SYNTHESIS, MOLECULAR DOCKING AND ANTITUBERCULAR ACTIVITY OF NEW BI HETEROCYCLIC COMPOUNDS ON BENZIMIDAZOLE MOIETY

Dhanaja Kotte1, Kumaraswamy Gullapelli 2, Ravichandar Maroju2
Ramchander Merugur3, Brahmeshwari Gavaji1,*

1Department of Chemistry, Kakatiya University, 506009, Warangal - India
2Department of Chemistry, Mahatma Gandhi Institute of Technology, 500075, Hyderabad -India
3Department of Bio-Chemistry, Mahatma Gandhi University, 508254, Nalgonda- India
*E-mail: gbrahmeshwari@gmail.com

ABSTRACT
A series of new and efficient Benzo [d] imidazole-2-yl -3, 5 substituted diphenyl -3,3a,5,6 –Tetrahydro 2H-pyrazole thiazole derivatives (4a-j) were synthesized from Schiff base derivatives of thiazolidinediones (3a-j) using hydrazine hydrate. The synthesized compounds were screened for their antitubercular and molecular docking studies. The results of docking studies are supporting antitubercular activity showing high inhibition constant and binding energy. The structures of synthesized compounds were characterized by IR, 1H NMR, Mass spectroscopic methods.

Keywords: Synthesis, Molecular Docking, Antitubercular Activity, Benzimidazole Derivatives

INTRODUCTION
The quest for synthesis of novel materials for specific applications has become a great challenge for researchers aiming to address urgent real-world demands. To meet this target, significant attention has been paid to design and develop heterocyclic molecules owning desirable properties. Heterocyclic chemistry is highly challenging especially in the growing demand for higher efficiency and eco-friendly synthesis. It always attracts the attention of scientists working in the area of natural products and synthesis of heterocyclic compounds, especially with nitrogen-containing heterocyclic molecules that occupy the key position in the area of drugs and pharmaceuticals. Majority of the pharmaceutical products are heterocyclic molecules that meet the expectations of biological and industrial requirements.

The present study involves the synthesis of high bioactive compounds like benzimidazole, thiazole and pyrazole which exhibit various biological activities like antitumor10, analgesic11, antimicrobial12-13, antibacterial14-15 and anti-inflammatory etc . Hence, in this direction, efforts have been undertaken to introduce most active and biologically versatile molecules containing nitrogen and sulphur triheterocyclic compounds like Benzo [d] imidazole-2-yl -3, 5 substituted diphenyl -3,3a, 5, 6 –Tetrahydro 2H-pyrazole thiazole derivatives which were synthesized from 2-amino-substituted benzimidazole.

EXPERIMENTAL
Materials and Methods
Progress of the reaction was observed by TLC plates. IR Spectra were recorded by Perkin Elmer BX series and 1H NMR spectra were recorded by Bruker 400 MHz instrument using DMSO as solvent and TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. Mass spectra were measured on a GC/MS-QP1000EX (EI, 70 eV) mass spectrometer. Elemental analysis was performed on PerkinElmer 240 CHN analyzer.
General Reaction Procedure for Compound 2
A mixture of Benzaldehyde (0.004 mol) and 2-amino benzimidazole (1) (0.004 mol) with few drops of glacial acetic acid was refluxed in ethanol for about 4 hours. Reaction progress was monitored by TLC. After the completion of the reaction, the product was cooled, filtered and dried then recrystallized with methanol to afford the compound Schiff base (2).

General Reaction Procedure for Compound 3:
An equimolar mixture of compound 2 (0.01), mercaptoacetic acid (0.01) and aromatic aldehyde (0.01) in 1,4-dioxane (30 ml) containing a small amount of ZnCl$_2$ was refluxed for about 6 hours. The resulting product was filtered and cooled in an ice bath to attain room temperature. The solid product was filtered and washed with 10% sodium bicarbonate and recrystallized with alcohol.

The remaining compounds (3b-3h) were prepared by similar procedure with minor changes as per the reaction conditions.

(Z)-3-(1H-benzo [d] imidazole -2-yl )-5-benzylidene-2-phenylthiazolidin-4-one (3a)
IR (KBr, cm$^{-1}$): 3328 (N-H), 1548 (C=N), 1230 (C=S), 3HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 5.92 (s, 1H CH-Ar), 7.12-7.22 (m, 4H, Ar-H), 7.26-7.48 (m, 5H, Ar-H), 7.56-7.74 (m, 5H, Ar-H), 9.85 (br, 1H, NH). MS, m/z (%), 383 (M$^+$); Anal. calcd for C$_{23}$H$_{17}$N$_3$OS: C, 72.08; H, 4.47; N, 10.97 %. Found C, 71.45; H, 4.24; N, 10.23%.

