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Unequivocal synthesis of substituted thiazolo[3,2-*a*]benzimidazoles

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Dedicated to Professor Jan Bergman on the occasion of his 80th birthday

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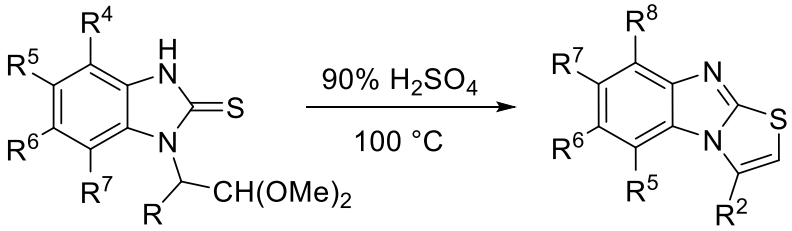
Abstract

An unequivocal route to individual substituted thiazolo[3,2-*a*]benzimidazole isomers has been developed, involving the acid-catalyzed intramolecular condensation of dialkylacetals with the sulfur atom of benzimidazole-2-thiones. Products are isolated without isomerization, in contrast to several literature methods.



Keywords: Thiazolo[3,2-*a*]benzimidazoles, unequivocal synthesis, benzimidazole-2-thiones, aminoacetals

Introduction

Thiazolo[3,2-*a*]benzimidazole (benzo[4,5]imidazo[2,1-*b*]thiazole) derivatives (**1**) have received attention over the years due to a variety of biological effects,[1,2] with the immunomodulator Tilomisole (Wy-18,251) (**2**),[3] and the allosteric antagonist of metabotropic glutamate receptor 1 (mGluR1) YM-298198 (**3**)[4] having probably received the most attention (Figure 1).[2]

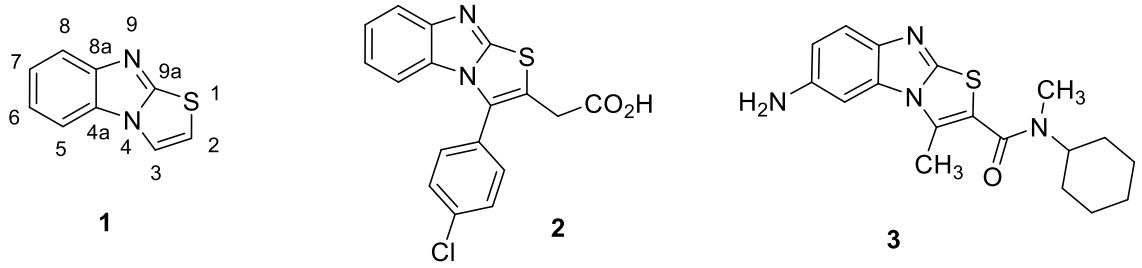
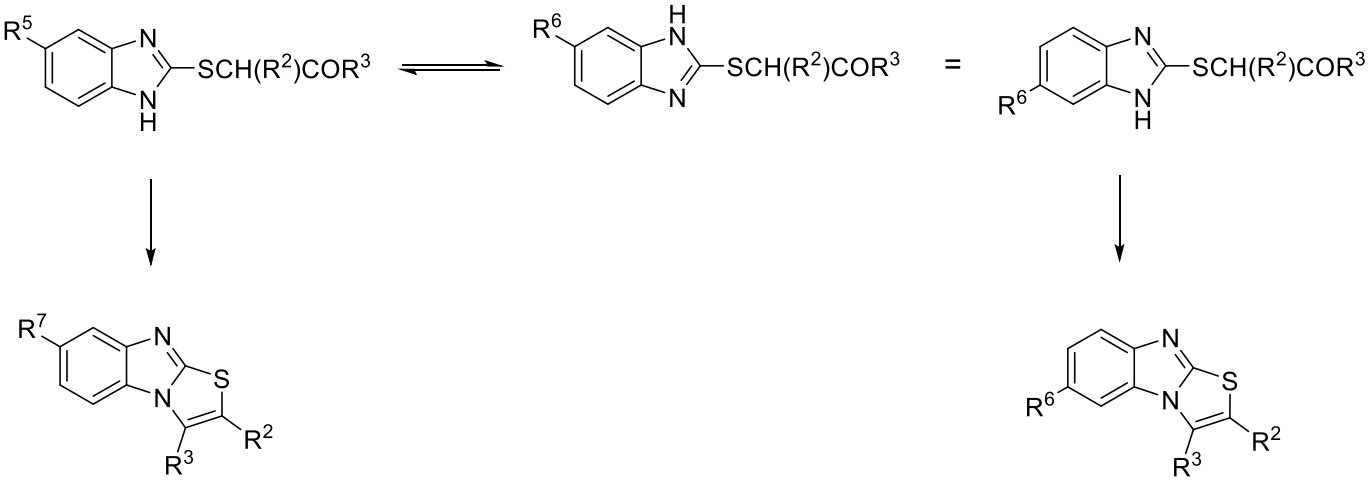


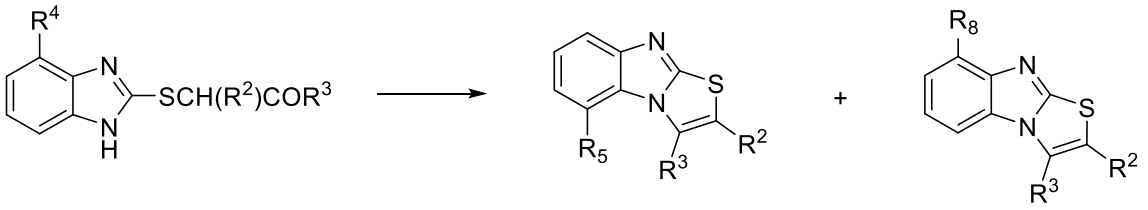
Figure 1.

As part of a drug development programme we wanted to prepare some 6- and 7-substituted thiazolo[3,2-*a*]benzimidazole derivatives, but soon found that none of the existing synthetic methods was able to prepare these compounds in an isomerically distinct manner. A standard route to thiazolo[3,2-*a*]benzimidazoles involves acid-catalyzed ring closure of 2-(acylmethylthio)benzimidazoles,[1,2,5] but for ring substituted benzimidazoles, two ring-closure routes are available, due to tautomerism of the benzimidazole nitrogens (Scheme 1). Thus the ring-closure of 5-substituted 2-(acylmethylthio)benzimidazoles gives rise to the production of isomeric mixtures of 6- and 7-substituted thiazolo[3,2-*a*]benzimidazole products.[6,7]



Scheme 1.

Similarly, 4-substituted 2-(acylmethylthio)benzimidazoles can undergo ring closure to give either 5- or 8-substituted thiazolo[3,2-*a*]benzimidazole products, although the latter are normally preferred for steric reasons (Scheme 2).[8]

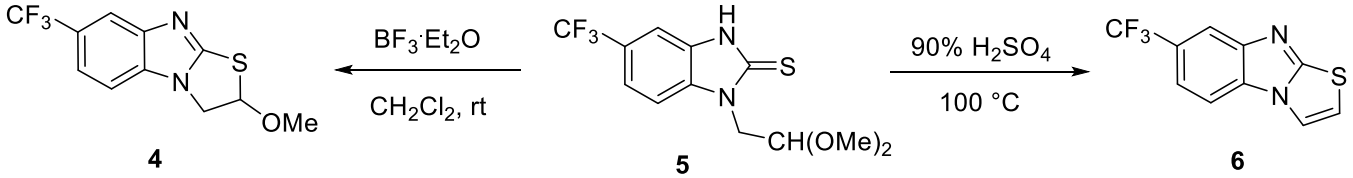


Scheme 2.

There are some reports in the literature claiming single isomeric products from the ring closure of 5-substituted 2-(acylmethylthio)benzimidazoles,[9-11] although NMR studies have confirmed that mixtures of both isomeric products are normally obtained.[6] It is probable that the reports of single products are the result of selective isolation of one isomer, and not of selective synthesis. Several new approaches to the synthesis of thiazolo[3,2-*a*]benzimidazoles have been reported in recent years,[12-19] but unfortunately, none of them provides a general route to individual substituted isomers. Therefore, a search for alternative routes that could result in unequivocal formation of individual isomers was initiated.

