Synthesis of 5-Amino-3-methylimidazolidine-2,4-dione and 1,3,5-Triazine Derivatives as Analogues of the Alkaloids Naamidine A and G

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Abstract: A simple two-step synthesis of 5-amino-3-methylimidazolidine-2,4-dione is described. Addition of this amine to cyanuric chloride followed by reaction with 4-methoxyphenol or 4-alkoxyanilines gives analogues of the imidazole alkaloids naamidine A and G with a 1,3,5-triazine core.

Key words: antitumor agents, imidazolidine, naamidine alkaloids, nucleophilic addition, *s*-triazine

Several imidazole alkaloids have been isolated from the bright yellow sponge *Leucetta chagosensis* including naamidines A (**1**) and G (**2**) (Figure 1).[1] These alkaloids possess novel, drug-like structures and indeed have been reported to show various types of potentially useful biological activity. For example, naamidine A (**1**) exhibits antitumor activity in a mouse xenograft model[2] and remains under active investigation as an anticancer agent.[3] There are at least two reported total syntheses[4] of naamidine A (**1**) and also a very recent report[5] of the total synthesis of naamidine G (**2**). We have also reported the synthesis and biological evaluation of analogues of **1** and **2** in which the central imidazole ring is replaced by a thiazole.[6]

It occurred to us that one interesting type of analogue of naamidines **1** and **2** would be compounds **3** in which the central imidazole ring is replaced with a 1,3,5-triazine core possessing two substituted phenyl rings attached via amino or ether linkages and an aminoimidazole-2,4-dione as the third substituent. In support of this idea it was noted that other workers have recently reported that a bis-anilinotriazine derivative has promising in vivo antitumor activity.[7] We thus set out to prepare compounds of general structure **3** using stepwise reaction of cyanuric chloride.

For introduction of the 3-methylimidazole-2,4-dione ring system we initially thought that 5-amino-3-methylimidazole-2,4-dione (**4**) (Figure 1) might be suitable for addition to cyanuric chloride. Compound **4** was reported in 1920, under the name 3-methylallantoxaidin,[8] however, more recent consideration of the chemistry has lead to the conclusion that the original structural assignment was incorrect.[9] Thus, it appears that compound **4** is actually unknown. However, a recent paper by Ohta[10] describes the amination of 3-methylparabanic acid (**5**) with various arylamines to give 5-(*N*-arylamino)-3-methylimidazole-2,4-diones **6**. We used the method of Ohta to prepare 5-benzylamino-3-methylimidazole-2,4-dione (**7**) which we hoped would debenzylate under catalytic hydrogenation conditions to give the amine **4** (Scheme 1).

However, it was found that transfer hydrogenation of **7** with ammonium formate in the presence of palladium on charcoal as catalyst gave 5-benzylamino-3-methylimidazolidine-2,4-dione (**8**), whilst prolonged hydrogenation at atmospheric pressure lead to the formation of 5-amino-3-methylimidazolidine-2,4-dione (**9**). The assignment of the reduced structure **9** is based on the ^{1}H spectrum in CD_3CN which, in addition to the *N*-methyl peak at 2.87 ppm, showed a one proton doublet at 4.68 ppm for the CH at the 5-position. The ^{13}C NMR spectrum confirmed the assignment showing a strong peak at 64 ppm for the C5 carbon and peaks at 24, 158, and 175 ppm for the *N*-methyl and carbonyl carbons. The only previous report of the synthesis of the amine **9** appears to be a 1926 paper[11] involving a three-step diacetylation, methylation, and deacetylation sequence from 5-aminohydantoin which itself can be ob-

