

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

Gordon W. Rewcastle*

Auckland Cancer Society Research Centre, School of Medical Sciences, Faculty of Medical and Health Sciences,
and Maurice Wilkins Centre for Molecular Biodiscovery, The University of Auckland, Private Bag 92019,
Auckland 1142, New Zealand
Email: g.rewcastle@auckland.ac.nz

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

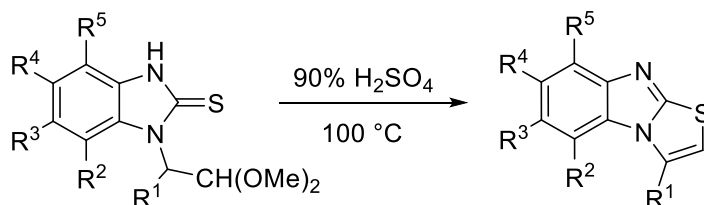
Received 08-18-2020

Accepted 09-29-2020

Published on line 11-01-2020

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 Tilomisolet (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

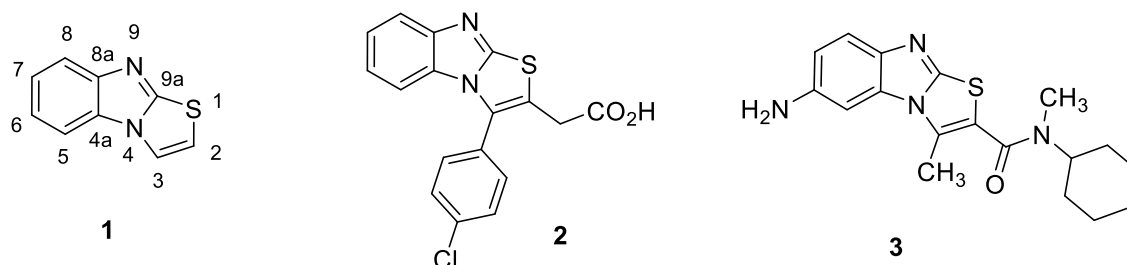
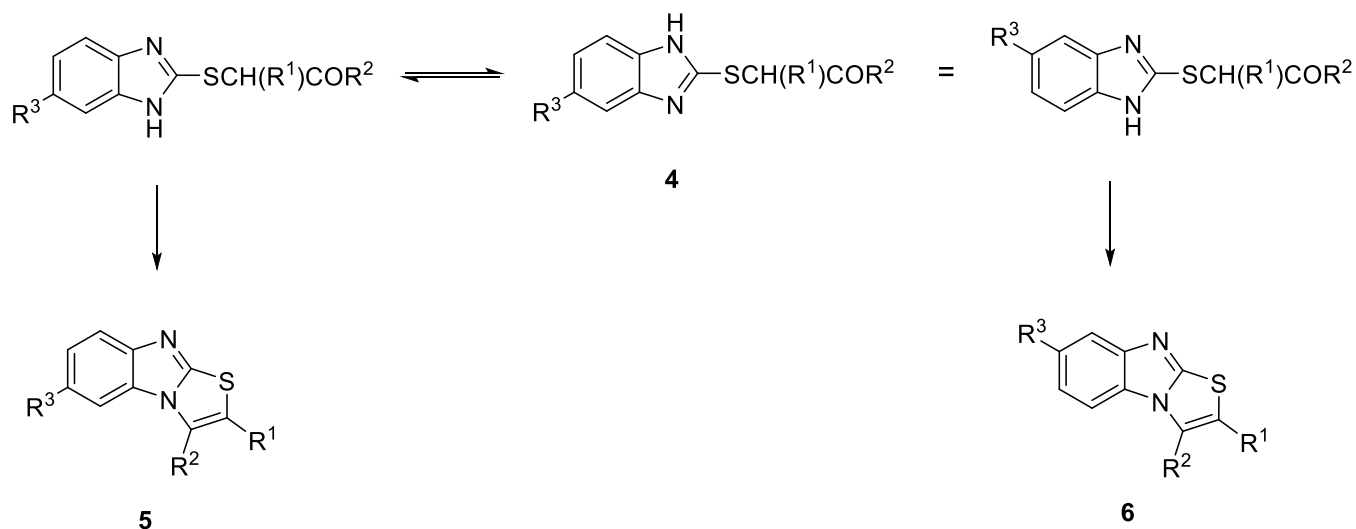


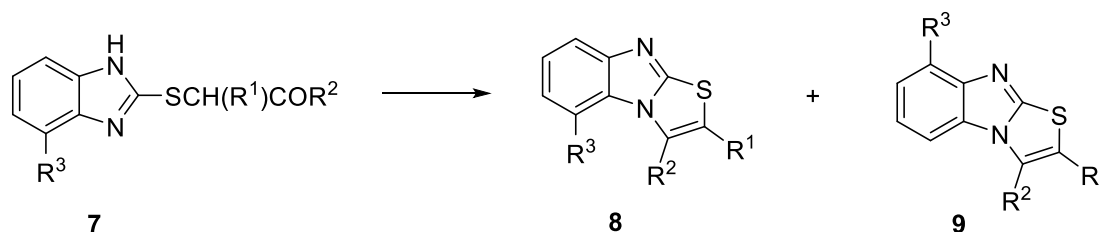
Figure 1

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 (**4**) gives rise to the production of isomeric mixtures of 6- and 7-substituted thiazolo[3,2-*a*]benzimidazole products (**5** and **6**).^{6,7}



Scheme 1

Similarly, 4-substituted 2-(acylmethylthio)benzimidazoles (**7**) can undergo ring closure to give either 5- or 8-substituted thiazolo[3,2-*a*]benzimidazole products (**8** and **9**), although the latter are normally preferred for steric reasons (Scheme 2).⁸

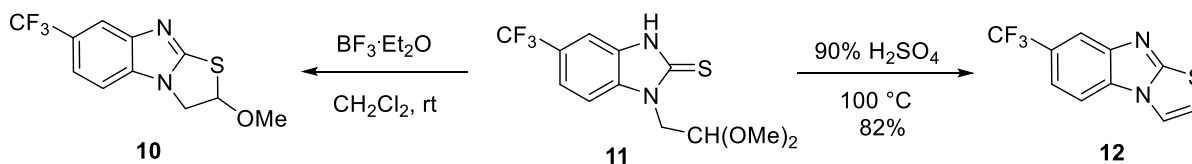


Scheme 2

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.

