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Total Synthesis and Cytotoxicity of *Leucetta* Alkaloids

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## Graphical Abstract

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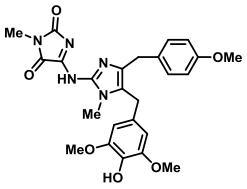


Naamidine H, $IC_{50}$ = 4.94 μM

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# Total Synthesis and Cytotoxicity of *Leucetta* Alkaloids

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ABSTRACT

The total synthesis of a number of representative natural products isolated from *Leucetta* and *Clathrina* sponges containing a polysubstituted 2-aminoimidazole are described. These syntheses take advantage of the site specific metallation reactions of 4,5-diiodoimidazoles resulting in the syntheses of three different classes of *Leucetta* derived natural products. The cytotoxicities of these natural products, along with several precursors in MCF7 cells were determined through an MTT growth assay. For comparative purposes a series of naphthimidazole-containing family members are included.



## 1. Introduction

The *Leucetta* and *Clathrina* families of marine sponges have been investigated as sources of novel bioactive secondary metabolites for several years.[1] Broadly speaking, these sponges produce either polyunsaturated fatty acid derivatives or a growing family of 2-aminoimidazole containing alkaloids (e.g., **1-7**, Figure 1).[2] These alkaloids vary in complexity from the simple monobenzyl substituted derivatives such as clathridine A (**1**) to the highly condensed kealiiquinone (**6**)[3] or the highly oxidized spiroleucettadine (**7**) (Figure 1).[4] In between these extremes are the two isomeric dibenzyl substituted systems exemplified by isonaamidine E (**2**)[5] or naamidine H (**5**).[6] The vast majority of these natural products are described as possessing "biological activity", but rarely are either the assays or the cell types the same from one isolation group to the next.[7] Furthermore, it is often times difficult to obtain extremely pure materials from natural isolates which influences both the magnitude and in some cases the reliability of these data. Lastly, the ability to conduct SAR studies is limited to derivatization of the natural material, which often can only be obtained in limited supply. To date, only the biological activity of naamidine A (**3**) has been extensively investigated by the Ireland lab which has demonstrated that it promotes caspase-dependent apoptosis in cultured tumor cells.[8] An Australian team has reported a modest exploration of the SAR of the naamine/naamidine A framework.[9] More recently, the Looper lab[10] and our group[11] have begun to evaluate the biological activity of synthetic versions of various other family members, specifically the naphthimidazole group. Very recently Jiang and coworkers have applied our synthetic methods to access the naamine framework to prepare derivatives at the 2-amino group with activity against P-glycoprotein mediated drug resistance in various cancer cell lines.[12] In order to pursue a medicinal chemistry campaign of these molecules, we needed reliable synthetic strategies that ideally were short and readily amenable to variation thus providing both the opportunity to access natural products but also permitting the construction of analogues around the imidazole core.

Several years ago, we began a synthetic program directed towards the total synthesis of several of the more complex members of the *Leucetta* alkaloids, specifically calcaridine A (**10**)[13] and spirocalcaridines A (**8**) and (**9**),[14] using a broadly bioinspired-synthetic strategy.[1a, 15] As a result we needed to access the basic framework found in the naamine group of alkaloids to perform a variety of biomimetic rearrangements. As we considered our options, it became clear that any strategy along these lines would provide an opportunity for the preparation of a selection of different family members. In this manuscript, we detail this strategy with the total synthesis of an example from each major class of *Leucetta* alkaloids. In addition, we describe the cytotoxicity of the synthesized natural products and selected precursors using an MTT based cell viability assay in MCF7 breast cancer cells, thereby obtaining direct comparative biological data for several members of the *Leucetta* alkaloids and their precursors for the first time.

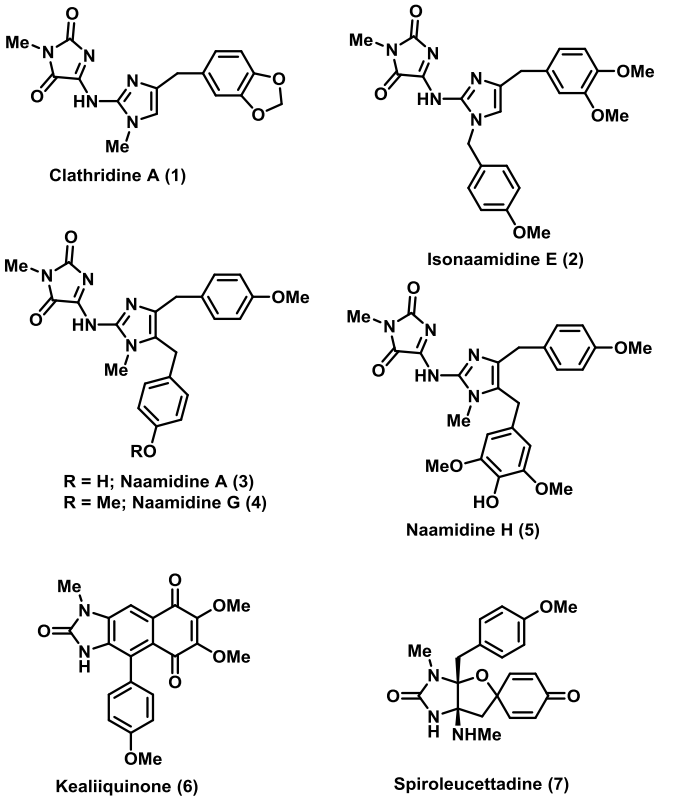



***Figure 1:*** Characteristic members of the *Leucetta* alkaloids

## 2. Results and Discussion

**Strategy**: As noted above, we wished to develop an approach to this group of molecules which was flexible, would readily deliver analogs and above all would be scalable. Several general strategies can be envisioned for the preparation of the polysubstituted imidazoles, either through the intermediacy of α–substituted ketones (**12**→**11**), hydroamination of alkynes[10b, 16] or through the functionalization of pre-formed imidazoles (**13**→**11**).[17] In each case, the strategies are executed to avoid introducing the polar 2-amino substituent until the end of the synthetic sequence. In this context we pursued the latter approach, relying on halogen-Grignard exchange reactions of 4,5-diiodoimidazole derivatives and subsequent electrophilic quench.[18] Based on literature reports, it was known that C5 would undergo exchange first, followed by C4, the remaining unsubstituted position at C2 could then be deprotonated with n-BuLi allowing the sequential and selective polyfunctionalization of the heterocycle. The majority of examples described in the literature prior to our work involved imidazoles with stabilizing N-substituents, whereas our substrates by necessity would have either methyl or benzyl groups which would not stabilize any adjacent negative charge character to any appreciable extent. As a consequence, when we initiated this effort it was uncertain whether this technique could be extrapolated to such systems.

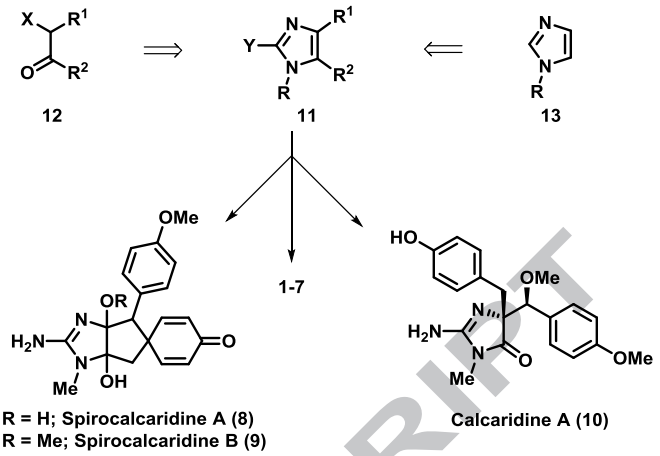



***Figure 2:*** Strategic approaches to the *Leucetta* alkaloids

Our initial target centered on the construction of the simple trisubstituted system clathridine A (**1**) and the related preclathridine A (**19**) (Scheme 1).[19] Our synthesis began with the preparation of 4,5-diiodo-1-methylimidazole (**14**);[20] while this material is commercially available through various sources, it can be prepared easily and in large quantities through the iodination of imidazole in basic solution and then *N*-methylation. No chromatography is required for either step; simply washing with solvent provides material of sufficient purity for further use. In order to access clathridine A (**1**), the 4-iodoimidazole **15** was required, this can be obtained by treatment of **14** with ethylmagnesium bromide and quenching with water.[21] At this stage we were in position to install the benzylic substituent. Previous experience in our lab had demonstrated that this would be difficult to achieve directly by using a benzyl halide with electron rich imidazoles due to competitive *N*-alkylation[13a] and therefore we employed an aldehyde and reduced the corresponding alcohol. In practice this involved metallation of C4 of **15** by treatment with ethylmagnesium bromide followed by treatment with piperanal, which delivered the doubly benzylic alcohol **16** in excellent yield. Ionic reduction occurred smoothly upon treatment of **16** with $Et_3SiH$ in a mixture of TFA and dichloromethane. At this stage the introduction of the 2-amino group was necessary and this was accomplished through a two-step sequence involving C2-metallation of **17** with n-BuLi and trapping with $TsN_3$.[22] The resulting 2-azido derivative **18** was subjected to catalytic hydrogenation (Pd-C/$H_2$) affording preclathridine A (**19**). Clathridine A (**1'**) was obtained by introduction of the methyl parabanic acid fragment using a literature procedure involving exposure of **19** to the silylated parabanic acid derivative **20**.[23] The resulting synthetic material had spectroscopic properties that nicely matched those reported for the natural material. In addition, the synthetic natural product was crystalline and so an X-ray crystal structure was obtained which nicely illustrated the location of all of the substituents and confirmed the structure of the natural product (Figure 3). Interestingly, the crystalline material obtained was tautomeric to the reported structure of clathridine A (**1**) (Figure 1) but this may simply reflect crystal packing forces.

