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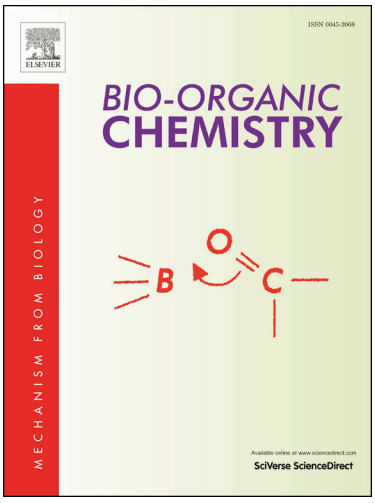

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Design, synthesis, docking and biological evaluation of chalcones as promising antidiabetic agents

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Abstract

Diabetes mellitus (DM) is a serious chronic metabolic disorder which occurs due to dysfunction of insulin and therapeutic approaches are poor. It is an under estimation that 387 million people currently suffering globally with diabetic and more than 592 million people may be affected by 2030. It makes an urgent necessity to discover novel drugs to control amplified diabetic populations. In this study, amino chalcones (3a-j) were synthesized and hydroxy chalcones (3g-j) were isolated from natural source such as *Sophora interrupta*, *Clerodendrum phlomidis* and *Andrographis macrobotrys*. Structural elucidation was carried out using Mass, ^{1}H and ^{13}C NMR Spectra. *In vivo* studies were carried out with alloxan induced diabetic rats (100 mg/kg) which reveals compounds 3c, 3a and 3h have significant antidiabetic efficacy with decreased blood glucose levels in the diabetic rats while compared with control rats. Besides, docking studies with aldose reductase, dipeptidyl peptidase, PPAR and glucosidase were monitored which accomplishes that the compounds 3c, 3i, 3a and 3d have eloquent binding affinity (kcal/mol) with aldose reductase, besides the chalcones 3c, 3b, 3d, 3e and 3i were also showed inhibition with DPP-IV, PPAR-α and α-glucosidase. Also, these compounds explicated distinct interactions i.e., π-π, π-cationic, polar, electrostatic and hydrophobic bonds were observed with key residues of binding pockets. Bioavailability is disclosed with Lipinski rule of five and the design pharmacokinetic as well as pharmacodynamic properties are reliable. Therefore, chalcones were implied as antidiabetic leads for in further studies and could be worthwhile for the development of new classes of effective antidiabetic agents.

Keywords: Diabetes mellitus, chalcones, docking, ADME

1. Introduction

Diabetes mellitus (DM) is a serious chronic metabolic disorder, categorized in to two types namely DM-I which is generated by dysfunction of β-pancreatic cells, whereas DM-II is caused from impairment of insulin secretion due to insulin resistance and occurs perturbations in the glucose homeostasis. This leads to originate several disorders like cardiovascular risks, blindness, skin infections and renal failure [1]. International Diabetes Federation (IDF) reported that 366 million people are currently suffering with DM and 552 million people will be affected by 2030 [2]. Now, biguanides, sulfonyl urease inhibitors, DPP4 inhibitors, trajenta, onglyza and Nesina, SGLT2 inhibitors, thiazolidinediones and α-glucosidase inhibitors are using in the diabetes clinical practices. However, several adverse effects have been reported such as diarrhea, liver diseases, renal failure, respiratory tract infections, musculoskeletal pain, enlarged urination and urinary tract infections [3, 4, 5]. In addition, passable remedial findings are also not optimistic. Therefore, there must be enormous contemplation is desired to deliberate peculiar antidiabetic agents with improved steered pharmacological action without adverse effects.

Chalcones are important classes of open chain flavonoids, essentially synthesized by plants and numerous synthetic methods also available [6]. Chalcone comprises two aromatic rings are united by three carbon system i.e., α, β unsaturated carbonyl system. It exhibits a wide range of therapeutic activities for instance, anticancer, antioxidants [7], anti-inflammatory [8], antihypertensive [9], antimalarial [10], antiulcer [11], antiviral [12], antiprotozoal [13], and antimutagenic [14]. Chalcone is a versatile molecule and easily allow to cyclize forming flavonoid structure. It is an isomeric key step for skeletal modification of biosynthetic pathway. Based on this feature, several synthetic attempts have been made to produce a new class of compounds, for example, azachalcones [15], oxazoles [16], pyrazoles [17] and indole grounded chalcones [18]. Also, amino chalcones were reported as anti-inflammatory and antimicrobial however antidiabetic activity has not yet been reported [19, 20]. So far, several chalcones have been rationalized that how their inhibitory modulation deliberates with essential pharmacological targets such as PPAR-g, DPP-4, a-glucosidase, PTP1B and aldose reductase in the diabetic clinical management [21]. In the current study, amino and hydroxy chalcones were achieved and examined their antidiabetic activity with alloxan induced diabetic rats through *in vivo* experiments. In addition, *in silico* studies were conducted with specific molecular targets of diabetes to confirm the chalcone structural significances for further comprehensive studies.

2. Material and methods

2.1. Chemistry

Chemicals and solvents were purchased from Merck, India and utilized in the present investigations. Melting points were recorded with Kofler hot stage apparatus and are uncorrected. The reactions were assessed by thin layer chromatography (TLC) on silica gel F_{254} plates. ^{1}H and ^{13}C NMR spectra were documented on Bruker Avance spectrophotometer operating at 600 and 400 MHz (**^{1}H**); 150 and 75 MHz (^{13}C) using DMSO-d_6 and $CDCl_3$ with TMS as an internal standard. Mass spectra was recorded on Micro Mass VG-7070H mass spectrometer for ESI and API Q-STAR PULSA i of applied bio-system in positive mode was used for ESI-TOFMS. The microanalyses were performed on Perkin-Elmer 240C elemental analyzer and Catalyst -4R microwave oven was used for synthesis reactions. Alloxan

monohydrate was obtained from HIMEDIA Ltd, India. The Accu Chek (Roche diabetes care, USA), glucometer and strips were purchased from local pharmacy.

2.2. Synthesis of amino chalcones

The preparation of amino chalcones was accomplished by microwave assisted synthesis [22]. An equimolar ratio of 4-aminoacetophenone (1 mmol) and aromatic aldehyde (1 mmol) were dissolved in 95% ethanol with catalytic quantity of NaOH (1-2 pellets). Further, the reaction mixture was irradiated under 180 microwave radiations for 10-15 mins and the progress of the reaction was confirmed with TLC using *n*-hexane-ethyl acetate (7:3). Subsequently, the reaction mixture was cooled at room temperature and poured into ice water. The solid was separated, filtered and recrystallized using ethanol (neutralize with dil. HCl, if precipitate is not appeared).

2.3. Natural chalcones

Hydroxy chalcones (3g-3j) were isolated from the medicinal plants such as 3g from *Sophora interrupta* [23], 3h and 3i from *Clerodendrum phlomidis* [24] and 3j from *Andrographis macrobotrys* [25] and were reported from our research laboratory. Therefore, these compounds were used in the present study to evaluate their antidiabetic activity.

2.3a.(E)-1-(4′-Aminophenyl)-3-(3,5-dimethoxy,4-hydroxyphenyl) prop-2-en-1-one (**3a**)

Pale Yellow Solid, Yield 71 %, M.P: 101°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.91 (6H, s, 3′ and 5′ OCH_3), 4.17 (2H, s, NH_2), 6.69 (2H, d, J = 9.6 Hz, H-3′and H-5′), 6.85 (2H, s, H-2 and H-6), 7.41 (1H, d, J=15.6 Hz, H_α), 7.74 (1H, d, J=15.6 Hz, H_β), 7.91 (2H, d, J =8.6 Hz, H-2′and H-6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 189.7, 162.6, 160.2, 150.7, 138.8, 130.9, 130.6, 120.4, 117.6, 113.8, 112.8,105.5, 98.6, 55.6, 55.5; ESI-MS (*m/z*); 322 for $[M+Na]^+$; Anal. calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.15; H, 5.70; N, 4.59.

2.3b.(E)-1-(4′-Aminophenyl)-3-(4-dimethylaminophenyl) prop-2-en-1-one (**3b**)

Pale Yellow Solid, Yield 87 %, M.P: 169°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.08 (6H, s, N,N CH_3), 4.11 (2H, s, NH_2), 6.77 (2H, d, J = 7.8 Hz, H-3 and H-5), 7.01 (2H, d, J = 8.6 Hz, H-3′and H-5′), 7.46 (1H, d, J = 15.2 Hz, H_α), 7.67 (2H, d, J = 7.8 Hz, H-2 and H-6), 7.81 (1H, d, J = 15.2 Hz, H_β), 7.97 (2H, d, J = 8.6 Hz, H-2′and H-6′);^{13}C NMR ($CDCl_3$, 75 MHz)δ: 188.8, 151.9, 145.7, 137.7, 131.0, 129.5, 127.3, 127.1, 121.4, 115.4, 110.7, 40.0; ESI-MS (*m/z*); 267 for $[M+H]^+$; Anal. calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.62; H, 6.77; N, 10.49.

2.3c.(E)-1-(4′-Aminophenyl)-3-(4-isopropylphenyl) prop-2-en-1-one (**3c**)

Pale Yellow Solid, Yield 82 %, M.P: 143°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (6H, J = 7.0 Hz, 2 CH_3), 2.90-2.99 (1H, m), 4.12 (2H, s, NH_2), 7.01 (2H, d, J = 8.6 Hz, H-3′and H-5′), 7.15 (2H, d, J = 8.0 Hz, H-3 and H-5), 7.36 (1H, d, J = 15.6 Hz, H_α), 7.55 (2H, d, J = 8.0 Hz, H-2 and H-6), 7.80 (2H, d, J = 8.6 Hz, H-2′and H-6′), 8.07 (1H, d, J = 15.5, H_β), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 188.3, 153.7, 152.2, 143.4, 133.7, 131.1, 128.6, 128.3, 126.0, 121.3, 114.5, 34.7, 23.6, ESI-MS (*m/z*); 266 for $[M+H]^+$; Anal. calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.44; H, 7.17; N, 5.19.

2.3d. (E)-1-(4′-Aminophenyl)-3-(4-fluorophenyl) prop-2en-1-one (**3d**)

Pale Yellow Solid, Yield 91 %, M.P: 143°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.16 (2H, s, NH_2), 6.63 (2H, d, *J*=8.6 Hz, H-3′ and H-5′), 7.01 (2H, d, *J* = 8.3 Hz, H-3 and H-5), 7.36 (1H, d, *J*=15.4 Hz, H_α), 7.51 (2H, d, *J* =8.6 Hz, H-2 and H-6), 7.64 (1H, d, *J*=15.4 Hz, H_β), 7.82 (2H, d, *J* = 8.6 Hz, H-2′and H-6′);^{13}C NMR ($CDCl_3$, 75 MHz)δ: 188.2, 162.3, 151.0, 141.5, 131.0,130.9, 129.9, 128.8, 128.1,119.8, 114.4, 113.9; ESI-MS (*m/z*): 264 for $[M+Na]^+$; Anal. calcd. for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; N, 5.81. Found: C, 74.62; H, 4.97; N, 5.79.

2.3e. (E)-1-(4′-Aminophenyl)-3-(pyridin-2-yl) prop-2-en-1-one (**3e**)

Pale Yellow Solid, Yield 78 %, M.P: 146°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.12(2H, s, NH_2), 6.68 (2H, d, *J* = 8.6 Hz, H-3′and H-5′), 7.21-7.25 (2H, m, H-4 and H_α), 7.63-7.68 (2H, m, H-3 and H-5), 7.87 (2H, d, *J* = 8.6 Hz, H-2′and H-6′), 8.01 (1H, d, *J*=15.4 Hz, H_β), 8.55 (1H, d, *J* = 7.3, H-6);^{13}C NMR ($CDCl_3$, 75 MHz) δ:187.0, 152.7, 150.3, 149.0, 140.1, 135.9, 130.3, 127.1, 124.2, 124.1, 123.0, 111.8; ESI-MS (*m/z*); 225 for $[M+H]^+$; Anal. calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.87; H, 5.37; N, 12.44.

