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SAR of Cocaine: Further Exploration of Structural Variations at the C-2 Center Provides Compounds of Subnanomolar Binding Potency

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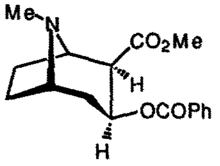
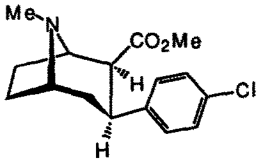
Abstract: *Syntheses of a variety of new analogues of cocaine are reported together with their binding affinities and dopamine uptake inhibition activities. The present work further expands the SAR data base for cocaine.*

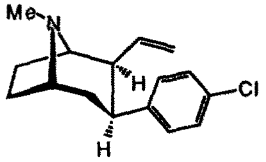
We have recently reported that substitution of a vinyl group for the ester group at cocaine's 2-position in the so-called "Win" series (phenyl replacing benzoate) still leads to compounds of high binding affinity.[1] Thus the vinyl compound **2** was found to be slightly more potent than its ester counterpart **1** (Table 1). We argued that this result provides evidence that specific hydrogen bond donor groups may not be present within the cocaine recognition site in the vicinity of its C-2 ester substituent. Since it might well be argued that the π-electrons of the vinyl group of **2** could provide a possible hydrogen bond donor site,[2,3] we felt that it would be important to probe this possibility through an examination of the activity of the Win-like analogue **3** in which the π-electrons of the vinyl group have been removed by hydrogenation. As is apparent from the data provided in Table 1, the binding potency and dopamine uptake inhibitory properties of **3** are not much different from **2**, with only about a two-fold decrease in binding affinity for **3** being observed. Likewise, **3** is only about two-fold less potent than the ester **1**. Clearly, a hydrogen bond acceptor group at cocaine's 2-position is not required for high binding affinity, for if this were the case, one could expect a loss in binding affinity of at least 10- to 100-fold.[3] However, caution



Cocaine



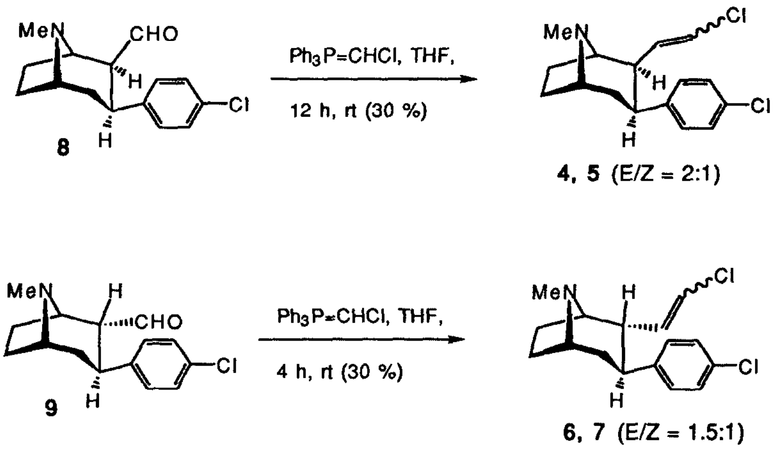
1, a Win analogue



2, a cocaine analogue containing two ester surrogates must be exercised in the interpretation of these data, for as we had suggested in our previous publication, different binding modalities may be available to the ester analogues relative to their alkyl or alkenyl counterparts.[1]

To probe the C-2 ester binding site further, we also investigated the effect of the stereochemistry of the C-2 substituent, both in regard to its location on either the α or β face of the tropane system and the effect of olefin configuration. We had reported previously that the E-vinyl chloride **4** was particularly potent in terms of its binding affinity and its ability to inhibit dopamine uptake. Three additional compounds (**5-7**) structurally related to **4** were synthesized by way of the routes delineated in Scheme 1.[1] The Z-olefin isomers were available as minor products in the Wittig reaction with the respective aldehydes, **8** and **9**.

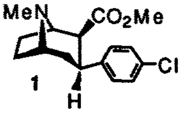
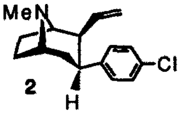
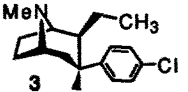
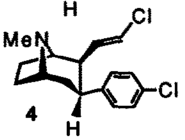
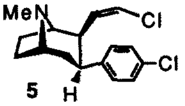
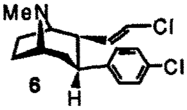
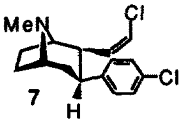
Scheme 1. Synthesis of other vinyl chlorides.



As is evident from the data in Table 1, the Z-configured β-isomer is two-fold more potent than its E counterpart, exhibiting a binding potency comparable to that of the best of the Win type analogues.[4,5] The two α isomers, **6** and **7**, are as much as 100-fold less potent. This is in line with previous observations recorded by Carroll and co-workers in which they show pseudococaine to be of lower binding potency compared to cocaine.[2]

Additionally, we have also examined the effect of sp^3 hybridization of the C-2 appendage in comparison to the sp^2 hybridization of this appendage as present in the majority of the preceding compounds (with the exception, of course, of the ethyl compound). Specifically, we examined the activity of the trifluoromethyl alcohols prepared by the reaction of the aldehydes **8** and **9** with (trifluoromethyl)trimethylsilane and tetra-*n*-butylammonium fluoride.[6] In the case of aldehyde **8**, only a single alcohol **10** resulted, which was expected to have R stereochemistry based on Si face addition to the energetically preferred conformer (see **8** in Scheme 2). This result was confirmed by single crystal X-ray analysis (see Figure 1). The two alcohols **12** and **13** resulting from

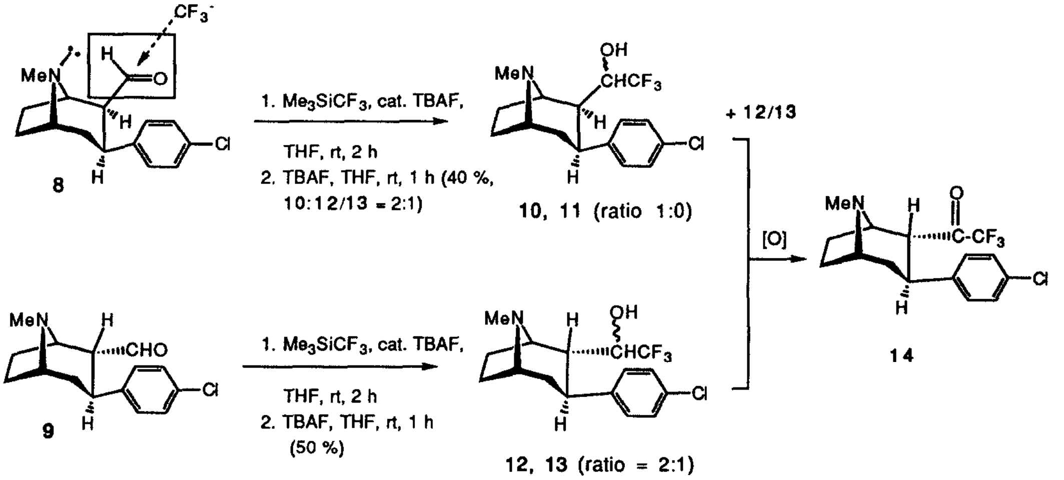
Table 1. IC_{50} values (nM) for cocaine and compounds 1-7 in dopamine uptake and mazindol binding experiments.

