Solid Phase Synthesis of Diamino-Substituted Pyrimidines

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2,4- and 4,6-Diamino-substituted pyrimidines are known for their biological activity in many therapeutic areas. A novel solid-phase synthesis of this class of compounds by nucleophilic aromatic substitution has been set up and the reactivity of differently substituted solid-supported pyrimidines with properly selected amines has been studied. Using this methodology a small library of diamino-substituted pyrimidines has been prepared.

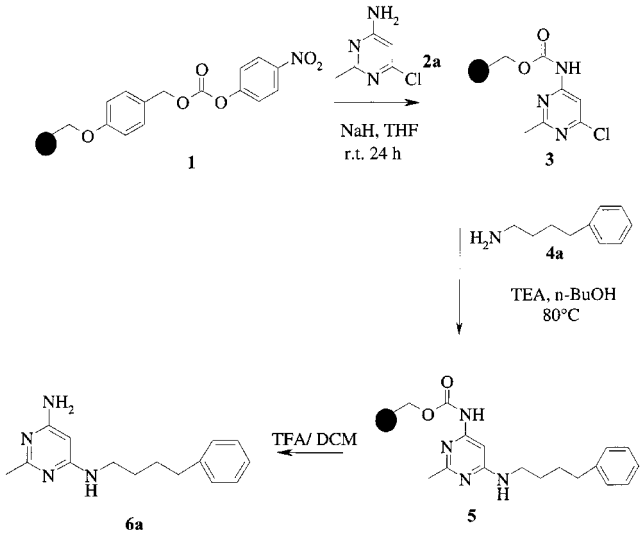
Introduction

The pyrimidine ring is present in many biologically active molecules and 2,4- and 4,6-diamino-substituted pyrimidines, in particular, are known for their antiviral,[1] antidepressant[2] and antiprotozoan activity.[3] In order to further investigate other possible biological activities of this class of compounds, the set up of a high throughput approach is desirable. For this reason we decided to develop a solid-phase synthesis for the creation of combinatorial libraries.

In addition to a number of reports describing the solution-phase synthesis of pyrimidines,[4] examples of solid-phase synthesis of these compounds can be found in the literature, either by de novo synthesis of the pyrimidine core onto the resin,[5,6] or by initial attachment of the pyrimidine to the resin and subsequent modification.[7,8]

For the synthesis of the 2,4- and 4,6-diamino-substituted pyrimidines described herein, we decided to follow the latter approach and to use one of the two amino groups as the point of attachment to the resin, while introducing the second one by nucleophilic aromatic substitution (S_NAr) (Scheme 1).

In previous literature examples,[8,9] Rink resin[10] was used as the solid support, thus introducing an amino group which caused deactivation of the pyrimidine nucleus, making it necessary to use very harsh reaction conditions (140 °C) to perform the subsequent S_NAr reaction. Attempts to solve this problem by using a very good leaving group, such as a fluorine instead of the more common chlorine, have been reported.[11] We decided to avoid deactivation of the ring by replacing the Rink resin by *p*-nitrophenyl carbonate Wang resin[12,13] (**1**), which allows attachment of the amino-chloro-substituted pyrimidine nucleus by a carbamic linkage, which is slightly electron withdrawing[14] and, as such, slightly activating towards nucleophilic substitution. This should permit the use of milder reaction conditions for subsequent substitution of the chlorine atom with amines. Moreover, this kind of solid support allows the use of milder cleavage conditions, which do not affect the products, and a shorter cleavage time than with Rink resin, thus facilitating the monitoring of the reaction progress.



Scheme 1. Solid-phase synthesis of 2-methyl-*N*-(4-phenylbutyl)pyrimidine-4,6-diamine

A small library of this class of compounds has been realized from four differently substituted pyrimidines and six amines; the reactivity to S_NAr has also been studied.

Results and Discussion

As shown in Scheme 1, 4-amino-6-chloro-2-methylpyrimidine (**2a**)[15] was attached to *p*-nitrophenyl carbonate Wang resin (**1**) by reaction with NaH in THF at room temp. for 24 h, giving compound **3**. To monitor this reaction, compound **2a** was recovered after treatment of the resin **3** with trifluoroacetic acid/dichloromethane (TFA/DCM; 15:85) for 15 minutes at room temp. in 78.4% yield, based on initial resin loading. A UV-based analysis method described

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in the literature[16] was also used to confirm the absence of *p*-nitrophenol on the resin at the end of the reaction.

