Synthesis of Fused Imidazoles and Benzothiazoles from (Hetero)Aromatic *ortho*-Diamines or *ortho*-Aminothiophenol and Aldehydes Promoted by Chlorotrimethylsilane

Sergey V. Ryabukhin,[a,b] Andrey S. Plaskon,[a,b] Dmitriy M. Volochnyuk,*[a,c] Andrey A. Tolmachev[b]

[a] Enamine Ltd., 23 A. Matrosova st., 01103 Kiev, Ukraine

[b] National Taras Shevchenko University, 62 Volodymyrska st., Kyiv-33, 01033 Kiev, Ukraine

[c] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska 5, Kyiv-94, 02094 Kiev, Ukraine
Fax +380(44)5373253; E-mail: D.Volochnyuk@enamine.net

Received 12 June 2006

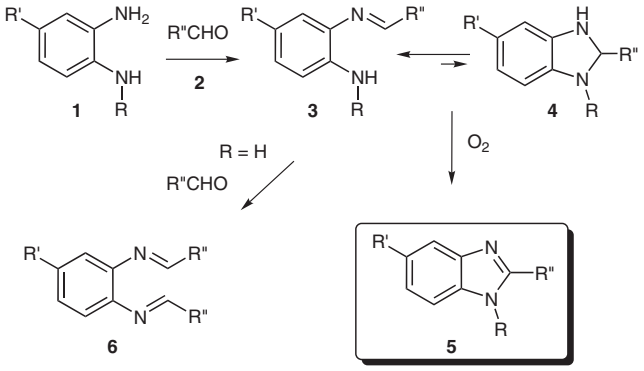
Abstract: New convenient conditions for benzimidazole and benzothiazole syntheses are described. A set of benzimidazoles, 3*H*-imidazo[4,5-*b*]pyridines, purines, xanthines and benzothiazoles was readily prepared from (hetero)aromatic *ortho*-diamines or *ortho*-aminothiophenol and aldehydes using chlorotrimethylsilane in DMF as a promoter and water-acceptor agent, followed by oxidation with air oxygen.

Key words: benzimidazoles, benzothiazoles, aldehydes, chlorotrimethylsilane, parallel synthesis

Benzimidazoles have found commercial applications as anti-ulcer, anti-hypertensive, antiviral, antifungal, anti-tumor, and antihistaminic agents as well as antihelmintic agents in veterinarian medicine.[1] The search for effective methods for the synthesis of benzimidazole libraries for high-throughput screening therefore remains a high priority.[2] The most popular synthetic approaches to the libraries are based on the cyclocondensation of arylidenediamines with carboxylic acid derivatives or on the condensation with aldehydes followed by oxidation. Taking into account the wide structural diversity of commercially available aldehydes, the second approach has recently become very popular.[3] Nitrobenzene, DMF or DMSO at elevated temperatures,[2d,4] as well as metal ions,[5] organic oxidants such as quinones,[6,2a,c] tetracyanoethylene,[7] benzofuroxan,[8] cumarins,[9] $PhI(OAc)_2$,[3b] inorganic sulfites,[2b,e,10] oxone®,[3a] air oxygen in the presence of a Lewis acid[3d] or activated carbon darco® KB[11] have all been used as oxidants in the reaction.

Examples of using aldehydes for a range of condensations in the presence of trimethylsilyl halides as promoting and dehydrating reagents have been recently reported.[12] Continuing our research on such reactions,[12a,b] we investigated the cyclocondensation of arylidenediamines with aldehydes in the presence of chlorotrimethylsilane (TMSCl).

It was found that heating (90 °C) equimolar amounts of the unsubstituted phenylendiamine **1a** (R = R′ = H) and the aldehyde **2b** (R = *p*-$MeOC_6H_4$-) in DMF, in the presence of two equivalents of TMSCl leads to a mixture of benzimidazole **5** and diimine **6** in the ratio ~2:1 (Scheme 1). As N-monosubstituted phenylendiamines cannot form diimines, we then chose to optimize the reaction of *N*-alkylphenylenediamine **1b** (R = Bn, R′ = Cl) with aldehyde **2b**. Under various conditions, in the presence of TMSCl, the reaction gave a mixture of benzimidazoline **4** and benzimidazole **5**. The reaction was carried out in a sealed tube in order to keep both the volatile TMSCl and the HCl formed, in the reaction mixture. After heating the mixture was to completion, benzimidazoline **4** was oxidized to benzimidazole **5** by ultrasonic irradiation in air for 1–3 hours.



Scheme 1

To optimize the reaction conditions, solvent, time, and the amount of TMSCl were varied. As seen from Tables 1 and 2, the optimal reaction conditions were found to be heating in DMF solution for two hours in the presence of two equivalents of TMSCl. The reaction mixtures were subsequently diluted with one to two volumes of water and the amorphous precipitate formed was triturated in an ultrasonic bath for several hours, providing the target product in high yield. The crude products **5**, isolated by simple filtration (except **5dk**, which was isolated by extraction with ethyl acetate), had from ~60% (in the case of diamine **1a** and **1f**) to >90% homogeneity, determined by RP-HPLC, so that washing the precipitates on the filter with methanol or acetonitrile was sufficient to obtain pure products.

SYNTHESIS 2006, No. 21, pp 3715–3726
Advanced online publication: 09.10.2006
DOI: 10.1055/s-2006-950289; Art ID: P07306SS

Table 1 Yields of **4** and **5** in the Reaction of **1b** and **2b** in the Presence of Two Equivalents of TMSCl in Various Solvents after Two Hours at 90 °C[a]

	Solvent	Yield **4** (%)	Yield **5** (%)
1	DMF	49	47
2	DMF–Et_3N	42	55
3	MeCN	34	26
4	MeCN–Et_3N	17	80
5	Dioxane	29	7
6	Dioxane–Et_3N	12	72
7	Pyridine	70	11
8	Pyridine–Et_3N	5	89

[a] According to HPLC-MS data of the reaction mixtures (APSI-MS, Agilent 1100\DAD\MSD VL G1965a).

Table 2 Yields of **4** and **5** in the Reaction of **1b** and **2b** Depending on the Quantity of TMSCl and the Reaction Time at 90 °C[a]

	Time (h)	Yield **4** (%)		Yield **5** (%)	
		1 equiv TMSCl	2 equiv TMSCl	3 equiv TMSCl	4 equiv TMSCl
1	2	55:38	49:47	35:56	30:56
2	5	36:46	35:58	31:56	27:56
3	10	32:59	29:60	24:56	24:56
4	15	24:67	8:78	21:56	16:60

[a] According to HPLC-MS data of the reaction mixtures (APSI-MS, Agilent 1100\DAD\MSD VL G1965a).

