# Synthesis of 6,7-Dimethoxypyrimido[4,5-*b*]-indoles as Potential Antihypertensive Agents †

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Using ethyl 5,7-dimethoxy-2-amino-3-indolecarboxylate as a synthon, routes are described for the synthesis of the title compounds bearing alkylamino moieties in the 2 and 4-positions. Some of the compounds displayed antihypertensive activity.

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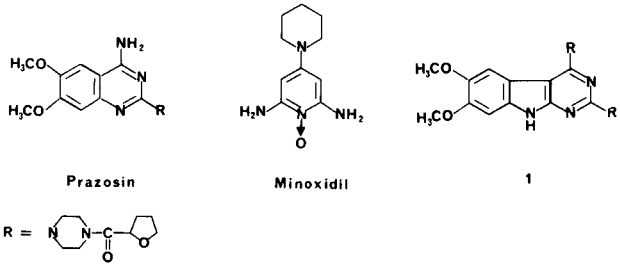
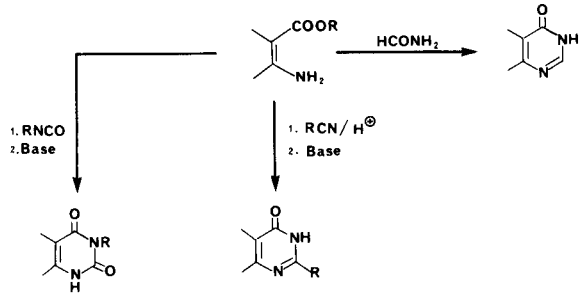
The presence of a pyrimidine ring in the antihypertensive drugs prazosin [1] and minoxidil [2] prompted us to develop synthetic routes leading to pyrimido[4,5-*b*]indoles **1** in order that a series of such compounds could be made for screening of their antihypertensive properties.

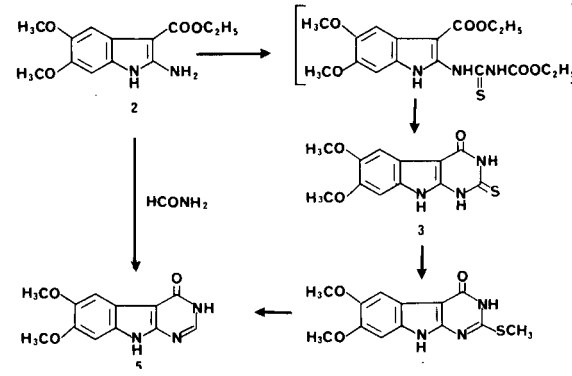



Enamino esters serve as a good synthon for the construction of a pyrimidine ring [3]. The synthesis of a pyrimidine ring could be achieved by the following ways: 1. Reaction of enamino esters with formamides [4]. 2. Reaction of enamino esters with nitriles in the presence of acid followed by base-catalysed cyclisation [5]. 3. Reaction of enamino esters with isocyanates followed by treatment with a base [4b,6,7].



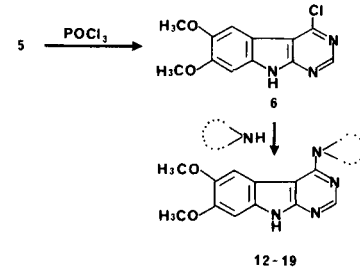

Herein we report the synthesis of mainly 5,7-dimethoxypyrimido[4,5-*b*]indoles and 7-chloropyrimido[4,5-*b*]indole, using the enamino ester ethyl 5,7-dimethoxy-2-amino-3-indolecarboxylate **2** [8] as a synthon. Treatment of **2** with ethyl carboxyisothiocyanate followed by reaction with potassium hydroxide gave the 2-thio-4-oxo-pyrimido[4,5-*b*]-indole [3]. Controlled methylation of **3** gave **4**, which upon Raney Nickel reduction gave the pyrimido indole **5**. The pyrimidoindole **5** was alternatively obtained by direct reaction of the enamino ester **2** with formamide as shown in Scheme I.

Scheme I



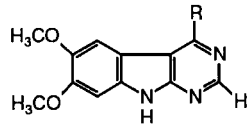

Treatment of the pyrimido[4,5-*b*]indol-4-one **5** with phosphoryl chloride gave the chloro compound **6**. Functionalisation of the chloro group with amines afforded a series of compounds for pharmacological evaluation as shown in Scheme II (Table I).