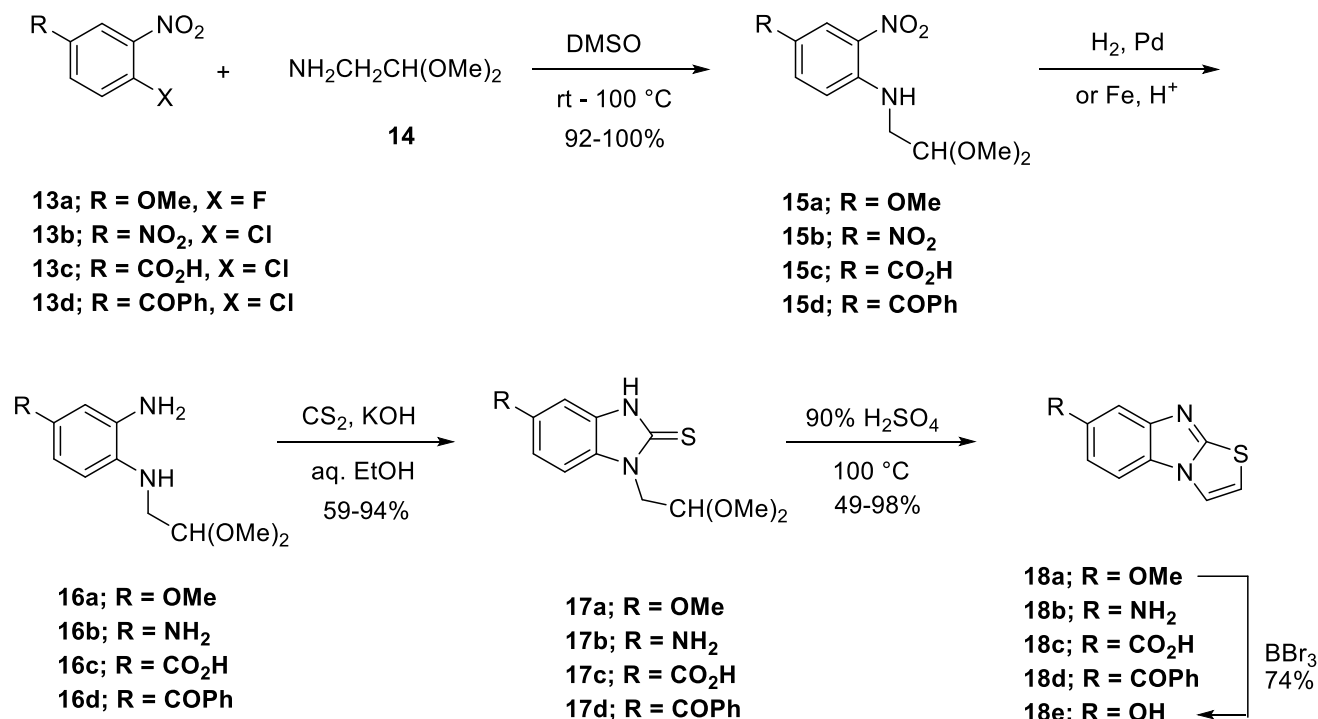
Results and Discussion

It had been reported that 2-methoxy-7-(trifluoromethyl)-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (**10**) could be prepared by treatment of the dimethylacetal **11** 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% H₂SO₄ at 100 °C, the analogous 7-(trifluoromethyl)thiazolo[3,2-*a*]benzimidazole (**12**) could be obtained, cleanly and in good yield (Scheme 3).



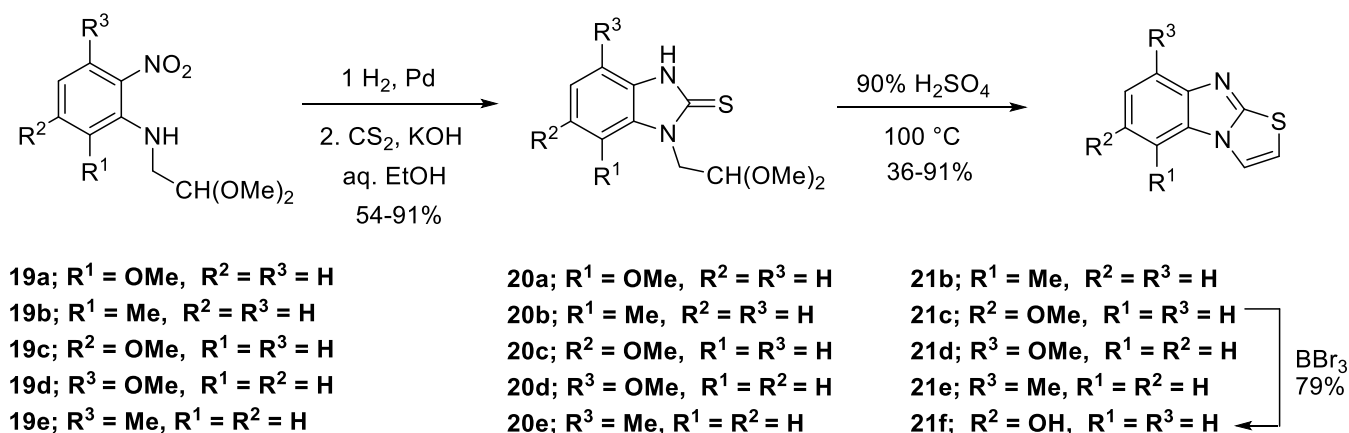
Scheme 3

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 (**13a-d**) with 2,2-dimethoxyethylamine (aminoacetaldehyde dimethylacetal) (**14**) (Scheme 4). The resulting 4-substituted-2-nitroaniline derivatives **15a-d** were then reduced to the corresponding diamines **16a-d**, which normally were not isolated, but treated directly with CS₂ and aqueous KOH in EtOH,²¹ to give the analogous benzimidazole-2-thiones **17a-d**. Ring closure with 90% H₂SO₄ at 100 °C then gave the desired 7-substituted thiazolo[3,2-*a*]benzimidazoles **18a-d** (Scheme 4). None of these compounds were previously known, although demethylation of the methoxy derivative **18a** with BBr₃ did give the 7-hydroxy derivative **18e**, which had been reported previously, but without characterization, in a patent.²²



