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IN-SILICO DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF PYRROLIDINE-2-CARBONITRILE DERIVED ANTI-DIABETIC AGENTS

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ABSTRACT

The design, synthesis and biological activity studies of series of the novel cyanopyrrolidines type II anti-diabetic agents reported in this paper. Three Dimensional Quantitative Structural Activity , pharmacophore, docking studies used for rational design of molecules, studies revealed that novel substituted cyanopyrrolidines were a promising candidate for further studies. Molecules were synthesized and evaluated for their anti-diabetic activity by using high-fat diet and multiple low doses STZ induced type II diabetes rat model. Amongst all the synthesized compounds 1-(2-(5- methylisoxazol-3-ylamino) acetyl) pyrrolidine-2-carbonitrile, 1- (2-(5-methyl-1, 2, 4-oxadiazol-3-ylamino) acetyl) pyrrolidine-2- carbonitrile and 1-(2-(1,2,4-thiadiazol-5- ylamino)acetyl)pyrrolidine-2-carbonitrile were found to be potent anti-diabetic agents.

Keywords: 3D QSAR; pharmacophore; docking Design; synthesis; pyrrolidine- 2-carbonitrile, acute toxicity; chronic toxicity; anti-diabetic ligands.

INTRODUCTION

Type II diabetes a disorder characterized by impaired management of blood sugar level, is prevalent worldwide, nearly 6 % of the population is affected by this disorder[1]. It's one amongst the quickest growing health issues worldwide and will have an effect on 366 million individuals within the next 30 years if preventive measures aren't enforced within the immediate future[2]. India turning into hub of diabetics[3]. The present oral treatment choices for type II diabetes include bigunides, sulfonylurea or PARR antagonist, glycosidase inhibitors, GLP-1 agonist and also the recently introduced dipeptidyl peptidase-4 (DPP-4) inhibitors[4,5]. DPP-4 inhibitors inhibit the enzyme DPP-4, a serine protease that degrades the incretin hormone, glucagon-like peptide-1(GLP-1), quickly to its inactive form. GLP-1 is free within the gut in response to the intake of food and stimulates insulin synthesis and secretion, whereas inhibiting the discharge of glucagon. Apart from many different helpful effects, GLP-1 regulates insulin in a strictly glucose-dependent manner[6]. Thus, inhibition of DPP-4 has been revealed to expand the half-life of GLP-1and to extend the helpful effects of this incretin secretion[7]. Additionally, DPP-4 inhibitors do not show undesirable side effects, like weight gain and hypoglycemia that are observed with the utilization of other anti-diabetic drugs[8]. Intense research in this field resulted in useful Sitagliptin and vildagliptin DPP-4 inhibitors and other are in pre-registration, e.g., saxagliptin and alogliptin[9]. Variety of review articles are currently out there that cover numerous aspects of DPP- 4 inhibitors extensively[10-15]. Clinical data reveals that the recent DPP-IV inhibitor offers many prospective advantages, counting no or less weight gain and no risk of hypoglycemia. Still, some side effects are with them, including throat infection, gastrointestinal problems like diarrhea and upper respiratory tract infection. Apart from these side effects, reported compounds are of less potent[16]. Hence, there's a necessity to spot new moiety which will not only treat hyperglycaemia but can also correct impaired glucose physiological state and preserve

β-cell function, because patients with freshly diagnosed diabetes have only about 50% normal β-cell function, with more progressive loss over time. Above observations indicates the need of present investigation on design and synthesis of novel cyanopyrrolidine derivatives as anti diabetic agents which will inhibit the action of dipeptidyl peptidase-IV on GLP-1 to achieve control on hyperglycemia without or with minimal adverse effects. If we will place rigid conformation on P2 site of DPP-IV inhibitors pharmacophore then potency of cynopyrrolidine containing DDP-IV inhibitors will increase. With this motivation, we herein disclosed Design, synthesis, and evaluation of novel cynopyrrolidine containing DDP-IV inhibitors.

