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Docking, synthesis and evaluation of *N*-(2-(4-methoxy-2-oxo-1-phenyl/methyl-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-substitutedphenylbenzenesulfonamide derivatives as hypoglycemic agents

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The current research work involves *in silico* docking studies, synthesis, characterisation and study on hypoglycemicactivity of a series of *N*-(2-(4-methoxy-1-methyl/phenyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-substitutedprimaryamino) -benzenesulfononamides [IVa/b (1-6)]. Compounds exhibit prominent anti-diabetic activity by glucose oxidase peroxidase (GOD-POD) method which involves measurement of average serum glucose levels in mg/dl as well as conserved hydrogen bonds with one or more amino acid residues in the active pocket of murine 11β-hydroxysteroid dehydrogenase domain. Among all the synthesized compounds, compound **IVb2** shows prominent anti-diabetic activity and higher Moldock score as compared to standard drug Glibenclamide. Structural analysis of the synthesized compounds has been done by standard spectroscopic techniques.

Keywords: Quinolin-2-one, sulphonamides, molecular docking, antidiabetic activity, glucose oxidase-peroxidase

Diabetes Mellitus is a group of metabolic disease resulting from deficiency of insulin secretion, insulin action or both. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic abnormalities. Uncontrolled diabetes may lead to stupor, coma and if not treated, death due to ketoacidosis or rare from nonketotic hyperosmolar syndrome[1]. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Ref. 2). Currently available drugs for the treatment do not restore normal glucose homeostasis for longer period and they are not free from side effects such as hypoglycaemia, kidney diseases, gastrointestinal(GIT) problems, hepatotoxicity, heart risk problems and insulinoma. The main disadvantage of current drugs is that they have to be taken throughout the life and thus produce side effects[3]. However, none of these medications are ideal due to their toxic side effects and decrease in response is observed sometimes in their prolonged use so search for newer drugs is necessary. Thus, the invention of a sustainable and efficient cure for this disorder appears to be a challenge to the scientists and hence numerous pharmaceutical companies and research institutes are concerned in development of drug with good therapeutic potential and less adverse effects for the treatment of Diabetes Mellitus[4].

The versatility of quinoline scaffold has attracted the interest of synthetic chemists to develop facile methods for its synthesis. This heterocyclic compound proved to be a promising pharmacophore in generating compounds with anticancer, antimicrobial, antimalarial, anti-inflammatory, anti-helminthic, analgesic, anti-diabetic, neuroprotective and antiviral activities[5-7]. Thus, quinolones are more known for their antibacterial activity, occasionally displaying hypoglycaemic activity[8].

On the other hand, sulphonamides have shown reduction of normoglycemia and when given by mouth it also possesses the ability to reduce elevated blood and urine sugar levels in diabetes to normal. Studies on sulphonamide bioactivities expanded when laboratories proved that sulfa drugs stimulated beta cell release of insulin[9].

The wide pharmacological activity range of sulphonamides and quinoline scaffold necessitates for further synthesis of novel quinolinoyl sulfonamide derivatives and screening of their activity against various diseases.

Results and Discussion

The synthesis of title compounds [**IV a/b(1-6)]** was accomplished by the synthetic sequence shown in the Figure 1. The starting material, 3-acetyl-4-methoxy-1-methyl/phenylquinolin-2(1*H*)-one **(I a/b)** was synthesized as per literature[10]. Further **(I a/b)** was subjected to bromination by reaction with *p*-toluenesulfonic acid (*p*-TsOH) and *N*-bromosuccinimide (NBS) to obtain 3-(2-bromoacetyl)-4-methoxy-1-methyl/phenylquinolin-2(1*H*)-one**(II a/b)**. Nucleophilic substitution with different aromatic primary amines resulted in synthesis of twelve corresponding amides of 4-methoxy-3-(2-(substitutedphenyl)amino)acetyl)-1-methyl/phenylquinolin-2(1*H*)-one **[III a/b(1-6)]**. In the final step, compounds were further treated with benzene sulfonyl chloride in presence of pyridine to obtain different quinolinylsulfonamide derivatives of *N*-(2-(4-methoxy-2-oxo-1-methyl/phenyl-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-(substitutedphenyl)benzene sulphonamide [**IV a/b(1-6)]**.

