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(54) Titre : LIGANDS SE FIXANT SUR LES RECEPTEURS DE COCAINE
(54) Title: COCAINE RECEPTOR BINDING LIGANDS

(57) **Abrégé/Abstract:**

The invention relates to novel compounds which show high affinity for cocaine receptors in the brain, particularly dopamine and serotonin transporter sites. The compounds may be used as imaging or pharmaceutical agents, in the diagnosis and treatment of drug addiction, depression, anorexia and neurodegenerative diseases.



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(21) International Application Number: PCT/US99/10456 (22) International Filing Date: 20 May 1999 (20.05.99) (30) Priority Data: 09/083,043 22 May 1998 (22.05.98) US (71) Applicant: RESEARCH TRIANGLE INSTITUTE [US/US]; 3040 Cornwallis Road, P.O. Box 12194, Research Triangle Park, NC 27709-2194 (US). (72) Inventors: CARROLL, Frank, I.; 5124 North Willowhave Drive, Durham, NC 27712 (US). KUHAR, Michael, J.; 2560 Echo Drive, N.E., Atlanta, GA 30345 (US). BOJA, John, W.; 926 Hardy Road, Cuyahoga Falls, OH 44223 (US). LEWIN, Anita, H.; 804 Cedar Falls Road, Chapel Hill, NC 27514 (US). ABRAHAM, Philip; 310 Homestead Drive, Cary, NC 27513 (US). (74) Agents: BEAUMONT, William, E. et al.; Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Suite 400, 1755 Jefferson Davis Highway, Arlington, VA 22202 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COCAINE RECEPTOR BINDING LIGANDS (57) Abstract The invention relates to novel compounds which show high affinity for cocaine receptors in the brain, particularly dopamine and serotonin transporter sites. The compounds may be used as imaging or pharmaceutical agents, in the diagnosis and treatment of drug addiction, depression, anorexia and neurodegenerative diseases.		

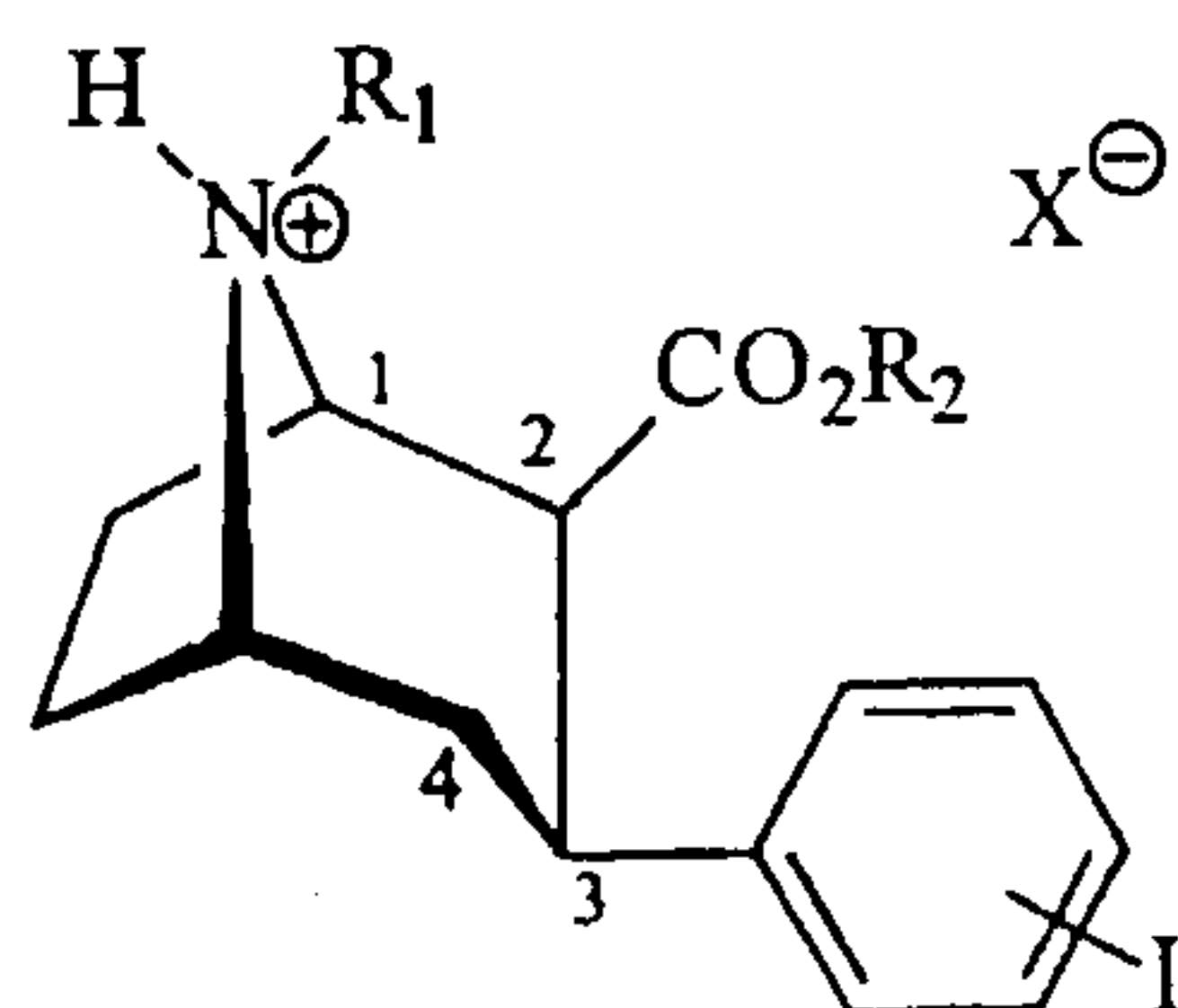
COCAINE RECEPTOR BINDING LIGANDS

Field of the Invention

This invention is directed to a class of binding ligands for cocaine receptors and other receptors in the brain. Specifically, a novel family of compounds shows high binding specificity and activity, and, in a radiolabeled form, can be used to bind to these receptors, for biochemical assays and imaging techniques. Such imaging is useful for determining effective doses of new drug candidates in human populations. In addition, the high specificity, slow onset and long duration of the action of these compounds at the receptors makes them particularly well suited for therapeutic uses, for example as substitute medication for psychostimulant abuse. Some of these compounds may be useful in treating Parkinson's Disease or depression, by virtue of their inhibitory properties at monoamine transporters.

BACKGROUND OF THE INVENTION

In U.S. patent No. 5,128,118, there is disclosure of a family of compounds exhibiting particularly high specificity and affinity for cocaine receptors and other neurotransmitter receptors in the brain of the formula:



Where the broken line represents an optional chemical bond and the substituents at 2 and 3 may be at any position;

The iodo substituent may be o, m, p, or multisubstituted;

$R_1 = \text{CH}_3, \text{CH}_2\text{CH}=\text{CH}_2, (\text{CH}_2)_n\text{C}_6\text{H}_5$ $n = 1-4$;

$R_2 = \text{CH}_3, \text{C}_2\text{H}_5, \text{CH}_3(\text{CH}_2)_3, (\text{CH}_3)_2\text{CH}, \text{C}_6\text{H}_5, \text{C}_6\text{H}_5\text{CH}_2, \text{C}_6\text{H}_5(\text{CH}_2)_2;$

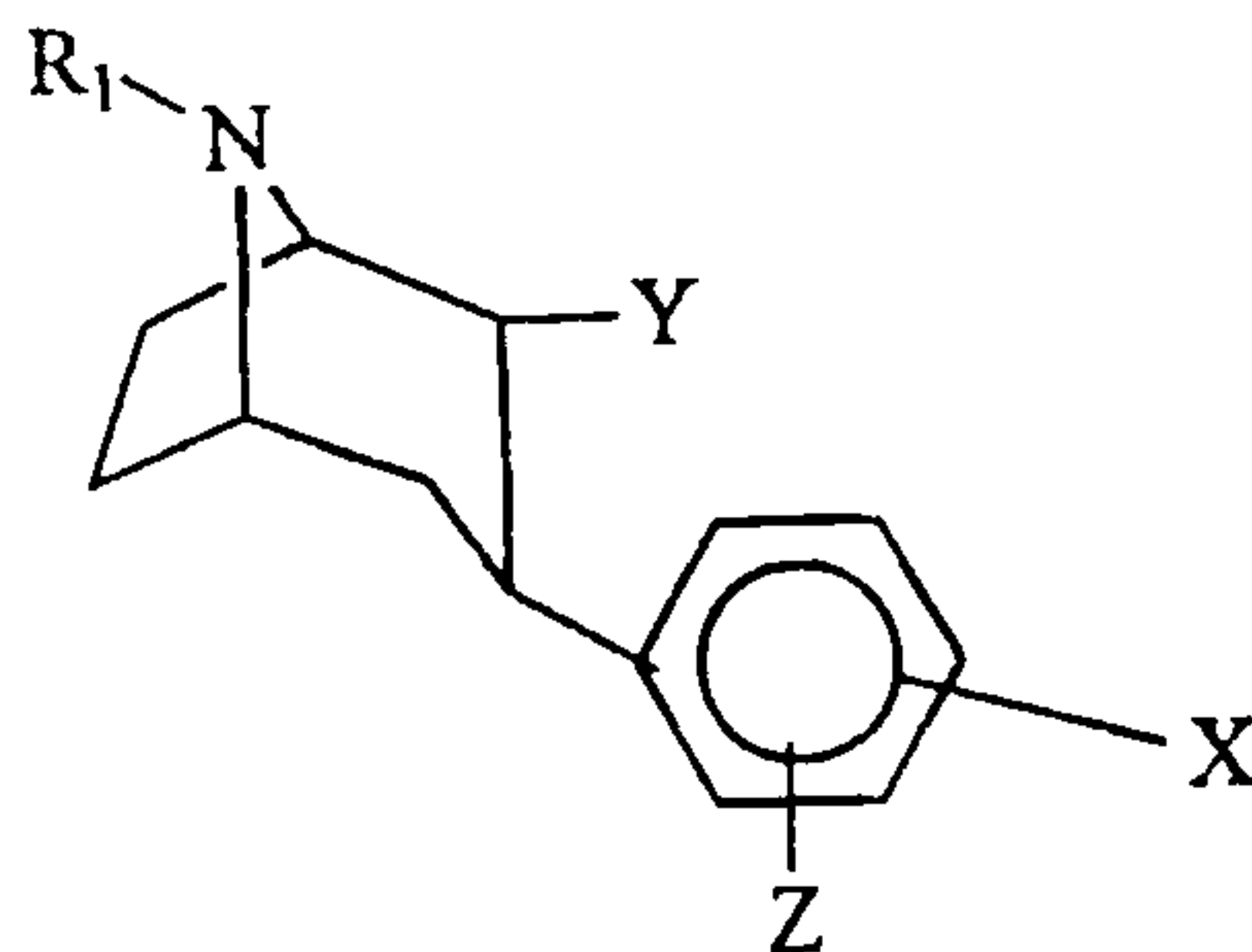
X = pharmacologically acceptable anion.

Sites of specific interest included cocaine receptors associated with dopamine (DA) transporter sites.

Subsequently, in the U.S. 5,413,779, the values for R_1 and R_2 were expanded, such that R_1 may be an alkyl of 1-7 carbon atoms, $\text{CH}_2\text{CR}_3=\text{CR}_4\text{R}_5$ wherein R_3 - R_5 are each, independently C_{1-6} alkyl, or phenyl compounds of the formula $\text{C}_6\text{H}_5(\text{CH}_2)_y$, wherein $y = 1-6$. R_2 may be any of those list above and
 10 also $\text{C}_6\text{H}_5(\text{CH}_2)_z$ wherein $z=1-6$. The PCT filing also reveals the affinity of these compounds for cocaine receptors associated with serotonin (5-hydroxytryptamine, 5-HT) transporters, and confirms, for the first time, that the *in vitro* binding reported in the earlier-filed application, is confirmed in *in vivo* testing. Specific disclosure for a variety of applications, including using the compounds in both PET and SPECT scanning, wherein either the iodine substituent, or one of the carbon groups is radioactive (I-123, 125 or 131 and C_{11}) thus providing methods for scanning for the presence of specific cocaine receptors. Such scanning processes may be used to determine physiological conditions associated with dopamine and serotonin re uptake inhibitors, which
 20 lead to behavioral and neurodegenerative disorders/diseases. Such disorders include depression, bipolar disorder, eating disorders, obesity, attention deficit disorder, panic attacks and disorders, obsessive-compulsive disorder, Parkinson's Disease, and cocaine, nicotine and alcohol addiction. These compounds, in addition to being used in treatment of these disorders, may be used to examine in general the density and distribution of specific cocaine receptors in various parts of the brain and/or body, to determine the efficacy of neurological treatments aimed at halting or reversing the degeneration of specific nerves in the brain, and for screening drugs, such as antidepressant drugs.

The affinity and specificity of these compounds is surprisingly high, and compared with prior art compounds, such as [³H]WIN 35,428, the novel compounds of these applications exhibit extremely low IC₅₀ values for binding inhibition.

In U.S. Patent 5,496,953, a family of compounds was disclosed, having the formula:



wherein:

10 Y is CONRR₂,

R₁ is hydrogen or C₁₋₅ alkyl,

X is H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₄ alkoxy, C₁₋₆ alkynyl, halogen amino or acylamido,

R and R₂ independently are H, C₁₋₆ alkyl, alkene or alkyne, phenyl, phenyl substituted with 1-3 of C₁₋₆ alkyl, alkene, alkyne or alkoxy, C₁₋₆ alkoxy, phenoxy, amine amino substituted with 1 or 2 C₁₋₆ alkyl, alkene, alkyne, alkoxy, phenyl or phenoxy, or R and R₂ may combine to form a cyclic structure selected from the group consisting of pyrrolidinyl, morpholinyl and piperidinyl moieties, and

20 Z is H, I, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₁, CO₂NH₂, CO₂R₁, C₁₋₆ alkyl, NR₄R₅, NHCOF₅, NHCOR₆, wherein R₄-R₆ are each C₁₋₆ alkyl.

These compounds exhibit unusually high affinity and specificity for binding to receptors for the dopamine transporter site, as well as the serotonin transporter site, based on inhibition of [³H]paroxetine binding. This high affinity

makes certain of these compounds particularly well suited for use as therapeutic agents, as well as for imaging agents for dopamine and serotonin transporters.

SUMMARY OF THE INVENTION

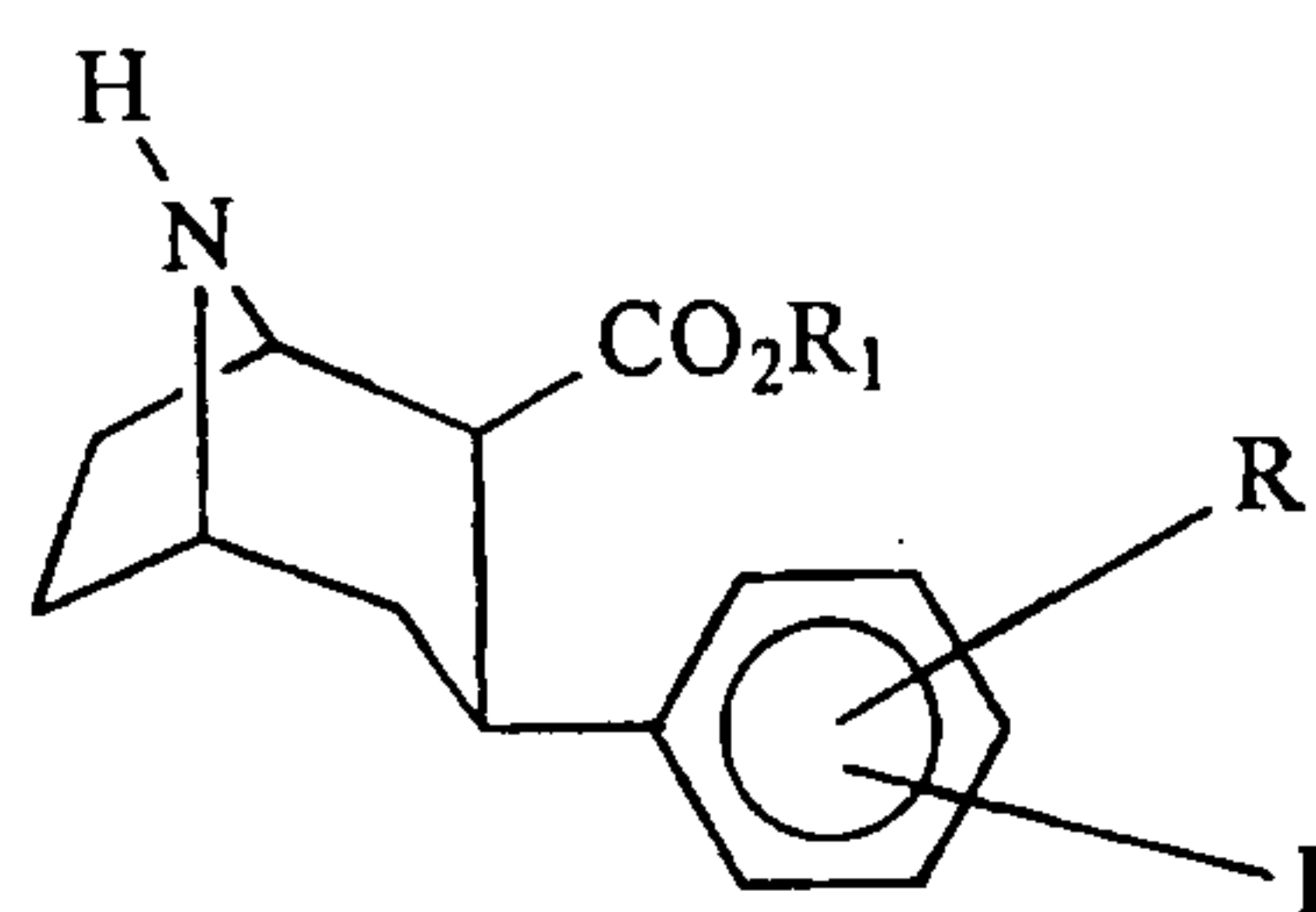
Accordingly, one object of this invention is to provide novel compounds which bind to cocaine receptors.

Another object of the invention is to provide novel 3-(substituted phenyl)-2-(substituted)tropane analogs which bind to cocaine receptors.

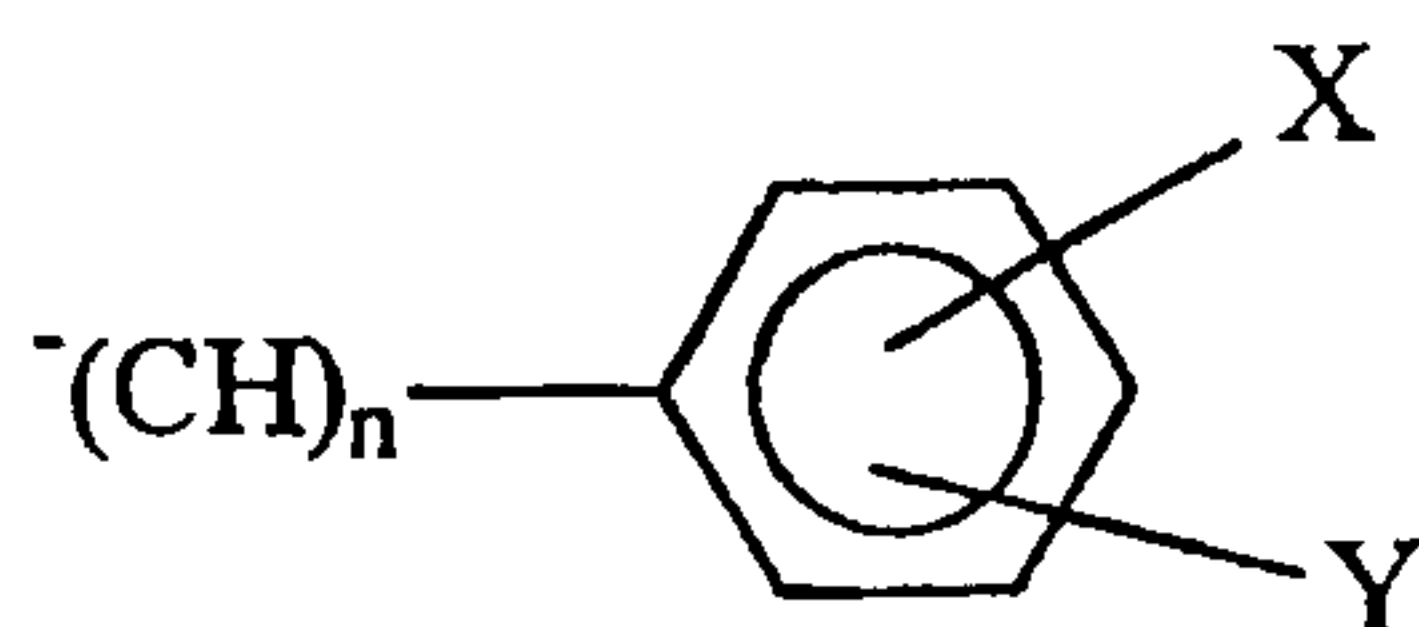
Still another object of the invention is to provide 3-(substituted phenyl)-2-(substituted)tropane analogs which bind preferentially to the dopamine transporter.

Yet another object of the invention is to provide 3-(substituted phenyl)-2-(substituted)tropane analogs which bind preferentially to the serotonin transporter.

The present invention as broadly disclosed provides a compound of the formula:

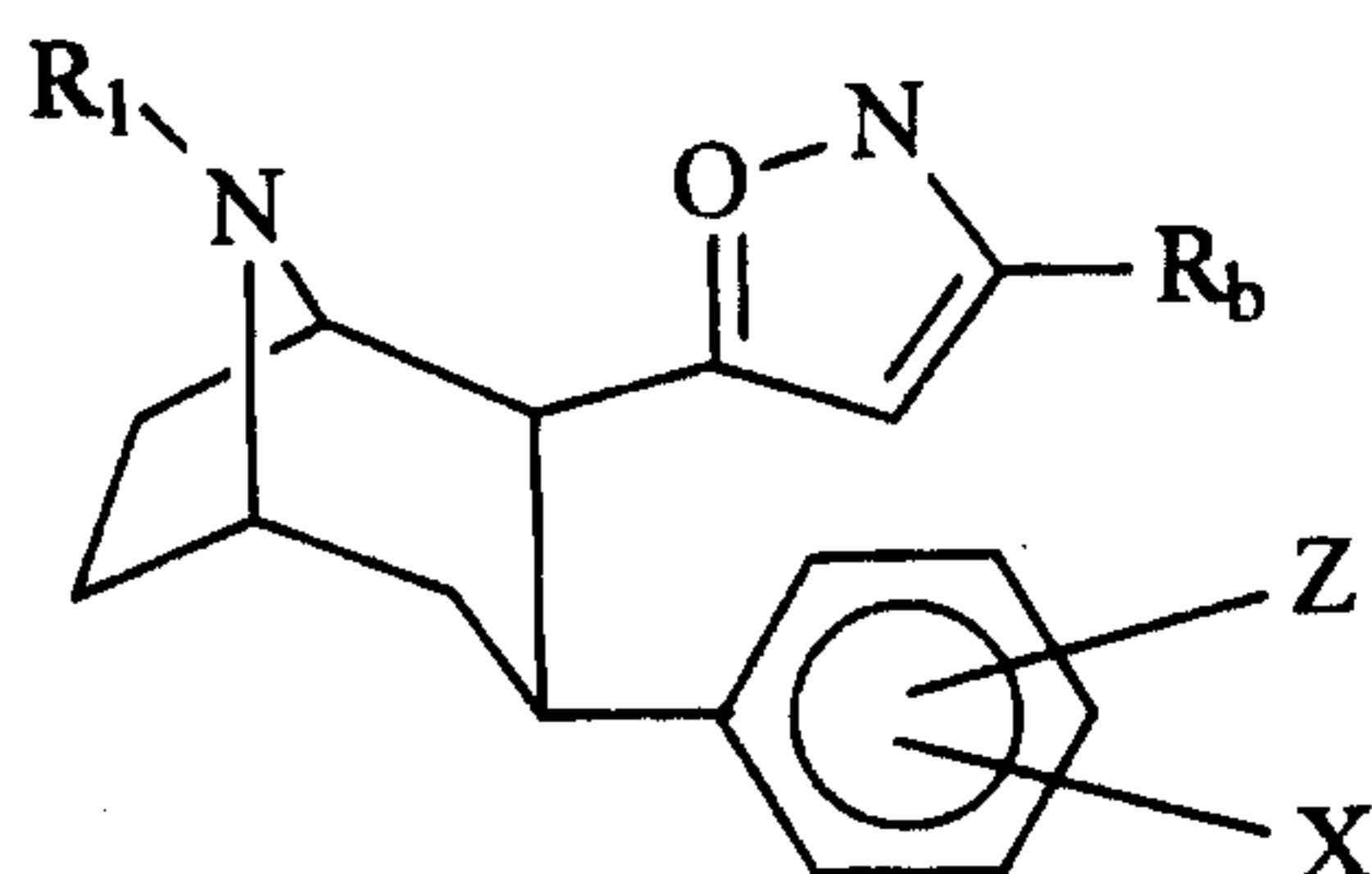


wherein R is CH₃, C₂H₅, CH₂CH₂CH₃, or CH(CH₃)₂, R₁ is CH₃, CH₂C₆H₅, (CH₂)₃C₆H₅, (CH₂)₃C₆H₅, or



wherein X is H, OCH₃, or Cl and Y is H, OCH₃, CO₂CH₃ or Cl, and n=1-8.

Another object of the invention is to provide compounds having the following formulas:



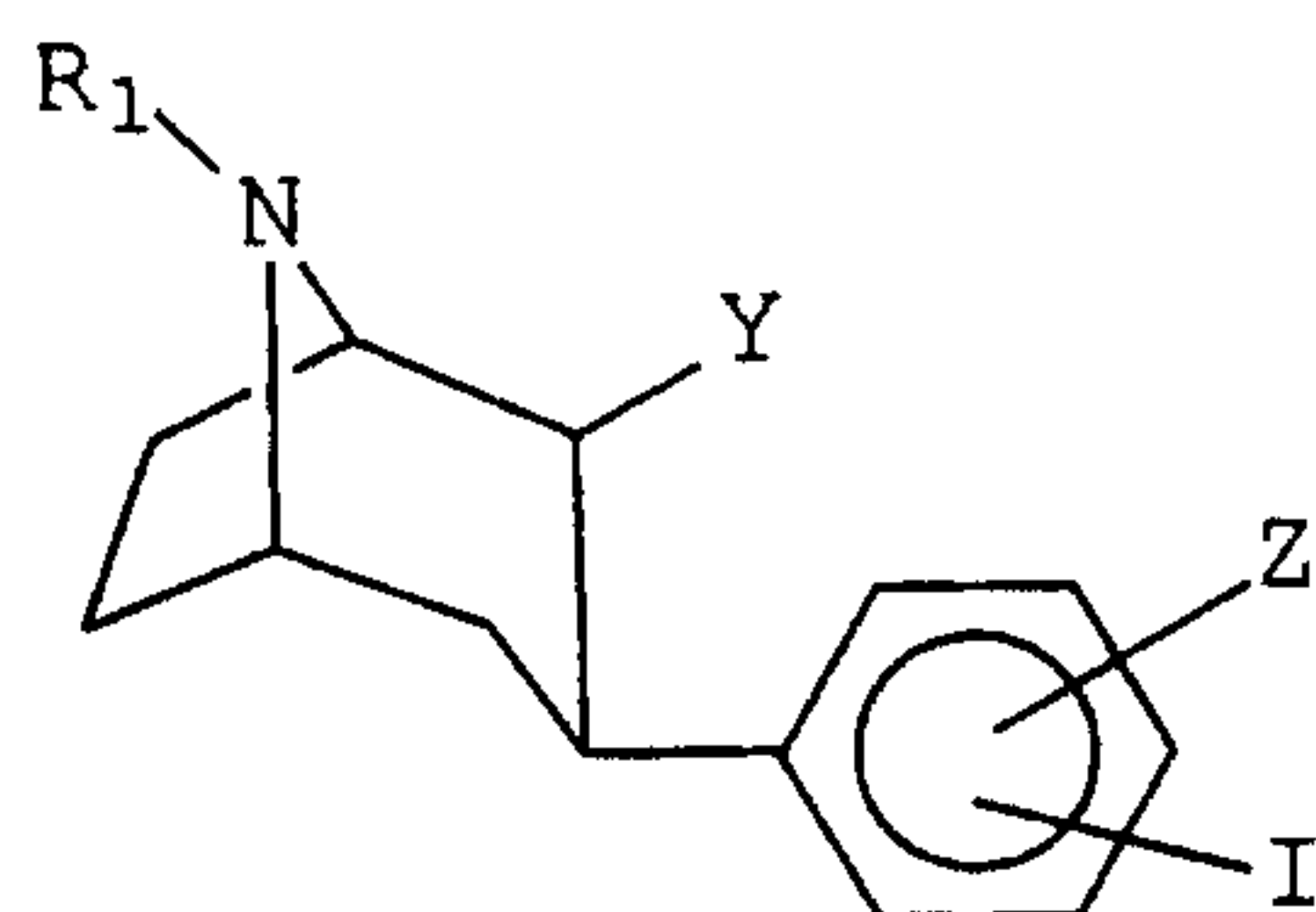
wherein

R₁=hydrogen, C₁₋₅ alkyl,

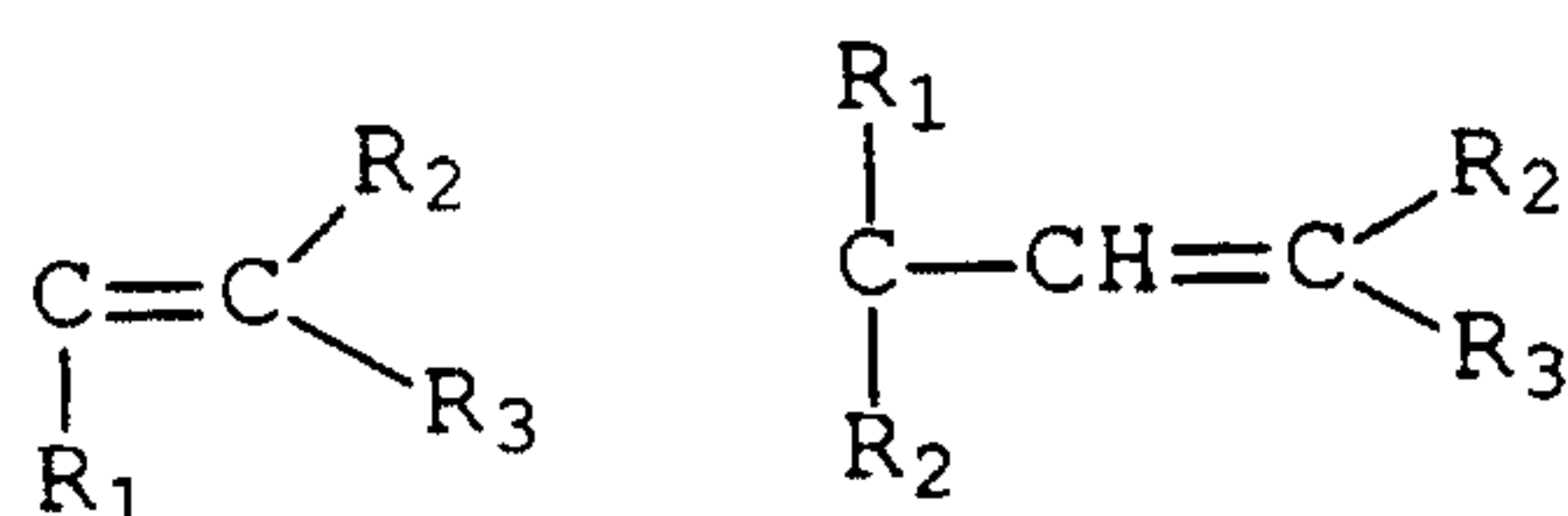
X=H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₄ alkoxy, C₁₋₆ alkynyl, halogen, amino, acylamido, and

Z=H, I, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₁, CONH₂, CO₂R₁, C₁₋₆ alkyl, NR₄R₅, NHCOR₅,
NHCO₂R₆,

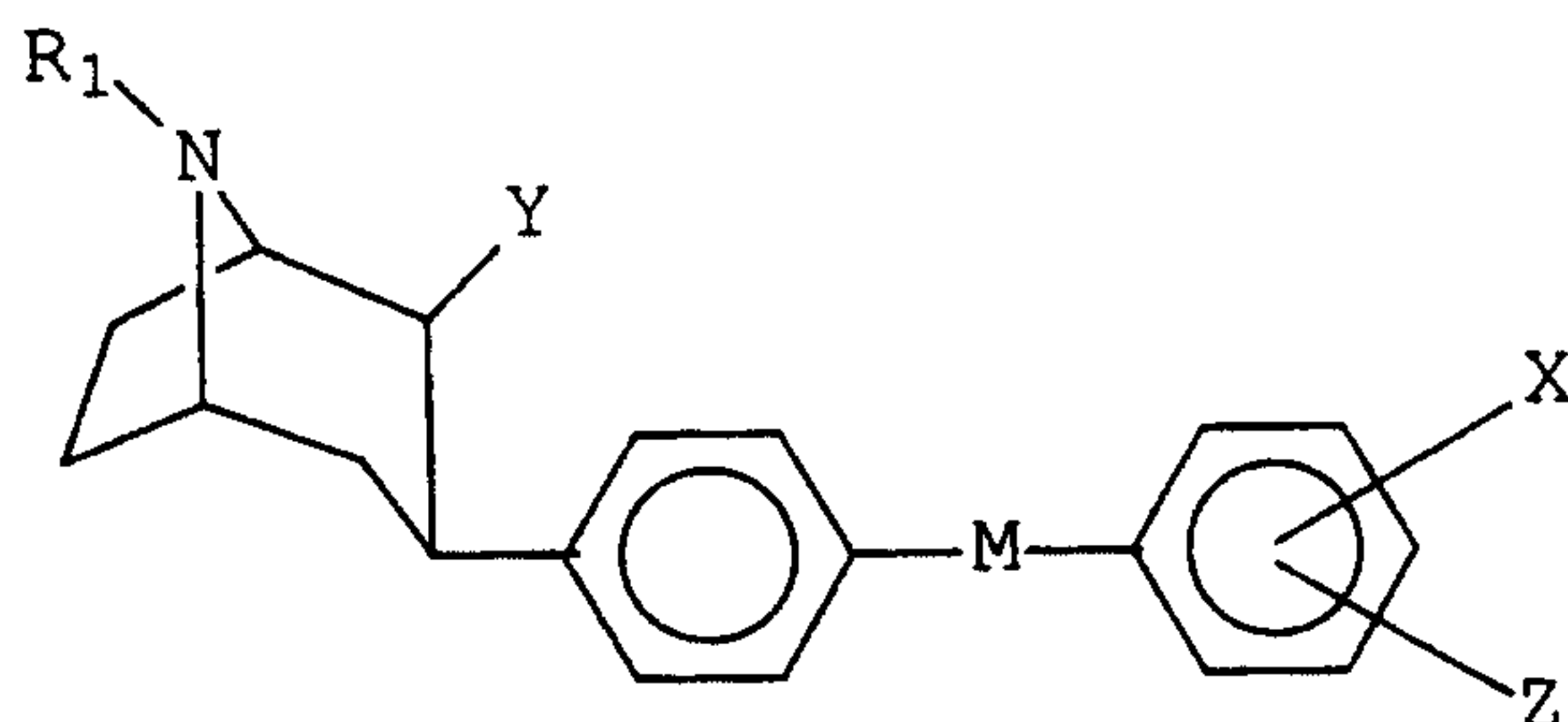
R_b is C₁₋₆ alkyl, C₁₋₆ alkenyl, phenyl, or phenyl substituted with C₁₋₆ alkyl, C₁₋₆ alkoxy, or halogen;



R, Y, and Z are as defined above
and Z may additionally be



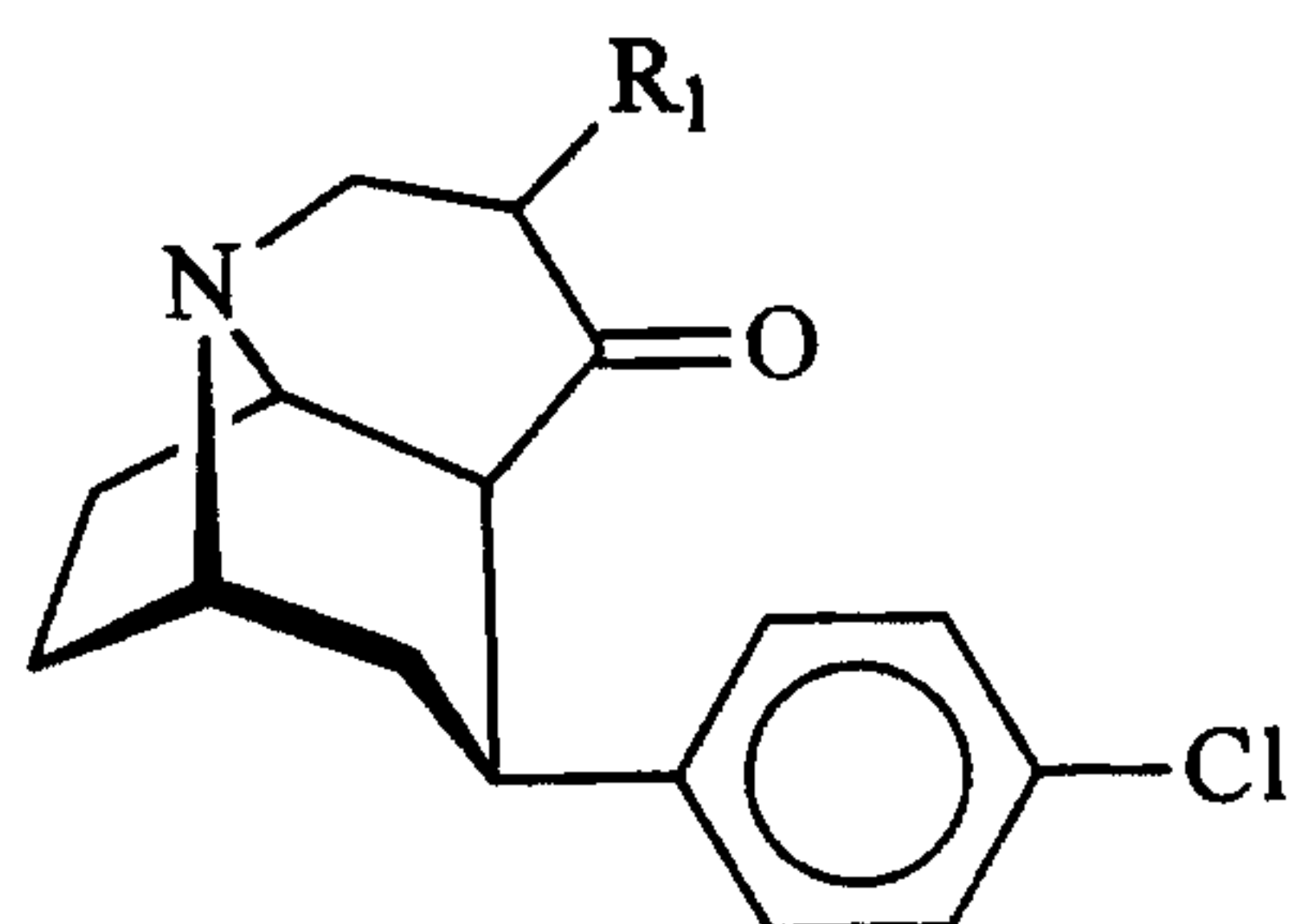
R₁, R₂, R₃ = H OR C₁₋₄ alkyl



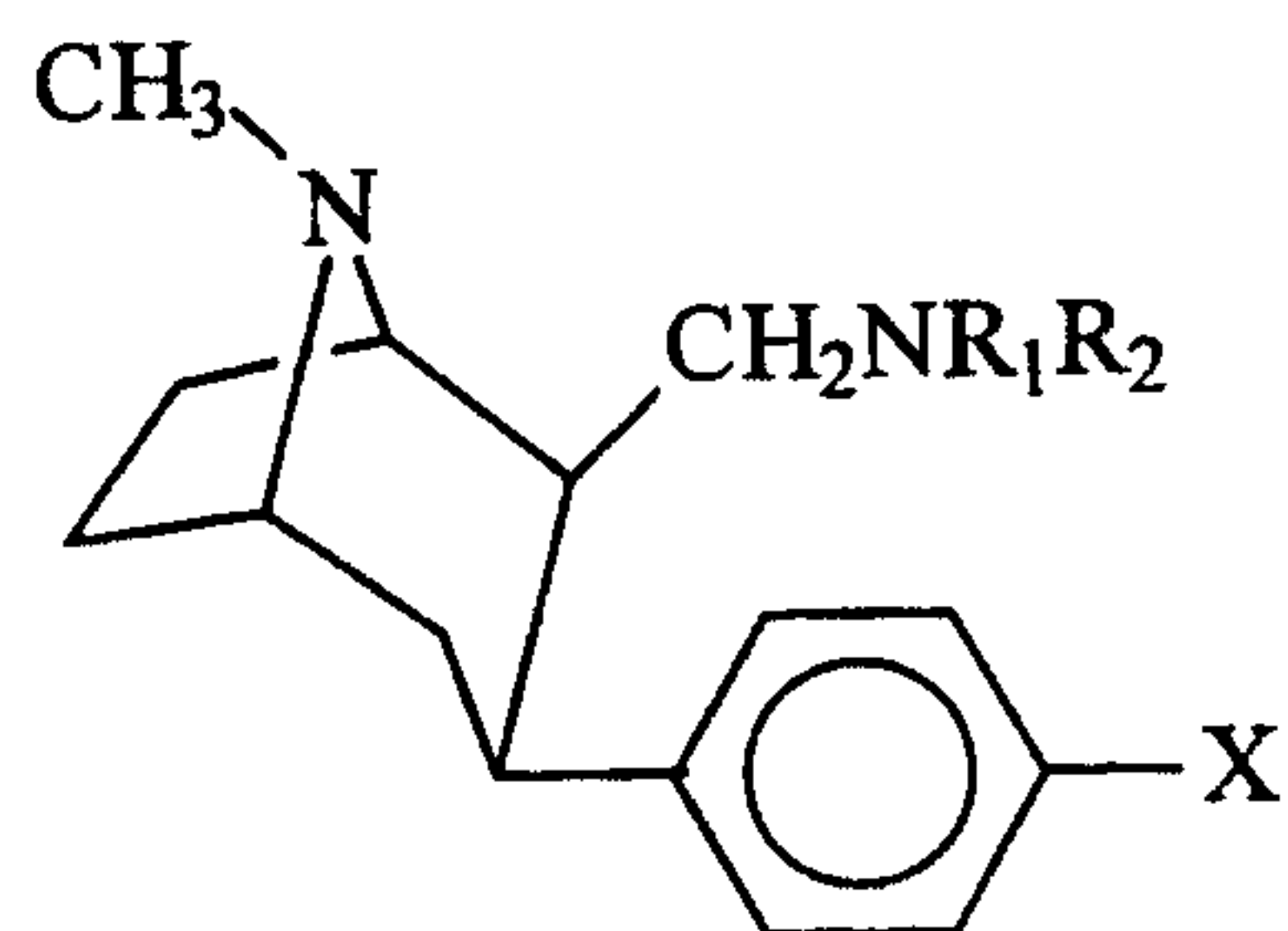
R₁, X, Y, Z are defined
above and M = (CH₂)₁₋₈ or
C≡C or HC=CH

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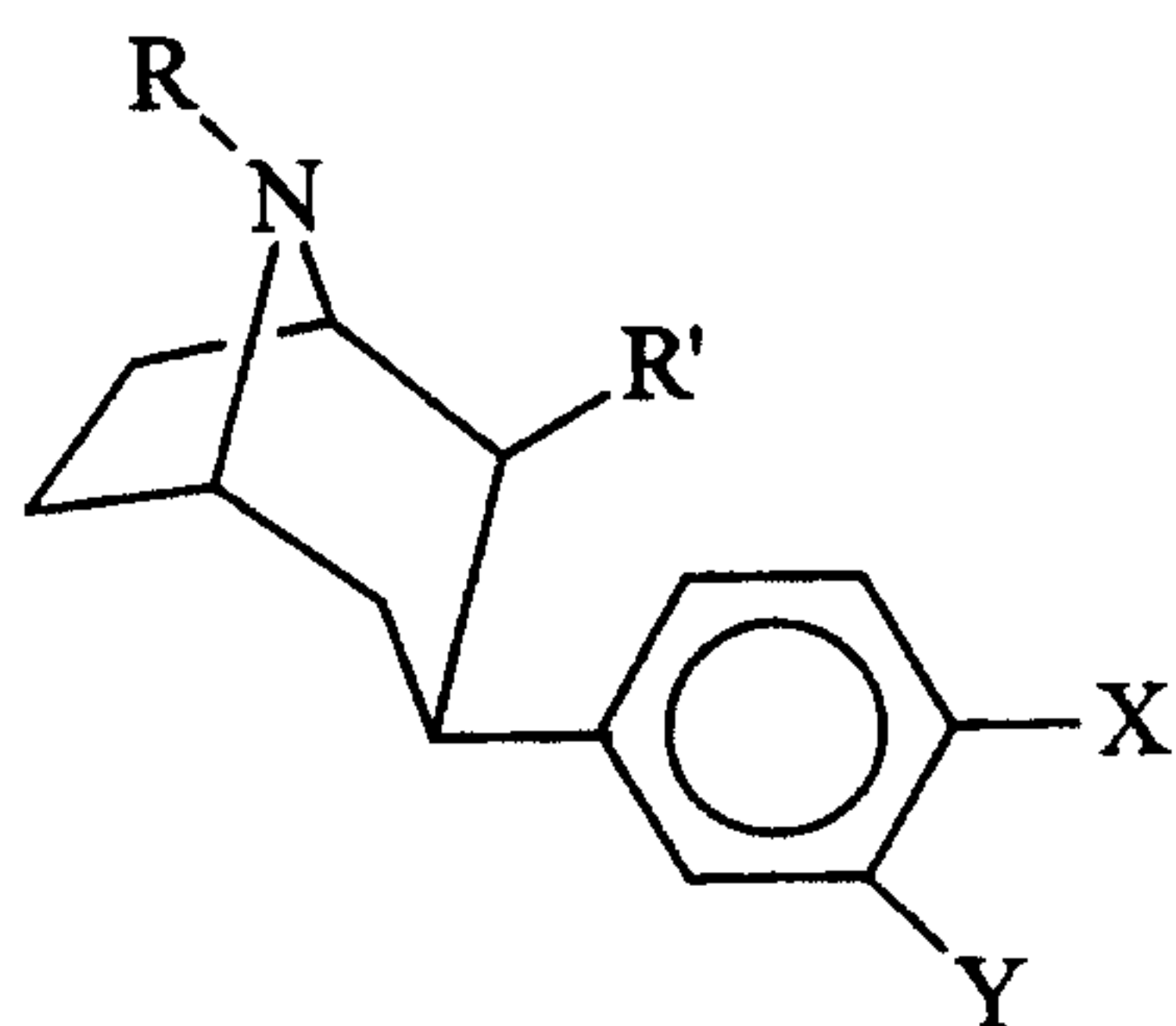
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wherein R₁=H or CO₂CH₃;



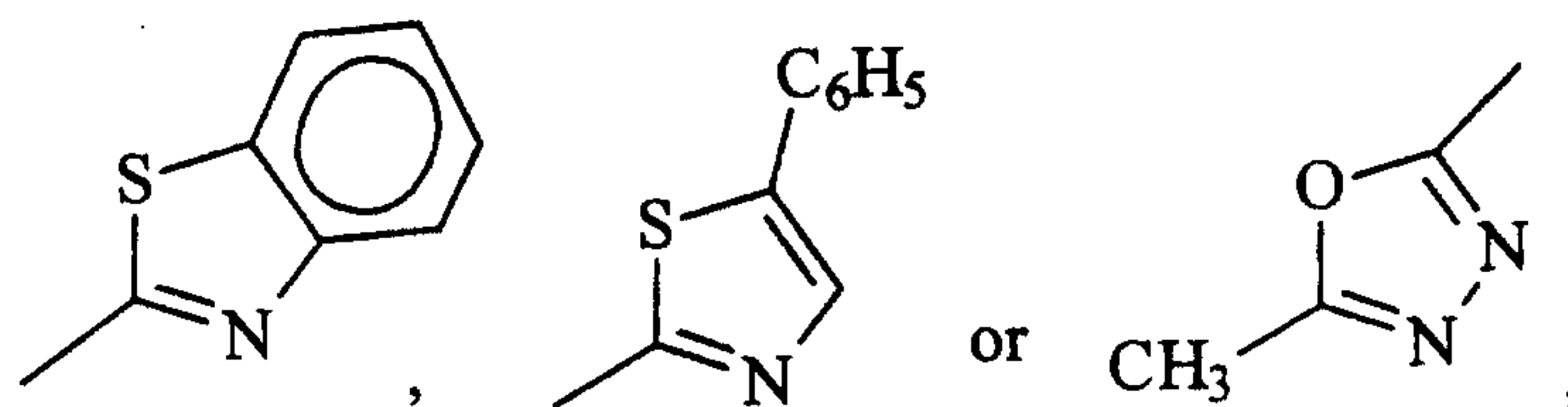
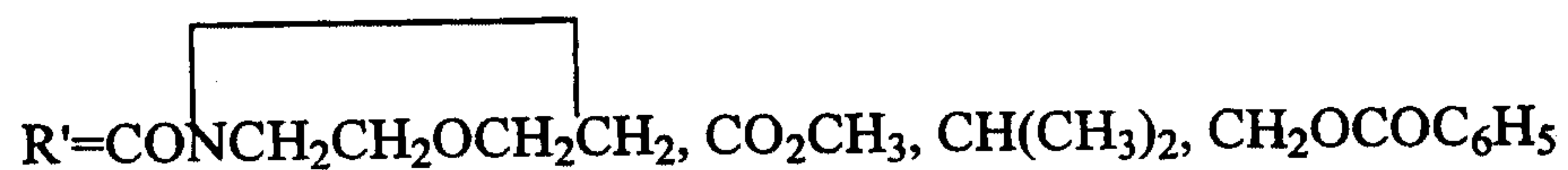
wherein R₁, R₂=H or CH₃ and X=CH₃;



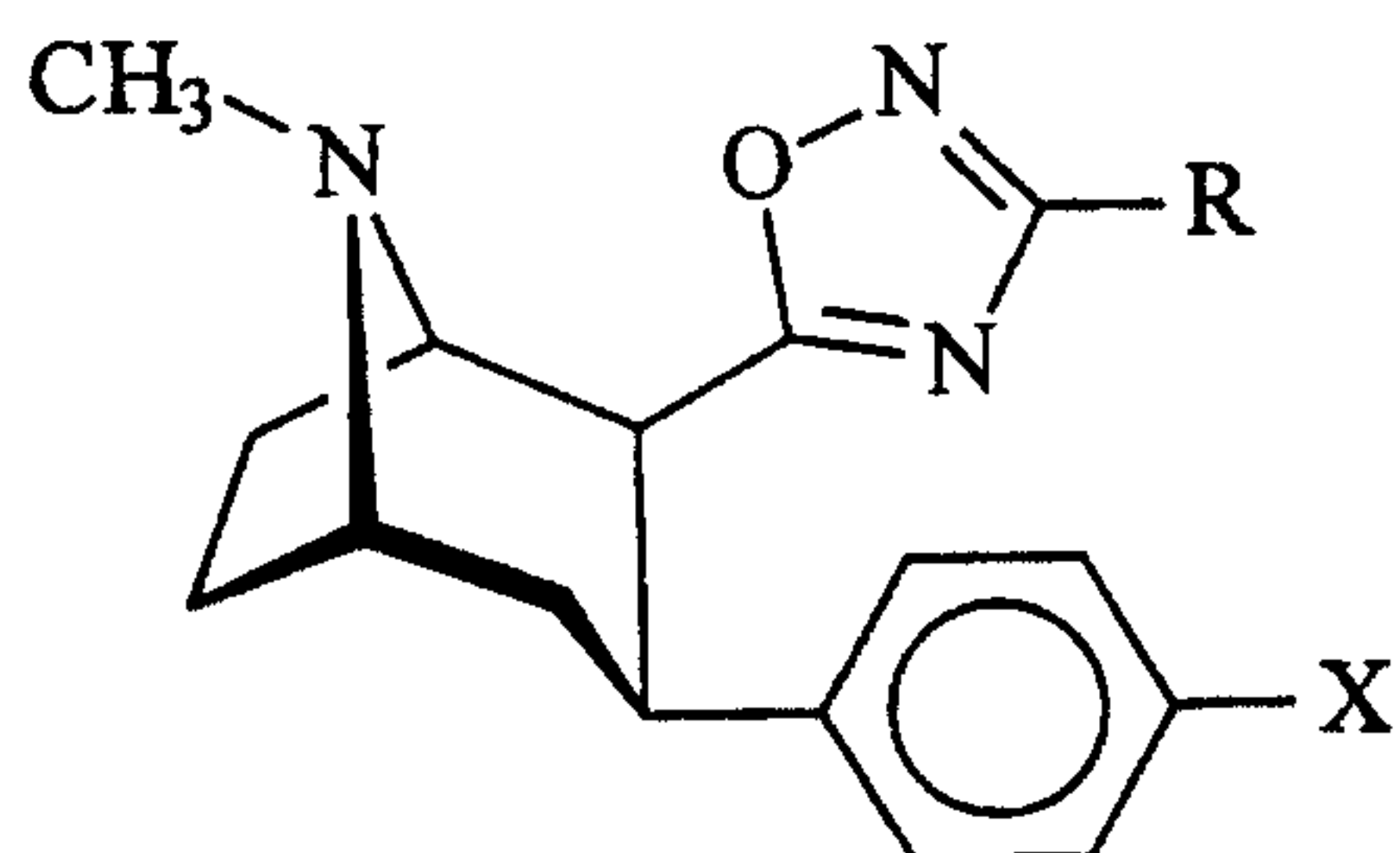
wherein R=H, CH₃ or CH₂CO₂C₂H₅,

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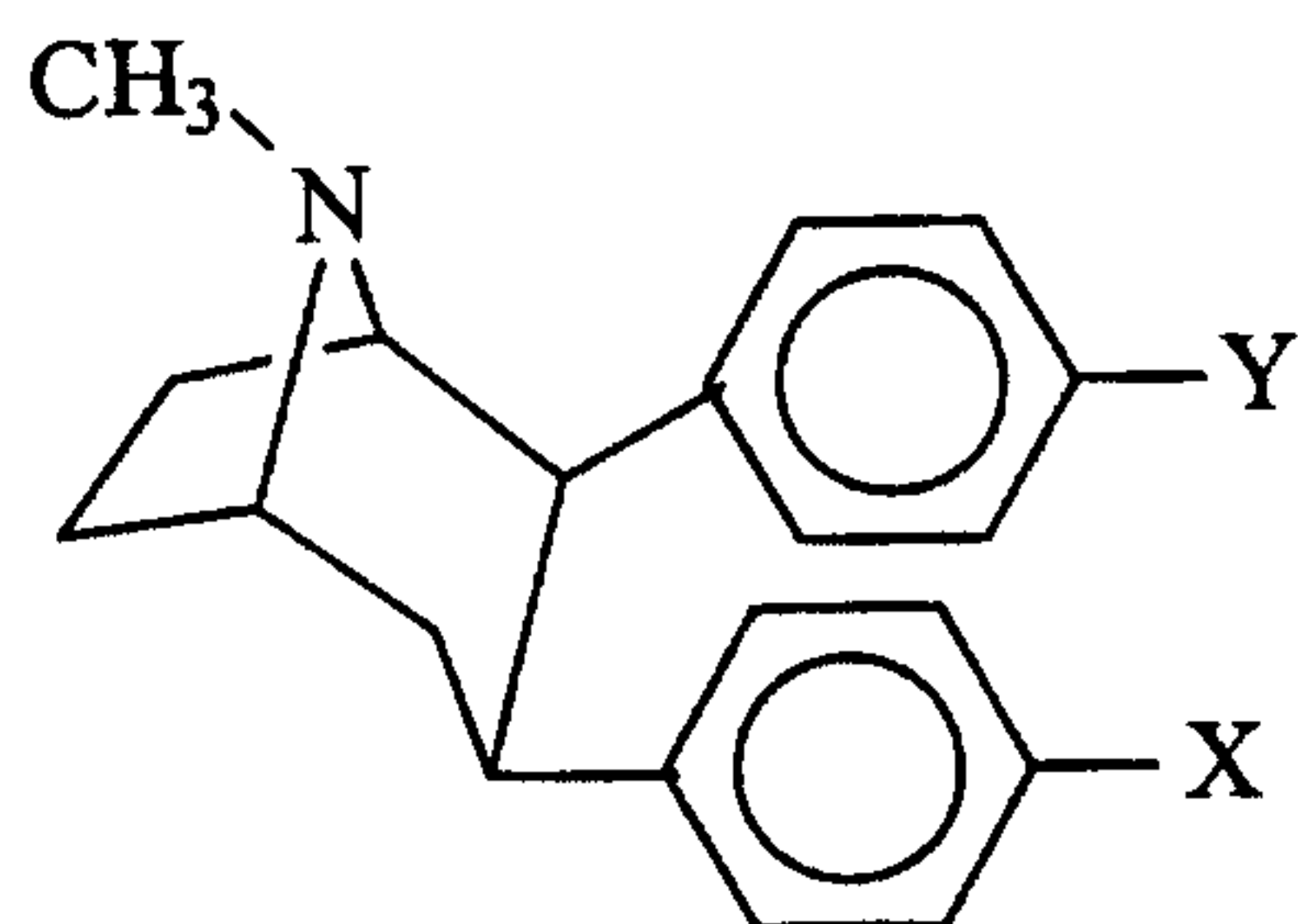
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and $Y = \text{H}$, $X = \text{CH}_3$, Cl , $t\text{-CH}_3\text{CH}=\text{CH}$ -, 2-naphthyl, or $\text{H}_2\text{C}=\text{C}$ -;

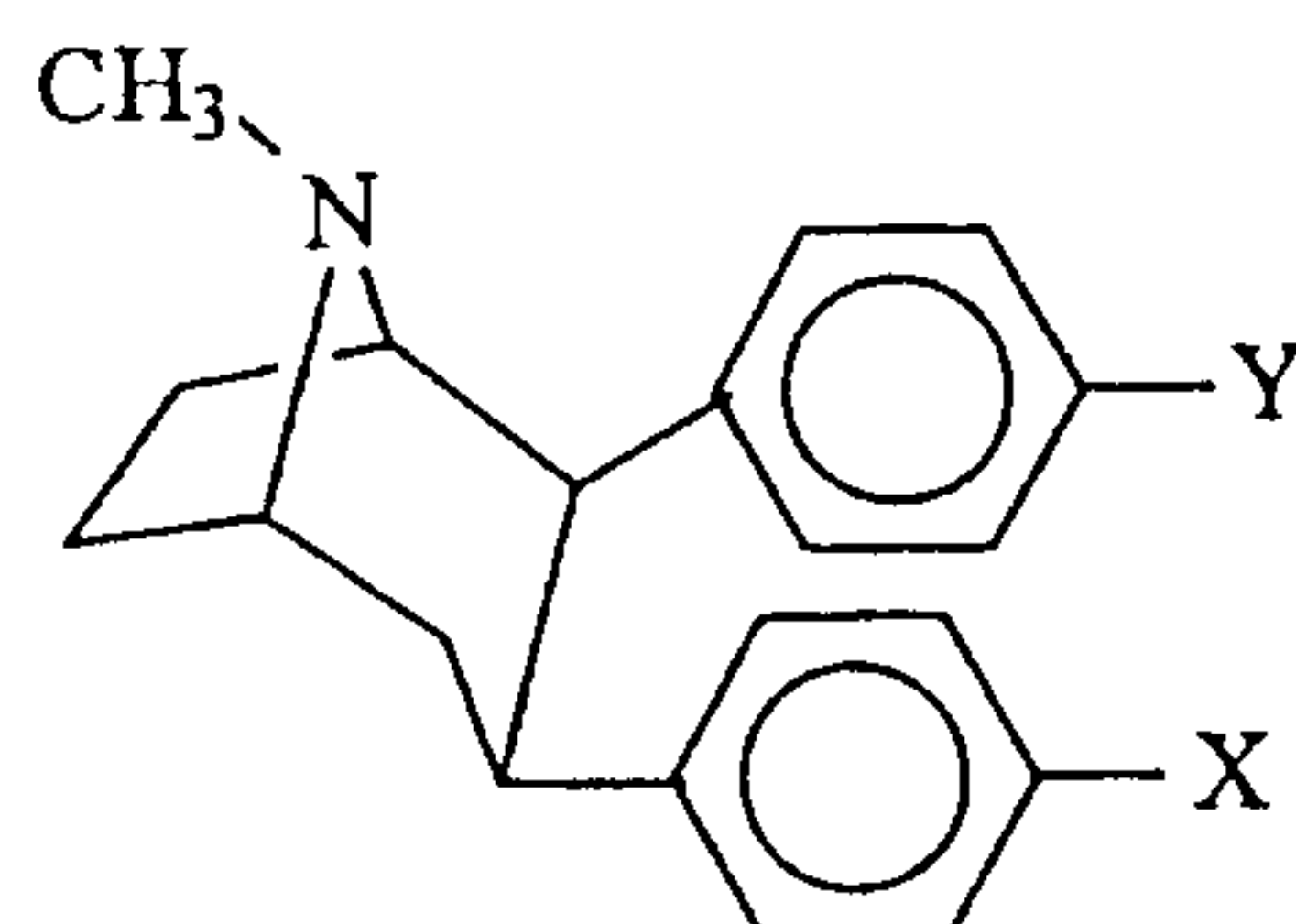


wherein $R = \text{CH}_3, \text{C}_6\text{H}_5, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4$, or $(\text{CH}_3)_2\text{CH}$ and $X = \text{Cl}, \text{CH}_3$ or H ; and



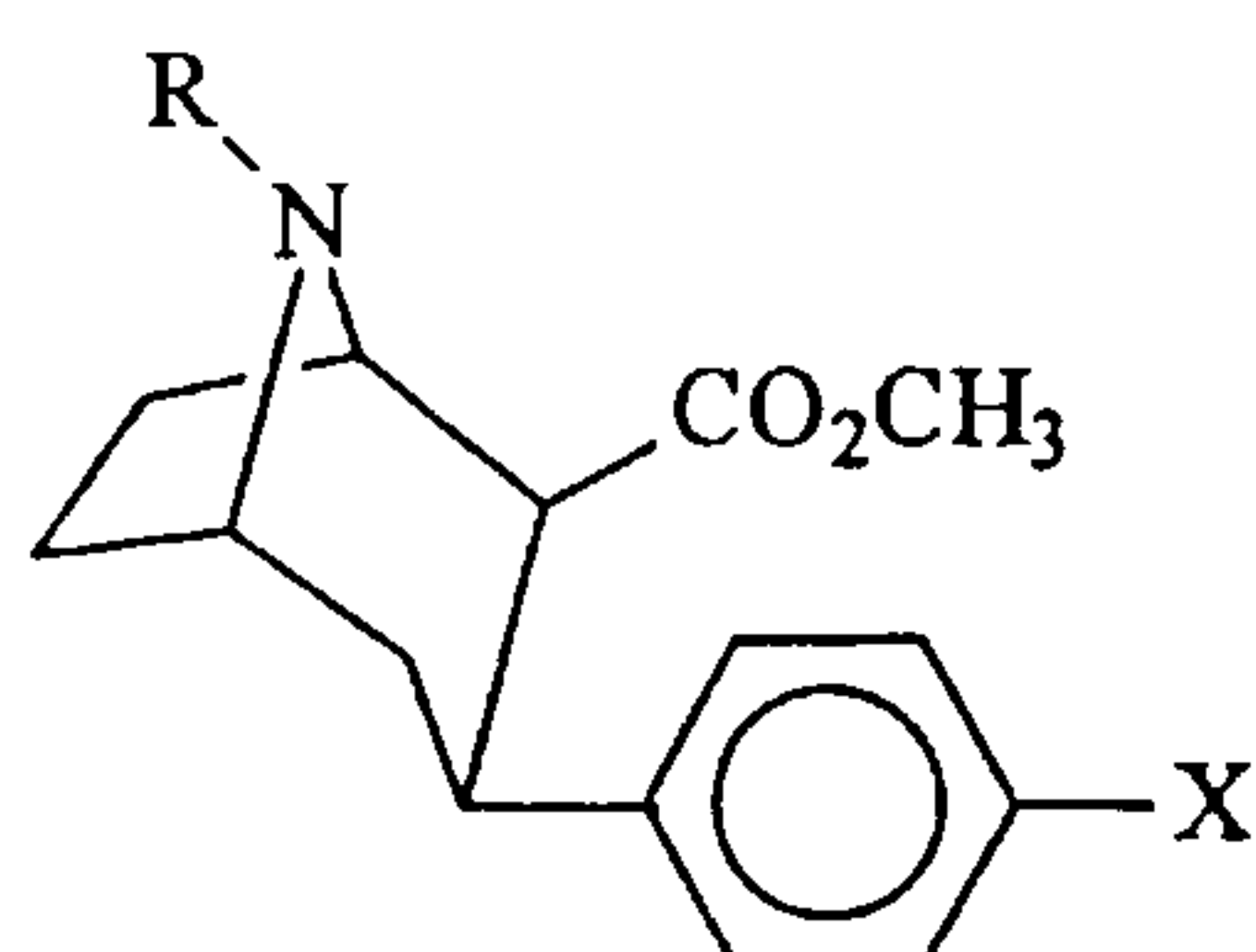
wherein $X = \text{CH}_3$ or H and $Y = \text{H}$ or CH_3 .

The invention as claimed more particularly concerns a compound of the formula:



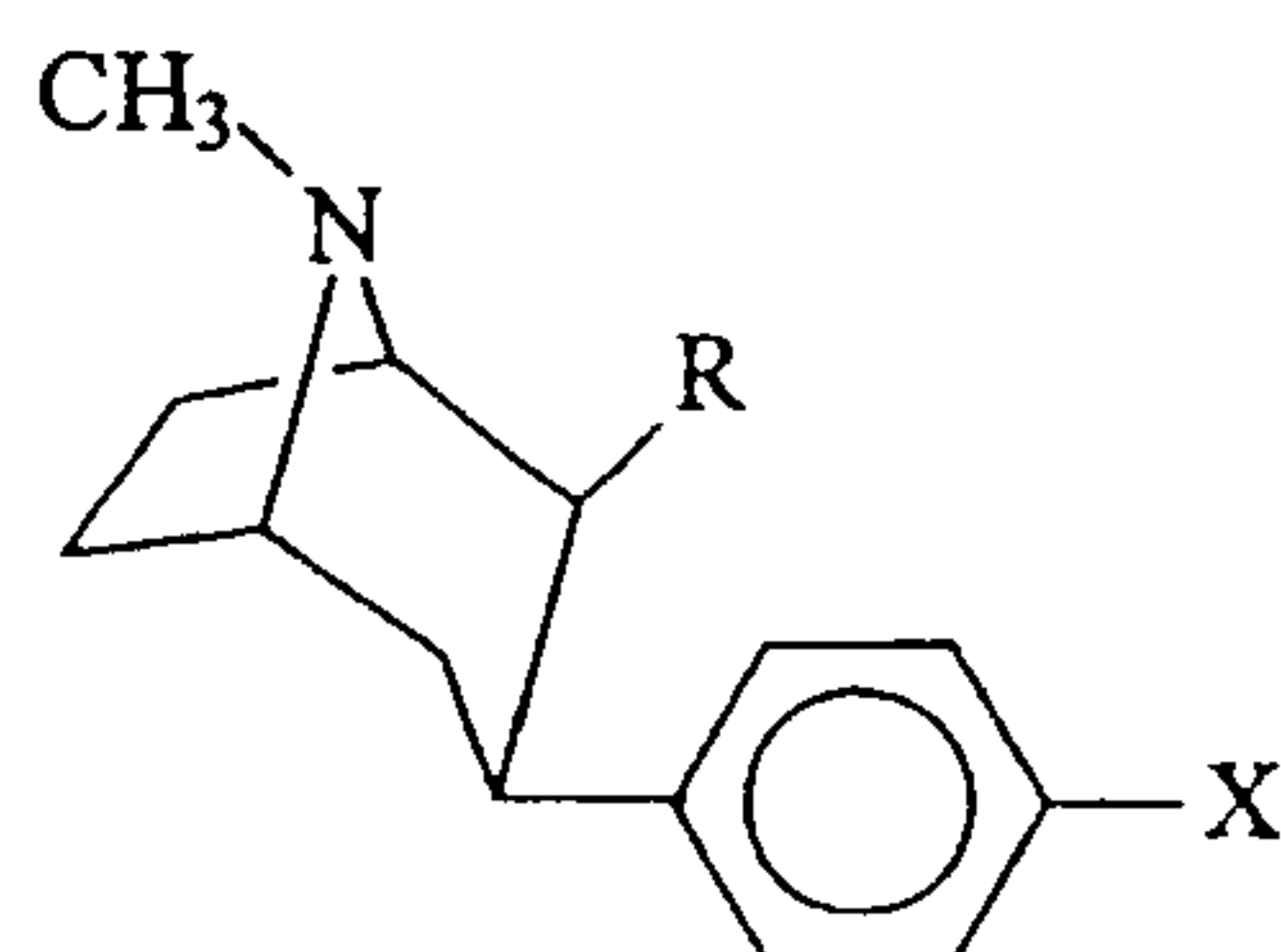
wherein X=CH₃ and Y=H.

It also concerns a compound of the formula:

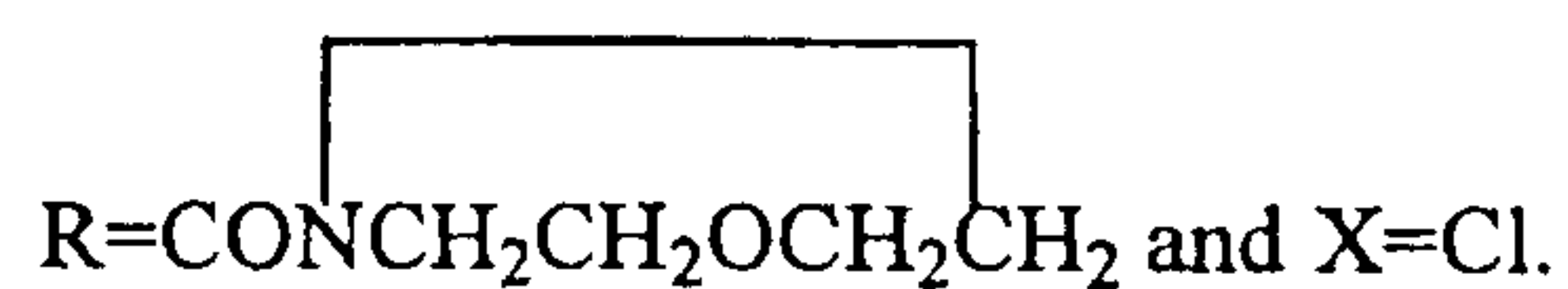


10 wherein X is 2-naphthyl and R is CH₃.

The invention is also directed to a compound of the formula:



wherein:



In another object the invention provides a method for treating psychostimulant abuse, by administering to a patient in need of such treatment a pharmaceutically effective amount of a 3-(substituted phenyl)-2-(substituted) tropane analog.

A still further object of the invention is to provide method for inhibiting the action of a psychostimulant, by administering to a patient in need of such treatment a psychostimulant-inhibiting amount of a 3-(substituted phenyl)-2-(substituted)tropane analog.

10

Still another object of the invention is to provide a method for inhibiting neurotransmitter re-uptake by administering to a patient in need of such treatment a neurotransmitter transporter-inhibiting amount of a 3-(substituted phenyl)-2-(substituted)tropane analog.

Another object of the invention is to provide a method for treating neurodegenerative disorders, by administering to a patient in need of such treatment a pharmaceutically effective amount of a 3-(substituted phenyl)-2-(substituted)tropane analog.

Still another object of the invention is to provide a method for treating depression, by administering to a patient in need of such treatment a pharmaceutically effective amount of a 3-(substituted phenyl)-2-(substituted)tropane analog.

20

Briefly, the invention pertains to the discovery that certain cocaine analogs are particularly well suited for therapeutic use as neurochemical agents. These particular cocaine analogs, in modulating neurotransmitter actions, may also be useful for modulating the actions of psychostimulant drugs, for modulating endocrine function, for modulating motor function, and for modulating complex behaviors.

With the foregoing and other objects, advantages and features of the invention that will become here in after apparent, the nature of the invention may be more clearly understood by reference to the following detailed description of the preferred embodiments of the invention and to the appended claims.

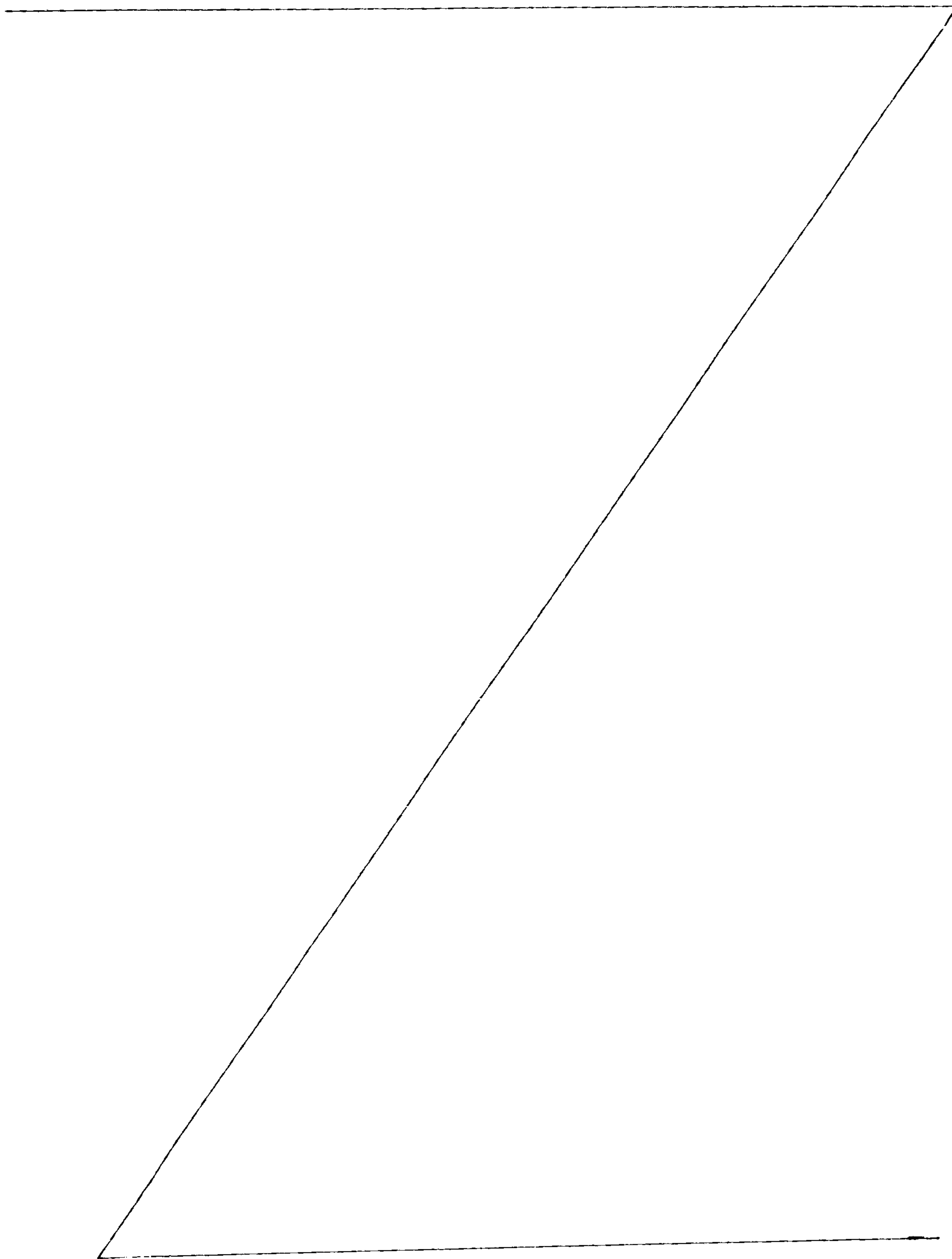
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BRIEF DESCRIPTION OF THE DRAWINGS:

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings,

wherein:

Figure 1 depicts the scheme for converting 3-(substituted phenyl)-2-tropane carboxylic acid (tropane acid) to 2-substituted tetrazoles, oxazoles, oxadiazoles, thiazoles, thiadiazoles and



benzothiazole.

Figure 2 depicts the scheme in which the carboxamide obtained from the tropane acid was treated to obtain nitriles and tetrazoles.

Figure 3 depicts the scheme used to prepare 3-substituted isoxazoles.

Figure 4 depicts the scheme for converting RTI-93 to RTI-123.

Figure 5 depicts the scheme for converting a 3 β -phenyltropane 2 β -ester analog(RTI-32) to a 3 β -phenyltropane 2 β -amide analog (RTI-129) and a 3 β -phenyltropane 2 β -aminomethyl analog (RTI-132).

Figure 6 depicts the scheme for converting a 3 β -phenyltropane analog (RTI-31) or a 3 β -phenyltropane 2 β -ester analog(RTI-32) into a 3 β -phenyltropane 2 β -(3'-substituted-1,2,4-oxadiazol-5-yl) analog (RTI-144) or a 3 β -phenyltropane 2 β -heterocyclic analog (RTI-194, RTI-219, and RTI-202).

Figure 7 depicts the scheme for converting a 3 β -phenyltropane analog (RTI-31) into a 3 β -phenyltropane 2 β -amide analog (RTI-214).

Figure 8 depicts the scheme for making a 3 β -phenyltropane 2 β -alkyl analog (RTI-239).

Figure 9 depicts the scheme for making a 3 β -phenyltropane analog (RTI-251) and an N,C2-fused 3 β -phenyltropane analog (RTI-242).

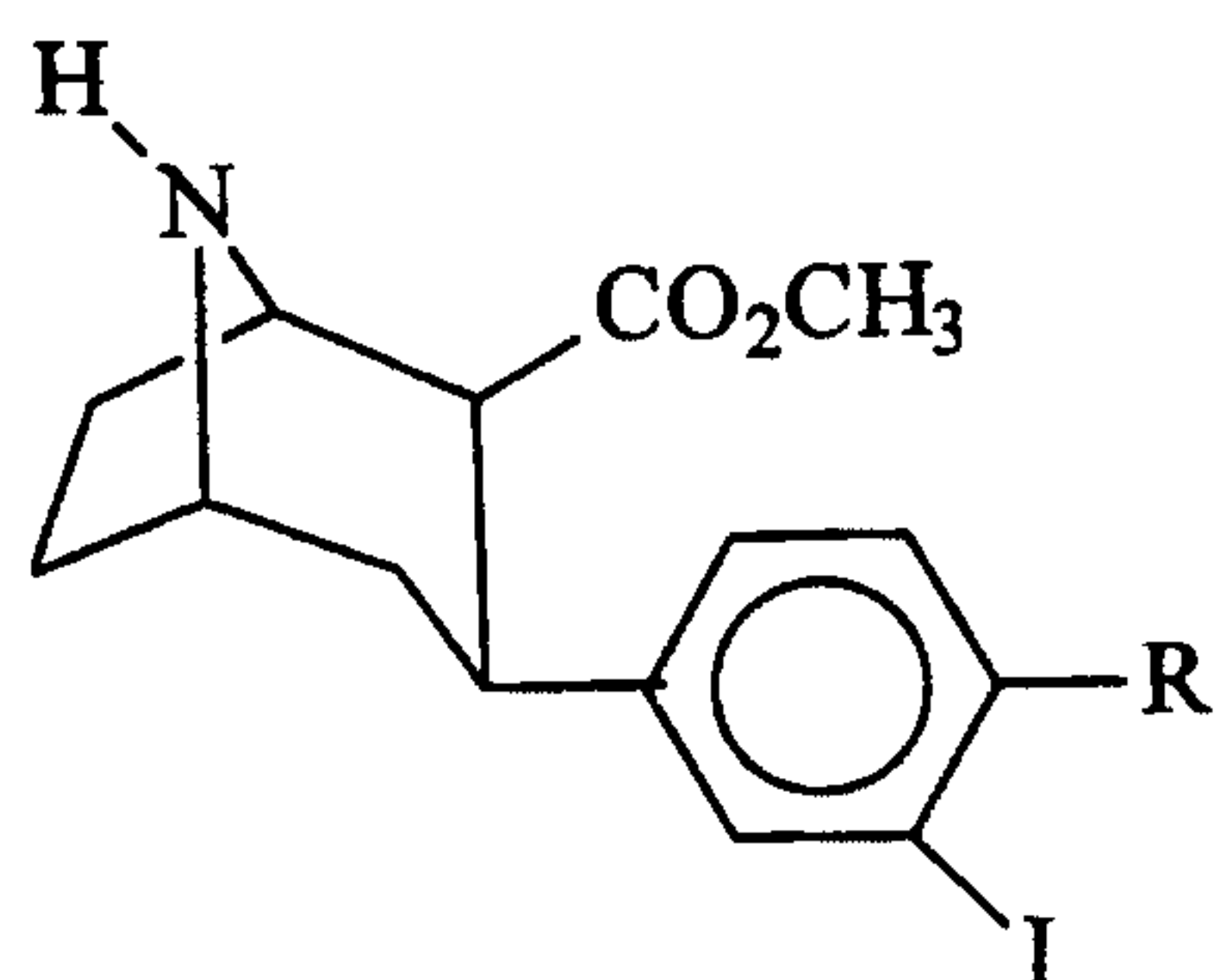
Figure 10 depicts the scheme for making RTI compounds 296, 298 and 309.

Figure 11 depicts the scheme for making RTI-318.

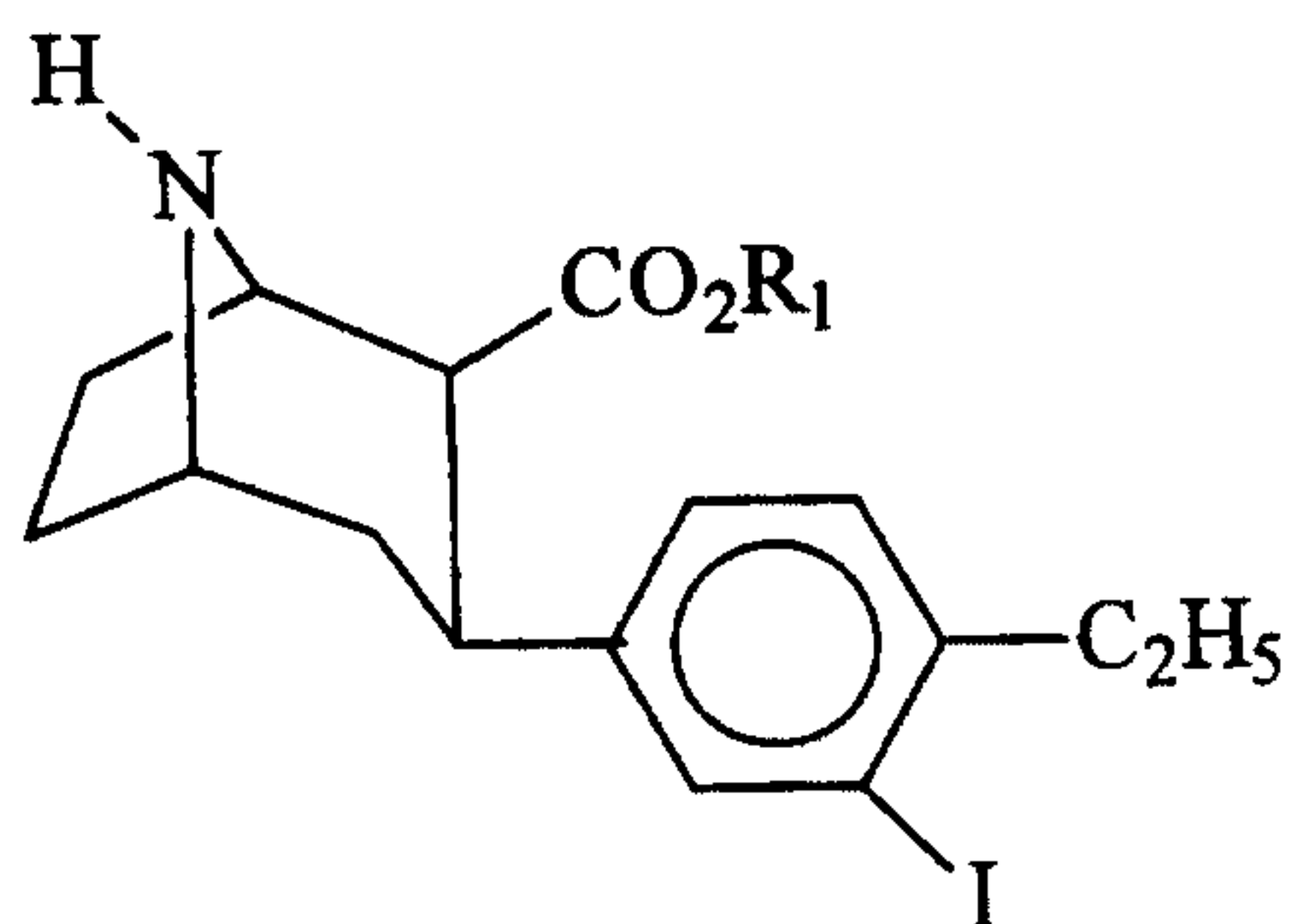
Figure 12 depicts the scheme for making a 2 β ,3 β -diphenyltropane analog (RTI-422).

