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Design, Synthesis and Evaluation of Piperidinyl Coumarin Derivatives as Potential Antidiabetic Agents

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Abstract : Coumarin derivatives have been reported to exhibit a promising therapeutic effect on diabetes. In present study preliminary *insilico* screening of various novel analogues of piperidinyl coumarin derivative were carried out. The analogues with highest doking score and hydrogen bond interaction were taken for wet lab synthesis. Synthesis was carried out by following steps, N- chloro acetylation of piperidine, amide formation, conversion of amide to nitrile group, coupling of piperidine derivative with various amino coumarin derivatives. The structure of the desired derivatives were confirmed at each level by spectroscopic studies like, FT-IR, ^{13}C-NMR, ^{1}H-NMR and Mass Spectra. After confirmation of structure, *in vitro* studies of synthesized derivatives were carried out by α-glucosidase inhibition assay and α-amylase inhibition assay method by using acarbose as standard. Among the proposed derivatives 1-(-(2-oxo-2H-chromen-6-yl)amino)acetyl)piperidine-2-carbonitrile (4C1) displayed significant α-glucosidase and α-amylase inhibition activity . The newly synthesized compounds may provide valuable template for future design and optimization to produce α-glucosidase analogues.

Key words : Coumarin, piperidine, α-glucosidase, α-amylase, Autodock vina.

Introduction

α – Glucosidase enzyme is one of the medication targets in diabetic management. The enzyme is involved in digestion of polysaccharide into monosaccharide that can be absorbed by the intestine. In this study, α-glucosidase isolated from *Saccharomyces cerevisiae* was chosen as the target enzyme.Inhibitors of *α*-glucosidase delay the breaking down of carbohydrate in the small intestine and diminish the postprandial blood glucose excursion in a person suffering from diabetes[1]. Acarbose, miglitol and voglibose act by competitively inhibiting the α-glucosidases. They decrease both postprandial and Hyperinsulinemia and thereby may improve sensitivity to insulin and release the stress on β-cells. These compounds do not induce hypoglycaemia and have a good safety profile, although gastrointestinal adverse effects may limit long term

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compliance to therapy[2]. However, synthetic α- glucosidase inhibitors like acarbose are often reported with gastrointestinal side effects which include flatulence, abdominal pain and diarrohea. Therefore, it is the need of our search for effective and safe alternative α- glucosidase inhibitors showing no side effects. One of the potential approaches to find out a new agent of drug for treating diabetes, especially type 2 DM is the mechanism of α-glucosidase inhibition.

Coumarins are secondary metabolites found widely in nature plants and used mainly in anticoagulation and antithrombotic therapy for cardiovascular diseases[3,4]. Given the frequent correlation between diabetes and cardiovascular complications, coumarins would be even more valuable if they were also effective against diabetes. Hypothetically, these drugs would not only lower blood glucose levels, but also synchronously improve outcomes from cardiovascular complications of diabetic patients. Natural coumarins such as umbelliferone, esculentin and osthole and other coumarin derivatives have been reported to exhibit a promising therapeutic effect on diabetes[5-9].

Piperidine and its derivatives are ubiquitous building blocks in the synthesis of pharmaceuticals and fine chemicals. Piperidine structure occurs in many pharmaceuticals such as paroxetine, risperidone, methylphenidate, raloxifene, minoxidil, thioridazine, haloperidol, droperidol, mesoridazine, meperidine etc. Piperidine derivatives are utilized for several pharmacological activities, much of these includes; antibacterial (Gram positive and Gram negative), antifungal, anti-inflammatory, antioxidant, anti-HIV and anticancer activities[10-13]. In the present study piperidinyl coumarin derivatives are synthesized by coupling various piperidine derivatives and aminocoumarin derivatives and study its α-glucosidase and α-amylase inhibitory activity.

