



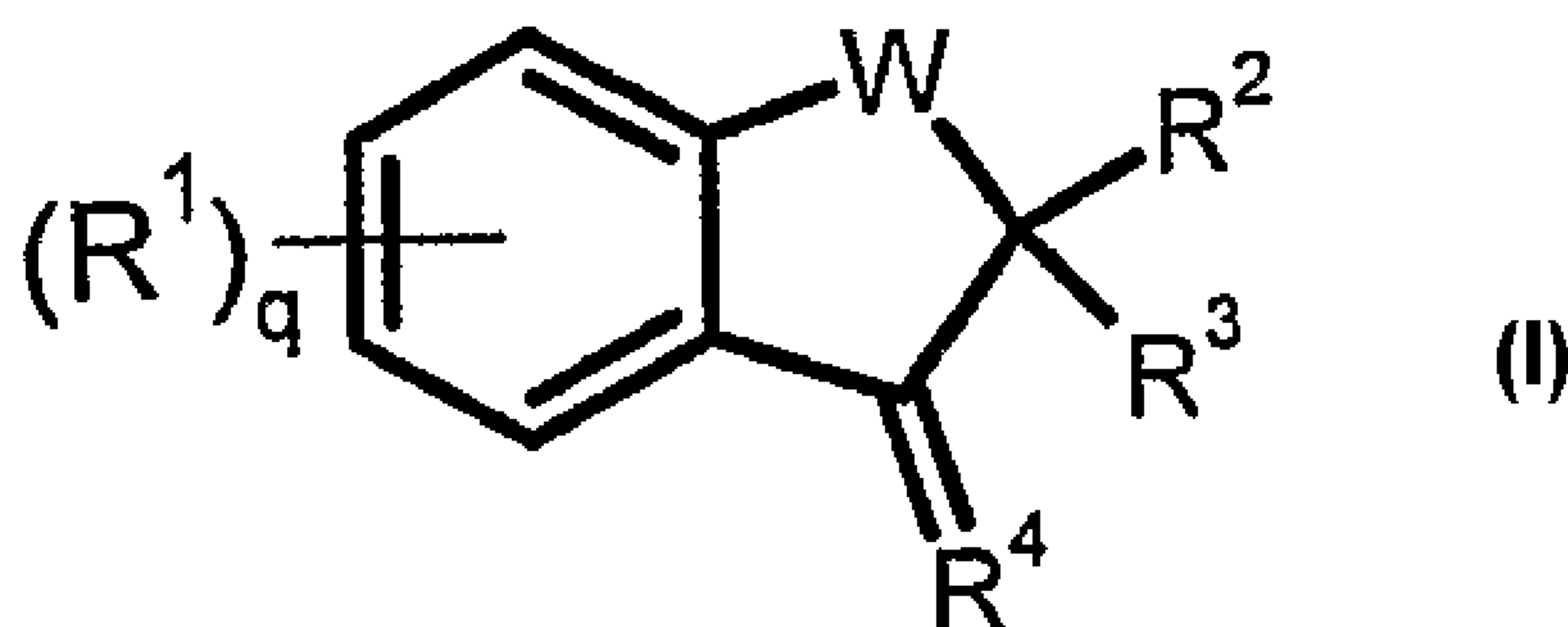
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(54) Titre : DIHYDROBENZOTHIOPHENE
(54) Title: DIHYDROBENZOTHIOPHENES



(57) **Abrégé/Abstract:**

The invention relates to compounds of formula (I), in which W, R¹, R², R³, R⁴, and q are defined as cited in claim 1. One application for said compounds is the treatment of tumours.

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ABSTRACT

The invention relates to compounds of formula (I), in which W, R¹, R², R³, R⁴, and q are defined as cited in claim 1. One application for said compounds is the treatment of tumours.

Dihydrobenzothiophenes

5 BACKGROUND OF THE INVENTION

The invention had the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

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The present invention relates to compounds of the formula I for the prophylaxis and treatment of diseases in which the inhibition, regulation and/or modulation of mitotic motor proteins, in particular the mitotic motor protein Eg5, plays a role, furthermore to pharmaceutical compositions which comprise these compounds.

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In detail, the present invention relates to compounds of the formula I which preferably inhibit, regulate and/or modulate one or more mitotic motor proteins, to compositions which comprise these compounds, and to methods for the use thereof for the treatment of diseases and complaints such as angiogenesis, cancer, tumour formation, growth and propagation, arteriosclerosis, ocular diseases, choroidal neovascularisation and diabetic retinopathy, inflammatory diseases, arthritis, neurodegeneration, restenosis, wound healing or transplant rejection. In particular, the compounds according to the invention are suitable for the therapy or prophylaxis of cancer diseases.

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During mitosis, various kinesins regulate the formation and dynamics of the spindle apparatus, which is responsible for correct and coordinated alignment and separation of the chromosomes. It has been observed that specific inhibition of a mitotic motor protein – Eg5 – results in collapse of the spindle fibres. The result of this is that the chromosomes can no longer be distributed correctly over the daughter cells. This results in mitotic arrest

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and can thus cause cell death. Upregulation of the motor protein Eg5 has been described, for example, in tissue from breast lung and colon tumours. Since Eg5 takes on a mitosis-specific function, it is principally rapidly
5 dividing cells and not fully differentiated cells that are affected by Eg5 inhibition. In addition, Eg5 regulates exclusively the movement of mitotic microtubuli (spindle apparatus) and not that of the cytoskeleton. This is crucial for the side-effect profile since, for example, neuropathies, as observed in the case of Taxol, do not occur or only do so to a weakened extent. The
10 inhibition of Eg5 by organic molecules is therefore a relevant therapy concept for the treatment of malignant tumours.

In general, all solid and non-solid tumours can be treated with the compounds of the formula I, such as, for example, monocytic leukaemia, brain,
15 urogenital, lymphatic system, stomach, laryngeal and lung carcinoma, including lung adenocarcinoma and small-cell lung carcinoma. Further examples include prostate, pancreatic and breast carcinoma.

Surprisingly, it has been found that the compounds according to the invention effect specific inhibition of mitotic motor proteins, in particular Eg5. The compounds according to the invention preferably exhibit an advantageous
20 biological activity which can easily be detected in the assays described herein, for example. In such assays, the compounds according to the invention preferably exhibit and cause an inhibiting effect, which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar
25 range and more preferably in the nanomolar range.

As discussed herein, effects of the compound according to the invention are relevant to various diseases. Accordingly, the compounds according to the invention are useful in the prophylaxis and/or treatment of diseases
30 which are influenced by inhibition of one or more mitotic motor proteins, in particular Eg5.
35

5 The present invention therefore relates to compounds according to the invention as medicaments and/or medicament active ingredients in the treatment and/or prophylaxis of the said diseases and to the use of compounds according to the invention for the preparation of a pharmaceutical for the treatment and/or prophylaxis of the said diseases, and also to a method for the treatment of the said diseases comprising the administration of one or more compounds according to the invention to a patient in need of such an administration.

10 It can be shown that the compounds according to the invention have an advantageous effect in a xenotransplant tumour model.

15 The host or patient can belong to any mammal species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cattle, dogs, cats, etc. Animal models are of interest for experimental investigations, providing a model for the treatment of a human disease.

20 The sensitivity of a certain cell to treatment with the compounds according to the invention can be determined by testing in vitro. Typically, a culture of the cell is combined with a compound according to the invention at various concentrations for a period which is sufficient to enable the active agents to induce cell death or inhibit migration, usually between approximately one hour and one week. For testing in vitro, cultivated cells from a biopsy sample can be used. The viable cells remaining after the treatment are then counted.

30 The dose varies depending on the specific compound used, the specific disease, the patient status, etc. Typically, a therapeutic dose is sufficient considerably to reduce the undesired cell population in the target tissue, while the viability of the patient is maintained. The treatment is generally continued until a considerable reduction has occurred, for example at least

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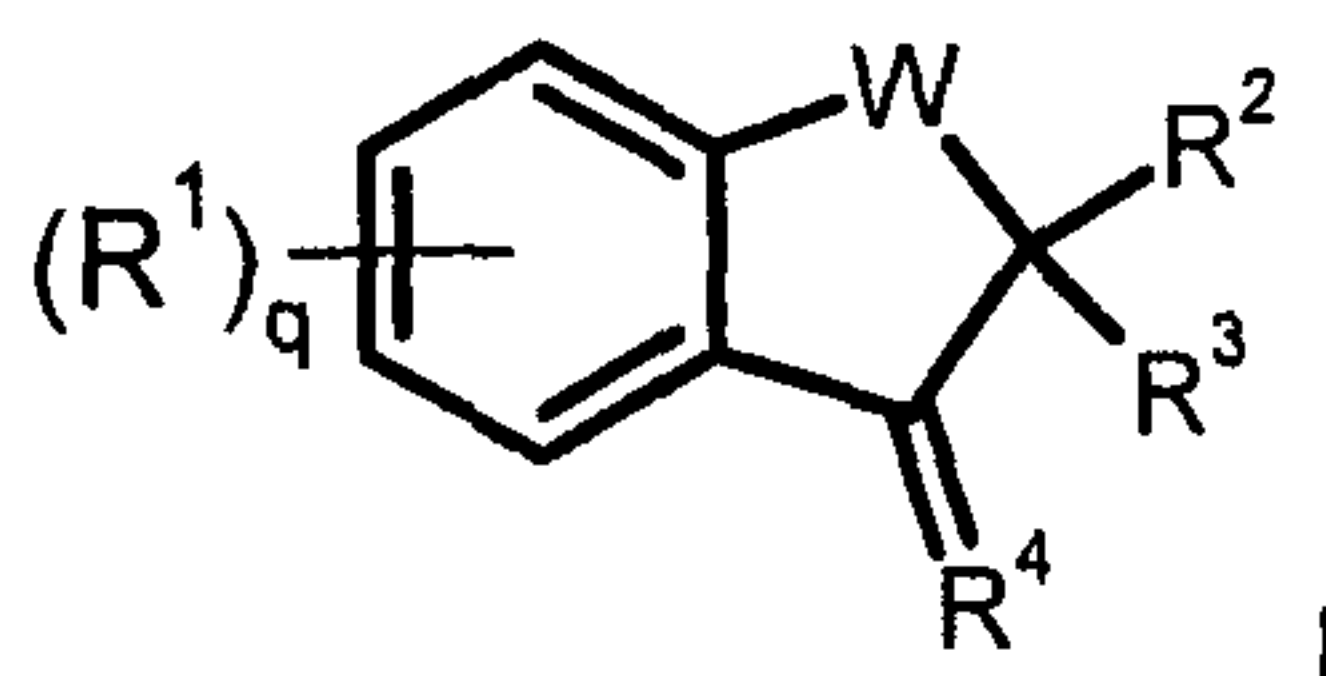
about a 50% reduction in the cell burden, and can be continued until essentially no undesired cells are detected in the body.

PRIOR ART

Similar compounds are described in US3328411, but are not mentioned in connection with cancer treatments and/or do not contain the features according to the invention.

SUMMARY OF THE INVENTION

The invention relates to compounds of the formula I:



where

W denotes S, SO or SO₂,

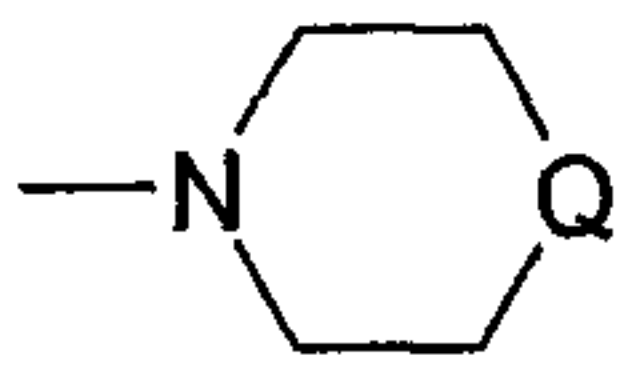
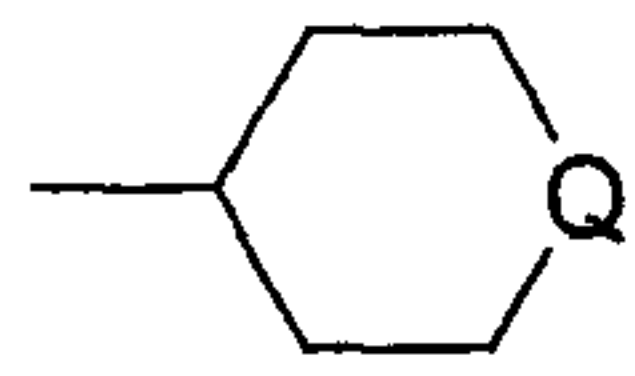
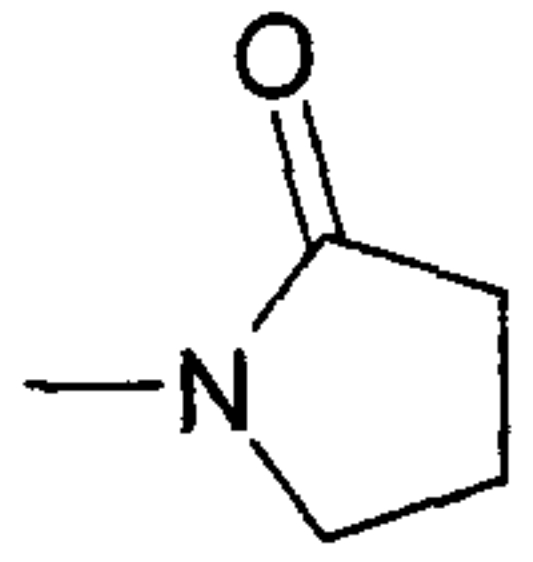
R¹ denotes H, A, Ar, Het, phenyl, methyl, OR⁵, SR⁵, OAr, SAr, N(R⁵)₂, N R⁵Ar, Hal, NO₂, CN, (CH₂)_mCOOR⁵, (CH₂)_mCOOAr, (CH₂)_mCON(R⁵)₂, (CH₂)_mCONHAr, COR⁵, COAr, S(O)_mA, S(O)_mAr, NHCOA, NHCOAr, NHSO₂A, NHSO₂Ar or SO₂N(R⁵)₂, heteroaryl, Hal, -(CY₂)_n-SA, -(CY₂)_n-SCF₃, -(CY₂)_n-SCN, -(CY₂)_n-CF₃, -(CY₂)_n-OCF₃, cycloalkyl, -SCH₃, -SCN, -CF₃, -OCF₃, -OA, -(CY₂)_n-OH, -(CY₂)_n-CO₂R⁵, -(CY₂)_n-CN, -(CY₂)_n-Hal, -(CY₂)_n-N(R⁵)₂, (CY₂)_n-OA, (CY₂)_n-OCOA, -SCF₃, (CY₂)_n-CON(R⁵)₂, -(CY₂)_n-NHCOA, -(CY₂)_n-NHSO₂A, SF₅, Si(CH₃)₃, CO-(CY₂)_n-CH₃, -(CY₂)_n-(N-pyrrolidone), and, if the R¹ occurs twice and vicinally on the aromatic ring, together also denote -N-C(CF₃)=N-, -N-CR=N-, -N-N=N-,

- R^2, R^3 , independently of one another, denote A, Het, H, -OH, -OA, -OAr, Ar, -O-CO-A, -OSO₃R⁵, -OSO₂R⁵, -OAr₂R⁵, SO₂R⁵, Hal, COOR⁵, CON(R⁵)₂, NHSO₂A, COA, CHO or SO₂N(R⁵)₂, -(CH₂)₀-Ar,
- 5 -(CH₂)₀-cycloalkyl, -(CH₂)₀-OH, -(CH₂)₀-N(R⁵)₂, NO₂, CN, -(CH₂)₀-COOR⁵, -(CH₂)₀-CON(R⁵)₂, -(CH₂)₀-NHCOA, NHCON(R⁵)₂, -(CH₂)₀-NHSO₂A, -(C(R⁵)₂)₀-Ar, or aryl or heteroaryl, each of which is unsubstituted or mono- or polysubstituted by aryl or heteroaryl,
- 10 which may be substituted by Hal, NO₂, CN, A, OR, OCOR, COR, NR₂, CF₃, OCF₃, OCH(CF₃)₂, or Hal, NO₂, CN, OR, A, -(CY₂)_n-OR, -OCO R⁵, -(CY₂)_n-CO₂ R⁵, -(CY₂)_n-CN, -NCO R⁵, -CO R⁵ or -(CY₂)_n-N(R⁵)₂, N[(CH₂)_nXCOOR⁵]CO(CH₂)_naryl, N[(CH₂)_nXR⁵]-CO(CH₂)_naryl, N[(CH₂)_nXR⁵]CO(CH₂)_nXaryl, N[(CH₂)_nXR⁵]SO₂-(CH₂)_naryl, N[(CH₂)_nNR⁵COOR⁵]CO(CH₂)_naryl, N[(CH₂)_nN(R⁵)₂]CO(CH₂)_naryl, N[(CH₂)_nN(R⁵)₂]CO(CH₂)_nNR⁵aryl, N[(CH₂)_nN(R⁵)₂]SO₂(CH₂)_naryl, N[(CH₂)_nXR⁵]CO(CH₂)_nheteroaryl, N[(CH₂)_nXR⁵]CO(CH₂)_nXheteroaryl, N[(CH₂)_nXR⁵]SO₂(CH₂)_nheteroaryl, N[(CH₂)_nNR⁵COOR⁵]-CO(CH₂)_nheteroaryl, N[(CH₂)_nN(R⁵)₂]CO(CH₂)_nheteroaryl or N[(CH₂)_nN(R⁵)₂]CO(CH₂)_nNR⁵heteroaryl,
- 15
- 20
- 25 R^4 denotes O, =CH-(CH₂)_nN(R⁵)₂, or cyclo[C(CH₂)_k (NY¹)-(CH₂)_p-], cyclo[C(CH₂)_k (CHY¹)-(CH₂)_p-] or E or Z - =CH(CH₂)_nX(CH₂)_l-Q(CH₂)_sT
- 30 R^5 denotes H or A, in the case of geminal radicals R^5 together also denote -(CH₂)₅-, -(CH₂)₄- or -(CH₂)_n-Q-(CH₂)_n,
- Y denotes H, A, Hal
- 35 Y^1 denotes R^2, R^5 , Ar, -(C(R⁵)₂)₀-Ar or -(C(R⁵)₂)₀-Het, X(CH₂)_lQ(CH₂)_sT, XCH₂T or T,

X denotes NR^5 , CH_2 , CO or SO_2 or a single bond

5 Q denotes CH_2 , NR^5 , O , S , CO , SO_2 , $\text{C}(\text{R}^5)_2$ or a single bond,
 $\text{CH}(\text{CH}_2)_n\text{NR}^5\text{COOR}^5$, $\text{CHNR}^5\text{COOR}^5$, NCO , $\text{CH}(\text{CH}_2)_n\text{COOR}^5$,
 NCOOR^5 , $\text{CHX}(\text{CH}_2)_n\text{OH}$, $\text{N}(\text{CH}_2)_n\text{OH}$, CHNH_2 , $\text{CH}(\text{CH}_2)_n\text{N}(\text{R}^5)_2$,
 $\text{CHX}(\text{CH}_2)_n\text{N}(\text{R}^5)_2$, $\text{C}(\text{OH})\text{R}^5$, CHNCOR^5 , $\text{CH}(\text{CH}_2)_n\text{aryl}$, $\text{CH}(\text{CH}_2)_n$ -
heteroaryl, $\text{CH}(\text{CH}_2)_n\text{R}^1$, $\text{N}(\text{CH}_2)_n\text{COOR}^5$, $\text{CH}(\text{CH}_2)_n\text{X}(\text{CH}_2)_n\text{aryl}$,
10 $\text{CH}(\text{CH}_2)_n\text{X}(\text{CH}_2)_n\text{heteroaryl}$, $\text{N}(\text{CH}_2)_n\text{CON}(\text{R}^5)_2$, $\text{CHCONR}^5(\text{CH}_2)_n$ -
 $\text{N}(\text{R}^5)_2$,

15

T denotes R^2 , Het, ,  or ,

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Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by Hal, A, $-(\text{CH}_2)_o\text{-Ar}$, $-(\text{CH}_2)_o\text{-cycloalkyl}$, $-(\text{CH}_2)_o\text{-OH}$, $-(\text{CH}_2)_o\text{-N}(\text{R}^5)_2$, NO_2 , CN , $-(\text{CH}_2)_o\text{-COOR}^5$, $-(\text{CH}_2)_o\text{-CON}(\text{R}^5)_2$, $-(\text{CH}_2)_o\text{-NHCOA}$, $\text{NHCON}(\text{R}^5)_2$, $-(\text{CH}_2)_o\text{-NHSO}_2\text{A}$, CHO , COA , SO_2NH_2 and/or $\text{S}(\text{O})_o\text{A}$,

25

Ar denotes aryl, or phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^5 , $\text{N}(\text{R}^5)_2$, NO_2 , CN , COOR^5 , $\text{CON}(\text{R}^5)_2$, NHCOA , $\text{NHCON}(\text{R}^5)_2$, NHSO_2A , CHO , COA , $\text{SO}_2\text{N}(\text{R}^5)_2$ or $\text{S}(\text{O})_o\text{A}$,

30

A denotes unbranched or branched alkyl having 1-10 C atoms, in which one or more H atoms may be replaced by Hal, in particular F or Ar,

35

Hal denotes F, Cl, Br or I,
o denotes 0, 1, 2 or 3,
m denotes 0, 1, 2 or 3,
5 n denotes 0, 1, 2, 3 or 4,
k,p,l,s denote 1, 2, 3, 4 or 5,

where

10 k + p denotes 2, 3, 4 or 5

and

15 q denotes 1, 2, 3 or 4

and pharmaceutically usable derivatives, solvates, tautomers, salts and stereoisomers thereof, including mixtures thereof in all ratios.

20 The invention also relates to the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds. The term solvates of the compounds is taken to mean adductions of inert solvent molecules onto the compounds which
25 form owing to their mutual attractive force. solvates are, for example, mono- or dihydrates or alkoxides.

The term pharmaceutically usable derivatives is taken to mean, for exam-
30 ple, the salts of the compounds according to the invention and also so-called prodrug compounds.

The term prodrug derivatives is taken to mean compounds of the formula I which have been modified by means of, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to
35 form the effective compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

5

The expression "effective amount" denotes the amount of a medicament or of a pharmaceutical active ingredient which causes in a tissue, system, animal or human a biological or medical response which is sought or desired, for example, by a researcher or physician.

10

In addition, the expression "therapeutically effective amount" denotes an amount which, compared with a corresponding subject who has not received this amount, results in the following:

15

improved healing treatment, healing, prevention or elimination of a disease, syndrome, condition, complaint, disorder or side-effects or also the reduction in the progress of a disease, condition or disorder.

The expression "therapeutically effective amount" also encompasses the amounts which are effective for increasing normal physiological function.

20

The invention also relates to the use of mixtures of the compounds according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

These are particularly preferably mixtures of stereoisomeric compounds.

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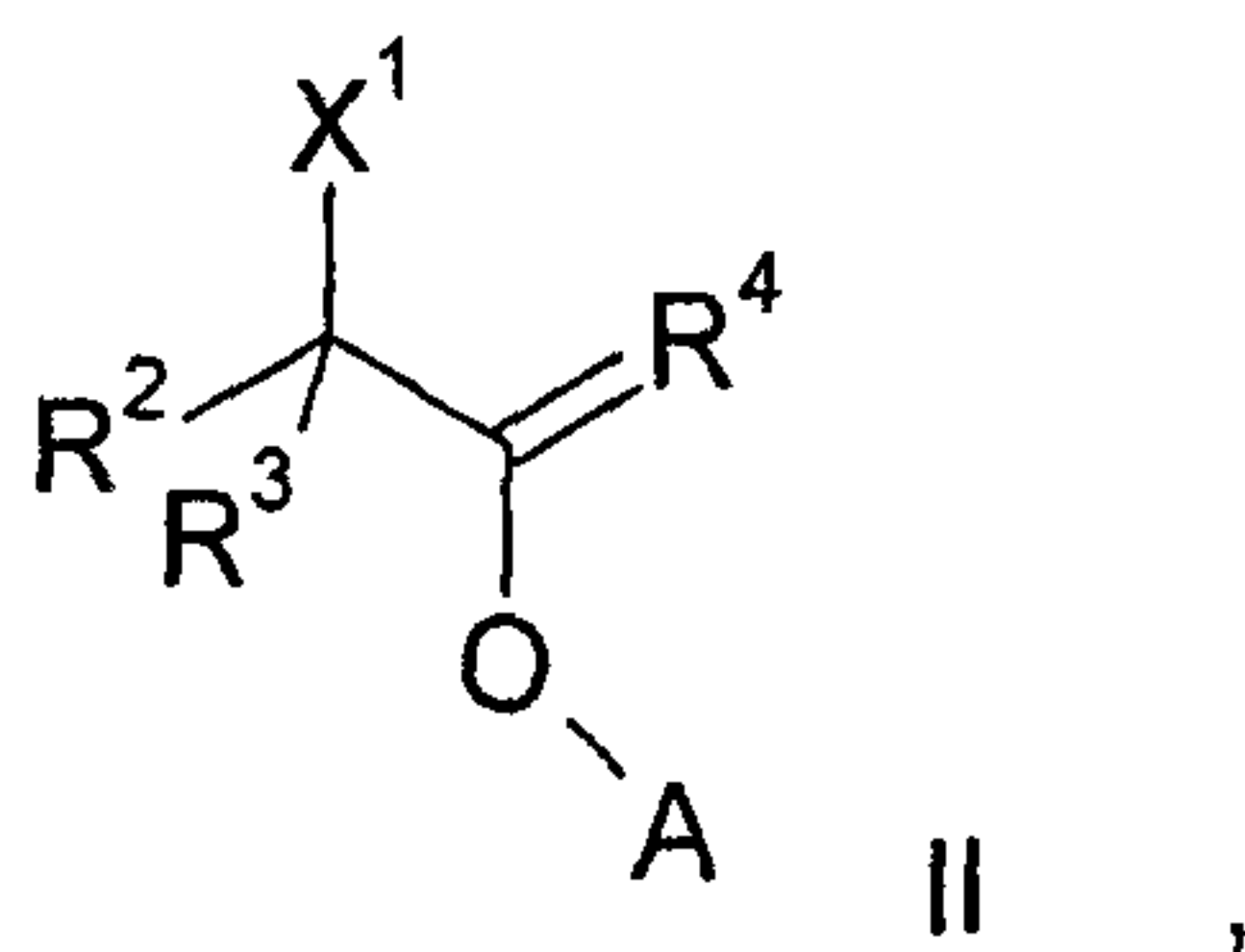
The invention relates to the compounds of the formula I and salts thereof and to a process for the preparation of compounds of the formula I according to the patent claims and pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, characterised in that

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a compound of the formula II

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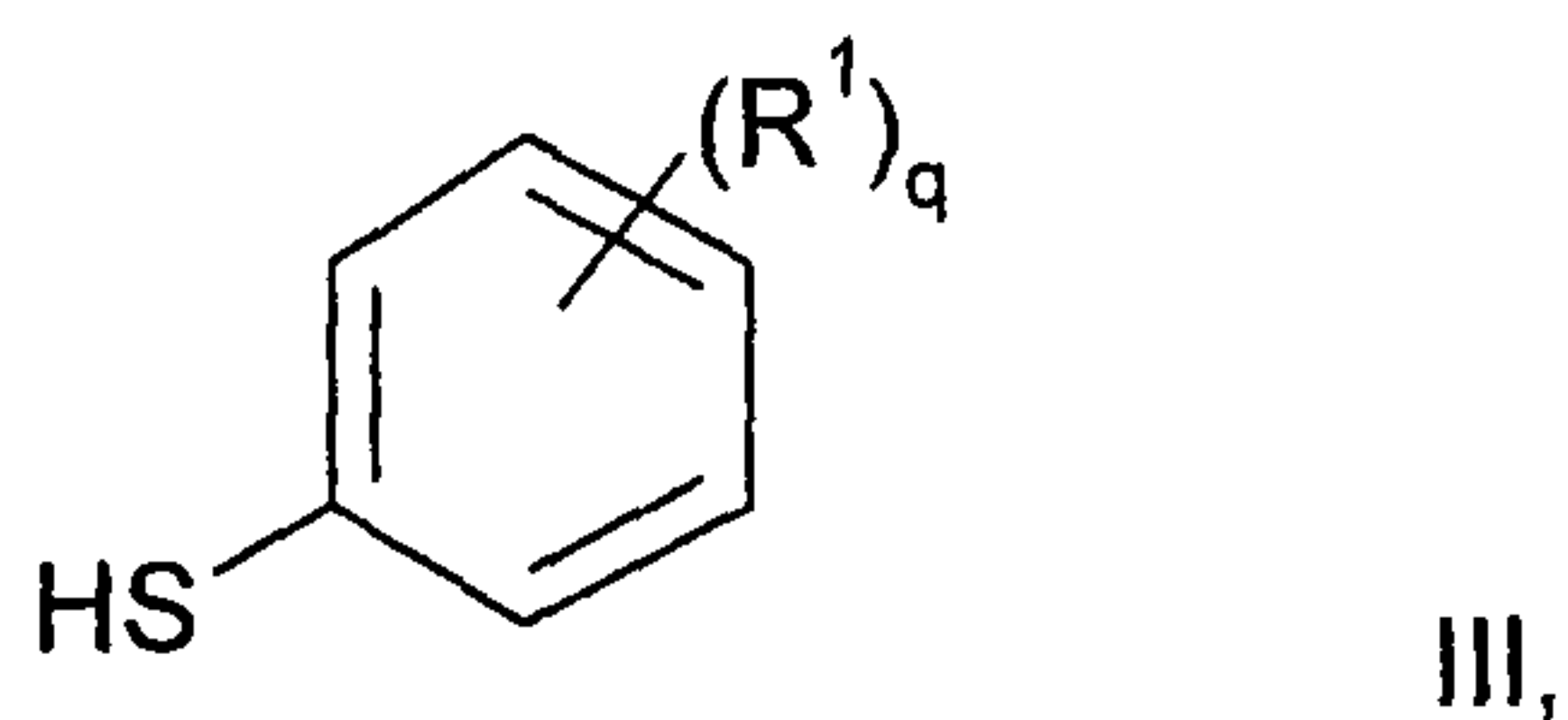
- 9 -



in which R^2 , R^3 and R^4 have the meanings indicated in Claim 1
 and X^1 can be a leaving group and preferably Hal or a reactive modified OH group, in particular tosyl or mesyl,

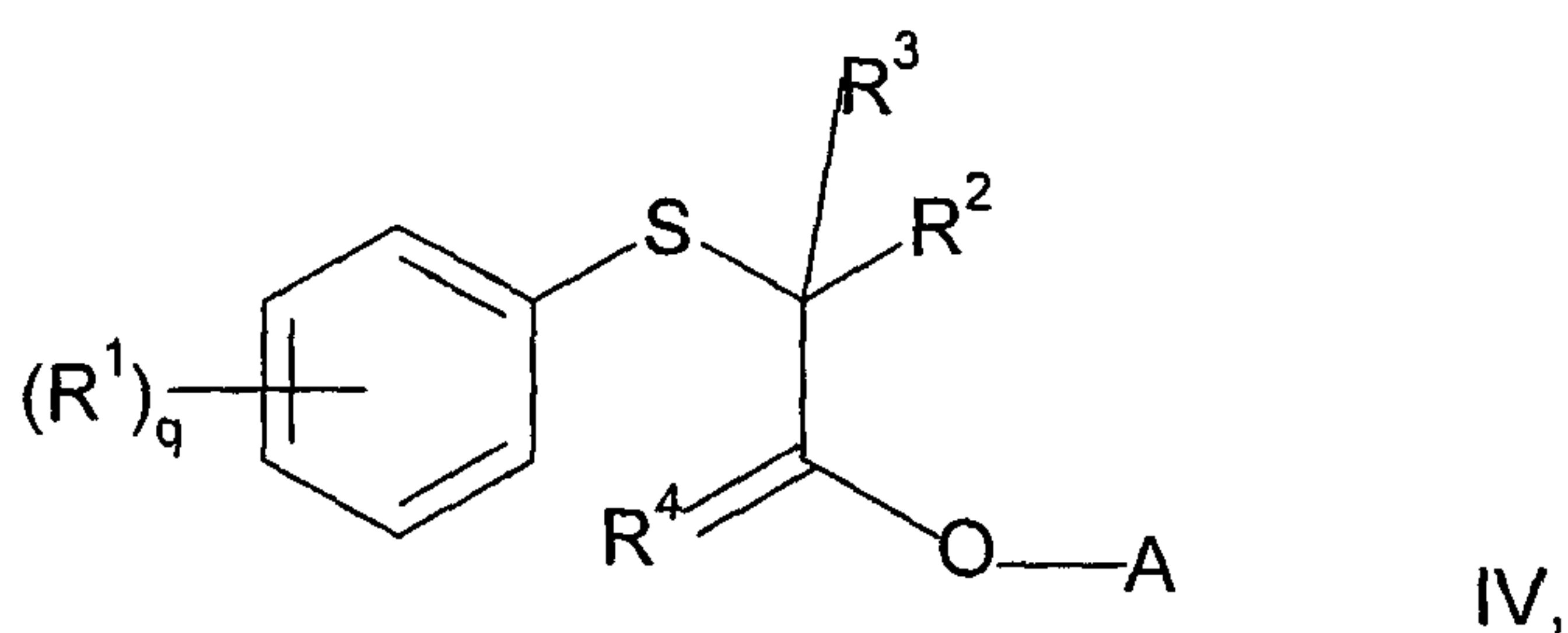
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is reacted with a compound of the formula III



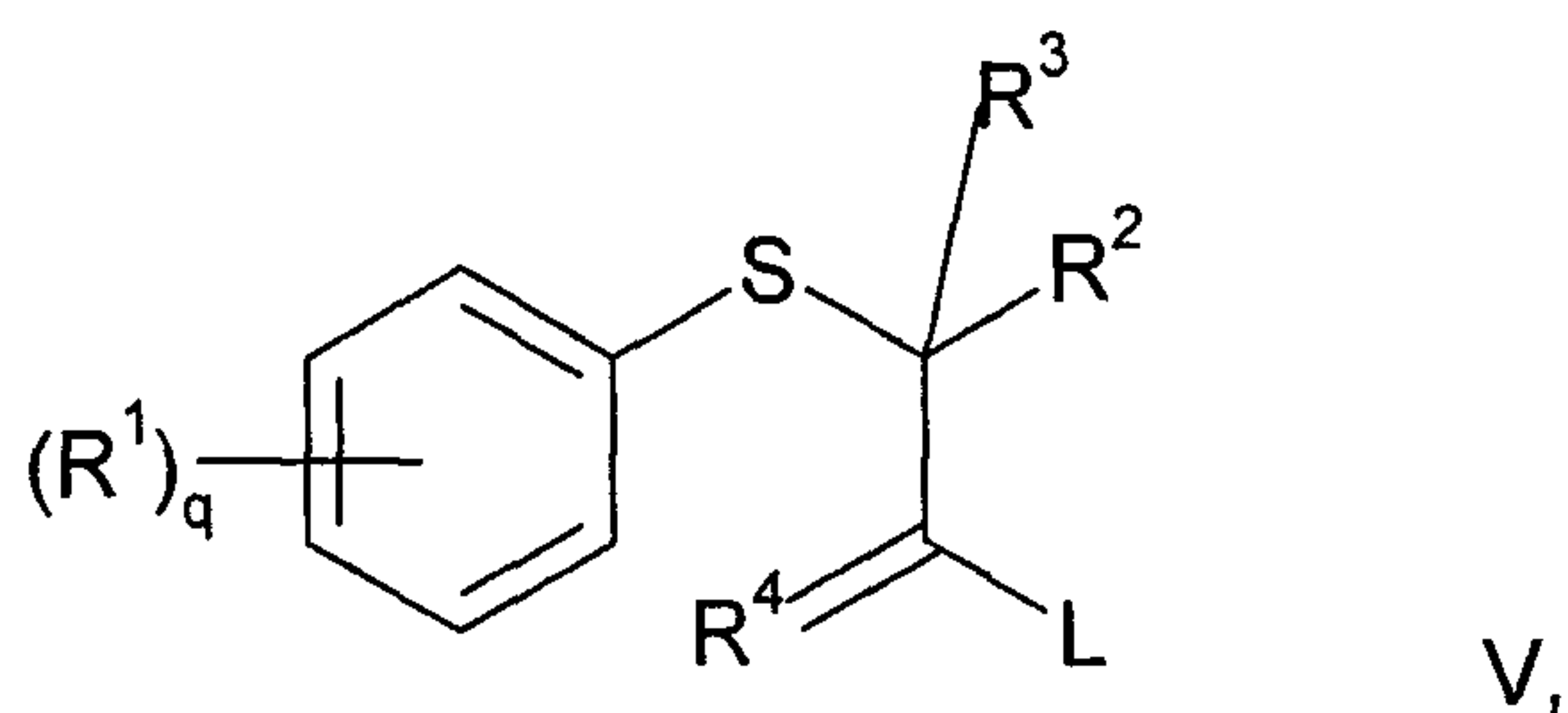
20 in which
 R^1 has the meanings indicated in Claim 1.

The resultant compound of the formula IV



in which
 R^1 , R^2 , R^3 , R^4 and q have the meanings indicated in Claim 1,
 is converted into the free acid by saponification, and this is subsequently
 converted by conventional methods into the corresponding formula V

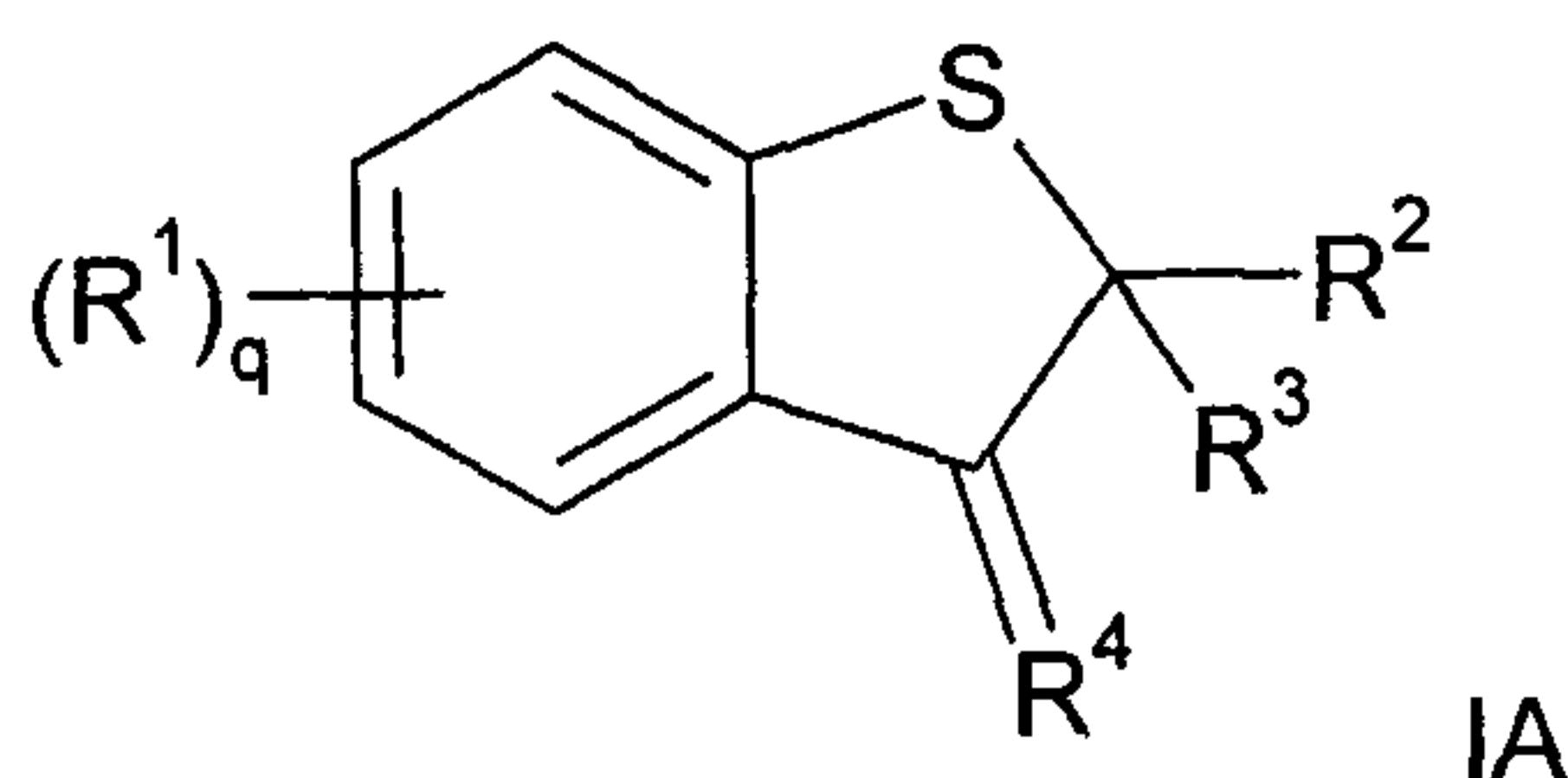
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in which

10 L denotes Hal or a reactive modified OH group, such as, for example, triflate, nonaflate, tosylate, mesylate or benzenesulfonate, but in particular tosylate or mesylate, and R^1 , R^2 , R^3 , R^4 and q have the meanings indicated in Claim 1.

