Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 1131–1133
Bioorganic & Medicinal Chemistry Letters

# Synthesis and monoamine transporter affinity of new 2β-carbomethoxy-3β-[4-(substituted thiophenyl)]phenyltropanes: discovery of a selective SERT antagonist with picomolar potency

Gilles Tamagnan,[a,c,*] David Alagille,[a] Xing Fu,[a] Nora S. Kula,[b] Ross J. Baldessarini,[b] Robert B. Innis[a] and Ronald M. Baldwin[a]

[a]*Department of Psychiatry, Yale University and VA Connecticut/116A2, 950 Campbell Avenue, West Haven, CT 06516, USA*
[b]*Department of Psychiatry and Neuroscience Program, Harvard Medical School and Mailman Research Center, McLean Division of Massachusetts General Hospital, Belmont, MA 02478-9106, USA*
[c]*Institute for Neurodegenerative Disorders, 60 Temple Street, Suite 8A, New Haven, CT 06510, USA*

Received 23 September 2004; revised 1 December 2004; accepted 6 December 2004
Available online 29 December 2004

**Abstract**—Preparation of cocaine analogues has been aimed largely at development of stable compounds with high affinity and selectivity for the dopamine transporter (DAT). We now report the synthesis and monoamine transporter affinity of 10 new 2β-carbomethoxy-3β-[4-(substituted thiophenyl)]phenyltropanes. Among these, compound **4b** exhibited very high affinity for the serotonin transporter (SERT: $K_i = 17$ pM) and good selectivity over dopamine (DAT: 710-fold) and norepinephrine transporters (NET: 11,100-fold).

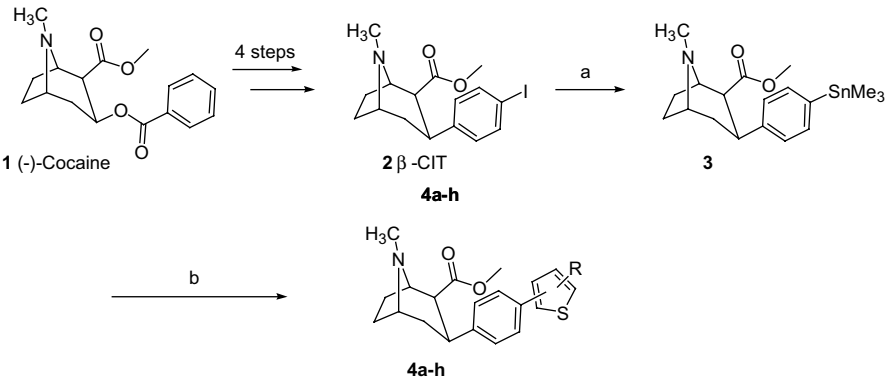

The naturally occurring alkaloid (−)-cocaine isolated from *Erythroxylom coca* remains one of the most abused drugs worldwide due to its powerful psychostimulant and self-reinforcing effects. Considerable effort has been directed toward understanding the neuropharmacological mechanisms of action and behavioral effects of cocaine.

It is hypothesized that stimulant and behavior-reinforcing effects of cocaine are mediated importantly by the central dopaminergic system.[1–3] Cocaine binds at the dopamine transporter (DAT) protein to result in inhibition of dopamine reuptake into presynaptic neurons, increased synaptic dopamine concentration, and enhanced dopaminergic neurotransmission.[1–4] Most efforts to develop a pharmacological treatment for cocaine abuse and addiction have targeted either dopamine receptors or DAT without clinical success to date.[5] The dopamine hypothesis of the actions of cocaine is a simplified model that focuses virtually exclusively on the interaction of cocaine with DAT, even though cocaine has multiple other neuropharmacological actions. Notably, cocaine binds with similar affinity to transporters for norepinephrine (NET) and serotonin (SERT) as well as dopamine, to inhibit the neuronal reuptake and inactivation of all three major monoamine neurotransmitters. Studies employing gene-knockout mice lacking expression of DAT proteins have found that cocaine provides its rewarding cues through its effects on others systems, and particularly through its interactions with the SERT.[6–8] Both DAT and SERT knockout mice have been generated, as well as combined DAT and SERT knockout mice. Whereas conditioned place preference was achieved with cocaine in mice lacking DAT and SERT,[8] no place preference for cocaine was observed in combined DAT and SERT knockout mice.[9] These findings suggest that, in the absence of DAT, the interaction of cocaine at the SERT might be sufficient to induce cocaine reward.

To further study the roles of different transporter systems in the behavioral effects of cocaine, ligands exhibiting selectivity for specific monoamine transporters would be valuable. The present study sought to provide additional tools for use in investigations of the

*Keywords*: Serotonin transporter; Tropane; Affinity.
* Corresponding author. Tel.: +1 203 401 4309; fax: +1 203 789 2119; e-mail: gtamagnan@indd.org

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.12.014




**Scheme 1.** Reagents and conditions: (a) $(SnMe_3)_2$, $Pd(PPh_3)_4$, DME, reflux; (b) halogenothiophene, $Pd(PPh_3)_4$, toluene, reflux.

