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Research Article

Pharmaceutical Chemistry for Novel drug discovery

Synthesis And Characterisation Of Some Novel 5-Chloro Benzimidazole-2-One Derivatives With Specific Docking Studies Against PPAR-γ

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Abstract: It is necessary to discover antidiabetic agents since diabetes is one of the most rapidly growing disorders . It is estimated by WHO that more than 420 million people are suffering from diabetes worldwide. It is very important to synthesize novel molecules for the treatment of diabetes. One of recent and very effective targets is Peroxisome Proliferator Activated Receptor γ (PPAR- γ) . In our current study, we have followed standard methods for the synthesis of novel molecules and docking. A series of 5-chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives have been synthesized and characterized by various spectroscopic techniques including FT-IR, Mass and ^{1}H NMR. All the synthesized molecules were analysed by suitable spectral methods i.e. FT-IR, Mass and ^{1}H NMR. The compounds were docked against PPAR-γ by using MCULE software. It was found that the synthesized molecules were active against PPAR-γ by their comparative docking scores with that of standard marketed drugs i.e. Rosiglitazone and Pioglitazone. In particular DSR-16, DSR-8 and DSR-5 are showing more binding capacity. The synthesized molecules were identified to have good binding capacity with PPAR- γ according to their docking data.

Keywords: Spectroscopy, NMR, MCULE, Docking, PPAR-γ, WHO .

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1. INTRODUCTION

Benzimidazole is a bicyclic nitrogen-containing aromatic heterocycle, which has a great role in the pharmaceutical industry for drug discovery. [1-2] Because of their special structural features and electron-rich environment via nonbonding electrons present on the two Nitrogens, Benzimidazole derivatives can bind to a variety of ligand binding domains [3], and they exhibit a broad spectrum of biological activities. Number of benzimidazole derivatives are used as drugs to treat many diseases with high therapeutic potential [4]. Benzimidazole is also as constituent in Vitamin B-12 structure. Drugs like Albendazole, Mebendazole and Thiabendazole contain benzimidazole as their basic nucleus which act as anthelmintics. Benzimidazole-2-one derivative is found in Domperidone which is an antiemetic [5-7]. Molecular docking is used to predict the orientation, conformation and native position of a ligand within the ligand binding pocket of the target receptor or protein. It is a combination of a search algorithm and a scoring function. There are several docking programs available viz. AutoDock, Gold, FlexX, MCULEetc[8-11]. Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The most common one is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin[12]. There are several targets to treat diabetes through drug therapy. One of the most recent targets is Peroxisome Proliferaror Activated Receptor γ (PPAR-γ) which is a nuclear receptor. PPAR-γ is mainly expressed in adipose tissue, but skeletal muscle is a major site for Thiazolidinedione (TZD) responsive glucose disposal. It is triggered by fatty acids naturally and synthetic molecules thiazolidinediones eg. Rosiglitazone and Pioglitazone. All these molecules act as agonists of the target. Literature survey revealed that Benzimidazole-2-one derivatives are active as PPAR-γ agonists[13]. PPAR-γ has Y-shaped ligand binding pocket so that it binds with multitude of fatty acids and synthetic ligands. This pocket can be divided into three arms i.e Arm-I, Arm-II, Arm-III. Arm-I consists of mainly polar residues which activates the transcription. Arm-II is a hydrophobic portion and Arm-III is a partly hydrophilic [14-1]The molecules for this current study, were designed based on binding pocket's structure. The best fit molecules were screened by their docking scores and were synthesized and characterized.

2. MATERIALS AND METHODS

2.1 Analytical Instruments and Chemicals

Nuclear Magnetic Resonance (Bruker.400.), ^{1}H-NMR spectra were recorded at 400 MHz, TMS as internal standard. The chemical shift values were reported in parts per million. IR spectra were recorded with a Bruker spectrophotometer (Bruker ALPHA). The melting points of the synthesized molecules were recorded by visual melting point apparatus from Lab India. All the commercially available reagent grade chemicals were used as received. Purity of the compound and progress of the reaction were monitored by thin layer chromatography (TLC), with detection by Ultra-Violet light and spots were visualized by exposure to iodine vapors.

