Published in final edited form as:
J Med Chem. 2008 October 9; 51(19): 6095–6109. doi:10.1021/jm800532x.

Structure–Activity Relationships for a Novel Series of Dopamine D2-like Receptor Ligands Based on N-Substituted 3-Aryl-8-azabicyclo[3.2.1]octan-3-ol

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Abstract

Discovering dopamine D2-like receptor subtype-selective ligands has been a focus of significant investigation. The D2R-selective antagonist 3-[4-(4-chlorophenyl)-4-hydroxypiperidinyl]methylindole (**1**, L741,626; K_i(D2R/D3R) = 11.2:163 nM) has previously provided a lead template for chemical modification. Herein, analogues have been synthesized where the piperidine was replaced by a tropane ring that reversed the selectivity seen in the parent compound, in human $hD2_LR$- or hD3R-transfected HEK 293 cells (**31**, K_i(D2R/D3R) = 33.4: 15.5 nM). Further exploration of both N-substituted and aryl ring-substituted analogues resulted in the discovery of several high affinity D2R/D3R ligands with 3-benzofurylmethyl-substituents (e.g., **45**, K_i(D2R/D3R) = 1.7:0.34 nM) that induced high affinity not achieved in similarly N-substituted piperidine analogues and significantly (470-fold) improved D3R binding affinity compared to the parent ligand **1**. X-ray crystallographic data revealed a distinctive spatial arrangement of pharmacophoric elements in the piperidinol vs tropine analogues, providing clues for the diversity in SAR at the D2 and D3 receptor subtypes.

Introduction

Dopamine is the primary neurotransmitter associated with the psychomotor stimulation and addictive liability of cocaine, methamphetamine, and other stimulant drugs of abuse that disrupt function of the dopamine transporter thereby increasing extracellular dopamine. Moreover, drugs that block dopamine D2-like receptors (e.g., haloperidol) are used clinically to treat hallucinations and other positive symptoms of schizophrenia and other neuropsychiatric disorders. Preponderance of debilitating extrapyramidal side effects, however, limits clinical efficacy and precludes use of these medications to treat drug addiction.[1]

Dopamine receptors are G-protein-coupled receptors (GPCRs) classified as either D1-like (D1R and D5R subtypes) or D2-like (D2R, D3R, and D4R subtypes), and there exists high

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Supporting Information Available: Elemental analysis results and X-ray crystallographic results. This material is available free of charge via the Internet at http://pubs.acs.org.

sequence homology (up to 75%) in the ligand-binding transmembrane regions among the members of each of these families.[2] Recently, D2-like receptors have received particular attention in psychostimulant abuse because their availability has been shown to be related to cocaine's pleasurable effects in both human[3,4] and primate studies.[5] Although antipsychotic medications targeting the D2-like receptors have been clinically utilized for over half a century, an understanding of the complex relationship between dopamine receptor subtype activity, clinical efficacy, and extrapyramidal side effects remains incomplete. Hence, D2-like receptors are clearly involved in drug reinforcement and addiction, and D3R-selective antagonists have recently shown efficacy in animal models of drug abuse without incapacitating motor side effects.[6–12] Continued study of the D3R using selective ligands has proven critical for the understanding of dopamine receptor-related mechanisms, yet it remains unclear which subtypes are necessary and have the most potential to target in medication discovery.[13,14] Given D2R antagonism has been implicated in the origin of cataleptic and other motor side effects,[15] the narrow therapeutic window of nonselective D2R antagonists might be improved with a critical ratio of D2R/D3R selectivity.[16–21] Thus, the discovery of subtype-selective ligands with which to determine specific roles of each of these receptor targets has been an imperative step toward the development of more effective medications for the treatment of schizophrenia, Parkinson's disease, obesity, and substance abuse.[22–25]

To provide tools with which to further explore the role of the dopamine receptor system, the development of high-affinity and D2R/D3R ligands was undertaken. The modestly D2R-selective antagonist **1** (L741,626, K_i(D2R/D3R) = 11.2:163 nM)[26] provided a template for chemical modification. SAR based on analogues of **1** has recently been exhaustively explored providing higher affinity D2R ligands such as compounds **2**[27] and **3**[28] in Figure 1. Despite these efforts, clear trends leading to D2R selectivity remain elusive. A recent report investigating the SAR of structurally rigid analogues of haloperidol, from which compound **4** was described, led us to explore this structural motif in a series of bicyclic analogues of **1**.[29] Hence, systematic 3-position aryl ring and 8-position heteroarylmethyl substitutions on the tropine template were investigated to determine their influence on D2R and D3R binding affinities in comparison to the more flexible piperidine analogues. Although highly D3R selective compounds (>100-fold) have been synthesized and their behavior in a number of models of drug abuse has been investigated, the discovery of new D3R ligands for in vivo investigation remains an important objective and it is anticipated that the resulting SAR from this study might provide clues to a novel class of D3R-selective ligands.[8,30–34]

Chemistry

Previously described SAR has suggested that the tropane 8-position N-substituent critically affects binding affinity for the D2-like receptor subtypes;[26–28] thus, a variety of heteroaryl ring systems were synthesized diverging from the indolyl side chains of compounds **1**, **2**, and **3** in order to explore new pharmacophoric elements. Hence, the benzofuryl and benzothienyl synthons (**11a–f**) were prepared as described in Scheme 1. 2′-Hydroxyacetophenones **5a–e** were alkylated with ethyl 2-chloroacetate under basic conditions to give the corresponding ethyl 2-(2-acetylphenoxy)acetates, which were recrystallized from acetone (**6a**,**b**) or carried on without further purification (**6c–e**).[35] Ester hydrolysis of **6a–e** gave 2-(2-acetylphenoxy)-acetic acids **7a–e**, which were cyclized in refluxing NaOAc/Ac_2O to yield 3-methylbenzofurans **8a–e**, and treatment of these resulting heterocycles with selenium dioxide afforded **9a–e** as major products.[36] The reduction of the intermediate aldehydes **9a–f** with $NaBH_4$, followed by mild chlorination with stoichiometric $SOCl_2$ in Et_2O yielded the desired 3-chloromethylbenzofurans **11a–e** and 3-chloromethylbenzothiophene **11f**.[37] Overall, this synthetic route was flexible because of the availability of a number of substituted 2-hydroxyacetophenones and was reliable, although

crystallization steps involving the naphthyl derivatives **6d**, **6e**, **7d**, and **7e** proceeded with more difficulty, thus lowering overall yields of compounds **11d** and **11e**.

The synthesis of 8-heteroarylmethyl-3-arylnortropines (**31–53**) relied on the protection of the 8-position nitrogen during installation of the 3-aryl substituent, then deprotection and functionalization of the 8-position with a specified side chain (Scheme 2). To begin, tropinone (**12**) was demethylated and protected in a one-step reaction with ethyl chloroformate to yield the ethyl carbamate **13**,[38] or in a two-step procedure using 1-chloroethyl chloroformate, then Boc_2O to yield the *tert*-butyl carbamate **14**.[39] The protected nortropinones **13** and **14** were then reacted with the appropriate ArLi or ArMgBr to yield 3-arylated **15–22**. The low yields observed in this reaction can be attributed to poor product solubility during the reaction, where the precipitated product salt traps the unreacted tropinone, preventing complete turnover. Reduction of this unreacted tropinone with $NaBH_4$ in the crude product was essential because of its coelution with pure target product during chromatography. The stereoselectivity of this reaction can be attributed to the sterically hindered nature of the bottom-face of the carbonyl group of **13** and **14** toward nucleophilic attack; thus, only *endo*-3-phenyltropines were produced.[29a,40,41] Removal of the ethyl carbamate protecting group of **15–21** was nontrivial, as reaction with 50% KOH(aq), EtOH, and hydrazine was required for complete deprotection and production of **23–29**.[29b] Since the 4-methylthiophenyl group of **22** was not stable under these harsh conditions, the *tert*-butyl carbamate analogues were developed. Unfortunately, Boc deprotection also proved problematic, as treatment of **22** with 3 M HCl in MeOH induced partial elimination of the 3-hydroxy group and an alternative deprotection method using TMSI in CH_2Cl_2 produced the Boc-protected alkene as the major product. Ultimately, deprotection of **22** was achieved at 185 °C for 5 min in the microwave reactor to give **30**.[42]

Indolyl- and related analogues **31–40** were synthesized via reaction of nortropines **23–26** and **28–30** with gramine, 3-(dimethylaminomethyl)indazole,[43] or 5-methoxygramine in refluxing pyridine to give reproducible yields of final product (40–70%). These gramine-type alkylating agents were used substoichiometrically (85–95 mol%) to avoid formation of side products that were not readily removed with flash chromatography or preparative TLC. Because of the limited structural diversity available using gramine-type reagents, other potential routes to final products were explored. The reaction of **23** with arylcarboxylic acid chlorides produced 8-amido derivatives in moderate yields; however, exposure of these amides to $LiAlH_4$ in refluxing THF failed to generate the expected amine product. Since an analogous system with a protected hydroxyl group reliably reduces to the amine, it was hypothesized that after the 3-OH group consumes 1 equiv of hydride, the reactant is precipitated as an insoluble salt, preventing reduction even under these robust conditions.[44] Likewise, the reductive amination of **23** with **9a** or **9f** using $NaBH_3CN$ was attempted but resulted in poor yield of **41** and no production of **44**. Ultimately, the alkylation of 3-arylnortropines **23–28** with heteroarylmethyl chlorides **11a–f** provided the most straightforward and reliable approach to obtaining products **41–53** in moderate to high yields. Unreacted **11a–f** frequently coeluted with the reaction products, so an excess of nortropine was preferred; however, purification of these products proved more facile than for those that involved gramine-type alkylating agents. Although K_2CO_3 in DMF provided reproducible and high-yielding alkylations, $NaHCO_3$ in CH_3CN was preferred because of the lower boiling point of the solvent and lower solubility of the base in the crude product mixture, allowing for simple filtration and evaporation to obtain the final products.[27] All products **31–53** were characterized by ^1H, ^{13}C, and ^{19}F (where applicable) NMR spectroscopy, IR spectroscopy, GC/MS analysis,[45] and elemental analysis. Oxalate salts were generated for all of the final products **31–53** except **36**.

Pharmacological Results and Discussion

The products **31–53** were tested for displacement of the high affinity and nonselective D2-like radioligand 2,3-dimethoxy-5-(^{125}I)-iodo-*N*-(9-benzyl-9-azabicyclo(3.3.1)nonan-3-yl) benzamide (^{125}I-IABN) in HEK 293 cells transfected with $hD2_LR$ or hD3R as described previously (Table 1).[32] Compound **31**, where the piperidinol motif of **1** was replaced with a tropine system, exhibited a 10-fold increase in affinity at D3R (K_i = 15.5 nM) and a 3-fold decrease in affinity at D2R (K_i = 33.4 nM), resulting in a reversal of selectivity compared to **1** (K_i(D2R/D3R) = 11.2:163 nM). Compound **32**, the tropine analogue of **2**,[27] the most potent and D2R-selective ligand to arise from the previous study, also exhibited a reversal in subtype selectivity compared to **2** because of improved D3R affinity (K_i = 6.35 nM) and decreased D2R affinity (K_i = 35.3 nM), which resulted in a 5-fold selectivity for D3R. The alternative 2,3-dichloro substitution in **33** resulted in a dramatic loss of affinity at both receptor subtypes compared to **32** that was not observed in the analogous piperidinol analogue (K_i(D2R) = 26 nM).[27] Conversely, the moderate and equivalent binding affinities of **34** at both receptor subtypes (K_i(D2R/D3R) = 41.4:31.0 nM) were unlike that of the piperidinol analogue (K_i(D2R/D3R) = 127:490 nM)[27] providing an example of the bicyclic ring system improving affinity at both receptors. Other 3-aryl substitutions, such as 2-napthyl, a classic 3,4-dichlorophenyl isostere, in **35** and the 2-methoxyphenyl in **36** were poorly tolerated at both D2R and D3R. Both compounds **33** and **36** possess aryl pharmacophores that when appended to piperazine-type ligands typically yield high affinity and selective D3R ligands, yet these structurally rigid tropines displayed low affinity for both receptor subtypes. This disparity may be explained by the presence of an intramolecular hydrogen bond between the tropine 3-OH and the ortho atom of the 3-aryl ring (the oxygen of 2-MeO or 2-Cl group) stabilizing a conformation of the 3-aryl ring that is disfavored for receptor binding. ^{1}H NMR spectral evidence supports this claim, as 2,3-dichloro analogues **33**, **43**, and **46** in $CDCl_3$ display –OH resonances (2.05, 1.81, and 1.95 ppm, respectively) that are downfield-shifted compared to the 3,4- dichloro isomers **32**, **42**, and **45** (1.57, 1.48, and 1.50 ppm), respectively), which is consistent with the presence of intramolecular hydrogen bonding.

During the course of this study, several analogues of **1** were published demonstrating high selectivity for D2R over D3R, and this effect was attributed to a pair of unique pharmacophores: the 4-methylthiophenyl group and the 5-methoxyindol-3-ylmethyl side chain, e.g. compound **3** in Figure 1.[28] These two substitutions were applied to the tropine framework individually and in concert, and the resulting SAR diverged from that of the previous report. Compound **37**, the 4-methylthiophenyl analogue of **31**, exhibited poor affinity at both receptor subtypes (K_i(D2R/D3R) = 565:541), corresponding to a 24-fold decrease in binding at D2R compared to the piperidinol analogue.[28] Similarly, the 5-methoxyindol-3-ylmethyl group of **39** failed to induce the selective D2R binding seen in the corresponding piperidinol ligand. The combination of these two pharmacophores in **40** resulted in a 100-fold decrease in binding at D2R compared to the unbridged analogue and poor affinity at both receptor subtypes. Thus, structural rigidification in compound **40**, the tropine analogue of **3**, is sufficient to greatly alter or even reverse the trends in SAR developed for the six-membered piperidinol series of analogues of **1**.

Given the results of N-containing compounds presented above, S- and O- analogues of the 8-(3-indolylmethyl) group were studied to further explore SAR of the 3-aryltropine pharmacophore. Although compound **41** maintained high affinity and a small but significant preference for D3R (K_i(D2R/D3R) = 12.9:3.62), the D3R affinity of the other S-analogues was diminished in the 3,4-dichlorophenyl analogue **42** (K_i(D2R/D3R) = 29.8:17.9 nM) and more so in the 2,3-dichlorophenyl compound **43** (K_i(D2R/D3R) = 280:431 nM),

demonstrating the failure of the benzothiophene moiety to consistently improve binding affinity at the D2-like receptors.

Conversely, the substitution of the N-heterocycle of **31** with a variety of benzofurans resulted in a new class of tropine-containing ligands (**44–53**) that demonstrate high binding affinity at both D2R and D3R and further underscore the significant divergence of SAR from piperidinol-based compounds. For example, compounds **44** and **45** exhibit low nanomolar affinities at both receptor subtypes (K_i(D2R/D3R) = 1.06:0.71 and 1.7:0.34 nM, respectively), which correspond to 20- to 30-fold increases in affinity at both receptor subtypes when compared to **31** and **32**. The high binding affinities of **44** and **45** due to the 3-benzofurylmethyl substituent were not observed in the previously described 4-chlorophenyl- and 3,4-dichlorophenylpiperidinol analogues (K_i(D2R/D3R) = 21:53 and 21:28 nM, respectively).[27] Notably, the combination of these chemical modifications to the parent ligand **1** improved binding affinity at D3R of **45** by 470-fold. Although **46** exhibited diminished affinity compared to the other analogues in the series (K_i(D2R/D3R) = 40.1:32.2 nM), this example highlighted the effectiveness of the 8-(3-benzofurylmethyl) group in imparting significant increases in affinity to an otherwise poor ligand (see **33** and **43**). Moreover, the 2,3-dichlorophenyl moiety is a classic D3R pharmacophore,[30] but this substitution on the tropane ring did not impart D3R selectivity in the present series. Compounds **47** and **48**, the F- and Br-congeners of **44**, demonstrated that high affinity could be maintained at both subtypes given a range of halide sizes, though in the absence of significant selectivity similar to **44**.

Since the benzofurylmethyl group emerged as a high affinity pharmacophore, further studies of the substituent effects were conducted. The affinity of **49** was similar to the parent **44**, an effect also seen in the addition of the 5-methoxy group to the indole of **31** to give **39**. The addition of a 5-fluoro substituent resulted in similar affinity at D2R for **50**. The substitution of the benzofuran heterocycle with either a naphtho[2,1-*b*]furan (**51**) or naphtho[1,2-*b*]furan (**52**) resulted in two high affinity, yet nonselective ligands. Likewise, no further selectivity was achieved in the combination of the 3,4-dichlorophenyl- and 5-fluorobenzofur-3-ylmethyl pharmacophores to give **53**, which displays binding affinities similar to those of both **45** and **50**. With the exception of **46**, the 3-benzofurylmethyl tropine analogues all exhibit affinities of less than 12 nM for one or both D2-like receptors and demonstrate the tolerance of this structure to limited modification. In total, these data illustrate the great divergence of SAR between compound classes based on **1** and **31**, suggesting that the tropine pharmacophore described herein warrants further study.

