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Synthesis, molecular docking and evaluation of hypolipidemic activities of novel benzophenonecarboxamide derivatives

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Fibrates are well known hypolipidemic agents and act by activating Peroxisome Proliferator-Activated Receptors (PPAR); this family of receptors is the main regulator for fatty acid metabolism. In the present study, a total of six novel benzophenonecarboxamide derivatives (**3-6, 9** and **10**) have been synthesized and evaluated for their hypolipidemic activity. Interestingly, compounds **4** and **6** show promising hypolipidemic activity and lower the level of TG by 71% and LDL-C by 26% and 29% respectively. Further, molecular docking studies have been carried out to gain insight into the binding interactions of all the newly synthesized compounds inside the PPARα receptor and the results are in consonance with the biological activity. The encouraging *in vivo*hypolipidemic activity of compounds **4** and **6** by lowering LDL-C levels as well as enhancing HDL-C indicates that these compounds can serve as promising lead compounds for further investigations for the development of novel hypolipidemic agents.

Keywords: Fibrates, PPARα, *in vivo*, hypolipidemic, benzophenone, molecular docking

Hyperlipidemia and atherosclerosis are the main underlying cause for the development of cardiovascular diseases which is recently being considered as the main leading cause of death worldwide[1]. Peroxisome proliferator-activated receptors (PPAR-α, β, δ and γ) are members of the ligand-activated nuclear receptor super family, considered as the key transcriptional regulators in fatty acids (FA) metabolism[2]. PPARs are important targets for drugs used in the treatment of atherosclerosis, dyslipidaemia, obesity, type-II diabetes, and other diseases caused by abnormal regulation of glucose and lipid metabolism. PPARs have recently drawn increased attention as a drug discovery target by regulating glucose and lipid metabolism[2]. PPAR-α primarily regulates fatty acid oxidation in addition to their role as regulators for many target genes such as apolipoprotein AI (Apo AI)[3], apolipoprotein CIII (Apo CIII)[4], apolipoprotein AV (Apo AV)[5], phospholipid transfer protein (PLTP)[6] and scavenger receptor class B, type I (SR-BI) in liver[7] that are intimately involved in lipoprotein metabolism.

A class of lipid-lowering drugs such as fenofibrate and gimfebrozil, specifically activate PPAR-α and decrease Triglyceride (TG) production by enhancing fatty acid oxidation in the liver and facilitates TG removal by stimulating lipoprotein lipase (LPL) production and suppressing Apo CIII production. PPAR-α activation also increases the levels of high density lipoprotein-cholesterol (HDL-C) by stimulating the production of Apo AI and AII[8]. The Figure 1 represents most commonly used Fibrates as well-known class of PPAR-α agonists currently used in practice. Fibrates lower HDL-cholesterol and TG levels by the activation of PPAR-α[5,9]. Long standing studies on these drugs have contributed to accumulation of considerable experimental data about their biological activity, stimulating an immense interest in the design of new agents toward the activation of PPAR-α for the treatment of dyslipidaemia.

Earlier, we have reported a series of anthraquinone-2-carboxamide derivatives as agonists PPAR-α receptor[10]. The encouraging *in vivo* hypolipidemic

