Bioorganic & Medicinal Chemistry Letters 20 (2010) 2186–2190

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of a novel tricyclic 1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline ring system and CXCR4 antagonists with potent activity against HIV-1

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ARTICLE INFO

Article history:
Received 8 January 2010
Revised 4 February 2010
Accepted 8 February 2010
Available online 12 February 2010

Keywords:
CXCR4
HIV
AIDS
Inhibitor
Antiviral
Viral
Entry
Chemokine

ABSTRACT

Stereorandom and diastereoselective syntheses of a novel 1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline ring system are described. Derivatives of all four diastereomers were prepared and isolated in >98% ee. The pure enantiomers were compared in order to determine the preferred absolute and relative configuration required for optimal anti-HIV activity. Anti-HIV potency and pharmacokinetic properties of the newly synthesized tricyclic octahydrophenanthroline inhibitors are presented and comparisons are made to previously reported bicyclic (8*S*)-*N*-methyl-5,6,7,8-tetrahydro-8-quinolinamine analogs.

CXCR4 is a G-protein coupled seven-transmembrane spanning receptor that has the rare characteristic of having only one known natural ligand, stromal cell-derived factor (SDF-1).[1] SDF-1 is a highly basic protein with about 20% of its 68 amino acids containing basic side-chains. CXCR4 is somewhat unusual among chemokine receptors in that it is strongly negatively charged. Recently there has been significant interest in CXCR4 inhibitors for the treatment of cancer, stem cell mobilization,[2] and HIV inhibition. CXCR4 is known to be a co-receptor for a number of specific strains of HIV-1,[3] and SDF-1 has been shown to inhibit infection of CD4+ cells by X4 HIV strains.[4,5] Furthermore, several classes of highly basic small molecule CXCR4 inhibitors have been reported in the literature to have anti-HIV activity.[6–10] HIV/AIDS continues to be a threat to public health. Potential treatments with new modes of action should be especially beneficial to clinicians struggling to treat patients with resistant HIV strains.

Our group previously reported examples of benzimidazole and imidazopyridine CXCR4 inhibitors, **1** and **2a**, respectively (Fig. 1).[9,10] In each series the benzimidazole/imidazopyridine core was substituted with a tethered basic amine side-chain, such as the 3-dimethylaminopropyl group shown for benzimidazole **1** or the *N*-methylpiperazine shown for imidazopyridine **2a**. Both the benzimidazole/imidazopyridine cores were additionally linked to the 8-position of a 5,6,7,8-tetrahydroquinoline ring system through a central unconstrained tertiary methyl amino moiety. As an evolution of this earlier work, we sought to conformationally restrain rotation about the 8-amino group of the bicyclic tetrahydroquinoline core by incorporating a novel tricyclic octahydrophenanthroline ring system.

The octahydrophenanthroline ring system encompasses four distinct stereoisomers and represents a previously unreported

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doi:10.1016/j.bmcl.2010.02.030

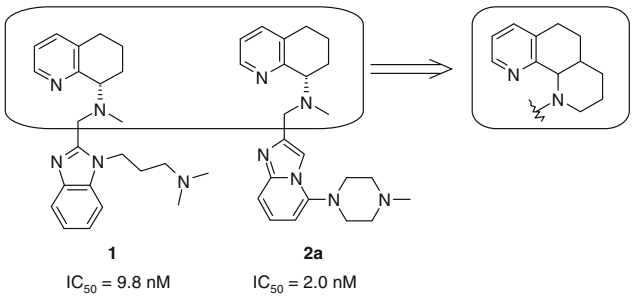
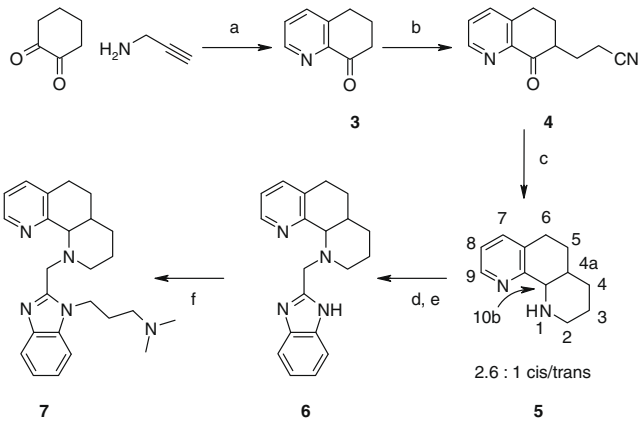


Figure 1.

scaffold. Our initial strategy was to target the ring system by achiral synthetic methods in order to obtain all four possible stereoisomers (Scheme 1). Subsequent resolution via chiral chromatography would then allow us to test single compounds.

