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Arylpropanolamines Incorporating an Antioxidant Function as Neuroprotective Agents

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A series of arylpropanolamines containing dipyrrolidinylpyrimidines as an antioxidant function have been synthesized and evaluated as dual function neuroprotective agents. Their in vitro efficacy as sodium channel blocking agents and antioxidants has been evaluated and compared with those of the ethanolamine derivative (1), which has been shown to be neuroprotective in a rat model of stroke. The ability of the present compounds to displace ^{3}H-BTX toxin from sodium-ion channels in a rat brain membrane fraction was shown to be largely independent of the substituents on the aryl ring, which suggests that this activity may be mainly associated with the aminopyrimidine moiety. Structure–activity relationships for antioxidant efficacy were less clear, but the unsymmetrical pyrimidines were consistently more active than their symmetrical isomers. A brief theoretical investigation of this observation is reported.

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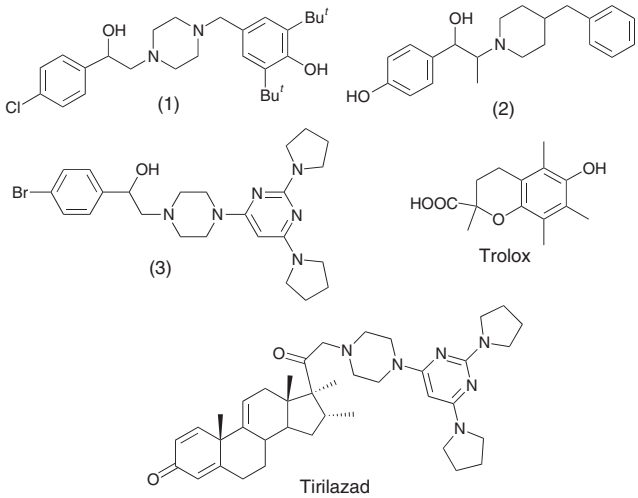
Introduction

The ethanolamine derivative (1), which contains some of the structural features of ifenprodil (2)[1] and an antioxidant function, has been shown to be neuroprotective in a rat model of stroke with a desirable therapeutic window of three hours (Scheme 1).[2,3] The patent application describing this compound also describes the preparation and pharmacological activity of a wide range of related compounds, many of which involve a combination of arylethanolamine derivatives and an antioxidant functionality.[4] The antioxidants incorporated into the structures were mainly phenolic in nature, i.e. Trolox or 2,6-di-*tert*-butylphenols.

In related studies, a series of compounds containing a different antioxidant moiety, amino-substituted pyrimidines, were prepared. The amino-substituted pyrimidine group is incorporated in the neuroprotective steroid tirilazad (Scheme 1).[5] Some of the compounds containing the aminopyrimidine antioxidant showed interesting activity both as Na^+ channel blockers and as antioxidants. For example, compound (3), whose preparation and antioxidant activity was reported recently by us,[6] showed comparable Na^+ channel blocking activity to compound (1) but was not quite as effective an antioxidant, as shown by the biological Sapphire assay[7,8] and by its oxidation potential (E_{pl}^{ox}), which was measured using cyclic voltammetry.[6]

It is noteworthy that several diamino-substituted pyrimidines,[9] such as BW 1003C87, BW 619C89, and the related compound lamotrigine (Scheme 2), have been shown to block voltage-gated Na^+ channels, and the Na^+ channel blocking activity of compound (3) and its analogues could, therefore, be due to both the arylethanolamine and aminopyrimidine functionalities.



Scheme 1.

It was thus decided to prepare and evaluate a series of arylpropanolamines (4) and (5) (see Scheme 3) which do not contain an arylethanolamine group but which retain the aminopyrimidine antioxidant moiety of (3) and the BW

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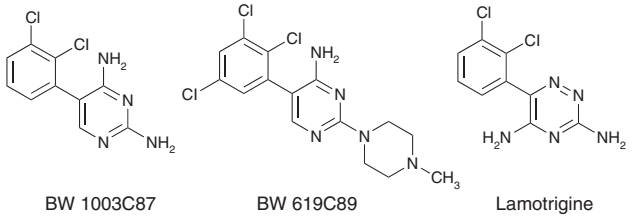
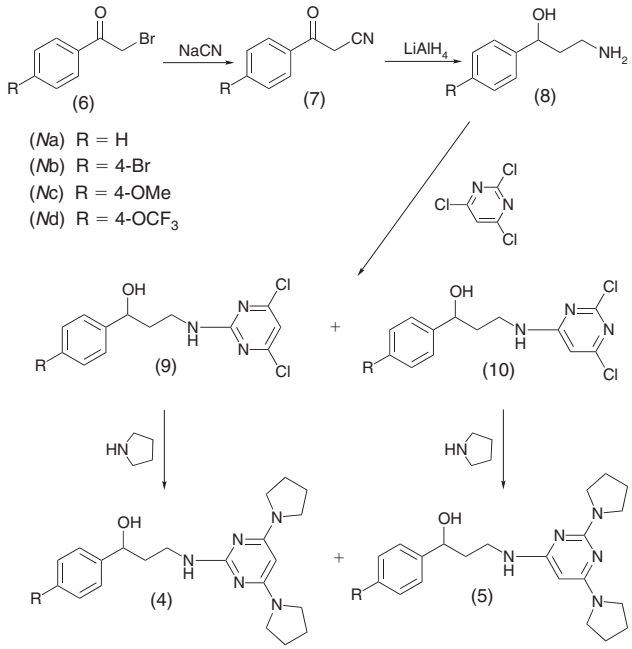


Scheme 2.



Scheme 3.

compounds. The arylethanol functionality was to be retained but was to be joined to the aminopyrimidine by a simple two-carbon spacer, thus eliminating the arylethanolamine moiety. Furthermore, any possible activity of the piperazine ring in (3) was also eliminated.

Results and Discussion

Synthesis of Propanolamine Derivatives (4) and (5)

A range of α-bromoacetophenones (6) were converted into the acetonitrile derivatives (7) which, in turn, were reduced with lithium aluminium hydride to the arylpropanolamines (8) in yields varying from 40 to 90% (Scheme 3). The amines (8) were treated with 2,4,6-trichloropyrimidine to give a mixture of symmetrical (9) and unsymmetrical (10) dichloropyrimidine derivatives in an approximately equimolar ratio under conditions described previously for preparation of the related ethanolamine derivatives.[6] The symmetrical and unsymmetrical compounds were readily separated and the pure compounds isolated with combined yields in the range of 64–89%. Conversion to the dipyrrolidinyl compounds (4) and (5) again followed the literature procedure[6] and gave pure compounds in yields varying from 30 to 75%.

Attempted preparation of the unsymmetrical isomer (5a) by treatment of amine (8a) with preformed 6-chloro-2,4-dipyrrolidinylpyrimidine failed, even under vigorous

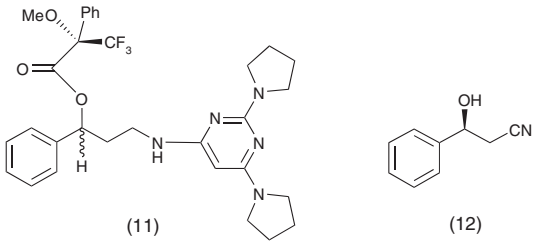


Diagram 1.

conditions, which shows that the electron-donating power of the pyrrolidino nitrogen atoms prevents the chlorine atom from undergoing nucleophilic substitution.

All of these compounds contain one chiral carbon atom and it was considered important to evaluate the pharmacological activity of individual enantiomers. The parent compound (5a) was converted into the ester (11) (Diagram 1) with (*S*)-(–)-Mosher's acid, but all attempts to separate the diastereomeric esters either by chromatography or fractional crystallization failed.

Enzymatic reduction of the cyanoketone (7a)[10] using yeast gave the (*S*)-configured isomer of the cyanoalcohol (12) with an optical rotation value of $[\alpha]_D^{20}$ −69°, which compared well with literature. Subsequent reduction of the cyano function in (12) with $LiAlH_4$ yielded the (*S*)-aminoalcohol (*S*)-(8a). The aminoalcohol was then converted, as described above, into the symmetrical and unsymmetrical dichloropyrimidines (9a) and (10a), which were separated and reacted individually with pyrrolidine to give the dipyrrolidinylpyrimidines (*S*)-(4a) and (*S*)-(5a), respectively. The unsymmetrical isomer (5a) was converted into its MTPA-ester (*S*)-(11). ^1H and ^{19}F NMR spectroscopy independently showed a 4 : 1 ratio of diastereomers, giving an enantiomeric excess (*e.e.*) of 64% for the (*S*)-enantiomer.

Na^+ Channel Activity

The ability of the compounds (4) and (5) to displace ^3H-batrachotoxin (BTX) from Na^+ channels in a rat brain membrane fraction was measured by a standard procedure[11] and the results are summarized in Table 1. IC_{50} (μM) values and their ranges are listed together with binding data at concentrations of 1 and 10 μM. Allowing for the uncertainty in the measurements, all compounds showed very similar BTX binding affinity at 1 and 10 μM concentrations and similar IC_{50} values. The *p*-bromo compounds (4b) and (5b) (Entries 3 and 4) gave indications of slightly less activity than the others (Entries 1, 2, 5–8). The two compounds with *para*-trifluoromethoxy substituents (4d) and (5d) (Entries 7 and 8) marginally showed the best activity. However, none of these compounds were as active as the lead compound (1) (Entry 12) or the key compound (3) (Entry 13), which were themselves comparable in activity (all having IC_{50} of ca. 0.3 μM) to dibucaine, a well known ^3H-BTX specific inhibitor.[12] No consistent differences were observed between the symmetrical (4) and unsymmetrical (5) isomers.

