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DESIGN, SYNTHESIS, AND ANTIDIABETIC EVALUATION OF COUMARIN FUSED OXADIAZOLE DERIVATIVES

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder that leads to severe complications worldwide. In the present study, a series of new coumarin fused oxadiazole Schiff base derivatives (PM1-PM10) were synthesized by treating coumarin oxadiazole amines with different aromatic aldehydes. The structure of synthesized compounds was confirmed by IR, Mass, and ^{1}H NMR. Further, these compounds were evaluated for ADME properties, molecular docking studies, and invitro α-glucosidase enzyme inhibition. The docking studies were performed with isomaltose from *Saccharomyces cerevisiae* (PDB Code 3A4A), with scores of -7.26 to -4.26 kcal/mol. Compound PM9 showed the best interaction among all these compounds having a ΔG of -7.26 kcal/mol compared with standard acarbose of -6.85 kcal/mol. The glucosidase inhibitory activity showed IC_{50} 31.10 to 21.33 µM and was compared with standard acarbose. Compound PM9 showed significant antidiabetic activity compared with the standard acarbose.

Keywords: Coumarin, Oxadiazole, α-glucosidase, ADME, Molecular Docking.

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INTRODUCTION

Coumarins and oxadiazoles are two different heterocyclic compounds possessing various pharmacological properties. Coumarins have a benzene and pyran ring and are chemically named 2*H*-1-benzopyran-2-ones.[1] This privileged heterocyclic scaffold possesses various biological activities like anticoagulant[2], anticancer[3], antioxidant[4], anti-inflammatory[5], anti-diabetic[6], antidepressant[7], antifungal[8], antiviral[9], antimicrobial[10,] and antitubercular[11] activities. Oxadiazole is a 5-membered nitrogen-containing heterocycle. 1,3,4-oxadiazole have three possible isomers that depend on the nitrogen atom's position: 1,2,4-oxadiazole, 1,2,3-oxadiazole, and 1,2,5-oxadiazole.[12] Oxadiazole derivatives exhibit a wide spectrum of activities such as anticancer[13], anti-inflammatory[14], antimicrobial[15], herbicidal[16], pesticidal, analgesic[17], anticonvulsant[18], anti-HIV, antidiabetic[19], and plant growth regulator activities[20]. Diabetes mellitus is a common metabolic disorder faced by the population worldwide. However, there are various classes of drugs available for treatment, but none of these drugs has complete control over this disorder and possesses various side effects[21]. Among the different methods to treat this disorder is by controlling the enzyme α-glucosidase, which is responsible for the digestion and absorption of carbohydrates.[22] Thus, inhibiting this enzyme delays the digestion and absorption of carbohydrates and prevents diabetes mellitus. Although there are marketed α- glucosidase inhibitors like voglibose, acarbose, and miglitol, these drugs possess gastrointestinal side effects.[23] Hence, there is a need to develop better therapeutic agents such as α-glucosidase inhibitors. The molecular hybridization method of drug development is followed here, in which two different pharmacophores are clubbed together, and their biological properties are evaluated. Therefore, we planned to synthesize new derivatives of coumarin fused oxadiazole since both heterocyclic molecules have proven to be good antidiabetic properties separately.

EXPERIMENTAL

Molecular Docking Study

To understand the binding pattern of compounds PM1-PM10 with the receptor isomaltase from *Saccharomyces cerevisiae* (PDB Code 3A4A), binding energy was calculated in terms of docking score.

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Docking studies were performed using Schrodinger 2019-3 suite using glide software installed on Dell Inc.27" having a configuration, processor Core i7-7700 CPU@3.60 Gx8 with 8GB RAM and 1000 GB hard disk. The protein (PDB Code 3A4A) was downloaded from the protein data bank and refined using the protein preparation wizard; similarly, the compounds PM1-PM10 were prepared using the lig prep wizard before the final operation of interaction studies. These studies are evaluated based on the docking score of compounds. Docking scores were obtained from the XP visualizer in the S-score expressed in kcal/mol.