The 6,7-dihydro-8(5*H*)-quinolinone **3** was synthesized by condensation of propargylamine with 1,2-cyclohexadione using conditions developed by Abbiati et al.[11] Although yields were generally poor, commercially available starting materials for this scalable one-step method were fairly inexpensive and isolation of the resulting ketone **3** was straight-forward.[12] Ketone **3** is now commercially available and several multi-step methods for its preparation have been reported.[13] The enolate of ketone **3** was formed by deprotonation with LDA and subsequent treatment of the anion with acrylonitrile gave nitrile **4**. Reduction of nitrile **4** with Raney nickel at 70 °C under 50–60 psi of hydrogen led to spontaneous cyclization via intramolecular reductive amination to afford the desired 1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline **5**.Octahydrophenanthroline **5** was carried forward as a mixture of diastereomers (2.6:1 cis/trans) and was condensed with *N*-Boc-2-chloromethyl benzimidazole.[14] At this stage, achiral chromatography gave two pairs of enantiomers with cis and trans relative configurations about the octahydrophenanthroline core. The unresolved pairs of enantiomers were carried forward separately. Removal of the *t*-butyl carbamate protecting group gave benzimidazole **6**, and the amine sidechain was incorporated by alkylation to give final products **7**. Resolved compounds **7a**–**d** were obtained via chiral reverse phase HPLC of the corresponding racemic mixtures.[15] Absolute stereochemistry was assigned by Ab Initio Vibrational Circular Dichroism (VCD) Spectroscopy.[16,17]



Scheme 1. Reagents and conditions: (a) Na_2AuCl_4 dihydrate, EtOH, 75 °C, 24 h, (20–25%); (b) *i*-Pr_2NH, *n*-BuLi, THF, −78 °C, 1.5 h, then acrylonitrile, −78 °C to 40 °C, 16 h, (72%); (c) Raney nickel, EtOH, H_2 (60 psi), 70 °C, 16 h, (43%); (d) *N*-Boc-2-chloromethyl benzimidazole, K_2CO_3, KI, CH_3CN, rt, 16 h; (e) TFA, CH_2Cl_2, 2 h, RT; (80–90%); (f) $Cl(CH_2)_3NMe_2$, K_2CO_3, KI, DMF, 80 °C, 16 h, (52–63%).

Testing for anti-HIV activity revealed that cis analog **7a** was the most potent of the isomers (Fig. 2). Compound **7a** had an IC_{50} of 35 nM against HIV-1 and was essentially equipotent to the analogous bicyclic tetrahydroquinoline derivative **1**. Activity for the cis isomer **7b** fell off more than 15-fold. Both trans diastereomers **7c** and **7d** were also less potent. An obvious preference for the *S* configuration at the 10b position was observed for both the cis and trans diastereomers, **7a** and **7c**, respectively, which was consistent with the preference for *S*-stereochemistry of tetrahydroquinoline **1**.

Having determined that the (4a*R*,10b*S*)-configuration of structure **7a** was the preferred replacement for the (8*S*)-*N*-methyl-5,6,7,8-tetrahydro-8-quinolinamine moiety of **1**, we developed a route to the favored cis diastereomer (Scheme 2). We also chose to incorporate the preferred imidazopyridine moiety found in compound **2a**. A pyrrolidine enamine was formed by reacting ketone **3** with pyrrolidine under Dean–Stark conditions and the resulting enamine reacted with ethyl acrylate to give keto ester **8**. Reductive amination with (*S*)-1-(4-methyloxyphenyl)ethylamine afforded the desired cis diastereomer **9** in good yield. Diastereomeric and enantiomeric control of reductive aminations between racemic α-substituted cyclohexanones and chiral α-methylbenzylamines are precedented.[18] The ester **9** was reduced with lithium aluminum hydride to give alcohol **10**. Treatment of **10** with methanesulfonyl chloride led to spontaneous cyclization and yielded the desired protected tricyclic octahydrophenanthroline ring system **11**. Deprotection with trifluoroacetic acid gave amine **12**, which was alkylated with 2-(chloromethyl)-5-fluoroimidazo[1,2-a]pyridine[19] to give the penultimate 5-fluoroimidazo[1,2-a]pyridine intermediate **13**. Final targets, such as **14a**[20], were realized by treating **13** with preferred amines.