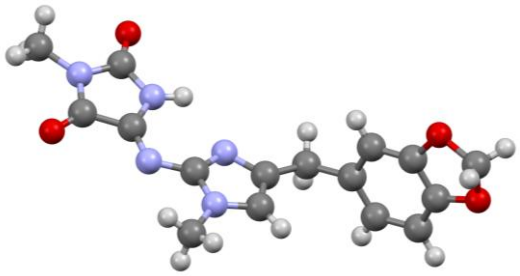
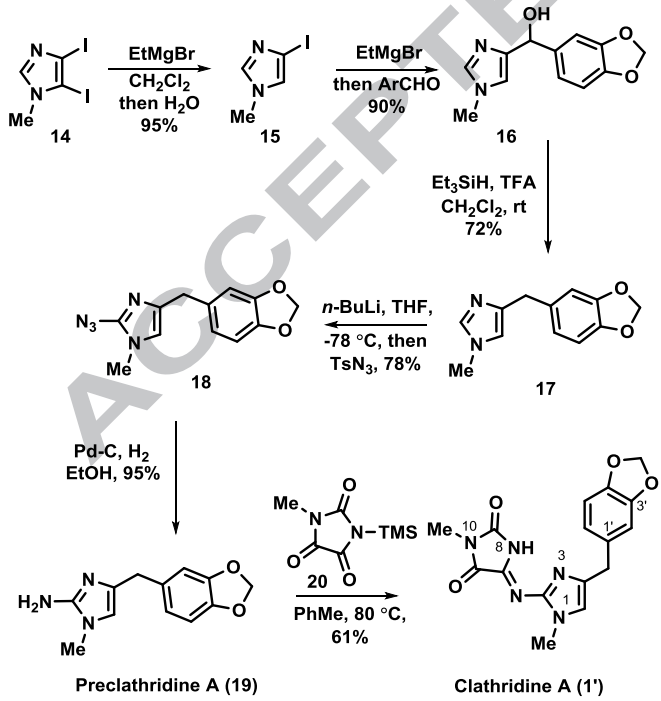
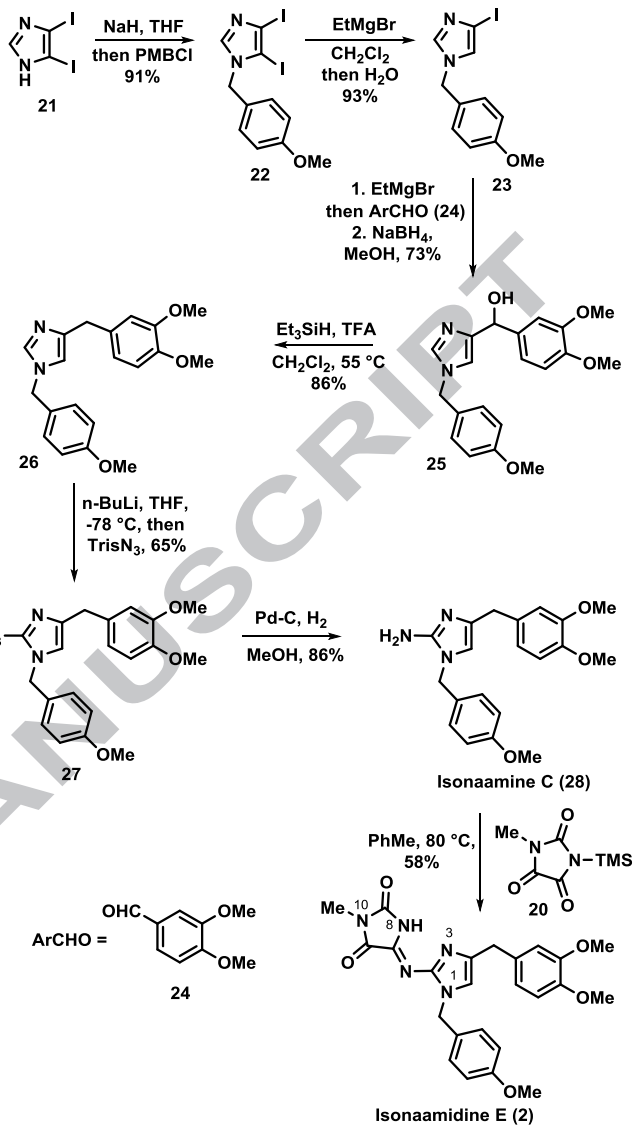


***Figure 3***: X-ray crystal structure of clathridine

With the synthesis of the two clathridine derivatives complete, we turned our attention to the isonaamidine series.[24] In this subfamily, the imidazole nitrogen is substituted with a benzyl moiety and thus the synthesis commenced with the 4,5-diiodoimidazole by alkylation with *p*-methoxybenzyl chloride resulting in the formation of **22** (Scheme 2). Treatment of **22** with ethylmagnesium bromide followed by quenching with water provided the 4-iodoimidazole **23**.[25] Exposure of **23** to ethylmagnesium bromide and treatment of the metallated imidazole with benzaldehyde **24** gave a mixture of the desired alcohol **25** and the corresponding ketone. Treatment of this unpurified mixture with $NaBH_4$ reduced the ketone to the alcohol, which upon purification delivered 73% of the required product **25**. Reduction of the doubly benzylic alcohol with $Et_3SiH$ and TFA provided **26**. At this stage we were in a position to introduce the C2-amine via metallation with n-BuLi and trapping with $TrisN_3$, however there was some concern *vis à vis* chemoselectivity as it is known that *N*-benzylimidazoles are prone to deprotonation at the benzylic position.[26] Fortunately, when **26** was exposed to n-BuLi followed by reaction with $TrisN_3$ the 2-azido derivative **27** was obtained in good yield. Reduction with Pd-C/$H_2$ delivered isonaamine C (**28**) which upon treatment with the silylated parabanic acid derivative **20** afforded isonaamidine E (**2**) in good yield (Scheme 2).



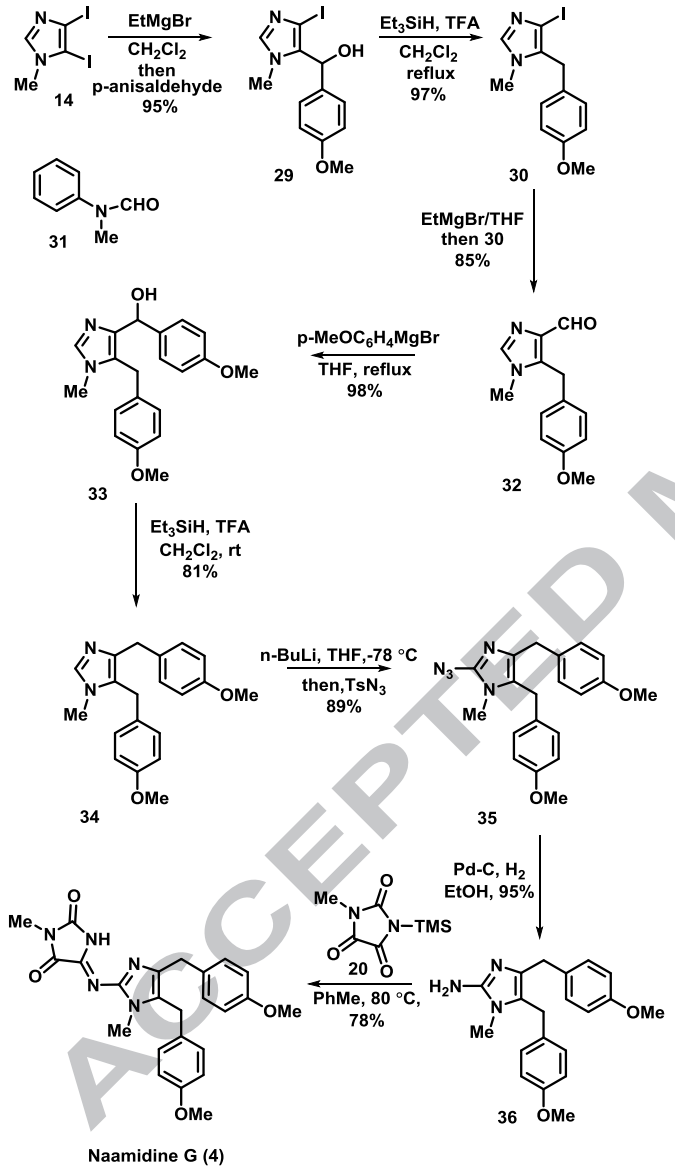

***Scheme 1:*** Total synthesis of preclathridine A (**19**) and clathridine A (**1'**)




***Scheme 2***: Total synthesis of isonaamine (**28**) and isonaamidine E (**2**)

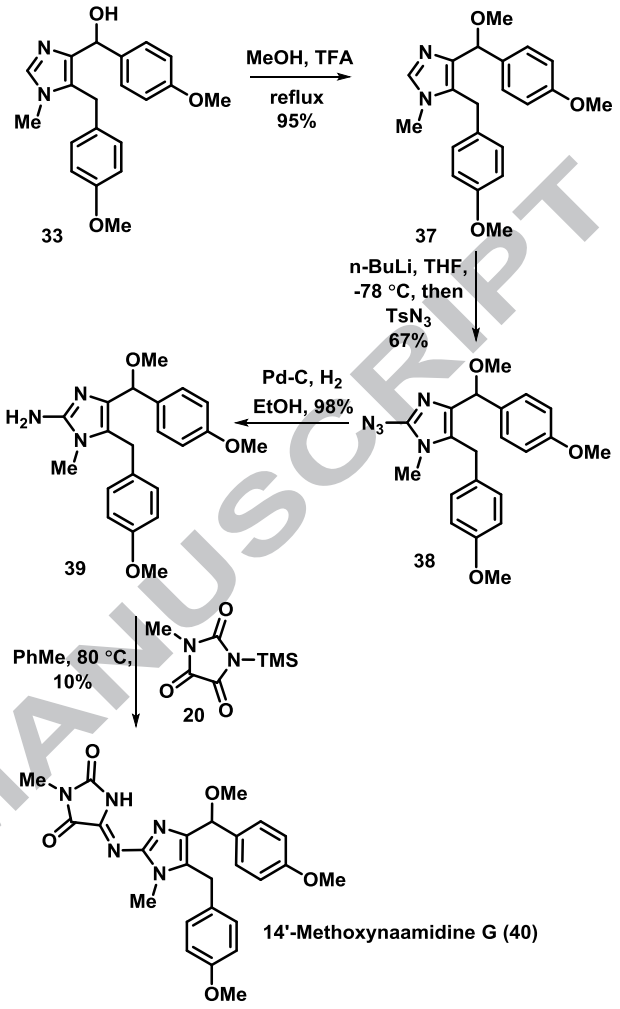
With approaches to examples of 4-substituted imidazoles secured, we turned our attention to the 4,5-disubstituted derivatives. Strategically, we anticipated that both benzyl moieties could be installed sequentially through metallation and trapping with the appropriate aldehydes. As initial targets, our attention was directed to naamidine G (**4**),[27] one of several molecules isolated by Pietra and coworkers.[28] The crude extract containing these molecules was described as being cytotoxic, but no details were described for the individual purified molecules and thus access to synthetic versions would help address the question of which of these several derivatives were responsible for the cytotoxicity. The synthesis commenced from the diiodoimidazole **14** which was subjected to transmetallation with EtMgBr. Exposure of the resulting organometallic to *p*-anisaldehyde delivered the corresponding alcohol **29**; ionic reduction of the doubly benzylic alcohol using $Et_3SiH$ and trifluoroacetic acid provides **30** (Scheme 3). In the context of our calcaridine A (**10**) synthesis we had attempted to introduce the second benzylic substituent by reaction of the Grignard derived from **30** and a protected benzaldehyde derivative, but this was not very efficient.[13] We were able to circumvent this problem by formylating first and then using an aryl Grignard reagent. Accordingly, formation of the Grignard reagent was accomplished by treatment of **30** with EtMgBr and then reaction with *N*-methyl formanilide (**31**) which delivered the aldehyde **32**

in excellent yield. Reaction of the aldehyde with *p*-anisylmagnesium bromide provided the corresponding alcohol **33** in good yield. Ionic reduction of the benzylic alcohol **33** was readily accomplished on exposure to $Et_3SiH$ and TFA. The synthesis naamidine G (**5**) was completed in short order by metallation of imidazole **34** at C2 with n-BuLi and reaction of the thus formed organolithium with $TsN_3$. The resulting azido derivative **35** was hydrogenated with Pd-C to provide the 2-amino derivative **36** which upon treatment with the activated parabanic acid derivative **20** afforded naamidine G **(4)** (Scheme 3). Compound **36** has not been reported as a natural product, but the desmethyl derivative (naamidine D) and the dimethyl derivative (N,N-dimethylnaamidine D)[2] have been described.