The reaction of 4-phenylbutylamine (**4a**) with the pyrimidine derivative **3** was used to determine the best conditions for the S_NAr reaction. Four different reaction conditions were tested. In those cases in which $NaHCO_3$ or triethylamine (TEA) in refluxing toluene were used, some starting material was still present after the first 24 hours, while after 48 hours a consistent impurity was clearly evident by TLC analysis. When *N,N*-diisopropylethylamine (DIPEA) in DMF at room temp. was used, the reaction was still not complete after three days and the reaction time was not extended. Finally, reaction with TEA in *n*-butyl alcohol at 80 °C for 24 hours gave after cleavage the desired product **6a** with high purity (93.7% by HPLC, determined at 254 nm).

Once the optimal reaction conditions had been determined, six amines and four differently substituted pyrimidines were chosen to set up a small library of diamino-substituted pyrimidines (Figure 1). All the reactions were followed by HPLC. In each case, after the first 24 hours the resin was washed, a sample of it was treated with TFA/DCM (15:85) at room temp. for 15 minutes and the recovered product was analysed by HPLC. In those cases in which starting material was still evident, more reactants were added to the resin and the reaction progress was monitored every 24 hours. Since our interest was focussed on studying the reactivity of solid supported pyrimidines towards nucleophilic substitution, single compounds were not purified at the end of the reactions and only the HPLC purity after cleavage from the resin was evaluated. For those compounds obtained with a high HPLC purity (>95%) it was verified that the amount obtained was very similar to that expected in relation to the initial resin loading, thus

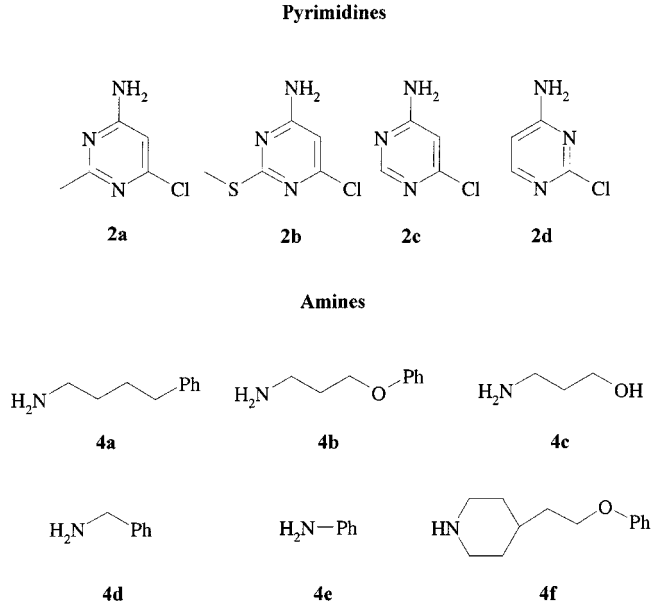
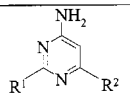
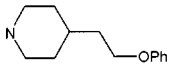
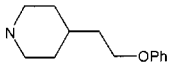
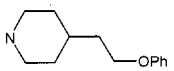
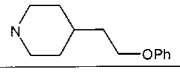


Figure 1. Pyrimidines and amines used to realize a library of diamino-substituted pyrimidines

Table 1. Reaction times of the S_NAr and HPLC% purity of compounds obtained after cleavage



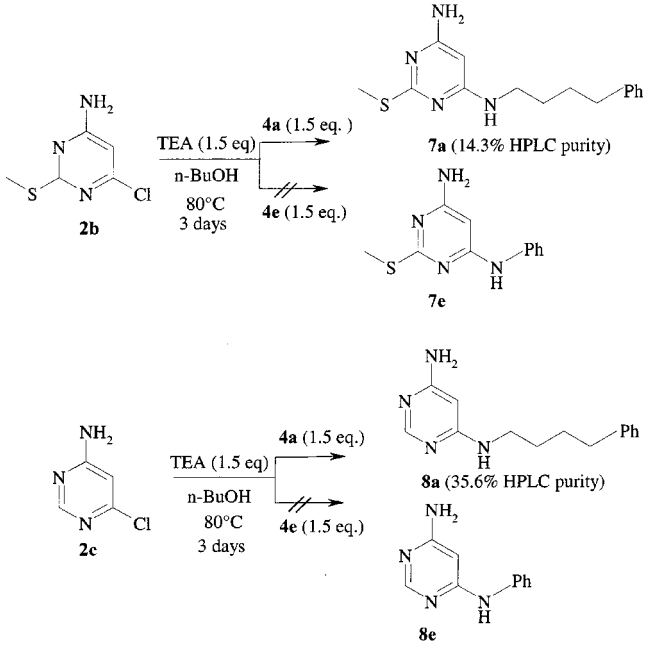
Compd.	R^1	R^2	HPLC purity[a] (%)	Reaction time (h)
6a	Me	$HN(CH_2)_4Ph$	93.6	24
6b	Me	$HN(CH_2)_3OPh$	79.7	72
6c	Me	$HN(CH_2)_3OH$	72.8	43
6d	Me	$NHCH_2Ph$	98.1	43
6e	Me	HNPh	10.0	120
6f	Me		91.0	24
7a	SMe	$HN(CH_2)_4Ph$	93.2	24
7b	SMe	$HN(CH_2)_3OPh$	95.0	72
7c	SMe	$HN(CH_2)_3OH$	90.8	72
7d	SMe	$NHCH_2Ph$	76.8	96
7e	SMe	HNPh	–	–
7f	SMe		94.6	24
8a	H	$HN(CH_2)_4Ph$	88.0	24
8b	H	$HN(CH_2)_3OPh$	78.0	72
8c	H	$HN(CH_2)_3OH$	62.3	24
8d	H	$NHCH_2Ph$	76.3	24
8e	H	HNPh	50.0	96
8f	H		95.0	24
9a	$HN(CH_2)_4Ph$	H	93.4	24
9b	$HN(CH_2)_3OPh$	H	78.7	43
9c	$HN(CH_2)_3OH$	H	89.9	24
9d	$NHCH_2Ph$	H	92.7	24
9e	HNPh	H	32.8	96
9f		H	71.0	24