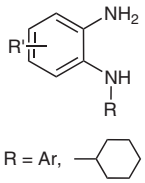
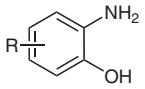
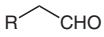
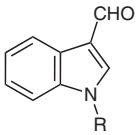
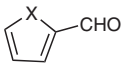
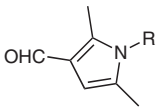
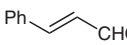
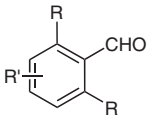
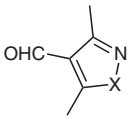
As seen from Table 4, the reaction proceeded in high yield with a wide range of mono N-alkylsubstituted diamines and in moderate yields with N-unsubstituted diamines and various aldehydes. Aromatic, heteroaromatic as well as aliphatic aldehydes could be used. Nevertheless, some limitations have been found, and are summarized in Table 3. *N*-Aryl diamines and diamines having a bulky substituent on the nitrogen, behaved poorly in the reaction. In this case, the reaction stopped at the stage of imine **3** and the target products were only obtained in 10–25% yields (Table 3, Entry 1). Under more drastic conditions such as higher temperature or longer reaction times, yields of the target products remained almost the same, but side processes led to various by-products. In most cases, unsuccessful reactions could be traced to the aldehyde components and their incompatibility towards the reaction conditions. Aliphatic aldehydes enter into crotonic condensation (Table 3, Entry 3), and some aldehydes, derivatives of π-electron rich heterocycles such as 2-furyl, 2(3)-pyrrolyl-, 3-indolylaldehydes (Table 3, Entry 4), gave complex reaction mixtures with the target benzimidazoles only formed in trace amounts. However, introduction of a substituent onto the nucleophilic carbon of the furan nucleus (aldehydes **2e** and **2f**) or an acceptor function onto the pyrrole nucleus (aldehyde **2g**) increased their stability so that they could tolerate the reaction conditions and successfully gave the target products (Table 4). α,β-Unsaturated aldehydes, as in the case of Oxone®,[3a] give complex reaction mixtures and using aromatic and heteroaromatic aldehydes having a formyl function shielded by two *ortho*-substituents was also problematic (Table 3, Entry 6). In the latter case, as with diamines with bulky substituents on the nitrogen, the reaction stopped at the stage of a mixture of imine **3** and benzimidazole **5**, and isolation of the target products required chromatographic separation. Nevertheless, aldehydes **2g**, **2h** and **2i**, bearing only one *ortho*-substituent, reacted readily.

ortho-Aminothiophenol **8**, under similar conditions for 1,2-phenylenediamines, also underwent the reaction, affording the corresponding benzothiazoles **9** in high yields (Scheme 2, Table 5). The limitations on the use of the aldehydes were similar to those for 1,2-phenylenediamines (Table 3).[13]

ortho-Aminophenol **11** did not give the desired products in the reaction.[14] In this case, imine **12** was isolated in high yield, with none of the target benzoxazole **13** observed (Scheme 3). These observations are consistent with the data obtained for an analogous condensation using Oxone® as oxidant.[3a]

The same chemistry could be used to close other fused imidazole ring systems, allowing easy assembly of substituted purines, xanthines and their analogues. 2,3-Diaminopyridine **14**, and diaminopyrimidines **16**, **18** and **20** underwent the reaction, affording the corresponding 3*H*-imidazo[4,5-*b*]pyridines **15**,[15] 2,6-diaminopurines **17**,[16] 2-aminopurin-6-ones **19** and xanthines **21**,[17] respectively, in high yields (Scheme 4, Tables 5 and 6). The synthesis of xanthines, starting from 5,6-diaminouracils and aldehydes, have previously been reported, however in these studies only uracils with unsubstituted amino groups were used. The reaction proceeded in two steps: formation of an imine of type **25**, with further oxidative cyclization by MCPBA,[17a] $FeCl_3$[17b] or DEAD[17c] to **26**. In some cases, the imines **25** were separated[17a] (Scheme 5). To the best of our knowledge, uracils with substituents on the C(5)-amino group were not used in the oxidative cyclocondensation with aldehydes due to the impossibility of formation of imines of type **25** and the low nucleophilicity of the C(6)-amino group for the alternative path of cyclization.[18] Under the conditions reported here however, uracil **22** smoothly underwent the reaction affording N(7)-methyl xanthines **23** in excellent yields. The success of the reaction could be rationalized by the formation of an intermediate of type **29** through silylation of the starting uracil (Scheme 6). Such a process would be analogous to the formation of arylideneaminium salts from aldehydes using the silylated amine-TMSCl system described by Jahn and co-workers.[19] The limitations of the method were found to be similar to those of the 1,2-phenylenediamines (Table 3).

Table 3 Limitations of the Methodology[a]

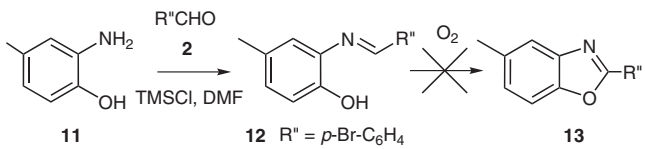
	Aniline	Aldehyde	Comments
1	 R = Ar,	**2a**, **2b**	Reaction stopped at the stage of imine **3**. Yield of products less than 10–25%.
2		**2b**, **2n**	Reaction stopped at the stage of imine **12**.
3	**1b**, **8**	 R = Ph, Et, *i*-Pr	Self-condensation of the aldehyde occurred.
4	**1b**, **8**	 R = H, CH_2Ph  X = O, NH, NMe  R = Me, Ph	Aldehydes unstable; target products formed in low yields (5–10%).
5	**1b**, **8**		Complex reaction mixture
6	**1b**, **8**	 R = Me, Cl  X = O, NPh, NBn	Reaction stopped at the stage of imine **3**. Yield of products 20–50%.

[a] According to HPLC-MS and ^1H NMR of the reaction mixtures (APSI-MS, Agilent 1100\DAD\MSD VL G1965a, Varian Mercury-400 spectrometer).

In summary, we have developed an efficient methodology for the preparation of substituted, fused imidazoles and benzothiazoles from (hetero)aromatic *ortho*-diamines or *ortho*-aminothiophenol and aldehydes, using TMSCl as a promoter and water scavenger. The methodology is applicable to a wide variety of aldehyde substrates (aliphatic, aromatic and heteroaromatic) and delivers the target products in good yields, excellent homogeneity and often in analytically pure form. The chemical procedure is very simple and could be easily adapted to semi-automated, solution-phase parallel synthesis of fused azole libraries.

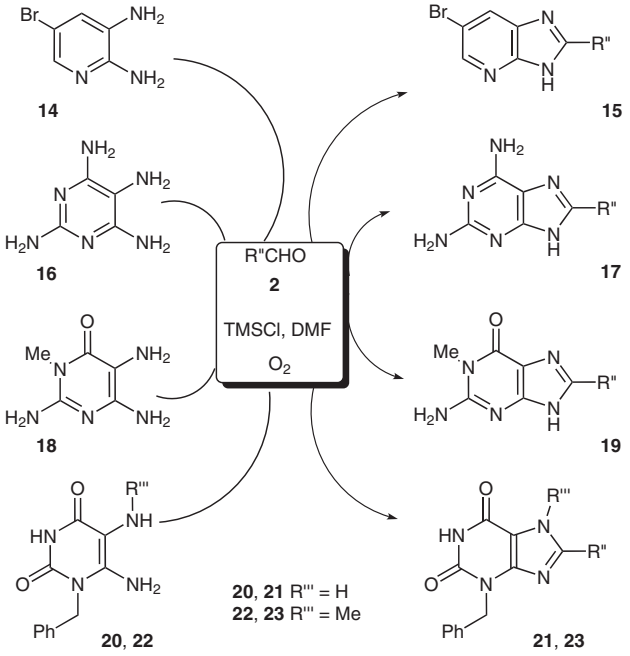
8 **2** **9**

Scheme 2

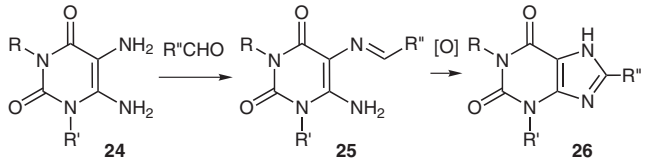


11 **12** R" = *p*-Br-C_6H_4 **13**

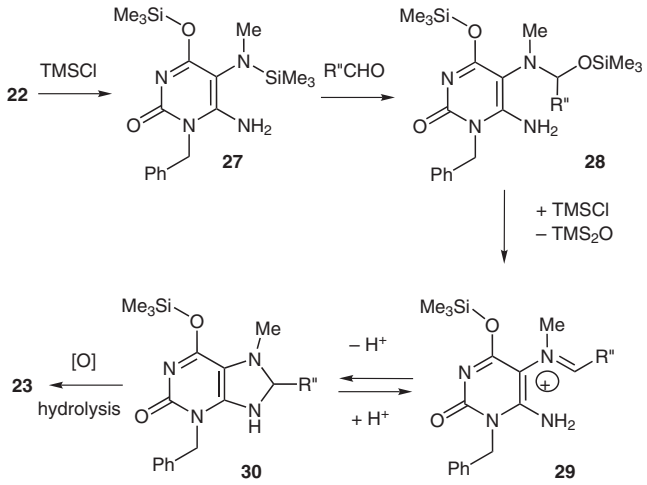
Scheme 3



Scheme 4



Scheme 5



Scheme 6

Table 4 Preparation of Benzimidazoles[e]

