

Supporting Information.

**High-Efficacy 5-HT_{1A} Agonists for Antidepressant Treatment: a Renew
Opportunity**

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and Bernard Vacher*

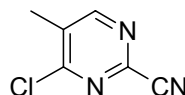
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1. Synthesis of diazine-methanamines.

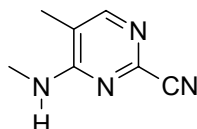
Pyrimidinemethanamines of the type XII. (Scheme 1)

2-Cyano-4-chloro-5-methylpyrimidine (II).



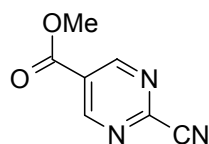
To a solution of 2,4-dichloro-5-methylpyrimidine **I** (9.91 g, 60.8 mmol) in diethyl ether (65 mL) was added NaCN (7.44 g, 152 mmol) in aqueous trimethylamine (65 mL). The mixture was stirred for 30 min at room temperature then filtered on Celite and the precipitate washed with water and diethyl ether. The filtrate was decanted, the organic layer washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate, 92:8) to provide **II** accompanied with 2,4-dicyanopyrimidine. This mixture was used as such in the next step.

2-Cyano-4-methylamino-5-methylpyrimidine (IIIa).



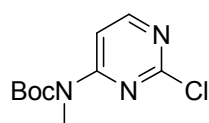
The mixture from step i was dissolved in ethanol (5 mL), aqueous methylamine (15 mL, 194 mmol) and stirred at room temperature for 20 min. The reaction mixture was extracted with ethyl acetate, the combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The solid obtained was washed with petroleum ether then dried in air to afford **IIIa** (R₁ = CH₃ and R = NHCH₃) as a gray solid (0.43 g, 5% over two steps); ¹H NMR (CDCl₃): δ 2.08 (s, 3H), 3.08 (d, *J* = 4.8 Hz, 3H), 4.85 (s, 1H), 7.98 (s, 1H).

2-Cyano-5-methoxycarbonylpyrimidine (IIIb).



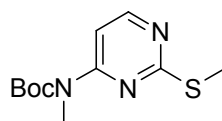
Compound **IV** (5.9 g, 27.3 mmol) was dissolved in DMSO (30 mL) and cooled to 15 °C. NaCN (1.4 g, 28.6 mmol) was added in one portion and the mixture stirred for 30 min at room temperature then poured into ice-cold saturated aqueous solution of NaHCO₃ and extracted with diethyl ether. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give a brown, oily residue. Purification by flash column chromatography (silica gel, heptane/ethyl acetate, 70:30) gave **IIIb** (R₁ = CO₂CH₃ and R = H) as a colorless oil which crystallized on standing (1.8 g, 40%). ¹H NMR (CDCl₃): δ 4.04 (s, 3H), 9.37 (s, 2H).

2-Chloro-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine.



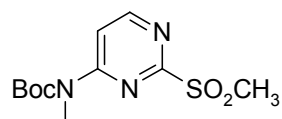
To a solution of compound **V** (4.5 g, 31.3 mmol) in THF (100 mL) and DMAP (3.82 g, 31.3 mmol) was added Boc-anhydride portion-wise (13.7 g, 62.68 mmol). The reaction mixture was stirred for 1 h at room temperature then concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 90:10) to give the 2-chloro-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine intermediate as a colorless oil (5.3 g, 69.7%); ¹H NMR (CDCl₃): δ 1.56 (s, 9H), 3.43 (s, 3H), 8.00 (d, *J* = 6.0 Hz, 1H), 8.35 (d, *J* = 6.0 Hz, 1H).

2-Methylthio-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine.



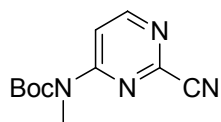
The 2-chloro-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine obtained in step iv (5.3 g, 21.7 mmol) was dissolved in DMF (30 mL) and NaSCH₃ was added in one portion under inert atmosphere. The mixture was stirred for 24 h at room temperature then poured into water and extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 90:10) to afford the 2-methylthio-pyrimidine derivative as a yellow oil (4.63 g, 83%); ¹H NMR (CDCl₃): δ 1.56 (s, 9H), 2.54 (s, 3H), 3.43 (s, 3H), 7.65 (d, *J* = 6.0 Hz, 1H), 8.29 (d, *J* = 6.0 Hz, 1H).

2-Methylsulfonyl-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine.



