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Preparation of Novel Cyanoguanidine Derivatives of Tryptamines

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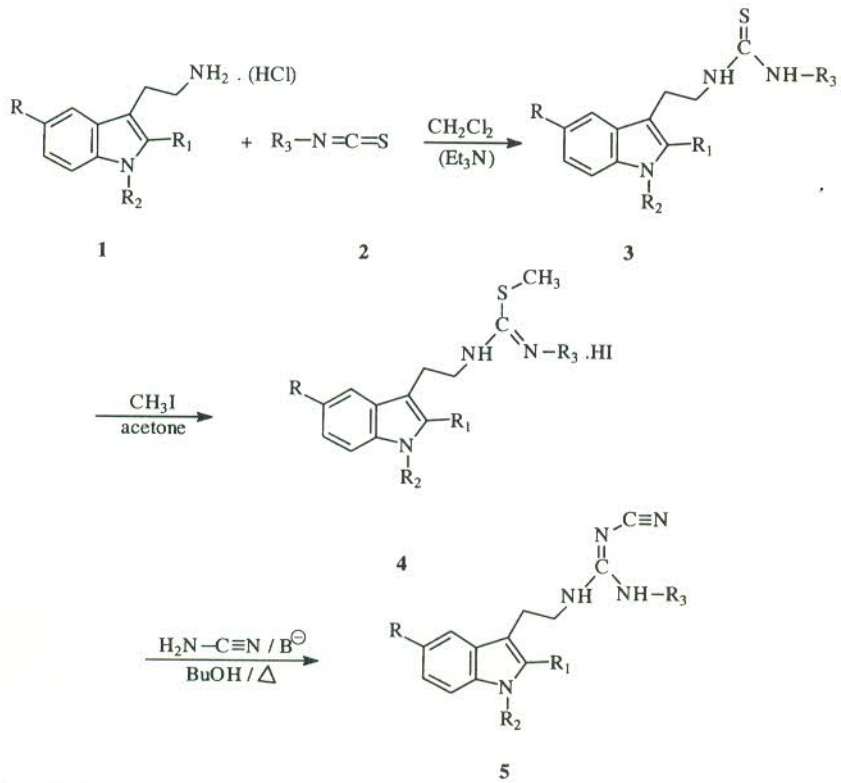
Abstract: A new class of cyanoguanidine derivatives (**5a–s**) bearing a tryptamine moiety was prepared in a three-step reaction sequence. The preparation of the starting materials and characterization of the intermediates and products are also described.

Key words: tryptamines, thioureas, thioethers, cyanoguanidines, cyanamide

Due to their remarkable chemical and biological importance, cyanoguanidine derivatives are desired products. These compounds find a wide-range applicability in different areas, for example Cimetidine is an antipeptic ulcer agent,[1] and Pinacidil is antihypertensive agent.[2] Therefore, the construction of the cyanoguanidine moiety is a challengeable task. Although numerous procedures for the building up of such derivatives are described,[3-5] these methods, however, lack the generality, compatibility, easy working-up procedures and high yields. So, it was worthwhile to develop a synthesis to overcome the previously mentioned disadvantages. We, therefore elaborated a straightforward three-step procedure for the preparation of trivial derivatives of cyanoguanidines.[6]

In this paper, we demonstrate the efficiency of our procedure for the preparation of a new class of cyanoguanidines bearing a tryptamine moiety, and diverse substituents (alkyl, aryl, or aralkyl) at the opposite nitrogen. As it is illustrated in the Scheme, tryptamine derivatives **1** were reacted with isothiocyanates **2** in CH_2Cl_2 affording thiourea derivatives **3** in almost quantitative yields. Methylation of the latter with methyl iodide in acetone furnished the hydrogen iodide salt of the thiother derivatives **4** in high yields. Upon treatment of these compounds with cyanamide in boiling butanol in the presence of catalytic amount (see experimental) of a strong base (1,4-diazabicyclo[2.2.2]octane), the desired cyanoguanidines **5** were isolated in moderate to good yields. Table 1 summarizes the yields and physical properties of the derivatives prepared by this method.



Preparation of cyanoguanidine derivatives **5**

Scheme

Table 1 Derivatives of the Cyanoguanidines and Intermediates Prepared

Entry	R	R_1	R_2	R_3	Yield (%)[a]	Mp (°C)	Yield (%)[a]	Mp (°C)	Yield (%)[a]	Mp (°C)
					3		**4**		**5**	
a	H	H	H	cyclohexyl	90	175–177	93	121–123	66	141–142
b	H	H	H	Ph	88	155[b]	87	oil	83	114–115
c	H	H	H	α-naphthyl	48	138–139	84	153–155	50	202
d	H	H	H	Allyl	92	94–96	83	140	0[e]	-
e	H	H	CH_3	Ph	86	oil	65	168–169	45	134–135
f	H	H	benzyl	Ph	66	164–166	86	oil	53	176–177
g	H	H	benzyl	cyclohexyl	86	oil	81	oil	47	121–122
h	CH_3	COOEt	H	cyclohexyl	93	162–163	97	126–127	29	223–224
i	CH_3	COOEt	H	Ph	87	202	77	162–163	72	198–99
j	CH_3	COOEt	H	α-naphthyl	90	200	72	140	72	246–248
k	$AcNHCH_2$	COOEt	H	Ph	90	190	60	155–156	26	192–193
l	CH_3O	H	H	Ph	64	109[c]	88	123–124[d]	65	137–138
m	CH_3O	COOEt	H	Ph	93	193–194	79	170	69	197–198
n	Cl	COOEt	H	CH_3	56	112–114	89	105–108	70	222–223
o	Cl	COOEt	H	Ph	83	203–204	88	175–176	75	225–226
p	Cl	COOEt	H	α-naphthyl	82	213–214	86	166–167	65	210
q	Br	H	H	cyclohexyl	94	oil	60	oil	43	147–148
r	Br	H	H	Ph	98	oil	71	155–156	68	156–157
s	Br	COOEt	H	Ph	96	205–206	84	185–186	81	223–225

[a]Yields refer to pure isolated products.
[b]Lit.[11b]: mp = 157-158 °C, Lit.[11a]: mp = 59-60 °C.
[c]Lit.[12]: mp = 108-110 °C.
[d]Lit.[12]: mp = 153-154 °C.
[e]Decomposition took place

NMR analyses showed that at room temperature thioethers **4a–s** existed in two stereoisomeric forms in approximately 1:1 ratio. At elevated temperature (373 K), however, these compounds showed a rapid interconversion and the characteristic signals coalesced. When the solution was re-cooled to room temperature, separate signals of the two isomers (*syn/anti* or *E/Z*) were observed again.

In the spectra of some thiourea derivatives **3**, a few signals were not detected [for example, in compound **3h**, C-2' (broad at 44.35 ppm), C-1", and C=S signals] therefore, the spectra were taken at elevated temperature (373 K). As it was expected, the signals became sharp and new signals were recognized; C-2' (44.00) and C-1" (51.45) ppm. However, the expected C=S signal (~182 ppm) was still not observed.

Although the reaction between thioethers **4** and cyan amide afforded the desired cyanoguanidines **5** in good yields, in some cases side products were also detected. For instance, besides compounds **5i** and **5p** (R_1 = COOEt), transesterified products (R_1 = COOBu) were isolated. On the other hand, compound **4d** bearing an allyl group, suffered a decomposition, and only traces of **5d** were formed.

We can conclude that the above described method is suitable not only for the preparation of trivial cyanoguanidines, but also for a new class of cyanoguanidines bearing a tryptamine nucleus. These new compounds are of biological and medicinal interest. Analytical data for the compounds prepared are summarized in Table 2.

Mps are uncorrected. IR spectra were recorded on Spekord 75 IR spectrometer. Unless otherwise stated, ^1H and ^{13}C NMR spectra were obtained with a Bruker DRX-500 spectrometer; internal standard TMS. Splitting patterns are designated as "s, d, t, q, m, and br"; these symbols indicate "singlet, doublet, triplet, quartet, multiplet, and broad", respectively. All solvents were dried by means of standard methods. Reactions were followed by TLC on Merck pre-coated silica gel 60 F_{254} plates. Merck Kieselgel® 60 was employed for