DETAILED DESCRIPTION OF THE INVENTION:

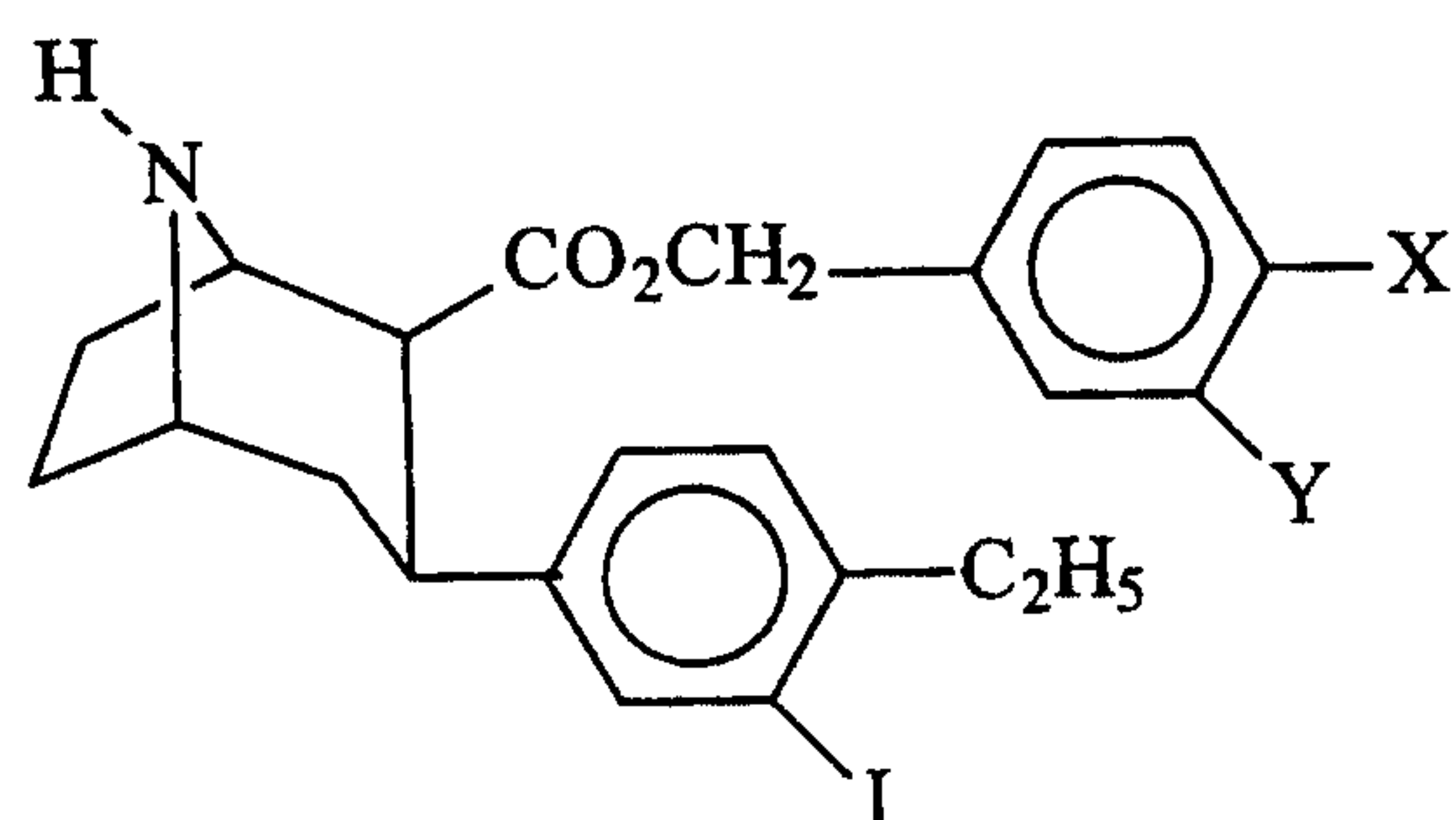
The present invention includes novel compounds having the following formula:



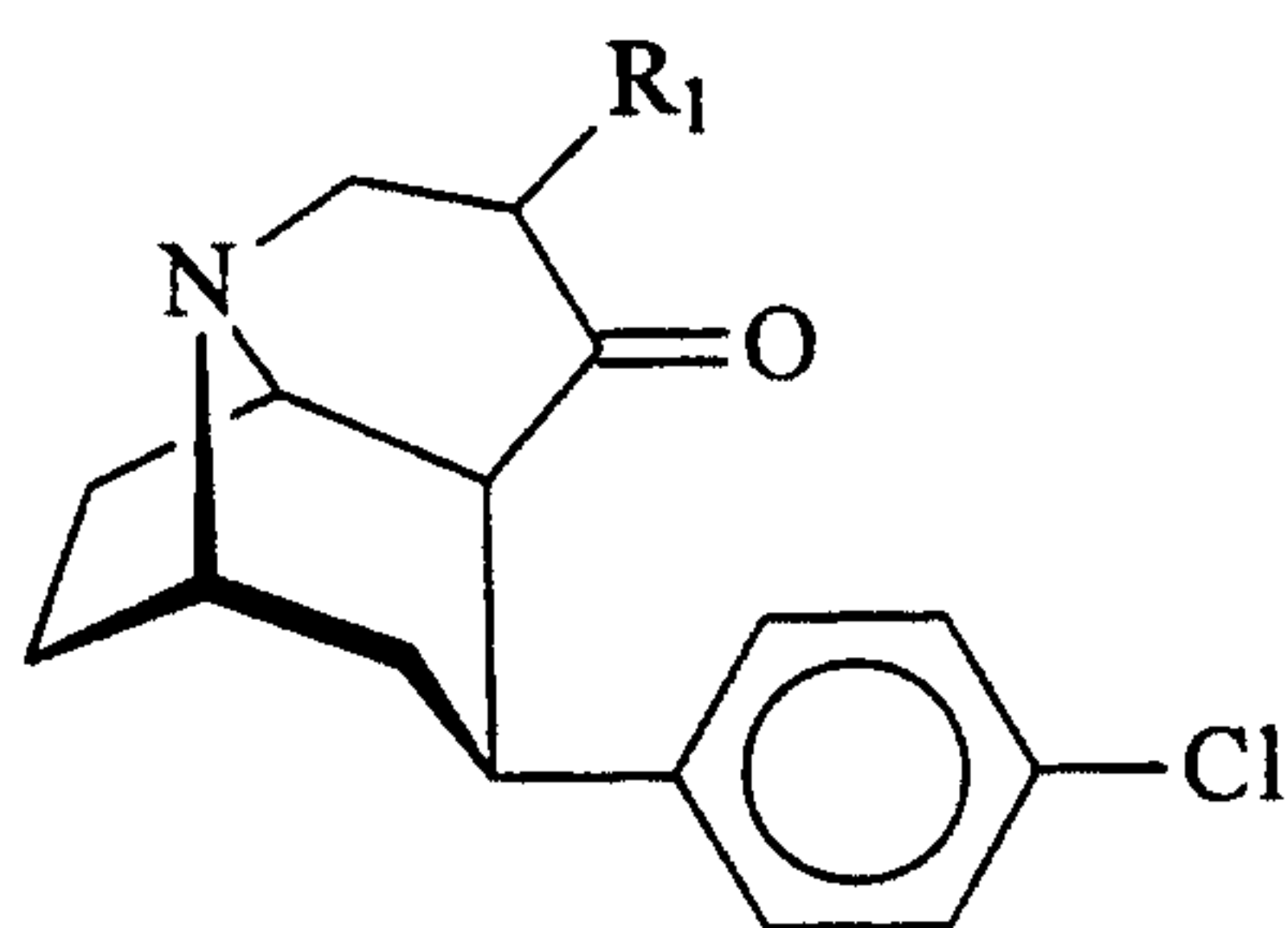
- 1a, $R = C_2H_5$
 b, $R = CH_2CH_2CH_3$
 c, $R = CH(CH_3)_3$



- 2a, $R_1 = CH_2C_6H_5$
 b, $R_1 = (CH_2)_2C_6H_5$
 c, $R_1 = (CH_2)_3C_6H_5$



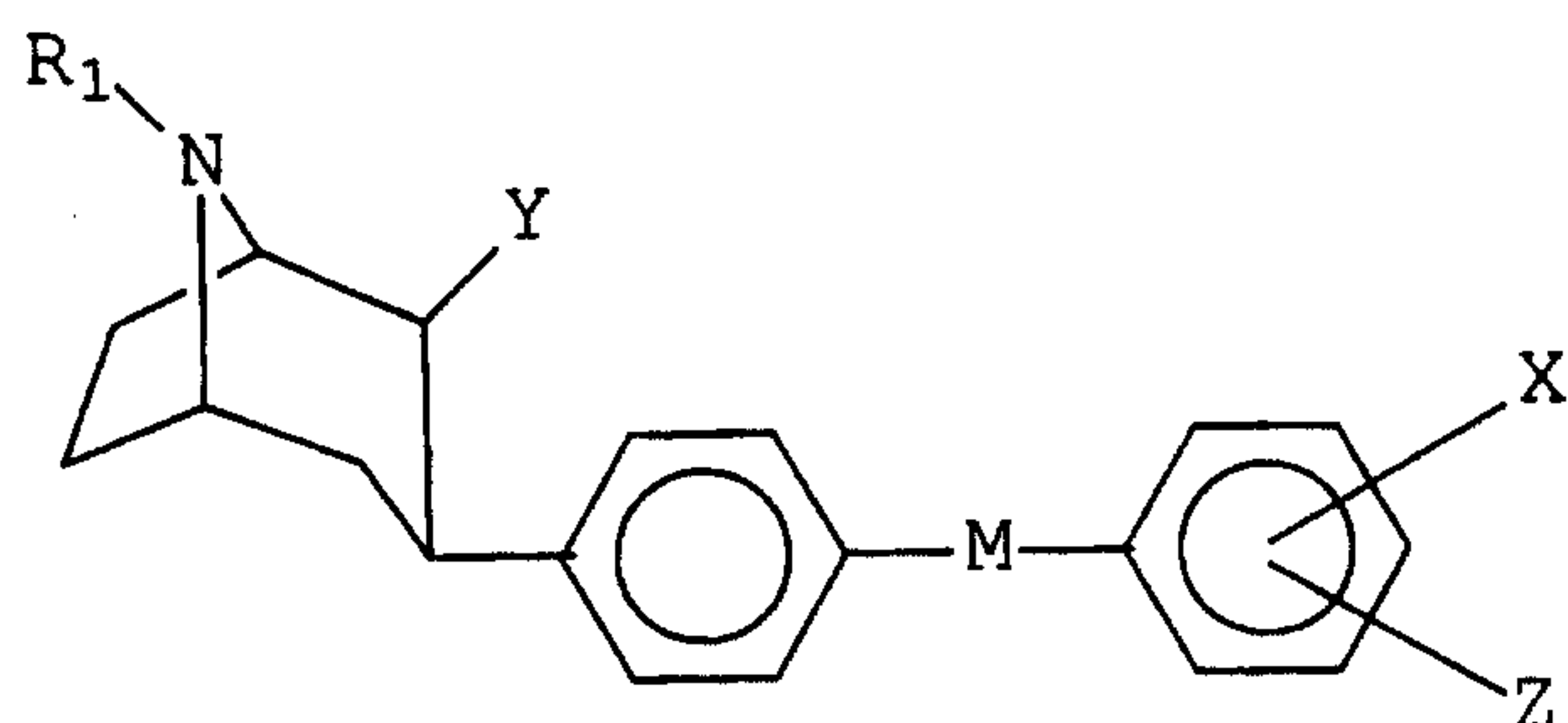
- 3a, $X = H, Y = OCH_3$
 b, $X = OCH_3, Y = H$
 c, $X = OCH_3, Y = OCH_3$
 d, $X = Cl, Y = H$
 e, $X = H, Y = Cl$
 f, $X = Cl, Y = Cl$



- 1a, $R_1 = H$
 1b, $R_1 = CO_2CH_3$

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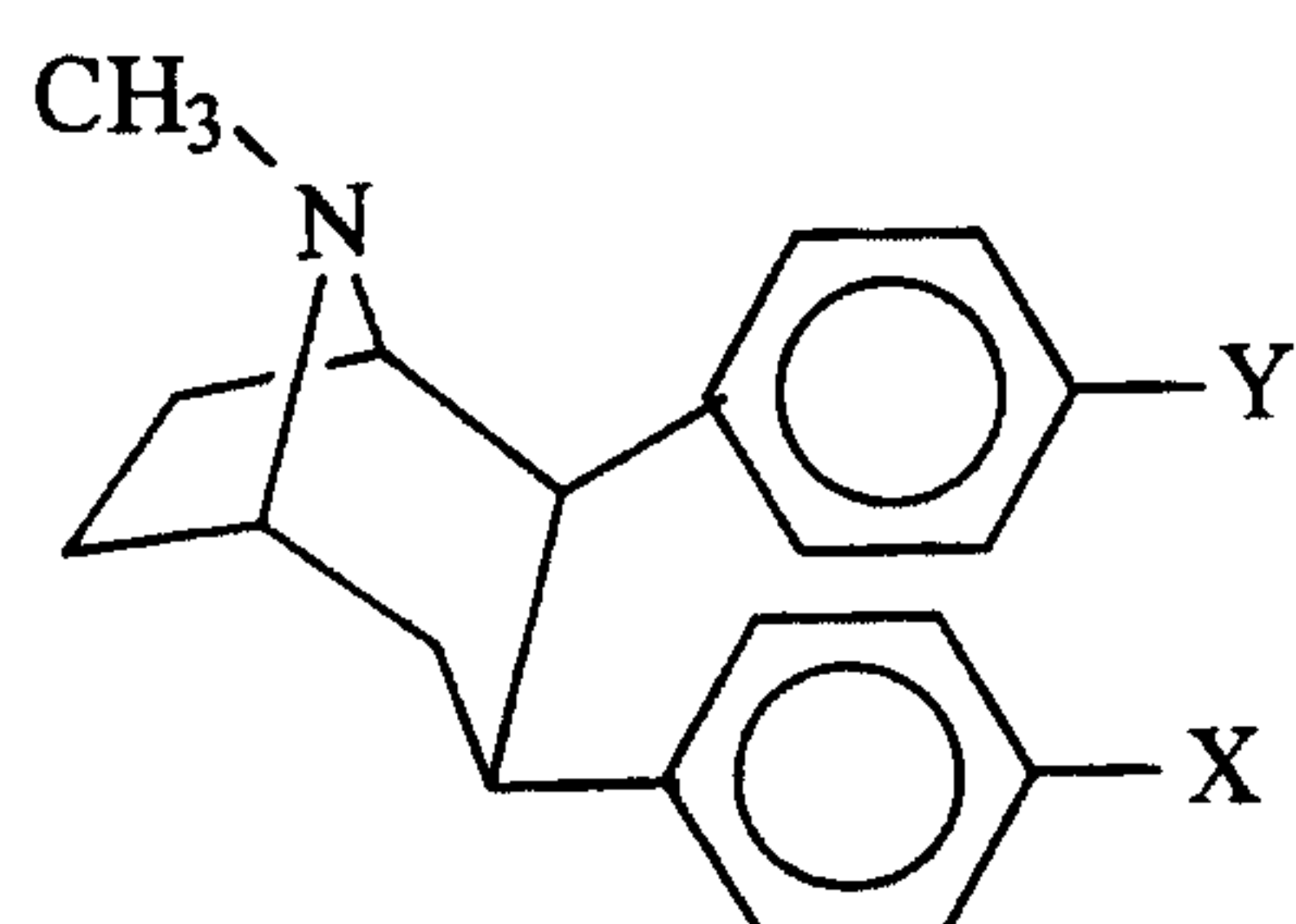


1a, $Y = \text{CO}_2\text{CH}_3$
 $M = \text{C}\equiv\text{C}$

$R_1 = \text{CH}_3$

$X = \text{H}$

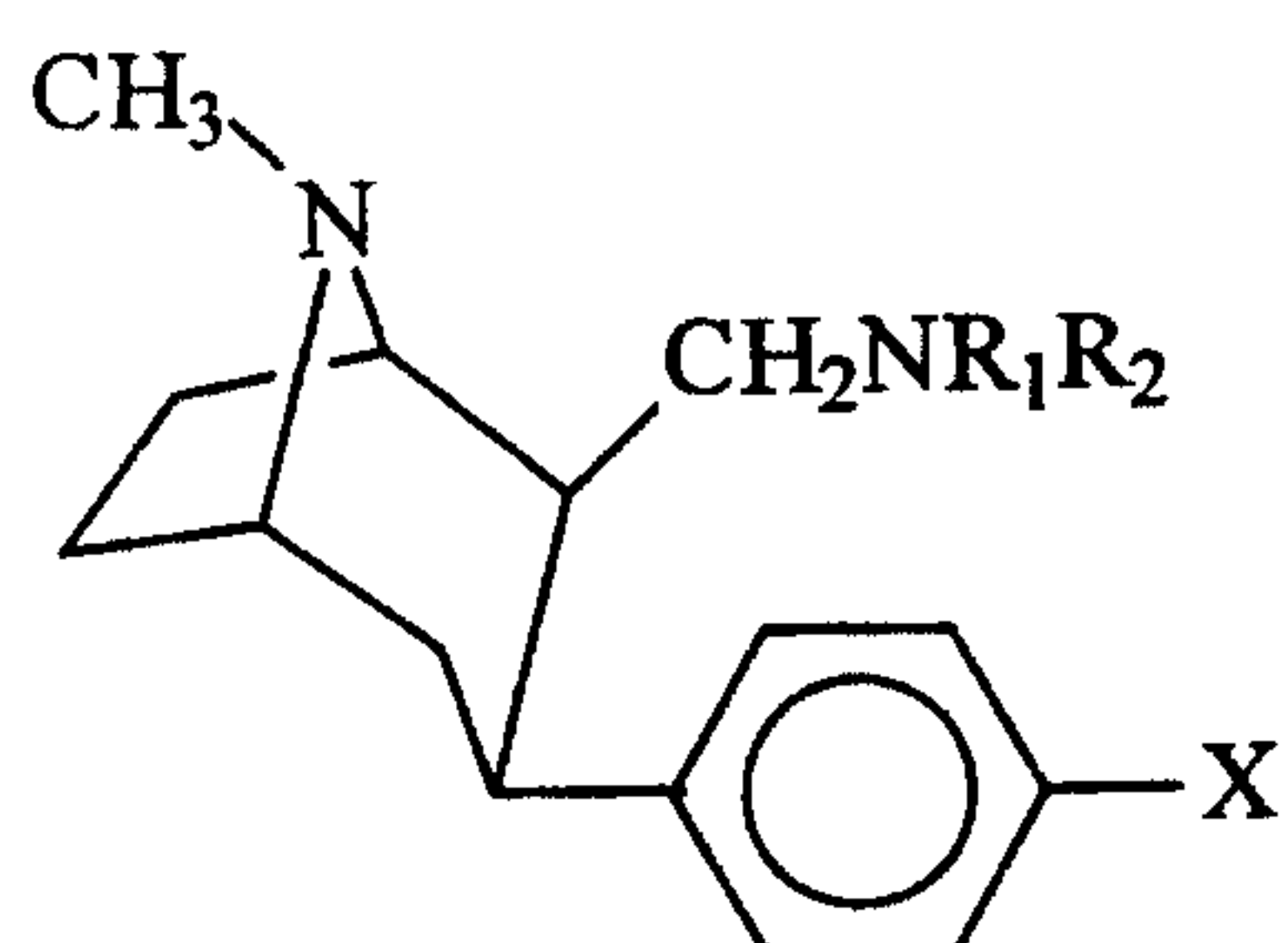
$Z = \text{H}$



1a, $X = \text{CH}_3$
 $Y = \text{H}$

1b, $X = \text{H}$
 $Y = \text{H}$

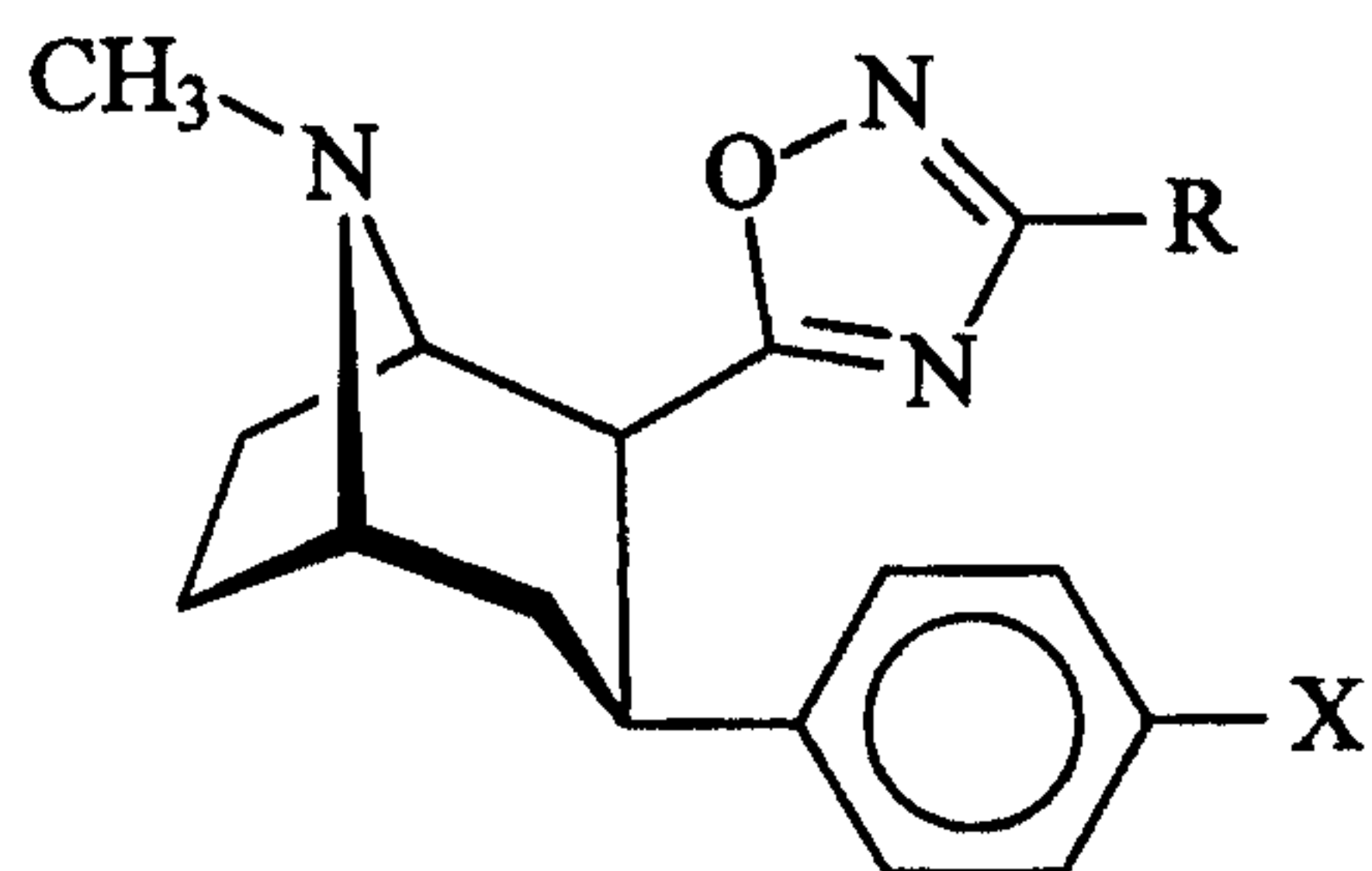
1c, $X = \text{H}$
 $Y = \text{CH}_3$



1a, $R_1, R_2, X = \text{CH}_3$

1b, $R_1, X = \text{CH}_3$
 $R_2 = \text{H}$

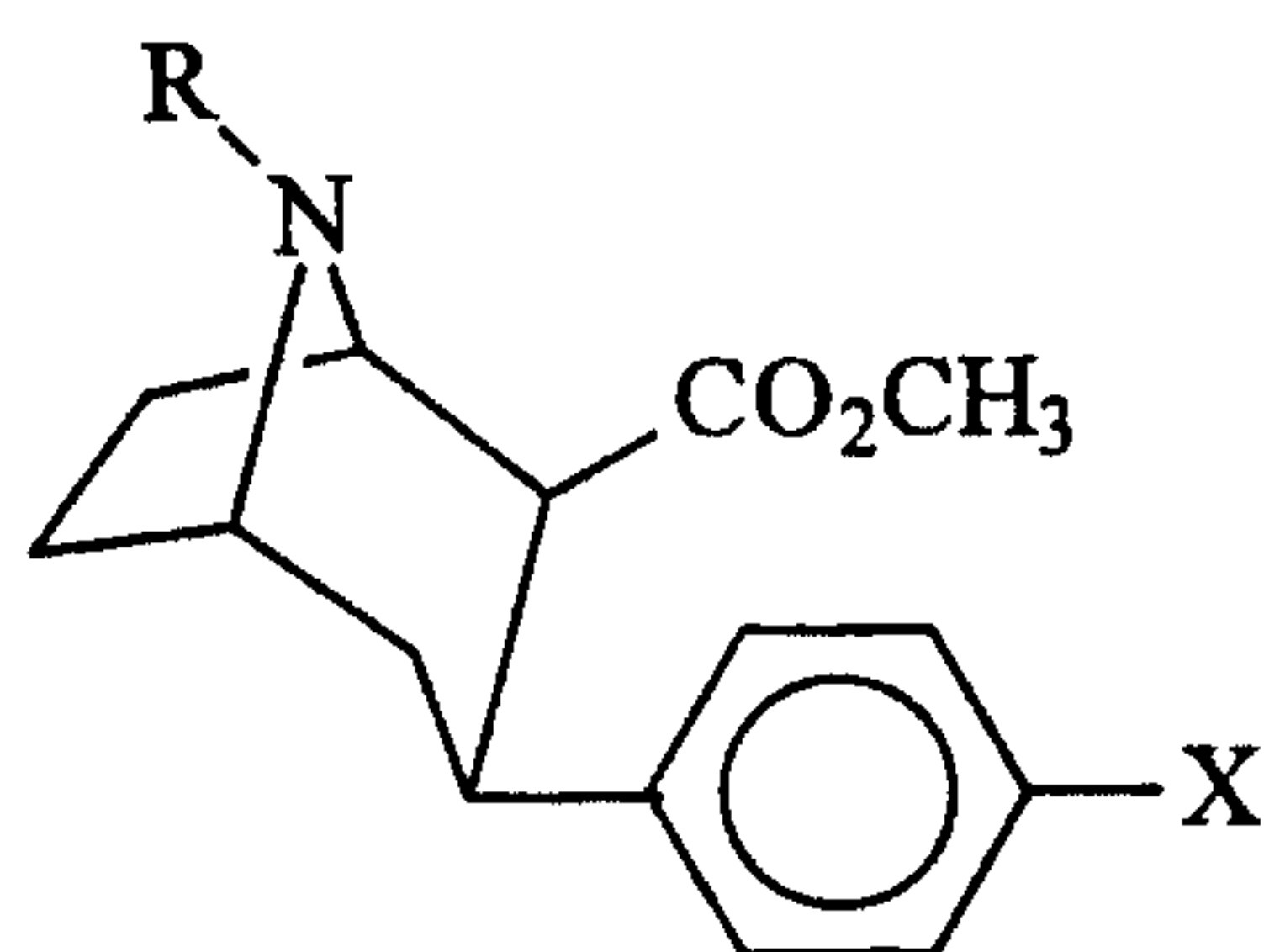
1c, $R_1, R_2 = \text{H}$
 $X = \text{CH}_3$



1a, R=C₆H₄
X=Cl

1b, R= 4-CH₃OC₆H₄
X= Cl

1c, R= C₆H₅
X= CH₃



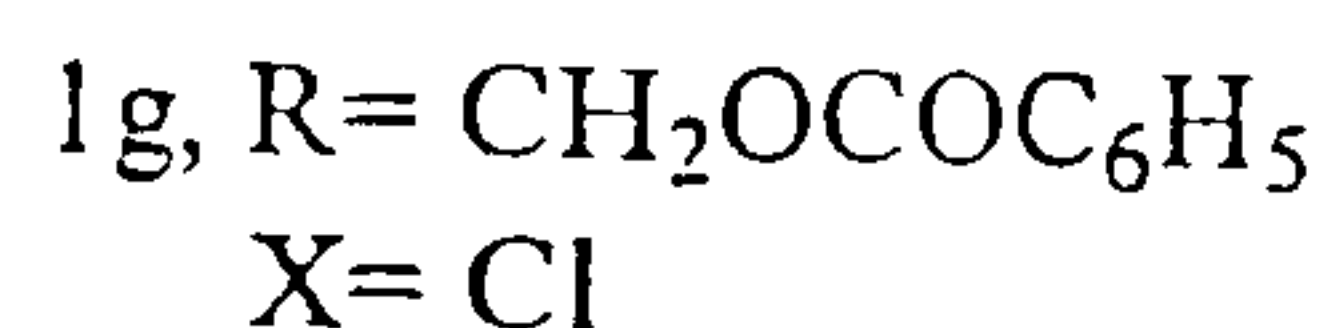
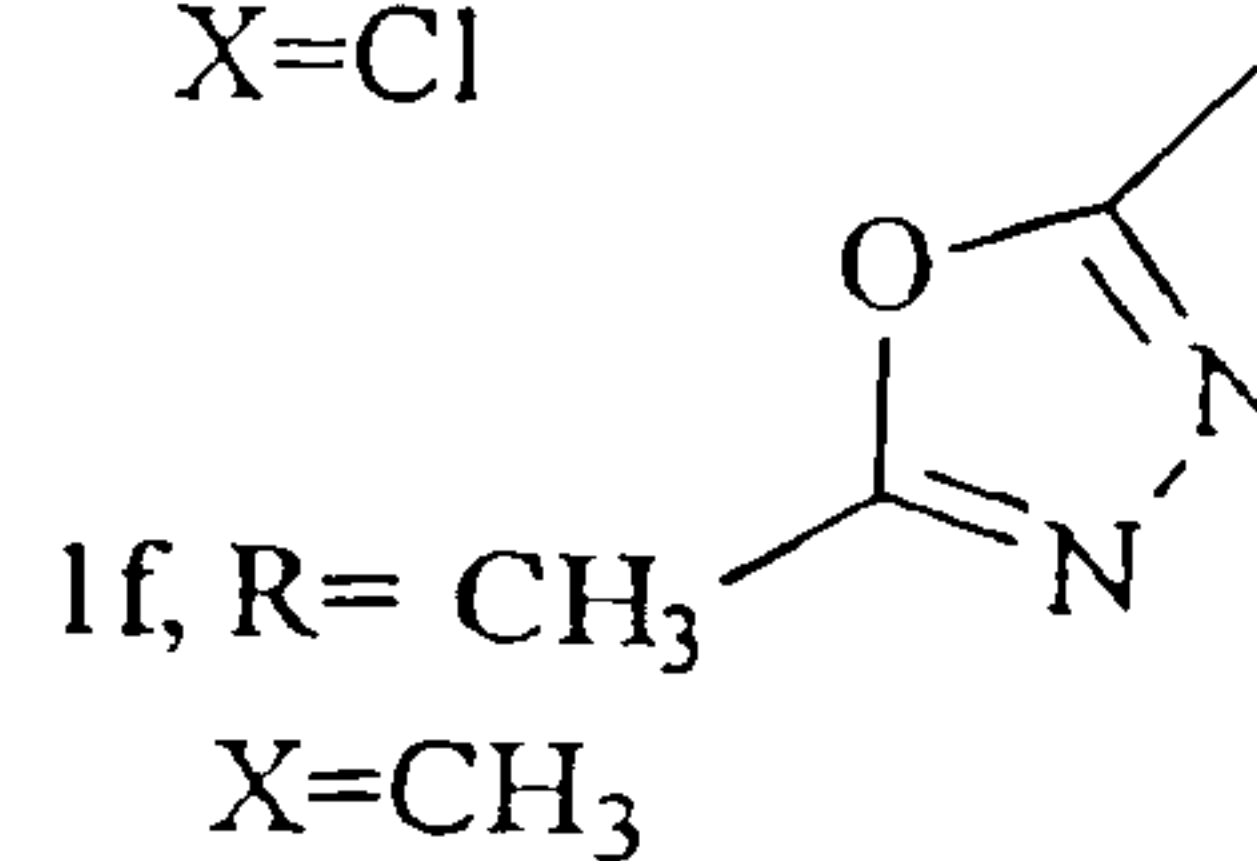
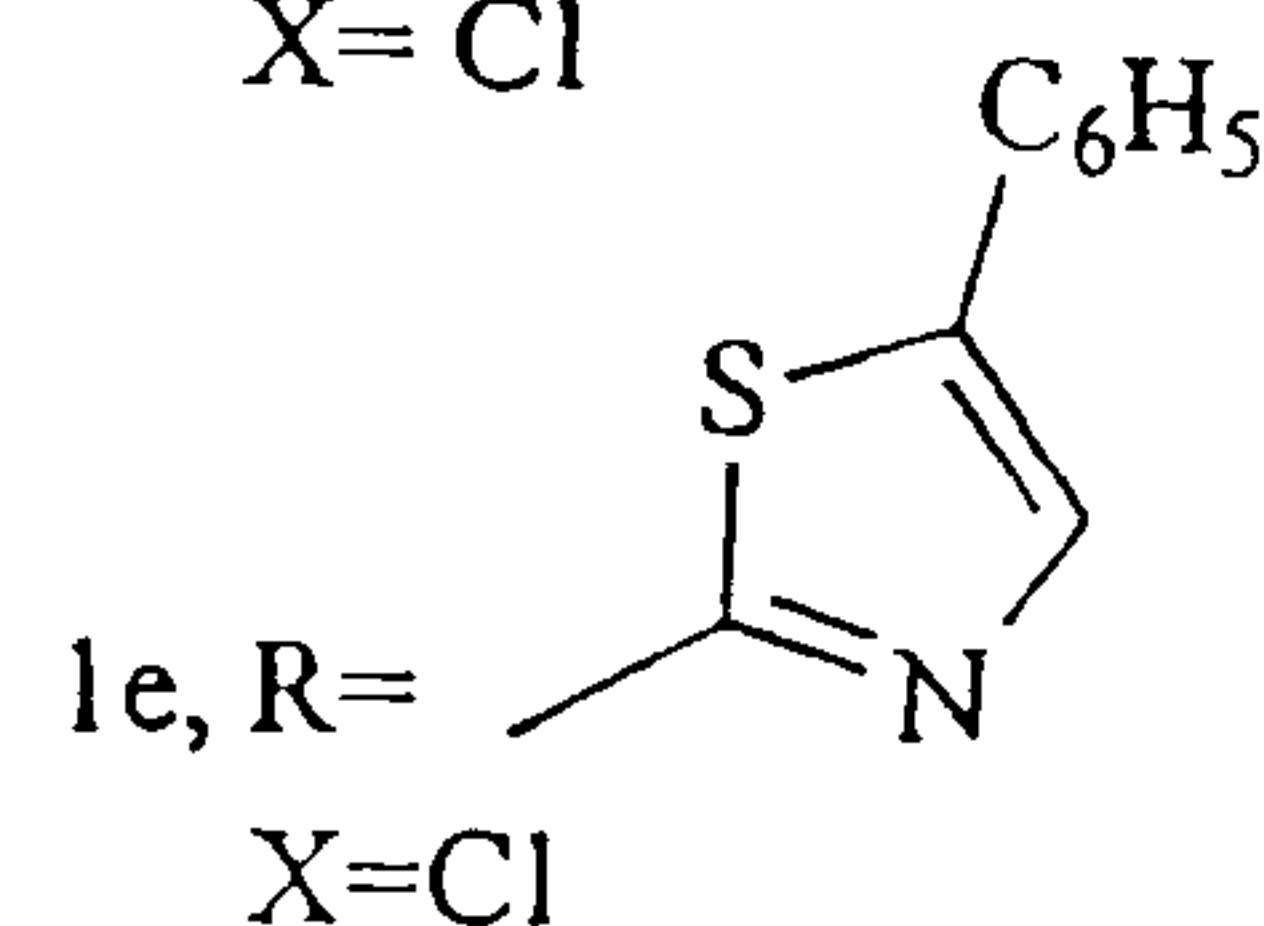
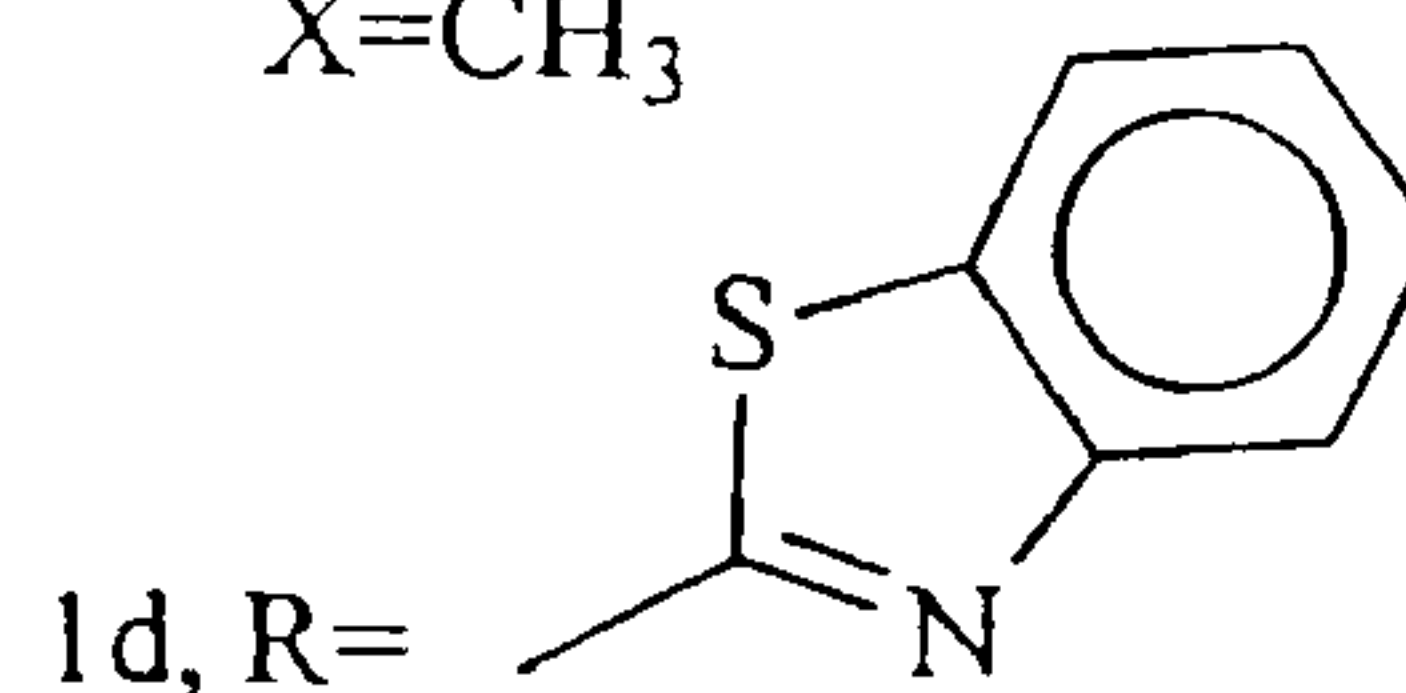
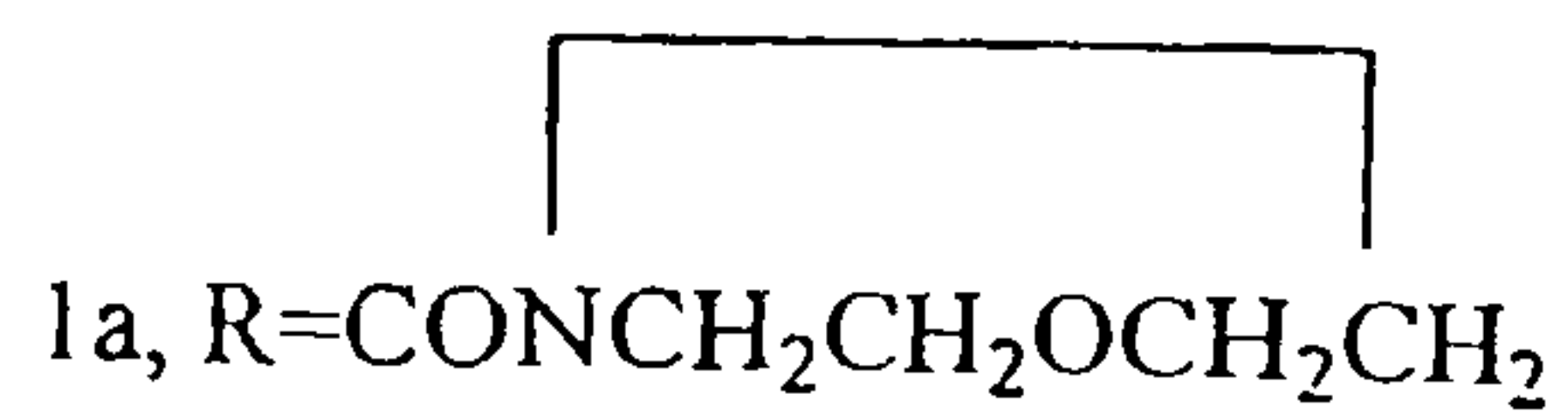
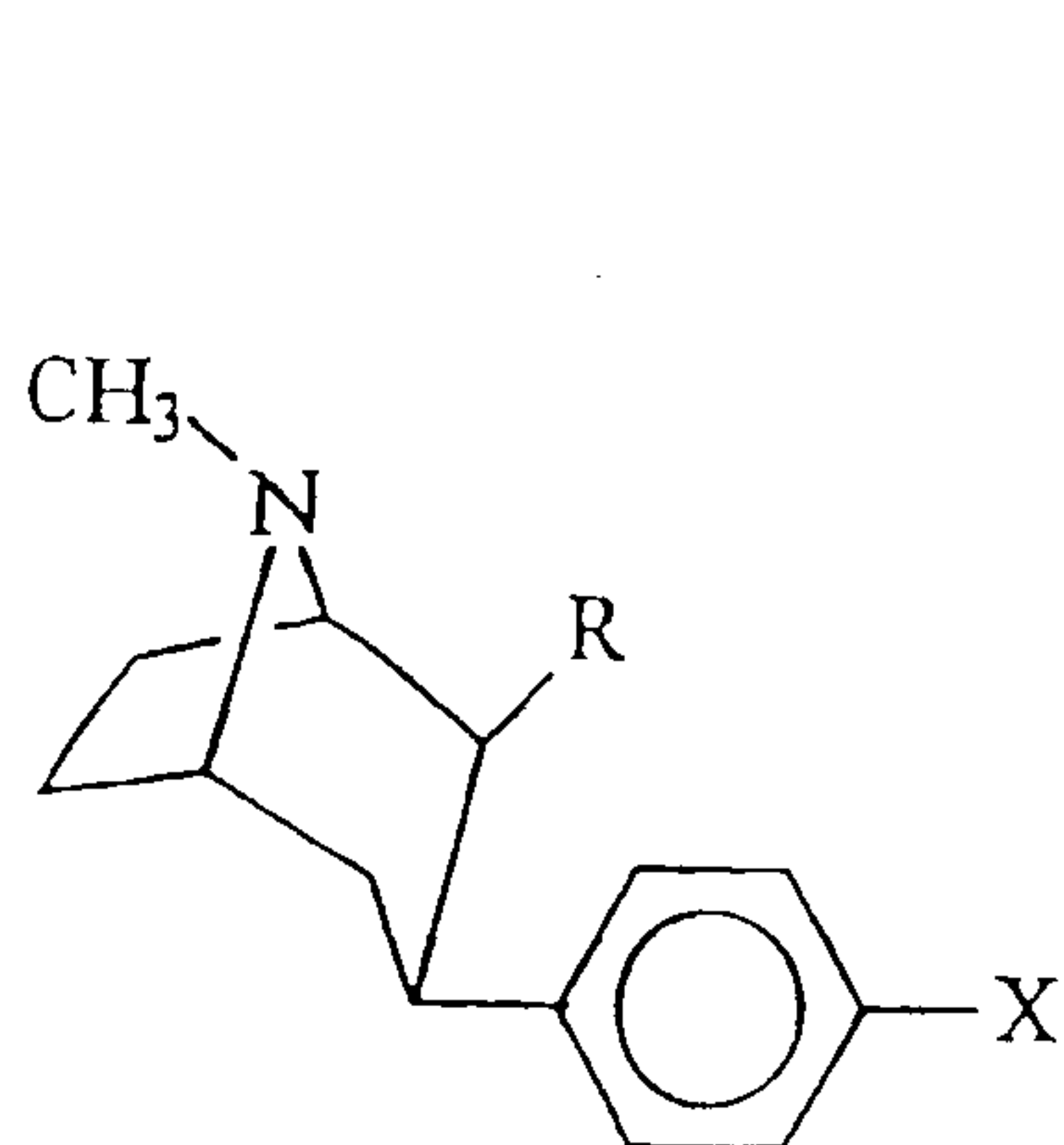
1a, R=CH₃,
X= t-CH₃CH=CH

1b, R=CH₃,
X=CH₃C≡C

1c, R=CH₃,
X=2-naphthyl

1d, R=H,
X=HC≡C

1e, R= CH₂CO₂C₂H₅
X= Cl



The compounds of this invention can be prepared according to the synthesis methods described in U.S. patent No. 5,413,779 and U.S. patent No. 5,128,118. Alternative synthesis for related compounds will be apparent to those of ordinary skill in the art. Particular synthesis schemes are exemplified in U. S. Patent No. 5,444,070. Additional schemes follow hereinbelow.

Preparation of 3 β -(Substituted phenyl)tropane-2 β -heterocyclic Analogues

Chemistry

The known 3 β -(substituted phenyl)-2 β -tropane carboxylic acid (tropane acid) (Carroll et al., *J. Med. Chem.* 35:1813-1817 (1992)) served as the starting material for the synthesis of 2 β -substituted tetrazoles, oxazoles, oxadiazoles, thiazoles, thiadiazoles and benzothiazole as shown in Figure 1.

The tropane acid was refluxed with N-acetyl and benzoic hydrazide in phosphorous oxychloride to obtain the corresponding 5-substituted 1,3,4-oxadiazoles (Afanasiadi et al., *Chem. Heterocyclic Compd.* 397-400 (1995)). N-benzoyl hydrazide amide obtained by the reaction of the acid chloride of tropane acid with N-benzoic hydrazide was cyclized with Lawesson's reagent (El-Barbary et al., *Acta Chimica Scandinavica* 597-601 (1980)) in refluxing THF to the 5-substituted 1,3,4-thiadiazoles. The N-phenylacetyl carboxamide obtained from tropane acid and 2-aminoacetophenone was cyclized by refluxing the amide in phosphorous oxychloride to obtain the required 5-substituted oxazoles (Carroll et al., *Med. Chem. Res.* 3:468 (1993)). Cyclization of the same amide with Lawesson's reagent (El-Barbary et al., 1980) in refluxing THF gave the 5-substituted thiazoles respectively. The benzothiazole was obtained without the cyclization step by the reaction of acid chloride obtained from the appropriate tropane acid with 2-aminothiophenol.

The previously reported carboxamide (Carroll et al., 1993) obtained from the tropane acid was dehydrated with trifluoroacetic acid and pyridine in THF to the nitriles (Campagna et al., *Tet. Letts.* 22:1813-1816 (1977)) as shown in Figure 2. Cycloaddition of trimethylsilylazide to the nitrile afforded the corresponding tetrazoles (Saunders et al., *Med. Chem.* 33:1128-1138 (1990)).

Figure 3 outlines the route used to prepare 3-substituted isoxazole. The known tropane compounds (Carroll et al., *J. Med. Chem.* 34:2719-2725 (1991)) were treated with dilithiated methyl or phenyl acetoneoximes, obtained by the treatment of acetone oxime, or acetophenoneoxime with n-BuLi at 0°C. The corresponding addition product was cyclized without isolation using sulfuric acid at reflux temperature to furnish the required isoxazoles (Saunders et al., 1990).

The therapeutic effects of the present cocaine analogs can be analyzed in various ways, many of which are well known to those of skill in the art. In particular, both *in vitro* and *in vivo*

assay systems may be used for the screening of potential drugs which act as agonists or antagonists at cocaine receptors, or drugs which are effective to modulate neurotransmitter level or activity, in particular by binding to a transporter of that neurotransmitter.

The compounds of the invention may be prepared and labeled with any detectable moiety, in particular a radioactive element, and may then be introduced into a tissue or cellular sample. After the labeled material or its binding partner(s) has had an opportunity to react with sites within the sample, the location and concentration of binding of the compound may be examined by known techniques, which may vary with the nature of the label attached.

Illustrative *in vitro* assays for binding are described in Boja et al *Ann. NY Acad. Sci.* 654:282-291 (1992), which is incorporated herein by reference in its entirety. A particularly preferred *in vitro* assay involves the ability of a compound in question to displace the binding of a known labeled compound at binding sites in a tissue sample, isolated membranes or synaptosomes. Alternatively, the compounds may be analyzed by their ability to inhibit reuptake of a labelled neurotransmitter in a sample, in particular, in synaptosomes.

The compound or its binding partner(s) can also be labeled with any detectable moiety, but are preferably labelled with a radioactive element. The radioactive label can be detected by any of the currently available counting procedures, including the imaging procedures detailed in the disclosures of the parent applications. The preferred isotope may be selected from ^3H , ^{11}C , ^{14}C , ^{32}P , ^{35}S , ^{36}Cl , ^{51}Cr , ^{57}Co , ^{58}Co , ^{59}Fe , ^{90}Y , ^{125}I , ^{131}I , and $^{186}\text{Re.c}$,

As noted in the parent disclosures, the binding of the labelled compounds may be analyzed by various imaging techniques, including positron emission tomography (PET), single photon emission computed tomography (SPECT), autoradiogram, and the like. Such imaging techniques are useful for determining effective doses of new drug candidates. By performing *in vivo* competition studies, it is possible to use brain imaging studies to determine the oral doses of new drug candidates, which produce significant receptor occupancy in the brain. *In vivo* displacement studies which determine *in vivo* IC₅₀'s which in turn reflect doses that occupy receptors *in vivo* are described in Cline et al ((1992) *Synapse* 12:37-46). In addition to its uses in determining *in vivo* potency/occupancy, these same brain imaging methods can be used to determine rate of entry of compounds into the brain (Stathis et al (1995) *Psychopharmacology* 119:376-384) and duration of action (Volkow et al (1995) *Synapse* 19:206-211).

The binding of the compounds of the invention may be at any location where a receptor for a particular psychostimulant is present, and more specifically, any location where a dopamine or serotonin transporter is present. Such locations are in general any area comprising a part of

the dopamine or serotonin pathway, in particular at synapses. Examples of locations known to be associated with dopamine transport include the cerebral cortex, hypothalamus, substantia nigra, nucleus accumbens, arcuate nucleus, anterior periventricular nuclei, median eminence and amygdala. Examples of locations known to be associated with serotonin include the striatum, cerebral cortex, hypothalamus, Raphe nuclei, pre-optic area and suprachiasmatic nucleus.

By "psychostimulant" is meant any compounds whose abuse is dependent upon mesolimbic and mesocortical dopaminergic pathways. In particular, psychostimulant relates to cocaine. However, the compounds of the invention may also be used to treat abuse of compounds not traditionally classified as "psychostimulants," but which act at a dopamine or serotonin transporter. Such abused compounds include ethanol and nicotine.

For *in vivo* studies, the compounds of the invention may be prepared in pharmaceutical compositions, with a suitable carrier and at a strength effective for administration by various means to a patient experiencing an adverse medical condition associated with cocaine receptor binding or neurotransmitter release and reuptake, for the treatment thereof. The action of the compounds may be analyzed by the imaging methods noted above, and also by behavioral studies. In particular, the pharmaceutical effects of the compounds of the invention may be reflected in locomotor activity, including the induction of ipsilateral rotation, stereotyped sniffing and the "swim test", in schedule-controlled operant behavior (i.e., response for food or shock termination) or drug self-administration. In general, maximal behavioral effects are seen at near complete occupancy of transporter sites. Such protocols are described in Boja et al (1992), Balster et al *Drug and Alcohol Dependence* 29:145-151 (1991), Cline et al *Pharm. Exp. Ther.* 260:1174-1179 (1992), and Cline et al *Behavioral Pharmacology* 3:113-116 (1992).

A variety of administration techniques may be utilized, among them oral or parenteral techniques such as subcutaneous, intravenous, intraperitoneal, intracerebral and intracerebroventricular injections, catheterizations and the like. Average quantities of the compounds may vary in accordance with the binding properties of the compound (i.e., affinity, onset and duration of binding) and in particular should be based upon the recommendations and prescription of a qualified physician or veterinarian.

The compounds of the invention preferably have a long duration of action, which is important to facilitate dosing schedules. In rats, the present compounds have a 7-10 fold longer duration of action than cocaine (Fleckenstein et al, "Highly potent cocaine analogs cause long-

lasting increases in locomotor activity, "*Eur. J. Pharmacol.*, 1996, vol. 311, n° 2-3, p.109-114. In addition, the present compounds also preferably have a slow rate of entry into the brain, which is important in decreasing the potential for abuse (Stathis et al, *supra*). The present compounds enter the brain more slowly than cocaine.

The therapeutic compositions useful in practicing the therapeutic methods of this invention may include, in admixture, a pharmaceutically acceptable excipient (carrier) and one or more of the compounds of the invention, as described herein as an active ingredient.

10

The preparation of therapeutic compositions which contain such neuroactive compounds as active ingredients is well understood in the art. Such compositions may be prepared for oral administration, or as injectables, either as liquid solutions or suspensions, however, solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, and pH buffering agents which enhance the effectiveness of the active ingredient. The compounds of the invention can be formulated into the therapeutic composition as neutralized pharmaceutically acceptable salt forms.

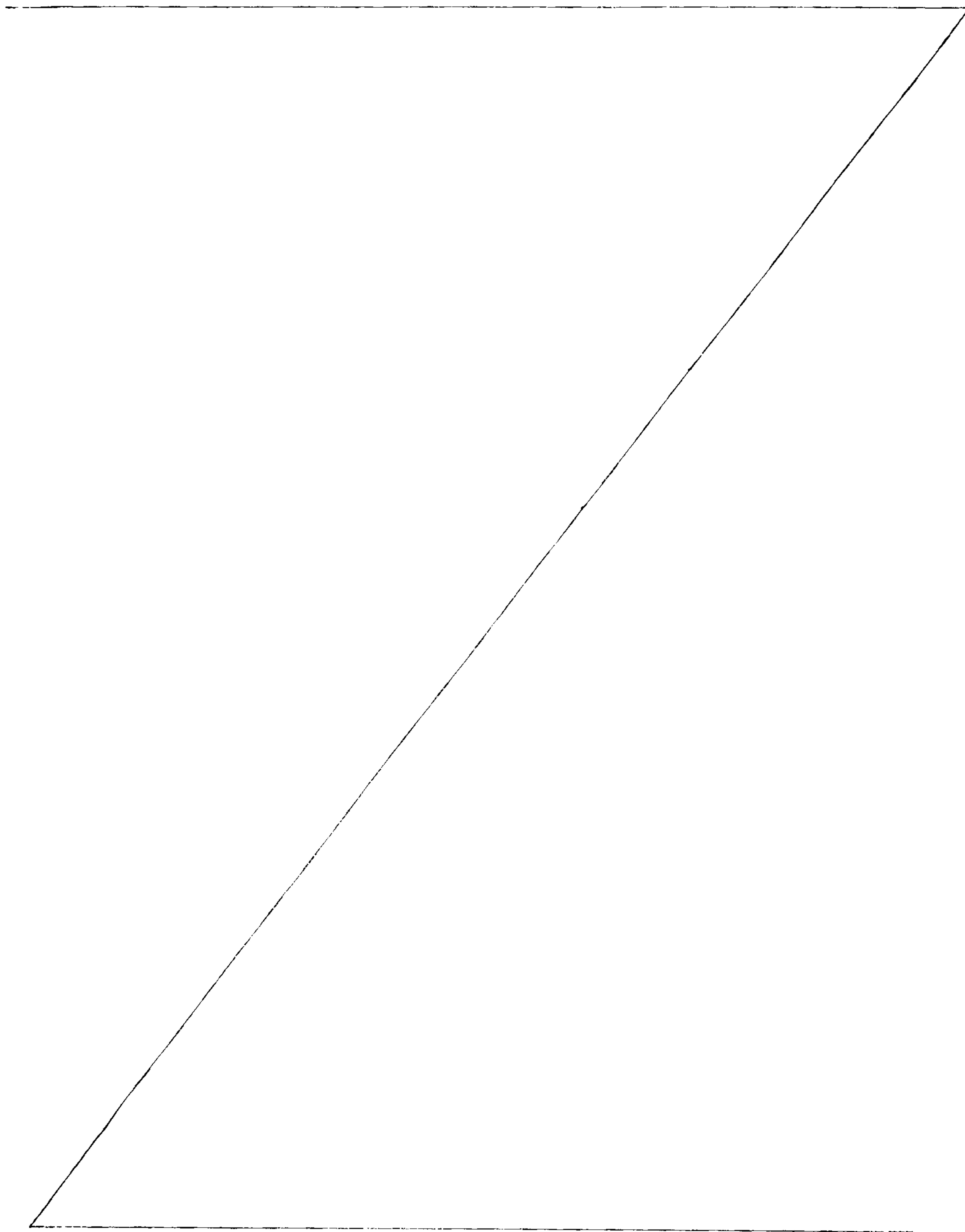
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The therapeutic compositions are conventionally administered orally, by unit dose, for example. The term "unit dose" when used in reference to a therapeutic composition of the present invention refers to physically discrete units suitable as unitary dosage for humans, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluent; i.e., carrier, or vehicle.

30

The compositions are administered in a manner compatible with the dosage formulation, and in a therapeutically effective amount. The quantity to be administered depends on the subject to be treated, the presence of other agonists and antagonists in the subject's system, and degree of binding or inhibition of binding desired. Precise amounts of active ingredient required to be administered depend on the judgment of the practitioner and are peculiar to each individual.

However, suitable dosages may range from about 0.01 to about 1000, preferably about .25 to about 500, and more preferably 10 to 50 milligrams of active ingredient per kilogram body weight of individual per day and depend on the route of administration. However, the exact dosage must be determined by factoring in rate of degradation in the stomach, absorption from



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the stomach, other medications administered, etc. Suitable regimes for administration are also variable, but are typified by an initial administration followed by repeated doses at one or more hour intervals by a subsequent injection or other administration. Alternatively, continuous intravenous infusion sufficient to maintain appropriate concentrations in the blood are contemplated.

The compounds of the present invention may be administered for their activities as surrogate agonist medications for cocaine, nicotine, alcohol, amphetamine and other psychostimulant abuse. Because of their favorable binding characteristics to transporters of neurotransmitters, they may be used for inhibiting the uptake of dopamine, norepinephrine, serotonin and other monoamines. The compounds of the present invention may find use as antipsychotics, antidepressants, local anesthetics, anti-Parkinsonian agents, anti-obesity drugs, drugs useful in the treatment of bipolar disorder, eating disorders, obesity, attention deficit disorder, panic attacks and disorder, obsessive-compulsive disorder, sexual dysfunction, as anticholinergic agents and as sigma receptor drugs.

The compounds of the invention may also be useful in treating neurodegenerative disorders, in particular for treating Parkinson's Disease, but also may be useful in the treatment of cocaine, nicotine and alcohol addiction.

The preferred compounds of the present invention are derived from the series of compounds designated RTI-4229. The physical properties of some of these compounds are given in Table I.

Table 1 Physical Properties of 2β-substituted Heterocyclic Analogs of 3β-(4-Substituted-phenyl) Tropane and Cocaine

<u>Code Name</u>	<u>Molecular Formulae²</u>	<u>mp °C</u>	<u>[α]_D (c) MeOH</u>	<u>Yield %</u>
RTI-188	C ₂₂ H ₂₃ Cl ₂ N ₃ O ^e	160-162	+84.59(0.36)	42
RTI-195	C ₂₃ H ₂₆ CN ₃ O ^e	175-178	+97.22 (0.25)	40
RTI-194	C ₁₈ H ₂₄ _{CN} ³ O ^d	146(dec)	-43.05(0.15)	58
RTI-200	C ₂₂ H ₂₃ Cl ₂ N ₃ S ^e	165-170	-42.81 (0.16)	58
RTI-199	C ₂₃ H ₂₆ CN ₃ S ^d	180-185	-33.50 (0.20)	58
RTI-189	C ₂₇ H ₂₉ CN ₂ O ₇ ^{b,e}	126 (dec)	+101.43(0.21)	49
RTI-178	C ₂₉ H ₃₂ N ₂ O ₇ ^{b,f}	175-181	-104.04(0.60)	72
RTI-219	C ₂₃ H ₂₄ CN ₂ S ^f	228-230	+27.43(0.11)	30
RTI-202	C ₂₁ H ₂₂ Cl ₂ N ₂ S ^e	140-150(dec)	-172.49(0.28)	41

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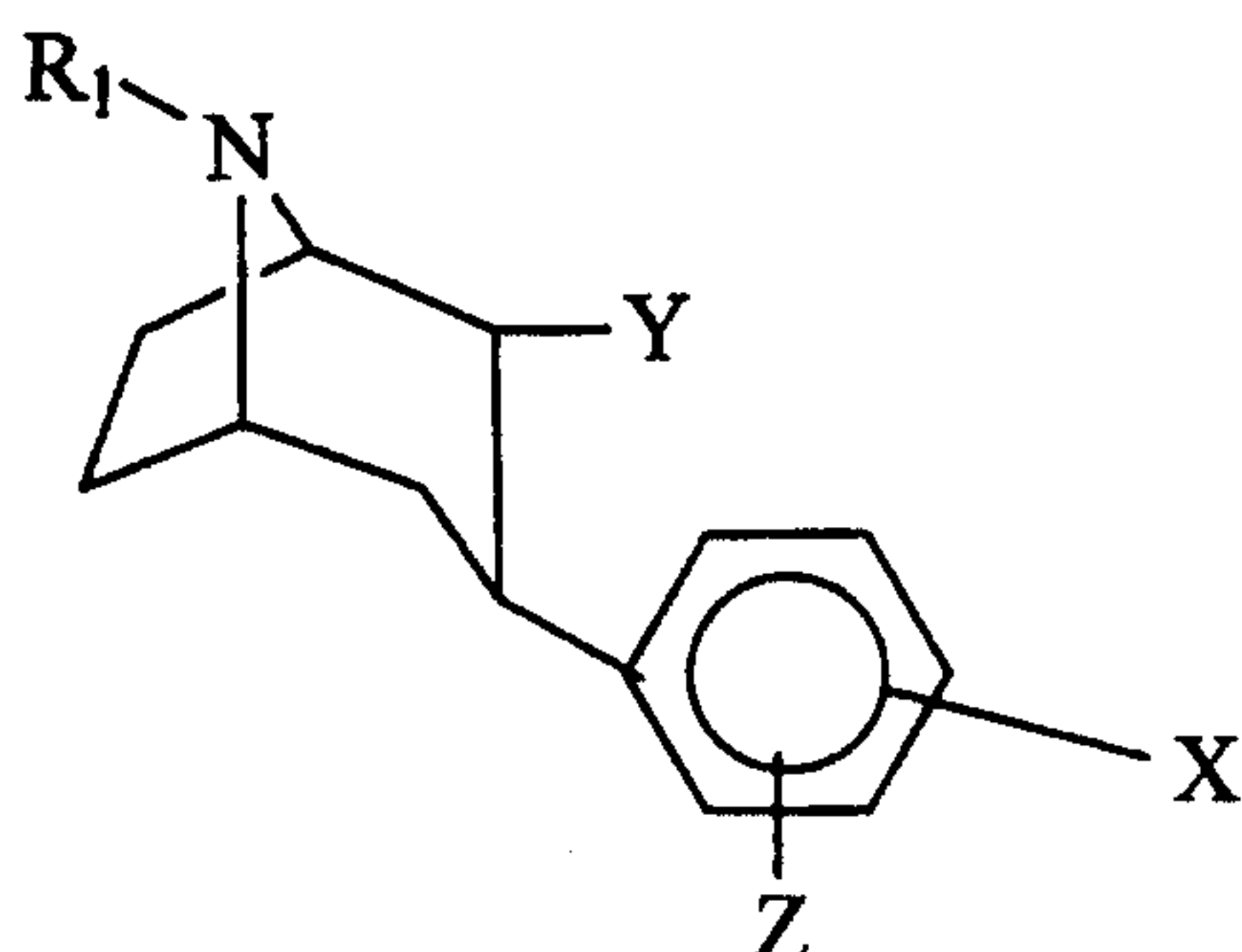
RTI-161	$C_{15}H_{18}Cl_2N_2^e$	>220(dec)	-71.00(0.50)	77
RTI-158	$C_{16}H_{21}CN_2$	270(dec)	-76.40(0.50)	67
RTI-163	$C_{15}H_{18}CN_5^e$	296-300	-124.94 (0.39)	33
RTI-157	$C_{16}H_{23}Cl_2N_5^e$	<212(dec)	-110.97 (0.16)	88
RTI-165	$C_{18}H_{22}Cl_2N_2O$	235(dec)	-102.89(0.46)	46
RTI-171	$C_{19}H_{25}CN_2O$	277	-107.28(0.71)	62
RTI-180	$C_{18}H_{22}CN_2O^e$	<235(dec)	-94.57(0.39)	49
RTI-177	$C_{23}H_{24}Cl_2N_2O^e$	287	-97.50(0.28)	50
RTI-176	$C_{24}H_{27}CN_2O$	270-295(dec)	-102.22(0.68)	77
RTI-181	$C_{23}H_{24}O_3^{CN_2d}$	<2679(dec)	-91.11(0.43)	56
RTI-184	$C_{19}H_{23}CN_2O_3^d$	117-121	-53.60 (0.25)	82
RTI-185	$C_{24}H_{25}CN_2O_3$	205	-56.71(0.43)	68

a. HCl Salt; b. Tartrate Salt c. 0.25 mol water; d. 0.5 mol water; e. 0.75 mol water;
f. 1 mol water.

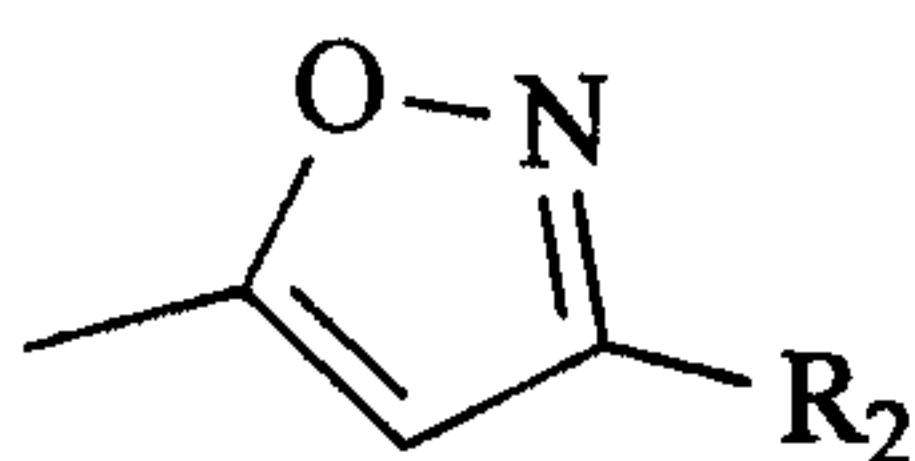
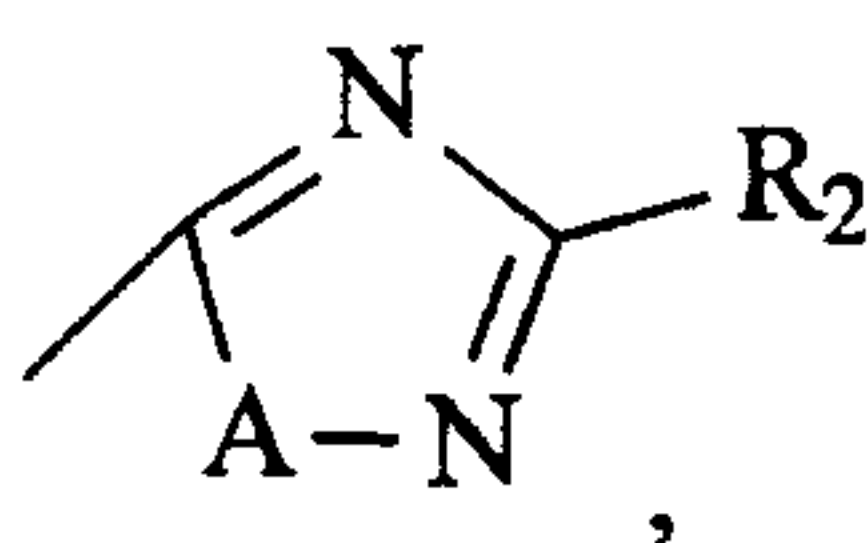
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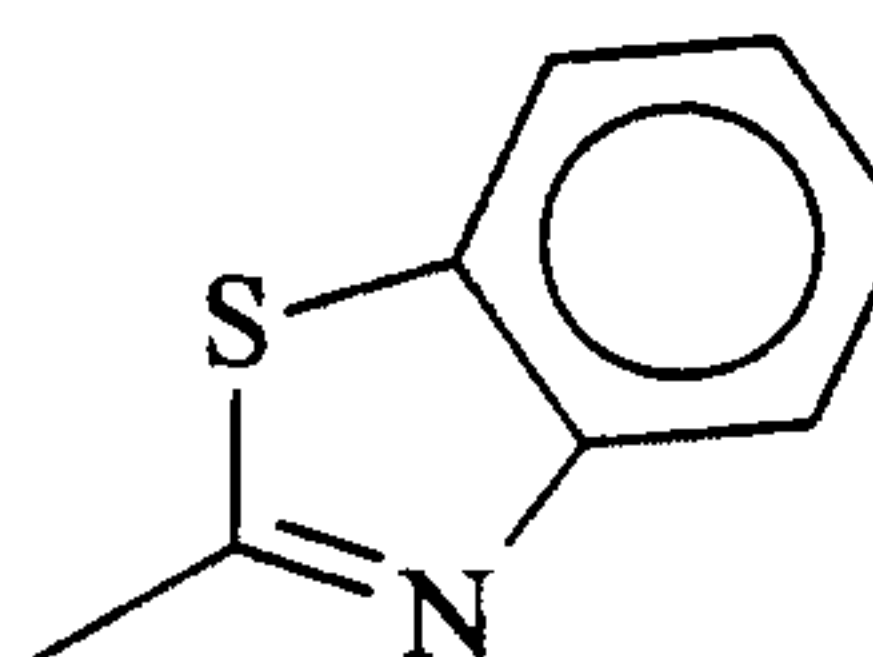
Many of the preferred compounds of the invention fall within the broad class of compounds described by the formula:



wherein $Y = CH_2R_3$, CO_2R_2 , $CONRR^1$,

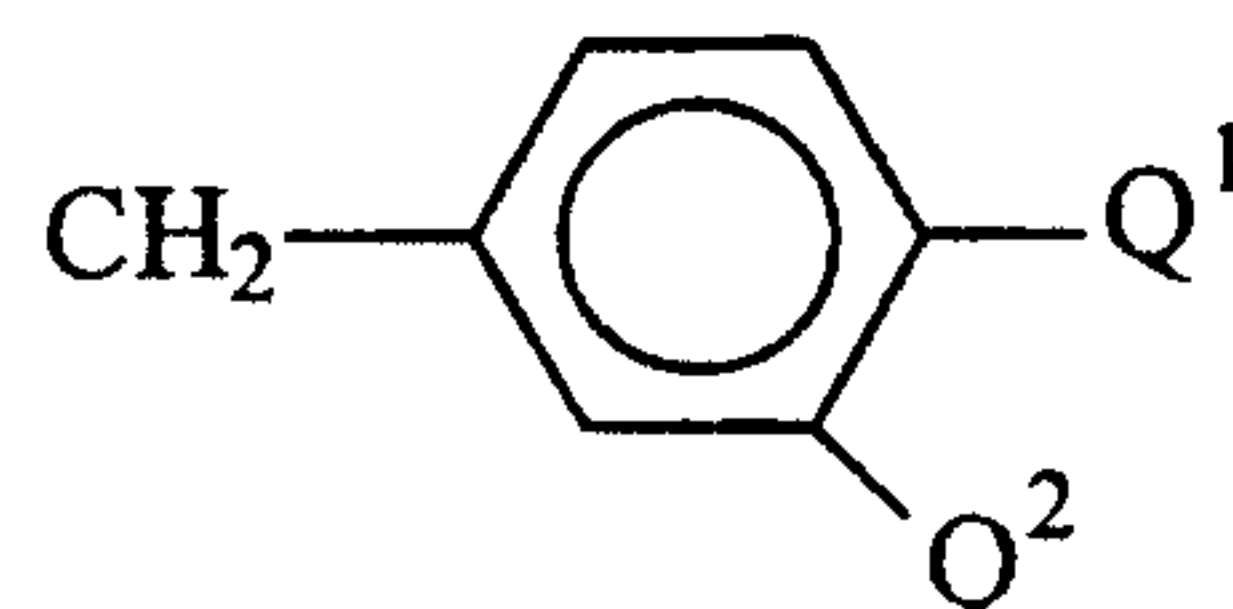


or



$R_1 =$ hydrogen, C_{1-5} alkyl,

$R_2 =$ hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkoxy, C_{1-6} alkynyl, halogen, amine, $CH_2C_6H_5$, $(CH_2)_2C_6H_5$, $(CH_2)_3C_6H_5$ or



$R_3 =$ OH, hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkoxy, Cl, Br, I, CN, NH_2 , NHC_{1-6} alkyl, NC_{1-6} alkyl, $OCOC_{1-6}$ alkyl, $OCOC_{1-3}$ alkylaryl,

$A =$ S, O or N

$X =$ H, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkoxy, C_{1-6} alkynyl, halogen, amino, acylamido, C_2H_5 , $CH_2CH_3CH_3$, $CH(CH_3)_2$,

$Z =$ H, I, Br, Cl, F, CN, CF_3 , NO_2 , N_3 , OR_1 , $CONH_2$, CO_2R_1 , C_{1-6} alkyl, NR_4R_5 , $NHCOR_5$, $NHCO_2R_6$, and

Q^1 and Q^2 may be the same or different and = H, OCH_3 , or Cl,

wherein R_4-R_6 are each C_{1-6} alkyl, R and R^1 are independently H, C_{1-6} alkyl, C_{1-6} alkene, C_{1-6} alkyne, phenyl, phenyl substituted with 1-3 of C_{1-6} alkyl, alkene, alkyl or alkoxy, C_{1-6} alkoxy,

phenoxy, amine, amine substituted with 1-2 of C₁₋₆ alkyl, alkene, alkyne, alkoxy or phenyl or phenoxy or R and R¹ may combine to form heterocyclic structure including pyrrolidinyl, piperidinyl and morpholino moieties, unsubstituted or substituted with 1-2 C₁₋₆ alkyl, alkene, alkyne or alkoxy groups.

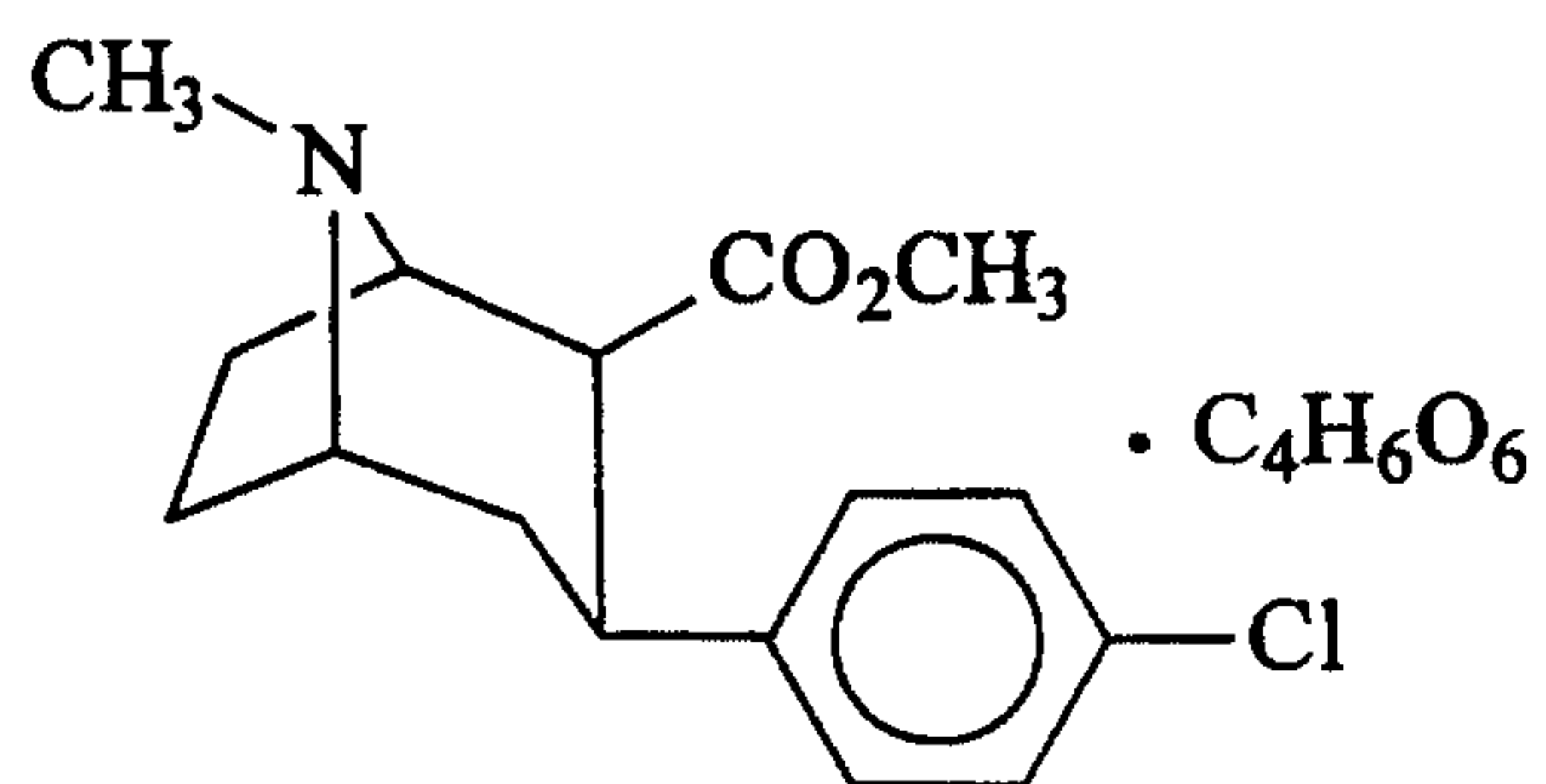
The present inventors have surprisingly found that certain of the RTI-4229 series of compounds are particularly potent pharmaceutical agents in accordance with the present invention.