Four tropine analogues were further evaluated for functional efficacy at D2R and D3R as well as for binding affinity at D4R, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} (Table 2). The functional assay confirmed that **31**, **32**, **41**, and **44** are antagonists for D2R and D3R, and these data correlate well with the binding data presented in Table 1. Overall, the additional binding experiments revealed that these compounds have uniformly low affinity for 5-HT_{1A}, 5-HT_{2C}, and D1R. Although **44** displayed moderate affinity at 5-HT_{2A} and D4R, this compound exhibited >100-fold selectivity for D2R/D3R over all the receptors tested. Compared to the parent **1**, **31** exhibited a 7-fold decrease in binding affinity at 5-HT_{2A} and served as another example of the tropine substitution disfavoring receptor binding compared to a ligand based on the piperidinol framework.

X-ray Crystallographic Results and Discussion

Binding data presented above revealed that structural differences between the piperidinol and tropine frameworks induce dissimilar binding affinity changes at the D2-like receptors. Thus, in an effort to collect additional conformational information, the oxalate salts of **1** and

31 were analyzed using single-crystal X-ray diffraction. Of note, the X-ray structure of **1** reveals a near-perpendicular alignment of the O(1)–C(12) bond with the C(15)–C(20) bond in the 3-aryl ring (–5.2 ± 0.2°) as well as an arrangement of the C(14)–N(2)–C(9)–C(7) torsion (−67.3 ± 0.2°) that allows the placement of the indole substituent on the same face of the molecule as the hydroxyl group (Figure 2). The X-ray structure of **31** shows similarities in the aryl ring conformation (O(1)–C(12)–C(15)–C(20) torsion angle of −6.82 ± 0.13°) but a significant divergence in the placement of the 8-position substituent (C(14)–N(2)–C(9)–C(7) torsion angle of +46.92 ± 0.13°) (Figure 3). An alignment of the two crystal structures revealed subtle differences in OH group and 3-aryl ring placement between the two structures but clearly shows a 114° relative rotation of the N(2)–C(9) bond from **1** to **31** (Figure 4).[46] Hence, the addition of an ethylene bridge between C(10) and C(14) in compound **31** precludes placement of the 8-position side chain on the same face as the hydroxyl group, as seen with compound **1**, as this would result in an unfavorable crystal packing interaction. Thus, the indolylmethyl substituent is positioned on the opposite face as the hydroxyl group in **31**, alleviating this high energy interaction. Because of a steric interaction with the ethylene bridge not present in piperidinol analogues like **1**, the 8-position substituent of the tropine analogue **31** may have access to a different low-energy binding mode than the piperidinol analogues, e.g., **1** and related structures, thus resulting in the unique SAR of the tropine analogues described in this series.

Summary and Conclusions

Ligands inspired by lead compound **1** but incorporating a 3-aryltropine substructure in place of 3-arylpiperidinol were synthesized, and their binding affinities for the dopamine D2 and D3 receptor subtypes were determined. The D2R-preferring properties of the piperidinol antagonists were reversed and diminished (**1** and **2** vs **31** and **32**) or completely eliminated (**3** vs **40**) when their respective pharmacophores were applied to a tropine framework. X-ray crystallographic data provided a three-dimensional explanation for the divergence in SAR between **1** and **31**, where comparison of the crystal structures indicated a unique low-energy conformation of the 8-position side chain in the tropine analogues. This likely affords access to a different subset of amino acid residues within the neurotransmitter binding sites of the D2R and D3R, and the conversion from D2R- to D3R-preferential binding could be due to either specific amino acid substitutions between the subtypes or differences in the overall contour of these two structurally related receptors. Primary structural analysis of D2R and D3R demonstrated extensive homology between the second and third helical transmembrane spanning (TMS) regions of these subtypes,[2] and subsequent molecular modeling and substituted-cysteine accessibility method (SCAM) studies of D2R indicated that the first TMS helix does not contribute contact residues to the agonist/antagonist binding site.[47,48] Therefore, it seems likely that the 3-aryltropine and 3-arylpiperidinol are exploiting differences in the remaining TMS regions (TMS IV, V, VI, and/or VII) of D2R and D3R, affording the unique SAR described herein.

In summary, a variety of high affinity ligands for both D2 and D3 dopamine receptors have been identified in this series of aryltropine analogues. Although the lead arylpiperidinol compounds (**1** and **2**) were more than 10-fold selective for the D2 receptor subtype, several of the corresponding aryltropine derivatives (**32**, **45**, and **47**) exhibited preferential (4- to 5-fold) binding at the D3 receptor subtype as well as significantly improved binding affinities.

Experimental Methods

Reaction conditions and yields were not optimized, and spectroscopic data refer to the free base. Microwave reactions were performed using a CEM Corp. (Matthews, NC) Discover LabMate system using the standard 10 mL reaction vessel. Thin-layer chromatography was

performed using analytical (Analtech Uniplate, catalog number 21521, 250 μm) or preparative (Analtech Uniplate, catalog number 02013, 20 cm × 20 cm, 1000 μm) silica gel plates, and flash chromatography was performed using silica gel (EMD Chemicals, Inc.; catalog number EMD-9385, 230–400 mesh, 60 Å). The ^{1}H, ^{13}C, and ^{19}F NMR spectra were acquired using a Varian Mercury Plus 400 spectrometer. Chemical shifts are reported in parts per million (ppm) and referenced according to deuterated solvent for ^{1}H spectra ($CDCl_3$, 7.26; CD_3OD, 3.31; $(CD_3)_2SO$, 2.50) and ^{13}C spectra ($CDCl_3$, 77.23; CD_3OD, 49.00; $(CD_3)_2SO$, 39.52) or an internal standard for ^{19}F spectra ($CFCl_3$, 0.00). Infrared spectra were recorded as a neat film on NaCl plates using a Perkin-Elmer Spectrum RX I FT-IR spectrometer. Gas chromatography–mass spectrometry (GC/MS) data were acquired using an Agilent Technologies (Santa Clara, CA) 6890 GC equipped with an HP-5MS column (cross-linked 5% PH ME siloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness) and a 5973 mass-selective ion detector in electron-impact mode. Ultrapure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line temperatures were 250 and 280 °C, respectively, and the oven temperature gradient used was as follows: the initial temperature (100 °C) was held for 3 min (0:00 to 3:00 min), then increased to 295 at 15.0 °C/min over 13 min (3:00 to 16:00 min), and finally maintained at 295 °C for 10 min (16:00 to 26:00 min). Combustion analysis was performed by Atlantic Microlab, Inc. (Norcross, GA), and results agree within 0.4% of calculated values. Melting point determination was conducted using a Thomas-Hoover melting point apparatus and are uncorrected. Anhydrous solvents were purchased from Aldrich (pyridine, acetonitrile, dichloromethane, chloroform, hydrazine) or JT Baker (diethyl ether) and were used without further purification except for tetrahydrofuran, which was freshly distilled from sodium benzophenone ketyl. Compounds **5a–e**, **9f**, and **12** were purchased from the Sigma- Aldrich Co. Methods for binding affinity determination at human dopamine D2 and D3 receptor subtypes have been previously reported.[32] Crystal structure alignment was achieved using Sybyl 7.3 using the nitrogen containing six-membered ring structure common between the two structures as a template.[46]

Ethyl 2-(2-Acetylphenoxy)acetate (6a)

6a was prepared from **5a** according to literature procedure[35] which was adapted below.

Ethyl 2-(2-Acetyl-4-methoxyphenoxy)acetate (6b). General Procedure A

A suspension of 2-hydroxy-5-methoxyacetophenone (**5b**) (25.00 g, 150.4 mmol), ethyl 2-chloroacetate (23.04 g, 188.0 mmol), and potassium carbonate (20.79 g, 150.4 mmol) in acetone (115 mL) was heated to reflux for 16 h under argon. The reaction mixture was cooled and filtered, and the filtrate was evaporated to yield a solid mass. The solid was transferred to a fritted filter and washed with cold acetone (−78 °C), then recrystallized from acetone (−40 °C) to yield **6b** (25.65 g, 101.7 mmol, 68%): mp 72–74 °C (acetone); R_f($CHCl_3$) = 0.07; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2, 3H), 2.72 (s, 3H), 3.80 (s, 3H), 4.27 (q, J = 7.2, 2H), 4.68 (s, 2H), 6.80 (d, J = 9.2, Hz, 1H), 7.00 (dd, J = 3.2, 9.2 Hz, 1H), 7.31 (d, J = 3.2 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.3, 32.2, 56.0, 61.7, 66.5, 114.2, 114.3, 120.4, 129.4, 151.6, 154.4, 168.6, 199.5; IR (thin film) 1660, 1755 cm^{-1}; GC/MS t_R = 11.0 min (252 $[M]^+$ *m/z*).

Ethyl 2-(2-Acetyl-4-fluorophenoxy)acetate (6c)

A suspension of 5-fluoro-2-hydroxyacetophenone (**5c**) (10.00 g, 64.88 mmol), ethyl 2-chloroacetate (9.94 g, 81.09 mmol), and potassium carbonate (8.97 g, 64.88 mmol) in acetone (52 mL) was reacted according to general procedure A. After the initial evaporation, the crystalline **6c** was carried on without further purification (15.58 g, 64.85 mmol, quant): mp 40–42 °C (acetone); R_f($CHCl_3$) = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 2.71 (s, 3H), 4.27 (q, J = 7.2 Hz, 2H), 4.69 (s, 2H), 6.80 (dd, 4.0, 9.2 Hz, 1H), 7.14

(ddd, J = 3.2, 7.2, 9.2 Hz, 1H), 7.47 (dd, J = 3.4, 9.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.3, 32.1, 61.9, 66.3, 114.1 (J = 7.6 Hz), 117.2 (J = 23.6 Hz), 120.1 (J = 23.5 Hz), 130.0 (J = 5.9 Hz), 153.4 (J = 1.7 Hz), 157.5 (240.4 Hz), 168.2, 198.4; ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −122.2 (dt, J = 4.0, 7.9 Hz); IR (thin film) 1678, 1759 cm^{-1}; GC/MS t_R = 9.2 min (240 $[M]^+$ *m/z*).

Ethyl 2-(1-Acetylnaphthalen-2-yloxy)acetate (6d)

A suspension of 2′-hydroxy-1′-acetonaphthone (**5d**) (25.00 g, 134.3 mmol), ethyl 2-chloroacetate (20.57 g, 81.09 mmol), and potassium carbonate (18.56 g, 134.3 mmol) in acetone (103 mL) was reacted according to general procedure A. After the initial evaporation, the resulting red oil **6d** was carried on without further purification (36.56 g, 134.3, quant); a small amount was purified by preparative TLC ($CHCl_3$) for characterization: mp 50–52 °C ($CHCl_3$); R_f($CHCl_3$) = 0.09; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 2.71 (s, 3H), 4.23 (q, J = 7.2 Hz, 2H), 4.75 (s, 2H), 7.09 (d, J = 8.8 Hz, 1H), 7.36 (dt, J = 0.8, 7.6 Hz, 1H), 7.46 (dt, J = 1.2, 7.6 Hz, 1H), 7.75 (br s, 1H), 7.77 (br s, 1H), 7.82 (d, J = 9.2 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.3, 32.9, 61.7, 66.4, 113.3, 124.1, 124.8, 126.2, 128.0, 128.4, 129.6, 130.5, 131.7, 152.3, 168.7, 205.0; IR (thin film) 1694, 1756 cm^{-1}; GC/MS t_R = 12.7 min (272 $[M]^+$ *m/z*).

Ethyl 2-(2-Acetylnaphthalen-1-yloxy)acetate (6e)

A suspension of 1′-hydroxy-2′-acetonaphthone (**5e**) (25.00 g, 134.3 mmol), ethyl 2-chloroacetate (20.57 g, 81.09 mmol), and potassium carbonate (18.56 g, 134.3 mmol) in acetone (103 mL) was reacted according to general procedure A. After the initial evaporation, the resulting red oil **6e** was carried on without further purification (36.56 g, 134.3, quant); a small amount was purified by preparative TLC ($CHCl_3$) for characterization; R_f($CHCl_3$) = 0.12; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 2.77 (s, 3H), 4.30 (q, J = 7.2 Hz, 2H), 4.69 (s, 2H), 7.59 (m, 2H), 7.67 (obs s, 1H), 7.68 (obs s, 1H), 7.87 (m, 1H), 8.30 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.3, 31.0, 61.5, 72.5, 123.4, 124.9, 125.4, 127.1, 127.7, 128.2, 128.5, 128.5, 136.8, 154.6, 168.6, 200.4; IR (thin film) 1682, 1756 cm^{-1}; GC/MS t_R = 12.4 min (272 $[M]^+$ *m/z*).

2-(2-Acetylphenoxy)acetic Acid (7a)

7a was prepared from **6a** according to literature procedure[35] which was adapted below.

2-(2-Acetyl-4-methoxyphenoxy)acetic Acid (7b). General Procedure B

A mixture of **6b** (25.11 g, 99.54 mmol) and potassium carbonate (15.27 g, 110.5 mmol) in H_2O (177 mL) was heated to reflux for 3 h. After cooling, the solution was adjusted to pH 1 with concentrated HCl (25 mL), and the resulting precipitate was collected in a (M) fritted filter and dried over high vacuum. Recrystallization from boiling H_2O (850 mL) yielded pure crystalline **7b** (20.52 g, 91.52 mmol, 92%): mp 141–142 °C (H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.61 (s, 3H), 3.73 (s, 3H), 4.78 (s, 2H), 7.03–7.10 (obs m, 3H), 13.09 (br s, 1H, –COO<u>H</u>); ^{13}C (100 MHz, DMSO-d_6) δ 31.7, 55.5, 65.6, 113.4, 114.9, 119.5, 128.6, 151.2, 153.3, 170.1, 198.7; IR (thin film) 1655, 1741 cm^{-1}.

2-(2-Acetyl-4-fluorophenoxy)acetic Acid (7c)

A mixture of **6c** (15.58 g, 64.85 mmol) and potassium carbonate (9.95 g, 72.00 mmol) in H_2O (116 mL) was reacted according to general procedure B, and subsequent recrystallization from H_2O yielded pure **7c** (9.38 g, 44.22 mmol, 68%): mp 121–123 °C (H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.62 (s, 3H), 4.84 (s, 2H), 7.15 (dd, J = 4.2, 9.0 Hz, 1H), 7.32–7.40 (obs m, 2H), 13.17 (br s, 1H, –COO<u>H</u>); ^{13}C (100 MHz, DMSO-d_6) δ 32.3, 66.2, 115.9 (d, J = 16.0 Hz), 116.1, 120.6 (d, J = 22.7 Hz), 129.8 (d, J = 5.8 Hz), 154.0

(d, J = 1.7 Hz), 156.9 (d, J = 237.0 Hz), 170.4, 198.6; ^{19}F NMR (376 MHz, DMSO-d_6/$CFCl_3$) δ −122.4 (dt, J = 4.0, 7.9 Hz); IR (thin film) 1661, 1747 cm^{-1}.

2-(1-Acetylnaphthalen-2-yloxy)acetic Acid (7d)

A mixture of **6d** (36.56 g, 134.3 mmol) and potassium carbonate (20.60 g, 149.00 mmol) in H_2O (240 mL) was reacted according to general procedure B, and subsequent recrystallization from H_2O yielded off-white **7d** (8.58 g, 35.13 mmol, 26%): mp 146–148 °C (H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.64 (s, 3H), 4.96 (s, 2H), 7.42 (obs, dt, J = 1.2, 6.6 Hz, 1H), 7.43 (obs d, J = 9.6 Hz, 1H), 7.51 (dt, J = 1.2, 6.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 9.6 Hz, 1H), 13.16 (s, 1H, –COO<u>H</u>); ^{13}C (100 MHz, DMSO- d_6) δ 32.5, 65.1, 113.8, 123.3, 124.2, 124.5, 127.6, 128.2, 128.6, 129.6, 131.2, 152.4, 170.2, 204.1; IR (thin film) 1682, 1716, 1739 cm^{-1}.

2-(2-Acetylnaphthalen-1-yloxy)acetic Acid (7e)

A mixture of **6e** (36.56 g, 134.3 mmol) and potassium carbonate (20.60 g, 149.02 mmol) in H_2O (240 mL) was reacted according to general procedure B, and subsequent recrystallization of the crude product resulted in fine light-brown needles of **7e** (2.69 g, 11.01 mmol, 8%): mp 122–125 °C (H_2O); ^{1}H NMR (400 MHz, CD_3OD) δ 2.74 (s, 3H), 4.69 (s, 2H), 7.61 (m, 2H), 7.71 (br s, 2H), 7.91 (m, 1H), 8.30 (m, 1H); ^{13}C (100 MHz, CD_3OD) δ 31.0, 73.0, 124.3, 125.7, 126.2, 128.1, 128.9, 129.2, 129.3, 129.6, 138.2, 155.8, 172.0, 202.1; IR (thin film) 1673, 1732 cm^{-1}.

