Synthesis of 5-[(4-Phenylpiperazin-1-yl)methyl]pyrrolo-[2,3-*d*]pyrimidine Derivatives as Potential Dopamine D4 Receptor Ligands

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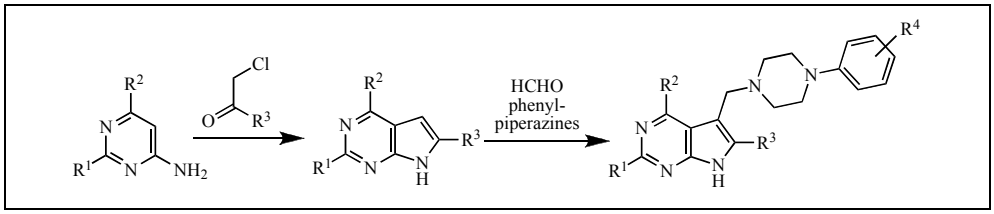

A series of pyrrolo[2,3-*d*]pyrimidine Mannich bases of type **9**, **12**, **15** and **16** have been prepared as potential dopamine D4 receptor ligands. The syntheses start from 4-aminopyrimidin-6-one **3** with pyrrole annulations and Mannich reactions with formaldehyde and phenylpiperazines **8** as new amine components.

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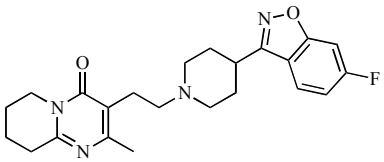
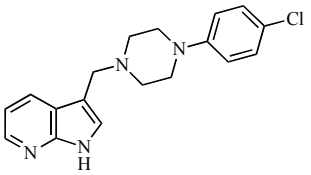
INTRODUCTION

The advances in molecular biology in the last decade have provided new insights into the mechanisms of various diseases. The family of dopamine receptor subtypes is a prime example for that [1]. The application of molecular cloning techniques led to the characterization of five different dopamine receptors, which can be distinguished into two classes, D1-like (D1 and D5) and D2-like (D2, D3, and D4), all belonging to the super family of G- protein-coupled receptors [2-4]. It is widely accepted that the dopaminergic system plays a key role in the manifestation of schizophrenic illnesses [5]. An association between the D4 receptor and schizophrenia was suggested by Seeman *et al.*, who had found elevated levels of the D4 receptor in the post-mortem brains of schizophrenic patients relative to controls [6]. For these reasons selective D4 antagonists were developed as a treatment for schizophrenia. Especially the atypical antipsychotics like clozapine or risperidone (**1**) show affinity for the D4 receptor. As a consequence many dopamine D4 receptor antagonists have been developed, *e.g.* 1*H*-pyrrolo[2,3-*b*]pyridines [7], isoxazoles [8,9], 2-naphthoate [10], benzamides [11], chromeno[3,4-*c*]pyridin-5-ones [12] and (aryloxy)-alkylamines [13]. The 7-azaindole derivative L-745,870 (**2**) was the farthest in development for this indication, but failed to demonstrate clinical efficacy [14]. Therefore we have been focused upon the development of aza-analogues of L-745,870 (**2**). Based on a combination of lead structures (**1**) and (**2**) we planned to prepare 5-aza analogues of L-745,870 (**2**) namely pyrrolo[2,3-*d*]pyrimidine derivatives with different residues (R^1 = -NMe_2; R^2 = -OH, -Cl, -H; R^3 = -H, -Me) (Scheme 1).

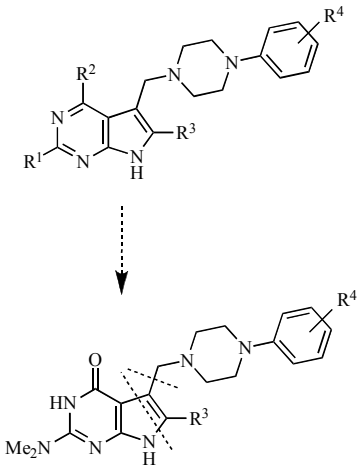
Scheme 1



Risperidone (1)



L-745,870 (2)



As L-745,870 (**2**) was prepared in a Mannich reaction, we planned to use the same approach because of its

simplicity. We found that Mannich bases of pyrrolo[2,3-*d*]-pyrimidines (R^1 = H, NH_2; R^2 = OH) had already been prepared with simple amines [15-17].

In this paper we are going to present the synthesis of 2-dimethylamino-pyrrolo[2,3-*d*]pyrimidine Mannich bases with 4-phenylpiperazines as new amine components.

