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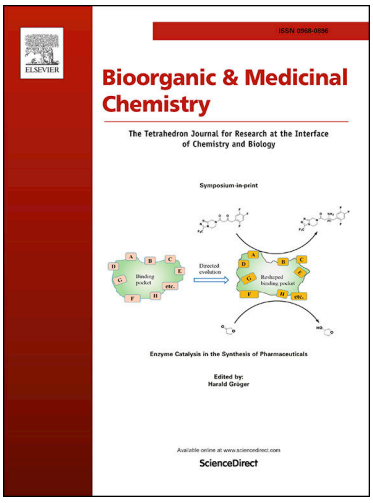

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Syntheses and Anti-HIV and Human Cluster of Differentiation 4 (CD4) Down-Modulating Potencies of Pyridine-Fused Cyclotriazadisulfonamide (CADA) Compounds

Liezel A. Lumangtad,[a,b] Elisa Claeys,[c] Sunil Hamal,[a] Amarawan Intasiri,[a,d] Courtney Basrai,[a] Expedite Yen-Pon,[a] Davison Beenfeldt,[a] Kurt Vermeire,[c] and Thomas W. Bell*,[a]

[a]Department of Chemistry, University of Nevada, Reno, Nevada, 89557-0216, USA

[c]KU Leuven Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory of Virology and Chemotherapy, 3000 Leuven, Belgium

[d]Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, 10330 Thailand

ABSTRACT

CADA compounds selectively down-modulate human cell-surface CD4 protein and are of interest as HIV entry inhibitors and as drugs for asthma, rheumatoid arthritis, diabetes and some cancers. Postulating that fusing a pyridine ring bearing hydrophobic substituents into the macrocyclic scaffold of CADA compounds may lead to potent compounds with improved properties, 17 macrocycles were synthesized, 14 with 12-membered rings having an isobutylene head group, two arenesulfonyl side arms, and fused pyridine rings bearing a para substituent. The analogs display a wide range of CD4 down-modulating and anti-HIV potencies, including some with greater potency than CADA, proving that a highly basic nitrogen atom in the 12-membered ring is not required for potency and that hydrophobic substituents enhance potency of pyridine-fused CADA compounds. Cytotoxicities of the new compounds compared favorably with those of CADA, showing that incorporation of a pyridine ring into the macrocyclic scaffold can produce selective compounds for potently down-modulating proteins of medicinal interest.

ARTICLE INFO

*Corresponding author. *E-mail address:* twb@unr.edu

[b]Present address: Nanosyn, 3100 Central Expressway, Santa Clara, California 95051, USA

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1. Introduction

Cyclotriazadisulfonamide (CADA) compounds selectively down-modulate expression of the cell-surface cluster of differentiation 4 (CD4) protein on primate cells and inhibit replication of human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV).[1–6] CD4 is expressed on T cells and other immune cells; it is required for entry of HIV into host cells.[7,8] Hence, CADA compounds act as HIV entry inhibitors, a class of compounds that are of continuing interest for treatment of HIV infection.[5,9–16] They are unique in that they do not simply inhibit direct binding of the virus to the cell; they reduce CD4 levels below the concentration required for entry of HIV.[2] Monoclonal antibodies that target CD4, such as iMabm36,[17] and small-molecule inhibitors[18–21] of the binding of viral gp120 to CD4 are of current interest as candidates for prophylactic and therapeutic drugs for HIV and acquired immunodeficiency syndrome (AIDS). The small-molecule drug fostemsavir (BMS663068),[19–21] which inhibits attachment by blocking the GP120-CD4 interaction, is in a phase III clinical trial for treatment of HIV-1 infected patients.[22] GSK3732394, a tri-specific entry inhibitor targeting CD4, viral gp41, and α-helical peptide fusion, has also entered clinical trials.[23,24]

Because antiretroviral therapy does not fully eradicate the virus, current research is aimed at a "kick and kill" strategy; the virus is first activated by an anti-latency drug, then eliminated by immune activation and/or antiviral or cytotoxic drugs.[15] Recent clinical trials of this approach have failed.[25] Combinations of anti-HIV drugs operating by different mechanisms may be required, as in current therapeutic regimens,[26] so there is a continuing demand for new HIV entry inhibitors.[15] CADA compounds are radically different from conventional anti-HIV agents that target viral proteins and are susceptible to resistance by mutation and selection mechanisms.[27] Instead, CADA

compounds target a host biochemical pathway for cellular expression of CD4, so it is difficult to generate a CADA-resistant virus with high infectivity.[28]

The availability of many conventional anti-HIV drugs suggests that CADA compounds may be less significant as anti-HIV agents and may be more significant as drugs for other diseases. Anti-CD4 antibodies have long been of interest for chemotherapy of various immune-based diseases involving CD4+ T cells,[29–31] including asthma, rheumatoid arthritis,[32–35] and diabetes. They are also being investigated as therapeutic agents for various cancers, such as neuroblastoma[36] and T cell lymphomas.[37,38] Thus, as CD4 receptor down-modulating drugs, CADA compounds are of potential interest as therapeutic agents for numerous autoimmune diseases and cancers. While CD4 down-modulation may at first appear to be a therapeutic strategy that could compromise the immune system, the African green monkey avoids progression to AIDS when infected by SIV_{agm} through decreased expression of CD4 on its T cells, and the resulting $CD4^-$ cells are immunocompetent.[39]

It has been found that the lead compound (CADA, **1**, Figure 1) down-modulates cell-surface CD4 by binding the signal peptide (SP) of the CD4 preprotein.[40] In mammals, more than one third of all proteins are bound to the cell membrane.[41,42] These proteins are translated by ribosomes that are docked onto the endoplasmic reticulum (ER) membrane. Cell-surface and secreted proteins consisting of more than 100 amino acids enter the interior (lumen) of the ER by crossing its membrane during translation, a process known as co-translational translocation.[43–50] Most type-1 transmembrane proteins, such as CD4, are targeted to the ER membrane by the SP, consisting of the first 15-40 amino acids at the *N*-terminus of the nascent protein (preprotein). For some membrane-bound proteins, such as G-protein coupled receptors (GPCRs), the first transmembrane domain serves as the signal sequence and is targeted in a similar manner. CADA

recognizes and binds to the SP of the human CD4 preprotein, preventing co-translational translocation of CD4 into the ER lumen, thus inhibiting cell-surface expression of this protein.[40] The significance of CADA compounds may go far beyond CD4 down-modulation in that the results of structure-activity and mechanistic studies could eventually enable the design of SP-targeting drugs for inhibiting expression of many cell-surface proteins of medicinal interest.[51]

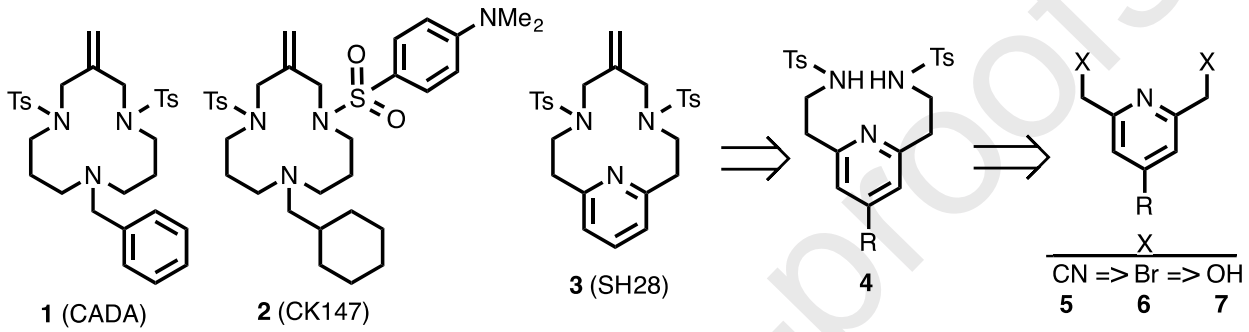


Figure 1. Structures of CADA (**1**), CK147 (**2**), pyridine-fused analog SH28 (**3**) and its retrosynthesis to key intermediate, diol **7** (R = H).

CADA specifically down-modulates CD4 among the numerous antigens expressed on T cells, but another human protein, sortilin, has been discovered as a secondary target for inhibition of ER translocation by CADA.[52] Sortilin has recently been identified as a potential drug target for many disorders,[53] including frontotemporal lobar degeneration,[54] autism,[55] Alzheimer's disease,[56] atherosclerosis,[57,58] and breast cancer.[59] The structure-activity relationships (SARs) described here focus on CD4 down-modulation potencies of pyridine-fused CADA compounds, but these compounds also contribute to the library of analogs that will be available for future SAR studies on sortilin down-modulation.

Previous SAR studies of CADA compounds focused on modifications of CADA's benzyl tail group,[2,6,60] its isobutylene head group,[2] and the two arenesulfonamide side arms.[2,6,60–62] Increasing the hydrophobicity of the tail[60] and the size of the dipole moment of one of the side

arms[62] were found to improve activity, leading to potent analog CK147 (**2**, Figure 1).[62] Hydrophobic tail groups decrease water solubility of CADA compounds, limiting biological studies. Introducing a pyridine ring into the structure was attractive for a number of reasons. Pyridine is second in abundance only to benzene as a 6-membered ring in drugs.[63] There are numerous examples of pyridine-containing drugs,[64,65] partly because its moderate pK_a (5.23) enables facile protonation/deprotonation during cell permeation and its metabolic reaction are readily adjustable via substitution.[66,67] It also has a large dipole moment (2.23 Debye)[68] and its nitrogen atom is a good hydrogen bond acceptor, enhancing attractive charge-dipole, dipole-dipole and hydrogen bonding interactions with drug targets. Of potential concern to this study was that pyridine is very polar and miscible with water in all proportions. Yet, the first pyridine-fused analog (SH28, **3**) had measurable CD4 down-modulation potency. We hypothesized that adding nonpolar groups to the para position of the pyridine ring would increase potency, without sacrificing water solubility. The retrosynthesis of **3** shown in Figure 1 was applied to each new analog, reducing the synthetic challenge for each target to obtaining diol **7** as the key intermediate.

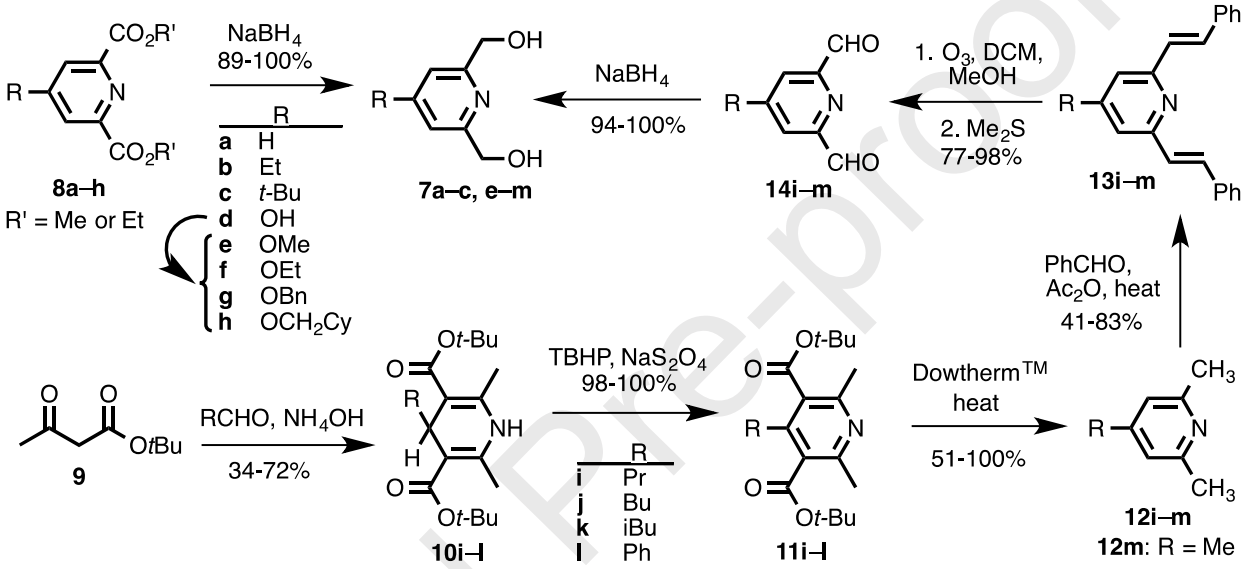
2. Results and discussion

2.1 Synthesis

The routes used for synthesis of the para substituted diols (**7**) are shown in Scheme 1. The shortest approach is reduction of diesters of pyridine-2,6-dicarboxylic acids, but only the unsubstituted dimethyl ester **8a** is commercially available at a price that is attractive for multistep synthesis. Reduction of **8a** and some *para*-substituted esters, including **8e**–**h**, with sodium borohydride in methanol or ethanol generally proceeds in high yields.[69–78] Dimethyl 4-ethylpyridine-2,6-dicarboxylate (**8b**) and diethyl 4-*t*-butylpyridine-2,6-dicarboxylate (**8c**) were prepared by free radical substitution reactions using H_2O_2, $FeSO_4$ and propionaldehyde or

pivaldehyde, respectively.[79,80] The 4-alkoxypyridinedicarboxylates **8e**–**h** were prepared by deprotonation and alkylation of **8d** (dimethyl 4-hydroxypyridine-2,6-dicarboxylate[70,72,78] or diethyl 4-hydroxypyridine-2,6-dicarboxylate).[71,75] Sodium borohydride reduction of all diesters **8a**–**c** and **8e**–**h** gave the corresponding diols **7a**–**c** and **7e**–**h** in very high yields, as shown in Scheme 1.

Scheme 1



Five additional para substituted diols with methyl, propyl, butyl, isobutyl, and phenyl substituents (**7i**–**m**, Scheme 1) were prepared by the Hantzsch pyridine synthesis[81–86] with the direct method, condensing the corresponding aldehydes with *t*-butyl acetoacetate and ammonium hydroxide.[81,83,84,86,87] Because of their ease of hydrolysis under acidic conditions, *t*-butyl esters were chosen for the general synthetic approach, modifying reactions reported for the 4-phenyl series.[88,89] Mild oxidizing conditions reported by Bai *et al*.[90] were chosen for standard conversion of **10** to **11**, rather than employing the traditional oxidant, nitric acid.[87] 4-Phenyl-1,4-dihydropyridine diester **10l**, obtained in 52% yield from benzaldehyde, was oxidized quantitatively under these conditions to **11l**. The HCl salt produced by acidic hydrolysis of this *t*-butyl diester was insoluble in the convenient pyrolysis solvent Dowtherm™ A,[91] and *t*-butyl esters of this type

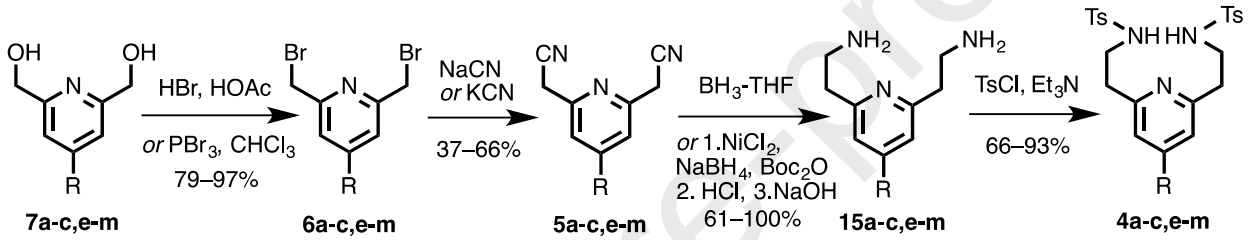
are resistant to alkaline saponification. Fortunately, **11l**[88,89] underwent quantitative dealkylcarboxylation to **12l** in boiling Dowtherm™ A. In contrast, saponification of the corresponding diethyl ester and neat pyrolysis of the intermediate diacid has been reported to give **12l** in 66% yield, overall.[92] This sequence of reactions was applied also to butyraldehyde, isobutyraldehyde, valeraldehyde, isovaleraldehyde and cyclohexanecarboxaldehyde, giving yields ranging from 34–72% for the condensation step (**9** to **10**). Excellent yields were obtained for the oxidation step (**10** to **11**), except that dealkylation of secondary substituents (isopropyl and cyclohexyl) was observed, apparently as a consequence of the single-electron transfer mechanism of this reaction.[90] Diesters **11i**–**k** underwent pyrolytic dealkylcarboxylation to 4-alkyl-2,6-dimethylpyridines **12i**–**k** in useful yields (51–100%).

Methyl groups in the 2 and 6 positions of pyridines can be selectively converted to aldehyde substituents by condensation with benzaldehyde, followed by ozonolysis.[93,94] As described in the literature,[94] this sequence of reactions was used to convert collidine (2,4,6-trimethylpyridine, **12m**) to 4-methyl-2,6-pyridinedicarboxaldehyde (**14m**) in 40% overall yield. As shown in Scheme 1, this route was also used to convert **12i**–**l** to dialdehydes **14i**–**l**. The intermediate 4-phenyl-2,6-distyrylpyridine (**13l**)[95] was obtained in 83% yield, while the yields of 4-alkyl analogs **13i**–**k** were lower due to side-products from condensation in the 4-position. All distyrylpyridines **13i**–**m** underwent ozonolysis in high yields and the resulting dialdehydes, including **14l**,[96] were reduced in very high yields to **14i**–**m**, including known diols **14l**[69,73] and **14m**.[74]

As shown in Scheme 2, twelve diols (**7a**–**c**, **e**–**m**) were converted to the corresponding open-chain ditosylamides to prepare for macrocyclization to the target fused pyridine CADA analogs. Preparation of 2,6-bis(bromomethyl)pyridine (**6a**) from diol **7a** has been reported frequently, generally with HBr in water[97–99] or acetic acid,[77,100] but PBr_3 in $CHCl_3$[75,78] was chosen

for the standard approach to the entire series, considering the potential lability of 4-alkoxypyridines under protic conditions. Conversions of **7e**–**g**[75,76,78,101] and **7l**[69] to **6e**–**g,l** have also been reported. The dibromides (**6**) were converted to dinitriles (**5**) via S_N2 displacement by cyanide, as described for **6a** to **5a**.[73,97] Dinitrile **5a** was reduced to diamine **15a** with BH_3•THF,[73,97] but higher yields were obtained in the remaining cases with $NaBH_4$ and $NiCl_2$.[102] Finally, the diamines were tosylated in high yield with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane, as described for **15a** to **4a**.[73]

Scheme 2

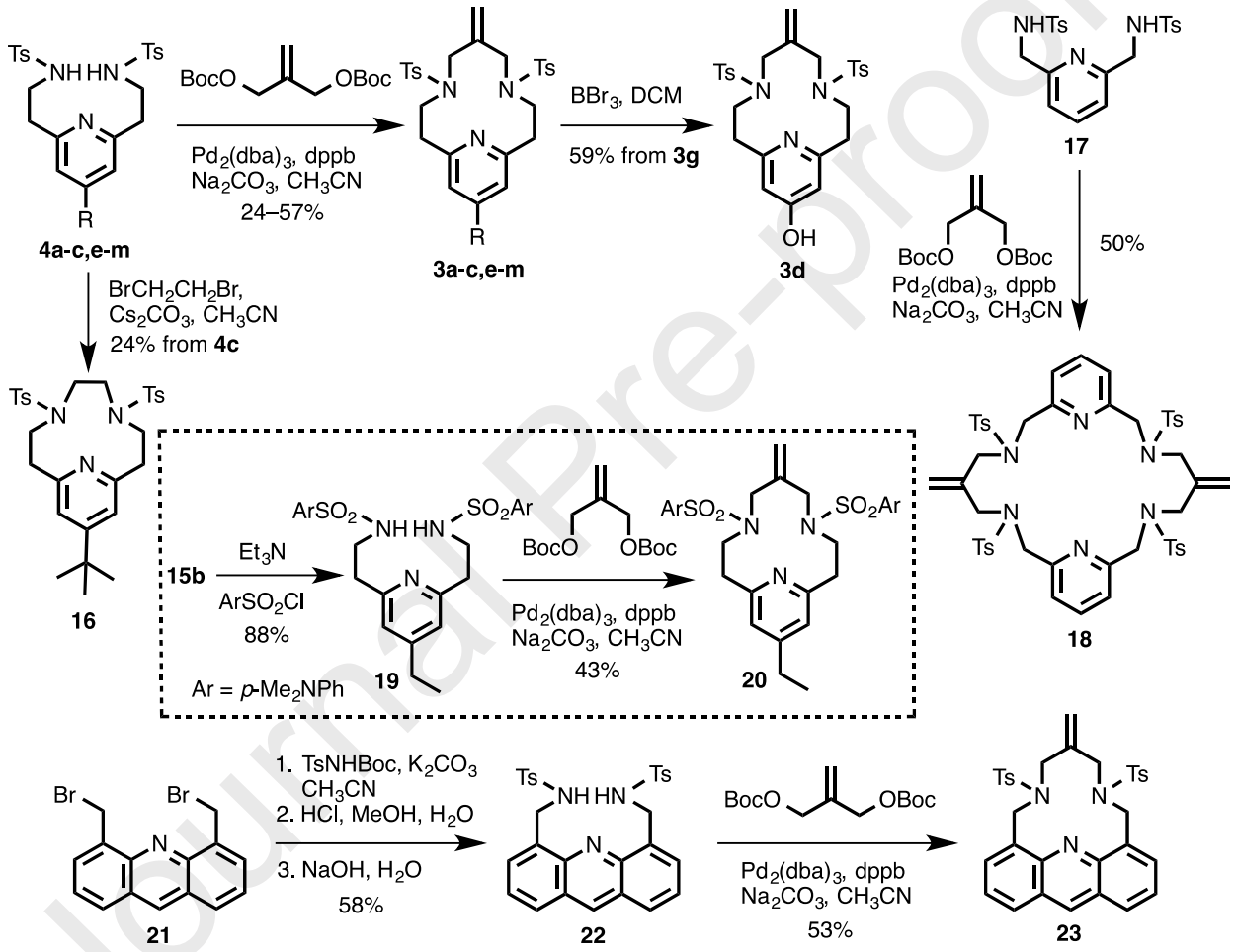


R = H (a), Et (b), *t*-Bu (c), OMe (e), OEt (f), OBn (g), OCH_2Cy (h), Pr (i), Bu (j), *i*-Bu (k), Ph (l), Me (m).