3-Methylbenzofuran (8a)

8a was prepared from **7a** according to literature procedure[35] which was adapted below.

5-Methoxy-3-methylbenzofuran (8b). General Procedure C

A solution of **7b** (20.52 g, 91.52 mmol) and sodium acetate (31.91 g, 389.0 mmol) in acetic anhydride (61 mL) was heated to reflux under Ar for 3 h. After the mixture was cooled, the reaction was quenched with H_2O (180 mL) and stirred for 16 h. The reaction mixture was extracted with benzene (200 mL), and the resulting organic layer was isolated, washed with 10% Na_2CO_3 solution, then H_2O (100 mL), dried with Na_2SO_4, and evaporated. The crude oil was purified by vacuum distillation to yield clear oil **8b** (13.00 g, 80.02 mmol, 88%): bp 64–65 °C at 0.6 mmHg; R_f($CHCl_3$) = 0.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.87 (s, 3H), 6.90 (dd, J = 2.6, 9.0 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 8.2, 56.2, 102.1, 112.0, 113.0, 115.9, 129.7, 142.5, 150.4, 156.0; GC/MS t_R = 6.4 min (162 $[M]^+$ m/z).

5-Fluoro-3-methylbenzofuran (8c)

A solution of **7c** (9.38 g, 44.22 mmol) and sodium acetate (15.42 g, 189.9 mmol) in acetic anhydride (29 mL) was reacted according to general procedure C. The crude product was vacuum-distilled to yield clear oil **8c** (4.41 g, 29.40 mmol, 66%): bp 22–25 °C at 0.15 mmHg; R_f($CHCl_3$) = 0.76; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (d, J = 1.2 Hz, 3H), 7.00 (dt, J = 2.4, 8.8, 1H), 7.17 (dd, J = 2.4, 8.8, 1H), 7.37 (dd, J = 4.0, 8.8 Hz, 1H), 7.44 (d, J = 1.2 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 8.1, 105.2 (d, J = 24.3 Hz), 112.0 (d, J = 36.1 Hz), 112.0, 116.1 (d, J = 3.4 Hz), 130.1 (d, J = 10.9 Hz), 143.3, 151.6, 159.3 (d, J = 236.1 Hz); ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −122.2 (dt, J = 4.0, 9.0); GC/MS t_R = 5.3 min (150 $[M]^+$ m/z).

1-Methylnaphtho[2,1-*b*]furan (8d)

A solution of **7d** (8.58 g, 35.15 mmol) and sodium acetate (12.25 g, 149.3 mmol) in acetic anhydride (23 mL) was reacted according to general procedure C. The crude product was purified using flash chromatography (3:1 hexane/$CHCl_3$) to yield pure **8d** (5.34 g, 29.30

mmol, 83%): mp 57–58 °C ($CHCl_3$); R_f(1:1 hexane/$CHCl_3$) = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 3H), 7.50 (br ddd, *J* = 1.2, 6.8, 8.4 Hz, 1H), 7.55 (s, 1H), 7.60 (br ddd, *J* = 1.2, 6.8, 8.4, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 11.6, 112.9, 117.8, 122.2, 123.3, 124.3, 125.5, 126.4, 129.1, 129.3, 130.8, 141.3, 153.5; GC/MS t_R = 9.3 min (182 $[M]^+$ *m/z*).

3-Methylnaphtho[1,2-*b*]furan (8e)

A solution of **7e** (2.69 g, 11.01 mmol) and sodium acetate (3.84 g, 46.80 mmol) in acetic anhydride (7 mL) was reacted according to general procedure C. The crude product was purified using flash chromatography (3:1 hexane/$CHCl_3$) to yield a colorless oil **8e** (1.49 g, 8.16 mmol, 74%); R_f(1:1 hexane/$CHCl_3$) = 0.65; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (d, *J* = 1.2 Hz, 3H), 7.49 (ddd, *J* = 1.2, 7.2 Hz, 8.0, 1H), 7.57 (obs s, 1H), 7.58 (obs dt, *J* = 1.2, 7.6 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.30 (dd, *J* = 0.8, 8.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 8.3, 116.9, 118.3, 120.2, 121.7, 123.1, 124.5, 125.1, 126.4, 128.5, 131.6, 140.9, 150.9; GC/MS t_R = 9.1 min (182 $[M]^+$ *m/z*).

Benzofuran-3-carbaldehyde (9a)

9a was prepared from **8a** according to literature procedure[36] which was adapted below.

5-Methoxybenzofuran-3-carbaldehyde (9b). General Procedure D

A solution of selenium dioxide (1.64 g, 14.81 mmol) and **8b** (2.09 g, 12.88 mmol) in 1,4-dioxane (16 mL) was heated to reflux for 16 h. The reaction mixture was filtered over Celite in a (M) fritted filter, and the solids were rinsed with THF (100 mL). The filtrate was evaporated and purified using flash chromatography ($CHCl_3$) to yield red-brown crystals of **9b** (1.45 g, 8.25 mmol, 64%): mp 75–77 °C ($CHCl_3$); R_f($CHCl_3$) = 0.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.00 (dd, *J* = 2.8, 9.0 Hz, 1H), 7.44 (d, *J* = 9.6 Hz, 1H), 7.64 (d, *J* = 2.8 Hz, 1H), 8.24 (s, 1H), 10.15 (s, 1H, –C<u>H</u>O); ^{13}C (100 MHz, $CDCl_3$) δ 56.1, 104.1, 112.4, 115.9, 123.7, 124.0, 151.0, 156.2, 157.6, 185.0; IR (thin film) 1675 cm^{-1}; GC/MS t_R = 8.1 min (176 $[M]^+$ *m/z*).

5-Fluorobenzofuran-3-carbaldehyde (9c)

A solution of selenium dioxide (1.79 g, 16.11 mmol) and **8c** (2.10 g, 14.01 mmol) in 1,4-dioxane (19 mL) was reacted according to general procedure D to yield peach-colored needles of **9c** (0.65 g, 3.98 mmol, 28%): mp 118–119 °C ($CHCl_3$); R_f($CHCl_3$) = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dt, *J* = 2.4, 8.8 Hz, 1H), 7.50 (dd, *J* = 4.0, 8.8 Hz, 1H), 7.86 (dd, *J* = 2.4, 8.0 Hz, 1H), 8.30 (s, 1H), 10.15 (s, 1H, –C<u>H</u>O); ^{13}C (100 MHz, $CDCl_3$) δ 108.6 (d, *J* = 26.0 Hz), 112.7 (d, *J* = 10.0 Hz), 114.4 (d, *J* = 26.1 Hz), 123.9 (d, *J* = 4.2 Hz), 124.1 (d, *J* = 11.7 Hz), 152.3, 156.6, 160.5 (d, *J* = 240.3 Hz), 184.6; ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −118.1 (dt, *J* = 4.0, 8.6 Hz); IR (thin film) 1673 cm^{-1}; GC/MS t_R = 5.8 min (164 $[M]^+$ *m/z*).

Naphtho[2,1-*b*]furan-1-carbaldehyde (9d)

A solution of selenium dioxide (1.80 g, 16.20 mmol) and **8d** (2.57 g, 14.09 mmol) in 1,4-dioxane (19 mL) was reacted according to general procedure D. After flash chromatography (1:1 hexane/$CHCl_3$), red-brown solid **9d** was obtained (1.05 g, 5.34 mmol, 38%): mp 96–98 °C ($CHCl_3$); R_f(1:1 hexane/$CHCl_3$) = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 1.2, 7.0, 8.0 Hz, 1H), 7.69 (obs d, *J* = 8.8 Hz, 1H), 7.70 (obs m, *J* = 1.2, 8.4 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.42 (s, 1H), 9.38 (d, *J* = 8.4 Hz, 1H), 10.21 (s, 1H, –C<u>H</u>O); ^{13}C (100 MHz, $CDCl_3$) δ 112.1, 118.5, 125.7, 126.8, 127.2, 127.7, 128.2, 128.3, 128.6, 131.4, 154.8, 157.5, 184.1; IR (thin film) 1676 cm^{-1}; GC/MS t_R = 10.6 min (196 $[M]^+$ *m/z*).

Naphtho[1,2-*b*]furan-3-carbaldehyde (9e)

A solution of selenium dioxide (0.88 g, 7.97 mmol) and **8e** (1.26 g, 6.93 mmol) in 1,4-dioxane (9 mL) was reacted according to general procedure D. After flash chromatography (1:1 hexane/$CHCl_3$), brown solid **9e** was obtained (1.04 g, 5.32 mmol, 77%): mp 91–93 °C ($CHCl_3$); R_f($CHCl_3$) = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (ddd, *J* = 1.2, 7.2, 8.0, 1H), 7.62 (ddd, *J* = 1.2, 7.2, 8.4, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.26 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.31 (s, 1H), 10.20 (s, 1H, –C<u>H</u>O); ^{13}C (100 MHz, $CDCl_3$) δ 119.1, 119.9, 120.1, 121.0, 124.7, 125.7, 126.3, 127.0, 128.5, 132.4, 152.0, 154.1, 185.2; IR (thin film) 1679 cm^{-1}; GC/MS t_R = 10.6 min (196 $[M]^+$ *m/z*).

Benzofuran-3-ylmethanol (10a)

10a was prepared from **9a** according to literature procedure[37] which was adapted below.

5-Methoxybenzofuran-3-ylmethanol (10b). General Procedure E

Sodium borohydride (0.30 g, 7.96 mmol) was added to a solution of **9b** (1.40, 7.96 mmol) in MeOH (20 mL), and the mixture was stirred at room temperature for 1 h. After quenching with saturated aqueous NH_4Cl (10 mL), the reaction mixture was extracted with $CHCl_3$ (100 mL), and the resulting aqueous layer was extracted with $CHCl_3$ (2 × 20 mL). The combined organic layer was dried with Na_2SO_4, evaporated, and dried over high vacuum to yield yellow solid **10b** (1.38 g, 7.76 mmol, 97%): mp 50–51 °C ($CHCl_3$); R_f(3% MeOH/$CHCl_3$) = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (obs t, *J* = 5.0 Hz, 1H, –O<u>H</u>), 3.86 (s, 3H), 4.82 (d, *J* = 5.0 Hz, 2H), 6.92 (dd, *J* = 2.8, 9.0 Hz, 1H), 7.12 (d, *J* = 2.8 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.59 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 55.9, 56.0, 102.3, 112.2, 113.7, 120.6, 127.4, 143.3, 150.7, 156.1; IR (thin film) 3296 cm^{-1}; GC/MS t_R = 9.0 min (178 $[M]^+$ *m/z*).

5-Fluorobenzofuran-3-ylmethanol (10c)

Sodium borohydride (0.14 g, 3.68 mmol) and **9c** (0.60 g, 3.68 mmol) were reacted in MeOH (9 mL) according to general procedure E to yield pure **10c** (0.55 g, 3.32 mmol, 90%): mp 64–66 °C ($CHCl_3$; R_f(3% MeOH/$CHCl_3$) = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (t, *J* = 5.4, 1H, –O<u>H</u>), 4.82 (d, *J* = 5.4, 2H), 7.04 (dt, *J* = 2.8, 8.8 Hz, 1H), 7.33 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.41 (dd, *J* = 4.0, 8.8 Hz, 1H), 7.65 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 55.9, 105.8 (d, *J* = 25.2 Hz), 112.5 (obs d, *J* = 9.3 Hz), 112.6 (obs d, *J* = 26.0 Hz), 120.8 (d, *J* = 3.4 Hz), 127.8 (d, *J* = 10.1 Hz), 144.2, 152.0, 159.4 (d, *J* = 237.8 Hz); ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −121.2 (dt, *J* = 4.0, 9.2 Hz); IR (thin film) 3289 cm^{-1}; GC/MS t_R = 6.6 min (166 $[M]^+$ *m/z*).

Naphtho[2,1-*b*]furan-1-ylmethanol (10d)

Sodium borohydride (0.19 g, 5.12 mmol) and **9d** (1.00 g, 5.12 mmol) were reacted in MeOH (25 mL) according to general procedure E, and the crude product was purified using flash chromatography ($CHCl_3$ to 3% MeOH/$CHCl_3$) to yield pure oil **10d** (0.73 g, 3.71 mmol, 72%); R_f(3% MeOH/$CHCl_3$) = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (br s, 1H, –O<u>H</u>), 5.12 (s, 2H), 7.51 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.63 (obs ddd, *J* = 1.6, 7.2, 8.4 Hz, 1H), 7.65 (obs d, *J* = 8.8 Hz, 1H), 7.75 (obs s, 1H), 7.76 (obs d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 57.0, 112.8, 120.8, 122.1, 124.3, 124.6, 126.2, 126.8, 128.3, 129.0, 130.8, 142.4, 153.9; IR (thin film) 3446 cm^{-1}; GC/MS t_R = 11.2 min (198 $[M]^+$ *m/z*).

Naphtho[1,2-*b*]furan-3-ylmethanol (10e)

Sodium borohydride (0.16 g, 4.19 mmol) and **9e** (0.82 g, 4.19 mmol) were reacted in MeOH (11 mL) according to general procedure E, and the crude product was purified using flash chromatography ($CHCl_3$ to 3% MeOH/$CHCl_3$) to yield yellow solid **10e** (0.62 g, 3.11 mmol,

74%): mp 93–94 °C ($CHCl_3$); R_f(3% MeOH/$CHCl_3$) = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (br s, 1H, –O<u>H</u>), 4.94 (s, 2H), 7.51 (ddd, *J* = 1.2, 6.8, 8.0 Hz, 1H), 7.60 (ddd, *J* = 1.2, 6.8, 8.0 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.77 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 56.2, 118.5, 120.2, 121.6, 121.7, 122.4, 123.7, 125.5, 126.6, 128.5, 131.7, 141.7, 151.4; IR (thin film) 3392 (br) cm^{-1}; GC/MS t_R = 11.3 min (198 $[M]^+$ *m/z*).

Benzo[*b*]thiophen-3-ylmethanol (10f)

Sodium borohydride (0.91 g, 24.00 mmol) and benzo[*b*]thiophene-3-carbaldehyde (**9f**) (3.89 g, 23.97 mmol) were reacted in MeOH (60 mL) according to general procedure E, and the crude product was purified using flash chromatography ($CHCl_3$ to 3% MeOH/$CHCl_3$) to yield pure yellow oil **10f** (3.88 g, 23.64 mmol, 98%); R_f(3% MeOH/$CHCl_3$) = 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (t, *J* = 5.6 Hz, 1H, –O<u>H</u>), 4.94 (d, *J* = 5.6 Hz, 2H), 7.35–7.43 (obs m, 2H), 7.39 (obs s, 1H), 7.86–7.89 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 59.9, 122.1, 123.1, 124.0, 124.4, 124.8, 136.1, 137.8, 140.9; IR (thin film) 3352 (br) cm^{-1}; GC/MS t_R = 8.6 min (164 $[M]^+$ *m/z*).

3-Chloromethylbenzofuran (11a)

11a was prepared from **10a** according to literature procedure[37] which was adapted below.

3-Chloromethyl-5-methoxybenzofuran (11b). General Procedure F

Thionyl chloride (0.21 g, 0.3 mL, 1.77 mmol) was added to a solution of **10b** (0.29 g, 1.61 mmol) in Et_2O (5 mL), and the mixture was stirred at room temperature for 3 h. After removal of solvents under vacuum, the residue was purified by flash chromatography (7:3 hexane/$CHCl_3$) to yield clear oil **11b** (0.24 g, 1.22 mmol, 76%); R_f(3% MeOH/$CHCl_3$) = 0.76; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.74 (s, 2H), 6.94 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.64 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 36.5, 56.2, 102.3, 112.5, 114.1, 117.8, 127.0, 144.1, 150.8, 156.4; GC/MS t_R = 8.5 min (196 $[M]^+$ *m/z*).

3-Chloromethyl-5-fluorobenzofuran (11c)

Thionyl chloride (0.33 g, 0.2 mL, 2.74 mmol) and **10c** (0.32 g, 1.94 mmol) were reacted in Et_2O (6 mL) according to general procedure F to yield pure solid **11c** (0.26 g, 1.40 mmol, 72%): mp 46–47 °C ($CHCl_3$); R_f(7:3 hexane/$CHCl_3$) = 0.56; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (s, 2H), 7.06 (dt, *J* = 2.8, 9.0 Hz, 1H), 7.35 (dd, *J* = 2.8, 8.4 Hz, 1H), 7.43 (dd, *J* = 4.4, 9.2 Hz, 1H), 7.70 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 36.0, 105.9 (d, *J* = 25.2 Hz), 112.7 (d, *J* = 9.3 Hz), 113.1 (d, *J* = 26.0 Hz), 118.1 (d, *J* = 4.2 Hz), 127.3 (d, *J* = 10.9 Hz), 145.0, 152.0, 159.5 (d, *J* = 237.8 Hz); ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −120.5 (dt, *J* = 3.9, 9.0 Hz); GC/MS t_R = 6.2 min (184 $[M]^+$ *m/z*).