RESULTS AND DISCUSSION

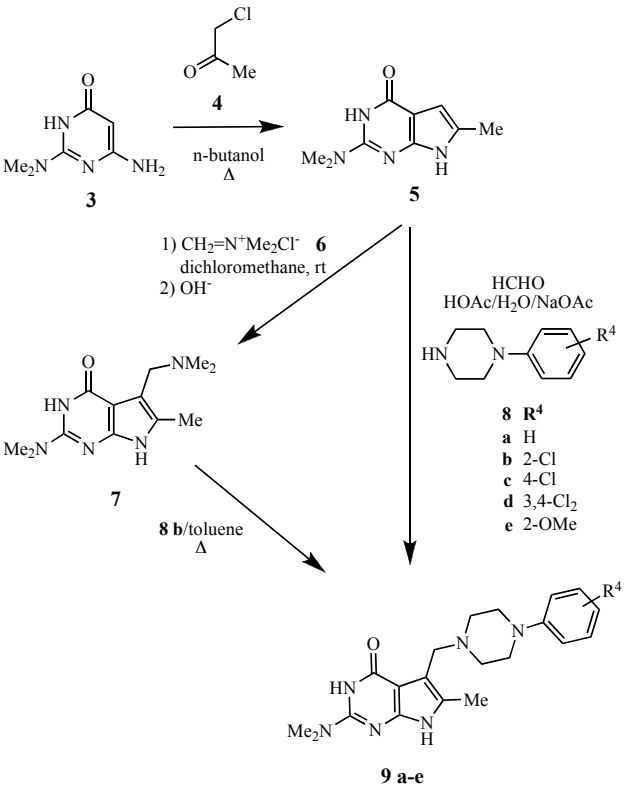
A short retrosynthetic consideration clarifies our approach. A pyrrole annulation on 6-aminopyrimidin-4(*3H*)-one with α-chloroacetone or α-chloroacetaldehyde will lead to pyrrolo[2,3-*d*]pyrimidin-4-ones and a subsequent Mannich reaction with formaldehyde and phenylpiperazines will give rise to the title compounds.

The starting material 6-aminopyrimidin-4(*3H*)-one **3** was easily prepared according to [18] by refluxing ethyl cyanoacetate and 1,1-dimethylaminoguanidine hydrochloride in a solution of sodium ethylate in ethanol for two hours. 6-Aminopyrimidin-4(*3H*)-one **3** was treated with α-chloroacetone (**4**) giving the new pyrrolo[2,3-*d*]pyrimidin-4-one **5**. Amongst others this methodology [19-21] was applied to synthesize the multi-targeted antifolate Pemetrexed [22]. In the range of this reaction other working groups have observed the formation of interesting by-products [21,23-25]. Already 1978 *Secrist et al*. had found out that besides the pyrrolo[2,3-*d*]pyrimidin-4-one derivative a furo[2,3-*d*]pyrimidine-2,4-diamine was formed [21]. Under our working conditions the pyrrolo[2,3-*d*]pyrimidone **5** was isolated as the main product ready for a Mannich reaction. There are two ways commonly used to prepare Mannich bases. On the one hand the introduction of a dimethylaminomethyl group with the help of *N,N*-dimethyl methyleneimmonium chloride followed by an amine exchange reaction with other amines *e.g*. phenylpiperazines and on the other hand the direct access, three-component-one-pot reaction, to the title compounds **9a-e**. We tried both ways in order to get the best yields.

The pyrrolo[2,3-*d*]pyrimidin-4-one **5** was stirred in dichloromethane solution with *N,N*-methyleneimmonium chloride (**6**) at rt overnight giving the Mannich base hydrochloride **7·HCl** from which the free base **7** was liberated with sodium hydroxide. Although amino-methylation of pyrrolo[2,3-*d*]pyrimidin-4-ones can take place at C-5 or C-6 [16,17], we made sure that substitution would occur only at C-5 by using the intermediate **5**, in which C-6 is already substituted with a methyl group. After that the amine exchange reaction was performed with Mannich base **7** and 2-chlorophenyl-piperazine (**8b**) in refluxing toluene. This long-known reaction is considered to involve an elimination-addition mechanism *via* an enimine intermediate [17].

We also tried to access the final products directly. Thus, compound **5**, formaldehyde (37% aqueous solution) and the phenylpiperazines **8 a-e** were each stirred in an acetic acid/water/sodium acetate solution [26] and the result were the 5-aminomethylpyrrolo[2,3-*d*]pyrimidine-4-ones **9 a-e**. Since the two methods did not differ significantly in the rate of yield, we preferred the direct access (Scheme 2).