15 The compound of the formula V is then converted in the presence of a suitable catalyst, such as, for example, a Friedel-Craft catalyst, in particular $AlCl_3$, into formula IA



in which

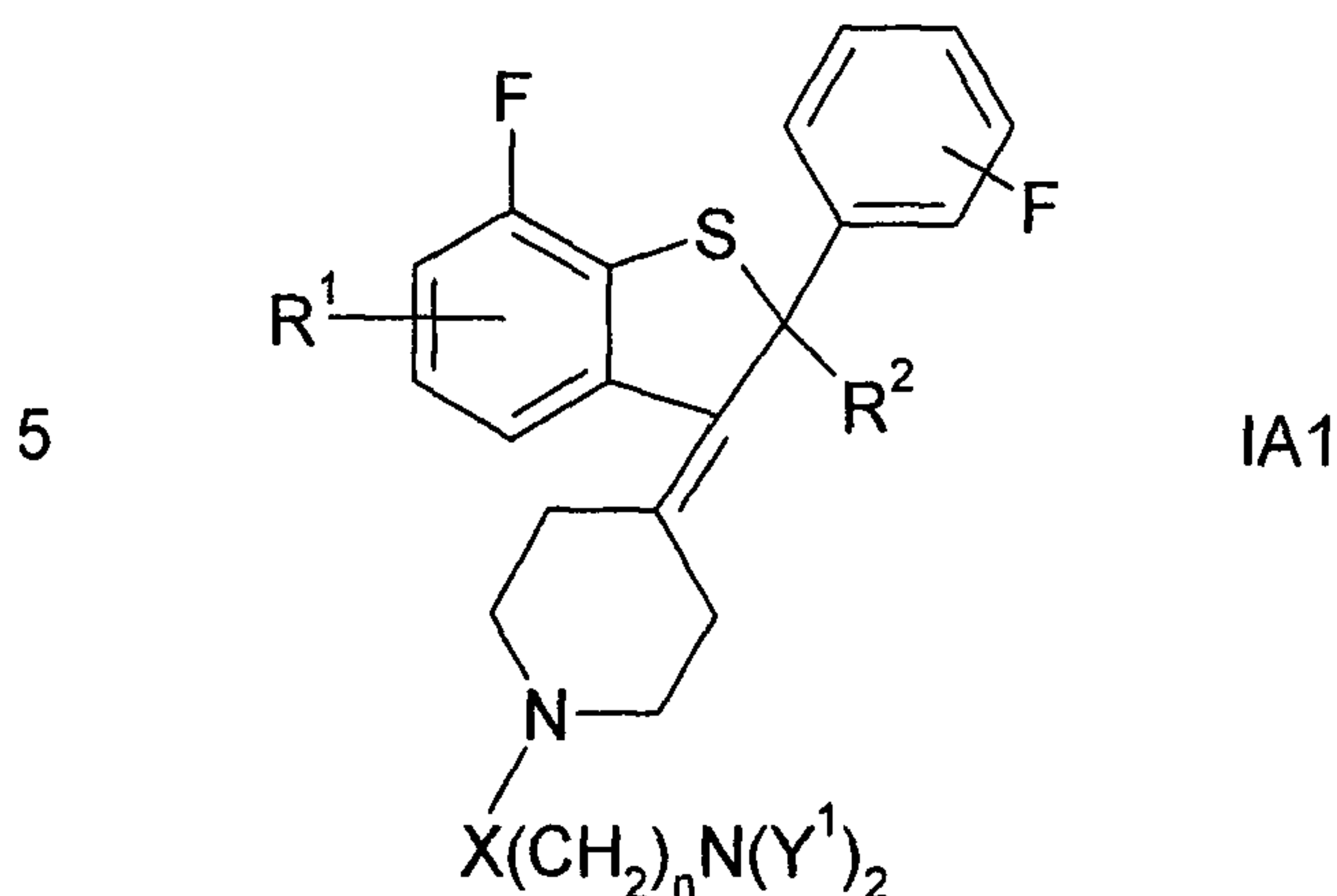
25 R^1 , R^2 , R^3 , R^4 and q have the meanings indicated in Claim 1.

The compounds of the formula IA are preferred.

Particular preference is given to the compounds of the formula IA1:

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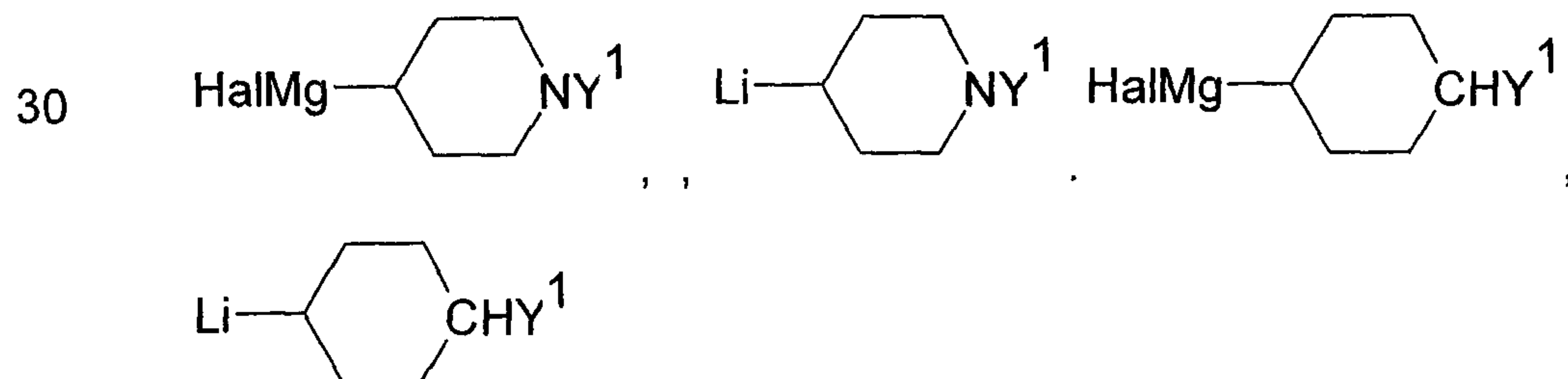


in which R^1 , R^2 , X , Y^1 and n have the meaning indicated above, and R^1 preferably denotes methyl.

Compounds of the formula I in which R^2 and/or R^3 denote H can be converted into the further compounds of the formula I in which R^2 and/or R^3 have a meaning other than H, for example by reaction with a base, such as, for example, sodium hydride, and an alkylating reagent.

Particular preference is given to alkylating reagents such as, for example, iodoalkane, alkyl sulfate, benzyl halides, sulfates, mesylates or tosylates, in particular iodomethane, methyl sulfate or benzyl chloride.

Compounds of the formula I in which R^4 denotes O are optionally converted into the further compounds of the formula I in which R^4 has the above-mentioned meaning by reaction with corresponding organometallic reagents, such as, for example, organolithium or Grignard compounds, in particular compounds of the formulae



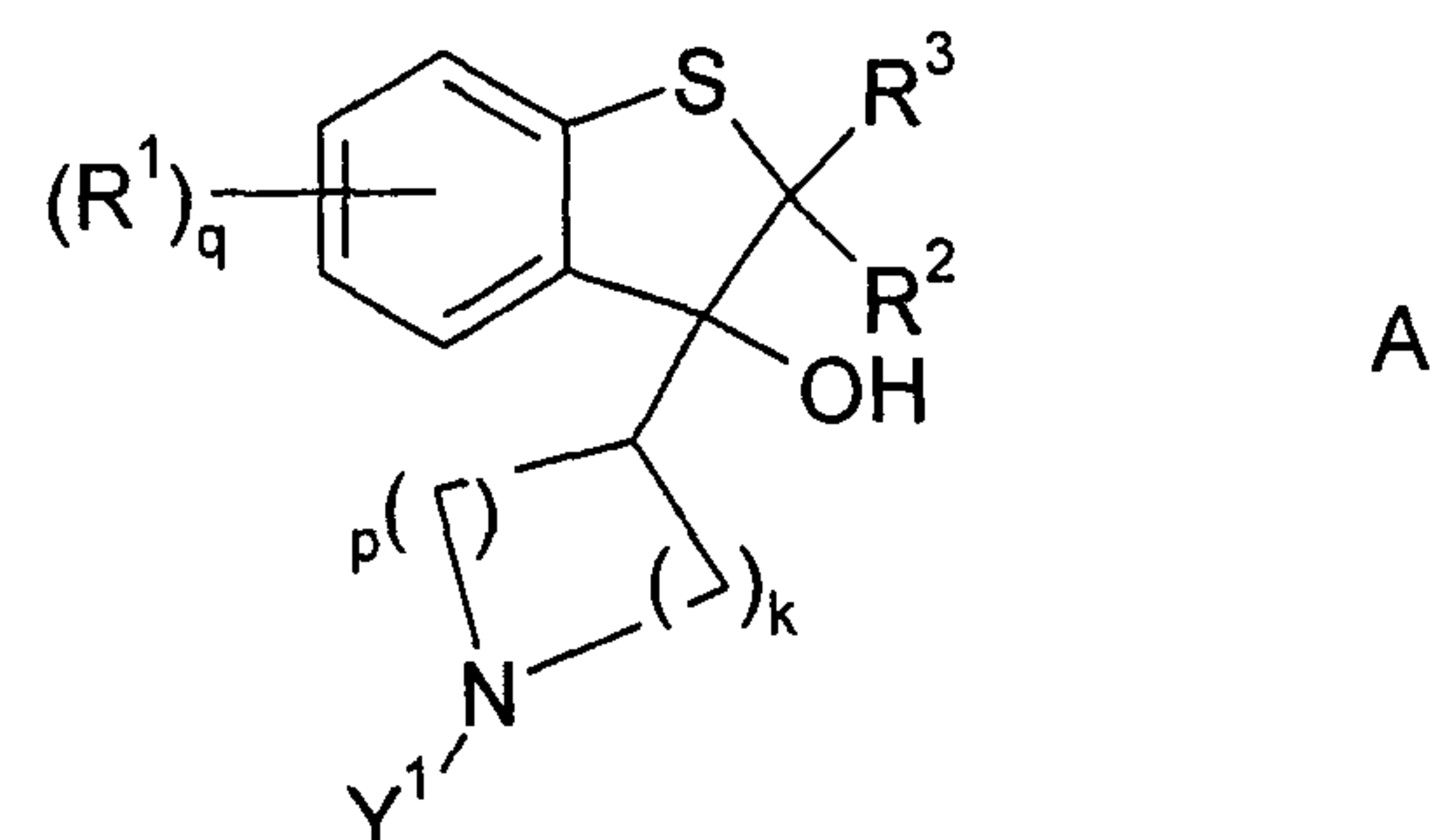
$\text{HalMg-CH}_2(\text{CH}_2)_n\text{X}(\text{CH}_2)_l\text{Q}(\text{CH}_2)_s\text{T}$ or $\text{Li-CH}_2(\text{CH}_2)_n\text{X}(\text{CH}_2)_l\text{Q}(\text{CH}_2)_s\text{T}$

and subsequent elimination. Any E/Z isomer mixtures obtained can be separated from one another by known, preferably chromatographic methods, or alternatively by crystallisation.

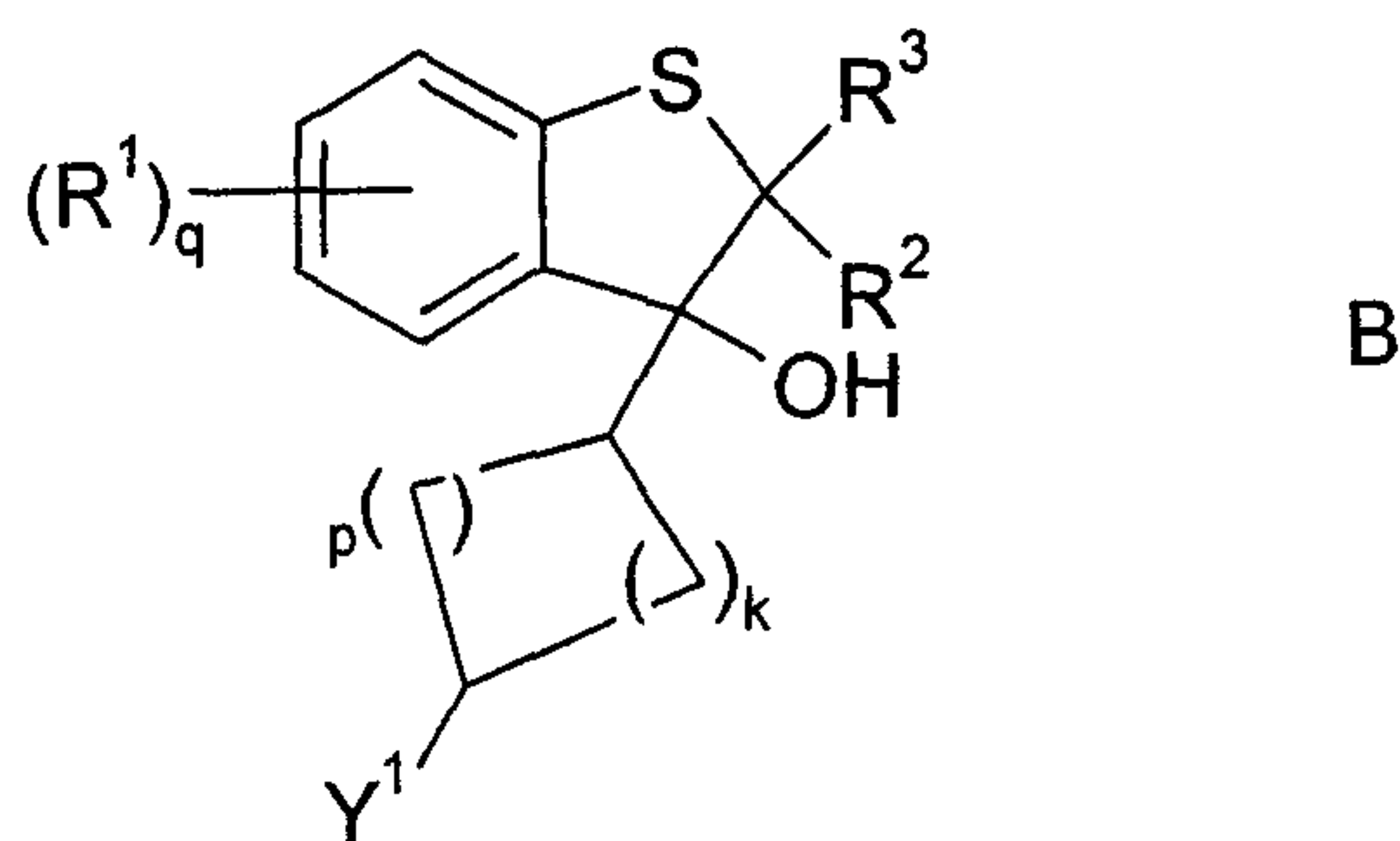
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Aqueous work-up of the by reaction of the compounds of the formula I in which R^4 denotes O with the said organometallic reagents preferably firstly gives the corresponding tertiary alcohols, which, as intermediates, are likewise a subject-matter of the invention. These are particularly preferably

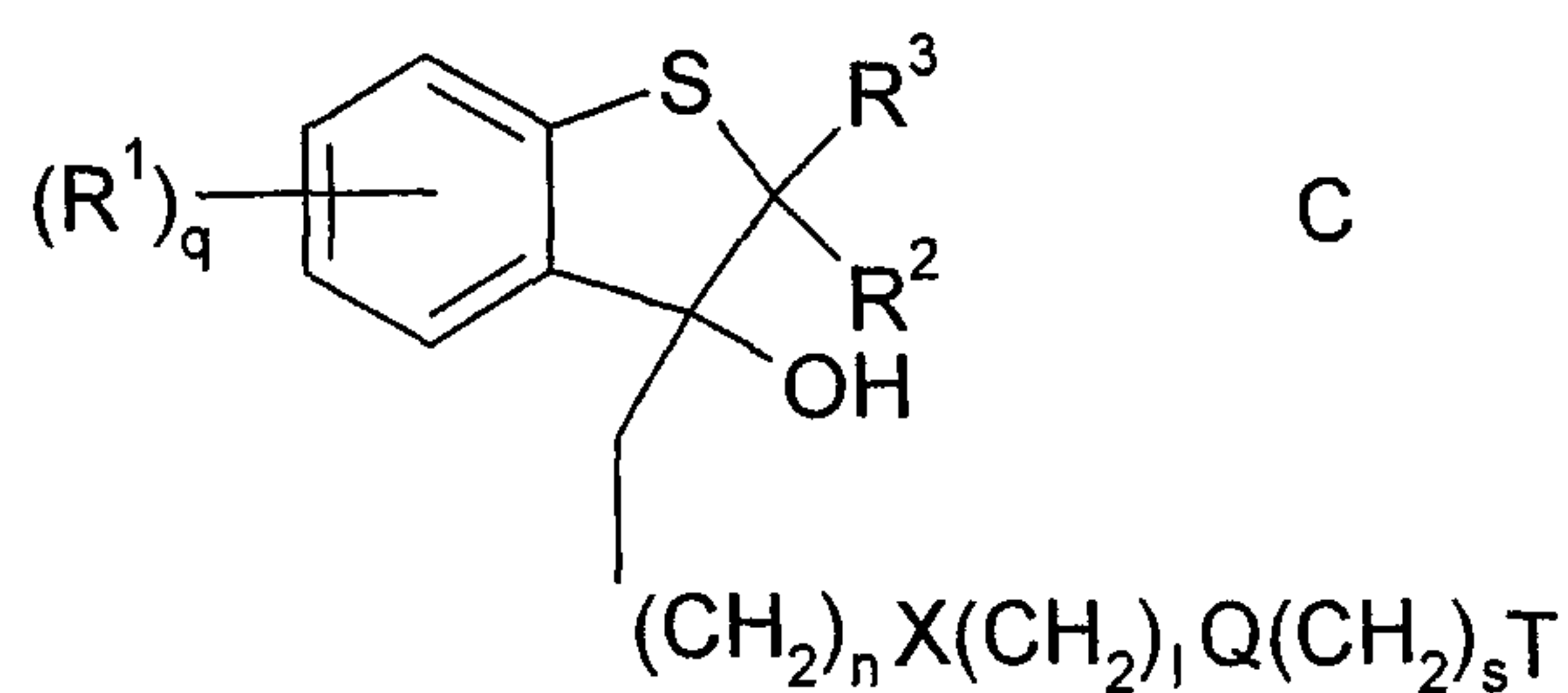
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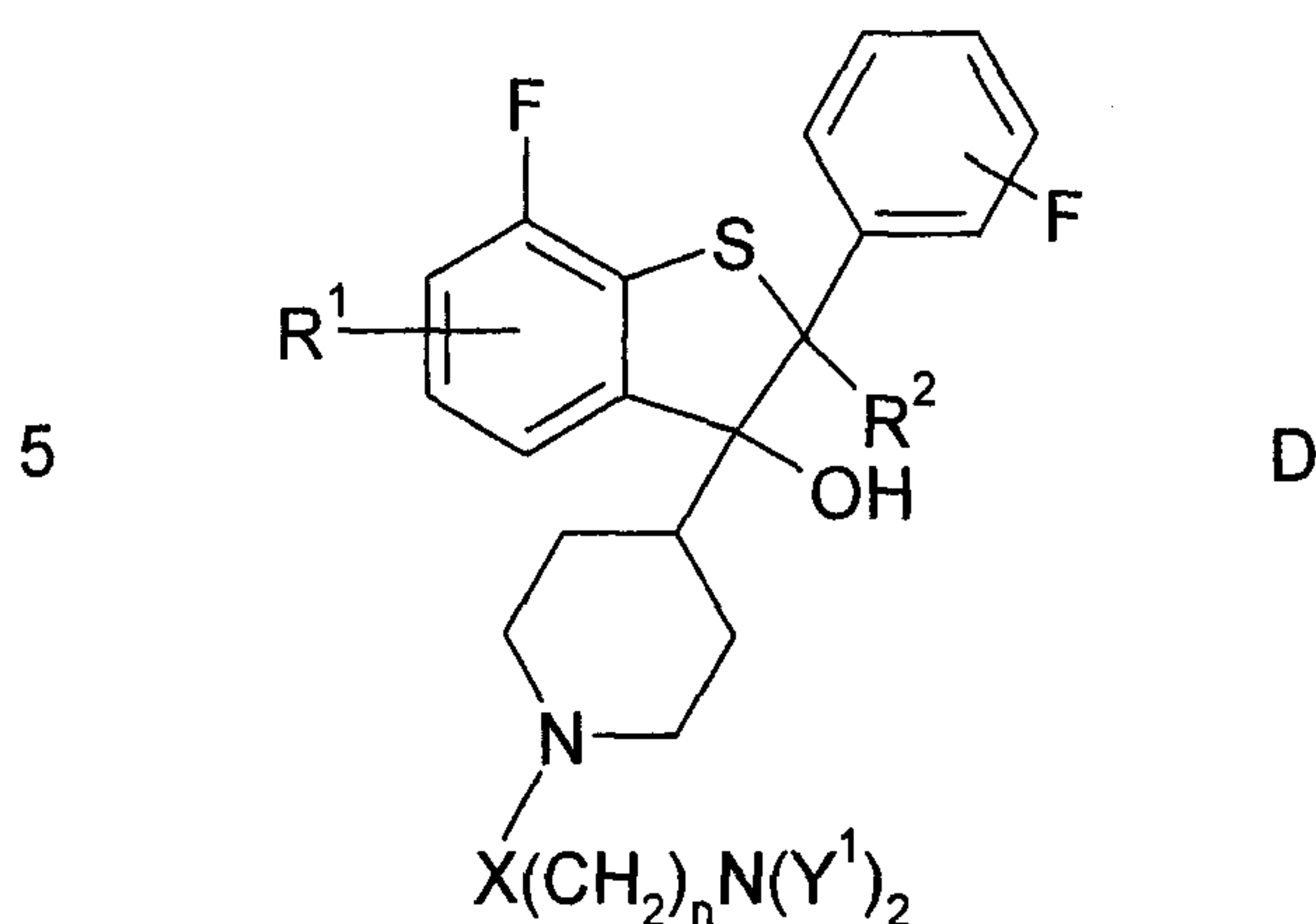


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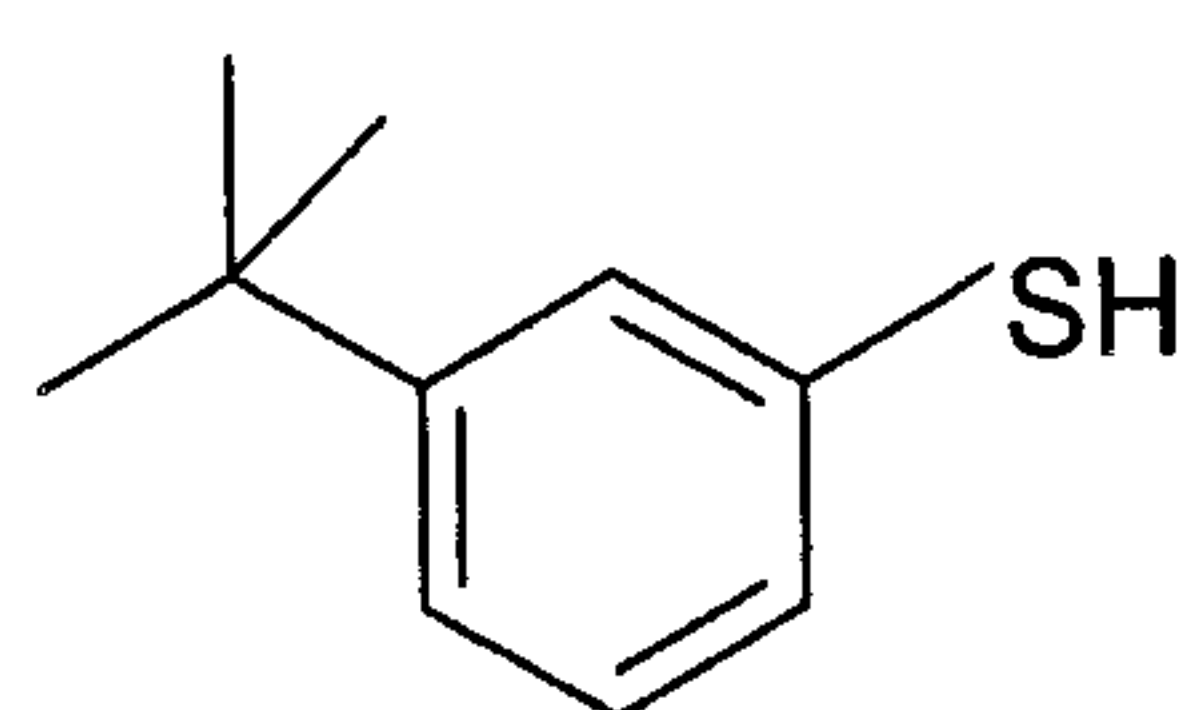
15 The sulfoxides ($W=SO$) and sulfones ($W=SO_2$) of the compounds of the formula I, A, B, C and D can preferably be prepared by oxidation of the compounds of the formula I in which W denotes S or SO. The compounds of the formula I, IA, VIA and VIB are preferably also employed as starting materials for oxidation of the sulfur atom. This is preferably carried out by use of H_2O_2 or other oxidants (for example according to Patai, "Supplement E, " Ref. 42, pt. 1, pp. 539-608; Org. Prep. Proced. Int. 14, 45-89 (1982); "The Chemistry of Sulfur," pp. 385-390, Plenum, New York, 1977; Tetra-

20 hedron Lett. 22, 1287 (1981)).

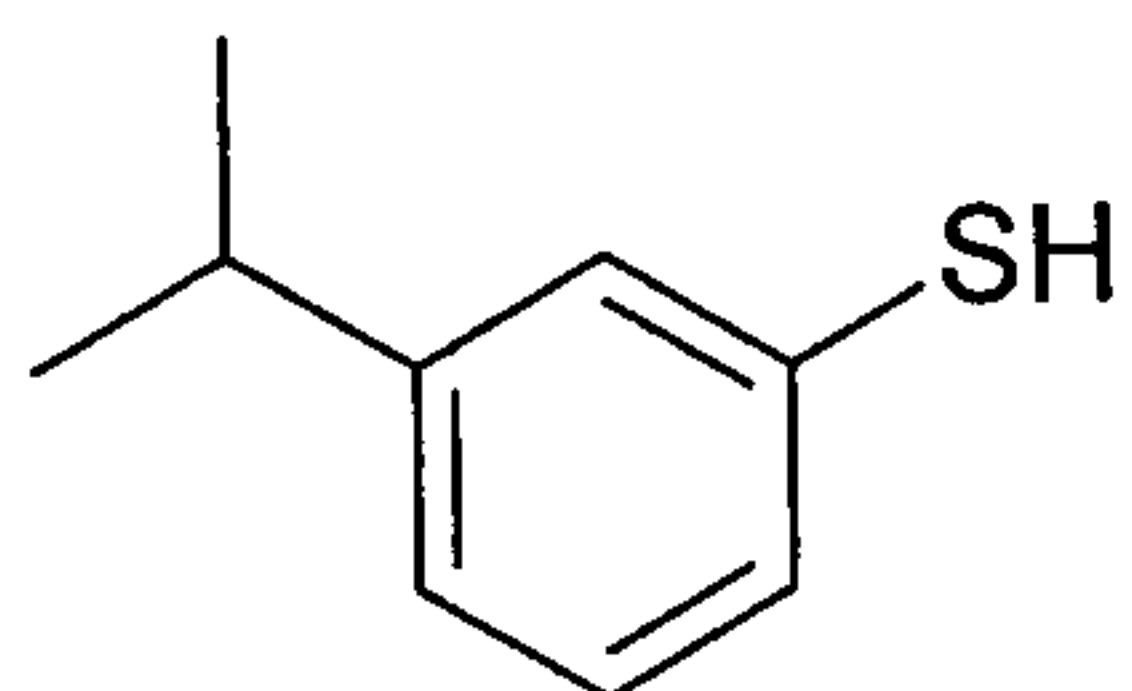
25 The compounds of the formula I in which W denotes SO or SO_2 are very particularly preferably prepared by starting from corresponding intermediates which are oxidised on the sulfur atom, which can be produced by oxidation of the thio compounds of the formula II, IV and V. The compounds oxidised to the sulfoxides or sulfones can be reacted like the parent thio compounds of the formula II, IV and V.

30 R^4 in the compounds of the formula II, IV and V preferably has the meaning O.

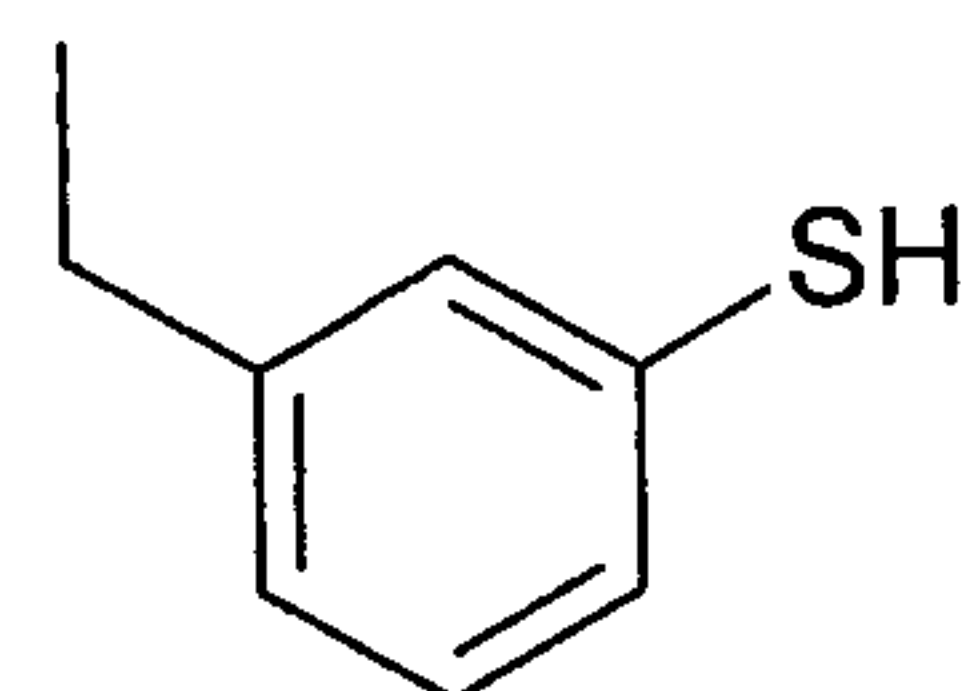
The following formulae III1- 15 are preferably employed for the formula III:



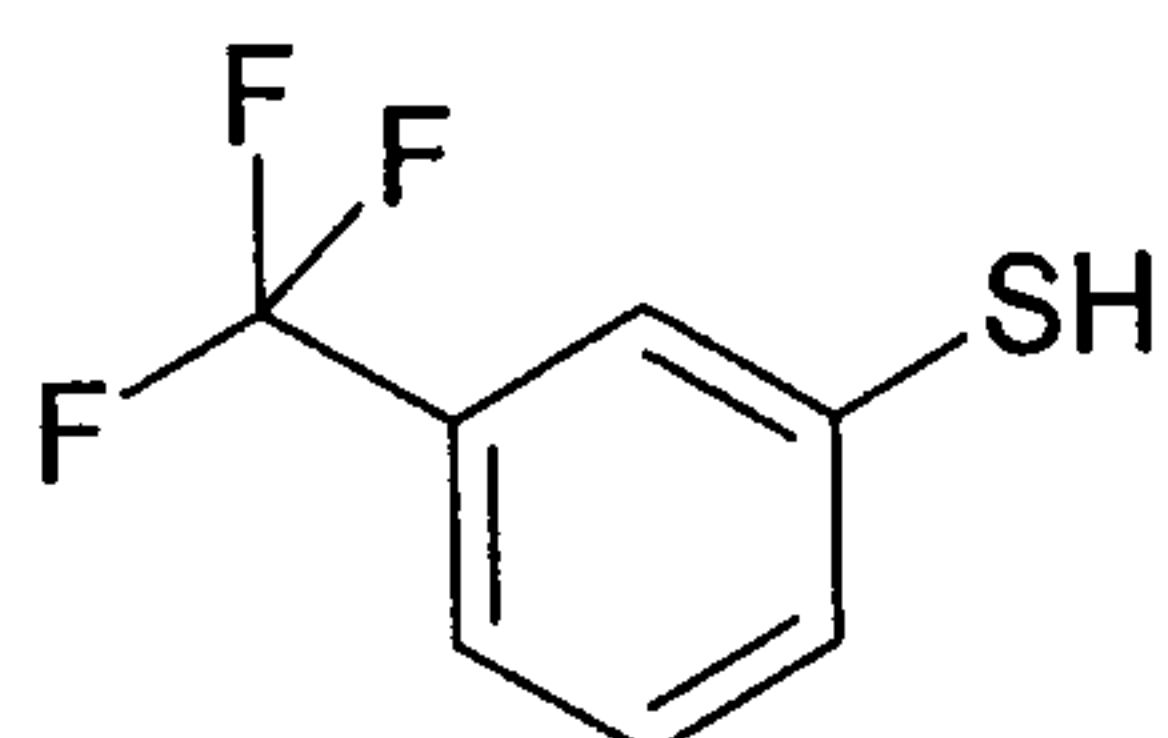
III1



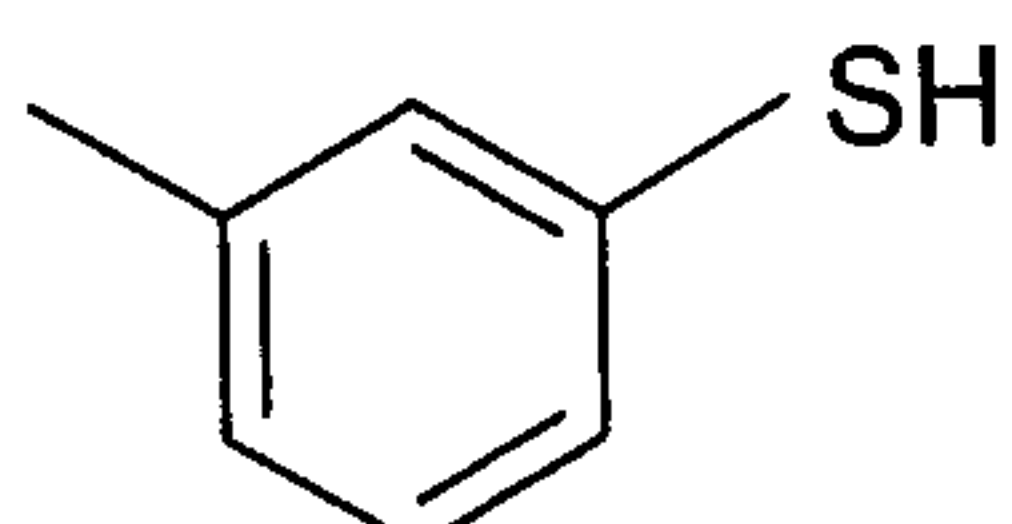
III2



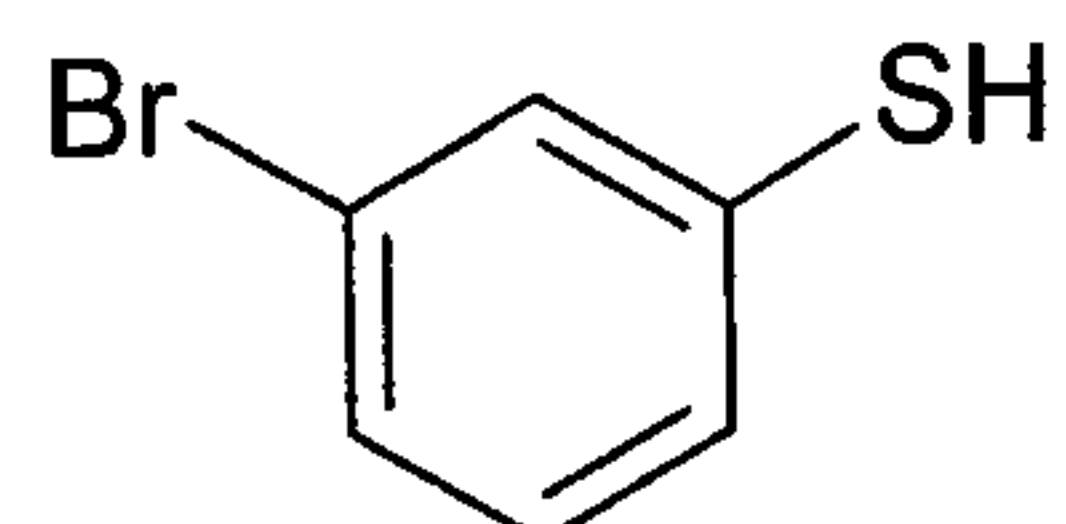
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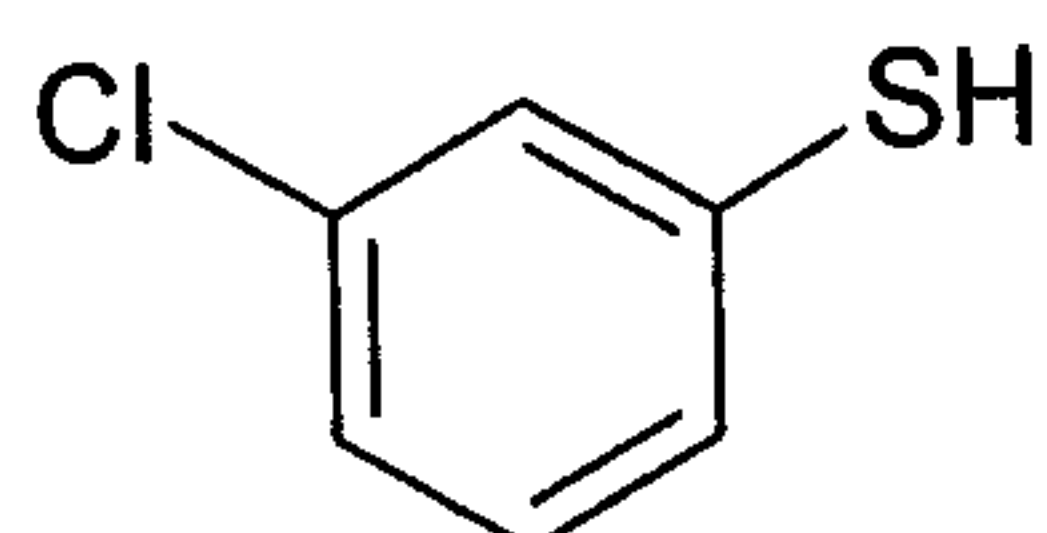
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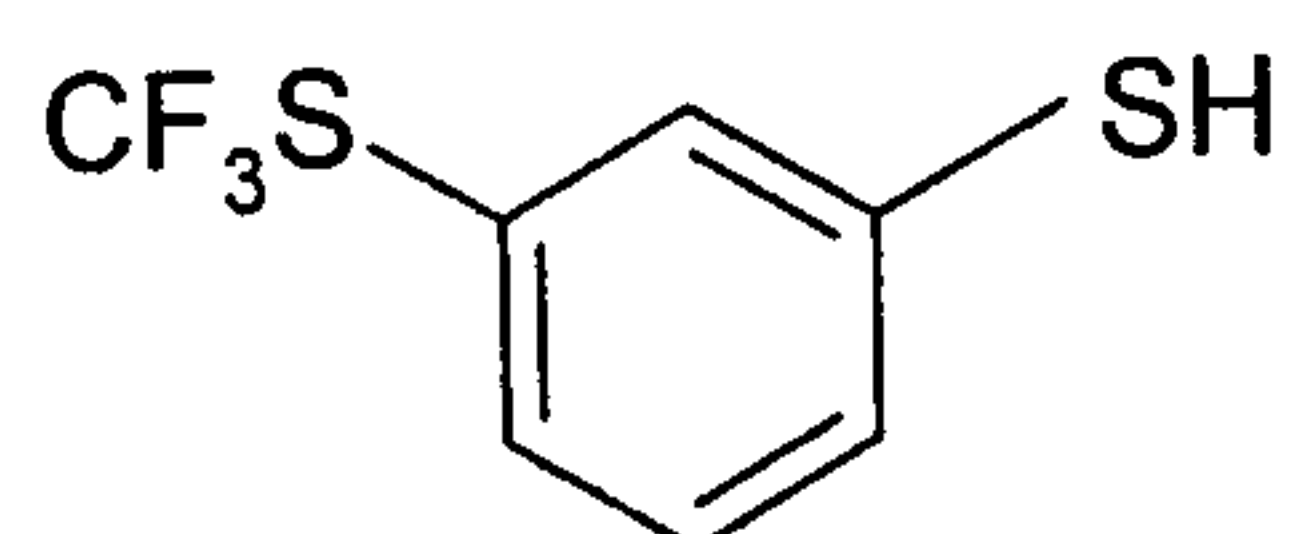
III5