As shown in Scheme 3, the 12 open-chain disulfonamides **4a-c**,**e-m** underwent palladium-catalyzed cyclization with 3-methylene-1,3-propanediyl bis(*t*-butylcarbonate), as previously reported for **4a** to **3a**.[103] To examine biological effects of a 4-hydroxypyridine (or the 4-pyridone tautomer), para benzyloxy analog **3g** was dealkylated to give compound **3d**. Also, Atkins-Richman cyclization[104,105] of para *t*-butyl open-chain disulfonamide **4c** with 1,2-dibromoethane gave 11-membered macrocycle **16** for further structural diversity. While an isobutylene head group has been essential for maximal potency in CADA compounds tested so far, **16** tests the combination of an ethylene head group with a fused pyridine ring. In an attempt to prepare a 10-membered macrocycle, Pd-catalyzed cyclization of disulfonamide **17** was attempted, but 20-membered 2+2 product **18** was isolated, as previously reported.[103] Considering that the electron donating dimethylamino side-arm substituent in compound **2** imparts high potency for CD4 down-modulation,[62] 2,6-bis(2-aminoethyl)-4-ethylpyridine **15b** was converted to the bis(4-

dimethylaminobenzenesulfonamide) **19**, which was then cyclized to analog **20** (Scheme 3, inset). Finally, replacement of the pyridine ring with acridine was considered desirable because acridine is a common scaffold in drugs.[106] For this purpose, readily available 1,8-bis(bromomethyl)acridine (**21**)[107] was converted to disulfonamide **22** by reaction with Boc-protected *p*-toluenesulfonamide,[108] then **22** was cyclized to acridine analog **23**.

Scheme 3



2.2 Potency

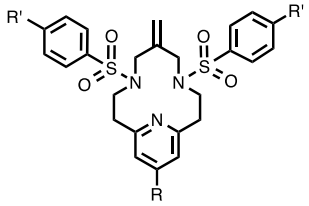
A total of 17 macrocycles were synthesized, 14 with 12-membered rings having an isobutylene head group, two arenesulfonyl side arms, and fused pyridine rings bearing an alkyl, aryl, hydroxy or alkoxy substituent in the para position. Each of these 17 compounds, including

previously reported[103] compounds **3a** (SH28) and **18**, was tested for CD4 down-modulation, either as its hydrochloride salt, hydrobromide salt, or free base form, as indicated in Table 1. As described in the Experimental Section, compositions and purities (>95%) were determined by combustion microanalysis. As for previous CADA compounds,[60–62] most of the samples tested were stoichiometric hydrates of the monohydrochloride salts. The CD4 down-modulation potencies are given in Table 1 as IC_{50} values, which are the concentrations producing a 50% decrease in CD4 expression, measured in Chinese hamster ovary (CHO) cells stably transfected with CD4 fused to yellow fluorescent protein (CD4-YFP), after 24 h of drug treatment. The structures, compound numbers/code names, anti-HIV potencies, and cytotoxicities of the 14 analogs are also given in Table 1, along with those of the previously reported reference compound **1** (CADA). Three of the new macrocycles, **16** (LAL039), **18** (LAL012), and **23** (LAL032), as well as all the open-chain disulfonamides, showed no observable CD4 down-modulation or anti-HIV activity and were not examined further.

The CD4 down-modulation and anti-HIV potencies given in Table 1 correlate well, as observed in previous studies of CADA compounds.[60–62] As anticipated from previous SAR studies,[60] increasing hydrophobicity in the tail region enhances CD4 down-modulation potency. The least potent fused pyridine CADA analog is **3d**, bearing a para-hydroxy group. IC_{50} values for CD4 down-modulation drop from 9.3 to 0.5 μM as the para substituent is modified as follows: OH => H => Me => Et => Pr => Bu in the **3d**, **3a**, **3m**, **3b**, **3i**, **3j** series. Branched or cyclic para substituents *i*Bu, *t*-Bu or Ph in **3c**, **3k**, and **3l** give slightly higher IC_{50} values in the range of 0.7 – 1.0 μM. Methoxy and ethoxy substituents in **3e** and **3f** reduce potency relative to methyl (**3m**) and ethyl (**3b**), increasing IC_{50} values by 0.2 and 0.6 μM, respectively, perhaps due to increased dipole moments of pyridine rings with para electron donating substituents. The more hydrophobic

benzyloxy group in **3g** give potency comparable to that of CADA, while cyclohexylmethoxy analog **3h** has the greatest potency in the entire series. Analog **20** with a *para*-ethylpyridine ring and *para*-dimethylamino groups on the benzenesulfonyl side arms is also more potent than CADA (by 50%), with an IC_{50} value that is smaller by 0.11 μM. Finally, 12 of the fused pyridine CADA compounds have undetectable cytotoxicities, and the remaining two, **3j** and **3k**, have therapeutic indices (CC_{50}/IC_{50} for CD4) exceeding 100.

Table 1. CD4 Down-Modulating and anti-HIV Potencies and Cytotoxicities of Pyridine-Fused CADA Compounds



Compound	R	R'	IC_{50} CD4 (μM)[a] mean ± SD	IC_{50} HIV (μM)[b] mean ± SD	CC_{50} (μM)[c]
1 (CADA•HCl)			0.33 ± 0.06	1.68 ± 1.00	> 100
3a (SH28)	H	Me	2.81 ± 0.21	> 50	> 100
3b (LAL028•HCl)	Et	Me	0.86 ± 0.10	3.40 ± 1.84	> 100
3c (LAL005•HCl)	*t*-Bu	Me	0.95 ± 0.14	2.70 ± 0.05	> 100
3d (LAL030•HBr)	OH	Me	9.30 ± 0.60	> 50	> 100
3e (LAL020•HCl)	OMe	Me	1.88 ± 0.10	12.59 ± 0.54	> 100
3f (LAL016•HCl)	OEt	Me	1.50 ± 0.17	10.40 ± 4.02	> 100
3g (LAL018•HCl)	OBn	Me	0.42 ± 0.11	2.18 ± 0.32	> 100
3h (LAL036•HCl)	OCH_2Cy	Me	0.13 ± 0.02	0.93 ± 0.75	> 100
3i (LAL026•HCl)	Pr	Me	0.83 ± 0.12	2.81 ± 0.28	> 100
3j (LAL022•HCl)	Bu	Me	0.54 ± 0.17	2.41 ± 0.62	65.8 ± 7.2
3k (LAL024•HCl)	iBu	Me	0.66 ± 0.03	2.30 ± 0.27	87.9 ± 17.1
3l (LAL014•HCl)	Ph	Me	0.74 ± 0.15	2.47 ± 0.94	> 100
3m (LAL001•HCl)	Me	Me	1.67 ± 0.24	> 50	> 100
20 (LAL042•HCl)	Et	NMe_2	0.22 ± 0.01	1.10 ± 0.15	> 100

[a] IC_{50}: inhibitory concentration 50%; concentration at which 50% down-modulation of CD4 expression measured in CD4-YFP transfected CHO cells after 24 h of drug treatment. Values are the mean ± standard deviation with n = 3.
[b] IC_{50}: inhibitory concentration 50%; concentration at which 50% reduction of HIV-1 NL4.3 (X4) replication in MT-4 cells was measured. Values are mean ± standard deviation with n = 2 or 3.
[c] CC_{50}: cytotoxic concentration 50%; concentration required to reduce viability of MT-4 cells by 50%.

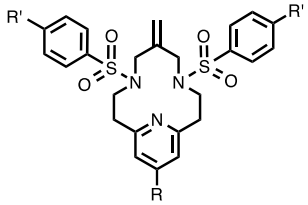
2.3 Solubility

A key rationale for investigating pyridine-fused CADA analogs was to determine whether the polar pyridine ring can enhance water solubilities in potent compounds. Drug solubility is perhaps one of the most important pharmacokinetic properties of an orally administered drug. A number of assays to determine solubility of drug candidates have been developed,[109] two of which have emerged as common and convenient. Kinetic solubility is measured by adding a concentrated solution of the drug in an organic solvent (e.g. DMSO) to an aqueous buffer (e.g. PBS) at various concentrations.[110] The drug is soluble at very low concentrations but becomes increasingly insoluble at higher aqueous concentrations. Nephelometry is commonly used to determine the kinetic solubility of a drug by measuring turbidity of mixtures of drug stock solutions diluted with buffer in wells of microtiter plates.[111] The concentration at which the nephelometer detects significant light scattering is the kinetic solubility of the drug. Alternatively, thermodynamic solubility is typically determined by agitating an excess of the drug and an aqueous buffer to achieve equilibrium between the crystalline and dissolved states. The concentration of the dissolved drug at equilibrium solubility can be determined conveniently by UV-Visible spectroscopy. Considering that many relatively hydrophobic drugs have such low aqueous concentrations that their molar absorptivities (extinction coefficients) are difficult to determine in water by Beer-Lambert[112] plots, the ε value is often determined in methanol and applied to the absorbance of the drug in water.

Listed in Table 2 are the molar absorptivities (ε) and the thermodynamic and kinetic solubilities of several selected pyridine-fused CADA compounds, as well as the lead compound, CADA. Only the thermodynamic or kinetic solubility was determined for some of the new compounds due to limitations of supply, but all of the results show that each of the fused-

pyridine analogs tested has greater aqueous solubility than CADA. This is not surprising for the compounds with small alkyl or alkoxy substituents in the *para*-pyridine position, but even LAL036 with the most hydrophobic substituent and greatest potency has greater kinetic solubility than CADA.

Table 2. Molar Absorptivities, Thermodynamic and Kinetic Solubilities of Pyridine-Fused CADA Compounds



Compound	R	R'	ε^a	λ_{max} (nm)	Therm. sol. (μM)[b]	Kinetic Sol. (μM)[c]
1 (CADA•HCl)			23,141	230	11 ± 1	43 ± 1
3c (LAL005•HCl)	*t*-Bu	Me	35,200	230	20 ± 1	ND
3d (LAL030•HBr)	OH	Me	27,150	230	27 ± 1	ND
3e (LAL020•HCl)	OMe	Me	32,950	230	28 ± 1	64 ± 2
3f (LAL016•HCl)	OEt	Me	ND	230	ND	54 ± 2
3h (LAL036•HCl)	OCH_2Cy	Me	ND	230	ND	65 ± 3
3i (LAL026•HCl)	Pr	Me	34,000	230	18 ± 1	ND
3k (LAL024•HCl)	iBu	Me	29,650	230	29 ± 1	ND
3l (LAL014•HCl)	Ph	Me	37,099	230	ND	61 ± 1

[a]Molar absorptivity determined from Beer-Lambert Law plots of absorbances measured at the λ_{max} value listed for the major absorption.
[b]Thermodynamic solubility measured by UV-Visible absorption spectroscopy in aqueous PBS buffer (pH 7.4).
[c] Kinetic solubility measured by nephelometry in aqueous PBS buffer (pH 7.4)/2.5% DMSO.

3. Conclusions

A total of 17 pyridine-fused macrocycles were synthesized with a wide range of structural variation. Many useful synthetic intermediates are reported, including intermediates in Hantzsch syntheses of *para*-propyl, butyl, isobutyl, and phenyl analogs. The new CADA analogs display a wide range of CD4 down-modulating and anti-HIV potencies, including some with greater potency than CADA. These results prove that a highly basic nitrogen atom in the 12-membered ring is not required for high potency and that hydrophobic substituents enhance the potency of pyridine-fused

CADA compounds. Moreover, thermodynamic and kinetic water solubilities were measured for many of the new compounds and they all compare favorably with those of CADA, validating the hypothesis that incorporation of a pyridine ring can enhance some drug-like properties of CADA compounds. In addition, the pyridine-fused analogs were determined to have low cytotoxicities and high therapeutic indices. These results may lead to improved candidates for studying the effects of CD4 down-modulation *in vivo* and may be useful for the design of novel SP-targeting drugs for down-modulating other proteins of medicinal interest.

4. Experimental section

4.1 Biological Evaluation

4.1.1 CD4 down-modulation

To study the effect of the CADA analogs on CD4 expression, CHO cells, stably expressing CD4-YFP (human CD4 fused at its COOH-terminus to the yellow fluorescent protein), were treated for 24 h with serial dilutions (1:5) of the compounds at 37 °C. Cells were then washed, fixed in 1% formaldehyde and analyzed immediately. Data were acquired with a FACSCanto flow cytometer (BD Biosciences) using the 488 nm laser line and the BD FACSDiva software application (BD Biosciences). Data were analyzed with FLOWJO software (Tree Star, San Carlos, CA). Down-modulation of CD4 was evaluated by the decrease in fluorescence intensity on CADA-treated cells relative to matched, untreated cells. To calculate the efficiency of CD4 down-modulation, the mean fluorescence intensity (MFI) for YFP for each sample was expressed as a percentage of the MFI of control cells (after subtracting the background MFI of the non-transfected control cells).

4.1.2 Viral replication

MT-4 cells (obtained from the American Type Culture Collection) were seeded in 96-well plates at 3.75×10^5 cells/mL (150 μL/well) filled with culture medium (Roswell Park Memorial Institute 1640, 10% (v/v) fetal bovine serum, 2 mM L-glutamine) and test compounds. Cells were pre-incubated with the compounds for 15 min before addition of the laboratory HIV-1 strain NL4.3 (obtained from the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH) at 50 μL (30 pg/well) and incubation at 37 °C. Four days after infection, cell viability was quantified by the MTS/phenazine ethosulfate (PES) method. Absorbance was measured at 490 and 700 nm and used to calculate the 50% inhibitory concentration (IC_{50}) of each compound for viral replication.

4.1.3 *Cytotoxicity*

MT-4 cells were seeded in transparent 96-well plates at 10^4 cells per well in Dulbecco's Modified Eagle Medium (Life Technologies, Waltham, MA, USA) with 10% (v/v) fetal bovine serum and 10 mM HEPES. Subsequently, compounds were added and the cell/compound mixture was incubated at 37 °C for 48 h. The 50% cytotoxic concentration (CC_{50}) of each compound was determined from the reduction of viability of cells exposed to the compound, as measured by the MTS/phenazine ethosulfate (PES) method.

4.2 Solubility

4.2.1 Thermodynamic solubility

Solutions of five different concentrations of each compound in methanol were prepared and analyzed by UV-Visible spectroscopy. The absorbance values obtained were plotted as a function of concentration and the ε value of each compound was determined by linear least squares curve fitting of the data to obtain the slope (ε). Thermodynamic solubility was analyzed using the traditional shake flask method.[109,110] For each compound tested in this assay, a small

amount (3-5 mg) of the compound was added to a glass vial containing 5 mL of PBS buffer (*pH* = 7.4) and agitated on a mechanical shaker for 72 h. In order to ensure the solutions remained saturated, the solutions were visually inspected at 24 and 48 h to ensure that some of the compound remained insoluble. After 72 h, the solutions were filtered using a PTFE syringe filter (0.45 μL) and the filtrate was analyzed by the standard addition method using UV-Visible spectroscopy in conjunction with the Beer-Lambert law to calculate the concentration of each compound.

4.2.2 Kinetic solubility

The following procedure[109,110] was used to determine the kinetic solubility of each compound tested. Solutions of each compound with various starting concentrations in 2.5% DMSO with a final volume of 100 μL were prepared in quadruplicate by serial dilution on sterile, 96-well microtiter plates, with wells arranged in 12 columns (1-12) and 8 rows (A-H). Using a micropipette, the appropriate amount of a 20 mM DMSO stock solution for each compound was added into a vial contained 858 μL of PBS buffer (*pH* = 7.4) and the appropriate amount of DMSO in order to keep the DMSO concentration constant. A second starting solution with lower concentration of the CADA compound was prepared in the same manner. Then, 100 μL of a solution of 2.5% DMSO in PBS buffer (*pH* = 7.4) was added into wells (A-H)2-8 and (A-H)11,12. Into wells (A-D)1, 200 μL of the first starting solution for each CADA compound tested was added. Also 200 μL of the second starting solution for each CADA compound tested was added to wells (E-H)1. Each solution in column 1 was mixed by pipetting 100 μL up and down five times, then 100 μL was transferred to the adjacent well in column (A-H)2. Each solution in column 2 was mixed by pipetting 100 μL up and down 5 times then 100 μL was transferred to well (A-H)3, and so on through column (A-H)8, after which 100 μL was removed

from each well in column 8 and placed in the waste container. Columns (A-H)11,12 served as blanks, containing only 100 μL of a solution of 2.5% DMSO in PBS buffer (*pH* = 7.4). Therefore, serial dilutions were performed from the starting solution with each well containing a final volume of 100 μL. Furthermore, four more solutions having CADA compound concentrations between the concentration of the first starting solution and half of the concentration of the first starting solution were prepared in the same manner. Aliquots (100 μL) of these solutions were placed in quadruplicate into wells (A-H)9,10. Plates were shaken for 2 min, incubated for 1 h at 37 ºC, and shaken again for 3 min before being analyzed using a nephelometer. Prior to use, a Nepheloskan Ascent nephelometer was allowed to warm up for at least 0.5 h. Each plate was placed in the nephelometer with the lid off, shaken for 2 min, incubated for 1 h at 37 ºC, and shaken again for 3 min before measuring each well. The raw data was adjusted by subtracting the average blank value and analyzed using Microsoft Excel.

4.3 Chemistry

4.3.1 General Methods

All reactions were performed under an atmosphere of dry nitrogen. Reagents and solvents purchased from Aldrich Chemical Company, Acros Organics, or Fisher Scientific were of ACS reagent grade or better and were used without purification, unless indicated otherwise. Anhydrous acetonitrile (AN) and THF were distilled from CaH_2 and from Na/benzophenone, respectively. Solutions of 2 N HCl in methanol/water was prepared from 42 mL of concentrated aq. HCl (12.1 N) and 210 mL of methanol. Trituration of HCl salts was done by sonication in anhydrous diethyl ether (5 – 15 mL, unless indicated otherwise) for 5 min and filtration, repeating the process two more times. “Overnight” periods are ca. 16 h. Organic solutions were dried with anhydrous Na_2SO_4, and sample drying *in vacuo* was performed at 0.1 mm at room temperature. Column

chromatography was performed with Sorbent Technologies neutral alumina (50-200 μm) or standard grade silica (32-63 μm), unless noted otherwise. Melting points were measured on a Thomas-Hoover or Mel-Temp apparatus and are uncorrected. ^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 125 MHz) spectra were acquired on a Varian 400 or a Varian Unity+ 500 spectrometer. All chemical shifts (δ) are reported in ppm units relative to solvent resonances, as follows: ^{1}H, $CDCl_3$/TMS = 0.00, DMSO-d_6 = 2.50, CD_3OD = 3.31; ^{13}C, $CDCl_3$ = 77.16, DMSO-d_6 = 39.7, CD_3OD = 49.15 ppm. Infrared spectra (IR) were recorded neat on a Nicolet 6700 FTIR spectrometer. Low-resolution mass spectra (MS) were acquired on a Waters Micromass ZQ electrospray ionization quadrupole mass spectrometer with positive ion detection (capillary voltage = 3.5 kV). High-resolution mass spectra (HRMS) were determined on an Agilent 6230 TOF mass spectrometer. Samples for combustion analysis were dried at 78 ºC (0.1 mm) for 2 d, unless stated otherwise, and microanalysis was performed by NuMega Resonance Labs, Inc. Samples for biological testing were at least 95% pure, as shown by combustion microanalysis.