***Scheme 3:*** Total synthesis of naamidine G (**4**)

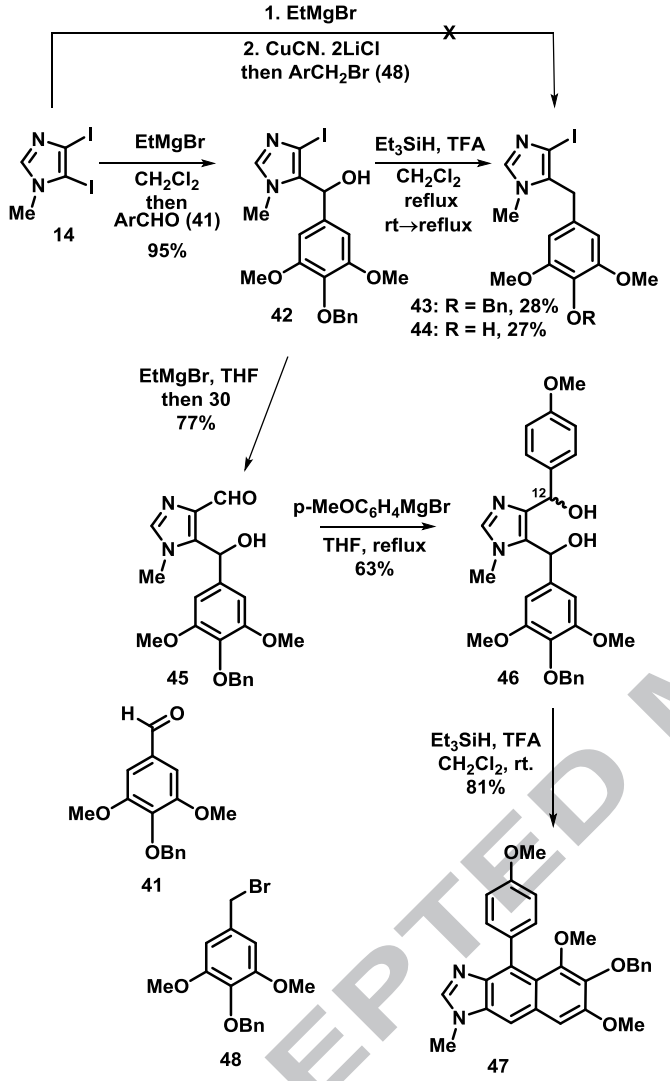
We noted that alcohol **33** might serve as a precursor to the C14-oxygenated derivatives exemplified by 14-methoxynaamidine G (**40**) (Scheme 4). Accordingly, alcohol **33** was converted to the methyl ether by treatment with TFA and methanol followed by C2-azidation and reduction to give the corresponding amine. Unfortunately, we were unable to obtain the naamidine derivative in useful amounts as the introduction of the parabanic acid fragment was not efficient using standard literature methods for its introduction. Presumably, residual BSA from the activation of the parabanic acid leads to competitive ionization of the methyl ether and non-productive side reactions.




**Scheme 4:** Total synthesis of 14'-Methoxynaamidine

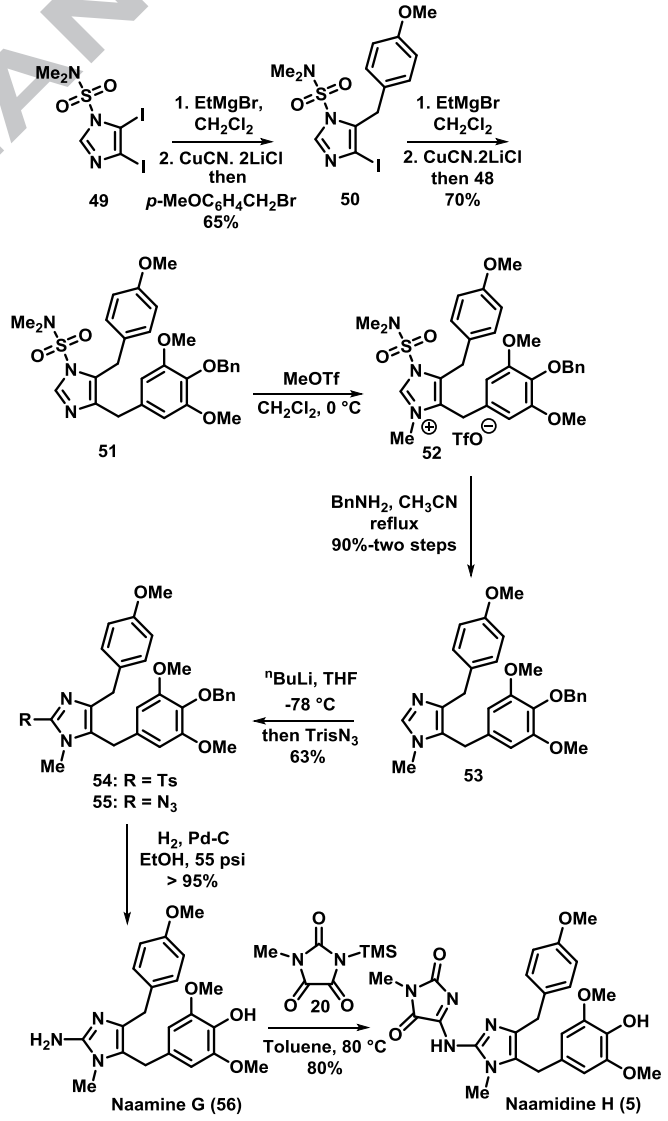
The last targets that we pursued were naamine G and naamidine H as these derivatives were reported to possess cytotoxicity against several cancer cell lines in the low micromolar range.[29] Our synthesis began from **14** and proceeded through halogen-metal exchange and subsequent reaction with the Bn-protected aldehyde **41** resulting in the formation of alcohol **42**. Attempts to reduce this alcohol under ionic conditions were not especially efficient, delivering less than 30% yield of the benzylic derivative **43**. In addition to the required product, the reductive debenzylation product **43** was obtained in a similar yield. However, rather than searching for conditions to optimize this reduction, we chose to introduce the second benzylic substituent and then remove both hydroxyl groups simultaneously. We were able to introduce this second substituent through similar chemistry to that employed above wherein the imidazolyl aldehyde **45** was prepared first and then reaction with *p*-anisylmagnesium bromide to deliver diol **46** as a mixture of diastereomers. With the crude diol in hand it was subjected to the standard conditions that had been successful previous for the ionic reduction of related derivatives, however, rather than reduction, the diol underwent an intramolecular Friedel-Crafts reaction followed by elimination to provide the naphthimidazole **47**. Presumably, a carbocation is formed and then this is trapped by the more electron rich aromatic system, dehydration then affords **47**. The initial formation and rearrangement of an *ipso* addition adduct cannot be ruled out. Indeed, in recently published work we have evidence of such

rearrangements resulting in the formation of naphthimidazoles.[14] While clearly in the context of our targets this outcome was not useful, the framework produced in this reaction maps very nicely onto other members of the *Leucetta* alkaloids, most notably the kealiinines and kealiiquinones. Indeed, we have used related chemistry to access both families of natural products.[11, 15]




Scheme 5: First generation approach to naamidine H (**5**)

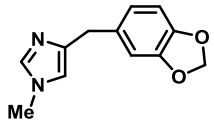
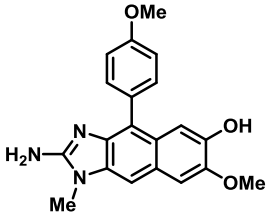
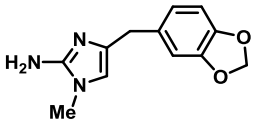
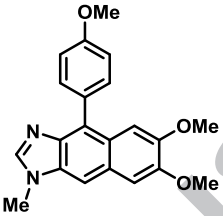
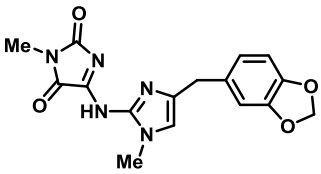
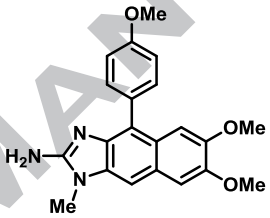
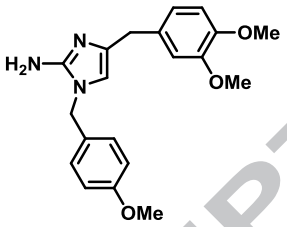
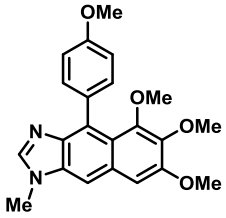
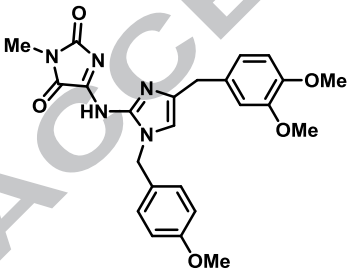
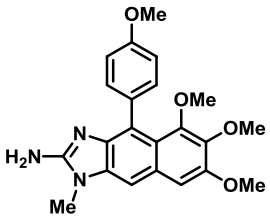
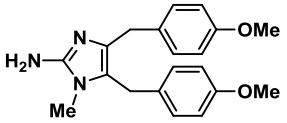
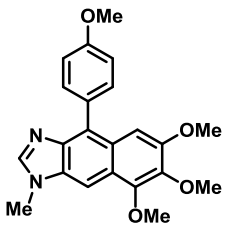
Given the propensity of this electron-rich system to undergo cyclization rather than reduction chemistry, we needed to develop an approach to circumvent this problem. An obvious way to accomplish this task was to avoid the generation of these benzylic carbocations. One way that this can be achieved is to use benzyl halides as electrophiles rather than aldehydes. We attempted to execute such a strategy with *N*-methylimidazole derivatives, e.g., **14**+**48**→**43**. Unfortunately this chemistry was not successful and led to the formation of monoiodinated imidazolium salts On the other hand, Lindell has demonstrated that C-alkylation can be feasible using dimethylsulfamoyl (DMAS)-protecting group via the corresponding organocuprate. While this was encouraging, this meant that an exchange of imidazole N-substituents was necessary and that this had to be accomplished in a position selective manner. Fortunately, Robiette,[30] Sames[31] and more recently Knochel[17b] have demonstrated that the DMAS-protecting group can be removed with a methyl group via the intermediacy of an imidazolium salt formed by reaction with methyl triflate or Meerwein's salt. Given this encouraging precedent, the corresponding DMAS-protected 4,5-diiodoimidazole was used as a starting material. Sequential treatment of **49** with EtMgBr then CuCN.2LiCl provided the corresponding cuprate which was then reacted with *p*-methoxybenzyl bromide to provide **50** in 65% yield. Essentially the same sequence of reactions was used to obtain the dibenzyl substituted imidazole this time using benzyl bromide **48** as the electrophile. At this stage, we chose to perform the protecting group exchange sequence by first converting **51** to the methyl imidazolium salt **52** by treatment with methyl triflate. Subsequent reaction with benzylamine in acetonitrile at reflux provided the N-methyl substituted derivative **53** in 90% yield for the two step sequence. At this point all that remained to be done was to introduce the 2-amino group and the parabanic acid moiety. Interestingly, it was found that metalation at C2 followed by treatment with $TsN_3$ resulted in sulfonylation, but substitution with $TrisN_3$ delivered the 2-azidoimidazole **55**. Catalytic hydrogenation resulted in reduction of the azido moiety to the corresponding amine and hydrogenolysis of the benzyl protecting group resulting in the synthesis of naamine G (**56**) in excellent yield. Treatment with activated *N*-methyl parabanic acid then delivered naamidine H (**5**) in good yield. The spectroscopic data for both synthetic naamine G and synthetic naamidine H were in good agreement with that obtained for the isolated materials.