Experimental

All the reagents and solvents used were purchased from Sigma Aldrich, S. D. Fine (India) and Qualigens(India). The purity of the compounds was checked by thin layer (TLC) on silica gel G (Merck) coated plates by using chloroform: methanol (7:3) as solventsystem. Iodine chamber was used for the visualization of TLC spots. Melting points were determined by the open capillary method using the electrical melting point apparatus and are uncorrected. IR spectra of the synthesized compounds were recorded using JASCO FT-IR spectrophotometer. Proton NMR spectra and ^{13}C NMR spectra of synthesized compounds were recorded in $CDCl_3$ on Bruker ultra shield DPX 400 spectrometer using tetramethylsilane(TMS) as internal reference (Chemical shift in δ ppm). Mass spectra of the synthesized compounds were recorded by using LC-MSD Trap-SL 2010 A- Shimadzu Mass spectrometer.

Molecular Docking Study:

In the present study different proposed piperidinyl coumarin derivatives were subjected to *in silico* evaluation using different softwares. Three-dimensional (3D) drawing of the proposed compounds was done using ACD Lab Chemsketch 12.0 The structure of enzymes (α-glucosidase, PPAR-γ, DPP4) with PDB id (3A4A, 3FEJ, 3W2T) was downloaded from protein data bank (http://www.rcsb.org/) and then prepared using discovery studio visualize software. The preparation process involve removing water molecule, ligand attached and adding hydrogen atoms. The binding site was visualised in discovery studio. Miglitol, rosiglitazone and sitagliptin were used as standards. Molecular docking of proposed molecules was done AutoDock Vina in PyRx Virtual screening tool[14] (1.1.2). The affinity of selected compounds with protein target of interest was analyzed in terms of energy. The 3D image of the docked structure was visualized by Discovery Studio Visualizer. Three piperidinyl coumarin derivatives were selected for synthesis with the help of *in silico* evaluation.

Chemistry:

Reaction of piperidine carboxylic acid with chloroacetyl chloride was followed by conversion of the carboxylic acid moiety of the resulting *N*-acylated product into thecarbonitrile via the corresponding amide intermediate[15]. Further coupling of acylated compound with amine derivative yield targeted product (Fig.1).

Synthesis of chloro acetyl derivative (2A, 2B, 2C)

To a suspension of piperidine/ piperidine 3-carboxylic acid (20.0 g, 0.174 mol) in THF (200 ml) was added chloroacetyl chloride (19.7 ml, 0.261 mol) at room temperature and the reaction mixture was refluxed for 2 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with water (20 ml) and stirred for 20 min. The precipitated crystalline white solid was filtered, washed with cold diisopropyl ether and dried at 40 °C under vacuum to afford compound (2)**.**

Synthesis of carboxamide derivative (3B, 3C)

To a solution of chloroacetylated compound (2)(10.0 g, 0.052 mol) in dichloromethane(200 mL) was added slowly a solution of dicyclohexylcarbodiimide (10.8 g, 0.052 mol) in dichloromethane at 10–15 °C and the mixture was stirred at room temperature for 1 h. To this was added ammonium bicarbonate (41.2 g, 0.522 mol) and precipitated, the mixture was stirred for 1 h. After completion of the reaction, the mixture was filtered and the residue was washed with DCM. The filtrates were collected, combined and concentrated under vacuumto afford amide derivative (3).

Synthesis of carbonitrile derivative (4B,4C)

To a suspension of amide (3)(4.0 g, 0.0209 mol) in THF (40 mL) was added trifluoroacetic anhydride (4.4 mL, 0.0315 mol) at 0–5 °C and the reaction mixture was then stirred at room temperature for 2 h. To this mixture was added portion wise (over 5 min) ammonium bicarbonate (12.4 g, 0.1573 mol) maintaining the temperature of the mixture at 5–10°C. The mixture was stirred at room temperature for 45 min and then concentrated under vacuum at 40 °C. The residue was stirred in toluene (60 mL) at room temperature for 1.0 h. After filtration, the filtrate was concentrated under vacuum at 40 °C to afford an oily mass which was stirred in hexane (20 mL) at room temperature for 30 min. The mixture was cooled to 0–5°C and allowed to stand at the same temperature for 30 min.The resulting crystalline solid was filtered and washed withcold hexane to give the nitrile derivative (4).