1-Chloromethylnaphtho[2,1-*b*]furan (11d)

Thionyl chloride (0.11 g, 66 μL, 0.91 mmol) and **10d** (0.16 g, 0.83 mmol) were reacted in Et_2O (3 mL) according to general procedure F to yield pure solid **11d** (99 mg, 0.46 mmol, 55%): mp 97–99 °C ($CHCl_3$); R_f(7:3 hexane/$CHCl_3$) = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 2H), 7.54 (ddd, *J* = 1.2, 6.8, 8.0 Hz, 1H), 7.66 (obs d, *J* = 8.4 Hz, 1H), 7.66 (obs ddd, *J* = 1.2, 6.8, 8.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.82 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 37.9, 112.8, 119.5, 120.1, 124.0, 124.8, 126.7, 127.0, 128.0, 129.2, 131.0, 143.4, 154.1; GC/MS t_R = 11.0 min (216 $[M]^+$ *m/z*).

3-Chloromethylnaphtho[1,2-*b*]furan (11e)

Thionyl chloride (66 mg, 40 μL, 0.55 mmol) and **10e** (0.10 g, 0.50 mmol) were reacted in Et_2O (2 mL) according to general procedure F to yield pure solid **11e** (66 mg, 0.30 mmol, 60%): mp 92–93 °C ($CHCl_3$); R_f(7:3 hexane/$CHCl_3$): 0.47; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 2H), 7.53 (br t, *J* = 7.6 Hz, 1H), 7.62 (br t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 0.8 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.30 (dd, *J* = 0.8, 8.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 36.4, 118.2, 119.0, 120.2, 121.6, 122.1, 124.0, 125.7, 126.7, 128.6, 131.9, 142.4, 151.6; GC/MS t_R = 11.0 min (216 $[M]^+$ *m/z*).

3-(Chloromethyl)benzo[*b*]thiophene (11f)

Thionyl chloride (0.69 g, 420 μL, 5.76 mmol) and **10f** (0.60 g, 3.68 mmol) were reacted in Et_2O (11 mL) as above to yield crude oil **11f** that was used without further purification (0.47 g, 2.58 mmol, 60%); R_f(3% MeOH/$CHCl_3$) = 0.82; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, *J* = 0.8 Hz, 2H), 7.40 (dt, *J* = 1.2, 7.4 Hz, 1H), 7.46 (dt, *J* = 1.2, 7.4 Hz, 1H), 7.49 (s, 1H), 7.88 (obs dd, *J* = 1.2, 7.4 Hz, 1H), 7.90 (obs dd, *J* = 1.2, 8.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 39.8, 122.2, 123.2, 124.7, 125.1, 126.5, 132.1, 137.5, 140.8; GC/MS t_R = 8.3 min (182 $[M]^+$ *m/z*).

endo-8-Ethoxycarbonyl-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]-octan-3-ol (15)

15 was prepared from **13** according to literature procedure[29a] which was adapted below.

endo-8-Ethoxycarbonyl-3-(3,4-dichlorophenyl)-8-azabicyclo-[3.2.1]octan-3-ol (16). General Procedure G

n-Butyllithium (12 mL of 2.5 M in hexane, 30.05 mmol) was added over 10 min to a solution of 1-bromo-3,4-dichlorobenzene (6.79 g, 30.05 mmol) in THF (37 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C, then removed from the cold bath and stirred for an additional 30 min. The mixture was again cooled to −78 °C, and a solution of 8-ethoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one (**13**) (2.96 g, 15.03 mmol) in THF (37 mL) was added over 3 min. The mixture was stirred for 1 h at −78 °C and then quenched with saturated aqueous NH_4Cl (70 mL) at −78 °C and allowed to warm to ambient temperature. After concentration under vacuum, the biphasic mixture was extracted with Et_2O (50 mL) and the organic layer was isolated. The resulting aqueous layer was extracted with Et_2O (2 × 25 mL), and the organic layers were combined and evaporated to yield a yellow oil. This crude product was dissolved in MeOH (75 mL), and sodium borohydride (0.188 g, 4.96 mmol) was added to the solution. After 1 h of stirring at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) while stirring over 30 min. After removal of MeOH under vacuum, the biphasic mixture was partitioned between Et_2O (150 mL) and H_2O (100 mL). The aqueous layer was isolated and extracted further with Et_2O (2 × 25 mL). The organic layers were combined, dried with Na_2SO_4, concentrated, and purified using flash chromatography (silica gel; 5:1:1 hexane/$CHCl_3$/EtOAc to 2:1:1 hexane/$CHCl_3$/EtOAc) to yield glassy solid **16** (1.04 g, 3.03 mmol, 20%); R_f(2: 1:1 hexane/EtOAc/$CHCl_3$) = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H, $–CH_2C\underline{H}_3$), 1.82 (br d, *J* = 11.6 Hz, 2H), 1.91 (br d, *J* = 3.6 Hz, 2H), 2.19 (br m, 4H), 2.87 (s, 1H, O<u>H</u>), 4.11 (br m, 6.8 Hz, 2H, $–C\underline{H}_2CH_3$), 4.31 (br s, 2H), 7.13 (dd, 2.4, 8.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.9, 28.0, 44.3, 53.4, 61.3, 73.0, 124.4, 127.1, 130.2, 130.7, 132.4, 150.3, 154.1; IR (thin film) 1687, 3431 cm^{-1}; GC/MS t_R = 15.0 min (270 $[M – CO_2Et]^+$, 343 $[M]^+$ *m/z*).

endo-8-Ethoxycarbonyl-3-(2-methoxyphenyl)-8-azabicyclo-[3.2.1]octan-3-ol (17). General Procedure H

A solution of 2-bromoanisole (4.81 g, 25.71 mmol) in Et_2O (10 mL) was added in portions to magnesium turnings (2.50 g, 102.84 mmol), and iodine crystals (2 mg) were suspended in Et_2O (5 mL) while heating briefly with a warm H_2O bath, then subsequently refluxed under its own heat for 30 min. A solution of 8-ethoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one (**13**) (2.65 g, 13.44 mmol) in Et_2O (20 mL) was added dropwise to the stirring Grignard reagent over 30 min, and then the mixture was stirred for an additional 30 min at room temperature. After the mixture was cooled to 0 °C, the reaction was quenched with saturated ammonium chloride (25 mL) and extracted with Et_2O (4 × 50 mL). The combined organic solution was dried with Na_2SO_4 and evaporated. The resulting crude product was dissolved in MeOH (45 mL) and treated with sodium borohydride (0.18 g, 4.34 mmol) at room temperature for 1 h. After the reaction was quenched with saturated NH_4Cl (12 mL) for 1 h, the solvents were completely evaporated and the solids were partitioned between H_2O (200 mL) and Et_2O (200 mL). The organic layer was isolated, the aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined organic layer was dried with $NaSO_4$, filtered, and evaporated. Purification via flash chromatography (5:1:1 hexane/$CHCl_3$/EtOAc to 2:1:1 hexane/$CHCl_3$/EtOAc) yielded pure **17** (1.62 g, 5.28 mmol, 39%): mp 154–156 °C ($CHCl_3$); R_f(2:1:1 hexane/$CHCl_3$/EtOAc) = 0.26; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.78 (br t, *J* = 16.0 Hz, 2H), 1.98 (m, 2H), 2.32 (m, 2H), 2.55 (br d, *J* = 12.0 Hz, 1H), 2.75 (br d, *J* = 12.0 Hz, 1H), 2.88 (s, 1H, OH), 3.84 (s, 3H), 4.19 (m, *J* = 7.0 Hz, 2H), 4.30 (br s, 1H), 4.38 (br s, 1H), 6.88 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.94 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.23 (dt, *J* = 2.0, 7.6 Hz, 1H), 7.40 (dd, *J* = 2.0, 7.6 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 15.0, 28.1, 28.7, 41.0, 42.0, 53.4, 55.2, 60.8, 73.5, 111.6, 120.8, 125.2, 128.4, 136.5, 154.0, 156.2; IR (thin film) 1673, 3442 cm^{-1}; GC/MS t_R = 13.9 min (305 $[M]^+$ *m/z*).

endo-8-Ethoxycarbonyl-3-(2,3-dichlorophenyl)-8-azabicyclo[3.2.1]-octan-3-ol (18)

1-Bromo-2,3-dichlorobenzene (10.67 g, 47.23 mmol), magnesium turnings (4.59 g, 188.81 mmol), and **13** (4.66 g, 23.63 mmol) were reacted according to general procedure H; however, after the initial Et_2O extraction, the crude was pumped over high vacuum overnight to yield a white precipitate in the clear crude oil, which after careful rinsing with cold Et_2O yielded white crystalline **18** (1.56 g, 4.53 mmol, 19%): mp 195–197 °C (Et_2O); R_f(2:1:1 hexane/$CHCl_3$/EtOAc) = 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.56 (br t, *J* = 13.6 Hz, 2H), 1.90 (s, 1H, OH), 2.03 (br d, *J* = 4.8 Hz, 2H), 2.24 (br m, *J* = 8.0 Hz, 2H), 2.98 (dd, *J* = 4.0, 14.4 Hz, 1H), 3.10 (dd, *J* = 4.0, 14.4 Hz, 1H), 4.18 (dq, *J* = 1.2, 7.2 Hz, 2H), 4.38 (br s, 1H), 4.46 (br s, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.70 (dd, *J* = 1.0, 8.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 15.1, 28.2, 29.0, 41.1, 41.5, 52.8, 53.0, 61.2, 74.7, 125.3, 127.3, 129.5, 129.7, 135.1, 147.6, 154.0; IR (thin film) 1668, 3436 cm^{-1}; GC/MS t_R = 15.0 min (270 [M –CO_2Et^+], 343 $[M]^+$ *m/z*).

endo-8-Ethoxycarbonyl-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]-octan-3-ol (19)

4-Fluorophenylmagnesium bromide (50.7 mL of 1.0 M in THF, 50.70 mmol) and **13** (5.00 g, 25.35 mmol) were reacted according to general procedure H, yielding pure **19** (1.97 g, 6.71 mmol, 26%): mp 113–115 °C ($CHCl_3$); R_f(3:1:1 hexane/$CHCl_3$/EtOAc) = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = Hz, 3H), 1.68 (s, 1H, OH), 1.82 (br s, 1H), 1.86 (br s, 1H), 1.97 (br m, 2H), 2.23 (obs br m, 1H), H2.30 (br m, 2H), 2.42 (br d, *J* = 12 Hz, 1H), 4.17 (br q, *J* = 6.4 Hz, 2H), 4.36 (br s, 1H), 4.40 (br s, 1H), 6.99 (m, 2H), 7.35 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 15.0, 27.7, 28.4, 44.2, 45.1, 53.4, 61.1, 73.3, 115.0 (d, *J* = 21.0 Hz), 126.3 (d, *J* = 8.4 Hz), 145.6 (d, *J* = 3.3 Hz), 154.2, 161.8 (d, *J* = 244.5 Hz); ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −117.0 (m); IR (thin film) 1668, 3441 cm^{-1}; GC/MS t_R = 12.6 min (293 $[M]^+$ *m/z*).

endo-8-Ethoxycarbonyl-3-(4-bromophenyl)-8-azabicyclo[3.2.1]-octan-3-ol (20)

1,4-Dibromobenzene (15.04 g, 63.76 mmol), *n*-butyllithium (20.4 mL of 2.5 M in hexanes, 51.00 mmol), and **13** (5.03 g, 25.50 mmol) were reacted according to general procedure G, yielding pure **20** (4.99 g, 14.44 mmol, 57%): mp 126–128 °C ($CHCl_3$); R_f(3:1:1 hexane/$CHCl_3$/EtOAc) = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 6.8 Hz, 3H), 1.65 (s, 1H, OH), 1.81 (br s, 1H), 1.84 (br s, 1H), 1.98 (br m, 2H), 2.21 (br d, *J* = 12.8 Hz, 1H), 2.29 (br m, 2H), 2.42 (br d, *J* = 12.8 Hz, 1H), 4.17 (br q, *J* = 6.4 Hz, 2H), 4.36 (br s, 1H), 4.40 (br s, 1H), 7.26 (dt, *J* = 2.0, 9.0 Hz, 2H), 7.44 (dt, *J* = 2.0, 9.0 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 15.0, 27.8, 28.4, 44.1, 45.0, 53.4, 61.2, 73.5, 120.9, 126.5, 131.5, 148.8, 154.2; IR (thin film) 1667, 3436 cm^{-1}; GC/MS t_R = 14.4 min (353 $[M]^+$ *m/z*).

endo-8-Ethoxycarbonyl-3-(2-naphthyl)-8-azabicyclo[3.2.1]octan-3-ol (21)

2-Bromonaphthalene (3.01 g, 14.54 mmol), magnesium turnings (0.53 g, 21.73 mmol), and **13** (1.90 g, 9.66 mmol) were reacted according to general procedure H, yielding pure glassy **21** (0.64 g, 1.96 mmol, 20%); R_f(2:1:1 hexane/$CHCl_3$/EtOAc) = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.0 Hz, 3H), 1.82 (s, 1H, OH), 1.90 (br m, 2H), 2.01 (m, 2H), 2.36 (br s, 3H), 2.61 (d, *J* = 12.8 Hz, 1H), 4.20 (br m, *J* = 6.0 Hz, 2H), 4.40 (br s, 1H), 4.47 (br s, 1H), 7.43 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.47 (t, *J* = 5.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H) 7.81 (obs m, 2H), 7.88 (d, *J* = 2.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.9, 27.6, 28.3, 43.7, 44.8, 53.5, 61.1, 73.5, 122.6, 123.6, 125.9, 126.2, 127.5, 128.1, 128.2, 132.3, 133.0, 147.0, 154.1; IR (thin film) 1667, 3436 cm^{-1}; GC/MS t_R = 16.2 min (325 $[M]^+$ *m/z*).

endo-8-*tert*-Butoxycarbonyl-3-(4-methylthiophenyl)-8-azabicyclo[3.2.1]octan-3-ol (22)

4-Bromothioanisole (6.00 g, 29.55 mmol), *n*-butyllithium (11.8 mL of 2.5 M in hexanes, 29.5 mmol), and *N*-*tert*-butoxycarbonylnortropinone (**14**) (3.33 g, 14.77 mmol) were reacted according to general procedure G, yielding pure **22** (1.77 g, 5.05 mmol, 34%): mp 119–121 °C ($CHCl_3$); R_f(6:1:1 hexane/$CHCl_3$/EtOAc) = 0.16; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.44 (s, 9H), 1.73 (br t, *J* = 14.0 Hz, 2H), 1.83 (br s, 2H), 2.02 (br d, *J* = 13.0 Hz, 1H), 2.14 (br d, *J* = 13.0 Hz, 1H), 2.25 (br s, 2H), 2.44 (s, 3H), 4.10 (s, 2H), 5.03 (s, 1H, OH), 7.20 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H); ^{13}C (100 MHz, DMSO-d_6) δ 14.9, 27.1, 27.7, 28.2, 42.6, 44.0, 52.9, 53.6, 71.8, 78.4, 125.2, 125.7, 135.5, 147.9, 153.0; IR (thin film) 1668, 3445 cm^{-1}; GC/MS t_R = 15.3 min (349 $[M]^+$ *m/z*).

endo-3-(4-Chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (23)

23 was prepared from **15** according to literature procedure[29b] which was adapted below.

endo-3-(3,4-Dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (24). General Procedure I

A solution of **16** (1.04 g, 3.02 mmol) in EtOH (10 mL) was heated to reflux with 50% aqueous KOH (10 mL, wt/wt) and hydrazine (6 mL) for 16 h. The mixture was cooled and evaporated, and the resulting white paste was suspended in H_2O (10 mL) and then filtered over a (M) frit. The white solid was triturated with $CHCl_3$ (5 mL) to yield pure **24** (0.70 g, 2.57 mmol, 85%): mp 190–192 °C ($CHCl_3$); R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.05; ^{1}H NMR (400 MHz, CD_3OD) δ 1.81 (obs m, 4H), 2.15 (dd, *J* = 3.6, 14.8 Hz, 2H), 2.33 (dd, *J* = 6.4, 13.6 Hz, 2H), 3.57 (br s, 2H), 7.43 (m, 2H), 7.69 (d, *J* = 1.6 Hz, 1H); ^{13}C (100 MHz, CD_3OD) δ 29.5, 46.3, 55.3, 73.6, 126.2, 128.4, 130.9, 131.0, 132.8, 153.3; IR (thin film) 3245 (br) cm^{-1}; GC/MS t_R = 13.1 min (271 $[M]^+$ *m/z*).