The cis antipode **14b** (Fig. 3) was obtained by following Scheme 2, but using (*R*)-1-(4-methyloxyphenyl)ethylamine for the reductive amination in step b. The single trans diastereomer **14c** was ob-

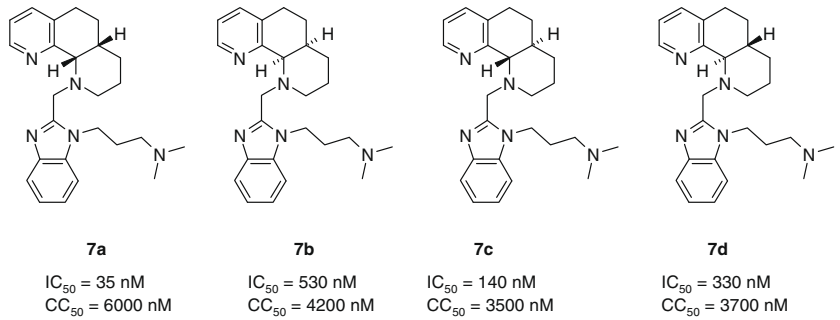
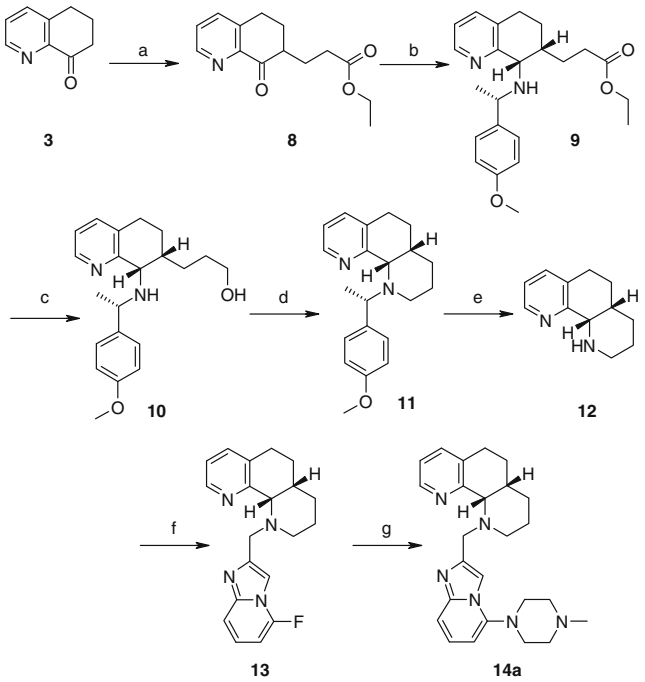


Figure 2. Comparison of anti-HIV activity between diastereomers of the benzimidazole series. HOS cells (expressing hCXCR4/hCCR5/hCD4/pHIV-LTR-luciferase), HIV-1, T-tropic CXCR4 strain (IIIB). Compounds were tested for their ability to block infection of the HOS cell line. IC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed. CC_{50} is the concentration at which 50% cytotoxicity is observed in the HOS cell line.



Scheme 2. Reagents and conditions: (a) (i) pyrrolidine, *p*-TosOH, benzene, reflux, Dean–Stark, 4 h; (ii) ethyl acrylate, ethanol, reflux, 6 h, then H_2O, 78 °C, 4 h (58%); (b) (i) (1*S*)-1-[4-(methyloxy)phenyl]ethanamine, *p*-TosOH, toluene, Dean–Stark, 4 h, (ii) $NaBH(OAc)_3$, 1,2-DCE, 16 h (61%); (c) $LiAlH_4$, THF, 0 °C, 1 h (64%); (d) MsCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 16 h, (98%); (e) TFA, CH_2Cl_2, 2 h; (98%); (f) 2-(chloromethyl)-5-fluoroimidazo[1,2-a]pyridine, K_2CO_3, KI, CH_3CN, RT, 16 h (56%); (g) 1-methylpiperazine, DMSO, 60 °C, 16 h, (63%).