Synthesis of piperidinyl-coumarin derivative (2A1-4C7)

A solution of piperidine derivative (5.24 mmol) in dichloro methane (20ml) was added drop wise over 10 minute to an ice water cooled mixture of 7-amino-4-methylcoumarin/ 3-aminocoumarin derivative (10.5 mmol) and K_2CO_3 (21.0 mmol) in dichloro methane (40ml). The reaction was then stirred at ice water temperature for 2 hours and then room temperature for 18 hours. The potassium salt was removed via filtration and filtrate was concentrate to obtain final product.

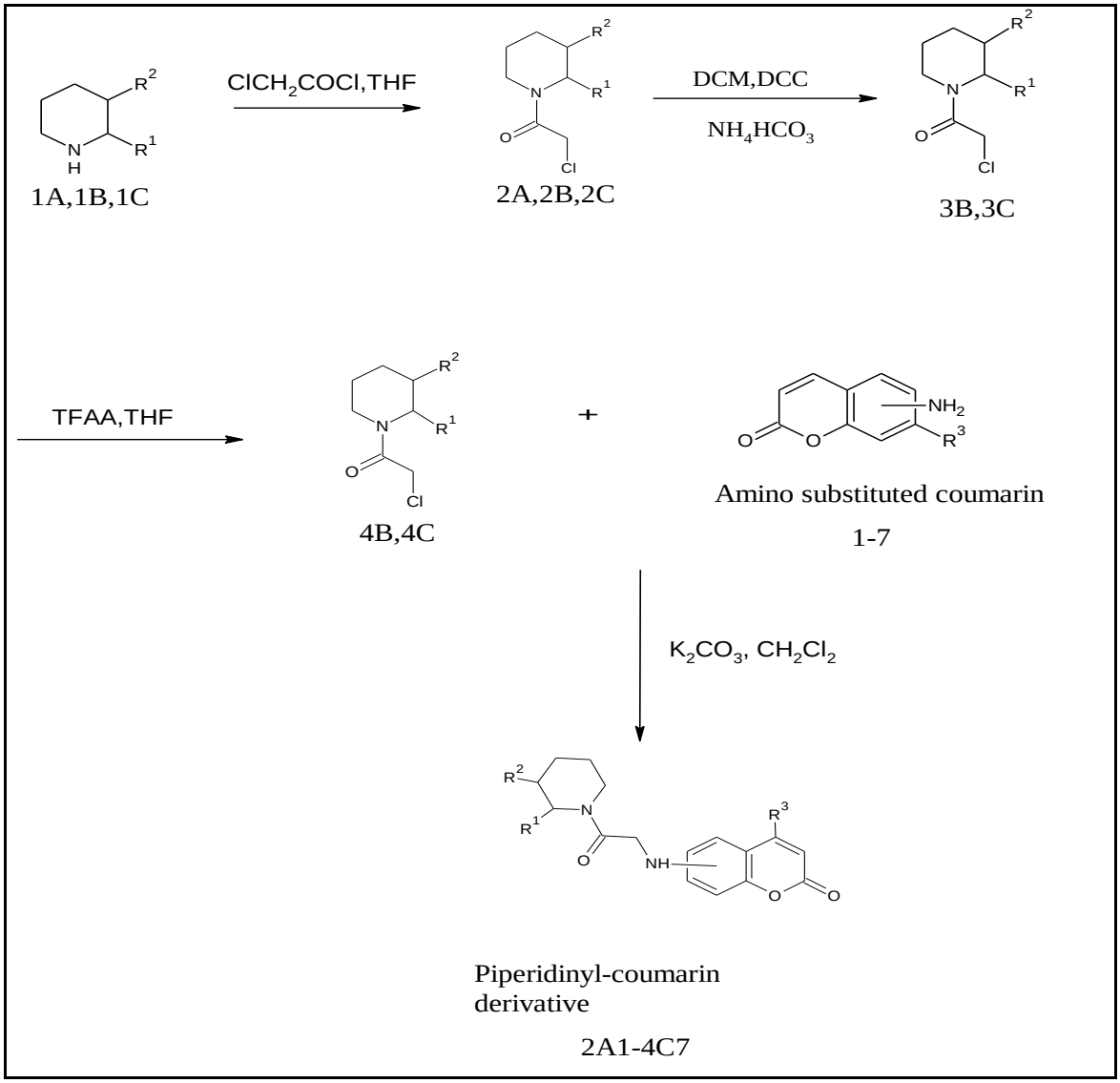

Fig:1 Synthesis of piperidinyl coumarin derivatives

***In-vitro* study**

- **α-Glucosidase inhibition assay method:** α-glucosidase reaction mixture contains 2.9 mM p-nitrophenyl-α-glucopyranoside (pNPG), varying concentrations (50, 100, 150, 200 μg/mL) of derivatives and 1.0 U/mL α-glucosidase in sodium phosphate buffer, pH 6.9. Negative control was enzyme and substrate, while positive controlcontains acarbose. Mixtures without enzyme and acarbose served as blanks. The reaction mixtures were incubated at 25 ºC for 5 min, after which the reaction was stopped by adding Na_2CO_3. Absorbance was determined at 405 nm using spectrophotometer and was considered directly proportional to the activity of the enzyme[16,17].

- **α-Amylase inhibition assay method:** Four different concentrations (50, 100, 150, 200 μg/mL) of samples and standard drug acarbose were prepared and made up to 1ml with DMSO. A total of 500 μl of sample and 500 μl of 0.02 M sodiumphosphate buffer (pH 6.9 with 0.006 M NaCl) containing α-amylase solution (0.5 mg/ml) were incubated for 10 min, at 