endo-3-(2-Methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol (25)

Compound **17** (1.52 g, 4.99 mmol) in EtOH (10 mL), 50% aqueous KOH (10 mL, wt/wt), and hydrazine (6 mL) were reacted according to general procedure I, yielding a glassy solid

25 (0.76 g, 3.24 mmol, 65%); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.23; ^{1}H NMR (400 MHz, CD_3OD) δ 1.64 (dd, *J* = 1.6, 16.0 Hz, 2H), 1.84 (m, 2H), 2.28 (m, *J* = 7.2 Hz, 2H), 2.59 (dd, *J* = 4.0, 14.4 Hz, 2H), 3.55 (br s, 2H), 3.88 (s, 3H), 6.91 (dt, 1.0, 8.0 Hz, 1H), 6.94 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.20 (ddd, *J* = 2.0, 7.2, 8.0 Hz, 1H), 7.49 (dd, *J* = 2.0, 7.6 Hz, 1H); ^{13}C (100 MHz, CD_3OD) δ 27.8, 41.7, 55.6, 56.0, 72.3, 112.5, 121.5, 126.9, 129.7, 136.9, 157.0; IR (thin film) 3392 (br) cm^{-1}; GC/MS t_R = 11.8 min (233 $[M]^+$ *m/z*).

endo-3-(2,3-Dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (26)

Compound **18** (1.14 g, 3.30 mmol) in EtOH (10 mL), 50% aqueous KOH (10 mL, wt/wt), and hydrazine (6 mL) were reacted according to general procedure I, yielding pure **26** (0.64 g, 2.36 mmol, 72%): mp 190–192 °C ($CHCl_3$); R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.05; ^{1}H NMR (400 MHz, CD_3OD) δ 1.81 (obs m, 4H), 2.15 (dd, *J* = 3.6, 14.8 Hz, 2H), 2.33 (dd, *J* = 6.4, 13.6 Hz, 2H), 3.57 (br s, 2H), 7.43 (m, 2H), 7.69 (d, *J* = 1.6 Hz, 1H); ^{13}C (100 MHz, CD_3OD) δ 29.2, 42.2, 55.1, 74.3, 127.3, 128.4, 129.9, 130.4, 135.5, 150.0; IR (thin film) 3307 (br) cm^{-1}; GC/MS t_R = 13.0 min (271 $[M]^+$ *m/z*).

endo-3-(4-Fluorophenyl)-8-azabicyclo[3.2.1]octan-3-ol(27)

Compound **19** (1.87 g, 6.39 mmol) in EtOH (15 mL), 50% aqueous KOH (15 mL, wt/wt), and hydrazine (9 mL) were reacted according to general procedure I. The crude solid was recrystallized from MeOH to yield pure **27** (0.84 g, 3.79 mmol, 59%): mp 171–174 °C ($CHCl_3$); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.14; ^{1}H NMR (400 MHz, CD_3OD) 1.79 (obs m, *J* = 3.2 Hz, 2H), 1.83 (obs d, *J* = 14.4 Hz, 2H), 2.18 (dd, *J* = 3.6, 14.8 Hz, 2H), 2.34 (m, 2H), 3.56 (br s, 2H), 7.00 (tt, *J* = 2.5, 8.4 Hz, 2H), 7.50 (ddt, *J* = 2.5, 5.6, 8.4 Hz, 2H); ^{13}C (100 MHz, CD_3OD) δ 29.6, 46.6, 55.4, 73.8, 115.3 (d, *J* = 21.9 Hz), 127.8 (d, *J* = 7.5 Hz), 148.1 (d, *J* = 2.5 Hz), 162.8 (d, *J* = 242.0 Hz); ^{19}F (376 MHz, $CD_3OD/CFCl_3$) δ −118.1 (m); IR (thin film) 3271 (br) cm^{-1}; GC/MS t_R = 10.2 min (221 $[M]^+$ *m/z*).

endo-3-(4-Bromophenyl)-8-azabicyclo[3.2.1]octan-3-ol (28)

Compound **20** (4.89 g, 13.80 mmol) in EtOH (45 mL), 50% aqueous KOH (45 mL, wt/wt), and hydrazine (27 mL) were reacted according to general procedure I, yielding pure **28** that quickly turned red in air (2.49 g, 8.81 mmol, 64%): mp 220–224 °C (dec) ($CHCl_3$); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.12; ^{1}H NMR (400 MHz, CD_3OD) δ 1.80 (obs t, *J* = 3.2 Hz, 2H), 1.83 (obs d, *J* = 14.4 Hz, 2H), 2.17 (dd, *J* = 3.6, 14.4 Hz, 2H), 2.34 (m, 2H), 3.58 (br s, 2H), 7.42 (s, 4H); ^{13}C (100 MHz, CD_3OD) δ 29.5, 46.2, 55.4, 73.8, 121.1, 128.1, 131.9, 151.4; IR (thin film) 3232 (br) cm^{-1}; GC/MS t_R = 12.5 min (281 $[M]^+$ *m/z*).

endo-3-(2-Naphthyl)-8-azabicyclo[3.2.1]octan-3-ol (29)

Compound **21** (0.64 g, 1.96 mmol) in EtOH (5 mL), 50% aqueous KOH (5 mL, wt/wt), and hydrazine (3 mL) were reacted according to general procedure I, yielding glassy solid **29** (0.23 g, 0.94 mmol, 48%); R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.11; ^{1}H NMR (400 MHz, CD_3OD) δ 1.85 (m, 2H), 1.92 (d, *J* = 14.8 Hz, 2H), 2.36 (dd, *J* = 3.6, 14.8 Hz, 2H), 2.42 (m, *J* = 3.2, 7.6 Hz, 2H), 3.66 (br s, 2H), 7.42 (dt, *J* = 2.0, 6.8, 10.8 Hz, 1H), 7.45 (dt, *J* = 2.0, 6.8, 10.8 Hz, 1H), 7.63 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.79 (s, 1H), 7.81 (obs s, 1H), 7.83 (obs dd, *J* = 2.0, 8.8 Hz, 1H), 7.96 (d, *J* = 1.6 Hz, 1H); ^{13}C (100 MHz, CD_3OD) δ 28.3, 44.6, 56.0, 73.2, 124.0, 124.7, 126.9, 127.1, 128.4, 128.9, 129.2, 133.8, 134.6, 148.1; IR (thin film) 3356 (br) cm^{-1}; GC/MS t_R = 14.4 min (253 $[M]^+$ *m/z*).

endo-3-(4-Methylthiophenyl)-8-azabicyclo[3.2.1]octan-3-ol (30)

Finely crushed **22** (0.31 g, 0.89 mmol) was heated (300 W max) without solvent to 185 °C and 275 psi (pressure max) in a microwave reaction tube for 5 min (hold time) and then cooled to room temperature; however, because of increased pressure, the tube was cooled in

dry ice prior to release from pressure lock. The crude residue was triturated with CH_2Cl_2 (2 mL) and the resulting solid precipitate was collected and rinsed with 0 °C CH_2Cl_2 (2 × 2 mL), yielding tan solid **30** (0.14 g, 0.56 mmol, 63%): mp 148–150 °C (CH_2Cl_2); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.18; ^{1}H NMR (400 MHz, CD_3OD) δ 1.80 (obs m, 2H), 1.82 (obs d, *J* = 14.4 Hz, 2H), 2.18 (dd, *J* = 3.4, 15.0 Hz, 2H), 2.34 (m, *J* = 6.2, 13.4 Hz, 2H), 2.44 (s, 3H), 3.56 (br s, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H); ^{13}C (100 MHz, CD_3OD) δ 15.9, 29.6, 46.4, 55.4, 73.8, 126.5, 127.4, 137.6, 149.1; IR (thin film) 1396, 2933, 3266 cm^{-1}; GC/MS t_R = 13.4 min (249 $[M]^+$ *m/z*).

endo-8-(1*H*-Indol-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo-[3.2.1]octan-3-ol (31). General Procedure J

Gramine (0.14 g, 0.80 mmol) was added to a solution of **23** (0.21 g, 0.88 mmol) in pyridine (9 mL), and the mixture was heated to reflux for 16 h. After the mixture was cooled to room temperature, the solvent was evaporated to yield a brown oil, which was purified using flash chromatography (3% MeOH/$CHCl_3$ + 1% NH_4OH to 10% MeOH/$CHCl_3$ + 1% NH_4OH) to yield off-white foam **31** (0.17 g, 0.46 mmol, 58%): mp 72–74 °C (CH_2Cl_2); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.32; R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.07; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (d, *J* = 14.0 Hz, 2H), 1.87 (br s, 1H, –O<u>H</u>), 2.12 (m, 2H), 2.22 (m, 2H), 2.32 (dd, *J* = 3.6, 14.4 Hz, 2H), 3.39 (br s, 2H), 3.78 (s, 2H), 7.14 (obs br d, *J* = 0.8 Hz, 1 H), 7.14 (obs td, *J* = 1.2, 7.4 Hz, 1 H), 7.20 (td, *J* = 1.2, 6.8 Hz, 1 H), 7.26 (dt, *J* = 2.3, 9.2 Hz, 2 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.84 (d, *J* = 7.6 Hz, 1 H), 8.13 (br s, 1H, –N<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 47.0, 48.6, 58.9, 73.7, 111.3, 115.1, 119.5, 120.0, 122.2, 123.0, 126.4, 127.9, 128.4, 132.5, 136.7, 149.3; IR (thin film) 3410, 3540 cm^{-1}.

Oxalate Salt Formation. General Procedure K

A solution of oxalic acid (46 mg, 0.51 mmol) in acetone (0.5 mL) was added dropwise to a solution of **31** (0.17 g, 0.46 mmol) in EtOH (0.5 mL), and a white solid precipitated. The solid was washed with cold acetone (0 °C, 3 × 1 mL) and dried over high vacuum to yield fine white crystals (94 mg, 0.18 mmol; 39%): mp 131–134 °C dec (EtOH). Anal. ($C_{22}H_{23}ClN_2O \cdot (COOH)_2 \cdot 1.5CH_3CH_2OH$) C, H, N.

endo-8-(1*H*-Indol-3-ylmethyl)-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (32)

Gramine (0.23 g, 1.30 mmol) and **24** (0.37 g, 1.36 mmol) in pyridine (13 mL) were reacted according to general procedure J, yielding pure **32** (0.19 g, 0.48 mmol, 37%): R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.54; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 1H, –O<u>H</u>), 1.76 (d, *J* = 14.0 Hz, 2H), 2.13 (m, 2H), 2.23 (m, 2H), 2.35 (br d, *J* = 12.8 Hz, 2H), 3.43 (br s, 2H), 3.82 (s, 2H), 7.15 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H), 7.21 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.23 (obs br s, 1H), 7.30–7.33 (m, 1H), 7.36 (obs d, *J* = 8.4 Hz, 1H), 7.37 (obs d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 8.22 (br s, 1H, –N<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 29.9, 46.6, 48.4, 58.9, 73.3, 111.4, 119.6, 119.7, 122.2, 123.6, 124.6, 127.3, 127.8, 130.2, 130.5, 132.3, 136.5, 150.9; IR (thin film) 3419, 3468 cm^{-1}. The product was converted to the oxalate salt using general procedure K (105 mg, 0.20 mmol, 42%): mp 166–170 °C dec (EtOH). Anal. ($C_{22}H_{22}Cl_2N_2O \cdot 0.5(COOH)_2 \cdot 1.5CH_3CH_2OH \cdot 0.25H_2O$) C, H, N.

endo-8-(1*H*-Indol-3-ylmethyl)-3-(2,3-dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (33)

Gramine (59 mg, 0.34 mmol) and **26** (102 mg, 0.37 mmol) in pyridine (4 mL) were reacted according to general procedure J, then purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% MeOH) to yield pure solid **33** (0.62 g, 0.16 mmol, 42%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (d, *J* = 13.6 Hz, 2H), 2.05 (br s, 1H, –

OH), 2.12 (m, 2H), 2.20 (m, 2H), 2.93 (dd, *J* = 4.0, 14.4 Hz, 2H), 3.44 (br s, 2H), 3.77 (s, 2H), 7.17 (m, 4H), 7.36 (obs d, *J* = 7.6 Hz, 1H), 7.39 (obs dd, *J* = 1.6, 8.4 Hz, 1H), 7.64 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 8.10 (s, 1H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 43.6, 49.1, 59.2, 74.9, 111.2, 115.1, 119.4, 120.2, 122.2, 123.0, 125.4, 127.2, 127.8, 129.4, 129.8, 135.0, 136.7, 148.2; IR (thin film) 3413, 3544 cm^{-1}. The product was converted to the oxalate salt using general procedure K (52 mg, 0.10 mmol, 63%): mp 175–179 °C dec (EtOH). Anal. ($C_{22}H_{22}Cl_2N_2O \cdot (COOH)_2 \cdot 0.5CH_3CH_2OH$) C, H, N.

endo-8-(1*H*-Indol-3-ylmethyl)-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (34)

Gramine (97 mg, 0.56 mmol) and **27** (0.15 g, 0.70 mmol) in pyridine (6 mL) were reacted according to general procedure J to yield pure **34** (0.11 g, 0.32 mmol, 57%); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.15; ^{1}H NMR (400 MHz, CD_3OH) δ 1.82 (d, *J* = 14.4 Hz, 2H), 2.19 (m, 2H), 2.25 (dd, *J* = 3.6, 14.8 Hz, 2H), 2.38 (m, *J* = 13.6 Hz, 2H), 3.46 (br s, 2H), 3.81 (s, 2H), 6.97 (m, *J* = 8.8 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.31 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.54 (m, *J* = 2.0 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OH) δ 26.3, 46.5, 48.1, 60.4, 73.6, 112.3, 112.4, 115.3 (d, *J* = 21.1 Hz), 119.4, 120.0, 122.4, 125.8, 127.8 (d, *J* = 7.5 Hz), 129.2, 137.8, 147.9 (d, *J* = 2.5 Hz), 162.8 (d, *J* = 241.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$) δ −118.0 (m); IR (thin film) 3292, 3407 cm^{-1}. The product was converted to the oxalate salt using general procedure K (79 mg, 0.16 mmol, 51%): mp 162–165 °C dec (acetone). Anal. ($C_{22}H_{23}FN_2O \cdot 0.66(COOH)_2 \cdot H_2O \cdot (CH_3)_2$-CO) C, H, N.

endo-8-(1*H*-Indol-3-ylmethyl)-3-(2-naphthyl)-8-azabicyclo[3.2.1]octan-3-ol (35)

Gramine (0.16 g, 0.91 mmol) and **29** (0.24 g, 0.94 mmol) in pyridine (9 mL) were reacted according to general procedure J, yielding pure **35** (0.25 g, 0.65 mmol, 71%); R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 1H, –OH), 1.85 (d, *J* = 14.0 Hz, 2H), 2.15 (m, 2H), 2.31 (m, 2H), 2.56 (br d, *J* = 13.2 Hz, 2H), 3.47 (br s, 2H), 3.87 (s, 2H), 7.17 (dt, *J* = 1.0, 7.0 Hz, 1H), 7.22 (dt, *J* = 1.0, 7.0 Hz, 1H), 7.26 (obs br s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.46 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.81 (obs m, 1H), 7.81 (obs s, 1H), 7.83 (obs s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 1.6 Hz, 1H), 8.14 (br s, 1H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 46.3, 48.3, 59.0, 73.8, 111.4, 114.0, 119.5, 119.7, 122.1, 122.6, 123.6, 124.1, 125.9, 126.2, 127.5, 127.9, 128.1, 128.4, 132.3, 133.1, 136.5, 147.7; IR (thin film) 3297, 3417 cm^{-1}. The product was converted to the oxalate salt using general procedure K except using *i*-PrOH as solvent (0.16 g, 0.32 mmol, 50%): mp 145–149 °C dec (*i*-PrOH). Anal. ($C_{26}H_{26}N_2O \cdot (COOH)_2 \cdot 0.75H_2O$) C, H, N.

endo-8-(1*H*-Indol-3-ylmethyl)-3-(2-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol (36)

Gramine (0.91 g, 5.25 mmol) and **25** (1.29 g, 5.53 mmol) in pyridine (55 mL) were reacted according to general procedure J, except the chromatographed material was triturated with $CHCl_3$ (5 mL) to yield white solid **36** (0.21 g, 0.58 mmol, 11%): R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.46; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (d, *J* = 12.8 Hz, 2H), 1.90 (br m, 2H), 2.19 (m, 2H), 2.61 (br dd, *J* = 3.4, 13.4 Hz, 2H), 3.18 (br s, 2H), 3.75 (s, 2H), 3.87 (s, 3H), 4.52 (s, 1H, –OH), 6.89 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.94 (dd, *J* = 0.8, 8.0 Hz, 1H), 6.99 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.06 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.17 (obs dt, *J* = 2.0, 8.0 Hz, 1H), 7.20 (obs d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 2.0, 7.6 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 10.79 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.0, 41.6, 47.8, 55.0, 58.0, 71.9, 111.3, 111.4, 113.6, 118.0, 119.8, 120.0, 120.9, 123.4, 126.7, 127.5, 127.6, 136.6, 138.4, 155.8; IR (thin film) 3438 cm^{-1}. Because of low solubility, the oxalate salt could not be generated: mp 209–212 °C ($CHCl_3$). Anal. ($C_{23}H_{26}N_2O_2 \cdot 0.5H_2O$) C, H, N.