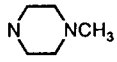
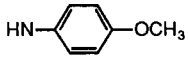
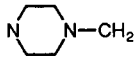
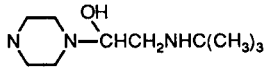
Scheme II




Nitriles on treatment with acid give rise to highly reactive imidoyl chlorides or nitrilium halides [9-14]. These reactive species can react further with an enamino ester to yield pyrimidones. As envisaged, treatment of the enamino ester 2 with acetonitrile in the presence of dry hydrogen chloride and followed by base treatment furnished 2-methylpyrimido[4,5-*b*]indol-4-one **7**. Similarly, the chloroacetonitrile underwent an acid catalysed nucleophilic addition reaction with the enamino ester **2** to give the inter-

Table I



| Compound | R | Mp (°C) | Crystallization solvent [a] | Yield (%) | Molecular Formula | Analysis (%) Calcd. (Found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| 12 |  | 218-219 | A | 48 | $C_{17}H_{21}HN_5O_2$ | 62.38<br>(61.90 | 6.42<br>6.63 | 21.40<br>21.50) |
| 13 |  | 238-239 | B | 76 | $C_{17}H_{20}N_4O_4$ | 65.38<br>(64.94 | 6.41<br>6.05 | 17.94<br>18.25) |
| 14 |  | 259-260 | B | 32 | $C_{16}H_{18}N_4O_3$ | 61.46<br>(61.68 | 5.73<br>5.67 | 17.83<br>18.21) |
| 15 |  | 272-273 | C | 55 | $C_{19}H_{18}N_4O_3$ | 65.13<br>(65.52 | 5.17<br>5.19 | 15.99<br>16.24) |
| 16 |  | > 310 | C | 52 | $C_{15}H_{17}N_5O_4$ | 54.37<br>(54.75 | 5.17<br>5.19 | 21.13<br>21.41) |
| 17 | $N(C_2H_5)_2$ | 220-221 | A | 92 | $C_{16}H_{21}N_4O_2$ | 63.76<br>(64.02 | 7.02<br>6.90 | 18.59<br>19.07) |
| 18 |  | 216-218 | A | 78 | $C_{23}H_{25}N_5O_2$ | 68.46<br>(68.86 | 6.24<br>6.10 | 17.36<br>17.11) |
| 19 |  | 234-235 | D | 68 | $C_{16}H_{19}N_5O_2$ | 61.32<br>(61.65 | 6.11<br>6.05 | 22.35<br>22.62) |
| 20 |  | 227-230 | D | 69 | $C_{23}H_{34}N_6O_3$ | 62.42<br>(62.36 | 7.74<br>8.27 | 18.99<br>18.43) |

mediate **8**. This intermediate **8** underwent both nucleophilic substitution and cyclisation in the presence of amine to furnish the pyrimido[4,5-*b*]indol-4-one **9**. The pyrimido indolones **7** and **9** were converted to **21-26** and **28-32** respectively as shown in Scheme III (Tables II and III).

This method was extended to the preparation of 2-amino pyrimido[4,5-*b*]indol-4-one **33**. Thus, cyanamide reacted with the enamino ester **2** in the presence of acid to yield the intermediate **10** which upon exposure to aqueous sodium hydroxide furnished the pyrimido indole **33**. Compound **33** was converted to **34-36** as shown in Scheme IV (Table IV).

Treatment of the enamino ester **2** with ethyl carboxyisocyanate followed by base treatment gave the pyrimido-[4,5-*b*]indole-2,4-dione **11**. Functionalisation of **11** using phosphoryl chloride followed by an amine gave the diamino compounds **37-38** as shown in Scheme V (Table V).

Scheme III

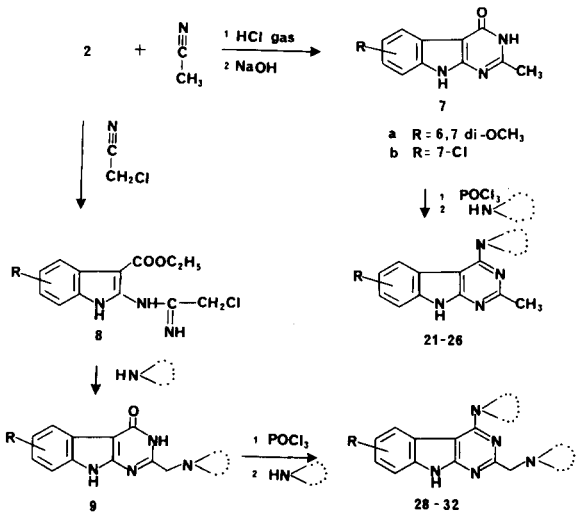
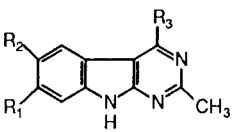
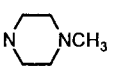
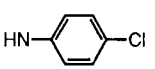
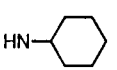
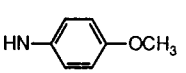