25^0C. After preincubation, 500 μl of 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M NaCl) was added to each tube. This reaction mixture was then incubated for 10 minutes at 25^0C. 1ml of di -nitro salicylic acid color reagent was added to stop the reaction. These test tubes were then incubated in a boiling water bath for 5 minutes and cooled to room temperature. Finally this reaction mixture was again diluted by adding 10 ml of distilled water. % of

inhibition by α-amylase can be calculated by using the following formula. Absorbance was measured at 540 nm[18].

$$\% \text{ Inhibition} = \frac{(\text{Abs of control} - \text{Abs of derivatives}) * 100}{\text{Abs of control}}$$

Results and Discussion

Molecular docking studies were performed on Autodock vina software. Compound 2A1 showed a good interaction with3A4A. In 2A1 carbonyl group of coumarin linked with ARG315 of 3A4A with a bond length of 2.42 Å. In compound 4C1 cyano group possess 2 hydrogen bonds with ARG213and HIS351 with a bond length of 2.26 and 2.25 respectively. Compound 4C1 have shown a good hydrogen bond interaction with 3W2T receptor. Carbonyl group and secondary amine of 4C1 form a hydrogen bond with ASP739 with bond length of 2.42 A^0.These results revealed that the interaction between 4C1 and 3A4A,3W2T and 3FEJ is very significant and compound exhibit a good antidiabetic activity.

Table 1: Docking score of proposed piperidinyl-coumarin derivatives

Compound	Binding energy in k.cal/mol		
	3A4A	3W2T	3FEJ
2A1	-9.0	-7.2	-8.8
2A2	-8.4	-7.0	-8.2
4C1	-9.2	-7.6	-9.1
4C2	-8.5	-7.3	-9. 0
Acarbose	-7.9	-	-
Vidagliptine	-	-6.2	-
Rosiglitzone	-	-	-6.9