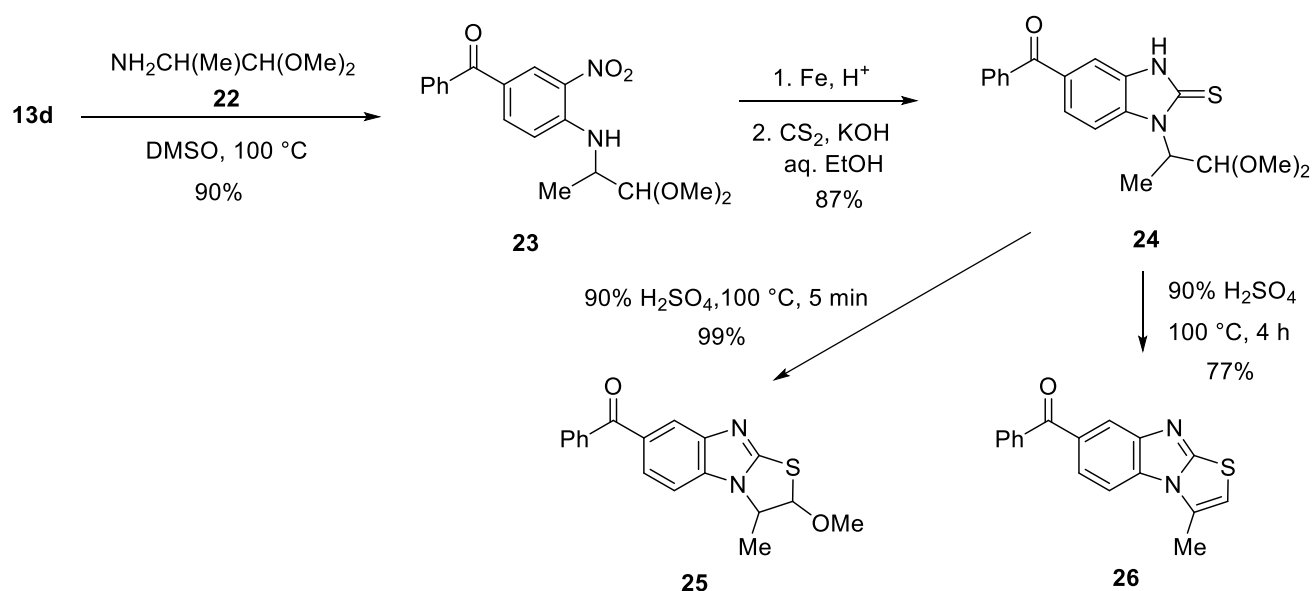
Scheme 4. Synthesis of 7-substituted thiazolo[3,2-*a*]benzimidazoles.

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 **19a** with CS₂ gave an amorphous solid, and not the desired thione **20a**, 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 **19b** which successfully gave both the thione **20b** and the thiazolo[3,2-*a*]benzimidazole **21b**. Similarly, the methoxy compounds **19c** and **19d** and methyl compound **19e**, all gave the desired thiones **20c-e** and thiazolo[3,2-*a*]benzimidazoles **21c-e** without any problems. Demethylation of **21c** then gave the known 6-hydroxy compound **21f**.²³



Scheme 5. Synthesis of 5-, 6-, 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 **10**, did occur rapidly, but the elimination step was much slower. For example, in the ring closure of thione **24** with 90% H₂SO₄, either the 2-methoxy-2,3-dihydro-compound **25** or the desired product **26** could be isolated, depending on the reaction time (Scheme 6). The ¹H NMR spectrum of crude **25** 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 **26** 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



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 Me₄Si or solvent resonances. Low-resolution atmospheric pressure chemical ionization (APCI) mass spectra were measured for methanol solutions on an Agilent Technologies 6120 Quadrupole LC/MS connected to an Agilent Technologies 1260 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 (12). A mixture of 1-chloro-2-nitro-4-(trifluoromethyl)-benzene (2.256 g, 10 mmol) and 2,2-dimethoxyethylamine (**14**) (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. ¹H NMR (CDCl₃): 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). ¹³C NMR (CDCl₃): 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, CF₃), 118.0 (q, *J*_{CF} 34.4 Hz, C-4), 114.8 (CH), 102.2 (CHO₂), 54.6 (CH₃O), 45.0 (CH₂). MS *m/z* 263.1 (100%) (M-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. CS₂ (4 mL) and aq. KOH (2.5 g in 20 mL H₂O) 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-thione²⁰ (**11**) as a white solid (2.39 g, 96%). mp (from aq. MeOH) 184-186 °C. ¹H NMR [(CD₃)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, CHO₂), 4.37 (t, *J* 5.4 Hz, 2H, CH₂N), 3.30 (s, 6H, 2 x CH₃O). ¹³C NMR [(CD₃)₂SO]: δ_C 170.6 (C-2), 135.8 (C), 130.6 (C), 124.5 (q, *J*_{CF} 271.7 Hz, CF₃), 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 (CHO₂), 54.5 (CH₃O), 45.8 (CH₂). MS *m/z* 307.1 (M+H)⁺.

A solution of **11** (0.306 g, 1 mmol) in a mixture of water (5 g) and conc. H₂SO₄ (45 g) was heated at 100 °C for 30 min and poured into ice-water. The mixture was diluted with aq. NH₃ until basic, and extracted with EtOAc to give **12** as a white solid (199 mg, 82%): mp (from *i*-Pr₂O) 200-203 °C. ¹H NMR [(CD₃)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). ¹³C NMR [(CD₃)₂SO]: δ_C 158.7 (C), 147.1 (C), 131.5 (C), 124.9 (q, *J*_{CF} 271.9 Hz, CF₃), 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 C₁₀H₆F₃N₂S: 243.0198

7-Methoxythiazolo[3,2-*a*]benzimidazole (18a). A mixture of 4-fluoro-3-nitroanisole (**13a**) (1.71 g, 10 mmol) and 2,2-dimethoxyethylamine (**14**) (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 CH₂Cl₂, gave *N*-(2,2-dimethoxyethyl)-4-methoxy-2-nitroaniline (**15a**) as a red oil (2.36 g, 92%). ¹H NMR (CDCl₃):

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, CHO₂), 3.80 (s, 3H, CH₃O), 3.45 (s, 6H, 2 x CH₃O), 3.44 (t, J 5.5 Hz, 2H, CH₂N). ¹³C NMR (CDCl₃): 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, CHO₂), 56.0 (CH₃O), 54.4 (2 x CH₃O), 45.2 (CH₂). HRMS (ESI): found m/z 225.0862 (M-OMe)⁺, Calc for C₁₀H₁₃N₂O₄: 225.0870.

A solution of **15a** (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 CS₂ and aqueous KOH as for the synthesis of **11**. 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-2H-benzimidazole-2-thione (**17a**) as white crystals (1.60 g, 60%): mp 132-133 °C (from aq. MeOH). ¹H NMR [(CD₃)₂SO]: δ_{H} 12.71 (br, 1H, exchangeable with D₂O, 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, CHO₂), 4.27 (d, J 5.5 Hz, 2H, CH₂N), 3.76 (s, 3H, CH₃O), 3.29 (s, 6H, 2 x CH₃O). ¹³C NMR [(CD₃)₂SO]: δ_{C} 168.0 (C), 156.1 (C), 131.3 (C), 127.4 (C), 110.9 (CH, C-7), 109.6 (CH, C-6), 101.5 (CHO₂), 94.3 (CH, C-4), 55.6 (CH₃O), 54.3 (2 x CH₃O), 45.6 (CH₂). MS m/z 269.2 (M+H)⁺. Anal. calcd for C₁₂H₁₆N₂O₃S (268.33): C, 53.71; H, 6.01; N, 10.44. Found: C, 53.39; H, 6.29; N, 10.24.

