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Sanjay Babu Katiyar [a] , Arun Kumar [a] & Prem M. S. Chauhan [a]
[a] Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, India
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Facile Synthesis of Pyrazolo[3,4-*d*]pyrimidines and Pyrimido[4,5-*d*]pyrimidin-4-one Derivatives

Sanjay Babu Katiyar, Arun Kumar, and Prem M. S. Chauhan
Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, India

Abstract: Pyrazolopyrimidine and pyrimidopyrimidine derivatives have shown a wide range of biological activities such as acting as A_1 adenosine receptors, kinase insert domain receptor (KDR), Rous sarcoma oncogene (Src), epidermal growth factor receptor (EGFR), antiproliferative, dihydrofolate reductase (DHFR), antimicrobial, antifungal, and lipid peroxidation. Because of this wide range of activities, we have synthesized pyrazolo[3,4-*d*]pyrimidines and pyrimido[4,5-*d*]pyrimidin-4-one derivatives.

Keywords: Pyrazolopyrimidine, pyrimidopyrimidine

INTRODUCTION

Pyrazolo[3,4-*d*]pyrimidine[1–4] derivatives were found to be selective ligands with antagonist activity for A_1 adenosine receptors (A_1AR). They may have therapeutical use as cognitive enhancers, antidementia drugs (e.g., for Alzheimer's disease and cerebrovascular dementia), psycostimulants, antidepressant drugs, and ameliorants of cerebral function.[5] A_1AR antagonists have also demonstrated promising therapeutic potential for renal and cardiac

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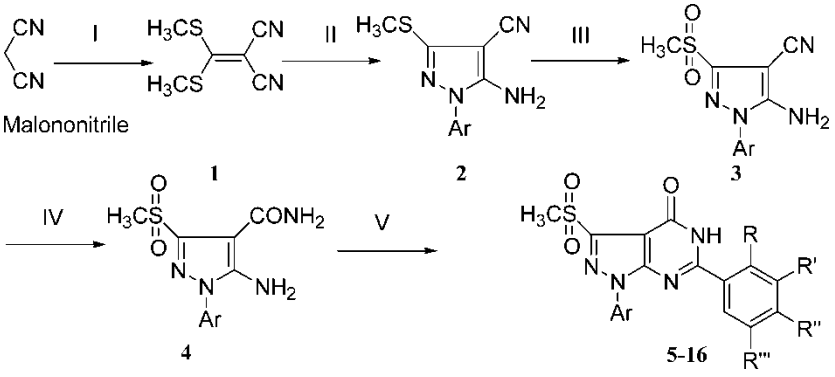
Address correspondence to Prem M. S. Chauhan, Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, India. E-mail: prem_chauhan_2000@yahoo.com

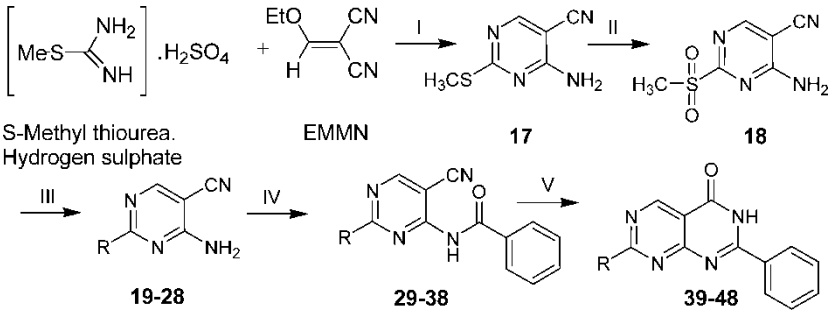


Scheme 1. Reagents and conditions: (I) CS_2, NaH, MeI, THF, 0°C–r.t.; (II) Ar-$NHNH_2$, EtOH, reflux; (III) m-CPBA, DCM, r.t.; (IV) NaOH, H_2O_2. (33%, v/v), 0–r.t.; (V) aromatic aldehydes, PTSA, benzene, reflux.

failure.[6,7] Because of this wide range of activities, we have synthesized the pyrazolopyrimidine derivatives using thiomethyl ketene acetal as intermediate and pyrimidopyrimidone derivatives.