Table 1. Results of pharmacological assays[A]

Entry	Substrate	R	^{3}H-BTX Specific Binding				Sapphire LPO-586 Colourimetric Assay		
			1 μM	10 μM	IC_{50} [μM]	IC_{50} range	IC_{50} [μM]	IC_{50} range	Max inhibition [%]
1	(4a)	H	27 ± 11	88 ± 3	2.8	0.9–8.4	184	152–224	81
2	(5a)	H	17 ± 4	78 ± 0	2.9	1.5–5.7	49	38–64	92
3	(4b)	Br	16 ± 5	83 ± 1	4.3	1.3–13.7	>1000	–	18
4	(5b)	Br	28 ± 6	81 ± 1	3.2	1.4–7.2	475	445–507	76
5	(4c)	OMe	20 ± 4	87 ± 0	2.9	2.1–4.1	722	601–878	56
6	(5c)	OMe	37 ± 4	97 ± 3	1.9	0.7–5.2	128	104–157	87
7	(4d)	OCF_3	45 ± 0	98 ± 0	1.1	0.5–2.0	>1000	–	4
8	(5d)	OCF_3	45 ± 3	100 ± 2	1.1	0.8–1.5	645	342–1216	78
9	(*S*)-(4a)[B]	H	44 ± 4	89 ± 0	2.0	1.5–2.7	>1000	–	28
10	(*S*)-(5a)[B]	H	58 ± 1	95 ± 1	1.0	0.8–1.3	822	549–1231	57
11	dibucaine	–	77 ± 6	97 ± 3	0.25	0.22–0.28	–[C]	–	–
12	(1)	–	69 ± 3	87 ± 1	0.28	0.14–0.42	62	46–82	81
13	(3)	–	75 ± 1	100 ± 1	0.31	0.24–0.41	123	87–180	87

[A] Replicates, $n = 2$–4. [B] These samples were enriched with the (*S*)-enantiomer. [C] Not tested (no antioxidant properties).

These results suggest that the ^{3}H-BTX specific inhibition observed in the series of compounds (4) and (5) is mainly associated with the aminopyrimidine moiety. Thus, the effect of changing substituents in the remote aryl ring on receptor binding is likely to be small. The compounds BW 1003C87, BW 619C89, and lamotrigine (Scheme 2) all have planar heterocyclic rings with two amino substituents and show Na^+ channel blocking activity. Such activity thus appears to be associated with a range of amino-substituted nitrogen-containing heterocycles including compounds (4) and (5). The greater activity of the aryl β-ethanolamine derivative (3) suggests that this moiety has Na^+ ion channel blocking activity which is additive to or greater than that facilitated by the aminopyrimidine moiety.

The enantiomerically enriched samples of (4a) and (5a) (Entries 9 and 10) showed evidence of being more active than the racemic samples, emphasizing the importance of assessing single enantiomers where possible.

Antioxidant Activity

The antioxidant activity was measured using the Sapphire colorimetric assay with modifications described previously by us.[6] Lipid peroxidation was stimulated by Fe^{3+} (100 μM) and the IC_{50} (μM) and maximum inhibition are given in Table 1. The unsymmetrical isomers (5) consistently showed better antioxidant activity than the symmetrical isomers (4) in both IC_{50} and maximum inhibition values. Compound (3) (Entry 13), which also contains the unsymmetrical pyrrolidinylpyrimidine structure, showed a maximum inhibition value similar to the isomers (5).

Compound (5a) was comparable in antioxidant activity to compound (1) (Entry 12), which has a di-*tert*-butylphenol as the antioxidant moiety. Compound (5c) (Entry 6) was comparable in antioxidant activity to compound (3) (Entry 13), both of which have the same unsymmetrical pyrimidine antioxidant moiety.

The large range of values for antioxidant activity obtained on changing the substituents in the remote aromatic ring is difficult to explain. Even more puzzling are the results for the enantiomerically enriched samples (4a) and (5a) (Entries 9 and 10), which showed a dramatic loss of activity relative to the racemic compounds (Entries 1 and 2). It should be noted that the Sapphire assay has previously been demonstrated to give results which were concordant with other biological (TBARS) and chemical (cyclic voltammetry) assays.[6] However, in this work, the much greater range of results obtained using this assay means that the results must not be over-interpreted. Although the results must be treated with caution, it appears that the least active compounds have a strong electron-withdrawing substituent in the *para*-position. Thus *para*-bromo and *para*-trifluoromethoxy substituents, with Hammett σ values of +0.2 and +0.35 respectively, show less activity than the unsubstituted and *para*-methoxy compounds with σ values of 0.0 and −0.27.

Only one clear trend was observed, namely, that the unsymmetrical isomers (5) were more active than the symmetrical isomers (4). Previous work by us has shown that it is necessary to have three amino substituents on the pyrimidine ring in order for antioxidant activity to be displayed.[6] Thus, a short theoretical study of the energies of the radical species obtained on oxidation of model analogues of symmetrical and unsymmetrical triamino-substituted pyrimidines was carried out.

Theoretical Studies

PM3 semi-empirical calculations for the radical cations (13) and (14), derived from the *N*-methyl-bis(dimethylamino)-pyrimidine analogues of (4) and (5), suggested electron-spin densities as illustrated in Figure 1. As expected, a significant portion of unpaired electron density resides on nitrogen. However, a significant amount of unpaired electron density also resides on carbon atoms, and the symmetrical (15) and unsymmetrical (16) canonical forms, which best represent these structures, are shown in Scheme 4. The symmetrical isomer can be seen to have a cross-conjugated structure in contrast to the fully conjugated unsymmetrical isomer, and thus could be expected to be of lower stability.

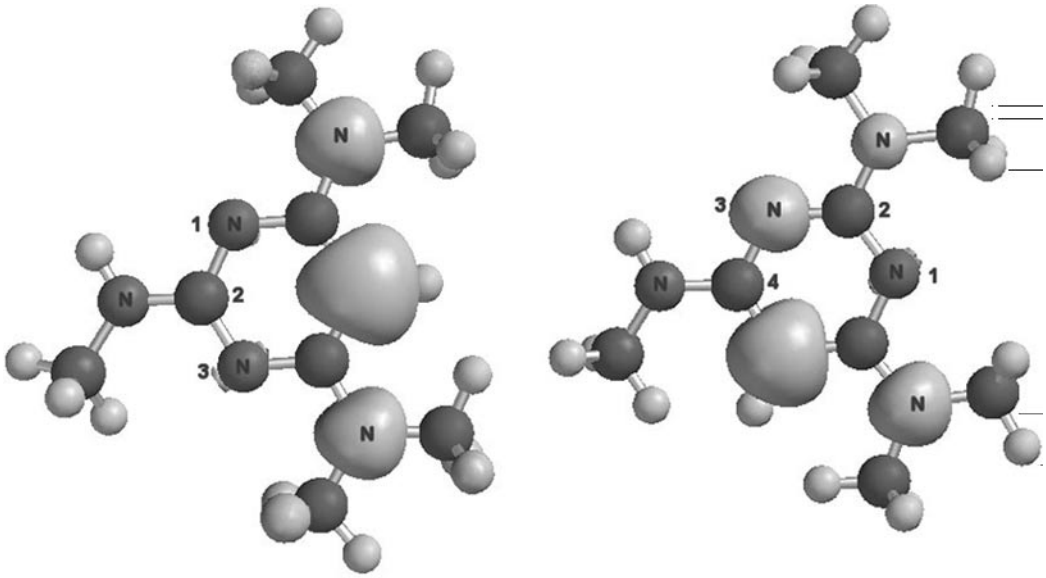
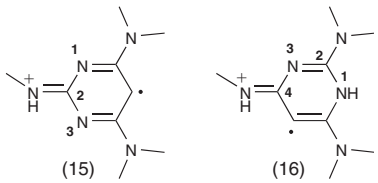


Fig. 1. Electron spin densities of the symmetrical (13), left, and unsymmetrical (14), right, radical cations.



Scheme 4.

This suggestion is consistent with the pK_a values of 5.69 for 4-aminopyrimidine itself and 3.45 for the 2-amino isomer.[13] The greater basicity of the former suggests that the cation which can be stabilized by linear conjugation is more stable than the cation from the 2-isomer where stabilization would involve cross-conjugation.

However, density functional calculations using Gaussian98 do not reveal any significant energy differences between the radical cations (13) and (14) relative to their parent molecules, i.e. the *N*-methyl-bis(dimethylamino) pyrimidine analogues of (4) and (5).

Conclusions

A range of arylpropanolamines with aminopyrimidine substituents have been prepared and evaluated as dual function neuroprotective agents. In vitro studies suggest that the sodium-channel blocking activity, as well as the antioxidant activity, is mainly associated with the aminopyrimidine moiety. The unsymmetrical aminopyrimidine isomers were found to be more active antioxidants.

Experimental

Syntheses

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using Bruker AM-300 and DRX-400 spectrometers for solutions in $CDCl_3$ unless otherwise stated. Mass spectra (ESI) were measured on a Bruker BioApex 47 e$^-$ Fourier transform mass spectrometer with a 4.7 T magnet and an Analytica electrospray source. Mass spectra (EI) were recorded on a VG TRIO-1 Quadrupole Mass Spectrometer at 70 eV with a source temperature of 200°C. Microanalyses were performed by Chemical and Microanalytical Services Pty Ltd, Melbourne. Merck Silica Gel 60 (230–400 mesh, no. 9385) was used for flash chromatography.