[a] HPLC conditions. Column: Simmetry C_{18} 3.5 μm, 4.6 × 75 mm; eluent: A (H_2O:CH_3CN:TFA 9:1:0.005) and B (H_2O:CH_3CN:TFA 1:9:0.005); elution: gradient of 5−100% B from 0 to 10 min, 100% B from 10 to 12 min and 100−0% B from 12 to 14 min; detection: UV absorption at 254 nm

indicating a quantitative yield. Table 1 shows reaction times and HPLC purities of the obtained products.

4-Phenylbutylamine (**4a**) and 4-(2-phenoxyethyl)piperidine (**4f**) were the most reactive amines, since they both gave the desired products (**6a**, **7a**, **8a**,[17] **9a and 6f**, **7f**, **8f**, **9f**) after 24 hours and with high HPLC purity in each case. 3-Phenoxy-1-propylamine (**4b**),[18,19] which has an oxygen atom in the alkylic chain instead of the methylene group of **4a**, proved to be less reactive than **4a** itself. 3-Hydroxy-1-propanol (**4c**) was slightly more reactive than **4b**, and showed the same reactivity as benzylamine (**4d**). Finally, aniline (**4e**), which is the only aromatic amine among the ones chosen, proved to be very poorly reactive in nucleophilic substitution with chloropyrimidines, in agreement with previous literature findings.[8]

4-Amino-2-chloropyrimidine (**2d**), which is the only compound with the chlorine atom at position 2, was the most reactive of the pyrimidines. 4-Amino-6-chloropyrimidine (**2c**) was the most reactive of the three 6-chloropyrimidines



Scheme 2. Solution-phase synthesis of some diamino-substituted pyrimidines

tested. 4-Amino-6-chloro-2-methylthiopyrimidine (**2b**) and 4-amino-6-chloro-2-methylpyrimidine (**2a**) showed a very similar reactivity.

To prove the real advantage of this synthetic approach, a solution-phase synthesis of some of these 4,6-diamino-substituted pyrimidines (**7a**, **7e**,[8] **8a**, **8e**[20]) was attempted, as shown in Scheme 2, with much lower results than those obtained for the synthesis of the same compounds on solid phase.

We attempted to extend this synthesis to other diamino-substituted heterocycles using 4-amino-2-chloropyridine and 2-amino-6-chloropyrazine, but they both proved to be unreactive to nucleophilic substitution with any of the six amines under the conditions used in the present study.

Conclusion

In summary, a novel solid-phase synthesis of diamino-substituted pyrimidines has been found. This approach can be considered to be better than the ones described thus far in the literature, since it allows the use of milder reaction and cleavage conditions. Moreover, the cleavage time is greatly reduced, thus facilitating the monitoring of the reaction progress, which is often the limiting step in the use of solid-phase synthesis. A study of reactivity towards nucleophilic substitution of differently substituted solid-supported pyrimidines with properly selected amines has been carried out. Using this methodology a small library of differently substituted diaminopyrimidines has been prepared, thus validating the synthetic strategy.

Experimental Section

General: ^{1}HNMR spectra were obtained with a Bruker ARX 300 spectrometer. The chemical shifts are given relative to TMS as internal standard. Mass spectra were obtained with a Finnigan TSQ 700/EI and Thermoquest AQA/ESI. HPLC analysis was performed with a Shimadzu analytical instrument, equipped with an automated injector system and UV diode-array detector. Gradient grade quality solvents for HPLC (Merck) were employed. Flash chromatography was performed on Merck silica gel 230−400 mesh ASTM. TLC was carried out on Merck 60F254 plates. The libraries were realized by using the automated synthesisers Myriad Personal Synthesiser and Myriad Remote Incubator (Mettler, Toledo).

