

Synthesis of (*E*)-8-(3-chlorostyryl)caffeine analogs leading to 9-deazaxanthine derivatives as dual A_{2A} antagonists /MAO-B inhibitors

Silvia Rivara,^{a*} Giovanni Piersanti,^{b*} Francesca Bartoccini,^b Giuseppe Diamantini,^b Daniele Pala,^a Teresa Riccioni,^c Maria Antonietta Stasi,^c Walter Cabri,^c Franco Borsini,^c Marco Mor,^a Giorgio Tarzia^b and Patrizia Minetti^{*c}

^a *Dipartimento di Farmacia, Università degli Studi di Parma, Viale G.P. Usberti 27 A, I-43124 Parma, Italy.*

^b *Department of Biomolecular Sciences, University of Urbino, Piazza Rinascimento 6, I-61029 Urbino (PU), Italy.*

^c *Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina Km 30,400, I-00040 Pomezia, Italy.*

SUPPORTING INFORMATION

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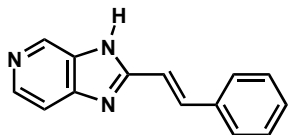
General methods.

All reactions were run in air except when differently noted. Column chromatography purifications were performed in flash conditions using Merck 230-400 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates (silica gel 60 F254), that were visualized by exposure to ultraviolet light. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 200 spectrometer, using CDCl_3 or $\text{DMSO-}d_6$ as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in Hertz (Hz). EI-MS spectra (70 eV) were taken on a Fison Trio 1000, molecular ions (M^+ or M^-) are given. ESI-MS spectra were taken on a Waters Micromass ZQ instrument, molecular ions ($M + 1$ or $M - 1$) is given. IR spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer, absorbance are reported in cm^{-1} . Melting points were determined on a Buchi SMP-510 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba analyzer and the results are within ± 0.4 of the theoretical values (C, H, N).

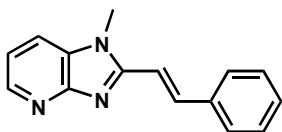
Starting Materials.

Pyridine-3,4-diamine (**1a**), biphenyl-4-carbaldehyde (**7a**), ethyl 5-(benzyloxy)-1*H*-indole-2-carboxylate (**9c**), 3-chlorostyrene, styrene, 3-methoxystyrene, 3-trifluoromethylstyrene, 4-fluorostyrene, 4-chlorostyrene, 4-(trifluoromethyl)styrene, 4-methoxystyrene, 4-bromostyrene, 3,4-dichlorostyrene, 2-methoxystyrene, 6-vinylpyridin-2-amine, 1-chloro-3-ethynylbenzene, 1-chloro-4-ethynylbenzene, 1-chloro-4-(prop-2-ynyl)benzene, (4-chlorophenyl)methanol, (4-chloro-3-(trifluoromethyl)phenyl)methanol, naphthalen-2-ylmethanol, 3-chlorophenol, biphenyl-3-ol, 4-chlorobenzamide and 1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**24**) are commercially available.

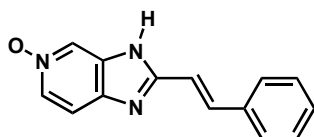
N^3 -methylpyridine-2,3-diamine (**1b**),¹ 1,3-dimethyl-5-(methylamino)pyrimidine-2,4(1*H*,3*H*)-dione (**5**),² 3'-chlorobiphenyl-4-carbaldehyde (**7b**),³ 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**15a**),⁴ 4-propoxystyrene,⁵ methylenedioxy styrene,⁶ 6-chlorobenzoxazole,⁷ 6-bromo-5-ethyl-1,3-dimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**15c**),⁴ and 6-bromo-1,3-diethyl-5-methyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**15d**)⁴ were prepared according to the reported procedures.



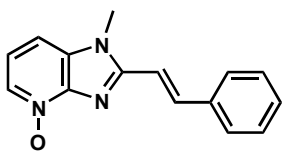
(E)-2-Styryl-3*H*-imidazo[4,5-*c*]pyridine (2a). POCl_3 (20 mL) was added to pyridine-3,4-diamine (**1a**) (1 g, 9.17 mmol) and *trans*-cinnamic acid (1.5 g, 10.09 mmol). The reaction mixture was stirred at 140 °C for 5 hours, poured into ice-water, basified with aqueous ammonia solution (10%) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5) to give 892 mg (44%) of **2a**. **MS** (ESI): 222 [$M+H$]⁺; **^1H NMR** ($\text{DMSO-}d_6$) δ 7.28 (d, $J = 16.5$ Hz, 1H), 7.37-7.49 (m, 3H), 7.53 (dd, $J_1 = 5.5$ and $J_2 = 1.0$ Hz, 1H), 7.67-7.72 (m, 2H), 7.78 (d, $J = 16.5$ Hz, 1H), 8.29 (d, $J = 5.5$ Hz, 1H), 8.89 (d, $J = 1.0$ Hz, 1H), 13.08 (br, 1H); **^{13}C NMR** ($\text{DMSO-}d_6$) δ 117.5, 127.7, 129.5, 129.7, 135.8, 136.9, 137.1, 139.2, 141.8, 143.5, 148.3, 153.5; **FTIR** (nujol, cm^{-1}): 3052, 2927; **mp**: 176-178 °C (acetone/ petrol ether); Anal. ($\text{C}_{14}\text{H}_{11}\text{N}_3$) C, H, N.



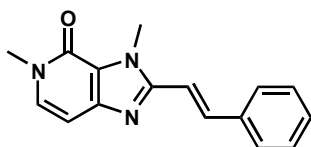
(E)-1-Methyl-2-styryl-1H-imidazo[4,5-b]pyridine (2b). Cinnamic aldehyde (2.06 g, 15.6 mmol) and AcOH (5 drops) were added to a solution of *N*³-methylpyridine-2,3-diamine (**1b**) (480 mg, 3.9 mmol) in MeOH (32 mL). The reaction mixture was stirred at room temperature for 1 hour, diluted with water (20 mL) and extracted with CHCl₃ (3 x 30 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 98:2) to give 370 mg (40%) of **2b**. **MS** (EI): 234 [M-1]⁺, 219; **¹H NMR** (CDCl₃) δ 3.87 (s, 3H), 7.08 (d, *J* = 16.0 Hz, 1H), 7.15 (dd, *J*₁ = 8.0 and *J*₂ = 5.0 Hz, 1H), 7.37-7.45 (m, 3H), 7.58-7.65 (m, 3H), 8.15 (d, *J* = 16.0 Hz, 1H), 8.53 (dd, *J*₁ = 5.0 and *J*₂ = 1.5 Hz, 1H); **¹³C NMR** (CDCl₃) δ 29.8, 112.0, 116.8, 117.4, 127.5, 128.4, 128.9, 129.5, 135.6, 139.9, 145.3, 153.3, 155.7; **FTIR** (nujol, cm⁻¹): 2925; **mp**: 158-159 °C (acetone/ petrol ether); Anal. (C₁₅H₁₃N₃) C, H, N.



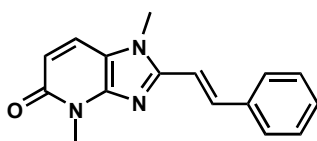
(E)-2-Styryl-3H-imidazo[4,5-c]pyridine-N-oxide (3a). *m*-Chloroperoxybenzoic acid (*m*-CPBA) (2.8 g, 16.2 mmol) was added to a solution of **2a** (600 mg, 2.7 mmol) in CH₂Cl₂ (10 mL) and MeOH (5 mL). The reaction mixture was stirred at room temperature for 1 hour. The solvents were evaporated under reduced pressure and the residue obtained was purified by flash chromatography (gradient from CH₂Cl₂ to CH₂Cl₂/MeOH 98:2) to give 440 mg (68%) of **3a**. **MS** (ESI): 238 [M+H]⁺; **¹H NMR** (DMSO-*d*₆) δ 7.23 (d, *J* = 16.5 Hz, 1H), 7.38-7.49 (m, 4H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.67-7.79 (m, 3H), 8.02 (dd, *J*₁ = 7.0 and *J*₂ = 2.0 Hz, 1H), 8.61 (br, 1H); **¹³C NMR** (DMSO-*d*₆) δ 116.8, 127.8, 129.5, 130.1, 134.7, 135.7, 137.3, 137.5, 141.7, 143.9, 148.6, 155.6; **FTIR** (nujol, cm⁻¹): 3319, 1419; **mp**: decomposition with color change starting from 250 °C (ethanol); Anal. (C₁₄H₁₁N₃O) C, H, N.



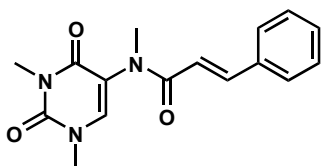
(E)-1-Methyl-2-styryl-1H-imidazo[4,5-b]pyridine-N-oxide (3b). *m*-Chloroperoxybenzoic acid (*m*-CPBA) (1 g, 6 mmol) was added to a solution of **2b** (350 mg, 1.5 mmol) in CHCl₃ (25 mL). The reaction mixture was stirred at room temperature for 30 minutes, then was added an 1 N NaHCO₃ solution (5 mL). The phases were separated and the aqueous phase was extracted with further CHCl₃ (2 x 15 mL). The combined organic phases were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/ MeOH 9:1) to give 330 mg (88%) of **3b**. **MS** (EI): 250 [M-1]⁺, 235; **¹H NMR** (CDCl₃) δ 3.93 (s, 3H), 7.02-7.14 (m, 2H), 7.27-7.66 (m, 6H), 8.30-8.38 (m, 2H); **¹³C NMR** (CDCl₃) δ 30.2, 112.6, 116.1, 117.9, 126.9, 128.9, 129.3, 129.8, 134.8, 140.3, 145.9, 152.6, 155.1; **FTIR** (nujol, cm⁻¹): 1422; **mp**: decomposition with color change starting from 180 °C (ethanol); Anal. (C₁₅H₁₃N₃O) C, H, N.



(E)-3,5-Dimethyl-2-styryl-3H-imidazo[4,5-c]pyridin-4(5H)-one (4a). A solution of **3a** (400 mg, 1.69 mmol) in acetic anhydride (7 mL) was stirred at 140 °C for 2 hours. The mixture was cooled at room temperature and diluted with water (30 mL). The volatiles were removed under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 9:1) to give 225 mg (56%) of (*E*)-2-styryl-3H-imidazo[4,5-c]pyridin-4(5H)-one. **MS** (EI): 237 [M]⁺; **¹H-NMR** (DMSO-*d*₆) δ 6.50 (d, *J* = 7.0 Hz, 1H), 7.08-7.16 (m, 2H), 7.34-7.46 (m, 4H), 7.60-7.69 (m, 2H), 11.18 (br, 1H), 13.31 (br, 1H). To a solution of (*E*)-2-styryl-3H-imidazo[4,5-c]pyridin-4(5H)-one (225 mg, 0.95 mmol) in DMF (4 mL) were added K₂CO₃ (394 mg, 2.85 mmol) and methyl iodide (0.18 mL, 2.85 mmol). The reaction mixture was stirred at room temperature for 60 hours, then diluted with water (30 mL) and CH₂Cl₂ (30 mL). The phases were separated and the aqueous phase was extracted with further CH₂Cl₂ (3 x 25 mL). The combined organic phases were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 95:5) to give 70 mg (28%) of **4a** as off-white solid. **MS** (ESI): 266 [M+H]⁺; **¹H NMR** (DMSO-*d*₆) δ 3.63 (s, 3H), 4.27 (s, 3H), 6.67 (d, *J* = 7.0 Hz, 1H), 7.02 (d, *J* = 16.0 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 1H), 7.37-7.47 (m, 3H), 7.60-7.65 (m, 2H), 7.98 (d, *J* = 16.0 Hz, 1H); **¹³C NMR** (DMSO-*d*₆) δ 31.7, 36.5, 100.7, 111.4, 122.8, 127.5, 128.9, 129.5, 132.9, 135.6, 138.8, 146.9, 151.9, 155.8; **FTIR** (nujol, cm⁻¹): 1662; **mp**: 234-236 °C (ethanol); Anal. (C₁₆H₁₅N₃O) C, H, N.

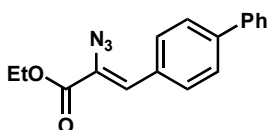


(E)-1,4-dimethyl-2-styryl-1H-imidazo[4,5-b]pyridin-5(4H)-one (4b). A solution of **3b** (300 mg, 1.19 mmol) in trifluoroacetic anhydride (3.3 mL, 24 mmol) was stirred at room temperature for 16 hours. The volatile was removed under reduced pressure and the residue obtained diluted with water (50 mL) and extracted with CHCl₃ (3 x 50 mL). The combined organic phases were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 95:5) to give 140 mg (47%) of (*E*)-1-methyl-2-styryl-1H-imidazo[4,5-b]pyridin-5(4H)-one. **MS** (EI): 250 [M-1]⁺; **¹H-NMR** (CDCl₃) δ 3.85 (s, 3H), 6.50 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 7.37-7.62 (m, 6H), 7.89 (d, *J* = 16.0 Hz, 1H). To a solution of (*E*)-1-methyl-2-styryl-1H-imidazo[4,5-b]pyridin-5(4H)-one (140 mg, 0.6 mmol) in 6 N NaOH solution (25 mL) was added methyl iodide (0.37 mL, 6 mmol). The reaction mixture was stirred at room temperature for 12 hours, then diluted with water (20 mL) and CH₂Cl₂ (20 mL). The phases were separated and the aqueous phase was extracted with further CH₂Cl₂ (3 x 20 mL). The combined organic phases were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 95:5) to give 87 mg (55%) of **4b** as yellow solid. **MS** (EI): 265 [M]⁺, 250, 235; **¹H NMR** (CDCl₃) δ 3.80 (s, 3H), 3.82 (s, 3H), 6.46 (d, *J* = 9.5 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 7.37-7.45 (m, 4H), 7.58-7.65 (m, 2H), 7.83 (d, *J* = 16.0 Hz, 1H); **¹³C NMR** (CDCl₃) δ 29.2, 30.1, 111.9, 113.9, 117.2, 122.8, 127.2, 128.9, 129.2, 135.8, 136.7, 146.2, 148.2, 162.5; **FTIR** (nujol, cm⁻¹): 2924, 2854, 1636, 1557; **mp**: 184-185 °C (ethanol/water); Anal. (C₁₆H₁₅N₃O) C, H, N.