(Z)- 3-(1H-benzo [d]imidazole -2-yl )-5-(4-methylbenzylidene)-2-phenylthiazolidin-4-one (3b)
IR (KBr, cm$^{-1}$): 3337 (N-H), 2960 (C-H), 1561 (C=N), 1672 (C=O), 1249 (C=S); 3HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 2.85 (s, 3H, CH$_3$), 5.86 (s, 1H, N-CH-Ar), 7.15-7.24 (m, 4H, Ar-H), 7.28-7.38 (m, 4H, Ar-H), 7.542-7.64 (m, 4H, Ar-H), 9.96 (br, 1H, NH). MS, m/z (%), 397 (M$^+$); Anal. calcd for C$_{24}$H$_{19}$N$_3$OS: C, 72.52; H, 4.82; N, 10.57 %. Found C, 71.81; H, 4.63; N, 10.24%.

(Z)- 3-(1H-benzo [d]imidazole -2-yl )-5-(4-methoxybenzylidene)-2-phenylthiazolidin-4-one (3c)
IR (KBr, cm$^{-1}$): 3341 (N-H), 3046 (C-H), 1561 (C=N), 1678 (C=O), 1239 (C=S); 3HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 3.45 (s, 3H, OCH$_3$), 5.72 (s, 1H, N-CH-Ar), 7.18-7.25 (m, 4H, Ar-H), 7.26-7.51 (m, 5H, Ar-H), 7.65 -7.84 (m, 4H, Ar-H), 10.05 (br, 1H, NH). MS, m/z (%), 413 (M$^+$); Anal. calcd for C$_{24}$H$_{19}$O$_2$N$_3$S: C, 69.71; H, 6.62; N, 10.16 %. Found C, 69.02; H, 4.36; N, 10.02%.

(Z)- 3-(1H-benzo [d]imidazole -2-yl )-5-(4-hydroxybenzylidene)-2-phenylthiazolidin-4-one (3d)
IR (KBr, cm$^{-1}$): 3514 (OH), 3346 (N-H), 1566 (C=N), 1678 (C=O), 1239 (C=S); 3HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 5.88 (s, 1HCH-Ar), 7.14-7.28 (m, 4H, Ar-H), 7.30-7.48 (m, 5H, Ar-H), 7.58-7.72 (m, 5H, Ar-H), 7.85-8.00 (m, 5H, Ar-H), 9.85 (br, 1H, NH). MS, m/z (%), 383 (M$^+$); Anal. calcd for C$_{25}$H$_{17}$N$_3$OS: C, 72.08; H, 4.47; N, 10.97 %. Found C, 71.45; H, 4.24; N, 10.23%.


ANTITUBERCULAR ACTIVITY OF NEW BI HETEROCYCLIC

Dhanaja Kotte et al.
10.01 (br, 1H, NH), 11.28(s,1H, OH); MS, m/z (%), 428 (M⁺); Anal. calcd for C$_{23}$H$_{16}$N$_4$O$_3$S: C, 64.47; H, 3.76; N, 13.08 %. Found C, 64.23; H, 3.84; N, 12.81%.

(Z)-3-(1H-benzo[d]imidazole-2-yl)-5-(4-nitrobenzylidene)-2-phenylthiazolidin-4-one (3e) 
IR (KBr, cm$^{-1}$): 3340 (N-H), 1572 (C=N), 1522 (-NO$_2$), 1684 (C=O), 1236 (C=S), 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 5.85 (s, 1HCH-Ar), 7.13-7.27 (m, 4H, Ar-H), 7.30-7.48 (m, 5H, Ar-H), 8.12-8.34 (m,4H, Ar-H), 10.18 (br, 1H, NH); MS, m/z (%), 399 (M⁺); Anal. calcd for C$_{23}$H$_{17}$N$_3$O$_2$: C, 68.45; H, 4.04; N, 10.40%.

(Z)-3-(1H-benzo[d]imidazole-2-yl)-5-(4-(dimethylamino)benzylidene)-2-phenylthiazolidin-4-one (3f) 
IR (KBr, cm$^{-1}$); 3328 (N-H), 1562 (C=N), 1675 (C=O), 1315(3°amine) 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 3.22 (s, 3H, OCH$_3$), 5.72  (s, 1H, N-CH-Ar) , 7.17-7.28 (m, 4H, Ar-H), 7.26-7.50 (m,4H, Ar-H), 7.55 -7.82 (m,4H, Ar-H), 10.14 (br, 1H, NH). MS, m/z (%), 426 (M⁺); Anal. calcd for C$_{25}$H$_{24}$N$_4$OS: C, 70.40; H, 5.20; N, 13.14 %. Found C, 69.82; H, 4.96; N, 12.62%.