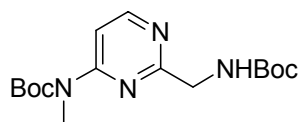
To a solution of the 2-methylthio-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine obtained in step v (4.6 g, 18.1 mmol) in dichloromethane (80 mL) maintained at 0 °C under inert atmosphere was added portion-wise mCPBA (9.4 g, 54.5 mmol). The reaction mixture was stirred overnight while the temperature allowed to rise to room temperature. The mixture was poured into aqueous NaHCO₃ (10%), decanted and the aqueous extracted with CH₂Cl₂ the organic layer washed with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The oil obtained was taken up in di-isopropyl ether and the precipitate formed was filtered out, washed with cyclohexane and dried at 50 °C to give the 2-methylsulfonyl-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine as a white powder (3.71 g, 71%); ¹H NMR (CDCl₃): δ 1.58 (s, 9H), 3.33 (s, 3H), 3.51 (s, 3H), 8.27 (d, *J* = 6.0 Hz, 1H), 8.59 (d, *J* = 6.0 Hz, 1H).

Preparation of 2-cyano-4-(*tert*-butoxycarbonyl-methylamino)-pyrimidine (IIIc).



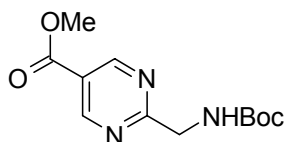
Applying the same conditions as those used to convert **IV** into **IIIb** provided **IIIc** ($R_1 = H$ and $R = NBocCH_3$). Purification by flash column chromatography (silica gel, cyclohexane/ethyl acetate, 70:30) furnished **IIIc** as an off-white solid (2.15 g, 71%); 1H NMR ($CDCl_3$): δ 1.53 (s, 9H), 3.36 (s, 3H), 8.19 (d, $J = 6.1$ Hz, 1H), 8.72 (d, $J = 6.1$ Hz, 1H).

2-(tert-Butoxycarbonyl-aminomethyl)-4-(tert-butoxycarbonyl-methylamino)-pyrimidine (VIc).



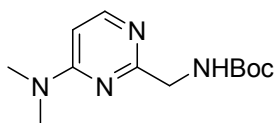
A solution of **IIIc** (2.15 g, 9.18 mmol) and Boc-anhydride (2.0 g, 9.18 mmol) in ethyl acetate (50 mL) was hydrogenated under low hydrogen pressure on Pd/C (10%, 0.6 g) for 3 h at room temperature. The solid was filtered off on Celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate, 70:30) to give **VIc** as a colorless oil (2.5 g, 81%); 1H NMR ($CDCl_3$): δ 1.43-1.56 (m, 18H), 3.44 (s, 3H), 4.48 (d, $J = 4.8$ Hz, 2H), 5.59 (s, 1H), 7.85 (d, $J = 5.9$ Hz, 1H), 8.43 (d, $J = 6.0$ Hz, 1H).

Preparation of 2-(tert-butoxycarbonyl-aminomethyl)-5-methoxycarbonylpyrimidine (VIb).



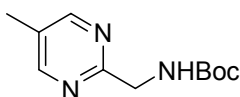
Applying the same conditions to **IIIb** produced intermediate **VIb** in quantitative yield; 1H NMR ($CDCl_3$): δ 1.48 (s, 9H), 3.98 (s, 3H), 4.67 (d, $J = 4.4$ Hz, 2H), 5.67 (s, 1H), 9.23 (s, 2H).

Preparation of 2-(*tert*-butoxycarbonyl-aminomethyl)-4-dimethylaminopyrimidine (VI_d).



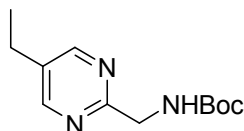
From **III_d** [500160-46-3] we obtained intermediate **VI_d** in 33% yield; ¹H NMR (CDCl₃): δ 1.47 (s, 9H), 3.11 (s, 6H), 4.34 (d, *J* = 4.4 Hz, 2H), 5.67 (s, 1H), 6.27 (d, *J* = 6.2 Hz, 1H), 8.12 (d, *J* = 6.2 Hz, 1H).

Preparation of 2-(*tert*-butoxycarbonyl-aminomethyl)-5-methylpyrimidine (VI_e).



