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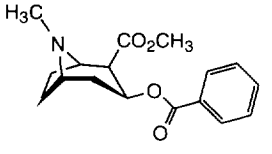
# N-PHTHALIMIDOALKYL DERIVATIVES OF 2β-CARBOMETHOXY-3β-(4'-IODOPHENYL)TROPANE (β-CIT): BRAIN MONOAMINE TRANSPORTER AFFINITY

Gilles Tamagnan,[a] John L. Neumeyer,[b,*] Yigong Gao,[a]
Shaoyin Wang,[a] Nora S. Kula,[a] and Ross J. Baldessarini,[c]

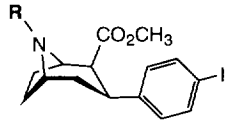
[a]*Research Biochemicals International, One Strathmore Road, Natick, MA 01760*
[b]*Alcohol and Drug Abuse Research Center–McLean Division of Massachusetts General Hospital, 115 Mill Street, Belmont, MA 02178*
[c]*Department of Psychiatry & Neuroscience Program, Harvard Medical School, Boston and Mailman Research Center–McLean Division of Massachusetts General Hospital, 115 Mill Street, Belmont, MA 02178*

**Abstract**: A series of novel N-phthalimidoalkyl analogs of the stable phenyltropane β-CIT were synthesized and evaluated by selective radioligand binding assays for affinity to transporters for dopamine (DA), serotonin (5-HT) and norepinephrine (NE) in corpus striatum tissue from rat forebrain. β-CIT and novel compounds with the phthalimido moiety separated by ≥4 methylene groups from the nitrogen atom of the tropane ring (**6–8**) showed similarly greater affinity at 5-HT than DA transporters; this affinity was lost with only 2 or 3 carbon atoms (**4** and **5**). These results are consistent with interference at a critical binding site for the tropane nitrogen on the transporter proteins and indicate that the tropane nitrogen atom can be substituted with large substituted alkyl moieties without loss of affinity or selectivity for amine transporters. 

The natural (–) isomer of the stimulant cocaine (**1**) has potent but short-lived inhibitory effects on the dopamine transporter ($DA_T$) at presynaptic terminals of neurons that produce and release DA as a neurotransmitter in mammalian brain. Cocaine also interacts with transporter proteins selective for norepinephrine ($NE_T$) and serotonin (5-hydroxytryptamine; 5-$HT_T$). These cell membrane proteins mediate the physiological inactivation of neurotransmitter amines following their release. Interactions with the $DA_T$ are believed to be critically involved in the behavioral arousal and reinforcing properties of cocaine.[1] This hypothesis is supported dramatically by loss of behavioral arousal by cocaine in "knock-out" mice genetically modified to lack expression of $DA_T$ protein.[2]




**1** Cocaine




**2** (β-CIT) **R** = $CH_3$

Pharmacological studies of the actions of cocaine have been facilitated by preparation of structural analogs, including stable, nonhydrolyzable, long-acting phenyltropanes with selectivity for specific monoamine transporters.[3] Modifications of the methyl substituent at the tropane nitrogen can modify the amine-transporter selectivity and the pharmacokinetics of phenyltropanes.[4–8] Compounds with high pharmacological specificity for particular neurotransmitter transporters, as well as chemical stability and ability to carry radioactive atoms or fluorescing moieties without loss of pharmacological activity or selectivity are of interest as research tools.[8]

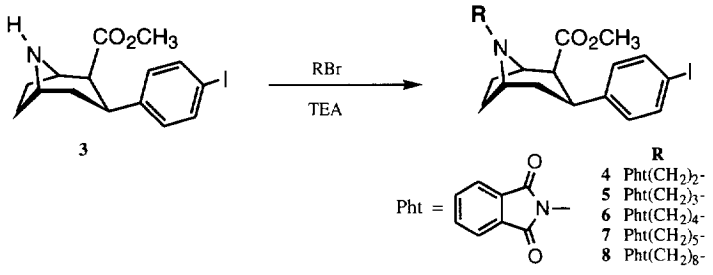
Radiolabeled derivatives also have clinical applications in neuroradiology, including positron emission tomography (PET) and single photon emission tomography (SPECT) imaging of brain.[8,9]

We previously reported on a series of N-substituted derivatives of the phenyltropane N-methyl-2β-carbomethoxy-3β-(4'-iodophenyl)tropane (β-CIT; **2**).[4,5] In competition with radioligands selective for $DA_T$, $NE_T$, and 5-$HT_T$ in rat forebrain tissue, even relatively bulky N-substituents, such as the phthalimidopropyl group (**5**), retained quite high $DA_T$ affinity and showed even higher 5-$HT_T$ affinity.[4] N-substituted phenyltropanes would be of interest if additional labeling moieties can be attached at the tropane nitrogen. The present study extends our earlier work by specifically investigating the effect of the spacing between the tropane nitrogen and that of a phthalimido moiety in derivatives with 2–8 carbon aliphatic chains on affinity to transporters in rat forebrain for DA, NE, and 5-HT, using methods reported previously.[4]

## Chemistry

Nor-β-CIT (**3**) prepared as previously reported[7] was starting material for the synthesis of N-phthalimidoalkyl analogs of β-CIT (**4–8**) by N-alkylation with a series of phthalimidoalkyl bromides in ethanol with triethylamine as shown in Scheme 1.