Table 2 Spectral Data for Derivatives Prepared

Product	IR (cm^{-1})	R_f	^1H NMR (solvent/TMS) δ, *J* (Hz)	^{13}C NMR (solvent/TMS) δ
3a	(KBr): 3405, 3320, 3280	0.74[a]	(80 MHz, DMSO-d_6): 1.15–1.65 (m, 10 H, H-2", H-3", H-4", H-5", H-6"), 2.90 (t, 2 H, H-1'), 3.65 (m, 3 H, H-1", H-2'), 6.95–7.55 (m, 6 H, ArH, NH), 10.80 (br s, 1 H, NH)	-
3c	(KBr): 3380, 3190	0.16[b]	(DMSO-d_6): 2.97 (t, 2 H, *J* = 6.9, H-1'), 3.77 (q, 2 H, *J* = 6.7, H-2'), 6.98 (t, 1 H, *J* = 7.4, H-5), 7.08 (t, 1 H, *J* = 7.4, H-6), 7.12 (br s, 1 H, H-2), 7.35 (d, 1 H, *J* = 8.1, H-7), 7.45 (d, 1 H, *J* = 7.1, H-2"), 7.50 (t, 1 H, *J* = 7.7, H-3"), 7.54 (m, ~3 H, C-6", C-7", NH), 7.64 (d, 1 H, *J* = 7.9, H-4), 7.84 (d, 1 H, *J* = 8.1, H-4"), 7.91 (m, 1 H, H-8"), 7.96 (m, 1 H, H-5"), 9.59 (br s, 1 H, NH), 10.77 (br s, 1 H, NH)	(DMSO-d_6): 24.81 (C-1'), 45.06 (C-2'), 111.44 (C-7), 111.77 (C-3), 118.32 (C-5), 118.61 (C-4), 121.03 (C-6), 122.80 (C-2), 123.01 (C-8"), 125.17 (C-2"), 125.78 (C-3"), 126.25 (C-6", C-7"), 126.72 (C-4"), 127.43 (C-3a), 128.19 (C-5"), 130.00 (C-8a"), 134.11 (C-4a"), 134.50 (C-1"), 136.41 (C-7a), 181.87 (C=S)
3d	(KBr): 3390, 3300, 3210 1560, 1540	0.58[c]	(80 MHz, $CDCl_3$): 2.95 (t, 2 H, *J* = 6, CH_2), 3.80 (q-m, 4 H, CH_2, 2NH), 4.80–5.70 (m, 3 H, CH=CH_2), 5.90 (m, 2 H, CH_2), 6.70–7.60 (m, 5 H, ArH), 8.20 (br s, 1 H, NH)	–
3e	(film): 3360, 3250 1580, 1540, 1520	0.5[c]	(80 MHz, $CDCl_3$): 2.95 (t, 2 H, *J* = 5, CH_2), 3.60 (s, 3 H, N-CH_3), 3.85 (q, 2 H, *J* = 5, CH_2-NH), 6.0 (m, 1 H, NH), 6.65–7.60 (m, 10 H, ArH), 8.30 (m, 1 H, NH)	–
3f	(KBr): 3380, 3200, 1560, 1550	0.86[d]	(80 MHz, $CDCl_3$/DMSO-d_6): 3.10 (m, 3 H, CH_2, NH), 3.90 (q, 2 H, *J* = 6, CH_2-N), 5.13 (s, 2 H, CH_2-N), 6.80–7.70 (m, 15 H, ArH), 9.10 (br s, 1 H, NH)	–
3g	(film) 3250, 3050, 2080, 1550	0.73[d]	(80 MHz, $CDCl_3$): 1.15–1.75 (m, 10 H, H-2", H-3", H-4", H-5", H-6"), 3.0 (t, 2 H, H-1'), 3.70 (m, 3 H, H-2', H-1"), 5.25 (s, 2 H, CH_2), 6.70 (br s, 1 H, NH), 6.95–7.75 (m, 10 H, ArH), 8.20 (br s, 1 H, NH)	–
3h	(KBr): 3330, 3240, 1700	0.70[a]	(DMSO-d_6): 1.12 (m, 3 H, H-2", H-4", H-6"), 1.24 (m, 2 H, H-3", H-5"), 1.36 (t, 3 H, *J* = 7.1, CH_3), 1.53 (m, 1 H, H-4"), 1.63 (m, 2 H, H-3", H-5"), 1.81 (m, 2 H, H-2", H-6"), 2.37 (s, 3 H, CH_3), 3.25 (t, 2 H, *J* = 6.5, H-1'), 3.61 (br s, 2 H, H-2'), 3.97 (br s, 1 H, H-1"), 4.34 (q, 2 H, *J* = 7.1, O-CH_2), 7.08 (d, 1 H, *J* = 8.3, H-6), 7.19 (br s, 1 H, NH), 7.31 (d, 1 H, *J* = 8.3, H-7), 7.52 (s, 1 H, H-4), 11.43 (br s, 1 H, NH)	(DMSO-d_6): 14.45 (CH_3), 21.40 (CH_3), 24.57 (C-1'), 24.68 (C-3", C-5"), 25.34 (C-4"), 32.47 (C-2", C-6"), 44.35 (C-2'), 60.31 (O-CH_2), 112.31 (C-7), 119.90 (C-4), 119.99 (C-3), 123.60 (C-2), 126.97 (C-6), 127.95 (C-3a), 128.23 (C-5), 134.91 (C-7a), 161.95 (C=O)
3i	(KBr): 3370, 3250, 1660	0.71[a]	(DMSO-d_6): 1.35 (t, 3 H, *J* = 7.1, CH_3), 2.37 (s, 3 H, H-1'"), 3.34 (t, 2 H, *J* = 7.0, H-1'), 3.74 (br s, 2 H, H-2'), 4.31 (q, 2 H, *J* = 7.1, O-CH_2), 7.09 (m, 2 H, *J* = 7.0, H-6, H-4"), 7.27 (t, 2 H, *J* = 8.2, H-3", H-5"), 7.28 (d, 2 H, *J* = 7.0, H-2", H-6"), 7.33 (d, 1 H, *J* = 8.4, H-7), 7.58 (br s, 1 H, H-4), 7.63 (br s, 1 H, NH), 9.47 (br s, 1 H, NH), 11.46 (br s, 1 H, NH)	(DMSO-d_6): 14.47 (CH_3), 21.45 (C-1'"), 24.08 (C-1'), 44.88 (C-2'), 60.37 (O-CH_2), 112.38 (C-7), 119.72 (C-3), 119.95 (C-4), 123.27 (C-2", C-6"), 123.80 (C-2), 124.32 (C-4"), 127.03 (C-6), 127.95 (C-3a), 128.34 (C-5), 128.77 (C-3", C-5"), 134.97 (C-7a), 139.23 (C-1"), 162.00 (CO), 180.55 (C=S)
3j	(KBr): 3410, 3260, 1690	0.76[a]	(DMSO-d_6): 1.32 (t, 3 H, *J* = 7.0, CH_3), 2.38 (s, 3 H, H-1'"), 3.32 (t, 2 H, *J* = 7.0, H-1'), 3.75 (q, 2 H, *J* = 6.0, H-2'), 4.26 (q, 2 H, *J* = 7.0, O-CH_2), 7.11 (d, 1 H, *J* = 8.5, H-6), 7.33 (t, 1 H, *J* = 8.5, H-7), 7.36 (d, 1 H, *J* = 7.5, H-2"), 7.45 (d, 1 H, *J* = 7.8, H-3"), 7.47 (br s, 1 H, NH), 7.48 (t, 1 H, *J* = 8.0, H-6"), 7.53 (t, 1 H, *J* = 7.0, H-7"), 7.61 (s, 1 H, H-4), 7.82 (d, 2 H, *J* = 8.0, H-4", H-8"), 7.94 (d, 1 H, *J* = 8.0, H-5"), 9.59 (br s, 1 H, NH), 11.40 (br s, 1 H, NH)	(DMSO-d_6): 14.43 (CH_3), 21.48 (C-1'"), 24.18 (C-1'), 45.15 (C-2'), 60.28 (O-CH_2), 112.36 (C-7), 119.77 (C-3), 119.98 (C-4), 122.96 (C-8"), 123.70 (C-2), 125.05 (C-2"), 125.80 (C-3"), 126.25 (C-6"), 126.32 (C-7"), 126.74 (C-4"), 126.99 (C-6), 127.98 (C-3a), 128.22 (C-5"), 128.27 (C-5), 129.95 (C-8a"), 134.13 (C-4"), 134.45 (C-1"), 134.93 (C-7a), 161.91 (CO), 181.94 (C=S)

Table 2 (continued)

