Full Paper

Synthesis of Non-Nucleosides: 7- and 1,3-Substituents of New Pyrrolo[2,3-*d*]pyrimidin-4-ones on Antiviral Activity

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A series of non-nucleosides **9–47** were synthesized. Compounds **1–4** were reacted with formic acid (85%) to afford compounds **5-8**. Then, the latter compounds were reacted with alkyl halides **a–f** (2-bromopropane, 2-bromobutane, benzyl bromide, benzyl chloromethyl ether, chloromethyl ethyl ether, phenacyl bromide) in the presence of NaH in dry DMF to give the desired compounds **9–47**, which were evaluated for activity against herpes simplex virus type-II (HSV-II).

Keywords: Pyrrolo[2,3-*d*]pyrimidin-4-ones / Synthesis / MIC / Antiviral activity against HSV-II

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Introduction

Pyrrolo[2,3-*d*]pyrimidines are known to possess a wide range of pharmacological activities like antifungal [1], antibacterial [2], antitumoral [3–7], antimalarial [8], and antiviral activities [9–19]. In view of the fact that some pyrrolo[2,3-*d*]pyrimidines possess antiviral activity, a series of some novel pyrrolo[2,3-*d*]pyrimidin-4-ones (**9–47**) were synthesized, with the aim of obtaining a new antiviral agent which would inhibit the replication of herpes simplex virus type-II (HSV-II).

Results and discussion

The target compounds were synthesized **9–47** as depicted in Scheme 1. The starting materials 2-amino-3-pyrrolecarbonitriles (**1–4**) [20, 21] were converted into pyrrolo[2,3-*d*]pyrimidin-4-ones *via* the reaction with formic acid. The latter compounds **5–8** were reacted with alkyl halides **a–f** (2-bromopropane, 2-bromobutane, chloromethyl ethyl ether, benzyl bromide, benzyl chloromethyl ether) in the presence of NaH and dry DMF to give the corresponding alkalized derivatives **9–30** and **31–47** according to the attachment of the alkyl group at 1- or 3-position, respectively.

All the synthesized compounds were characterized by their physical, analytical, and spectral data (see Experimental). The IR spectra of compounds **5–8** showed the presence of characteristic absorption peak at 3080, 3089, 3090, and 3108 cm^{-1} (NH stretching) and also at 1680, 1688, 1677, and 1682 cm^{-1} (C=O stretching). Moreover, the ^{1}H-NMR spectra showed a broad single at δ 10.09-10.77 ppm characteristic for the NH group, besides the ^{13}C-NMR showed δ 157.13–162.94 ppm (C=O). The IR spectra of the compounds **9–47** showed the presence of band around 1676–1689 cm^{-1} (C=O stretching) and the absence of a peak at 3080–3090 cm^{-1} for (NH stretching), due to the alkylation at 1- or 3- position of compounds **5–8**. The disappearance of δ 10.09–10.77 ppm (1H) due to the ring NH proton, and the presence of δ 157.13–162.94 ppm (C=O) for the compounds **9–47**, confirm the alkylation of compounds **5–8**. Besides, the chemical structure of isomers was based on the UV, ^{1}H- and ^{13}C-NMR spectral results. Furthermore, the ^{1}H- and ^{13}C-NMR spectral data of all the synthesized compounds are in conformity with the structure assigned.

All the tested compounds **9–47** were assayed *in vitro* for antiviral activity against herpes simplex type-II (HSV-II). The minimum inhibitory concentration (MIC) mmol/mL was determined by tissue culture with Vero cells. The MICs values illustrated that the most potent compounds are **9**, **10**, **13**, **14**, **15**, **25**, **26**, **31**, **40**, **42**, the lesser potent

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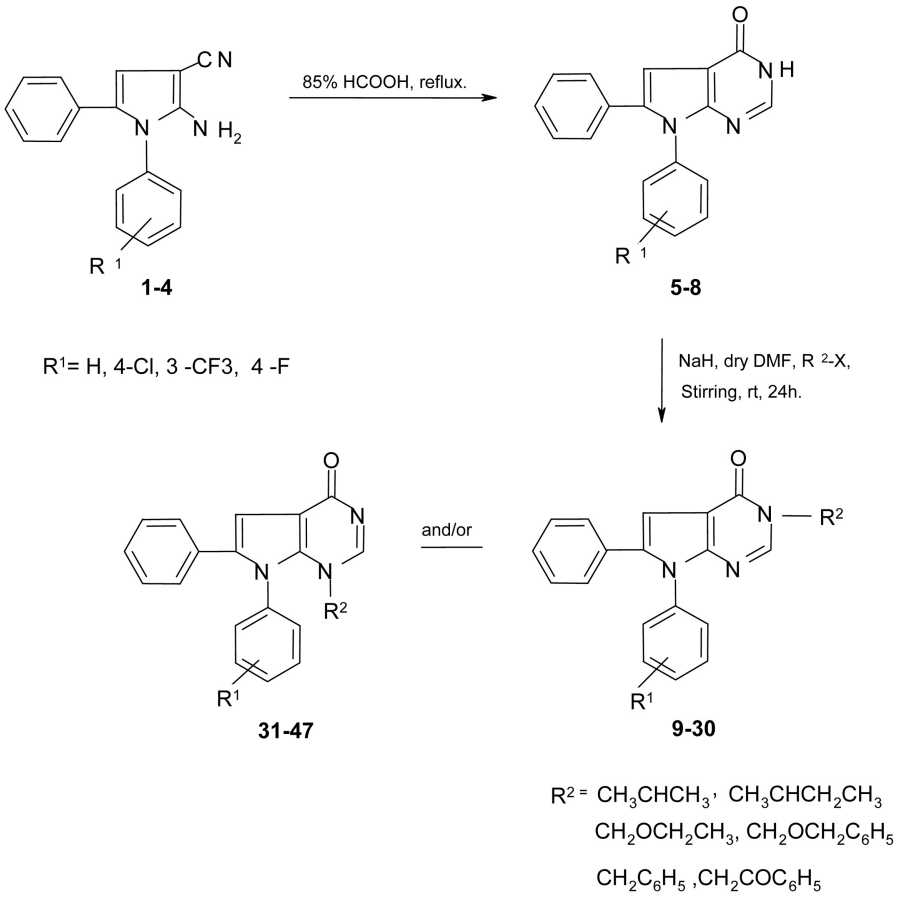

Scheme 1. Synthesis of **7** and 1,3-substituents of new pyrrolo[2,3-*d*]pyrimidin-4-ones.

compounds are **20**, **21**, **38**, **41**, **46**, while compounds **16**, **23**, **43** showed weak anti-HSV-II activity (Table 1).