2.3f. (E)-1-(4′-Aminophenyl)-3-(thiophen-2-yl) prop-2-en-1-one (**3f**)

Pale Yellow Solid, Yield 66 %, M.P: 119°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.12(2H, s, NH_2), 6.78 (2H, d, *J* = 8.6 Hz, H-3′and H-5′), 7.03 (1H, t, *J* = 4.5 Hz, H-6), 7.31- 7.37 (2H, m, H-3 and H_α), 7.85-7.96 (4H, m, H-4, H-2′, H-6′ and H_β),^{13}C NMR ($CDCl_3$, 75 MHz) δ: 186.25, 152.73, 140.09, 133.72, 131.51, 130.88, 129.11, 128.16, 124.87, 120.56, 112.51; ESI-MS (*m/z*); 252 for $[M+Na]^+$; Anal. calcd. for $C_{13}H_{11}NOS$: C, 68.09; H, 4.84; N, 6.11. Found: C, 68.01; H, 4.79; N, 5.09.

2.3g. (E)-1-(2′-Hydroxy-4′,6′-dimethoxyphenyl)-3-(2,4,5-trimethoxyphenyl) prop-2en-1-one (**3g**)

Yellow amorphous solid (Me_2CO), M.P: 184°C; ^{1}H NMR**:** (DMSO-d_6, 600 MHz) δ 13.68 (1H, s, OH-2'), 7.89 (1H, d, *J*=15.7 Hz, H-*β*), 7.73 (1H, s, H-*α*),7.19 (1H, s, H-6), 6.74 (1H, s, H-3), 6.13 (1H, d, *J*=2.3 Hz, H-3′), 6.10 (1H, d, *J*=2.3 Hz, H-5′), 3.88 (3H, s, OMe-2), 3.87 (3H, s, OMe-6′), 3.86 (3H, s, OMe-4), 3.80 (3H, s, OMe-4′), 3.77 (3H, s, OMe-5);^{13}C NMR: (DMSO-d_6, 150 MHz) δ 191.9, 165.5, 165.1, 161.7, 154.2, 152.7, 143.1, 138.0, 124.8, 114.4, 111.7, 106.4, 97.8, 93.9, 91.0, 57.0, 56.2, 56.0, 55.8, 55.6; ESITOFMS (*m/z*) : 375.1430 for $[M+H]^+$; Anal. calcd. for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.13; H, 5.91.

2.3h. (E)-1-(2′-Hydroxy-4′,6′-dimethoxyphenyl)-3-(3-hydroxyphenyl) prop-2en-1-one (**3h**)

Pale yellow solid (Me_2CO), M.P: 147°C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 13.50 (1H, s, OH-2′), 9.65 (1H, s, OH-3), 7.69 (1H, d, *J* = 15.7 Hz, H-α), 7.55 (1H, d, *J* = 15.7 Hz, H-β), 7.24 (1H, dd, *J* = 7.9, 7.8 Hz, H-5), 7.12 (1H, brd, *J* = 7.8 Hz, H-6), 7.06 (1H, dd, *J* = 2.0, 1.7 Hz, H-2), 6.84 (1H, ddd, *J* = 7.9, 2.0, 0.9 Hz, H-4), 6.12 (1H, d, *J* = 2.3 Hz, H-5′), 6.15 (1H, d, *J* = 2.3 Hz, H-3′), 3.89 (3H, s, OMe-6′), 3.81 (3H, s, OMe-4′); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 192.4, 165.6, 165.7, 161.9, 157.8, 142.5, 136.0, 130.1, 127.2, 119.7, 117.7, 114.4, 106.2, 93.9, 91.2, 56.2, 55.7; ESI-TOFMS (*m/z*): 301.0991 for $[M+H]^+$; Anal. calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.93; H, 5.30.

2.3i. (E)-1-(2′,3′-Dihydroxy-4′-methoxyphenyl)-3-(3-hydroxyphenyl) prop-2en-1-one (**3i**)

Orange yellow solid (Me_2CO), M.P: 129°C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 12.97 (1H, s, OH-2′), 9.65 (1H, s, OH-3), 8.69 (1H, s, OH-3′), 7.90 (1H, d, *J* = 15.4 Hz, H-α), 7.84 (1H, d, *J* =

9.2 Hz, H-6′), 7.72 (1H, d, *J* = 15.4 Hz, H-β), 7.32 (1H, m, H-6), 7.26 (1H, m, H-5), 7.24 (1H, m, H-2), 6.88 (1H, dd, *J* = 8.0, 1.7 Hz, H-4), 6.67 (1H, d, *J* = 9.2 Hz, H-5′), 3.88 (3H, s, OMe-4′); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 192.6, 157.8, 153.6, 152.2, 144.2, 135.8, 133.8, 129.9, 122.4, 121.2, 120.1, 118.0, 115.5, 114.9, 103.5, 56.0; ESI-TOFMS (*m/z*): 287.0880 for $[M+H]^+$; Anal. calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.11; H, 4.89.

2.3j. (E)-1-(2′-Hydroxy-4′-methoxyphenyl)-3-(2,3-dimethoxyphenyl) prop-2en-1-one (**3j**)

Yellow solid ($CHCl_3$), M.P: 185°; ^{1}H NMR : (DMSO-d_6, 400 MHz) δ 13.40 (1H, s, OH-2′), 8.21 (1H, d, *J* = 9.0 Hz, H-6′), 8.07 (1H, d, *J* = 15.7 Hz, H-β), 7.93 (1H, d, *J* = 15.7 Hz, H-α), 7.65 (1H, dd, *J* = 9.0, 2.0 Hz, H-6), 7.12 (1H, dd, *J* = 9.0, 9.0 Hz, H-5), 7.08 (1H, dd, *J* = 9.0, 2.0 Hz, H-4), 6.54 (1H, dd, *J* = 9.0, 2.4 Hz, H-5′), 6.49 (1H, d, *J* = 2.4 Hz, H-3′), 3.82 (6H, s, OMe-3, 4′), 3.79 (3H, s, OMe-2); ^{13}C NMR : (DMSO-d_6, 75 MHz) δ 191.8, 166.0, 165.7, 152.7, 148.3, 137.9, 132.6, 128.0, 124.2, 121.9, 119.3, 115.1, 113.9, 107.4, 100.9, 61.0, 55.7; ESITOFMS (*m/z*): 315.1206 for $[M + H]^+$; Anal. cald. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.73; H, 5.69.

2.4. *In vivo* studies

2.4.1. Animals

Wistar male albino rats (180-200 g) were utilized in the present study and ethical committee clearance (No.27/2012-2013/(i)/a/CPCSEA/IAEC/SVU/CAR-MSA) was approved from Sri Venkateswara Univeristy, Tirupati, India. The rats were maintained under standard laboratory conditions at 25ºC with 12 hours light and dark by giving standard pelleted as feed and water with not more than five animals per cage.

2.4.2. Experimental design and induction of diabetes

The antidiabetic evaluation of chalcones (3a-3j) was performed according to the experimental design described by Satyanarayana, *et. al.,* 2004 [26]. The animals were randomly divided into ten groups and each group consists of five rats. Group-I is treated as normal control and given normal diet and water throughout the experiment. Group-II is treated with simply alloxan monohydrate and treated as positive control. Group-III is preserved as negative control and treated with alloxan monohydrate followed by 0.025 units of insulin (1 IU/kg body weight). The groups IV-XIII are consisting of diabetic induced arts and monitored with chalones (3a-3j). The rats were fasted for 10-12 hrs and alloxan monohydrate (150 mg/kg body weight) was administered intraperitoneally to induce the diabetes [26]. Subsequently, animals were feed with on standard pellets and water. The blood glucose levels of the rats were monitored by tail tipping method using glucometer. After two days, the blood glucose levels were predicted and are considered as diabetic rats if blood glucose is above 200 mg/dl and conducted further studies.

2.4.3. Blood sampling and blood glucose determination

The portion of albino rat tail was wiped off with warm water, subsequently with 10% alcohol nipping, squeeze gently to collect the blood drops at specific time intervals. The rat tail was sterilized by swabbing with 70% alcohol and the blood glucose levels were measured with a glucose analyzer model (Accu Chek, Roche diabetes care, USA) and were calculated according to AUC method and expressed results in percentage (%).

2.5. Statistical analysis

All the experiments were carried out in triplicates and calculated using SPSS v16. The data was expressed as Mean±Standard error of the mean (SEM) and analyzed by one-way analysis of variance (ANOVA) followed by student ″t″ test and statistically significant findings were considered as *P*-value is <0.05.

2.6. *In silico* studies

2.6.1. Protein preparation

Crystal structures of aldose reductase (PDBID:4GCA) [27], DPP-IV (PDBID:4N8D) [28], PPAR-α (PDBID:1K7L) [29] and α-glucosidase (PDBID:5NN5) [30] were retrieved from Protein Data Bank (PDB). Co-crystal ligands, water and ions were removed and hydrogens were added. Energy minimization was employed using steepest descent algorithms [31, 32].

2.6.2. Binding cavity volume and shape calculations

CastP was employed to determine binding cavities, volume and key residues of targets [33]. Shape analysis of binding cavity of the protein was achieved with Metapocket2.0 [34].

2.6.3. Ligand preparation

Chalcones and reference inhibitors were drawn in 3D and optimized using Marvin Skech. The hydrogens were added and energy minimized molecules were used for docking studies.

2.6.4 Molecular docking

Auto Dock Vina 4.05 was used to dock into active site of the proteins [35, 36]. Ligand molecules were uploaded and energy minimized with universal force field using conjugate-gradient algorithm with 200 run iterations and converted as PDBQT files. Docking grid box was prepared and positioned to cover binding pockets according to the location of key residues (Table 1). The grid box and sizes were followed as aldose reductase (center_x = -9.1, center_y = 4, center_z = 4.3; size_x = 26.2, size_y = 24.6 and size_z = 25.9), DPPIV (center_x = 13.6, center_y = 26.4, center_z =55.8; size_x = 25, size_y = 25 and size_z = 25), PPAR-α (center_x = -20.6, center_y = -12.5, center_z = -2.8; size_x = 25.0, size_y = 25.0) and α-glucosidase (center_x = -8.9, center_y = -34.9, center_z = 94.4; size_x = 25.0, size_y = 25.0, size_z = 25.0 and size_z = 25.0) and exhaustiveness was set to 8. Moreover, Lamarckian genetic algorithm was used for docking with following parameters: the number of individuals in the population was 150; the maximum number of energy evaluations was 25,000; and the maximum number of generations was 27,000. Top individuals to survive to next generation were 1; Gene mutation rate was 0.02; Crossover rate was 0.8; Cauchy beta was 1.0 and genetic algorithm window size was set to 10.0. The best docked ligand conformations, bond angles, bond lengths and bonding interactions were analysed using PyMOL [37].

2.6.5. Bioavailability

Molecular properties, Lipinski rule of five, ADME (absorption, distribution, metabolism and excretion) and drug likeness of chalcones were appraised using Molsoft molecular property prediction and Swiss ADME server [38].

3. Results and discussion

3.1. Chemistry

Synthesis of amino chalcones (3a-f) were achieved by microwave irradiation of 4-aminoacetophenone with the corresponding aryl aldehydes with varied substituents, resulting moderate to high yields of 66-91% (Figure 1a). Natural hydroxy chalcones (3g-j) were isolated from various medicinal plants and represented in Figure 1b. The structural elucidation of chalcones was employed by Mass, ^{1}H and ^{13}C NMR spectra. A characteristic pair of doublets of olefinic double bond protons with coupling constant ranges from 15.2 to 15.7 Hz indicating that the two aryl rings in the chalcone moiety were in trans configuration.^{13}C NMR spectra reveals chemical shifts ranging from 192.6 to 186.3 ppm which attributed to carbonyl group of prop-2-enone bridge and are the evidence for the formation of open chain chalcone structures.

