Synthesis of various novel heterocyclic N-Mannich bases from variety of dihydropyrimidones and octahydropyrimidopyrimidones

Ritika Mahajan* & R L Sharma
Department of Chemistry, University of Jammu, Jammu 180 006, India
E-mail: ritikamahajanchem1985@gmail.com

Received 8 April 2016; accepted (revised) 10 July 2017

Two series of Mannich bases 3a-c and 4a-c have been prepared by Mannich reaction of octahydropyrimidopyrimidones 2a-c with heterocyclic-2°-amines (benzimidazole and indole) and HCHO in molar ratio 1:4:4. Two more series of Mannich bases 5a-c and 6a,b have been prepared by Mannich reaction of dihydropyrimidine 1a and tetrahydrospiro[indoline-3,4’-pyrimidine]-2,2’-dione 1d with same heterocyclic-2°-amines and HCHO in the molar ratio 1:2:2. The chemical structures of all the Mannich bases have been elucidated by elemental analysis and spectral studies (IR, NMR).

Keywords: Dihydropyrimidines, octahydropyrimidopyrimidines, N-Mannich bases, antimicrobial activity

In recent years, dihydropyrimidiones and their derivatives occupy an important role in the realm of natural and synthetic organic chemistry because of their therapeutic and pharmacological properties. They have emerged as integral backbone of several calcium channel blockers, antihypertensive agents, α-1a-antagonists1,2 and neuropeptide Y(NPY) antagonists.

Similarly, various spiro-derivatives3,5 based on heterocyclics have antibacterial, anticonvulsant, antitumor and anti cancer activities. The pyrimidine ring forms an integral part of the structure of a number of important natural products. The biodynamic property of the ring system prompted us to design pyrimidine derivatives stimulating pharmachore and substituents responsible for diverse pharmacological activities6-9. As the pyrimidine ring system is highly biologically active, therefore, it was thought of interest to construct it alone as well as condensed with the same moiety i.e. the creation of pyrimidopyrimidine to see the additive effect of these rings towards antifungal activities. Further, a considerable amount of work has been done on the synthesis and pharmacological activities like analgesic, antispasmodic, anesthetic and antimicrobial activity of various N-Mannich bases derived from these dihydropyrimidones as well as intermediates obtained during such drug synthesis10-12.

Keeping in view the biological importance of various heterocyclic nuclei i.e., pyrimidiones, pyrimidopyrimidines and N-Mannich bases especially derived from DHPM, an attempt has been made to synthesize the novel heterocyclic N-Mannich bases derived from 3,4-dihydropyrimid-2(1H)-one moieties and 5-aryl-1,2,3,4,5,6,7,8 octahydropyrimido[4,5-d]pyrimidine-2,4,7-triones with indole, carbazole and benzimidazole as the most interesting structural systems and as the most likely biologically potent reagents. Their synthesis may open a wide area for investigation of pharmacological activities like analgesic, antispasmodic, anesthetic and antimicrobial activity.

The present paper describes the synthesis of N-Mannich bases of OHPMs, DHPMs and spiro analogue. The heterocyclic precursors (1a and 1d) and (2a-c) were synthesized by Biginelli reaction of variety of aromatic and heterocyclic aldehydes, active methylene compounds and urea according to the literature procedure24-29 (Scheme I). Four series of N-Mannich bases of OHPMs, DHPMs and spiro analogue (3a-c), (4a-c), (5a-c) and (6a,b) have been synthesized by Mannich reaction of OHPMs (2a-c), DHPM (1a) and spiro analogue (1d) with different heterocyclic secondary amines and formaldehyde (Scheme II). All these OHPMs, DHPMs, spiro analogue and their N-Mannich bases have been characterized by elemental and spectral studies. The analytical data of these N-Mannich bases are given in Table I.
Results and Discussion

The one pot multicomponent Biginelli reaction leading to the formation of novel dihydropyrimidones and octahydropyrimido[4,5-d]pyrimidinetrione precursors starting from three components is outlined in Scheme I. In this section, we describe a general and practical route for the synthesis of 3,4-dihydropyrimid-2(1H)-ones (1a and 1d) and octahydropyrimido[4,5-d]pyrimidinetriones (2a-c) by Biginelli condensation reaction in good yields (>75%). This is a novel method for the synthesis of precursors of N-Mannich bases (3a-c), (4a-c), (5a-c) and (6a,b) in the present study with 70-80% yield. The analytical and spectral data of all the N-Mannich bases obtained are in good agreement with calculated values based on the proposed structures shown in Scheme II.