The different substituents in compounds **9–47** over the side chain at the 1- and 3-positions of pyrrolo[2,3-*d*]pyrimidin-4-one ring exert significant influence on the biological activity. In general, substituted compounds at the 1- and 3-positions (R^1 = H, 3-CF_3) were found to be biologically more active than substituted compounds (R^1 = 4-Cl, 4-F). Thus, the study suggested that this class of compounds could be used as potent antiviral agents to treat various clinical condition associated with viral infection of HSV-II. Furthermore, studies are in progress to optimize these lead compounds and fully characterize their mode of action.

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Experimental

Chemistry

Analytical data were recorded for the compounds described below using the following general procedures. IR spectra were recorded on KBr pellets on a Perkin Elmer 1720, Infrared Fourier Transform Spectrometer (Perkin Elmer, Norwalk, CT, USA). UV spectra were measured with solutions in DMF on Unicam UV/VIS spectrometer (Pye Unicam Ltd. Cambridge, England). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer (Varian, Palo Alto, CA, USA) at 300 MHz for ^{1}H- and 75.5 MHz for ^{13}C-NMR with TMS (tetramethylsilane) as an internal standard. Chemical shifts were recorded in ppm (δ) from an internal TMS standard in deuterochloroform or deuterodimethyl sulphoxide as specified below. EI spectra were recorded on a Finnigan MAT SSQ 710 (Finnigan Mat, San José, CA, USA). All the above analytical data were recorded at the University of Southern Denmark. The progress of the reaction was monitored by TLC analytical silica gel plates. 60 F_{254} Merck silica gel (0.040–0.063 mm) was used for column chromatography (Merck, Darmstadt, Germany). Solvents were of reagent grade and, when necessary, were purified and dried by standards methods. Solvents were removed under reduced pressure. Melt-

Table 1. *In vitro* antiviral activity test of compounds against HSV-II.

Compd.	R^1	R^2	Antiviral activity (MIC[#]) [μM mL^{-1}]
9	H	CH_3CHCH_3	0.19
10	H	$CH_3CHCH_2CH_3$	0.19
11	H	$CH_2OCH_2CH_3$	–
12	H	$CH_2OCH_2C_6H_5$	–
13	H	$CH_2C_6H_5$	0.39
14	H	$CH_2COC_6H_5$	0.19
15	4-Cl	CH_3CHCH_3	0.39
16	4-Cl	$CH_3CHCH_2CH_3$	25.00
17	4-Cl	$CH_2OCH_2CH_3$	–
18	4-Cl	$CH_2OCH_2C_6H_5$	–
19	4-Cl	$CH_2C_6H_5$	–
20	3-CF_3	CH_3CHCH_3	6.30
21	3-CF_3	$CH_3CHCH_2CH_3$	6.30
22	3-CF_3	$CH_2OCH_2C_6H_5$	–
23	3-CF_3	$CH_2C_6H_5$	25.00
24	3-CF_3	$CH_2COC_6H_5$	–
25	4-F	CH_3CHCH_3	0.78
26	4-F	$CH_3CHCH_2CH_3$	0.78
27	4-F	$CH_2OCH_2CH_3$	–
28	4-F	$CH_2OCH_2C_6H_5$	–
29	4-F	$CH_2C_6H_5$	–
30	4-F	$CH_2COC_6H_5$	–
31	H	CH_3CHCH_3	0.19
32	H	$CH_3CHCH_2CH_3$	–
33	H	$CH_2OCH_2C_6H_5$	–
34	H	$CH_2COC_6H_5$	–
35	4-Cl	CH_3CHCH_3	–
36	4-Cl	$CH_3CHCH_2CH_3$	–
37	4-Cl	$CH_2OCH_2CH_3$	–
38	4-Cl	$CH_2OCH_2C_6H_5$	5.00
39	4-Cl	$CH_2COC_6H_5$	–
40	3-CF_3	CH_3CHCH_3	0.78
41	3-CF_3	$CH_3CHCH_2CH_3$	6.30
42	3-CF_3	$CH_2OCH_2CH_3$	0.78
43	3-CF_3	$CH_2OCH_2C_6H_5$	12.50
44	4-F	CH_3CHCH_3	–
45	4-F	$CH_3CHCH_2CH_3$	–
46	4-F	$CH_2OCH_2CH_3$	6.30
47	4-F	$CH_2OCH_2CH_3$	–
ACV			0.4

[#] MIC: minimum inhibitory concentration.

ing points were taken on an electro thermal melting point apparatus and are uncorrected. Elemental analyses data (±0.4%) were performed by Micro lab, Chemistry Department, Copenhagen University, Denmark.

*General procedure for the preparation of Pyrrolo{2,3-d]pyrimidin-4-ones **5-8***

Compounds **1–4** [20, 21] (0.01 mol) were added to formic acid 85% (10 mL). The reaction mixture was refluxed for 10 h, and then poured onto cold water. The solid product was collected by filtration, washed with water several times, dried, and recrystallized from DMF.

6,7-Diphenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one 5

Yield 48%; m.p. 292–293°C; IR (KBr) cm^{-1}: 3108 (NH), 1680 (CO); ^{1}H-NMR (DMSO-d_6) ppm: 6.85–7.92 (m, 11H, $H_{arom.}$ and $H_{pyrrole}$), 8.20 (s, 1H, pyrimidine-2-CH), 10.12 (s, 1H, NH); ^{13}C-NMR ppm: 157.69, 149.35, 144.15, 143.11, 136.78, 134.10, 131.12, 130.31, 128.86, 127.97, 108.40, 102.55; EI MS m/z 287 (M^+) Anal. calcd. for $C_{18}H_{13}N_3O$ (287.32): C, 75.25; H, 4.56; N, 14.62. Found: C, 75.50; H, 4.43; N, 14.67.

*7-(4-Chloro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one **6***

Yield 51%; m.p. 261–262°C; IR (KBr) cm^{-1}: 3090 (NH), 1688 (CO); ^{1}H-NMR (DMSO-d_6) ppm: 6.94–7.51 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 7.82 (s, 1H, pyrimidine-2-CH), 10.09 (s, 1H, NH); ^{13}C-NMR: 158.08, 149.41, 144.43, 143.11, 135.78, 135.42, 132.49, 130.95, 130.03, 128.94, 128.65, 127.64, 108.63, 102.92; EI MS m/z 321 (M^+). Anal. calcd. for $C_{18}H_{12}ClN_3O$ (321.77): C, 67.19; H, 3.76; N, 13.06; Cl, 11.02. Found: C, 66.89; H, 4.06; N, 12.80; Cl, 11.20.