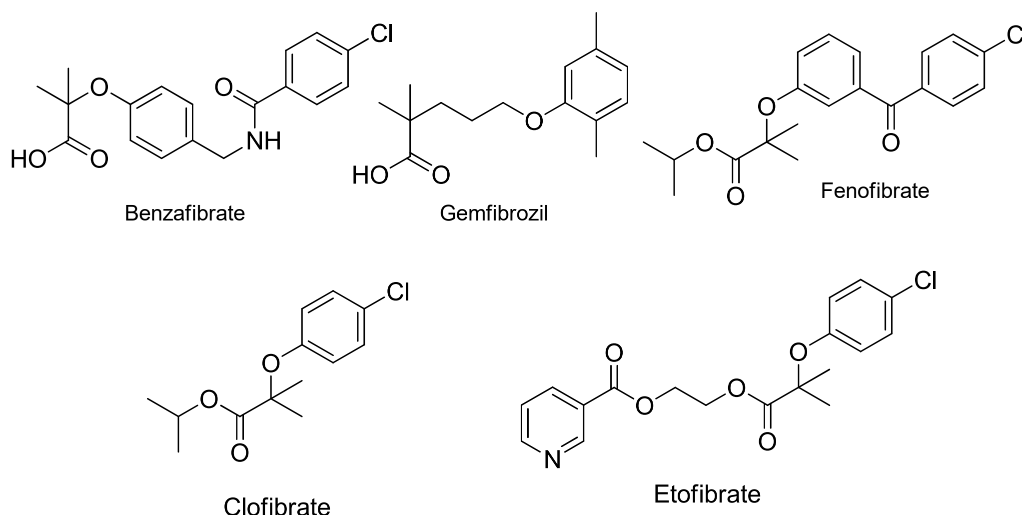


Figure 1 — The most common Fibrates

activity of almost all our previously reported anthraquinone carboxamide derivatives gave us an impetus to farther design and investigates some novel benzophenone carboxamide derivatives for their agonistic activity on PPAR-α receptor. Herewith, we report the design, synthesis, molecular docking and biological evaluation of some novel benzophenone carboxamide derivatives as promising agonists of PPAR-α receptor.

Experimental Section

Melting points were determined in open capillaries using a Stuart Scientific electrothermal melting point apparatus (Stone, Staffordshire, UK) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were collected on a Varian Oxford NMR300 spectrometer (Santa Clara, CA, USA). High-resolution (HR) mass spectra were measured in the negative ion mode using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker Apex-4 (Tesla) instrument (Bremen, Germany). The samples were dissolved in acetonitrile, diluted in spray solution (methanol/water, 5:4.9, v/v +0.1 part formic acid), and infused using a syringe pump with a flow rate of 2 mL/min. External calibration was done using an arginin cluster in the mass range m/z 175 – 871. Infrared (IR) spectra were recorded on a Shimadzu 8400F FT-IR spectrophotometer (Kyoto, Japan). Thin-layer chromatography (TLC) was performed on aluminium plates pre-coated with fluorescent silica gel, and the spots were visualized by UV light at 254 and/or 360 nm. Elemental analyses (EA) of C, H, and N were performed using Euro Vector elemental analyzer (Milan, Italy).

Synthesis of *N*-[substituted]-1*H*-indole-2-carboxamide, 3-6

The 1*H*-indole-2-carboxylic acid (**1**) on reaction (70-80 °C) with thionyl chloride in presence of dichloromethane (DCM) resulted in the formation of 1*H*- indole-2-carbonyl chloride (**2**). Further, indole-2-carbonyl chloride (**2**) (0.36 g, 2.0 mmol) was added to a solution of 2-aminobenzophenone (0.39 g, 2.0 mmol) and $NaOC_2H_5$ (0.36 g, 5.30 mmol) in 20 mL anhydrous dichloromethane (DCM). The mixture was refluxed for 12 h at 80 °C, and then cooled, washed with 1N HCl, followed by 1M sodium hydroxide and brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered. Finally, the organic layer was removed by evaporation under reduced pressure and the residue was purified by column chromatography using chloroform / methanol (95:5) as eluent to afford a spongy yellow solid (**3-6**).

***N*-[2-Benzoylphenyl]-1*H*-indole-2-carboxamide, 3**: Yield 21%, mp: 226-229 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.75 (br s, 1H, NH-indole), 10.89 (s, 1H, NHCO), 7.89 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.77 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.72-7.56 (m, 4H, Ar-H), 7.55- 7.43 (m, 3H, Ar-H), 7.40 (d, *J* = 8.24 Hz, 1H, Ar-H), 7.31 (dd, *J* = 7.95, 6.30 Hz, 1H, Ar- H), 7.25-7.15 (m, 2H, Ar-H), 7.03 (dd, *J* = 7.11, 1.0 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 196.33 (CO-ketone), 159.96 (CONH), 137.78, 137.34 (CH-Ar), 137.29 (CHAr), 133.0 (CH-Ar), 132.75 (CH-Ar), 131.38 (CH-Ar), 131.14 (CH-Ar), 130.32, 130.24 (CH-Ar), 128.67 (CH-Ar), 127.37 (CH-Ar), 124.44 (CH-Ar), 124.38 (CH-Ar), 123.97 (CH-Ar), 122.25 (CH-Ar), 120.44 (CH-Ar), 112.84 (CH-Ar), 104.15

