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Synthesis and monoamine transporter binding properties of 2β-[3′-(substituted benzyl)isoxazol-5-yl]- and 2β-[3′-methyl-4′-(substituted phenyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes

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ABSTRACT

A series of 2β-[3′-(substituted benzyl)isoxazol-5-yl]- and 2β-[3′-methyl-4′-(substituted phenyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes were prepared and evaluated for affinities at dopamine, serotonin, and norepinephrine transporters using competitive radioligand binding assays. The 2β-[3′-(substituted benzyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**3a–h**) showed high binding affinities for the dopamine transporter (DAT). The IC_{50} values ranged from 5.9 to 22 nM. On the other hand, the 2β-[3′-methyl-4′-(substituted phenyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**4a–h**), with IC_{50} values ranging from 65 to 173 nM, were approximately 3- to 25-fold less potent than the corresponding 2β-[3′-(substituted benzyl)isoxazol]tropanes. All tested compounds were selective for the DAT relative to the norepinephrine transporter (NET) and serotonin transporter (5-HTT). 3β-(4-Methylphenyl)-2β-[3′-(4-fluorobenzyl)isoxazol-5-yl]tropane (**3b**) with IC_{50} of 5.9 nM at the DAT and K_is of 454 and 113 nM at the NET and 5-HTT, respectively, was the most potent and DAT-selective analog. Molecular modeling studies suggested that the rigid conformation of the isoxazole side chain in **4a–h** might play an important role on their low DAT binding affinities.

1. Introduction

Cocaine abuse continues to be a significant medical problem in the United States. An estimated 2 million Americans currently use cocaine (past-month) according to the National Survey on Drug Use and Health (NSDUH).[1] In addition to its direct effects, cocaine abuse has also contributed to the increase of the spread of human immunodeficiency virus (HIV) infection and drug-resistant tuberculosis.[2] At present, no effective medication is in clinical use for the treatment of cocaine abuse. In the central nervous system (CNS), cocaine (**1a**, Fig. 1) binds to the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (5-HTT), and inhibits presynaptic reuptake of the respective neurotransmitters. It also has effects on the cholinergic, muscarinic, and σ receptors and sodium channels.[3,4] It is believed that the DAT is the key recognition site for cocaine, mediating the behavioural and reinforcing effects that contribute to its abuse liability.[4–8] The dopamine hypothesis of cocaine addiction has received further support from molecular biological studies involving DAT knockout mice and positron emission tomography (PET).[9,10] Accordingly, the discovery and development of potent and selective DAT inhibitors represents one of the promising approaches in the treatment of cocaine abuse.

Many research groups have sought to develop the 3-phenyltropane class of DAT inhibitors, with 3β-phenyltropane-2β-carboxylic acid methyl ester (WIN35,065-2, **1b**) as the lead compound.[11–19] A large part of our structure–activity relationships (SAR) studies was directed toward modification of the 4′-chloro and 4′-methyl analogs **1c,d**.[16] Over the last several years, we have synthesized a large number of 3-phenyltropane analogs and evaluated them for binding at monoamine transporters. We have shown that a variety of 2β-esters, amides, and heterocyclic groups possessing either a 4′-chloro or 4′-methylphenyl group at the 3β-position had high-affinity for the DAT, in some cases, with considerably reduced affinity at the NET and 5-HTT.[16] One of the more interesting classes of compounds in the heterocyclic series is the 2β-[3′-(substituted phenyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**2a–h**).[20] The DAT-selective inhibitor RTI-336 (**2e**) is currently in advanced preclinical development.[21,22] This study was undertaken to further explore the effect of substituents on the isoxazole ring of the 3β-phenyltropanes. In this paper, we describe the synthesis of several 2β-[3′-(substituted benzyl) isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**3a–h**) and 2β-[3′-methyl-4′-(substituted phenyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**4a–h**), and report their monoamine transporter binding properties.

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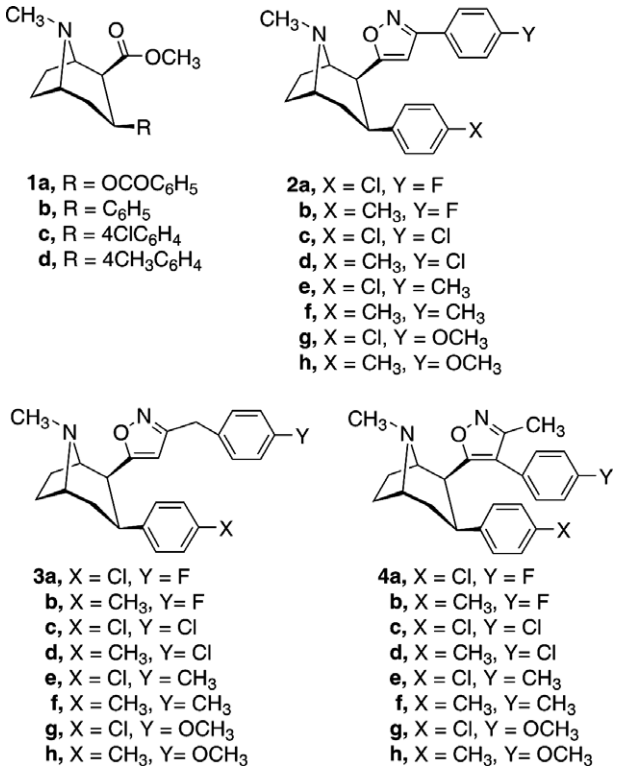
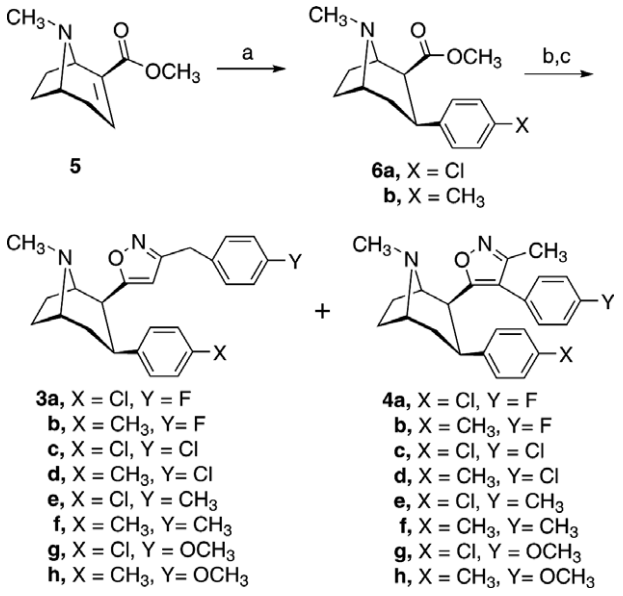


Figure 1. Structures of cocaine (**1a**) and 3-phenyltropanes.