Product	IR (cm^{-1})	R_f	^1H NMR (solvent/TMS) δ, *J* (Hz)	^{13}C NMR (solvent/TMS) δ
3k	(KBr): 3350, 3310, 3260 1690, 1675	0.28[b]	(DMSO-d_6): 1.36 (t, 3 H, *J* = 7.1, CH_3), 1.88 (s, 3 H, CH_3), 3.37 (t, 2 H, *J* = 7.0, H-1'), 3.75 (br s, 2 H, H-2'), 4.32 (q, 4 H, *J* = 7.1, O-CH_2, H-1'"), 7.10 (t, 1 H, *J* = 7.1, H-4"), 7.20 (d, 1 H, *J* = 8.5, H-6), 7.29 (t, 2 H, *J* = 8.0, H-3", H-5"), 7.32 (d, 2 H, *J* = 8.0, H-2", 6"), 7.40 (d, 1 H, *J* = 8.5, H-7), 7.70 (br s, 1 H, NH), 7.71 (s, 1 H, H-4), 8.29 (t, 1 H, *J* = 5.5, NH), 9.53 (br s, 1 H, NH), 11.57 (br s, 1 H, NH)	(DMSO-d_6): 14.47 (CH_3), 22.85 (CH_3), 24.16 (C-1'), 42.91 (C-1'"), 44.88 (C-2'), 60.47 (O-CH_2), 112.65 (C-7), 119.25 (C-4), 120.02 (C-3), 123.30 (C-2", C-6"), 124.13 (C-2), 124.34 (C-4"), 125.47 (C-6), 127.49 (C-3a), 128.79 (C-3", 5"), 130.88 (C-5), 135.71 (C-7a), 139.27 (C-1"), 161.96 (COO), 169.20 (CO), 180.60 (C=S)
3l	(KBr): 3250, 3160, 1580, 1540	0.51[c]	(80 MHz, $CDCl_3$): 2.95 (t, 2 H, *J* = 5, CH_2), 3.75 (s, 3 H, CH_3O), 3.95 (t, 2 H, *J* = 5, CH_2), 6.10 (br s, 1 H, NH), 6.70–8.00 (m, 10 H, 2NH, ArH)	–
3m	(KBr): 3370, 3250, 1660	0.65[c]	($CDCl_3$): 1.35 (t, 3 H, *J* = 7.0, CH_3), 1.57 (br s, 2 H, H_2O crystal), 3.41 (t, 2 H, *J* = 6.5, CH_2), 3.87 (s, 3 H, O-CH_3), 3.96 (m, 2H, CH_2-N), 4.25 (q, 2 H, *J* = 7.0, O-CH_2), 6.26 (br s, 1 H, NH), 6.86 (br s, 2 H, ArH), 7.01 (dd-m, 1 H, *J* = 8.8, 1.0, ArH), 7.18 (m, 2 H, ArH), 7.23 (m, 2 H, ArH), 7.28 (d, 1 H, *J* = 8.8, ArH), 7.56 (br s, 1 H, NH), 8.65 (br s, 1 H, NH)	–
3n	(KBr): 3310, 3220, 1670, 1560	0.48[c]	(80 MHz, $CDCl_3$/DMSO-d_6): 1.40 (t, 3 H, *J* = 7, CH_3), 2.90 (d, 3 H, *J* = 5, N-CH_3), 3.35 (m, 2 H, CH_2), 3.70 (m, 2 H, CH_2), 4.35 (q, 2 H, *J* = 7, O-CH_2), 6.70–7.70 (m, 5 H, 2NH, ArH), 10.90 (br s, 1 H, NH)	–
3o	(KBr): 3290, 3200, 1680, 1520, 1500	0.62[c]	(80 MHz, $CDCl_3$/DMSO-d_6): 1.35 (t, 3 H, *J* = 6, CH_3), 3.38 (t, 2 H, *J* = 6, CH_2), 3.90 (q, 2 H, *J* = 6, CH_2-N), 4.30 (t, 2 H, *J* = 6, CH_2-O), 6.85 (t~m, 1 H, NH), 6.90–7.70 (m, 8 H, ArH), 8.90 (br s, 1 H, NH), 10.90 (br s, 1 H, NH)	–
3p	(KBr): 3350, 3310, 3260, 1675	0.76[a]	(DMSO-d_6): 1.33 (t, 3 H, *J* = 7.0, CH_3), 3.32 (t, 2 H, *J* = 6.5, H-1'), 3.74 (q, 2 H, *J* = 6.5, H-2'), 4.30 (q, 2 H, *J* = 7.0, O-CH_2), 7.28 (dd, 1 H, *J* = 8.5, 1.5, H-6), 7.33 (t, 1 H, *J* = 7.2, H-2"), 7.45 (d, 1 H, *J* = 8.5, H-7), 7.46 (t, 1 H, *J* = 5, NH), 7.50 (m, 2 H, H-3", H-6"), 7.52 (t, 1 H, *J* = 6.8, H-7"), 7.81 (d, 1 H, *J* = 8.7, H-8"), 7.83 (d, 1 H, *J* = 8.4, H-4"), 7.93 (d, 1 H, *J* = 1.5, H-4), 7.93 (d, 1 H, *J* = 8.4, H-5"), 9.60 (br s, 1 H, NH), 11.74 (br s, 1 H, NH)	(DMSO-d_6): 14.41 (CH_3), 24.13 (C-1'), 44.96 (C-2'), 60.61 (O-CH_2), 114.29 (C-7), 119.91 (C-3), 120.03 (C-4), 123.02 (C-8"), 124.42 (C-2), 125.18 (C-6), 125.22 (C-5, C-2"), 125.84 (C-3"), 126.30 (C-6"), 126.34 (C-7"), 126.90 (C-4"), 128.21 (C-5"), 128.91 (C-3a), 130.06 (C-8a"), 134.14 (C-4a"), 134.39 (C-1"), 134.77 (C-7a), 161.60 (CO), 181.95 (C=S)
3q	(film): 3400, 3300, 3250	0.64[c]	(80 MHz, $CDCl_3$): 0.80–1.80 (m, 10 H, $5CH_2$), 2.90 (t, 2 H, *J* = 6, CH_2), 3.70 (q~m, 3 H, *J* = 6, CH_2-N, CH-N), 5.90 (m, 2 H, 2NH), 6.85 (d, 1 H, *J* = 1, ArH), 7.10 (m, 2 H, ArH), 7.65 (m, 1 H, ArH), 8.50 (br s, 1 H, NH)	–
3r	(film): 3350, 3280, 3230	0.86[d]	(80 MHz, $CDCl_3$): 2.95 (t, 2 H, *J* = 6, CH_2), 3.90 (q, 2 H, *J* = 6, CH_2-N), 6.10 (br s, 1 H, NH), 6.80–7.80 (m, 9 H, ArH), 8.00 (br s, 1 H, NH), 8.40 (br s, 1 H, NH)	–
3s	(KBr): 3330 1690, 1680	0.75[c]	($CDCl_3$): 1.36 (t, 3 H, *J* = 7.1, CH_3), 3.36 (q, 2 H, *J* = 6.5, CH_2), 3.96 (m, 2 H, CH_2), 4.28 (q, 2 H, *J* = 7.1, O-CH_2), 6.17 (br s, 1 H, NH), 6.95 (br s, 2 H, ArH), 7.20 (m~t, 1 H, ArH), 7.26 (d, 1 H, *J* = 8.5, ArH), 7.27 (m, 2 H, ArH), 7.42 (dd, 1 H, *J* = 8.5, 1.5, ArH), 7.54 (br s, 1 H, NH), 7.86 (d, 1 H, *J* = 1.5, ArH), 8.77 (br s, 1 H, NH)	–

Table 2 (continued)