(CH-Ar) ppm; IR (thin film): ν_{max} cm^{-1} = 3302 (NH-indole), 3188 (NHCO), 1667 (br CO), 1632, 1582, 1535, 1447, 1312, 1258, 1157, 930, 810, 745 cm-1; hMS (ESI, negative mode): m/z (M+H) 339.11390 ($C_{22}H_{16}N_2O_2$) requires 339.11335; Elemental analysis calculated for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23, Found: C, 77.91; H, 4.49; N, 8.41.

***N*-[3-Benzoylphenyl]-1*H*-indole-2-carboxamide, 4**: Yield 23%, mp: 226-229 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.83 (br s, 1H, NH-indole), 10.52 (s, 1H, NHCO), 8.28 (s, 1H, Ar-H), 8.19 (d, *J* = 7.04 Hz, 1H, Ar-H), 7.80 (d, *J* = 6.88 Hz, 1H, Ar-H), 7.74-7.30 (m, 9H, Ar-H), 7.24 (dd, *J* = 6.38, 7.74 Hz, 1H, Ar-H), 7.08 (dd, *J* = 7.11, 6.64 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 196.13 (CO-ketone), 160.43 (CONH), 139.69, 137.91, 137.56, 137.38, 133.16 (CH-Ar), 131.63, 130.11 (CH-Ar), 129.54 (CH-Ar), 129.06 (CH-Ar), 127.46, 125.08 (CH-Ar), 124.39 (CH-Ar), 122.29 (CH-Ar), 121.55 (CH-Ar), 120.44 (CH-Ar), 112.87 (CH-Ar), 104.79 (CH-Ar) ppm; IR (thin film): ν_{max} cm^{-1} = 3364 (NH-indole), 3291 (NHCO), 3051, 1647 (br CO), 1585, 1543, 1435, 1315, 1285, 1242, 1204, 860, 750 cm-1; hMS (ESI, negative mode): m/z (M+ - H+) 339.11390 ($C_{22}H_{16}N_2O_2$) requires 339.11335; Elemental analysis calculated for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.41; H, 4.49; N, 8.09.

3-(3-(1*H*-Indole-2-carboxamido)benzoyl)benzoic acid, 5: Yield 50%, mp: 339-340 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 14.21 (br s, 1H, COOH), 12.42 (br s, 1H, NH-indole), 11.82 (s, 1H, NHCO), 8.53 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.86-7.80 (m, 1H, Ar-H), 7.69 (d, *J* = 7.94 Hz, 1H, Ar-H), 7.57-7.45 (m, 2H, Ar-H), 7.44-7.36 (m, 2H, Ar-H), 7.28-7.15 (m, 4H, Ar-H), 7.12-7.00 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 202.12 (CO-ketone), 169.18 (COOH), 159.90 (CONH), 142.14, 140.10, 139.25, 137.51, 132.67 (CH-Ar), 132.24, 131.46 (CH-Ar), 129.69 (CH-Ar), 128.85 (CH-Ar), 128.81 (CH-Ar), 128.31, 127.58, 125.32 (CH-Ar), 124.36 (CH-Ar), 122.72 (CH-Ar), 122.26 (CH-Ar), 121.04 (CH-Ar), 120.50 (CH-Ar), 112.93 (CH-Ar), 103.84 (CH-Ar) ppm; IR (thin film): ν_{max} cm^{-1}= 2600-3500 (OH), 3435 (NH-indole), 3318 (NHCO), 3071, 1670 (br CO), 1624 (CO), 1605, 1585, 1535, 1450, 1423, 1385, 1312, 1269, 1200, 1157, 933, 814, 748 cm-1; hMS (ESI, negative mode): m/z (M-1) 383.10373 ($C_{23}H_{15}N_2O_4$) requires 383.10318; Elemental analysis calculated for $C_{23}H_{16}N_2O_4$: C, 71.87; H, 4.20; N, 7.29. Found: C, 71.71; H, 3.99; N, 6.95.