*6-Phenyl-7-(3-trifluoromethyl-phenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one **7***

Yield 55%; m.p. 272-273°C; IR (KBr) cm^{-1}: 3089 (NH), 1677 (CO); ^{1}H-NMR (DMSO-d_6) ppm: 6.98-7.89(m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.31(s, 1H, pyrimidine-2-CH), 10.33 (s, 1H, NH); ^{13}C-NMR: 162.95, 158.00, 149.34, 144.61, 135.65, 135.50, 132.28, 130.74, 130.02, 128.43, 128.36, 128.32, 128.01, 124.91, 124.45, 113.50, 108.66, 103.09; EI MS m/z 355 (M^+). Anal. calcd. for $C_{19}H_{12}F_3N_3O$ (355.32): C, 64.23; H, 3.40; N, 11.83. Found: C, 64.04; H, 3.25; N, 11.93.

*7-(4-Fluoro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one **8***

Yield 61%; m.p. 287–286°C; IR (KBr) cm^{-1}: 3080 (NH), 1682 (CO); ^{1}H-NMR (DMSO-d_6) ppm: 7.03–7.92 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.15 (s, 1H, pyrimidine-2-CH), 10.77 (s, 1H, NH); ^{13}C-NMR: 162.81, 159.55, 158.04, 149.46, 144.28, 135.65, 135.41, 132.19, 130.98, 130.51, 130.21, 128.98, 128.42, 128.26, 126.65, 127.53, 115.81, 115.80, 108.41, 102.54; EI MS m/z 305 (M^+). Anal. calcd. for $C_{18}H_{12}FN_3O$ (305.31): C, 70.81; H, 3.96; N, 13.76. Found: C, 70.63; H, 3.77; N, 13.61.

*General procedure for the preparation of 1,3-Substituent of Pyrrolo[2,3-d]pyrimidin-4-ones **9–47***

Compounds **5–8** (0.006 mol) were suspended in dry DMF (30 mL). To this suspension was added sodium hydride 60%, 0.24 g, 0.006 mol. The mixture was stirred at room temperature for 20 min and then the alkyl halide (0.006 mol) was added. The reaction mixture was refluxed for 5 h. Then the mixture was cooled to room temperature and the solvent was evaporated under vacuum. The residue was dissolved in (200 mL) dichloromethane and the organic phase was washed with water (2 × 50 mL). Then organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography on a silica gel column and the product was eluted with $C_2H_5COOCH_3$/$CHCl_3$ (1:4).

*3-Isopropyl-6,7-diphenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one **9***

Yield 34%; m.p. 195–196°C; IR (KBr) cm^{-1}: 1678 (CO); UV max 306 nm (ε 31392); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.46,1.48 (d, 6H, $2CH_3$),

5.32–5.42 (m, 1H, CH), 6.95-7.42 (m, 11H, $H_{arom.}$ and $H_{pyrrole}$), 7.91 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 157.86, 148.58, 142.42, 136.89, 135.99, 131.37, 128.95, 128.40, 128.16, 127.91, 127.88, 127.41, 108.38, 103.20, 45.01, 22.43; EI MS m/z 329 (M^+). Anal. calcd. for $C_{21}H_{19}N_3O$ (329.41): C, 76.57; H, 5.81; N, 12.76. Found: C, 76.51; H, 5.78; N, 12.65.

3-sec-Butyl-6,7-diphenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***10***

Yield 33%; m.p. 156–157°C; IR (KBr) cm^{-1}: 1685 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.12–1.15 (t, 3H, CH_3), 1.38, 1.40 (d, 3H, CH_3), 1.81–1.86 (m, 2H, CH_2), 5.49–5.53 (q, 1H, CH), 6.81–7.44 (m, 11H, $H_{arom.}$ and $H_{pyrrole}$), 8.30 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 159.62, 151.63, 138.74, 136.31, 131.54, 129.10, 128.72, 128.22, 127.97, 127.55, 127.20, 108.23, 104.71, 73.33, 29.09, 19.41, 9.77; EI MS m/z 343 (M^+). Anal. calcd. for $C_{22}H_{21}N_3O$ (343.42): C, 76.94; H, 6.16; N, 12.24. Found: C, 76.88; H, 6.19; N, 12.19.

3-Ethoxymethyl-6,7-diphenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***11***

Yield 63%; m.p. 157–158°C; IR (KBr) cm^{-1}: 1680 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.20–1.22 (t, 3H, CH_3), 3.63–3.65 (q, 2H, CH_2), 5.50 (s, 2H, CH_2),7.00–7.75 (m, 11H, $H_{arom.}$ and $H_{pyrrole}$), 8.10 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.62, 149.21, 145.47, 137.37, 136.05, 131.43, 129.22, 128.67, 128.40, 128.29, 128.17, 127.76, 108.51, 103.64, 74.55, 65.25, 15.07.EI MS m/z 345 (M^+). Anal. calcd. for $C_{21}H_{19}N_3O_2$ (345.40): C, 73.03; H, 5.54; N, 12.17. Found: C, 73.13; H, 5.50; N, 12.12.

3-Benzyloxymethyl-6,7-diphenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***12***

Yield 33%; m.p. 144–145°C; IR (KBr) cm^{-1}: 1688 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.52 (s, 2H, CH_2), 5.51 (s, 2H, CH_2), 6.91-7.50 (m, 16H, $H_{arom.}$ and $H_{pyrrole}$), 8.00 (s,1H, pyrimidine-2-CH); ^{13}C-NMR: 158.50, 148.50, 145.43, 137.30, 136.93, 131.27, 129.09, 128.54, 128.43, 128.29, 128.19, 128.04, 127.95, 127.88, 127.65, 108.38, 103.53, 74.03, 71.44. EI MS m/z 407 (M^+). Anal. calcd. for $C_{26}H_{21}N_3O_2$ (407.48): C, 76.64; H, 5.19; N, 10.31. Found: C, 76.58; H, 5.04; N, 10.19.

3-Benzyl-6,7-diphenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***13***

Yield 69%; m.p. 208–209°C; IR (KBr) cm^{-1}: 1680; ^{1}H-NMR ($CDCl_3$-d_6) ppm: 5.52 (s, 2H, CH_2), 7.00–7.51 (m, 16H, $H_{arom.}$ and $H_{pyrrole}$), 7.97 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.88,148.78, 145.32, 137.17, 136.37, 136.00, 131.38, 129.05, 128.88, 128.54, 128.27, 128.05, 128.02 127.98, 127.59, 108.78,103.37, 49.11. EI MS m/z 377 (M^+). Anal. calcd. for $C_{25}H_{19}N_3O$ (377.45): C, 79.55; H, 5.07; N, 11.13. Found: C, 79.39; H, 4.94; N, 10.97.

3-(2-Oxo-2-phenyl-ethyl)-6,7-diphenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***14***

Yield 43%; m.p. 282–283°C; IR (KBr) cm^{-1}: 1683,1677 (2 CO); ^{1}H-NMR (DMSO-d_6) ppm: 5.81 (s, 2H, CH_2), 7.13–7.82 (m, 16H, $H_{arom.}$ and $H_{pyrrole}$), 8.11 (s,1H, pyrimidine-2-CH); ^{13}C-NMR: 160.23, 153.41, 148.13, 147.51, 136.52, 136.41, 134.01, 134.00, 132.21, 130.46, 130.11, 128.31, 128.21, 128.00, 127.61, 125.04, 125.01, 124.23, 107.44, 120.06, 49.15. EI MS m/z 405 (M^+). Anal. calcd. for $C_{26}H_{19}N_3O_2$ (405.46): C, 77.02; H, 4.72; N; 10.36. Found: C, 76.89; H, 4.63; N, 10.33.

7-(4-Chloro-phenyl)-3-isopropyl-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***15***

Yield 38%; m.p. 233–134°C; IR (KBr) cm^{-1}: 1685 (CO); UV max 308 nm (ε 27106); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.45, 1.64 (d, 6H, $2CH_3$), 5.22–5.50 (m, 1H, CH), 6.95–7.48 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 7.97 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 157.92, 142.65, 136.84, 134.61, 133.85, 131.18, 129.33,129.21, 129.08, 128.58, 128.46, 128.37, 127.76, 108.67, 103.65, 45.23, 22.55. EI MS m/z 363 (M^+). Anal. calcd. for $C_{21}H_{18}ClN_3O$ (363.85): C, 69.32; H, 4.99; N, 11.55. Found: C, 69.26; H, 4.88; N, 11.44.

3-sec-Butyl-7-(4-chloro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***16***

Yield 33%; m.p. 199–200°C; IR (KBr) cm^{-1}: 1687 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.10–1.14 (t, 3H, CH_3), 1.40,1.44 (d, 3H, CH_3), 1.81–1.85 (m, 2H, CH_2), 5.25–5.48 (q, 1H, CH), 6.92–7.43 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 7.96 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.36, 143.10, 136.89, 134.71, 133.92, 131.30, 129.38, 129.32, 128.68, 128.56, 127.85, 108.72, 103.83, 50.78, 29.63, 20.84, 10.77. Anal. calcd. for $C_{22}H_{20}ClN_3O$ (377.88): C, 69.93; H, 5.33; N, 11.12. Found: C, 69.71; H, 5.36; N, 10.96.

7-(4-Chloro-phenyl)-3-ethoxymethyl-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***17***

Yield 29%; m.p. 125–126°C; IR (KBr) cm^{-1}: 1684 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.21–1.29 (t, 3H, CH_3), 3.60–3.65 (q, 2H, CH_2), 4.92 (s, 2H, CH_2), 6.97–7.48 (m, 10H, $H_{arom.}$ and Hpyrrole), 8.00 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.25, 150.02, 146.28, 134.07, 129.31, 129.21, 128.58, 128.23, 127.89, 101.01, 98.91, 72.28, 65.15, 14.23. EI MS m/z 379 (M^+). Anal. calcd. for $C_{21}H_{18}ClN_3O_2$(379.85): C, 66.40; H, 4.78; N, 11.06. Found: C, 66.23; H, 4.80; N, 10.89.

3-Benzyloxymethyl-7-(4-chloro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***18***

Yield 33%; m.p. 170–171°C; IR (KBr) cm^{-1}: 1683 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.70 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 6.90-7.41 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.11 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.36, 148.42, 145.54, 137.06, 136.85, 134.34, 133.99, 130.92, 129.28, 129.18, 128.55, 128.43, 128.41, 127.94, 127.84, 108.52, 103.81, 74.04, 71.45. EI MS m/z 441 (M^+). Anal. calcd. for $C_{26}H_{20}ClN_3O_2$ (411.89): C, 70.67; H, 4.56; N, 9.51. Found: C, 70.49; H, 4.53; N, 9.42.

3-Benzyl-7-(4-chloro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***19***

Yield 63%; m.p. 224–225°C; IR (KBr) cm^{-1}: 1679 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 5.11 (s, 2H, CH_2), 6.75–7.48 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.25 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: C, 157.13, 148.80, 147.10, 137.29, 136.14, 134.61, 132.55, 130.76, 130.00, 128.94, 128.48, 128.22, 128.02, 127.72, 127.47, 127.44, 106.86, 102.91, 48.25. EI MS m/z 411 (M^+). Anal. calcd. for $C_{25}H_{18}ClN_3O$ (411.89): C, 72.90; H, 4.40; N, 10.20. Found: C, 72.79; H, 4.21; N, 9.98.

3-Isopropyl-6-phenyl-7-(3-trifluoromethyl-phenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***20***

Yield 37%; m.p. 150–151°C; IR (KBr) cm^{-1}: 1688 (CO); UV max 309 nm (ε 19870); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.47, 1.51 (d, 6H, $2CH_3$), 5.42–5.48 (m, 1H, CH), 6.90–7.70 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.01 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.21, 151.54, 142.80, 136.78, 136.58, 131.21, 130.98, 129.52, 128.86, 128.64, 128.48, 127.89, 125.04, 124.99, 124.94, 124.51, 124.46, 103.96, 45.26, 22.54. EI MS m/z 397 (M^+). Anal. calcd. for $C_{22}H_{18}F_3N_3O$ (397.40): C, 66.49; H, 4.57; N, 10.57. Found: C, 66.35; H, 4.51; N, 10.41.

3-sec-Butyl-6-phenyl-7-(3-trifuloromethyl-phenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***21***

Yield 53%; m.p. 138–139°C; IR (KBr) cm^{-1}: 1689 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.01–1.23 (t, 3H, CH_3), 1.48, 1.54 (d, 3H, CH_3), 1.80–1.90 (m, 2H, CH_2), 5.15–5.28 (q, 1H, CH), 7.00–7.68 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 7.92 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.26, 147.40, 143.15, 136.76, 136.58, 131.21, 130.99, 129.53, 128.66, 128.49, 127.90, 125.05, 125.00, 124.55, 124.51, 124.46, 50.74, 29.55, 20.75, 10.67. EI MS m/z 411 (M^+). Anal. calcd. for $C_{23}H_{20}F_3N_3O$ (395.44): C, 67.15; H, 4.90; N, 10.21. Found: C, 66.89; H, 4.87; N, 10.14.