(Z)-3-(1H-benzo[d]imidazol-2-yl)-5-(4-chlorobenzylidene)-2-phenylthiazolidin-4-one(3g) 
IR (KBr, cm$^{-1}$); 3366 (N-H), 1561(C=N), 1694 (C=O), 875 (C-Cl); 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 5.84 (s, 1H, N-CH-Ar) ,7.14-7.26 (m, 4H, Ar-H), 7.25-7.48 (m, 4H, Ar-H), 7.51 -7.82 (m,4H, Ar-H), 10.04 (br, 1H, NH). MS, m/z (%), 433 (M⁺); Anal. calcd for C$_{23}$H$_{16}$ClN$_3$:  C, 66.10; H, 3.85; N, 10.04 %. Found C, 65.82; H, 3.13; N, 9.82%.

(Z)-5-(4-aminobenzylidene)-3-(1H-benzo[d]imidazol-2-yl)- 2-phenylthiazolidin-4-one (3h) 
IR (KBr, cm$^{-1}$); 3365 (N-H), 1563(C=N), 1697(C=O); 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 5.85 (s, 1H, N-CH-Ar) ,6.22( s, 2H,NH$_2$), 7.15-7.26 (m, 4H, Ar-H), 7.31-7.49 (m, 5H, Ar-H) , 7.58 -7.82 (m,4H, Ar-H), 10.08 (br, 1H, NH). MS, m/z (%), 398 (M⁺); Anal. calcd for C$_{23}$H$_{18}$N$_4$: C, 69.32; H, 4.55; N, 10.04 %. Found C, 68.82; H, 4.13; N, 12.82%.

General Reaction Procedure for Compound 4a
Equimolar mixture of 3a (0.03 mol), hydrazine hydrate (0.03mol) and anhydrous CH$_3$COONa (0.001 mol) in glacial acetic acid (30ml) were heated under reflux for about 6.5 hours, the resulting compound was cooled at room temperature and poured in to crushed ice. The product was filtered, washed with water and recrystallized with ethanol to afford the pure compound. The remaining compound (4b-4h) was prepared by similar procedure with minor changes as per the reaction conditions.

6-(1H-benzo[d]imidazole-2-yl)-3,5-diphenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4a) 
IR (KBr, cm$^{-1}$): 3348 (N-H), 3078 (C-H), 1564 (C=N), 1671 (C=O), 1238(C=S), 1042 (N-N); 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 4.42(d,1H, CH-S), 4.85 (d, 1H, CH-N), 5.90 (s,1H, CH=CH), 7.10-7.22 (m,4H,Ar-H), 7.26-7.45 (m,5H, Ar-H), 9.75 (br, 1H,NH); MS, m/z (%) 397 (M⁺) ; Anal. Calcd for C$_{23}$H$_{19}$N$_5$: C, 69.50; H, 4.87; N, 17.97%. Found: C, 69.50; H, 4.52; N, 17.62%.

6-(1H-benzo[d]imidazole-2-yl)-5-phenyl-3-(p-tolyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4b) 
IR (KBr, cm-1): 3348 (N-H), 3078 (C-H), 1564 (C=N), 1671 (C=O), 1238 (C=S), 1042 (N-N); 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 2.85 (s, 3H, OCH$_3$), 4.60 (d, 1H, CH-S), 4.83 (d,1H, CH=CH), 7.10-7.22 (m,4H,Ar-H), 7.26-7.45 (m,5H, Ar-H), 9.75 (br, 1H,NH); MS, m/z (%) 411 (M⁺); Anal. Calcd for C$_{24}$H$_{21}$N$_5$: C, 69.32; H, 4.55; N, 17.04 %. Found C, 68.82; H, 4.13; N, 12.82%.

6-(1H-benzo[d]imidazole-2-yl)-5-phenyl-3-(toly)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4c) 
IR (KBr, cm-1): 3348 (N-H), 3078 (C-H), 1564 (C=N), 1671 (C=O), 1238 (C=S), 1042 (N-N); 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 3.48 (s, 3H, OCH$_3$), 4.62 (d, 1H, CH-S), 4.83 (d,1H, CH=CH), 7.10-7.22 (m,4H,Ar-H), 7.26-7.45 (m,5H, Ar-H), 9.75 (br, 1H,NH); MS, m/z (%) 411 (M⁺); Anal. Calcd for C$_{24}$H$_{21}$N$_5$: C, 70.15; H, 5.17; N, 17.07%. Found: C, 69.81; H, 4.92; N, 16.82%.