General Procedure for the Synthesis of Coumarinyl-Oxadiazole Schiff Base Derivatives

All the reagents obtained were of analytical grade: Salicylaldehyde, diethyl malonate, hydrazine hydrate, cyanogen bromide, substituted aromatic aldehydes, piperidine, HCl, glacial acetic acid, sodium bicarbonate, and ethanol. The open capillary tube method was employed to determine the compounds' melting points. TLC was done using a Silica gel G plate to check the compound's purity using the solvent n-hexane and ethyl acetate (8:2). To characterize and confirm the synthesized compounds, spectral studies were performed. These spectral studies include IR, NMR, and mass spectra; these were recorded using the instrument Alpha Bruker from the ATR technique for IR spectra, ^{1}H NMR spectra using $CDCl_3$, and DMSO solvent and internal standards as TMS on the 400M Bruker Advance II NMR spectrometer and mass spectra using electron impact ionization technique on GC MS Perkin Elmer Clarus 680 spectrometer respectively.

Step-1: Synthesis of ethyl 2-oxo-2*H*-1-benzopyran-3-carboxylate

Salicylaldehyde (10.0 mmol) and diethyl malonate (10.0 mmol) were mixed and stirred for 5 minutes, with the addition of a catalytic amount of piperidine. The room temperature was maintained. Further, this mixture was neutralized by dilute HCl. The obtained product was processed through filtration and washing to obtain 3-ethoxy-carbonyl coumarin. The synthesized compound was recrystallized from ethanol. The reaction progression was analyzed through TLC analysis. Yield: 73.39%.[24]

Step-2: Synthesis of 2-oxo-2*H*-1-benzopyran-3-carbohydrazide

In a round bottom flask, the equimolar concentration of ethyl-3-coumarin carboxylate and hydrazine hydrate were taken, and methanol was added as the solvent. The reaction mixture was refluxed for 24 hrs. The reaction progress was monitored through TLC analysis. The mixture was evaporated after the completion of the reaction, and the product obtained was recrystallized from ethanol. % Yield: 69.55%.[25]

Step-3: Synthesis of 3-(5-amino-1,3,4-oxadiazol-2-yl)-2*H*-1-benzopyran-2-one

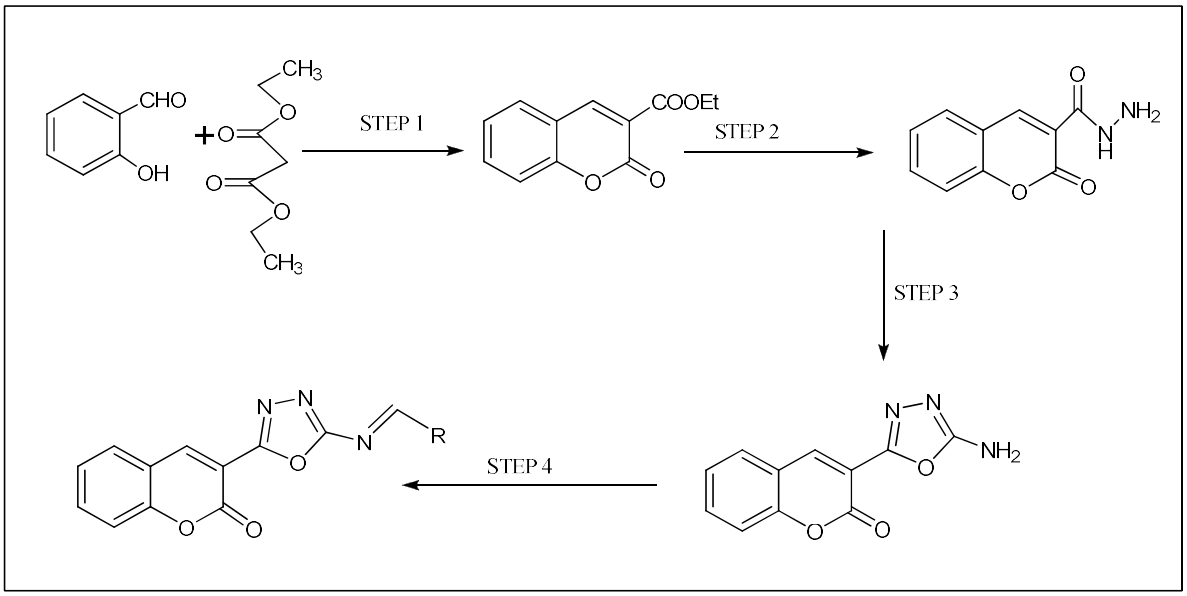
To an ethanolic solution of carbohydrazide in the round bottom flask, cyanogen bromide was added and warmed at 55-60^{o}C for 90 min, refluxed for the period of 16-18 hrs. The resulting reaction mixture was cooled and neutralized using sodium bicarbonate solution. The resultant product was solid, filtered, and then recrystallized using ethanol. TLC was carried out to monitor the reaction progression. % Yield: 63.83%.[26]

