Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Information

Green, efficient and large-scale synthesis of benzimidazoles, benzoxazoles and benzothiazoles derivatives using ligand-free cobalt-nanoparticles: as potential anti-estrogen breast cancer agents, and study of their interactions with estrogen receptor by molecular docking

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1. Experimental

1.1 Materials

All general chemicals were supplied by Merck Chemicals (Germany). All of the reagents were used without any further purification. The products were purified via crystallization process to obtain the corresponding products in to 83-96 % yields. Melting points were determined using Stuart Scientific SMP2 apparatus. ^{1}H and ^{13}C NMR were performed on Bruker-avance 500 MHz spectrometer in $CDCl_3$ using TMS as internal standard. The Fourier transform infrared (FT-IR) spectra were recorded on a Jasco-680 (Japan) spectrophotometer in KBr pellets and reported in cm^{-1}. A scanning electron microscope (SEM) (Philips XL 20) was used to observe the size and morphology of the catalyst. XRD patterns were recorded by an Xpert MPD, X-ray diffractometer using CuKα radiation.

1.2. General procedure for preparation of cobalt (II) nanoparticles

In a typical procedure, a solution of 0.5 M (10 mL) of cobalt sulfate was prepared using dematerialized water. Then, required amount of hydrazine (2 M, 10 mL) and NaOH solution (10 mL, 60%) was added in sequence. The entire Co^{2+} ion in the solution was allowed to precipitate under ultra-sonication process. The reduced black powder was washed thoroughly with dilute HCl to remove traces of alkali and finally with ethanol, the powder was dried under vacuum at 50 ºC for overnight.

1.3. General procedure for synthesis of benzimidazoles, benzoxazoles, benzothiozoles

Benzoxazole: In a round-bottomed flask equipped with a condenser and a magnetic stirrer, 2-bromoaniline (172 mg, 1 mmol) and 4-hydroxy-benzoyl chloride (166 µL, 1.5 mmol), reacted together in aqueous sodium hydroxide (10 mL, 30 %) to obtain bromoamids. *N*-(2-bromo-phenyl)-4-hydroxy-benzamide (204 mg, 0.7 mmol), K_2CO_3 (207 mg, 1.5 mmol) and cobalt nanostructure (5 mg, 10 mol%) was stirred in ethanol (2 mL) under air atmosphere for the appropriate time (Table 1). The progress of the reaction was monitored by TLC (eluent: n-hexane /ethyl acetate, 4:1). After completion of the reaction CH_2Cl_2 (15 mL) was added and the catalyst was separated by centrifuge. The catalyst was washed and dried. The residue was purified by recrystallization from ethanol to obtain the corresponding products in 87-95 % yields.

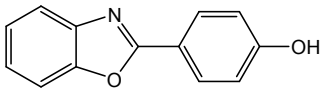
Benzothiazole: In a round-bottomed flask equipped with a condenser and a magnetic stirrer, 2-bromoaniline (172 mg, 1 mmol) and 4-hydroxy-benzoyl chloride (166 µL, 1.5 mmol), reacted together in aqueous sodium hydroxide (10 mL, 30 mol%) to obtain bromoamids; Next, *N*-(2-bromo-phenyl)-4-hydroxy-benzamide (204 mg, 0.7 mmol) was dispersed in toluene (15 mL), and HMDO (162 mg, 1.0 mmol) was added with stirring. The mixture was heated to 60 °C, phosphorus pentasulfide (220 mg, 0.5 mmol) was added with further toluene (5 mL), and then the mixture was heated under reflux for 5 h. After cooling, toluene was evaporated under reduced pressure.[1] The product was purified by column chromatography (hexane: ethyl acetate 3:2) to give desired product as a yellow-orange solid. *N*-(2-Bromo-phenyl)-4-hydroxy-thiobenzamide (154mg, 0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol) and cobalt nanostructure (4 mg, 10 mol%) was stirred in ethanol (2 mL) under air

atmosphere for the appropriate time (Table 1). The progress of the reaction was monitored by TLC (eluent: n-hexane /ethyl acetate, 4:1). After completion of the reaction CH_2Cl_2 (15 mL) was added and the catalyst was separated by centrifuge. The catalyst was washed and dried. The residue was purified by recrystallization from ethanol to obtain the corresponding products in 88-96 % yields.

Benzimidazole: In a round-bottomed flask equipped with a condenser and a magnetic stirrer, 2-bromoaniline (0.172 g, 1 mmol) and 4-hydroxy-benzoyl chloride (166 μL, 1.5 mmol) reacted together to obtain bromoamids. In a round bottom flask, *p*-toluenesulfonic acid (10 mg, 6 mol%) was slowly added to a mixture of a *N*-(2-bromo-phenyl)-4-hydroxy-benzamide (203 mg, 0.7 mmol) and 4-amino-phenol (109 mg, 1.0 mmol) in 2 mL EtOH. [2] The resulting mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. The product was obtained upon recrystallization. N-(2-Bromo-phenyl)-N'-(4-hydroxy-phenyl)-benzamidine (183 mg, 0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol) and cobalt nanostructure (4 mg, 10 mol %) was added to reaction mixture and refluxed in ethanol (2 mL) under air atmosphere. The progress of the reaction was monitored by TLC (eluent: n-hexane /ethyl acetate, 4:1). After completion of the reaction, the resulting mixture was diluted with ethyl acetate, and washed with brine. The organic layer was dried and concentrated under vacuum. The resulting residue was separated by silica gel column (eluent: n-hexane /ethyl acetate, 9:1) to yield final compounds (83-91%).

