Heterocycles of biological importance. Part 5.[1] The formation of novel biologically active pyrimido[1,2-*a*]benzimidazoles from allenic nitriles and aminobenzimidazoles

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The reaction of allenic nitriles with 2-aminobenzimidazoles gives 2-aminopyrimido[1,2-*a*]benzimidazoles **5** in very good yields. The pharmacological screening of compound **5a**, **5d** and **5i** shows that they possess slight antibiotic and antiarrythmic properties.

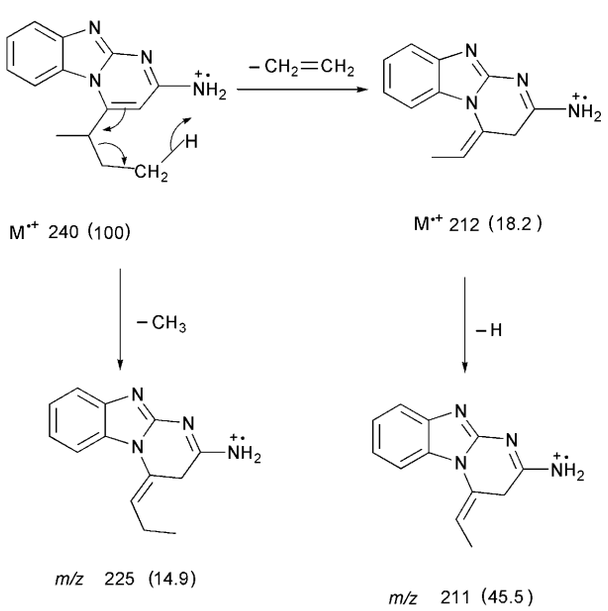
The usefulness of allenic nitriles as starting materials in heterocyclic syntheses has been clearly demonstrated.[2–12] As a continuation of that work, we decided to study the synthesis and biological activity of heterocycles that could be readily obtained by the reaction of various substituents with allenic and acetylenic nitriles.[13–15] In this paper, we report the reaction of substituted or unsubstituted aminobenzimidazoles **1** with nitriles **2** to give pyrimidobenzimidazoles **5** that possess some biological activity. The allenic nitriles **2** were treated with aminobenzimidazoles **1** under reflux in *N*,*N*-dimethylformamide for 3–4 days, the reaction being monitored by TLC. When the reaction was stopped after 36 hours, spectral data showed that traces of the starting materials, unconjugated enaminic nitrile **3**, traces of conjugated enaminic nitrile **4** and some of the pyrimidobenzimidazole **5** were in the mixture. However, after 4 days of reaction, all the starting materials had been used up and the intermediate enaminic nitriles converted to the final product in near quantitative yield. When the reaction was carried out in ethanol for 3 days, the unconjugated adduct **3** was the sole product.

The rate of the reaction is determined by the rate of conversion of the unconjugated enaminic nitrile **3** to the conjugated enaminic nitrile **4**.[16]

Compounds **3** and **4** show broad twin stretching bands in the IR spectra between 3150–3450 cm^{-1} due to NH_2, intense stretching bands due to C=N between 1640–1650 cm^{-1} and to C=C between 1600–1610 cm^{-1} (see Table 3). The UV spectra showed strong absorption maxima between 218–224 nm (ε 11 500–13 800 $dm^3\ mol^{-1}\ cm^{-1}$) and between 258–264 nm (ε 35 100–40 500 $dm^3\ mol^{-1}\ cm^{-1}$) (see Table 3). The ^1H NMR spectra show signals for the vinylic protons between δ 6.15–6.28 (see Table 4) and the mass fragmentation data (Scheme 1) all fit neatly with the assigned structures.

The reaction of aminobenzimidazoles with allenic nitriles may proceed by two possible mechanistic pathways (Schemes 2 or 3) depending on whether the initial attack of the allenic nitrile is by ring nitrogen (Scheme 2) or by the nitrogen of the side chain (Scheme 3), to give the isomeric pyrimidobenzimidazoles **5** or **8**.