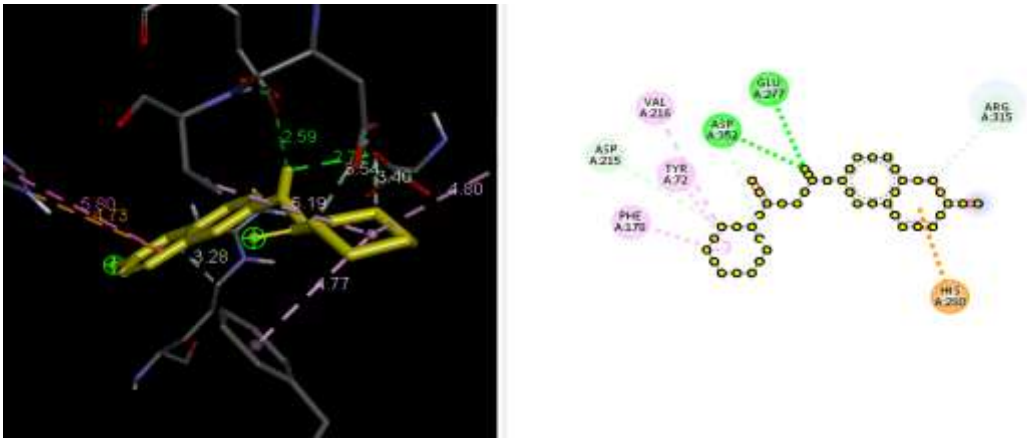

Fig 2: Hydrogen bond interaction of 2A1 with 3A4A

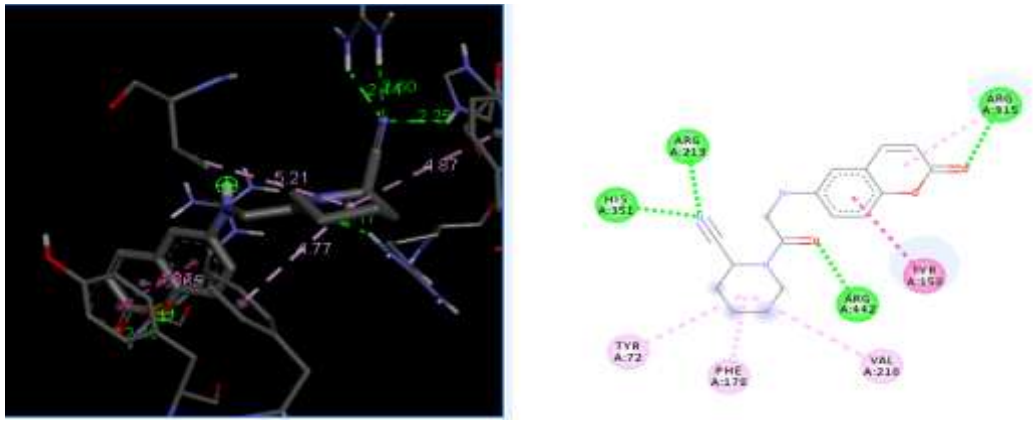

Fig 3: Hydrogen bond interaction of 4C1 with 3A4A

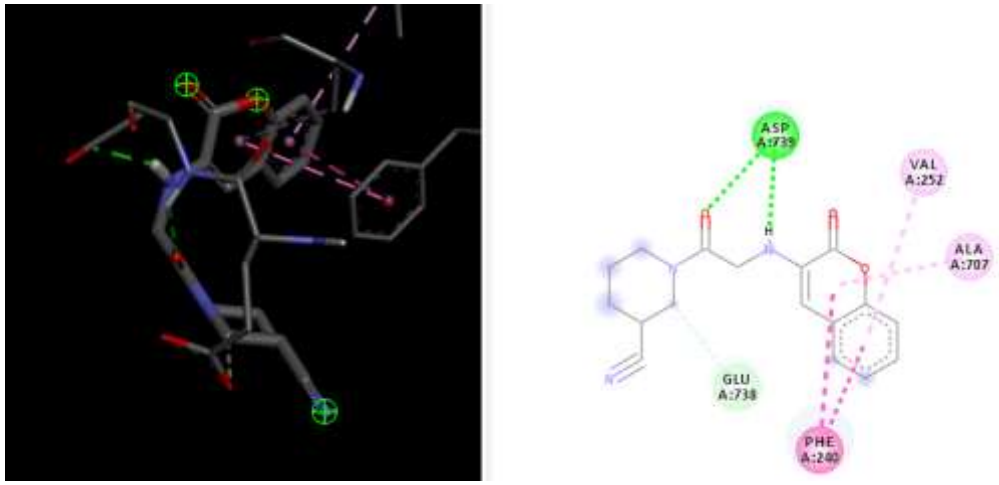

Fig 4:Hydrogen bond interaction of 4C1 with 3W2T

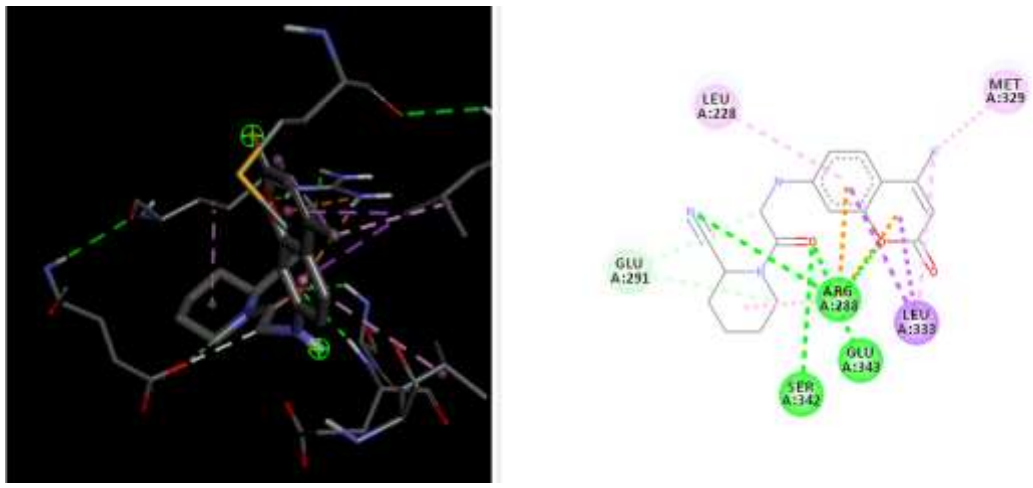

Fig 5: Hydrogen bond interaction of 4C1 with 3FEJ

Analogues designed by *Insilico* studies were selected for wet lab synthesis based on the better scores obtained by docking. The reaction sequence leading to the formation of title compound was shown in the scheme. Piperidine/ piperidine 3-carboxylic acid was *N*-acylated with chloroacetyl chloride in refluxing THF to afford 1-(2-chloroacetyl) piperidine-carboxylic acid then converted the carboxylic acid moiety of this compound to the amide. The amide substituted piperidine derivative coupled with coumarin to get piperidinyl-coumarin derivative.acylation of piperidine proceeds faster in THF at an elevated temperature. All the

synthesized compounds were obtained in good yield (Table 2). Structures of all the compounds were established by combined use of IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data of synthesized compounds.

Table 2: Physico-chemical characterization of synthesized compounds