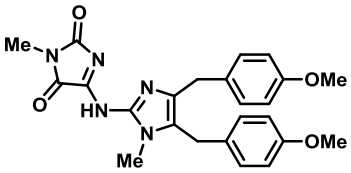
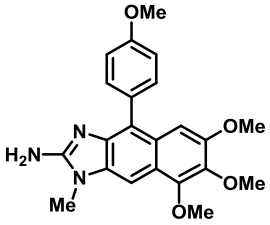
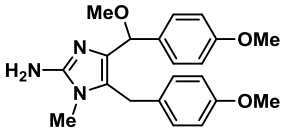
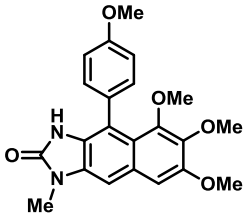
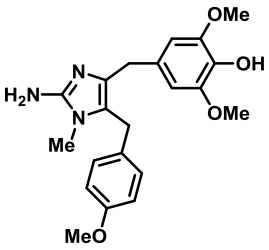
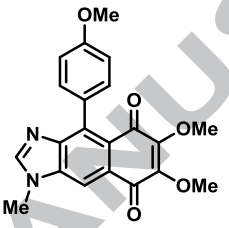
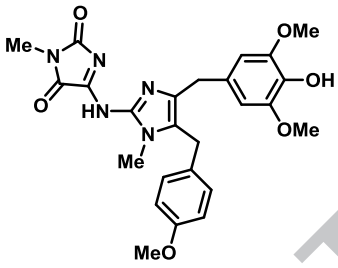
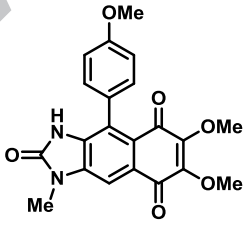
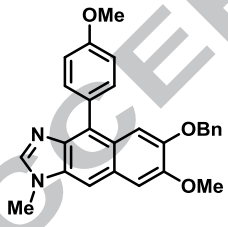
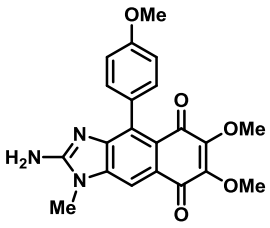
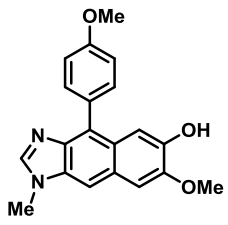



Scheme 6: Second generation total syntheses of naamine G (**56**) and naamidine G (**5**)

With this group of natural products in hand they were subjected to cytotoxicity testing using an MTT assay with MCF7 cells; the outcomes of these experiments are reported in Table 1 (entries 1-10). In addition to the naamine/naamidine group of compounds, we also include the naphthimidazole based family that we have reported previously for comparative purposes (entries 12-23, Table 1).[11] Generally speaking for the synthetic versions of the natural products, the systems substituted with *N*-methyl parabanic acid are substantially more active than the corresponding 2-amino derivatives or desamino derivatives. Interestingly, there appears to be broad tolerance with respect to the identity and location of the other substituents around the imidazole moiety. In cases where cytotoxicity has been determined on material isolated from natural sources, our synthetic materials display similar values – typically $IC_{50}$ < 10 μM. One notable exception was with isonaamine C (**28**) (entry 4), for which the naturally occurring material was reported to have an $IC_{50}$ value of 2-5 μM, although this was obtained in different cell lines, whereas our synthetic material had an $IC_{50}$ >100 μM. Our data are consistent with respect to the naamine vs naamidine activities, with the latter being more active. In the cases of the naphthimidazole derivatives, the cytotoxicities were not determined on natural materials, only on the synthetic materials.[11, 32] In general terms the presence of a C2-amino substituent increases their cytotoxicity as evidenced by the kealiinines, but the presence of quinone in the C-ring as found in kealiiquinone (**6**) and 2-deoxy-2-aminokealiiquinone (**68**) appears to reduce activity. Interestingly, kealiinine C (**63**) is almost devoid of activity, whereas the isomeric congener **65** (entry 19) is about equipotent with the other two family members **59** and **61** (entries 13 and 15). At one point in our synthetic studies we were concerned that the structure of kealiinine C had been misassigned, however, HPLC studies suggested that the original assignment does in fact appear to be correct.[11, 32a]

**Table 1.** Cytotoxicity data for several Leucetta-derived alkaloids and analogs in MCF7 cells using an MTT growth assay.

| Entry | Compound | IC50/μMol | Entry | Compound | IC50/μMol |
|---|---|---|---|---|---|
| 1 |  **17** | >100 | 13 |  Kealiinine A (**59**) | 23.4±1.9 |
| 2 |  Preclathridine A (**19**) | >100 | 14 |  **60** | 28.0±1.3 |
| 3 |  Clathridine A (**1**) | 5.78±0.04 | 15 |  Kealiinine B (**61**) | 28.8±1.2 |
| 4 |  Isonaamine C (**28**) | >100 | 16 |  **62** | 99.8±0.9 |
| 5 |  Isonaamidine E (**2**) | 4.4±0.2 | 17 |  Kealiinine C (**63**) | >100 |
| 6 |  **36** | 19.5±1.5 | 18 |  **64** | 68.2±1.6 |

| | | | | | |
|---|---|---|---|---|---|
| 7 |  Naamidine G (**4**) | 5.08±0.05 | 19 |  Isokealiinine C (**65**) | 22.7±1.0 |
| 8 |  **39** | 16.3±0.4 | 20 |  2-Deamino-2-oxokealiinine C (**66**) | 29.9±0.3 |
| 9 |  Naamine G (**56**) | 76.9±0.97 | 21 |  2-Deoxykealiiquinone (**67**) | 41.1±0.1 |
| 10 |  Naamidine H (**5**) | 4.94±0.12 | 22 |  Kealiiquinone (**6**) | 91.9±0.5 |
| 11 |  **57** | 92.0±2.2 | 23 |  2-Deoxy-2-aminokealiiquinone (**68**) | 43.8±0.4 |
| 12 |  **58** | >100 | | | |

**Conclusion**

Our initial approach to these molecules relied on the formation of Grignards by *in situ* metal-halogen exchange reactions followed by trapping with carbonyl derivatives. In most cases this was followed by ionic reduction to deliver the net C-alkylated product. This strategy worked well for the production a number of representative members of the *Leucetta* alkaloids, however, in at least one case the ionic reduction chemistry was

compromised by the presence of an electron rich aromatic ring that led to an unanticipated Friedel-Craft's pathway and the formation of a naphthimidazole. To circumvent this pathway, an electron poor imidazole derivative was alkylated at carbon thereby avoiding the non-productive cyclization pathway and ultimately delivering naamidine H. This latter strategy, while requiring the use of an *N*-protecting group, results in an overall shorter synthetic sequence and would appear to represent the best approach to this family of natural products. In general terms, synthetic variants of the natural products containing the methyl parabanic acid moiety exhibited higher cytotoxicities.

## Experimental

Chemicals were used as received unless indicated otherwise. NMR spectra were obtained at either 500 MHz (for $^{1}$H NMR spectra) and 125 MHz (for $^{13}$C NMR spectra) in $CDCl_3$ unless indicated otherwise. Infrared (IR) spectra were obtained on neat samples (ATR spectroscopy) or using either KBr pellets for solids or neat films on NaCl plates for liquids (transmission). Analytical thin-layer chromatography (TLC) was performed on silica gel plates, 200 mesh with F254 indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of $KMnO_4$. Flash column chromatography was performed with 230−400 silica gel. High resolution mass spectra (HRMS) were recorded by electrospray ionization (ESI-TOF) or atmospheric-pressure chemical ionization (APCI-TOF) unless otherwise indicated.

**4-Iodo-1-methyl-1*H*-imidazole (15)**: EtMgBr (3.0 M solution in ether, 11.00 mL, 32.9 mmol) was added to a solution of **14** (10.00 g, 29.9 mmol) in dry $CH_2Cl_2$ (150 mL) at rt. over ~15 min. The resulting mixture was stirred for 20 min and water (20 mL) was added to the reaction mixture after running a TLC experiment to confirm all the starting material is consumed. Then, the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3x50 mL) and the combined organic layers were dried ($Na_2SO_4$) and concentrated to isolate **15** as pale yellow oil (5.86 g, 94%).

**4-(Benzo[1,3]dioxol-5-yl)hydroxymethyl-1-methyl-1*H*-imidazole (16):** EtMgBr (3.0 M solution in ether, 9.76 mL, 29.3 mmol) was added to a solution of **15** (5.80 g, 27.9 mmol) in dry THF (100 mL) at 0 ºC over ~10 min. The resulting mixture was stirred at rt. for 30 min and piperonal (4.65 mL, 30.7 mmol) was added to the reaction slowly at rt. After stirring overnight at rt., satd. aq. $NH_4Cl$ (20 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried ($Na_2SO_4$) and concentrated to provide the crude product, which was purified by flash column chromatography on silica gel (100% EtOAc → 100% Acetone) to isolate **16** (5.82 g, 90%) as an orange semi-solid: $^{1}$H NMR: δ = 7.35 (s, 1H), 6.90 (s, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.45 (s, 1H), 5.88 (s, 2H), 5.66 (s, 1H), 5.27 (br, 1H), 3.54 (s, 3H); $^{13}$C NMR: δ = 147.5, 146.8, 146.0, 137.8, 137.4, 120.1, 117.2, 107.9, 107.4, 101.0, 70.0, 33.5; IR (neat, cm$^{-1}$): = 3114, 2891, 1493, 1442, 1243, 1037, 927, 794, 756; HR-ESIMS (*m/z*): Calcd. for $C_{12}H_{13}N_2O_3$ $[M+H]^+$ 233.0921, found 233.0925.

**4-(Benzo[1,3]dioxol-5-yl)methyl-1-methyl-1*H*-imidazole (17):** TFA (7.00 mL, 91.4 mmol) and $Et_3SiH$ (17.00 mL, 106.4 mmol were added to a solution of **16** (5.31 g, 22.9 mmol) in dry $CH_2Cl_2$ (150 mL) at rt. The resulting mixture was stirred for 48 h; the reaction mixture was then quenched by the addition of sat. $NaHCO_3$ solution until effervescence ceased. The resulting mixture was extracted with $CH_2Cl_2$ several times and the combined extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified by chromatography (acetone/EtOAc, 3/7) to isolate a pale yellow semi-solid: **17** (3.55 g, 72%); $^{1}$H NMR: δ = 7.27 (s, 1H), 6.71 (s, 1H), 6.67 (s, 2H), 6.46 (s, 1H), 5.82 (s, 2H), 3.76 (s, 2H), 3.52 (s, 3H); $^{13}$C NMR: δ = 147.6, 145.8, 142.8, 137.4, 134.4, 121.6, 117.0, 109.4, 108.2, 101.0, 34.7, 33.2; IR (neat, cm$^{-1}$): = 3367, 2900, 2778, 1492, 1441, 1246, 1185, 1038, 928, 815, 773; HR-ESIMS (*m/z*): Calcd. for $C_{12}H_{13}N_2O_2$ $[M+H]^+$ 217.0972, found 217.0991.

**2-Azido-4-(benzo[1,3]dioxol-5-yl)methyl-1-methyl-1*H*-imidazole (18):** *n*-Butyl lithium (1.4 M solution in hexanes, 11.34 mL, 15.9 mmol) was added dropwise to a solution of **17** (3.12 g, 14.4 mmol) in THF at -78 ºC and $TsN_3$ (3.41 g, 17.3 mmol) were used to afford the crude product, which was purified by chromatography (15% → 20% EtOAc in hexanes) to isolate **18** (2.93 g, 78%) as a reddish brown oil: $^{1}$H NMR: δ = 6.76 (s, 1H), 6.72 (s, 2H), 6.24 (s, 1H), 5.90 (s, 2H), 3.74 (s, 2H), 3.31 (s, 3H); $^{13}$C NMR: δ = 147.7, 146.0, 140.2, 140.0, 133.6, 121.7, 116.1, 109.5, 108.2, 100.9, 34.8, 31.5; IR (neat, cm$^{-1}$): = 2896, 2154, 2125, 1494, 1441, 1245, 1039, 929, 812; HR-ESIMS (*m/z*): Calcd. for $C_{12}H_{12}N_5O_2$ $[M+H]^+$ 258.0986, found 258.0987.

**2-Amino-4-(benzo[1,3]dioxol-5-yl)methyl-1-methyl-1*H*-imidazole (Preclathridine A) (19):** Azide **18** (2.80 g, 10.9 mmol) was dissolved in EtOH (30 mL) and stirred under a hydrogen atmosphere (1 atm) in the presence of 10% Pd-C on charcoal (0.30 g) at rt overnight to afford **19** (2.59 g, quant) as a yellow solid: m.p. = 116-118 ºC; $^{1}$H NMR ($CDCl_3$): δ = 6.73 (s, 1H), 6.69 (s, *2*H), 6.08 (s, 1H), 5.86 (s, 2H), 4.14 (br, 2H), 3.63 (s, 2H), 3.26 (s, 3H); $^{13}$C NMR δ = 148.0, 147.5, 145.8, 137.1, 134.5, 121.7, 112.8, 109.5, 108.1, 100.8, 34.7, 31.3; IR (KBr, cm$^{-1}$): = 3432, 3299, 3109, 1643, 1547, 1505, 1442, 1244, 1034, 921, 814; HR-ESIMS (*m/z*): Calcd. for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081, found 232.1094.