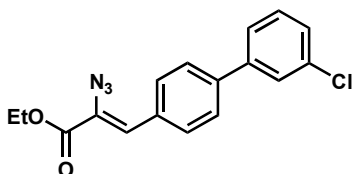


N-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-N-methylcinnamamide (6). A solution of 1,3-dimethyl-5-(methylamino)pyrimidine-2,4(1*H*,3*H*)-dione (**5**) (200 mg, 1.18 mmol), *trans*-cinnamic acid (177 mg, 1.20 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) (231 mg, 1.21 mmol) in MeOH (10 mL) was stirred at room temperature for 20 hours. The solvent was evaporated under reduced pressure and the residue obtained was diluted with CH₂Cl₂ (30 mL). The organic phase was washed with 0.5 N HCl solution (1 x 30 mL), 0.5 N Na₂CO₃ solution (1 x 30 mL) and brine (1 x 30 mL). The organic phase was dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 98:2) to give 131 mg (37%) of **6** as white solid. **MS** (EI): 299 [M]⁺, 169, 131, 103; ¹H NMR (CDCl₃) δ 3.23 (s, 3H), 3.43 (s, 3H), 3.46 (s, 3H), 6.43 (d, *J* = 15.5 Hz, 1H), 6.33-6.41 (m, 6H), 7.71 (d, *J* = 15.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 28.6, 36.6, 37.5, 117.2, 117.7, 128.0, 128.8, 129.9, 134.9, 142.1, 143.3, 151.1, 160.5, 167.0; **FTIR** (nujol, cm⁻¹): 1708, 1654, 1616; **mp**: 122-123 °C (ethanol); Anal. (C₁₆H₁₅N₃O) C, H, N.

General procedure for the synthesis of azido acrylate derivatives (8a,b). A solution of the appropriate arylaldehyde (**7a,b**) (13.7 mmol) and ethyl azidoacetate (25% in EtOH) (8.2 mL, 54.8 mmol) in anhydrous EtOH (55 mL) was added to an ethanolic solution of sodium ethoxide, prepared from sodium (1.6 g, 68 mmol) in EtOH (30 mL), at 0°C. The reaction mixture was stirred at 0 °C for 2 hours, poured into ice-water saturated with ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ ethyl acetate 9:1).

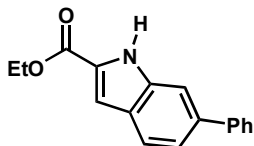


Ethyl 2-azido-3-(biphenyl-4-yl)acrylate (8a): Yellow solid; (2.2 g, 55%); **MS** (EI): 293 [M]⁺, 265, 219; ¹H NMR (CDCl₃) δ 1.43 (t, *J* = 7.0 Hz, 3H), 4.40 (q, *J* = 7.0 Hz, 2H), 6.97 (s, 1H), 7.38-7.51 (m, 3H), 7.62-7.66 (m, 4H), 7.90-7.94 (m, 2H); ¹³C NMR (CDCl₃) δ 14.2, 62.3, 124.8, 125.5, 127.1, 127.8, 128.9, 131.0, 131.1, 132.2, 140.2, 142.0, 164.1; **FTIR** (nujol, cm⁻¹): 2126, 1708; **mp**: 99-103 °C (ethanol); Anal. (C₁₇H₁₅N₃O₂) C, H, N.

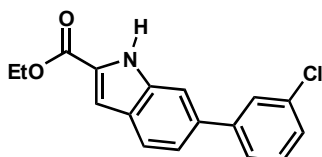


Ethyl 2-azido-3-(3'-chlorobiphenyl-4-yl)acrylate (8b): Yellow solid; (2.6 g, 58%); **MS** (EI): 327-329 [M]⁺, 299-301; ¹H NMR (CDCl₃) δ 1.43 (t, *J* = 7.0 Hz, 3H), 4.40 (q, *J* = 7.0 Hz, 2H), 6.95 (s, 1H), 7.27-7.96 (m, 8H); ¹³C NMR (CDCl₃) δ 14.2, 62.4, 124.5, 125.2, 125.9, 127.0, 127.2, 127.7, 130.1, 131.1, 132.8, 134.8, 140.4, 142.1, 163.5; **FTIR** (nujol, cm⁻¹): 2125, 1716; **mp**: 71-73 °C (ethanol); Anal. (C₁₇H₁₄ClN₃O₂) C, H, N.

General procedure for the synthesis of ethyl 1*H*-indole-2-carboxylate derivatives (9a,b). A solution of the appropriate azido acrylate (8a,b) (5.4 mmol) in *p*-xylene (70 mL) was stirred at 150 °C for 2 hours. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (gradient from cyclohexane to cyclohexane/ ethyl acetate 85:15).

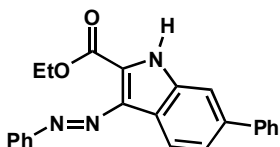


Ethyl 6-phenyl-1*H*-indole-2-carboxylate (9a): Yellowish solid; (1.4 g, 98%); **MS** (EI): 265 [M]⁺; ¹H NMR (CDCl₃) δ 1.44 (t, *J* = 7.0 Hz, 3H), 4.44 (q, *J* = 7.0 Hz, 2H), 7.25 (d, *J* = 1.0 Hz, 1H), 7.41-7.78 (m, 8H), 8.91 (br s, 1H); ¹³C NMR (CDCl₃) δ 14.4, 61.1, 108.5, 110.1, 121.0, 122.8, 126.8, 127.2, 127.4, 128.0, 128.8, 137.3, 138.8, 141.6, 161.9; **FTIR** (nujol, cm⁻¹): 3278, 1693; **mp**: 130-133 °C (ethanol); Anal. (C₁₇H₁₅NO₂) C, H, N.

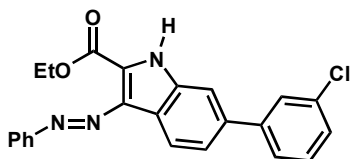


Ethyl 6-(3-chlorophenyl)-1*H*-indole-2-carboxylate (9b): Yellowish solid; (1.2 g, 78%); **MS** (EI): 299-301 [M]⁺, 253-255, 190-192; ¹H NMR (CDCl₃) δ 1.45 (t, *J* = 7.0 Hz, 3H), 4.44 (q, *J* = 7.0 Hz, 2H), 7.26-7.74 (m, 8H), 8.99 (br s, 1H); ¹³C NMR (CDCl₃) δ 14.4, 61.2, 108.5, 110.2, 120.7, 123.0, 125.5, 127.1, 127.2, 127.5, 128.3, 130.0, 134.6, 137.2, 137.3, 143.5, 161.8; **FTIR** (nujol, cm⁻¹): 3322, 1690; **mp**: 127-129 °C (ethanol); Anal. (C₁₇H₁₄ClNO₂) C, H, N.

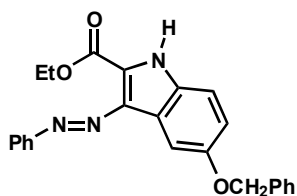
General procedure for the synthesis of ethyl 3-(phenyldiazenyl)-1*H*-indole-2-carboxylate derivatives (10a-c). Aniline (3.33 mL, 37 mmol) was diazotized by treatment with 6 N HCl solution (17 mL), followed by NaNO₂ (2.78 g, 40 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 minutes. An amount of this cold solution was added to a solution of the appropriate ethyl 1*H*-indole-2-carboxylate derivatives (9a-c) (3.7 mmol) in DMF (20 mL) and 2 N Na₂CO₃ solution (13 mL). The reaction mixture was stirred at 0 °C for 1 hour and then was added water. The aqueous layer was extracted with ethyl acetate and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ ethyl acetate 8:2).



Ethyl 6-phenyl-3-(phenyldiazenyl)-1*H*-indole-2-carboxylate (10a): Yellow solid; (410 mg, 30%); **MS** (EI): 369 [M]⁺, 292, 265, 220, 165; ¹H NMR (CDCl₃) δ 1.56 (t, *J* = 7.0 Hz, 3H), 4.58 (q, *J* = 7.0 Hz, 2H), 7.43-7.70 (m, 10H), 8.01-8.05 (m, 2H), 8.65 (d, *J* = 8.5 Hz, 1H), 9.43 (br s, 1H); ¹³C NMR (CDCl₃) δ 14.4, 62.0, 110.0, 122.5, 124.0, 125.1, 127.4, 127.5, 127.9, 128.9, 129.1, 130.4, 135.7, 135.8, 140.1, 141.1, 161.5; **FTIR** (nujol, cm⁻¹): 3442, 1692, 1467; **mp**: 127-129 °C (ethanol); Anal. (C₂₃H₁₉N₃O₂) C, H, N.

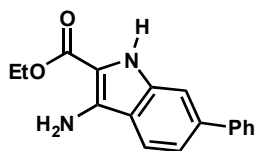


Ethyl 6-(3-chlorophenyl)-3-(phenyldiazenyl)-1H-indole-2-carboxylate (10b): Yellow solid; (970 mg, 65%); **MS** (EI): 403-405 $[M]^+$, 292, 265, 220, 165; **$^1\text{H NMR}$** (CDCl_3) δ 1.51 (t, $J = 7.0$ Hz, 3H), 4.59 (q, $J = 7.0$ Hz, 2H), 7.38-8.05 (m, 12H), 8.63 (br s, 1H); **$^{13}\text{C NMR}$** (CDCl_3) δ 14.4, 62.1, 110.1, 122.6, 123.7, 125.4, 125.6, 127.5, 127.5, 128.2, 129.1, 130.1, 130.5, 134.7, 135.6, 138.6, 142.9, 161.4; **FTIR** (nujol, cm^{-1}): 3300, 1676; **mp**: 220-222 °C (ethanol); Anal. ($\text{C}_{23}\text{H}_{18}\text{ClN}_3\text{O}_2$) C, H, N.

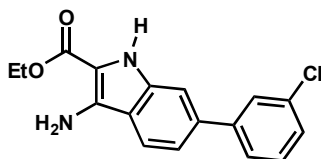


Ethyl 5-(benzyloxy)-3-(phenyldiazenyl)-1H-indole-2-carboxylate (10c): Yellow solid; (1.2 g, 80%); **MS** (ESI): 400 $[M+1]^+$; **$^1\text{H NMR}$** (CDCl_3) δ 1.54 (t, $J = 7.0$ Hz, 3H), 4.56 (q, $J = 7.0$ Hz, 2H), 5.18 (s, 2H), 7.13-7.52 (m, 10H), 7.99 (d, $J = 7.0$ Hz, 1H), 9.43 (br s, 1H); **$^{13}\text{C NMR}$** (CDCl_3) δ 14.4, 61.9, 70.6, 106.7, 112.7, 118.3, 118.8, 122.5, 127.7, 127.9, 128.0, 128.6, 129.0, 130.1, 130.5, 135.6, 137.2, 153.9, 156.5, 161.6; **FTIR** (nujol, cm^{-1}): 3279, 1678; **mp**: 195-197 °C (ethanol); Anal. ($\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_2$) C, H, N.

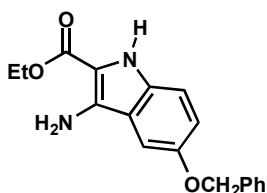
General procedure for the synthesis of ethyl 3-amino-1H-indole-2-carboxylate derivatives (11a-c). To a solution of the appropriate ethyl 3-(phenyldiazenyl)-1H-indole-2-carboxylate derivatives (**10a-c**) (1.7 mmol) in isopropanol (60 mL) were added con HCl (24 mL) and Sn (2 g, 17.2 mmol), at 0 °C. The reaction mixture was stirred at 85 °C for 2 hours. The solution was filtered, washed with aqueous ammonia solution (30%) and the suspension so obtained was filtered over Celite and ethyl acetate (80 mL) was added. The phases were separated and the aqueous phase was extracted with further ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2).



Ethyl 3-amino-6-phenyl-1H-indole-2-carboxylate (11a): Yellowish oil; (220 mg, 46%); **MS** (EI): 280 $[M]^+$, 234, 207; **$^1\text{H NMR}$** ($\text{DMSO}-d_6$) δ 1.33 (t, $J = 7.0$ Hz, 3H), 4.30 (q, $J = 7.0$ Hz, 2H), 7.18 (d, $J = 8.5$ Hz, 1H), 7.22-7.67 (m, 8H), 7.83 (d, $J = 8.5$ Hz, 1H), 10.48 (br s, 1H); **$^{13}\text{C NMR}$** ($\text{DMSO}-d_6$) δ 15.3, 59.2, 108.2, 110.1, 117.9, 119.1, 121.2, 127.2, 127.7, 131.8, 135.8, 137.4, 137.9, 143.1, 161.8; **FTIR** (nujol, cm^{-1}): 3550, 3460, 1701; **mp**: undeterminable-rubber-like substance; Anal. ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$) C, H, N.