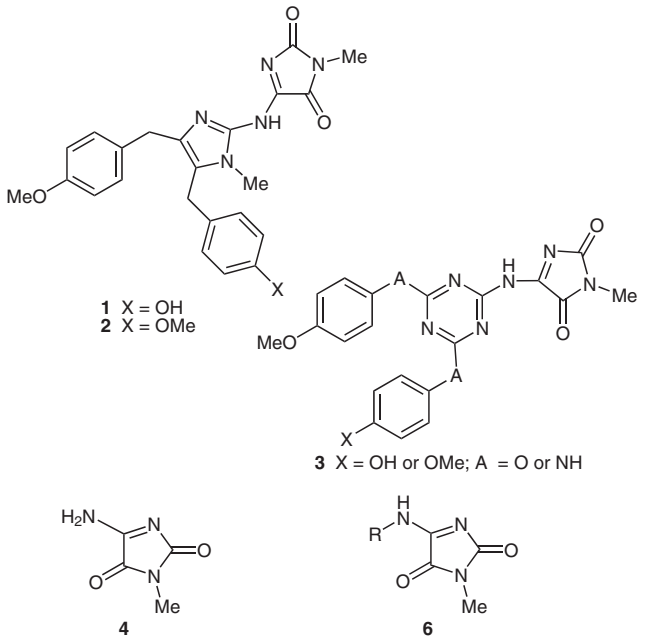

Figure 1 Naamidine A (**1**), naamidine G (**2**), triazine targets **3**, and imidazoles **4** and **6**

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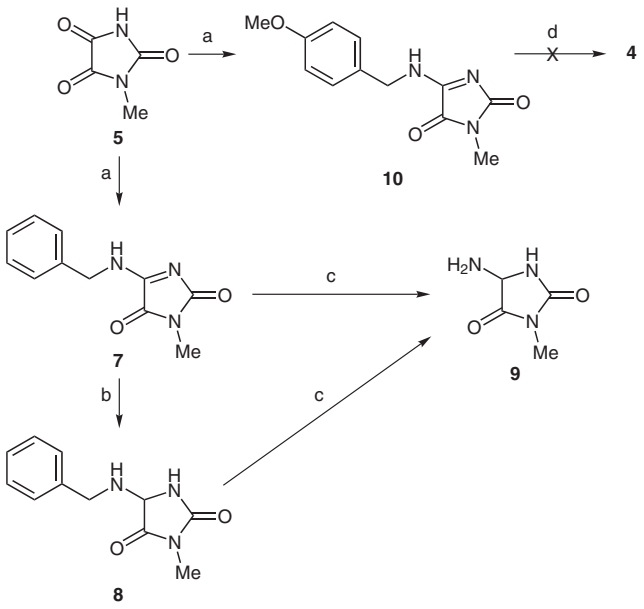


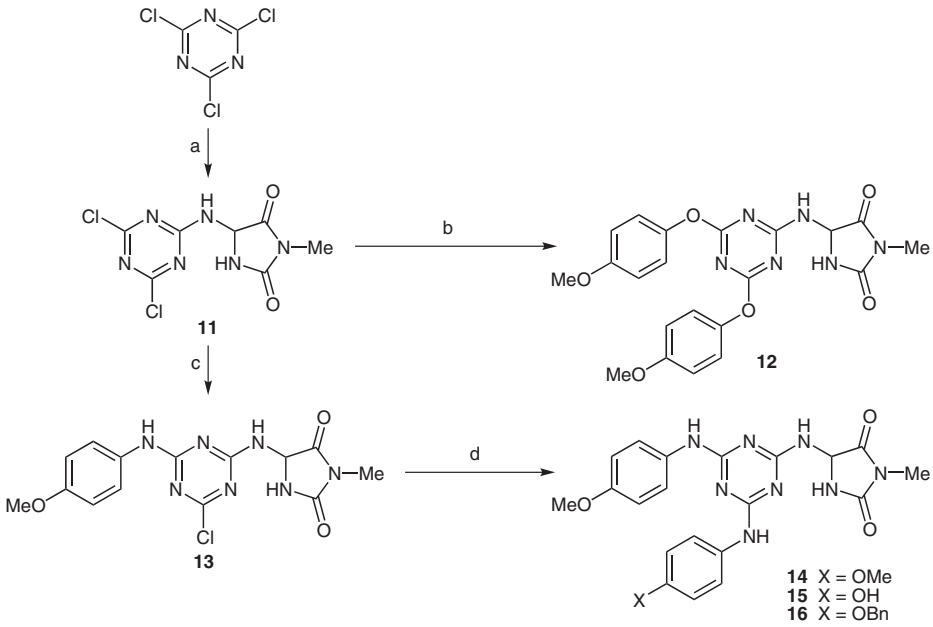
Scheme 1 Synthesis of 5-amino-3-methylimidazolidine-2,4-dione (**9**). *Reagents and conditions*: (a) imidazole, Et_3N, DMAP, Me_3SiCl, (4-MeO)$PhCH_2NH_2$, $CHCl_3$, 56–62%; (b) Pd/C, HCO_2NH_4, MeOH, 45%; (c) H_2, Pd/C, EtOH–EtOAc, 90%; (d) TFA, CH_2Cl_2, or CAN, MeCN–H_2O.