N	Starting material	R″CHO **2**	Product	Yield[a] (crude) (%)	Homogeneity[b] (crude) (%)	Crystallization solvent	Yield[c] (%)	Mp (°C)[d] [Lit.]
5aa	**1a**	**2a**		66	87	*i*-PrOH–H_2O	55	293–294 [292][3d]
5ab	**1a**	**2b**		69	90	*i*-PrOH	65	220–223 [226][3d]
5ac	**1a**	**2c**		58	86	*i*-PrOH	51	228–229 [233][20a]
5bb	**1b**	**2b**		99	93	MeCN	90	141–142
5bd	**1b**	**2d**		99	88	MeOH	87	158–159
5be	**1b**	**2e**		97	85	MeOH	81	147–148

Table 4 Preparation of Benzimidazoles[e] (continued)

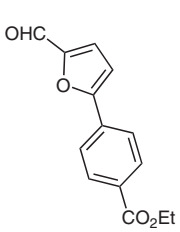
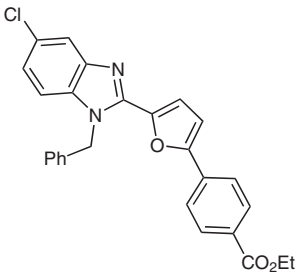
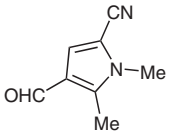
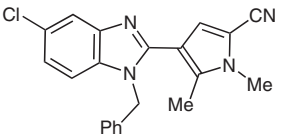
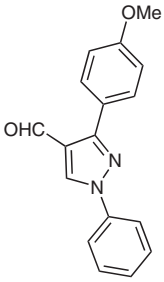
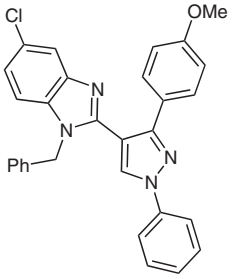
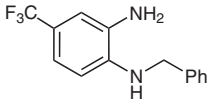
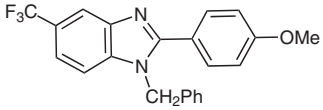
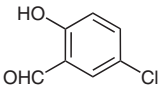
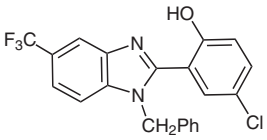
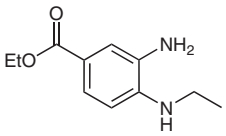
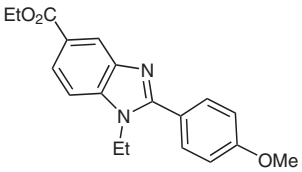
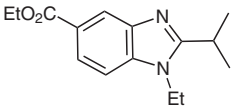
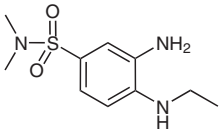
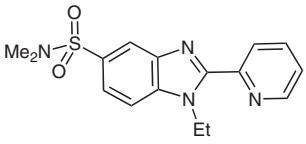
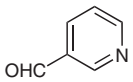
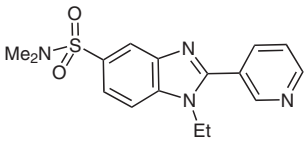
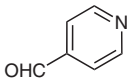
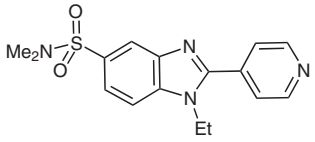
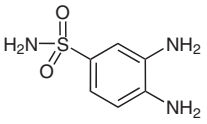
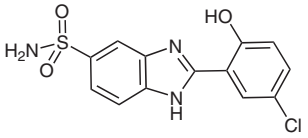
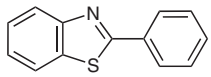
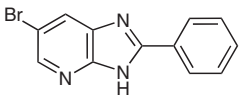
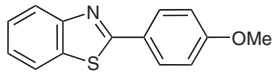
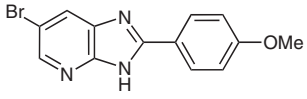
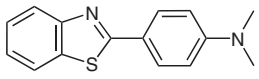
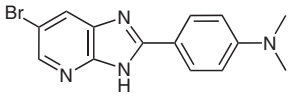
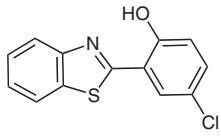
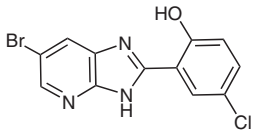
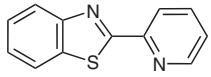
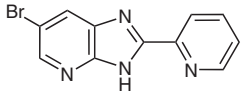
N	Starting material	R″CHO **2**	Product	Yield[a] (crude) (%)	Homogeneity[b] (crude) (%)	Crystallization solvent	Yield[c] (%)	Mp (°C)[d] [Lit.]
5bf	**1b**	 **2f**		99	90	DMF–MeOH	94	177–178
5bg	**1b**	 **2g**		96	91	MeCN	92	182–183
5bh	**1b**	 **2h**		95	88	DMF–MeOH	91	171–172
5cb	 **1c**	**2b**		99	92	MeOH	88	124–125
5ci	**1c**	 **2i**		95	89	MeCN	90	209–210
5db	 **1d**	**2b**		100	92	MeOH	94	103–104
5dj	**1d**	 **2j**		96	85	–	85	oil
5ek	 **1e**	**2k**		94	89	MeOH	81	137–138

Table 4 Preparation of Benzimidazoles[e] (continued)

N	Starting material	R″CHO **2**	Product	Yield[a] (crude) (%)	Homogeneity[b] (crude) (%)	Crystallization solvent	Yield[c] (%)	Mp (°C)[d] [Lit.]
5el	**1e**	 **2l**		98	93	MeOH	84	152–153
5em	**1e**	 **2m**		95	90	MeOH	85	184–185
5fi	 **1f**	**2i**		65	88	*i*-PrOH	58	>300

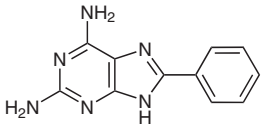
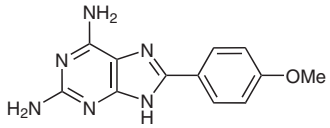
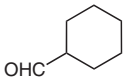
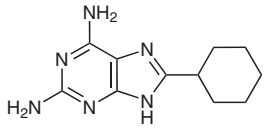
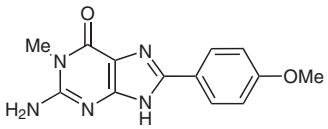
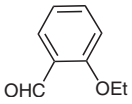
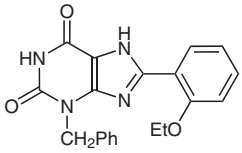
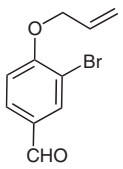
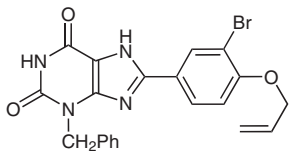
[a] Yield of crude material obtained after dilution of reaction mixture with 2 volumes of aq K_2CO_3 (~10%) and collection of the precipitate by filtration or extraction with EtOAc
[b] Reversed-phase HPLC homogeneity of the crude products.
[c] Yields refer to pure isolated products.
[d] Melting points are uncorrected.
[e] Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25.