4.3.2 Synthesis

4-Ethyl-2,6-bis(hydroxymethyl)pyridine (7b). A solution of 1.6 g (7.2 mmol) of dimethyl 4-ethylpyridine-2,6-dicarboxylate[79] in 100 mL of absolute ethanol was stirred at 0 ºC as 4.0 g (0.1 mol) of $NaBH_4$ was added in portions, then the mixture was stirred at 0 ºC for 1 h, at room temperature for 1 h, then boiled under reflux for 24 h. Acetone (150 mL) was added and the mixture was boiled for 1 h, then concentrated by rotary evaporation. A mixture of the residue and 60 mL of saturated aq. Na_2CO_3 solution (60 mL) was boiled under reflux for 1 h, then cooled to room temperature and extracted with DCM (5 x 80 mL). The combined extracts were dried, filtered and concentrated to dryness by rotary evaporation. The residue was dried *in vacuo* overnight, yielding 1.2 g (100%) of **7b** as a viscous oil, which was used in the next step without further

purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 2 H, Py), 4.70 (d, 8.1 Hz, 4 H, CH_2O), 4.09 (br, 2 H, OH), 2.64 (q, 7.4 Hz, 2 H, CH_2Me), 1.24 (t, 7.8 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) 159.1, 154.8, 118.8, 64.0, 28.0, 13.9.

Diethyl 4-*tert*-butylpyridine-2,6-dicarboxylate (8c).[79,80] A solution of 20.8 g (90 mmol) of diethyl pyridine-2,6-dicarboxylate[100] in 185 mL of 30% (v/v) aq. H_2SO_4 was stirred at 0 ºC as 25 g (0.29 mol) of pivaldehyde was added dropwise over 45 min. The reaction mixture was stirred for 1 h at 0 ºC, initially forming a white solid that re-dissolved. A solution of 10.4 g (70 mmol) of $FeSO_4$•$7H_2O$ in 75 mL of water was added dropwise over 45 min and the reaction mixture was stirred for 1 h at 0 ºC. A solution of 30% aq. hydrogen peroxide (23.3 mL, 25.7 g, 0.19 mol) was added dropwise over 45 min, the reaction mixture was stirred at 0 ºC for 2 h, then allowed to warm to room temperature and was stirred for 48 h. The reaction mixture was adjusted to pH 3 by dropwise addition of a saturated aq. solution of K_2CO_3. The mixture (5 L) was divided into 10 parts, which were separately extracted with ethyl acetate (5 x 100 mL). The combined extracts were dried, filtered and concentrated by rotary evaporation with a water bath temperature of 60 ºC. The resulting brownish residue was dried *in vacuo* overnight giving a brownish solid, which was purified by column chromatography on silica, eluting with 4:6 (v/v) ethyl acetate/cyclohexane, yielding 6.8 g (26%) of **8c** as a white solid, mp 66-68 ºC; lit.[80] 68 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 2 H, Py), 4.50 (q, 7.6 Hz, 4 H, OCH_2), 1.47 (t, 7.1 Hz, 6 H, $CH_2C\mathit{H_3}$), 1.39 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 26.9, 30.3, 35.2, 62.2, 124.8, 148.5, 162.9, 165.0. IR (cm^{-1}) 2972 (m), 2060 (w), 1719 (s), 1371 (m), 1248 (s), 1023 (s). MS *m/z* 280.54 $(MH)^+$. Anal. calcd for $C_{15}H_{21}NO_4$: C, 63.47; H, 7.64; N, 4.93; Found: C, 63.44; H, 7.95; N, 5.32.

4-*tert*-Butyl-2,6-bis(hydroxymethyl)pyridine (7c). A solution of (0.20 g, 0.72 mmol) of

diethyl 4-*tert*-butylpyridine-2,6-dicarboxylate (**8c**) in 10 mL of absolute ethanol was stirred at 0 ºC as a suspension of 0.15 g (4.0 mmol) of $NaBH_4$ in 10 mL of absolute ethanol was added in portions. The reaction mixture was stirred for 3 h at room temperature, boiled under reflux for 5 h, cooled to room temperature and concentrated by rotary evaporation. A mixture of the residue and 100 mL of saturated aq. K_2CO_3 solution was stirred at 60 ºC for 2 h, cooled to room temperature, and extracted with chloroform (8 x 25 mL). The combined extracts were dried, filtered, and concentrated to dryness by rotary evaporation. The residue was dried *in vacuo* overnight to give 0.13 g (93%) of **7c** as a brown solid, mp 105-107 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (s, 2 H, Py), 5.33 (t, 6.3 Hz, 2 H, OH), 4.50 (d, 5.9 Hz, 4 H, CH_2), 1.28 (s, 9 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2, 30.5, 64.5, 115.1, 160.4, 160.9. IR (cm^{-1}) 3349 (br), 2965 (w), 2911 (w), 2748 (w), 2060 (w), 1607 (s). MS *m/z* 218.24 $(M+Na)^+$. Anal. calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17; Found: C, 67.29; H, 9.00; N, 7.17.

2,6-Bis(hydroxymethyl)-4-methoxypyridine (7e).[72,73,101,113,114] By the method described for **7b**, 4.0 g (18 mmol) of dimethyl 4-methoxypyridine-2,6-dicarboxylate[72,73,101,113] gave 3.0 g (100%) of **7e** as a white solid, mp 121 ºC; lit.[114] 121-122 ºC; lit.[113] 125-127 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.86 (s, 2 H, Py), 5.35 (t, 5.4 Hz, 2 H, OH), 4.46 (d, 5.2 Hz, 4 H, CH_2), 3.82 (s, 3 H, OMe). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.6, 162.9, 103.9, 64.0, 55.1.

4-Ethoxy-2,6-bis(hydroxymethyl)pyridine (7f).[75] By the method described for **7b**, 5.3 g (19 mmol) of diethyl 4-ethoxypyridine-2,6-dicarboxylate[75] gave 3.30 g (97%) of **7f** as a white solid, mp 117-118 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (s, 2 H, Py), 5.32 (t, 5.9 Hz, 2 H, OH), 4.44 (d, 6.8 Hz, 4 H, CH_2OH), 4.10 (q, 6.7 Hz, 4 H, OCH_2CH$_3$), 1.34 (t, 7.1 Hz, 3 H, OCH$_2$CH_3).

4-Benzyloxy-2,6-bis(hydroxymethyl)pyridine (7g).[70–72,76,78,115] A mixture of 0.18 g (4.8

mmol) of $NaBH_4$, 0.28 g (0.92 mmol) of dimethyl 4-benzyloxypyridine-2,6-dicarboxylate,[70–72,76,78] and 11 mL of anhydrous THF was stirred and heated to boiling, then 2.5 mL of MeOH was added over 10 min. The reaction mixture was boiled under reflux for 3 h then cooled to room temperature and 5 mL of water was added dropwise. Most of the MeOH was removed by rotary evaporation, resulting in a cloudy solution, which was diluted with 100 mL of water and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight, yielding 0.23 g (100%) of **7g** as a white solid, mp 295-298 ºC (dec); lit.[76] 298 ºC (dec); lit.[115] 268 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43-7.38 (m, 5 H, Ph), 7.06 (s, 2 H, Py), 5.20 (s, 2 H, OCH_2Ph), 4.63 (s, 4 H, CH_2OH).

Dimethyl 4-cyclohexylmethoxy-2,6-dicarboxylate (8h). A mixture of 0.30 g (1.42 mmol) of dimethyl chelidamate,[70] 0.80 g (5.8 mmol) of K_2CO_3, and 15 mL of anhydrous DMF was stirred at 90 ºC for 30 min. After cooling to room temperature, 1.0 g (5.7 mmol) of cyclohexylmethyl bromide was added in one portion. The tube was sealed and the reaction mixture was stirred at 90 ºC for 48 h. Water (200 mL) was added, then the mixture was extracted with DCM (5 x 50 mL). The combined extracts were dried, filtered, and concentrated by rotary evaporation. A solution of the resulting oil in 200 mL of diethyl ether was washed with water (3 x 100 mL). The organic layer was dried, filtered, and concentrated by rotary evaporation, then the resulting yellow oil was dried *in vacuo* overnight. Recrystallization from diethyl ether gave 0.10 g (23%) of pure product as a white solid. Concentration of the mother liquor by rotary evaporation gave a white residue, which was dried *in vacuo* for 3 h, then purified by column chromatography on silica gel, eluting with DCM, followed by 9:1 (v/v) DCM/EtOAc, giving an additional 0.22 g of the product as a white solid. Total yield: 0.32 g (73%), mp 105 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2 H, Py), 4.01 (s, 6 H, CH_3), 3.93 (d, 6.0 Hz, 2 H, OCH_2Cy*),* 1.88-1.04 (m, 11 H, Cy). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 167.4, 165.4, 149.8, 114.7, 74.5, 53.4, 37.5, 29.8, 26.4, 25.8. IR (cm^{-1}) 2930 (s), 2853 (s), 1744 (s), 1718 (s), 1592 (s), 1436 (s). MS *m/z* 308.3 $(MH)^+$. Anal. calcd for $C_{16}H_{21}NO_5 \cdot 2H_2O$: C, 55.97; H, 7.34; N, 4.08; Found: C, 56.27; H, 7.20; N, 4.00.

4-Cyclohexylmethoxy-2,6-bis(hydroxymethyl)pyridine (7h). By the method described for **7b**, 1.8 g (5.86 mmol) of dimethyl 4-cyclohexylmethoxy-2,6-dicarboxylate (**8h**) gave 1.4 g (92%) of **7h** as a white solid, mp 114-115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 2 H, Py), 4.67 (s, 4 H, CH_2O), 3.79 (d, 6.1 Hz, 2 H, OC*H*$_2$Cy*),* 3.31 (s, 2 H, OH), 1.84-0.94 (m, 11 H, Cy). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 160.2, 105.7, 73.7, 64.6, 37.6, 29.9, 26.5, 25.8. IR (cm^{-1}) 3340 (m), 3070 (br), 2927 (m), 2850 (m), 1600 (s), 1566 (m). HRMS calcd for $C_{14}H_{21}NO_3$ $(MH)^+$: *m/z* 252.1600; Found: 252.1593. Anal. calcd for $C_{14}H_{21}NO_3 \cdot 0.25H_2O$: C, 65.73; H, 8.47; N, 5.48; Found: C, 65.32; H, 7.86; N, 5.38.

3,5-Di(*tert*-butoxycarbonyl)-2,6-dimethyl-4-propyl-1,4-dihydropyridine (10i). A solution of 18 g (0.11 mol) of *t*-butyl acetoacetate, 3.6 g (50 mmol) of butyraldehyde and 15 mL of ethanol (15 mL) was stirred at room temperature as 3.8 mL (56 mmol) of concentrated aq. ammonium hydroxide solution was added slowly. The mixture was boiled under reflux for 6 h, cooled to room temperature and concentrated by rotary evaporation. Aq. 2 N HCl solution (100 mL) and 200 mL of DCM were added to the residue and the layers were separated. The aqueous phase was extracted with DCM (3 x 75 mL). The combined organic solutions were washed with saturated aq. $NaHCO_3$ solution (2 x 100 mL), saturated aq. NaCl solution (100 mL), then dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight then recrystallized from aq. isopropanol to give 6.04 g (34%) of **10i** as a pale yellow, crystalline solid, mp 133-134 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 1 H, NH), 3.85 (t, 5.7 Hz, 1 H, CH), 2.23

(s, 6 H, C=CCH_3), 1.49 (s, 18 H, *t*-Bu), 1.24 (m, 4 H, CH_2CH_2), 0.85 (t, 7.0 Hz, 3 H, $CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 143.5, 105.1, 79.4, 39.5, 33.4, 28.5, 19.5, 18.5, 14.6. IR (cm^{-1}) 3322 (s), 2968 (s), 2931 (m), 1691 (s), 1645 (s). MS *m/z* 374.69 $(M+Na)^+$. Anal. calcd for $C_{20}H_{33}NO_4 \cdot 0.25H_2O$: C, 67.48; H, 9.49; N, 3.93; Found: C, 67.18; H, 9.16; N, 4.07.

3,5-Di(*tert*-butoxycarbonyl)-2,6-dimethyl-4-propylpyridine (11i). A mixture of 5.1 g (15 mmol) of 3,5-di(*tert*-butoxycarbonyl)-2,6-dimethyl-4-propyl-1,4-dihydropyridine (**10i),** 5.3 g (30 mmol) of $Na_2S_2O_4$ and 380 mL of EtOAc was stirred at room temperature as 8.7 mL (8.2 g, 60 mmol) of 70% *t*-butyl hydroperoxide was added in one portion. The reaction mixture was stirred at room temperature for 4 d, then 150 mL of saturated aq. $NaHCO_3$ solution and 60 mL of H_2O were added, and the mixture was stirred for 30 min at room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 75 mL). The combined organic solutions were washed with saturated aq. $NaHCO_3$ solution (2 x 100 mL) and saturated aq. NaCl solution (100 mL), then dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* for 2 d, yielding 5.1 g (100%) of **11i** as a pale orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (m, 2 H, CH_2Py), 2.51 (s, 6 H, CH_3Py), 1.60 (s, 18 H, *t*-Bu), 1.25 (m, 2 H, $CH_2CH_2CH_3$), 0.98 (t, 7.53 Hz, 3 H, $CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 154.0, 145.1, 128.4, 82.6, 33.3, 28.1, 24.3, 22.6, 14.6. IR (cm^{-1}) 2970 (m), 2933 (w), 2875 (w), 1719 (s), 1567 (s). HRMS calcd for $C_{20}H_{31}NO_4$ $(MH)^+$: *m/z* 350.2331; Found: 350.2349.

4-Propyl-2,6-distyrylpyridine (13i).[116,117] A mixture of 10.3 g (30 mmol) of 3,5-di-*t*-butoxycarbonyl-2,6-dimethyl-4-propylpyridine (**11i**) and 150 mL of Dowtherm A was stirred and boiled under reflux for 30 min (in an open apparatus to allow emission of white fumes) and then boiled at reflux under nitrogen for 24 h. After cooling to room temperature, 200 mL of 6 N aq. HCl solution and 100 mL of DCM were added and the mixture was stirred for 18 h at room

temperature. The mixture was filtered, washing the residue with water (2 x 100 mL). The layers of the filtrate were separated and the aqueous layer was washed with DCM (5 x 100 mL). The aqueous layer was basified (pH 14) with NaOH pellets added in portions with shaking, then saturated with NaCl. The resulting solution was stirred with 300 mL of DCM at room temperature for 18 h. The layers were separated and the aqueous layer was extracted with DCM (3 x 75 mL). The combined organic solutions were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight, yielding 2.88 g (65%) of 2,6-dimethyl-4-propylpyridine (**12i**)[116] as a brown oil, which was not purified further. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 2 H, Py), 2.48 (m, 7.3 Hz, 8 H, CH_3Py, CH_2Py), 1.62 (sext, 7.6 Hz, 2 H, $CH_2CH_2CH_3$), 0.93 (t, 7.4 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 152.0, 120.5, 37.2, 24.4, 23.5, 13.8. A solution of 2.9 g (20 mmol) of 2,6-dimethyl-4-propylpyridine (**12i**), 11 g (0.10 mol) of benzaldehyde, and 40 mL of acetic anhydride was stirred and boiled under reflux for 87 h. After cooling to room temperature, 100 mL of 5% (w/v) aq. sodium hydroxide solution was added and the mixture was stirred at room temperature for 3 h. The layers were separated and the aqueous layer was extracted with DCM (5 x 50 mL). The combined organic solutions were dried, filtered, and concentrated by rotary evaporation. A mixture of the residue, 11 g (0.11 mol) of $NaHSO_3$, 80 mL of ethyl acetate, 50 mL of EtOH, and 17 mL of water (17 mL) was stirred at 40 ºC for 24 h, then filtered, washing with DCM (3 x 50 mL). The filtrate was concentrated by rotary evaporation and extracted with DCM (3 x 100 mL). The combined extracts were washed with 100 mL of saturated aq. NaCl solution, dried, filtered, and concentrated by rotary evaporation. A mixture of the residue and 300 mL of 2 N HCl in aq. MeOH was stirred at room temperature for 6 h then stored in a refrigerator overnight. The precipitate was collected by filtration, washed with cold MeOH (2 x 30 mL) and dried *in vacuo* overnight, yielding 2.0 g (27%) of 4-propyl-2,6-

distyrylpyridine HCl salt (**13i•**HCl) as a greenish yellow solid, mp 222-223 ºC; lit.[117] 225 ºC ($CHCl_3$). The HCl salt was converted to the free base by stirring with 200 mL of DCM, 200 mL of saturated aq. NaCl solution, and 200 mL of 2 N aq. NaOH solution for 5 h. The layers were separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic solutions were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight giving 1.80 of a yellow solid. The filtrate from collection of the HCl salt was concentrated by rotary evaporation to give a black oil, which was dried *in vacuo* for 3 d, then mixed with diethyl ether and acetone, but no precipitate formed. The solution was again concentrated by rotary evaporation. The residue was dried *in vacuo* overnight then stirred with 200 mL of DCM, 200 mL of 2 N aq. NaOH solution, and 200 mL of saturated aq. NaCl solution for 7 h. The layers were separated and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic solutions were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight then subjected to column chromatography on silica, eluting with DCM/hexane (1:1, 7:3, then 9:1 v/v), yielding 0.76 g of 4-propyl-2,6-distyrylpyridine (**13i**) as a glassy yellow solid. Total yield: 2.6 g (41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 16.1 Hz, 2 H, C=C*H*Py), 7.56 (d, 8.4 Hz, 4 H, *o*-Ph), 7.31 (m, 7.4 Hz, 6 H, *m,p*-Ph), 7.14 (d, 16.1 Hz, 2 H, C=CHPh), 6.96 (s, 2 H, Py), 2.46 (t, 7.6 Hz, 2 H, CH_2Py), 1.59 (sext, 8.0 Hz, 2 H, $CH_2CH_2CH_3$), 0.90 (t, 7.6 Hz, 3 H, $CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.0, 136.8, 132.4, 128.6, 128.4, 128.0, 127.0, 120.8, 37.1, 23.3, 13.7. IR (neat, cm^{-1}) 2962 (w), 2871 (w), 2234 (s), 1952 (s), 1616 (s), 1494 (m), 1451 (s).

2,6-Bis(hydroxymethyl)-4-propylpyridine (7i). A solution of 1.77 g (5.44 mmol) of 4-propyl-2,6-distyrylpyridine (**13i**), 40 mL of DCM, and 10 mL of MeOH was cooled to -78 ºC by means of a dry ice/acetone bath, and a stream of O_3/O_2 was bubbled through the solution until it

turned a pale greenish color. Nitrogen was bubbled through the solution for 15 min, and then 4.2 g (70 mmol) of Me_2S was added in one portion. The solution was stirred at room temperature overnight then concentrated by rotary evaporation. The resulting oil was dried *in vacuo* overnight and subjected to column chromatography on silica, eluting with 95:5 then 9:1 (v/v) hexane/ethyl acetate, yielding 0.79 g (82%) of 4-propylpyridine-2,6-dicarboxaldehyde (**14i**) as a pale yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 2 H, CHO), 8.01 (s, 2 H, Py), 2.80 (t, 7.6 Hz, 2 H, C*H*$_2$Py), 1.76 (sext, 8.1 Hz, 2 H, $CH_2CH_2CH_3$), 1.00 (t, 7.8 Hz, 3 H, $CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 154.8, 153.1, 125.5, 37.2, 23.3, 13.6. IR (cm^{-1}) 2962 (m), 2933 (m), 2872 (m), 1708 (s), 1600 (s), 1452 (m). A solution of 0.63 g (3.6 mmol) of 4-propylpyridine-2,6-dicarboxaldehyde (**14i**) in 40 mL of absolute ethanol was stirred at 0 ºC as 1.2 g of $NaBH_4$ (30 mmol) was added in one portion. The mixture was stirred at 0 ºC for 1 h, at room temperature for 1 h, then boiled and stirred under reflux for 22 h. After cooling, 40 mL of acetone was added and the mixture was boiled for 1 h, then concentrated by rotary evaporation. A mixture of the residue and 25 mL of saturated aq. Na_2CO_3 solution (25 mL) was boiled under reflux for 1 h. After cooling to room temperature, the mixture was diluted with 10 mL of water and extracted with chloroform (8 x 30 mL). The combined extracts were dried, filtered, and concentrated by rotary evaporation. The residual oil was dried *in vacuo* overnight, yielding 0.60 g (94%) of 2,6-bis(hydroxymethyl)-4-propylpyridine (**7i**) as a pale yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 2 H, Py), 4.70 (s, 2 H, CH_2O), 4.16 (br, 2 H, OH), 2.58 (t, 7.5 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.64 (sext, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 0.93 (t, 7.4 Hz, 3 H, $CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 153.6, 119.8, 64.5, 37.4, 23.5, 13.8. IR (cm^{-1}) 3246 (br), 2959 (m), 2930 (m), 2869 (m), 1610 (s), 1564 (s), 1427 (s). HRMS calcd for $C_{10}H_{15}NO_2$ $(MH)^+$: *m/z*

182.1181; Found: 182.1204.