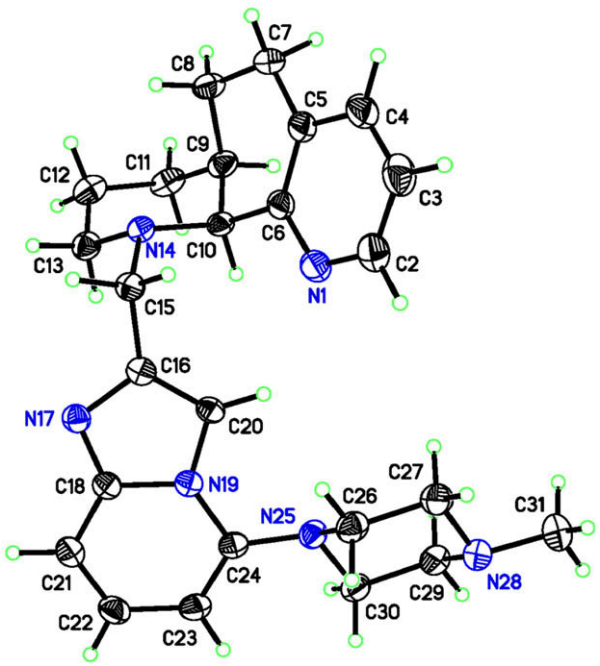
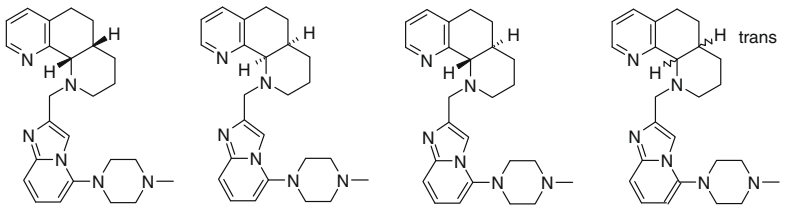


Figure 4. ORTEP diagram of 1-{[5-(4-methyl-1-piperazinyl)imidazo[1,2-a]pyridine-2-yl]methyl}1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline **14a** showing atomic numbering scheme and 50% anisotropic displacement ellipsoids for non-hydrogen atoms. Hydrogen atoms are displayed with an arbitrarily small radius. Cambridge Crystallographic Data Centre deposition number CCDC 760486.[21]

tained by carrying a minor trans by-product to the final stage of Scheme 2, and then isolating by silica gel chromatography. The (+/-) trans mixture **14d** was obtained by following the achiral route, but replacing the benzimidazole core in Scheme 1 with the imidazopyridine core. Absolute configuration for **14a** was tentatively assigned by Ab Initio Vibrational Circular Dichroism (VCD) Spectroscopy and then confirmed by X-ray crystallography (Fig. 4).[16,17,21]

The SAR trend for the imidazopyridine diastereomers **14a–d** (Fig. 3) was consistent with that observed for benzimidazole diastereomers **7a–d**. The (4a*R*,10b*S*)-configuration was preferred over the other isomers in both series. Imidazopyridine analog **14a** was 50-fold more potent than antipode **14b** and roughly 25-fold more potent than the single trans diastereomer **14c**. The racemic trans mixture **14d** was equipotent to **14c**, indicating that the antipode to **14c** was less potent or equipotent. As with the benzimidazole core, the imidazopyridine example **14a** was equipotent with the previously reported bicyclic derivative **2a**.

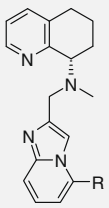
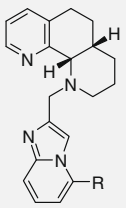
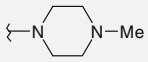
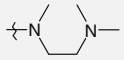
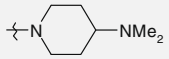
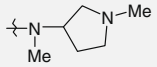
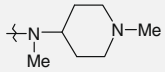
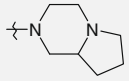
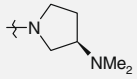
A number of additional compounds were synthesized in order to further compare tricyclic octahydrophenanthroline derivatives, **14a** and **14e–k**, to previously reported bicyclic tetrahydroquinoline analogs **2a–h**[9] (Table 1). The subset of comparable analogs presented in Table 1 demonstrates that SAR tracked fairly well between the two series, regardless of overall potency. Potent analogs such as **2a** and **14a** had very similar anti-HIV activity, as did the much less potent morpholine derivatives **2b** and **14e**. The R-group entries in Table 1 all impart less than a fourfold potency difference between comparable analogs of the two series. No clear general preference for either core was observed and this trend in SAR generally held true throughout a much broader series of similar analogs that are not presented herein. Overall, the anti-HIV activity of the tricyclic analogs (**14a**, **14e–k**) compared with the tetrahydroquinolines (**2a–h**), establishing the tricyclic core as a