Scheme 1. Reagents and conditions: (a) Grignard reagent, −45 °C, 2 h, then −78 °C, TFA; (b) 1-(4-substituted phenyl)propan-2-one oxime, BuLi, THF, 0–70 °C; (c) 3 N HCl, THF, reflux.

2. Chemistry

The synthesis of 2β-[3′-(substituted benzyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**3a–h**) and 2β-[3′-methyl-4′-(substituted phenyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**4a–h**) starting with anhydroecgonine methyl ester (**5**) is outlined in Scheme 1. Briefly, conjugate addition of **5** with the appropriate Grignard reagent at −45 °C in ethyl ether followed by trifluroacetic acid (TFA) yielded 3β-aryltropanes **6a,b**.[23] Following our previously reported procedure,[20,24] a solution of **6a** was added at 0 °C to the oxime dilithium salt, generated from the oxime of 1-(4-fluorophenyl)propan-2-one with *n*-butyllithium in tetrahydrofuran (THF) at room temperature, and the reaction mixture was warmed to room temperature. After 20 h, the reaction mixture was added to a 1:1 mixture of 3 N hydrochloric acid and THF, and was refluxed for 5 h. Column chromatography purification of the crude product afforded 2β-[3′-(4-fluorobenzyl)isoxazol-5-yl]-3β-(4-chlorophenyl)tropane (**3a**) in 41% yield. Under these conditions, none of the desired 2β-[3′-methyl-4′-(4-fluorophenyl)isoxazol-5-yl]-3β-(4-chlorophenyl)tropane (**4a**) was obtained. Alternatively, treatment of the oxime of 1-(4-fluorophenyl)propan-2-one with *n*-butyllithium in THF at 70 °C for 30 min followed by addition of **6a** and refluxing for 3 h afforded the corresponding mixture of addition intermediates. Subsequent cyclization in refluxing 3 N hydrochloric acid and THF furnished a mixture of **3a** and **4a**, which were obtained in 4% and 7% yields, respectively, after careful column chromatography. The low yields of **3a** and **4a** were due to the formation of multiple by-products under the reaction conditions. However, none of the by-products was formed in quantities justifying isolation and identification. The stereochemistry of **3a** and **4a** was determined by ^{1}H NMR spectral analysis, particularly with the aid of coupling constants of C(2)–H and C(3)–H. The vicinal couplings of $J_{2eq,3ax}$ = 5.9 Hz and $J_{3ax,4ax}$ = 13.0 Hz for **3a**, and $J_{2eq,3ax}$ = 6.0 Hz and $J_{3ax,4ax}$ = 12.9 Hz for **4a**, respectively, are in good agreement with stereochemical assignments. By employing the modified reaction conditions, 2β-(substituted isoxazol)tropane analogs **3b–h** and **4b–h** were prepared in the range of 3–43% and 4–18% yields, respectively. The yields obtained along with the analytical data of target compounds are given in Table 1.

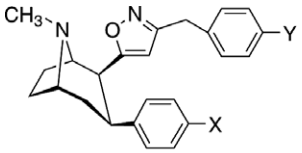
3. Biology

The binding affinities for the target compounds at the DAT, NET, and 5-HTT were determined via competitive binding assays using the previously reported procedures.[25,26] The final concentration of radioligands in the assays was 0.5 nM [^{3}H]WIN35,428 for the DAT, 0.5 nM [^{3}H]nisoxetine for the NET, and 0.2 nM [^{3}H]paroxetine for the 5-HTT. The results of the binding studies along with binding data of cocaine, WIN35,065-2,[21] and **2a–h**[20] for comparison are listed in Table 2. Since the DAT has two binding sites, IC_{50} values are reported. The NET and 5-HTT have only one binding site, thus K_i values were calculated for inhibition of binding at these two transporters.

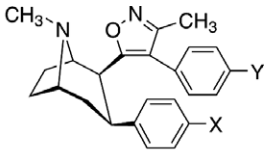
4. Results and discussion

SAR studies from our laboratory as well as others have shown that a variety of functional groups and substituents are well tolerated at the C(2)-position of 3β-phenyltropanes without loss of high-affinity for the DAT.[16,27–29] Results from some of the analogs suggest an electrostatic interaction between the 2β-substituent and the binding site, whereas results from other analogs are more consistent with a hydrophobic or steric interaction, which is important for the high binding potency at the DAT. A possible explanation for the wide range of substituents that can be accommodated at the C(2)-position is the existence of more than one binding mode. Although the DAT tolerates ligands having a broad variety of 2β-substituents with little change in the affinity of the ligand, the nature of the substituents has a profound effect on the monoamine transporter selectivity.[16] To obtain analogs with increased metabolic stability, we have replaced the metabolically labile 2β-ester group of the 3β-phenyltropanes by stable bioisosteric heterocyclic groups, which led to several analogs with high-affinity and selectivity for the DAT.[20,24,30,31] Computational analyses of the electrostatic (molecular electrostatic potential), hydrophobic (calculated log*P*), and steric (substituted volume) properties of these 2β-heterocyclic analogs strongly

