Synthesis and Monoamine Transporter Binding Properties of 2,3-Cyclo Analogues of 3β-(4′-Aminophenyl)-2β-tropanemethanol

F. Ivy Carroll,*,† Bruce E. Blough,† Xiaodong Huang,† Zhe Nie,† S. Wayne Mascarella,† Jeffrey Deschamps,‡ and Hernán A. Navarro†

Center for Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, North Carolina 27709-2194, and Laboratory for the Structure of Matter, Naval Research Laboratory, 4555 Overlook Avenue, Washington, D.C. 20375-5341

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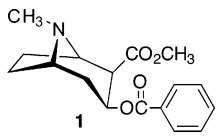
A series of cyclo-3β-(4-aminophenyl)-2β-tropanemethanol analogues (**5a**−**m**) possessing varying linker groups between the 2- and 3-position on the tropane ring were synthesized and evaluated for their monoamine transporter binding properties. The results show that binding to the dopamine and serotonin transporters (DAT and 5-HTT) is highly dependent on the specific linker used. Cyclo-3β-(4-aminophenyl)-2β-tropanemethanol pimelic acid ester/amide (**5b**) had an IC_{50} of 3.8 nM at the DAT. Cyclo-3β-(4-aminophenyl)-2β-tropanemethanol sebacic acid ester/amide (**5e**) had a K_i of 1.9 nM at the 5-HTT and was 68- and 737-fold selective for the 5-HTT relative to the DAT and NET. Small changes to the size as well as the electrostatic and hydrophobic properties of the 2,3-linker in **5b** or **5e** led to much less potent analogues at all three transporters. These results suggest that the high affinity for **5b** and **5e** at the DAT and 5-HTT may be due to their specific conformational properties.

Introduction

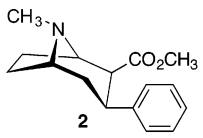
Cocaine (**1**) abuse continues to be a problem of national significance.[1] In addition to its direct effects, cocaine abuse indirectly results in the increase of the spread of HIV-1, hepatitis B and C, and drug-resistant tuberculosis.[2] Cocaine binds to dopamine, serotonin, and norepinephrine transporters (DAT, 5-HTT, and NET) with similar affinities. However, many of cocaine's stimulant and reinforcing effects in animals have been attributed to its action at the DAT.[3−5] A positive correlation between the reinforcing and DAT binding for a variety of dopamine (DA) uptake inhibitors resulted in the dopamine hypothesis of cocaine addiction.[3−5] These research findings resulted in considerable effort being devoted to the characterization of the cocaine-binding site on the DAT. One approach, used by a number of laboratories, is structure−activity relationships (SAR) studies. These studies have been summarized in recent reviews.[6−8]

Studies directed toward the 3-phenyltropane class of DAT uptake inhibitors, where **2** (WIN 35,065-2)[9] served as a lead structure, have provided valuable information about the pharmacophore for the DAT as well as for the 5-HTT and NET. In broad terms, (a) substitution of the 3-phenyl ring controls potency but also can affect transporter selectivity; (b) a substituent in the 2-position is required for high potency, but a wide variety of substituents are allowed; (c) the stereochemistry about the tropane 2- and 3-position can have large effects on both potency and selectivity (for more details see refs 10−13 and references cited therein). Even though much has been learned about the cocaine-binding site on the DAT, much still remains to be done before the site is well characterized. Sometimes the design, synthesis, and evaluation of conformationally constrained analogues can help identify a pharmacophore for a target-binding site. For example, the conformationally constrained 3-phenyltropanes **3** and **4** and their analogues have provided valuable information.[14,15] Compound **3** bridges the 8-amino and 2-position, while **4** bridges the 8-amino and 3-position on the tropane ring. Compound **4** is a potent and selective NET uptake inhibitor.

The present studies were undertaken to explore the effect of reducing the conformational freedom of rotation about the 2- and 3-positions of the tropane ring. Specifically, we designed, synthesized, and determined the monoamine transporter binding properties of **5a**−**m**, where the linker M connecting the 2- and 3-positions was changed both in length and in structural character. The study also revealed the effect of changing the character of the linker group. Surprisingly, only **5b**, which has five methylenes between the ester and amide carbonyls, showed high affinity for the DAT and only **5e**, which possesses eight methylenes, showed high affinity for the 5-HTT.



1



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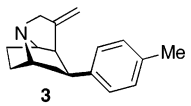

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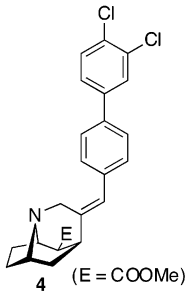
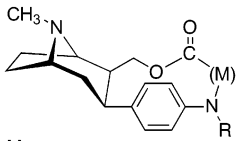
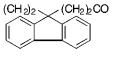


4 (E = COOMe)



5a, M = $(CH_2)_4CO$, R = H
b, M = $(CH_2)_5CO$, R = H
c, M = $(CH_2)_6CO$, R = H
d, M = $(CH_2)_7CO$, R = H
e, M = $(CH_2)_8CO$, R = H
f, M = $(CH_2)_{10}CO$, R = H
g, M = $CH_2C_6H_4CH_2CO$, R = H
h, M = $(CH_2)_2CO(CH_2)_2CO$, R = H
i, M = $(CH_2)_2S(CH_2)_2CO$, R = H
j, M =  , R = H
k, M = $(CH_2)_8CO$, R = CH_3
l, M = $(CH_2)_9$, R = CH_3
m, M = $(CH_2)_{11}$, R = CH_3

* To whom correspondence should be addressed. Telephone: 919-541-6679. Fax: 919-541-8868. E-mail: fic@rti.org.
† Research Triangle Institute.
‡ Naval Research Laboratory.