Synthesis of pyrazolo[3,4-*d*]-pyrimidine derivatives **5–16** were carried out as shown in Scheme 1. 2-(bis-Methylsulfanylmethylene)-malononitrile[8] (**1**) was obtained by the reaction of malononitrile with CS_2 in the presence of NaH followed by methylation with methyl iodide at 0°C–r.t. Compound **1** was cyclized with hydrazine hydrate[9,10] in methanol to obtain 5-amino-4-cyano-3-methylsulfanyl-1-phenyl-1H-pyrazole (**2**). Compound **2** was oxidized to the corresponding sulphone 5-amino-4-cyano-3-methanesulfonyl-1-phenyl-1H-pyrazole-4-carbonitrile[11] (**3**) in the presence of chloroperbenzoic acid (m-CPBA). Compound **3** was converted into 5-amino-3-methanesulfonyl-1-phenyl-1H-pyrazole-4-carboxylic acid amide[12] (**4**) by means of H_2O_2 in the presence of NaOH at 0°C–40°C. Compound **4** was cyclized[13] with different aromatic aldehydes in the presence of p-toluenesulfonic acid (PTSA) to obtain the target products **5–16**.

Compound 4-amino-5-cyano-2-methylthiopyrimidine (**17**) was synthesized by the reaction of S-methyl thiourea hydrogen sulphate and ethoxymethylene malonitrile (EMMN) in the presence of diisopropylethylamine in dry DMF at 0°C to r.t.[14] Compound **17** was oxidized with m-chloroperoxybenzoic acid to obtain the sulphone (**18**), which on nucleophilic substitution with various amines furnished the compounds **19–28**.[15] Compounds **19–28** were benzoylated separately with benzoyl chloride in the presence of potassium tert. butoxide in dry DMF at 0°C–r.t. to obtain compounds **29–38**, which were cyclized in the presence of hydrogen peroxide/sodium hydroxide and methanol to give the final products **39–48** (Scheme 2).



Scheme 2. Reagents and conditions: (I) diisopropylethyl amine, DMF, 0°C–r.t.; (II) 3-chloro peroxybenzoic acid, THF, 0°C–r.t.; (III) amines, THF, reflux; (IV) benzoyl chloride, potassium tert. butoxide, DMF, 0°C–r.t., (V) $NaOH/H_2O_2$, MeOH, 0°C–r.t.

EXPERIMENTAL

Melting points were recorded on a capillary melting-point apparatus and are uncorrected. Both ^1H and ^{13}C NMR spectra were recorded on a 200-MHz Bruker FT-NMR (Avance DPX200) spectrometer using tetramethylsilane as internal standard, and the chemical shifts are reported in δ units. Fast atom bombardment (FAB) mass spectra were recorded on Jeol SX 102/DA 6000 mass spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas. Elemental analyses were carried out on a Carlo-Erba 1108 instrument or Elementar's Vario EL III microanalyzer. All chromatographic purification was performed with silica gel 60 (or 100–200 mesh), whereas all thin-layer chromatography (TLC) (silica gel) development was performed on silica gel coated (Merck Kiesel 60 GF-254, 0.2 mm thickness) sheets. All chemicals were purchased from Aldrich Chemical Ltd. (Milwaukee, WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade and were used without further purification unless otherwise stated.

General Experimental Procedure for the Synthesis of Compounds 5–16

The solution of compound **4** (1 equiv), appropriate aromatic aldehydes (1 equiv), and PTSA (1 equiv), in dry benzene was refluxed for 12 h. The solvent was removed under reduced pressure to get a solid mass, which was dissolved in $CHCl_3$, washed with water three times, dried over anhyd. Na_2SO_4, and crystallized with methanol–ether to afford targeted compounds **5–16**.