3,5-Di(*tert*-butoxycarbonyl)-4-butyl-2,6-dimethyl-1,4-dihydropyridine (10j). By the method described for **10i**, 18 g (0.11 mol) of *tert*-butyl acetoacetate and 4.3 g (50 mmol) of valeraldehyde gave 12.5 g (68%) of **10j** as a yellow solid, mp 143-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1 H, NH), 3.85 (t, 5.0 Hz, 1 H, CH), 2.24 (s, 6 H, C=CCH_3), 1.49 (s, 18 H, *t*Bu), 1.24 (m, 6 H, CH_2CH_2CH_2CH_3), 0.86 (t, 7.0 Hz, 3 H, $CH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 143.4, 104.9, 79.2, 36.7, 33.5, 28.4, 27.6, 23.0, 19.4, 14.2. IR (neat, cm^{-1}) 3323 (s), 3237 (m), 2968 (s), 2925 (s), 1692 (s), 1644 (s), 1486 (s). Anal. calcd for $C_{21}H_{35}NO_4$: C, 69.01; H, 9.65; N, 3.83; Found: C, 68.98; H, 10.00; N, 4.03.

3,5-Di(*tert*-butoxycarbonyl)-4-butyl-2,6-dimethylpyridine (11j). By the method described for **11i**, 12 g (30 mmol) of 3,5-di(*tert*-butoxycarbonyl)-4-butyl-2,6-dimethyl-1,4-dihydropyridine (**10j**) gave 12 g (100%) of **11j** as an orange oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (m, 2 H, CH_2Py), 2.51(s, 6 H, PyCH_3), 1.60 (s, 18 H, *t*Bu), 1.36 (m, 4 H, CH_2CH_2CH_2CH_3), 0.93 (t, 7.5 Hz, 3 H, $CH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 154.0, 145.2, 128.4, 82.6, 33.0, 31.1, 28.1, 23.4, 22.7, 13.8. IR (neat, cm^{-1}) 2962 (s), 2931 (m), 2874 (m), 1720 (s), 1565 (s), 1457 (s). HRMS calcd for $C_{21}H_{33}NO_4$ $(MH)^+$: *m/z* 364.2489; Found: 364.2469.

4-Butyl-2,6-bis(hydroxymethyl)pyridine (7j). By the method described for conversion of **11i** to **12i**, 12 g (0.03 mol) of 3,5-di(*tert*-butoxycarbonyl)-4-butyl-2,6-dimethylpyridine (**11j**) gave 2.65 g (51%) of 4-butyl-2,5-dimethylpyridine (**12j**)[118] as a brown oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 2 H, Py), 2.51 (m, 7.8 Hz, 8 H, CH_2Py, CH_3Py), 1.57 (m, 2 H, CH_2C$H_2CH_2CH_3$), 1.34 (m, 2 H, CH_2CH_2CH_2CH_3), 0.93 (t, 7.5 Hz, 3 H, $CH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 152.2, 120.4, 34.9,

32.5, 24.4, 22.4, 13.9. The method described for conversion of **12i** to **13i** was applied to 2.64 g (20 mmol) of **12j**, except that after aq. workup and treatment with $NaHSO_3$, the residue from the combined DCM extracts were subjected to column chromatography on alumina, eluting with DCM/hexane (1:4, 1:1, then 4:1, v/v), yielding 3.37 g (61%) of 4-butyl-2,6-distyrylpyridine (**13j**), a yellow solid, mp 65-67 ºC, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, 2.3 Hz, 16.4 Hz, 2 H, C=CHPy), 7.60 (d, 7.6 Hz, 4 H, *o*-Ph), 7.38 (td, 2.4 Hz, 7.5 Hz, 4 H, *m*-Ph), 7.29 (m, 2 H, *p*-Ph), 7.20 (dd, 2.3 Hz, 16.1 Hz, 2 H, C=CHPh), 7.10 (s, 2 H, Py), 2.62 (t, 7.6 Hz, 2 H, CH_2Py), 1.66 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.39 (m, 2 H, $CH_2CH_2CH_2CH_3$), 0.96 (t, 7.5 Hz, 3 H, $CH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 152.4, 137.1, 132.7, 128.8, 128.7, 128.3, 127.2, 121.0, 35.2, 32.7, 22.5, 14.1. By the method described for conversion of **13i** to **14i**, 3.2 g (9.5 mmol) of 4-butyl-2,6-distyrylpyridine (**13j**) gave 1.4 g (77%) of 4-butylpyridine-2,6-dicarboxaldehyde (**14j**) as a pale yellow oil, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 2 H, CHO), 8.00 (s, 2 H, Py), 2.81 (t, 7.5 Hz, 2 H, CH_2Py), 1.69 (m, 7.6 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.38 (m, 7.4 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 0.96 (t, 7.4 Hz, 3 H, $CH_2CH_2CH_2CH_3$). By the method described for **7i**, 0.95 g (5.0 mmol) of **14j** gave 0.98 g (100%) of 4-butyl-2,6-bis(hydroxymethyl)pyridine (**7j**) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 2 H, Py), 5.32 (br, 2 H, OH), 4.63 (s, 4 H, CH_2O), 2.55 (t, 7.5 Hz, 2 H, CH_2Py), 1.77 (m, 7.7 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.30 (m, 7.5 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 0.89 (t, 7.4 Hz, 3 H, $CH_2CH_2CH_2CH_3$). HRMS calcd for $C_{11}H_{17}NO_2$ $(MH)^+$: *m/z* 196.1337; Found: 196.1335.

3,5-Di-(*tert*-butoxycarbonyl)-4-isobutyl-2,6-dimethyl-1,4-dihydropyridine (10k). By the method described for **10i**, 18 g (0.11 mol) of *tert*-butyl acetoacetate, 4.3 g (50 mmol) of isovaleraldehyde gave 13.2 g (72%) of a (**10k**) as a yellow solid, mp 157-158 ºC. ^{1}H NMR (400

MHz, $CDCl_3$): δ 5.53 (s, 1 H, NH), 3.90 (t, 7.0 Hz, 1 H, C=CCH), 2.25 (s, 6 H, C=CCH_3), 1.49 (m, 20 H, *t*Bu, CH_2CH(CH_3)$_2$), 1.08 (t, 7.0 Hz, 1 H, CH_2C*H*(CH_3)$_3$), 0.90 (d, 6.5 Hz, 6 H, CH_2CH(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 143.5, 105.7, 79.4, 46.9, 31.5, 28.5, 23.7, 23.5, 19.5. IR (neat, cm^{-1}) 3318 (s), 2969 (s), 1690 (s), 1643 (s), 1491 (s). Anal. calcd for $C_{21}H_{35}NO_4$: C, 69.01; H, 9.65; N, 3.83; Found: C, 68.90; H, 10.05; N, 4.08.

3,5-Di-(*tert*-butoxycarbonyl)-4-isobutyl-2,6-dimethylpyridine (11k). By the method described for **11i**, 20 g (55 mmol) of 3,5-di-(*tert*-butoxycarbonyl)-4-isobutyl-2,6-dimethyl-1,4-dihydropyridine (**10k**) gave 19.5 g (98%) of **11k** as pale orange oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62 (d, 7.4 Hz, 2 H, CH_2Py), 2.52(s, 6 H, PyCH_3), 1.93 (m, 1 H, CH_2C*H*(CH_3)$_2$), 1.60 (s, 18 H, *t*Bu), 0.89 (d, 7.2 Hz, 6 H, CH_2CH(CH_3)$_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 154.1, 144.6, 128.9, 82.7, 39.1, 29.5, 28.1, 22.9, 22.7. IR (neat, cm^{-1}) 2968 (s), 1718 (s), 1565 (s), 1457 (s). HRMS calcd for $C_{21}H_{33}NO_4$ $(MH)^+$: *m/z* 364.2488; Found: 364.2458.

4-Isobutyl-2,6-distyrylpyridine (13k). By the method described for conversion of **11i** to **12i**, 11 g (30 mmol) of 3,5-di-(*tert*-butoxycarbonyl)-4-isobutyl-2,6-dimethylpyridine (**11k**) gave 2.5 g (51%) of 4-isobutyl-2,6-dimethylpyridine (**12k**),[119] which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (s, 2 H, Py), 2.49 (s, 6 H, CH_3Py), 2.38 (d, 7.3 Hz, 2 H, CH_2Py), 1.88 (m, 1 H, CH_2C*H*(CH_3)$_2$), 0.90 (d, 7.0 Hz, 6 H, CH_2CH(CH_3)$_2$). ^{13}C NMR (125 MHz, CDCl3) δ 157.3, 151.2, 121.2, 44.7, 29.6, 24.4, 22.5. By the method described for conversion of **12j** to **13j**, 2.5 g (20 mmol) of 4-isobutyl-2,6-dimethylpyridine (**12k**) gave 2.3 g (43%) of 4-isobutyl-2,6-distyrylpyridine (**13k**) as a yellow solid, mp 79-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, 2.3 Hz, 16.1 Hz, 4 H, C=CHPy), 7.61 (d, 7.6 Hz, 4 H, *o*-Ph), 7.38 (t, 7.1 Hz, 4 H, *m*-Ph), 7.29 (m, 2 H, *p*-Ph), 7.18 (dd, 2.3 Hz, 16.1 Hz, 2 H, C=CHPh), 7.07 (s, 2 H, Py), 2.50

(d, 7.4 Hz, 2 H, CH_2CH(CH$_3$)$_2$), 1.96 (m, 1 H, CH$_2$CH(CH$_3$)$_2$), 0.95 (t, 7.5 Hz, 3 H, CH$_2$CH(CH_3)$_2$). ^{13}C NMR (100 MHz, CDC3) δ 155.0, 151.2, 136.7, 132.4, 128.5, 128.3, 128.0, 126.9, 121.3, 44.6, 29.4, 22.2. IR (neat, cm^{-1}) 3021 (m), 2955 (s), 2926 (m), 2868 (m), 2360 (m), 2341 (m), 1635 (s), 1589 (s). HRMS calcd for $C_{25}H_{25}N$ (MH)$^+$: *m/z* 340.2065; Found: 340.2047.

2,6-Bis(hydroxymethyl-4-isobutylpyridine (7k). By the method described for conversion of **13i** to **14i**, 1.1 g (3.2 mmol) of 4-isobutyl-2,6-distyrylpyridine (**13k**) gave 0.54 g (89%) of 4-isobutylpyridine-2,6-dicarboxaldehyde (**14k**) as a pale orange oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.16 (s, 2 H, CHO), 7.96 (s, 2 H, Py), 2.67 (d, 7.5 Hz, 2 H, CH_2Py), 2.00 (m, 1 H, CH$_2$CH(CH$_3$)$_2$), 0.96 (t, 7.4 Hz, 6 H, CH$_2$CH(CH_3)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 192.9, 154.0, 153.1, 126.1, 44.7, 29.7, 22.3. By the method described for **7i**, 0.72 g (3.8 mmol) of 4-isobutylpyridine-2,6-dicarboxaldehyde (**14k**) gave 0.73 g (99%) of 2,6-bis(hydroxymethyl)-4-isobutylpyridine (**7k**) as a pale yellow solid, mp 75-76 ºC. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.99 (s, 2 H, Py), 4.72 (s, 4 H, CH$_2$O), 4.22 (br, 2 H, OH), 2.47 (d, 7.2 Hz, 2 H CH$_2$Py,), 1.90 (m, 1 H, CH(CH$_3$)$_2$), 0.90 (d, 7.6 Hz, 6 H, CH(CH_3)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.6, 152.7, 120.3, 64.5, 44.8, 29.6, 22.4. IR (neat, cm^{-1}) 3249 (br), 2968 (s), 2873 (s), 1610 (s), 1564 (s). HRMS calcd for $C_{11}H_{17}NO_2$ (MH)$^+$: *m/z* 196.1338; Found: 196.1360.

3,5-Di-(*tert*-butoxycarbonyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (10l).[88] By the method described for **10i**, 18 g (0.11 mol) of *tert*-butyl acetoacetate and 5.3 g (50 mmol) of benzaldehyde gave 10.1 g (52%) of 3,5-di-(*tert*-butoxycarbonyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**10l**) as an orange solid, mp 185-186 ºC (lit.[88] 168-171.5 ºC). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26-7.31 (m, 2 H, *o*-Ph), 7.18-7.21 (m, 2 H, *m*-Ph), 7.10 (m, 1 H, *p*-Ph), 5.50 (s, 1 H, NH), 4.91 (s, 1 H, CH), 2.27 (s, 6 H, C=CCH$_3$), 1.39 (s, 18 H, *t*Bu).

3,5-Di-(*tert*-butoxycarbonyl)-2,6-dimethyl-4-phenylpyridine (11l).[88–90] By the method described for **11i**, 8.1 g (21 mmol) of 3,5-di-(*tert*-butoxycarbonyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**10l**) gave 8.1 g (100%) of 3,5-di-(*tert*-butoxycarbonyl)-2,6-dimethyl-4-phenylpyridine (**11l**) as a light yellow solid, mp 89-90 ºC (lit.[89] 88-92 ºC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.37 (m, 3 H, *o,p*-Ph), 7.20 (m, 2 H, *m*-Ph), 7.27 (m, 2 H, Py), 2.58 (s, 6 H, CH_3Py), 1.18 (s, 18 H, *t*Bu).

2,6-Dimethyl-4-phenylpyridine (12l).[91,120] By the method described for **12i**, 0.30 g (0.78 mmol) of 3,5-di(*tert*-butoxycarbonyl)-2,6-dimethyl-4-phenylpyridine (**11l**) gave 0.14 g (100%) of 2,6-dimethyl-4-phenylpyridine (**12l**) as a white solid, mp 58-60 ºC (lit.[121] 49-50 ºC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (m, 2 H, *o*-Ph), 7.44 (m, 3 H, *m,p*-Ph), 7.18 (s, 2 H, Py), 2.59 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 149.2, 138.8, 129.1, 128.9, 127.1, 118.5, 24.7.

4-Phenyl-2,6-distyrylpyridine (13l). A solution of 2.7 g (15 mmol) of 2,6-dimethyl-4-phenylpyridine (**12l**), 7.5 mL (7.8 g, 70 mmol) of benzaldehyde, and 14 mL (15 g, 0.15 mol) of acetic anhydride was stirred and boiled under reflux for 73 h. After cooling to room temperature, 15 mL of 5% (w/v) aq. NaOH solution was added. The mixture was stirred at room temperature for 3 h and extracted with DCM (3 x 50 mL), and the combined organic solutions were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight then stirred with 100 mL of 6 N aq. HCl solution and 50 mL of DCM at room temperature for 5 h. The layers were separated and the aq. phase was extracted with DCM (3 x 75 mL). The combined extracts were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* and triturated with anhydrous diethyl ether (5 x 50 mL). The resulting yellow solid was dried *in vacuo* overnight yielding the HCl salt as a yellow solid, which was converted to the free base by stirring with 300 mL of DCM, 300 mL of 2 N aq. NaOH solution, and 300 mL of saturated aq. NaCl

solution for 5 h. The layers were separated and the aq. layer was extracted with DCM (3 x 75 mL). The combined extracts were dried, filtered, and concentrated by rotary evaporation. Recrystallization of the residue with DCM/hexane gave 2.7 g (75%) of a yellow-green powder. The mother liquor was subjected to column chromatography on neutral alumina, eluting with 3:7, then 1:1 (v/v) DCM/hexane to give 1.7 g (47%) of a pale yellow powder. Total yield of **13l**: 4.36 g (83%). Spectroscopic data are consistent with those reported in the literature.[94,95]

4-Phenylpyridine-2,6-dicarboxaldehyde (14l).[94,96] By the method described for conversion of **13i** to **14i**, 2.1 g (5.8 mmol) of 4-phenyl-2,6-distyrylpyridine (**13l**) gave the crude product as a yellow solid, which was recrystallized from diethyl ether yielding 1.1 g (90%) of ***14l*** as a pale yellow solid, mp 104-105 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.23 (s, 2 H, CHO), 8.41 (s, 2 H, Py), 7.76 (d, 7.8 Hz, 2 H, *o*-Ph), 7.58-7.52 (m, 3 H, *m,p*-Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 153.6, 152.2, 136.0, 130.4, 129.6, 127.2, 122.9.

2,6-Bis(hydroxymethyl)-4-phenylpyridine (7l).[72,88] By the method described for **7i**, 2.3 g (10 mmol) of 4-phenylpyridine-2,6-dicarboxaldehyde (**14l**) gave 2.17 g (94%) of **7l** as a brown solid, mp 94-95 ˚C (lit.[69] 105-108 ˚C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (m, 2 H, *o*-Ph), 7.47 (m, 3 H, *m,p*-Ph), 7.41 (s, 2 H, Py), 4.82 (s, 4 H, CH_2), 3.70 (br, 2 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 150.3, 138.1, 129.4, 129.2, 127.2, 117.5, 64.7.

4-Methyl-2,6-distyrylpyridine (13m).[94] A solution of 4 mL (30 mmol) of collidine, 15 mL (0.15 mol) of benzaldehyde, and 28 mL (0.3 mol) of acetic anhydride was stirred at 170 ˚C for 45 h. Most of the acetic anhydride (ca. 15 mL) was distilled off under reduced pressure, then 30 mL of 5% (w/v) aq. NaOH solution was added. The mixture was stirred at room temperature for 3 h then extracted with DCM (3 x 50 mL). The combined extracts were dried, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography on silica, eluting with

9:1 (v/v) pentane/EtOAc to give 0.56 g of yellow solid. Flash column chromatography on slilica gel, eluting with 9:1 (v/v) pentane/EtOAc gave 1.77 g of **13m** as a yellow solid. Total yield: 2.33 g (26%), mp 119-122 ˚C (lit.[94] 130-131 ˚C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 16.1 Hz, 2 H, C=CHPy), 7.61 (dd, 7.1, 1.4 Hz, 4 H, *o*-Ph), 7.42–7.30 (m, 6 H, *m,p*-Ph), 7.19 (d, 16.1 Hz, 2 H, C=CHPh), 7.13 (s, 2 H, Py), 2.37 (s, 3 H, Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 147.7, 136.9, 132.6, 128.7, 128.4, 128.1, 127.1, 121.5, 21.0.

4-Methylpyridine-2,6-dicarboxaldehyde (14m). By the method described for conversion of **13i** to **14i**, 1.8 g (5.9 mmol) of 2,6-dibenzylidene-4-methylpyridine gave 0.86 g (98%) of **14m** as a brownish solid, mp 164-165 ˚C (lit.[94] 162 ˚C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.15 (s, 2 H, CHO), 7.99 (s, 2 H, Py), 2.55 (s, 3 H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.6, 153.0, 150.3, 126.1, 21.1.

2,6-Bis(hydroxymethyl)-4-methylpyridine (7m) By the method described for **7i**, 0.95 g (6.4 mmol) of 4-methylpyridine-2,6-dicarboxaldehyde (**14m**) gave 0.86 g (89%) of **7m** as an off white solid, mp 95-97 ˚C (lit.[72] 85-86 ˚C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.12 (s, 2 H, Py), 5.30 (t, 6.1 Hz, 2 H, OH), 4.46 (d, 6.1 Hz, 4 H, CH_2), 2.30 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 147.7, 119.1, 64.3. 21.1.

General procedure for conversion of diols (7) to dibromides (6) with PBr_3. A suspension or solution of 20 mmol of the diol (**7**) in 200 mL of $CHCl_3$ was stirred at room temperature as a solution of 0.13 mol of PBr_3 was added dropwise over 30 min. The reaction mixture was stirred and boiled under reflux overnight, then cooled to room temperature and stirred with 350 mL of 5% (w/v) aq. $NaHCO_3$ solution for 1 hr. The layers were separated and the clear organic layer was washed with water (2 x 150 mL), dried, filtered and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight.

2,6-Bis(bromomethyl)-4-ethylpyridine (6b).[122] Following the general procedure, 0.70 g (4.2 mmol) of 4-ethyl-2,6-bis(hydroxymethyl)pyridine (**7b**) gave 1.05 g (85%) of **6b** as a pale pinkish orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 2 H, Py), 4.52 (s, 4 H, CH_2Br), 2.67 (q, 7.4 Hz, 2 H, CH_2CH_3), 1.27 (t, 7.8 Hz, 3 H, CH_3).