tained in four steps from parabanic acid.[12] As an alternative approach to making the desired amino compound **4** we prepared the 5-(4-methoxybenzyl)amino-3-methylimidazole-2,4-dione (**10**) again using the Ohta method.[10] Attempted removal of the methoxybenzyl group with trifluoroacetic acid in dichloromethane did not give any identifiable product. Initially we thought that oxidative removal of the methoxybenzyl group with ceric ammonium nitrate in aqueous acetonitrile had given compound **4**, but microanalysis of the product revealed that we had only reformed the starting 3-methylparabanic acid (**5**). It thus appears that compound **4** may not be stable under aqueous acidic conditions, possibly because it exists predominantly in the 5-imino form which is readily hydrolyzed.

Given the novelty of amino compound **9** and its similarity to **4**, we decided to go ahead with the preparation of triazine derivatives incorporating the reduced 5-amino-3-methylimidazolidine-2,4-dione (**9**). Reaction of cyanuric chloride with amine **9** was carried out in anhydrous acetonitrile at 0–20 °C in the presence of sodium bicarbonate (Scheme 2). The crude dichlorotriazine product **11** was isolated by chromatography in 78% yield and, being fairly unstable towards hydrolysis, was not fully characterized, but reacted immediately with 4-methoxyphenol in acetonitrile, using potassium carbonate as the base and stirring for 18 hours at room temperature. A mixture of products was obtained and the bis-ether **12** was isolated in low yield by column chromatography.

To prepare the amino-linked compounds, the dichlorotriazine **11** was first reacted with one equivalent of 4-methoxyaniline in acetonitrile at room temperature for 25 hours, using sodium bicarbonate as base. These conditions allowed clean monosubstitution to give intermediate **13** in high yield with one remaining chlorine atom on the triazine ring. Reaction of **13** with three different anilines was carried out in dimethylformamide with gentle warming and in the presence of a base such as potassium or cesium carbonate to give the triaminotriazines **14**–**16** in modest yields after chromatographic purification.

A recent publication[13] has reported that a variety of bis-(4-methoxybenzylamino)-1,3,5-triazines, together with the analogous purine derivative myoseverin, are active as microtubulin destabilizing agents. Given the structural simi-



Scheme 2 Synthesis of imidazolidine–aminotriazine conjugates **12**–**16**. *Reagents and conditions*: (a) **9**, $NaHCO_3$, MeCN, 0–20 °C, 78%; (b) 4-methoxyphenol, K_2CO_3, MeCN, 20 °C, 13%; (c) 4-methoxyaniline, $NaHCO_3$, MeCN, 96%; (d) 4-substituted phenol, inorganic base, DMF, 20–35 °C, 33–62%.

larity between these compounds and our triazines **12** and **14**, we are exploring the tubulin-binding properties of our imidazolidine–aminotriazine conjugates.

Melting point determinations were carried out on a Barnstead Electrothermal A9200 Digital Melting Point apparatus and are uncorrected. Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, Dunedin, New Zealand. Electrospray ionization (ESI) mass spectra were determined in positive ion mode using a Micromass Platform II Mass Spectrometer or a Thermo Electron LCQ Advantage MAX ion trap. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75.4 MHz, respectively, using a Bruker DRX 300 or a Bruker Advance DPX 300 spectrometer equipped with a Silicon Graphics workstation. ^{1}H NMR spectra were recorded in the specified deuterated solvent, and referenced to the residual nondeuterated solvent signal. Chemical shifts (δ) in ppm were measured relative to the internal standard. Analytical TLC analyses were carried out on Merck silica gel 60 F_{254} precoated aluminum plates with a thickness of 0.2 mm. All column chromatography was performed under 'flash' conditions on Merck Silica gel 60 (230–400 mesh). Chromatography solvent mixtures were measured by volume. Organic solvent extracts were dried with anhyd $MgSO_4$, and the solvent removed under reduced pressure with a Büchi rotary evaporator. All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and TLC analysis. Starting materials and reagents were purchased from Sigma-Aldrich Pty Ltd and were used as received.

