Synthesis of cyclic guanidines: 2-arylamino-1,4,5,6-tetrahydropyrimidines

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Dedicated to Professor Rosa Maria Claramunt on the occasion of her 65th anniversary

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Abstract
Considering the biological and chemical relevance of guanidine containing derivatives, we have devised a novel and efficient two-step synthesis of 2-arylamino-1,4,5,6-tetrahydropyrimidines. We have found that the coupling of aryl bromides with 2-aminopyrimidine is a very effective method for the high yielding synthesis of 2-arylaminopyrimidines. Moreover, the employment of Pd-catalysed hydrogenation to selectively reduce the pyrimidine ring generates a very high-yielding pathway to 2-arylamino-1,4,5,6-tetrahydropyrimidines of biological interest.

Keywords: Cyclic guanidine, 2-arylaminopyrimidine, Buchwald-Hartwig reaction, 2-arylamino-1,4,5,6-tetrahydropyrimidine

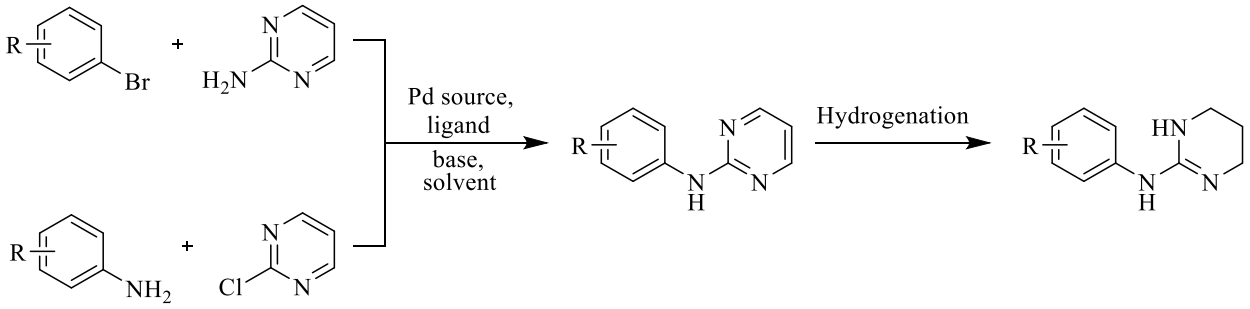
Introduction

Compounds embodying the guanidine functional group are prevalent throughout chemistry[1] and their synthesis has been of interest for many years.[2] Many biologically active molecules containing guanidine or cyclic guanidine functionalities (*e.g.* the 2-aminoimidazoline system) exhibit a wide range of applications from minor groove binders[3] to potential antidepressant agents.[4] Continuing with our interest in the guanidine system[4] and, in particular, in guanidines embedded in aliphatic rings, the synthesis of 2-arylamino-1,4,5,6-tetrahydropyrimidines, which are compounds that incorporate a cyclic guanidine moiety in a six-membered ring was highly interesting to us. We now present a flexible, two-step synthesis of these compounds, using either aryl bromides or anilines as starting materials.

Literature methods for the formation of 2-arylamino-1,4,5,6-tetrahydropyrimidines are often dated and low-yielding. These include formation of 2-chlorotetrahydropyrimidine followed by

nucleophilic displacement of the chlorine by an aniline to form the C–N bond,[5] or reduction of the pyrimidine moiety of 2-aminopyrimidines using an excess of triethylsilane under acidic conditions.[6] We aimed to find a more efficient, high-yielding synthetic method for the production of the required 2-arylamino-1,4,5,6-tetrahydropyrimidines.

Our approach consists in the initial preparation first of 2-arylaminopyrimidines with the intention of later transforming them into the corresponding 2-arylamino-1,4,5,6-tetrahydropyrimidines as presented in Scheme 1.

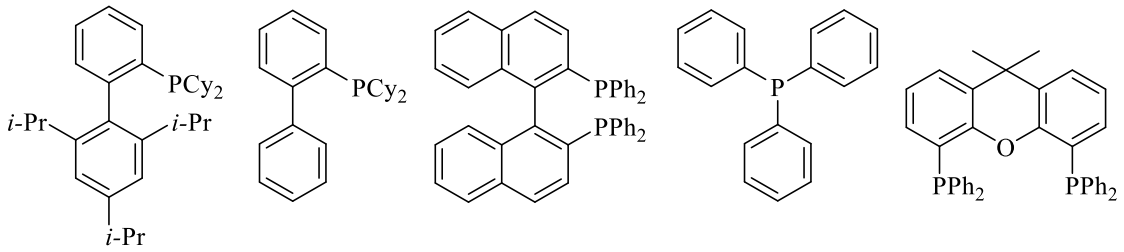


Scheme 1. Possible approaches to the synthesis of 2-arylaminopyrimidines.

Results and Discussion

We began our investigation by examining complementary methods for the formation of the C–N bond, by reacting either an aryl bromide with 2-aminopyrimidine or an aniline with 2-chloropyrimidine, using the Buchwald-Hartwig reaction as a tool in each case (Scheme 1).
Publications dealing with these particular couplings are scarce[7] and there have been no investigations into the effects of substituted aryl groups on the coupling process. As the 2-aminopyrimidine moiety is also found throughout many therapeutically-active compounds[8] a comparative study on each of the complementary routes to the formation of 2-arylaminopyrimidines (Scheme 1) was undertaken to determine the most effective and flexible synthetic pathway.

Initially, the coupling of 4-bromoanisole with 2-aminopyrimidine was investigated using chemistry developed in the laboratories of Buchwald[9] and Hartwig.[10] $Pd_2(dba)_3$ was chosen as the source of catalytic Pd and different bases, solvents and temperatures were examined for their effect on the reaction. A range of ligands **1** – **5** (Figure 1) was investigated but, as previously discovered,[7] we found that Xantphos **5** was the most successful ligand for this coupling process.