3.2. *In vivo* studies

In vivo studies were carried out with alloxan induced diabetic wistar male albino rats to evaluate the antidiabetic activity of chalcones. Initially, diabetes was induced with alloxan (100 mg/kg) and found that blood glucose levels are high in group II i.e., 301.12±1.85, 286.00±1.20 and 265.42±2.10 mg/dL at various time intervals (1, 2 and 3 hours) when compared with normal control group I rats 84.78 ±0.78, 81.45±0.58 and 78.12±1.25 mg/dL, respectively. Further, acute antidiabetic activities of chalcones (3a-j) were assessed by perceiving lower the blood glucose levels in diabetic rats in the range of 50-29% (Figure 2). The compound 3c significantly inhibited 50% of blood glucose levels (150.60±1.50 mg/dL) in the diabetic rats when compared with control rats. Amino chalcone 3c possesses amphipathic properties owing to presence of isopropyl and amino phenyl group which could able to implicate formation of hydrophilic and hydrophobic bonds with targets. Another amino chalcone 3a is having amino phenyl, one hydroxyl and two methoxy groups which contributed to reduce 41% blood glucose (156.50±1.30 mg/dL). Further, compound 3e showed moderate antidiabetic activity with 39% glucose inhibition (160.60±1.58 mg/dL) due to its hydrophobic property. In addition, 3d, 3b and 3f compounds conferred sensible antidiabetic activity by decreasing blood glucose with percentage of 35% (170.60±1.44 mg/dL), 33% (176.40±1.90 mg/dL) and 31% (181.10±2.40 mg/dL), respectively. Also, the hydroxyl chalcone 3h has two methoxy, two hydroxy and one carbonyl as function groups and able to reduce excess blood glucose levels (158.60±1.58 mg/dL) to 40% in alloxan induced diabetic rats. Another chalcone 3g revealed considerable blood glucose inhibition with 33% percentage when compared with control diabetic rats. The hydroxyl chalcone 3i has three hydroxy, one methoxy and one carbonyl group functions which showed moderate activity. While the chalcone 3j has three methoxy, one hydroxy and one carbonyl group which showed 29% of glucose inhibition with least antidiabetic activity.

Diabetic drug targets

Earlier reports have shown that chalcones are potent inhibitors of several key enzymes such as aldose reductase, dipeptidyl peptidase-IV, peroxisome proliferator activated receptor-g and α-glucosidase with reference to diabetic complications [21]. Henceforth, in the present study intended to *in silico* studies of chalcones to ascertain the active diabetic target(s). Hence, binding pockets, volume, shape, key residues and docking with chalcones will be discussed more details in below.

3.3. Volumetric evaluation of binding cavities

Volumetric analysis for aldose reductase, dipeptidyl peptidase-IV, and peroxisome proliferator activated receptor-α, and α-glucosidase were assessed. It is a reliable approach to distinguish binding cavity volumes to identify the related ligands (Figure 3). DPP-IV has largest binding cavity volume (9903.2 Å) and area (4530.9) with predicted key residues such as Glu205, Glu206, Arg358, Phe357, Tyr547, Tyr585, Tyr666, Tyr662. PPARα pocket has volume of 470.2 Å and area is 884.7, aligned with Phe351, Ile354, Phe243, His440, Phe318, Tyr314, Tyr646, Cys275, Ala333 and Thr279. Aldose reductase pocket has 228.7 Å volume and area is 443.9 that formed with critical residues of Thr113, Trp111, His110, Tyr48, Trp20, Tyr209, Leu300 and Cys303. α-Glucosidase pocket has smallest binding cavity volume is 216.1 Å and area is 195.1 including key residues of Trp376, Asp404, Ile441, Met519, Asp518, Trp516, Arg600, Trp613, Asp616, His674, Phe649 (Table 1).

3.4. Redocking and validation

The docking method is necessary to be validated by reproducing and hence co-crystal ligands from the targets were retracted and redocked into specific identified binding pockets. RMSD was computed with overlay of best docked pose with crystal pose of ligand. RMSD of docked pose is within 2.0 Å that denoting reliable docking that helps in the endorsement of consistency and reproducibility. Redocking studies explicated that IDD1219 has volume is 312 A^3 and showed binding energy of -11.0 kcal/mol. RMSD was measured to be 1.0 Å with crystal pose of aldose reductase. Syn-7aa is a crystal inhibitor of DPP-IV has volume of 351.15 A^3 that showed binding energy of -8.5 kcal/mol and RMSD was calculated as 1.8 Å with crystal pose. DW409544 is a bound inhibitor of PPARα and has volume of 537.24 A^3. It showed binding energy -9.7 kcal/mol and measured RMSD of 1.2 Å. α-Glucosidase has bound crystal inhibitor 1-deoxynojirimycin and has volume of 142.95 A^3. Docking study showed binding affinity -4.5 kcal/mol and calculate RMSD was found to be 1.7 Å with crystal pose (Figure 4). Based on this result, further we carried out docking by using reproducible protocol.

Protein-chalcone interactions

Docking experiment was assessed with aldose reductase, DPP-IV, PPARα and α-glucosidase and chalcones, and depicted binding affinities in Table 2. Chalcones interacted through a variety of interfaces i.e., hydrogen bonds, hydrophobic and π-π interactions. Aldose reductase is belonging to the aldo-keto reductase superfamily and involved in polyol pathway. Chalcones were docked into binding pocket of energy minimized aldose reductase and measured binding affinities (kcal/mol). The best docked conformation of chalcone was exposed and extracted critical interaction with key residues in the pocket (Figure 5). Compound 3c showed binding interactions with Thr113 (2.9 Å), the ring A of 3c formed π-π bond with Trp111 and isopropyl forms π-π bonds with Trp20 (3.9 Å and 3.7 Å). Similarly, chalcone 3d bonds with Thr113 (2.8 Å), ring A forms π-π bond with Trp111 (2.7 Å) and fluorophenyl exhibited π-π and polar bonds with Trp20 (4.0 Å and 4.1 Å). While, 3a compound exerted four bonds such as one bond with Thr113 (2.8 Å), π-π bond with Trp111 (2.7 Å), 5-methoxy phenyl formed two bonds i. e., π-π and polar bonds with Trp20 (3.9 Å and 3.0 Å). Likewise, the chalcone 3b showed bonds with Thr113 (2.8 Å), ring A forms π-π bond with Trp111 (3.6 Å), amino phenyl formed two bonds such as π-π and polar bonds with Trp20 (4.1 Å and 4.0 Å). The compound 3e

demonstrated one bond with Thr113 (2.8 Å), ring A and pyridine forms π-π interactions with Trp111 (3.7 Å) and Trp20 (4.0 Å). Whereas the chalcone 3f showed interactions such as, one bond with Thr113 (3.1 Å), ring A and thiophene ring forms π-π bonds with Trp111 (3.8 Å) and Trp20 (3.6 Å). The compound 3i with Thr113 (2.5 Å) and Trp111 (3.7 Å) through di-hydroxy phenyl bonds with Tyr48 (3.4 Å), forms π-π and polar bonds with Trp20 (3.8 Å, 3.2 Å). 3h exhibited bonding with Thr113 (4.3 Å) and Trp111 (3.7 Å), 2′-hydroxy, 4′, 6′-dimethoxy phenyl ring bonds with Tyr48 (3.3 Å), π-π and polar bond with Trp20 (3.9 Å and 4.7 Å) and Tyr209 (4.9 Å). Chalcone 3j showed one bond each with Cys303 (4.3 Å) and Trp111 (3.8 Å) and, 2′-hydroxy phenyl formed π-π and polar bonds with Trp20 (3.1 Å and 4.1 Å), respectively.

In addition, docking studies for DPP4 revealed that compounds 3c and 3i have revealed highest binding energies and oriented in the S1 binding pocket **(**Figure 6**)**. Chalcone 3c illustrated binding interactions *via* isopropyl formed two π-cation interactions with Tyr547 and Glu206 (3.3 Å and 3.3 Å), polar bonds with Tyr666 and Tyr662 (3.3 Å and 3.4 Å) and carbonyl group showed two bonds with Arg358 (2.8 Å). The amino group of 3c bonds with Tyr585 (4.7 Å) and phenyl formed π-π bond with Phe357 (3.8 Å). Similarly, 3i compound formed π-π bond with Phe357 (3.8 Å), OH with Arg358 (3.1 Å), 17OH with Glu206 (2.8 Å), 21OH with Glu205 (2.7 Å), 16MeO with Tyr662 (4.3 Å) and one π-cationic bond with Tyr547 (3.5 Å)**.** Also, the chalcone 3a made π-π bond with Phe357 (3.8 Å), carbonyl with Arg358 (3.9 Å), dimethyl with Glu205 (3.4 Å) and 4-OH with Tyr662 (3.2 Å). Another chalcone 3d displayed two π-π bonds with Phe357 (3.5 Å) and Arg358 (4.2 Å), carbonyl with Glu206 (3.2 Å), π-cationic interaction with Tyr662 (3.5 Å). The compound 3b formed π-π and polar bonds with Tyr585 (4.3 Å), carbonyl with Arg358 (2.8 Å) and methyl amine bonds with Tyr666 (4.0 Å) and Tyr662 (3.7 Å). In the same way, the compound 3e showed interactions with Phe357 (3.7 Å), carbonyl with Arg358 (3.3 Å) and pyridine with Tyr666 (4.0 Å) and Tyr662 (3.5 Å). The chalcone 3f exhibited bonds with Phe357 (3.8 Å), carbonyl with Arg358 (3.3 Å) and thiophene with Tyr666 (3.8 Å) and Tyr662 (3.4 Å).

Further, the molecular docking of chalcones 3d, 3b, 3e and 3i exhibited best binding energy with PPARα and explicate interactions with key residues and, depicted in Figure 7**.** 3d compound showed π-π and polar bonds with Phe351 (3.3 Å) and Ile272 (3.7 Å) and, fluorophenyl formed π-π and polar bonds with Tyr314 (3.1 Å) and Tyr464 (3.7 Å). The compound 3b presented two bonds with Cys275 (4.3 Å) and Thr279 (3.7 Å) and, one π-π bond with Phe318 (4.2 Å). Whereas, chalcone 3e showed polar bond with Tyr314 (3.0 Å), carbonyl with Ile354 (4.3 Å) and pyridine with Phe351 (3.4 Å). Also, 3i compound disclosed π-π bond with Phe351 (3.7 Å), π-cationic bond with Phe273 (2.9 Å), 3OH with Tyr464, 4OH with Tyr314 and π-cationic bond with Phe318. Furthermore, binding interactions of 3g, 3h, 3c, 3a, 3f and 3j compounds with PPARα were also depicted.

The α-glucosidase is a member of exo-acting enzyme which is actively involved in the carbohydrate metabolism and regulation. Hence, the docking studies of chalcones revealed that the compounds 3c, 3i and 3b showed best binding energies with significant binding interaction with key residues of α-glucosidase (Figure 8). The chalcone 3c displayed crucial interactions π-π bond with Trp376 (3.4 Å). Another chalcone 3i formed four bonds i.e., polar bond with Asp616 (3.3 Å), π-π bond with Phe649 (3.5 Å) and Trp376 (3.6 Å). Further, 3b compound exhibited two bonds such as one polar bond with Asp616 (4.1 Å) and one π-π bond with Phe376 (3.5 Å).

Likewise, the chalcones 3a, 3d, 3e, 3f, 3g, 3h and 3j formed bonds with Asp616, Trp376, Phe649 and Asp518.

3.7. Molecular properties, Lipinski rule and ADME

Pharmacokinetic and pharmacodynamic properties are playing an important role in the optimization of lead molecules and in the drug discovery process which minimizes the pharmacokinetic failures at various clinical phases. In this perspective, *in silico* prediction is an effective alternative approach for prediction of ADME (Absorption, Distribution, Metabolism and Elimination) to experimental estimations. Bioavailability radar hat denotes reliable drug-likeness by considering lipophilicity (-0.7-+0.5), size (150g/mol >500g), polarity (20A-130A), solubility (<6), flexibility (<9) and saturation (0.25<1) and shown in Figure 9. Further, Lipinski's rule of five (molecular weight (<500), H-bond donor (<5), H-bond acceptor (<10) and cLogP (<5)) are specifically describing the relationships between physicochemical and pharmacokinetic properties and were establish to be satisfied (Table 3). Similarly, lipophilicity is calculated to be less than five. Solubility is another majorly concerning property about the absorption of drug by assessing either drug to be soluble or moderately soluble. Further, pharmacokinetic property evaluation revealed the skin permeability, gastrointestinal absorption and blood brain barrier (BBB) permeability and interactions with different isoform of cytochrome p450 which play a key role in the drug elimination. Based on the bioavailability, clearly drug likeness could be deliberated as oral drug from the analysis of Lipinski rule, Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) (Table 4). Therefore, these optimized chalcones could be recommended for further studies and ratified as anti-diabetes agents.