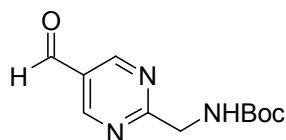
To a solution of CH₃ONa (1.39 mol) in methanol (2.5 L) was added successively at room temperature 3-ethoxymethacroleine (70 g, 613 mmol) and *tert*-butoxycarbonyl-acetamidine (69.3 g, 400 mmol). The mixture was heated at reflux for 5 h then concentrated under vacuum. The residue was taken up in dichloromethane, washed with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The product was precipitated by addition of cold hexane. The solid formed was filtered off, washed with hexane and dried to furnish **VI_e** as a white powder (67.4 g, 75%); ¹H NMR (CDCl₃): δ 1.47 (s, 9H), 2.31 (s, 3H), 4.55 (d, *J* = 4Hz, 2H), 5.69 (s, 1H), 8.53 (s, 2H).

Preparation of 2-(*tert*-butoxycarbonyl-aminomethyl)-5-ethylpyrimidine (VI_f).



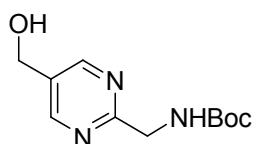
The same procedure starting from the amidine **VII** and 2-ethyl-3-dimethylaminoacroleine led to **VI_f** in 23% yield; ¹H NMR (CDCl₃): δ 1.28 (t, *J* = 7.6Hz, 3H), 1.43 (s, 9H), 2.45 (q, *J* = 7.6 Hz, 2H), 4.56 (d, *J* = 4.4 Hz, 2H), 5.68 (s, 1H), 8.54 (s, 2H).

Preparation of 2-(*tert*-butoxycarbonyl-aminomethyl)-5-pyrimidinecarboxaldehyde (**VIII**).



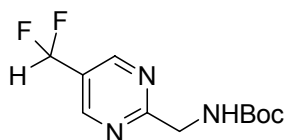
The reaction between amidine **VII** and 2-dimethylaminomethylene-1,3-bis(dimethylimmonio)propane bisperchlorate according to the above procedure gave **VIII** in 33% yield; $^1\text{H NMR}$ (CDCl_3): $^1\text{H NMR}$ (CDCl_3): δ 1.48 and 1.54 (2s, 9H), 4.69 (d, $J = 5.2$ Hz, 2H), 5.64 (s, 1H), 9.14 (s, 2H), 10.14 (s, 1H).

2-(*tert*-Butoxycarbonyl-aminomethyl)-5-hydroxymethylpyrimidine (**VIg**).



To a solution of the aldehyde **VIII** (0.8 g, 3.37 mmol) in ethanol (10 mL) cooled at 0 °C was added NaBH_4 (0.13 g, 3.63 mmol). The mixture was stirred for 30 min then HCl (4N) was added dropwise until gas evolution ceased. The mixture was filtered on Celite and the filtrate concentrated under vacuum to give **VIg** as a pale yellow solid (0.82 g, quantitative yield) which was used as such in the next step; $^1\text{H NMR}$ (CDCl_3): δ 1.47 (s, 9H), 4.59 (s, 2H), 4.74 (s, 2H), 8.70 (s, 2H).

2-(*tert*-Butoxycarbonyl-aminomethyl)-5-difluoromethylpyrimidine (**VIh**).

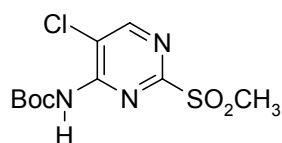


The aldehyde **VIII** (1.0 g, 4.21 mmol) was dissolved in dichloromethane (20 mL), cooled to 0 °C under inert atmosphere then was added dropwise (diethylamino)sulfur trifluoride (0.6 mL, 4.89 mmol) and the mixture stirred at 0 °C for 30 min. The reaction was quenched by addition of a small volume of saturated solution of NaHCO_3 , the mixture was decanted then the dichloromethane layer dried over

Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, dichloromethane/ethyl acetate, 80:20) to give **VIIh** as a colorless oil (0.25 g, 23%); ¹H NMR (CDCl₃): δ 1.48 and 1.55 (2s, 9H), 4.66 (d, *J* = 4.4 Hz, 2H), 5.62 (s, 1H), 6.75 (t, *J* = 55.3 Hz, 1H), 8.85 (s, 2H).

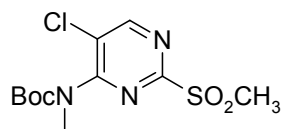
Preparation of 2-cyano-4-(*tert*-butoxycarbonyl-methylamino)-5-chloropyrimidine (**XI**).