2.2 Scheme-1

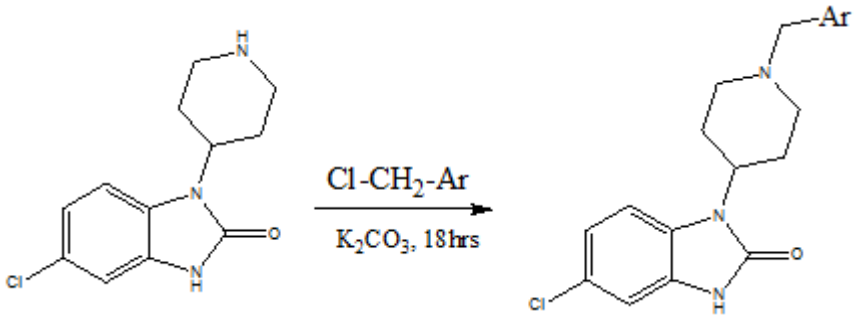

Fig 1. Synthesis of 1-(1-aryl methyl piperidin-4yl)-5-chloro-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives.

2.2.1 General procedure for the scheme-1

5-chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole-2(3*H*)-one (0.01 mol, 1 eq) was dissolved in Acetonitrile (50 mL) and 1.2 equivalents of different aryl methyl halides and 3 equivalents of K_2CO_3 were added. The reaction was refluxed for 18 h. After reflux, the progress of the reaction was monitored by thin layer chromatography (TLC) by using Hexane and ethyl acetate as mobile phase. Then the reaction mixture is cooled to room temperature and K_2CO_3 was filtered off and subsequently washed with Acetonitrile (2 × 50 mL) to get pure product. The scheme of the reaction is shown in Fig-1

2.2.2 Characterization of synthesised compounds: (DSR-1 to DSR-8)

1-(1-benzylpiperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-1): yield 42.5; m.p 196 °C; Anal. calc for $C_{19}H_{20}ClN_3O$: C, 66.76; H, 5.90; Cl, 10.37; N, 12.29; O, 4.68; found: C, 63.63; H, 4.60; Cl, 8.3; N, 11.4; O, 3.56; IR (KBr) υ max: cm^{-1}: 3157, 1685, 1398, 1159, 1105 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.77 (4H, d, J=18.1); 1.87 (d, J=16.8); 2.45(2H, d, J=13.3); 2.69 (2H, d); 3.65 (2H, d, J=10.3); 4.05 (1H, t, J=10.2); 7.10 (1H, d, J=8.5); 7.22 (d, J=7.8); 7.53(1H, d, J=1.7); ESI MS m/z: 343 [M+1].
1-(1-(4-chlorobenzyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-2): yield 38.6; m.p 240 °C; Anal. calc for $C_{19}H_{19}Cl_2N_3O$: C, 60.65; H, 5.09; Cl, 18.84; N, 11.17; O, 4.25; found: C, 58.25; H, 4.30; Cl, 16.7; N, 10.14; O, 3.25; IR (KBr) υ max: cm^{-1}: 3165, 1710, 1450, 1238, 1110 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.74 (4H, d, J=17.8); 1.82 (d, J=16.8); 2.34(2H, d, J=13.6); 2.72 (2H, d, J=13.4); 3.67 (2H, s); 4.25 (1H, t, J=10.2); 7.15 (1H, d, J=8.5); 7.21 (1H, d, J=8.5); 7.44 (d, J=8.3); ESI MS m/z: 377 [M+1].