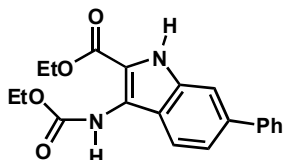


Ethyl 3-amino-6-(3-chlorophenyl)-1H-indole-2-carboxylate (11b): Off-white solid; (273 mg, 51%); **MS** (ESI): 315-317 [M+H]⁺; **¹H NMR** (DMSO-*d*₆) δ 1.33 (t, *J* = 7.0 Hz, 3H), 4.30 (q, *J* = 7.0 Hz, 2H), 5.75 (s, 2H), 7.22 (dd, *J* = 8.5 and 1.5 Hz, 1H), 7.39-7.67 (m, 5H), 7.85 (d, *J* = 8.5 Hz, 1H), 10.51 (s, 1H); **¹³C NMR** (DMSO-*d*₆) δ 15.1, 59.6, 107.8, 110.5, 117.2, 118.7, 121.9, 126.0, 126.9, 127.4, 131.2, 134.1, 136.2, 137.0, 137.4, 143.8, 162.7; **FTIR** (nujol, cm⁻¹): 3465, 3367, 3299, 1667; **mp**: 167-169 °C (ethanol); Anal. (C₁₇H₁₅ClN₂O₂) C, H, N.

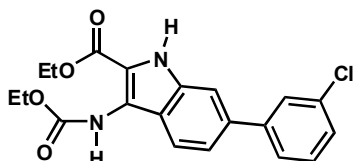


Ethyl 3-amino-5-(benzyloxy)-1H-indole-2-carboxylate (11c): Yellowish solid; (365 mg, 69%); **MS** (ESI): 311 [M+H]⁺; **¹H NMR** (DMSO-*d*₆) δ 1.41 (t, *J* = 7.0 Hz, 3H), 4.50 (q, *J* = 7.1 Hz, 2H), 5.14 (s, 2H), 7.07-7.49 (m, 8H), 8.37 (s, 1H); **¹³C NMR** (DMSO-*d*₆) δ 14.8, 60.1, 69.6, 105.7, 112.1, 113.7, 119.8, 120.1, 124.6, 128.3, 128.9, 131.8, 138.5, 139.1, 153.8, 162.3; **FTIR** (nujol, cm⁻¹): 3435, 3309, 1671; **mp**: 165-167 °C (ethanol); Anal. (C₁₈H₁₈N₂O₃) C, H, N.

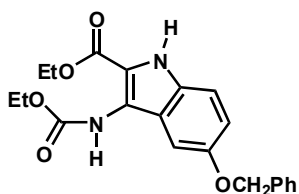
General procedure for the synthesis of ethyl 3-(ethoxycarbonylamino)-1H-indole-2-carboxylate derivatives (11a-c). Ethyl chloroformate (0.5 mL, 4.8 mmol) was added to a solution of the appropriate 3-amino-1H-indole-2-carboxylate derivatives (**11a-c**) (0.8 mmol) in *p*-xylene (15 mL). The reaction mixture was stirred at 140 °C for 24 hours. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 98:2).



Ethyl 3-(ethoxycarbonylamino)-6-phenyl-1H-indole-2-carboxylate (12a): colourless oil; (169 mg, 60%); **MS** (ED): 352 [M]⁺, 306, 260; **¹H NMR** (DMSO-*d*₆) δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 4.16 (q, *J* = 7.0 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 7.29-7.74 (m, 8H), 8.94 (s, 1H), 11.75 (s, 1H); **¹³C NMR** (DMSO-*d*₆) δ 14.9, 15.9, 59.8, 60.6, 108.7, 110.5, 117.1, 119.6, 120.7, 127.8, 128.2, 132.6, 135.9, 137.8, 138.2, 143.8, 153.8, 162.3; **FTIR** (nujol, cm⁻¹): 3465, 3367, 3299, 1667; **mp**: undeterminable-rubber-like substance; Anal. (C₂₀H₂₀N₂O₄) C, H, N.

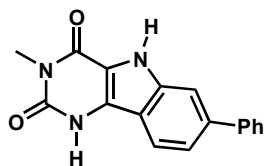


Ethyl 6-(3-chlorophenyl)-3-(ethoxycarbonylamino)-1H-indole-2-carboxylate (12b): Yellowish solid; (257 mg, 83%); **MS** (ESI): 387-389 [M+H]⁺; **¹H NMR** (CDCl₃) δ 1.42 (t, *J* = 7.0 Hz, 3H), 1.50 (t, *J* = 7.0 Hz, 3H), 4.30 (q, *J* = 7.0 Hz, 2H), 4.46 (q, *J* = 7.0 Hz, 2H), 7.32-7.63 (m, 7H), 8.26 (s, 1H), 8.46 (s, 1H); **¹³C NMR** (CDCl₃) δ 14.5, 14.6, 61.1, 61.7, 109.8, 119.9, 120.1, 124.5, 125.1, 125.5, 126.0, 127.3, 127.4, 130.0, 134.6, 135.8, 138.3, 143.2, 154.1, 161.8; **FTIR** (nujol, cm⁻¹): 3337, 3309, 1706, 1678; **mp**: 187-189 °C (ethanol); Anal. (C₂₀H₁₉ClN₂O₄) C, H, N.

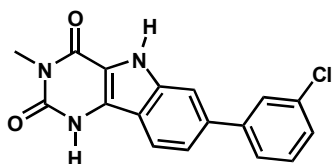


Ethyl 5-(benzyloxy)-3-(ethoxycarbonylamino)-1H-indole-2-carboxylate (12c): Yellowish solid; (122 mg, 40%); **MS** (ESI): 383 [M+H]⁺; **¹H NMR** (CDCl₃) δ 1.36 (t, *J* = 7.0 Hz, 3H), 1.47 (t, *J* = 7.0 Hz, 3H), 4.29 (q, *J* = 7.0 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 5.11 (s, 2H), 7.08-7.53 (m, 8H), 7.70 (s, 1H), 8.37 (s, 1H); **¹³C NMR** (CDCl₃) δ 14.4, 14.6, 60.9, 61.6, 70.6, 105.2, 112.6, 114.4, 119.2, 120.9, 123.9, 127.9, 128.5, 131.0, 137.3, 139.9, 153.1, 154.2, 161.9; **FTIR** (nujol, cm⁻¹): 3413, 3322, 1739, 1704; **mp**: 185-187 °C (ethanol); Anal. (C₂₁H₂₂N₂O₅) C, H, N.

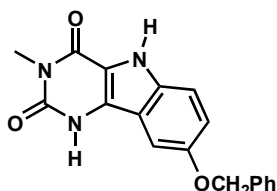
General procedure for the synthesis of 3-methyl-1H-pyrimido[5,4-*b*]indole-2,4(3*H*,5*H*)-dione derivatives (13a-c). Methyl amine (15 mL, 40% aqueous) was added to a solution of the appropriate ethyl 3-(ethoxycarbonylamino)-1H-indole-2-carboxylate derivatives (12a-c) (0.48 mmol) in isopropanol (15 mL). The reaction mixture was stirred at 85 °C for 24 hours. The solvent was evaporated under reduced pressure and the residue obtained was used for the following reaction without further purification.



3-Methyl-7-phenyl-1H-pyrimido[5,4-*b*]indole-2,4(3*H*,5*H*)-dione (13a): An analytical sample was purified by flash chromatography (CH₂Cl₂/ MeOH 94:6) for the characterization. Colourless oil; (21 mg, 15%); **MS** (ESI): 292 [M+H]⁺; **¹H NMR** (DMSO-*d*₆) δ 3.34 (s, 3H), 7.34-7.71 (m, 7H), 8.00 (d, *J* = 8.5 Hz, 1H), 11.88 (s, 1H), 12.01 (s, 1H); **¹³C NMR** (DMSO-*d*₆) δ 27.6, 110.9, 114.5, 121.6, 121.5, 126.1, 127.4, 128.0, 129.5, 139.0, 139.6, 141.0, 151.6, 157.1; **FTIR** (nujol, cm⁻¹): 3173, 3164, 1722, 1627; **mp**: undeterminable-rubber-like substance; Anal. (C₁₇H₁₃N₃O₂) C, H, N.

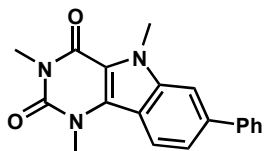


7-(3-Chlorophenyl)-3-methyl-1H-pyrimido[5,4-b]indole-2,4(3H,5H)-dione (13b): An analytical sample was purified by flash chromatography (CH₂Cl₂/ MeOH 94:6) for the characterization. Colourless oil; (70 mg, 45%); **MS** (ESI): 326-328 [M+H]⁺; **¹H NMR** (DMSO-*d*₆) δ 3.30 (s, 3H), 7.42-7.74 (m, 6H), 8.01 (d, *J* = 8.5 Hz, 1H), 11.94 (s, 1H), 12.01 (s, 1H); **¹³C NMR** (DMSO-*d*₆) δ 28.9, 108.2, 113.8, 115.1, 120.8, 121.7, 125.1, 127.2, 127.8, 127.9, 130.8, 135.3, 139.4, 140.6, 143.2, 151.9, 157.6; **FTIR** (nujol, cm⁻¹): 3145, 3073, 1722, 1623; **mp**: undeterminable-rubber-like substance; Anal. (C₁₇H₁₂ClN₃O₂) C, H, N.

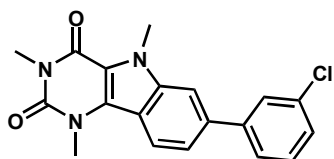


8-(Benzyloxy)-3-methyl-1H-pyrimido[5,4-b]indole-2,4(3H,5H)-dione (13c): An analytical sample was purified by flash chromatography (CH₂Cl₂/ MeOH 94:6) for the characterization. Yellowish oil; (80 mg, 52%); **MS** (ESI): 323 [M+H]⁺; **¹H NMR** (DMSO-*d*₆) δ 3.28 (s, 3H), 5.09 (s, 2H), 7.11 (dd, *J* = 9.0 and 2.4 Hz, 1H), 7.30-7.51 (m, 7H), 11.62 (s, 1H), 11.82 (s, 1H); **¹³C NMR** (DMSO-*d*₆) δ 28.5, 71.5, 104.1, 111.6, 114.2, 118.1, 126.5, 127.3, 128.5, 128.9, 135.8, 137.1, 151.6, 153.5, 157.8; **FTIR** (nujol, cm⁻¹): 3147, 3095, 1722, 1671; **mp**: undeterminable-rubber-like substance; Anal. (C₁₈H₁₅N₃O₃) C, H, N.

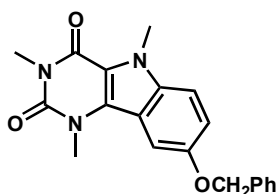
General procedure for the synthesis of 1,3,5-trimethyl-1H-pyrimido[5,4-b]indole-2,4(3H,5H)-dione derivatives (14a-c). NaH (80%, 5 mg, 0.21 mmol) was added to a solution of the appropriate 3-methyl-1H-pyrimido[5,4-b]indole-2,4(3H,5H)-dione derivatives (**13a-c**) (0.07 mmol) in dry DMF (2 mL), under N₂. The reaction mixture was stirred at room temperature for 30 minutes, then was added methyl iodide (8.6 μl, 0.14 mmol). The reaction mixture was stirred at room temperature for 24 hours, diluted with water (15 mL) and CH₂Cl₂ (15 mL). The phases were separated and the aqueous phase was extracted with further CH₂Cl₂ (3 x 15 mL). The combined organic phases were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/MeOH 98:2).



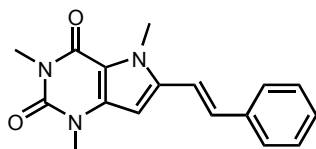
1,3,5-Trimethyl-7-phenyl-1H-pyrimido[5,4-b]indole-2,4(3H,5H)-dione (14a): Off-white solid; (19 mg, 86%); **MS** (ESI): 320 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.53 (s, 3H), 4.00 (s, 3H), 4.23 (s, 3H), 7.41-7.55 (m, 4H), 7.60 (s, 1H), 7.68-7.72 (m, 2H), 8.07 (d, *J* = 8.5 Hz, 1H); **¹³C NMR** (CDCl₃) δ 28.4, 31.1, 32.9, 108.7, 114.2, 120.3, 122.0, 127.5, 127.8, 129.0, 140.3, 140.5, 140.9, 151.6, 157.0; **FTIR** (nujol, cm⁻¹): 1691, 1645; **mp**: 234-236 °C (ethanol); Anal. (C₁₉H₁₇N₃O₂) C, H, N.



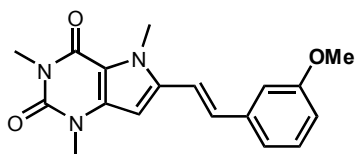
7-(3-Chlorophenyl)-1,3,5-trimethyl-1H-pyrimido[5,4-*b*]indole-2,4(3H,5H)-dione (14b): Yellowish solid; (13 mg, 51%); **MS** (ESI): 354 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.53 (s, 3H), 4.00 (s, 3H), 4.24 (s, 3H), 7.40-7.68 (m, 6H), 8.07 (d, *J* = 8.5 Hz, 1H); **¹³C NMR** (CDCl₃) δ 28.4, 31.1, 32.9, 108.8, 114.6, 115.7, 120.0, 122.1, 125.6, 127.5, 127.5, 127.7, 130.2, 134.8, 139.0, 140.1, 142.8, 151.5, 157.0; **FTIR** (nujol, cm⁻¹): 1687, 1646; **mp**: 232-234 °C (CH₂Cl₂/ petrol ether); Anal. (C₁₉H₁₆ClN₃O₂) C, H, N.