The structures of the newly synthesized compounds were confirmed by spectral and analytical data. The supporting information can be seen from the spectral data which confirms the formation of claimed compounds. Synthesized compounds were tested *in vivo* to evaluate their oral hypoglycemic activity by GOD-POD method and molecular docking studies were carried out using Molegro Virtual Docker (MVD-2013, 6.0) software. The compound *N*-(2-(4-methoxy-1-phenyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-(4-chlorophenyl)benzenesulfonamide) **IV b2** showed most significant hypoglycemic activity by decreasing the average serum glucose level and also the MolDock Score was higher than that of the standard drug Glibenclamide and comparably similar to that of ligand.

Hypoglycaemic activity studies[11,12]

Glucose oxidase oxidises glucose to give D-gluconic acid and hydrogen peroxide. The hydrogen peroxide released then in the presence of enzyme peroxidase oxidizes phenol which combines with 4-aminoantipyrine dyes to give pink colour. The

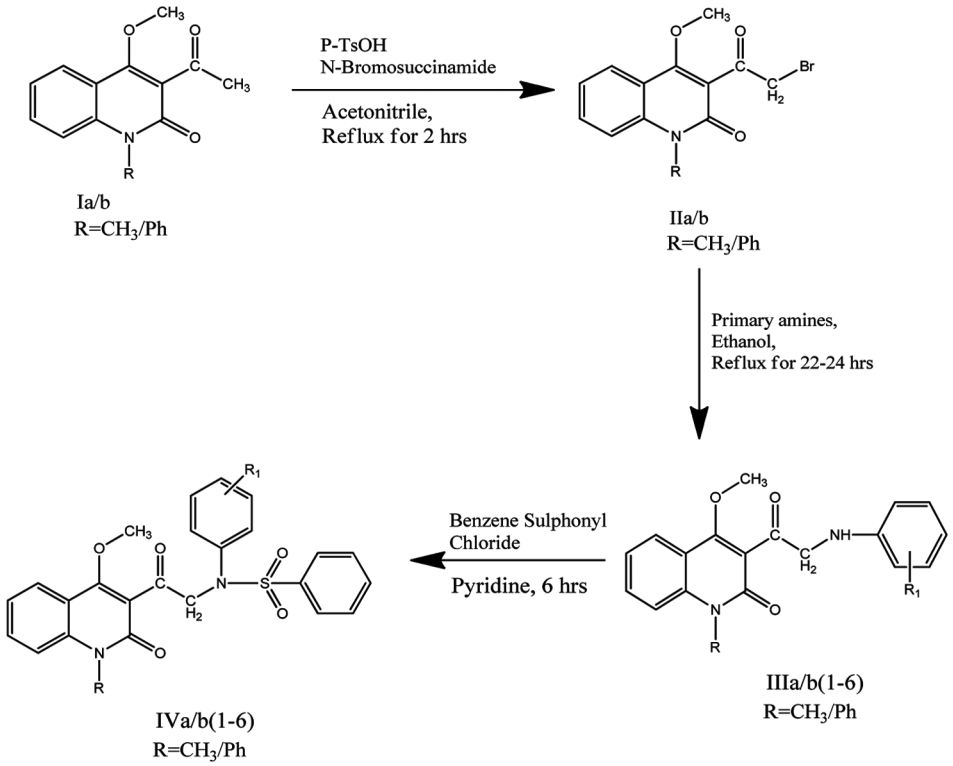

Figure 1 — Scheme for synthesis of *N*-(2-(4-methoxy-2-oxo-1-phenyl/methyl-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-substitutedphenylbenzenesulfonamide derivatives as hypoglycemic agents

intensity of the pink colour formed is proportional to the glucose concentration in the sample and can be measured photometrically at 546 nm.

On the basis of the results obtained by carrying out docking studies, selected *N*-(2-(4-methoxy-2-oxo-1-methyl/phenyl-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-substitutedphenyl benzenesulfonamide derivatives were tested for their *in vivo* oral hypoglycaemic activity using the GOD-POD method. Most of the compounds exhibited high activity after two hours of administration. Anti-diabetic activity was also displayed by some compounds even after 6 hours of administration thus claiming for some novel leads.

Statistical analysis

The Standard error of mean (SEM) of the average blood glucose level was calculated for each group by the following formula:

$$\text{Glucose} = \frac{\text{Absorbance of test} \times \text{concentration of standard (mg/dl}}{\text{Absorbance of standard}}$$

Values are expressed as mean ±SEM.*p<0.05, ** p<0.01, ***p<0.001 by comparing to diabetic control in Table I. Statistical comparisons were performed by one-way ANOVA followed by Dunnett's Multiple Comparison Test.

