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Synthesis and monoamine transporter affinity of new 2β-carbomethoxy-3β-[aryl or heteroaryl]phenyltropanes

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Abstract—A series of 16 new 2β-carbomethoxy-3β-[aryl or heteroaryl]phenyltropane derivatives was synthesized and evaluated for binding to monoamine transporters. Most of the compounds exhibited nanomolar affinity for the serotonin transporter (SERT). Four compounds (**29**, **14**, **11**, and **10)** presented a particularly attractive pharmacological profile, with very high SERT affinity (K_i 0.15–0.5 nM) and selectivity versus the dopamine transporter of 25- to 77-fold.

Neurotransmission mediated by serotonin (5-hydroxytryptamine; 5-HT) plays an important role in the central nervous system. The serotonin transporter (SERT) is critical for regulating availability of 5-HT at the synapse by neuronal reuptake and is a protein that is uniquely expressed by 5-HT neurons. Alterations in SERT densities have been reported in numerous neuropsychiatric conditions, including drug abuse, schizophrenia, major depression, anxiety and eating disorders, alcoholism, Parkinson's and Alzheimer's disease.[1–6]

Cocaine (**1**, Fig. 1) exerts its physiological and behavioral effects by interaction with the three major monoamine transporters (for dopamine [DAT] and norepinephrine [NET] as well as SERT). Therefore, structurally related tropane (8-azabicyclo[3.2.1]octane) derivatives have been extensively studied in recent years to develop compounds with defined selectivities at particular monoamine transport sites.[7,8] We have recently explored structure–activity relationships of tropane analogues related to their binding affinity to the SERT,[9–13] In these studies, we discovered that introduction of a substituted aryl or heteroaryl moiety in the *para* position of the 3β-phenyltropane ring (**2**–**4**,[10,13] Fig. 1) resulted in increased affinity and selectivity for SERT versus dopamine (DAT) and norepinephrine (NET) transporters. Another approach that usually leads compounds with SERT selectivity has been the use of *N*-demethylated tropane.[14] The purpose of the present study was to extend the library of *para*-aryl and heteroaryl 3β-phenyltropane as well as some of their nor analogues in search of compounds with increased SERT selectivity.

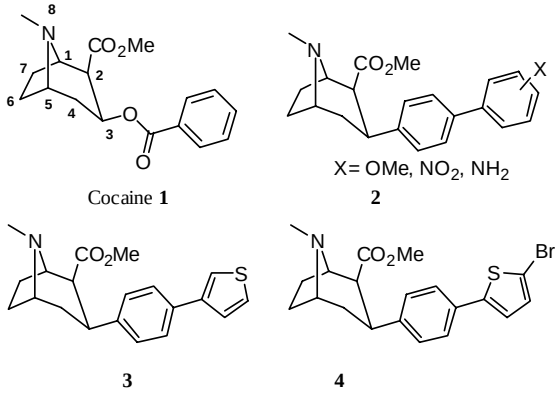

Figure 1.

Keywords: Transporter; Serotonin; Dopamine; Norepinephrine; Tropane.
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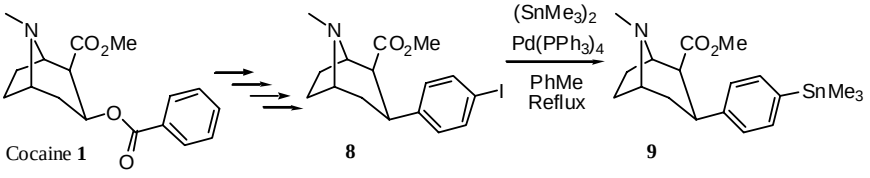
The key tin derivative **9** was synthesized from β-CIT (**8**), which was made from natural cocaine in four steps.[15] Treatment of **8** with hexamethylditin in the presence of tetrakis-triphenylphosphine palladium gave 82% yield of trimethylstannyl β-CIT (**9**) in 82% yield (Scheme 1). The new *para*-aryl and heteroaryl 3β-phenyltropanes (**10**–**23**) were prepared by Stille cross-coupling between **9** and the desired bromoaryl and bromoheteroaryl as illustrated in Scheme 2. β-CIT was selectively *N*-demethylated by the action of 1-chloroethyl chloroformate (ACE-Cl) and methanol to provide nor-β-CIT (**23**) in 75% yield (Scheme 3).