2,6-Bis(bromomethyl)-4-*tert*-butylpyridine (6c). Following the general procedure, 1.5 g, (7.4 mmol) of 4-*tert*-butyl-2,6-bis(hydroxymethyl)pyridine (**7c**) gave 2.1 g (90%) of **6c** as a white solid, mp 108-110 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 2 H, Py), 4.54 (s, 4 H, CH_2), 1.33 (s, 9 H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7, 34.1, 35.2, 120.2, 156.8, 162.8. IR (cm^{-1}) 2962 (s), 2864 (s), 2060 (w), 1628 (s), 1599 (s), 1554 (s). MS *m/z* 322.47 $(MH)^+$, 324.43 $(M+2)^+$. Anal. calcd for $C_{11}H_{15}Br_2N$: C, 41.15; H, 4.71; N, 4.36; Found: C, 41.22; H, 5.08; N, 4.49.

2,6-Bis(bromomethyl)-4-methoxypyridine (6e).[75,101] Following the general procedure, 2.8 g (20 mmol) of 2,6-bis(hydroxymethyl)-4-methoxypyridine (**7e**) gave 4.38 g (90%) of **6e** as a white solid, mp 98-99 ˚C (lit.[101] 99 ˚C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (s, 2 H, Py), 4.46 (s, 4 H, CH_2), 3.88 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 158.3, 109.0, 55.6, 33.7.

2,6-Bis(bromomethyl)-4-ethoxypyridine (6f).[75] Following the general procedure, 1.3 g (6.8 mmol) of 4-ethoxy-2,6-bis(hydroxymethyl)pyridine (**7f**) gave 1.85 g (87%) of **6f** as a white solid, mp 71-72 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 2 H, Py), 4.48 (s, 4 H, CH_2Br), 4.12 (s, 7.0 Hz, 2 H, OCH_2), 1.44 (t, 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 158.2, 109.5, 64.2, 33.6, 14.6.

4-Benzyloxy-2,6-bis(bromomethyl)pyridine (6g).[76] Following the general procedure, 0.24 g (1.0 mmol) of 4-benzyloxy-2,6-bis(hydromethyl)pyridine (**7g**) gave 0.30 g (83%) of **6g** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.39 (m, 5 H, Ph), 6.99 (s, 2 H, Py), 5.14 (s, 2 H, OCH_2), 4.51 (s, 4 H, CH_2Br).

2,6-Bis(bromomethyl)-4-cyclohexylmethoxypyridine (6h). Following the general procedure, 0.13 g (0.52 mmol) of 4-cyclohexylmethoxy-2,6-bis(hydroxymethyl)pyridine (**7h)** gave 0.19 g (97%) of **6h** as a pale yellow solid, mp 94-95 ^{0}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (s, 2 H, Py), 4.49 (s, 4 H, CH_2Br), 3.81 (d, 6.1 Hz, 2 H, OCH_2), 1.86-1.01 (m, 11 H, Cy). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 158.1, 109.5, 73.8, 37.5, 33.6, 29.8, 26.5, 25.8. IR (cm^{-1}) 2921 (s), 2849 (s), 1622 (s), 1595 (s). HRMS calcd for $C_{14}H_{19}Br_2NO$ $(M+2)^+$: *m/z* 377.9846; Found: 377.9843. Anal. calcd for $C_{14}H_{19}Br_2NO$: C, 44.59; H, 5.08; N, 3.71; Found: C, 44.24; H, 5.68; N, 3.63.

2,6-Bis(bromomethyl)-4-propylpyridine (6i). Following the general procedure, 0.53 g (2.9 mmol) of 2,6-bis(hydroxymethyl)-4-propylpyridine (**7i**) gave 0.75 g (84%) of **6i** as a pale orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2 H, Py), 4.51 (s, 2 H, CH_2Br), 2.58 (t, 7.5 Hz, 2 H, CH_2CH_2Py), 1.65 (sext, 7.7 Hz, 2 H, $CH_2CH_2CH_3$), 0.93 (t, 7.4 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 153.9, 122.9, 36.9, 33.6, 23.1, 13.6. IR (cm^{-1}) 2959 (m), 2870 (m), 2511 (br), 1627 (s), 1560 (m). HRMS calcd for $C_{10}H_{13}Br_2N$ $(MH)^+$: *m/z* 305.9447; Found: 305.9479.

2,6-Bis(bromomethyl)-4-butylpyridine (6j). Following the general procedure, 0.98 g (5.0 mmmol) of 4-butyl-2,6-bis(hydroxymethyl)pyridine (**7j**) gave 1.58 g (98%) of **6j** as a light pink oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 2 H, Py), 4.50 (s, 4 H, CH_2Br), 2.60 (t, 7.6 Hz, 2 H, CH_2CH_2Py), 1.61 (m, 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 1.35 (m, 7.5 Hz, 2 H, CH_2CH_3), 0.92 (t, 7.4 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 154.0, 122.8, 34.6, 33.5, 32.0, 22.1, 13.7. IR (cm^{-1}) 2959 (s), 2869 (s), 2508 (br), 1626 (s), 1560 (s), 1437 (s). HRMS calcd for $C_{11}H_{15}Br_2N$ $(M+2)^+$: *m/z* 321.9629; Found: 321.9656. Anal. calcd for $C_{11}H_{15}Br_2N$: C, 41.15; H, 4.71; N, 4.36; Found: C, 40.87; H, 5.10; N, 4.57.

2,6-Bis(bromomethyl)-4-isobutylpyridine (6k). Following the general procedure, 0.72 g (3.7 mmol) of 2,6-bis(hydroxymethyl)-4-isobutylpyridine (**7k**) gave 1.05 g (89%) of **6k** as a pale pinkish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 2 H, Py), 4.51 (s, 4 H, CH_2Br), 2.49 (d, 7.4 Hz, 2 H, CHCH_2Py), 1.91 (m, 1 H, CH_2CH), 0.90 (d, 7.3 Hz, 6 H, $CH(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 153.2, 123.8, 44.7, 33.8, 29.6, 22.4. IR (cm^{-1}) 2955 (s), 2928 (s), 2860 (s), 2509 (br), 2361 (s), 2342 (s), 1627 (s), 1606 (s), 1560 (s). HRMS calcd for $C_{11}H_{15}Br_2N$ $(M+2)^+$: *m/z* 321.9629; Found: 321.9634.

2,6-Bis(bromomethyl)-4-phenylpyridine (6l).[69,75] Following the general procedure, 2.16 g (10 mmol) of 2,6-bis(hydroxymethyl)-4-phenylpyridine (**7l**) gave 3.0 g (88%) of **6l** as a a brown solid, mp 159-160 ºC (lit.[69] 167-169 ºC). ^{1}H NMR (400 MHz, CDCl3): δ 7.64 (m, 2 H, *o*-Ph), 7.58 (s, 2 H, Py), 7.49 (m, 3 H, *m,p*-Ph), 4.60 (s, 4 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 151.0, 137.5, 129.6, 129.4, 127.2, 121.1, 33.7.

2,6-Bis(bromomethyl)-4-methylpyridine (6m). Following the general procedure, 0.10 g (0.66 mmol) of 2,6-bis(hydroxymethyl)-4-methylpyridine (**7m**) gave 0.16 g (87%) of **6m** as white crystals, mp 84-85 ˚C (lit.[123] 85-85.5 ºC). ^{1}H NMR (400 MHz, CDCl3): δ 7.19 (s, 2 H, Py), 4.49 (s, 4 H, CH_2), 2.36 (s, 3 H, CH_3).

General procedure for conversion of dibromides (6) to dinitriles (5) with NaCN. A mixture of 10 mmol of the dibromide **(6)**, 60 mmol of NaCN and 100 mL of MeOH was stirred and boiled under reflux for 5–6.5 h, cooled to room temperature, then the reaction mixture or the residue after rotary evaporation was partitioned between 100 mL of water and 100 mL of chloroform or DCM. The layers were separated and the aq. layer was extracted with chloroform or DCM (3 x 50 mL). The combined organic solutions were washed with 100 mL of water, 100 mL of saturated aq. NaCl solution, dried, filtered and concentrated to dryness by rotary

evaporation. The residue was purified by column chromatography on silica, eluting with EtOAc/$CHCl_3$ or EtOAc/DCM.

2,6-Bis(cyanomethyl)-4-ethylpyridine (5b). Following the general procedure, except that the reaction mixture was partitioned between DCM and saturated aq. NaCl solution (instead of water), 1.65 g (5.63 mmol) of 2,6-bis(bromomethyl)-4-ethylpyridine (**6b**) gave 0.66 g (63%) of **5b** as a reddish brown solid, mp 75-76 ^{0}C. ^{1}H NMR (500 MHz, CDCl3) δ 7.24 (s, 2 H, Py), 3.89 (s, 4 H, CH_2CN), 2.71 (q, 7.6 Hz, 2 H, $CH_3C\mathit{H}_2$), 1.28 (t, 7.6 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 150.9, 121.3, 117.0, 28.4, 26.5, 14.4. IR (cm^{-1}) 2968 (s), 2924 (m), 2245 (s), 1609 (s), 1562 (s), 1441 (s). HRMS calcd for $C_{11}H_{11}N_3$ $(MH)^+$: *m/z* 186.1031; Found: 186.1024.

4-*tert*-Butyl-2,6-bis(cyanomethyl)pyridine (5c). Following the general procedure, 5.9 g (0.02 mol) of 2,6-bis(bromomethyl)-4-*tert*-butylpyridine (**6c**) was converted to 3.3 g (84%) of **5c** as a reddish brown solid, mp 79-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 2 H, Py), 3.91 (s, 4 H, CH_2), 1.34 (s, 9 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 30.6, 35.3, 117.1, 118.9, 150.9, 163.9. IR (cm^{-1}) 2968 (s), 2252 (m), 1605 (s), 1555 (s). HRMS calcd for $C_{13}H_{15}N_3$ $(M+Na)^+$; *m/z* 236.1164; Found: 236.1145. Anal. calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70; Found: C, 72.56; H, 7.43; N, 19.50.

2,6-Bis(cyanomethyl)-4-methoxypyridine (5e). Following the general procedure, 0.51 g, (1.7 mmol) of 2,6-bis(bromomethyl)-4-methoxypyridine (**6e**) gave 0.16 g (49%) of **5e** as a brown solid, mp 58-60 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (s, 2 H, Py), 3.91 (s, 4 H, CH_2), 3.88 (s, 3 H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 152.4, 116.8, 107.8, 55.9, 26.6. IR (cm^{-1}) 2949 (w), 2921 (m), 2259 (m), 1738 (m), 1600 (s), 1572 (s), 1464 (s). MS *m/z* 210.40 $(M+Na)^+$. Anal. calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45; Found: C, 63.85; H, 4.94; N, 22.13.

2,6-Bis(cyanomethyl)-4-ethoxypyridine (5f). Following the general procedure, 2.4 g (7.7 mmol) of 2,6-bis(bromomethyl)-4-ethoxypyridine (**6f**) gave 0.57 g (37%) of **5f** as a brown solid, mp 91-92 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (s, 2 H, Py), 4.13 (q, 7.2 Hz, 2 H, CH_2CH$_3$), 3.85 (s, 4 H, CH_2CN), 1.46 (t, 6.8 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 152.1, 116.6, 107.9, 64.2, 26.3, 14.2. IR (cm^{-1}) 2983 (w), 2949 (w), 2905 (m), 2258 (m), 1608 (s), 1567 (s). HRMS calcd for $C_{11}H_{11}N_3O$ $(M+Na)^+$: *m/z* 224.0800; Found: 224.0786. Anal. calcd for $C_{11}H_{11}N_3O \cdot 1.5H_2O$: C, 57.88; H, 6.18; N, 18.41; Found: C, 57.97; H, 5.64; N, 18.47.

4-Benzyloxy-2,6-bis(cyanomethyl)pyridine (5g). Following the general procedure, 4.2 g (0.01 mol) of 4-benzyloxy-2,6-bis(bromomethyl)pyridine (**6g**) gave 1.19 g (40%) of **5g** as a brown solid, mp 87-89 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.47 (m, 5 H, Ph), 6.99 (s, 2 H, Py), 5.17 (s, 2 H, OCH_2), 3.86 (s, 4 H, CH_2CN). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 152.5, 134.9, 131.1, 129.0, 127.8, 116.8, 108.6, 70.6, 26.7. IR (cm^{-1}) 2256 (m), 1739 (m), 1603 (s), 1573 (s), 1453 (s). MS *m/z* 286.28 $(M+Na)^+$, 100%; 287.54 $(M+Na+H)^+$, 20%. Anal. calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96; Found: C, 72.71; H, 5.33; N, 16.00.

2,6-Bis(cyanomethyl)-4-cyclohexylmethoxypyridine (5h). Following the general procedure, 1.8 g (4.7 mmol) of 2,6-bis(bromomethyl)-4-cyclohexylmethoxypyridine (**6h**) gave 0.64 g (51%) of **5h** as a reddish brown solid, mp 85-86 ^{0}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (s, 2 H, Py), 3.85-3.84 (m, 6 H, CH_2Br, OCH_2Cy*),* 1.86-1.03 (m, 11 H, Cy). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 152.3, 116.8, 108.2, 74.1, 37.5, 29.8, 26.6, 25.8. IR (cm^{-1}) 2921 (s), 2851 (s), 2258 (m), 1598 (s), 1568 (s), 1450 (s). HRMS calcd for $C_{16}H_{19}N_3O$ $(M+Na)^+$: *m/z* 292.1426; Found: 292.1455. Anal. calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60; Found: C, 70.96; H, 7.59; N, 15.56.

2,6-Bis(cyanomethyl)-4-propylpyridine (5i). Following the general procedure, 0.72 g (2.4 mmol) of 2,6-bis(bromomethyl)-4-propylpyridine (**6i**) gave 0.18 g (39%) of **5i** as an orange brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 2 H, Py), 3.91 (s, 2 H, CH_2Br), 2.64 (t, 7.7 Hz, 2 H, CH_2Py), 1.68 (sext, 7.7 Hz, 2 H, $CH_2CH_2CH_3$), 0.94 (t, 7.4 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 150.6, 121.7, 116.9, 37.1, 26.3, 23.4, 13.6. IR (cm^{-1}) 2962 (s), 2933 (m), 2873 (m), 2254 (s), 1608 (s), 1564 (s), 1432 (m), 1408 (s). HRMS calcd for $C_{12}H_{13}N_3$ $(M+Na)^+$: *m/z* 222.1007; Found: 222.1025.

4-Butyl-2,6-bis(cyanomethyl)pyridine (5j). Following the general procedure, 1.5 g (4.6 mmol) of 2,6-bis(bromomethyl)-4-butylpyridine (**6j**) gave 0.50 g (51%) of **5j** as a brown solid, mp 72-73 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 2 H, Py), 3.90 (s, 4 H, CH_2CN), 2.66 (t, 7.5 Hz, 2 H, CH_2Py), 1.62 (m, 7.5 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.37 (m, 7.6 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 0.95 (t, 7.5 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 150.7, 121.7, 116.9, 35.0, 32.4, 26.4, 22.3, 13.8. IR (cm^{-1}) 2962 (s), 2933 (s), 2873 (s), 2254 (s), 1608 (s), 1564 (s), 1432 (s), 1408 (s). HRMS calcd. for $C_{13}H_{15}N_3$ $(M+Na)^+$: *m/z* 236.1164; Found: 236.1194.

2,6-Bis(cyanomethyl)-4-isobutylpyridine (5k). Following the general procedure, 1.0 g (3.1 mmol) of 2,6-bis(bromomethyl)-4-isobutylpyridine (**6k**) gave 0.34 g (52%) of **5k** as a reddish brown solid, mp 67-69 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2 H, Py), 3.90 (s, 4 H, CH_2CN), 2.53 (d, 7.3 Hz, 2 H, CH_2Py), 1.93 (m, 1 H, CH), 0.90 (d, 7.1 Hz, 6 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 150.7, 122.3, 116.9, 44.6, 29.7, 26.5, 22.4. IR (cm^{-1}) 2962 (s), 2933 (m), 2873 (m), 2253 (s), 1608 (s), 1564 (s), 1432 (m), 1408 (s). HRMS calcd for $C_{13}H_{15}N_3$ $(MH)^+$: *m/z* 214.1344; Found: 214.1325.

2,6-Bis(cyanomethyl)-4-phenylpyridine (5l). Following the general procedure, 1.2 g (3.4 mmol) of 2,6-bis(bromomethyl)-4-phenylpyridine (**6l**) gave 0.30 g (38%) of **5l** as a beige solid,

mp 127-128 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (m, 2 H, *o*-Ph), 7.61 (s, 2 H, Py), 7.51 (m, 3 H, *m,p*-Ph), 3.98 (s, 4 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 151.5, 136.8, 130.1, 129.5, 127.2, 119.6, 116.8, 26.7. IR (cm^{-1}) 2913 (w), 2253 (w), 1732 (m), 1604 (s), 1553 (s). MS *m/z* 256.39 $(M+Na)^+$. Anal. calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01; Found: C, 76.85; H, 5.15; N, 17.80.

2,6-Bis(cyanomethyl)-4-methylpyridine (5m). Following the general procedure, 1.5 g (5.5 mmol) of 2,6-bis(bromomethyl)-4-methylpyridine (**6m**) gave 0.57 g (57%) of **5m** as a beige solid, mp 93-95 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 2 H, Py), 3.88 (s, 4 H, CH_2), 2.40 (s, 3 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 26.5, 117.0, 122.6, 131.6, 150.8. IR (cm^{-1}) 2971 (m), 2946 (w), 2252 (s), 1607 (s), 1561 (s), 1448 (s), 1405 (s). HRMS calcd for $C_{10}H_9N_3$ $(M+Na)^+$: *m/z* 194.0694; Found: 194.0680. Anal. calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54; Found: C, 69.50; H, 5.66; N, 24.86.

General procedure for conversion of dinitriles (5) to diamines (15) with $NaBH_4$. A mixture of 2 mmol of **5**, 8 mmol of di-*t*-butyl dicarbonate, 0.5 mmol of $NiCl_2$•$6H_2O$ and 40 mL of dry MeOH was stirred at 0 ˚C as 40 mmol of $NaBH_4$ was added in small portions over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 18–48 h, then 5 mmol of diethylenetriamine was added. The mixture was stirred for 30 min then concentrated by rotary evaporation. The black residue was partitioned between 100 mL of EtOAc and 100 mL of saturated aq. $NaHCO_3$ solution. The organic layer was separated, dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight to give the crude Boc-protected amine, which was stirred with 50 mL of 2 N HCl in methanol/water for 6 h at room temperature then concentrated to dryness by rotary evaporation. The residue was dried *in vacuo*, triturated with diethyl ether and dried *in vacuo*. The crude HCl salt was converted to the free base by stirring with

50 mL of 2 N aq. NaOH solution, 50 mL of saturated aq. NaCl solution, and 50 mL of DCM for 5 h at room temperature. The layers were separated and the aq. layer was saturated with K_2CO_3 and NaCl, then extracted with DCM (5 x 50 mL). The combined organic solutions were dried, filtered, and concentrated by rotary evaporation to give diamine **15**, which was dried *in vacuo.*

2,6-Bis(2-aminoethyl)-4-ethylpyridine (15b). Following the general procedure, 0.24 g (1.3 mmol) of 2,6-bis(cyanomethyl)-4-ethylpyridine (**5b**) gave 0.22 g (88%) of **15b** as an orange brown oil, which was used in the next step without further purification. **15b•HCl:** ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (s, 2 H, Py), 3.51 (s, 8 H, CH_2N, CH_2Py), 2.97 (q, 7.6 Hz, 2 H, CH_2CH_3), 1.38 (t, 7.7 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 168.3, 153.1, 127.4, 39.6, 31.9, 30.3, 14.0. IR (cm^{-1}) 3129 (br), 2809 (br), 2576 (br), 2049 (m), 1629 (s), 1451 (m), 1402 (s). HRMS calcd for $C_{11}H_{19}N_3$ $(MH)^+$: *m/z* 194.1657; Found: 194.1687. **15b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 2 H, *m*-Py), 3.08 (t, 7.0 Hz, 4 H, CH_2Py), 2.86 (t, 7.0 Hz, 4 H, CH_2N), 2.59 (q, 8.2 Hz, 2 H, CH_2CH_3), 1.41 (br, 4 H, NH), 1.23 (t, 8.3 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 153.6, 120.5, 42.2, 42.1, 28.1, 14.4.