1-Methylimidazolidine-2,4,5-trione (5)

1-Methylimidazolidine-2,4,5-trione (1-methylparabanic acid, **5**) was prepared following a literature procedure;[14] yield: 94%; mp 146–149 °C (Lit.[14,15] mp 153–155 °C, 145–148 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.96 (br s, 1 H, NH), 2.91 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.2, 158.5, 154.8, 24.2.

5-Benzylamino-3-methylimidazole-2,4-dione (7)

To a solution of 1- methylparabanic acid (**5**; 800 mg, 6.25 mmol), imidazole (467 mg, 6.87 mmol), *N*,*N*-dimethylaminopyridine (5 mg, cat.), and Et_3N (1.82 mL, 13.1 mmol) in $CHCl_3$ (13 mL) was added Me_3SiCl (1.67 mL, 13.1 mmol) dropwise at r.t. under a N_2 atmosphere, and the reaction mixture was stirred for 2 h. Benzylamine (0.75 mL, 6.87 mmol) was added and the mixture was stirred for a further 22.5 h. The mixture was diluted with $CHCl_3$ (20 mL), washed with H_2O (2 × 20 mL), and the $CHCl_3$ extracts were dried and evaporated. The crude product was purified by column chromatography (silica gel; CH_2Cl_2–EtOAc, with ratio decreasing from 10:1 to 3:1) to give **7** as a colorless solid; yield: 838 mg (62%); mp 152–154 °C.

^{1}H NMR (300 MHz, CD_3CN): δ = 7.95 (v br s, 1 H, NH), 7.41–7.27 (m, 5 H, C_6H_5), 4.64 (s, 2 H, CH_2), 2.95 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 163.6, 161.9, 134.7, 128.6, 128.2, 128.1, 46.7, 24.8.

MS (ESI): *m*/*z* (%) = 218 (79, $[M + H]^+$), 91 (100).

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.80; H, 5.06; N, 19.28.

5-Benzylamino-3-methylimidazolidine-2,4-dione (8)

A solution of **7** (650 mg, 3.0 mmol) and ammonium formate (1.5 g, 24 mmol) in MeOH (40 mL) was stirred at r.t. under an atmosphere of N_2. Pd/C (10%, 100 mg) was added to the solution and the resultant suspension was stirred vigorously at r.t. for 48 h. The suspension was filtered and the filtrate was concentrated by evaporation to give a clear colorless oil, which was purified by chromatography on silica gel ($CHCl_3$, then 1% MeOH–$CHCl_3$), to give the product as a colorless solid; yield: 300 mg (45%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (br s, 5 H, C_6H_5), 5.93 (s, 1 H, NH), 4.84 (s, 1 H, CH), 3.89 (d, *J* = 12.9 Hz, 1 H, CH_2), 3.78 (d, *J* = 12.9 Hz, 1 H, CH_2), 2.99 (s, 3 H, CH_3), 2.5 (br, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 156.6, 138.5, 128.7, 128.4, 127.7, 69.1, 48.5, 24.4.

MS (ESI): *m*/*z* (%) = 220 (100, $[M + H]^+$).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.10; H, 5.96; N, 19.26.

5-Amino-3-methylimidazolidine-2,4-dione (9)

To a solution of **7** (400 mg, 1.84 mmol) in EtOH–EtOAc (50 mL, 1:1) was added Pd/C catalyst (10%, 195 mg). The flask was evacuated and filled with H_2 three times and then stirred under a H_2 atmosphere at r.t. for 23 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to give the product **9** as a colorless solid; yield: 214 mg (90%); mp 122–125 °C.