EXPERIMENTAL

Design of Inhibitors

A library of cyanopyrrolidinesanalogs was designed considering our recently published article on 3D QSAR; pharmacophore modeling studies and other published articles on cyanopyrrolidine derivatives [17]. The basic characteristic used for designing library is illustrated in Fig.-1. To screen out potent analogs from designed library docking studies performed using Vlife MDS suit installed in Dell Inspiron 15 having Windows 8 operating system. Protein Structure and ligand preparation were performed and ligands selections were done by applying Lipinski's Rule of Five. Batch Docking Module of Vlife MDS used for docking[18-25].

Synthesis

Chemicals and solvents were procured from Aldrich India Ltd., E. Merck India Ltd. These solvents and reagents were of LR grade and if necessary purified before use. Melting points were obtained in the laboratory with melting point device by an open capillary method and are uncorrected. The IR,1H NMR and mass spectra obtained on Bruker AT-FT-IR spectrophotometer, NMR spectrometer, and mass spectrometer respectively. To obtain NMR spectra DMSO-d_6 used as solvent and TMS used as an internal standard. The purity of the compounds was checked by thin-layer chromatography. All tested compounds' purity was greater than 95%. The scheme for synthesis shown in Scheme-1.

Synthesis of 1-(2-chloroacetyl) pyrrolidine-2-carbonitrile

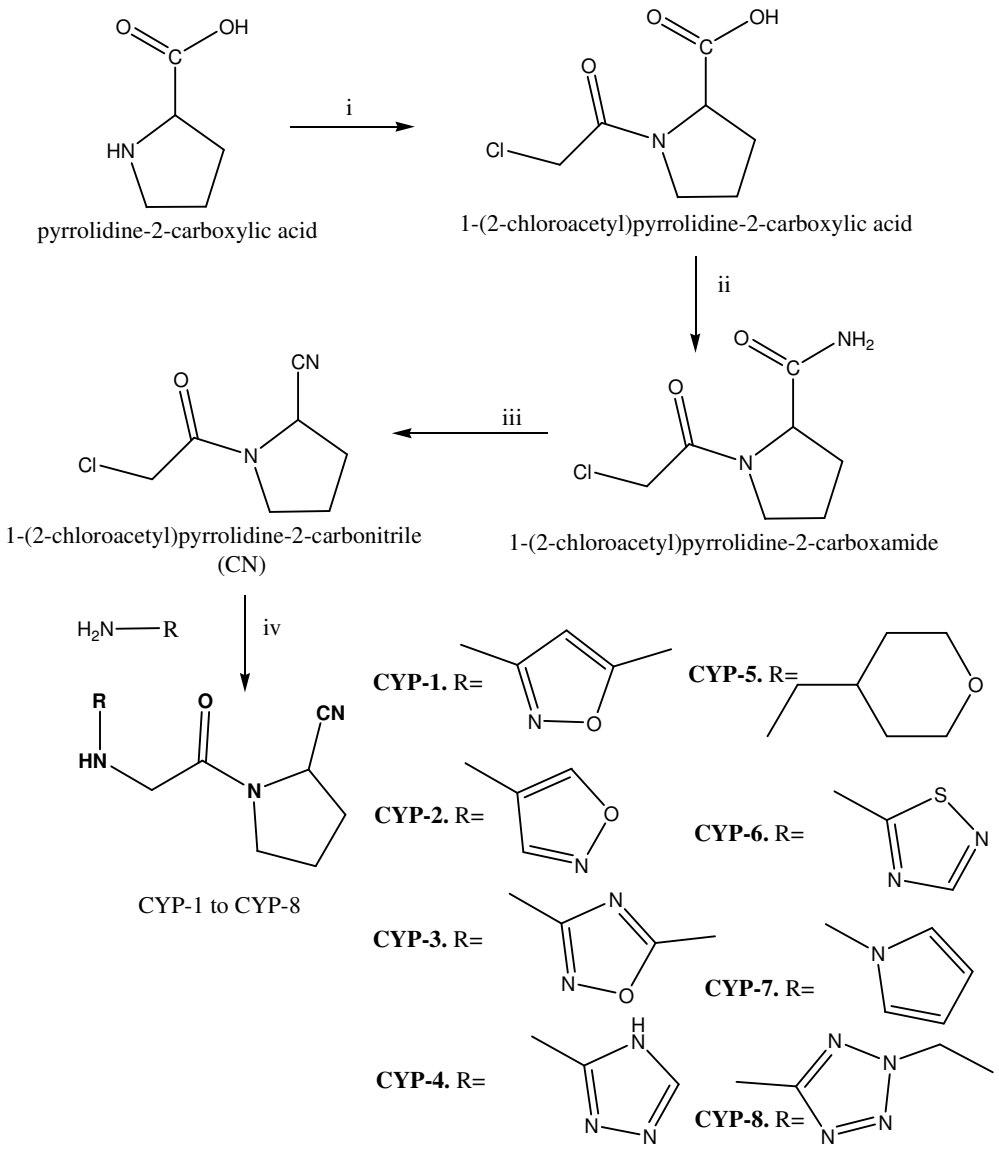
We synthesized key intermediates, 1-(2-chloroacetyl) pyrrolidine-2-carbonitrile (4), from L-proline (1) as per literature protocol (scheme-1)[26]. The pure compound was obtained as a brownish white solid, Yield =55 %; mp = 50-56 0C; Rf=0.6 (Methanol: Chloroform = 8:2); ATR-FT-IR (cm-1): (C-C-H) 2910, (C=C-H) 3052, (C≡N) 2219, (C=O) 1660, (C-N) 1253, 1294, (C-O) 1149, (Cl) 767. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.700.1–2.101(s, 2.17H, CH_2), 2.600 δ (s, 2.27 H, CH_2) 3.520(s, 2.28 H, CH_2) 3.477-4.503 (m, 3.21 H, Cl-CH_2). LC-MS m/z: M + 172 (100%)