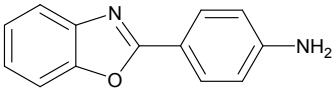
2. Characterization of products

1a)



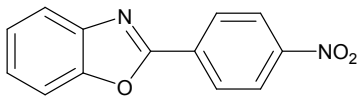
White solid; yield 95%; mp 156–157 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (m, 2H), 7.63–7.61 (m, 1H), 7.32–7.13 (m, 2H), 7.07–7.01 (m, 1H), 6.97–6.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 151.2, 142.6, 133.4, 129.6, 126.8, 153.4, 143.9, 139.9, 138.3, 110.6,. FT-IR (neat) 3520, 3060, 2949, 2920, 2857, 1642, 1610, 1505, 1472, 1455, 1441, 1378, 1326, 1305, 1265, 1074, 1136, 1155, 1192 cm^{-1}; Anal. Calcd (%) for $C_{13}H_9NO_2$: C, 73.9; H, 4.2; N, 6.6; found: C, 74.1; N, 6.8

1b)



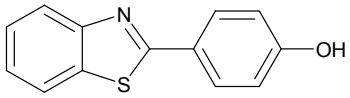
White solid; yield 92%; mp 116–117 ºC; ^{1}H NMR $CDCl_3$, 500 MHz: δ 7.92–7.90 (d, J = 8.4 Hz, 2H), 7.74–7.72 (m, 1H), 7.59–7.56 (m, 1H), 7.34–7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.5, 156.8, 145.3, 134.4, 130.1, 127.6, 127.6, 124.2, 120,7, 110.3; FT-IR (KBr) 3430, 3281, 2967, 2924, 2855, 1651, 1459, 1437, 1411, 1346, 1242, 1175, 1021 cm^{-1}, Anal. Calcd (%) for $C_{13}H_{10}N_2O$: C, 74.3; H, 4.8; N, 13.3; found: C, 74.8; N, 13.9.[3]

1c)



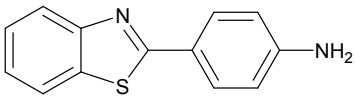
White solid; yield 56%; mp 93–94 ºC; ^{1}HNMR ($CDCl_3$, 500 MHz): δ 8.13–8.09 (m, 2H), 7.61–7.59 (d, J = 8.0 Hz, 2H) 7.47-7.50 (m, 4H), ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.7, 150.1, 140.3, 134.7, 130.9, 128.4, 127.9, 126.8, 125.3, 123.9, 121.2; FT-IR (KBr) 3054, 2920, 2856, 1424, 1657, 1615, 1554, 1481, 1448, 1351, 1337, 1242, 1021, 1175, cm^{-1}. Anal. Calcd (%) for $C_{13}H_8N_2O_3$: C, 60; H, 3; N, 17; found: C, 62.1; N, 16.8. [4]

2a)



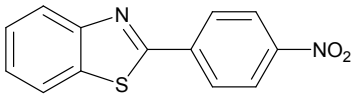
White solid; yield: 96%; m.p: 100–101 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66–7.63 (m, 2H), 7.42–7.48 (m ,2 H), 7.50–7.46 (m, 2H), 7.33–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.2, 149.9, 143.2, 131.2, 129.8, 126.8, 126.1, 125.3, 124.4, 120.2; FT-IR (KBr) 3520, 3059, 2966, 1645, 1619, 1557, 1479, 1450, 1344, 1314, 1241, 1186, 1052, 1020 cm^{-1}. Anal. Calcd (%) for $C_{13}H_9NSO$: C, 68.7; H, 4.0; N, 6.16; S, 14; found: C, 69.1; H, 4.03; N, 6.08; S, 13.87.[5]

2b)



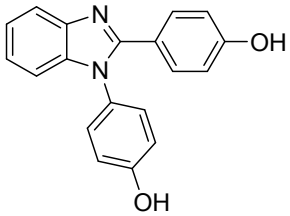
White solid; yield 94 %; m.p. 93–94 ◦C; ^{1}HNMR ($CDCl_3$, 500 MHz): δ 7.73–7.69 (m, 2H), 7.61–7.57 (m, 2H) 7.37-7.48 (m, 4H), ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.7, 150.1, 144.3, 135.7, 131.9, 128.4, 128.1, 127.8, 126.3, 125.9, 121.2; FT-IR (KBr) 3424, 3056, 2930, 2858, 1647, 1617, 1559, 1489, 1441, 1424, 1330, 1238, 1021, 1172, cm^{-1}. Anal. Calcd (%) for $C_{13}H_{10}N_2S$: C, 74.3; H, 4.8; N, 12.9; found: C, 74.45; H, 4.47; N, 12.60.[3]

2c)



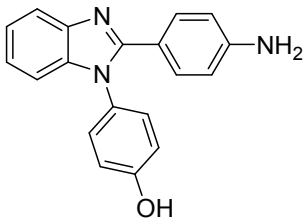
White solid; yield 88 %; mp 93–94 ◦C; ^{1}HNMR ($CDCl_3$, 500 MHz): δ 7.93–7.89 (m, 2H), 7.64–7.61 (m, 2H) 7.45-7.49 (m, 4H), ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.7, 153.1, 139.3, 136.7, 129.9, 128.1, 127.3, 126.8, 125.5, 124.2, 120.2; FT-IR (KBr) 3050, 2925, 2858, 1427, 1625, 1552, 1484, 1449, 1335, 1246, 1022, 1165 cm^{-1}. Anal. Calcd (%) for $C_{13}H_8N_2O_2S$: C, 60.9; H, 3.1; N, 10.9; found: C, 60.65; H, 3.27; N, 10.60.[4]