IR (KBr): 3375, 1713, 1470 cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN): δ = 6.31 (br s, 1 H, NH), 4.68 (d, *J* = 1.5 Hz, 1 H, CH), 2.87 (s, 3 H, CH_3).

^{1}H NMR (300 MHz, D_2O): δ = 4.95 (s, 1 H, CH), 2.96 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, D_2O): δ = 175.6, 158.5, 64.0, 24.3.

Anal. Calcd for $C_4H_7N_3O_2$: C, 37.21; H, 5.46; N, 32.54. Found: C, 38.20; H, 5.34; N, 31.13.

5-(4-Methoxy)benzylamino-3-methylimidazole-2,4-dione (10)

To a solution of **5** (1.02 g, 7.97 mmol), imidazole (596 mg, 8.77 mmol), *N*,*N*-dimethylaminopyridine (cat.), and Et_3N (2.33 mL, 16.7 mmol) in $CHCl_3$ (15 mL) was added Me_3SiCl (2.13 mL, 16.7 mmol) dropwise at r.t. under a N_2 atmosphere. The reaction mixture was stirred for 2 h and 4-methoxybenzylamine (1.14 mL, 8.77 mmol) was added and the mixture was stirred for a further 20 h. The mixture was diluted with $CHCl_3$ (30 mL), washed with H_2O (2 × 20 mL), and the $CHCl_3$ extracts were dried and evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc, ratio decreasing from 10:1 to 5:1) to give the product **10** as a colorless solid; yield: 1.10 g (56%); mp 141–143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (br s, 1 H, NH), 7.24 (d, *J* = 8.6 Hz, 2 H, ArH), 6.83 (d, *J* = 8.6 Hz, 2 H, ArH), 4.60 (br s, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.02 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 163.5, 162.0, 159.4, 129.6, 126.8, 114.0, 54.9, 46.2, 24.8.

MS (ESI): *m*/*z* (%) = 248 (15, $[M + H]^+$), 121 (100).

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.54; H, 5.29; N, 16.87.

Attempted Preparation of 5-Imino-3-methylimidazolidine-2,4-dione (4)

A solution of **10** (1.10 g, 4.45 mmol) and ceric ammonium nitrate (4.88 g, 8.91 mmol) in MeCN–H_2O (4:1; 30 mL) was stirred at r.t. for 19 h. The reaction mixture was diluted with EtOAc (40 mL), washed with H_2O (2 × 20 mL), and the EtOAc extracts were dried and evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc, 3:1) to give **5** as a pale cream solid; yield: 516 mg (91%); mp 155–156 °C (Lit.[14] mp 153–155 °C).

^{1}H NMR (300 MHz, CD_3OD): δ = 3.05 (s, 3 H, CH_3).

Anal. Calcd for $C_4H_4N_2O_3$: C, 37.51; H, 3.15; N, 21.87. Found: C, 38.03; H, 3.17; N, 21.42.

5-(4,6-Dichloro[1,3,5]triazin-2-ylamino)-3-methylimidazolidine-2,4-dione (11)

An ice-cold suspension of **9** (266 mg, 2.06 mmol), cyanuric chloride (415 mg, 2.27 mmol), and $NaHCO_3$ (191 mg, 2.27 mmol) in MeCN (15 mL) was stirred with ice-cooling under a N_2 atmosphere for 1 h, and then allowed to stir at r.t. for 22 h. The solvent was evaporated, and residue was extracted with EtOAc (2 × 20 mL). The EtOAc extracts were dried, filtered, and evaporated, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc ratio increasing from 10:1 to 1:1) to afford **11** as a pale cream solid; yield: 448 mg (78%).

^{1}H NMR (300 MHz, CD_3CN): δ = 7.50 (br s, 1 H, NH), 6.56 (br s, 1 H, NH), 5.60 (dd, *J* = 7.8, 1.8 Hz, 1 H, CH), 2.97 (s, 3 H, CH_3).

MS (ESI): *m*/*z* (%) = 277 (10, $[M + H]^+$), 259 (46), 241 (100).