Table 1
2β-Isoxazol-3β-(substituted phenyl)tropanes, yields, and analytical data



3a-h

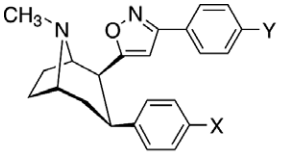


4a-h

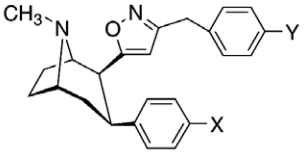
Compound[a]	X	Y	Yield (%)	$[\alpha]_D^{20}$ (g/100 mL, CH_3OH)	Mp (°C)	Molecular formula	Analysis
3a	Cl	F	4	−47.7° (0.34)	192 (dec)	$C_{24}H_{25}Cl_2FN_2O{\cdot}H_2O$	C, H, N
3b	CH_3	F	7	−66.6° (0.29)	165 (dec)	$C_{25}H_{28}ClFN_2O{\cdot}1.5H_2O$	C, H, N
3c	Cl	Cl	5	−88.3° (0.31)	192 (dec)	$C_{24}H_{25}Cl_3N_2O{\cdot}0.75H_2O$	C, H, N
3d	CH_3	Cl	3	−75.4° (0.40)	180 (dec)	$C_{25}H_{28}Cl_2N_2O{\cdot}0.5H_2O$	C, H, N
3e	Cl	CH_3	17	−70.0° (0.37)	108 (dec)	$C_{25}H_{28}Cl_2N_2O{\cdot}0.5H_2O$	C, H, N
3f	CH_3	CH_3	39	−61.9° (0.43)	193 (dec)	$C_{26}H_{31}ClN_2O{\cdot}0.75H_2O$	C, H, N
3g	Cl	OCH_3	33	−62.4° (0.34)	178 (dec)	$C_{25}H_{28}Cl_2N_2O_2{\cdot}0.75H_2O$	C, H, N
3h	CH_3	OCH_3	43	−68.7° (0.53)	168 (dec)	$C_{26}H_{31}ClN_2O_2{\cdot}1.5H_2O$	C, H, N
4a	Cl	F	7	+22.2° (0.79)	231 (dec)	$C_{24}H_{25}Cl_2FN_2O{\cdot}H_2O$	C, H, N
4b	CH_3	F	18	+18.0° (0.25)	208 (dec)	$C_{25}H_{28}ClFN_2O{\cdot}1.75H_2O$	C, H, N
4c	Cl	Cl	12	+71.4° (0.37)	248 (dec)	$C_{24}H_{25}Cl_3N_2O{\cdot}0.25H_2O$	C, H, N
4d	CH_3	Cl	11	+51.1° (0.33)	245 (dec)	$C_{25}H_{28}Cl_2N_2O{\cdot}1.25H_2O$	C, H, N
4e	Cl	CH_3	9	+61.5° (0.35)	248 (dec)	$C_{25}H_{28}Cl_2N_2O{\cdot}0.5H_2O$	C, H, N
4f	CH_3	CH_3	7	+44.7° (0.34)	249 (dec)	$C_{26}H_{31}ClN_2O{\cdot}1.25H_2O$	C, H, N
4g	Cl	OCH_3	7	+69.4° (0.39)	243 (dec)	$C_{25}H_{28}Cl_2N_2O_2{\cdot}1.25H_2O$	C, H, N
4h	CH_3	OCH_3	4	+50.7° (0.28)	238 (dec)	$C_{26}H_{31}ClN_2O_2{\cdot}1.25H_2O$	C, H, N

[a] HCl salt used to characterize the compound.

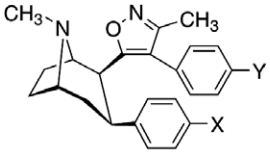
Table 2
Monoamine transporter binding affinities of 2β-isoxazol-3β-(substituted phenyl)tropanes



2a-h



3a-h



4a-h

Compound[a]	*c*log*P*	X	Y	DAT, IC_{50}[b] (nM) [^{3}H]WIN35,428	NET, K_i[b] (nM) [^{3}H]Nisoxetine	5-HTT, K_i[b] (nM) [^{3}H]Paroxetine
Cocaine[c]				89.1	1990	95
WIN35,065-2[c]				23	556	182
2a[d]	4.48	Cl	F	1.86 ± 0.09	553 ± 65	660 ± 19
2b[d]	4.34	CH_3	F	6.45 ± 1.6	552 ± 18	> 2000
2c[d]	5.12	Cl	Cl	6.42 ± 0.46	>2000	> 2000
2d[d]	4.98	CH_3	Cl	8.74 ± 1.7	>2000	> 2000
2e[d]	5.01	Cl	CH_3	4.09 ± 0.44	1030 ± 24	522 ± 48
2f[d]	4.87	CH_3	CH_3	13 ± 2.1	> 2000	>2000
2g[d]	4.36	Cl	OCH_3	1.57 ± 0.1	454 ± 23	535 ± 16
2h[d]	4.23	CH_3	OCH_3	3.93 ± 0.49	455 ± 89	366 ± 2.9
3a	4.98	Cl	F	8.6 ± 3.0	435 ± 40	72 ± 8
3b	4.85	CH_3	F	5.9 ± 1.5	454 ± 30	113 ± 8
3c	5.53	Cl	Cl	17.5 ± 1	677 ± 60	79 ± 36
3d	5.39	CH_3	Cl	22.2 ± 5.5	840 ± 70	85 ± 12
3e	5.39	Cl	CH_3	22.1 ± 2.8	1100 ± 140	42.9 ± 5
3f	5.26	CH_3	CH_3	6.9 ± 2.2	770 ± 40	89.7 ± 3.5
3g	4.85	Cl	OCH_3	6.1 ± 1.4	347 ± 20	14.4 ± 1
3h	4.71	CH_3	OCH_3	9.6 ± 5	357 ± 50	41.1 ± 11
4a	5.09	Cl	F	111 ± 23	466 ± 40	908 ± 170
4b	4.96	CH_3	F	76 ± 12	349 ± 70	>2000
4c	5.73	Cl	Cl	68.7 ± 4	788 ± 120	387 ± 130
4d	5.60	CH_3	Cl	65.7 ± 22	519 ± 20	864 ± 250
4e	5.62	Cl	CH_3	135 ± 34	>2000	297 ± 20
4f	5.49	CH_3	CH_3	173 ± 40	>2000	1000 ± 100
4g	4.98	Cl	OCH_3	81.6 ± 22	>2000	1800 ± 300
4h	4.84	CH_3	OCH_3	119 ± 16	1300 ± 100	>2000

[a] All compounds were tested as the HCl salt.
[b] All values are means ± standard error of three or four experiments performed in duplicate.
[c] Data taken from Ref. 21.
[d] Data taken from Ref. 20.

suggested that electrostatic interactions predominately contributed to their DAT binding affinities.[24]