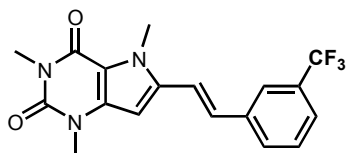
8-(Benzyloxy)-1,3,5-trimethyl-1H-pyrimido[5,4-*b*]indole-2,4(3H,5H)-dione (14c): Yellowish solid; (11 mg, 46%); **MS** (ESI): 350 [M]⁺; **¹H NMR** (CDCl₃) δ 3.47 (s, 3H), 3.87 (s, 3H), 4.11 (s, 3H), 5.13 (s, 2H), 7.22-7.50 (m, 8H); **¹³C NMR** (CDCl₃) δ 28.3, 31.1, 32.6, 71.2, 104.5, 111.4, 114.8, 118.8, 126.9, 127.5, 128.1, 128.7, 135.6, 136.9, 151.4, 153.1, 157.1; **FTIR** (nujol, cm⁻¹): 1689, 1642; **mp**: 217-219 °C (CH₂Cl₂/ petrol ether); Anal. (C₂₀H₁₉N₃O₃) C, H, N.



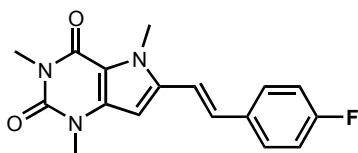
(*E*)-1,3,5-Trimethyl-6-styryl-1H-pyrrolo[3,2-*d*]pyrimidine-2,4(3H,5H)-dione (17b):⁸ Obtained following the general procedure A. Off-white solid; (83 mg, 76%); **MS** (ESI): 296 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.43 (s, 3H), 3.50 (s, 3H), 4.11 (s, 3H), 6.20 (s, 1H), 7.00 (d, *J* = 16.0 Hz, 1H), 7.16 (d, *J* = 16.0 Hz, 1H), 7.45-7.36 (m, 3H), 7.55-7.50 (m, 2H); **¹³C NMR** (CDCl₃): δ 27.9, 31.7, 31.8, 90.6, 111.1, 114.7, 126.7, 128.7, 128.9, 133.1, 135.7, 136.2, 140.2, 151.6, 155.8; **FTIR** (nujol, cm⁻¹): 1687, 1651; **mp**: 142-144 °C (ethanol); Anal. (C₁₇H₁₇N₃O₂) C, H, N.



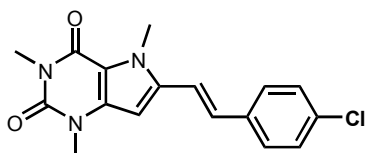
(*E*)-6-(3-Methoxystyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-*d*]pyrimidine-2,4(3H,5H)-dione (17c): Obtained following the general procedure A. Off-white solid; (103 mg, 86%); **MS** (ESI): 326 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.43 (s, 3H), 3.50 (s, 3H), 3.89 (s, 3H), 4.10 (s, 3H), 6.20 (s, 1H), 7.0-6.9 (m, 4H), 7.12 (d, *J* = 16 Hz, 1H), 7.34 (d, *J* = 8 Hz, 1H); **¹³C NMR** (CDCl₃): δ 27.9, 31.7, 31.8, 55.3, 90.6, 111.1, 112.2, 114.0, 115.0, 111.3, 129.9, 133.0, 135.7, 137.6, 140.0, 151.6, 155.8, 160.0; **FTIR** (nujol, cm⁻¹): 1688, 1651; **mp**: 175-177 °C (ethanol); Anal. (C₁₈H₁₉N₃O₃) C, H, N.



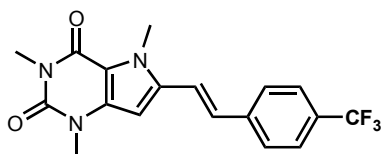
(E)-1,3,5-Trimethyl-6-(3-(trifluoromethyl)styryl)-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17d): Obtained following the general procedure A. White solid; (50 mg, 37%); **MS** (ESI): 364 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.43 (s, 3H), 3.50 (s, 3H), 4.14 (s, 3H), 6.23 (s, 1H), 7.06 (d, *J* = 16.0 Hz, 1H), 7.18 (d, *J* = 16.0 Hz, 1H), 7.48-7.57 (m, 4H); ¹³C NMR (CDCl₃): δ 27.0, 31.7, 31.9, 91.0, 107.6 (q, *J* = 265.5 Hz), 111.2, 116.5, 123.2 (q, *J* = 3.5 Hz), 125.0 (q, *J* = 3.5 Hz), 129.4, 129.7, 131.3, 131.4 (q, *J* = 32.5 Hz), 135.6, 137.0, 139.3, 151.5, 155.9; **FTIR** (nujol, cm⁻¹): 1683, 1650, 1578; **mp**: 248-250 °C (ethanol); Anal. (C₁₈H₁₆F₃N₃O₂) C, H, N.



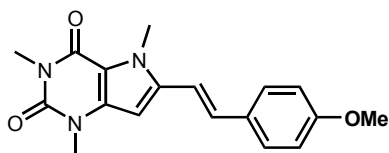
(E)-6-(4-Fluorostyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17e): Obtained following the general procedure A. Off-white solid; (46 mg, 40%); **MS** (ESI): 314 [M+H]⁺; ¹H NMR (CDCl₃) δ 3.43 (s, 3H), 3.50 (s, 3H), 4.11 (s, 3H), 6.19 (s, 1H), 6.92 (d, *J* = 16.0 Hz, 1H), 7.14-7.08 (m, 2H), 7.12 (d, *J* = 16.0 Hz, 1H), 7.53-7.47 (m, 2H); ¹³C NMR (CDCl₃) δ 27.9, 31.6, 31.8, 90.5, 111.1, 114.5 (d, *J* = 2.5 Hz), 116.0 (d, *J* = 22.0 Hz), 128.2 (d, *J* = 8.0 Hz), 131.8, 132.44 (d, *J* = 4.0 Hz), 135.7, 140.0, 151.5, 155.8, 162.8 (d, *J* = 249.0 Hz); **FTIR** (nujol, cm⁻¹): 1681, 1648; **mp**: 175-177 °C (ethanol); Anal. (C₁₇H₁₆FN₃O₂) C, H, N.



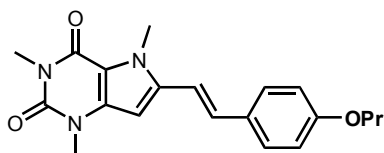
(E)-6-(4-Chlorostyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17f): Obtained following the general procedure A. Orange solid; (24 mg, 20%); **MS** (ESI): 330-332 [M+H]⁺; ¹H NMR (CDCl₃) δ 3.43 (s, 3H), 3.50 (s, 3H), 4.11 (s, 3H), 6.19 (s, 1H), 6.97 (d, *J* = 16.0 Hz, 1H), 7.10 (d, *J* = 16.0 Hz, 1H), 7.34-7.42 (m, 4H); ¹³C NMR (CDCl₃) δ 27.9, 31.7, 31.8, 90.7, 111.2, 115.2, 127.8, 129.1, 131.6, 134.3, 134.7, 135.7, 139.8, 151.5, 155.8; **FTIR** (nujol, cm⁻¹): 1675, 1639, 1579; **mp**: 233-235 °C (ethanol). Anal. (C₁₇H₁₆ClN₃O₂) C, H, N.



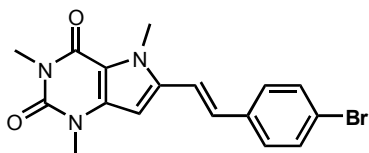
(E)-1,3,5-Trimethyl-6-(4-(trifluoromethyl)styryl)-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17g): Obtained following the general procedure A. Yellowish solid; (34 mg, 25%); **MS** (ESI): 364 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.43 (s, 3H), 3.50 (s, 3H), 4.13 (s, 3H), 6.24 (s, 1H), 7.08 (d, *J* = 16.5 Hz, 1H), 7.17 (d, *J* = 16.5 Hz, 1H), 7.63 (s, 4H); ¹³C NMR (CDCl₃): δ 27.9, 31.7, 31.9, 91.2, 114.3 (q, *J* = 278 Hz), 125.8 (q, *J* = 4 Hz), 126.7, 128.8, 129.7, 130.1 (q, *J* = 30 Hz), 131.2, 135.6, 139.3, 139.6 (q, *J* = 2 Hz), 151.5, 155.9; **FTIR** (nujol, cm⁻¹): 1655, 1686; **mp**: 212-214 °C (ethanol); Anal. (C₁₈H₁₆F₃N₃O₂) C, H, N.



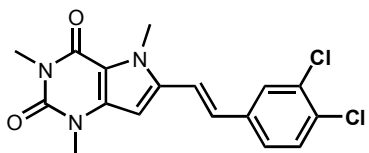
(E)-6-(4-methoxystyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17h): Obtained following the general procedure A. Yellowish solid; (94 mg, 78%); **MS** (ESI): 326 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.43 (s, 3H), 3.50 (s, 3H), 3.86 (s, 3H), 4.10 (s, 3H), 6.16 (s, 1H), 6.86 (d, *J* = 16.0 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 2H); **¹³C NMR** (CDCl₃): δ 27.8, 31.6, 31.8, 55.4, 90.1, 110.8, 112.5, 114.3, 128.0, 129.0, 132.8, 135.8, 140.7, 151.6, 155.8, 160.1; **FTIR** (nujol, cm⁻¹): 1686, 1647; **mp**: 191-193 °C (acetone/ petrol ether); Anal. (C₁₈H₁₉N₃O₃) C, H, N.



(E)-1,3,5-Trimethyl-6-(4-propoxystyryl)-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17i): Obtained following the general procedure A. Yellow solid; (59 mg, 45%); **MS** (ESI): 354 [M+H]⁺; **¹H NMR** (CDCl₃): δ 1.06 (t, *J* = 6.5 Hz, 3H), 1.89-1.79 (m, 2H), 3.41 (s, 3H), 3.48 (s, 3H), 3.96 (t, *J* = 6.5 Hz, 2H), 4.08 (s, 3H), 6.14 (s, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 16.0 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H); **¹³C NMR** (CDCl₃): δ 10.5, 22.5, 27.8, 31.6, 31.7, 69.6, 90.0, 110.7, 112.3, 114.9, 128.0, 128.7, 132.9, 135.8, 140.7, 151.6, 155.7, 159.7; **FTIR** (nujol, cm⁻¹): 1696, 1676; **mp**: 173-175 °C (ethanol); Anal. (C₂₀H₂₃N₃O₃) C, H, N.

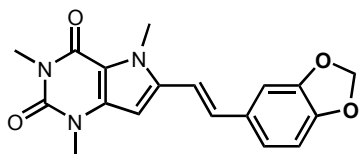


(E)-6-(4-Bromostyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17j): Obtained following the general procedure A. Yellow solid; (30 mg, 22%); **MS** (ESI): 374-376 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.43 (s, 3H), 3.50 (s, 3H), 4.10 (s, 3H), 6.20 (s, 1H), 7.98 (d, *J* = 16.0 Hz, 1H), 7.08 (d, *J* = 16.0 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H); **¹³C NMR** (CDCl₃) δ 27.8, 31.7, 31.8, 90.8, 111.3, 115.3, 122.5, 128.1, 131.7, 132.1, 135.2, 135.7, 139.7, 151.5, 155.8; **FTIR** (nujol, cm⁻¹): 1694, 1658; **mp**: 227-229 °C (ethanol); Anal. (C₁₇H₁₆BrN₃O₂) C, H, N.

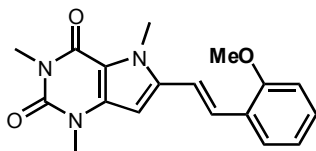


(E)-6-(3,4-Dichlorostyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17k): Obtained following the general procedure A. Yellow solid; (52 mg, 39%); **MS** (ESI): 363-365-367 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.43 (s, 3H), 3.49 (s, 3H), 4.12 (s, 3H), 6.20 (s, 1H), 7.01 (s, 2H), 7.33 (dd, *J* = 8.5 and 2.0 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H); **¹H NMR** (DMSO-*d*₆): δ 3.23 (s, 3H), 3.38 (s, 3H), 4.05 (s, 3H), 6.60 (s, 1H), 7.27 (d, *J* = 16.0 Hz, 1H), 7.45 (d, *J* = 16.0 Hz, 1H), 7.63 (s, 2H), 8.09 (s, 1H); **¹³C NMR** (CDCl₃): δ 27.9, 31.7, 31.9, 91.1, 111.5,

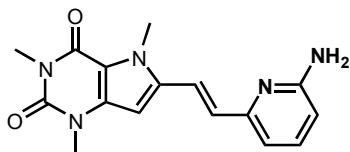
116.5, 125.7, 128.1, 130.2, 130.8, 132.2, 133.1, 135.6, 136.3, 139.2, 151.5, 155.9; **FTIR** (nujol, cm^{-1}): 1689, 1651, 1545; **mp**: 220-222 °C (ethanol). Anal. ($\text{C}_{17}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_2$) C, H, N.



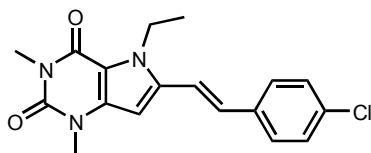
(E)-6-(2-(Benzo[d][1,3]dioxol-5-yl)vinyl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17l): Obtained following the general procedure A. Yellowish solid; (107 mg, 85%); **MS** (ESI): 340 $[\text{M}+\text{H}]^+$; **^1H NMR** (CDCl_3): δ 3.43 (s, 3H), 3.50 (s, 3H), 4.09 (s, 3H), 6.02 (s, 2H), 6.15 (s, 1H), 6.82 (d, $J = 16.0$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 7.06 (s, 1H), 7.06 (d, $J = 16.0$ Hz, 1H); **^{13}C NMR** (CDCl_3) δ 27.8, 31.6, 31.8, 90.4, 101.4, 105.4, 108.2, 108.4, 108.6, 112.9, 122.1, 123.3, 130.8, 132.9, 135.8, 140.4, 148.2, 148.4; **FTIR** (nujol, cm^{-1}): 1686, 1647; **mp**: decomposition with color change starting from 250 °C (ethanol); Anal. ($\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$) C, H, N.