Product	IR (cm^{-1})	R_f	^1H NMR (solvent/TMS) δ, *J* (Hz)	^{13}C NMR (solvent/TMS) δ
4a	(KBr): 3330, 3200	0.15[a]	(DMSO-d_6): 1.11 (m, 1 H, H-4"), 1.29 (m, 2 H, H-3", H-5"), 1.39 (m, 2 H, H-2", H-6"), 1.58 (m, 1 H, H-4"), 1.70 (m, 2 H, H-3", H-5"), 1.76 (m, 2 H, H-2", H-6"), 2.57 (s, 3 H, S-CH_3), 3.08 (m, 2 H, H-1'), 3.66 (m, 1 H, H-1"), 3.77 (m, 2 H, H-2'), 7.00 (t, 1 H, *J* = 7.2, H-5), 7.08 (t, 1 H, *J* = 7.3, H-6), 7.20 (br s, 1 H, H-2), 7.39 (d, 1 H, *J* = 7.9, H-7), 7.58 (d, 1 H, *J* = 7.6, H-4), 8.32 (br s, 1 H, NH), 8.73 (br s, 1 H, NH), 10.64 (br s, 1 H, NH)	(DMSO-d_6): 14.75 (S-CH_3), 23.95 (C-3", C-5"), 24.05 (C-4"), 24.19 (C-1'), 31.10 (C-2"), 45.15 (C-2'), 54.02 (C-1"), 109.91 (C-3), 111.09 (C-7), 117.72 (C-4), 118.09 (C-5), 120.69 (C-6), 122.98 (C-2), 126.85 (C-3a), 136.07 (C-7a), 166.07 (N-C-N)
4b	(film): 3310, 3220	0.30[f]	(80 MHz, $CDCl_3$/DMSO-d_6): 2.45 (s, 3 H, S-CH_3), 3.20 (t, 2 H, *J* = 5, CH_2), 3.90 (q, 2 H, *J* = 5, CH_2-N), 6.90–7.50 (m, 10 H, ArH), 8.90 (m, 1 H, NH), 10.70 (br s, 1 H, NH)	–
4c	(KBr): 3420	0.78[a]	(80 MHz, DMSO-d_6): 2.25 (s, 3 H, CH_3), 3.15 (t, 2 H, *J* = 5.0, H-1'), 3.65 (m, 2 H, H-2'), 6.80–7.85 (m, 13 H, ArH NH), 10.80 (br s, 1 H, NH)	–
4d	(KBr): 3350, 3250, 3200, 3150 1600, 1520	0.17[c]	(DMSO-d_6, 373 K): 2.61 (s, 3 H, CH_3), 3.09 (t~m, 2 H, CH_2), 3.75 (t~m, 2 H, CH_2), 4.04 (m, 2 H, CH_2), 5.22 (m, 2 H, =CH_2), 5.82 (m, 1 H, =CH), 7.02 (t, 1 H, *J* = 7.0, H-5), 7.09 (t, 1 H, *J* = 7.3, H-6), 7.20 (s, 1 H, H-2), 7.39 (d, 1 H, *J* = 8.0, H-7), 7.57 (d, 1 H, *J* = 7.7, H-4), 8.89 (br s, 2 H, 2NH), 10.62 (br s, 1 H, NH)	(DMSO-d_6, 373 K): 14.23 (CH_3), 23.89 (C-1'), 45.04 (C-2'), 45.82 (N-CH_2), 109.90 (C-3), 111.12 (C-7), 117.28 (=CH_2), 117.69 (C-4), 118.11 (C-5), 120.73 (C-6), 122.91 (C-2), 126.83 (C-3a), 131.50 (=CH), 136.12 (C-7a), 167.43 (C=N)
4e	(KBr): 3250	0.63[c]	(80 MHz, $CDCl_3$/DMSO-d_6): 2.55 (s, 3 H, S-CH_3), 3.20 (t, 2 H, *J* = 5, CH_2), 3.75 (s, 3 H, N-CH_3), 3.90 (q, 2 H, *J* = 5, CH_2-N), 6.90–7.50 (m, 10 H, ArH), 8.90 (m, 1 H, NH)	–
4f	(film): 3410	0.92[d]	(80 MHz, $CDCl_3$): 2.05 (s, 3 H, S-CH_3), 2.90 (t, 2 H, *J* = 6, CH_2), 3.55 (t, 2 H, *J* = 6, CH_2-N), 4.40 (br m, 1 H, NH), 5.05 (s, 2 H, CH_2-N), 6.70–7.70 (m, 15 H, ArH)	–
4g	(film): 3250, 1610	0.83[d]	(80 MHz, $CDCl_3$): 1.15–1.75 (m, 10 H, H-2", H-3", H-4", H-5", H-6"), 2.25 (s, 3 H, S-CH_3), 3.0 (t, 2 H, *J* = 5.0, H-1'), 3.48 (m, 1 H, H-1"), 3.60 (m, 2 H, H-2'), 4.40 (br s, 1 H, NH), 5.30 (s, 2 H, CH_2), 6.95–7.30 (m, 10 H, ArH), 7.65 (m, 1 H, NH)	–
4h	(KBr): 3410, 3250, 1675	0.50[g]	(DMSO-d_6): 1.12 (m, 1 H, H-4"), 1.28 (m, 2 H, H-3", H-5"), 1.40 (m, 5 H, H-2", H-6", CH_3), 1.60 (m, 1 H, H-4"), 1.73 (m, 4 H, H-2", H-3", H-5", H-6"), 2.42 (s, 3 H, CH_3), 2.50 (s, 3 H, S-CH_3), 3.38 (m, 2 H, H-1'), 3.57 (m, 1 H, H-1"), 3.80 (m, 2 H, H-2'), 4.41 (m, 2 H, O-CH_2), 7.12 (d, 1 H, *J* = 8.0, H-6), 7.39 (d, 1 H, *J* = 8.0, H-7), 7.49 (s, 1 H, H-4), 8.31 and 8.75 (br s, 2 H, 2NH), 11.23 (br s, 1 H, NH)	(DMSO-d_6, 373 K): 13.97 (S-CH_3), 14.37 (CH_3), 20.68 (CH_3), 23.54 (C-4"), 23.95 (C-3", C-5"), 24.21 (C-1'), 31.07 (C-2", C-6"), 44.76 (C-2'), 53.80 (C-1"), 59.89 (O-CH_2), 112.04 (C-7), 117.77 (C-3), 118.69 (C-4), 123.71 (C-2), 126.57 (C-6), 127.39 (C-3a), 128.25 (C-5), 134.53 (C-7a), 161.24 (CO), 166.09 (C=N)
4i	(KBr): 3360, 3250, 1660	0.83[a]	(DMSO-d_6): 1.35 (t, 3 H, *J* = 7.1, CH_3), 2.13 (s, 3 H, S-CH_3), 2.33 (s, 3 H, H-1'"), 3.36 (t, 2 H, *J* = 7, H-1'), 3.52 (q, 2 H, *J* = 5.5, H-2'), 4.33 (q, 2 H, *J* = 7.1, O-CH_2), 6.45 (br s, 1 H, NH), 6.77 (d, 2 H, *J* = 7.7, H-2", H-6"), 6.92 (t, 1 H, *J* = 7.3, H-4"), 7.08 (d, 1 H, *J* = 8.3, H-6), 7.21 (t, 2 H, *J* = 7.7, H-3", 5"), 7.32 (d, 1 H, *J* = 8.4, H-7), 7.48 (s, 1 H, H), 7.59 (br s, 1 H, NH), 11.40 (br s, 1 H, NH)	(DMSO-d_6): 13.39 (S-CH_3), 14.49 (CH_3), 21.32 (C-1'"), 24.13 (C-1'), 43.51 (C-2'), 60.25 (O-CH_2), 112.28 (C-7), 120.00 (C-4), 120.64 (C-3), 121.77 (C-4"), 122.29 (C-2", C-6"), 123.52 (C-2), 126.92 (C-6), 128.12 (C-5), 128.19 (C-3a), 128.64 (C-3", 5"), 134.90 (C-7a), 150.50 (C-1"), 152.13 (C=N), 162.03 (CO)

Table 2 (continued)