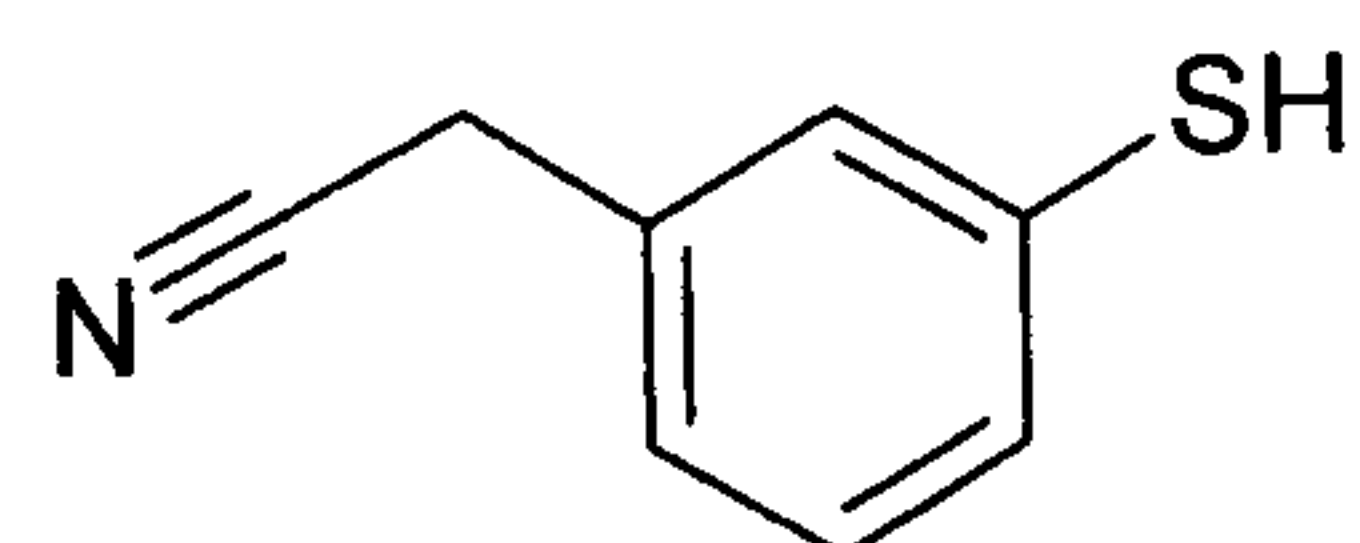
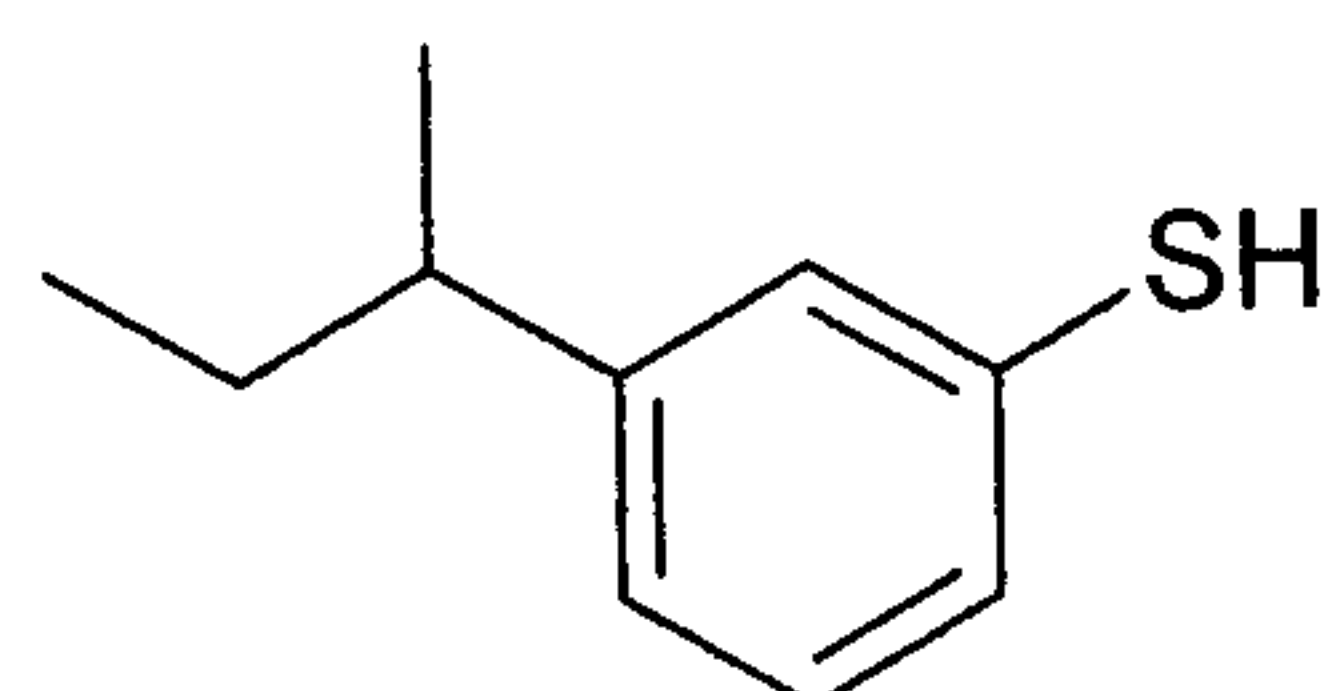
III6



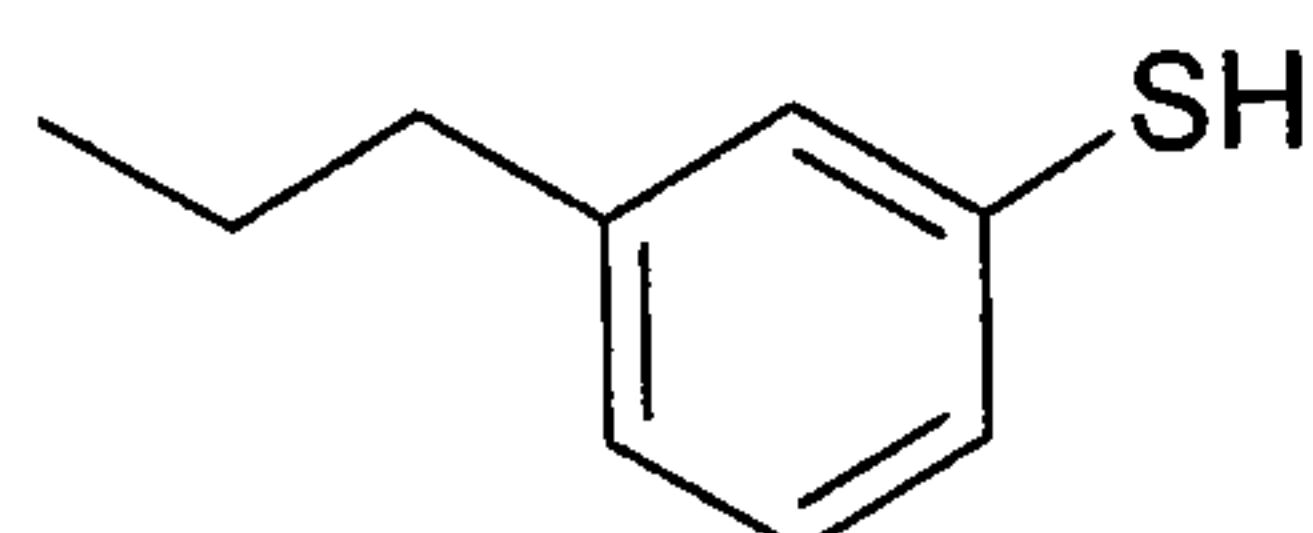
III7



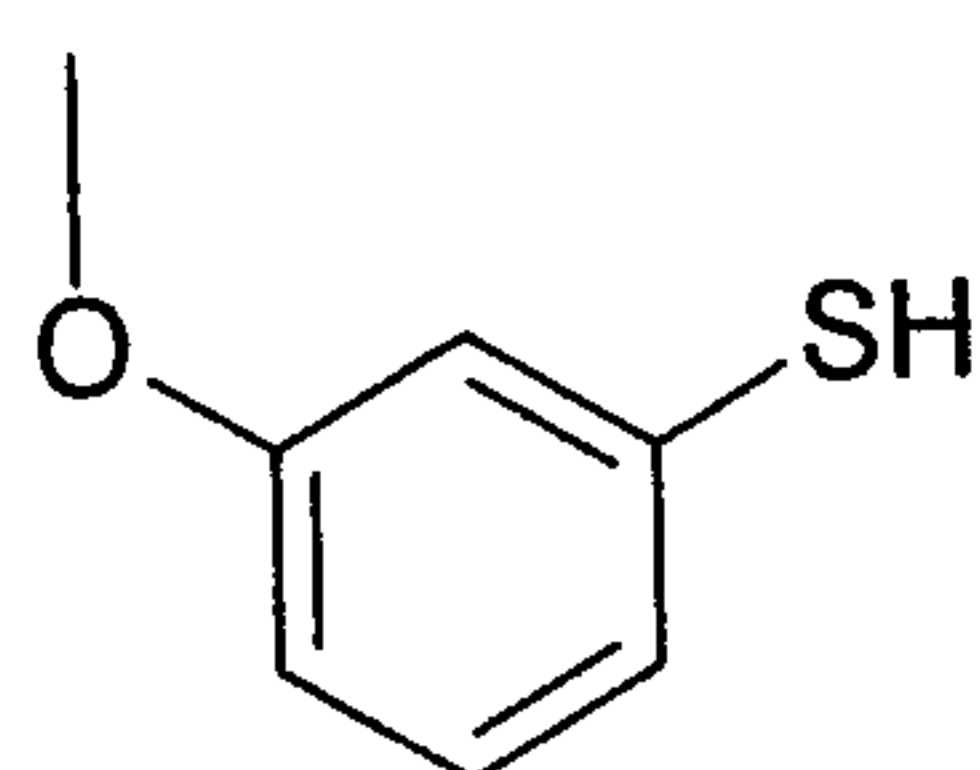
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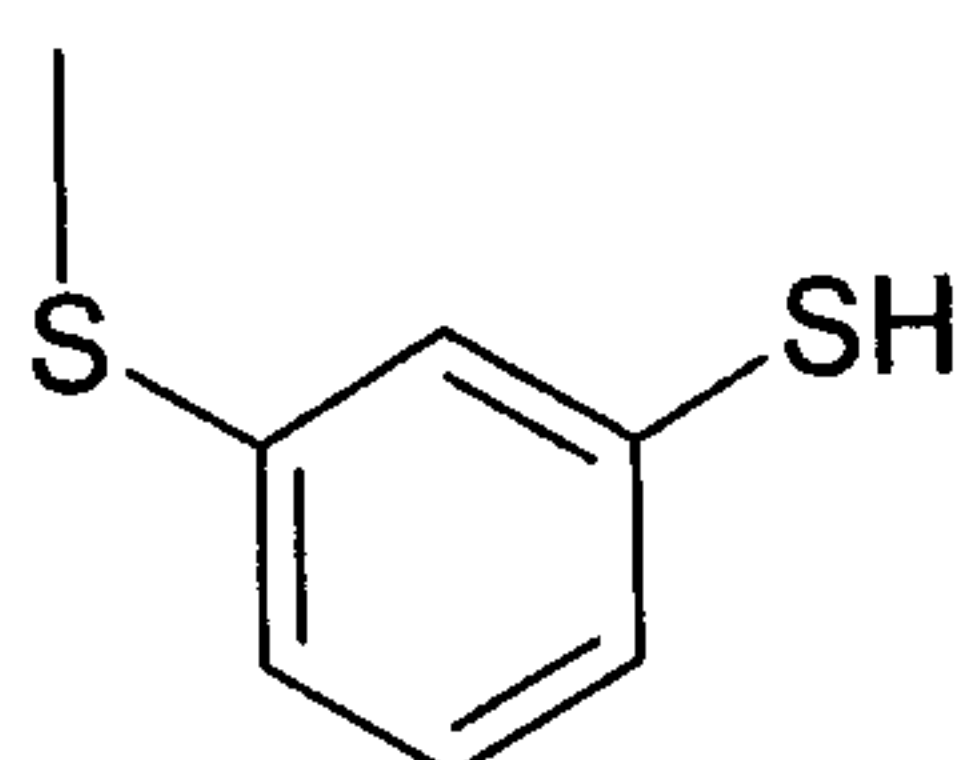
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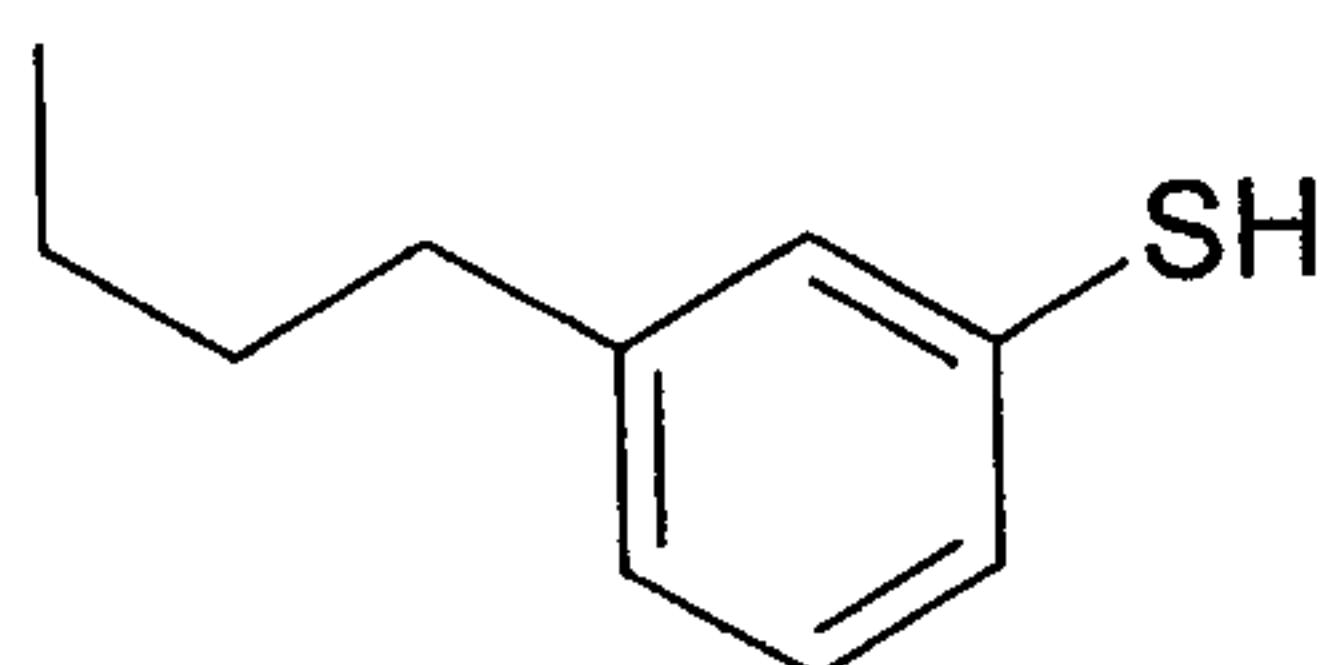
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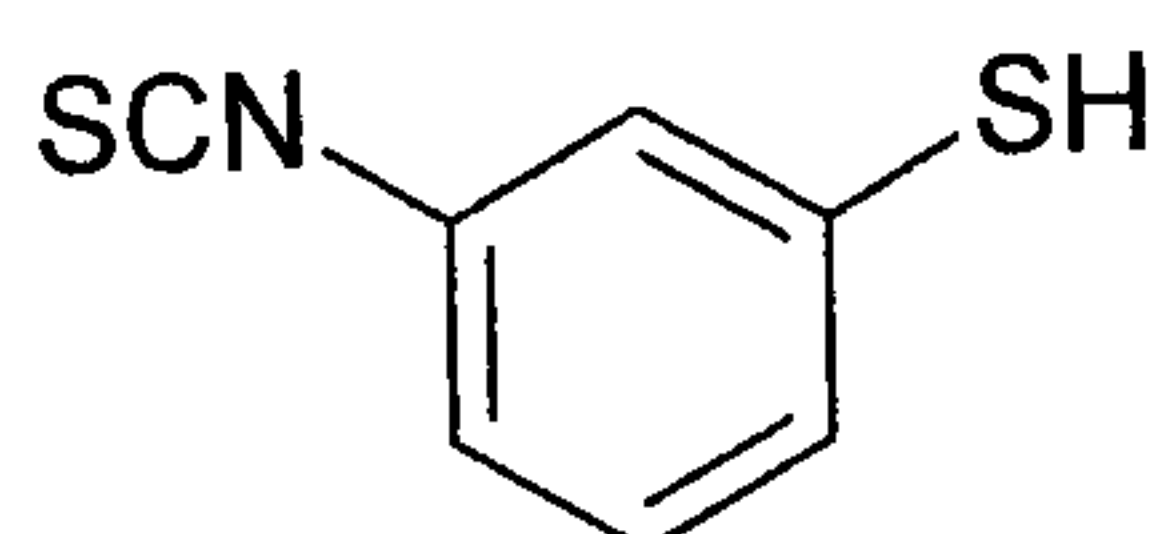
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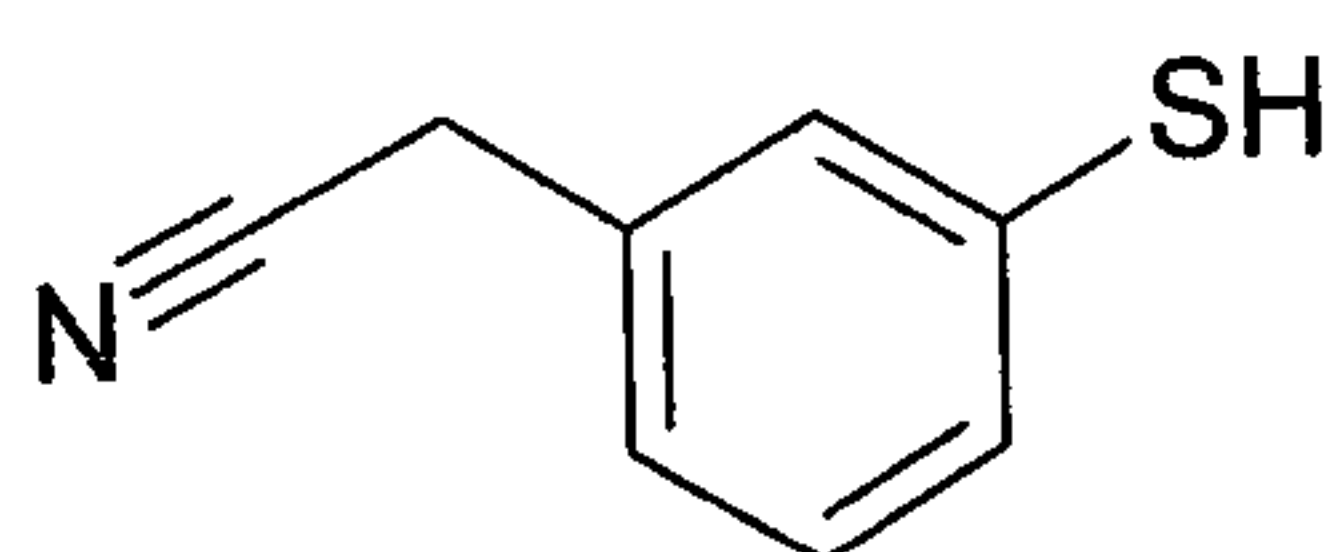
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III13



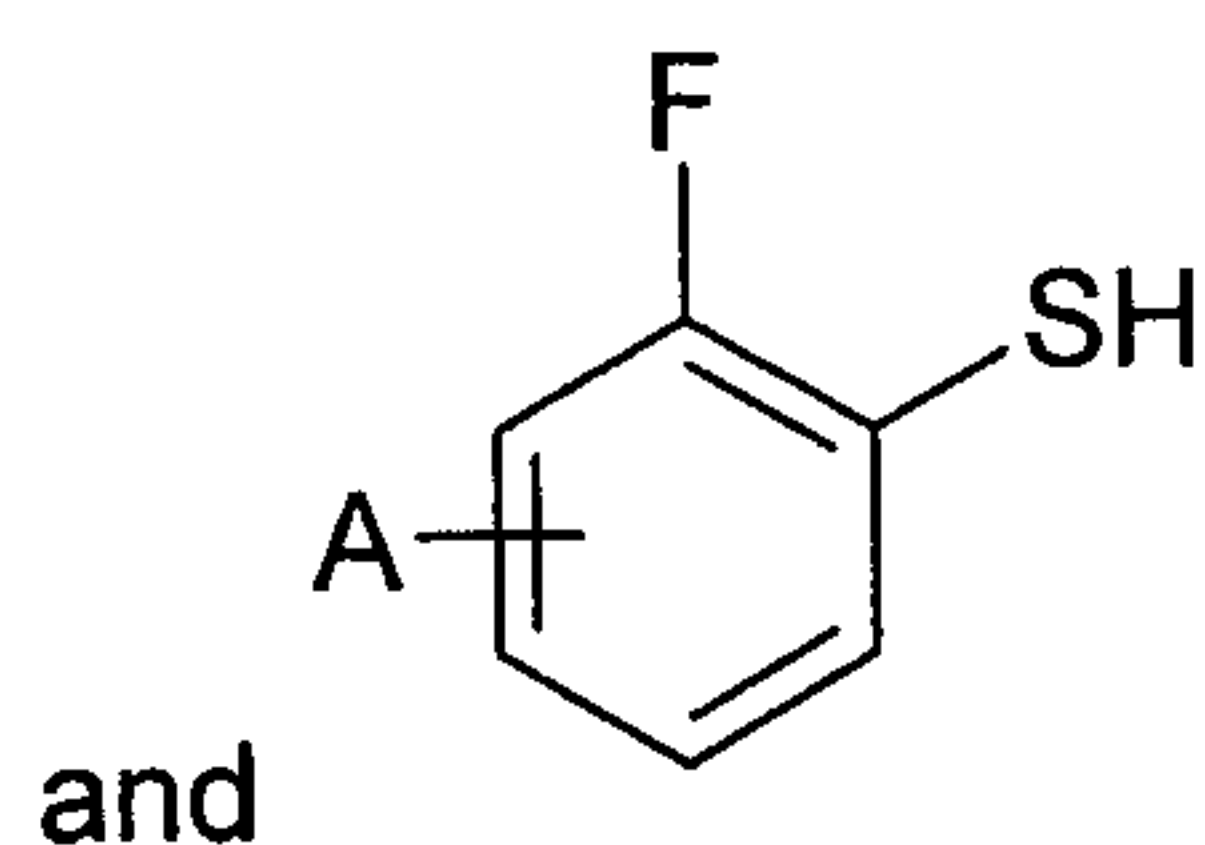
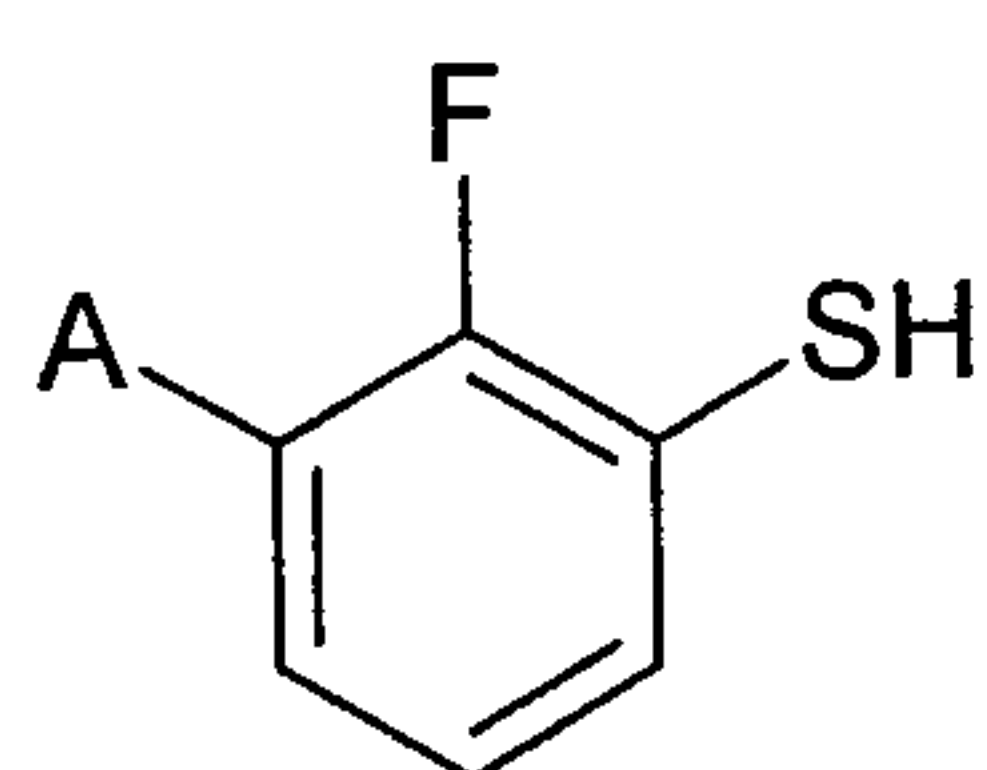
III14



III15

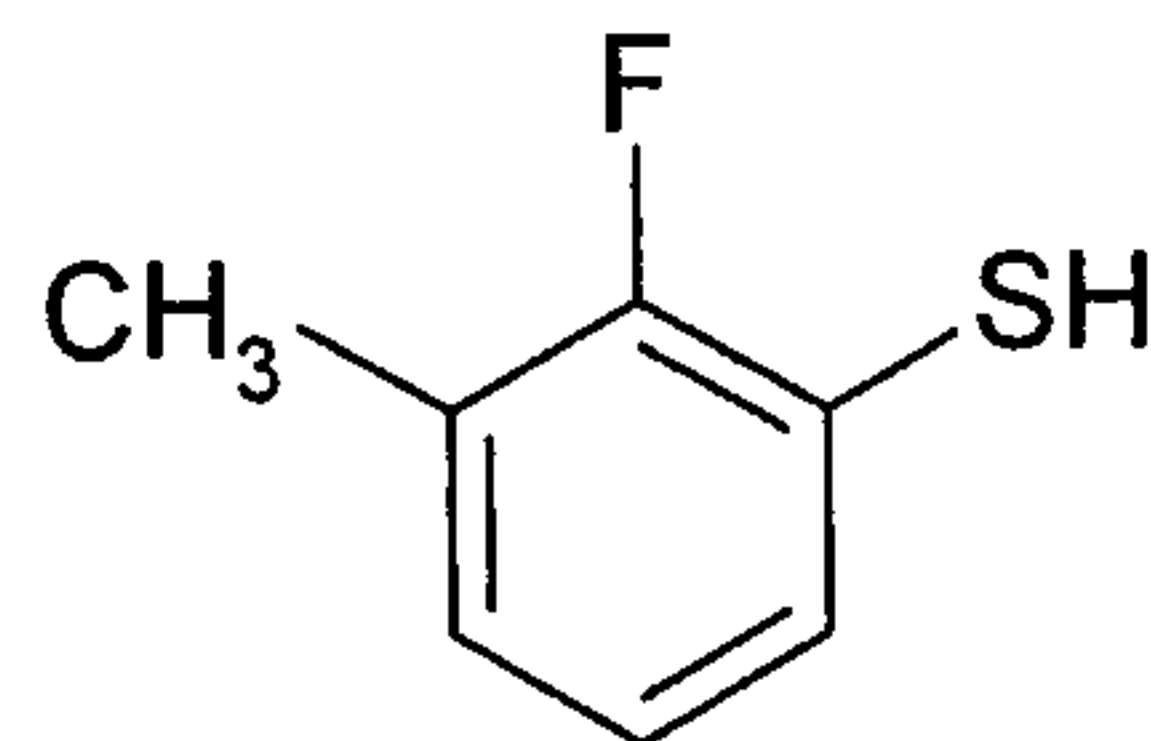
where preference is given to compounds which have, with the exception of F, no substituents on C-5, C-7 or C-8 (based on formula I). The following compounds are furthermore preferred:

5



and

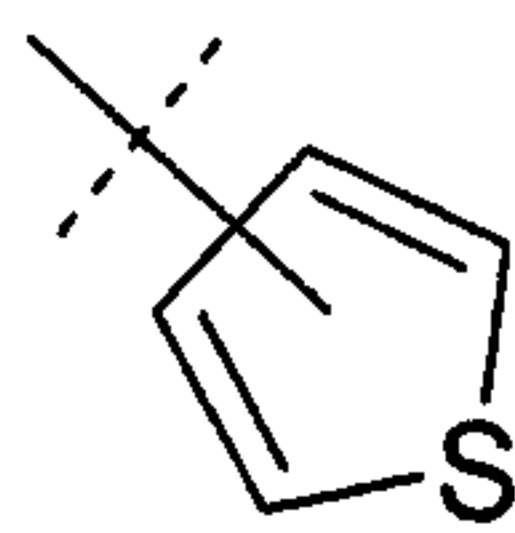
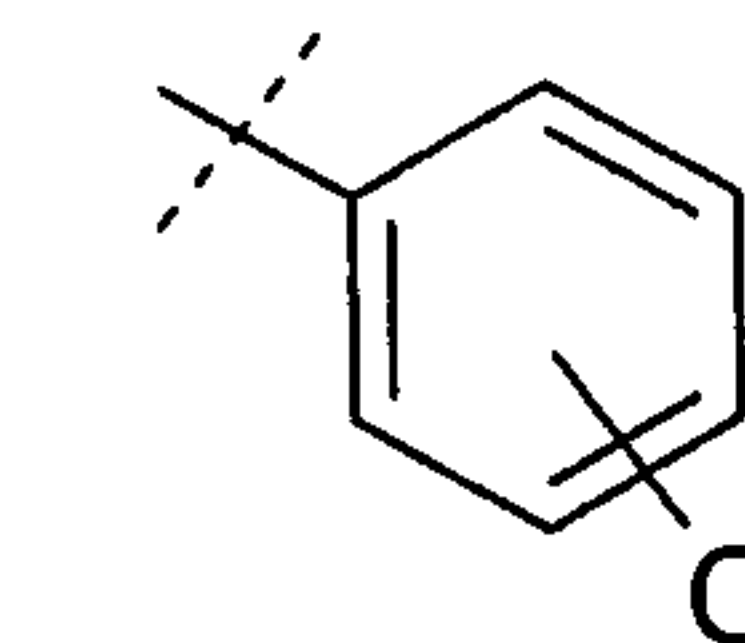
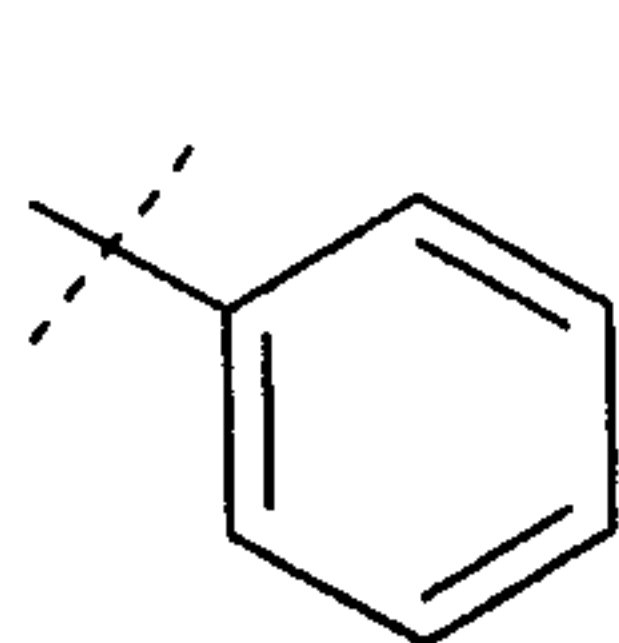
, in particular



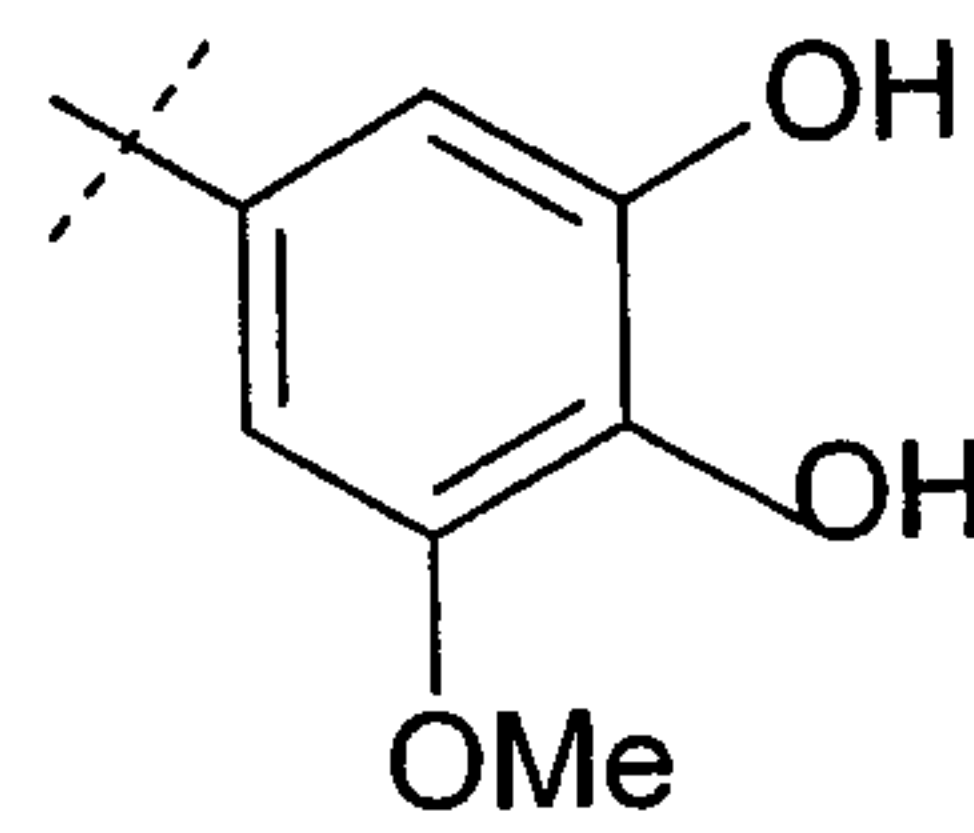
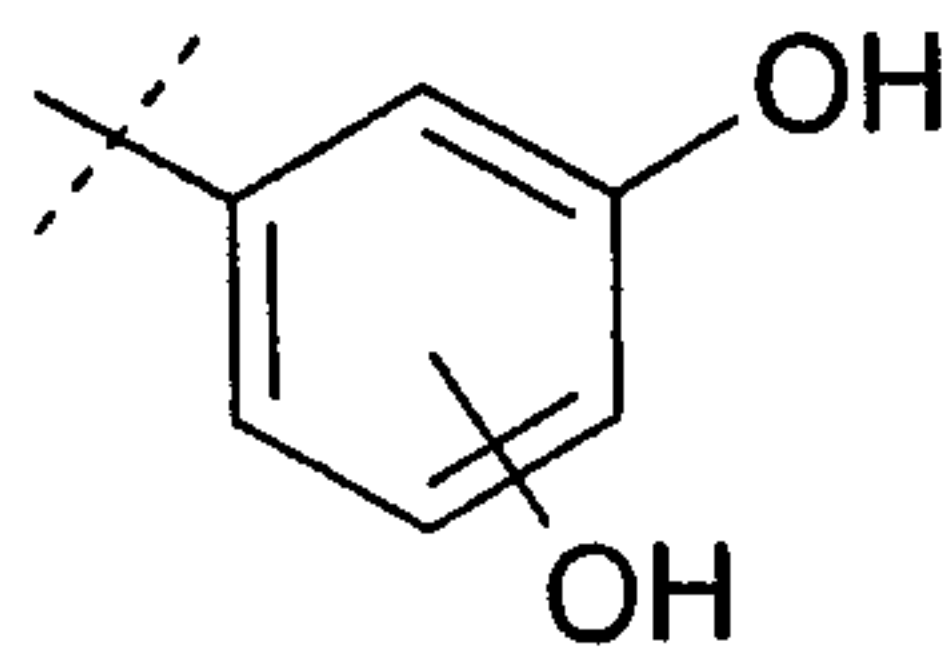
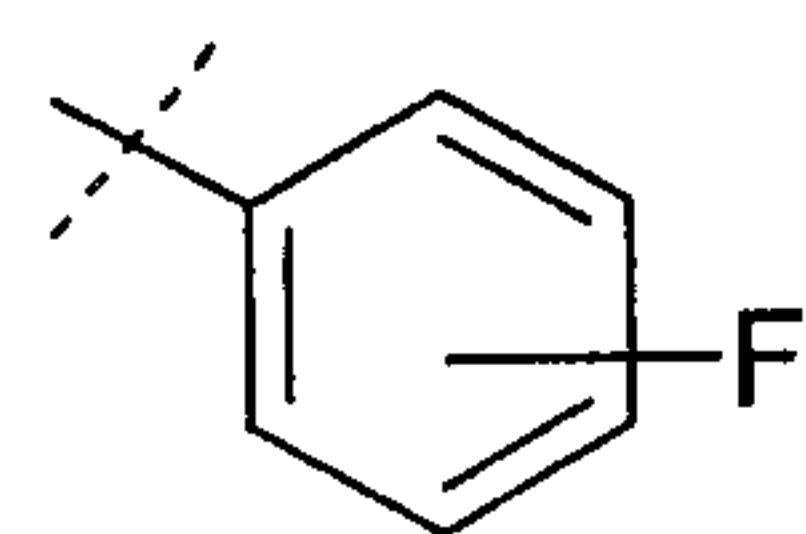
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The following groups are particularly preferred for R² and/or R³:

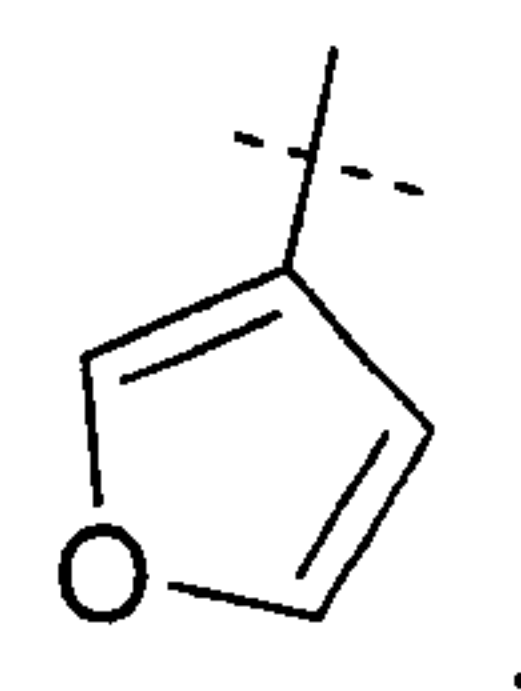
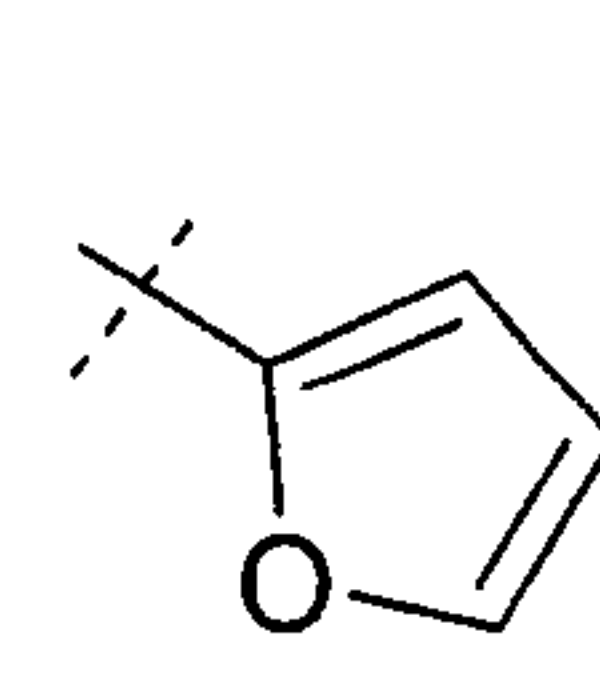
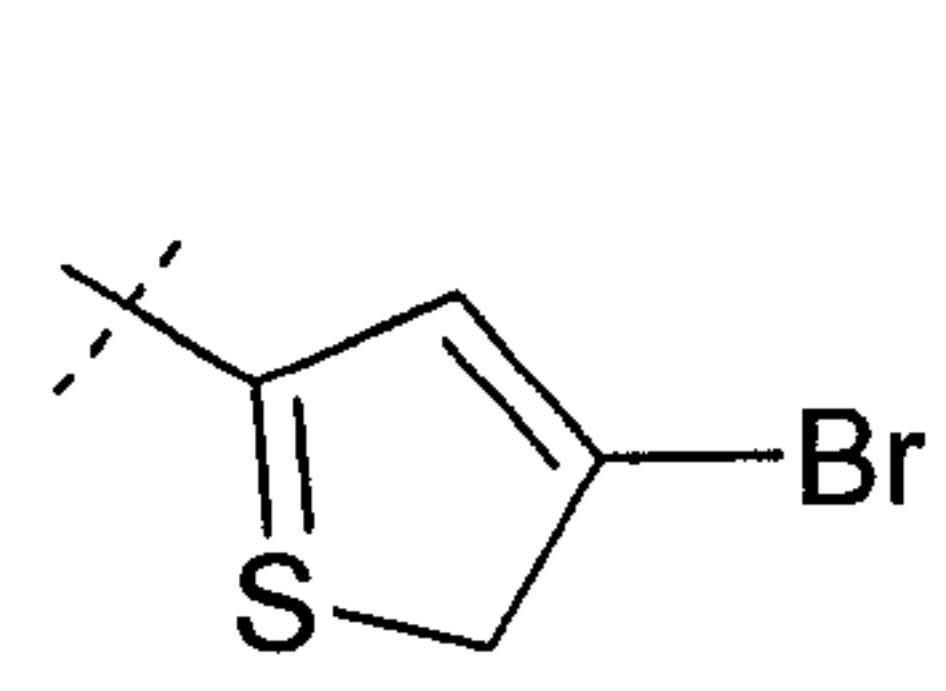
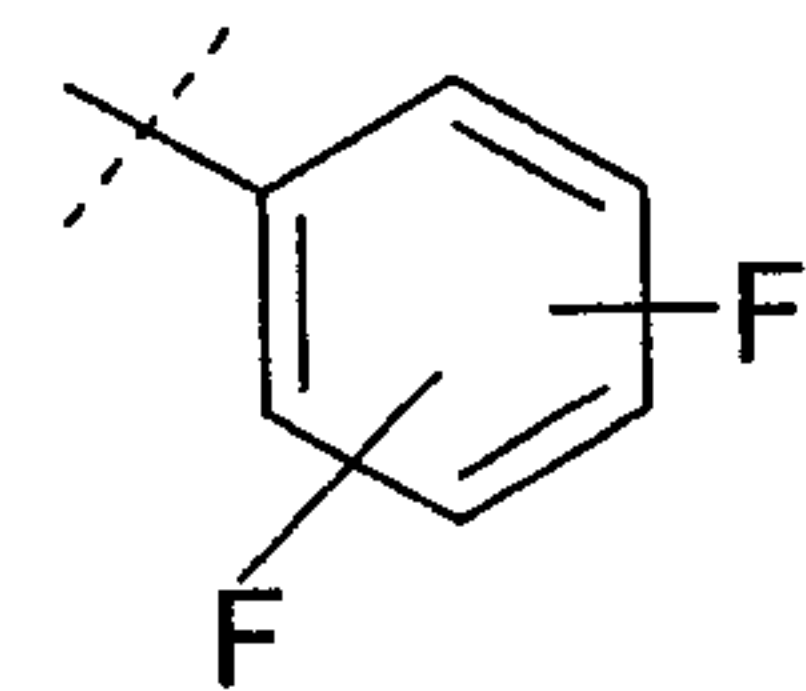
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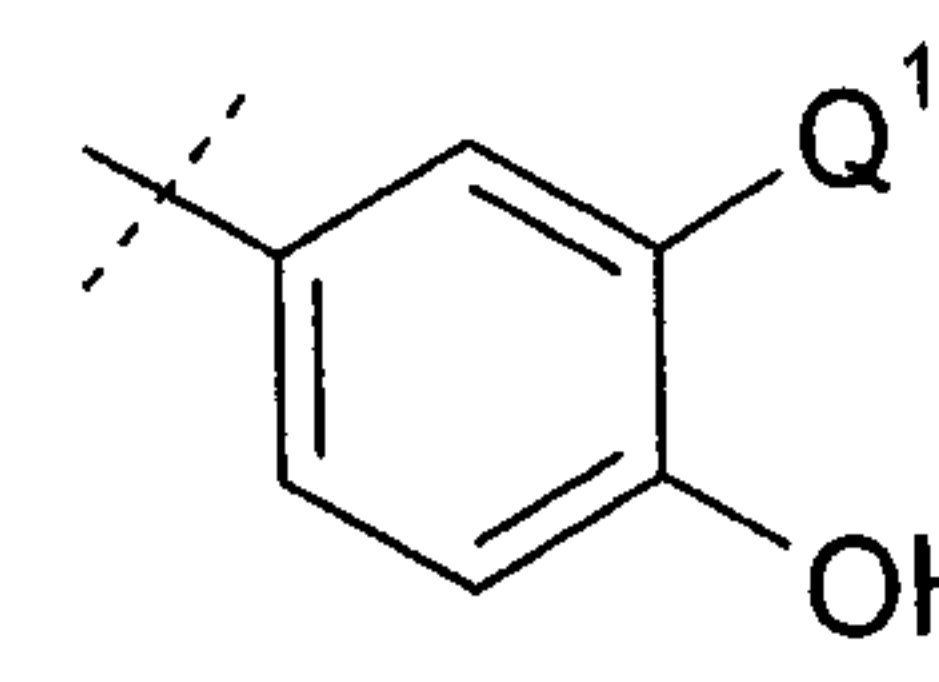
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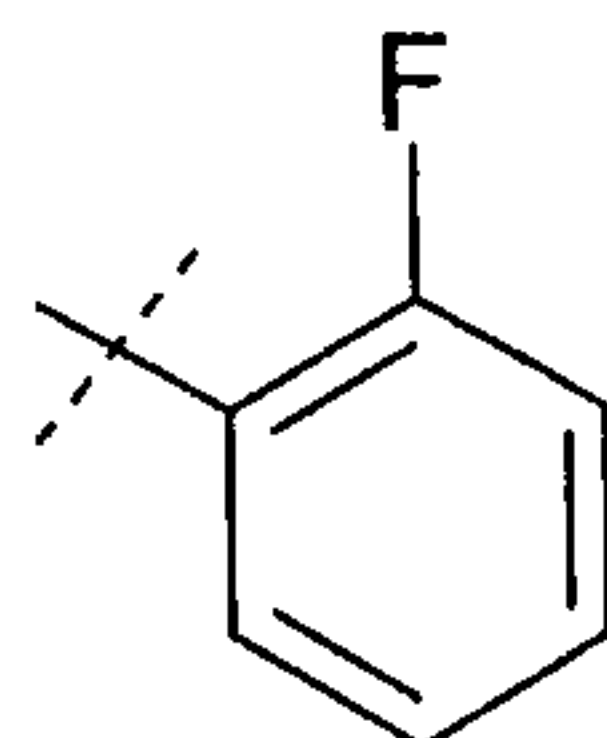
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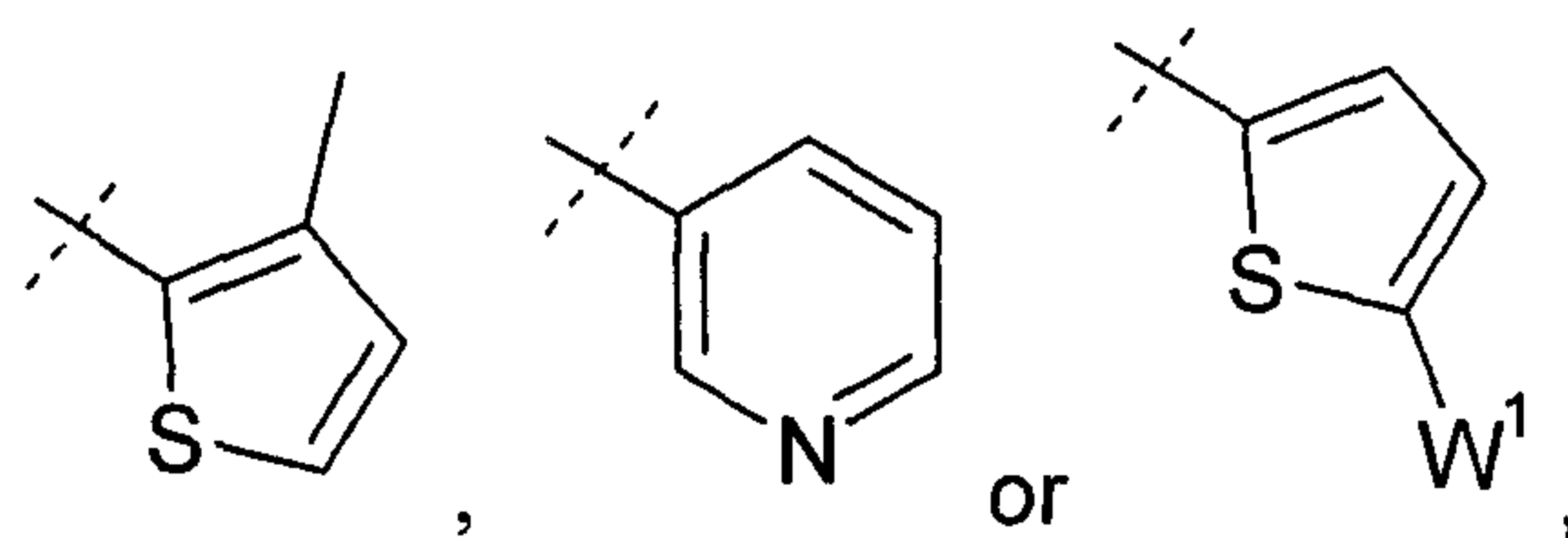


, in particular



35

where Q¹ stands for F, Cl, Br, or A, in particular ethyl or methyl,



where Q¹ and W¹ stand for Cl, Br, A, in particular methyl and ethyl, or SA, and in particular Smethyl and Sethyl, and in which R³ preferably denotes H or alkyl, in particular methyl. R² is preferably p- or m-hydroxyphenyl, and o, m or p-fluorophenyl.