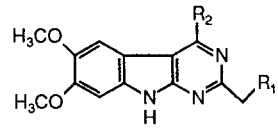
Table II

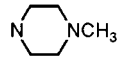
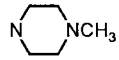
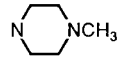
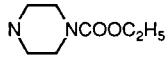
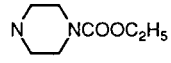
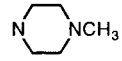


| Compound | R | $R_2$ | $R_3$ | Mp (°C) | Crystallization solvent [a] | Yield (%) | Molecular Formula | Analysis (%) Calcd. (Found) C | H | N | Cl |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **21** | $OCH_3$ | $OCH_3$ |  | 210-211 | A | 64 | $C_{18}H_{22}N_4O_4$ | 66.23 (66.23 | 6.69 6.55 | 17.17 17.42) | |
| **22** | $OCH_3$ | $OCH_3$ | $HN(CH_2)_2N(C_2H_5)_2$ | 193-194 | B | 46 | $C_{19}H_{27}N_5O_2$ | 63.84 (63.98 | 7.62 7.45 | 19.59 19.66) | |
| **23** | H | H |  | 257-259 | A | 77 | $C_{16}H_{19}N_5$ | 68.30 (68.03 | 6.81 6.52 | 24.89 25.31) | |
| **24** | Cl | H |  | > 330 | C | 47 | $C_{17}H_{11}Cl_2N_4$ | 59.66 (59.38 | 3.24 3.38 | 16.37 16.42 | 20.72 20.54) |
| **25** | $OCH_3$ | $OCH_3$ |  | 265-267 | B | 82 | $C_{19}H_{24}N_4O_2$ | 67.03 (67.11 | 7.10 6.76 | 16.46 16.20) | |
| **26** | $OCH_3$ | $OCH_3$ |  | 258-260 | B | 52 | $C_{20}H_{20}N_4O_3$ | 65.92 (65.92 | 5.53 5.54 | 15.37 15.17) | |

[a] A, Methanol-dichloromethane; B, dichloromethane-petroleum ether (60-80°); C, acetone.

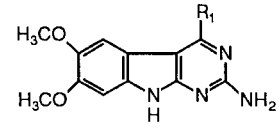
Table III

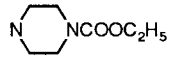
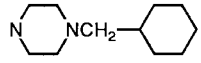


| Compound | R | $R_2$ | Mp (°C) | Crystallization solvent [a] | Yield (%) | Molecular Formula | Analysis (%) Calcd. (Found) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| **28** |  |  | 176-178 | B | 32 | $C_{23}H_{33}N_7O_2$ | 62.84<br>(62.98 | 7.57<br>7.76 | 22.29<br>22.05) |
| **29** |  | $N(C_2H_5)_2$ | 153-154 | C | 30 | $C_{22}H_{32}N_6O_2$ | 64.04<br>(63.68 | 7.80<br>7.64 | 20.37<br>19.87) |
| **30** |  |  | 173-175 | E | 30 | $C_{27}H_{37}N_7O_6$ | 58.36<br>(57.89 | 6.71<br>6.39 | 17.65<br>17.56) |
| **31** | $N(C_2H_5)_2$ |  | 115-117 | A | 58 | $C_{22}H_{32}N_6O_2$ | 64.05<br>(64.25 | 7.82<br>7.66 | 20.37<br>20.40) |
| **32** | $N(C_2H_5)_2$ |  | 134-136 | C | 53 | $C_{22}H_{31}N_5O_2$ | 66.46<br>(66.28 | 7.86<br>7.69 | 17.62<br>17.41) |

[a] A, Ether-pentane; B, dichloromethane-petroleum ether (60-80°); C, ether-petroleum ether (60-80°); D, methanol; E, ethyl acetate-petroleum ether (60-80°).