***N*-(4-Amino-methyl benzoic acid)-1*H*-indole-2-carboxamide, 6**: Yield 11%, mp: 184 °C, hMS (ESI, negative mode): m/z (M-1) 293.09317 ($C_{17}H_{13}N_2O_3$) requires 293.09262; IR (thin film): ν = 3441 (NH-indole), 3298 (NHCO), 2982, 2947, 1659 (CO), 1639 (CO), 1589, 1524, 1404, 1315, 1281, 1238, 1200, 1177, 926, 826, 739 cm-1; Elemental analysis calculated for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.39; H, 4.33; N, 9.43.

Synthesis of *N*-[substituted]-1*H*-pyrrole-2-carboxamides, 9-10

The 1*H*-pyrrole-2-carboxylic acid (**7**) on reaction (70-80 °C) with thionyl chloride in presence of dry dichloromethane (DCM) resulted in the formation of 1*H*-pyrrole-2-carbonyl chloride (**8**). Further, a mixture of 1*H*-pyrrole-2-carbonyl chloride (**8**) (3.2 mmol) in 15 mL of acetonitrile was added to a solution of 2-aminobenzophenone / 3-aminobenzophenone (1.8 mmol) in 20 mL of dry 1,4-dioxane and refluxed for 12 h at 120 °C. The organic layer was removed by evaporation under reduced pressure and the residue was crystallized using chloroform / methanol to afford compounds **9** and **10** as black solid.

***N*-[2-Benzoylphenyl]-1*H*-pyrrole-2-carboxamide, 9**: Yield 38%, mp: 182 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ= 11.70 (br s, 1H, NH-pyrrole), 10.56 (br s, 1H, NHCO), 7.91 (d, *J* = 7.39 Hz, 1H, Ar-H), 7.74 (d, *J* = 6.20 Hz, 2H, Ar-H), 7.68 – 7.55 (m, 2H, Ar-H), 7.51 (d, *J* = 6.57 Hz, 2H, Ar-H), 7.43 (d, *J* = 6.98 Hz, 1H, Ar-H), 7.25 (dd, *J* = 6.40, 6.40 Hz, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.14 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 196.62 (CO-ketone), 159.23 (CONH), 138.08, 137.96, 132.87 (CH-Ar), 132.84 (CH-Ar), 131.34 (CH-Ar), 130.19 (CH-Ar), 129.31, 128.64 (CH-Ar), 126.08, 123.66 (CH-Ar), 123.37 (CH-Ar), 111.65 (CH-Ar), 109.54 (CH-Ar) ppm; Elemental analysis calculated for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.20; H, 4.55; N, 9.42.

***N*-[4-Benzoylphenyl]-1*H*-pyrrole-2-carboxamide, 10**: Yield 20%, mp: 185 °C (decomposed); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.70, 11.82 (2br s, 1H, NH-pyrrole), 10.23, 9.85 (2br s, 1H, NHCO), 8.01-6.15 (5m, 12H, Ar-H): [(8.01-7.89, m; 7.85-7.45, m; 7.40-6.88, m; 6.80-6.45, m; 6.35 6.15, m)]; ^{13}C NMR (DMSO-d_6): δ = 195.15 (CO-ketone), 160.15, 159.95 (CONH), 154.21, 138.13, 133.04 (CH-Ar), 132.74 (CH-Ar), 131.50 (CH-Ar), 129.81 (CH-Ar), 129.22 (CH-Ar), 128.95 (CH-Ar), 128.65 (CH-Ar), 120.33, 119.34, 113.02 (CH-Ar) ppm; IR (thin film): ν_{max} cm^{-1} = 3364 (NH-pyrrole), 3291 (NHCO), 3129, 1701 (CO), 1639 (CO), 1589, 1520, 1412, 1319, 1281,

1246, 1126, 845, 741; hMS (ESI, negative mode): m/z (M+H) 289.09769 ($C_{18}H_{13}N_2O_2$) 289.09770; Elemental analysis calculated for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.28; H, 4.72; N, 9.43.

Biological activity

Triton WR-1339 was obtained from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals (fine super grade) were purchased from Acros Organics (Amman, Jordan).

