Facile multi-components one-pot synthesis of dipyrazolo[1,5-a:3’,4’-d]pyrimidine as potent bioactive scaffolds

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ABSTRACT

An efficient, three-component, catalyst free synthesis of dipyrazolo[1,5-a:3’,4’-d]pyrimidines scaffolding has been carried out using 3-methyl-1H-pyrazol-5(4H)-one (1), 5-amino pyrazole (2a-b) and substituted aromatic aldehydes. The reaction underwent cyclocondensation reaction in reflux condition with moderate to good (62%-90 %) yields. The twenty newly prepared molecules were analyzed by means of 1H & 13C NMR, Mass, and IR spectroscopies and their activities against the bacterial and fungal strains were screened. Some of tested compounds have shown excellent antibacterial activities while another four were found to have good antifungal activity.

1. Introduction

Pyrimidine scaffold is found in several naturally occurring compounds and they make the core structures of many biologically active scaffolds and much more pharmaceutical industrial materials. For the most part, significant fused dipyrazoloes is dipyrazolopyrimidine derivative which acquires a range of biological potent molecules. The MCRs (Multi-components reaction) approach is more convenient in comparison to conventional synthesis because of flexibility and atom-efficient character. We used the MCRs for an optimization of a synthesis of dipyrazolo[1,5-a:3’,4’-d]pyrimidines. Pyrazolopyrimidines have shown different types of pharmacological activities such as antitumor, anticancer, DPP-4 inhibitory activity, PDE-4 inhibitory, antiproliferative, COX-2-inhibitory, 11β-HSD1 inhibitory, antibacterial and many others. Thus, the synthesis of these moieties has been widely accounted in the most recent couple of years. Despite the potential utility of previously mentioned synthetic methods, many of them suffer from usage of organic solvent and catalysts as well as strong acidic/basic conditions, long reaction times, and low yields of the target products.

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Herein, we report an efficient catalyst free synthesis of these important biologically active pyrazolopyrimidines based on cyclocondensation reaction of 3-methyl-1H-pyrazol-5(4H)-one (1), 3-phenyl-1H-pyrazol-5-amine (2a), 3-(4-chlorophenyl)-1H-pyrazol-5-amine (2b) and substituted aromatic aldehydes (3a-j) run in a reflux condition.

2. Results and Discussion

2.1 Chemistry

Our preliminary study involving the synthesis of 3-methyl-1H-pyrazol-5(4H)-one (1), 3-phenyl-1H-pyrazol-5-amine (2a) and 3-(4-chlorophenyl)-1H-pyrazol-5-amine (2b) were based on earlier reported procedures. The catalyst free, one-pot, high yielding condensation reaction of 3-methyl-1H-pyrazol-5(4H)-one (1), 3-(4-substitutedphenyl)-1H-pyrazol-5-amines (2a-b) and aromatic aldehydes (3a-j) was carried out using methanol as a solvent at reflux temperature to furnish desired dipyrazolo[1,5-a:3',4'-d]pyrimidine (4a-t) (Scheme 1).

The reaction run at room temperature with constant stirring, gives a poor yield, what could be easily understanding taking in consideration a low solubility of 3-methyl-1H-pyrazol-5(4H)-one (1) in methanol at that temperature. Thus, we found that this MCRs reaction was more efficient under a reflux condition with utilization of an equimolar mixture of the starting materials in methanol, and good yields of the products were obtained after 3-5 hr. Unfortunately trace amount of Hantzsch-type dihydropyridines were also formed in the reaction.
The chemical structures of newly synthesized compounds (4a-t) were proved by the spectral and microanalytical techniques. The compounds 4a-t showed IR absorption bands at 3410-3430 cm\(^{-1}\) of cyclic secondary amine (\(-NH\)) stretching. The \(^1\)H NMR spectra of newly prepared scaffolds 4a-t possess characteristic peaks at: 4.82 ppm (hydro pyrimidine CH); two signals for two NH groups at 2.06 ppm (pyrimidine) and 10.45 ppm (pyrazole). The \(^{13}\)C NMR spectrum possess characteristic peaks at: 159.41 and 149.14 ppm (pyrazole rings); 64.28 ppm (hydro pyrimidine CH). The mass spectra molecular ion peak of compound 4c was detected at m/z 362.21 and 364.22 (M+).