Cpd code	Physical appearance	Melting point in ^{0}C	R_f value	Percentage yield
2A1	White	154	0.62	86
2A2	Pale yellow	168	0.71	85
4C1	Pale white	150	0.63	88
4C2	Yellow	172	0.74	84

Spectral data:

Compound 2A:FT-IR (KBr) cm^{-1}:3250 (SP^{2}C-H), 3055 (cyclic C-H), 1875 (C=0), 1362 (3^0 N)

1165 (C-N), 749 (C-Cl)

Compound 2C: FT-IR (KBr) cm^{-1} 3235 (SP^2 C-H), 3040 (cyclic C-H), 1363 (3^0 N) , 1167 (C-N), 752 (C-Cl) , 1869 (C=0), 2902 (-OH)

Compound 3C:FT-IR (KBr) cm^{-1}3200 (SP^2 C-H), 3050 (cyclic C-H), 1360 (3^0 N) , 1166 (C-N), 750 (C-Cl), 1870 (C=0), 3350-3200(-NH)

Compound 4C: FT-IR (KBr) cm^{-1}3243 (SP^2 C-H), 3053 (cyclic C-H), 1366 (3^0 N), 1167 (C-N), 755 (C-Cl), 1876 (C=0), 2251 (CN)

2A1, 4-methyl-7-(2-oxo-2(piperidinyl)ethyl)amino)-2H-chromen-2-one: $C_{17}H_{20}N_2O_3$,FT-IR (KBr) cm^{-1} 3207 (SP^2 C-H), 1873 (C=O), 1081 (C-0-C),1369 (3^0 N), 3358s (2^0 N), ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm):1.42-1.68 (m,6H,Piperidine), 2.4 (s,3H,Methyl), 3.35 (m,4H,Piperidine), 3.67 (s,2H,Methylene), 5.81 (s,1H,Ethylene), 6.56-7.78 (d,3H,Benzene), 4.0 (s,1H,Aromatic-C-NH), ^{13}C NMRδ (ppm): 103.3, 108.4, 111.4, 116., 144.35, 152.5, 155.3, 161.4, 167.4, 45.6, 45.6, 25.7, 25.6,44.9, 24.1, 19.1, MS: m/z 184.24, 218.56, 132.34 (Base peak), 300.15 (Molecular ion peak M+H).