Molecular docking[13]

Molecular docking studies of the title compounds were carried out using Molegro Virtual Docker (MVD-2013, 6.0) software. The compounds exhibited well-conserved hydrogen bonds with one or more amino acid residues in the active pocket of NADPH-dihydro ligand (Ligand NDP_1 [A]) (PDB ID: 1y5m). Amongst all of the synthesised derivatives, the compound *N*-(2-(4-methoxy-1-phenyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-(4-chlorophenyl)benzenesulfonamide) **IV b2** showed a MolDock score of (−153.434); which is higher to that of the standard drug (−95.765) and comparably similar to that of ligand (−180.898).Most of the synthesized novel analogues of quinolin-2-one exhibited better affinity towards NADPH-dihydro ligand than standard drug. These results show that the novel quinolin-2-one possess higher affinity than standard drug towards the active site of the NADPH-dihydro ligand, thus the synthesized derivatives possessed a potential to bind with some of the residues of the active site.

The crystal structure of the target enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyses the conversion of 11-dehydrocorticosterone to its active form corticosterone in rodents (or cortisone to cortisol in humans). The reductive reaction of the 11-keto to 11-hydroxyl is the pivotal switch in the activation of glucocorticoids. An excess of active glucocorticoids has been shown to play a key role in metabolic disorders such as diabetes and obesity. Therefore, 11β-HSD1 represents an important therapeutic target for the treatment of these diseases. To facilitate the iterative design of inhibitors, we have crystallized and determined the three-dimensional structures of a binary complex of murine 11β-HSD1 with NADP(H) to a resolution of 2.3 A and of a ternary complex with corticosterone and NADP(H) to a resolution of 3.0 A by X-ray crystallography. The enzyme forms a homodimer in the crystal and has a fold similar to those of other members of the family

Table I — Result of molecular docking of title compounds, *N*-(2-(4-methoxy-2-oxo-1-phenyl/methyl-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-substitutedphenylbenzenesulfonamide derivatives as hypoglycemic agents

Name	MolDock Score	Rerank Score	H Bond
Standard	−95.765	−76.3581	−4.5105
IV a1	−123.05	−97.8769	−5.01089
IV a2	−143.132	−99.914	−4.33364
IV a3	−139.255	−98.927	−4.60919
IV a4	−141.982	−110.74	−6.0734
IV a5	−98.956	−30.9827	−6.0734
IV a6	−137.085	−76.616	−3.65616
IV b1	−123.597	−79.9372	−8.60829
IV b2	−153.434	−93.713	−4.64763
IV b3	−126.681	−82.2137	−2.81888
IV b4	−152.093	−90.7046	−5.78174
IV b5	−150.539	−95.6954	−5.92412
IV b6	−151.322	−23.674	−2.48913
Ligand NDP_1 [A]	−180.898	−94.113	−20.4794

of short chain steroid dehydrogenases/reductases (SDRs). The structure shows a novel folding feature at the C-terminus of the enzyme. The C-terminal helix insertions provide additional dimer contacts, exert an influence on the conformations of the substrate binding loops, and present hydrophobic regions for potential membrane attachment. The site at which the known NADPH dihydro ligand binds with the target protein was selected as the active site (Figure 2). It is lined with the amino acids such as Thr124, Gln123, Lys44, Arg66, Thr222, Asn119, *etc.* Hence to identify other residual interactions of the tested compounds, a grid box (includes residues within a 15.0 A radius) large enough to accommodate the active site was constructed. Since NADPH dihydro ligand is known, the center of this site was considered as the center of search space for docking. Docking of the synthesized compounds with murine 11β-hydroxysteroid dehydrogenase domain exhibited well conserved hydrogen bonding with the amino acids residues at the active site. The MolDock scores of the test compounds ranged from -98.956 to -153.434. Glibenclamide was used as the standard for the comparison of efficiency and exhibited MolDock score of -95.765. Most of the designed molecules exhibited MolDock score higher than that exhibited by standard drug; with compound IV b2 having the a highest MolDock score of -153.434. The MolDock scores of synthesized compounds are summarized in Table II. These results show that the novel benzenesulfonamide derivatives possess higher affinity than standard drug towards the active site of the target protein 11β-hydroxysteroid dehydrogenase.