Results and Discussion

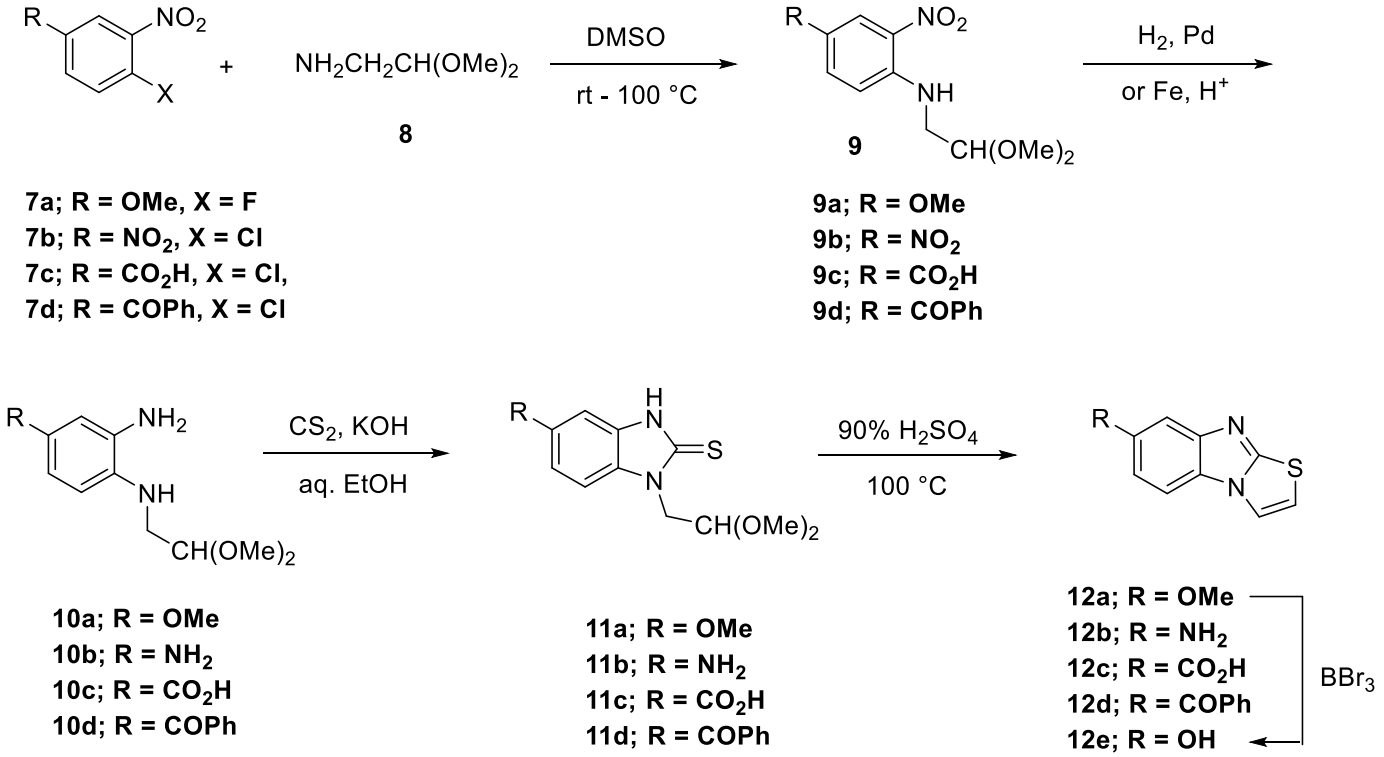
It had been reported that 2-methoxy-7-(trifluoromethyl)-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (**4**) could be prepared by treatment of the dimethylacetal **5** with boron trifluoride diethyl etherate at room temperature (Scheme 3).[20] This result was investigated further, and it was found that by using the stronger ring closure conditions of 90% H_2SO_4 at 100 °C, the analogous 7-(trifluoromethyl)thiazolo[3,2-*a*]benzimidazole (**6**) could be obtained, cleanly and in good yield (Scheme 3).



Scheme 3.

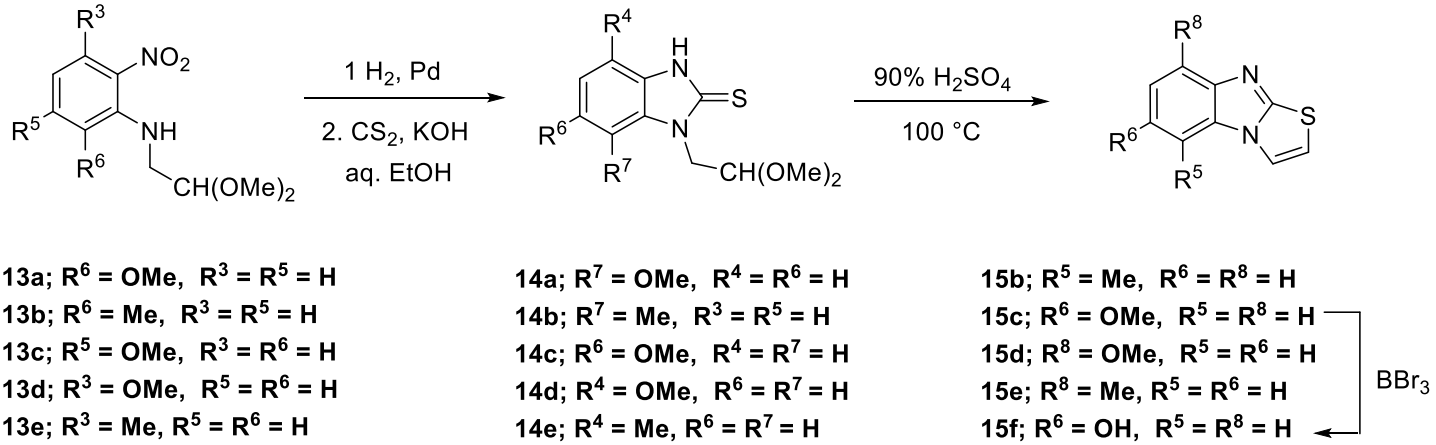
This new route was next investigated for the unequivocal synthesis of other 7-substituted thiazolo[3,2-*a*]benzimidazoles, starting by reaction of the appropriate 4-substituted-1-halo-2-nitrobenzenes (**7a-d**) with 2,2-dimethoxyethylamine (aminoacetaldehyde dimethylacetal) (**8**) (Scheme 4). The resulting 4-substituted-2-nitroaniline derivatives **9a-d** were then reduced to the corresponding diamines **10a-d**, which normally were not isolated, but treated directly with CS_2 and aqueous KOH in EtOH,[21] to give the analogous benzimidazole-2-

thiones **11a-d**. Ring closure with 90% H_2SO_4 at 100 °C then gave the desired 7-substituted thiazolo[3,2-*a*]benzimidazoles **12** (Scheme 4). None of these compounds were previously known, although demethylation of the methoxy derivative **12a** with BBr_3 did give the 7-hydroxy derivative **12e**, which had been reported previously, but without characterization, in a patent.[22]



Scheme 4. Synthesis of 7-substituted thiazolo[3,2-*a*]benzimidazoles

Having established that a variety of 7-substituted thiazolo[3,2-*a*]benzimidazoles could be synthesized in an unequivocal manner, the synthesis of 5-, 6-, and 8-substituted thiazolo[3,2-*a*]benzimidazoles was next investigated (Scheme 5). Unfortunately, the reduction and subsequent reaction of the 6-methoxy derivative **13a** with CS_2 gave an amorphous solid, and not the desired thione **14a**, presumably because of steric inhibition of the ring closure step by the adjacent methoxy group. However, no such problem was observed with the less sterically hindered 6-methyl compound **13b** which successfully gave both the thione **14b** and the thiazolo[3,2-*a*]benzimidazole **15b**. Similarly, the methoxy compounds **13c** and **13d** and methyl compound **13e**, all gave the desired thiones **14c-e** and thiazolo[3,2-*a*]benzimidazoles **15c-e** without any problems. Demethylation of **15c** then gave the known 6-hydroxy compound **15f**.[23]