3a)



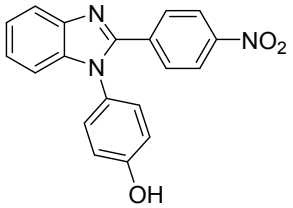
Yellow solid; yield 91%; mp 109–110 ºC, ^{1}H NMR (500 MHz, $CDCl_3$): δ: 7.68-7.62 (m, 2H), 7.45-7.43 (m, 4H), 7.40-7.19 (m, 4H), 7.47-7.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.3, 132.5, 132.3, 132.4, 132.2, 131.7, 131.6, 131.5, 128.7, 128.6, 128.5; FT-IR (KBr) 3520, 3050, 3022, 2982, 1658, 1597, 1490, 1476, 1451, 1387, 1322, 1301, 1274, 1255, 1178, 1071, 1024 cm^{-1}. Anal. Calcd (%) for $C_{19}H_{14}N_2O_2$: C, 75.50; H, 4.63; N, 9.27; found: C, 74.89; H, 4.23; N, 9.28.

3b)



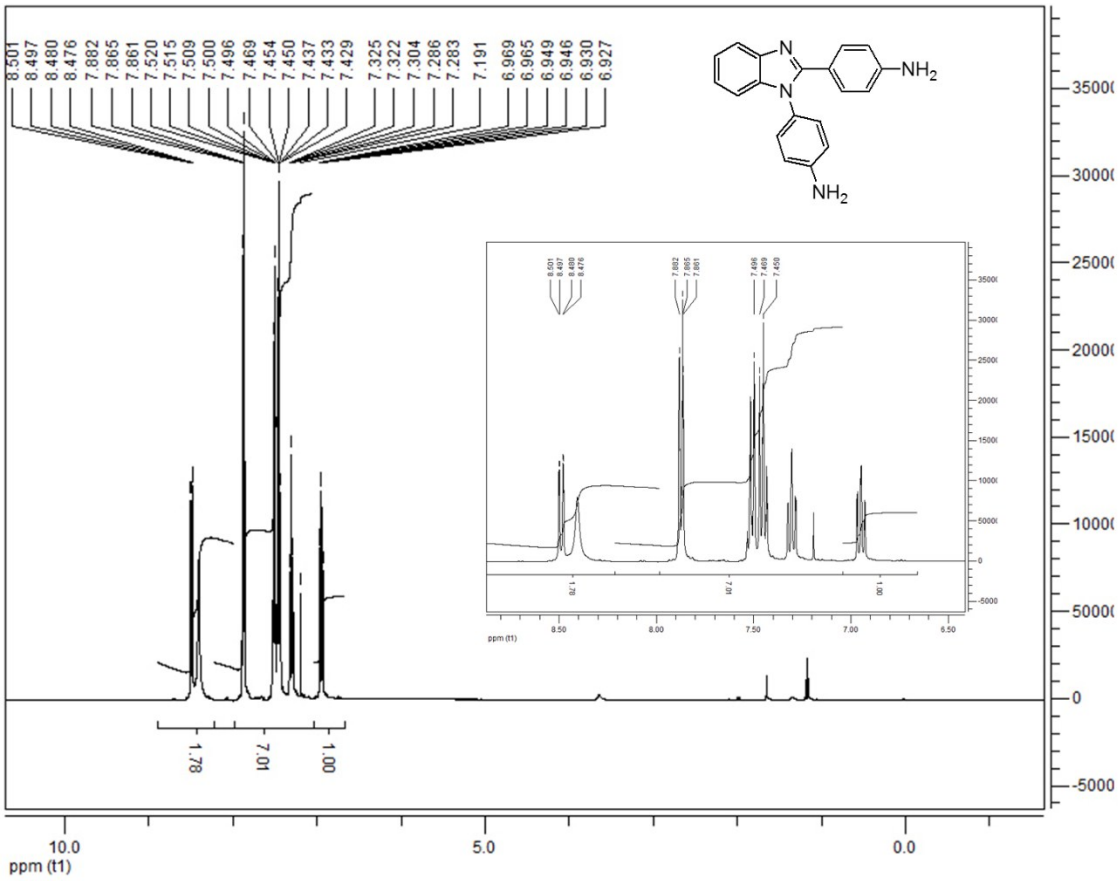
Yellow liquid; yield 79 %; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87-8.50 (m, 2H), 7.88-7.86 (m, 2H), 7.52-7.50 (m, 2H), 7.47-7.42 (m, 2H), 7.32-7.19 (m, 2H), 6.97-6.93 (m, 2H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 135.8, 134.6, 132.3, 132.2, 129.0, 127.1, 125.3, 121.8, 113.8; FT-IR (KBr) 3451, 3058, 2932, 1649, 1606, 1554, 1447, 1401.1, 1372.1, 1261, 1019 cm^{-1}. Anal. Calcd (%) for $C_{19}H_{15}N_3O$: C, 75.75; H, 5.00; N, 13.95; found: C, 74.60; H, 5.04; N, 14.06