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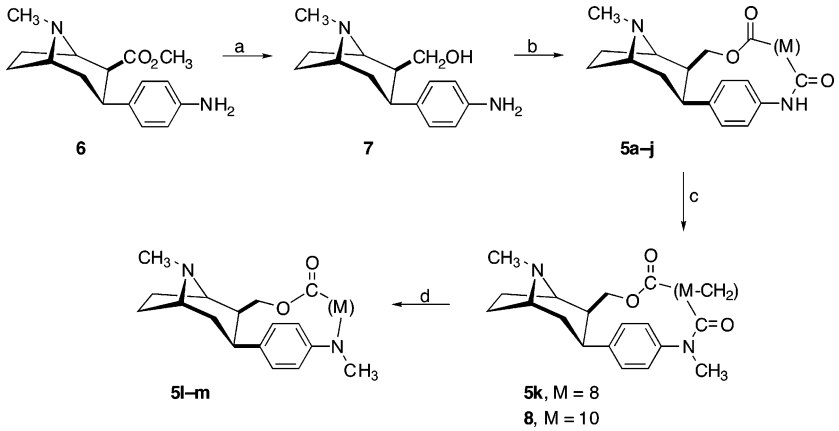
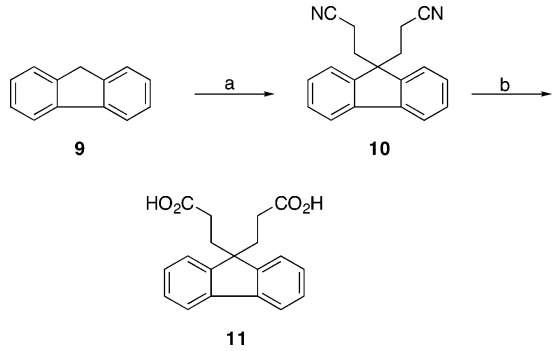
Scheme 1[a]



[a] Reagents: (a) $LiAlH_4$, THF; (b) ClCO(M)COCl, Et_3N, CH_2Cl_2; (c) NaH, DMF, CH_3I; (d) 9-BBN, THF.

Scheme 2[a]



[a] Reagents: (a) CH_2═CHCN, Triton-B, dioxane; (b) 10 N KOH ethylene glycol, reflux.

Chemistry

The 2,3-cyclo-3β-(4-aminophenyl)-2β-tropanemethanol ester/amides (**5a**−**j**) were synthesized from 3β-(4-aminophenyl)-2β-tropane-2β-carboxylic acid methyl ester (**6**)[16] as shown in Scheme 1. Reduction of **6** using lithium aluminum hydride in tetrahydrofuran provided an 85% yield of 3β-(4-aminophenyl)-tropane-2β-methanol (**7**). Slow addition of the appropriate diacid chloride to a dilute solution of **7** in methylene chloride containing excess triethylamine afforded the desired **5a**−**j** in yields varying from 6% to 48% yield. The diacid chlorides of adipic, pimelic, suberaic, azelaic, sebacic, and dodecanedioic acids needed to synthesize **5a**−**f** were all commercially available. 1,2-Phenylenediacetic, 4-ketopimelic, and 3,3-thiodipropionic acid needed to synthesize **5g**−**i** were converted to their diacid chlorides using oxalyl chloride. 3-[9-(2-Carboxyethyl)-9*H*-fluoren-9-yl]propionic acid (**11**) needed to prepare **5i** was synthesized as outlined in Scheme 2. Triton B catalyzed addition of acrylonitrile to fluorene (**9**) afforded the addition product **10**. Hydrolysis of **10** using 10 N potassium hydroxide in refluxing ethylene glycol followed by acid workup gave the desired diacid **11**.

The ester/amides **5k**−**m** were prepared from **5d**−**f** (Scheme 1). Treatment of **5d**−**f** with sodium hydride in dimethylformamide followed by methylation with iodomethane provided **8** and **5k**. Reduction with 9-borabicyclo[3.3.1]nonane (9-BBN) in tetrahydrofuran affected selective reduction of the amide carbonyl to yield **5l**−**m**.

The structure assignments for compounds **5a**−**m** were based on elemental analyses and mass spectral and ^1H and ^{13}C NMR properties. The mass spectrum of each of the compounds showed the expected *m*/*z*. In addition, the signals in the ^1H NMR spectrum were very sharp, suggesting some conformational rigidity. The structure of **5b**, the compound showing the highest affinity at the DAT, was confirmed by single-crystal X-ray analysis (Figure 1). This solid-state structure also provided information about the conformational properties of **5b** in the solid state. It is interesting to note that all of the analogues except **5b** have a negative optical rotation under the conditions used. The reason for this is not apparent.

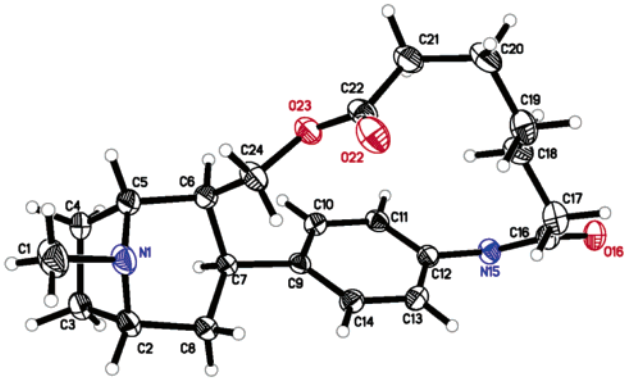


Figure 1. Structure of compound **5b** showing labeling of the non-hydrogen atoms. Displacement ellipsoids are at the 20% probability level.

Molecular Modeling

Molecular modeling studies were performed to determine whether conformational differences exist among **5b**−**e** that may account for the observed receptor-binding selectivity. The minimum-energy conformations of **5c**, **5d**, and **5e** (for comparison to the conformation of the X-ray crystal structure of **5b**) were determined via simulated annealing calculations. For all four compounds, there were no significant differences in the relative conformations of the tropane ring, the phenyl ring attached at C3, or the ester group attached at C2 (Figure 2). However, significant differences in the position and amide C−O bond direction are revealed by the alignment of minimum-energy conformations shown in Figure 2. Also, there is a pronounced steric difference between the conformations of the smallest ring system (**5b**) compared to the larger ring systems of **5c**, **5d**, and **5e**. The centers of the alkyl bridges of compounds **5c**−**e** all occupy a somewhat similar region spaced at ∼10 Å from the tropane nitrogen atom, while the analogous alkyl bridge center of **5b** is at a distance of ∼8 Å from the nitrogen.