10

Above and below, all radicals, such as, for example, the radicals R¹, R², R³, R⁴, R⁵, X, Q, Q¹, Y, Y¹, m, n, y, T, k, p, q, l and s, have the meanings indicated for the formula I unless expressly stated otherwise. If individual radicals occur more than once within a compound, the radicals adopt, independently of one another, the meanings indicated.

15

Y¹ preferably denotes COCH₂NMe₂.

20

Alkyl and is preferably unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. Alkyl preferably denotes methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl.

25

30

Alkyl very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl. Alkyl also denotes cycloalkyl.

35

Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

R^1 preferably denotes A, SR^5 , OR^5 , Hal, CN, NO_2 , $N(R^5)_2$. In particular, R^1 denotes methyl, ethyl, isopropyl, tert-butyl, F, Cl, CN, or OH.

5

R^2 preferably denotes H, A, such as, for example, ethyl, phenyl, methyl, aryl or Het. In particular, R^2 denotes A or Ar.

W preferably denotes S.

10

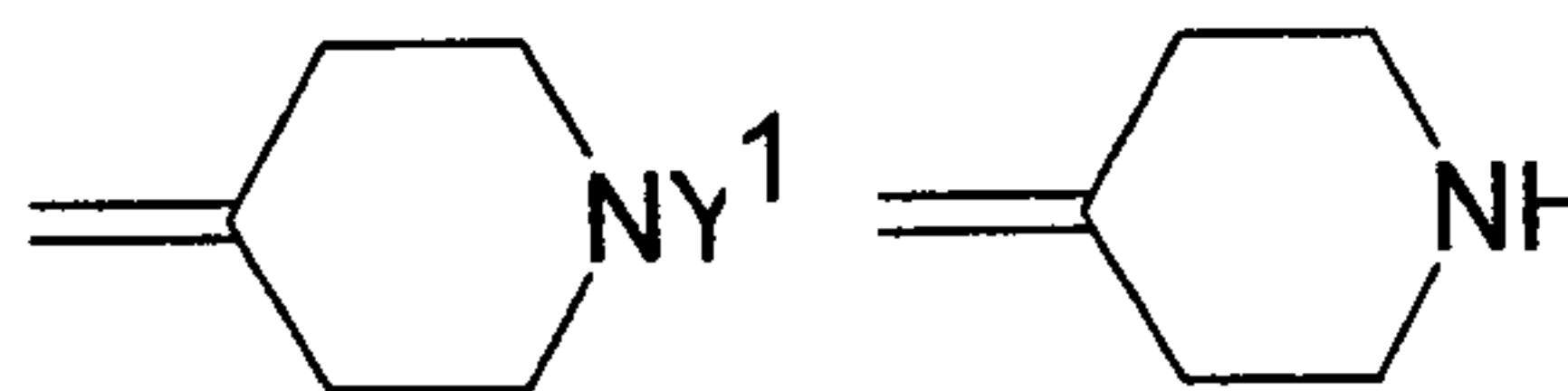
R^3 preferably denotes H, A, Ar or $-(C(R^5)_2)_oAr$. In particular, R^3 denotes H or A.

In particularly preferred compounds of the formula I, R^2 denotes Ar and R^3 simultaneously denotes A.

15

R^4 preferably denotes $cyclo[-C(CH_2)_k(NY^1)-(CH_2)_p-]$, or E or Z

$=CH(CH_2)_nX(CH_2)_lQ(CH_2)_sT$, in particular,

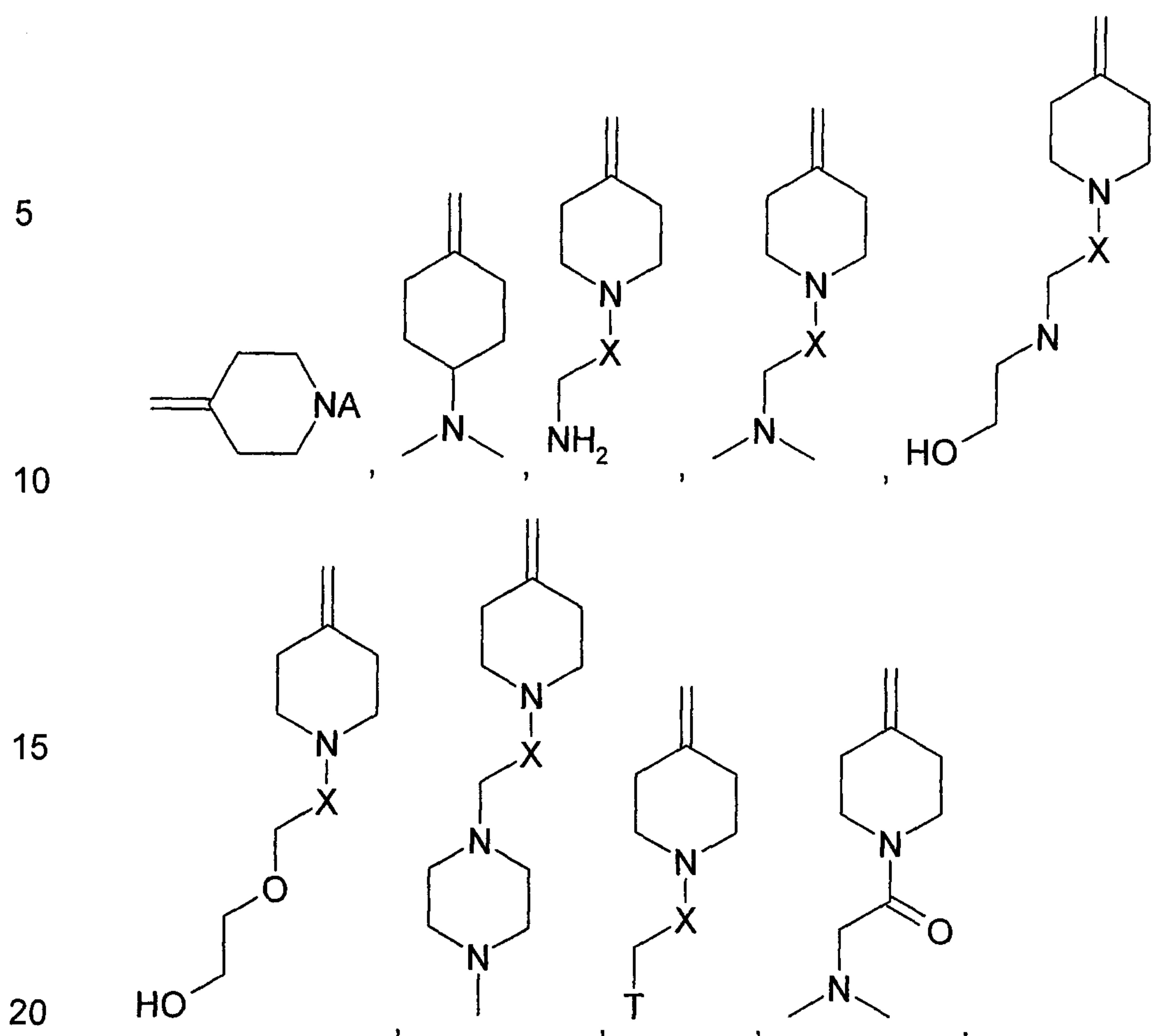


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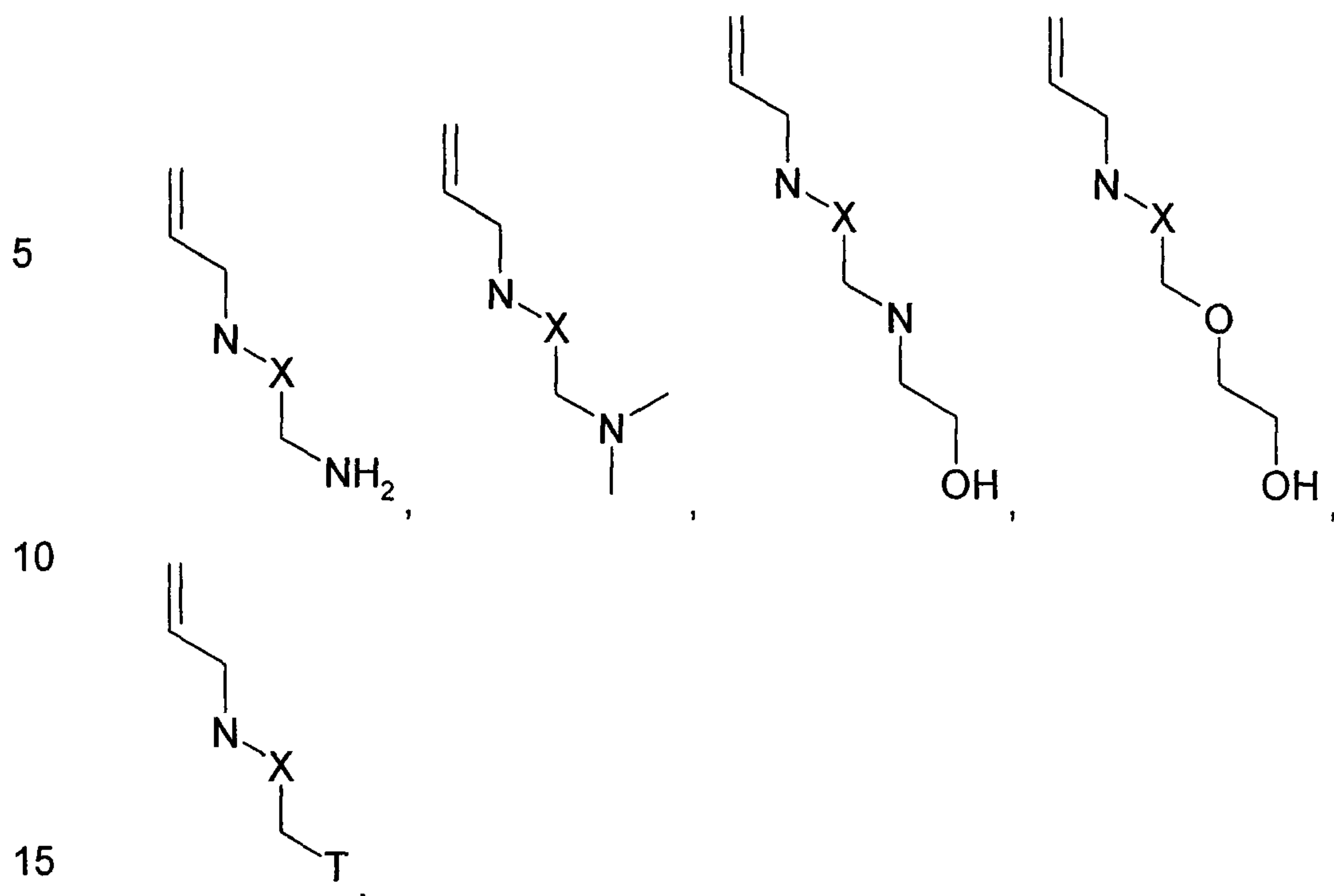
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- 19 -



in which X, n, l, Q, s and T have the meaning indicated above.

Essentially diastereomerically pure compounds of the formula I, i.e. pure E or Z diastereomers, are preferred.

Ar preferably denotes phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitro-

phenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Het preferably denotes a mono- or bicyclic aromatic or saturated heterocycle having one or more N, O and/or S atoms which may be unsubstituted or mono-, di- or trisubstituted by Hal, methyl, NO₂, NHA, NA₂, OA, COOA or CN. Aromatic groups Het are preferred.

Irrespective of further substitutions, Het denotes unsubstituted heteroaryl. This is, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-

benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

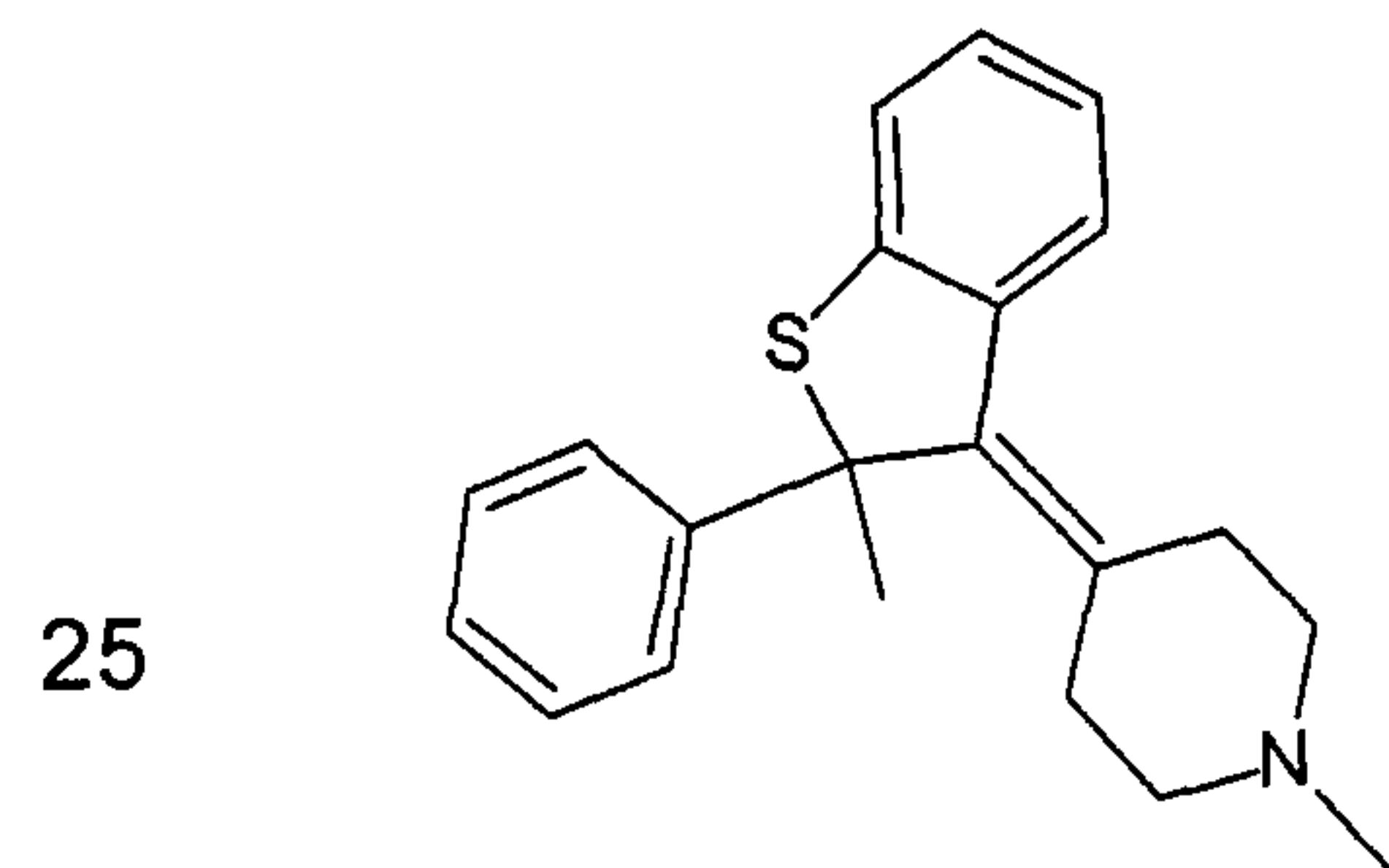
5 Hal preferably denotes F, Cl or Br, but also I, particularly preferably F or Cl.

Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

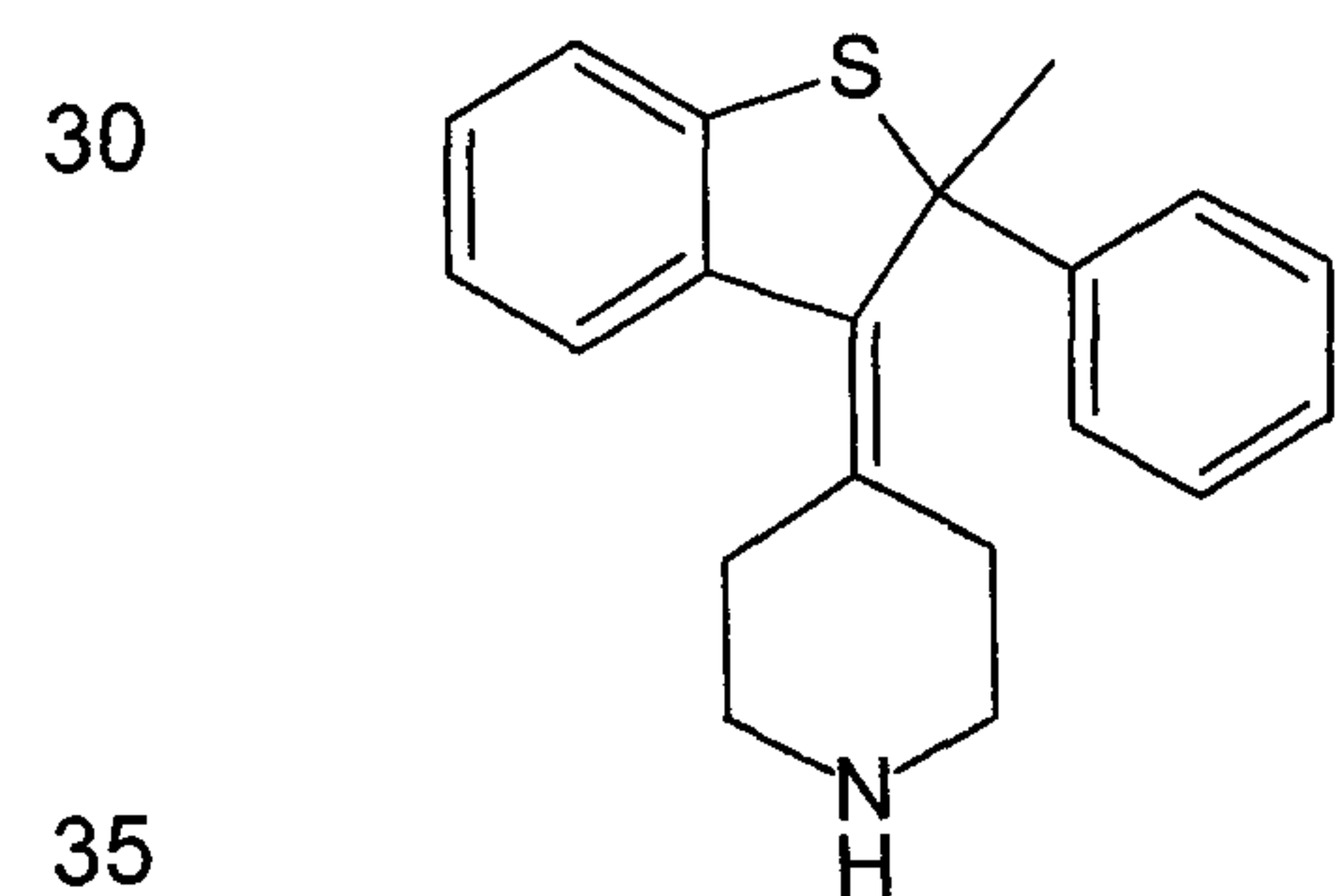
10 The compounds of the formula I may have one or more chiral centres and therefore exist in various stereoisomeric forms. The formula I encompasses all these forms.

Accordingly, the invention relates, in particular, to the compounds of the
15 formula I in which at least one of the said radicals has one of the preferred meanings indicated above.

Some preferred groups of compounds may be expressed by the following
20 sub-formulae I1 to I64:



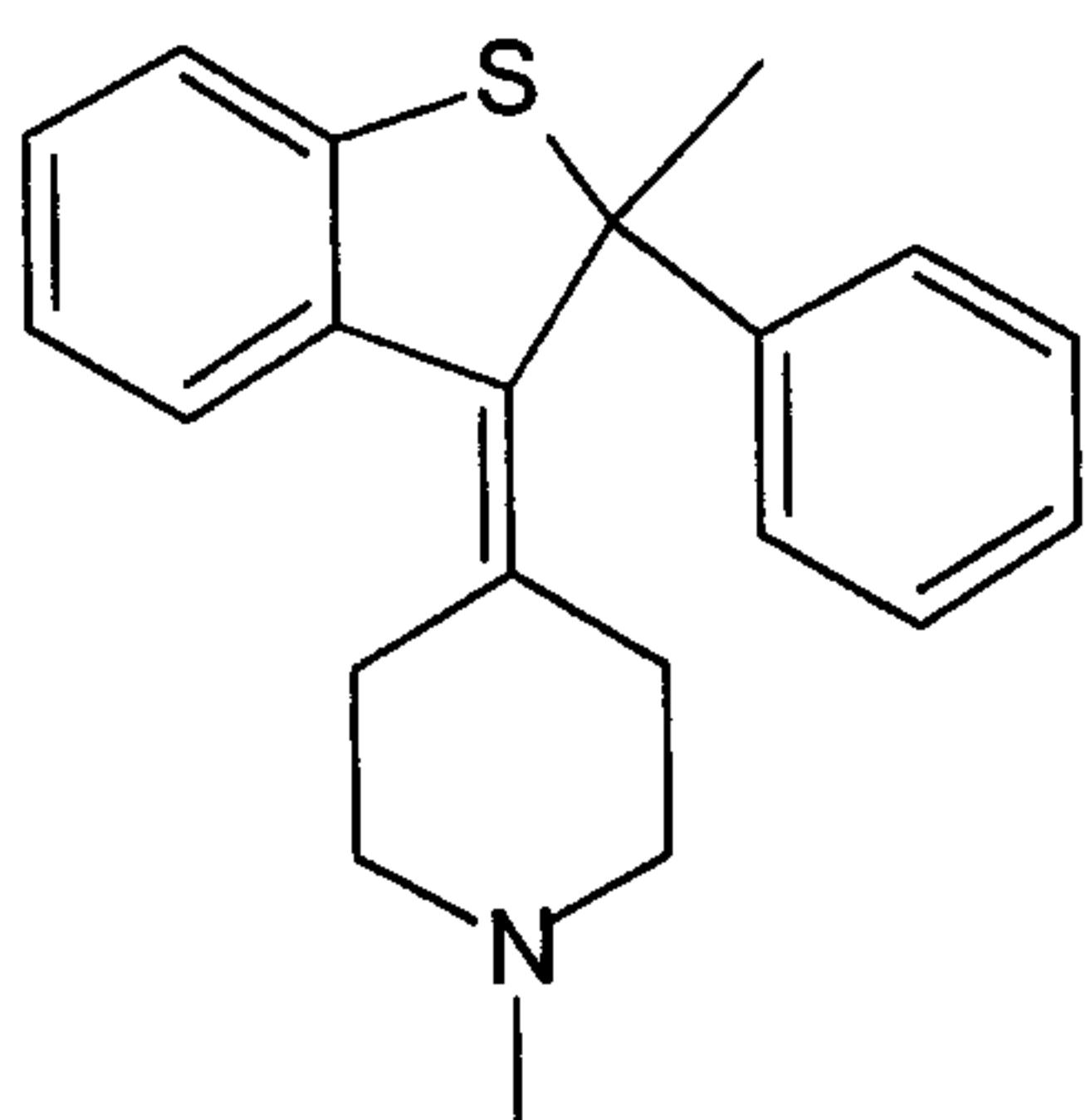
I1



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I2

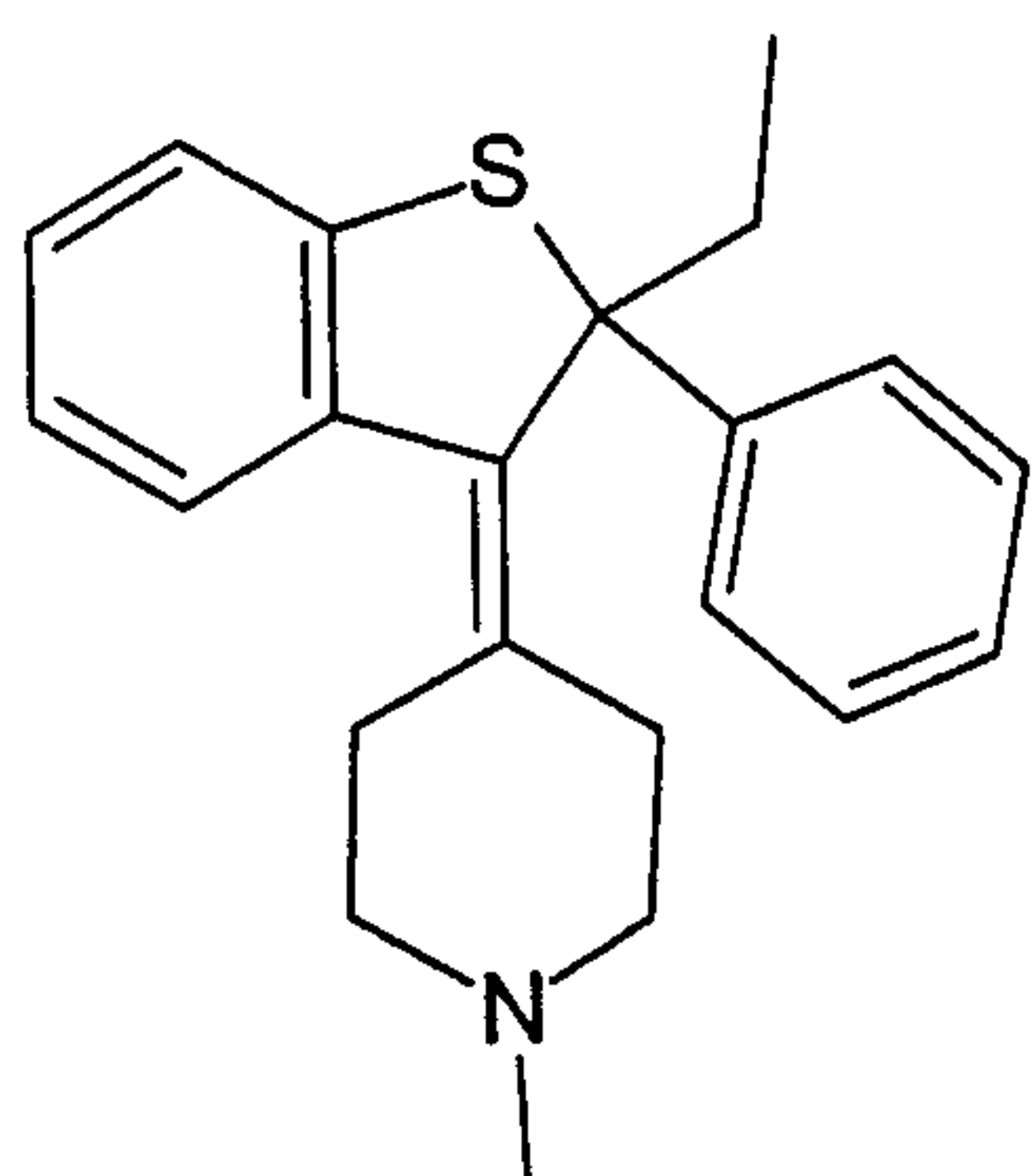
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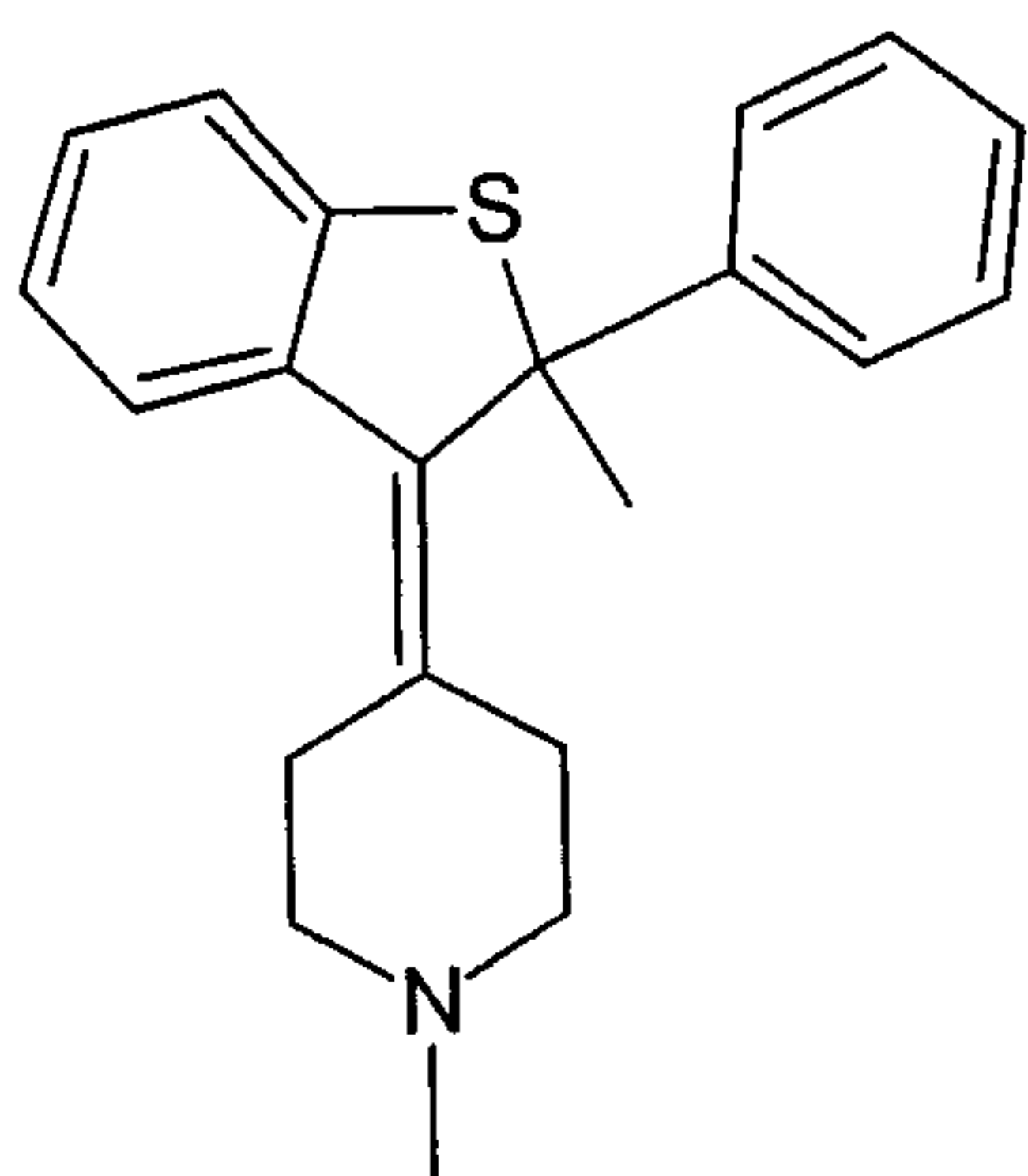
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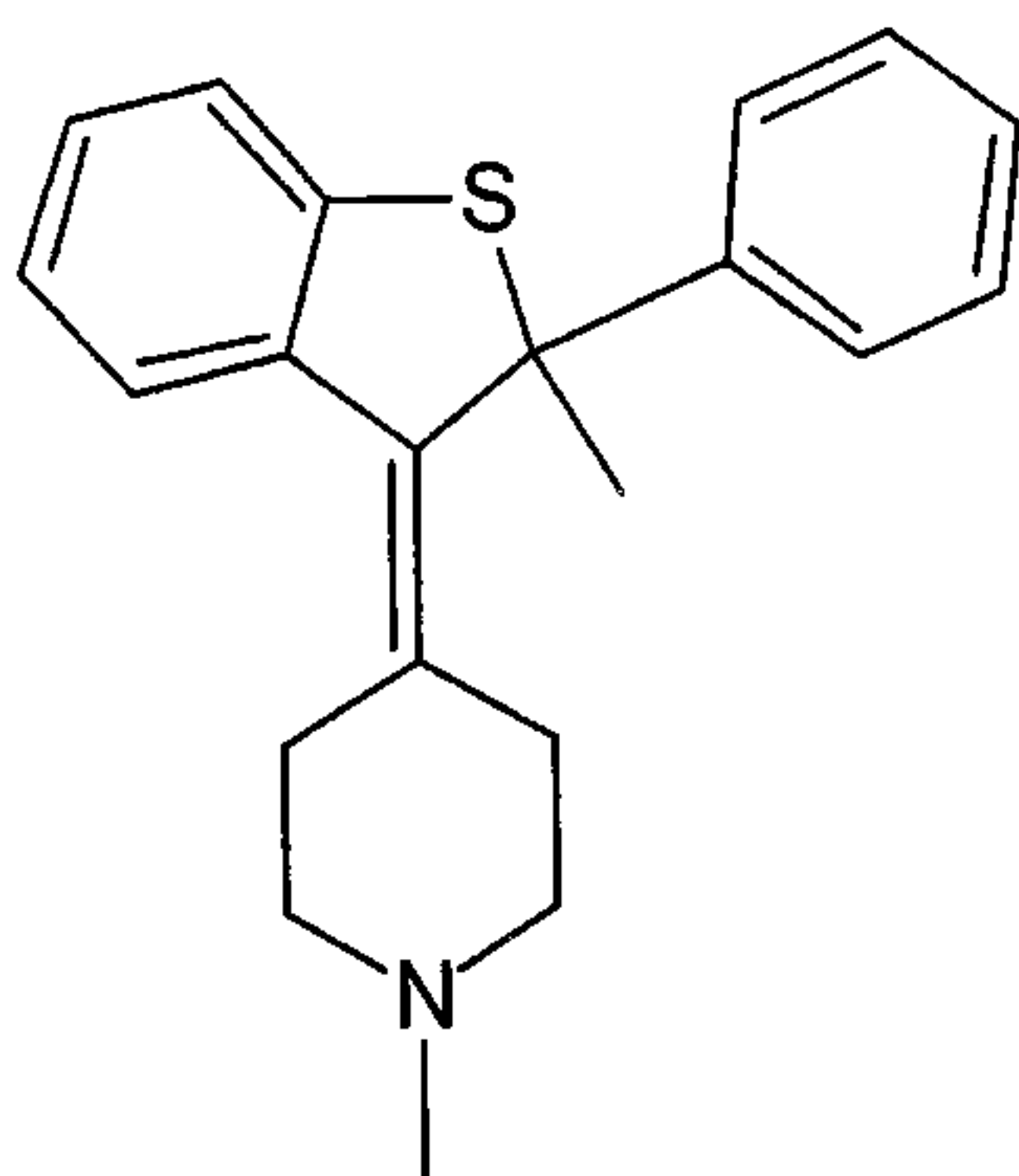