Scheme 2

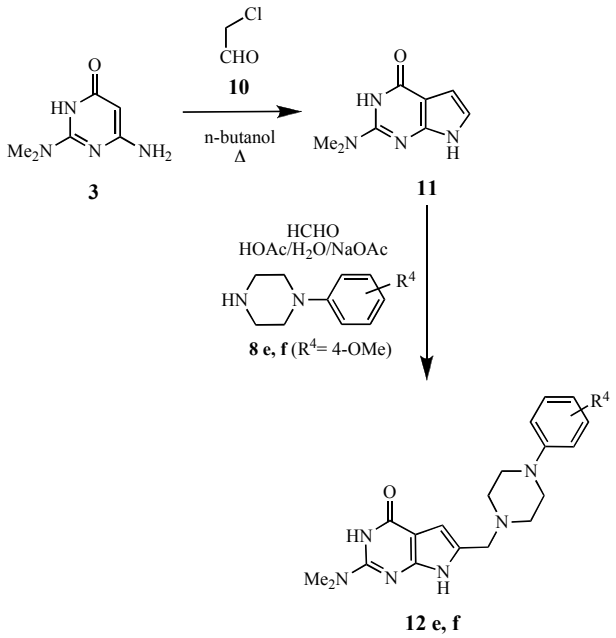


In a similar manner 6-aminopyrimidin-4(*3H*)-one **3** was treated with α-chloroacetaldehyde (**10**) giving the new pyrrolo[2,3-*d*]pyrimidin-4-one **11**. Mannich reaction with **11**, formaldehyde and phenylpiperazines **8 e, f** led to the pyrrolo[2,3-*d*]pyrimidines **12 e, f** (Scheme 3). An attack of the methyleneimmonium ion at C-6 instead of C-5 is favoured due to the better resonance stabilization of the carbenium ion in the σ-complex [16]. Here the dimethyl amino group and the pyrimidine ring are part of the delocalization area of the positive charge [16]. It was unequivocally proved by a Heteronuclear Multiple Quantum Correlation (HMQC) experiment that C-5 of **12 e, f** is unsubstituted. H-5 of the pyrrolo[2,3-*d*]pyrimidines **12 e, f** shows a strong CH coupling with C-5.

In order to learn more about the influence of the substituents at the pyrrolo[2,3-*d*]pyrimidine part on the effect as dopamine D4 receptor antagonist we varied it. We exchanged the hydroxyl function by a chloro substituent by refluxing **5** in phosphorous oxychloride to afford the 4-chloro derivative **13**. The corresponding Mannich bases **16 a, c-f** were then formed by stirring **13**

with formaldehyde and phenylpiperazines **8 a, c-f**. The chlorine at C-4 of **13** was removed by hydrogenation over palladium/carbon catalysis [27]. Finally the 7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-amine **14** was amino-methylated with formaldehyde and phenylpiperazines **8 e, f** to the title compounds **15 e, f** (Scheme 4).

Scheme 3



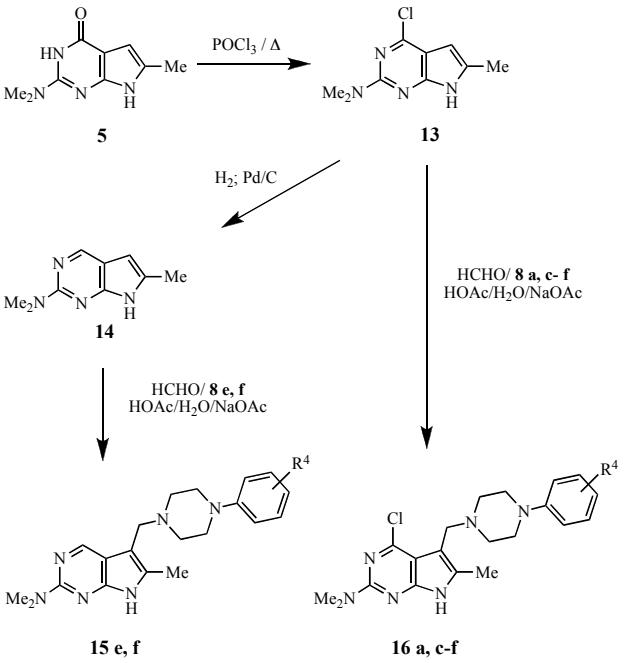
Dopamine D1 receptor binding was determined by measuring the ability to displace [^{3}H]SCH 23390 from porcine D1 receptors [28]. To assess $D2_{long}$, $D2_{short}$ [29], D3 [30] and D4.4 [31] affinities cloned human dopamine receptor subtypes stably expressed in Chinese hamster ovary cells (CHO) and the radioligand [^{3}H]spiperone were used for competition experiments.

The title compounds **9 a-e**, **12 e, f**, **15 e, f** and **16 a**, **c-f** possessed no appreciable affinity for any of the dopamine receptors tested. The title compounds **12 e** and **15 e** showed the best binding properties at the dopamine D4.4 receptor with Ki-values of 2,4 and 1,9 nm.

EXPERIMENTAL

Starting materials were obtained from commercial sources and were used without further purification. Solvents were dried through standard procedures. The reaction progress was observed by thin layer chromatography on commercial silica gel plates (Merck, silica gel F_{254} on aluminium sheets). Preparative chromatography was done on silica gel 60 (Merck). The medium pressure liquid chromatography (mplc) apparatus consisted of a Buechi B688 chromatography pump, a LKB Multirac 2111 fraction collector, and Buechi glass columns of different sizes. Melting points were determined in open capillary tubes on a Buechi 510 melting point apparatus and are uncorrected.

Scheme 4



Elemental analyses were performed by the *Institut für Organische Chemie* (University of Erlangen/Nürnberg) using Carlo Erba Elemental Analyzer 1108. ^{1}H nuclear magnetic resonance (^{1}H-nmr) spectra were determined with a Bruker Avance 360 (360 MHz) and Bruker Avance 600 (600MHz) spectrometer in appropriate deuterated solvents and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). Nmr data are given as multiplicity (s, singlet; d, doublet; t, triplett; m, multiplet), coupling constants (J), and number of protons. Mass spectra (MS) were taken with a Finnigan MAT TSQ 700 and Joel JMS-GCMATE II mass spectrometer in the electron impact mode (70eV). Infrared (ir) spectra were obtained on a Jasco FT/IR 410.