**2-(3-Methylimidazolidine-2,4-dione)imino-4-(4-benzo[1,3]dioxol-5-ylmethyl-1-methyl-1*H*-imidazole (Clathridine A) (1'):** *N,O*-Bis(trimethysilyl)acetamide (5.18 mL, 21.2 mmol) was added to a solution of 1-methylparabanic acid (2.26 g, 17.7 mmol) in dry $CH_3CN$ (30 mL) under an $N_2$ atmosphere and the resulting mixture was heated at reflux temperature for 1.5 h. The solvent was removed by vacuum distillation, and to the resulting yellow residue **20** was dissolved in dry toluene (5 mL) and then added amine **19** (817 mg, 3.5 mmol) under $N_2$ atmosphere. After, this mixture was heated at 85 ºC overnight (product starts to form after 10 min as a yellow solid at the bottom of the flask), the product was filtered and solid was washed with methanol (10 mL) to deliver **1'** as a yellow solid (730 mg, 61%): m.p. = 253-254 ºC (lit.[7] m.p. = 260-262 ºC); $^{1}$H NMR: δ = 6.75 (d, *J* = 8.3 Hz, 1H), 6.71 (s, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.52 (s, 1H), 5.93 (s, 2H), 3.80 (s, 2H), 3.71 (s, 3H), 3.18 (s, 3H); $^{13}$C NMR: δ = 162.0, 155.0, 147.8, 147.1, 146.3, 144.3, 139.7, 132.7, 121.7, 117.7, 109.3, 108.4, 101.0, 34.5, 32.2, 24.8; IR (KBr, cm$^{-1}$): = 3204, 3122, 2914, 1789, 1738, 1665, 1444, 1391, 1323, 1249, 1209, 1114, 1034, 925, 732; HR-ESIMS (*m/z*): Calcd. for $C_{16}H_{16}N_5O_4$ $[M+H]^+$ 342.1197, found 342.1201.

**4,5-Diiodo-1-(4-methoxybenzyl)-1H-imidazole (22):** 4,5-Diiodo-1H-imidazole **21** (0.50 g, 1.6 mmol) in THF ( 15 mL) was cooled to 0 ºC and NaH (60% suspension in mineral oil) (0.10 g, 2.5 mmol) was added slowly. The reaction was allowed to come to rt and stir under $N_2$ for 30 min. 4-Methoxybenzyl chloride (0.28 mL, 2.0 mmol) was added and stirred at 50 ºC for 18 h. The reaction was allowed to cool to rt, quenched with water

(10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic solutions were washed with water (10 mL), brine (10 mL), dried (anhyd. $Na_2SO_4$) and concentrated. The resulting crude residue was purified by column chromatography (4:6 EtOAc/Hexane) to give **22** as a yellow solid (0.63 g, 91%). m.p. = 158-160 °C; $^1$H NMR: δ = 7.55 (s, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.07 (s, 2H), 3.80 (s, 3H); $^{13}$C NMR: δ = 159.9, 141.2, 129.2, 126.7, 114.5, 96.1, 82.4, 55.4, 53.1; IR (cm-1): 3099, 2929, 2832, 1611, 1510, 1433, 1298, 1241, 1174, 1024, 816, 760, 629; HR-ESIMS (*m/z*): Calcd. for $[M+H]^+$ $C_{11}H_{11}N_2OI_2$ is 440.8955 found 440.8956.

**4-Iodo-1-(4-methoxybenzyl)-1H-imidazole (23):**[25b] Diiodoimidazole **22** (16.2 g, 36.8 mmol) in $CH_2Cl_2$ (250 mL) was cooled to 0 °C under $N_2$ and EtMgBr (3.0 M in $Et_2O$) (12.3 mL, 36.8 mmol) was added slowly. The reaction mixture was allowed to come to rt and stirred for 1.5 h. Water (5 mL) was slowly added and then the mixture was stirred at rt for an additional 1 h. The reaction was partitioned with water and the organic layer separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic extracts were washed with brine, dried (anhyd. $Na_2SO_4$), and concentrated. The resulting residue was purified by column chromatography (1:1 EtOAc/Hexane) to give **23** as a pale yellow solid (9.6 g, 83%). m.p. = 49-51 °C; $^1$H NMR ($CDCl_3$+DMSO-$d_6$): δ = 7.37 (d, *J* = 1.7 Hz, 1H), 7.08, (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.97 (s, 2H), 3.76 (s, 3H); $^{13}$C NMR ($CDCl_3$+DMSO-$d_6$): δ = 159.9, 138.7, 129.2, 127.2, 124.7, 114.5, 81.9, 55.4, 50.8; IR ($cm^{-1}$): 3127, 3005, 2959, 2836, 1612, 1512, 1441, 1244, 1223, 1179, 1095, 1033, 934, 837, 813, 760, 619.

**4-[Hydroxy-(3,4-dimethoxyphenyl)]methyl-1-(4-methoxybenzyl)-1H-imidazole (25):** Iodoimidazole **23** (1.0 g, 3.2 mmol) in THF (15 mL) was added EtMgBr (3.0 M in $Et_2O$) (1.28 mL, 3.83 mmol) under $N_2$ and stirred at rt for 30 min. The resulting Grignard solution was then added to aldehyde **24** (0.53 g, 3.2 mmol) in THF (30 mL) and the mixture was stirred at rt for 18 h. The reaction was quenched with water (30 mL) and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, dried (anhyd. $Na_2SO_4$), and concentrated. The crude residue was dissolved in MeOH (10 mL) and $NaBH_4$ (0.060 g, 1.6 mmol) was added and stirred at rt for 3 h. The reaction was quenched with water (10 mL) and extracted with $CH_2Cl_2$ (2 x 15 mL). The combined organics were dried (anhyd. $Na_2SO_4$) and concentrated. The resulting residue was purified by column chromatography (5% MeOH in EtOAc) to give **25** as an off-white solid (0.82 g, 73%). m.p. = 115-117 °C; $^1$H NMR: δ = 7.45 (d, *J* = 1.2 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.96 (dd, *J* = 2.3, 8.0 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 5.72 (s, 1H), 4.93 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H); $^{13}$C NMR: δ = 159.7, 148.9, 148.5, 146.3, 137.0, 135.6, 129.0, 127.8, 119.0, 116.0, 114.4, 110.9, 109.9, 70.6, 56.0, 55.9, 55.4, 50.6; IR ($cm^{-1}$): 3125 (br), 2838, 1612, 1505, 1417, 1302, 1248, 1134, 792, 746, 630; HR-ESIMS (*m/z*): Calcd. for $[M+H]^+$ $C_{20}H_{23}N_2O_4$ is 355.1652 found 355.1642.

**4-(3,4-Dimethoxybenzyl)-1-(4-methoxybenzyl)-1H-imidazole (26):** Alcohol **25** (0.82 g, 2.3 mmol) in $CHCl_3$ (25 mL) was added TFA (1.10 mL, 13.9 mmol) followed by $Et_3SiH$ (1.85 mL, 11.6 mmol) and heated to 55 °C under $N_2$ for 30 h. The reaction was quenched with 2M $Na_2CO_3$ until neutral and then extracted with $CH_2Cl_2$ (2 x 20 mL), dried (anhyd. $Na_2SO_4$), and concentrated. The resulting residue was purified by column chromatography (100% EtOAc to 5% MeOH in EtOAc) to give **26** as a colorless oil (0.67 g, 86%). $^1$H NMR: δ = 7.42 (d, *J* = 1.2 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 1.7 Hz, 1H), 6.78 (d, *J* = 1.7 Hz, 1H), 6.77 (s, 1H), 6.49 (d, *J* = 1.2 Hz, 1H), 4.93 (s, 2H), 3.83 (s, 5H), 3.81 (s, 3H), 3.78 (s, 3H); $^{13}$C NMR: δ = 159.6, 148.8, 147.4, 143.2, 136.8, 133.1, 128.9, 128.3, 120.8, 116.0, 114.3, 112.2, 111.2, 56.0, 55.8, 55.4, 50.4, 34.8; IR ($cm^{-1}$): 2998, 2933, 2834, 1611, 1510, 1463, 1246, 1175, 1137, 1025, 818, 764, 686; HR-ESIMS (*m/z*): Calcd. for $[M+H]^+$ $C_{20}H_{23}N_2O_3$ is 339.1703 found 339.1718.

**2-Azido-4-(3,4-dimethoxybenzyl)-1-(4-methoxybenzyl)-1H-imidazole (27):** Imidazole **26** (0.10 g, 0.30 mmol) in THF (15 mL) was cooled to -78 °C under $N_2$. n-BuLi (1.6 M in hexane) (0.22 mL, 0.36 mmol) was added and stirred at -78 °C for 7 min. Tris$N_3$ (0.11 g, 0.36 mmol) was added in one portion and then the mixture was stirred at -78 °C for 30 min. The reaction was quenched by the addition of water (15 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried (anhyd. $Na_2SO_4$), and concentrated. The resulting residue was purified by column chromatography (35% EtOAc in hexane) to give **27** as a yellow oil (0.072 g, 65%). $^1$H NMR: δ = 7.08 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.80 (s, 1H), 6.78 (m, 2H), 6.24 (s, 1H), 4.72 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.77 (s, 2H); $^{13}$C NMR: δ = 159.5, 148.8, 147.5, 140.7, 139.6, 132.2, 128.9, 128.2, 120.8, 114.9, 114.3, 112.3, 111.2, 56.0, 55.9, 55.4, 48.2, 34.8; IR ($cm^{-1}$): 2934, 2907, 2128, 1734, 1611, 1512, 1244, 1175, 1137, 1027; HR-ESIMS (*m/z*): Calcd. for $[M+H]^+$ $C_{20}H_{22}N_5O_3$ is 380.1717 found 380.1727.

**2-Amino-4-(3,4-dimethoxybenzyl)-1-(4-methoxybenzyl)-1H-imidazole (28): Isonaamine C** 10% Pd/C (0.020 g, 0.018 mmol) was added to azide **26** (0.069 g, 0.18 mmol) in MeOH (5 mL) and stirred under $H_2$ (1 atm) at rt for 20 h. The catalyst was filtered through Celite and washed with $CH_2Cl_2$. The filtrate was reduced and the resulting residue purified by column chromatography using Biotage KP-NH Silica (100% EtOAc to 1% MeOH in EtOAc) to give **28** as a yellow solid (0.055 g, 86%). m.p. = 103-106 °C; $^1$H NMR: δ = 7.06 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.78 (s, 1H), 6.16 (s, 1H), 4.74 (s, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.70 (s, 2H); $^{13}$C NMR: δ = 159.4, 148.8, 147.5, 147.4, 137.4, 132.9, 128.3, 128.1, 120.8, 114.5, 112.5, 112.3, 111.2, 56.0, 55.9, 55.4, 48.2, 34.6; IR ($cm^{-1}$): 3367, 3075, 2997, 2939, 2838, 1612, 1587, 1512, 1442, 1232, 1151, 1024, 803; HR-ESIMS (*m/z*): Calcd. for $[M+H]^+$ $C_{20}H_{24}N_3O_3$ is 354.1812, found 354.1824.