Brominated Acetophenones

The compounds (6b)–(6d) were prepared as described in the literature.[14,15]

2-Bromo-4′-trifluoromethoxyacetophenone (6d)

Prepared in 83% yield as a white solid,[16] mp 52–54°C (Found: $[M+Na]^{+\bullet}$, 304.9399. $C_9H_6{}^{79}BrF_3O_2$ requires $[M+Na]^{+\bullet}$, 304.9401). δ_H (300 MHz) 8.05 (2 H, d, *J* 8.7, H2′ and H6′), 7.32 (2 H, d, *J* 8.7, H3′ and H5′), 4.41 (2 H, s, H2). δ_C (75 MHz) 190.0 (C1), 153.3 (q, $^3J_{CF}$ 1.7, C4′), 132.2 (C1′), 131.2 (C2′ and C6′), 120.7 (q, $^4J_{CF}$ 1.2, C3′ and C5′), 120.4 (q, $^1J_{CF}$ 259.4, OCF_3), 30.5 (C2).

Propanenitriles (7a)–(7d)

The propanenitriles were prepared as described by Long.[17]

3-Oxo-3-phenylpropanenitrile (7a)

A solution of sodium cyanide (0.74 g, 15.07 mmol) in water (10 mL) was added slowly to a stirred solution of 2-bromoacetophenone (6a) (1.00 g, 5.02 mmol) in methanol (15 mL) under nitrogen. The mixture was allowed to stir at ambient temperature for 3 h and was then concentrated under reduced pressure. Water (10 mL) was added followed by acetic acid (to pH 3) to give a precipitate which was collected by filtration to give 3-oxo-3-phenylpropanenitrile (7a) as a pale cream, crystalline solid (1.59 g, 80%), mp 79.6–79.8°C (lit.[18] 80.5–80.7°C).

3-(4′-Bromophenyl)-3-oxopropanenitrile (7b)

2,4′-Dibromoacetophenone (6b) (1.00 g, 3.59 mmol) gave the nitrile (7b) as a pale cream, crystalline solid (0.71 g, 88%), mp 159.3–160.3°C (lit.[19] 159°C, 164–165°C). δ_H (300 MHz) 7.71 (2 H, d, *J* 8.6, H2′ and H6′), 7.60 (2 H, d, *J* 8.6, H3′ and H5′), 3.95 (2 H, s, H2). δ_C (75 MHz) 186.4 (C3), 133.2 (C1′), 132.8 (C2′ and C6′), 130.5 (C4′), 130.1 (C3′ and C5′), 113.6 (CN), 29.5 (C2).

3-Oxo-3-(4′-methoxyphenyl)propanenitrile (7c)

2-Bromo-4′-methoxyacetophenone (6c) (4.00 g, 17.46 mmol) gave the nitrile (7c) as a cream, crystalline solid (2.04 g, 67%), mp 127.4–127.6°C (lit.[20] 132–133°C, lit.[21] 125–127°C). δ_H (300 MHz) 7.91

(2 H, d, *J* 9.0, H2′ and H6′), 6.98 (2 H, d, *J* 9.0, H3′ and H5′), 4.00 (2 H, s, H2), 3.90 (3 H, s, OCH_3). δ_C (75 MHz) 185.5 (C3), 164.9 (C4′), 131.1 (C2′ and C6′), 127.5 (C1′), 114.5 (C3′ and C5′), 114.2 (CN), 55.8 (OCH_3), 29.1 (C2).

3-Oxo-3-(4′-trifluoromethoxyphenyl)propanenitrile (7d)

2-Bromo-4′-trifluoromethoxyacetophenone (6d) (1.00 g, 3.71 mmol) gave the nitrile (7d) as a cream, crystalline solid (0.69 g, 85%), mp 74.0–75.4°C (lit.[22] 79–81°C). δ_H (300 MHz) 8.00 (2 H, d, *J* 8.9, H2′ and H6′), 7.36 (2 H, d, *J* 8.9, H3′ and H5′), 4.07 (2 H, s, H2). δ_C (75 MHz) 185.9 (C3), 153.9 (q, $^3J_{CF}$ 1.7, C4′), 132.4 (C1′), 130.8 (C2′ and C6′), 120.9 (q, $^4J_{CF}$ 1.2, C3′ and C5′), 120.3 (q, $^1J_{CF}$ 259.8, OCF_3), 113.6 (CN), 29.6 (C2).

Preparation of Propanolamines (8a)–(8d)

3-Amino-1-phenylpropanol (8a)

A solution of 3-oxo-3-phenylpropanenitrile (7a) (1.00 g, 6.89 mmol) in THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.61 g, 6.90 mmol) in THF (20 mL) at 0°C. The mixture was warmed to ambient temperature and stirred for 15 min at which point TLC analysis indicated the absence of any starting material. The mixture was cooled, $Na_2SO_4{\cdot}10H_2O$ (10 g) was added portionwise until the effervescence ceased, and the mixture was allowed to stir for a further 15 min. The suspension was filtered and the filter cake was washed with ether (20 mL). The filtrate was reduced under vacuum to yield a yellow oil (0.68 g). Kugelrohr distillation gave the amine (8a) as a colourless liquid that solidified to a colourless solid (0.67 g, 64%), bp 150°C/0.1 mmHg (lit.[23] 107–110°C/0.5 mmHg), mp 57.4–58.2°C (lit.[23] 63–64°C). δ_H (300 MHz) 7.40–7.22 (5 H, m, ArH), 4.96 (1 H, dd, *J* 8.5, 3.2, H1), 3.08 (1 H, m, H3), 2.95 (1 H, m, H3), 2.78 (3 H, br s, exchangeable OH and NH_2), 1.91–1.69 (2 H, m, H2). δ_C (75 MHz) 145.3 (C1′), 128.4 (C3′ and C5′), 127.2 (C4′), 125.8 (C2′ and C6′), 75.8 (C1), 41.0 (C3), 40.2 (C2).

3-Amino-1-(4′-bromophenyl)propanol (8b)

Reaction of 3-(4′-bromophenyl)-3-oxopropanenitrile (7b) (0.70 g, 3.14 mmol) with $LiAlH_4$ (0.72 g, 18.84 mmol) gave a yellow oil (0.47 g). Spectroscopic data (^{1}H NMR) showed a mixture of (8b) and the debrominated compound, 3-amino-1-phenylpropanol (8a) in a ratio of 3 : 1. Kugelrohr distillation gave the *amino alcohol* (8b) as a colourless oil (0.35 g, 49%), bp 180–200°C/0.2 mmHg (Found: $[M+H]^{+\bullet}$, 229.0094; 231.0073. $C_9H_{12}{}^{79}BrNO$ requires $[M+H]^{+\bullet}$, 229.0103; $C_9H_{12}{}^{81}BrNO$ requires $[M+H]^{+\bullet}$, 231.0082). ν_{max} (neat)/cm^{-1} 3360bs, 2937s, 2870s, 1673m, 1590s, 1401s, 1338m, 1199m, 1176m, 1071s, 1010s, 996m, 824s, 702s, 467s. δ_H (300 MHz) 7.46 (2 H, d, *J* 8.4, H3′ and H5′), 7.30 (2 H, d, *J* 8.3, H2′ and H6′), 4.92 (1 H, dd, *J* 8.6, 3.0, H1), 2.89 (1 H, ddd, *J* 12.4, 5.7, 3.9, H3), 2.75 (1 H, ddd, *J* 12.4, 9.4, 3.6, H3), 1.67–1.59 (1 H, m, H2), 1.54–1.42 (1 H, m, H2). δ_C (75 MHz) 144.4 (C1′), 131.4 (C3′ and C5′), 127.6 (C2′ and C6′), 120.3 (C4′), 75.3 (C1), 40.8 (C3), 39.6 (C2). Mass spectrum (ESI) *m*/*z* 232 (92%, $[M(^{81}Br)+H]^+$), 230 (100, $[M(^{79}Br)+H]^{+\bullet}$).

Reactions using a lesser excess of $LiAlH_4$ (substrate (7b)/$LiAlH_4$ ratio 1 : 2) or for a shorter time (5 min) were attempted but in all cases the debromination compound (8a) still formed.

3-Amino-1-(4′-methoxyphenyl)propanol (8c)

Reaction of 3-oxo-3-(4′-methoxyphenyl)propanenitrile (7c) (2.00 g, 11.4 mmol) with $LiAlH_4$ gave a cream solid (1.82 g) which was triturated with ether to give the amino alcohol (8c) as a white solid (1.78 g, 86%), mp 102–104°C (lit.[24] 123–125°C, but with incorrect elemental analysis) (Found: C, 66.1; H, 8.4; N, 7.6%; $[M+H]^{+\bullet}$, 181.1103. $C_{10}H_{15}NO_2$ requires C, 66.2; H, 8.4; N, 7.7%; $[M+H]^{+\bullet}$, 181.1102). ν_{max} (KBr)/cm^{-1} 3354s, 2854bs, 1610s, 1509s, 1459m, 1299m, 1248s, 1169s, 1081s, 1029s, 977m, 919m, 829m. δ_H (300 MHz) 7.29 (2 H, d, *J* 8.4, H2″ and H6″), 6.87 (2 H, d, *J* 8.4, H3″ and H5″), 4.88 (1 H, dd, *J* 8.1, 3.5, H1), 3.79 (3 H, s, OCH_3), 3.04 (1 H, m, H3), 2.92 (1 H, m, H3), 2.78 (3 H, br s, exchangeable OH and NH_2), 1.86–1.69 (2 H, m, H2). δ_C (75 MHz) 158.8 (C4′), 137.5 (C1′), 127.0 (C2′ and C6′), 113.8 (C3′ and C5′), 75.1 (C1), 55.4 (OCH_3), 40.7 (C3), 40.2 (C2). Mass spectrum (EI) *m*/*z* 181 (10%, $M^{+\bullet}$), 164 (32), 163 (100), 137 (45), 135 (62), 133 (78), 109 (28), 94 (48), 91 (46), 78 (18), 77 (95), 66 (22), 65 (45), 63 (47), 55 (15).