A solution of **17a** (1.24 g, 4.6 mmol) in 85% H₂SO₄ (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 CH₂Cl₂/EtOAc (9:1) gave **18a** as a white solid (0.46 g, 49%): mp 115-116 °C (from aq. MeOH). ¹H NMR (CDCl₃): 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, CH₃O). ¹³C NMR (CDCl₃): 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 (CH₃O). MS m/z 205.1 (M+H)⁺. Anal. calcd for C₁₀H₈N₂OS (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 (18b). A mixture of 1-chloro-2,4-dinitrobenzene (**13b**) (10.13 g, 5 mmol), 2,2-dimethoxyethylamine (**14**) (12.6 g, 6 mmol), and Et₃N (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 (**15b**) as a yellow oil (13.6 g, 100%): mp 61-62 °C (from EtOH). ¹H NMR (CDCl₃): δ_{H} 9.13 (d, J 2.7 Hz, 1H, H-3), 8.68 (br, 1H, NH), 8.28 (dd, J 9.5, 2.7 Hz, 1H, H-5), 6.96 (d, J 9.5 Hz, 1H, H-6), 4.67 (t, J 5.3 Hz, 1H, CHO₂), 3.56 (t, J 5.3 Hz, 2H, CH₂N), 3.48 (s, 6H, 2 x CH₃O). ¹³C NMR (CDCl₃): δ_{C} 148.4 (C), 136.5 (C), 130.9 (C), 130.5 (CH, C-5), 124.4 (CH, C-3), 114.3 (CH, C-6), 102.0 (CHO₂), 54.8 (2 x CH₃O), 45.3 (CH₂). MS m/z 240.1 (100%) (M-OMe)⁺, 272.1 (20%) (M+H)⁺. Anal. calcd for C₁₀H₁₃N₃O₆ (271.23): C, 44.28; H, 4.83; N, 15.49. Found: C, 44.45; H, 4.56; N, 15.70.

A solution of **15b** (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 CS₂/KOH as for above examples. After being heated under gentle reflux for 1h, the mixture was acidified with acetic acid, and concentrated. Aqueous NaHCO₃ was added, and the mixture was extracted with EtOAc to give 5-amino-1,3-dihydro-1-(2,2-dimethoxyethyl)-2H-benzimidazole-2-thione (**17b**) as a white solid (3.1 g, 61%): mp 202-204 °C (from MeOH). ¹H NMR [(CD₃)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, NH₂), 4.74 (t, J 5.5 Hz, 1H, CHO₂), 4.19 (d, J 5.5 Hz, 2H, CH₂N), 3.28 (s, 6H, 2 x CH₃O). ¹³C NMR [(CD₃)₂SO]: δ_{C} 166.3 (CS), 145.4 (C), 131.7 (C), 124.7 (C), 110.6 (CH, C-7), 109.7 (CH, C-6), 101.4 (CHO₂), 94.2 (CH, C-4), 54.2 (2 x CH₃O), 45.5 (CH₂). MS m/z 254.2 (M+H)⁺. Anal. calcd for C₁₁H₁₅N₃O₂S (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 **17b** (1.01 g, 4 mmol) in 90% H₂SO₄ 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 **18b** as a

white solid (0.74 g, 98%): mp 219-221 °C (from aq. MeOH). ^1H NMR $[(\text{CD}_3)_2\text{SO}]$: 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 $[(\text{CD}_3)_2\text{SO}]$: 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). MS m/z 190.2 (M+) $^+$. Anal. calcd for $\text{C}_9\text{H}_7\text{N}_3\text{S}$ (189.24): C, 57.12; H, 3.73; N, 22.21. Found: C, 57.23; H, 3.87; N, 22.51.

Thiazolo[3,2- α]benzimidazole-7-carboxylic Acid (18c). A mixture of 4-chloro-3-nitrobenzoic acid (**13c**) (5.04 g (25 mmol), 2,2-dimethoxyethylamine (**14**) (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 (**15c**) as a yellow solid (6.21 g, 92%): mp 187-189.5 °C (from MeOH). ^1H NMR $[(\text{CD}_3)_2\text{SO}]$: 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). ^{13}C NMR $[(\text{CD}_3)_2\text{SO}]$: δ_{C} 165.8 (C), 147.3 (C), 136.0 (CH, C-6), 130.6 (C), 128.3 (CH, C-2), 117.5 (C), 115.0 (CH, C-5), 101.8 (CHO_2), 53.9 (2 x CH_3O), 44.2 (CH_2). MS m/z 269.1 (M-H) $^-$. Anal. calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_6$ (270.24): C, 48.89; H, 5.22; N, 10.37. Found: C, 49.05; H, 5.20; N, 10.61.

A mixture of **15c** (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-1H-benzimidazole-5-carboxylic acid (**17c**) as a white solid (4.02 g, 59%): mp 248 °C (dec) (from MeOH). ^1H NMR $[(\text{CD}_3)_2\text{SO}]$: 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). ^{13}C NMR $[(\text{CD}_3)_2\text{SO}]$: δ_{C} 170.3 (CS), 167.1 (CO_2), 136.3 (C), 130.5 (C), 125.3 (C), 123.9 (CH, C-6), 110.4 (CH, C-4), 110.1 (CH, C-7), 101.4 (CHO_2), 54.4 (2 x CH_3O), 45.7 (CH_2). MS m/z 281.1 (M-H) $^-$. Anal. calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$ (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-1H-benzimidazole-6-carboxylic acid (**17c**) (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 **18c** as a white solid (2.13 g, 98%): mp 307-309 °C (from MeOH). ^1H NMR $[(\text{CD}_3)_2\text{SO}]$: 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 $[(\text{CD}_3)_2\text{SO}]$: 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). MS m/z 217.0 (M-H) $^-$. Anal. calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_5\text{S}$ (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- α]benzimidazole (18d). A mixture of 4-chloro-3-nitrobenzophenone (**13d**) (5.23 g, 20 mmol) and 2,2-dimethoxyethylamine (**14**) (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 (**15d**) as a yellow solid (6.11 g, 93%). mp 98-99.5 °C (from MeOH). ^1H NMR $[(\text{CD}_3)_2\text{SO}]$: 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). ^{13}C NMR (CDCl_3): δ_{C} 193.7 (CO), 147.7 (C), 137.7 (C), 137.2 (CH, C-6), 132.4 (CH, C-4'), 131.4 (C), 130.9 (CH, C-2), 129.7 (CH, C-2', 6'), 128.7 (CH, C-3', 5'), 125.1 (C), 114.1 (CH, C-5), 102.1 (CH, CHO_2), 54.6 (2 x CH_3O), 45.0 (CH_2). MS m/z 331.2 (M+) $^+$. Anal. calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5$ (330.34): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.97; H, 5.64; N, 8.75.