2-Methylsulfonyl-4-*tert*-butoxycarbonylamino-5-chloropyrimidine.



To a solution of 2-methylsulfonyl-5-chloro-4-pyrimidine carboxylic acid **IX** (7.2 g, 30 mmol) in *tert*-butanol (200 mL) and triethylamine (5.1 mL, 36 mmol) was added dropwise diphenylphosphoryl azide (7.9 mL, 36 mmol). The mixture was heated at 85 °C for 8 h and the cooled reaction mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate, washed with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The oily material obtained was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 50:50) to provide the intermediate 2-methylsulfonyl-4-(*tert*-butoxycarbonylamino)-5-chloropyrimidine as an off-white solid (4.82 g, 52%); ¹H NMR (CDCl₃): δ 1.57 (s, 9H), 3.39 (s, 3H), 7.57 (s, 1H), 8.66 (s, 1H).

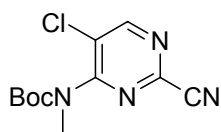
2-Methylsulfonyl-4-(*tert*-butoxycarbonyl-methylamino)-5-chloropyrimidine (**X**).



The intermediate obtained above (4.8 g, 15 mmol) was dissolved in THF (50 mL) under inert atmosphere then sodium hydride (0.6 g, 15 mmol) was added and the mixture stirred for 15 min at room temperature. Neat dimethylsulfate (1.7 mL, 16 mmol) was added dropwise then the mixture heated at 70

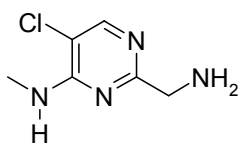
°C for 8 h. The mixture was concentrated under reduced pressure, the residue taken up in ethyl acetate, washed HCl (0.5 N) then with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The mixture was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 60:40) to give the intermediate 2-methylsulfonyl-4-(*tert*-butoxycarbonyl-methylamino)-5-chloropyrimidine **X** as a white solid (1.96 g, 41%); ¹H NMR (CDCl₃): δ 1.50 (s, 9H), 3.36 (s, 3H), 3.42 (s, 3H), 8.75 (s, 1H).

2-Cyano-4-(*tert*-butoxycarbonyl-methylamino)-5-chloropyrimidine (**XI**).



The compound **X** (1.9 g, 5.9 mmol) was treated as described before (see the formation of **IIIb** from **IV**). Purification by flash column chromatography (silica gel, heptane/ethyl acetate, 88:12) gave **XI** as a yellow oil (1.62 g, quantitative yield); ¹H NMR (CDCl₃): δ 1.49 (s, 9H), 3.37 (s, 3H), 8.69 (s, 1H).

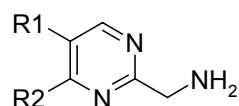
Preparation of 2-aminomethyl-4-methylamino-5-chloropyrimidine (**XIIj**).



Compound **XI** (2.5 g, 9.3 mmol) was hydrogenated on Pd/C (10%, 0.25 g) under low hydrogen pressure in methanol (20 mL) for 3 h at room temperature. The solid was filtered off on Celite, washed with ethyl acetate and the filtrate concentrated under reduced pressure. The residue consisted of two products: the expected intermediate **XIIi** (R₁ = Cl and R₂ = NBocCH₃) and the compound in which the Boc-group had migrated from the *sec*-amine function in 4-position onto the primary amine one. This mixture was taken up in dichloromethane (10 mL) then a solution of trifluoroacetic acid (15 mL) in dichloromethane (15 mL) was added over 5 min. The reaction mixture was stirred at room temperature for 40 min then concentrated under vacuum. The residue was taken up in dichloromethane then concentrated NaOH was added. The mixture was decanted and the aqueous extracted with

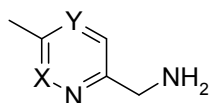
dichloromethane, the combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to yield **XIIj** (R₁ = Cl and R₂ = NHCH₃) as a pink solid (0.81 g, 51% over two steps); ¹H NMR (CDCl₃): δ 2.88 (d, *J* = 8 Hz, 3H), 3.66 (s, 2H), 8.14 (s, 1H).

2-Aminomethylpyrimidine (**XIIa-h**).



The compound **VI** (300 mmol.L⁻¹) was stirred at room temperature in a solution of HCl (5 N) in 2-propanol. After dissolution the chlorhydrate of the amine **XII** precipitate out. The solid formed was filtered off, washed with hexane and dried to give the amines **XIIa-h** which were used without further purification.