Experimental Section

All the chemicals and reagents were purchased from SD Fine-Chem limited Mumbai or Molychem, Mumbai. Melting points of synthesized compounds were determined by Thiele's melting point apparatus and are uncorrected. The absorbance was recorded on Ultraviolet (UV)-1800 Shimadzu UV spectrophotometer. Fourier transform-infrared (IR spectra were recorded on Shimadzu IRAFFINITY-1 spectrophotometer using KBr pellets. The ^{1}H and ^{13}C NMR spectral data of the derivatives were recorded on BrukerAvance II 400 NMR spectrometer using dimethyl sulfoxide (DMSO)-$d_6$as the solvent and tetramethylsilane as an internal standard; chemical shifts are expressed as delta (δ) values (ppm).

Synthesis of 3-(2-bromoacetyl)-4-methoxy-1-methyl/phenylquinolin-2(1*H*)-one (IIa/b)

A solution of (I a/b) (10 mmol) and *p*-toluenesulfonic acid (*p*-TsOH) (20 mmol) was taken in a RBF. *N*-bromosuccinimide (NBS) (10 mmol) was slowly added to the mixture and stirred. The reaction mixture was refluxed for 2 hours and cooled to RT. The solvent was distilled out by using distillation apparatus and the obtained residue was dissolved in chloroform (50 mL). Three portions (20 mL each) of distilled water were used to wash and the chloroform layer obtained was evaporated to obtain solid product. Product was recrystallized from benzene to afford the pure α-bromo ketone(II a/b).

Spectral data of 3-(2-bromoacetyl)-4-methoxy-1-methylquinolin-2(1*H*)-one, IIa: Yield: 82.95%. m.p.224°C. UV-Vis λ_{max}: 234.05nm; IR (KBr): 3028.24

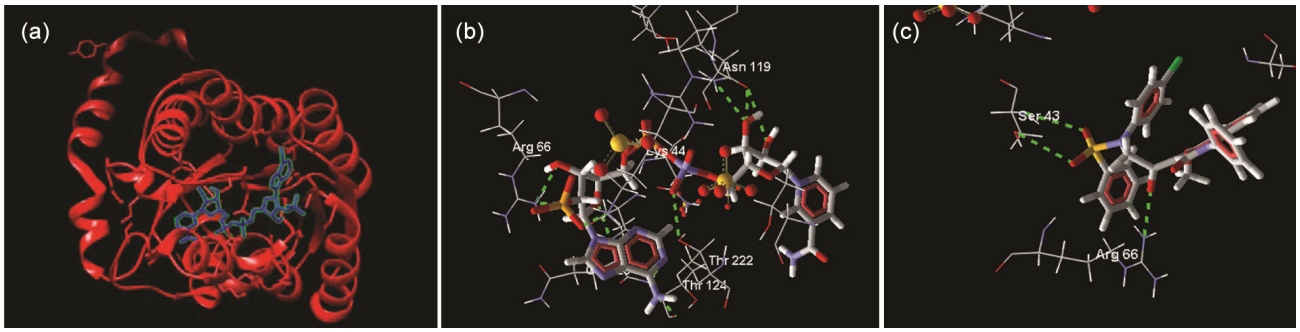

Figure 2 — **(a)** Structure of murine 11β-hydroxysteroid dehydrogenase domain complexed with NADPH dihydro (PDB: 1Y5M). **(b)**Ligand NADPH-dihydro docked in best of its conformation (pose) into the binding site of 1y5m. The -N at 3rd position of the purine ring forms H bonds with NH of Thr 124 and 4th position NH_2 forms interaction with oxygen of Thr 124. The -O of tetrahydrofuran ring forms H bonds with -NH of Gln 123. One -O of dihydrogen phosphate forms H bonds with -NH of Lys 44 and other -O form interaction with -NH of Arg 66. One -O of diphosphoric acid forms H bonds with oxygen of Thr 222. Two -O of tetrahydrofurandiol ring forms H bonds with oxygen of Asn 119 and one -O forms interaction with -NH of Asn 119. **(c)** Compound IV b-2 docked in best of its conformation (pose) into the binding site of 1y5m. The -C=O present on the side chain of quinoline-2-one nucleus showed interaction with -NH of Arg 66. One -O of -S=O present in the side chain of nucleus showed H bonding with -O of serine 43 and other -O showed interaction with -O of serine 43.