IC_{50} = 2.0 nM, CC_{50} = 9600 nM
IC_{50} = 100 nM, CC_{50} = 8500 nM
IC_{50} = 50 nM, CC_{50} = 9900 nM
IC_{50} = 32 nM, CC_{50} = 9600 nM

Figure 3. Anti-HIV activity of 1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline diastereomers. HOS cells (expressing hCXCR4/hCCR5/hCD4/pHIV-LTR-luciferase), HIV-1, T-tropic CXCR4 strain (IIIB). Compounds were tested for their ability to block infection of the HOS cell line. IC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed. CC_{50} is the concentration at which 50% cytotoxicity is observed in the HOS cell line.

Table 1
Anti-HIV activity of imidazopyridine-1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline derivatives compared to imidazopyridine-tetrahydro-8-quinolinamine derivatives

R		IC_{50}[b] (nM)		IC_{50}[b] (nM)	CC_{50}[c] (nM)
	**2a**[a]	2.0	**14a**	2.0	9500
	**2b**[a]	690	**14e**	1200	6600
	**2c**[a]	17	**14f**	5.0	1450
	**2d**[a]	4.0	**14g**	15	3850
	**2e**[a]	30	**14h**	9.0	1570
	**2f**[a]	49	**14i**	38	1300
	**2g**[a]	2.0	**14j**	2.0	2980
	**2h**[a]	8.0	**14k**	21	1600

[a] Compounds with data were reported previously.[10]
[b] HOS cells (expressing hCXCR4/hCCR5/hCD4/pHIV-LTR-luciferase), HIV-1, T-tropic CXCR4 strain (IIIB). Compounds were tested for their ability to block infection of the HOS cell line. IC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed.
[c] CC_{50} is the concentration at which 50% cytotoxicity is observed in the HOS cell line. CC_{50} data for compounds **2a**–**h** were reported previously.[10]

Table 2
Pharmacokinetic data for imidazopyridien-1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline derivative compared to imidazopyridine-tetrahydro-8-quinolinamine derivative

Compound Species	**2a** Rat	**14a** Rat	**2a** Dog	**14a** Dog
Cl (mL/min/kg)	14	5.4	18	5.1
V_{dss} (L/kg)	5.5	4.5	7.6	4.7
$T_{1/2}$ (h)	4.9	12	8.5	11
F (%, solution)	11	16	13	30
DNAUC (mg h/mL/mg/kg)	100	390	160	850

Clearance (Cl) and volume of distribution (V_{dss}) were calculated following a 1 mg/kg iv dose. Half life ($T_{1/2}$), oral bioavailability (*F*), and dose-normalized area under the curve (DNAUC) (mg h/mL/mg/kg) were calculated following solution doses of 3 mg/kg.

very promising conformationally restricted alternative scaffold to the bicyclic tetrahydroquinoline.

Based on promising anti-HIV activity, the octahydrophenanthroline derivative **14a** was chosen for further studies (Table 2). Compound **14a** showed a good overall pharmacokinetic profile in rat and dog, and showed a general improvement over the tetrahydroquinoline analog **2a**. Clearance of **14a** was lower in both rat and dog with moderate improvements in half-life over **2a**. Oral bioavailability of **14a** was also improved compared to **2a** in both species, as was overall oral exposure as indicated by the dose-normalized AUCs (DNAUCs), which were nearly fourfold higher for **14a** in the rat and greater than fivefold higher than **2a** in the dog.

In conclusion, the tricyclic (4a*R*,10b*S*)-1,2,3,4,4a,5,6,10b-octahydro-1,10-phenanthroline scaffold was found to be a good alternative to the bicyclic (8*S*)-*N*-methyl-5,6,7,8-tetrahydro-8-quinolinamine core. Given the similar SAR profile between these two cores, we speculate that the tetrahydroquinoline scaffold efficiently adopts a conformation similar to that of the more restricted octahydro phenanthroline system. So although significant gains in potency were not realized by restricting conformational rotation, metabolic stability seems to have been positively affected. Further studies showed that **14a** displayed a suitable cytochrome P450 profile and screening against a panel of enzymes and receptors (Panlabs) revealed little risk of unwanted enzyme and receptor inhibition. Because of the promising anti-HIV potency and oral bioavailability, compound **14a** was progressed into toxicology studies and served as a novel core for synthesis of additional analogs.