2-(Dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]-pyrimidin-4-one (5). 6-Amino-2-(dimethylamino)pyrimidin-4(*3H*)-one (**3**) (1.03 g, 6.7 mmol) was suspended in 15 ml water. Sodium acetate (0.45 g, 5.5 mmol) was added and the reaction mixture was stirred over 30 min at 100 °C in an oil bath. α-Chloroacetone (**4**) (0.87 g, 6.7 mmol) in a sodium acetate/water mixture (0.15 g NaOAc/ml water) was added in drops before the whole mixture was heated for 1.5 h at 100 °C. After cooling down, the product precipitated, was filtered off, washed with a small amount of acetone and dried in vacuo. 0.87 g (68 %) of a white powder was obtained, mp 283-284 °C; ir: NH 3363, CH 3203, CO 1680, C=C 1651cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.14 (s, 3H, 6-CH_3); 2.99 (s, 6H, N(CH_3)$_2$); 5.85 (s, 1H, 5-H); 10.30 (s, 1H, CONH); 10.94 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 13.0 (6-CH_3); 37.7 (N(CH_3)$_2$); 98.3 (5-C); 99.3 (4a-C); 126.6 (6-C); 150.7 (7a-C); 151.9 (2-C); 159.0 (4-C); ms: m/z 192 (M^+), 163, 148, 122. *Anal.* Calcd. for $C_9H_{12}N_4O$ (192.22): C, 56.24; H, 6.29; N, 29.15; Found: C, 56.32; H, 6.19; N, 29.29.

2-(Dimethylamino)-5-[(dimethylamino)methyl]-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (7). 2-(Dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**5**) (0.38 g, 2.0 mmol) was dissolved in dry

dichloromethane with *N,N*-dimethyl methyleneimmonium chloride (**6**) (0.24 g, 2.6 mmol) and stirred over night. The reaction mixture was quenched with 10 ml of water and after 2-3 min, the aqueous phase was made basic with a 10 % NaOH solution. The mixture was extracted three times with ethyl acetate. The combined organic extracts were washed with a saturated solution of sodium chloride and dried over sodium sulfate. The crude isolated product obtained on rotary evaporation was purified by column chromatography with ethyl acetate as the eluent to yield 0.37 g (75 %) as a pale-yellow powder, mp 261-262 °C; ir: NH 3223, CH 2929, C=C 1624 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.13 (s, 3H, 6-CH_3); 2.19 (m, 6H, $CH_2N(CH_3)_2$); 3.00 (s, 6H, $N(CH_3)_2$); 3.51 (m, 2H, $CH_2N(CH_3)_2$); 10.19 (s, 1H, CONH); 10.82 (s, 1H, NH); ms: m/z 249 (M^+), 204, 192. *Anal.* Calcd. for $C_{12}H_{19}N_5O$ (249.31): C, 57.81; H, 7.68; N, 28.09. Found: C, 57.46; H, 7.59; N, 27.73.

5-{[4-(2-Chlorophenyl)piperazin-1-yl]methyl}-2-(dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (9 b). 2-Chlorophenylpiperazine (**8 b**) (0.45 g, 2.3 mmol) was added to a solution of 2-(dimethylamino)-5-[(dimethylamino)methyl]-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**7**) (0.37 g, 1.5 mmol) and the mixture was refluxed for 5 h. The solvent was removed *in vacuo* and the crude **9 b** was purified by mplc using cyclohexane:ethyl acetate:methanol (7:2:1) as eluent to yield 0.39 g (61 %) as a pale-yellow powder, mp 245-246 °C; ir: NH 3091, CH 2923, CO 1662, C=C 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.18 (s, 3H, 6-CH_3); 2.63 (m, 4H, 2× $N^1CH_2CH_2$); 2.96 (m, 4H, 2× $N^1CH_2CH_2$); 3.02 (s, 6H, $N(CH_3)_2$); 3.70 (s, 2H, $ArCH_2N$); 7.03 (t, 1H, 4'-H, J = 7 Hz); 7.15 (d, 1H, 6'-H, J = 7 Hz); 7.29 (t, 1H, 5'-H, J = 7 Hz); 7.40 (d, 1H, 3'-H, J = 7 Hz); 10.19 (s, 1H, CONH); 10.92 (s, 1H, NH); ms: m/z 402 (M^+), 400 (M^+), 204, 196. *Anal.* Calcd. for $C_{20}H_{25}ClN_6O$ (400.90): C, 59.92; H, 6.29; N, 20.96 Found: C, 59.58; H, 6.44; N, 20.59.

General procedure for preparation of Mannich bases 9 a-e. The appropriate phenylpiperazine **8** (1.0 mmol) and sodium acetate (0.14 g, 1.0 mmol) were dissolved in acetic acid (4 ml) and water (2 ml). 37 % aqueous formaldehyde (0.9 ml, 1.2 mmol) was added and the reaction mixture was stirred for five minutes. 2-(Dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**5**) (0.19 g, 1.0 mmol) was added and the resulting solution was stirred at room temperature overnight. The reaction mixture was basified with 2 *M* sodium hydroxide and double-extracted with ethyl acetate. The extracts were washed with brine (50 ml), combined and dried over sodium sulfate. The ethyl acetate solution was concentrated. The crude products were purified by column chromatography using cyclohexane:ethyl acetate:methanol (7:2:1) as eluent.

