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Synthesis and structure–activity relationship studies of 3-biaryl-8-oxabicyclo[3.2.1]octane-2-carboxylic acid methyl esters

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ABSTRACT

Stille cross coupling protocols were utilized for the synthesis of 3-(biaryl)-8-oxabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl esters, which furnished products in high yields where in some cases Suzuki coupling under the conditions utilized provided complex reaction mixture. Samarium iodide reduction of the resulting coupling products produced both of the 2β-carbomethoxy-3-biaryl-8-oxabicyclo[3.2.1]octane diastereomers and the 2α-carbomethoxy-3-biaryl-8-oxabicyclo[3.2.1]octane diastereomers. Among the series synthesized, the benzothiophene substituted compounds demonstrated significant binding profiles of inhibition of WIN 35,438 with 177-fold selectivity for DAT versus SERT.

1. Introduction

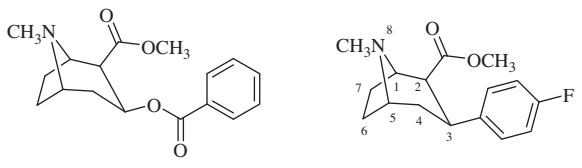
Cocaine abuse is a serious international public health problem that results from its powerful psychostimulant and reinforcing effects. Chronic use of cocaine can impair central nervous system function by blockade of neurotransmitter uptake by dopamine, serotonin and norepinephrine reuptake systems.[1–5] Cocaine abuse has profound effects on other organ systems, in particular the cardiovascular system.

Considerable research has been devoted to gaining an understanding of the mechanism of action by which cocaine produces its pharmacological effects. In the brain, the neurotransmitter dopamine (DA) is released by presynaptic neurons into the synapse for signal transduction, where it can then bind at dopamine receptors of neighboring neurons. Under normal circumstances, excess synaptic DA is recycled back into the presynaptic neurons by the dopamine active transporter (DAT). Cocaine (**1**) binds to the DAT and thus inhibits dopamine reuptake from the synapse, thereby causing an accumulation of dopamine in the synapse. This, in turn, leads to an increase in dopaminergic neurotransmission and continuous stimulation of receiving postsynaptic neurons.

Cocaine's addictive properties are thought to depend largely on its ability to inhibit DAT.[1,6–10] In addition to the DAT, cocaine also binds at the serotonin reuptake transporter (SERT) and norepinephrine (NET) transporters with moderate affinity.[11–14]

The DAT has been a prime focus for development of medications for cocaine abuse and there have been intensive research efforts over the last few decades toward discovery of cocaine pharmacotherapies based on this dopamine hypothesis[1]

The prototypical tropane (−)-2β-carbomethoxy-3β-(4-fluorophenyl)tropane (WIN 35,428, compound **2**), an analog of cocaine (Fig. 1), has provided a lead for many researchers working in this field.[15] These analogs of WIN 35,428 have provided significant insights and a large number of analogs have been reported to



1 Cocaine

2 WIN35,428

Figure 1. Structures of cocaine and WIN 35,428.

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manifest selective and potent binding to monamine reuptake systems.[16–20]

Despite extensive research on this subject,[11,12] a comprehensive understanding of the mechanism of action of cocaine and its tropane analogs at the molecular level has been elusive. We[21,22] have reported that the 8-amine functionality present in WIN 35,428 is not essential for inhibitory potency at the DAT. Indeed, this amine can be exchanged for an ether,[23] a thioether[23] and even a methylene[24] with very limited effect on DAT or SERT inhibition.[25] Davies[26] and Fu[27] have reported the synthesis and binding profile of 3-heterobiaryl systems in the 8-azabicyclo[3.2.1]octane series and shown a preferred selectivity of the SERT over the DAT for 4-(2-pyrrolyl)phenyl[10] and 4-(2-thiophenyl)phenyl[17] at the 3-position. In contrast 3-monoaryl systems demonstrated DAT selectivity.[28]

We have reported that within the broad class of 8-heterobicyclo[3.2.1]octane systems, the 2β-carbomethoxy-3β-aryl configured compounds showed interesting structure–activity relationship (SAR) profiles.[29–31] The chair configured diastereomers demonstrated potency at DAT and SERT while the 2β-carbomethoxy-3α-aryl ones manifested far weaker potency at SERT.

To further develop a comprehensive picture about the substituent role in the inhibition effect of DAT and SERT, the synthesis of the ligands with the *para*- and *meta*-aryl phenyl groups and various heteroaryl substituents at the 3-position of oxatropanes would be important. In this regard, the present study undertook the synthesis of several oxatropene series and evaluated SAR profiles of both oxatropenes synthesized and some of their corresponding SmI_2 reduction products. We now present synthesis and binding profiles of Series of II–V.

2. Results and discussion

2.1. Chemistry

The primary goal of this study was to develop a broader understanding about the type and the nature of the side groups at the 3-position of the oxatropane skeleton on the effect of inhibiting DAT and SERT. The derivatives of the first series contained benzene units with five-membered heteroaryl groups at the *para*-position. The second series provided compounds with heteroaryl substituents at the *meta*-position of the benzene unit. Series III furnished derivatives with heterobiarly substituents. In Series IV and V, the biaryl substituents were directly connected to the tropane skeleton through the heteroring of the side groups. We recently reported the synthesis and DAT and SERT inhibitory potencies of a small series of 3-biaryloxatropanes (Series I, in Fig. 2).[32] We now report an extension of this study to include remaining series (Fig. 2).

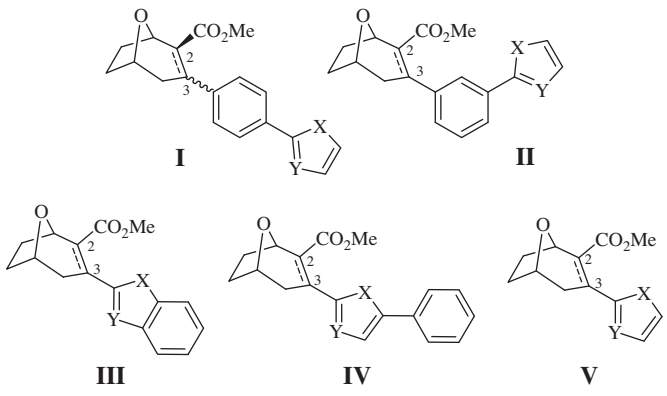


Figure 2. Structures of 8-oxa[3.2.1]octan(en)es.

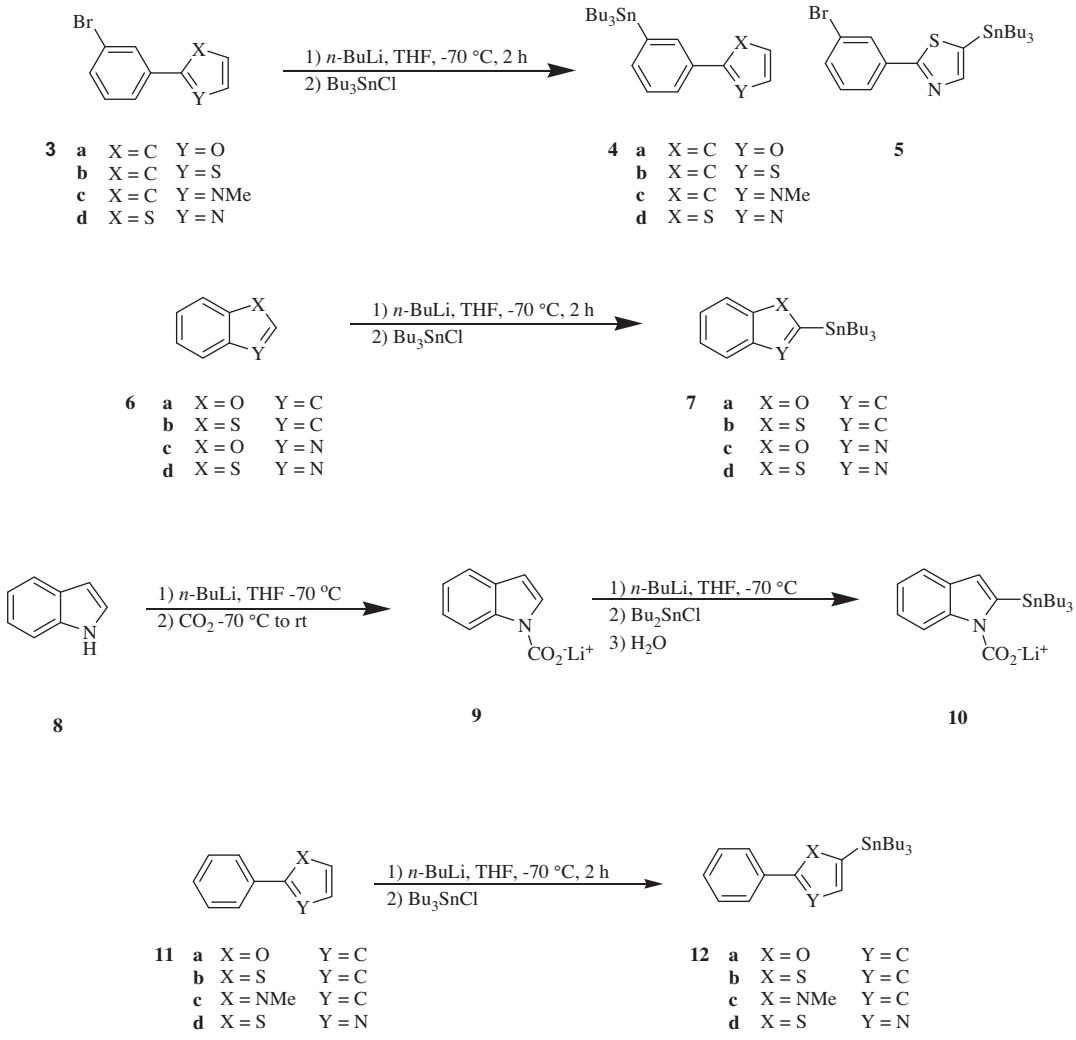
Syntheses of organostannane *building blocks* used to construct the targeted compounds are presented in Scheme 1. Compounds **3a–d** were prepared under Stille conditions in the presence of $Pd[P(Ph_3)]_4$ in dioxane by the treatment of 3-bromo-1-iodobenzene with the corresponding arylstannanes and purified by column chromatography. These compounds were then treated with *n*-BuLi at −70 °C in THF and reacted with Bu_3SnCl to furnish the intermediates **4a–d**. Compound **4d** was obtained along with **5** in approximately 1:1 ratio from the reaction of **3d** as evidenced by the presence of $(M+H)^+$ peaks at 452 and 529 in the mass spectra of the mixture, which correspond to the protonated molecular ion peaks of **4d** and **5**, respectively. In addition the coupling between compound **13** and mixture of **4d** and **5** resulted in the formation of the corresponding compounds **14i** and **14j** in 42% and 40% yields, respectively, providing conclusive evidence for the ratio of compounds **4d** and **5**. Purification of the organostannane intermediates **4a–d** by chromatographic methods resulted in significant destannylation. Therefore, they were used without purification and in slight excess in the subsequent coupling reactions. Intermediate stannanes **7a–d** could be purified by fractional distillation at reduced pressure. Intermediates **10** and **12a–d** were synthesized similarly.