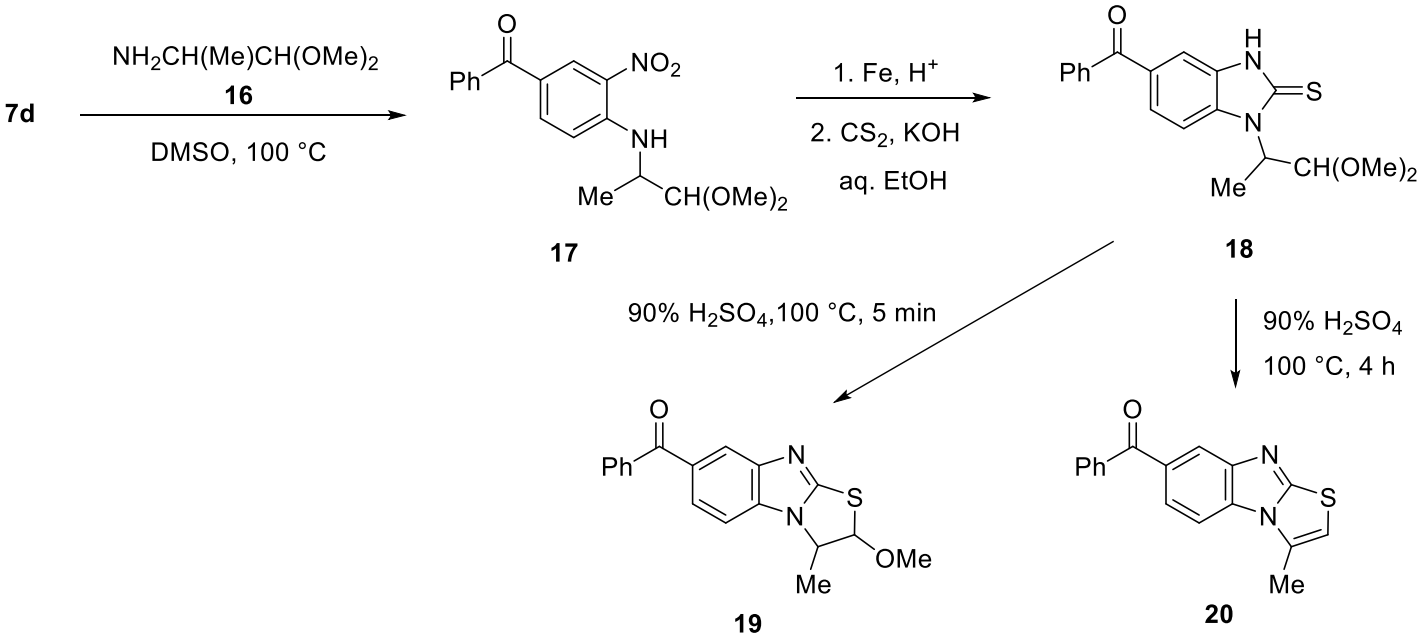
13a; R^6 = OMe, R^3 = R^5 = H
13b; R^6 = Me, R^3 = R^5 = H
13c; R^5 = OMe, R^3 = R^6 = H
13d; R^3 = OMe, R^5 = R^6 = H
13e; R^3 = Me, R^5 = R^6 = H

14a; R^7 = OMe, R^4 = R^6 = H
14b; R^7 = Me, R^3 = R^5 = H
14c; R^6 = OMe, R^4 = R^7 = H
14d; R^4 = OMe, R^6 = R^7 = H
14e; R^4 = Me, R^6 = R^7 = H

15b; R^5 = Me, R^6 = R^8 = H
15c; R^6 = OMe, R^5 = R^8 = H
15d; R^8 = OMe, R^5 = R^6 = H
15e; R^8 = Me, R^5 = R^6 = H
15f; R^6 = OH, R^5 = R^8 = H

Scheme 5. Synthesis of 5-, 7-, and 8-substituted thiazolo[3,2-*a*]benzimidazoles

The synthesis of 3-methylthiazolo[3,2-*a*]benzimidazoles was also investigated, although it was found that longer reaction times were necessary. Formation of the intermediate 2-alkoxy compounds, analogous to compound **4**, did occur rapidly, but the elimination step was much slower. For example, in the ring closure of thione **18** with 90% H_2SO_4, either the 2-methoxy-2,3-dihydro-compound **19** or the desired product **20** could be isolated, depending on the reaction time (Scheme 6). The ^{1}H NMR spectrum of crude **19** showed two isomers in approximate proportions of 77% and 33%. Recrystallization from aqueous MeOH cleanly gave the major component, which was assigned as the *trans* isomer due to the absence of ^3J coupling between the H-2 and H-3 protons. The minor component, which displayed a ^3J coupling of 3.5 Hz, was therefore assigned as the *cis* isomer, although it was never isolated cleanly. Compound **20** had previously been reported as the hydrochloride,[24] although it was probably a mixture of the 6- and 7-benzoyl isomers, due to being produced by a procedure similar to Scheme 1. No evidence to support the 7-isomer structure over the 6-isomer was provided.[24]



17 **18** **19** **20**

Scheme 6. Synthesis of 3-methylthiazolo[3,2-*a*]benzimidazoles

Attempts to extend the acetal procedure to the synthesis of 3-phenylthiazolo[3,2-*a*]benzimidazole derivatives were not successful, with long reaction times being required, which resulted in mixtures of products being obtained, from which the desired compounds could not be isolated in synthetically useful yields.

Conclusions

An efficient route for the unequivocal synthesis of individual substituted thiazolo[3,2-*a*]benzimidazole isomers has been developed, with both 3-unsubstituted, and 3-alkylthiazolo[3,2-*a*]benzimidazoles able to be prepared. Single isomeric products are isolated cleanly, in contrast to the results from several literature methods.

Experimental Section

General. Elemental analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal IA9100 melting point apparatus and are as read. NMR spectra were obtained on a Bruker Avance 400 spectrometer at 400 MHz for proton spectra, and 100 MHz for carbon spectra, referenced to Me_4Si or solvent resonances. Low-resolution atmospheric pressure chemical ionization (APCI) mass spectra were measured for methanol solutions on an Agilent Technologies 6120 Quadrapole LC/MS connected to an Agilent Technologies1260 Infinity autosampler. High-resolution mass spectra were obtained with organic solutions on an Agilent Technologies 6500 Series quadrupole time-of-flight (Q-TOF) LC/MS system. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F254), with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel, (Merck 230 - 400 mesh) unless otherwise stated. Tested compounds were >95% purity, as determined by combustion analysis, or by HPLC conducted on an Agilent 1100 system, using a reversed-phase C8 column with diode array detection.

7-(Trifluoromethyl)thiazolo[3,2-*a*]benzimidazole (**6**)**.** A mixture of 1-chloro-2-nitro-4-(trifluoromethyl)-benzene (2.256 g, 10 mmol) and 2,2-dimethoxyethylamine (**8**) (2.31 g, 22 mmol) in DMSO (10 mL) was stirred at room temperature overnight. Dilution with water gave a yellow solid which was collected by filtration, and dried, to give *N*-(2,2-dimethoxyethyl)-2-nitro-4-(trifluoromethyl)aniline (2.76 g, 94%): mp (from aq. MeOH) 51-53 °C. ^{1}H NMR ($CDCl_3$): δ_H 8.47 (dd, *J* 1.8, 0.6 Hz, 1H), 8.37 (br s, 1H), 7.63 (dd, *J* 9.0, 2.2 Hz, 1H), 6.97 (d, *J* 9.0 Hz, 1H), 4.65 (t, *J* 5.4 Hz, 1H), 3.49 (t, *J* 5.4 Hz, 2H), 3.46 (s, 6H). ^{13}C NMR ($CDCl_3$): δ_C 146.9 (C), 132.3 (q, J_{CF} 3.1 Hz, CH), 131.5 (C), 125.2 (q, J_{CF} 4.1 Hz, CH), 123.8 (q, J_{CF} 270.8 Hz, CF_3), 118.0 (q, J_{CF} 34.4 Hz, C-4), 114.8 (CH), 102.2 (CHO_2), 54.6 (CH_3O), 45.0 (CH_2). MS m/z 263.1 (100%) $(M\text{-}OMe)^+$, m/z 295.1 (80%) $(M+H)^+$.

A solution of *N*-(2,2-dimethoxyethyl)-2-nitro-4-(trifluoromethyl)aniline (2.38 g, 8 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on carbon, and filtered through celite to remove the catalyst. CS_2 (4 mL) and aq. KOH (2.5 g in 20 mL H_2O) were added, and the mixture was heated under gentle reflux for 2 h. After removal of the EtOH, the mixture was diluted with water, and neutralized with HOAc to give 1,3-dihydro-1-(2,2-

dimethoxyethyl)-5-(trifluoromethyl)-2*H*-benzimidazole-2-thione[20] (**5**) as a white solid (2.39 g, 96%). mp (from aq. MeOH) 184-186 °C. ^{1}H NMR [$(CD_3)_2SO$]: δ_H 12.21 (br, 1H, NH), 7.58 (d, *J* 8.5 Hz, 1H, H-7), 7.54 (dd, *J* 8.6, 1.2 Hz, 1H, H-6), 7.41 (br s, 1H, H-4), 4.76 (t, *J* 5.4 Hz, 1H, CHO_2), 4.37 (t, *J* 5.4 Hz, 2H, CH_2N), 3.30 (s, 6H, 2 x CH_3O). ^{13}C NMR [$(CD_3)_2SO$]: δ_c 170.6 (C-2), 135.8 (C), 130.6 (C), 124.5 (q, J_{CF} 271.7 Hz, CF_3), 123.3 (q, J_{CF} 32.2 Hz, C-5), 119.3 (q, J_{CF} 3.7 Hz, C-6), 111.0 (C-7), 106.3 (q, J_{CF} 3.9 Hz, C-4), 101.5 (CHO_2), 54.5 (CH_3O), 45.8 (CH_2). MS m/z 307.1 $(M+H)^+$.