2-(Dimethylamino)-6-methyl-5-[(4-phenylpiperazine-1-yl) methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (9 a). This compound was obtained as a white powder; yield 0.20 g (54 %); mp 237-238 °C; ir: NH 3262, CH 2925, CO 1654, C=C 1597 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.30 (s, 3H, 6-CH_3); 2.57 (m, 4H, 2× $N^1CH_2CH_2$); 3.02 (s, 6H, $N(CH_3)_2$); 3.09 (m, 4H, 2× $N^1CH_2CH_2$); 3.69 (s, 2H, $ArCH_2N$); 6.75 (m, 1H, 4'-H); 6.89 (m, 2H, 2'- and 6'-H); 7.18 (m, 2H, 3'- and 5'-H); 10.21 (s, 1H, CONH); 10.89 (s, 1H, NH); ms: m/z 366 (M^+), 204, 162.

Anal. Calcd. for $C_{20}H_{26}N_6O$ (366.46): C, 65.55; H, 7.15; N, 22.93. Found: C, 65.68; H, 7.33; N, 22.56.

5-{[4-(2-Chlorophenyl)piperazin-1-yl]methyl}-2-(dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (9 b). This compound was obtained as a pale-yellow powder; yield 0.21 g (52 %). See above for analysis.

5-{[4-(4-Chlorophenyl)piperazin-1-yl]methyl}-2-(dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (9 c). This compound was obtained as a pale-yellow powder; yield 0.20 g (49 %); mp 242-243 °C; ir: NH 3322, CH 3168, CO 1681, C=C 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.15 (s, 3H, 6-CH_3); 2.56 (m, 4H, 2× $N^1CH_2CH_2$); 3.00 (s, 6H, $N(CH_3)_2$); 3.08 (m, 4H, 2× $N^1CH_2CH_2$); 3.65 (s, 2H, $ArCH_2N$); 6.90 (m, 2H, 2'- and 6'-H); 7.20 (m, 2H, 3'- and 5'-H); 10.20 (s, 1H, CONH); 10.90 (s, 1H, NH); ms: m/z 404 (M^+), 402 (M^+), 400 (M^+), 204, 196. *Anal.* Calcd. for $C_{20}H_{25}ClN_6O$ (400.90): C, 59.92; H, 6.29; N, 20.96. Found: C, 59.94; H, 6.20; N, 20.72.

5-{[4-(3,4-Dichlorophenyl)piperazin-1-yl]methyl}-2-(dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (9 d). This compound was obtained as a pale-yellow powder; yield 0.22 g (51 %); mp 238-239 °C; ir: NH 3320, CH 2958, CO 1661, C=C 1651 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.15 (s, 3H, 6-CH_3); 2.55 (m, 4H, 2× $N^1CH_2CH_2$); 2.99 (s, 6H, $N(CH_3)_2$); 3.13 (m, 4H, 2× $N^1CH_2CH_2$); 3.66 (s, 2H, $ArCH_2N$); 6.89 (dd, 1H, 6'-H, J = 2.5 Hz, 8.9 Hz); 7.08 (d, 1H, 2'-H, J = 2.5 Hz); 7.36 (d, 1H, 5'-H, J = 8.9 Hz); 10.17 (s, 1H, CONH); 10.90 (s, 1H, NH); ms: m/z 438 (M^+), 436 (M^+), 434 (M^+), 230, 204, 188. *Anal.* Calcd. for $C_{20}H_{24}Cl_2N_6O$ (435.35): C, 55.18; H, 5.56; N, 19.30. Found: C, 55.54; H 5.81; N, 18.93.

2-(Dimethylamino)-5-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (9 e). This compound was obtained as a pale-yellow powder; yield 0.20 g (51 %), mp 211-212 °C; ir: NH 3262, CH 2954, CO 1651, C=C 1595 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.18 (s, 3H, 6-CH_3); 2.56 (m, 4H, 2× $N^1CH_2CH_2$); 2.95 (m, 4H, 2× $N^1CH_2CH_2$); 3.03 (s, 6H, $N(CH_3)_2$); 3.69 (s, 2H, $ArCH_2N$); 3.77 (s, 3H, OMe); 6.91 (m, 4H, 3'- to 6'-H); 10.15 (s, 1H, CONH); 10.90 (s, 1H, NH); ms: m/z 396 (M^+), 204, 192. *Anal.* Calcd. for $C_{21}H_{28}N_6O_2$ (396.49): C, 63.62; H, 7.12; N, 21.20. Found: C, 63.25; H, 7.33; N, 20.82.