Spectral studies of N-Mannich bases have shown the following characteristic features. The characteristic absorption bands of OHPMs, DHPMs and spiro component in IR spectra of N-Mannich bases resembles the pattern observed for parent OHPMs, DHPMs and spiro substrate reported in Experimental Section with the exception that absorption band at 3208.6 cm\(^{-1}\), 3240 cm\(^{-1}\) and 3258.6 cm\(^{-1}\) due to the...
3a: \( R_1 = R_2 = H, R_3 = OCH_3 \)
3b: \( R_1 = H, R_2 = R_3 = OCH_3 \)
3c: \( R_1 = H, R_2 = OCH_3, R_3 = OH \)

4a: \( R_1 = R_2 = H, R_3 = OCH_3 \)
4b: \( R_1 = H, R_2 = R_3 = OCH_3 \)
4c: \( R_1 = H, R_2 = OCH_3, R_3 = OH \)
Scheme II — Synthesis and evaluation of N-Mannich bases

2° (-NH) group of OHPM, DHPM and spiro substrate disappeared in the IR spectra of their respective N-Mannich bases. Moreover, two strong bands in the region 2898-2870 cm\(^{-1}\) and 1430-1420 cm\(^{-1}\) due to –CH stretching and bending vibrations are also observed in the IR spectra of N-Mannich bases of OHPMs, DHPMs and spiro analogue which indicates the presence of methylene linkages between pyrimidine/pyrimidopyrimidine substrate and heterocyclic 2° amines. \(^1\)H NMR spectra of different N-Mannich bases have shown the absence of four (1H, -NH), two (1H, -NH) and two (1H, -NH) singlets of four 2° amino groups of OHPMs substrate and two 2° amino groups of both DHPMs and spiro substrate respectively. This suggests that the hydrogen atom of the 2° amino groups have reacted with HCHO and heterocyclic amino compounds to form tetrasubstituted and disubstituted N-Mannich bases. This can be further confirmed from the appearance of new \(^1\)H NMR signals due to the methylene linkages between pyrimidine/pyrimidopyrimidine substrate and heterocyclic 2° amines. All these inferences support the predicted chemical structure of novel N-Mannich bases as shown in Scheme II.
Table I — Analytical characterization data of N-Mannich bases 1a, 1d, 2a-c, 3a-c, 4a-c, 5a-c and 6a,b