Table 5 Preparation of Benzothiazoles **9** and Imidazo[4,5-*b*]pyridines **15** Starting from **8** and **14**, Respectively[c]

R″CHO	Product **9**	Yield[a] (%)	Mp (°C)[b] [Lit.]	Product **15**	Yield[a] (%)	Mp (°C)[c] [lit]
2a	 **9a**	94	113–114 [114][20b]	 **15a**	74	>300 [>310][20g]
2b	 **9b**	96	124–125 [123–125][20c]	 **15b**	80	>300 [299–300][20h]
2c	 **9c**	92	170–171 [173][20d]	 **15c**	87	>300
2i	 **9i**	91	152–153 [149–150][20e]	 **15i**	79	>300
2k	 **9k**	88	129–130 [132][20f]	 **15k**	64	284–285

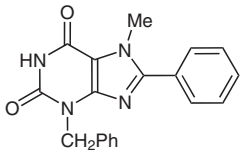
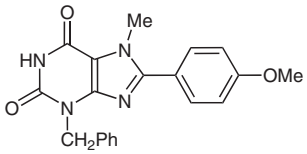
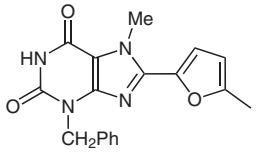
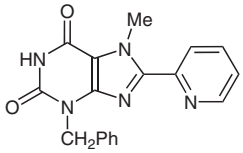
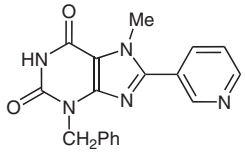
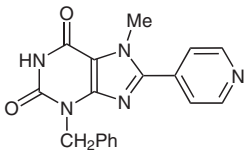
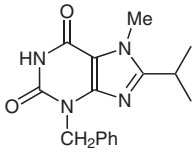
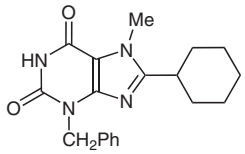
[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25.

Table 6 Preparation of N(7)-Unsubstituted Purines **17**, **19** and Xanthines **21**[d]

N	Diamine	R″CHO **2**	Product	Yield[a] (%)	Mp (°C)[b] [Lit.]	^{1}H NMR, δ (ppm), *J* (Hz)	[M + H]$^{+}$[c]
17a	**16**	**2a**		95	>300 [>300][16], [303][21a]	7.54 (5 H, m, CH + NH_2), 8.09 (4 H, m, CH + NH_2)	227
17b	**15**	**2b**		99	283–284	3.84 (3 H, s, OCH_3), 7.13 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.31 (2 H, br s, NH_2), 8.05 (2 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 8.43 (2 H, br s, NH_2), 14.50 (1 H, br s, NH)	257
17n	**15**	 **2n**		97	224–225	1.23 (2 H, m, CH_2), 1.37 (2 H, m, CH_2), 1.51 (2 H, m, CH_2), 1.67 (2 H, m, CH_2), 1.76 (2 H, m, CH_2), 2.79 (1 H, m, CH), 7.13 (2 H, br s, NH_2), 8.36 (2 H, br s, NH_2), 13.57 (1 H, br s, NH)	233
19	**18**	**2b**		76	>300	3.36 (3 H, s, NCH_3), 3.82 (3 H, s, OCH_3), 7.08 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.28 (2 H, m, NH_2), 8.03 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH)	272
21o	**20**	 **2o**		86	277–278	1.47 (3 H, t, $^3J_{HH}$ = 7.0 Hz, OCH_2CH_3), 4.26 (2 H, q, $^3J_{HH}$ = 7.0 Hz, OCH_2CH_3), 5.18 (2 H, s, NCH_2), 7.02 (1 H, t, $^3J_{HH}$ = 8.0 Hz, CH), 7.10 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.23 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.29 (2 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.40 (1 H, t, $^3J_{HH}$ = 8.4 Hz, CH), 7.45 (2 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.99 (1 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 11.01 (1 H, br s, NH), 12.42 (1 H, br s, NH)	363
21p	**20**	 **2p**		90	261–262	4.72 (2 H, m, OCH_2), 5.16 (2 H, s, NCH_2), 5.30 (1 H, d, $^3J_{HH}$ = 11.2 Hz, CH), 5.46 (1 H, d, $^3J_{HH}$ = 11.2 Hz, CH), 6.05 (1 H, m, CH), 7.25 (2 H, m, CH), 7.31 (2 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.37 (2 H, m, CH), 8.07 (1 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 8.32 (1 H, s, CH), 11.21 (1 H, br s, NH), 13.78 (1 H, br s, NH)	454

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] APSI-MS, Agilent 1100\DAD\MSD VL G1965a instrument.
[d] Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25.

Table 7 Preparation of N(7) Methyl Xanthines **23** from **22**[d]

N	R″CHO **2**	Product	Yield[a] (%)	Mp (°C)[b] [Lit.]	^{1}H NMR, δ (ppm), *J* (Hz)	[M + H]$^{+c}$
23a	**2a**		87	263–264 [–][21b]	3.96 (3 H, s, NCH_3), 5.14 (2 H, s, NCH_2), 7.26 (1 H, t, $^3J_{HH}$ = 8.4 Hz, CH), 7.32 (2 H, t, $^3J_{HH}$ = 8.4 Hz, CH), 7.37 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.57 (3 H, m, CH), 7.78 (2 H, m, CH), 11.28 (1 H, br s, NH)	333
23b	**2b**		91	247–248	3.84 (3 H, s, OCH_3), 3.96 (3 H, s, NCH_3), 5.14 (2 H, s, NCH_2), 7.09 (2 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 7.23–7.39 (5 H, m, CH), 7.73 (2 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 11.17 (1 H, br s, NH)	363
23e	**2e**		80	285–286	2.39 (3 H, s, CH_3), 4.08 (3 H, s, NCH_3), 5.13 (2 H, s, NCH_2), 6.37 (1 H, d, $^3J_{HH}$ = 3.3 Hz, CH), 7.07 (1 H, d, $^3J_{HH}$ = 3.3 Hz, CH), 7.26 (1 H, m, CH), 7.32 (4 H, m, CH), 11.20 (1 H, br s, NH)	337
23k	**2k**		85	>300	4.33 (3 H, s, NCH_3), 5.16 (2 H, s, NCH_2), 7.25 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.32 (2 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.39 (2 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.52 (1 H, m, CH), 8.00 (1 H, td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.6 Hz, CH), 8.15 (1 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 8.72 (1 H, m, CH), 11.31 (1 H, br s, NH)	334
23l	**2l**		90	252–253	4.00 (3 H, s, NCH_3), 5.15 (2 H, s, NCH_2), 7.25 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.32 (2 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.37 (2 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.59 (1 H, m, CH), 8.20 (1 H, dt, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.0 Hz, CH), 8.73 (1 H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.0 Hz, CH), 8.98 (1 H, d, $^4J_{HH}$ = 2.0 Hz, CH), 11.32 (1 H, br s, NH)	334
23m	**2m**		87	>300	4.04 (3 H, s, NCH_3), 5.14 (2 H, s, NCH_2), 7.24 (1 H, t, $^3J_{HH}$ = 8.0 Hz, CH), 7.31 (2 H, t, $^3J_{HH}$ = 8.0 Hz, CH), 7.36 (2 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 7.79 (2 H, d, $^3J_{HH}$ = 6.0 Hz, CH), 8.76 (2 H, d, $^3J_{HH}$ = 6.0 Hz, CH), 11.35 (1 H, br s, NH)	334
23j	**2j**		83	218–219	1.32 [6 H, d, $^3J_{HH}$ = 6.9 Hz, $CH(CH_3)_2$], 3.14 [1 H, hept, $^3J_{HH}$ = 6.9 Hz, $CH(CH_3)_2$], 3.87 (3 H, s, NCH_3), 5.09 (2 H, s, NCH_2), 7.24 (3 H, m, CH), 7.42 (2 H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, CH), 10.81 (1 H, br s, NH)	299
23n	**2n**		89	194–195	1.38 (4 H, m, 2 × CH_2), 1.65 (2 H, m, CH_2), 1.85 (4 H, m, 2 × CH_2), 3.13 (1 H, m, CH), 3.86 (3 H, s, NCH_3), 5.08 (2 H, s, NCH_2), 7.25 (3 H, t, $^3J_{HH}$ = 7.8 Hz, CH), 7.41 (2 H, d, $^3J_{HH}$ = 7.8 Hz, CH), 10.80 (1 H, br s, NH)	339

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] APSI-MS, Agilent 1100\DAD\MSD VL G1965a instrument.
[d] Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25.