Acknowledgments

The authors wish to thank David McCoy, Richard Hazen and Wendell Lawrence for providing HIV-1 data, as well as Amanda G. Culp, Rachel M. Robeson, and Manon Villeneuve for chiral resolutions. We additionally wish to acknowledge Jeanette A. Krause (University of Cincininati) for crystallographic determination of **14a**, as well as funding for the SMART6000 diffractometer through NSF-MRI Grant CHE-0215950 (University of Cincinnati).

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15. Separation was performed on ChiralPak ADH column (250 × 10 mm id, 5 μm; ChiralTechnologies, West Chester, PA) under supercritical conditions maintained at 40 °C, 140 bar, with methanol, containing 0.5% DEA (diethylamine), modified CO_2 (30% MeOH, 70% CO_2) delivered at a combined flow rate of 10 mL/min on a Thar Discovery Series SFC system (Thar Instruments, Inc.; Pittsburgh, PA). The geoisomers were monitored using a Gilson selectable wavelength 151 UV–vis detector at 230 nm.
16. Absolute configurations by ab initio vibrational circular dichroism (VCD) were assigned as follows. Experimental VCD spectra were acquired for samples in D-chloroform (approx. 10 mg/125 μL) using a BioTools ChiralIR FT-VCD spectrometer operating at 4 cm^{-1} resolution between 2000 and 800 cm^{-1}. Model VCD and IR spectra were simulated at the quantum mechanical level using the GAUSSIAN 03 software suite. Stereochemical assignments were made by comparing baseline-corrected experimental VCD spectra with VCD spectra calculated for corresponding models.
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19. 2,6-difluoropyridine (31.5 mL, 0.348 mol) was diluted with 30% ammonium hydroxide (200 mL) in a steel bomb and heated to 110 °C overnight. The bomb was cooled to room temperature over 2 h then further cooled to 0 °C for 2 h. The resulting solid was filtered and rinsed with water to obtain 26.39 g as a white solid. The filtrate was extracted with dichloromethane, dried over sodium sulfate and concentrated to afford an additional 9.3 g (92% overall yield) of 6-fluoro-2-pyridinamine. A portion of the solid (5 g, 0.044 mol) was dissolved in 1,2-dichloroethane (20 mL) and 1,3-dichloro-2-propanone (34.2 mL, 4.34 mol) was added in two portions. The reaction was stirred at 40 °C over 2 days. The resulting solid was collected by filtration, dissolved in absolute ethanol (100 mL), and refluxed at 90 °C overnight. The solvent was evaporated and dichloromethane added to the residue followed by saturated aqueous sodium bicarbonate. The mixture was added to a separatory funnel and the phases separated. The aqueous layer was extracted two additional times with dichloromethane and once with a 3:1 chloroform:isopropanol mixture. The combined organic layers were dried over sodium sulfate and concentrated to give 3.61 g (62%) of 2-(chloromethyl)-5-fluoroimidazo[1,2-a]pyridine as a black oil, which solidified upon standing. ^{1}H NMR (400 MHz, DMSO-d_6) d 5.02 (s, 2H), 7.29 (d, 1H), 7.74 (d, 1H), 7.88 (m, 1H), 8.41 (s, 1H); MS *m*/*z* 185 (M+1).
20. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.7 (m, 5H), 2.1 (m, 1H), 2.4 (m, 5H), 2.7 (m, 5H), 3.0 (m, 1H), 3.1 (m, 5H), 3.6 (m, 1H), 3.6 (d, *J* = 14.6 Hz, 1H), 4.0 (d, *J* = 14.5 Hz, 1H), 6.4 (d, *J* = 7.3 Hz, 1H), 7.2 (m, 3H), 7.5 (d, *J* = 9.1 Hz, 1H), 7.6 (s, 1H), 8.3 (d, *J* = 6.4 Hz, 1H); MS *m*/*z* 417 (M+1).
21. The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 760486.