2.2 Biological Activities

The newly synthesized compounds (4a-t) were evaluated by Lipinski filter.\(^{25}\) Only four compounds have a logP value >5 (4l-4o), remaining all compounds follow the Lipinski rules of five. The in-vitro antibacterial activity of the 20 new synthesized compounds was evaluated using the agar well diffusion method.\(^{26-28}\) The compounds were dissolving and tested at 1mg/ml concentration in dimethylsulfoxide (DMSO). The tested bacteria were: Staphylococcus aureus (S.a) and Enterococcus facialis (E.f) a gram (+Ve) and Escherichia coli (E.c) and Salmonella typhi (S.t) as a gram (-Ve) bacteria. The in-vitro antifungal analysis was screened against two fungi: Candida albicans (C.a) and Aspergillus niger (A.n). The agar well diffusion analysis was performed using nutrient agar medium, as described previously.\(^{29, 30}\)

After making agar mediated petri dishes to make well 5mm sterilize cork borer was used, and the solutions of tested compounds in DMSO at concentrations of 0, 25, 50, 75 and 100 µg/ml were poured into each well The two reference drugs clarithromycin and cefixime were used as antibacterial references and ketoconazole as an antifungal agent. The inhibition % was calculated using the Equation 1. Antibacterial and antifungal activity was determined by calculate the zone of inhibition in mm.

\[
\text{%Inhibition} = \frac{I}{M} \times 100,
\]

where, \(I= \text{Diameter zone of inhibition (mm)} \) and \(M= \text{Diameter of petri dish (90 mm)} \).

Lipophilicity of the molecules delivers the good antimicrobial effect. The lipophilicity of the molecules, expressed as logP, clarifies the principal indicator for the action. The o/w partition coefficient ClogP was computed utilizing the product ACD/logP.

**Table 1.** Antibacterial activity of dipyrrolopyrimidine derivatives

<table>
<thead>
<tr>
<th>Sample code</th>
<th>S. a</th>
<th>E. f</th>
<th>E. c</th>
<th>S. t</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Z.I</td>
<td>% Inhibition</td>
<td>Z.I</td>
<td>% Inhibition</td>
</tr>
<tr>
<td>4g</td>
<td>19</td>
<td>21.11</td>
<td>14</td>
<td>15.55</td>
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<td>20.00</td>
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<td>22.22</td>
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<td>22.22</td>
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<tr>
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<td>27.77</td>
<td>23</td>
<td>25.55</td>
</tr>
<tr>
<td>Cefixime</td>
<td>23</td>
<td>25.55</td>
<td>24</td>
<td>26.66</td>
</tr>
</tbody>
</table>

\(Z.I = \text{Zone of inhibition, zone diameter of growth inhibition (mm) after 24 h.}\)

The results of antibacterial evaluation of synthesized dipyrrolopyrimidine and comparison their activities with the activities of known reference drugs are shown in the Table 1. The only compounds 4h, 4q, and 4t have shown higher antibacterial activity against gram +Ve bacteria Staphylococcus aureus and Enterococcus faecalis, while 4g and 4j were moderately active. The only compounds 4g, 4j, and 4t have shown good antibacterial activity against gram -Ve bacteria Escherichia coli and Salmonella typhi. All other obtained compounds appears to be inactive. The active compounds have a lipophilic nature with logP value below 5.
The \textit{in-vitro} antifungal zone of inhibition results are shown in Table 2.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Sample code & \multicolumn{2}{c|}{\textbf{Fungal strains}} & \multicolumn{2}{c|}{\textbf{C. a.}} \\
\cline{2-5}
 & \textbf{\textit{A. n.}} & \textit{\% Inhibition} & \textbf{\textit{C. a.}} & \textit{\% Inhibition} \\
\hline
4c & 25 & 23.33 & 17 & 18.89 \\
4i & 27 & 26.67 & 30 & 24.44 \\
4n & 23 & 25.56 & 28 & 23.33 \\
4s & 26 & 28.89 & 28 & 31.11 \\
\hline
Ketoconazole & 28 & 31.11 & 34 & 37.78 \\
\hline
\end{tabular}
\caption{Antifungal activity of dipyrazolopyrimidine derivatives.}
\end{table}

\textit{Z.I} = Zone of inhibition, zone diameter of growth inhibition (mm) after 7 days.