1-(1-(4-bromobenzyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-3): yield 34.4; m.p 226 °C; Anal. calc for $C_{19}H_{19}BrClN_3O$: C, 54.24; H, 4.55; Br,18.99; Cl, 8.43; N, 9.99; O, 3.80; found: C, 52.30; H, 4.40; Br, 15.25; Cl, 6.7; N, 8.9; O, 3.35; IR (KBr) υ max: cm^{-1}: 3260, 1670, 1480, 1340, 1250 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.78 (4H, d, J=18.4); 1.85 (d, J=16.4); 2.48(2H, d, J=13.4); 2.69 (2H, d, J=13.8); 3.64 (2H, s); 4.05 (1H, t, J=10.6); 7.10 (1H, d, J=8.8); 7.28 (1H, d, J=8.6); 7.62 (1H, d, *J*=1.7); ESI MS m/z: 422 [M+1].
1-(1-(4-hydroxybenzyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-4): yield 36.2; m.p 185 °C; Anal. calc for $C_{19}H_{19}ClN_3O_2$: C, 63.77; H, 5.63; Cl, 9.91; N, 11.74; O, 8.94; found: C, 61.7; H, 5.32; Cl, 8.6; N, 9.2; O, 6.35; IR (KBr) υ max: cm^{-1}: 3170, 1685, 1390, 1350, 1150 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.87 (4H, d, J=18.4); 2.45(2H, d, J=12.1); 2.79 (2H, d, J=13.6); 3.54 (2H, s); 4.25 (1H, t, J=10.2); 7.18 (3H, d, J=8.4); 7.22 (1H, d, J=8.5); 7.67 (1H, d, J=1.7); ESI MS m/z: 359 [M+1].
1-(1-(4-methylbenzyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-5): yield 45.4; m.p 226 °C; Anal. calc for $C_{20}H_{22}ClN_3O$: C, 67.50; H, 6.23; Cl, 9.96; N, 11.81; O, 4.50; found: C, 65.6; H, 5.47; Cl, 9.46; N, 10.1; O, 3.75; IR (KBr) υ max: cm^{-1}: 3250, 3100, 1690, 1425, 1375, 1175 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.78 (4H, d, J=18.1); 1.87 (d, J= 18.1); 2.26(3H, s); 2.45 (2H, d, J=13.4); 2.69 (2H, d, J=13.4); 3.64 (2H, s); 4.05 (1H, t, J=10.2); 6.94 (2H, d, J=8.0); 7.10 (3H, d, J=8.5); 7.21 (1H, d, J=8.5); 7.62 (1H, d, J=1.7); ESI MS m/z: 357 [M+1].
1-(1-(2-chlorobenzyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-6): yield 24.2; m.p 214 °C; Anal. calc for $C_{19}H_{19}Cl_2N_3O$: C, 60.65; H, 5.09; Cl, 18.84; N, 11.17; O, 4.25; found: C, 56.4; H, 4.56; Cl, 17.29; N, 10.41; O, 3.25; IR (KBr) υ max: cm^{-1}: 3275, 1675, 1335, 1240, 1145 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.88 (4H, d, J=18.4); 2.46(2H, d, J=13.4); 2.68 (2H, d, J=13.4); 3.75 (2H, s); 4.05 (1H, t, J=10.2); 7.24 (2H, d, J=8.1); 7.44 (1H, d, J=8.1); 7.64 (1H, d, J=1.5); ESI MS m/z: 377 [M+1].
1-(1-(2-hydroxybenzyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-7): yield 32.8; m.p 184 °C; Anal. calc for $C_{19}H_{20}ClN_3O_2$: C, 63.77; H, 5.63; Cl, 9.91; N, 11.74; O, 8.94; found: C, 60.24; H, 4.87; Cl, 8.9; N, 10.51; O, 7.82; IR (KBr) υ max: cm^{-1}: 3180, 1690, 1360, 1270, 1135 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.79 (4H, d, J=18.1); 1.87 (d, J=18.1); 2.46 (2H, d, J=13.3); 2.67 (2H, d J=13.5); 3.74 (2H, s); 4.15 (1H, t, J=10.4); 6.72 (1H, d, J=8.3); 6.87 (1H, d, J= 7.9); 7.19 (2H, d, J=8.5); 7.25 (d, J=8.3); 7.29 (1H, d, J=7.9); 7.62 (1H, d, J=1.7); ESI MS m/z: 359 [M+1].
1-(1-(2-methylbenzyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-8): yield 29.6; m.p 178 °C; Anal. calc for $C_{20}H_{22}ClN_3O$: C, 67.50; H, 6.23; Cl, 9.96; N, 11.81; O, 4.50; found: C, 65.74; H, 5.26; Cl, 9.02; N, 10.12; O, 3.26; IR (KBr) υ max: cm^{-1}: 3015, 1710, 1470, 1340,1275, 1135 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.81 (4H, d, J=18.3); 1.87 (d, J=18.1); 2.20 (3H, s); 2.45 (2H, d J=13.4); 2.70 (2H, d, J=13.4); 3.69 (2H, s); 4.05 (1H, t, J=10.2); 6.94 (1H, d, J=7.9); 6.97 (4H, d, J= 8.5); 7.08 (d, J=8.0); 7.04 (d, J=8.0); 7.21 (1H, d, J=8.5); 7.62 (1H, d, J=1.7); ESI MS m/z: 357 [M+1].