3.8. Structure Activity Relationship (SAR) Studies

Chalcones possess broad spectrum therapeutic profiles which are believed to be owing to their structural substitutions on the ring A and B. It is a fascinating note to mention that the chalcones having electron releasing groups such as dimethyl amino, alkyl and amino groups at C-4 position of either on the ring A or the ring B flourished extensive pharmacological activities than heteroaryl chalcones. In case of 3c, amino and isopropyl groups act as electron donors and substituted at para position incite electron delocalization and implicates stabilization of the molecule. Also, the 2′-hydroxyl group is an essential feature that deliberates the significant biological activity and retains the structural stability. Furthermore, the chalcones having either 2′-hydroxylation or 2′,3′-dihydroxylation substitution pattern exhibits augmented inhibitory activities. Especially, 2′-hydroxylation is in chelation with carbonyl group, is greatly enhances the biological activities [39, 40]. Thus, the chalcone 3i showed effective diabetic activity is believed due to the presence of 2′, 3′-dihydroxylations on the ring A. Similarly, the antidiabetic activity of chalcone 3a may be assumed due to the unique tri-oxygenation in the ring B.

4. Conclusions

In conclusion, the present study discloses the antidiabetic activity of chalcones. The results revealed that the chalcones 3c, 3a, 3e, 3h and 3i were presented significant antidiabetic properties. In addition, the molecular docking studies reveal the target specificity with aldose reductase. Hence, these findings would be helpful for the further *in vitro* studies with quantified target. Furthermore, these molecules might be endorsed as plausible antidiabetic agents and to ensure therapeutic profiles must be evaluated in the subsequent clinical phases for the effective treatment of diabetes.

Conflict of Interest

All the authors declare no conflict of interest.

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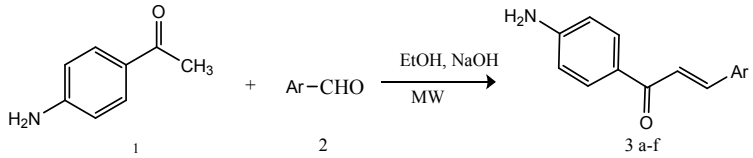
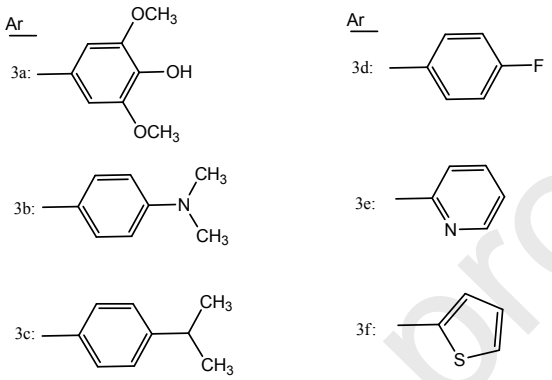
a).





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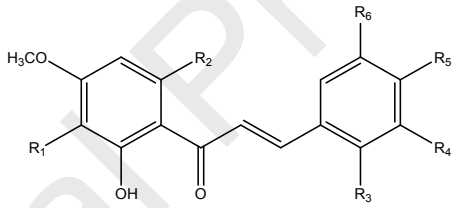


3g R_1=R_4=H, R_2=OCH_3, R_3=R_5=R_6=OCH_3
3h R_1=R_3=R_5=R_6=H, R_2=OCH_3, R_4=OH
3i R_1=R_4=OH, R_2=R_3=R_5=R_6=H
3j R_1=R_2=R_5=R_6=H, R_3= R_4=OCH_3

Fig. 1. a). Synthesis of amino chalcones (3a-3f); **b).** natural hydroxy chalcones (3g-3j) were isolated from medicinal plants.

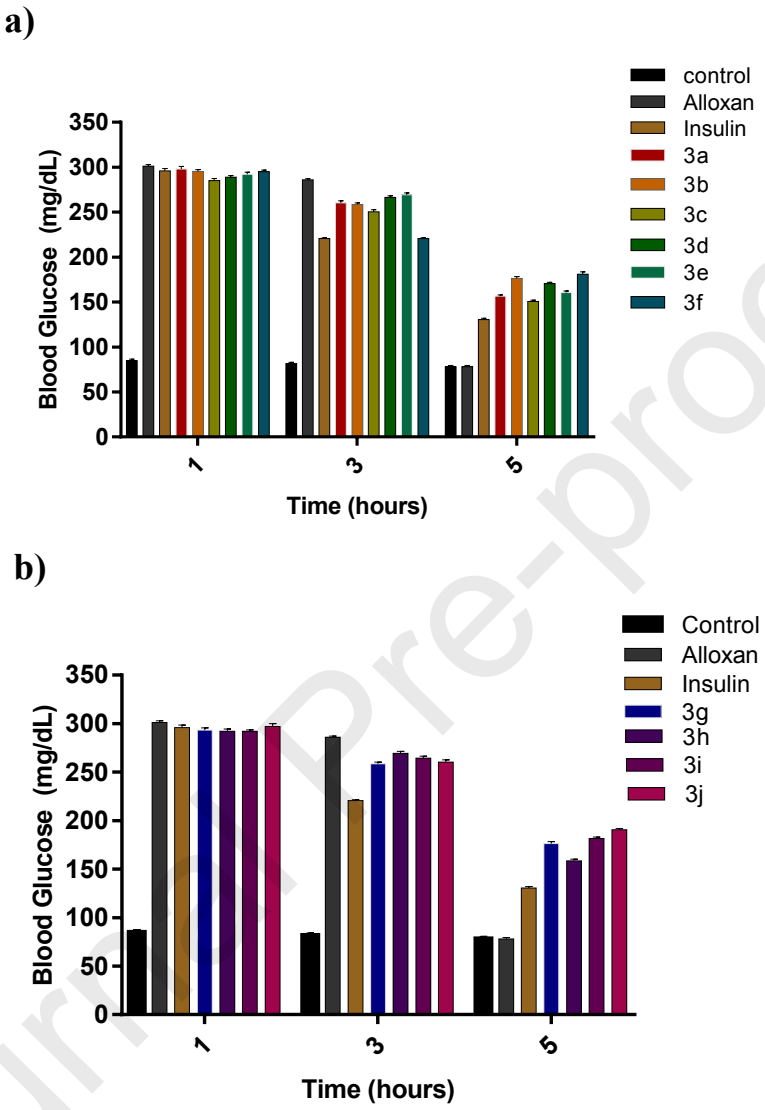


Fig. 2. a). Antidiabetic activity of amino chalcones (3a-3f); **b).** hydroxy chalcones (3g-3j). The data are presented as means ± SD from three independent experiments: $p < 0.05$ as determined by Student's *t* test.

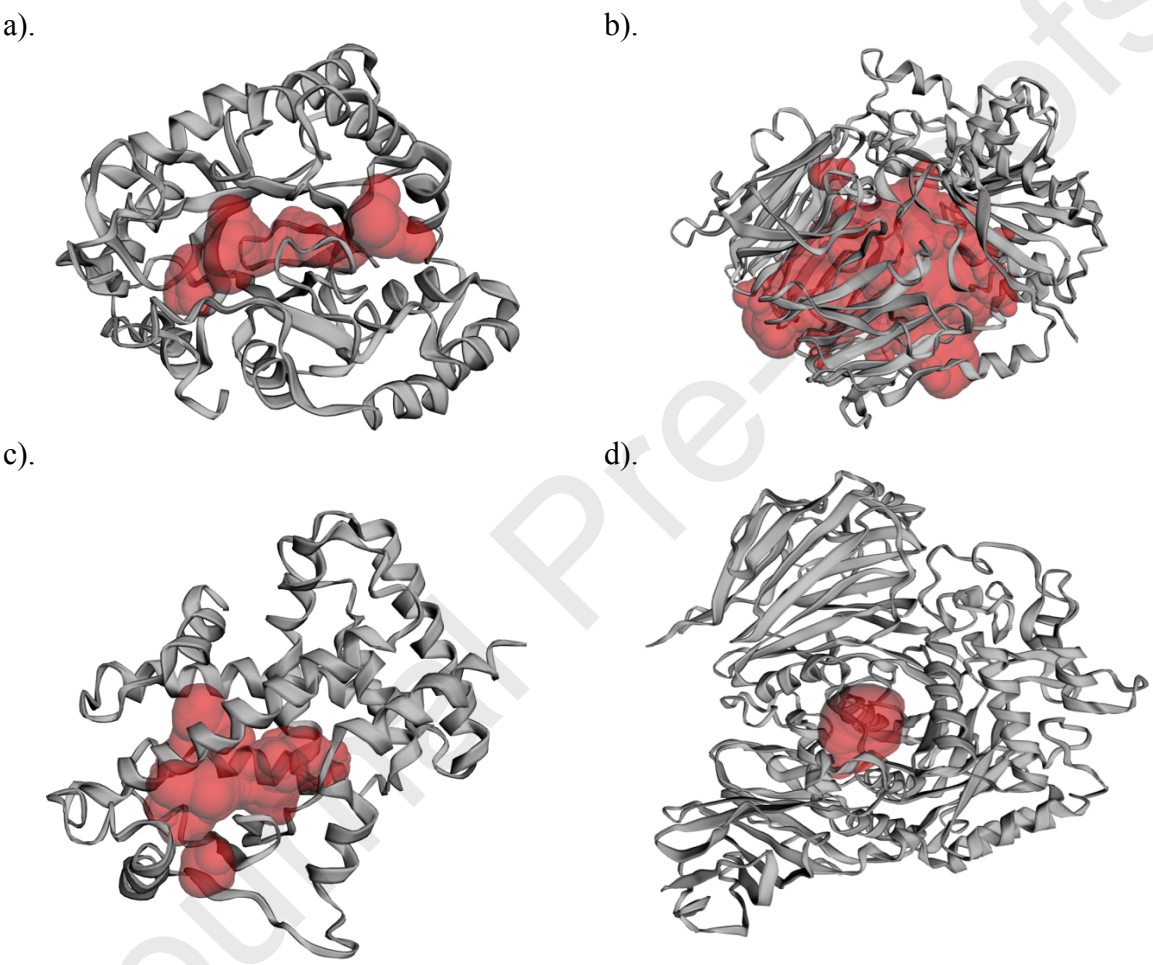


Fig. 3. Binding pocket volumes and shapes of **a).** Aldose reductase, **b).** DPP-IV, **c).** PPARα and **d).** α-Glucosidase.

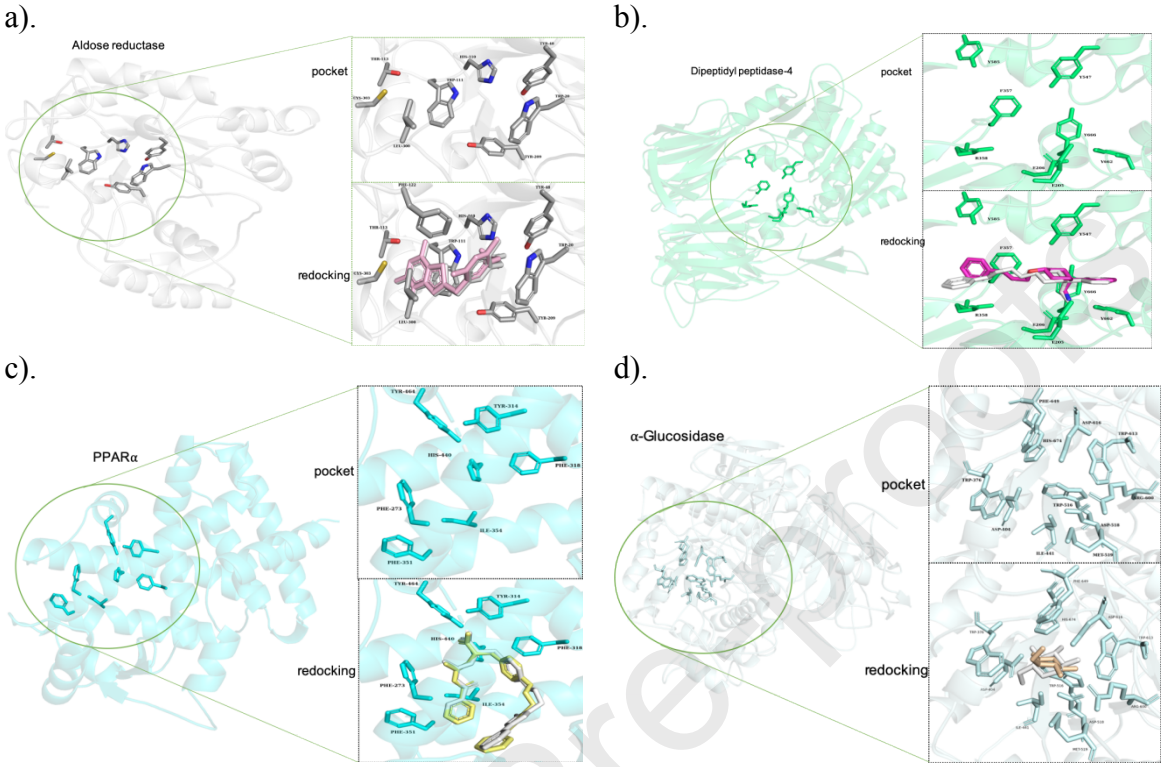


Fig. 4. Binding pocket residues of putative drug targets of diabetes such as **a).** aldose reductase, **b).** dipeptidyl peptidase-IV, **c).** PPARα and **d).** α-glucosidase. Critical residues are rendered as sticks with labeling and crystal ligands (white) and docked poses were overlaid.