4-(2-Phenoxyethyl)piperidine (4f): 10% NaOH and di-*tert*-butyl-dicarbonate (15 g, 85.7 mmol) were added to a solution of 4-(2-hydroxyethyl)piperidine (5 g, 38 mmol), and the mixture was stirred at room temp. for 1 hour. After extracting the aqueous phase with ethyl acetate and evaporating the solvent, flash chromatography with ethyl acetate/hexane (1:1) was performed. The resulting product (4.8 g, 20.8 mmol) was dissolved in THF together with phenol (2.3 g, 25 mmol) and triphenylphosphane (8.7 g, 33.3 mmol). The mixture was cooled to 0 °C and, after dropwise addition of diisopropyl azadicarboxylate (6.6 mL, 33.3 mmol) dissolved in THF, it was stirred for 1 hour at room temp. The solvent was evaporated and flash chromatography with ethyl acetate/hexane (5:95) was performed. The resulting product (1.8 g, 5.7 mmol) was then dissolved in methanol with addition of an excess of HCl/Et_2O and the mixture was stirred at room temp. for 2 hours, to give a precipitate of **4f** as a white solid (460 mg, 2.2 mmol). Evaporation of the solvent and addition of 2-propanol to the residue allowed precipitation of the remaining product (**4f**) as a white solid (780 mg, 3.8 mmol; 15.6% yield). EIMS: *m*/*z* = 205 [M^+], 128, 112, 99, 84. ^{1}H NMR ($CDCl_3$): δ = 1.83−1.66 (m, 6 H, piperidine: CH_2axCH, CH_2CH, NH; chain: CH_2CH), 1.97 (br. d, *J* = 14.2 Hz, 2 H, piperidine: CH_2eqCH), 2.87 (dt, *J* = 13.0, 3.1 Hz, 2H piperidine: CH_2axNH), 3.49 (br. d, *J* = 13.0 Hz, 2 H, piperidine: CH_2eqNH), 4.01 (t, *J* = 5.7 Hz, 2 H, OCH_2), 6.87 (d, *J* = 8.8 Hz, 2 H, *o*Ph), 6.94 (dd, *J* = 7.6, 7.6 Hz, 1 H, *p*Ph), 7.28 (dd, *J* = 8.8, 7.6 Hz, 2 H, *m*Ph).

Attachment of 4-Amino-6-chloro-2-methylpyrimidine to the Resin (3): A solution of 4-amino-6-chloro-2-methylpyrimidine (**2a**)[15] (450 mg, 3.1 mmol) in THF was added dropwise to a suspension of NaH (112 mg, 4.65 mmol) in THF at 0 °C. After stirring the mixture at 0 °C for 15 minutes, *p*-nitrophenyl carbonate Wang resin (**1**; 520 mg, 0.31 mmol, loading 0.6 mmol/g) was added and the suspension was stirred at room temp. overnight. The resin was then washed with DCM (3 ×), MeOH (3 ×), DCM (3 ×), MeOH (3 ×) and dried under vacuum.

The same procedure was followed for attachment of the other pyrimidine rings **2b**, **2c**, **2d** to the resin.

2-Methyl-*N*-(4-phenylbutyl)pyrimidine-4,6-diamine (6a): 4-Phenylbutylamine (**4a**; 0.5 mL, 3.15 mmol) and TEA (0.44 mL, 3.15 mmol) were added to a suspension of the resin **3** (350 mg, 0.21 mmol) in *n*-butyl alcohol, and the mixture was stirred at 80 °C for 24 hours. After washing the resin with MeOH (3 ×), DCM (3 ×), diethyl ether (3 ×), MeOH (3 ×) and drying it under vacuum at 30 °C, it was treated with TFA/DCM (15:85) for 15 min at room temp. The resin was then filtered, the filtrate was basified with Na_2CO_3 and extracted with dichloromethane. After drying the organic layer over Na_2SO_4, the solvent was evaporated to give compound **6a** with 93.8% HPLC purity. ESIMS: *m*/*z* = 257 [MH^+]. ^{1}H NMR ($CDCl_3$, 333 K): δ = 1.80−1.63 (m, 4 H, chain: CH_2), 2.47

(s, 3 H, CH_3), 2.68 (t, J = 6.92 Hz, 2 H, CH_2Ph), 3.21 (m, 2 H, CH_2NH), 4.76 (br. s, 3 H, NH_2, NH), 5.20 (s, 1 H, pyrimidine H), 7.17 (d, J = 7.8 Hz, 2 H, *o*Ph), 7.19 (dd, J = 6.9, 6.9 Hz, 1 H, *p*Ph), 7.28 (dd, J = 7.8, 6.9 Hz, 2 H, *m*Ph). IR (KBr): $\tilde{\nu}$ = 3457, 3243, 3086, 2929, 1641, 1590 cm^{-1}.