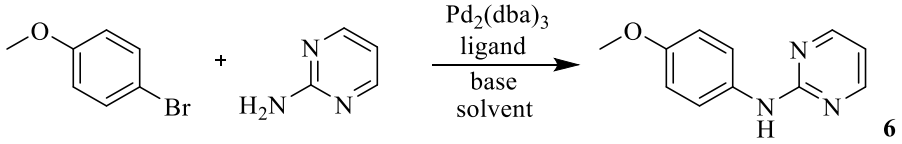


1 XPhos **2** **3** BINAP **4** PPh_3 **5** Xantphos

Figure 1. Ligands used in the optimisation process.

Different combinations of base, solvent and temperature were explored and the results obtained are gathered in Table 1. The highest yields were obtained by using NaO^tBu as base and toluene as solvent (Table 1, entry 13).

Table 1. Optimisation of the Pd catalysed coupling of 2-aminopyrimidine with 4-bromoanisole[a]



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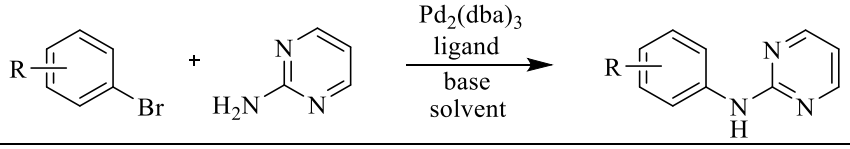
Entry	Pd	Ligand	Base	Solvent	Temp. (°C)	Yield (%)
1	-	-	NaO^tBu	toluene	90	-
2	$Pd_2(dba)_3$	**1**	NaO^tBu	toluene	90	45
3	$Pd_2(dba)_3$	**1**	NaO^tBu	toluene	100	50
4	$Pd_2(dba)_3$	**2**	NaO^tBu	toluene	90	35
5	$Pd_2(dba)_3$	**1**	Cs_2CO_3	toluene	90	23
6	$Pd_2(dba)_3$	**1**	K_3PO_4	toluene	90	34
7	$Pd_2(dba)_3$	**1**	NaO^tBu	toluene	90	52
8	$Pd_2(dba)_3$	**1**	NaO^tBu	toluene	100	54
9	$Pd_2(dba)_3$	**3**	NaO^tBu	toluene	90	9
10	$Pd_2(dba)_3$	**1**	NaO^tBu	DME	75	32
11	$Pd_2(dba)_3$	**1**	NaO^tBu	1,4-dioxane	90	27
12	$Pd_2(dba)_3$	**4**	NaO^tBu	toluene	100	<5
13	$Pd_2(dba)_3$	**5**	NaO^tBu	toluene	100	90
14	$Pd_2(dba)_3$	**1**	NaO^tBu	toluene	100	58[b]
15	$Pd_2(dba)_3$	**1**	NaO^tBu	toluene	100	57[c]
16	$Pd_2(dba)_3$	**1**	K_2CO_3	^{t}BuOH	110	45

[a]2-Aminopyrimidine (2 mmol), NaO^tBu (2 mmol), aryl halide (1 mmol), $Pd_2(dba)_3$ (2 mol %), ligand (3 mol %), toluene (1 mL/mmol aryl halide), 18 h. [b]24 h. [c]48 h.

These optimised conditions were then applied to a range of aryl bromides possessing different electronic and steric features to yield a variety of 2-arylaminopyrimidines **6-16** (Table 2). The reagent combination was tolerant of most functional groups. However, when strongly electron-withdrawing substituents were present on the aryl halide, the use of K_3PO_4 as base gave optimal results. The presence of sterically bulky groups adjacent to the displaced halogen atom had no detrimental effects on the reaction, and in nearly all cases very good to excellent yields were obtained. The presence of electron-withdrawing substituents gave slightly lower yields than expected but the yields obtained were still acceptable. These results were very satisfactory and were replicable on a multi-gram scale.[11]

Table 2. Aryl bromides successfully coupled with 2-aminopyrimidine[a]

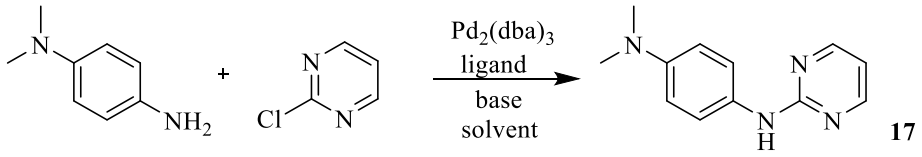


Entry	R	Product	Yield (%)
1	H	**7**	98
2	*p*-OCH_3	**6**	90
3	*m*-OCH_3	**8**	95
4	*o*-OCH_3	**9**	90
5	*p*-F	**10**	85
6	*m*-Br	**11**	94
7	*o*-F	**12**	92
8	*p*-CN	**13**	78[b]
9	*m*-CN	**14**	66[b]
10	*o*-CN	**15**	82[b]
11	*o*-Ph	**16**	98

[a]2-Aminopyrimidine (2 mmol), NaO^{t}Bu (2 mmol), aryl halide (1 mmol), $Pd_2(dba)_3$ (2 mol %), ligand (3 mol %), toluene (1 mL/mmol aryl halide), 18 h. 95 °C. [b]K_3PO_4 used as base.