A mixture of **15d** (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. NH₃ 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 (**16d**) as a red oil (4.50 g, 100%). ¹H NMR [(CD₃)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, NH₂), 4.56 (t, *J* 5.4 Hz, 1H, CHO₂), 3.36 (s, 6H, 2 x CH₃O) 3.28 (t, *J* 5.5 Hz, 2H, CH₂N).

A mixture of crude **16d** (4.5 g, 15 mmol), CS₂ (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 (**17d**) as a white solid (4.83 g, 94%): mp 170-180 °C (from MeOH). ¹H NMR [(CD₃)₂SO]: δ_H 13.11 (br s, 1H, NH), 7.74-7.50 (m, 8H), 4.80 (t, *J* 5.4 Hz, 1H, CHO₂), 4.38 (d, *J* 5.4 Hz, 2H, CH₂N), 3.32 (s, 6H, 2 x CH₃O). ¹³C NMR [(CD₃)₂SO]: δ_C 194.9 (CO), 170.5 (CS), 137.6 (C), 136.4 (C), 132.3 (CH, C-4'), 131.5 (C), 130.5 (C), 129.4 (CH, C-2', 6'), 128.5 (CH, C-3', 5'), 124.9 (CH, C-6), 111.0 (CH, C-4), 110.2 (CH, C-6), 101.4 (CHO₂), 54.5 (2 x CH₃O), 45.8 (CH₂). MS *m/z* 343.1 (M+H)⁺. Anal. calcd for C₁₈H₁₈N₂O₃S (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 **17d** (2.0 g, 5.8 mmol) in 90% H₂SO₄ (100 mL) was heated at 100 °C for 5 min, cooled, and poured onto ice. After being made basic with conc. aq. NH₃ solution, the mixture was extracted with EtOAc, to give **18d** as a white solid (1.58 g, 97%): mp 162-163 °C (from MeOH). ¹H NMR [(CD₃)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). ¹³C NMR [(CD₃)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). MS *m/z* 279.1 (M+H)⁺. Anal. calcd for C₁₆H₁₀N₂OS (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 (18e).²² A mixture of 7-methoxythiazolo[3,2-*a*]benzimidazole (**18a**) (0.204 g, 1 mmol) and BBr₃ (1*M* in CH₂Cl₂, 4 mL, 4 mmol) in CH₂Cl₂ (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 NaHCO₃, to give **18e** as a white solid (0.14 g, 74%). mp 294-296 °C (from aq. MeOH). ¹H NMR [(CD₃)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). ¹³C NMR [(CD₃)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). MS *m/z* 191.1 (M+H)⁺. Anal. calcd for C₉H₆N₂OS (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 (21b). A mixture of 2-fluoro-3-nitrotoluene (1.55 g, 1 mmol), 2,2-dimethoxyethylamine (**14**) (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 (**19b**) (2.30 g, 96%): ¹H NMR (CDCl₃): 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, CHO₂), 3.36 (s, 6H, 2 x CH₃O), 3.30 (t, *J* 5.8 Hz, 2H, CH₂N), 2.39 (s, 3H, CH₃). ¹³C NMR (CDCl₃): δ_C 145.0 (C), 140.1 (C), 137.5 (CH, C-3), 131.0 (C), 124.2 (CH, C-5), 119.4 (CH, C-4), 103.4 (CHO₂), 54.3 (2 x CH₃O), 49.1 (CH₂), 20.3 (CH₃). MS *m/z* 241.2 (M+H)⁺.

A solution of crude **19b** (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 H₂O (10 mL) and CS₂ (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 (**20b**) as a white solid (1.645 g, 68%). mp (from MeOH) 210-212 °C. ¹H NMR [(CD₃)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, CHO₂), 4.51

(d, *J* 5.6 Hz, 2H, CH₂N), 3.29 (s, 6H, 2 x CH₃O), 2.64 (s, 3H, CH₃). ¹³C NMR [(CD₃)₂SO]: δ_c 168.4 (CS), 131.2 (C), 131.0 (C), 125.4 (CH, C-5), 122.7 (CH), 121.0 (C), 107.8 (CH), 101.8 (CHO₂), 55.1 (2 x CH₃O), 47.1 (CH₂), 18.6 (CH₃). HRMS (ESI): found *m/z* 221.0737 (M-OMe)⁺, Calc for C₁₁H₁₃N₂O₅: 221.0748.

A solution of **20b** (0.252 g, 1 mmol) in a mixture of H₂SO₄ (45 g) and H₂O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. Neutralization with aq NH₃ and extraction with EtOAc gave **21b** as a white solid (91 mg, 48%). mp (from aq. MeOH) 171-173 °C. ¹H NMR (CDCl₃): 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, CH₃). ¹³C NMR (CDCl₃): 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 (CH₃). HRMS (ESI): found *m/z* 189.0481 (M+H)⁺, calcd for C₁₀H₉N₂S: 189.0481.

6-Methoxythiazolo[3,2-*a*]benzimidazole (21c). A mixture of 3-fluoro-4-nitroanisole (1.71 g, 10 mmol), 2,2-dimethoxyethylamine (**14**) (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 (**19c**) as a yellow solid (2.42 g, 94%): mp 76-78 °C (from MeOH). ¹H NMR (CDCl₃): 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, CHO₂), 3.86 (s, 3H, CH₃O), 3.46 (s, 6H, 2 x CH₃O), 3.42 (t, *J* 5.4 Hz, 2H, CH₂N). ¹³C NMR (CDCl₃): δ_c 166.1 (C-2), 147.7 (C-5), 129.5 (CH, C-3), 127.1 (C-1), 104.9 (CH, C-4), 102.4 (CHO₂), 95.7 (CH, C-6), 55.9 (CH₃O), 54.4 (2 x CH₃O), 45.0 (CH₂). MS *m/z* 257.2 (M+H)⁺. Anal. calcd for C₁₁H₁₆N₂O₅ (256.26): C, 51.56; H, 6.29; N, 10.93. Found: C, 51.74; H, 6.54; N, 11.10.

A solution of **19c** (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 CS₂ 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 (**20c**) as a white solid (2.0 g, 83%): mp 127-129 °C (from MeOH). ¹H NMR [(CD₃)₂SO]: δ_H 12.67 (br, 1H, 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, CHO₂), 4.30 (d, *J* 5.5 Hz, 2H, CH₂N), 3.78 (s, 3H, CH₃O), 3.31 (s, 6H, 2 x CH₃O). ¹³C NMR [(CD₃)₂SO]: δ_c 168.3 (CO), 155.7 (CS), 134.0 (C), 124.7 (C), 109.99 (CH, C-5), 109.95 (CH, C-4), 101.6 (CH, CHO₂), 95.9 (CH, C-7), 55.7 (CH₃O), 54.4 (2 x CH₃O), 45.5 (CH₂). MS *m/z* 269.1 (M+H)⁺. Anal. calcd for C₁₂H₁₆N₂O₃S·0.75H₂O (281.84): C, 51.13; H, 6.33; N, 9.94. Found: C, 50.86; H, 5.77; N, 9.91.