Preferred compounds of the RTI-4229 series include the following: RTI-4229-31, 32, 51, 55, 83, 96, 97, 98, 101, 105, 108, 110, 111, 112, 116, 121, 122, 123, 127, 132, 139, 140, 142, 145, 146, 147, 150, 153, 173, 178, 188, 189, 190, 191, 193, 195, 199, 200, 203, 204, 205, 206, 214, 219, 230, 239, 240, 241, 242, 243, 251, 252, 274, 277, 278, 279, 280, 281, 282, 283, 286, 287, 296, 304, 305, 307, 309, 318, 330 and 422. The chemical structures of these compounds, along with their IC₅₀ values for inhibition of radioligand binding are given below. DA is dopamine, 5-HT is 5-hydroxytryptamine (serotonin), and NE is norepinephrine, DA=[³H]WIN 35,428; 5-HT = [³H] paroxetine and NE_N = [³H] nisofetine:

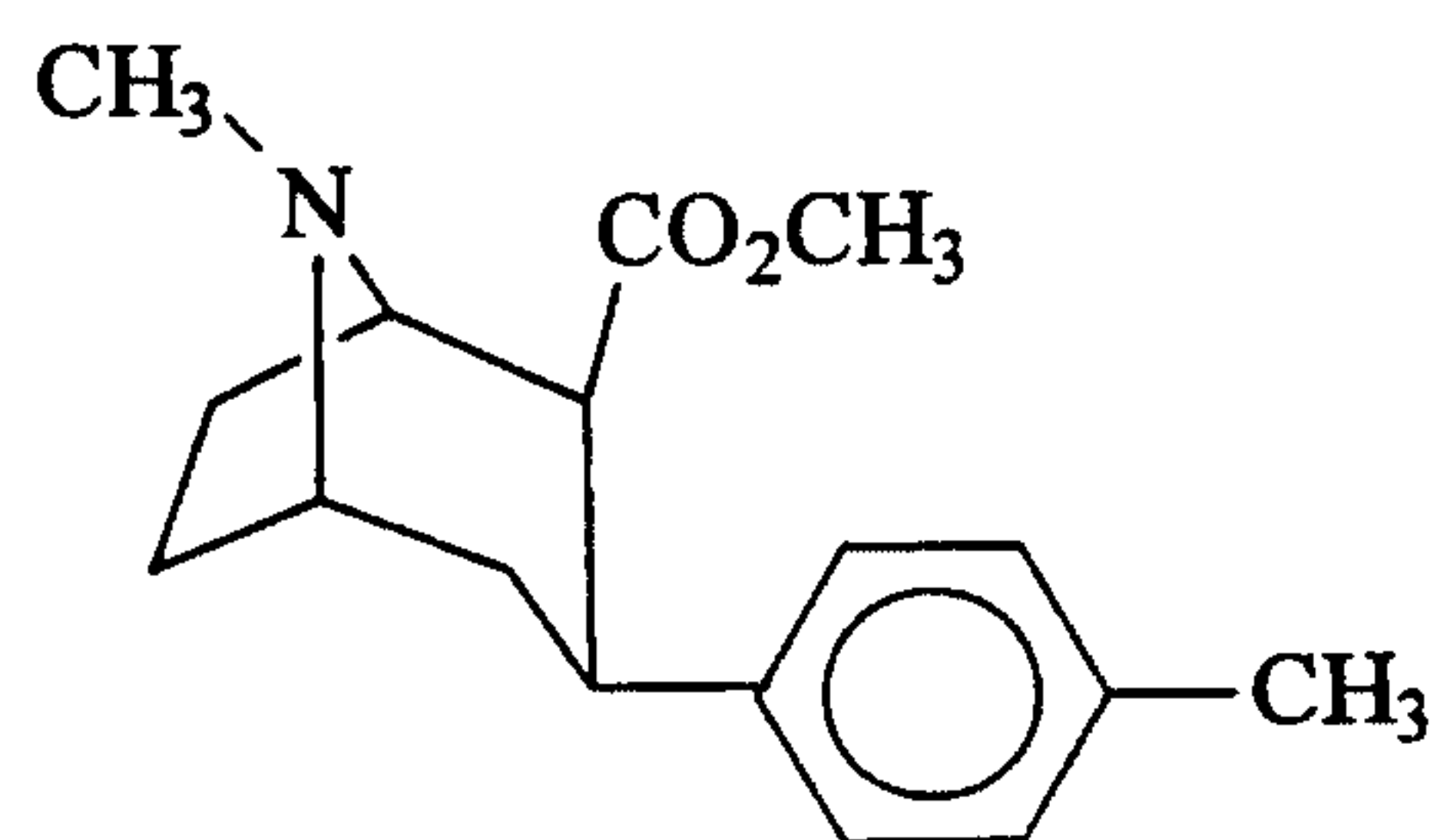
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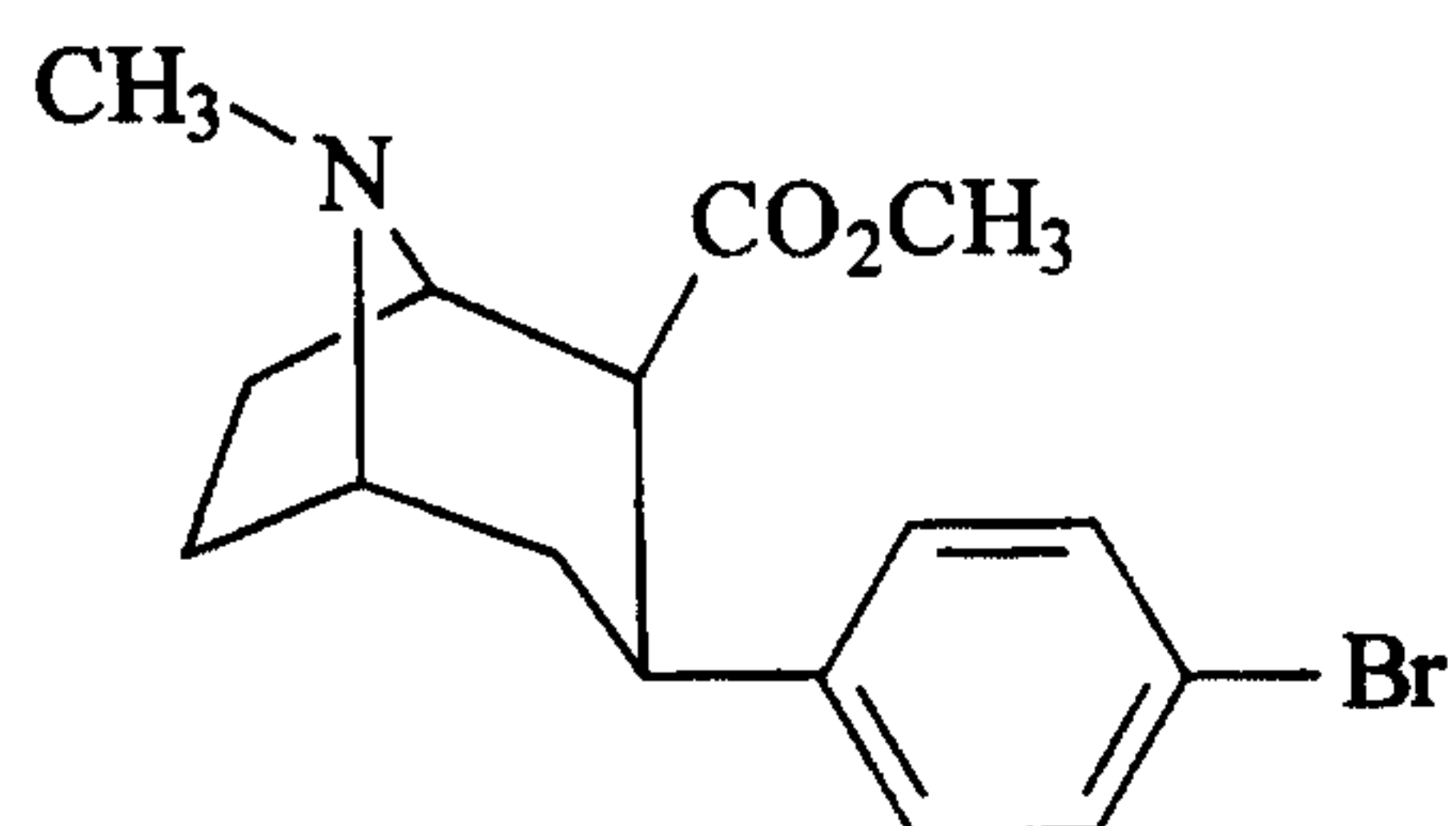
RTI-4229-31

DA 1.12 ± 0.1 5-HT 44.5 ± 1.34 NE_N 37 ± 2.1 

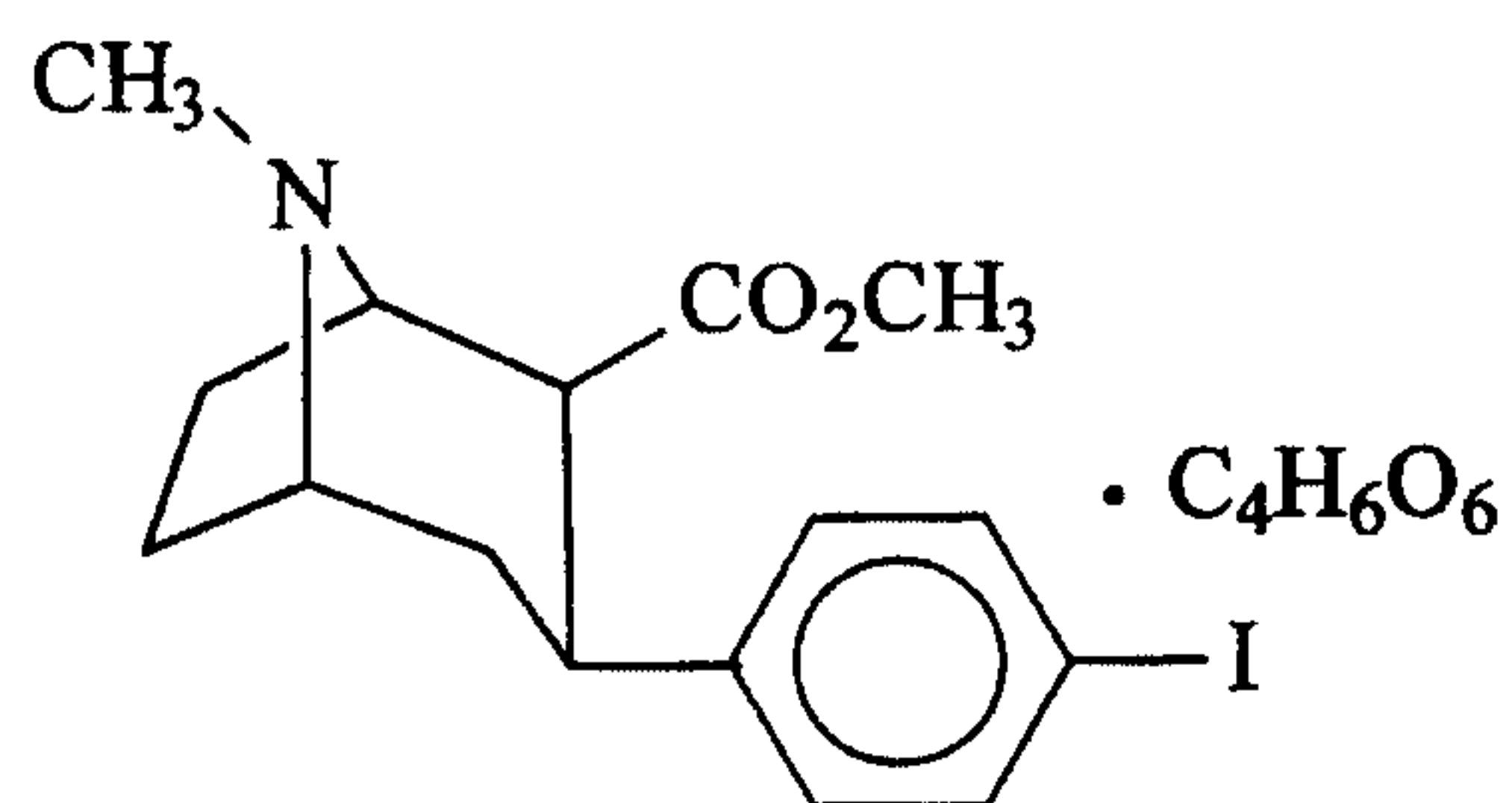
RTI-4229-32

DA 1.71 ± 0.31 5-HT 240 ± 27 NE_N 60 ± 0.53 

RTI-4229-51

DA 1.69 ± 0.23 5-HT 240 ± 0.24 NE_N 37.4 ± 5.2 

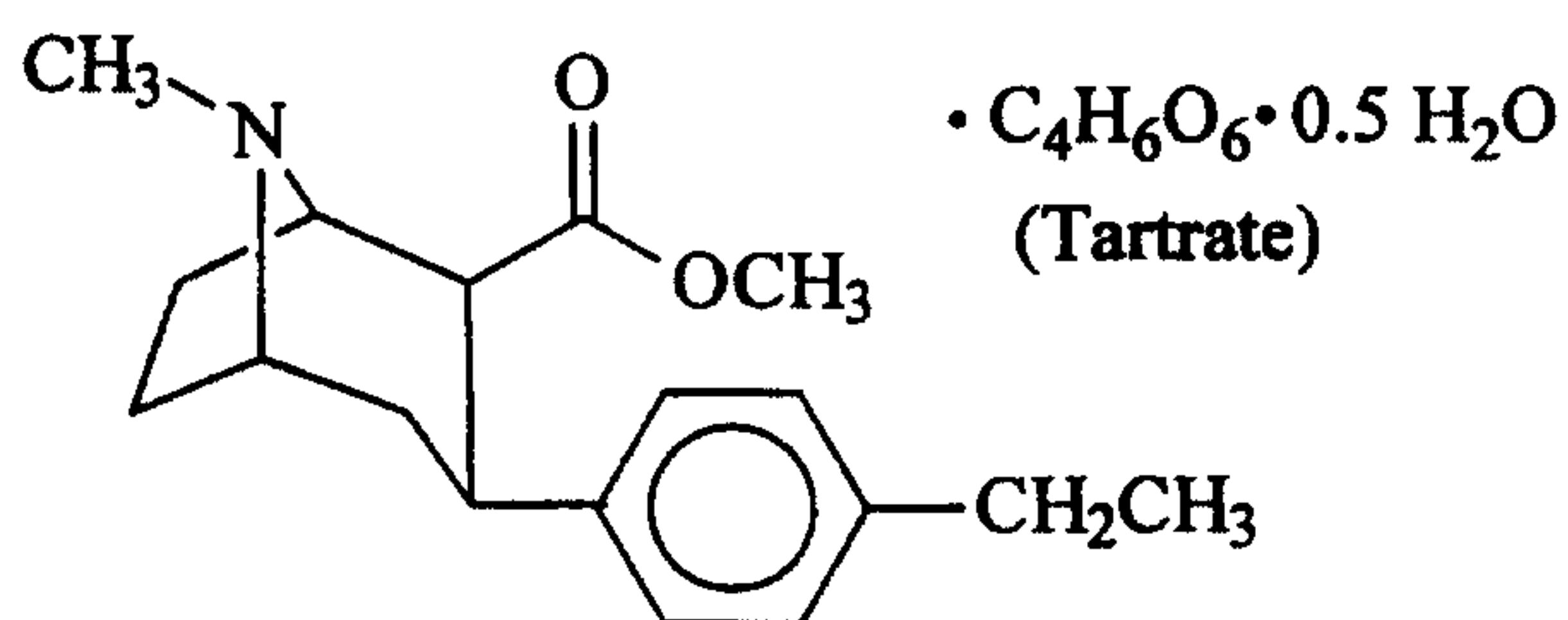
RTI-4229-55

DA 1.26 ± 0.04 5-HT 4.21 ± 0.34 NE_N 36 ± 3 

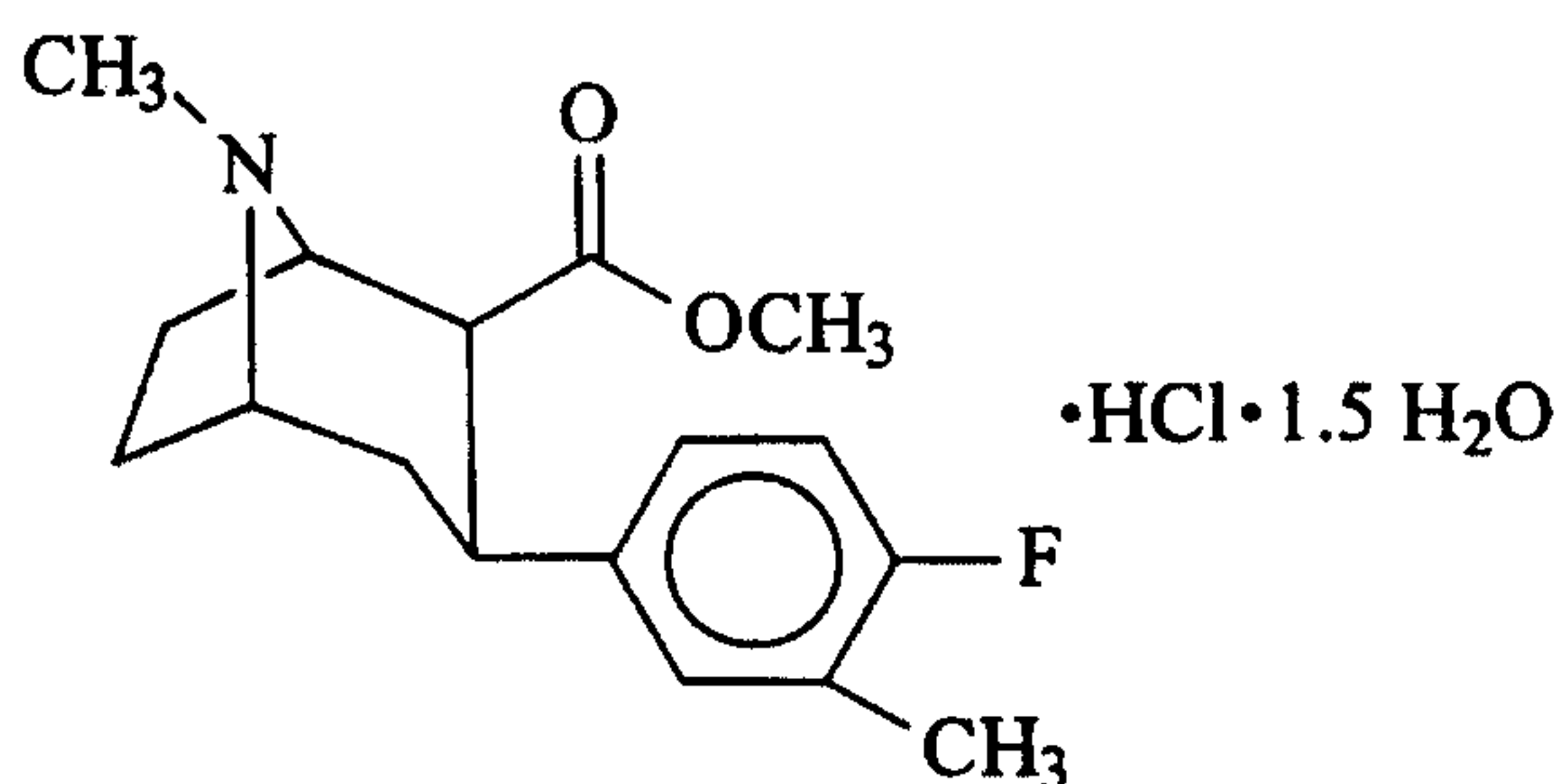
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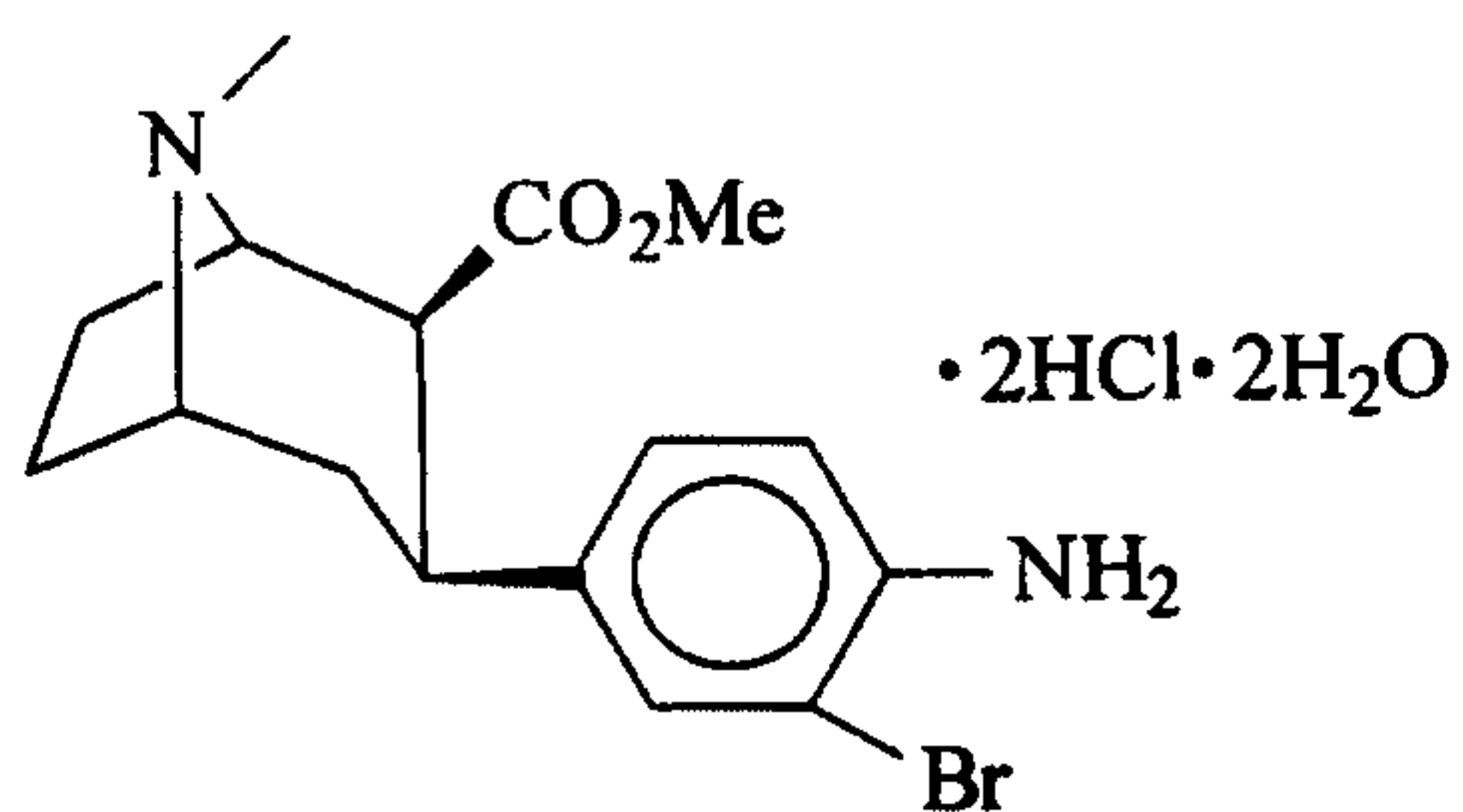
RTI-4229-83

DA 55 ± 2 5-HT 28.4 ± 3.83 NE_N $4.027.87 \pm 380.70$ 

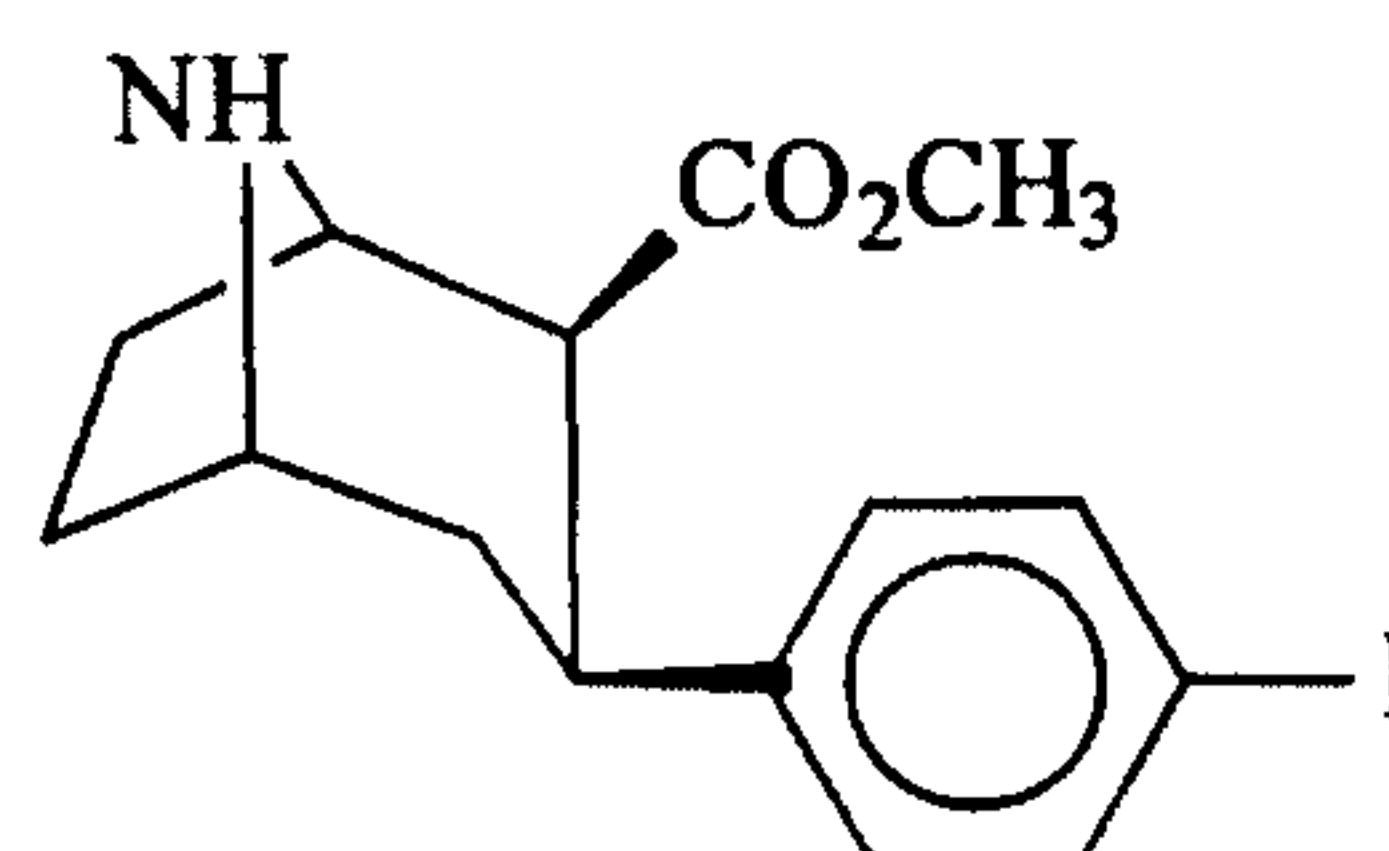
RTI-4229-96

DA 2.95 ± 0.58 5-HT 76 ± 2.8 NE_N 520 ± 10.4 

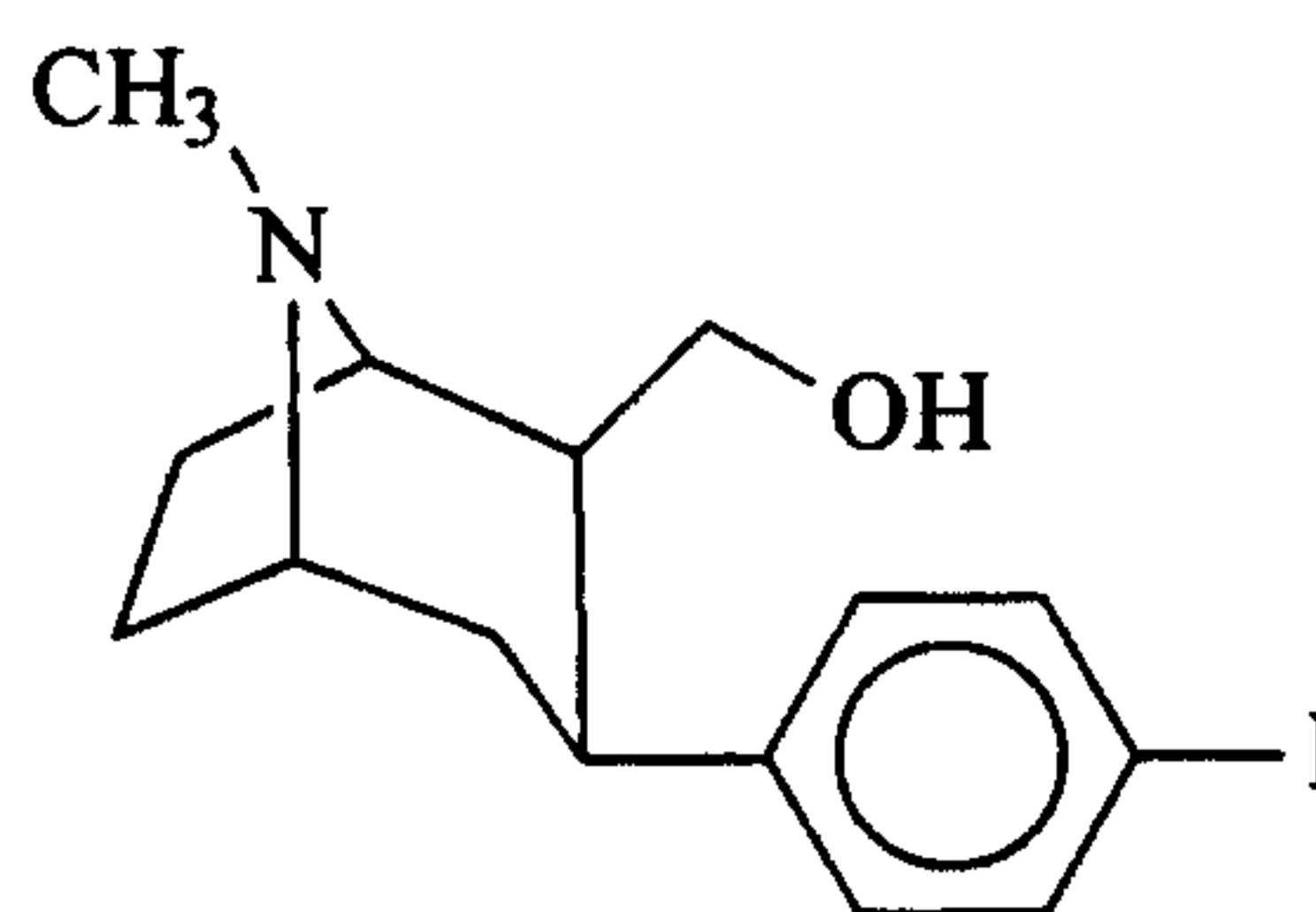
RTI-4229-97

DA 3.91 ± 0.59 5-HT 181 ± 14 NE_N 282 ± 30 

RTI-4229-98

DA 0.69 ± 0.2 5-HT 0.36 ± 0.047 NE_N 10.97 ± 0.88 

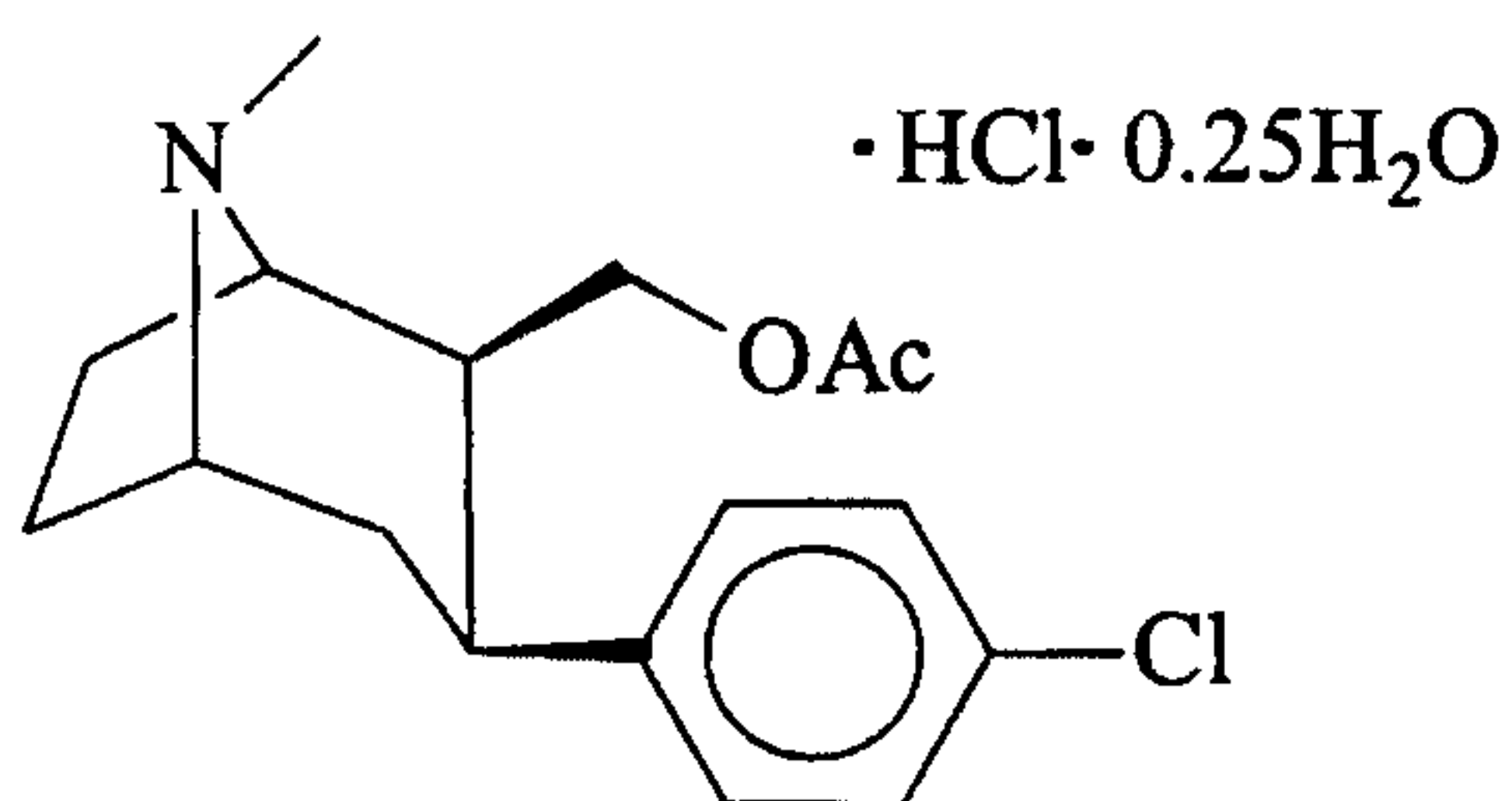
RTI-4229-101

DA 2.2 ± 0.19 5-HT 26 ± 3.2 NE_N $\pm$ 

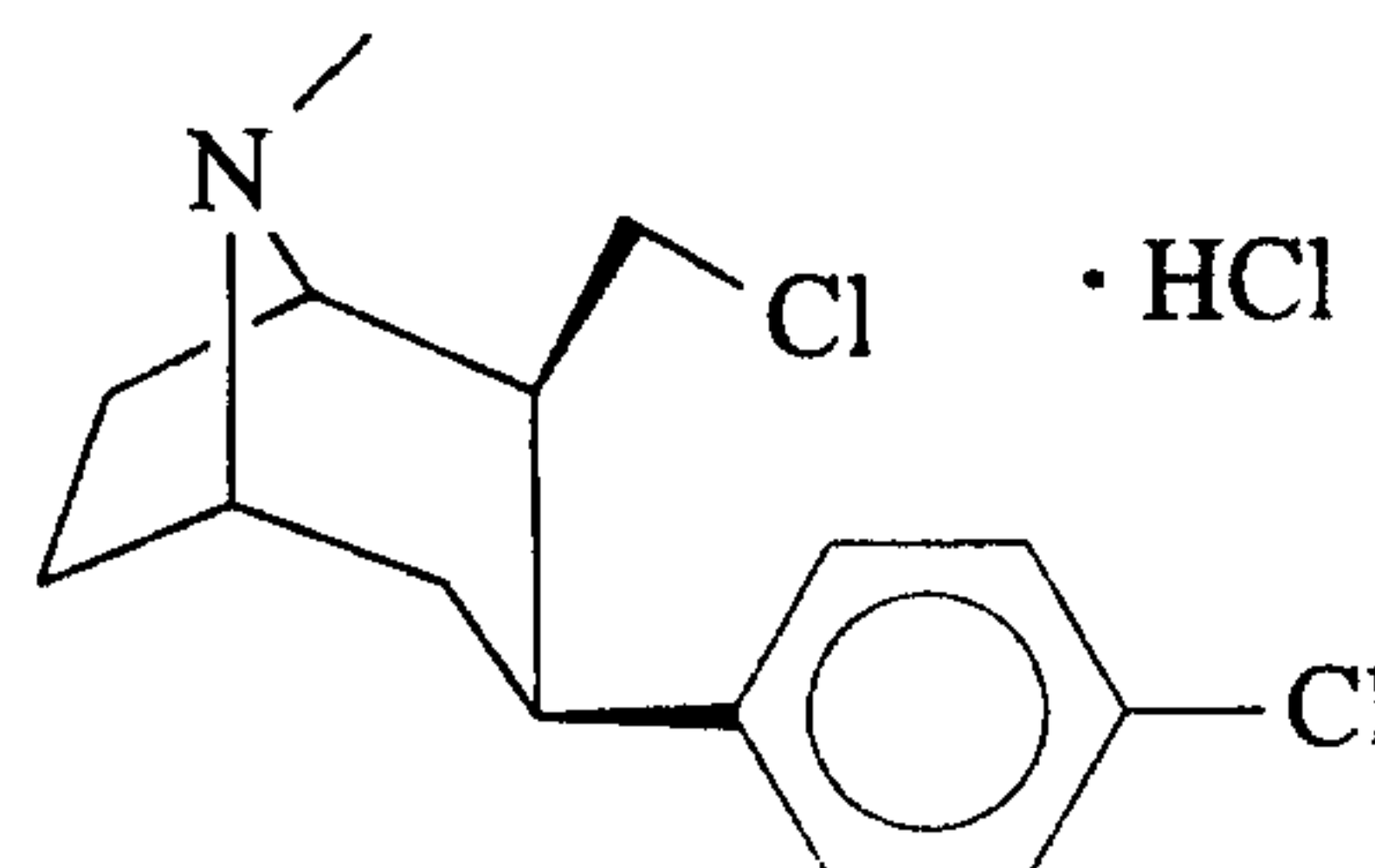
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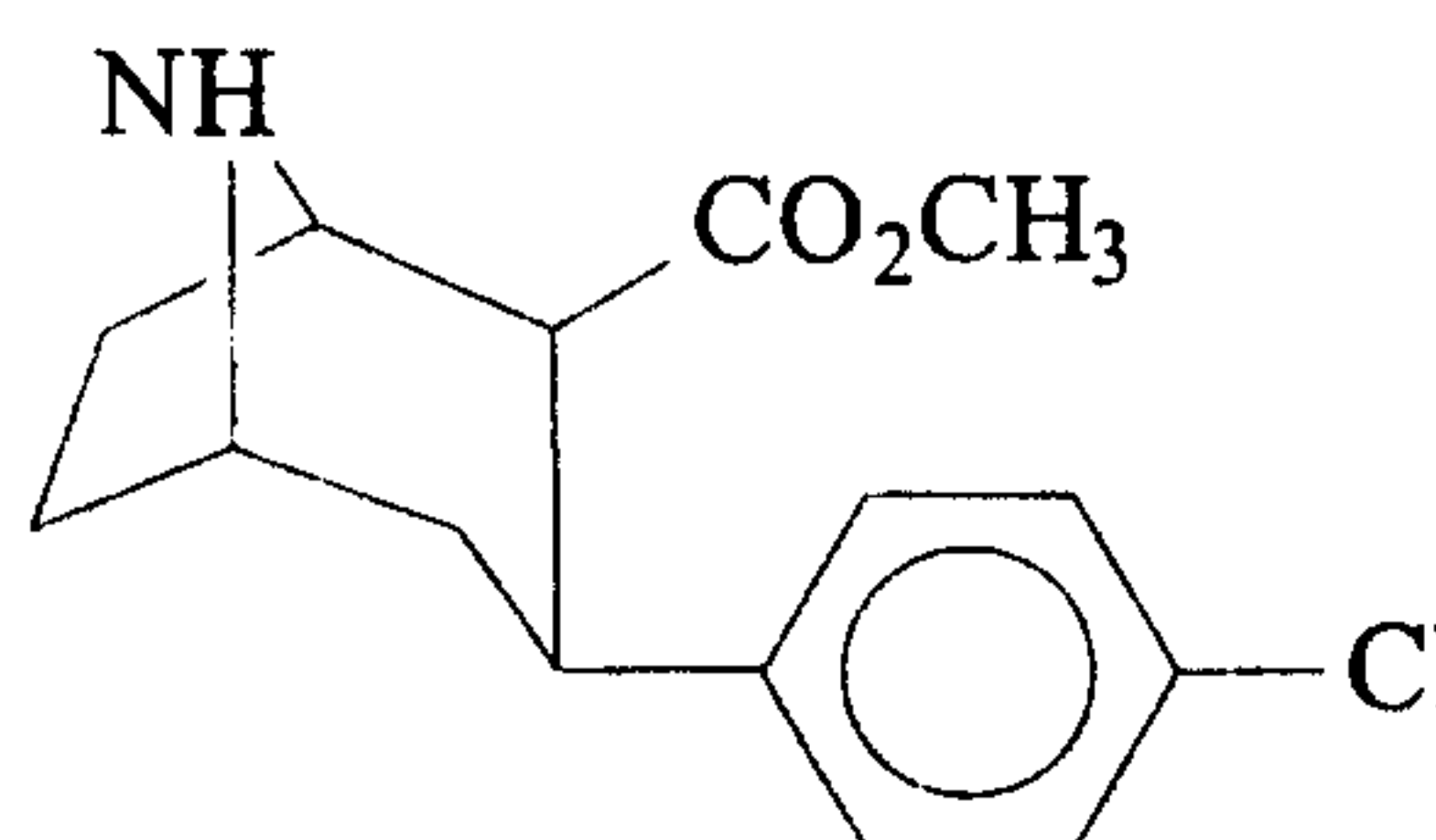
RTI-4229-105

DA 1.60 ± 0.05 5-HT 1.43 ± 25 NE_N 127.2 ± 5.9 

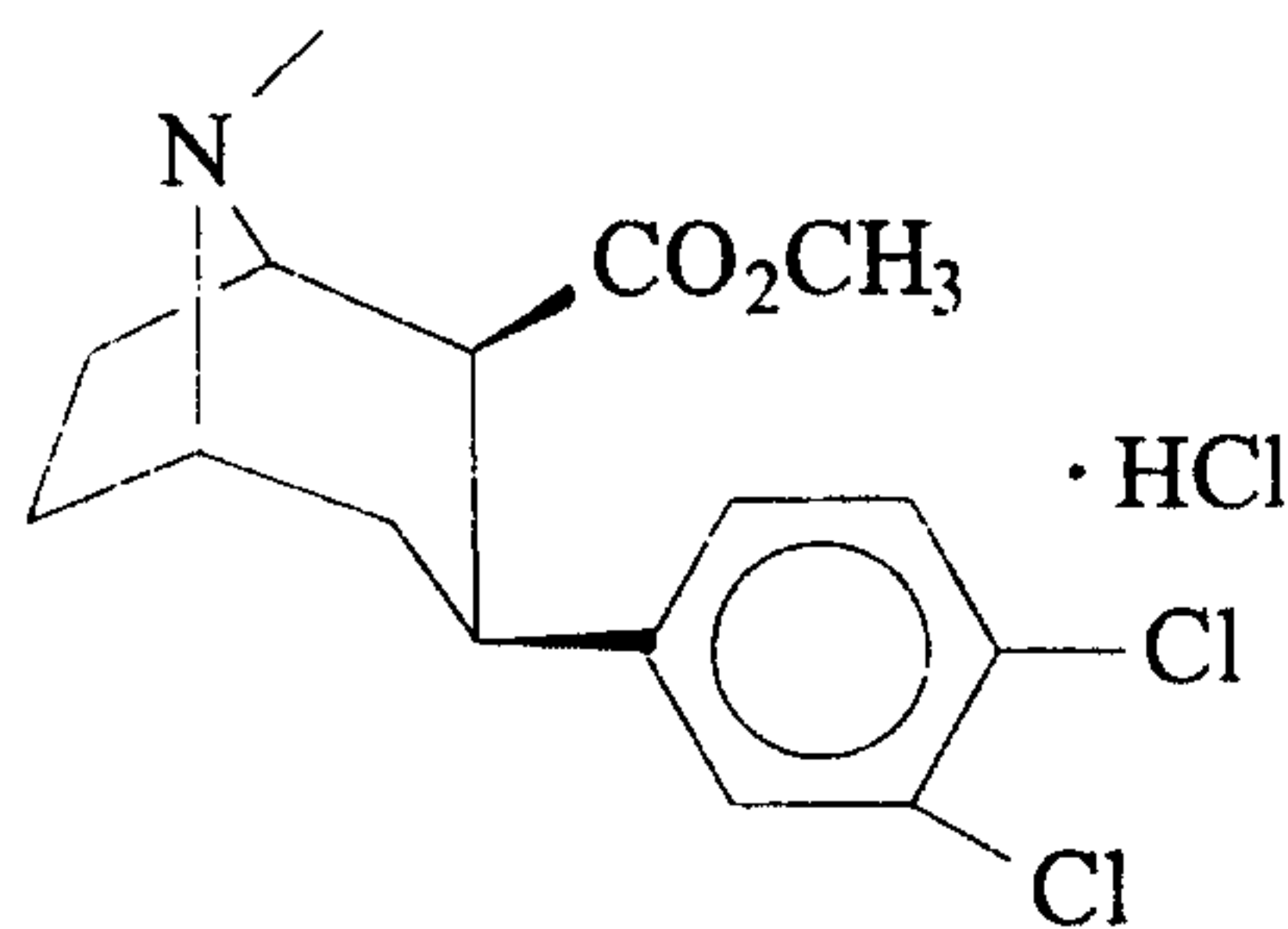
RTI-4229-108

DA 2.64 ± 0.31 5-HT 98 ± 8.7 NE_N 129.3 ± 15 

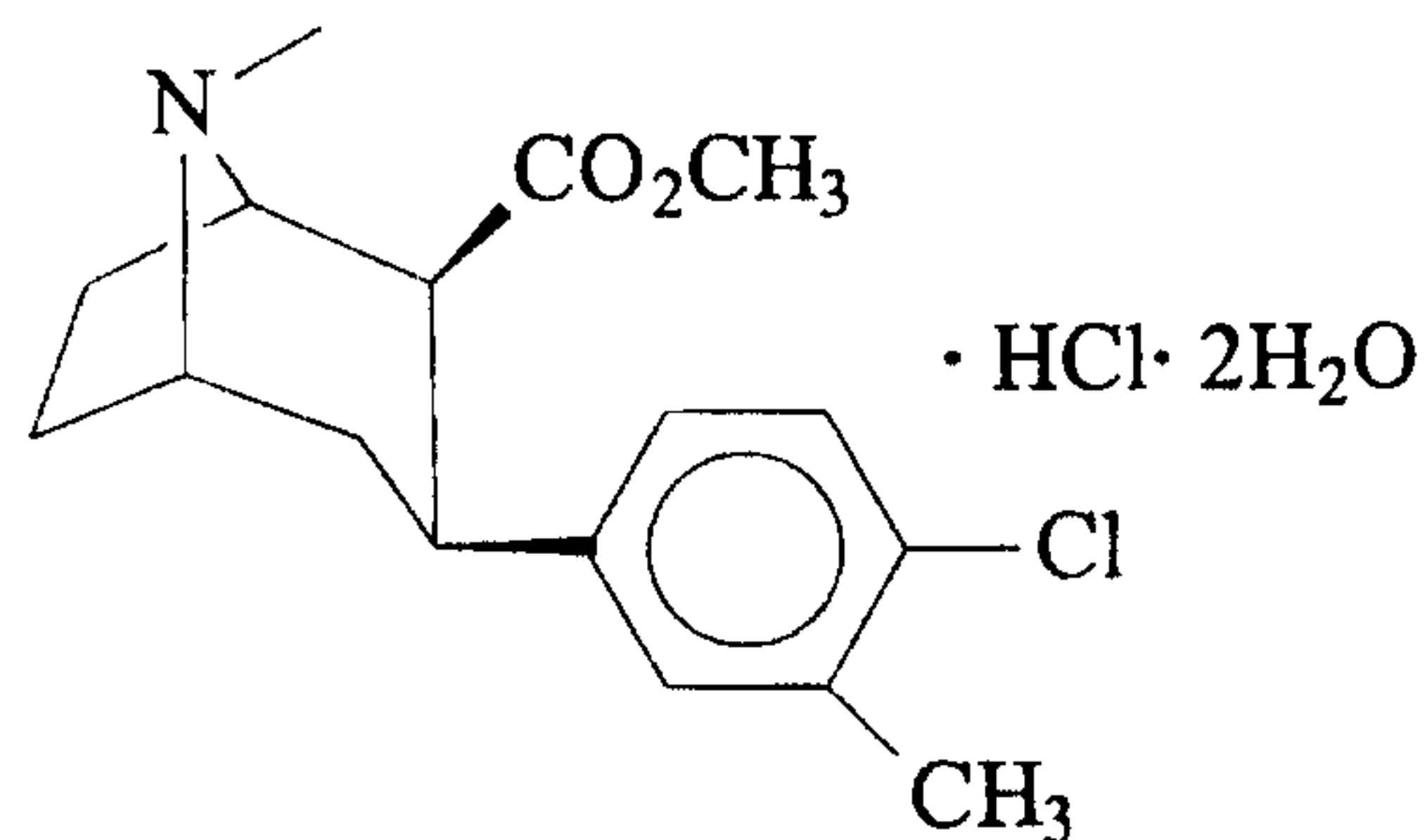
RTI-4229-110

DA 0.62 ± 0.09 5-HT 4.13 ± 0.62 NE_N 5.45 ± 0.21 

RTI-4229-111

DA 0.79 ± 0.08 5-HT 3.13 ± 0.36 NE_N 17.96 ± 0.85 

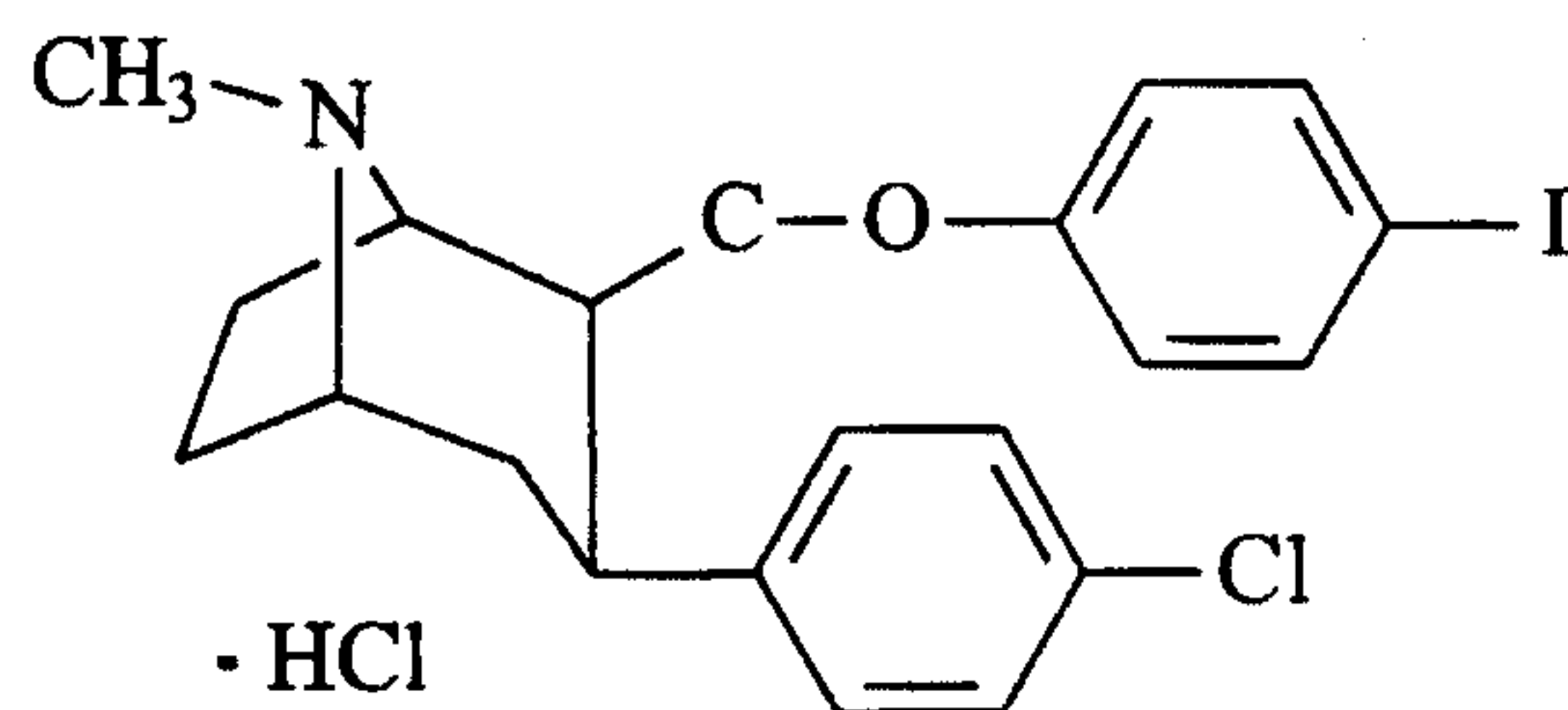
RTI-4229-112

DA 0.82 ± 0.05 5-HT 10.5 ± 0.41 NE_N 36.2 ± 1.02 

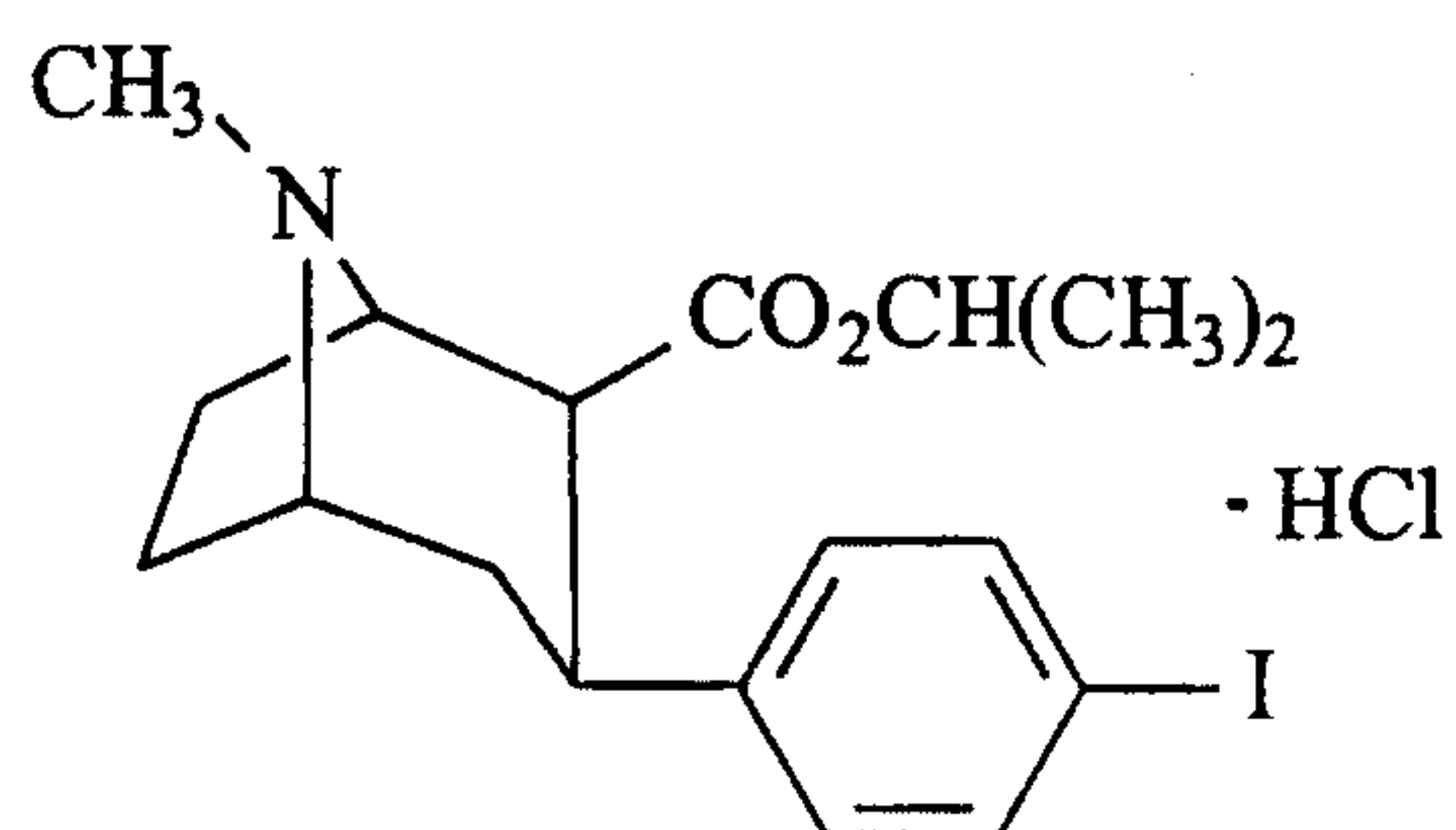
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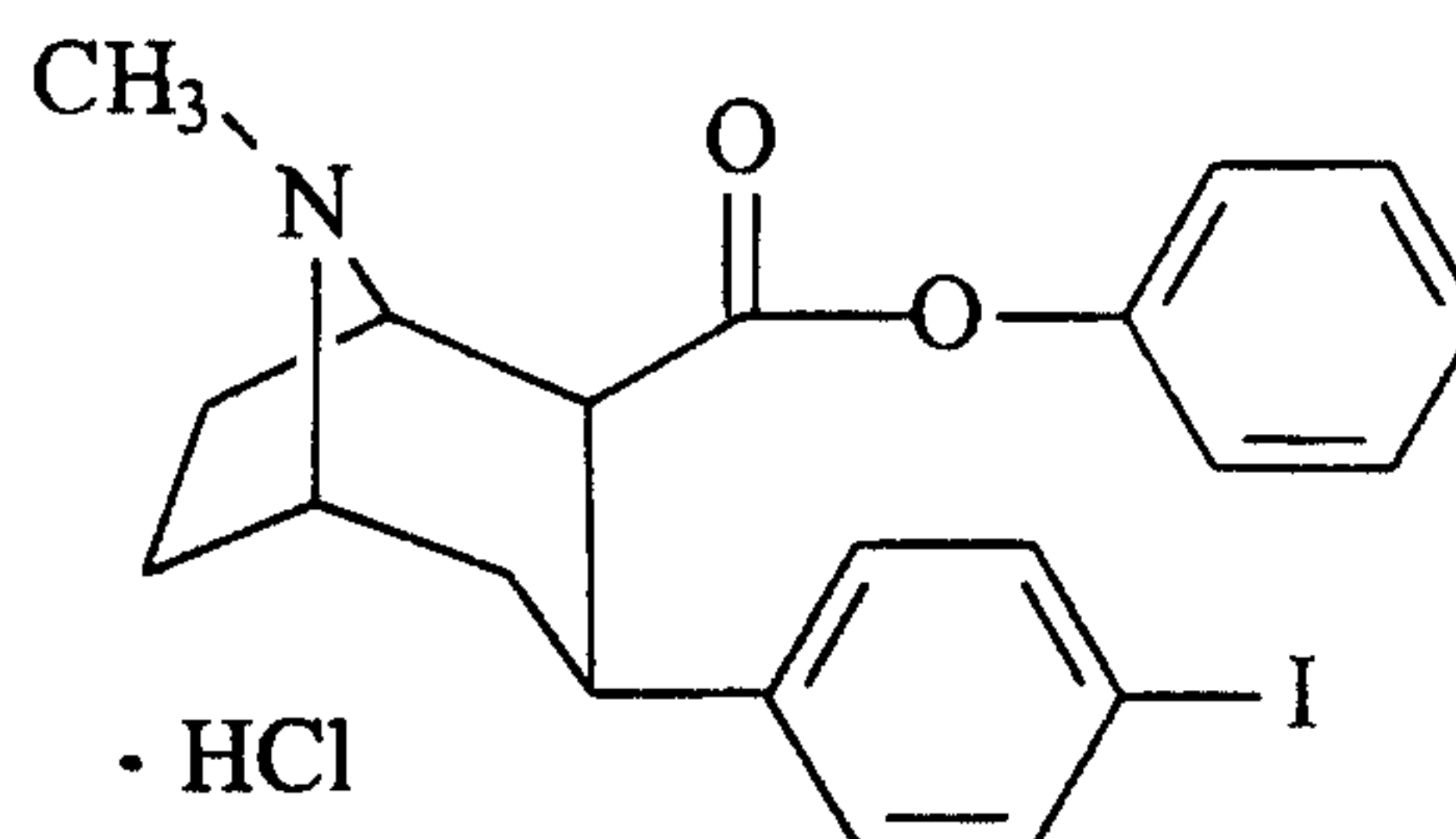
RTI-4229-116

DA 33 ± 3.9 5-HT 1.227 ± 176 NE_N 967.55 ± 26.25 

RTI-4229-121

DA 0.43 ± 0.05 5-HT 55.84 ± 6.53 NE_N 285 ± 7.6 

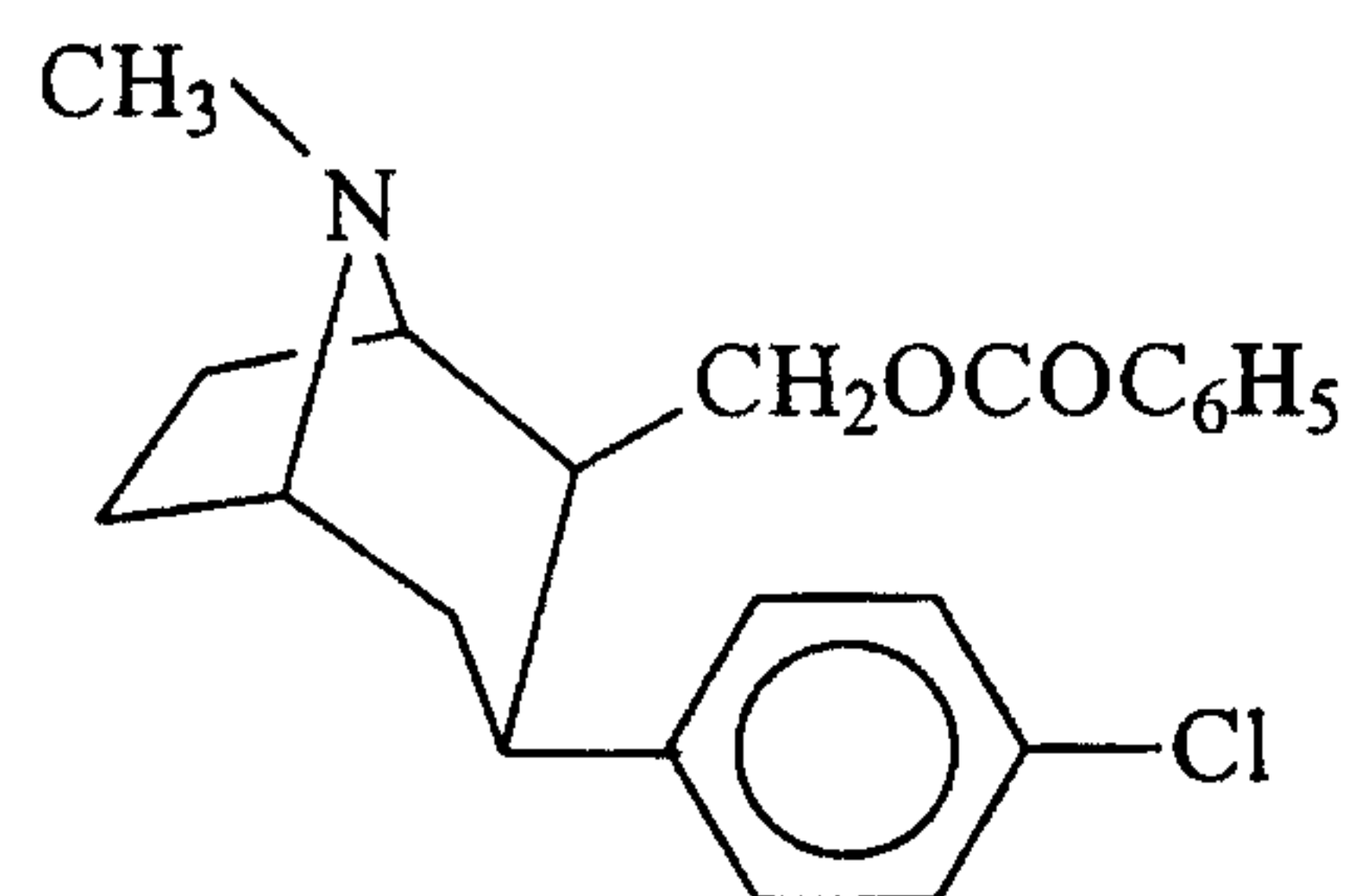
RTI-4229-122

DA 1.50 ± 0.35 5-HT 184.38 ± 21.91 NE_N 3.791 ± 149 

RTI-4229-123

DA 1.78

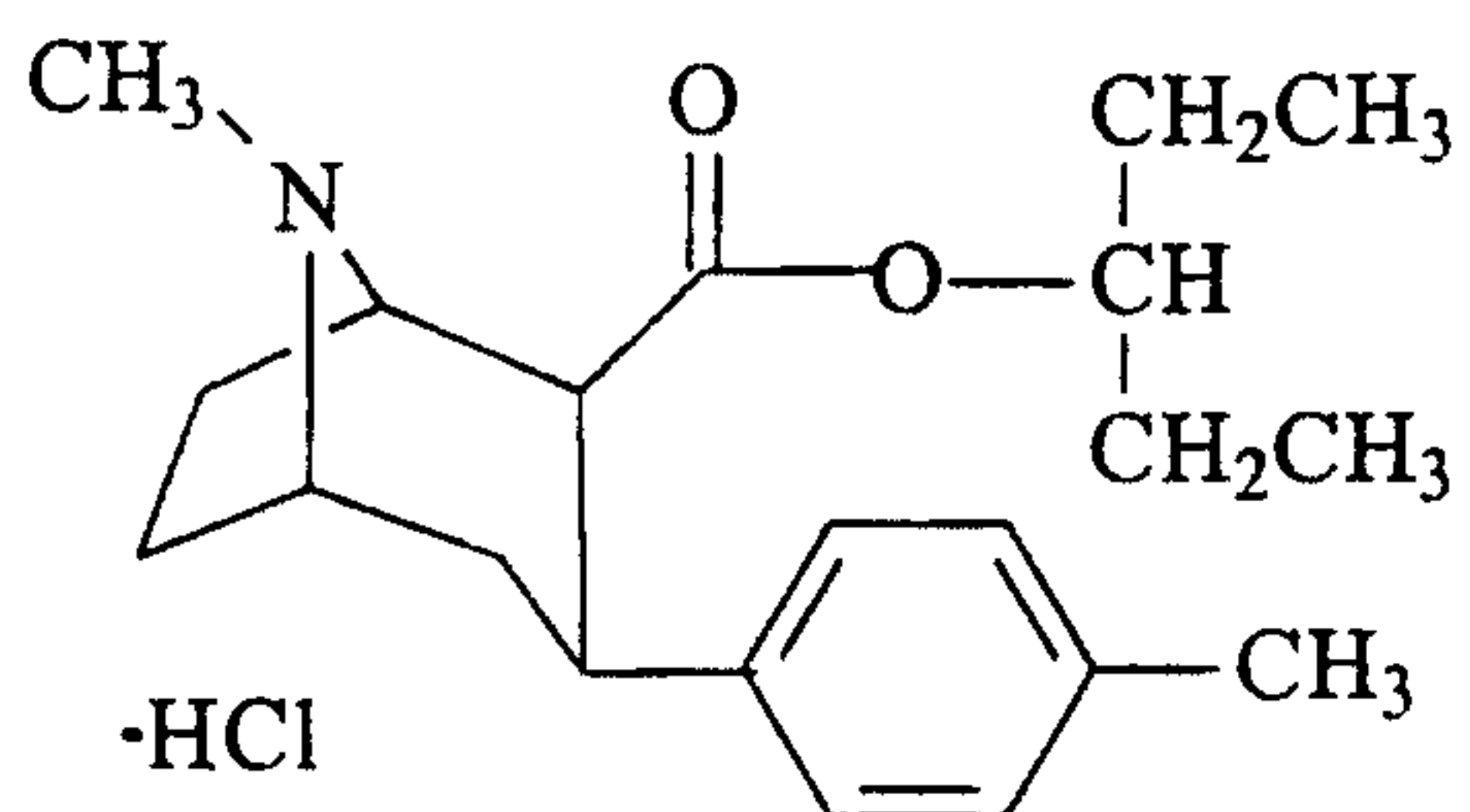
5-HT 3.53

NE_N 393

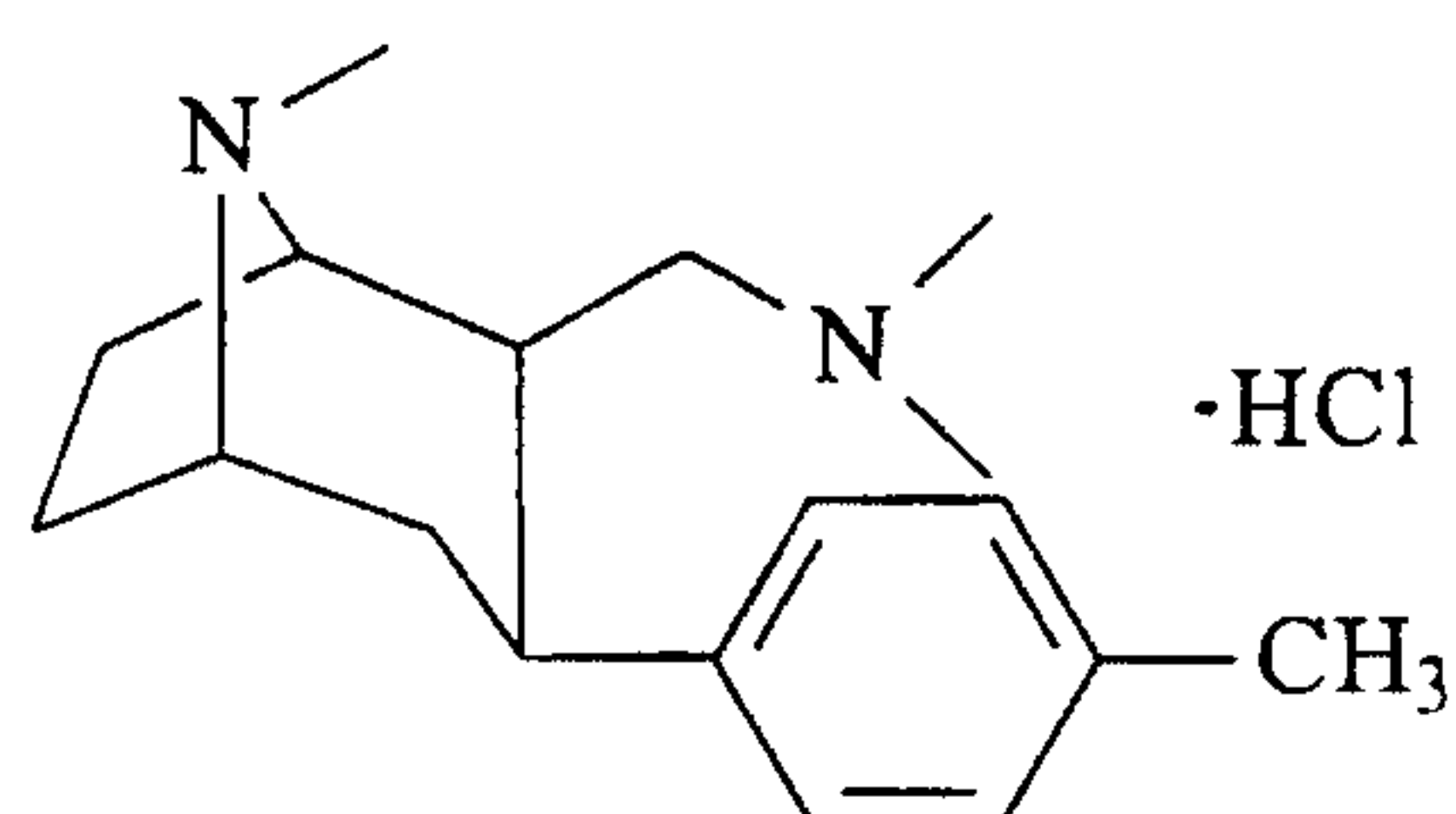
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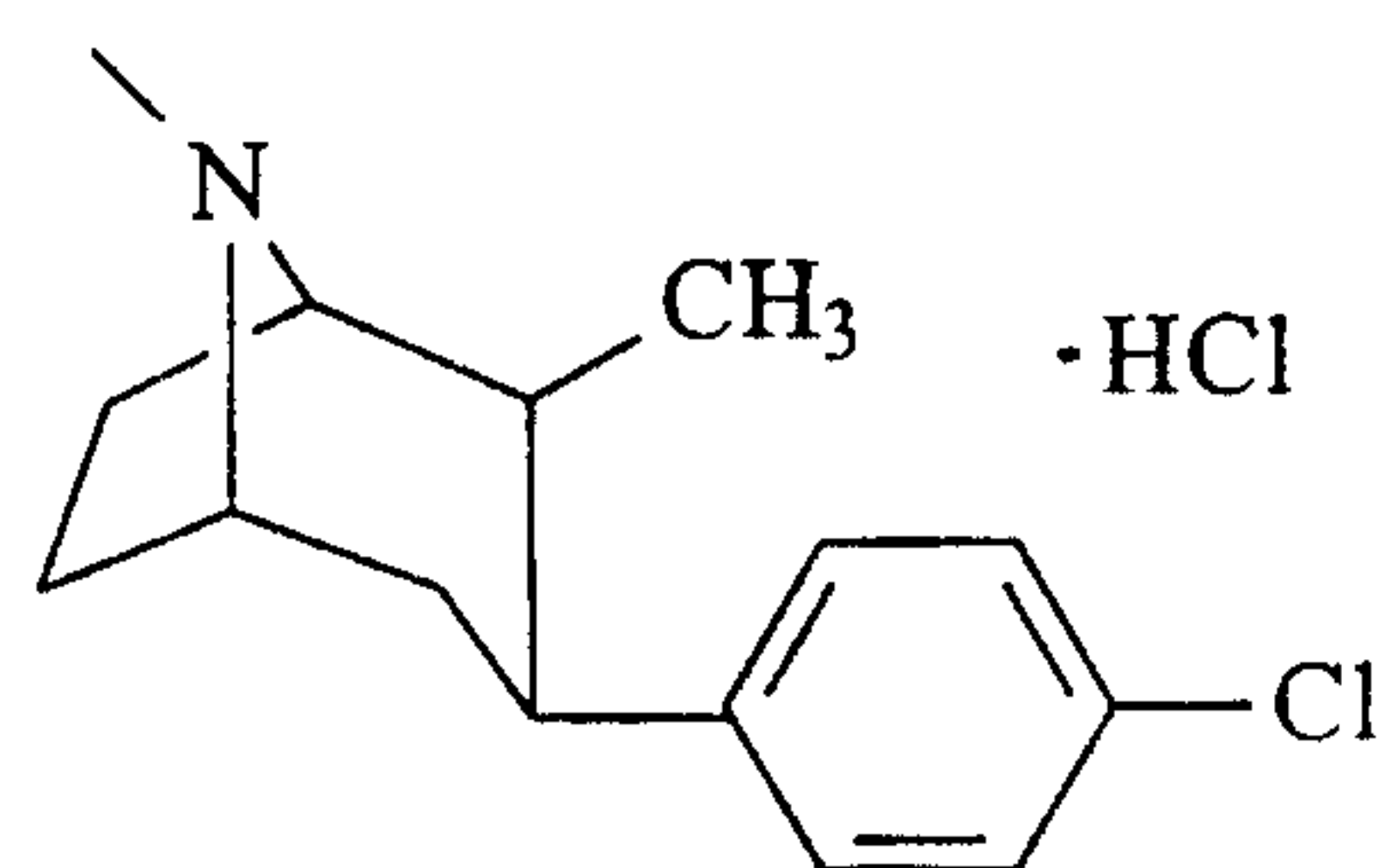
RTI-4229-127

DA 19 ± 1 5-HT 4.499 ± 557 NE_N 3.444 ± 44 

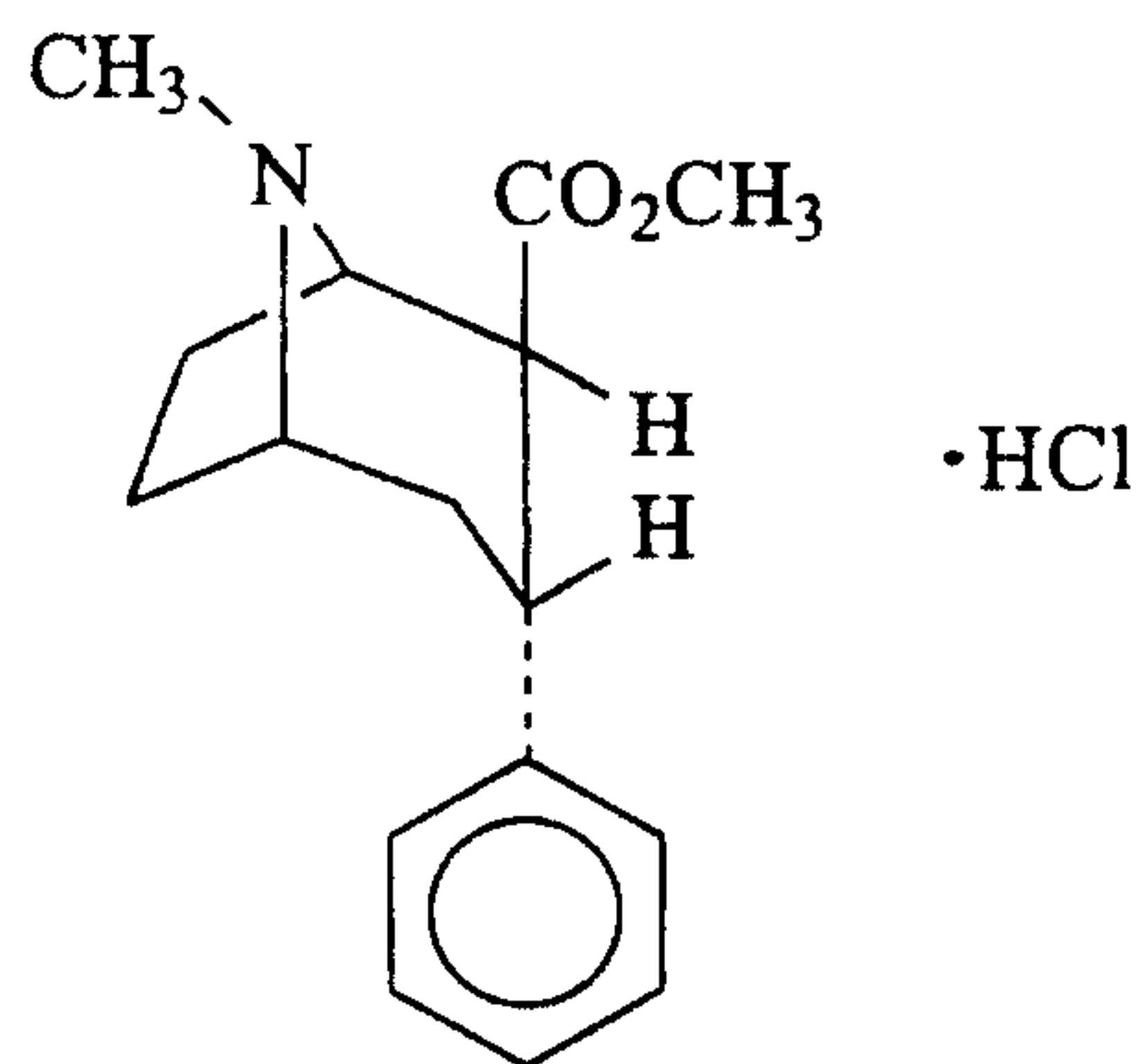
RTI-4229-132

DA 3.48 ± 0.11 5-HT 208 ± 18 NE_N 137.3 ± 10.5 

RTI-4229-139

DA 1.67 ± 0.13 5-HT 85 ± 9.3 NE_N 56.9 ± 2.6 

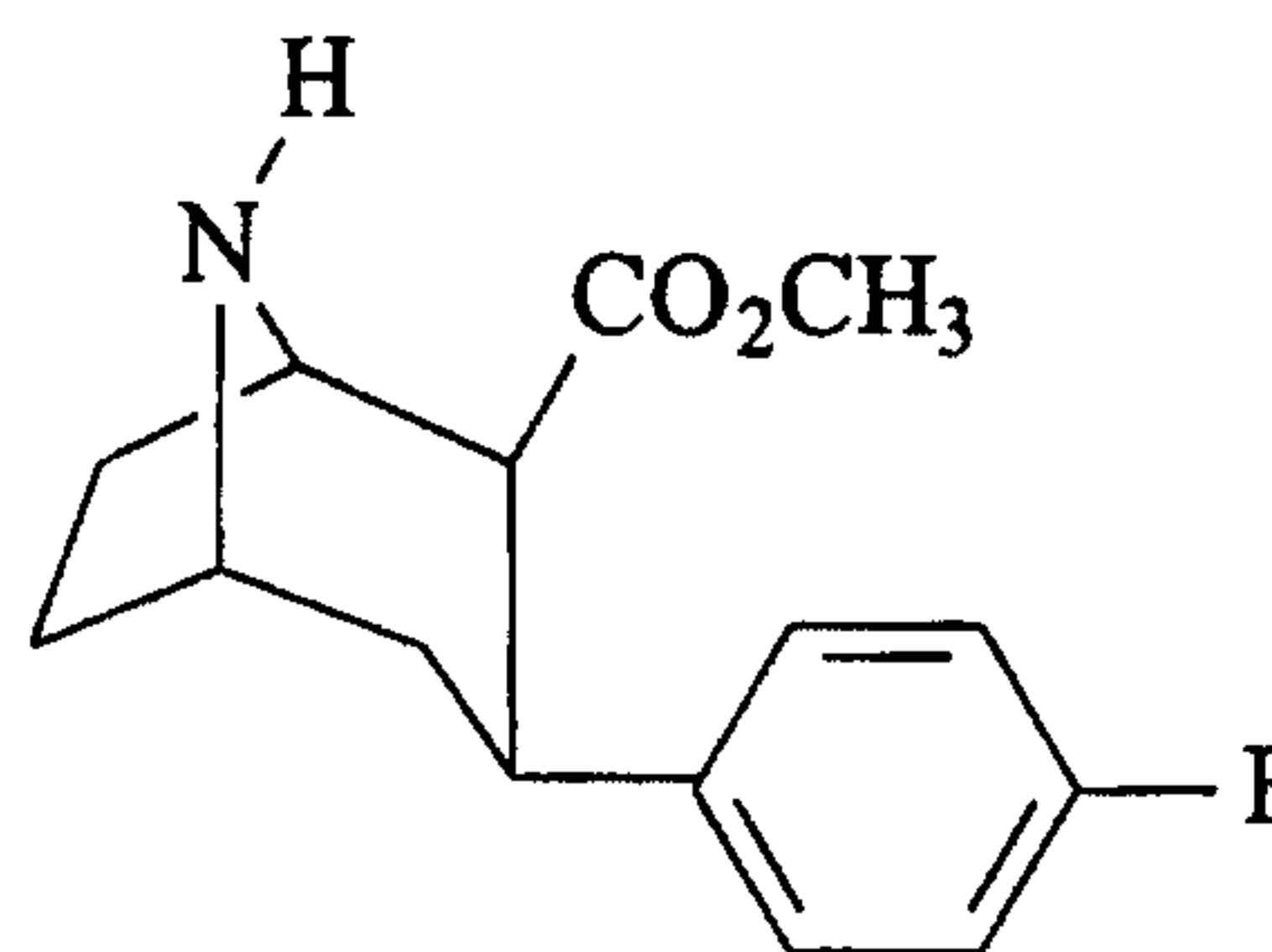
RTI-4229-140

DA 101 ± 16 5-HT 5.701 ± 721 NE_N 2.076 ± 285 

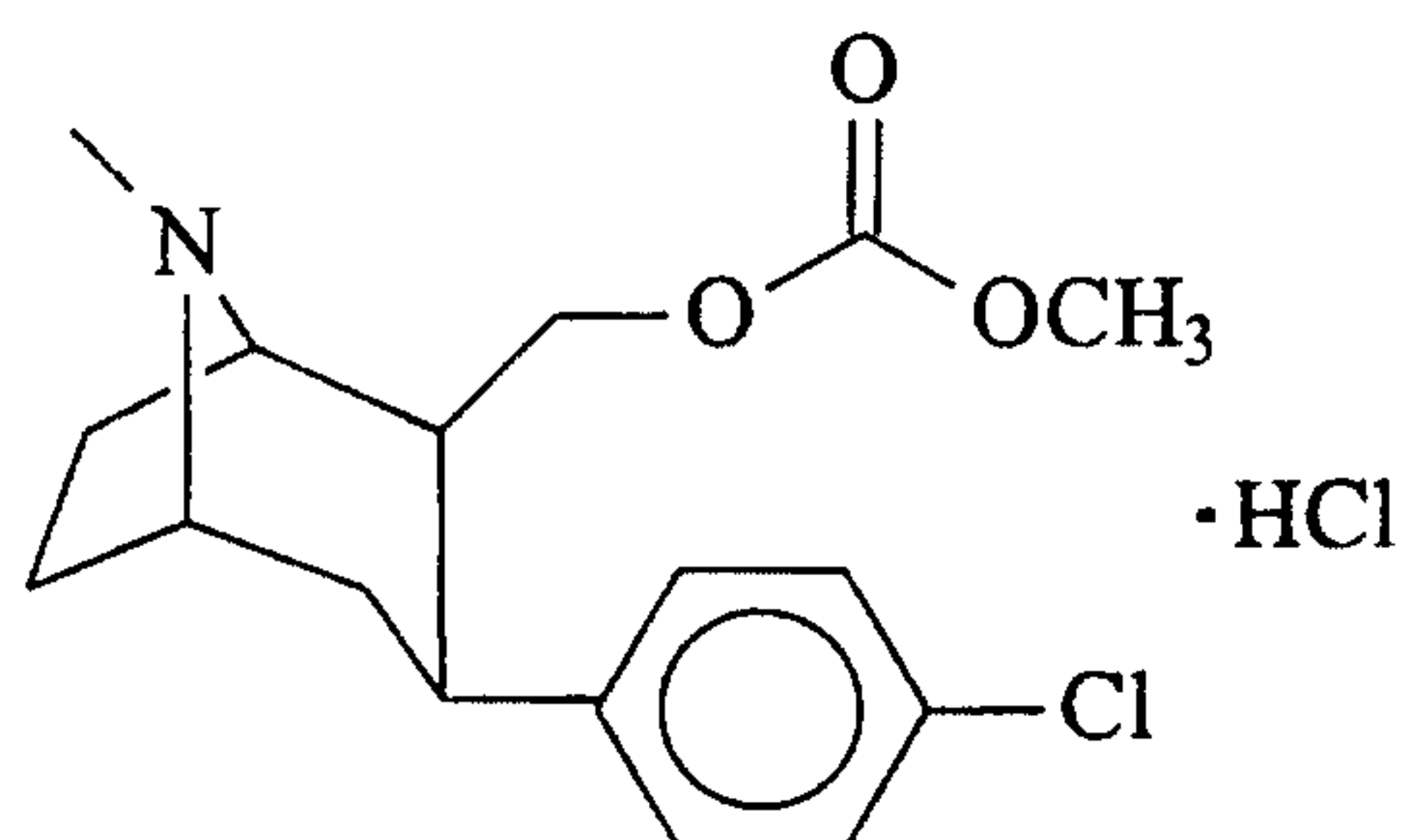
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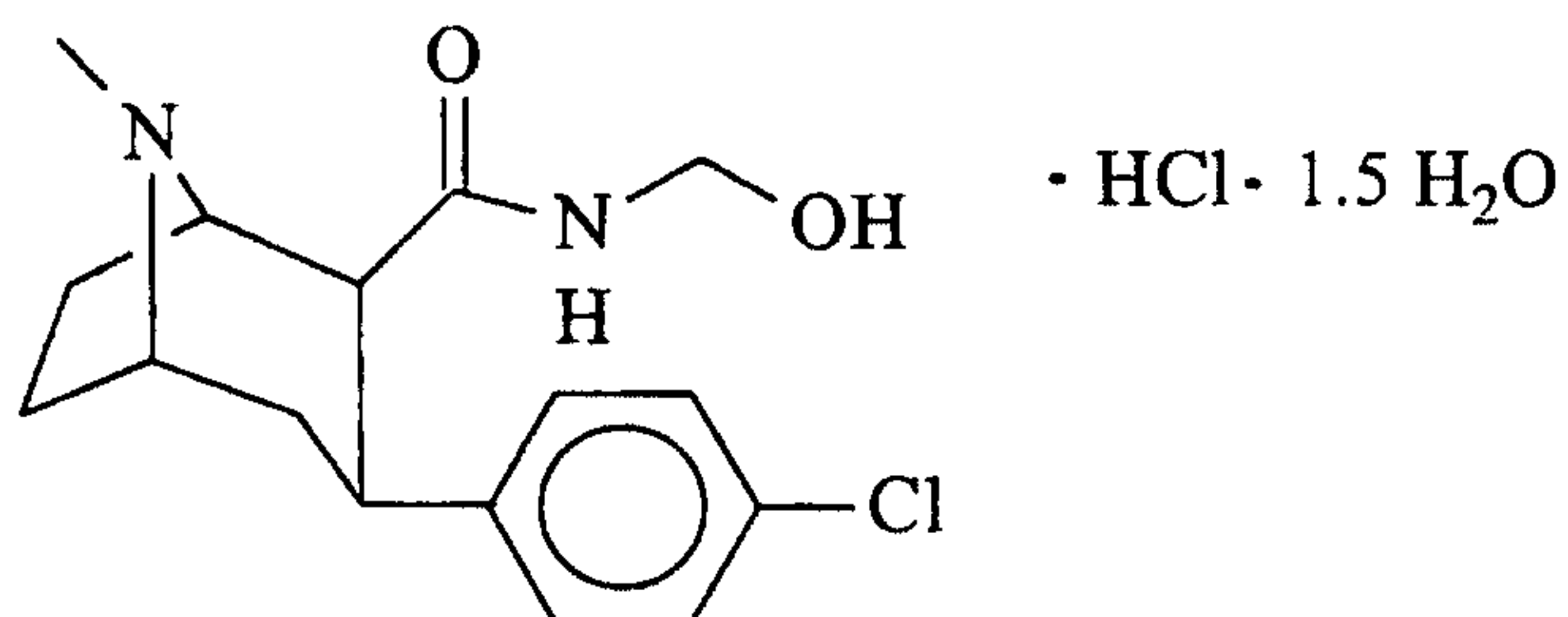
RTI-4229-142