<table>
<thead>
<tr>
<th>Compd</th>
<th>Yield (%)</th>
<th>m.p. °C</th>
<th>Mol. formula</th>
<th>Found (%)</th>
<th>(Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>86</td>
<td>180</td>
<td>C_{15}H_{13}N_{3}O_{3}</td>
<td>58.79</td>
<td>5.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(58.82)</td>
<td>5.88</td>
</tr>
<tr>
<td>1b</td>
<td>86</td>
<td>210</td>
<td>C_{15}H_{13}N_{3}O_{3}</td>
<td>51.9</td>
<td>5.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(52.38)</td>
<td>5.15</td>
</tr>
<tr>
<td>2a</td>
<td>90</td>
<td>210</td>
<td>C_{15}H_{13}N_{3}O_{3}</td>
<td>54.08</td>
<td>4.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(54.16)</td>
<td>4.16</td>
</tr>
<tr>
<td>2b</td>
<td>80</td>
<td>179</td>
<td>C_{15}H_{13}N_{3}O_{3}</td>
<td>52.56</td>
<td>4.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(52.83)</td>
<td>4.4</td>
</tr>
<tr>
<td>2c</td>
<td>89</td>
<td>185</td>
<td>C_{15}H_{13}N_{3}O_{3}</td>
<td>51.24</td>
<td>3.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(51.31)</td>
<td>3.94</td>
</tr>
<tr>
<td>3a</td>
<td>75</td>
<td>195</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>73.01</td>
<td>4.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(73.13)</td>
<td>4.9</td>
</tr>
<tr>
<td>3b</td>
<td>79</td>
<td>215</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>74.23</td>
<td>5.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(74.62)</td>
<td>5.22</td>
</tr>
<tr>
<td>3c</td>
<td>85</td>
<td>225</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>71.49</td>
<td>4.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(71.70)</td>
<td>4.87</td>
</tr>
<tr>
<td>4a</td>
<td>88</td>
<td>205</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>66.71</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(66.83)</td>
<td>4.45</td>
</tr>
<tr>
<td>4b</td>
<td>87</td>
<td>202</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>65.61</td>
<td>4.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(65.87)</td>
<td>4.53</td>
</tr>
<tr>
<td>4c</td>
<td>80</td>
<td>189</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>65.31</td>
<td>4.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(65.53)</td>
<td>4.36</td>
</tr>
<tr>
<td>5a</td>
<td>78</td>
<td>199</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>73.89</td>
<td>5.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(74.09)</td>
<td>5.42</td>
</tr>
<tr>
<td>5b</td>
<td>88</td>
<td>209</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>65.89</td>
<td>5.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(66.09)</td>
<td>5.42</td>
</tr>
<tr>
<td>5c</td>
<td>79</td>
<td>195</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>65.69</td>
<td>5.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(65.79)</td>
<td>5.32</td>
</tr>
<tr>
<td>6a</td>
<td>77</td>
<td>214</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>85.43</td>
<td>4.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(85.69)</td>
<td>4.74</td>
</tr>
<tr>
<td>6b</td>
<td>78</td>
<td>204</td>
<td>C_{16}H_{14}N_{3}O_{3}</td>
<td>68.43</td>
<td>4.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(68.57)</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Experimental Section

Laboratory grade ethyl acetoacetate, ethyl cyanoacetate, barbituric acid, urea, different aldehydes and other solvents were used after purifying as and when required. Indole, carbazole and benzimidazole used were synthesized by the literature method. Melting points of N-Mannich bases were determined by open capillary method and are uncorrected. Elemental analysis for C, H and N were carried out on Perkin-Elmer 2400 (USA) instrument. IR spectra ($\nu_{\text{max}}$ in cm$^{-1}$) were recorded on Perkin-Elmer FT-IR instrument and $^1$H and $^{13}$C NMR were scanned in CDCl$_3$ on Bruker AC-90 MHz FT-NMR instrument using TMS as an internal standard.

General procedure for the synthesis of (1a and 1d) and (2a-c)

A mixture of aromatic aldehyde (0.05 mol), active methylene compound (0.05 mol) and urea (0.05 mol) with a few drops of HCl as catalyst was refluxed in methanol at 70-75°C for 8-10 h. After the completion of the reaction as monitored by TLC, the reaction mixture was cooled to RT and poured into crushed ice. The solid thus formed was filtered, washed with cold water and purified by recrystallization from ethanol to get (1a and 1d) and (2a-c).

The synthesis and spectral data of precursors (1a and 1d) and (2a-c) are provided as follows.