General procedure for the synthesis of 1-(2-chloroacetyl) pyrrolidine-2-carbonitrile derivatives (CYP-1 to CYP-8)

The reported method was used for the synthesis of 1-(2-chloroacetyl) pyrrolidine-2-carbonitrile derivatives (CYP-1 to CYP-8)[27, 28]. A 250 ml reactor with a thermometer, condenser and magnetic stirrer was charged with THF (50 ml), powdered K_2CO_3 0.08 mol, 0.05 mol, 1-chloroacetyl-2-cyanopyrrolidine 0.02 mol and KI 0.001 mol. The resulting slurry was heated to reflux until complete conversion by TLC (approx. 2 h). The warm suspension was filtered and the solids washed with 20 ml of THF. Solvents were distilled off to obtain a solid. This solid was suspended in 30 ml of MEK and heated to reflux. The resulting clear solution was allowed to cool and the product crystallized as a white solid. The slurry was stirred at 0° C. for 1 hour, filtered, washed dried under vacuum to obtain the final product.

Synthesis of 1-(2-(5-methylisoxazol-3-ylamino) acetyl) pyrrolidine-2-carbonitrile (CYP-1): White solid compound with 59% yield was obtained, mp = 176-178 ^{0}C; Rf=0.8 (Hexane: Ethyl acetate (9: 1); ATR-FT-IR (cm^{-1}): (C-C-H) 2911, (C=C-H) 2983, (NH) 3357, (C≡N) 2360, (C=O) 1662. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.400.1δ (s, 2.12H, CH_2), 2.120-2.270 (d, 2.02 H, CH_2) 2.779 δ (s, 3.10 H, CH_3)

3.635- 3.662 (d, 2.11 H, CH_2), 4.116-4.140 (s, 2.87H, C-CH_2- NH). LCMS m/z: 234 (100%), 235 (12%), 234 (2%), 233 (8%).



Scheme-1: Synthesis of 1-(2-chloroacetyl) pyrrolidine-2-carbonitrile derivatives. Reagents and Conditions: (i) Chloroacetyl chloride, THF, reflux, 2 h.; (ii) **1:** DCC, DCM, stir, RT, 2 h.; **2:** NH_4HCO_3 , stir, RT, 1h.; (iii)**1:** TFA, THF, 15^OC- RT, 1 h.; **2:** NH_4HCO_3 , $C_6H_5CH_3$, RT, 1 h.; (iv) K_2CO_3, KI, THF, reflux, 2 h.