2A2, 3-(-(2-oxo-2(piperidinyl)ethyl)amino)-2H-chromen-2-one: $C_{16}H_{18}N_2O_3$, FT-IR (KBr) cm^{-1} 1872 (C=O), 1081 (C-O-C), 1364 (3^0 N), 3352 (2^0 N), ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.42-1.68 (m,6H,Piperidine)2.4 (s,3H,Methyl), 3.35 (m,4H,Piperidine), 3.71 (s,2H,Methylene), 7.03-7.12 (s,2H,Benzene), 2.0 (s,1H,Aromatic-C-NH), ^{13}C NMRδ (ppm):158.23, 116.47, 149.87, 125.98, 131.35, 130.64, 167.75, 120.83, 24.13, 25.68, 25.69, 44.93, 45.62, 45.60, MS: m/z 113.64, 212.45 (Base peak), 287.14 (Molecular ion peak M+H).

4C1, 1-(-(2-oxo-2H-chromen-6-yl)amino)acetyl)piperidine-2-carbonitrile: C_{18} $H_{19}N_3O_3$,FT-IR (KBr) cm^{-1} 3208 (SP^2 C-H), 1830 (C=O), 1082 (C-0-C), 1367 (3^0 N), 3350 (2^0 N), 2500 (CN), ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm):1.77-1.97 (m,4H,Piperidine), 2.41 (s,3H,Methyl), 3.12-3.42 (m,5H,Piperidine), 3.67 (s,2H,methylene), 5.81 (s,1H,-NH), 6.56-7.78 (d,4H,Benzene), ^{13}C NMRδ (ppm) : 161.02, 103.32, 167.74, 116.43, 155.35, 127.47, 144.32, 122.30, 26.85, 30.03, 30.06, 21.14, 49.68, 44.94, MS: m/z 185.43, 220.56, 137.48 (Base peak), 325.14 (Molecular ion peak M+H).

4C2, 1-(-(2-oxo-2H-chromen-3-yl)amino)acetyl)piperidine-2-carbonitrile: C_{17} $H_{17}N_3O_3$, FT-IR (KBr) cm^{-1} 1870 (C=O), 1084 (C-O-C), 1367 (3^0 N), 3350 (2^0 N), 2509 (CN), ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm):1.77-1.97 (m,4H,Piperidine), 3.12-3.42 (m,5H,Piperidine), 3.71 (s,2H,Methylene), 7.03-7.35 (d,5H,Benzene), 2.03 (S,1H,-NH), ^{13}C NMRδ (ppm) : 119.82, 121.93, 149.84, 125.15, 116.44, 167.76, 132.10, 131.39, 158.27, 125.84, 122.38, 30.02, 30.04, 26.83, 49.62, 49.64, 44.98, MS: m/z 187.94, 212.67, 272.48 (Base peak), 312.13 (Molecular ion peak M+H).

IR spectrum of compound 4C1exhibited strong band at 3350 cm^{-1} for the -NH stretching, another strong band at 1830 cm^{-1} for carbonyl group of coumarin ring and 2500 cm^{-1} for nitrile group.^{1}H NMR spectrum of compound 4C1 showed a multiplet resonating between δ 1.77 and 1.97 ppm, whichwas assigned to the four protons of piperidine ring. All aromatic protons observed at δ 6.56-7.78 and -NH at δ 5.81 as a singlet. The

methylene protons were observed as a singlet at δ 3.67 and methyl group at δ 2.41. In the ^{13}C NMR spectrum, thelactone carbonyl carbon of coumarin ring observed at δ 161,all aromatic carbons observed from δ 155-116, methylene carbon at δ 49 and methyl carbon at δ 30.The above spectral analysis suggested successful synthesis of titled compounds 2A1-4C2. This fact was further supported by MS spectra of title compounds.

