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Design and synthesis of novel heterocyclic compounds as a PPAR-γ agonist

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ABSTRACT

The multifarious metabolic syndrome, diabetes mellitus (DM), is a diseaseof concern all over the world and is approximate to affect 400 million individuals by the 2020. Several classes of drugs at the moment are available to lessen hyperglycemia in diabetes mellitus especially in Type-II. These drugs mostly have dangerous side effects and thus incisive for a new class of compounds is necessary to conquer this inconvenience. A series of 6 novel 5-nitrobenzofuran-2yl-carbamides derivatives were synthesized and molecular docking studies were performed on PPAR-γ target using (PDB code-4rfm).The preparation of5-nitro-1-benzofuran-2-carbohydrazide(4) on action with acetic acid, 1, 4-diaxone and sodium nitrite resulted in 5-nitro-1-benzofuran-2-carbonyl azide (5).The related compound (5) on action with substituted aromatic substituted amines undergoes Curtis type of rearrangement to give 5-nitro-*N*-(sub. carbamoyl)-1-benzofuran-2-carboxamide.The characterization and identification of prepared compounds were identified on the basis of NMR, IR, Mass and elemental analysis. Docking study of targeted compounds were done using software Autodock Tools 1.5.6 and visualisation done by Discovery Studio 3.5 software (Accelrys Inc. San Diego, CA USA). Molecular docking studies, the binding energies are determined to be in the range of –5.90 to –9.80 kcal/mol, with peroxisome proliferator activated receptor γ (PPAR-γ) receptors (PDB ID: 4RFM). The prepared compounds have been studied for their oral glucose tolerance test to distinguish the effect on plasma glucose level.

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INTRODUCTION

Worldwide researchers and scientist are trying to manufacture new drugs moieties with improved pharmacokinetic and pharmacodynamic properties with lesser unfavourable effects.

The available anti-diabetic agents include biguanides, sulfonylureas, glycosidase inhibitors, thiazolidinediones, and DPP-4 inhibitors. These antidiabetic agents containing drugs are commonly used to manage hyperglycemia, but have proved unsuccessful to modify the course of diabetic complications and have inadequate use because of unwanted side effects and high rates of inferior failure. The literature reviews and survey reveals that the benzofuran boast to be high-quality bioactive and perceptive molecules. Benzofuran is heterocyclic containing compounds of enormous significance in the field of pharmacy and various different fields such as cinematography, crop growing, medical sciences etc. (Vaidya *et al.*, 1975;

Ghabgharan *et al.*, 1976).

Benzofuran and its similar derivatives have been suggested to possess large variety of pharmacological and biological activities such as antibacterial, anti-fungal, anti-diabetic, anti- inflammatory, analgesic, anti-depressant, insecticidal, central nervous system stimulants and depressant effects etc (Basawaraj *et al.*, 2007, 2001). Having understood the qualities of benzofuran with the aforesaid observations and explanations, it is of interest to synthesize pharmacological and biological study and their evaluation to arrive a number of benzofuran derivatives (Basavaraj and Agasimundin, 2002).

The present research plan is to amalgamate some substituted benzofuran derivates and their pharmacological and biological activities (Mahajan *et al.*, 1976; Basavaraja and Agasimundin, 1983). Different substituted alcohols, other phenols and appropriate amines were treated with substituted novel benzofuran moiety to provide different derivatives (Basawaraj *et al.*, 2001).

The final structures of the prepared compounds were identified and confirmed by Infra Red spectroscopy and 1H-Neuclear Magnetic Resonance Spectroscopy (Sangapure and Basawaraj, 2004). The proposed and planned compounds were screened for anti-diabetic activity using PPAR-γ as at target with the standard drugs and STZ induced rat model in the well operational and developed pharmacology laboratory by using standard appropriate methods (Zambare *et al.*, 2019; Bhole *et al.*, 2019).

MATERIALS AND METHODS

Melting point was identified by ANA Lab instrument, Thermocal and is uncorrected. Infra Red spectroscopy were recorded in KBr on instrument like SHIMADZU FT-IR version8400S and prepared compound were recorded on FT-NMR BRUCKER spectrometer version 500 MHz PMR spectra at the same frequency using DMSO and TMS used as internal standard.