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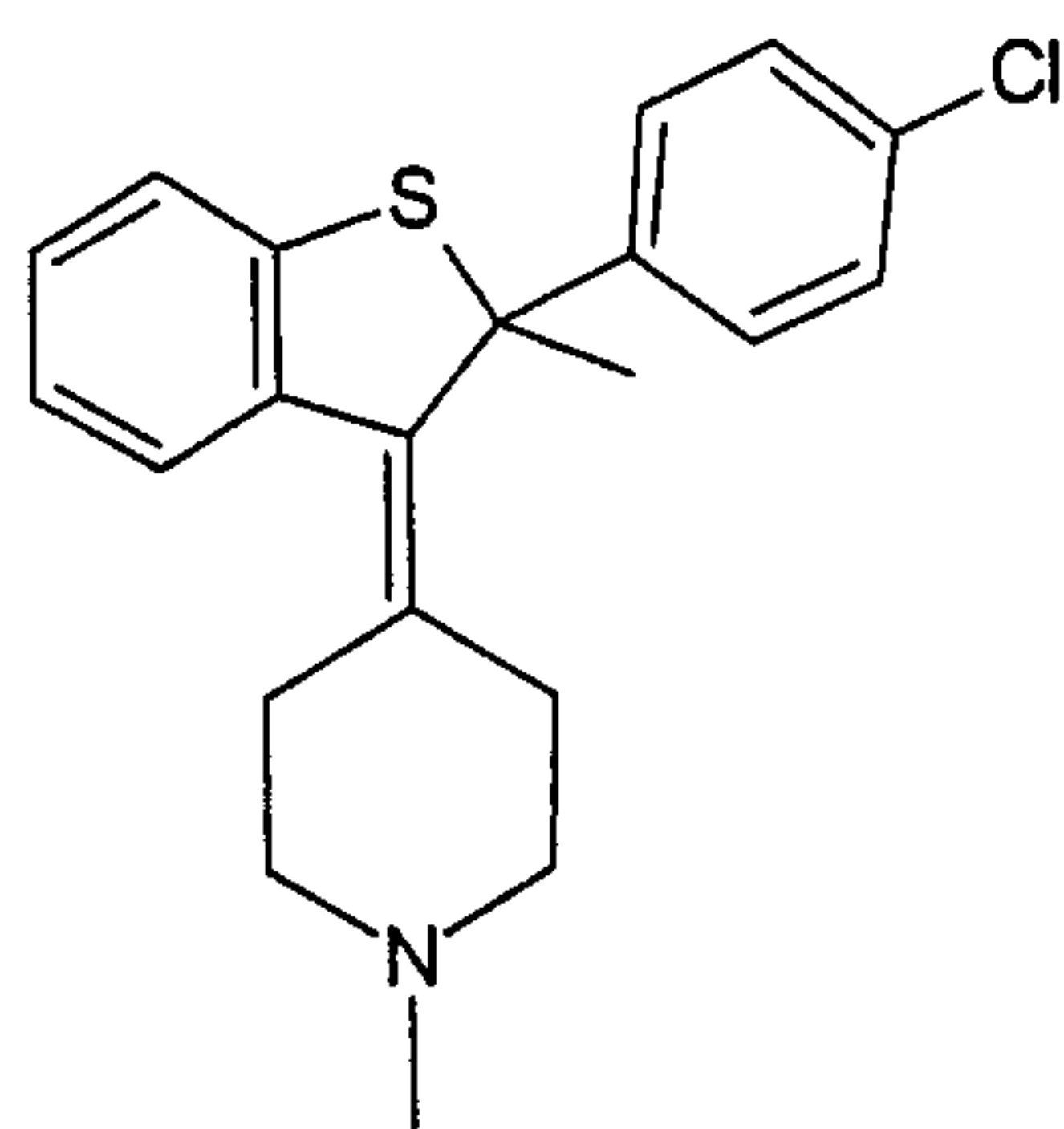
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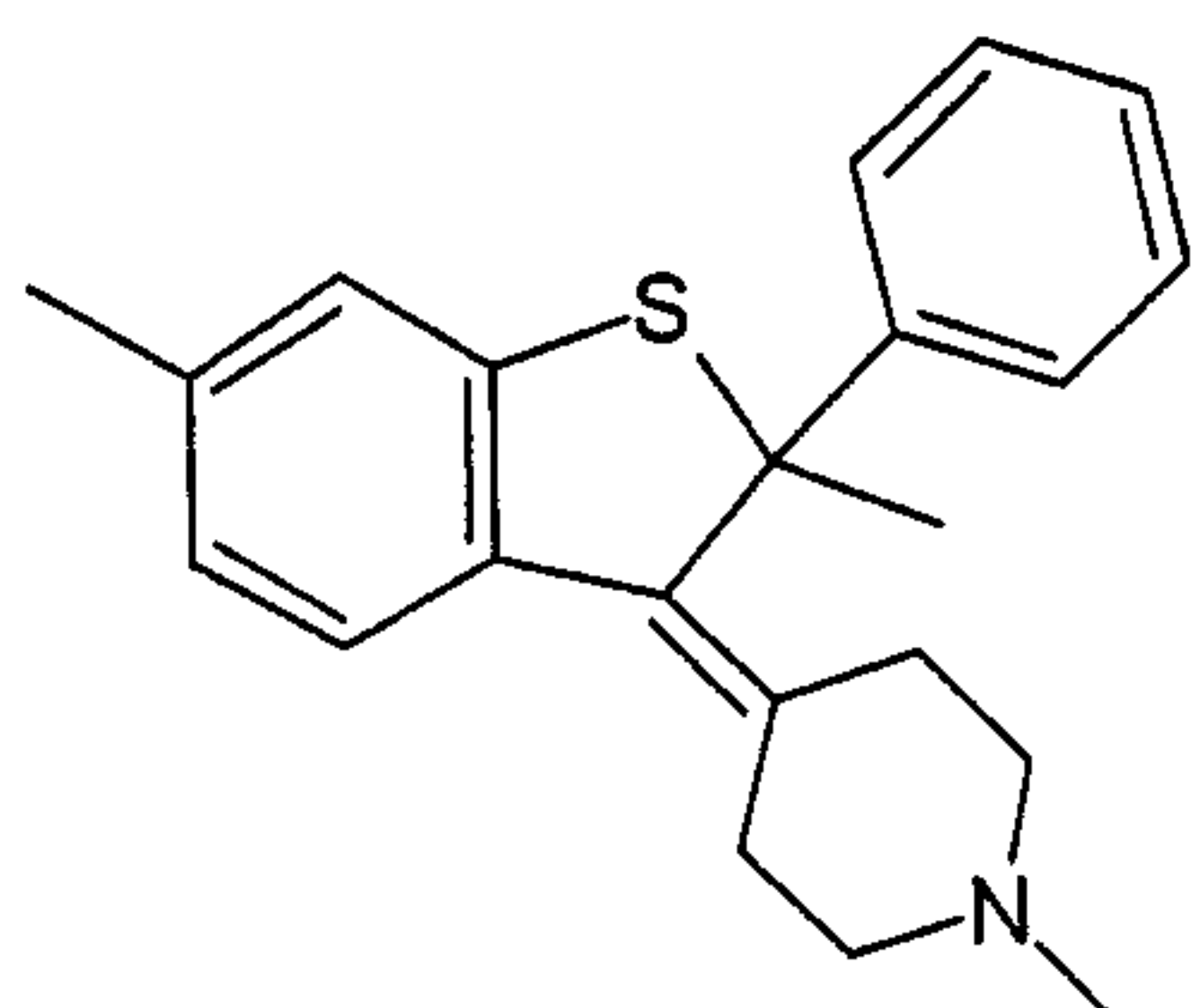
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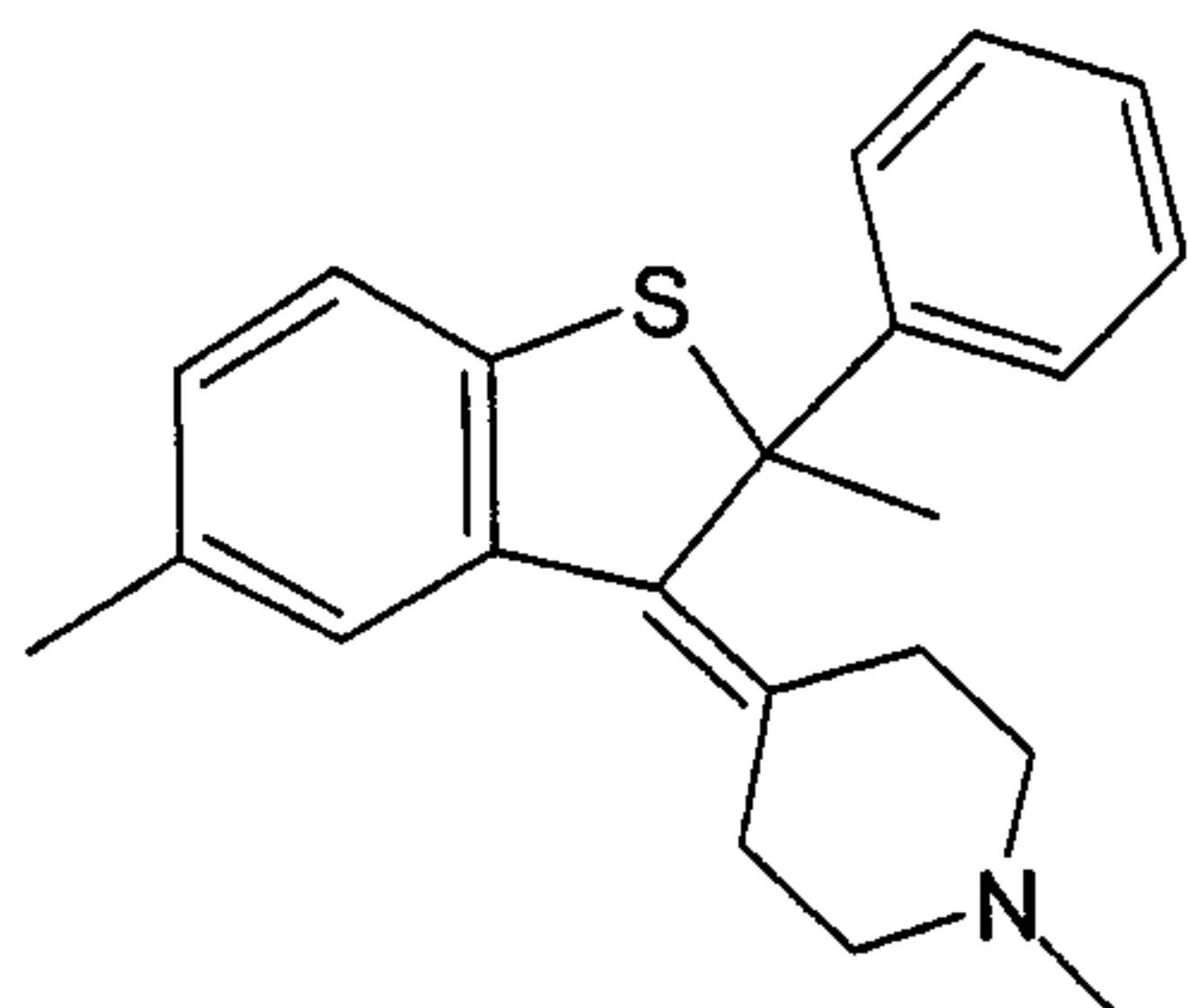
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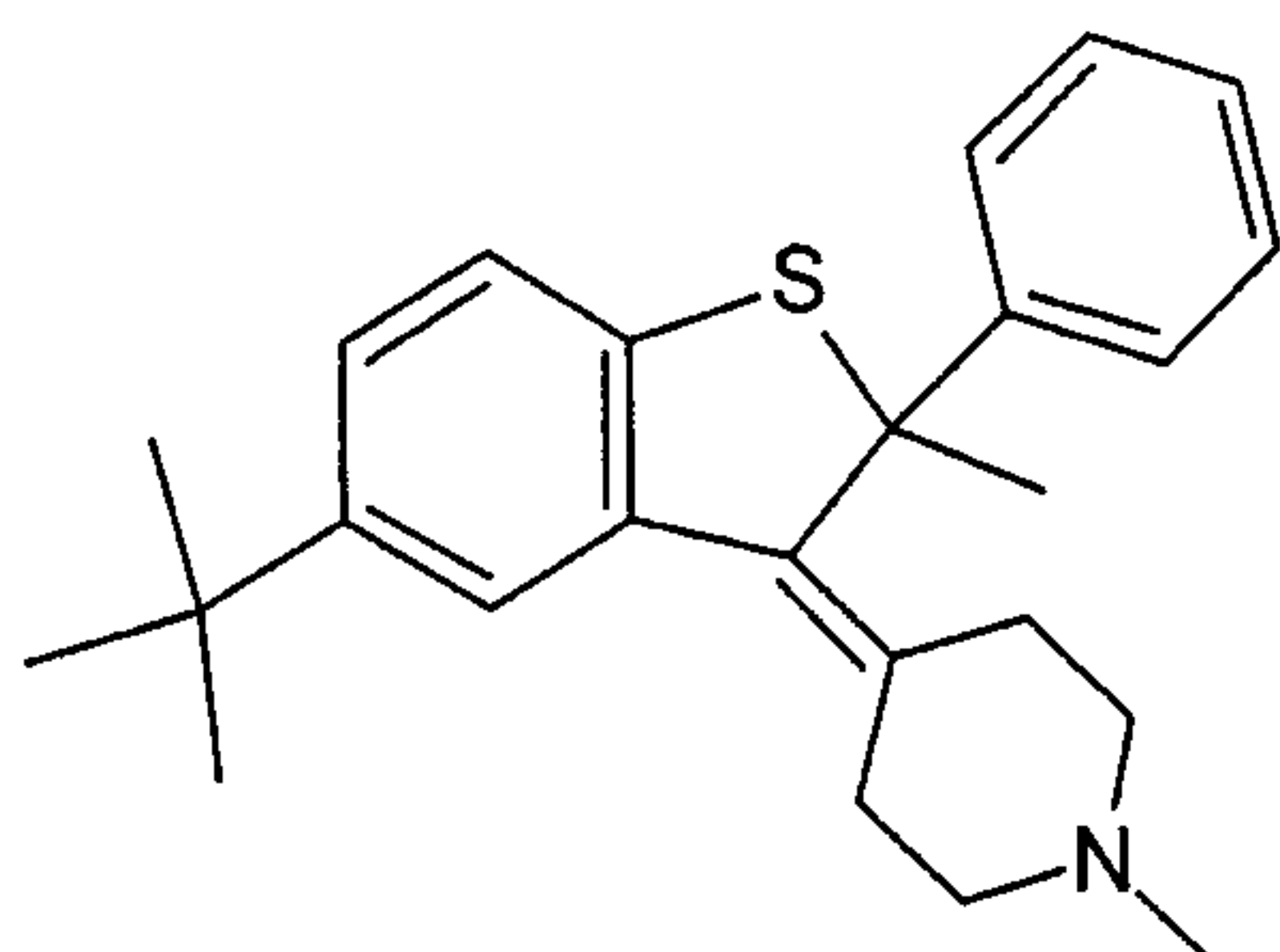


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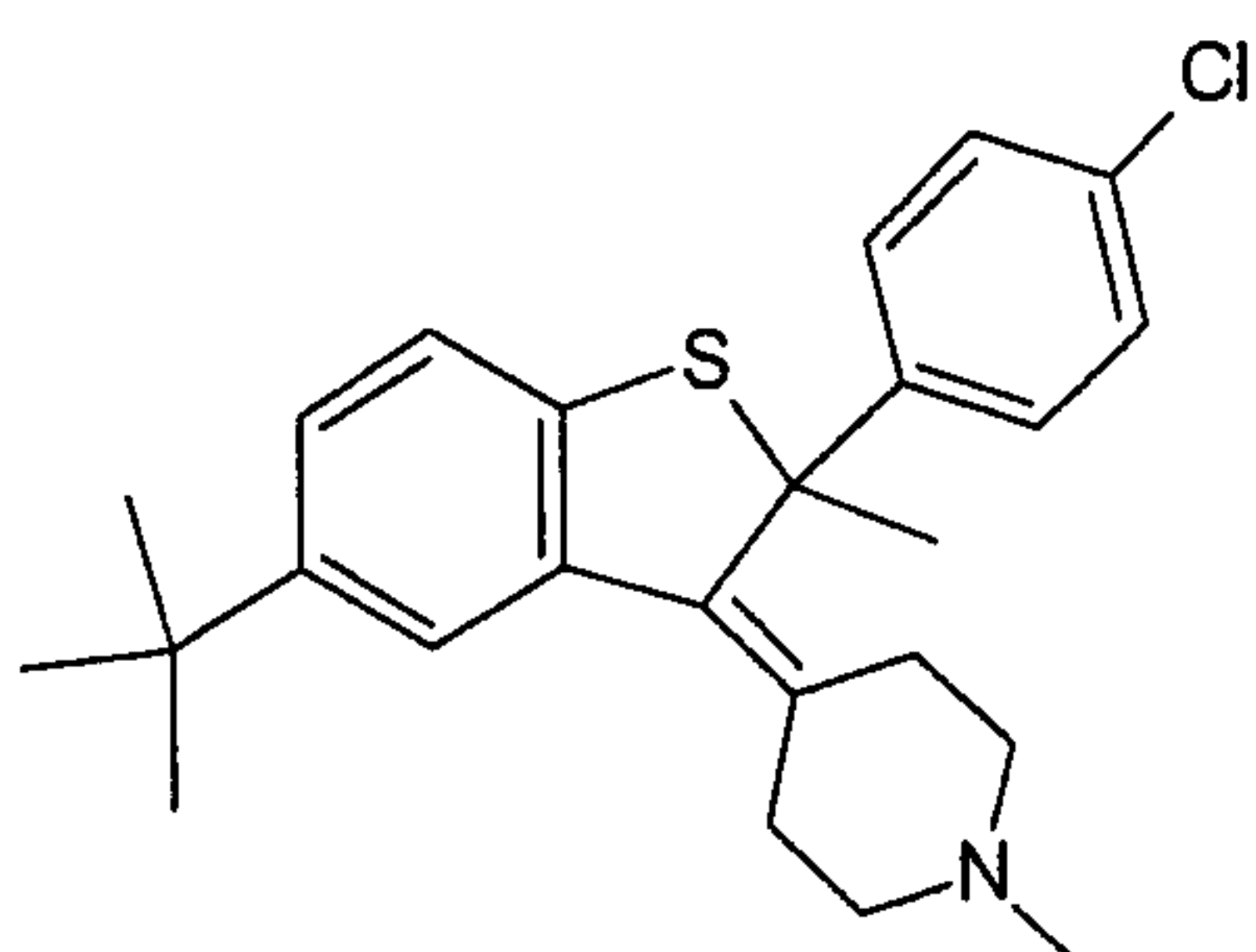
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I10

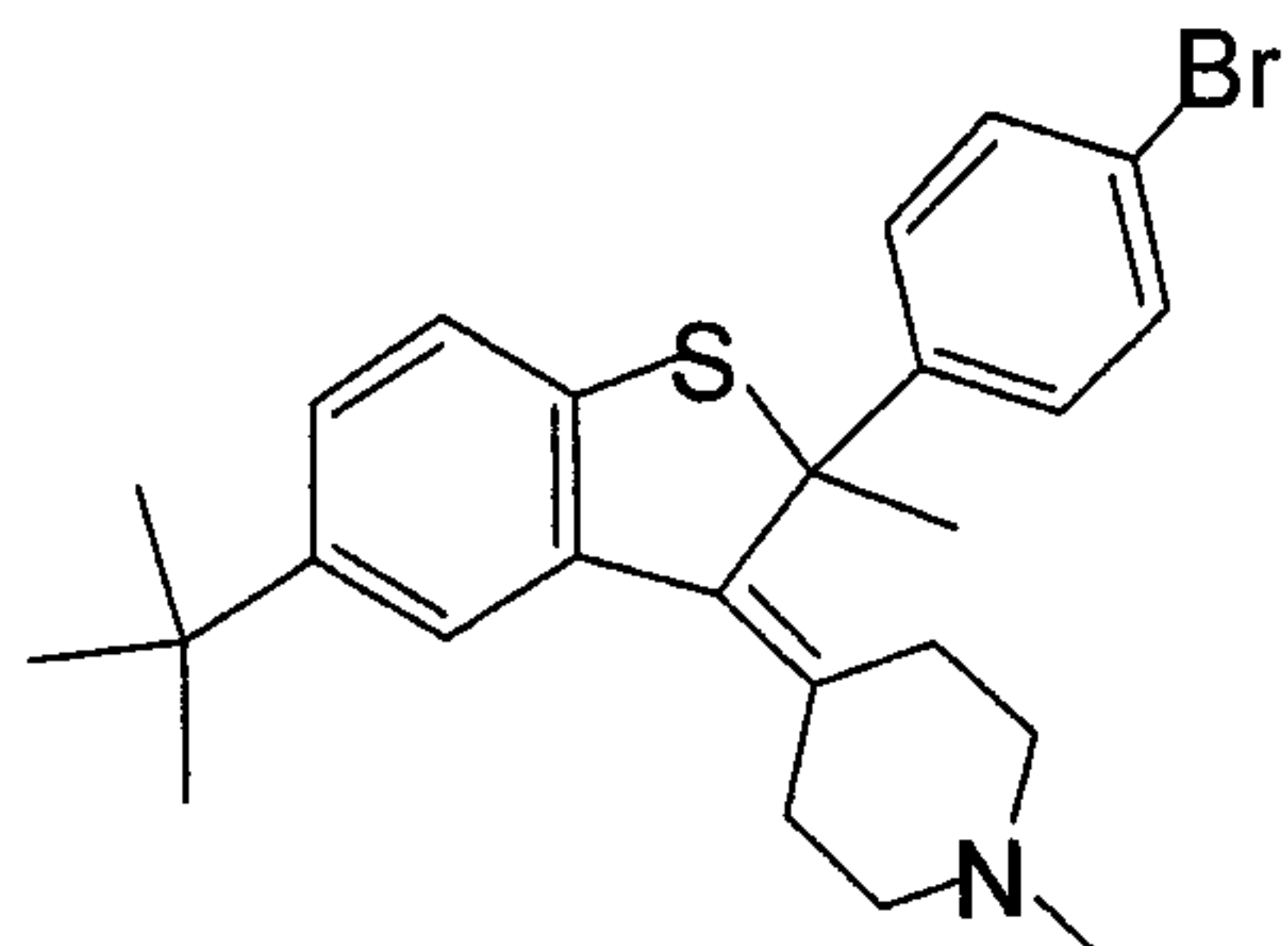
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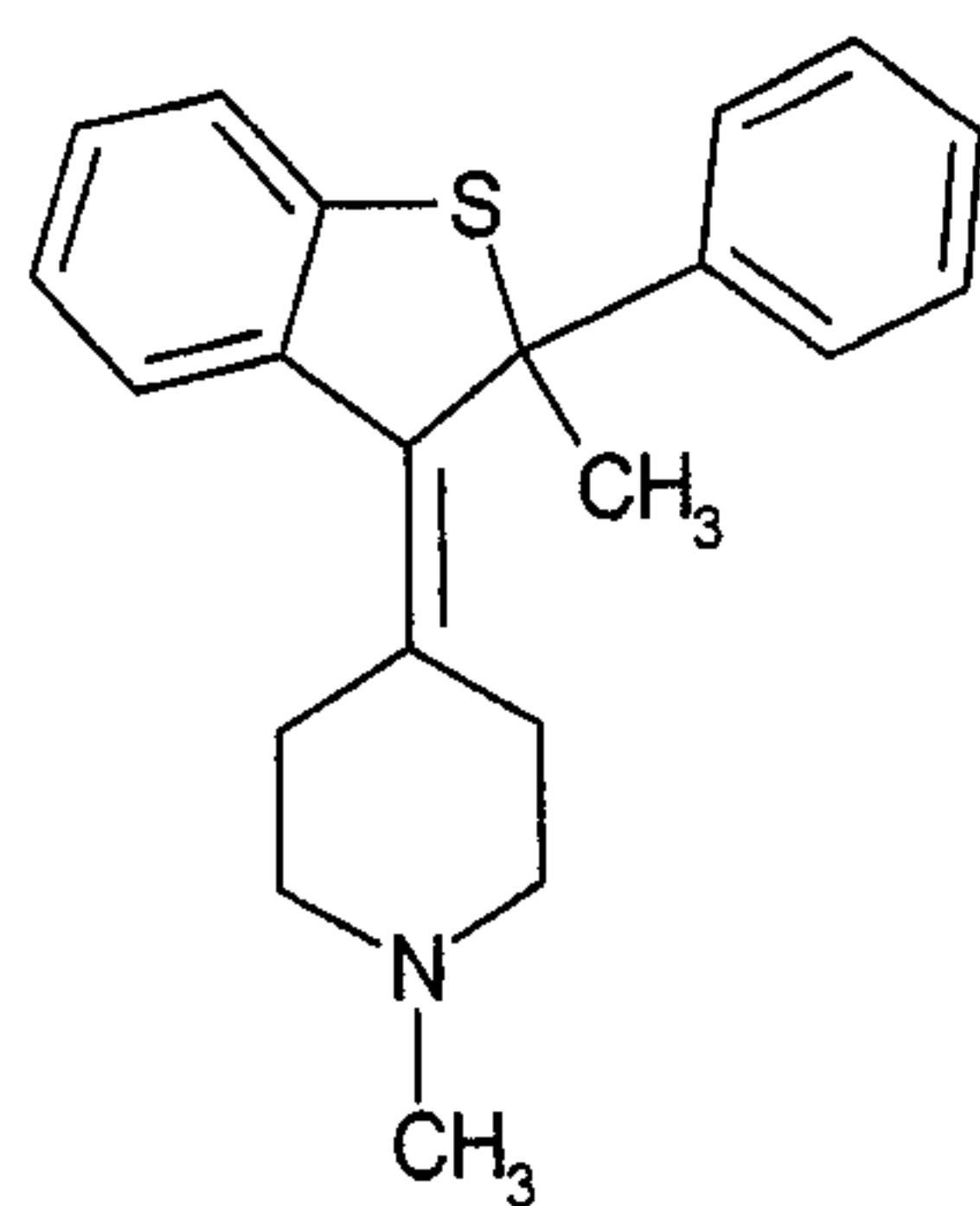
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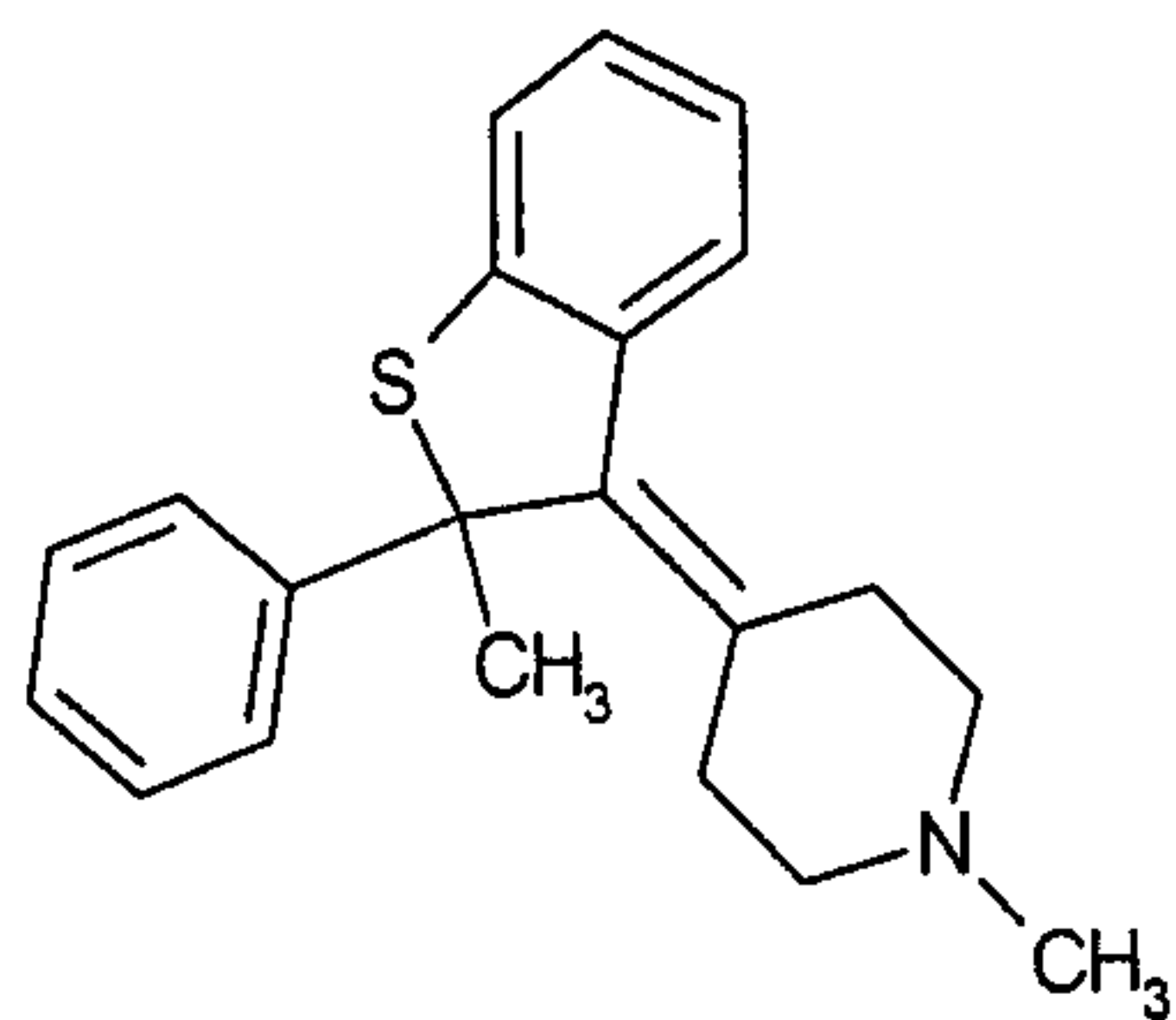
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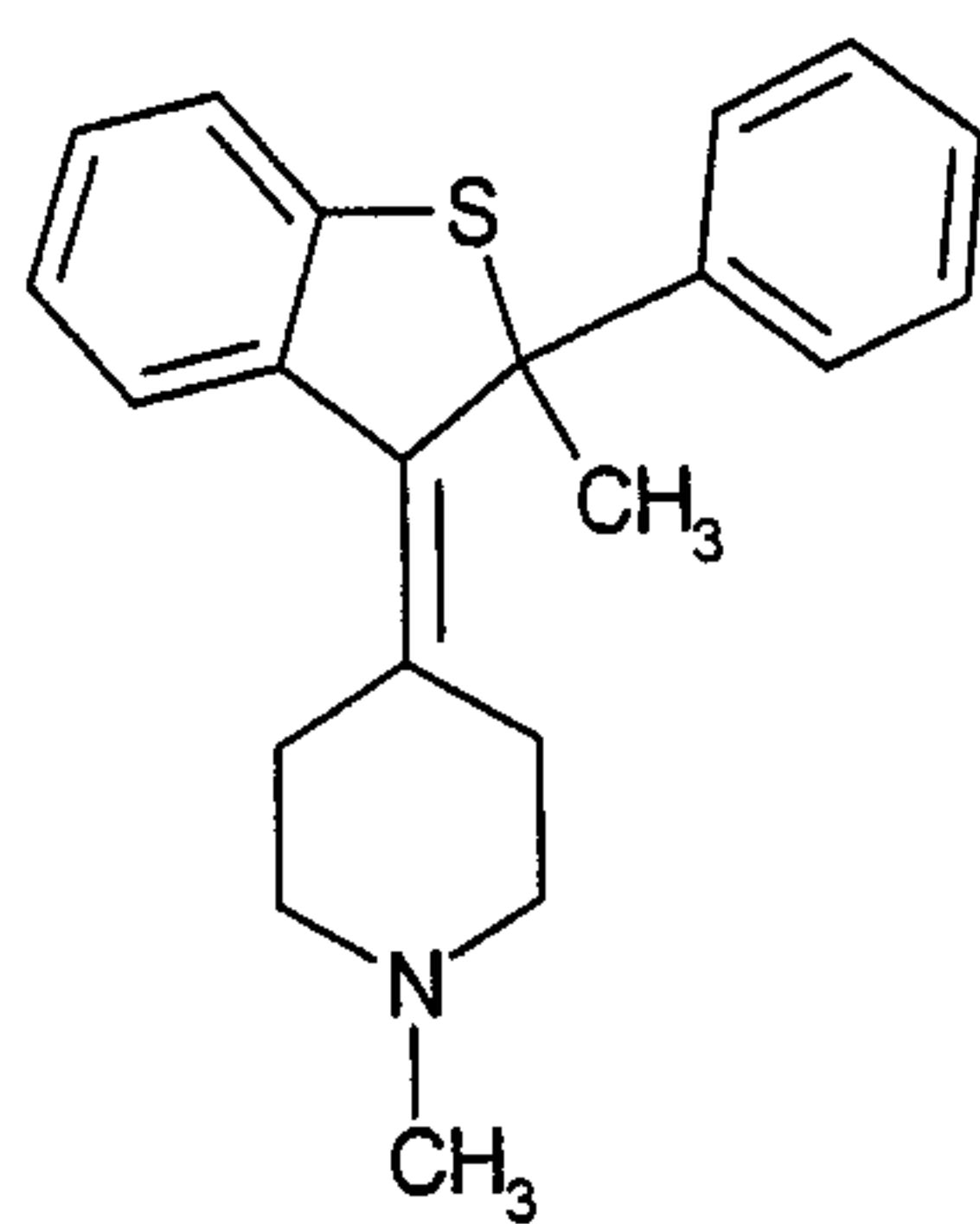
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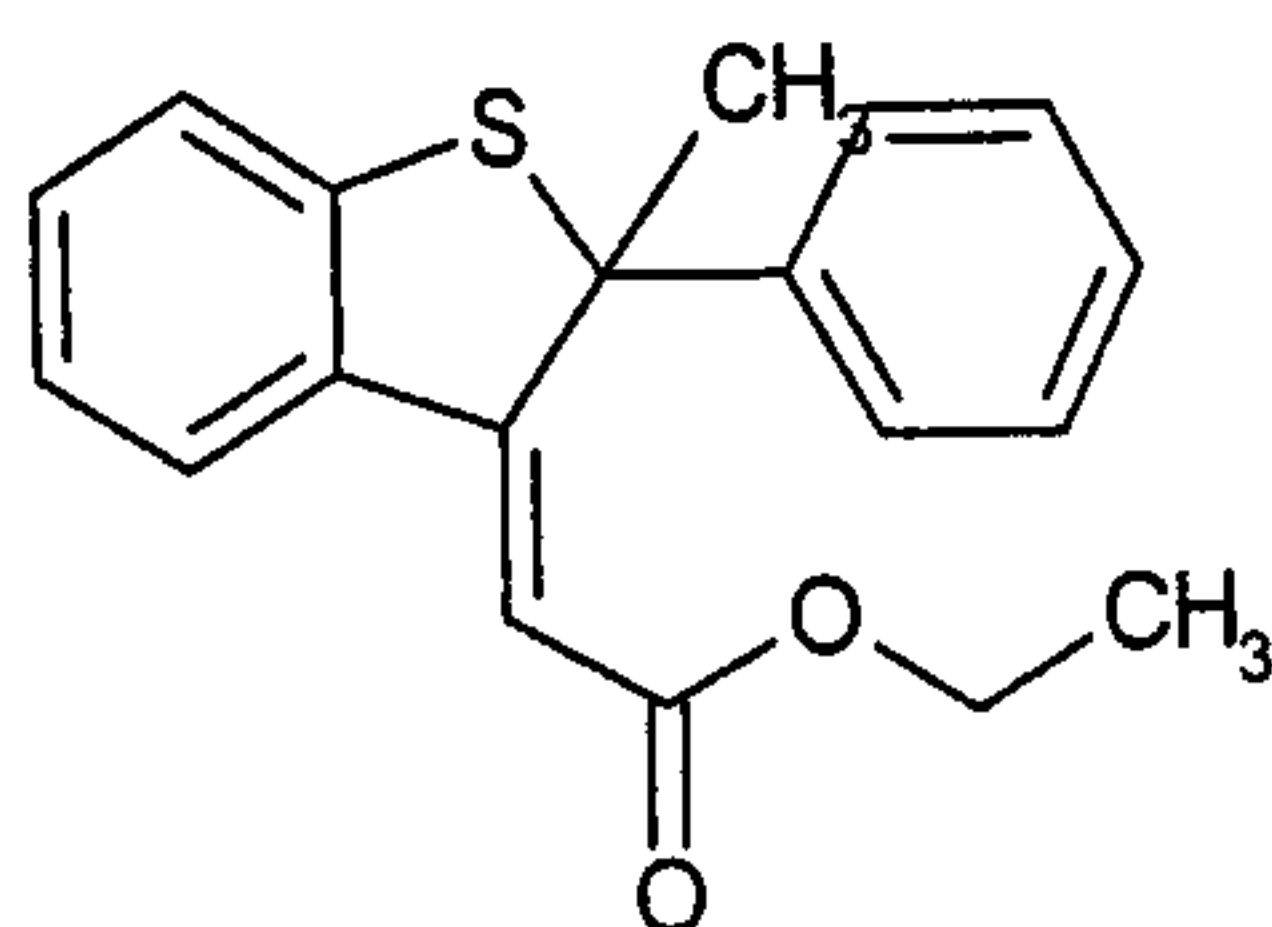
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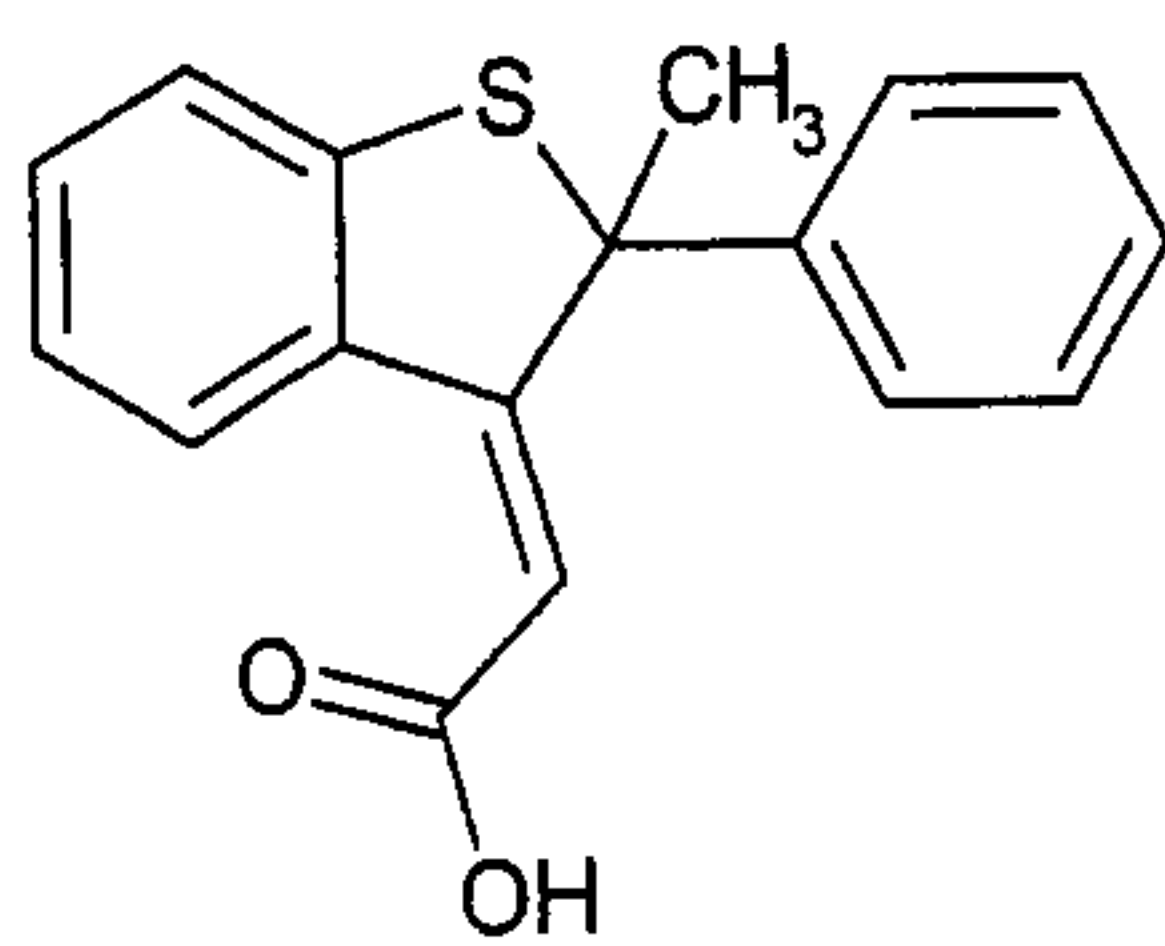
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I16

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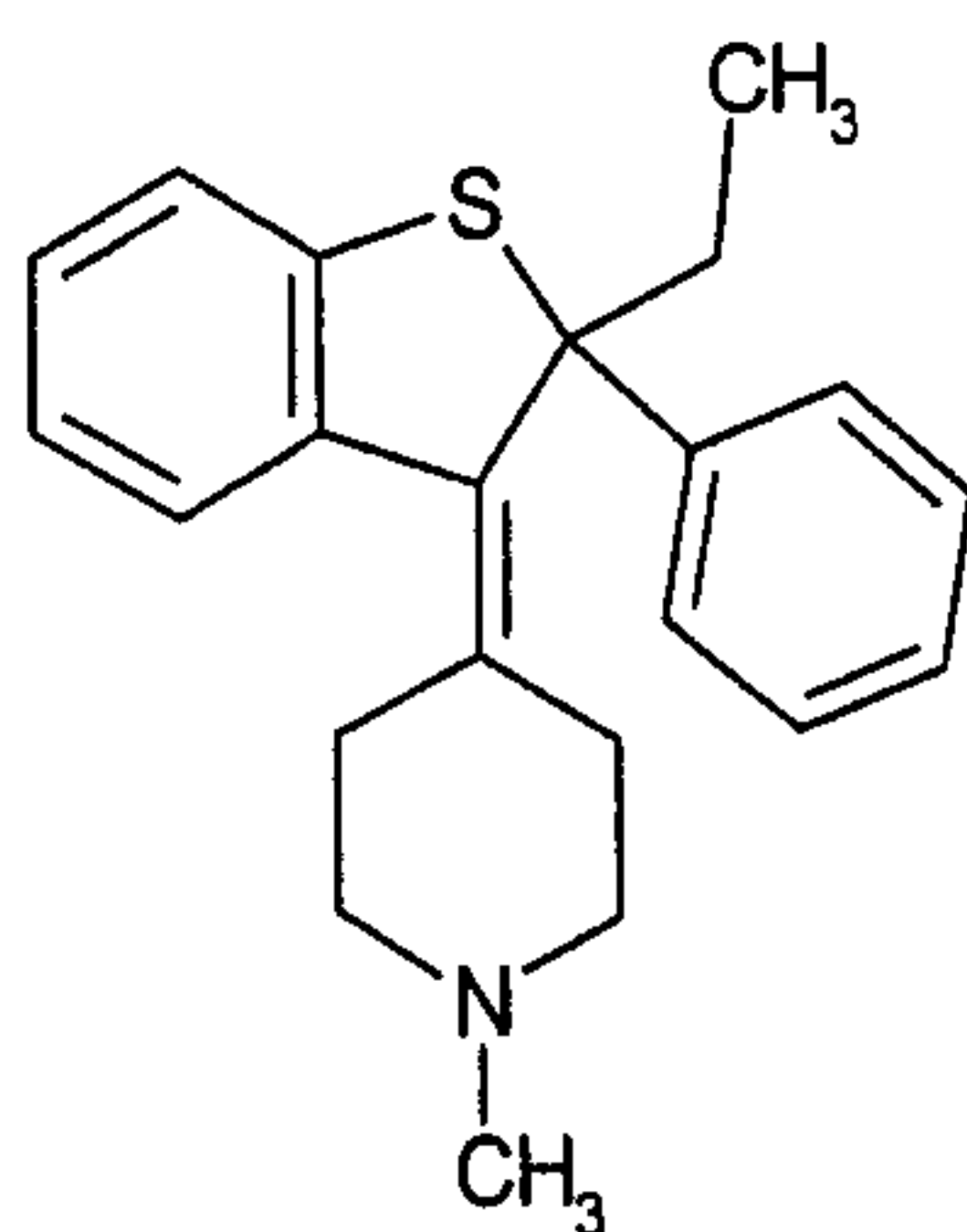
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I17