Step-4: Synthesis of 3-{5-[(benzylideneamino]-1,3,4-oxadiazol-2-yl}-2*H*-1-benzopyran-2-one Derivatives (PM1-PM10)

Equimolar quantities (0.02 mol) of compound 3 and various aromatic aldehydes were added to the round bottom flask and followed by the addition of a few drops of glacial acetic acid. The mixture was heated under reflux conditions for 14 hrs. Ethanol was used as a solvent. The residue obtained after distilling off the solvent (ethanol) was poured onto crushed ice with a continued stirring of 20 min. The products formed were filtered, ice-cold water was used for occasional washing and then dried, and recrystallization was carried out using alcohol. TLC was carried out to monitor the progress of the reaction.[27]

***In-vitro* α- glucosidase Inhibitory Assay**

The enzyme α-glucosidase was prepared using potassium phosphate buffer (pH 6.8, 50 mM). DMSO was used to dissolve the synthesized compounds PM1-PM10 (10-50 µg/ml). 10 µL α-glucosidase and 20 µL samples were incubated at 37^{o}C for 15 minutes. To this p- nitrophenyl glucopyranoside was added and incubated for another 20 minutes. The absorbance at 405 nm was measured. DMSO is used as a control and acarbose as the standard drug.[28]



R: p- OCH_3, p-Cl, p-CH_3, 3,4 (OCH_3, OH), 3-NO_2, p-$N(CH_3)_3$, p-Br, 3,4-$(OCH_3)_2$,p-OH, 3-Cl

Fig.-1: Scheme Coumarin Fused Oxadiazole Schiff Base Derivatives (PM1-PM10)

RESULTS AND DISCUSSION

Ethyl 2-oxo-2*H*- benzopyran-3-carboxylate (STEP 1): IR (ν $cm^{-1)}$: 3260 (C-H str Aromatic), 1480 (C=C str Aromatic), 1750 (C=O str), 1370 (C-C str), 1150(C-O-C str). ^{1}H NMR (400 M, DMSO-d_6): δ 1.25 (3H, t, J = 7.1), 4.12 (2H, q, J = 7.2), 7.36-7.61 (2H, 7.45 (m, J = 7.4, 7.3, 1.2), 7.61 (m, J = 7.9, 1.3, 0.6), 7.51 (1H, m, J = 8.2, 7.6, 1.2), 8.12 (1H, m, J = 7.8, 1.5, 0.4), 8.85 (1H, s). Mass (m/z): 219 (M^+).