2,6-Bis(2-aminoethyl)4-*tert*-butylpyridine (15c). A solution of 2.3 g (0.01 mol) of 4-*tert*-butyl-2,6-bis(cyanomethyl)pyridine (**5c**) in 60 mL of anhydrous THF was stirred at room temperature as 95 mL of 1 M BH_3/THF was added over 90 min by syringe. The reaction mixture was stirred at room temperature for 24 h then 40 mL of water was added over 30 min by syringe, followed by 40 mL of 6 N aq. HCl solution, added over 30 min by syringe. THF was removed by distillation at atmospheric pressure under nitrogen at 85-90˚C (3 h) then the solution was cooled to room temperature. The resulting white crystals were collected by filtration, washing the filter paper with 6 N aq. HCl followed by water. The filtrate was washed with DCM (5 x 75 mL) then basified with 6 N aq. NaOH (pH 14), saturated with K_2CO_3 and NaCl, then extracted with DCM (6 x 100

mL). The combined extracts were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight giving 1.64 g (70% yield) of **15c** as an orange oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 2 H, Py), 3.07 (t, 6.1 Hz, 4 H, CH_2Py), 2.87 (t, 6.1 Hz, 4 H, CH_2N), 1.29 (s, 9 H, CH_3), 1.57 (br, 4 H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 30.6, 34.5, 42.3, 117.9, 159.4, 160.7. MS *m/z* 224.19 $(M+3H)^+$.

2,6-Bis(2-aminoethyl)-4-methoxypyridine (15e). Following the general procedure, 0.40 g (2.1 mmol) of 2,6-bis(cyanomethyl)-4-methoxypyridine (**5e**) gave 0.34 g (81%) of **15e** as a yellow orange oil, which was used in the next step without further purification. **15e•HCl**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.46 (s, 2 H, Py), 4.17 (s, 3 H, CH_3), 3.51-3.40 (m, 12 H, CH_2N, CH_2Py, NH_2). ^{13}C NMR (100 MHz, CD_3OD): δ 172.9, 153.4, 111.9, 57.3, 37.9, 30.4. IR (cm^{-1}) 2831 (br, s), 2255 (m), 1623 (s), 1486 (s). MS *m/z* 196.25 $(MH)^+$. Anal. calcd for $C_{10}H_{17}N_3O$•3HCl•1.25H_2O: C, 36.71; H, 6.93; N, 12.84; Found: C, 36.72; H, 7.28; N, 12.70. **15e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (s, 2 H, Py), 3.81 (s, 3 H, OCH_3), 3.07 (t, 7.6 Hz, 2H, CH_2Py), 2.84 (t, 7.5 Hz, 2 H, CH_2N), 1.93 (br, 2 H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 161.0, 106.6, 54.7, 42.1, 41.9.

2,6-Bis(2-aminoethyl)-4-ethoxypyridine (15f). Following the general procedure, 0.40 g (2 mmol) of 2,6-bis(cyanomethyl)-4-ethoxypyridine (**5f**) gave 0.24 g (91%) of **15f** as an orange oil. **15f•HCl**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.41 (s, 2 H, Py), 4.45 (q, 7.0 Hz, 2 H, CH_2CH_3), 3.48-3.41 (m, 8 H, CH_2CH_2N), 1.50 (t, 7.1 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 154.9, 113.8, 68.7, 39.6, 32.0, 14.6. IR (cm^{-1}) 2867 (br, s), 2258 (m), 1624 (s), 1486 (s). MS *m/z* 210.26 $(MH)^+$. Anal. calcd for $C_{11}H_{19}N_3O$·3HCl·1.75H_2O: C, 37.73; H, 7.34; N, 12.00; Found: C, 37.54; H, 6.95; N, 12.42. **15f**: ^{1}H NMR (400 MHz, CD_3OD): δ 6.68 (s, 2 H, Py), 4.10 (q, 7.2 Hz, 2 H,

C*H*$_2$CH$_3$*),* 2.96 (t, 7.1 Hz, 4 H, CH$_2$Py), 2.83 (t, 7.1 Hz, 4 H, CH$_2$N), 1.39 (t, 7.0 Hz, 3 H, CH$_3$). ^{13}C NMR (100 MHz, CD$_3$OD): δ 168.0, 162.4, 109.0, 64.9, 42.9, 42.1, 15.1.

2,6-bis(2-aminoethyl)-4-benzyloxypyridine (15g). Following the general procedure, 0.84 g (3.19 mmol) of 4-benzyloxy-2,6-bis(cyanomethyl)pyridine (**5g**) gave 0.32 g (86%) of **15g** as an orange oil. **15g•HCl**: ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.55 (s, 2 H, Py), 7.53-7.36 (m, 5 H, Ph), 5.48 (s, 2 H, OCH$_2$), 3.52-3.41 (m, 8 H, CH$_2$Py, CH$_2$N).^{13}C NMR (100 MHz, CD$_3$OD): δ 173.5, 155.1, 135.7, 130.2, 130.0, 129.7, 114.1, 74.1, 39.5, 32.0. IR (cm^{-1}) 2831 (s, br), 1624 (s), 1484 (s). Anal. calcd for C$_{16}$H$_{21}$N$_3$O•3HCl•2.5H$_2$O: C, 45.14; H, 6.87; N, 9.87; Found: C, 45.10; H, 6.68; N, 10.03. MS *m/z* 272.42 (MH)$^+$, 100%; 297.41 (M+Na+3H)$^+$, 39%. **15g**: ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.43-7.25 (m, 5 H, Ph), 6.77 (s, 2 H, Py), 5.14 (s, 2 H, OCH$_2$), 2.94 (t, 7.2 Hz, 4H, CH$_2$Py), 2.83 (t, 7.2 Hz, 4 H, CH$_2$N). ^{13}C NMR (100 MHz, CD$_3$OD): δ 167.7, 162.5, 137.8, 129.8, 129.4, 128.9, 109.4, 71.0, 42.9, 42.1.

2,6-Bis(2-aminoethyl)-4-cyclohexylmethoxypyridine (15h). Following the general procedure, 0.50 g (1.9 mmol) of 2,6-bis(cyanomethyl)-4-cyclohexylmethoxypyridine (**5h**) gave 0.52 g (100%) of **15h** as a yellow-orange oil, which was used in the next step without further purification. **15h•HCl**: ^{1}H NMR (500 MHz, CD$_3$OD): δ 7.46 (s, 2 H, Py), 4.20 (d, 6.1 Hz, 2 H, CH$_2$Cy*),* 3.49 (t, 7.0 Hz, 4 H, CH$_2$Py), 3.43 (m, 4 H, CH$_2$N), 1.91-1.12 (m, 11 H, Cy). ^{13}C NMR (125 MHz, CD$_3$OD) δ 174.0, 154.9, 113.7, 77.6, 39.5, 38.7, 32.0, 30.6, 27.5, 26.9. IR (cm^{-1}) 2849 (br), 1626 (s). HRMS calcd for C$_{16}$H$_{27}$N$_3$O (MH)$^+$: *m/z* 278.2232; Found: 278.2260. Anal. calcd for C$_{16}$H$_{27}$N$_3$O•H$_2$O•3HCl: C, 47.36; H, 7.26; N, 10.44; Found: C, 47.47; H, 7.97; N, 10.38. **15h**: ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.53 (s, 2 H, Py), 3.76 (d, 6.1 Hz, 2 H, CH$_2$Cy*),* 3.04 (t, 7.6 Hz, 4 H, CH$_2$Py), 2.82 (t, 7.4 Hz, 4 H, CH$_2$N), 1.85-1.02 (m, 11 H, Cy). ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.1, 161.1, 107.3, 73.1, 42.3, 42.0, 37.5, 29.8, 26.4, 25.7.

2,6-Bis(2-aminoethyl)-4-propylpyridine (15i). Following the general procedure, 0.18 g (0.90 mmol) of 2,6-bis(cyanomethyl)-4-propylpyridine (**5i**) gave 0.16 g (86%) of **15i** as an orange oil, which was used in the next step without further purification. **15i•HCl:** ^{1}H NMR (400 MHz, CD_3OD): δ 7.84 (br, 2 H, Py), 3.44 (br, 8 H, CH_2CH_2N), 2.87 (br, 2 H, $CH_2CH_2CH_3$), 1.80 (br, 2 H, $CH_2CH_2CH_3$), 1.01 (br, 3 H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 166.9, 153.0, 128.0, 39.7, 39.0, 31.8, 24.1, 14.2. HRMS calcd for $C_{12}H_{21}N_3$ $(MH)^+$: *m/z* 208.1813; Found: 208.1842. **15i:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 2 H, Py), 3.08 (t, 7.7 Hz, 4 H, CH_2Py), 2.86 (t, 7.7 Hz, 4 H, CH_2N), 2.52 (t, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 1.63 (sext, 7.7 Hz, 2 H, $CH_2CH_2CH_3$), 0.95 (t, 7.7 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 152.2, 121.2, 42.3, 42.2, 37.3, 23.6, 13.9.

4-Butyl-2,6-bis(2-aminomethyl)pyridine (15j). Following the general procedure, 0.47 g (2.2 mmol) of 4-butyl-2,6-bis(cyanomethyl)pyridine (**5j**) gave 0.41 g (85%) of **15j** as a greenish brown oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2 H, Py), 3.08 (t, 6.5 Hz, 4 H, $CH_2CH_2NH_2$, 2.88 (t, 6.5 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 2.55 (t, 7.7 Hz, 4 H, CH_2N), 1.57 (m, 2 H, $CH_2CH_2CH_3$), 1.36 (m, 2 H, CH_2CH_3), 1.26 (s, 4 H, NH), 0.91 (t, 7.4 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.4, 121.1, 42.3, 42.2, 34.9, 32.4, 22.4, 13.9. MS *m/z* 223.49 $(M+2)^+$.

2,6-Bis(2-aminoethyl)-4-isobutylpyridine (15k). Following the general procedure, 0.30 g (1.4 mmol) of 2,6-bis(cyanomethyl)-4-isobutylpyridine (**5k**) gave 0.27 g (87%) of the free base **15k** as a yellow orange oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (s, 2 H, Py), 2.93 (t, 7.2 Hz, 4 H, $CH_2CH_2NH_2$), 2.73 (t, 7.2 Hz, 4 H, CH_2N), 2.27 (d, 7.3 Hz, 2 H, CH_2CH), 1.74 (m, 1 H, $CH(CH_3)_2$), 0.77 (d, 7.0 Hz, 6 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 150.9, 121.5, 44.5, 42.0, 41.9, 29.4, 22.2. MS *m/z* 224.04 $(M+3H)^+$.

2,6-Bis(2-aminomethyl)-4-phenylpyridine (15l). Following the general procedure 0.20 g (0.86 mmol) of 2,6-bis(cyanomethyl)-4-phenylpyridine (**5l**) gave 0.21 g (100%) of **15l** as a yellow orange oil, which was used in the next step without further purification. **15l•HCl:** ^{1}H NMR (500 MHz, CD_3OD): δ 8.31 (m, 1 H, *p*-Ph), 8.06 (m, 2 H, *m*-Ph), 7.62 (m, 2 H, *o*-Ph), 7.57 (s, 2 H, Py) 3.59 (s, 8 H, CH_2CH_2N). ^{13}C NMR (125 MHz, CD_3OD) δ 160.0, 153.8, 136.0, 133.4, 131.0, 129.6, 125.1, 39.7, 32.2. IR (cm^{-1}) 2800 (br), 2060 (w), 1626 (s), 1466 (m). MS *m/z* 242.53 $(MH)^+$. Anal. calcd for $C_{15}H_{19}N_3 \cdot 2.25HCl \cdot 2.5H_2O$: C, 48.90; H, 7.18; N, 11.41; Found: C, 48.94; H, 7.38; N, 11.33. **15l:** ^{1}H NMR (500 MHz, CD_3OD): δ 7.62 (d, 8.6 Hz, 2 H, *o*-Ph), 7.45 (m, 3 H, *m*-Ph), 7.22 (s, 2 H, Py), 3.14 (t, 6.9 Hz, 4 H, CH_2Py), 2.97 (t, 6.7 Hz, 4 H, CH_2N). ^{13}C NMR (125 MHz, CD_3OD) δ 160.3, 149.2, 138.7, 129.1, 128.9, 127.1, 119.1, 42.5, 42.4.

2,6-Bis(2-aminoethyl)-4-methylpyridine (15m). Following the general procedure, 0.47 g (2.8 mmol) of 2,6-bis(cyanomethyl)-4-methylpyridine (**5m**) gave 0.40 g (81%) of **15m** as an orange oil, which was used in the next step without further purification. **15m•HCl:** ^{1}H NMR (400 MHz, CD_3OD): δ 7.82 (s, 2 H, Py), 3.49 (s, overlap, 8 H, CH_2CH_2), 2.66 (s, 3 H, Me). ^{13}C NMR (100 MHz, CD_3OD) δ 163.2, 152.8, 128.5, 39.6, 31.8, 22.5. IR (cm^{-1}) 2826-2584 (br), 2060 (w), 1628 (s). MS *m/z* 180.01 $(MH)^+$. Anal. calcd for $C_{10}H_{17}N_3 \bullet 3HCl \bullet H_2O$: C, 39.17; H, 7.23; N, 13.70; Found: C, 39.02; H, 7.35; N, 13.50. **15m:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 2 H, Py), 3.08 (t, 6.4 Hz, 4 H, CH_2Py), 2.85 (t, 6.6 Hz, 4 H, CH_2N), 2.29 (s, 3 H, Me), 1.69 (br, 4 H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 147.5, 121.8, 42.2, 26.2, 20.9.

General procedure for conversion of diamines (15) to disulfonamides (4) with *p*-toluenesulfonyl chloride. A filtered solution of 7 mmol of *p*-toluenesulfonyl chloride in 40 mL of DCM was added dropwise over 30 min to a vigorously stirred solution of 2 mmol of **15** and 7 mmol of triethylamine in 50 mL of DCM. The solution was stirred at room temperature for 18–24 h,

washed with saturated aq. $NaHCO_3$ solution (2 x 100 mL) then with 100 mL of saturated aq. NaCl solution. The organic layer was separated, dried, filtered, and concentrated to dryness by rotary evaporation. The residue was dried *in vacuo* overnight then subjected to column chromatography on alumina, eluting with DCM/EtOAc. In some cases, a portion of the free base was converted to the HCl salt for elemental analysis and biological testing by stirring with 50 mL of 2 N HCl in methanol/water for 5 h, followed by rotary evaporation, trituration with anhydrous diethyl ether, and drying *in vacuo.*

4-Ethyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4b). Following the general procedure, 0.31 g (1.6 mmol) of 2,6-bis(2-aminoethyl)-4-ethylpyridine (**15b**) gave 0.70 g (88%) of **4b** as a glassy brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 8.5 Hz, 4 H, *o*-Ts), 7.27 (d, 8.5 Hz, 4 H, *m*-Ts), 6.76 (s, 2 H, Py), 5.64 (s, 2 H, NH), 3.32 (t, 6.0 Hz, 4 H, CH_2N), 2.86 (t, 6.5 Hz, 4 H, C*H*$_2$$CH_2N$), 2.54 (q, 7.6 Hz, 2 H, C*H*$_2$$CH_3$), 2.40 (s, 6 H, $ArCH_3$), 1.19 (t, 7.4 Hz, 3 H, CH_2C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 154.4, 143.1, 137.0, 129.6, 126.9, 121.3, 42.1, 36.3, 28.0, 21.4, 14.1. **4b•HCl:** mp 140-145 ^{0}C (dec). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, 7.8 Hz, 4 H, *o*-Ts), 7.38 (s, 2 H, Py), 7.25 (d, 7.6 Hz, 4 H, *m*-Ts), 6.54 (s, 2 H, NH), 3.51 (br, 4 H, CH_2N), 3.39 (t, 5.7 Hz, 4 H, CH_2Py), 2.86 (br, 2 H, C*H*$_2$$CH_3$), 2.40 (s, 6 H, $ArCH_3$), 1.34 (br, 3 H, CH_2C*H*$_3$). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.5, 153.7, 143.4, 137.2, 129.8, 127.0, 125.7, 42.4, 33.5, 29.3, 21.7, 13.7. IR (cm^{-1}) 3090 (s), 2679 (s), 1633 (s), 1598 (m), 1439 (s). MS *m/z* 502.59 $(MH)^+$. Anal. calcd for $C_{25}H_{31}N_3O_4S_2 \cdot HCl$: C, 55.80; H, 5.99; N, 7.81; Found: C, 55.56; H, 6.39; N, 7.78.

4-*tert*-Butyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4c). Following the general procedure, 1.51 g (6.82 mmol) of 4-*tert*-butyl-2,6-bis(2-aminoethyl)pyridine (**15c**) gave 2.38 g (66%) of **4c** as a glassy brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 8.8 Hz, 4 H, *o*-Ts),

7.27 (d, 8.5 Hz, 4 H, *m*-Ts), 6.90 (s, 2 H, Py), 5.82 (br, 2H, NH), 3.30 (t, 6.9 Hz, 4 H, CH_2N), 2.86 (t, 6.5 Hz, 4 H, CH_2Py), 2.39 (s, 6 H, $ArCH_3$), 1.23 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 30.6, 34.8, 36.8, 42.4, 118.8, 127.2, 129.8, 137.2, 143.3, 158.0, 161.9. IR (cm^{-1}) 2959 (w), 1600 (m), 1555 (w), 1416 (w). MS *m/z* 530.80 $(MH)^+$. Anal. calcd for $C_{27}H_{35}N_3O_4S_2$: C, 61.22; H, 6.66; N, 7.93; Found: C, 61.35; H, 6.86; N, 8.21.

4-Methoxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4e). Following the general procedure, 0.18 g (0.92 mmol) of 2,6-bis(2-aminoethyl)-4-methoxypyridine (**15e**) gave 0.43 g (93%) of **4e** as a glassy brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 8.4 Hz, 4 H, *o*-Ts), 7.27 (d, 8.3 Hz, 4 H, *m*-Ts), 6.47 (s, 2 H, Py), 3.79 (s, 3 H, OCH_3), 3.31 (t, 6.0 Hz, 4 H, CH_2N), 2.84 (t, 4 H, CH_2Py), 2.41 (s, 6 H, $ArCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 159.6, 143.2, 137.1, 129.7, 127.0, 107.8, 55.2, 42.1, 36.7, 21.5. IR (cm^{-1}) 2942 (w), 1597 (s), 1573 (w), 1493 (w), 1438 (m). MS *m/z* 504.48 $(M+Na)^+$. Anal. calcd for $C_{24}H_{29}N_3O_5S_2$: C, 57.24; H, 5.80; N, 8.34; Found: C, 56.97; H, 6.10; N, 8.33.

4-Ethoxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4f). Following the general procedure, 0.24 g (1.15 mmol) of 2,6-bis(2-aminoethyl)-4-ethoxypyridine (**15f**) gave 0.54 g (92%) of **4f** as a brown glassy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 8.3 Hz, 4 H, *o*-Ts), 7.26 (d, 8.2 Hz, 4 H, *m*-Ts), 6.47 (s, 2 H, Py), 4.02 (q, 7.3 Hz, 2H, OCH_2), 3.30 (t, 6.5 Hz, 4 H, CH_2N), 2.85 (t, 6.5 Hz, 4 H, CH_2Py), 2.39 (s, 6 H, $ArCH_3$), 1.39 (t, 6.7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 159.3, 143.3, 137.2, 129.8, 127.1, 108.5, 63.9, 42.3, 36.5, 21.6, 14.5. IR (cm^{-1}) 1628 (m), 1599 (w), 1455 (m). MS *m/z* 518.41 $(MH)^+$, 100%; 540.25 $(M+Na)^+$, 15%. Anal. calcd for $C_{25}H_{31}N_3O_5S_2 \cdot 0.5H_2O$: C, 57.01; H, 6.12; N, 7.98; Found: C, 57.06; H, 6.28; N, 8.18.

4-Benzyloxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4g). Following the general procedure, 0.55 g (2.0 mmol) of 4-benzyloxy-2,6-*bis*(2-aminoethyl)pyridine (**15g**) gave 1.1 g

(93%) of **4g** as a brown glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 8.2 Hz, 4 H, *o*-Ts), 7.38 (m, 5 H, Ph), 7.26 (d, 8.3 Hz, 4 H, *m*-Ts), 6.54 (s, 2 H, Py), 5.02 (s, 2 H, OCH_2), 3.29 (t, 6.2 Hz, 4 H, CH_2N), 2.83 (t, 6.4 Hz, 4 H, CH_2Py), 2.38 (s, 6 H, $ArCH_3$). ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.0, 159.6, 143.2, 137.0, 135.4, 129.7, 128.7, 128.4, 127.5, 127.0, 108.5, 69.9, 42.1, 36.6, 21.5. IR (cm^{-1}) 1596 (s), 1572 (m), 1449 (w). MS *m/z* 580.50 $(MH)^+$, 100%; 581.41 $(M+2)^+$, 41%; 602.49 $(M+Na)^+$, 18%. Anal. Calcd. for $C_{30}H_{33}N_3O_5S_2$: C, 62.15; H, 5.74; N, 7.25; Found: C, 61.90; H, 6.12; N, 7.54.