Among the tested compounds a significant antifungal activity (in comparison with reference ketoconazole) against fungal strains \textit{A. niger} and \textit{C. Albicans} exhibit the compounds 4n and 4s. The compounds 4c and 4i showed moderate only.

3. Conclusions

In conclusion, we have developed a facile, simple reaction procedure for the synthesis of biologically significant dipyrazolo[1,5-\textit{a}:3',4'-\textit{d}]pyramid scaffold. The procedure has such features as: one pot synthesis, catalyst free, short reaction times, simple work up, and moderate to excellent yields. Preliminary \textit{in-vitro} antibacterial study indicates that compounds 4g, 4h, 4j, 4q and 4t have antibacterial activities and compounds 4c, 4i, 4n, and 4s have antifungal activity, which are almost comparable with reference drugs.

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4. Experimental

4.1. Materials and Methods

Ethyl acetoacetate, aromatic aldehyde and analytical grade solvents were purchase from commercial sources and used as received. All the reaction continuously monitored by TLC Plate (Merck silica gel PF\textsubscript{254} plates) with Ethyl acetate/ hexane mixtures as mobile phase and spot visualized in iodine and UV chamber. Melting point measured in open capillary tube. Microanalysis was carried out on Perkin Elmer 2400 CHNS analyzer, the FT-IR spectra were recorded from 400 to 4000 cm\textsuperscript{-1} with SHIMADZU FT-IR system using KBr pellet method. NMR \textit{\textsuperscript{1}H} and \textit{\textsuperscript{13}C} spectra were recorded on Bruker F113V (600 MHz) and referenced internally with TMS and DMSO-\textit{d}_6 solvent. Mass spectrum was recorded on MS Micromass.

4.2. General procedure

\textbf{Synthesis of 3-methyl-7-(substituted phenyl)-4-(substituted phenyl)-4,9-dihydro-1H-dipyrazolo[1,5-\textit{a}:3',4'-\textit{d}]pyrimidine(4a-t).}

A mixture of the 3-methyl-1\textit{H}-pyrazol-5(4\textit{H})-one (1, 0.01 mol), 3- substituted phenyl-1\textit{H}-pyrazol-5-amine (2\textit{a-b}, 0.01 mol) and substituted aromatic aldehydes (3\textit{a-j}, 0.01 mol) in methanol (15 mL) was
refluxed for 4 to 5 hr. Reaction time was measured by TLC. After completion, the reaction mixture was kept at room temperature for 12 hours and filtered to get the solid dipyrazolopyrimidine products (4a-t), which were washed with methanol and dried in air.

4.3 Physical and Spectral Data

3-methyl-4,7-diphenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4a)

Yield: 69%; light yellow solid; IR (KBr): \( \nu \) 3411, 3385, 3012, 2911, 2834, 1605, 1520, 1444, 703, 692 cm\(^{-1}\); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \( \delta \) 1.72 (s, 3H), 2.32 (s, b, 1H), 5.21 (s, 1H), 6.9 (s, 1H), 7.43-7.68 (m, 8H), 7.83 (d, 2H, \( J = 8.2 \) Hz), 12.71 (s, 1H); \(^1^3\)C NMR (150 MHz, DMSO-\(d_6\)): \( \delta \) 159.8, 152.8, 150.5, 141.6, 138.3, 135.6, 128.5, 126.1, 123.3, 101.5, 97.4, 58.8, 15.8; mp: 181-183 °C; Anal. Calcd for C\(_{20}\)H\(_{17}\)N\(_5\): C, 73.37; H, 5.23; N, 21.39; Found: C, 73.47; H, 5.20; N, 21.29; m/z 327.9 (M+1).