Table 8 ^{1}H NMR and APSI-MS Data of Benzimidazoles **5**[a]

N	^{1}H NMR, δ (ppm), *J* (Hz)	$[M + H]^+$
5ac	3.03 [6 H, s, $N(CH_3)_2$], 6.92 (2 H, d, $^3J_{HH}$ = 9.0 Hz, CH), 7.47 (2 H, td, $^3J_{HH}$ = 6.3 Hz, $^4J_{HH}$ = 3.0 Hz, CH), 7.73 (2 H, dd, $^3J_{HH}$ = 6.3 Hz, $^4J_{HH}$ = 3.0 Hz, CH), 8.23 (2 H, d, $^3J_{HH}$ = 9.0 Hz, CH)	238
5bb	3.89 (3 H, s, OCH_3), 5.74 (2 H, s, CH_2), 7.15 (4 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.31 (3 H, m, CH), 7.42 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.2 Hz, CH), 7.65 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.85 (2 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.91 (1 H, d, $^4J_{HH}$ = 1.2 Hz, CH)	349
5bd	2.55 (3 H, s, CH_3), 5.71 (2 H, s, CH_2), 6.82 (1 H, d, $^4J_{HH}$ = 3.6 Hz, CH), 7.08 (2 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.20 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.2 Hz, CH), 7.30 (3 H, m, CH), 7.41 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.67 (1 H, d, $^4J_{HH}$ = 3.6 Hz, CH), 7.90 (1 H, d, $^4J_{HH}$ = 1.2 Hz, CH)	339
5be	2.38 (3 H, s, CH_3), 5.73 (2 H, s, CH_2), 6.20 (1 H, d, $^4J_{HH}$ = 3.2 Hz, CH), 6.96 (1 H, d, $^4J_{HH}$ = 3.2 Hz, CH), 7.11 (2 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.14 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.2 Hz, CH), 7.24 (3 H, m, CH), 7.40 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.58 (1 H, d, $^4J_{HH}$ = 1.2 Hz, CH)	323
5bf	1.41 (3 H, t, $^3J_{HH}$ = 6.8 Hz, CH_2CH_3), 4.34 (2 H, q, $^3J_{HH}$ = 6.8 Hz, CH_2CH_3), 5.91 (2 H, s, CH_2), 7.17 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.30 (4 H, m, CH), 7.43 (1 H, d, $^4J_{HH}$ = 3.2 Hz, CH), 7.56 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.2 Hz, CH), 7.67 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.71 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.90 (1 H, d, $^4J_{HH}$ = 1.2 Hz, CH), 7.94 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH)	457
5bg	2.49 (3 H, s, CH_3), 3.74 (3 H, s, NCH_3), 5.48 (2 H, s, CH_2), 6.87 (1 H, s, CH), 6.99 (2 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.11 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.6 Hz, CH), 7.29 (4 H, m, CH), 7.63 (1 H, d, $^4J_{HH}$ = 1.6 Hz, CH)	361
5bh	3.79 (3 H, s, OCH_3), 5.19 (2 H, s, CH_2), 6.82 (2 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 6.90 (2 H, m, CH), 7.14 (4 H, m, CH), 7.32 (2 H, m, CH), 7.47 (4 H, m, CH), 7.69 (1 H, s, CH), 7.90 (2 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 8.71 (1 H, s, CH)	491
5cb	3.86 (3 H, s, OCH_3), 5.57 (2 H, s, CH_2), 6.99 (2 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.08 (2 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.29 (3 H, m, CH), 7.43 (2 H, s, CH), 7.64 (2 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.98 (1 H, s, CH)	383
5ci	5.50 (2 H, s, CH_2), 7.04 (3 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.25 (3 H, m, CH), 7.32 (1 H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.4 Hz, CH), 7.39 (1 H, d, $^4J_{HH}$ = 2.4 Hz, CH), 7.44 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.51 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.99 (1 H, s, CH), 10.82 (1 H, br s, OH)	403
5db	1.43 (6 H, t, $^3J_{HH}$ = 6.8 Hz, OCH_2CH_3 and NCH_2CH_3), 3.89 (3 H, s, OCH_3), 4.37 (4 H, q, $^3J_{HH}$ = 6.8 Hz, OCH_2CH_3 and NCH_2CH_3), 7.08 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.56 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.70 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.90 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 8.27 (1 H, s, CH)	325
5dj	1.35 [6 H, d, $^3J_{HH}$ = 7.2 Hz, $CH(CH_3)_2$], 1.43 (6 H, t, $^3J_{HH}$ = 6.8 Hz, OCH_2CH_3 and NCH_2CH_3), 4.17 [1 H, hept, $^3J_{HH}$ = 7.2 Hz, $CH(CH_3)_2$], 4.37 (4 H, q, $^3J_{HH}$ = 6.8 Hz, OCH_2CH_3 and NCH_2CH_3), 7.61 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.87 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 8.18 (1 H, s, CH)	261
5ek	1.50 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 2.67 [6 H, s, $N(CH_3)_2$], 4.97 (2 H, q, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 7.50 (1 H, dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 5.2 Hz, CH), 7.66 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.78 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.99 (1 H, t, $^3J_{HH}$ = 8.0 Hz, CH), 8.07 (1 H, s, CH), 8.41 (1 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 8.73 (1 H, d, $^3J_{HH}$ = 5.2 Hz, CH)	331
5el	1.47 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 2.68 [6 H, s, $N(CH_3)_2$], 4.45 (2 H, q, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 7.57 (1 H, dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 5.2 Hz, CH), 7.68 (1 H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.6 Hz, CH), 7.82 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 8.08 (1 H, d, $^4J_{HH}$ = 1.6 Hz, CH), 8.19 (1 H, dt, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.6 Hz, CH), 8.75 (1 H, dd, $^3J_{HH}$ = 5.2 Hz, $^4J_{HH}$ = 1.6 Hz, CH), 8.96 (1 H, d, $^4J_{HH}$ = 1.6 Hz, CH)	331
5em	1.47 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 2.67 [6 H, s, $N(CH_3)_2$], 4.51 (2 H, q, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 7.70 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.6 Hz, CH), 7.86 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.89 (2 H, d, $^3J_{HH}$ = 5.2 Hz, CH), 8.10 (1 H, d, $^4J_{HH}$ = 1.6 Hz, CH), 8.86 (2 H, d, $^3J_{HH}$ = 5.2 Hz, CH)	331
5fi	7.00 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.15 (2 H, s, NH_2), 7.30 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.2 Hz, CH), 7.73 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.78 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 8.12 (1 H, s, CH), 8.14 (1 H, d, $^4J_{HH}$ = 1.2 Hz, CH), 10.20 (1 H, br s, OH)	324

[a] DMSO-d_6

All commercially available starting materials were used without additional purification. All solvents were purified by standard methods. All procedures were carried out under an open atmosphere with no precautions taken to exclude ambient moisture. ^{1}H and ^{13}C (400 and 100 MHz, respectively) were recorded on a Varian Mercury-400 spectrometer with TMS as an internal standard. HPLC APSI MS spectra were recorded on Agilent 1100\DAD\MSD VL G1965a instrument. A Branson 2510E-MT ultrasonic bath was used.