A solution of **20c** (1.34 g, 5 mmol) in 85% H₂SO₄ (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 CH₂Cl₂/EtOAc (9:1) gave **21c** as a white solid (0.37 g, 36%): mp 137-139 °C (from MeOH). ¹H NMR (CDCl₃): 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, CH₃O). ¹³C NMR (CDCl₃): 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 (CH₃O). MS *m/z* 205.1 (M+H)⁺. Anal. calcd for C₁₀H₈N₂O₅ (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 (21d). A mixture of 3-fluoro-2-nitroanisole (3.42 g, 20 mmol) and 2,2-dimethoxyethylamine (**14**) (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 (**19d**) as red oil, which solidified on standing (4.85 g, 95%). mp 36-38 °C (from *i*-Pr₂O). ¹H NMR (CDCl₃): 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, CHO₂), 3.87 (s, 3H, CH₃O), 3.42 (s, 6H, 2 x CH₃O), 3.31 (t, *J*, 5.5 Hz, 2H, CH₂N). ¹³C NMR (CDCl₃): δ_c 155.1 (C), 143.8 (C), 133.6 (CH, C-5), 128.2 (C), 105.4 (CH), 102.4 (CHO₂), 100.3 (CH), 56.6 (CH₃O), 54.3 (2 x CH₃O), 45.3 (CH₂). HRMS (ESI): found *m/z* 257.1128 (M+H)⁺, calcd for C₁₁H₁₆N₂O₅: 257.1137.

A solution of **19d** (1.024 g, 4 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite. CS₂ (2 mL) and KOH (1.6 g in 10 mL H₂O) 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-2H-benzimidazole-2-thione (**20d**) as a white solid (0.58 g, 54%). mp 179-181 °C (from aq. MeOH). ¹H NMR (CDCl₃): 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, CHO₂), 4.28 (d, *J* 5.5 Hz, 2H, CH₂N), 3.88 (s, 3H, CH₃O), 3.28 (s, 6H, 2 x CH₃O). ¹³C NMR (CDCl₃): δ_C 168.1 (C), 143.9 (C), 134.4 (C), 123.0 (CH), 120.1 (C), 105.0 (CH), 103.3 (CHO₂), 101.4 (CH), 55.8 (CH₃O), 54.3 (2 x CH₃O), 45.8 (CH₂). HRMS (ESI): found *m/z* 237.0658 (M-OMe)⁺, calcd for C₁₁H₁₃N₂O₂S: 237.0697.

A solution of **20d** (0.268 g, 1 mmol) in a mixture of H₂SO₄ (45 g) and H₂O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. After neutralization with aq. NH₃ the mixture was extracted with EtOAc to give **21d** as a white solid (78 mg, 38%). mp (from aq. MeOH) 166-168 °C. ¹H NMR (CDCl₃): 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, CH₃O). ¹³C NMR (CDCl₃): 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 (CH₃O). HRMS (ESI): found *m/z* 205.0432 (M+H)⁺, calcd for C₁₀H₉N₂O₂S: 205.0430.

8-Methylthiazolo[3,2-*a*]benzimidazole (21e). A mixture of 3-fluoro-2-nitrotoluene (3.10 g, 20 mmol) and 2,2-dimethoxyethylamine (**14**) (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 (**19e**) as an orange oil which solidified on standing (4.82 g, 100%). mp (from *i*-Pr₂O) 38-39 °C. ¹H NMR (CDCl₃): 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, CHO₂), 3.43 (s, 6H, 2 x CH₃O), 3.33 (t, *J*, 5.5 Hz, 2H, CH₂N), 2.46 (s, 3H, CH₃). ¹³C NMR (CDCl₃): δ_C 143.5 (C), 136.7 (C), 135.5 (C), 133.3 (CH), 119.8 (CH), 111.4 (CH), 102.4 (CHO₂), 54.3 (CH₃O), 45.3 (CH₂), 21.3 (CH₃). HRMS (ESI): found *m/z* 241.1186 (M+H)⁺, calcd for C₁₁H₁₆N₂O₄ 241.1188.

A solution of **19e** (2.40 g, 1 mmol) in EtOH (50 mL) was hydrogenated over 5% Pd on C, and filtered through celite. CS₂ (5 mL) and KOH (2.5 g in 10 mL H₂O) were added and the mixture was heated under reflux for 3 h. The solution was concentrated, diluted with water and neutralized with HOAc to give 1-(2,2-dimethoxyethyl)-4-methyl-1,3-dihydro-2H-benzimidazole-2-thione (**20e**) as a white solid (2.306 g, 91%). mp (from aq. MeOH) 171-174 °C. ¹H NMR [(CD₃)₂SO]: δ_H 12.89 (s, 1H), 7.19 (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, CHO₂), 4.30 (d, *J* 5.5 Hz, 2H, CH₂N), 3.29 (s, 6H, 2 x CH₃O), 2.39 (s, 3H, CH₃). ¹³C NMR [(CD₃)₂SO]: δ_C 168.4 (CS), 132.9 (C), 129.8 (C), 123.7 (CH), 122.2 (CH), 119.8 (C), 107.8 (CH, C-6), 101.4 (CHO₂), 54.3 (2 x CH₃O), 45.6 (CH₂), 16.1 (CH₃). HRMS (ESI): found *m/z* 221.0730 (M-OMe)⁺, calcd for C₁₁H₁₃N₂O₂S 221.0749.

A solution of **20e** (0.505 g, 0.2 mmol) in a mixture of H₂SO₄ (45 g) and H₂O (5 g) was heated at 100 °C for 30 min, and poured into ice-water. After neutralization with aq. NH₃ the mixture was extracted with EtOAc to give **21e** as a white solid (0.318 g, 84%). mp (from aq. MeOH) 150-152 °C. ¹H NMR (CDCl₃): 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, CH₃). ¹³C NMR (CDCl₃): 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 (CH₃). HRMS (ESI): found *m/z* 189.0480 (M+H)⁺, calcd for C₁₀H₉N₂S: 189.0481.