3-Benzyloxymethyl-6-phenyl-7-(3-trifluoromethyl-phenyl)-3,7-dihydro- pyrrolo[2,3-d] pyrimidin-4-one ***22***

Yield 40%; m.p. 119–120°C; IR (KBr) cm^{-1}: 1681 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.70 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 7.00–7.75 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.10 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.40, 145.71, 137.10, 136.88, 136.38, 131.26, 130.77, 129.58, 128.69, 128.51, 128.46, 128.25, 127.89, 125.11, 125.06, 125.01, 124.78, 124.73, 124.68, 74.13, 71.55. EI MS m/z 475 (M^+). Anal. calcd. for $C_{27}H_{20}F_3N_3O_2$ (475.47): C,68.21; H, 4.24; N, 8.84. Found: C, 67.94; H, 4.25; N, 8.76.

3-Benzyl-6-phenyl-7-(3-trifluoromethyl-phenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***23***

Yield 70%; m.p. 171–172°C; IR (KBr) cm^{-1}: 1685 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 5.38 (s, 2H, CH_2), 7.00–7.65 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 7.98 (s,1 H, pyrimidine-2-CH); ^{13}C-NMR: C, 158.17, 148.21, 145.61, 136.95, 136.49, 136.27, 131.22, 130.88, 129.52, 128.94, 128.68, 128.50, 128.15, 128.01, 125.05, 125.00, 124.57, 124.52, 49.17. EI MS m/z 445 (M^+). Anal. calcd. for $C_{26}H_{18}F_3N_3O$ (445.45): C, 70.11; H, 4.07; N, 9.43. Found: C, 69.89; H, 3.94; N, 9.52.

1-(2-Oxo-2-phenyl-ethyl)-6-phenyl-7-(3-trifluoro-phenyl)-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***24***

Yield 64%; m.p. 202–203°C; IR (KBr) cm^{-1}: 1686, 1677 (2 CO); ^{1}H-NMR (DMSO-d_6) ppm: 5.72 (s, 2H, CH_2), 6.90–7.82 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.23 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.94, 157.13, 148.75, 147.70, 136.40, 136.19, 134.31, 134.09, 132.35, 130.65, 130.22, 128.69, 128.52, 128.40, 128.00, 127.82, 125.06 , 125.01, 124.69, 107.76, 103.11, 51.74. EI MS m/z 473 (M^+). Anal. calcd. for $C_{27}H_{18}F_3N_3O_2$ (473.46): C, 68.50; H, 3.83; N, 8.88. Found: C, 68.33; H, 3.39; N, 8.73.

7-(4-Fluoro-phenyl)-3-isopropyl-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***25***

Yield 40%; m.p. 196–197°C; IR (KBr) cm^{-1}: 1687 (CO); UV max 308 nm (ε 40922); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.49, 1.51 (d, 6H, $2CH_3$), 5.40–5.47 (m, 1H, CH), 6.97–7.41 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 7.97 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.63, 160.12, 158.03, 142.73, 137.10, 131.37, 129.85, 129.74, 128.67, 128.49, 127.80, 116.36, 116.06, 103.49, 45.30, 22.05. EI MS m/z 347 (M^+). Anal. calcd. for $C_{21}H_{18}FN_3O$ (347.40): C, 72.61; H, 5.22; N, 12.10. Found: C, 72.52; H, 5.13; N, 12.07.

3-sec-Butyl-7-(4-fluoro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]yrimidin-4-one ***26***

Yield 35%; m.p. 186–187°C; IR (KBr) cm^{-1}: 1681 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.01–1.21 (t, 3H, CH_3), 1.44, 1.50 (d, 3H, CH_3), 1.61–1.81 (m, 2H, CH_2), 5.18–5.48 (q, 1H, CH), 6.98–7.47 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 7.91 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.49, 160.20, 158.25, 149.21, 142.92, 136.92, 131.24, 129.72, 129.60, 128.54, 128.36, 127.65, 116.22, 115.91, 108.44, 103.42, 50.60, 29.51, 20.71, 10.64. EI MS m/z 361 (M^+). Anal. calcd. for $C_{22}H_{20}FN_3O$ (361.42): C, 73.11; H, 5.58; N, 11.63. Found: C, 73.01; H, 5.53; N, 11.41.

3-Ethoxymethyl-7-(4-fluoro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-0ne ***27***

Yield 50%; m.p. 179–180°C; IR (KBr) cm^{-1}: 1682 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.18–1.25 (t, 3H, CH_3), 3.61–3.66 (q, 2H, CH_2), 5.51 (s, 2H, CH_2), 6.98–7.32 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.10 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.61, 160.31, 158.41, 148.65, 145.44, 137.21,131.89, 131.08, 129.77, 129.66, 128.58, 128.40, 127.80, 116.29, 115.99, 108.42, 103.58, 74.46, 65.18, 14.94. EI MS m/z 363 (M^+). Anal. calcd. for $C_{21}H_{18}FN_3O_2$ (363.39): C,69.41; H, 4.99; N, 11.56. Found: C, 69.27; H, 4.94; N, 11.47.

3-Benzyloxymethyl-7-(4-fluoro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***28***

Yield 51%; m.p. 152–153°C; IR (KBr) cm^{-1}: 1685 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.73 (s, 2H, CH_2), 5.62 (s, 2H, CH_2), 6.98–7.40 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.00 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.50, 160.30, 158.42, 148.32, 145.53, 137.26, 136.89, 131.04, 129.76, 129.65, 128.88, 128.58, 128.43, 128.40, 127.96, 127.87, 127.81, 124.51, 116.28, 115.98, 74.05, 71.47. EI MS m/z 425 (M^+). Anal. calcd. for $C_{26}H_{20}FN_3O_2$ (425.47): C, 73.40; H, 4.74; N, 9.88. Found: C, 73.21; H, 4.63; N, 9.66.

3-Benzyl-7-(4-fluoro-phenyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***29***

Yield 66%; m.p. 210–211°C; IR (KBr) cm^{-1}: 1689 (CO); UV max 311 nm (ε 31408); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 5.33 (s, 2H, CH_2), 6.98-7.43 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 7.92 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: C, 163.67, 160.37, 158.32, 145.54, 137.27, 136.44, 132.13, 131.28, 129.86, 129.75, 129.03, 128.71, 128.52, 128.43, 128.22, 128.11, 127.89, 116.37, 116.06, 108.93, 103.56, 49,27. EI MS m/z 395 (M^+). Anal. calcd. for $C_{25}H_{18}FN_3O$ (395.44): C, 75.94; H, 4.59; N, 10.63. Found: C, 75.79; H, 4.52; N, 10.49.