Product	IR (cm^{-1})	R_f	^1H NMR (solvent/TMS) δ, *J* (Hz)	^{13}C NMR (solvent/TMS) δ
4j	(KBr): 3410, 1695	0.63[a]	(DMSO-d_6): 1.33 (t, 3 H, *J* = 7.1, CH_3), 2.14 (s, 3 H, S-CH_3), 2.20 (s, 3 H, 1'''), 3.48 (t, 2 H, *J* = 7.0, H-1'), 3.71 (q, 2 H, *J* = 5.8, H-2'), 4.33 (q, 2 H, *J* = 7.1, O-CH_2), 6.74 (m, 1 H, NH), 6.83 (d, 1 H, *J* = 7.2, H-2''), 7.06 (d, 1 H, *J* = 8.4, H-6), 7.34 (d, 1 H, *J* = 8.4, H-7), 7.35 (t, 1 H, *J* = 8.4, H-6''), 7.39 (t, 1 H, *J* = 8.0, H-7''), 7.44 (t, 1 H, *J* = 7.5, H-3''), 7.48 (d, 1 H, *J* = 8.2, H-4''), 7.50 (s, 1 H), 7.64 (br s, 1 H, NH), 7.81 (d, 1 H, *J* = 8.1, H-5''), 7.88 (d, 1 H, *J* = 8.3, H-8''), 11.45 (br s, 1 H, NH)	(DMSO-d_6): 13.47 (S-CH_3), 14.49 (CH_3), 21.18 (C-1'''), 24.69 (C-1'), 43.60 (C-2'), 60.27 (O-CH_2), 112.33 (C-7), 116.49 (C-2''), 120.05 (C-4), 120.61 (C-3), 121.64 (C-4''), 123.59 (C-2), 124.00 (C-8''), 124.86 (C-7''), 125.85 (C-3''), 126.13 (C-6''), 126.93 (C-6), 127.73 (C-5''), 128.16 (C-5), 128.20 (C-3a), 128.33 (C-8a''), 134.14 (C-4a''), 134.96 (C-7a), 146.91 (C-1''), 152.94 (C=N), 162.05 (CO)
4k	(KBr): 3395, 3250, 1680	0.32[a]	(DMSO-d_6): 1.35 (t, 3 H, *J* = 7.1, CH_3), 1.83 (s, 3 H, CH_3), 2.14 (s, 3 H, S-CH_3), 3.36 (t, 2 H, *J* = 7.4, H-1'), 3.51 (q, 2 H, *J* = 6.0, H-2'), 4.27 (d, 2 H, *J* = 5.5, H-1'''), 4.33 (q, 2 H, *J* = 7.1, O-CH_2), 6.44 (br s, 1 H, NH), 6.75 (d, 2 H, *J* = 7.7, H-2'', H-6''), 6.91 (t, 1 H, *J* = 8.0, H-4''), 7.17 (d, 1 H, *J* = 8.0, H-6), 7.20 (t, 2 H, *J* = 7.8, H-3'', 5''), 7.38 (d, 1 H, *J* = 8.5, H-7), 7.66 (s, 1 H, H-4), 8.21 (t, 1 H, *J* = 5.5, NH), 11.51 (br s, 1 H, NH)	(DMSO-d_6): 13.47 (S-CH_3), 14.47 (CH_3), 22.77 (CH_3), 24.16 (C-1'), 42.94 (C-1'''), 43.55 (C-2'), 60.37 (O-CH_2), 112.60 (C-7), 119.34 (C-4), 120.94 (C-3), 121.84 (C-4''), 122.33 (C-2'', C-6''), 123.90 (C-2), 125.41 (C-6), 127.71 (C-3a), 128.67 (C-3'', 5''), 130.67 (C-5), 135.66 (C-7a), 150.38 (C-1''), 152.27 (C=N), 161.96 (COO), 169.10 (CO)
4l	(KBr): 3400, 3180	0.63[c]	(80 MHz, $CDCl_3$): 2.05 (s, 3 H, S-CH_3), 2.90 (t, 2 H, *J* = 5, CH_2), 3.62 (t, 2 H, *J* = 5, CH_2-N), 3.85 (s, 3 H, O-CH_3), 6.80–7.30 (m, 10 H, NH, ArH), 7.95 (br s, 1 H, NH)	–
4m	(KBr): 3360, 3250, 1660	0.25[f]	($CDCl_3$): 1.40 (t, 3 H, *J* = 7.0, CH_3), 2.15 (s, 3 H, S-CH_3), 3.39 (t, 2 H, *J* = 6.0, CH_2), 3.69 (m, 2 H, CH_2), 3.80 (s, 3 H, O-CH_3), 4.38 (q, 2 H, *J* = 7.0, O-CH_2), 4.81 (br s, 1 H, NH), 6.79 (d, 2 H, *J* = 7.3, H-2', H-6'), 6.93 (t, 1 H, *J* = 7.3, H-4'), 7.00 (d, 1 H, *J* = 8.8, H-6), 7.11 (br s, 1 H, H-2), 7.19 (t, 2 H, *J* = 7.5, H-3', 5'), 7.25 (d, 1 H, *J* = 8.8, H-7), 8.65 (br s, 1 H, NH)	–
4n	(KBr): 3410, 1700	0.23[g]	(80 MHz, DMSO-d_6/$CDCl_3$): 1.35 (t, 3 H, *J* = 7, CH_3), 2.25 (s, 3 H, S-CH_3), 2.85 (s, 3 H, N-CH_3), 3.40 (dd~m, 4 H, 2CH_2), 4.40 (q, 2 H, *J* = 7, O-CH_2), 6.90–7.60 (m, 4 H, ArH, NH)	–
4o	(KBr): 3420, 3410, 1700	0.92[g]	(80 MHz, DMSO-d_6/$CDCl_3$): 1.40 (t, 3 H, *J* = 7, CH_3), 2.06 (s, 3 H, S-CH_3), 3.35 (d~m, 2 H, CH_2), 3.50 (m, 2 H, CH_2), 4.35 (q, 2 H, *J* = 7, O-CH_2), 5.10 (m, 1 H, NH), 6.70–7.70 (m, 8 H, ArH), 10.90 (br s, 1 H, NH)	–
4p	(KBr): 3410, 1695	0.50[a]	(DMSO-d_6): 1.32 (t, 3 H, *J* = 7.1, CH_3), 2.13 (s, 3 H, S-CH_3), 3.44 (t, 2 H, *J* = 6.5, H-1'), 3.70 (q, 2 H, *J* = 6.5, H-2'), 4.33 (q, 2 H, *J* = 7.1, O-CH_2), 6.73 (t, 1 H, *J* = 5.5, NH), 6.87 (d, 1 H, *J* = 7.3, H-2''), 7.24 (dd, 1 H, *J* = 8.7, 2.0, H-6), 7.33 (t, 1 H, *J* = 7.8, H-5''), 7.37 (t, 1 H, *J* = 8.0, H-7''), 7.43 (t, 1 H, *J* = 8.0, H-3''), 7.45 (d, 1 H, *J* = 8.6, H-7), 7.46 (d, 1 H, *J* = 6.5, H-4''), 7.71 (d, 1 H, *J* = 8.3, C-8''), 7.80 (d, 1 H, *J* = 8.1, H-5''), 7.89 (d, 1 H, *J* = 2.0, H-4), 11.80 (s, 1 H, NH)	(DMSO-d_6): 13.46 (S-CH_3), 14.41 (CH_3), 24.63 (C-1'), 43.34 (C-2'), 60.60 (O-CH_2), 114.29 (C-7), 116.49 (C-2''), 119.97 (C-4), 120.68 (C-3), 121.65 (C-4''), 123.86 (C-8''), 124.35 (C-2), 124.87 (C-7''), 125.07 (C-5), 125.12 (C-6), 125.83 (C-3''), 126.10 (C-6''), 127.70 (C-5''), 128.26 (C-3a), 129.05 (C-8a''), 134.09 (C-4a''), 146.88 (C-1''), 152.97 (C=N), 161.72 (CO)
4q	(film): 3420, 3200	0.12[a]	(80 MHz, $CDCl_3$): 1.10–1.90 (m, 10 H, 5CH_2), 2.20 (s, 3 H, S-CH_3), 2.95 (t, 2 H, *J* = 6, CH_2), 3.60 (m, 3 H, CH_2-N, CH-N), 4.40 (m, 1 H, NH), 6.90 (m, 1 H, ArH), 7.10–7.80 (m, 3 H, ArH)	–

Table 2 (continued)

Product	IR (cm^{-1})	R_f	^1H NMR (solvent/TMS) δ, *J* (Hz)	^{13}C NMR (solvent/TMS) δ
4r	(KBr): 3450, 3150	0.90[a]	(80 MHz, $CDCl_3$/DMSO-d_6): 2.10 (s, 3 H, S-CH_3), 2.95 (t, 2 H, *J* = 7, CH_2), 3.60 (t~m, 2 H, CH_2-NH), 5.00 (m, 1 H, NH), 6.70–7.80 (m, 9 H, ArH), 10.00 (s, 1 H, NH)	–
4s	(KBr): 3400, 1700	0.31[f]	($CDCl_3$): 1.40 (t, 3 H, *J* = 7.0, CH_3), 2.16 (s, 3 H, S-CH_3), 3.36 (m~t, 2 H, *J* = 6.0, CH_2), 3.66 (m~t, 2 H, *J* = 6.0, CH_2), 4.39 (q, 2 H, *J* = 7.0, O-CH_2), 4.70 (br s, 1 H, NH), 6.80 (d, 2 H, *J* = 7.2, ArH), 6.94 (t, 1 H, *J* = 7.2, ArH), 7.20 (t, 2 H, *J* = 7.5, ArH), 7.24 (d, 1 H, *J* = 8.5, ArH), 7.40 (dd, 1 H, *J* = 8.5, 1.0, ArH), 7.87 (d, 1 H, *J* = 1.0, ArH), 8.73 (br s, 1 H, NH)	–
5a	(KBr): 3375, 3240, 2180, 1600, 1580	0.61[a]	(DMSO-d_6): 1.06 (m, 1 H, H-4"), 1.21 (m, 4 H, H-2", H-3", H-5", H-6"), 1.55 (m, 1 H, H-4"), 1.66 (m, 2 H, H-3", H-5"), 1.72 (m, 2 H, H-2", H-6"), 2.88 (t, 2 H, *J* = 7.3, H-1'), 3.40 (m, 3 H, H-2', H-1"), 6.43 (d, 1 H, *J* = 8.2, NH), 6.87 (m, 1 H, NH), 6.98 (t, 1 H, *J* = 7.4, H-5), 7.07 (t, 1 H, *J* = 7.5, H-6), 7.15 (d, 1 H, *J* = 1.0, H-2), 7.34 (d, 1 H, *J* = 8.1, H-7), 7.55 (d, 1 H, *J* = 7.9, H-4), 10.83 (s, 1 H, NH)	(DMSO-*d*): 24.92 (C-3", C-5"), 25.19 (C-1'), 25.24 (C-4"), 32.50 (C-2", C-6"), 42.13 (C-2'), 50.33 (C-1"), 111.51 (C-3), 111.58 (C-7), 118.35 (C≡N), 118.47 (C-5), 118.50 (C-4), 121.18 (C-6), 123.05 (C-2), 127.36 (C-3a), 136.43 (C-7a), 158.52 (N-C-N)
5b	(KBr): 3375, 3240, 2180, 1600, 1580	0.76[g]	(DMSO-d_6): 2.94 (t, 2 H, *J* = 7.5, CH_2), 3.51 (m~q, 2 H, CH_2), 6.99 (t, 1 H, *J* = 7.4, H-5), 7.08 (t, 1 H, *J* = 7.5, H-6), 7.13 (t, 1 H, *J* = 7.4, H-4"), 7.15 (d, 2 H, *J* = 7.4, H-2", H-6"), 7.18 (s, 1 H, H-2), 7.19 (m~t, 1 H, NH), 7.30 (t, 2 H, *J* = 7.5, H-3", H-5"), 7.35 (d, 1 H, *J* = 8.1, H-7), 7.58 (d, 1 H, *J* = 7.9, H-4), 8.95 (br s, 1 H, NH). 10.84 (br s, 1 H, NH)	–
5c	(KBr): 3400, 3190, 2170, 1590	0.56[a]	(DMSO-d_6): 2.92 (br s, 2 H, H-1'), 3.48 (br s, 2 H, H-2'), 6.92 (br s, 1 H, NH), 6.98 (t, 1 H, *J* = 7.4, H-5), 7.07 (t, 1 H, *J* = 7.5, H-6), 7.13 (br s, 1 H, H-2), 7.33 (d, 1 H, *J* = 7.3, H-2"), 7.35 (d, 1 H, *J* = 8.2, H-7), 7.51 (t, 1 H, *J* = 8.0, H-3"), 7.56 (m, 3 H, H-4, H-6", H-7"), 7.81 (br s, 1 H, C-8"), 7.89 (d, 1 H, *J* = 8.3, H-4"), 7.97 (m, 1 H, H-5"), 9.18 (s, 1 H, NH), 10.82 (s, 1 H, NH)	(DMSO-d_6): 25.33 (C-1'), 42.42 (C-2'), 111.45 (C-3), 111.59 (C-7), 117.81 (C≡N), 118.46 (C-5), 118.55 (C-4), 121.17 (C-6), 122.95 (C-8"), 123.06 (C-2), 125.57 (C-2"), 125.99 (C-3"), 126.49 (C-6"), 126.65 (C-7"), 127.40 (C-3a), 128.54 (C-4"), 128.36 (C-5"), 130.26 (C-8a"), 133.10 (C-1"), 134.19 (C-4a"), 136.44 (C-7a), 159.40 (C=N)
5e	(KBr): 3370, 3190, 2180, 1590	0.47[a]	(DMSO-d_6): 2.93 (t, 2 H, *J* = 7.3, CH_2), 3.49 (q, 2 H, *J* = 6.5, CH_2-N), 3.72 (s, 3 H, N-CH_3), 7.03 (t, 1 H, *J* = 7.4, H-5), 7.12 (m, 2 H, H-6, H-4"), 7.14 (s, 1 H, H-2), 7.15 (d, 2 H, *J* = 8.5, H-2", H-6"), 7.16 (m, 1 H, NH), 7.31 (t, 2 H, *J* = 7.5, H-3", H-5"), 7.37 (d, 1 H, *J* = 8.3, H-7), 7.59 (d, 1 H, *J* = 8.0, H-4), 8.97 (s, 1 H, NH)	(DMSO-d_6): 25.01 (C-1'), 32.48 (CH_3), 42.53 (C-2'), 109.82 (C-7), 110.82 (C-3), 117.64 (C≡N), 118.66 (C-5), 117.84 (C-4), 121.40 (C-6), 123.86 (C-2", C-6"), 125.01 (C-4"), 127.61 (C-2), 127.73 (C-3a), 129.18 (C-3", C-5"), 136.91 (C-7a), 137.82 (C-1"), 158.25 (C-5), 158.18 (C=N)
5f	(KBr): 3190, 2180, 1590	0.49[c]	(DMSO-d_6): 2.96 (t, 2 H, *J* = 7.4, CH_2), 3.53 (q, 2 H, *J* = 6.6, CH_2-N), 5.36 (s, 2 H, CH_2), 7.02 (t, 1 H, *J* = 7.4, H-5), 7.10 (t, 1 H, *J* = 7.8, H-6), 7.13 (t, *J* = 8.2, 1 H, H-4"), 7.16 (d, 2 H, *J* = 7.9, H-2", H-6"), 7.19 (d, 2 H, *J* = 7.5, H-2', H-6'), 7.20 (s, 1 H, NH), 7.23 (t, 1 H, *J* = 7.4, H-4'), 7.28 (t, 2 H, *J* = 7.4, H-3', H-5'), 7.29 (t, 2 H, *J* = 7.7, H-3", H-5"), 7.33 (s, 1 H, H-2), 7.40 (d, 1 H, *J* = 8.2, H-7), 7.61 (d, 1 H, *J* = 7.8, H-4), 8.97 (br s, 1 H, NH)	(DMSO-d_6): 25.02 (C-1'), 32.39 (C-2'), 49.15 (CH_2), 110.24 (C-7), 110.46 (C-3), 117.55 (C≡N), 118.80 (C-5), 118.96 (C-4), 121.48 (C-6), 123.82 (C-2", C-6"), 124.88 (C-4"), 126.94 (C-2), 127.20 (C-2', C-6'), 127.43 (C-4'), 127.99 (C-3a), 128.68 (C-3', C-5'), 129.07 (C-3", C-5"), 136.26 (C-7a), 137.78 (C-1"), 138.50 (C-1'), 158.20 (C=N)