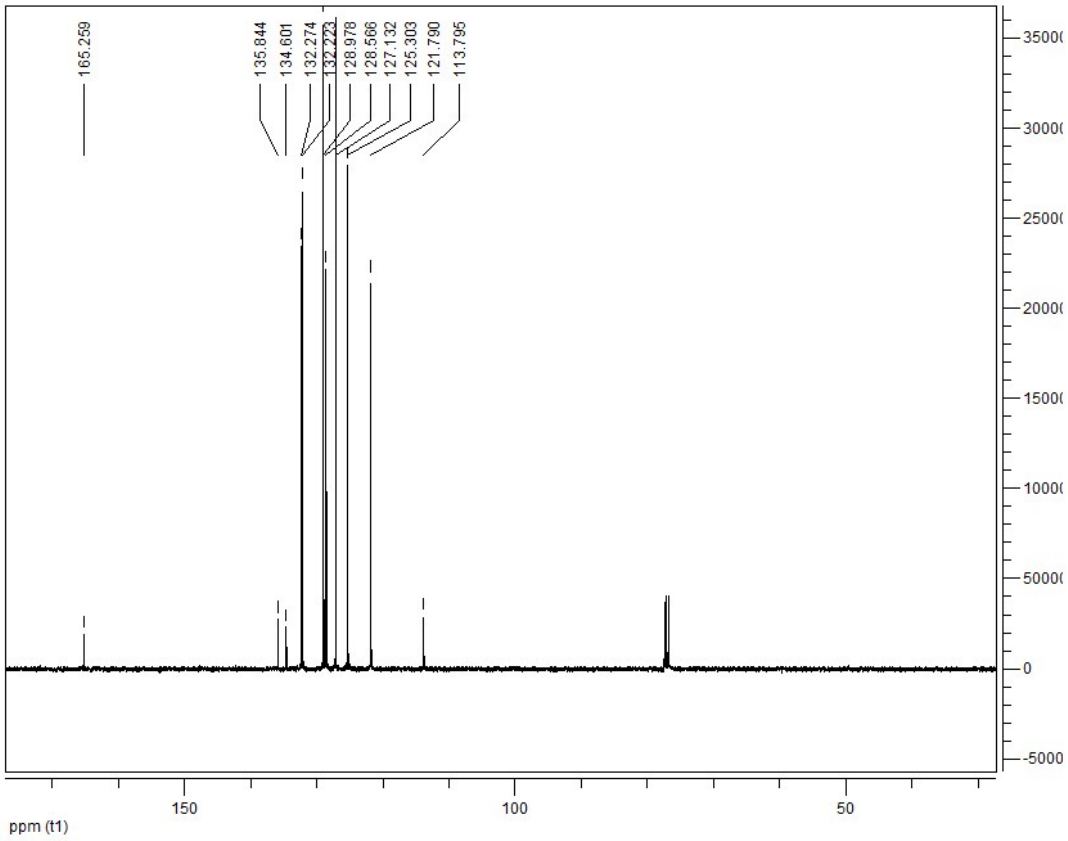
3c)

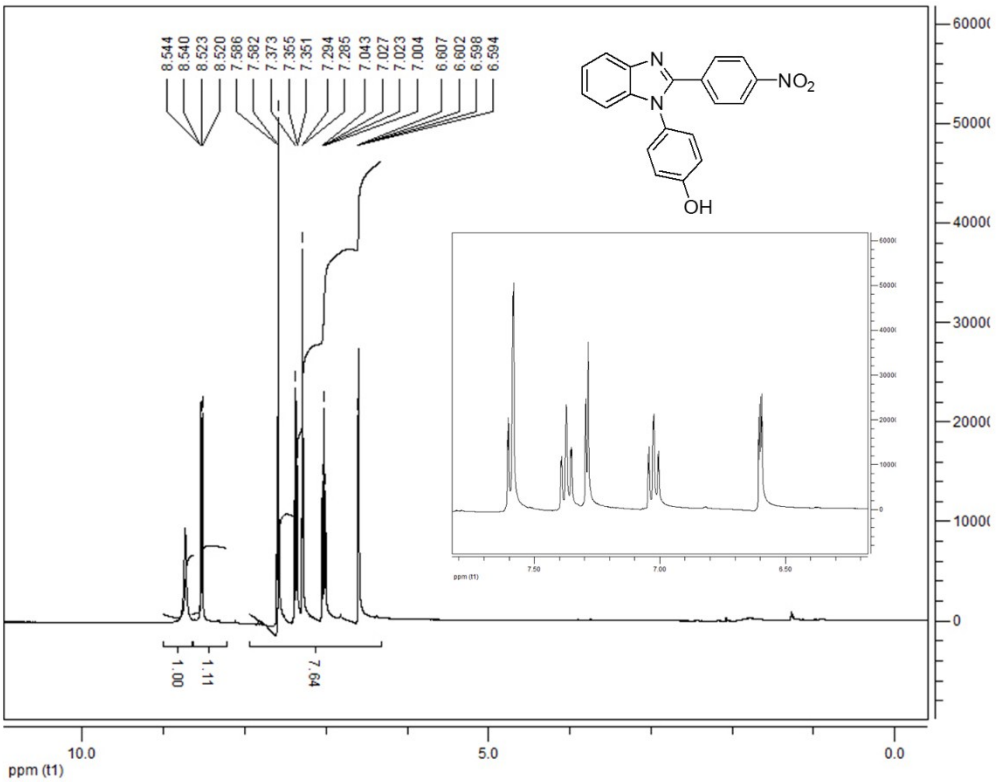


White solid; yield 83 %; mp 119–120 ◦C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54-8.52 (m, 2H), 7.59-7.58 (m, 4H), 7.37-7.35 (m, 2H), 7.29-7.28 (m, 2H), 7.05-7.00 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 147.7, 135.4, 132.3, 128.5, 125.2, 121.6, 115.7, 113.4, 112.7; FT-IR (KBr) 3543, 3062, 2957, 2839, 1606, 1546, 1514, 1472, 1458, 1442, 1353, 1325, 12285, 1210, 1186, 1074, 1028 cm^{-1}. Anal. Calcd (%) for $C_{19}H_{14}N_3O_3$: C, 68.68; H, 4.22; N, 12.65; found: C, 70.01; H, 4.35; N, 12.24.