6-Hydroxythiazolo[3,2-*a*]benzimidazole (21f).²³ A mixture of 6-methoxythiazolo[3,2-*a*]benzimidazole (**21c**) (0.23 g, 1.13 mmol) and BBr₃ (1M in CH₂Cl₂, 4 mL, 4 mmol) in CH₂Cl₂ (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 **21f** as a white solid (0.17 g, 79 %). mp 298-303 °C (from aq. MeOH) (lit.²³ mp > 280 °C). ¹H NMR [(CD₃)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). ¹³C NMR [(CD₃)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). MS *m/z* 191.2 (M+H)⁺. Anal. calcd for C₉H₆N₂OS (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-propylamine²⁶ (**22**). 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 NaBH₄ (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 NaBH₄, and the solvent was removed under vacuum. The residue was made basic with aqueous ammonia, and extracted with CH₂Cl₂. Elution through alumina with CH₂Cl₂ gave *N*-benzyl-1,1-dimethoxy-2-propylamine²⁵ as an oil (36.8 g, 88%): ¹H NMR (CDCl₃): δ_H 7.34-7.30 (m, 4H, ArH), 7.26-7.21 (m, 1H, ArH), 4.14 (d, *J* 6.3 Hz, 1H, CHO₂), 3.89 (d, *J* 13.1 Hz, 1H, benzyl CH), 3.70 (d, *J* 13.2 Hz, 1H, benzyl CH), 3.38 (s, 3H, CH₃O), 3.35 (s, 3H, CH₃O), 2.84 (pentet, *J* 6.3 Hz, 1H, CHN), 1.82 (br s, 1H, NH), 1.10 (d, *J* 6.5 Hz, 3H, CH₃). ¹³C NMR (CDCl₃): δ_c 140.4 (C), 128.4 (2 x CH), 128.1 (2 x CH), 126.8 (CH), 107.9 (CHO₂), 54.7 (CH₃O), 54.5 (CH₃O), 53.5 (CHN), 51.1 (CH₂N), 14.9 (CH₃). MS *m/z* 210.2 (M+H)⁺.

Hydrogenation of the above amine over 10% Pd on carbon in MeOH, gave 1,1-dimethoxy-2-propylamine²⁶ (**22**) as an oil: ¹H NMR (CDCl₃): δ_H 3.98 (d, *J* 6.0 Hz, 1H, CHO₂), 3.43 (s, 3H, CH₃O), 3.40 (s, 3H, CH₃O), 3.01 (pentet, *J* 6.4 Hz, 1H, CHN), 1.67 (s, 2H, NH₂), 1.09 (d, *J* 6.6 Hz, 3H, CH₃). ¹³C NMR (CDCl₃): δ_c 109.5 (CHO₂), 55.2 (CH₃O), 54.9 (CH₃O), 48.5 (CHN), 18.4 (CH₃). MS *m/z* 120.2 (M+H)⁺.

trans-7-Benzoyl-2-methoxy-3-methyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (**25**). A mixture of 4-chloro-3-nitrobenzophenone (**13d**) (2.62 g, 10 mmol), **22** (1.54 g, 13 mmol) and Et₃N (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 Na₂CO₃ solution, dried, and the solvent was removed, to give (**23**) as a yellow solid (3.1 g, 90%): mp 92-94 °C (from *i*-PrOH). ¹H NMR (CDCl₃): δ_H 8.66 (d, *J* 2.1 Hz, 1H, H-2), 8.64 (d, *J* 8.4 Hz, 1H, NH), 8.03 (dd, *J* 9.1, 2.1 Hz, 1H, H-6), 7.76-7.72 (m, 2H, H-2', 6'), 7.62-7.57 (m, 1H, H-4'), 7.53-7.47 (m, 2H, H-3', 5'), 7.01 (d, *J* 9.2 Hz, 1H, H-5), 4.36 (t, *J* 4.1 Hz, 1H, CHO₂), 4.00-3.91 (m, 1H, CHN), 3.52 (s, 3H, CH₃O), 3.50 (s, 3H, CH₃O), 1.34 (d, *J* 6.6 Hz, 3H, CH₃). ¹³C NMR (CDCl₃): δ_c 193.7 (CO), 147.3 (C), 137.8 (C), 137.0 (CH, C-6), 132.4 (CH, C-4'), 131.2 (CH, C-2), 131.17 (C), 129.7 (CH, C-2', 6'), 128.7 (CH, C-3', 5'), 124.7 (C), 114.4 (CH, C-5), 106.8 (CH, CHO₂), 56.7 (CH₃O), 56.6 (CH₃O), 51.0 (CHN), 15.6 (CH₃). MS *m/z* 345.2 (M+H)⁺. Anal. calcd for C₁₈H₂₀N₂O₅ (344.37): C, 62.78; H, 5.85; N, 8.13. Found: C, 62.96; H, 6.12; N, 8.16.

A solution of **23** (3.0 g, 8.7 mmol) in 65% aqueous EtOH was reduced with Fe powder as for the reduction of **15d**, to give crude 3-amino-4-[*N*-(1,1-dimethoxy-2-propyl)amino]benzophenone (2.7 g). ¹H NMR [(CD₃)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, NH₂), 4.32 (t, *J* 4.6 Hz, 1H, CHO₂), 3.78-3.72 (m, 1H, CHN), 3.36 (s, 3H, CH₃O), 3.34 (s, 3H, CH₃O), 1.14 (d, *J* 6.5 Hz, 3H, CH₃).

Crude diamino product was treated with an excess of CS₂ and aqueous KOH in MeOH, as for the synthesis of **17d**. 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 CH₂Cl₂/EtOAc (9:1), gave 5-benzoyl-1,3-dihydro-1-(1,1-dimethoxy-2-propyl)-2*H*-benzimidazole-2-thione (**24**) (2.7 g, 87%): mp 151-152.5 °C (from aq. MeOH). ¹H NMR [(CD₃)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, CHO₂), 3.41 (s, 3H, CH₃O), 3.21 (s, 3H, CH₃O), 1.48 (d, *J* 5.5 Hz, 3H, CH₃). ¹³C NMR [(CD₃)₂SO]: δ_c 194.8 (CO), 170.5 (CS), 137.6 (C), 134.4 (C), 132.3 (CH, C-4'), 131.3 (C), 130.7 (C), 129.4 (CH, C-2', 6'), 128.5 (CH, C-3', 5'), 124.7 (CH, C-6), 111.1 (CH, C-4), 110.9 (CH, C-7), 102.8 (CHO₂), 55.0 (CH₃O),

52.8 (CH₃O), 52.6 (CHN), 13.5 (CH₃). MS *m/z* 357.1 (M+H)⁺. Anal. calcd for C₁₉H₂₀N₂O₃S (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 **24** (0.20 g, 0.56 mmol) in 90% H₂SO₄ (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 **25**: mp 136-137 °C. ¹H NMR (CDCl₃): 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, CH₃O), 1.52 (d, *J* 6.8 Hz, 3H, CH₃). ¹³C NMR (CDCl₃): 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 (CH₃O), 17.0 (CH₃). MS *m/z* 325.1 (M+H)⁺. Anal. calcd for C₁₈H₁₆N₂O₂S (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 (26). A solution of 5-Benzoyl-1,3-dihydro-1-(1,1-dimethoxy-2-propyl)-2H-benzimidazole-2-thione (**24**) (0.20 g, 0.56 mmol) in 90% H₂SO₄ (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 CH₂Cl₂ gave 7-benzoyl-3-methylthiazolo[3,2-*a*]benzimidazole (**26**): mp 122-123.5 °C (from aq. MeOH). ¹H NMR [(CD₃)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, CH₃). ¹³C NMR [(CD₃)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 (CH₃). MS *m/z* 293.1 (M+H)⁺. Anal. calcd for C₁₇H₁₂N₂OS (292.36): C, 69.84; H, 4.14; N, 9.58. Found: C, 70.03; H, 3.99; N, 9.45.

