Synthesis of 1,2,3-Benzotriazin-4(3*H*)-one derivatives as α-glucosidase inhibitor and their *in-silico* study

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Abstract

α-Glucosidase inhibition is considered as an effective strategy for the treatment of diabetes mellitus. Currently, three α-glucosidase inhibitors are being used as drugs; Acarbose, Voglibose and Miglitol. The side effects of these drugs are forcing researchers to search for new and effective molecules. In this research work, novel 1,2,3-benzotriazin-4(3*H*)-one sulfonamides were synthesized and investigated for their α-glucosidase inhibition activity. TCT: DMF adduct have been utilized for the direct synthesis of targeted sulfonamides. All reactions were performed at room temperature under mild conditions. *In-vitro* enzyme inhibition studies led us to discover many potent inhibitors demonstrating good to excellent activity. The compound **5c** with dimethyl substituent was found to be more potent inhibitor than acarbose with the IC_{50} value of 29.75±0.14 μM. Compounds **5a, 5b, 5d, 5e, 5f** and **5m** showed good inhibition results with IC_{50} value 31.97±0.03, 33.24±0.01, 33.76±1.05, 35.98±0.03, 30.87±0.51 and 37.24±0.04 μM respectively. Further structure activity relationship was analyzed by molecular docking studies.

Introduction

Diabetes mellitus is a chronic disorder that is adversely affecting the quality of life of a large population worldwide. In type 2 diabetes mellitus, cell secretes insulin, but body become irresponsive leads to uncontrol blood glucose level. α-Glucosidase inhibitors, Voglibose, Acarbose and Miglitol are being utilized to treat this health condition. These inhibitors control blood sugar by inhibiting α-glucosidase that is responsible for starch and disaccharides conversion to glucose. The available α-glucosidase inhibitors are associated with a number of side effects and thus, there is an urgent need to discover new drugs for the treatment of diabetes [1]. The sulfonamides based on heterocyclic systems are emerging as potent α-glucosidase inhibitors. Various sulfonamide molecules based on indole [2], chalcone [3], Celebrex [4], sulfaguanidine [5], and quinoline [6], have demonstrated effective α-glucosidase inhibition activity as compared to the available drug, acrobase.

In general, sulfa compounds are known for their applications in pharmaceuticals and agrochemicals. The sulfadizine (antibacterial), darunavir (antiviral drug) and celecoxib (anti-inflammatory drug) are among the well-known examples of sulfa-drugs [7]. According to a survey, 15% of the most prescribed drugs in cardiovascular, neurological and infectious diseases belong to the family of sulfonamides [8].

On the other hand, 1,2,3-benzotriazin-4(3*H*)-one compounds have been reported as active antiproliferative agent [9], anti-inflammatory [10, 11], anti-depressant [12], anticancer [13], antidiarrhoeal [14] and as anesthetics [15] (Fig. 1). Benzotriazinonephenyllthio-N-hydroxy-propionamides have been found as potent matrix metalloprotease inhibitor. 3-Indolylmethyl1,2,3-benzotriazinones have been reported as excellant chorismate mutase inhibitor [16]. Recently some benzotriazinone (Fig. 1) derivatives have tested as efficient inhibitor of HepG2 liver carcinoma [17]. Structure of all active 1,2,3-benzotriazin-4(3*H*)-ones are shown in Fig. 1 prompted us to synthesize their dervatives. In stated work 1,2,3-Benzotriazin-4(3*H*)-one nucleus was selected and derivatized with sulfonamide functionality to evaluate their α-glucosidase inhibition potency.

In this research work, the synthesis of *N*-alkyl / aryl-4-(4-oxobenzo[1, 2, 3]triazin-3(4*H*)-yl)benzenesulfonamides were achieved through one pot, simple and low cost methodology under mild conditions. The most common method for sulfonamide synthesis is by the reaction of sulfonyl chloride and amine under basic conditions. But this reaction is two step and undesired di-sulfonamides are formed [18]. Only a few sulfonyl chlorides are commercially available due to their instability. To avoid these problems, different reagents have been developed to replace sulfonyl chlorides, such as pentafluorophenyl vinylsulfonate and sulfonylbenzotriazole followed by aminolysis [19]. In-addition, triphenylphosphine/pyridine or triethylamine salt, sodium salt sulfonic acid/ TCT [18] and alkylisocyanides have also been reported for the direct conversion of sulfonic acid to sulfonamides [20].

In continuation of our strategy employed for the direct conversion of sulfonic acid to sulfonamides by using cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) and *N*, *N*-dimethylformamide (DMF). Synthesized products were evaluated for their antidiabetic potential and structure activity relationship was explained by molecular docking studies.

Result And Discussion

Chemistry

Isatin (**1**) was used as basic precursor to prepare isatoic anhydride (**2**) by the oxidation reaction with hydrogen peroxide in the presence of formic acid. Compound **2** was treated with sulfanilic acid to form 4-(2-aminobenzamido)benzenesulfonic acid (**3**) that was subjected to cyclization with the help of nitrous acid to 4-(4-Oxobenzo[1, 2, 3]triazin-3(4*H*)-yl)benzenesulfonic acid **(4**). Then triazin-based sulfonic acid (**4)** was directly converted to series of sulfonamide compounds **5a-m** (Scheme 1) by using TCT:DMF adduct.

For direct conversion of sulfonic acid to sulfonamide, cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) was taken in cold DMF and stirred until all TCT changed to TCT: DMF adduct then dried DCM and DMF was used in 1:1 ratio. 4-(4-Oxobenzo[1, 2, 3]triazin-3(4*H*)-yl)benzenesulfonic acid (4) and *p*-bromo aniline was added to adduct mixture and 85% product yield was obtained. Reaction was also tried in DMF and DCM: DMSO mixture but no product was observed. Then all reactions were done in DCM:DMF (1:1) solvent.

The reaction conditions and results of all reactants are explained in Table 1. Aliphatic amine, heteroaryl amine and aniline were utilized in reaction. Anilines with electron donating groups showed better yield rather than anilines with electron withdrawing groups. Among all reactants nitro anilines and amino pyridines did not give any result. All products were confirmed by IR, ^{1}HNMR and ^{13}CNMR.

2.2 α-Glucosidase inhibition studies

Among the members of the series **5a-5m**, the α-glucosidase inhibition results were found in moderate to excellent activity **(**Table 2**)**. Compound **5c** proved excellent inhibition results with IC_{50} value 29.75±0.14 µM that is better than acrobase (37.38±0.12). Compounds **5a, 5b, 5d, 5e, 5f** and **5m** showed good

inhibition results with IC_{50} value 31.97±0.03, 33.24±0.01, 33.76±1.05, 35.98±0.03, 30.87±0.51 and 37.24±0.04 µM. Compounds **5a-5f** were aryl sulfonamide group while compounds **5g, 5h, 5i, 5j, 5k, 5l** were alkyl sulfonamide group that just showed moderate activity towards this enzyme.