Data

6-(3-Bromo-phenyl)-3-methanesulfonyl-1-phenyl-1,5-dihydro-pyrazolo-[3,4-*d*]-pyrimidin-4-one (5)

Yield: 73% mp $> 270^{\circ}$C; FAB-MS: 446 (M + 1); IR (KBr): 3428, 3029, 2930, 2818, 197, 1588, 1498, 1464, 1394, 1352 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.29 (s, 1H, Ar-H), 8.08 (d, 1H, $J = 7.92$ Hz, Ar-H), 7.98 (d, 2H, $J = 7.98$ Hz, Ar-H), 7.63 (d, 1H, $J = 7.98$ Hz, Ar-H), 7.53–7.46 (m, 3H, Ar-H), 7.41–7.35 (m, 1H, Ar-H), 3.53 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 172.42, 165.88, 144.65, 139.97, 135.23, 133.90, 130.87, 129.55, 129.96, 127.56, 126.75, 125.25, 123.33, 119.34, 111.42, 41.13. Anal. calcd. for $C_{18}H_{13}BrN_4O_3S$: C, 48.55; H, 2.94; N, 12.58. Found: C, 48.23; H, 3.13; N, 12.25%.

3-Methanesulphonyl-6-(4-methoxy-phenyl)-1-phenyl-1,5-dihydro-pyrazolo-[3,4-*d*]-pyrimidin-4-one (6)

Yield: 69%; mp $> 270^{\circ}$C; FAB-MS: 397 (M + 1); IR (KBr): 3441, 3065, 2956, 2856, 1698, 1599, 1553, 1498, 1397, 1335 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-D_6): δ (ppm) 8.12 (d, 2H, $J = 8.80$ Hz, Ar-H), 8.01 (d, 2H, $J = 7.84$ Hz, Ar-H), 7.61–7.40 (m, 3H, Ar-H), 7.04 (d, 2H, $J = 8.80$ Hz, Ar-H), 3.78 (s, 3H, OCH_3), 3.56 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 171.44, 165.89, 162.44, 145.56, 129.67, 128.12, 127.12, 126.45, 125.67, 119.85, 114.23, 110.11, 56.71, 41.53. Anal. calcd. for $C_{19}H_{16}N_4O_4S$: C, 57.57; H, 4.07; N, 14.13. Found: C, 57.73; H, 4.34; N, 14.09%.

6-(2,3-Dimethoxy-phenyl)-3-methanesulfonyl-1-phenyl-1,5-dihydro-pyrazolo-[3,4-*d*]-pyrimidin-4-one (7)

Yield: 53%; mp 210–213°C; FAB-MS: 427 (M + 1); IR (KBr): 3429, 3009, 2962, 2835, 1698, 1594, 1549, 1496, 1467, 1396 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.12 (d, 2H, $J = 8.74$ Hz, Ar-H), 7.96 (dd, 1H, $J = 1.74$, 7.84 Hz, Ar-H), 7.60–7.45 (m, 3H, Ar-H), 7.28 (dd, 1H, $J = 7.28$ & 8.70 Hz, Ar-H), 7.17 (dd, 1H, $J = 1.74$, 8.18 Hz, Ar-H), 4.03 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.59 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 172.89, 164.98, 147.85, 144.42, 145.67, 140.11, 129.41, 128.74, 126.45, 122.17, 119.89, 119.28, 118.87, 41.15, 116.55, 111.12, 56.89, 56.34. Anal. calcd. for $C_{20}H_{18}N_4O_5S$: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.15; H, 4.43; N, 13.24%.