2-Oxo-2*H*- benzopyran -3-carbohydrazide (STEP 2): IR (ν $cm^{-1)}$: 3310 (N-H str), 3260 (Ar C-H str), 1490 (Ar C=C str), 1720 (C=O str), 1360 (C-C str). ^{1}H NMR (400 M, DMSO-d_6): δ 1.25 (3H, t, J = 7.1), 4.12 (2H, q, J = 7.1), 7.33-7.54 (2H, 7.36 (m, J = 7.7, 7.1, 1.2), 7.48 (m, J = 8.2, 1.3, 0.5), 7.76 (1H, m, J = 8.5, 7.7, 1.4), 8.13 (1H, m, J = 7.7, 1.6, 0.5), 8.86 (1H, s). Mass (m/z): 205 (M^+).

3-(5-amino-1,3,4-oxadiazol-2-yl)-2*H*-benzopyran -2-one (STEP 3): IR (ν $cm^{-1)}$: 3340 (N-H str), 3270 (Ar C-H str), 1485 (Ar C=C str), 1700 (C=O str), 1250 (C-O-C str). ^{1}H NMR (400 M, DMSO-d_6): δ 7.23-7.51 (3H, 7.20 (m, J = 8.4, 1.2, 0.6), 7.42 (m, J = 7.7, 7.3, 1.2), 7.41 (m, J = 8.4, 7.7, 1.6), 7.65 (1H, m, J = 7.6 1.5, 0.5), 7.71 (1H, s). Mass (m/z): 231 (M^+).

3-(5--[(4-methoxyphenyl) methylidene] amino}-1,3,4-oxadiazol-2-yl)-2*H*-1-benzopyran-2-one:(PM1) Yield: 70.02%, mp: 171-174°C, IR (ν cm^{-1}): 1678 (C=O), 1611 (C=N), 1194 (C-O). ^{1}H NMR: δ 3.92 (2H, s), 7.14 (2H, m, J = 8.1, 1.3, 0.5), 7.24 (1H, dd, J = 8.6, 1.2, 0.5), 7.54 (2H, dd, J = 7.7, 7.5, 1.1), 7.77 (1H, d, J = 8.3, 1.5), 7.94 (1H, m, J = 7.6, 1.4), 7.81 (2H, dd, J = 8.1, 1.7, 0.5), 8.37 (1H, s), 9.54 (1H, s). Mass m/z: 348 (M^+).

3-(5-[(4-chlorophenyl) methylidene] amino}-1,3,4-oxadiazol-2-yl)-2*H*-1-benzopyran-2-one: (PM2) Yield: 72.81%, mp: 168-171°C, IR (ν cm^{-1}): 1690 (C=O), 1628 (C=N), 1194 (C-O), 815 (C-Cl). ^{1}H NMR: δ 7.39 (1H, m, J = 8.4, 1.2, 0.5), 7.51 (1H, dd, J = 7.6, 7.5, 1.1), 7.56 (2H, m, J = 7.8, 1.1, 0.5), 7.76 (1H, m, J = 8.3, 7.6, 2.1), 7.84-7.94 (3H, 7.87 (m, J = 7.8, 1.9, 0.5), 7.91 (m, J = 7.7, 1.5, 0.4), 8.25 (2H, d), 9.45 (2H, s). Mass, m/z: 352(M^+).

3-(5-[(4-hydroxy-3-methoxyphenyl) methylidene] amino}-1,3,4-oxadiazol-2-yl)-2*H*-1benzopyran-2-one:(PM4) Yield: 69.54%, mp: 283-286 °C, IR (ν cm^{-1}): 1687 (C=O), 1593 (C=N), 1220 (C=N). ^{1}H NMR: δ 3.84 (3H, d), 6.81 (1H, m, J = 8.6, 0.4), 7.25 (1H, m, J = 8.1, 1.3, 0.5), 7.36 (1H, m, J = 1.6, 0.6), 7.41 (1H, d, J = 7.6, 7.4, 1.4), 7.52 (2H, m, J = 8.5, 1.4), 7.72 (1H, m, J = 8.1, 7.6, 1.4), 7.92 (1H, m, J = 7.8, 1.4, 0.5), 8.31 (1H, s), 9.37 (1H, s). Mass m/z: 364(M^+).