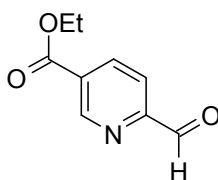
Diazines of the type **XIII**.



The cyano-diazine (1 equiv) was dissolved in acetic acid (0.5 M) and concentrated hydrochloric acid (10 N, 1 equiv). Hydrogenation was carried out under low hydrogen pressure using Pd on barium sulfate (5%) as catalyst (0.15 g per g of substrate). The reaction mixture was efficiently stirred at room temperature for 5 h then the catalyst was filtered out and washed with methanol. The solvents were concentrated in vacuo and the residue purified by flash column chromatography (silica gel, dichloromethane/methanol/ammonia) to give amines **XIII** which were immediately engaged in the reductive-amination.

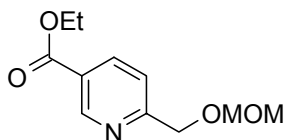
2. Preparation of heteroarylcarboxaldehyde

Preparation of 5-ethoxycarbonyl-2-pyridinecarboxaldehyde (**XVIIIa**). (Scheme 3)



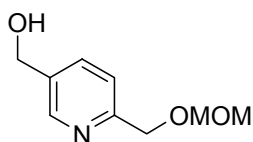
The alcohol **XV** (1.0 g, 5.5 mmol) in chloroform (30 mL) was oxidized with MnO₂ (5 g) at room temperature for 4 h. The usual treatment (see step iii) gave **XVIIIa** as a yellow oil 0.9 g (91%); ¹H NMR (CDCl₃): δ 1.46 (t, *J* = 7.2 Hz, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 8.03 (d, *J* = 7.6 Hz, 1H), 8.47 (d, *J* = 7.8 Hz, 1H), 9.36 (s, 1H), 10.15 (s, 1H).

5-Ethoxycarbonyl-2-methoxymethylpyridine.



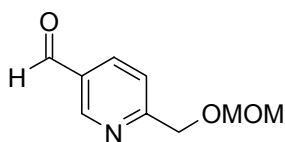
The alcohol **XV** (7.0 g, 38.6 mmol) was dissolved in DMF (70 mL), cooled to -15 °C under inert atmosphere, and sodium hydride (1.85 g, 46.3 mmol) was added by fractions over 15 min. After the gas evolution ceased, the reaction mixture was stirred for 15 min at -15 °C then neat chloromethylmethyl ether was added dropwise. The reaction mixture was stirred for 5 min then quenched with saturated aqueous NaHCO₃ solution (100 mL) and extracted with diethyl ether. The combined organic layer was washed with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The oily material obtained was distilled bulb-to-bulb, bp = 130-135 °C (P = 7.0 Pa) to yield the methoxymethyl ether of the 6-hydroxymethylnicotinic acid ethyl ester as a yellow oil 6.0 g (69%); ¹H NMR (DMSO-*d*₆): δ 1.34 (t, *J* = 7.2 Hz, 3H), 3.33 (s, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.70 (s, 2H), 4.75 (s, 2H), 7.61 (d, *J* = 8.2 Hz, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 9.20 (s, 1H).

5-Hydroxymethyl-2-methoxymethylpyridine (XVI).



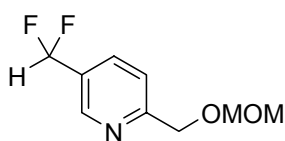
To a suspension of LiAlH_4 (9 g, 218 mmol) in THF (200 mL), cooled at -75°C under inert atmosphere, was added dropwise the 5-ethoxycarbonyl-2-methoxymethoxymethyl-pyridine (20.5 g, 91 mmol) dissolved in THF (100 mL). The reaction mixture was stirred for 30 min at -81°C then water (18 mL) was added dropwise followed by aqueous sodium hydroxide (10%, 23 mL), THF (200 mL) and water (53 mL). The temperature was allowed to rise to room temperature then ammonium acetate (20 g, 260 mmol) was added and the mixture filtered on Celite. The filtrate was concentrated under vacuum, the residue taken up in dichloromethane, the organic layer washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, dichloromethane/methanol, 96:4) to afford **XVI** as a white solid 13.0 g (78%); ^1H NMR (CDCl_3): δ 2.43 (s, 1H), 3.42 (s, 3H), 4.71 (s, 4H), 4.77 (s, 2H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 8.50 (s, 1H).