2-(Dimethylamino)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (11). Preparation and purification according to **5** using 0.52 g of α-chloroacetaldehyde (**10**) (6.7 mmol) to yield 0.75 g (63 %) as a pale-yellow powder, mp 259-260 °C; ir: NH 3365, CH 3213, CO 1679, C=C 1652 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.04 (s, 6H, $N(CH_3)_2$); 6.20 (d, 1H, 5-H, J = 2.5 Hz); 6.64 (d, 1H, 6-H, J = 2.5 Hz); 10.36 (s, 1H, CONH); 11.07 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 38.0 ($N(CH_3)_2$); 99.5 (4a-C); 101.5 (5-C); 117.1 (6-C); 150.9 (7a-C); 152.4 (2-C); 159.3 (4-C); ms: m/z 178 (M^+), 134. *Anal.* Calcd. for $C_8H_{10}N_4O$ (178.19): C, 53.92; H, 5.66; N, 31.44. Found: C, 53.79; H, 5.53; N, 31.29.

2-(Dimethylamino)-6-{[4-(2-methoxyphenyl)piperazine-1-yl]methyl}-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidine-4-one (12 e). Preparation and purification according to **9 a-e** using 2-(dimethylamino)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**11**) (0.18 g, 1.0 mmol) and 2-methoxyphenylpiperazine (**8 e**) (0.19 g, 1.0 mmol) to yield 0.18 g (48 %) as a beige powder; mp 211-212 °C; ir: NH 3155, CH 2938, CO 1656, C=C 1589 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.69 (m, 4H, 2× $N^1CH_2CH_2$); 3.11 (m, 4H, 2× $N^1CH_2CH_2$); 3.17 (s, 6H, $N(CH_3)_2$); 3.60 (s, 2H, $ArCH_2N$); 3.89 (s, 3H, 2'-OCH_3); 6.38 (s, 1H, 5-H); 6.87-7.06 (m, 4H, 2'-H to 6'-H); 8.50 (s, 1H, CONH); 8.98 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 37.7 ($N(CH_3)_2$); 50.7 (2×$N^1CH_2CH_2$); 53.3 (2× $N^1CH_2CH_2$); 55.4 ($ArCH_2N$); 55.6 (OCH_3); 99.5 (4a-C); 101.2 (5-C); 111.3 (3'-C); 118.2 (6'-C); 121.0 (5'-C); 122.9 (4'-C); 128.1 (6-C); 141.3 (7a-C); 151.8 (1'- and 2'-C); 152.3 (2-C); 159.9 (4-C); ms:

m/z 382 (M^+), 192, 150. *Anal.* Calcd. for $C_{20}H_{26}N_6O_2$ (382.46): C, 62.81; H, 6.85; N, 21.97. Found: C, 62.46; H, 7.18; N, 21.63.

2-(Dimethylamino)-6-{[4-(4-methoxyphenyl)piperazin-1-yl]methyl}-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (12 f). Preparation and purification according to **9 a-e** using 0.18 g (1.0 mmol) 2-(dimethylamino)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**11**) and 0.19 g 4-methoxyphenylpiperazine (**8 f**) (1.0 mmol) to yield 0.19 g (49 %) as a beige powder; mp 226-227 °C; ir: NH 3155, CH 2930, CO 1660, C=C 1589 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.61 (m, 4H, 2× $N^1CH_2CH_2$); 3.08 (m, 4H, 2× $N^1CH_2CH_2$); 3.13 (s, 6H, $N(CH_3)_2$); 3.55 (s, 2H, $ArCH_2N$); 3.77 (s, 3H, 4'-OCH_3); 6.34 (s, 1H, 5-H); 6.80-6.94 (m, 4H, 2'-H to 6'-H); 8.43 (s, 1H, CONH); 8.78 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 37.6 ($N(CH_3)_2$); 50.6 (2×$N^1CH_2CH_2$); 53.1 (2× $N^1CH_2CH_2$); 55.6 ($ArCH_2N$); 55.6 (OCH_3); 99.5 (4a-C); 101.3 (5-C); 114.5 (2'- and 6'-C); 118.2 (3'- and 5'-C); 128.1 (6-C); 145.6 (7a-C); 151.8 (1'- and 4'-C); 153.9 (2-C); 159.8 (4-C); ms: m/z 382 (M^+), 192, 150 *Anal.* Calcd. for $C_{20}H_{26}N_6O_2$ (382.46): C, 62.81; H, 6.85; N, 21.97. Found: C, 62.51; H, 6.82; N, 21.85.

4-Chloro-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (13). 2-(Dimethylamino)-6-methyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**5**) (0.96 g, 5.0 mmol) was suspended in 30 ml of phosphorous oxychloride, cautiously heated and finally refluxed for 1.5 h. After cooling the reaction mixture was concentrated in vacuo. Some ice and later water was very cautiously added to the residue and the mixture was neutralized with sodium hydrogen carbonate salt. The product precipitated, was filtered off and dried. Purification by flash chromatography with cyclohexane : ethyl acetate : methanol (8 : 1.5 : 0.5) as eluent. Yield 0.68 g (63 %) as a white powder; mp 169-170 °C; ir NH 3221, CH 2925, C=C 1624 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.33 (s, 3H, 6-CH_3); 3.18 (s, 6H, $N(CH_3)_2$); 6.03 (s, 1H, 5-H); 8.34 (s, 1H, NH); ms: m/z 212 (M^+), 210 (M^+), 195, 181. *Anal.* Calcd. for $C_9H_{11}ClN_4$ (210.66): C, 51.31; H, 5.26; N, 26.60. Found: C, 51.01; H, 5.06; N, 26.52.