3-Amino-1-(4′-trifluoromethoxyphenyl)propanol (8d)

In a similar manner, 3-oxo-3-(4′-trifluoromethoxyphenyl)propanenitrile (7d) (0.50 g, 2.18 mmol) gave a yellow oil (0.41 g) which was purified by acid–base extraction. The crude mixture was poured into 2M HCl (20 mL), CH_2Cl_2 (20 mL) was added, and the organic layer was separated. The aqueous layer was basified to pH 14 by addition of NaOH pellets and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were dried and the solvent removed under vacuum to give the *amino alcohol* (8d) as a clear oil (0.21 g, 41%) (Found: C, 51.0; H, 4.5; N, 5.9%; $[M+H]^{+\bullet}$, 236.0892. $C_{10}H_{12}F_3NO_2$ requires C, 51.1; H, 5.1; N, 6.0%; $[M+H]^{+\bullet}$, 236.0898). ν_{max} (neat)/cm^{-1} 3360bm, 2936bm, 2874bm, 1595m, 1510m, 1268bs, 1161bs, 1070bm, 1018m, 922m. δ_H (400 MHz) 7.31 (2 H, d, *J* 8.5, H2′ and H6′), 7.08 (2 H, d, *J* 8.5, H3′ and H5′), 4.88 (1 H, dd, *J* 8.8, 2.9, H1), 3.06–3.01 (1 H, m, H3), 2.91–2.85 (1 H, m, H3), 2.70–2.20 (3 H, br s, exchangeable OH and NH_2), 1.76 (1 H, m, H2), 1.61 (1 H, m, H2). δ_C (100 MHz) 148.4 (q, $^3J_{CF}$ 1.5, C4′), 144.2 (C1′), 127.2 (C2′ and C6′), 121.0 (q, $^4J_{CF}$ 0.40, C3′ and C5′), 120.8 (q, $^1J_{CF}$ 256.7, OCF_3), 75.8 (C1), 41.0 (C3), 39.7 (C2). Mass spectrum (ESI) *m*/*z* 236 $[M+H]^{+\bullet}$.

Arylpropanolamino Dichloropyrimidines (9a)–(9d) and (10a)–(10d)

A solution of 2,4,6-trichloropyrimidine (4 mmol) in dry 1,4-dioxane (10 mL) was added dropwise at ambient temperature to a stirred solution of the amino alcohol (8a)–(8d) (4 mmol) in dry 1,4-dioxane (20 mL). Once addition was complete, $NaHCO_3$ (24 mmol) was added and the resulting mixture was heated at reflux for 2–6 h. The mixture was cooled to ambient temperature, quenched with water (20 mL), and basified to pH 12 by addition of 2M NaOH. The mixture was extracted with CH_2Cl_2 (3 × 40 mL), dried, filtered, and concentrated. In all cases, the ^{1}H NMR spectrum indicated that the compounds (9) and (10) were present in ca. 1 : 1 ratio. Flash chromatography (SiO_2, 50% ether/light petroleum) gave the symmetrical isomer (9) followed by the unsymmetrical isomer (10).

4,6-Dichloro-2-(3′-hydroxy-3′-phenylpropylamino)pyrimidine (9a) and 2,4-Dichloro-6-(3′-hydroxy-3′-phenylpropylamino) pyrimidine (10a)

Reaction of 2-amino-1-phenylpropanol (8a) (0.60 g, 3.97 mmol) after reflux for 2 h gave a yellow gum (0.95 g).

Compound (9a). Isolated as a *white solid* (0.40 g, 34%), mp 120.9–121°C (Found: C, 52.3; H, 4.4; N, 14.0%. $C_{13}H_{13}Cl_2N_3O$ requires C, 52.4; H, 4.4; N, 14.1%). ν_{max} (KBr)/cm^{-1} 3376bs, 3269bs, 3116m, 2363m, 2345m, 1654m, 1637m, 1599bs, 1582bs, 1519s, 1455s, 1426m, 1238m, 1122m, 1093s, 1067m, 1012m, 816m, 794m, 766m, 702m, 538m. δ_H (300 MHz) 7.36–7.26 (5 H, m, ArH), 6.59 (1 H, s, H5), 5.85 (1 H, br s, exchangeable OH or NH), 4.78 (1 H, m, H3′), 3.74 (1 H, m, H1′), 3.47 (1 H, m, H1′), 2.84 (1 H, d, *J* 3.3, exchangeable OH or NH), 2.00–1.94 (2 H, m, H2′). δ_C (75 MHz) 162.05 (C2), 162.0 (C4 and C6), 144.1 (C1″), 128.8 (C3″ and C5″), 127.9 (C4″), 125.9 (C2″ and C6″), 109.3 (C5), 72.5 (C3′), 39.4 (C1′), 39.2 (C2′). Mass spectrum (ESI) *m*/*z* 322 (67%, $[M(^{35}Cl)(^{37}Cl)+Na]^{+\bullet}$), 320 (100, $[M(^{35}Cl)_2+Na]^{+\bullet}$), 300 (52, $[M(^{35}Cl)(^{37}Cl)+H]^{+\bullet}$), 298 (72, $[M(^{35}Cl)_2+H]^{+\bullet}$).

Compound (10a). Isolated as a *white solid* (0.47 g, 40%), mp 98.1–98.6°C (Found: C, 52.3; H, 4.4; N, 14.1%. $C_{13}H_{13}Cl_2N_3O$ requires C, 52.4; H, 4.4; N, 14.1%). ν_{max} (KBr)/cm^{-1} 3630m, 3395bs, 3320bs, 3200m, 2872m, 1592bs, 1528m, 1508m, 1499m, 1458m, 826m, 701m. δ_H (300 MHz) 7.32–7.19 (5 H, m, ArH), 6.18 (1 H, s, H5), 5.85 (1 H, br s, exchangeable OH or NH), 4.78 (1 H, m, [4.84 (t, *J* 6.3 on D_2O exchange)], H3′), 3.72 (1 H, br s, H1′), 3.42 (1 H, br s, H1′), 2.62 (1 H,

br s, exchangeable OH or NH), 1.96–1.93 (2 H, m, H2′). δ_C (75 MHz) 178.0 (C6), 164.3 (C2 and C4), 143.8 (C1″), 128.9 (C3″ and C5 ″), 128.3 (C4″), 125.8 (C2″ and C6″), 100.6 (C5), 73.5 (C3′), 39.7 (C1′), 38.0 (C2′). Mass spectrum (ESI) *m/z* 302 (12%, $[M(^{37}Cl)_2 + H]^{+\bullet}$), 300 (54, $[M(^{35}Cl)(^{37}Cl) + H]^{+\bullet}$), 298 (84, $[M(^{35}Cl)_2 + H]^{+\bullet}$).

2-[3′-(4″-Bromophenyl)-3′-hydroxypropylamino]-4,6-dichloropyrimidine (9b) and 6-[3′-(4″-Bromophenyl)-3′-hydroxypropylamino]-2,4-dichloropyrimidine (10b)

Reaction of 3-amino-1-(4′-bromophenyl)propanol (8b) (0.50 g, 2.17 mmol) after reflux for 6 h gave an orange oil (0.81 g).

Compound (9b). Isolated as a *white solid* (0.26 g, 32%), mp 115.4–115.6°C (Found: C, 41.6; H, 3.0; N, 11.2%. $C_{13}H_{12}BrCl_2N_3O$ requires C, 41.6; H, 3.2; N, 11.1%). ν_{max} (KBr)/cm^{-1} 3752s, 3413bm, 2365m, 1654s, 1610s, 1560m, 1523s, 1491m, 1458m, 1256m, 1094m, 1010s, 817m, 786m. δ_H (300 MHz) 7.47 (2 H, d, *J* 8.4, H3″ and H5″), 7.24 (2 H, d, *J* 8.4, H2″ and H6″), 6.62 (1 H, s, H5), 5.80 (1 H, br s, exchangeable OH or NH), 4.74 (1 H, m, H3′), 3.84–3.74 (1 H, m, H1′), 3.72–3.36 (1 H, m, H1′), 3.13 (1 H, br d, *J* 3.5, exchangeable OH or NH), 1.97–1.90 (2 H, m, H2′). δ_C (75 MHz) 162.0 (C4 and C6), 161.9 (C2), 143.1 (C1″), 131.8 (C3″ and C5″), 127.5 (C2″ and C6″), 121.5 (C4″), 109.3 (C5), 71.4 (C3′), 39.2 (C1′), 38.8 (C2′). Mass spectrum (ESI) *m/z* 378 (56%, $[M(^{81}Br)(^{37}Cl)(^{35}Cl) - H]^{-\bullet}$), 376 (100, $[M(^{81}Br)(^{35}Cl)_2 - H]^{-\bullet}$), 374 (68, $[M\ (^{79}Br)(^{35}Cl)_2 - H]^{-\bullet}$).

Compound (10b). Isolated as a *white solid* (0.26 g, 32%), mp 54.3–54.7°C (Found: C, 41.0; H, 3.0; N, 10.8%; $[M + H]^{+\bullet}$, 375.9607. $C_{13}H_{12}Cl_2BrN_3$ requires C, 41.0; H, 3.2; N, 11.1%; $[M(^{79}Br^{35}Cl_2) + H]^{+\bullet}$, 375.9641). ν_{max} (KBr)/cm^{-1} 3413bs, 2346m, 1594bs, 1528m, 1480m, 1490m, 1448m, 1364m, 1278m, 1208m, 1121m, 1072m, 1010m, 975m. δ_H (300 MHz) 7.50 (2 H, d, *J* 8.4, H3″ and H5″), 7.22 (2 H, d, *J* 8.4, H2″ and H6″), 6.27 (1 H, s, H5), 6.18–5.59 (1 H, br s, exchangeable OH or NH), 4.80 (1 H, m, H3′), 3.67 (1 H, m, H1′), 3.46 (1 H, m, H1′), 2.97 (1 H, br s, exchangeable OH or NH), 2.16–1.94 (2 H, m, H2′). δ_C (75 MHz) 165.0 (C4), 164.0 (C2), 142.7 (C1″), 131.7 (C3″ and C5″), 127.33 (C2″ and C6″), 121.5 (C4″), 102.9 (C5), 72.1 (C3′), 39.2 (C1′), 38.5 (C2′), C6 not detected. Mass spectrum (ESI) *m/z* 378 (52%, $[M(^{81}Br)(^{37}Cl)(^{35}Cl) - H]^{-\bullet}$), 376 (100, $[M(^{81}Br)(^{35}Cl)_2 - H]^{-\bullet}$), 374 (60, $[M(^{79}Br)(^{35}Cl)_2 - H]^{-\bullet}$).