Table 2 (continued)

Product	IR (cm^{-1})	R_f	^1H NMR (solvent/TMS) δ, *J* (Hz)	^{13}C NMR (solvent/TMS) δ
5g	(KBr): 3350, 2170, 1540	0.31[c]	(DMSO-d_6): 1.03 (m, 1 H, H-4"), 1.20 (m, 4 H, H-2", H-3", H-5", H-6"), 1.53 (m, 1 H, H-4"), 1.64 (m, 2 H, H-3", H-5"), 1.71 (m, 2 H, H-2", H-4"), 2.90 (t, 2 H, *J* = 7.0, CH_2), 3.42 (m, 3 H, CH_2, H-1"), 5.35 (s, 2 H, CH_2), 6.46 (d, 1 H, *J* = 8.0, NH), 6.94 (br s, 1 H, NH), 7.02 (t, 1 H, *J* = 7.3, H-5), 7.09 (t, 1 H, *J* = 7.5, H-6), 7.20 (d, 2 H, *J* = 7.3, H-1', H-6'), 7.24 (d, 1 H, *J* = 7.1, H-4'), 7.29 (m, 3 H, H-2, H-3', H-5'), 7.39 (d, 1 H, *J* = 8.1, H-7), 7.59 (d, 1 H, *J* = 7.8, H-4)	(DMSO-d_6): 24.96 (C-3"', C-5"'), 25.17 (C-4"'), 25.20 (C-1'), 32.51 (C-2"', C-6"'), 42.05 (C-2'), 49.18 (CH_2), 50.37 (C-1"'), 110.27 (C-7), 111.55 (C-3), 118.40 (C≡N), 118.82 (C-5), 118.95 (C-4), 121.50 (C-6), 126.96 (C-2), 127.26 (C-2', C-6'), 127.48 (C-4'), 128.01 (C-3a), 128.72 (C-3', C-5'), 136.26 (C-7a), 138.54 (C-1'), 158.52 (C=N)
5h	(KBr): 3350, 2170, 1690	0.66[a]	(DMSO-d_6): 1.06 (m, 1 H, H-4"), 1.20 (m, 4 H, H-2", H-3", H-5", H-6"), 1.36 (t, 3 H, *J* = 7.1, CH_3), 1.53 (m, 1 H, H-4"), 1.66 (m, 4 H, H-2", H-3", H-5", H-6"), 2.38 (s, 3 H, H-1"'), 3.21 (t, 2 H, *J* = 7.0, H-1'), 3.35 (m, 3 H, H-2', H-1"), 4.35 (q, 2 H, *J* = 7.1, O-CH_2), 6.38 (d, 1 H, *J* = 8.0, NH), 6.84 (t, 1 H, *J* = 6.0, NH), 7.09 (d, 1 H, *J* = 8.4, H-6), 7.31 (d, 1 H, *J* = 8.4, H-7), 7.45 (s, 1 H, H-4), 11.45 (br s, 1 H, NH)	(DMSO-d_6): 14.44 (CH_3), 21.40 (C-1"'), 24.55 (C-1'), 24.86 (C-3", C-5"), 25.16 (C-4"), 23.42 (C-2", C-6"), 42.11 (C-2'), 50.23 (C-1"), 60.41 (O-CH_2), 112.39 (C-7), 118.19 (C≡N), 119.57 (C-3, C-4), 123.65 (C-2), 127.04 (C-6), 127.76 (C-3a), 128.38 (C-5), 134.90 (C-7a), 158.49 (C=N), 162.00 (CO)
5i	(KBr): 3370, 3250, 2170, 1670	0.62[a]	(DMSO-d_6): 1.35 (t, 3 H, *J* = 7.1, CH_3), 2.39 (s, 3 H, H-1"'), 3.29 (t, 2 H, *J* = 6.9, H-1'), 3.50 (q, 2 H, *J* = 6.1, H-2'), 4.32 (q, 2 H, *J* = 7.1, O-CH_2), 7.09 (br s, 1 H, NH), 7.11 (m, 4 H, *J* = 7.9, H-6, H-2", H-4", H-6"), 7.28 (t, 2 H, *J* = 7.8, H-3", H-5"), 7.33 (d, 1 H, *J* = 8.4, H-7), 7.50 (s, 1 H, H-4), 8.89 (br s, 1 H, NH), 11.47 (br s, 1 H, NH)	(DMSO-d_6): 14.30 (CH_3), 21.44 (C-1"'), 24.47 (C-1'), 42.45 (C-2'), 60.43 (O-CH_2), 112.43 (C-7), 117.47 (C≡N), 119.37 (C-3), 119.71 (C-4), 123.67 (C-2", C-6"), 123.85 (C-2), 124.83 (C-4"), 127.05 (C-6), 127.84 (C-5), 128.44 (C-3a), 129.03 (C-3", 5"), 134.98 (C-7a), 137.76 (C-1"), 158.20 (C=N), 162.04 (CO)
5j	(KBr): 3410, 2175, 1695	0.84[a]	(DMSO-d_6): 1.33 (t, 3 H, *J* = 7.1, CH_3), 2.38 (br s, 3 H, CH_3), 3.24 (br s, 2 H, H-1'), 3.42 (br s, 2 H, H-2'), 4.27 (q, 2 H, *J* = 7.1, O-CH_2), 6.58 and 6.72 (br s, 2 H, NH), 7.10 (d, 1 H, *J* = 8.3, H-6), 7.17 (d, 1 H, *J* = 7.3, H-2"), 7.32 (d, 1 H, *J* = 8.4, H-7), 7.45 (t, 1 H, *J* = 8.0, H-7"), 7.47 (d, 1 H, *J* = 7.0, H-6"), 7.49 (s, 1 H, H-4), 7.53 (t, 1 H, *J* =7.0, H-3"), 7.69 and 7.70 (br s, 1 H, H-8"), 7.85 (d, 1 H, *J* = 8.2, H-4"), 7.94 (d, 1 H, *J* = 8.1, H-5"), 9.08 (br s, 1 H, NH), 11.40 (br s, 1 H, NH)	(DMSO-d_6): 14.45 (CH_3), 21.50 (CH_3), 24.60 (C-1'), 42.47 (C-2'), 60.41 (O-CH_2), 112.45 (C-7), 117.47 (C≡N), 119.42 (C-3), 119.80 (C-4), 122.88 (C-8"), 123.84 (C-2), 125.46 (C-2"), 125.96 (C-7"), 126.48 (C-6"), 126.55 (C-3"), 127.05 (C-6), 127.56 (C-4"), 127.95 (C-3a), 128.32 (C-5"), 128.45 (C-5), 130.25 (C-8a"), 134.18 (C-4a"), 134.98 (C-7a), 159.31 (C-1"), 159.37 (C=N), 162.03 (CO)
5k	(KBr): 3395, 3250, 2170, 1690, 1680	0.37[g]	(DMSO-d_6): 1.29 and 1.35 (t, 3H, *J* = 7.0, CH_3), 1.84 and 1.86 (s, 3 H, CH_3), 3.29 (t, 2 H, *J* = 6.8, H-1'), 3.48 (m, 2 H, H-2'), 4.30 (m, 4 H, H-1"', O-CH_2), 7.08 (d, 2 H, *J* = 7.5, H-2", H-6"), 7.12 (t, 1 H, *J* = 7.5, H-4"), 7.19 (d, 1 H, *J* = 9.0, H-6), 7.28 (t, 2 H, *J* = 7.8, H-3", H-5"), 7.38 (d, 1 H, *J* = 8.6, H-7), 7.59 (s, 1 H, H-4), 8.26 (t, 1 H, *J* = 5.5, NH), 8.89, 7.52, 7.36 and 7.17 (br s, 2 H, NH), 11.57 (br s, 1 H, NH)	(DMSO-d_6): 14.47 (CH_3), 22.87 (CH_3), 24.47 (C-1'), 42.55 (C-2'), 43.05 (C-1"'), 60.61 (O-CH_2), 112.78 (C-7), 117.58 (C≡N), 119.16 (C-4), 119.78 (C-3), 123.76 (C-2", C-6"), 124.25 (C-2), 124.97 (C-4"), 125.60 (C-6), 127.46 (C-3a), 129.12 (C-3", 5"), 130.95 (C-5), 135.75 (C-7a), 137.75 (C-1"), 158.26 (C=N), 162.03 (COO), 169.35 (CO)
5l	(KBr): 3420, 2180	0.37[c]	(DMSO-d_6): 2.93 (t, 2 H, *J* = 7.3, CH_2), 3.52 (q~m, 2 H, CH_2-N), 3.79 (s, 3 H, O-CH_3), 6.74 (m, 1 H, ArH), 7.12 (s, 1 H, ArH), 7.17 (m, 2 H, ArH), 7.18 (d, 2 H, *J* = 9.0, ArH), 7.19 (br s, 1 H, NH), 7.25 (d, 1 H, *J* = 8.8, ArH), 7.32 (t, 2 H, *J* = 7.7, ArH), 8.97 (br s, 1 H, NH), 10.69 (br s, 1 H, NH)	(DMSO-d_6): 25.19 (C-1'), 42.37 (C-2'), 55.53 (O-CH_3), 100.43 (C-4), 111.17 (C-3), 111.36 (C-6), 112.21 (C-7), 117.68 (C≡N), 123.72 (C-2", C-6"), 123.76 (C-2), 124.84 (C-4"), 127.73 (C-3a), 129.08 (C-3", 5"), 131.59 (C-7a), 137.84 (C-1"), 153.24 (C-5), 158.18 (C=N)