***N,N*,6-Trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (14).** 4-Chloro-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**13**) (0.59 g, 2.8 mmol) and palladium carbon (0.26 g; 10 % Pd) are dissolved in a mixture of 25 ml dry methanol with concentrated ammonia (0.2 ml, 3.0 mmol) and stirred for 7 h under a hydrogen atmosphere. Thereafter the catalyst was filtered off and the filtrate was concentrated in vacuo. Purification by flash chromatography with cyclohexane : ethyl acetate : methanol (8 : 1.5 : 0.5) as eluent. Yield 0.42 g (86 %) as white crystals, mp 153-154 °C; ir: NH 3220, CH 2927, C=C 1623 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.34 (s, 3H, 6-CH_3); 3.20 (s, 6H, $N(CH_3)_2$); 6.01 (s, 1H, 5-H); 8.10 (s, 1H, NH); 8.48 (s, 1H, 4-H); ms: m/z 176 (M^+), 161, 147. *Anal.* Calcd. for $C_9H_{12}N_4$ (176.22): C, 61.34; H, 6.86; N, 31.79. Found: C, 61.32; H, 6.81; N, 31.42.

5-[4-(2-Methoxyphenyl)piperazin-1-ylmethyl]-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (15 e). Preparation and purification according to **9 a-e** using *N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**14**) (0.18 g, 1.0 mmol) and 2-methoxyphenylpiperazine (**8 e**) (0.19 g, 1.0 mmol) to yield 0.21 g (56 %) as a pale-yellow powder; mp 177-178 °C; ir: NH 3167, CH 2935, C=C 1628 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.32 (s, 3H, 6-CH_3); 2.66 (m, 4H, 2× $N^1CH_2CH_2$); 3.06 (m, 4H, 2× $N^1CH_2CH_2$); 3.20 (s, 6H, $N(CH_3)_2$); 3.61 (s, 2H, $ArCH_2N$); 3.84 (s, 3H, 2'-OCH_3); 6.84 (m, 1H, 6'-H); 6.91 (m, 2H, 3'- and 5'-H); 6.97 (m, 1H, 4'-H); 7.91 (s, 1H, NH); 8.69 (s, 1H, H-4); ms: m/z 380 (M^+), 192, 150. *Anal.* Calcd. for $C_{21}H_{28}N_6O$ (380.49): C, 66.29; H, 7.42; N, 22.09. Found: C, 66.20; H, 7.23; N, 21.88.

5-[4-(4-Methoxyphenyl)piperazin-1-ylmethyl]-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (15 f). Preparation and purification according to **9 a-e** using *N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**14**) (0.18 g, 1.0 mmol) and 4-methoxyphenylpiperazine (**8 f**) (0.19 g, 1.0 mmol) to yield 0.21 g (54 %) as a pale-yellow powder; mp 192-193 °C, ir: NH 3168, CH 2933, C=C 1631 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.32 (s, 3H, 6-CH_3); 2.62 (m, 4H, 2× $N^1CH_2CH_2$); 3.07 (m, 4H, 2× $N^1CH_2CH_2$); 3.20 (s, 6H, $N(CH_3)_2$); 3.60 (s, 2H, $ArCH_2N$); 3.76 (s, 3H, 4'-OCH_3); 6.79-6.97 (m, 4H, 2'-, 3'-, 5'- and 6'-H); 7.94 (s, 1H, NH); 8.67 (s, 1H, 4-H); ms: m/z 380 (M^+), 192, 150. *Anal.* Calcd. for $C_{21}H_{28}N_6O$ (380.49): C, 66.29; H, 7.42; N, 22.09. Found: C, 66.21; H, 7.16; N, 21.88.

4-Chloro-*N,N*,6-trimethyl-5-[(4-phenylpiperazin-1-yl)-methyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (16 a). Preparation and purification according to **9 a-e** using 4-chloro-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**13**) (0.21 g, 1.0 mmol) and phenylpiperazine (**8 a**) (0.16 g, 1.0 mmol) to yield 0.24 g (62 %) as a pale-yellow powder; mp 194-195 °C, ir: NH 3189, CH 2823, C=C 1626 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.32 (s, 3H, 6-CH_3); 2.67 (m, 4H, 2× $N^1CH_2CH_2$); 3.15 (m, 4H, 2× $N^1CH_2CH_2$); 3.16 (s, 6H, $N(CH_3)_2$); 3.72 (s, 2H, $ArCH_2N$); 6.82 (m, 1H, 4'-H); 6.91 (m, 2H, 2'- and 6'-H); 7.23 (m, 2H, 3'- and 5'-H); 8.08 (s, 1H, NH); ms: m/z 386 (M^+), 384 (M^+), 222, 162. *Anal.* Calcd. for $C_{20}H_{25}ClN_6$ (384.91): C, 62.41; H, 6.55; N, 21.83. Found: C, 62.24; H, 6.49; N, 21.45.