endo-8-(1*H*-Indol-3-ylmethyl)-3-(4-(methylthio)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (37)

Gramine (92 mg, 0.53 mmol) and **30** (0.15 g, 0.59 mmol) in pyridine (6 mL) were reacted according to general procedure J and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH) to yield pure **37** (0.13 g, 0.34 mmol, 64%); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.26; ^{1}H NMR (400 MHz, CD_3OD) δ 1.82 (d, *J* = 14.4 Hz, 2H), 2.21 (br m, 2H), 2.26 (br dd, *J* = 3.2, 14.8 Hz, 2H), 2.39 (m, 2H), 2.42 (s, 3H, –SC<u>H</u>$_3$), 3.49 (br s, 2H), 3.85 (s, 2H), 7.05 (dt, *J* = 0.8, 7.2 Hz, 1H), 7.11 (dt, *J* = 0.8, 7.2 Hz, 1H), 7.18 (dt, *J* = 1.4, 8.0 Hz, 2H), 7.33 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.46 (dt, *J* = 2.0, 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 15.9, 26.3, 46.3, 48.1, 60.5, 73.6, 112.2, 112.3, 119.4, 120.0, 122.4, 125.9, 126.5, 127.3, 129.2, 137.6, 137.8, 148.9; IR (thin film) 3391 (br) cm^{-1}. The product was converted to the oxalate salt using general procedure K except using *i*-PrOH as solvent (0.11 g, 0.23 mmol, 70%): mp 135–143 °C dec (*i*-PrOH); Anal. ($C_{23}H_{26}N_2OS \cdot (COOH)_2 \cdot 0.5CH_3OH$) C, H, N.

endo-8-(1*H*-Indazol-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (38)

3-(Dimethylaminomethyl)indazole[43] (0.20 g, 1.13 mmol) and **23** (0.30 g, 1.26 mmol) in pyridine (3 mL) were reacted according to general procedure J, yielding pure **38** (0.27 g, 0.73 mmol, 64%): mp 90–95 °C ($CHCl_3$); R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.30; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.71 (d, *J* = 13.2 Hz, 2H), 1.97 (m, 2H), 2.06 (br dd, *J* = 2.8, 14.0 Hz, 2H), 2.34 (m, 2H), 3.25 (br s, 2H), 3.91 (s, 2H), 4.83 (s, 1H, –O<u>H</u>), 7.10 (t, *J* = 7.2 Hz, 1H), 7.32 (obs dt, *J* = 0.8, 8.4 Hz, 1H), 7.33 (obs d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 12.75 (s, 1H, –N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.5, 45.1, 49.4, 58.5, 71.5, 110.1, 119.6, 121.1, 122.0, 125.9, 126.8, 127.6, 130.5, 141.1, 143.8, 150.8; IR (thin film) 3227 (br) cm^{-1}. The product was converted to the oxalate salt using general procedure K (0.17 g, 0.36 mmol, 49%): mp 171–174 °C (EtOH). Anal. ($C_{21}H_{22}$-$ClN_3O \cdot (COOH)_2 \cdot 0.25H_2O$) C, H, N.

endo-8-(5-Methoxy-1*H*-indol-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (39)

5-Methoxygramine (79 mg, 0.38 mmol) and **23** (96 mg, 0.40 mmol) in pyridine (4 mL) were reacted according to general procedure J and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH) to yield pure solid **39** (0.10 g, 0.25 mmol, 66%); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (br s, 1H, –O<u>H</u>), 1.77 (d, *J* = 14.0 Hz, 2H), 2.11 (br m, 2H), 2.25 (br m, 2H), 2.38 (br d, *J* = 13.6 Hz, 2H), 3.41 (br s, 2H), 3.79 (s, 2H), 3.87 (s, 3H), 6.86 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.18 (br s, 1H), 7.24 (obs d, *J* = 8.8 Hz, 2H), 7.26 (obs d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 8.10 (br s, 1H, –N<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 46.9, 48.7, 56.1, 58.9, 73.6, 101.9, 112.0, 112.4, 112.5, 124.1, 126.4, 128.3, 128.4, 131.8, 132.5, 149.1, 154.1; IR (thin film) 3307 (br) cm^{-1}. The product was converted to the oxalate salt using general procedure K (81 mg, 0.15 mmol, 60%): mp 134–140 °C dec (EtOH). Anal. ($C_{23}H_{25}ClN_2O_2 \cdot (COOH)_2 \cdot CH_3CH_2OH$) C, H, N.

endo-8-(5-Methoxy-1*H*-indol-3-ylmethyl)-3-(4-methylthiophenyl)-8-azabicyclo[3.2.1]octan-3-ol (40)

5-Methoxygramine (0.10 g, 0.49 mmol) and **30** (0.14 g, 0.55 mmol) in pyridine (5 mL) were reacted according to general procedure J and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH) to yield pure solid **40** (0.14 g, 0.35 mmol, 71%); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.19; ^{1}H NMR (400 MHz, CD_3OD) δ 1.82 (d, *J* = 14.0 Hz, 2H), 2.20 (br m, 2H), 2.27 (br dd, *J* = 3.2, 14.8 Hz, 2H), 2.38 (m, 2H), 2.43 (s, 3H, –SC<u>H</u>$_3$), 3.47 (br s, 2H), 3.81 (s, 2H), 3.83 (s, 3H, –OC<u>H</u>$_3$), 6.77 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.28 (s, 1H), 7.45 (d, *J* = 8.4 Hz,

2H); ^{13}C NMR (100 MHz, CD_3OD) δ 15.9, 26.4, 46.2, 48.1, 56.2, 60.2, 73.7, 101.6, 112.2, 112.7, 113.0, 126.5, 126.5, 127.3, 129.5, 133.1, 137.6, 149.0, 155.1; IR (thin film) 3306 (br) cm^{-1}. The product was converted to the oxalate salt using general procedure K except using *i*-PrOH as solvent (0.15 g, 0.30 mmol, 84%): mp 130–137 °C dec (*i*-PrOH/acetone). Anal. ($C_{24}H_{28}N_2O_2S \cdot (COOH)_2 \cdot 0.5H_2O \cdot 0.25(CH_3)_2CO$) C, H, N.

endo-8-(Benzothien-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (41). General Procedure L

A solution of **11f** (76 mg, 0.42 mmol), **23** (90 mg, 0.38 mmol), and sodium bicarbonate (0.10 g, 1.23 mmol) in acetonitrile (1 mL) was refluxed for 16 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (3 mL) and the entire solution was filtered over a (M) fritted filter. The solids were rinsed with CH_2Cl_2 (3 × 1 mL), the filtrate was evaporated, and the resulting residue was purified by preparative TLC (3% MeOH/$CHCl_3$ + 1% NH_4OH), yielding the glass **41** (0.11 g, 0.28 mmol, 74%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 1H, –OH), 1.80 (d, *J* = 13.6 Hz, 2H), 2.10 (br m, 2H), 2.26 (m, 2H), 2.34 (dd, *J* = 3.6, 14.4 Hz, 2H), 3.38 (br s, 2H), 3.83 (s, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.35 (obs s, 1H), 7.38 (obs dt, *J* = 1.2, 7.2 Hz, 1H), 7.42 (obs d, *J* = 8.8 Hz, 2H), 7.42 (obs dt, *J* = 1.2, 7.2 Hz, 1H), 7.88 (dd, *J* = 1.2, 7.2 Hz, 1H), 8.07 (dd, *J* = 1.2, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 47.0, 51.8, 59.3, 73.4, 122.9, 123.2, 123.9, 124.4, 126.3, 128.3, 132.4, 135.2, 139.0, 141.0, 149.1; IR (thin film) 3355 cm^{-1}; GC/MS t_R = 17.7 min (365 $[M - H_2O]^+$ *m/z*), 18.8 min (383 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K and was recrystallized from acetone (50 mg, 0.11 mmol, 39%): mp 219–221 °C (acetone). Anal. ($C_{22}H_{22}ClNOS \cdot 0.5(COOH)_2 \cdot 0.75H_2O$) C, H, N.

endo-8-(Benzothien-3-ylmethyl)-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (42)

Compound **11f** (77 mg, 0.42 mmol), **24** (100 mg, 0.37 mmol), and sodium bicarbonate (92 mg, 1.09 mmol) in acetonitrile (1 mL) were reacted according to procedure L and purified using preparative TLC (3% MeOH/$CHCl_3$ + 1% NH_4OH), yielding solid **42** (0.12 g, 0.28 mmol, 76%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.75; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 1H, –OH), 1.79 (d, *J* = 14.0 Hz, 2H), 2.10 (m, 2H), 2.24 (m, 2H), 2.31 (br d, *J* = 13.2 Hz, 2H), 3.38 (br s, 2H), 3.83 (s, 2H), 7.28–7.43 (obs m, 5H), 7.59 (d, *J* = 1.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 47.1, 51.9, 59.3, 73.4, 123.0, 123.0, 123.4, 124.0, 124.5, 124.5, 127.3, 130.3, 130.7, 132.4, 135.0, 139.0, 141.0, 151.0; IR (thin film) 3436 cm^{-1}; GC/MS t_R = 22.0 min (417 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (92 mg, 0.18 mmol, 64%): mp 231–233 °C dec (EtOH). Anal. ($C_{22}H_{21}Cl_2NOS \cdot (COOH)_2$) C, H, N.

endo-8-(Benzothien-3-ylmethyl)-3-(2,3-dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (43)

Compound **11f** (78 mg, 0.43 mmol), **26** (102 mg, 0.37 mmol), and sodium bicarbonate (94 mg, 1.12 mmol) in acetonitrile (1 mL) were reacted according to procedure L and purified using preparative TLC (3% MeOH/$CHCl_3$ + 1% NH_4OH), yielding solid **43** (88 mg, 0.21 mmol, 57%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.77; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, *J* = 14.4 Hz, 2H), 1.81 (s, 1H, –OH), 2.10 (m, 2H), 2.17 (m, 2H), 2.95 (dd, *J* = 4.0, 14.4 Hz, 2H), 3.38 (br s, 2H), 3.77 (s, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.32–7.39 (obs m, 4H), 7.65 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 43.9, 52.5, 59.6, 74.8, 122.8, 123.2, 123.4, 123.9, 124.5, 125.5, 127.2, 129.5, 129.7, 135.0, 135.5, 139.0, 141.0, 148.3; IR (thin film) 3451, 3563 cm^{-1}; GC/MS t_R = 22.0 min (417 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (90 mg, 0.18 mmol, 84%): mp 195–198 °C dec (EtOH). Anal. ($C_{22}H_{21}Cl_2NOS \cdot (COOH)_2$) C, H, N.

endo-8-(Benzofur-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (44)

Compound **11a** (75 mg, 0.45 mmol), **23** (0.12 g, 0.50 mmol), and sodium bicarbonate (0.11 g, 1.35 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (3% MeOH/$CHCl_3$ + 1% NH_4OH), yielding glass **44** (0.15 g, 0.41 mmol, 91%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.72; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 1H, –OH), 1.79 (d, *J* = 14.0 Hz, 2H), 2.07 (m, 2H), 2.24 (m, 2H), 2.32 (dd, *J* = 3.2, 14.4 Hz, 2H), 3.37 (br s, 2H), 3.70 (s, 2H), 7.26 (obs dt, *J* = 1.0, 7.2 Hz, 1H), 7.29 (obs d, *J* = 8.4 Hz, 2H), 7.31 (obs dt, *J* = 1.6, 7.6 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.56 (s, 2H), 7.81 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 46.9, 47.3, 59.1, 73.4, 111.6, 119.4, 121.0, 122.5, 124.4, 126.3, 128.2, 128.4, 132.5, 142.5, 149.1, 155.8; IR (thin film) 3434 cm^{-1}; GC/MS t_R = 16.9 min (349 $[M]^+$ – H_2O *m/z*), 17.9 min (367 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (0.13 g, 0.29 mmol, 71%): mp 223–225 °C (EtOH). Anal. ($C_{22}H_{22}ClNO_2 \cdot (COOH)_2$) C, H, N.

endo-8-(Benzofur-3-ylmethyl)-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (45)

Compound **11a** (30 mg, 0.18 mmol), **24** (54 mg, 0.20 mmol), and sodium bicarbonate (50 mg, 0.60 mmol) in acetonitrile (0.5 mL) were reacted according to general procedure L and purified using preparative TLC (3% MeOH/$CHCl_3$ + 1% NH_4OH), yielding solid **45** (56 mg, 0.14 mmol, 78%); R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.64; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 1H, –OH), 1.77 (d, *J* = 14.0 Hz, 2H), 2.07 (m, 2H), 2.22 (br m, 2H), 2.29 (br d, *J* = 13.2 Hz, 2H), 3.37 (br s, 2H), 3.70 (s, 2H), 7.25–7.33 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.56 (obs s, 1H), 7.58 (obs d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 1.6, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 47.0, 47.4, 59.1, 73.3, 111.6, 119.3, 120.9, 122.6, 124.5, 124.5, 127.3, 128.2, 130.3, 130.7, 132.4, 142.6, 151.0, 155.8; IR (thin film) 3460, 3564 cm^{-1}; GC/MS t_R = 19.2 min (401 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (52 mg, 0.11 mmol, 79%): mp 210–211 °C dec (EtOH). Anal. ($C_{22}H_{21}Cl_2NO_2 \cdot (COOH)_2$) C, H, N.

endo-8-(Benzofur-3-ylmethyl)-3-(2,3-dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (46)

Compound **11a** (55 mg, 0.33 mmol), **26** (101 mg, 0.37 mmol), and sodium bicarbonate (93 mg, 1.11 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (2% MeOH/$CHCl_3$ + 1% NH_4OH), yielding solid **46** (62 mg, 0.15 mmol, 45%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.69; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, *J* = 14.0 Hz, 2H), 1.95 (s, 1H, –OH), 2.09 (m, 2H), 2.21 (m, 2H), 2.94 (dd, *J* = 4.0, 14.0 Hz, 2H), 3.42 (br s, 2H), 3.67 (s, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.27 (obs dt, *J* = 1.2, 7.6 Hz, 1H), 7.31 (obs dt, *J* = 1.6, 7.2 Hz, 1H), 7.39 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.48 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.57 (s, 1H), 7.67 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.85 (dd, *J* = 1.6, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 43.6, 47.8, 59.4, 74.8, 111.5, 119.7, 121.3, 122.4, 124.4, 125.5, 127.2, 128.1, 129.5, 129.7, 135.0, 142.5, 148.2, 155.9; IR (thin film) 3458, 3559 cm^{-1}; GC/MS t_R = 19.4 min (401 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (61 mg, 0.12 mmol, 80%): mp 201–204 °C dec (EtOH). Anal. ($C_{22}H_{21}Cl_2NO_2 \cdot (COOH)_2$) C, H, N.

endo-8-(Benzofur-3-ylmethyl)-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (47)

Compound **11a** (0.11 g, 0.66 mmol), **27** (0.16 g, 0.72 mmol), and sodium bicarbonate (0.18 g, 2.16 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH), yielding glass **47** (0.16 g, 0.46 mmol, 70%); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.67; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 1H, –OH), 1.81 (d, *J* = 14.0 Hz, 2H), 2.07 (m, 2H), 2.25 (br m, 2H), 2.34 (dd, *J* = 2.8, 14.0 Hz, 2H), 3.38 (br s, 2H), 3.71 (s, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 7.26 (obs

dt, *J* = 1.0, 7.4 Hz, 1H), 7.31 (obs dt, *J* = 1.0, 7.4 Hz, 1H), 7.44 (dd, *J* = 5.4, 8.6 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.81 (dd, *J* = 1.2, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 47.0, 47.3, 59.2, 73.4, 111.6, 115.0 (d, *J* = 21.0 Hz), 119.4, 121.0, 122.5, 124.4, 126.4 (d, *J* = 7.6 Hz), 128.2, 142.6, 146.3 (d, *J* = 2.6), 155.8, 161.7 (d, *J* = 243.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$) δ −117.4 (m); IR (thin film) 3452, 3564 cm^{-1}; GC/MS t_R = 16.1 min (351 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (0.12 g, 0.26 mmol, 57%): mp 219–221 °C dec (EtOH). Anal. ($C_{22}H_{22}FNO_2 \cdot 0.5(COOH)_2 \cdot H_2O \cdot 0.5CH_3CH_2$-OH) C, H, N.

endo-8-(Benzofur-3-ylmethyl)-3-(4-bromophenyl)-8-azabicyclo-[3.2.1]octan-3-ol (48)