A solution of **5** (0.306 g, 1 mmol) in a mixture of water (5 g) and conc. H_2SO_4 (45 g) was heated at 100 °C for 30 min and poured into ice-water. The mixture was diluted with aq. NH_3 until basic, and extracted with EtOAc to give **6** as a white solid (199 mg, 82 %): mp (from *i*-Pr_2O) 200-203 °C. ^{1}H NMR [$(CD_3)_2SO$]: δ_H 8.49 (d, *J* 4.5 Hz, 1H, H-3), 8.22 (d, *J* 8.5 Hz, 1H, H-5), 8.03 (br s, 1H, H-8), 7.60 (dd, *J* 8.5, 1.0 Hz, 1H, H-6), 7.42 (d, *J* 4.5 Hz, 1H, H-2). ^{13}C NMR [$(CD_3)_2SO$]: δ_c 158.7 (C), 147.1 (C), 131.5 (C), 124.9 (q, J_{CF} 271.9 Hz, CF_3), 124.0 (q, J_{CF} 31.0 Hz, C-7), 119.6 (C-3), 117.1 (q, J_{CF} 3.6 Hz, C-6), 115.6 (q, J_{CF} 4.1 Hz, C-8), 113.1 (C-2), 112.6 (C-5). HRMS (ESI): found m/z 243.0201 $(M+H)^+$, calcd for $C_{10}H_6F_3N_2S$: 243.0198

7-Methoxythiazolo[3,2-*a*]benzimidazole (12). A mixture of 4-fluoro-3-nitroanisole (**7a**) (1.71 g, 10 mmol) and 2,2-dimethoxyethylamine (**8**) (2.31 g, 22 mmol) in DMSO (12 mL) was stirred at room temperature overnight, and diluted with water. Extraction with EtOAc, followed by chromatography on silica, eluting with CH_2Cl_2, gave *N*-(2,2-dimethoxyethyl)-4-methoxy-2-nitroaniline (**9a**) as a red oil (2.36 g, 92 %). ^{1}H NMR ($CDCl_3$): δ_H 8.03 (br s, 1H, NH), 7.62 (d, *J* 3.0 Hz, 1H, H-3), 7.16 (dd, *J* 9.3, 3.1 Hz, 1H, H-5), 6.85 (d, *J* 9.3 Hz, 1H, H-6), 4.62 (t, *J* 5.5 Hz, 1H, CHO_2), 3.80 (s, 3H, CH_3O), 3.45 (s, 6H, 2 x CH_3O), 3.44 (t, *J* 5.5 Hz, 2H, CH_2N). ^{13}C NMR ($CDCl_3$): δ_C 150.0 (C), 141.2 (C), 131.5 (C), 127.3 (CH, C-5), 115.5 (CH, C-6), 107.4 (CH, C-3), 102.5 (CH, CHO_2), 56.0 (CH_3O), 54.4 (2 x CH_3O), 45.2 (CH_2). HRMS (ESI): found m/z 225.0862 $(M-OMe)^+$, Calc for $C_{10}H_{13}N_2O_4$: 225.0870.

A solution of **9a** (2.56 g, 10 mmol) in MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the solution was treated with an excess of CS_2 and aqueous KOH as for the synthesis of **5**. After being heated under gentle reflux for 1 h, the mixture was neutralized with acetic acid, concentrated, and diluted with water, to give 1,3-dihydro-1-(2,2-dimethoxyethyl)-5-methoxy-2*H*-benzimidazole-2-thione (**11a**) as white crystals (1.60 g, 60 %): mp 132-133 °C (from aq. MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 12.71 (br, 1H, exchangeable with D_2O, NH), 7.28 (d, *J* 8.8 Hz, 1H, H-7), 6.79 (dd, *J* 8.8, 2.4 Hz, 1H, H-6), 6.70 (d, *J* 2.4 Hz, 1H, H-4), 4.75 (t, *J* 5.5 Hz, 1H, CHO_2), 4.27 (d, *J* 5.5 Hz, 2H, CH_2N), 3.76 (s, 3H, CH_3O), 3.29 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{12}H_{16}N_2O_3S$ (268.33): C, 53.71; H, 6.01; N, 10.44. Found: C, 53.39; H, 6.29; N, 10.24.

A solution of **11a** (1.24 g, 4.6 mmol) in 85 % H_2SO_4 (50 mL) was heated at 100 °C for 30 min, cooled, and poured onto ice. The resulting aqueous solution was filtered through celite and made basic with aqueous ammonia, to give a precipitate which was collected and dried. Chromatography on alumina, eluting with CH_2Cl_2/EtOAc (9:1) gave **12** as a white solid (0.46 g, 49 %): mp 115-116 °C (from aq. MeOH). ^{1}H NMR ($CDCl_3$): δ_H 7.62 (d, *J* 4.5 Hz, 1H, H-3), 7.51 (d, *J* 8.8 Hz, 1H, H-5), 7.26 (d, *J* 2.4 Hz, 1H, H-8), 6.89 (dd, *J* 8.8, 2.4 Hz, 1H, H-6), 6.77 (d, *J* 4.5 Hz, 1H, H-2), 3.89 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ_C 157.2 (C), 149.6 (C), 124.5 (C), 117.8 (CH, C-3), 110.8 (CH, C-6), 110.7 (CH, C-5), 110.4 (CH, C-2), 101.8 (CH, C-8), 56.0 (CH_3O). MS m/z 205.1 $(M+H)^+$. Anal. calcd for $C_{10}H_8N_2OS$ (204.25): C, 58.80; H, 3.95; N, 13.72. Found: C, 58.68; H, 3.70; N, 13.57.

7-Aminothiazolo[3,2-*a*]benzimidazole (12b). A mixture of 1-chloro-2,4-dinitrobenzene (**7b**) (10.13 g, 5 mmol), 2,2-dimethoxyethylamine (**8**) (12.6 g, 6 mmol), and Et_3N (15 g, 7.5 mmol) in DMSO (50 mL) at room temperature was stirred for 5 min, acidified with acetic acid, diluted with water, and extracted with EtOAc, to give *N*-(2,2-dimethoxyethyl)-2,4-dinitroaniline (**9b**) as a yellow oil (13.6 g, 100 %): mp 61-62 °C (from EtOH). ^{1}H

NMR [$(CD_3)_2SO$]: δ_H 8.85 (d, *J* 2.7 Hz, 1H, H-3), 8.74 (br, 1H, NH), 8.26 (dd, *J* 9.6, 2.7 Hz, 1H, H-5), 7.30 (d, *J* 9.7 Hz, 1H, H-6), 4.66 (t, *J* 5.2 Hz, 1H, CHO_2), 3.56 (t, *J* 5.4 Hz, 2H, CH_2N), 3.35 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{10}H_{13}N_3O_6$ (271.23): C, 44.28; H, 4.83; N, 15.49. Found: C, 44.45; H, 4.56; N, 15.70.

A solution of **9b** (5.43 g, 20 mmol) in MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the resulting solution was treated with excess CS_2/KOH as for above examples. After being heated under gentle reflux for 1h, the mixture was acidified with acetic acid, and concentrated. Aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc to give 5-amino-1,3-dihydro-1-(2,2-dimethoxyethyl)-2*H*-benzimidazole-2-thione (**11b**) as a white solid (3.1 g, 61 %): mp 202-204 °C (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 12.31 (br s, 1H, NH), 7.03 (d, *J* 8.5 Hz, 1H, H-7), 6.44 (dd, *J* 8.5, 2.0 Hz, 1H, H-6), 6.40 (d, *J* 1.8 Hz, 1H, H-4), 5.02 (br, 2H, NH_2), 4.74 (t, *J* 5.5 Hz, 1H, CHO_2), 4.19 (d, *J* 5.5 Hz, 2H, CH_2N), 3.28 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{11}H_{15}N_3O_2S$ (253.32): C, 52.16; H, 5.97; N, 16.59; S, 12.66. Found: C, 52.36; H, 6.24; N, 16.72; S, 12.90.

A solution of **11b** (1.01 g, 4 mmol) in 90 % H_2SO_4 was heated at 100 °C for 5 min, cooled, and poured onto ice. The resulting solution was made basic with aqueous ammonia, and extracted with EtOAc, to give **12b** as a white solid (0.74 g, 98 %): mp 219-221 °C (from aq. MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 8.21 (d, *J* 4.5 Hz, 1H, H-3), 7.61 (d, *J* 8.4 Hz, 1H, H-5), 7.13 (d, *J* 4.5 Hz, 1H, H-2), 6.78 (d, *J* 2.0 Hz, 1H, H-8), 6.57 (dd, *J* 8.6, 2.0 Hz, 1H, H-6), 4.95 (br s, 2H, NH_2). ^{13}C NMR [$(CD_3)_2SO$]: δ_C 155.3 (C), 149.3 (C), 145.3 (C), 122.1 (C), 119.8 (CH), 111.1 (CH), 109.8 (CH), 109.6 (CH), 101.5 (CH). Anal. calcd for $C_9H_7N_3S$ (189.24): C, 57.12; H, 3.73; N, 22.21. Found: C, 57.23; H, 3.87; N, 22.51.