Table II — Average serum glucose levels of *N*-(2-(4-methoxy-2-oxo-1-phenyl/methyl-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-*N*-substitutedphenylbenzenesulfonamide derivatives. All values are expressed as a mean ± SEM, n=6, The minimum value of **p*<0.05,***p*<0.01,****p*<0.001 as compared to control group (one way Analysis of variance (ANOVA) followed by multiple comparison Dunnet's test.

Group	Treatment	Average serum glucose level (mg/dL)					
		0h	1 h	2 h	3 h	4 h	6 h
Group I	Control (Glucose 3 mg/kg)	86.83± 2.088	115.8± 1.302	121.2± 0.7923	120.8± 0.9458	115± 1.693	106.5± 6.174
Group II	Glibenclamide (5 mg/kg)	86.83± 2.088	112.7± 1.856 ^{ns}	83.67± 2.404 ***	82.33± 1.838 ***	86.17± 1.778 ***	85.67± 1.145 **
Group III	**IV a1** **R_1=4-NO_2**	86.83± 2.088	113.8± 2.574 ^{ns}	80.50± 2.837 ***	82.67± 3.169 ***	88.33± 3.694 ***	107.3± 5.976 ^{ns}
Group IV	**IV a2** **R_1=Cl**	86.83± 2.088	116.5± 1.668 ^{ns}	81.17± 2.136 ***	79± 3.445 ***	90.67± 3.896 **	101.5± 5.778 ^{ns}
Group V	**IV a3** **R_1=Br**	86.83± 2.088	118.7± 0.881^{ns}	82± 1.77 ***	81.5± 1.384 ***	86.17± 2.845 ***	90.33± 2.629 ^{ns}
Group VI	**IV a4** **R_1=CH_3**	86.83± 2.088	119± 0.730 ^{ns}	116.5± 1.765 ^{ns}	108.7± 4.745 ^{ns}	111± 4.83 ^{ns}	110.5± 2.997 ^{ns}
Group VII	**IV a5** **R_1=2-NO_2**	86.83± 2.088	116.3± 1.909 ^{ns}	80.67± 1.145 ***	79.67± 1.145 ***	86.83± 0.945 ***	85.17± 1.956 **
Group VIII	**IV a6** **R_1=F**	86.83± 2.088	117± 1.461 ^{ns}	111.7± 6.766 ^{ns}	111.7± 6.786 ^{ns}	98.33± 6.76 ^{ns}	107.8± 4.135 ^{ns}
Group IX	**IV b1** **R_1=4-NO_2**	86.83± 2.088	116.2± 1.869 ^{ns}	86.67± 3.084 ***	84.33± 1.476 ***	90.67± 4.425 **	89.5± 3.452 *
Group X	**IV b2** **R_1=Cl**	86.83± 2.088	117.8± 0.833 ^{ns}	81± 1.633 ***	81.67± 2.186 ***	88± 1.751***	88.17± 4.061*
Group XI	**IV b3** **R_1=Br**	86.83± 2.088	111.5± 5.673 ^{ns}	110.5± 5.993 ^{ns}	103± 6.909 *	106.2± 7.863 ^{ns}	106± 4.933 ^{ns}
Group XII	**IV b4** **R_1=CH_3**	86.83± 2.088	110.2± 3.772 ^{ns}	106.7± 7.246 ^{ns}	112± 4.817 ^{ns}	111.8± 5.468 ^{ns}	109.7± 5.004 ^{ns}
Group XIII	**IV b5** **R_1=2-NO_2**	86.83± 2.088	116.7± 1.626 ^{ns}	79.33± 1.256 ***	94.83± 5.85 ***	104.5± 7.571^{ns}	115.2± 3.28 ^{ns}
Group XIV	**IV b5** **R_1=F**	86.83± 2.088	110.8± 3.825^{ns}	90± 4.472 ^{ns}	107.2± 2.469^{ns}	107.8± 1.108^{ns}	106.7± 2.679 ^{ns}

(Aromatic –CH), 2954.95, 2920.23, 2848.86 (aliphatic -C-H); 1724.36 (-C=O acetyl); 1641.42 (-C=O amide); 1238.30 (-C-O-C); 1072.42 cm^{-1} (C-Br); ^{1}H NMR (DMSO-d_6): δ 7.88-7.35 (q, 4H, Ar-H); 4.15 (s, 2H, -$COCH_2$); 3.37 (s, 3H, -OCH_3); 2.50 (s, 3H, -NCH_3).