We previously reported that 2β-[3′-(substituted phenyl)isoxazol-5-yl]-3β-(substituted phenyl)tropanes (**2a–h**) possessed

high binding affinities (IC_{50} = 1.57–13 nM) at the DAT with lower affinities at the NET and 5-HTT.[24] One of the most potent and selective compounds in the series, RTI-336 (**2e**), had an IC_{50} of 4.09 nM at the DAT and K_is of 1030 nM and 522 nM at the NET and 5-HTT, respectively, and is currently in advanced preclinical development.[21,22] In this study, we expanded the 2β-(substituted isoxazol)tropanes including 2β-[3′-(substituted benzyl)isoxazol] tropanes **3a–h** and 2β-[3′-methyl-4′-(substituted phenyl)isoxazol]tropanes **4a–h** to further explore the effect of the substituents on the isoxazole ring. All of the analogs **3a–h** exhibited high DAT binding affinities similar to the corresponding 2β-[3′-(substituted phenyl)isoxazol]tropanes **2a–h**. The IC_{50} values ranged from 5.9 to 22 nM. On the other hand, the 2β-[3′-methyl-4′-(substituted phenyl)isoxazol]tropanes **4a–h**, with IC_{50} values ranging from 65 to 173 nM, were approximately 8- to 60-fold less potent than **2a–h**, and 3- to 25-fold less potent than **3a–h**. The particular substituents (F, Cl, CH_3, OCH_3) on the phenyl group of the isoxazole moiety appeared to have only a subtle effect on the DAT affinities. No correlation was observed between the DAT binding affinities and the calculated log*P* (*c*log*P*) of the compounds. All tested compounds in this study were selective for the DAT relative to the NET and 5-HTT. However, none of the compounds was as selective as the corresponding 2β-[3′-(substituted phenyl)isoxazol]tropanes 2a–**h**.

A molecular modeling study was performed to determine whether conformational differences between **3a–h** and **4a–h** account for the observed DAT binding properties. The minimum-energy conformations (Fig. 2) of **3a** and **4a** were generated using the MMFF94 force field in Spartan'06 (Wavefunction, Inc., Irvine, CA). There were no significant differences in the relative conformations of the tropane ring and the benzene ring attached at C(3)-position. However, significant difference in the relative conformations of the isoxazole ring attached at C(2)-position was revealed by the alignment of minimum-energy conformations shown in Figure 2. It is worthy to note that the isoxazole oxygen atom in **4a** is pointed in an almost opposite direction compared to that in **3a**. The two benzene rings in **4a** are proximal, and the resultant steric hindrance increases the rigidity of the isoxazole side chain and perhaps decreases the ability of the ligand to adopt a higher affinity conformation at the DAT.

In summary, a new series of 3β-phenyltropanes with various 2β-[3′-(substituted benzyl)isoxazol] and 2β-[3′-methyl-4′-(substituted phenyl)isoxazol] substituents were synthesized and evaluated for their monoamine transporter binding affinities. The 2β-[3′-(substituted benzyl)isoxazol]tropanes **3a–h** exhibited high affinities (IC_{50} = 5.9–22 nM) at the DAT, which is similar to that of the corresponding 2β-[3′-(substituted phenyl)isoxazol]tropanes 2a–**h**. On the other hand, the 2β-[3′-methyl-4′-(substituted phenyl)isoxazol]tropanes **4a–h** were approximately 3- to 25-fold less potent than the corresponding **3a–h**. Molecular modeling studies suggested that the conformational properties of the isoxazole moiety of **3a–h** and **4a–h** might play an important role on their DAT binding affinities.

5. Experimental

Melting points were determined using a MEL-TEMP II capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained on a Bruker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Mass spectra (MS) were obtained by electron impact at 70 eV on a Hewlett Packard 5989A instrument. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Optical rotations were measured on an AutoPol III polarimeter, purchased from Rudolf Research. Analytical thin-layer chromatography (TLC) was carried out using EMD silica gel 60 F_{254} TLC plates. TLC visualization was achieved with a UV lamp or in an iodine chamber. Flash column chromatography was done on a CombiFlash Companion system using Isco prepacked silica gel columns or using EM Science silica gel 60 Å (230–400 mesh). Unless otherwise stated, reagent-grade chemicals were obtained from commercial sources and were used without further purification. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen. All compounds described herein were prepared from natural (−)-cocaine, and therefore, they all possess the same absolute configuration as (−)-cocaine.

5.1. 3β-(4-Chlorophenyl)-2β-[3′-(4-fluorobenzyl)isoxazol-5-yl]-tropane (3a)

To a stirred solution of 1-(4-fluorophenyl)propan-2-one (5.00 g, 33.0 mmol) in EtOH (75 mL) at room temperature under nitrogen was added K_2CO_3 (12.4 g, 99.0 mmol) followed by hydroxylamine hydrochloride (4.17 g, 66.0 mmol). After stirring for 5 h, the reaction mixture was filtered through a plug of Celite and the filtrate was concentrated under reduced pressure. The resultant residue was dissolved in Et_2O (200 mL), washed with brine (3× 100 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 1-(4-fluorophenyl)propan-2-one oxime (5.40 g) as an oil, which was used in the next step without further purification.

To a stirred solution of 1-(4-fluorophenyl)propan-2-one oxime (1.84 g, 11.0 mmol) in anhydrous THF (20 mL) at 0 °C under nitrogen was added a solution of BuLi in hexanes (1.6 M, 13.7 mL, 22.0 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. A solution of **6a**[23] (1.07 g, 3.66 mmol) in anhydrous THF (5 mL) was then added. After stirring at room temperature for 20 h, the reaction was quenched by addition of a 20% NH_4Cl aqueous solution (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3× 50 mL). The combined organic phases were washed with brine (3× 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resultant residue was then dissolved in a 1:1 mixture of 3 N HCl aqueous solution and THF (20 mL), and refluxed for 5 h. After cooling to room temperature, the mixture was washed with Et_2O (3× 10 mL). The aqueous layer was made basic with $NaHCO_3$ and extracted with EtOAc (3× 50 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concen-

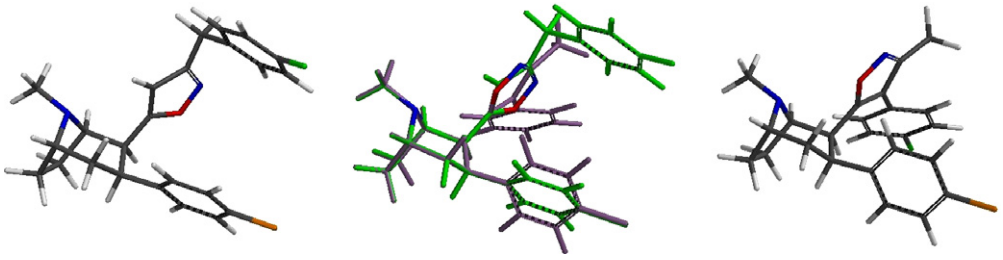


Figure 2. Overlay (center; green: **3a** and purple: **4a**) of the calculated minimum-energy conformations of **3a** (left) and **4a** (right) (black, carbon; blue, nitrogen; red, oxygen; orange, chlorine; and green, fluorine).

