formed less number of hydrogen bonding, electrostatic and hydrophobic interactions as compared to compound **5d** (R=4-OCH₃), resulting in decrease in inhibitory potential of compound **5e**. The binding of compound **5f** (R=4-Br) facilitated two pi-pi T shaped and one pi-pi stacked interaction of *para* bromo substituted phenyl ring with Tyr:258, Phe:188, Trp:177 amino acid residues and two pi-pi stacked interactions of *para* chloro substituted phenyl ring with Phe:188, Tyr:92 amino acid residues with other interactions, which made compound **5f** more active than compounds **5g** (R=3-Br) and **5h** (R=2-Br). Considering the moderate active compound **5q** (R=4-NO₂), additional hydrophobic interaction such as pi-pi T shaped, pi-pi stacked interactions with Tyr:258 and Trp:177 residues were observed as compared

to compounds **5k** (R=2-NO₂) and **5r** (R=3-NO₂). In comparison to compounds bearing aromatic anilines, a decrease in inhibitory potential was observed in compounds **5s** (R=*n*-propyl), and **5t** (R=*n*-butyl), due to less pi-pi interactions between the inhibitory compounds and amino acid residues. The binding interaction of compound **5u** (R=C₄H₃O-CH₂ (2-furfuryl)) with residues of α -amylase was nearly same as **5v** (R=C₅H₅N- (pyridine-2-yl)) but the difference was that 2-furfuryl ring exhibited pi-pi T shaped interaction with Trp:177 residue and four hydrogen bond interactions with Asp:329, Arg:376, His:90, Trp:93 residues of α -amylase with other interactions while compound **5v** formed three hydrogen bond interactions, which made **5u** more active than **5v** against α -amylase.

Molecular dynamics study

A stable protein backbone atoms RMSD vs time is an indication of the near-equilibrium system. As shown in Fig. 3a and b, the protein backbone in both systems attains a constant phase after an initial surge. Whereas, due to the extensive involvement of water molecules (-500 kJ/mol) the ligand-bound protein backbone has higher RMSD fluctuations compared to the naked protein as represented in Fig. 3a. Figure 4 represent that electrostatic interactions are dominated between the ligand **5o** and protein.

The results obtained from the MD simulations demonstrated that water molecules are predominately involved in ligand-protein interactions (Fig. 5). As shown in the figure, the fall in electrostatic energy that corresponds to the ligand-protein interactions is compensated by the water molecules.

In silico ADMET properties prediction

Lipinski's rule of five, topological polar surface area, aqueous solubility and number of rotatable bonds, these calculated parameters are presented in Additional file 1: Table S1. The human intestinal absorption values were found in range of 93.10 to 95.93% which established the moderate to good absorption capacity of synthesized compounds and supported their interaction with target cell.

The in vitro Caco-2 cell permeable property in the range of 0.36–0.55 nm/s, in vitro MDCK cell permeability in range of 0.01–0.97 nm/s designated low permeability of target compounds with the concerned cell line. The synthesized compounds displayed values in range of 95.75–100% confirmed their strong binding capacity with proteins. The in vivo blood brain barrier penetration ranges from 0.01 to 0.32 supported their low to moderate distribution in vivo with medium to good penetration capacity (Additional file 1: Table S2). Bioactivity and

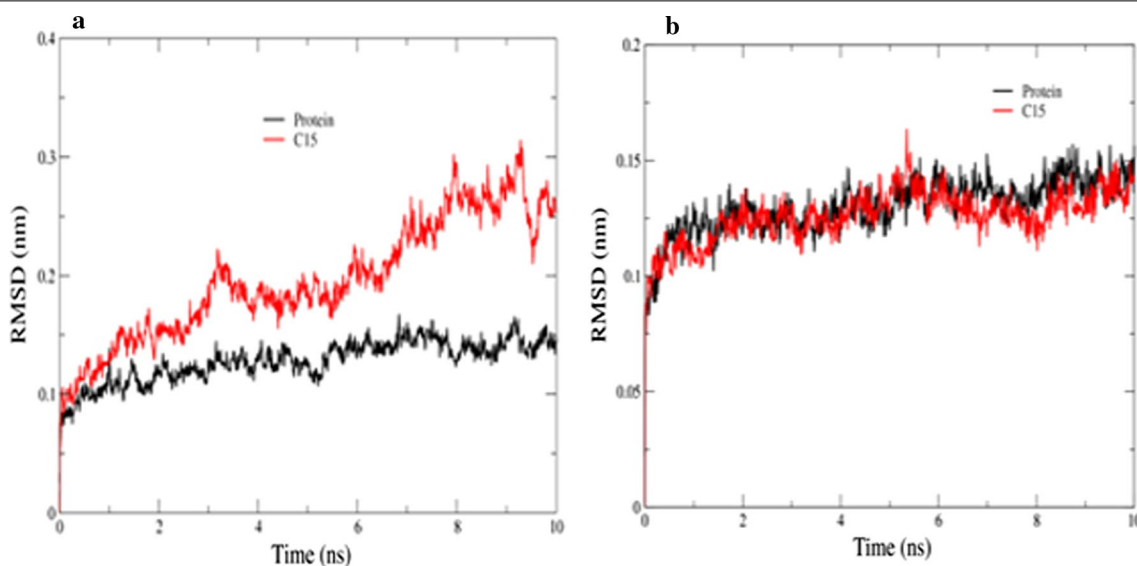


Fig. 3 Plot of protein backbone RMSD against time where red color line represent 5o bound modeled protein and black line represent naked protein. **a** For 3aj7 modeled protein with 5o. **b** For 1qho with 5o