In order to distinguish between the isomeric benzimidazoles



Scheme 1

5 and **8**, ^1H nuclear Overhauser effect (NOE) experiments involving the spectral substitution technique (difference NOE)[17,18] was used. Enhancement of the H-6 signal (26%) was observed when the C-12 methine proton was irradiated in compound **5c**, whereas irradiation of H-6 induced enhancement of H-7 (23%) and H-12 (20%) signals, thus indicating that H-6 and H-12 protons are in close spatial proximity. These results confirm that the pyrimidobenzimidazoles obtained in this work are of structure **5** and not **8**. The NOE experiment also permitted the unambiguous assignment of all the proton signals in structure **5**.

X-Ray crystallographic analyses of reaction products from the reaction of 2-aminobenzimidazoles and dimethyl allene-1,3-dicarboxylate[19] have proved that the product obtained results from the attack of the allene by the ring nitrogen and not the nitrogen of the side chain. The assignment of structure **5**

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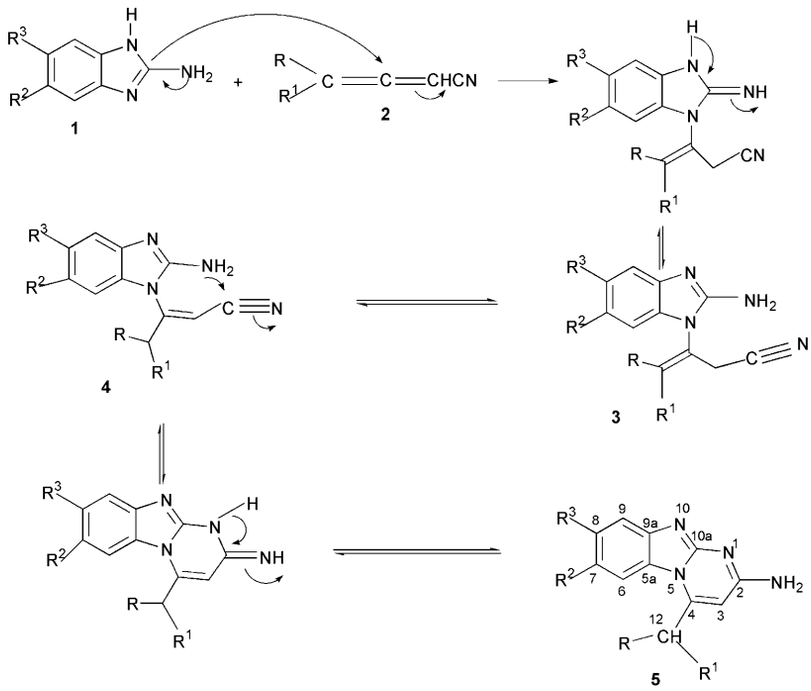
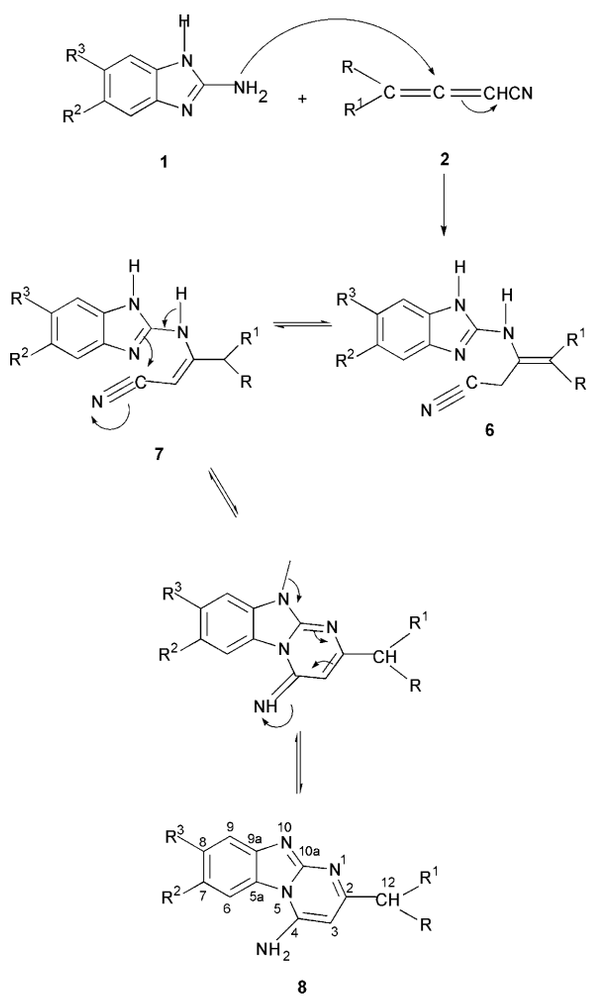