Nature and position of substituent on the phenyl ring influence the inhibition activity. Aryl sulfonamides make more pi-stacking and pi-cation interactions with enzyme cavity as compared to alkyl sulfonamide. From results it was noticed that with two methyl groups containing compound **5c** showed strong inhibition as compared to mono methyl substituted compounds **5d** and **5f** because hydrophobic interactions increase with methyl groups. Compounds **5a** and **5b** contains chloro and bromo substituent that showed better result than methoxy **5e** because halogens make strong H-bonds than methoxy group. It is noticeable that compounds **5g, 5h, 5i, 5j, 5k** and **5l** contain alkyl groups and their enzyme inhibition potential increases as number of carbons atoms increase in alkyl chain i.e., **5g** with propyl chain showed 79.33±0.97% (102.16±0.41) while **5l** with octyl chain had 88.74±0.17% (50.66±0.05) inhibition. This reason of increase in inhibition from **5g** to **5l** is due to increase in alkyl chains hydrophobic interactions. However, for the inhibitory activity, one generalization can be postulated that sulfonamide with aryl substitution shows better results as compared to alkyl groups.

Table 2
Results of α-Glucosidase Inhibition studies

Sr. NO.	Compounds	Inhibition (%) At 0.5mm	IC_{50}(µM)
1.	5a	93.58±0.20	31.97±0.03
2.	5b	92.54±0.11	33.24±0.01
3.	5c	94.53±0.42	29.75±0.14
4.	5d	92.29±1.43	33.76±1.05
5.	5e	92.88±0.12	35.98±0.03
6.	5f	93.01±0.93	30.87±0.51
7.	5g	79.33±0.97	102.16±0.41
8.	5h	81.88±1.57	95.57±1.03
9.	5i	83.97±1.59	75.52±1.06
10.	5j	85.69±0.15	57.51±0.01
11.	5k	86.13±0.39	54.54±0.09
12.	5l	88.74±0.17	50.66±0.05
13.	5m	91.93±0.66	37.24±0.04
14.	Acrobase	92.23±0.16	37.38±0.12

2.3. In Silico Docking Studies

In order to define enzyme inhibition, Auto Dock Vina computational studies were applied to explore possible interaction mechanism of α-glucosidase and ligand. In docking studies, ligand and enzyme best orientation and confirmation was chosen and α-glucosidase counting function algorithm was used to calculate their binding affinity.

All synthesized compounds (**5a-5m)** interacted with the binding sites of α-glucosidase and their inhibition potency was justified. These novel compounds presented good binding energies against α-glucosidase (Cat No. 5003-1KU Type I) (Table 3). Among all ligands, **5c** have highest free binding energy **9.7 kcal.mol^{-1}** proves as potent inhibitor of target proteins. Ligands **5a, 5b, 5d, 5f** and **5m** were also found as good glucosidase inhibitor with binding energy **9.5 kcal. mol^{-1}**. Remaining analogues, **5e, 5g, 5h, 5i, 5j and 5k** presented less interactions as compared to other compounds with binding energy **8.4-9.2 kcal. mol^{-1}**.

Table 3
Docking binding energies (kcal mol-1) of the docked compounds 5a-m into the active site of α-glucosidase

Compound	Free binding energy (kcal mol^{-1})
5a	-9.5
5b	-9.5
5c	-9.7
5d	-9.5
5e	-9.2
5f	-9.5
5g	-8.5
5h	-8.4
5i	-8.5
5j	-8.7
5k	-8.5
5l	-8.5
5m	-9.5

For complete docking studies, ligand **5c** was selected against α-glucosidase (Cat No. 5003-1KU Type I). 2D and 3D structural interactions were appeared with the several amino acid residues and its picture

shown in Fig. 1. These results demonstrated that ligand **5c** fits perfectly at the catalytic sites of α-glucosidase with a binding energy of -9.7 kcal/mol.

The interaction studies displayed that ligand bonded to the active site through five H-bonds. There is one hydrogens bond exists in Phe157 with the distance of 2.39 Å (Table: 4a). Asn241 interacted through H-bond have distance of 2.77 Å. Two oxygen atoms of SO_2 make H-bonding with the cavity amino acid residues i.e., Arg312 and Asp408 make H-bond with the distance of 2.78 Å and 2.86 Å. His279 form another hydrogen bond with the oxygen atom of benzotriazinone motif with the distance of 3.40 Å.

Table 4
a Hydrogen Bonding

Index	Residue	AA	Distance H-A	Distance D-A	Donar Angle	Donar Atom	Acceptor Atom
1.	157X	PHE	2.39	3.30	146.32	9435[Npl]	2528[O_2]
2.	241X	ASN	2.77	3.65	145.77	3858[Nam]	9433[Nar]
3.	279X	HIS	3.40	4.04	122.64	4486[Npl]	9457[O_2]
4.	312X	ARG	2.78	3.56	134.24	4975[Ng^+]	9459[O_2]
5.	408X	ASP	2.86	3.59	133.55	6548[O^-]	9458[O_2]

Table 4
b Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1.	157X	PHE	3.35	9454	2532
2.	158X	PHE	3.31	9450	2553
3.	300X	PHE	3.83	9456	4792
4.	304X	GLU	3.90	9445	4856
5.	309X	PRO	3.55	9446	4918
6.	312X	ARG	3.61	9440	4972

Alkyl and pi-alkyl bonds found to have hydrophobic interactions at six sides of enzyme cavity (Table 4b) and they observed in Phe177X, Phe157, Phe158, Glu304, Pro309, Arg312 with the distance of 3.35, 3.31. 3.83, 3.90, 3.55, 3.61 Å.

Table 4
c Π-Stacking

Index	Residue	AA	Distance	Ligand Atom	Offset	Stacking Type	Ligands Atoms
1.	177X	PHE	5.21	69.32	1.55	T	9449, 9450, 9451, 9452, 9453, 9454

Table 4
d Π- Cation Interactions

Index	Residue	AA	Distance	Offset	Ligand Group	Ligands Atoms
1.	279X	HIS	4.24	1.39	Aromatic	9442, 9443, 9444, 9445, 9446, 9447
2.	279X	HIS	4.31	1.60	Aromatic	9432, 9433, 9434, 9443, 9444, 9448

In ligand there are number of non-polar and aromatic residues that build π-stacking interactions with Phe177 (Table 4c**)**. Pi-cation interactions were also formed because of phenyl rings and these interactions were located at two points with residue His279 (Table 4d**)**.

The analogue structures 5a, 5b, 5d, 5f and 5m demonstrated the second level inhibitory results with α-glucosidase binding energy 9.5 kcal/mol. These compounds form one or two hydrogen bonds with enzyme cavity while **5c** showed strong interactions because of five H-bonds. These compounds 5a, 5b, 5d, 5f and 5m make same type of hydrophobic interactions with Phe158, Phe300 and Phe177 at two sides of enzyme cavity while Thr215, Glu304 have these interactions at one side. **5a, 5b, 5d** and **5f** form interactions with the active site Glu276 through the hydrogen bond with the distance of 2.34-2.36Å but **5m** make its three H-bonds with Glu276 (2.74Å), His279 (3.20Å), Arg312 (3.16Å). His279 in all these compounds bonded to vicinity residues through Pi-cation interaction.

These interactions stabilize the ligand protein complex and forms its strong inhibition effect. From docking studied result elucidated that 5c have strong binding within enzyme protein. **5a, 5b, 5d, 5f, 5m** have low binding energy than **5c** because of less hydrogen bonds. **5g, 5h, 5i, 5j, 5k** and **5l** are alkyl sulfonamides and have less hydrophobic and pi stacking interactions to amino acid residues that reduce its binding energy as compared to **5c**.

Conclusion

TCT: DMF adduct has been used successfully for the synthesis of *N*-alkyl or aryl 4-(4-oxobenzo[1, 2, 3]triazin-3(4*H*)-yl)benzenesulfonamides. All reactions were done at the same time under same conditions. This method is simple one step conversion that provides rapid and good yield product under mild conditions. So, it is efficient method to convert 1,2,3-benzotriazin-4(3*H*)-one sulfonic acid to their corresponding sulfonamides. In comparison to acarbose all synthesized compounds were screened for their potency to inhibit α-glucosidase. Compound **5c** found potent inhibitor (IC_{50}= 29.75±0.14μM) than

acrobase (IC_{50}= 37.38±0.12) and most of the elaborated benzotriazinone derivatives showed inhibitory activity close to acarbose. Molecular docking studies clearly demonstrate that structures 5a-m bind to the active sites of α-glucosidase and possesses strong inhibitory potential.

Material And Methods

Experimental

Synthesis of Isatoic anhydride (2)

In conical flask, 14.7 g Isatin (0.1 mol) was taken in formic acid (80 mL). Hydrogen peroxide (30%, 20 mL) was added dropwise with slight cooling. The reaction contents were stirred for one hour at 25 ℃ and precipitates were filtered. Product was washed with methanol and dried at 70 ℃. Light yellow precipitates, m.p.: 240℃ (Lit. m.p.: 240-243℃) [21] Yield: 13.85 g (85%), Appearance: FT-IR (v-cm^{-1}): 3170 (N-H), 1765 (C=O), 1722 (C=O), 1035 (C-O-C)

Synthesis of 4'-(2-Aminobenzamido)benzenesulfonic acid (3):
Sulfanilic acid (3.46 g, 20 mmol) was dissolved in pyridine (70 mL). On heating, isatoic anhydride (3.26 g, 20 mmol) was added in small installments. The reaction mixture was heated at reflux for five hours. Then pyridine was removed under reduced pressure. Residue was added to acidified ice cooled water (pH: 3). Precipitates formed that were filtered and washed with methanol.

Grey precipitates, m.p.: > 300℃, Yield: 4.50 g (77%), FT-IR (v-cm^{-1}): 3394 (NH_2), 3184 (N-H), 1765 (C=O), 1305 (C-N), 1376 (S=O), 1161 (S=O), ^{1}H NMR (DMSO, 400 MHz): δ: 5.27 (2H, s, NH_2), 7.01 (1H, t, *J* = 7.4 Hz, Ar-*H*), 7.68 (1H, d, *J* = 8 Hz, Ar-*H*), 7.40 (1H, t, *J* = 7.6 Hz, Ar-*H*), 7.56 (2H, d, *J* = 8.4 Hz, Ar-*H*), 7.67 (2H, d, *J* = 8.4 Hz, Ar-*H*) 7.77 (1H, d, *J*= 7.6 Hz, Ar-*H*), 8.30 (1H, s, NH). EI-MS (m/z): ($C_{13}H_{12}N_2O_4S$) [M^+] 292 (1%), 238 (9), 194 (2), 172 (9), 120 (57), 108 (14), 93 (100).

4-(4-Oxobenzo[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonic acid (4)**

4-(2-Aminobenzamido)benzene sulfonic acid (3 g, 10.26 mmol) was suspended in ice cold water (30 mL) and 30% HCl solution (20 mL) was added. Sodium nitrite (5.1 g, 52 mmol) solution in distilled water (10 mL) was added slowly to mixture and the temperature was maintained at 0-5 ℃. The it was stirred for 1 hour, precipitates were filtered and recrystallized with methanol. Off white precipitate, m.p.:> 300℃, Yield: 2.80 g (90%), FT-IR (v-cm-1): 3383 (OH), 1697 (C=O) 1140 (S=O), 1030 (S=O) ^{1}H NMR: (DMSO, 400 MHz): δ: 7.60 (2H, d, *J* = 8.4 Hz, Ar-*H*), 7. 78 (2H, t, *J* = 8.0 Hz, Ar-*H*), 7.98 (1H, t, *J* = 7.4 Hz, Ar-*H*), 8.13 (1H, t, *J* = 7.6 Hz, Ar-*H*), 8.27 (1H, d, *J* = 8.0 Hz, Ar-*H*), 8.33 (1H, d, *J* = 7.6 Hz, Ar-*H*). ^{13}C NMR: (126 MHz, DMSO): δ: 155.31, 150.49 (2C), 148.82, 143.71, 139.40, 136.24, 133.90, 128.78, 126.70 (2C), 125.55, 120.49. EI-MS (m/z): (C13H9N3O4S) [M+HCl] 339 (0.4%), 269 (7), 195 (53), 167 (41), 139 (17), 119 (7), 93 (83), 64 (100).

General Preparation for the preparation of N**-alkyl or aryl-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamides (5a-5k)**

2,4,6-Trichloro-1,3,5-triazine (0.182 g, 0.99 mmol) was added to cold *N*,*N*-dimethylformamide (0.39 mL, 0.99 mmol) and temperature maintained below 25 °C. After 30 minutes stirring, white solid was formed. Then adduct was dissolved in dichloromethane (10 mL). 4-(4-Oxobenzo[1, 2, 3]triazin-3(4*H*)-yl) benzenesulfonic acid (**4**) (300 mg, 0.99 mmol) was dissolved in DMF (10 mL) and poured to adduct solution followed by the amine (0.99 mmol) addition. After reaction completion precipitates formed that were filtered and washed with 1N HCl followed by recrystallization with methanol to have pure *N*-alkyl or aryl sulfonamides. But in case of *N*-alkyl sulfonamides, product was purified by chloroform: n-hexane mixture.

N **-(4-Chlorophenyl)-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide (5a)**

Beige brown precipitates, m.p.: > 300 °C, Yield: 0.30 g (75%), FT-IR (v-cm^{-1}): 2865 (NH), 1684 (C=O), 1331 (S=O), 1160 (S=O), ^{1}H NMR: (DMSO, 400 MHz): δ 7.17 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.42 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.58 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.75 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.96 (t, *J* = 7.8, 1H, Ar-*H*), 8.11 (t, *J* = 7.5, 1H, Ar-*H*), 8.26 (d, *J* = 8.0, 1H, Ar-*H*), 8.31 (d, *J* = 8.0, 1H, Ar-*H*), 11.15 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.26 (C=O), 150.43, 149.15, 143.79, 139.40, 136.21, 133.89, 130.10 (2C), 128.84, 126.65 (3C), 126.64 (3C), 125.56, 123.84, 120.65.

N **-(4-Bromophenyl)-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)- yl)benzenesulfonamide (5b)**

Apricot pink precipitates, m.p.: > 300 °C, Yield: 0.38 g (85%), FT-IR (v-cm^{-1}): 2866 (NH), 1685 (C=O), 1328 (S=O), 1150 (S=O), ^{1}H NMR: (DMSO, 500 MHz): δ 6.84 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.36 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.58 (dd, *J* = 8.5 Hz, 2.0 Hz, 2H, Ar-*H*), 7.74 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.96 (t, *J* = 8.0 Hz, 1.0 Hz, 1H, Ar-*H*), 8.11 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 8.26 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.30 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 11.15 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 120.60, 125.55, 126.49 (4C), 126.65 (4C), 128.75, 132.86, 133.78, 143.82, 149.33 (2C), 150.54, 152.46, 155.25 (C=O).

N **-(3,4-Dimethylphenyl)-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide (5c)**

Off white precipitates, m.p.: > 300 °C, Yield: 0.21 g (64%), FT-IR (v-cm^{-1}): 2871 (NH), 1685 (C=O), 1330 (S=O), 1165 (S=O), ^{1}H NMR: (DMSO, 500 MHz): δ: 2.16 (s, 3H, CH3), 2.19 (s, 3H, CH3), 6.91-6.95 (m, 2H, Ar-*H*), 7.14 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.74 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 8.11 (t, *J* = 8.5, 4.4 Hz, 1H, Ar-*H*), 8.30 (t, *J* = 8.5 Hz, 1H, Ar-*H*), 8.28 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.31 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 9.22 (s, 1H, NH). ^{13}C NMR: (126 MHz, DMSO): δ: 19.41 (CH_3), 19.43 (CH_3), 116.38, 120.68, 122.93, 125.43, 126.61 (4C), 126.65 (4C), 128.87, 131.02, 133.67, 139.13 (2C), 141.78, 151.07 (C=O).

N **-(3-Methylphenyl)- 4-(4- oxobenzo**[1, 2, 3]**triazin-3(4**H**)- yl)benzenesulfonamide (5d)**

Pale pink precipitates, m.p.: > 300 °C Yield: 0.30 g (78%) FT-IR (v-cm^{-1}): 2865 (NH), 1683 (C=O), 1331 (S=O), 1155 (S=O) ^{1}H NMR: (DMSO, 400 MHz): δ 2.93 (3H, s, CH3), 7.02-7.09 (m, 3H, Ar-*H*), 7.28 (t, *J* = 8.1 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.75 (d, *J* =8.4 Hz, 2H, Ar-*H*), 7.96 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 8.12 (t, *J* = 8.25 Hz, 1H, Ar-*H*), 8.25 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.31 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 9.54 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.28 (C=O), 150.43 (4C), 149.25, 143.81, 139.94, 139.20, 136.21, 133.82, 130.10, 128.77, 126.69 (2C), 126.62 (2C), 125.49, 120.52, 21.44 (CH_3).

N **-(4-Methoxyphenyl)-4-(4-oxobenzo[1,2,3]triazin-3(4** H **)-yl)benzenesulfonamide (5e)**

Persion orange precipitates, m.p.: > 300°C, Yield: 0.32 g (79%) FT-IR (v-cm^{-1}): 2971 (NH), 1678 (C=O), 1360 (S=O), 1179 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 3.72 (s, 3H, CH_3), 7.00 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 7.24 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 7.59 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.75 (d, *J* = 8.4Hz, 2H, Ar-*H*), 7.95 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 8.11 (t, *J* = 7.9, 1.0 Hz, 1H, Ar-*H*), 8.25 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 9.79 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 159.29 (C=O), 155.32, 148.83, 143.73, 139.40, 136.22, 133.89, 128.78, 126.72 (2C), 126.64 (2C), 125.56, 124.80 (2C), 124.52, 120.53, 115.46 (2C), 55.92 (OCH_3).

N **-(4-Methylphenyl)-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide (5f)**

Off white precipitates, m.p.: > 300°C, Yield: 0.30 g (72%) FT-IR (v-cm^{-1}): 2886 (NH), 1684 (C=O), 1333 (S=O), 1169 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 2.28 (s, 3H, CH_3), 7.19 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.25 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.58 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.75 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.95 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 8.11 (t, *J* =8.0 Hz, 1H, Ar-*H*), 8.24 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.30 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 9.79 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.29 (C=O), 150.48 (4C), 149.21, 143.76, 138.04, 136.18, 133.84, 130.70 (2C), 128.79, 126.65 (2C), 125.57, 123.40 (2C), 120.60, 21.06.

N **-Propyl-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide** (**5g**)

Off white precipitates, m.p.: > 300°C, Yield: 0.29 g (85%), FT-IR (v-cm^{-1}): 2865 (NH), 1698 (C=O), 1315 (S=O), 1042 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 0.85 (t, *J* = 7.5 Hz, 3H, CH_3), 1.50 (sex, *J* = 7.5 Hz, 2H, CH_2), 2.70 (t, *J* = 7.5 Hz, 2H, CH_2), 7.59 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.77 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.95 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 8.11 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 8.24 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 8.29 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar-*H*), 11.19 (s, NH, 1H) ^{13}C NMR: (126 MHz, DMSO): δ 155.32 (C=O), 150.48, 148.85, 143.73, 139.39, 136.23, 133.89, 128.78, 126.71 (2C), 126.66 (2C), 120.52, 41.01, 20.96, 11.33.

N **-Butyl-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide** (**5h**)

Off white precipitates, m.p.: > 300°C, Yield: 0.27 g (79%), FT-IR (v-cm^{-1}): 2865 (NH), 1698 (C=O), 1315 (S=O), 1042 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 0.83 (t, *J* = 7.5 Hz, 3H, CH_3), 1.48-1.52 (m, 4H, CH_2), 2.69 (t, *J* = 7.5 Hz, 2H, CH_2), 7.60 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.76 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.95 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 8.11 (t, *J*= 7.8 Hz, 1H, Ar-*H*), 8.25 (d, *J* = 7.8Hz, 1H, Ar-*H*), 8.29 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 11.19 (s,

NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.31 (C=O), 150.47, 148.92, 143.74, 139.37, 136.22, 133.89, 128.78, 126.76 (2C), 126.66 (2C), 120.53, 28.41, 27.15, 22.14, 14.26.