4,6-Dichloro-2-[3′-hydroxy-3′-(4″-methoxyphenyl) propylamino] pyrimidine (9c) and 2,4-Dichloro-6-[3′-hydroxy-3′-(4″-methoxyphenyl)propylamino]pyrimidine (10c)

Reaction of 3-amino-1-(4′-methoxyphenyl)propanol (8c) (1.00 g, 5.52 mmol) after reflux for 4 h gave a yellow gum (1.80 g).

Compound (9c). Isolated as a *white solid* (0.58 g, 32%), mp 87.0–87.2°C (Found: C, 51.3; H, 4.6; N, 12.8%. $C_{14}H_{15}Cl_2N_3O_2$ requires C, 51.4; H, 4.6; N, 12.8%). ν_{max} (KBr)/cm^{-1} 3425bs, 3281bs, 1604s, 1560s, 1523s, 1257s, 1094m, 819m, 787m. δ_H (300 MHz) 7.28 (2 H, d, *J* 8.7, H2″ and H6″), 6.89 (2 H, d, *J* 8.7, H3″ and H5″), 6.60 (1 H, s, H5), 5.82 (1 H, br s, exchangeable OH or NH), 4.75 (1 H, m, H3′), 3.80 (3 H, s, OCH_3), 3.70 (1 H, m, H1′), 3.50 (1 H, m, H1′), 2.63 (1 H, d, *J* 3.3, exchangeable OH or NH), 2.01–1.91 (2 H, m, H2′). δ_C (75 MHz) 162.0 (C2), 161.9 (C4 and C6), 159.4 (C4″), 136.3 (C1″), 127.1 (C2″ and C6″), 114.1 (C3″ and C5″), 109.1 (C5), 72.2 (C3′), 55.5 (OCH_3), 39.2 (C1′), 38.7 (C2′). Mass spectrum (ESI) *m/z* 352 (70%, $[M(^{35}Cl)(^{37}Cl) + Na]^{+\bullet}$), 350 (100, $[M(^{35}Cl)_2 + Na]^{+\bullet}$).

Compound (10c). Isolated as a *white solid* (0.65 g, 36%), mp 88.6–90.6°C (Found: C, 52.0; H, 5.0; N, 13.1%; $[M + H]^{+\bullet}$, 328.0618. $C_{14}H_{15}Cl_2N_3O_2$ requires C, 51.4; H, 4.6; N, 12.8%; $[M(^{35}Cl_2) + H]^{+\bullet}$, 328.0619). ν_{max} (KBr)/cm^{-1} 3414bs, 2980m, 1594s, 1512s, 1442m, 1248m, 1176m, 1121m, 1033m, 828m. δ_H (300 MHz) 7.16 (2 H, d, *J* 8.6, H2″ and H6″), 6.75 (2 H, d, *J* 8.7, H3″ and H5″), 6.24 (1 H, s, H5), 5.95–5.89 (1 H, br s, exchangeable OH or NH), 4.80 (1 H, m, H3′), 3.80 (3 H, s, OCH_3), 3.72 (1 H, m, H1′), 3.50 (1 H, br s, H1′), 2.31 (1 H, br s, exchangeable OH or NH), 2.01–1.97 (2 H, br m, H2′). δ_C (75 MHz) 166.6 (C4), 164.2 (C2), 158.5 (C4″), 136.6 (C1″), 126.7 (C2″ and C6″), 113.5 (C3″ and C5″), 102.7 (C5), 71.3 (C3′), 55.1 (OCH_3), 38.6 (C1′), 38.1 (C2′), C6 not observed. Mass spectrum (ESI) *m/z* 330 (55%, $[M(^{35}Cl)(^{37}Cl) + H]^{+\bullet}$), 328 (100, $[M(^{35}Cl)_2 + H]^{+\bullet}$).

4,6-Dichloro-2-[3′-hydroxy-3′-(4″-trifluoromethoxyphenyl) propylamino]pyrimidine (9d) and 2,4-Dichloro-6-[3′-hydroxy-3′-(4″-trifluoromethoxyphenyl)propylamino]pyrimidine (10d)

Reaction of 3-amino-1-(4′-trifluoromethoxyphenyl)propanol (8d) (0.48 g, 2.04 mmol) after reflux for 3 h gave an orange gum (0.75 g).

Compound (9d). Isolated as a *white solid* (0.37 g, 47%), mp 112.9–114.9°C (Found: C, 44.0; H, 3.1; N, 11.0%; $[M + H]^{+\bullet}$, 382.0326. $C_{14}H_{12}Cl_2F_3N_3O_2$ requires C, 44.1; H, 3.1; N, 11.0%; $[M(^{35}Cl_2) + H]^{+\bullet}$, 382.0337). ν_{max} (KBr)/cm^{-1} 3282bm, 1604m, 1560m, 1523m, 1454m, 1278s, 1164m, 789m. δ_H (300 MHz) 7.40 (2 H, d, *J* 8.8, H2″ and H6″), 7.22 (2 H, d, *J* 8.8, H3″ and H5″), 6.63 (1 H, s, H5), 5.88 (1 H, br s, exchangeable OH or NH), 4.78 (1 H, m, H3′), 3.79 (1 H, m, H1′), 3.48 (1 H, m, H1′), 3.30 (1 H, d, *J* 3.6, exchangeable OH or NH), 2.03–1.87 (2 H, m, H2′). δ_C (75 MHz) 162.2 (C2), 162.1 (C4 and C6), 148.7 (q, $^3J_{CF}$ 1.9, C4″), 142.8 (C1″), 127.2 (C2″ and C6″), 121.4 (q, $^4J_{CF}$ 1.1, C3″ and C5″), 120.6 (q, $^1J_{CF}$ 256.9, OCF_3), 71.2 (C3′), 39.3 (C1′), 38.9 (C2′). Mass spectrum (ESI) *m/z* 384 (52%, $[M(^{37}Cl)(^{35}Cl) + H]^{+\bullet}$), 382 (92, $[M(^{35}Cl)_2 + H]^{+\bullet}$).

Compound (10d). Isolated as a *white solid* (0.31 g, 40%), mp 78–80°C (Found: $[M + H]^{+\bullet}$, 382.0327. $C_{14}H_{12}{}^{35}Cl_2F_3N_3O_2$ requires $[M + H]^{+\bullet}$, 382.0337). ν_{max} (KBr)/cm^{-1} 3412bs, 3284m, 1638m, 1618s, 1560m, 1508m, 1236bm, 1213m, 1157m, 1198m, 1075m. δ_H (300 MHz) 7.40 (2 H, d, *J* 8.1, H2″ and H6″), 7.22 (2 H, d, *J* 8.1, H3″ and H5″), 6.28 (1 H, s, H5), 5.99–5.21 (1 H, br s, exchangeable OH or NH), 4.86 (1 H, s, H3′), 3.63 (1 H, m, H1′), 3.47 (1 H, m, H1′), 3.01 (1 H, br s, exchangeable OH or NH), 1.96–1.94 (2 H, m, H2′). δ_C (75 MHz) 174.3 (C6), 164.3 (C4), 160.1 (C2), 148.9 (q, $^3J_{CF}$ 1.5, C4″), 142.5 (C1″), 127.2 (C2″ and C6″), 121.3 (C3″ and C5″), 120.6 (q, $^1J_{CF}$ 257.2, OCF_3), 102.8 (C5), 72.2 (C3′), 39.3 (C1′), 38.2 (C2′). Mass spectrum (ESI) *m/z* 382 $[M + H]^{+\bullet}$.

Arylpropanolamino Dipyrrolidinylpyrimidines (4a)–(4d) and (5a)–(5d)

A stirred mixture of the arylpropanolamino dichloropyrimidines (9a)–(9d) or (10a)–(10d) (ca. 1 mmol) and pyrrolidine (20 mL) was heated under reflux for 10 h. The excess pyrrolidine was removed under vacuum and the resulting yellow oil was dissolved in CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL), dried, filtered, and concentrated to yield the product as a crude solid. In all cases, the ^1H NMR spectrum of the crude material indicated mainly the desired product. Recrystallization from ethyl acetate or chromatography gave the dipyrrolidinylpyrimidine compounds.