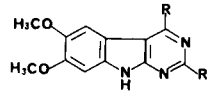
Table IV



| Compound | $R_1$ | Mp (°C) | Crystallization solvent [a] | Yield (%) | Molecular Formula | Analysis (%) Calcd. (Found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **34** |  | 218-222 | B | 25 | $C_{19}H_{24}N_6O_4$ | 57.35<br>(57.05 | 6.05<br>6.04 | 21.07<br>21.01) |
| **35** |  | 210-212 | C | 13 | $C_{16}H_{20}N_6O_2$ | 58.52<br>(58.89 | 6.14<br>5.94 | 25.60<br>25.16) |
| **36** |  | 202-203 | A | 33 | $C_{23}H_{26}N_6O_2$ | 65.99<br>(66.00 | 6.21<br>6.26 | 19.70<br>20.10) |

[a] A, Dichloromethane-petroleum ether (60-80°); B, methanol-dichloromethane; C, methanol-dichloromethane-petroleum ether (60-80°); D, dimethylsulfoxide-water.

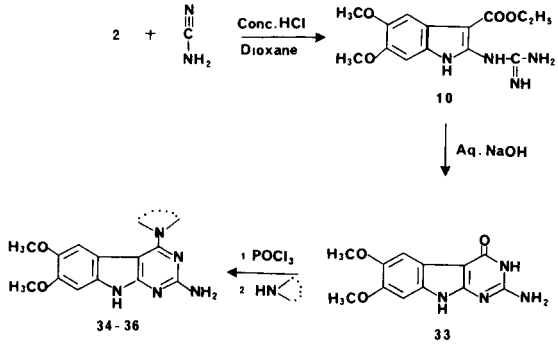
Table V



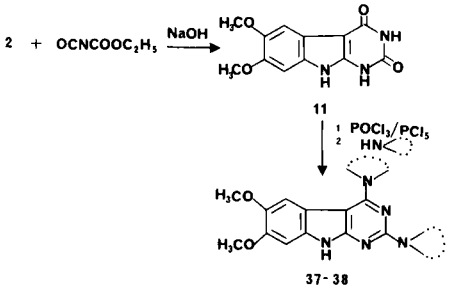
| Compound | R | Mp (°C) | Crystallisation Solvent [a] | Yield (%) | Molecular Formula | Analysis (%) Calcd./(Found) C | H | N |
|---|---|---|---|---|---|---|---|---|
| **37** | N $NCH_3$ | 210-212 | A | 7 | $C_{22}H_{31}N_7O_2$ | 62.09 (62.30) | 7.34 (7.67) | 23.04 (22.67) |
| **38** | N | 170-172 | B | 11 | $C_{22}H_{29}N_5O_2$ | 66.81 (67.20) | 7.39 (6.94) | 17.71 (17.51) |

[a] A, Chloroform-petroleum ether (60-80°); B, dichloromethane-petroleum ether (60-80°).

Scheme IV



Scheme V



A number of these compounds has shown significant hypotensive activity. Biological test results will be described elsewhere.

## EXPERIMENTAL

All the melting points are uncorrected. Infrared spectra were taken in potassium bromide using a Perkin Elmer 157 spectrophotometer. The $^1H$ nmr spectra were run on a Varian T-60 spectrometer chemical shifts ($\delta$) are in parts per million relative to tetramethylsilane.

6,7-Dimethoxy-3,4-dihydro-9*H*-pyrimido[4,5-*b*]indol-4-one (**5**).

Method I.

To dry sodium methoxide prepared from 250 mg of sodium and 10 ml of dry methanol, was added a solution of 2.64 of (0.01 mole) of 5,6-dimethoxy-2-amino-3-carbethoxyindole **2** [8] in 250 ml of formamide. The reaction mixture was refluxed for 3 hours and poured into ice water. The solid separating out was filtered, dried and recrystallised from aqueous DMSO, mp 315° dec, yield 2.2 g (80%); ir (potassium bromide): 1670 $cm^{-1}$; $^1H$ nmr (DMSO-$d_6$): $\delta$ 7 (s, 1H), 7.42 (s, 1H), 8 (s, 1H), 3.82 (s, 6H), 11.95 (b s, 2H).

Method II.

To a solution of **2**, 15 g (0.06 mole) in 150 ml of dry benzene, was added 7 ml of carbethoxy isothiocyanate. The reaction mixture was heated to 90° for 1 hour. A solid was precipitated. It was filtered and washed with petroleum ether (60-80°), yield, 16 g.

This crude solid was treated with 32 g of potassium hydroxide in 480 ml of water. The reaction mixture was refluxed for 15 hours at 100°, cooled and acidified. The precipitate (8.4 g) was filtered dried, and recrystallised from DMSO/methanol to give **3**, mp 299-301°; ir (potassium bromide): ($cm^{-1}$) 3500, 3200 (broad), 1600, $^1H$ nmr (DMSO-$d_6$): $\delta$ 3.9 (s, 6H), 7.1 (s, 1H), 11.6 (s, 1H), 12.2 (s, 1H), 7.3 (s, 1H), 13.6 (s, 1H).