N **-Pentyl-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide** (**5i**)

Off white precipitates, m.p.: > 300°C, Yield: 0.27 g (77%), FT-IR (v-cm^{-1}): 2857 (NH), 1689 (C=O), 1309 (S=O), 1041 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 0.81 (t, *J* = 6.9 Hz, 3H, CH_3), 1.21-1.24 (m, 4H, CH_2), 1.46–1.49 (m, 2H, CH_2), 2.71 (t, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.77 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 8.09 (td, *J* = 6.5, 1.0 Hz, 1H, Ar-*H*), 8.12 (td, *J* = 6.5, 1.0 Hz, 1H, Ar-*H*), 8.24 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 8.29 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 11.25 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.31 (C=O), 150.47, 148.92, 143.74, 139.37, 136.22, 133.89, 128.78, 126.68 (2C), 126.66 (2C), 120.53, 31.33, 28.41, 27.15, 22.14, 14.26.

N **-Hexyl-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide** (**5j**)

Off white precipitates, m.p.: > 300 °C, Yield: 0.26 g (71%) FT-IR (v-cm^{-1}): 2867 (NH), 1698 (C=O), 1316 (S=O), 1045 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 0.81 (t, *J* = 6.9 Hz, 3H, CH_3), 1.17-1.27 (m, 6H, CH_2), 1.48 (quin, 7.3 Hz, 2H, CH_2), 2.71 (t, *J* = 7.5 Hz, 2H, CH_2), 7.60 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.77 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.95 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 8.11 (t, *J* = 8.3 Hz, 1H, Ar-*H*), 8.24 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.29 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 11.18 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.31 (C=O), 150.48, 148.73, 143.72, 139.43, 136.22, 133.91, 128.78, 126.68 (2C), 125.55 (2C), 120.44, 34.74.01, 31.21, 27.40, 25.98, 22.42, 14.36.

N **-Heptyl-4-(4-oxobenzo[** d **]**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide** (**5k**)

Off white precipitates, m.p.: > 300°C, FT-IR (v-cm^{-1}): 2860 (NH), 1696 (C=O), 1312 (S=O), 1044 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 0.81 (t, *J* = 6.9 Hz, 3H, CH_3), 1.15-1.26 (m, 8H, CH_2), 1.48 (quin, *J* = 6.9 Hz, 2H, CH_2), 2.71 (t, *J* = 7.5 Hz, 2H, CH_2), 7.60 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.77 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.95 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 8.11 (t, *J* = 8.3 Hz, 1H, Ar-*H*), 8.24 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.29 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 11.21 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.30 (C=O), 150.47, 148.94, 143.75, 138.47, 136.28, 133.79, 128.75, 126.70 (2C), 126.66 (2C), 120.43, 45.51, 39.43, 33.34, 28.46, 27.18, 22.15, 14.24.

N **-Octyl-4-(4-oxobenzo[** d **]**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide** (**5l**)

Off white precipitates, Melting Point: > 300°C, Yield: 0.32 g (74%), FT-IR (v-cm-1): 2865 (NH), 1698 (C=O), 1315 (S=O), 1042 (S=O), ^{1}H NMR: (500 MHz, DMSO): δ 0.85 (t, *J* = 6.9 Hz, 3H, CH_3), 1.22-1.25 (m, 4H, CH2, Ar-*H*), 2.73-2.76 (m, 4H, CH_2, Ar-*H*), 3.18-3.24 (m, 2H, CH_2), 3.45-3.47 (m, 4H, CH_2), 7.73 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.84 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.98 (t, *J* = 7.25 Hz, 1H, Ar-*H*), 8.05 (t, *J* = 7.75 Hz, 1H, Ar-*H*), 8.21 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.41 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 11.18 (s, 1NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.30 (C=O), 150.47, 148.94, 143.75, 138.47, 136.28, 133.79, 128.75, 126.70 (2C), 126.66 (2C), 120.43, 50.05, 44.91, 39.57, 33.24, 28.56, 26.82, 22.11, 13.99.

N **-(** l,d **-Benzyl)-4-(4-oxobenzo**[1, 2, 3]**triazin-3(4**H**)-yl)benzenesulfonamide (5j)** Light brown precipitates, m.p.; > 300°C, Yield: 0.30 g (74%), FT-IR (v-cm^{-1}): 2855 (NH), 1689 (C=O), 1299 (S=O), 1041 (S=O), ^{1}H NMR: (300 MHz, DMSO): δ 1.49 (d, *J* = 6.9 Hz, CH_2), 4.37 (q, *J* = 6.0 Hz, NH), 7.39 (m, 3H, Ar-*H*), 7.49 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.61 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.73 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.98 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 8.13 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 8.27 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 8.32 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 8.46 (s, NH, 1H). ^{13}C NMR: (126 MHz, DMSO): δ 155.32 (C=O), 150.49 (5C), 148.85, 143.73 139.38, 136.24, 135.21, 133.93, 128.79, 126.71 (2C), 126.68 (2C), 125.56, 120.52, 34.67.

Procedure for α-Glucosidase Inhibition Studies:

α-Glucosidase (Cat No. 5003-1KU Type I) belongs to *Saccharomyces cereviciae* was used for the enzyme inhibition studies because its structure and function is like yeast/ mammalian enzymes. Pierre *et al*. method was adopted with some changes.

In tubes,10 µl test compound (0.5 mM), 70 µl saline phosphate buffer (50 mM at pH 6.8) and 10 µl α-glucosidase enzyme (0.0234 units) was added. Then tubes were incubated for ten minutes at 37 °C and absorbance was observed at 400 nm. In test tube, 10 µl *p*-nitrophenyl-α-D-glucopyranoside (0.5 mM, 'substrate', code No. N1377 from Sigma) was added to start the reaction and tubes were placed for 30 minutes. Then to observe free substrate change, absorbance of all tubes was measured at 400 nm. The percentage inhibition was calculated by the formula given below and IC_{50} values were calculated at 'EZ-Fit enzyme kinetics software.

% Inhibition = [(Abs. of control – Abs. of test) / Abs. of control] x 100

Molecular modeling studies

The crystal structure of eukeryotic yeast (*Saccharomyces cerevisiae*) was not found on Protein Data Bank (PDB), only some bacterial glucosidase structures were available. The sequence of saccharomyces cerevisiae's *α*-glucosidase is based on sequence of 584 amino acid residues (uniprot ID: P53341). NCBI's BLAST algorithm was used to have suitable template for homology modelling of target protein. For homology modeling, highest sequence similarity was observed in oligo-1,6-glucosidase (P53051) and selected to be used as a basic pattern. Sequence alignment was conducted by using Needleman-Wunsch Global Alignment Algorithm via Chimera. Structure modelling was processed on Modeller. Quality of the new structure was checked by using Ramachandran plot, which showed 97.3% residues were in the favored region, and 99.7% residues were in the allowed region. To review the quality of created homology model, molecular dynamics simulation was carried out on NAMD. Visualization of molecular dynamics trajectories was done on VMD. Protein molecule was solvated and equilibrated in a water box and modeled at physiological temperature of 310 K for 10 ps. Finally optimized structure was applied for further docking studies on BioSolveIT's LeadtIT. Discovery Studio visualizer was used for presentation of docked conformations.