DA 4.39 ± 0.20 5-HT 68.59 ± 2.02 NE_N 18.78 ± 0.68 

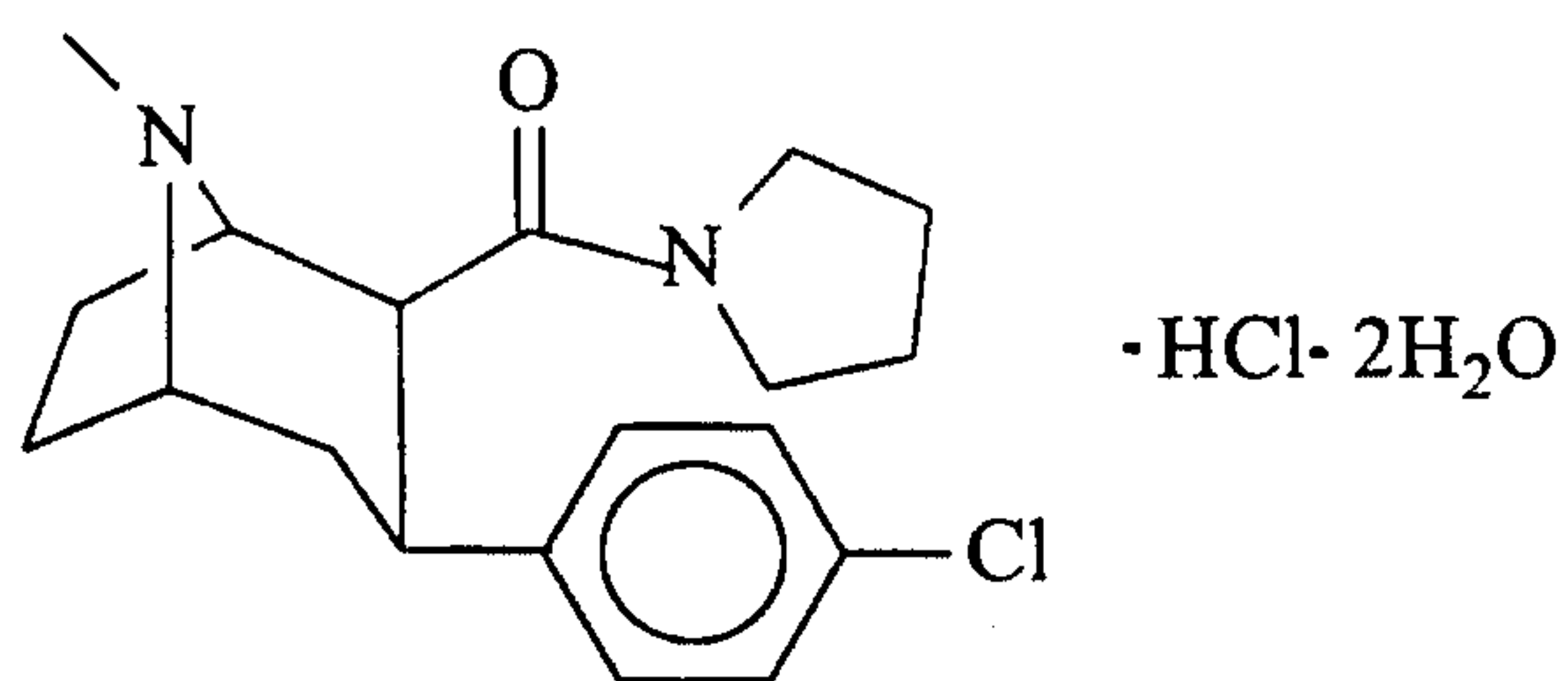
RTI-4229-145

DA 9.60 ± 0.42 5-HT 2.932 ± 181 NE_N 1.478 ± 96 

RTI-4229-146

DA 2.05 ± 0.23 5-HT 98 ± 10 NE_N 144 ± 3 

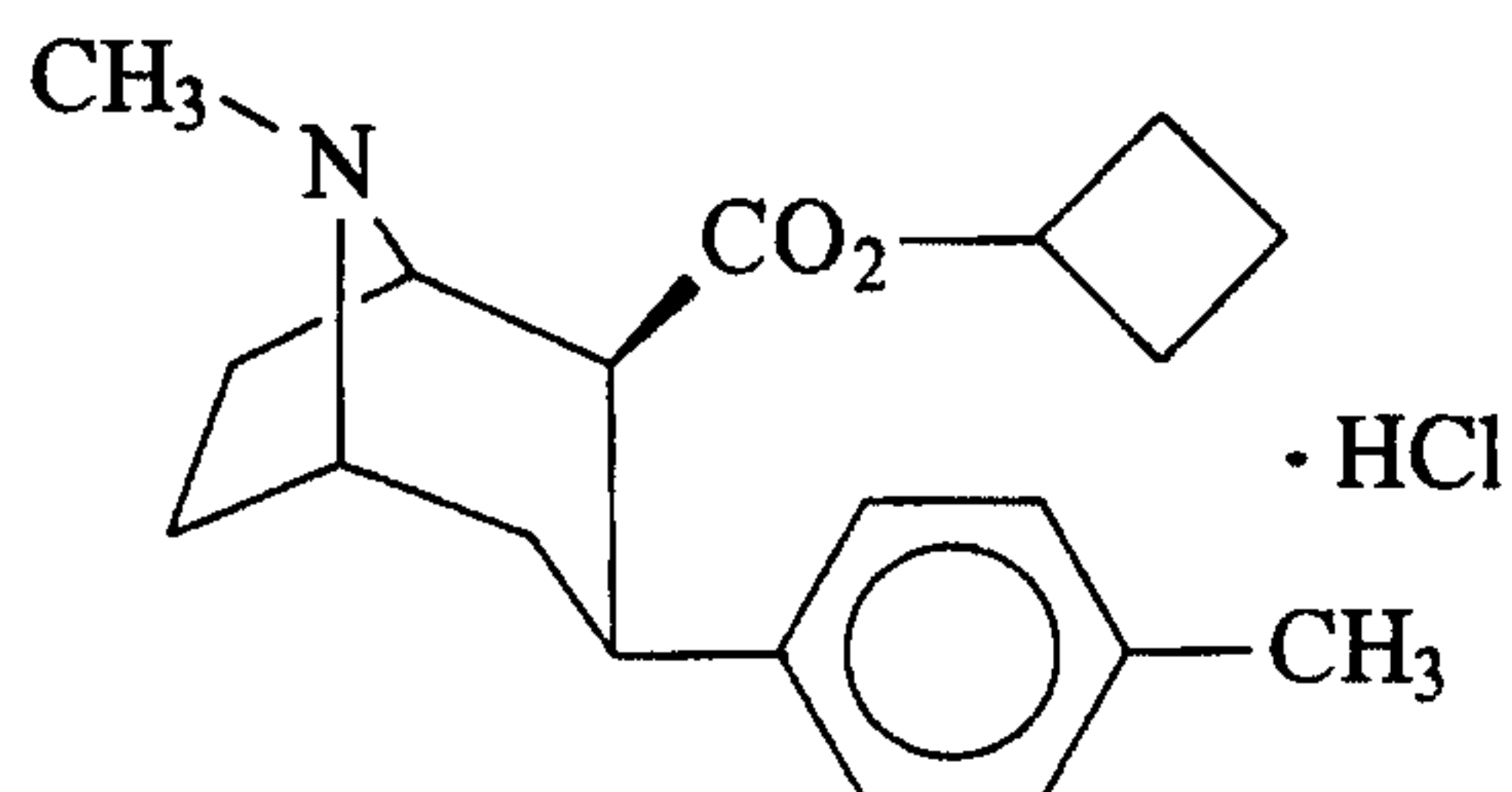
RTI-4229-147

DA 1.38 ± 0.03 5-HT $12.393.99 \pm 1207.03$ NE_N 3.949 ± 72 

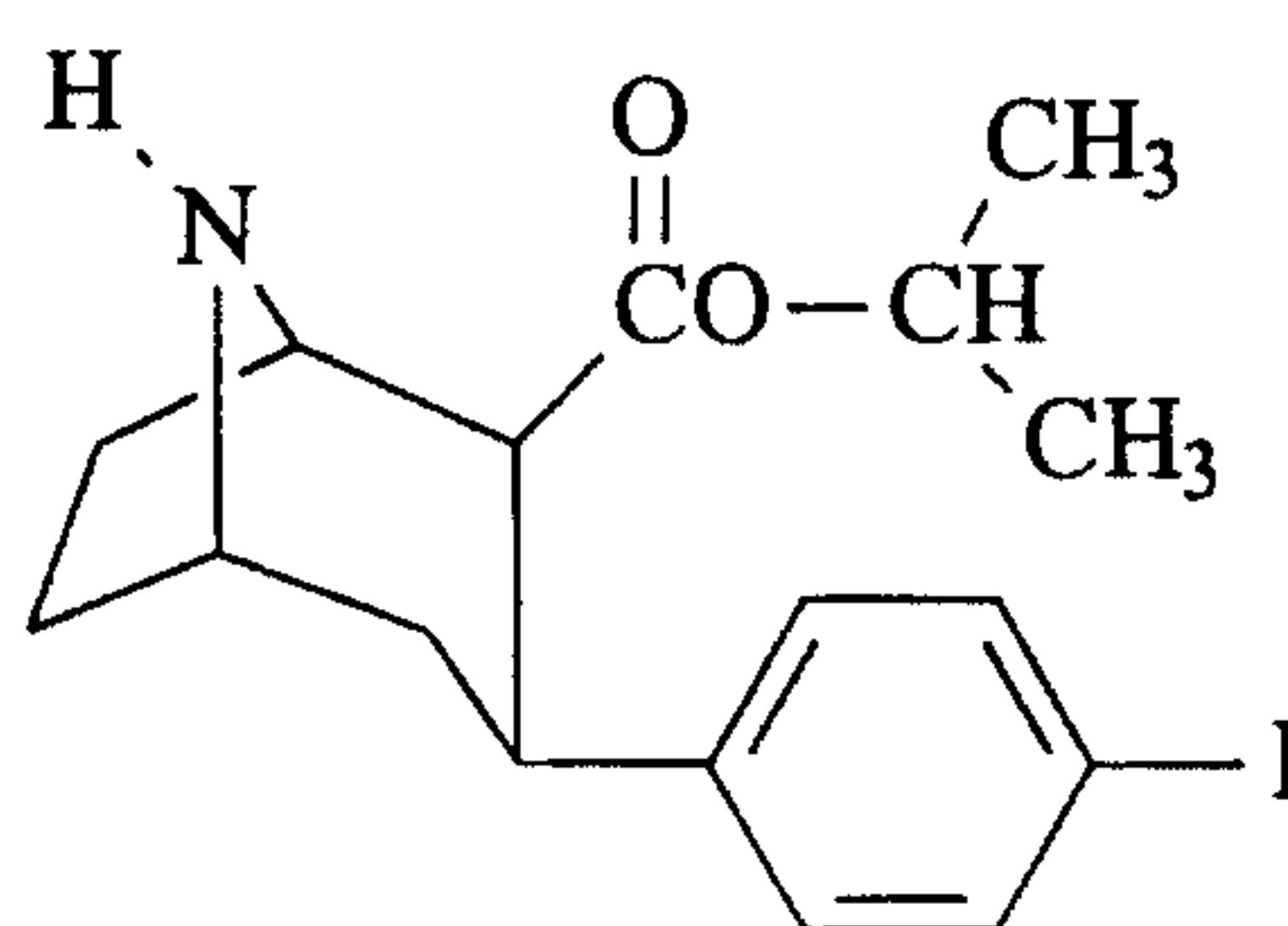
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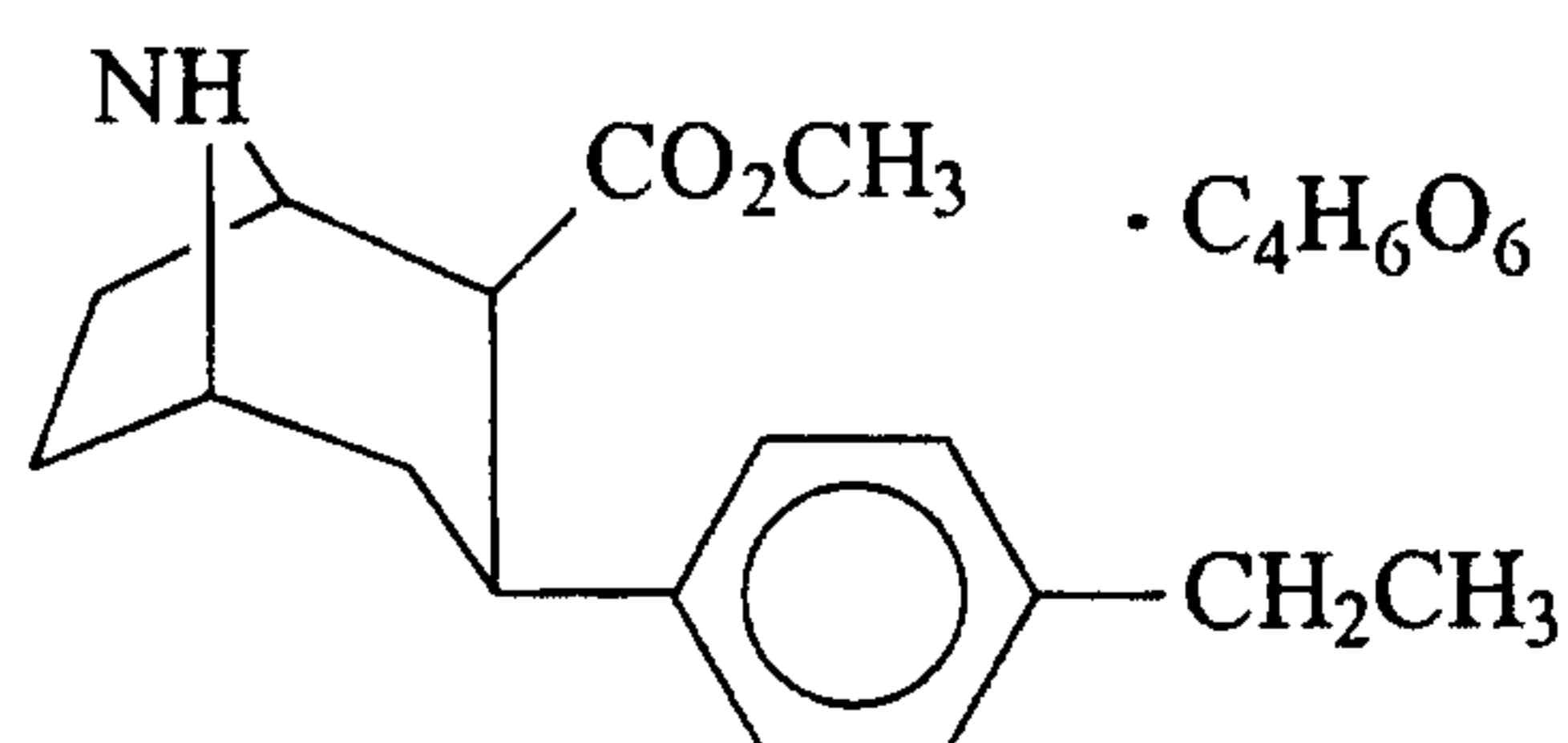
RTI-4229-150

DA 3.74 ± 0.52 5-HT 2.019 ± 133 NE_N 4.738 ± 322 

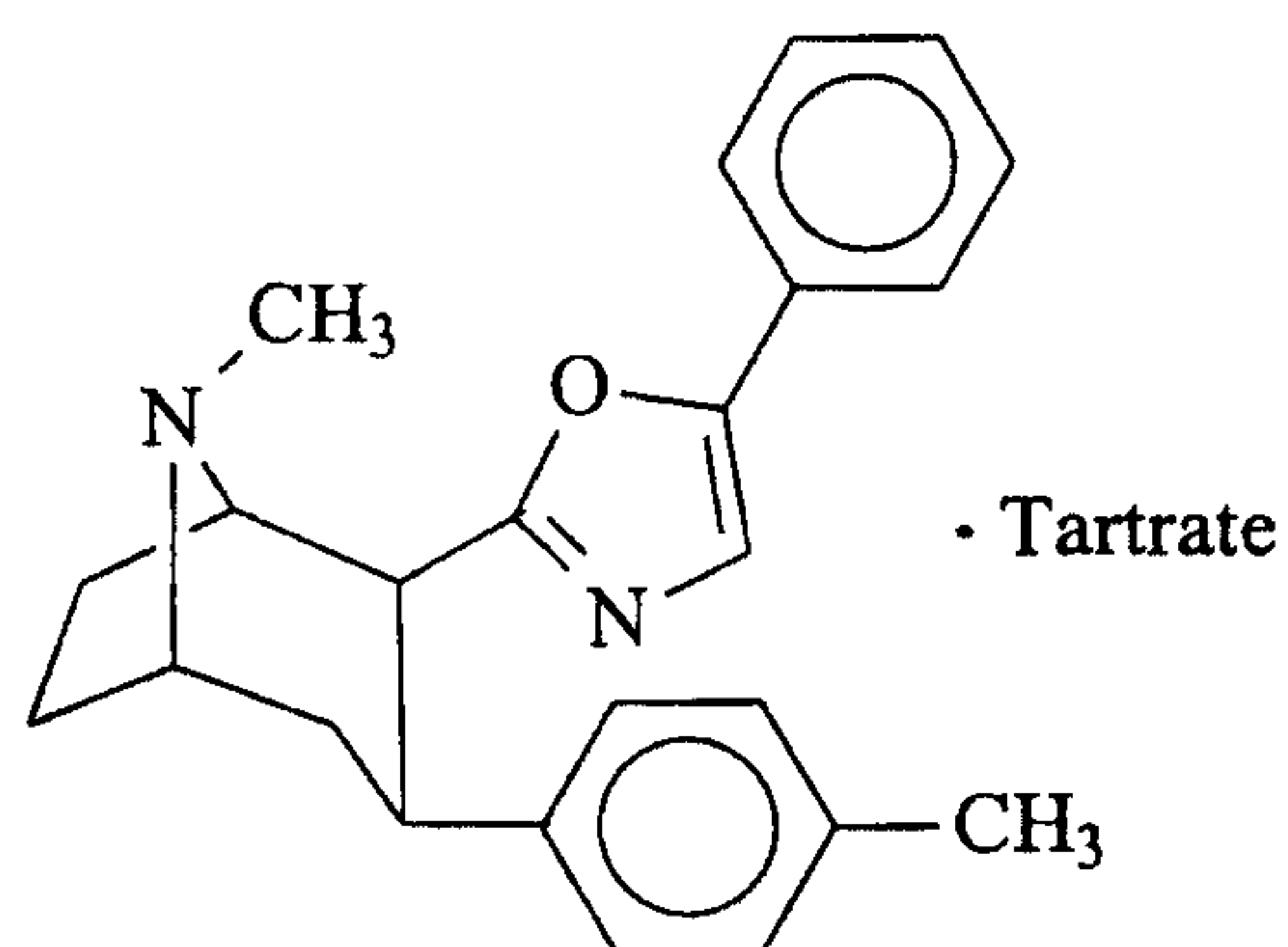
RTI-4229-153

DA 1.06 ± 0.12 5-HT 3.59 ± 0.27 NE_N 132 ± 5 

RTI-4229-173

DA 49.9 ± 7.3 5-HT 8.13 ± 0.30 NE_N 122 ± 12 

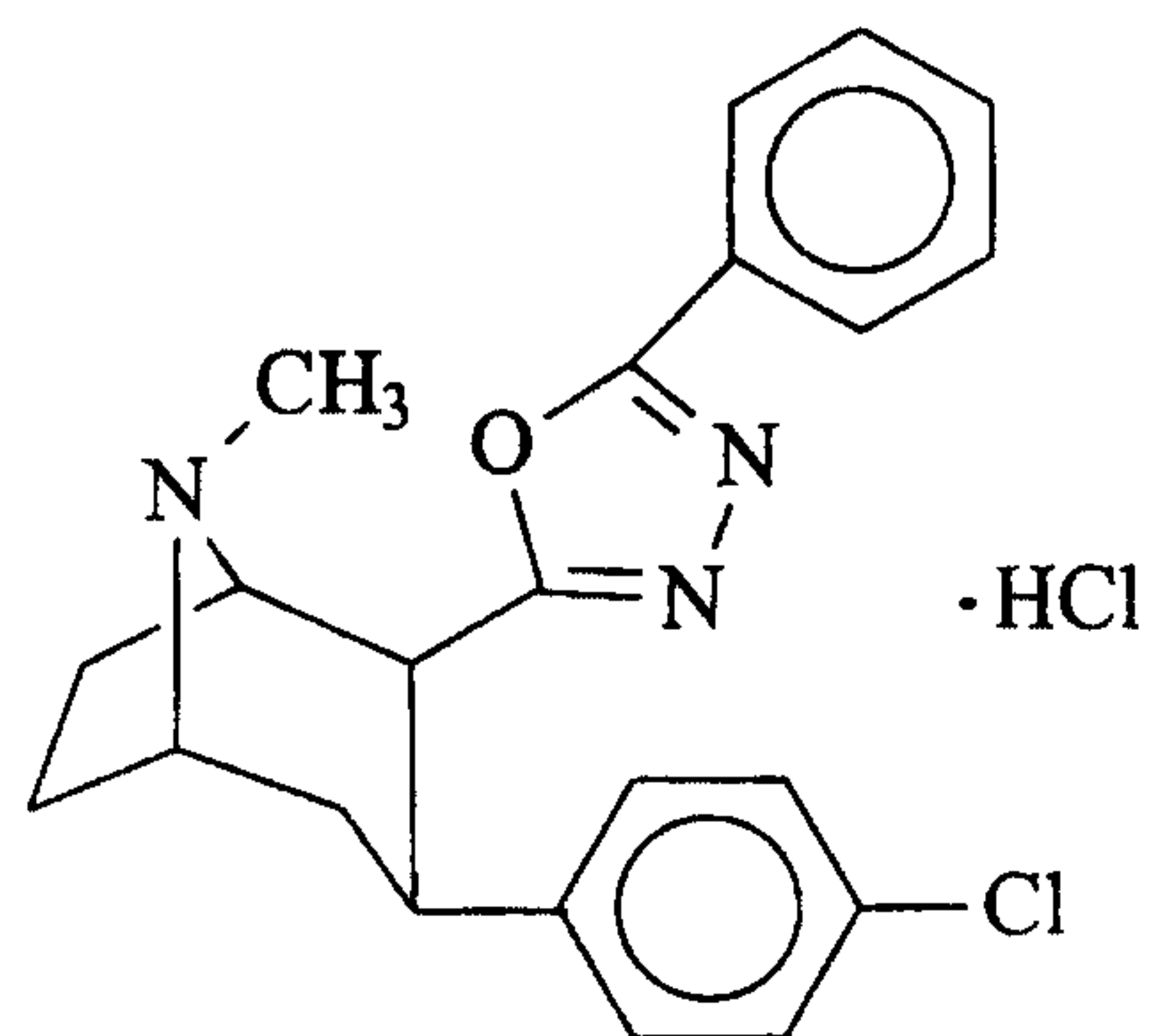
RTI-4229-178

DA 35.4 ± 1.74 5-HT $1.698.77 \pm 166.68$ NE_N 677 ± 67.5 

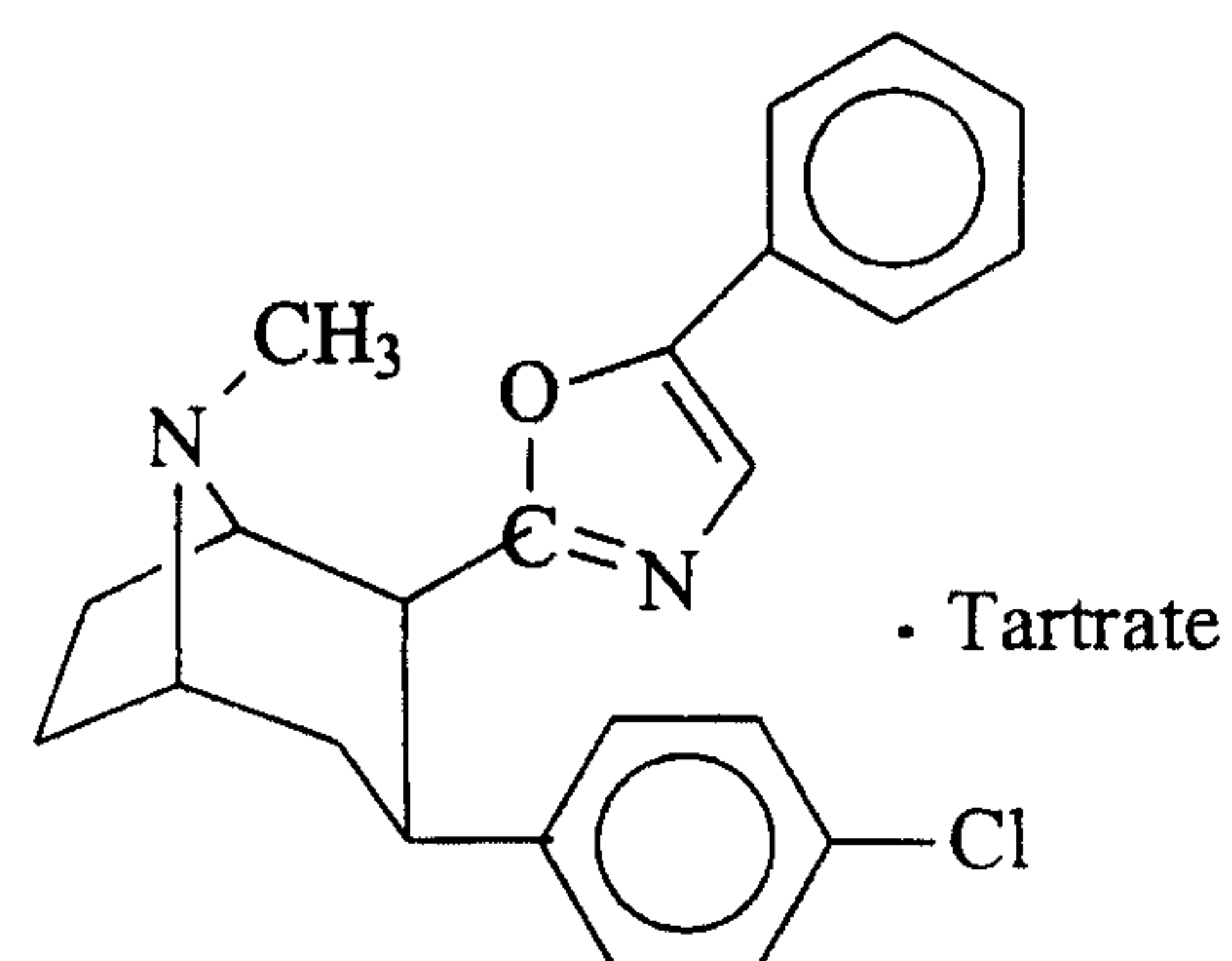
WO 99/61023

PCT/US99/10456

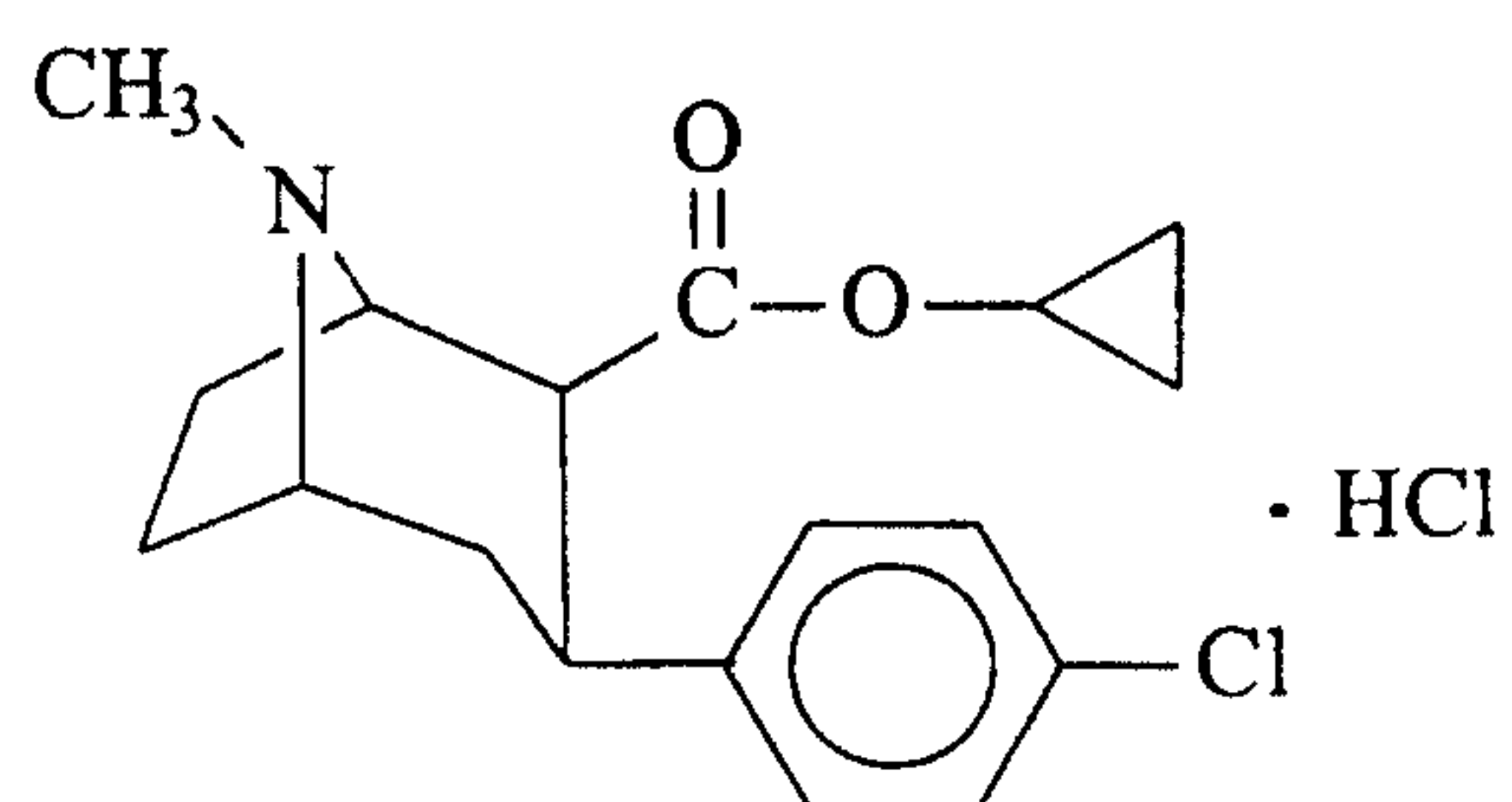
RTI-4229-188

DA 12.56 $\pm$ 1.035-HT 3.303.76 $\pm$ 195.85NE_N 929 $\pm$ 88.1

RTI-4229-189

DA 19.71 $\pm$ 1.985-HT 1.116.18 $\pm$ 107.148NE_N 496 $\pm$ 42.1

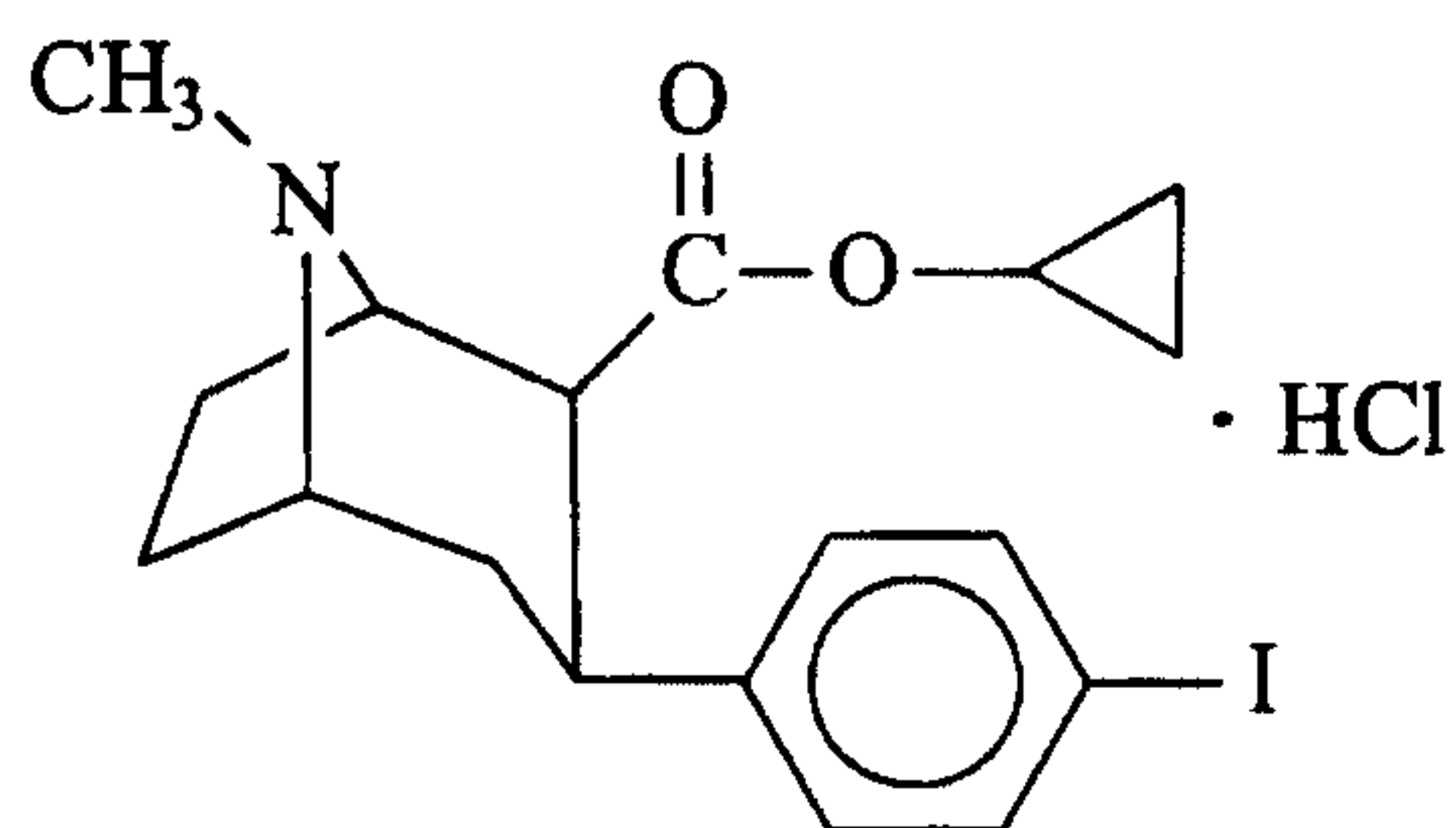
RTI-4229-190

DA 0.96 $\pm$ 0.105-HT 168 $\pm$ 1.8NE_N 235 $\pm$ 8.39

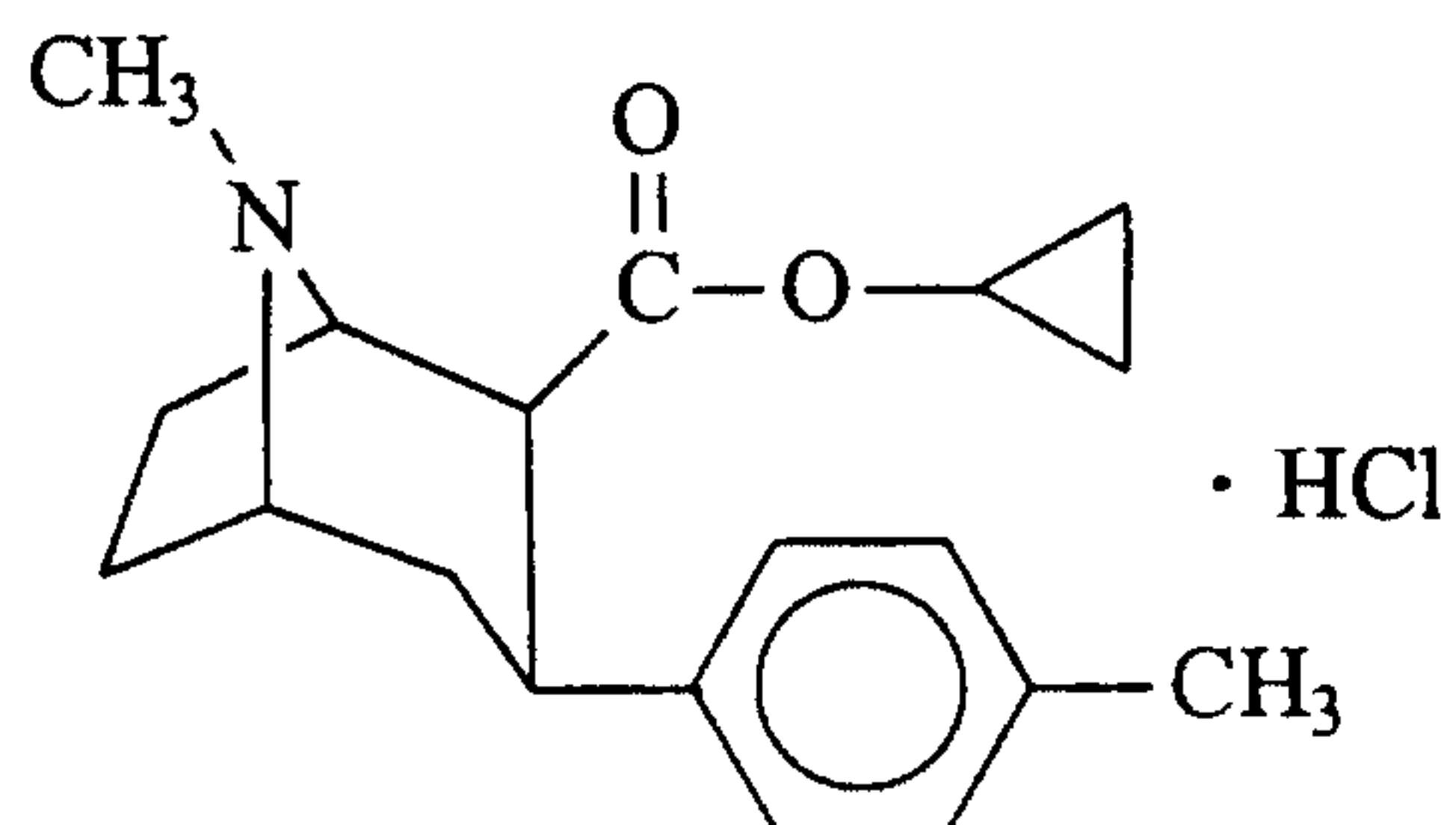
WO 99/61023

PCT/US99/10456

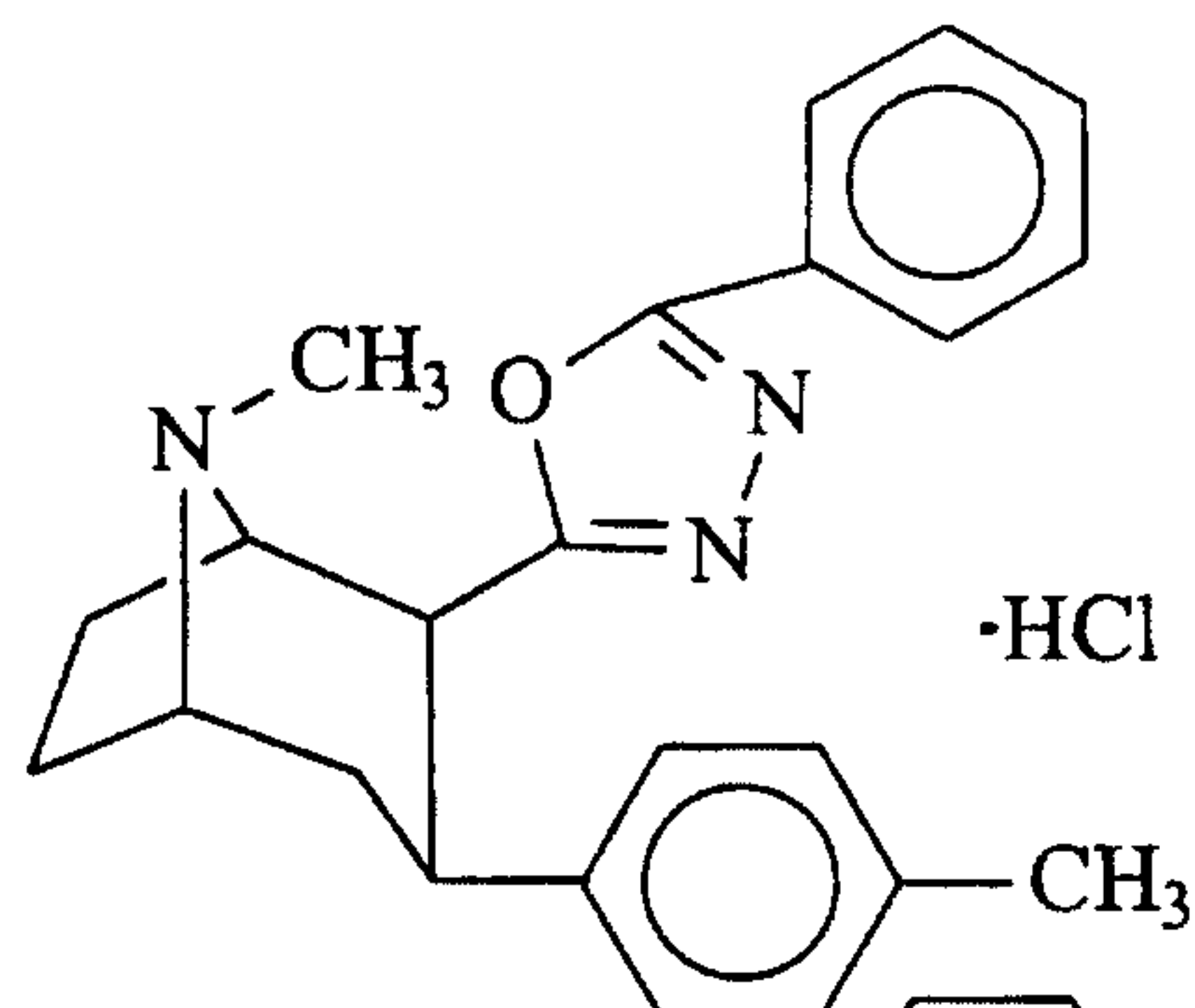
RTI-4229-191

DA 0.61 ± 0.08 5-HT 15.5 ± 0.72 NE_N 101.7 ± 10.5 

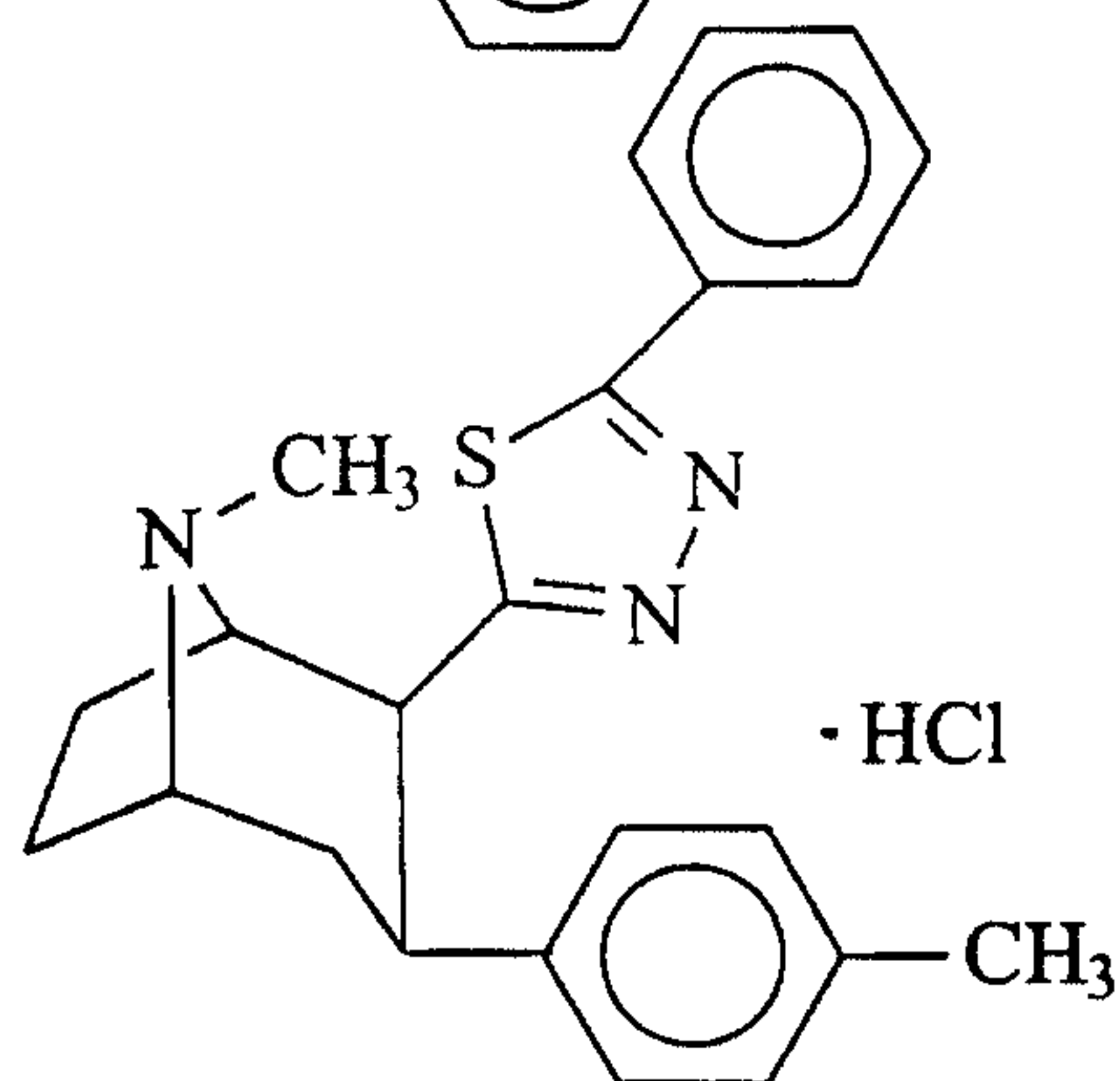
RTI-4229-193

DA 1.68 ± 0.14 5-HT $1.066.38 \pm 109.12$ NE_N 544 ± 27.7 

RTI-4229-195

DA 47.48 ± 4.76 5-HT $22.310.9 \pm 822.83$ NE_N 1.310 ± 36.7 

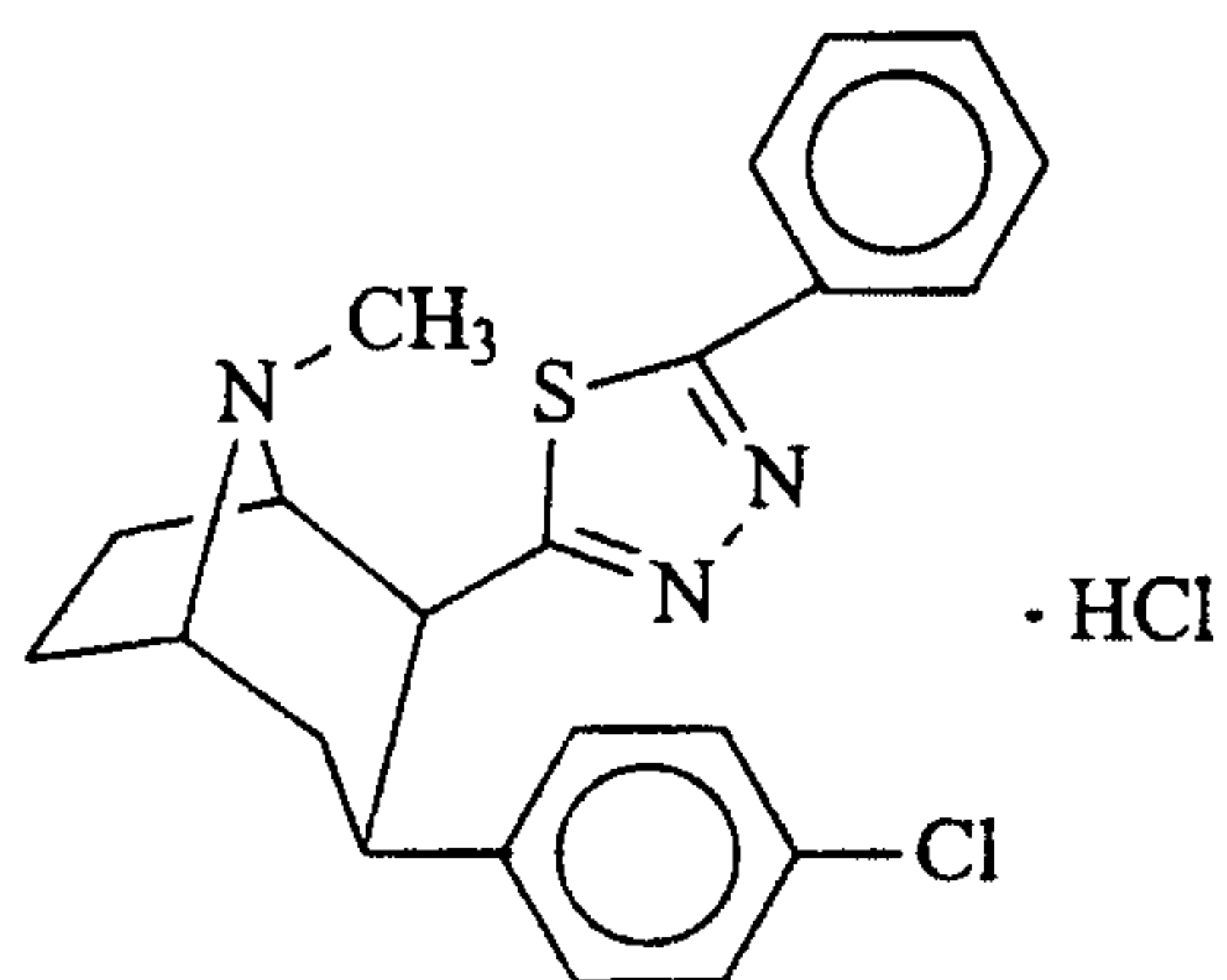
RTI-4229-199

DA 35.88 ± 3.40 5-HT $51.459.7 \pm 4.513.10$ NE_N $24.320.8 \pm 3.822.61$ 

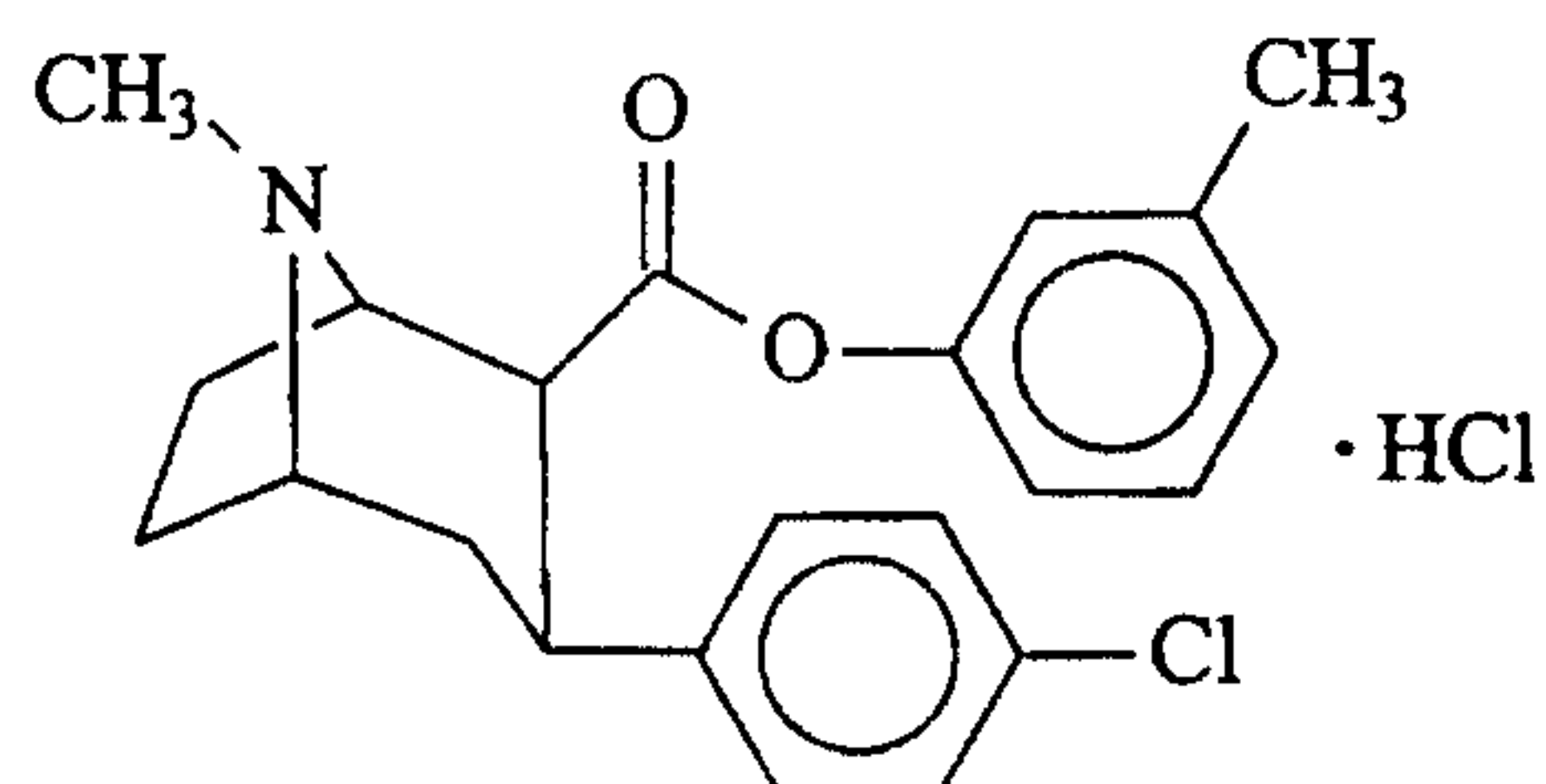
WO 99/61023

PCT/US99/10456

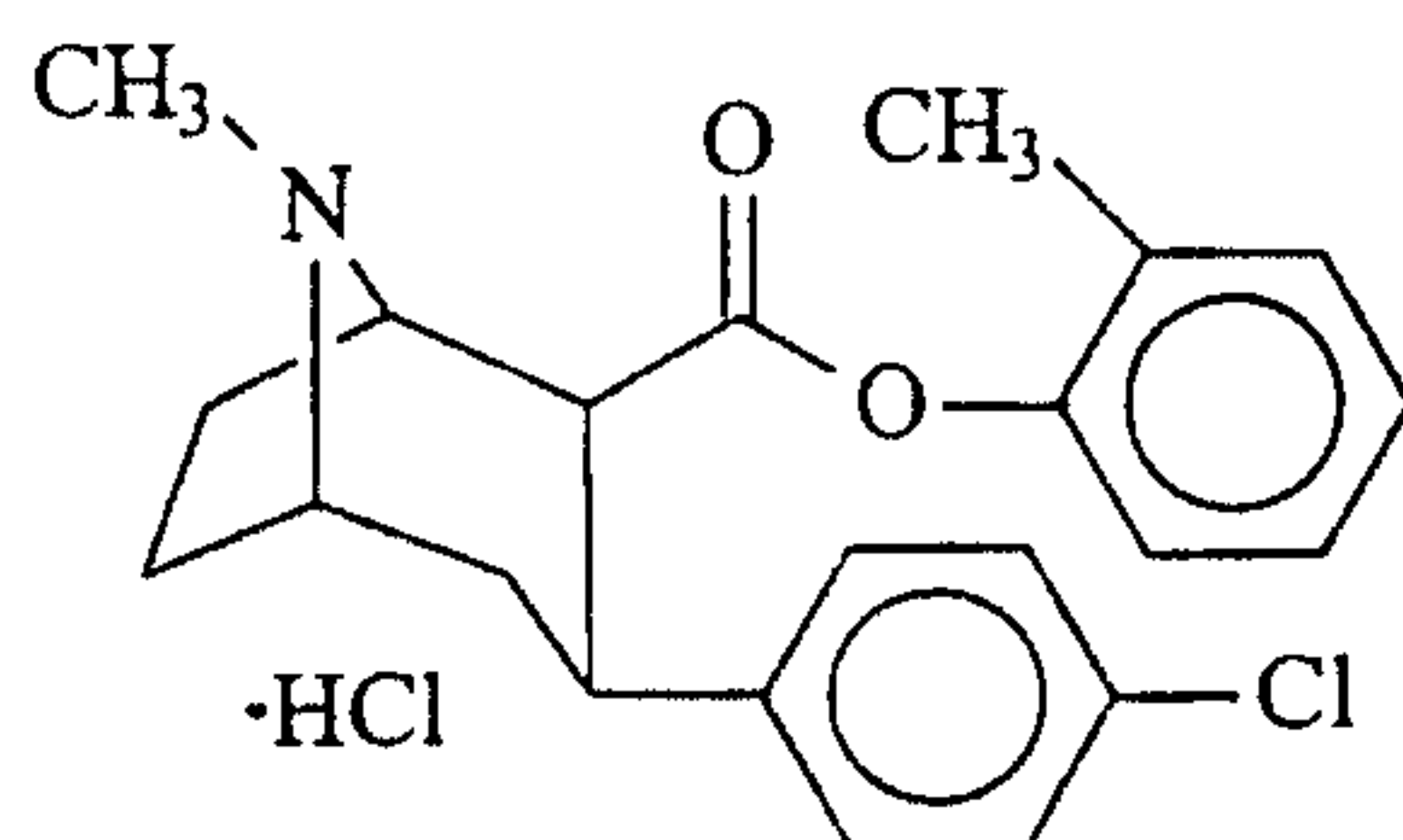
RTI-4229-200

DA 15.29 ± 2.43 5-HT $18.416.5 \pm 1.508.79$ NE_N $4.142.08 \pm 466.07$ 

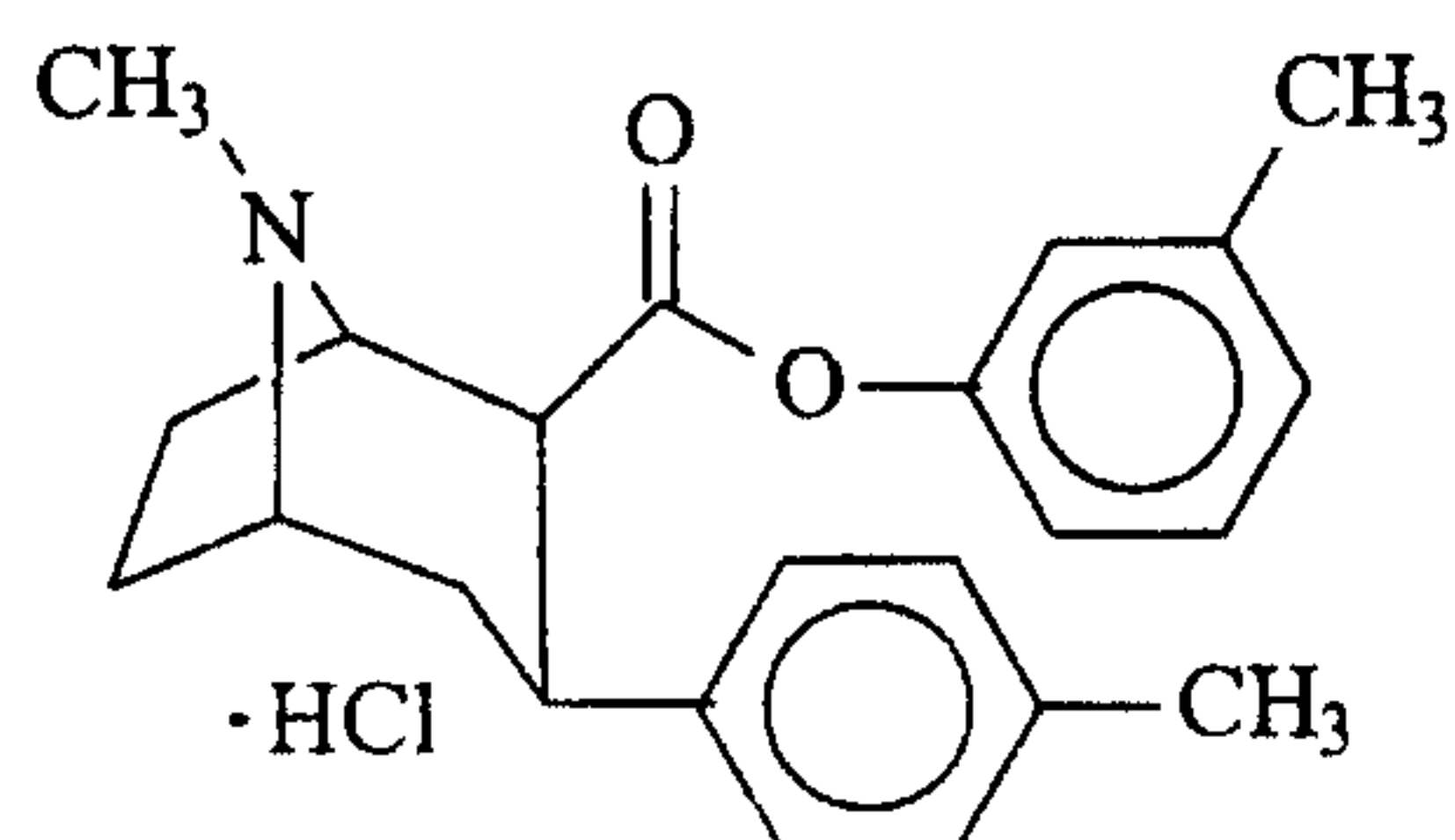
RTI-4229-203

DA 9.37 ± 0.52 5-HT $2.153.39 \pm 143.18$ NE_N $2.743.73 \pm 140.92$ 

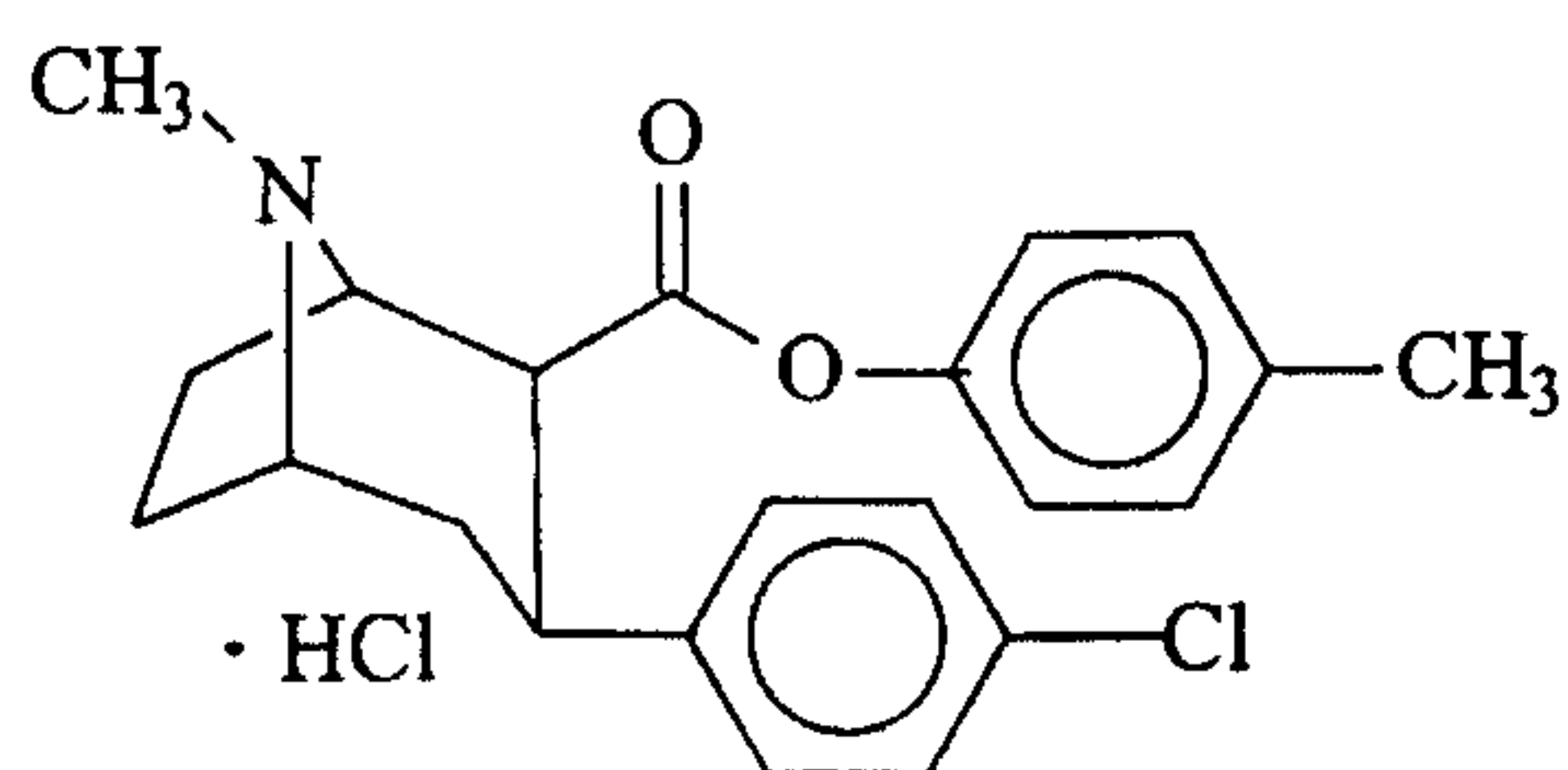
RTI-4229-204

DA 3.91 ± 0.23 5-HT $3.772.17 \pm 383.64$ NE_N $4.782.70 \pm 487.10$ 

RTI-4229-205

DA 8.19 ± 0.90 5-HT $5.237.30 \pm 453.397$ NE_N $2.136.62 \pm 208.52$ 

RTI-4229-206

DA 27.38 ± 1.47 5-HT $1.203.39 \pm 41.79$ NE_N $1.277.60 \pm 117.68$ 

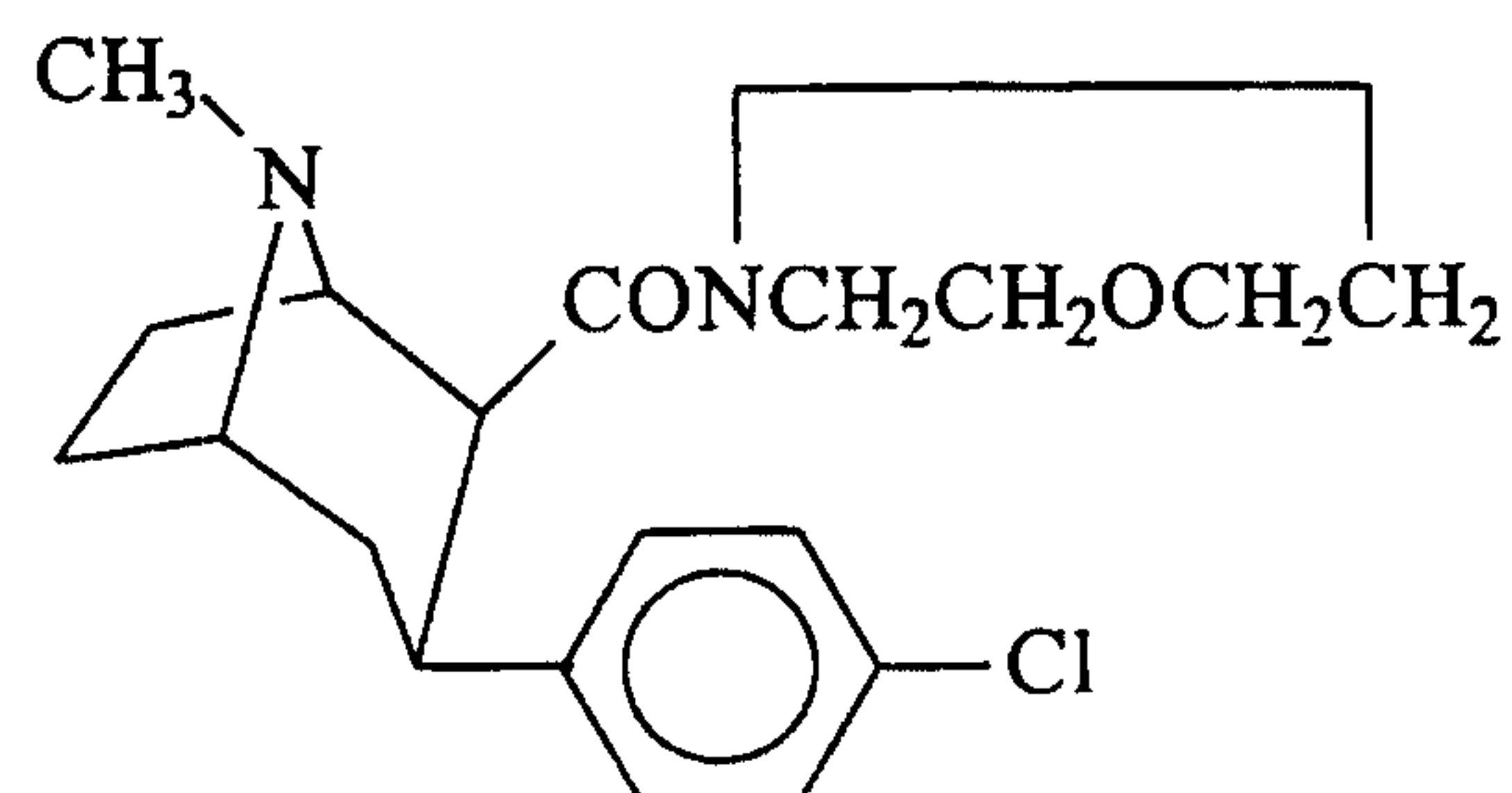
WO 99/61023

PCT/US99/10456

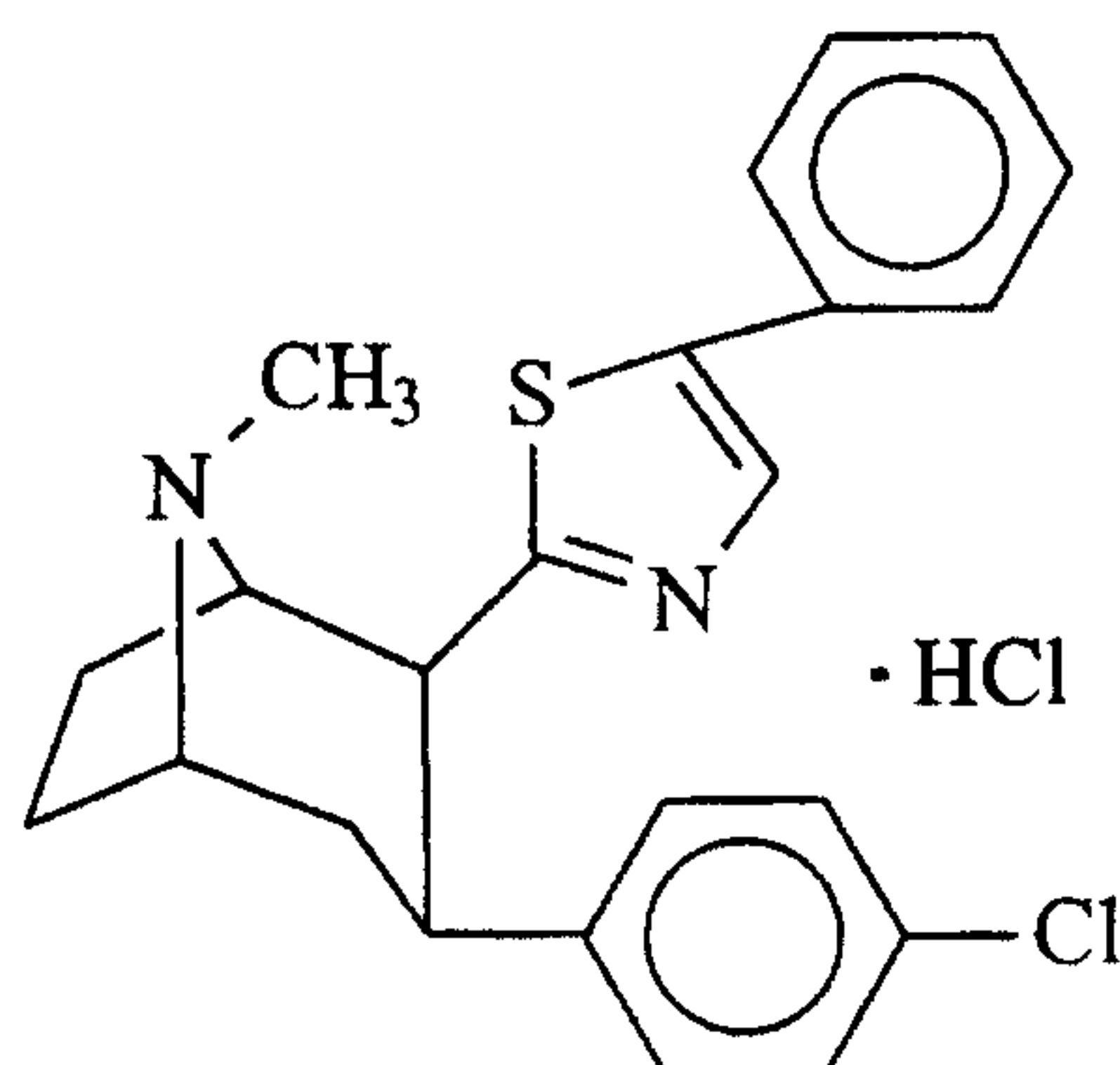
RTI-4229-214

DA 2.90

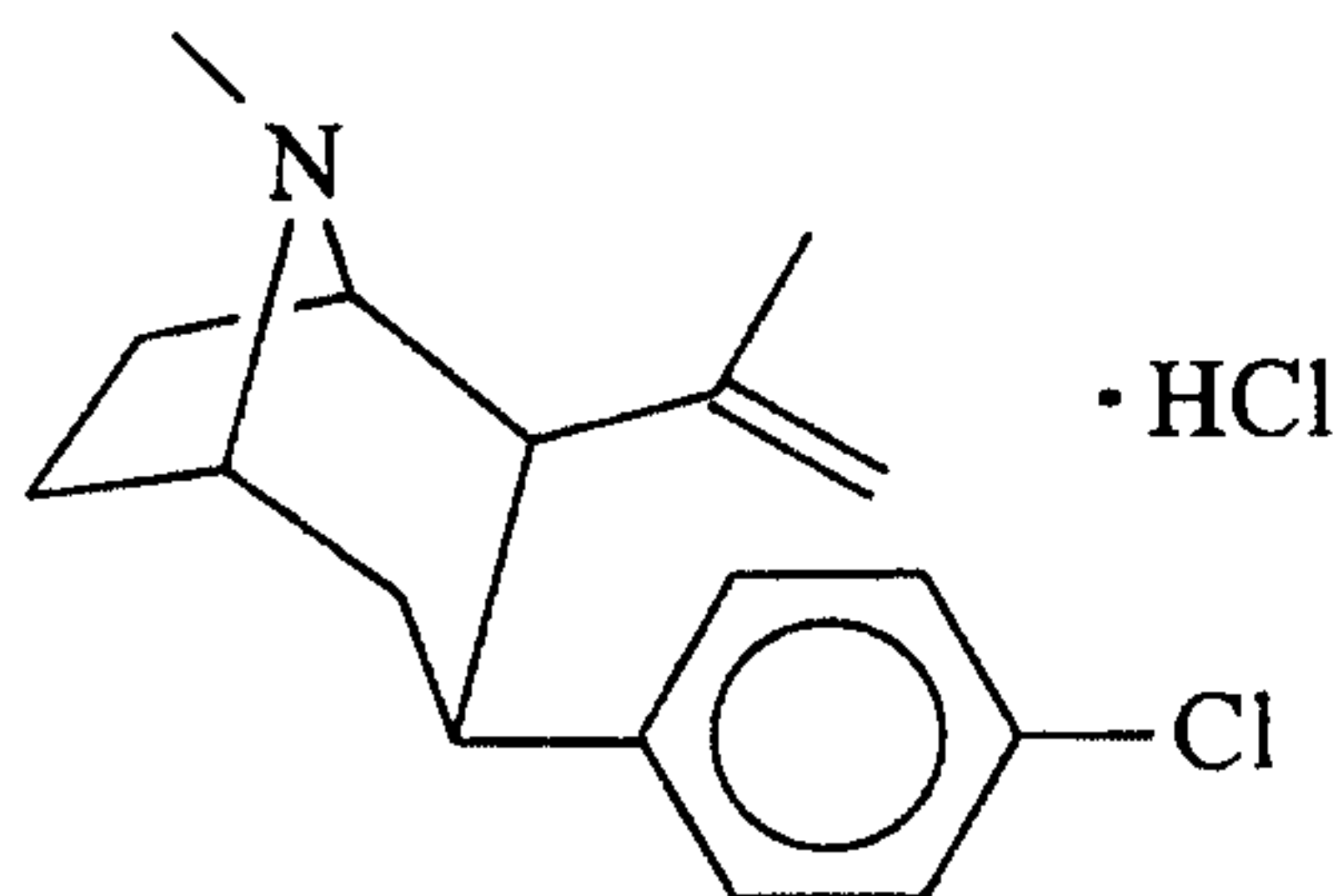
5-HT 88,800

NE_N 8550

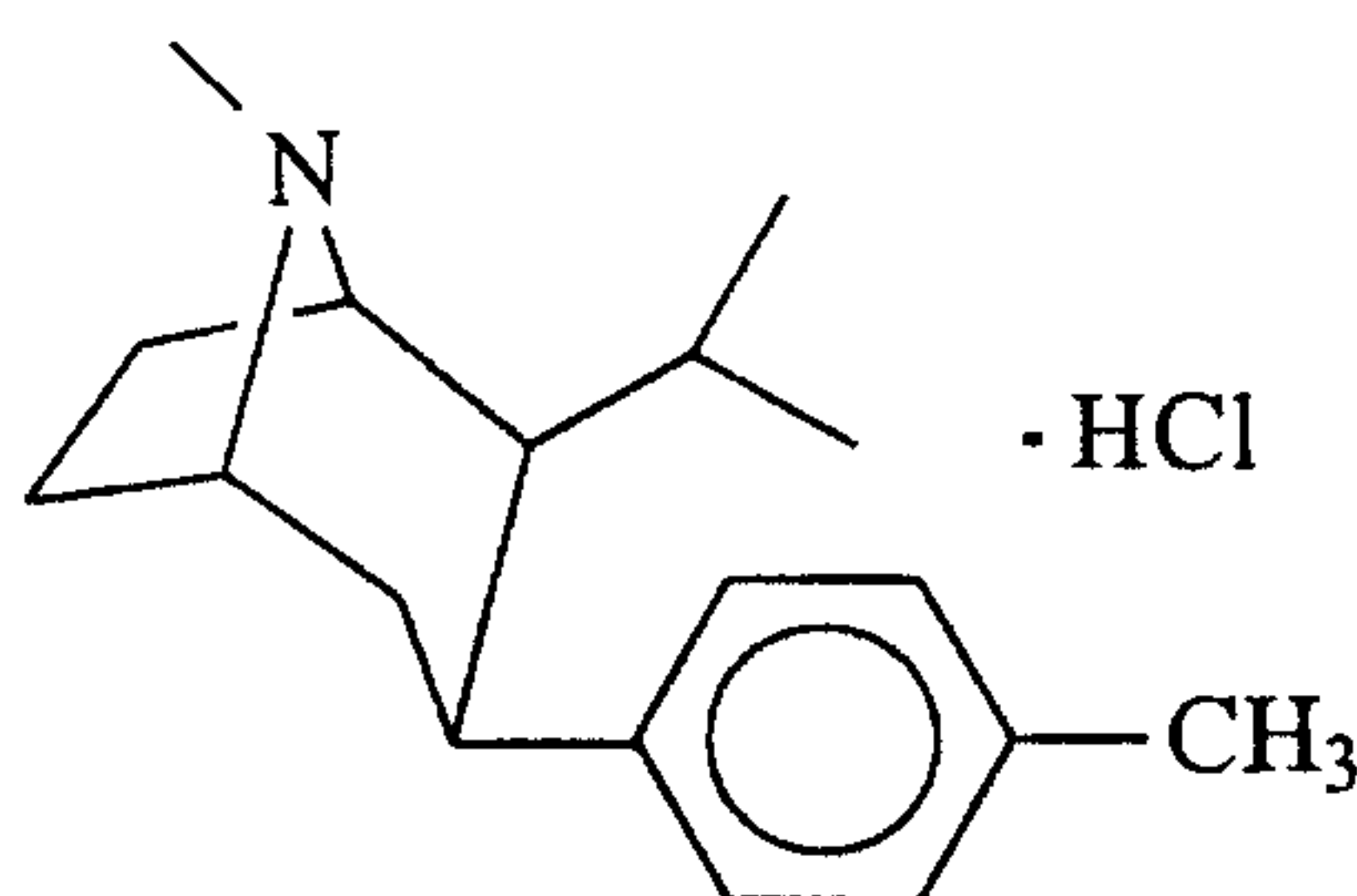
RTI-4229-219

DA 5.71 ± 0.36 5-HT 10.3415 ± 76.11 NE_N 8.563 ± 824 

RTI-4229-230

DA 1.26 ± 0.17 5-HT 57.41 ± 5.04 NE_N 141 ± 16.1 

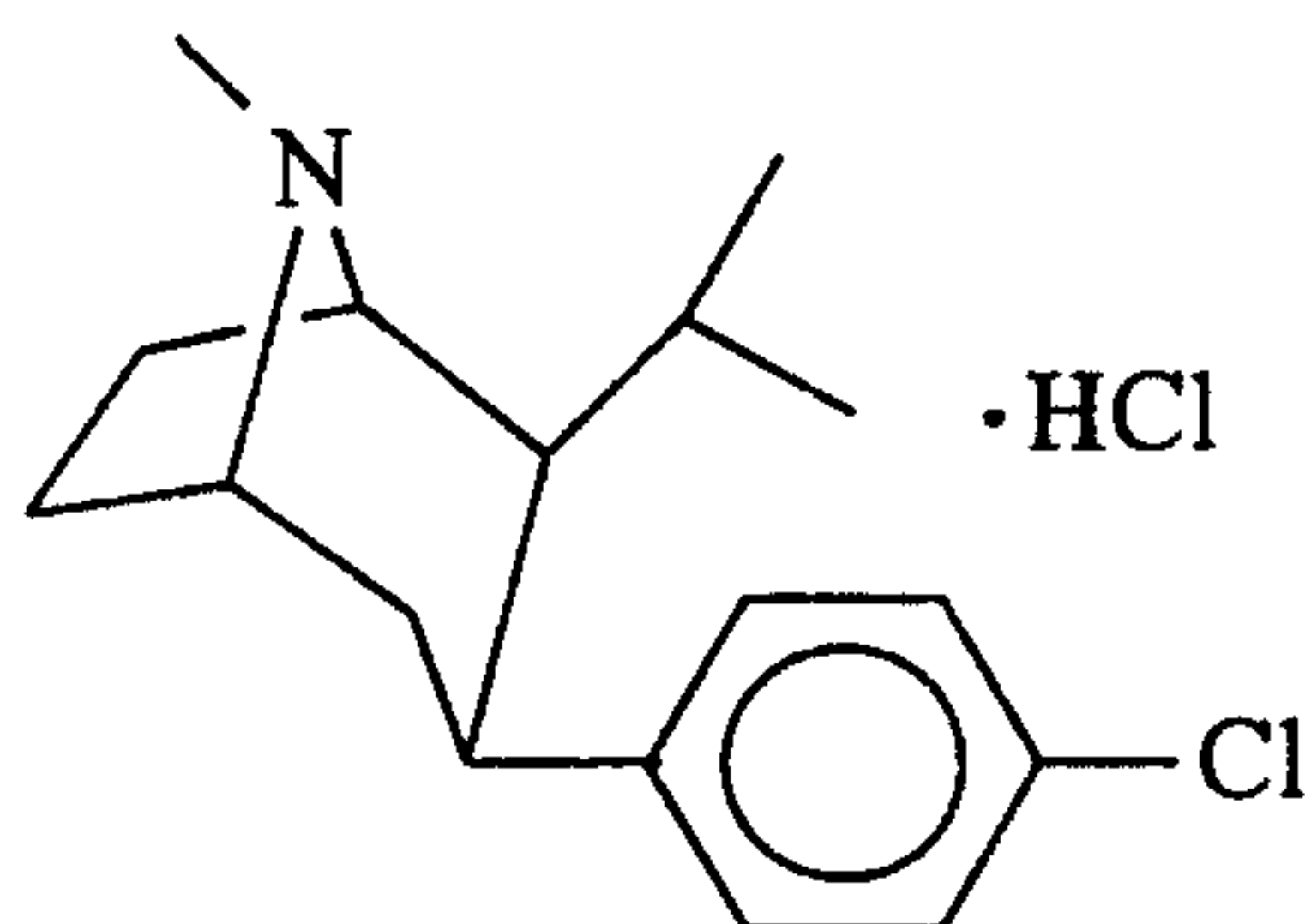
RTI-4229-239

DA 0.61 ± 0.07 5-HT 114.3 ± 3.69 NE_N 35.6 ± 2.57 

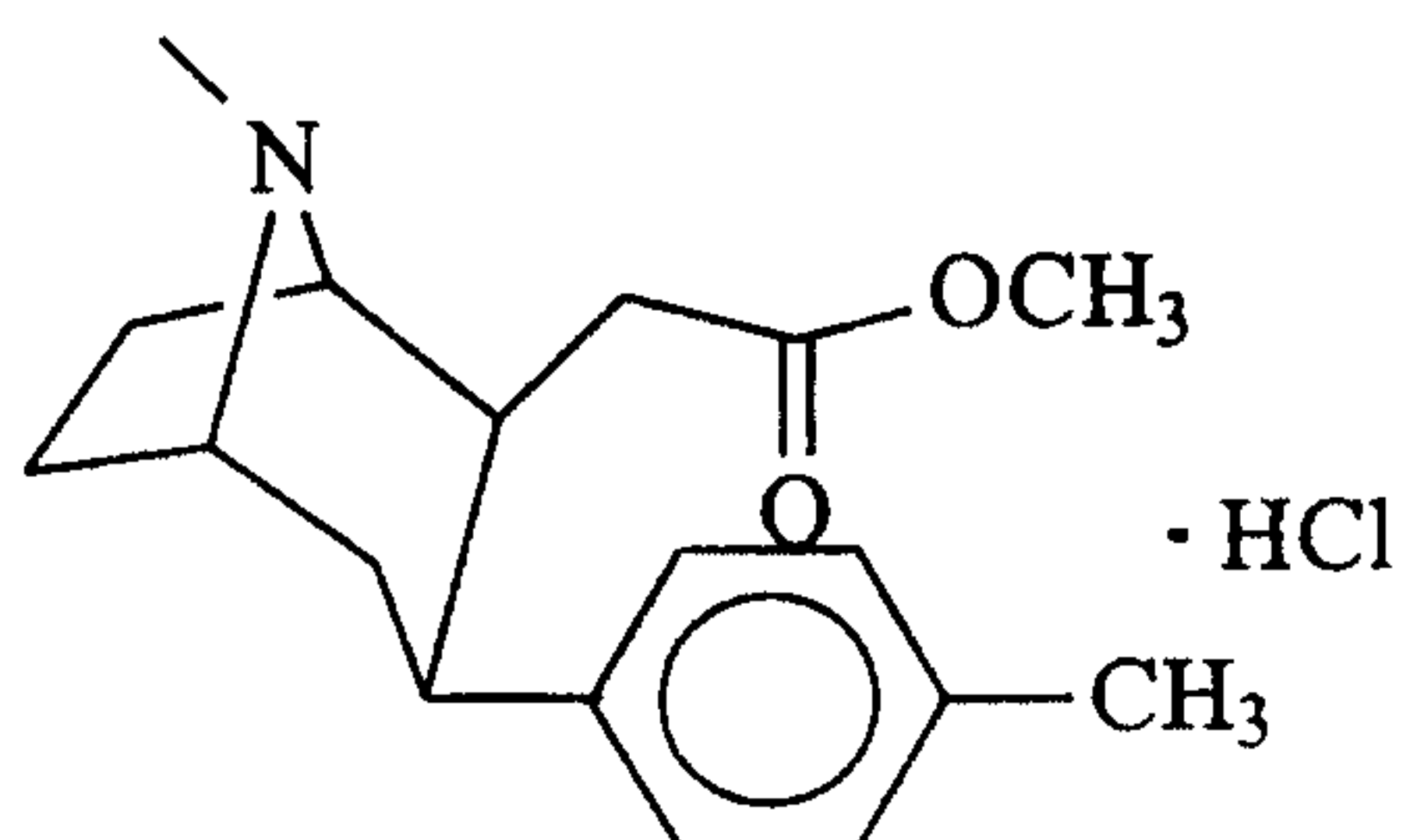
WO 99/61023

PCT/US99/10456

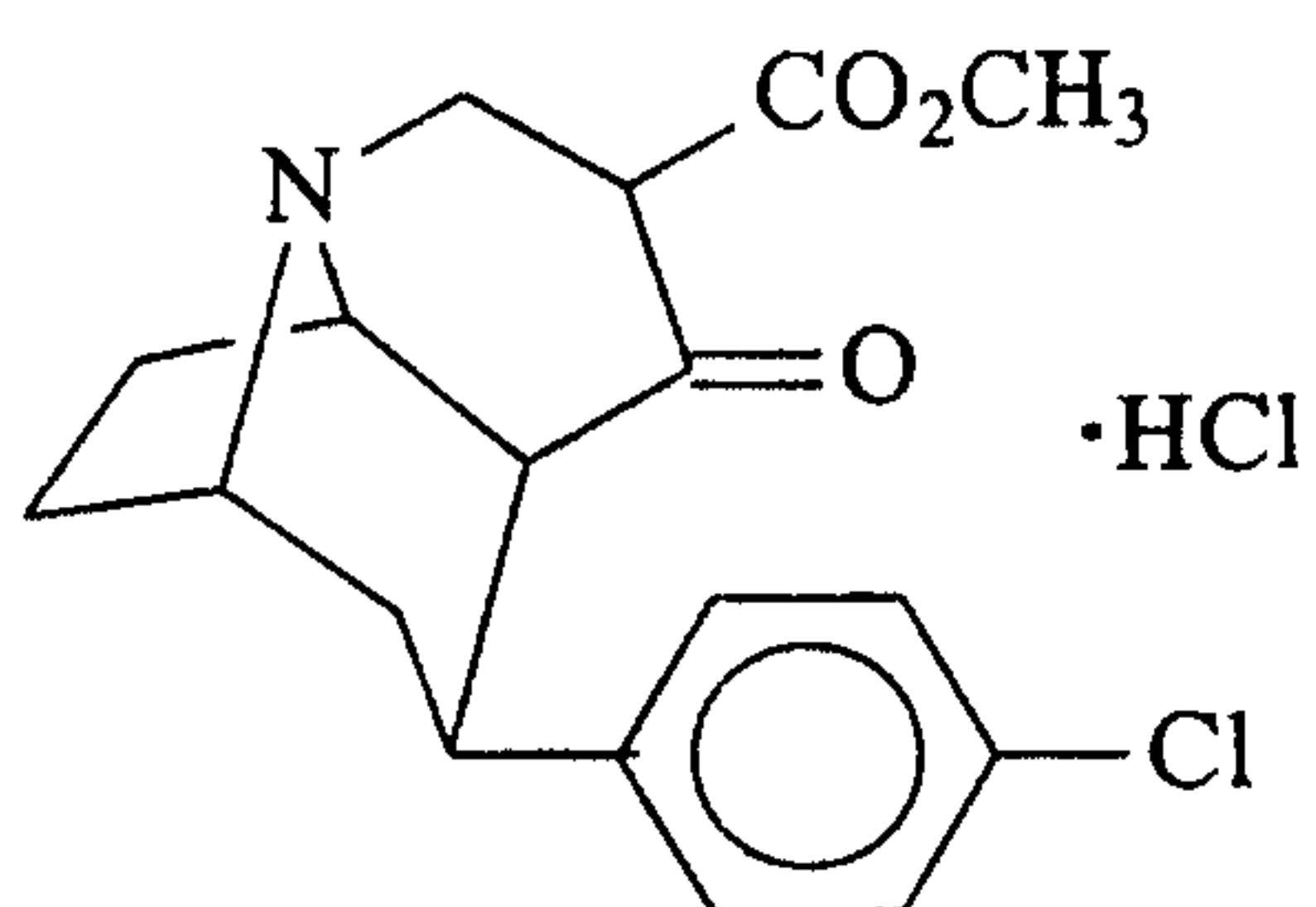
RTI-4229-240

DA 1.38 ± 0.03 5-HT 38.4 ± 2.31 NE_N 84.5 ± 3.09 

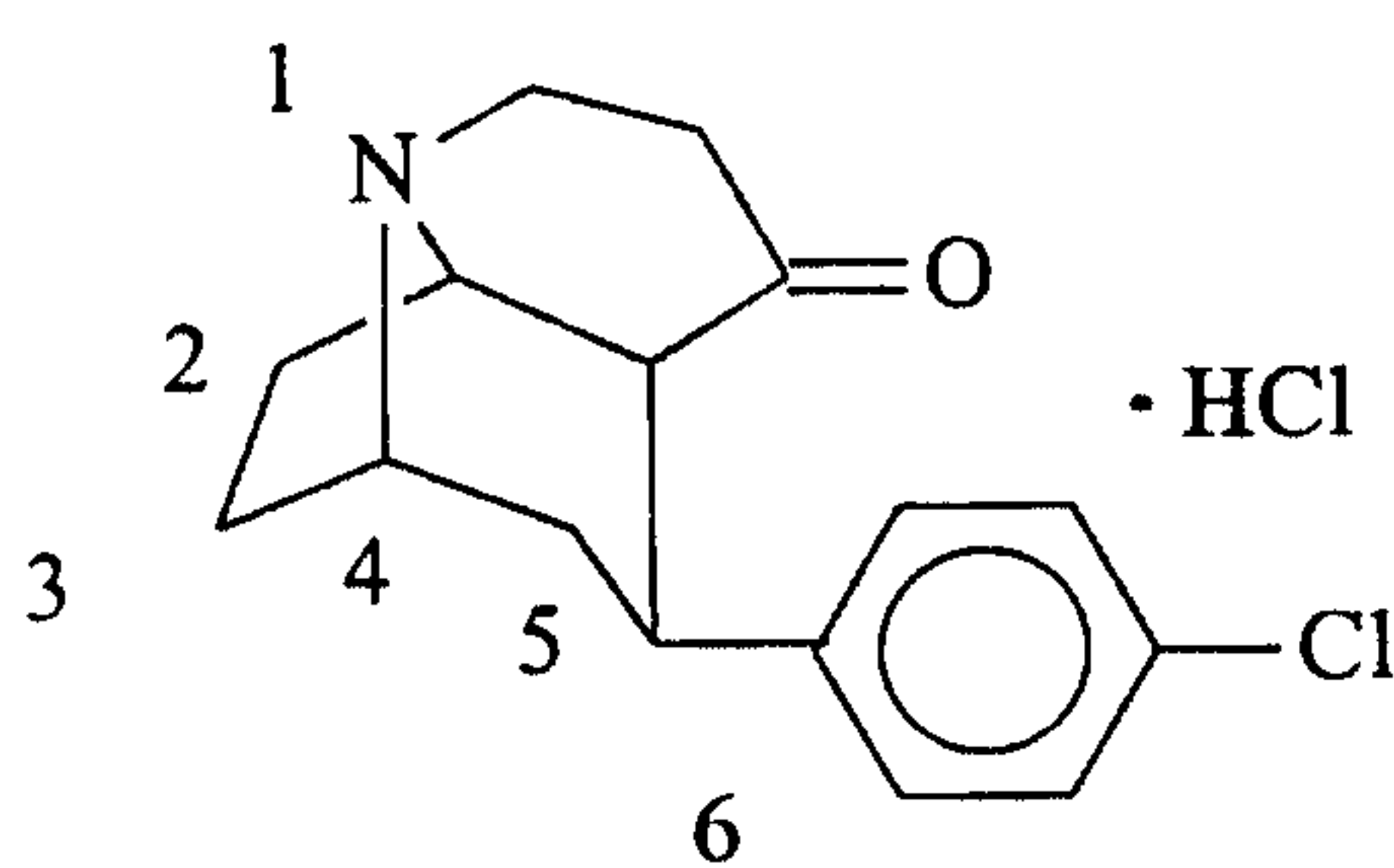
RTI-4229-241

DA 1.02 ± 0.06 5-HT 618.5 ± 28 NE_N 124 ± 3.56 

RTI-4229-242

DA 7.57 ± 0.31 5-HT 226.54 ± 27.37 NE_N 510.1 ± 51.4 

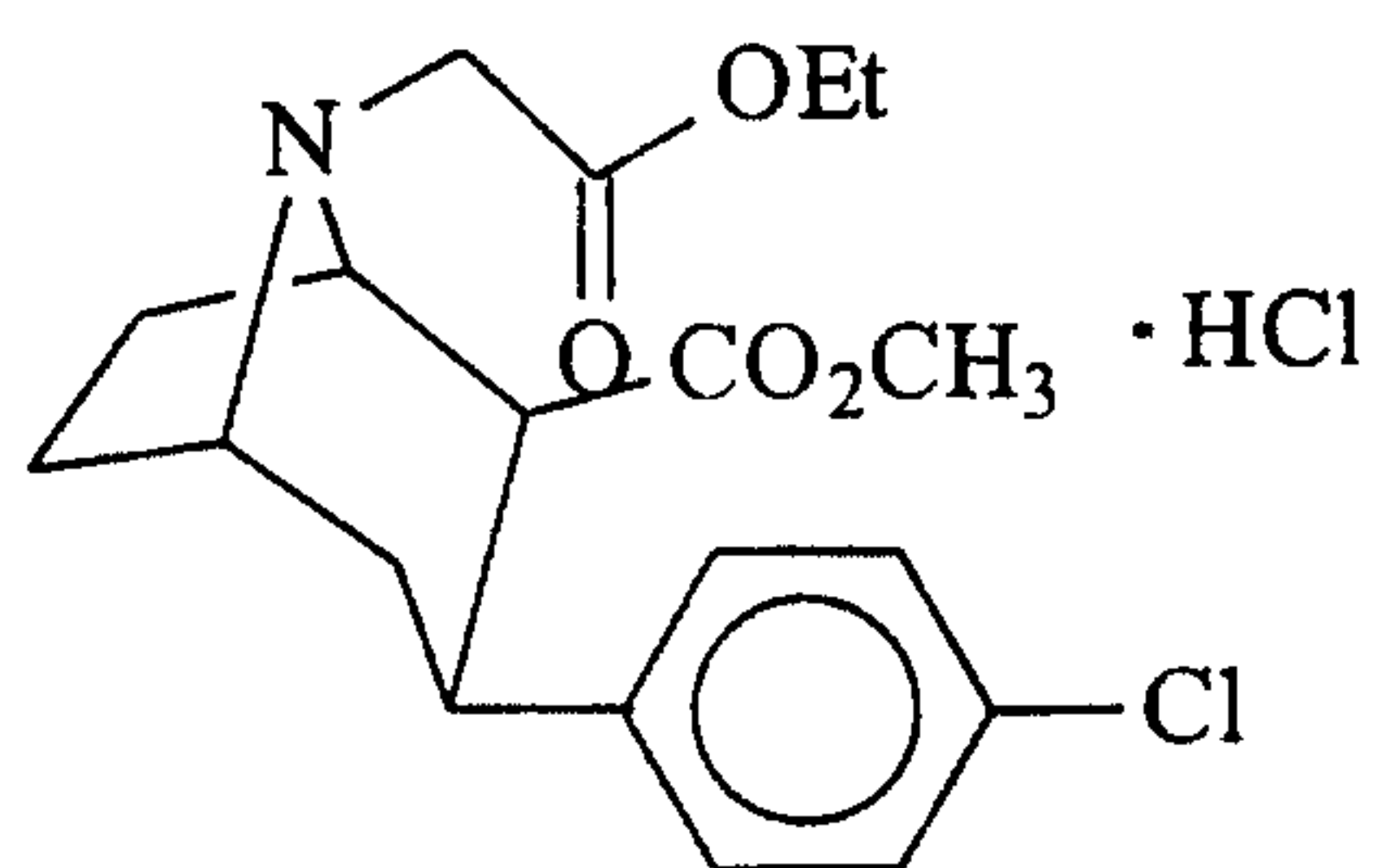
RTI-4229-243

DA 129 ± 19.6 5-HT 155.93 ± 15.27 NE_M $\pm$ NE_N $540 \pm$ 

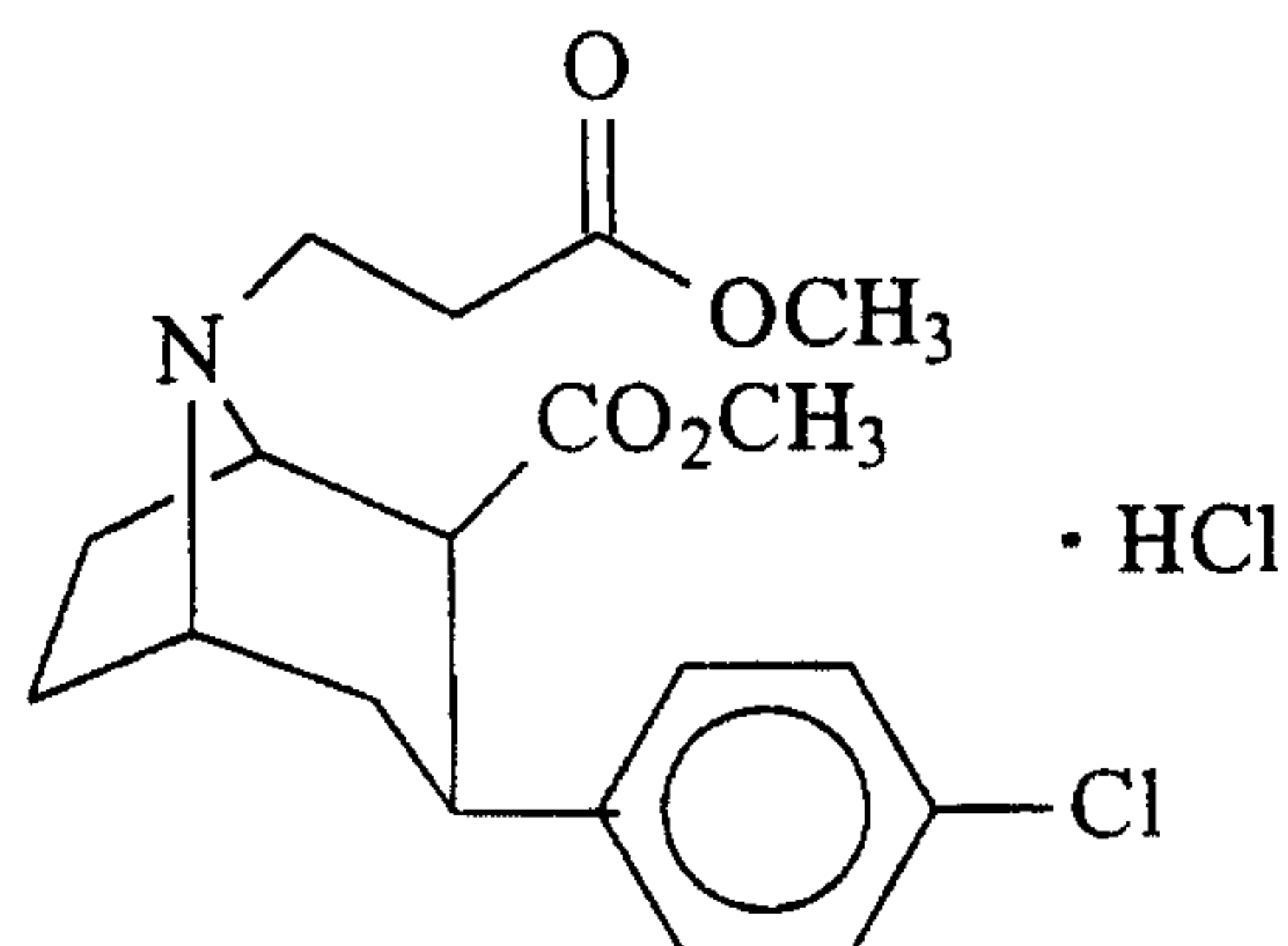
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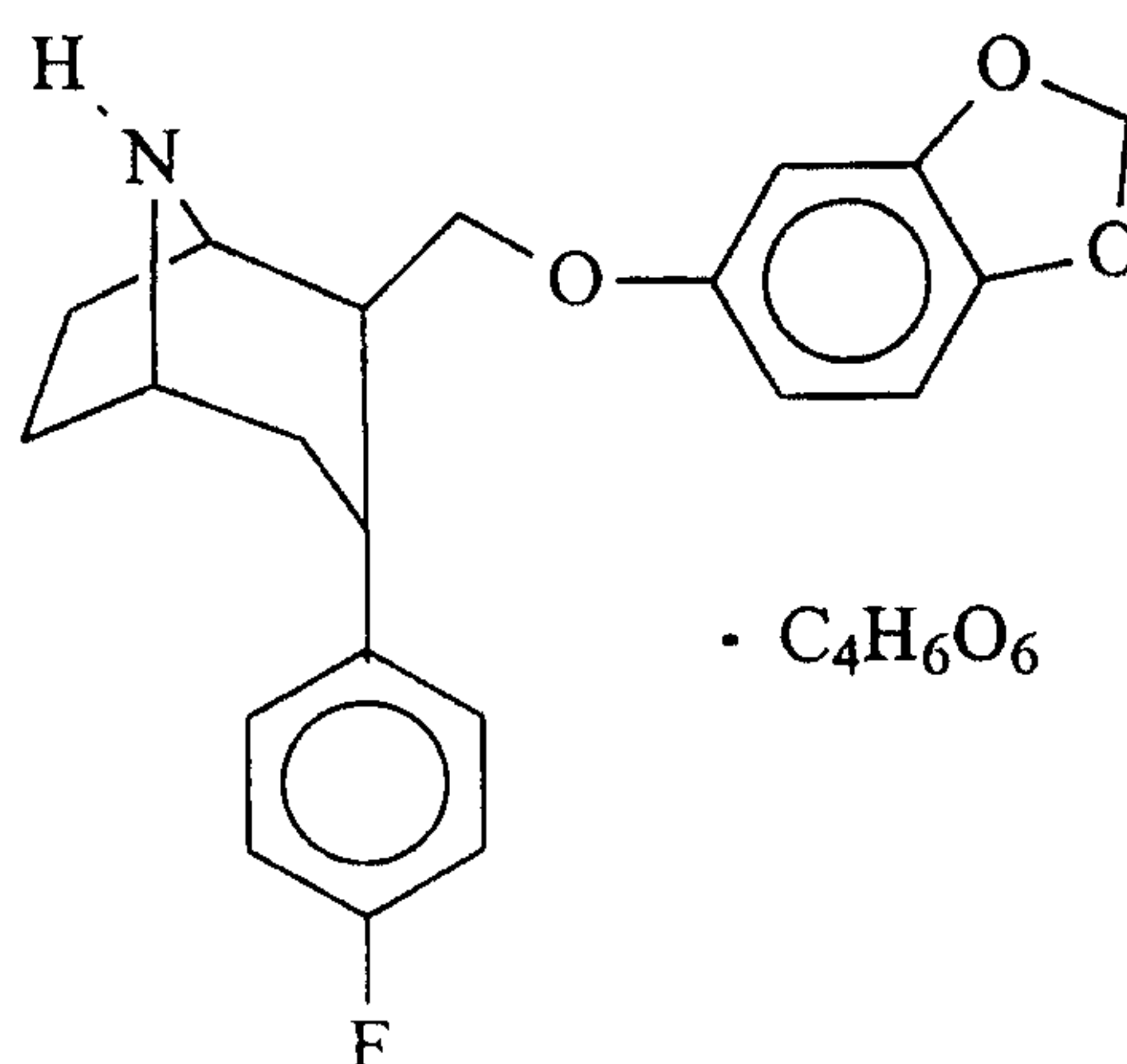
RTI-4229-251

DA 1.93 ± 0.14 5-HT 10.1 ± 1.1 NE_N 114 ± 13.1 

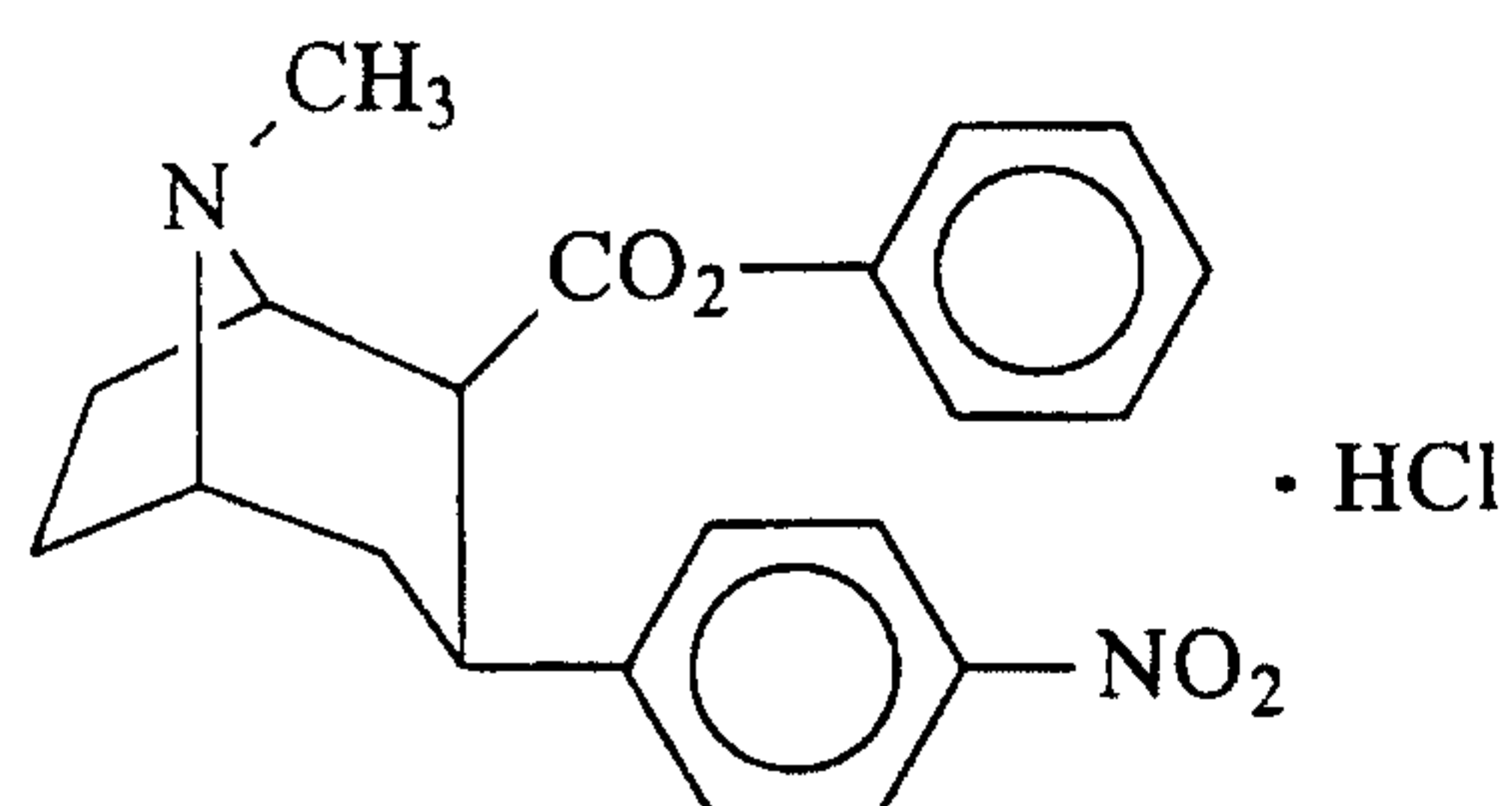
RTI-4229-252

DA 2.56 ± 0.22 5-HT 35.2 ± 2.45 NE_N 124.6 ± 8.3 

RTI-4229-274

DA 3.96 ± 0.2 5-HT 5.62 ± 0.2 NE_N 14.4 ± 1.3 

RTI-4229-277

DA 5.94 ± 0.61 5-HT $2.909.71 \pm 255.41$ NE_N $5.695.38 \pm 214.72$ 

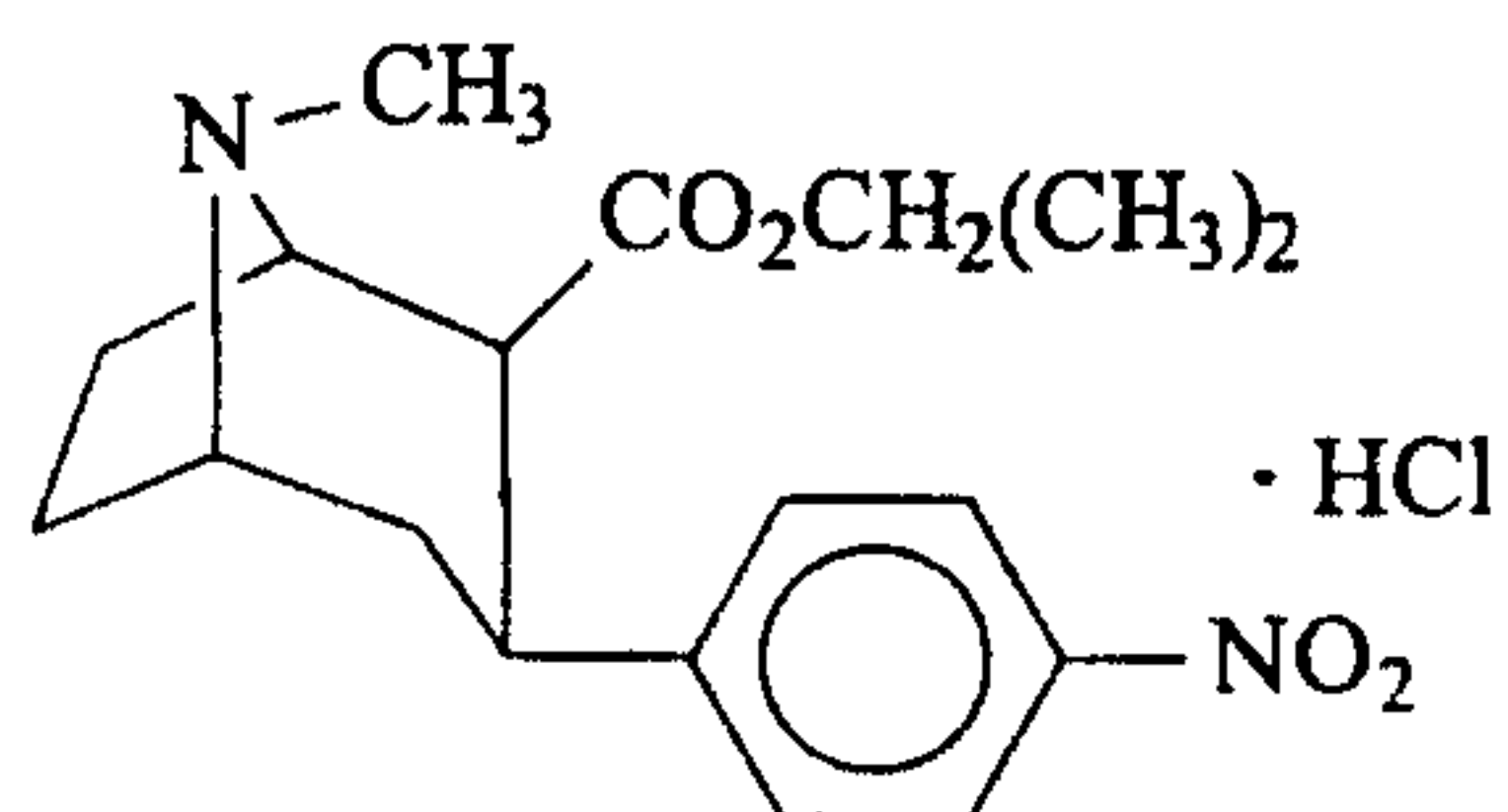
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RTI-4229-278

DA 8.14 ± 0.73

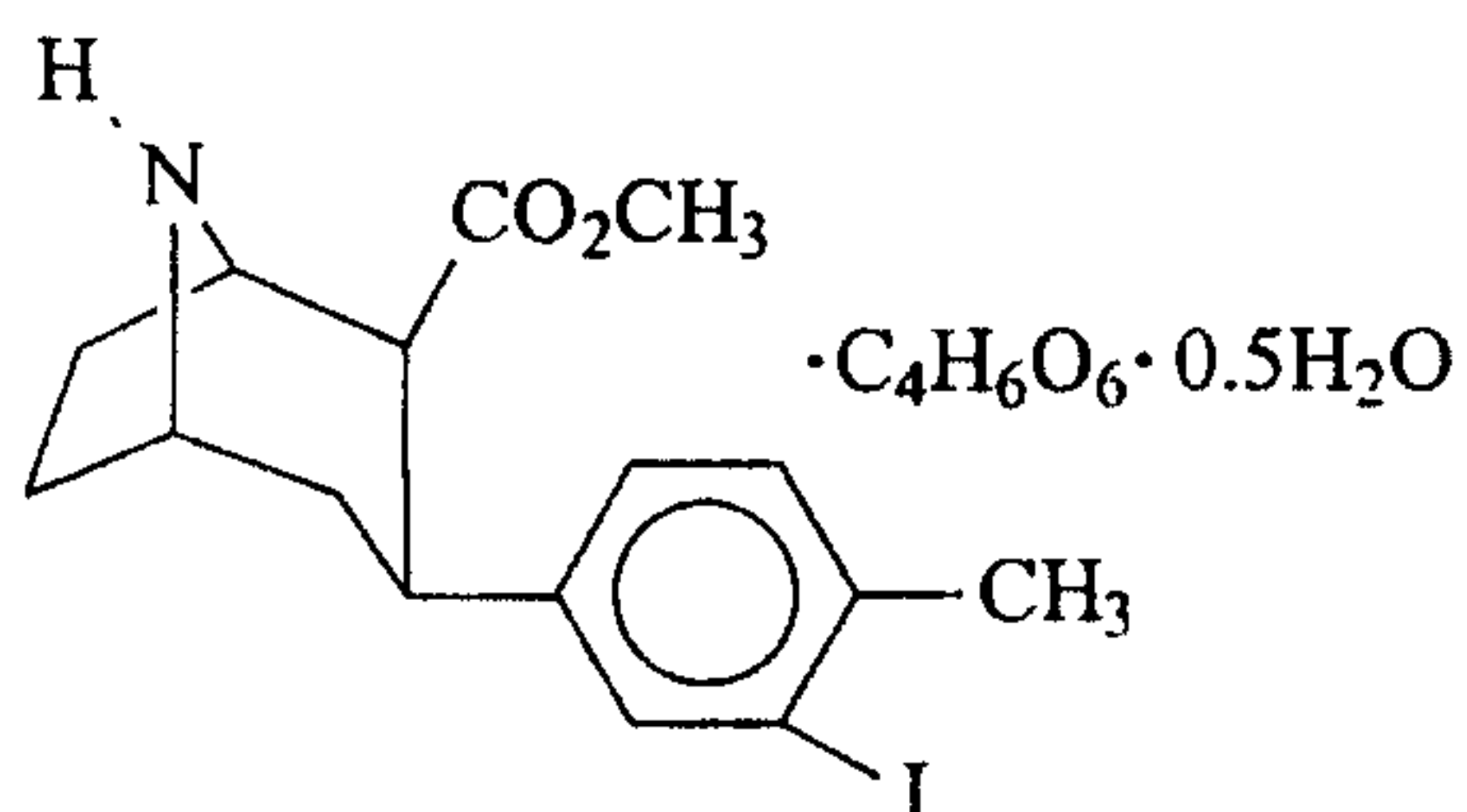
5-HT 2.146.50 ± 138.71

NE_N 4.095.01 ± 413.45

RTI-4229-279

DA 5.96 ± 0.48

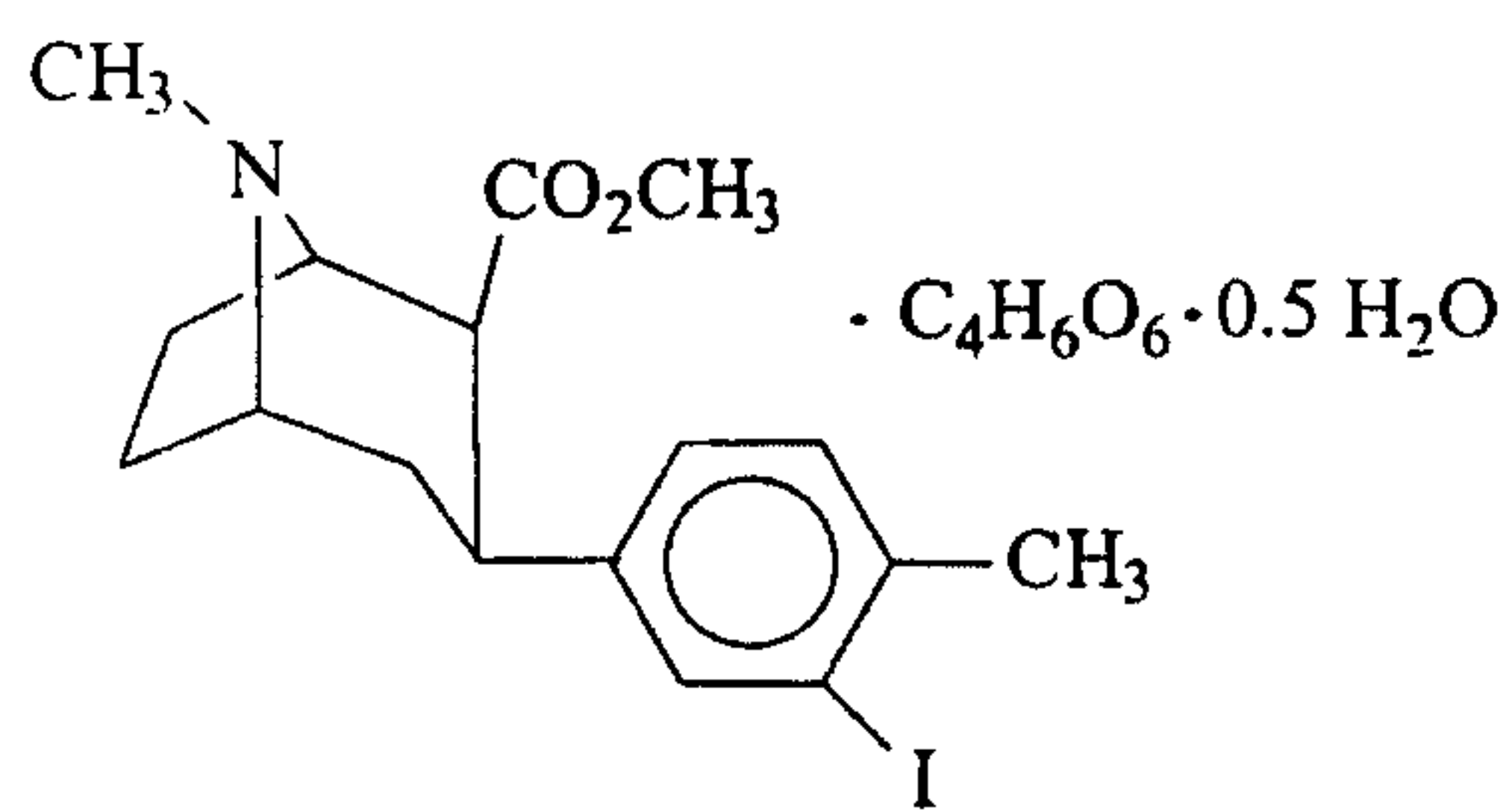
5-HT 1.06 ± 0.10

NE_N 74.3 ± 3.8

RTI-4229-280

DA 3.12 ± 0.39

5-HT 6.81 ± 0.41

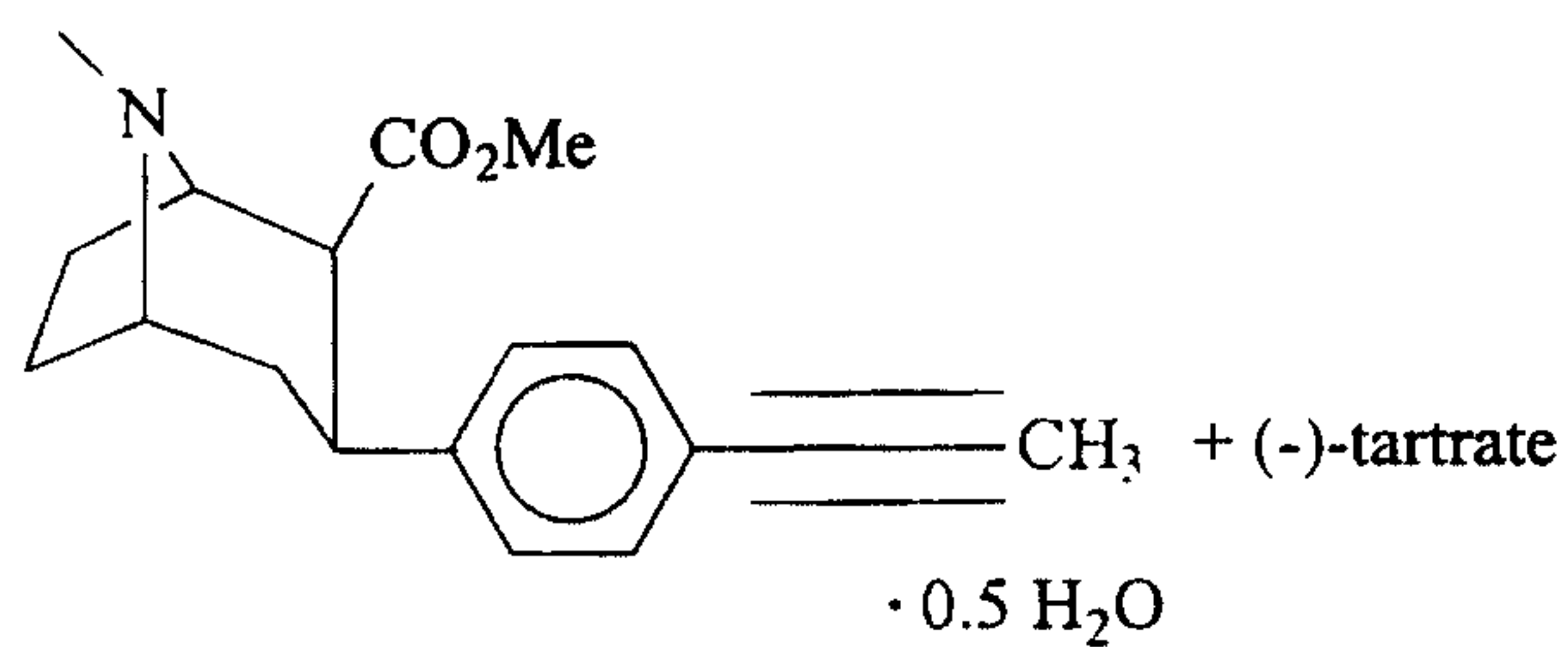
NE_N 484.13 ± 51.6

RTI-4229-281

BIH-141-7

DA 2.37 ± 0.28

5-HT 15.69 ± 1.5

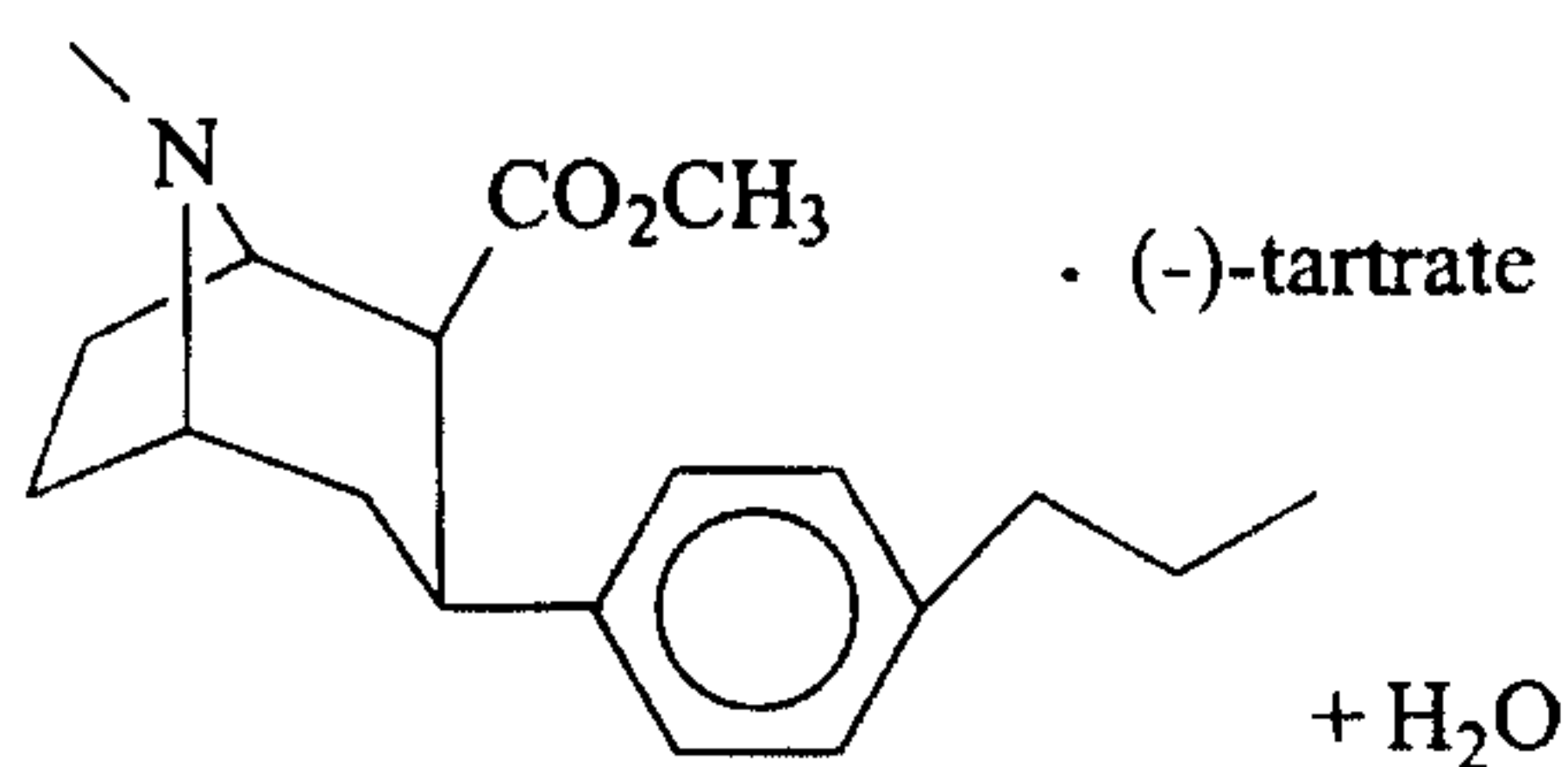
NE_N 820.5 ± 45.8

RTI-4229-282

BIH-141-2

DA 68.53 ± 7.08

5-HT 70.38 ± 4.13

NE_N 3921.58 ± 130

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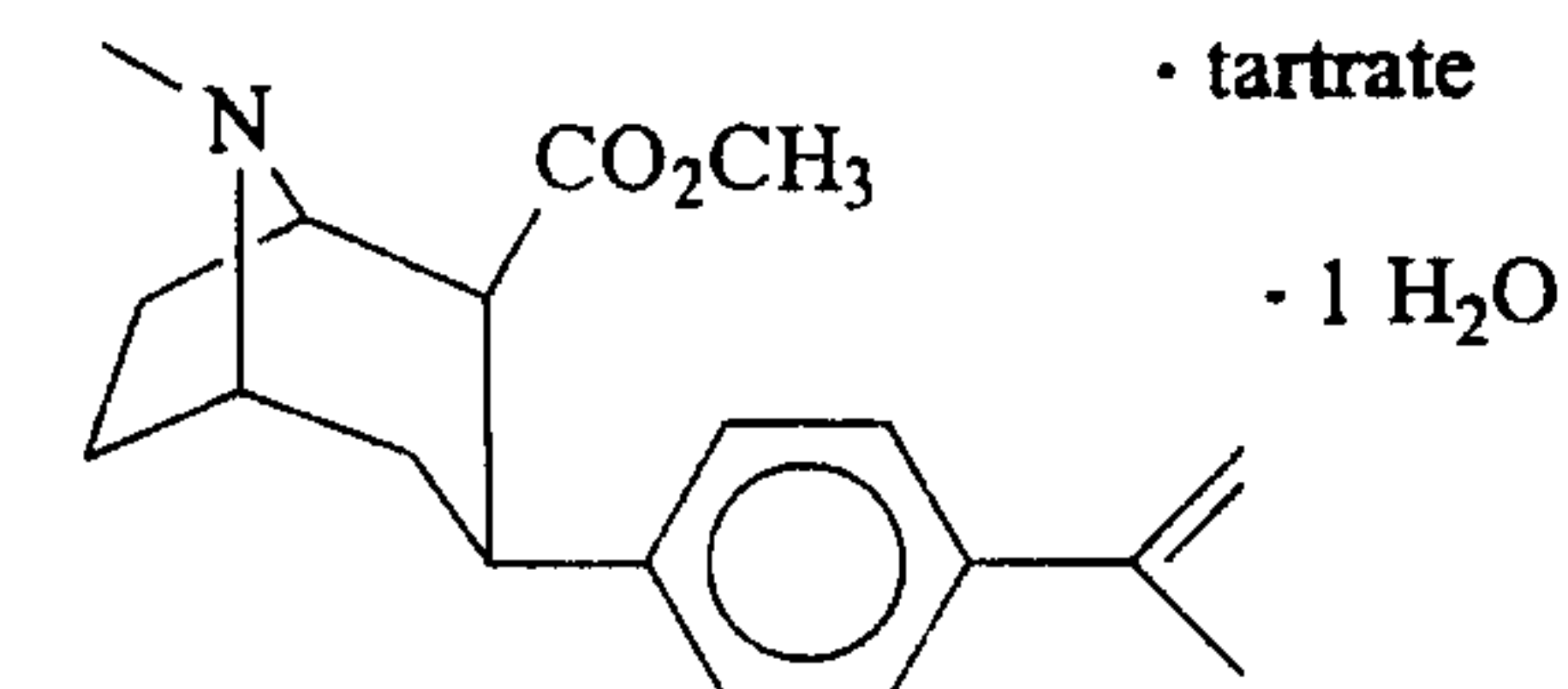
PCT/US99/10456

RTI-4229-283

BIH-141-2

DA 14.35 ± 0.3

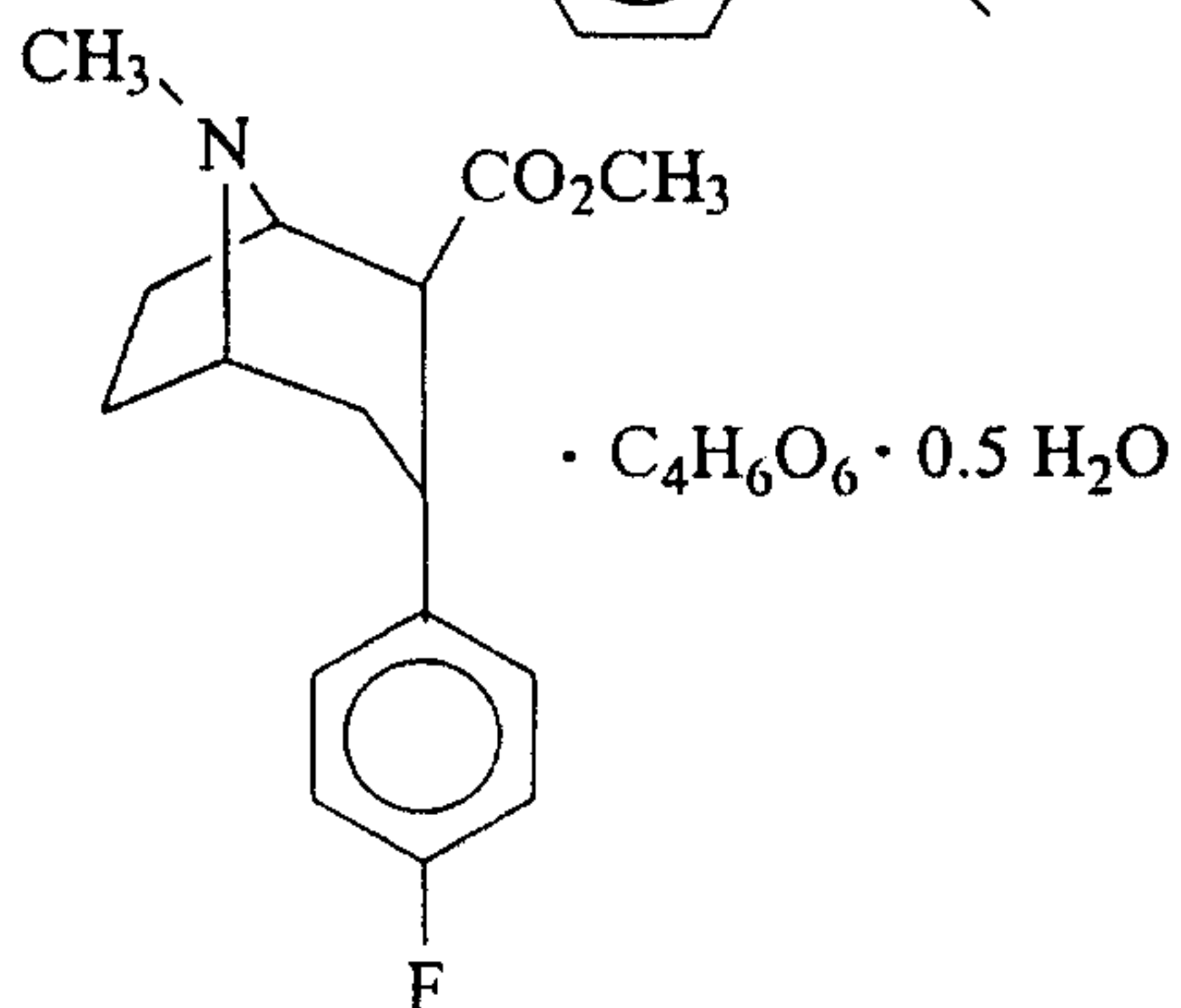
5-HT 3.13 ± 0.16

NE_N 3125 ± 333

RTI-4229-286

DA 20.7 ± 0.57

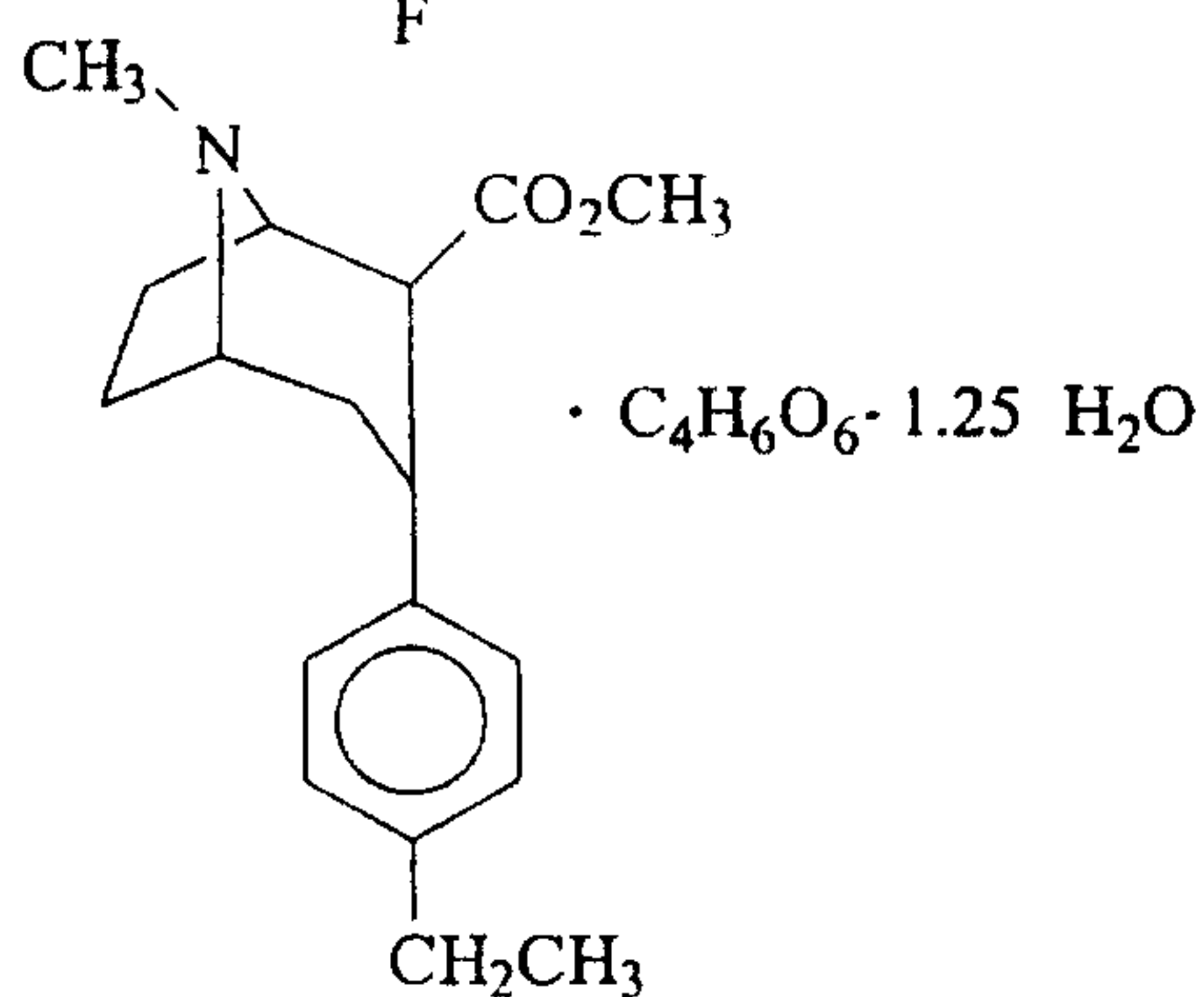
5-HT 5062 ± 485

NE_N 1231 ± 91

RTI-4229-287

DA 325 ± 20

5-HT 1686 ± 140

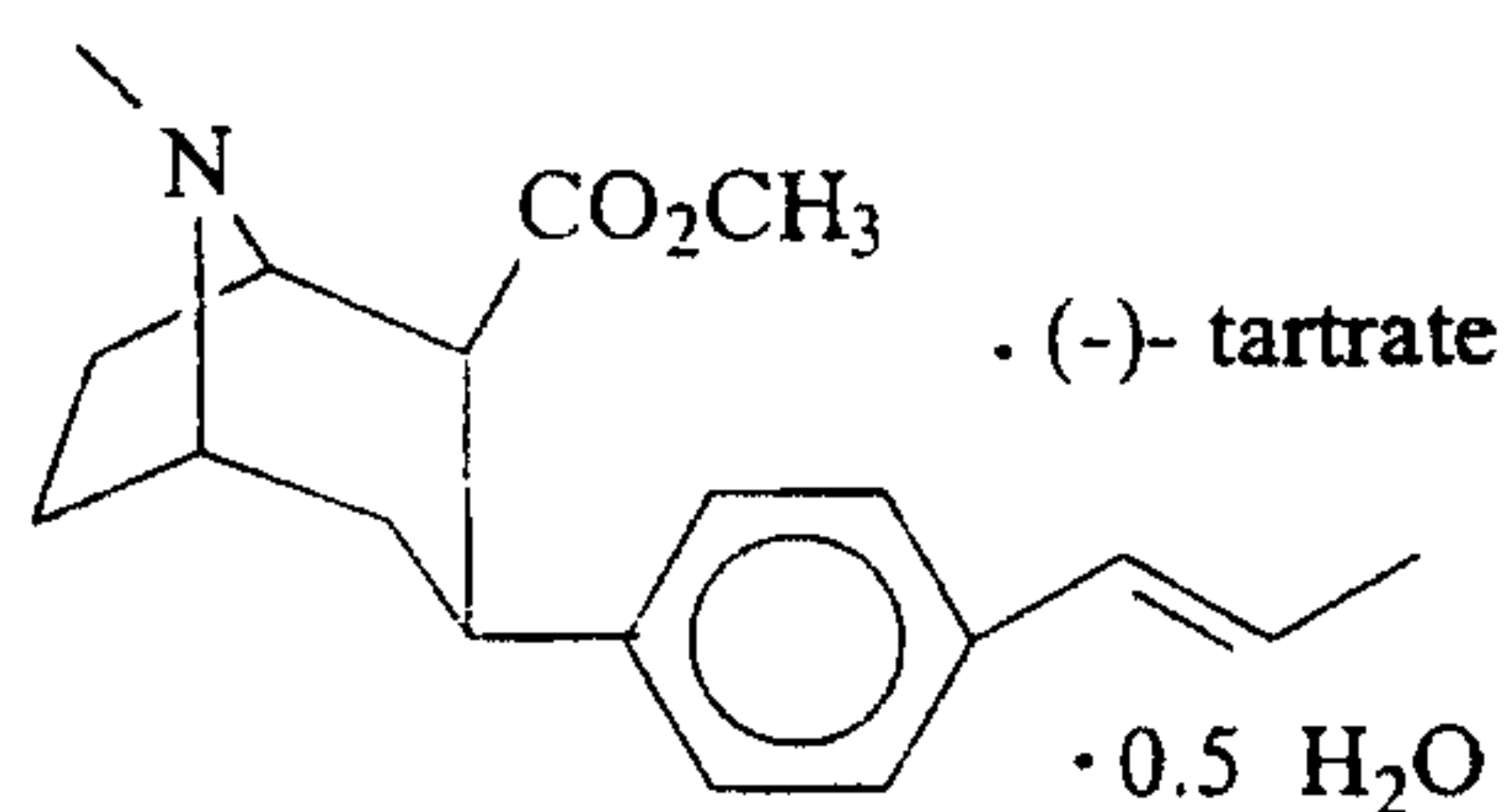
NE_N 17.819 ± 440

RTI-4229-296

BIH-141-1

DA 5.29 ± 0.53

5-HT 11.39 ± 0.28

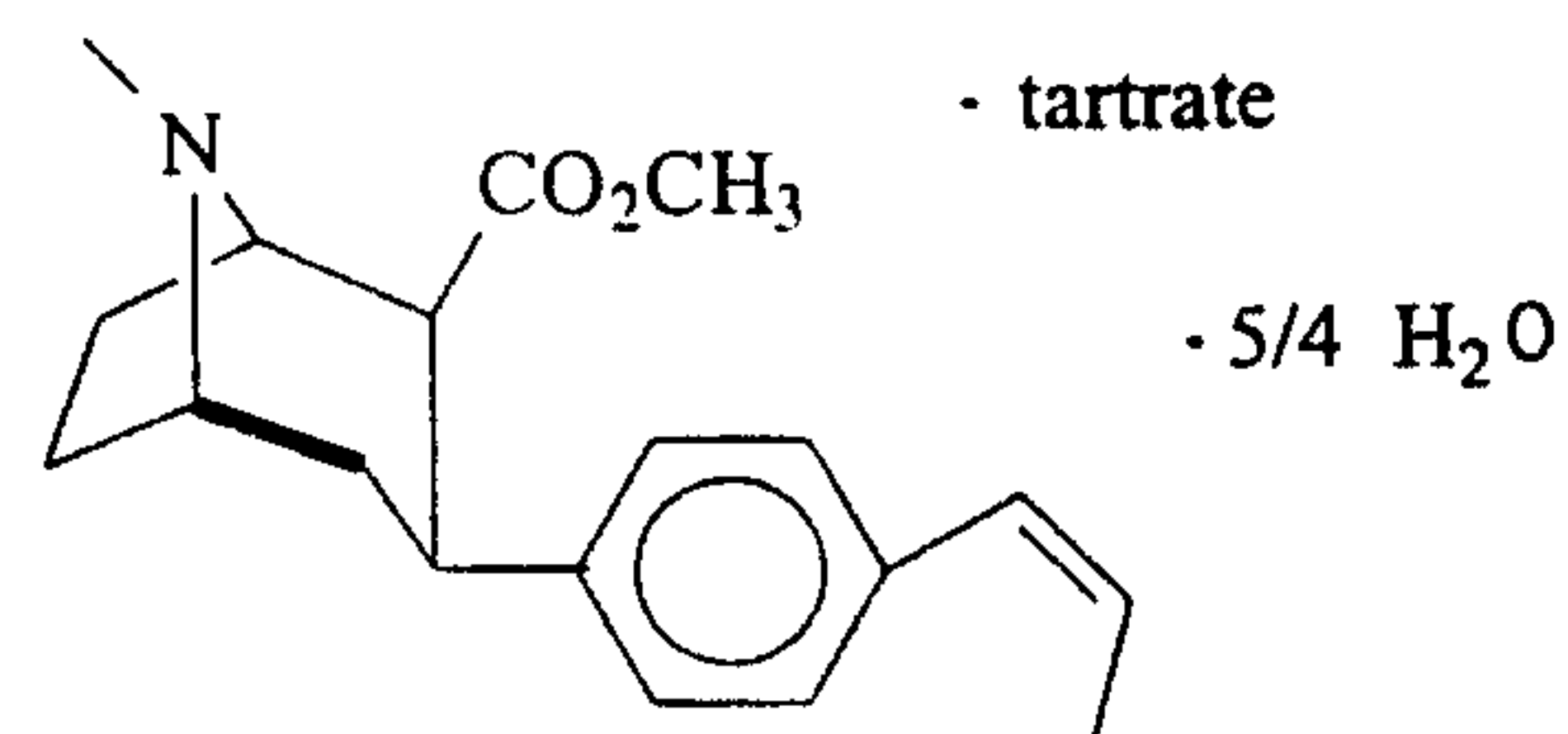
NE_N 1592.23 ± 93.4

RTI-4229-304

BIH-141-11

DA 15.04 ± 1.2

5-HT 7.09 ± 0.71

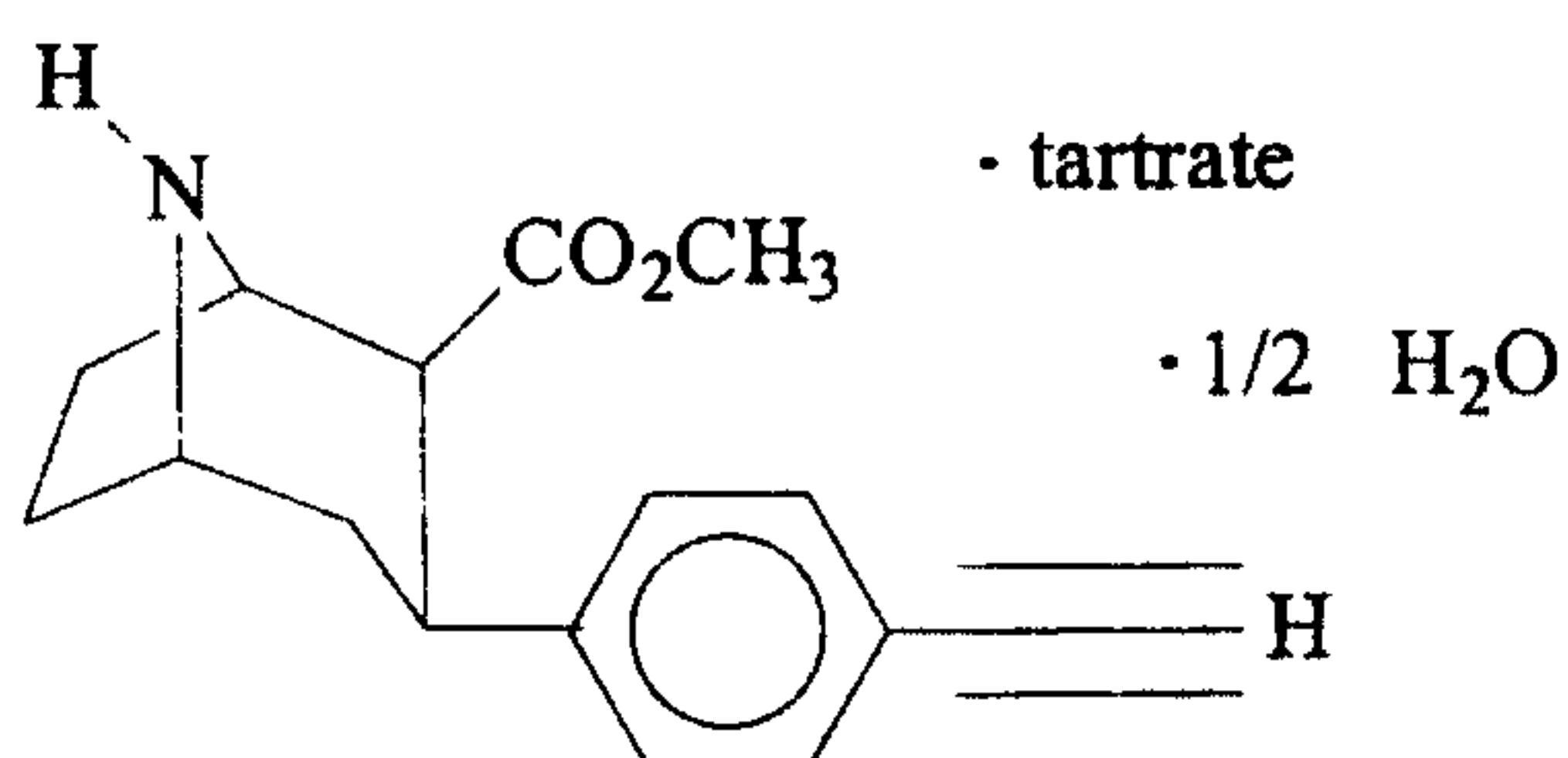
NE_N 2799 ± 300

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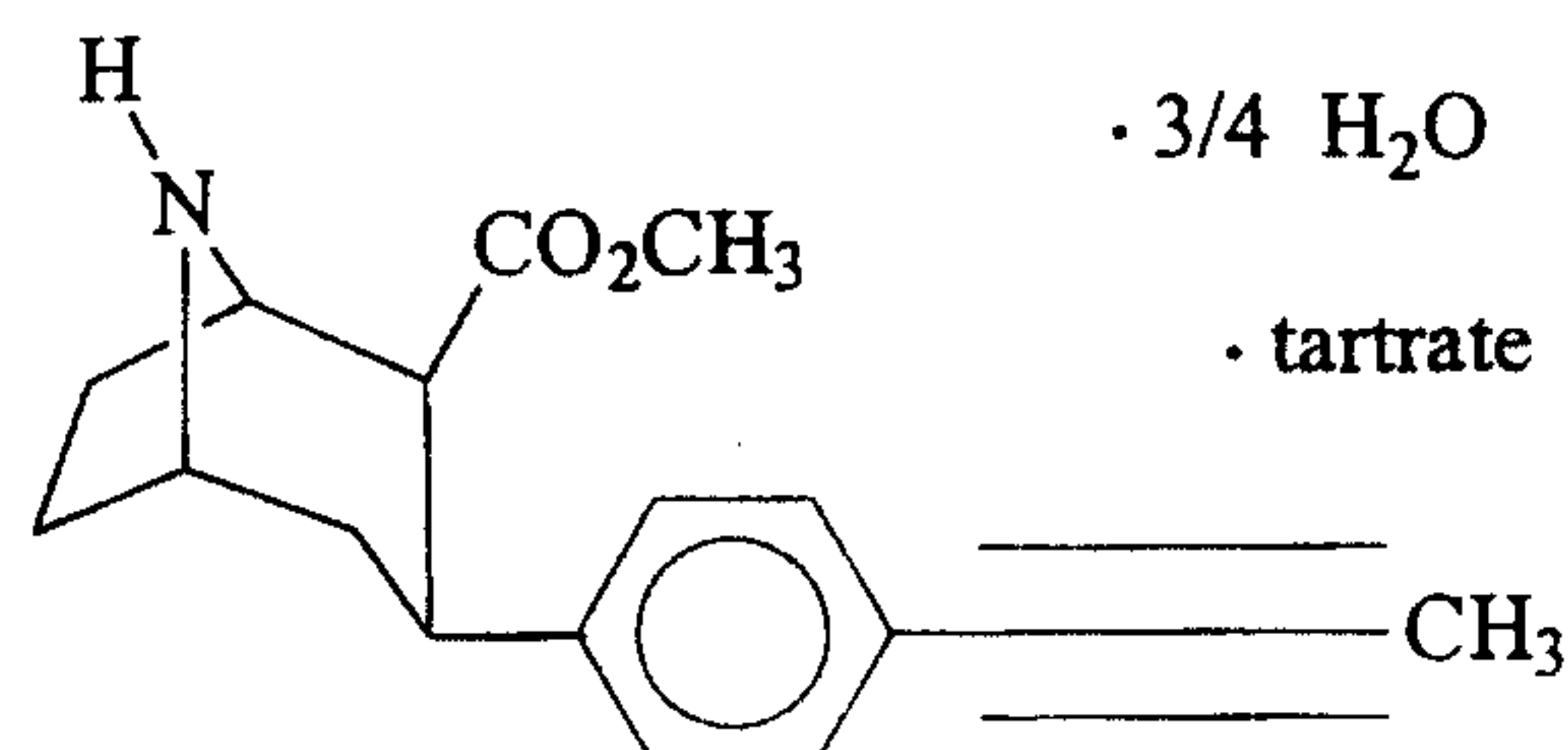
RTI-4229-305

BIH-141-18

DA 1.24 ± 0.11 5-HT 1.59 ± 0.2 NE_N 21.8 ± 1.0 

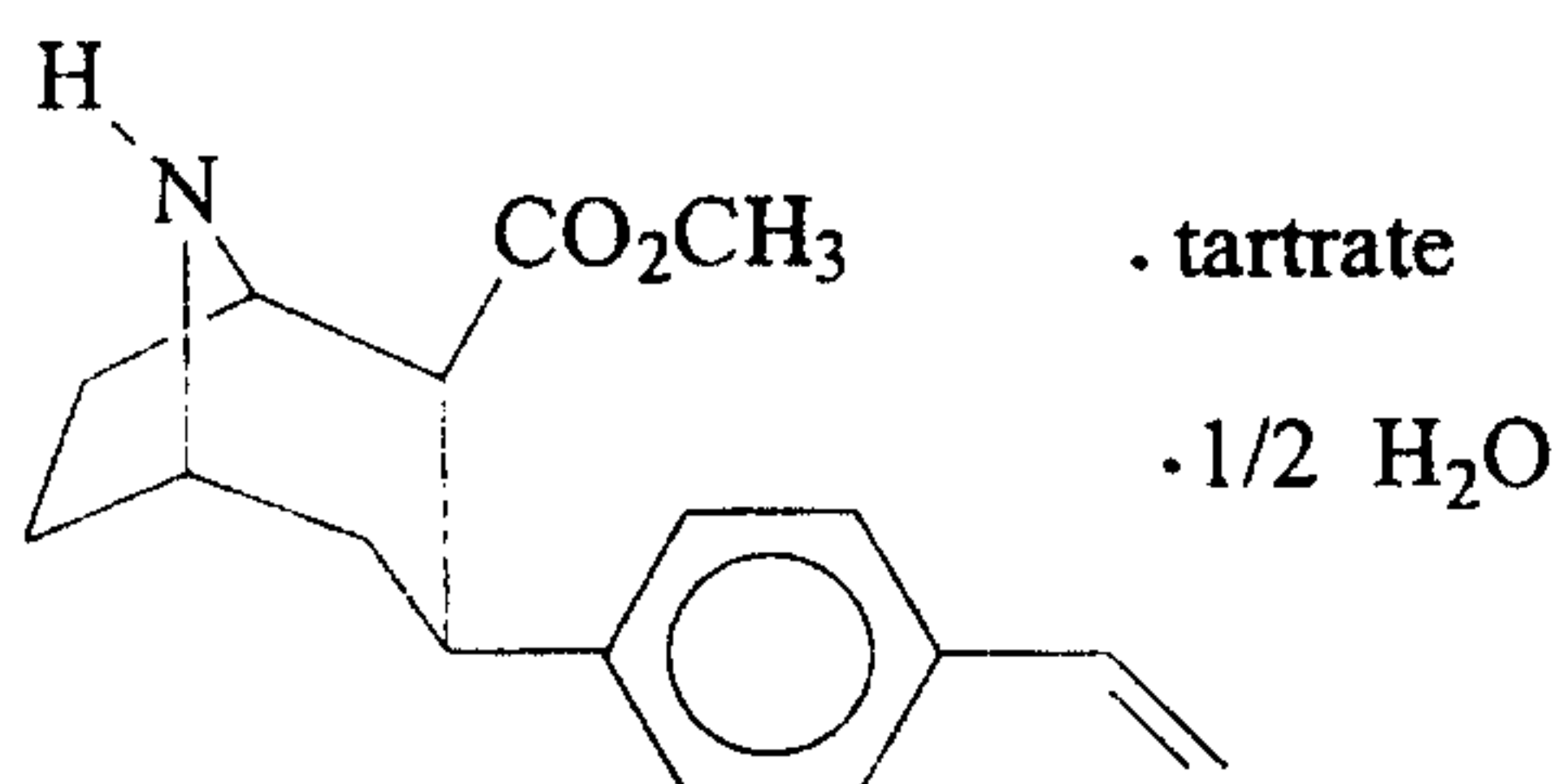
RTI-4229-307

BIH-141-15

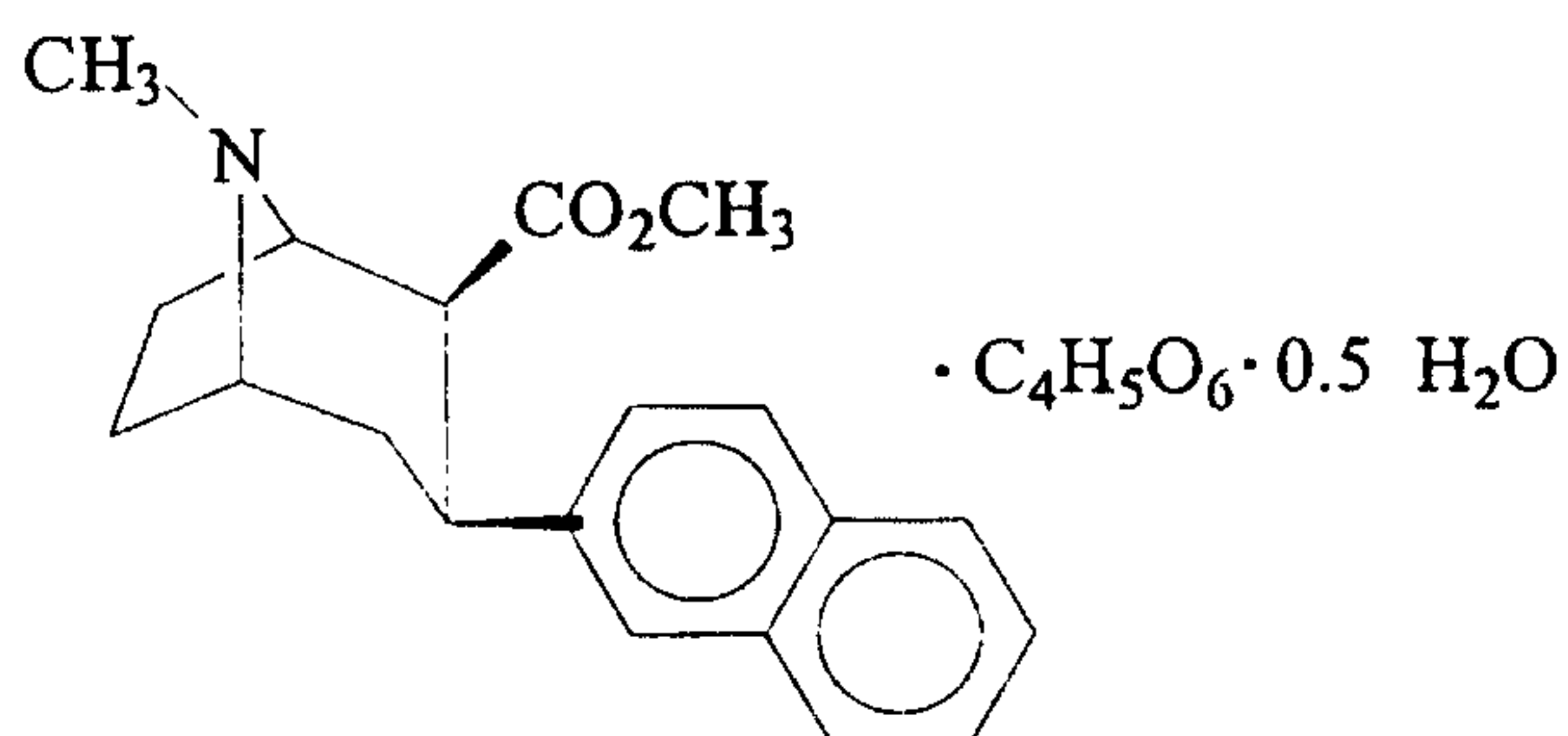
DA 6.11 ± 0.67 5-HT 3.16 ± 0.33 NE_N 115.8 ± 5.1 

RTI-4229-309

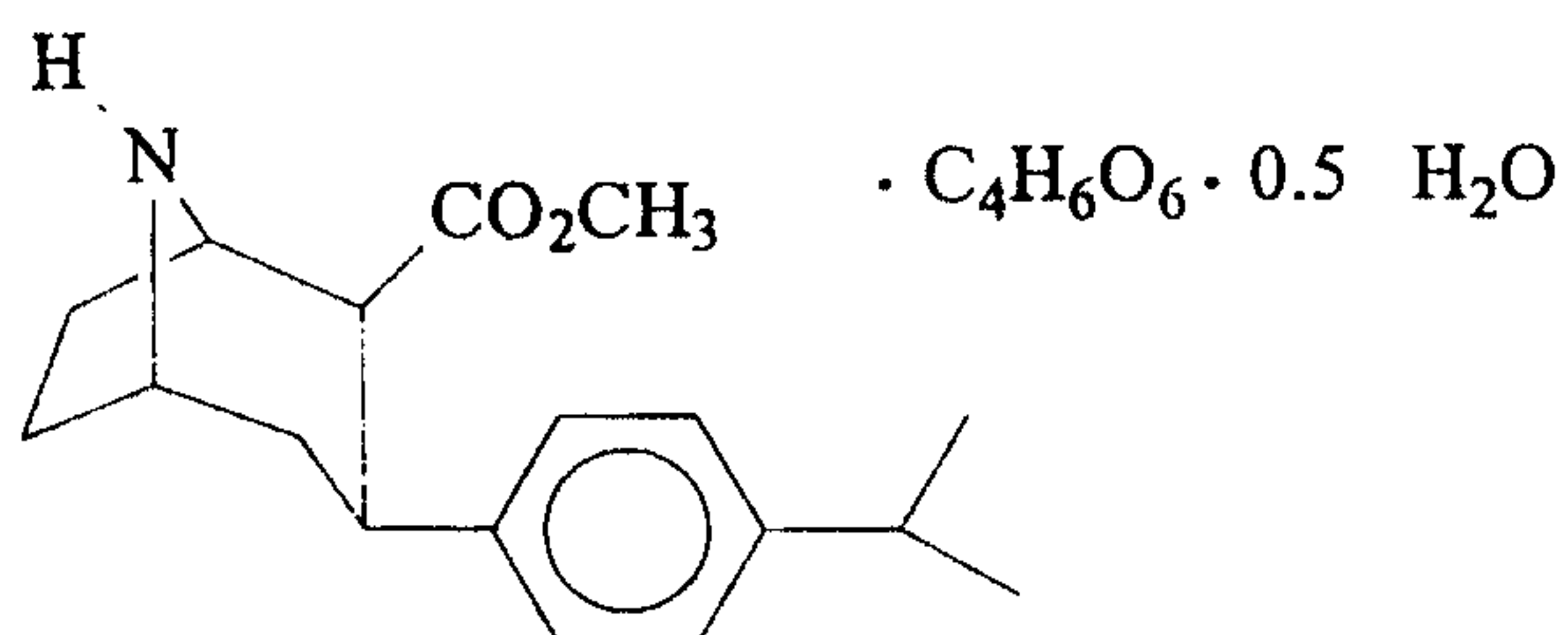
BIH-141-17

DA 1.73 ± 0.05 5-HT 2.25 ± 0.17 NE_N 14.9 ± 1.18 

RTI-4229-318

DA 0.51 ± 0.03 5-HT 0.80 ± 0.06 NE_N 21.1 ± 1.0 

RTI-4229-330

DA 310.2 ± 21 5-HT 15.1 ± 0.97 NE_N ±

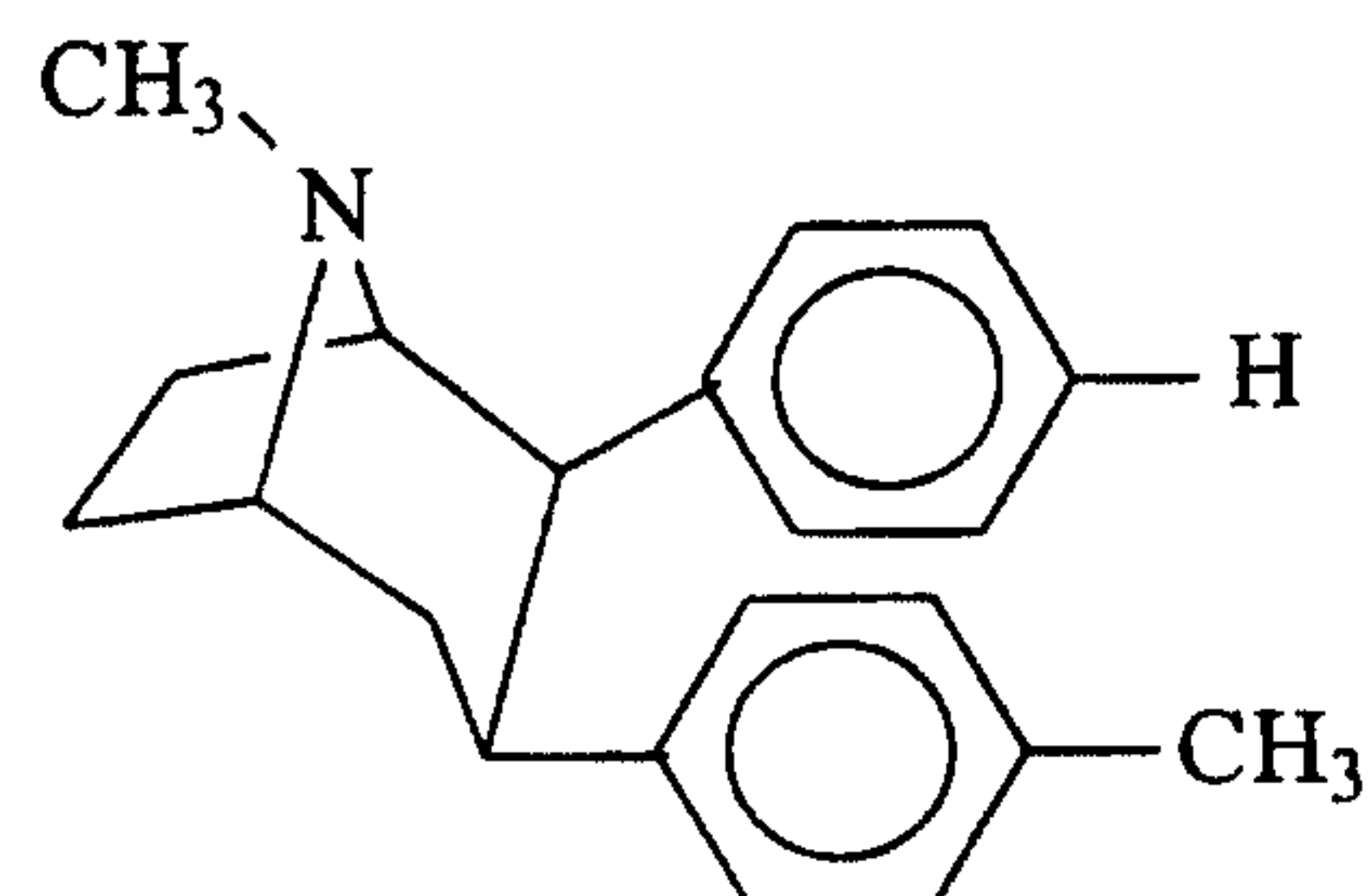
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RTI-4229-422

DA 1.96

5-HT 1,100

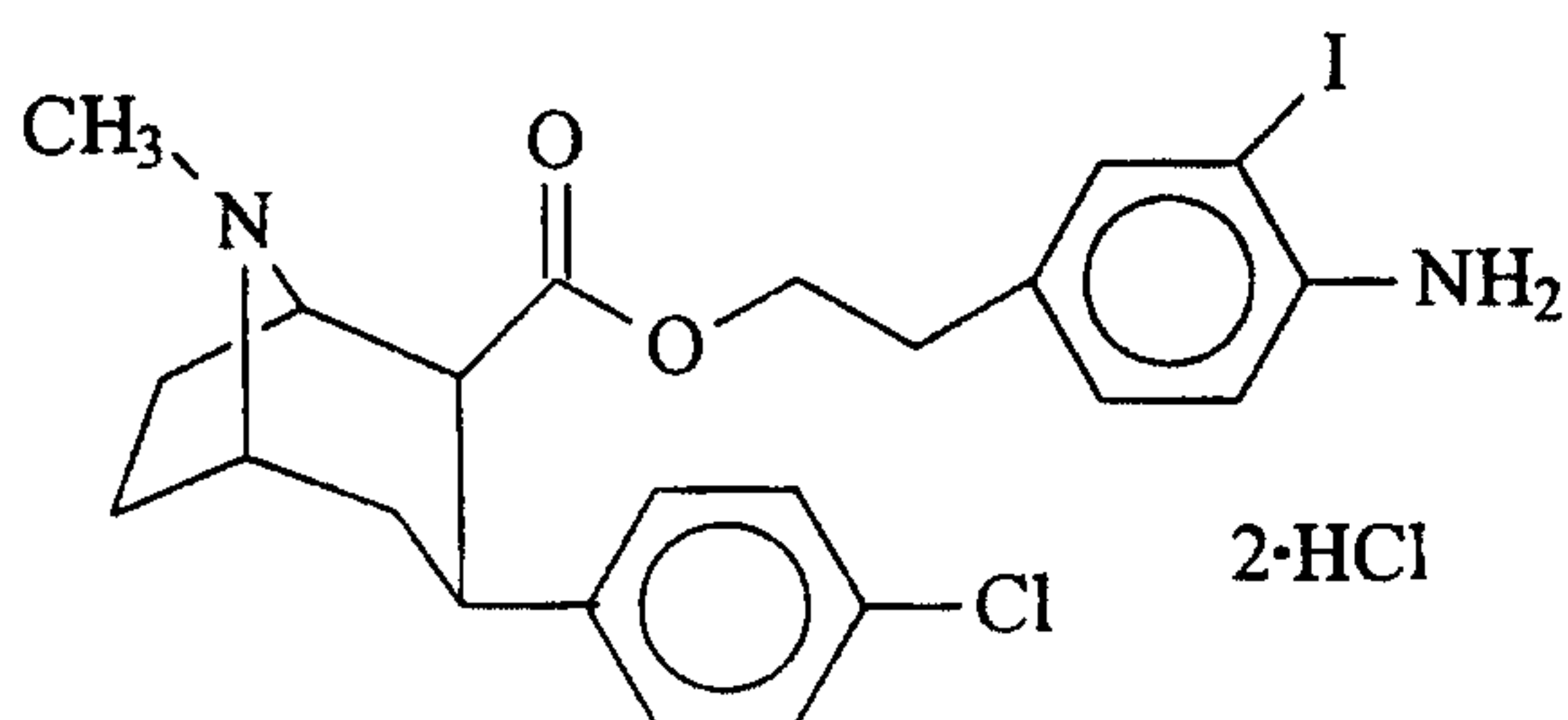
NE_N 6090

Particularly preferred compounds include RTI-4229-77, 87, 113, 114, 117, 119, 120, 124, 125, 126, 130, 141, 143, 144, 151, 152, 154, 165, 171, 176, 177, 180, 181, 194, 202, 252, 295, 298, 319, 334, 335, 336, 337, 338, 345, 346, 347, 348, 352 and 353. The chemical structures of these compounds are given below:

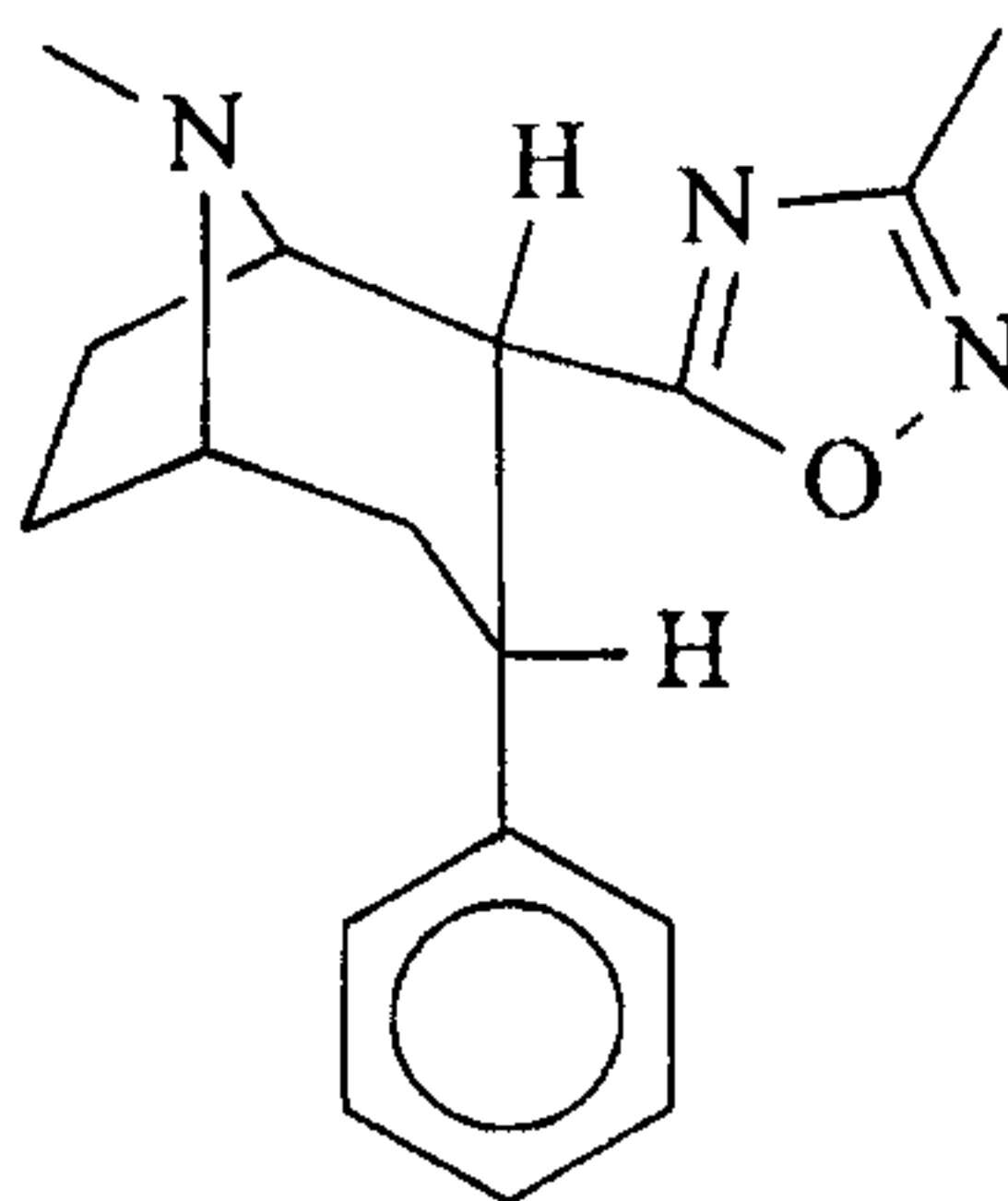
WO 99/61023

PCT/US99/10456

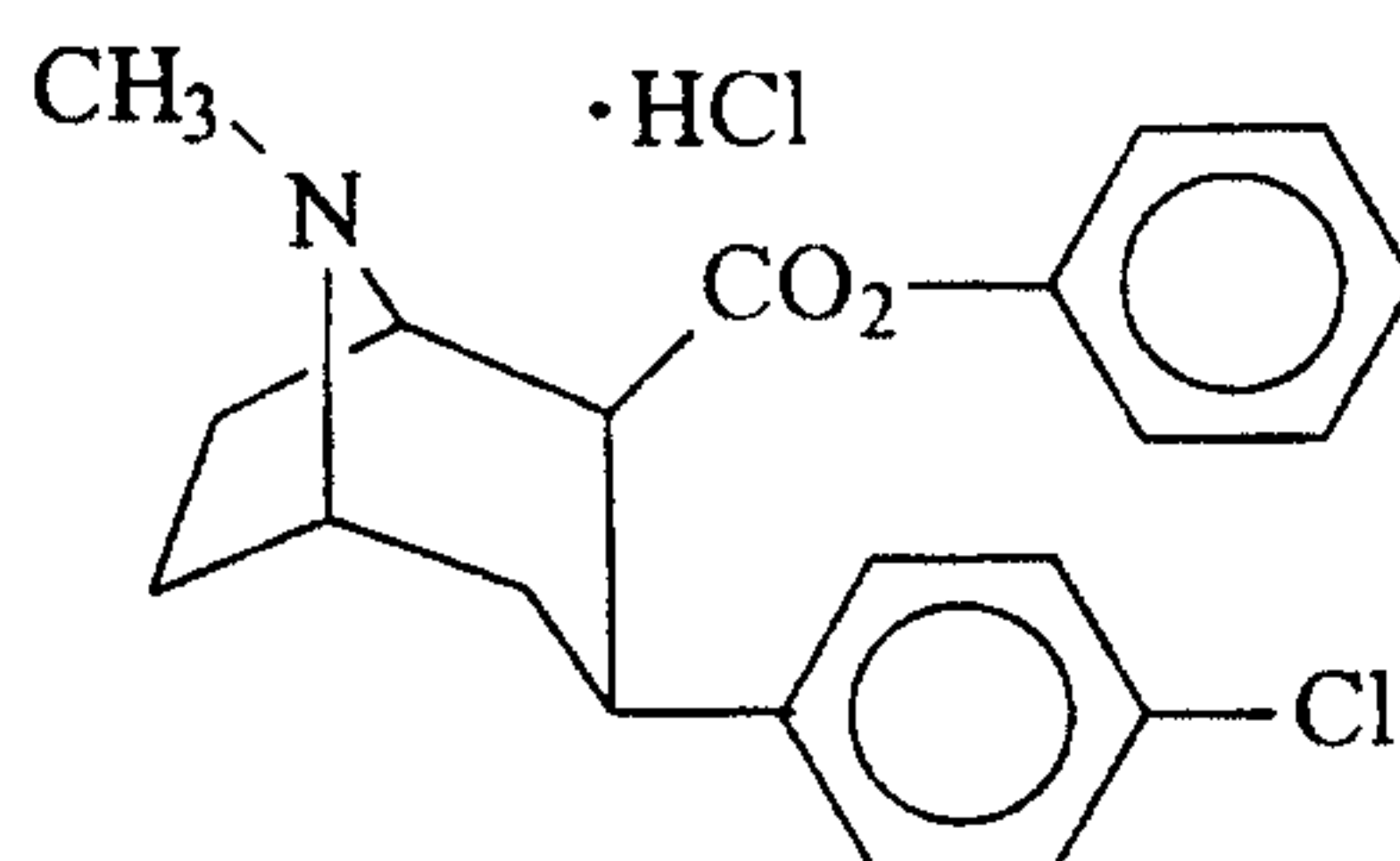
RTI-4229-77

DA 2.51 ± 0.25 5-HT $\pm$ NE_N $2.246.86 \pm 238.99$ 

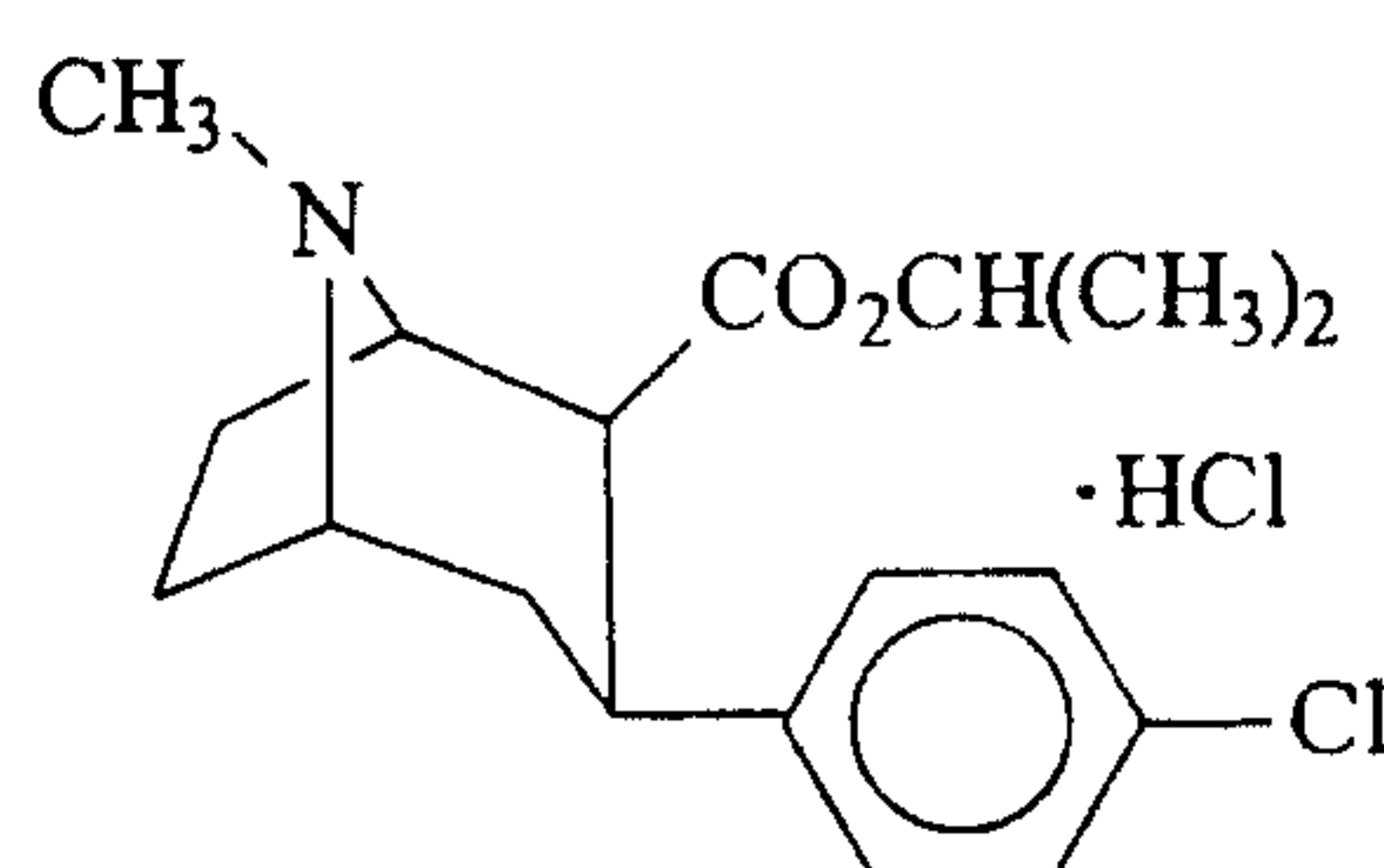
RTI-4229-87

DA 204 ± 29 5-HT 28.391 ± 2.324 NE_N 35.782 ± 6.245 

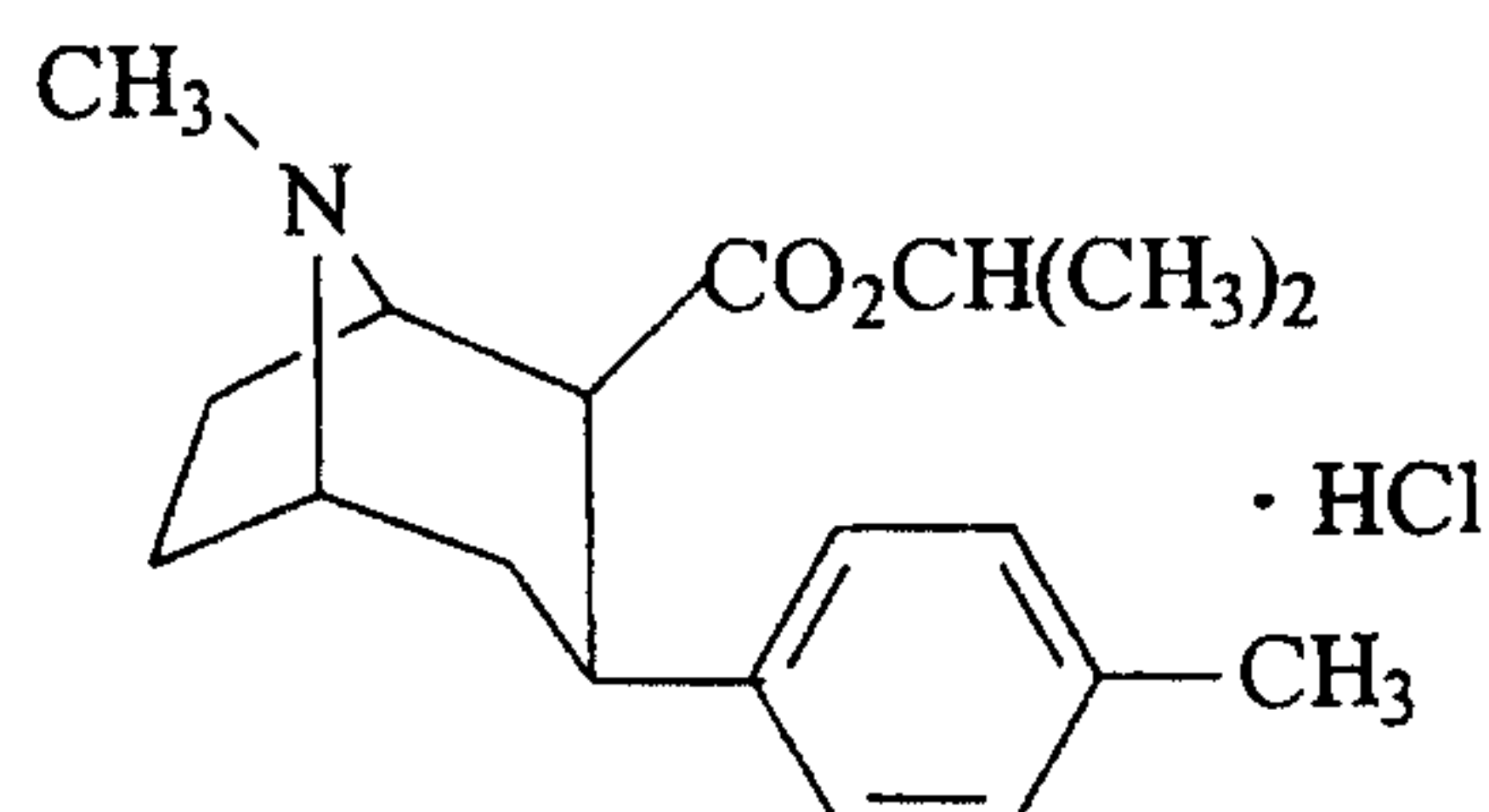
RTI-4229-113

DA 1.98 ± 0.05 5-HT 2.3336 ± 176 NE_N 2.955 ± 223 

RTI-4229-114

DA 1.40 ± 0.13 5-HT 1.404 ± 7.1 NE_N 778 ± 21 

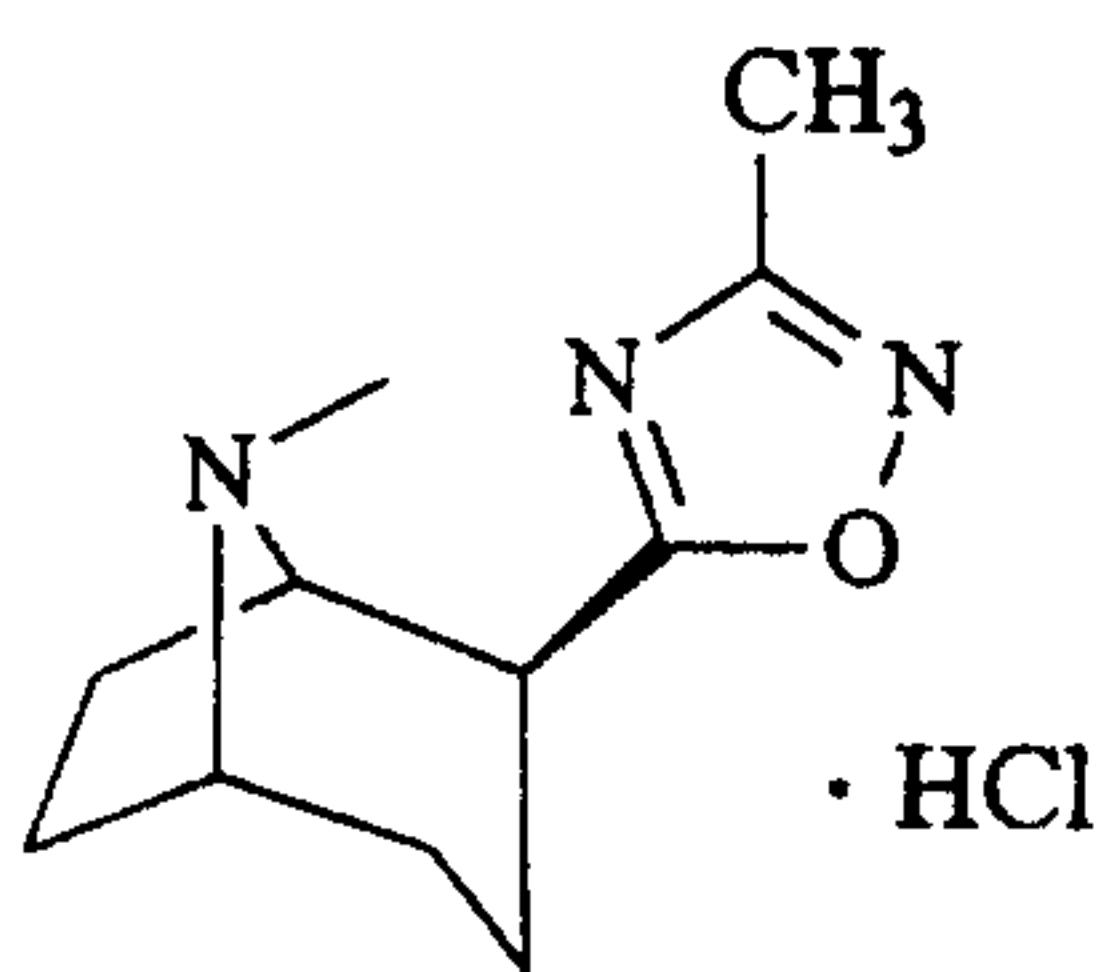
RTI-4229-117

DA 6.45 ± 0.85 5-HT 6.090 ± 488 NE_N 1.926 ± 38 

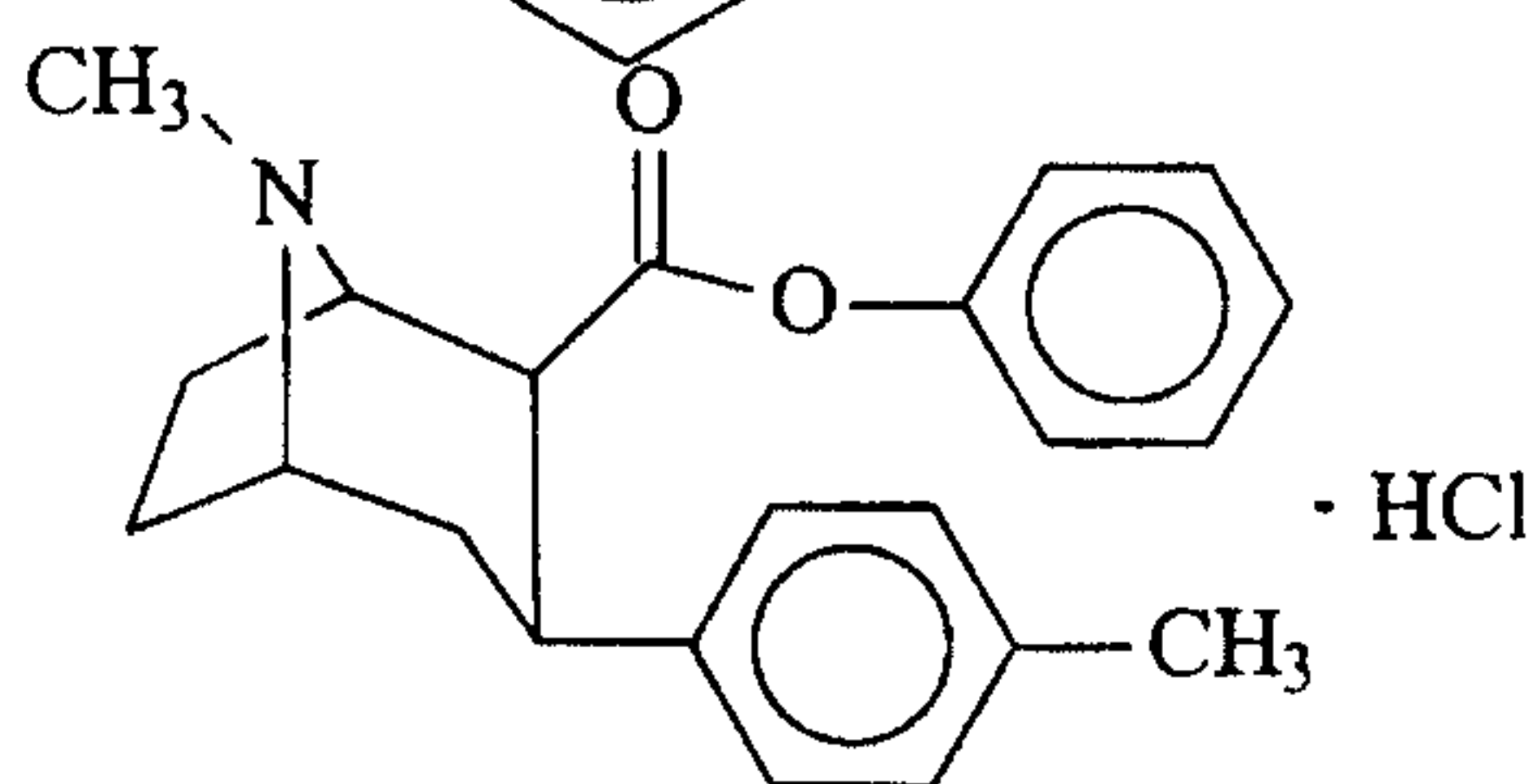
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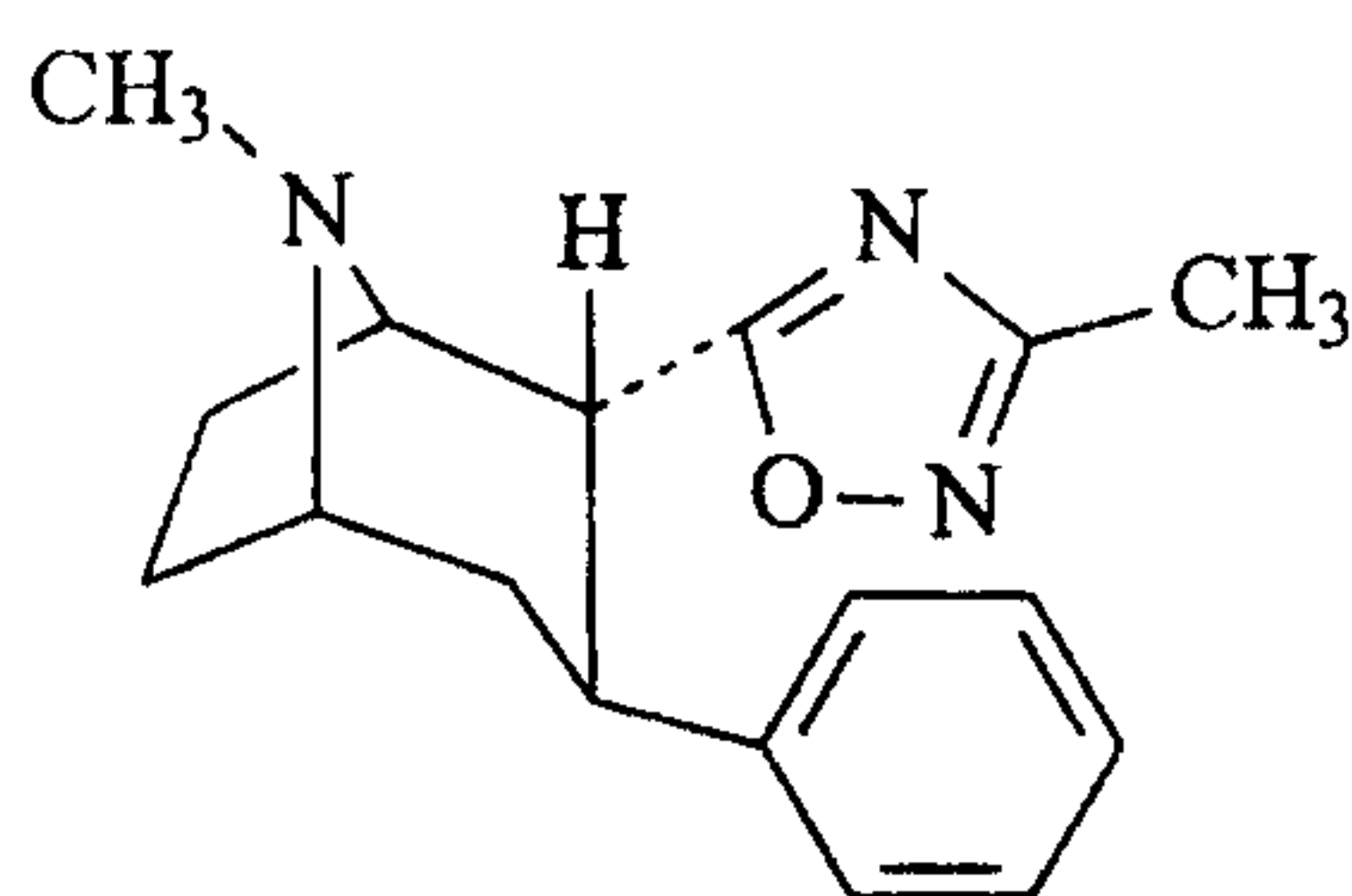
RTI-4229-119

DA 167 ± 13 5-HT 40.615 ± 9.416 NE_N 6.985 ± 635 

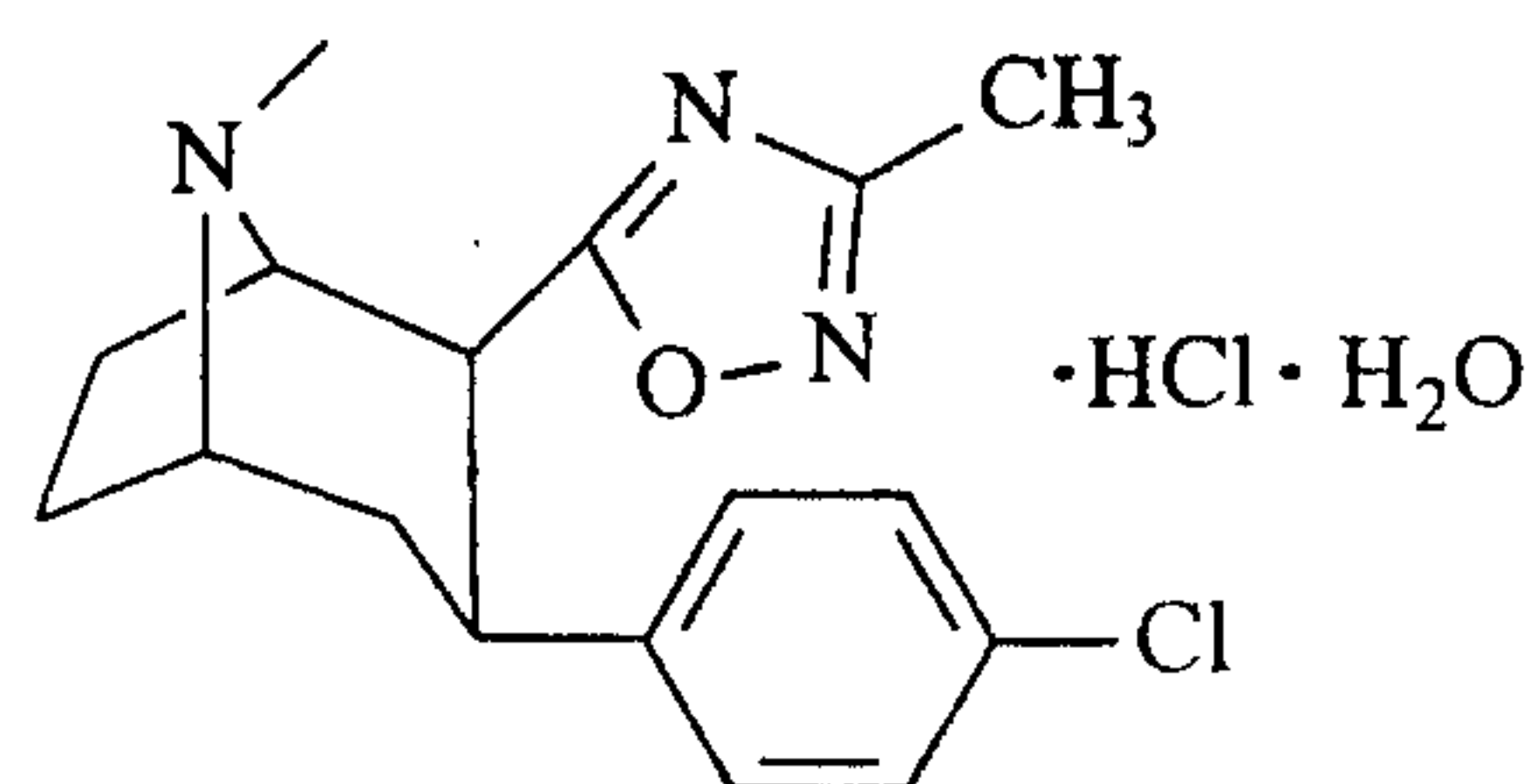
RTI-4229-120

DA 3.26 ± 0.06 5-HT 24.47 ± 1.515 NE_N 5.833 ± 373 

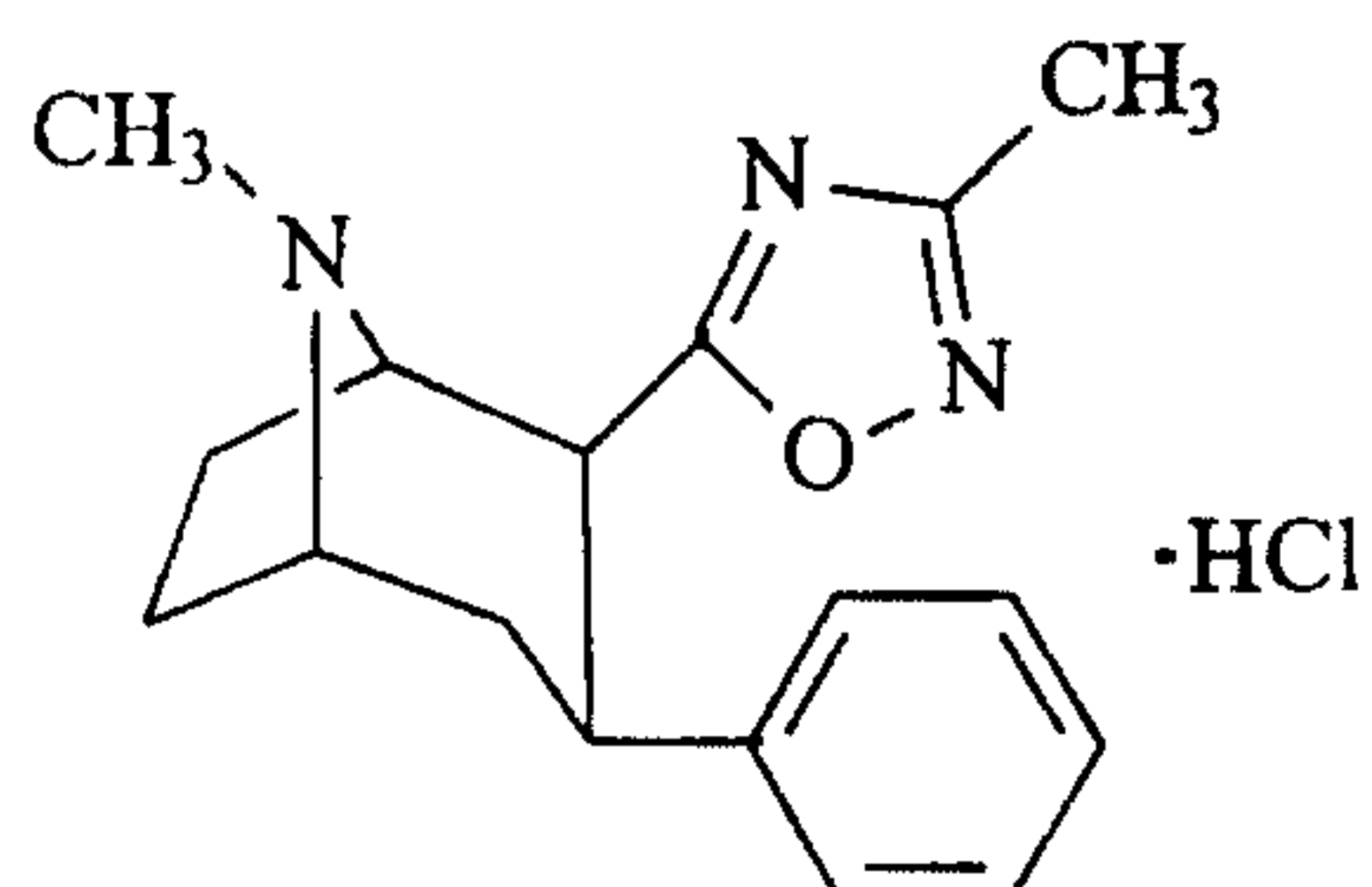
RTI-4229-124

DA 1.028 ± 65 5-HT 33.085 ± 5.434 NE_N 70.993 ± 3.563 

RTI-4229-125

DA 4.05 ± 0.57 5-HT 2.584 ± 799 NE_N 363 ± 36 

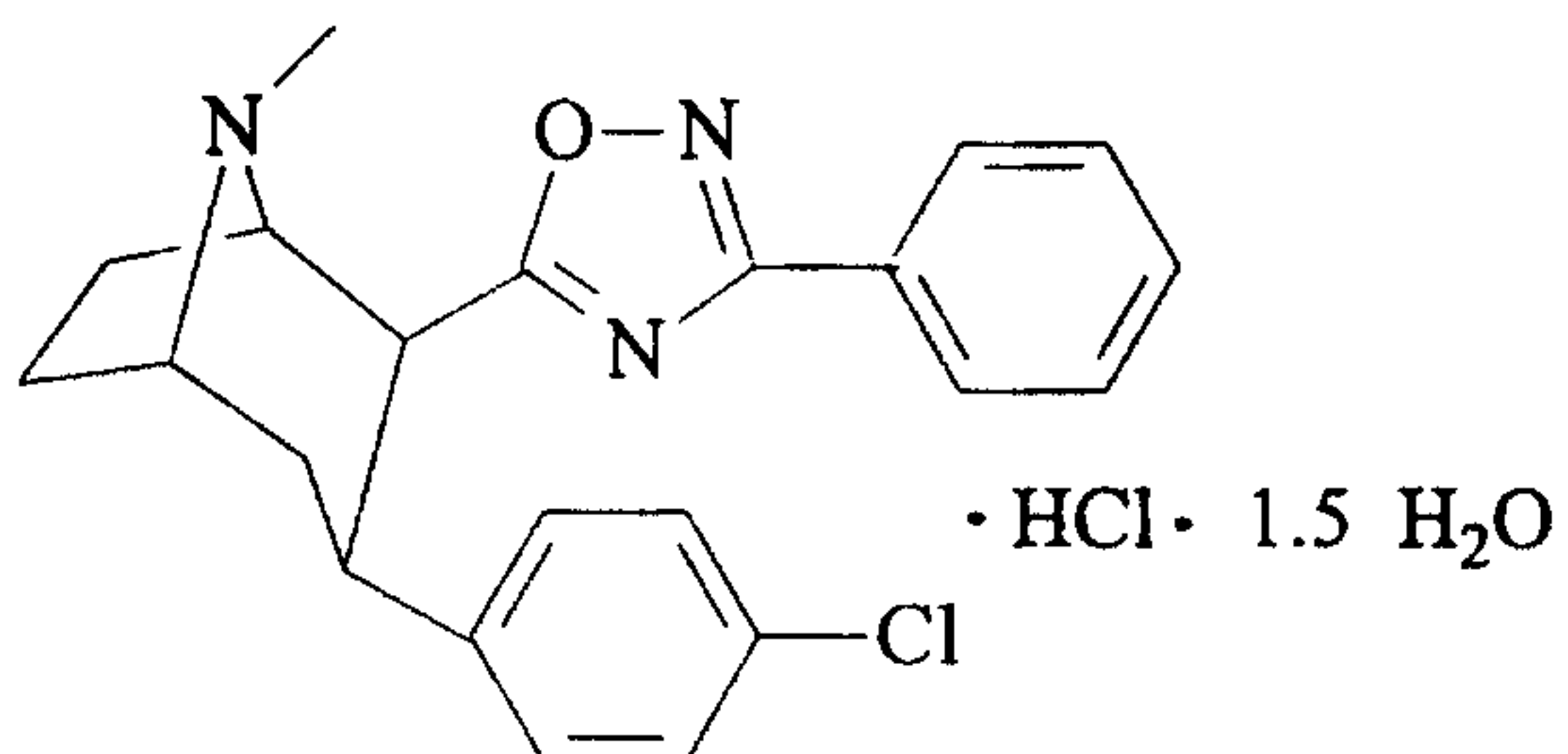
RTI-4229-126

DA 100 ± 6.3 5-HT 3.824 ± 418 NE_N 7.876 ± 551 

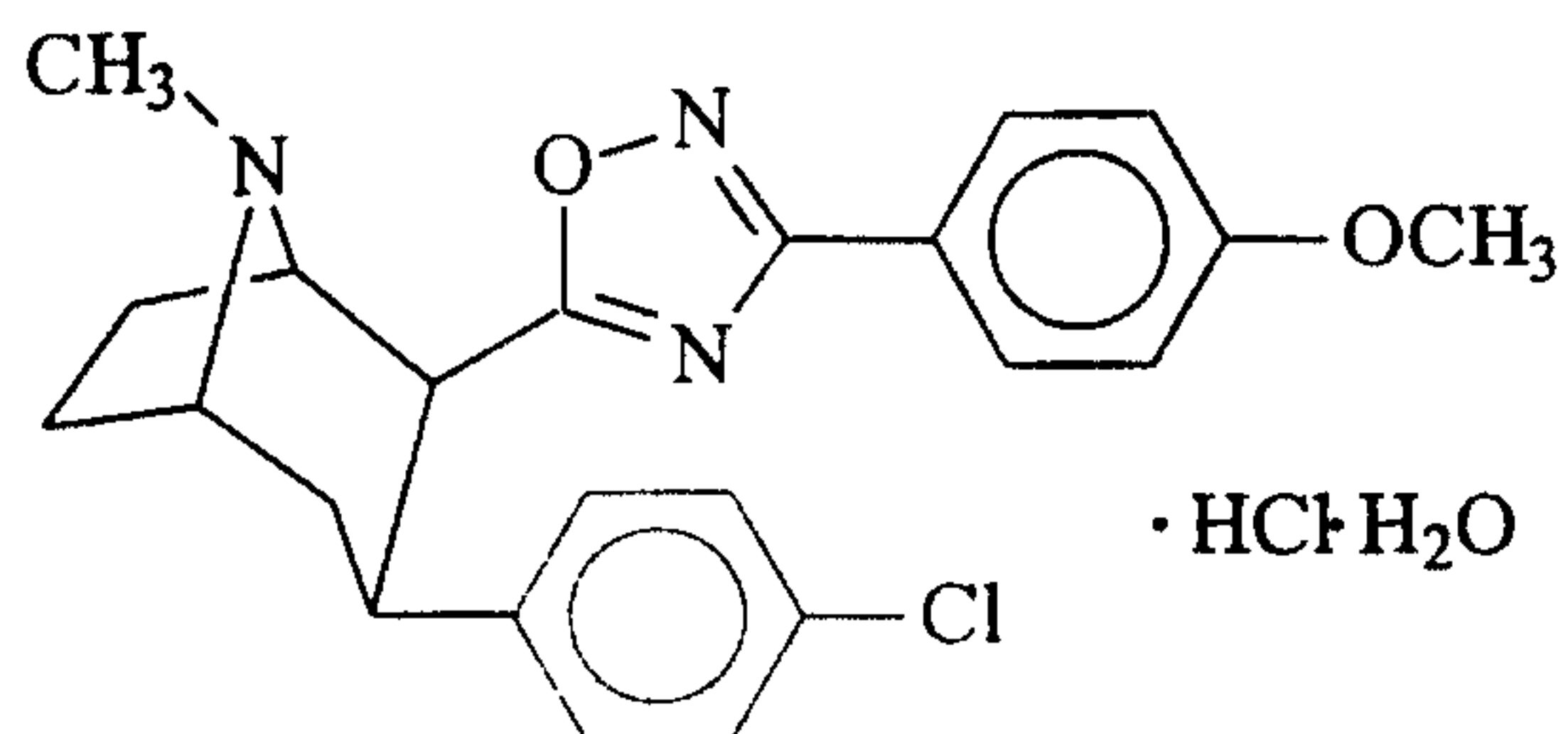
WO 99/61023

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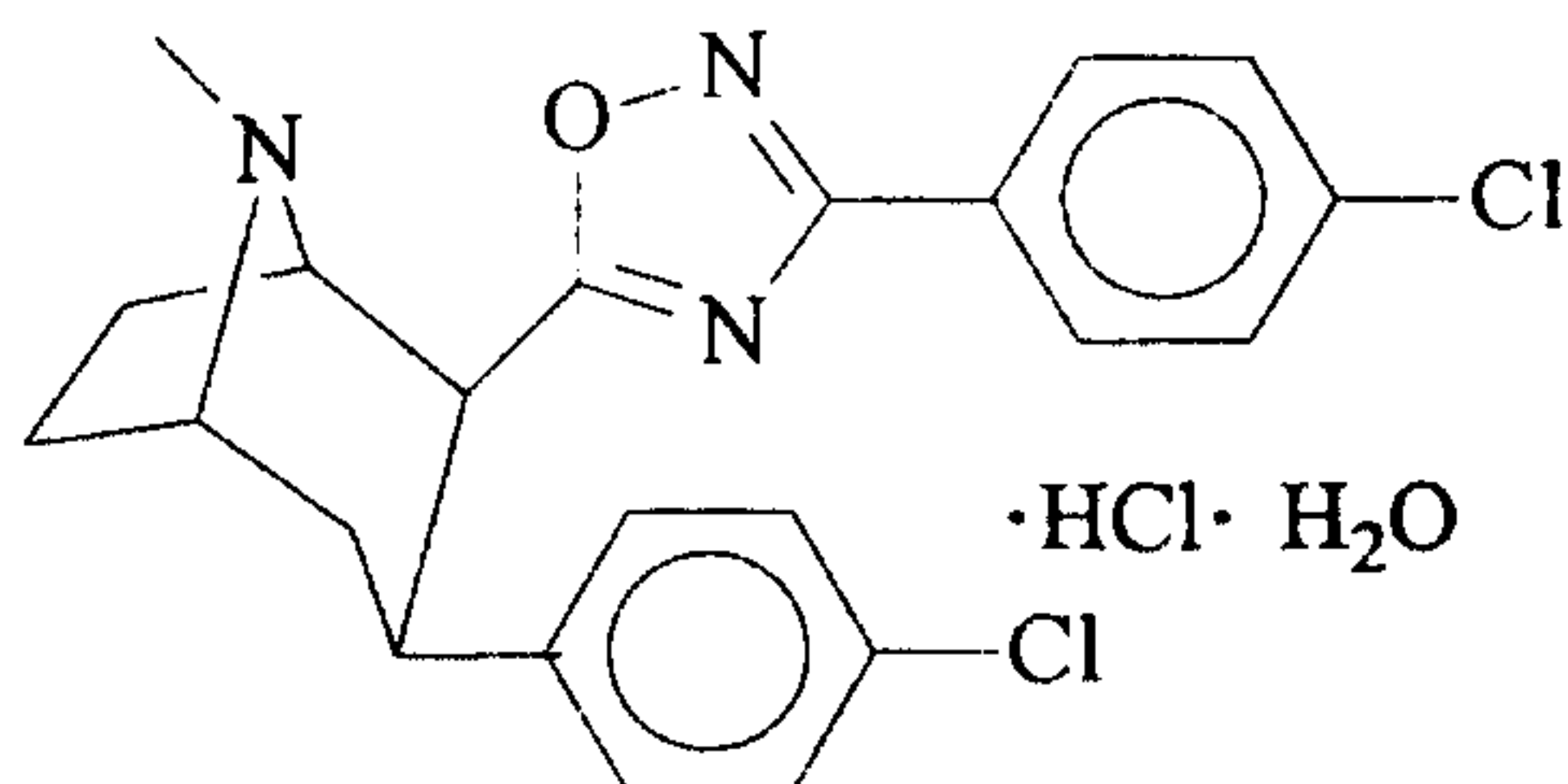
RTI-4229-130

DA 1.62 ± 0.02 5-HT 195 ± 4.8 NE_N 245 ± 13 

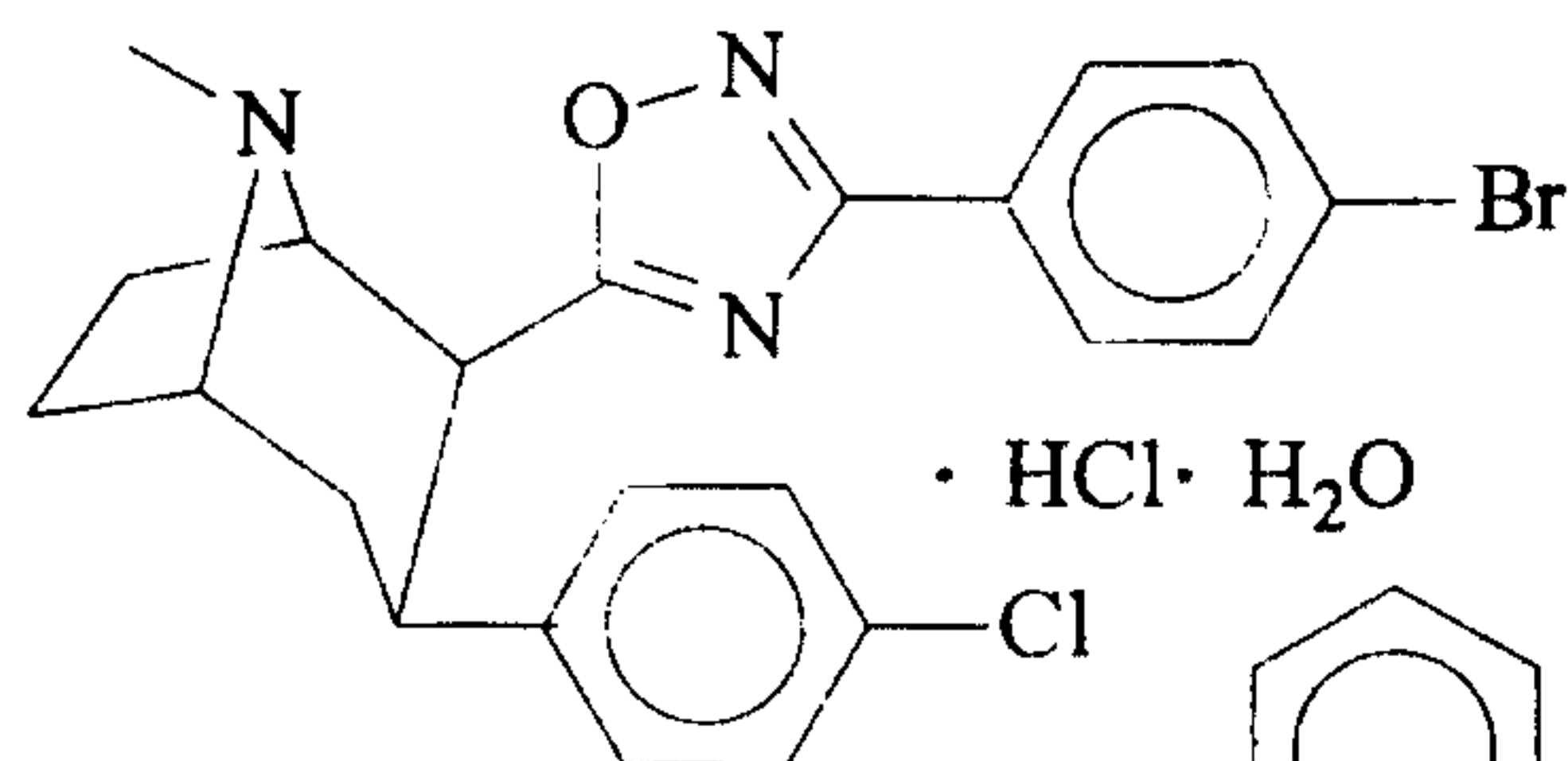
RTI-4229-141

DA 1.81 ± 0.19 5-HT 337 ± 43 NE_N 835 ± 7.5 

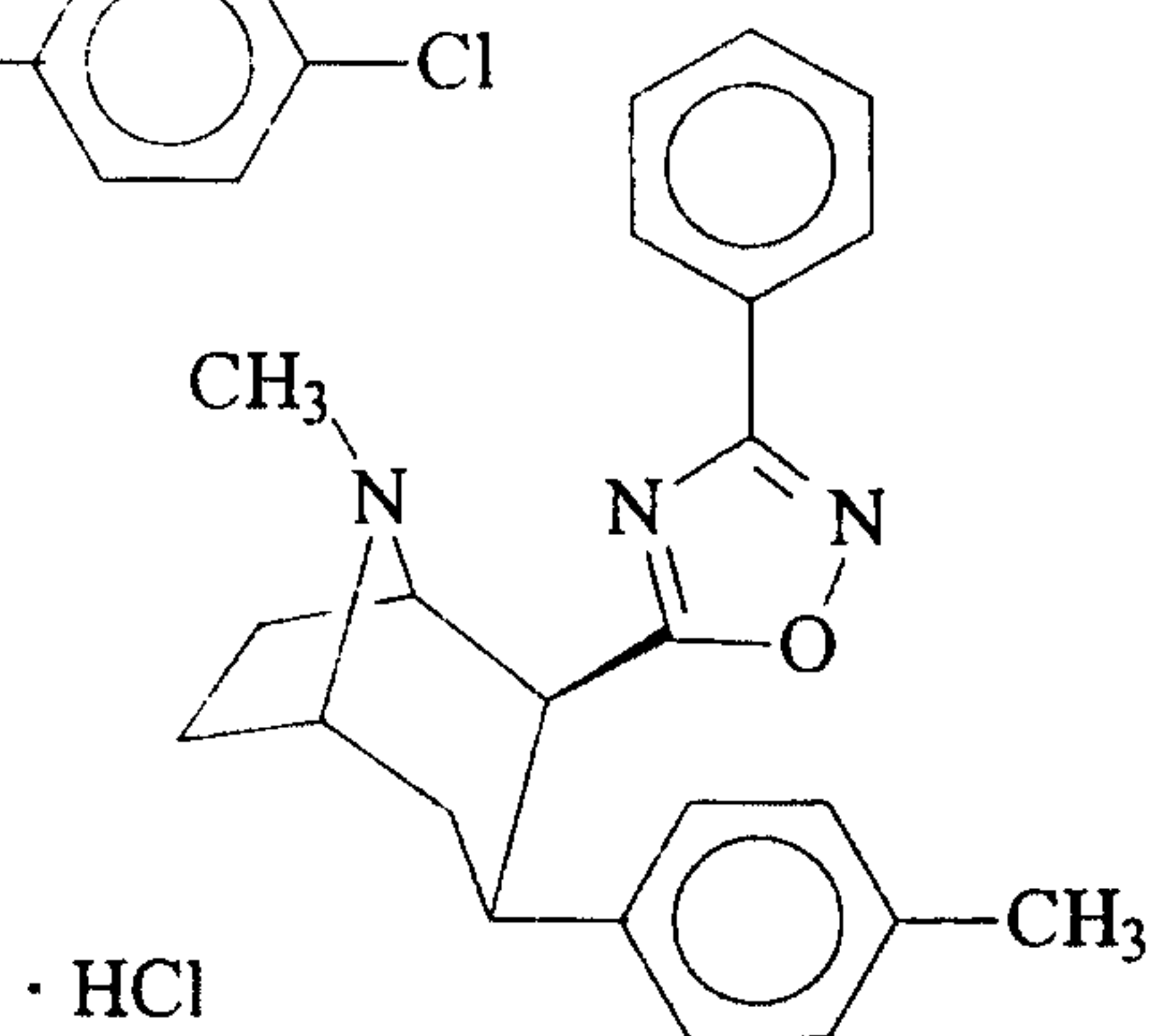
RTI-4229-143

DA 4.1 ± 0.22 5-HT 404 ± 58 NE_N 4.069 ± 177 

RTI-4229-144

DA 3.44 ± 0.36 5-HT 106 ± 10 NE_N 1.825 ± 166 

RTI-4229-151

DA 2.33 ± 0.26 5-HT 1.074 ± 125 NE_N 60 ± 2 

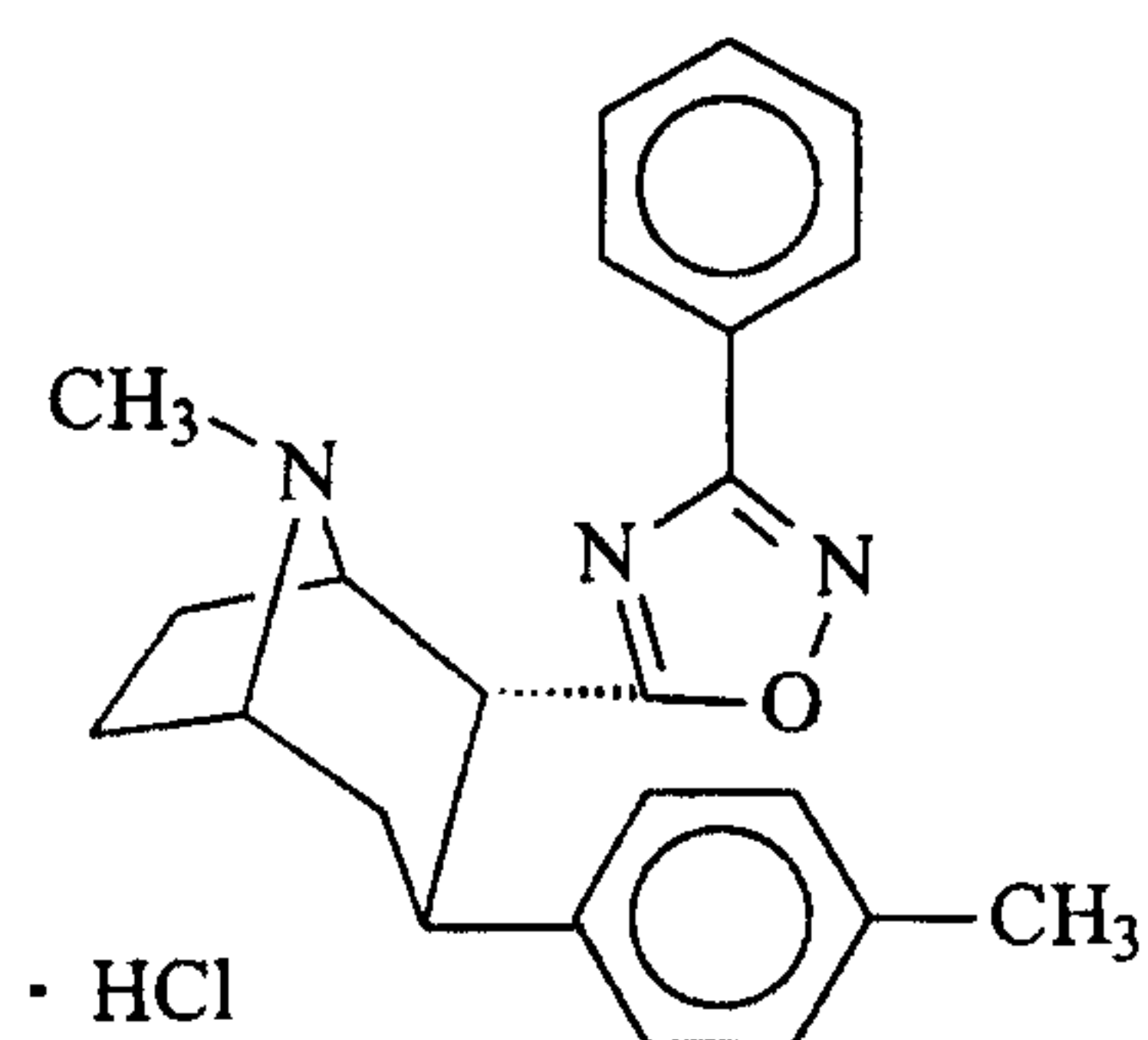
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RTI-4229-152

DA 494 ± 37

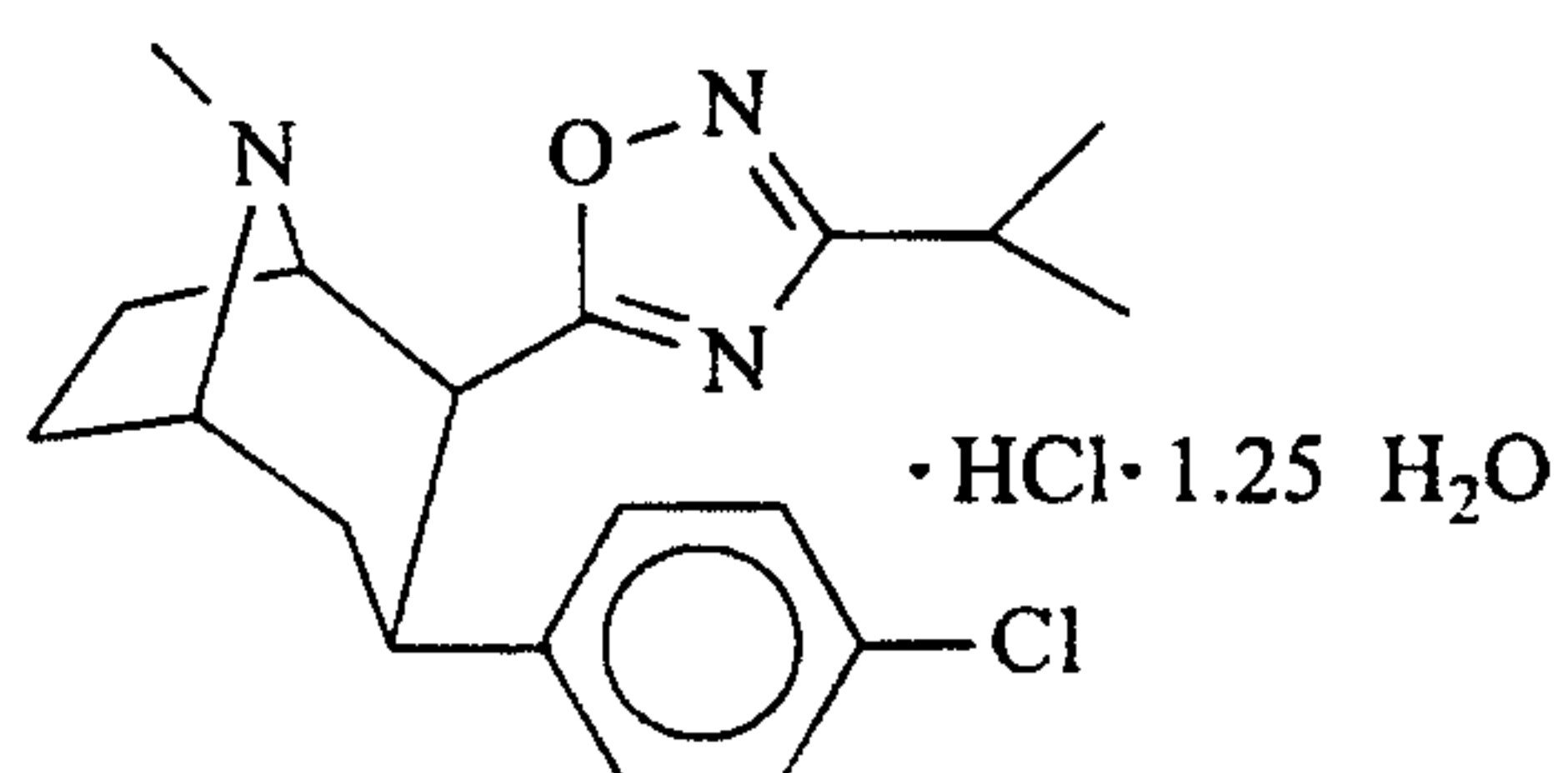
5-HT 1.995 ± 109

NE_N 22.689 ± 1.957

RTI-4229-154

DA 6.0 ± 0.55

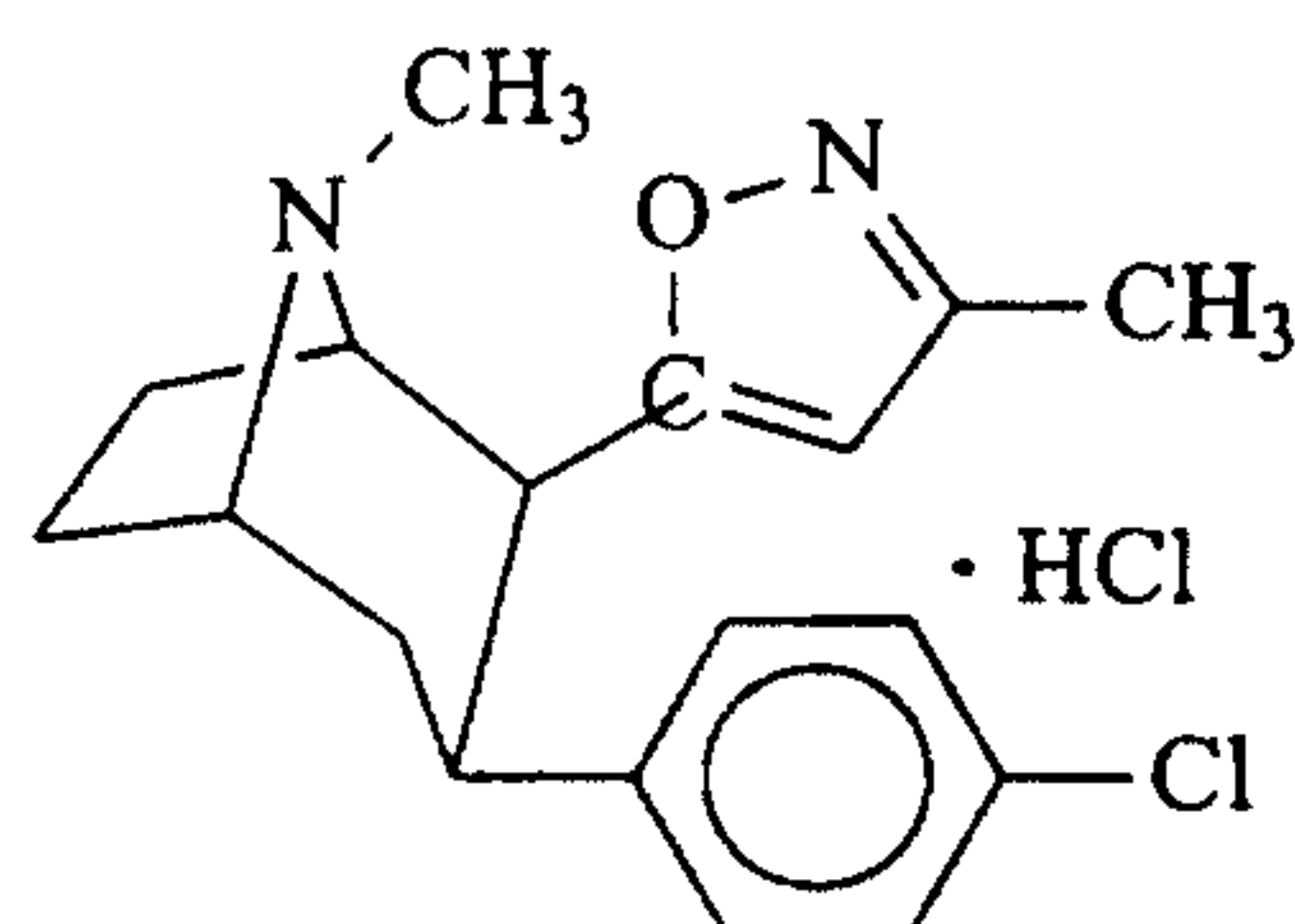
5-HT 3.460 ± 245

NE_N 135 ± 13

RTI-4229-165

DA 0.59 ± 0.04

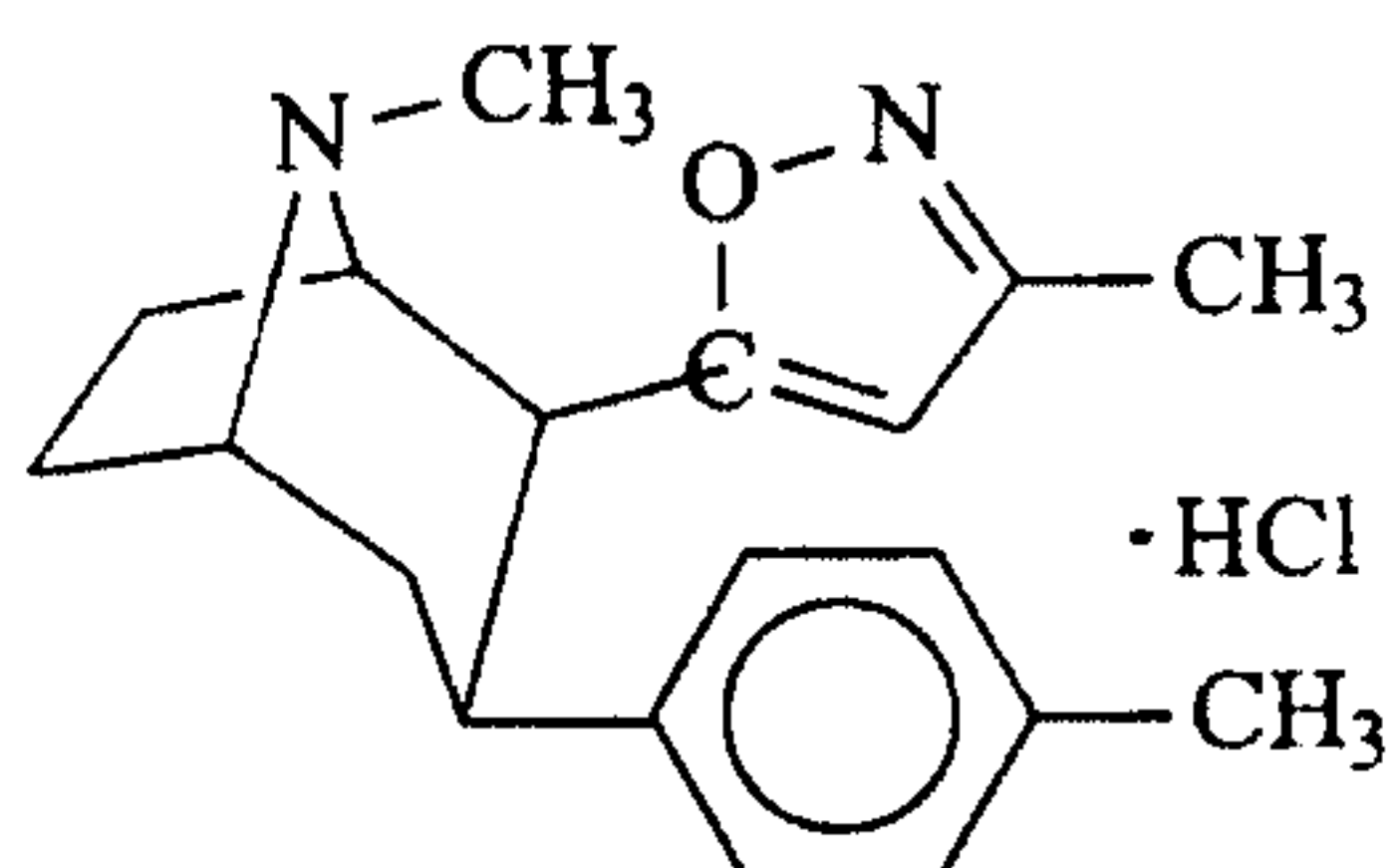
5-HT 572 ± 58

NE_N 161 ± 12

RTI-4229-171

DA 0.93 ± 0.09

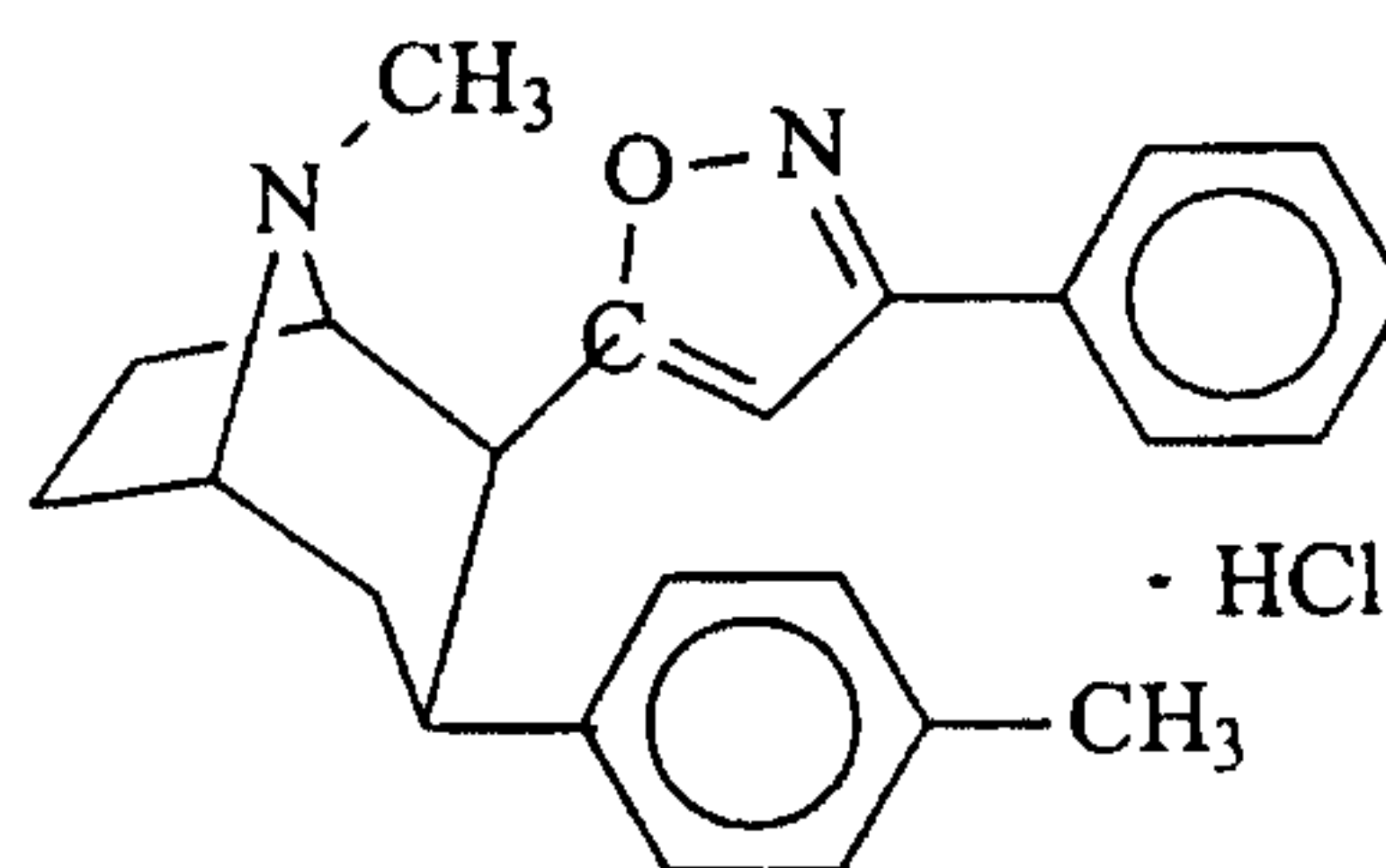
5-HT 3.818.25 ± 346.14

NE_N 254 ± 31

RTI-4229-176

DA 1.58 ± 0.02

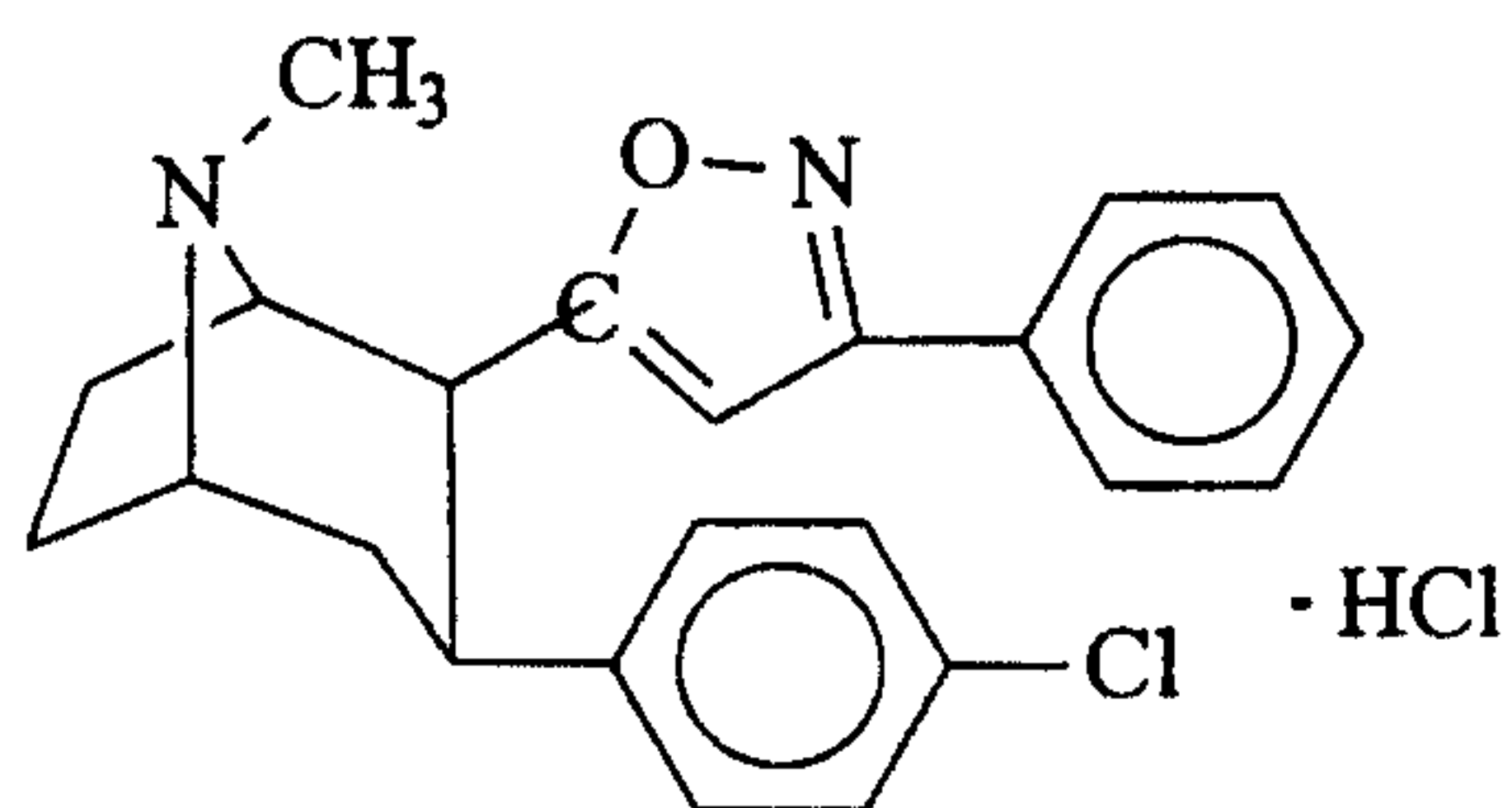
5-HT 5.109.72 ± 187.101

NE_N 398 ± 17.6

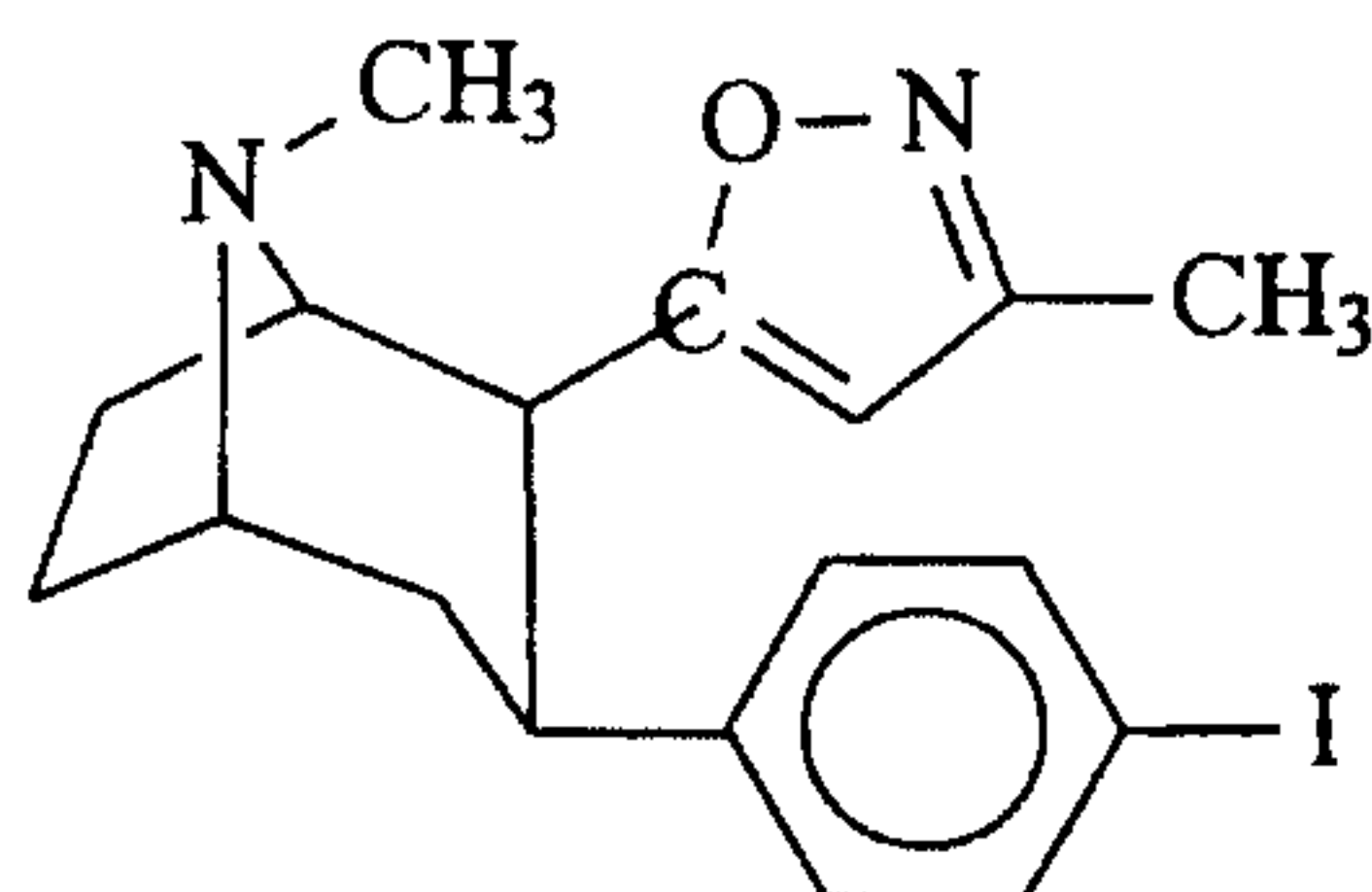
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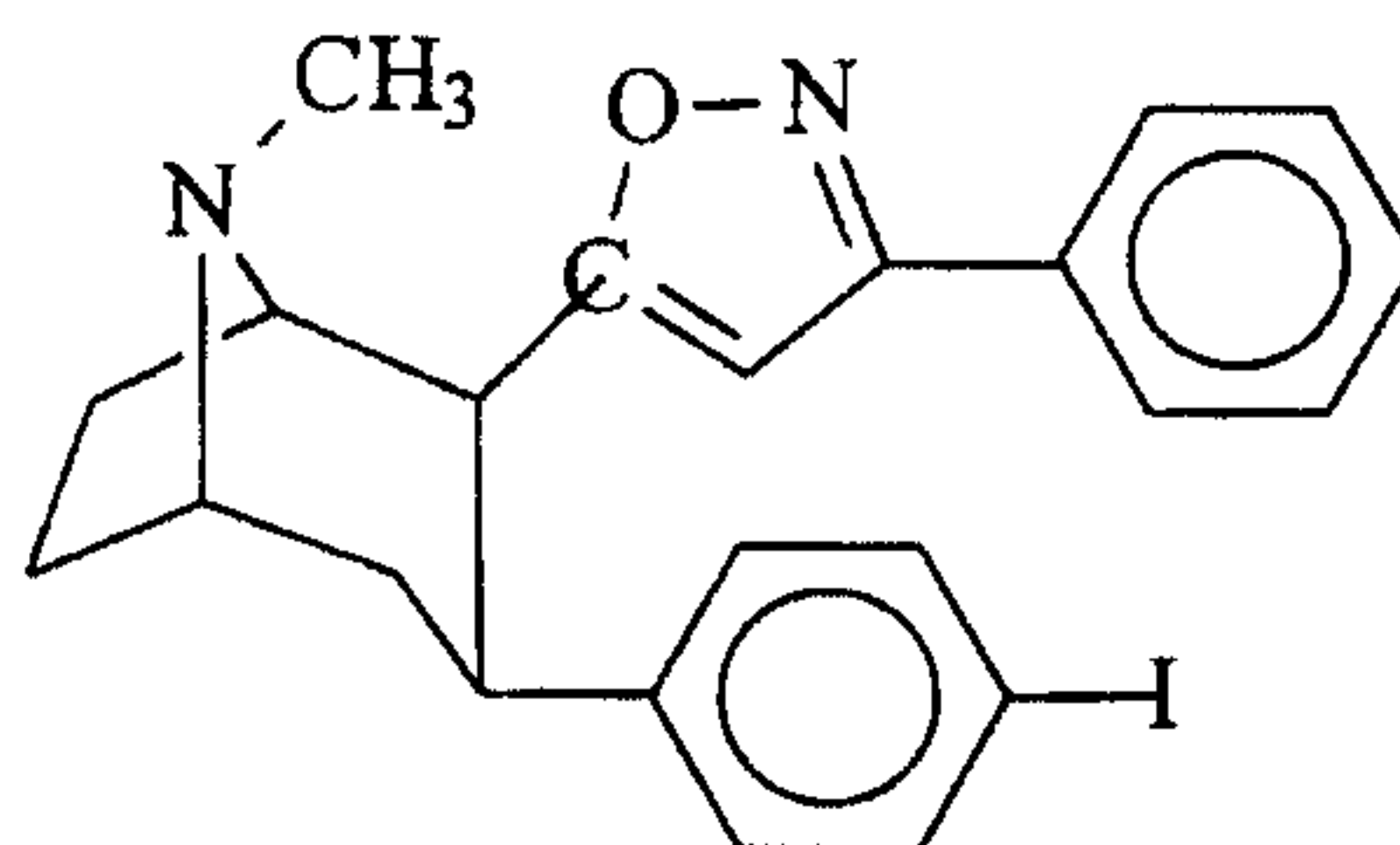
RTI-4229-177

DA 1.28 ± 0.18 5-HT $2.418.21 \pm 135.68$ NE_N 504 ± 29 

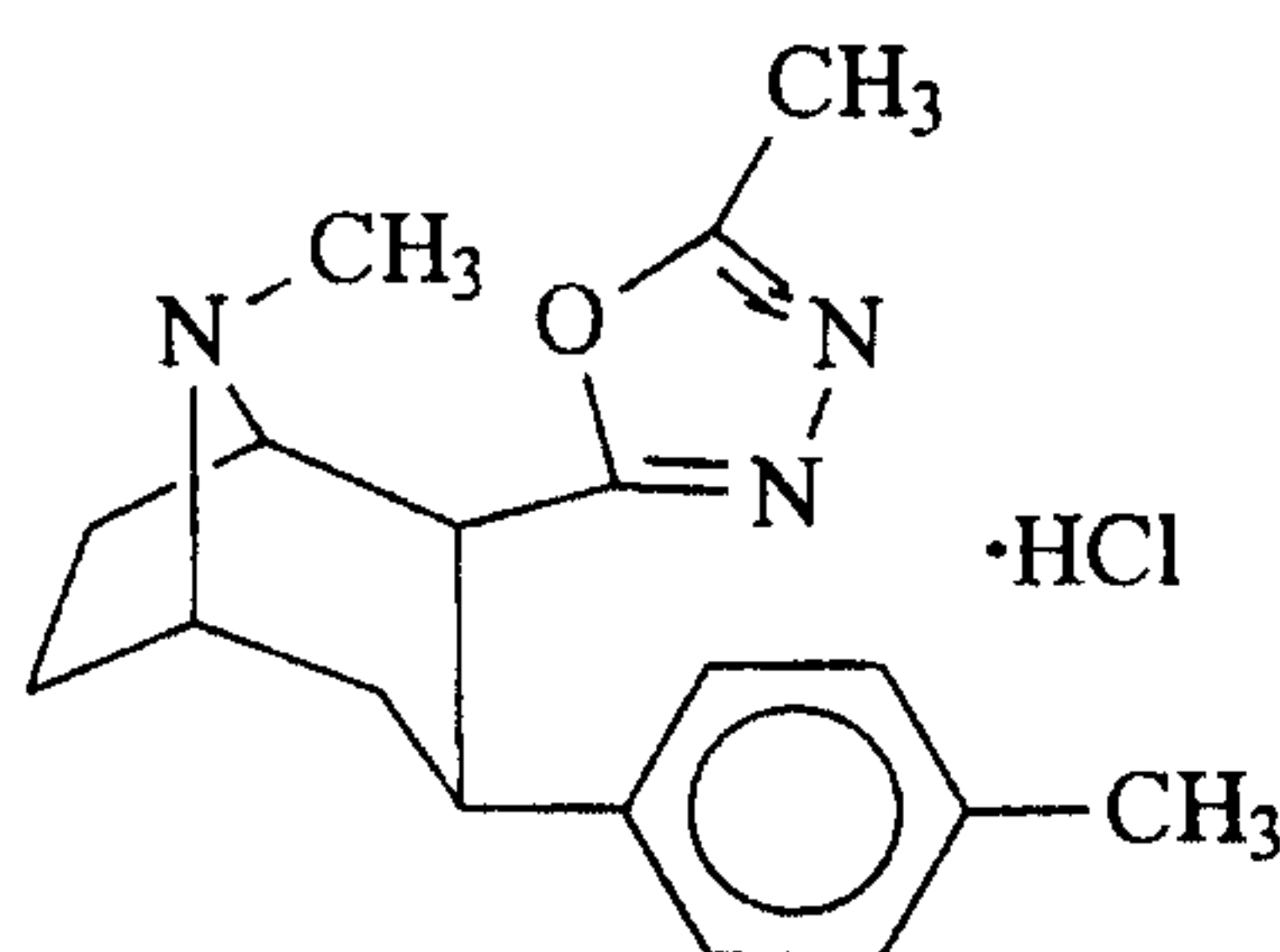
RTI-4229-180

DA 0.73 ± 0.04 5-HT 36.35 ± 4.99 NE_N 67.9 ± 5.25 

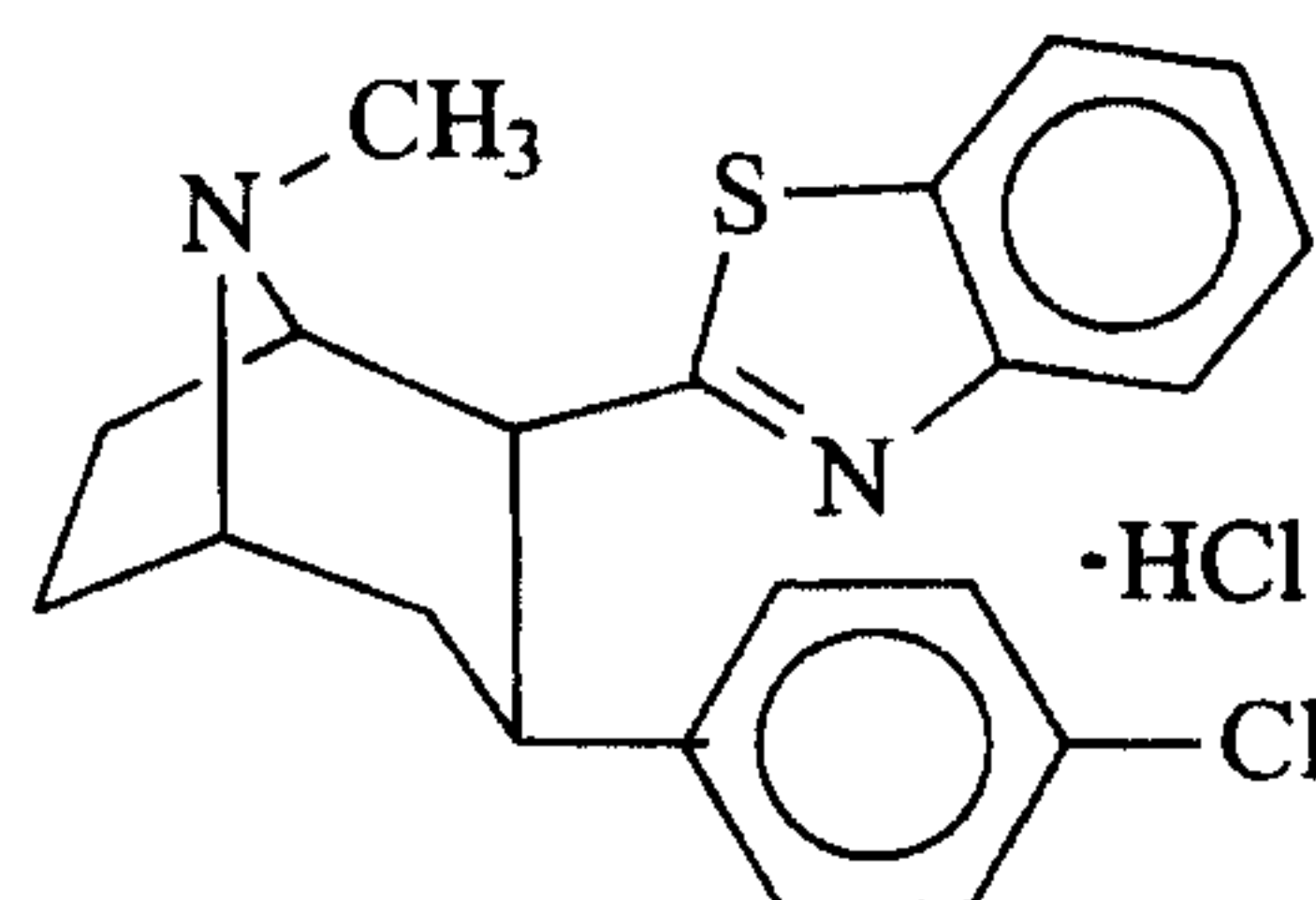
RTI-4229-181

DA 2.57 ± 0.14 5-HT 100 ± 9.0 NE_N 868 ± 95 

RTI-4229-194

DA 4.45 ± 0.12 5-HT $4.884.47 \pm 155.42$ NE_N 253 ± 18.9 

RTI-4229-202

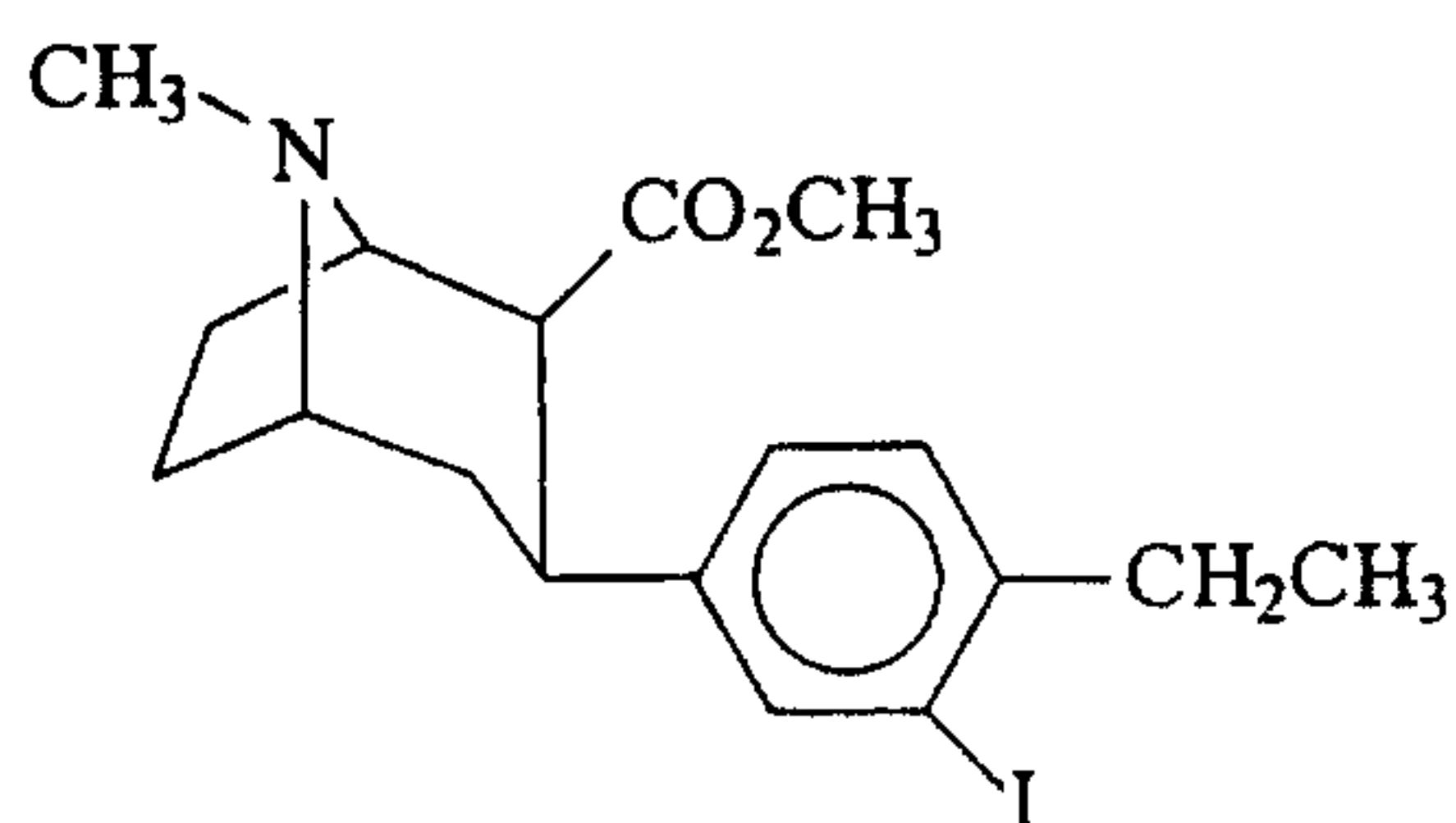
DA 1.37 ± 0.14 5-HT $1.118.85 \pm 120.00$ NE_N 402.8 ± 29.5 

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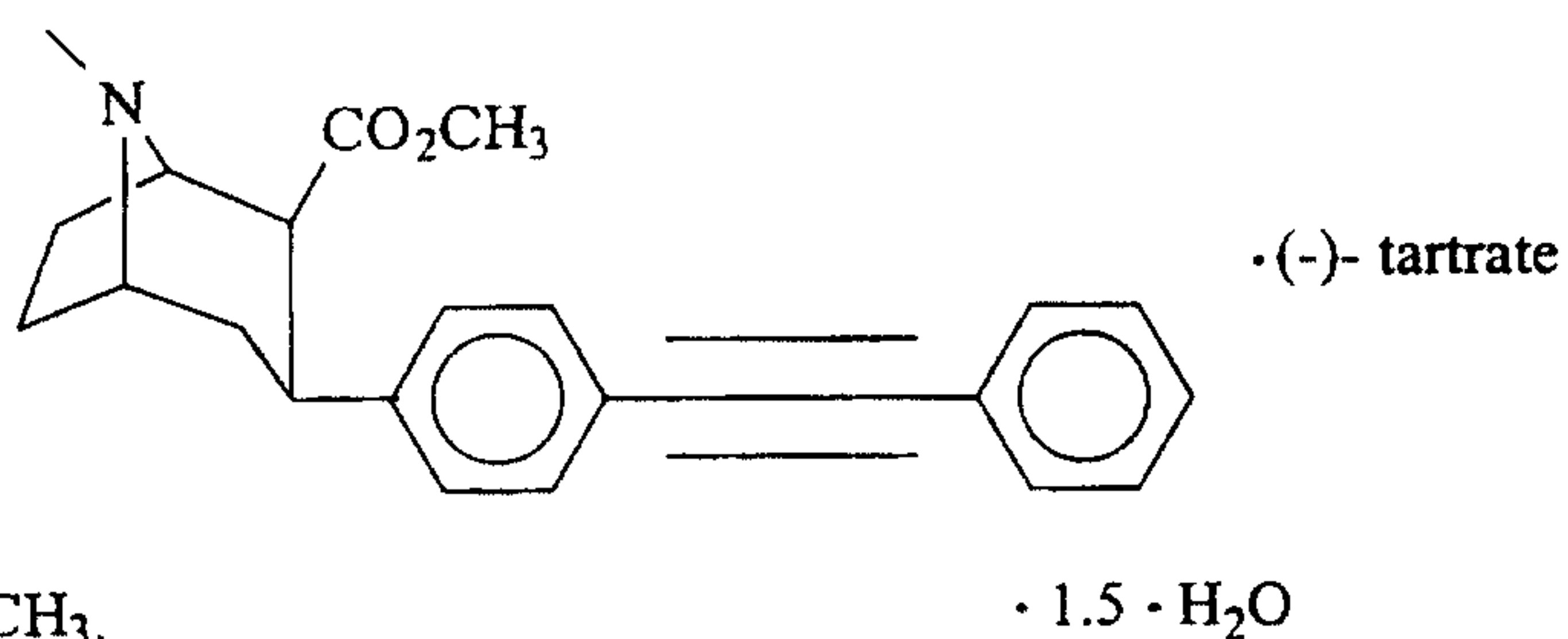
RTI-4229-295

BIH 141-4

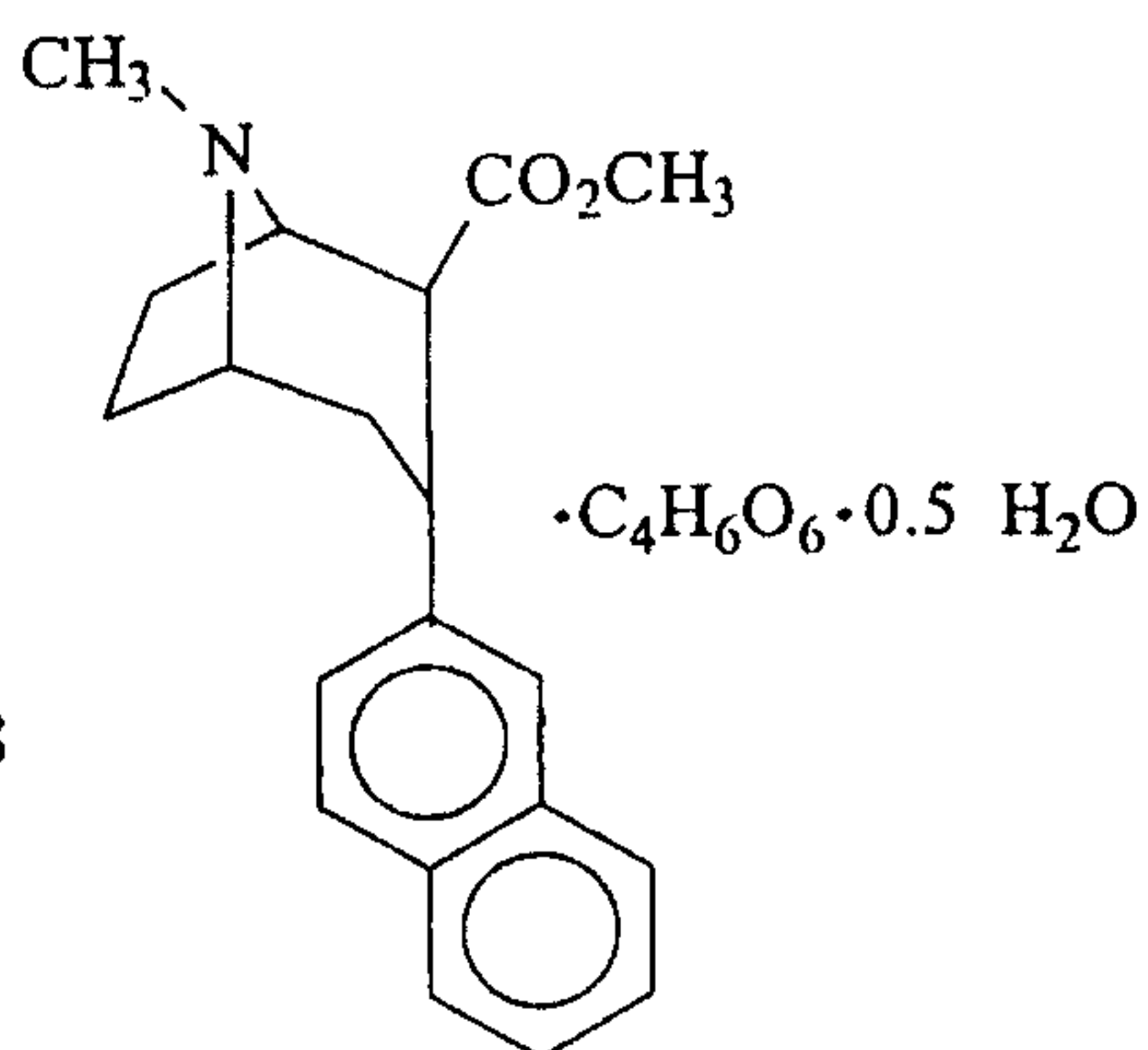
DA 21.31 ± 0.87 5-HT 2.96 ± 0.04 NE_N 1349 ± 105 

RTI-4229-298

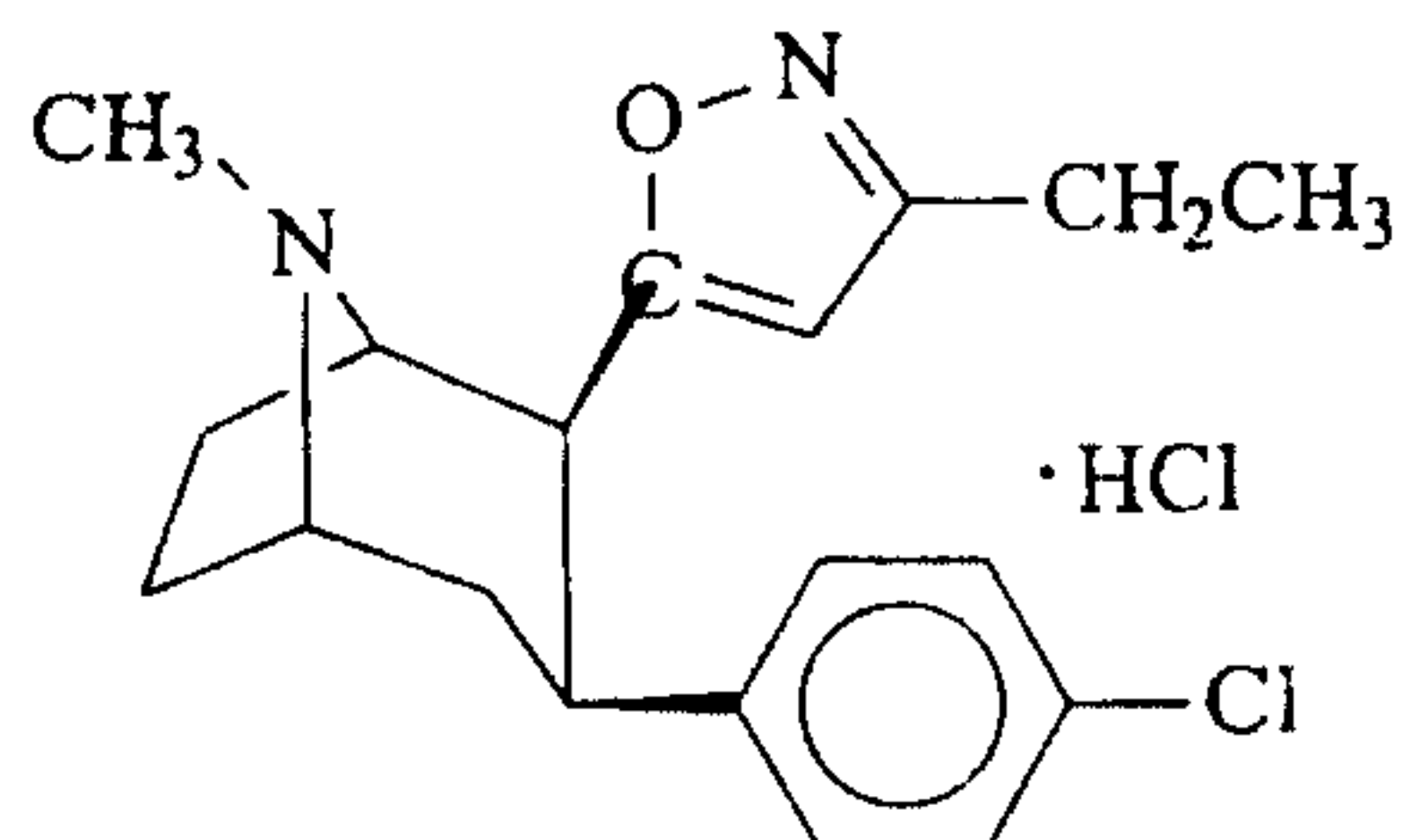
BIH-141-4

DA 3.7 ± 0.16 5-HT 46.8 ± 5.8 NE_N 346.6 ± 25 

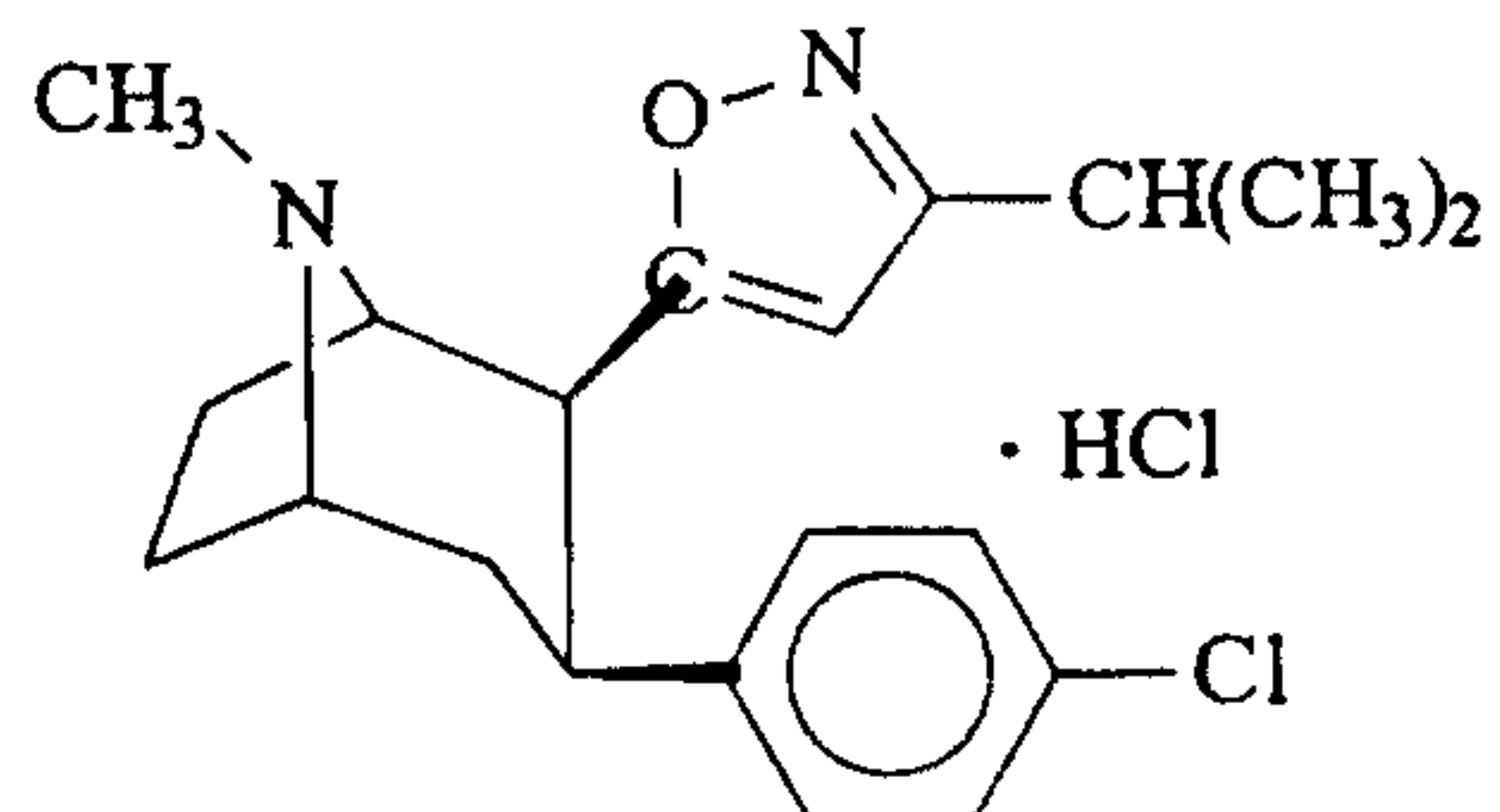
RTI-4229-319

DA 1.1 ± 0.09 5-HT 11.4 ± 1.3 NE_N 70.2 ± 6.28 

RTI-4229-334

DA 0.50 ± 0.03 5-HT 3086 ± 153 NE_N 120 ± 10.4 

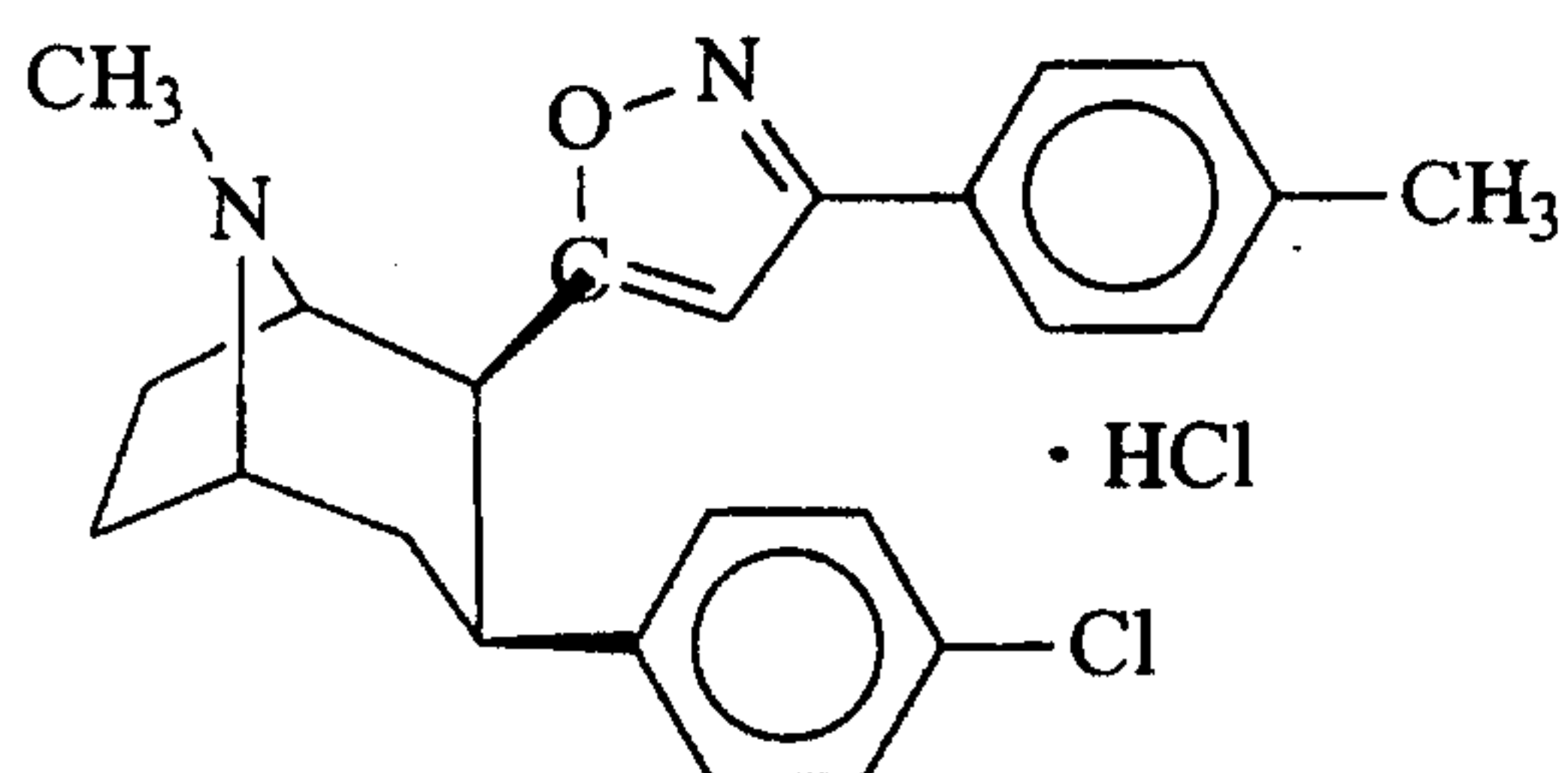
RTI-4229-335

DA 1.19 ± 0.12 5-HT 2318 ± 153 NE_N 954 ± 97.3 

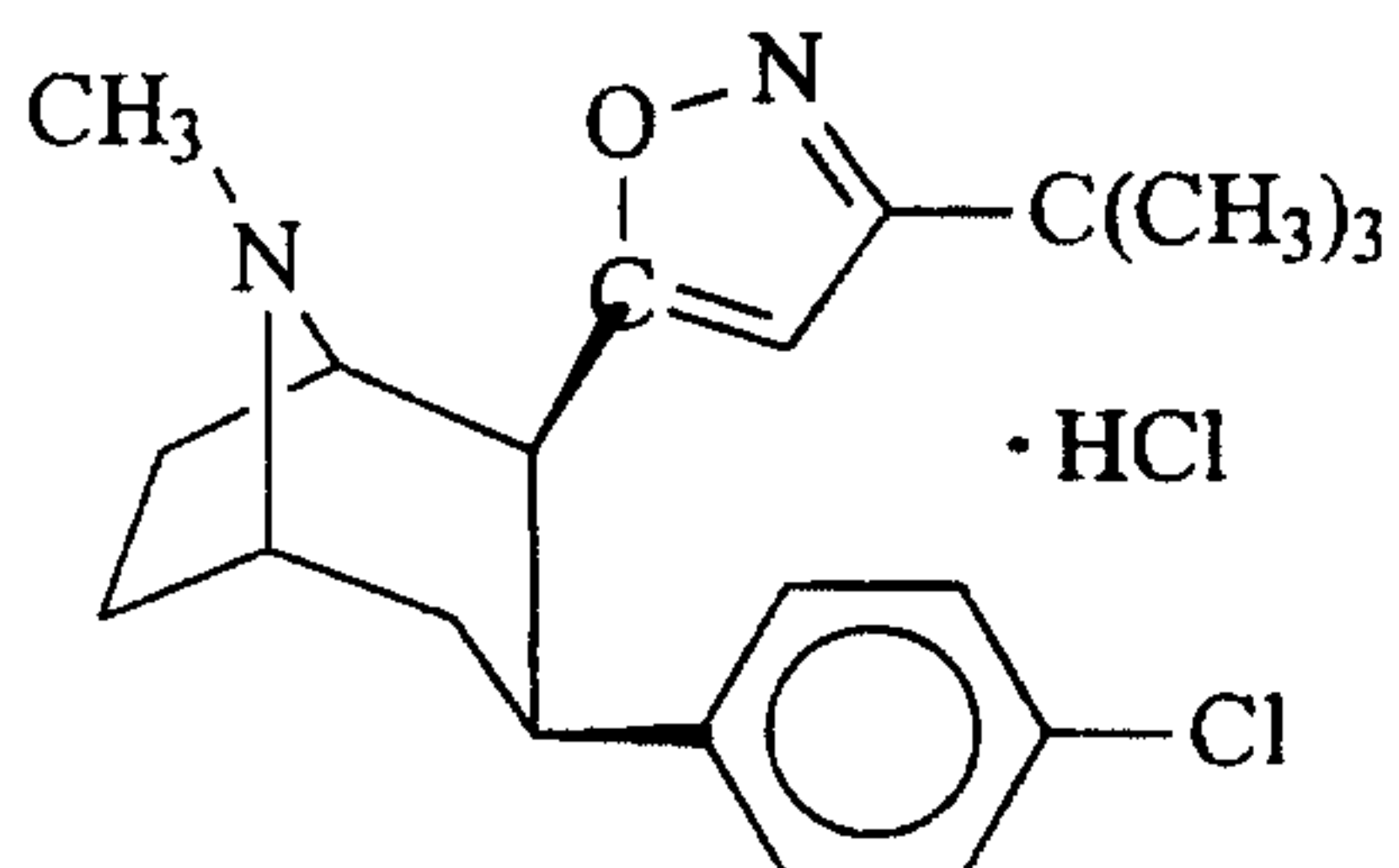
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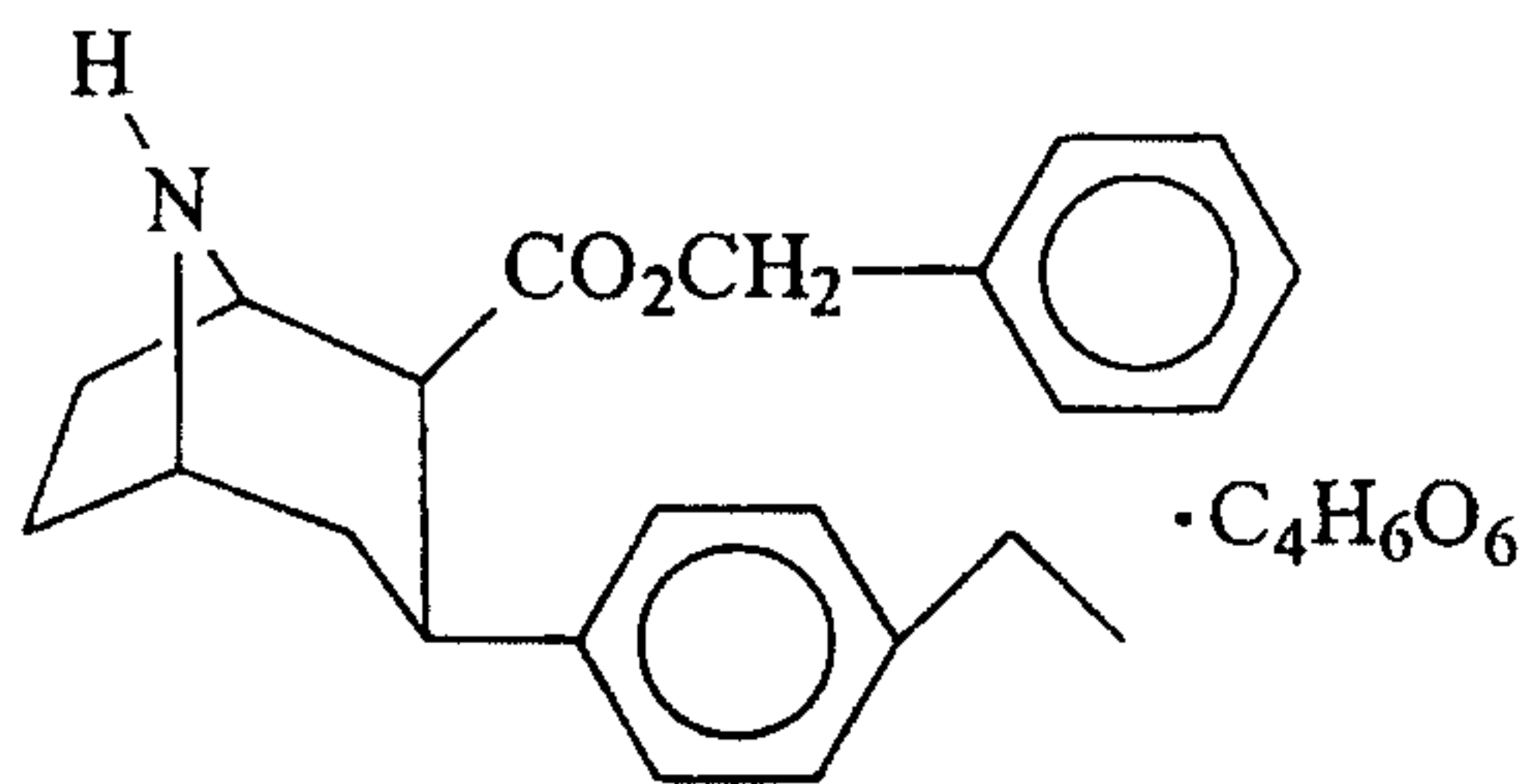
RTI-4229-336

DA 4.09 ± 0.44 5-HT 5741 ± 421 NE_N 1714 ± 38.5 

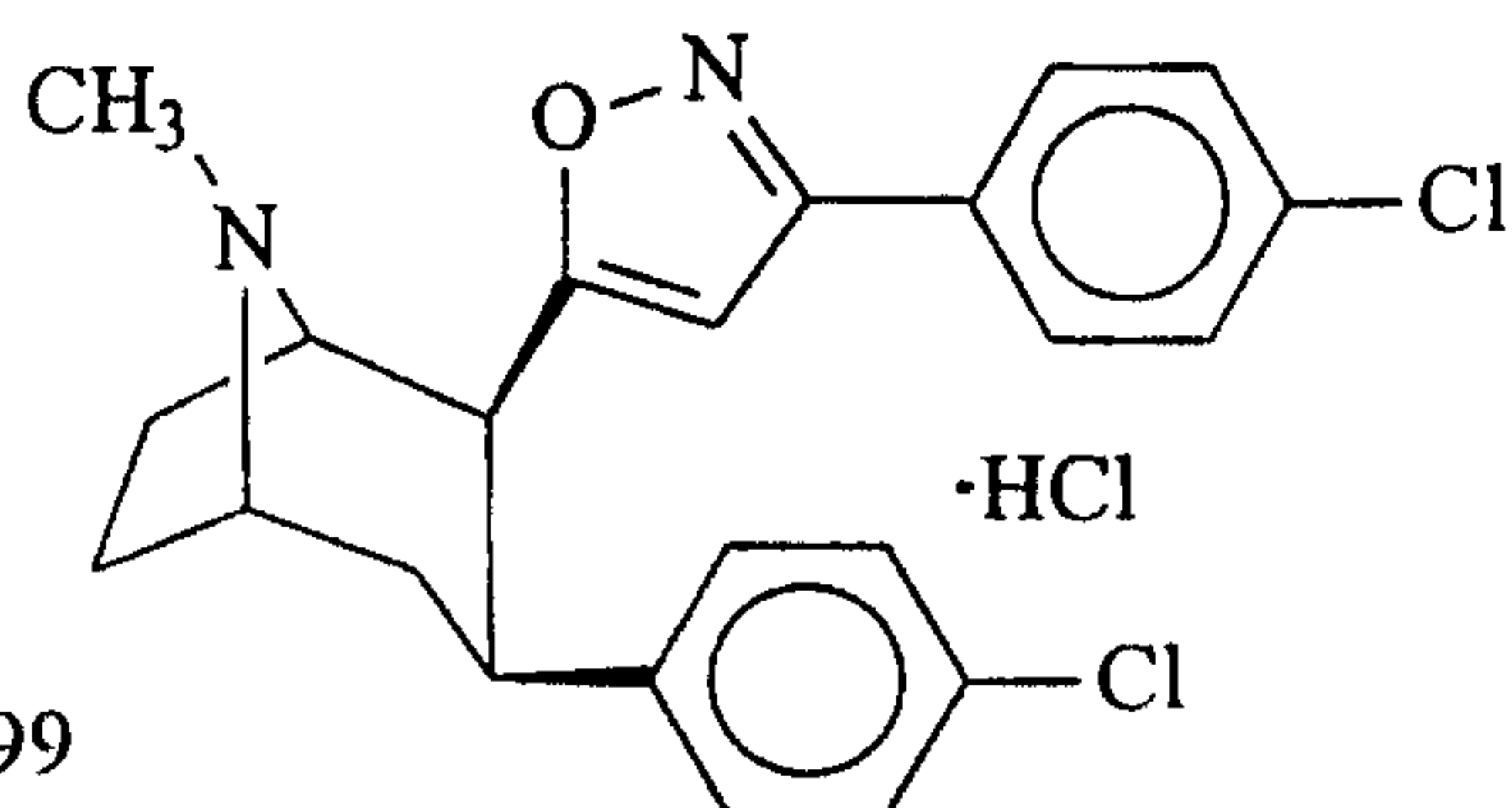
RTI-4229-337

DA 7.31 ± 0.61 5-HT 36.842 ± 3616 NE_N 6321 ± 703 

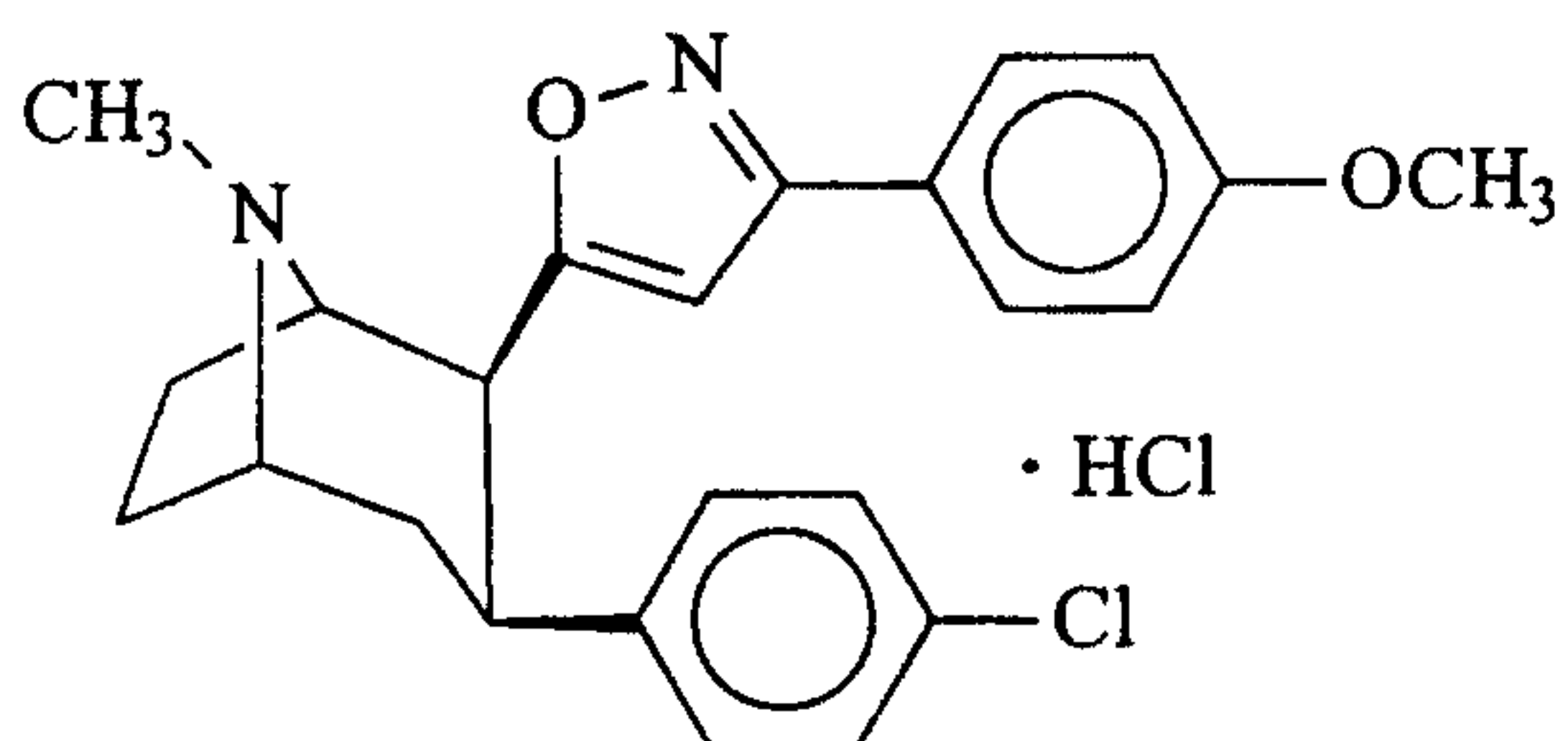
RTI-4229-338

DA 1104.2 ± 54.6 5-HT 7.41 ± 0.55 NE_N 3366 ± 584 

RTI-4229-345

DA 6.42 ± 0.46 5-HT $>76.000 \pm$ NE_N 5290.4 ± 448.99 

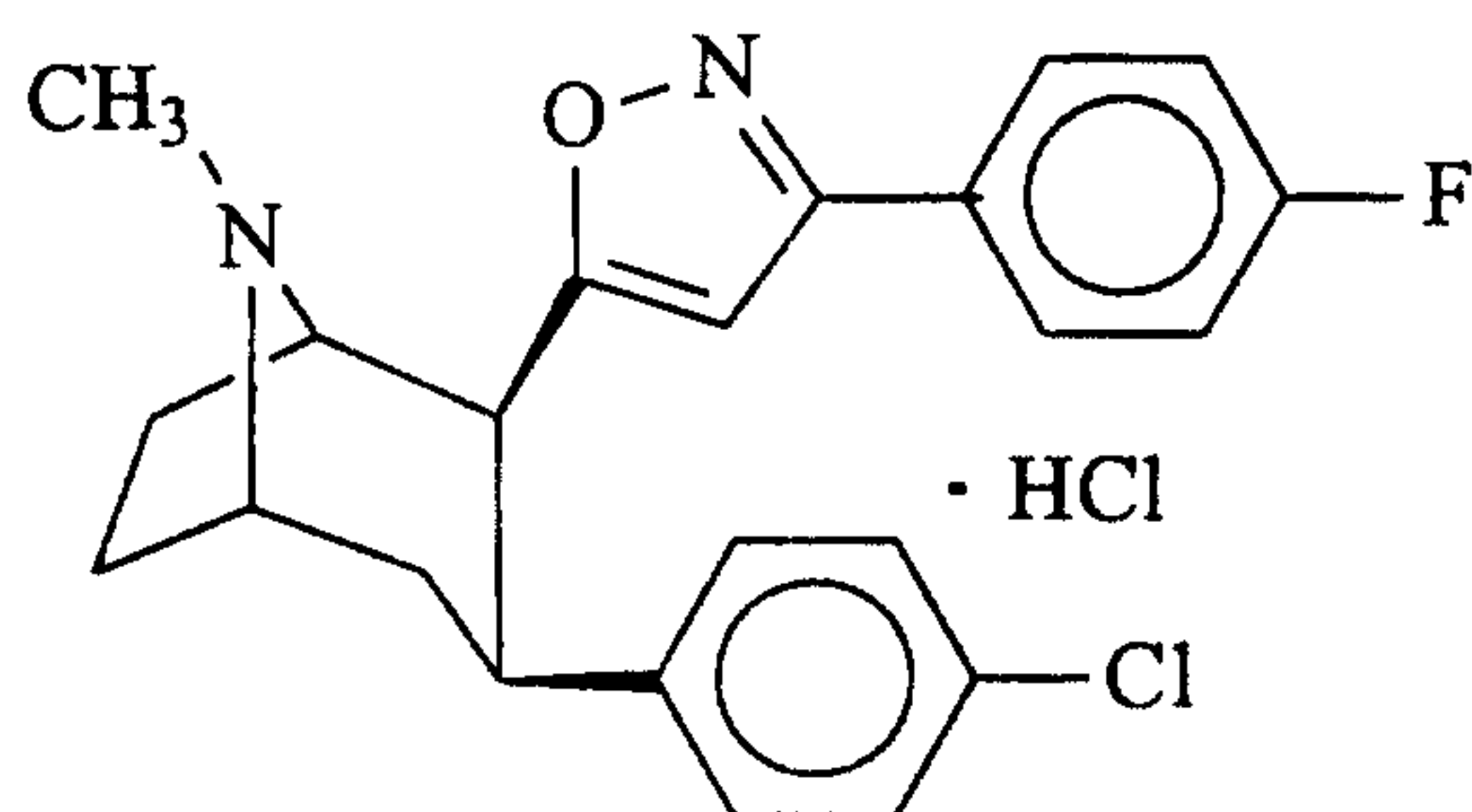
RTI-4229-346

DA 1.57 ± 0.10 5-HT 5880 ± 179 NE_N 762.01 ± 37.8 

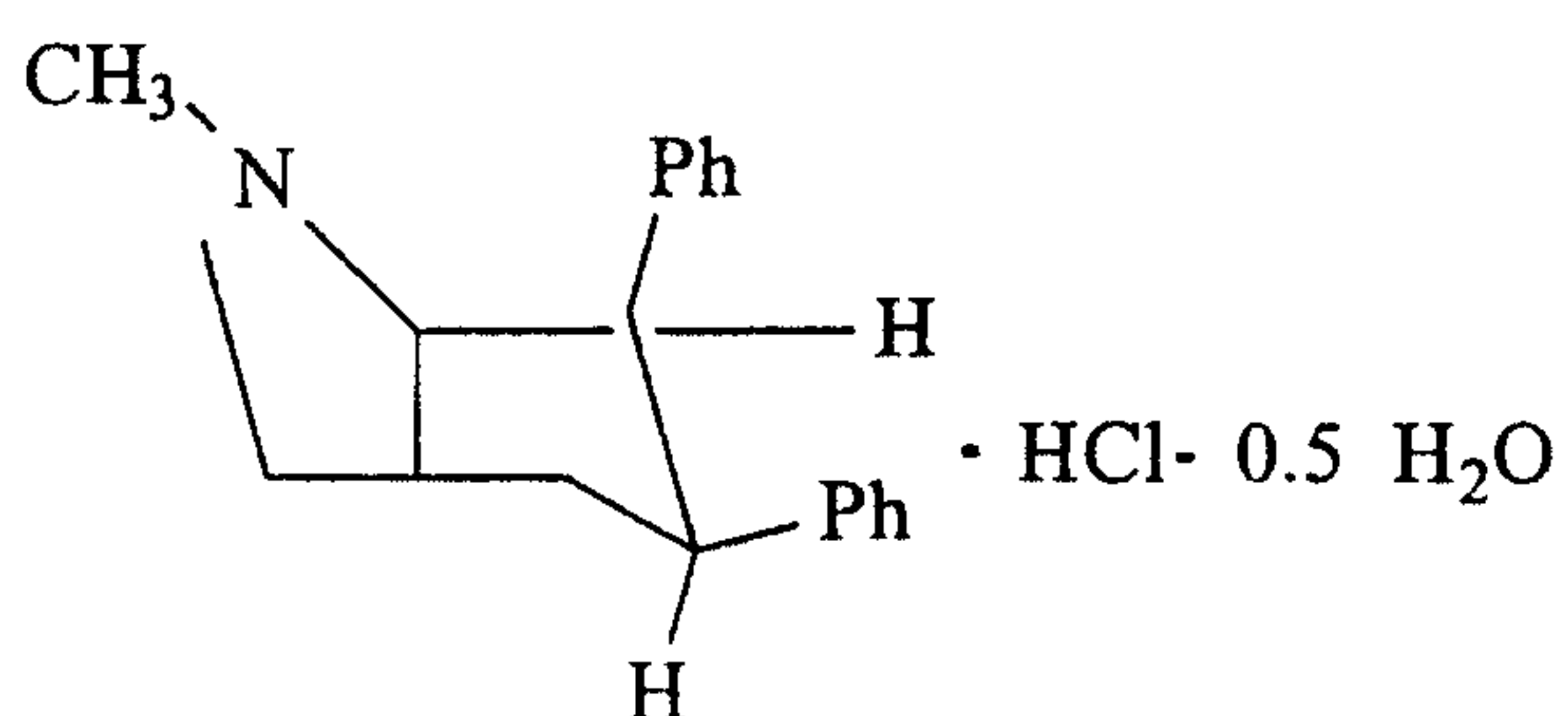
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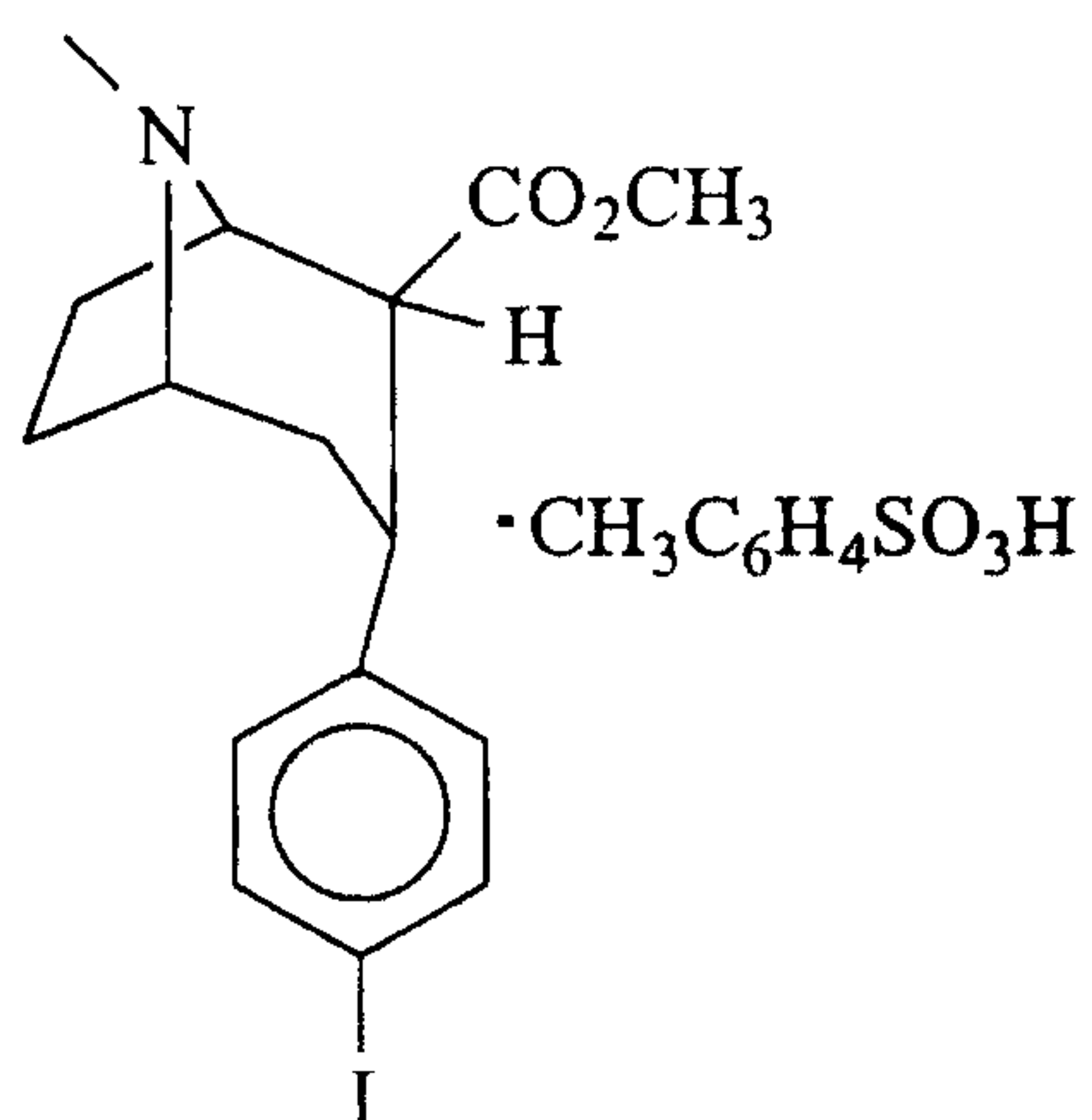
RTI-4229-347

DA 1.86 ± 0.09 5-HT 7256.95 ± 210 NE_N 918.4 ± 108.34 

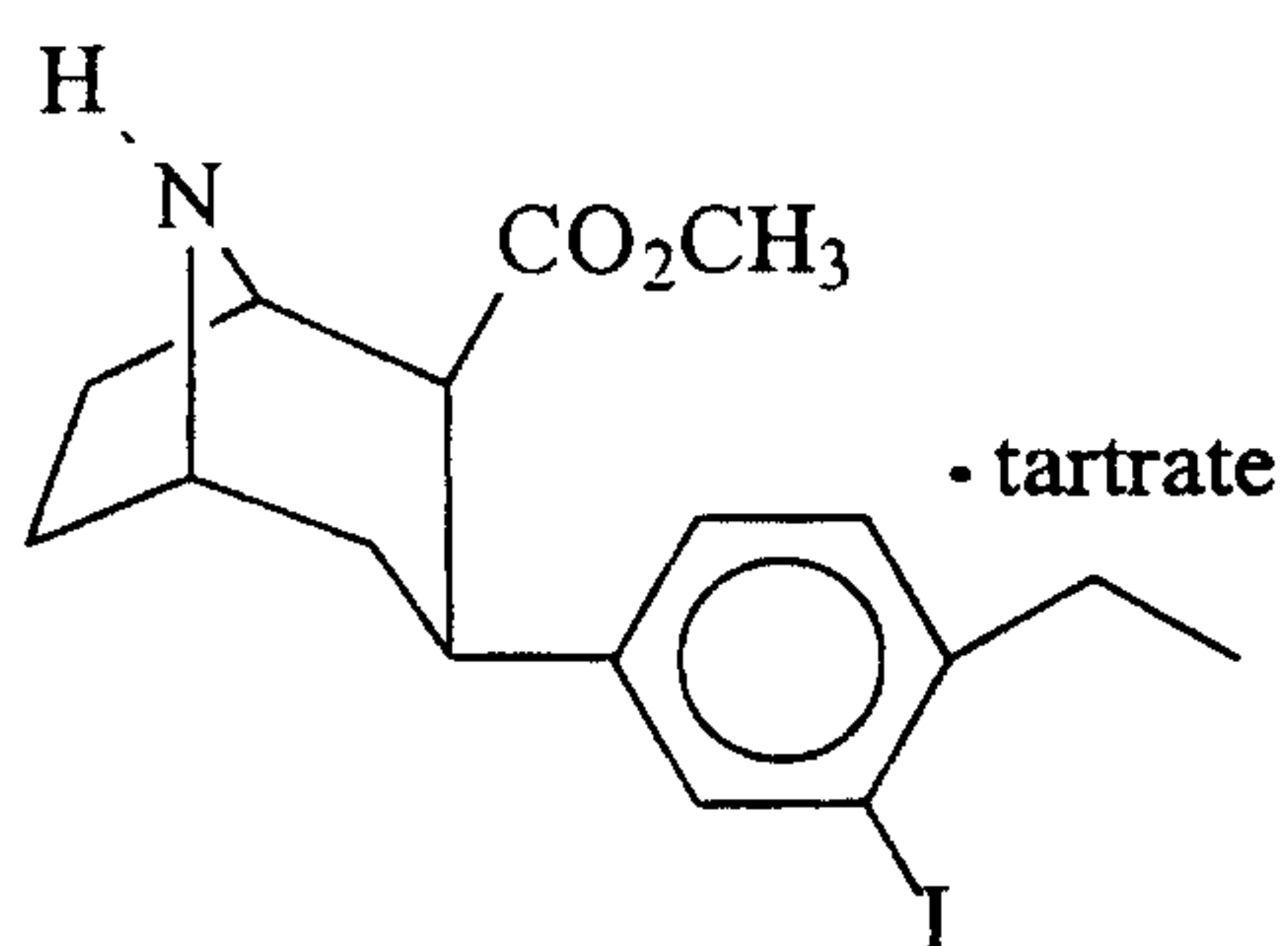
RTI-4229-348

DA 28.2 ± 1.9 5-HT 34.674 ± 3954 NE_N 2667.2 ± 6267.3 

RTI-4229-352

DA 2.86 ± 0.21 5-HT 64.9 ± 1.97 NE_N 52.4 ± 4.9 

RTI-4229-353

DA 330.54 ± 17.12 5-HT 0.69 ± 0.07 NE_N 148.4 ± 9.15 

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It should be noted that compound RTI-353 is a highly potent compound at the serotonin site, and is selective relative to the dopamine and norepinephrine sites. This compound is particularly useful as an antidepressant, and as an imaging agent for serotonin transporters.

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

EXAMPLES

All certified grade reagents or solvents were purchased from Aldrich Chemical Co. or Fluka Chemical Co. All reagents were normally used without further purification. When anhydrous conditions were required, solvents were distilled and dried by standard techniques immediately prior to use.

All air and moisture sensitive reactions were conducted under a prepurified nitrogen atmosphere in flame-dried glassware, previously dried at 150°C. Anhydrous solvents were transferred using conventional syringe or steel canula techniques under an inert atmosphere. Removal of solvents in vacuo was done on a Buchi rotavapor rotary evaporator operated at water aspirator pressure.

¹H NMR and ¹³C NMR spectra were recorded at 250 Mhz on a Bruker AM250 spectrometer. Optical rotations were recorded on at the Sodium D line on a Rudolph Research Autopol III polarimeter (1 dm cell). Melting point was recorded on a Uni-melt Thomas Hoover capillary melting point apparatus in open capillary tubes and were uncorrected. Elemental analysis were performed by Atlantic Microlab, Inc., Norcross, Georgia.

Reaction products were purified by flash column chromatography using silica gel (mesh size 230-400) purchased from VWR Scientific. Thin layer chromatography (TLC) was performed on Whatman 254 nm fluorescent silica gel 60A (1 x 3 inches, 250 [μm thickness]) precoated TLC plates using the solvent systems indicated. Developed chromatograms were evaluated under 254 nm UV light or with iodine.

EXAMPLE 1

General Procedure For the Preparation of Amides

To a solution of 1 mmol of 3β-(4-Chlorophenyl)-tropane-2β-carboxylic acid or 3β-(4-Methylphenyl)tropane-2β-carboxylic acid in 5 ml of methylene chloride was added dropwise with stirring under nitrogen 2.0 eq oxalyl chloride (2 M solution in methylene chloride). The

resulting solution was stirred at room temperature for an hour after evolution of gas has ceased. The solvent was removed in vacuo at room temperature and then at high vacuum to remove residual traces of oxalyl chloride. The resulting residue of acid chloride was suspended in 5 ml methylene chloride under nitrogen at 0 °C, and 2.0 eq of the amine hydrochloride containing 4.0 eq of triethylamine, or 2.5 eq of the amine free base was added. The mixture was stirred at room temperature overnight. Aqueous 3N NaOH (5 ml) was added to basify the reaction mixture, the organic layer was separated and the aqueous layer extracted with 3 x 10 ml chloroform. The combined organic layers were dried (Na₂SO₄), filtered and the solvent removed in vacuo to give crude product. The crude was purified by flash column chromatography or crystallization.

EXAMPLE 2

3β-(4-Chlorophenyl)-2β-(5-phenyl-1,3,4-oxadiazol-2-yl)-tropane Hydrochloride (RTI-188)

To a solution of 0.59 g (2 mmol) of 3β-(4-Chlorophenyl)-tropane-2β-carboxylic acid (chloro acid) in 2 ml of POCl₃ was added 0.31 g (2.2 mmol) of N-benzoic hydrazide and refluxed under nitrogen for 2 hours. The reaction mixture was cooled, poured into ice and rendered basic to pH 7-8 using concentrated NH₄OH. To the ice cold aqueous layer was added 10 ml brine and extracted thrice with 10 ml methylene chloride. The organic layers were combined, dried (NaSO₄), filtered, and the solvent removed in vacuo to give 0.9 g of crude residue. Purification of the residue by flash column chromatography [50% (ether/triethylamine 9:1) in hexane] gave 0.33 g (42%) of pure oxadiazole (RTI-188) which was recrystallized from ether/petroleum ether: ¹H NMR (CDCl₃) 1.81 (m, 3 H), 2.18 (s, 3 H), 2.26 (m, 2 H), 2.66 (m, 1 H), 3.33 (m, 2 H), 3.51 (m, 2 H), 7.16 (m, 4 H), 7.45 (m, 3 H), 7.86 (m, 2 H); IR (CHCl₃) 2950, 1550, 1490, 1450, 1340, 1090 cm⁻¹; [α]_D -106.25° (c = 0.08, CHCl₃).

The oxadiazole was converted into hydrochloride salt: ¹H NMR (MeOD) 2.08 (m, 1 H), 2.57 (m, 5 H), 3.0 (s, 3 H), 4.01 (m, 2 H), 4.15 (m, 1 H), 4.39 (m, 1 H), 7.24 (m, 4 H), 7.52 (m, 5 H); mp 160-162°C; Anal calcd for C₂₂H₂₃Cl₂N₃O.0.75H₂O; C = 61.47; H = 5.74, N = 9.78; Cl = 16.50; found C = 61.47, H = 5.73, N = 9.76; Cl = 16.56; [α]_D +84.59° (c = 0.36, CH₃OH).

Further elution gave as a second fraction 0.1 g (13%) of white solid which was characterized to be 3β-(4-Chlorophenyl)-2α-(5-phenyl-1,3,4-oxadiazol-2-yl)-tropane: ¹H NMR (CDCl₃) 1.76 (m, 3 H), 2.06 (s, 3 H), 2.45 (s, 3 H), 3.36 (m, 2 H), 3.51 (m, 1 H), 3.65 (m, 1 H), 7.21 (m, 4 H), 7.47 (m, 3 H), 7.91 (m, 2 H); mp 170-171°C; Anal calcd for C₂₂H₂₂ClN₃O; C = 69.55; H = 5.84, N = 11.06; Cl = 9.33; found C = 69.49, H = 5.85, N = 11.01; Cl = 9.41; [α]_D +33.06° (c = 0.18, CHCl₃).

EXAMPLE 3**3 β -(4-Methylphenyl)-2 β -(5-phenyl-1,3,4-oxadiazol-2-yl)-tropane Hydrochloride (RTI-195)**

Reaction of 0.65 g (2.5 mmol) of 3 β -(4-Methylphenyl)-tropane-2 β -carboxylic acid (Methyl acid) as described above for RTI-188 gave after work-up and purification by flash column chromatography [(50% (ether/triethylamine 9 : 1) in hexane] 0.36 g (40%) of pure oxadiazole (RTI-195) which was recrystallized from ether/petroleum ether: ¹H NMR (CDCl₃) 1.83 (m, 3 H), 2.18 (s, 3 H), 2.21 (s, 3 H), 2.3 (m, 2 H), 2.67 (m, 1 H), 3.33 (m, 1 H), 3.41 (m, 1 H), 3.53 (m, 1 H), 3.61 (m, 1 H) 7.0 (m, 2 H). 7.13 (m, 2 H), 7.44 (m, 3 H), 7.86 (m, 2 H); IR (CHCl₃) 2990, 1545, 1505, 1440, 1350. cm⁻¹; [α]_D -163.92° (c = 0.2, CHCl₃).

The oxadiazole was converted into hydrochloride salt: ¹H NMR (MeOD) 2.05 (m, 1 H), 2.21 (s, 3 H), 2.51 (m, 5 H), 2.99 (s, 3 H), 3.86 (m, 1 H), 3.95 (m, 1 H), 4.14 (m, 1 H), 4.35 (m, 1 H), 7.02 (m, 4 H) 7.53 (m, 5 H); mp 175-178°C; Anal calcd for C₂₃H₂₆ClN₃O.0.75H₂O; C = 67.47; H = 6.77, N = 10.26; Cl = 8.66; found C = 67.58, H = 6.79, N = 10.34; Cl = 8.78; [α]_D +97.22° (c = 0.25, CH₃OH).

Further elution gave as a second fraction 0.18g (20%) of solid which was characterized to be 3 β -(4-Methylphenyl)-2 α -(5-phenyl-1,3,4-oxadiazol-2-yl)-tropane which was recrystallized from ether/ petroleum ether: ¹H NMR (CDCl₃) 1.77 (m, 2 H), 2.0 (m, 4 H), 2.25 (s, 3 H), 2.47 (s, 3 H), 3.33 (m, 2 H), 3.51 (m, 1 H), 3.69 (d of d, J = 2.6, 12 Hz, 1 H), 6.91 (m, 2 H) 7.03 (m, 2 H). 7.45 (m, 2 H), 7.45 (m, 3 H), 7.89 (m, 2 H); IR (CHCl₃) 3020, 1540, 1510, 1415, 1250, 1215. cm⁻¹; Anal calcd for C₂₃H₂₅N₃O; C = 76.85; H = 7.01, N = 11.69; found C = 76.60, H = 7.12, N = 11.55; [α]_D +40.73° (c = 0.28, CHCl₃).

EXAMPLE 4**3 β -(4-Methylphenyl)-2 β -(5-methyl-1,3,4-oxadiazol-2-yl)-tropane Hydrochloride (RTI-194)**

Reaction of 0.65g (2.5 mmol) of methyl acid as described above for RTI-195 using 0.21 g (2.75 mmol) of N-acetic hydrazide gave after work-up and Purification by flash column chromatography [(75% (ether/triethylamine 9:1) in hexane] 0.29 g (39%) of pure oxadiazole (RTI-194) which was recrystallized from ether/petroleum ether: ¹H NMR (CDCl₃) 1.75 (m, 3 H), 2.18 (s, 3 H), 2.22 (s, 3 H), 2.25 (m, 2 H), 2.35 (s, 3 H), 2.56 (m, 1 H), 3.24 (m, 1 H), 3.4 (m, 2 H), 3.47 (m, 1 H) 7.0 (m, 4 H); ¹³C NMR (CDCl₃) 11.06, 20.9, 25.08, 26.32, 34.11, 34.6, 41.83, 45.73, 61.97, 66.21, 127.11, 128.85, 135.85, 138.19, 162.5, 167.44; IR (CHCl₃) 2950, 1590, 1510, 1450, 1350, 1215 cm⁻¹; [α]_D -108.47° (c = 0.14, CHCl₃).

The oxadiazole was converted into hydrochloride salt: ¹H NMR (MeOD) 1.99 (m, 1 H),

2.23 (s, 3 H), 2.27 (s, 3 H), 2.47 (m, 5 H), 2.94 (s, 3 H), 3.72 (m, 1 H), 3.79 (m, 1 H), 4.10 (m, 1 H), 4.23 (m, 1 H), 7.05 (m, 4 H); mp 146°C.(dec); Anal calcd for $C_{18}H_{24}ClN_3O \cdot 0.5H_2O$; C = 63.06; H = 7.35, N = 12.26; Cl = 10.34; found C = 63.21, H = 7.40, N = 12.07; Cl = 10.27; $[\alpha]_D -43.05^\circ$ (c = 0.15, CH_3OH).

EXAMPLE 5

3 β -(4-Chlorophenyl)-2 β -(5-phenyl-1,3,4-thiadiazol-2-yl)-tropane Hydrochloride (RTI-200).

Reaction of 0.59g (2 mmol) of 3 β -(4-Chlorophenyl)tropane-2 β -carboxylic acid as described above for the preparation of amides gave after purification of the crude by crystallizing from ethyl acetate/ether 0.52 g (66%) of pure N-[3 β -(4-Chlorophenyl)-tropane-2 β -carboxylic]-N'-benzoylhydrazide: ^1H NMR ($CDCl_3$) δ 1.76 (m, 3 H), 2.24 (m, 2 H), 2.41 (s, 3 H), 2.51 (m, 1 H), 2.68 (m, 1 H), 3.18 (m, 1 H), 3.44 (m, 2 H), 7.22 (m, 4 H), 7.46 (m, 3 H), 7.78 (m, 2 H), 9.02 (br s, 1 H), 12.97 (br s, 1 H); IR ($CHCl_3$) 3385, 3035, 3000, 1620, 1570, 1485, 1450, 1215 cm^{-1} .

A solution of 0.4 g (1 mmol) of N-[3 β -(4-Chlorophenyl)-tropane-2 β -carboxylic]-N'-benzoyl-hydrazide and 0.8g (2 mmol) of Lawesson's reagent in 10 ml toluene was refluxed for 4 h under nitrogen. The reaction mixture was cooled and solvent removed in vacuo to give a yellow residue. To the residue was added 3 g of silica gel and 10 ml of methylene chloride, the resulting slurry was mixed properly and the solvent removed in vacuo. The crude compound impregnated on silica gel was loaded on a column and purified by flash column chromatography [50% ether/triethylamine(9 : 1) in hexane] to obtain 0.23 g (58%) of pure thiadiazole (RTI-200) which was further purified by recrystallizing from ether: ^1H NMR ($CDCl_3$) δ 1.75 (m, 3 H), 2.20 (m, 3 H), 2.32 (s, 3 H), 3.30 (m, 3 H), 3.78 (m, 1 H), 6.86 (m, 2 H), 7.08 (m, 2 H), 7.43 (m, 3 H), 7.97 (m, 2 H); ^{13}C NMR 25.55, 25.88, 34.60, 36.09, 41.55, 49.73, 61.48, 65.33, 127.59, 128.28, 128.78, 128.88, 130.37, 130.88, 132.19, 139.27, 168-29, 169.56; IR (CCl_4) 2940, 1490, 1460, 1340, 1245, 1100, 1010 cm^{-1} .

The thiadiazole was converted into hydrochloride salt: ^1H NMR (MeOD) δ 2.06 (m, 1 H), 2.53 (m, 5 H), 2.97 (s, 3 H), 3.92 (m, 1 H), 4.17 (m, 2 H), 4.39 (m, 1 H), 7.11 (m, 2 H), 7.26 (m, 2 H), 7.51 (m, 3 H), 7.79 (m, 2 H); mp 165-170°C; Anal calcd for $C_{22}H_{23}Cl_2N_3S \cdot 0.75H_2O$; C = 59.26, H = 5.54, N = 9.42, Cl = 15.90; S = 7.19. found C = 59.27, H = 5.52, N = 9.40, Cl = 15.99; S 7.09; $[\alpha]_D -42.81^\circ$ (c = 0.16, MeOH).

Further elution gave 0.08 g (21%) as a second fraction which was characterized to be 3 β -(4-chlorophenyl)-2 α -(5-phenyl-1,3,4-oxadiazol-2-yl)-tropane.

EXAMPLE 6**3 β -(4-Methylphenyl)-2 β -(5-phenyl-1,3,4-thiadiazol-2-yl)-tropane Hydrochloride (RTI-199)**

Reaction of 0.65 g (2.5 mmol) of 3 β -(4-Methylphenyl)-tropane-2 β -carboxylic acid as described above for preparation of amides gave after work up and purification by flash column chromatography [(50% CMA-80 in methylene chloride)] 0.48 g (51%) pure N-[3 β -(4-Methylphenyl) Tropane-2 β -carboxylic]-N'-benzoyl-hydrazide which was further purified by recrystallizing from ether/pet ether: ^1H NMR (CDCl_3) δ 1.75 (m, 3 H), 2.20 (m, 2 H), 2.27 (s, 3 H), 2.42 (s, 3 H), 2.51 (m, 1 H), 2.67 (m, 1 H), 3.18 (m, 1 H), 3.47 (m, 2 H), 7.11 (m, 4 H), 7.48 (m, 3 H), 7.81 (m, 2 H), 9.06 (br s, 1 H), 13.09 (br s, 1 H); IR (CHCl_3) 3385, 3045, 1625, 1570, 1460, 1420, 1100 cm^{-1} ;

Reaction of 0.29 g (0.75 mmol) of N-[3 β -(4-Methylphenyl)-tropane-2 β -carboxylic]-N'-benzoyl-hydrazide as described above for **RTI-200** gave after work and purification by flash chromatography [40% ether/triethylamine(9 : 1) in hexane] 0.16 g (58%) of pure thiadiazole (**RTI-199**): ^1H NMR (CDCl_3) δ 1.70 (m, 1 H), 1.88 (m, 2 H), 2.20 (s, 3 H), 2.23 (m, 2 H), 2.21 (s, 3 H), 2.38 (m, 1 H), 3.21 (m, 1 H), 3.32 (m, 1 H), 3.39 (m, 1 H), 3.78 (m, 1 H), 6.81 (m, 2 H), 6.92 (m, 2 H), 7.43 (m, 3 H), 7.97 (m, 2 H); ^{13}C NMR 20.98, 25.65, 25.95, 34.79, 36.25, 41.65, 50.05, 61.68, 65.49, 127.32, 127.65, 128.89, 128.95, 130.29, 131.11, 135.94, 137.68, 168.83, 169.45; IR (CCl_4) 2935, 1510, 1450, 1250, 1120, 1100, 1060 cm^{-1}

The thiadiazole was converted into hydrochloride salt; ^1H NMR (MeOD) δ 1.95 (m, 1 H), 2.17 (s, 3 H), 2.41 (m, 5 H), 2.89 (s, 3 H), 3.76 (m, 1 H), 4.05 (m, 2 H), 4.30 (m, 1 H), 4.22 (m, 1 H), 6.89 (m, 2 H), 6.99 (m, 2 H), 7.39 (m, 3 H), 7.67 (m, 2 H); mp 180-185°C; Anal calcd for $\text{C}_{23}\text{H}_{26}\text{ClN}_3\text{S}\cdot\text{H}_2\text{O}$; C = 65.62, H = 6.46, N = 9.98, Cl = 18.42; S = 7.62. found C = 65.57, H = 6.63, N = 9.91, Cl = 18.24; S = 7.55; $[\alpha]_D -33.5^\circ$ (c = 0.2, MeOH)

Further elution gave 0.04 g (15%) of a second fraction which was characterized to be 3 β -(4-Methylphenyl)-2 α -(5-phenyl-1,3,4-oxadiazol-2-yl)-tropane.

EXAMPLE 7**3 β -(4-Chlorophenyl)-2 β -(5-phenyl-oxazol-2-yl)-tropane Tartrate RTI-189)**

Reaction of 0.73 g (2.5 mmol) of 3 β -(4-Chlorophenyl)-tropane-2 β carboxylic acid as described above for the preparation of amides gave after purification by flash column chromatography (15% CMA 80 in methylene chloride) 0.8 g (81%) of pure 3 β -(4-Chlorophenyl)-tropane-2 β -N-(phenylacyl)carboxamide: ^1H NMR (CDCl_3) δ 1.71 (m, 3 H), 2.19 (m, 2 H), 2.39 (s, 3 H), 2.46 (m, 1 H), 2.58 (m, 1 H), 3.13 (m, 1 H), 3.43 (m, 2 H), 4.74 (m, 2 H), 7.13 (m, 4 H),

7.49 (m, 2 H), 7.59 (m, 1 H), 7.96 (m, 2 H), 10.57 (br s, 1 H); IR (CHCl₃) 3135, 3010, 2930, 1695, 1650, 1590, 1530, 1485, 1450, 1355, 1220 cm⁻¹.

A solution of 0.725 g (1.83 mmol) of 3β-(4-Chlorophenyl)-tropane-2β-N-(phenylacyl)carboxamide in 6 ml POCl₃ was heated at 125°C under nitrogen for 2 hours. The reaction mixture was cooled and poured into ice and rendered basic to pH 7-8 using concentrated NH₄OH. To the ice cold aqueous layer was added 10 ml brine and extracted thrice with 10 ml methylene chloride. The organic layers were combined dried (NaSO₄), filtered, and the solvent removed in vacuo to 0.63 g crude oxazole. Purification of the crude by flash column chromatography [(40% (ether/triethylamine 9 : 1) in hexane)] gave 0.34 g (49%) of pure oxazole (**RTI-189**) which was further purified by recrystallizing from ether/petroleum ether: ¹H NMR (CDCl₃) 1.79 (m, 3 H), 2.22 (s, 3 H), 2.27 (m, 2 H), 2.66 (m, 1 H), 3.27 (m, 1 H), 3.40 (m, 2 H), 3.53 (m, 1 H), 7.11 (s, 1 H), 7.16 (s, 4 H) 7.31 (m, 5 H); IR (CHCl₃) 2950, 1540, 1490, 1445, 1350, 1120, 1090 CM⁻¹; [α]_D -70.37° (c = 0.19, CHCl₃).

The oxazole was converted into tartrate salt: ¹H NMR (MeOD) 2.14 (m, 1 H), 2.54 (m, 5 H), 2.96 (s, 3 H), 3.75 (m, 2 H), 4.12 (m, 1 H), 4.25 (m, 1 H), 4.41 (s, 2 H), 7.05 (m, 2 H), 7.29 (m, 7 H), 7.45 (s, 1 H), 7.43 (s, 1 H); mp 126°C (dec); Anal calcd for C₂₇H₂₉ClN₂O₇·0.75H₂O; C = 59.78; H = 5.67, N = 5.16; Cl = 6.54; found C = 59.78, H = 5.58, N = 4.93; Cl = 6.31; [α]_D +101.43° (c = 0.21, CH₃OH).

EXAMPLE 8

3β-(4-Methylphenyl)-2β-(5-phenyl-oxazol-2-yl)-tropane Tartrate (RTI-178)

Reaction of 0.52 g (2 mmol) of 3β-(4-Methylphenyl)-tropane-2β-carboxylic acid as described above for preparation of amides gave after work up and purification by flash column chromatography (15% CMA in methylene chloride) 0.54 g (72%) of pure 3β-(4-Methylphenyl)-tropane-2β-N-(phenylacyl)carboxamide: ¹H NMR (CDCl₃) δ 1.73 (m, 3 H), 2.14 (m, 2 H), 2.26 (s, 3 H), 2.40 (s, 3 H), 2.47 (m, 1 H), 2.59 (m, 1 H), 3.14 (m, 1 H), 3.42 (m, 2 H), 4.74 (m, 2 H), 7.05 (m, 4 H), 7.48 (m, 2 H), 7.59 (m, 2 H), 7.97 (m, 2 H), 10.62 (br s, 1 H); IR (CHCl₃) 3155, 3005, 2930, 1690, 1650, 1520, 1450, 1355, 1215 cm⁻¹

Reaction of 0.5 g (1.33 mmol) of 3β-(4-Methylphenyl)-tropane-2β-N-(phenylacyl)carboxamide as described above for **RTI-189** gave after workup and purification by flash column chromatography [(40% (ether/triethylamine 9 : 1) in hexane)] 0.1 g (31%) **RTI-158** as a first fraction. Further elution gave 0.19 g (42%) of pure oxazole **RTI-178**: ¹H NMR (CDCl₃)

1.8 (m, 3 H), 2.18 (m, 2 H), 2.21 (s, 3 H), 2.22 (s, 3 H), 2.67 (m, 1 H), 3.28 (m, 1 H), 3.42 (m, 2 H), 3.53 (m, 1 H), 6.98 (m, 2 H), 7.11 (m, 3 H), 7.30 (m, 5 H).

The oxazole was crystallized as the tartrate salt: ^1H NMR (MeOD) 1.99 (m, 1 H), 2.19 (s, 3 H), 2.54 (m, 5 H), 2.95 (s, 3 H), 3.74 (m, 2 H), 4.13 (m, 1 H), 4.26 (m, 1 H), 4.4 (s, 2 H), 6.91 (m, 2 H), 7.0 (m, 2 H), 7.25 (m, 2 H), 7.33 (m, 3 H), 7.43 (s, 1 H); mp 175-181 C; Anal calcd for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_7 \cdot 1\text{H}_2\text{O}$; C = 63.87; H = 6.51, N = 5.32; found C = 64.21, H = 6.40, N = 5.19; $[\alpha]_{\text{D}} -104.04^\circ$ (c = 0.6, CH_3OH).

EXAMPLE 9

3 β -(4-Chlorophenyl)-2 β -(5-phenylthiazol-2-yl)-tropane Hydrochloride (RTI-219)

To a solution of 0.74 g (1.86 mmol) of 3 β -(4-Chlorophenyl)-tropane-2 β -N-(phenylacyl)carboxamide and 1.51 g (7.45 mmol) of Lawesson's reagent in 18 ml of toluene was refluxed under N_2 for 5 hours. The reaction mixture was cooled and solvent removed in vacuo to give crude residue. To the residue was added 3 g of silica gel and 10 ml of methylene chloride, the resulting slurry was mixed properly and the solvent removed in vacuo. The crude compound impregnated on silica gel was loaded on a column and purified by flash column chromatography [(40% (ether/triethylamine 9 : 1) in hexane)] to give 0.21 g (30%) of pure thiazole **RTI-219**: ^1H NMR (CDCl_3) 1.61 (m, 1 H), 1.82 (m, 2 H), 2.22 (m, 2 H), 2.34 (s, 3 H), 2.39 (m, 1 H), 3.28 (m, 2 H), 3.39 (m, 1 H), 3.49 (m, 1 H), 6.8 (m, 2 H) 7.07 (m, 2 H). 7.32 (m, 3 H), 7.57 (m, 2 H), 7.60 (s, 1 H); ^{13}C NMR (MeOD) 25.51, 25.99, 35.01, 36.92, 41.72, 52.97, 61.58, 65.70, 126.45, 127.60, 128.13, 128.89, 129.05, 131.91, 132.43, 136.11, 139.91, 140.27, 168.97; IR (CHCl_3) 2945, 1590, 1485, 1445, 1350, 1125, 1090. cm^{-1} .

The thiazole was converted into hydrochloride salt: ^1H NMR (MeOD) 1.99 (m, 1 H), 2.51 (m, 5 H), 2.93 (s, 3 H), 3.79 (m, 2 H), 4.15 (m, 1 H), 4.28 (m, 1 H), 7.02 (d, J = 8.5 Hz, 2 H) 7.21 (d, J = 8.5 Hz, 2 H), 7.39 (m, 5 H), 8.06 (s, 1 H); mp 228-230°C; Anal calcd for $\text{C}_{23}\text{H}_{24}\text{ClN}_2\text{S} \cdot \text{H}_2\text{O}$; C = 61.47, H = 5.83, N = 6.23, S = 7.13, Cl = 15.78; found C = 61.61, H = 5.76, N = 6.20, S = 7.51, Cl = 15.84; $[\alpha]_{\text{D}} +27.43^\circ$ (c = 0.11, CH_3OH).

EXAMPLE 10

3 β -(4-Chlorophenyl)-2 β -(benzothiazol-2-yl)-tropane Hydrochloride (RTI-202)

Reaction of 0.59 g (2 mmol) of 3 β -(4-Chlorophenyl)-tropane-2 β -carboxylic acid as described above for preparation of amides gave after purification of the crude by flash column chromatography (50% CMA-80 in methylene chloride) 0.3 g (41 %) of pure **RTI-202** which was

further purified by recrystallizing from ether/hexane: ^1H NMR (CDCl_3) δ 1.65 (m, 1 H), 1.87 (m, 2 H), 2.24 (m, 2 H), 2.34 (s, 3 H), 2.41 (m, 1 H), 3.28 (m, 2 H), 3.40 (m, 1 H), 3.62 (m, 1 H), 6.8 (m, 2 H), 6.81 (m, 2 H), 7.29 (m, 2 H), 7.70 (m, 1 H), 7.84 (m, 1 H); ^{13}C NMR (CDCl_3) δ 25.58, 26.07, 35.40, 36.95, 41.56, 53.09, 61.57, 65.47, 120.95, 122.42, 124.11, 125.20, 128.05, 129.03, 131.87, 136.72, 139.91, 151.33, 171.11; IR (CHCl_3) 2940, 2795, 1495, 1445, 1305, 1130, 1105, 1015, 907 cm^{-1} ; $[\alpha]_{\text{D}} -233.89^\circ$ ($c = 0.09$, CHCl_3).

The benzothiazole was converted into hydrochloride salt: ^1H NMR (MeOD) δ 2.02 (m, 1 H), 2.43 (m, 4 H), 2.89 (m, 1 H), 2.98 (s, 3 H), 3.90 (m, 2 H), 4.23 (m, 1 H), 4.34 (m, 1 H), 7.02 (m, 2 H), 7.13 (m, 2 H), 7.45 (m, 2 H), 7.81 (m, 1 H), 8.16 (m, 1 H); mp 140-150°C (dec); Anal calcd for $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{N}_2\text{S} \cdot 0.75\text{H}_2\text{O}$ C = 60.21, H = 5.65, N = 6.69, Cl = 16.93; S = 7.65; found C = 60.14, H = 5.74, N = 6.60, Cl = 16.89; S = 7.71; $[\alpha]_{\text{D}} -172.49^\circ$ ($c = 0.28$, MeOH).

EXAMPLE 11

3 β -(4-Chlorophenyl)-tropane-2 β -nitrile (RTI-161)

To a solution of 0.95g (3.5 mmol) of 3 β -(4-Chlorophenyl)-tropane-2 β -carboxamide in 20 ml dry THF was added 0.56 ml (7 mmol) pyridine. To the resulting solution at room temperature was added dropwise with stirring under nitrogen 0.35 ml (4.2 mmol) of trifluoroacetic anhydride. The reaction was stirred at room temperature for 30 minutes, and quenched with 10 ml water. The solvent was removed under vacuo and the residue was taken in 10 ml saturated aqueous K_2CO_3 and extracted thrice with 10 ml CHCl_3 . The organic layers were combined and washed with 20 ml brine dried (NaSO_4), filtered, and the solvent removed in vacuo to give 0.26 g crude product. Purification of the crude by flash column chromatography (10% CMA in methylene chloride) gave 0.68 g (77%) of pure nitrile **RTI-161** which was recrystallized from methylene chloride and hexane: ^1H NMR (CDCl_3) δ 1.70 (m, 3 H), 2.22 (m, 3 H), 2.35 (s, 3 H), 2.80 (m, 1 H), 3.04 (m, 1 H), 3.34 (m, 1 H), 3.43 (m, 1 H), 7.26 (m, 4 H); IR (CHCl_3) 3700, 2950, 2225, 1490, 1470, 1090, 900 cm^{-1} ; mp 167-173°C; Anal calcd for $\text{C}_{15}\text{H}_{18}\text{Cl}_2\text{N}_2 \cdot 0.75\text{H}_2\text{O}$; C = 57.98, H = 6.32, N = 9.02, Cl = 22.82; found C = 58.22, H = 6.12, N = 8.48, Cl = 22.89; $[\alpha]_{\text{D}} -73.33^\circ$ ($c = 0.48$, MeOH).

EXAMPLE 12

3 β -(4-Methylphenyl)-tropane-2 β -nitrile Hydrochloride (RTI-158)

Reaction of 0.26g (1 mmol) of 3 β -(4-Methylphenyl)-tropane-2 β -carboxamide as described above for **RTI-161** gave after work up and purification 0.16 g (67%) of pure nitrile

(RTI-158): ^1H NMR (CDCl_3) δ 1.68 (m, 3 H), 2.18 (m, 3 H), 2.32 (s, 3 H), 2.35 (s, 1 H), 2.82 (m, 1 H), 3.02 (m, 1 H), 3.36 (m, 1 H), 3.43 (m, 1 H), 7.18 (m, 4 H); IR (CHCl_3) 3675, 3000, 2950, 2200, 1600, 1510, 1450, 1350, 1220, 1100 cm^{-1} .

The crude product was crystallized as the HCl salt: ^1H NMR (MeOH) δ 2.08 -2.58 (m, 9 H), 2.92 (s, 3 H), 3.54 (m, 1 H), 3.69 (br s, 1 H), 4.12 (br s, 1 H), 4.29 (m, 1 H), 7.21 (m, 4 H); mp 270°C (dec.); Anal calcd for $\text{C}_{16}\text{H}_{21}\text{ClN}_2$; C = 69.42, H = 7.65 N = 10.12, Cl = 12.81; found C = 69.31, H = 7.70, N = 10.12, Cl = 12.81; $[\alpha]_D$ -76.4° (c = 0.5, MeOH).

EXAMPLE 13

3 β -(4-Chlorophenyl)-tropane-2 β -tetrazole (RTI-163)

To a solution of 0.13 g (0.5 mmol) of **RTI-161** in 5 ml dry THF was added 0.28 ml (5 mmol) azidotrimethylsilane and the mixture was placed in a PTFE-lined autoclave. The solution was heated to 150°C for 24 hours in an oil bath. The reaction mixture was cooled and transferred using MeOH. The solvent was removed in vacuo to give a brownish residue. Purification of the crude by flash column chromatography (20%-50% CMA in methylene chloride) gave 0.05 g (33%) of pure tetrazole (**RTI-163**): ^1H NMR (CDCl_3 + 1 drop MeOD) δ 1.73 (m, 1 H), 2.44 - 2.02 (m, 4 H), 2.6 (m, 1 H), 2.68 (s, 3 H), 3.33 (m, 1 H), 3.65 (m, 1 H), 3.73 (m, 1 H), 3.97 (m, 1 H), 6.68 (d, J = 8 Hz, 2 H), 7.07 (d, J = 8 Hz, 2 H); mp 296-300°C; Anal calcd for $\text{C}_{15}\text{H}_{18}\text{ClN}_5 \cdot 0.75\text{H}_2\text{O}$; C = 56.78, H = 6.19 N = 22.07, Cl = 11.17; found C = 56.69, H = 6.22, N = 22.09, Cl = 11.15; $[\alpha]_D$ -124.94° (c=0.39, MeOH).