Preparation of 2-methoxymethoxymethyl-5-pyridinecarboxaldehyde.



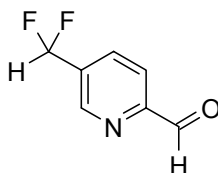
The alcohol **XVI** was oxidized with MnO_2 as described in step i to give the corresponding 5-carboxaldehyde derivative (90% yield) which was used as such in the next step; ^1H NMR (CDCl_3): δ 3.44 (s, 3H), 4.82 (s, 4H), 7.65 (d, $J = 8.1$ Hz, 1H), 8.19 (d, $J = 8.1$ Hz, 1H), 9.12 (s, 1H), 10.14 (s, 1H).

2-Methoxymethoxymethyl-5-difluoromethylpyridine (XVII).



To the aldehyde prepared above (3.2 g, 17.6 mmol) in chloroform (26 mL) was added dropwise diethylaminosulfur trifluoride (3.5 mL, 26.5 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was poured into saturated solution of NaHCO₃ (50 mL) then the aqueous extracted with chloroform, the combined organic layer washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate, 85:15) to give **XVII** as a yellow oil 2.33 g (65%). ¹H NMR (CDCl₃): δ 3.43 (s, 3H), 4.77 (s, 2H), 4.80 (s, 2H), 6.72 (t, *J* = 55.8 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 8.70 (s, 1H).

5-Difluoromethyl-2-pyridinecarboxaldehyde (**XVIIIb**).

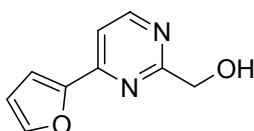


The compound **XVII** (2.85 g, 14 mmol) is stirred at room temperature for 12 h in a solution of HCl in ethanol (2.9 N, 50 mL). The reaction mixture was concentrated under vacuum then the residue taken up in water and the solution made basic by addition of an aqueous solution of NaOH (30%, 2 mL). The mixture was extracted with dichloromethane, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, dichloromethane/ethyl acetate, 50:50) to give the corresponding primary alcohol derivative as a yellow oil 1.78 g (78%); ¹H NMR (CDCl₃): δ 3.60 (t, *J* = 4.8 Hz, 1H), 4.82 (d, *J* = 4.0 Hz, 2H), 6.72 (t, *J* = 55.8 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.70 (s, 1H). This compound was oxidized with MnO₂ (cf. step v) to give the aldehyde **XVIIIb** (75% yield) as an off-white solid which was used as such in the next step; ¹H NMR (CDCl₃): δ 6.80 (t, *J* = 55.4 Hz, 1H), 8.03-8.08 (m, 2H), 8.93 (s, 1H), 10.13 (s, 1H).

4-(Fur-2-yl)-2-methylpyrimidine *N*-oxide.

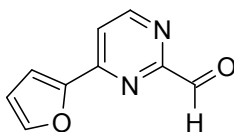
To a solution of 4-(fur-2-yl)-2-methylpyrimidine (8.1 g, 51 mmol) in chloroform (150 mL) at 0°C under inert atmosphere was added portion-wise *m*-CPBA (70%, 20 g, 115 mmol). The reaction mixture was stirred overnight at room temperature then heated at reflux for 1 h. The cooled reaction mixture was poured into saturated aqueous NaHCO₃ then extracted with dichloromethane. The combined organic layer was washed with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give an off-white solid 3.8 g (42%); ¹H NMR (CDCl₃): δ 2.76 (s, 3H), 6.58 (m, 1H), 7.15 (d, *J* = 3.5 Hz, 1H), 7.48 (d, *J* = 6.9 Hz, 1H), 7.57 (s, 1H), 8.35 (d, *J* = 6.9 Hz, 1H).

4-(Fur-2-yl)-2-hydroxymethylpyrimidine.



The 4-(fur-2-yl)-2-methylpyrimidine *N*-oxide (3.65 g, 24.6 mmol) was dissolved in THF (60 mL) at 0°C under inert atmosphere then trifluoroacetic anhydride (9 mL, 62.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight then cooled to 0°C and NaOH (5 N, 45 mL, 225 mmol) was added slowly. The mixture was stirred at room temperature for 30 min then concentrated under reduced pressure, the aqueous taken up in brine and extracted with dichloromethane, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, dichloromethane/methanol, 98:2) to afford 4-(fur-2-yl)-2-hydroxymethylpyrimidine as a white solid 1.37 g (34%); ¹H NMR (CDCl₃): δ 3.73 (s, 1H), 4.84 (s, 2H), 6.60 (m, 1H), 7.32 (d, *J* = 3.4 Hz, 1H), 7.51 (d, *J* = 5.3 Hz, 1H), 7.63 (s, 1H), 8.71 (d, *J* = 5.3 Hz, 1H).