4-Cyclohexylmethoxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4h). Following the general procedure, 0.53 g (1.91 mmol) of 2,6-bis(2-aminoethyl)-4-cyclohexylmethoxypyridine (**15h**) gave 0.65 g (58%) of **4h** as a brown solid, mp 80-85 ^{0}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 8.4 Hz, 4 H, *o*-Ts), 7.27 (d, 8.3 Hz, 4 H, *m*-Ts), 6.49 (s, 2 H, Py), 5.58 (s, 2 H, NH), 3.75 (d, 6.5 Hz, 2 H, CH_2Cy), 3.32 (t, 6.3 Hz, 4 H, CH_2N), 2.87 (br, 4 H, CH_2Py), 2.40 (s, 6 H, $ArCH_3$), 1.84-1.0 (m, 11 H, Cy). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 159.2, 143.3, 137.2, 129.8, 127.1, 108.7, 73.7, 42.3, 37.5, 36.5, 29.9, 26.5, 25.8, 21.6. IR (cm^{-1}) 2923 (m), 2851 (m), 1628 (m), 1597 (m), 1570 (w), 1485 (w), 1450 (m). MS *m/z* 586.73 $(MH)^+$ Anal. calcd for $C_{30}H_{39}N_3O_5S_2 \cdot 2.5H_2O$: C, 57.12; H, 7.03; N, 6.66; Found: C, 57.45; H, 6.81; N, 6.59.

4-Propyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4i). Following the general procedure, 0.16 g (0.77 mmol) of 2,6-bis(2-aminoethyl)-4-propylpyridine (**15i**) gave 0.30 g (75%) of **4i** as a glassy brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 8.2 Hz, 4 H, *o*-Ts), 7.27 (d, 8.6 Hz, 4 H, *m*-Ts), 6.78 (s, 2 H, Py), 3.33 (t, 6.0 Hz, 4 H, CH_2N), 2.89 (t, 6.8 Hz, 4 H, CH_2CH_2N), 2.48 (t, 7.2 Hz, 2 H, $CH_2CH_2CH_3$) 2.40 (s, 6 H, $ArCH_3$), 1.60 (m, 7.6 Hz, 2 H, CH_2CH_3), 0.93 (t, 7.4 Hz, 3 H, CH_2CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.5, 154.1, 143.2, 137.1, 129.7, 127.0, 122.3, 45.8, 42.2, 37.2, 23.4, 21.5, 13.8. **4i•HCl:** mp 148-153 ^{0}C. ^{1}H NMR (500 MHz, CD_3OD):

δ 7.68 (d, 8.4 Hz, 4 H, *o*-Ts), 7.62 (s, 2 H, Py), 7.36 (d, 8.4 Hz, 4 H, *m*-Ts), 3.19 (m, 8 H, CH_2CH_2N), 2.84 (t, 7.6 Hz, 2 H, CH_2CH_2N), 2.41 (s, 6 H, $ArCH_3$), 1.78 (m, 2 H, CH_2CH_3), 1.31 (t, 7.4 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 165.7, 154.7, 145.1, 138.8, 131.0, 128.1, 127.4, 42.9, 39.0, 35.1, 24.3, 21.6, 14.1. IR (cm^{-1}) 3065 (br), 2678 (br), 2361 (s), 2341 (s), 1633 (s), 1598 (m), 1437 (s). MS *m/z* 516.80 $(MH)^+$. Anal. calcd for $C_{26}H_{33}N_3O_4S_2 \cdot 1.5H_2O \cdot HCl$: C, 53.92; H, 6.44; N, 7.26; Found: C, 53.72; H, 6.82; N, 7.30.

4-Butyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4j). Following the general procedure, 0.30 g (1.36 mmol) of 2,6-bis(2-aminomethyl)-4-butylpyridine (**15j**) gave 0.68 g (95%) of **4j** as a glassy brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 8.0 Hz, 4 H, *o*-Ts), 7.26 (d, 8.1 Hz, 4 H, *m*-Ts), 6.73 (s, 2 H, Py), 5.79 (t, 6.1 Hz, 2H, NH), 3.30 (q, 6.2 Hz, 4 H, CH_2N), 2.84 (t, 6.5 Hz, 4 H, CH_2CH_2N), 2.47 (t, 8.1 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 2.39 (s, 6 H, $ArCH_3$), 1.52 (m, 2 H, $CH_2CH_2CH_3$), 1.30 (m, 2 H, CH_2CH_3), 0.91 (t, 7.5 Hz, 3 H,) CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 153.7, 143.2, 137.2, 129.7, 127.1, 122.0, 42.3, 36.5, 34.9, 32.4, 22.4, 21.6, 13.9. **4j•HCl:** mp 143-150 ^{0}C (dec). ^{1}H NMR (400 MHz, CD_3OD): δ 7.68 (d, 8.3 Hz, 4 H, *o*-Ts), 7.62 (s, 2 H, Py), 7.36 (d, 8.5 Hz, 4 H, *m*-Ts), 3.17 (t, 6.8 Hz, 4 H, CH_2N), 2.86 (t, 7.6 Hz, 4 H, CH_2CH_2N), 2.42 (m, 8 H, $ArCH_3$, $CH_2CH_2CH_2CH_3$), 1.72 (m, 2 H, $CH_2CH_2CH_3$), 1.43 (m, 2 H,) CH_2CH_3, 0.99 (t, 7.3 Hz, 3 H,) CH_2CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 165.9, 154.7, 145.1, 138.8, 131.0, 128.0, 127.3, 42.9, 36.8, 35.1, 33.1, 23.5, 21.6, 14.2. IR (cm^{-1}) 3064 (s), 2929 (s), 2861 (s), 2648 (br), 2362 (w), 1632 (s), 1598 (m), 1438 (s). MS *m/z* 530.80 $(MH)^+$. Anal. calcd for $C_{27}H_{35}N_3O_4S_2 \cdot 2.25H_2O$: C, 56.87; H, 6.98; N, 7.37; Found: C, 56.96; H, 7.32; N, 7.44.

4-Isobutyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4k). Following the general procedure, 0.27 g (1.22 mmol) of 2,6-bis(2-aminoethyl)-4-isobutylpyridine (**15k**) gave 0.50 g (77%) of **4k** as a dark brown glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 8.4 Hz, 4 H, *o*-

Ts), 7.27 (d, 8.4 Hz, 4 H, *m*-Ts), 6.74 (s, 2 H, Py), 5.68 (br, 2 H, NH), 3.33 (t, 6.4 Hz, 4 H, CH_2N), 2.89 (t, 6.9 Hz, 4 H, CH_2CH_2N), 2.40 (s, 6 H, $ArCH_3$), 2.37 (d, 6.9 Hz, 2 H, CH_2CH), 1.84 (m, 1 H, $CH(CH_3)_2$), 0.88 (d, 7.0 Hz, 6 H, $CH(CH_3)_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 152.5, 143.1, 137.1, 129.6, 127.0, 122.6, 44.5, 42.3, 36.4, 29.4, 22.3, 21.5. **4 k • HCl:** ^1H NMR (500 MHz, CD_3OD): δ 7.68 (d, 8.1 Hz, 4 H, *o*-Ts), 7.61 (s, 2 H, Py), 7.36 (d, 8.2 Hz, 4 H, *m*-Ts), 3.31 (br, 4 H, CH_2N), 3.20 (t, 7.2 Hz, 4 H, CH_2CH_2N), 2.74 (d, 7.5 Hz, 2 H, CH_2CH), 2.41 (s, 6 H, $ArCH_3$), 2.03 (m, 1 H, $CH(CH_3)_2$), 0.99 (d, 6.3 Hz, 6 H, $CH(CH_3)_2$). ^{13}C NMR (125 MHz, CD_3OD) δ 165.0, 154.8, 145.3, 138.9, 131.2, 128.3, 128.2, 46.4, 43.2, 35.4, 31.2, 23.0, 21.8. IR (cm^{-1}) 3065 (s), 2957 (m), 2868 (m), 2678 (m), 1632 (s), 1597 (s), 1516 (w), 1495 (w), 1440 (s). MS *m/z* 530.59 $(MH)^+$. Mp 138-145 ^0C (dec). Anal. calcd for $C_{27}H_{35}N_3O_4S_2 \cdot HCl$: C, 57.28; H, 6.41; N, 7.42; Found: C, 57.55; H, 6.80; N, 7.46.

4-Phenyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4l). Following the general procedure, 0.23 g (0.95 mmol) of 2,6-bis(2-aminomethyl)-4-phenylpyridine (**15l**) gave 0.45 g (87%) of **4l** as a glassy brown solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, 8.6 Hz, 4 H, *o*-Ts), 7.54 (m, 2 H, *o*-Ph), 7.46 (m, 3 H, *m,p*-Ph), 7.26 (d, 8.4 Hz, 4 H, *m*-Ts), 7.12 (s, 2 H, Py), 3.39 (t, 6.4 Hz, 4 H, CH_2Py), 2.96 (t, 6.3 Hz, 4 H, CH_2N), 2.38 (s, 6 H, $ArCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 149.8,143.1, 137.6, 137.0, 129.6, 129.1, 129.0, 126.9, 126.9, 119.6, 42.1, 36.6, 21.4. IR (cm^{-1}) 2919 (w), 1601 (s), 1553 (m), 1495 (w). MS *m/z* 550.75 $(MH)^+$, 572.73 $(M+Na)^+$. Anal. calcd for $C_{29}H_{31}N_3O_4S_2 \cdot 2H_2O$: C, 59.47; H, 6.02; N, 7.17; Found: C, 59.85; H, 6.42; N, 7.17.

4-Methyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (4m). Following the general procedure, 0.40 g (2.23 mmol) of 2,6-bis(2-aminoethyl)-4-methylpyridine (**15m**) gave 0.85 g (78%) of **4m** as an orange, glassy residue. ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, 9.7 Hz, 4 H, *o*-Ts), 7.24 (d, 8.2 Hz, 4 H, *m*-Ts), 6.71 (s, 2 H, Py), 3.29 (t, 6.3 Hz, 4 H, CH_2N), 2.80 (t, 6.3 Hz, 4

H, CH_2Py), 2.39 (s, 6 H, $TsCH_3$), 2.20 (s, 3 H, $PyCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 148.6, 143.2, 137.1, 129.7, 127.1, 122.6, 42.3, 36.5, 21.5, 20.9. IR (neat, cm^{-1}) 2923 (w), 1607 (s), 1564 (w), 1446 (w), 1321 (s), 1152 (s), 1091 (s), 933 (w), 851 (w), 813 (s), 658 (s). MS *m/z* 488.73 $(MH)^+$. Anal. calcd for $C_{24}H_{29}N_3O_4S_2$: C, 59.11; H, 5.99; N, 8.62; Found: C, 58.72; H, 6.21; N, 8.46.

General procedure for palladium-catalyzed conversion of disulfonamides (4, **19**, **or 22) to macrocycles (3**, **20**, **or 23).** Glassware and equipment used in macrocyclization reactions, including magnetic stir bars, spatulas, syringes and needles, were dried overnight at 110 ºC. A mixture of 0.5 mmol of **4**, **19**, or **22**, 2 mmol of 2-methylene-1,3-propanebis(*tert*-butylcarbonate), 0.05 mmol of 1,4-bis(diphenylphosphinobutane) (dppb), 0.025 mmol of tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$), 0.25 mmol of Na_2CO_3 and 30 mL of anhydrous MeCN was stirred and boiled under reflux for 24 h then cooled to room temperature and concentrated by rotary evaporation. A solution of the residue in 50 mL of DCM was washed with sat. aq. $NaHCO_3$ solution (2 x 50 mL) then with 50 mL of sat. aq. NaCl solution, dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight then subjected to column chromatography on alumina, eluting with DCM/EtOAc, chloroform/EtOAc, or hexanes/EtOAc. A solution of the resulting free base in 30 mL of 2 N HCl in methanol/water was stirred at room temperature for 6 h then concentrated to dryness by rotary evaporation. The residue was dried *in vacuo*, triturated with anhydrous diethyl ether, then dried *in vacuo* yielding the HCl salt of **3**, **20**, or **23**.

13-Ethyl-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3b). Following the general macrocyclization procedure, 0.25 g (0.50 mmol) of 4-ethyl-2,6-bis(2-*p*-

toluenesulfonamidoethyl)pyridine (**4b**) gave 0.12 g (40%) of the **3b•HCl** as pale yellow solid, mp 134-140 ^{0}C (dec). ^{1}H NMR (500 MHz, CD_3OD): δ 7.77 (d, 8.1 Hz, 4 H, *o*-Ts), 7.62 (s, 2 H, Py), 7.45 (d, 8.1 Hz, 4 H, *m*-Ts), 4.63 (s, 2 H, C=CH_2), 3.65 (t, 5.4 Hz, 4 H, H3,9), 3.42 (s, 4 H, H5,7), 3.39 (t, 5.7 Hz, 4 H, H2,10), 2.88 (q, 7.2 Hz, 2 H, C$H_2$$CH_3$), 2.46 (s, 6 H, Ar$CH_3$), 1.34 (t, 7.7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 167.8, 156.0, 146.1, 139.9, 135.8, 131.3, 129.0, 128.0, 116.8, 55.5, 52.2, 36.2, 30.2, 21.7, 14.2. IR (cm^{-1}) 1631 (s), 1596 (m), 1445 (m). MS *m/z* 555.79 $(M+2)^+$. Anal. calcd for $C_{29}H_{35}N_3O_4S_2 \cdot HCl \cdot H_2O$: C, 57.27; H, 6.30; N, 6.91; Found: C, 57.01; H, 6.03; N, 6.77.

13-*tert*-Butyl-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3c). Following the general macrocyclization procedure, 0.18 g (0.34 mmol) of 4-*tert*-butyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4c**) gave 0.10 g (48%) of **3c•HCl**, mp 154-160 ˚C (dec). ^{1}H NMR (400 MHz, CD_3OD): ^{1}H NMR (400 MHz, CD_3OD): δ 7.89 (s, 2 H, Py), 7.82 (d, 8.9 Hz, 4 H, *o*-Ts), 7.51 (d, 8.3 Hz, 4 H, *m*-Ts), 4.62 (s, 2 H, C=CH_2), 3.69 (t, 5.7 Hz, 4 H, H3,9), 3.47 (s, 4 H, H5,7), 3.34 (t, 6.0 Hz, 4 H, H2,10), 2.47 (s, 6 H, ArCH_3), 1.47 (s, 9 H, C$(CH_3)_3$). ^{13}C NMR (100 MHz, CD_3OD): δ 174.6, 156.0, 146.1, 140.2, 135.8, 131.4, 129.0, 126.0, 116.6, 55.7, 52.7, 37.8, 36.6, 30.4, 21.7. IR (cm^{-1}) 2964 (m), 1979 (m), 1631 (s), 1596 (m), 1447 (s). MS *m/z* 582.18 $(MH)^+$. Anal. calcd for $C_{31}H_{39}N_3O_4S_2 \cdot HCl$: C, 60.23; H, 6.52; N, 6.80; Found: C, 60.01; H, 6.46; N, 6.51.

13-Methoxy-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3e). Following the general macrocyclization procedure, 0.60 g (1.19 mmol) of 4-methoxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4e**) gave 0.20 g (53%) of **3e·HCl** as a pale yellow solid, mp

170-175 ^{0}C (dec). ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, 8.3 Hz, 4 H, *o*-Ts), 7.46 (d, 8.5 Hz, 4 H, *m*-Ts), 7.28 (s, 2 H, Py), 4.71 (br, 2 H, C=CH_2), 4.13 (s, 3H, OCH_3), 3.62 (t, 5.5 Hz, 4 H, H3,9), 3.46 (s, 4 H, H5,7), 3.31 (br, 4 H, H2,10), 2.46 (s, 6 H, $ArCH_3$). ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 157.9, 146.1, 140.1, 135.8, 131.3, 129.0, 116.7, 113.9, 58.7, 55.6, 52.1, 36.3, 21.7. IR (cm^{-1}) 1624 (m), 1488 (m). MS *m/z* 556.49 $(MH)^+$. Anal. calcd for $C_{28}H_{33}N_3O_5S_2 \cdot HCl \cdot 0.5H_2O$: C, 55.94; H, 5.87; N, 6.99; Found: C, 55.83; H, 6.18; N, 7.22.

13-Ethoxy-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3f). Following the general macrocyclization procedure, 0.15 g (0.29 mmol) of 4-ethoxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4f**) gave 90 mg (52%) of **3f·HCl** as a beige solid, mp 160-165 ˚C (dec). ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (br, 4 H, *o*-Ts), 7.46 (br, 4 H, *m*-Ts), 7.20 (br, 2 H,-Py), 4.74 (br, 2 H, C=CH_2), 4.40 (br, 2H, OCH_2), 3.63 (br, 4 H, H3,9), 3.45 (br, 4 H, H5,7), 3.31 br, 4 H, H2,10), 2.46 (s, 6 H, $ArCH_3$), 1.51 (br, 3 H, $CH_2C\mathit{H_3}$). ^{13}C NMR (100 MHz, CD_3OD): δ 173.3, 157.6, 145.9, 139.7, 135.6, 131.2, 128.9, 116.9, 114.2, 68.4, 55.3, 51.7, 36.2, 21.6, 14.6. IR (cm^{-1}) 1624 (m), 1596 (w), 1488 (m). MS *m/z* 570.49 $(MH)^+$. Anal. calcd for $C_{29}H_{35}N_3O_5S_2 \cdot HCl$: C, 57.46; H, 5.99; N, 6.93; Found: C, 57.08; H, 6.38; N, 7.00.

13-Benzyloxy-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3g). Following the general macrocyclization procedure, 0.19 g (0.33 mmol) of 4-benzyloxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4g**) gave 10 mg (48%) of **3g·HCl** as a beige solid, mp 145-150 ˚C (dec). ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, 8.2 Hz, 4 H, *o*-Ts), 7.53-7.37 (m, 9 H, *m*-Ts, Ph), 7.30 (s, 2 H, Py), 5.44 (s, 2 H, OCH_2), 4.60 (s, 2 H, C=CH_2), 3.59 (t, 5.5 Hz, 4 H, H3,9), 3.45 (s, 4 H, H5,7), 3.30 (m, 4 H, H2,10), 2.45 (s, 6 H, $ArCH_3$). ^{13}C NMR (125 MHz, CD_3OD):

δ 172.9, 158.0, 146.0, 140, 135.7, 131.2, 130.2, 130.0,129.5, 128.9, 116.6, 114.3, 111.6, 73.5, 55.5, 51.9, 36.3, 21.5. IR (cm^{-1}) 2420 (w), 1944 (w), 1624 (m), 1597 (w), 1481 (m). MS *m/z* 633.01 $(MH)^+$. Anal. calcd for $C_{34}H_{37}N_3O_5S_2 \cdot 0.5HCl \cdot H_2O$: C, 61.13; H, 5.96; N, 6.29; Found: C, 61.49; H, 6.22; N, 6.53.

13-Cyclohexylmethoxy-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3h). Following the general macrocyclization procedure, 0.30 g (0.51 mmol) of 4-cyclohexylmethoxy-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4h**) gave 0.19 g (54%) of **3h·HCl** as a beige solid, mp 145-150 ^{0}C (dec). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 8.4 Hz, 4 H, *o*-Ts), 7.33 (d, 8.5 Hz, 4 H, *m*-Ts), 6.91 (s, 2 H, Py), 4.86 (s, 2 H, C=CH_2), 4.21 (br, 2 H, OCH_2), 4.03 (br, 2 H, H3,9), 3.22 (br, 10 H, H5,7, H2,10, CH_2Cy), 2.44 (s, 6 H, $ArCH_3$), 1.83 (m, 6 H, Cy), 1.22 (m, 5 H, Cy). ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.0, 156.6, 144.1, 134.0, 129.8, 127.4, 118.8, 112.6, 75.6, 51.9, 46.0, 37.0, 33.8, 29.4, 26.1, 25.4, 21.4. IR (cm^{-1}) 2924 (m), 2851 (m), 1625 (s), 1596 (m), 1485 (m), 1450 (m). MS *m/z* 638.75 $(MH)^+$. Anal. calcd for $C_{34}H_{43}N_3O_5S_2 \cdot HCl$: C, 60.56; H, 6.58; N, 6.23; Found: C, 60.90; H, 6.91; N, 6.08.

6-Methylene-13-propyl-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3i). Following the general macrocyclization procedure, 0.21 g (0.41 mmol) of 4-propyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4i**) gave 0.10 g (40%) of **3i·HCl** as a beige solid, mp 167-180 ^{0}C (dec). ^{1}H NMR (500MHz, CD_3OD): δ 7.77 (d, 8.7 Hz, 4 H, *o*-Ts), 7.61 (s, 2 H, Py), 7.45 (d, 8.7 Hz, 4 H, *m*-Ts), 4.65 (s, 2 H, C=CH_2), 3.66 (br, 4 H, H3,9), 3.39 (br, 8 H, H5,7, H2,10), 2.82 (t, 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.46 (s, 6 H, $ArCH_3$), 1.76 (sext, 7.4 Hz, 2 H, CH_2CH_3), 1.03 (t, 7.3 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 166.7, 155.9, 146.0, 139.6, 135.8,

131.3, 129.0, 128.6, 117.1, 55.3, 51.9, 38.9, 36.1, 24.4, 21.7, 14.3. IR (cm^{-1}) 2967 (m), 2286 (s), 2012 (s), 1632 (s), 1596 (m), 1493 (w), 1447 (s). MS *m/z* 569.72 $(M+2)^+$. Anal. calcd for $C_{30}H_{37}N_3O_4S_2 \cdot 0.5H_2O \cdot HCl$: C, 58.76; H, 6.41; N, 6.85; Found: C, 58.95; H, 6.67; N, 7.07.