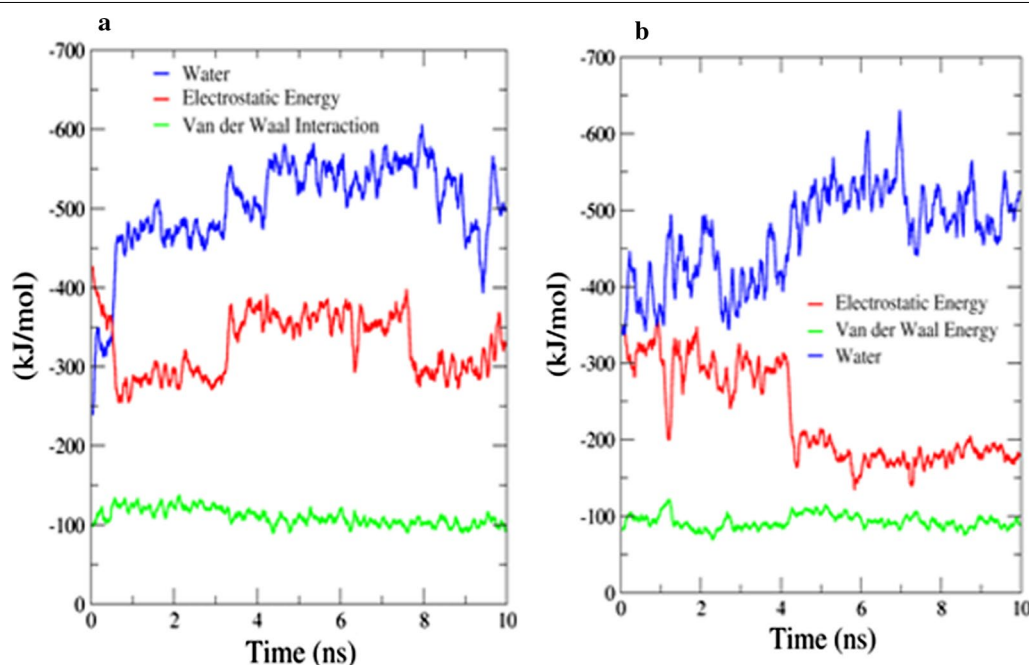


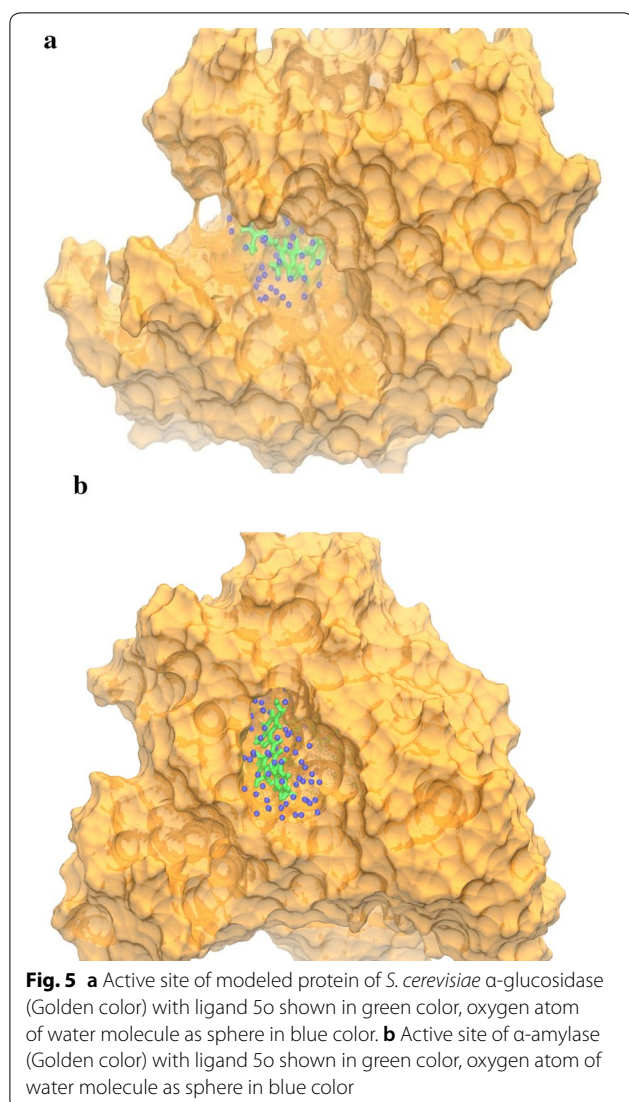
Fig. 4 Plot of binding energy (electrostatic and Van der Waal) vs time: **a** For 3aj7 modeled protein with 5o. **b** For 1qho with 5o

toxicity risk values of synthesized compounds are illustrated in Additional file 1: Table S3.

Conclusion

A series of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(alkyl/aryl)-4-nitrobenzamide derivatives (**5a-5v**) has been synthesized and all the compounds were found

to possess potent to moderate inhibitory potential against α -glucosidase and α -amylase. Compound **5o** (2-chloro-5-[(4-chlorophenyl) sulfamoyl]-*N*-(2-methyl-5-nitrophenyl)-4-nitrobenzamide) was found to be highly active having fourfold inhibitory potential against α -glucosidase and around six times inhibitory activity against α -amylase in comparison to standard drug



acarbose. Molecular docking results of antidiabetic study showed reasonable dock score and binding interactions of synthesized molecules with their respective targets. Analysis of RMSD of ligand protein complex during molecular dynamic simulations suggested stability of the most active compounds **5o** in binding site of respective target proteins i.e. α -glucosidase and α -amylase enzymes. Prediction of computational drug like properties showed that most of synthesized compounds are safe with acceptable ADMET and druggable properties.

Materials and methods

Chemicals

The analytical grade chemicals and reagents were used as such in experiments without any purification. Decibel melting point apparatus was used for checking the melting point of the synthesized compounds and are reported

as uncorrected. The silica gel-precoated aluminum sheets for thin-layer chromatography (TLC) were employed to keep a vigil of the reaction progress. FT-IR (Diffuse Reflectance Method (DRS) -8000A, Shimadzu, Japan) spectrophotometer was utilized for recording infrared spectra and the Bruker Avance III, 400 MHz NMR spectrometer was employed for nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR; Chemical shift δ values-ppm). α -Glucosidase from *Saccharomyces cerevisiae* (EC 3.2.1.20, Sigma Aldrich) and α -amylase from malt (232-588-1, HiMedia) have been used for in vitro studies.

General procedure for synthesis of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(alkyl/aryl)-4-nitrobenzamide (**5a–5v**)

Synthesis of 2-chloro-5-(chlorosulfonyl)-4-nitro benzoic acid (**2**)

Compound **2** was synthesized from 2-chloro-4-nitro benzoic acid (**1**) as previously reported method in literature [32].

Synthesis of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzoic acid (**3**)

2-Chloro-5-(chlorosulfonyl)-4-nitrobenzoic acid (**1** g, 0.003 mol) was refluxed with *p*-nitro aniline (0.003 mol) using dimethyl formamide as solvent, till the completion of reaction [34]. The reaction progress was monitored by TLC. The reaction mixture was cooled and yielded precipitates were washed and recrystallized.

Synthesis of 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(alkyl/aryl)-4-nitrobenzamide (**5a–5o**)

Compound **3** (0.5 g, 0.0012 mol) was further treated with excess of thionyl chloride in presence of catalytic amount of DMF with calcium chloride (CaCl_2) guard tube to get 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzoylchloride (**4**). Compound **4** was dissolved in DMF and refluxed with anilines/amines/heterocyclic amines to get the desired products in appropriate yield [41]. After refluxing, mixture was cooled and poured on crushed ice, separated product was filtered and washed with dilute HCl and dried.

Physicochemical and spectral characterization

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-*N*-(4-methylphenyl)-4-nitrobenzamide (**5a**)

% Yield: 37.70; m.p.: 90–92 °C; R_f : 0.81 (Chloroform); FTIR (KBr): ν_{max} (cm^{-1}): 3502.79 (N–H str.), 3171.70 (C–H str., Ar), 2977.30, 2889.01 (C–H str., Aliphatic), 1641.45 (C=O), 1600.41 (N–H bend), 1586.48 (asym. NO_2 str.), 1349.25 (sym. NO_2 str.), 1315.47 (asym. SO_2 str.), 1157.31 (sym. SO_2 str.), 733.44 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 2.15 (s, 3H, CH_3), 4.01 (s, 1H, NH),

6.78–6.80 (d, 2H, CH of C₃, C₅ of –CONH–C₆H₅CH₃–), 7.11–7.13 (d, 2H, CH of C₂, C₆ of –CONH–C₆H₅CH₃–), 7.60 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.88–7.89 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 8.23 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 8.42–8.43 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 10.69 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 163.59 (C=O), 148.75 (C–S), 142.92 (C–NO₂), 136.44 (C–NH), 133.79 (C–Cl), 131.62, 130.79, 130.34, 129.71, 125.76, 123.26, 120.15, 119.55, 117.91, 21.00.

2-Chloro-5-[(4-chlorophenyl)

sulfamoyl]-N-(3-methylphenyl)-4-nitrobenzamide (5b)

% Yield: 50.81; m.p.: 102–104 °C; R_f: 0.82 (H:E— 8:2); FTIR (KBr): ν_{max} (cm⁻¹): 3502.97 (N–H str.), 3117.98 (C–H str., Ar), 2982.94, 2882.00 (C–H str., Aliphatic), 1621.03 (C=O), 1602.20 (N–H bend), 1544.11 (asym. NO₂ str.), 1370.45 (asym. SO₂ str.), 1340.55 (sym. NO₂ str.), 1170.07 (sym. SO₂ str.), 766.16 (C–Cl); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 2.35 (s, 3H, CH₃), 3.92 (s, 1H, NH), 5.48 (s, 1H, CH of C₂ –CONH–C₆H₅CH₃–), 6.88 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.10–7.12 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 7.19 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 7.23–7.25 (d, 1H, CH of C₆ of –CONH–C₆H₅CH₃–), 7.35–7.40 (m, 2H, CH of C₄, C₅ –CONH–C₆H₅CH₃–), 7.51–7.53 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 10.31 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 168.51 (C=O), 151.75 (C–S), 143.40 (C–NO₂), 139.92 (C–NH), 138.59 (C–Cl), 132.07, 130.56, 130.11, 129.23, 128.68, 124.09, 120.89, 119.21, 115.21, 21.41.