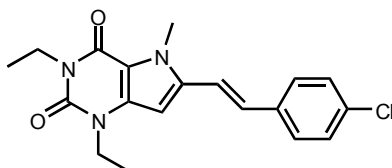
(E)-6-(2-methoxystyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17m): Obtained following the general procedure A. Yellowish solid; (49 mg, 41%); **MS** (ESI): 326 $[\text{M}+\text{H}]^+$; **^1H NMR** (CDCl_3): δ 3.43 (s, 3H), 3.50 (s, 3H), 3.93 (s, 3H), 4.09 (s, 3H), 6.21 (s, 1H), 6.9-7.1 (m, 3H), 7.6-7.3 (m, 3H); **^{13}C NMR** (CDCl_3): δ 27.5, 31.9, 31.2, 55.8, 90.6, 110.1, 112.2, 114.8, 115.1, 121.3, 128.2, 129.5, 133.2, 135.2, 141.2, 151.2, 155.9, 160.6; **FTIR** (nujol, cm^{-1}): 1681, 1654; **mp**: 169-171 °C (ethanol); Anal. ($\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3$) C, H, N.



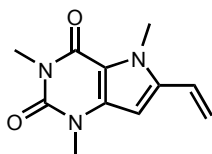
(E)-6-(2-(6-Aminopyridin-2-yl)vinyl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17n): Obtained following the general procedure A. Yellowish solid; (43 mg, 37%); **MS** (ESI): 312 $[\text{M}+\text{H}]^+$; **^1H NMR** (CDCl_3): δ 3.36 (s, 3H), 3.49 (s, 3H), 4.10 (s, 3H), 6.52 (d, $J = 7.0$ Hz, 1H), 6.54 (s, 1H), 6.76 (d, $J = 7.0$ Hz, 1H), 7.14 (d, $J = 16.0$ Hz, 1H), 7.46 (t, $J = 7.0$ Hz, 1H), 7.55 (d, $J = 16.0$ Hz, 1H); **^{13}C NMR** (CDCl_3): δ 28.7, 31.4, 31.9, 96.5, 111.9, 112.7, 113.8, 119.0, 120.7, 129.8, 135.5, 138.6, 143.5, 150.4, 151.5, 155.9; **FTIR** (nujol, cm^{-1}): 3425, 3341, 1681, 1642; **mp**: decomposition with color change starting from 250 °C (ethanol); Anal. ($\text{C}_{16}\text{H}_{17}\text{N}_5\text{O}_2$) C, H, N.



(E)-6-(4-Chlorostyryl)-5-ethyl-1,3-dimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17x): Obtained following the general procedure A. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 8:2); yellow solid (57 mg, 45%); **MS** (ESI): 344-346 [M+H]⁺; **¹H NMR** (CDCl₃): δ 1.43 (t, *J* = 7.0 Hz, 3H), 3.44 (s, 3H), 3.50 (s, 3H), 4.58 (q, *J* = 7.0 Hz, 2H), 6.20 (s, 1H), 6.96 (d, *J* = 16.0 Hz, 1H), 7.12 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H); **¹³C NMR** (CDCl₃): δ 17.0, 27.8, 31.7, 39.8, 90.8, 110.4, 115.1, 127.8, 129.1, 131.7, 134.2, 134.8, 135.8, 138.8, 151.5, 155.3; **FTIR** (nujol, cm⁻¹): 1685, 1647; **mp**: 178-180 °C (ethanol); Anal. (C₁₈H₁₈ClN₃O₂) C, H, N.

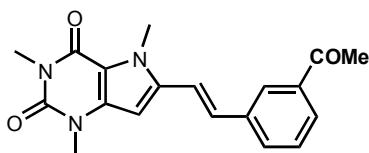


(E)-6-(4-Chlorostyryl)-1,3-diethyl-5-methyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17y): Obtained following the general procedure A. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 8:2); yellow solid (57 mg, 43%); **MS** (ESI): 358-360 [M+H]⁺; **¹H NMR** (CDCl₃): δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 4.00 (q, *J* = 7.0 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 4.11 (s, 3H), 6.18 (s, 1H), 6.96 (d, *J* = 16.0 Hz, 1H), 7.09 (d, *J* = 16.0 Hz, 1H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H); **¹³C NMR** (CDCl₃): δ 12.8, 13.4, 31.8, 36.2, 40.2, 90.5, 111.7, 115.4, 127.8, 129.1, 131.5, 134.2, 134.7, 134.8, 139.7, 150.6, 155.6; **FTIR** (nujol, cm⁻¹): 1680, 1652; **mp**: 186-188 °C (ethanol); Anal. (C₁₉H₂₀ClN₃O₂) C, H, N.

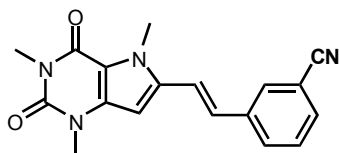


1,3,5-Trimethyl-6-vinyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (16)⁴

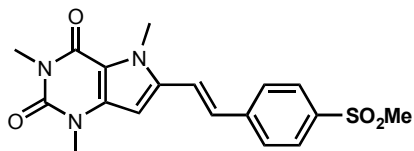
A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**15a**) (100 mg, 0.37 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (91 mg, 0.59 mmol), PdCl₂(PPh₃)₂ (26 mg, 0.037 mmol), DME (0.84 mL), H₂O (0.16 mL) and TEA (155 μL, 0.59 mmol). The mixture was stirred at 80 °C for 16 hours. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ethyl acetate 7:3) to give 54 mg (67%) of desired product (**16**) as a off-white solid. **MS** (ESI): 220 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.40 (s, 3H), 3.46 (s, 3H), 4.01 (s, 3H), 5.47 (d, *J* = 11.0 Hz, 1H), 5.80 (d, *J* = 17.5 Hz, 1H), 6.07 (s, 1H), 6.66 (dd, *J*₁ = 17.5 and *J*₂ = 11.0 Hz, 1H); **¹³C NMR** (CDCl₃): δ 27.8, 31.6, 31.7, 90.7, 110.8, 118.6, 123.8, 135.4, 140.0, 151.5, 156.0; **FTIR** (nujol, cm⁻¹): 2924, 1684, 1646; **mp**: 216-218 °C (ethanol); Anal. C₁₁H₁₃N₃O₂: C, H, N.



(E)-6-(3-Acetylstyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17o): Obtained following the general procedure B. Yellow solid, (80 mg, 66%); **MS** (EI): 337 [M]⁺; **¹H NMR** (CDCl₃): δ 2.67 (s, 3H), 3.43 (s, 3H), 3.51 (s, 3H), 4.14 (s, 3H), 6.23 (s, 1H), 7.09 (d, *J* = 16.0 Hz, 1H), 7.20 (d, *J* = 16.0 Hz, 1H), 7.51 (dd, *J*₁ = *J*₂ 7.5 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 8.11 (s, 1H); **¹³C NMR** (CDCl₃): δ 26.7, 27.9, 31.7, 31.9, 90.9, 111.4, 116.1, 126.1, 128.4, 129.2, 130.9, 131.9, 135.7, 136.8, 137.7, 139.6, 151.5, 155.9, 197.8; **FTIR** (nujol, cm⁻¹): 1678, 1642; **mp**: decomposition with color change starting from 250 °C (ethanol); Anal. (C₁₉H₁₉N₃O₃) C, H, N.

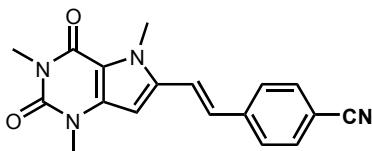


(E)-3-(2-(1,3,5-Trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl)vinyl)benzonitrile (17p): Obtained following the general procedure B. Yellow solid; (97 mg, 84%); **MS** (EI): 320 (M)⁺; **¹H NMR** (CDCl₃): δ 3.44 (s, 3H), 3.51 (s, 3H), 4.14 (s, 3H), 6.24 (s, 1H), 7.09 (s, 2H), 7.52 (dd, *J*₁ = *J*₂ = 7.5 Hz, 1H), 7.63-7.59 (m, 1H), 7.76-7.72 (m, 1H), 7.79 (s, 1H); **¹H NMR** (Acetone-d₆): δ 3.29 (s, 3H), 3.45 (s, 3H), 4.15 (s, 3H), 6.58 (s, 1H), 7.38 (d, *J* = 16.5 Hz, 1H), 7.57 (d, *J* = 16.5 Hz, 1H), 7.61 (dd, *J*₁ = *J*₂ = 7.5 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.98-7.94 (m, 1H), 8.12 (s, 1H); **¹³C NMR** (CDCl₃): δ 27.8, 31.6, 31.9, 91.3, 111.7, 113.3, 117.4, 118.4, 129.7, 129.9, 130.1, 130.5, 131.5, 135.6, 137.6, 138.9, 151.5, 155.9; **FTIR** (nujol, cm⁻¹): 2226, 1687, 1647; **mp**: decomposition with color change starting from 250 °C (ethanol); Anal. (C₁₈H₁₆N₄O₂) C, H, N.



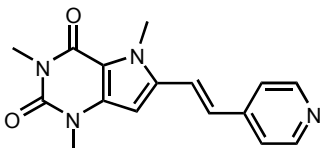
(E)-1,3,5-Trimethyl-6-(4-(methylsulfonyl)styryl)-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17r): Obtained following the general procedure B. Yellow solid; (70 mg, 52%); **MS** (ESI): 374 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.08 (s, 1.05H), 3.10 (s, 3H), 3.32 (s, 3H), 3.42 (s, 1.05H), 3.44 (s, 3H), 3.51 (s, 3H), 3.90 (s, 1.05H), 4.15 (s, 3H), 5.71 (s, 0.35H), 6.27 (s, 1H), 6.57 (d, *J* = 12.5 Hz, 0.35H), 6.84 (d, *J* = 12.5 Hz, 0.35H), 7.17 (s, 2H), 7.49 (d, *J* = 8.5 Hz, 0.7H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 0.7H), 7.96 (d, *J* = 8.5 Hz, 2H); **¹H NMR** (acetone-d₆) δ 3.12 (s, 1.05H), 3.14 (s, 3H), 3.25 (s, 1.05H), 3.27 (s, 1.05H), 3.29 (s, 3H), 3.45 (s, 3H), 3.93 (s, 1.05H), 4.16 (s, 3H), 5.89 (s, 0.35H), 6.63 (s, 1H), 6.75 (d, *J* = 12.0 Hz, 0.35H), 6.99 (d, *J* = 12.0 Hz, 0.35H), 7.44 (d, *J* = 16.0 Hz, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 0.7H), 7.88 (d, *J* = 8.5 Hz, 0.7H), 7.93 (s, 4H); **¹³C NMR** (CDCl₃): δ 27.8, 27.9, 31.7, 31.9, 32.4, 44.4, 44.6, 46.2, 91.5, 93.9, 118.4, 120.1, 127.2, 127.7, 128.1, 129.4, 130.3, 132.7, 135.5, 138.9, 139.6, 139.8, 141.6, 141.8, 151.2, 155.9; **FTIR** (nujol, cm⁻¹): 2222, 1683, 1642; **mp**: decomposition with color change starting from 210 °C (ethanol); Anal. (C₁₈H₁₉N₃O₄S) C, H, N.

Note: ¹H and ¹³C NMR spectra of compound 17r indicate the presence of two isomers cis and trans. The isomerization might be promoted by photochemical factor or acid agents (silica gel, CDCl₃, acetone).⁹



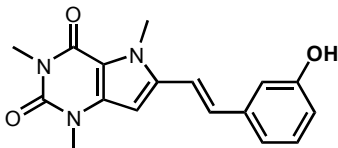
(E)-4-(2-(1,3,5-Trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl)vinyl)benzonitrile (17s): Obtained following the general procedure B. Yellow solid; (35 mg, 30%); **MS** (ESI): 321 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.32 (s, 0.6H), 3.41 (s, 0.6H), 3.42 (s, 3H), 3.49 (s, 3H), 3.91 (s, 0.6H), 4.13 (s, 3H), 5.68 (s, 0.2H), 6.24 (s, 1H), 6.55 (d, *J* = 12.5 Hz, 0.2H), 6.81 (d, *J* = 12.5 Hz, 0.2H), 7.12 (s, 2H), 7.38 (d, *J* = 8.5 Hz, 0.8H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H); **¹H NMR** (acetone-d₆) δ 3.26 (s, 0.6H), 3.27 (s, 0.6H), 3.29 (s, 3H), 3.44 (s, 3H), 3.92 (s, 0.6H), 4.16 (s, 3H), 5.90 (s, 0.2H), 6.62 (s, 1H), 6.75 (d, *J* = 12.0 Hz, 0.2H), 6.96 (d, *J* = 12.0 Hz, 0.2H), 7.41 (d, *J* = 16.0 Hz, 1H), 7.59 (d, *J* = 16.1 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 0.4H), 7.72 (d, *J* = 8.5 Hz, 0.4H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 2H); **¹³C NMR** (CDCl₃): δ 27.8, 31.6, 31.8, 91.5, 111.6, 111.8, 118.2, 126.9, 129.2, 130.5, 132.6, 135.6, 138.8, 140.6, 151.4, 155.8; **FTIR** (nujol, cm⁻¹): 2222, 1683, 1642; **mp**: decomposition with color change starting from 250 °C (ethanol); Anal. (C₁₈H₁₆N₄O₂) C, H, N.