4-(3-chlorophenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4b)

Yield: 78%; light pink solid; IR (KBr): \( \nu \) 3423, 2980, 2874, 1601, 1545, 1447, 810, 773, 690 cm\(^{-1}\); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \( \delta \) 1.71 (s, 3H), 2.31 (s, b, 1H), 5.21 (s, 1H), 6.95 (s, 1H), 7.10-7.11 (d, 1H, \( J = 3.2 \) Hz), 7.23-7.56 (m, 6H), 7.71 (d, 2H, \( J = 7.2 \) Hz), 12.52 (s, 1H); \(^1^3\)C NMR (150 MHz, DMSO-\(d_6\)): \( \delta \) 163.1, 155.2, 152.7, 139.2, 134.8, 130.7, 129.4, 128.1, 126.4, 118.4, 104.8, 99.7, 62.3, 15.1; mp: 216-218 °C; Anal. Calcd for C\(_{20}\)H\(_{16}\)ClN\(_5\): C, 66.39; H, 4.46; Cl, 9.80; N, 19.36; Found: C, 66.36; H, 4.53; Cl, 9.40; N, 19.71; m/z 361.4, 363.6 (M+).

4-(4-chlorophenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4c)

Yield: 82%; light pink solid; IR (KBr): \( \nu \) 3403, 2924, 2812, 2729, 1595, 1500, 1447, 814, 761, 692 cm\(^{-1}\); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \( \delta \) 1.67 (s, 3H), 2.08 (s, b, 1H), 5.07 (s, 1H), 7.1 (s, 1H), 7.15-7.16 (d, 2H, \( J = 8.2 \) Hz), 7.34-7.49 (m, 5H), 7.58-59 (d, 2H, \( J = 8.0 \) Hz), 12.61 (s, 1H); \(^1^3\)C NMR (150 MHz, DMSO-\(d_6\)): \( \delta \) 161.3, 158.7, 150.2, 143.5, 131.2, 130.3, 128.1, 126.4, 118.4, 100.7, 59.7, 16.4; mp: 208-210 °C; Anal. Calcd for C\(_{20}\)H\(_{16}\)ClN\(_5\): C, 66.39; H, 4.46; Cl, 9.80; N, 19.36; Found: C, 66.53; H, 4.50; Cl, 9.29; N, 19.68; m/z 362.2 (M+1), 364.2 (M+2).

4-(3-bromophenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4d)

Yield: 78%; yellow solid; IR (KBr): \( \nu \) 3360, 3117, 2878, 1592, 1507, 1470, 1432, 883, 765, 668 cm\(^{-1}\); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \( \delta \) 1.89 (s, 3H), 2.9 (s, b, 1H), 5.12 (s, 1H), 6.79 (s, 1H), 7.04-7.11 (m, 2H), 7.21-7.42 (m, 5H), 7.76 (d, 2H, \( J = 8.2 \) Hz), 12.65 (s, 1H); \(^1^3\)C NMR (150 MHz, DMSO-\(d_6\)): \( \delta \) 160.2, 156.7, 151.9, 140.4, 133.7, 130.1, 129.8, 128.1, 122.6, 104.6, 89.9, 65.1, 15.9; mp: 190-192 °C; Anal. Calcd for C\(_{20}\)H\(_{16}\)BrN\(_5\): C, 59.13; H, 3.97; Br, 19.67; N, 17.24; Found: C, 59.51; H, 4.03; Br, 19.47; N, 17.01; m/z 405.5, 407.8 (M+).