Thiazolo[3,2-*a*]benzimidazole-7-carboxylic Acid (12c). A mixture of 4-chloro-3-nitrobenzoic acid (**7c**) (5.04 g (25 mmol), 2,2-dimethoxyethylamine (**8**) (7.90 g, 75 mmol) and Et_3N (4 mL) in DMSO (30 mL) was heated at 100 °C for 14 h, acidified with acetic acid, and diluted with water, to give 4-[(2,2-dimethoxyethyl)amino]-3-nitrobenzoic acid (**9c**) as a white solid (6.21 g, 92 %): mp 187-189.5 °C (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 12.92 (br, 1H, CO_2H), 8.61 (d, *J* 2.1 Hz, 1H, H-2), 8.44 (t, *J* 5.5 Hz, 1H, NH), 7.97 (dd, *J* 9.1, 2.0 Hz, 1H, H-6), 7.19 (d, *J* 9.1 Hz, 1H, H-5), 4.66 (t, *J* 5.2 Hz, 1H, CHO_2), 3.56 (t, *J* 5.4 Hz, 2H, CH_2N), 3.35 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{11}H_{14}N_2O_6$ (270.24): C, 48.89; H, 5.22; N, 10.37. Found: C, 49.05; H, 5.20; N, 10.61.

A mixture of **9c** (5.40 g, 20 mmol) and KOH (1.5 g) in aqueous MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the resulting solution was treated with an excess of CS_2 and KOH as for previous examples. After being heating at gentle reflux over night, the reaction mixture was concentrated, filtered through celite, and acidified with acetic acid, to give 2,3-dihydro-1-(2,2-dimethoxyethyl)-2-thioxo-1*H*-benzimidazole-5-carboxylic acid (**11c**) as a white solid (4.02 g, 59 %): mp 248 °C (dec) (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 13.10 (br s, 1H, NH), 12.92 (br, 1H, CO_2H), 7.82 (dd, *J* 8.3, 1.5 Hz, 1H, H-6), 7.70 (d, *J* 1.4 Hz, 1H, H-4), 7.47 (d, *J* 8.4 Hz, 1H, H-7), 4.77 (t, *J* 5.4 Hz, 1H, CHO_2), 4.35 (d, *J* 5.4 Hz, 2H, CH_2N), 3.30 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{12}H_{14}N_2O_4S$ (282.31): C, 51.05; H, 5.00; N, 9.92. Found: C, 51.14; H, 4.84; N, 10.02.

A suspension of 2,3-dihydro-1-(2,2-dimethoxyethyl)-2-thioxo-1*H*-benzimidazole-6-carboxylic acid (**11c**) (2.82 g, 1 mmol) in 90 % H_2SO_4 (100 mL) was heated at 100 °C for 10 min to give a clear solution. After cooling, the solution was poured onto ice, and aqueous ammonia was added until the mixture was just basic. After filtration, the solution was acidified with acetic acid, to give **12c** as a white solid (2.13 g, 98 %): mp 307-309 °C (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 13.0 (br, 1H, CO_2H), 8.47 (d, *J* 4.6 Hz, 1H, H-3), 8.28 (br s, 1H, H-8), 8.11 (d, *J* 8.4 Hz, 1H, H-5), 7.92 (dd, *J* 8.4, 1.3 Hz, 1H, H-6), 7.39 (d, *J* 4.6 Hz, 1H, H-2). ^{13}C NMR [$(CD_3)_2SO$]: δ_C 167.7 (C), 158.1 (C), 147.3 (C), 132.2 (C), 125.8 (C), 121.7 (CH), 120.0 (CH), 119.4 (CH), 112.8 (CH), 111.4 (CH). Anal. calcd for $C_{11}H_{10}N_2OS$ (218.23): C, 55.04; H, 2.77; N, 12.84. Found: C, 55.09; H, 2.85; N, 13.00.

7-Benzoylthiazolo[3,2-*a*]benzimidazole (12d). A mixture of 4-chloro-3-nitrobenzophenone (**7d**) (5.23 g, 20 mmol) and 2,2-dimethoxyethylamine (**8**) (5.26 g, 50 mmol) in DMSO (50 mL) was heated at 100 °C overnight. After treatment with aqueous acetic acid, to hydrolyze imine byproducts, the solution was diluted with water to give 4-[(2,2-dimethoxyethyl)amino]-3-nitrobenzophenone (**9d**) as a yellow solid (6.11 g, 93%). mp 98-99.5 °C (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 8.57 (t, *J* 5.5 Hz, 1H, NH), 8.44 (d, *J* 2.1 Hz, 1H, H-2), 7.95 (dd, *J* 9.0, 2.1 Hz, 1H, H-6), 7.73-7.65 (m, 3H, H-2´ ,4´,6´), 7.58 (t, *J* 7.5 Hz, 2H, H-3´, 5´), 7.29 (d, *J* 9.2 Hz, 1H, H-5), 4.68 (t, *J* 5.2 Hz, 1H, CHO_2), 3.61 (t, *J* 5.5 Hz, 2H, CH_2N), 3.37 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{17}H_{18}N_2O_5$ (330.34): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.97; H, 5.64; N, 8.75.

A mixture of **9d** (4.95 g, 15 mmol), Fe powder (5.04 g, 60 mmol) and HOAc (1 mL) in 65 % aqueous EtOH (150 mL) was heated under reflux for 30 min. Excess aq. NH_3 was added and the mixture was boiled to coagulate Fe salts. The mixture was filtered through celite, washing with EtOH. Removal of the EtOH under vacuum, and extraction with EtOAc gave 3-amino-4-[(2,2-dimethoxyethyl)amino]benzophenone (**10d**) as a red oil (4.50 g, 100 %). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 7.61-7.54 (m, 3H, H-2´,4´,6´), 7.49 (t, *J* 6.7 Hz, 2H, H-3´, 5´), 7.12 (d, *J* 2.0 Hz, 1H, H-2), 6.99 (dd, *J* 8.3, 2.0 Hz, 1H, H-6), 6.54 (d, *J* 8.4 Hz, 1H, H-5), 5.40 (t, *J* 5.7 Hz, 1H, NH), 4.86 (br s, 2H, NH_2), 4.56 (t, *J* 5.4 Hz, 1H, CHO_2), 3.36 (s, 6H, 2 x CH_3O) 3.28 (t, *J* 5.5 Hz, 2H, CH_2N).

A mixture of crude **10d** (4.5 g, 15 mmol), CS_2 (2.3 g, 30 mmol) and KOH (2.0 g, 36 mmol) in 80 % aqueous EtOH (100 mL) was heated under gentle reflux for 1 h and cooled. Neutralization with acetic acid then gave 5-benzoyl-1,3-dihydro-1-(2,2-dimethoxyethyl)-2*H*-benzimidazole-2-thione (**11d**) as a white solid (4.83 g, 94 %): mp 170-180 °C (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 13.11 (br s, 1H, NH), 7.74-7.50 (m, 8H), 4.80 (t, *J* 5.4 Hz, 1H, CHO_2), 4.38 (d, *J* 5.4 Hz, 2H, CH_2N), 3.32 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{18}H_{18}N_2O_3S$ (342.41): C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found: C, 63.05; H, 5.04; N, 8.27; S, 9.30.

A solution of **11d** (2.0 g, 5.8 mmol) in 90 % H_2SO_4 (100 mL) was heated at 100 °C for 5 min, cooled, and poured onto ice. After being made basic with conc. aq. NH_3 solution, the mixture was extracted with EtOAc, to give **12d** as a white solid (1.58 g, 97 %): mp 162-163 °C (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 8.51 (d, *J* 4.6 Hz, 1H), 8.17 (d, *J* 8.4 Hz, 1H), 8.02 (d, *J* 1.1 Hz, 1H), 7.79-7.68 (m, 4H), 7.59 (t, *J* 7.5 Hz, 2H), 7.42 (d, *J* 4.6 Hz, 1H). ^{13}C NMR [$(CD_3)_2SO$]: δ_C 195.6 (CO), 158.3 (C), 147.0 (C), 137.7 (C), 132.2 (CH), 132.1 (C), 132.0 (C), 129.5 (2 x CH), 128.4 (2 x CH), 122.2 (CH), 120.8 (CH), 119.4 (CH), 112.9 (CH), 111.6 (CH). Anal. calcd for $C_{16}H_{10}N_2OS$ (278.33): C, 69.05; H, 3.62; N, 10.06. Found: C, 69.05; H, 3.68; N, 10.21.