trated under reduced pressure. Flash column chromatography of the crude product on silica gel (40 g Isco prepacked column) using 0 → 10% Et_2O in hexanes with 5% Et_3N afforded **3a** (610 mg, 41%) as an oil: ^1H NMR ($CDCl_3$) δ 7.12–6.90 (m, 6H), 6.88–6.78 (m, 2H), 6.11 (s, 1H), 3.89 (d, J = 15.6 Hz, 1H), 3.80 (d, J = 15.6 Hz, 1H), 3.32–3.12 (m, 4H), 2.30–2.02 (m, 6H), 1.81–1.52 (m, 3H); ^1H NMR (300 MHz; C_6D_6) δ 7.05 (d, J = 8.7 Hz, 2H), 6.80–6.72 (m, 4H), 6.58 (d, J = 8.7 Hz, 2H), 6.11 (s, 1H), 3.67 (d, J = 15.3 Hz, 1H), 3.53 (d, J = 15.3 Hz, 1H), 2.93 (dd, J = 5.9, 2.6 Hz, 1H), 2.88–2.80 (m, 2H), 2.74 (ddd, J = 13.0, 5.9, 5.6 Hz, 1H), 1.91 (ddd, J = 13.0, 12.9, 2.7 Hz, 1H), 1.86 (s, 3H), 1.80–1.60 (m, 2H), 1.30–1.13 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 162.1, 161.8 (d, $J_{C,F}$ = 243 Hz), 140.3, 133.6 (d, $J_{C,F}$ = 3.2 Hz), 132.1, 130.2 (d, $J_{C,F}$ = 7.9 Hz), 128.8, 128.2, 115.3 (d, $J_{C,F}$ = 21.1 Hz), 103.6, 65.4, 61.6, 46.3, 42.0, 35.4, 34.9, 31.7, 26.4, 25.0; MS (EI) m/z 410 (M^+). The free base was converted to the hydrochloride salt: mp 192 °C (dec); $[\alpha]_D^{20}$ −47.7° (c 0.34, CH_3OH); Anal. Calcd for $C_{24}H_{25}Cl_2FN_2O{\cdot}H_2O$: C, 61.94; H, 5.85; N, 6.02. Found: C, 61.95; H, 5.74; N, 5.97.

5.2. 3β-(4-Chlorophenyl)-2β-[3′-(4-fluorobenzyl)isoxazol-5-yl]-tropane (3a) and 3β-(4-chlorophenyl)-2β-[3′-methyl-4′-(4-fluorophenyl)isoxazol-5-yl]tropane (4a)

To a stirred solution of 1-(4-fluorophenyl)propan-2-one oxime (1.84 g, 11.0 mmol) in anhydrous THF (20 mL) at 0 °C under nitrogen was added a solution of BuLi in hexanes (1.6 M, 13.7 mL, 22.0 mmol). The reaction mixture was warmed to room temperature over 30 min, and then heated to 70 °C for another 30 min. A solution of **6a** (1.07 g, 3.66 mmol) in anhydrous THF (5 mL) was added. The resultant mixture was refluxed for 3 h. After cooling to room temperature, the reaction was quenched by addition of a 20% NH_4Cl aqueous solution (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3× 50 mL). The combined organic phases were washed with brine (3× 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was partitioned between Et_2O (100 mL) and 2 N HCl (50 mL). The aqueous layer was separated, made basic with $NaHCO_3$, and extracted with EtOAc (3× 50 mL). The combined EtOAc extracts were washed with brine (3× 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resultant residue was then dissolved in a 1:1 mixture of 3 N HCl aqueous solution and THF (10 mL), and refluxed for 5 h. After cooling to room temperature, the mixture was made basic with $NaHCO_3$ and extracted with EtOAc (3× 50 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel (40 g Isco prepacked column) using 0 → 10% Et_2O in hexanes with 10% Et_3N afforded **3a** (55.0 mg, 4%) and **4a** (101 mg, 7%).

Compound **4a**: oil; ^1H NMR ($CDCl_3$) δ 7.17–6.88 (m, 6H), 6.77–6.67 (m, 2H), 3.54–3.44 (m, 1H), 3.27–3.08 (m, 2H), 3.04 (dd, J = 6.0, 2.1 Hz, 1H), 2.65 (ddd, J = 12.9, 12.9, 2.7 Hz, 1H), 2.30–2.08 (m, 5H), 2.02 (s, 3H), 1.78-1.62 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 168.9, 164.1, 159.3 (d, $J_{C,F}$ = 221 Hz), 140.8, 132.1, 131.4 (d, $J_{C,F}$ = 8.0 Hz), 129.2, 128.3, 126.6 (d, $J_{C,F}$ = 3.5 Hz), 117.6, 115.8 (d, $J_{C,F}$ = 21.4 Hz), 66.3, 62.0, 45.6, 42.1, 36.4, 35.8, 26.9, 25.2, 10.5; MS (EI) m/z 410 (M^+). The free base was converted to the hydrochloride salt: mp 231 °C (dec); $[\alpha]_D^{20}$ +22.2° (c 0.79, CH_3OH); Anal. Calcd for $C_{24}H_{25}Cl_2FN_2O{\cdot}H_2O$: C, 61.94; H, 5.85; N, 6.02. Found: C, 61.69; H, 5.85; N, 5.80.

5.3. 3β-(4-Methylphenyl)-2β-[3′-(4-fluorobenzyl)isoxazol-5-yl]-tropane (3b) and 3β-(4-methylphenyl)-2β-[3′-methyl-4′-(4-fluorophenyl)isoxazol-5-yl]tropane (4b)

The procedure for **3a** and **4a** was followed using 1.00 g (3.66 mmol) of **6b**[23] and 1.84 g (11.0 mmol) of 1-(4-fluorophenyl)propan-2-one oxime to give 105 mg (7%) of **3b** and 250 mg (18%) of **4b**.