6-(3′-Hydroxy-3′-phenylpropylamino)-2,4-di(pyrrolidin-1-yl)pyrimidine (5a)

Reaction of 2,4-dichloro-6-(3′-hydroxy-3′-phenylpropylamino)pyrimidine (10a) (0.40 g, 1.34 mmol) and pyrrolidine gave a crude solid (0.52 g). Recrystallization from ethyl acetate gave the *pyrimidine* (5a) as a white, crystalline solid (0.27 g, 55%), mp 126°C (dec.) (Found: C, 68.6; H, 8.0; N, 19.0%; $[M + H]^{+\bullet}$, 368.2441. $C_{21}H_{29}N_5O$ requires C, 68.6; H, 8.0; N, 19.0%; $[M + H]^{+\bullet}$, 368.2450). ν_{max} (KBr)/cm^{-1} 3347bs, 3172bm, 2958bs, 2853bs, 1570bs, 1506bs, 1439bs, 1345bs, 1250m, 1172m, 975m, 788s, 764s, 701s. δ_H (400 MHz; [D$_6$]DMSO) 7.24–7.09 (5 H, m, ArH), 6.01 (1 H, br s, exchangeable OH or NH), 5.27 (1 H, br s, exchangeable OH or NH), 4.61 (1 H, s, H5), 4.50 (1 H, m, H3′), 3.29–3.00 (10 H, m, H1′ and NCH_2CH_2), 1.77–1.67 (10 H, m, H2′ and NCH_2CH_2). δ_C (100 MHz; [D$_6$]DMSO) 163.3 (C6), 161.0 (C4), 159.7 (C2), 146.0 (C1″), 127.9 (C3″ and C5″), 126.5 (C4″), 125.7 (C2″ and C6″), 72.2 (C5), 70.1 (C3′), 45.8, 45.5 (NCH_2CH_2), 40.0 (C1′), 37.3 (C2′); 25.0, 24.7 (NCH_2CH_2). Mass spectrum (ESI) *m/z* 368 $[M + H]^{+\bullet}$.

6-[3′-(4″-Bromophenyl)-3′-hydroxypropylamino]-2,4-di(pyrrolidin-1-yl)pyrimidine (5b)

Reaction of 6-[3′-(4″-bromophenyl)-3′-hydroxypropylamino]-2,4-dichloropyrimidine (10 b) (0.30 g, 0.80 mmol) and pyrrolidine gave a crude solid (0.32 g). Recrystallization from ethyl acetate gave the *pyrimidine* (5b) as a cream, crystalline solid (0.12 g, 32%), mp 136°C (dec.) (Found: C, 52.4; H, 6.1; N, 14.6%. $C_{21}H_{29}N_5OBrCl$ requires C, 52.4; H, 6.0; N, 14.4%). ν_{max} (KBr)/cm^{-1} 3413bm, 2966bm, 1572s, 1508m, 1474m, 1438m, 1346m. δ_H (300 MHz) 7.41 (2 H, d, *J* 8.4, H3″ and H5″), 7.24 (2 H, d, *J* 8.4, H2″ and H6″), 6.26 (1 H, br s, exchangeable OH or NH), 4.73 (1 H, s, H5), 4.65 (1 H, dd, *J* 10.0, 3.7, H3′), 4.31 (1 H, br s, exchangeable OH or NH), 4.21–4.08 (1 H, m, H1′), 3.67–3.40 (8 H, br m, NC*H*$_2$CH$_2$), 3.24–3.15 (1 H, m, H1′), 1.96–1.66 (10 H, m, H2′ and NCH$_2$C*H*$_2$). δ_C (75 MHz) 163.7 (C6), 161.4 (C4), 159.8 (C2), 143.8 (C1″), 131.3 (C3″ and C5″), 127.7 (C2″ and C6″), 120.5 (C4″), 72.7 (C5), 68.6 (C3′), 46.6, 46.2 (N*C*H$_2$CH$_2$), 41.7 (C1′), 37.1 (C2′), 25.7, 25.6 (NCH$_2$*C*H$_2$). Mass spectrum (ESI) *m*/*z* 448 (100%, [M(^{81}Br) + H]$^{+\bullet}$), 446 (96, [M(^{79}Br) + H]$^{+\bullet}$).

6-[3′-Hydroxy-3′-(4″-methoxyphenyl)propylamino]-2,4-di(pyrrolidin-1-yl)pyrimidine (5c)

Reaction of 2,4-dichloro-6-[-3′-hydroxy-3′-(4″-methoxyphenyl)propylamino]pyrimidine (10c) (0.40 g, 1.22 mmol) gave a crude, cream solid (0.50 g). Recrystallization from ethyl acetate gave the *pyrimidine* (5c) as a cream, crystalline solid (0.36 g, 75%), mp 134.7°C (dec.) (Found: C, 60.9; H, 7.3; N, 16.0%; [M + H]$^{+\bullet}$, 398.2547. $C_{22}H_{32}N_5O_2Cl$ requires C, 60.9; H, 7.4; N, 16.2%; [M + H]$^{+\bullet}$, 398.2556). ν_{max} (KBr)/cm^{-1} 3344bs, 2968bs, 2855bs, 1578s, 1500bs, 1344s, 1315s, 1303s, 1245s, 1172s, 1102m, 1071m, 1032s, 978s, 820s, 788s, 704m. δ_H (300 MHz) 7.28 (2 H, d, *J* 8.6, H2″ and H6″), 6.84 (2 H, d, *J* 8.7, H3″ and H5″), 5.69 (1 H, br s, exchangeable OH or NH), 4.73 (1 H, s, H5), 4.67 (1 H, dd, *J* 8.7, 3.9, H3′), 4.37 (1 H, br s, exchangeable OH or NH), 4.15–4.01 (1 H, m, H1′), 3.76 (3 H, s, OCH$_3$), 3.62–3.23 (8 H, br m, NC*H*$_2$CH$_2$), 3.22–3.14 (1 H, m, H1′), 1.94–1.73 (10 H, m, H2′ and NCH$_2$C*H*$_2$). δ_C (75 MHz) 164.0 (C4), 161.7 (C2), 158.8 (C4″), 137.0 (C1″), 127.2 (C2″ and C6″), 113.8 (C3″ and C5″), 72.6 (C5), 69.2 (C3′), 55.4 (OCH$_3$), 46.5, 46.1 (N*C*H$_2$CH$_2$), 41.3 (C1′), 37.3 (C2′), 25.7, 25.5 (NCH$_2$*C*H$_2$), C6 not detected. Mass spectrum (ESI) *m*/*z* 398 [M + H]$^{+\bullet}$.

6-[3′-Hydroxy-3′-(4″-trifluoromethoxyphenyl)propylamino]-2,4-di(pyrrolidin-1-yl)pyrimidine (5d)

Reaction of 2,4-dichloro-6-[3′-hydroxy-3′-(4″-trifluoromethoxyphenyl) propylamino]pyrimidine (10d) (0.20 g, 0.52 mmol) and pyrrolidine (15 mL) gave a brown solid (0.21 g). Recrystallization from ethyl acetate gave the *pyrimidine* (5d) as a cream, crystalline solid (0.08 g, 34%), mp 175.8–176.9°C (dec.) (Found: [M + H]$^{+\bullet}$, 452.2266. $C_{22}H_{28}F_3N_5O_2$ requires [M + H]$^{+\bullet}$, 452.2273). ν_{max} (KBr)/cm^{-1} 3327s, 3184m, 2966s, 2856s, 1745m, 1576s, 1506s, 1474s, 1438s, 1372m, 1347s, 1305m, 1260s, 1166s, 1079s, 1019m, 975m, 789s, 692m. δ_H (400 MHz) 7.40 (2 H, d, *J* 8.4, H2″ and H6″), 7.14 (2 H, d, *J* 8.4, H3″ and H5″), 6.40 (1 H, br s, exchangeable OH or NH), 4.75 (1 H, s, H5), 4.70 (1 H, dd, *J* 10.1, 3.6, H3′), 4.33–4.26 (1 H, br s, exchangeable OH or NH), 4.23–4.10 (1 H, m, H1′), 3.60–3.28 (8 H, br m, NC*H*$_2$CH$_2$), 3.27–3.15 (1 H, m, H1′), 1.99–1.75 (10 H, m, H2′ and NCH$_2$C*H*$_2$). δ_C (100 MHz) 164.4 (C6), 161.7 (C4), 160.2 (C2), 148.2 (q, $^3J_{CF}$ 1.8, C4″), 143.6 (C1″), 127.4 (C2″ and C6″), 120.9 (q, $^4J_{CF}$ 0.9, C3″ and C5″), 120.7 (q, $^1J_{CF}$ 256.6, OCF$_3$), 72.8 (C5), 68.6 (C3′), 46.5, 46.1 (N*C*H$_2$CH$_2$), 41.8 (C1′), 37.0 (C2′), 25.7, 25.5 (NCH$_2$*C*H$_2$). Mass spectrum (ESI) *m*/*z* 452 [M + H]$^{+\bullet}$.

2-(3′-Hydroxy-3′-phenylpropylamino)-4,6-di(pyrrolidin-1-yl)pyrimidine (4a)

A stirred mixture of 4,6-dichloro-2-[(3′-hydroxy-3′-phenyl)propylamino]pyrimidine (9a) (0.40 g, 1.34 mmol) and pyrrolidine (20 mL) was heated at reflux for 10 h. Workup as described above gave the crude solid (0.49 g). Purification by flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate/methanol, 4 : 4 : 1) gave the *pyrimidine* (4a) as a white, crystalline solid (0.34 g, 70%), mp 112.7–112.9°C (Found: C, 68.5; H, 7.8; N, 19.0%; [M + H]$^{+\bullet}$, 368.2428. $C_{21}H_{29}N_5O$ requires C, 68.6; H, 8.0; N, 19.0%; [M + H]$^{+\bullet}$, 368.2450). ν_{max} (KBr)/cm^{-1} 3415bs, 2966bm, 2867bm, 1594bs, 1559s, 1509s, 1456s, 1352m, 1318m. δ_H (300 MHz) 7.39–7.17 (5 H, m, ArH), 6.41 (1 H, br s, exchangeable OH and NH), 4.91 (1 H, br s, exchangeable OH and NH), 4.78 (1 H, dd, *J* 13.7, 3.2, H3′), 4.64 (1 H, s, H5), 4.20–4.07 (1 H, m, H1′), 3.51–3.41 (8 H, m, NC*H*$_2$CH$_2$), 3.29–3.22 (1 H, m, H1′), 2.04–1.68 (10 H, m, H2′ and NCH$_2$C*H*$_2$). δ_C (75 MHz) 162.5 (C4 and C6), 161.4 (C2), 144.9 (C1″), 128.4 (C3″ and C5″), 127.0 (C4″), 126.1 (C2″ and C6″), 73.5 (C5), 70.0 (C3′), 46.7 (N*C*H$_2$CH$_2$), 42.2 (C1′), 37.6 (C2′), 25.7 (NCH$_2$*C*H$_2$). Mass spectrum (ESI) *m*/*z* 368 [M + H]$^{+\bullet}$.