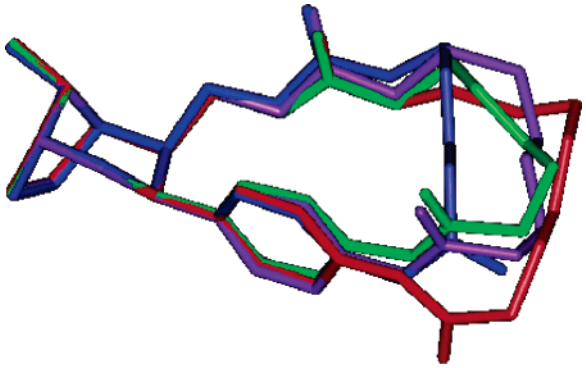


Figure 2. Overlay of the observed X-ray crystal structure of **5b** (blue) and the calculated minimum-energy conformations of **5c** (green), **5d** (purple), and **5e** (red).

Biology

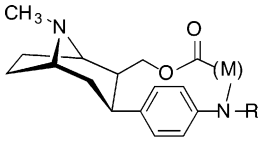
The IC_{50} values for the inhibition of radioligand binding at the DAT, 5-HTT, and NET for **5a**−**m** are listed in Table 1. Since the 5-HTT and NET have only one binding site, K_i values were calculated for inhibition of binding at these two transporters. For comparison, the previously reported values for cocaine and **2** are also listed. The binding affinities at the DAT, 5-HTT, and NET were determined via competitive binding assays using previously reported procedures.[17,18]

Results and Discussion

Previous studies from our laboratory as well as others have shown that the structure of the substituent in the 2-position ester or reverse ester of the 3-phenyltropane has only minor effects on DAT affinity.[6,19] However, the size of the substituent can have large affects on the affinity at the NET and 5-HTT. This information led to the development of a number of high-affinity DAT selective compounds. Previous studies also show that as the size of the 4′-acylamino group increased, the DAT, NET, and 5-HTT affinity decreased.[20] To gain additional information about the cocaine-binding site(s) on the DAT, 5-HTT, and NET, we designed, synthesized, and evaluated the monoamine binding properties of a series of 2,3-cyclo-3β-(4-aminophenyl)-2-substituted tropane analogues **5a**−**m**. The compounds are macrocyclic in nature, where the 2- and 3-positions on the tropane ring are connected through a linker that varies in length, size, electrostatic, and hydrophobic properties. The connection at the 2-position is via an ester function to a 2β-hydroxymethyl group. The connection in the 3-position is via an amide (**5a**−**j**) or amine (**5k**−**m**) group to a 3β-(4-aminophenyl) substituent. These structural variations affected selectivity for the DAT and 5-HTT to a greater extent than at the NET such that affinities at the DAT and 5-HTT differed by approximately 500- and 900-fold, respectively, compared to only a 76-fold spread at the NET. The two most interesting observations were that **5b** had an IC_{50} of 3.8 nM for the DAT and that **5e** possessed a K_i of 1.9 nM for the 5-HTT. Cyclo analogue **5b** also showed K_i values of 20 and 50 nM at the NET and 5-HTT and thus was not selective for the DAT relative to the NET and 5-HTT. In contrast, **5e** had K_i values of 130 and 1400 nM at the DAT and NET and thus was 68- and 737-fold selective for the 5-HTT relative to the DAT and NET. The cyclo analogue **5b** has five methylenes between the ester and amide carbonyl groups. Cyclo analogues **5a** and **5c**, which possess one less and one more methylene group in the linker, show DAT IC_{50} values of 890 and 70 nM. Replacement of one methylene with a carbonyl (**5h**) or sulfur (**5i**) did not lead to analogues with high affinity at the DAT. These analogues also possessed low affinity at the 5-HTT and NET. Analogues **5g** and **5j**, which have an aromatic and fluorenyl group in the linker, show weak affinity at the DAT as well as at the 5-HTT and NET.

The 5-HTT selective cyclo analogue **5e** has an eight-methylene linker between the ester and amide carbonyl group. However, the cyclo analogues **5d** and **5f**, which have one less and two more methylenes in the linker, have K_i values of >2000 and 290 nM at the 5-HTT, respectively. Compound **5l**, which can be considered an analogue of **5e** with one additional methylene and no amide carbonyl, retained similar selectivity for the DAT and NET but with a K_i of 94 nM at the 5-HTT was 50 times less potent than **5e**. The overall compound design goal of reducing the conformational freedom of the 2- and 3-positions appears to have been achieved. The observed solid-state structure of **5b** confirms the calculated prediction that the phenyl ring and ester group will exhibit limited conformational variability in low-energy conformations of compounds from this

Table 1. Monoamine Transporter Binding Properties of 2,3-Cyclo-2β-(4-aminophenyl)-2β-substituted Tropanes