2.3 Scheme-2

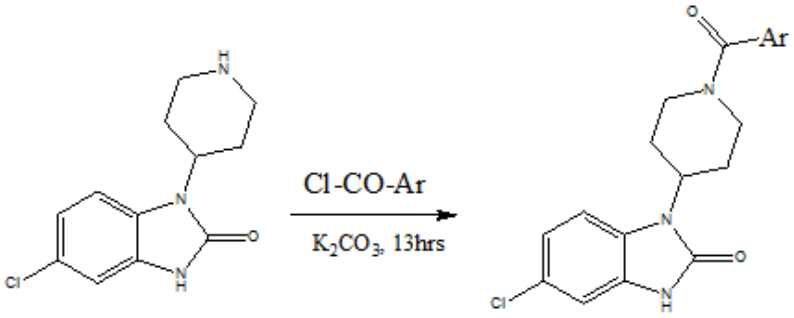

Fig 2. Synthesis of 1-(1-aryl carbonyl piperidin-4yl)-5-chloro-1*H*-benzo[d]imidazole-2(3*H*)-one derivatives.

2.3.1 General procedure for the scheme-2

5-chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole-2(3*H*)-one (0.01 mol, 1 eq) was dissolved in Acetonitrile (50 mL) and 0.012 mol (1.2 eq) of different aryl halides and 0.03 mol (3 eq) of K_2CO_3 were added. The reaction was refluxed for 13 h. After reflux, the progress of the reaction was monitored by thin layer chromatography (TLC) by using Hexane and ethyl acetate as mobile phase. Then the reaction mixture was cooled to room temperature and K_2CO_3 was filtered off and subsequently washed with Acetonitrile (2 × 50 mL) to get pure product. The scheme of the reaction is shown in Fig-2.

3. RESULTS

3.1.1 Characterization of synthesised compounds: (DSR-9 to DSR-16)

1-(1-benzoylpiperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-9): yield 42.8; m.p 215 °C; Anal. calc for $C_{19}H_{18}ClN_3O_2$: C, 64.13; H, 5.10; Cl, 9.96; N, 11.81; O, 8.99; found: C, 62.34; H, 4.53; Cl, 8.09; N, 9.23; O, 8.26; IR (KBr) υ max: cm^{-1}: 3100, 1690, 1340, 1260, 1180, 1135 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.74 (4H, d, J=14); 1.84 (d, J=14); 3.30 (4H, d, J=15); 3.36 (d, J=15.0); 4.09 (1H, t, J=10.3); 7.08 (1H, d, J=8.0); 7.21 (1H, d, J=8.0); 7.46 (3H, d, J=8.5); 7.54 (2H, d, J=8.5); ESI MS m/z: 357 [M+1].
1-(1-(4-chlorobenzoyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-10): yield 37.4; m.p 284 °C; Anal. calc for $C_{19}H_{17}Cl_2N_3O_2$: C, 58.47; H, 4.39; Cl, 18.17; N, 10.77; O, 8.20; found: C, 56.20; H, 4.30; Cl, 15.7; N, 9.14; O, 6.25; IR (KBr) υ max: cm^{-1}: 3155, 1690, 1350, 1138 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.78 (4H, d, J=14.0); 1.88 (d, J=14.8); 3.34(4H, d, J=14.7); 3.36 (d, J=14.4); 3.94 (1H, t, J=10.3); 7.10 (1H, d, J=8.5); 7.25 (1H, d, J=8.7); 7.54 (2H, d, J=8.7); ESI MS m/z: 391 [M+1].
1-(1-(4-bromobenzoyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-11): yield 33.6; m.p 292 °C; Anal. calc for $C_{19}H_{17}BrClN_3O_2$: C, 52.50; H, 3.94; Br, 18.38; Cl, 8.16; N, 9.67; O, 7.36; found: C, 51.50; H, 3.02; Br, 17.70; Cl, 7.07; N, 9.21; O,

6.53; IR (KBr) υ max: cm^{-1}: 3075, 1710, 1420, 1237 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.88 (4H, d, J=14.4); 3.38 (4H, d, J=14.3); 3.36 (d, J=13); 3.94 (1H, t, J=10.7); 7.25 (1H, d, J=8.7); 7.40 (1H, d, J=85); 7.62 (1H, d, J=1.7); ESI MS m/z: 437 [M+2].