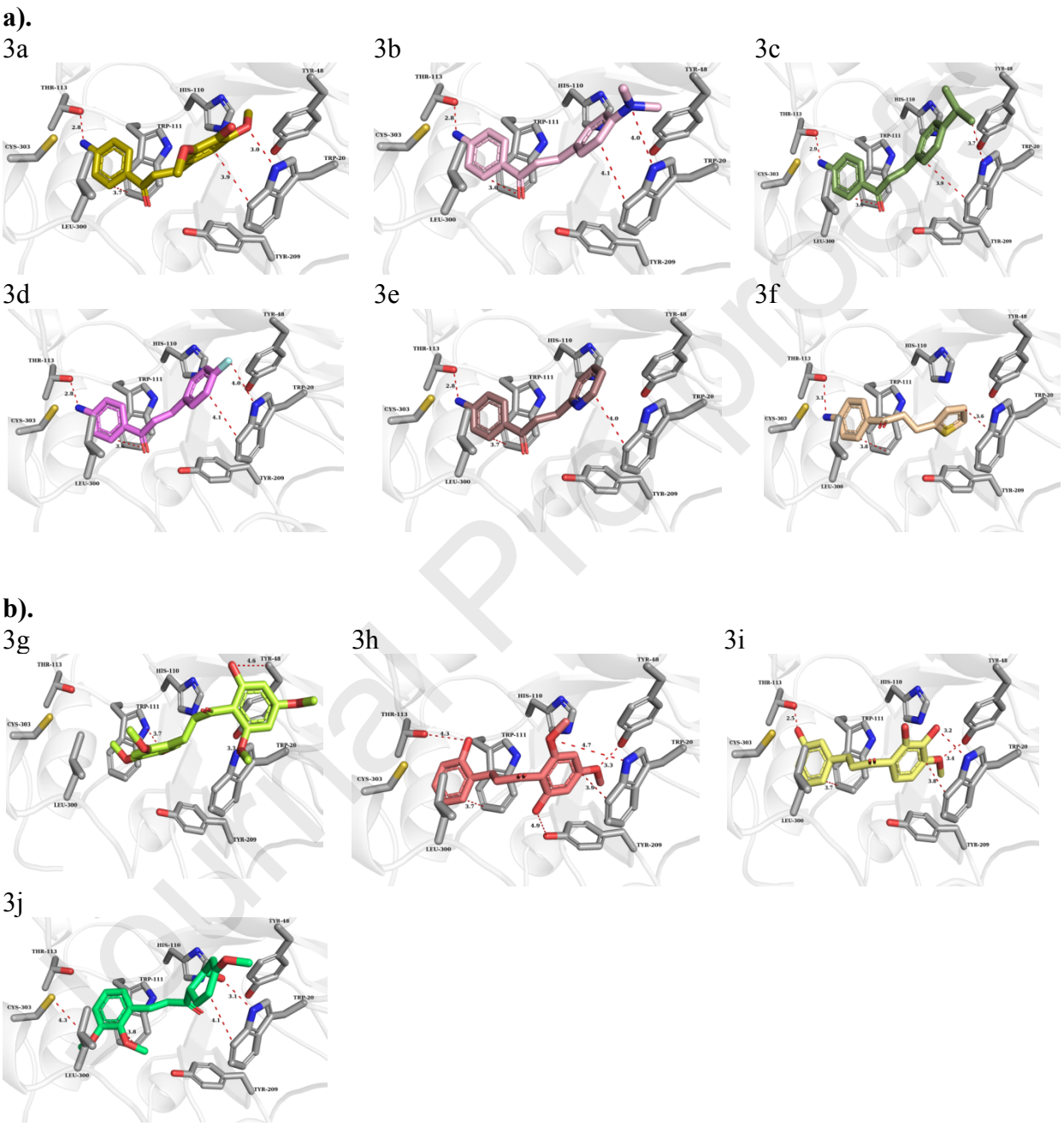


Fig. 5. a). Amino chalcones (3a-3j) and **b).** hydroxy chalcones (3g-3j) binding interactions and distances with active site residues of aldose reductase.

a). b).

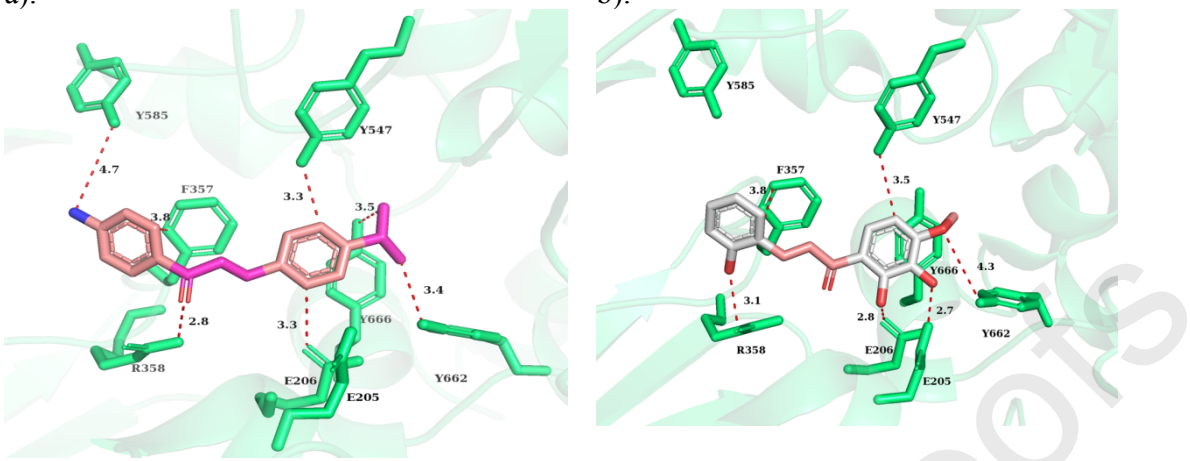
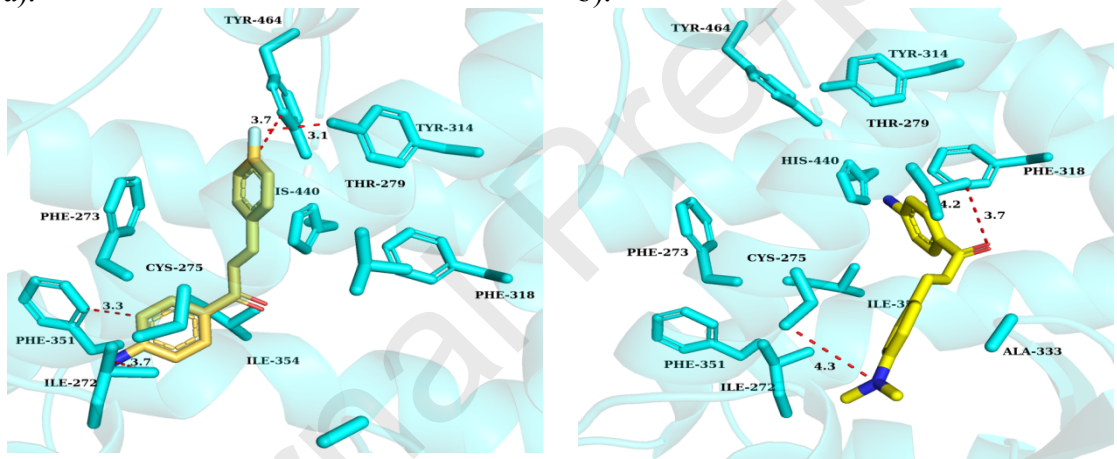


Fig. 6. 3c and 3i binding interactions and distances with key residues of DPP-IV.

a). b).



e). i).

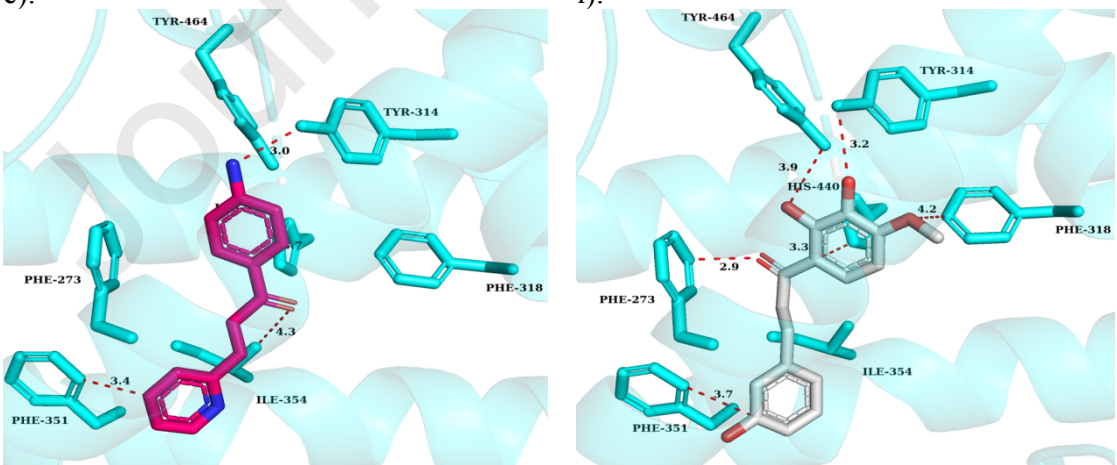
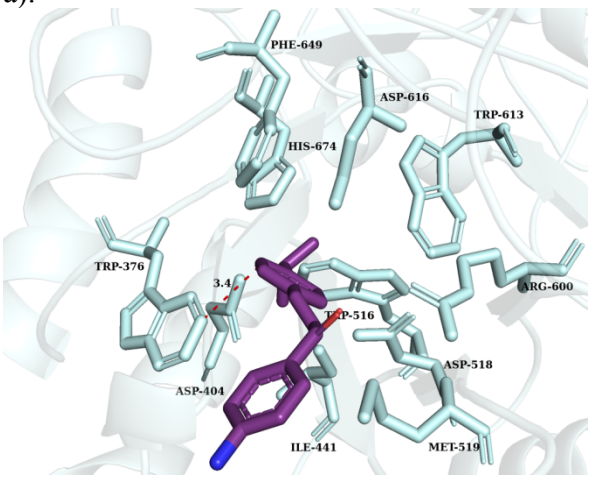
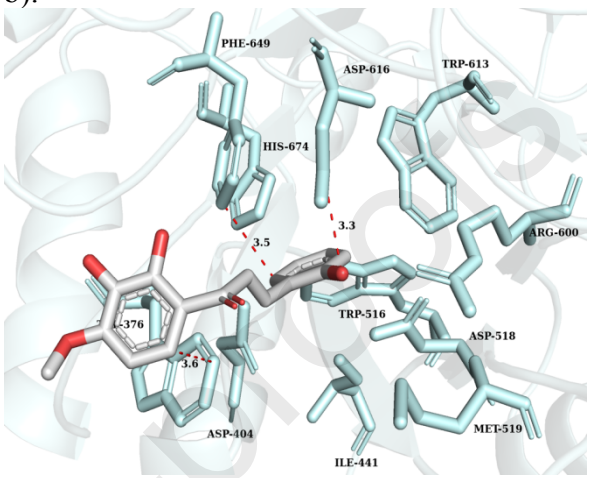


Fig. 7. a). 3d, **b).** 3b, **c).** 3e and **d).** 3i binding interactions and bond distances with pocket residues of PPARα.

a).



b).



c).