Compound **11a** (80 mg, 0.48 mmol), **28** (151 mg, 0.53 mmol), and sodium bicarbonate (134 mg, 1.60 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH), yielding glass **48** (167 mg, 0.40 mmol, 83%); R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 1H, –O<u>H</u>), 1.77 (d, *J* = 14.0 Hz, 2H), 2.05 (m, 2H), 2.23 (m, 2H), 2.30 (dd, *J* = 3.2, 14.4 Hz, 2H), 3.35 (br s, 2H), 3.69 (s, 2H), 7.25 (obs dt, *J* = 1.2, 7.6 Hz, 1H), 7.30 (obs dt, *J* = 1.2, 7.6 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.80 (dd, *J* = 1.6, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 46.8, 47.3, 59.1, 73.4, 111.6, 119.3, 120.6, 120.9, 122.5, 124.4, 126.7, 128.1, 131.3, 142.5, 149.6, 155.8; IR (thin film) 3445, 3564 cm^{-1}; GC/MS t_R = 18.5 min (411 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (165 mg, 0.31 mmol, 78%): mp 222–224 °C dec (EtOH). Anal. ($C_{22}H_{22}BrNO_2 \cdot (COOH)_2 \cdot 0.5CH_3$-$CH_2OH$) C, H, N.

endo-8-(5-Methoxybenzofur-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (49)

Compound **11b** (96 mg, 0.49 mmol), **23** (130 mg, 0.55 mmol), and sodium bicarbonate (139 mg, 1.65 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH), yielding solid **49** (101 mg, 0.25 mmol, 51%): R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 1H, –O<u>H</u>), 1.80 (d, *J* = 14.4 Hz, 2H), 2.06 (m, 2H), 2.24 (m, 2H), 2.33 (dd, *J* = 3.6, 14.4 Hz, 2H), 3.37 (br s, 2H), 3.68 (s, 2H), 3.87 (s, 3H), 6.91 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.28 (obs d, *J* = 8.4 Hz, 2H), 7.30 (obs d, *J* = 2.8 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 47.1, 47.4, 56.1, 59.1, 73.5, 103.5, 112.0, 113.2, 119.3, 126.3, 128.4, 128.7, 132.5, 143.4, 149.2, 150.8, 155.8; IR (thin film) 3446, 3564 cm^{-1}; GC/MS t_R = 19.2 min (397 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (90 mg, 0.18 mmol, 72%): mp 192–193 °C dec (EtOH). Anal. ($C_{23}H_{24}ClNO_3 \cdot (COOH)_2 \cdot 0.75H_2O$) C, H, N.

endo-8-(5-Fluorobenzofur-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (50)

Compound **11c** (104 mg, 0.56 mmol), **23** (149 mg, 0.63 mmol), and sodium bicarbonate (158 mg, 1.88 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (3% MeOH/$CHCl_3$ + 1% NH_4OH) to yield solid **50** (170 mg, 0.44 mmol, 79%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 1H, –O<u>H</u>), 1.79 (d, *J* = 14.0 Hz, 2H), 2.06 (m, 2H), 2.25 (m, 2H), 2.31 (dd, *J* = 3.6, 14.4 Hz, 2H), 3.34 (br s, 2H), 3.66 (d, *J* = 0.8 Hz, 2H), 7.02 (dt, *J* = 2.8, 8.8 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.38 (obs d, *J* = 4.4 Hz, 1H), 7.41 (obs d, *J* = 8.8 Hz, 2H), 7.52 (dd, *J* = 2.8, 8.4 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 46.9, 47.2, 59.1, 73.4, 106.7 (d, *J* = 25.2 Hz), 112.0 (d, *J* = 5.0 Hz), 112.2 (d, *J* = 11.7 Hz), 119.6 (d, *J* = 4.2 Hz), 126.2, 128.4, 129.0 (d, *J* = 10.1 Hz), 132.5, 144.1, 149.0, 152.0, 159.1 (d, *J* = 236.1 Hz); ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −121.7 (dt, *J* = 4.0, 9.4 Hz); IR (thin film) 3459, 3584 cm^{-1}; GC/MS t_R = 17.3 min (385 $[M]^+$ *m/z*). The product was converted to the oxalate salt

using general procedure K (188 mg, 0.38 mmol, 86%): mp 251–217 °C dec (EtOH). Anal. ($C_{22}H_{21}ClFNO_2 \cdot 0.75(COOH)_2 \cdot CH_3CH_2OH$) C, H, N.

endo-8-(Naphtho[2,1-*b*]fur-1-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (51)

Compound **11d** (99 mg, 0.46 mmol), **23** (121 mg, 0.51 mmol), and sodium bicarbonate (128 mg, 1.52 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH), yielding solid **51** (179 mg, 0.43 mmol, 93%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.77; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 1H, –OH), 1.79 (d, *J* = 14.0 Hz, 2H), 2.13 (m, 2H), 2.30 (m, 4H), 3.48 (br s, 2H), 3.94 (s, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.53 (ddd, *J* = 1.2, 6.8, 8.4 Hz, 1H), 7.62 (ddd, *J* = 1.2, 6.8, 8.4 Hz, 1H), 7.66 (obs d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.97 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 47.7, 48.4, 59.0, 73.7, 112.9, 121.2, 122.0, 124.5, 125.9, 126.0, 126.3, 126.3 128.3, 128.8, 129.0, 130.9, 132.4, 142.6, 149.2, 154.1; IR (thin film) 3564 cm^{-1}; GC/MS t_R = 21.7 (399 $[M - H_2O]^+$), 23.7 min (417 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K except with *i*-PrOH/$CHCl_3$ as solvent (213 mg, 0.37 mmol, 86%): mp 225–226 °C dec (*i*-PrOH/$CHCl_3$). Anal. ($C_{26}H_{24}ClNO_2 \cdot (COOH)_2 \cdot (CH_3)_2$-CHOH · $0.33H_2O$) C, H, N.

endo-8-(Naphtho[1,2-*b*]fur-3-ylmethyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (52)

Compound **11e** (100 mg, 0.46 mmol), **23** (137 mg, 0.58 mmol), and sodium bicarbonate (116 mg, 1.38 mmol) in acetonitrile (1 mL) were reacted according to general procedure L and purified using preparative TLC (10% MeOH/$CHCl_3$ + 1% NH_4OH), yielding solid **52** (146 mg, 0.35 mmol, 76%): R_f(10% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.78; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 1H, –OH), 1.80 (d, *J* = 14.4 Hz, 2H), 2.10 (m, 2H), 2.26 (m, 2H), 2.33 (dd, *J* = 3.0, 14.4 Hz, 2H), 3.40 (br s, 2H), 3.78 (s, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.50 (ddd, *J* = 1.2, 6.4, 7.6 Hz, 1H), 7.59 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.69 (obs d, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 47.0, 47.4, 59.1, 73.5, 119.7, 120.2, 120.5, 121.7, 123.1, 123.7, 125.3, 126.3, 126.4, 128.4, 128.5, 131.6, 132.5, 141.8, 149.1, 151.4; IR (thin film) 3564 cm^{-1}; GC/MS t_R = 23.0 (399 $[M - H_2O]^+$), 25.7 min (417 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K except with *i*-PrOH as solvent (178 mg, 0.32 mmol, 92%): mp 237–239 °C dec (*i*-PrOH). Anal. ($C_{26}H_{24}$-$ClNO_2 \cdot (COOH)_2 \cdot 0.75(CH_3)_2CHOH$) C, H, N.

endo-8-(5-Fluorobenzofur-3-ylmethyl)-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (53)

Compound **11c** (45 mg, 0.24 mmol), **24** (70 mg, 0.26 mmol), and sodium bicarbonate (64 mg, 0.76 mmol) in acetonitrile (0.5 mL) were reacted according to general procedure L and purified using preparative TLC (3% MeOH/$CHCl_3$ + 1% NH_4OH) to yield solid **53** (83 mg, 0.20 mmol, 83%): R_f(3% MeOH/$CHCl_3$ + 1% NH_4OH) = 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 1H, –OH), 1.79 (d, *J* = 14.0 Hz, 2H), 2.06 (m, 2H), 2.23 (br m, 2H), 2.28 (d, *J* = 14.4 Hz, 2H), 3.35 (br s, 2H), 3.66 (s, 2H), 7.02 (dt, *J* = 2.4, 9.2 Hz, 1H), 7.28 (br d, *J* = 9.2 Hz, 1H), 7.39 (obs m, 1H), 7.40 (obs d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.58 (obs br s, 1H), 7.59 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 46.9, 47.3, 59.1, 73.3, 106.7 (d, *J* = 24.4 Hz), 112.1 (d, *J* = 5.1 Hz), 112.3 (d, *J* = 12.6 Hz), 119.5, 124.5, 127.2, 129.0 (d, *J* = 10.9 Hz), 130.3, 130.7, 132.4, 144.3, 150.9, 152.0, 159.1 (d, *J* = 236.1 Hz); ^{19}F (376 MHz, $CDCl_3$/$CFCl_3$) δ −121.6 (dt, *J* = 4.0, 7.9 Hz); IR (thin film) 3448, 3568 cm^{-1}; GC/MS t_R = 20.3 min (419 $[M]^+$ *m/z*). The product was converted to the oxalate salt using general procedure K (70 mg, 0.13 mmol, 65%): mp 224–226 °C dec (EtOH/acetone). Anal. ($C_{22}H_{20}Cl_2FNO_2 \cdot (COOH)_2 \cdot 0.5(CH_3)_2CO$) C, H, N.

X-ray Crystal Structure of Compounds 1 and 31

Single-crystal X-ray diffraction data on compounds **1** and **31** were collected at 113 K using Mo Kα radiation and a Bruker APEX 2 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream on the diffractometer. Corrections were applied for Lorentz, polarization, and absorption effects. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL, version 6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C–H distance set at 0.96 Å.

Data were collected on a 0.12 × 0.20 × 0.23 mm^3 crystal of **1**. The crystal was monoclinic in space group $P2_1$ with unit cell dimensions a = 10.2395(3) Å, b = 18.2952(5) Å, c = 11.1875(3) Å, and β = 90.302(1)°. Data were 99.0% complete to 29.15° θ (approximately 0.73 Å) with an average redundancy of 2.77.

Data were collected on a 0.19 × 0.28 × 0.71 mm^3 crystal of **31**. The crystal was triclinic in space group $P\bar{1}$ with unit cell dimensions a = 9.3193(8) Å, b = 11.0905(9) Å, c = 12.0185(10) Å, α = 79.202(1)°, β= 67.397(1)°, and γ = 72.184(1)°. Data were 97.1% complete to 29.15° θ (approximately 0.73 Å) with an average redundancy of 2.01.

Atomic coordinates for compounds **1** and **31** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 686186 and 686185). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ,U.K.[fax,+44(0)-1223-336033; e-mail, deposit@ccdc.cam.ac.uk].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIDA-IRP, NIH Grant DA13584-03S1, and NIH Grant DA13584-01. N.M.P. was supported by a NIH Postdoctoral Intramural Research Training Award (IRTA) Fellowship. Crystallographic studies were supported by NIDA Contract Y1-DA6002.

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45. GC/MS runs of the indolylmethyl and indazolylmethyl compounds **31**–**40** are inconclusive because of decomposition of the 8-arylmethyl linkage in the gas chromatograph, though dealkylated products are observed.
46. Alignment of **31** to the N(2)-C(10)-C(11)-C(12)-C(13)-C(14) atoms of **1** was produced using Sybyl 7.3 by Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144.
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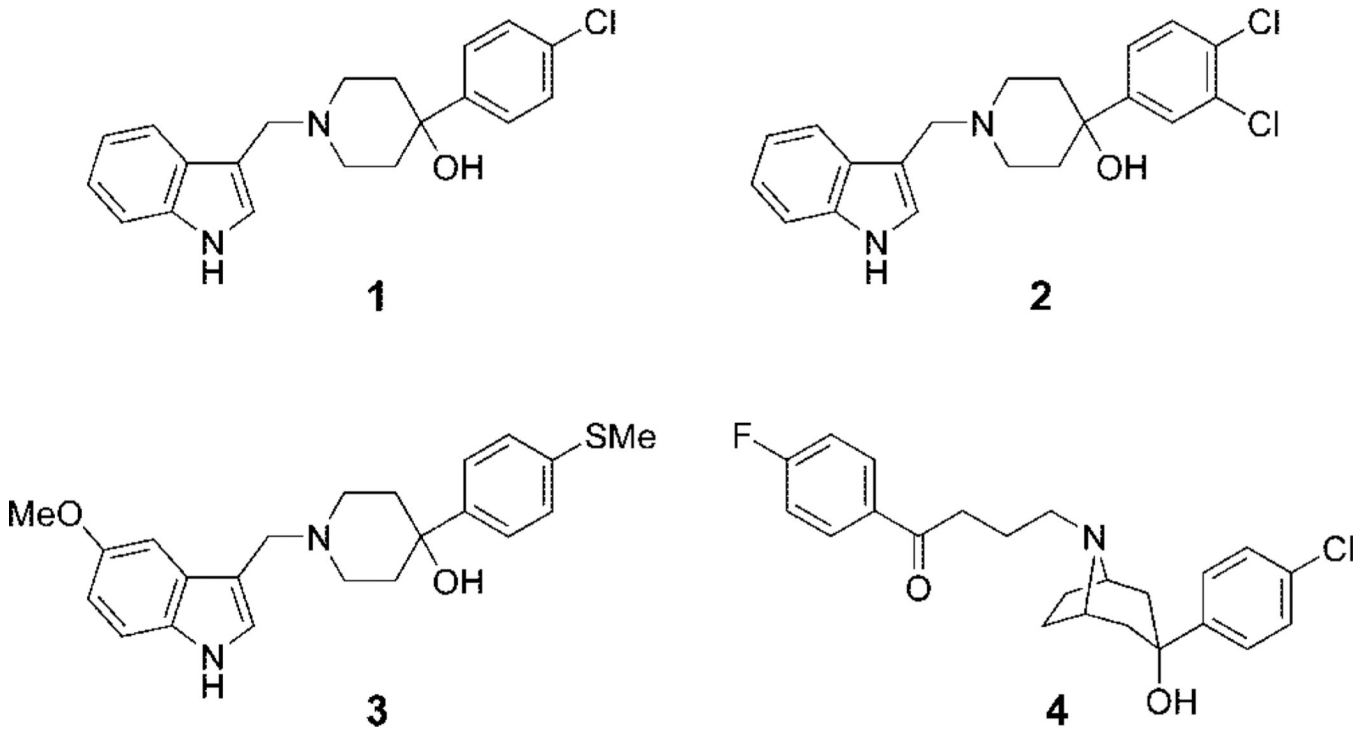


Figure 1.
Structurally related D2-like compounds.

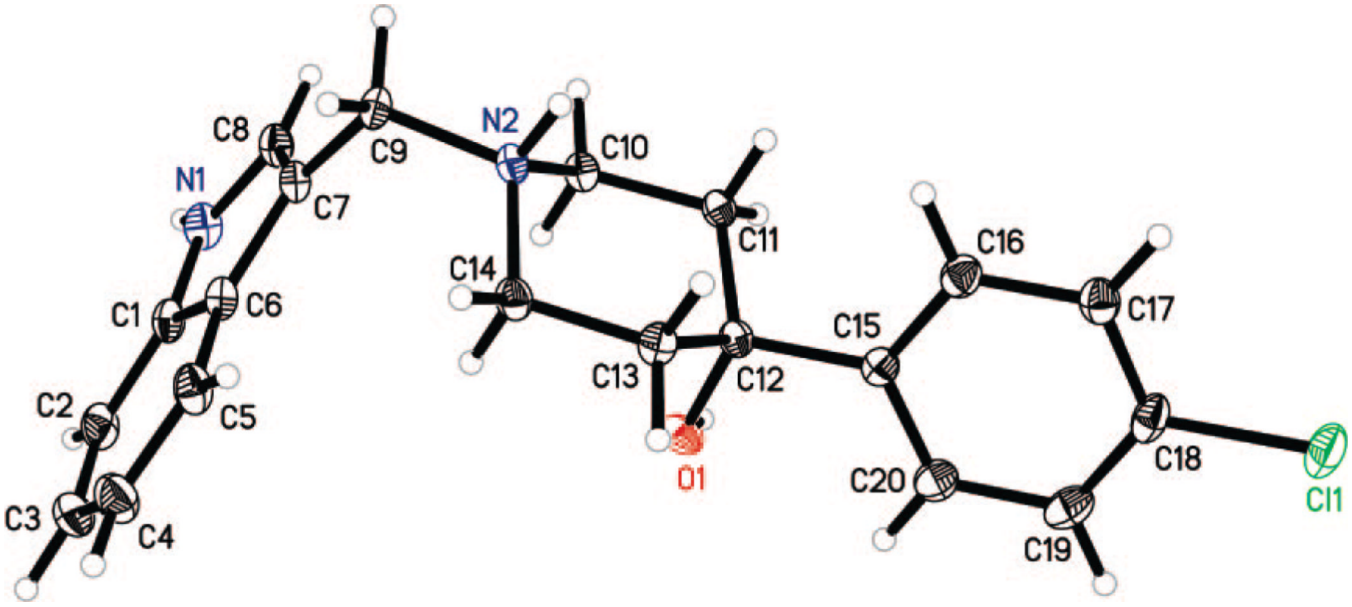


Figure 2.
X-Ray crystal structure of **1**. Displacement ellipsoids are at the 50% level, and the counterions (oxalate) and solvent (water) have been omitted for clarity. Only one of the two molecules in the asymmetric unit is shown.