**4-(3,4-dimethoxybenzyl)-1-(4-methoxybenzyl)-2-(3-methylimidazolidine-2,4-dione)imino-1H-imidazole (Isonaamidine E) (2):** 1-Methylparabanic acid (0.11 g, 0.85 mmol) in dry $CH_3CN$ (8 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (0.25 mL, 1.0 mmol) and heated to reflux for 1.5 h. The solvent was removed by vacuum distillation and the resulting residue was dissolved in dry toluene (5 mL). Amine **28** (0.060 g, 0.17 mmol) was added and stirred at 85 °C under $N_2$ for 18 h. The reaction was quenched with water (10 mL) and extracted with EtOAC (2 x 10 mL). The combined organic extracts were dried (anhyd. $Na_2SO_4$) and concentrated. The resulting residue was purified by column chromatography (1:1 EtOAc/Hexane) to give **2** as an orange solid (0.078 g, 51%). m.p. = 121-124 °C; $^1$H NMR: δ = 7.16 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.80-6.74 (m, 3H), 6.47 (s, 1H), 5.19 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 (s, 2H), 3.77 (s, 3H), 3.18 (s, 3H); $^{13}$C NMR: δ = 162.0, 159.5, 155.1, 149.0, 147.5, 147.7, 146.8, 144.6, 140.0, 131.3, 129.5, 128.4, 120.8, 116.1, 114.3, 112.1, 111.3, 56.0, 55.9, 55.4, 48.4, 34.4, 24.8; IR ($cm^{-1}$): 3001, 2936, 2839, 1789, 1728, 1661, 1609, 1512, 1440, 1389, 1343, 1245,

1226, 1137, 1105, 1025, 822, 603; HR-ESIMS (*m/z*): Calcd. for $[M+H]^+$ $C_{24}H_{26}N_5O_5$ is 464.1928 found 464.1915.

**4-Iodo-5-(4-methoxybenzyl)-1-methyl-1*H*-imidazole (30):** $Et_3SiH$ (13.9 mL, 87.2 mmol) and TFA (5.60 mL, 72.6 mmol) were added to a solution of benzyl alcohol **29** (5.00 g, 14.5 mmol) in anhydrous $CH_2Cl_2$ (100 mL) at rt, then the resulting mixture was heated at reflux for 60 h under $N_2$ atmosphere. After cooling to rt, the reaction was quenched by the addition of sat. aq. solution of $NaHCO_3$. The resulting mixture was extracted with $CH_2Cl_2$ several times and the combined extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified by chromatography (hexane/EtOAc, 1/3) to isolate **30** (4.65 g, 97%) as a pale yellow solid: m.p. = 97-99 ºC; $^1$H NMR (Acetone–D6): δ = 7.50 (s, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2 H), 3.92 (s, 2H), 3.74 (s, 3H), 3.51 (s, 3H); $^{13}$C NMR: δ = 158.6, 139.4, 133.4, 129.3, 129.1, 114.3, 84.9, 55.4, 32.6, 30.0; IR (KBr, $cm^{-1}$): = 3005, 3001, 2957, 2834, 1608, 1508, 1444, 1280, 1247, 1176, 1030, 981, 821, 770, 694; HR-ESIMS (*m/z*): Calcd. for $C_{12}H_{14}IN_2O$ $[M+H]^+$ 329.0145, found 329.0142.

**5-(4-Methoxybenzyl-1-methyl-1*H*-imidazole-4-carbaldehyde (32):** EtMgBr (3.0 M in ether, 5.2 mL, 15.7 mmol) was added into a solution of **30** (4.90 g, 14.9 mmol) in dry THF (50 mL) at 0 ºC, and the resulting mixture was stirred at rt. for 2 h. Then, *N*-methylformanilide (**31**) (2.23 mL, 17.9 mmol) was added at 0 ºC and the resulting mixture was stirred at rt overnight. Saturated aq. $NH_4Cl$ (20 mL) was added to quench the reaction and the organic layer was extracted with EtOAc, dried ($Na_2SO_4$) and concentrated to provide the crude product, which was purified through a short plug of silica gel (EtOAc) to isolate **32** (3.10 g, 90%) as a white solid: m.p. = 120-121 ºC; $^1$H NMR: δ = 9.99 (s, 1H), 7.40 (s, 1H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 4.32 (s, 2H), 3.3.75 (s, 3H), 3.45 (s, 3H); $^{13}$C NMR: δ = 187.7, 158.6, 138.8, 138.4, 137.7, 129.3, 128.5, 114.4, 55.3, 31.6, 28.5; IR (KBr, $cm^{-1}$): = 3105, 3022, 2957, 2818, 2770, 1669, 1552, 1511, 1344, 1244,1022, 824, 789; HR-ESIMS (*m/z*): Calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$ 231.1128, found 231.1139.

**4-[Hydroxy-(4-methoxyphenyl)]methyl-5-(4-methoxy-benzyl)-1-methyl-1*H*-imidazole (33):** p-Anisylmagnesium bromide was prepared from *p*-bromoanisole (6.67 mL, 52.1 mmol) and magnesium turnings (1.25 g, 52.1 mmol) in THF. A solution of **32** (3.00 g, 13.0 mmol) in THF (20 mL) was added dropwise. to afford a crude product, which was purified through a short plug of silica gel (EtOAc) to isolate **33** (4.34 g, 98%) as an off-white solid: m.p. = 134-135 ºC; $^1$H NMR: δ = 7.33 (d, *J* = 8.7 Hz, 2H), 7.33 (s, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.74 (s, 1H), 3.81 (s, 2H), 3.75 (s, 6H), 3.30 (s, 3H); $^{13}$C NMR: δ = 158.5, 158.1, 141.4, 136.8, 136.7, 130.2, 129.2, 127.8, 126.2, 113.9, 113.4, 69.4, 55.1, 55.1, 31.4, 28.0; IR (KBr, $cm^{-1}$): = 3112 (br), 2835, 2710, 1608, 1582, 1511, 1461, 1298, 1250, 1173, 1042, 846, 820, 787; HR-ESIMS (*m/z*): Calcd. for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.1703, found 339.1701.

**4,5-Bis(4-methoxybenzyl)-1-methyl-1*H*-imidazole (34):** $Et_3SiH$ (1.88 mL, 11.8 mmol) and TFA (0.73 mL, 9.5 mmol) were added to a solution of **33** (800 mg, 2.4 mmol) in anhydrous $CH_2Cl_2$ (20 mL) at rt, then the resulting mixture was stirred overnight. The reaction was quenched by the addition of satd. aq. solution of $NaHCO_3$ and the resulting mixture was extracted with $CH_2Cl_2$ several times. The combined extracts were dried ($Na_2SO_4$), concentrated and the residue was purified by chromatography (acetone) to provide **34** (615 mg, 81%) as a pale yellow oil: $^1$H NMR: δ = 7.32 (s, 1H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 2H), 3.85 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.30 (s, 3H); $^{13}$C NMR: δ = 158.3, 157.9, 139.0, 136.7, 133.2, 130.4, 129.6, 129.0, 125.7, 114.1, 113.9, 55.3, 33.1, 31.7, 28.3; IR (neat, $cm^{-1}$): = 3000, 2908, 2835, 1610, 1509, 1461, 1245,1178, 1034,819; HR-ESIMS (*m/z*): Calcd. for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ 323.1754, found 323.1774.

**2-Azido-4,5-bis(4-methoxybenzyl)-1-methyl-1*H*-imidazole (35):** *n*-Butyl lithium (1.4 M solution in hexanes, 1.50 mL, 2.1 mmol) was added dropwise to a stirred solution of **34** (613 mg, 1.9 mmol) in dry THF (15 mL) at -78 ºC. The reaction was stirred for 1 h at the same temperature. The cooling bath was removed for 10 min, then the reaction mixture was re-cooled to -78 ºC, and $TsN_3$ (0.80 g, 4.1 mmol) in THF (3 mL) was added dropwise. After stirring for 40 min at -78 ºC, the reaction mixture was allowed to come to rt. and was quenched by the addition of satd. aq. $NH_4Cl$ (3 mL). The aqueous layer was extracted with EtOAc (3x20 mL), and the combined organic extracts were dried ($Na_2SO_4$) and concentrated to provide a pale brown oil, which was purified through a short column of silica gel (hexane/EtOAc, 4:1) to isolate **35** (615 mg, 89%) as a pale yellow oil: $^1$H NMR: δ = 7.17 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 3.84 (s, 2H), 3.79 (s, 2H), 3.76 (s, 6H), 3.06 (s, 3H); $^{13}$C NMR: δ = 158.3, 158.0, 139.0, 136.3, 132.8, 130.2, 129.5, 129.0, 125.0, 114.1, 113.9, 55.3, 32.8, 29.5, 28.7; IR (neat, $cm^{-1}$): = 3000, 2944, 2835, 2132, 1609, 1508, 1247, 1176, 1034, 821; HR-ESIMS (*m/z*): Calcd. for $C_{20}H_{22}N_5O_2$ $[M+H]^+$ 364.1773, found 364.1768.

**2-Amino-4,5-bis(4-methoxybenzyl)-1-methyl-1*H*-imidazole (36):** Azide **35** (475 mg, 1.3 mmol) was dissolved in EtOH (10 mL) and stirred overnight under a hydrogen atmosphere (1 Atm) in the presence of 10% Pd-C on charcoal (47 mg) at rt. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to isolate amine, **36** (440 mg, quant) as a pale yellow solid: m.p. = 175-176 ºC; $^1$H NMR: δ = 7.09 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 5.79 (br, 2H), 3.75 (s, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.68 (s, 2H), 3.03 (s, 3H); $^{13}$C NMR: δ = 158.4, 158.0, 147.4, 132.4, 130.4, 130.4, 129.6, 128.9, 121.0, 114.1, 113.9, 55.3, 55.3, 31.8, 29.5, 28.5; IR (KBr, $cm^{-1}$): = 3374, 3296, 3123, 2954, 2838, 1764, 1610, 1550, 1510, 1462, 1249, 1178, 1033, 819, 758; HR-ESIMS (*m/z*): Calcd. for $C_{20}H_{24}N_3O_2$ $[M+H]^+$ 338.1863, found 338.1871.

**4,5-Bis(4-methoxybenzyl)-1-methyl-2-(3-methyl-imidazolidine-2,4-dione)imino-1*H*-imidazole (Naamidine G) (4):** *N*,*O*-Bis(trimethysilyl)acetamide (1.00 mL, 4.1 mmol) was added to a solution of 1-methylparabanic acid (526 mg, 4.1 mmol) in dry $CH_3CN$ under an $N_2$ atmosphere and the resulting mixture was heated at reflux for 1 h. Then, the solvent was removed by distillation and to the resulting yellow residue in toluene (3 mL) was added amine **36** (277 mg, 0.8 mmol) under $N_2$. After, this mixture was heated at 85 ºC overnight, water (5 mL) was added and the organic layer was extracted in to EtOAc. The dried organic layer ($Na_2SO_4$) was concentrated to afford a yellow residue, which was purified over silica gel (EtOAc/hexanes, 3/7) to provide **4** (287 mg, 78%) as a yellow powder: m.p. = 195-196 ºC (lit.[28] m.p. = 94 ºC); $^1$H NMR: δ = 10.04 (br, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 2H), 3.88 (s, 2H), 3.76 (s, 6H), 3.47 (s, 3H), 3.15 (s, 3H); $^{13}$C NMR: δ = 162.3, 158.6, 158.3, 155.7, 146.5, 145.0, 135.7, 131.5, 129.4, 129.1, 129.0, 127.0, 114.3, 114.1, 55.4, 32.3, 30.0, 28.7, 24.7; IR (KBr, cm-1): = 3241, 2931, 2835, 1788, 1738, 1656, 1511, 1451, 1302, 1248, 1177, 1036, 744, 697; HR-ESIMS (*m/z*): Calcd. for $C_{24}H_{26}N_5O_4$ $[M+H]^+$ 448.1979, found 448.1984.