Synthesis of 1-(2-(isoxazol-4-ylamino) acetyl) pyrrolidine-2-carbonitrile (CYP-2): White solid compound with 68% yield was obtained, mp = 130-136^{0}C; Rf=0.7 (Hexane: Ethyl acetate (9: 1); ATR-FT-IR (cm^{-1}): (C-C-H) 2907, (C=C-H) 2999, (NH) 3280, (C≡N) 2212, (C=O) 1654. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.920 (s, 2.01H, CH_2), 2.620-2.650 (s, 2.11 H, CH_2) 3.620-3.629 (m, 4.17 H, CH_2) 4.309 (s, 0.71 H, -NH-), 4.915- 5.062 (d, 3.10 H2, CH). LCMS m/z: 220 (100%), 221 (10.5%), 222(7%)219 (5%), 218(1%)

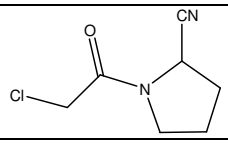
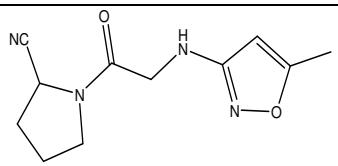
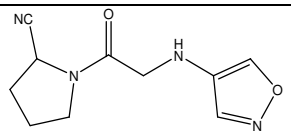
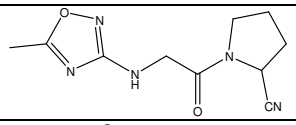
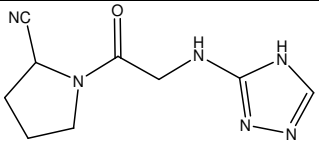
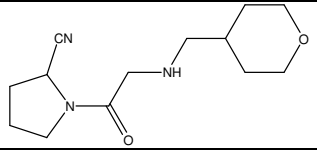
Synthesis of 1-(2-(5-methyl-1, 2, 4-oxadiazol-3-ylamino) acetyl) pyrrolidine-2- carbonitrile (CYP-3): White solid compound with 58% yield was obtained, mp = 118-120 ^{0}C; Rf=0.7 (Hexane: Ethyl acetate (8: 2); ATR-FT-IR (cm^{-1}): (C-C-H) 2907, (C=CH) 2999, (NH) 3285 (C≡N) 2227, (C=O) 1654. ^{1}H NMR

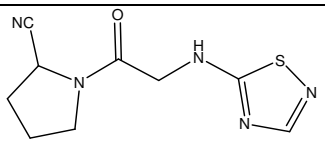
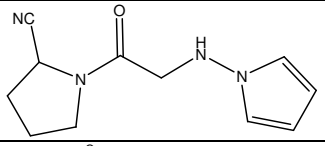
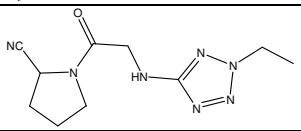
(300 MHz, $CDCl_3$): δ (ppm) 1.420- 1.510 (d, 2.00 H, CH_2), 2.120 (d, 2.82 H H, CH_3) 2.410 (s, 2.13 H, CH2) 3.540 (t, 3.83 H, CCH2-NH-). 4.413-4.439 (d, 0.83 H, -NH-), 4.820-4.917 (m, 1.30H, CH2), LCMS m/z: m/e: 235 (100.0%), 236 (11.0%), 237.11(2%)

Synthesis of 1-(2-(4H-1, 2, 4-triazol-3-ylamino) acetyl) pyrrolidine-2-carbonitrile (CYP-4): White solid compound with 59% yield was obtained, mp = 120-122 ^{0}C; Rf=0.7 (Hexane: Ethyl acetate (8: 2); ATR-FT-IR (cm^{-1}): (C-C-H) 2883, (C=C-H) 3003, (NH) 3279, (C≡N) 2245, (C=O) 1666. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.441-2.632 (d, 3.82 H, CH_2), 3.672 (d, 1.83 H, CH_2) 4.021 (d, 1.10 H, NH_2) 4.141 (s, 2.02 H, C-CH_2- NH-), 4.404 (s, 0.77 H,-NH-), 4.844 (s, 1.23H, -CH-). 7.646 (s, 0.71H, -CH-). LCMS m/z: m/e: 235 (100.0%), 236 (11.0%), 237.11(2%)

Synthesis of 1-(2-((tetrahydro-2H-pyran-4-yl) methylamino) acetyl) pyrrolidine-2- carbonitrile (CYP-5): White solid compound with 80% yield was obtained, mp = 198-202^{0}C; Rf=0.8 (Hexane: Ethyl acetate (9: 1); ATR-FT-IR (cm^{-1}): (C-C-H) 2926,, (C=CH) 2991, (NH) 3325, (C≡N) 2204, (C=O) 1660, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.308.1–1.317 (m, 4.97H, CH_2), 2.120-2.341 (m,7.02 H, -NH-,CH_2) 3.287-3.341 (d, 2.29 H, CH_2) 3.513 (s, 1.12 H, -CH_2-NH-), 3.598 (d, 3.74H, CH_2), 4.607 (s, 1.03 H, CH_2). LCMS m/z: 220 (100%), 221 (10%), 222 (9%) 223 (2 %)

Table-1: Physiochemical characterizations of synthesized compounds

S. No.	Code	Structural Formula	Chemical Name
1	CN		1-(2-chloroacetyl)pyrrolidine-2-carbonitrile
2	CYP-1		1-(2-(5-methylisoxazol-3-ylamino)acetyl)pyrrolidine-2-carbonitrile
3	CYP-2		1-(2-(isoxazol-4-ylamino)acetyl)pyrrolidine-2-carbonitrile
4	CYP-3		1-(2-(5-methyl-1,2,4-oxadiazol-3-ylamino)acetyl)pyrrolidine-2-carbonitrile
5	CYP-4		1-(2-(4H-1,2,4-triazol-3-ylamino)acetyl)pyrrolidine-2-carbonitrile
6	CYP-5		1-(2-((tetrahydro-2H-pyran-4-yl)methylamino)acetyl)pyrrolidine-2-carbonitrile

7	CYP-6		1-(2-(1,2,4-thiadiazol-5-ylamino)acetyl)pyrrolidine-2-carbonitrile
8	CYP-7		1-(2-(1H-pyrrol-1-ylamino)acetyl)pyrrolidine-2-carbonitrile
9	CYP-8		1-(2-(2-ethyl-2H-tetrazol-5-ylamino)acetyl)pyrrolidine-2-carbonitrile

CN= 1-(2-chloroacetyl) pyrrolidine-2-carbonitrile
CYP= Cyanopyrrolidines

Synthesis of 1-(2-(1,2,4-thiadiazol-5-ylamino) acetyl) pyrrolidine-2-carbonitrile (CYP-6): White solid compound with 90% yield was obtained, mp = 130-134 ^{0}C; Rf=0.6 (Hexane: Ethyl acetate (9: 1); ATR-FT-IR (cm^{-1}): (C-C-H) 2919, (C=C-H) 3068, (NH) 3295 (C≡N) 2218, (C=O) 1672, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.371–2.350 (d, 3.42H, CH_2), 3.550 (m, 4.27 H, CH_2) 4.367-4.394 (d, 1.20 H, -NH-) 4.474-4.999 (m, 1.17 H, CH_2), 7.169 (m, 1.03 H, CH) LCMS m/z: 251.16 (100%), 252 (14%), 253 (3%), 254 (1%)

Synthesis of 1-(2-(1H-pyrrol-1-ylamino) acetyl) pyrrolidine-2-carbonitrile (CYP-7): White solid compound with 88% yield was obtained, mp = 110-112 ^{0}C; Rf=0.7 (Hexane: Ethyl acetate (9: 1); ATR-FT-IR (cm^{-1}): (C-C-H) 2888, (C=C-H) 3090, (NH) 3696 (C≡N) 2261, (C=O) 1661. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.432–1.533 (d, 1.39 H, - NH-), 2.050 (s, 1.91 H, CH_2) 2.869-3.059 (s, 2.21 H, CH_2) 3.222-3.572 (d, 4.14H, CH_2). 4.150 (s, 1.07 H, CH_2) 6.352 (s, 4.13 H, CH), LCMS m/z: 237 (100%), 238 (10.5%), 239 (4%)