The same procedure was followed for the synthesis of all the other pyrimidine compounds whose spectroscopic data are reported below.

6b: EIMS: m/z = 258 [M^+.], 165, 151, 138, 124. ^1H NMR ($CDCl_3$): δ = 2.06 (m, 2 H, chain: CH_2), 2.32 (s, 3 H, CH_3), 3.41 (dt, J = 6.5, 6.3 Hz, 2 H, CH_2NH), 4.06 (t, J = 6.0 Hz, 2 H, OCH_2), 4.39 (br. s, 2 H, NH_2), 4.86 (br. t, J = 6.3 Hz, 1 H, NH), 5.26 (s, 1 H, pyrimidine H), 6.90 (d, J = 8.8 Hz, 2 H, *o*Ph), 6.95 (dd, J = 7.6, 7.6 Hz, 1 H, *p*Ph), 7.29 (dd, J = 8.8, 7.6 Hz, 2 H, *m*Ph).

6c: ESIMS: m/z = 183 [MH^+], 205 [MNa^+]. ^1H NMR (DMSO): δ = 1.61 (m, 2 H, chain: CH_2), 2.10 (s, 3 H, CH_3), 3.14 (dt, J = 7.3, 7.3 Hz, 2 H, CH_2NH), 3.44 (t, J = 6.3 Hz, 2 H, OCH_2), 5.18 (s, 1 H, pyrimidine H), 5.88 (br. s, 2 H, NH_2), 6.32 (br. t, J = 6.0 Hz, 1 H, NH). IR (KBr): $\tilde{\nu}$ = 3364, 3161, 2924, 2853, 1599, 1463 cm^{-1}.

6d: 21.8 mg (89% overall yield) of compound **6d** were obtained from 190 mg of resin (loading 0.6 mmol/g). ESIMS: m/z = 215 [MH^+]. ^1H NMR (DMSO): δ = 2.26 (s, 3 H, CH_3), 4.43 (d, J = 5.4 Hz, 2 H, CH_2), 5.36 (s, 1 H, pyrimidine H), 6.80 (br. s, 2 H, NH_2), 7.36- 7.21 (m, 5 H, Ph), 7.93 (br. s, 1 H, NH). IR (KBr): $\tilde{\nu}$ = 3157, 1592, 1451 cm^{-1}.

6e:[21] ESIMS: m/z = 201 [MH^+].

6f: ESIMS: m/z = 313 [MH^+]. ^{1}HNMR ($CDCl_3$): δ = 1.86−1.69 (m, 7 H), 2.36 (s, 3 H, CH_3), 2.81 (dt, J = 13.2, 2.8 Hz, 2 H, piperidine CH_2axN), 4.03 (t, J = 6.3 Hz, 2 H, OCH_2), 4.32 (br. d, J = 13.2 Hz, 2 H, piperidine CH_2eqN), 4.46 (br. s, 2 H, NH_2), 5.43 (s, 1 H, pyrimidine H), 6.89 (d, J = 8.8 Hz, 2 H, *o*Ph), 6.94 (dd, J = 7.2 Hz, 1 H, *p*Ph), 7.28 (dd, J = 8.8, 7.2 Hz, 2 H, *m*Ph). IR (KBr): $\tilde{\nu}$ = 3370, 2919, 1587, 1504 cm^{-1}.

7a: ESIMS: m/z = 289 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.77−1.56 (m, 4 H, chain CH_2), 2.45 (s, 3 H, CH_3), 2.65 (t, J = 7.2 Hz, 2 H, CH_2Ph), 3.19 (dt, J = 6.9, 6.9 Hz, 2 H, CH_2NH), 4.46 (br. s, 2 H, NH_2), 4.63 (br. t, J = 6.9 Hz, 1 H, NH), 5.08 (s, 1 H, pyrimidine H), 7.21−7.15 (m, 3 H, *o*-*p*Ph), 7.28 (m, 2 H, *m*Ph). IR (KBr): $\tilde{\nu}$ = 3404, 3285, 3148, 2929, 1631, 1591, 1492 cm^{-1}.