7-(4-Fluoro-phenyl)-3-(2-oxo-2-phenyl-ethyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***30***

Yield 58%; m.p. 280–281°C; IR (KBr) cm^{-1}: 1686, 1679 (2 CO); ^{1}H-NMR (DMSO-d_6) ppm: 5.96 (s, 2H, CH_2), 6.70-7.88 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.34 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.98, 162.45, 160.62, 158.12, 145.32, 137.01, 136.65, 132.13, 131.22, 129.56, 129.32, 129.01, 126.55, 128.32, 128.12, 128.01, 127.87,

116.23, 115.89, 108.92, 103.56, 49.12. EI MS m/z 423 (M^+). Anal calcd. for $C_{26}H_{18}FN_3O_2$ (423.45): C, 73.75; H, 4.28; N, 9.92. Found: C, 73.51; H, 4.18; N, 9.78.

1-Isopropyl-6,7-diphenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***31***

Yield 40%; m.p. 199–200°C; IR (KBr) cm^{-1}: 1683 (CO); UV max 304 nm (ε 29992); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.46–1.48 (d, 6H, 2 CH_3), 5.42-5.52 (m, 1H, CH), 6.56–7.50 (m, 11H, $H_{arom.}$ and $H_{pyrrole}$), 8.30 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.50, 151.74, 138.95, 136.47, 131.70, 129.21, 128.89, 128.37, 128.10, 127.90, 127.86, 106.41, 99.63, 59.28, 22.23; EI MS m/z 329 (M^+). Anal. calcd. for $C_{21}H_{19}N_3O$ (329.39): C, 76.57; H, 5.81; N, 12.76. Found: C, 76, 54; H, 5.76; N, 12.72.

1-sec-Butyl-6,7-diphenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***32***

Yield 33%; m.p. 145–146°C; IR (KBr) cm^{-1}: 1687 (CO); ^{1}H-NMR; ($CDCl_3$-d_6) ppm: 1.11–1.13 (t, 3H, CH_3), 1.37, 1.40 (d, 3H, CH_3), 1.83–1.87 (m, 2H, CH_2), 5.47–5.52 (q, 1H, CH), 6.85–7.51 (m, 11H, $H_{arom.}$ and $H_{pyrrole}$), 8.30 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.68, 151.63,138.79,136.35, 131.58, 129.08, 128.76, 128.24, 127.97, 127.77, 127.17, 106.27, 99.52, 73.77, 29.09, 19.56, 9.79; EI MS m/z 343 (M^+). Anal. calcd. for $C_{22}H_{21}N_3O$ (343.42): C, 76.94; H, 6.16; N, 12.24. Found: C, 76.81; H, 6.18; N, 12.14.

1-Benzyloxymethyl-6,7-diphenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***33***

Yield 41%; m.p. 171–172°C; IR (KBr) cm^{-1}: 1689 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.51 (s, 2H, CH_2), 5.51 (s, 2H, CH_2), 6.50-7.20 (m, 16H, $H_{arom.}$ and $H_{pyrrole}$), 8.11 (s,1H, pyrimidine-2-CH); ^{13}C-NMR: 161.51, 154.41, 151.36, 139.56, 137.17, 136.16, 131.38, 129.14, 128.84, 128.43, 128.40, 127.96, 127.87, 127.86, 106.06, 99.23, 89.95, 71.52. EI MS m/z 407 (M^+). Anal. calcd. for $C_{26}H_{21}N_3O_2$ (407.46): C, 76.64; H, 5.19; N, 10.31. Found: C, 76.51; H, 5.04; N, 10.25.

1-(2-Oxo-2-phenyl-ethyl)-6,7-diphenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***34***

Yield 37%; m.p. 290–291°C; IR (KBr) cm^{-1}: 1681,1679 (2 CO); ^{1}H-NMR (DMSO-d_6) ppm: 5.62 (s, 2H, CH_2), 7.08-7.89 (m, 16H, $H_{arom.}$ and $H_{pyrrole}$), 8.07 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.66, 157.41, 148.66, 147.53, 136.44, 136.23, 134.33, 134.26, 132.33, 130.46, 130.21, 128.94, 128.49, 128.38, 128.11, 127.82, 125.06, 125.03, 124.69, 107.68, 103.01, 51.69. EI MS m/z 405 (M^+). Anal. calcd. for $C_{26}H_{19}N_3O_2$ (405.46): C,77.02; H, 4.72; N, 10.36. Found: C, 76.99; H, 4.69; N, 10.13.

7-(4-Chloro-phenyl)-1-isopropyl-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***35***

Yield 37%; m.p. 189–190°C; IR (KBr) cm^{-1}: 1683 (CO); UV max 301 nm (ε 31436); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.86, 1.91 (d, 6H, 2CH_3), 5.50–5.65 (m, 1H, CH), 6.82–7.45 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.49 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.43, 151.70, 138.56, 134.84, 133.51, 131.25, 129.29, 129.12, 128.79, 128.43, 128.00, 106.37, 99.91, 69.29, 22.28. EI MS m/z 363 (M^+). Anal. calcd. for $C_{21}H_{18}ClN_3O$ (363.85): C, 69.32; H, 4.99; N, 11.55. Found: C, 69.23; H, 4.78; N, 11.39.

1-sec-Butyl-7-(4-chloro-phenyl)-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***36***

Yield 42%; m.p. 136–137°C; IR (KBr) cm^{-1}: 1689 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.10–1.14 (t, 3H, CH_3), 1.42, 1.48 (d, 3H, CH_3), 1.83–1.87 (m, 2H, CH_2), 5.50–5.56 (q, 1H, CH), 6.71–7.48 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.50 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.74, 154.27, 151.72, 138.54, 134.85, 133.50, 131.27, 129.29, 129.11, 128.79, 128.43, 127.99, 106.36, 99.91, 73.90, 29.06, 19.53, 9.77. EI MS m/z 377 (M^+). Anal. calcd. for $C_{22}H_{20}ClN_3O$ (377.88): C, 69.93; H, 5.33; N, 11.12. Found: C, 69.79; H, 5.28; N, 10.99.

7-(4-Chloro-phenyl)-1-ethoxymethyl-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***37***

Yield 33%; m.p. 182–183°C; IR (KBr) cm^{-1}: 1686 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.21–1.27 (t, 3H, CH_3), 3.60–3.65 (q, 2H, CH_2), 5.46 (s, 2H, CH_2), 6.88–7.41 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 7.95 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.37, 148.78, 145.47, 137.03, 134.40, 134.01, 130.98, 129.83, 129.12, 128.58, 128.45, 127.85, 108.55, 103.84, 74.46, 65.19, 14.49. EI MS m/z 379 (M^+). Anal. calcd. for $C_{21}H_{18}ClN_3O_2$ (379.85): C, 66.40; H, 4.78; N, 11.06. Found: C, 66.19; H, 4.63; N, 10.96.

1-benzyloxymethyl-7-(4-chloro-phenyl)-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***38***

Yield 49%; m.p. 120–121°C; IR (KBr) cm^{-1}: 1685 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.86 (s, 2H, CH_2), 5.88 (s, 2H, CH_2), 6.81–7.48 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.31 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 161.60, 154.34, 139.32, 137.13, 134.67, 133.69, 131.07, 129.36, 129.12, 128.87, 128.51, 128.41, 128.23, 127.96, 127.89, 106.17, 99.62, 90.01, 71.58. EI MS m/z 441 (M^+). Anal. calcd. for $C_{26}H_{20}ClN_3O_2$ (411.89): C, 70.67; H, 4.56; N, 9.51. Found: C, 70.49; H, 4.53; N, 9.42.

7-(4-chloro-phenyl)-3-(2-oxo-2-phenyl-ethyl)-6-phenyl-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***39***

Yield 56%; m.p. 277–278°C; IR (KBr) cm^{-1}: 1676 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 5.82 (s, 2H, CH_2), 6.88–7.49 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.11 (s, 1H, pyrimidine-2-CH); EI MS m/z 439 (M^+). Anal. calcd. for $C_{28}H_{18}ClN_3O_2$ (439.91): C, 70.99; H, 4.12; N, 9.55. Found: C, 70.79; H, 3.98; N, 9.32.

1-Isopropyl-6-phenyl-7-(3-trifluoromethyl-phenyl)-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***40***

Yield 41%; m.p. 125–126°C; IR (KBr) cm^{-1}: 1684 (CO); UV max 305 nm (ε 27063); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.47, 1.51 (d, 6H, 2CH_3), 5.48–5.67 (m, 1H, CH), 6.80–7.70 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.50 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.50, 151.84, 138.55, 136.84, 131.15, 131.07, 129.57, 124.31, 124.26, 124.22, 124.17, 106.46, 100.29, 69.38, 22.09. EI MS m/z 397 (M^+). Anal. calcd. for $C_{22}H_{18}F_3N_3O$ (397.40): C, 66.49; H, 4.57; N, 10.57. Found: C, 66.31; H, 4.63; N, 10.29.

1-sec-Butyl-6-phenyl-7-(3-trifuloromethyl-phenyl)-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***41***

Yield 42%; m.p. 105–106°C; IR (KBr) cm^{-1}: 1683 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.01–1.21 (t, 3H, CH_3), 1.45 & 1.51 (d, 3H, CH_3), 1.80–1.90 (m, 2H, CH_2), 5.15–5.45 (q, 1H,CH), 7.80–7.59 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.38 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 162.83, 153.91, 151.86, 138.54, 136.86, 131.16, 131.09, 129.59, 128.88,

128.48, 128.16, 125.03, 124.98, 124.93, 124.27, 124.22, 124.17, 74.01, 29.08, 19.54, 9.78. EI MS m/z 411 (M^+). Anal. calcd. for $C_{23}H_{20}F_3N_3O$ (395.44): C, 67.14; H, 4.90; N, 10.21. Found: C, 67.10; H, 4.85; N, 10.13.

3-Ethoxymethyl-6-phenyl-7-(3-trifluoromethyl-phenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***42***

Yield 67%; m.p. 164–165°C; IR (KBr) cm^{-1}: 1680 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.49-1.55 (t, 3H, CH_3), 3.51–3.56 (q, 2H, CH_2), 5.51 (s, 2H, CH_2), 7.00–7.54 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.10 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 158.36, 145.61, 131.25, 130.79, 129.56, 128.67, 128.49, 128.01, 125.09, 125.03, 124.98, 124.68, 124.63, 124.58, 108.67, 104.14, 74.50, 62.21, 14.94. EI MS m/z 413 (M^+). Anal. calcd. for $C_{22}H_{18}F_3N_3O_2$ (413.40): C, 63.92; H, 4.39; N, 10.16. Found: C, 63.74; H, 4.31; N, 10.11.

1-Benzyloxymethyl-6-phenyl-7-(3-trifluoromethyl-phenyl)-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***43***

Yield 35%; m.p. 68–69°C; IR (KBr) cm^{-1}: 1682 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.85 (s, 2H, CH_2), 5.82 (s, 2H, CH_2), 6.90–7.70 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.42 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 161.77, 151.71, 139.40, 137.24, 136.76, 131.24, 130.97, 129.73, 129.05, 128.65, 128.53, 128.48, 128.08, 128.01, 125.07, 125.02, 124.51, 124.47, 106.34, 100.10, 90.17, 71.72. EI MS m/z 475 (M^+). Anal. calcd. for $C_{27}H_{20}F_3N_3O_2$ (475.47): C, 68.21; H, 4.24; N, 8.84. Found: C, 67.98; H, 4.28; N, 8.75.

7-(4-Fluoro-phenyl)-1-isopropyl-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***44***

Yield 34%; m.p. 177–178°C; IR (KBr) cm^{-1}: 1686 (CO); UV max 302 nm (ε 40479); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.41, 1.46 (d, 6H, $2CH_3$), 5.42–5.49 (m,1H, CH), 6.58–7.38 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.33 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.38, 162.42, 160.12, 154.01, 151.67, 138.76, 131.34, 129.67, 129.56, 128.80, 128.37, 127.94, 116.26, 115.96, 106.28, 99.60, 69.26, 22.09. EI MS m/z 347 (M^+). Anal. calcd. for $C_{21}H_{18}FN_3O$ (347.40): C, 72.61; H, 5.22; N, 12.10. Found: C, 72.46; H, 5.19; N, 11.99.

1-sec-Butyl-7-(4-fluoro-phenyl)-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***45***

Yield 36%; m.p. 146–147°C; IR (KBr) cm^{-1}: 1683 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.05–1.27 (t, 3H,CH_3), 1.47 & 1.50 (d, 3H, CH_3), 1.63–1.83 (m, 2H, CH_2), 5.53–5.59 (q, 1H, CH), 6.73–7.43 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.38 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.38, 162.72, 160.09, 153.63, 151.69, 138.73, 132.32, 131.36, 129.66, 129.55, 128.80, 128.37, 127.93, 116.26, 115.95, 106.26, 99.60, 73.88, 29.08, 19.54, 9.78. EI MS m/z 361 (M^+). Anal. calcd. for $C_{22}H_{20}FN_3O$ (361.42): C, 73.11; H, 5.58; N, 11.63. Found: C, 72.98, H, 5.56; N, 11.49.

1-Ethoxymethyl-7-(4-fluoro-phenyl)-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***46***

Yield 33%; m.p. 127–128°C; IR (KBr) cm^{-1}: 1680 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 1.39–1.44 (t, 3H, CH_3), 3.90–3.96 (q, 2H, CH_2), 5.97 (s, 2H, CH_2), 6.81–7.43 (m, 10H, $H_{arom.}$ and $H_{pyrrole}$), 8.39 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.43, 161.66, 160.14, 151.48, 139.41, 132.13, 131.15, 129.71, 129.33, 128.93, 128.85, 128.42, 128.12, 125.02, 116.29, 115.99, 106.02, 99.30, 90.95, 65.89, 15.19. EI MS m/z 363 (M^+). Anal. calcd. for $C_{21}H_{18}FN_3O_2$ (363.39): C, 69.41; H, 4.99; N, 11.56. Found: C, 69.33; H, 4.94; N, 11.44.