Selected spectra:



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8.520
7.586
7.582
7.373
7.355
7.351
7.294
7.285
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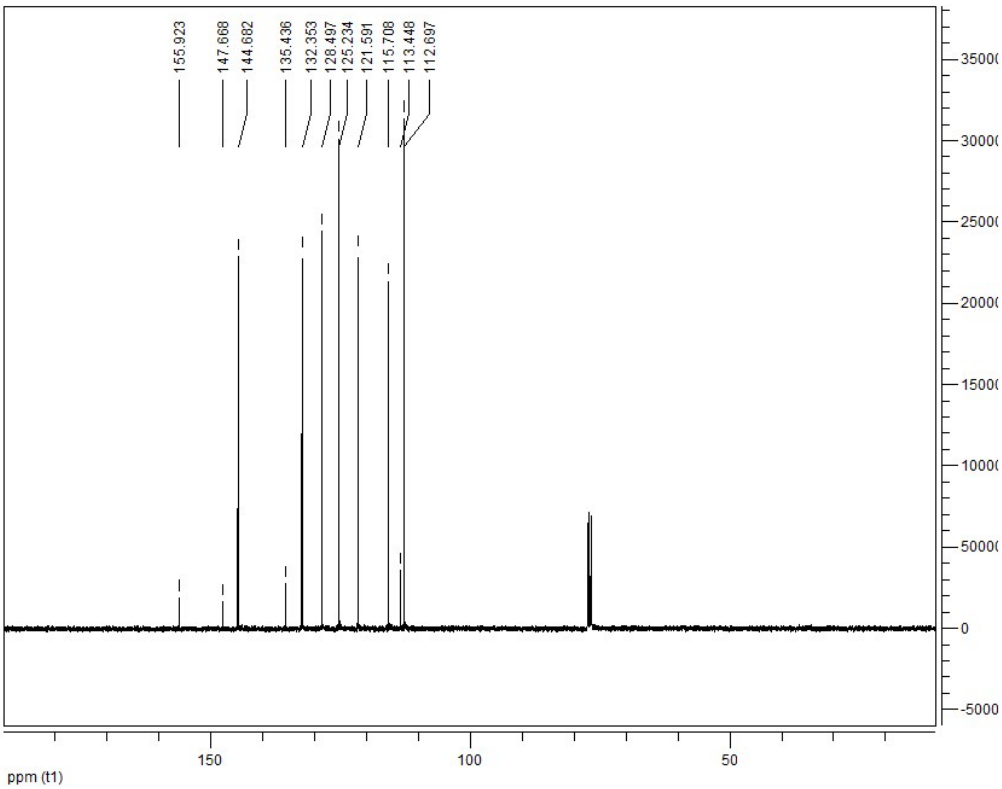
7.027
7.023
7.004
6.607
6.602
6.598
6.594
N
N
NO2
OH
1.00
1.11
7.64
10.0
5.0
0.0
ppm (t1)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135.436
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125.234
121.591
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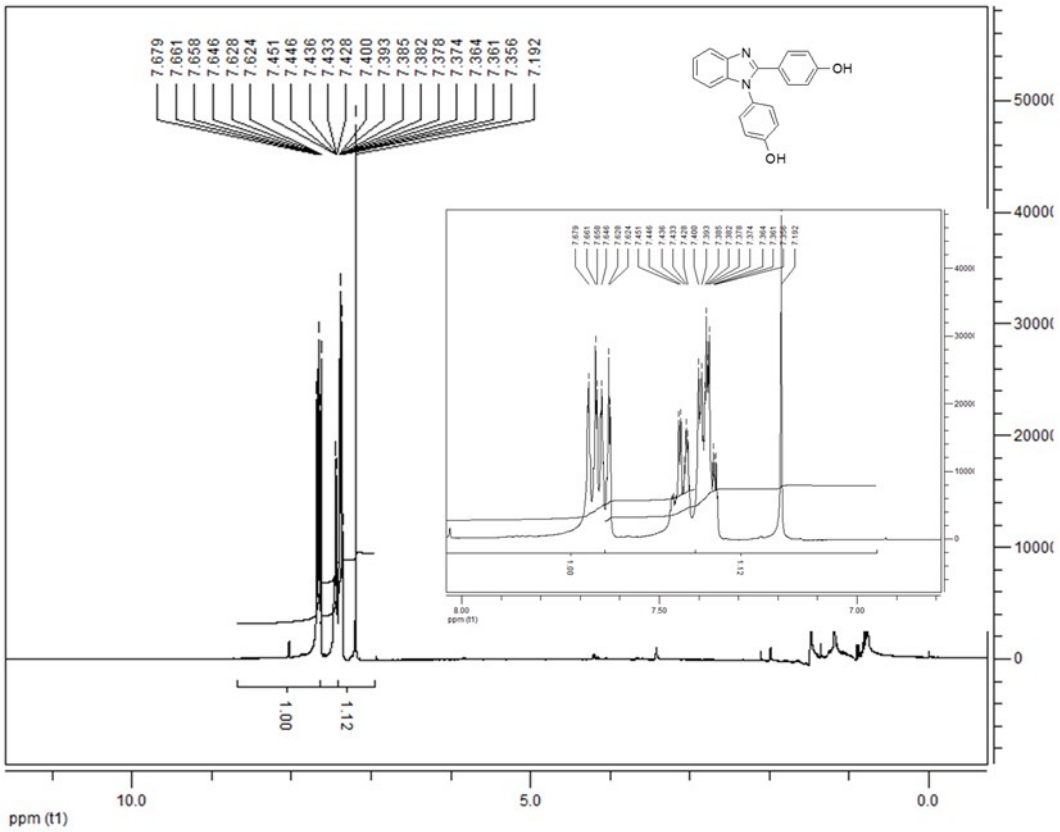