6-(1H-benzo[d]imidazole-2-yl)-3-(4-methoxyphenyl)-5-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d] thiazole (4d) 
IR (KBr, cm-1): 3343 (N-H), 3085 (C-H), 1564 (C=N), 1675 (C=O), 1245 (C=S), 1048 (N-N); 1HNMR (DMSO-d$_6$, 400MHz, δ in ppm): 2.85 (s, 3H,CH$_3$), 4.60 (d, 1H, CH-S), 4.83 (d,1H, CH=CH), 7.18-7.26 (m,4H,Ar-H), 7.28-7.38 (m,4H,Ar-H), 7.45-7.68 (m,4H,Ar-H), 9.95 (br, 1H,NH); MS, m/z (%) 411 (M⁺); Anal. Calcd for C$_{24}$H$_{21}$N$_5$: C, 70.15; H, 5.17; N, 17.07%. Found: C, 69.81; H, 4.92; N, 16.82%.
ANTITUBERCULAR ACTIVITY OF NEW BI HETEROCYCLIC

Dhanaja Kotte et al.

IR (KBr, cm\(^{-1}\)): 3346 (N-H), 1569 (C=N), 1528 (N=O) , 1682 (C=O), 1235 (C=S), 872 (C-Cl), 1052 (N-N); \(^1\)HNMR (DMSO-d\(_6\), 400MHz, \(\delta\) in ppm): 4.73 (d, 1H, CH-S), 4.91 (d, 1H, N-CH-Ar), 5.84 (s, 1H, N-CH-Ar), 7.18-7.32 (m, 4H, Ar-H), 7.60-7.85 (m, 4H, Ar-H), 10.16 (br, 1H, NH); MS, m/z (%) 431 (M\(^+\)) ; Anal. Calcd for C\(_{23}\)H\(_{26}\)N\(_5\)S: C, 66.96; H, 4.26; N, 15.82%.

RESULTS AND DISCUSSION

The present study reports the synthesis of thiazolo-pyrazole derivatives linked with benzimidazole with an appreciable yield. The compound 2 (Schiff base) is synthesized using 2-aminobenzimidazole with Benzaldehyde under simple conditions. The compound 3 (Chalcone derivatives of thiazolidinone) is synthesized by one-pot three-component cyclization using compound 2, mercaptoacetic acid and aromatic aldehyde using anhydrous ZnCl\(_2\). Later, the Chalcone derivative of thiazolidinone (3) undergoes cyclization with hydrazine hydrate in the presence of anhydrous acetic acid to afford the compound 4.

The structures of synthesized compounds were established based on spectral and analytical data. The compounds showed IR absorption bands at 3366 cm\(^{-1}\) (NH), 1569 cm\(^{-1}\) (C=O), 1232 cm\(^{-1}\) (C=S), 584 cm\(^{-1}\) (C-Cl), 1052 cm\(^{-1}\) (N-N); \(^1\)HNMR spectra of test compounds displayed singlet signals at 5.49 for N-CH-Ar, doublet signals at 4.62 CH-S, 4.72 CH-N, and 9.78 ppm for NH protons and also phenylic protons as
multiplet in the range of 7.10-8.10 ppm. Mass spectra of synthesized compounds showed a molecular ion peak at m/z concerning their molecular weights.

Table 1: Physical Data of Synthesized Compounds (3a-3h) and (4a-4h)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>3a</th>
<th>3b</th>
<th>3c</th>
<th>3d</th>
<th>3e</th>
<th>3f</th>
<th>3g</th>
<th>3h</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Ar</td>
<td>4-CH3- Ar</td>
<td>4-OCH3- Ar</td>
<td>4-OH- Ar</td>
<td>4-NO2- Ar</td>
<td>4- Ni(CH3)2-Ar</td>
<td>4-Cl-Ar</td>
<td>4-NH2-Ar</td>
</tr>
<tr>
<td>M.P (°C)</td>
<td>208-12</td>
<td>215-17</td>
<td>220-22</td>
<td>213-14</td>
<td>221-23</td>
<td>225-28</td>
<td>215-17</td>
<td>210-12</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>80</td>
<td>82</td>
<td>78</td>
<td>81</td>
<td>76</td>
<td>75</td>
<td>76</td>
<td>80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compounds</th>
<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4g</th>
<th>4h</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Ar</td>
<td>4-CH3- Ar</td>
<td>4-OCH3- Ar</td>
<td>4-OH- Ar</td>
<td>4-NO2- Ar</td>
<td>4- Ni(CH3)2-Ar</td>
<td>4-Cl-Ar</td>
<td>4-NH2-Ar</td>
</tr>
<tr>
<td>M.P (°C)</td>
<td>238-40</td>
<td>245-47</td>
<td>250-52</td>
<td>243-46</td>
<td>250-52</td>
<td>255-57</td>
<td>246-48</td>
<td>241-42</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>82</td>
<td>80</td>
<td>75</td>
<td>72</td>
<td>74</td>
<td>76</td>
<td>73</td>
<td>72</td>
</tr>
</tbody>
</table>