To a suspension of **3** (1.4 g, 0.005 mole) in acetone (100 ml) was added anhydrous potassium carbonate (550 mg) followed by methyl iodide (0.5 ml). The reaction mixture was stirred at room temperature for 1 hour and poured into water. The solid which precipitated was further purified by passing through a column of silica gel. Elution with chloroform/methanol (5%) furnished the 6,7-dimethoxy-2-thiomethyl-3,4-dihydro-9*H*-pyrimido[4,5-*b*]indol-4-one, **4** as a white solid, mp 315° dec, yield 518 mg (35%); ir (potassium bromide): ($cm^{-1}$) 3100 (broad), 1670; $^1H$ nmr (DMSO-$d_6$): $\delta$ 2.6 (s, 3H), 3.8 (s, 6H), 7 (s, 1H), 7.4 (s, 1H), 12.6 (b s, 1H), 12 (s, 1H).

To a solution of **4**, 290 mg (1 mmole) in 10 ml of ethanol was added 500 mg of Raney Nickel. The reaction mixture was refluxed for 15 hours and filtered. The solvent was removed and the crude reaction product was passed through a column of silica gel. Elution with chloroform/methanol (5%) furnished 6,7-dimethoxy-3,4-dihydro-9*H*-pyrimido[4,5-*b*]indol-4-one **5**, mp 315° dec, yield 31%; the ir and $^1H$ nmr were identical with those of **5** obtained by the method I.

6,7-Dimethoxy-4-chloro-9*H*-pyrimido[4,5-*b*]indole (**6**).

A suspension of **5** (1 g, 0.004 mole) in phosphoryl chloride (10 ml) was refluxed at 120° for 6 hours. The reaction mixture became clear. Excess phosphoryl chloride was distilled off under vacuum. The reaction mixture was cooled and poured into ice water. The solid was separated, filtered an passed through a column of silica gel. Elution with chloroform/methanol (1%) furnished the compound **6**, mp >300°, yield 0.64 g (60%); $^1H$ nmr (DMSO-$d_6$): $\delta$ 3.95 (two s, 6H), 7.1 (s, 1H), 7.6 (s, 1H), 8.6 (s, 1H), 12.4 (b s, 1H).

6,7-Dimethoxy-4-piperidino-9*H*-pyrimido[4,5-*b*]indole (**13**).

To a solution of **6** in dry dimethylformamide (10 ml), was added 7.5 ml of piperidine. The reaction mixture was heated at 110-130° for 40 hours and poured into ice water. The solid which separated was filtered, washed with water and recrystallised from chloroform/petroleum ether (60-80°) to give **13**, mp 238-239°, yield 76%; ir (potassium bromide): 1560 $cm^{-1}$; $^1H$ nmr (DMSO-$d_6$): δ 1.7 (b s, 6H), 3.5 (b s, 4H), 3.9 (s, 6H), 7 (S, 1H), 7.2 (s, 1H), 8.4 (s, 1H), 11.9 (s, 1H).

*Anal.* Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.38; H, 6.41; N, 17.94. Found: C, 64.94; H, 6.05; N, 18.25.

Similarly compounds **12** and **14-18** were prepared (Table I).

6,7-Dimethoxy-4-piperazino-9*H*-pyrimido[4,5-*b*]indole (**19**).

To a solution of **6**, 1.77 g (0.007 mole) in dioxane (130 ml), was added piperazine (1.74 g, 0.02 mole). The reaction mixture was refluxed for 1.5 hours. The solvent was removed and the reaction mixture was poured into water. The solid which separated was filtered and recrystallised from methylene chloride/methanol/petroleum ether (60-80°) to give **19**, mp 234-235°, yield 68%; ir (potassium bromide): 1610 $cm^{-1}$; $^1H$ nmr (DMSO-$d_6$): δ 3 (b s), 3.9 (s), 7.1 (s), 7.2 (s), 8.4 (s).

*Anal.* Calcd. for $C_{16}H_{19}N_5O_2$: C, 61.65; H, 6.05; N, 22.62. Found: C, 61.32; H, 6.11; N, 22.35.

6,7-Dimethoxy-4-[*N*-(3-*t*-butylamino-2-hydroxypropyl)piperazino]-9*H*-pyrimido[4,5-*b*]indole (**20**).