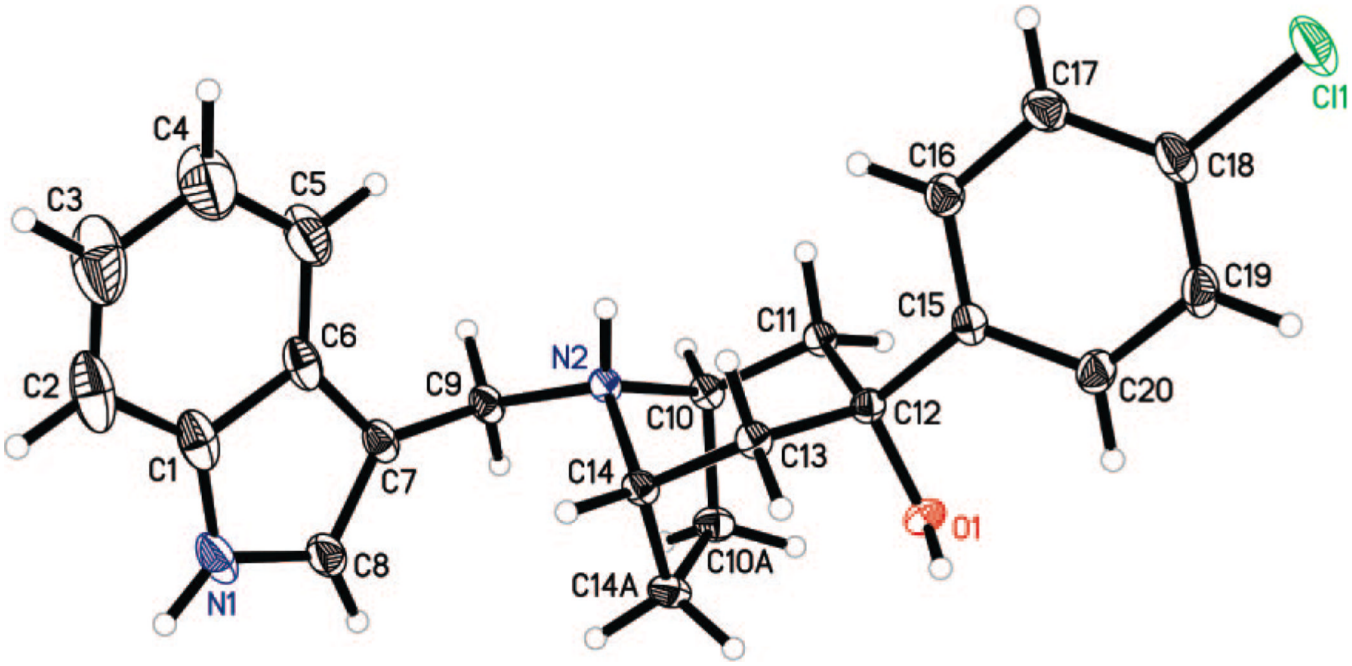


Figure 3.
X-ray crystal structure of **31**. Displacement ellipsoids are at the 50% level, and the counterion (oxalate) and solvent (water) have been omitted for clarity.

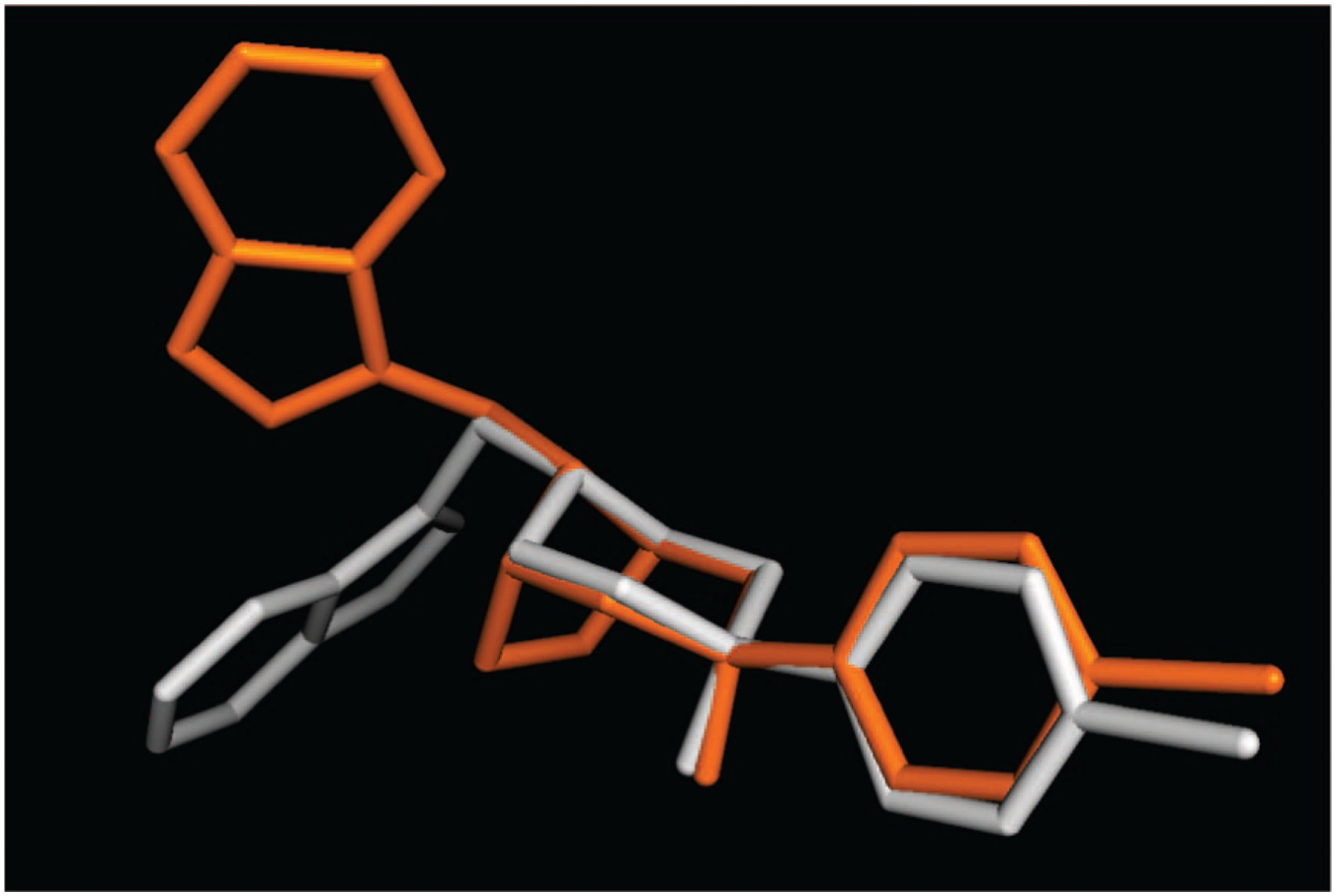
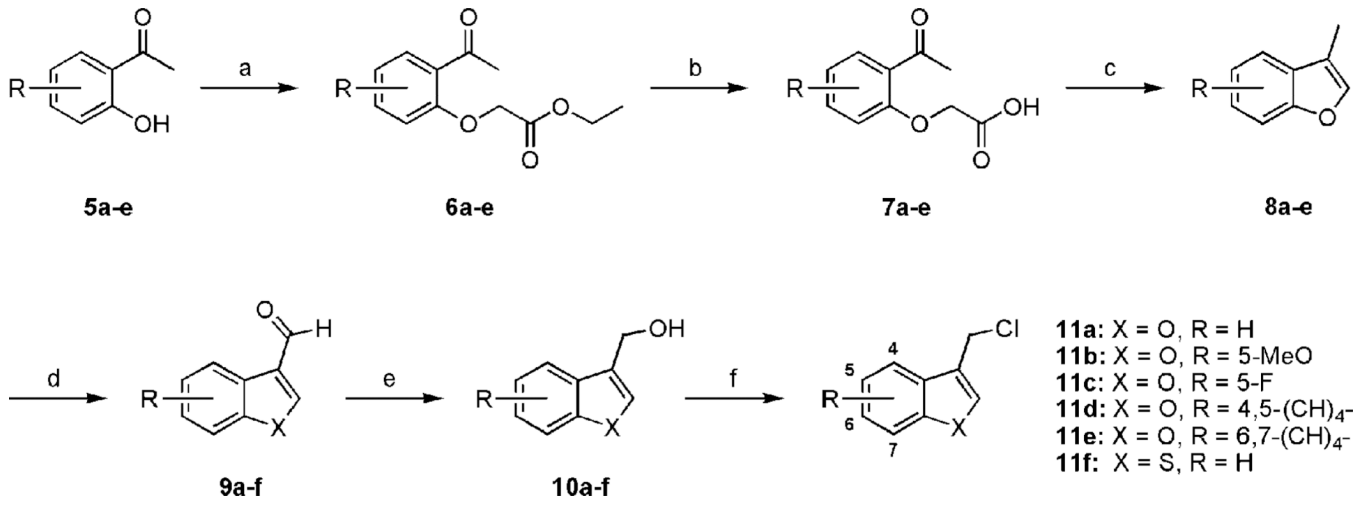


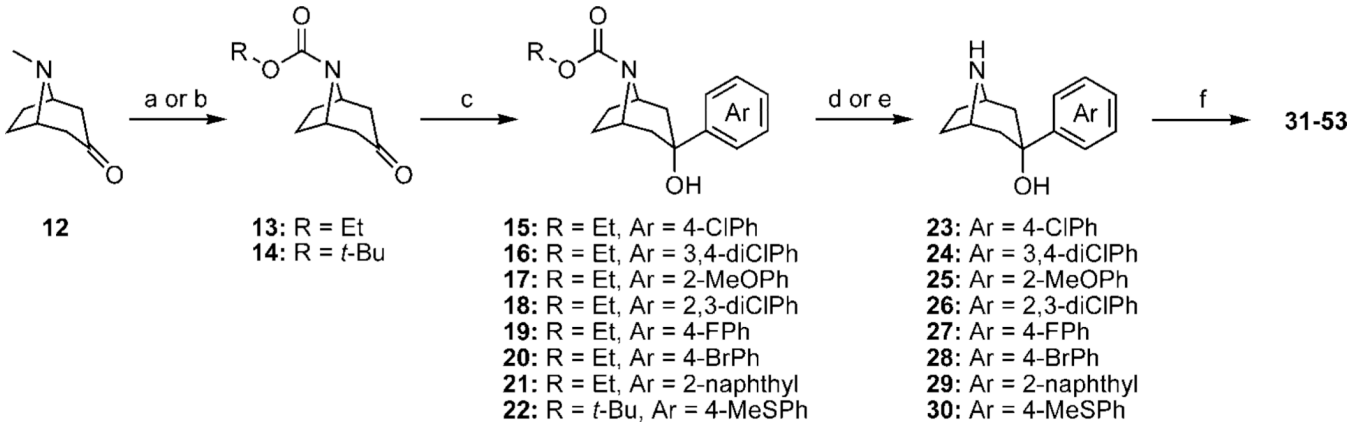
Figure 4.
Superimposed X-ray crystal structures of **1** (white) and **31** (orange).



Scheme 1.

Synthesis of Benzofuran and Benzothiophene Side Chains[a]

[a] (a) Ethyl 2-chloroacetate, K_2CO_3, acetone, reflux, 16 h; (b) K_2CO_3, H_2O, reflux, 3 h; (c) NaOAc, AcO_2, reflux, 3 h; (d) SeO_2, dioxane, reflux, 16 h; (e) $NaBH_4$, MeOH, room temp, 1 h; (f) $SOCl_2$, Et_2O, room temp, 3 h.



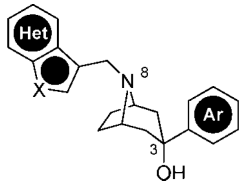
Scheme 2.

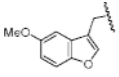
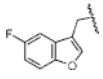
Synthesis of D2R/D3R Tropinesa

[a] (a) R = Et, ethyl chloroformate, K_2CO_3, toluene, reflux, 16 h; (b) (i) R = *t*-Bu, 1-chloroethyl chloroformate, $ClCH_2CH_2Cl$, reflux, 3 h, then MeOH, (ii) Boc_2O, MeOH, Et_3N, reflux, 30 min; (c) ArLi, THF, −78 °C, 1 h or ArMgBr, Et_2O, room temp, 1 h, followed by $NaBH_4$, MeOH, room temp, 1 h; (d) R = Et, 3:3:1 EtOH/50% KOH(aq)/NH_2NH_2, reflux, 16 h; (e) R = *t*-Bu, microwave (neat), 185 °C, 5 min; (f) gramine, pyridine, reflux, 16 h or **11a–f**, $NaHCO_3$, CH_3CN, reflux, 16 h.

Table 1

Human $D2_L$ and D3 Receptor Subtype Binding Data in HEK 293 Cells



	8-heteroarylmethyl	3-aryl	D2R (K_i ± SEM, nM)	D3R (K_i ± SEM, nM)		8-heteroarylmethyl	3-aryl	D2R (K_i ± SEM, nM)	D3E (K_i ± SEM, nM)
31			33.4 ± 2.9	15.5 ± 1.6	**43**			280 ± 40	431 ± 35
32			35.3 ± 1.3	6.35 ± 1.1	**44**			1.06 ± 0.09	0.71 ± 0.14
33			545 ± 51	480 ± 81	**45**			1.7 ± 0.26	0.34 ± 0.03
34			41.4 ± 7.0	31.0 ± 6.2	**46**			40.1 ± 2.2	32.2 ± 0.26
35			196 ± 13	224 ± 35	**47**			4.9 ± 0.70	1.2 ± 0.12
36			2070 ± 1400	6410 ± 1600	**48**			1.5 ± 0.03	0.92 ± 0.12
37			565 ± 20	541 ± 45	**49**			1.5 ± 0.12	2.1 ± 0.26
					50			1.2 ± 0.18	0.37 ± 0.05

	8-heteroarylmethyl	3-aryl	D2R	D3R		8-heteroarylmethyl	3-aryl	D2R	D3E
			(K_i ± SEM, nM)					(K_i ± SEM, nM)	
38			225 ± 26	84.7 ± 5.3	**51**			11.7 ± 0.97	8.40 ± 1.3
39			39.4 ± 5.5	21.2 ± 3.5	**52**			5.6 ± 0.74	2.0 ± 0.22
40			554 ± 67	1210 ± 170	**53**			1.4 ± 0.26	0.53 ± 0.08
41			12.9 ± 1.3	3.62 ± 0.45	**1**			11.2 ± 0.46[22]	163 ± 18[27]
42			29.8 ± 4.0	17.9 ± 1.3	**2**			6.9 ± 0.99[27]	111 ± 12[27]

Table 2

In Vitro Binding and Functional Data for Selected Compounds[a]

	K_i ± SEM, nM					functional IC_{50} ± SEM, nM	
	5-HT_{1A} [^{3}H]-8-OH-DPAT	**5-HT_{2A} [^{3}H]ketanserin**	**5-HT_{2C} [^{3}H]mesulergine**	**D1R [^{3}H]SCH23390**	**D4R[b] [^{125}I]IABN**	**D2R**	**D3R**
31	>10000	4770 ± 170	>10000	1220 ± 260	>5000	48.3 ± 11	12.3 ± 0.42
32	>10000	2800 ± 500	2390 ± 96	1710 ± 120	364 ± 64	210 ± 56	10.2 ± 3.6
41	1720 ± 250	70.1 ± 1.4	>10000	3000 ± 270	140 ± 26	26.2 ± 4.5	4.20 ± 0.08
44	1780 ± 500	171 ± 15.5	>10000	3930 ± 250	195 ± 44	1.92 ± 0.24	0.85 ± 0.08
1	6300 ± 210	695 ± 160	6570 ± 1500	722 ± 12	1100 ± 210	4.46 ± 0.85[27]	90.4 ± 15[27]

[a] Unless otherwise noted, data were obtained through the NIDA Addiction Treatment Discovery Program contract with Southern Research Institute (Contract N01DA-1-8816).

[b] Binding inhibition values determined using HEK 293 cells transfected with hD4 dopamine receptor and [^{125}I]IABN radioligand as previously reported.[32]