1-(1-(4-hydroxybenzoyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-12): yield 37.7; m.p 284 °C; Anal. calc for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; Cl, 9.54; N, 11.30; O, 12.91; found: C, 59.60; H, 4.12; Cl, 8.25; N, 9.15; O, 11.25; IR (KBr) υ max: cm^{-1}: 3240, 3125, 1685, 1440, 1137 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.98 (4H, d, J=14.0); 3.35 (4H, d, J=14.7); 3.38(d, J=14.7); 4.09 (1H, t, J=10.3); 7.02 (1H, d, J=8.5); 7.10 (1H, d, J=8.5); 7.64 (1H, d, J=1.7);7.89 (2H, d, J= 8.5); ESI MS m/z: 373 [M+1].

1-(1-(4-methylbenzoyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-13): yield 39.2; m.p 278 °C; Anal. calc for $C_{20}H_{20}ClN_3O_2$: C, 64.95; H, 5.45; Cl, 9.59; N, 11.36; O, 8.65; found: C, 62.65; H, 4.45; Cl, 8.53; N, 9.57; O, 7.32; IR (KBr) υ max: cm^{-1}: 3170, 1678, 1340, 1235 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.74 (4H, d, J=14.3); 2.31 (3H, s); 3.29 (4H, d, J=15); 3.38(d, J=14.7); 4.15 (1H, t, J=10.7); 7.10 (1H, d, J=8.5); 7.14 (3H, d, J=8.5); 7.62 (1H, d, J=1.5);7.88 (2H, d, J= 8.5); ESI MS m/z: 371 [M+1].

1-(1-(2-chlorobenzoyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-14): yield 28.3; m.p 244 °C; Anal. calc for $C_{19}H_{17}Cl_2N_3O_2$: C, 58.47; H, 4.39; Cl, 18.17; N, 10.77; O, 8.20; found: C, 56.45; H, 2.36; Cl, 16.71; N, 8.45; O, 6.05; IR (KBr) υ max: cm^{-1}: 3166, 1692, 1376, 1160 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.75 (4H, d, J=14.1); 3.26 (4H, d, J=15); 3.37(d, J=14.7); 3.94 (1H, t, J=10.3), 7.10 (1H, d, J=8.5); 7.21 (1H, d, J=8.7); 7.62 (1H, d, J=1.7); 7.89 (1H, d, J=8.1); ESI MS m/z: 391 [M+1].

1-(1-(2-hydroxybenzoyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-15): yield 24.5; m.p 212 °C; Anal. calc for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; Cl, 9.54; N, 11.30; O, 12.91; found: C, 56.60; H, 3.25; Cl, 7.85; N, 9.25; O, 10.15; IR (KBr) υ max: cm^{-1}: 3200, 1687, 1400, 1158 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.88 (4H, d, J=14.0); 3.38 (4H, d, J=14.9); 3.96 (1H, t, J=10.6), 7.02 (1H, d, J=8.3); 7.10 (1H, d, J=8.3); 7.65 (1H, d, J=1.9); 7.74 (1H, d, J=8.4); ESI MS m/z: 373 [M+1].

1-(1-(2-methylbenzoyl)piperidin-4-yl)-5-chloro-1H-benzo[d]imidazol-2(3H)-one (DSR-16): yield 32.7; m.p 234 °C; Anal. calc for $C_{20}H_{20}ClN_3O_2$: C, 64.95; H, 5.45; Cl, 9.59; N, 11.36; O, 8.65; found: C, 60.75; H, 3.32; Cl, 7.20; N, 8.40; O, 7.24; IR (KBr) υ max: cm^{-1}: 3170, 2978, 1684, 1420, 1154 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) ; 1.85 (4H, d, J=14.0); 2.39 (3H,s); 3.39 (4H, d, J=15.0); 3.94 (1H, t, J=10.3), 7.10 (1H, d, J=8.5); 7.21 (2H, d, J=8.5); 7.38 (2H, d, J=8.1); 7.62 (1H, d, J=1.7); ESI MS m/z: 371 [M+1].