5a R = Me, R^1 = Et, R^2 = H, R^3 = H
5b R = Me, R^1 = Et, R^2 = Me, R^3 = Me
5c R = Et, R^1 = Et, R^2 = H, R^3 = H
5d R =Et, R^1 = Et, R^2 = Me, R^3 = Me
5e R = Me, R^1 = Pr, R^2 = H, R^3 = H
5f R = Me, R^1 = Pr, R^2 = Me, R^3 = Me
5g R = Me, R^1 = Bu^i, R^2 = H, R^3 = H
5h R = Me, R^1 = Bu^i, R^2 = Me, R^3 = Me
5i R—R^1 = —$CH_2(CH_2)_3CH_2$, R^2 = H, R^3 = H
5j R—R^1 = —$CH_2(CH_2)_3CH_2$, R^2 = Me, R^3 = Me

Scheme 2



Scheme 3

Table 1 Microbial activity of compounds **5a**, **5d** and **5i**

Test	Dose/ μg ml^{-1}	Response of compounds			
		5a	**5d**	**5i**	Ref. compound
Staphylococcus aureus	5	+	+	+	+
Staphylococcus aureus	1	−	−	−	+
Staphylococcus aureus	0.06	−	−	−	+
Mycobacterium ranae	20	+	+	+	+
Mycobacterium ranae	5	−	−	−	+
Mycobacterium ranae	0.5	−	−	−	+

and not **8** to the compounds obtained in this work is thus confirmed conclusively.

Biological activity

Some of the pyrimidobenzimidazoles, compounds **5a**, **5d** and **5i**, were subjected to various biological activity tests[20] and found to possess slight microbial activity and some antiarrhythmic effect.

a) Microbial activity

Minimal inhibitory concentrations (MIC) of compound **5a**, **5d** and **5i** were determined by standard tube dilution techniques *versus* representative Gram +ve and −ve bacterial organisms, fungi and protozoa. They were slightly active against *S. aureus* and *M. ranae* when compared against ampicillin (*Staphylococcus aureus*) and gentamycin (*Mycobacterium ranae*) as reference compounds (Table 1).

b) Antiarrhythmic effect

Thirty minutes after intraperitoneally (ip) dosing, if less than 2 mice display cardiac arrhythmias and heart rates above 200 beats per minute (ECG) when exposed to deep chloroform anesthesis, potential antiarrhythmic activity is

Table 2 Antiarrhythmic effects of compounds **5a**, **5d** and **5i**

Test	Dose/ mm kg^{-1}	Response of compounds			
		5a	**5d**	**5i**	Ref. compound
Antiarrythmic	100	1 MED[a]	1 MED[a]	1 MED[a]	0 ED 100[b]
Antiarrythmic	50	3	3	3	

[a] MED = minimum effective dose. [b] ED 100 = dose which is always active in the test system.