3-{5-[3-(dimethylamine) phenyl] methylidene} amino]-1,3,4-oxadiazol-2-yl}-2*H*-1-benzopyran-2-one:(PM6) Yield: 82.45%, mp: 223-227 °C, IR (ν cm^{-1}): 1679 (C=O), 1594 (C=N), 1231 (C-O). ^{1}H NMR: δ 2.94 (6H, s), 6.70 (2H, d, J = 8.1, 1.6, 1.1), 7.22 (1H, m, J = 8.4, 1.3, 0.5), 7.42 (1H, m, J = 7.6, 7.4, 1.3), 7.70 (1H, m, J = 8.4, 7.6, 1.6), 7.84 (2H, m, J = 7.7, 1.6, 0.5), 8.11 (1H, dd, J = 7.6, 1.4, 0.5), 8.17 (1H, s), 9.35(1H, s). Mass: m/z: 361(M^+).

3-(5-[(3-bromophenyl) methylidene] amino}-1,3,4-oxadiazol-2-yl)-2*H*-1-benzopyran-2-one: (PM7) Yield: 62.5%, mp: 228-231°C, IR (ν cm^{-1}): 1700 (C=O), 1619 (C=N), 1198 (C-O). ^{1}H NMR: δ 2.92 (6H, s), 6.69 (2H, m, J = 7.9, 1.4, 0.4), 7.25 (1H, m, J = 8.3, 1.2, 0.4), 7.41 (1H, m, J = 7.7, 7.5, 1.2), 7.69 (1H, d, J = 7.4, 7.6,1.4), 7.86 (2H, m, J = 7.9, 1.9, 0.4), 8.06 (1H, m, J = 7.6, 1.5, 0.4), 8.16 (2H, s), 9.37 (1H, s).Mass m/z: 397(M^+).

Table-1: Physical Data of Coumarin Fused Oxadiazole Derivatives (PM1-PM10)

Comp. Code	R	Molecular Formula	Molecular Weight	M.P °C	Percentage Yield
PM1	P- OCH_3	$C_{19}H_{13}N_3O_4$	347	172-74	70.02%
PM2	P-Cl	$C_{18}H_{10}ClN_3O_3$	352	168-70	72.81%
PM3	P-CH_3	$C_{19}H_{13}N_3O_3$	333	160-62	67.92%
PM4	3-OCH_3,4-OH	$C_{19}H_{13}N_3O_5$	363	284-86	69.54%
PM5	3-$N0_2$	$C_{18}H_{10}N_4O_5$	362	242-44	76.66%
PM6	P-$N(CH_3)_2$	$C_{20}H_{16}N_4O_3$	360	223-27	82.45%
PM7	P-Br	$C_{18}H_{10}BrN_3O_3$	396	228-31	62.50%
PM8	3,4-$(OCH_3)_2$	$C_{20}H_{15}N_3O_5$	377	247-50	74.56%
PM9	P-OH	$C_{18}H_{11}N_3O_4$	333	237-39	65.66%
PM10	3-Cl	$C_{18}H_{10}ClN_3O_3$	351	168-72	77.76%

Table-2: In Silico ADME Properties of Coumarin Fused Oxadiazole Derivatives

Comp.Code	Predicted Caco-2permeability (nm/sec)	Percentage of human oral absorption	Total area accessed using a solvent (SASA)	Polar Surface area
PM1	528.24	90.76	636.28	93.95
PM2	528.17	93.39	624.11	85.59
PM3	528.12	92.33	632.15	85.60
PM4	172.24	79.74	649.38	115.57
PM5	65.92	69.85	636.63	130.42
PM6	498.76	92.43	680.06	90.16
PM7	528.93	93.85	629.04	85.58
PM8	528.29	91.13	674.52	101.36
PM9	159.95	78.47	612.42	108.14
PM10	528. 21	93.81	624.08	85.59