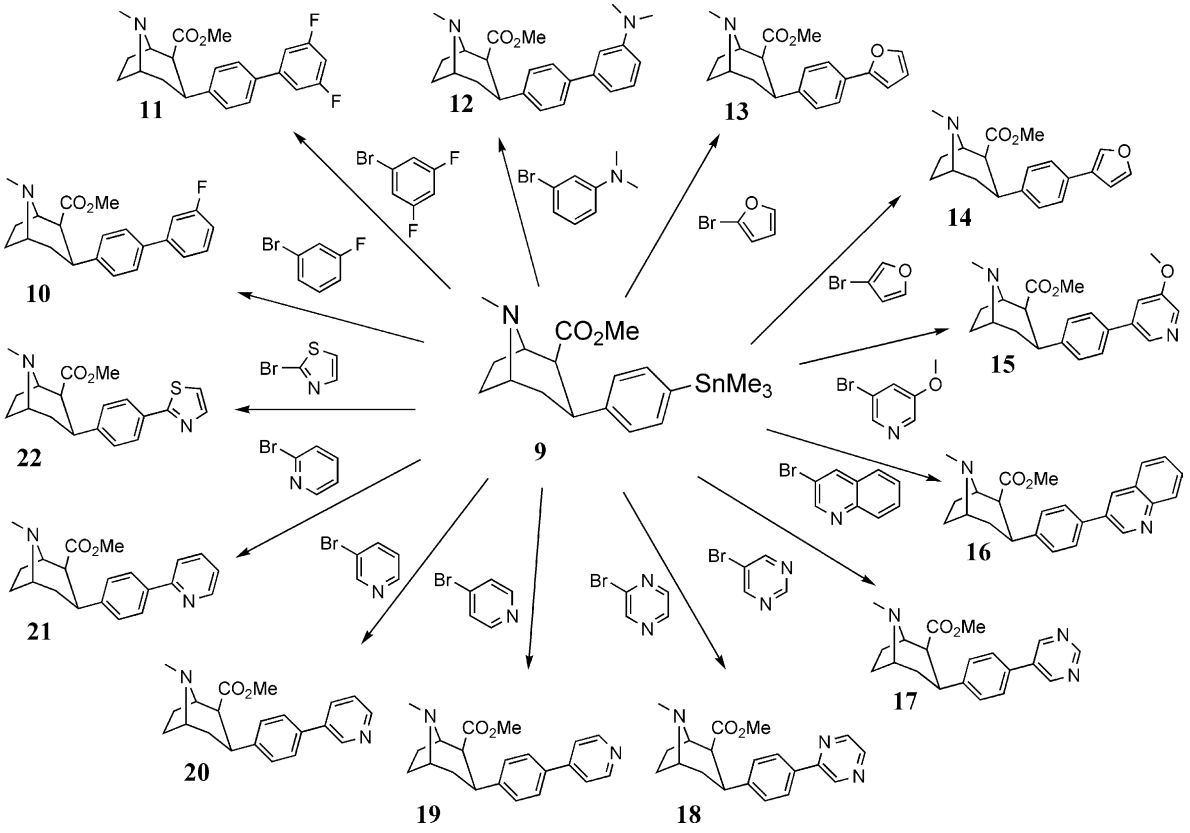
Treatment of **23** with trichloroethyl chloroformate (Troc-Cl) led to the corresponding *N*-protected carbamate **24**. The same sequence of stannylation (compound **25**) and Stille cross-coupling led to **26**–**28**, and subsequent removal of the Troc-protecting group with cadmium amalgam provided the desired nor analogues (**29**–**31**) of **13**, **15**, and **22** (Scheme 3).

Compounds **2**–**4** are 2β-carbomethoxy-3β-phenyltropanes substituted by an aromatic or a thiophene moiety in the *para* position of the 3β-phenyl ring, with relatively high affinity and selectivity for SERT.

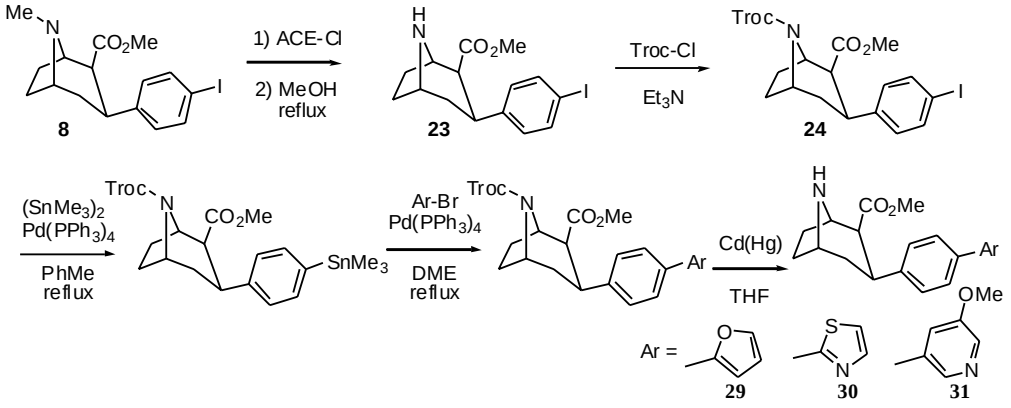
We modulated the *para*-aryl or heteroaryl 3β-phenyltropane structures to extend knowledge of the molecular requirements for high affinity to the SERT proteins, and selectivity for SERT compared to DAT or NET proteins, based on testing with cell membrane-containing homogenates of rat cerebral cortex (SERT, NET) or caudate nucleus tissue (DA) as transporter sources. Transporter potencies and SERT-selectivities of novel compounds are summarized in Table 1. All compounds tested showed at least moderate affinity for SERT



Scheme 1.

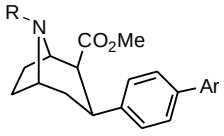


Scheme 2. Reagents and conditions: $Pd(PPh_3)_4$, toluene, reflux, 4 h.



Scheme 3.

Table 1. Affinity (K_i, nM; mean ± SEM) of new *para*-aryl and heteroaryl 3β-phenyltropane to monoamine transporters[a]



Compound	R	Ar	SERT	DAT	NET	Selectivity SERT versus DAT
29	H	2′-Furyl	0.15 ± 0.02	3.76 ± 0.48	12.7 ± 1.3	25
14	Me	3′-Furyl	0.35 ± 0.09	14.2 ± 3.3	127 ± 6.0	40
11	Me	3′,5′-F_2-Ph	0.41 ± 0.05	31.7 ± 4.1	109 ± 9.5	77
10	Me	3′-F-Ph	0.50 ± 0.11	25.2 ± 1.8	249 ± 19	50
13	Me	2′-Furyl	1.13 ± 0.21	7.14 ± 1.1	1400 ± 59	6
31	H	3′-MeO-pyridin-3-yl	1.56 ± 0.24	332 ± 99	739 ± 231	212
22	Me	2′-Thiazolyl	1.67 ± 0.31	520 ± 72	>10,000	311
20	Me	Pyridin-3-yl	3.51 ± 0.35	26.1 ± 3.1	1407 ± 154	7
15	Me	3′-MeO-pyridin-3-yl	3.91 ± 0.22	587 ± 55	1595 ± 198	150
30	H	2′-Thiazolyl	5.15 ± 0.76	69.6 ± 7.4	213 ± 48	13
18	Me	Pyrazin-2-yl	11.3 ± 0.2	121 ± 11	213 ± 26	10
16	Me	Quinolin-3-yl	20.0 ± 1.1	59.8 ± 2.9	>30,000	3
17	Me	Pyrimidin-5-yl	33.1 ± 0.9	344 ± 52	>10,000	110
21	Me	Pyridin-2-yl	161 ± 1.9	44 ± 2.8	>10,000	0.27
19	Me	Pyridin-4-yl	>1000	1566 ± 254	>30,000	—
12	Me	3′-Me_2N-Ph	>1000	545 ± 259	>30,000	—

[a] Assays of novel compounds employed cell membrane-containing homogenates of rat forebrain (frontoparietal cerebral cortex for SERT and NET, caudate-putamen for DAT), with [^{3}H]paroxetine (0.17 nM) for SERT (blank = 10 μM *R*,*S*-fluoxetine, Sigma-RBI), [^{3}H]GBR-12935 (0.20 nM) for DAT (blank = 10 μM GBR-12909, Sigma-RBI), and [^{3}H]nisoxetine (0.40 nM) for NET (blank = 10 μM desipramine, Sigma-RBI); results are expressed as mean ± SE, based on at least three separate determinations. Test agents are ranked by SERT potency.

(K_i < 100 nM) and greater affinity than for DAT or NET. In the phenyl series, the 3′,5′-difluoro- and 3-fluoro-compounds **11** and **10** displayed high affinity (K_i = 0.41 and 0.5 nM, respectively) for SERT and selectivity versus DAT (77- and 50-fold) or NET (265- and 498-fold), whereas the 3′-*N*,*N*-dimethyl analogue **12** was inactive at all three monoamine transporters. These findings accord with our previous results showing good affinity and selectivity at SERT for phenyltropanes with small electronegative substituents at the *meta* position.[10] To investigate the effect of replacing the phenyl (**2**) or thiophenyl (**3** and **4**) rings with a heteroaromatic ring, we synthesized and evaluated analogues bearing a furan (**13** and **14**), pyridine (**15** and **19**–**21**), quinoline (**16**), pyrimidine (**17**), pyrazine (**18**), or thiazole (**22**) moiety. The furan analogues were the most potent at SERT. The 3′-furyl (**13**) displayed higher SERT potency (K_i = 0.35 SERT) and selectivity (40-fold, SERT vs DAT) than the 2′-furyl (**14**), 2.7 times less potent and 7 times less selective at the SERT; these results are consistent with our previous findings with thiophenytropanes.[13] The 2′-thiazolyl (**22**) isostere of the 2′-furyl derivative (**14**) presented the same range of affinity with K_i = 1.67 nM at SERT; however, the pharmacological profile of this compound differed by the higher selectivity versus DAT (330- and 6-fold, respectively) than the 3′-furyl analogue (**13**). Introducing a pyridine moiety led to less SERT-potent and selective compounds, ranked 3′-pyridyl (**20**) > 2′-pyridyl (**21**) > 4′-pyridyl (**20**). A 5-methoxy group as a 3′-pyridyl substituent (**15**) did not appreciably alter SERT affinity (K_i = 3.91 and 3.51 nM, for **15** and **20**) but markedly increased

SERT selectivity versus DAT, from 7- to 150-fold (**20** vs **15**). The quinoline (**16**), pyrimidine (**17**), and pyrazine (**18**) analogues showed weaker affinity for the SERT (K_i = 11.3, 20.0, and 33.1 nM respectively). Among nortropane analogues, as expected, **29** was more active and selective than the parent tropane **13** (in fact, it was the most potent at SERT of the compounds reported in this study), with a K_i = 0.15 nM and a selectivity versus DAT of 25-fold. The same phenomenon was observed for **31** (desmethyl analogue of **20**), but, interestingly, not for the 2′-thiazolyl analogues (**30** vs **22**).

In conclusion, we report the synthesis of 16 new *para*-aryl or heteroaryl 3β-phenyltropanes and their evaluation for potency and selectivity at monoamine transporter proteins in mammalian forebrain tissue. Four new compounds (**29**, **14**, **11**, and **10**) showed equal or higher affinity for SERT than β-CIT, a radiotracer used to quantify SERT proteins in brain tissue (SERT K_i = 0.46, selectivity vs DAT = 2),[15] with improved, 22- to 77-fold, selectivity versus DAT.

Acknowledgments

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