Table 3 UV, IR and CHN analysis data of compounds **5a**–**j**

Compounds Nº	ν(KBr)/cm^{-1}				λ_{max}/nm (ε/10^2 dm^3 mol^{-1} cm^{-1})		Empirical formula	Found (%)			Required (%)		
	NH_2 def	C=N	C=C	N–H				C	H	N	C	H	N
5a	3300, 3150	1640	1640	1560	218 (115)	258 (351)	$C_{14}H_{16}N_4$	69.97	6.60	23.36	70.00	6.67	23.33
5b	3400, 3250	1640	1600	1560	220 (121)	260 (358)	$C_{16}H_{20}N_4$	71.80	7.58	20.72	71.64	7.46	20.89
5c	3400, 3200	1650	1010	1550	220 (135)	260 (401)	$C_{15}H_{18}N_4$	70.71	7.22	21.98	70.87	7.09	22.05
5d	3450, 3250	1650	1610	1560	220 (130)	261 (395)	$C_{17}H_{22}N_4$	72.21	7.86	20.01	72.34	7.80	19.86
5e	3400, 3250	1650	1610	1550	220 (125)	259 (362)	$C_{15}H_{18}N_4$	70.93	7.18	21.89	70.87	7.09	22.05
5f	3400, 3250	1650	1610	1550	220 (120)	261 (401)	$C_{17}H_{22}N_4$	72.32	7.75	20.01	72.34	7.80	19.86
5g	3350, 3150	1650	1575	1525	222 (130)	260 (404)	$C_{16}H_{20}N_4$	71.63	7.45	20.64	71.61	7.51	20.87
5h	3350, 3150	1650	1575	1525	222 (135)	262 (401)	$C_{18}H_{24}N_4$	72.84	8.34	18.92	72.94	8.16	18.90
5i	3350, 3150	1650	1575	1525	220 (138)	260 (405)	$C_{16}H_{18}N_4$	72.06	6.62	21.10	72.16	6.81	21.03
5j	3300, 3200	1650	1575	1550	220 (140)	259 (420)	$C_{18}H_{22}N_4$	73.38	7.54	18.95	73.47	7.48	19.05

Table 4 ^{1}H (300 MHz) NMR data (δ; multiplicity) for compounds **5a**–**j** in DMSO-d_6

H	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**
3	6.22; s	6.12; s	6.20; s	6.25; s	6.23; s	6.20; s	6.21; s	6.15; s	6.15; s	6.18; s
6	7.88; d	7.56; d	7.85; d	7.70; s	7.78; d	7.55; s	7.81; d	7.58; s	7.67; d	7.46; s
7	7.12; dd	—	7.15; dd	—	7.14; dd	—	7.13; dd	—	7.13; dd	—
8	7.30; dd	—	7.30; dd	—	7.30; dd	—	7.30; dd	—	7.27; dd	—
9	7.56; d	7.34; s	7.55; d	7.30; s	7.55; d	7.34; s	7.54; d	7.31; s	7.53; d	7.32; s
12	3.52–3.66; m	3.50–3.66; m	3.50–3.60; m	3.50–3.70; m	3.58–3.72; m	3.50–3.60; m	2.48–2.51; m	2.48–2.51; m	—	—
NH_2	7.26; s	7.10; s	7.29; s	7.40; s	7.26; s	7.10; s	7.22; s	7.09; s	7.22; s	7.42; s
7-CH_3	—	2.35; s	—	2.35; s	—	2.40; s	—	2.35; s	—	2.35; s
8-CH_3	—	2.35; s	—	2.35; s	—	2.40; s	—	2.35; s	—	2.35; s

Table 5 ^{13}C (75 MHz) NMR data (δ) for compounds **5a**–**j** in DMSO-d_6

H	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**
2	127.7	131.9	127.8	132.9	127.7	131.9	127.9	132.1	127.9	132.6
3	94.8	94.2	95.8	96.2	94.7	94.1	94.9	94.2	94.6	94.5
4	144.6	143.1	144.7	139.4	144.6	143.1	144.8	144.1	114.8	142.0
5a	153.7	154.0	153.4	152.0	153.7	153.2	153.8	153.3	153.8	153.0
6	119.1	113.9	119.0	114.4	119.1	113.9	119.4	114.0	119.6	114.2
7	113.7	126.0	113.7	125.6	113.6	126.0	113.9	—	113.6	126.0
8	117.3	127.2	119.0	128.4	117.4	127.2	117.7	—	117.6	128.0
9	129.6	117.8	123.6	116.4	123.6	117.8	127.8	117.9	123.8	117.5
9a	155.3	155.0	153.8	153.5	155.5	155.2	156.1	156.8	155.3	155.3
10a	160.6	160.2	160.4	160.6	160.6	160.6	160.9	160.3	160.8	160.8
12	34.8	34.7	39.9	40.9	33.4	33.3	31.7	31.6	38.4	38.4
7-CH_3	—	19.8	—	19.7	—	19.3	—	20.1	—	20.1
8-CH_3	—	19.8	—	19.9	—	19.8	—	20.1	—	20.1