5-[4,6-Bis-(4-methoxyphenoxy)[1,3,5]triazin-2-ylamino]-3-methylimidazolidine-2,4-dione (12)

A suspension of **11** (80 mg, 0.29 mmol), 4-methoxyphenol (39 mg, 0.32 mmol), and K_2CO_3 (88 mg, 0.64 mmol) in MeCN (5 mL) was stirred at r.t. under a N_2 atmosphere for 18 h. The reaction mixture was diluted with EtOAc (20 mL) and H_2O (30 mL), and the organic layer was separated, and dried. The solvent was evaporated, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc ratio increasing from 10:1 to 1:2). Recrystallization from MeCN gave **12** as a colorless solid; yield: 17 mg (13%).

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.81 (d, *J* = 8.1 Hz, 1 H, NH), 7.40 (s, 1 H, NH), 7.08 (d, *J* = 9.0 Hz, 2 H, ArH), 7.07 (d, *J* = 9.0 Hz, 2 H, ArH), 6.92 (d, *J* = 9.0 Hz, 4 H, ArH), 5.73 (d, *J* = 8.1 Hz, 1 H, CH), 3.81 (s, 6 H, OCH_3), 2.77 (s, 3 H, NCH_3).

MS (ESI): *m*/*z* (%) = 453 (100, $[M + H]^+$).

Anal. Calcd for $C_{21}H_{20}N_6O_6$: C, 55.75; H, 4.46; N, 18.58. Found: C, 55.46; H, 4.66; N, 18.39.

5-[4-Chloro-6-(4-methoxyphenylamino)[1,3,5]triazin-2-ylamino]-3-methylimidazolidine-2,4-dione (13)

A suspension of **11** (228 mg, 0.82 mmol), 4-methoxyaniline (111 mg, 0.90 mmol), and $NaHCO_3$ (76 mg, 0.90 mmol) in MeCN (7 mL) was stirred at r.t. under a N_2 atmosphere for 25 h. The solvent was evaporated, and the crude product was extracted with EtOAc (2 × 20 mL). The organic layer was dried and evaporated and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc starting with 10:1 and increasing the polarity to pure EtOAc) to afford **13** as a cream solid; yield: 288 mg (96%).

^{1}H NMR (300 MHz, acetone-d_6): δ = 8.88 (br d, 1 H, NH), 7.9–7.7 (br m, 2 H, NH), 7.51 (d, *J* = 8.7 Hz, 2 H, ArH), 6.88 (d, *J* = 8.7 Hz, 2 H ArH), 5.82 (br d, 1 H, CH), 3.79 (s, 3 H, OCH_3), 2.95 and 2.73 (2 s, 3 H, NCH_3).

MS (ESI): *m*/*z* (%) = 364 (100, $[M + H]^+$).

5-[4,6-Bis-(4-methoxyphenylamino)[1,3,5]triazin-2-ylamino]-3-methylimidazolidine-2,4-dione (14)

A suspension of **13** (50 mg, 0.14 mmol), 4-methoxyaniline (25 mg, 0.21 mmol), and K_2CO_3 (48 mg, 0.34 mmol) in anhyd DMF (5 mL) was stirred under a N_2 atmosphere for 18.5 h. The reaction mixture was diluted with H_2O (30 mL) and the crude product was extracted with EtOAc (2 × 20 mL). The organic layer was dried and evaporated, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc starting with a solvent ratio of 10:1 and increasing the polarity to CH_2Cl_2–MeOH, 10:1) to afford **14** as a pale cream solid; yield: 36 mg (58%).

^{1}H NMR (300 MHz, acetone-d_6): δ = 8.14 (br s, 2 H, NH), 7.60 (br s, 4 H, ArH), 7.43 (br s, 1 H, NH), 6.91 (br d, 1 H, NH), 6.85 (d, *J* = 9.0 Hz, 4 H, ArH), 5.91 (d, *J* = 7.8 Hz, 1 H, CH), 3.77 (s, 6 H, OCH_3), 2.86 and 2.73 (2 s, total 3 H, NCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.5, 165.3, 164.0, 156.5, 154.5, 132.8, 121.9, 113.6, 61.8, 55.1, 24.0.

MS (ESI): *m*/*z* (%) = 451 (100, $[M + H]^+$).

Anal. Calcd for $C_{21}H_{22}N_8O_4$: C, 55.99; H, 4.92; N, 24.88. Found: C, 57.02; H, 5.52; N, 23.22.

5-[4-(4-Hydroxyphenylamino)-6-(4-methoxyphenylamino)[1,3,5]triazin-2-ylamino]-3-methylimidazolidine-2,4-dione (15)

A suspension of **13** (76 mg, 0.21 mmol), 4-aminophenol (50 mg, 0.46 mol), and KOAc (25 mg, 0.25 mmol) in anhyd DMF (3 mL) was stirred under a N_2 atmosphere at 35 °C for 22 h. The reaction mixture was diluted with H_2O (25 mL), and the crude product was extracted with EtOAc (2 × 20 mL). The organic layer was dried and evaporated and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc starting with a solvent ratio of 10:1 and increasing the polarity to CH_2Cl_2–MeOH, 10:1) to afford **15** as a fawn solid; yield: 24 mg (33%).

^{1}H NMR (300 MHz, CD_3CN): δ = 7.49 (br d, *J* = 8.7 Hz, 2 H, ArH), 7.37 (br s, 4 H, NH and ArH), 6.87 (d, *J* = 8.7 Hz, 2 H, ArH), 6.75 (d, *J* = 8.7 Hz, 2 H, ArH), 6.70 (s, 1 H, OH), 6.48 (s, 1 H, NH), 6.09 (br d, 1 H, NH), 5.67 (d, *J* = 7.8 Hz, 1 H, CH), 3.78 (s, 3 H, OCH_3), 2.88 (s, 3 H, NCH_3).

^{13}C NMR (75 MHz, CD_3CN): δ = 171.4, 166.3, 156.9, 156.0, 153.2, 122.9, 114.9, 113.8, 62.2, 55.3, 24.0.

MS (ESI): *m*/*z* (%) = 437 (100, $[M + H]^+$).

Anal. Calcd for $C_{20}H_{20}N_8O_4$·MeOH: C, 53.84; H, 5.16; N, 23.92. Found: C, 54.11; H, 4.89; N, 24.26.

5-[4-(4-Benzyloxyphenylamino)-6-(4-methoxyphenylamino)[1,3,5]triazin-2-ylamino]-3-methylimidazolidine-2,4-dione (16)

A suspension of **13** (93 mg, 0.26 mmol), 4-benzyloxyaniline hydrochloride (132 mg, 0.56 mmol), Cs_2CO_3 (184 mg, 0.56 mmol) in anhyd DMF (5 mL) was stirred under a N_2 atmosphere at 30 °C for 19 h. The reaction mixture was diluted with H_2O (25 mL) and the aqueous mixture was extracted with EtOAc (2 × 20 mL). The organic layer was dried and evaporated, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc starting with a solvent ratio of 10:1 and increasing the polarity to CH_2Cl_2–MeOH, 20:1). The main fractions from the column were combined and the crude product was recrystallized from hexane–CH_2Cl_2–EtOAc gave **16** as a cream solid; yield: 90 mg (62%).

^{1}H NMR (300 MHz, CD_3CN): δ = 7.58–7.30 (m, 11 H, ArH, C_6H_5, and NH), 6.94 (d, *J* = 8.7 Hz, 2 H, ArH), 6.87 (d, *J* = 8.7 Hz, 2 H, ArH), 6.49 (br s, 1 H, NH), 6.14 (br, 1 H, NH), 5.67 (d, *J* = 7.2 Hz, 1 H, CH), 5.09 (s, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 2.88 (br s, 3 H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 156.6, 155.4, 137.2, 131.5, 128.6, 128.0, 127.5, 123.2, 115.1, 114.1, 70.3, 62.4, 55.5, 24.7.

MS (ESI): *m*/*z* (%) = 527 (100, $[M + H]^+$).

Anal. Calcd for $C_{27}H_{26}N_8O_4$: C, 61.59; H, 4.98; N, 21.28. Found: C, 61.50; H, 5.10; N, 21.22.

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