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Structural Remodeling of Cocaine: Design and Synthesis of Trisubstituted Cyclopropanes as Selective Serotonin Reuptake Inhibitors

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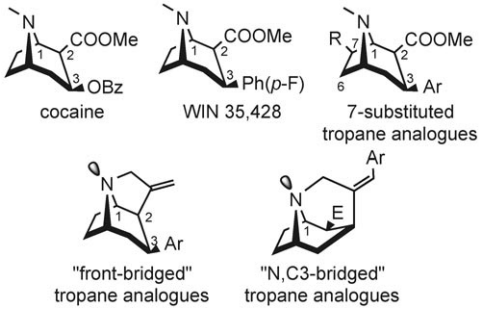
Cocaine, one of the most powerful stimulants of the mammalian central nervous system, binds all monoamine transporters (dopamine transporter (DAT), serotonin transporter (SERT) and norepinephrine transporter (NET)) with similar potency.[1–3] As the reinforcing effects of cocaine are believed to be due primarily to its activity toward DAT, over the past decades, several different classes of DAT-selective ligands have been designed for use as cocaine treatment medications. However, compounds that are selective solely for the DAT and NET have not yet resulted in clinically effective medications against cocaine abuse.[4–11] For this reason, ligands selective for the SERT transporter or various central nervous system (CNS) receptors have been investigated for use in the treatment of cocaine abuse as well.[9–17] The selective serotonin reuptake inhibitors (SSRIs) have been long known to be valuable in the treatment of certain affective disorders including depression.[18]

Our recent work in this area has led to the discovery of several different series of compounds with novel structures that are distinct from those of the traditional tropane analogues belonging to the Sterling–Winthrop (WIN) series.[19–27] Structure–activity relationship (SAR) studies have shown that some of these newer ligands exhibit good to excellent potency and selectivity for the DAT, SERT, or NET. For example, conformationally constrained tricyclic tropane analogues of the (*Z*)-9-(arylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane[25–27] class are highly potent and selective for the SERT over the DAT and NET, whereas several piperidine-based ligands display selectivity for the DAT and NET.[21–24] One of these piperidine ligands ("Nocaine") has been found to antagonize cocaine-induced locomotor effects in rodents while acting as a weak positive reinforcer compared with cocaine in primates.[24,28] Such results encouraged us to explore further structural modifications of cocaine without alteration to its essential pharmacophore. Specifically, we envisioned the excision of C6 from the piperidine structure and the connection of C3 with C5 by a single bond to form a cyclopropane ring (Figure 1). Herein we report the synthesis of representative compounds of this class and their SAR at monoamine transporters. Related compounds in which the ester function is located at the same position on the cyclopropane ring as the aryl group were previously investigated by Bonnaud et al., and several congeners were found to exhibit activity profiles suggestive of their suitability as antidepressants.[29]



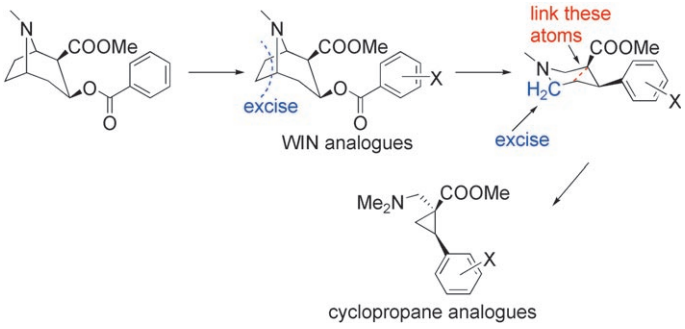


Figure 1. General plan for the synthesis of cyclopropane analogues that retain the pharmacophore of the parent cocaine.