indicated (Table 2). Compounds **5a**, **5d** and **5i** indicated an antiarrhythmic effect.

The biological activity tests show that the activity of these compounds comes from the pyrimidobenzimidazole moiety exclusively and is not influenced by the alkyl side chain of the molecules.

Experimental

The infrared (IR) spectra (potassium bromide pellets) were taken with a Perkin-Elmer Grating Infrared spectrometer model 337 and with a Varian 2290 and a Perkin-Elmer 298 spectrophotometer. The ultraviolet (UV) spectra were determined in ethanolic solutions on a Perkin-Elmer 137 instrument, and on Beckmann 25 and Lambda 40 spectrophotometers. The high field ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were performed on a Bruker WH 300 spectrometer with tetramethylsilane as internal standard. The observation frequency for ^{1}H NMR spectra was 300 MHz and that for ^{13}C NMR spectra was 75 MHz. Chemical shifts (δ) are reported in ppm. Mass spectra were recorded at 70 eV on a LKB 9000 machine, updated MS 12 and MS 9025 instruments with direct insert and with a JEOL JMS-SX102 spectrometer. Purity of the sample was checked by TLC. Melting points were determined on a Kofler Block, Buchi SMP-20 apparatus, and on a Reichert thermovar microscope and are uncorrected. Alumina of activity 5 for column chromatography was prepared by mixing 15 ml of distilled water and 100 g of neutral alumina which had been

preheated for 4 h at 120 °C. Combustion analyses were performed on CHN elemental analyser Carlo Erba Model 1106. The allenic nitriles were prepared as previously reported.[21]

4-Ethyl-3-(2′-amino-1′*H*-benzimidazol-1′-yl)hex-3-enenitrile (3c)

4-Ethylhexa-2,3-dienenitrile (0.665 g, 5 mmol) and 2-aminobenzimidazole (0.605 g, 5 mmol) were refluxed in ethanol (25 ml) for 38 hours. Evaporation of solvent gave a crude product as a thick dark brown oil. Purification of the crude product by column chromatography on neutral alumina (150 g, activity 5) and elution with methylene dichloride–hexane (8:2) gave a crystalline compound which on recrystallization from methylene dichloride–hexane gave 4-ethyl-3-(2′-amino-1′*H*-benzimidazol-1′-yl)hex-3-enenitrile (1.06 g, 85%), mp 177 °C (from methylene dichloride–hexane) (Found: C, 70.78; H, 7.11; N, 22.07. $C_{15}H_{18}N_4$ requires C, 70.83; H, 7.13; N, 22.03%); λ_{max} (EtOH)/nm 215 (ε/dm^3 mol^{-1} cm^{-1} 31600), 254 (8900), 283 (7200); ν_{max} (KBr)/cm^{-1} 3363 and 3307 (NH_2), 2261 (C≡N), 1643 (C=N), 1611 (C=C), 1546 (N–H); δ_H (300 MHz, $CDCl_3$) 0.92 (3 H, t, 6-CH_3), 1.27 (3 H, t, CH_3CH$_2$-), 1.99 (2 H, m, 5-H), 2.42 (2 H, q, CH$_3$CH_2-), AB: 3.42 (H_A), 3.34 (H_B, $|J_{AB}|$ = 17.6 Hz, 2-H), 4.74 (2 H, br s, NH), 6.95 (1 H, d, 4′-H), 7.04 (1 H, dd, 6′-H), 7.14 (1H, dd, 5′-H), 7.45 (1 H, d, 7′-H); δ_C (75 MHz, $CDCl_3$) 12.3 (C-6), 12.8 (*C*H$_3$CH$_2$-), 19.9 (C-2), 24.1 (C-5), 24.5 (CH$_3$*C*H$_2$-), 108.0 (C-4′), 116.0 (C-4), 116.6 (C-3), 116.9 (C-7′), 120.5 (C-6′), 122.4 (C-5′), 133.6 (C-3′a), 142.5 (C-7′a), 152.3 (C-2′), 154.4 (C-1); *m*/*z* 254 (M$^+$, 100%), 253 (7), 240 (9), 239 (51), 225 (14), 223 (6), 214 (11), 212 (7), 209 (6), 198 (9), 197 (13), 186 (5), 184 (5), 158 (5), 144 (7), 134 (11), 133 (25), 117 (6), 105 (6), 92 (6), 90 (11), 77 (5), 41 (7).