7-Hydroxythiazolo[3,2-*a*]benzimidazole (12e).[22] A mixture of 7-methoxythiazolo[3,2-*a*]benzimidazole (**12a**) (0.204 g, 1 mmol) and BBr_3 (1*M* in CH_2Cl_2,, 4 mL, 4 mmol) in CH_2Cl_2 (20 mL) was heated under reflux for 5 h, and the solvent was removed. The residue was mixed with ice-water, and neutralized with aqueous $NaHCO_3$, to give **12e** as a white solid (0.14 g, 74 %). mp 294-296 °C (from aq. MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 9.27 (s, 1H, OH), 8.28 (d, *J* 4.5 Hz, 1H, H-3), 7.75 (d, *J* 8.7 Hz, 1H, H-5), 7.19 (d, *J* 4.5 Hz, 1H, H-2), 6.97 (d, *J* 2.1 Hz, 1H, H-8), 6.74 (dd, *J* 8.7, 2.3 Hz, 1H, H-6). ^{13}C NMR [$(CD_3)_2SO$]: δ_c 156.2 (C), 154.1 (C), 149.0 (C), 123.5 (C), 119.4 (CH, C-3), 111.4 (CH, C-5), 110.4 (CH, C-2), 110.0 (CH, C-6), 103.1 (CH, C-8). Anal. calcd for $C_9H_6N_2OS$ (190.22): C, 56.83; H, 3.18; N, 14.73. Found: C, 56.94; H, 3.29; N, 14.95.

5-Methylthiazolo[3,2-*a*]benzimidazole (15b). A mixture of 2-fluoro-3-nitrotoluene (1.55 g, 1 mmol), 2,2-dimethoxyethylamine (**8**) (1.26 g, 1.2 mmol), and DIEPA (1.55 g, 1.2 mmol) in DMSO (10 mL) was stirred at 100 °C for 4 h, cooled, acidified with acetic acid, diluted with water, and extracted with EtOAc, to give N-(2,2-dimethoxyethyl)-2-methyl-6-nitroaniline (**13b**) (2.30 g, 96%): ^{1}H NMR ($CDCl_3$): δ_H 7.88 (dd, *J* 8.4, 1.1 Hz, 1H, H-

5), 7.31 (br d, *J* 7.3 Hz, 1H, H-4), 6.82 (dd, *J* 8.3, 7.4 Hz, 1H, H-3), 6.70 (br s, 1H, NH), 4.38 (t, *J* 5.6 Hz, 1H, CHO_2), 3.36 (s, 6H, 2 x CH_3O), 3.30 (t, *J* 5.8 Hz, 2H, CH_2N), 2.39 (s, 3H, CH_3). MH^+ 241.2

A solution of crude **13b** (2.30 g, 0.96 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite to remove the catalyst. A solution of KOH (0.56 g, 10 mmol) in H_2O (10 mL) and CS_2 (0.76 g, 10 mmol) were added and the mixture was heated under gentle reflux overnight. After being concentrated, the solution was diluted with water and neutralized with HOAc to give 1-(2,2-dimethoxyethyl)-4-methyl-1,3-dihydro-2*H*-benzimidazole-2-thione (**14b**) as a white solid (1.645 g, 68%). mp (from MeOH) 210-212 °C. ^{1}H NMR [$(CD_3)_2SO$]: δ_H 12.84 (br, 1H, NH), 7.07-7.01 (m, 2H), 6.96-6.92 (m, 1H), 4.80 (t, *J* 5.6 Hz, 1H, CHO_2), 4.51 (d, *J* 5.6 Hz, 2H, CH_2N), 3.29 (s, 6H, 2 x CH_3O), 2.64 (s, 3H, CH_3). MH^+ 253.2

A solution of **14b** (0.252 g, 1 mmol) in a mixture of H_2SO_4 (45 g) and H_2O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. Neutralization with aq NH_3 and extraction with EtOAc gave **15b** as a white solid (91 mg, 48%). mp (from aq. MeOH) 171-173 °C. ^{1}H NMR ($CDCl_3$): δ_H 7.84 (d, *J* 4.6 Hz, 1H, H-3), 7.62 (d, *J* 8.2 Hz, 1H, H-8), 7.25 (dd, *J* 8.1, 7.5 Hz, 1H, H-7), 7.02 (dt, *J* 7.3, 0.8 Hz, 1H, H-6), 6.78 (d, *J* 4.6, 1H, H-2), 2.72 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 157.1 (C), 148.5 (C), 129.5 (C), 123.7 (CH, C-7), 122.5 (CH, C-6), 121.6 (C), 119.5 (CH, C-3), 117.1 (CH, C-8), 110.5 (CH, C-2), 18.1 (CH_3). HRMS (ESI): found m/z 189.0481 $(M+H)^+$, calcd for $C_{10}H_9N_2S$: 189.0481.

6-Methoxythiazolo[3,2-*a*]benzimidazole (15c). A mixture of 3-fluoro-4-nitroanisole (1.71 g, 10 mmol), 2,2-dimethoxyethylamine (**8**) (2.11 g, 20 mmol) in DMSO (12 mL), was stirred at room temperature for 1 h and diluted with water, to give *N*-(2,2-dimethoxyethyl)-5-methoxy-2-nitroaniline (**13c**) as a yellow solid (2.42 g, 94 %): mp 76-78 °C (from MeOH). ^{1}H NMR ($CDCl_3$): δ_H 8.37 (br, 1H, NH), 8.15 (d, *J* 9.5 Hz, 1H, H-3), 6.26 (dd, *J* 9.5 , 2.6 Hz, 1H, H-4), 6.19 (d, *J* 2.5 Hz, 1H, H-6), 4.65 (t, *J* 5.5 Hz, 1H, CHO_2), 3.86 (s, 3H, CH_3O), 3.46 (s, 6H, 2 x CH_3O), 3.42 (t, *J* 5.4 Hz, 2H, CH_2N). Anal. calcd for $C_{11}H_{16}N_2O_5$ (256.26): C, 51.56; H, 6.29; N, 10.93. Found: C, 51.74; H, 6.54; N, 11.10.

A solution of **13c** (2.30 g, 9 mmol) in MeOH was hydrogenated over Pd/C, and after filtration to remove the catalyst, the solution was treated with an excess of CS_2 and aqueous KOH. After being heated under gentle reflux for 1 h, the mixture was concentrated, diluted with water, and acidified with HOAc,to give 1,3-dihydro-1-(2,2-dimethoxyethyl)-6-methoxy-2*H*-benzimidazole-2-thione (**14c**) as a white solid (2.0 g, 83 %): mp 127-129 °C (from MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 12.67 (br, 1 H, NH), 7.07 (d, *J* 8.7 Hz, 1H, H-4), 6.99 (d, *J* 2.3 Hz, 1H, H-7), 6.78 (dd, *J* 8.6, 2.3 Hz, 1H, H-5), 4.78 (t, *J* 5.4 Hz, 1H, CHO_2), 4.30 (d, *J* 5.5 Hz, 2H, CH_2N), 3.78 (s, 3H, CH_3O), 3.31 (s, 6H, 2 x CH_3O). Anal. calcd for $C_{12}H_{16}N_2O_3S{\cdot}0.75H_2O$ (281.84): C, 51.13; H, 6.33; N, 9.94. Found: C, 50.86; H, 5.77; N, 9.91.

A solution of **14c** (1.34 g, 5 mmol) in 85 % H_2SO_4 (50 mL) was heated at 100 °C for 30 min, cooled, and poured onto ice. The resulting aqueous solution was filtered through celite and made basic with aqueous ammonia, to give a precipitate, which was collected and dried. Chromatography on alumina, eluting with CH_2Cl_2/EtOAc (9:1) gave **15c** as a white solid (0.37 g, 36 %): mp 137-139 °C (from MeOH). ^{1}H NMR ($CDCl_3$): δ_H 7.67 (d, *J* 8.9 Hz, 1H, H-8), 7.62 (d, *J* 4.6 Hz, 1H, H-3), 7.14 (d, *J* 2.4 Hz, 1H, H-5), 7.01 (dd, *J* 8.9, 2.5 Hz, 1H, H-7), 6.79 (d, *J* 4.6 Hz, 1H, H-2), 3.90 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ_C 155.6 (C), 155.4 (C), 143.1 (C), 130.0 (C), 120.0 (CH, C-8), 117.4 (CH, C-3), 112.8 (CH, C-7), 110.8 (CH, C-2), 94.5 (CH, C-5), 56.2 (CH_3O). MS m/z 205.1 $(M+H)^+$. Anal. calcd for $C_{10}H_8N_2OS$ (204.25): C, 58.80; H, 3.95; N, 13.72. Found: C, 58.98; H, 4.01; N, 13.86.

8-Methoxythiazolo[3,2-*a*]benzimidazole (15d). A mixture of 3-fluoro-2-nitroanisole (3.42 g, 20 mmol) and 2,2-dimethoxyethylamine (**8**) (4.21 g, 40 mmol) in DMSO (20 mL) was heated at 60 °C for 6h, cooled and diluted with water. Extraction with EtOAc gave *N*-(2,2-dimethoxyethyl)-3-methoxy-2-nitroaniline (**13d**) as red oil, which solidified on standing (4.85 g, 95%). mp 36-38 °C (from *i*-Pr_2O). ^{1}H NMR ($CDCl_3$): δ_H 7.24 (t, *J* 8.4 Hz, 1H, H-5), 6.38 (d, *J* 8.5 Hz, 1H), 6.30 (d, *J* 8.3 Hz, 1H), 6.10 (br, 1H, NH), 4.56 (t, *J* 5.6 Hz, 1H, CHO_2), 3.87 (s, 3H, CH_3O), 3.42 (s, 6H, 2 x CH_3O), 3.31 (t, *J*, 5.5 Hz, 2H, CH_2N). ^{13}C NMR ($CDCl_3$): δ_C 155.1 (C), 143.8 (C), 133.6 (CH, C-5), 128.2 (C), 105.4 (CH), 102.4 (CHO_2), 100.3 (CH), 56.6 (CH_3O), 54.3 (2 x CH_3O), 45.3 (CH_2). MS m/z 257.2 $(M+H)^+$.