13-Butyl-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3j). Following the general macrocyclization procedure, 0.37 g (0.70 mmol) of 4-butyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4j**) gave 60 mg (23%) of **3j·HCl** as a beige solid, mp 120-125 ^{0}C (dec). ^{1}H NMR (500 MHz, CD_3OD): δ 7.78 (d, 8.5 Hz, 4 H, *o*-Ts), 7.64 (s, 2 H, Py), 7.47 (d, 8.5 Hz, 4 H, *m*-Ts), 4.61 (s, 2 H, C=CH_2), 3.62 (t, 5.8 Hz, 4 H, H3,9), 3.43 (s, 4 H, H5,7), 3.37 (t, 5.9 Hz, 4 H, H2,10), 2.87 (t, 7.4 Hz, 2 H, C$H_2$$CH_2CH_2CH_3$), 2.46 (s, 6 H, $ArCH_3$), 1.73 (m, 2 H, C$H_2$$CH_2CH_3$), 1.45 (m, 2 H, C$H_2$$CH_3$), 1.00 (t, 7.4 Hz, 3 H CH_2CH_3).^{13}C NMR (125 MHz, CD_3OD) δ 166.7, 156.0, 146.1, 139.8, 135.8, 131.3, 129.0, 128.5, 117.0, 55.4, 52.0, 36.8, 36.3, 33.3, 23.66, 21.7, 14.3. IR (cm^{-1}) 2927 (m), 2297 (w), 1981 (w), 1738 (m), 1631 (s), 1596 (m), 1444 (s). MS *m/z* 582.53 $(MH)^+$. Anal. calcd for $C_{31}H_{39}N_3O_4S_2 \cdot 2.0H_2O \cdot HCl$: C, 56.91; H, 6.78; N, 6.42; Found: C, 57.16; H, 7.15; N, 6.55.

13-Isobutyl-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3k). Following the general macrocyclization procedure, 0.32 g (0.60 mmol) of 4-isobutyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4k**) gave 0.18 g (57%) of **3k•HCl**, mp 162-170 ^{0}C (dec). ^{1}H NMR (500 MHz, CD_3OD): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 8.0 Hz, 4 H, *o*-Ts), 7.58 (s, 2 H, Py), 7.45 (d, 8.0 Hz, 4 H, *m*-Ts), 4.71 (s, 2 H, C=CH_2), 3.68 (br, 4 H, H3,9), 3.41 (br, 4 H, H2,10), 3.36 (s, 4 H, H5,7), 2.70 (d, 7.7 Hz, 2 H, CH_2CH), 2.45 (s, 6 H, $ArCH_3$), 2.03 (m,

1 H, C*H*(CH_3)$_2$), 0.98 (t, 7.4 Hz, 6 H, CH(C*H*$_3$)$_2$). ^{13}C NMR (125 MHz, CD_3OD) δ 165.8, 155.7, 146.0, 139.1, 135.8, 131.3, 129.1, 129.0, 117.6, 54.9, 51.0, 46.0, 35.8, 30.9, 22.9, 21.7. IR (cm^{-1}) 2957 (w), 2866 (m), 2231 (m), 1962 (s), 1741 (m), 1630 (s), 1597 (m), 1493 (w), 1454 (s). MS *m/z* 583.72 $(M+2)^+$. Anal. calcd for $C_{31}H_{39}N_3O_4S_2 \cdot HCl$: C, 60.23; H, 6.52; N, 6.80; Found: C, 59.90; H, 6.92; N, 6.49.

6-Methylene-13-phenyl-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3l). Following the general macrocyclization procedure, 0.36 g (0.58 mmol) of 4-phenyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4l**) gave 0.15 g (36%) of **3l·HCl** as a white solid, mp 162-171 ^{0}C (dec). ^{1}H NMR (400 MHz, CD_3OD): δ 8.07 (s, 2 H, Py), 7.79 (d, 8.3 Hz, 4 H, *o*-Ts), 7.95 (m, 2 H, *o*-Ph), 7.65 (m, 3H, *m,p*-Ph), 7.45 (d, 8.3 Hz, 4 H, *m*-Ts), 4.64 (s. 2 H, C=CH_2), 3.69 (br, 4 H, H3,9), 3.47 (br, 8 H, H5,7,2,10), 2.45 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, CD_3OD): δ 160.1, 156.7, 146.1, 140.3, 135.8, 133.4, 131.4, 131.1, 129.4, 129.0, 125.8, 116.6, 55.8, 52.8, 36.5, 35.4, 21.7. IR (cm^{-1}) 2487 (m), 1630 (s), 1597 (m), 1444 (m). MS *m/z* 602.77 $(MH)^+$. Anal. calcd for $C_{33}H_{35}N_3O_4S_2 \cdot HCl$: C, 62.10; H, 5.69; N, 6.58; Found: C, 61.81; H, 5.57; N, 7.02.

13-Methyl-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (3m). Following the general macrocyclization procedure, 0.27 g (0.57 mmol) of 4-methyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4m**) gave 40 mg (32%) of **3m•HCl**, mp 175-185 ˚C (dec). ^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (d, 8.9 Hz, 4 H, *o*-Ts), 7.61 (d, 8.3 Hz, 4 H, *m*-Ts), 7.45 (s, 2 H, Py), 4.85 (s. 2 H, C=CH_2), 3.63 (t, 5.7 Hz, 4 H, H3,9), 3.44 (s, 4 H, H5,7), 3.36 (t, 6.0 Hz, 4 H, H2,10), 2.61 (s, 6 H, TsCH_3), 2.46 (s, 3 H, PyCH_3). ^{13}C NMR (100 MHz, CD_3OD): δ 162.6, 155.6, 145.9, 140.0, 135.7, 131.2, 128.9, 116.5, 55.6, 52.4, 36.2, 22.2, 21.5. IR (cm^{-1}) 2918 (m), 1979

(w), 1633 (s), 1607 (s), 1493 (s), 1448 (s). MS *m/z* 539.13 $(M)^+$. Anal. calcd for $C_{28}H_{33}N_3O_4S_2 \cdot HCl$: C, 58.37; H, 5.95; N, 7.29; S, 11.13; Found: C, 58.18; H, 6.34; N, 7.10; S, 11.52.

6-Methylene-4,8-bis(4-*p*-toluenesulfonyl-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-trien-13-ol (3d). A solution of 0.19 g (0.30 mmol) of 13-benzyloxy-6-methylene-4,8-di(*p*-toluenesulfonyl)-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**3g**) in 10 mL of dry DCM was stirred at -10 ºC as 3 mL of a 1 M solution of BBr_3 in DCM was added. The mixture was allowed to warm to room temperature and stirred for 17 h, 6 mL of water was added and the mixture and was stirred for 30 min. The aq. layer was separated and extracted with DCM (5 x 30 mL). The combined organic solutions were dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight, triturated with anhydrous diethyl ether (5 x 5 mL) and dried *in vacuo* overnight giving 0.11 g (59%) of **3d·HBr** as a brown powder, mp 180-190 ^{0}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, 8.4 Hz, 2 H, *o*-Ts), 7.32 (d, 8.2 Hz, 2 H, *m*-Ts), 7.00 (s, 2 H, Py), 4.85 (s, 2 H, $C=CH_2$), 3.76 (br, 4 H, H3,9), 3.35 (s, 4 H, H5,7), 3.30 (t, 6.0 Hz, 4 H, H2,10), 2.43 (s, 6 H, $ArCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 155.2, 144.4, 135.5, 134.0, 130.0, 127.5, 118.8, 114.4, 52.8, 48.0, 33.9, 21.6. IR (cm^{-1}) 2758 (m), 1628 (s), 1596 (m), 1484 (s), 1447 (m). MS *m/z* 542.49 $(MH)^+$. Anal. calcd for $C_{27}H_{31}N_3O_5S_2 \cdot HBr$: C, 52.09; H, 5.18; N, 6.75; Found: C, 52.15; H, 5.53; N, 6.68.

12-*tert*-Butyl-4,7-bis(*p*-toluenenesulfonyl)-4,7,14-triazabicyclo[8.3.1]tetradeca-1(14),10,12-triene (16). A mixture of 0.20 g (0.38 mmol) of 4-*tert*-butyl-2,6-bis(2-*p*-toluenesulfonamidoethyl)pyridine (**4c**), 0.49 g (1.5 mmol) of Cs_2CO_3 and 25 mL of acetonitrile was stirred and boiled under reflux for 1 h, then a solution of 0.05 mL (0.11 g, 0.58 mmol) of 1,3-dibromoethane in 5 mL of acetonitrile was added by syringe pump over 2 h. The reaction mixture was stirred and boiled under reflux for 21 h, cooled to room temperature and filtered, washing the

flask and residue with 50 mL of acetonitrile. The filtrate was concentrated by rotary evaporation, and the resulting brown oil was dried *in vacuo* overnight then submitted to column chromatography on silica, eluting with DCM, then 9:1 (v/v) DCM/ethyl acetate, giving 50 mg of **16** as a clear oil. A solution of this sample of **16** in 10 mL of 2 N HCl in methanol/water was stirred at room temperature for 5 h then concentrated by rotary evaporation. The residue was dried *in vacuo*, triturated with anhydrous diethyl ether (3 x 10 mL) and dried *in vacuo* overnight, giving 50 mg (23%) of **16•HCl**, mp 140-148 ^{0}C (dec). **16:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, 8.4 Hz, 4 H, *o*-Ts), 7.33 (d, 8.3 Hz, 4 H, *m*-Ts), 6.91 (s, 2 H, Py), 3.55 (br, 12 H, CH_2CH_2), 2.44 (s, 6 H, $ArCH_3$), 1.47 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (500 MHz, $CDCl_3$) δ 161.2, 158.3, 143.4, 135.9, 129.8, 127.4, 118.4, 53.2, 50.0, 39.3, 34.7, 30.7, 21.6. **16•HCl:** IR (cm^{-1}) 2361 (m), 1999 (m), 1630 (s), 1596 (m). MS *m/z* 556.49 $(MH)^+$. Anal. calcd for $C_{29}H_{37}N_3O_4S_2 \cdot HCl$: C, 58.82; H, 6.47; N, 7.10; Found: C, 58.43; H, 6.67; N, 6.89.

4-Ethyl-2,6-bis[2-*p*-(dimethylamino)benzenesulfonamidoethyl]pyridine (19). A solution of 0.26 g (1.4 mmol) of 2,6-bis(2-aminoethyl)-4-ethylpyridine (**15b**), 0.80 mL (0.58 g, 5.7 mmol) of triethylamine and 50 mL of DCM was stirred at room temperature as a solution of 1.26 g (5.74 mmol) of *p*-(dimethylamino)benzenesulfonyl chloride[124,125] in 30 mL of DCM was added dropwise over 30 min. The resulting solution was stirred at room temperature for 24 h, washed with saturated aq. $NaHCO_3$ solution (2 x 50 mL), then with 50 mL of saturated aq. NaCl solution. The organic layer was separated, dried, filtered, and concentrated by rotary evaporation. The residue was subjected to column chromatography on alumina, eluting with DCM, 1:9 (v/v) DCM/EtOAc, EtOAc, and 1:9 (v/v) EtOH/EtOAc, giving 0.66 g (88%) of pure **19** as a glassy light brown solid. As described for **16**, a portion was converted to the HCl salt for elemental analysis and biological testing. **19:** δ 7.72 (d, 8.3 Hz, 4 H, *o*-Ts), 7.27 (d, 8.6 Hz, 4 H, *m*-Ts), 6.76 (s, 2 H, Py), 5.64 (s, 2

H, NH), 3.32 (t, 7.2 Hz, 4 H, CH_2N), 2.86 (t, 7.4 Hz, 4 H, CH_2CH_2N), 2.40 (s, 12 H, NCH_3), 2.54 (q, 7.4 Hz, 2 H, CH_2CH_3), 1.19 (t, 7.6 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 157.9, 154.7, 143.2, 137.1, 129.7, 127.0, 121.4, 42.4, 36.4, 28.1, 21.4, 14.2. **19·HCl:** mp 150-155 ^{0}C (dec). ^{1}H NMR (500 MHz, CD_3OD): δ 7.86 (d, 8.2 Hz, 4 H, *o*-Ts), 7.66 (s, 2 H, Py), 7.48 (d, 8.2 Hz, 4 H, *m*-Ts), 3.35 (br, 4 H, CH_2N), 3.22 (br, 20 H, CH_2CH_2N, NCH_3), 2.89 (q, 7.3 Hz, 2 H, CH_2CH_3), 1.33 (t, 7.6 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 164.88, 152.66, 148.86, 133.08, 128.16, 124.78, 115.86, 41.84, 40.99, 32.84, 28.16, 12.13. IR (cm^{-1}) 2861 (m), 2563 (br), 1981 (m), 1633 (s), 1594 (s), 1516 (s), 1444 (s). MS *m/z* 560.83 $(MH)^+$. Anal. calcd for $C_{27}H_{37}N_5O_4S_2 \cdot 1.5HCl \cdot H_2O$: C, 51.28; H, 6.45; N, 11.07; Found: C, 51.59; H, 6.81; N, 10.82.

4,8-Di[(*p*-dimethylamino)benzenesulfonyl]-13-ethyl-6-methylene-4,8,15-triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (20). By the general macrocyclization procedure, 0.25 g (0.45 mmol) of 4-ethyl-2,6-bis[2-*p*-(dimethylamino)benzenesulfonamidoethyl]pyridine **19** gave 0.15 g (46%) of **20·HCl** as a pale yellow solid, mp 153-158 ^{0}C (dec). ^{1}H NMR (500 MHz, CD_3OD): δ 7.74 (br, 4 H, *o*-Ts), 7.60 (s, 2 H, Py), 7.02 (br, 4 H, *m*-Ts), 4.66 (s, 2 H, $C=CH_2$), 3.66 (br, 4 H, H3,9), 3.38 (br, 8 H, H2,5,7,10), 3.11 (s, 12 H, NCH_3), 2.87 (br, 2 H, CH_2CH_3), 1.33 (t, 7.5 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 167.9, 155.9, 153.8, 140.0, 130.8, 128.0, 126.2, 116.9, 114.3, 55.4, 52.0, 41.6, 36.0, 30.2, 14.3. IR (cm^{-1}) 1632 (s), 1593 (s), 1515 (s), 1444 (s). MS *m/z* 612.50 $(MH)^+$, 613.83 $(M+2)^+$. Anal. calcd for $C_{31}H_{41}N_5O_4S_2 \cdot H_2O \cdot HCl$: C, 55.88; H, 6.66; N, 10.51; Found: C, 56.06; H, 6.95; N, 10.41.

4,5-Bis(*p*-toluenesulfonamidomethyl)acridine (22). A mixture of 1.3 g (3.5 mmol) of 4,5-bis(bromomethyl)acridine[107] (**21**), 2.1 g (7.7 mmol) of Boc-protected *p*-toluenesulfonamide,[108] 2.1 g (15 mmol) of K_2CO_3 and 100 mL of acetonitrile were stirred and

boiled under reflux for 24 h, cooled to room temperature and concentrated by rotary evaporation. A mixture of the residue and 300 mL of water was extracted with DCM (4 x 100 mL). The combined extracts were dried, washed with 400 mL of a saturated aq. NaCl solution, dried, filtered, and concentrated by rotary evaporation. The residue was dried *in vacuo* overnight then stirred with 100 mL of DCM and 100 mL of 2 N HCl in MeOH/water at room temperature for 5 h, then the mixture was concentrated to dryness by rotary evaporation. The residue was dried *in vacuo* for 2 d, triturated with anhydrous diethyl ether (3 x 20 mL) and dried *in vacuo* overnight. The crude HCl salt was converted to the free base by stirring with 200 mL of DCM, 100 mL of saturated aq. NaCl solution, and 100 mL of 2 N aq. NaOH solution at room temperature for 5 h. The aq. layer was separated, extracted with DCM (5 x 100 mL). The combined extracts were dried, filtered, concentrated by rotary evaporation. The residue was dried *in vacuo* overnight and subjected to column chromatography on alumina, eluting with 9:1, 1:1, and 3:7 (v/v) DCM/EtOAc giving 1.1 g (58%) of **22** as a yellowish solid, mp 210-211 ^{0}C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1 H, H9), 7.87 (d, 8.5 Hz, 2 H, H1,8), 7.63 (d, 6.8 Hz, 2 H, H3,6), 7.58 (d, 8.2 Hz, 4 H, *o*-Ts), 7.40 (m, 2 H, H2,7), 7.06 (d, 8.2 Hz, 4 H, *m*-Ts), 6.05 (t, 6.7 Hz, 2 H, NH), 4.80 (d, 6.6 Hz, CH_2N), 2.32 (s, 6 H, ArMe). ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.1, 143.1, 137.3, 137.2, 133.7, 130.7, 129.4, 128.3, 126.9, 126.5, 125.6, 45.6, 21.4. IR (cm^{-1}) 3277 (m), 1739 (m), 1625 (m), 1598 (w), 1531 (m), 1496 (w), 1413 (s). MS *m/z* 546.69 $(MH)^+$. Anal. calcd for $C_{29}H_{27}N_3O_4S_2$: C, 63.83; H, 4.99; N, 7.70; Found: C, 63.51; H, 5.36; N, 7.81.

9-Methylene-7,11,19-7,11-bis(*p*-toluenesulfonyl)-triazatetracyclo[15.3.1.0^{5,20}.0^{13,18}]henicosa-1(21),2,4,13,15,17,19-heptaene (23). By the general macrocyclization procedure, 1.0 g (1.8 mmol) of 4,5-bis(*p*-toluenesulfonamidomethyl)acridine (**22**) gave 0.10 g (50%) of **23·HCl** salt as a bright yellow solid, mp 200-210 ^{0}C (dec). ^{1}H NMR

(400 MHz, $CDCl_3$): δ 8.68 (s, 1 H, H21), 7.92 (d, 8.5 Hz, 2 H, H2,16), 7.84 (d, 6.5 Hz, 2 H, H4,14), 7.59 (d, 8.5 Hz, 4 H, *o*-Ts), 7.45 (t, 7.5 Hz, 2 H, H3,15), 7.15 (d, 8.8 Hz, 4 H, *m*-Ts), 5.42 (br, 2 H, H6,12), 5.26 (s, 2 H, $C=CH_2$), 4.72(br, 2 H, H6,12), 3.90 (s, 4 H, H8,10), 2.37 (s, 6 H, ArMe). ^{13}C NMR (126 MHz, CDCl3) δ 147.3, 143.1, 138.4, 137.6, 136.8, 134.4, 133.9, 129.5, 128.9, 127.4, 126.4, 125.9, 113.7, 50.6, 45.0, 21.6. IR (neat, cm^{-1}) 1739 (m), 1633 (w), 1596 (m), 1534 (m), 1493 (m), 1428 (m). MS *m/z* 598.78 $(MH)^+$. Anal. calcd for $C_{33}H_{31}N_3O_4S_2 \cdot 1.25H_2O$: C, 63.90; H, 5.44; N, 6.77; Found: C, 63.92; H, 5.86; N, 6.97.

AUTHOR INFORMATION

Author Contributions

The major contributor to the research presented in this publication is LAL, followed by EC, KV, and TWB. LAL and TWB contributed equally to the preparation of this manuscript.

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ABBREVIATIONS USED

AIDS, aquired immunodeficiency syndrome; CD4, cluster of differentiation 4; CADA, cyclotriazadisulfonamide; ER, endoplasmic reticulum; HIV, human immunodeficiency virus; SP, signal peptide; SIV, simian immunodeficieny virus.

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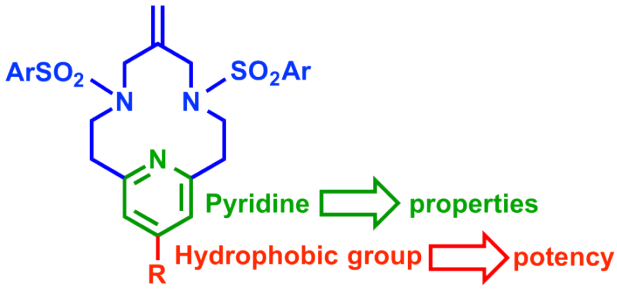
Graphical abstract



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: