Synthesis and Pharmacological Evaluation of Tricyclic Carbazole Annulated with Substituted Benzothiazole-2-Amine Under Microwave Irradiation

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Abstract

Tricyclic carbazole nucleus is an integral part of naturally occurring alkaloids and synthetic derivatives, possessing various potential biological activities such as anticancer, antimicrobial and antiviral. Binding mechanism of carbazole with target receptor as molecule or fused molecule exhibit potential lethal effect. In the present work, development of microwave assisted organic synthesis (MAOS) methods for synthesis of a novel series of N-Mannich bases of carbazole annulled with substituted benzothiazole-2-amine with carbazole (secondary aromatic amine) and aldehyde derivatives has been presented. All the synthesized compounds were characterized by physicochemical and spectral methods viz. ultra-violet, FT-IR, 1H-NMR, Mass and elemental analysis. The newly developed MAOS method evident the improvement in percentage yield (% yield) and reaction time compared to conventional method. The synthesized compounds were screened for antibacterial (B. subtilis, S. aureus, E. coli and P. aeruginosa) and antifungal activities (A. niger and C. albicans) using impregnated paper-disc diffusion method. Compounds posses electronegative functional group at C5 and C6 position showed significant potential for antibacterial (compd. 2c and 3c) and antifungal (compd. 1b, 2b and 7b). Furthermore, in silico (PASS prediction) analysis predicts the possible mechanism of synthesized compounds could be a glycosylphosphatidylinositol phospholipase D inhibitor (antifungal action) and potassium channel blocker (antibacterial action).

Keywords: Microwave assisted organic synthesis (MAOS); Carbazole; Benzothiazole; Antimicrobial activity; N-Mannich bases

Introduction


This high affinity is based on their intercalation property in the minor groove of DNA, which is attributed to the secondary amine (>NH) group of carbazole moiety [11,12] In recent research, the development of N-Mannich bases of heterocyclic moieties significantly become important due to the rendering of molecule aqueous solubility when transferred to the ammonium salt [13]. The N-Mannich bases are the compounds with powerful bond between carbon atoms having wide application to prepare diverse amino alkyl derivatives containing molecules with aldehyde and primary or secondary amine [14]. The existing literature suggested the synthesis of N-Mannich bases derived from different heterocyclic moieties i.e. carbazole, triazole, benimidazole possessing wide spectrum pharmacological activities [15-18].

Recently, the integration of microwave assisted organic synthesis (MAOS) in drug discovery has become an invaluable technique. Indeed, the use of microwave irradiation is simplified and improves the classical organic reactions which lead to the higher yields, cleaner reaction and shorter time of reaction [19]. Thus, based on the expectation of the wide application of carbazole nucleus and MAOS reaction, the present work employs the development of MAOS methods for the synthesis of new series of N-Mannich bases of carbazole. The developed MAOS method
was compared with conventional adopted method including the percentage yield (% yield) and reaction time. MAOS reactions showed the better % yield and less reaction time. The synthesized compounds were experimentally screened for antibacterial activity against gram positive (*S. aureus* and *B. subtilis*) and gram negative (*P. aeruginosa* and *E. coli*) bacteria while antifungal activity was screened against *A. niger* and *C. albicans*. Later on, the in-silico predicted biological activities were compared with experimentally performed activities.

**Experimental**

**Materials and Reagents**

Carbazole was purchased from *M/s Sigma Aldrich* (India). All other chemicals like ammonium thiocyanate, glacial acetic acid, toluene, methanol, ethanol, *n*-octanol, bromine, concentrated hydrochloric acid (conc. HCl), formaldehyde, aniline derivatives and *m*-hydroxybenzaldehyde used were of analytical grade. All the solvents used in the synthesis and chromatographic analysis were distilled before use and store properly when not in use.

**General Procedure for Synthesis of Substituted Benzo[D] Thiazol-2-Amine (1a-7a): Conventional Method**

Equimolar quantity of substituted anilines (20 mmol) and ammonium thiocyanate (20 mmol) were dissolved in ethanol (40 mL) followed by addition of 2.0 mL of conc. HCl in a round bottom flask. To the above solution, separately prepared bromine in glacial acetic acid (50 mmol) mixture was added under ice-cold condition and refluxed. TLC was performed to investigate the completion of the reactions. On the basis of TLC performance, the reaction mixture was cooled overnight in ice cold condition and filtered. The obtained product was dried and recrystallized from absolute ethanol.

**Microwave Assisted Organic Synthesis (MAOS)**

Similarly, the equimolar quantity of all reagents were taken and added in iodine flask (quantities explained in conventional method). The reaction mixture was irradiated in microwave at 750 W with intermittent cooling and mixing after 1 minute (unless the condition was not optimized). Completion of the reaction was monitored by TLC after every 1 minute in toluene: methanol (7:3). Based on TLC performance, the reaction mixture was carried out and cooled in ice cold conditions. Crystalline product was filtered out and dried. The dried product was again recrystallized from absolute ethanol.

**Characterization**

**Physicochemical Analysis:** The melting point ranges of the newly synthesized compounds were determined by open capillary method, using the melting point apparatus and were uncorrected. The solubility was evaluated in various solvents (distilled water and organic solvents) to optimize the conditions for further spectral analysis. Thin layer chromatography (TLC) was carried out on silica gel-G coated plates to monitor the reaction conditions and to determine the purity of the products. The mobile phase was selected according to the polarity of the compounds and a mixture of toluene to ethanol (7:3) was optimized in further experimentation. Visualization was achieved by exposure to iodine vapors and UV light (254 nm, short wavelength) for calculation of RI values. The partition coefficient (octanol/phosphate buffer pH 7.4) of synthesized compounds was determined at room temperature by the flask shake method. Theoretical logP for synthesized compounds was compared with the experimental logP data. Structure and molecular weight of synthesized compounds were elucidated on the basis of spectral analysis.

**Spectroscopical Characterization:** UV absorption measurements were performed to determine the absorption maxima (λmax) in absolute ethanol on UV-Visible Spectrophotometer Pharma spec-1700 (M/s SHIMADZU). Fourier transform infrared spectrum (FTIR) was recorded on Fourier Transform Infrared Spectrophotometer (FTIR-8400S, M/s SHIMADZU, Japan) using the KBr disk method. 1H NMR (300 MHz) and D2O exchange spectrum were performed at room temperature by the flask shake method. Theoretical logP for synthesized compounds was compared with the experimental logP data. Structure and molecular weight of synthesized compounds were elucidated on the basis of spectral analysis.

**Software Analysis:** Chem draw ultra and Chem Draw 3D software were used to draw the chemical structure and to determine the IUPAC nomenclature, molecular weight and molecular formula of newly synthesized compounds. For structural elucidation, theo-
Theoretical obtained elemental fragmentation was compared with the experimentally obtained results.

**Data Set Modeling**

Schrodinger’s Maestro 3D module was used for data set modeling (www.schrodinger.com). The partial atomic charges were assigned using the Gasteiger method. Energy optimization cycles were used for the initial geometry optimization of the molecules. Annealing dynamics was used for conformational scanning with user defined attributes: required temperature-450 K, dynamic time step- 0.01 ps, and iteration-10000, at NVE (constant number of moles, volume and energy). Simulated annealing dynamics were followed by energy minimization using MMFF94 force field and molecules were minimized to the high convergence using 1000 iterations or more as required. 2.5. Pharmacological Screening

The newly synthesized compounds (1b-7b and 1c-7c) were screened for their in vitro antibacterial activity against Gram positive (*B. subtilis* and *S. aureus*) and Gram negative (*E. coli* and *P. aeruginosa*) bacteria using paper disc diffusion method [20]. In brief, the test compounds were dissolved in DMSO at concentration 25, 50 and 100 µg/mL and paper disc were impregnated. For control, the disc impregnated with DMSO was used.

The microorganism culture was spread over nutrient agar media in petri dishes and each plate area was divided into 5 equal portions. Three discs of test sample, one disc of reference drug ciprofloxacin (50 µg/mL) and one control were placed in different sections. Thus, the plates were incubated at 35°C for next 24 hrs to determine the antibacterial activities. After incubation, the zones of inhibition were calculated from triplicate measurements. Similarly, the in vitro antifungal screening was carried out against two fungal strains (*A. niger* and *C. albicans*). A spore suspension in normal saline was prepared from the culture of the test fungi in sabouraud’s broth media. Fluconazole (50 µg/mL) was used as standard drug and disc impregnated with the solvent (DMSO) used as negative control. The three different concentration test compounds, i.e. 50, 100 and 200 µg/mL in DMSO were used for antifungal measurements. The petri plates inoculated with fungal cultures with standard and test compounds were incubated at 25°C for 48 hrs. Antifungal activity was determined by measuring and calculating the diameter of zone of inhibition in triplicate.

**Result and Discussion**

In the twostep reaction for the synthesis of N-Mannich bases of carbazole, initially the synthesis of substituted benzothiazole precursors (1a-7a) was accomplished by the reaction of ammonium thiocyanate followed using bromine cyclization mechanism Figure 1. Thus, based on the synthesis of substituted benzothiazole attention turns towards the synthesis of N-Mannich bases. Further, the synthesized compounds were evaluated for in vitro antimicrobial activities.

![Figure 1: Synthesis of benzothiazole precursors and N-Mannich bases of carbazole.](image-url)
Synthesis of Substituted Benzothiazole Precursors (1a-7a)

Substituted benzothiazoles (1a-7a) were synthesized from substituted anilines and ammonium thiocyanate using bromine cyclization mechanism. On the basis of TLC, the substituted benzothiazole precursors were characterized and used in the next step. The reaction performance of conventional and MAOS method was compared. Encouragingly, the developed MAOS shows better % yield and less reaction time to accomplished reaction in comparison to the conventional reflux method as shown in Figure 2. The obtained results are summarized in supplementary table ST 1.

3.2. Synthesis of N-[(9H-carbazol-9-yl) methyl]-halobenzo[d]thiazol-2-amine (1b-7b) and 3-[(Halobenzo[d]thiazol-2-ylamino) (9H-carbazol-9-yl) methyl] phenol (1c-7c) N-Mannich bases of carbazole were synthesized by the reaction of carbazole, aldehydes and substituted benzothiazole derivatives. Both the conventional as well as developed MAOS methods were adopted for the synthesis of N-Mannich bases.

Figure 2: Comparative results of conventional and MAOS method substituted benzothiazole-2-amine (1a-7a) showing (a) % yield and (b) reaction time.

All newly synthesized compounds were physicochemical (Rf, log P) and spectroscopically characterized using FT-IR, 1H-NMR, Mass and elemental analysis. The 1H-NMR spectra showed characteristic peak in DMSO-d6 at 5.643-5.698 δ (singlet 2H) -CH2 methylene bridge, 10.438-10.644 δ (singlet 1H) of –NH in 1b-7b. Similarly, the NMR peak of 5.09-6.120 δ (singlet 1H) –CHC6H5, 9.043-9.103 δ (br. singlet 1H) of -OH, 10.892-10.993 δ (singlet 1H) of –NH in 1c-7c confirm the formation of mannich bases. The FTIR spectrum characteristic peaks were obtained at (KBr) v cm⁻¹ at approximate ly 3409, 3047, 2923, 1649, 1487 and 1058. The spectral analysis results confirm the formations of compounds. The obtained results are summarized in Tables 1 & 2. Experimentally obtained elemental results were in good agreements to the theoretical obtained value. The developed MAOS showed the significant improvement in % yield and reaction time as shown in Table 2.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Rf</th>
<th>log P</th>
<th>Melting point</th>
<th>Molecular formula (M_w)</th>
<th>Found/calcd. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>1b</td>
<td>0.59</td>
<td>6.18</td>
<td>215-216°C</td>
<td>C_{20}H_{21}N_{3}O_{3}S (364)</td>
<td>66.02</td>
</tr>
<tr>
<td>2b</td>
<td>0.63</td>
<td>4.78</td>
<td>201-202°C</td>
<td>C_{20}H_{20}N_{3}O_{2}S (374)</td>
<td>64.16</td>
</tr>
<tr>
<td>3b</td>
<td>0.84</td>
<td>4.73</td>
<td>191-192°C</td>
<td>C_{20}H_{19}N_{3}O_{2}S (374)</td>
<td>64.16</td>
</tr>
<tr>
<td>4b</td>
<td>0.54</td>
<td>5.81</td>
<td>219-220°C</td>
<td>C_{20}H_{18}N_{3}S_{2} (361)</td>
<td>66.45</td>
</tr>
<tr>
<td>5b</td>
<td>0.78</td>
<td>5.5</td>
<td>182-183°C</td>
<td>C_{20}H_{17}N_{3}S (359)</td>
<td>70.17</td>
</tr>
<tr>
<td>6b</td>
<td>0.7</td>
<td>6.74</td>
<td>211-212°C</td>
<td>C_{20}H_{16}ClN_{3}O_{2}S (397)</td>
<td>60.31</td>
</tr>
<tr>
<td>7b</td>
<td>0.73</td>
<td>6.18</td>
<td>191-192°C</td>
<td>C_{20}H_{15}ClN_{3}S (364)</td>
<td>66.02</td>
</tr>
<tr>
<td>1c</td>
<td>0.76</td>
<td>7.69</td>
<td>189-190°C</td>
<td>C_{20}H_{14}ClN_{3}O_{5} (456)</td>
<td>68.49</td>
</tr>
</tbody>
</table>

Table 2: Spectral analysis data for synthesized compounds 1b-7b and 1c-7c.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>FT-IR (v, cm⁻¹)</th>
<th>¹H NMR signals (8, ppm)</th>
<th>MS (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>3417, 3047, 2932, 2954, 1647, 1506, 1492.</td>
<td>5.698 (2H, s, CH₂), 7.144-7.178 (2H, t, Ar-H), 7.488-7.512 (2H, d, Ar-H), 7.733-7.761 (2H, d, Ar-H), 8.256-8.311 (2H, d, Ar-H), 8.415 (1H, s, Ar-H), 10.602 (1H, s-NH, D₀ exchangeable).</td>
<td>374</td>
</tr>
<tr>
<td>4b</td>
<td>3413, 3049, 2941, 2609, 1654, 1484.</td>
<td>3.493 (1H, s, 5H, D₀ exchangeable), 5.644 (2H, s, CH₂), 7.141-7.179 (2H, t, Ar-H), 7.368-7.409 (3H, t, Ar-H), 7.479-7.515 (2H, t, Ar-H), 7.594-7.609 (1H, d, Ar-H), 7.719-7.739 (2H, d, Ar-H), 7.991-8.006 (1H, d, Ar-H), 10.644 (1H, s-NH, D₀ exchangeable).</td>
<td>361</td>
</tr>
<tr>
<td>6b</td>
<td>3423, 3045, 2923, 1651, 1486, 1054.</td>
<td>5.644 (2H, s, CH₂), 7.130-7.179 (2H, t, Ar-H), 7.457-7.478 (2H, t, Ar-H), 7.496-7.509 (1H, t, Ar-H), 7.729-7.755 (2H, d, Ar-H), 7.978-7.994 (1H, d, Ar-H), 10.478 (1H, s-NH, D₀ exchangeable).</td>
<td>397</td>
</tr>
<tr>
<td>2c</td>
<td>3631, 3415, 3051, 2925, 1648, 1500, 1482, 1240.</td>
<td>6.14 (1H, s, CHC₆H₃), 6.987 (1H, s, Ar-H), 7.106-7.126 (2H, d, Ar-H), 7.139-7.192 (3H, t, Ar-H), 7.359-7.413 (1H, t, Ar-H), 7.417-7.450 (1H, t, Ar-H), 7.492-7.514 (2H, d, Ar-H), 7.725-7.741 (1H, Ar-H), 7.781-7.804 (1H, d, Ar-H), 8.253-8.282 (2H, s, Ar-H), 8.329 (1H, s, Ar-H), 9.043 (1H, br.s, OH, D₀ exchangeable), 10.983 (1H, s-NH, D₀ exchangeable).</td>
<td>466</td>
</tr>
<tr>
<td>3c</td>
<td>3634, 3419, 3054, 2930, 1649, 1498, 1485, 1253.</td>
<td>6.113 (1H, s, CHC₆H₃), 6.988 (1H, s, Ar-H), 7.104-7.124 (2H, d, Ar-H), 7.136-7.194 (3H, t, Ar-H), 7.361-7.409 (1H, t, Ar-H), 7.413-7.452 (1H, t, Ar-H), 7.490-7.514 (2H, d, Ar-H), 7.739-7.756 (1H, d, Ar-H), 7.794-7.805 (1H, d, Ar-H), 8.258-8.304 (2H, s, Ar-H), 8.415 (1H, s, Ar-H), 9.103 (1H, br.s, OH, D₀ exchangeable), 10.993 (1H, s-NH, D₀ exchangeable).</td>
<td>453</td>
</tr>
<tr>
<td>4c</td>
<td>3634, 3419, 3047, 2948, 2605, 1654, 1485, 1235.</td>
<td>3.530 (s, 1H, Ar-SH, D₀ exchangeable), 6.09 (s, 1H, CH₂C₆H₃), 6.987 (s, 1H, Ar-H), 7.110-7.126 (2H, d, Ar-H), 7.136-7.173 (1H, Ar-H), 7.368-7.409 (2H, t, Ar-H), 7.414-7.439 (3H, t, Ar-H), 7.489-7.524 (2H, d, Ar-H), 7.594-7.604 (1H, d, Ar-H), 7.709-7.728 (1H, Ar-H), 7.784-7.799 (1H, d, Ar-H), 7.989-8.001 (1H, d, Ar-H), 9.099 (br.s, 1H, CH₂C₆H₃, D₀ exchangeable), 10.979 (s, 1H, Ar-SH, D₀ exchangeable).</td>
<td>453</td>
</tr>
</tbody>
</table>
In Silico Prediction Using Pass Program

Towards an endeavor of convergence in terms of pharmacological activity with our experimental study, the prediction of biological activity was performed by computer assisted in-silico program using PASS [21,22] a knowledge base biological activity prediction tool. The mechanism of this software is based on the SAR base of the hundred of thousand of compounds with known biological activity stored in the respective database with a diverse spectrum of chemical space. The PASS based preliminary screening of the large database with a similar and diverse structural determinant could increase the probability of finding a molecule to be active with a similar or divergent structural requirements. The PASS [23] program generally uses the two common parameters, i.e. Pa and Pi value where, Pa is defined by the probability of a compound being active with a certain applicability domain and the Pi is the exact opposite.

Herein, we set the [Pa] value a little higher to raise the level of constraint for a molecule to be pharmacologically active and to be sure about the consistency of the result extracted out from the program. In this prediction results, compound 2b, 4b and 5b has not shown any kind of activity rather they also showed some kind of adverse effect. Additionally, on performance of adverse effect analysis, compound of similar type of molecular surface and the interaction profile showed similarities in adverse effects. The compounds 1c-7c showed the antibacterial effect possessing potassium channel blocking activity. For each and every compound in the dataset, near about 4000 types of the spectrum of activity was estimated by PASS [24,25]. A threshold for activity was chosen 0.7 and unexpectedly almost all the compound was overtaking the constraint comprehensively. The detailed result has been stipulated in the Table 3.

Biological Evaluation

In the present work, the newly synthesized derivatives (1b-7b) and (1c-7c) were screened via computer assisted in silico program and compared with experimentally performed biological activities. The newly synthesized compounds 1c-7c possess similar type of activity which predicted by PASS program as shown in Table 3 and Figure 2, the compounds 2c and 3c showed good antibacterial activity. Compounds 1c and 7c were having moderate to good activity against E. coli and against B. subtilis. As shown in Figure 2 the compounds 2c, 3c and 5c were having good activity against B. subtilis and 5c having moderate activity against all bacterial strains. It was observed that the derivatives having electronegative substitution at C-5 and C-6 increase the antimicrobial potential.

In vitro antifungal screening of newly synthesized compounds was performed against a fifteen days old culture of A.

Figure 3: Comparative results of conventional and MAOS method of N-Mannich bases (1b-7b and 1c-7c) showing (a) % yield and (b) reaction time.
niger and *C. albicans*. As shown in Figure 4 the compounds 1b, 3b and 7b showed good antifungal activity against *C. albicans* and *A. niger* in comparison to standard drug Fluconazole at conc. 50 µg mL⁻¹. No potential of biological activity was shown by compounds 2b, 4b and 5b as depicted in the Figure 3 & 4. However, the 2b, 4b and 5b possess the severe side effects as shown in Table 3. It is noteworthy to mention here that, almost a similar type of compound series shown identical type of activity as predicted by PASS program in silico. Thus, the obtained result suggested, it is noteworthy to further explore the derivatives which showed side effects such as neutrophilic dermatosis (Sweet’s syndrome) and postural (orthostatic) hypotension and no biological activity as shown in Table 3.

![Figure 4](image)

**Figure 4:** (a) Antibacterial activities bar graph of N-Mannich bases of carbazole; (b) Antifungal activities bar graph of N-Mannich bases of carbazole.

**Table 3:** Prediction results from PASS program.

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Pa</th>
<th>Pi</th>
<th>Predicted mechanism of action (MOA)</th>
<th>Pa</th>
<th>Pi</th>
<th>Predicted biological activity</th>
<th>Pa</th>
<th>Pi</th>
<th>Predicted adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>0.792</td>
<td>0.015</td>
<td>Glycosylphosphatidylinositol phospholipase D inhibitor</td>
<td>0.812</td>
<td>0.012</td>
<td>Antifungal</td>
<td>0.792</td>
<td>0.016</td>
<td>Postural (orthostatic) hypotension</td>
</tr>
<tr>
<td>2b</td>
<td>0</td>
<td>0</td>
<td>Nil</td>
<td>0</td>
<td>0</td>
<td>Nil</td>
<td>0.752</td>
<td>0.036</td>
<td>Neutrophilic dermatosis (Sweet’s syndrome)</td>
</tr>
<tr>
<td>3b</td>
<td>0.716</td>
<td>0.015</td>
<td>Arylacetonitrilase inhibitor</td>
<td>0.712</td>
<td>0.014</td>
<td>Antifungal</td>
<td>0.719</td>
<td>0.046</td>
<td>Neutrophilic dermatosis (Sweet’s syndrome)</td>
</tr>
<tr>
<td>4b</td>
<td>0</td>
<td>0</td>
<td>Nil</td>
<td>0</td>
<td>0</td>
<td>Nil</td>
<td>0</td>
<td>0</td>
<td>Nil</td>
</tr>
<tr>
<td>5b</td>
<td>0</td>
<td>0</td>
<td>Nil</td>
<td>0</td>
<td>0</td>
<td>Nil</td>
<td>0.725</td>
<td>0.025</td>
<td>Postural (orthostatic) hypotension</td>
</tr>
<tr>
<td>6b</td>
<td>0.766</td>
<td>0.02</td>
<td>Glycosylphosphatidylinositol phospholipase D inhibitor</td>
<td>0.715</td>
<td>0.008</td>
<td>Antibacterial</td>
<td>0.747</td>
<td>0.072</td>
<td>Twitching</td>
</tr>
<tr>
<td>7b</td>
<td>0.846</td>
<td>0.006</td>
<td>Glycosylphosphatidylinositol phospholipase D inhibitor</td>
<td>0.711</td>
<td>0.006</td>
<td>Antifungal</td>
<td>0.796</td>
<td>0.024</td>
<td>Neutrophilic dermatosis (Sweet’s syndrome)</td>
</tr>
<tr>
<td>1c</td>
<td>0.801</td>
<td>0.003</td>
<td>Potassium channel blocker</td>
<td>0.814</td>
<td>0.006</td>
<td>Antibacterial</td>
<td>0.716</td>
<td>0.09</td>
<td>Twitching</td>
</tr>
</tbody>
</table>
Conclusion

In conclusion, two new series of N-Mannich bases of carbazole has been successfully synthesized. All synthesized derivatives were characterized by physicochemical and spectral analysis. The developed MAOS method revealed improved reaction condition (% yield and reaction time) in comparison to conventional methods. Further, MAOS method can be successfully employed to increase the yield of the organic compounds. The in vitro evaluation of newly synthesized compounds revealed the potential for biological activity. Some of the derivatives showed the potent or equipotent biological potential in comparison to standard drug. In silico prediction of PASS program suggested that the similar type of compounds possess similar type of biological potential, mechanism of action and adverse effects. Prediction studies suggested that it is of quite essential to further explore the derivatives which only possess severe side effects no biological potential.

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References