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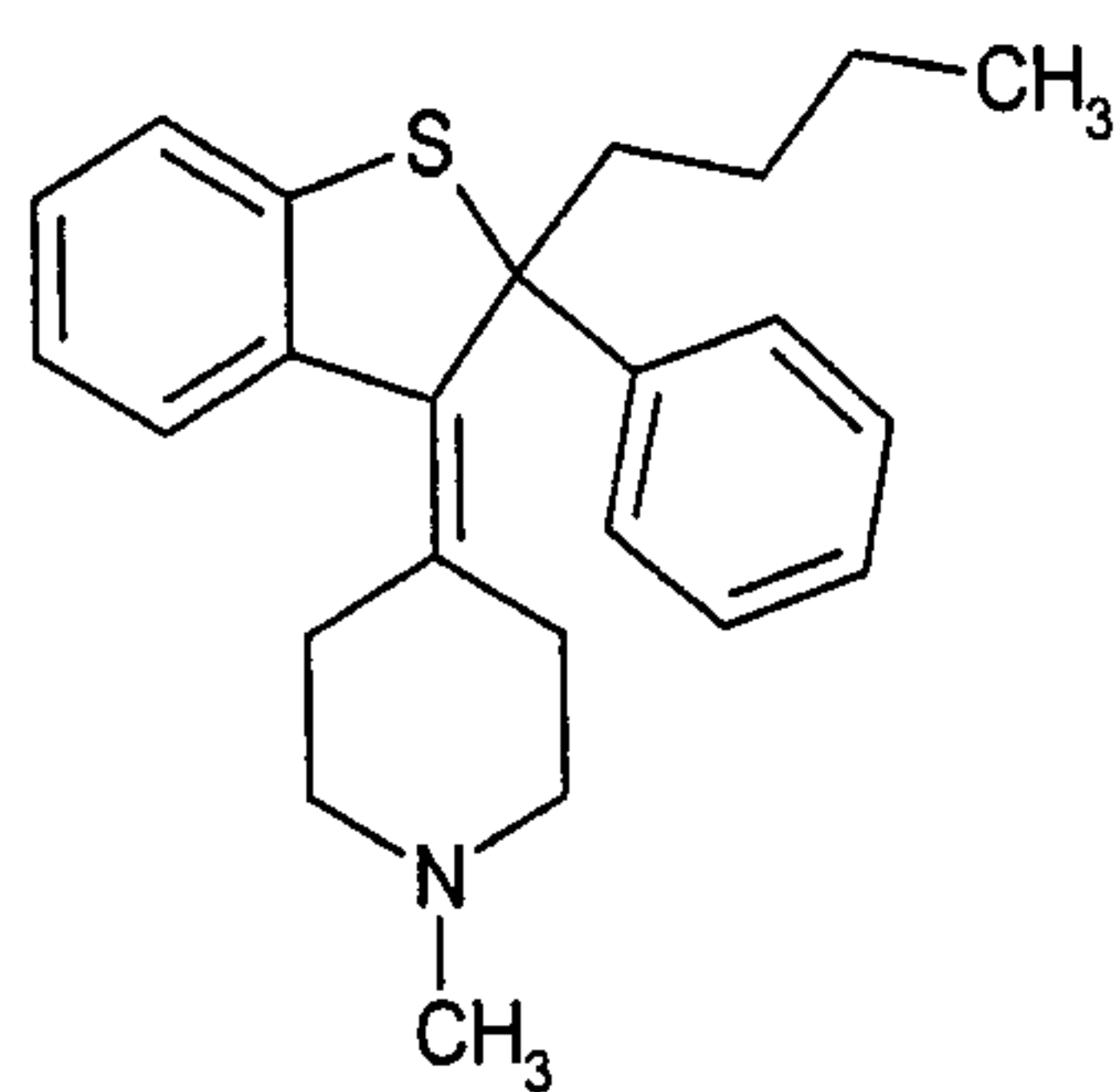
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I18

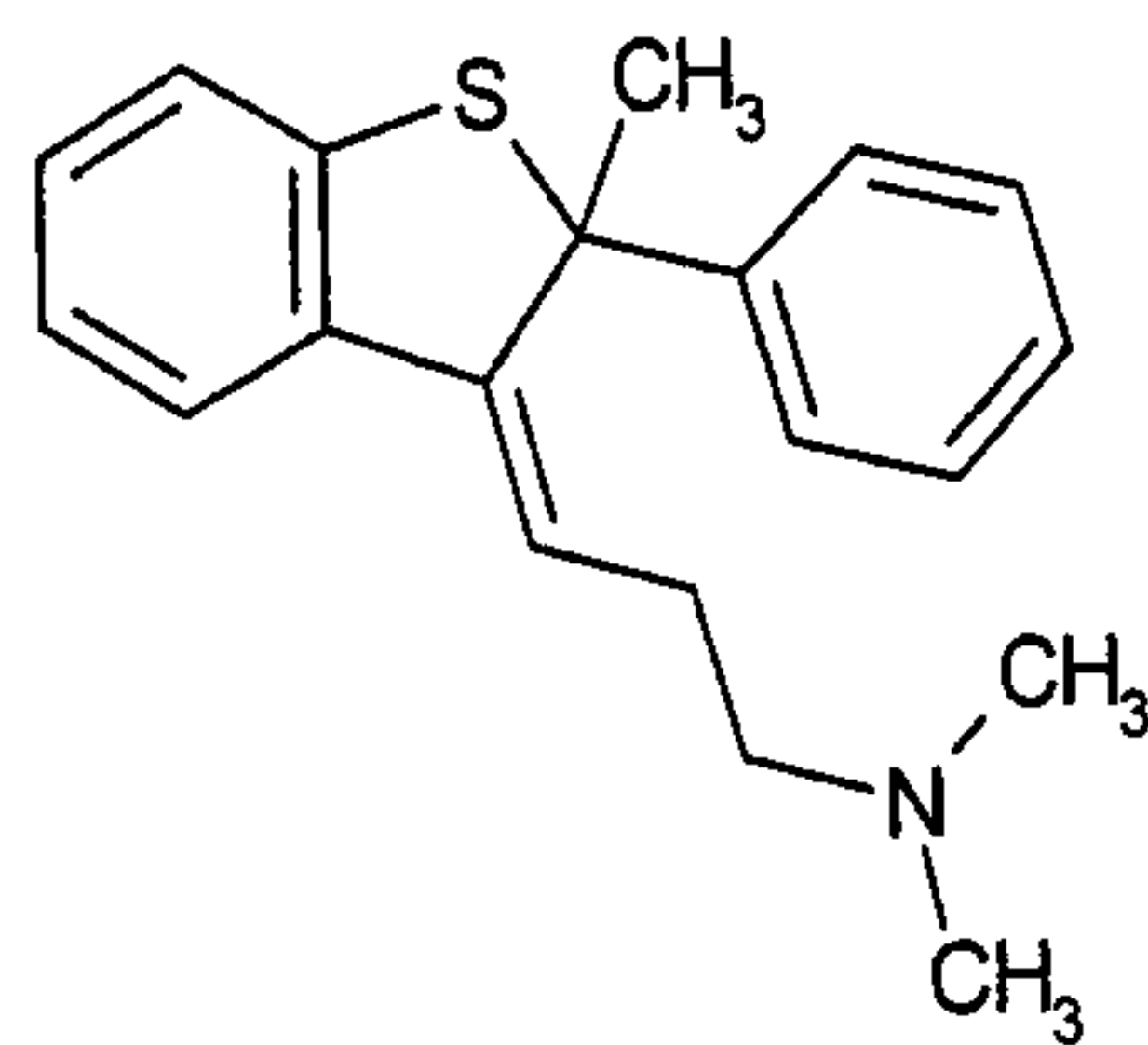
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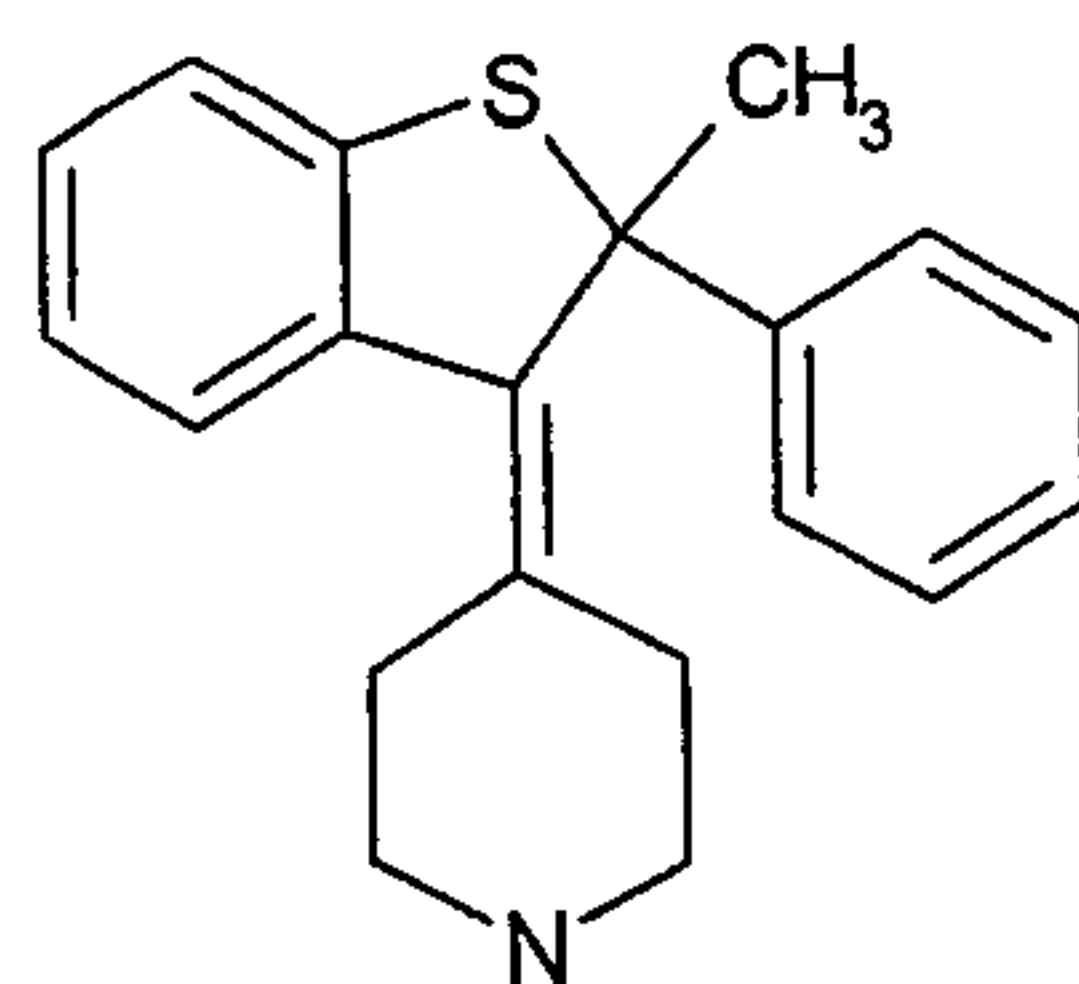
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I20

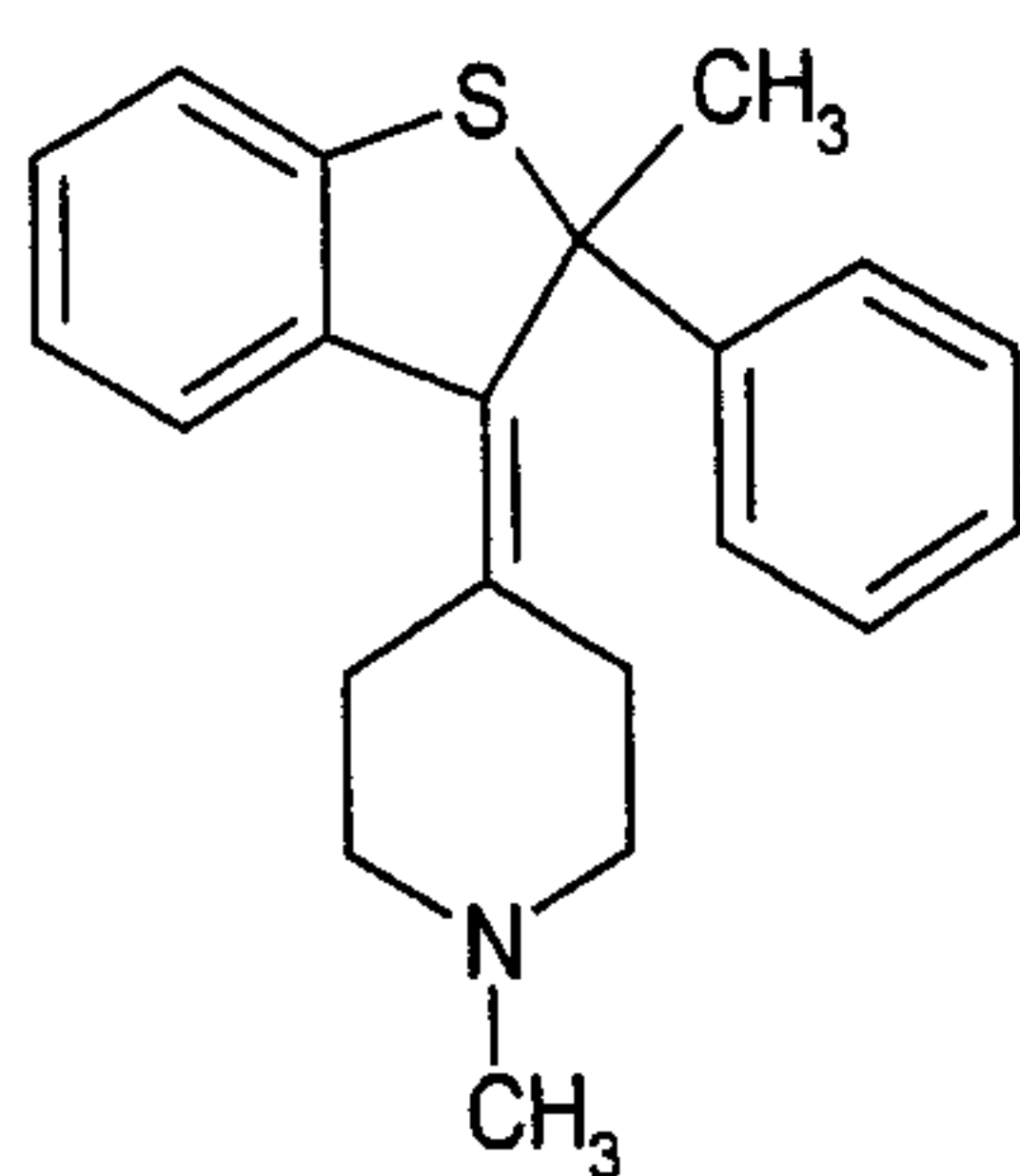
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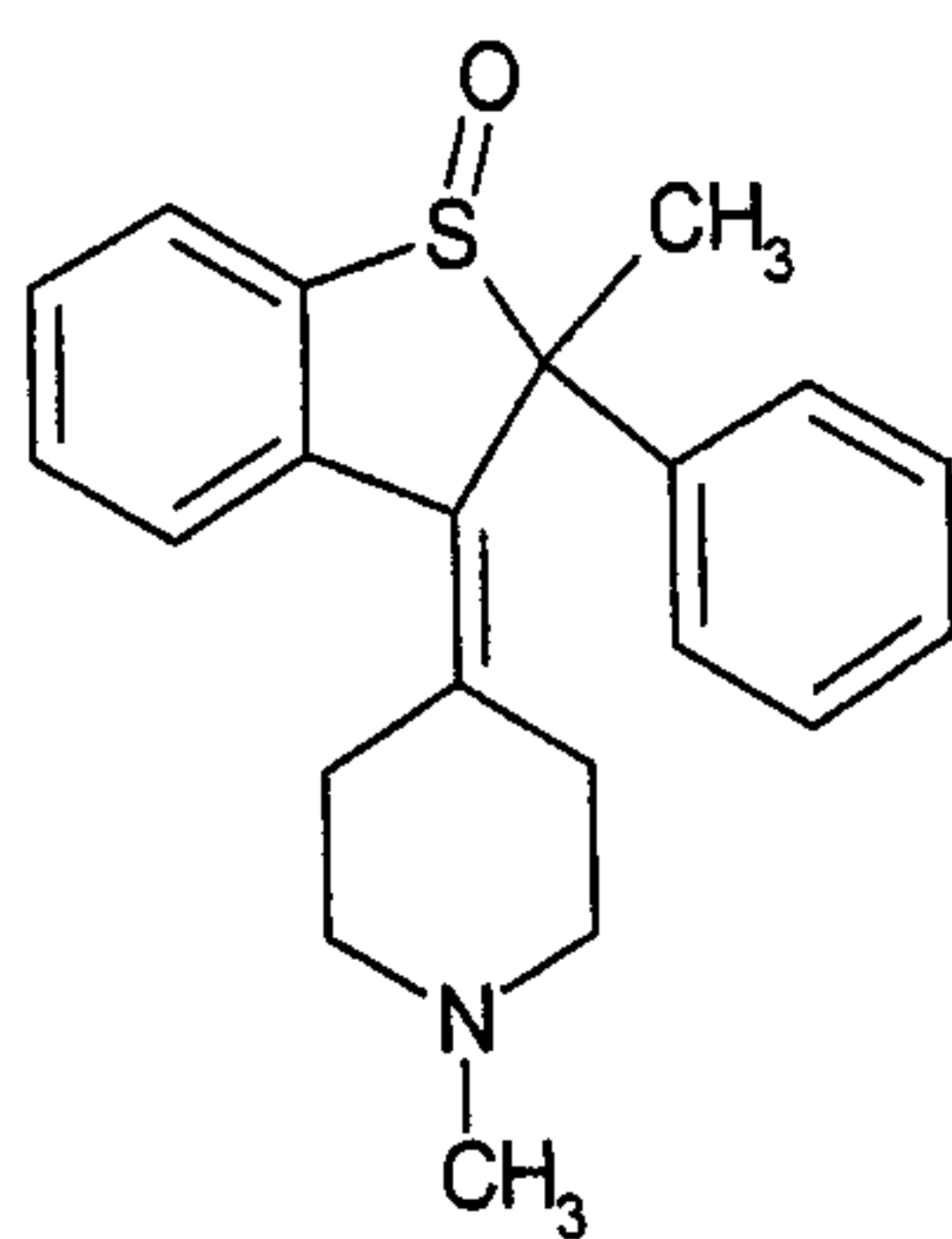
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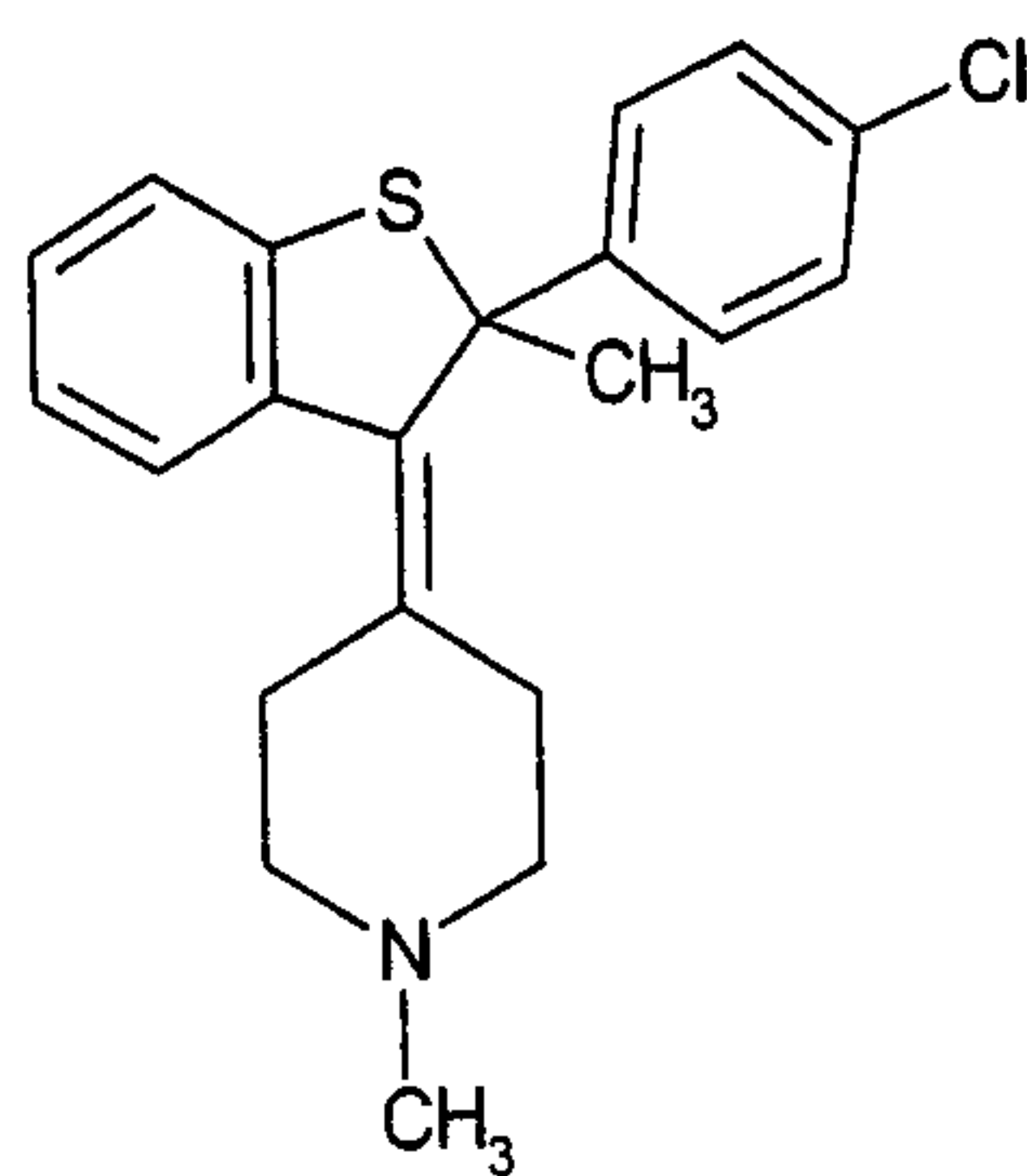
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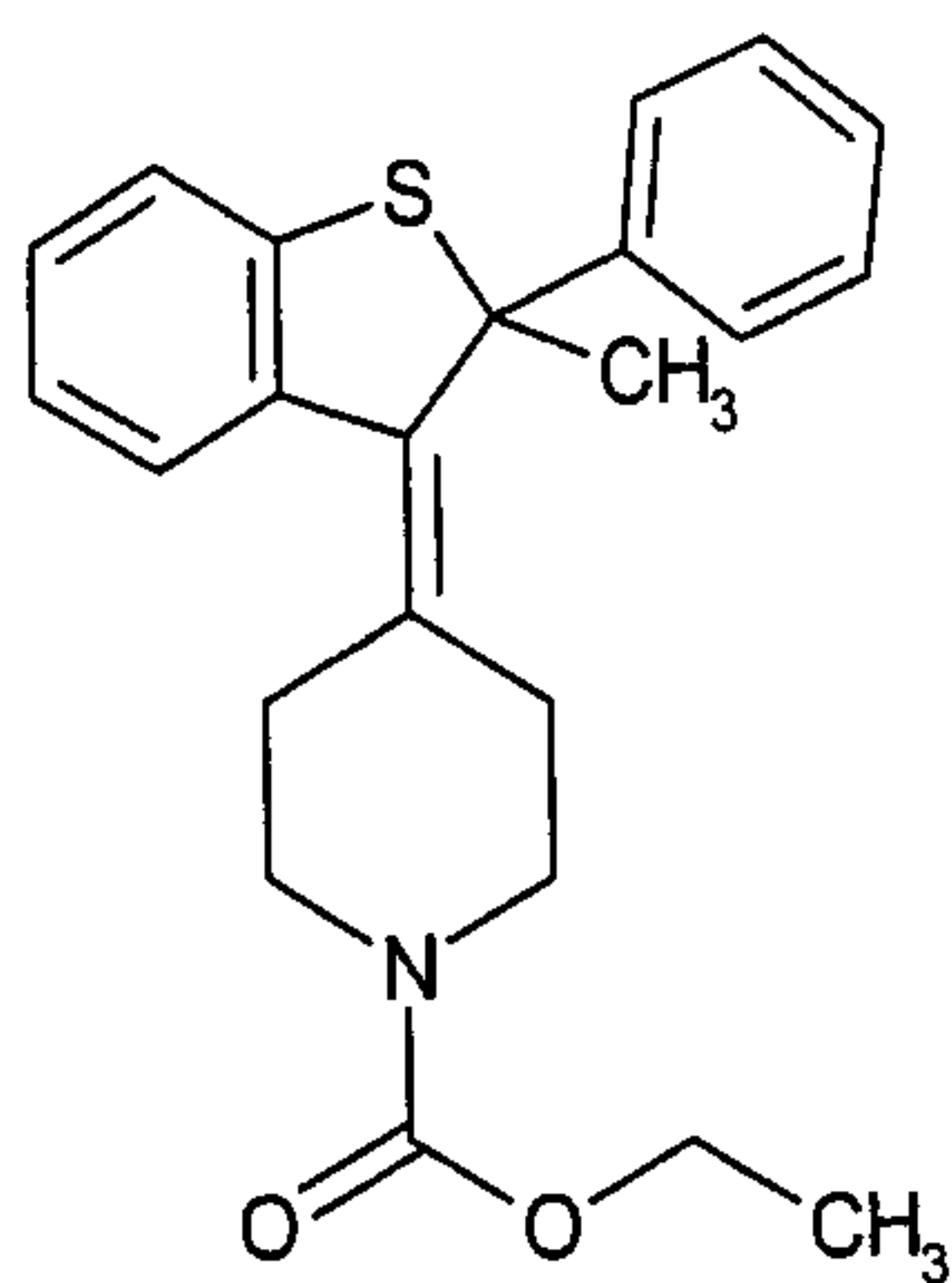
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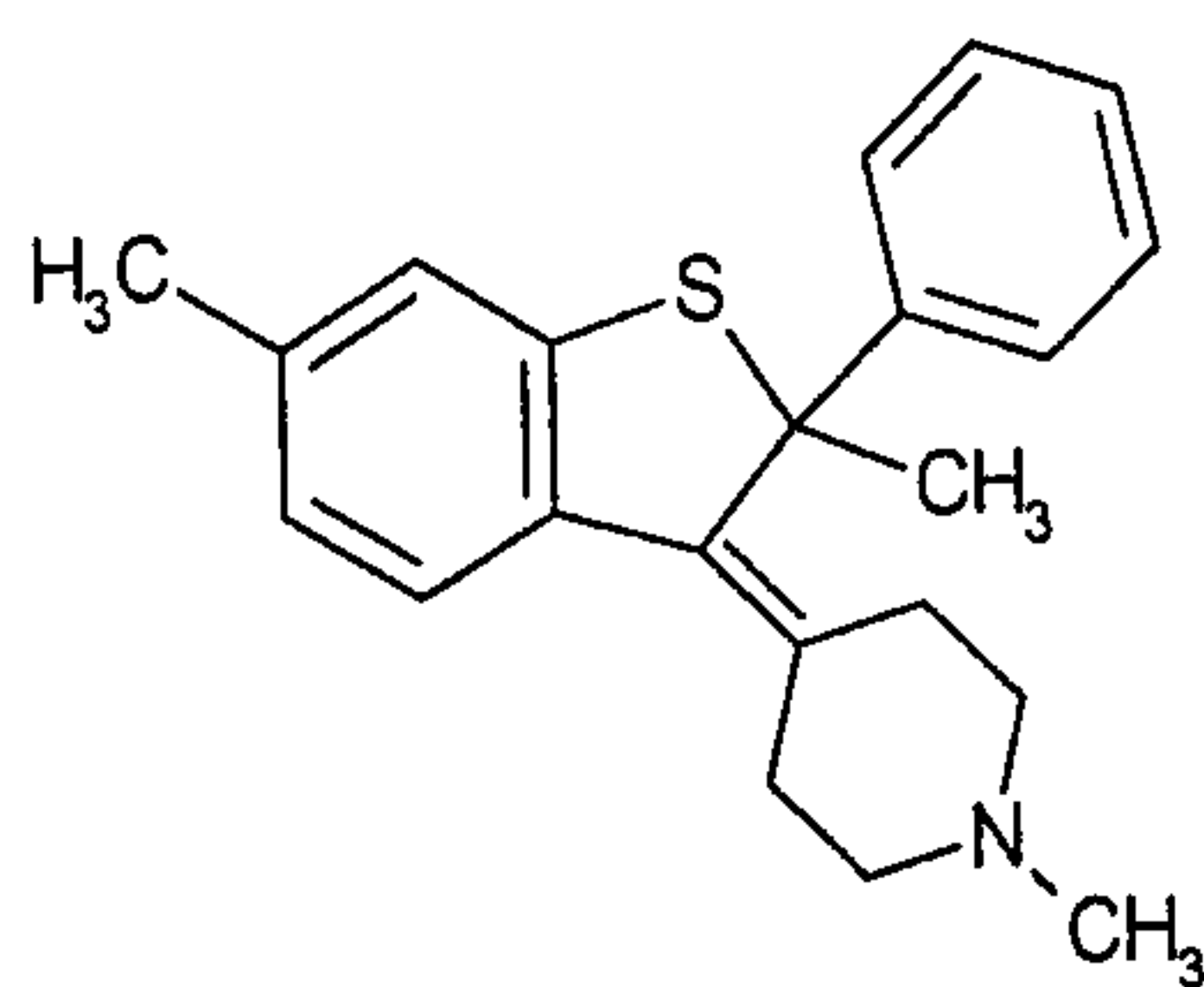
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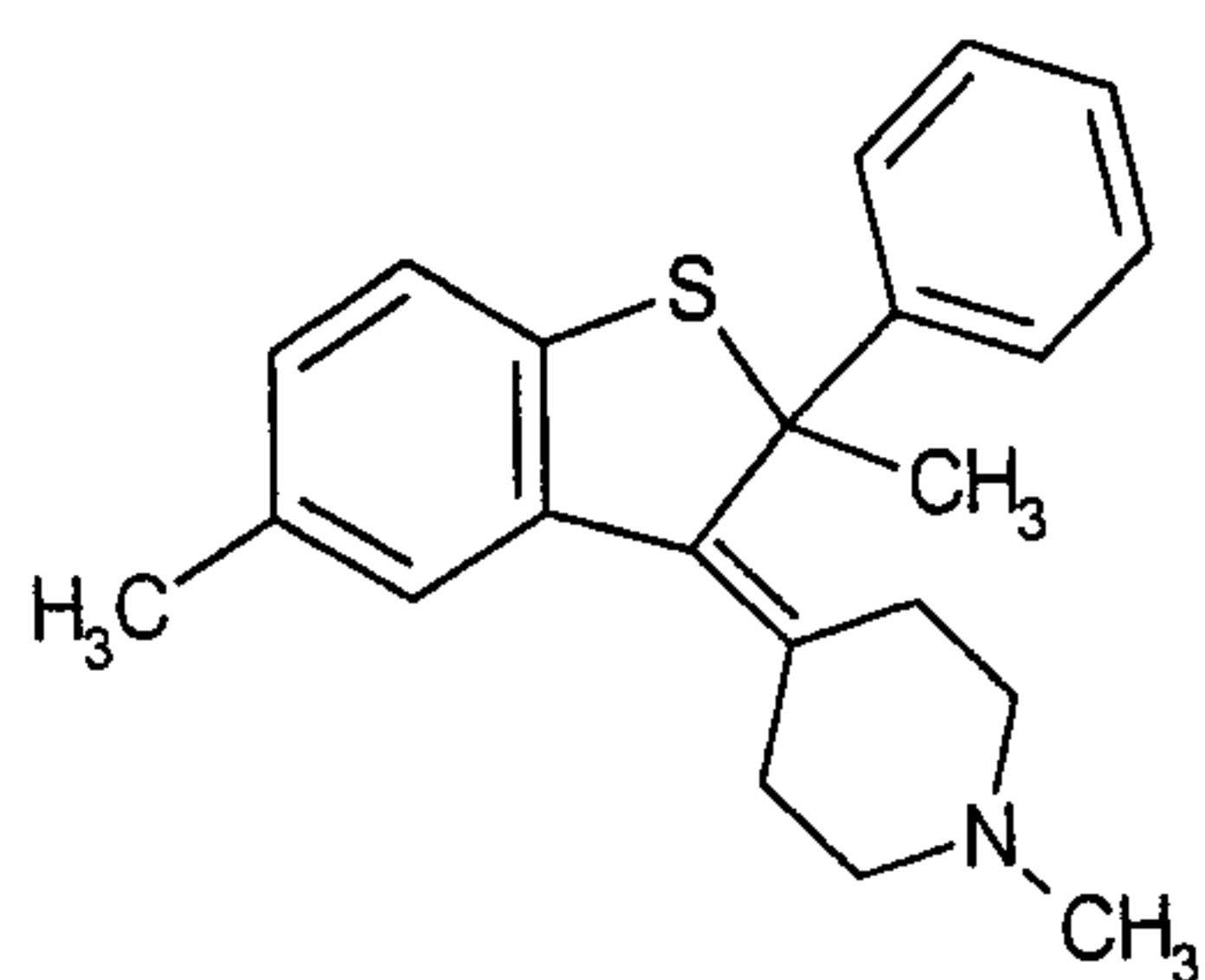
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I26

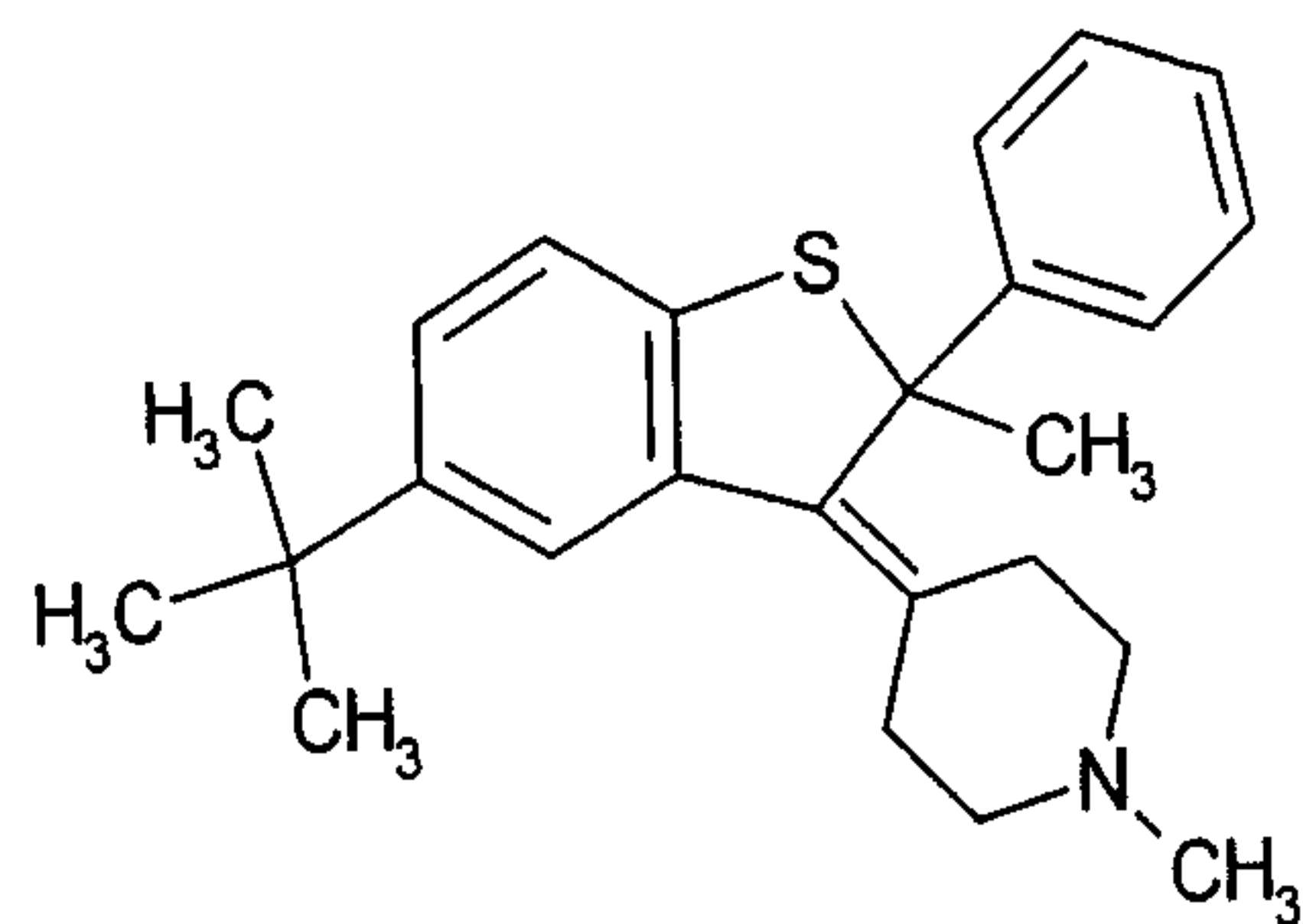
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I27

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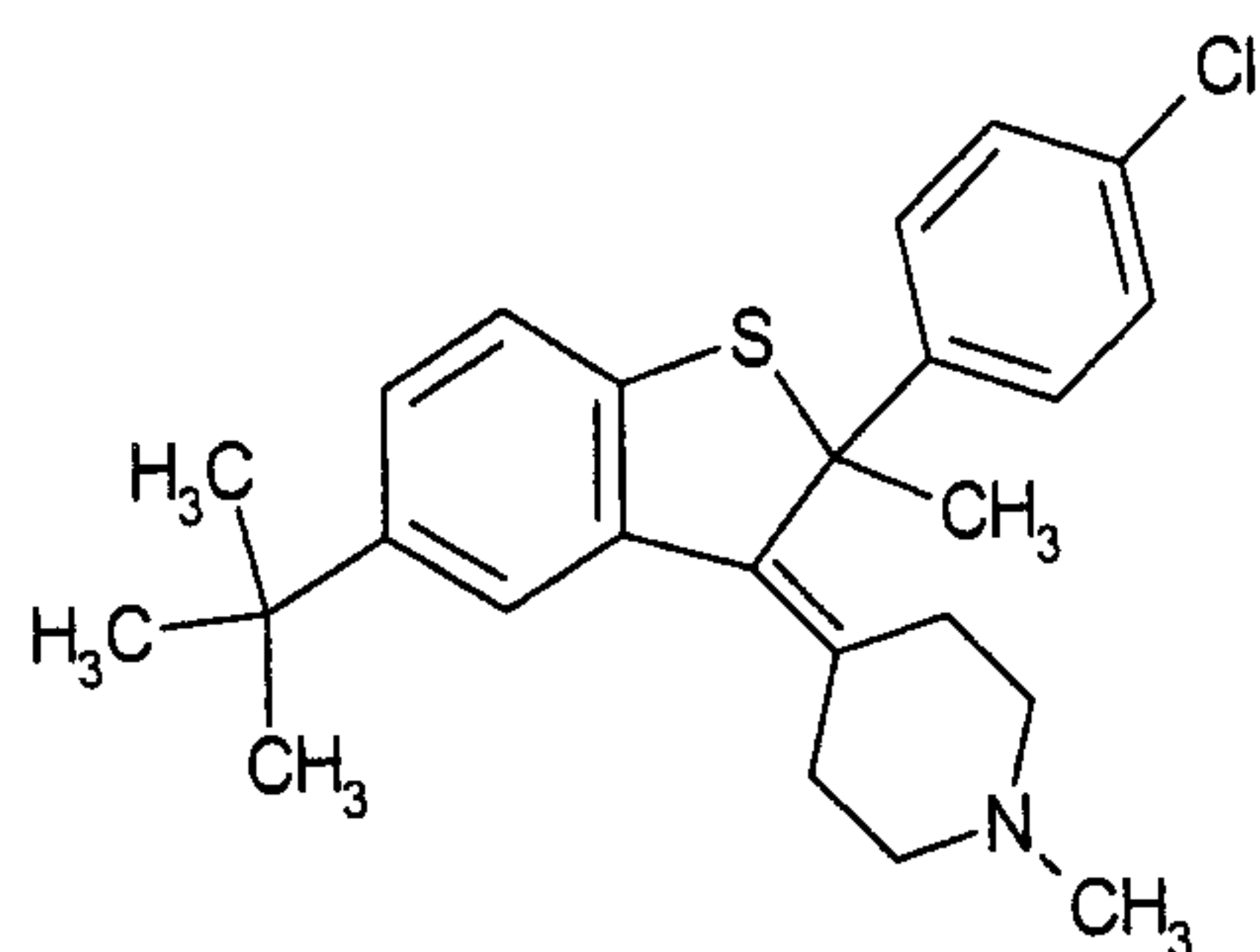


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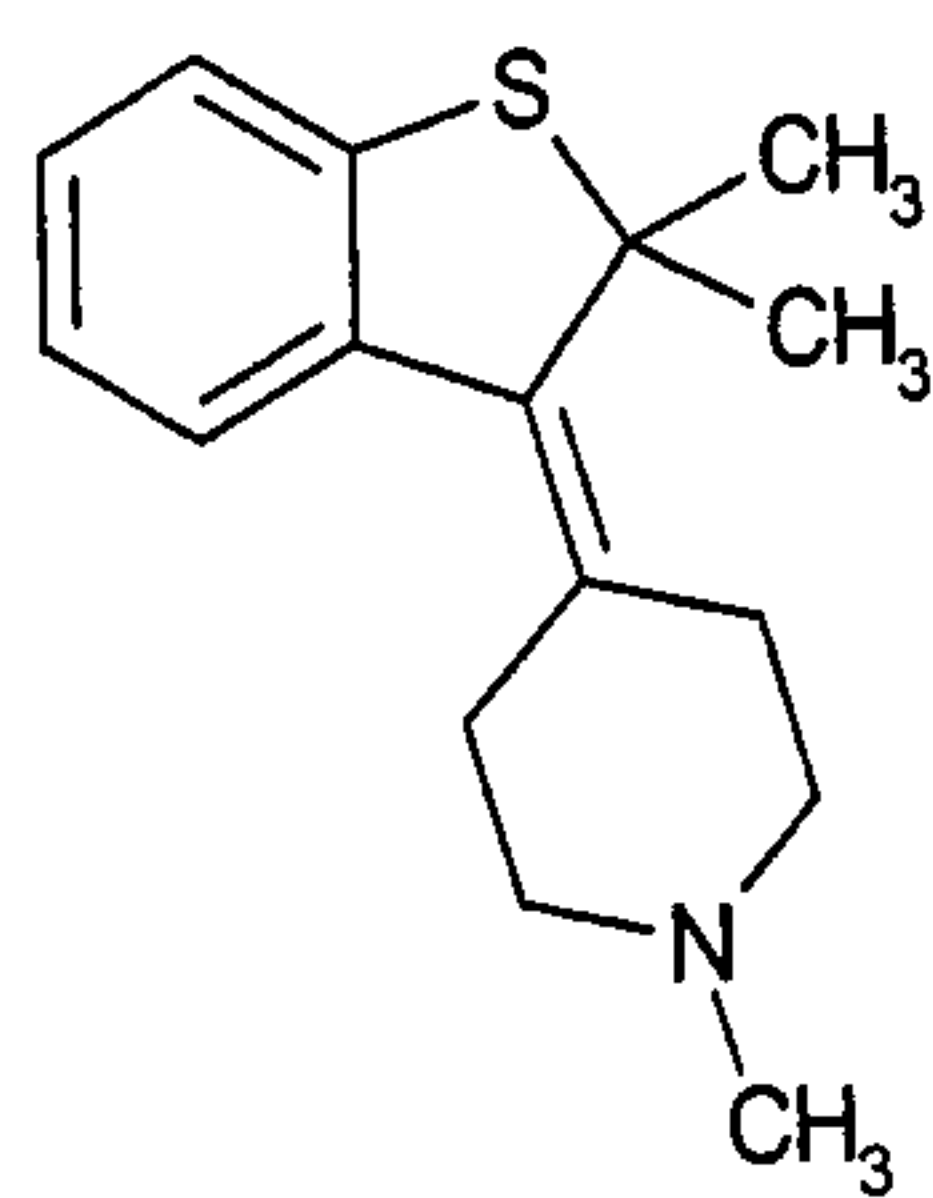
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129

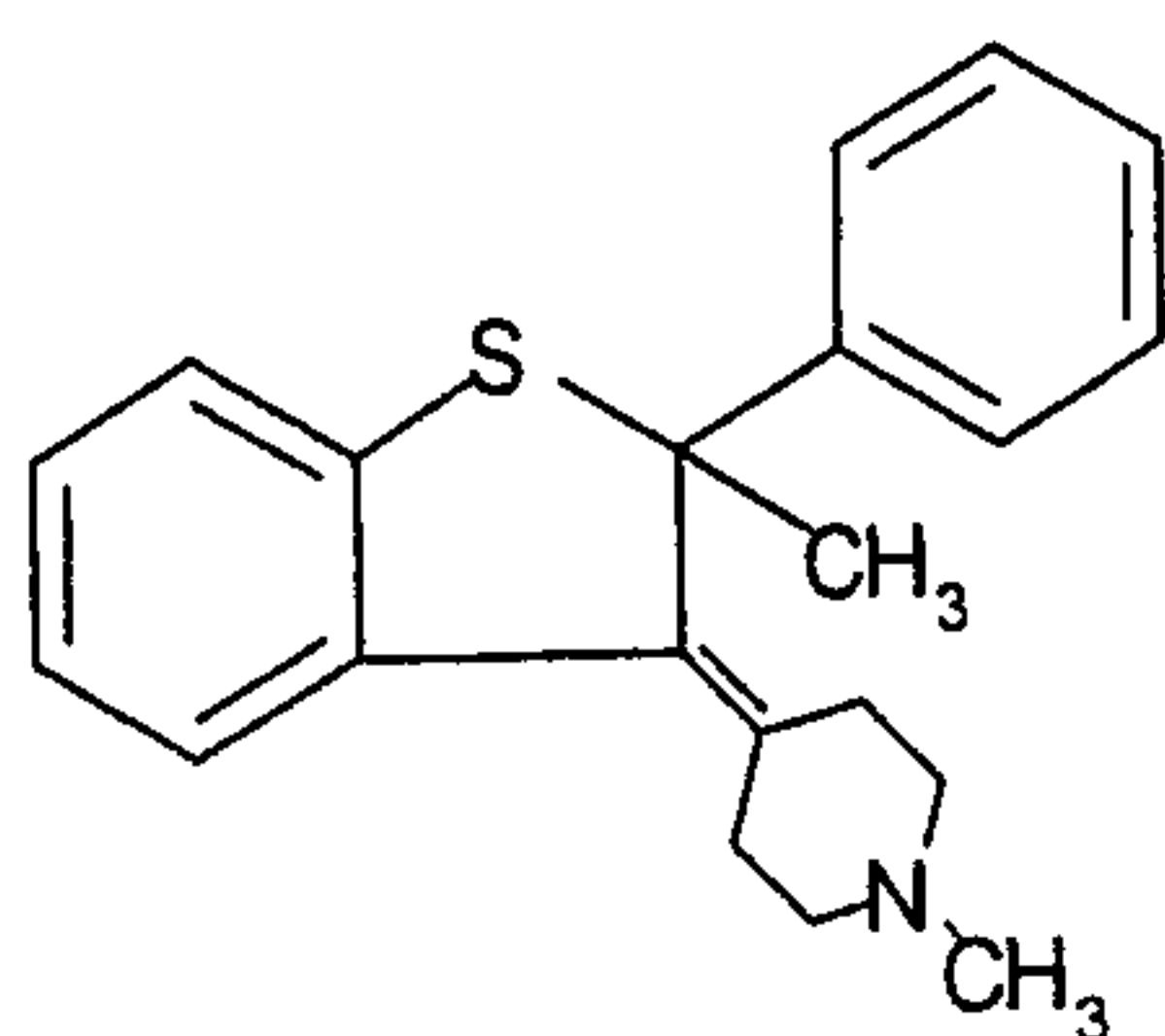
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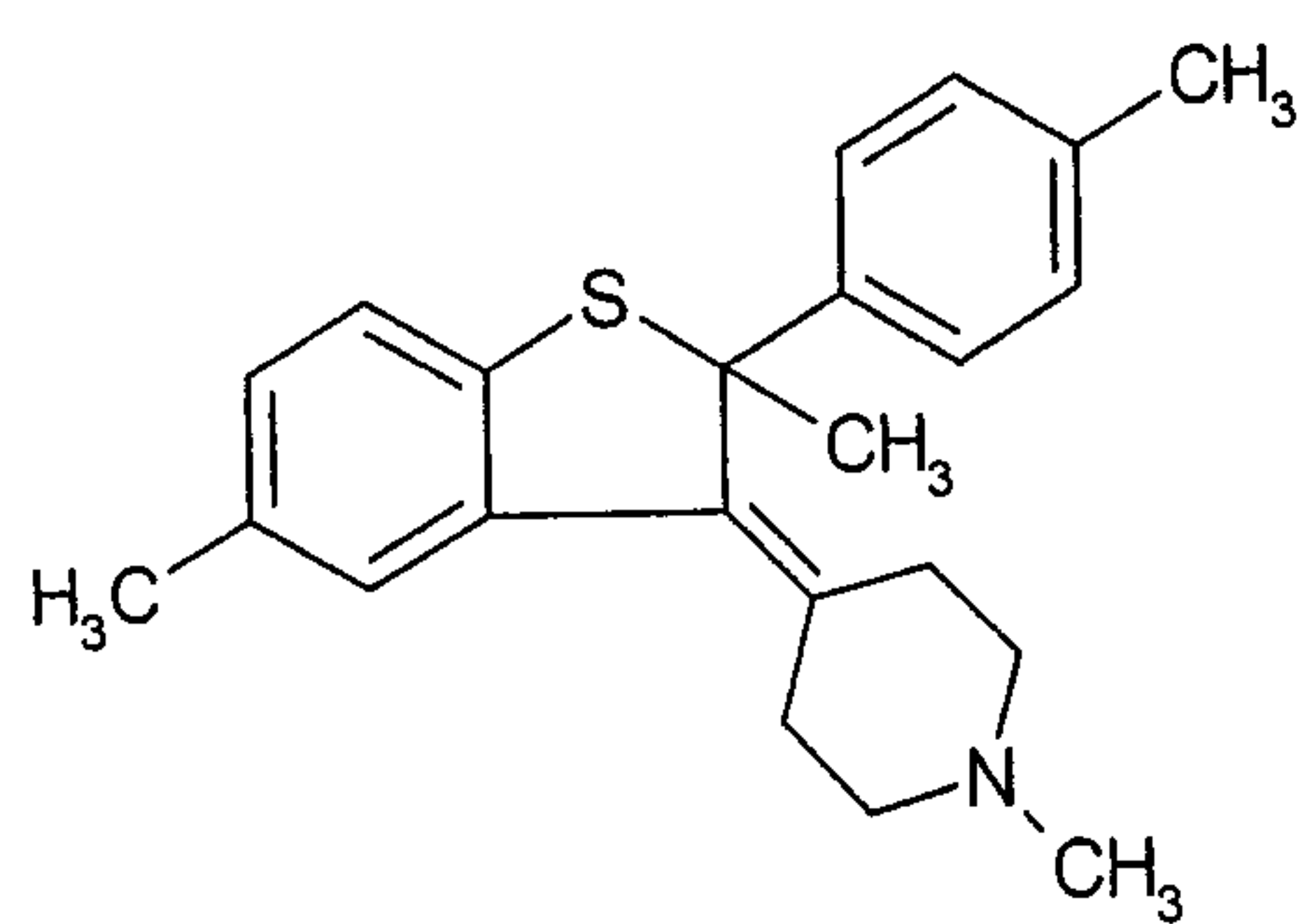
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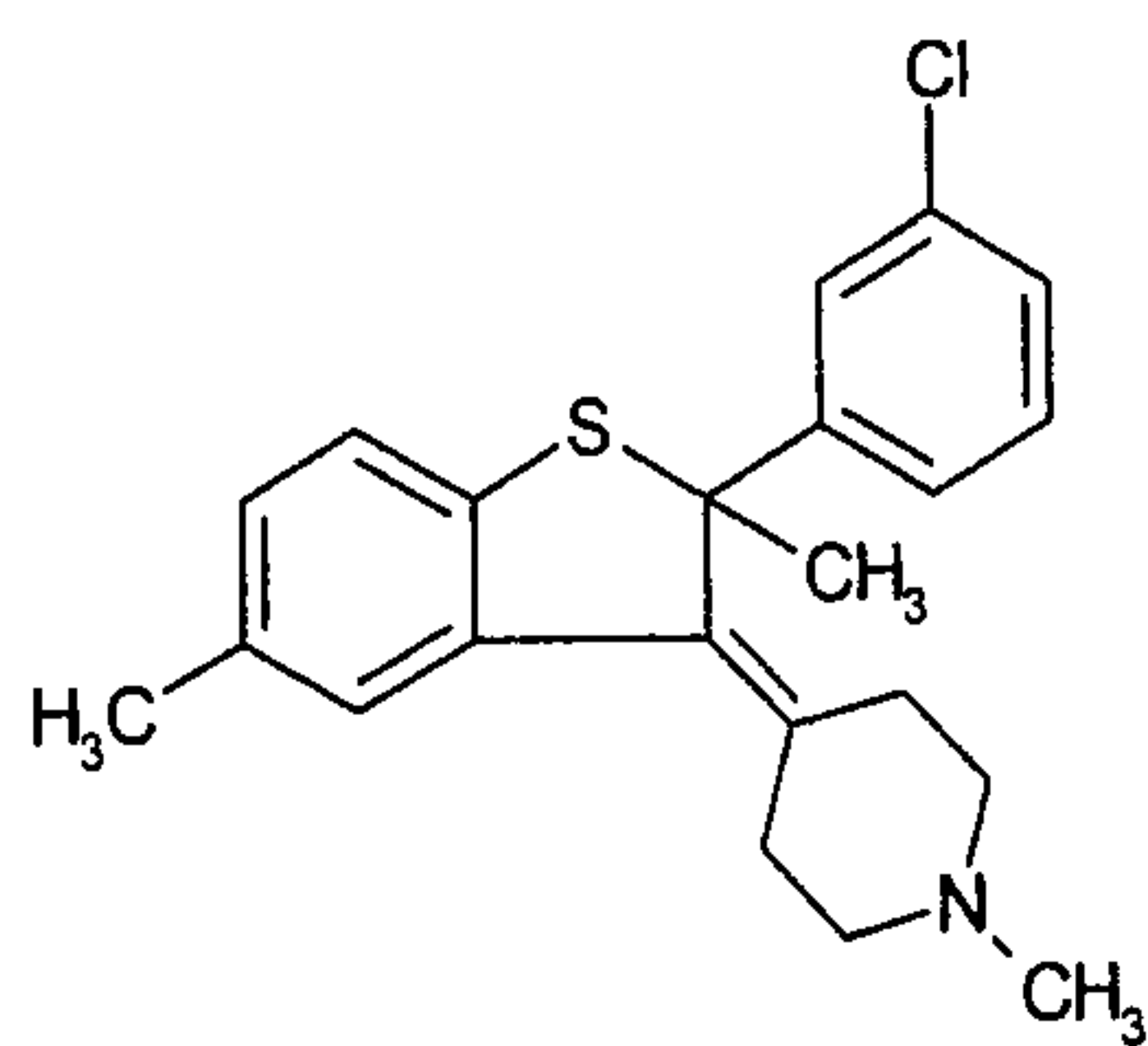


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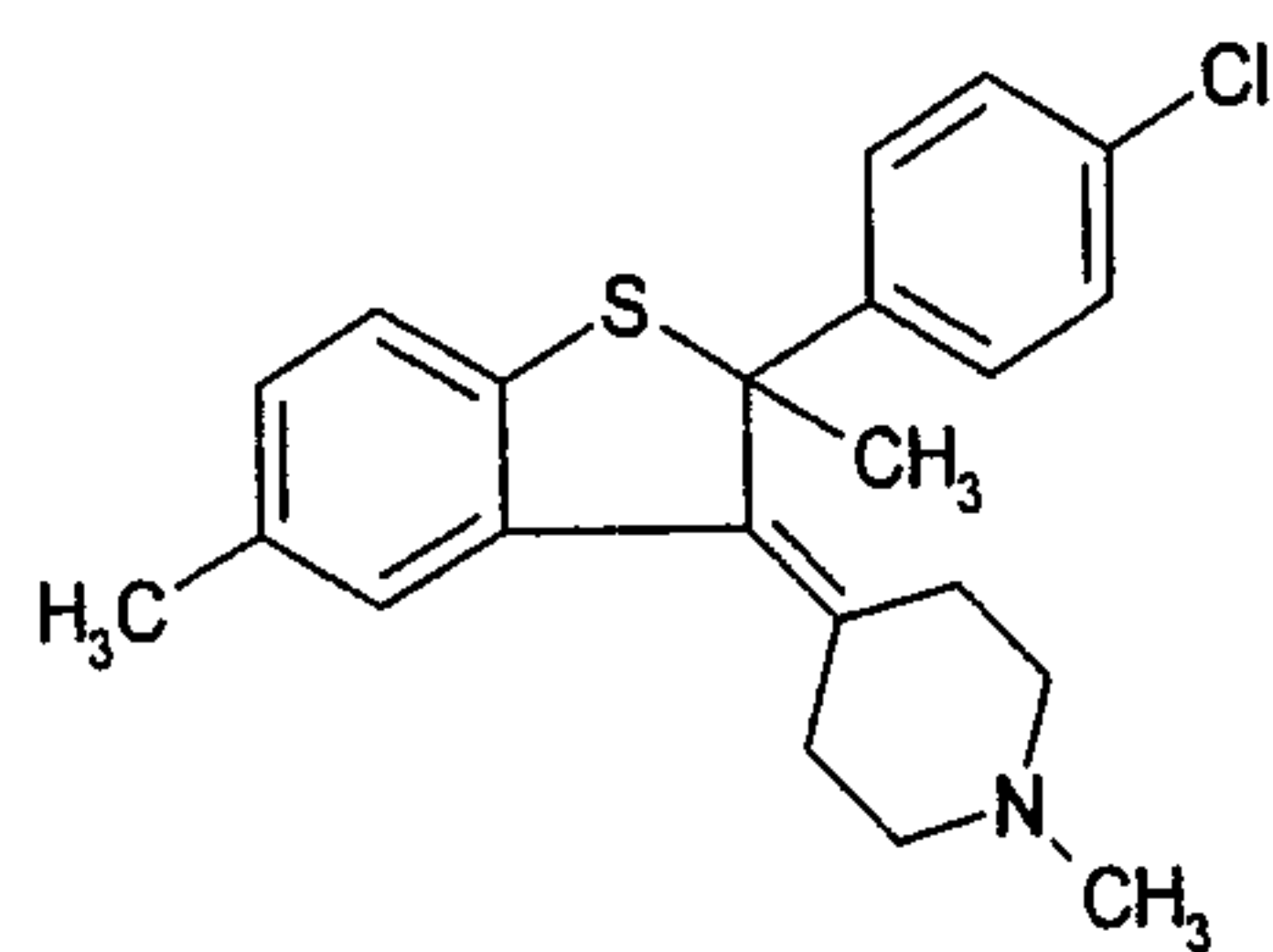
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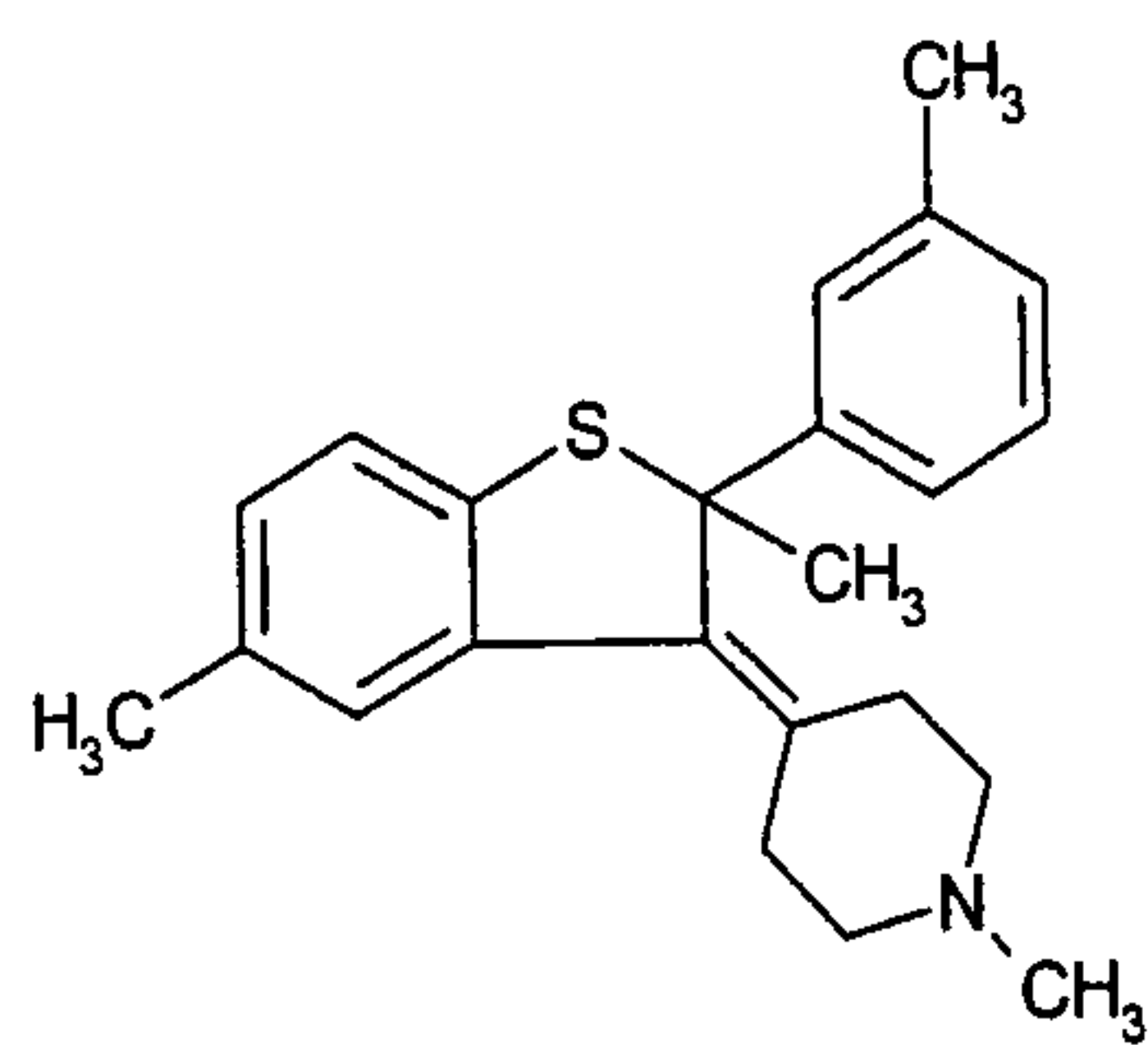
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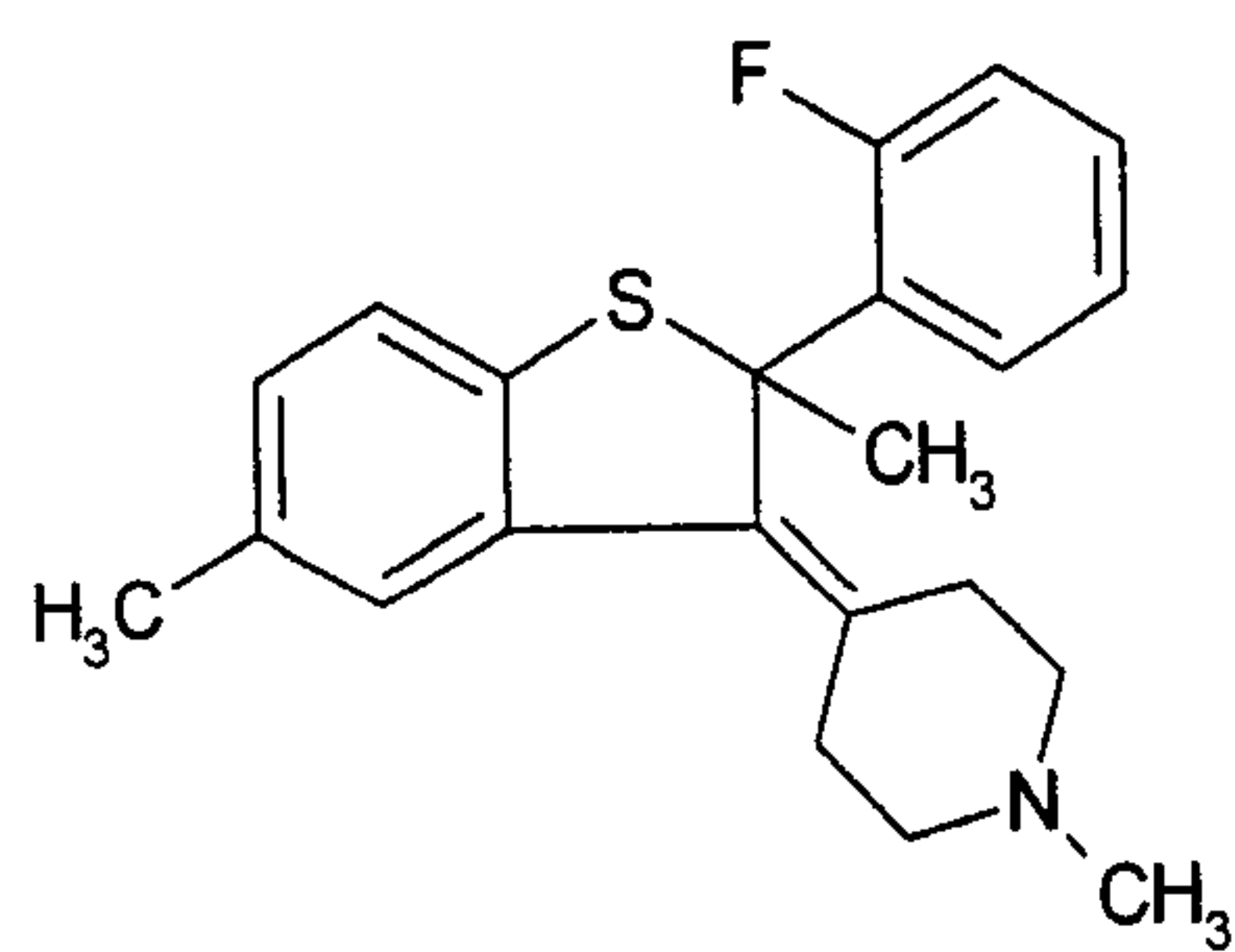
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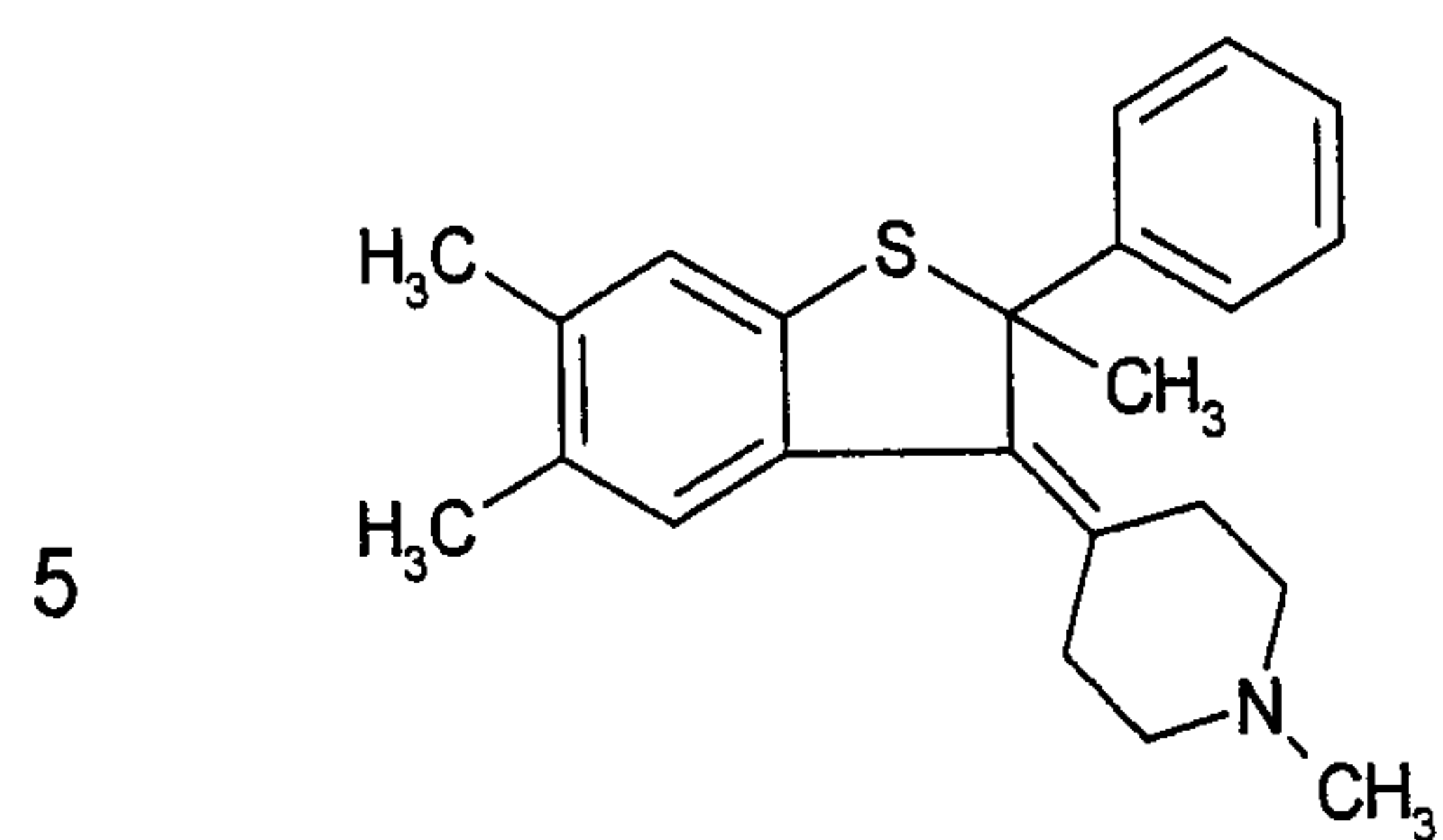