To a solution of 6,7-dimethoxy-4-piperazino-9*H*-pyrimido[4,5-*b*]indole **19**, 1.5 g (5 mmoles) in 75 ml of dry acetone, was added anhydrous potassium carbonate (820 mg, 5 mmole) and epibromohydrine (0.5 ml, 6 mmoles). The reaction mixture was refluxed for 3 hours. It was then filtered. The filtrate was evaporated and passed through a column of neutral alumina. Elution with 1% ethyl acetate and methanol furnished the compound, 6,7-dimethoxy-4-[*N*-(2,3-propylenoxy)piperazino]-9*H*-pyrimido[4,5-*b*]indole. It was crystallised from methylene chloride/petroleum ether (60-80°), mp 192-194°, yield 46%.

To a solution of the above solid (780 mg, 0.002 mole) in 80 ml of recitifed spirit, was added *t*-butylamine (4 ml). The reaction mixture was refluxed for 4 hours. The solvent was removed and the reaction mixture was triturated with petroleum ether (60-80°). The solid which precipitated was recrystallised from methylene chloride/methanol (1 drop)/petroleum ether (60-80°) to give the amino alcohol **20** mp 227-230°; yield 69%; ir: (potassium bromide): 1600, 3600 $cm^{-1}$; $^1H$ nmr (deuteriochloroform and perdeuteriomethanol): δ 1.2 (s, 9H), 2.75 (m, 9H), 3.8 (m, 4H) 4.1 (s, 6H), 7.1 (s, 1H), 7.2 (s, 1H), 8.4 (s, 1H).

*Anal.* Calcd. for $C_{23}H_{34}N_6O_3$: C, 62.42; H, 7.74; N, 18.99. Found: C, 62.36; H, 8.27; N, 18.43.

6,7-Dimethoxy-2-methyl-3,4-dihydro-9*H*-pyrimido[4,5-*b*]indol-4-one (**7a**).

To a solution of **2** (6 g, 0.022 mole) in 200 ml of acetonitrile, was passed dry hydrogen chloride gas at room temperature for 1.5 hour. After a few minutes, a solid precipitated. The reaction mixture was kept at room temperature for 15 hours. The solid was filtered, dissolved in water, and the resulting solution basified with sodium carbonate. The solid which precipitated was filtered, washed with water and dried. Recrystallisation with aqueous dimethylsulfoxide afforded the intermediate 5,6-dimethoxy-2-acetamidino-3-carboethoxy-9*H*-indole, mp >300°, yield 5.7 g (82%); ir (ptassium bromide(: ($cm^{-1}$) 3600, 3400, 1600; $^1H$ nmr (DMSO-$d_6$): δ 1.3 (t, 3H), 1.9 (s, 3H), 3.8 (s, 6H), 4.2 (q, 2H), 6.8 (s, 3H), 7.2 (s, 1H).

*Anal.* Calcd. for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.81; H, 6.13; N, 13.93.

This intermediate (5 g) was dissolved in 100 ml of ethanol and 15 ml of 6% aqueous sodium hydroxide. The reaction mixture was refluxed for 6 hours. The solvent was evaporated and the reaction mixture was dissolved in water and acidified. The solid which precipitated was filtered and recrystallised from aqueous dimethylsulfoxide, to give **7a**, mp >300°, yield 4.0 g (98%); ir (potassium bromide): ($cm^{-1}$) 1680, 2850; $^1H$ nmr (DMSO-$d_6$): δ 2.4 (s, 3H), 3.8 (s, 6H), 7 (s, 1H), 12.6 (s, 1H).

*Anal.* Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.12; H, 4.53; N, 16.35.

Similarly 7-chloro-2-methyl-3,4-dihydro-9*H*-pyrimido[4,5-*b*]indole **7b** was prepared, mp 294-296°.

6,7-Dimethoxy-2-methyl-4-cyclohexylamino-9*H*-pyrimido[4,5-*b*]indole (**25**).

A suspension of **7a** (500 mg, 0.0019 mole) in phosphoryl chloride (5 ml) was refluxed for 6 hours. Excess phosphoryl chloride was removed under vacuum. The reaction mixture was treated with water. The solid which precipitated was passed through a column neutral alumina. Elution with chloroform followed by recrystallisation of the appropriate fractions furnished 6,7-dimethoxy-2-methyl-4-chloro-9*H*-pyrimido[4,5-*b*]indole, mp >300°; (methylene chloride/methanol), yield 450 mg (84%); $^1H$ nmr (DMSO-$d_6$): δ 2.8 (s, 3H), 4.4 (s, 6H), 7.2 (s, 1H), 7.8 (s, 1H), 11.6 (s, 1H).

*Anal.* Calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.22; H, 4.36; N, 15.13; Cl, 12.77. Found: C, 55.93; H, 4.53; N, 15.15; Cl, 13.10.

A solution of 6,7-dimethoxy-2-methyl-4-chloro-9*H*-pyrimido[4,5-*b*]-indole (277 mg, 1 mmole) in 2 ml of cyclohexylamine was refluxed for 18 hours. The reaction mixture was cooled and diluted with petroleum ether (60-80°). The solid which separated was filtered and recrystallised from methylene chloride/petroleum ether (60-80°) to give an analytical sample of **25**, mp 265-267°, yield 82%; ir (potassium bromide): 1580 $cm^{-1}$ nmr (deuteriochloroform and DMSO-$d_6$): δ 1.7 (m, 11H), 2.6 (s, 3H), 3.9 (s, 3H), 7 (s, 1H), 7.4 (s, 1H), 11.4 (s, 1H).

*Anal.* Calcd. for $C_{19}H_{24}N_4O_2$; C, 67.03; H, 7.10; N, 16.46. Found: C, 67.11; H, 6.76; N, 16.20.

Similarly compounds **21-24** and **26** were prepared.

6,7-Dimethoxy-2-(4-methylpiperazino)methylpyrimido[4,5-*b*]indol-4-one (**27**).

To an ice cold solution of **2** (10 g, 0.037 mole) in 60 ml of chloroacetonitrile was passed dry hydrogen chloride gas for 1.5 hours and then kept at room temperature for 15 hours. The solid which precipitated was filtered and dissolved in water. The solution was basified with sodium carbonate. The solid which precipitated was filtered and dried, yield 10 g. One g of this dry solid was dissolved in 10 ml of *N*-methylpiperazine. The reaction mixture was stirred at room temperature for 15 hours. The excess of amine was removed under vacuum and the residue was treated with ice. The solid which precipitated was filtered and recrystallised from methanol to give an analytical sample of **27**, mp 275-276°, yield 700 mg (66%); ir (potassium bromide): 1660 $cm^{-1}$; $^1H$ nmr (deuteriochloroform and DMSO-$d_6$): δ 2.2; (s, 3H), 2.6 (b s, 4H), 3.4 (b s, 4H), 3.6 (s, 2H), 4 (s, 6H), 7 (s, 1H), 7.6 (s, 1H), 11.6 (s, 1H).

*Anal.* Calcd. for $C_{18}H_{23}N_5O_3$: C, 60.49; H, 6.48; N, 19.60. Found: C, 60.89; H, 6.46; N, 19.93.

6,7-Dimethoxy-2-(4-methylpiperazino)methyl-4-(4-methylpiperazino)-pyrimido[4,5-*b*]indole (**28**).

A suspension of pyrimidoindolone **27** (1 g, 0.0028 mole) in 20 ml of phosphoryl chloride was refluxed for 6 hours. The excess of phosphoryl chloride was removed under vacuum. The reaction mixture was then treated with 15 ml of *N*-methylpiperazine, and heated at 130-140° for 18 hours. The excess of *N*-methylpiperazine was removed under vacuum. The residue was diluted with water and extracted with chloroform. The organic layer was washed thrice with 2*N* hydrochloric acid solution. The aqueous hydrochloric acid extract was then basified with dilute sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulphate, and concentrated and the residue passed through a column of neutral alumina. Elution with chloroform gave a pure crystalline solid which was recrystallised from methylene chloride/petroleum ether (60-80°) to give an analytical sample of **28**, mp 176-178°, yield 32%; ir (potassium bromide): 1560 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.2-2.8 (b s, 18H), 3.8-4 (b s, 12H), 7 (s, 1H), 7.2 (s, 1H).

*Anal.* Calcd. for $C_{23}H_{33}N_7O_2$: C, 62.84; H, 7.57; N, 22.29. Found: C, 62.98; H, 7.76; N, 22.05.

Similarly compounds **29-32** were prepared (Table III).

6,7-Dimethoxy-2-aminopyrimido[4,5-*b*]indol-4-one (**33**).

To a solution of **2** (6 g, 0.022 mole) in 200 ml of dioxane was added 1.2 g (0.028 mole) of cyanamide and 1.1 ml of concentrated hydrochloric acid. The reaction mixture was refluxed under nitrogen atmosphere for 48 hours. The solid which precipitated was filtered and washed with dry ether, yield 5.2 g (77%) mp >320°.