The first step of this project involved a literature search for methods of synthesis of the required cyclopropane scaffold. Although the synthesis of this particular scaffold has been reported,[30,31] there is a general lack of detailed procedures, and little substantive biological activity has been reported for such ligands. The chemistry that we developed to gain access to compounds **7a**–**h** is illustrated in Scheme 1. Dimethyl or dibenzyl (*para*-substituted benzylidene)malonates **3** were synthesized by the Knoevenagel condensation of *para*-substituted benzaldehydes **1** and malonates **2**.[32] Treatment of compounds **3** with dimethylsulfoxonium methylide in *N*,*N*-dimethylformamide (DMF) gave cyclopropanes **4**.[33] The sterically more accessible ester group *trans* to the aromatic ring was selectively hydrolyzed in high yield with methanolic NaOH to give monoesters **5**. The carboxyl group of these intermediates was then con-

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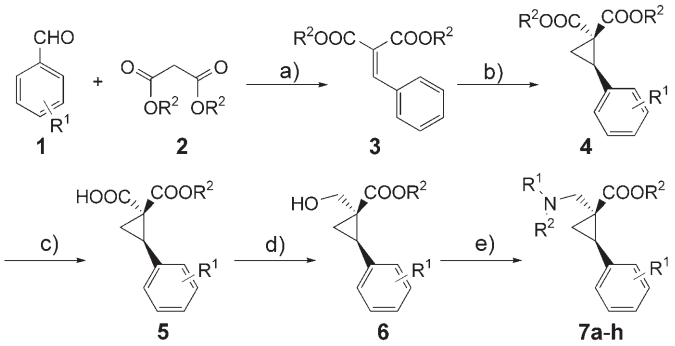
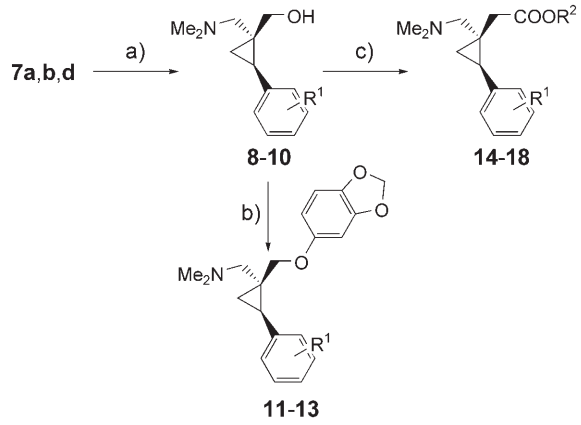


Scheme 1. Reagents and conditions: a) piperidine, AcOH, benzene, reflux, 6 h; b) NaH, $Me_3S(O)I$, DMF, RT→40 °C, 2 h; c) NaOH (1 N), MeOH, RT, 2 h; d) *N*-methylmorpholine, isobutyl chloroformate, THF, 0 °C, 15 min, then $NaBH_4$, THF/MeOH (2:1), −78 °C, 2 h; e) Tf_2O, 2,4,6-trimethylpyridine, CH_2Cl_2, −78 °C, 40 min, then amine, −78 °C→−40 °C, overnight. Tf = trifluoromethanesulfonyl.



Scheme 2. Reagents and conditions: a) $LiAlH_4$, THF; b) MsCl, Et_3N, CH_2Cl_2, 0 °C→RT, 3 h, then sodium salt of sesamol, 18-crown-6, THF/DMF (5:1), reflux, overnight; c) acetic anhydride or acid chloride, Et_3N, THF, 0 °C→RT. Ms = methanesulfonyl.

verted into a mixed anhydride with isobutyl chloroformate and *N*-methylmorpholine followed by reduction with sodium borohydride to give the corresponding alcohols **6** in high yield.[34,35] Alcohols **6** were converted into the corresponding triflates, which underwent nucleophilic displacement with amines to yield the desired compounds **7a**–**h**. Amino alcohols **8**–**10** were obtained by reduction of the esters **7** with $LiAlH_4$. The *trans* relationship between the aryl and amino groups in this series of compounds was confirmed by X-ray crystallographic analysis of compound **8** (Figure 2). Further treatment of intermediates