**Scheme 1**




## Results and Discussion

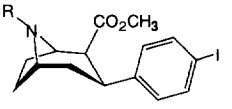
Five novel N-substituted *p*-iodophenylnortropanes (compounds **4–8**) with 2, 3, 4, 5, or 8 methylene groups separating the tropane and phthalimido nitrogen atoms were prepared; their structures were verified chemically and they were evaluated for affinity in binding assays with radioligands selective for $DA_T$ ([$^3$H]GBR-12935),[10,11] $NE_T$ ([$^3$H]nisoxetine),[12] and 5-$HT_T$ ([$^3$H]paroxetine)[13] in homogenates of rat forebrain (Table 1) as reported previously.[4]

The prototype compound β-CIT (**2**)[4] had relatively high affinity at both 5-$HT_T$ and $DA_T$, and somewhat less affinity at $NE_T$ sites in rat brain tissue; among N-phthalimidoalkyl derivatives (**4–8**), alkyl chain length affected transporter affinity, particularly for the 5-$HT_T$ (Table 1). Derivatives with ≥4 methylenes separating the tropane and phthalimido rings had greater 5-$HT_T$ affinity than β-CIT, and $DA_T$ affinity was lower. Compound **8**, with an 8-methylene spacer, had high 5-$HT_T$ affinity ($K_i$ = 0.2 nM), 15-fold selectivity over $DA_T$ sites, and 373-fold 5-$HT_T$ vs. $NE_T$ selectivity. Compounds with only 2 or 3 methylene groups between tropane and phthalimido rings

had lower affinity at 5-$HT_T$ and $DA_T$ sites than those with longer alkyl chains. These trends suggest that the N-substituent in phenyltropanes can effect selectivity and affinity for specific monoamine transporters. Bulky substituents with electronegative charge may interfere sterically or electronically with a possibly crucial tropane N-binding site on 5-$HT_T$ and $DA_T$ proteins.

In summary, we synthesized a series of derivatives of iodophenylnortropane analogs of cocaine with alkyl chains of 2–8 carbons separating the tropane nitrogen from a bulky phthalimido substituent. These substituents showed a gain in affinity for 5-$HT_T$ when the spacer was ≥4 carbons long. The 8-carbon derivative (N-[8-phthalimido-octyl]-2β-carbomethoxy-3β-[4'-iodophenyl]nortropane; **8**) showed particularly high affinity and selectivity for the 5-$HT_T$ in rat forebrain. Compound **8** or other congeners may lead to novel agents for experimental or neuroradiological applications as markers of serotonin neurons, or perhaps to selective serotonin reuptake inhibitor drugs with antidepressant or antianxiety effects.[14]

**Table 1**. *In Vitro Binding Affinities of N-Substituted nor-β-CITs at Transporters (T)for Serotonin (5-HT), Dopamine (DA), and Norepinephrine (NE) in Rat Forebrain Tissue.*




| | | Transporter Affinity ($K_i$ ± SEM, nM) | | | 5-$HT_T$ vs $DA_T$ |
|---|---|---|---|---|---|
| **Compound** | **R** | **5-$HT_T$** | **$DA_T$** | **$NE_T$** | *Selectivity* |
| **2** | $CH_3$ | 0.44 ± 0.04 | 0.96 ± 0.20 | 2.80 ± 0.40 | 2.2 |
| **4** | Pht$(CH_2)_2$ | 0.84 ± 0.02 | 4.23 ± 0.48 | 441± 66.0 | 5.0 |
| **5*** | Pht$(CH_2)_3$ | 0.59 ± 0.07 | 9.10 ± 1.10 | 74.0 ± 11.6 | 15.4 |
| **6** | Pht$(CH_2)_4$ | 0.21 ± 0.02 | 2.38 ± 0.22 | 190 ± 18.0 | 11.3 |
| **7** | Pht$(CH_2)_5$ | 0.34 ± 0.03 | 2.40 ± 0.17 | 60.0 ± 3.10 | 7.1 |
| **8** | Pht$(CH_2)_8$ | 0.20 ± 0.02 | 2.98 ± 0.30 | 75.0 ± 3.60 | 14.9 |

Pht = phthalimido. Selectivity is indicated as the ratio of $K_i$ values for $DA_T$/5-$HT_T$. (*)Compound **5** was reported previously.[4]

## Experimental

### General procedure for N-alkylation of nor-β-CIT

An appropriate alkyl bromide (0.4 mmol) and KI (10 mg) were added to nor-β-CIT (0.27 mmol) and triethylamine (46 mmol) in absolute EtOH (10 mL) and refluxed under nitrogen (1–24 h, depending on reactivity of each alkyl bromide). Reaction progress was monitored with TLC. Solvent was removed under the reduced pressure; residue was passed through a silica gel column (eluted with hexane/ether in triethylamine in optimized vol. ratios) to yield pure products.