Declarations

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Scheme

Scheme 1 is available in the Supplemental File section.

Figures

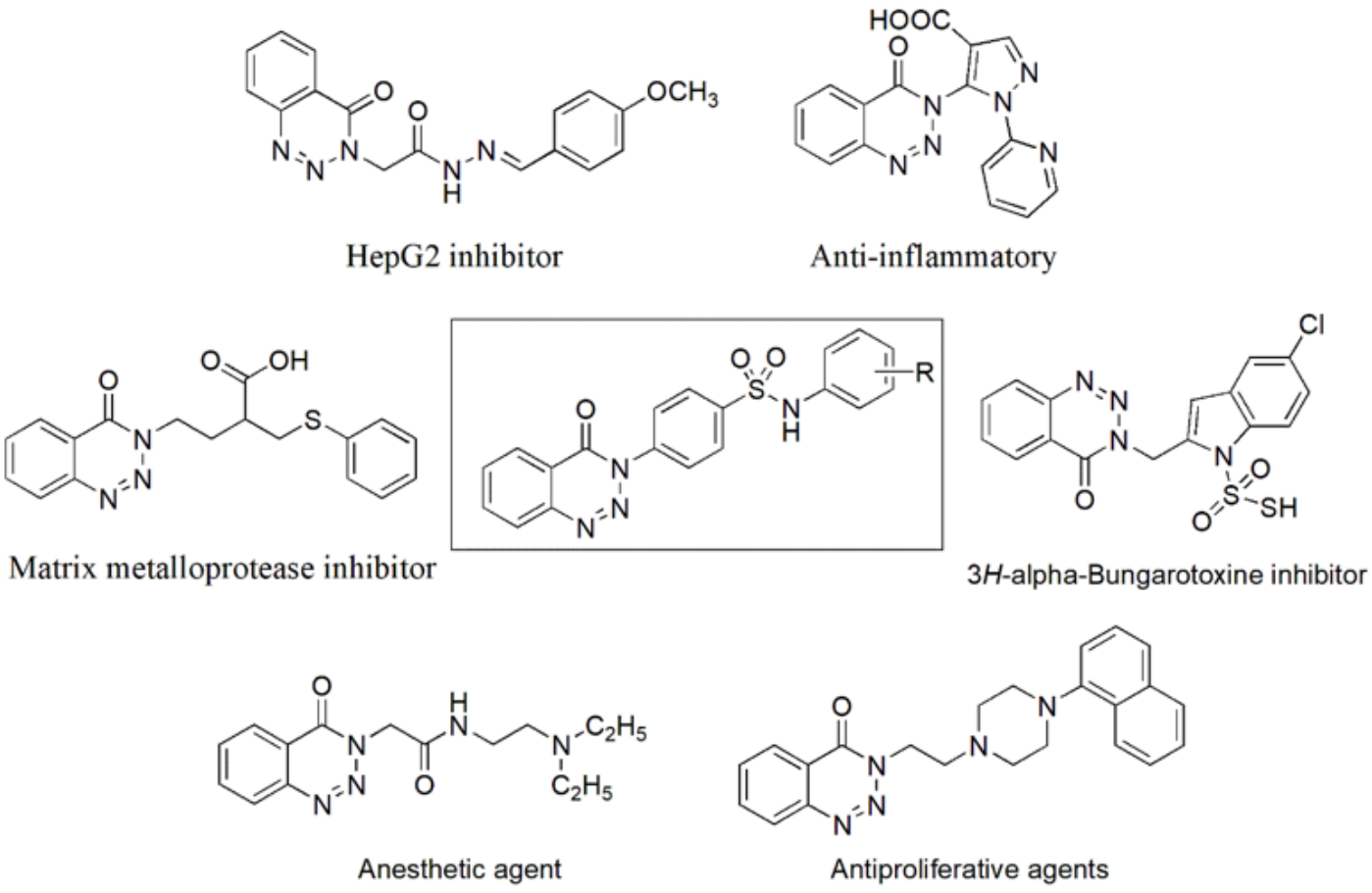

Figure 1

Different bioactive 1,2,3-benzotriazin-(3*H*)-ones lead to current synthesis.

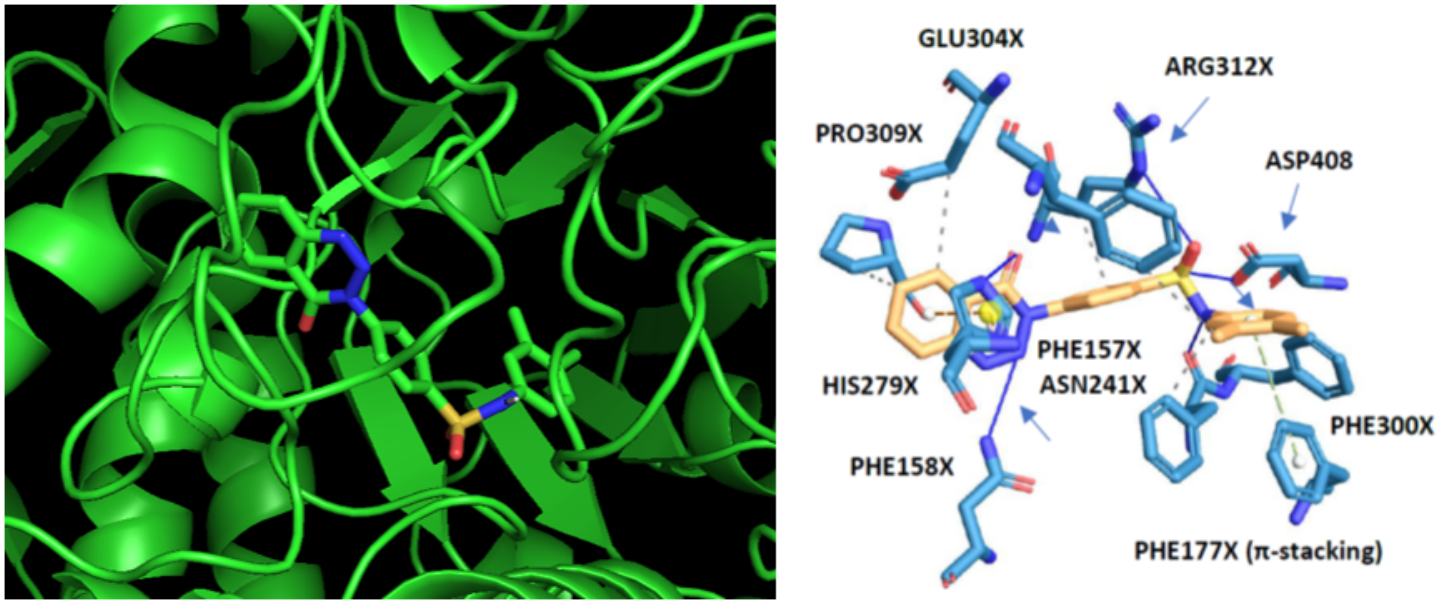

Figure 2

2D and 3D interactions between amino acid residues of α-glucosidase and ligand 5c

