Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 845–847

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis of Iodinated 3β-Aryltropanes with Selective Binding to either the Dopamine or Serotonin Transporters

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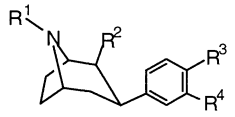
Received 1 October 2001; accepted 23 December 2001

Abstract—Iodinated 3β-aryltropanes functionalized appropriately at the 2β-, 8- and aryl positions display selective binding to either the dopamine or serotonin transporters.

In recent years, there has been considerable interest in the application of neuroimaging techniques such as single-photon emission tomography (SPECT) and positron emission tomography (PET) to the study of drug addiction and neurodegenerative diseases. As the monoamine neurotransmitters are intimately involved in these disease states, the design of selective radioligands for the monoamine binding sites is of central importance.[1,2] Great progress has been made in the preparation of radioligands for the dopamine transporter (DAT) and in recent years various 3β-aryl substituted tropanes have been developed as radioligands.[3] Iodinated tropanes have been most commonly used as SPECT ligands[4] but the positioning of the iodine can alter the binding affinity of the ligand. In this paper, we demonstrate the rational design of new iodinated 3β-aryltropanes that are selective for either the DAT or serotonin transporter (SERT).



3β-aryltropane

Considerable progress has been made in the understanding of the structure–activity relationships that exist for the monoamine transporter binding affinities of the 3β-aryl tropanes.[5–7] By appropriate structural modifications, binding selectivity for either the DAT or SERT can be achieved. Introduction of large substituents at C-2 results in compounds that are selective for the DAT.[8] Small substituents at the 3′ or 4′ positions of the phenyl group increases potency to both transporters,[9] and replacement of the phenyl ring with a 2-naphthyl ring results in extremely potent but non-selective tropanes.[10] Larger substituents at the 4′ position of the aryl ring have been shown by Carroll,[11,12] Tamaganen[13] and us[14–16] to lead to tropanes that are highly selective for the SERT. Also, conformationally constrained tropanes can lead to compounds that are selective for the SERT.[17,18] Even though the normethyl tropanes can be up to ten times more selective for the SERT than the *N*-methyltropanes,[16,19] a larger *N*-alkyl group appears to be reasonably well-tolerated by both transporters.

We describe here the synthesis of a series of highly selective iodinated 3β-aryl tropanes by applying the general structure–activity considerations described above. Our synthetic strategy for the construction of tropanes is distinctive from the work of others in the field, as it is based on a 3+4 cycloaddition between rhodium-stabilized vinylcarbenoids and pyrroles.[20] The key intermediates, the 2-propanoyltropanes, **1a** and **1b**, are readily prepared by this method. They offer a major advantage for the convergent synthesis of complex 3β-aryltropanes because elaborate Grignard reagents will undergo effective copper catalyzed 1,4-additions to **1a** and **1b**. This is not the case for the reaction of the unsaturated ester corresponding to **1**, which has typically been used for the synthesis of 3β-aryl tropanes.

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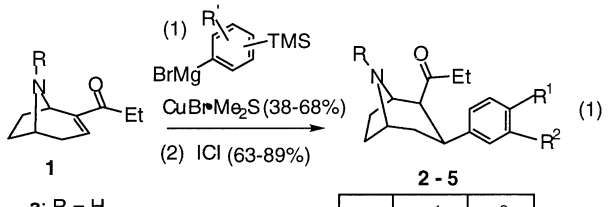
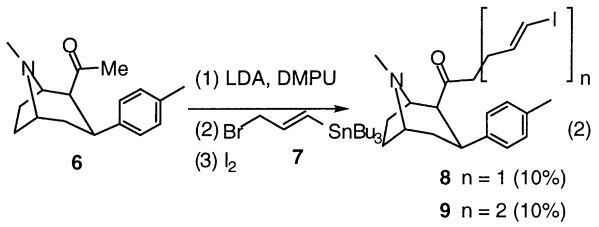
0960-894X/02/$ - see front matter
PII: S0960-894X(02)00048-3

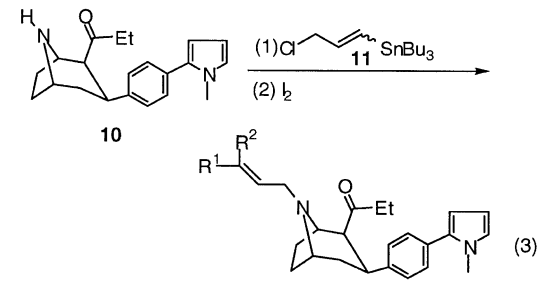
Two approaches were explored for the synthesis of dopamine selective iodinated 3β-aryltropanes. A series of 3′-, 4′-, and 3′,4′-substituted tropanes **2**–**5** was prepared as illustrated in eq 1. Copper catalyzed 1,4-addition of the appropriate TMS-substituted Grignard reagent to **1a** or **1b** followed by conversion of the TMS group to an iodo group by treatment with iodine monochloride gave rise to **2**–**5** (eq 1). The second approach was to introduce bulky iodinated functionality at C-2. This was achieved by alkylation of the enolate of the tolyl tropane **6** with the bromovinylstannane **7** followed by iododestannylation (eq 2). This resulted in the formation of both the monoalkylated (**8**) and the dialkylated product **9**.