Compound **3b:** oil; ^1H NMR ($CDCl_3$) δ 7.12–6.90 (m, 6H), 6.86–6.74 (m, 2H), 6.10 (s, 1H), 3.90 (d, J = 15.6 Hz, 1H), 3.80 (d, J = 15.6 Hz, 1H), 3.35–3.12 (m, 4H), 2.30–2.02 (m, 9H), 1.82–1.52 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.6, 161.9, 161.7 (d, $J_{C,F}$ = 244 Hz), 138.6, 135.8, 133.8 (d, $J_{C,F}$ = 3.2 Hz), 130.2 (d, $J_{C,F}$ = 7.9 Hz), 128.8, 127.3, 115.3 (d, $J_{C,F}$ = 21.1 Hz), 103.6, 65.5, 61.8, 46.5, 42.0, 35.5, 35.0, 31.7, 26.4, 25.1, 21.1; MS (EI) m/z 390 (M^+). The free base was converted to the hydrochloride salt: mp 165 °C (dec); $[\alpha]_D^{20}$ −66.6° (c 0.29, CH_3OH); Anal. Calcd for $C_{25}H_{28}ClFN_2O{\cdot}1.5H_2O$: C, 66.14; H, 6.88; N, 6.17. Found: C, 65.74; H, 6.51; N, 6.07.

Compound **4b:** oil; ^1H NMR ($CDCl_3$) δ 7.05–6.84 (m, 6H), 6.69–6.59 (m, 2H), 3.51–3.43 (m, 1H), 3.23–3.08 (m, 2H), 3.03 (dd, J = 6.0, 2.1 Hz, 1H), 2.65 (ddd, J = 12.6, 12.6, 2.4 Hz, 1H), 2.35–2.08 (m, 8H), 2.01 (s, 3H), 1.75–1.62 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 169.4, 164.0, 159.2 (d, $J_{C,F}$ = 226 Hz), 139.1, 135.8, 131.5 (d, $J_{C,F}$ = 8.0 Hz), 128.8, 127.8, 126.8 (d, $J_{C,F}$ = 3.4 Hz), 117.4, 115.5 (d, $J_{C,F}$ = 21.3 Hz), 66.3, 62.1, 45.7, 42.1, 36.6, 36.1, 26.8, 25.2, 21.1, 10.5; MS (EI) m/z 390 (M^+). The free base was converted to the hydrochloride salt: mp 208 °C (dec); $[\alpha]_D^{20}$ +18.0° (c 0.25, CH_3OH); Anal. Calcd for $C_{25}H_{28}ClFN_2O{\cdot}1.75H_2O$: C, 65.49; H, 6.92; N, 6.11. Found: C, 65.24; H, 6.53; N, 6.03.

5.4. 3β-(4-Chlorophenyl)-2β-[3′-(4-chlorobenzyl)isoxazol-5-yl]-tropane (3c) and 3β-(4-chlorophenyl)-2β-[3′-methyl-4′-(4-chlorophenyl)isoxazol-5-yl]tropane (4c)

The procedure for **3a** and **4a** was followed using 1.07 g (3.66 mmol) of **6a** and 2.02 g (11.0 mmol) of 1-(4-chlorophenyl)propan-2-one oxime to give 85.0 mg (5%) of **3c** and 180 mg (12%) of **4c**.

Compound **3c:** oil; ^1H NMR ($CDCl_3$) δ 7.31–7.22 (m, 2H), 7.14–7.07 (m, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.11 (s, 1H), 3.90 (d, J = 15.6 Hz, 1H), 3.81 (d, J = 15.6 Hz, 1H), 3.36–3.14 (m, 4H), 2.30–2.04 (m, 6H), 1.82–1.53 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 161.8, 140.3, 136.5, 132.6, 132.2, 130.1, 128.9, 128.7, 128.3, 103.7, 65.5, 61.7, 46.4, 42.1, 35.5, 34.9, 31.9, 26.5, 25.1; MS (EI) m/z 426 (M^+). The free base was converted to the hydrochloride salt: mp 192 °C (dec); $[\alpha]_D^{20}$ −88.3° (c 0.31, CH_3OH); Anal. Calcd for $C_{24}H_{25}Cl_3N_2O{\cdot}0.75H_2O$: C, 60.39; H, 5.60; N, 5.87. Found: C, 60.70; H, 5.85; N, 5.62.

Compound **4c:** oil; ^1H NMR ($CDCl_3$) δ 7.35–7.27 (m, 2H), 7.14–7.05 (m, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 3.54–3.42 (m, 1H), 3.22–3.08 (m, 2H), 3.04 (dd, J = 6.0, 2.1 Hz, 1H), 2.64 (ddd, J = 12.9, 12.9, 2.7 Hz, 1H), 2.30–2.06 (m, 5H), 2.03 (s, 3H), 1.77–1.63 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0, 157.7, 140.7, 133.9, 132.2, 131.0, 129.2, 129.0, 128.3, 117.5, 66.3, 62.0, 45.7, 42.1, 36.4, 35.8, 26.8, 25.2, 10.5; MS (EI) m/z 426 (M^+). The free base was converted to the hydrochloride salt: mp 248 °C (dec); $[\alpha]_D^{20}$ +71.4° (c 0.37, CH_3OH); Anal. Calcd for $C_{24}H_{25}Cl_3N_2O{\cdot}0.25H_2O$: C, 61.55; H, 5.49; N, 5.89. Found: C, 61.49; H, 5.75; N, 5.78.

5.5. 3β-(4-Methylphenyl)-2β-[3′-(4-chlorobenzyl)isoxazol-5-yl]-tropane (3d) and 3β-(4-methylphenyl)-2β-[3′-methyl-4′-(4-chlorophenyl)isoxazol-5-yl]tropane (4d)

The procedure for **3a** and **4a** was followed using 1.00 g (3.66 mmol) of **6b** and 2.02 g (11.0 mmol) of 1-(4-chlorophenyl)propan-2-one oxime to give 40.0 mg (3%) of **3d** and 160 mg (11%) of **4d**.

Compound **3d:** oil; ^1H NMR ($CDCl_3$) δ 7.31–7.20 (m, 2H), 7.10–6.77 (m, 6H), 6.10 (s, 1H), 3.91 (d, J = 15.6 Hz, 1H), 3.81 (d, J = 15.6 Hz, 1H), 3.40–3.17 (m, 4H), 2.40–2.03 (m, 9H), 1.88–1.57 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 161.8, 138.6, 136.6, 136.1, 132.5, 131.1, 130.2, 129.0, 128.7, 127.4, 103.8, 65.6, 62.0, 46.5, 42.1, 35.5, 34.9, 31.9, 26.6, 25.1, 21.2; MS (EI) m/z 406 (M^+). The free base was converted to the hydrochloride salt: mp 180 °C (dec); $[\alpha]_D^{20}$

−75.4° (*c* 0.40, CH_3OH); Anal. Calcd for $C_{25}H_{28}Cl_2N_2O{\cdot}0.5H_2O$: C, 66.37; H, 6.46; N, 6.19. Found: C, 66.38; H, 6.61; N, 5.87.

Compound **4d:** oil; ^1H NMR ($CDCl_3$) δ 7.30–7.23 (m, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.67–7.57 (m, 2H), 3.53–3.44 (m, 1H), 3.23–3.09 (m, 2H), 3.04 (dd, *J* = 6.0, 2.0 Hz, 1H), 2.66 (ddd, *J* = 12.9, 12.9, 2.7 Hz, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 2.24–2.04 (m, 2H), 2.02 (s, 3H), 1.78–1.63 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.4, 157.6, 139.0, 136.0, 133.7, 131.2, 129.4, 128.9, 128.8, 127.8, 117.4, 66.3, 62.2, 45.7, 42.1, 36.6, 36.0, 26.9, 25.2, 21.1, 10.6; MS (EI) *m/z* 406 (M^+). The free base was converted to the hydrochloride salt: mp 245 °C (dec); $[\alpha]_D^{20}$ +51.1° (*c* 0.33, CH_3OH); Anal. Calcd for $C_{25}H_{28}Cl_2N_2O{\cdot}1.25H_2O$: C, 64.45; H, 6.60; N, 6.01. Found: C, 64.50; H, 6.42; N, 5.92.

5.6. 3β-(4-Chlorophenyl)-2β-[3′-(4-methylbenzyl)isoxazol-5-yl]-tropane (3e) and 3β-(4-chlorophenyl)-2β-[3′-methyl-4′-(4-methylphenyl)isoxazol-5-yl]tropane (4e)

The procedure for **3a** and **4a** was followed using 1.07 g (3.66 mmol) of **6a** and 1.79 g (11.0 mmol) of 1-(4-methylphenyl)propan-2-one oxime to give 250 mg (17%) of **3e** and 130 mg (9%) of **4e**.

Compound **3e:** oil; ^1H NMR ($CDCl_3$) δ 7.16–6.96 (m, 6H), 6.88–6.79 (m, 2H), 6.13 (s, 1H), 3.91 (d, *J* = 16.5 Hz, 1H), 3.80 (d, *J* = 16.5 Hz, 1H), 3.33–3.13 (m, 4H), 2.34 (s, 3H), 2.30–2.03 (m, 6H), 1.82–1.53 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8, 162.3, 140.3, 136.0, 134.8, 132.1, 129.2, 128.9, 128.5, 128.2, 103.8, 65.4, 61.6, 46.3, 41.9, 35.5, 34.9, 32.0, 26.4, 25.0, 21.1; MS (EI) *m/z* 406 (M^+). The free base was converted to the hydrochloride salt: mp 108 °C (dec); $[\alpha]_D^{20}$ −70.0° (*c* 0.37, CH_3OH); Anal. Calcd for $C_{25}H_{28}Cl_2N_2O{\cdot}0.5H_2O$: C, 66.37; H, 6.46; N, 6.19. Found: C, 66.26; H, 6.64; N, 6.04.

Compound **4e:** oil; ^1H NMR ($CDCl_3$) δ 7.20–7.03 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 3.52–3.44 (m, 1H), 3.27–2.96 (m, 3H), 2.67 (ddd, *J* = 12.0, 12.0, 2.1 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 2.26–2.07 (m, 2H), 2.03 (s, 3H), 1.76–1.62 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 158.0, 140.8, 137.4, 132.0, 129.5, 129.4, 129.2, 128.2, 127.6, 118.3, 66.4, 62.0, 45.4, 42.1, 36.2, 35.8, 26.8, 25.1, 21.3, 10.6; MS (EI) *m/z* 406 (M^+). The free base was converted to the hydrochloride salt: mp 248 °C (dec); $[\alpha]_D^{20}$ +61.5° (*c* 0.35, CH_3OH); Anal. Calcd for $C_{25}H_{28}Cl_2N_2O{\cdot}0.5H_2O$: C, 66.37; H, 6.46; N, 6.19. Found: C, 66.62; H, 6.42; N, 6.07.

5.7. 3β-(4-Methylphenyl)-2β-[3′-(4-methylbenzyl)isoxazol-5-yl]-tropane (3f) and 3β-(4-methylphenyl)-2β-[3′-methyl-4′-(4-methylphenyl)isoxazol-5-yl]tropane (4f)

The procedure for **3a** and **4a** was followed using 1.00 g (3.66 mmol) of **6b** and 1.79 g (11.0 mmol) of 1-(4-methylphenyl)propan-2-one oxime to give 550 mg (39%) of **3f** and 105 mg (7%) of **4f**.

Compound **3f:** oil; ^1H NMR ($CDCl_3$) δ 7.10 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 7.8 Hz, 2H), 6.15 (s, 1H), 3.92 (d, *J* = 15.0 Hz, 1H), 3.81 (d, *J* = 15.0 Hz, 1H), 3.35–3.13 (m, 4H), 2.33 (s, 3H), 2.30–2.02 (m, 9H), 1.85–1.50 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.1, 161.9, 138.1, 135.6, 135.4, 134.8, 128.9, 128.6, 128.4, 127.2, 103.4, 65.2, 61.5, 46.3, 41.8, 35.4, 34.8, 31.7, 26.2, 24.8, 20.9, 20.8; MS (EI) *m/z* 386 (M^+). The free base was converted to the hydrochloride salt: mp 193 °C (dec); $[\alpha]_D^{20}$ −61.9° (*c* 0.43, CH_3OH); Anal. Calcd for $C_{26}H_{31}ClN_2O{\cdot}0.75H_2O$: C, 71.54; H, 7.50; N, 6.42. Found: C, 71.61; H, 7.37; N, 6.34.