Note: ¹H and ¹³C NMR spectra of compound 17r indicate the presence of two isomers cis and trans. The isomerization might be promoted by photochemical factor or acid agents (silica gel, CDCl₃, acetone).⁹



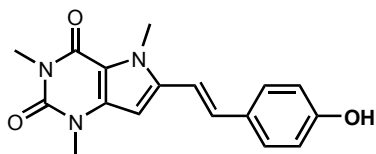
(E)-1,3,5-trimethyl-6-(2-(pyridin-4-yl)vinyl)-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17t): Obtained following the general procedure B. Yellow solid; (70 mg, 66%); **MS** (EI): 296 [M]⁺; **¹H NMR** (CDCl₃) δ 3.44 (s, 3H), 3.51 (s, 3H), 4.14 (s, 3H), 6.27 (s, 1H), 7.05 (d, *J* = 16.0 Hz, 1H), 7.23 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 6.0 Hz, 2H), 8.64 (d, *J* = 6.0 Hz, 2H); **¹³C NMR** (CDCl₃): δ 27.9, 31.7, 31.9, 91.7, 111.9, 119.0, 120.7, 129.8, 135.5, 138.6, 143.5, 150.4, 151.5, 155.9; **FTIR** (nujol, cm⁻¹): 1686, 1640; **mp**: 239-241 °C (acetone/ petrol ether); Anal. (C₁₆H₁₆N₄O₂) C, H, N.

General Procedure for the Synthesis of Styryl Derivatives (17u-w). Boron tribromide (5.4 mL, 1M in dichloromethane, 5.4 mmol) was added to a solution of the appropriate styryl derivatives (**17c**, **17h**, **17m**) (175 mg, 0.54 mmol). The mixture was stirred at 0°C for 1 hour, diluted with water (5 mL) and basified with saturated aqueous NaHCO₃ solution. The phases were separated and the aqueous phase was extracted with further CH₂Cl₂ (3 x 15 mL). The combined organic phases were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ ethyl acetate 1:1).

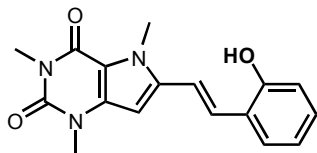


(E)-6-(3-Hydroxystyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17u): off-white solid; (151 mg, 90%); **MS** (ESI): 312 [M+H]⁺; **¹H NMR** (CD₃OD): δ 3.35 (s, 3H), 3.48 (s, 3H), 4.07 (s, 3H), 6.48 (s, 1H), 7.1-6.7 (m, 5H), 7.23 (d, *J* = 16.0 Hz, 2H); **¹³C NMR** (CD₃OD): δ 28.3, 31.2, 32.3, 91.3, 111.5, 112.8, 114.3, 115.9, 111.1, 130.6, 133.3, 136.6, 138.3, 140.5, 151.1,

155.2, 160.3; **FTIR** (nujol, cm^{-1}): 3287, 1668, 1631; ; **mp**: 262-264 °C (ethanol); Anal. ($\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$) C, H, N.

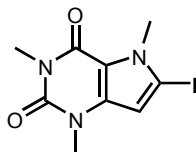


(E)-6-(4-Hydroxystyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17v): yellow solid; (134 mg, 80%); **MS** (ESI): 312 $[\text{M}+\text{H}]^+$; **^1H NMR** ($\text{DMSO}-d_6$) δ 3.21 (s, 3H), 3.34 (s, 3H), 3.99 (s, 3H), 6.50 (s, 1H), 6.79 (d, $J = 8.5$ Hz, 2H), 7.03 (d, $J = 16.0$ Hz, 1H), 7.20 (d, $J = 16.0$ Hz, 1H), 7.48 (d, $J = 8.5$ Hz, 2H), 9.66 (s, 1H); **^{13}C NMR** ($\text{DMSO}-d_6$): δ 27.8, 31.8, 31.9, 90.9, 110.0, 112.4, 116.1, 128.0, 128.8, 133.3, 136.0, 141.3, 151.2, 155.2, 158.4; **FTIR** (nujol, cm^{-1}): 3284, 1670, 1629; **mp**: 293-295 °C (ethanol); Anal. ($\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$) C, H, N.

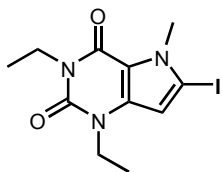


(E)-6-(2-Hydroxystyryl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (17w): yellow solid; (45 mg, 27%); **MS** (ESI): 312 $[\text{M}+\text{H}]^+$; **^1H NMR** (CDCl_3): δ 3.43 (s, 3H), 3.50 (s, 3H), 4.09 (s, 3H), 6.21 (s, 1H), 6.8-7.0 (m, 3H), 7.12 (d, $J = 16.0$ Hz, 1H), 7.40 (d, $J = 16.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H); **^{13}C NMR** (CDCl_3): δ 27.8, 32.3, 31.8, 90.2, 110.6, 112.7, 115.3, 115.5, 121.6, 128.7, 130.2, 133.6, 135.7, 140.6, 151.6, 156.3, 161.3; **FTIR** (nujol, cm^{-1}): 3283, 1671, 1628; **mp**: 246-248 °C (ethanol); Anal. ($\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$) C, H, N.

General Procedure for the Synthesis of 6-iodo-1,3,5-alkyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (15b,e). 6-Bromo-1,3,5-alkyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**15a,d**) (1 mmol), CuI (10.8 mg, 0.056 mmol), KI (243 mg, 1.46 mmol) were placed in a flame-dried Schlenk, which was evacuated and backfilled with nitrogen five times. *n*-Butanol (1 mL) and *N,N'*-dimethylethylenediamine (12.6 mL, 0.12 mmol) were added and the flask was evacuated and backfilled with nitrogen a further five times. The stirred mixture was then heated at 120 °C for 36 hours. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with dilute aqueous ammonia solution (20 mL, 5%) followed by water (3 x 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 , the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3).

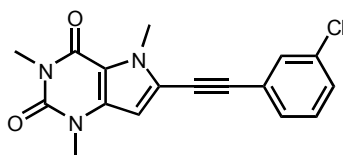


6-Iodo-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (15b): off-white solid (230 mg, 72%); **MS** (ESI): 320 $[\text{M}+\text{H}]^+$; **^1H NMR** (CDCl_3): δ 3.40 (s, 3H), 3.43 (s, 3H), 3.99 (s, 3H), 6.20 (s, 1H); **^{13}C NMR** (CDCl_3): δ 28.0, 32.4, 34.6, 91.6, 98.4, 111.7, 136.4, 151.3, 154.8; **FTIR** (nujol, cm^{-1}): 1701, 1647; **mp**: 211-213 °C (ethanol); Anal. ($\text{C}_9\text{H}_{10}\text{IN}_3\text{O}_2$) C, H, N.

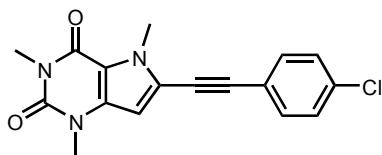


1,3-Diethyl-6-iodo-5-methyl-1H-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (15e): off-white solid (225 mg, 65%); **MS** (ESI): 348 [M+H]⁺; **¹H NMR** (CDCl₃): δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 3.92 (q, *J* = 7.0 Hz, 2H), 4.11 (s, 3H), 4.16 (q, *J* = 7.0 Hz, 2H), 6.35 (s, 1H); **¹³C NMR** (CDCl₃): δ 13.5, 13.8, 28.2, 32.0, 34.9, 90.9, 98.7, 111.3, 136.1, 151.6, 154.4; **FTIR** (nujol, cm⁻¹): 1705, 1641; **mp**: 219-221 °C (ethanol); Anal. (C₁₁H₁₄IN₃O₂) C, H, N.

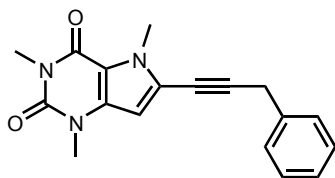
General Procedure for the Synthesis of Ethynyl Derivatives (18a-d). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**15a**) (108 mg, 0.4 mmol), Pd(PPh₃)₂Cl₂ (14 mg, 0.02 mmol), CuI (8 mg, 0.04 mmol), dioxane (1.6 mL) and TEA (84 μL, 0.6 mmol), under N₂. The opportune ethynyl derivative (0.44 mmol) was then added and the resulting black reaction mixture was stirred at 100 °C for 20 hours. The mixture was diluted with CH₂Cl₂ (3 mL), filtered through a pad of Celite and washed with CH₂Cl₂ (3 x 10 mL). The solvent were evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ ethyl acetate 8:2).



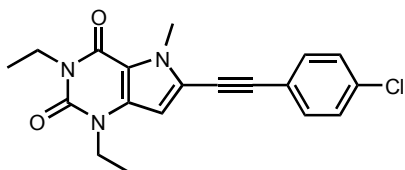
6-((3-Chlorophenyl)ethynyl)-1,3,5-trimethyl-1H-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (18a): yellowish solid; (71 mg, 54%); **MS** (ESI): 328-330 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.43 (s, 3H), 3.47 (s, 3H), 4.10 (s, 3H), 6.19 (s, 1H), 7.46-7.32 (m, 3H), 7.53 (s, 1H); **¹³C NMR** (CDCl₃): δ 27.9, 31.7, 33.5, 80.0, 95.6, 98.5, 111.6, 123.3, 123.5, 129.5, 129.6, 129.8, 131.3, 134.5, 134.6, 151.5, 155.5; **FTIR** (nujol, cm⁻¹): 2250, 1685, 1652; **mp**: 233-235 °C (acetone/ petrol ether); Anal. (C₁₇H₁₄ClN₃O₂) C, H, N.



6-((4-Chlorophenyl)ethynyl)-1,3,5-trimethyl-1H-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (18b): yellowish solid; (81 mg, 62%); **MS** (ESI): 328-330 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.43 (s, 3H), 3.46 (s, 3H), 4.09 (s, 3H), 6.18 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H); **¹³C NMR** (CDCl₃): δ 28.3, 32.1, 33.9, 80.2, 96.3, 98.6, 111.8, 120.6, 123.9, 129.3, 133.1, 135.0, 135.8, 151.8, 155.9; **FTIR** (nujol, cm⁻¹): 2247, 1690, 1647; **mp**: 196-198 °C (acetone/ petrol ether); Anal. (C₁₇H₁₄ClN₃O₂) C, H, N.

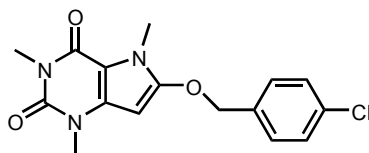


1,3,5-Trimethyl-6-(3-phenylprop-1-ynyl)-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (18c): white solid; (52 mg, 42%); **MS** (ESI): 308 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.41 (s, 3H), 3.44 (s, 3H), 3.92 (s, 2H), 4.03 (s, 3H), 6.07 (s, 1H), 7.40-7.31 (m, 5H); **¹³C NMR** (CDCl₃): δ 25.2, 28.7, 31.9, 33.7, 86.9, 88.2, 111.3, 121.3, 123.6, 129.1, 132.4, 133.4, 135.1, 151.6, 154.6; **FTIR** (nujol, cm⁻¹): 2223, 1688, 1650; **mp**: 143-145 °C (ethanol); Anal. (C₁₈H₁₇N₃O₂) C, H, N.

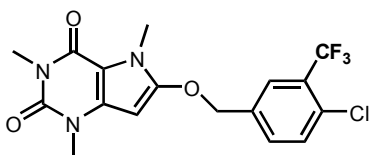


6-((4-Chlorophenyl)ethynyl)-1,3-diethyl-5-methyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (18d): white solid; (64 mg, 45%); **MS** (EI): 355-357 [M]⁺; **¹H NMR** (CDCl₃) δ 1.27 (t, *J* = 7 Hz, 3H), 1.33 (t, *J* = 7 Hz, 3H), 3.97 (q, *J* = 7 Hz, 2H), 4.10 (s, 3H), 4.11 (q, *J* = 7 Hz, 2H), 6.19 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H); **¹³C NMR** (CDCl₃): δ 12.8, 13.4, 33.5, 36.3, 40.3, 79.9, 95.8, 98.1, 111.8, 120.3, 123.4, 129.0, 132.7, 133.7, 135.3, 150.5, 155.3; **FTIR** (nujol, cm⁻¹): 2208, 1685, 1652; **mp**: 144-146 °C (ethanol); Anal. (C₁₉H₁₈ClN₃O₂) C, H, N.

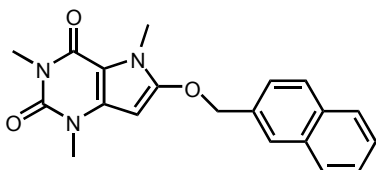
General Procedure for the Synthesis of Ethynyl Derivatives (19a-d). A flame-dried Schlenk tube was charged with the appropriate 6-iodo-1,3,5-trialkyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**15b,e**) (0.3 mmol), CuI (6 mg, 0.03 mmol), Cs₂CO₃ (195 mg, 0.6 mmol), phenantroline (12 mg, 0.06 mmol), the appropriate alcohol (126 mg, 0.6 mmol) and toluene over molecular sieves (0.2 mL), under N₂. The mixture was stirred at 100 °C for 5 hours. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/ MeOH 98:2).



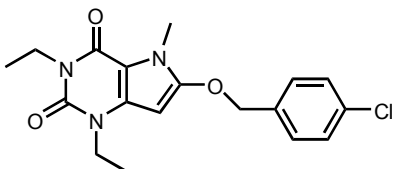
6-(4-Chlorobenzoyloxy)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (19a): white solid; (46 mg, 41%); **MS** (ESI): 334-336 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.40 (s, 3H), 3.42 (s, 3H), 3.80 (s, 3H), 5.12 (s, 2H), 5.23 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H); **¹³C NMR** (CDCl₃): δ 27.6, 29.8, 31.7, 72.2, 74.2, 128.9, 129.1, 133.5, 134.7, 135.5, 145.9, 151.7, 152.7, 155.3; **FTIR** (nujol, cm⁻¹): 2208, 1685, 1652; **mp**: 183-18 °C (ethanol); Anal. (C₁₆H₁₆ClN₃O₃) C, H, N.