Adult male Wistar rats, weighing around 250 g, bred in the animal care centre of the Faculty of Pharmacy, Al-Zaytoonah Private University, Amman, Jordan, were given *ad libitum* access only to tap water throughout the experimental duration (24 h). Rats were maintained in a 12 h light/ 12 h dark under constant humidity and at 22°C. All experiments had been approved by and were performed in accordance with the guidelines of the Animal Welfare Committee of Al-Zaytoonah Private University.

Triton WR-1339 (tyloxapol; Sigma-Aldrich) was dissolved in normal saline (*p*H 7.4) and administered intraperitoneally (i.p.) to the rats [250 mg/kg body weight (BW)] for induction of hyperlipidemia by following reported method[11].

Overnight fasted rats were randomly divided into five groups of six animals each. The first group, serving as a negative normal control group (CG), received an *i.p.* administration of 1 mL normal saline. The second group, serving as a positive control group (PCG), received an *i.p*. administration of 4% DMSO. The third hyperlipidemic group (HG) received an *i.p* .injection of TritonWR-1339 and was gavaged with 4% DMSO (in distilled water). In the fourth group, rats were *i.p.* injected with Triton WR-1339, followed by intragastric administration of 1 mL of a 57 mM solution of the target compounds (**3-6**, **9** and **10**) dissolved in 4% DMSO. The last group was *i.p*. injected with Triton WR-1339 and intragastrically treated with Bezafibrate (BF) (100 mg/kg BW) dissolved in 4% DMSO as a positive reference compound[12]. After 8 h of treatment, animals were anaesthetized with diethyl ether, and blood was collected. The blood samples were immediately centrifuged (1500 g for 10 min), and the plasma was used for lipid analysis by an enzymatic method with an automatic analyzer (Model Erba XL-300, ERBA Diagnostics, Mannheim, Germany).

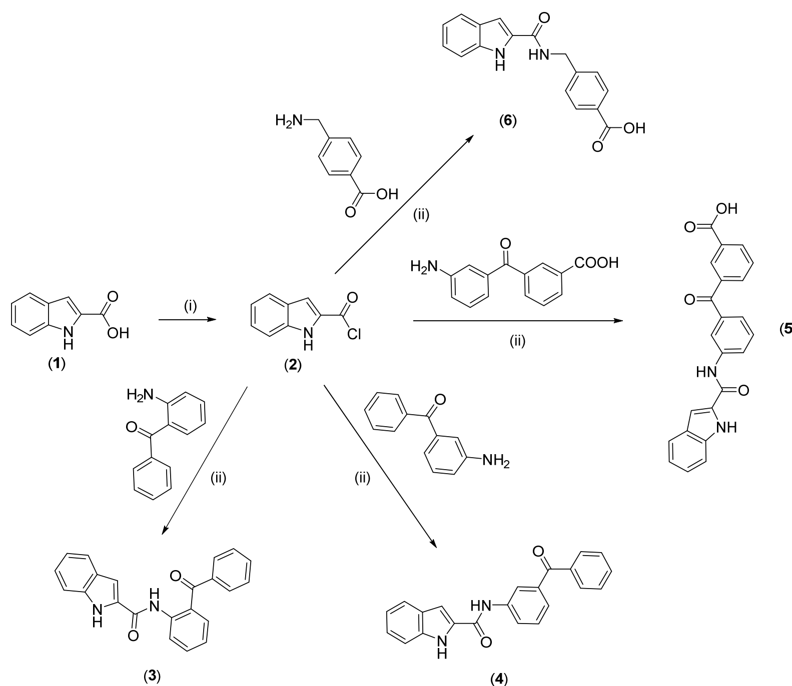
Results were expressed as means_SEM. Data obtained were analysed using the Student's t-test, and differences with p < 0:05 were considered statistically significant.