Synthesis of the target compounds was readily achieved by the Stille cross-coupling protocol (Scheme 2). Thus reaction of triflate **13**[30] with the corresponding arylstannane intermediates in Scheme 1 produced the desired products **14a–u** in high yields. Reactions were carried out in 1-methyl-2-pyrrolidinone at room temperature in the presence of $ZnCl_2$, tri-2-furylphosphine and tris(dibenzylideneacetone)dipalladium(0) for overnight or in dioxane at reflux temperature in the presence of tetrakis(triphenylphosphine)palladium(0) ($Pd[(PPh_3)]_4$) for overnight. The crude reaction mixtures were treated with 10% aq KF to remove the tin by-product by converting it into insoluble tributyltin fluoride. Further purification was accomplished by flash chromatography on silica gel with ethyl acetate/hexane (1:9) as the eluent. When necessary, products were further purified by recrystallization. The compounds were characterized by ^1H NMR, mass spectrometry and elemental analysis.

The Stille cross-coupling reaction conditions were quite successful in producing the target compounds (**14e–u**) in reasonably high yields (67–93%) as seen in Table 1, comparable to the reported reactions of Series I[32] (**14a–d**). The exception was the reaction with the benzoxazole stannane **7c** intermediate for the synthesis of **14k** which was obtained in 10% yield.[33]

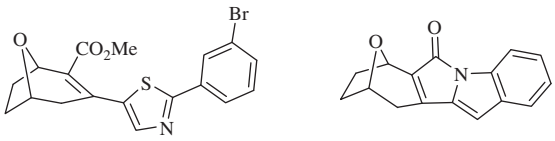
Compounds **14h** and **14i** were obtained nearly equal quantities. The unintended compound **14i** was the product from the coupling with the intermediate **5.** The reaction with indolestannane **10** produced the target compounds **14n** with 56% yields as the major product along with lactam **15** in 10% yields, which was conceivably formed via intramolecular lactamization. Structures of the compounds synthesized were confirmed by spectroscopic means and spectral data are provided in Section 5.

We also utilized Suzuki conditions for the synthesis of some oxatropenes. Under the Suzuki conditions employed ($Pd(PPh_3)_4$, LiCl, Na_2CO_3, dioxane, reflux, **4h**) the reaction between triflate **13** and benzofuranboronic acid provided compound **14j** in 82% yield. On the other hand, the reaction between compound **13** with thiophenboronic acid furnished a complex reaction mixture. H NMR spectrum of the crude reaction mixture showed three well-resolved carbomethoxy signals with comparable intensities,



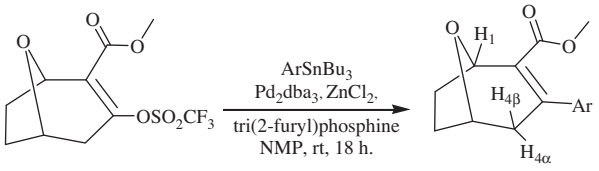
Scheme 1. Synthesis of organostannane intermediates.

indicating the presence of **14m** (2,3-unsaturated) and two other products, which are presumably 3,4-unsaturated compounds one with 2α-CO_2CH_3 and the other with 2β-CO_2CH_3 orientation.



14i

15



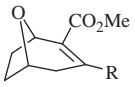
Scheme 2. Synthesis of 3-biaryloxatropenes via Stille coupling.

The ^1H NMR spectral data for the bicyclic skeleton of compounds **14e–u** are in good agreement with the previous assignments for the 2-carbomethoxy-3-(4-heteroaryl)-8-oxa-[3.2.1]octene systems (**14a–d)**. The chemical shifts of diagnostic skeletal protons are given in Table 2. The H_1 proton shows a doublet between δ 4.97–5.01 while H_5 appears as multiplet at δ 4.65–4.68. In addition, $H_{4\beta}$ appears as a double doublet at δ 2.98–3.09 with the $H_{4\alpha}$ proton as a doublet at δ 2.08–2.18.

The saturated target compounds (**16a–u**) were obtained by reduction of the 2,3-ene precursors (**14a–u**). Catalytic reduction provides mainly 2α-$COOCH_3$ compounds (diastereomer **C**, Fig. 3) due to the preferred β-face reduction. As previously reported, 2α-$COOCH_3$ diastereomers are generally not effective inhibitors of DAT and SERT.[6] Therefore our method of choice employed SmI_2 in a protic solvent, which furnished 2β-carbomethoxy configured compounds (Table 4) as the predominant reduction products.[30,34] This route produced the biologically more interesting 2β,3α-configured diastereomer (**A**, Fig. 3) in minor quantity.

Reduction of the bicyclo[3.2.1]octene systems with SmI_2 in THF/MeOH at −78 °C led to substrate dependent product distributions. For example, biaryl groups attached to the bicyclooctene skeleton through the phenyl ring, as in **14a–h**, produced the 2β,3α (diastereomer **A**) compounds **16a–d, 16g** and **16h** and the 2β,3β (diastereomer **B**) compounds **16e, 16f** and **16j** as the two isolable diastereomers, with the 2β,3β-chair conformer dominating (ca.

Table 1
The 3-biaryloxatropenes **13a–u**



R

	X	Y	Yield (%)		X	Y	Yield (%)		X	Y	Yield (%)		X	Y	Z	Yield (%)
14a	O	C	82	**14e**	O	C	75	**14j**	O	C	81	**14o**	S	C	H	85
b	S	C	85	**f**	S	C	91	**k**	O	N	10	**p**	O	C	H	93
c	NMe	C	79	**g**	NMe	C	93	**l**	S	N	67	**q**	NMe	C	H	80
d	S	N	79	**h**	S	N	42	**m**	S	C	78	**r**	S	N	H	85
								n	NH	C	56	**s**	O	C	Ph	80
												t	S	C	Ph	85
												u	NMe	C	Ph	80

Table 2
Diagnostic ^{1}H NMR data for compounds **14e–u**

Chemical shifts (ppm)					
Compounds	H_1	$H_{4\beta}$(dd)	$H_{4\alpha}$(d)	H_5	Compounds
O-2784	**14e**	5.03	2.98	2.16	4.65
O-2550	**14f**	4.94	3.05	2.25	4.68
O-2569	**14g**	5.02	2.99	2.15	4.64
O-2755	**14h**	4.97	3.08	2.26	4.68
O-2738	**14i**	4.97	3.09	2.22	4.68
O-2551	**14j**	4.86	3.04	2.30	4.71
O-2835	**14k**	4.87	3.15	2.49	4.76
O-2695	**14l**	4.94	3.13	2.43	4.74
O-2688	**14m**	4.95	3.08	2.26	4.68
O-2856	**14n**	5.02	3.25	2.53	4.64
O-2799	**14o**	4.92	3.03	2.23	4.65
O-2785	**14p**	4.83	2.95	2.23	4.66
O-2800	**14q**	5.08	2.90	2.14	4.61
O-2786	**14r**	4.81	3.02	2.33	4.64
O-2810	**14s**	4.87	2.99	2.25	4.69
O-2811	**14t**	4.93	3.04	2.24	4.65
O-2809	**14u**	5.11	2.95	2.21	4.64

3:1 ratio). These two diastereomers (**A** and **B**) have the C2-carbomethoxyl group pointing toward the 8-oxygen of the bicyclic system. The thiazole substituent on the 3-aryl ring had a significant influence on the SmI_2 reduction. For example, compound **14d** (4-thiazole: Series I) produced diastereomer **A**, compound **16d**, in 9% yield as compared to compound **14h** (3-thiazole) in Series II provided diastereomer **C**, compound **16k** in 23% yield as the only isolable products.

The trend of the diastereoselectivity is less clear and the product distribution is more complex with compounds **14j–u** where the heterocyclic ring is attached to the bicyclic skeleton. For example, the diastereofacial selectivity was reversed in the case of thiofuran **14o** producing 2α3β (diastereomer **D**, **16t**) as the major product with 74% yield and 2β,3α (diastereomer **A**, **16u**; 9% yield), while the indole substituted compound **14n** resulted in diastereomers **B, C** and **D** (**16o–q**) in comparable yields (14%, 20% and 15% yields, respectively). In contrast, the benzofuran derivative **14j**, produced diastereomer **C**, **16l**, as the only isolable product in 60% yield, while the benzothiofuran derivative **14m** provided **A** and **D** diastereomers, compounds **16m** and **16n**, with 48% and 6% yields, respectively.

3. Discussion

There has been extensive research in the developing potential medications for cocaine abuse. Much effort has been devoted for synthesis and biological evaluation of cocaine-like compounds where substituents at certain position were systematically changed. In this regard 3β-aryl-8-azabicyclo[3.2.1]octane-2β-carboxylates are among the most widely studied oxatropanes. Introduction of a naphthyl group into the tropane-based cocaine analogs established much significant effect in SERT affinity. Davies et al. showed that 2-naphthyl derivative at the 3β position resulted in a very potent tropane analog.[35] In addition, the 4-isopropyl phenyl derivative demonstrated good selectivity for SERT transporter.[28] The N-methylated 3β-(4(2-pyrrolyl)phenyl derivative showed 585-fold selectivity for SERT transporter over DAT

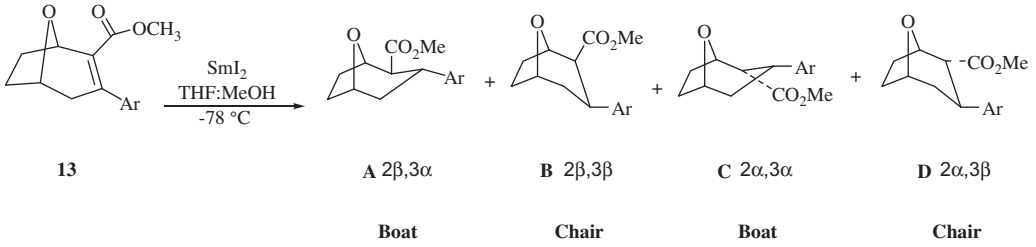


Figure 3. Synthesis of 3-(biaryl)-8-oxabicyclo[3.2.1]octane-2-carboxylic acid methyl esters.

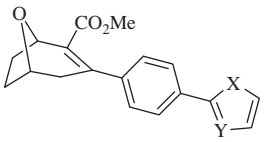
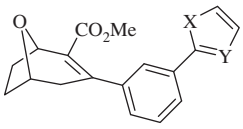
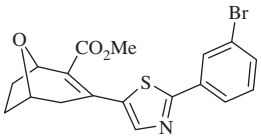
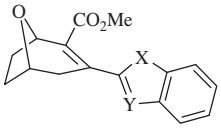
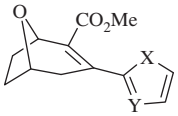
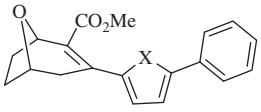
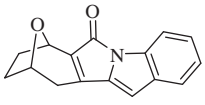
(1.05 nM vs 614 nM), respectively.[26] On the other hand, the 3β-(5-indlyl)-8-azabicyclo[3.2.1]octanes showed binding affinities to both DAT and SERT transporters at 0.7–5.5 nM range with lack of selectivity.[26,41] In contrast, Dutta and co-workers showed that replacement of the benzylic group by naphthyl moiety in structurally constrained 1,4-diazabicyclo[3.3.1]nonane systems resulted in reduction of the affinity for DAT.[36] However, the 2-naphthyl derivatives demonstrated about threefold more potency as compared to the 1-naphthyl derivative.

Fu and co-workers reported binding profiles of series of tropane analogs of cocaine. They saw that introduction of aryl or heteroaryl groups in the *para* position of 3β-phenylazatropane ring provided an increase in affinity and selectivity for SERT versus DAT and NET transporters.[37]

From our laboratories, we reported high inhibition profile for 2β-carbomethoxy-3β-(2-naphthyl)-8-aza-bicyclo[3.2.1]octanes (0.49 nM for DAT and 2.19 nM for SERT).[21] In addition, we also observed remarkable binding profiles of 2β-carbomethoxy-3β-(3,4-dichlorophenyl)-8-aza-, 8-oxa-, and 8-thia-bicyclo[3.2.1]octanes, which showed comparable nanomolar potency at DAT and SERT (1.1, 3.3, 2.0 for DAT and 2.5, 4.7, 3.0 for SERT, respectively).[25]

A preliminary report[32] from these laboratories described the synthesis and DAT and SERT inhibitory potencies of compounds in Series I (Scheme 2). We reported that within a series of carboxylic acid methyl esters of (*R,S*)3-(4-heteroarylphenyl)-8-oxabicyclo[3.2.1]octan(en)e, the saturated 3α-aryl and 3β-aryl diastereomers were more potent inhibitors of the SERT compared with their inhibition of the DAT. We have now extended the SAR

Table 3
2-Carbomethoxy-3-aryl-8-oxabicylclo[3.2.1]octenes, **17a**–**u**: Inhibition of [^{3}H]WIN 35,428[a] binding to the human dopamine transporter (hDAT) and [^{3}H]citalopram binding[b] to the human serotonin transporter (hSERT)[c]

Series	Org#	Compd	X,Y	DAT	SERT	DAT/SERT[c]
				IC_{50} (nM)		
	**O-2546**	**14a**	O,C	102	248	0.4
	O-2783	**14b**	S	272	242	1
	O-2547	**14c**	NCH_3,C	>3 μM	>3 μM	1
	O-2861	**14d**	S,N	>3 μM	>3 μM	1
Series I						
	**O-2784**	**14e**	O,C	>10 μM	710	>14
	O-2550	**14f**	S,C	>10 μM	>1 μM	< 0.7
	O-2569	**14g**	NCH_3,C	>3 μM	870	>14
	O-2755	**14h**	S,N	>3 μM	>3 μM	1
Series II						
	**O-2738**	**14i**		>3 μM	>3 μM	1
	**O-2551**	**14j**	O,C	349	>3 μM	<0.1
	O-2835	**14k**	O,N	>3 μM	>3 μM	1
	O-2695	**14l**	S,N	>1 μM	>3 μM	<0.5
	O-2668	**14m**	S,C	13	>2 μM	<0.004
	O-2856	**14n**	NH,C	336	>3 μM	<0.1
Series III						
	**O-2799**	**14o**	S,C	>3 μM	>3 μM	1
	O-2785	**14p**	O,C	>3 μM	>3 μM	1
	O-2800	**14q**	NCH_3,C	>3 μM	>3 μM	1
	O-2768	**14r**	S,N	>3 μM	>3 μM	1
Series IV						
	**O-2810**	**14s**	O	>3 μM	>3 μM	1
	O-2811	**14t**	S	>3 μM	>3 μM	1
	O-2809	**14u**	NCH_3	>3 μM	>3 μM	1
Series V						
	**O-2862**	**15**		>3 μM	>3 μM	1

[a] Binding affinity[38] DAT: 12.9 nM; SERT: 160 nM.
[b] Binding affinity DAT:[39] 17.7 μm, SERT[23]: 2.43 nM.
[c] Compounds are racemic. Each value is the mean of two or more independent experiments, each conducted in triplicate.

in this class by introduction of new aryl substituents at the 3-position of the 8-oxabicyclo[3.2.1]octane systems.

In this study we synthesized new series of 2,3-ene compounds **14e–u**, and 2,3-oxatropanes, compounds **16e–u**, and investigated their inhibitory potencies of DAT and SERT. Triflate **13** was reacted under Stille conditions with arylstannanes in Scheme 1 to obtain corresponding oxatropese **14e–u** in high yields, which then were subjected to SmI_2 reduction conditions to obtain the 2,3-oxatropane diastereomers **16e–u**.

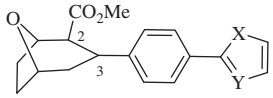
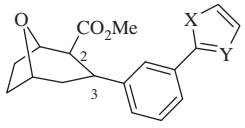
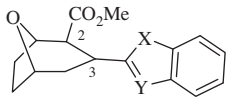
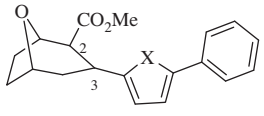
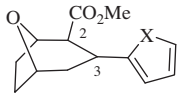
The data obtained for inhibition of ligand binding at both DAT and SERT for the compounds in Tables 3 and 4 are striking. In general, these compounds show very limited, if any, inhibitory potencies. Thus, within these series of 2,3-unsaturated compounds in Table 3, all the compounds are, at best, weak inhibitors of the DAT, **14a** (102 nM), **14b** (248 nM), **14j** (349 nm), **14n** (336 nm) and SERT **14a** (248 nm), **14b** (242 nm). The remaining compounds are effectively inactive at both transporters (IC_{50} >1 μM). This is quite unlike the activity profiles we previously reported for 8-oxatropanes devoid of a 3-biaryl or a 3-(5-membered ring) system.[25] In that case, 2,3-ene-3-phenyl-(or 3-naphthyl)-8-oxatropanes manifest substantial inhibition of the DAT, as well as some considerable selectivity versus SERT inhibition.

The exception was observed with benzothiophene substituted compound **14m** in Series III with 13 nm potency and significant selectivity (<0.004) at the DAT. The benzufora **14j**, benzoxazole **14k**, benzothiazole **14l** and indole **14n** analogs have IC_{50} values at the DAT of 349 nM, >3 μM, >1 μM and 336 nM, respectively, which showed the loss of selectivity and potency. The high binding affinity of benzothiophene could be due to electronic or interaction with distant binding location or both.

In the case of 2,3-'ane' compounds, although not selective, the most potent tropane analogs are and found in Series III. In this series, the benzothiophene substituted 2,3-saturated 2β3β-benzothiophene **16m** demonstrated 9 nM and its 2α3β counterpart **16n** showed 18 nM potencies at the DAT while they manifest IC_{50} values of 10 and 79 nM, respectively for SERT. It is noteworthy to mention that the azatopane derivative of compound **16e** as reported by Tamagnan et al. demonstrated significantly higher binding profile and SERT selectivity.[37] 2β-Carbomethoxy-3β-[2-furylphenyl]-8-aza-bicyclo[3.2.1]tropane and its N-methylated derivative showed 3.76 nM and 7.14 nM for DAT and 0.15 nm and 1.13 nM for SERT, respectively. In contrast, compound **16e** showed 64 nM for DAT and 30 nM for SERT potencies.

It is also clear that the influence of substituent bulk at the C3 position is important. A comparison of the IC_{50} values of the *meta* substituted compounds **14e,f** and **16g,h** to the *para* substituted counterparts **14a,b** and **16a,b**, respectively, shows that the extension site of the 5-membred heteroring, which increases bulkiness of the ligand as in the case of *meta* substitution, resulted in the significant loss of the binding ability to the DAT. Similar results were also reported for oxatropene with 1-naphthyl (1720 nM),

Table 4
2α,β-Carbomethoxy-3α,β-8-oxabicyclo[3.2.1]octanes **16a–u**: Inhibition of [^{3}H]WIN 35,428 binding to the human dopamine transporter (hDAT) and [^{3}H]citalopram binding to the human serotonin transporter (hSERT)[a]

Series	Org#	Compd	X,Y	Diast[b,d] (Scheme 3)	DAT	SERT	DAT/SERT[c]
					IC_{50} (nM)		
 Series I[d]	**O-2504**	**16a**	O,C	A: 2β, 3α	139	32	4
	O-2501	**16b**	S,C	A: 2β, 3α	356	35	10
	O-2570	**16c**	NCH_3,C	A: 2β, 3α	>1 μM	395	>2.5
	O-2993	**16d**	S,N	A: 2β, 3α	>1 μM	128	>7
	O-2502	**16e**	O,C	B: 2β, 3β	64	30	2
	O-2823	**16f**	NCH_3,C	B: 2β, 3β	>1 μM	566	>2
 Series II	**O-2608**	**16g**	O,C	A: 2β, 3α	>1 μM	77	>13
	O-2572	**16h**	S,C	A: 2β, 3α	>1 μM	287	> 4
	O-2573	**16j**	NCH_3,C	B: 2β, 3β	>1 μM	142	> 7
	O-3232	**16k**	S,N	C: 2α, 3β	>1 μM	>1 μM	1
 Series III	**O-2607**	**16l**	O,C	C: 2α, 3α	39	>1 μM	<0.04
	O-3245	**16m**	S,C	A: 2β, 3β	9	10	1
	O-2758	**16n**	S,C	D: 2α, 3β	18	79	0.2
	O-2967	**16o**	NH,C	C: 2α, 3α	350	>1 μM	<0.3
	O-2969	**16p**	NH,C	B: 2β, 3β	110	556	0.2
	O-2968	**16q**	NH,C	D: 2α, 3β	370	>1 μM	0.4
 Series IV	**O-2918**	**16r**	S	C: 2α, 3α	487	78	6
	O-2917	**16s**	O	C: 2α, 3α	>1 μM	640	<2
 Series V	**O-3230**	**16t**	S	D: 2α, 3β	>1 μM	>1 μM	1
	O-3231	**16u**	S	A: 2β, 3α	>1 μM	>1 μM	1

[a] Each value is the mean of two or more independent experiments, each conducted in triplicate.
[b] Compounds are racemic.
[c] Ratio of SERT inhibition to DAT inhibition.
[d] A–D refer to the diastereomers (Fig. 3).

2-naphthyl (20 nM), and 2-anthracenyl (>40,000 nM) substitution at the C3 position. The least bulkier 2-naphthyl manifests substantial DAT inhibitory potency.[40] Accordingly, these results support the notion that there is a significant steric barrier to binding if the substituents lay transverse to the tropane skeleton as in the compounds in Series II.

4. Conclusions

In this report we utilized Stille protocols for the synthesis of four novel series of oxabicyclo[3.2.1]octenes containing aryl substituents at the 3-position. SmI_2 reduction of the Series II furnished 2β3α and 2β3β diastereomers as the isolable products while the remaining series produced complex product distributions. Analysis of the inhibition data obtained for these compounds demonstrates that the biaryl substitution at the 3-position of the bicyclooctene **14a–u** did not have significant effect on the inhibition of WIN 35,438 nor the selectivity between DAT versus SERT. Compound **14m** was striking in that it was a DAT inhibitor (IC_{50} = 13 nM) and quite selective (SERT IC_{50} = >3 μM, 177-fold), while its saturated counterpart, **16m**, was the most potent, but non-selective DAT and SERT inhibitor (DAT IC_{50} = 9 nM; SERT IC_{50} = 10 nM) in all series. The bicyclic aryl substituted oxatropenes, Series III in general, and the corresponding reduction products have the strongest interaction with the binding site of DAT as compared to the remaining series.

It is important to note the fact that the relative positions of the heteroatoms in **14j–l** and less so **16l–q** have such an impact on potency and selectivity. In addition, compounds **14m** and **16m** are more similar to our 3-naphthyl compounds[21] in the earlier 8-hetero series, in contrast to that compounds in Series I, II, IV and V look very different that our earlier 3-aryl analogs.[40] This difference could be the subject of further studies including perhaps modeling studies.

5. Experimental section

All compounds are racemates (1*R*/1*S*). NMR spectra were recorded in $CDCl_3$ on a JEOL 300 NMR spectrometer operating at 300.53 MHz for ^1H and 75.58 MHz for ^{13}C. TMS was used as internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Thin-layer chromatography (TLC) was carried out on Baker Si250F plates. Visualization was accomplished with either UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker silica gel 40 mm. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. All reactions were conducted under an inert (N_2) atmosphere.

5.1. General procedure for organostannane building blocks

A mixture of 1-bromo-3-iodobenzene (25 mmol), 1.0 equiv of arylstannanes and 0.05 equiv of $Pd(PPh_3)_4$ was refluxed under nitrogen for 5 h in dioxane (100 mL) (Scheme 1). After cooling and evaporation of the volatiles, the residue was dissolved in EtOAc (100 mL). KF solution (10%, 50 mL) was added and the solution was stirred at room temperature for 30 min. The resultant precipitate was removed by suction filtration. The organic layer was washed with water (3 × 50 mL), dried over Na_2SO_4 and concentrated. The product was purified by flash column chromatography (eluent: hexane)

The resulting biarylbromides **2a–d** (5 mmol) were treated in THF (25 mL) with *n*-BuLi (1.05 equiv, 2.5 M in THF) at −70 °C for 1 h followed by addition of tributyltin chloride (1.0 equiv) via syringe. The reaction was allowed to warm to room temperature with stirring over 30 min. Hexane (50 mL) was added and the solution was washed with KF solution (10%, 20 mL) and brine (2 × 30 mL). The organic layer was dried over Na_2SO_4 and concentrated. Attempts to purify the crude materials by column chromatography on deactivated silica or neutral alumina resulted in significant decomposition of the stannanes. Therefore, the resulting crude materials were used in the coupling reactions with the triflate without further purification.

5.1.1. 2(3-Bromophenyl)furan (3a)

Colorless oil 80%. ^1H NMR ($CDCl_3$) 7.80–7.79 (m, 1H), 7.57–7.54 (dt, 1H), 7.45–7.44 (d, 1H), 7.34–7.33 (m, 1H), 7.23–7.18 (t, 1H), 6.64–6.63 (d, 1H), 6.46–6.45 (m, 1H). ^{13}C NMR δ 152.3, 142.6, 132.7, 130.2, 130.1, 126.6, 122.8, 122.2, 111.8, 106.0. Mass $(M+H)^+$ = 223/225.

5.1.2. 2(3-Bromophenyl)thiophen (3b)

Pale yellow oil 66%. ^1H NMR ($CDCl_3$ 7.74–7.72 (m, 1H), 7.50–7.47 (m, 1H), 7.39–7.35 (m, 1H), 7.28 (s, 1H), 7.26 (s, 1H), 7.22–7-16 (t, 1H), 7.06–7.03 (m 1H). Mass $(M+H)^+$ = 239/241.

5.1.3. 2-(3-Bromophenyl)-1-meyhyl-1*H*-pyrrole (3c)

Colorless oil 58%. ^1H NMR δ 7.55–7.54 (t, 1H), 7.42–7.38 (dt, 1H), 7.33–7.30 (dt, 1H), 7.26–7.20 (t, 1H), 7.71–7.69 (t, 1H), 6.24–6.22 (m, 1H), 6.19–6.17 (m, 1H), 3.64 (s, 3H). δ 135,3, 132.9, 131.2, 129.8, 129.5, 126.9, 124.3, 122.4, 109.4, 107.9, 35.0. Mass $(M+H)^+$ = 236/238 (100%).

5.1.4. 2-(3-Bromophenyl)thiazole (3d)

Colorless oil 57%. ^1H NMR ($CDCl_3$) δ 8.13–8.12 (t, 1H), 7.86–7.85 (d, 1H), 7.83–7.82 (m, 1H), 7.53–7.49 (m, 1H), 7.33–7.32 (d, 1H), 7.29–7.24 (t, 1H). ^{13}C NMR ($CDCl_3$) δ 166.4, 143.8, 135.3, 132.7, 130.3, 129.3, 125.0, 123.0, 119.9. Mass $(M+H)^+$ = 240/242 (100%).

5.1.5. Tributyl-(3-furan-2-yl-phenyl)-stannane (4a)

Mass $(M+H)^+$ = 435. The stannyl intermediate was used directly in the following step without further purification.

5.1.6. Tributyl-(3-thiophen-2-yl-phenyl)-stannane (4b)

Mass $(M+H)^+$ = 451, The stannyl intermediate was used directly in the following step without further purification.

5.1.7. 1-Methyl-2-(3-tributylstannyl-phenyl)-1*H*-pyrrole (4c)

Mass $(M+H)^+$ = 448. The stannyl intermediate was used directly in the following step without further purification.

5.1.8. 2-(3-Tributylstannanyl-phenyl)-thiazole (4d) and 2-(3-tributylstannanyl-phenyl)-5-bromo-thiazole (5)

Brown oil $(M+H)^+$ = 529/531, $(M+H)^+$ = 449/451. The stannyl intermediates were used directly in the following step without further purification.

5.1.9. Benzofuran-2-yl-tributylstannane (7a)

Pale yellow oil 90%, bp 164 °C at 0.13 mm Hg. ^1H NMR ($CDCl_3$) δ 7.56–7.48 (m, 2H), 7.22–7.16 (m, 2H), 6.90–6.89 (m, 1H), 1.65–1.54 (m, 6H), 1.39–1.29 (m, 6H), 1.27–1.12 (m, 6H), m 0.92–0.87 (m, 9H). ^{13}C NMR ($CDCl_3$) 165.34, 158.62, 128.03, 123.29, 121.98, 120.22, 117.99, 110.94, 28.95, 27.19, 13.65, 10.14. Mass spectrum did not have $(M+H)^+$ peak at *m*/*z* = 408. A common fragment ion at *m*/*z* = 291 for $(C_{12}H_{27}Sn)^+$ was present (100%). Anal. ($C_{20}H_{32}OSn$) C, H.

5.1.10. Benzo[*b*]thiophen-2-yl-tributylstannane (7b)

Pale yellow oil 67.4%, bp 174 °C at 0.13 mm Hg. ^1H NMR ($CDCl_3$) δ 7.90–7.87 (m, 1H), 7.82–7.80 (m, 1H), 7.42–7.23 (m, 3H), 1.69–1.50 (m, 6H), 1.42–1.30 (m, 6H), 1.27–1.05 (m, 6H), m 0.93–0.88 (m, 9H). ^{13}C NMR ($CDCl_3$) 144.31, 141.03, 139.74, 132.03, 123.66, 123.27,

122.68, 121.79, 28.97, 27.27, 13.67, 10.75. Mass spectrum did not have $(M+H)^+$ peak at $m/z = 424$. A common fragment ion at $m/z = 291$ $(C_{12}H_{27}Sn)^+$ was present (100%). Anal. ($C_{20}H_{32}SSn$) C, H.

5.1.11. 2-Tributylstannyl-benzooxazole (7c)

Pale yellow oil 49%, bp >140 °C at 0.13 mm Hg. ^1H NMR ($CDCl_3$) δ 7.79–7.75 (m, 1H), 7.57–7.54 (m, 1H), 7.32–7.26 (m, 2H), 1.68–1.57 (m, 6H), 1.42, 1.20 (m, 12H), 0.92–0.87 (t, 9H) ^{13}C NMR ($CDCl_3$) 175.92, 152.01, 141.34, 124.32, 123.43, 119.64, 110.28, 28.76, 27.11, 13.60, 10.74. Mass $(M+H)^+ = 410$ (100%).

5.1.12. 2-Tributylstannyl-benzothoazole (7d)

Pale yellow oil 84%, bp 165 °C at 0.13 mm Hg. ^1H NMR ($CDCl_3$) δ 8.18–8.16 (m, 1H), 7.97–7.94 (m, 1H), 7.46–7.43 (m, 1H), 7.39–7.33 (m, 1H), 1.67–1.58 (m, 6H), 1.40–1.23 (m, 12H), 0.94–0.86 (m, 9H). ^{13}C NMR ($CDCl_3$) 177.66, 156.06, 136.25, 125.26, 124.35, 122.76, 121.28, 28.82, 27.20, 13.61, 11.23. Mass: $(M+H)^+ = 426$ (100%). Anal. ($C_{19}H_{31}NSSn$) C, H.

5.1.13. Synthesis of tributylstannanylindol-1-carboxylic acid lithium salt (10)

n-Butyllithium (2.5 M, 36 mL) was added to indole solution (10.0 g, 85.5 mmol) in THF (170 mL) under nitrogen at −70 °C. After stirring for 30 min, excess of dry ice was added and stirring was continued at that temperature for 1 h and then allowed to warm to room temperature. Volatiles were removed to dryness and 21.5 g of white/gray solid was obtained. The solid was then dissolved in 200 mL of anhydrous THF and cooled to −70 °C. *n*-BuLi (36 mL, 2.5 M), was added and mixture was stirred for 2 h. Bu_3SnCl (23.2 mL) was added via syringe and mixture was allowed to warm to room temperature. Ethyl acetate (150 mL) were added and mixtures was washed with brine (100 mL) and water (2 × 50 mL), dried over Na_2SO_4 and concentrated. The reddish oil (44.8 g) was used in the next step.

5.1.14. 2-Phenylfuran (11a)

Pale yellow oil 79%. ^1H NMR ($CDCl_3$) δ 7.70–7.66 (m, 2H), 7.47–7.46 (m, 1H), 7.41–7.35 (m, 2H), 7.28–7.23 (m, 1H), 6.65–6.64 (d, 1H), 6.43–6.46 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 153.9, 141.9, 130.8, 128.2, 127.3, 123.7, 111.6, 104.9.

5.1.15. 2-Phenylthiophen (11b)

White solid 84% yield, mp 33–34 °C. ^1H NMR ($CDCl_3$) δ 7.63–7.60 (m, 2H), 7.41–7.35 (m, 2H), 7.32–7.25 (m, 3H), 7.09–7.07 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 144.3, 134.3, 128.8, 127.9, 127.4, 125.8, 124.7, 123.

5.1.16. 1-Methyl-2-phenylpyrrole (11c)

Colorless oil 78%. ^1H NMR ($CDCl_3$) δ 7.39–7.33 (m, 4H), 7.31–7.25 (m, 1H), 6.69–6.68 (m, 1H), 6.24–6.17 (m, 2H), 3.63 (s, 3H). Mass $(M+H)^+ = 158$ (100%).

5.1.17. Tributyl-(5phenyl-furan-2-yl)-stannane (12a)

^1H NMR ($CDCl_3$) δ 7.69–7.66 (m, 2H), 7.39–7.34 (m, 2H), 7.24–7.19 (m, 1H), 6.68–6.67 (dt, 1H), 6.22–6.21 (d, 1H), 1.66–1.55 (m, 6H), 1.42–1.30 (m, 6H), 1.14–1.09 (m, 6H), 0.94–0.88 (t, 9H). ^{13}C NMR $CDCl_3$) δ 160.9, 158.4, 131.4, 131.4, 128.6, 123.7, 123.4, 204.9, 28.9, 27.2, 13.7, 10.2.

5.1.18. 1-Methyl-2-phenyl-5-tributylstannanyl-1*H*-pyrrole (12c)

$(M+H)^+ = 448$.

5.1.19. General synthesis of (*R*/*S*), 3-aryl-8-oxabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl esters

5.1.19.1. Method I. Triflate **13** (1.75 g, 5.5 mmol), arylstannane (1.2 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.6 g, 10 mol %) were refluxed under nitrogen in dioxane (100 mL) for overnight. Ethyl acetate (150 mL) and 10% aqueous KF (100 mL) were added and stirring was continued for 20 min. Precipitate formed was filtered off and the filtrate was washed with water (3 × 500 mL), dried over Na_2SO_4 and concentrated in vacuo. Further purification was done on silica gel column using EtOAc/Hexanes (1:9) as the eluent. Hexanes (1:9) as the eluent.

5.1.19.2. Method II. Triflate **13** (1.75 g, 5.5 mmol), arylstannane (1.2 equiv), $ZnCl_2$ (11.0 mmol), tri-2-furylphosphine (0.25 g, 1.1 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.5 g, 0.5 mmol) were stirred in 1-methyl-2-pyrrolidinone (100 mL) at room temperature for overnight under nitrogen. Ethyl acetate (150 mL) and 10% aqueous KF (100 mL) were added and stirring was continued for 20 min. Precipitate formed was filtered off and the filtrate was washed with water (3 × 500 mL), dried over Na_2SO_4 and concentrated in vacuo. Further purification was done on silica gel column using EtOAc/Hexanes (1:9) as the eluent. Hexanes (1:9) as the eluent.

5.1.20. Spectral data

5.1.20.1. (*R*,*S*) 3-(3-Furan-2-yl-phenyl)-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14e). White solid 75% yield, mp 81–81 °C. ^1H NMR ($CDCl_3$) δ 7.60–7.57 (m, 1H), 7.45–7.43 (m, 2H), 7.36–7.31 (t, 1H), 7.02–6.99 (m, 1H), 6.64–6.63 (d, 1H), 6.47–6.46 (m, 1H). 5.03–5.02 (d, 1H), 4.67–4.63 (m, 1H), 3.49 (s, 3H), 3.02–2.94 (dd, 1H), 2.22–2.13 (m, 4H), 1.84–1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 166.4, 153.6, 144.6, 142.0, 141.4, 130.6, 128.3, 125.7, 122.9, 122.0, 11.7, 105.2, 73.4, 73.1, 51.3, 41.5, 35.6, 29.8. Mass $(M+H)^+ = 311$ (60%), $(M-OCH_3)^+ = 279$ (100%). Anal. ($C_{19}H_{18}O_4$) C, H.

5.1.20.2. (R,S) 3-(3-Thiophen-2-yl-phenyl)-8-oxa-bicyclo[3.2.1] oct-2-ene-2-carboxylic acid methyl ester (14f). Pale yellow solid 91% yield, mp 93–94 °C. ^1H NMR ($CDCl_3$) δ 7.59–7.56 (m, 2H), 7.39–7.35 (m, 2H), 7.35–7.24 (m, 1H), 7.20–7.18 (d, 1H), 7.01–7.00 (m, 1H), 4.95–4.93 (d, 1H), 4.69–4.67 (m, 1H), 3.71 (s, 3H), 3.09–3.02 (dd, 1H), 2.29–2.05 (m, 4H), 1,84–1.72 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 167.5, 144.8, 140.5, 133.9, 133.1, 132.0, 128.9, 127.7, 127.4, 125.7, 122.8, 74.00, 73.1, 51.8, 40.5, 35.2, 29.6. Mass $(M+H)^+ = 327$ (100%), $(M-OCH_3)^+ = 295$ (15 %). Anal. ($C_{19}H_{18}O_3S$) C, H.

5.1.20.3. (*R*,*S*) 3-[3-(1-Methyl-1H-pyrrol-2-yl)-phenyl]-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14g). Pale yellow oil 93% yield. ^1H NMR ($CDCl_3$) δ 7.37–7.29 (m, 2H), 7.14–7.13 (m, 1H), 7.06–7.02 (dt, 1H), 6.71–6.70 (t, 1H), 6.22–6.16 (m, 2H), 5.04–5.00 (d, 1H), 4.67–4.62 (m, 1H), 3.64 (s, 3H), 3.51 (s, 3H), 3.03–2.95 (dd, 1H), 2.26–2.04 (m, 4H), 1.83–1.73 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 166.3, 144.8, 141.0, 134.2, 133.0, 131.7, 128.0, 127.7, 127.0, 125.0, 123.7, 108.6, 107.7, 73.4, 73.1, 51.3, 41.7, 35.6, 35.0, 29.8. Mass $(M+H)^+ = 324$ (100%). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

5.1.20.4. (*R*,*S*) 3-(3-Thiazol-2-yl-phenyl)-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14h). Pale yellow 42% yield, mp 92–94 °C. ^1H NMR ($CDCl_3$) δ 7.94–7.91 (m, 2H), 7.75 (s, 1H), 7.45–7.40 (m, 3H), 4.98–4.96 (d, 1H), 4.69–4.67 (m, 1H), 3.72 (s, 3H), 3.12–3.04 (dd, 1H), 2.28–2.04 (m, 4H), 1.80–1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 168.4, 166.6, 142.5, 135.6, 133.6, 133.3, 130.9, 129.2, 128.9, 126.4, 73.8, 72.9, 51.9, 40.8, 35.1, 29.6. Mass $(M+H)^+ = 328$ (100%). Anal. ($C_{18}H_{17}NO_3S$) C, H, N.

5.1.20.5. (*R*,*S*)-3-[2-(3-Bromophenyl)-thiazol-5-yl]-8-oxa-bicyclo [3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14i). Pale yellow solid 40% yield, mp 92–94 °C. ^1H NMR ($CDCl_3$) δ 8.11–8.10 (t, 1H), 7.85–7.82 (m, 1H), 7.76 (s, 1H), 7.56–7.52 (m, 1H), 7.33–7.27 (t,

1H), 4.98–4.96 (d, 1H), 4.70–4.66 (m, 1H), 3.73 (s, 3H), 3.12–3.05 (dd, 1H), 2.28–2.05 (m, 4H), 1.79–1.72 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 166.4, 142.7, 136.3, 135.2, 134.0, 132.9, 130.9, 130.4, 129.2, 125.0, 123.1, 73.8, 72.9, 51.9, 40.9, 35.2, 29.6. Mass $(M+H)^+$ = 406/408 (100%). Anal. ($C_{18}H_{16}BrNO_3S$) C, H, N.

5.1.20.6. Synthesis of (*RS*), 3-Benzofuran-2-yl-8-oxa-bicyclo[3.2.1] oct-2-ene-2–carboxylic acid methyl ester (14j). White solid 81% yield, mp 95–96 °C. ^{1}H NMR ($CDCl_3$) δ 7.55–7.52 (m, 1H), 7.40–7.37 (m, 1H), 7.30–7.25 (dt, 1H), 7.22–7.17 (dt, 1H), 6.74–6.71 (d, 1H), 4.87–4.85 (d, 1H), 4.74–4.69 (m, 1H), 3.81 (S, 3H), 3.08–3.01 (dd, 1H), 2.32–2.09 (m, 4H), 1.82–1.77 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 168.4, 154.6, 153.3, 135.6, 133.1, 128.1, 125.0, 122.9, 121.3, 110.9, 105.6, 74.0, 72.9, 52.0, 35.4, 35.1, 29.4. Mass. $(M+H)^+$ = 285 (70%), $(M-OCH_3)^+$ = 253 (100%). Anal. (C17H16O4) C, H.

5.1.20.7. Synthesis of (*RS*), 3-Benzoxazol-2-yl-8-oxa-bicyclo[3.2.1] oct-2-ene-2–carboxylic acid methyl ester (14k). Pale yellow solid 10% yield, mp 85–86 °C. ^{1}H NMR ($CDCl_3$) δ 7.75–7.70 (m, 1H), 7.50–7.45 (m, 1H), 7.38–7.31 (m, 2H), 4.88–4.86 (d, 1H), 4.79–4.74 (m, 1H), 3.81 (s, 3H), 3.19–3.11 (dd, 1H), 2.53–2.47 (d, 1H), 2.32–2.20 (m, 2H), 2.18–2.10 (m, 1H), 1.86–1.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ. 167.4, 160.9, 150.3, 141.3, 141.1, 125.6, 124.6, 123.2, 120.3, 110.5, 73.9, 73.0, 52.4, 35.2, 29.5. Mass. $(M+H)^+$ = 286 (100%). Anal. ($C_{16}H_{15}NO_4$) C, H, N.

5.1.20.8. (*R,S*) 3-Thiazole-2-yl-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14l). Method II, colorless oil 67% yield. ^{1}H NMR ($CDCl_3$) δ 8.03–8.00 (m, 1H), 7.89–7.86 (m, 1H), 7.55–7.45 (m, 1H), 7.42–7.36 (m, 1H), 4.95–4.93 (d, 1H), 4.76–4.72 (m, 1H), 3.70 (s, 3H), 3.17–3.09 (dd, 1H), 2.47–2.41 (d, 1H), 2.31–2.11 (m, 3H), 1.92–1.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 166.8, 165.7, 153.1, 137.7, 135.2, 132.4, 126.2, 125.4, 123.4, 121.5, 73.7, 73.1, 52.1, 38.4, 35.2, 29.7. Mass. $(M+H)^+$ = 302 (100%), $(M-OCH_3)^+$ = 270 (10%).

5.1.20.9. (*R,S*)-3-[2-Benzothiophen-2-yl]-8-oxa-bicyclo[3.2.1]oct-2-ene-2carboxylic acid methyl ester (14m). White solid 78% yield, mp 84–86 °C. ^{1}H NMR ($CDCl_3$) δ 7.79–7.76 (m, 1H), 7.74–7.71 (m, 1H), 7.37–7.30 (m, 2H), 7.18 (s, 1H), 4.96–4.94 (d, 1H), 4.70–4.66 (m, 1H), 3.65 (s, 3H), 3.11–3.04 (dd, 1H), 2.30–2.20 (m, 4H), 1.85–1.76 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 167.1, 141.6, 139.7, 139.4, 134.2, 133.8, 124.6, 124.4, 123.7, 122.4, 122.1, 73.9, 73.1, 51.9, 40.8, 35.3, 29.7. Mass. $(M+H)^+$ = 301 (60%), $(M-OCH_3)^+$ = 269 (100%). Anal. ($C_{17}H_{16}O_3S$) C, H.

5.1.20.10. (*RS*), 3-(1*H*-Indol-2-yl)-8-oxa-bicyclo[3.2.1]oct-2-ene-2–carboxylic acid methyl ester (14n). Method II, light yellow solid 56% yield, mp 132–134 °C. ^{1}H NMR ($CDCl_3$) δ 7.59–7.56 (d, 1H), 7.41–7.38 (m, 1H), 7.23–7.18 (m, 1H), 7.09–7.03 (m, 1H), 6.74–6.73 (m, 1H), 5.03–5.01 (m, 1H), 4.66–4.62 (m, 1H), 3.79 (s, 3H), 3.28–3.21 (dd, 1H), 2.56–2.50 (d, 1H), 2.16–2.07 (m, 3H), 1.69–1.62 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 168.3, 136.4, 135.3, 127.2, 127.1, 123.7, 120.8, 119.8, 111.6, 105.6, 73.9, 72.8, 52.2, 37.9, 35.4, 29.3. Mass. $(M+H)^+$ = 284 (100%). Anal. ($C_{17}H_{17}NO_4$) C, H, N.

5.1.20.11. (*R,S*) 3-Thiophen-2-yl-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14o). Method I, yellow solid 85% yield. ^{1}H NMR ($CDCl_3$) δ 7.29–7.26 (m, 1H), 7.01–7.98 (m, 2H), 4.92–4.91 (d, 1H), 4.67–4.63 (m, 1H), 3.67 (s, 3H), 3.07–2.99 (dd, 1H), 2.25–2.04 (m, 4H), 1.81–1.72 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 167.4, 1412.3, 133.3, 132.3, 126.8, 126.1, 125.8, 73.8, 73.1, 51.7, 40.8, 35.1, 29.6. Mass $(M+H)^+$ = 251 (50%) $(M-OCH_3)^+$ = 219 (100%). Anal. ($C_{13}H_{14}O_3S$) C, H, S.

5.1.20.12. (*R,S*) 3-Furan-2-yl-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14p). Method I, yellow solid 93% yield, mp 56–57 °C. ^{1}H NMR ($CDCl_3$) δ 7.37–7.36 (d, 1H), 7.52–7.52 (d, 1H), 6.40–6.38 (m, 1H), 4.84–4.82 (d, 1H), 4.68–4.64 (m, 1H), 3.77 (s, 3H), 2.99–2.91 (dd, 1H), 2.26–2.02 (m, 4H), 1.78–1.72 (m, 1H) ^{13}C NMR ($CDCl_3$) δ 168, 151.4, 142.5, 130.1, 111.1, 109.8, 73.7, 72.7, 51.6, 35.4, 35.3, 29.3. Mass $(M+H)^+$ = 235 (100%) $(M-OCH_3)^+$ = 203 (80%). Anal. ($C_{13}H_{14}O_4$) C, H.

5.1.20.13. (*R,S*) 3-(1-Methyl-1*H*-pyrrol-2-yl-8-oxa-bicyclo[3.2.1] oct-2-ene-2-carboxylic acid methyl ester (14q). Method I, pale yellow oil 80% yield. ^{1}H NMR ($CDCl_3$) δ 6.65–6.63 (M, 1H), 6.15–6.13 (M, 1H), 6.01–5.99 (M, 1H), 5.09–5.07 (M, 1H), 4.63–4.59 (M, 1H), 3.62 (S, 3H), 3.41 (S, 3H), 2.94–2.86 (DD, 1H), 2.20–2.06 (M, 4H), 1.79–1.69 (M, 1H). ^{13}C NMR ($CDCl_3$) δ 165.5, 137.2, 133.4, 131.9, 107.8, 107.7, 73.4, 73, 71.7, 42.4, 33.9, 29.6. Mass $(M+H)^+$ = 248 (100%) $(M-OCH_3)^+$ = 216 (30%). Anal. $C_{14}H_{17}NO_3$) C, H, N.

5.1.20.14. (*R,S*) 3-Thiazol-2-yl-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14r). Method I, yellow oil 85% yield. ^{1}H NMR ($CDCl_3$) 7.81–7.80 (d, 1H), 7.35–7.34 (d, 1H), 4.89–4.87 (d, 1H), 4.74–4.70 (m, 1H), 3.72 (s, 3H), 3.13–3.05 (dd, 1H), 2.44–2.38 (d, 1H), 2.29–2.17 (m, 2H), 2.15–2.07 (m, 1H), 1.88–1.74 (m, 1H). ^{13}C NMR ($CDCl_3$) 167.43, 165.1, 142.9, 135.9, 130.9, 119.7, 73.7, 73.1, 52, 38.1, 35.1, 29.5. Mass $(M+H)^+$ = 252 (100%) $(M-OCH_3)^+$ = 220 (20%). Anal. ($C_{12}H_{13}NO_3S$) C, H, S, N.

5.1.20.15. (*R,S*) 3-(5-Phenyl-furan-2-yl)-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (14s). Method I, white solid 80% yield, mp 85–87 °C. ^{1}H NMR ($CDCl_3$) δ 7.62–7.60 (m, 2H), 7.40–7.35 (m, 2H), 7.28–7.26 (m, 1H), 6.67–6.65 (d, 1H), 6.61–6.58 (d, 1H), 4.87–4.86 (d, 1H), 4.71–4.67 (m, 1H), 3.77 (s, 3H), 3.05–3.98 (dd, 1H), 2.30–2.04 (m, 4H), 1.82–1.67 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 169, 154, 150, 130.3, 130, 129, 128, 125, 124, 112, 107, 74, 73, 52, 35, 30. Mass $(M+H)^+$ = 310 (100%) $(M-OCH_3)^+$ = 279 (30%). Anal. ($C_{19}H_{18}O_4$) C, H.

5.1.20.16. (*R,S*) 3-(5-Phenyl-thiophrn-2-yl)-8-oxa-bicyclo[3.2.1] oct-2-ene-2-carboxylic acid methyl ester (14t). Method I, yellow solid 85% yield, mp 92–93 °C. ^{1}H NMR ($CDCl_3$) δ 7.58–7.55 (m, 2H), 7.39–7.33 (m, 2H), 7.30–7.24 (m, 1H), 7.19–7.18 (d, 1H), 7.00–6.99 (d, 1H), 4.94–4.92 (d,1H), 4.68–4.63 (m, 2H), 3.70 (s, 3H), 3.08–3.01 (dd, 1H), 2.28–2.13 (m, 4H), 1.79–1.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 167.5, 144.8, 133.9, 133, 128.8, 127.7, 125.7, 122.8, 73.9, 73.1, 51.8, 40.4, 35.1, 29.6. Mass $(M+H)^+$ = 327 (100%) $(M-OCH_3)^+$ = 295 (20%). Anal. ($C_{19}H_{18}O_3S$) C, H, S.

5.1.20.17. (*R,S*) 3-(1-Methyl-1*H*-pyrrol-4-phenyl)-2-yl-8-oxa-bicyclo[3.2.1]oct-2-ene-2-carboxylic Acid Methyl Ester (14u). Method I, pale yellow oil 80% yield. ^{1}H NMR ($CDCl_3$) δ 6.65–6.63 (M, 1H), 6.15–6.13 (M, 1H), 6.01–5.99 (M, 1H), 5.09–5.07 (M, 1H), 4.63–4.59 (M, 1H), 3.62 (S, 3H), 3.41 (S, 3H), 2.94–2.86 (DD, 1H), 2.20–2.06 (M, 4H), 1.79–1.69 (M, 1H). ^{13}C NMR ($CDCl_3$) δ 165.5, 137.2, 133.4, 131.9, 107.8, 107.7, 73.4, 73, 71.7, 42.4, 33.9, 29.6. Mass $(M+H)$+ = 248 (100%) $(M-OCH_3)$+ = 216 (30%). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

5.1.20.18. Compound 15. Yellow solid 10% yield, mp 171–172 °C. ^{1}H NMR ($CDCl_3$) δ 7.64–7.61 (m, 1H), 7.36–7.33 (d, 1H), 7.26–7.20 (dt, 1H), 7.07–7.01 (dt, 1H), 6.28 (s, 1H), 4.94–4.92 (m, 1H), 4.78–4.73 (m, 1H), 3.03–2.95 (dd, 1H), 2.31–2.08 (m, 4H), 1.77–1.70 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 162.5, 140.7, 140.6, 138.6, 134.4, 133.5, 127.3, 122.8, 122.6, 112.0, 105.8, 72.3, 70.3, 35.6, 31.9, 29.8. Mass. $(M+H)^+$ = 252 (100%). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

5.2. General procedure for SmI_2 reduction

Compounds **14** (2–5 mmol) were dissolved in THF/MeOH or THF:2-propanol (9:1, 30 mL) in pre-degassed flask and cooled to −78 °C. Samarium iodide (0.1 M in pentane, 3 equiv) was added via syringe and, after stirring for 15 min, solution was allowed to warm up to room temperature. Solvent was removed and residue was taken into EtOH/brine, and washed with brine, dried over Na_2SO_4 and concentrated. Further purification was done on column (silica gel, ~100 g) using 10% ethyl acetate in hexane as the eluent.

5.2.1. (*R,S*) 3α-(3-(2-Furyl)phenyl)-8-oxa-bicyclo[3.2.1]octane-2 β-carboxylic acid methyl ester (16g)

White solid 65% yield, mp 94–96 °C. ^{1}H NMR ($CDCl_3$) δ 7.54–7.46 (m, 3H), 7.32–7.27 (t, 1H), 7.14–7.11 (d, 1H), 6.65–6.64 (dd, 1H), 6.48–6.46 (m, 1H), 4.55–4.50 (m, 2H), 3.58 (s, 3H), 3.35–3.26 (m, 1H), 2.61–2.57 (dd, 1H), 2.49–2.40 (m, 1H), 2.20–1.95 (m, 2H), 1.85–1.76 (m, 1H), 1.73–1.64 (m, 1H), 1.50–1.42 (dt, 1H). ^{13}C NMR ($CDCl_3$) δ 174.5, 153.9, 143.4, 142.0, 130.9, 128.7, 126.7, 122.9, 122.1, 111.6, 105.0, 74.6, 72.3, 54.9, 51.8, 36.8, 36.1, 31.6, 31.5. Mass $(M+H)^+$ = 313 (100%), $(M-OCH_3)^+$ = 285 (85%), $(M-COOCH_3)^+$ = 253 (7%). Anal. ($C_{19}H_{20}O_4$) C, H.

5.2.2. (*R,S*) 3α-(3-(2-*N*-Methylpyrrol)phenyl)-8-oxa-bicyclo[3.2.1]octane-2 β-carboxylic acid methyl ester (16h)

Colorless oil 57% yield. ^{1}H NMR ($CDCl_3$) δ 7.34–7.27 (m, 2H), 7.24–7.21 (m, 1H), 7.19–7.16 (m, 1H), 6.71–6.70 (t, 1H), 6.21–6.19 (m, 2H), 4.70–4.66 (m, 2H), 3.65 (s, 3H), 3.49 (s, 3H), 3.27–3.21 (m, 1H), 2.89–2.77 (m, 2H), 2.1902.01 (m, 2H), 1.98–1.89 (m, 1H), 1.85–1.78 (m, 1H), 1.69–1.63 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.6, 142.3, 134.7, 133.0, 128.1, 127.6, 126.6, 125.6, 123.5, 108.4, 107.7, 75.4, 51.6, 51.3, 35.0, 33.4, 32.3, 29.1, 28.1. Mass $(M+H)^+$ = 326. Anal. ($C_{20}H_{23}NO_3$) C, H, N.

5.2.3. (*R,S*) 3β-(3-(2-Furyl)phenyl)-8-oxa-bicyclo[3.2.1]octane-2 β-carboxylic acid methyl ester (16i)

^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 7.50–7.47 (dd, 1H), 7.45–7.44 (dd, 1H), 7.32–7.27 (t, 1H), 7.17–7.14 (m, 1H), 6.63–6.62 (dd, 1H), 6.46–6.44 (m, 1H), 4.71–4.66 (m, 2H), 3.48 (s, 3H), 3.28–3.20 (m, 1H), 2.89–2.76 (m, 2H), 2.22–1.90 (m, 3H), 1.85–1.77 (m, 1H), 1.68–1.62 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.6, 154.0, 142.7, 141.8, 130.6, 128.4, 126.1, 122.6, 121.8, 111.5, 104.8, 76.6, 75.3, 51.6, 51.2, 33.4, 32.2, 29.0, 28.0. Mass $(M+H)^+$ = 313 (100%), $(M-OCH_3)^+$ = 285 (90%). Anal. ($C_{19}H_{20}O_4$) C, H.

5.2.4. (*R,S*) 3β-(3-(2-*N*-Methylpyrrol)phenyl)-8-oxa-bicyclo[3.2.1]octane-2β-carboxylic acid methyl ester (16j)

Colorless oil 17% yield. ^{1}H NMR ($CDCl_3$) δ 7.33–7.21 (m, 3H), 7.18–7.15 (dt, 1H), 6.72–6.71 (t, 1H), 6.22–6.19 (m, 2H), 4.54–4.49 (m, 2H), 3.64 (s, 3H), 3.59 (s, 3H), 3.34–3.25 (m, 1H), 2.58–2.54 (dd, 1H), 2.47–2.40 (m, 1H), 2.16–2.09 (m, 1H), 2.06–1.95 (m, 1H), 1.83–1.75 (m, 1H), 1.70–1.61 (m, 1H), 1.49–1.38 (dt, 1H). ^{13}C NMR ($CDCl_3$) δ 174.5, 143.0, 134.6, 133.3, 128.6, 128.1, 126.8, 123.6, 108.5, 107.7, 74.6, 72.2, 55.1, 51.8, 37.1, 36.1, 35.0, 31.7, 31.6. Mass $(M+H)^+$ = 326. Anal. $C_{20}H_{23}NO_3$) C, H, N.

5.2.5. (*R,S*) 3α-(3-(2-Thiazole)phenyl)-8-oxa-bicyclo[3.2.1]octane-2α-carboxylic acid methyl ester (16k)

White solid, mp 134–135 °C. ^{1}H NMR ($CDCl_3$) δ 7.90–7.87 (m, 2H), 7.59 (s, 1H), 7.44–7.40 (m, 3H), 7.26 (s, 1H), 4.57–4.55 (m, 2H), 3.67–3.64 (m, 1H), 3.63 (s, 3H), 3.05–3.01 (dd, 1H), 2.09–1.97 (m, 3H), 1.96–1.87 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 171.8, 166.7, 141.8, 140.5, 133.7, 129.8, 128.9, 128.8, 128.3, 126.2, 75.9, 75.1, 54.1, 53.9, 50.0, 39.6, 39.4, 30.0, 29.6, 28.4, 25.7. Mass $(M+H)^+$ = 330. Anal. ($C_{18}H_{19}NO_3S$) C, H, N, S.

5.2.6. (*R,S*) 3α-Benzofuran-2-yl-8-oxa-bicyclo[3.2.1]octane-2α-carboxylic acid methyl ester (16l)

Semi solid 60% yield. ^{1}H NMR ($CDCl_3$). δ 7.51–7.48 (m, 1H), 7.42–7.39 (m, 1H), 7.26–7.17 (m, 2H), 6.53–6.52 (m, 1H), 4.80–4.48 (d, 1H), 4.50–4.46 (t, 1H), 3.86–3.81 (m, 1H), 3.80 (s, 3H), 3.21 (s, 1H), 2.54–2.46 (m, 1H), 2.07–2.02 (m, 1H), 1.98–1.81 (m, 2H), 1.78–1.71 (m, 1H), 1.65–1.57 (m, 1H). ^{13}C NMR ($CDCl_3$). δ 173.4, 160.4, 154.2, 128.6, 123.5, 122.7, 120.3, 110.8, 101.3, 75.00, 74.0, 52.2, 48.0, 30.5, 29.2, 28.4, 28.1. Mass $(M+H)^+$ = 287 (100%), $(M-OCH_3)^+$ = 255 (65%), $(M-CO_2CH_3)^+$ = 227 (35%). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.39; H, 6.50.

5.2.7. (*R,S*) 3α-Benzo[*b*]thiophen-2-yl-8-oxa-bicyclo[3.2.1]-octane-2β-carboxylic acid methyl ester (16m)

White solid 48% yield, mp 117–119 °C. ^{1}H NMR ($CDCl_3$) δ 7.77–7.74 (m, 1H), 7.67–7.64 (m, 1H), 7.34–7.24 (m, 2H), 7.11–7.10 (d, 1H), 4.71–4.69 (d, 1H), 4.50–4.47 (m, 1H), 3.87–3.84 (m, 1H), 3.74 (s, 3H), 2.91–2.89 (d, 1H), 2.64–2.55 (m, 1H), 2.01–1.92 (m, 1H), 1.90–1.71 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 173.6, 149.5, 139.8, 138.6, 124.2, 123.7, 122.9, 122.0, 119.7, 74.9, 73.4, 52.8, 52.2, 34.8, 31.6, 29.3. Mass $(M+H)^+$ = 303 (100%), $(M-OCH_3)^+$ = 271 (60%), $(M+CO_2CH_3)^+$ = 243 (10%). Anal. ($C_{17}H_{18}O_3S$) C, H, S.

5.2.8. (*R,S*) 3β-Benzo[*b*]thiophen-2-yl-8-oxa-bicyclo[3.2.1]-octane-2α-carboxylic acid methyl ester (16n)

Yellow oil 6% yield. ^{1}H NMR ($CDCl_3$) δ. 7.75–7.72 (m, 1H), 7.68–7.65 (m, 1H), 7.32–7.21 (m, 2H), 7.06 (s, 1H), 4.70–4.64 (m, 2H), 3.65 (s, 3H), 3.54–3.45 (m, 1H), 2.93–2.91 (d, 1H), 2.86–2.77 (m, 1H), 2.22–2.03 (m, 2H), 1.97–1.90 (m, 1H), 1.89–1.78 (m, 2H). ^{13}C NMR ($CDCl_3$) δ. 171.4, 147.5, 139.9, 138.6, 124.1, 123.6, 122.1, 119.9, 76.5, 75.3, 51.7, 45.6, 33.9, 31.1, 28.8, 28.1. Mass $(M+H)^+$ = 303.

5.2.9. (*R,S*) 3α-(1*H*-Indol-2-yl)-8-oxa-bicyclo[3.2.1]-octane-2α-carboxylic acid methyl ester (16o)

Pale yellow solid 14% yield, mp 176–178 °C. ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1H), 7.54–7.51 (d, 1H), 7.283–7.280 (d, 1H), 7.13–7.07 (m, 2H), 6.298–6.294 (d, 1H), 4.65–4.63 (d, 1H), 4.54–4.49 (m, 1H), 3.75 (s, 3H), 3.71–3.62 (m, 1H), 2.73–2.70 (dd, 1H), 2.61–2.52 (m, 1H), 2.07–1.93 (m, 1H), 1.92–1.83 (m, 1H), 1.82–1.70 (m, 3H), ^{13}C NMR ($CDCl_3$) δ Mass. $(M+H)^+$ = 286. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

5.2.10. (*R,S*) 3β-(1*H*-Indol-2-yl)-8-oxa-bicyclo[3.2.1]-octane-2-β-carboxylic acid methyl ester (16p)

Pale yellow solid 20% yield, mp 222–224 °C. ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 7.53–7.50 (d, 1H), 7.35–7.32 (d, 1H), 7.12–7.05 (m, 2H), 6.278–6.273 (d, 1H), 4.72–4.68 (d, 1H), 4.62–4.58 (m, 1H), 3.65 (s, 3H), 3.48–3.40 (m, 1H), 2.83–2.73 (m, 2H), 2.21–2.05 (m, 2H), 2.02–1.82 (m, 2H), 1.57–1.55 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 173.4, 139.7, 136.0, 127.6, 121.2, 119.8, 119.4, 110.8, 100.5, 75.4, 51.7, 51.1, 34.2, 29.5, 29.6, 28.0. Mass. $(M+H)^+$ = 286. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

5.2.11. (*R,S*) 3β-(1*H*-Indol-2-yl)-8-oxa-bicyclo[3.2.1]-octane-2-α-carboxylic acid methyl ester (16q)

Pale yellow solid 15% yield, mp decomposed > 150 °C. ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.54–7.51 (d, 1H), 7.307–7.305 (d, 1H), 7.12–7.05 (m, 2H), 6.274–6.270 (d, 1H), 4.59–4.56 (m, 2H), 3.64 (s, 3H), 3.56–3.45 (m, 1H), 3.00–2.95 (dd, 1H), 2.24–2.15 (dt, 1H), 2.09–2.02 (m, 1H), 1.99–1.93 (m, 1H), 1.91–1.80 (m, 3H), ^{13}C NMR ($CDCl_3$) δ Mass. $(M+H)^+$ = 286. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

5.2.12. (*R,S*) 3α-(5-Phenyl-thiophen-2-yl)-8-oxa-bicyclo[3.2.1]octane-2α-carboxylic acid methyl ester (16r)

Colorless semi-solid. ^{1}H NMR ($CDCl_3$) δ 7.56–7.54 (m, 2H), 7.37–7.32 (m, 2H), 7.32–7.24 (m, 1H), 7.13–7.11 (d, 1H), 6.85–6.84 (m, 1H), 4.68–4.66 (m, 1H), 4.50–4.48 (m, 1H), 3.79–3.69 (m, 4H), with a singlet at 3.74 for 3H), 2.82–2.80 (dd, 1H), 2.62–2.52 (m, 1H), 1.99–1.75 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 173.8, 148.2, 141.9, 134.3, 128.8, 127.2, 125.4, 124.2, 123, 74.9, 73.3, 53.3, 52.2, 35.2, 31.2, 29.5. Mass $(M+H)^+$ = 329 (100%). Anal. ($C_{19}H_{20}O_3S$) C, H, S.

5.2.13. (*R,S*) 3α-(5-Phenyl-furan-2-yl)-8-oxa-bicyclo[3.2.1] octane-2α-carboxylic Acid Methyl Ester (16s)

Colorless oil. ^{1}H NMR ($CDCl_3$) 7.62–7.59 (m, 2H), 7.39–7.32 (m, 2H), 7.24–7.19 (m,2H), 6.59–6.56 (d, 1H), 6.18–6.17 (m, 1H), 4.78–4.76 (d, 1H), 4.45–4.42 (m, 1H), 3.78 (s, 3H), 3.12 (s, 1H), 2.49–2.41 (m, 1H), 1.99–1.87 (m, 2H), 1.87–1.71 (m, 1H), 1.68–1.65 (m, 1H), 1.65–1.60 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 173.4, 156.7, 151.9, 130.7, 128.5, 126.9, 123.3, 106.4, 105.7, 74, 73.7, 52.1, 48, 30.5, 28.8, 27.9. Mass $(M+H)^+$ = 313 (100%). Anal. ($C_{19}H_{20}O_4$) C, H.

5.2.14. (*R,S*) 3β-Thiophen-2-yl-8-oxa-bicyclo[3.2.1]octane-2α-carboxylic Acid Methyl Ester (16t)

Pale yellow oil, 74% yield. ^{1}H NMR ($CDCl_3$) δ 7.09–7.06 (m, 1H), 6.84–6.8-0 (m, 2H), 4.59–4.57 (m, 1H), 4.42–4.48 (m, 1H), 3.70–3.60 (m, 4H), 3.67 (s, 3H), 2.72–2.70 (dd, 1H), 2.54–2.44 (m, 1H), 1.94–1.60 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 173.8, 148.6, 126.6, 123.2, 123, 74.9, 73.3, 53.7, 52.1, 35.5, 30.9, 29.5. Mass $(M+H)^+$ = 252 (90%) $(M-OCH_3)^+$ = 221 (100%). Anal. ($C_{13}H_{16}O_3S$) C, H, S.

5.2.15. (*R,S*) 3α-Thiophen-2-yl-8-oxa-bicyclo[3.2.1]octane-2α-carboxylic Acid Methyl Ester (16u)

White solid 9% yield, mp 102–103 °C. ^{1}H NMR ($CDCl_3$) δ 7.12–7.10 (dd, 1H), 6.93–6.90 (m, 1H), 6.84–6.83 (m, 1H), 4.67–4.60 (m, 2H), 3.57 (s, 3H), 3.48–3.41 (m, 1H), 2.86–2.84 (d, 1H), 2.78–2.69 (dt, 1H), 2.20–2.00 (m, 2H), 1.94–1.86 (m, 2H), 1.83–1.71 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 171.2, 146.7, 123.3, 122.9, 75.3, 52.1, 51.4, 34.4, 30.3, 28.8, 28. Mass $(M+H)^+$ = 252 (90%) $(M-OCH_3)^+$ = 221 (100%). Anal. ($C_{13}H_{16}O_3S$) C, H, S.

5.3. Biology

The affinities of 2,3-unstaurated 'ene' and 2,3-saturated 'ane' compounds for the DAT and SERT are presented in Tables 3 and 4, respectively. The affinities (IC_{50}) for the dopamine and serotonin transporters were determined in competition studies using [^{3}H]3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester (WIN 35,438) or [^{3}H]CFT) to label the DAT and [^{3}H]citalopram to label the serotonin transporter. Nonspecific binding was measured with fluoxetine (10 μM).[41] Each compound was tested 2–5 times in monkey striatum because these compounds were part of an ongoing SAR study of DAT in this tissue.[9,21–23,29–31] Competition studies were conducted with a fixed concentration of radioligand and a range of concentrations of test drug. All compounds inhibited [^{3}H]WIN 35,438 and [^{3}H]citalopram in a concentration dependent manner. All compounds tested are racemic.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2012.01.053. These data include MOL files and InChiKeys of the most important compounds described in this article.

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