A solution of **13d** (1.024 g, 4 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite. CS_2 (2 mL) and KOH (1.6 g in 10 mL H_2O) were added and the mixture was heated under reflux for 4 h. The solution was concentrated, diluted with water and neutralized with HOAc to give 1-(2,2-dimethoxyethyl)-4-methoxy-1,3-dihydro-2*H*-benzimidazole-2-thione (**14d**) as a white solid (0.58 g, 54%). mp 179-181 °C (from aq. MeOH). ^{1}H NMR ($CDCl_3$): δ_H 12.99 (s, 1H, NH), 7.12 (t, *J* 8.1 Hz, 1H, H-6), 6.99 (d, *J* 7.9 Hz, 1H), 6.81 (d, *J* 8.1 Hz, 1H), 4.78 (t, *J* 5.5 Hz, 1H, CHO_2), 4.28 (d, *J* 5.5 Hz, 2H, CH_2N), 3.88 (s, 3H, CH_3O), 3.28 (s, 6H, 2 x CH_3O). ^{13}C NMR ($CDCl_3$): δ_C 168.1 (C), 143.9 (C), 134.4 (C), 123.0 (CH), 120.1 (C), 105.0 (CH), 103.3 (CHO_2), 101.4 (CH), 55.8 (CH_3O), 54.3 (2 x CH_3O), 45.8 (CH_2). MS m/z 269.1 $(M+H)^+$.

A solution of **14d** (0.268 g, 1 mmol) in a mixture of H_2SO_4 (45 g) and H_2O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. After neutralization with aq. NH_3 the mixture was extracted with EtOAc to give **15d** as a white solid (78 mg, 38%). mp (from aq. MeOH) 166-168 °C. ^{1}H NMR ($CDCl_3$): δ_H 7.64 (d, *J* 4.6 Hz, 1H, H-3), 7.26 (dd, *J* 8.1, 0.9 Hz, 1H), 7.18 (t, *J* 8.0 Hz, 1H, H-6), 6.81 (dd, *J* 8.0, 0.6 Hz, 1H), 6.80 (d, *J* 4.6 Hz, 1H, H-2), 4.05 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ_C 155.4 (C), 150.9 (C), 138.7 (C), 130.9 (C), 121.8 (CH), 117.7 (CH, C-3), 111.3 (CH, C-2), 104.4 (CH), 103.4 (CH), 56.1 (CH_3O). HRMS (ESI): found m/z 205.0432 $(M+H)^+$, calcd for $C_{10}H_9N_2OS$: 205.0430.

8-Methylthiazolo[3,2-*a*]benzimidazole (15e). A mixture of 3-fluoro-2-nitrotoluene (3.10 g, 20 mmol) and 2,2-dimethoxyethylamine (**8**) (4.60 g, 44 mmol) in DMSO (10 mL) was heated at 100 °C overnight**.** Dilution with water and extraction with EtOAc gave *N*-(2,2-dimethoxyethyl)-3-methyl-2-nitroaniline (**13e**) as an orange oil which solidified on standing (4.82 g, 100%). mp (from *i*-Pr_2O) 38-39 °C. ^{1}H NMR ($CDCl_3$): δ_H 7.22 (t, *J* 8.0 Hz, 1H, H-5), 6.67 (d, *J* 8.5 Hz, 1H), 6.56 (d, *J* 7.4 Hz, 1H), 6.48 (br, 1H, NH), 4.58 (t, *J* 5.6 Hz, 1H, CHO_2), 3.43 (s, 6H, 2 x CH_3O), 3.33 (t, *J*, 5.5 Hz, 2H, CH_2N), 2.46 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 143.5 (C), 136.7 (C), 135.5 (C), 133.3 (CH), 119.8 (CH), 111.4 (CH), 102.4 (CHO_2), 54.3 (CH_3O), 45.3 (CH_2), 21.3 (CH_3). MS m/z 241.2 $(M+H)^+$.

A solution of **13e** (2.40 g, 1 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite. CS_2 (5 mL) and KOH (2.5 g in 10 mL H_2O) were added and the mixture was heated under reflux for 3 h. The solution was concentrated, diluted with water abd neutralized with HOAc to give 1-(2,2-dimethoxyethyl)-4-methyl-1,3-dihydro-2H-benzimidazole-2-thione (**14e**) as a white solid (2.306 g, 91%). mp (from aq. MeOH) 171-174 °C. ^{1}H NMR [$(CD_3)_2SO$]: δ_H 12.89 (s, 1H), 7.20 (d, *J* 8.0 Hz, 1H), 7.08 (t, *J* 7.8 Hz, 1H, H-6), 6.97 (d, *J* 7.5 Hz, 1H), 4.79 (t, *J* 5.5 Hz, 1H, CHO_2), 4.30 (d, *J* 5.5 Hz, 2H, CH_2N), 3.29 (s, 6H, 2 x CH_3O), 2.39 (s, 3H, CH_3). MS m/z 253.2 $(M+H)^+$.

A solution of **14e** (0.505 g, 0.2 mmol) in a mixture of H_2SO_4 (45 g) and H_2O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. After neutralization with aq. NH_3 the mixture was extracted with EtOAc to give **15e** as a white solid (0.318 g, 84%). mp (from aq. MeOH) 150-152 °C. ^{1}H NMR ($CDCl_3$): δ_H 7.64 (d, *J* 4.6 Hz, 1H, H-3), 7.48 (dd, *J* 6.8, 2.2 Hz, 1H, H-6), 7.19-7.14 (m, 2H, H-5, 7), 6.78 (d, *J* 4.6 Hz, 1H, H-2), 2.70 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ_C 156.2 (C), 147.8 (C), 129.4 (C), 129.3 (C), 124.1 (CH), 121.0 (CH), 117.8 (CH, C-3), 110.8 (CH, C-2), 107.9 (CH, C-6), 17.1 (CH_3). HRMS (ESI): found m/z 189.0480 $(M+H)^+$, calcd for $C_{10}H_9N_2S$: 189.0481.

6-Hydroxythiazolo[3,2-*a*]benzimidazole (15f).[23] A mixture of 6-methoxythiazolo[3,2-*a*]benzimidazole (0.23 g, 1.13 mmol) and BBr_3 (1*M* in CH_2Cl_2,, 4 mL, 4 mmol) in CH_2Cl_2 (20 mL) was heated under reflux for 6 h, and the solvent was removed. The residue was then mixed with ice-water, and neutralized with aqueous ammonia, to give **15f** as a white solid (0.17 g, 79 %). mp 298-303 °C (from aq. MeOH) (lit.[23] mp > 280 °C). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 9.39 (s, 1H, OH), 8.27 (d, *J* 4.6 Hz, 1H, H-3), 7.45 (d, *J* 8.7 Hz, 1H, H-8), 7.32 (d, *J* 2.3 Hz, 1H, H-5), 7.18 (d, *J* 4.6 Hz, 1H, H-2), 6.83 (dd, *J* 8.8, 2.4 Hz, 1H, H-7). ^{13}C NMR [$(CD_3)_2SO$]: δ_c 154.1 (C), 152.3 (C), 141.3 (C), 130.0 (C), 119.1 (CH, C-3), 118.7 (CH, C-8), 112.8 (CH, C-7), 110.7 (CH, C-2), 97.0 (CH, C-5). Anal. calcd for $C_9H_6N_2OS$ (190.22): C, 56.83; H, 3.18; N, 14.73. Found: C, 56.73; H, 3.11; N, 14.85.

1,1-Dimethoxy-2-propylamine[26] **(16).** A mixture of 1,1-dimethoxyacetone (23.6 g, 0.2 mol) and benzylamine (21.4 g, 0.2 mol) in toluene (100 mL) was heated under reflux with a Dean-Stark condenser until water evolution ceased. The toluene was removed under vacuum and the residue was dissolved in EtOH (100 mL). The solution was treated with $NaBH_4$ (3.78 g, 0.1 mol) and the resulting mixture was heated under reflux for 30 min. After cooling, acetic acid was added to destroy excess $NaBH_4$, and the solvent was removed under vacuum. The residue was made basic with aqueous ammonia, and extracted with CH_2Cl_2. Elution through alumina with CH_2Cl_2 gave *N*-benzyl-1,1-dimethoxy-2-propylamine[25] as an oil (36.8 g, 88 %): ^{1}H NMR ($CDCl_3$): δ_H 7.34-7.30 (m, 4H, ArH), 7.26-7.21 (m, 1H, ArH), 4.14 (d, *J* 6.3 Hz, 1H, CHO_2), 3.89 (d, *J* 13.1 Hz, 1H, benzyl CH), 3.70 (d, *J* 13.2 Hz, 1H, benzyl CH), 3.38 (s, 3H, CH_3O), 3.35 (s, 3H, CH_3O), 2.84 (pentet, *J* 6.3 Hz, 1H, CHN), 1.82 (br s, 1H, NH), 1.10 (d, *J* 6.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 140.4 (C), 128.4 (2 x CH), 128.1 (2 x CH), 126.8 (CH), 107.9 (CHO_2), 54.7 (CH_3O), 54.5 (CH_3O), 53.5 (CHN), 51.1 (CH_2N), 14.9 (CH_3).