3.2 Molecular docking by using MCULE software

Peroxisome Prolifirative Activated Receptor is one of the recent targets that has different biological activities. Its subtypes are the good targets for Atherosclerosis, Diabetes and Obesity etc. In our study we have focused on one of its subtypes PPAR-γ since its derivatives are good antidiabetic agents viz. rosiglitazone, pioglitazone. Since our compounds, which are structurally similar to the molecules has good binding capacity to the receptors as per recent reports.[15] The molecules DSR-1 to DSR-16 were docked against PPAR-γ by using MCULE[17] which is an online software. The crystal structure of the PPAR- γ was taken from sc-PDB[18] and its ID is 1i7i with 2.350 resolution.

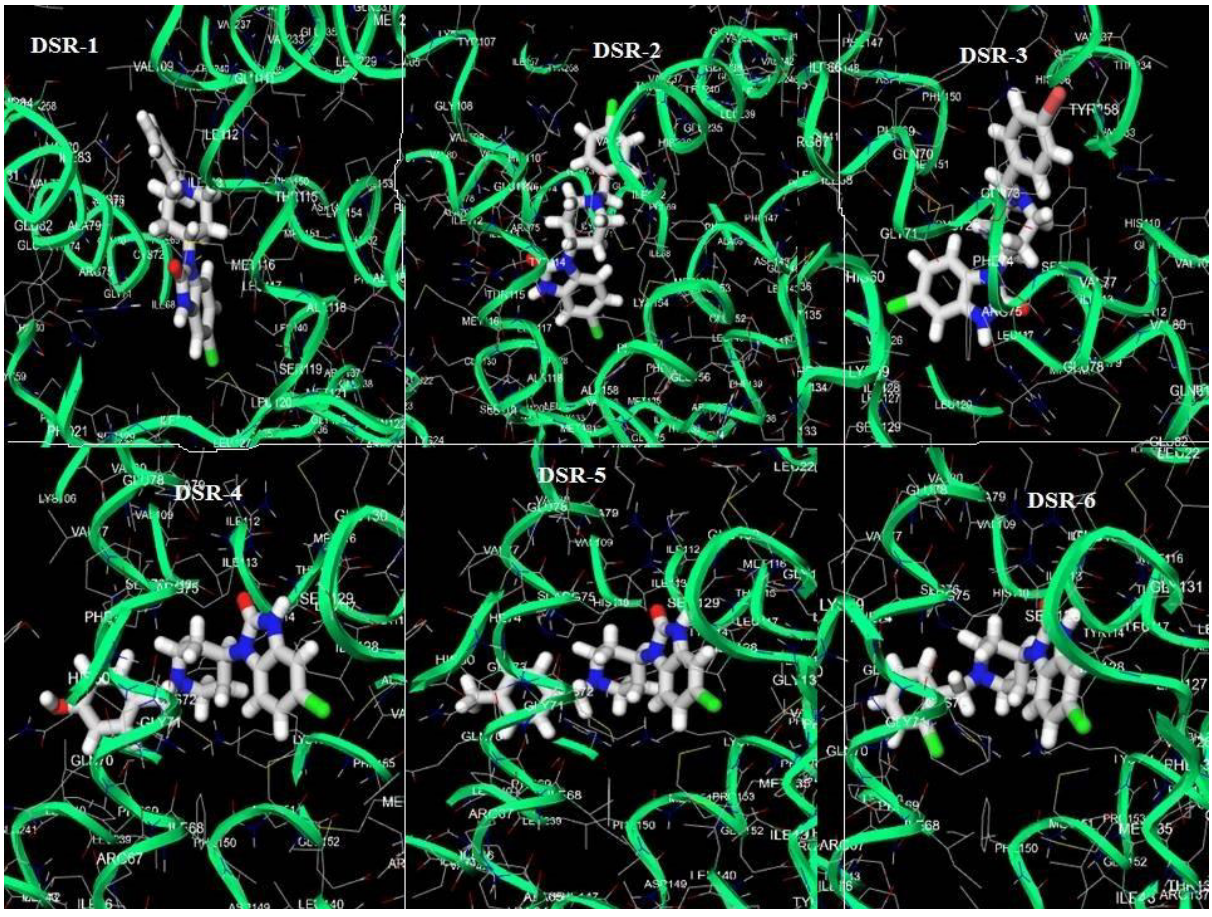

Fig 3. Docking poses of the synthesised molecules. (DSR-1 to DSR-6)

Table 1. Synthesized and standard marketed molecules with their corresponding docking scores.