compd	RTI compd	M	R	IC_{50}, nM (K_i, nM)[a] DAT [^{3}H]WIN 35,428	NET [^{3}H]nisoxetine	5-HTT [^{3}H]paroxetine
cocaine[b]				89.1	3300 (1990)	1050 (45)
2[b]				23	920 (550)	1960 (178)
5a	672	$(CH_2)_4CO$	H	890 ± 200	(>2000)	>2000
5b	614	$(CH_2)_5CO$	H	3.8 ± 0.4	40 ± 6 (20 ± 3)	200 ± 20 (50 ± 6)
5c	659	$(CH_2)_6CO$	H	70 ± 10	3040 ± 250 (1520 ± 130)	2090 ± 513 (513 ± 126)
5d	658	$(CH_2)_7CO$	H	410 ± 120	(>2000)	(>2000)
5e	615	$(CH_2)_8CO$	H	130 ± 25	2800 ± 500 (1400 ± 260)	7.8 ± 0.8 (1.9 ± 0.2)
5f	657	$(CH_2)_{10}CO$	H	390 ± 130	2320 ± 230 (1160 ± 110)	1200 ± 49 (290 ± 12)
5g	667	$CH_2C_6H_4CH_2CO$	H	>2000	(>2000)	(>2000)
5h	668	$(CH_2)_2CO(CH_2)_2CO$	H	160 ± 30	1400 ± 66 (710 ± 33)	5010 ± 1030 (1230 ± 250)
5i	669	$(CH_2)_2S(CH_2)_2CO$	H	170 ± 31	990 ± 62 (500 ± 31)	6730 ± 510 (1650 ± 130)
5j	671	$(CH_2)_2C(R,R')(CH_2)_2CO$[c]	H	290 ± 19	980 ± 71 (490 ± 36)	>2000
5k	660	$(CH_2)_8CO$	CH_3	1920 ± 300	(>2000)	(>2000)
5l	661	$(CH_2)_9$	CH_3	150 ± 21	2130 ± 78 (1060 ± 39)	380 ± 15 (94 ± 4)
5m	662	$(CH_2)_{11}$	CH_3	490 ± 140	(>2000)	450 ± 98 (110 ± 24)

[a] The numbers in the parenthesis are K_i values. [b] Taken from ref 18; [c] R,R′ = 

series. Taken together, the conformational analysis and X-ray crystallographic results suggest that differences in the geometry of the methylene linker and amide group are the most likely source for the observed monoamine transporter binding selectivity. The five methylenes of **5b** are about 2 Å closer to the nitrogen of the tropane ring than that of the eight methylenes in **5e**. Thus, the space occupied by these groups could account for their monoamine transporter binding properties. It is also interesting to note that the amide carboxyl in **5e** is pointed in an almost opposite direction for **5b**. Somewhat surprising, the ester carboxyls and the aromatic rings of **5b**−**e** are closely aligned.

In summary, a series of 2,3-cyclo-3β-(4-aminophenyl)-2β-substituted tropane analogues (**5a**−**m**) were designed, synthesized, and evaluated for their monoamine transporter binding properties. The linker connecting the 2- and 3-positions on the tropane ring varied in size and electrostatic and hydrophobic properties. 3β-(4-Aminophenyl)-2β-tropanemethanol pimelic acid ester/amide (**5b**) showed high affinity for the DAT, and 3β-(4-aminophenyl)-2β-tropanemethanol sebacic acid ester/amide (**5e**) showed potent and selective affinity for the 5-HTT. Small changes to the linkers in **5b** and **5e** led to much less potent compounds. The results suggest that the conformational properties of **5b** and **5e** may play an important part in their potent affinity at the DAT and 5-HTT, respectively.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker 300 spectrometer at 300 and 75 MHz, respectively, using tetramethylsilane as an internal standard. Mass spectral data were obtained using a Finnegan LCQ electrospray mass spectrometer in positive ion mode at atmospheric pressure. Optical rotations were measured on an AutoPol III polarimeter. Silica gel 60 (230−400 mesh) was used for column chromatography. All reactions were followed by thin-layer chromatography using Whatman silica gel 60 TLC plates and were visualized by UV or by charring using 5% phosphomolybdic acid in ethanol. All solvents were reagent grade. Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl and distilled prior to use. Methylene chloride and chloroform were distilled from calcium hydride if used as reaction solvents. HCl in dry diethyl ether was purchased from Aldrich Chemical Co. and used while fresh before discoloration.

Cocaine was obtained via the Research Technology Branch, NIDA. [^{3}H]WIN 35,428, [^{3}H]paroxetine, and [^{3}H]nisoxetine were obtained from Perkin-Elmer Inc. (Boston, MA). CMA-80 is a mixture of 80% chloroform, 18% methanol, and 2% concentrated ammonium hydroxide.

Note that with the exception of **5g**, CAS names were used.

3β-(4-Aminophenyl)tropane-2β-methanol (7). To a solution of 2.75 g (10 mmol) of **6**[15] in THF (100 mL) was added dropwise 20 mL (20 mmol) of $LiAlH_4$ in THF at 0 °C. The resulting mixture was stirred at room temperature for 3 h, cooled to 0 °C, and quenched with saturated ammonium chloride (25 mL). The mixture was then extracted with ethyl acetate, followed by 3:1 CH_2Cl_2/THF. The organic extracts were dried (Na_2SO_4) and purified by flash column chromatography (elution 1:1 CMA80/EtOAc), giving 2.1 g (85%) of **7**. ^{1}H NMR ($CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 3.74 (dd, J = 2.2, 10.9 Hz, 1H), 3.57 (s, 1H), 3.47 (dd, J = 2.2, 10.7 Hz, 1H), 3.30 (s, 1H), 2.98 (m, 1H), 2.45 (dt, J = 3.1, 13.1 Hz, 1H), 2.26 (s, 3H), 2.20−2.00 (m, 2H), 1.80−1.55 (m, 6H), 1.06 (s, 1H).

4,5,6,7,8,9,10,11,12,13,15,19a,20,21,22,23,24,24a-Octadecahydro-25-methyl-16,19-etheno-21,24-imino-1*H*-cyclohept[*c*][1,9]-oxaazacycloheneicosine-3,14-dione (5f) Dihydrochloride. To a solution of 100 mg (0.4 mmol) of **7** in dry CH_2Cl_2 (80 mL) and triethylamine (556 μL, 4 mmol) was slowly added a solution of dodecanedioyl chloride (100 μL, 0.4 mmol) in 20 mL of dry CH_2Cl_2 through a dropping funnel over a period of 4 h. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (50 mL), washed consecutively with sodium bicarbonate (20 mL), water (20 mL), and brine (20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by column chromatography (silica gel, 1:2 CMA/ethyl acetate) to afford 85 mg (48%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 4.16 (dd, J = 7.8, 11.9 Hz, 1H), 4.01 (d, J = 11.8 Hz, 1H), 3.21 (m, 2H), 3.00 (m, 1H), 2.40−1.00 (m, 27H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.7, 171.3, 138.4, 136.2, 128.3, 119.0, 66.9, 65.5, 62.0, 46.4, 42.1, 37.1, 34.6, 34.1, 33.9, 29.3, 29.1, 28.0, 27.6, 27.5, 27.3, 26.7, 26.6, 26.0, 25.0, 24.6, 24.5; LCMS (APCI) m/z 441.7 $(M + 1)^+$.