2-Chloro-5-[(4-chlorophenyl)

sulfamoyl]-N-(2-methylphenyl)-4-nitrobenzamide (5c)

% Yield: 84.91; m.p.: 88–90 °C; R_f: 0.75 (Chloroform); FTIR (KBr): ν_{max} (cm⁻¹): 3354.96 (N–H str.), 3197.07 (C–H str., Ar), 2915.46, 2837.25 (C–H str., Aliphatic), 1602.25 (C=O), 1578.76 (N–H bend), 1511.25 (asym. NO₂ str.), 1374.26 (asym. SO₂ str.), 1348.27 (sym. NO₂ str.), 1146.44 (sym. SO₂ str.), 753.00 (C–Cl); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 2.35 (s, 3H, CH₃), 3.45 (s, 1H, NH), 6.58–6.60 (d, 1H, CH of C₃ –CONH–C₆H₅CH₃–), 7.26–7.33 (t, 2H, CH of C₄, C₅ of –CONH–C₆H₅CH₃–), 7.40–7.41 (d, H, CH of C₆ –CONH–C₆H₅CH₃–), 7.81 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 8.00–8.02 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 8.36–8.37 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.51 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.31 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 162.32 (C=O), 153.39 (C–S), 142.32 (C–NO₂), 136.24 (C–NH), 133.93 (C–Cl), 131.57, 129.24, 127.88, 125.93, 123.22, 120.56, 117.54, 115.14, 17.72.

2-Chloro-5-[(4-chlorophenyl)

sulfamoyl]-N-(4-methoxyphenyl)-4-nitrobenzamide (5d)

% Yield: 88.69; m.p.: 150–152 °C; R_f: 0.23 (Chloroform); FTIR (KBr): ν_{max} (cm⁻¹): 3438.05 (N–H str.), 3083.26 (C–H str., Ar), 1614.01 (C=O), 1594.19 (N–H bend), 1555.62 (asym. NO₂ str.), 1352.32 (sym. NO₂ str.), 1304.87 (asym. SO₂ str.), 1261.51 (C–O–C str.), 1175.58 (sym. SO₂ str.), 727.73 (C–Cl); ¹HNMR (300 MHz, DMSO-d₆), δ: 3.38 (s, 3H, OCH₃ of –CONH–C₆H₅OCH₃–), 3.89 (s, 1H, NH), 7.02–7.03 (d, 2H, CH of C₃, C₅ of –CONH–C₆H₅OCH₃–), 7.34–7.37 (d, 2H, CH of C₂, C₆ of –CONH–C₆H₅OCH₃–), 7.52 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.81–7.83 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 8.09–8.11 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.50 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.32 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 164.63 (C=O), 154.30 (C–S), 144.57 (C–NO₂), 138.48 (C–NH), 136.24 (C–Cl), 131.58, 129.95, 128.12, 126.09, 124.46, 123.24, 120.20, 32.90.

2-Chloro-5-[(4-chlorophenyl)

sulfamoyl]-N-(2-methoxyphenyl)-4-nitrobenzamide (5e)

% Yield: 85.30; m.p.: 164–166 °C; R_f: 0.53 (B:EA–7:3); FTIR (KBr): ν_{max} (cm⁻¹): 3447.82 (N–H str.), 3012.86 (C–H str., Ar), 1682.45 (C=O), 1597.64 (N–H bend), 1530.54 (asym. NO₂ str.), 1378.16 (sym. NO₂ str.), 1307.76 (asym. SO₂ str.), 1252.68 (C–O–C str.), 1174.67 (sym. SO₂ str.), 752.65 (C–Cl); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 3.38 (s, 3H, OCH₃), 3.89 (s, 1H, NH), 7.07–7.09 (d, 1H, CH of C₃ –CONH–C₆H₅OCH₃–), 7.27–7.33 (m, 3H, CH of C₄, C₅, C₆ of –CONH–C₆H₅OCH₃–), 7.52 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.81–7.82 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 8.28–8.30 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.49 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.48 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 164.21 (C=O), 157.32 (C–S), 145.07 (C–NO₂), 139.07 (C–NH), 136.16 (C–Cl), 131.34, 129.45, 128.24, 127.14, 125.18, 121.68, 121.51, 120.55, 35.60.

N-(4-Bromophenyl)-2-chloro-5-[(4-chlorophenyl)

sulfamoyl]-4-nitrobenzamide (5f)

% Yield: 91.30; m.p.: 200–202 °C; R_f: 0.56 (Chloroform); FTIR (KBr): ν_{max} (cm⁻¹): 3392.85 (N–H str.), 3012.55 (C–H str., Ar), 1614.45 (C=O), 1591.36 (N–H bend), 1562.37 (asym. NO₂ str.), 1353.50 (sym. NO₂ str.), 1308.72 (asym. SO₂ str.), 1145.63 (sym. SO₂ str.), 732.07 (C–Cl), 691.49 (C–Br); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 3.60 (s, 1H, NH), 7.46 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.54–7.55 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 8.00–8.02 (d, 2H, CH of

C₂, C₆ of –CONH–C₆H₅Br–), 8.24–8.26 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.36–8.37 (d, 2H, CH of C₃, C₅ –CONH–C₆H₅CH₃–), 8.51 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.55 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 166.34 (C=O), 158.33 (C–S), 144.35 (C–NO₂), 140.21 (C–NH), 135.49 (C–Cl), 132.90, 130.58, 129.89, 129.21, 128.24, 127.08, 120.18.

***N*-(3-Bromophenyl)-2-chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5g)**

% Yield: 44.92; m.p.: 181–183 °C; R_f: 0.73 (Chloroform); FTIR (KBr): ν_{max} (cm⁻¹): 3502.79 (N–H str.), 3058.19 (C–H str., Ar), 1614.45 (C=O), 1588.41 (N–H bend), 1566.61 (asym. NO₂ str.), 1372.38 (asym. SO₂ str.), 1302.95 (sym. NO₂ str.), 1175.63 (sym. SO₂ str.), 778.76 (C–Cl), 675.80 (C–Br); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 3.71 (s, 1H, NH), 7.37 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.51 (s, 1H, CH of –CONH–C₆H₅Br–), 7.71–7.80 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH–), 7.93–7.98 (m, 3H, CH C₄, C₅ and C₆ of –CONH–C₆H₅Br–), 8.21–8.23 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.48 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.40 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 165.33 (C=O), 157.35 (C–S), 143.24 (C–NO₂), 139.51 (C–NH), 136.54 (C–Cl), 133.05, 130.77, 129.10, 128.39, 128.17, 127.63, 126.71, 126.12, 121.49.

***N*-(2-Bromophenyl)-2-chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5h)**

% Yield: 55.07; m.p.: 180–182 °C; R_f: 0.70 (Chloroform); FTIR (KBr): ν_{max} (cm⁻¹): 3392.85 (N–H str.), 3028.29 (C–H str., Ar), 1614.62 (C=O), 1594.19 (N–H bend), 1565.96 (asym. NO₂ str.), 1349.23 (sym. NO₂ str.), 1377.20 (asym. SO₂ str.), 1152.15 (sym. SO₂ str.), 754.34 (C–Cl), 661.15 (C–Br); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 3.83 (s, 1H, NH), 6.57–6.61 (t, 1H, CH of C₅ of –CONH–C₆H₅Br–), 6.90–6.92 (d, 1H, CH of C₆ –CONH–C₆H₅Br–), 7.12–7.14 (t, 1H, CH of C₄ of –CONH–C₆H₅Br–), 7.32–7.40 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 7.51–7.52 (d, 1H, CH of C₃ of –CONH–C₆H₅Br–), 7.82 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 8.16–8.18 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.50 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.39 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 167.04 (C=O), 156.56 (C–S), 143.06 (C–NO₂), 138.20 (C–NH), 135.47 (C–Cl), 135.07, 130.23, 129.04, 128.93, 126.13, 125.34, 122.21.

***2-Chloro-N*-(3-chlorophenyl)-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5i)**

% Yield: 93.25; m.p.: 220–222 °C; R_f: 0.72 (B:EA– 7:3); FTIR (KBr): ν_{max} (cm⁻¹): 3455.53 (N–H str.), 3056.96

(C–H str., Ar), 1687.80 (C=O), 1592.15 (N–H bend), 1542.11 (asym. NO₂ str.), 1366.59 (sym. NO₂ str.), 1308.72 (asym. SO₂ str.), 1165.99 (sym. SO₂ str.), 782.92 (C–Cl); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 3.39 (s, 1H, NH), 7.51 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.80–7.83 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 8.01–8.04 (m, 3H, CH C₄, C₅ and C₆ of –CONH–C₆H₅Cl–), 8.23 (s, 1H, CH of –CONH–C₆H₅Cl–), 8.30–8.32 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.49 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.20 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 167.04 (C=O), 155.28 (C–S), 145.02 (C–NO₂), 139.44 (C–NH), 136.10 (C–Cl), 132.12, 130.16, 129.12, 128.14, 127.33, 127.17, 126.39, 124.17.

***2-Chloro-N*-(2-chlorophenyl)-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5j)**

% Yield: 87.71; m.p.: 176–178 °C; R_f: 0.5 (B:EA– 7:3); FTIR (KBr): ν_{max} (cm⁻¹): 3337.42 (N–H str.), 3060.18 (C–H str., Ar), 1665.56 (C=O), 1592.43 (N–H bend), 1533.43 (asym. NO₂ str.), 1377.20 (sym. NO₂ str.), 1392.63 (asym. SO₂ str.), 1173.70 (sym. SO₂ str.), 755.22 (C–Cl); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 3.89 (s, 1H, NH), 7.44 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.85–7.90 (m, 3H, CH of C₄, C₅ and C₆ –CONH–C₆H₅Cl–), 7.98–8.00 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 8.21–8.22 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.31–8.33 (d, 1H, CH of C₃ of –CONH–C₆H₅Cl–), 8.52 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.19 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 166.34 (C=O), 157.02 (C–S), 146.93 (C–NO₂), 139.24 (C–NH), 135.56 (C–Cl), 131.57, 131.25, 129.53, 128.55, 127.21, 125.24, 121.86.

***2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitro-N*-(2-nitrophenyl)benzamide (5k)**

% Yield: 44.61; m.p.: 150–152 °C; R_f: 0.8 (B:EA– 7:3); FTIR (KBr): ν_{max} (cm⁻¹): 3524.01 (N–H str.), 3198.03 (C–H str., Ar), 1614.45 (C=O), 1593.50 (N–H bend), 1563.33 (asym. NO₂ str.), 1376.23 (asym. SO₂ str.), 1347.30 (sym. NO₂ str.), 1146.26 (sym. SO₂ str.), 746.55 (C–Cl); ¹HNMR (300 MHz, DMSO-d₆), δ ppm: 3.64 (s, 1H, NH), 7.26–7.28 (d, 1H, CH of C₆ of –CONH–C₆H₅NO₂–), 7.46–7.48 (d, 1H, CH of C₃ of –CONH–C₆H₅NO₂–), 7.65 (s, 1H, CH of C₆ of ClNO₂C₆H₂CONH–), 7.81–7.82 (d, 2H, CH of C₂ and C₆ of ClC₆H₄NH), 7.90–7.96 (m, 2H, CH of C₄, C₅ of –CONH–C₆H₅NO₂–), 8.16–8.19 (d, 2H, CH of C₃ and C₅ of ClC₆H₄NH), 8.50 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.30 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO-d₆), δ ppm: 167.03 (C=O), 156.04 (C–S), 149.28 (C–NO₂), 141.14 (C–NH), 137.43 (C–Cl), 135.29, 133.38, 132.21, 130.67, 130.22, 129.18, 128.15, 126.02.

2-Chloro-N-(3-chloro-2-methylphenyl)-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5l)

% Yield: 57.62; m.p.: 212–214 °C; R_f : 0.65 (B:EA– 7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3447.82 (N–H str.), 3096.77 (C–H str., Ar), 2947.05, 2885.31 (C–H str., Aliphatic), 1692.29 (C=O), 1592.79 (N–H bend), 1531.51 (asym. NO_2 str.), 1380.09 (asym. SO_2 str.), 1306.80 (sym. NO_2 str.), 1174.67 (sym. SO_2 str.), 772.81 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 2.26 (s, H, CH_3), 3.45 (s, 1H, NH), 7.24–7.30 (m, 2H, CH C_4 , C_5 and C_6 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{Cl}-$), 7.63 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.81–7.82 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.28–8.30 (d, 2H, CH of C_3 and C_5 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.58 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.59 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 165.37 (C=O), 158.36 (C–S), 147.85 (C– NO_2), 140.10 (C–NH), 138.55 (C–Cl), 137.21, 135.46, 130.80, 129.61, 129.04, 125.15, 121.47, 118.28, 23.57.

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(2-methyl-3-nitrophenyl)-4-nitrobenzamide (5m)

% Yield: 38.29; m.p.: 170–172 °C; R_f : 0.61 (C:T– 9:1); FTIR (KBr): ν_{\max} (cm^{-1}): 3469.45 (N–H str.), 3095.80 (C–H str., Ar), 2882.55 (C–H str., Aliphatic), 1692.32 (C=O), 1598.62 (N–H bend), 1530.06 (asym. NO_2 str.), 1351.59 (sym. NO_2 str.), 1302.76 (asym. SO_2 str.), 1177.56 (sym. SO_2 str.), 734.45 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 2.14 (s, H, CH_3 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 3.37 (s, 1H, NH), 7.45 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.94–7.95 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.09–8.13 (m, 2H, CH C_4 , C_5 and C_6 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 8.46–8.47 (d, 2H, CH of C_3 and C_5 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.72 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.50 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 166.48 (C=O), 158.10 (C–S), 146.02 (C– NO_2), 138.52 (C–NH), 137.46 (C–Cl), 136.78, 136.15, 131.20, 129.89, 129.25, 128.19, 126.71, 126.26, 117.19, 22.76.

2-Chloro-N-(2-chloro-4-nitrophenyl)-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5n)

% Yield: 79.16; m.p.: 214–216 °C; R_f : 0.34 (B:EA– 7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3461.39 (N–H str.), 3187.49 (C–H str., Ar), 1626.02 (C=O), 1587.77 (asym. NO_2 str.), 1378.16 (asym. SO_2 str.), 1320.40 (sym. NO_2 str.), 1127.06 (sym. SO_2 str.), 747.47 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 3.37 (s, 1H, NH), 7.53 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.80–7.81 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.11–8.13 (d, 2H, CH of C_3 and C_5 of $\text{NO}_2\text{C}_6\text{H}_4\text{NH}$), 8.25–8.26 (d, H, CH

of C_6 of $-\text{CONH}-\text{C}_6\text{H}_5\text{ClNO}_2$), 8.36–8.38 (d, H, CH of C_5 of $-\text{CONH}-\text{C}_6\text{H}_5\text{ClNO}_2$), 8.51 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 8.61 (s, H, CH of C_3 of $-\text{CONH}-\text{C}_6\text{H}_5\text{ClNO}_2$), 10.53 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 168.41 (C=O), 160.22 (C–S), 145.06 (C– NO_2), 138.02 (C–NH), 136.61 (C–Cl), 132.42, 130.59, 128.62, 128.41, 126.57, 124.78, 122.38, 118.76, 26.08.

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(2-methyl-5-nitrophenyl)-4-nitrobenzamide (5o)

% Yield: 93.61; m.p.: 203–205 °C; R_f : 0.30 (B:EA– 7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3488.67 (N–H str.), 3082.35 (C–H str., Ar), 2979.35, 2899.74 (C–H str., Aliphatic), 1630.01 (C=O), 1511.16 (asym. NO_2 str.), 1382.02 (asym. SO_2 str.), 1345.60 (sym. NO_2 str.), 1138.02 (sym. SO_2 str.), 737.34 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 2.14 (s, H, CH_3 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 3.37 (s, 1H, NH), 7.24–7.29 (m, 2H, CH C_3 , C_4 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 7.62 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.84–7.87 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.32 (d, 2H, CH of C_3 and C_5 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.41 (d, H, CH of C_6 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 8.29–8.58 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.67 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 163.88 (C=O), 153.37 (C–S), 147.61 (C– NO_2), 139.52 (C–NH), 137.36 (C–Cl), 130.91, 129.21, 128.35, 127.24, 124.82, 122.63, 118.04, 110.49, 18.53.

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(2-methyl-4-nitrophenyl)-4-nitrobenzamide (5p)

% Yield: 56.66; m.p.: 104–106 °C; R_f : 0.50 (B:EA– 7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3473.73 (N–H str.), 3090.98 (C–H str., Ar), 2838.62 (C–H str., Aliphatic), 1640.49 (C=O), 1586.11 (N–H bend), 1529.58 (asym. NO_2 str.), 1396.49 (asym. SO_2 str.), 1350.19 (sym. NO_2 str.), 1154.21 (sym. SO_2 str.), 740.69 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 2.12 (s, H, CH_3 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 3.46 (s, 1H, NH), 7.51 (s, H, CH of C_3 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 7.67 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.84–7.87 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.21–8.25 (m, 2H, CH C_5 , C_6 of $-\text{CONH}-\text{C}_6\text{H}_5\text{CH}_3\text{NO}_2-$), 8.47–8.48 (d, 2H, CH of C_3 and C_5 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.64 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.70 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 167.72 (C=O), 154.62 (C–S), 148.40 (C– NO_2), 141.67 (C–NH), 135.94 (C–Cl), 130.20, 128.44, 126.61, 124.87, 124.39, 120.86, 112.81, 17.59.

2-Chloro-N-(4-chlorophenyl)-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5q)

% Yield: 95.24; m.p.: 177–179 °C; R_f : 0.65 (B:EA–7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3483.02 (N–H str.), 3108.34 (C–H str., Ar), 1633.74 (C=O), 1599.82 (N–H bend), 1530.54 (asym. NO_2 str.), 1396.49 (asym. SO_2 str.), 1353.09 (sym. NO_2 str.), 1183.49 (sym. SO_2 str.), 754.34 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 3.67 (s, 1H, NH), 7.44–7.46 (d, 2H, CH of C_2 and C_6 of $-\text{ClC}_6\text{H}_4\text{NH}-$), 7.60 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.95–7.96 (d, 2H, CH of C_2 and C_6 of $-\text{CONHC}_6\text{H}_5\text{Cl}-$), 8.00–8.02 (d, 2H, CH of C_3 and C_5 of $-\text{CONH}-\text{C}_6\text{H}_5\text{Cl}-$), 8.24–8.26 (d, 2H, CH of C_3 and C_5 of $-\text{ClC}_6\text{H}_4\text{NH}-$), 8.36 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.63 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 166.17 (C=O), 156.21 (C–S), 149.28 (C– NO_2), 138.40 (C–NH), 138.06 (C–Cl), 136.11, 131.94, 132.52, 129.89, 126.84, 125.71, 123.20, 112.90.

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitro-N-(3-nitrophenyl)benzamide (5r)

% Yield: 84.37; m.p.: 135–137 °C; R_f : 0.59 (B:EA–7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3294.47 (N–H str.), 3102.55 (C–H str., Ar), 1618.98 (C=O), 1569.12 (N–H bend), 1549.18 (asym. NO_2 str.), 1398.42 (asym. SO_2 str.), 1353.37 (sym. NO_2 str.), 1133.20 (sym. SO_2 str.), 732.87 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 4.08 (s, 1H, NH), 7.05 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.34–7.49 (t, 1H, CH of C_5 of $-\text{CONH}-\text{C}_6\text{H}_5\text{NO}_2-$), 7.91–7.93 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.00–8.02 (d, 1H, CH of C_6 of $-\text{CONH}-\text{C}_6\text{H}_5\text{NO}_2-$), 8.24–8.26 (d, 2H, CH of C_3 and C_5 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.36–8.39 (d, 1H, CH of C_4 of $-\text{CONH}-\text{C}_6\text{H}_5\text{NO}_2-$), 8.64 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 8.95 (s, 1H, CH of C_2 of $-\text{CONH}-\text{C}_6\text{H}_5\text{NO}_2-$), 10.81 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 165.98 (C=O), 161.31 (C–S), 149.25 (C– NO_2), 139.61 (C–NH), 132.26 (C–Cl), 130.24, 125.93, 124.56, 123.59, 118.85, 113.87.

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitro-N-propylbenzamide (5s)

% Yield: 57.89; m.p.: 116–118 °C; R_f : 0.66 (Chloroform); FTIR (KBr): ν_{\max} (cm^{-1}): 3524.01 (N–H str.), 3089.05 (C–H str., Ar), 2967.82, 2874.42 (C–H str., Aliphatic), 1650.13 (C=O), 1598.78 (N–H bend), 1533.43 (asym. NO_2 str.), 1372.38 (sym. SO_2 str.), 1309.34 (sym. NO_2 str.), 1168.88 (sym. SO_2 str.), 755.90 (C–Cl). ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 1.82–1.90 (m, 7H, $-\text{CONH}-\text{C}_3\text{H}_7$), 3.39 (s, 1H, NH), 7.50 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.80–7.83 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.21–8.23 (d, 2H, CH of C_3 and C_5 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.51 (s, 1H, CH of C_3

of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.32 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 162.67 (C=O), 158.75 (C–S), 146.08 (C– NO_2), 139.51 (C–NH), 135.49 (C–Cl), 132.72, 128.73, 128.06, 126.60, 31.15, 26.04, 21.41.

N-Butyl-2-chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitrobenzamide (5t)

% Yield: 84.54; m.p.: 111–113 °C; R_f : 0.54 (Chloroform); FTIR (KBr): ν_{\max} (cm^{-1}): 3446.85 (N–H str.), 3186.46 (C–H str., Ar), 2959.53, 2871.74 (C–H str., Aliphatic), 1658.64 (C=O), 1597.82 (N–H bend), 1531.51 (asym. NO_2 str.), 1372.38 (asym. SO_2 str.), 1309.80 (sym. NO_2 str.), 1174.67 (sym. SO_2 str.), 750.37 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 2.08–2.18 (m, 9H, $-\text{CONH}-\text{C}_4\text{H}_9$), 3.71 (s, 1H, NH), 7.46 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.79–7.80 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.22–8.24 (d, 2H, CH of C_3 and C_5 of $\text{NO}_2\text{C}_6\text{H}_4\text{NH}$), 8.50 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.51 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 160.69 (C=O), 155.52 (C–S), 144.08 (C– NO_2), 138.84 (C–NH), 136.60 (C–Cl), 133.53, 129.57, 128.48, 127.57, 32.15, 27.34, 18.99.