S.No	Molecule	Docking score	S.No	Molecule	Docking score
1	DSR-1	-8.7	10	DSR-9	-8.7
2	DSR-2	-9.2	11	DSR-10	-9.2
3	DSR-3	-9.1	12	DSR-11	-9.1
4	DSR-4	-8.8	13	DSR-12	-8.8
5	DSR-5	-9.3	14	DSR-13	-9.3
6	DSR-6	-9.2	15	DSR-14	-9.2
7	DSR-7	-8.7	16	DSR-15	-8.7
8	DSR-8	-9.4	17	DSR-16	-9.4
9-	Rosiglitazone	-8.4	18	Pioglitazone	-8.5

A total of sixteen 5-chlorobenzimidazole-2-one derivatives were synthesized by using established protocols. The compounds were purified and obtained in good yield. The synthesized molecules were characterized by using spectral analysis including NMR, IR and Mass. The newly synthesized molecules were subjected for docking studies by using MCULE software which was shown in Fig 3 had shown good binding capacity with PPAR-γ when compared with standard marketed drugs i.e. Rosiglitazone and Pioglitazone. Especially DSR-16, DSR-8 and DSR-5 had shown remarkable binding capacity with PPAR-γ when compared to other synthesized molecules and marketed drugs. The results are shown in Table-1.

4. DISCUSSION

The need for antidiabetic agents with suitable rationality is required , since Diabetic cases are increasing day by day. According to the statistics from WHO, about 422 million people have diabetes particularly in low and medium income countries. It is not a wonder to know that diabetes is one of the leading causes of death in the world. Treatment and drug therapy are sufficiently not available for diabetes with rationality. There are several classes of drugs available in the market and most of them have severe side effects. The newly introduced class of antidiabetic agents are thiazolidinediones whose common target is PPAR-γ. It arouses our interest to make PPAR-γ as our target. Extensive literature survey suggests that benzimidazole-2-one derivatives are active against PPAR-γ and can reduce elevated blood glucose levels. Based on the need and urgency, we had synthesized different 5-chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives and analyzed by using 1HNMR, I.R, Mass spectral studies were done to determine the structures of the synthesized molecules. They were docked by PPAR-γ as our target of interest by using MCULE online software. Among all, DSR-16 had shown greater binding capacity with the docking score of -9.6. DSR-8 and DSR-5 had also shown the good binding capacity with the docking score of -9.4 and -9.3 respectively. All the synthesized molecules were having druggable nature according to the Lipiski rule.The series of sixteen molecules were designed based on their ligand binding capacity[14]. DSR-16, 2-methylbenzoyl derivative have shown highest binding capacity and DSR-8, 2-methylbenzyl derivative shows good binding capacity indicates methyl group on second position of phenyl ring indicates good binding properties. DSR-5, a 4-methylbenzyl derivative which also shows good binding capacity to the receptor.

Abbreviations

NMR: Nuclear Magnetic Resonance
I.R:Infra red
$CDCl_3$: Deuterochloroform
TLC: Thin layer chromatography
RBF: Round bottom flask
WHO: world health organisation.

5. CONCLUSION

We have synthesized sixteen 5-chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives. These compounds were purified and analysed by spectral analysis. All the sixteen compounds were docked against PPAR-γ by using online software i.e. MCULE. Among all DSR-16 followed by DSR-8 and DSR-5 had shown good binding capacity with their docking score. These molecules had greater binding capacity than that of marketed drugs viz. Rosiglitazone and Pioglitazone.

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7. AUTHORS CONTRIBUTION STATEMENT

Mr. D. Suryanarayana Raju has conceptualized, designed and executed current research work. Dr. R.L.C Sasidhar has supervised the work. Dr. S. Vidyadhara has reviewed and corrected the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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