Compound **5f** (20 mg, 0.046 mol) was then dissolved in CH_2Cl_2 (2 mL) and HCl (1 M in diethyl ether) (50 μL, 1.1 equiv) and was added to this solution. The solvent was removed under reduced pressure, and the product was dried under vacuum overnight to afford the hydrochloride salt: mp 163−165 °C; $[\alpha]^{20}_D$ −34.1° (c 0.39, CH_3OH). Anal. ($C_{27}H_{42}Cl_2N_2O_3 \cdot H_2O$) C, H, N.

4,5,6,7,9,13a,14,15,16,17,18,18a-Dodecahydro-19-methyl-10,-13-etheno-15,18-imino-1*H*-cyclohept[*m*][1,8]oxaazacyclopentadecine-3,8-dione (5a) Hydrochloride. A procedure similar to that described for **5f** but using adipoyl chloride was used to prepare **5a** in 8% yield: $[\alpha]^{20}_D$ −156.5° (c 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.23−7.01 (m, 4 H), 4.50 (dd, J = 7.7, 12 Hz, 1H), 3.57 (d, J = 8.4, 12 Hz, 1H), 3.27 (br s, 1H), 3.18 (m, 2H), 2.53 (t, J = 12.9 Hz, 1H), 2.21 (s, 3H), 2.30−1.50 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 176.1, 171.6, 141.4, 135.3, 131.0, 128.1, 127.5, 126.7, 67.1, 65.2, 61.9, 46.8, 41.7, 34.4, 33.1, 32.7, 30.2, 26.1, 24.2, 23.3, 22.7; LCMS (APCI) m/z 357.2 $(M + 1)^+$. The hydrochloride salt had mp 223−225 °C. Anal. ($C_{21}H_{29}ClN_2O_3 \cdot 2.5H_2O$) C, H, N.

5,6,7,8,10,14a,15,16,17,18,19,19a-Dodecahydro-20-methyl-11,-14-etheno-16,19-iminocyclohept[*c*][1,9]oxaazacyclohexadecine-3,9(1*H*,4*H*)-dione (5b) Dihydrochloride. A procedure similar to that described for **5f** but using pimeloyl chloride was used to prepare **5b** in 15% yield. $[\alpha]^{20}_D$ +36.2° (c 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.75 (br s, 1H, NH), 7.07−7.29 (m, 4H, Ar−H), 4.21 (m, 1H), 4.08 (d, J = 12.0 Hz, 1H), 3.16−3.28 (m, 3H), 2.68 (m, 1H), 2.02−2.28 (m and s, 8H), 1.35−1.88 (m, 8H), 1.09−1.16 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 176.0, 172.9, 142.5, 135.4, 131.0, 126.8, 126.7, 126.1, 66.8, 65.5, 62.0, 46.3, 42.1, 34.9, 33.5, 32.5, 31.2, 26.3, 26.1, 24.4, 23.8, 22.1; LCMS (APCI) m/z 371.5 $(M + 1)^+$. The hydrochloride salt had mp 222−224 °C. Anal. ($C_{22}H_{32}Cl_2N_2O_3 \cdot 0.2H_2O$) C, H, N.

4,5,6,7,8,9,11,15a,16,17,18,19,20,20a-Tetradecahydro-21-methyl-12,15-etheno-17,20-imino-1*H*-cyclohept[*c*][1,9]oxaazacycloheptadecine-3,10-dione (5c) Hydrochloride. A procedure similar to that described for **5f** but using suberoyl chloride was followed to prepare **5c** in 17% yield. ^{1}H NMR ($CDCl_3$) δ 7.22 (br s, 2 H), 7.12 (br s, 2 H), 7.06 (s, 1 H), 4.06−3.66 (m, 2 H), 3.21−3.06 (m, 3 H), 2.20 (s, 3 H), 2.29−1.10 (m, 19 H); ^{13}C NMR ($CDCl_3$) δ 175.9, 173.3, 142.2, 135.4, 130.7, 129.0, 126.8, 117.6, 67.2, 65.5, 61.8, 46.7, 42.2, 38.9, 35.0, 34.3, 31.9, 26.5, 25.9, 24.9, 24.5, 24.1, 23.1; LCMS (APCI) m/z 385.3 $(M + 1)^+$. The hydrochloride salt had mp 205−207 °C; $[\alpha]^{20}_D$ −75.5° (c 0.33, CH_3OH). Anal. ($C_{23}H_{33}ClN_2O_3 \cdot 2H_2O$) C, H, N.

5,6,7,8,9,10,12,16a,17,18,19,20,21,21a-Tetradecahydro-22-methyl-13,16-etheno-18,21-iminocyclohept[*c*][1,9]oxaazacyclooctadecine-3,11(1*H*,4*H*)-dione (5d) Hydrochloride. A procedure similar to that described for **5f** but using azeloyl chloride was used to prepare **5d** in 36% yield. ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.14 (m, 3H), 4.24 (dd, J = 9.3, 11.6 Hz, 1H), 3.81 (d, J = 12 Hz, 1H), 3.25 (br s, 1H), 3.10 (m, 2H), 2.18 (s, 3H), 2.30−1.20 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 173.4, 172.4, 138.5, 136.7, 130.5, 125.9, 118.3, 66.9, 65.6, 62.0, 46.6, 42.1, 38.3, 34.7, 33.3, 33.2, 27.5, 26.2, 25.0, 24.4, 23.7, 15.3; LCMS (APCI) m/z 399.4 $(M + 1)^+$. The hydrochloride salt had mp 223−225 °C; $[\alpha]^{20}_D$ −41.8° (c 0.40, CH_3OH). Anal. ($C_{24}H_{35}ClN_2O_3 \cdot 2H_2O$) C, H, N.