6-(2,5-Dimethoxy-phenyl)-3-methanesulphonyl-1-phenyl-1,5-dihydro-pyazolo-[3,4-*d*]-pyrimidin-4-one (8)

Yield: 57%; mp 205–228°C; FAB-MS: 427 (M + 1); IR (KBr): 34029, 3015, 2923, 2836, 1701, 1596, 1553, 1492, 1435, 1398, 1329 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.13 (d, 2H, $J = 8.26$ Hz, Ar-H), 8.02 (d, 1H, $J = 3.02$ Hz, Ar-H), 7.59–7.44 (m, 3H, Ar-H), 7.12 (dd, 1H, $J = 3.04$ & 8.74 Hz, Ar-H), 7.03 (d, 1H, $J = 8.74$ Hz, Ar-H), 4.07 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.59 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 172.75, 165.66, 154.55, 151.91, 145.12, 139.99, 129.33, 127.55, 126.76, 119.56, 118.43, 116.78, 115.67, 112.23, 110.98, 56.84, 56.19, 40.78. Anal. calcd. for $C_{20}H_{18}N_4O_5S$: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.13; H, 4.34; N, 13.35%.

6-(4-Isopropyl-phenyl)-3-methanesulphonyl-1-phenyl-1,5-dihydro-pyrazolo-[3,4-*d*]-pyrimidin-4-one (9)

Yield: 55%; mp > 270°C; FAB-MS: 409 (M + 1); IR (KBr): 3432, 3065, 2962, 2856, 1693, 1595, 1555, 1498, 1396, 1328 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.30 (d, 2H, $J = 8.34$ Hz, Ar-H), 8.14 (d, 2H, $J = 7.66$ Hz, Ar-H), 7.62–7.46 (m, 5H, Ar-H), 3.54 (s, 3H, SO_2CH_3), 3.09–3.02 (m, 1H, CH), 1.35 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 172.42, 165.97, 151.55, 144.43, 139.86, 130.75, 129.12, 128.55, 127.85, 126.49, 125.68, 118.89, 110.11, 40.98, 31.75, 24.54. Anal. calcd. for $C_{21}H_{20}N_4O_3S$: C, 61.75; H, 4.94; N, 13.72. Found: C, 61.82; H, 4.73; N, 13.85%.

3-Methanesulfonyl-1-phenyl-6-(3,4,5-trimethoxy-phenyl)-1,5-dihydro-pyrazolo-[3,4-*d*]-pyrimidin-4-one (10)

Yield: 52%; mp > 270°C; FABMS: 457 (M + 1); IR (KBr): 3443, 3016, 2939, 2836, 1712, 1598, 1495, 1459, 1301 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.08 (d, 2H, $J = 7.94$ Hz, Ar-H), 7.53–7.43 (m, 3H, Ar-H), 7.39 (s, 2H, Ar-H), 3.89 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 3.41 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 171.89, 165.43, 148.76, 144.87, 140.74, 134.68, 129.87, 128.12, 127.74, 126.88, 119.43, 111.23, 105.57, 56.32, 56.77, 41.63. Anal. calcd. for $C_{21}H_{20}N_4O_6S$: C, 55.26; H, 4.42; N, 12.27. Found: C, 55.12; H, 4.23; N, 12.45%.

3-Methanesulfonyl-1-phenyl-6-p-tolyl-1,5-dihydro-pyrazolo-[3,4-*d*]-pyrimidin-4-one (11)

Yield: 59%; mp > 270°C; FABMS: 381 (M + 1); IR (KBr): 3434, 3090, 2960, 2865, 1695, 1594, 1479, 1394 1349 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 12.96 (bs, 1H, NH), 8.10–8.02 (m, 4H, $J = 8.14$ Hz,

Ar-H), 7.71–7.49 (m, 3H, Ar-H), 7.43 (d, 2H, $J = 8.28$ Hz, Ar-H), 3.64 (s, 3H, SO_2CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 172.45, 165.79, 145.34, 141.23, 139.76, 130.45, 129.67, 129.12, 127.87, 126.98, 125.91, 119.34, 111.67, 40.98, 21.96. Anal. calcd. for $C_{19}H_{16}N_4O_3S$: C, 59.99; H, 4.24; N, 14.73. Found: C, 59.45; H, 4.64; N, 14.56%.