7b: 17.7 mg (90% overall yield) of compound **7b** were obtained from 113 mg of resin (loading 0.6 mmol/g). ESIMS: m/z = 291 [MH^+]. ^1H NMR ($CDCl_3$): δ = 2.06 (m, 2 H, chain CH_2), 2.46 (s, 3 H, CH_3), 3.44(dt, J = 6.6, 6.6 Hz, 2 H, CH_2NH), 4.06 (t, J = 6.3 Hz, 2 H, OCH_2), 4.46 (br. s, 2 H, NH_2), 4.96 (br. s, 1 H, NH), 5.14 (s, 1 H, pyrimidine H), 6.90 (d, J = 8.8 Hz, *o*Ph), 6.96 (dd, J = 7.5, 7.5 Hz, 1 H, *p*Ph), 7.29 (dd, J = 8.8, 7.5 Hz, 2 H, *m*Ph). IR (KBr): $\tilde{\nu}$ = 3385, 2924, 1582, 1496 cm^{-1}.

7c: ESIMS: m/z = 215 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.82 (m, 2 H, chain CH_2), 2.01 (br. s, 1 H, OH), 2.49 (s, 3 H, CH_3), 3.43 (br. s, 2 H, CH_2NH), 3.74 (t, J = 5.7 Hz, 2 H, OCH_2), 5.17 (s, 1 H, pyrimidine H), 5.39 (br. s, 3 H, NH_2, NH). IR (KBr): $\tilde{\nu}$ = 3333, 2890, 1651, 1557 cm^{-1}.

7d:[8] ESIMS: m/z = 247 [MH^+]. ^1H NMR ($CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 4.43 (d, J = 6.0 Hz, 2 H, CH_2), 4.64 (br. s, 3 H, NH, NH_2), 5.12 (s, 1 H, pyrimidine H), 7.38−7.25 (m, 5 H, Ph). IR (KBr): $\tilde{\nu}$ = 3380, 2924, 1578, 1495 cm^{-1}.

7f: ESIMS: m/z = 345 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.33−1.17 (m, 2 H, piperidine: CH_2axCH), 1.84−1.71 (m, 5 H), 2.47 (s, 3 H, CH_3), 2.82 (dt, J = 13.2, 2.8 Hz, 2 H, piperidine CH_2axN), 4.03 (t, J = 6.3 Hz, 2 H, OCH_2), 4.31 (br. d, J = 13.2 Hz, 2 H, piperidine CH_2eqN), 4.40 (br. s, 2 H, NH_2), 5.31 (s, 1 H, pyrimidine H), 6.90 (d, J = 8.5 Hz, 2 H, *o*Ph), 6.94 (dd, J = 7.2, 7.2 Hz, 1 H, *p*PH), 7.28 (dd, J = 8.5, 7.2 Hz, 2 H, *m*Ph). IR (KBr): $\tilde{\nu}$ = 3373, 2923, 1577, 1492 cm^{-1}.

8a: ESIMS: m/z = 243 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.77−1.55 (m, 4 H, chain CH_2), 2.66 (t, J = 7.5 Hz, 2 H, CH_2Ph), 3.19 (dt, J = 6.6, 6.6 Hz, 2 H, CH_2NH), 4.58 (br. s, 2 H, NH_2), 4.77 (br. s, 1 H, NH), 5.34 (s, 1 H, pyrimidine 5-H), 7.31−7.13 (m, 5 H, Ph), 8.08 (s, 1 H, pyrimidine 2-H). IR (KBr): $\tilde{\nu}$ = 3456, 3234, 1594, 1477 cm^{-1}.

8b: ESIMS: m/z = 245 [MH^+], 267 [MNa^+]. ^1H NMR ($CDCl_3$): δ = 2.09 (m, 2 H, chain CH_2), 3.45 (dt, J = 6.6, 6.3 Hz, 2 H, CH_2NH), 4.07 (t, J = 5.7 Hz, 2 H, OCH_2), 4.81 (br. s, 2 H, NH_2), 5.40 (br. s, 1 H, NH), 5.40 (s, 1 H, pyrimidine 5-H), 6.91 (d, J = 8.5 Hz, 2 H, *o*Ph), 6.96 (dd, J = 7.2, 7.2 Hz, 1 H, *p*Ph), 7.30 (dd, J = 8.5, 7.2 Hz, 2 H, *m*Ph), 8.07 (s, 1 H, pyrimidine 2-H). IR (KBr): $\tilde{\nu}$ = 3445, 1686, 1442 cm^{-1}.

8c. ESIMS: m/z = 169 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.7 (br. s, 1 H), 2.15 (m, 2 H), 3.82 (t, J = 5.6 Hz, 2 H), 4.48 (t, J = 6.0 Hz, 2 H), 4.81 (br. s, 2 H), 5.40 (br. s, 1 H), 5.42 (s, 1 H), 8.05 (s, 1 H). IR (KBr): $\tilde{\nu}$ = 3397, 2885, 1669 cm^{-1}.