Preparation and Identification procedure of 5-Nitrosalicylaldehyde (2):

Salicylaldehyde (25.0 gm, 0.2 mol) in 100 ml of glacial acetic acid. Added gradually 48.3 gm of calcium nitrate tetra hydrate (48.3gm, 0.2 mol) was allowed to dissolve. It was heated gradually to reflux on hot plate with continuous stirring. Heated under reflux approximately for about 3 hours. At room temperature, cooled it, poured in RBF containing 500ml ice-cold water contained in 1L beaker with continuous stirring.

These solid precipitates were filtered under vacuum using suction pump and dried under air. The solid was dissolved using ethyl acetate and the insoluble were filtered under vacuum. The ethyl-acetate filtrate was dried over powder of sodium sulphate and evaporated under given reduced pressure to get yellow coloured solid. Melting point was 123-124ºC; the yield is72.3% (Basawaraj *et al.*, 2007).

Preparation and Identification procedure of ethyl 5-nitro-1-benzofuran-2-carboxylate (3):

Mixture of 5-nitrosalicylaldehyde (2) (3.00gm,0.017mol) was dissolved in acetone (40ml), add potassium carbonate (6gm) and other reagent diethyl bromo-malonate (4.47gm,0.017mol) respectively in a 100 ml flask. Heated, reflux it on water bath, maintained the temperature up to 12 hours. The completion of the reaction was observed by using TLC. When the reaction was complete, cooled at room temperature, mixture is filtered by vacuum under suction, potassium salts were washed with dry ether as a solvent.

The dry compounds salt was added in water and cooled thoroughly by ice-cold water. The suspension of compounds was carefully acidified with dilute hydrochloric acid and the Ethyl 5-nitrobenzofuran-2-carboxylate solids were collected and separated by filtration. Methanol used for recystallizing the product and to acquire pure compound 3, as yellow crystal. Melting point of prepared compounds were observed between 145-147ºC; the yield is 52% (Basawaraj *et al.*, 2001; Sangapure and Basawaraj, 2004).

Synthesis of 5-Nitrobenzofuran-2-carbohydrazide (4):

Ethyl 5-nitrobenzofuran-2-carboxylate (3) (1.0gm, 0.004 mole) was dissolved in 5-ml methanol, added Hydrazine hydrate (0.25gm,0.004mol). Heated to reflux and maintained for 2 hours. The solid product was insoluble in methanol starts precipitating. The completed reaction was examined by TLC. The solvent was allowed to evaporate to get a solid product, water was added to remove excess hydrazine hydrate and extracted using ethyl acetate. Layer of Ethyl acetate was washed using water and dried over sodium sulphate powder and evaporated to get solid final compound. Melting point is 252-2540C; the yield is 60.63% (Basawaraj *et al.*, 2001; Sangapure and Basawaraj, 2004).

Synthesis of 5-Nitrobenzofuran-2-carboxyazide(5):

5-Nitrobenzofuran-2-carboxyhydrazide (4) (5.0gm,0.02mole)was dissolved in a equimolar

Table 1: Physicochemical parameters of Benzofuranderivatives 6(a-f)

Compoun	Molecular Formula	Molecular weight	Melting point (^{0}C)	% Yield	CHN analysis		
					C %	H %	N%
6a	$C_{15}H_{11}N_3O_4$	298	230-233	63.4	60.57	3.74	14.16
6b	$C_{16}H_{13}N_3O_4$	312	240-242	71.1	61.72	4.25	13.54
6c	$C_{16}H_{13}N_3O_4$	312	283-285	74.3	61.76	4.18	13.49
6d	$C_{16}H_{13}N_3O_5$	327	250-251	68.4	58.73	3.98	12.86
6e	$C_{16}H_{13}N_3O_5$	327	220-223	69.4	58.69	4.03	12.83
6f	$C_{15}H_{10}ClN_3O_4$	331.5	222-224	78.3	54.29	3.06	10.71

Table 2: Spectral data of Benzofuran derivatives 6(a-f)