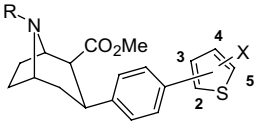
role of selective SERT inhibitors in the pharmacology of cocaine and potential agents for use in the treatment of stimulant addiction. We report the synthesis and in vitro evaluation of 2β-carbomethoxy-3β-[4-(substituted-thiophenyl)]phenyltropanes as potent and selective SERT inhibitors.

β-CIT (**2**) was synthesized in four steps starting from cocaine (**1**) in good yield.[10] The key intermediary **3** was obtained by treatment of **2** with hexamethyl-ditin in presence of a catalytic amount of tetrakis(triphenylphosphine)palladium (Scheme 1). The desired 4′-thiophenylphenyltropane **4** was obtained by Stille cross-coupling between **3** and the desired halogenothiophene (Scheme 1, Table 1).

β-CIT was selectively demethylated by treatment with 1-chloroethyl chloroformate (ACE-Cl) and methanol in 75% yield. Treatment of nor-β-CIT with trichloroethyl chloroformate (Troc-Cl) led to the corresponding *N*-protected carbamate **7** (Scheme 2). The same sequence of stannylation (compound **8**) and Stille cross-coupling led to **9a**–**b**, and subsequent treatment with diluted NaOH in methanol led to the *N*-desmethyl analogues of **4a**–**b** (Scheme 2, Table 1).

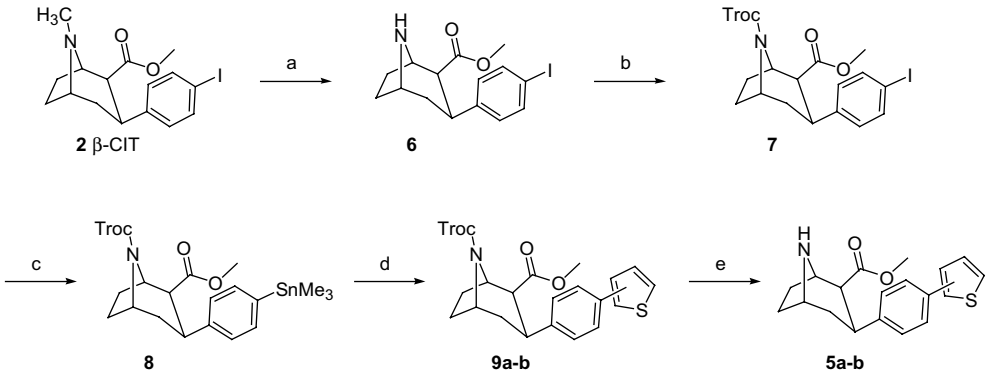
All final compounds were tested for their ability to inhibit high-affinity binding of selective index radioligands to SERT, DAT, or NET using cell membrane-containing homogenates of rat caudate (DA) and rat cerebral cortex (SERT, NET) as transporters sources.

**Table 1.** Neuropharmacological characterization of novel and comparison compounds[a]




| Compound | Substitution | R | SERT | DAT | NET | Selectivity SERT versus DAT | Selectivity SERT versus NET |
|---|---|---|---|---|---|---|---|
| **4b** | 3-Thiophene | $CH_3$ | 0.017 ± 0.004 | 12.1 ± 3 | 189 ± 82 | 710 | 11,118 |
| **5a** | 2-Thiophene | H | 0.11 ± 0.006 | 12.2 ± 0.9 | 75.3 ± 9.6 | 111 | 685 |
| **4a** | 2-Thiophene | $CH_3$ | 0.15 ± 0.015 | 52 ± 12.8 | 158 ± 12 | 346 | 1053 |
| **5b** | 3-Thiophene | H | 0.23 ± 0.02 | 6.4 ± 0.27 | 39 ± 0.8 | 28 | 170 |
| **4c** | 2-(5-Br)-Thiophene | $CH_3$ | 0.38 ± 0.008 | 6.43 ± 0.9 | 324 ± 19 | 17 | 853 |
| **2** | β-CIT | | 0.46 ± 0.06 | 0.96 ± 0.15 | 2.80 ± 0.40 | 2.1 | 6.1 |
| **4d** | 2-(5-Cl)-Thiophene | $CH_3$ | 0.64 ± 0.04 | 4.42 ± 1.64 | 311 ± 25 | 6.9 | 486 |
| | *R,S*-Citalopram | | 1.60 | 16,540 | 6190 | 10,338 | 3869 |
| **4h** | 3-(4-Br)-Thiophene | $CH_3$ | 4.02 ± 0.34 | 183 ± 69 | >10,000 | 46 | >2488 |
| **4e** | 2-(5-I)-Thiophene | $CH_3$ | 4.56 ± 0.84 | 22.1 ± 3.2 | 1137 ± 123 | 4.9 | 249 |
| **4f** | 2-(5-$NH_2$)-Thiophene | $CH_3$ | 64.7 ± 3.7 | >10,000 | >30,000 | >155 | >464 |
| **4g** | 2-(4,5-$NO_2$)-Thiophene | $CH_3$ | 5,000 | >30,000 | >10,000 | >6.0 | >2.0 |
| **1** | (−)-Cocaine | | 1050 | 89 | 3320 | 0.08 | 3.2 |