2-[3′-(4″-Bromophenyl)-3′-hydroxypropylamino]-4,6-di(pyrrolidin-1-yl)-pyrimidine (4b)

Reaction of 2-[3′-(4″-bromophenyl)-3-hydroxypropylamino]-4,6-dichloropyrimidine (9b) (0.25 g, 0.66 mmol) gave a crude solid (0.32 g). Recrystallization from ethyl acetate gave the *pyrimidine* (4b) as a cream, crystalline solid (0.16 g, 54%), mp 211.2°C (dec.) (Found: C, 52.4; H, 6.1; N, 14.6%. $C_{21}H_{29}N_5OBrCl$ requires C, 52.4; H, 6.1; N, 14.3%). ν_{max} (KBr)/cm^{-1} 3316bs, 2971bs, 2363m, 2350m, 1726m, 1638s, 1586m, 1557m, 1509s, 1477s, 1459s, 1350m, 1316m. δ_H (300 MHz) 7.42 (2 H, d, *J* 8.3, H3″ and H5″), 7.25 (2 H, d, *J* 8.3, H2″ and H6″), 6.33 (1 H, br s, exchangeable OH or NH), 5.78 (1 H, br s, exchangeable OH or NH), 4.74 (1 H, dd, *J* 10.8, 2.9, H3′), 4.63 (1 H, s, H5), 4.16–4.02 (1 H, m, H1′), 3.67–3.41 (8 H, m, NC*H*$_2$CH$_2$), 3.32–3.23 (1 H, m, H1′), 2.00–1.65 (10 H, m, H2′ and NCH$_2$C*H*$_2$). δ_C (75 MHz) 171.3 (C4 and C6), 167.5 (C2), 143.9 (C1″), 131.4 (C3″ and C5″), 127.5 (C2″ and C6″), 120.6 (C4″), 73.2 (C5), 68.9 (C3′), 41.5 (N*C*H$_2$CH$_2$), 37.3 (C1′), 29.8 (C2′), 25.4 (NCH$_2$*C*H$_2$). Mass spectrum (ESI) *m*/*z* 448 (98%, [M(^{81}Br) + H]$^{+\bullet}$), 446 (100, [M(^{79}Br) + H]$^{+\bullet}$).

2-[3′-Hydroxy-3′-(4″-methoxyphenyl)propylamino]-4,6-di(pyrrolidin-1-yl)pyrimidine (4c)

Reaction of 4,6-dichloro-2-[3′-hydroxy-3′-(4″-methoxyphenyl)propylamino]pyrimidine (9c) (0.50 g, 1.52 mmol) gave a crude solid (0.37 g). Purification by flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate/methanol, 4 : 4 : 1) gave the *pyrimidine* (4c) as a cream, crystalline solid (0.35 g, 58%), mp (HCl salt) 201.9–202.9°C (Found: C, 66.5; H, 7.9; N, 17.6%. $C_{22}H_{32}ClN_5O_2$ (HCl salt) requires C, 66.5; H, 7.9; N, 17.6%). ν_{max} (KBr)/cm^{-1} 3414bm, 2966bm, 2868bm, 1583s, 1560s, 1510s, 1459s, 1352s, 1318m, 1246m, 1172m, 1129m, 1074m, 1034m, 829m, 788m. δ_H (300 MHz) 7.29 (2 H, d, *J* 8.7, H2″ and H6″), 6.83 (2 H, d, *J* 8.7, H3″ and H5″), 6.49 (1 H, br s, exchangeable OH or NH), 4.74–4.70 (2 H, br m, H3′ and exchangeable OH or NH [4.75–4.70 (1H, dd, *J* 9.1, 4.1, H3′) on D_2O exchange]), 4.62 (1 H, s, H5), 4.17–4.07 (1 H, m, H1′), 3.76 (3 H, s, OCH$_3$), 3.66–3.38 (8 H, br m, NC*H*$_2$CH$_2$), 3.27–3.21 (1 H, m, H1′), 2.04–1.70 (10 H, m, H2′ and NCH$_2$C*H*$_2$). δ_C (75 MHz) 177.3 (C4 and C6), 161.6 (C2), 158.7 (C4″), 137.1 (C1″), 127.2 (C2″ and C6″), 113.8 (C3″ and C5″), 68.6 (C5), 66.0 (C3′), 55.4 (OCH$_3$), 46.3 (N*C*H$_2$CH$_2$), 41.9 (C1′), 37.4 (C2′), 25.4 (NCH$_2$*C*H$_2$). Mass spectrum (ESI) *m*/*z* 398 [M + H]$^{+\bullet}$.

2-[3′-Hydroxy-3′-(4″-trifluoromethoxyphenyl)propylamino]-4,6-di(pyrrolidin-1-yl)pyrimidine (4d)

Reaction of 4,6-dichloro-2-[3′-hydroxy-3′-(4″-trifluoromethoxyphenyl) propylamino]pyrimidine (9d) (0.20 g, 0.52 mmol) gave a crude solid (0.20 g). Purification by flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate/methanol, 4 : 4 : 1) gave the *pyrimidine* (4d) as a cream, crystalline solid (0.07 g, 30%), mp 122.4–124.3°C (Found: [M + H]$^{+\bullet}$, 452.2266. $C_{22}H_{28}F_3N_5O_2$ requires [M + H]$^{+\bullet}$, 452.2273). ν_{max} (KBr)/cm^{-1} 3416bm, 2971bm, 1584s, 1508s, 1460s, 1353s, 1264s, 1160m. δ_H (300 MHz) 7.32 (2 H, d, *J* 8.4, H2″ and H6″), 7.06 (2 H, d, *J* 8.4, H3″ and H5″), 6.55 (1 H, br s, exchangeable OH or NH), 4.92 (1 H, br s, exchangeable OH or NH), 4.70 (1 H, dd, *J* 10.8, 2.6, H3′), 4.57 (1 H, s, H5), 4.11–4.02 (1 H, m, H1′), 3.37–3.33 (8 H, m, NC*H*$_2$CH$_2$), 3.22–3.16 (1 H, m, H1′), 2.08–1.60 (10 H, m, H2′ and NCH$_2$C*H*$_2$). δ_C

(100 MHz) 162.2 (C4 and C6), 161.3 (C2), 148.1 (q, $^3J_{CF}$ 1.8, C4″), 143.7 (C1″), 127.2 (C2″ and C6″), 120.8 (q, $^4J_{CF}$ 0.6, C3″ and C5″), 120.7 (q, $^1J_{CF}$ 256.5, OCF_3), 73.4 (C5), 68.4 (C3′), 46.3 (NCH_2CH_2), 41.8 (C1′), 37.3 (C2′), 25.6 (NCH_2CH_2). Mass spectrum (ESI) m/z 452 $[M+H]^{+\bullet}$.

Attempted Preparation of the Di(pyrrolidinyl)pyrimidine (5a) Using 6-Chloro-2,4-di(pyrrolidin-1-yl)pyrimidine

A solution of 2-amino-1-phenylpropanol (8a) (0.10 g, 0.40 mmol), 6-chloro-2,4-di(pyrrolidin-1-yl)pyrimidine[25] (0.07 g, 0.40 mmol), and pyridine (10 mL) was heated at 100°C for 4 days followed by reaction at room temperature for 4 days. The mixture was concentrated, saturated $NaHCO_3$ (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried, filtered, and reduced under vacuum to yield a brown solid (0.12 g). The ^1H NMR spectrum of this solid indicated only recovered 6-chloro-2,4-di(pyrrolidin-1-yl)pyrimidine and the alcohol (8a).

Mosher's Esters of 6-(3′-Hydroxy-3′-phenylpropylamino)-2,4-di(pyrrolidin-1-yl)pyrimidine (11)

A solution of 1,3-dicyclohexylcarbodiimide (0.41 g, 1.98 mmol) in dry CH_2Cl_2 (5 mL) and 4-dimethylaminopyridine (0.05 g, 0.40 mmol) was added to a stirred solution of 6-(3′-hydroxy-3′-phenylpropylamino)-2,4-di(pyrrolidin-1-yl)pyrimidine (5a) (0.48 g, 1.31 mmol) and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(−)-MTPA] (0.36 mL, 1.98 mmol) in dry CH_2Cl_2 (5 mL). The reaction was stirred under nitrogen at room temperature for 1 h. The mixture was filtered and the filtrate was diluted with ethyl acetate (20 mL), washed with water (20 mL × 2), saturated aqueous NaCl (20 mL), dried, filtered, and concentrated to yield a crude solid (0.71 g). ^1H and ^{19}F NMR spectra of this crude material showed the *diastereomeric esters* (11) in a ca. 1 : 1 ratio. Column chromatography (SiO_2, 25% ethyl acetate/ether) gave a ca. 1 : 1 mixture of both isomers of the ester (11) as a cream solid (0.30 g, 40%) (Found: $[M+H]^{+\bullet}$, 584.2837. $C_{31}H_{35}F_3N_5O_3$ requires $[M+H]^{+\bullet}$, 584.2848). ν_{max} (KBr)/cm^{-1} 3630s, 3422bs, 2949m, 1751m, 1654m, 1560s, 1499m, 1450s, 1346m, 1247m, 1169m, 1121m, 1016m, 916m. δ_H (300 MHz) (for both isomers) 7.34–7.09 (20 H, m, ArH), 6.00 (1 H, m, H3′), 5.94 (1 H, m, H3′), 4.54 (1 H, s, H5), 4.51 (1 H, s, H5), 3.44–3.21 (26 H, m, H2′, OCH_3 and NCH_2CH_2), 2.33–2.14 (4 H, m, H1′), 2.11–1.79 (16 H, m, NCH_2CH_2). δ_C (75 MHz) 166.1 (C6 and CO), 163.4 (C4), 162.0 (C2), 138.9, 138.8, 132.4, 132.2, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.5, 127.0, 126.7 (ArCH), 123.6 (q, $^1J_{CF}$ 288.5, CF_3), 76.9 (C5′), 71.8 (C3′), 55.7, 55.5 (OCH_3), 46.3, 46.1 (NCH_2CH_2), 38.1, 37.9 (C1′), 36.2, 36.0 (C2′), 25.6, 25.4 (NCH_2CH_2), $COCH_3$ not detected. δ_F (282.4 MHz) −71.67 (s, CF_3), −72.10 (s, CF_3). Mass spectrum (ESI) m/z 584 $[M+H]^{+\bullet}$.