4-(Fur-2-yl)-2-pyrimidinecarboxaldehyde (XIX).



The 4-(fur-2-yl)-2-hydroxymethylpyrimidine (1.35 g, 7.7 mmol) was dissolved in chloroform (50 mL) then manganese dioxide (7 g) was added and the mixture stirred at reflux for 4 h. The hot reaction mixture was filtered on Celite and the precipitate washed with chloroform then the filtrate concentrated under vacuo to provide **XIX** as a yellow solid 0.86 g 65%); $^1\text{H NMR}$ (CDCl_3): δ 6.64 (m, 1H), 7.48 (d, $J = 3.5$ Hz, 1H), 7.67 (s, 1H), 7.73 (d, $J = 5.2$ Hz, 1H), 8.94 (d, $J = 5.2$ Hz, 1H), 10.1 (s, 1H).

Compd	Salt	Calculated (C,H,N)	Found
2	methanolate	C, 56.67; H, 4.75; N, 9.91	C, 55.32; H, 5.30; N, 9.22
3	fumarate	C, 54.81; H, 4.98; N, 7.99	C, 54.61; H, 5.13; N, 7.86
4	fumarate	C, 54.60; H, 4.77; N, 7.96	C, 54.42; H, 4.65; N, 7.75
5	fumarate	C, 52.80; H, 4.45; N, 7.70	C, 52.75; H, 4.47; N, 7.55
6	fumarate	C, 52.09; H, 4.37; N, 7.92	C, 52.04; H, 4.38; N, 7.84
7	2.HCl, 0.5.H ₂ O ^a	C, 47.86; H, 5.07; N, 11.75	C, 48.03; H, 5.12; N, 11.50; H ₂ O, 2.0
8	HCl, 0.5.H ₂ O ^a	C, 51.82; H, 5.15; N, 12.72	C, 52.03; H, 5.14; N, 12.63; H ₂ O, 2.0
9	tosylate	C, 55.07; H, 5.15; N, 9.88	C, 55.14; H, 5.22; N, 9.80
10	fumarate, H ₂ O ^a	C, 51.30; H, 4.89; N, 10.87	C, 51.54; H, 4.76; N, 10.86; H ₂ O, 3.4
11	1.5.fumarate	C, 50.94; H, 4.44; N, 9.14	C, 49.26; H, 4.51; N, 8.50
12	4.5.fumarate, 0.5.H ₂ O ^a	C, 47.16; H, 4.17; N, 5.94	C, 47.42; H, 4.35; N, 5.81; H ₂ O, 0.84
13	fumarate	C, 54.91; H, 5.18; N, 10.67	C, 54.63; H, 5.37; N, 10.57
14	fumarate	C, 50.51; H, 4.24; N, 10.24	C, 50.70; H, 4.24; N, 10.40
15	fumarate, H ₂ O ^a	C, 48.10; H, 4.40; N, 10.20	C, 48.33; H, 4.38; N, 10.40; H ₂ O, 3.2
16	fumarate	C, 52.43; H, 4.78; N, 10.63	C, 52.38; H, 4.90; N, 10.35
17	1.5.oxalate	C, 48.48; H, 4.62; N, 12.85	C, 48.00; H, 4.80; N, 12.63
18	fumarate, 0.25.H ₂ O ^a	C, 52.50; H, 5.23; N, 12.75	C, 52.16; H, 5.30; N, 12.40; H ₂ O, 0.4
19	hemifumarate	C, 57.07; H, 4.59; N, 11.09	C, 56.70; H, 4.53; N, 10.78
20	difumarate.H ₂ O ^a	C, 49.89; H, 5.08; N, 10.39	C, 49.98; H, 5.25; N, 9.69; H ₂ O, 2.6
21	difumarate.H ₂ O ^a	C, 46.62; H, 4.63; N, 10.07	C, 46.53; H, 4.50; N, 9.98; H ₂ O, 3.2

Elemental analyses. ^a Water percentage was determined by the Karl Fisher method with a coulometer.