3-methyl-7-phenyl-4-(p-tolyl)-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4e)

Yield: 72%; yellow solid; IR (KBr): \( \nu \) 3360, 3117, 2878, 1592, 1507, 1470, 1432, 883, 765, 668 cm\(^{-1}\); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \( \delta \) 1.81 (s, 3H), 2.18 (s, 3H), 2.7 (s, b, 1H), 5.12 (s, 1H), 6.89 (s, 1H), 7.35-7.49 (m, 4H), 7.54-7.68 (m, 5H), 12.73 (s, 1H); \(^1^3\)C NMR (150 MHz, DMSO-\(d_6\)): \( \delta \) 158.8, 156.5, 149.9, 140.1, 138.8, 132.6, 129.4, 128.9, 126.4, 105.4, 98.6, 55.9, 23.3, 15.6; mp: 175-177 °C; Anal. Calcd for C\(_{21}\)H\(_{18}\)N\(_5\): C, 73.88; H, 5.61; N, 20.51; Found: C, 73.79; H, 5.66; N, 20.58; m/z 341.3 (M+).
3-methyl-4-(4-nitrophenyl)-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4f)
Yield: 78%; Dark yellow solid; IR(KBr): \( \nu \) 3389, 3330, 3093, 2875, 2812, 1597, 1509, 1454, 1344, 1176, 878, 770, 697 cm\(^{-1}\); \( ^1\)H NMR (600 MHz, DMSO-\( d_6 \)): \( \delta \) 1.68 (s, 3H), 2.1 (s, b, 1H), 5.09 (s, 1H), 6.91 (s, 1H), 7.38-7.51 (m, 5H), 7.63-7.72 (m, 4H), 12.72 (s, 1H); \( ^{13} \)C NMR (150 MHz, DMSO-\( d_6 \)):

2,6-dimethoxy-4-(3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)phenol (4g)
Yield: 65%; light orange solid; IR(KBr): \( \nu \) 3497, 3404, 3045, 2898, 1601, 1539, 1512, 1457, 1423, 1214, 916, 770, 697 cm\(^{-1}\); \( ^1\)H NMR (600 MHz, DMSO-\( d_6 \)):

4-(3-ethoxy-4-methoxyphenyl)-3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4h)
Yield: 63%; yellow solid; IR(KBr): \( \nu \) 3412, 3388, 2995, 2937, 1515, 1458, 1425, 1260, 1028, 812, 765 cm\(^{-1}\); \( ^1\)H NMR (600 MHz, DMSO-\( d_6 \)):

5-chloro-2-methoxy-4-(3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)phenol (4i)
Yield: 67%; orange solid; IR(KBr): \( \nu \) 3545, 3455, 3049, 2921, 1587, 1518, 1462, 1427, 1245, 1028, 812, 765 cm\(^{-1}\); \( ^1\)H NMR (600 MHz, DMSO-\( d_6 \)):

2-chloro-5-(3-methyl-7-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)phenol (4j)
Yield: 71%; pale yellow solid; IR(KBr): \( \nu \) 3505, 3398, 3013, 2879, 1541, 1514, 1458, 1423, 1093, 882, 830, 639 cm\(^{-1}\); \( ^1\)H NMR (600 MHz, DMSO-\( d_6 \)):

7-(4-chlorophenyl)-3-methyl-4-phenyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4k)
Yield: 73%; yellow solid; IR(KBr): \( \nu \) 3403, 3010, 2920, 2832, 1595, 1520, 1457, 825, 790, 767 cm\(^{-1}\);
1H NMR (600 MHz, DMSO-d6): δ 1.80 (s, 3H), 2.81 (s, b, 1H), 5.11 (s, 1H), 6.72 (s, 1H), 7.13-7.23 (m, 5H), 7.45-7.46 (d, 2H, J = 8.2 Hz) 8.02-8.03 (d, 2H, J = 8.0 Hz), 12.31 (s, b, 1H); 13C NMR (150 MHz, DMSO-d6): δ 160.1, 155.7, 152.6, 140.2, 137.2, 130.9, 129.1,126.2, 105.5, 94.9, 59.2, 15.7; mp: 175-178°C; Anal. Calcd for C20H16ClN5: C, 66.39; H, 4.46; Cl, 9.80; N, 19.36; Found: C, 66.42; H, 4.49; N, 19.33; Cl, 9.76; m/z 361.25, 363.12 (M+).

4-(3-chlorophenyl)-7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4l)

Yield: 81%; light yellow solid; IR(KBr): v 3391, 3012, 2980, 2832, 1592, 1537, 1463, 832, 803, 753 cm⁻¹; 1H NMR (600 MHz, DMSO-d6): δ 1.83 (s, 3H), 3.01 (s, b, 1H), 5.34 (s, 1H), 6.86 (s, 1H), 7.10-7.11 (d, 1H, J = 4.6 Hz), 7.26-7.29 (m, 3H) 7.48-7.49 (d, 2H, J = 8.0 Hz) 8.01-8.02 (d, 2H, J = 7.8 Hz) 11.9 (s, b, 1H); 13C NMR (150 MHz, DMSO-d6): δ 159.3, 154.6, 150.1, 141.5, 135.9, 134.3, 132.3, 131.3, 129.7,128.2, 125.9, 124.5, 104.8, 93.6, 61.7, 15.2; mp: 207-209 oC; Anal. Calcd for C20H15Cl2N5: C, 60.62; H, 3.82; Cl, 17.89; N, 17.67; Found: C, 60.58; H, 3.83; N, 17.71; Cl, 17.67; m/z 395.21, 397.45 (M+).

4,7-bis(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4m)

Yield: 90%; light yellow solid; IR(KBr): v 3394, 3010, 2986, 2825, 1590, 1535, 1461, 828, 803, 764 cm⁻¹; 1H NMR (600 MHz, DMSO-d6): δ 1.88 (s, 3H), 2.98 (s, b, 1H), 5.51 (s, 1H), 6.67 (s, 1H), 7.17-7.18 (d, 2H, J = 7.6 Hz), 7.28 (d, 2H, J = 7.8 Hz) 7.58 (d, 2H, J = 7.8 Hz) 8.12 (d, 2H, J = 8.0 Hz), 12.1 (s, b, 1H); 13C NMR (150 MHz, DMSO-d6): δ 159.7, 153.4, 150.5, 140.6, 135.1, 132.6, 129.3, 128.8, 104.6, 93.2, 61.3, 15.6; mp: 171-174oC; Anal. Calcd for C20H15Cl2N5: C, 60.62; H, 3.82; Cl, 17.89; N, 17.67; Found: C, 60.65; H, 3.79; N, 17.72; Cl, 17.67; m/z 395.26, 397.40 (M+).

4-(3-bromophenyl)-7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4n)

Yield: 86%; dark yellow solid; IR(KBr): v 3413, 3060, 2926, 2875, 1595, 1545, 1464, 810, 684 cm⁻¹; 1H NMR (600 MHz, DMSO-d6): δ 1.81 (s, 3H), 2.67 (s, b, 1H), 5.71 (s, 1H), 6.61 (s, 1H), 7.12-7.13 (m, 2H), 7.29-7.31 (m, 2H) 7.51-7.52 (d, 2H, J = 7.6 Hz) 8.09-8.10 (d, 2H, J = 8.0 Hz), 12.3 (s, b, 1H); 13C NMR (150 MHz, DMSO-d6): δ 159.1, 153.4, 150.9, 139.6, 135.3, 134.6, 132.3, 129.6, 128.2, 124.5, 104.8, 93.9, 60.3, 15.2; mp: 210-212oC; Anal. Calcd for C20H15ClBrN5: C, 54.50; H, 3.43; Br, 18.13; Cl, 8.04; N, 15.89; Found: C, 54.52; H, 3.41; N, 15.89; Cl, 8.08; Br, 18.10; m/z 439.12, 439.42 (M+).