In response to nitrate, *Mycobacterium* which causes tuberculosis produces nitrate reductase by NarL. 17-19 NarL is a cytoplasmic response regulator that is involved in regulating gene expression of this bacterium. NarL has been identified as a potential drug target due to its role in nitrate respiration. 20 The Docking studies were conducted on NarL similar to that reported by Prashantha et al 21 using docking server software. 22-23 The protein structure was downloaded from the Protein data bank and was docked to the ligand. The estimated free energy of binding was found to be -7.16 kcal/mol while the inhibition constant was found to be 5.60 uM and ARG63 was involved in polar bond formation with the ligand (Tables 2, 3 and 4). The docking pose of the ligand with NarL is shown in Fig.-1.
### Table-2: Free Energy of Binding between the Ligand and the Protein

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>-7.16 kcal/mol</td>
<td>5.60 uM</td>
<td>-7.73 kcal/mol</td>
<td>-0.07 kcal/mol</td>
<td>-7.79 kcal/mol</td>
<td>50%</td>
<td>809.37</td>
</tr>
</tbody>
</table>

### Table-3: Decomposed Interaction Energies in Kcal/mole

<table>
<thead>
<tr>
<th>Polar</th>
<th>Hydrophobic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARG63 (0)</td>
<td>PRO65 (0)</td>
<td>ARG115 (0)</td>
</tr>
<tr>
<td>PRO65 (0)</td>
<td>ARG115 (0)</td>
<td>ASP68 (0)</td>
</tr>
<tr>
<td>VAL119 (0)</td>
<td>ASP68 (0)</td>
<td>GLU117 (0)</td>
</tr>
<tr>
<td>ARG115 (0)</td>
<td>GLU117 (0)</td>
<td>LYS120 (0)</td>
</tr>
<tr>
<td>ASP68 (0)</td>
<td>LYS120 (0)</td>
<td>THR116 (0)</td>
</tr>
</tbody>
</table>

### Table-4: Interaction Showing the Various Bonds between the Ligand and the Protein

<table>
<thead>
<tr>
<th>Polar</th>
<th>Hydrophobic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>N4 (15) [3.06]</td>
<td>ARG63 (CZ, NE, NH2)</td>
<td>C17 (23) [3.01] - VAL119 (CB, CG2)</td>
</tr>
<tr>
<td>N5 (16) [2.66]</td>
<td>ARG63 (CZ, NE, NH2)</td>
<td>C18 (24) [3.19] - VAL119 (CB, CG1, CG2)</td>
</tr>
<tr>
<td>H8 (37) [2.74]</td>
<td>ARG63 (CZ, NE, NH2)</td>
<td>C16 (22) [3.85] - VAL119 (CG2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C10 (14) [3.40] - PRO65 (CB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S1 (13) [3.16] - THR116 (CB, CG2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C19 (25) [2.93] - THR116 (CB, OGl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C20 (26) [3.13] - THR116 (CB, OGl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C18 (24) [3.33] - THR116 (CB, CG2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C13 (19) [3.52] - THR116 (CG2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C17 (23) [3.75] - THR116 (CG2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C20 (26) [3.74] - GLU117 (CG)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H8 (37) [2.15] - VAL119 (CB, CG1, CG2)</td>
</tr>
</tbody>
</table>
CONCLUSION
The experimental results conclude that a new series of thiazolo–pyrazole containing benzimidazole nucleus and its derivatives are successfully synthesized. It has been reported in the present work that the title compounds (i.e., tri heterocyclic compounds) are exhibiting antitubercular activity based on In silico studies.
ACKNOWLEDGMENT

The authors are thankful to the Department of Chemistry, Kakatiya University for its constant support during the work and also thankful to the Department of Bio-Chemistry, Mahatma Gandhi University-Nalgonda, India.

REFERENCES

1. A. C. Valery, V. Fokin, Chemical Reviews, 109(2), 725 (2009), DOI: 10.1021/cr800448q

[RJC-5465/2019]