4-Chloro-5-{[4-(4-chlorophenyl)piperazin-1-yl]methyl}-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (16 c). Preparation and purification according to **9 a-e** using 4-chloro-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**13**) (0.21 g, 1.0 mmol) and 4-chlorophenylpiperazine (**8 c**) (0.20 g, 1.0 mmol) to yield 0.24 g (58 %) as a pale-yellow powder; mp 212-213 °C, ir: NH 3186, CH 2823, C=C 1626 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.32 (s, 3H, 6-CH_3); 2.64 (m, 4H, 2× $N^1CH_2CH_2$); 3.11 (m, 4H, 2× $N^1CH_2CH_2$); 3.17 (s, 6H, $N(CH_3)_2$); 3.67 (s, 2H, $ArCH_2N$); 6.81 (m, 2H, 2'- and 6'-H); 7.17 (m, 2H, 3'- and 5'-H); 8.05 (s, 1H, NH); ms: m/z 422 (M^+), 420 (M^+), 418 (M^+), 222, 196. *Anal.* Calcd. for $C_{20}H_{24}Cl_2N_6$ (419.35): C, 57.28; H, 5.77; N, 20.04. Found: C, 57.02; H, 5.75; N, 19.68.

4-Chloro-5-{[4-(3,4-dichlorophenyl)piperazin-1-yl]methyl}-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (16 d). Preparation and purification according to **9 a-e** using 4-chloro-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**13**) (0.21 g, 1.0 mmol) and 3,4-dichlorophenylpiperazine (**8 d**) (0.24 g, 1.0 mmol) to yield 0.29 g (65 %) as a pale-yellow powder; mp 210-211 °C, ir: NH 3197, CH 2823, C=C 1628 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.32 (s, 3H, 6-CH_3); 2.62 (m, 4H, 2× $N^1CH_2CH_2$); 3.12 (m, 4H, 2× $N^1CH_2CH_2$); 3.17 (s, 6H, $N(CH_3)_2$); 3.66 (s, 2H, $ArCH_2N$); 6.70 (dd, 1H, 6'-H, J = 3.0, 8.9 Hz); 6.92 (d, 1H, 2'-H, J = 3.0 Hz); 7.24 (d, 1H, 5'-H, J = 8.9 Hz); 7.94 (s, 1H, NH); ms: m/z 456 (M^+), 454 (M^+), 452 (M^+), 222, 188. *Anal.* Calcd. for $C_{20}H_{23}Cl_3N_6$ (453.80): C, 52.94; H, 5.11; N, 18.52. Found: C, 52.81; H, 5.16; N, 18.18.

4-Chloro-5-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (16 e). Preparation and purification according to **9 a-e** using 4-chloro-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**13**) (0.21 g, 1.0 mmol) and 2-methoxyphenylpiperazine (**8 e**) (0.19 g, 1.0 mmol) to yield 0.26 g (63 %) as a pale-yellow powder; mp 195-196 °C, ir: NH 3290, CH 2937, C=C 1624 cm^{-1}; ^1H nmr

($CDCl_3$): δ 2.33 (s, 3H, 6-CH_3); 2.70 (m, 4H, 2× $N^1CH_2CH_2$); 3.04 (m, 4H, 2× $N^1CH_2CH_2$); 3.17 (s, 6H, $N(CH_3)_2$); 3.71 (s, 2H, $ArCH_2N$); 3.85 (s, 3H, OCH_3); 6.81-7.00 (m, 4H, 3'- to 6'-H); 7.95 (s, 1H, NH); ms: m/z 416 (M^+), 414 (M^+), 222, 192. *Anal.* Calcd. for $C_{21}H_{27}ClN_6O$ (414.93): C, 60.79; H, 6.56; N, 20.25. Found: C, 60.86; H, 6.56; N, 20.00.

4-Chloro-5-{[4-(4-methoxyphenyl)piperazin-1-yl]methyl}-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (16 f). Preparation and purification according to **9 a-e** using 4-chloro-*N,N*,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**13**) (0.21 g, 1.0 mmol) and 4-methoxyphenylpiperazine (**8 f**) (0.19 g, 1.0 mmol) to yield 0.29 g (69 %) as a pale-yellow powder; mp 195-196 °C, ir: NH 3294, CH 2935, C=C 1626 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.32 (s, 3H, 6-CH_3); 2.67 (m, 4H, 2× $N^1CH_2CH_2$); 3.05 (m, 4H, 2× $N^1CH_2CH_2$); 3.17 (s, 6H, $N(CH_3)_2$); 3.69 (s, 2H, $ArCH_2N$); 3.76 (s, 3H, OCH_3); 6.80-6.84 (m, 2H, 2'- and 6'-H); 6.86-6.89 (m, 2H, 3'- and 5'-H); 8.12 (s, 1H, NH); ms: m/z 416 (M^+), 414 (M^+), 222, 192. *Anal.* Calcd. for $C_{21}H_{27}ClN_6O$ (414.93): C, 60.79; H, 6.56; N, 20.25. Found: C, 60.51; H, 6.41; N, 19.91.

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