Molecular Docking

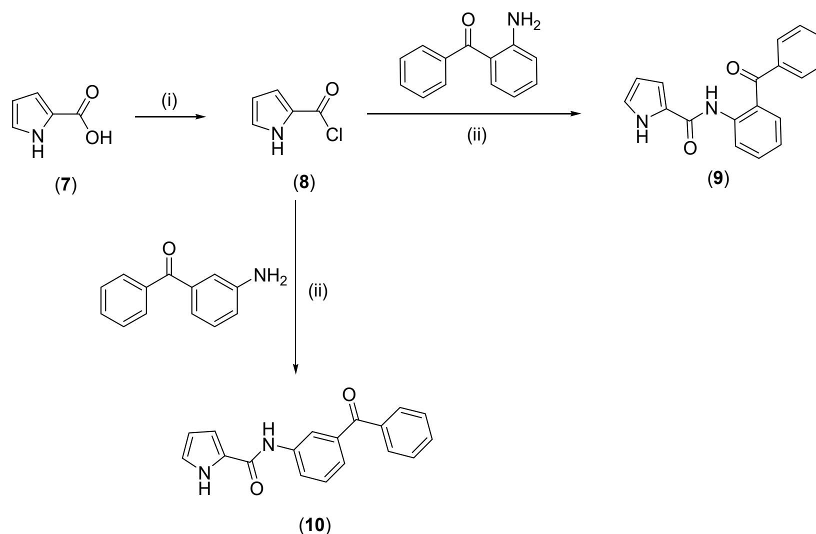
The crystal structures for PPAR-α (PDB: 1K7L) bound with an agonist **GW4095544** was taken from the Protein Data Bank (RCSB) for carrying out the molecular docking studies. Protein preparation was carried out by using the "Prepare Protein Protocol" of Accelrys Discovery Studio (DS) software version 5.2.2, in which the ligand was removed followed by addition of Hydrogen atoms and energy minimization of the whole structure by using the CHARMm forcefield[13]. The *p*H for protonation was set to 7.4 and energy cutoff by 0.9. All the target compounds (**3-6, 9** and **10**) were sketched, converted into 3D structures and energy minimized by using ACD Free ChemSketch software. A total of 50 lowest energy conformers for each compound were generated using Conformation Generation Protocol, and then all conformations were docked into the PPAR-α binding domain after assigning the binding site (10Å) around the nitrogen atom of Cys 275, where all the amino acids within 10Å area were considered as part of the binding domain. Dock Ligand (GOLD) Protocol was used for docking all energy minimized conformations by using four different Fitness Scoring Functions *viz*. GoldScore, ChemScore, ChemPLP and ASP respectively. A total of 50 docking poses were obtained, one for each conformer that were visually inspected regardless its score ranking to have better idea about the different possible poses that compound could accommodate. Molecular modeling studies were carried out by following the standard reported protocol[14-16].

Results and Discussion

All the target compounds **3-6**, **9** and **10** were synthesized by following Scheme I and Scheme II and characterized based on their physical and spectral data (Experimental Section). These compounds **1-6** were tested (*in vivo*) on hyperlipidemic rats after administering 1 mL of a drug solution containing 57 μg in 4% DMSO (corresponding to 0.021 mg/ rat of 250g weight); drugs were administered intragastrically and bezafibrate was used as a reference in a dose of 1mg of 276 mM. The levels of TC, TG, HDL-C and LDL-C for compounds **3-6**, **9**, **10** and bezafibrate were measured 8 hour after the administration of Triton WR-1339 and are shown in Table I. Compounds **4** and **6** have shown promising hypolipidemic activity and lowered the level of TG by 71% and LDL-C by 26% and 29% respectively. These results suggest that the mechanism of cholesterol lowering



Scheme I — Synthesis of N-[substituted]-1*H*-indole-2-carboxamide (**3-6**): (i) $SOCl_2$, DCM, 70-80°C; (ii) $NaOC_2H_5$, DCM, 80°C.



Scheme II — Synthesis of N-[substituted]-1*H*-pyrrole-2-carboxamides (**9-10**): (i) $SOCl_2$, DCM, 70-80°C; (ii) acetonitrile, 1,4-dioxane, 120°C.

activity of these two compounds depends on improving the catabolism of LDL-C by the activation of hepatic receptors[12]. On the other hand, both **4** and **6** have increased the level of HDL-C by 64%. HDL-C is known for its important role in facilitating the mobilization of TG and cholesterol from plasma to the liver[17]. Interestingly, compound **6** has lowered TC level by 23% whereas compound **2** did not affect the level of TC which strongly suggests that this compound might lower lipid level by another mechanism in addition to that know for the Fibrates which needs more investigation in future.