Table 2 (continued)

Product	IR (cm^{-1})	R_f	^1H NMR (solvent/TMS) δ, *J* (Hz)	^{13}C NMR (solvent/TMS) δ
5m	(KBr): 3420, 2175, 1690	0.47[e]	(DMSO-d_6): 1.34 (t, 3 H, *J* = 7.0, CH_3), 3.27 (t, 2 H, *J* = 7.0, CH_2), 3.48 (q, 2 H, *J* = 5.7, CH_2), 3.78 (s, 3H, O-CH_3), 4.31 (q, 2 H, *J* = 7.0, O-CH_2), 6.92 (dd, 1 H, *J* = 8.9, 1.9, H-6), 7.03 (m, 2H, H-2", H-6"), 7.09 (br s, 1 H, NH), 7.10 (t, 1 H, *J* = 7.5, H-4"), 7.17 (d, 1 H, *J* = 1.5, H-4), 7.25 (t, 2 H, *J* = 7.7, H-3", H-5"), 7.32 (d, 1 H, *J* = 8.9, H-7), 8.90 (br s, 1 H, NH), 11.45 (s, 1 H, NH)	–
5n	(KBr): 3380, 3230, 2150, 1680	0.10[c]	(DMSO-d_6): 1.37 (t, 3 H, *J* = 7.1, CH_3), 2.60 (d, 3 H, *J* = 4.5, N-CH_3), 3.22 (t, 2 H, *J* = 7.0, CH_2), 3.33 (q, 2 H, *J* = 6.4, CH_2), 4.35 (q, 2 H, *J* = 7.1, O-CH_2), 6.90 (m, 2 H, 2NH), 7.26 (dd, 1 H, *J* = 8.8, 2.0, H-6), 7.43 (d, 1 H, *J* = 8.8, H-7), 7.75 (d, 1 H, *J* = 2.0, H-4), 11.77 (s, 1 H, NH)	(DMSO-d_6): 14.37 (CH_3), 24.59 (C-1'), 28.37 (N-CH_3), 41.91 (C-2'), 60.72 (O-CH_2), 114.34 (C-7), 118.40 (C≡N), 119.56 (C-3), 119.65 (C-4), 124.40 (C-2), 125.16 (C-6), 125.26 (C-5), 128.67 (C-3a), 134.79 (C-7a), 160.25 (C=N), 161.73 (CO)
5o	(KBr): 3400, 3330, 2170, 1680	0.35[c]	(DMSO-d_6): 1.35 (t, 3 H, *J* = 7.1, CH_3), 3.26 (t, 2 H, *J* = 6.8, CH_2), 3.48 (q, 2 H, *J* = 6.0, CH_2), 4.34 (q, 2 H, *J* = 7.1, O-CH_2), 7.07 (br s, 1 H, NH), 7.09 (d, 2 H, *J* = 7.7, H-2", H-6"), 7.13 (t, 1 H, *J* = 7.3, H-4"), 7.27 (dd, 1 H, *J* = 8.0, 1.5, H-6), 7.29 (t, 2 H, *J* = 7.8, H-3", H-5"), 7.44 (d, 1 H, *J* = 8.8, H-7), 7.78 (d, 1 H, *J* = 1.5, H-4), 8.90 (br s, 1 H, NH), 11.80 (s, 1 H, NH)	(DMSO-d_6): 14.35 (CH_3), 24.40 (C-1'), 42.20 (C-2'), 60.72 (O-CH_2), 114.35 (C-7), 117.35 (C≡N), 119.37 (C-3), 119.73 (C-4), 123.79 (C-2", C-6"), 124.48 (C-2), 124.93 (C-4"), 125.20 (C-6), 125.34 (C-5), 128.63 (C-3a), 129.05 (C-3", C-5"), 134.79 (C-7a), 137.65 (C-1"), 159.17 (C=N), 161.68 (CO)
5p	(KBr): 3430, 3320, 2180	0.55[a]	(DMSO-d_6): 1.34 (t, 3 H, *J* = 7.1, CH_3), 3.23 (br s, 2 H, H-1'), 3.44 (br s, 2 H, H-2'), 4.33 (q, 2 H, *J* = 7.1, O-CH_2), 6.71 (br s, 1 H, NH), 7.22 (d, 1 H, *J* = 7.3, H-2"), 7.27 (dd, 1 H, *J* = 8.5, 2.0, H-6), 7.44 (d, 1 H, *J* = 8.4, H-7), 7.47 (t, 1 H, *J* = 7.8, H-3"), 7.50 (m, 1 H, H-6"), 7.54 (t, 1 H, *J* = 7.0, H-7"), 7.72 (m, 1 H, H-8"), 7.76 (br s, 1 H, C-4), 7.87 (d, 1 H, *J* = 8.2, H-4"), 7.95 (d, 1 H, *J* = 7.9, H-5"), 9.12 (br s, 1 H, NH), 11.75 (s, 1 H, NH)	(DMSO-d_6): 14.36 (CH_3), 24.50 (C-1'), 42.20 (C-2'), 60.67 (O-CH_2), 114.34 (C-7), 117.62 (C≡N), 119.41 (C-3), 119.73 (C-4), 122.81 (C-8"), 124.46 (C-2), 125.17 (C-6), 125.28 (C-5), 125.55 (C-2"), 125.93 (C-3"), 126.44 (C-6"), 126.51 (C-7"), 127.58 (C-4"), 128.27 (C-5"), 128.72 (C-3a), 130.24 (C-8a"), 134.14 (C-4a"), 134.76 (C-7a, C-1"), 159.31 (C=N), 161.64 (CO)
5q	(KBr): 3410, 3310, 3280, 2140	0.46[c]	(DMSO-d_6): 1.05 (m, 1 H, H-4"), 1.21 (m, 4 H, H-2", H-3", H-5", H-6"), 1.55 (m, 1 H, H-4"), 1.65 (m, 2 H, H-3", H-5"), 1.73 (m, 2 H, H-2", H-6"), 2.86 (t, 2 H, *J* = 7.3, H-1'), 3.38 (m, 3H, H-2', H-1"), 6.45 (d, 1 H, *J* = 8.1, NH), 6.87 (m, 1 H, NH), 7.17 (dd, 1 H, *J* = 8.6, 1.5, H-6), 7.22 (s, 1 H, H-2), 7.31 (d, 1 H, *J* = 8.6, H-6), 7.74 (s, 1 H, H-4), 11.05 (s, 1 H, NH)	(DMSO-d_6): 24.95 (C-3", C-5"), 25.03 (C-1'), 25.21 (C-4"), 32.52 (C-2", C-6"), 42.10 (C-2'), 50.38 (C-1"), 111.26 (C-3), 111.48 (C-5), 113.59 (C-7), 118.33 (C≡N), 120.87 (C-4), 123.62 (C-6), 124.88 (C-2), 129.31 (C-3a), 135.09 (C-7a), 158.53 (N-C-N)
5r	(KBr): 3430, 3320, 3150, 2150, 1600, 1580	0.40[c]	(DMSO-d_6): 2.92 (t, 2 H, *J* = 7.4, CH_2), 3.48 (t, 2 H, *J* = 6.6, CH_2), 6.58 (br s, 4 H, $2H_2O$), 7.14 (t, 1 H, *J* = 7.4, H-4'), 7.16 (d, 2 H, *J* = 9.3, H-2', H-6'), 7.17 (br s, 1 H, NH), 7.18 (m, 1 H, *J* = 1.7, H-6), 7.25 (d, 1 H, *J* = 1.6, H-2), 7.31 (t, 2 H, *J* = 7.8, H-3', H-5'), 7.33 (d, 1 H, *J* = 8.6, H-7), 7.78 (d, 1 H, *J* = 1.3, H-4), 8.97 (br s, 1 H, NH). 11.07 (br s, 1 H, NH)	(DMSO-d_6): 24.95 (C-1'), 42.40 (C-2'), 111.28 (C-3), 111.38 (C-5), 113.61 (C-7), 117.58 (C≡N), 120.93 (C-4), 123.65 (C-6), 123.86 (C-2', C-6'), 124.94 (C-4'), 129.10 (C-3', C-5'), 129.30 (C-3a), 135.12 (C-7a), 137.79 (C-1'), 158.21 (C=N)
5s	(KBr): 3400, 3330, 2170, 1680	0.61[e]	(DMSO-d_6): 1.35 (t, 3 H, *J* = 7.0, CH_3), 3.26 (m~t, 2 H, *J* = 6.6, CH_2), 3.47 (m~q, 2 H, CH_2), 4.34 (q, 2 H, *J* = 7.0, O-CH_2), 7.09 (br s, 1 H, NH), 7.10 (m~d, 2 H, *J* = 7.3, H-2", H-6"), 7.13 (t, 1 H, *J* = 7.8, H-4"), 7.29 (t, 2 H, *J* = 7.6, H-3", H-5"), 7.37 (d, 1 H, *J* = 9.0, H-6), 7.39 (d, 1 H, *J* = 9.0, H-7), 7.92 (s, 1 H, H-4), 8.90 (br s, 1 H, NH), 11.81 (s, 1 H, NH)	–