Transformation of 4-ethyl-3-(2′-amino-1′*H*-benzimidazol-1′-yl)-hex-3-enenitrile (3c) into 2-amino-4-(1-ethylpropyl)pyrimido-[1,2-*a*]benzimidazole (5c)

4-Ethyl-3-[2′-amino-1′H-benzimidazol-1′-yl]hex-3-enenitrile (0.500 g, 2 mmol) was refluxed in *N*,*N*-dimethylformamide for 2 days. Removal of solvent under reduced pressure gave a crude product as a dark brown oil which solidified after some days standing at room temperature. Recrystallisation from methylene dichloride gave compound **5c** (0.475 g, 95%).

2-Amino-4-(1-methylpropyl)pyrimido[1,2-*a*]benzimidazole (5a)

4-Methylhexa-2,3-dienenitrile (2.14 g, 20 mmol) dissolved in *N*,*N*-dimethylformamide (25 ml) was reacted with 2-aminobenzimidazole (2.70 g, 20 mmol) in *N*,*N*-dimethylformamide (25 ml) under reflux for 4 days. Evaporation of solvent under reduced pressure gave the crude product as a dark brown oil. Purification of 4.80 g of crude product by column chromatography on neutral alumina (300 g, activity 5) and elution with ethyl acetate–hexane (8:2) gave the crude product as a solid. Recrystallization from methylene dichloride–hexane gave 2-amino-4-(1-methylpropyl)pyrimido[1,2-***a***]benzimidazole (4.30 g, 90%), mp 258 °C; *m*/*z* (EI) 240 (M$^+$, 100%), 225 (15), 212 (18), 211 (46), 209 (21), 156 (15), 133 (11), 129 (10), 106 (1), 90 (22), 42 (2), 41 (11). Full NMR data for compounds **5a**–**j** are given in Tables 3–5.

2-Amino-4-(1-methylpropyl)-7,8-dimethylpyrimido[1,2-*a*]-benzimidazole (5b)

Was similarly prepared from 2-amino-5,6-dimethylbenzimidazole and 4-methylhexa-2,3-dienenitrile as white crystals (90%), mp 301 °C; *m*/*z* (EI) 268 (M$^+$, 100%), 253 (30), 240 (18), 239 (59), 237 (25), 224 (14), 233 (22), 91 (14), 44 (41), 42 (3), 41 (13).

2-Amino-4-(1-ethylpropyl)pyrimido[1,2-*a*]benzimidazole (5c)

Was similarly prepared from 2-aminobenzimidazole and 4-ethylhexa-2,3-dienenitrile as white crystals (87%), mp 280 °C; *m*/*z* (EI) 254 (M$^+$, 100%), 226 (9), 225 (20), 211 (11), 210 (11), 209 (30), 156 (6), 106 (1), 90 (9), 42 (2), 41 (4), 28 (4).

2-Amino-4-(1-ethylpropyl)-7,8-dimethylpyrimido[1,2-*a*]-benzimidazole (5d)

Was similarly prepared from 2-amino-5,6-dimethylbenzimidazole and 4-ethylhexa-2,3-dienenitrile as white crystals (92%), mp 307 °C; *m*/*z* (EI) 282 (M$^+$, 100%), 253 (30), 238 (18), 237 (30), 223 (11), 106 (2), 91 (10), 42 (5), 41 (11), 36 (13), 29 (26), 27 (13).