5-(Ethoxycarbonyl)-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 1a: It was obtained from ethyl acetoacetate, vanillin and urea as a brown powder, crystallized from ethanol. IR (KBr): 3280 (OH), 3240 (NH), 3016 (C-H of aromatic ring), 1720 (>C=O), 1548 (C=O of aromatic ring), 1220 cm$^{-1}$ (C-O stretch); $^1$H NMR (CDCl$_3$): $\delta$ 6.50-6.40 (m, 3H, ArH), 6.0 (s, 1H, NH), 7.25 (s, 1H, NH), 5.56 (d, 1H, CH), 6.5 (s, 1H, OH), 4.19 (q, 2H, CH$_2$ of OCH$_2$CH$_3$), 3.73 (s, 3H, OCH$_3$), 1.71 (s, 3H, CH$_3$), 1.30 (s, 3H, CH$_3$ of OCH$_2$CH$_3$); ESI-MS: m/z 307 (M$^+$).
6'-Amino-5'-ethoxycarbonyl-1',2',3',4',4'-tetrahydrospiro[indoline-3',4'-pyrimidine]-2',2'-dione, 1d: It was obtained from ethyl cyanoacetate, isatin, and urea as a red crystalline solid, crystallized from ethanol. IR (KBr): 3396 (NH of indole), 3350 (NH), 1545.6 (C=O), 1674 and 1750 (>C=O), 1598.4 (C=O of aromatic ring), 1570 (C=C stretch), 1223 cm⁻¹ (C-O); 1H NMR (CDCl₃): δ 8.0 (s, 1H, NH), 7.68-75 (m, 4H, ArH), 6.0 (s, 1H, NH), 7.65 (s, 1H, NH), 4.19 (d, 2H, CH₂ of OCH₂CH₃), 2.0 (s, 2H, NH₂), 1.30 (s, 3H, CH₃ of OCH₂CH₃); ESI-MS: m/z 303 (M⁺).

5-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione, 2a: It was obtained from barbituric acid, vanillin and urea as a red crystalline solid. IR (KBr): 3290.6 (NH), 3071.5 (C-H of aromatic ring), 1674 & 1730 (>C=O), 1598.4 (C=O of aromatic ring), 1570 (C=C stretch), 1223 cm⁻¹ (C-O); 1H NMR (CDCl₃): δ 8.0 (s, 1H, NH), 7.68-75 (m, 4H, ArH), 6.0 (s, 1H, NH), 7.65 (s, 1H, NH), 4.19 (d, 2H, CH₂ of OCH₂CH₃), 2.0 (s, 2H, NH₂), 1.30 (s, 3H, CH₃ of OCH₂CH₃); ESI-MS: m/z 289 (M⁺).

5-(3,4-Dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione, 2b: It was obtained from barbituric acid, vanillin and urea as a red crystalline solid. IR (KBr): 3290.6 (NH), 3065.5 (C-H of aromatic ring), 1674 and 1750 (>C=O), 1545.4 (C=O of aromatic ring), 1570 (C=C stretch), 1223 cm⁻¹ (C-O); 1H NMR (CDCl₃): δ 8.0 (s, 1H, NH), 6.65-6.45 (s, 3H, ArH), 7.34 (s, 2H, 2×NH), 5.85 (s, 1H, NH), 3.73 (s, 6H, 2×OCH₃); ESI-MS: m/z 319 (M⁺).

5-(4-Hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione, 2c: It was obtained from barbituric acid, vanillin and urea as a brown powder. IR (KBr): 3290.3 (-OH of aromatic ring), 3045 (C=O of aromatic ring), 1679 & 1616 (>C=O), 1545.4 (C=O of aromatic ring), 1570 (C=C stretch), 1223 cm⁻¹ (C-O); 1H NMR (CDCl₃): δ 10.4 (s, 1H, OH), 6.40-6.56 (m, 3H, ArH), 7.59 (s, 2H, 2×NH), 5.65 (s, 1H, NH), 4.85 (s, 1H, OH), 3.56 (s, 3H, OCH₃); ESI-MS: m/z 305 (M⁺).

General procedure for the synthesis of N-Mannich bases (3a-c), (4a-c), (5a-c) and (6a,b)

To a solution of above prepared heterocyclic compounds (1a and 1d) and (2a-c) in DMF, formaldehyde was added. The reaction mixture was stirred at RT for 2-3 h to yield methylol derivative. To this, a solution of heterocyclic-2°-amine in DMF was added drop-wise and refluxed for further 7-8 h. The reaction mixture was poured into ice cold water and the product formed was filtered and washed with hot water. Finally, it was dried and purified by recrystallisation from chloroform to get (3a-c) (with indole) and (4a-c) (with benzimidazole) [if the reactants were taken in molar ratio 1:4:4] and (5a-c) (with carbazole, benzimidazole and indole respectively) and (6a,b) (with benzimidazole and indole respectively) [if the reactants were taken in molar ratio 1:2:2].

