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3α-(4-Substituted Phenyl)nortropane-2β-carboxylic Acid Methyl Esters Show Selective Binding at the Norepinephrine Transporter

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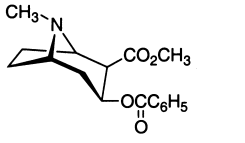
Abstract—A series of 3α-(4-substituted)nortropane-2β-carboxylic acid methyl esters was synthesized and evaluated for the ability to inhibit radioligand binding at the dopamine, serotonin, and norepinephrine transporters. 3α-(4-Methylphenyl)nortropane-2β-carboxylic acid methyl ester (**4c**) was found to be selective and highly potent for the norepinephrine transporter (NET) relative to the dopamine and serotonin transporters.

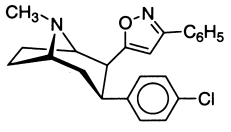
The pharmacology of cocaine (**1**) is believed to center around its interaction with the dopamine, serotonin, and norepinephrine transporters (DAT, 5-HTT, and NET, respectively). As part of a program to study the biochemical mechanism of action of cocaine, we have conducted a structure–activity relationship (SAR) study to investigate the monoamine transporter binding properties of the 3-phenyltropane class of compounds.[1] These studies have led to the discovery of analogues selective for the DAT such as 3β-(4-chlorophenyl)-2β-(3-phenylisoxazol-5′-yl)tropane (**2**, RTI-177)[2,3] as well as analogues selective for the 5-HTT such as 3β-(4-ethyl-3-iodophenyl)nortropane-2β-carboxylic acid methyl ester (**3**, RTI-353, EINT) (Chart 1).[4,5] As a continuation of these SAR studies, we now report the synthesis of the 3α-(4-substituted phenyl)nortropane-2β-carboxylic acid methyl esters (**4a–c**), some of which possess greater affinity at the NET than that at the DAT and 5-HTT.

Chemistry

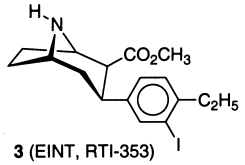
The 3α-(4′-fluoro, -chloro, and -methylphenyl)nortropane-2β-carboxylic acid methyl esters (**4a–c**, respectively) were synthesized by refluxing the known 3α-(4′-substituted phenyl)tropane-2β-carboxylic acid methyl esters (**5a–c**)[6] with α-chloroethyl chloroformate (ACE-Cl) in dichloroethane under a nitrogen atmosphere to give an (α-chloroethyl)urethane, which was not isolated but converted directly to the *N*-nor analogues by solvolysis with methanol (Scheme 1).[7] Concentration of the reaction mixture followed by the addition of ethyl ether provided **4a–c** as their hydrochloride salts. Each compound gave satisfactory elemental analyses for carbon, hydrogen, and nitrogen, and the ^{1}H NMR spectra were in



1 (cocaine)



2 (RTI-177)



3 (EINT, RTI-353)

Chart 1.

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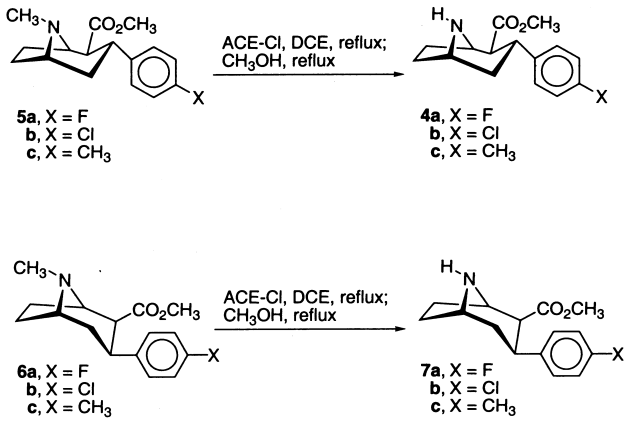


Scheme 1.

agreement with the assigned structures. The 2β,3β-phenyltropanes, **6a–c**, and 2β,3β-phenylnortropanes, **7a–c**, were prepared as previously described.[7,8] Depiction of the 2β,3α isomers as boats and 2β,3β isomers as chairs is intentional. Previous NMR analysis suggests that the ring of the 2β,3β compounds inverts when the center is epimerized to the 2β,3α isomers.[6]

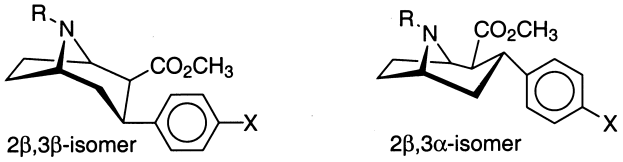
Biological Studies

The in vitro binding affinities of the compounds at the DAT, 5-HTT, and NET were determined via competitive binding assays using the previously reported procedures.[7,9,10] The radioligands were 0.5 nM [^{3}H]WIN 35,428 for the DAT, 0.2 nM [^{3}H]paroxetine for the 5-HTT, and 0.5 nM [^{3}H]nisoxetine for the NET. The binding data for the 2β,3α-phenylnortropane analogues, **4a–c**, along with previously reported data of the 2β,3β-phenyltropane (**6a–c**), 2β,3β-phenylnortropane (**7a–c**), and 2β,3α-phenyltropane (**5a–c**) analogues as well as cocaine (**1**) for comparison are given in Table 1.

Results and Discussion

A SAR study of the 3β-(4′-substituted phenyl)nortropane-2β-carboxylic acid methyl esters revealed that removing the *N*-methyl group from the tropane analogue resulted in increased binding at NET and 5-HTT with little change in binding at the DAT.[4,7] This can be seen by comparing the affinity of the 3-phenyltropane analogues, **6a–c**, to the nortropane analogues, **7a–c** (Table 1), respectively. In all three cases, binding at the DAT remained relatively constant while binding to the

Table 1. Comparison of transporter binding properties of 3-phenyltropane and 3-phenylnortropane 2β-carboxylic acid methyl ester analogues



	Isomer				IC_{50} nM (K_i nM)[a]		
RTI compound[b]	2	3	R	X	NE [^{3}H]nisoxetine	DA [^{3}H]WIN 35,428	5-HT [^{3}H]paroxetine
WIN 35, 428 (**6a**)[c]	β	β	CH_3	F	835±45 (503±27)	15.7±1.4	760±47 (69±4)
142 (**7a**)[c]	β	β	H	F	18.80±0.68 (11.3±0.41)	4.4±0.2	68.6±2.0 (6.24±0.18)
286 (**5a**)[d]	β	α	CH_3	F	1200±91 (741±54.8)	21.0±0.50	5060±485 (460±44)
367 (**4a**)	β	α	H	F	9.8±0.7 (5.9±0.40)	32.6±2.6	92.4±7.7 (8.40±0.70)
31 (**6b**)[c]	β	β	CH_3	Cl	37±2.1 (22.0±1.3)	1.12±0.10	45.0±1.3 (4.00±0.12)
110 (**7b**)[c]	β	β	H	Cl	5.45±0.21 (3.28±0.13)	0.62±0.09	4.13±0.62 (0.38±0.06)
355 (**5b**)[d]	β	α	CH_3	Cl	60±2.40 (36.0±1.5)	2.4±0.2	998±120 (91±11)
389 (**4b**)	β	α	H	Cl	5.14±1.08 (3.1±0.60)	3.1±1.0	53±3 (4.80±0.26)
32 (**6c**)[d]	β	β	CH_3	CH_3	60.0±0.50 (36.0±0.30)	1.70±0.30	240±27 (22.0±2.5)
404 (**7c**)	β	β	H	CH_3	7.20±0.45 (4.40±0.27)	0.84±0.09	135±28 (12±3)
356 (**5c**)[d]	β	α	CH_3	CH_3	270±24 (160±14)	10.2±0.8	4250±422 (390±38)
362 (**4c**)	β	α	H	CH_3	9.0±0.3 (5.20±0.18)	33.6±4.1	500±30 (46±3)
Cocaine (**1**)	—	—	—	—	3300±290 (1900±170)	89.1±4.8	1050±89 (95±8)

[a]The numbers under the IC_{50} value in parentheses are the K_I values.
[b]Compounds **4a–c**, **5a** and **6a–c** and **5b–c** were assayed as their hydrochloride, tartrate, and tosylate salts, respectively. Compounds **7a–c** were assayed as free bases.
[c]The IC_{50} values are from ref 7.
[d]The IC_{50} values are from ref 6.

NET increased 44-, 6.8-, and 8.3-fold, and binding to the 5-HTT increased 11-, 11-, and 2-fold for the 4′-fluoro, 4′-chloro, and 4′-methyl analogues, respectively. In a separate SAR study we reported that 3α-(4′-substituted phenyl)tropane-2β-carboxylic acid methyl esters showed decreased binding at all three transporters relative to the corresponding 2β,3β-isomer; however, binding at the NET was sometimes affected less than the other two transporters.[6] This trend is evidenced when comparing compounds **6a–c** to **5a–c** (Table 1). The data shows that epimerization at the 3-position caused binding to the NET to decrease only 1.4- to 4.5-fold, but binding to the DAT and 5-HTT became worse.

Since previous binding studies have shown that trends of the WIN 35,065-2 analogues are often additive, combining these two trends would suggest that 3α-(substituted phenyl)nortropane-2β-carboxylic acid methyl esters might be more potent and selective for the NET than at the DAT and 5-HTT. As expected, 3α-(4′-fluoro, -chloro, and -methylphenyl)nortropane-2β-carboxylic acid methyl esters, **4a–c**, were found to have the highest potency for NET. A comparison of the affinity at the NET of the 2β,3α-phenylnortropane analogues to that of the 2β,3β-phenylnortropanes reveals that they have approximately the same affinities. For example, 3β-(4′-chlorophenyl) nortropane-2β-carboxylic acid methyl ester **7b** was found to bind with a K_i value of 3.3 nM, while its 2β,3α-nortropane isomer **4b** possesses a K_i value of 3.1 nM. The NET K_i values for the 4′-methyl analogues, **7c** and **4c**, were 4.4 and 5.2 nM, respectively. The fluoro analogue **4a** was the only analogue to show an increase in potency, roughly 2-fold over its epimer. The 4-methylphenyl analogue **4c** was found to bind to the NET 7 and 9 times better than at the DAT and the 5-HTT, respectively. To our knowledge, **4c** is the first 3-phenyltropane analogue to show selectivity for the NET and, thus, represents a lead structure for the development of even more NET-selective analogues. The 4-fluorophenyl analogue **4a** shows approximately equal affinity for the NET and 5-HTT with 6-fold selectivity relative to the DAT. The 4-chlorophenyl analogue **4b** showed about equal affinity for all three transporters.

In summary, we have compared the monoamine transporter binding properties of the 2β,3β- and 2β,3α-isomers of 3-(4-substituted phenyl)tropane-2-carboxylic acid methyl ester to the corresponding 3-(4-substituted phenyl)nortropane-2-carboxlic acid methyl esters and have shown that the 2β,3α-nortropane analogues, **4a–c**, possess the greatest selectivity for the NET. 3α-(4-Methylphenyl)nortropane-2β-carboxylic acid methyl ester (**4c**) is the first 3-phenyltropane analogue to show high potency and selectivity at the NET relative to the DAT and 5-HTT.

Additional analogues are currently under investigation to exploit these trends further. The discovery of NET-selective compounds also completes a set of WIN 35,065-2 compounds selective for each transporter affected by cocaine.

Acknowledgements

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