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-N-[(furan-2-yl)methyl]-4-nitrobenzamide (5u)

% Yield: 67.48; m.p.: 191–193 °C; R_f : 0.40 (B:EA–7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3503.75 (N–H str.), 3056.03 (C–H str., Ar), 2981.34 (C–H str., Aliphatic), 1665.16 (C=O), 1596.15 (N–H bend), 1506.43 (asym. NO_2 str.), 1396.80 (asym. SO_2 str.), 1376.23 (sym. NO_2 str.), 1149.59 (sym. SO_2 str.), 743.60 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ : 2.59 (s, 2H, CH of $\text{CONH}-\text{CH}_2-\text{C}_4\text{H}_3\text{O}$), 3.71 (s, 1H, NH), 7.61 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.79–7.87 (m, 3H, CH of C_2 , C_3 and C_4 of $\text{CONH}-\text{CH}_2-\text{C}_4\text{H}_3\text{O}$), 7.92–7.93 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.22–8.24 (d, 2H, CH of C_3 and C_5 of $\text{ClC}_6\text{H}_4\text{NH}$), 8.50 (s, 1H, CH of C_3 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 10.58 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), δ ppm: 165.97 (C=O), 157.03 (C–S), 145.82 (C– NO_2), 142.54 (C–NH), 136.72 (C–Cl), 130.46, 129.18, 125.49, 121.85, 120.80, 113.64, 32.59.

2-Chloro-5-[(4-chlorophenyl)sulfamoyl]-4-nitro-N-(pyridin-4-yl)benzamide (5v)

% Yield: 71.32; m.p.: 197–199 °C; R_f : 0.31 (B:EA–7:3); FTIR (KBr): ν_{\max} (cm^{-1}): 3503.75 (N–H str.), 3113.16 (C–H str., Ar), 1665.56 (C=O), 1598.05 (N–H bend), 1548.50 (asym. NO_2 str.), 1371.07 (asym. SO_2 str.), 1316.44 (sym. NO_2 str.), 1170.81 (sym. SO_2 str.), 755.14 (C–Cl); ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 3.71 (s, 1H, NH), 7.57 (s, 1H, CH of C_6 of $\text{ClNO}_2\text{C}_6\text{H}_2\text{CONH}-$), 7.80–7.83 (d, 2H, CH of C_2 and C_6 of $\text{ClC}_6\text{H}_4\text{NH}$), 7.93–7.96 (d, 2H, CH of C_2 and C_6 of $-\text{CONH}-\text{C}_5\text{H}_4\text{NH}-$), 8.24–8.26 (d, 2H,

CH of C₃ and C₅ of ClC₆H₄NH–), 8.36–8.39 (d, 2H, C₃ and C₅ CH of –CONH–C₅H₄NH), 8.50 (s, 1H, CH of C₃ of ClNO₂C₆H₂CONH–), 10.56 (s, 1H, NH); ¹³CNMR (300 MHz, DMSO–d₆), δ ppm: 164.70 (C=O), 156.22 (C–S), 148.17 (C–NO₂), 144.89 (C–NH), 138.96 (C–Cl), 130.34, 128.50, 125.55, 120.17.

In vitro antidiabetic studies

α-Glucosidase inhibitory assay

The method adopted for performing *α*-glucosidase inhibitory assay was similar to our previous study, Thakral and Singh [32]. Graph Pad Prism program, version 5 was employed for calculation of the 50% inhibitory concentration (IC₅₀) of all compound [32, 42, 43].

α-Amylase inhibitory assay

Xiao et al., and Yoshikawa et al., illustrated a method, with little modification this method has been adopted for measuring the activity [32, 44].

Homology modeling

The 3D model for *α*-glucosidase is developed by comparative homology modeling technique using SWISS-MODEL web server (<https://swissmodel.expasy.org/>) [45] and then the quality of modeled structure was validated by Ramachandran plot (RAMPAGE) (<http://mordred.bioc.cam.ac.uk/~rapper/rampage.php>). The details are available in our previous report [32].

Molecular docking

Ligand molecules were prepared as per reported method [32] using MarvinSketch and AutoDock tools. The crystal structures of *α*-amylase, 1qho [32, 46] from *Bacillus stercorophilus*, maltose/acarbose complex downloaded from the protein data bank (<http://www.rcsb.org>) and *α*-glucosidase modeled structure [32] was used for docking in antidiabetic evaluation. Docking studies were carried out as reported in our previous study and literature using AutoDock Vina program [32, 47].

Molecular dynamic simulations

The respective structures placed in the center of the cubic box, the remaining volume of the box was filled by SPCE [48] water molecules. The whole box is then neutralized by adding the respective number of positive and negative ions using GROMACS 5.4 [49] by replacing the equal number of water molecules. Further energy minimization followed by 10 ns equilibration performed by using OPLS [50] force fields integrated into GROMACS 5.4 package to represent the potential energy of the system.

Computation of drug like parameters and ADMET profiling

Molinspiration (<http://www.molinspiration.com/>) online tool kit and OSIRIS property explorer was used for computing drug like characteristics from 2D chemical structures of aforementioned compounds [51–54]. Pre-ADMET online server (<https://preadmet.bmdrc.kr/>) was used for calculating pharmacokinetic parameters like adsorption, distribution, metabolism and excretion and some of the computed properties are human intestinal absorption (HIA %), Caco-2 cell permeability (nm/s), MDCK (Medin-Darbey Canine Kidney Epithelial Cells) cell permeability (nm/s), plasma protein binding (%), blood brain barrier penetration (C. brain/C. blood) and Pgp inhibition [55]. Bioactivity of synthesized compounds was predicted by Molinspiration (<http://www.molinspiration.com/>) online tool kit [56] and toxicity parameters like mutagenicity, tumorigenicity irritating effects and reproductive effects were computed by OSIRIS property explorer [57].

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13065-020-00703-4>.

Additional file 1: Table S1. Topological polar surface area, aqueous solubility, number of rotatable bonds, and calculated Lipinski's rule of five for the synthesized 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(alkyl/aryl)-4-nitrobenzamide derivatives; **Table S2.** ADME property values of synthesized 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(alkyl/aryl)-4-nitrobenzamide derivatives using Pre-ADMET online server; **Table S3.** Bioactivity and toxicity risk of synthesized 2-chloro-5-[(4-chlorophenyl)sulfamoyl]-N-(alkyl/aryl)-4-nitrobenzamide derivatives

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Authors' contributions

The authors (ST, RN, MK and VS) have done synthetic work, in vitro and in silico evaluation. All authors have read and approved the manuscript.