Compound **4f:** oil; ^1H NMR ($CDCl_3$) δ 7.11 (d, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 8.1 Hz, 2H), 3.50–3.41 (m, 1H), 3.22–3.08 (m, 3H), 2.68 (ddd, *J* = 12.3, 12.3, 2.1 Hz, 1H), 2.40 (s, 3H), 2.24 (s, 6H), 2.21–2.06 (m, 2H), 2.01 (s, 3H), 1.72–1.60 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.1, 157.8, 139.2, 137.2, 135.7, 129.6, 129.2, 128.8, 127.9, 127.7, 118.1, 66.5, 62.1, 45.6, 42.1, 36.4, 36.1, 26.8, 25.2, 21.3, 21.1, 10.6; MS (EI) *m/z* 386 (M^+). The free base was converted to the hydrochloride salt: mp 249 °C (dec); $[\alpha]_D^{20}$ +44.7° (*c* 0.34, CH_3OH); Anal. Calcd for $C_{26}H_{31}ClN_2O{\cdot}1.25H_2O$: C, 70.10; H, 7.58; N, 6.29. Found: C, 70.22; H, 7.36; N, 6.35.

5.8. 3β-(4-Chlorophenyl)-2β-[3′-(4-methoxybenzyl)isoxazol-5-yl]-tropane (3g) and 3β-(4-chlorophenyl)-2β-[3′-methyl-4′-(4-methoxyphenyl)isoxazol-5-yl]tropane (4g)

The procedure for **3a** and **4a** was followed using 1.07 g (3.66 mmol) of **6a** and 1.97 g (11.0 mmol) of 1-(4-methoxylphenyl)propan-2-one oxime to give 510 mg (33%) of **3g** and 101 mg (7%) of **4g**.

Compound **3g:** oil; ^1H NMR ($CDCl_3$) δ 7.14–6.99 (m, 4H), 6.90–6.80 (m, 4H), 6.10 (s, 1H), 3.89 (d, *J* = 15.6 Hz, 1H), 3.81 (s, 3H), 3.77 (d, *J* = 15.6 Hz, 1H), 3.34–3.13 (m, 4H), 2.30–2.05 (m, 6H), 1.83–1.56 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 162.6, 158.4, 140.4, 132.1, 130.0, 129.7, 128.9, 128.3, 114.0, 103.8, 65.4, 61.7, 55.4, 46.4, 42.0, 35.5, 35.0, 31.6, 26.5, 25.1; MS (EI) *m/z* 422 (M^+). The free base was converted to the hydrochloride salt: mp 178 °C (dec); $[\alpha]_D^{20}$ −62.4° (*c* 0.34, CH_3OH); Anal. Calcd for $C_{25}H_{28}Cl_2N_2O_2{\cdot}0.75H_2O$: C, 63.49; H, 6.29; N, 5.92. Found: C, 63.20; H, 6.38; N, 5.78.

Compound **4g:** white solid; mp 58.0–59.0 °C; ^1H NMR ($CDCl_3$) δ 7.14–7.08 (m, 2H), 6.95–6.80 (m, 4H), 6.72–6.63 (m, 2H), 3.82 (s, 3H), 3.52–3.42 (m, 1H), 3.24–3.06 (m, 3H), 2.66 (ddd, *J* = 12.3, 12.3, 2.4 Hz, 1H), 2.25 (s, 3H), 2.24–2.05 (m, 2H), 2.02 (s, 3H), 1.75–1.62 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 168.6, 159.2, 158.1, 140.9, 132.0, 130.9, 129.2, 128.2, 122.9, 118.1, 114.2, 66.5, 62.0, 55.4, 45.5, 42.1, 36.3, 35.8, 26.9, 25.2, 10.6; MS (EI) *m/z* 422 (M^+). The free base was converted to the hydrochloride salt: mp 243 °C (dec); $[\alpha]_D^{20}$ +69.4° (*c* 0.39, CH_3OH); Anal. Calcd for $C_{25}H_{28}Cl_2N_2O_2{\cdot}1.25H_2O$: C, 62.31; H, 6.38; N, 5.81. Found: C, 62.34; H, 6.42; N, 5.77.

5.9. 3β-(4-Methylphenyl)-2β-[3′-(4-methoxybenzyl)isoxazol-5-yl]tropane (3h) and 3β-(4-methylphenyl)-2β-[3′-methyl-4′-(4-methoxyphenyl)isoxazol-5-yl]tropane (4h)

The procedure for **3a** and **4a** was followed using 1.00 g (3.66 mmol) of **6b** and 1.97 g (11.0 mmol) of 1-(4-methoxylphenyl)propan-2-one oxime to give 631 mg (43%) of **3h** and 52.0 mg (4%) of **4h**.

Compound **3h:** oil; ^1H NMR ($CDCl_3$) δ 7.08–6.90 (m, 4H), 6.86–6.77 (m, 4H), 6.13 (s, 1H), 3.89 (d, *J* = 15.3 Hz, 1H), 3.80 (s, 3H), 3.79 (d, *J* = 15.3 Hz, 1H), 3.32–3.10 (m, 4H), 2.30–2.01 (m, 9H), 1.84–1.53 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 162.2, 158.2, 138.6, 135.6, 130.0, 129.6, 128.7, 127.3, 113.8, 103.5, 65.3, 61.7, 55.1, 46.4, 41.9, 35.5, 34.9, 31.4, 26.3, 24.9, 21.0; MS (EI) *m/z* 402 (M^+). The free base was converted to the hydrochloride salt: mp 168 °C (dec); $[\alpha]_D^{20}$ −68.7° (*c* 0.53, CH_3OH); Anal. Calcd for $C_{26}H_{31}ClN_2O_2{\cdot}1.5H_2O$: C, 67.01; H, 7.35; N, 6.01. Found: C, 66.72; H, 7.33; N, 5.80.

Compound **4h:** oil; ^1H NMR ($CDCl_3$) δ 7.00–6.76 (m, 6H), 6.66–6.55 (m, 2H), 3.82 (s, 3H), 3.50–3.40 (m, 1H), 3.20–3.02 (m, 3H), 2.67 (ddd, *J* = 12.3, 12.3, 2.1 Hz, 1H), 2.24 (s, 6H), 2.21–2.05 (m, 2H), 2.01 (s, 3H), 1.75–1.60 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.1, 159.1, 158.10, 139.3, 135.8, 131.0, 128.8, 127.8, 123.2, 117.9, 114.0, 66.5, 62.2, 55.4, 45.7, 42.2, 36.5, 36.2, 26.9, 25.2, 21.1, 10.6; MS (EI) *m/z* 402 (M^+). The free base was converted to the hydrochloride salt: mp 238 ° C (dec); $[\alpha]_D^{20}$ +50.7° (*c* 0.28, CH_3OH); Anal. Calcd for $C_{26}H_{31}ClN_2O_2{\cdot}1.25H_2O$: C, 67.67; H, 7.32; N, 6.07. Found: C, 67.56; H, 7.35; N, 5.96.

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