6-(4-Dimethylamino-phenyl)-3-methanesulfonyl-1-phenyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one (12)

Yield: 59%; mp $> 270^\circ$C; FAB-MS: 410 (M + 1); IR (KBr): 3425, 3093, 2925, 2833, 1690, 1595, 1555, 1453, 1376, 1321 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.14 (d, 2H, $J = 8.16$ Hz, Ar-H), 8.00 (d, 2H, $J = 7.94$ Hz, Ar-H), 7.68–7.52 (m, 3H, Ar-H), 6.84 (d, 2H, $J = 7.96$ Hz, Ar-H), 3.60 (s, 3H, SO_2CH_3), 2.10 (s, 6H, NCH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 171.99, 166.23, 145.92, 144.96, 140.24, 129.53, 127.55, 126.80, 126.33, 123.77, 119.25, 113.44, 111.75, 44.76, 44.82, 41.22. Anal. calcd. for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 17.10. Found: C, 58.86; H, 4.55; N, 17.25%.

3-Methanesulfonyl-6-(4-methylsulfanyl-phenyl)-1-phenyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one (13)

Yield: 60%; mp $> 270^\circ$C; FAB-MS: 413 (M + 1); IR (KBr): 3435, 3095, 2935, 2830, 1691, 1590, 1551, 1463, 1377, 1311 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.12 (d, 2H, $J = 8.26$ Hz, Ar-H), 8.04 (d, 2H, $J = 8.18$ Hz, Ar-H), 7.69–7.48 (m, 3H, Ar-H), 6.80 (d, 2H, $J = 8.16$ Hz, Ar-H), 3.63 (s, 3H, SO_2CH_3), 2.52 (s, 3H, SCH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 172.56, 165.66, 145.43, 139.97, 137.33, 129.22, 129.76, 128.12, 127.58, 126.21, 126.79, 119.34, 111.53, 40.98, 21.35. Anal. calcd. for $C_{19}H_{16}N_4O_3S_2$: C, 55.32; H, 3.91; N, 13.58. Found: C, 55.52; H, 3.77; N, 13.45%.

6-(4-Fluoro-phenyl)-3-methanesulfonyl-1-phenyl-1,5-dihydro-pyrazolo[3,4-*d*]-pyrimidin-4-one (14)

Yield: 61%; mp $> 270^\circ$C; FAB-MS: 385 (M + 1); IR (KBr): 3429, 3080, 2974, 2831, 1688, 1597, 1555, 1493, 1391 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 13.07 (bs, 1H, NH), 8.26 (d, 2H, $J = 8.62$ Hz, Ar-H), 8.08 (d, 2H, $J = 7.88$ Hz, Ar-H), 7.62 (d, 2H, $J = 8.60$ Hz, Ar-H), 7.57–7.42 (m, 3H, Ar-H), 3.64 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 171.997, 165.57, 163.52, 145.34, 140.14, 129.15, 128.76, 127.23, 127.79, 126.55, 118.92, 115.72, 111.35, 4176. Anal. calcd. for $C_{18}H_{13}FN_4O_3S$: C, 56.24; H, 3.41; N, 14.58. Found: C, 56.83; H, 3.08; N, 14.72%.

6-(3,4-Dimethoxy-phenyl)-3-methanesulfonyl-1-phenyl-1,5-dihydro-pyrazolo-[3,4-*d*]-pyrimidin-4-one (15)

Yield: 60%; mp $> 270^{\circ}$C; FAB-MS: 427 ($M^{+}1$); IR (KBr): 3433, 3107, 2933, 2835, 1706, 1599, 1560, 1498, 1396, 1323 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.04 (d, 2H, $J = 7.80$ Hz, Ar-H), 7.83 (d, 1H, $J = 8.64$ Hz, Ar-H), 7.77 (d, 1H, $J = 1.78$ Hz, Ar-H), 7.64–7.45 (m, 3H, Ar-H), 7.10 (dd, 1H, $J = 1.76$, 8.62 Hz, Ar-H), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.56 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 171.79, 166.24, 149.45, 147.75, 145.79, 139.97, 129.66, 127.93, 126.33, 126.95, 119.87, 118.80, 115.64, 112.50, 111.59, 56.32, 56.85, 41.33. Anal. calcd. for $C_{20}H_{18}N_4O_5S$: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.56; H, 4.37; N, 13.08%.