Spectral data of 3-(2-bromoacetyl)-4-methoxy-1-phenylquinolin-2(1*H*)-one, IIb: Yield: 88.95%. m.p.224°C. UV-Vis λ_{max}: 222.8nm; IR (KBr): 3057.17 (aromatic -C-H); 2954.95, 2916.37, 2848.86 (aliphatic -C-H), 1716.65 (-C=O acetyl), 1654.92 (-C=O amide), 1265.30 (-C-O-C), 1072.42 cm^{-1} (C-Br); ^{1}H NMR (DMSO-d_6): δ 9.01-7.00 (m, 9H, Ar-H), 4.90 (s, 2H, -$COCH_2$), 3.45 (s, 3H, -OCH_3).

Synthesis of 4-methoxy-3-(2-(substitutedphenyl) amino)acetyl)-1-methyl/phenylquinolin-2(1*H*)-ones [IIIa/b (1-6)]

Compound (**IIa/b**) (1mmole) and a primary amine (1mmol) was refluxed at 85ºC in ethanol with a catalytic amount (0.2g) of sodium bicarbonate as a base for a period of 22-24 hours. After 24 hours the solution was allowed to evaporate to obtain crystalline product. The crystalline product was then recrystallized using methanol.

Spectral data of 4-methoxy-1-methyl-3-(2-((4-chlorophenyl)amino)acetyl)quinolin-2(1*H*)-one, IIIa2: Yield:72.99%. m.p.138°C. UV-Vis λ_{max}: 231.6nm; IR (KBr): 3412.08 (-NH), 3062.96 (aromatic -C-H), 2954.95, 2922.16, 2850.79 (aliphatic -C-H), 1637.56 (-C=O acetyl), 1616.35 (-C=O amide), 1213.23(-C-O-C), 1091.71 cm^{-1} (C-Cl); ^{1}H NMR (DMSO-d_6): 7.95-7.18 (m, 8H, Ar-H), 4.52 (s, 2H, -$COCH_2$), 4.05 (s, 1H, NH), 2.50 (s, 3H, -OCH_3), 2.29 (s, 3H, -N-CH_3).

Spectral data of 4-methoxy-1-phenyl-3-(2-((4-nitrophenyl)amino)acetyl)quinolin-2(1*H*)-one, IIIb1: Yield: 74.51%. m.p.143°C. UV-Vis λ_{max}: 233.6nm; IR (KBr): 3460.30 (-NH); 3066.82 (aromatic -C-H), 2956.67, 2924.09, 2852.72 (aliphatic

-C-H), 1629.85 (-C=O acetyl), 1597.06 (-C=O amide), 1487.12 and 1303.88 (NO_2), 1224.80 cm^{-1} (-C-O-C); ^{1}H NMR (DMSO-d_6): δ 9.00-6.95 (m, 13H, Ar-H), 4.64 (s, 2H, -$COCH_2$), 3.40 (s, 1H, NH), 2.30 (s, 3H, -OCH_3).

Synthesis of *N*-(2-(4-methoxy-2-oxo-1-methyl-1,2- dihydroquinolin-3-yl)-2-oxoethyl)-*N*-(phenyl substituted)benzenesulfonamide [IVa/b (1-6)]

A mixture of compound (III a/b -1) (0.05mol) and benzene sulfonylchloride (0.05mol) were added in pyridine (15 mL) and solution was refluxed for interval of 6 hours. The completion of reaction was confirmed by TLC (n-hexane: ethyl acetate; 2:8). After completion of the reaction, the reaction mixture was poured in 50 mL of ice water and refrigerated overnight. The solid product precipitated out. Precipitate was filtered and washed with multiple portions of distilled water and dried. Recrystallization was performed with methanol as the solvent.

Spectral data of *N*-(2-(4-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-N-(4-chlorophenyl)benzenesulfonamide), IVa2: Yield: 59.21%. m.p.134°C. UV-Vis λ_{max}: 207.2nm; IR (KBr): 3062.96 (aromatic -C-H), 2922.16, 2850.79 (aliphatic -C-H), 1670.35 (-C=O acetyl), 1639.49 (-C=O amide), 1330.88 and 1161.15 (S=O), 1228.66(-C-O-C), 1089.78 cm^{-1} (C-Cl); ^{1}H NMR (DMSO-d_6): δ 7.88-6.78 (m, 13H, Ar-H), 4.83 (s, 2H, -$COCH_2$), 3.39 (s, 3H, -OCH_3), 3.25 (s, 3H, -N-CH_3); ^{13}C NMR (DMSO-d_6): δ 205.90 (1C, -C=O-CH_2), 189.17 (1C, -C-O-CH_3), 173.40 (1C, -C=O), 141.09-105.43 (12C, Ar-C), 60.22 (1C, O-CH_3), 50.17 (1C, -C=O-CH_2), 30.64 (1C,-N-CH_3).