**2-Azido-5-[4-methoxybenzyl]-4-[methoxy-(4-methoxy-phenyl)]methyl-1-methyl-1*H*-imidazole (38):** TFA (0.60 mL, 7.8 mmol) was added to a solution of **33** (1.31 g, 3.9 mmol) in anhyd MeOH (20 mL) at rt. and the mixture was then heated at 55 ºC overnight. Satd. aq. solution of $NaHCO_3$ was used to neutralize the above reaction mixture, and the aqueous layer was extracted with EtOAc (3x 30 mL). Combined organic layers were washed with water and brine, then dried ($Na_2SO_4$) and concentrated to provide **37** (1.37 g, >95%) as a pale yellow oil which was used directly in the next step: $^1$H NMR: δ = 7.34 (d, *J* = 8.7 Hz, 2H), 7.23 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 5.26 (s, 1 H), 3.93 (s, 2H), 3.75 (s, 6H), 3.34 (s, 3H), 3.29 (s, 3H). Following the general procedure for azidation, *n*-Butyl lithium (1.4 M solution in hexanes, 2.66 mL, 3.7 mmol), **37** (1.45 g, 3.4 mmol) in dry THF (20 mL) and $TsN_3$ (0.80 g, 4.1 mmol) were used to obtain the crude product, which was purified through a short column of silica gel (hexane/EtOAc, 4:1) to isolate **38** (891 mg, 67%) as a reddish brown oil: $^1$H NMR: δ = 7.41 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.23 (s, 1 H), 3.85 (s, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.35 (s, 3H), 3.03 (s, 3H); $^{13}$C NMR: δ = 159.0, 158.4, 139.8, 136.9, 133.4, 129.9, 129.1, 128.4, 126.1, 114.1, 113.7, 79.1, 56.8, 55.3, 55.3, 29.4, 28.6; IR (neat, cm$^{-1}$) = 2937, 2834, 2138, 1508, 1246, 1174, 1087, 1033, 829; HR-ESIMS (*m/z*): Calcd. for $C_{21}H_{23}N_5NaO_3$ $[M+Na]^+$ 416.1693, found 416.1677.

**2-Amino-5-(4-methoxybenzyl)-4-[methoxy-(4-methoxy-phenyl)]methyl-1-methyl-1*H*-imidazole (39):** Following the general procedure for catalytic reduction, azide **38** (800 mg, 2.0 mmol) in EtOH (10 mL) and 10% Pd-C on charcoal (80 mg) at 1 atm hydrogen were used to afford amine **39** (745 mg, quant) as a pale yellow solid: m.p. = 139-140 ºC; $^1$H NMR ($CD_3OD$): δ = 7.29 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.21 (s, 1H), 3.86 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.30 (s, 3H), 3.08 (s, 3H); $^{13}$C NMR: δ = 159.0, 158.4, 148.9, 133.8, 131.8, 130.7, 128.7, 127.9, 123.0, 113.6, 113.1, 78.5, 55.4, 54.4, 54.4, 28.0, 27.7; IR (KBr, cm$^{-1}$) = 3129, 1671, 1510, 1459, 1248, 1176, 1084, 1031, 830, 746; HR-ESIMS (*m/z*): Calcd. for $C_{21}H_{26}N_3O_3$ $[M+H]^+$ 368.1969, found 368.1970.

**5-(4-Methoxybenzyl)-4-[methoxy-(4-methoxy-phenyl)]methyl-1-methyl-2-(3-methylimidazolidine-2,4-dione)imino-1*H*-imidazole (4-Methoxynaamidine G) (40):** Following the general procedure, *N*,*O*-Bis(trimethysilyl)acetamide (0.33 mL, 1.4 mmol) and 1-methylparabanic acid (174 mg, 1.4 mmol) in dry $CH_3CN$ (15 mL) were used to produce a yellow residue, which was treated with amine **39** (100 mg, 0.3 mmol) to obtain the product **40** (13 mg, 11%) as a yellow solid after the purification over silica gel (EtOAc/hexanes, 2/3): $^1$H NMR: δ = 7.34 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H) , 6.87 (d, *J* = 8.8 Hz, 2H) , 6.78 (d, *J* = 8.8 Hz, 2H) , 5.29 (s, 1H), 3.98 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.45 (s, 3H), 3.35 (s, 3H), 3.17 (s, 3H);

**5-(4-Benzyloxy-3,5-dimethoxyphenyl)hydroxymethyl-4-iodo-1-methyl-1H-imidazole (42):** EtMgBr (3.0 M solution in ether, 7.54 mL, 22.6 mmol) was added to a solution of **14** (7.19 g, 21.5 mmol) in dry $CH_2Cl_2$ (100 mL) at rt. over ~10 min. After stirring at rt. for 20 min, aldehyde **41** (6.46 g, 23.7 mmol) was added to the reaction followed by 48 h stirring. Then, satd. aq. NH4Cl (10 mL) was added to the reaction and the resulting pale yellow solid was filtered and the filtrate was partitioned with $CH_2Cl_2$. The organic layer was dried ($Na_2SO_4$) and concentrated to provide a pale yellow solid. The resulting solid was triturated with hexanes, recrystallized with $CH_2Cl_2$ to isolate **42** (9.68 g, 95%) as a white solid: m.p. = 173-175 ºC; $^1$H NMR: δ = 7.44 (d, *J* = 7.8 Hz, 2H), 7.31-7.24 (m, 4H), 6.57 (s, 2H), 5.98 (s, 1H), 5.18 (s, 1H), 4.98 (s, 2H), 3.75 (s, 6H), 3.43 (s, 3H); $^{13}$C NMR: δ = 153.6, 141.1, 137.8, 136.6, 135.9, 135.2, 128.6, 128.2, 127.9, 102.7, 84.6, 75.0, 67.1,56.3, 33.5; IR (neat, cm$^{-1}$): = 3253 (br), 3104, 1585, 1501, 1411, 1338, 1226, 1140, 1033, 908 ; HR-DARTMS (*m/z*): Calc. for $C_{20}H_{21}IN_2O_4$ $[M]^+$ 480.0546; found: 480.0546; Calc. for $C_{20}H_{22}IN_2O_4$ $[M+H]^+$ 481.0624, found 481.0624.

**5-(4-Benzyloxy-3,5-dimethoxybenzyl)-4-iodo-1-methyl-1H-imidazole (43):** $Et_3SiH$ (1.00 mL, 6.2 mmol) and TFA (0.40 mL, 5.2 mmol) were added to a solution of **42** (0.50 g, 1.0 mmol) in anhydrous $CHCl_3$ (20 mL) at rt. and the resulting mixture was heated at reflux temperature for 24 h under nitrogen atmosphere. After cooling to rt., reaction was quenched by the addition of satd. aq. $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$ and the combined organic extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified by chromatography (EtOAc) to isolate **43** (0.14 g, 28%) as a pale brown semi solid: $^1$H NMR: δ = 7.44 (d, *J* = 6.9 Hz, 2H), 7.36 (s, 1H), 7.30 (t, *J* = 6.9 Hz, 2H), 7.25 (d, *J* = 6.9 Hz, 1H), 6.31 (s, 2H), 4.95 (s, 2H), 3.87 (s, 2H), 3.73 (s, 6H), 3.40 (s, 3H); $^{13}$C NMR: δ = 153.8, 139.6, 137.9, 135.9, 133.1, 128.5, 128.2, 127.9, 105.2, 85.0, 75.1, 56.3, 32.7, 31.0; IR (neat, cm-1): = 3107, 2939, 1588, 1494, 1460, 1420, 1237, 1215, 1187, 1100, 978,758 ; HR-ESIMS (*m/z*): Calc. for $C_{20}H_{22}IN_2O_3$ $[M+H]^+$ 465.0670, found 465.0669.

**5-[(3,5-Dimethoxy-4-hydroxy)benzyl]-4-iodo-1-methyl-1H-imidazole (44):** A second product was obtained from above reaction in which the *O*-benzyl protecting group has been removed **44** (0.11 g, 27%) as a pale yellow solid: m.p. = 210-212 ºC; $^1$H NMR (DMSO-$D_6$): δ = 7.40 (s, 1H), 6.34 (s, 2H), 5.47 (br, 1H), 3.90 (s, 2H), 3.82 (s, 6H), 3.45 (s, 3H); $^{13}$C NMR: δ = 148.6, 140.6, 134.7, 133.7, 128.4, 106.1, 85.1, 56.5, 32.6, 30.0; IR (neat, cm$^{-1}$): = 3107, 2936 (br), 1595, 1514, 1499, 1413, 1242, 1214, 1113, 1037, 838, 811, 765, 737; HR-ESIMS (*m/z*): Calc. for $C_{13}H_{15}IN_2O_3$ $[M+H]^+$

**5-(4-Benzyloxy-3,5-dimethoxyphenyl)hydroxymethyl-1-methyl-1H-imidazole-4-carbaldehyde (45):** EtMgBr (3.0 M in ether, 13.8 mL, 41.4 mmol) was added into a solution of **42** (9.03 g, 18.8 mmol) in dry THF (200 mL) at rt., and the resulting mixture was stirred for 20 min. Then, *N*-methylformanilide (**30**) (2.78 mL, 22.6 mmol) was added to the reaction mixture followed by stirring for 33 h. Half saturated $NH_4Cl$ (30 mL) was added to quench the reaction and the organic layer was extracted with EtOAc, dried ($Na_2SO_4$) and concentrated to provide the crude product, which was purified through a short plug of silica gel (EtOAc→Acetone) to isolate **45** as a pale yellow solid (5.52 g, 77%): m.p. = 132-134 ºC; $^1$H NMR: δ = 9.82 (s, 1H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.38 (s, 1H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.25 (m, 1H), 6.50 (s, 2H), 6.23 (s, 1H), 4.94 (s, 2H), 3.71 (s, 6H), 3.47 (s, 3H); $^{13}$C NMR: δ = 188.4, 153.8, 141.7, 139.9, 138.0, 137.7, 136.6, 136.2, 128.5, 128.2, 127.9, 103.4, 75.1, 66.7, 56.3, 33.1; IR (neat, cm$^{-1}$): = 3253 (br), 3106, 2938, 1680, 1587, 1502, 1450, 1415, 1230, 1100, 1056, 824 ; HR-DARTMS (*m/z*): Calc. for $C_{21}H_{23}N_2O_5$ $[M+H]^+$ 383.1601, found 383.1597.

**6-Benzyloxy-5,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-1H-naphtho[2,3-d]imidazole (47):** A Grignard reagent was prepared from *p*-bromoanisole, (7.23 mL, 56.5 mmol), magnesium turnings (1.35 g, 56.5 mmol) and a small crystal of iodine in THF (100 mL) and a solution of **45** (5.40 g, 14.1 mmol) in THF (50 mL) were used to obtain a crude product, which was purified through a short plug of silica gel (EtOAc) to isolate **46** (4.38 g, 63%) as a pale yellow oil, which was used in the next

step directly without further characterization. $Et_3SiH$ (11.41 mL, 71.4 mmol) and TFA (4.81 mL, 62.5 mmol) were added to a solution of **45** (4.38 g, 8.9 mmol) in anhydrous $CH_2Cl_2$ (100 mL) at rt. and the resulting mixture was stirred for 24 h under nitrogen atmosphere. Then, the reaction was quenched by the addition of satd. aq. solution of $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ several times and the combined extracts were dried ($Na_2SO_4$), and concentrated. The residue was purified by chromatography (EtOAc → acetone) to provide **47** (3.30 g, 81%) as a pale brown solid; m.p. = 194-197 ºC; $^1$H NMR: δ = 7.87 (s, 1H), 7.61 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8,7 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.08 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 5.10 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H); $^{13}$C NMR: δ = 158.2, 152.1, 150.6, 146.6, 142.9, 139.8, 138.0, 134.4, 132.4, 131.6, 130.9, 129.7, 128.4, 128.3, 127.9, 119.6, 112.7, 104.0, 102.3, 75.2, 60.9, 55.8, 55.4, 31.0; IR (neat, cm$^{-1}$): = 2929, 2831, 1607, 1514, 1451, 1330, 1274, 1236, 1145, 1075, 1027, 826, 740; HR-DARTMS (*m/z*): Calc. for $C_{28}H_{27}N_2O_4$ $[M+H]^+$ 455.1971, found 455.1983.