8d:[22] ESIMS: m/z = 201 [MH^+].

8e: ESIMS: m/z = 187 [MH^+].

8f: ESIMS: m/z = 299 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.26 (m, 2 H, piperidine CH_2axCH), 1.88−1.70 (m, 5 H), 2.86 (dt, J = 12.9, 2.8 Hz, 2 H, piperidine CH_2axN), 4.03 (t, J = 6.3 Hz, 2 H, OCH_2), 4.30 (br. d, J = 12.9 Hz, 2 H, piperidine CH_2eqN), 4.65 (br. s, 2 H, NH_2), 5.58 (s, 1 H, pyrimidine 5-H), 6.90 (d, J = 8.8 Hz, 2 H, *o*Ph), 6.94 (dd, J = 7.2.7.2 Hz, 1 H, *p*Ph), 7.28 (dd, J = 8.8, 7.2 Hz, 2 H, *m*Ph), 8.17 (s, 1 H, pyrimidine 2-H). IR (KBr): $\tilde{\nu}$ = 3345, 3189, 2923, 1659, 1597, 1493 cm^{-1}.

9a: ESIMS: m/z = 243 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.77−1.56 (m, 4 H, chain CH_2), 2.65 (t, J = 7.6 Hz, 2 H, CH_2Ph), 3.38 (dt, J = 6.9, 6.6 Hz, 2 H, CH_2NH), 4.56 (br. s, 2 H, NH_2), 4.90 (br. s, 1 H, NH), 5.76 (d, J = 5.7 Hz, 1 H, pyrimidine 5-H), 7.20−7.13 (m, 3 H, *o,p*Ph), 7.3−7.23 (m, 2 H, *m*Ph), 7.87 (d, J = 5.7 Hz, 1 H, pyrimidine 6-H). IR (KBr): $\tilde{\nu}$ = 3306, 2890, 1557 cm^{-1}.

9b: ESIMS: m/z = 245 [MH^+]. ^1H NMR ($CDCl_3$): δ = 2.08 (m, 2 H, chain CH_2), 3.58 (dt, J = 6.9, 6.6 Hz, 2 H, CH_2NH), 4.06 (t, 6.0 Hz, 2 H, OCH_2), 4.70 (br. s, 2 H, NH_2), 4.76 (br. s, 1 H, NH), 5.77 (d, J = 6.0, 1 H, pyrimidine 5-H), 6.95−6.88 (m, 3 H, *o,p*Ph), 7.27 (m, 2 H, *m*Ph), 7.8 (d, J = 6.0 Hz, 1 H, pyrimidine 6-H). IR (KBr): $\tilde{\nu}$ = 3334, 2887, 1651, 1359 cm^{-1}.

9c: ESIMS: m/z = 169 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.87 (br. s, 1 H, OH), 2.09 (m, 2 H, chain CH_2), 3.58 (m, 2 H, CH_2NH), 4.45 (t, J = 6.0 Hz, 2 H, OCH_2), 5.63 (br. s, 2 H, NH_2), 5.92 (d, J = 6.9 Hz, 1 H, pyrimidine 5-H), 7.69 (d, J = 6.9 Hz, 1 H, pyrimidine 6-H), 9.38 (br. s, 1 H, NH). IR (KBr): $\tilde{\nu}$ = 3395, 3054, 2986, 1651 cm^{-1}.

9d: ESIMS: m/z = 201 [MH^+]. ^1H NMR ($CDCl_3$): δ = 4.6 (br. s, 2 H, NH_2), 4.6 (d, J = 6.0 Hz, 2 H, CH_2), 5.34 (br. s, 1 H, NH), 5.81 (d, J = 5.7 Hz, 1 H, pyrimidine 5-H), 7.36−7.21 (m, 5 H, Ph), 7.89 (d, J = 5.7 Hz, 1 H, pyrimidine 6-H). IR (KBr): $\tilde{\nu}$ = 3471, 3328, 3190, 1641, 1589, 1430 cm^{-1}.

9e:[23,24] ESIMS: m/z = 187 [MH^+].

9f: ESIMS: m/z = 299 [MH^+]. ^1H NMR ($CDCl_3$): δ = 1.24 (m, 2 H, piperidine CH_2axCH), 1.84−1.70 (m, 5 H), 2.82 (dt, J = 12.9, 2.2 Hz, 2 H, piperidine CH_2axN), 4.03 (t, J = 6.3 Hz, 2 H, OCH_2), 4.52 (br. s, 2 H, NH_2), 4.70 (dt, J = 13.2, 2.2 Hz, 2 H, piperidine CH_2eqN), 5.72 (d, J = 5.7 Hz, 1 H, pyrimidine 5-H), 6.90 (d, J = 8.8 Hz, 2 H, *o*Ph), 6.93 (dd, J = 7.6, 7.6 Hz, 1 H, *p*Ph), 7.28 (dd, J = 8.8, 7.6 Hz, 2 H, *m*Ph), 7.93 (d, J = 5.7 Hz, 1 H, pyrimidine 6-H). IR (KBr): $\tilde{\nu}$ = 3378, 2918, 1586, 1452 cm^{-1}.