2-Amino-4-(1-methylbutyl)pyrimido[1,2-*a*]benzimidazole (5e)

Was similarly prepared from 2-aminobenzimidazole and 4-methylhepta-2,3-dienenitrile as white crystals (91%), mp 282 °C; *m*/*z* (EI) 254 (M$^+$, 100%), 212 (54), 211 (48), 209 (24), 156 (15), 133 (13), 106 (2), 90 (24), 42 (9), 41 (22), 39 (15), 27 (26).

2-Amino-4-(1-methylbutyl)-7,8-dimethylpyrimido[1,2-*a*]-benzimidazole (5f)

Was similarly prepared from 2-amino-5,6-dimethylbenzimidazole and 4-methylhepta-2,3-dienenitrile as white needles (88%), mp 309 °C; *m*/*z* (EI) 282 (M$^+$, 100%), 281 (10), 240 (26), 239 (31), 238 (9), 237 (16), 223 (14), 91 (10), 42 (5), 41 (14), 27 (15).

2-Amino-4-(1,3-dimethylbutyl)pyrimido[1,2-*a*]benzimidazole (5g)

Was similarly prepared from 2-aminobenzimidazole and 4,6-dimethylhepta-2,3-dienenitrile as white crystals (75%), mp 279 °C; *m*/*z* (EI) 268 (M$^+$, 100%), 267 (4), 225 (4), 223 (3), 213 (13), 212 (89), 211 (39), 210 (6), 209 (16), 198 (4), 197 (7), 184 (6), 172 (5), 170 (4), 156 (7), 134 (7), 133 (16), 129 (5), 118 (4), 105 (6), 92 (3), 90 (8), 83 (3), 57 (4), 44 (20), 43 (5), 41 (8), 40 (11), 39 (11).

2-Amino-7,8-dimethyl-4-(1,3-dimethylbutyl)pyrimido[1,2-*a*]-benzimidazole (5h)

Was similarly prepared from 2-amino-5,6-dimethylbenzimidazole and 4,6-dimethylhepta-2,3-dienenitrile as white crystals (79%), mp 305 °C; *m*/*z* 296 (M$^+$, 100%), 295 (7), 281 (3), 253 (4), 241 (9), 240 (52), 239 (25), 238 (5), 237 (10), 225 (12), 224 (4), 223 (10), 212 (5), 184 (3), 161 (3), 160 (3), 44 (5).

2-Amino-4-cyclohexylpyrimido[1,2-*a*]benzimidazole (5i)

Was similarly prepared from 2-aminobenzimidazole and 3-cyclohexylidenepropenenitrile as white crystals (71%), mp 327 °C; *m*/*z* (EI) 266 (M$^+$, 100%), 265 (13), 250 (10), 249 (66), 248 (5), 237 (5), 223 (8), 222 (3), 212 (4), 211 (18), 210 (3), 209 (9), 208 (14), 199 (3), 198 (9), 158 (6), 156 (6), 144 (5), 134 (3), 133 (7), 129 (4), 124 (8), 118 (9), 111 (3), 105 (4), 92 (4), 91 (4), 90 (8), 65 (4).

2-Amino-4-cyclohexyl-7,8-dimethylpyrimido[1,2-*a*]-benzimidazole (5j)

Was similarly prepared from 2-amino-5,6-dimethylbenzimidazole and 3-cyclohexylidenepropenenitrile as white crystals (80%), mp 343 °C; *m*/*z* (EI) 294 (M$^+$, 100%), 293 (14), 280 (2), 279 (8), 265 (2), 251 (4), 249 (1), 240 (2), 238 (1), 237 (4), 236 (2), 235 (2), 226 (3), 225 (1), 223 (2), 211 (1), 184 (2), 161 (1), 160 (2), 147 (2), 118 (2), 116 (1), 111 (1), 91 (29), 73 (11), 44 (7), 42 (3), 41 (1).

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