A mixture of 2.1 g (0.068 mole) of the above solid and a solution of 2.5 g of sodium hydroxide in 100 ml of water was heated on a water bath for 3 hours. To the cooled reaction mixture, dilute hydrochloric acid was added to get a clear solution. It was then basified with dilute sodium carbonate. The solid which precipitated was filtered and washed with water followed by methanol to give 33, yield 1.6 g (89%), mp >300°; ir (potassium bromide): 1660, 1610 ($cm^{-1}$); $^1H$ nmr (DMSO-$d_6$): δ 3.9 (s, 6H), 6.4 (b s, 2H), 7 (s, 1H), 7.4 (s, 1H), 10.6 (b s, 1H), 11.2 (b s, 1H).

*Anal.* Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.40; H 4.65; N, 21.54. Found: C, 55.46; H, 4.89, N, 21.89.

6,7-Dimethoxy-2-amino-4-(*N*-carbethoxypiperazino)pyrimido[4,5-*b*]indole (**34**).

A suspension of 6,7-dimethoxy-2-aminopyrimidoindol-4-one **33** (2 g, 0.0076 mole) in 30 ml of phosphoryl chloride was refluxed for 15 hours. The excess of phosphoryl chloride was removed under vacuum. The residue was diluted with water and then basified with aqueous sodium carbonate solution. The aqueous solution was freeze dried and the residue was treated with 5 g of *N*-carbethoxypiperazine in 50 ml of dioxane. The reaction mixture was refluxed for 15 hours. The excess of the solvent was removed and the residue was extracted with chloroform, washed, dried and evaporated. The resulting product was passed through a column of neutral alumina. Elution with chloroform and methanol (2%) yielded the pyrimidoindole **34**. Recrystallisation of the solid from methanol and methylene chloride furnished the analytical sample, mp 218-222°, yield 25%; ir (potassium bromide): 1750, 1650, 1580 ($cm^{-1}$); $^1H$ nmr (deuteriochloroform and DMSO-$d_6$): δ 1.3 (t, 3H), 3.7-4 (m, 16H), 5.6 (b s, 2H), 6.9-7 (two s, 2H), 7.8 (s, 1H), 11 (s, 1H).

*Anal.* Calcd. for $C_{19}H_{24}N_6O_4$: C, 57.05; H, 6.04; N, 21.01. Found: C, 57.35; H, 6.05; N, 21.07.

Similarly compounds **35** and **36** were prepared (Table IV).

6,7-Dimethoxy-2,4-dipiperidino-9*H*-pyrimido[4,5-*b*]indole (**38**).

To an ice cold solution of **2**, 5.28 g (0.02 mole) in 100 ml of dry benzene was added dropwise a solution of 2.5 ml of carbethoxyisocyanate in 10 ml of dry benzene. After the addition was completed, the reaction mixture was refluxed for 3 hours. The solid precipitated was filtered and dried, yield 6.4 g (84%).

A suspension of 6.4 g (0.016 mole) of the above solid in 100 ml of 6% aqueous sodium hydroxide was treated at 90° for 6 hours under a nitrogen atmosphere. The reaction mixture was cooled and acidified with concentrated hydrochloric acid. The solid which precipitated was filtered and dried to give compound **11**, yield 2.8 g (67%); ir (potassium bromide): 1750, 1675 ($cm^{-1}$).

To a suspension of the above solid (8 g, 0.03 mole) in 60 ml of phosphoryl chloride, was added 8 g of phosphorus pentachloride. The reaction mixture was refluxed for 3.5 days. The excess of phosphoryl chloride was removed and 20 ml of piperidine was added. The reaction mixture was refluxed for 2 days. The excess of piperidine was removed under vacuum and diluted with water. The reaction mixture was extracted with chloroform, dried and concentrated. The residue was passed through a column of neutral alumina. On elution with benzene/ethyl acetate (5%), a viscous gum was obtained. This gum was dissolved in dry methylene chloride and 3 ml of ethereal hydrogen chloride was added. The solid which precipitated was crystallised from dry methanol/methylene chloride/ether. The recrystallised solid was then passed through a column of ion exchange resin. Elution with ethanol furnished the desired product as a solid. Recrystallisation of the solid from methylene chloride/petroleum ether (60-80°) afforded an analytical sample of **38**, yield 11% mp 170-172°; ir (potassium bromide): 1610, 1560 ($cm^{-1}$); $^1H$ nmr (deuteriochloroform): δ 1.6-1.8 (m, 12H), 3.6-4.0 (m, 14H), 6.8 (s, 1H), 7.1 (s, 1H), 9.4 (b s, 1H).

*Anal.* Calcd. for $C_{22}H_{29}N_5O_2$: C, 66.81; H, 7.39; N, 17.71. Found: C, 67.20; H, 6.94; N, 17.5.

Similarly compound **37** was made (Table V).

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## REFERENCES AND NOTES

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