Synthesis of 1-(2-(2-ethyl-2H-tetrazol-5-ylamino) acetyl) pyrrolidine-2-carbonitrile (CYP-8): White solid compound with 86% yield was obtained, mp = 150-152 ^{0}C; Rf=0.8 (Hexane: Ethyl acetate (8: 2); ATR-FT-IR (cm^{-1}): (C-C-H) 2871, (C=C-H) 3055, (NH) 3301, (C≡N) 2267, (C=O) 1655. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.210 (s, 3.12 H, CH_3), 2.050 (m, 3.53 H, CH_2) 3.151 (s, 2.10 H, CH_2) 3.567-3.797 (m, 3.89 H, Cl-CH_2), 4.110 (s, 0.97 H, NH), 4.472-4.511 (s, 1.09 H, CH_2). LCMS m/z: 218(100%), 219 (12%), 220 (2%), 221 (1%)

Pharmacological Evaluation

Protocol for animal studies was approved by the Institute Animal Ethics Committee (IAEC), Satara College of Pharmacy, Satara, Maharashtra, India (Ref no. SCOP/IEAC/43/14-15) and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines were followed for the maintenance of experimental animals.

Table-2: Selected compounds for synthesis with code, formula and chemical name

S. No.	Name of compound	Mole. Formula (Mole. Wt.)	M.P. ^{0}C	% Yield	rf value	Elemental Analysis Calculated (%)		
						C	H	N
1	CN	$C_7H_9ClN_2O$ 172.61	50-56	55	0.6	48.71	5.26	16.23
2	CYP-1	$C_{11}H_{14}N_4O_2$ 234.25	176-178	59	0.8	56.40	6.02	23.92

3	CYP-2	$C_{10}H_{12}N_4O_2$ 220.23	130-136	68	0.7	54.54	5.49	25.44
4	CYP-3	$C_{10}H_{13}N_5O_2$ 235.24	118-120	58	0.7	51.06	5.57	29.77
5	CYP-4	$C_9H_{12}N_6O$ 220.23	120-121	59	0.7	49.08	5.49	38.16
6	CYP-5	$C_{13}H_{21}N_3O_2$ 251.32	198-202	80	0.8	62.13	8.42	16.72
7	CYP-6	$C_9H_{11}N_5OS$ 237.28	130-134	90	0.6	45.56	4.67	29.51
8	CYP-7	$C_{11}H_{14}N_4O$ 218.26	110-112	88	0.7	60.53	6.47	25.67
9	CYP-8	$C_{10}H_{15}N_7O$ 249.27	150-152	86	0.8	48.18	6.07	39.33

Type II Anti-diabetic activity by using high-fat diet and multiple low-dose streptozotocin-induced type II diabetes rat model

40 Wistar rats were divided into two dietary regimens; normal pellet diet (6 rats) and high-fat diet regimen (34) given high-fat diet. High-fat diet prepared in-house as per the literature search (Protein: casein 254.1g/kg, lipid: lard 364.5 g/kg and carbohydrates: Corn starch 305 g/kg + sucrose33.8 g/kg) for 4 weeks and injected for next 2 days intraperitoneally with 30 mg/kg doses of STZ whereas the control rats were given vehicle citrate buffer (pH 4.4) in a dose volume of 0.25 ml/kg IP, respectively. After 72 hrs of STZ injection, all the rats fasted for 12 hours; the fasting blood glucose determined and rats with 300mg/dl blood glucose were considered as diabetic so used in further study. Out of 40 animals, 2 died before grouping and 2 are omitted from the study because of mild hyperglycemia. Remaining 30 diabetic animals were separated into 5 groups each group having 6 rats of either sex. Group 1: Vehicle Control rats, fed normal pellet diet, received only single i.p. injection of citrate buffer (1 ml/kg) and served as Vehicle control group. Group 2: diabetic rats received Vildagliptin as standard drug. Group 3: Diabetic control rats received the only vehicle and served as diabetic control group. Group 4 (MTD): diabetic rats received Maximum Therapeutic Dose Group 5 (MTD/ 2): diabetic rats received half of Maximum Therapeutic Dose Group. 6 (MTD* 2): diabetic rats received double of Maximum Therapeutic Dose[29, 30].