Attempts to separate the two isomers by fractional recrystallization also failed.

Preparation of Enantiomerically Enriched 6-(3′-Hydroxy-3′-phenylpropylamino)-2,4-di(pyrrolidin-1-yl)pyrimidine (5a)

(S)-3-Hydroxy-3-phenylpropanenitrile (12)

Using the method described by Smallridge et al.,[10] 3-oxo-3-phenylpropanenitrile (7a) (3.00 g, 20.67 mmol) was added to a pre-cooled (4°C) suspension of baker's yeast (414 g) in water (1860 mL) and the mixture stirred at 4°C for 7 days. The mixture was filtered, the filtrate extracted with ethyl acetate (7 × 150 mL), and the combined extracts were dried and evaporated. Flash-pad chromatography (SiO_2, 50% ether/light petroleum) of the crude product gave the (*S*)-alcohol (12) as a colourless oil (1.00 g, 33%), $[\alpha]_D^{20}$ −69° (*c* 0.4 in EtOH) [lit.[10] −57° (*c* 1.1 in EtOH), lit.[26] −52.5° (*c* 2.6 in EtOH), lit.[27] −57.7° (*c* 2.6 in EtOH) > 96% *e.e.* (*S*)]. δ_H (300 MHz) 7.40–7.31 (5 H, m, ArH), 5.01 (1 H, t, *J* 6.2, H1), 2.74 (2 H, d, *J* 6.3, H2), 2.66 (1 H, br s, exchangeable OH). δ_C (75 MHz) 141.3 (C1′), 129.1 (C3′ and C5′), 129.0 (C4′), 125.8 (C2′ and C6′), 117.5 (CN), 70.3 (C2), 28.1 (C1). The ^1H NMR data were consistent with literature data.[26,28]

(S)-3-Amino-1-phenylpropanol (S)-(8a)

A solution of (*S*)-3-hydroxy-3-phenylpropanenitrile (12) (0.20 g, 1.36 mmol) in dry THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.26 g, 6.80 mmol) in dry THF (5 mL) at 0°C. The reaction was worked up as described in the preparation of 3-amino-1-phenylpropanol (8a) to give the alcohol (*S*)-(8a) as a cream solid (0.18 g, 88%), $[\alpha]_D^{20}$ −34° (*c* 0.2 in MeOH) (lit.[27] for (*S*)-(8a) −43.65° (*c* 1.0 in MeOH), lit.[25] $[\alpha]_D^{25}$ −46.3° (*c* 1.46 in MeOH), 98% *e.e.*). The amino alcohol was predominantly (*S*), based on the literature[26,28] $[\alpha]_D$ values. The spectral data was consistent with the data for 3-amino-1-phenylpropanol (8a) and for literature data for the (*S*)-isomer.[26,28]

(S)-4,6-Dichloro-2-(3′-hydroxy-3′-phenylpropylamino)pyrimidine (S)-(9a) and (S)-2,4-Dichloro-6-(3′-hydroxy-3′-phenylpropylamino)pyrimidine (S)-(10a)

(*S*)-3-Amino-1-phenylpropanol (*S*)-(8a) (0.57 g, 3.77 mmol) was coupled with 2,4,6-trichloropyrimidine (0.44 mL, 3.77 mmol) in dioxane (20 mL) and $NaHCO_3$ (1.90 g, 22.62 mmol), and the isomers formed were separated as described above for the synthesis of the racemic dichloro compounds (9a) and (10a). The symmetrical compound (*S*)-(9a) (0.36 g, 32%) and the unsymmetrical compound (*S*)-(10a) (0.34 g, 30%) had spectral data consistent with those of the racemic symmetrical (9a) and unsymmetrical (10a) isomers.

(S)-6-(3′-Hydroxy-3′-phenylpropylamino)-2,4-di(pyrrolidin-1-yl)pyrimidine (S)-(5a)

(*S*)-2,6-Dichloro-6-(3′-hydroxy-3′-phenylpropylamino)pyrimidine (*S*)-(10a) (0.30 g, 1.01 mmol) was reacted with pyrrolidine (20 mL) and purified as described in the preparation of the racemic pyrimidine (5a). This gave the expected, predominantly (*S*)-(5a) as a cream solid (0.30 g, 81%). Spectral data was consistent with the data for the racemic compound (5a).

(S)-2-(3′-Hydroxy-3′-phenylpropylamino)-4,6-di(pyrrolidin-1-yl)pyrimidine (S)-(4a)

Similarly, (*S*)-4,6-dichloro-2-(3′-hydroxy-3′-phenylpropylamino) pyrimidine (*S*)-(9a) (0.30 g, 1.01 mmol) was reacted with pyrrolidine (20 mL) and purified as described in the preparation of the racemic pyrimidine (4a). This gave the predominantly (*S*)-(4a) as a white solid (0.32 g, 86%). Spectral data was consistent with the data of the racemic compound (4a).

(S)-6-(3′-Hydroxy-3′-phenylpropylamino)-2,4-di(pyrrolidin-1-yl)pyrimidine-(−)-MTPA Ester (S)-(11)

A solution of 1,3-dicyclohexylcarbodiimide (0.013 g, 0.06 mmol) and a few crystals of 4-dimethylaminopyridine in dry CH_2Cl_2 (5 mL) was reacted with a stirred solution of the predominantly (*S*)-6-(3′-hydroxy-3′-phenylpropylamino)-2,4-(dipyrrolidin-1-yl)pyrimidine (*S*)-(5a) (0.015 g, 0.04 mmol) and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(−)-MTPA] (0.011 mL, 0.06 mmol) in dry CH_2Cl_2 (5 mL) as described above for the synthesis of the Mosher's esters (11) to give crude (*S*)-6-(3′-hydroxy-3′-phenylpropylamino-2,4-di(pyrrolidin-1-yl)pyrimidine-(−)-MTPA ester (11) as a solid (0.02 g). Partial spectral data* δ_H (500 MHz) 4.55 (s, H5, (*R*)-isomer), 4.50 (s, H5, (*S*)-isomer), 6.05 (dd, *J* 9.0, 4.7, H3′, (*S*)-isomer), 6.00 (dd, *J* 8.1, 5.7, H3′, (*R*)-isomer). * δ_F (282.4 MHz) −71.40 (s, CF_3, (*R*)-isomer), −72.00 (s, CF_3, (*S*)-isomer). The ratios of corresponding pairs of peaks in the ^1H and ^{19}F NMR spectra showed two diastereisomers in the ratio of ca. 4 : 1, giving an enantiomeric excess of ca. 64% for the (*S*)-enantiomer (*S*)-(11).

* (*R*) and (*S*) isomers were assigned on the basis that the major diastereoisomer expected was the (*S*,*S*) compound since the pyrimidine (5a) was derived from the predominantly (*S*)-alcohol (12).

^{3}H-BTX Specific Binding

This Na^+ channel binding assay involves the use of a steroidal alkaloid, BTX, as a specific tritiated radioligand for the Na^+ channel neurotoxin binding site 2 in the rat brain homogenate.[29] The competitive ability of the compounds to displace the toxin at this site was measured.[30] The results are summarized in Table 1. Table 1 gives IC_{50} values (i.e. the amount of compound that leads to 50% inhibition of ^{3}H-BTX in the rat brain homogenate) and their ranges. The IC_{50} values were obtained from concentration response curves constructed using concentrations in the range of 0.1–100 μM using GraphPad Prism software ($n = 2$–4). Table 1 also displays the results for binding data at two specific concentrations (1 and 10 μM) and their confidence intervals. The binding data for dibucaine, the lead compound (1), and its pyrrolidinylpyrimidine analogue (3) are also included for comparison.

Sapphire Assay[6–8]

The procedures outlined in the Sapphire LPO-586 kit were carried out with the modifications described previously.[6]

Theoretical Calculations

The semi-empirical calculations were carried out using the PM3 method as implemented in the commercial Titan[31] software package. The *N*-methyl-bis(dimethylamino)pyrimidine radicals (13) and (14) first underwent a full geometry optimization at the PM3 level before the wave function for each was determined. The spin density was then calculated using the methods internal to this software.

The density functional calculations were carried out using the Gaussian98[32] software package. Calculations were performed using the B3LYP/6-311+G(d,p) method as implemented by this program. Calculations were performed on the *N*-methyl-bis(dimethylamino)pyrimidine radicals (13) and (14), as well as their closed shell counterparts. All structures were first fully optimized at the B3LYP/6-311+G(d,p) level before the final wave function was calculated.

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