To gain insight into the binding interactions of the synthesized compounds inside PPARα, first the active

binding site of this receptor was investigated. It comprised of two domains; hydrophobic and hydrophilic pocket respectively. The hydrophobic pocket is formed by amino acids Val332, Leu344, ILe272, ILe241, Leu247 and Cys275 whereas the hydrophilic pocket characterized by Ser280, Tyr314, Tyr464 and His440 respectively as shown in Figure 2. The binding of agonists to the hydrophilic pocket has been extensively studied and found responsible for the PPARα activation[9,18]. Docking studies for fibrates revealed that bezafibrate preferred binding pattern with the polar pocket by forming more than one H-bond especially with His440, while lipophilic end of the molecule characterized by the presence of halogenated benzene rings were docked into PPARα hydrophobic binding domain (Figure 2). All the newly synthesized compounds were also found to be docked well inside the binding pocket of PPARα. In particular, compound **4** occupied the binding pocket by forming H-bonding with His440 and Ser280 as well as π-π stacking interaction with His440 and Phe273 inside the hydrophilic pocket (Figure 3).

Table I — Effect of target compounds (**3-6**, **9** and **10**) on plasma lipid levels in Triton WR-1339-induced hyperlipidemic rats after 8 h

Lipid Profile	TC (mg/mL)	TG (mg/mL)	HDL-C (mg/mL)	LDL-C (mg/mL)
CG	1.07 ±0.15	1.27 ± 0.40	0.49 ± 0.11	0.31 ±0.01
HG	2.23 ±0.07	15.11 ±.22	0.31 ±0.03	0.63 ±0.02
3	2.78 ±0.19	15.89 ±0.09	0.37 ±0.03	0.67 ±0.06
4	2.34 ±0.10	4.40 ±0.25	0.51 ±0.03	0.47 ±0.03
5	2.90 ±0.29	14.89 ±0.19	0.31 ±0.02	0.57 ±0.03
6	1.72 ±0.06	4.41 ±0.03	0.50 ±0.01	0.45 ±0.02
9	2.28 ±0.08	15.23 ±0.13	0.30 ±0.02	0.60 ±0.03
10	2.69 ±0.17	15.38 ±0.18	0.28 ±0.027	0.65 ±0.02
BF	2.18 ±0.06	5.65 ±0.18	0.43 ±0.01	0.63 ±0.02

CG: normal control group; HG: hyperlipidemic + 4% DMSO control group; BF: Bezafibrate + 4% DMSO group; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol. Values are means _SEM from six rats in each group.