Compound	[^{3}H]Dopamine Uptake	[^{3}H]Mazindol Binding
(-)-cocaine	350 ± 11	490 ± 110
 1	3.2 ± 0.1	1.7 ± 0.1
 2	2.8 ± 0.6	1.2 ± 0.3
 3	2.6 ± 0.6	3.5 ± 0.4
 4	1.3 ± 0.3	0.73 ± 0.06
 5	$\boxed{0.99 \pm 0.05}$*	$\boxed{0.36 \pm 0.04}$*
 6	19 ± 2	24 ± 9
 7	16 ±0.3	18 ± 1

*The K_i values calculated from the Cheng-Prusoff relationship are 0.88 ± 0.05 and 0.22 ± 0.02 for [^{3}H]dopamine uptake and [^{3}H]mazindol binding, respectively.

addition to the α-aldehyde were formed in a 2:1 ratio, and NMR and X-ray studies are underway in order to establish their stereochemistry. Lastly, we have examined the oxidation of these alcohols to the respective trifluoromethyl ketones, since we were interested in the possibility that such compounds might interact irreversibly with the cocaine recognition site.[7] Unfortunately,

Scheme 2. Synthesis of the trifluoromethyl bearing cocaine analogues.



oxidation of **10** with a host of oxidants led to apparent rapid epimerization with isolation of only the α-ketone **14**. This was confirmed by oxidation of the α-alcohol mixture **12/13** to the same trifluoromethyl ketone **14**.

The binding and uptake inhibition data for the trifluoromethyl series are shown in Table 2. While the isomeric pair **12/13** is less potent than **10**, this is to be expected based on the observation that β stereochemistry is preferred at the C-2 center. No irreversible binding was found for the "incorrect" α-configured trifluoromethyl ketone **14** thus suggesting the absence of certain types of amino acid residues (e.g., lysine) within this region of the cocaine recognition site.[7] Irreversible binding could, however, be precluded by the possible hydration of the trifluoromethyl ketone. Of further interest is the finding that **10** is about 10-fold less potent than its ester counterpart, 3β-(*p*-chlorophenyl)tropane-2β-carboxylic acid methyl ester (data not shown), a result which can be attributed to any of a number of factors including unfavorable steric or electronic factors associated with the sp^3 hybridized C-2 substituent of **10**.

In summary, the present work provides further support for either : (a) the lack of specific hydrogen bond donor groups within the region of the cocaine recognition site which surrounds the C-2 ester group, and/or (b) the possibility of a different binding modality being available to the C-2 alkyl or alkenyl analogues of cocaine relative to their C-2 ester counterparts. The binding affinity reported for the Z-vinyl chloride **5** is one of the highest ever reported for a Win type analogue, and thus this compound provides further information as to the electronics of the cocaine recognition site.[8] Lastly, the binding data obtained for compound **10** reveal unfavorable steric or electronic factors to be associated with sp^3 hybridization of the C-2 appendage. This work *in toto* thus confirms and further extends the SAR data base which is emerging for cocaine and its analogues.

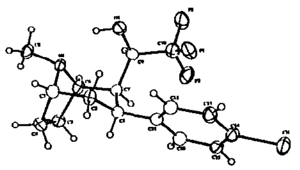
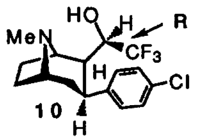
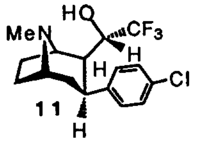
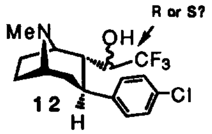
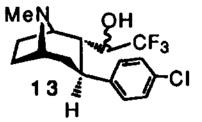
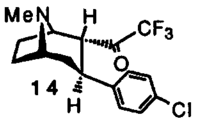
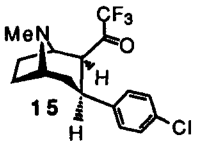


Figure 1. Single crystal X-ray structure of trifluoromethyl alcohol **10** (note intramolecular H-bonding).

Table 2. IC_{50} values (nM) for compounds **10-15** in dopamine uptake and mazindol binding experiments.

Cocaine Analogue	$[^3H]$Dopamine Uptake	$[^3H]$Mazindol Binding
 10	10.5 ± 0.2	9.2 ± 0.35
 11	not isolated from the reaction of the precursor aldehyde with the trifluoromethyl carbanion species	
 12	125 ± 5 (less polar isomer)	166 ± 11
 13	525 ± 30 (more polar isomer)	1105 ± 23
 14	377 ± 21	1190 ± 96
 15	presently unable to isolate this compound due to rapid epimerization to 14 upon attempted purification	

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