6-(4-Chloro-3-(trifluoromethyl)benzyloxy)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (19b): white solid; (52 mg, 38%); **MS** (ESI): 402-404 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.40 (s, 3H), 3.43 (s, 3H), 3.83 (s, 3H), 5.17 (s, 2H), 5.24 (s, 1H), 7.62-7.53 (m, 2H), 7.75 (s, 1H); **¹³C NMR** (CDCl₃): δ 27.6, 29.9, 31.7, 71.4, 74.1, 126.6, 127.7, 129.1 (*J* = 27 Hz), 129.1 (*J* = 258 Hz), 130.1, 131.7, 132.0, 134.1, 135.5, 151.7, 152.2, 155.3; **FTIR** (nujol, cm⁻¹): 1684, 1648; **mp**: 184-186 °C (ethanol); Anal. (C₁₇H₁₅ClF₃N₃O₃) C, H, N.

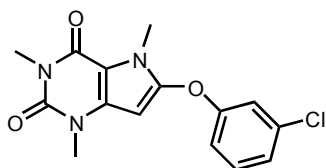


1,3,5-Trimethyl-6-(naphthalen-2-ylmethoxy)-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (19c): white solid; (51 mg, 43%); **MS** (ESI): 350 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.41 (s, 3H), 3.43 (s, 3H), 3.84 (s, 3H), 5.30 (s, 1H), 5.33 (s, 2H), 7.59-7.751 (m, 3H), 7.94-7.87 (m, 4H); **¹³C NMR** (CDCl₃): δ 27.6, 29.8, 31.7, 73.2, 74.3, 103.2, 124.9, 126.6, 126.8, 127.8, 128.0, 128.8, 132.4, 133.1, 133.3, 135.6, 151.8, 153.0, 155.3; **FTIR** (nujol, cm⁻¹): 1687, 1647; **mp**: 172-174 °C (acetone/ petrol ether); Anal. (C₂₀H₁₉N₃O₃) C, H, N.

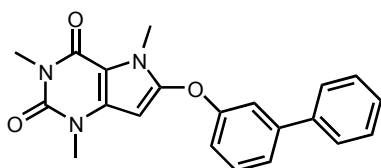


6-(4-Chlorobenzoyloxy)-1,3-diethyl-5-methyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (19d): off-white solid; (49 mg, 40%); **MS** (EI): 361-363 [M]⁺; **¹H NMR** (CDCl₃) δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 3.80 (s, 3H), 3.92 (q, *J* = 7.0 Hz, 2H), 4.07 (q, *J* = 7.0 Hz, 2H), 5.12 (s, 2H), 5.23 (s, 1H), 7.43-7.34 (m, 4H); **¹³C NMR** (CDCl₃): δ 12.9, 13.5, 29.8, 36.0, 40.2, 72.1, 73.9, 103.6, 128.9, 129.0, 133.5, 134.6, 134.7, 150.7, 152.7, 155.0; **FTIR** (nujol, cm⁻¹): 1686, 1641; **mp**: 137-139 °C (acetone/ petrol ether); Anal. (C₁₈H₂₀ClN₃O₃) C, H, N.

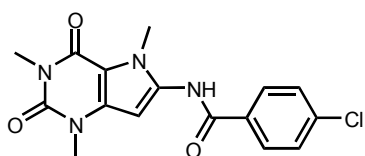
General Procedure for the Synthesis of Phenol Derivatives (20a,b). A flame-dried Schlenk tube was charged with 6-iodo-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**15b**) (96 mg, 0.3 mmol), the appropriate phenol (58 mg, 0.45 mmol), Cs₂CO₃ (244 mg, 0.75 mmol), FeCl₃ (5 mg, 0.03 mmol), 2,2,6,6-Tetramethyl-3,5-heptanedione (49 μL, 0.24 mmol) and dry DMF (0.4 mL), under N₂. The mixture was stirred at 130 °C for 72 hours. The mixture was diluted with CH₂Cl₂ (3 mL), filtered through a pad of Celite and washed with CH₂Cl₂ (3 x 10 mL). To the was added water (15 mL). The phases were separated and the aqueous phase was extracted with further CH₂Cl₂ (15 mL). The combined organic phases were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash-chromatography (CH₂Cl₂/ MeOH 99:1).



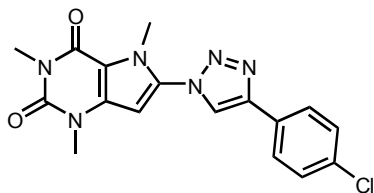
6-(3-Chlorophenoxy)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (20a): white solid; (41 mg, 43%); **MS** (ESI): 320-322 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.40 (s, 3H), 3.42 (s, 3H), 3.88 (s, 3H), 5.28 (s, 1H), 7.39-6.99 (m, 4H); **¹³C NMR** (CDCl₃): δ 27.7, 30.3, 31.8, 79.2, 104.2, 116.3, 118.7, 125.3, 130.9, 134.9, 135.5, 149.3, 151.7, 155.6, 156.2; **FTIR** (nujol, cm⁻¹): 1686, 1657; **mp**: 189-191 °C (acetone/ petrol ether); Anal. (C₁₅H₁₄ClN₃O₃) C, H, N.



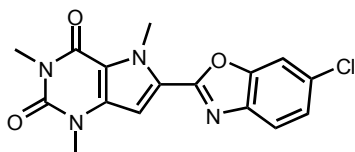
6-(Biphenyl-3-yloxy)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (20b): white solid; (40 mg, 37%); **MS** (ESI): 362 [M+H]⁺; **¹H NMR** (CDCl₃) δ 3.37 (s, 3H), 3.43 (s, 3H), 3.93 (s, 3H), 5.24 (s, 1H), 7.11-7.13 (m, 1H), 7.36-7.61 (m, 8H); **¹³C NMR** (CDCl₃): δ 27.7, 30.3, 31.8, 103.9, 117.1, 117.2, 123.9, 127.1, 128.0, 129.0, 130.4, 135.1, 139.8, 143.6, 150.5, 151.7, 155.5, 156.0; **FTIR** (nujol, cm⁻¹): 1700, 1647; **mp**: 134-136 °C (acetone/ petrol ether); Anal. (C₂₁H₁₉N₃O₃) C, H, N.



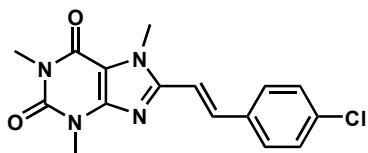
4-Chloro-N-(1,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl)benzamide (21). A flame-dried Schlenk tube was charged with 6-iodo-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**15b**) (110 mg, 0.34 mmol), CuI (0.6 mg, 0.0034 mmol), racemic trans-*N,N'*-dimethyl-1,2-cyclohexanediamine (5 μL, 0.034 mmol), K₂CO₃ (52 mg, 0.37 mmol), 4-chlorobenzamide (53 mg, 0.34 mmol) and dry dioxane (0.35 mL), under N₂. The mixture was stirred at 100 °C for 20 hours. The mixture was diluted with CH₂Cl₂ (3 mL), filtered through a pad of Celite and washed with CH₂Cl₂ (3 x 10 mL). The solvent were evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH₂Cl₂/ acetone 96:4) to give 41 mg (35%) of desired product (**21**) as a off-white solid. **MS** (ESI): 347-349 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.42 (s, 3H), 3.47 (s, 3H), 3.97 (s, 3H), 6.24 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 8.33 (br s, 1H); **¹³C NMR** (CDCl₃): δ 22.7, 29.3, 32.0, 88.4, 128.8, 128.9, 129.3, 130.4, 131.6, 138.4, 151.7, 152.7, 155.3, 168.2; **FTIR** (nujol, cm⁻¹): 1682, 1652, 1643; **mp**: 268-270 °C (ethanol); Anal. (C₁₆H₁₅ClN₄O₃) C, H, N.



6-(4-(4-Chlorophenyl)-1H-1,2,3-triazol-1-yl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (22). 6-iodo-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**15b**) (110 mg, 0.34 mmol), 4-chlorophenylacetylene (46 mg, 0.34 mmol), L-proline (8 mg, 0.068 mmol), Na₂CO₃ (7.2 mg, 0.068 mmol), sodium azide (26 mg, 0.41 mmol), sodium ascorbate (7 mg, 0.034 mmol), CuSO₄·5H₂O (4 mg, 0.017 mmol) and DMSO/H₂O 9:1 (0.3 mL) were placed in a flame-dried Schlenk, which was evacuated and backfilled with nitrogen five times. The mixture was stirred at 60 °C for 18 hours. The mixture was filtered and washed with dilute aqueous ammonia solution (5%). The solid obtained was purified by flash chromatography (cyclohexane/ ethyl acetate 1:1) to give 49 mg (39%) of desired product (**22**) as a off-white solid. **MS** (ESI): 371-373 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.46 (s, 3H), 3.51 (s, 3H), 3.99 (s, 3H), 6.18 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 8.03 (s, 1H); **¹³C NMR** (CDCl₃): δ 28.1, 31.9, 32.6, 90.7, 110.0, 121.7, 127.2, 127.8, 129.3, 131.9, 134.1, 134.8, 147.1, 151.3, 156.0; **FTIR** (nujol, cm⁻¹): 1697, 1650; **mp**: 268-270 °C (acetone/ petrol ether); Anal. (C₁₇H₁₅ClN₆O₂) C, H, N.



6-(6-Chlorobenzo[d]oxazol-2-yl)-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (23). 6-Iodo-1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**15b**) (34 mg, 0.11 mmol), 6-chlorobenzooxazole (14 mg, 0.09 mmol), Cs₂CO₃ (36 mg, 0.11 mmol), CuBr (3 mg, 0.02 mmol), Pd(OAc)₂ (1 mg, 0.0044 mmol), tri tert-butylphosphine (2 μl, 0.009 mmol) and dry DMF (0.8 mL) were placed in a flame-dried Schlenk, which was evacuated and backfilled with nitrogen five times. The reaction mixture was stirred at 150 °C for 2 hours. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ ethyl acetate 1:1) to give 15 mg (39%) of desired product (**23**) as an off-white solid. **MS** (ESI): 345-347 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.46 (s, 3H), 3.55 (s, 3H), 4.57 (s, 3H), 6.77 (s, 1H), 7.39 (dd, *J*₁ = 8.0 and *J*₂ = 2.0 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H); **¹³C NMR** (CDCl₃): δ 28.4, 31.7, 32.8, 98.3, 109.8, 111.5, 115.8, 120.1, 125.8, 126.3, 134.9, 140.7, 150.6, 151.3, 155.4, 162.5; **FTIR** (nujol, cm⁻¹): 1695, 1648; **mp**: decomposition with color change starting from 250 °C (acetone/ petrol ether); Anal. (C₁₆H₁₃ClN₄O₃) C, H, N.



(E)-8-(4-Chlorostyryl)-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (25). A flame-dried Schlenk tube was charged with 1,3,5-trimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**24**) (100 mg, 0.5 mmol), Cu(OAc)₂ (300 mg, 1.5 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), Ag₂CO₃ (414 mg, 1.5 mmol), 4-chlorostyrene (125 μl, 1 mmol) and pivalic acid (1.2 mL), under N₂. The mixture was stirred at 90 °C for 72 hours. The mixture was diluted with CH₂Cl₂ (3 mL), washed with 1 N NaHCO₃ solution (15 mL) and saturated solution of NH₄Cl (15 mL). The organic phase were dried

over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ ethyl acetate 7:3) to give 100 mg (60%) of desired product (**21**) as a off-white solid. **MS** (ESI): 331-333 [M+H]⁺; **¹H NMR** (CDCl₃): δ 3.42 (s, 3H), 3.63 (s, 3H), 4.08 (s, 3H), 6.90 (d, *J* = 16.0 Hz, 1H), 7.27-7.55 (m, 4H), 7.77 (d, *J* = 16.0 Hz, 1H); **¹³C NMR** (CDCl₃): δ 28.1, 30.1, 31.7, 107.9, 111.6, 128.4, 129.4, 139.9, 135.3, 136.8, 148.3, 149.8, 151.6, 155.5; **FTIR** (nujol, cm⁻¹): 1699, 1666; **mp**: 268-270 °C (ethanol); Anal. (C₁₆H₁₅ClN₄O₂) C, H, N.

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Table S1. Elemental Analysis.