Compound	IR bands (In cm^{-1})	Types of vibrations	δppm	Nature of proton
6a	3360,1715, 1430, 2910	(-NH-),(>C=O), (-C=C-), Aromatizing	—-	—-
6b	3290,1650, 1470, 3080	(-NH-),(>C=O), (-C=N-), Aromatizing	9.05, 8.90, 6.6-8.4, 2.3	1H, NH 1H, NH 7H, Ar-H 3H, CH_3
6c	3280,1670, 1450, 3060	(-NH-),(>C=O), (-C=N-), Aromatizing	9.1, 9.0, 6.9-8.7, 2.1	1H, NH 1H, NH 7H, Ar-H 3H, CH_3
6d	3410,1640, 1470, 3080	(-NH-),(>C=O), Ar-(C=C), Aromatizing	—-	—-
6e	3420,1620, 1530, 3130	(-NH-),(>C=O), Ar-(C=C), Aromatizing	—-	—-
6f	3380,1720, 1430, 3030	(-NH-),(>C=O), Ar-(C=C), Aromatizing	—-	—-

Table 3: Molecular docking study of compounds (6a-6f)

Compound Code	R-(Substituted Benzaldehyde)	Binding Energy (Kcal/mol)	Inhibition constant (Nm)	No. of H Bonds
6a	-C_6H_5	-5.90	8.85	2
6b	-$C_6H_4CH_3$(O)	-8.20	16.46	2
6c	-$C_6H_4OCH_3$(P)	-6.90	11.18	1
6d	-$C_6H_4OCH_3$(P)	-4.50	2.07	2
6e	-$C_6H_4OCH_3$(O)	-7.28	16.64	2
6f	-C_6H_4Cl	-9.28	19.64	2
Std	Glibenclamide	-11.25	17.63	2

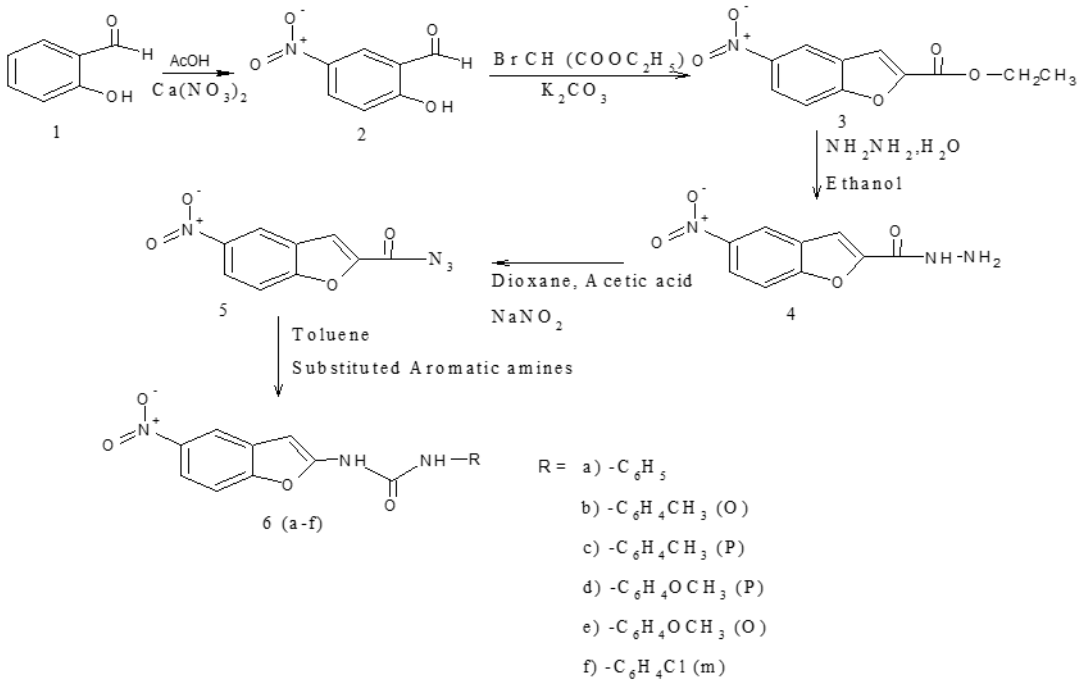

Figure 1: Synthetic scheme of preparation of Benzofuran derivatives

Table 4: Antidiabetic effect by Oral Glucose Tolerance Test

Group	R	Treatment (mg/kg)	Blood Glucose Concentration (mg/dl)		
			0 min.	60 min.	120 min.
Normal Control (Normal Saline)	-	10ml/kg	72.16±0.52	95.20±0.70	84.01±0.65
6a	$-C_6H_5$	200 mg/kg	82.10±0.75	100.10±0.52	92.15±0.50
6b	$-C_6H_4CH_3$(O)	200 mg/kg	78.60±0.34	96.92±0.46	86.84±0.42
6c	$-C_6H_4OCH_3$(P)	200 mg/kg	80.65±0.50	98.33±0.63	99.66±0.52
6d	$-C_6H_4OCH_3$(P)	200 mg/kg	82.45±0.49	92.22±0.70	82.81±0.77
6e	$-C_6H_4OCH_3$(O)	200 mg/kg	76.12±0.56	98.86±0.55	86.81±0.48
6f	$-C_6H_4Cl$	200 mg/kg	76.86±0.35	96.45±0.36	86.31±0.32
Standard (10 mg/kg)	Glibenclamide	200 mg/kg	50.41±0.44	70.55±0.41	60.65±0.45

mixture of (30ml) of pure glacial acetic acid and (30ml)of1,4-dioxane and cooled at 0^0C using ice bath containing salt. An ice-cold sodium nitrite solution (1.6 gm, 0.02 mole) in water (10 ml) was added in small portions while stirring vigorously, the temperature of the mixture was maintained below 2ºC. When the addition was completed, reacted mixture was allowed to stand at room temperature for about 30 min and then cream colour solid that precipitatesd was collected, washed few times in cold water. In desiccators, solid compounds were dried and immediately used in next step reaction. Melting point is 95-97ºC; the yield is 57.25% (Basawaraj *et al.*, 2007, 2001).

General procedure And identification for the preparation of aryl-5- nitro benzofuran -2- carbamides. 6(a-f):

A mixture of 5- Nitrobenzofuran-2-carboxyazide (5) (0.3 gm, 0.0013 mole), suitable substituted amine (0.0013 mole) and anhydrous toluene (15 ml) were heated and reflux at 120ºC by using oil bath for 4 hours. Completed reaction was observed under TLC. Recrysatllised from ethanol. Report final yield (Basawaraj *et al.*, 2007, 2001). The systematic scheme for the preparation of benzofuran mentioned in (Figure 1). Physicochemical and analytical data of the synthesized compound thus prepared and depicted in (Table 1) and (Table 2).