113.448
112.697
150
100
50
ppm (t1)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7.385
7.382
7.378
7.374
7.364
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7.356
7.192
OH
OH
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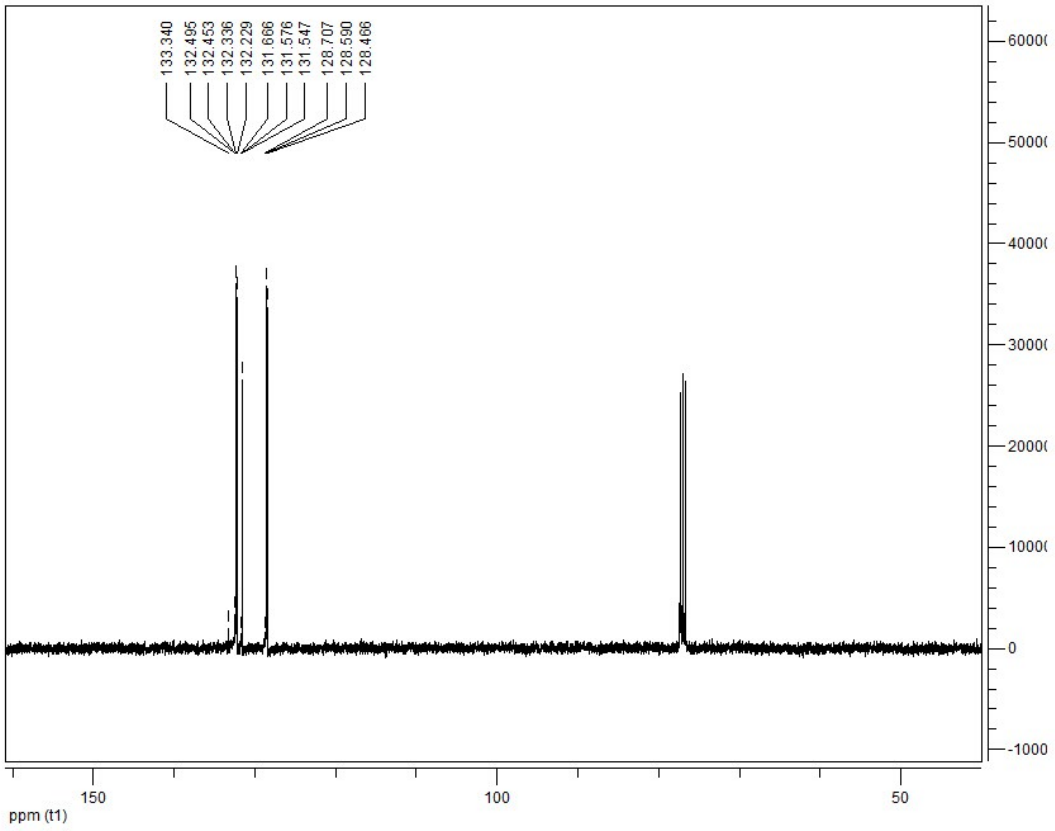
1.12
10.0
5.0
0.0
ppm (t1)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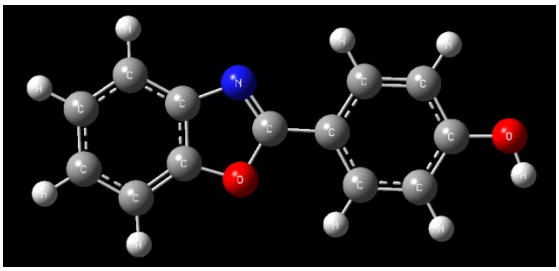
132.229
131.666
131.576
131.547
128.707
128.590
128.466
150
100
50
ppm (t1)