1-Benzyloxymethyl-7-(4-fluoro-phenyl)-6-phenyl-1,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one ***47***

Yield 42%; m.p. 143–144°C; IR (KBr) cm^{-1}: 1684 (CO); ^{1}H-NMR ($CDCl_3$-d_6) ppm: 4.84 (s, 2H, CH_2), 5.95 (s, 2H, CH_2), 6.80–7.93 (m, 15H, $H_{arom.}$ and $H_{pyrrole}$), 8.00 (s, 1H, pyrimidine-2-CH); ^{13}C-NMR: 163.47, 161.59, 160.19, 156.13, 151.44, 139.52, 137.16, 131.16, 129.69, 129.58, 128.89, 128.62, 128.46, 128.42, 128.18, 127.98, 127.89, 116.33, 116.03, 106.08, 99.32, 90.00, 71.56. EI MS m/z 425 (M^+). Anal. calcd. for $C_{26}H_{20}FN_3O_2$ (425.47): C, 73.40; H, 4.74; N, 9.88. Found: C, 73.27; H, 4.60; N, 9.69.

Pharmacology

Cells and virus

Herpes simplex Virus type-Π (HSV-II) was kindly supplied by The National Research Center, Dokki, Egypt. The virus was propagated in Vero cells, which were commercially obtained from The Egyptian Organization of Serum and Vaccines. Minimal essential medium (MEM) was used as growth and maintenance medium for tissue culture with 10% or 2% fetal calf serum (FCS), respectively.

Titration of HSV-Π by plaque assay [22]

Cell suspension (3 mL) with the concentration 10^5 cells/mL GM was dispensed into each of the wells of 6-well plates (Falcon). Plates were incubated at 37 °C in a 0.5% CO_2 for 24–48 hrs to obtain a confluent sheet. Ten-fold dilution of the virus stock (10^{-1}–10^{-7}) was done as mentioned under titration of HSV by $TCID_{50}$ endpoint. Then growth medium was aspirated from the wells and 0.2 mL/well of each virus dilution was added in duplicate manner. For each plate, two wells were left uninoculated as cell control, each contained 0.2 mL MEM only; incubation at 37 °C in a 0.5% CO_2 incubator for one hour, to permit virus adsorption. Then 30 mL 1% agarose solution was melted at 48 °C in a water bath, and mixed with 2 × 30 mL MEM (supplied with 1% antibiotic solution and 2% FCS) in a ratio of 1:1 to prepare an overlay mixture. Then 3 mL of overlay mixture was added quickly to each well in the plate. After overlay solidification, plates were inverted and incubated at 37°C in a 0.5% CO_2 incubator. Daily observation was carried out for early plaque detection; usually it takes 2–3 days for plaque detection. After plaques development, cells were fixed by flooding with 10% formalin solution for 1 h at room temperature. Agarose overlay was removed with forceps; cell monolayers were washed under tap water and stained with 10% crystal violet solution for 10 min. Plaques were recorded as clear unstained areas against a violet background of stained viable cells and counted either visually or using a stereomicroscope. The infectivity titer represented as number of plaque forming unit/mL (PFU/mL) of the stock virus suspension. It was calculated form the following equation:

PFU/mL = No. of plaques × reciprocal of dilution × reciprocal of volume in mL.

Determination of the solvent cytotoxicity

Growth medium was decanted from 96 well micro titer plate after a confluent sheet of cells was formed. Ten-fold serial dilutions of pyrrolo[2,3-*d*]pyrimidin-4-one derivatives were made in MEM medium without FCS, starting from 5000 μm/mL till 10^{10}

dilution. 0.2 mL of each dilution was tested in 3 different wells leaving two wells/row as control, receiving only maintenance medium. The plate was incubated in a CO_2 incubator at 37°C and examined for up to 3 days. Cells were checked for any physical signs of toxicity, partial or complete loss of the monolayers, shrinkage, or cell granulation. Then, the non-toxic concentration of each substance was used in this study.

HSV-Π yield reduction assay [22]

Vero cells were seeded into 96-well tissue culture plates at a concentration of 10,000 cells in 0.2 mL of minimal essential medium with Earle salts, MEM(E), supplemented with 10% FCS, and incubated at 37°C in a humidified 3% CO_2 – 97% air atmosphere. After 24 h, plates were inverted over a waste vessel, medium was shaken out, and the plates were allowed to drain for 5 to 10 s on a sterile paper towel. Cultures were incubated with HSV-Π at a multiplicity of infection (MOI) of 5 PFU/cell in 0.2 mL of MEM (E) supplemented with 5% FCS, 100 U penicillin/mL, and 100 μg streptomycin sulfate/mL. Cultures were incubated at 37°C for 2 h to permit virus adsorption. Virus inoculum was replaced with 0.2 mL of fresh medium and test compounds were added to the cultures.

The first row of 12 wells was left undisturbed and served as virus controls. Each well in the second row received an additional 0.1 mL of MEM (E) containing 5% FCS, antibiotics, and test compound at three times the desired final concentration. The contents of the 12 wells were mixed by repeated pipetting and then serially diluted 1:3 down the plate by repeated transfer and mixing of 0.1 mL of drug-containing medium. In this manner, six compounds could be tested in duplicate on a single plate with a concentrations range of nearly 1000-fold between the highest and the lowest dilutions (0.10 μM to 80 μM minuscule example). Plates were incubated at 37°C over night and then subjected to one cycle of freezing at −76°C and thawing at 37°C to disrupt the cells. Aliquots of 0.1 mL from each of the eight wells of a given row were transferred to the row of a fresh 96-well monolayers culture of Vero cells. Contents were mixed and serially diluted 1:3 across the remaining 11 rows of the second plate. Each row of the original primary plate was diluted across a separate plate in this manner. Cultures was incubated at 37°C for 2 h to permit virus adsorption and then the virus inoculum was replaced with 0.2 mL of fresh medium. Cultures were incubated for 2 days, medium was removed, and the cell sheets were stained with 0.1% crystal violet in 20% methanol. Plaques were counted under 20-fold magnification in the row of wells having the dilution which gave 5 to 20 plaques per well. Virus titers were calculated according to following formula: titer (PFU/mL) = number of plaques $\times 5 \times 3^n$; where n represents the n^{th} dilution of the virus used to infect the well in which plaques were counted.

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