Next, the 'inverse' reaction of *N,N*-dimethyl-*p*-aminoaniline with 2-chloropyrimidine to give compound **17** under Buchwald-Hartwig conditions was investigated (Table 3). This reaction is known to occur without the use of Pd catalysis.[12] However, in our experience, the yields varied greatly and harsh reaction conditions were required. A zinc-promoted version of this reaction has recently been published.[13]

Table 3. Optimisation of the Pd catalysed coupling of 2-chloropyrimidine with *N,N*-dimethyl-*p*-aminoaniline[a]



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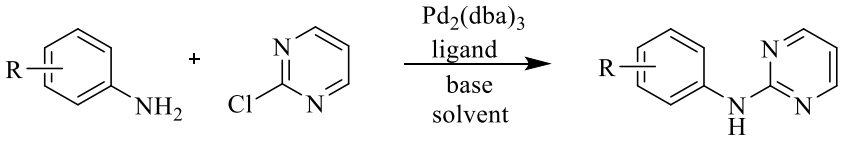
Entry	Pd	Ligand	Base	Solvent	Temp. (°C)	Yield (%)
1	-	-	NaO^{t}Bu	Toluene	100	23
2	$Pd_2(dba)_3$	**1**	NaO^{t}Bu	Toluene	90	56
3	$Pd_2(dba)_3$	**1**	NaO^{t}Bu	Toluene	100	56
4	$Pd_2(dba)_3$	**2**	NaO^{t}Bu	Toluene	90	47
5	$Pd_2(dba)_3$	**1**	Cs_2CO_3	Toluene	90	29
6	$Pd_2(dba)_3$	**1**	K_3PO_4	Toluene	90	22
7	$Pd_2(dba)_3$	**1**	NaO^{t}Bu	Toluene	90	55
8	$Pd_2(dba)_3$	**3**	NaO^{t}Bu	Toluene	90	<5
9	$Pd_2(dba)_3$	**1**	NaO^{t}Bu	DME	75	<5
10	$Pd_2(dba)_3$	**1**	NaO^{t}Bu	1,4-dioxane	90	11
11	$Pd_2(dba)_3$	**4**	NaO^{t}Bu	Toluene	100	<5
12	$Pd_2(dba)_3$	**5**	NaO^{t}Bu	Toluene	100	72
13	$Pd_2(dba)_3$	**1**	NaO^{t}Bu	Toluene	100	64[b]
14	$Pd_2(dba)_3$	**1**	NaO^{t}Bu	Toluene	100	63[c]
15	$Pd_2(dba)_3$	**1**	K_2CO_3	^{t}BuOH	110	12

[a]*N,N*-Dimethyl-*p*-aminoaniline (2 mmol), base (2 mmol), 2-chloropyrimidine (1 mmol), $Pd_2(dba)_3$ (2 mol %), ligand (3 mol %), solvent (1 mL/mmol 2-chloropyrimidine), 18 h. [b]24 h. [c]48 h.

The Pd-mediated cross-coupling reaction was optimised and it was found that satisfactory yields could be obtained under the same conditions that we earlier found to be successful for the coupling of aryl bromides with 2-aminopyrimidine (Table 3, entry 12). This reagent combination and conditions were then applied to the coupling of 2-chloropyrimidine to a selection of anilines containing both electron-withdrawing and -donating groups to produce the corresponding 2-arylaminopyrimidines (Table 4). It was found that the more nucleophilic anilines were the most effective coupling partners with 2-chloropyrimidine, but that reaction still occurred with electron-deficient anilines.

Table 4. Anilines successfully coupled with 2-chloropyrimidine[a]



Entry	R	Products	Yield (%)
1	H	**7**	88
2	*p*-OCH_3	**8**	87
3	*p*-$N(CH_3)_2$	**17**	72
4	*p*-F	**11**	50
5	*m*-CN	**14**	55[b]
6	*p*-NO_2-*m*-CH_3	**18**	54[b]

[a]Aniline (2 mmol), NaO^tBu (2 mmol), 2-chloropyrimidine (1 mmol), $Pd_2(dba)_3$ (2 mol %), ligand (3 mol %), toluene (1 mL/mmol 2-chloropyrimidine), 18 h. 95 °C. [b] K_3PO_4 used as base.

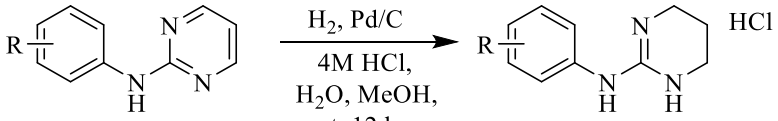
Overall, in the synthesis of 2-arylaminopyrimidines, we have found that the coupling of aryl bromides with 2-aminopyrimidine is a much more efficient method than the 'inverse' coupling of anilines with 2-chloropyrimidine.

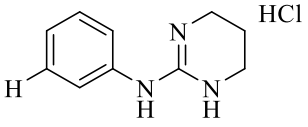
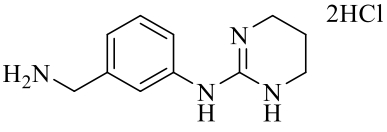
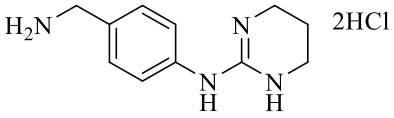
With an efficient and robust method for the synthesis of 2-arylaminopyrimidines in hand, we turned our attention towards an effective method for the reduction of the pyrimidine ring to generate the desired tetrahydropyrimidines. Hydrogenation of the pyrimidine ring as described by Ajito *et al.*[14] offered a particularly attractive pathway to the desired compounds.

Gratifyingly, after some optimisation of the reaction conditions, a slightly modified version of Ajito's procedure gave 2-anilino-1,4,5,6-tetrahydropyrimidinium salts (**19**-**29**, Table 5) in high yields with very little purification required. Ajito's hydrogenation involved the use of acetic acid but with our systems these conditions did not result in an increase in yields. However, the use of methanol as a co-solvent in conjunction with aqueous HCl led to higher yields and allowed for a more facile purification of our target compounds. Optimum reactions times varied between 10 and 13 hours, depending on the substrate.