Commercially unavailable starting 1,2-phenylenediamines **1b–d**,[22] **1e**, **1f**,[23] heterocyclic diamines **18**,[24] **20**,[21b] **22**[21b] and aldehydes **2f**[25] and **2h**[26] were obtained according to the literature procedures. See Tables 6, 7 and 8 for ^{1}H NMR data.

***N*^{1}-Benzyl-4-chlorobenzene-1,2-diamine (1b)**
Mp 77–78 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.27 (2 H, d, $^3J_{HH}$ = 4.4 Hz, CH_2), 4.93 (2 H, s, NH_2), 5.25 (1 H, d, $^3J_{HH}$ = 4.4 Hz, NH), 6.26 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 6.38 (1 H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.0 Hz, CH), 6.57 (1 H, d, $^4J_{HH}$ = 2.0 Hz, CH), 7.23 (1 H, t, $^3J_{HH}$ = 8.2 Hz, CH), 7.29–7.37 (4 H, m, CH).

N^1-Benzyl-4-(trifluoromethyl)benzene-1,2-diamine (1c)
Mp 87–88 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.35 (2 H, s, CH_2), 4.58 (2 H, br s, NH_2), 5.48 (1 H, br s, NH), 6.33 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 6.68 (1 H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.8 Hz, CH), 6.81 (1 H, d, $^4J_{HH}$ = 1.8 Hz, CH), 7.20 (1 H, t, $^3J_{HH}$ = 8.4 Hz, CH), 7.30 (2 H, t, $^3J_{HH}$ = 8.4 Hz, CH), 7.34 (2 H, t, $^3J_{HH}$ = 8.4 Hz, CH).

Ethyl 3-Amino-4-(ethylamino)benzoate (1d)
Mp 94–95 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.38 (3 H, t, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 4.25 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 4.75 (2 H, br s, NH_2), 5.06 (1 H, br s, NH), 6.50 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 6.91 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 6.98 (1 H, s, CH).

3-Amino-4-(ethylamino)-*N*,*N*-dimethylbenzenesulfonamide (1e)
Mp 155–156 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.29 (3 H, t, $^3J_{HH}$ = 7.0 Hz, NCH_2CH_3), 2.57 [6 H, s, $N(CH_3)_2$], 3.24 (2 H, q, $^3J_{HH}$ = 7.0 Hz, NCH_2CH_3), 4.70 (2 H, br s, NH_2), 5.01 (1 H, br s, NH), 6.44 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 6.88 (2 H, d + s, $^3J_{HH}$ = 8.4 Hz, CH).

4-Formyl-1,5-dimethylpyrrole-2-carbonitrile (2g)
To a stirring solution of 1,5-dimethyl-1*H*-pyrrole-2-carbonitrile (5 g, 0.042 mol) in DMF (20 mL) was added, dropwise, $POCl_3$ (6.37 g, 0.042 mol). The reaction mixture was maintained at r.t. for 3 h then H_2O (30 mL) was added in one portion and the resulting mixture was diluted with aq NaOH (40%, 20 mL) at 0 °C. The precipitate formed was filtered, dried and washed with Et_2O (50 mL) affording **2g**.

Yield: 4.6 g, (75%); mp 116–117 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.57 (3 H, s, CH_3), 3.71 (3 H, s, NCH_3), 7.19 (1 H, s, CH), 9.75 (1 H, s, CHO).

Preparation of Benzimidazoles; General Procedure
Aniline **1** (4 mmol) and an appropriate aldehyde **2** (4 mmol) were placed in a 15 mL pressure tube and dissolved in DMF (10 mL). TMSCl (10 mmol) was added dropwise to the solution and the tube was thoroughly sealed and heated on a water-bath for 2–4 h. After cooling, the flask was opened (*Caution! Excess pressure inside*) and the reaction mixture was poured into H_2O (20 mL) and allowed to stand at r.t. in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH and then with MeOH. Recrystallization from an appropriate solvent yielded the targeted compound (see Table 4).

5dj
Obtained following the above general procedure, but the mixture obtained after dilution with H_2O was extracted with EtOAc (2 × 10 mL). The organic layer was dried ($MgSO_4$), the solvent was evaporated under reduced pressure and the crude product was purified by flash silica gel column chromatography (neat EtOAc).

5aa and 5ab
Spectral data of compounds were in agreement with those previously reported.[3d]

5bg
^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.6, 33.4, 47.7, 103.5, 111.1, 112.6, 114.0, 118.8, 119.0, 122.8, 126.6, 126.9, 128.0, 129.3, 134.6, 137.2, 138.6, 144.0, 150.5.

5ci
^{13}C NMR (125 MHz, DMSO-d_6): δ = 48.3, 112.6, 117.1, 118.5, 118.9, 119.8, 123.2, 123.3 ($^1J_{CF}$ = 270 Hz), 123.5 ($^2J_{CF}$ = 31 Hz), 127.2, 128.1, 129.1, 131.2, 132.0, 136.7, 137.9, 142.6, 153.6, 155.2.

5db
^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.7, 15.4, 48.2, 55.8, 61.0, 111.2, 114.8, 121.0, 122.5, 123.7, 124.2, 131.1, 139.2, 142.7, 155.3, 161.1, 166.8.

5dj
^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.2, 15.2, 21.7, 25.7, 37.9, 60.4, 110.0, 120.2, 122.7, 123.1, 138.0, 142.0, 161.6, 166.3.

5em
^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.5, 34.5, 38.2, 112.8, 120.2, 123.0, 125.0, 129.6, 138.8, 140.2, 142.2, 148.2, 152.3.

Preparation of Benzothiazoles 9; General Procedure
Compounds **9** were prepared from **8** and **2** using the above procedure for **5**. Compounds **9a–c** and **9k** were recrystallized from *i*-PrOH–H_2O, **9i** from neat *i*-PrOH. Spectral data of all compounds were in agreement with those previously reported.[20b–f]

2-{[(4-Bromophenyl)methylene]amino}-4-methylphenol (12)
o-Aminophenole **11** (4 mmol) and *p*-bromobenzaldehyde **2** (4 mmol) were placed in a 15 mL pressure tube and dissolved in DMF (10 mL). TMSCl (10 mmol) was added dropwise to the solution and the tube was thoroughly sealed and heated on a water-bath for 2–4 h. After cooling, the flask was opened (*Caution! Excess pressure inside*), Et_3N was added dropwise and the reaction mixture was allowed to stand at r.t. in an ultrasonic bath for 1 h. The reaction mixture was then poured into H_2O (20 mL) and allowed to stand at r.t. in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH and then with MeOH.

Yield: 70%; mp 123–124 °C (Lit.[27] 83–84 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (3 H, s, OCH_3), 6.60 (1 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 6.69 (1 H, s, CH), 7.12 (1 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 7.60 (2 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 7.94 (2 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 8.68 (1 H, s, CH), 11.10 (1 H, br s, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 115.3, 115.6, 120.9, 125.8, 129.9, 132.1, 132.4, 134.8, 139.8, 152.3, 154.1.

Preparation of Imidazo[4,5-*b*]pyridines 15; General Procedure
Compounds **15** were prepared from **14** and **2** using the above procedure for **5**. Compounds **15a–c** and **15i** were recrystallized from MeCN, **15k** from MeOH.