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[1] A. G. Arvanitis, P. J. Gilligan, R. J. Chorvat, R. S. Cheeseman, T. E. Christos, R. Bakthavatchalam, J. P. Beck, A. J. Cocuzza, F. W. Hobbs, R. G. Wilde, C. Arnold, D. Chidester, M. Curry, L. He, A. Hollis, J. Klaczkiewicz, P. J. Krenitsky, J. P. Rescinito, E. Scholfield, S. Culp, E. B. De Souza, L. Fitzgerald, D. Grigoriadis, S. W. Tam, Y. N. Wong, S.-M. Huang, H. L. Shen, *J. Med. Chem.* **1999**, *42*, 805−818.
[2] P. Franchetti, L. Cappellacci, G. Abu Sheikha, M. Grifantini, A. G. Loi, A. De Montis, M. G. Spiga, P. La Colla, *Nucleosides Nucleotides* **1995**, *14*, 607−610.
[3] K. E. Kinnamon, R. R. Engle, B. T. Poon, W. Y. Ellis, J. W. McCall, M. T. Dzimianski, *Ann. Trop. Med. Parasitol.* **1999**, *93*, 851−858.
[4] H. Vorbrueggen, *Adv. Heterocyclic Chem.* **1990**, *49*, 117−192.
[5] D. Obrecht, C. Abrecht, A. Grieder, J. M. Villalgordo, *Helv. Chim. Acta* **1997**, *80*, 65−72.
[6] T. Masquelin, D. Sprenger, R. Baer, F. Gerber, Y. Mercadal, *Helv. Chim. Acta* **1998**, *81*, 646−659.
[7] C. Zucca, P. Bravo, A. Volonterio, M. Zanda, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2001**, *42*, 1033−1035.
[8] F. Guillier, P. Roussel, H. Moser, P. Kane, M. Bradley, *Chem. Eur. J.* **1999**, *5*, 3450−3458.
[9] R. Di Lucrezia, I. H. Gilbert, C. D. Floyd, *J. Comb. Chem.* **2000**, *3*, 249−253.
[10] I. W. James, *Tetrahedron* **1999**, *55*, 4855−4946.
[11] C. Gibson; H. Kessler, *Tetrahedron Lett.* **2000**, *41*, 1725−1728.
[12] B. A. Dressman, L. A. Spangle, S. W. Kaldor, *Tetrahedron Lett.* **1996**, *37*, 937−940.
[13] D. M. Dixit, C. C. Leznoff, *Isr. J. Chem.* **1978**, *17*, 248−252.
[14] C. Hansch, A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology* John Wiley & Sons, **1979**.
[15] Z. Budesinsky, *Collect. Czech. Chem. Commun.* **1949**, *14*, 223−235.
[16] G. Reginat, E. Grandini, A. Paio, P. Seneci, S. Gehanne, *Combinatorial Chemistry 2000. New Horizons for accelerated discovery in the Chemical and Biological Sciences* London, UK, **2000**, Poster Glaxo-Wellcome.
[17] C. W. Whitehead, J. J. Traverso, *J. Am. Chem. Soc.* **1958**, 2185−2189.
[18] J. von Braun, *Ber. Dtsch. Chem. Ges.*, **1937**, *70B*, 979−985.
[19] J. C. Schaeffer, A. K. Cho, J. F. Fischer, *J. Pharm. Sci.* **1976**, *65*, 122−126.
[20] C. A. H. Rasmussen, H. C. Van der Plas, P. Grotenhuis, A. Koudijs, *J. Heterocycl. Chem.* **1978**, *15*, 1121−1125.
[21] Y. Fumio, S. Fukazawa, *J. Chem. Soc., Chem. Commun.* **1972**, *9*, 503−504.
[22] S. Takahashi, T. Yatsunami, K. Shudo, T. Okamoto, K. Yamada, Y. Isogai, *Chem. Pharm. Bull.* **1978**, *26*, 2286−2287.
[23] E. A. Arutyunyan, V. I. Gunar, S. I. Zav′yalov, *Ser. Khim.* **1970**, *4*, 904−909.
[24] H. C. Van der Plas, B. Zuurdeeg, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 426−438.

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