Table-3: Effect of CYP-1, CYP-3 and CYP-6 on Body weight and Blood glucose

Para.	Group	CYP-1		CYP-3		CYP-6	
		0	90	0	90	0	90
BW (g)	Control	256±6.1	36.37±4.2	251.3±1.6	380.2±2.9	253.7±1.4	323.7±5.7
	Diabetic	254.5±1.3	163.2±4.5^{c}	278.7±16^{a}	162.3±4.9^{c}	243.5±7.6	167.7±4.9^{c}
	Standard	251.8±1.8	311±2.7^{c}	249.8±4.2^{a}	316.5±3.8^{c}	239.7±1.3	306.7±4^{c}
	MTD	255±2.8	308±2.4^{c}	254.3±2.8	314±4.1^{c}	248±2.2	235.5±7.3^{c}
	MTD/2	250.7±3.7	280±5^{c}	255±1.5	280.7±2.6^{c}	250.2±1.4	275.2±1.4^{c}
	MTD*2	251.7±1.8	306.7±4.1^{c}	252±2^{a}	325.5±3	254.2±1.1	304.7±2.8^{c}
BG (mg/dl)	Control	113±4.4	115±5.5	99±7.7	100.3±3.4	118.8±3	117.7±6.5
	Diabetic	326.8±2.3^{c}	254.8±1.9^{c}	349.8±7.3^{c}	356.5±5.9^{c}	342.5±4.5^{c}	254.8±1.2^{c}
	Standard	344.3±3.7^{a}	115.7±2.2^{c}	356.8±2.7^{a}	142.3±17.7^{c}	336.8±8.6	123.5±8.1^{b}
	MTD	339.8±4.3	104.5±2.7^{c}	353.5±7.4	105.5±3.1^{c}	341.5±3.2	114.2±6.4
	MTD/2	338.5±4.5	134±1.1^{c}	342.2±6.7	177.7±14.9^{c}	335.2±6.7	184.8±15.9
	MTD*2	344.7±2.8^{b}	98±5.1^{c}	354±11.3	108.5±2.6^{c}	342.8±6.4	104±5.9^{c}

All the data were expressed as mean ± S.E.M. (n=6). Statistical significance was determined by one way ANOVA (Analysis of Variance) followed by Dunnet multiple comparison tests by using the Graph pad Prism version 6. a= P<0.05, b=P<0.01 and c= P<0.001 were regarded as significant.

RESULTS AND DISCUSSION

All the compounds were designed on basis of pharmacophore and SAR studies. The rational design illustrated in Fig.-1. In designing molecules aliphatic, hydrogen bond donor, hydrogen bond acceptor and aromatic pharmacophore features were considered.