### N-(2-Phthalimidoethyl)-2β-carbomethoxy-3β-(4'-iodophenyl)nortropane·HCl (4)

Prepared as a white solid HCl salt (45%): mp 160-162 °C. $^1$H NMR (250 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.67 (m, 2H), 7.53 (d, $J$ = 8.4 Hz, 2H), 6.94 (d, $J$ = 8.4 Hz, 2H), 3.83 (m, 1H), 3.62 (m, 3H), 3.09 (s, 1H), 2.92 (m,

1H), 2.82 (m, 1H), 2.54 (m, 2H), 2.43 (m, 1H), 2.01 (m, 2H), 1.72 (m, 3H), 1.52 (m, 2H). Anal. ($C_{25}H_{25}N_2O_4I$·HCl·2.5 $H_2O$): CHN.

**N-(4-Phthalimidobutyl)-2β-carbomethoxy-3β-(4'-iodophenyl)nortropane·HCl (6)**

Prepared as a white solid HCl salt (69%): mp 151-153 °C. $^1H$ NMR (250 MHz, $CDC1_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.54 (d, $J$ = 8.4 Hz, 2H), 6.98 (d, $J$ = 8.4 Hz, 2H), 3.70 (m, 3H), 3.42 (m, 4H), 2.88 (m, 2H), 2.50 (m, 1H), 2.26 (m, 1H), 1.88 (m, 4H), 1.68 (m, 4H), 1.42 (m, 2H) Anal. ($C_{27}H_{29}N_2O_4I$·HCl·2.5 $H_2O$): CHN.

**N-(5-Phthalimidopentyl)-2β-carbomethoxy-3β-(4'-iodophenyl)nortropane·HCl (7)**

Prepared as a white solid HCl salt (45%): mp 78-80 °C, $[\alpha]^{20}_D$ –66.3° (C = 0.15, MeOH). $^1H$ NMR (250 MHz, $CDC1_3$) δ 7.83 (m, 2H), 7.70 (m, 2H), 7.55 (d, $J$ = 8.4 Hz, 2H), 7.00 (d, $J$ = 8.4 Hz, 2H), 3.70 (m, 3H), 3.42 (m, 4H), 2.88 (m, 2H), 2.50 (m, 1H), 2.26 (m, 1H), 1.88 (m, 41-1), 1.68 (m, 4H), 1.42 (m, 4H). MS (FAB, NBA): 559 (27%), 445 (22%), 444 (100%), 417 (27%). Anal. ($C_{28}H_{31}N_2O_4I$·HCl·2.5 $H_2O$): CHN.

**N-(8-Phthalimidooctyl)-2β-carbomethoxy-3β-(4'-iodophenyl)nortropane (8)**

Obtained as a colorless oil (59%). $^1H$ NMR (250 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.70 (m, 2H), 7.56 (d, $J$ = 8.4 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 2H), 3.66 (m, 3H), 3.46 (s, 3H), 3.37 (m, 1H), 2.87 (m, 2H), 2.52 (m, 1H), 2.20 (m, 2H), 2.04 (m, 2H), 1.66 (m, 6H), 1.29 (m, 9H). Anal. ($C_{31}H_{36}N_2O_4I$): CHN.

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**References and Notes**

1. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219.
2. Giros, B.; Jaber, M.; Jones, S. R.; Wightman, R. M.; Caron, M. G. *Nature (London)* **1996**, *379*, 606.
3. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.
4. Neumeyer, J. L.; Tamagnan, G.; Wang, S.; Gao, Y.; Milius, R. A.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1996**, *39*, 543.
5. Neumeyer, J. L.; Wang, S.; Gao, Y.; Milius, R. A.; Kula, N. S.; Campbell, A.; Baldessarini, R. J.; Zea-Ponce, Y.; Baldwin, R. M.; Innis, R. B. *J. Med. Chem.* **1994**, *37*, 1558.
6. Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem.* **1994**, *37*, 1262.
7. Milius, R. A.; Saha, J. K.; Madras, B. K.; Neumeyer, J. L. *J. Med. Chem.* **1991**, *34*, 1728.
8. Tamagnan, G.; Gao, Y.; Baldwin, R. M.; Zoghbi, S. S.; Neumeyer, J. L. *Tetrahedron Lett.* **1996**, *37*, 4353.
9. Baldessarini, R. J. In *The Dopamine Receptors*; Neve, R. L., Neve, K. A., Eds.; Humana: Totowa, 1997; pp 457–498.
10. Andersen, P. H. *J. Neurochem.* **1987**, *48*, 1887.
11. Kula, N. S.; Baldessarini, R. J. *Neuropharmacology* **1990**, *30*, 89.
12. Tejani-Butt, S. M. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 427.
13. Habert, E.; Graham, D.; Tahraoui, L.; Claustre, Y.; Langer, S. Z. *Eur. J. Pharmacol.* **1985**, *118*, 107.
14. Baldessarini, R. J. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; Hardman, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W.; Gilman, A. G., Eds.; McGraw-Hill: New York, 1996; pp 399–430.

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