Table-3**:** Physiochemical Properties of Coumarin Fused Oxadiazole Derivatives

Comp. Code	Molecular Weight	Molecular Volume	LOG P	H-Bond Donors	H Bond Acceptors	N violation
PM1	347.329	1077.78	2.577	0.000	6.750	0
PM2	351.748	1047.161	3.026	0.000	6.000	0
PM3	331.330	1062.934	2.845	0.000	6.000	0
PM4	363.329	1102.076	2.182	1.000	7.500	0
PM5	362.301	1074.077	1.768	0.000	7.000	0

PM6	360.371	1158.452	2.938	0.000	7.000	0
PM7	396.199	1055.966	3.104	0.000	6.000	0
PM8	377.356	1153.140	2.639	0.000	7.500	0
PM9	333.303	1025.720	2.064	1.000	6.750	0
PM10	351.75	1047.173	3.072	0.000	6.000	0

Table-4: Docking score of coumarin fused oxadiazole derivatives (PM1-PM10)

Compounds Code	PM1	PM2	PM3	PM4	PM5	PM6	PM7	PM8	PM9	PM10
Docking Score (kcal/mol)	-4.76	-5.06	-4.70	-4.92	-4.89	-4.26	-4.41	-4.76	-7. 26	-5.00

Table-5: List of Amino Acids That Participated in the Interaction between Receptor and Coumarin Fused Oxadiazole Derivatives

Compound Code	Hydrogen bonding	Hydrophobic interaction	pi-pi stacking
PM1	Asn 235, Asn 317, Ser 311,	Ile 419, Ala 418,Phe 314, Leu 313	Phe 314
PM2	Asn235, Asn 317, Ser 311,	Ile 419, Ala 418, Phe 314, Leu 313, Trp 238	Phe 314
PM3	Asn 235,Asn 317, Ser 311,	Ile 419, Ala 418, Phe 314, Leu 313, Trp 238	Phe 314
PM4	Asn 317, Ser 311, Asn 415, Asn 235	Ile 419, Ala 418, Phe 314, Leu 313	
PM5	Arg 315, Asn 317, Ser 311	Phe 314, Pro 312, Tyr 158, Ala418, Ile 419, Phe 314, Leu 313	Phe 314
PM6	Lys 156	Tyr 316, Tyr 158, Phe 314, Leu 313, Pro 312, Val 232, Pro 243, Phe 303	
PM7	Asn 317, Ser 311, Asn 235	Trp 238, Phe 314, Leu 313, Ala 418	Phe 314
PM8	Asn 317, Ser 311, Asn 235	Trp 238, Phe 314, Leu 313, Ile 419, Ala 418	
PM9	Arg 315, Thr 310, Ser 241, Lys 156	Pro 312, Tyr 150, Trp 155, Leu 177	Tyr 150
PM10	Arg 315, Ser 241	Tyr 158, Phe 314, Pro 312	Hid 280

Table-6: In vitro Antidiabetic Activity of Coumarin Fused Oxadiazole Derivatives

ADME and Docking Studies

	Percentage Inhibition										
Conc	STD	PM1	PM2	PM3	PM4	PM5	PM6	PM7	PM8	PM9	PM10
10	31.41	19.91	28.65	20.84	20.33	20.27	19.53	18.65	17.03	26.75	27.06
20	44.93	34.19	39.27	36.52	35.48	35.19	34.00	36.44	34.34	40.07	39.84
30	47.97	48.48	46.96	43.38	48.52	49.41	48.96	45.93	42.19	48.43	47.60
40	60.49	56.71	56.98	55.74	55.58	56.33	55.65	54.61	53.28	57.88	57.23
50	81.27	81.38	77.64	74.26	79.61	79.05	78.44	78.50	76.88	78.07	77.62
IC 50	17.21	28.71	22.82	24.20	31.10	26.51	24.13	23.92	28.07	21.33	21.51

Designed analogs of coumarin fused oxadiazole derivatives (PM1-PM10) were studied for their physicochemical properties using a computational tool Qikprop. It predicted the ADME properties such as gut-blood barrier permeability (non-active transport) in nm/sec by measuring QPPCaco, percentage of oral absorption, the quantum of the solvent accessible area in square angstroms (SASA), polar surface area, molecular weight, molecular volume, log P, Hydrogen bond donors, and acceptors.