Spectral data of *N*-(2-(4-methoxy-1-phenyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoethyl)-N-(4-nitrophenyl)benzenesulfonamide), IVb: Yield: 49.98%. m.p.121°C. UV-Vis λ_{max}: 211.7; IR (KBr): 3064.89 (aromatic -C-H), 2955.87, 2918.30, 2848.86 (aliphatic -C-H), 1629.85 (-C=O acetyl), 1595.13 (-C=O amide), 1489.05 and 1307.74 (NO_2), 1338.60 and 1159.22 (S=O), 1238.30 cm^{-1} (-C-O-C); ^{1}H NMR (DMSO-d_6): δ 8.14-6.59 (m, 18H, Ar-H); 3.61 (s, 2H, -$COCH_2$), 3.17 (s, 3H, -OCH_3); ^{13}C NMR (DMSO-d_6): δ 189.17 (1C, -C=O), 172.05 (1C, -C-O-CH_3), 165.60 (1C, -C=O), 141.09-114.21 (16C, Ar-C), 59.43 (1C, O-CH_3), 53.19 (1C, -C=O-CH_2).

Hypoglycemia Activity[11,12]

Wister albino rats weighing between (180—240g) procured from AditaBiosysPvt. Ltd. Tumkur (1868/PO/Bt/S/16/CPCSEA) were used in carrying out the activity. The rats were housed in animal house of P.E.S.'s Rajaram and TarabaiBandekar College of Pharmacy, Farmagudi, Ponda Goa. The animals were housed at RT (22-28°C) under standard laboratory conditions and fed with synthetic pellet feed and clean water *ad libitum*. The animals were deprived of food but were allowed free access to drinking water before the start of activity. The institutional animal ethics committee (IAEC) under the guidance of committee framed for the purpose of control and supervision of experiments on animals (CPCSEA) approved animal activity of this study with resolution number PESRTBCOP/IAEC;clear/2018-19/R-57.

Acute oral toxicity studies

Acute oral toxicity of the synthesized compounds was carried out as per the guidelines set by the Organization for Economic Co-operation and Development (OECD), revised draft guidelines 425. No toxicity was observed in all of the doses given. Thus, for the screening of antidiabetic activity the dose selected was 100 mg/kg of body weight as per OECD guidelines.

Collection of blood sample

Blood was withdrawn from the retro orbital plexus of the eye (around 0.5 mL) under light ether anaesthesia using capillary tubes at intervals of 0, 1, 2, 3, 4 and 6 hours from all the groups. The blood was collected in 2 mL micro centrifuge tubes containing EDTA as an anticoagulant and was centrifuged at 3000 rpm for 10 minutes to obtain serum. Serum was analysed immediately for glucose by using GOD-POD method using commercially available kit (manufactured by BIOLAB DIAGNOSTICS (I) PVT. LTD).

Animal Studies design

Fasted animals were divided into 14 groups, with 6 rats in each group. Group I served as control (3 g glucose/kg body weight), Group II received a standard drug Glibenclamide (5 mg/kg body weight) and Group III to Group XIV were orally administered test compounds (100 mg/kg body weight). The effect of blood sugar lowering agents was studied in glucose loaded rats. All the groups were loaded with 3 g/kg of glucose, 30 min after drug administration. Blood samples were collected from the tail vein just prior to drug administration and at 0, 1, 2, 3, 4 and 6 hour after glucose loading. Serum glucose levels were measured immediately.

Conclusion

From the obtained results of the research work, it can be concluded that compound with R=C_6H_5 and R_1=4-chloro aniline (IV b2) exhibited the highest MolDock score of (−153.434) which is higher to that of the standard drug (−95.765) and comparably similar to that of ligand (−180.898) probably because of presence of halogen. The compound IV b2 was also found to be the most potent hypoglycemic compound by decreasing the average serum glucose level in rats by GOD-POD method.

Acknowledgement

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