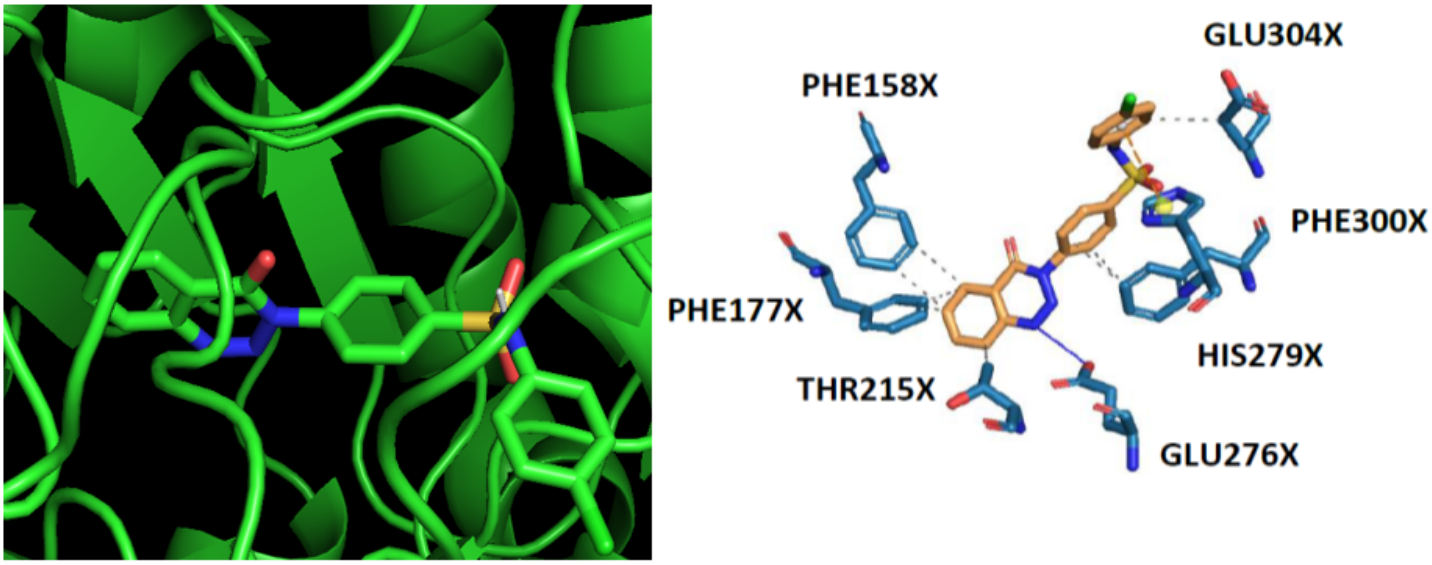

Figure 3

2D and 3D structure represents 5a ligand and α-glucosidase interactions

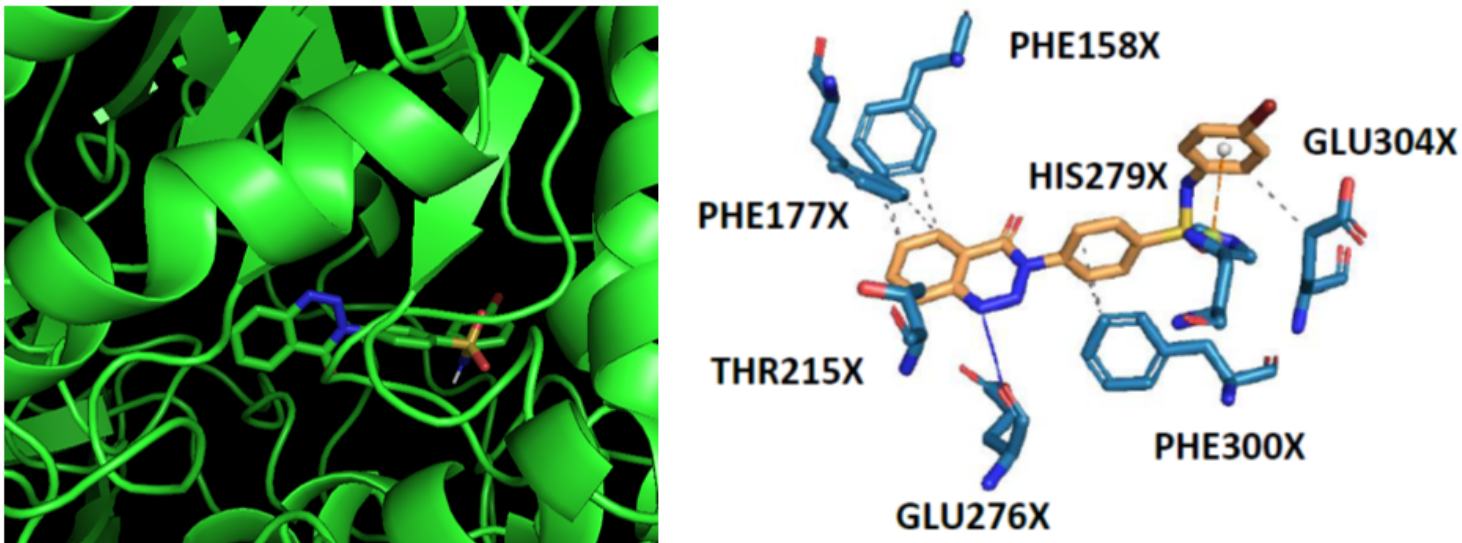

Figure 4

2D and 3D structure represents 5b ligand and α-glucosidase interactions

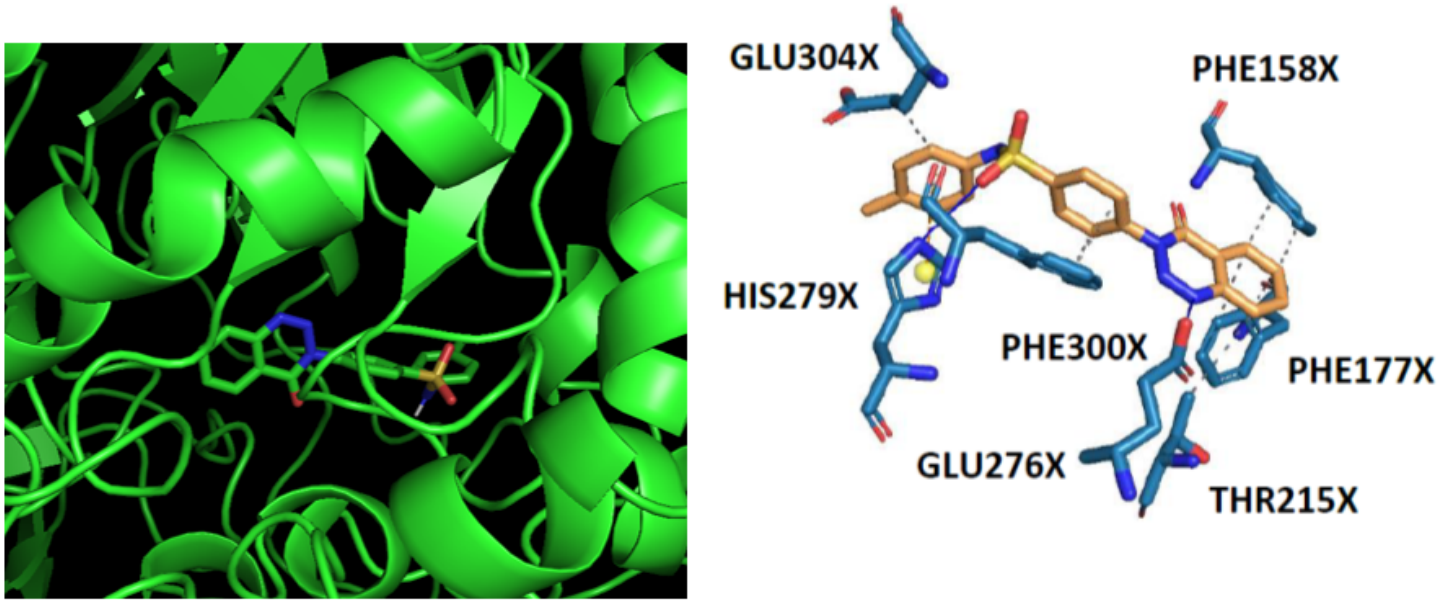

Figure 5

2D and 3D structures represent 5d ligand and α-glucosidase interactions