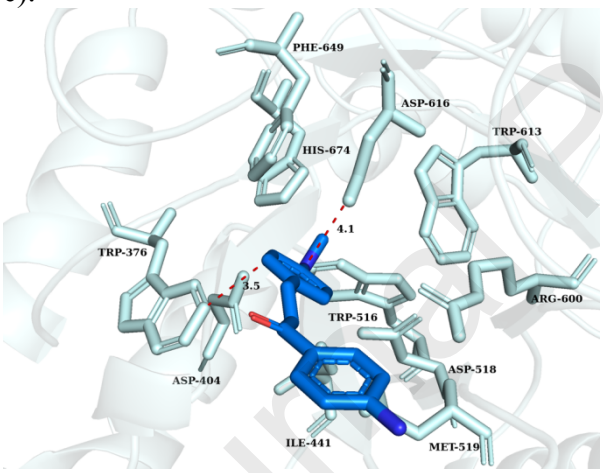


Fig. 8. a). 3c, **b).** 3i and **c).** 3b binding interaction and distances with active site residues of α-glucosidase.

Fig. 9. Drug-likeness of chalcones were predicted using Bioavailability radar. The pink is depicted optimal range of each property (Lipo:Lipophilicity, Size:Molecular weight, POLAR: Total Polar Surface Area, INSOLU: Insolubility, INSATU: Insaturation, FLEX: Flexibility).

Table 1. Binding pocket residues, volume and area of diabetic drug targets**.**

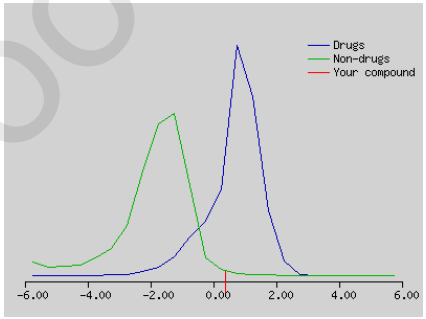
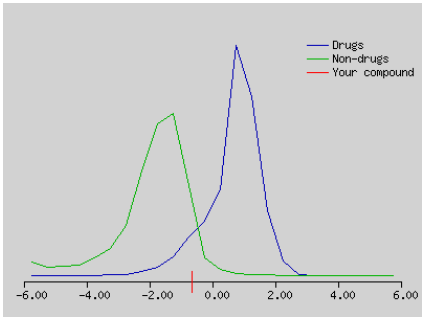
S. No	Targets	PDBID	Key Residues	Volume (Å)	Area (SA)
1	Aldose reductase	4GCA	Thr113, Trp111, His110, Tyr48, Trp20, Tyr209, Leu300, Cys303	228.7	443.9
2	DPP-IV	4N8D	E205, E206, R358, F357, Y547, Y585, Y666, Y662	9903.2	4530.9
3	PPAR-α	1K7L	Phe351, Ile354, Phe243, His440, Phe318, Tyr314, Tyr646, Cys275, Ala333, Thr279	470.2	884.7
4	α-Glucosidase	5NN5	Trp376, Asp404, Ile441, Met519, Asp518, Trp516, Arg600, Trp613, Asp616, His674, Phe649	216.1	195.1

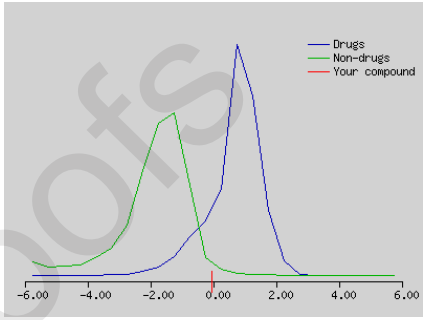
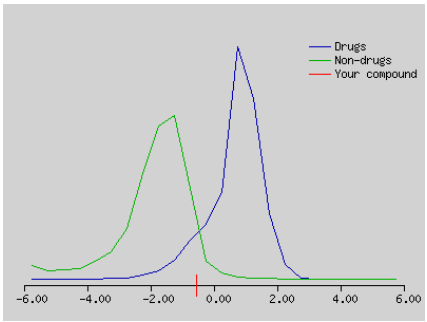
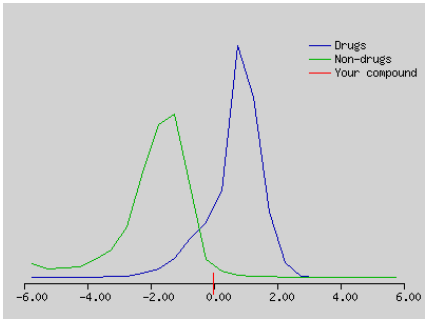
Table 2. Binding energies of chalcones with diabetic drug targets.

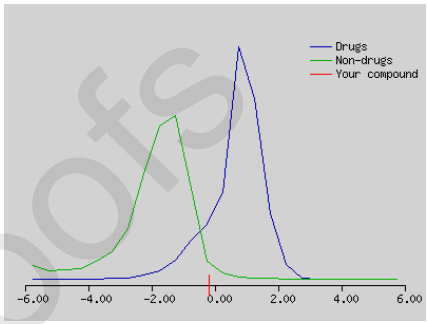
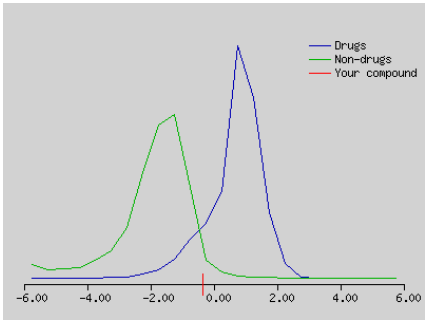
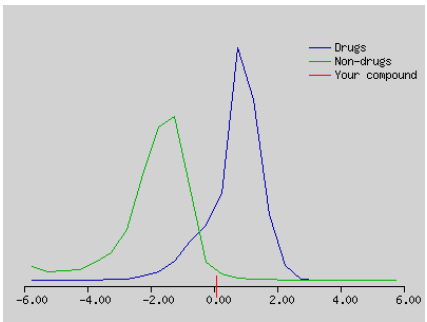
Chalcones	IUPAC name	Binding affinity ΔG (kcal/mol)			
		Aldose reductase (PDBID:4GCA)	DPP-IV (PDBID:4N8D)	PPARα (PDBID:1K7L)	α-Glucosidase (PDBID:5NN5)
3a	(E)-1-(4′-aminophenyl)-3-(4-hydroxy-3,5 dimethoxyphenyl) prop-2-en-1-one	-10.0	-7.5	-7.4	-6.8
3b	3-[4-(dimethylamino)cyclohexyl]-1-(4-iminocyclohexyl)propan-1-one octadecahydrogen	-9.6	-7.2	-7.9	-7.1
3c	(E)-1-(4′-aminophenyl)-3-(4-isopropylphenyl)prop-2-en-1-on	-10.7	-8.6	-7.5	-7.5
3d	(E)1-(4′-aminophenyl)-3-(4-fluorophenyl)-2-propen-1-one	-10.0	-7.5	-8.3	-6.6
3e	(E)-1-(4′-aminophenyl)-3-(pyridin-2-yl)prop-2-en-1-one	-9.2	-7.1	-7.9	-6.9
3f	(E)-1-(4′-aminophenyl)-3-(thiophen-2-yl)prop-2-en1-one	-8.7	-6.4	-7.3	-5.8
3g	(E)-(1-(2′-hydroxy, 4′,6′-dimethoxyphenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en1-one)	-9.2	-7.2	-7.8	-6.2
3h	(E)-1-(2′-hydroxy,4′,6′-dimethoxyphenyl)-3-(3-hydroxyphenyl)prop-2-en1-one)	-9.3	-7.8	-7.8	-6.8

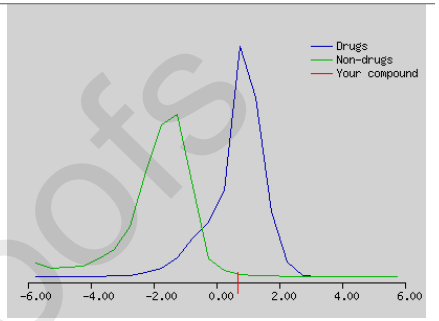
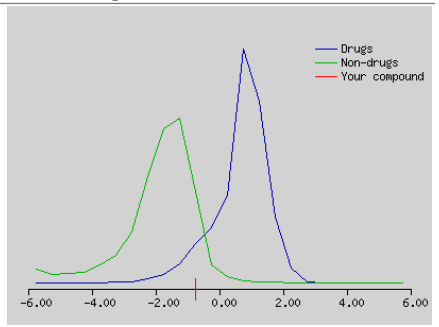
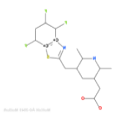
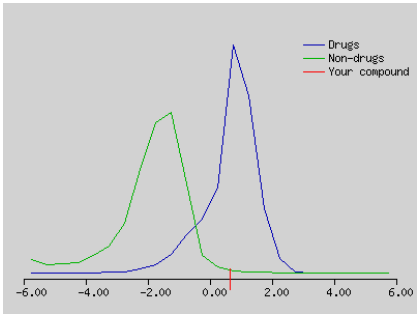
3i	(E)-1-(2′,3′-dihydroxy,4′-methoxyphenyl)-3-(3-hydroxyphenyl)prop-2-en1-one)	-10.3	-8.5	-7.9	-7.2
3j	(E)-1-(2′-hydroxy,4′-methoxyphenyl)-3-(2,3-dimethoxyphenyl)prop-2-en1-one)	-8.7	-7.3	-7.3	-6.8
		-11.0	-8.5	-9.7	-4.5
	Cocrystal ligand	2,6-dimethyl-5-[(4,5,7-trifluoro-1,3-benzothiazol-2-yl)methyl]pyridin-3-yl}acetic acid (2x9)	**1-(cis-1-phenyl-4-{[(2E)-3-phenylprop-2-en-1-yl]oxy}cyclohexyl) methanamine** (syn-7aa)	2-(1-methyl-3-oxo-3-phenyl-propylamino)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (GW409544)	1-deoxynojirimycin (NOJ)

Table 3. SMILES**,** Lipinski rule of five and drug likeness of chalcones.

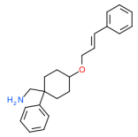
S. No	Chalcones	SMILES	Molecular properties	Drug likeliness
1	3a	COC1=C(O)C(=CC(=C1)\C=C\C(=O)C2=CC=C(N)C=C2)OC	Molecular formula: C_{17} H_{17} NO_4 Molecular weight: 299.12 Number of HBA: 4 Number of HBD: 3 MolLogP : 3.12 MolLogS : -3.79 (in Log(moles/L)) 48.50 (in mg/L) MolPSA : 64.76 A^2 MolVol : 301.62 A^3 Number of stereo centers: 0	 Drug-likeness score: 0.37
2	3b	CN(C)C1=CC=C(\C=C\C(=O)C2=CC=C(N)C=C2)C=C1	Molecular formula: C17 H18 N_2O Molecular weight: 266.14 Number of HBA: 1 Number of HBD: 2 MolLogP : 3.56 MolLogS : -4.59 (in Log(moles/L)) 6.83 (in mg/L) MolPSA : 36.82 A^2 MolVol : 277.23 A^3 Number of stereo centers: 0	 Drug-likeness score: -0.64

3	3c	CC(C)C1=CC=C(\C=C\C(=O)C2=CC=C(N)C=C2)C=C1	Molecular formula: C_{18} H_{19} N O Molecular weight: 265.15 Number of HBA: 1 Number of HBD: 2 MolLogP : 4.56 MolLogS : -5.50 (in Log(moles/L)) 0.84 (in mg/L) MolPSA : 34.02 A^2 MolVol : 280.74 A^3 Number of stereo centers: 0	 Drug-likeness score: -0.05
4	3d	NC1=CC=C(C=C1)C(=O)\C=C\C2=CC=C(F)C=C2	Molecular formula: C_{15} H_{12} F N O Molecular weight: 241.09 Number of HBA: 1 Number of HBD: 2 MolLogP : 3.71 MolLogS : -4.78 (in Log(moles/L)) 4.02 (in mg/L) MolPSA : 34.02 A^2 MolVol : 233.59 A^3 Number of stereo centers: 0	 Drug-likeness score: -0.54
5	3e	NC1=CC=C(C=C1)C(=O)\C=C\C2=CC=CC=N2	Molecular formula: C_{14} H_{12} N_2 O Molecular weight: 224.09 Number of HBA: 2 Number of HBD: 2 MolLogP : 2.50 MolLogS : -3.26 (in Log(moles/L)) 123.40 (in mg/L) MolPSA : 43.56 A^2 MolVol : 223.12 A^3 Number of stereo centers: 0	 Drug-likeness score: -0.00