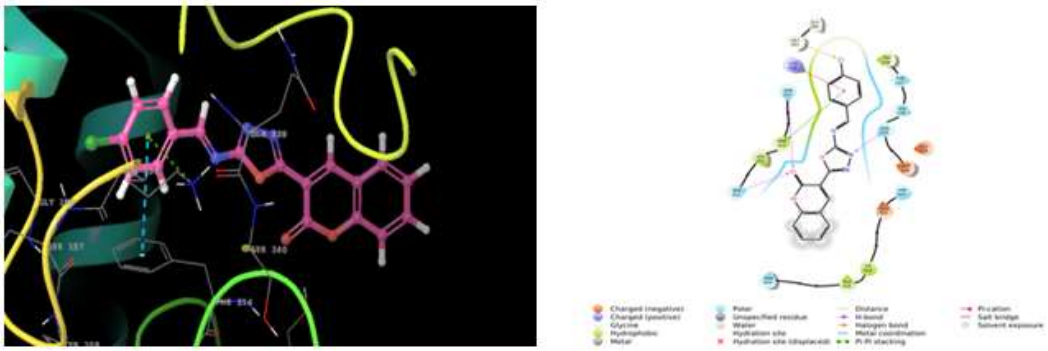


Fig.-2: 2D and 3D Interaction Image of Compound PM2 with Receptor 3A4A

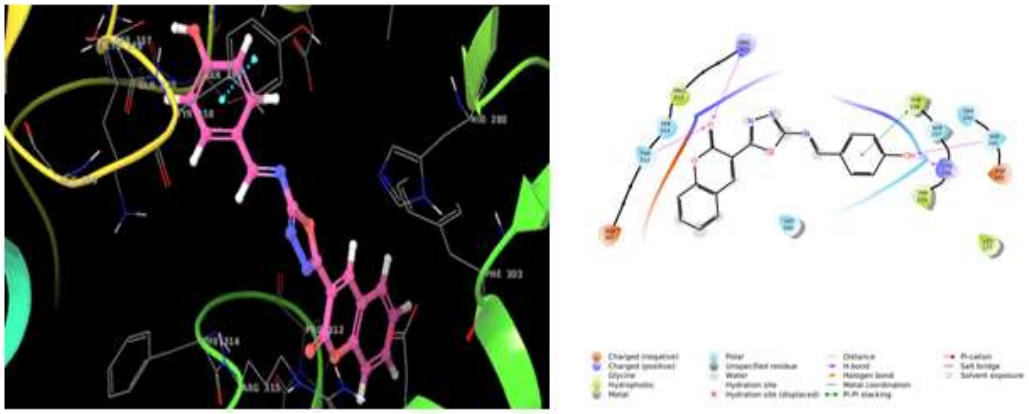


Fig.-3: 2D and 3D Interaction Image of Compound PM9 with Receptor 3A4A

It obeyed Lipinski's rule of five by showing no more than 5 and 10 hydrogen bond donors and acceptors respectively, molecular mass <500 Daltons and (log P) that does not exceed 5. With all these obtained physiochemical data from Qikprop, it has been observed that coumarin-fused oxadiazole derivatives (PM1-PM10) possess excellent druggable properties. Physiochemical and ADME properties of PM1-PM10 are shown in Tables-2 and 3**.** From the molecular docking studies, the interaction pattern of compounds (PM1-PM10) with the active site of receptor 3A4A was studied using glide software. Derivatives PM1-PM10 showed binging energy with receptors in the ranges of -7.268 to -3.594 kcal/mol respectively shown in Table-4. Compound C9 displayed the maximum binding energy i.e., -7.26 kcal/mol with the highest affinity among the entire compound with protein 3A4A. Different forces through which the compounds interact with receptor 3A4A are polar interactions, charged negative, charged positive, hydrophobic, pi-pi stacking, and hydrogen bonds. The best fit compound PM9 hydroxy group and its carbonyl function form four hydrogen bonds with Arg 315, Thr 310, Ser 241, Lys 156 amino acid and hydrophobic interaction with ASP215, hydrophobic interaction with Pro 312, Tyr 150, Trp 155, Leu 177, and pi-pi stacking with Tyr 150 amino acids of receptor 3A4A. Docking interactions of the compound PM9 and PM2 are represented in the form of 2D and 3D in Figures 2 & 3. The chemical bonding between the amino acid of the receptor and PM1-PM10 with different forces and shown in Table-5.