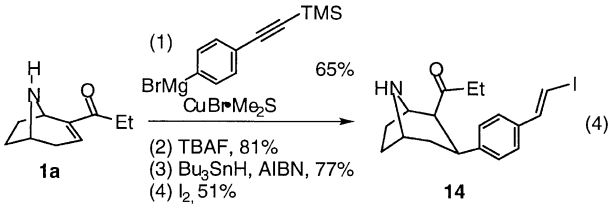
	R^1	R^2
2	I	H
3	H	I
4	I	F
5	I	Cl

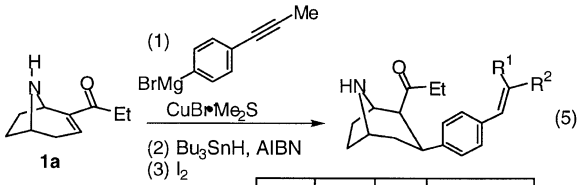


SERT selective 3β-aryltropanes were prepared by introduction of appropriate functionality at the 4-position of the phenyl ring. The first approach began with *N*-methylpyrrole derivative **10**, which has been shown to be highly selective for the serotonin transporter. *N*-alkylation of **10** with either *E* or *Z* chlorovinylstannane **11** followed by iododestannylation generated either *E* or *Z* *N*-(iodoallyl)tropane **12** and **13** (eq 3). A second strategy began with the normethyl tropane **1a** (eqs 4 and 5) Cuprate addition of the 4-alkynylphenyl cuprate followed by radical induced addition of tin hydride across the triple bond and then iododestannylation generated various iodovinyl substituted aryltropanes **14**–**16**.



	R^1	R^2	Yield (%)
12	I	H	50
13	H	I	45





	R^1	R^2	Yield (%)
15	I	Me	13
16	Me	I	32

Binding of the 3β-aryl tropane analogues to the DAT and SERT was determined as previously described (Table 1).[15] The binding affinities for the 3′-, 4′-, and 3′,4′-substituted tropanes followed the general trends that have been observed for the related 2β-methoxycarbonyl analogues. The 3′,4′-disubstituted analogues **4** and **5**, in particular exhibit sub-nanomolar binding affinity and moderate selectivity to the DAT. In the case of the highly potent DAT selective ligands, the usual enhanced binding affinity to the SERT of the normethyl analogues (**2b**–**5b**) compared to the *N*-methyl analogues (**2a**–**5a**) was not observed. The rather unusual C-2 iodinated derivatives **8** and **9** also displayed moderate selectivity to the DAT. The effect on binding of a large ketone group at C-2 was considerably less than had been seen with large ester groups in the related 2β-carboxylates (Table 1).[8]

We have previously described that the pyrrolylphenyltropane **10** is highly SERT selective.[14] Even though introduction of an alkyl group in **10** has a slight detrimental effect on binding to the SERT,[15] the iodoallyl derivatives **12** and **13** still bind selectively to the SERT. Interestingly, the *E*-iodoallyl derivative **12** is more potent than the *Z*-isomer **13**. Carroll and we have previously reported that 3β-(4-alkenylphenyl) groups strongly enhance selective binding to the serotonin transporter.[11,12,14,15] A similar trend was found for the iodovinyl derivatives **14**–**16**, as these compounds exhibit sub-nanomolar affinity and high selectivity for the SERT.

These studies demonstrate that iodinated tropanes with selective binding to either the SERT or DAT can be readily prepared. The most important site for control of the binding selectivity is the 3β-aryl position. Especially promising are the highly SERT selective analogues, such as **12**, **13**, and **14**–**16**. Further studies are in progress to

Table 1. IC_{50} and K_i values of tropane analogues in displacing [^{125}I]RTI-55 binding in rat striatal membranes and [^{3}H]paroxetine binding in rat frontal cortex membranes

Compd	Dopamine IC_{50} (nm)[21]	5-HT K_i (nm)[21]	5HT/DA potency ratio
2a	2.20±0.71	2.44±	0.90
2b	1.69±0.49	1.88±0.29	0.90
3a	19.8±4.3	15.7±3.4	1.3
3b	56.5±8.2	19.7±4.8	2.9
4a	1.08±0.54	7.26±2.83	0.15
4b	0.38±0.15	9.07±1.04	0.041
5a	0.085±0.006	1.08±0.34	0.079
5b	0.077±0.007	1.14±0.34	0.067
8	13.3±4.5	50.8±6.87	0.26
9	47.2±17.1	>1100	>0.05
12	753±332	2.82±1.19	270
13	1120±395	13.1±1.60	86
14	51.3±5.6	0.62±0.08	83
15	66.5±11.1	0.13±0.03	510
16	401±72	0.57±0.03	710

develop radioligands of various members of these iodinated compounds.

Acknowledgements

This research was supported by PHS grants DA-06301 and DA-06634 from the National Institute on Drug Abuse. Partial support from Resolution Pharmaceuticals is also gratefully acknowledged.

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21. K_i and IC_{50} values in binding assays were calculated from displacement curves using 7–10 concentrations of unlabeled analogues. All data are mean values±SEM of at least three separate experiments, each of which was conducted in triplicate. Potencies of all analogues in displacing [^{125}I]RTI-55 binding are expressed as IC_{50} values because the biphasic nature of radiolabeled tropane binding to striatal membranes makes determination of accurate K_i values difficult. However, potencies of analogues in displacing [^{3}H]paroxetine binding are expressed as K_i values, as calculated by the method of Cheng and Prusoff using a K_d value of 0.15 nM for [^{3}H]paroxetine binding. For a detailed description, see refs 14 and 15.