4,5,6,7,8,9,10,11,13,17a,18,19,20,21,22,22a-Hexadecahydro-23-methyl-14,17-etheno-19,22-imino-1*H*-cyclohept[*c*][1,9]oxaazacyclononadecine-3,12-dione (5e) Hydrochloride. A procedure similar to that described for **5f** but using sebacoyl chloride was

used to prepare **5e** in 19% yield. $[\alpha]^{20}_D$ −60.8° (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.65 (br s, 1H, NH), 7.51 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 4.38 (m, 1H), 3.75 (d, J = 11.8 Hz, 1H), 3.15−3.25 (m, 3H), 1.57−2.35 (m, 18H), 1.09−1.27 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 173.2, 171.7, 138.1, 136.3, 128.4, 118.4, 67.1, 65.5, 61.9, 46.5, 42.2, 38.2, 34.6, 34.4, 33.8, 28.1, 27.8, 27.5, 26.9, 26.0, 24.9, 24.5, 23.4; LCMS (APCI) *m*/*z* 413.6 $(M + 1)^+$. The hydrochloride salt had mp 212−214 °C. Anal. ($C_{25}H_{37}ClN_2O_3 \cdot 1.5H_2O$) C, H, N.

Ester/Amide of 3-(4-Aminophenyl)-8-methyl-8-azabicylo-[3.2.1]octane-2-methanol and *p*-Phenylenediacetic Acid (5g) Hydrochloride. To a suspension of 200 mg (1 mmol) of 1,2-phenylenediacetic acid in dry benzene (7 mL) was added dry DMF (1 drop), followed by the dropwise addition of 0.54 mL (6 mmol) of oxalyl chloride. The reaction mixture was stirred at room temperature until all solid dissolved. Another drop of DMF was added, and stirring was continued for 2 h. Benzene and the excess oxalyl chloride were removed under reduced pressure. The product was used directly in the next step without further purification.

A procedure similar to that described for **5f** but using the acid chloride above was used to prepare **5g** in 24% yield. ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 7.5 Hz, 1H), 7.23−7.10 (m, 4H), 7.00 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.81(d, J = 8.1 Hz, 1H), 4.46 (dd, J = 8.9, 12.1 Hz, 1H), 3.81 (d, J = 12.2 Hz, 1H), 3.50 (s, 2H), 3.30−2.90 (m, 5H), 2.17 (s, 3H), 2.19−1.50 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 173.7, 170.0, 141.8, 134.9, 133.1, 131.4, 130.7, 130.3, 129.2, 128.5, 128.1, 127.3, 126.8, 126.4, 66.7, 65.7, 62.3, 46.7, 41.7, 36.9, 36.6, 34.7, 32.4, 26.2, 24.1; LCMS (APCI) *m*/*z* 405.5 $(M + 1)^+$. The hydrochloride salt had mp 260 °C (dec); $[\alpha]^{20}_D$ −99.3° (*c* 0.2, CH_3OH). Anal. ($C_{25}H_{29}ClN_2O_3 \cdot 2.5H_2O$) C, H, N.

4,5,7,8,10,14a,15,16,17,18,19,19a-Dodecahydro-20-methyl-11,-14-theno-16,19-iminocyclohept[*c*][1,9]oxaazacyclohexadecine-3,6,9(1*H*)-trione (5h) Hydrochloride. To a suspension of 61 mg (0.35 mmol) of 4-ketopimelic acid in dry benzene (3 mL) was added dry DMF (1 drop), followed by the dropwise addition of 65 μL (0.73 mmol) of oxalyl chloride. The reaction mixture was stirred at room temperature until all solid dissolved. Another drop of DMF was added, and stirring was continued for 2 h. The reaction solution was diluted with 15 mL of dry CH_2Cl_2 and used directly in the next step.

A procedure similar to that described for **5f** but using the acid chloride above was used to prepare **5h** in 6% yield. ^{1}H NMR ($CDCl_3$) δ 7.29−7.09 (m, 3H), 6.99 (d, J = 8.2 Hz, 1H), 4.50 (dd, J = 8.9, 11.8 Hz, 1H), 4.17 (br s, 1H), 3.32−3.10 (m, 3H), 2.90−2.60 (m, 2H), 2.22 (s, 3H), 2.50−1.50 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 174.4, 171.8, 171.3, 142.8, 133.3, 131.1, 130.6, 128.1, 126.7, 66.8, 65.9, 65.4, 61.8, 48.5, 47.0, 42.1, 36.8, 34.7, 33.9, 28.7, 26.5, 24.3; LCMS (ESI) *m*/*z* 385.5 $(M + 1)^+$. The hydrochloride salt had mp 214−216 °C; $[\alpha]^{20}_D$ −34° (*c* 0.2, CH_3OH). Anal. ($C_{22}H_{29}ClN_2O_4 \cdot 2H_2O$) C, H, N.

4,5,7,8,10,14a,15,16,17,18,19,19a-Dodecahydro-20-methyl-11,-14-etheno-16,19-imino-3*H*-cyclohept[*n*][1,5,9]oxathiaazacyclohexadecine-3,9(1*H*)-dione (5i) Hydrochloride. To a suspension of 500 mg (2.8 mmol) of 3,3′-thiodipropionic acid in dry benzene (10 mL) was added dry DMF (1 drop), followed by the dropwise addition of 1.5 mL (17.2 mmol) of oxayl chloride. The reaction mixture was stirred at room temperature until all solid dissolved. Another drop of DMF was added, and stirring was continued for 2 h. Benzene and the excess oxalyl chloride were removed under reduced pressure. The product was used directly in the next step without further purification.