[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); potencies are as inhibitory constant ($K_i$) ± SE, in nanomolar (nM), based on at least three separate determinations. Test agents are ranked by SERT-potency. Note that for comparison, (−)-*cocaine* was evaluated in very similar assays with rat forebrain tissue, using [$^3$H]citalopram for SERT, the phenyltropane [$^3$H]WIN-35,428 for DAT, and [$^3$H]nisoxetine for NET, as reported elsewhere.[11] *R,S-Citalopram* was evaluated with cell membranes from cell lines genetically transfected with human genes for each transporter protein, assaying with [$^3$H]citalopram for SERT, the phenyltropane [$^3$H]RTI-55 for DAT, and again [$^3$H]nisoxetine for NET.[12]




**Scheme 2.** Reagents and conditions: (a) (i) ACE-Cl, $CH_2Cl_2$, reflux; (ii) methanol, reflux; (b) Troc-Cl, $Et_3N$, THF; (c) $(SnMe_3)_2$, $Pd(PPh_3)_4$, DME, reflux; (d) bromothiophen, $Pd(PPh_3)_4$, toluene, reflux; (e) MeOH, NaOH 0.01 M.

Transporter potencies and SERT-selectivities of compounds tested are provided in Table 1, along with data for (−)-cocaine **1**, β-CIT **2**, and *R*,*S*-citalopram for comparison. All compounds exhibited greater affinity for SERT than DAT and NET. The most potent compounds at SERT were non-substituted thiophenes (compounds **4a**–**b** and **5a**–**b**). The most potent compound, the *N*-methyltropane **4b** ($K_i$ = 17 pM), was 710-times more potent at SERT than at DAT, and over 11,000-times more selective for SERT than NET. Its nor-analogue **5b** showed somewhat less potency at SERT ($K_i$ = 230 pM) and much less selectivity (only 28-fold vs DAT). This contrast appears to contradict the general observation of higher SERT affinity and selectivity over DAT for nortropanes than their corresponding tropanes.[11] In the 2-thiophene series the 2-thiophene-tropane **4a** was slightly less potent for SERT than the nortropane **5a** (110 vs 150 pM) and **4a** had somewhat greater selectivity for SERT over DAT (111- vs 346-times) and NET (685- vs 1050-times). Introduction of 4- or 5-substituents yielded compounds with relatively lower potency and selectivity for SERT than the corresponding non-substituted thiophenes.

In conclusion, we report the synthesis of 10 new 4′-thiophenephenyltropanes and their evaluation for the monoamine transporter potencies and selectivity. The 3-thiophenphenyltropane **4b** exhibited high potency ($K_i$ = 17 pM) and selectivity for SERT over DAT (710-fold) and NET (over 11,000-fold). These new ligands provide additional pharmacological tools of potential value in attempting to correlate structure and transporter selectivity with in vivo studies of behavioral outcomes.

## Acknowledgements

This work was supported by the National Institutes of Health (MH67066-01) and from Department of Veterans Affairs, National Center for PTSD Alcohol Research Center and NARSAD to G.D.T. and by an award from the Bruce J. Anderson Foundation and the McLean Private Donors Neuropharmacology Research Fund to R.J.B.

## References and notes

1. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219.
2. Kuhar, M. J.; Ritz, M. C.; Boja, J. W. *TiNS* **1991**, *14*, 299.
3. Robinson, T. E.; Berridge, K. C. *Brain Res. Rev.* **1993**, *18*, 247.
4. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.
5. Singh, S. *Chem. Rev.* **2000**, *100*, 925.
6. Spanagela, R.; Weissb, F. *TiNS* **1999**, *22*, 521.
7. Walsh, S. G.; Cunningham, K. A. *Psychopharmacology* **1997**, *130*, 41.
8. Sora, I.; Wichems, C.; Takahashi, N.; Li, X. F.; Zeng, Z.; Revay, R.; Lesh, K. P.; Murphy, D. L.; Uhl, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 7699.
9. Sora, I.; Hall, F. S.; Andrews, A. M.; Itokawa, M.; Li, X. F.; Wei, H. B.; Wichems, C.; Lesch, K. P.; Uhl, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5300.
10. Tamagnan, G.; Baldwin, R. M.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1783.
11. Boja, J. W.; Kuhar, M. J.; Kopajtic, T. A.; Yang, E.; Abraham, P.; Lewin, A. H.; Carroll, F. I. *J. Med. Chem.* **1994**, *37*, 1220.
12. Dutta, A. K.; Fei, X.-S.; Beardsley, P. M.; Newman, J. L.; Reith, M. E. A. *J. Med. Chem.* **2001**, *44*, 937.