Hydrogenation of the brominated 2-anilinopyrimidine not surprisingly resulted in dehalogenation of the aryl ring to leave the unsubstituted compound **19** (entry 7, Table 5). Interestingly, hydrogenation of the nitrile substituted 2-arylaminopyrimidines resulted in reduction of the nitrile moiety to the corresponding primary amine (entries 9 and 10, Table 5) except in the case of the *ortho*- substituted compound where the nitrile remained intact throughout the acid-promoted reduction (entry 8, Table 5).

Table 5. Hydrogenation of the 2-aminopyrimidine ring[a]



Entry	R	Product	Yield (%)
1	H	**19**	97
2	*o*-OCH_3	**20**	98
3	*m*-OCH_3	**21**	91
4	*p*-OCH_3	**22**	92
5	*o*-F	**23**	95
6	*p*-F	**24**	95
7	*m*-Br	 **19**	90[b]
8	*o*-CN	**25**	64
9	*m*-CN	 **26**	71[c]
10	*p*-CN	 **27**	78[c]
11	*o*-Ph	**28**	92

[a]2-Anilinopyrimidine (1 mmol), Pd/C 10% (150 mg) MeOH (4 mL), aq HCl (1M, 1 mL), rt, 10-12 hrs. [b]Concomitant debromination. [c]Concomitant reduction of the nitrile moiety.

Conclusions

We have found that the coupling of aryl bromides with 2-aminopyrimidine is a more effective method for the high yielding synthesis of 2-arylaminopyrimidines than the coupling of anilines with 2-chloropyrimidine.
In addition, the employment of Pd-catalysed hydrogenation to selectively reduce the pyrimidine ring generates a very high-yielding pathway to 2-arylamino-1,4,5,6-tetrahydropyrimidines that are potentially of biological interest.

Experimental Section

General. All commercial chemicals were obtained from Sigma-Aldrich or Fluka and used without further purification. Deuteriated solvents for NMR use were purchased from Apollo. Dry solvents were prepared using standard procedures, according to Vogel, with distillation prior to use. Chromatographic columns were run using a Biotage SP4 flash purification system with Biotage SNAP silica cartridges. Solvents for synthesis purposes were used at GPR grade. Analytical TLC was performed using Merck Kieselgel 60 F254 silica gel plates or Polygram Alox N/UV254 aluminium oxide plates. Visualisation was by UV light (254 nm). NMR spectra were recorded on Bruker DPX–400 Avance spectrometers, operating at 400.13 MHz for ^{1}H NMR and at 150.9 MHz for ^{13}C-NMR. Shifts are referenced to the internal solvent signals. NMR data were processed using Bruker TOPSPIN software. HRMS spectra were measured on a Micromass LCT electrospray TOF instrument with a WATERS 2690 autosampler and methanol/acetonitrile as carrier solvent. Melting points were determined using a Stuart Scientific Melting Point SMP1 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer equipped with a Universal ATR sampling accessory.

General method A. Preparation of 2-arylaminopyrimidines using the Buchwald-Hartwig reaction between aryl bromide and 2-aminopyrimidine. To a Schlenk tube charged with $Pd_2(dba)_3$ (2 mol %) and Xantphos (3 mol %) was added 2-aminopyrimidine (1 mmol) and NaO^tBu (1 mmol). The tube was evacuated and backfilled with Ar three times. Toluene (1 mL / mmol aryl halide) was then added via syringe followed by aryl bromide (0.5 mmol) by syringe. The mixture was heated to 95 °C. Once deemed complete (TLC) the reaction mixture was cooled, filtered through a pad of Celite, washed with EtOAc (20 mL) and diluted with water (20 ml), then extracted with EtOAc (3 x 20 mL). The organic layers were then combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product was then purified using column chromatography (hexanes: ethyl acetate, gradient from 20-70% ethyl acetate).

General method B. Preparation of 2-arylaminopyrimidines using the Buchwald-Hartwig reaction between an aniline and 2-chloropyrimidine. To a Schlenk tube charged with $Pd_2(dba)_3$ source (1 mol %) and Xantphos (1.5 mol %) was added aniline (1 mmol) and NaO^tBu (1 mmol). 2-Chloropyrimidine (0.5 mmol) was added to this mixture. The tube was evacuated and backfilled with Ar three times. Toluene (1 mL / mmol aniline) was then added via syringe. The mixture was heated to 90 °C. Once deemed complete (TLC) the reaction mixture was cooled, filtered through a pad of Celite, washed with EtOAc (20 mL) and diluted with water (50 mL). The product was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product was then purified using column chromatography (hexane: ethyl acetate 20-70%)**.**

General method C. Hydrogenation of 2-arylaminopyrimidines. To 2-arylaminopyrimidine (1 mmol) in MeOH (4 mL) was added 10% Pd/C (150 mg). To this was added aqueous HCl (1M, 1 mL). The mixture was then hydrogenated at atmospheric pressure for 10-12 hrs with vigorous stirring. If the reaction had not gone to completion after said time another equivalent of aqueous HCl acid was added and the vessel resubmited to the hydrogenation conditions previously mentioned. It was then filtered through a pad of Celite and concentrated. The residue was then purified by passing through a reverse phase silica plug, by diluting the compound in the minimum amount of H_2O then using 95/5 H_2O-MeCN as the eluent. This yielded the title compounds as the tetrahydropyrimidinium hydrochloride salts.

***2*-Phenyl-2-aminopyrimidine (7)**. Yield: 98% (1962 mg). Mp: 112-115 °C. IR: ν_{max} (film)/cm^{-1}: 3254 (NH), 3054, 1609, 1576, 1444, 793, 746, 698. δ_H (400 MHz, $CDCl_3$): 6.75 (t, 1H, J 5.0), 7.09 (t, 1H, J 7.3), 7.38 (app t, 2H,),7.43 (br s, NH) 7.64 (d, 2H, J 7.3), 8.45 (d, 2H, J 5.0). δ_C (100 MHz, $CDCl_3$): 112.1 (CH), 119.1 (2CH), 122.2 (CH), 128.5 (2CH), 138.9 (q), 157.6 (2CH), 159.7 (q). HRMS (*m/z* ES): Found 172.0875 (M^+ + H. $C_{10}H_{10}N_3$ Requires 172.0867).

***2*-(4-Methoxyanilino)pyrimidine (6)**. Yield: 90% (91 mg). Mp: 129-131 °C. IR: ν_{max} (film)/cm^{-1}: 3260, 2980, 1712, 1620, 1584, 1208, 1155, 852, 819, 777. δ_H (400 MHz, $CDCl_3$): 3.82 (s, 3H, OCH_3), 6.68 (t, 1H, J 5.0), 6.91 (d, 2H, J 9.0), 7.34(br s, NH), 7.49 (d, 2H, J 9.0), 8.39 (d, 2H, J 5.0). δ_C (100 MHz, $CDCl_3$): 55.0(CH_3), 111.6 (CH), 113.8 (2CH), 119.8 (q), 121.9 (2CH), 131.8 (q), 157.6 (2CH), 160.2 (q). HRMS (*m/z* ES): Found 202.0980 (M^+ + H. $C_{11}H_{11}N_3O$ Requires 202.0982).

***2*-(3-Methoxyanilino)pyrimidine (8)**. Yield: 95% (96 mg). Mp: 127-129 °C. IR: ν_{max} (film)/cm^{-1}: 3259, 2971, 1712, 1620, 1584, 1507, 1412, 1155, 791, 777. δ_H (400 MHz, $CDCl_3$): 3.86 (s, 3H, OCH_3), 6.64 (d, 1H, J 7.8), 6.76 (t, 1H, J 5.0), 7.12 (d, 1H, J 7.8), 7.26 (app t, 1H), 7.31 (br s, NH), 7.43 (s, 1H), 8.45 (d, 2H, J 5.0). δ_C (100 MHz, $CDCl_3$): 54.8 (CH_3-1), 105.1 (CH-5), 107.4 (CH-4), 111.4 (CH), 112.2 (CH-6), 129.2 (CH-3), 140.1 (q, C-2), 157.5 (2CH), 159.6 (q, C), 159.8 (q, C). HRMS (*m/z* ES): Found 202.0980 (M^+ + H. $C_{11}H_{11}N_3O$ Requires 202.0988).

***2*-(2-Methoxyanilino)pyrimidine (9)**. Yield: 90% (91 mg). Mp: 121-124 °C. IR: ν_{max} (film)/cm^{-1}: 3255, 2972, 1608, 1576, 1444, 1251, 973, 793, 779, 693, 669. δ_H (400 MHz, $CDCl_3$): 3.91 (s, 3H, OCH_3), 6.71 (t, 1H, J 5.0), 6.92 (d, 1H, J 7.0), 7.02(m, 2H), 7.83 (br s, NH), 8.45 (d, 2H, J

5.0), 8.53 (d, 1H, J 7.0). δ_C (100 MHz, $CDCl_3$): 55.2 (CH_3), 109.5 (CH-4), 111.9 (CH), 118.1 (CH-5), 120.4 (CH-3), 121.4 (CH-6), 128.7 (q, C-2), 147.5 (q, C-7), 157.5 (2CH), 159.5 (q, C). HRMS (*m/z* ES): Found 202.0980 (M^+ + H. $C_{11}H_{11}N_3O$ Requires 202.0982).

***2*-(4-Fluoroanilino)pyrimidine (10)**. Yield: 66% (62 mg). Mp: 146-150 °C. IR: ν_{max} (film)/cm^{-1}: 3259, 2972, 1713, 1619, 1584, 1506, 1416, 1280, 791, 709. δ_H (400 MHz, $CDCl_3$): 6.74 (t, 1H, J 5.0), 7.06 (t, 2H, J 8.5), 7.51 (br s, NH), 7.57 (m, 2H, J 8.5), 8.43 (d, 2H, J 5.0). δ_C (100 MHz, $CDCl_3$): 112.1 (CH), 114.9 (2CH-2), 121.1 (2CH-3), 134.8 (q, C-4), 157.0 (q, C-1), 157.6 (2CH), 159.4 (q, C). HRMS (*m/z* ES): Found 190.0781 (M^+ + H. $C_{10}H_9N_3F$ Requires 190.0789).

***2*-(3-Bromoanilino)pyrimidine (11)**. Yield: 94% (117 mg). Mp: 93-94 °C. IR: ν_{max} (film)/cm^{-1}:3267, 3175, 1603, 1377, 1357, 1279, 1176, 1079, 889, 792, 769, 662. δ_H (400 MHz, $CDCl_3$): 6.80 (t, 1H, J 5.0), 7.21 (m, 2H), 7.42(br s, NH), 7.48 (d, 1H, J 7.5), 8.02 (s, 1H), 8.48 (d, 2H, J 5.0). δ_C (100 MHz, $CDCl_3$): 112.7 (CH), 117.2 (CH-4), 121.4 (CH-3), 122.3 (q, C-2), 124.9 (CH-5), 129.7 (CH-1), 140.3 (q, C-6), 157.6 (2CH), 159.2 (q, C). HRMS (*m/z* ES): Found 249.9980 (M^+ + H. $C_{10}H_9N_3Br$ Requires 249.9979).

***2*-(2-Fluoroanilino)pyrimidine (12)**. Yield: 92% (86 mg). Mp: 110-114 °C. IR: ν_{max} (film)/cm^{-1}: 3249, 3014, 1576, 1489, 1439, 1252, 1106, 1030, 795, 753. δ_H (400 MHz, $CDCl_3$): 6.73 (t, 1H, J 5.0), 6.97 (m, 1H), 7.09(m, 2H), 7.98 (br s, NH), 8.38 (d, 1H, J 7.6), 8.43(d, 2H, J 5.0). δ_C (100 MHz, $CDCl_3$): 112.5 (CH), 114.3 (CH-3), 114.5 (CH-4), 122.2 (CH-1), 123.7 (CH-5), 127.5 (q, C-2), 151.3 (q, C-6), 157.5 (2CH), 159.5 (q, C). HRMS (*m/z* ES): Found 190.0781 (M^+ + H. $C_{10}H_9N_3F$ Requires 190.0785).

***2*-(4-Cyanoanilino)pyrimidine (13)**. Yield: 78% (86 mg). IR: ν_{max} (film)/cm^{-1}: 3266, 3086, 2212, 1606, 1539, 1580, 1493, 1391, 1248, 1172, 1090, 1016, 914, 881, 832, 789, 710, 683. δ_H (400 MHz, DMSO): 6.95 (t, 1H, J 4), 7.69 (d, 2H, J 8), 7.95 (d, 2H, J 8), 8.55 (d, 2H, J 4), 10.18 (s, NH). δ_C (100 MHz, DMSO): 102.4 (q, C), 114.3 (CH), 118.5 (2CH), 120.0 (q, C), 133.2 (2CH), 144.9 (q, C), 158.4 (2CH), 159.8 (q, C). HRMS (*m/z* ES): Found 197.6790 (M^+ + H. $C_{11}H_9N_4$ Requires 197.6795).

***2*-(3-Cyanoanilino)pyrimidine (14).** Yield: 64% (76 mg). IR: ν_{max} (film)/cm^{-1}: 3265, 3087, 2227, 1603, 1577, 1493, 1308, 1179, 1094, 1004, 965, 856, 778, 705, 682. δ_H (400 MHz, $CDCl_3$): 6.88 (t, 1H, J 4.0), 7.35 (d, 1H, J 8.0), 7.44 (app t, 1H), 7.63 (br s, NH), 7.69 (d, 1H, J 8), 8.31 (s, 1H), 8.51 (d, 2H, J 4). δ_C (100 MHz, $CDCl_3$): 112.5 (q, C), 113.1 (CH), 118.5 (q, C), 121.4 (CH), 122.5 (CH), 125.2 (CH), 129.2 (CH), 139.7 (q, C), 157.6 (2CH), 158.9 (q, C). HRMS (*m/z* ES): Found 197.0781 (M^+ + H. $C_{11}H_9N_4$ Requires 197.0785).

***2*-(2-Cyanoanilino)pyrimidine (15)**. Yield: 82% (80 mg). IR: ν_{max} (film)/cm^{-1}: 3107, 2227, 1602, 1578, 1539, 1493, 1463, 1311, 1273, 1171, 1028, 1004, 965, 788, 753, 709, 682. δ_H (400 MHz, $CDCl_3$): 6.89 (t, 1H, J 4), 7.10 (app t, 1H), 7.61 (m, 2H), 7.69 (br s, NH), 8.53 (d, 2H, J 4), 8.61 (d, 1H, J 8). δ_C (100 MHz, $CDCl_3$): 100.8 (q, C), 113.8 (CH), 116.4 (q, C), 119.2 (CH), 121.7 (CH), 132.2 (CH), 133.3 (CH), 141.7 (q, C), 157.6 (2CH), 158.9 (q, C). HRMS (*m/z* ES): Found 195.0679 (M^+ - H. $C_{11}H_7N_4$ Requires 195.0671).

***2*-(2-phenylanilino)tetrahydropyrimidine (16).** Yield: 98% (96 mg). Mp: 167-169 °C. IR: ν_{max} (film)/cm^{-1}: 3175, 2883, 2343, 2212, 1619, 1562, 1504, 1480, 1439, 1422, 1376, 1320, 1276,

1194, 1073, 952, 882, 831, 766, 743, 703. δ_H (400 MHz, $CDCl_3$): 6.72 (t, 1H, J 4), 7.2 (app t, 2H), 7.29 (m, 1H), 7.30 (br s, NH), 7.39-7.51 (m, 6H), 8.41 (d, 2H, J 4). δ_C (100 MHz, $CDCl_3$): 112.1 (CH), 120.1 (CH), 122.5 (CH), 127.3 (CH), 127.7 (CH), 128.6 (2CH), 129.0 (2CH), 129.9 (CH), 131.8 (CH), 136.7 (q, C), 138.2 (q, C), 157.5 (2CH), 159.6 (q, C). HRMS (*m/z* ES): Found 248.1176 (M^+ + H. $C_{16}H_{14}N_3$ Requires 248.1188).

***2*-(*N, N*-dimethyl-4-aminoanilino)pyrimidine (17).** Yield: 69% (74 mg). Mp: 137-140 °C. IR: ν_{max} (film)/cm^{-1}: 3237, 3155, 2849, 1600, 1582, 1564, 1364, 991, 793, 704. δ_H (400 MHz, D_2O): 3.19 (s, 3H), 7.13 (t, 1H, J 5.0), 7.37 (br S, NH), 7.57 (q, 4H, J 7.5), 8.48 (d, 2H, J 5.0). δ_C (100 MHz, D_2O): 45.9 ($2CH_3$-1), 112.2(CH), 121.1 (4CH), 137.4 (q, C), 138.6 (q, C), 154.6 (q, C), 1 57.4 (2CH). HRMS (*m/z* ES): Found 215.1217 (M^+ + H. $C_{12}H_{15}N_4$ Requires 215.1218).

***2*-(4-Nitro-2-methylanilino)tetrahydropyrimidine (18).** Yield: 74% (85 mg). Mp: 178-180 °C. IR: ν_{max} (film)/cm^{-1}: 3260, 3060, 1712, 1620, 1538, 1412, 1253, 1155, 1081, 852, 818, 750, 703. δ_H (400 MHz, $CDCl_3$): 2.46 (s, 3H, CH_3), 6.92 (t, 1H, J 5.0), 7.31 (br s, NH), 8.13 (s, 1H), 8.16 (d, 1H, J 8.9), 8.55 (d, 2H, J 5.0), 8.67 (d, 1H, J 8.9). δ_C (100 MHz, $CDCl_3$): 17.6 (CH_3-1), 113.9 (CH), 117.5 (CH-6), 122.7 (CH-5), 125.3 (CH-4), 139.9 (q, C-7), 141.3 (q, C-2), 143.4 (q, C-3), 157.7 (2CH), 158.8 (q, C). HRMS (*m/z* ES): Found 231.0882 (M^+ + H. $C_{11}H_{11}N_4O_2$ Requires 231.0871).

2-Anilino-1,4,5,6-tetrahydropyrimidine (19). Yield: 97% (94 mg). IR: ν_{max} (film)/cm^{-1}: 3181, 2971, 2344, 1611, 1583, 1494, 1456, 1440, 1422, 1373, 1347, 1318, 1192, 1150, 1078, 1025, 1002, 967, 913, 881, 848, 763, 691. ^{1}H NMR δ_H (400 MHz, D_2O): 1.80 (quintet, 2H, J 4), 3.19 (t, 4H, J 4), 7.11 (d, 2H, J 8), 7.21 (t, 1H, J 8), 7.32 (app t, 2H). ^{13}C NMR δ_C (100 MHz, D_2O): 19.1 (CH_2), 38.0 ($2CH_2$), 125.3 (2CH), 127.3 (CH), 129.5 (2CH), 133.9 (q, C), 152.3 (q, C). HRMS calcd for $C_{10}H_{14}N_3$: MH^+ 176.1188 ; found MH^+ 176.1168.

2-(2-Methoxyanilino)-1,4,5,6-tetrahydropyrimidine (20). Yield: 98% (104 mg). IR: ν_{max} (film)/cm^{-1}: 3183, 2970, 2883, 2382, 1619, 1568, 1502, 1463, 1438, 1376, 1320, 1277, 1244, 1219, 1043, 1020, 966, 933, 851, 755, 709, 685. ^{1}H NMR δ_H (400 MHz, D_2O): 1.80 (quintet, 2H, J 4), 3.18 (t, 4H, J 4), 3.72 (s, 3H), 6.91 (app t, 1H), 7.01 (d, 1H, J 8), 7.10 (d, 1H, J 8), 7.25 (app t, 1H). ^{13}C NMR δ_C (100 MHz, D_2O): 19.3 (CH_2), 38.3 (CH_3), 55.8 ($2CH_2$), 112.9 (CH), 121.2 (CH), 122.0 (q, C), 128.1 (CH), 129.6 (CH), 152.4 (q, C), 154.2 (q, C). HRMS calcd for $C_{11}H_{16}N_3O$: MH^+ 206.1350; found MH^+ 206.1348.

2-(3-Methoxyanilino)-1,4,5,6-tetrahydropyrimidine (21). Yield: 91% (79 mg). IR: ν_{max} (film)/cm^{-1} 3188, 2961, 2345, 1624, 1583, 1561, 1491, 1455, 1441, 1374, 1322, 1209, 1191, 1141, 1032, 1002, 968, 880, 849, 780, 766, 705, 681. ^{1}H NMR δ_H (400 MHz, D_2O): 1.85 (quintet, 2H, J 4), 3.23 (t, 4H, J 4), 3.70 (s, 3H), 6.72 (s, 1H), 6.75 (d, 1H, J 8), 6.83 (d, 1H, J 8), 7.27 (app t, 1H). ^{13}C NMR δ_C (100 MHz, D_2O): 19.5 (CH_2), 38.0 (CH_2), 55.2 (CH_3), 111.0 (CH), 112.5 (CH), 117.8 (CH), 130.6 (CH), 135.3 (q, C), 152.3 (q, C), 159.8 (q, C). HRMS calcd for $C_{11}H_{16}N_3O$: MH^+ 206.1293; found MH^+ 206.1295.

2-(4-Methoxyanilino)-1,4,5,6-tetrahydropyrimidine (22). Yield: 92% (110 mg). IR: ν_{max} (film)/cm^{-1}: 3197, 2971, 2886, 2837, 1615, 1509, 1463, 1440, 1422, 1375, 1347, 1294, 1242, 1181, 1116, 1081, 1025, 967, 933, 884, 843, 823, 797, 766. ^{1}H NMR δ_H (400 MHz, D_2O): 1.77

(quintet, 2H, J 4), 3.14 (t, 4H, J 4), 3.65 (s, 3H), 6.85 (d, 2H, J 8), 7.01 (d, 2H, J 8). ^{13}C NMR δ_C (100 MHz, D_2O): 18.9 (CH_2), 38.2 ($2CH_2$), 52.2 (CH_3), 115.3 (2CH), 126.9 (q, C), 127.8 (2CH), 153.0 (q, C), 157.9 (q, C). HRMS calcd for $C_{11}H_{16}N_3O$: MH^+ 206.1318; found MH^+ 206.1311.

2-(2-Fluoroanilino)-1,4,5,6-tetrahydropyrimidine (23). Yield: 95% (90 mg). IR: ν_{max} (film)/cm^{-1}: 3184, 2971, 2887, 2359, 1621, 1601, 1567, 1501, 1459, 1441, 1424, 1377, 1289, 1265, 1237, 1151, 1101, 1027, 1022, 950, 878, 800, 750, 730, 706, 680. ^{1}H NMR δ_H (400 MHz, D_2O): 1.84 (quintet, 2H, J 4), 3.23 (t, 4H, J 4), 7.16 (m, 2H), 7.26 (m, 2H). ^{13}C NMR δ_C (100 MHz, D_2O): 19.2 (CH_2), 38.2 ($2CH_2$), 116.6 (CH), 125.3 (CH), 128.6 (CH), 129.7 (CH), 152.3 (q, C), 156.0 (q, C), 158.5 (q, C). HRMS calcd for $C_{10}H_{13}N_3F$: MH^+ 194.1094; found MH^+ 194.1103.

2-(4-Fluoroanilino)-1,4,5,6-tetrahydropyrimidine (24). Yield: 95% (80 mg). IR: ν_{max} (film)/cm^{-1}: 3236, 2965, 2880, 2393, 2225, 2136, 1911, 1621, 1598, 1569, 1461, 1421, 1378, 1321, 1288, 1180, 1165, 1023, 1001, 966, 927, 843, 829, 819, 770, 708. ^{1}H NMR δ_H (400 MHz, D_2O): 1.81 (quintet, 2H, J 4), 3.18 (t, 4H, J 4), 7.04 (m, 2H), 7.10 - 7.14 (m, 2H). ^{13}C NMR δ_C (100 MHz, D_2O): 18.9 (CH_2), 38.0 ($2CH_2$), 116.4 (CH), 116.6 (CH), 128.3 (CH), 128.4 (CH), 129.9 (q, C), 152.8 (q, C), 162.6 (q, C). HRMS calcd for $C_{10}H_{13}N_3F$: MH^+ 194.0462; found MH^+ 194.0464.

2-(2-Cyanoanilino)-1,4,5,6-tetrahydropyrimidine (25). Yield: 64% (86 mg). IR: ν_{max} (film)/ cm^{-1}: 2971, 2332, 1682, 1633, 1603, 1553,1489, 1380, 1340, 1291, 1265, 1121, 1108,1080, 1001, 955, 893, 881, 752, 710, 681. δ_H (400 MHz, D_2O): 1.94 (quintet, 2H, J 4), 3.22 (t, 2H, J 4), 3.58 (t, 2H, J 4), 7.03 (m, 2H), 7.25 (d, 1H, J 8), 7.47 (app t, 1H). δ_C (100 MHz, D_2O): 18.2 (CH_2), 37.3 (CH_2), 43.3 (CH_2), 109.2 (q, C), 113.6 (CH), 123.9 (CH), 124.8 (CH), 135.3 (CH), 138.5 (q, C), 151.4 (q, C), 160.2 (q, C). HRMS calcd for $C_{11}H_{13}N_4$: MH^+ 201.1140; found MH^+ 201.1144.

2-(3-Methylaminoanilino)-1,4,5,6-tetrahydropyrimidine (26). Yield: 71% (16 mg). IR: ν_{max} (film)/cm^{-1}: 3260, 3060, 1712, 1620, 1538, 1412, 1253, 1155, 1081, 852, 818, 750, 703. δ_H (400 MHz, D_2O): 1.86 (quintet, 2H, J 4), 3.24 (t, 4H, J 4), 4.07 (s, 2H), 7.20 (m, 2H), 7.27 (d, 1H, J 8), 7.40 (app t, 1H). δ_C (100 MHz, D_2O): 19.1 (CH_2), 38.3 ($2CH_2$), 42.6 (CH_2), 110.0 (q, C), 125.6 (CH), 125.9 (CH), 127.4 (CH), 130.6 (CH), 134.3 (q, C), 135.0 (q, C). HRMS calcd for $C_{11}H_{17}N_4$: MH^+ 205.1453; found MH^+ 205.1461.

2-(4-Methylaminoanilino)-1,4,5,6-tetrahydropyrimidine (27). Yield: 67% (14 mg). IR: ν_{max} (film)/cm^{-1}: 3383, 3235, 2968, 2855, 2394, 2210, 2134, 1621, 1568, 1505, 1482, 1462, 1439, 1372, 1205, 1146, 1081, 1028, 1001, 958, 913, 895, 808, 765, 709. δ_H (400 MHz, D_2O): 1.85 (quintet, 2H, J 4), 3.24 (t, 4H, J 4), 4.07 (s, 2H), 7.19 (d, 2H, J 8), 7.37 (d, 2H, J 8). δ_C (100 MHz, D_2O): 18.9 (CH_2), 38.3 ($2CH_2$), 42.4 (CH_2), 125.6 (2CH), 129.9 (2CH), 131.1 (q, C), 136.1 (q, C), 152.1 (q, C). HRMS calcd for $C_{11}H_{17}N_4$ MH^+ 205.1386; found MH^+ 205.1381.

2-(2-Phenylanilino)-1,4,5,6-tetrahydropyrimidine (28). Yield: 92% (100 mg).IR: ν_{max} (film)/cm^{-1}: 3175, 2883, 2343, 2212, 1619, 1562, 1504, 1480, 1439, 1422, 1376, 1320, 1276, 1194, 1073,. 952, 882, 831, 766, 743, 703. δ_H (400 MHz, D_2O): 1.31 (quintet, 2H, J 4), 2.86 (t, 4H, J 4), 7.19 (m, 1H), 7.28 (m, 3H), 7.34 (m, 5H). δ_C (100 MHz, D_2O): 19.1 (CH_2), 37.9

(2CH_2), 122.7 (CH), 128.1 (CH), 128.5 (2CH), 128.6 (2CH), 128.6 (CH), 129.1 (CH), 131.0 (CH), 131.3 (q, C), 138.2 (q, C), 138.9 (q, C), 151.8 (q, C). HRMS calcd for $C_{16}H_{18}N_3$: MH^+ 252.1440; found MH^+ 252.1432**.**

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