6-(4-Chloro-phenyl)-3-methanesulfonyl-1-phenyl-1,5-dihydro-pyrazolo[3,4-*d*]-pyrimidin-4-one (16)

Yield: 59%; mp $> 270^{\circ}$C; FAB-MS: 401 ($M + 1$); IR (KBr): 3430, 3094, 2965, 2860, 1686, 1592, 1492, 1394 1352 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.18 (d, 2H, $J = 8.62$ Hz, Ar-H), 8.06 (d, 2H, $J = 7.44$ Hz, Ar-H), 7.69–7.48 (m, 5H, Ar-H), 3.62 (s, 3H, SO_2CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 172.55, 165.44, 145.23, 139.76, 135.42, 131.37, 129.55, 129.15, 127.39, 127.68, 126.63, 119.45, 111.79, 41.39. Anal. calcd. for $C_{18}H_{13}ClN_4O_3S$: C, 53.93; H, 3.27; N, 13.98. Found: C, 53.23; H, 3.34; N, 13.85%.

General Experimental Procedure for the Synthesis of Compounds 39–48

To an ice-cold solution of compounds **29–38** (2.5 mmol) in methanol (20 ml) and 10% NaOH solution (10 ml), 33% (v/v) H_2O_2 (10 ml) was added dropwise. The reaction mixture was stirred at r.t. for 6 h. The methanol was distilled in vacuum, and the reaction mixture was neutralized with dil. HCl to pH = 7. The precipited solid was filtered and washed with cold water. The precipitate was dissolved in chloroform, and the solution was dried with Na_2SO_4. Distillation of solvent in vacuum yielded compounds **39–48**.

Data

7-Morpholin-4-yl-2-phenyl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (39)

Yield: 59%; mp 230–235°C (dec.); IR (KBr): 3167, 3088, 2957, 2856, 1678, 1556 cm^{-1}; FAB MS: 310 ($M^{+} + 1$); ^{1}H NMR (200 MHz, $CDCl_3$): δ

(ppm) 9.16 (s, 1H, Py-H), 8.24 (d, 2H, $J = 7.2$ Hz, Ar-H), 7.52 (m, 3H, Ar-H), 4.02 (t, 4H, $J = 4.43$ Hz, N-CH_2), 3.77 (t, 4H, 4.54 Hz, O-CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 184.10, 172.15, 169.55, 164.32, 159.50, 132.98, 129.68, 128.63, 125.78, 110.38, 58.92, 71.40. Anal. calcd. for $C_{16}H_{15}N_5O_2$: C, 62.19; H, 4.88; N, 22.63. Found: C, 61.77; H, 4.96; N, 22.21%.

2-Phenyl-7-piperidin-1-yl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (40)

Yield: 60%; mp $> 250^\circ$C; IR (KBr): 3319, 3087, 2923, 2859, 1676, 1599, 1526 cm^{-1}; FAB MS: 308 ($M^+ + 1$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.14 (s, 1H, Py-H), 8.24 (d, 2H, $J = 6.46$ Hz, Ar-H), 7.52–7.49 (m, 3H, Ar-H), 4.02 (t, 4H, $J = 5.12$ Hz, N-CH_2), 1.69 (m, 6H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 184.35, 171.94, 169.22, 164.66, 159.77, 133.08, 129.44, 128.15, 125.54, 111.23, 54.74, 25.20, 26.38. Anal. calcd. for $C_{17}H_{17}N_5O$: C, 66.44; H, 5.57; N, 22.77. Found: C, 66.11; H, 5.59; N, 22.58%.