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Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Kar K, Krithika U, Mithuna BP, Kumar SS, Reji A, Kumar BRP (2014) Design, synthesis and glucose uptake activity of some novel glitazones. *Bioorg Chem* 56:27–33
2. Li K, Yao F, Xue Q, Fan H, Yang L, Li X, Sun L, Liu Y (2015) Inhibitory effects against α -glucosidase and α -amylase of the flavonoids-rich extract from *Scutellaria baicalensis* shoots and interpretation of structure–activity relationship of its eight flavonoids by a refined assign-score method. *Chem Cent J* 12(1):82
3. Chinthala Y, Thakur S, Tirunagari S, Chinde S, Kumar A, Domatti AK, Arigari NK, Srinivas KVNS, Alam S, Jonalla K, Khan F, Tiwari A, Grover P (2015) Synthesis, docking and ADMET studies of novel chalcone triazoles for anti-cancer and anti-diabetic activity. *Eur J Med Chem* 93:564–573
4. Kim KY, Nguyen TH, Kurihara H, Kim SM (2010) α -Glucosidase inhibitory activity of bromophenol purified from the red alga *Polypops lancifolia*. *J Food Sci* 75(5):145–150
5. Wang G, Li X, Wang J, Xie Z, Li L, Chen M, Chen S, Peng Y (2017) Synthesis, molecular docking and α -glucosidase inhibition of 2-((5, 6-diphenyl-1, 2, 4-triazin-3-yl) thio)-*N*-arylacetamides. *Bioorg Med Chem Lett* 27(5):1115–1118
6. Lopéz D, Cherigo L, Mejía LC, Loza-Mejía MA, Martínez-Luis S (2019) α -Glucosidase inhibitors from a mangrove associated fungus, *Zasmidium* sp. strain EM5-10. *BMC Chem* 13(1):22
7. Abuelizz HA, Iwana NA, Ahmad R, Anouar EH, Marzouk M, Al-Salahi R (2019) Synthesis, biological activity and molecular docking of new tricyclic series as α -glucosidase inhibitors. *BMC Chem* 13(1):52
8. Barakat A, Ali M, Al-Majid AM, Yousuf S, Choudhary MI, Khalil R, UI-Haq Z (2017) Synthesis of thiobarbituric acid derivatives: in vitro α -glucosidase inhibition and molecular docking studies. *Bioorg Chem* 75:99–105
9. Gollapalli M, Taha M, Javid MT, Almandil NB, Rahim F, Wadood A, Mosadik A, Ibrahim M, Alqahtani MA, Bamarouf YA (2019) Synthesis of benzothiazole derivatives as a potent α -glucosidase inhibitor. *Bioorg Chem* 85:33–48
10. Imran S, Taha M, Ismail NH, Kashif SM, Rahim F, Jamil W, Hariono M, Yusuf M, Wahab H (2015) Synthesis of novel flavone hydrazones: in vitro evaluation of α -glucosidase inhibition, QSAR analysis and docking studies. *Eur J Med Chem* 105:156–170
11. El-Karim SSA, Anwar MM, Syam YM, Nael MA, Ali HF, Motaleb MA (2018) Rational design and synthesis of new tetralin-sulfonamide derivatives as potent anti-diabetics and DPP-4 inhibitors: 2D & 3D QSAR, in vivo radiolabeling and bio distribution studies. *Bioorg Chem* 81:481–493
12. Naaz F, Srivastava R, Singh A, Singh N, Verma R, Singh VK, Singh RK (2018) Molecular modeling, synthesis, antibacterial and cytotoxicity evaluation of sulfonamide derivatives of benzimidazole, indazole, benzothiazole and thiazole. *Bioorgan Med Chem* 26(12):3414–3428
13. Krishnaiah M, de Almeida NR, Udumula V, Song Z, Chhonker YS, Abdelmoaty MM, do Nascimento VA, Murry DJ, Conda-Sheridan M (2018) Synthesis, biological evaluation, and metabolic stability of phenazine derivatives as antibacterial agents. *Eur J Med Chem* 143:936–947
14. Ahmed A, Channar PA, Saeed A, Kalesse M, Kazi MA, Larik FA, Abbas Q, Hassan M, Raza H, Seo SY (2019) Synthesis of sulfonamide, amide and amine hybrid pharmacophore, an entry of new class of carbonic anhydrase II inhibitors and evaluation of chemo-informatics and binding analysis. *Bioorg Chem* 86:624–630
15. Navarrete-Vázquez G, Morales-Vilchis MG, Estrada-Soto S, Ramírez-Espinosa JJ, Hidalgo-Figueroa S, Nava-Zuazo C, Tlahuext H, Leon-Rivera I, Medina-Franco JL, López-Vallejo F, Webster SP (2014) Synthesis of 2-{2-[(α / β -naphthalen-1-ylsulfonyl) amino]-1, 3-thiazol-4-yl} acetamides with 11 β -hydroxysteroid dehydrogenase inhibition and in combo anti-diabetic activities. *Eur J Med Chem* 74:179–186
16. Ghareb N, El-Sayed NM, Abdelhameed R, Yamada K, Elgawish MS (2019) Toward a treatment of diabetes: rational design, synthesis and biological evaluation of benzene-sulfonamide derivatives as a new class of PTP-1B inhibitors. *Bioorg Chem* 86:322–338
17. Durgapal SD, Soman SS (2019) Evaluation of novel coumarin-proline sulfonamide hybrids as anticancer and antidiabetic agents. *Synth Commun*. <https://doi.org/10.1080/00397911.2019.1647439>
18. Singh V, Pacitto A, Donini S, Ferraris DM, Boros S, Illyés E, Szokol B, Rizzi M, Blundell TL, Ascher DB, Pato J (2019) Synthesis and structure–activity relationship of 1-(5-isoquinolinesulfonyl) piperazine analogues as inhibitors of *Mycobacterium tuberculosis* IMPDH. *Eur J Med Chem* 174:309–329
19. Ugwu DI, Okoro UC, Ahmad H (2017) New carboxamide derivatives bearing benzenesulphonamide as a selective COX-II inhibitor: design, synthesis and structure-activity relationship. *PLoS ONE* 12(9):e0183807
20. Banupriya G, Sribalan R, Padmini V (2018) Synthesis and characterization of curcumin-sulfonamide hybrids: biological evaluation and molecular docking studies. *J Mol Struct* 1155:90–100
21. Ji Y, Chen X, Chen H, Zhang X, Fan Z, Xie L, Ma B, Zhu C (2019) Designing of acyl sulphonamide based quinoxalones as multifunctional aldose reductase inhibitors. *Bioorg Med Chem* 27(8):1658–1669
22. Abbas A, Murtaza S, Tahir MN, Shamim S, Sirajuddin M, Rana UA, Naseem K, Rafique H (2016) Synthesis, antioxidant, enzyme inhibition and DNA binding studies of novel *N*-benzylated derivatives of sulfonamide. *J Mol Struct* 1117(5):269–275
23. Gatadi S, Gour J, Shukla M, Kaul G, Dasgupta A, Madhavi YV, Chopra S, Nanduri S (2019) Synthesis and evaluation of new 4-oxoquinazolin-3(4H)-yl benzoic acid and benzamide derivatives as potent antibacterial agents effective against multidrug resistant *Staphylococcus aureus*. *Bioorg Chem* 83:569–579
24. Dev J, Poornachandra Y, Kumar N, Ravikumar N, Ranjithreddy P, Kumar S, Nanubolu JB, Kumar G, Narsaiah B (2017) Synthesis of novel pyrazolo [3, 4-*b*] quinolinyl acetamide analogs, their evaluation for antimicrobial and anticancer activities, validation by molecular modeling and CoMFA analysis. *Eur J Med Chem* 130:223–239
25. Caliendo G, Santagada V, Perissutti E, Severino B, Fiorino F, Warner TD, Wallace JL, Iffa DR, Antunes E, Cirino G, de Nucci G (2001) Synthesis of substituted benzamides as anti-inflammatory agents that inhibit preferentially cyclooxygenase 1 but do not cause gastric damage. *Eur J Med Chem* 36(6):517–530
26. Tian Y, Zhang T, Long L, Li Z, Wan S, Wang G, Yu Y, Hou J, Wu X, Zhang J (2018) Design, synthesis, biological evaluation and molecular modeling of novel 2-amino-4-(1-phenylethoxy) pyridine derivatives as potential ROS1 inhibitors. *Eur J Med Chem* 143:182–199
27. Guo J, Zhu M, Wu T, Hao C, Wang K, Yan Z, Huang W, Wang J, Zhao D, Cheng M (2017) Discovery of indolin-2-one derivatives as potent PAK4 inhibitors: structure-activity relationship analysis, biological evaluation and molecular docking study. *Bioorg Med Chem* 25(13):3500–3511
28. Avalakki AS, Jadhav SB, Bandawane DD, Bhalekar PA (2019) Synthesis and antidiabetic evaluation of some novel compounds. *Indian J Chem* 58:849–854
29. Giacobbo BC, Pissinate K, Rodrigues-Junior V, Villela AD, Grams ES, Abbadi BL, Subtil FT, Sperotto N, Trindade RV, Back DF, Campos MM (2017) New insights into the SAR and drug combination synergy of 2-(quinolin-4-yloxy) acetamides against *Mycobacterium tuberculosis*. *Eur J Med Chem* 126:491–501
30. Foster JE, Nicholson JM, Butcher R, Stables JP, Edafiogho IO, Goodwin AM, Henson MC, Smith CA, Scott KR (1999) Synthesis, characterization and anticonvulsant activity of enamines Part 6: Synthesis of substituted vinylic benzamides as potential anticonvulsants. *Bioorg Med Chem* 7(11):2415–2425
31. Carson JR, Coats SJ, Codd EE, Dax SL, Lee J, Martinez RP, Neilson LA, Pitis PM, Zhang SP (2004) N, N-Dialkyl-4-[(8-azabicyclo [3.2.1]oct-3-ylidene) phenylmethyl] benzamides, potent, selective δ opioid agonists. *Bioorg Med Chem Lett* 14(9):2109–2112
32. Thakral S, Singh V (2019) 2, 4-Dichloro-5-[(N-aryl/alkyl) sulfamoyl] benzoic acid derivatives: in vitro antidiabetic activity, molecular modeling and in silico ADMET screening. *Med Chem* 15(2):186–195
33. Thakral S, Singh V (2019) Synthesis, biological evaluation, QSAR, molecular docking and ADMET studies of *N*-aryl/*N,N*-dimethyl substituted sulfonamide derivatives. *Anti-Infect Agents*. <https://doi.org/10.2174/2211352517666190902130014>
34. Singh R, Lather V, Pandita D, Judge V, Arumugam KN, Grewal AS (2017) Synthesis, docking and antidiabetic activity of some newer benzamide derivatives as potential glucokinase activators. *Lett Drug Des Discov* 14(5):540–553