7-(4-chlorophenyl)-3-methyl-4-(p-tolyl)-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4o)

Yield: 72%; off white solid; IR(KBr): v 3408, 3020, 2933, 2812, 1594, 1515, 1469, 844, 760 cm⁻¹; 1H NMR (600 MHz, DMSO-d6): δ 1.91 (s, 3H), 2.34 (1H, s), 3.23 (s, b, 1H), 5.72 (s, 1H), 6.75 (s, 1H), 7.11 (s, 4H), 7.45 (d, 2H, J = 7.8 Hz) 7.81 (d, 2H, J = 7.8 Hz), 12.72 (s, b, 1H); 13C NMR (150 MHz, DMSO-d6): δ 160.2, 154.3, 151.5, 139.9, 136.9, 135.4, 132.3, 129.8, 128.4, 127.8, 104.9, 93.8, 60.7, 24.7, 15.6; mp: 164-166°C; Anal. Calcd for C21H18ClN5: C, 67.50; H, 3.43; Br, 18.13; Cl, 8.04; N, 15.89; Found: C, 54.52; H, 3.41; N, 15.89; Cl, 8.08; Br, 18.10; m/z 375.76, 377.40 (M+).

7-(4-chlorophenyl)-3-methyl-4-(4-nitrophenyl)-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine (4p)

Yield: 82%; dark yellow solid; IR(KBr): v 3408, 3025, 2981, 2856, 1590, 1510, 1535, 1461, 1339, 844, 795 cm⁻¹; 1H NMR (600 MHz, DMSO-d6): δ 1.79 (s, 3H), 3.27 (s, b, 1H), 5.82 (s, 1H), 6.93 (s, 1H), 7.52-7.54 (m, 4H), 7.88-789 (d, 2H, J = 7.8 Hz) 8.13 (d, 2H, J = 8.0 Hz), 12.61 (s, b, 1H); 13C NMR (150
4-(7-(4-chlorophenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidin-4-yl)-2,6-dimethoxyphenol(4q)

Yield: 62%; orange solid; IR(KBr): $\nu 3484, 3392, 3025, 2913, 1595, 1542, 1452, 1423, 1224, 912, 774, 696$ cm$^{-1}$; $^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$ 1.85 (s, 3H), 3.82 (s, 6H), 5.72 (s, 1H), 5.72 (s, 1H), 6.43 (s, 2H), 6.92 (s, 1H), 7.58-7.59 (d, 2H, $J = 7.8$ Hz), 7.89 (d, 2H, $J = 7.8$ Hz); $^{13}$C NMR (150 MHz, DMSO-d$_6$): $\delta$ 159.2, 153.4, 149.6, 148.8, 148.8, 134.9, 132.1, 130.4, 129.1, 127.2, 108.3, 103.7, 95.3, 65.1, 57.2, 15.1; mp: 168-170°C; Anal. Calcd for C$_{20}$H$_{15}$ClN$_6$O$_2$: C, 59.05; H, 3.72; Cl, 8.71; N, 20.66%; Found: C, 59.09; H, 3.71; N, 20.63; Cl, 8.69; m/z 406.23, 408.48 (M+).

7-(4-chlorophenyl)-4-(3-ethoxy-4-methoxyphenyl)-3-methyl-4,9-dihydro-1H-dipyrazolo[1,5-a:3',4'-d]pyrimidine(4r)

Yield: 65%; orange solid; IR(KBr): $\nu 3404, 3392, 3015, 2957, 1593, 1515, 1458, 1425, 1260, 1028, 842, 812, 765$ cm$^{-1}$; $^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$ 1.21 (t, 3H), 1.71 (s, 3H), 3.25 (s, 1H), 3.97-4.03 (q, 2H), 5.73 (s, 1H), 6.70-6.78 (m, 4H), 7.58-7.59 (d, 2H, $J = 7.4$ Hz), 7.87 (d, 2H, $J = 7.4$ Hz), 12.82 (s, 1H); $^{13}$C NMR (150 MHz, DMSO-d$_6$): $\delta$ 158.2, 152.3, 149.1, 148.8, 148.6, 147.4, 138.5, 135.4, 132.4, 129.6, 128.8, 126.7, 122.1, 115.2, 112.3 103.5, 94.2, 65.2, 57.3, 14.2,15.7; mp: 198-201°C; Anal. Calcd for C$_{23}$H$_{22}$ClN$_5$O$_2$: C, 63.37; H, 5.09; Cl, 8.13; N, 16.07; Found: C, 63.30; H, 5.11; N, 16.15; Cl, 8.13; m/z 435.34, 437.23(M+).

References


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