7-(4-Benzyl-piperazin-1-yl)-2-phenyl-3-pyrimido-[4,5-*d*]-pyrimidin-4-one (41)

Yield: 76%; mp $> 235–240^\circ$C; IR (KBr): 3167, 3085, 2912, 2795, 1683, 1593, 1526 cm^{-1}; FAB MS: 399 ($M^+ + 1$); ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 9.10 (s,1H, Py-H), 8.22 (d, 1H, $J = 6.62$ Hz, Ar-H), 7.57–7.49 (m, 3H, Ar-H), 7.34–7.27 (m, 5H, Ar-H), 4.03 (t, 4H, $J = 4.60$ Hz, N-CH_2), 3.55 (s, 2H, N-CH_2-Ar), 2.55 (t, 4H, $J = 5.56$ Hz, N-CH_2); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 184.50, 171.80, 169.12, 164.20, 159.60, 144.50, 132.48, 129.80, 129.44, 128.70, 125.92, 118.24, 113.10, 110.39, 59.10, 57.60, 54.50. Anal. calcd. for $C_{23}H_{22}N_6O$: C, 69.33; H, 5.56; N, 21.09. Found: C, 68.67; H, 5.62; N, 20.24%.

7-[4-(2-methoxyphenyl)-piperazin-1-yl]-2-phenyl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (42)

Yield: 55%; mp 130–133°C; IR (KBr): 3319, 3086, 2909, 1676, 1594, 1525 cm^{-1}; FAB MS: 414 ($M^+ + 1$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.07 (s, 1H, Py-H), 8.19 (d, 2H, $J = 7.4$ Hz, Ar-H), 7.64–7.52 (m, 3H, Ar-H), 6.97–6.92 (m, 4H, Ar-H), 4.06 (t, 4H, $J = 4.74$ Hz, N-CH_2), 3.82 (s, 3H, O-CH_3), 3.02 (t, 4H, $J = 5.20$ Hz, N-CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 184.55, 171.54, 169.38, 164.76, 159.32, 146.60, 132.92, 130.10, 129.69, 128.75, 125.32, 121.78, 119.15, 115.23, 114.35, 110.39, 57.92, 57.22, 56.56. Anal. calcd. for $C_{23}H_{22}N_6O_2$: C, 66.65; H, 5.35; N, 20.27. Found: C, 66.30; H, 5.45; N, 20.02%.

7-(3,4-Dihydro-2H-quinolin-1-yl)-2-phenyl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (43)

Yield: 50%; mp 215–217°C (dec.); IR (KBr): 3319, 3086, 2924, 1681, 1598, 1516, 1422 cm^{-1}; FAB MS: 356 ($M^+ + 1$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.21 (s, 1H, Py-H), 8.25 (d, 2H, $J = 6.56$ Hz, Ar-H), 7.61–7.51 (m, 3H, Ar-H), 7.21–7.18 (m, 4H, Ar-H), 5.11 (t, 2H, $J = 5.78$ Hz, N-CH_2), 4.25 (t, 2H, $J = 5.76$ Hz, Ar-CH_2), 2.98 (m, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): 184.55, 172.15, 169.28, 164.37, 159.56, 143.35, 132.85, 129.92, 129.14, 128.58, 126.66, 125.65, 122.62, 117.00, 112.46, 110.45, 60.69, 33.91, 29.25. Anal. calcd. for $C_{21}H_{17}N_5O$: C, 69.98; H, 4.82; N, 19.9. Found: C, 69.32; H, 4.61; N, 19.39%.

7-(4-Methyl-piperazin-1-yl)-2-phenyl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (44)

Yield: 68%; mp 233–235°C (dec.); IR (KBr): 3420, 3170, 3086, 2924, 1681, 1598, 1516, 1422 cm^{-1}; FAB MS: 323 ($M^+ + 1$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.19 (s, 1H, Py-H), 8.27 (d, 2H, $J = 7.80$ Hz, Ar-H), 7.63–7.52 (m, 3H, Ar-H), 4.09 (t, 4H, $J = 4.86$ Hz, N-CH_2), 2.51 (t, 4H, $J = 5.08$ Hz, N-CH_2), 2.35 (s, 3H, N-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 184.55, 172.10, 169.18, 164.35, 159.48, 132.97, 129.92, 128.68, 125.75, 110.38, 57.72, 48.43, 38.70. Anal. calcd. for $C_{17}H_{18}N_6O$: C, 63.34; H, 5.62; N, 26.06. Found: C, 63.11; H, 5.82; N, 25.87%.