EXAMPLE 14

3 β -(4-Methylphenyl)-tropane-2 β -tetrazole Hydrochloride (RTI-157)

Reaction of 0.12 g (0.5 mmol) of **RTI-158** as described above for **RTI-163** gave after workup and purification of the crude by flash column chromatography (100% CMA) 0.14 g (88%) of pure tetrazole (**RTI-157**): ^1H NMR (CDCl_3 + 1 drop MeOD) δ 1.8 (m, 1 H), 2.14 (s, 3 H), 2.35 (m, 5 H), 2.71 (s, 3 H), 3.36 (m, 1 H), 3.75 (m, 2 H), 4.02 (m, 1 H), 6.48 (d, J = 8 Hz, 2 H), 6.82 (d, J = 8 Hz, 2 H).

The purified product was converted into HCl salt: ^1H NMR (MeOD) δ 2.01 (m, 1 H), 2.27 (s, 3 H), 2.69 (m, 5 H), 2.97 (s, 3 H), 3.81 (m, 2 H), 4.18 (m, 2 H), 5.5 (s, 1 H), 6.76 (d, J = 8 Hz, 2 H), 7.02 (d, J = 8 Hz, 2 H); mp 212°C (dec); Anal calcd for $\text{C}_{16}\text{H}_{23}\text{Cl}_2\text{N}_5 \cdot 0.25\text{H}_2\text{O}$; C = 53.26, H = 6.56 N = 19.41; found C = 53.41, H = 6.50, N = 19.02; $[\alpha]_D$ -110.97° (c = 0.16, MeOH).

EXAMPLE 15**3 β -(4-Chlorophenyl)-2 β -(3-methylisoxazol-5-yl)tropane Hydrochloride (RTI-165)**

A solution of n-butyl lithium in hexane 5.9 ml (2.5 M, 14.6 mmol) was added to a stirred solution of acetone oxime 0.55 g (7.3 mmol) in dry THF (15 ml) at 0 °C under nitrogen. After 1 hour, a solution of 1.65 g (5.62 mmol) 3 β -(4-Chlorophenyl)-2 β -(carbomethoxy)tropane in 10 ml dry was added dropwise with stirring at 0°C. The solution was allowed to warm to room temperature over 18 hours. The mixture was poured into a stirred solution of concentrated sulfuric acid (3.2 g) in THF (15 ml) and water (4 ml) and was heated under reflux for 1 hour. The cooled solution was made basic using saturated aqueous K₂CO₃ (10 ml) and extracted thrice with 10 ml methylene chloride. The combined organic layers were dried (Na₂SO₄), filtered and solvent removed in vacuo to give 1.8 g of crude isoxazole. Purification of the crude residue by flash column chromatography (10% CMA in methylene chloride) gave 0.74 g (46%) of pure isoxazole **RTI-165** which was further purified by crystallization from methylene chloride/hexane: ¹H NMR (CDCl₃) δ 1.71 (m, 3 H), 2.10 (m, 3 H), 2.18 (s, 3 H), 2.24 (s, 3 H), 3.20 (m, 2 H), 3.32 (m, 2 H), 6.18 (s, 1 H), 6.9 (d, J = 8 Hz, 2 H), 7.14 (d, J = 8, Hz, 2 H); IR (CCl₄) 2950, 1590, 1490, 1420, 1350, 1020, 910 cm⁻¹; mp 154-156°C; Anal calcd for C₁₈H₂₁N₂OCl; C = 68.28, H = 6.68, N = 8.84, Cl = 11.19; found C = 68.22, H = 6.69, N = 8.87, Cl = 11.19; [α]_D -125.58° (c = 0.43, MeOH).

The isoxazole was crystallized as the hydrochloride salt: ¹H NMR (MeOD) δ 2.04 (s, 3 H), 2.19 (m, 1 H), 2.30 (m, 1 H), 2.48 (m, 2 H), 2.60 (m, 1 H), 2.70 (m, 1 H), 2.90 (s, 3 H), 3.68 (m, 1 H), 3.81 (m, 1 H), 4.04 (m, 1 H), 4.15 (m, 1 H), 5.55 (s, 1 H), 7.04 (d, J = 8 Hz, 2 H), 7.14 (d, J = 8 Hz, 2 H); mp >235°C (dec); Anal calcd for C₁₈H₂₂Cl₂N₂O; C = 61.19, H = 6.28, N = 7.93, Cl = 20.07; found c = 60.98, H = 6.38, N = 7.91, Cl = 19.96; [α]_D -102.89° (c = 0.46, MeOH).

EXAMPLE 16**3 β -(4-Methylphenyl)-2 β -(3-methylisoxazol-5-yl)tropane Hydrochloride (RTI-171)**

Reaction of 1.09 g (4 mmol) of 3 β -(4-Methylphenyl)-2 β -(carbomethoxy)tropane as described above for **RTI-165** gave after workup 1.21 g crude isoxazole. Purification of the crude by flash column chromatography (15% CMA in methylene chloride) gave 0.73 g (62%) pure isoxazole (**RTI-171**): ¹H NMR (CDCl₃) δ 1.73 (m, 3 H), 2.11 (m, 3 H), 2.17 (s, 3 H), 2.23 (s, 3 H), 2.25 (s, 3 H), 3.20 (m, 2 H), 3.32 (m, 2 H), 6.13 (s, 1 H), 6.97 (m, 4 H); IR (CCl₄) 2935, 2785, 1590, 1510, 1460, 1421, 1350, 1125, 1010, 910 cm⁻¹.

The isoxazole was crystallized as the hydrochloride salt: ^1H NMR (MeOD) δ 2.01 (s, 3 H), 2.24 (s, 3 H), 2.32 (m, 2 H), 2.42 (m, 4 H), 2.81 (s, 3 H), 3.61 (m, 1 H), 3.78 (m, 1 H), 4.03 (m, 1 H), 4.15 (m, 1 H), 5.45 (s, 1 H), 6.96 (m, 4 H); mp 277°C ; Anal calcd for $\text{C}_{19}\text{H}_{25}\text{ClN}_2\text{O}$; C = 68.55, H = 7.57, N = 8.42, Cl = 10.65; found C = 68.65, H = 7.62, N = 8.42, Cl = 10.56; $[\alpha]_{\text{D}} -107.28^\circ$ (c = 0.71, MeOH).

EXAMPLE 17

3 β -(4-Iodophenyl)-2 β -(3-methylisoxazol-5-yl)tropane Hydrochloride (RTI-180)

Reaction of 0.73 g (1.9 mmol) of 3 β -(4-Iodophenyl)-2 β -(carbomethoxy)tropane as described above for **RTI-165** gave after workup 0.77 g of crude isoxazole. Purification of the crude by flash column chromatography (5% CMA80 in methylene chloride) gave 0.37 g (49%) of pure isoxazole **RTI-180**: ^1H NMR (CDCl_3) δ 1.71 (m, 3 H), 2.12 (m, 3 H), 2.18 (s, 3 H), 2.24 (s, 3 H), 3.17 (m, 2 H), 3.33 (m, 2 H), 6.18 (s, 1 H), 6.74 (m, 2 H), 7.49 (m, 2 H); IR (CHCl_3) 2940, 1600, 1485, 1450, 1420, 1355 cm^{-1} .

The isoxazole was crystallized as the hydrochloride salt: ^1H NMR (MeOD) δ 2.11 (s, 3 H), 2.50 (m, 6 H), 2.89 (s, 3 H), 3.70 (m, 1 H), 3.90 (m, 1 H), 4.14 (m, 1 H), 4.22 (m, 1 H), 5.66 (s, 1 H), 6.96 (m, 2 H), 7.56 (m, 2 H); mp $>235^\circ\text{C}$ (dec); Anal calcd for $\text{C}_{18}\text{H}_{22}\text{ClIN}_2\text{O}\cdot 0.25\text{H}_2\text{O}$ C = 48.12, H = 5.05, N = 6.24, Cl = 15.79; I = 56.50; found C = 47.84, H = 5.05, N = 6.19, Cl = 15.77; I = 56.46; $[\alpha]_{\text{D}} -94.57^\circ$ (c = 0.39, MeOH).

EXAMPLE 18

3 β -(4-Chlorophenyl)-2 β -(3-phenylisoxazol-5-yl)tropane Hydrochloride (RTI-177)

Reaction of 1.18 g (4 mmol) of 3 β -(4-Chlorophenyl)-2 β -(carbomethoxy)tropane as described above for **RTI-165** gave after work up 1.46 g of crude isoxazole. Purification of the crude by flash column chromatography [20% (ether/triethylamine 9 : 1) in hexane] gave 0.75 g (50%) of pure isoxazole **RTI-177** which was further purified by crystallizing from ether/petroleum ether: ^1H NMR (CDCl_3) δ 1.74 (m, 3 H), 2.22 (m, 3 H), 2.27 (s, 3 H), 3.24 (m, 2 H), 3.36 (m, 2 H), 6.80 (s, 1 H), 6.94 (m, 2 H), 7.12 (m, 2 H), 7.40 (m, 3 H), 7.76 (m, 2 H); IR (CHCl_3) 2940, 1600, 1590, 1490, 1450, 1405, 1350 cm^{-1} .

The isoxazole was crystallized as the hydrochloride salt: ^1H NMR (MeOD) δ 2.35 (m, 6 H), 2.84 (s, 3 H), 3.73 (m, 1 H), 4.09 (m, 1 H), 4.21 (m, 1 H), 6.12 (s, 1 H), 7.14 (m, 4 H), 7.34 (m, 3 H), 7.57 (m, 2 H); mp 287°C ; Anal calcd for $\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{IN}_2\text{O}\cdot 0.25\text{H}_2\text{O}$ C = 65.79, H = 5.88,

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N 6.67, Cl = 16.89; found C = 65.94, H = 5.79, N = 6.68, Cl = 17.00; $[\alpha]_D -97.5^\circ$ (c = 0.28, MeOH).

EXAMPLE 19

3 β -(4-Methylphenyl)-2 β -(3-phenylisoxazol-5-yl)tropane Hydrochloride (RTI-176)

Reaction of 1.09 g (4 mmol) of 3 β -(4-Methylphenyl)-2 β -(carbomethoxy)tropane as described above for RTI-165 gave after work up 1.56 g of crude isoxazole. Purification of the crude by flash column chromatography [25% (ether/triethylamine 9 : 1) in hexane] gave 1.1 g (77%) of pure isoxazole RTI-176 which was further purified by crystallizing from methylene chloride/hexane: ^1H NMR (CDCl_3) δ 1.76 (m, 3 H), 2.23 (m, 3 H), 2.24 (s, 3 H), 2.27 (s, 3 H), 3.23 (m, 2 H), 3.36 (m, 2 H), 6.74 (s, 1 H), 6.93 (m, 4 H), 7.41 (m, 3 H), 7.76 (m, 2 H); IR (CCl_4) 2935, 1590, 1455, 1410, 1215 cm^{-1}

The isoxazole was crystallized as the hydrochloride salt: ^1H NMR (MeOD) δ 2.08 (m, 1 H), 2.15 (s, 3 H), 2.45 (m, 5 H), 2.84 (s, 3 H), 3.68 (m, 1 H), 3.88 (m, 1 H), 4.07 (m, 1 H), 4.22 (m, 1 H), 5.97 (s, 1 H), 7.0 (m, 4 H), 7.33 (m, 3 H), 7.54 (m, 2 H); mp 270-295°C (dec); Anal calcd for $\text{C}_{24}\text{H}_{27}\text{ClN}_2\text{O}$; C = 72.99, H = 6.89, N = 7.10, Cl = 8.98; found C = 72.91, H = 6.91, N = 7.15, Cl = 8.98; $[\alpha]_D -102.22$ (c = 0.68, MeOH).

EXAMPLE 20

3 β -(4-Iodophenyl)-2 β -(3-phenylisoxazol-5-yl)tropane Hydrochloride (RTI-181)

Reaction of 0.73 g (1.9 mmol) of 3 β -(4-Iodophenyl)-2 β -(carbomethoxy)tropane as described above for RTI-181 gave after workup 1.46 g of crude isoxazole. Purification of the crude by flash column chromatography [20% (ether/triethylamine 9 : 1) in hexane] gave 0.5 g (56%) of pure isoxazole RTI-181 which was further purified by crystallizing from methylene chloride/hexane: ^1H NMR (CDCl_3) δ 1.72 (m, 3 H), 2.15 (m, 2 H), 2.28 (s, 3 H), 3.22 (m, 2 H), 3.35 (m, 2 H), 6.74 (m, 2 H), 6.79 (s, 1 H), 7.44 (m, 5 H), 7.75 (m, 2 H); IR (CHCl_3) 2940, 1580, 1480, 1475, 1450, 1400, 1355, 1005 cm^{-1}

The isoxazole was crystallized as the hydrochloride salt: ^1H NMR (MeOD) δ 2.54 (m, 6 H), 2.92 (s, 3 H), 3.79 (m, 1 H), 4.05 (m, 1 H), 4.19 (m, 1 H), 4.33 (m, 1 H), 6.18 (s, 1 H), 7.02 (m, 2 H), 7.43 (m, 3 H), 7.63 (m, 4 H); mp >267°C (dec); Anal calcd for $\text{C}_{23}\text{H}_{24}\text{ClIN}_2\text{O} \cdot 0.5\text{H}_2\text{O}$ C = 53.55, H = 4.89, N = 5.43, Cl = 13.75; I = 49.21; found C = 53.75, H = 4.87, N = 5.41, Cl = 13.68; I = 48.95; $[\alpha]_D -91.11^\circ$ (c = 0.43, MeOH).

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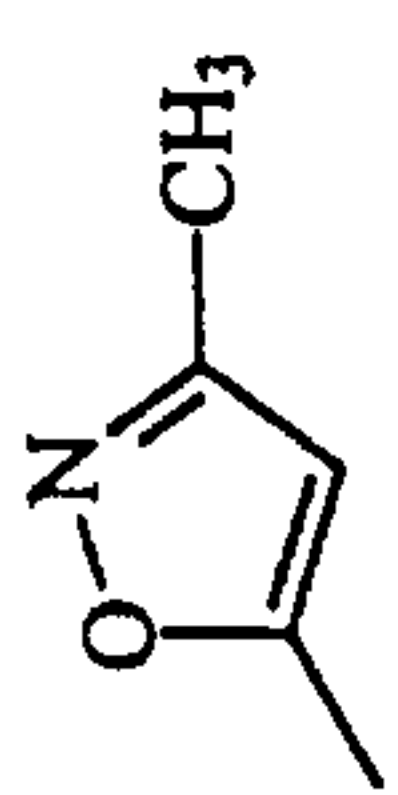
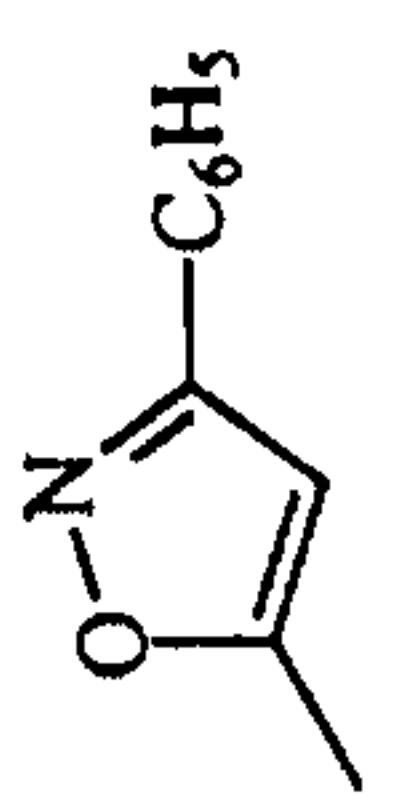
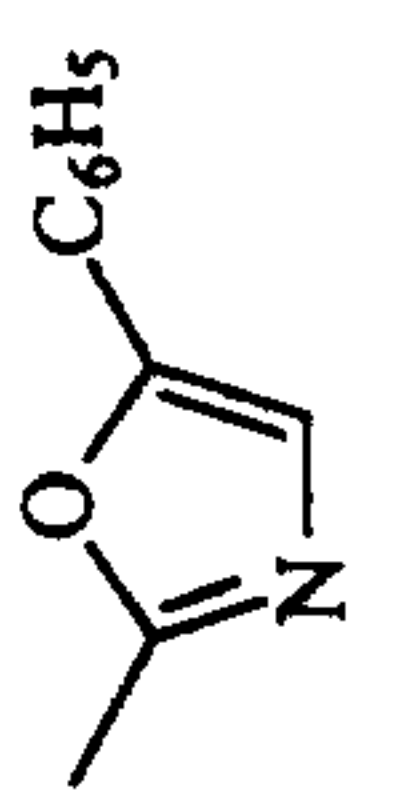
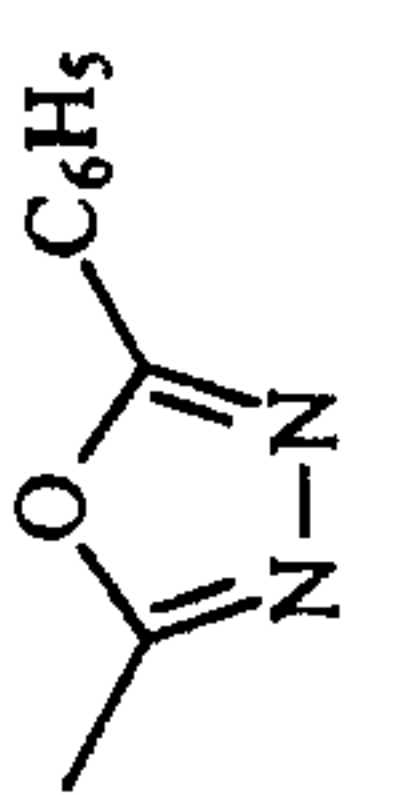
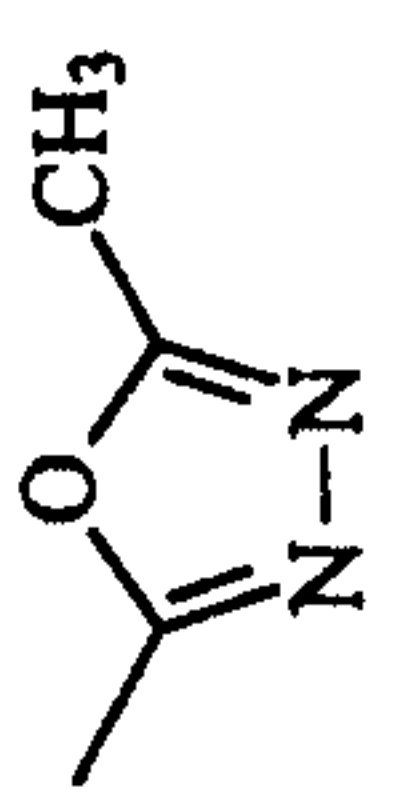
PCT/US99/10456

EXAMPLE 21**Biochemistry of 3 β -(Substituted phenyl)-2 β -(heterocyclic)tropanes**

Inhibition of radioligand binding data at the dopamine, serotonin, and norepinephrine transporters are listed in Tables II, III and IV.

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RTI-165		Cl	0.59 ± 0.04	181 ± 12	572 ± 58	307	97
RTI-171		CH ₃	0.93 ± 0.09	254 ± 31	3818 ± 346	273	410
RTI-180		I	0.73 ± 0.04	67.9 ± 5.25	36.4 ± 5.0	93	49
RTI-177		Cl	1.28 ± 0.18	504 ± 29	2418 ± 136	393	188
RTI-176		CH ₃	1.58 ± 0.02	398 ± 18	5110 ± 187	251	323
RTI-181		I	2.57 ± 0.14	868 ± 95	100 ± 9.0	337	3
RTI-189		Cl	19.7 ± 1.98	496 ± 42	1116 ± 107	25	5
RTI-178		CH ₃	35.4 ± 1.74	677 ± 68	1699 ± 167	19	4
RTI-188		Cl	12.6 ± 1.03	929 ± 88	3304 ± 196	73	26
RTI-195		CH ₃	47.5 ± 4.76	1310 ± 37	23,310 ± 822	28	49
RTI-194		CH ₃	4.45 ± 0.12	253 ± 19	4885 ± 155	57	109

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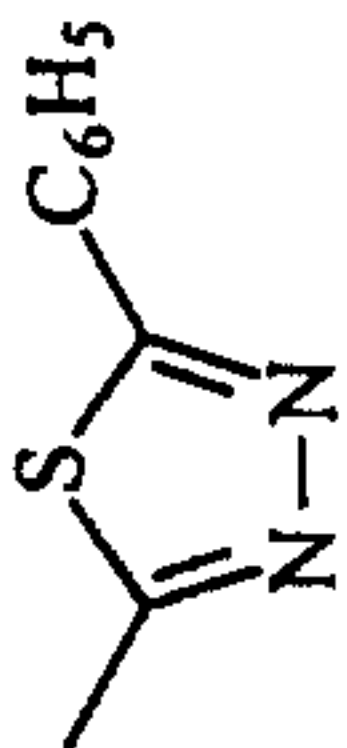
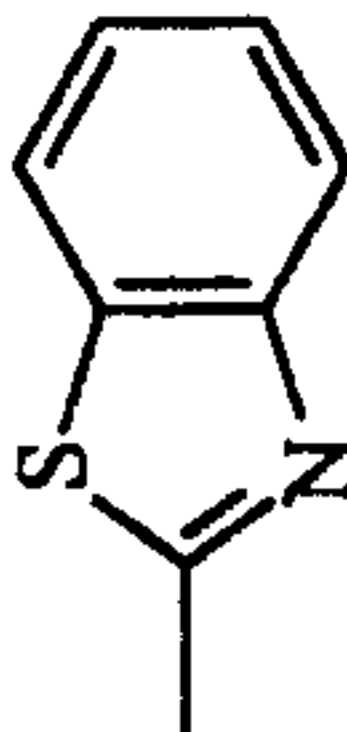
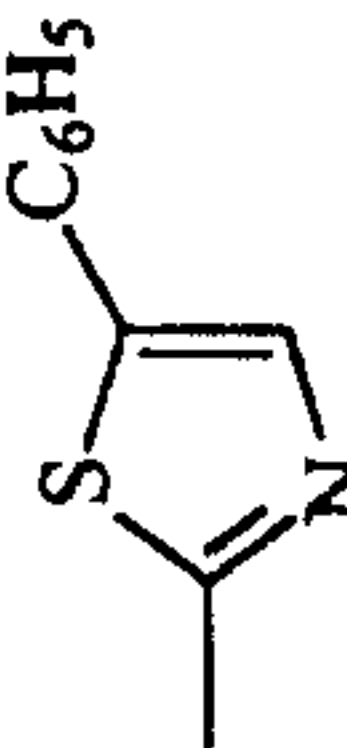
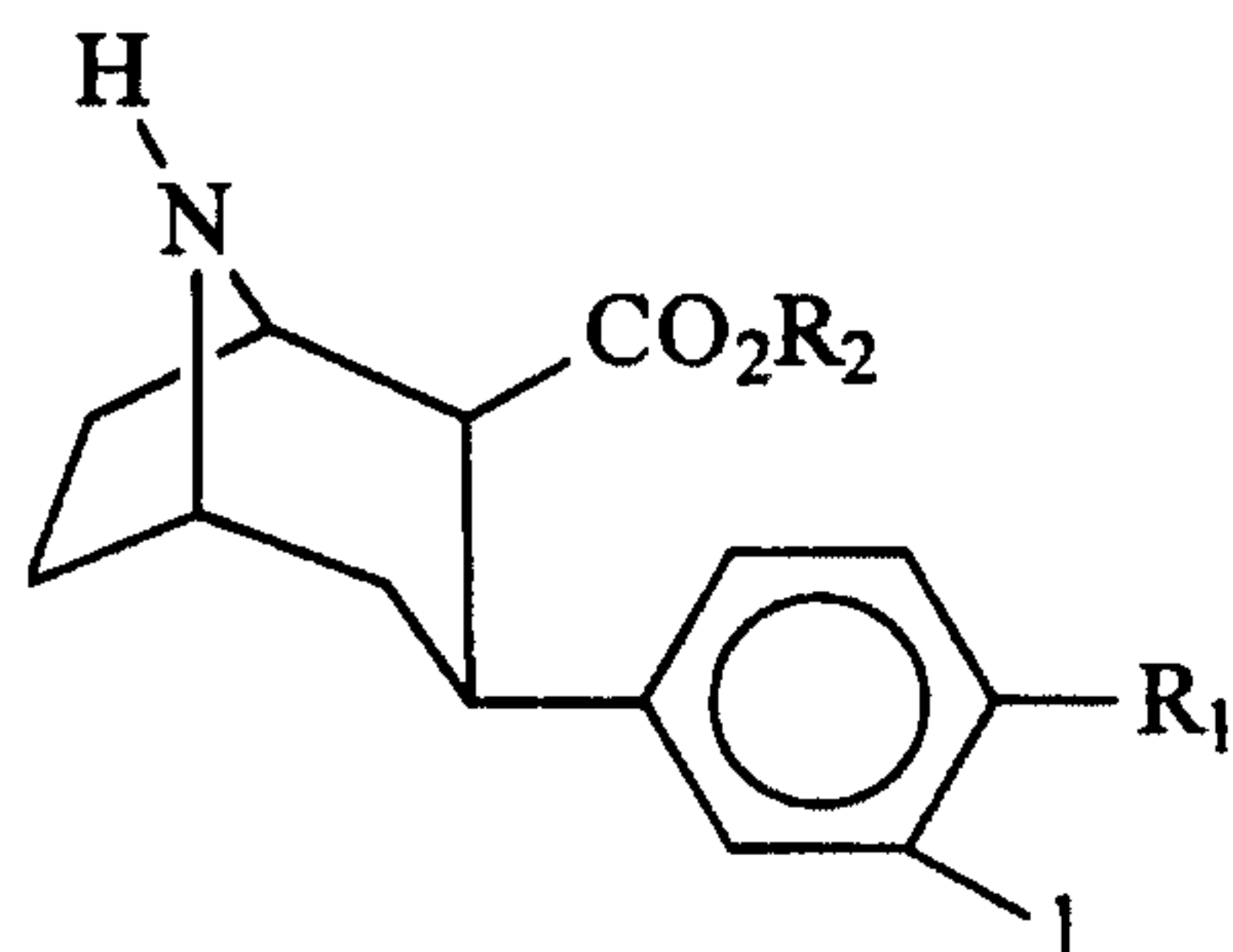
RTI-200		Cl	15.3 ± 2.43	4142 ± 466	$18,417 \pm 1509$	271	120
RTI-199		CH ₃	35.9 ± 3.4	$24,321 \pm 3822$	$51,460 \pm 4513$	677	143
RTI-202		Cl	1.37 ± 0.14	403 ± 30	1119 ± 120	294	81
RTI-219		Cl	5.71 ± 0.36	8563 ± 824	$10,342 \pm 76$	1500	181

TABLE III

Comparison of Transporter Binding Potencies



RTI No.	R ₁	R ₂	IC ₅₀ (Nm)		
			5-HT	DA	NE
			[³ H] Paroxetine	[³ H] WIN 35,428	[³ H] Nisoxetine
279	CH ₃	CH ₃	1.06 ± 0.39	5.98 ± 0.48	74.3 ± 3.8
353	C ₂ H ₅	CH ₃	0.69 ± 0.07	331 ± 17	148 ± 9.2
Paroxetine*			0.28 ± 0.02	623 ± 25	313

5-

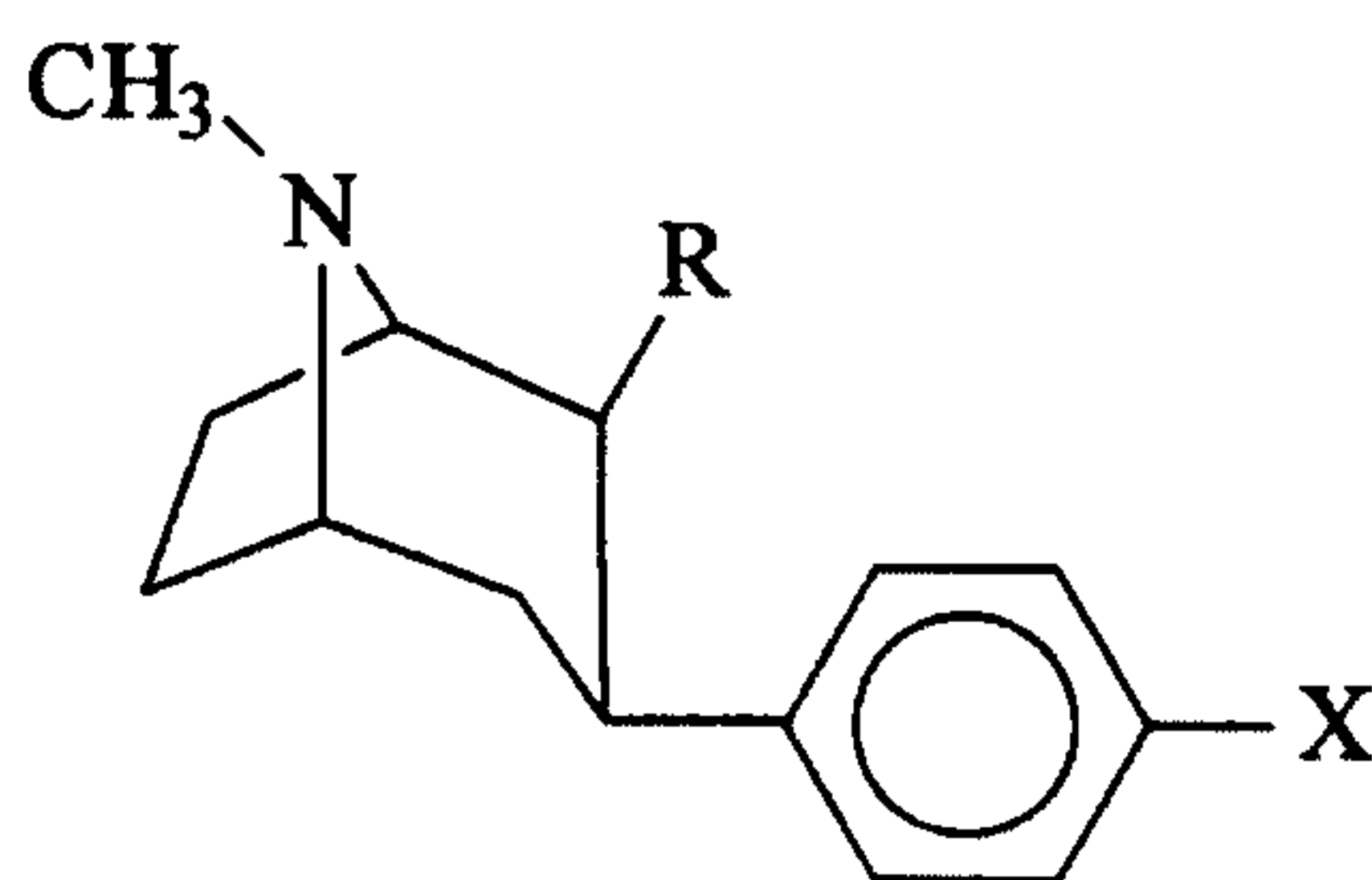
HT = serotonin

DA = dopamine

NE = norepinephrine

* Aropax: Seroxat; see Merck Index.

Table IV
3 β -(Substituted phenyl)-2 β -(substituted)tropanes



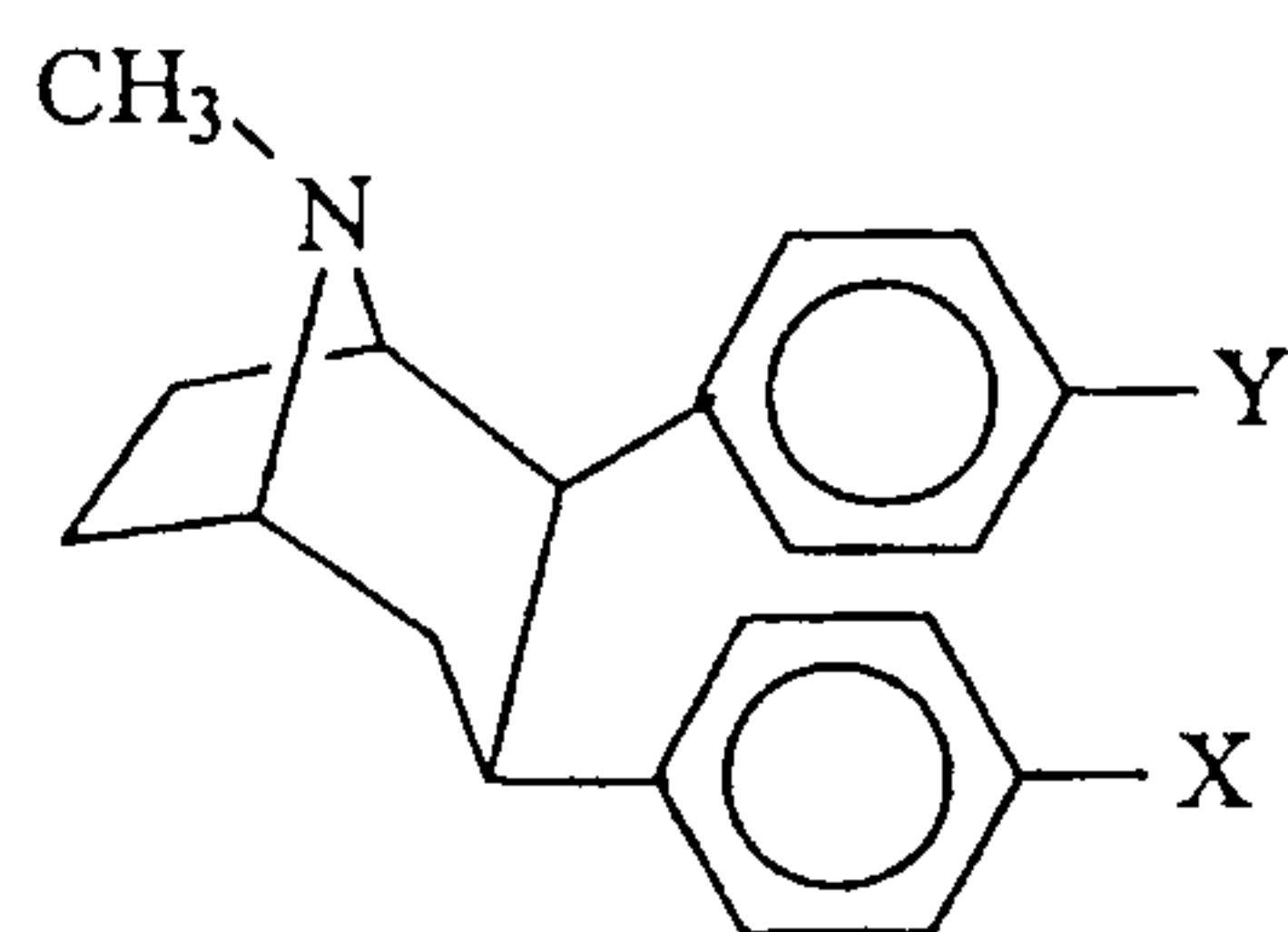
Code Name	R	X	IC ₅₀ (nM)		
			DA [³ H]-WIN 35,428	NE [³ H]-nisoxetine	5-HT [³ H]- paroxetine
RTI-93	CH ₂ OH	Cl	1.53 ± 0.15	43.8 ± 6.4	204 ± 16
RTI-99	CH ₂ OH	Br	1.49 ± 0.06		51 ± 4.5
RTI-100	CH ₂ OH	F	47 ± 4.6		4741 ± 335
RTI-101	CH ₂ OH	I	2.2 ± 0.19		26 ± 3.2
RTI-102	CO ₂ H	I	474 ± 57	43,400 ± 5500	1928 ± 120
RTI-103	CO ₂ H	Br	278 ± 43	17,400 ± 1400	3070 ± 208
RTI-104	CO ₂ H	F	2744 ± 141	>100,000	>100.00
RTI-105	CH ₂ OAc	Cl	1.60 ± 0.05	127 ± 5.9	143 ± 25
RTI-108	CH ₂ Cl	Cl	2.64 ± 0.31	129 ± 15	96 ± 8.7
RTI-123	CH ₂ OCOC ₆ H ₅	Cl	1.78 ± 0.09	393 ± 30	3.53 ± 0.58
RTI-131	CH ₂ NH ₂	CH ₃	10.5 ± 1.7	120 ± 20	855 ± 52
RTI-132	CH ₂ N(CH ₃) ₂	CH ₃	3.48 ± 0.11	137 ± 11	208 ± 18
RTI-139	CH ₃	Cl	1.67 ± 0.13	57 ± 2.6	85 ± 9.3
RTI-145	CH ₂ OCO ₂ CH ₃	Cl	9.6 ± 0.42	1478 ± 94	2930 ± 181
RTI-158	CN	CH ₃	57 ± 7.3	1624 ± 136	5095 ± 315
RTI-161	CN	Cl	13.1 ± 0.78	2516 ± 253	1887 ± 134
RTI-164	CH ₂ NHCH ₃	CH ₃	13.6 ± 2.03	280 ± 19	2246 ± 94
RTI-230	-C(CH ₃)CH ₂	Cl	1.26 ± 0.17	141 ± 16	57 ± 5.0
RTI-239	CH(CH ₃) ₂	CH ₃	0.61 ± 0.07	35.6 ± 2.57	114 ± 3.69
RTI-240	CH(CH ₃) ₂	Cl	1.38 ± 0.03	84.5 ± 3.09	38.4 ± 2.31
RTI-241	CH ₂ CO ₂ CH ₃	CH ₃	1.02 ± 0.06	124 ± 3.56	616 ± 28

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This invention has been described in both generic terms, and by reference to specific description. No specific description or example is considered binding, unless so identified. Alternate forms and methods will occur to those of ordinary skill in the art, without the exercise of inventive faculty, and remain within the scope of this invention, save as limited by the claims set forth below.

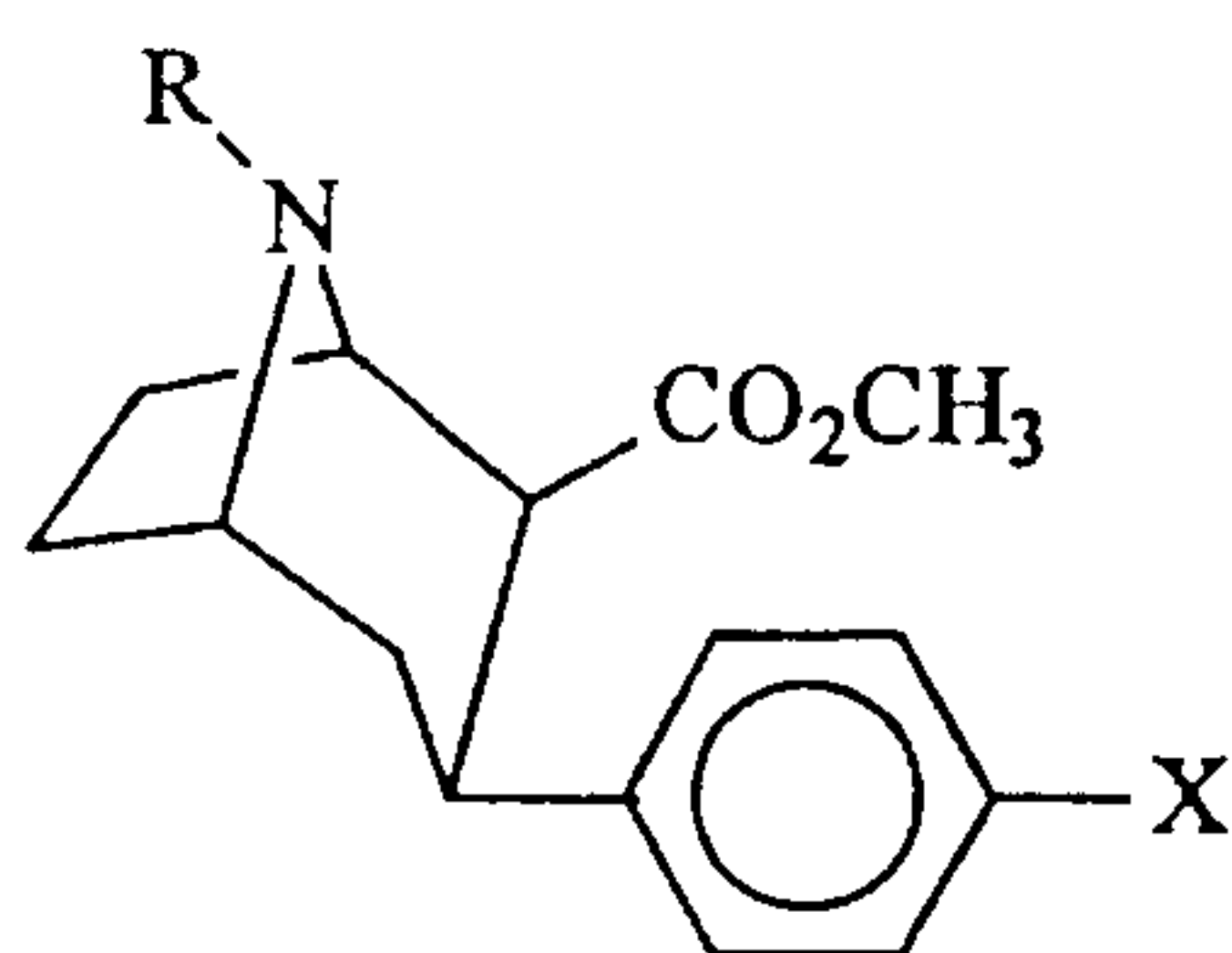
WHAT IS CLAIMED IS:

1. A compound of the formula:



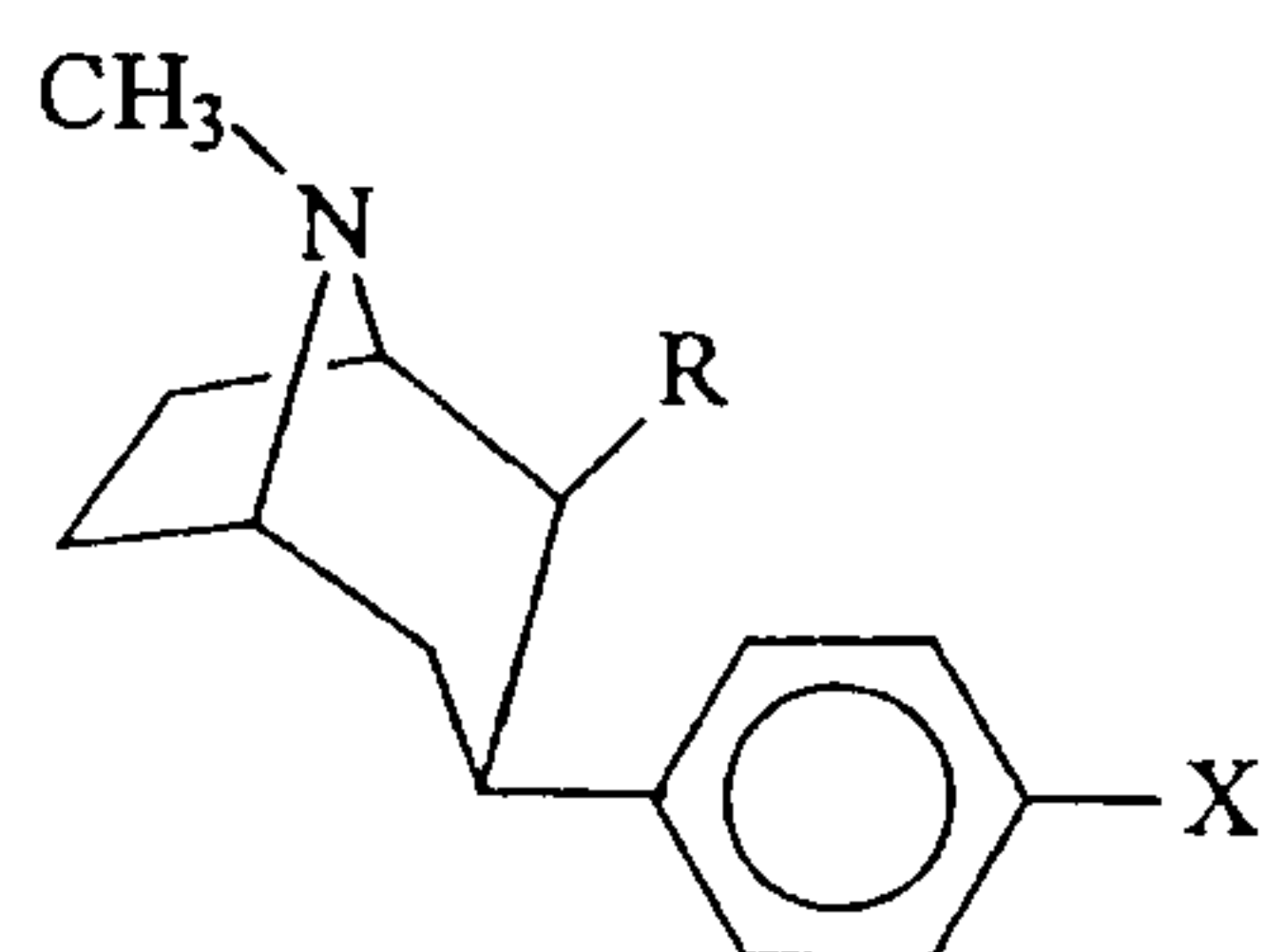
wherein X=CH₃ and Y=H.

2. A compound of the formula:

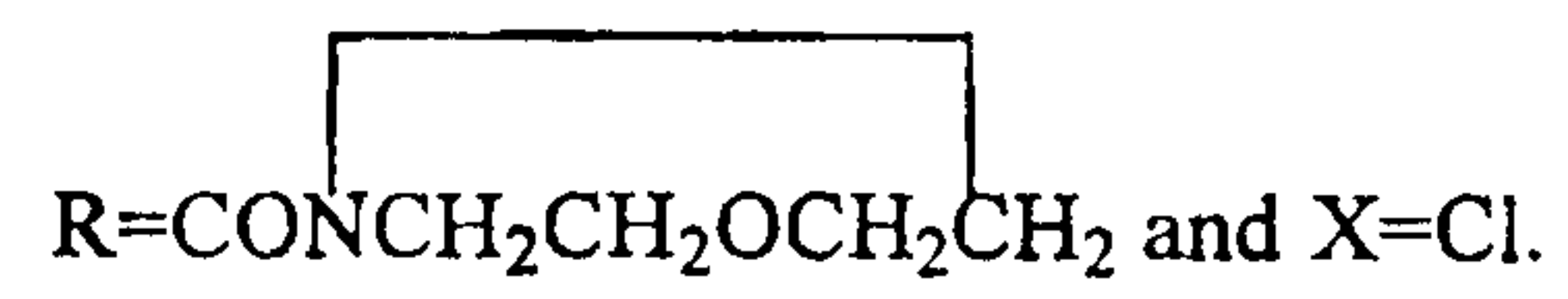


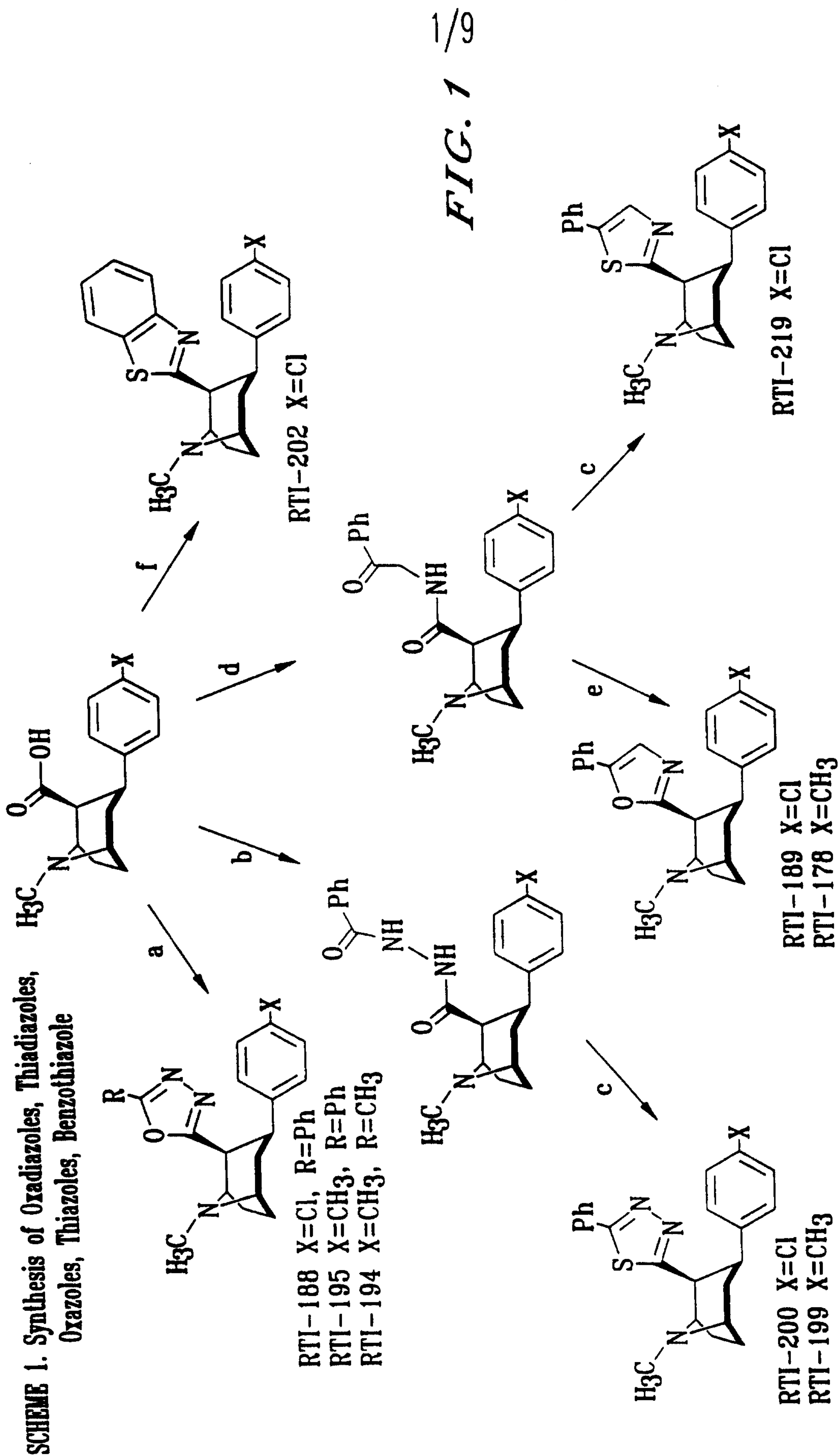
10 wherein X is 2-naphthyl and R is CH₃.

3. A compound of the formula:

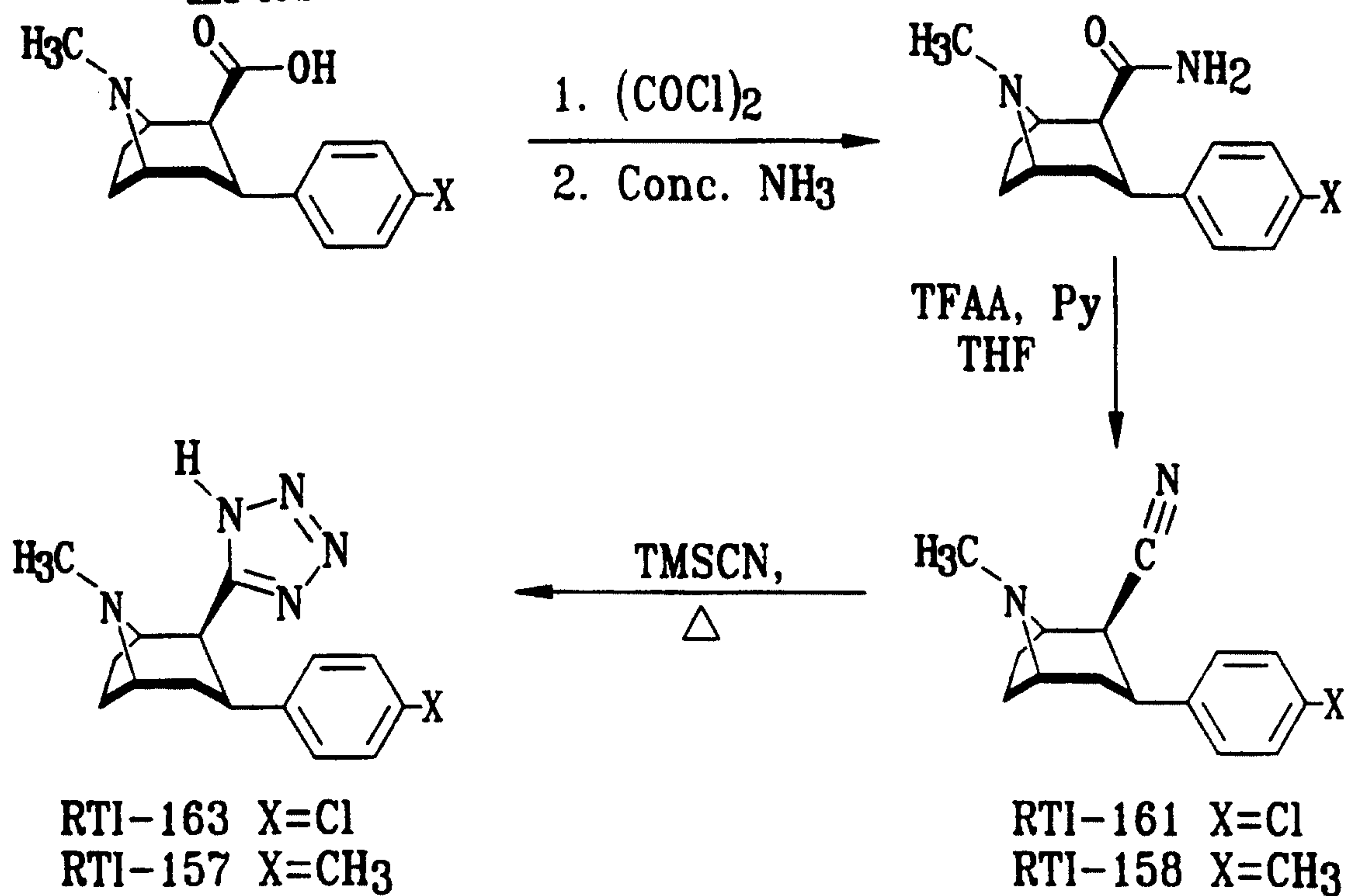
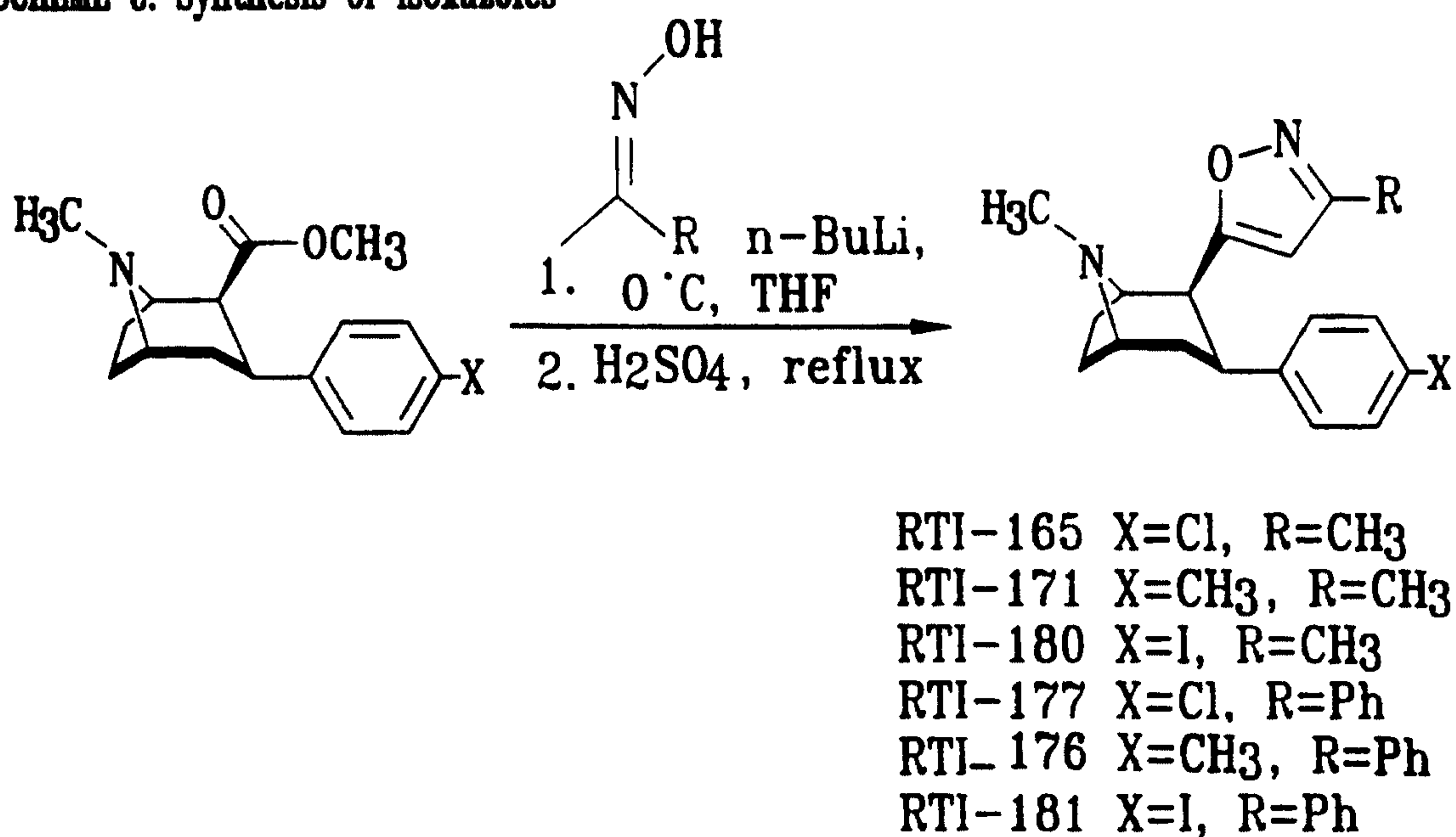


wherein:

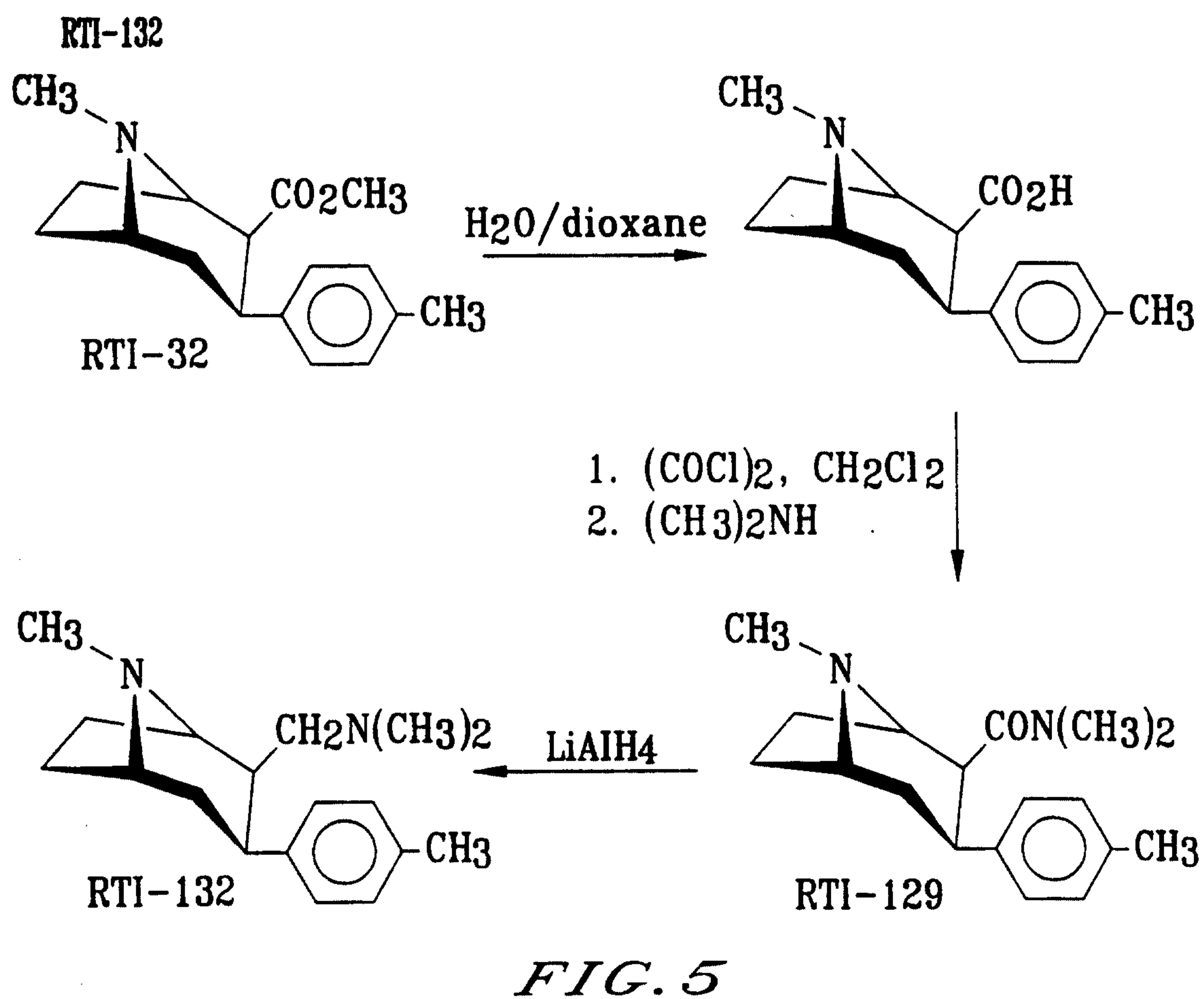
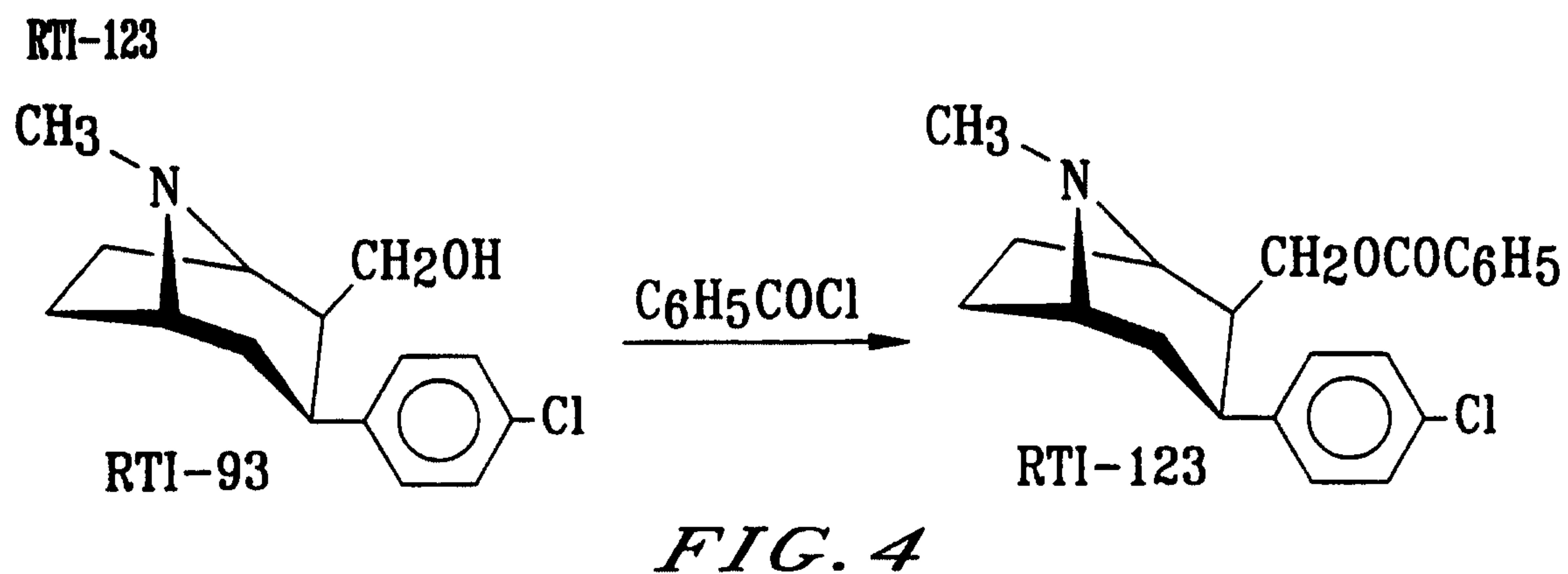




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SCHEME 2. Synthesis of Nitriles and Tetrazoles**FIG. 2****SCHEME 3. Synthesis of Isoxazoles****FIG. 3**

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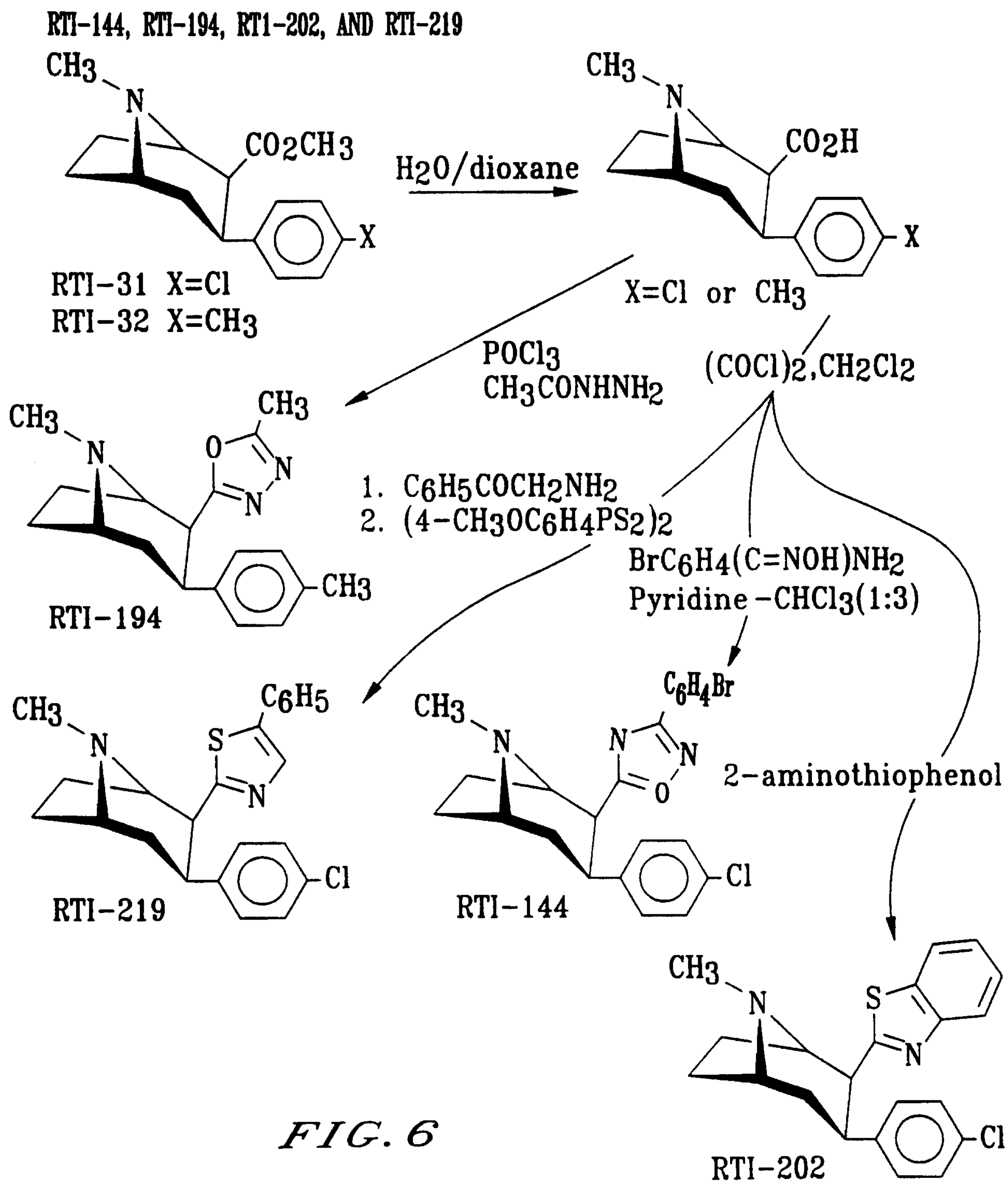
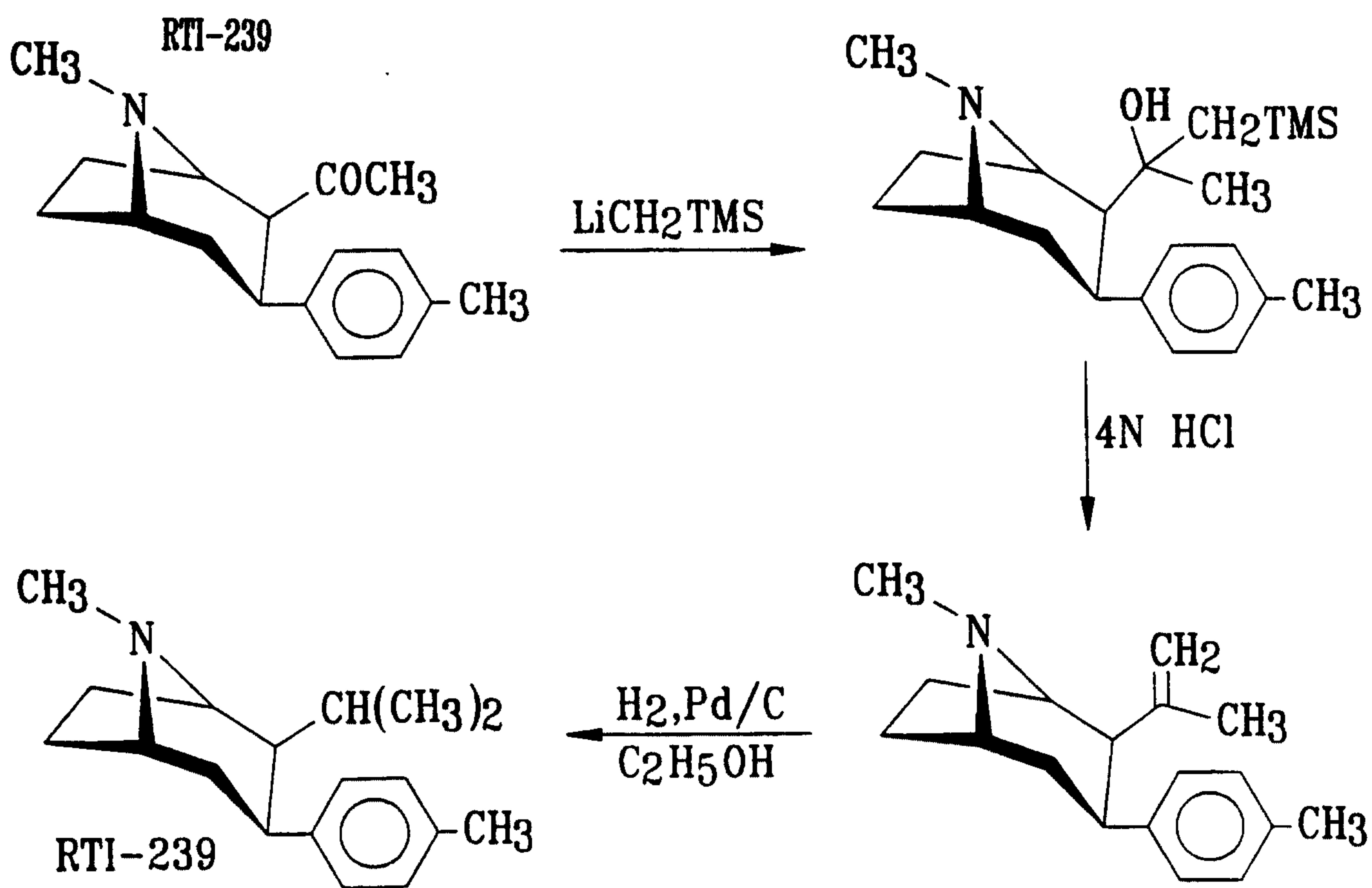
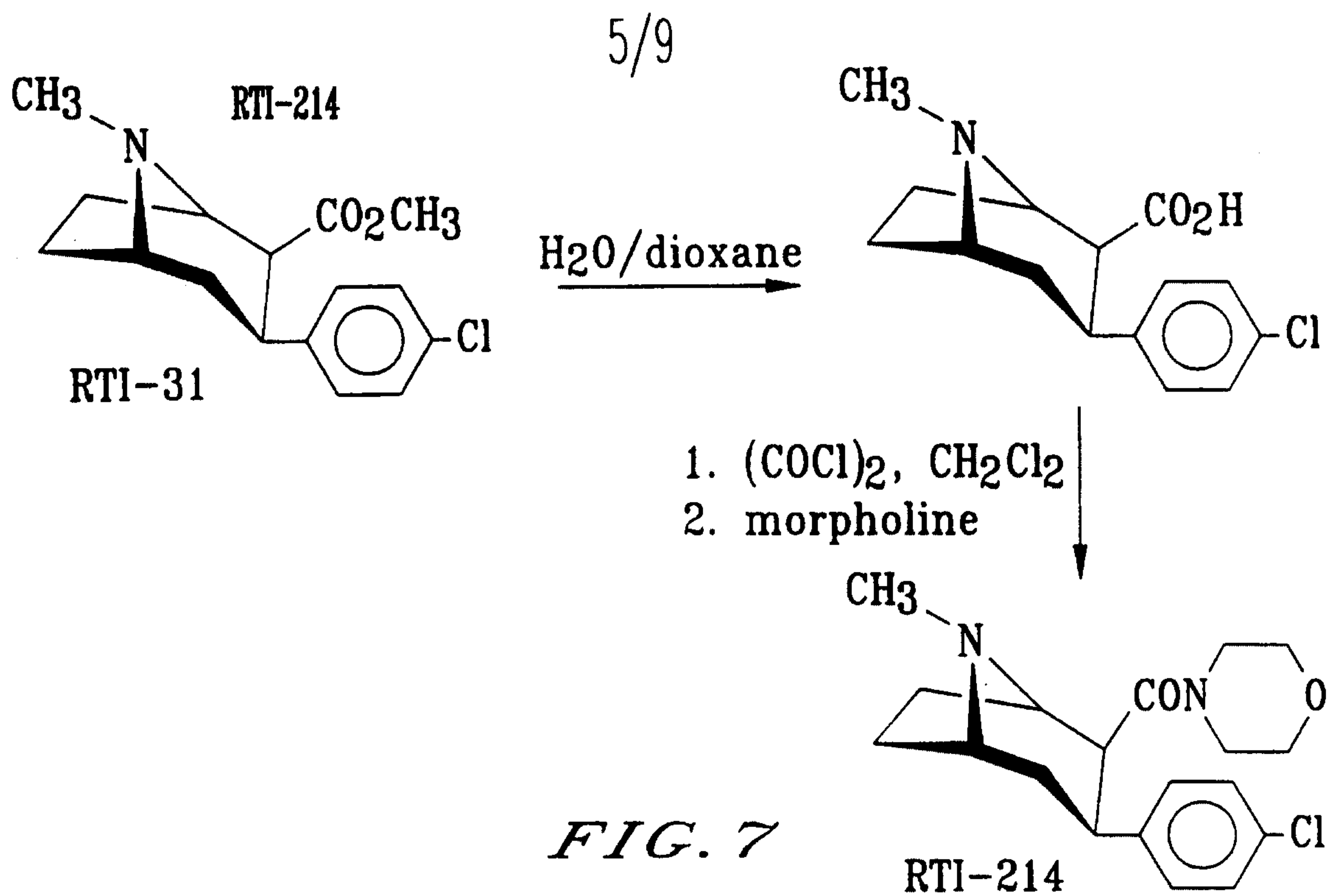


FIG. 6

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*FIG. 8*

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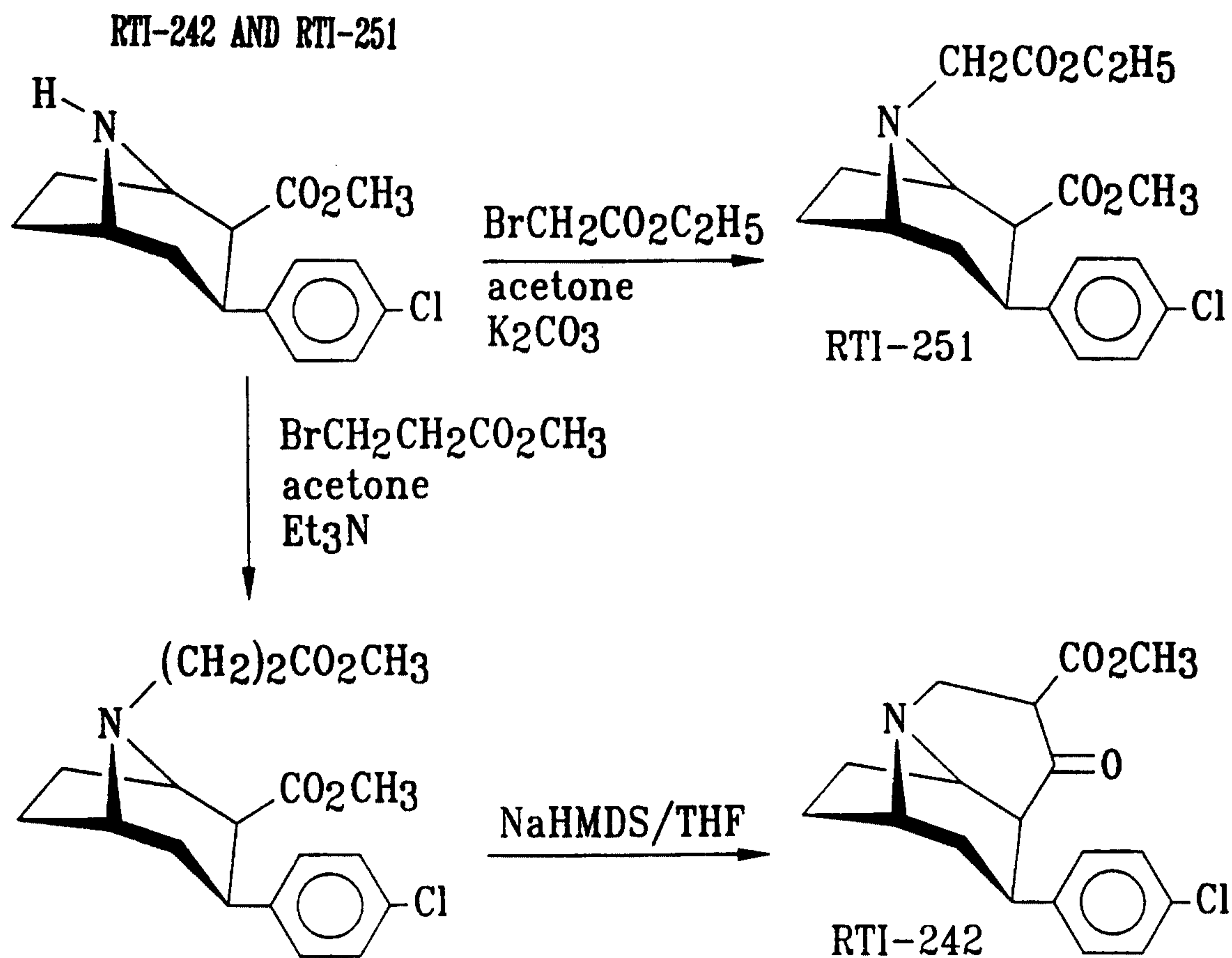


FIG. 9

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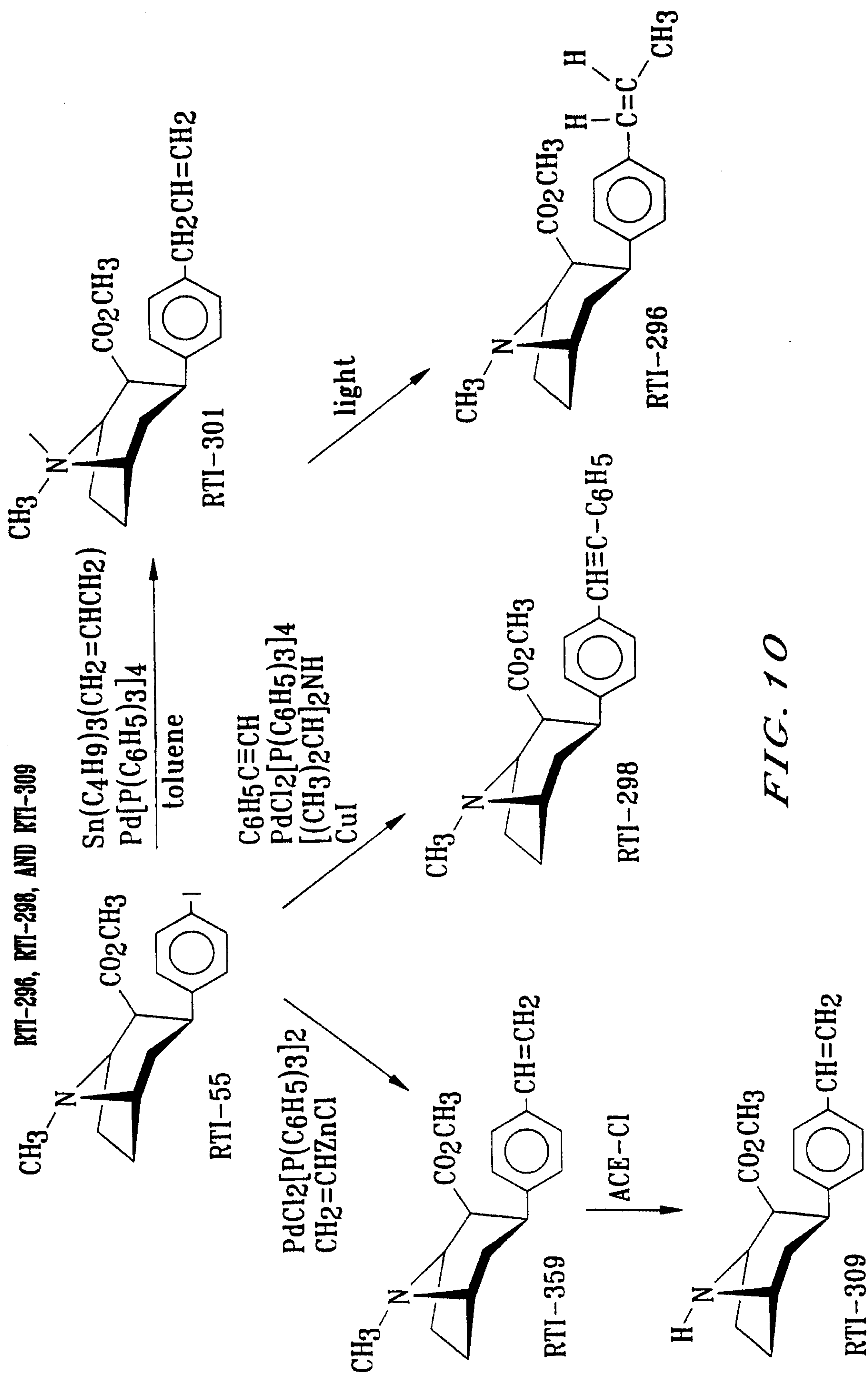


FIG. 10

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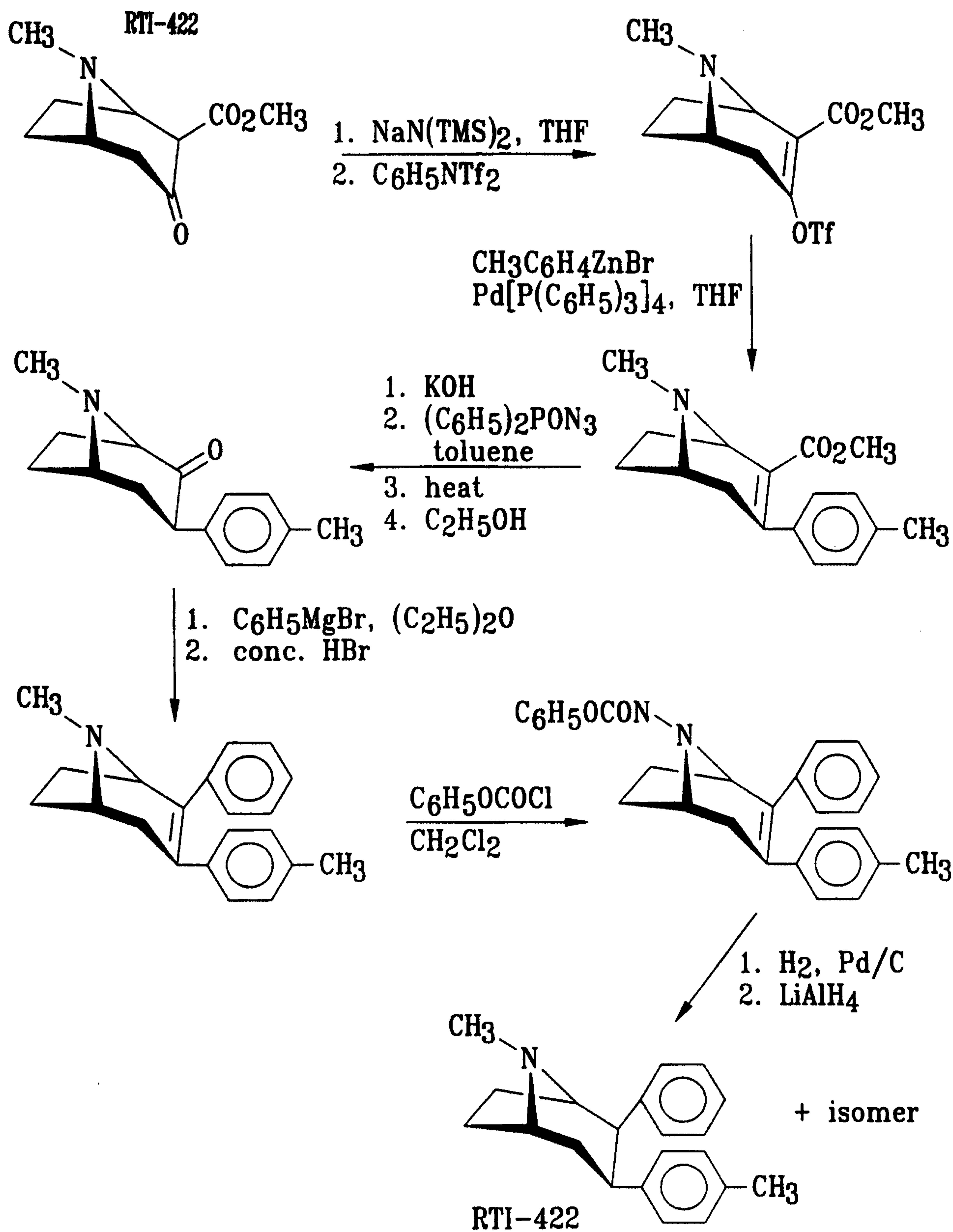


FIG. 12