6	3f	NC1=CC=C(C=C1)C(=O)\C=C\C2=CC=CS2	Molecular formula: $C_{13}H_{11}NOS$ Molecular weight: 229.06 Number of HBA: 2 Number of HBD: 2 MolLogP : 3.31 MolLogS : -4.01 (in Log(moles/L)) 22.44 (in mg/L) MolPSA : 35.04 A^2 MolVol : 225.89 A^3 Number of stereo centers: 0	 Drug-likeness score: -0.17
7	3g	COC1=CC(O)C(C=C1)C(=O)\C=C\C2=C(OC)C(=CC=C2)OC	Molecular formula: $C_{20}H_{22}O_7$ Molecular weight: 374.14 Number of HBA: 7 Number of HBD: 1 MolLogP : 3.59 MolLogS : -3.78 (in Log(moles/L)) 61.63 (in mg/L) MolPSA : 67.83 A^2 MolVol : 390.54 A^3 Number of stereo centers: 0	 Drug-likeness score: -0.35
8	3h	COC1=CC(=C(C(=C1)O)C(=O)\C=C\C2=C(O)C=CC=C2)OC	Molecular formula: $C_{17}H_{16}O_5$ Molecular weight: 300.10 Number of HBA: 5 Number of HBD: 2 MolLogP : 3.18 MolLogS : -3.35 (in Log(moles/L)) 134.02 (in mg/L) MolPSA : 61.48 A^2 MolVol : 307.19 A^3 Number of stereo centers: 0	 Drug-likeness score: 0.08

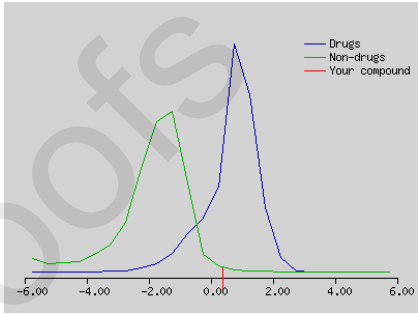
9	3i	COC1=CC=C(C(=C1O)O)C(=O)\C=C\C2=CC(=CC=C2)O	Molecular formula: C_{16} H_{14} O_5 Molecular weight: 286.08 Number of HBA: 5 Number of HBD: 3 MolLogP : 2.83 MolLogS : -3.28 (in Log(moles/L)) 150.91 (in mg/L) MolPSA : 69.42 A^2 MolVol : 283.18 A^3 Number of stereo centers: 0	 Drug-likeness score: 0.68
10	3j	COC1=CC(O)C(C=C1)C(=O)\C=C\C2=C(OC)C(=CC=C2)OC	Molecular formula: C_{18} H_{20} O_5 Molecular weight: 316.13 Number of HBA: 5 Number of HBD: 1 MolLogP : 1.84 MolLogS : -2.85 (in Log(moles/L)) 441.97 (in mg/L) MolPSA : 51.66 A^2 MolVol : 356.82 A^3 Number of stereo centers: 2	 Drug-likeness score: -0.76
	2x9 	Cc:1:n:c(C):c(:[cH]:c:1Cc(:o):o)Cc:2:n:c:3:c(F):c(F):[cH]:c(F):c:3:s:2	Molecular formula: C17 H16 F3 N2 O2 S Molecular weight: 369.09 Number of HBA: 5 Number of HBD: 2 MolLogP : 4.07 MolLogS : -4.46 (in Log(moles/L)) 12.79 (in mg/L) MolPSA : 49.22 A^2 MolVol : 312.63 A^3 Number of stereo centers: 0	 Drug-likeness score: 0.65

syn-7aa



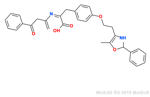
NCC1(CCC(CC1)OC\C=C\C2=CC=CC=C2)C3=CC=CC=C3

Molecular formula: C22 H27 N O
Molecular weight: 321.21
Number of HBA: 2
Number of HBD: 2
MolLogP : 4.35
MolLogS : -6.13 (in Log(moles/L)) 0.24 (in mg/L)
MolPSA : 28.48 A^2
MolVol : 351.15 A^3
Number of stereo centers: 0



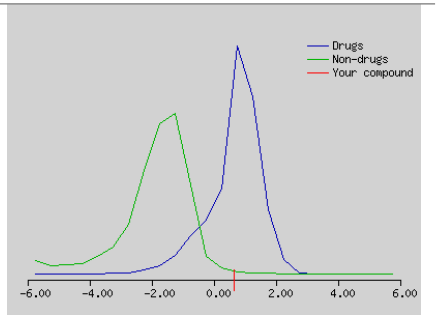
Drug-likeness score: 0.39

GW409544



CC1=C(CCOC2=CC=C(CC(=NC(=C)CC(=O)C3=CC=CC=C3)C(O)=O)C=C2)NC(O1)C4=CC=CC=C4

Molecular formula: C31 H30 N2 O5
Molecular weight: 510.22 (> 500)
Number of HBA: 6
Number of HBD: 2
MolLogP : 4.39
MolLogS : -6.15 (in Log(moles/L)) 0.36 (in mg/L)
MolPSA : 78.97 A^2
MolVol : 537.24 A^3
Number of stereo centers: 1

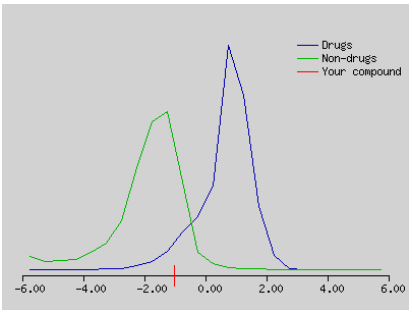


Drug-likeness score: 0.64

NOJ

OCC1NCC(O)C(O)C1O

Molecular formula: C6 H13 N O4
Molecular weight: 163.08
Number of HBA: 5
Number of HBD: 5
MolLogP : -3.14
MolLogS : 0.14 (in Log(moles/L)) 224203.08 (in mg/L)
MolPSA : 76.49 A^2
MolVol : 142.95 A^3
Number of stereo centers: 4



Drug-likeness score: -1.01

Table 4. Physicochemical properties, lipophilicity, solubility, pharmacokinetics, drug likeness and medicinal chemistry of chalcones predicted using SwissADME.

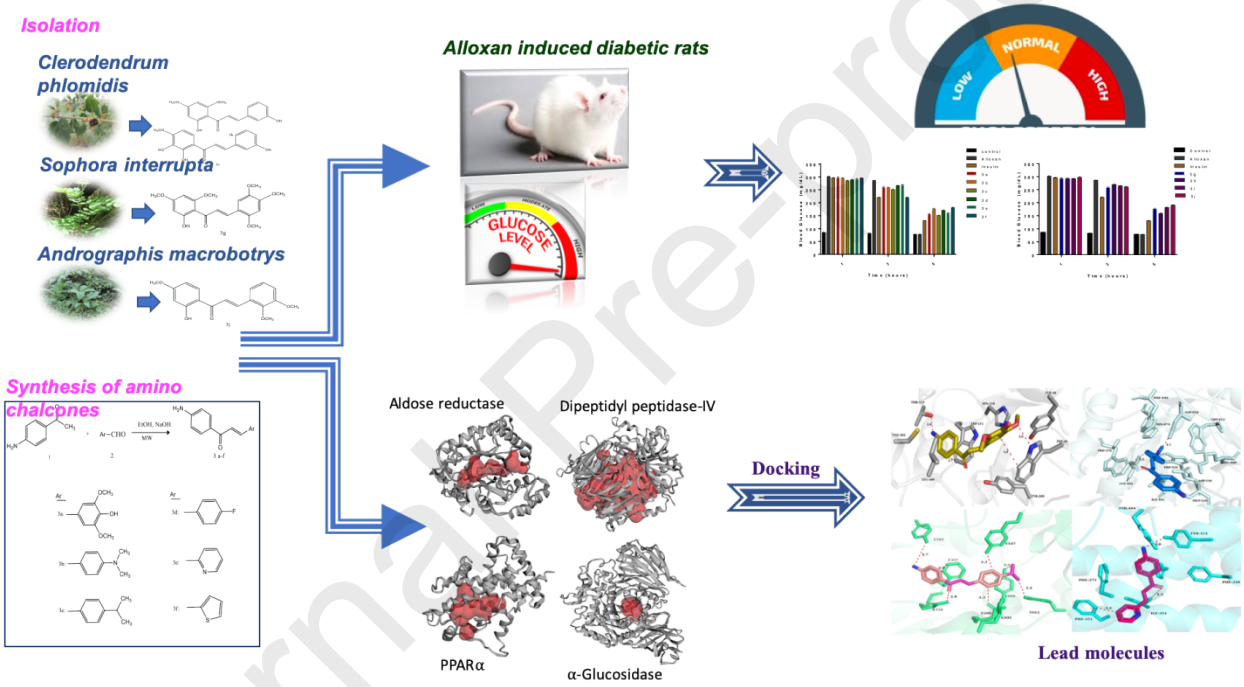
S. No	Physicochemical Properties	Lipophilicity	Water Solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
3a	Formula: C17H17NO4 Molecular weight: 299.32 g/mol Num. heavy atoms: 22 Num. arom. heavy atoms: 12 Fraction Csp3: 0.12 Num. rotatable bonds: 5 Num. H-bond acceptors: 4 Num. H-bond donors: 2 Molar Refractivity: 85.66 TPSA:81.78 Å	Log $P_{o/w}$ (iLOGP): 2:.45 Log $P_{o/w}$ (XLOGP3):2.60 Log $P_{o/w}$ (WLOGP) :2.79 Log $P_{o/w}$ (MLOGP): 1.52 Log $P_{o/w}$ (SILICOS-IT):2.83 Consensus Log $P_{o/w}$:2.44	Log *S* (ESOL):-3.41 Solubility:1.17e-01 mg/ml; 3.91e-04 mol/l Class:Soluble Log *S* (Ali):-3.97 Solubility:3.23e-02 mg/ml; 1.08e-04 mol/l Class:Soluble Log *S* (SILICOS-IT):-4.26 Solubility:1.63e-02 mg/ml ; 5.45e-05 mol/l Class:Moderately soluble	GI absorption: High BBBpermeant: No P-gp substrate: No CYP1A2inhibitor:Yes CYP2C19inhibitor:Yes CYP2C9 inhibitor:Yes CYP2D6 inhibitor:No CYP3A4 inhibitor:Yes Log Kp (skinpermeation): -6.28 cm/s	Lipinski:Yes Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability Score:0.55	PAINS:0 alert Brenk:2 alerts: aniline, michael_acceptor_1 Leadlikeness:Yes Synthetic accessibility:2.66
3b	Formula:C17H18N2O Molecularweight:266.34 g/mol Num. heavy atoms:20 Num. arom. heavy	Log Po/w (iLOGP):2.46 Log Po/w (XLOGP3):3.64 Log Po/w (WLOGP):3.13	Log S (ESOL):-3.96 Solubility:2.89e-02 mg/ml ; 1.09e-04 mol/l Class:Soluble Log S (Ali):-4.30	GI absorption:High BBB permeant:Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:Yes	Lipinski:Yes;0 violation Ghose:Yes Veber:Yes Egan:Yes	PAINS:1 alert: anil_di_alk_B Brenk:2 alerts: aniline, michael_acceptor_1 Leadlikeness:No; 1