15a and 15b
Spectral data of compounds were in agreement with those previously reported.[20g,h]

15c
^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.01 [3 H, s, $N(CH_3)_2$], 6.79 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 8.00 (1 H, d, $^4J_{HH}$ = 1.6 Hz, CH), 8.10 (2 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 8.24 (1 H, d, $^4J_{HH}$ = 1.6 Hz, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.6, 112.2, 113.6, 113.9, 124.7, 129.2, 144.1, 149.8, 152.9, 153.6, 155.0.

APSI-MS: m/z $[M + 1]^+$ = 317.

15i

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.09 (1 H, d, $^3J_{HH}$ = 8.8 Hz, CH), 7.45 (1 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.6 Hz, CH), 8.21 (1 H, d, $^4J_{HH}$ = 2.0 Hz, CH), 8.36 (1 H, s, CH), 8.49 (1 H, d, $^4J_{HH}$ = 2.0 Hz, CH), 12.90 (1 H, br s, OH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 113.6, 113.7, 119.0, 119.2, 123.1, 126.5, 132.3, 145.1, 149.1, 151.8, 153.0, 156.9.

APSI-MS: *m*/*z* $[M + H]^+$ = 325.

15k

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.50 (1 H, dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 5.2 Hz, CH), 7.97 (1 H, td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.8 Hz, CH), 8.06 (1 H, d, $^4J_{HH}$ = 1.6 Hz, CH), 8.36 (1 H, d, $^4J_{HH}$ = 2.0 Hz, CH), 8.41 (1 H, d, $^3J_{HH}$ = 8.0 Hz, CH), 8.74 (1 H, d, $^3J_{HH}$ = 5.2 Hz, CH).

APSI-MS: *m*/*z* $[M + 1]^+$ = 276.

Preparation of 2,6-Diaminopurines 17; General Procedure

2,4,5,6-Tetraaminopyrimidine sulphate **16** (3 mmol) and an appropriate aldehyde **2** (3.5 mmol) were placed in a 15 mL pressure tube and dissolved in DMF (10 mL). TMSCl (12 mmol) was added dropwise to the solution and the tube was thoroughly sealed and heated on a water-bath for 8 h. After cooling, the flask was opened (*Caution! Excess pressure inside*) and the reaction mixture was poured into H_2O (20 mL) and allowed to stand at r.t. in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH and then with MeCN. Compounds **17a** and **17b** were recrystallized from DMF–MeOH, **17n** was recrystallized from DMF–*i*-PrOH.

17b

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.5, 113.8, 114.7, 120.8, 128.0, 151.1, 152.6, 153.7, 153.9, 161.3.

2-Amino-8-(4-methoxyphenyl)-1-methyl-1,7-dihydro-6*H*-purin-6-one (19)

Prepared from **18** and **2b** using the above procedure for **17** and recrystallized from DMF–*i*-PrOH.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.8, 55.9, 97.1, 114.1, 115.0, 120.4, 128.6, 137.6, 154.7, 161.6, 162.8.

Preparation of Xanthines 21 and 23; General Procedure

Uracil **20** or **22** (3 mmol) and an appropriate aldehyde **2** (4 mmol) were placed in a 15 mL pressure tube and dissolved in DMF (10 mL). TMSCl (10 mmol) was added dropwise to the solution and the tube was thoroughly sealed and heated on a water-bath for 8–12 h. After cooling, the flask was opened (*Caution! Excess pressure inside*) and the reaction mixture was poured into H_2O (20 mL) and allowed to stand at r.t. in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH and then with MeCN. Solvent for crystallization: **21o**, **21p**, **23j**, **23 k–m**, **23q**: DMF–*i*-PrOH; **23a**, **23b**, **23e**: DMF–MeOH.

21o

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.8, 45.5, 64.2, 108.0, 113.1, 117.9, 121.0, 127.8, 128.1, 128.9, 130.8, 132.2, 137.7, 148.4, 149.8, 151.3, 154.8, 156.4.

23a

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.2, 45.2, 108.9, 127.8, 128.1, 128.7, 128.9, 129.2, 129.5, 130.7, 137.5, 149.3, 151.1, 151.6, 155.6.

23e

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.9, 33.8, 45.1, 107.9, 109.1, 115.3, 127.7, 128.9, 137.4, 142.1, 143.1, 149.4, 151.0, 155.3, 155.35.

23k

^{13}C NMR (125 MHz, DMSO-d_6): δ = 35.6, 45.3, 109.8, 124.8, 124.9, 127.8, 128.1, 128.9, 137.5, 138.1, 147.9. 148.9, 149.0, 149.5, 151.1, 155.7.

23m

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.3, 45.3, 109.7, 123.4, 127.9, 128.1, 128.9, 136.1, 137.4, 148.7, 149.2, 150.6, 151.0, 155.6.

23j

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.2, 25.6, 31.6, 45.1, 107.2, 127.8, 128.3, 128.8, 137.6, 149.1, 151.1, 155.3, 159.0.

References

(1) (a) Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimiva, V. A. *Pharm. Chem. J.* **1999**, *33*, 232. (b) Preston, P. N. In *The Chemistry of Heterocyclic Compounds, Benzimidazoles and Congeneric Tricyclic Compounds*, Part 2, Vol. 40; John Wiley and Sons: New York, **1980**, Chap. 10. (c) Preston, P. N. *Chem. Rev.* **1974**, *74*, 279.

(2) For recent examples, see: (a) Buerli, R. W.; McMinn, D.; Kaizerman, J. A.; Hu, W.; Ge, Y.; Pack, Q.; Jiang, V.; Gross, M.; Garcia, M.; Tanaka, R.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1253. (b) Ryu, C.-K.; Song, E.-H.; Shim, J.-Y.; You, H.-J.; Choi, K. U.; Choi, I. H.; Lee, E. Y.; Chae, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 17. (c) Hranjec, M.; Grdisa, M.; Pavelic, K.; Boykin, D. W.; Karminski-Zamola, G. *Farmaco* **2003**, *58*, 1319. (d) Tawar, U.; Jain, A. K.; Dwarakanath, B. S.; Chandra, R.; Singh, Y.; Chaudhury, N. K.; Khaitan, D.; Tandon, V. *J. Med. Chem.* **2003**, *46*, 3785. (e) Guemues, F.; Demirci, A. B.; Oezden, T.; Eroglu, H.; Diril, N. *Pharmazie* **2003**, *58*, 303. (f) Yang, D.; Fokas, D.; Li, J.; Yu, L.; Baldino, C. M. *Synthesis* **2005**, 47.

(3) For recent examples, see: (a) Beaulieu, P. L.; Haché, B.; von Moos, E. *Synthesis* **2003**, 1683. (b) Jung, M. H.; Park, J. M.; Lee, I.-Y. C.; Ahn, M. *J. Heterocycl. Chem.* **2003**, *40*, 37. (c) Reddy, G. V.; Rao, V. V. V. N. S. R.; Narsaiah, B.; Rao, P. S. *Synth. Commun.* **2002**, *32*, 2467. (d) Nagata, K.; Itoh, T.; Ishikawa, H.; Ohsawa, A. *Heterocycles* **2003**, *61*, 93. (e) Ben-Alloum, A.; Bougrin, S.; Soufiaoui, M. *Tetrahedron Lett.* **2003**, *44*, 5935.

(4) (a) Blettner, C. G.; König, W. A.; Rühter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, 307. (b) Sun, Q.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **1995**, *38*, 3638. (c) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1998**, *39*, 4481. (d) Satz, A. L.; Bruice, T. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3261. (e) Rangarajan, M.; Kim, J. S.; Sim, S.-P.; Liu, A.; Liu, L. R.; LaVoie, E. J. *Bioorg. Med. Chem.* **2000**, *8*, 2591. (f) Black, D. S. C.; Kumar, N.; Wong, L. C. H. *Synthesis* **1986**, 474.