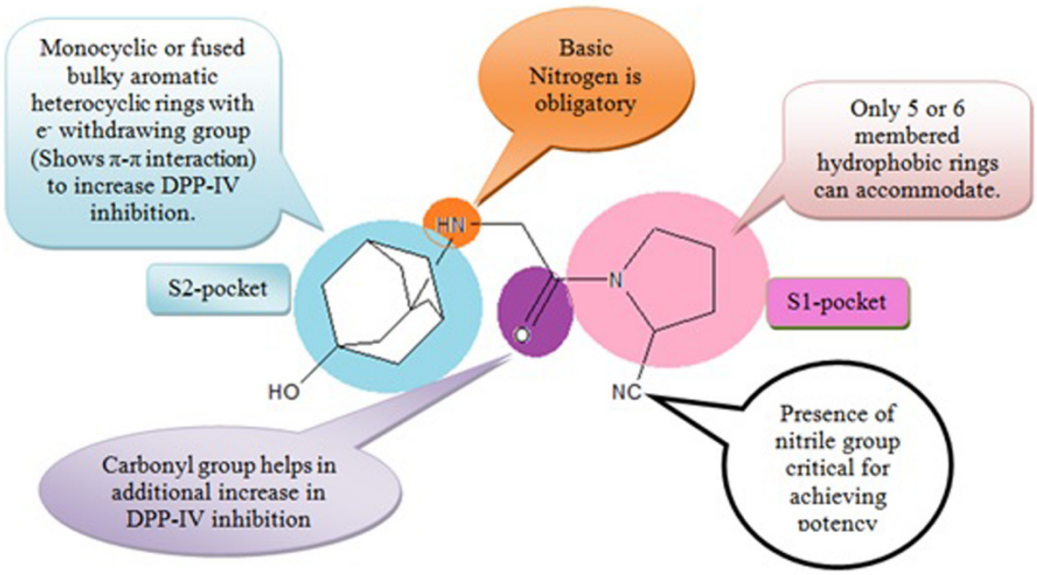


Fig.-1: Design of novel Cyanopyrrolidines

When molecules in literature compare with a designed set of molecules it was found that designed set molecules possess similar structural features. Designed set molecules and molecules in literature contain nitrile group, a pyrrolidine ring, a carbonyl group and an amine group in common.

Type II Anti-diabetic Activity Studies

Type II Anti-diabetic activity by using high-fat diet multiple low dose STZ diabetes animal models

CYP-1, CYP-3 and CYP-6 were found to be equally effective in decreasing blood levels as Vildagliptin. CYP-1, CYP-3 and CYP-6 showed dose dependant anti-diabetic activity with the ability to restore weight loss occurred in diabetics.

Histopathology of Pancreas

Histopathological changes in the pancreas were illustrated in Fig.-2. In Normal control (A) acinar cells were seen to be normal. The islet present in adequate proportion beta cells. There was no evidence of infiltration or fibrosis. MTDx2 (B) demonstrates a section of the regular pancreas of the rat. It explains the normal acinar pattern, islet cells and no evidence of infiltration. Numbers of islets of β-cells were found to be increased as compared to a therapeutic dose. Mainly regeneration of pancreatic β-cells was observed. The acinar cells are seen to be normal.

CONCLUSION

Rational drug design including 3D QSAR, pharmacophore modeling and docking studies provided a list of eight potential novel type II antidiabetic agents. Screened compounds CYP- 1 to CYP-8 were synthesized. The purity of the compounds was accessed by thin-layer chromatography and melting points. Structures of all were confirmed by interpretation of IR, ^{1}H NMR and Mass spectra. All the synthesized cyanopyrrolidine derivatives subjected to pharmacological evaluation. Type II anti-diabetic activity of

synthesized compounds was performed in high-fat diet and multiple low-dose streptozotocin-induced type 2 diabetes rat model in which synthesized drugs tested in three dose levels MTD, MTD/2 and MTDx2. CYP-1, CYP-3 and CYP-6 found to be promising one in decreasing increased serum glucose level as standard vildagliptin.

All these observations and results it can be concluded that design and synthesis of novel type II anti diabetic's agent were carried out successfully with fruitful results as CYP-1, CYP-3 and CYP-6 showing outstanding results in animal models they can be the most promising candidates for human studies.

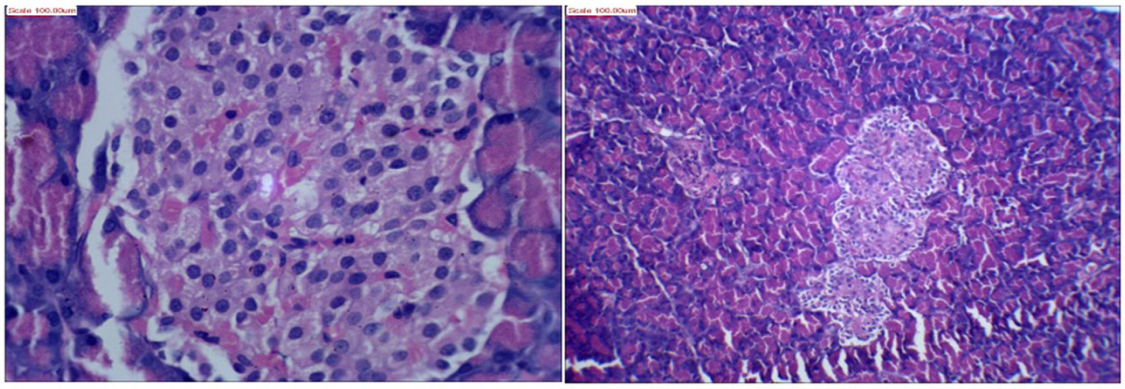


Fig.-2: Microphotographs of Histopathological study of pancreas: A-Control group B- MTD*2

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