	atoms:12 Fraction Csp3:0.12 Num. rotatable bonds:4 Num. H-bond acceptors:1 Num. H-bond donors:1 Molar Refractivity:84.86 TPSA:46.33 Å²	Log Po/w (MLOGP):2.66 Log Po/w (SILICOS-IT):2.86 Consensus Log Po/w:2.95	Solubility:1.33e-02 mg/ml ; 5.00e-05 mol/l Class:Moderately soluble Log S (SILICOS-IT):-4.71 Solubility:5.24e-03 mg/ml ; 1.97e-05 mol/l Class: Moderately soluble	CYP2C9 inhibitor:Yes CYP2D6 inhibitor:Yes CYP3A4 inhibitor:Yes Log Kp (skin permeation):-5.34 cm/s	Muegge:Yes Bioavailability Score:0.55	violation: XLOGP3>3.5 Synthetic accessibility:2.55
3c	Formula:C18H19NO Molecularweight:265.35 g/mol Num. heavy atoms:20 Num. arom. heavy atoms:12 Fraction Csp3:0.17 Num. rotatable bonds:4 Num. H-bond acceptors:1 Num. H-bond donors:1 Molar Refractivity:85.23 TPSA:43.09 Å²	Log Po/w (iLOGP):2.84 Log Po/w (XLOGP3):3.53 Log Po/w (WLOGP):4.19 Log Po/w (MLOGP):3.51 Log Po/w (SILICOS-IT):4.31 Consensus Log Po/w:3.68	Log S (ESOL):-3.89 Solubility:3.43e-02 mg/ml ; 1.29e-04 mol/l Class:Soluble Log S (Ali):-4.12 Solubility:2.02e-02 mg/ml ; 7.60e-05 mol/l Class:Moderately soluble Log S (SILICOS-IT): -5.42 Solubility:1.01e-03 mg/ml ; 3.81e-06 mol/l Class:Moderately soluble	GI absorption:High BBB permeant:Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:Yes CYP2C9 inhibitor:Yes CYP2D6 inhibitor:Yes CYP3A4 inhibitor:Yes Log Kp (skin permeation):-5.41 cm/s	Lipinski:Yes; 0 violation Ghose :Yes Veber :Yes Egan:Yes Muegge:Yes Bioavailability Score:0.55	PAINS:0 alert Brenk:2 alerts: aniline, michael_acceptor_1 Leadlikeness :No; 1 violation: XLOGP3>3.5 Synthetic accessibility:2.64
3d	Formula:C15H12FNO Molecular weight:241.26 g/mol Num. heavy atoms:18 Num. arom. heavy atoms:12 Fraction Csp3:0.00 Num. rotatable bonds:3 Num. H-bond acceptors:2 Num. H-bond donors:1 Molar Refractivity:70.61 TPSA:43.09 Å²	Log Po/w (iLOGP):2.27 Log Po/w (XLOGP3):2.50 Log Po/w (WLOGP):3.62 Log Po/w (MLOGP):3.17 Log Po/w (SILICOS-IT):3.62 Consensus Log Po/w:3.04	Log S (ESOL):-3.21 Solubility:1.50e-01 mg/ml ; 6.22e-04 mol/l Class:Soluble Log S (Ali):-3.05 Solubility:2.15e-01 mg/ml ; 8.91e-04 mol/l Class:Soluble Log S (SILICOS-IT):-4.88 Solubility:3.18e-03 mg/ml ; 1.32e-05 mol/l Class:Moderately soluble	GI absorption:High BBB permeant:Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:Yes CYP2C9 inhibitor:No CYP2D6 inhibitor:No CYP3A4 inhibitor:Yes Log Kp (skin permeation):-6.00 cm/s	Lipinski:Yes; 0 violation Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability Score:0.55	PAINS:0 alert Brenk:2 alerts: aniline, michael_acceptor_1 Leadlikeness:No; 1 violation: MW<250 Synthetic accessibility:2.33
3e	Formula:C14H12N2O Molecular weight:224.26 g/mol Num. heavy atoms:17 Num. arom. heavy atoms:12 Fraction Csp3:0.00	Log Po/w (iLOGP):1.95 Log Po/w (XLOGP3):1.97 Log Po/w (WLOGP):2.46 Log Po/w (MLOGP):1.25	Log S (ESOL):-2.80 Solubility:3.59e-01 mg/ml ; 1.60e-03 mol/l Class:Soluble Log S (Ali):-2.77 Solubility:3.80e-01 mg/ml ; 1.69e-03 mol/l	GI absorption:High BBB permeant:Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:Yes CYP2C9 inhibitor:No CYP2D6 inhibitor:No	Lipinski:Yes; 0 violation Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability	PAINS:0 alert Brenk:2 alerts: aniline, michael_acceptor_1 Leadlikeness:No; 1 violation: MW<250 Synthetic accessibility:2.46

	Num. rotatable bonds:3 Num. H-bond acceptors:2 Num. H-bond donors:1 Molar Refractivity:68.45 TPSA:55.98 Å²	Log Po/w (SILICOS-IT):2.66 Consensus Log Po/w:2.06	Class:Soluble Log S (SILICOS-IT):-4.23 Solubility:1.32e-02 mg/ml ; 5.90e-05 mol/l Class:Moderately soluble	CYP3A4 inhibitor:No Log Kp (skin permeation):-6.27 cm/s	Score:0.55	
3f	Formula:C13H11NOS Molecular weight:229.30 g/mol Num. heavy atoms:16 Num. arom. heavy atoms:11 Fraction Csp3:0.00 Num. rotatable bonds:3 Num. H-bond acceptors:1 Num. H-bond donors:1 Molar Refractivity:68.53 TPSA:71.33 Å²	Log Po/w (iLOGP):2.19 Log Po/w (XLOGP3):2.73 Log Po/w (WLOGP):3.13 Log Po/w (MLOGP):1.91 Log Po/w (SILICOS-IT):3.84 Consensus Log Po/w:2.76	Log S (ESOL):-3.29 Solubility:1.17e-01 mg/ml ; 5.10e-04 mol/l Class:Soluble Log S (Ali):-3.88 Solubility:3.01e-02 mg/ml ; 1.31e-04 mol/l Class:Soluble Log S (SILICOS-IT):-3.87 Solubility:3.09e-02 mg/ml ; 1.35e-04 mol/l Class:Soluble	GI absorption:High BBB permeant :Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:Yes CYP2C9 inhibitor:Yes CYP2D6 inhibitor:No CYP3A4 inhibitor:No Log K_p (skin permeation):-5.76 cm/s	Lipinski:Yes; 0 violation Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability Score:0.55	PAINS:0 alert Brenk:2 alerts: aniline, michael_acceptor_1 Leadlikeness:No; 1 violation: MW<250 Synthetic accessibility:2.61
3g	Formula:C18H20O5 Molecular weight:316.35 g/mol Num. heavy atoms:23 Num. arom. heavy atoms:6 Fraction Csp3:0.28 Num. rotatable bonds:6 Num. H-bond acceptors:5 Num. H-bond donors:1 Molar Refractivity:87.36 TPSA:64.99 Å²	Log Po/w (iLOGP):2.95 Log Po/w (XLOGP3):2.72 Log Po/w (WLOGP):2.25 Log Po/w (MLOGP):0.90 Log Po/w (SILICOS-IT):2.46 Consensus Log Po/w:2.26	Log S (ESOL):-3.31 Solubility:1.54e-01 mg/ml ; 4.88e-04 mol/l Class:Soluble Log S (Ali):-3.74 Solubility:5.78e-02 mg/ml ; 1.83e-04 mol/l Class:Soluble Log S (SILICOS-IT):-2.71 Solubility:6.11e-01 mg/ml ; 1.93e-03 mol/l Class: Soluble	GI absorption:High BBB permeant:Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:No CYP2C9 inhibitor:No CYP2D6 inhibitor:No CYP3A4 inhibitor:No Log Kp (skin permeation):-6.30 cm/s	Lipinski:Yes; 0 violation Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability Score:0.55	PAINS:0 alert Brenk:1 alert: michael_acceptor_1 Leadlikeness:Yes Synthetic accessibility:4.41
3h	Formula:C17H16O5 Molecular weight:300.31 g/mol Num. heavy atoms:22 Num. arom. Heavy atoms:12 Fraction Csp:30.12	Log Po/w (iLOGP):2.49 Log Po/w (XLOGP3):3.47 Log Po/w (WLOGP):2.90 Log Po/w (MLOGP):1.52 Log Po/w (SILICOS-IT):3.06 Consensus Log	Log *S* (ESOL):-3.96 Solubility:3.28e-02 mg/ml ; 1.09e-04 mol/l Class:Soluble Log *S* (Ali): -4.75 Solubility:5.37e-03 mg/ml ; 1.79e-05 mol/l	GI absorption:High BBB permeant:Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:No CYP2C9 inhibitor:Yes CYP2D6 inhibitor:No	Lipinski:Yes; 0 violation Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability	PAINS:0 alert Brenk:1 alert: michael_acceptor_1 Leadlikeness:Yes Synthetic accessibility:2.92

	Num. rotatable bonds:5 Num. H-bond acceptors:5 Num. H-bond donors:2 Molar Refractivity:83.28 TPSA:75.99 Å²	Po/w:2.69	Class:Moderately soluble Log *S* (SILICOS-IT):-4.05 Solubility:2.69e-02 mg/ml ; 8.95e-05 mol/l Class: Moderately soluble	CYP3A4 inhibitor:Yes Log Kp (skin permeation):-5.67 cm/s	Score:0.55	
3i	Formula:C16H14O5 Molecular weight:286.28 g/mol Num. heavy atoms:21 Num. arom. heavy atoms:12 Fraction Csp3:0.06 Num. rotatable bonds:4 Num. H-bond acceptors:5 Num. H-bond donors:3 Molar Refractivity:78.81 TPSA:86.99 Å²	Log Po/w (iLOGP):1.99 Log Po/w (XLOGP3):3.15 Log Po/w (WLOGP):2.60 Log Po/w (MLOGP):1.27 Log Po/w (SILICOS-IT):2.53 Consensus Log Po/w:2.31	Log S (ESOL):-3.76 Solubility:4.99e-02 mg/ml ; 1.74e-04 mol/l Class:Soluble Log S (Ali):-4.65 Solubility:6.46e-03 mg/ml ; 2.26e-05 mol/l Class:Moderately soluble Log S (SILICOS-IT):-3.35 Solubility:1.28e-01 mg/ml ; 4.46e-04 mol/l Class: Soluble	GI absorption:High BBB permeant:No P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:No CYP2C9 inhibitor:Yes CYP2D6 inhibitor:No CYP3A4 inhibitor:Yes Log Kp (skin permeation):-5.81 cm/s	Lipinski:Yes; 0 violation Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability Score:0.55	PAINS:1 alert: catechol_A Brenk:2 alerts: catechol, michael_acceptor_1 Leadlikeness:Yes Synthetic accessibility:2.77
3j	Formula:C18H20O5 Molecular weight:316.35 g/mol Num. heavy atoms:23 Num. arom. heavy atoms:6 Fraction Csp3:0.28 Num. rotatable bonds:6 Num. H-bond acceptors:5 Num. H-bond donors:1 Molar Refractivity:87.36 TPSA:64.99 Å²	Log Po/w (iLOGP):2.95 Log Po/w (XLOGP3):2.72 Log Po/w (WLOGP):2.25 Log Po/w (MLOGP):0.90 Log Po/w (SILICOS-IT):2.46 Consensus Log Po/w:2.26	Log S (ESOL):-3.31 Solubility:1.54e-01 mg/ml ; 4.88e-04 mol/l Class:Soluble Log S (Ali):-3.74 Solubility:5.78e-02 mg/ml ; 1.83e-04 mol/l Class:Soluble Log S (SILICOS-IT):-2.71 Solubility:6.11e-01 mg/ml ; 1.93e-03 mol/l Class: Soluble	GI absorption:High BBB permeant:Yes P-gp substrate:No CYP1A2 inhibitor:Yes CYP2C19 inhibitor:No CYP2C9 inhibitor:No CYP2D6 inhibitor:No CYP3A4 inhibitor:No Log Kp (skin permeation):-6.30 cm/s	Lipinski:Yes; 0 violation Ghose:Yes Veber:Yes Egan:Yes Muegge:Yes Bioavailability Score:0.55	PAINS:0 alert Brenk:1 alert: michael_acceptor_1 Leadlikeness:Yes Synthetic accessibility:4.41

Graphical Abstract



Research Highlights

- Amino chalcones (3a-3f) were synthesized and hydroxy chalcones (3g-3j) from *Clerodendrum phlomidi, Sophora interrupta* and *Andrographis macrobotrys*.
- *In vivo* studies with alloxan induced diabetic rats unveiled 3c, 3a and 3h have shown significant antidiabetic activity.
- Molecular docking resolved that chalcones has shown strong affinity with aldose reductase and might be considered as potent antidiabetic agents for the treatment of diabetes.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: