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Synthesis, Characterization, Screening and Docking Studies of Some Novel 5-Chloro benzimidazole-2-one Derivatives as Potent Antitubercular Agents

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ABSTRACT

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 FTIR, mass and ^{1}H NMR. In current study, we have followed standard methods for the synthesis of novel molecules, docking and screening against mycobacterium species. The compounds were docked against 2Q1Y protein by using MCULE software and screened them by MABA. Out of sixteen synthesized molecules, two molecules *i.e.* **DSR-14** and **DSR-9** had shown good antitubercular activity.

KEYWORDS

5-Chloro benzimidazole-2-ones, Antitubercular agents.

INTRODUCTION

Benzimidazole is a bicyclic nitrogen-containing aromatic heterocycle, which has 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]. We also observe benzimidazole 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 are available today *viz.* AutoDock, Gold, FlexX, MCULE, *etc*. [8-11].

Tuberculosis (TB) is one of the ancient communicable diseases. There are many efforts made by the scientists, still

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its spread remained consistent in many parts of the globe. The latest anti-TB drug resistance surveillance data shows that 4.1 % of new and 19 % of previously treated TB cases in the world, are estimated to have rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB). In 2016, an estimation of 6,00,000 new cases of MDR/RR-TB emerged globally. MDR/RR-TB caused 2,40,000 deaths in 2016. About 6.2 % of MDR-TB cases have additional drug-resistance, extensively drug-resistant TB (XDR-TB) [12].

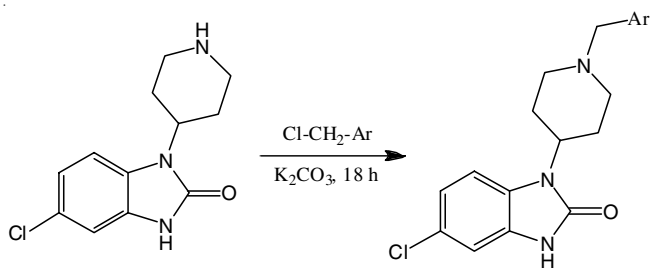
Many classes of drugs target limited to either cellwall synthesis or RNA biosynthesis [13]. Filamentous temperature-sensitive protein Z (FtsZ) is an attractive and trending target for the discovery of novel antibacterial. Prokaryotic cell division is a dynamic process that requires a concentration-dependent, temporal and spatial septation of the cell membrane and cell wall [14]. FtsZ is a structurally related protein to tubulin and it is the most abundant bacterial cell-division protein involved in septation. In the presence of cytoplasmic protein and essential GTPase, FtsZ polymerizes bi directionally at the centre of the cell on the inner membrane to form a highly dynamic helical structure known as the 'Z-ring' [15,16]. This Z-ring structure is essential in the septum formation and inhibiting this target leads to bacterial cell division arrest [17].

In our current research we have used MCULE software for molecular docking studies for all the synthesized compounds [18,19].

EXPERIMENTAL

Nuclear magnetic resonance (Bruker), ^{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. 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 vapours.

General procedure for the synthesis of 1-(1-arylmethylpiperidin-4yl)-5-chloro-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives: 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, a progress of the reaction was monitored by thin layer chromatography (TLC) by using hexane and ethylacetate as mobile phase (2:1). Then the reaction mixture was cooled to room temperature and excess K_2CO_3 was filtered off and subsequently washed with acetonitrile (2 × 50 mL) to get pure product (**Scheme-I**).



Scheme-I: Synthesis of 1-(1-arylmethylpiperidin-4yl)-5-chloro-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives

Characterization data of synthesized compounds (DSR 1-8)

1-(1-Benzylpiperidin-4-yl)-5-chloro-1*H*-benzo[*d*]-imidazol-2(3*H*)-one (DSR-1): Yield: 42.5; m.p.: 196 °C; Anal. calcd. (%) for $C_{19}H_{20}N_3OCl$: 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, ν_{max}, cm^{-1}): 3157, 1685, 1398, 1159, 1105; ^{1}H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-2): Yield: 38.6; m.p.: 240 °C; Anal. calcd. (%) for $C_{19}H_{19}N_3OCl_2$: 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, ν_{max}, cm^{-1}): 3165, 1710, 1450, 1238, 1110; ^{1}H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-3): Yield: 34.4; m.p.: 226 °C; Anal. calcd. (%) for $C_{19}H_{19}N_3OBrCl$: 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, ν_{max}, cm^{-1}): 3260, 1670, 1480, 1340, 1250; ^{1}H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-4): Yield: 36.2; m.p.: 185 °C; Anal. calcd. (%) for $C_{19}H_{19}N_3O_2Cl$: 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, ν_{max}, cm^{-1}): 3170, 1685, 1390, 1350, 1150; ^{1}H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-5): Yield: 45.4; m.p.: 226 °C; Anal. calcd. (%) for $C_{20}H_{22}N_3OCl$: 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, ν_{max}, cm^{-1}): 3250, 3100, 1690, 1425, 1375, 1175; ^{1}H NMR ($CDCl_3$, 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].

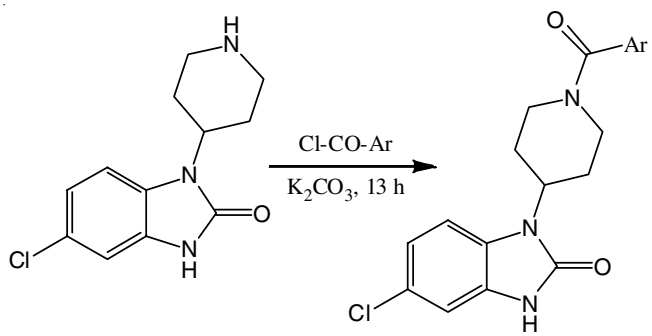
1-(1-(2-Chlorobenzyl)piperidin-4-yl)-5-chloro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-6): Yield: 24.2; m.p.: 214 °C; Anal. calcd. (%) for $C_{19}H_{19}N_3OCl_2$: C, 60.65; H, 5.09; Cl, 18.84; N, 11.17; O, 4.25; found (%): C, 56.4; H, 4.56; Cl,

17.29; N, 10.41; O, 3.25; IR (KBr, ν_{max}, cm^{-1}): 3275, 1675, 1335, 1240, 1145; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-7): Yield: 32.8; m.p.: 184 °C; Anal. calcd. (%) for $C_{19}H_{20}N_3O_2Cl$: 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, ν_{max}, cm^{-1}): 3180, 1690, 1360, 1270, 1135; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-8): Yield: 29.6; m.p.: 178 °C; Anal. calcd. (%) for $C_{20}H_{22}N_3OCl$: 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, ν_{max}, cm^{-1}): 3015, 1710, 1470, 1340, 1275, 1135; ^1H NMR ($CDCl_3$, 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].

General procedure for the synthesis of 1-(1-arylcarbonylpiperidin-4yl)-5-chloro-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives: 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 aroyl 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 ethylacetate 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 (**Scheme-II**).



Scheme-II: Synthesis of 1-(1-arylcarbonylpiperidin-4yl)-5-chloro-1*H*-benzo[*d*]imidazole-2(3*H*)-one derivatives

Characterization of synthesized compounds (DSR 9-16)

1-(1-Benzoylpiperidin-4-yl)-5-chloro-1*H*-benzo[*d*]-imidazol-2(3*H*)-one (DSR-9): Yield: 42.8; m.p.: 215 °C; Anal. calcd. (%) for $C_{19}H_{18}N_3O_2Cl$: 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, ν_{max}, cm^{-1}): 3100, 1690, 1340, 1260, 1180, 1135; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-10): Yield: 37.4; m.p.: 284 °C; Anal. calcd. (%) for $C_{19}H_{17}N_3O_2Cl_2$: 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, ν_{max}, cm^{-1}): 3155, 1690, 1350, 1138; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-11): Yield: 33.6; m.p.: 292 °C; Anal. calcd. (%) for $C_{19}H_{17}N_3O_2BrCl$: 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, ν_{max}, cm^{-1}): 3075, 1710, 1420, 1237; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-12): Yield: 37.7; m.p.: 284 °C; Anal. calcd. (%) for $C_{19}H_{18}N_3O_3Cl$: 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, ν_{max}, cm^{-1}): 3240, 3125, 1685, 1440, 1137; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-13): Yield: 39.2; m.p.: 278 °C; Anal. calcd. (%) for $C_{20}H_{20}N_3O_2Cl$: 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, ν_{max}, cm^{-1}): 3170, 1678, 1340, 1235; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-14): Yield: 28.3; m.p.: 244 °C; Anal. calcd. (%) for $C_{19}H_{17}N_3O_2Cl_2$: 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, ν_{max}, cm^{-1}): 3166, 1692, 1376, 1160; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-15): Yield: 24.5; m.p.: 212 °C; Anal. calcd. (%) for $C_{19}H_{18}N_3O_3Cl$: 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, ν_{max}, cm^{-1}): 3200, 1687, 1400, 1158; ^1H NMR ($CDCl_3$, 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-1*H*-benzo[*d*]imidazol-2(3*H*)-one (DSR-16): Yield: 32.7; m.p.: 234 °C; Anal. calcd. (%) for $C_{20}H_{20}N_3O_2Cl$: 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, ν_{max}, cm^{-1}): 3170, 2978, 1684, 1420, 1154; ^1H NMR ($CDCl_3$, 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].

Antitubercular activity: All the synthesized compounds (**DSR 1-16**) were tested for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv by Microplate Alamar Blue assay (MABA) under aerobic conditions. All the solutions were prepared by using Millipore water and all media was sterilized by autoclave. Prepared media was protected from direct light and stored at 4 ºC. MABA cell stock and MABA solutions were prepared by established protocols.

***in vitro* Cytotoxicity screening by MTT assay:** The MTT assay has been widely used to assess cell viability due to its effective and less time consuming process. The method involved in this reaction is the enzymatic reduction of 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT) to MTT-formazan is catalyzed by mitochondrial succinate dehydrogenase. The MTT assay is dependent on mitochondrial respiration and indirectly serves to assess the cellular energy capacity of a cell. The solutions were prepared and measured its absorbance as per established procedures [20].

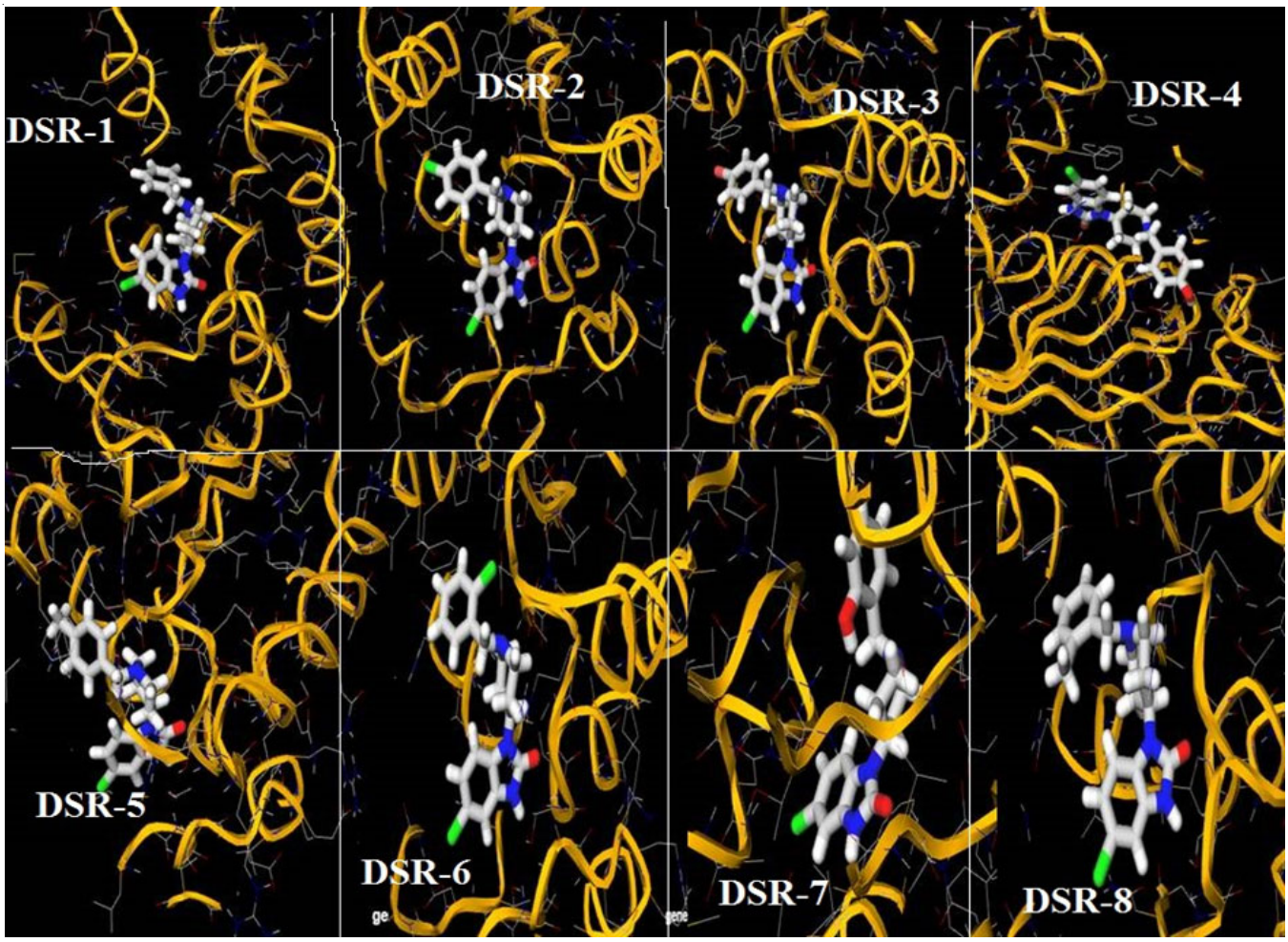
RESULTS AND DISCUSSION

A total of sixteen 5-chlorobenzimidazole-2-one derivatives were synthesized by using established protocols. The compounds were purified and obtained in good yields. The synthesized molecules were characterized by using spectral analysis including NMR, IR and Mass. All the synthesized molecules were having druggable nature according to the Lipiski rule.

Antitubercular activity: The synthesized compounds were screened for antitubercular activity by using MABA. Among the sixteen compounds, DSR-9 and DSR-16 have shown excellent antitubercular activity with an MIC 4.16 and 2.35 µg/mL, respectively.

***in vitro* Cytotoxicity screening by MTT assay:** Compound **DSR-14** was evaluated for cytotoxicity on normal and cancer cell lines which shows non-toxicity to normal cells at 50 µg/mL.

Molecular docking studies: Molecular docking studies were performed by using MCule software. The target protein mtFtsZ (2Q1Y) was obtained from protein data bank. The synthesized molecules (**DSR 1-16**) were docked against the target by using 1-click docking application in the software. Out of sixteen compounds **DSR-12**, **DSR-14** and **DSR-16** got good docking scores *i.e.* -9.2 kcal/mol. The resulting docking poses are presented in Fig. 1.



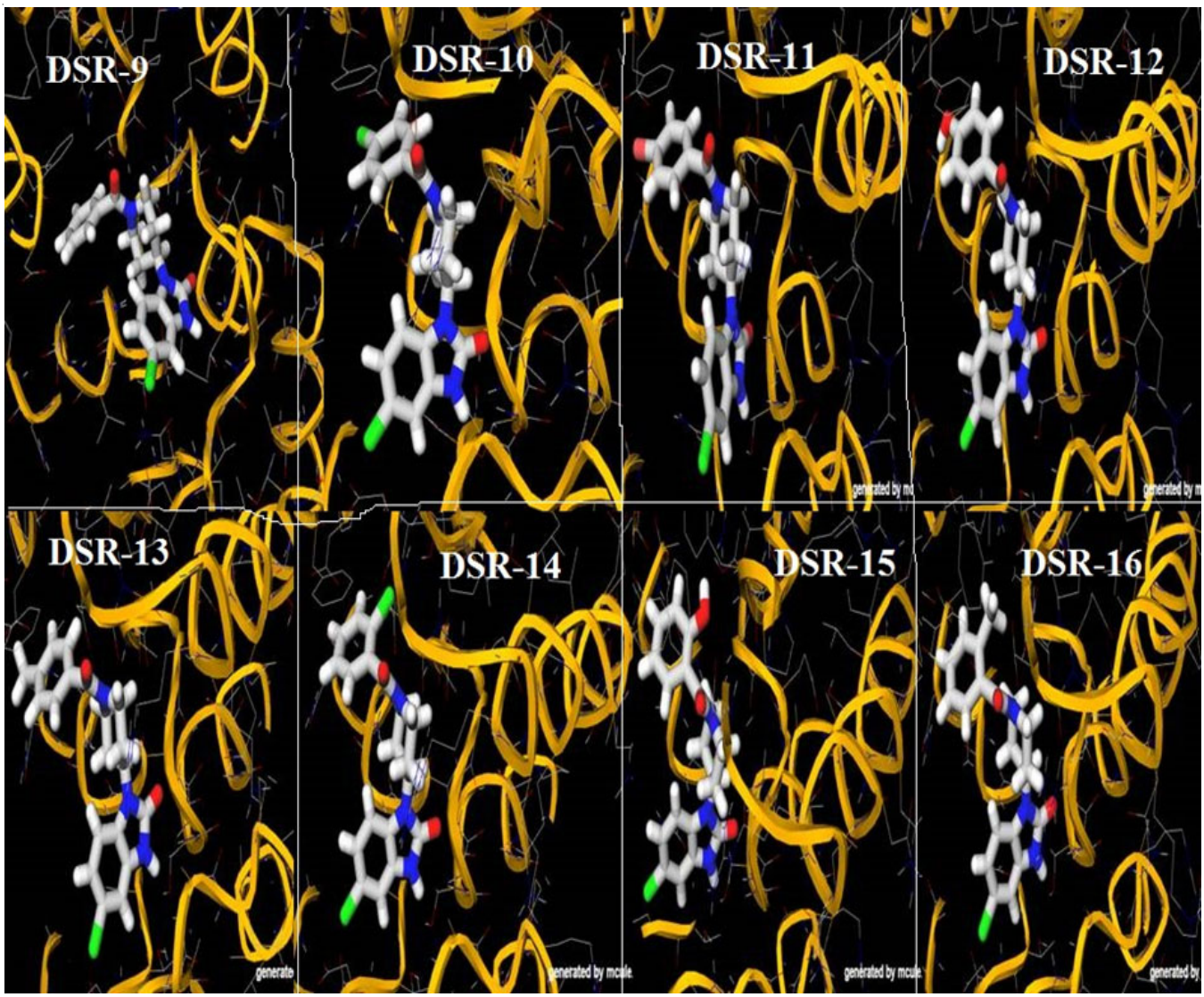


Fig. 1. Generated docking pose of synthesized molecules

TABLE-1
ANTITUBERCULAR ACTIVITY AND DOCKING SCORES OF THE COMPOUNDS **DSR 1-16**

Compound	Antitubercular activity		Docking score (kcal/mol)
	MABA MIC (µg/mL)	MTT assay (% inhibition)	
DSR-1	48	68	-8.0
DSR-2	50	54	-8.0
DSR-3	50	64	-7.8
DSR-4	36	78	-8.5
DSR-5	42	59	-8.1
DSR-6	7.25	62	-8.1
DSR-7	13.4	76	-8.3
DSR-8	6.79	72	-8.2
DSR-9	4.16	84	-8.8
DSR-10	5.24	79	-8.9
DSR-11	9.98	80	-8.7
DSR-12	7.80	55	-9.2
DSR-13	13.44	58	-9.1
DSR-14	2.35	86	-9.2
DSR-15	38.7	74	-8.8
DSR-16	5.55	80	-9.2
Rifampicin	–	85	–
Pyrazinamide	3.225	–	–

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