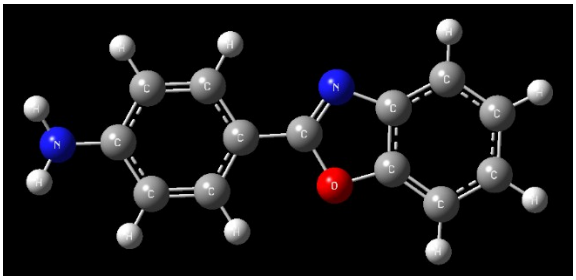
3. Results of docking studies

Figure 1. The optimized structure of ligands obtained at B3lyp/6-31+G(d,p) level of theory

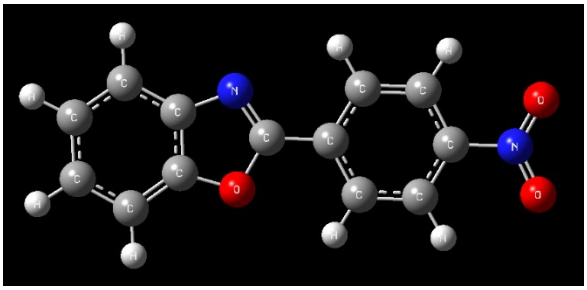
1a



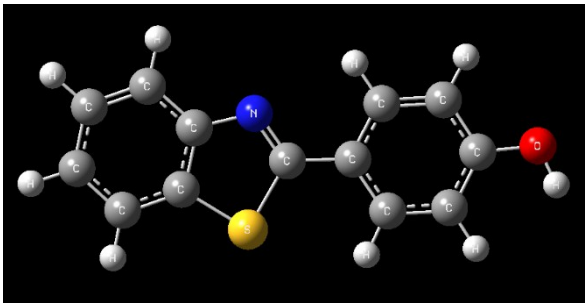
1b



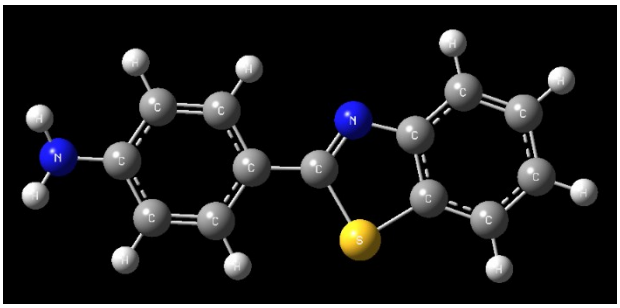
1c



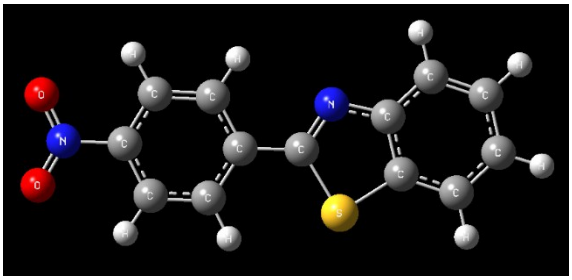
2a



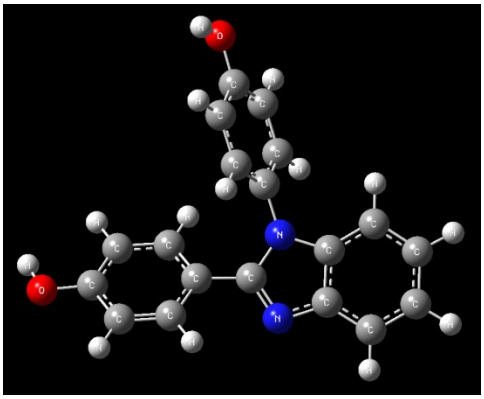
2b



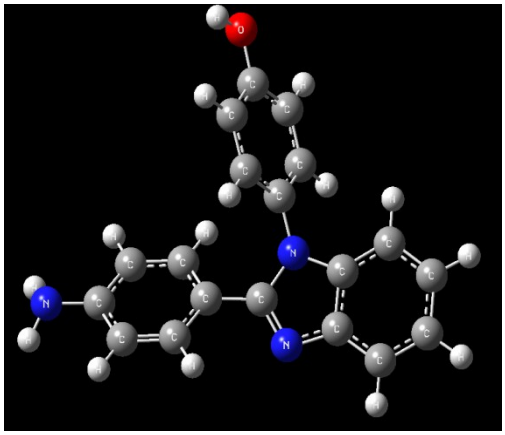
2c



3a



3b



3c

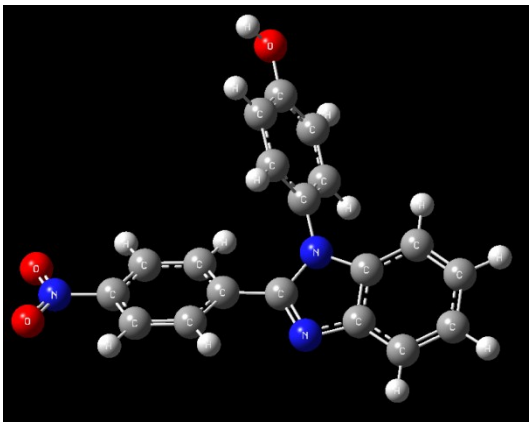
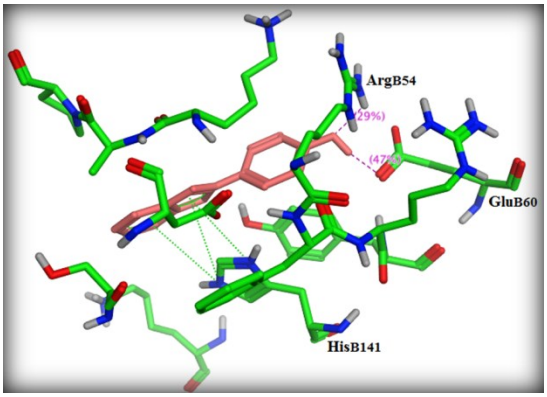
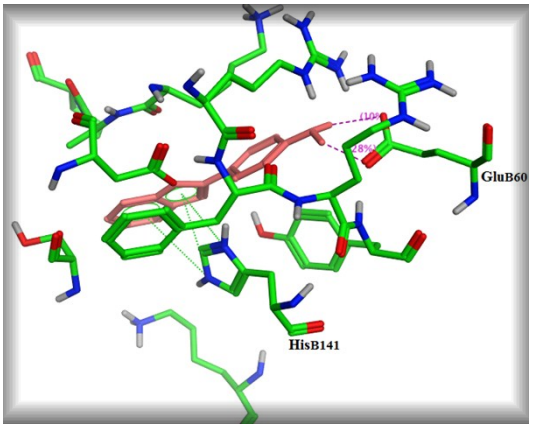