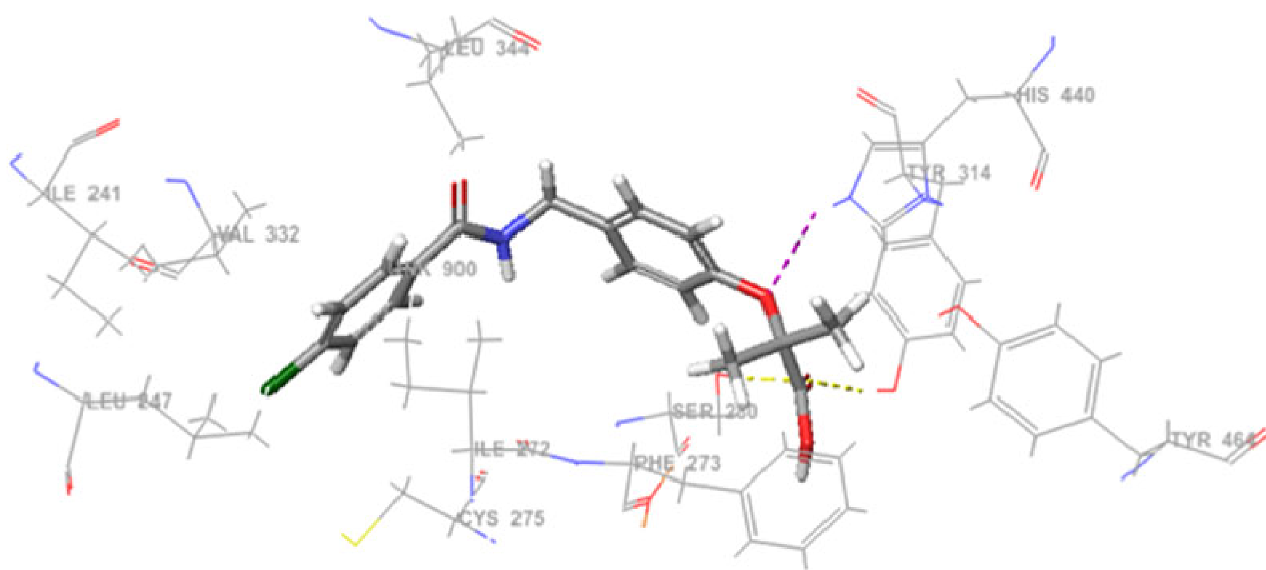


Figure 2 — Binding orientation of Bezafibrate (in stick) inside the PPAR-α binding domain forming H-bond (dashed green line) with Tyr314, Ser280 and His440

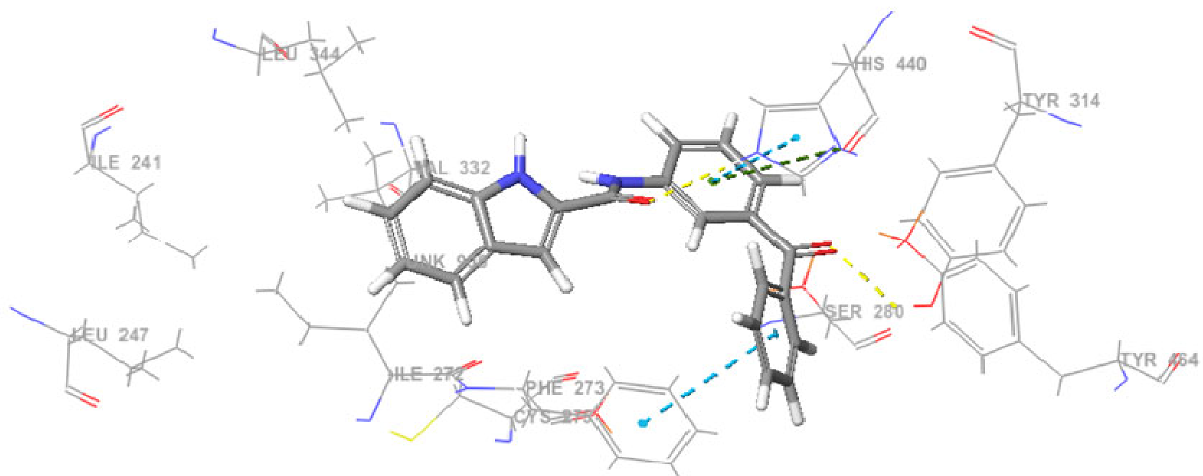


Figure 3 — Binding orientation of compound **4** docked inside PPAR-α active site forming H-bonding (dashed yellow lines) and π-π stacking interaction (cyan lines)

Conclusions

In the present study, a total of six novel benzophenonecarboxamide derivatives (**3-6, 9** and **10**) were synthesized by following Scheme I and Scheme II and evaluated for their hypolipidemic activity. Interestingly, compounds **4** and **6** showed promising hypolipidemic activity and lowered the level of TG by 71% and LDL-C by 26% and 29% respectively. Further, molecular docking studies were carried out to gain insight into the binding interactions of all the newly synthesized compounds inside PPARα receptor. All the compounds were found to be docked well inside the binding pocket of the receptor by forming required H-bonding with His440 and Ser280 as well as π-π stacking interaction with His440 and Phe273 inside the hydrophilic pocket of the receptor on par with the bezafibrate. The encouraging *in vivo* hypolipidemic activity of compounds **4** and **6** by lowering LDL-C levels as well as enhancing HDL-C indicates that these compounds could serve as promising lead compounds for farther investigation for the development of novel hypolipidemic agents.

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