A procedure similar to that described for **5f** but using the acid chloride above was used to prepare **5i** in 44% yield. ^{1}H NMR ($CDCl_3$) δ 7.41−7.13 (m, 4H), 4.55 (br s, 1H), 4.25 (d, J = 11.4 Hz, 1H), 3.55−3.43 (m, 2H), 3.17 (m, 1H), 2.78−2.61 (m, 4H), 2.44 (s, 3H), 2.30−1.60 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 173.4, 170.8, 142.6, 135.3, 131.0, 127.1, 126.7, 66.6, 65.6, 62.2, 46.2, 41.9, 34.9, 34.5, 33.2, 32.7, 29.7, 27.3, 26.2, 25.1, 24.3; LCMS (APCI) *m*/*z* 389.7 $(M + 1)^+$. The hydrochloride salt had mp 205−207 °C; $[\alpha]^{20}_D$ −25.8° (*c* 0.26, CH_3OH). Anal. ($C_{21}H_{29}ClN_2O_3S \cdot 2H_2O$) C, H, N.

3-[9-(2-Cyanoethyl)-9*H*-fluoren-9-yl]propionitrile (10). To a solution of 5.0 g (30.1 mmol) of fluorene in 50 mL of dioxane and 0.5 g of Triton-B was added dropwise 3.3 g (63 mmol) of acrylonitrile. The temperature was kept between 30 and 40 °C with an ice bath. Stirring was continued at room temperature for 3 h. The reaction was quenched with 0.1 N HCl until pH 8−9 was attained. Water (80 mL) was added, and the mixture was vigorously stirred until the oil layer became the granular solid. The solid was filtered, washed with water, and then air-dried. Recrystallization from absolute ethanol afforded 4.5 g (55%) of **10** as colorless needles. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 6.0 Hz, 2H), 7.42 (m, 6H), 2.45 (t, J = 9.0 Hz, 4 H), 1.51 (t, J = 9.0 Hz, 4H).

3-[9-(2-Carboxyethyl)-9*H*-fluoren-9-yl]propionic Acid (11). A solution of 1.0 g (3.67 mmol) of nitrile **10** in 10 mL of 10 N potassium hydroxide and 4 mL of ethylene glycol was heated to reflux, stirred for 30 min, and cooled to room temperature, and 50 mL of water was added. The solution was acidified with concentrated HCl to pH 1. The solid precipitate was filtered, washed with water, and air-dried to give 280 mg (28%) of **11** as white powder. ^{1}H NMR (CD_3OD) δ 7.78 (m, 2H), 7.44 (m, 2H), 7.37 (m, 4H), 2.38 (m, 4H), 1.44 (m, 4H).

20-Methyl-4,5,7,8,10,14a,15,16,17,18,19,19a-dodecahydro-3*H*-spiro[16,19-epimino-11,14-ethenocyclohepta[*c*][1,9]oxazacyclohexadecine-6,9′-fluorene]-3,9(1*H*)-dione (5j). To a suspension of 75 mg (0.24 mmol) of diacid **11** in dry benzene (3 mL) was added dry DMF (1 drop), followed by the dropwise addition of 120 μL (1.44 mmol) of oxalyl chloride. The reaction mixture was stirred at room temperature until all solid dissolved. Benzene and the excess oxalyl chloride were removed under reduced pressure. The 3-[9-(2-chlorocarbonylethyl)-9*H*-fluoren-9-yl]propionyl chloride was used directly in the next step without further purification.

A procedure similar to that described for **5f** but using the acid chloride above was used to prepare **5j** in 18% yield. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 7.4 Hz, 2H), 7.39−7.29 (m, 6H), 7.23 (m, 2H), 7.13 (d, J = 7.1 Hz, 2H), 4.20 (m, 2H), 3.30−3.10 (m, 3H), 2.95 (dt, J = 3.4, 12.0 Hz, 1H), 2.56 (m, 1H), 2.19 (s, 3H), 2.40−1.20 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 175.6, 172.4, 149.4, 148.7, 143.4, 140.0, 139.9, 135.6, 131.3, 128.4, 127.5, 127.3, 127.1, 127.0, 123.7, 123.0, 120.2, 120.1, 67.0, 65.4, 62.0, 51.8, 46.7, 42.1, 35.6, 35.5, 33.9, 29.8, 29.7, 29.4, 29.2, 26.0, 24.4; LCMS (APCI) *m*/*z* 521.7 $(M + 1)^+$. The hydrochloride salt of **5j** had mp 230−232 °C; $[\alpha]^{20}_D$ −39.3° (*c* 0.28, CH_3OH). Anal. ($C_{34}H_{37}ClN_2O_3 \cdot 2H_2O$) C, H, N.

23,29-Dimethyl-10-oxa-23,29-diazatetracyclo[22.2.2.1^{4,7}.0^{2,8}]-nonacosa-1(27),24(28),25-triene-11,22-dione (8). To a solution of 65 mg (0.144 mmol) of **5f** in 1.5 mL of dry DMF was added 8.7 mg (0.22 mmol) of 60% NaH. After the mixture was stirred at room temperature for 15 min, 9 μL of iodomethane was added. The reaction mixture was stirred for another 1 h, diluted with ethyl acetate (100 mL), washed with water (10 mL × 3) and brine (10 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by column chromatography (silica gel, 1:1:1 CMA/ethyl acetate/CH_2Cl_2) to afford 51 mg (77%) of **8** as off-white solid. $[\alpha]^{20}_D$ −20.8° (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 4.46 (t, J = 10.2 Hz, 1H), 3.37 (dd, J = 3.3, 10.5 Hz, 1H), 3.28 (s, 1H), 3.23 (s, 3H), 3.20 (m, 1H), 2.25 (s, 3H), 2.22−1.13 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 174.0, 173.5, 143.6, 137.9, 128.9, 127.9, 64.5, 64.0, 61.7, 45.5, 40.3, 37.2, 34.3, 33.8, 33.0, 30.9, 29.5, 28.2, 28.1, 27.9, 27.5, 27.4, 26.7, 26.0, 25.3, 23.6; LCMS (APCI) *m*/*z* 455.5 $(M + 1)^+$.