**1-(*N*,*N*-dimethylaminosulfonyl)-4-iodo-5-(4-methoxybenzyl)-1H-imidazole (50):** EtMgBr (3.0 M solution in ether, 8.60 mL, 25.8 mmol) was added to a solution of **49** (7.19 g, 21.5 mmol) in dry $CH_2Cl_2$ (150 mL) at rt. The resulting mixture was stirred at rt. for 20 min and 1.0 M solution of CuCN.2LiCl in dry THF (26.0 mL, 26.0 mmol) was added followed by *p*-methoxybenzyl bromide (3.80 mL, 25.8 mmol). The orange reaction solution was stirred at rt. for 48 h and poured into half sat. $NH_4Cl$ containing 2% concentrated $NH_3$ (50 mL). After stirring for 20 min, the resulting solid was filtered off and the filtrate was partitioned with $CH_2Cl_2$ (3x50 mL). The organic layer was dried ($Na_2SO_4$), concentrated and purified by chromatography (EtOAc/hexane, 3:7) to afford **50** (6.41 g, 65%) as a pale yellow solid: m.p. = 76-78 ºC; $^1$H NMR: δ = 7.87 (s. 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.37 (s, 2H), 4.09 (s, 2H), 3.71 (s, 3H), 2.49 (s, 6H); $^{13}$C NMR: δ = 158.5, 139.7, 137.9, 132.5, 129.1, 114.0, 90.6, 55.4, 37.6, 29.9; IR (neat, cm$^{-1}$): = 3111, 2919, 1514, 1459, 1415, 1240, 1173, 1174, 1095, 960, 802 ; HR-DARTMS (*m/z*): Calc. for $C_{13}H_{17}IN_3O_3S$ $[M+H]^+$ 422.0030, found 422.0047.

**4-(4-Benzyloxy-3,5-dimethoxybenzyl)-1-(*N*,*N*-dimethylsulfonyl)-5-(4-methoxybenzyl)-1H-imidazole (51):** EtMgBr (3.0 M solution in ether, 4.98 mL, 14.9 mmol), **50** (5.72 g, 13.6 mmol) in dry $CH_2Cl_2$ (150 mL), 1.0 M solution of CuCN.2LiCl in dry THF (16.3 mL, 16.3 mmol) and 206 (6.87 g, 20.4 mmol) were used to synthesize **51** (5.18 g, 70%) as a pale yellow oil after the purification by chromatography (EtOAc:hexane, 1:1): $^1$H NMR: δ = 7.94 (s. 1H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.33 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.37 (s, 2H), 4.94 (s, 2H), 4.14 (s, 2H), 3.78 (s, 2H), 3.75 (s, 3H), 3.71 (s, 6H), 2.57 (s, 6H); $^{13}$C NMR: δ = 158.4, 153.4, 141.3, 138.1, 138.0, 135.6, 134.8, 130.3, 129.9, 128.9, 128.5, 128.2, 127.8, 114.0, 106.0, 75.1, 56.1, 55.4, 37.5, 34.0, 28.1; IR (neat, cm$^{-1}$): = 2929, 2857, 1691, 1507, 1393, 1252, 1124, 909, 836, 779 ; HR-DARTMS (*m/z*): Calc. for $C_{29}H_{34}N_3O_6S$ $[M+H]^+$ 552.2163, found 552.2180.

**5-(4-Benzyloxy-3,5-dimethoxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazole (53):** Methyl trifluoromethanesulfonate (0.95 mL, 8.7 mmol) was added dropwise to a solution of **51** (3.96 g, 7.2 mmol) in $CH_2Cl_2$ (50 mL), at 0 ºC under $N_2$ and stirred for 4 h at the same temperature. Then, the solvent was evaporated under reduced pressure and the crude pale yellow oil was dissolved in dry acetonitrile (30 mL), and benzylamine (0.95 mL, 8.7 mmol) was added to it. After heating at 80 ºC for 10 h, the solvent was evaporated to provide a crude oil, which was purified with a gradient column (EtOAc:hexanes, 3:1→EtOAc:acetone; 1:1) to isolate **53** (2.96 g, 90%) as a light brown oil: $^1$H NMR: δ = 7.45 (d, *J* = 7.3 Hz, 2H), 7.40 (s, 1H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.15 (s, 2H), 4.96 (s, 2H), 3.88 (s, 2H), 3.87 (s, 2H), 3.75 (s, 3H), 3.64 (s, 6H), 3.34 (s, 3H); $^{13}$C NMR: δ = 157.9, 153.8, 138.8, 137.9, 136.8, 135.5, 134.1, 133.1, 129.5, 128.5, 128.2, 127.9, 125.5, 113.9, 105.1, 75.1, 56.1, 55.3, 32.8, 31.9, 29.5; IR (neat, cm$^{-1}$): = 2929, 2857, 1691, 1507, 1391, 1251, 1176, 1150, 910; HR-ESIMS (*m/z*): Calc. for $C_{28}H_{31}N_2O_4$ $[M+H]^+$ 459.2278, found 459.2278.

**2-Azido-5-(4-benzyloxy-3,5-dimethoxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazole (55):** n-Butyl lithium (1.6 M solution in hexanes, 1.31 mL, 2.1 mmol) was added dropwise to a stirred solution of **52** (870 mg, 1.9 mmol) in dry THF (20 mL) at -78 ºC, and the reaction was stirred for 1 h. The cooling bath was removed for 10 min, then the reaction mixture was re-cooled to -78 ºC, and then $TrisN_3$ (706 mg, 2.3 mmol) was added. After stirring for an additional 45 min at -78 ºC, the reaction mixture was quenched by the addition of satd. aq. $NH_4Cl$ (5 mL). The aqueous layer was extracted with EtOAc (3x15 mL), and the combined organic extracts were dried ($Na_2SO_4$) and concentrated to provide a pale brown oil, which was purified through a short column of silica gel (hexane/EtOAc, 7:3) to isolate azide **55** (600 mg, 63%) as a pale brown oil: $^1$H NMR: δ = 7.46 (d, *J* = 7.4 Hz, 2H), 7.38-7.26 (m, 3H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.16 (s, 2H), 4.95 (s, 2H), 3.85 (s, 2H), 3.80 (s, 2H), 3.76 (s, 3H), 3.64 (s, 6H), 3.08 (s, 3H); $^{13}$C NMR: δ = 158.0, 153.7, 139.2, 137.9, 136.5, 135.5, 134.0, 132.9, 129.5, 128.6, 128.2, 127.9, 124.6, 113.9, 105.0, 75.0, 56.1, 55.3, 32.7, 30.0, 29.6; IR (neat, cm-1): = 2929, 2857, 2129, 1691, 1507, 1391, 1252, 1150, 1124, 909, 836, 779 ; HR-ESIMS (*m/z*): Calc. for $C_{28}H_{30}N_5O_4$ $[M+H]^+$ 500.2292, found 500.2290.

**2-Amino-5-(3,5-dimethoxy-4-hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1H-imidazole (Naamine G) (56):** Azide **55** (600 mg, 1.2 mmol) was dissolved in EtOH (15 mL) and stirred overnight under a hydrogen atmosphere (55 psi) in the presence of 20% $Pd(OH)_2$ on charcoal (100 mg) at rt. The catalyst was filtered through a pad of Celite and the filtrate was concentrated to isolate naamine G, (**56**) (430 mg, 95%) as a greenish-yellow solid; m.p. = 218-220 ºC; $^1$H NMR ($CD_3OD$): δ = 7.17 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.34 (s, 2H), 3.92 (s, 2H), 3.84 (s, 2H), 3.74 (s, 3H), 3.69 (s, 6H), 3.23 (s, 3H); $^{13}$C NMR: δ = 158.8, 148.3, 146.5, 134.3, 129.8, 129.2, 127.3, 122.8, 122.4, 114.0, 105.2, 55.5, 54.5, 28.8, 28.3, 27.9; IR (neat, cm$^{-1}$): = 3244 (br), 3004, 2836, 1667, 1654, 1609, 1500, 1461, 1429, 1245, 1216, 1110, 1022; HR-DARTMS (*m/z*): Calc. for $C_{21}H_{26}N_3O_4$ $[M+H]^+$ 384.1918, found 384.11907.

**5-(3,5-Dimethoxy-4-hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-2-(3-methylimidazolidine-2,4-dione)imino-1H-imidazole (Naamidine H) (5):** Following the general procedure for this reaction, *N*,*O*-Bis(trimethysilyl)acetamide (0.63 mL, 2.6 mmol) and 1-methylparabanic acid (331 mg, 4.1 mmol) in dry $CH_3CN$ (10 mL) were used to produce 3-trimethylsilyl-1-methylparabanic acid. After removing the solvent, naamine G, 1 h (198 mg, 0.5 mmol) was added and the mixture was heated at 80 ºC overnight in dry toluene (5 mL). Usual workup and purification over silica gel (EtOAc/hexanes, 4/6) provided naamidine H (**5**) as a yellow amorphous solid (205 mg, 80%): m.p. = 204-205 ºC; $^1$H NMR: δ = 7.14 (d, *J* = 8.7 Hz, 2H), 6.98 (br, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.14 (s, 2H), 3.89 (s, 2H), 3.88 (s, 2H), 3.75 (s, 3H), 3.69 (s, 6H), 3.49 (s, 3H), 3.47 (s, 3H), 3.16 (s, 3H); $^{13}$C NMR: δ = 162.3, 158.3, 155.5, 147.4, 146.6, 144.7, 136.1, 133.7, 131.7, 129.4, 128.1, 126.7, 114.1, 104.7, 56.3, 55.4,

32.3, 30.0, 29.7, 24.8; IR (neat, $cm^{-1}$): = 3501, 3212, 2929, 2837, 1784, 1718, 1652, 1511, 1392, 1113, 1039, 1020, 918 ; HR-DARTMS (*m/z*): Calc. for $C_{25}H_{28}N_5O_6$ [M+H]+ 494.2034, found 494.2049.

**Cytotoxicity assay ($IC_{50}$ measurement):** Human breast adenocarcinoma cell line (MCF7, ATCC) was maintained in growth medium containing Dulbeco's modified Eagles media (DMEM, Sigma) with 10% heat inactivated fetal bovine serum (FBS, Sigma), 2 mM L-glutamine, 100 units of penicillin, and 0.1 mg/mL streptomycin. Cells were incubated in a water-jacketed humidified CO2 incubator with 5% CO2 and at 37 °C. To measure the cytotoxicity of the test compounds, approximately 10,000 MCF7 cells were cultivated in each well of a 96-well microtiter plate and maintained overnight in 150 180 µL of the growth medium and the conditions described above. Each compound was initially dissolved in DMSO and then was serially dilutedion also made (in DMSO) for (10 µL for each concentration). 10 µL andof each diluted stock was further then diluted within 990 µL of above growth medium to have desired concentration. To treat the cells, 50 20 µL of growth medium containing the appropriate amount of each compound was added to each well to obtain required final concentration (200 µL final volume and 0.1 µL of DMSO in each well). An equivalent volume of the vehicle (0.1 % DMSO) was added to each control well. After 96 h of incubation, the cell viability was analyzed by using the MTT assay. In brief, 20 µL of MTT solution (stock 5 mg/ml in PBS) was added into each well and incubated for 2 h under normal growth conditions to allow the viable cell to convert MTT to formazan. Then the media was discarded and formazan crystals were dissolved by adding 100 µL of DMSO and incubating 2 h with continuous shaking. The absorbance of the lysates was measured directly at 560 nm using a micro plate reader (Fluostar-omega, BMG Labtech). The percent viable cells (calculated based on absorbance of the untreated control sample) were plotted as a function of concentration to obtain the IC50 values. Each experiment was repeated at least twice (with 5 replicates each time).

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