2-Phenyl-7-(4-phenyl-piperazin-1-yl)-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (45)

Yield: 61%; mp 210–213°C; IR (KBr): 3418, 3166, 3084, 2911, 2812, 1679, 1594, 1523 cm^{-1}; FAB MS: 385 ($M^+ + 1$); ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 9.06 (s, 1H, Py-H), 8.16 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.63–7.52 (m, 3H, Ar-H), 7.25–6.77 (m, 5H, Ar-H), 4.04 (t, 4H, $J = 5.08$ Hz, N-CH_2), 3.24 (t, 4H, $J = 5.08$ Hz, N-CH_2); ^{13}C NMR (50 MHz, DMSO-d_6): δ (ppm) 184.53, 171.98, 169.14, 164.25, 159.62, 144.50, 132.45, 129.81, 129.45, 128.75, 125.90, 118.25, 113.12, 110.39, 57.58, 54.52. Anal. calcd. for $C_{22}H_{20}N_6O$: C, 68.73; H, 5.25; N, 21.87. Found: C, 68.57; H, 5.23; N, 20.86%.

7-Butylamino-2-phenyl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (46)

Yield: 55%; mp 220–222°C; IR (KBr): 3446, 3169, 3083, 2958, 1675, 1592 cm^{-1}; FAB MS: 296 ($M^+ + 1$); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 8.97 (s, 1H, Py-H), 8.21 (d, 2H, $J = 7.50$ Hz, Ar-H), 7.59–7.49 (m, 3H, Ar-H), 3.47 (t, 2H, $J = 6.9$ Hz, N-CH_2), 1.62–1.59 (m, 2H, CH_2), 1.42–1.39 (m, 2H, CH_2), 0.94 (t, 3H, $J = 7.2$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 184.73, 172.09, 169.14,

164.35, 159.52, 132.85, 129.91, 128.60, 125.90, 110.34, 51.32, 34.00, 20.55, 13.76. Anal. calcd. for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.34; H, 5.96; N, 23.27%.

7-Hexylamino-2-phenyl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (47)

Yield: 58%; mp 218–220°C; IR (KBr): 3344, 3169, 3080, 2956, 1675, 1595 cm^{-1}; FAB MS: 324 ($M^+ + 1$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.03 (s, 1H, py-H), 8.24 (d, 2H, $J = 6.82$ Hz, Ar-H), 7.55–7.50 (m, 3H, Ar-H), 3.49 (t, 2H, N-CH_2), 2.02–1.33 (m, 8H, CH_2), 0.88 (t, 3H, $J = 6.33$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 184.23, 172.35, 169.45, 164.15, 159.44, 131.98, 129.68, 128.73, 125.68, 110.38, 51.66, 31.82, 32.25, 27.40, 23.12, 14.00. Anal. calcd. for $C_{18}H_{21}N_5O$: C, 66.85; H, 6.55; N, 21.66. Found: C, 66.43; H, 6.77; N, 21.34%.

7-Cyclohexylamino-2-phenyl-3H-pyrimido-[4,5-*d*]-pyrimidin-4-one (48)

Yield: 52%; mp 176–179°C; IR (KBr): 3433, 3261, 3089, 1675, 1594, 1518 cm^{-1}; FAB MS: 322 ($M^+ + 1$) ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.06 (s, 1H, Py-H), 8.24 (d, 2H, $J = 6.93$ Hz, Ar-H), 7.58–7.47 (m, 3H, Ar-H), 4.10 (m, 1H, N-CH), 1.80–1.27 (m, 10H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 184.10, 172.15, 169.55, 164.32, 159.50, 132.98, 129.68, 128.63, 125.78, 110.38, 53.66, 33.32, 27.15, 22.32. Anal. calcd. for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 66.89; H, 6.13; N, 21.67%.

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