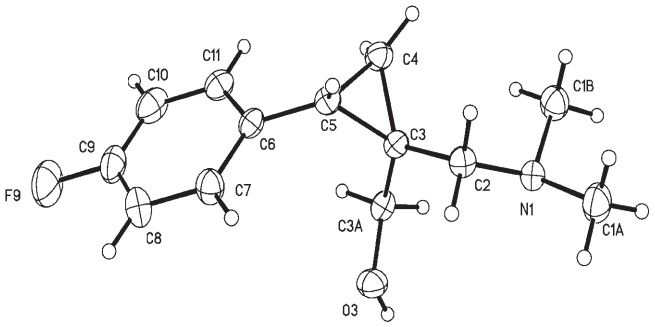
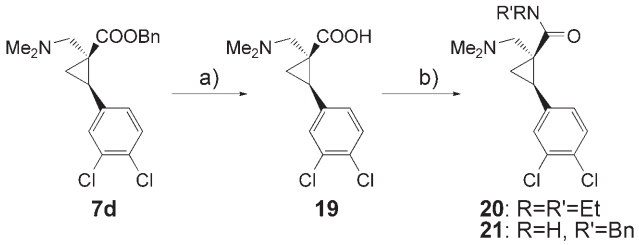


Figure 2. View of compound **8** showing the labeling of non-hydrogen atoms. Displacement ellipsoids are shown at the 30% probability level.

8–**10** with methanesulfonyl chloride, followed by reflux of the resulting mesylate with the sodium salt of sesamol in THF/DMF (5:1) containing a small amount of 18-crown-6, afforded the ethers **11**-**13** (Scheme 2).[36] The reverse esters **14**–**18** were prepared by esterification of the alcohols **8**–**10** with acetic anhydride or acid chlorides.[25] The amides **20** and **21** were obtained by hydrolysis of the ester **7d** with HCl (6 N) followed by reaction of the crude acid with oxalyl chloride to give the intermediate acid chloride, which was subsequently treated with the appropriate amines (Scheme 3).

For racemate resolution, acid **19** was treated with oxalyl chloride; the resulting acid chloride reacted with (−)-8-phenylmenthol in ether to give a mixture of esters **22a** and **22b** (Scheme 4), which are readily separable by column chromatography on silica gel. The pure diastereomers were hydrolyzed in HCl (6 N, reflux), and the resulting enantiomeric acids were



Scheme 3. Reagents and conditions: a) HCl (6 N), reflux; b) oxalyl chloride, CH_2Cl_2, RT, 2 h, then amine, CH_2Cl_2, RT, overnight. Bn = benzyl.

converted into the corresponding benzyl esters (−)-(1*S*, 2*S*)-**7d** and (+)-(1*R*, 2*R*)-**7d** (Scheme 4). The diastereomeric esters **24a** and **24b** (Scheme 5) were prepared in the same manner, and the relative configuration of **24a** was established by X-ray crystallographic analysis (Figure 3). The relative configuration of **22a**, and thus the absolute configuration of (−)-**7d**, follow by analogy.

All final compounds were tested for their ability to inhibit the high-affinity reuptake of dopamine (DA), 5-hydroxy-L-tryptamine (5-HT), and norepinephrine (NE) into nerve endings (synaptosomes) prepared from brain regions enriched in transporters for these biogenic amine neurotransmitters.[37,38] The uptake data and selectivity profiles (based on the K_i values) of these compounds are listed in Table 1. All data are mean values ± SEM from at least three independent experiments, each of which consisted of six drug concentrations in triplicate. Nearly all compounds exhibit weak or no inhibition of reuptake at the DA and NE transporters, but modest to good potency toward the 5-HT transporter. These results contrast with the transporter inhibition data reported for the piperidine ana-

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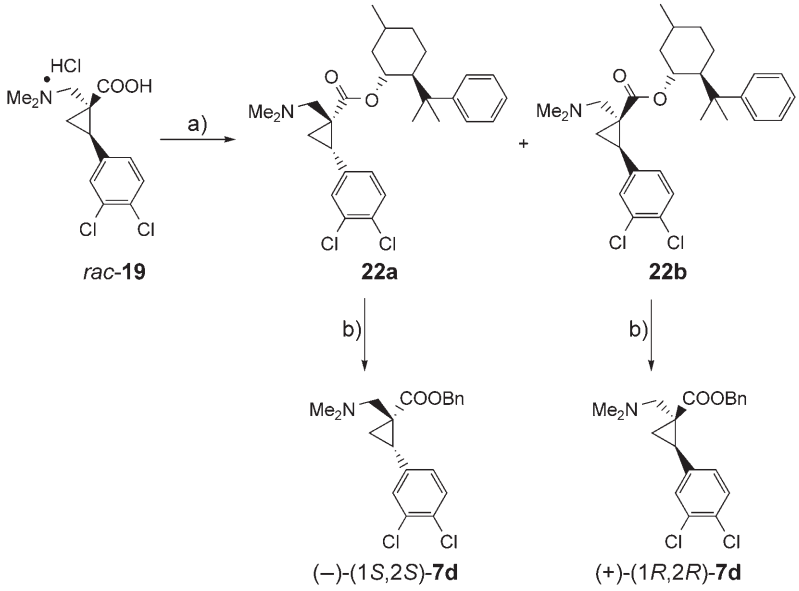
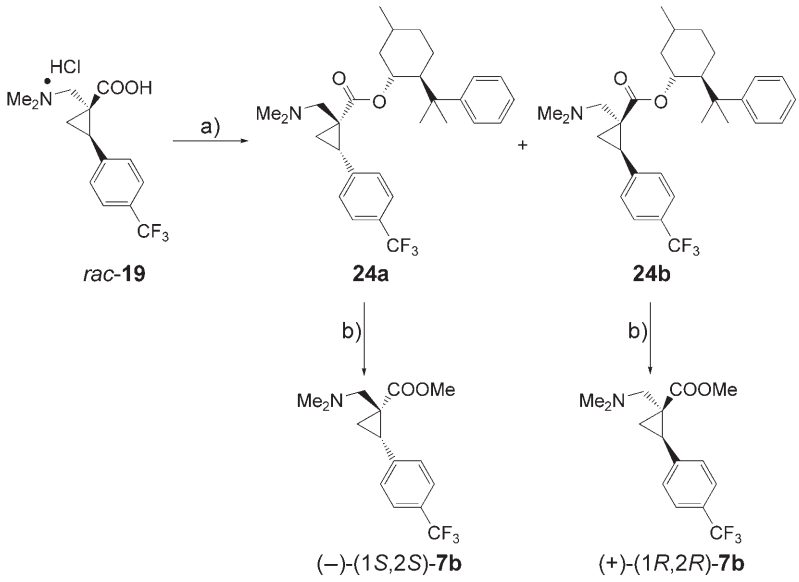


Scheme 4. Reagents and conditions: a) oxalyl chloride, CH_2Cl_2, RT, 2 h, then (−)-8-phenylmenthol, *n*BuLi, ether, RT, overnight; b) HCl (6 N), reflux, 12 h, then oxalyl chloride, CH_2Cl_2, RT, 2 h, then $PhCH_2OH$, *n*BuLi, THF, RT, overnight.



Scheme 5. Reagents and conditions: a) oxalyl chloride, CH_2Cl_2, RT, 2 h, then (−)-8-phenylmenthol, *n*BuLi, ether, RT, overnight; b) HCl (6 N), reflux, 12 h, then oxalyl chloride, CH_2Cl_2, RT, 2 h, then CH_3OH, *n*BuLi, THF, RT, overnight.

logues, which are potent DA and NE reuptake inhibitors.[21–24] By using compound **7a** as a starting point, we investigated the effects of structural modifications made to the tropane series similar to modifications previously reported by us or other research groups.[6,25–27] Compound **7a** displayed no activity at the DAT and NET and only weak inhibitory activity at the SERT (K_i = 1.6 μM). Replacement of the 4-fluoro substituent in **7a** with a trifluoromethyl group gave compound **7b**, which exhibited a fourfold increase in potency against SERT. The benzyl ester **7c** was even more potent toward the SERT, with a K_i value of 98 nM. Replacement of the 4-substituent with the 3,4-dichloro substitution pattern gave the analogue **7d**, which displayed fairly good inhibitory activity at the SERT (K_i = 55 nM). Introduction of a larger group in the ester moiety (compounds **7e** and **7f**) resulted in a ninefold decrease in potency for the SERT.[6,39,40]

Modification of the amino group revealed that the primary and secondary amines **7h** and **7g** are eight- and fivefold less active at the SERT than is compound **7d**. Interestingly, in the WIN series, N-demethylation generally leads to an improvement in SERT activity.[23,41,42]

As the ester group in the WIN series of tropanes is generally tolerant to a variety of structural changes,[6,7] we examined the effect of modification at this site in the cyclopropanes. First, esters **7a**, **c**, and **d** were reduced to the corresponding alcohols **8**–**10**. Alcohol **8** displayed the same low activity at the SERT as the parent compound **7a**, alcohol **9** displayed a 12-fold decreased potency at the SERT compared with the parent compound **7c**, and alcohol **10** was fourfold less potent than its parent **7d**. On the other hand, the ethers **11**–**13** prepared from their corresponding alcohols had improved potency at the SERT. Compound **11** showed a sixfold improvement in activity over ester **7a**, ether **12** exhibited a twofold increase relative to ester **7c**, and ether **13** was twofold more potent than the parent **7d,** with a K_i value of 22 nM. Compound **13** also displayed some activity at the NET (K_i = 451 nM); the DAT/SERT uptake ratio is 81:1, and the NET/SERT uptake ratio is 20:1.

In recent studies on some conformationally constrained tropane analogues,[25–27] we found that replacement of the ester group with a benzoyloxymethyl group resulted in the most potent and selective SERT ligands. It was therefore reasonable to apply this type of modification to the current series as well. Acetate **14** is almost equipotent to ester **7d** at the SERT, but it is somewhat less potent than ether **13**. Benzoate **15** is more potent than acetate **14** and almost equipotent to ether **13**. The SERT selectivity of benzoate **15** is, however, higher than that of **13** or **14**. Benzoate **16** also displayed a twofold increase in SERT inhibition relative to the ester **7c**, and it is more potent than the ether **12**. The benzoate **17** was even more potent at the SERT, with a K_i value of 20 nM, which is 10-fold higher than that of ether **11**. The most potent compound in the current series is naphthoate **18**, which displayed a K_i value of 13 nM, a DAT/SERT uptake ratio of 366:1, and a NET/SERT uptake ratio of 248:1. However, its calculated log*P* is 5.7 (determined with Daylight software[43]), and thus this compound may not be the most suitable drug candidate in this series. The Clog*P* of benzoate **17** is 4.6, which falls within the range of typical druglike molecules.

Replacement of the ester group by an amide group caused a significant decrease in potency of SERT inhibition. Although

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Table 1. Inhibition of Reuptake at Monoamine Transporters.

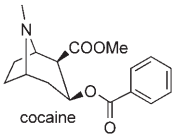
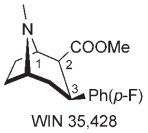
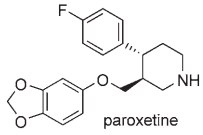
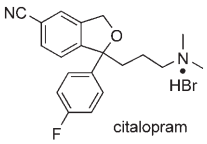
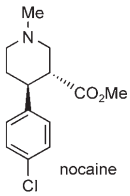
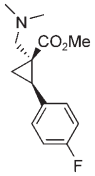
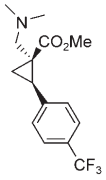
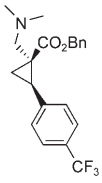
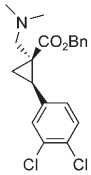
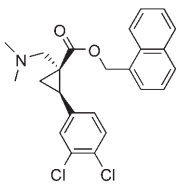
Compound		Clog P[a]	[^{3}H]DA Uptake [nM][b]	[^{3}H]5-HT Uptake [nM][b]	[^{3}H]NE Uptake [nM][b]	$K_{i(DA)}/K_{i(5\text{-}HT)}$	$K_{i(NE)}/K_{i(5\text{-}HT)}$
 cocaine		2.57	259 ± 19.9	155 ± 0.40	108 ± 3.50	1.7	0.7
 WIN 35,428		2.96	26.1	31.9	127	0.8	4.0
 paroxetine		4.24	–	0.25	312	–	1248
 citalopram		3.13	10000	5.4	> 1000	4000	> 185
 nocaine		3.22	233 ± 62	8490 ± 1430	252 ± 43	0.03	0.03
	(±)-**7a**	2.54	> 10000	1600 ± 290	> 10000	> 6.3	> 6.3
	(±)-**7b**	3.28	> 10000	424 ± 42.1	> 10000	> 23.6	> 23.6
	(±)-**7c**	5.00	> 10000	98.3 ± 7.2	> 10000	> 10.2	> 10.2
	(±)-**7d**	5.43	5950 ± 1030	55.4 ± 4.3	4560 ± 170	107	82.3
	(±)-**7e**	6.60	9730 ± 1580	511 ± 38.0	5910 ± 10	19	11.5

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Table 1. (Continued)

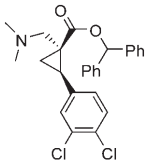
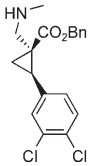
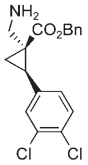
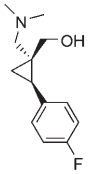
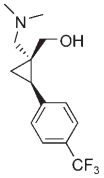
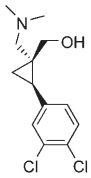
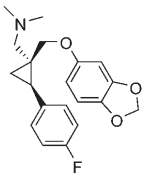
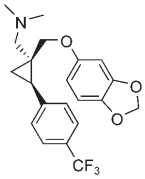
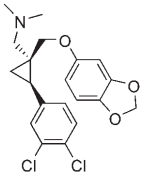
Compound		Clog P[a]	[^{3}H]DA Uptake [nM][b]	[^{3}H]5-HT Uptake [nM][b]	[^{3}H]NE Uptake [nM][b]	$K_{i(DA)}/K_{i(5\text{-}HT)}$	$K_{i(NE)}/K_{i(5\text{-}HT)}$
	(±)-**7f**	6.78	> 10000	539 ± 44.7	> 10000	> 18.6	> 18.6
	(±)-**7g**	4.83	> 10000	297 ± 0.8	2020 ± 190	> 33.7	6.8
	(±)-**7h**	4.53	1760 ± 90	435 ± 57.0	3730 ± 540	4.0	8.6
	(±)-**8**	1.88	> 10000	1750 ± 243	> 10000	5.7	5.7
	(±)-**9**	2.62	> 10000	1230 ± 144	> 10000	> 8.1	> 8.1
	(±)-**10**	3.04	7650 ± 211	221 ± 36	1740 ± 263	36.2	7.9
	(±)-**11**	4.53	1090 ± 100	272 ± 0.9	816 ± 60.1	4.0	3.0
	(±)-**12**	5.27	10200 ± 290	59.8 ± 11.7	2140 ± 200	170	35.8
	(±)-**13**	5.70	1800 ± 200	22.1 ± 4.5	451 ± 44.0	81.4	20.4

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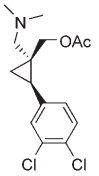
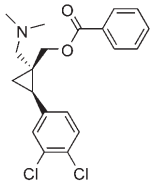
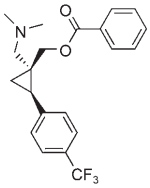
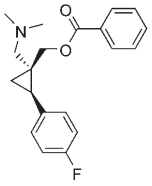
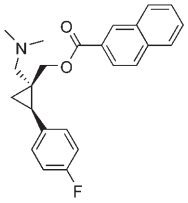
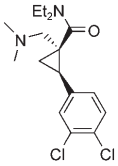
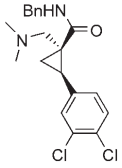
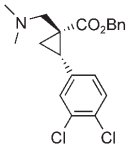
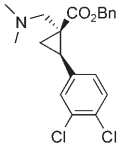
Table 1. (Continued)

Compound		Clog P[a]	[^{3}H]DA Uptake [nM][b]	[^{3}H]5-HT Uptake [nM][b]	[^{3}H]NE Uptake [nM][b]	$K_{i(DA)}/K_{i(5\text{-}HT)}$	$K_{i(NE)}/K_{i(5\text{-}HT)}$
	(±)-**14**	3.95	9231 ± 993	53.7 ± 2.1	3039 ± 158	172	56.6
	(±)-**15**	5.70	9590 ± 1740	29.2 ± 4.4	2650 ± 116	328	90.8
	(±)-**16**	5.28	> 10000	48.8 ± 5.6	> 10000	205	205
	(±)-**17**	4.53	> 10000	20.5 ± 2.4	4780 ± 215	> 488	233
	(±)-**18**	5.71	4900 ± 59	13.4 ± 3.0	3330 ± 326	366	248
	(±)-**20**	4.23	> 10000	3780 ± 550	> 10000	> 2.6	> 2.6
	(±)-**21**	4.68	> 10000	1690 ± 100	> 10000	> 5.9	> 5.9
	(−)-**7d**	5.43	> 10000	184 ± 1.0	> 10000	> 54.3	> 54.3
	(+)-**7d**	5.43	7720 ± 170	64.6 ± 6.9	3450 ± 220	119	53.4

[a] Clog P calculated by using the web-based program from Daylight (ref. [43]). [b] Data are mean K_i ± SEM from two to four independent experiments, each consisting of six drug concentrations (in triplicate) that were selected on the basis of preliminary screening experiments to bracket the approximate IC_{50} value.

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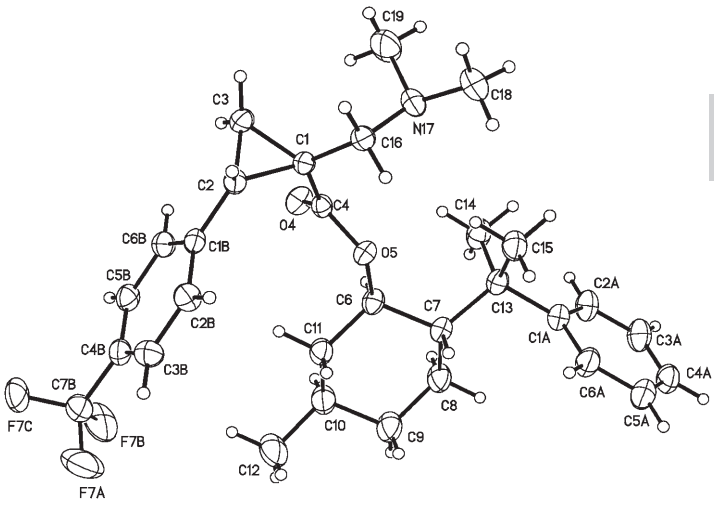

Figure 3. View of compound **24a** showing the labeling of non-hydrogen atoms. Displacement ellipsoids are shown at the 30% probability level.

amides **20** and **21** have K_i values in the micromolar range, they remain SERT-selective.

Whereas all compounds discussed above were prepared in racemic form, in one case, cyclopropane **7d** was resolved chemically into its individual enantiomers. Both enantiomers were active against SERT. Compound (+)-**7d** is approximately threefold more potent than (−)-**7d**, but is roughly equipotent with the racemic mixture.

In summary, a series of cyclopropane analogues was synthesized through a cyclopropanation reaction of a benzylidenemalonate. These cyclopropanes bear the same pharmacophore elements as those found in the WIN series of cocaine analogues. Through modifications of ester, aryl, and amino groups, ligands were identified that show good selectivity and potency at the SERT. The ether **13** and the benzoates **15** and **17** are roughly equipotent at the SERT with K_i values around 20 nM. The 2-naphthyl-bearing ligand **18** represents the most potent ligand in this series, with $K_i = 13$ nM, a DAT/SERT uptake ratio of 366:1, and a NET/SERT uptake ratio of 248:1. Ether **13** likely represents one of the more promising candidates of the series presented herein for in vivo study, owing to its relative metabolic stability. As both selective and mixed monoamine transporter reuptake inhibitors have proven useful as medications in the treatment of depression, anxiety and eating disorders, schizophrenia, Alzheimer's disease, and other CNS disorders,[44,45] we believe that the compounds described herein are worthy of continued investigation. Accordingly, further pharmacological experiments are planned along with assessments of the behavioral activity of selected compounds.

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Keywords: cocaine · cyclopropane · monoamine inhibitors · neurochemistry · neurotransmitters

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