Figure 2. Superposition of the best docked poses of ligands in the active site of Ligands

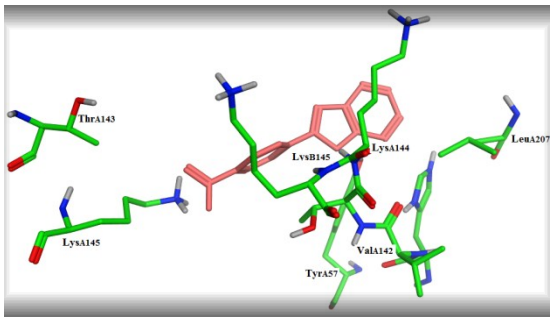
1a)



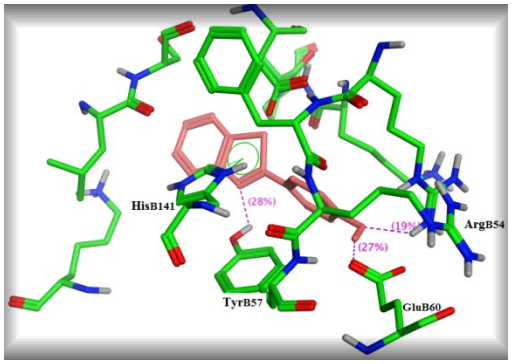
1b)


GluB60
HisB141

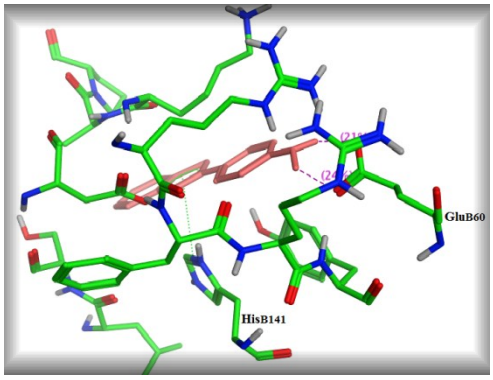
1c)


ThrA143
LysB145
LysA144
LeuA207
LysA145
ValA142
TyrA57

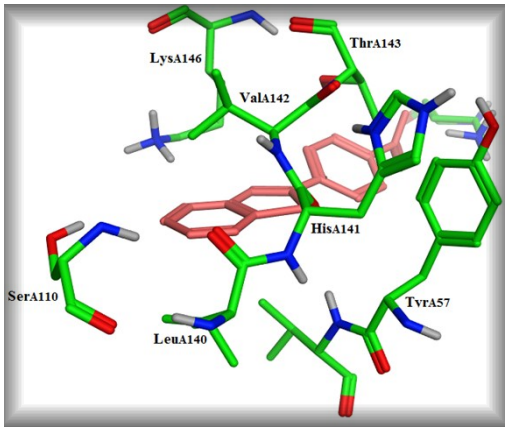
2a)


HisB141
(28%)
(19%)
(27%)
ArgB54
TyrB57
GluB60

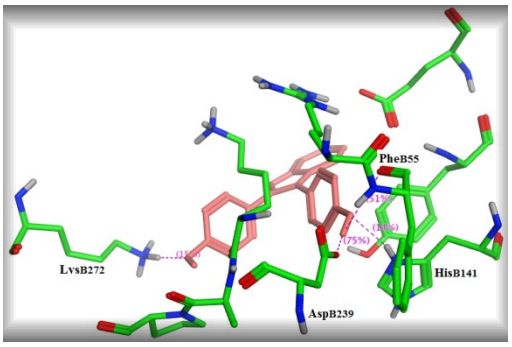
2b)


GluB60
HisB141

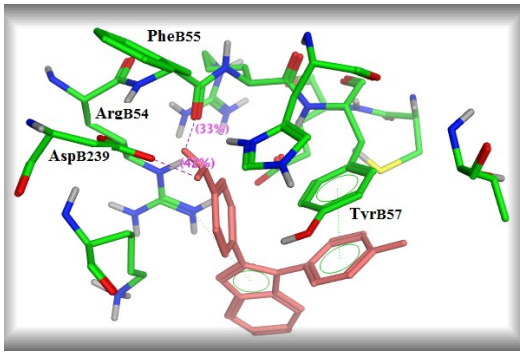
2c)


ThrA143
LysA146
ValA142
HisA141
SerA110
TyrA57
LeuA140

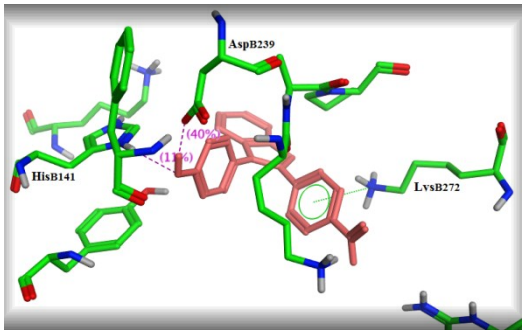
3a)


PheB55
LysB272
HisB141
AspB239

3b)


PheB55
ArgB54
(33%)
AspB239
TyrB57

3c)


AspB239
(40%)
(11%)
HisB141
LysB272

4. References

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