[a] Hexane/acetone, 1:1.
[b] Hexane/acetone, 5:2.
[c] Hexane/acetone, 5:3.
[d] CH_2Cl_2/hexane/acetone, 7:5:2.
[e] CH_2Cl_2/toluene/MeOH, 10:2:1.
[f] Toluene/hexane/acetone, 6:2:1.
[g] $CHCl_3$/MeOH, 10:1.

column chromatography. The isothiocyanates and the other reagents were purchased from suppliers. 5-Bromotryptamine, 5-methoxytryptamine and their corresponding ethyl esters were prepared by known procedure,[7] while other tryptamine derivatives **1** were prepared according to the literature procedure we recently reported.[8] 1-Methyltryptamine was prepared according to literature procedure.[9]

1-Benzyltryptamine

To a stirred solution of tryptamine (14.4 g, 30 mmol) in DMF (100 mL) was added NaH (60% in mineral oil, 4 g, 100 mmol) in portions at r.t. The resulting residue was stirred for 30 min, then a solution of benzyl chloride (12.6 g, 100 mmol) in DMF (10 mL) was added dropwise. The mixture was stirred at 50 °C for 2 h. The solvent was then evaporated under reduced pressure and to the residue was added $CHCl_3$ (150 mL). The organic phase was washed with sat. Na_2CO_3 (30 mL), H_2O (50 mL), and dried ($MgSO_4$). After evaporation of the solvent, purification by flash column chromatography afforded the desired product (12.5 g, 55%) as an oil.[10]

R_f = 0.25 (CH_2Cl_2/hexane/acetone, 7:5:2).

Lit.[10]: mp = 93–94 °C.

IR (film): ν = 3300 cm^{-1}.

^1H NMR (80 MHz, $CDCl_3$): δ = 2.90 (m, 4H, $2CH_2$), 4.40 (m, 2H, CH_2), 5.00 (m, 2H, NH_2), 6.80–7.60 (m, 10H, ArH).

Thioureas 3a-s; General Procedure

To a stirred suspension of the amine **1** (10.4 mmol) and isothiocyanate **2** (11.44 mmol) in CH_2Cl_2 (50 mL) was added dropwise Et_3N (3.0 mL, 21.5 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred at r.t. for 3 h. The solvent was then evaporated, and the residue was stirred with MeOH (40 mL) for 20 min, followed by filtration or evaporation of the solvent affording the desired thiourea derivatives **3a–s**.

Hydrogen Iodide Salts of Thioethers 4a–s; General Procedure

To a stirred solution of the thiourea **3a–s** (7 mmol) in acetone (70 mL), CH_3I (2.98 g, 21 mmol) and Et_3N (2 drops) were added and the mixture was stirred at r.t. for 3 h. The solvent was then evaporated under reduced pressure, H_2O (30 mL) was added to the residue, and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was washed with 10% Na_2CO_3 (25 mL), H_2O (25 mL), and brine (20 mL). After evaporating the solvent, the product, if solid, was recrystallized from alcohol. Otherwise, it was used in the next step without further purification.

Cyanoguanidines 5a–s; General Procedure

A solution of the thioether derivative **4a–s** (9.2 mmol), cyanamide (0.84 g, 20 mmol), and 1,4-diazabicyclo[2,2,2]octane (100 mg, 0.90 mmol) was refluxed in BuOH (50 mL) for 4–6 h. The work-up procedure was continued by one of the following methods affording the cyanoguanidines **5a–s** (Table 3).

Procedure A

Upon cooling the mixture, a precipitate dropped out which was filtered, washed with alcohol, and dried on air.

Procedure B

The solvent was evaporated and the residue was diluted with CH_2Cl_2. The organic phase was washed with 5% HCl, and H_2O, and then dried ($MgSO_4$). Concentration of the solution afforded crystals, which were filtered and washed with Et_2O.

Procedure C

The solvent was evaporated and the residue was separated by column chromatography.

Table 3 Work-up Methods for Cyanoguanidine Derivatives **5a–s**

Compound[a]	Procedure	Eluent, v/v	Recrystallisation Solvent
5a	C	CH_2Cl_2/MeOH, 10: 0.1	–
5b	C	$CHCl_3$/MeOH, 5:1	–
5c	A	–	EtOH/H_2O
5d	-	–	–
5e	B	–	EtOH
5f	B	–	EtOH
5g	C	hexane/EtOAc, 1:1	–
5h	B	–	EtOH
5i	C	hexane/acetone, 5:1	–
5j	C	$CHCl_3$/MeOH, 10:1	–
5k	B	–	–
5l	B	–	EtOH
5m	A	–	EtOH
5n	A	–	EtOH
5o	A	–	EtOH
5p	C	hexane/acetone, 5:1	–
5q	C	EtOAc/hexane, 3:2	–
5r[b]	B	–	–
5s	A	–	EtOH

[a] All compounds showed saticfactory microanalysis: C ± 0.33; H ± 0.30; N ± 0.34.

[b] This compound contained two moles of crystalline water.

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