The synthesis and spectral data of N-Mannich bases (3a-c), (4a-c), (5a-c) and (6a,b) are provided as follows.

1,3,6,8-Tetakisindol-1-yl-methyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione, 3a: It was obtained from (2a), formaldehyde and indole as a crystalline solid. IR (KBr): 3071.5 (C-H of aromatic ring), 1674 and 1730 (>C=O), 1620 (C=C stretch), 1598.4 (C=O of aromatic ring), 1103.1 cm⁻¹ (C-O-C); 1H NMR (CDCl₃, 200 MHz): δ 7.12 (m, 16H, ArHs of 4×indole), 6.92-6.65 (m, 4H, ArH), 6.82 (d, 4H, 4×CH), 6.48 (d, 4H, 4×CH), 5.72 (s, 8H, 4×CH₂), 5.56 (s, 1H, CH), 3.73 (s, 3H, OCH₃); 13C NMR (CDCl₃, 50 MHz): δ 162.3, 159.0, 151.2, 141.8, 136.6, 127.4, 122.2, 121.0, 119.0, 112, 104, 87.6, 69.8, 67.7, 65.9, 55.5; ESI-MS: m/z 805 (M⁺).

1,3,6,8-Tetakisindol-1-yl-methyl-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione, 3b: It was obtained from (2b), formaldehyde and indole as a crystalline solid. IR (KBr): 3035 (C=O of aromatic ring), 1720 and 1616 (>C=O), 1654.6 (C=O of aromatic ring), 1212.3 cm⁻¹ (C-O-C stretch); 1H NMR (CDCl₃, 200 MHz): δ 7.14 (m, 16H, ArHs of 4×indole), 6.80 (d, 4H, 4×CH), 6.45-6.35 (m, 3H, ArH), 6.45 (d, 4H, 4×CH), 5.70 (s, 8H, 4×CH₂), 5.45 (s, 1H, CH), 3.73 (s, 6H, 2×OCH₃); 13C NMR (CDCl₃, 50 MHz): δ 162.3, 151.2, 149.6, 148.1, 141.3, 136.6, 131.3, 128.4, 122.2, 120.1, 119.0, 117.1, 115.7, 113.0, 102.3, 87.6, 69.8, 67.7, 65.9, 55.5; ESI-MS: m/z 819 (M⁺).

1,3,6,8-Tetakisindol-1-yl-methyl-5-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-d]pyrimidine-2,4,7-trione, 3c: It was obtained from (2c), formaldehyde and indole as a crystalline solid. IR (KBr): 3296 (OH of aromatic ring), 3015 (C=O of aromatic ring), 1720 and 1616 (>C=O), 1654.6 (C=O of aromatic ring), 1232.3 cm⁻¹ (C-O-C stretch); 1H NMR (CDCl₃, 200 MHz): δ 7.21 (m, 16H, ArHs of 4×indole), 6.81 (d, 4H, 4×CH), 6.50-6.40 (m,
3H, ArH), 6.46 (d, 4H, 4xCH), 5.72 (s, 8H, 4xCH₂), 5.55 (s, 1H, CH), 4.9 (s, 1H, OH), 3.73 (s, 3H, OCH₃); ¹³C NMR (CDCl₃, 50 MHz): δ 162.3, 151.2, 149.6, 148.1, 144.3, 141.3, 136.6, 131.3, 128.4, 122.2, 120.1, 119.0, 117.1, 115.7, 113.0, 102.3, 87.6, 69.8, 67.7, 65.9, 55.5; ESI-MS: m/z 805 (M⁺).

1,3,6,8-Tetrasubstituted pyrimidine-1-yl-methyl-5-(4-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimidine[4,5-d]pyrimidine-2,4,7-trione, 4a: It was obtained from (2a), formaldehyde and benzimidazole as a crystalline solid. IR (KBr): 3071.5 (C=O of aromatic ring), 1674 and 1730 (C=O), 1598.4 (C=O of aromatic ring), 1101.3 cm⁻¹ (O-C=C); ¹¹H NMR (CDCl₃, 200 MHz): δ 8.08 (s, 4H, 4xCH), 7.70–7.2 (m, 16H, ArHs of 4xbenzenimidazole), 6.92–6.61 (m, 4H, ArH), 5.65 (s, 8H, 4xCH₂), 5.45 (s, 1H, CH), 3.73 (s, 3H, OCH₃); ¹³C NMR (CDCl₃, 50 MHz): δ 162.3, 159.0, 151.5, 151.2, 143.8, 141.1, 138.9, 134.6, 130.3, 129.4, 123.2, 112.5, 110.5, 87.6, 67.7, 63.1, 55.5; ESI-MS: m/z 805 (M⁺).

1,3,6,8-Tetrasubstituted pyrimidine-1-yl-methyl-5-(3,4-dimethoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimidine[4,5-d]pyrimidine-2,4,7-trione, 4b: It was obtained from (2b), formaldehyde and benzimidazole as a crystalline solid. IR (KBr): 3031.5 (C=O of aromatic ring), 1654 and 1710 (C=O of aromatic ring), 1210.8 cm⁻¹ (OCH₃ of aromatic ring); ¹¹H NMR (CDCl₃, 200 MHz): δ 8.08 (s, 4H, 4xCH of benzimidazole), 7.70–7.26 (m, 16H, ArHs of 4xbenzenimidazole), 6.55–6.46 (m, 3H, ArH), 5.65 (s, 8H, 4xCH₂), 5.45 (s, 1H, CH), 3.73 (s, 6H, 2xCH₂); ¹³C NMR (CDCl₃, 50 MHz): δ 162.3, 159.0, 151.5, 149.5, 148.6, 143.2, 138.9, 134.6, 130.3, 123.4, 122.2, 117.0, 115.3, 113.0 87.6, 67.7, 63.1, 56.2; ESI-MS: m/z 823 (M⁺).

1,3,6,8-Tetrasubstituted pyrimidine-1-yl-methyl-5-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrimidine[4,5-d]pyrimidine-2,4,7-trione, 4c: It was obtained from (2c), formaldehyde and benzimidazole as crystalline solid. IR (KBr): 3306 (OH of aromatic ring), 3041.5 (C=O of aromatic ring), 1654 and 1710 (C=O of aromatic ring), 1498.4 (C=O of aromatic ring), 1220 cm⁻¹ (O-C=C); ¹¹H NMR (CDCl₃, 200 MHz): δ 7.17–7.06 (m, 8H, ArHs of indole), 6.8 (d, 2H, CH), 6.48 (d, 2H, CH), 6.50–6.40 (m, 3H, ArH), 5.72 (s, 4H, 2xCH₂), 5.55 (s, 1H, CH), 5.03 (s, 1H, OH), 4.19 (q, 2H, CH₂), 3.73 (s, 3H, OCH₃), 2.73 (s, 3H, OCH₃), 1.71 (s, 3H, CH₃), 1.30 (t, 3H, CH₃); ¹³C NMR (CDCl₃, 50 MHz): δ 167.3, 151.2, 150.5, 144.1, 143.2, 138.9, 134.3, 131.6, 123.4, 121.2, 116.7, 113.4, 113.3, 106.4, 66.7, 61.7, 56.1, 15.4; ESI-MS: m/z 757 (M⁺).

1,3,6-Bisindolyl-1-ylmethyl-5-ethoxyxybenzyl-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-4-dihydropyrimidin-2(1H)-one, 5a: It was obtained from (1a), formaldehyde and carbazole as crystalline solid. IR (KBr): 3396 (OH of aromatic ring), 2936.9.5 (C=O of aromatic ring), 2898 (aliphatic C=H stretch), 1632 (>C=O), 1565.4 (C=O of aromatic ring), 1234 cm⁻¹ (C-O-C stretch); ¹¹H NMR (CDCl₃, 200 MHz): δ 7.36–7.08 (m, 16H, ArHs of carbazole), 6.50–6.40 (m, 3H, ArH), 5.70 (s, 4H, 2xCH₂), 5.55 (s, 1H, CH), 5.03 (s, 1H, OH), 4.19 (q, 2H, CH₂), 3.72 (s, 3H, OCH₃), 1.71 (s, 3H, CH₃), 1.30 (t, 3H, CH₃); ¹³C NMR (CDCl₃, 50 MHz): δ 167.3, 151.2, 150.5, 144.1, 143.2, 138.9, 134.3, 131.6, 123.4, 121.2, 116.7, 113.4, 113.3, 106.4, 102.7, 66.7, 61.7, 56.1, 14.4; ESI-MS: m/z 755 (M⁺).

1',3'-Bisbenzimidazol-1-ylmethyl-6'-amino-5'-ethoxycarbonyl-1,2',3',4'-tetrahydropyrido[5-]indoline-3,4'-pyrimidine]-2,2'-dione, 6a: It was obtained from (1d), formaldehyde and benzimidazole as a crystalline solid. IR (KBr): 3375 (NH₂), 3180 (NH of spiro str.),
3027.2 (C-H of aromatic ring ), 1631.9 & 1509.1 (C=C of aromatic ring), 1216.0 cm\(^{-1}\) (C=O); \(^{1}H\) NMR (CDCl\(_3\), 200 MHz): \(\delta\) 8.08 (s, 2H, 2\timesCH), 8.0 (s, 1H, NH), 7.70-7.26 (m, 8H, ArH of 2\timesbenzimidazole), 7.52-6.88 (m, 4H, ArH), 5.60 (s, 4H, 2\timesCH\(_2\)), 4.19 (q, 2H, CH\(_2\)), 2.0 (s, 2H, NH\(_2\)), 1.30 (t, 3H, CH\(_3\)); \(^{13}C\) NMR (CDCl\(_3\), 50 MHz): \(\delta\) 168.2, 167.1, 150.4, 143.8, 141.2, 138.9, 134.8, 127.4, 127.1, 124.6, 123.0, 122.1, 115.3, 85.8, 64.0, 61.9, 14.1; ESI-MS: \(m/z\) 549 (M\(^{+}\)).

1′, 3′-Bisindo 1-1-ylmethyl-6'-amino - 5'-ethoxy-carbonyl 1′,2′,3′,4′-tetrahydrospiro[indoline-3,4′-pyrimidine]-2,2′-dione, 6b: It was obtained from (1d), formaldehyde and indole as a crystalline solid. IR (KBr): 3450 (NH\(_2\)), 1631.9 & 1509.1 (>C=O), 1580.4 (C=N); \(^{1}H\) NMR (CDCl\(_3\), 200 MHz): \(\delta\) 8.0 (s, 1H, NH), 7.17-7.04 (m, 4H, ArH), 7.52-6.82 (m, 8H, ArH of 2\timesbenzimidazole), 7.52-6.88 (m, 4H, ArH), 5.60 (s, 4H, 2\timesCH\(_2\)), 4.19 (q, 2H, CH\(_2\)), 2.0 (s, 2H, NH\(_2\)), 1.30 (t, 3H, CH\(_3\)); \(^{13}C\) NMR (CDCl\(_3\), 50 MHz): \(\delta\) 168.2, 167.1, 150.4, 143.8, 141.2, 138.9, 134.8, 127.4, 127.1, 124.6, 123.0, 122.1, 115.3, 85.8, 64.0, 61.9, 14.1; ESI-MS: \(m/z\) 561 (M\(^{+}\)).

**Conclusion**

This paper reports a convenient one pot multicomponent synthesis of precursors of Mannich bases (1a and 1d) and (2a-c) and some tetrasubstituted and disubstituted novel Mannich bases (3a-c), (4a-c), (5a-c) and (6a,b).

**Acknowledgements**

Authors are thankful to the Department of Chemistry of IIIM, Jammu for \(^{1}H\) and \(^{13}C\) NMR spectral analysis and Department of Chemistry, Jammu University for IR spectral analysis.

**References**

34. Biginelli P, *Chem Ber*, 24 (1891) 2962;