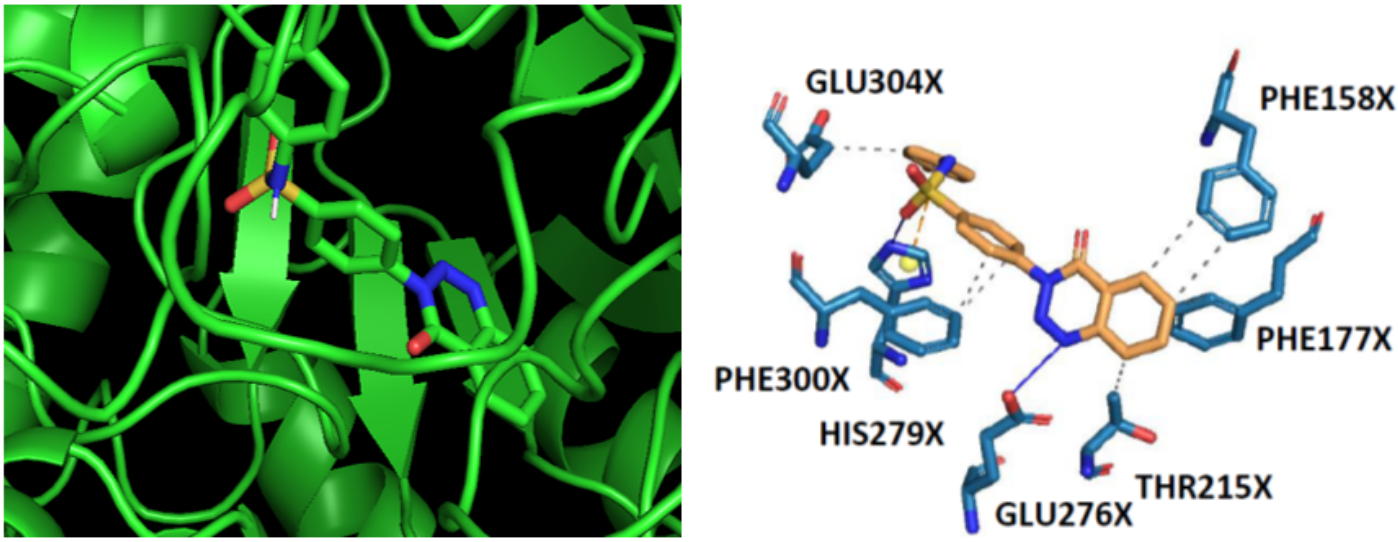

Figure 6

2D and 3D structures represent 5f ligand and α-glucosidase interactions

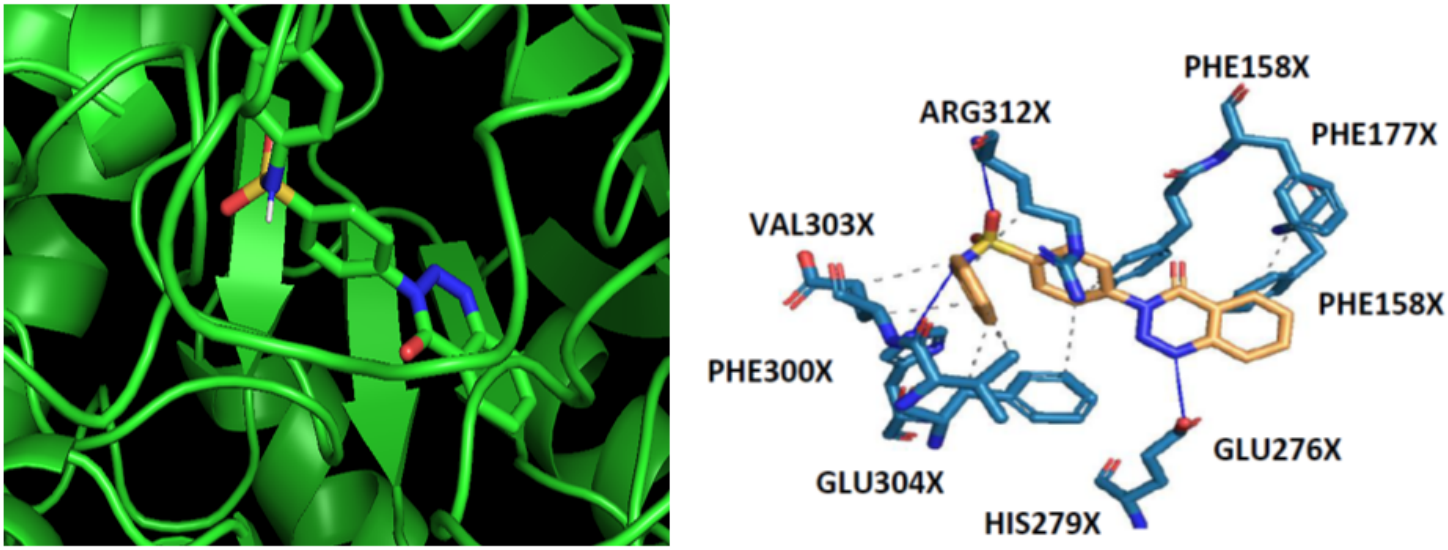

Figure 7

2D and 3D structure represents 5m ligand and α-glucosidase interactions

Supplementary Files

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- GraphicalAbstract.png
- Scheme1.png
- SUPPORTINGDATANMR.docx
- Table1.docx