35. Charaya N, Pandita D, Grewal AS, Lather V (2018) Design, synthesis and biological evaluation of novel thiazol-2-yl benzamide derivatives as glucokinase activators. *Comput Biol Chem* 73:221–229
36. Grewal AS, Kharb R, Prasad DN, Dua JS, Lather V (2019) N-pyridin-2-yl benzamide analogues as allosteric activators of glucokinase: design, synthesis, in vitro, in silico and in vivo evaluation. *Chem Biol Drug Des* 93(3):364–372
37. Grewal AS, Sharma K, Singh S, Singh V, Pandita D, Lather V (2018) Design, synthesis and antidiabetic activity of novel sulfamoyl benzamide derivatives as glucokinase activators. *J Pharm Tech Res Manag* 6(2):113–122
38. Adegboye AA, Khan KM, Salar U, Aboaba SA, Chigurupati S, Fatima I, Taha M, Wadood A, Mohammad JI, Khan H, Perveen S (2018) 2-Aryl benzimidazoles: synthesis, in vitro α -amylase inhibitory activity, and molecular docking study. *Eur J Med Chem* 150:248–260
39. Taha M, Irshad M, Imran S, Chigurupati S, Selvaraj M, Rahim F, Ismail NH, Nawaz F, Khan KM (2017) Synthesis of piperazine sulfonamide analogs as diabetic-II inhibitors and their molecular docking study. *Eur J Med Chem* 141:530–537
40. Kumar CA, Veeresh B, Ramesha KC, Raj CA, Mahadevaiah KM, Prasad SB, Naveen S, Madaiah M, Rangappa KS (2017) Antidiabetic studies of 1-benzhydryl-piperazine sulfonamide and carboxamide derivatives. *J Applicable Chem* 6(2):232–240
41. Lad NP, Manohar Y, Mascarenhas M, Pandit YB, Kulkarni MR, Sharma R, Salkar K, Suthar A, Pandit SS (2017) Methylsulfonyl benzothiazoles (MSBT) derivatives: search for new potential antimicrobial and anticancer agents. *Bioorg Med Chem Lett* 27(5):1319–1324
42. Kim KY, Nguyen TH, Kurihara H, Kim SM (2010) α -Glucosidase inhibitory activity of bromophenol purified from the red alga *Polyopes lancifolia*. *J Food Sci* 75:145–150
43. Nguyen TH, Kim SM (2015) α -Glucosidase inhibitory activities of fatty acids purified from the internal organ of sea cucumber *Stichopus japonicus*. *J Food Sci* 80:841–847
44. Rani N, Sharma SK, Vasudeva N (2012) Assessment of antiobesity potential of *Achyranthes aspera* Linn. seed. *Evid Based Complement Alternat Med*. <https://doi.org/10.1155/2012/715912>
45. Biasini M, Bienert S, Waterhouse A, Arnold K, Studer G, Schmidt T, Kiefer F, Cassarino TG, Bertoni M, Bordoli L, Schwede T (2014) SWISS-MODEL: modeling protein tertiary and quaternary structure using evolutionary information. *Nucleic Acids Res* 42:W252–W258
46. Dauter Z, Dauter M, Brzozowski AM, Christensen S, Borchert TV, Beier L, Wilson KS, Davies GJ (1999) X-ray structure of novamyl, the five-domain "maltogenic" α -amylase from *Bacillus stearothermophilus*: maltose and acarbose complexes at 1.7 Å resolution. *Biochemistry* 38(26):8385–8392
47. Trott O, Olson JA (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem* 31:455–461
48. Berendsen HJC, Grigera JR, Straatsma TP (1987) The missing term in effective pair potentials. *J Phys Chem* 91(24):6269–6271
49. Van Der Spoel D, Lindahl E, Hess B, Groenhof G, Mark AE, Berendsen HJ (2005) GROMACS: fast, flexible, and free. *J Comput Chem* 26(16):1701–1718
50. Jorgensen WL, Tirado-Rives J (1988) The OPLS [optimized potentials for liquid simulations] potential functions for proteins, energy minimizations for crystals of cyclic peptides and crambin. *J Am Chem Soc* 110(6):1657–1666
51. El-Gohary NS, Shaaban MI (2015) Antimicrobial and antiquorum-sensing studies. Part 3: synthesis and biological evaluation of new series of [1, 3, 4] thiadiazoles and fused [1, 3, 4] thiadiazoles. *Arch Pharm* 348:283–297
52. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 46:3–26
53. Cardoso MF, Rodrigues PC, Oliveira MEI, Gama IL, da Silva IM, Santos IO, Rocha DR, Pinho RT, Ferreira VF, de Souza MCB, da Silva FDC (2014) Synthesis and evaluation of the cytotoxic activity of 1, 2-furanonaphthoquinones tethered to 1, 2, 3-1H-triazoles in myeloid and lymphoid leukemia cell lines. *Eur J Med Chem* 84:708–717
54. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD (2002) Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem* 45:2615–2623
55. Murugavel S, Kannan D, Bakthadoss M (2016) Experimental and computational approaches of a novel methyl (2E)-2-[[N-(2-formylphenyl) (4-methylbenzene) sulfonamido] methyl]-3-(4-chlorophenyl) prop-2-enoate: a potential antimicrobial agent and an inhibition of penicillin-binding protein. *J Mol Struct* 1115:33–54
56. Balam SK, Krishnammagari SK, Harinath JS, Sthanikam SP, Cheredy SS, Pasupuleti VR, Yellapu NK, Peddiahgari VGR, Cirandur SR (2015) Synthesis of N-(3-picoly)-based 1, 3, 2 λ 5-benzoxazaphosphinamides as potential 11 β -HSD1 enzyme inhibitors. *Med Chem Res* 24:1119–1135
57. de Oliveira KN, Souza MM, Sathler PC, Magalhaes UO, Rodrigues CR, Castro HC, Palm PR, Sarda M, Perotto PE, Cezar S, de Brito MA (2012) Sulphonamide and sulphonyl-hydrazone cyclic imide derivatives: antinociceptive activity, molecular modeling and in silico ADMET screening. *Arch Pharm Res* 35:1713–1722

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