α-Glucosidase Inhibition Assay

Table 3: Determination of IC_{50} value of piperidinyl coumarin derivatives by α-glucosidase inhibition assay method

Sample	Concentration (µg/ml)	Percentage inhibition (mean ± SEM)	IC_{50} µg/ml
Standard acarbose	50	45.40±0.01	61.89
	100	60.26±0.02	
	150	78.81±0.01	
	200	85.24±0.01	
2A1	50	37.74±0.01	93.2
	100	39.65±0.01	
	150	45.53±0.01	
	200	52.27±0.66	
2A2	50	42.09±0.16	89.4
	100	48.37±0.18	
	150	63.52±0.03	
	200	69.91±0.05	
4C1	50	37.82±0.02	74.5
	100	43.94±0.01	
	150	56.01±0.3	
	200	76.43±0.02	
4C2	50	39.82±0.41	90.5
	100	47.10±0.1	
	150	56.44±0.07	
	200	58.41±0.02	

Table 4: Determination of IC_{50} values of piperidinyl coumarin derivatives by α-amylase inhibition assay method

Sample	Concentration (µg/ml)	Percentage inhibition (mean ± SEM)	IC_{50} µg/ml
Standard (acarbose)	50	38.51±O.27	114.9
	100	44.03±0.5	
	150	56.83±0.38	
	200	73.90±0.25	
2A1	50	22.85±0.22	123.4
	100	38.93±0.26	
	150	48.16±0.42	
	200	59.83±0.23	
2A2	50	31.45±0.36	121.1
	100	35.18±0.25	
	150	52.94±0.29	
	200	68.05±0.25	
4C1	50	37.15±0.26	118.3
	100	43.19±0.01	
	150	57.55±0.28	

	200	71.75±0.11	
4C2	50	31.38±0.02	120.2
	100	42.07±0.17	
	150	51.38±0.02	
	200	61.07±0.17	

The synthesized derivatives were evaluated for α-amylase inhibitiory and α- glucosidase inhibitiory activity as *invitro* method by using acarbose as standard drug. All samples show gradual increase in inhibition of α-amylase and α-glucosidase, where the sample concentration increased from 50 to 200μg/ml. Compound 1-(-(2-oxo-2H-chromen-6-yl)amino)acetyl)piperidine-2-carbonitrile (4C1) displayed significant inhibition of enzyme.Notably, 4C1 (IC_{50} 74.5 and 118.3 µg/ml) had relatively strong activity, which was a little weaker than acarbose (IC_{50} 61.89 and 114.9µg/ml) against α- glucosidase and α-amylase respectively.

Conclusion

Present study involved the preliminary *insilico* screening of various novel analogues for quantifying their drug likeness using Autodock vina software. The analogues with highest doking score and hydrogen bond interaction were taken for wet lab synthesis.Piperidine-3-carboxylicacid was *N*-acylated with chloroacetyl chloride in refluxing THF to afford 1-(2-chloroacetyl)piperidine-3-carboxylic acid Synthesis was carried out by following steps, N- chloro acetylation of piperidine, amide formation,conversion of amide to nitrile group, coupling of piperidine derivative with various amino coumarin derivative. The structure of the desired derivatives were confirmed at each level by spectroscopic studies like, FT-IR, ^{13}C- NMR, ^{1}H-NMR and Mass Spectra. After confirmation of structure, *in vitro* studies of synthesized derivatives were carried out by α-glucosidase inhibition assay and α- amylase inhibition assay method by using acarbose as standard. Among the proposed derivatives 1-(-(2-oxo-2H-chromen-6-yl)amino)acetyl)piperidine-2-carbonitrile (4C1) displayed significant α-glucosidase and α-amylase inhibition activity.Presence of nitrile group on piperidine increase nanomolar absorption and chemical stability. The newly synthesized compounds may provide valuable template for future design and optimization to produce α-glucosidase analoguues.

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