Chemistry

Synthesis of different coumarin-fused oxadiazole Schiff base derivatives was carried out through a four-step method shown in Fig.-1 (Scheme). Proof of the synthesis of the compound of step 1 was confirmed by the bands attributed to 1710 (C=O str), 1355 (C-C str), 1145 (C-O-C str) in the IR spectrum, and mass spectra peak at 219 (M^+). The compound of step 2 was confirmed with IR peaks value for functional group 3320 (N-H str), 3270 (Ar C-H str), 1480 (Aromatic C=C str), 1710 (C=O str). In step 3 the presence of IR peak 3340 confirms the presence of the amino-functional group. ^{1}H-NMR showed signals

for protons of the NH group at δ 7.41 ppm beside signals in the range of 7.22-7.56 ppm attributed to coumarin protons, respectively. The final compounds of step 4, PM2 and PM9, showed IR bands attributed to C-Cl, and OH at 810 (C-Cl) and 3210 (O-H), respectively.

Antidiabetic Activity

The antidiabetic screening of PM1-PM10 compounds was done in vitro by inhibiting the α-glucosidase enzyme. These compounds were examined at different concentrations (10-50 µg/ml) using acarbose as the standard drug. These synthesized compounds have shown significant activity of α-glucosidase inhibition with an IC_{50} range of 31.1-21.33 µM, whereas acarbose IC_{50} is 17.21 µM. PM9 showed the best α-glucosidase inhibition with IC_{50} 21.33 µM. Compounds PM2 and PM10 have also shown good α-glucosidase inhibitory activity with IC_{50} 21.51 and 22.82. Compounds PM4 and PM8 have shown the least active against glucosidase inhibition having IC_{50} 31.4 and 28.07, respectively. The IC_{50} of all the compounds is shown in Table-6. From IC_{50} results, it is obvious that glucosidase inhibitory activity of synthesized compounds PM1-PM10 depends on critical parameters of structural factors such as the nature of substituent present on the phenyl ring attached to the methylidene amino oxadiazole**.** The inclusion of a para-hydroxy group, meta, and para-chloro groups on the phenyl ring increases the glucosidase inhibitory potential, whereas decreases due to the meta and para methoxy group present on the phenyl ring.

CONCLUSION

In the present study, a new series of coumarin fused oxadiazole Schiff base derivatives were synthesized and characterized using different spectral methods, and the yield of compounds PM1-PM10 was in the range of 62.5-82.45 percent. These compounds were also studied for physiochemical properties for their draggability and show all the parameters well within the range of prescribed limits. Docking studies of these compounds have good interaction with the receptor 3A4A, and forces like hydrogen bond, polar, hydrophobic bond, and charged positive and charged negative interaction forces were found to be important in the compound binding to the receptors. Compound PM9 showed the best docking score of -7.26 kcal/mol compared with the standard acarbose of -6.85 kcal/mol. Anti-diabetic activity of compounds PM1-PM10 was evaluated by α-glucosidase inhibition activity at different concentrations (10-50 µg/ml) and compared with the standard drug acarbose. Compound PM9 showed significant antidiabetic activity compared with the standard acarbose. Based on the above result it can be concluded that the compound PM9, with further modification, can be a useful lead molecule for pharmaceutical application as an anti-diabetic molecule.

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