Compd.	Formula	Calculated	Found
2a	C ₁₄ H ₁₁ N ₃ (221.10)	C, 76.00; H, 5.01; N, 18.99	C, 75.93; H, 5.07; N, 18.86
2b	C ₁₅ H ₁₃ N ₃ (235.11)	C, 76.57; H, 5.57; N, 17.86	C, 76.66; H, 5.51; N, 17.95
3a	C ₁₄ H ₁₁ N ₃ O (237.09)	C, 70.87; H, 4.67; N, 6.74	C, 70.81; H, 4.62; N, 6.86
3b	C ₁₄ H ₁₁ N ₃ O (237.09)	C, 70.87; H, 4.67; N, 6.74	C, 70.75; H, 4.71; N, 6.63
4a	C ₁₆ H ₁₅ N ₃ O (265.12)	C, 72.43; H, 5.70; N, 15.84	C, 72.55; H, 5.60; N, 15.71
4b	C ₁₆ H ₁₅ N ₃ O (265.12)	C, 72.43; H, 5.70; N, 15.84	C, 72.31; H, 5.66; N, 15.71
6	C ₁₆ H ₁₇ N ₃ O ₃ (299.13)	C, 64.20; H, 5.72; N, 14.04	C, 64.12; H, 5.66; N, 13.95
8a	C ₁₇ H ₁₅ N ₃ O ₂ (293.12)	C, 69.61; H, 5.15; N, 14.33	C, 69.74; H, 5.09; N, 14.25
8b	C ₁₇ H ₁₄ ClN ₃ O ₂ (327.08)	C, 62.30; H, 4.31; N, 12.82	C, 62.46; H, 4.39; N, 12.73
9a	C ₁₇ H ₁₅ NO ₂ (265.11)	C, 76.96; H, 5.70; N, 5.28	C, 77.06; H, 5.66; N, 5.37
9b	C ₁₇ H ₁₄ ClNO ₂ (299.07)	C, 68.12; H, 4.71; N, 4.67	C, 68.01; H, 4.64; N, 4.78
10a	C ₂₃ H ₁₉ N ₃ O ₂ (369.15)	C, 74.78; H, 5.18; N, 11.37	C, 74.99; H, 5.14; N, 11.48
10b	C ₂₃ H ₁₈ ClN ₃ O ₂ (403.11)	C, 68.40; H, 4.49; N, 10.40	C, 68.58; H, 4.38; N, 10.49
10c	C ₂₄ H ₂₁ N ₃ O ₃ (399.16)	C, 72.16; H, 5.30; N, 10.52	C, 72.32; H, 5.21; N, 10.63
11a	C ₁₇ H ₁₆ N ₂ O ₂ (280.12)	C, 72.84; H, 5.75; N, 9.99	C, 72.71; H, 5.81; N, 10.06
11b	C ₁₇ H ₁₅ ClN ₂ O ₂ (314.08)	C, 64.87; H, 4.80; N, 8.90	C, 64.99; H, 4.88; N, 8.82
11c	C ₁₈ H ₁₈ N ₂ O ₃ (310.13)	C, 69.66; H, 5.85; N, 9.03	C, 69.79; H, 5.92; N, 9.11
12a	C ₂₀ H ₂₀ N ₂ O ₄ (352.14)	C, 68.17; H, 5.72; N, 7.95	C, 68.06; H, 5.66; N, 7.83
12b	C ₂₀ H ₁₉ ClN ₂ O ₄ (386.10)	C, 62.10; H, 4.95; N, 7.24	C, 62.38; H, 5.01; N, 7.35
12c	C ₂₁ H ₂₂ N ₂ O ₅ (382.15)	C, 65.96; H, 5.80; N, 7.33	C, 65.82; H, 5.85; N, 7.26
13a	C ₁₇ H ₁₃ N ₃ O ₂ (291.10)	C, 70.09; H, 4.50; N, 14.42	C, 69.96; H, 4.58; N, 14.52
13b	C ₁₇ H ₁₂ ClN ₃ O ₂ (325.06)	C, 62.68; H, 3.71; N, 12.90	C, 62.79; H, 3.75; N, 13.08
13c	C ₁₈ H ₁₅ N ₃ O ₃ (321.11)	C, 67.28; H, 4.71; N, 13.08	C, 67.16; H, 4.66; N, 13.21
14a	C ₁₉ H ₁₇ N ₃ O ₂ (319.13)	C, 71.46; H, 5.37; N, 13.16	C, 71.32; H, 5.48; N, 13.25
14b	C ₁₉ H ₁₆ ClN ₃ O ₂ (353.09)	C, 64.50; H, 4.56; N, 11.88	C, 64.62; H, 4.67; N, 11.99
14c	C ₂₀ H ₁₉ N ₃ O ₃ (349.14)	C, 68.75; H, 5.48; N, 12.03	C, 68.61; H, 5.44; N, 12.12
15b	C ₉ H ₁₀ IN ₃ O ₂ (318.98)	C, 33.88; H, 3.16; N, 13.17	C, 33.76; H, 3.08; N, 13.25
15e	C ₁₁ H ₁₄ IN ₃ O ₂ (347.01)	C, 38.06; H, 4.06; N, 12.10	C, 38.23; H, 4.13; N, 12.14
17a	C ₁₇ H ₁₆ ClN ₃ O ₂ (329.09)	C, 61.91; H, 4.89; N, 12.74	C, 62.08; H, 4.96; N, 12.68
17b	C ₁₇ H ₁₇ N ₃ O ₂ (295.13)	C, 69.14; H, 5.80; N, 14.23	C, 69.02; H, 5.89; N, 14.31
17c	C ₁₈ H ₁₉ N ₃ O ₃ (325.14)	C, 66.45; H, 5.89; N, 12.91	C, 66.58; H, 5.96; N, 13.02
17d	C ₁₈ H ₁₆ F ₃ N ₃ O ₂ (363.12)	C, 59.50; H, 4.44; N, 11.57	C, 59.42; H, 4.51; N, 11.45
17e	C ₁₇ H ₁₆ FN ₃ O ₂ (313.12)	C, 65.17; H, 5.15; N, 13.41	C, 65.03; H, 5.19; N, 13.56
17f	C ₁₇ H ₁₆ ClN ₃ O ₂ (329.09)	C, 61.91; H, 4.89; N, 12.74	C, 61.84; H, 4.88; N, 12.47
17g	C ₁₈ H ₁₆ F ₃ N ₃ O ₂ (363.12)	C, 59.50; H, 4.44; N, 11.57	C, 59.42; H, 4.53; N, 11.69
17h	C ₁₈ H ₁₉ N ₃ O ₃ (325.14)	C, 66.45; H, 5.89; N, 12.91	C, 66.23; H, 5.79; N, 12.85
17i	C ₂₀ H ₂₃ N ₃ O ₃ (353.17)	C, 67.97; H, 6.56; N, 11.89	C, 68.06; H, 6.48; N, 11.97
17j	C ₁₇ H ₁₆ BrN ₃ O ₂ (373.04)	C, 54.56; H, 4.31; N, 11.23	C, 54.69; H, 4.24; N, 11.15
17k	C ₁₇ H ₁₅ Cl ₂ N ₃ O ₂ (363.05)	C, 56.06; H, 4.15; N, 11.54	C, 56.08; H, 4.12; N, 11.48
17l	C ₁₈ H ₁₇ N ₃ O ₄ (339.12)	C, 63.71; H, 5.05; N, 12.38	C, 63.86; H, 5.16; N, 12.51
17m	C ₁₈ H ₁₉ N ₃ O ₃ (325.14)	C, 66.45; H, 5.89; N, 12.91	C, 66.57; H, 5.96; N, 13.03
17n	C ₁₆ H ₁₇ N ₅ O ₂ (311.14)	C, 61.72; H, 5.50; N, 22.49	C, 61.86; H, 5.41; N, 22.38
17o	C ₁₉ H ₁₉ N ₃ O ₃ (337.14)	C, 67.64; H, 5.68; N, 12.46	C, 67.48; H, 5.76; N, 12.32
17p	C ₁₈ H ₁₆ N ₄ O ₂ (320.13)	C, 67.49; H, 5.03; N, 17.49	C, 67.32; H, 5.09; N, 17.38
17q	C ₁₉ H ₁₉ N ₃ O ₃ (337.14)	C, 67.64; H, 5.68; N, 12.46	C, 67.79; H, 5.76; N, 12.57
17r	C ₁₈ H ₁₉ N ₃ O ₄ S (373.11)	C, 57.89; H, 5.13; N, 11.25	C, 57.73; H, 5.05; N, 11.18

17s	C ₁₈ H ₁₆ N ₄ O ₂ (320.13)	C, 67.49; H, 5.03; N, 17.49	C, 67.63; H, 5.12; N, 17.62
17t	C ₁₆ H ₁₆ N ₄ O ₂ (296.13)	C, 64.85; H, 5.44; N, 18.91	C, 64.98; H, 5.52; N, 19.03
17u	C ₁₇ H ₁₇ N ₃ O ₃ (311.13)	C, 65.58; H, 5.50; N, 13.50	C, 65.72; H, 5.44; N, 13.62
17v	C ₁₇ H ₁₇ N ₃ O ₃ (311.13)	C, 65.58; H, 5.50; N, 13.50	C, 65.67; H, 5.41; N, 13.41
17w	C ₁₇ H ₁₇ N ₃ O ₃ (311.13)	C, 65.58; H, 5.50; N, 13.50	C, 65.66; H, 5.57; N, 13.44
17x	C ₁₈ H ₁₈ ClN ₃ O ₂ (343.11)	C, 62.88; H, 5.28; N, 12.22	C, 62.75; H, 5.37; N, 12.31
17y	C ₁₉ H ₂₀ ClN ₃ O ₂ (357.12)	C, 63.77; H, 5.63; N, 11.74	C, 63.82; H, 5.56; N, 11.65
18a	C ₁₇ H ₁₄ ClN ₃ O ₂ (327.08)	C, 62.30; H, 4.31; N, 12.82	C, 62.42; H, 4.39; N, 12.95
18b	C ₁₇ H ₁₄ ClN ₃ O ₂ (327.08)	C, 62.30; H, 4.31; N, 12.82	C, 62.23; H, 4.24; N, 12.95
18c	C ₁₈ H ₁₇ N ₃ O ₂ (307.13)	C, 70.34; H, 5.58; N, 13.67	C, 70.48; H, 5.63; N, 13.75
19a	C ₁₆ H ₁₆ ClN ₃ O ₃ (333.09)	C, 57.58; H, 4.83; N, 12.59	C, 57.72; H, 4.90; N, 12.74
19b	C ₁₇ H ₁₅ ClF ₃ N ₃ O ₃ (401.08)	C, 50.82; H, 3.76; N, 10.46	C, 50.95; H, 3.76; N, 10.46
19c	C ₂₀ H ₁₉ N ₃ O ₃ (349.14)	C, 68.75; H, 5.48; N, 12.03	C, 68.69; H, 5.45; N, 12.13
19d	C ₁₈ H ₂₀ ClN ₃ O ₃ (361.12)	C, 59.75; H, 5.57; N, 11.61	C, 59.64; H, 5.62; N, 11.67
20a	C ₁₅ H ₁₄ ClN ₃ O ₃ (319.07)	C, 56.35; H, 4.41; N, 13.14	C, 56.22; H, 4.36; N, 13.06
20b	C ₂₁ H ₁₉ N ₃ O ₃ (361.14)	C, 69.79; H, 5.30; N, 11.63	C, 69.66; H, 5.22; N, 11.48
21	C ₁₆ H ₁₅ ClN ₄ O ₃ (346.08)	C, 55.42; H, 4.36; N, 16.16	C, 55.31; H, 4.41; N, 16.27
22	C ₁₇ H ₁₅ ClN ₆ O ₂ (370.09)	C, 55.07; H, 4.08; N, 22.66	C, 54.93; H, 4.16; N, 22.74
23	C ₁₆ H ₁₃ ClN ₄ O ₃ (344.07)	C, 55.74; H, 3.80; N, 16.25	C, 55.65; H, 3.83; N, 16.29
25	C ₁₆ H ₁₅ ClN ₄ O ₂ (330.09)	C, 58.10; H, 4.57; N, 16.94	C, 58.23; H, 4.51; N, 17.06

Table S2. Binding profile^a for compound 17f at the concentration of 10 μ M.

Receptor	% Inhibition of control specific binding
A ₁ (h) (antagonist radioligand)	59
A _{2A} (h) (agonist radioligand)	91
A ₃ (h) (agonist radioligand)	60
α_1 (non-selective) (antagonist radioligand)	5
α_2 (non-selective) (antagonist radioligand)	3
β_1 (h) (agonist radioligand)	4
β_2 (h) (agonist radioligand)	11
AT ₁ (h) (antagonist radioligand)	-2
BZD (central) (agonist radioligand)	23
B ₂ (h) (agonist radioligand)	1
CB ₁ (h) (agonist radioligand)	9
CCK ₁ (CCK _A) (h) (agonist radioligand)	6
D ₁ (h) (antagonist radioligand)	31
D _{2s} (h) (antagonist radioligand)	2
ET _A (h) (agonist radioligand)	-3
GABA (non-selective) (agonist radioligand)	8
GAL ₂ (h) (agonist radioligand)	-11
CXCR2 (IL-8B) (h) (agonist radioligand)	-10
CCR1 (h) (agonist radioligand)	-11
H ₁ (h) (antagonist radioligand)	12
H ₂ (h) (antagonist radioligand)	-13

MC ₄ (h) (agonist radioligand)	16
MT ₁ (ML _{1A}) (h) (agonist radioligand)	45
M ₁ (h) (antagonist radioligand)	29
M ₂ (h) (antagonist radioligand)	23
M ₃ (h) (antagonist radioligand)	0
NK ₂ (h) (agonist radioligand)	75
NK ₃ (h) (agonist radioligand)	24
Y ₁ (h) (agonist radioligand)	-11
Y ₂ (h) (agonist radioligand)	-13
NTS ₁ (NT ₁) (<i>h</i>) (agonist radioligand)	-7
δ ₂ (DOP) (h) (agonist radioligand)	17
κ (KOP) (agonist radioligand)	10
μ (MOP) (h) (agonist radioligand)	29
NOP (ORL1) (h) (agonist radioligand)	5
TP (h) (TXA ₂ /PGH ₂) (antagonist radioligand)	18
5-HT _{1A} (h) (agonist radioligand)	19
5-HT _{1B} (antagonist radioligand)	-23
5-HT _{2A} (h) (antagonist radioligand)	42
5-HT _{2B} (h) (agonist radioligand)	72
5-HT ₃ (h) (antagonist radioligand)	-1
5-HT _{5A} (h) (agonist radioligand)	28
5-HT ₆ (h) (agonist radioligand)	27
5-HT ₇ (h) (agonist radioligand)	7
sst (non-selective) (agonist radioligand)	-4
VPAC ₁ (VIP ₁) (h) (agonist radioligand)	-4
V _{1a} (h) (agonist radioligand)	4
K _V channel (antagonist radioligand)	-8
SK _{Ca} channel (antagonist radioligand)	13
Na ⁺ channel (site 2) (antagonist radioligand)	31
Cl ⁻ channel (GABA-gated) (antagonist radioligand)	45
norepinephrine transporter (h) (antagonist radioligand)	57
dopamine transporter (h) (antagonist radioligand)	47
5-HT transporter (h) (antagonist radioligand)	20

^a For experimental details, see <http://www.cerep.fr/cerep/users/pages/catalog/assay/catalog.asp>.