Molecular Docking study

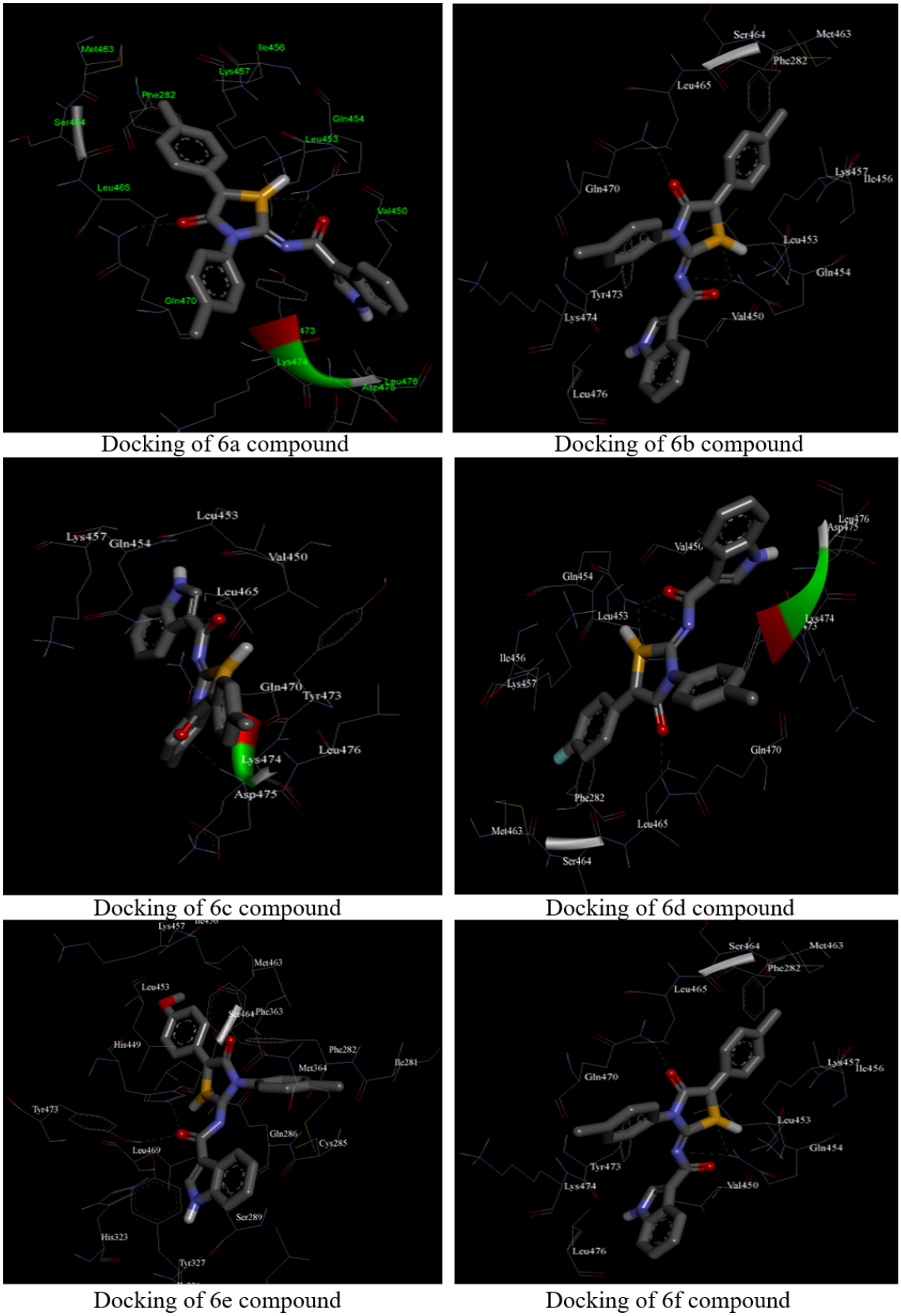

Figure 2: Images of the compounds (6C) in PPAR-γ active site

Docking study of targeted compounds were done using software Autodock Tools 1.5.6 and visualisation done by Discovery Studio 3.5 software (Accelrys Inc. San Diego, CA USA) depicted in (Figure 2), (Saptarini *et al.*, 2014; Darwish *et al.*, 2018). All dock score were performed to inspect the complete intermolecular interaction between the ligand-target proteins (Zapata-Sudo *et al.*, 2012; Kharbanda *et al.*, 2015). The observed binding energies takes place between ligand and receptors were recorded in (Table 3).

Oral glucose tolerance test

All the prepared compounds were first of all evaluated for the stage of oral glucose tolerance test (OGTT) to distinguish the effect on plasma glucose level (Dixit and Saxena, 2008). The compounds efficacies 6a-6f were compared by standard drug glibenclamide (Semple, 2006; Janani and Kumari, 2015). The results and analysis of the compounds showed that all the six compounds (6a, 6b, 6c, 6d, 6e and 6f) does not show significant antidiabetic compared to standard drugs. The results are mentioned in (Table 4).

RESULTS AND DISCUSSION

A new series of 5-nitrobenzofuran carbamides derivatives is prepared and characterized, analysed by spectroscopic techniques Infrared, 1H NMR, and LC Mass spectra. All the compounds 6a-6f do not show the significant activity as compared to standard glibenclamide. According to molecular docking studies, the binding energies are determined to be in the range of –5.90 to –9.80 kcal/mol, with peroxisome proliferator activated receptor γ (PPAR-γ) receptors (PDB ID: 4RFM). All the compound do not exhibits the binding affinity. The accumulated data can be helpful in designing and optimizing the studied hybrid molecules as new oral antidiabetic agents.

CONCLUSION

As we have prepared the 5-nitrobenzofuran carbamides derivatives but the entire compound does not produce any significant activity for the antidiabetic study. So present derivatives not being suitable for the antidiabetic activity.

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