Hydrogenation of the above amine over 10% Pd on carbon in MeOH, gave 1,1-dimethoxy-2-propylamine[26] (**16**) as an oil: ^{1}H NMR ($CDCl_3$): δ_H 3.98 (d, *J* 6.0 Hz, 1H, CHO_2), 3.43 (s, 3H, CH_3O), 3.40 (s, 3H, CH_3O), 3.01 (pentet, *J* 6.4 Hz, 1H, CHN), 1.67 (s, 2H, NH_2), 1.09 (d, *J* 6.6 Hz, 3H, CH_3).

***trans*-7-Benzoyl-2-methoxy-3-methyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (19).** A mixture of 4-chloro-3-nitrobenzophenone (**7d**) (2.62 g, 10 mmol), **16** (1.54 g, 13 mmol) and Et_3N (2 mL) in DMSO (30 mL) was heated at 100 °C for 14 h. The mixture was diluted with water and acetic acid, and extracted into EtOAc. The organic layer was washed with aqueous Na_2CO_3 solution, dried, and the solvent was removed, to give (**17**) as a yellow solid (3.1 g, 90 %): mp 92-94 °C (from *i*-PrOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 8.57 (d, *J* 8.5 Hz, 1H, NH), 8.44 (d, *J* 2.1 Hz, 1H, H-2), 7.95 (dd, *J* 9.2, 2.0 Hz, 1H, H-6), 7.73-7.65 (m, 3H, H-2′,4′,6′), 7.57 (t, *J* 7.5 Hz, 2H, H-3′,5′), 7.33 (d, *J* 9.3 Hz, 1H, H-5), 4.49 (t, *J* 3.9 Hz, 1H, CHO_2), 4.17 (m, 1H, CHN), 3.43 (s, 3H, CH_3O), 3.42 (s, 3H, CH_3O), 1.22 (d, *J* 6.6 Hz, 3H, CH_3). Anal. calcd for $C_{18}H_{20}N_2O_5$ (344.37): C, 62.78; H, 5.85; N, 8.13. Found: C, 62.96; H, 6.12; N, 8.16.

A solution of **17** (3.0 g, 8.7 mmol) in 65 % aqueous EtOH was reduced with Fe powder as for the reduction of **9d,** to give crude 3-amino-4-[*N*-(1,1-dimethoxy-2-propyl)amino]benzophenone (2.7 g). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 7.60-7.55 (m, 3H, H-2′,4′,6′), 7.49 (t, *J* 7.5 Hz, 2H, H-3′,5′), 7.12 (d, *J* 2.0 Hz, 1H, H-2), 6.98 (dd, *J* 8.3, 2.0 Hz, 1H, H-6), 6.57 (d, *J* 8.5 Hz, 1H, H-5), 5.08 (d, *J* 8.2 Hz, 1H, NH), 4.85 (br s, 2H, NH_2), 4.32 (t, *J* 4.6 Hz, 1H, CHO_2), 3.78-3.72 (m, 1H, CHN), 3.36 (s, 3H, CH_3O), 3.34 (s, 3H, CH_3O), 1.14 (d, *J* 6.5 Hz, 3H, CH_3).

Crude diamino product was treated with an excess of CS_2 and aqueous KOH in MeOH, as for the synthesis of **11d**. After being heated under gentle reflux for 1 h, the reaction mixture was concentrated, diluted with

water, cooled, and acidified with acetic acid, to give an oil, which was extracted into EtOAc. Chromatography on silica, eluting with CH_2Cl_2/EtOAc (9:1), gave 5-benzoyl-1,3-dihydro-1-(1,1-dimethoxy-2-propyl)-2*H*-benzimidazole-2-thione (**18**) (2.7 g, 87 %): mp 151-152.5 °C (from aq. MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 13.10 (br s, 1H, NH), 7.79-7.72 (m, 3H, 3 x ArH), 7.68 (t, *J* 7.4 Hz, 1H, ArH), 7.59-7.55 (m, 3H, 3 x ArH), 7.51 (d, *J* 1.3 Hz, ArH), 5.42 (m, 1H, CHN), 4.38 (m, 1H, CHO_2), 3.41 (s, 3H, CH_3O), 3.21 (s, 3H, CH_3O), 1.48 (d, *J* 5.5 Hz, 3H, CH_3). Anal. calcd for $C_{19}H_{20}N_2O_3S$ (356.44): C, 64.02; H, 5.66; N, 7.86; S, 8.99. Found: C, 64.16; H, 5.80; N, 7.87; S, 9.06.

A solution of **18** (0.20 g, 0.56 mmol) in 90 % H_2SO_4 (10 mL) was heated at 100 °C for 5 min, cooled, and poured onto ice. The solution was made basic with conc. ammonia solution to give a white solid which was collected by filtration and recrystallized from aqueous MeOH to give **19**: mp 136-137 °C. ^{1}H NMR ($CDCl_3$): δ_H 8.06 (dd, *J* 1.5, 0.5 Hz, 1H, H-8), 7.82-7.78 (m, 3H, H-6, 2′, 6′), 7.60-7.55 (m, 1H, H-4′), 7.50 (m, 2H, H-3′, 5′), 7.32 (dd, *J* 8.4, 0.5 Hz, 1H, H-5), 5.56 (s, 1H, H-2), 4.80 (q, *J* 6.8 Hz, 1H, H-3), 3.48 (s, 3H, CH_3O), 1.52 (d, *J* 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ_C 196.8 (CO), 157.7 (C), 148.6 (C), 138.5 (C), 136.1 (C), 132.2 (CH, C-4′), 131.8 (C), 130.2 (CH, C-2′, 6′), 128.4 (CH, C-3′, 5′), 124.7 (CH, C-6), 122.3 (CH, C-8), 108.5 (CH, C-5), 100.9 (CH, C-2), 59.7 (CH, C-3), 57.0 (CH_3O), 17.0 (CH_3). MS m/z 325.1 $(M+H)^+$. Anal. calcd for $C_{18}H_{16}N_2O_2S$ (324.40): C, 66.65; H, 4.97; N, 8.64 Found: C, 67.02; H , 5.05; N, 8.74.

7-Benzoyl-3-methylthiazolo[3,2-*a*]benzimidazole (20). A solution of 5-Benzoyl-1,3-dihydro-1-(1,1-dimethoxy-2-propyl)-2*H*-benzimidazole-2-thione (**18**) (0.20 g, 0.56 mmol) in 90 % H_2SO_4 (10 mL) was heated at 100 °C for 3 h, cooled, and poured onto ice. After being made basic with conc. ammonia solution, the mixture was extracted with EtOAc. Chromatography on alumina, eluting with CH_2Cl_2 gave 7-benzoyl-3-methylthiazolo[3,2-*a*]benzimidazole (**20**): mp 122-123.5 °C (from aq. MeOH). ^{1}H NMR [$(CD_3)_2SO$]: δ_H 8.13 (d, *J* 8.4 Hz, 1H, H-5), 8.01 (d, *J* 1.4 Hz, 1H, H-8), 7.76-7.72 (d, *J* 7.5 Hz, 2H, H-2′, 6′), 7.72-7.68 (m, 2H, H-6, H-6, 4′), 7.59 (br t, *J* 7.5 Hz, 2H, H-3′, 5′), 6.97 (d, *J* 1.3 Hz, 1H, H-2), 2.78 (d, *J* 1.1 Hz, 3H, CH_3). ^{13}C NMR [$(CD_3)_2SO$]: δ_C 195.5 (s, CO), 158.4 (C), 147.1 (C), 137.7 (C), 132.4 (C), 132.2 (CH), 131.7 (C), 130.1 (C), 129.5 (2 x CH), 128.4 (2 x CH), 121.9 (CH), 120.6 (CH), 111.4 (CH), 106.6 (CH), 13.7 (CH_3). Anal. calcd for $C_{17}H_{12}N_2OS$ (292.36): C, 69.84; H, 4.14; N, 9.58. Found: C, 70.03; H, 3.99; N, 9.45.

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Supplementary Material

Copies of ^{1}H NMR spectra are available in the supplementary material associated with this paper

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