Acknowledgements

This work was originally funded by the Parke-Davis Pharmaceutical Division of the Warner-Lambert Company (now Pfizer). Recent funding is from the Maurice Wilkins Centre for Molecular Biodiscovery at the University of Auckland, and the Auckland/Northland Division of the Cancer Society of New Zealand. Adrian Blaser and Maruta Boyd are thanked for NMR services, and Wilson Sun, Sisira Kumara and Sree Sreebhavan are thanked for technical assistance.

Supplementary Material

Copies of ¹H and ¹³C NMR spectra are available in the supplementary material associated with this paper

References

- Chimirri, A.; Grasso, S.; Romeo, G.; Zappala, M. *Heterocycles* **1988**, *27*, 1975-2003.
<https://doi.org/10.3987/REV-88-391>
- Al-Rashood, K. A.; Abdel-Aziz, H. A. *Molecules* **2010**, *15*, 3775-3815.
<https://doi.org/10.3390/molecules15063775>
- Bell, S. C.; Wei, P. H. L. *J. Med. Chem.* **1976**, *19*, 524-530.
<https://doi.org/10.1021/jm00226a016>
- Kohara, A.; Toya, T.; Tamura, S.; Watabiki, T.; Nagakura, Y.; Shitaka, Y.; Hayashibe, S.; Kawabata, S.; Okada, M. *J. Pharm. Exper. Therapeut.* **2005**, *315*, 163-169.

- <https://doi.org/10.1124/jpet.105.087171>
5. Alper, A. E.; Taurins, A. *Can. J. Chem.* **1967**, *45*, 2903-2912.
<https://doi.org/10.1139/v67-471>
 6. Bercin, E.; Eroglu, Y.; Noyanalpan, N. *J. Fac. Pharm. Gazi.* **1993**, *10*, 93-104.
 7. Hayashibe, S.; Kamikubo, T.; Tsukamoto, S.; Sakamoto, S. *Heterocycles* **2004**, *62*, 815-819.
[https://doi.org/10.3987/COM-03-S\(P\)27](https://doi.org/10.3987/COM-03-S(P)27)
 8. Gupta, R. P.; Handa, R. N.; Pujari, H. K. *Indian J. Chem.* **1979**, *17B*, 572-574.
 9. Chadha, V. K.; Sharma, K. S.; Pujari, H. K. *Indian J. Chem.* **1971**, *9*, 913-915.
 10. Mohan, J.; Pujari, H. K. *Indian J. Chem.* **1972**, *10*, 274-276.
 11. Singh, A.; Handa, R.N.; Pujari, H. K. *Indian J. Chem.* **1978**, *16B*, 478-480.
 12. Xu, J.; Deng, R.; Chen, J.; Tang, X.; Zhao, J. *Adv. Synth. Catalysis* **2019**, *361*, 5144-5148.
<https://doi.org/10.1002/adsc.201900909>
 13. Kuang, J.; Xia, Y.; Yang, A.; Zhang, H.; Su, C.; Lee, D. *Chem. Commun.* **2019**, *55*, 1813-1816.
<https://doi.org/10.1039/C8CC09122F>
 14. Jana, S.; Chakraborty, A.; Shirinian, V. Z.; Hajra, A. *Adv. Synth. Catalysis* **2018**, *360*, 2402-2408.
<https://doi.org/10.1002/adsc.201800393>
 15. Shen, G.; Yang, B.; Huang, X.; Hou, Y.; Gao, H.; Cui, J.; Cui, C.; Zhang, T. *J. Org. Chem.* **2017**, *82*, 3798-3805.
<https://doi.org/10.1021/acs.joc.7b00162>
 16. Veltri, L.; Grasso, G.; Rizzi, R.; Mancuso, R.; Gabriele, B. *Asian J. Org. Chem.* **2016**, *5*, 560-567.
<https://doi.org/10.1002/ajoc.201600042>
 17. Gao, J.; Zhu, J.; Chen, L.; Shao, Y.; Zhu, J.; Huang, Y.; Wang, X.; Lv, X. *Tetrahedron Lett.* **2014**, *55*, 3367-3373.
<https://doi.org/10.1016/j.tetlet.2014.04.070>
 18. Zhang, X.; Jia, J.; Ma, C. *Org. Biomol. Chem.* **2012**, *10*, 7944-7948.
<https://doi.org/10.1039/c2ob26211h>
 19. Roussel, C.; Andreoli, F.; Vanthuyne, N. D. P. PCT Int. Appl. 2010/052670, 2010; *Chem. Abstr.* **2010**, *152*, 548109.
 20. Lee, K.-J. Jeong, J. U.; Choi, D. O.; Kim, S. H.; Kim, S.; Park, H. *Bull. Korean Chem. Soc.* **1991**, *12*, 360-361.
 21. Van Allan, J. A.; Deacon, B. D. *Org. Syntheses Coll. Vol. IV* **1963**, 569-570.
 22. Rudner, B. U.S. Patent 2,790,172, 1957; *Chem. Abstr.* **1957**, *51*, 77156.
 23. Sahu, M.; Sahu, J. K.; Nayak, A. *Indian J. Chem.* **1986**, *25B*, 1266-1268.
 24. Grant, N.; EL-Desoky, S. I.; Hammad, M. A.; EL-Telbany, E. M.; Abdel Rahmann, A. H. *Boll. Chim. Farmaceut.* **1996**, *135*, 442-446.
 25. Bellizzi, M. E.; Bhatia, A. V.; Cullen, S. C.; Gandarilla, J.; Kruger, A. W.; Welch D.S. *Org. Process Res. Dev.* **2014**, *18*, 303-309.
<https://doi.org/10.1021/op400184f>
 26. Gall, M.; Kamdar, B. V. *J. Org. Chem.* **1981**, *46*, 1575-1585.
<https://doi.org/10.1021/jo00321a010>

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)