4,5,6,7,8,9,10,11,13,17a,18,19,20,21,22,22a-Hexadecahydro-13,23-dimethyl-14,17-etheno-19,22-imino-1*H*-cyclohept[*c*][1,9]-oxaazacyclononadecine-3,12-dione (5k). A procedure similar to that used to prepare **8** was followed to yield 79% of **5k**. ^{1}H NMR ($CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.47 (dd, J = 5.8, 11.2 Hz, 1H), 3.54 (dd, J = 4.2, 11.3 Hz, 1H), 3.23 (s, 3H), 3.10 (m, 1H), 2.24 (s, 3H), 2.14−1.12 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 174.5, 173.9, 143.1, 129.3, 127.6, 65.8, 64.4, 62.6, 47.2, 42.1, 37.6, 34.9, 34.4, 33.9, 28.2, 27.3, 26.9, 26.4, 24.9, 23.9; LCMS (APCI) *m*/*z* 426.9 $(M + 1)^+$. The hydrochloride salt had

mp 75−77 °C; $[\alpha]^{20}_D$ −20.9° (*c* 0.63, CH_3OH). Anal. ($C_{26}H_{39}ClN_2O_3 \cdot 1.75H_2O$) C, H, N.

5,6,7,8,9,10,11,12,13,14,16,20a,21,22,23,24,25,25a-Octadecahydro-16,26-dimethyl-17,20-etheno-22,25-iminocyclohept[*c*][1,9]-oxaazacyclodocosine-3(1*H*,4*H*)-one (5m) Dihydrochloride. To a solution of 65 mg (0.143 mmol) of **8** in 2 mL of dry THF was added 0.86 mL (0.43 mmol) of 0.5 M 9-BBN in THF solution. The reaction mixture was stirred at room temperature for 8 h, diluted with 100 mL of ethyl acetate, washed with saturated sodium bicarbonate solution, water, and brine, and dried over sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by column chromatography (silica gel, 1:1:2 CMA/ethyl acetate/hexanes) to afford 7 mg (11%) of **5m** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.02 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.7 Hz, 2H), 4.29 (dd, J = 6.7, 11.0 Hz, 1H), 3.64 (dd, J = 5.0, 11.0 Hz, 1H), 3.41 (m, 1H), 3.20 (m, 3H), 3.00 (m, 1H), 2.86 (s, 3H), 2.22 (s, 3H), 2.09−1.18 (m, 27H); LCMS (APCI) m/z 441.5 $(M + 1)^+$. The hydrochloride salt had mp 115−117 °C; $[\alpha]^{20}_D$ −28.0° (*c* 0.20, $CHCl_3$). Anal. ($C_{28}H_{46}Cl_2N_2O_2 \cdot 2H_2O$) C, H, N.

5,6,7,8,9,10,11,12,14,18a,19,20,21,22,23,23a-Hexadecahydro-14,24-dimethyl-15,18-etheno-5620,23-iminocyclohept[*c*][1,9]oxa-azacycloeicosine-3(1*H*,4*H*)-one (5l) Dihydrochloride. A procedure similar to the preparation of **5m** was followed to prepare **5l**. The eluent for column chromatography was ethyl 3:1 ether/hexanes with 1% of NH_4OH. The yield of product was 4% as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.02 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 4.14 (d, J = 11.8 Hz, 1H), 3.96 (dd, J = 6.7, 11.6 Hz, 1H), 3.38 (m, 1H), 3.24 (m, 3H), 3.00 (m, 1H), 2.89 (s, 3H), 2.20 (s, 3H), 2.11−1.15 (m, 23H); LCMS (APCI) m/z 413.2 $(M + 1)^+$. The hydrochloride salt had mp 149−151 °C; $[\alpha]^{20}_D$ −20.0° (*c* 0.20, $CHCl_3$). Anal. ($C_{26}H_{42}Cl_2N_2O_2 \cdot 2.5H_2O$) C, H, N.

Single-Crystal X-ray Diffraction Analysis of 5b. Crystallographic data are as follows: $C_{22}H_{30}N_2O_3$, $0.5(C_{0.8}H_{3.2}O_{0.8})$, FW = 383.23, monoclinic space group *C*2, a = 23.910(8) Å, b = 8.620(3) Å, c = 10.820(4) Å, and β = 112.925(7)°, V = 2054.0(12) Å^3, Z = 4, density (calcd) = 1.239 Mg/m^3, λ (Mo Kα) = 0.710 73 Å, μ = 0.083 mm^{-1}, $F(000)$ = 828.7, T = 93 K. A clear colorless 0.85 mm × 0.66 mm × 0.50 mm crystal was used for data collection with a Bruker SMART 1000 CCD detector on a four-circle goniometer using SMART (version 1a). Lattice parameters were determined using SAINT (version 2b) from 1627 reflections within 2.54° < θ < 28.24°. Data were 94.7% complete to θ = 28.24°. Reflections (8871) were collected using a combination of ϕ and $2\theta/\omega$ scans. There were 2570 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL (version 3a) and refined with the aid of the SHELX system of programs. The full-matrix least-squares refinement on F_2 used three restraints and varied 266 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms on carbon atoms were included using a riding model (coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96−0.93 Å, H angles idealized, U_{iso}(H) values were set to (1.2−1.5)U_{eq}(C)). Final residuals were R1 = 0.0541 for the 2280 observed data with $F_o > 4\sigma(F_o)$ and 0.0623 for all data. Final difference Fourier excursions were 0.394 and −0.258 e Å^{-3}. The asymmetric unit contains one molecule of **5b**, plus a disordered methanol molecule at partial occupancy. Tables of coordinates, bond distances, bond angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge, CB2 and 1EW, England.

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Supporting Information Available: Crystal data, structural refinement analysis, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters of **5b** and elemental analysis data for compounds **5a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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