(5) (a) Denny, W. A.; Rewcastle, G. W.; Baguley, B. C. *J. Med. Chem.* **1990**, *33*, 814. (b) Dang, Q.; Brown, B. S.; Erion, M. D. *Tetrahedron Lett.* **2000**, *41*, 6559. (c) Singh, M. P.; Sasmal, S.; Lu, W.; Chatterjee, M. N. *Synthesis* **2000**, 1380. (d) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **1994**, *37*, 4338. (e) Das, T. M.; Rao, C. P.; Kalle, N.; Rissanen, K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2003**, *42*, 661.

(6) (a) Vanden Eynde, J. J.; Delfosse, F.; Lor, P.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 5813. (b) Hopkins, K. T.; Wilson, W. D.; Bender, B. C.; McCurdy, D. R.; Hall, J. E.; Tidwell, R. R.; Kumar, A.; Bajic, M.; Boykin, D. W. *J. Med. Chem.* **1998**, *41*, 3872. (c) Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. *J. Med. Chem.* **1996**, *39*, 1452. (d) Starcevic, K.; Boykin, D. W.; Karminski-Zamola, G. *Heterocycl. Commun.* **2002**, *8*, 221.
(7) Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 737.
(8) Pätzold, F.; Zeuner, F.; Heyer, T. H.; Niclas, H.-J. *Synth. Commun.* **1992**, *22*, 281.
(9) Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. *Heterocycles* **2001**, *55*, 1311.
(10) (a) Ridley, H. F.; Spickett, R. G. W.; Timmis, G. M. *J. Heterocycl. Chem.* **1965**, *2*, 453. (b) Göker, H.; Kus, C.; Boykin, D. W.; Yildiz, S.; Altanlar, N. *Bioorg. Med. Chem.* **2002**, *10*, 2589. (c) Meric, A.; Incesu, Z.; Isikdag, I. *Farmaco* **2002**, *57*, 543.
(11) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713.
(12) For use of Me_3SiCl as a condensation agent, see: (a) Ryabukhin, S. V.; Plaskon, A. S.; Tverdokhlebov, A. V.; Tolmachev, A. A. *Synth. Commun.* **2004**, *34*, 1483. (b) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2004**, 2287. (c) Zhu, Y.-L.; Huang, S.-L.; Pan, Y.-J. *Eur. J. Org. Chem.* **2005**, 2354. (d) Zhu, Y.-L.; Pan, Y.-J.; Huang, S.-L. *Synth. Commun.* **2004**, *34*, 3167. (e) Heaney, H.; Papageorgeogu, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941 . For use of Me_3SiI as a condensation agent, see: (f) Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. *Synthesis* **2004**, 263. (g) Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Synlett* **2003**, 858. (h) Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129.
(13) For recent examples of the synthesis of benzothiazoles starting from *o*-aminothiophenol and aldehydes, see: (a) Itoh, T.; Nagata, K.; Ishikawa, H.; Ohsawa, A. *Heterocycles* **2004**, *62*, 197. (b) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 6395.
(14) For recent examples of the synthesis of benzoxazoles starting from *o*-aminophenoles and aldehydes, see ref. 11 and: Chang, J.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951.
(15) For recent examples of the synthesis of 3*H*-imidazo[4,5-*b*]pyridines from 2,3-diaminopyridines and aldehydes, see ref. 5c and: (a) Singh, A. K.; Lown, J. W. *Synth. Commun.* **2000**, *30*, 923. (b) Oguchi, M.; Wada, K.; Honma, H.; Tanaka, A.; Kaneko, T.; Sakakibara, S.; Ohsumi, J.; Serizawa, N.; Fujiwara, T.; Horikoshi, H.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 3052. (c) Blettner, C. G.; Koenig, W. A.; Ruehter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, 307.
(16) For examples of the synthesis of 2,6-diaminopurines starting from 2,4,5,6-tetraaminopyrimidine and aldehydes, see: Gangjee, A.; Vasudevan, A.; Queener, S. F. *J. Med. Chem.* **1997**, *40*, 3032.
(17) For recent examples of synthesis of xanthines from 5,6-diaminouracils and aldehydes, see: (a) De Araujo, A. D.; Bacher, E.; Demnitz, F. W. J.; Santos, D. A. *Heterocycles* **1999**, *51*, 29. (b) Mueller, C. E.; Shi, D.; Manning, M. Jr.; Daly, J. W. *J. Med. Chem.* **1993**, *36*, 3341. (c) Kuefner-Muehl, U.; Weber, K. H.; Walther, G.; Stransky, W.; Ensinger, H.; Schingnitz, G.; Kuhn, F. J.; Lehr, E. DE 03843117, **1991**; *Chem. Abstr.* **1991**, *114*, 164265p.
(18) For the synthesis of purines from 6-(substituted)amino-5-aminopyrimidines and aldehydes using $FeCl_3/SiO_2$, see: Liu, J.; Dang, Q.; Wei, Z.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 627.
(19) (a) Jahn, U.; Schroth, W. *Tetrahedron Lett.* **1993**, *34*, 5863. (b) Schroth, W.; Jahn, U.; Stroehl, D. *Chem. Ber.* **1994**, *127*, 2013.
(20) (a) Kalle, A.-G. DE 1137625, **1958**, *Chem. Abstr.* **1963**, *59*, 11515c. (b) Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, *83*, 1691. (c) Nagase, R.; Kawashima, T.; Yoshifuji, M. *Heterocycles* **1977**, *8*, 243. (d) Cerniani, A.; Passerini, R. *J. Chem. Soc.* **1954**, 2261. (e) Anthony K., Brown R. G., Hepworth J. D., Hodson K. W., May B., West M. A.; *J. Chem. Soc., Perkin Trans. 2*; **1984**, 2111. (f) CohenV, V. I. *J. Heterocycl. Chem.* **1979**, *16*, 13. (g) Szczepankiewicz, B. G.; Rohde, J. J.; Kurukulasuriya, R. *Org. Lett.* **2005**, *7*, 1833. (h) Dubey, P. K.; Kumar, R.; Vino, D. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2000**, *39*, 746.
(21) (a) Young, R. C.; Jones, M.; Milliner, K. J.; Rana, K. K.; Ward, J. G. *J. Med. Chem.* **1990**, *33*, 2073. (b) Mueller, C. E.; Thorand, M.; Qurishi, R.; Diekmann, M.; Jacobson, K. A.; Padgett, W. L.; Daly, J. W. *J. Med. Chem.* **2002**, *45*, 3440.
(22) Nicolai, E.; Goyard, J.; Benchetrit, T.; Teulon, J. M.; Caussade, F.; Virone, A.; Delchambre, C.; Cloarec, A. *J. Med. Chem.* **1993**, *36*, 1175.
(23) Sato, K.; Kitaguchi, H.; Takechi, M.; Tsukase, M.; Kato, M. JP 182039, **1986**; *Chem. Abstr.* **1987**, *106*, 147020x.
(24) Curran, W. V.; Angier, R. B. *J. Am. Chem. Soc.* **1958**, *80*, 6095.
(25) McClure, M. S.; Roschangar, F.; Hodson, S. J.; Millar, A.; Osterhout, M. H. *Synthesis* **2001**, 1681.
(26) Bebernitz, G. R.; Argentieri, G.; Battle, B.; Brennan, C.; Balkan, B.; Burkey, B. F.; Eckhardt, M.; Gao, J.; Kapa, P.; Stroehschein, R. J.; Schuster, H. F.; Wilson, M.; Xu, D. D. *J. Med. Chem.* **2001**, *44*, 2601.
(27) Kristek, F.; Klicnar, J.; Vetersnik, P. *Collect. Czech. Chem. Commun.* **1971**, *36*, 3608.