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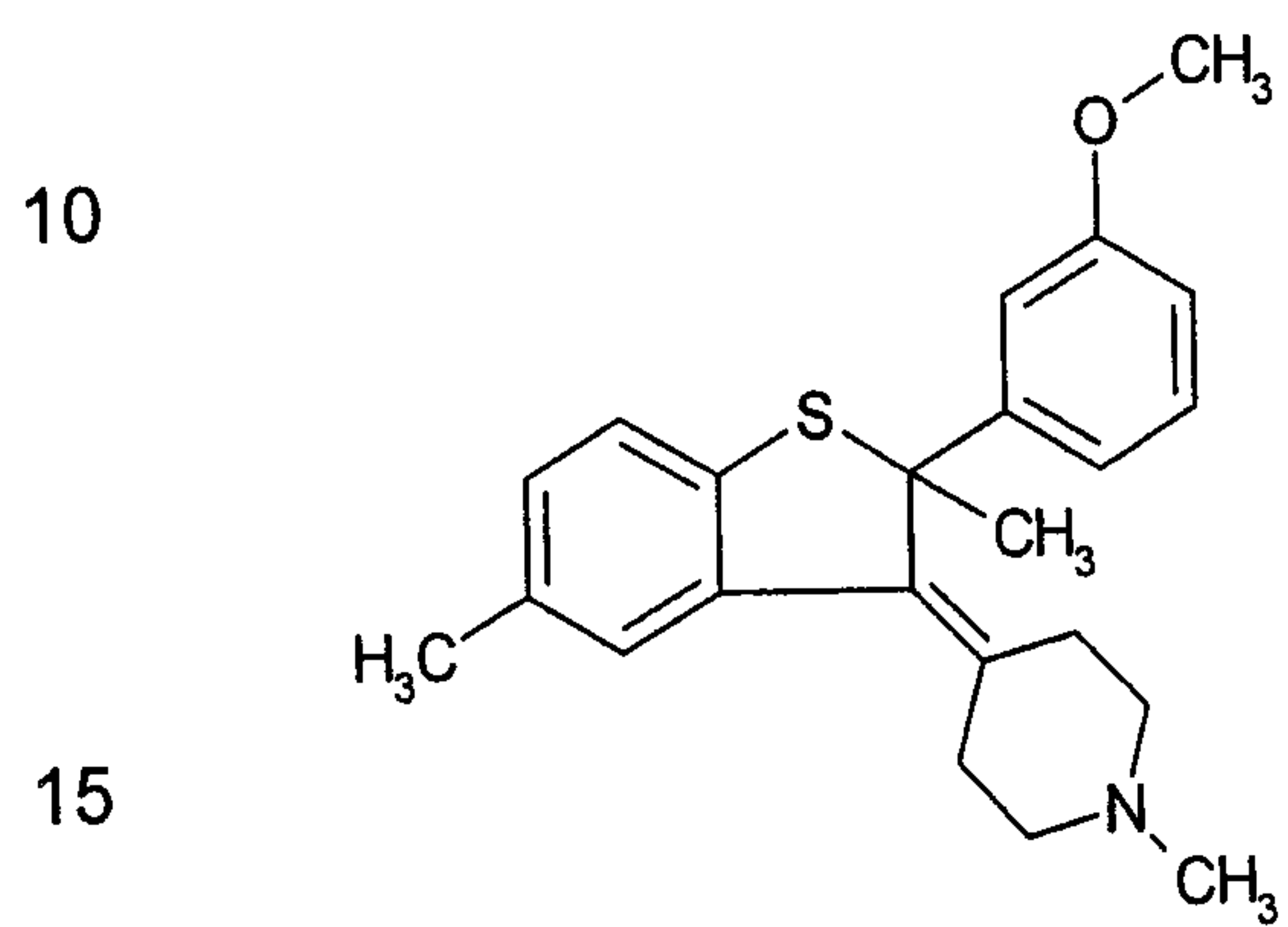
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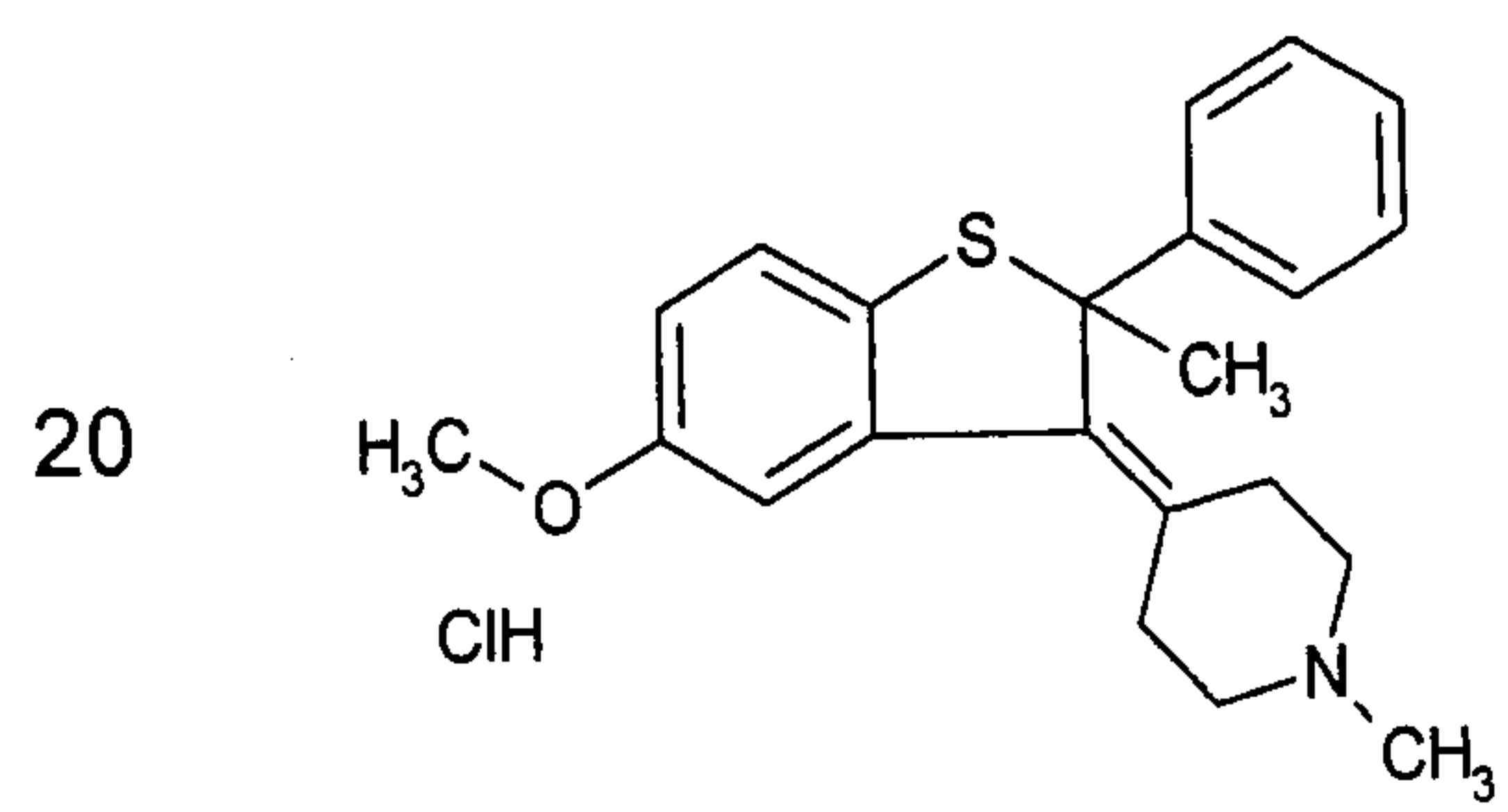
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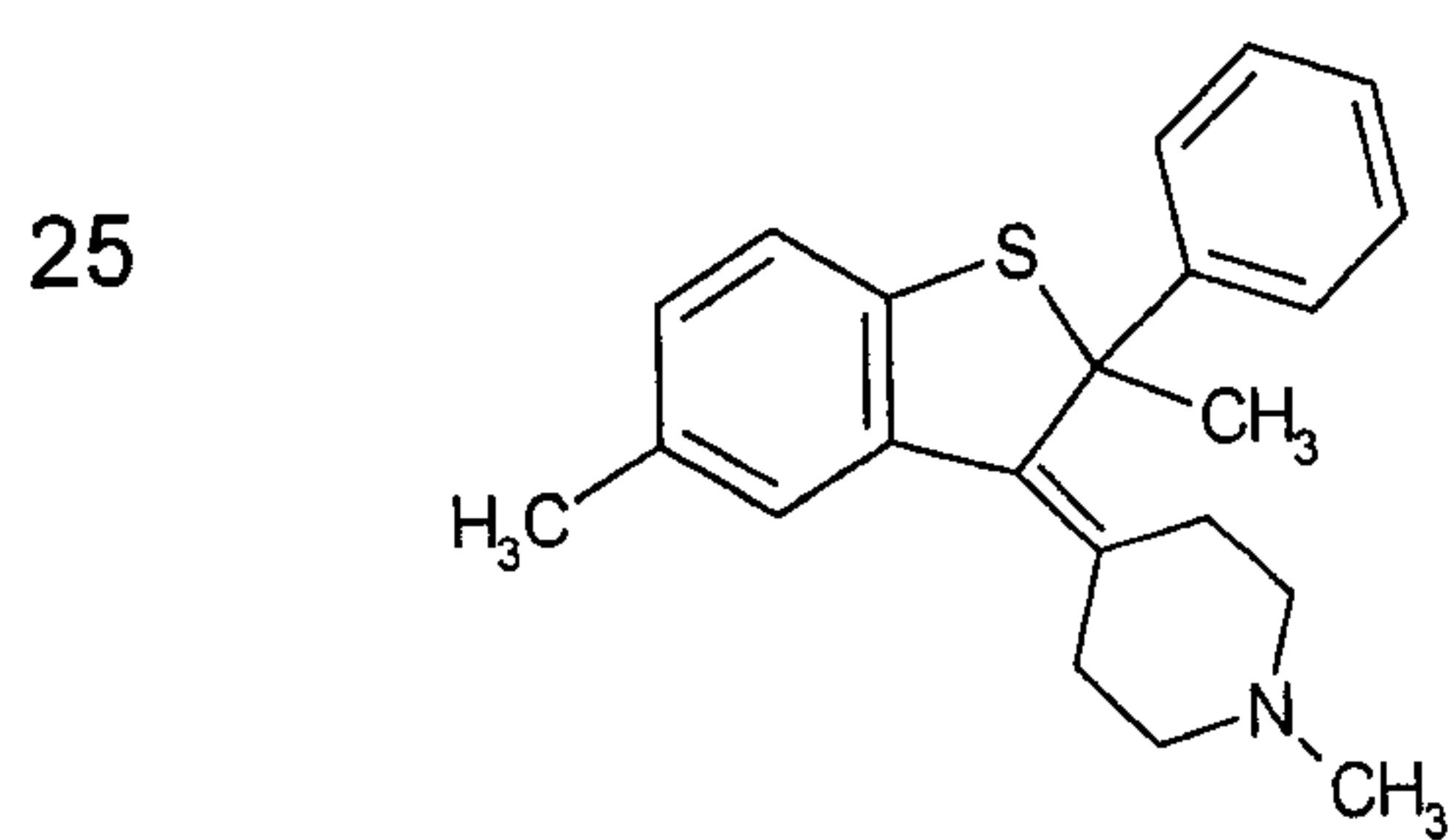
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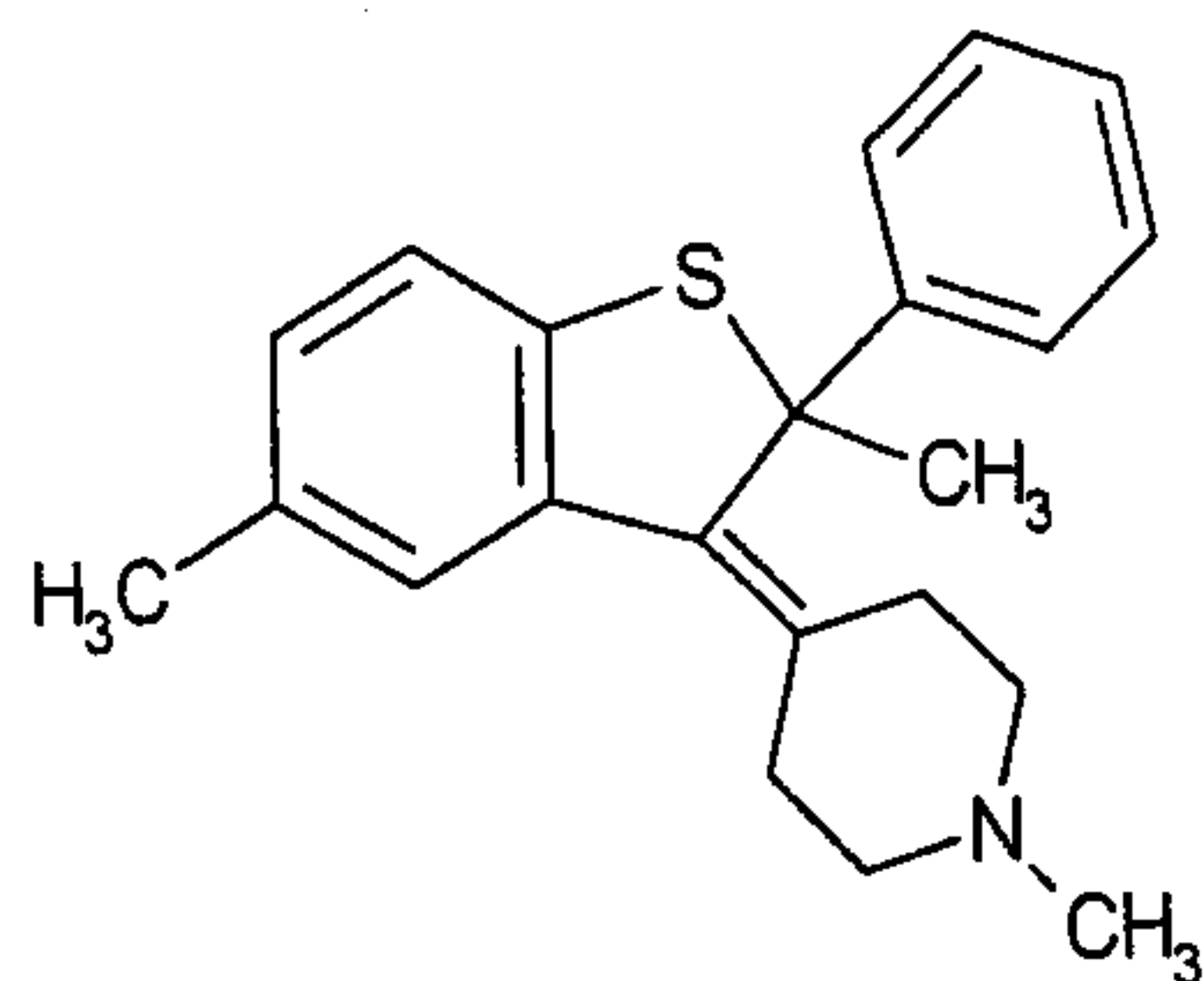
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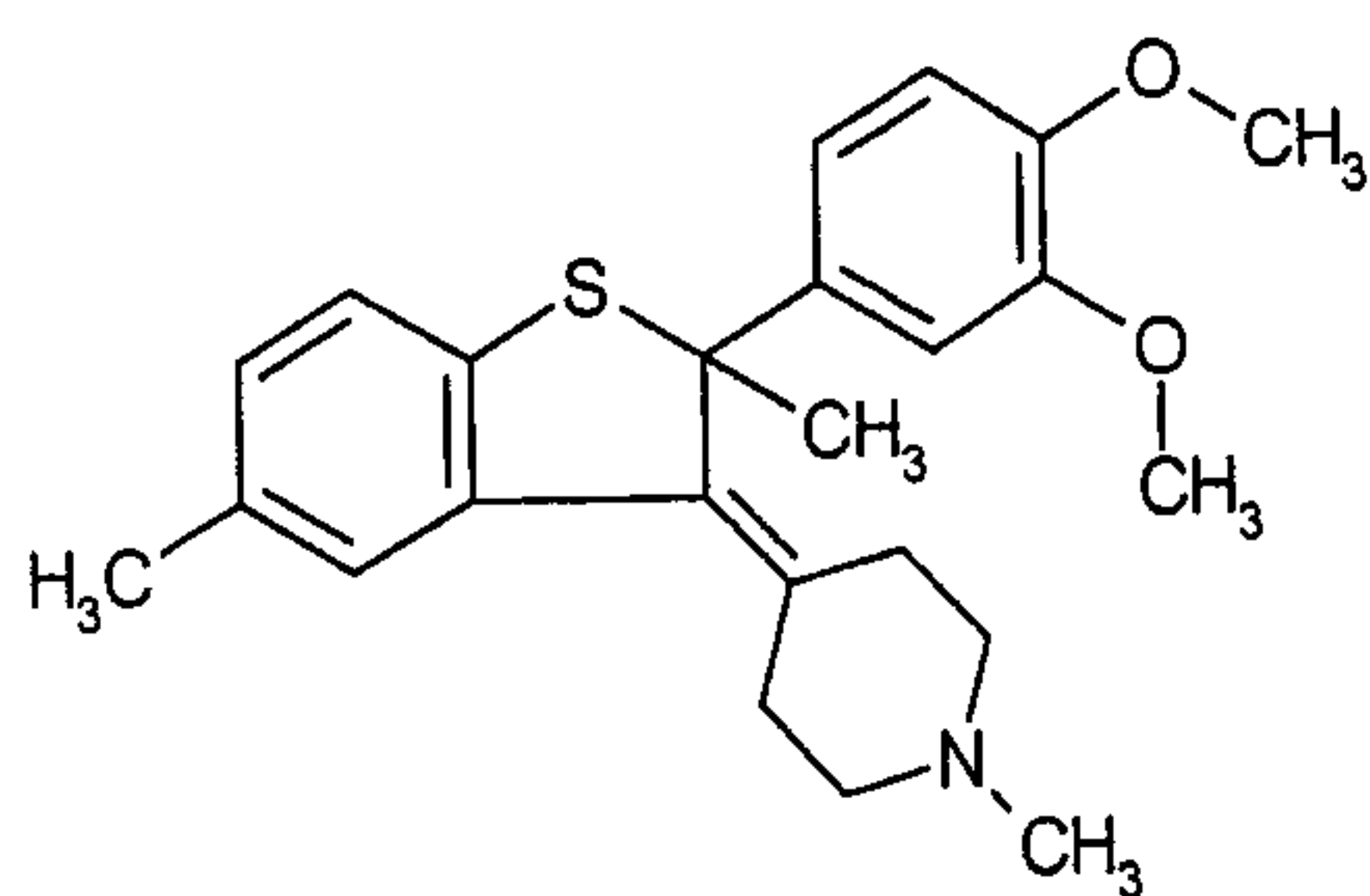
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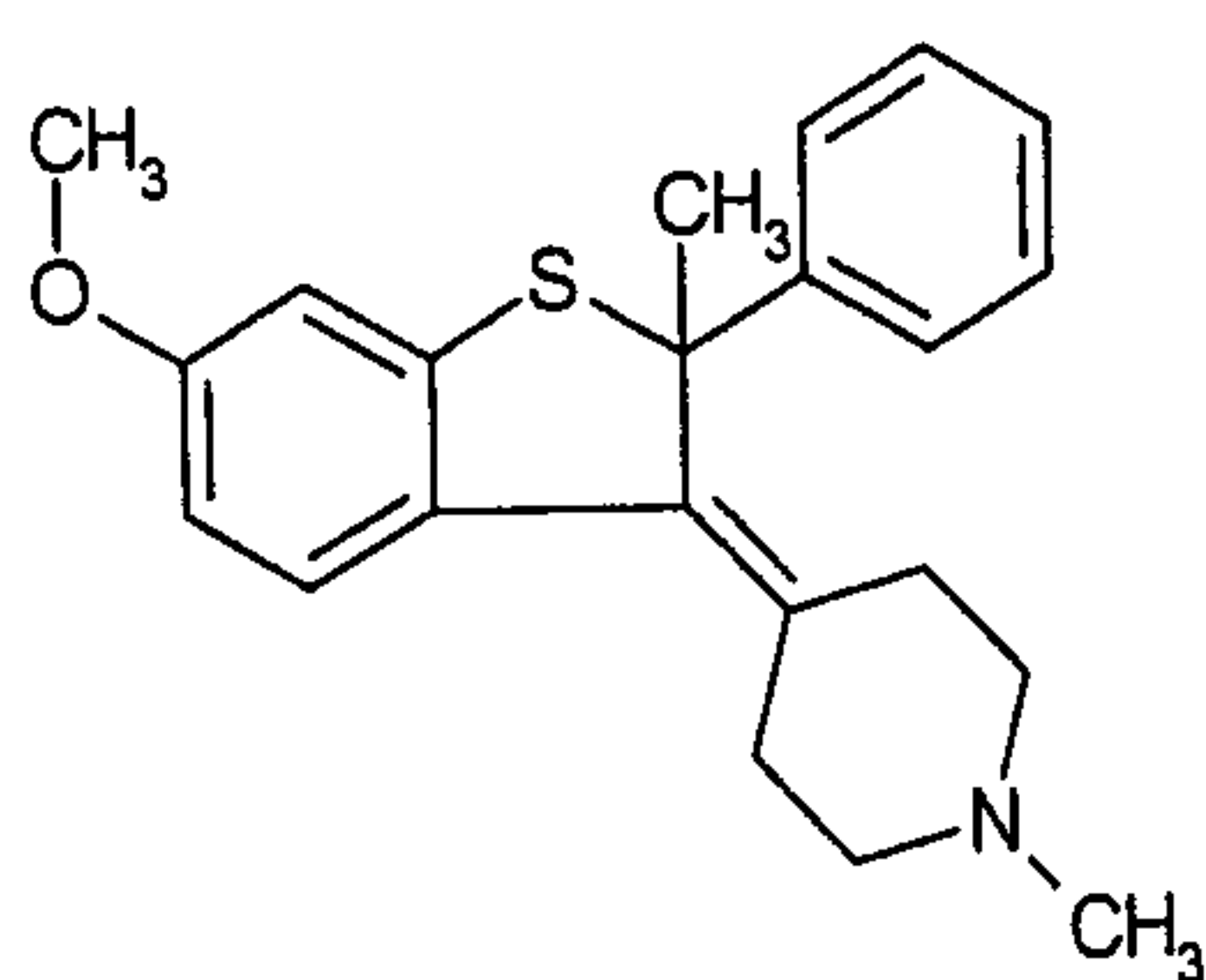
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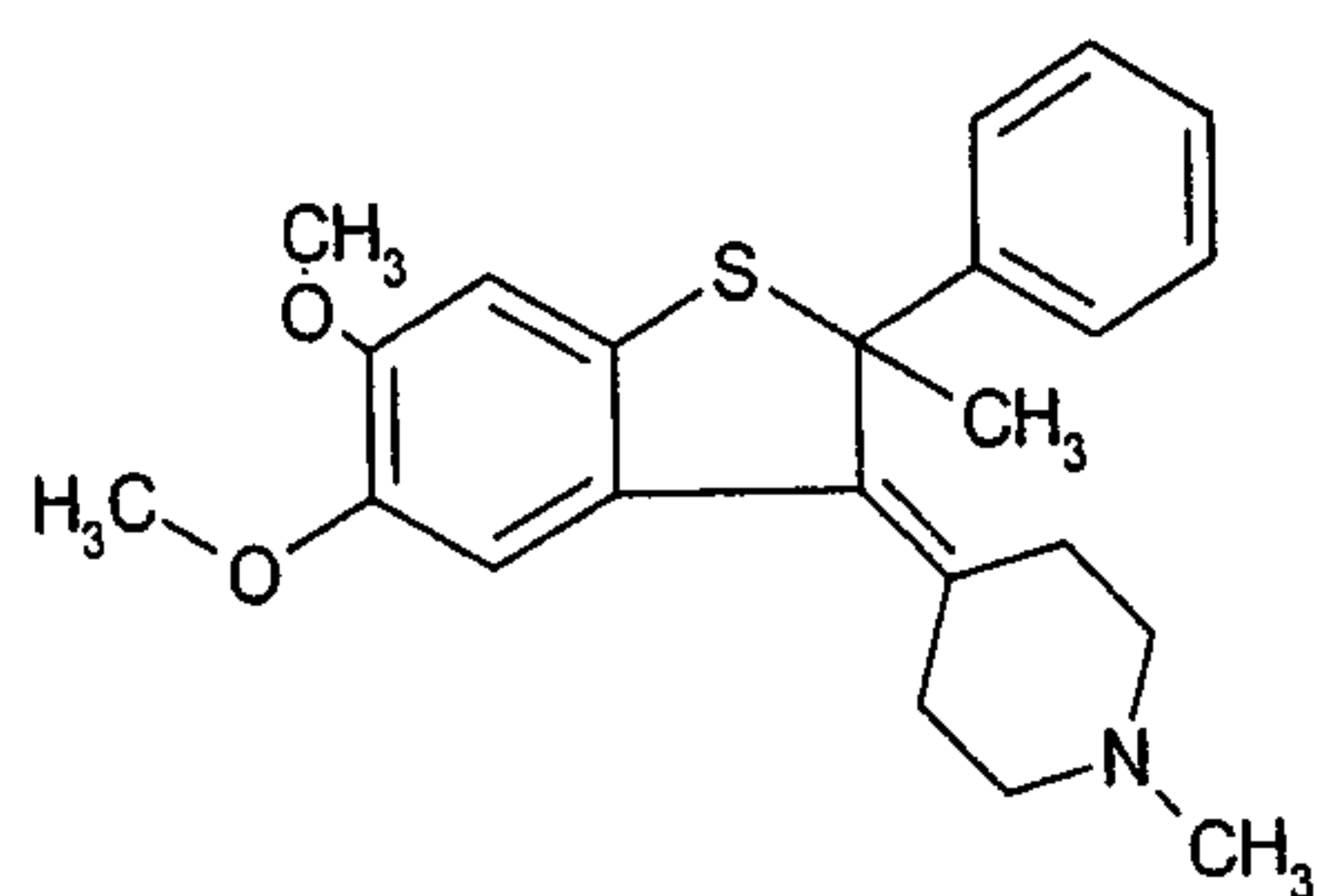
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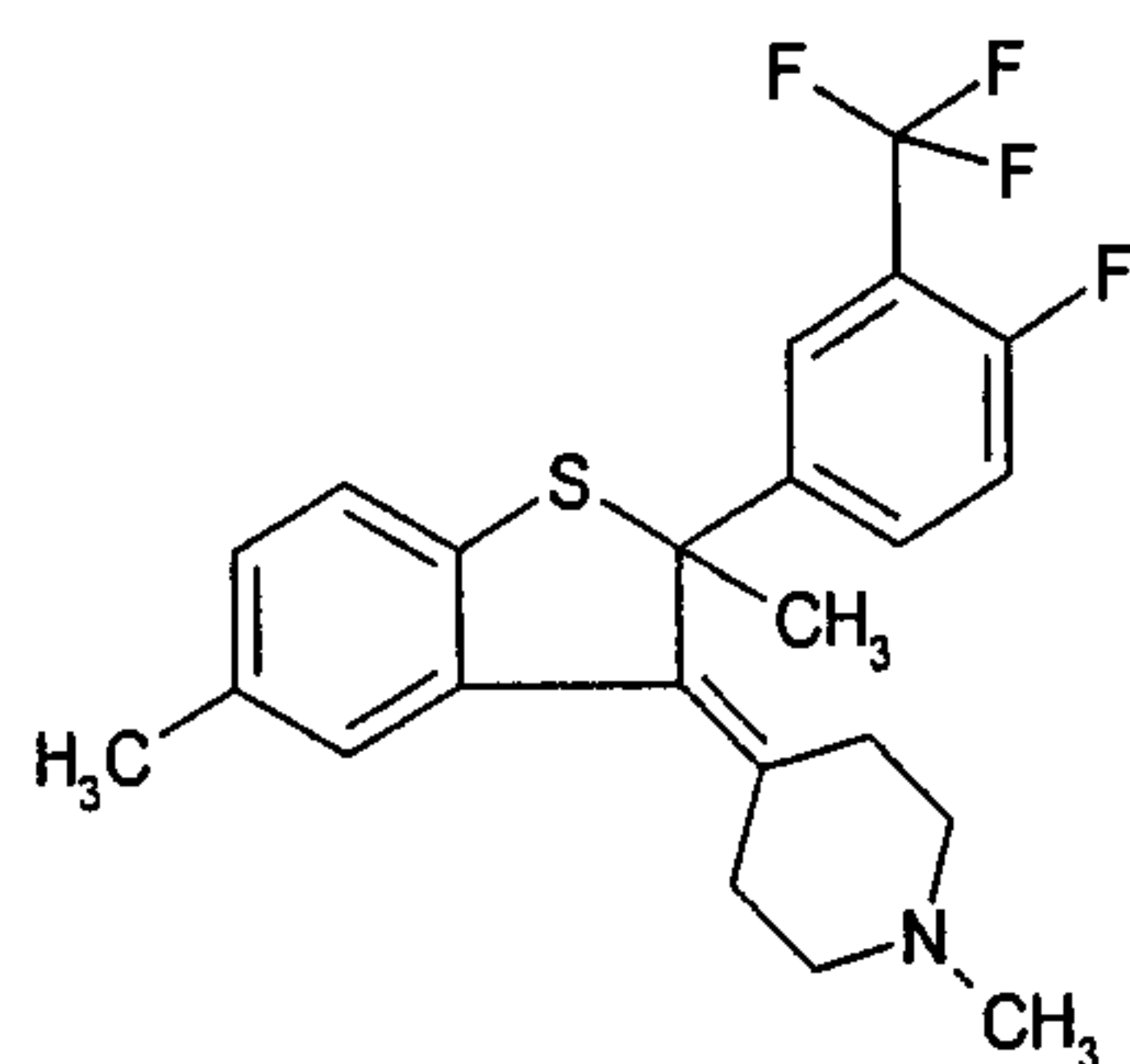


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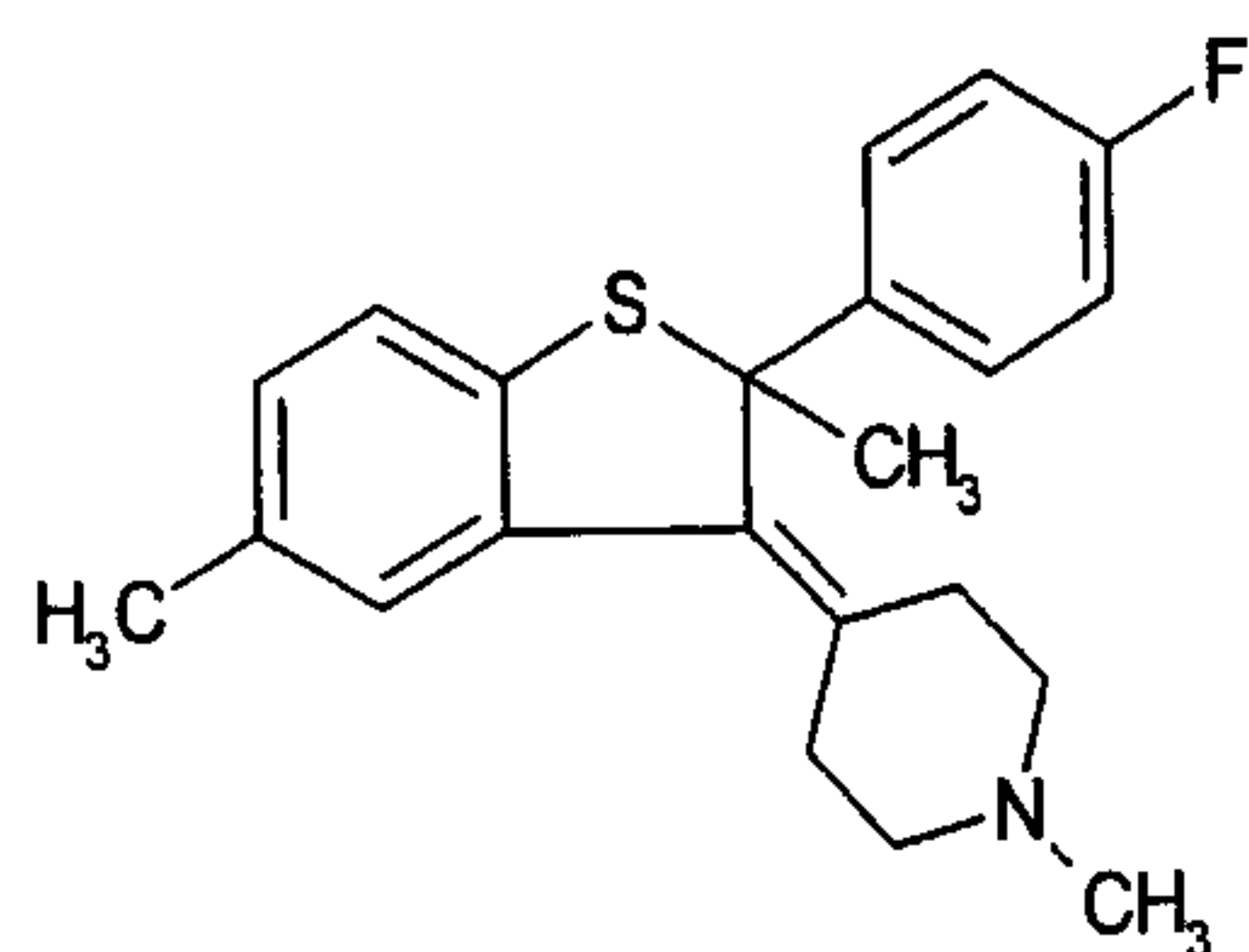
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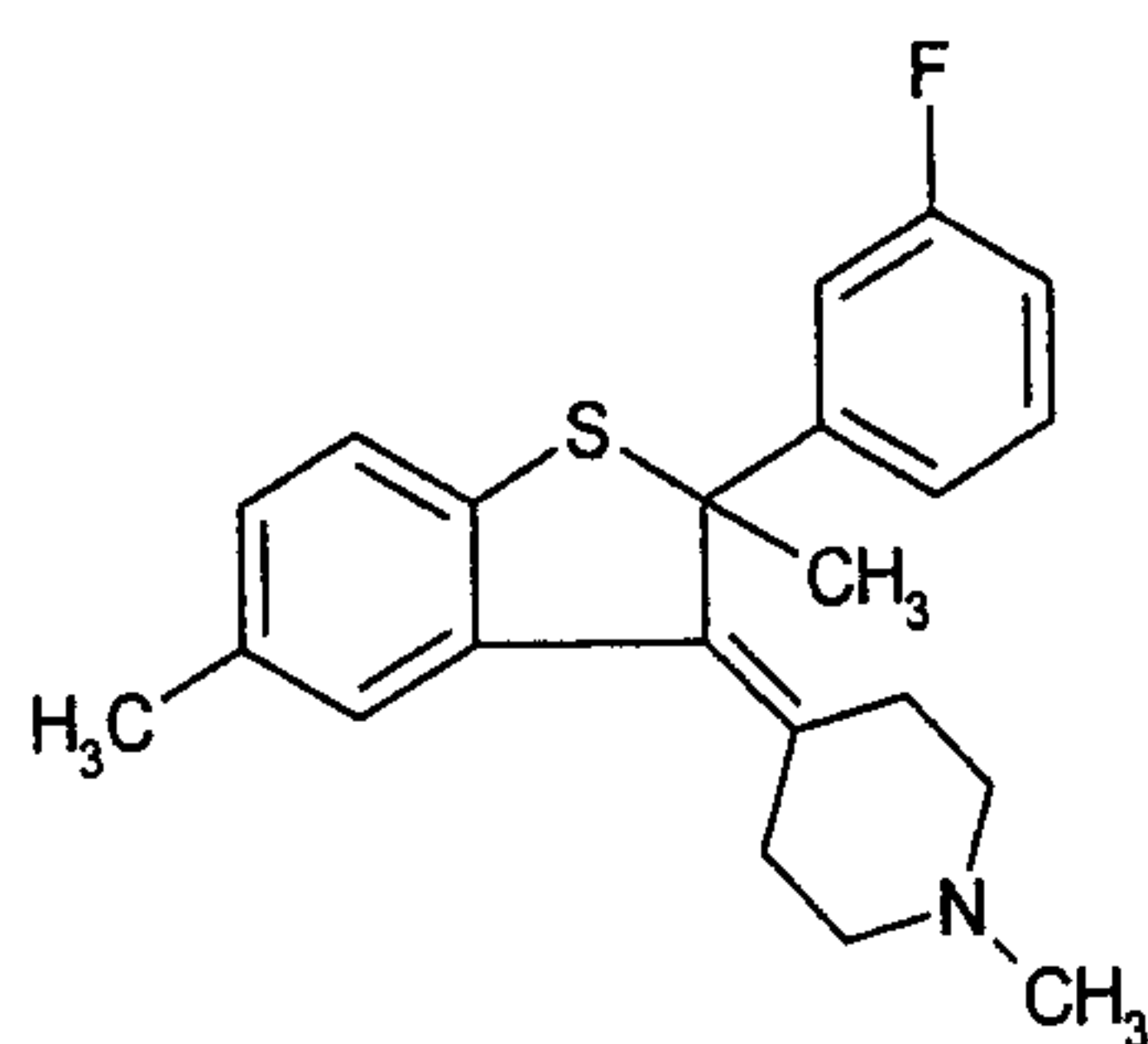
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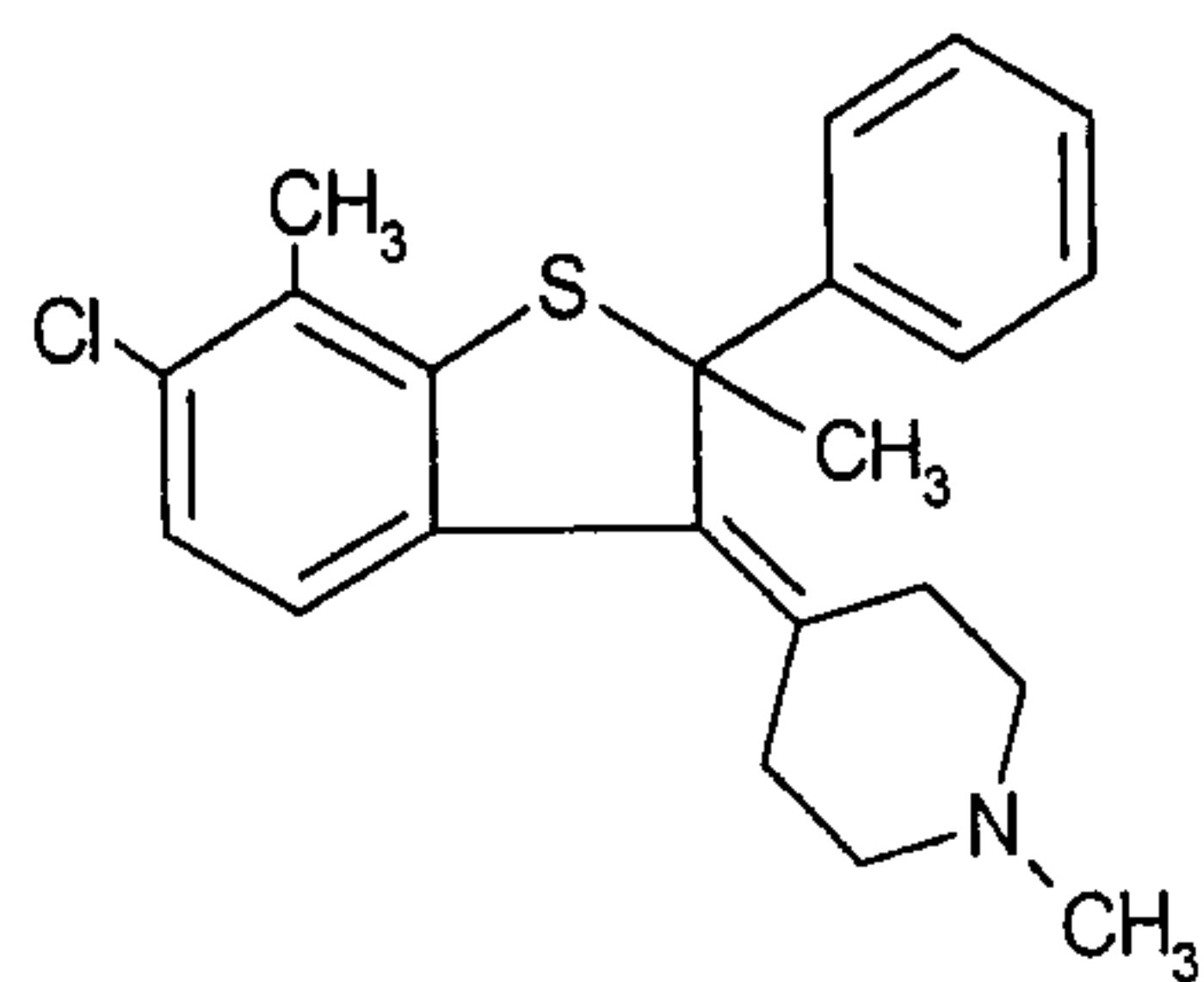
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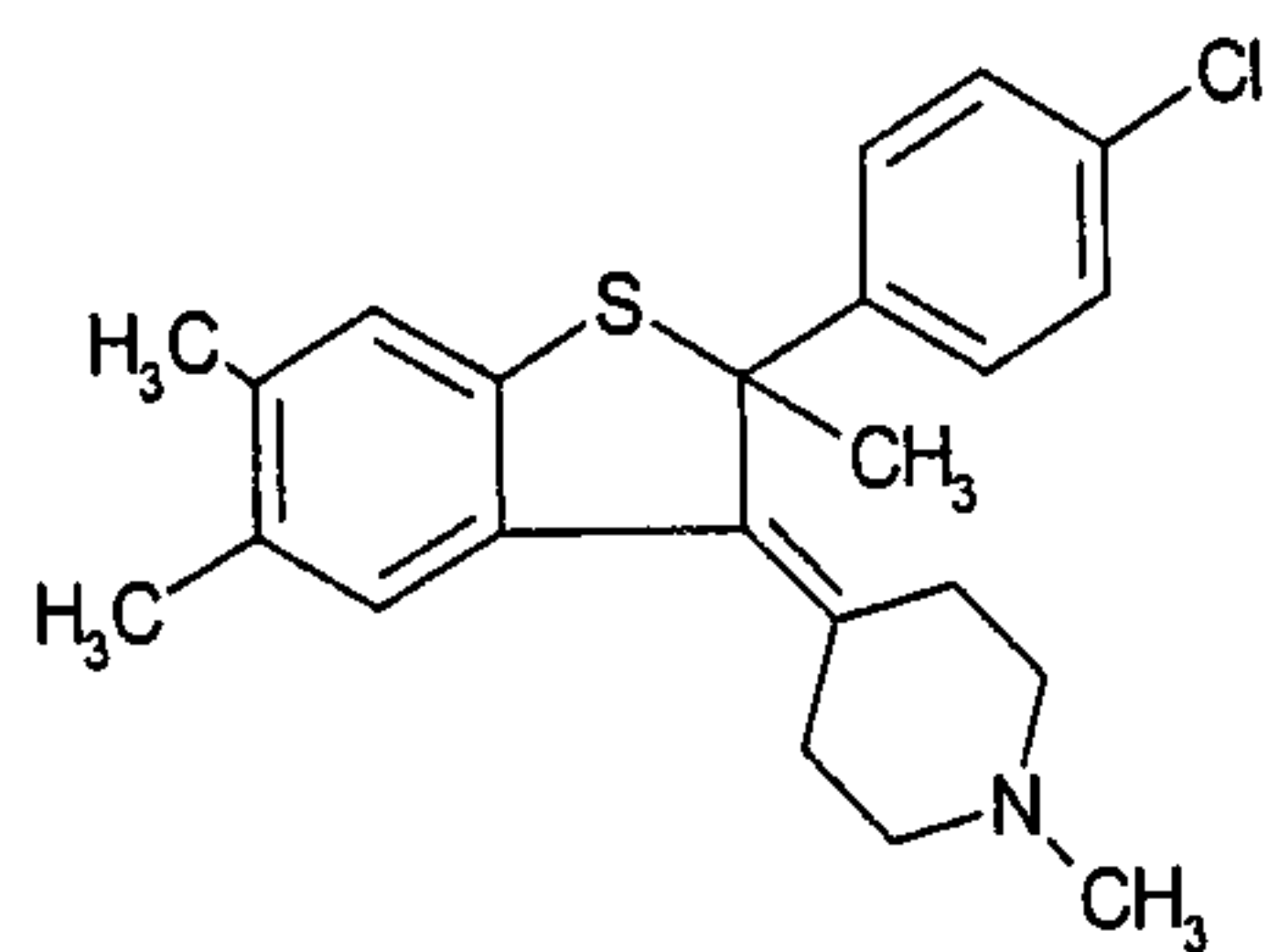


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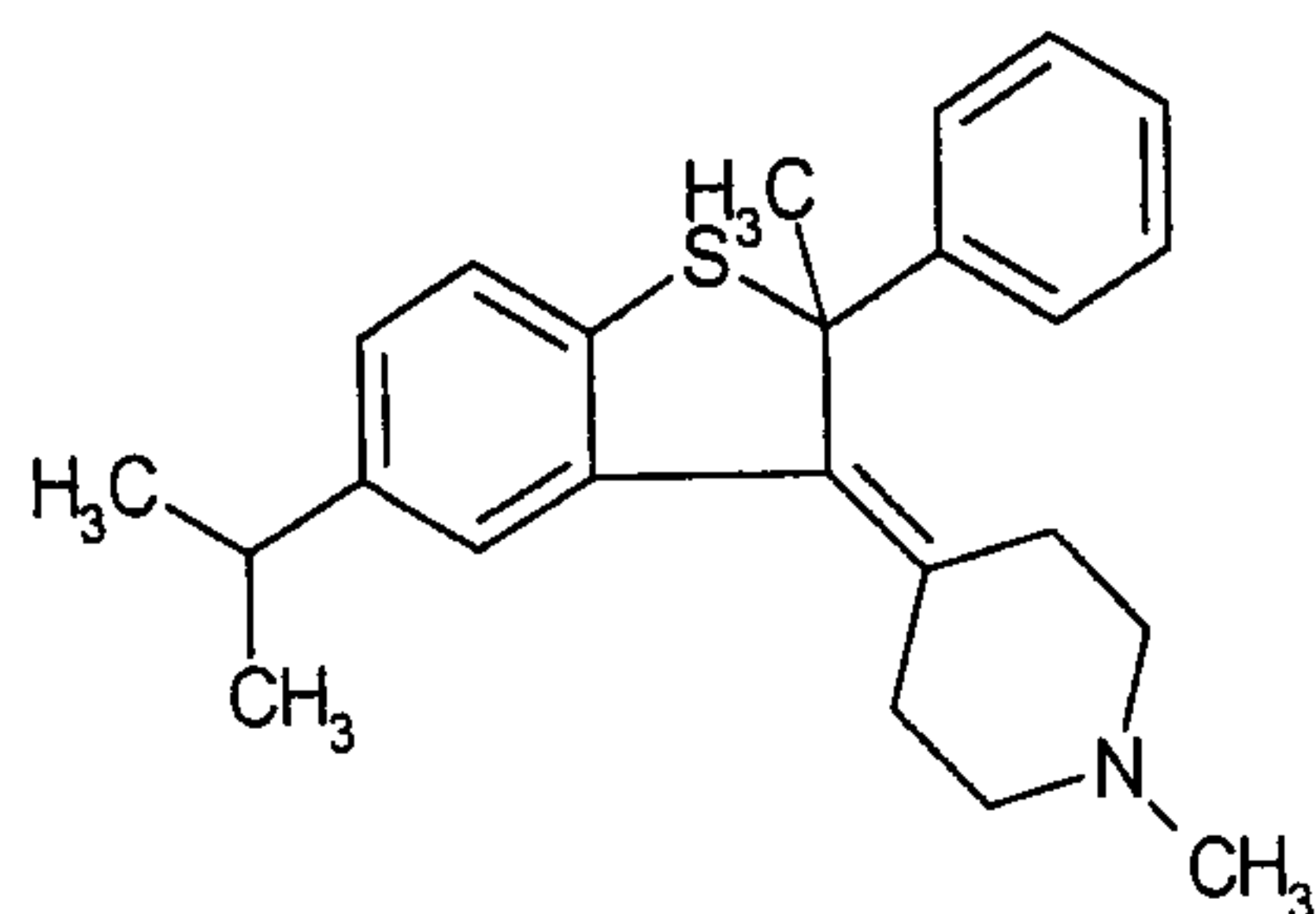
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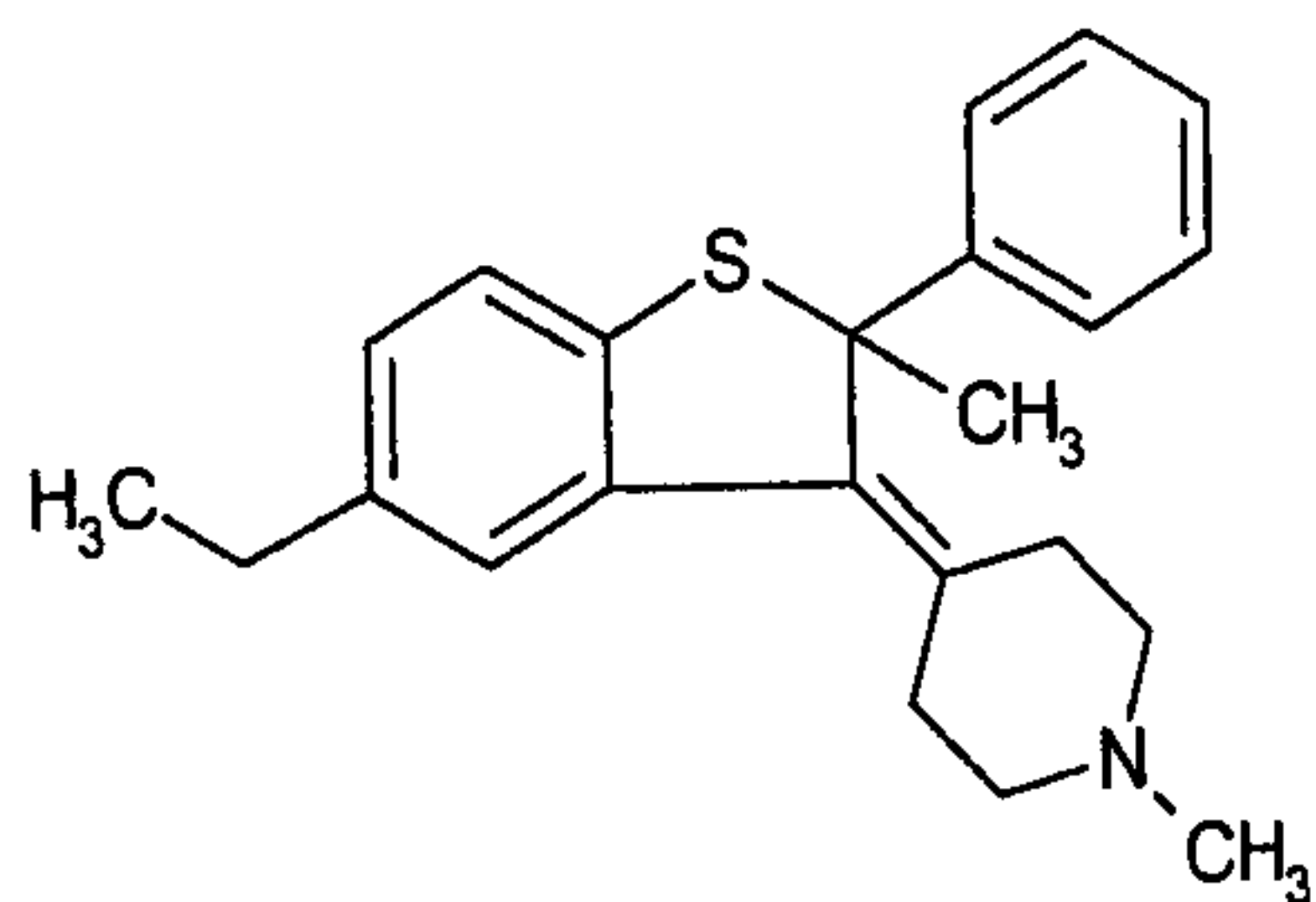
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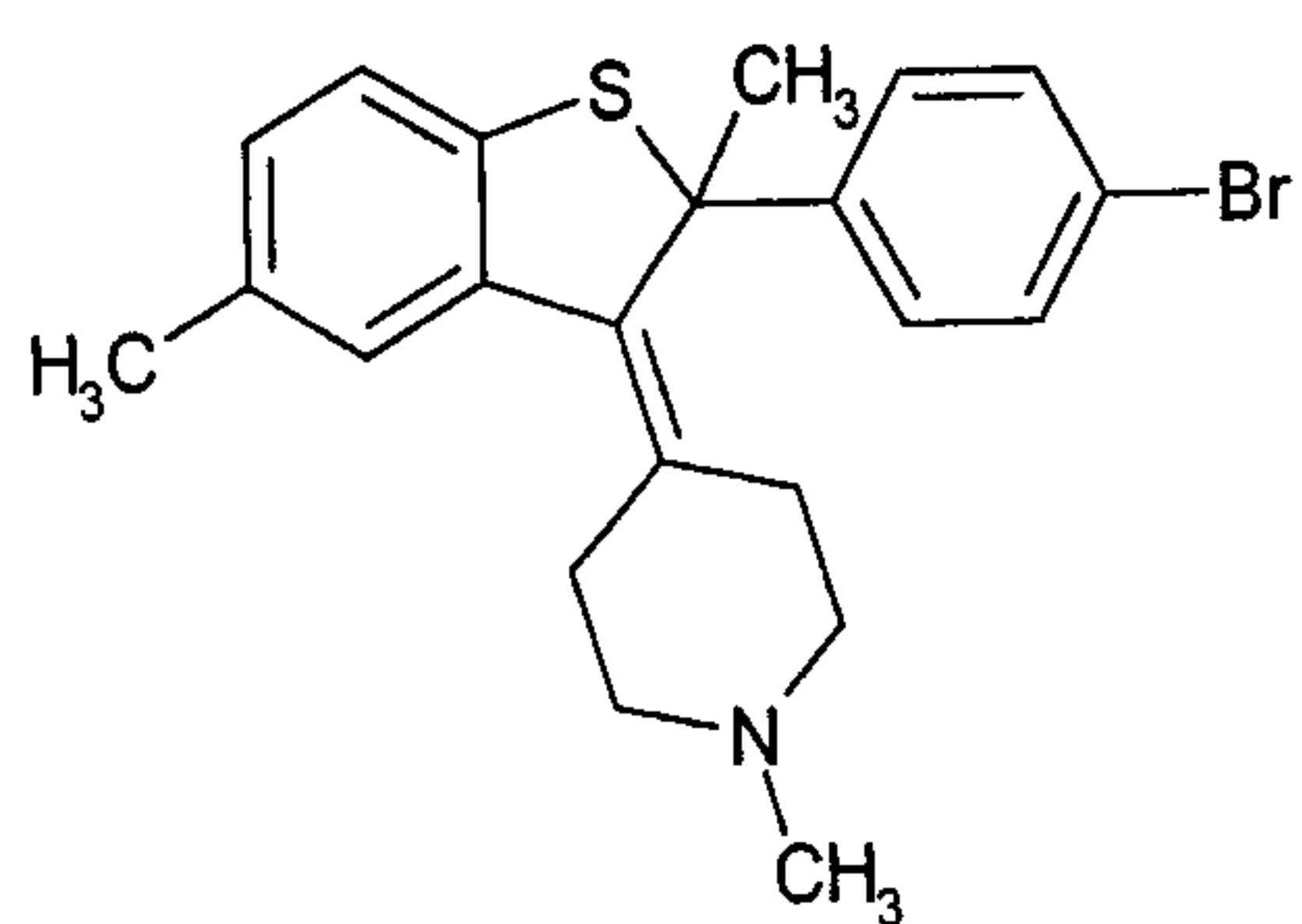
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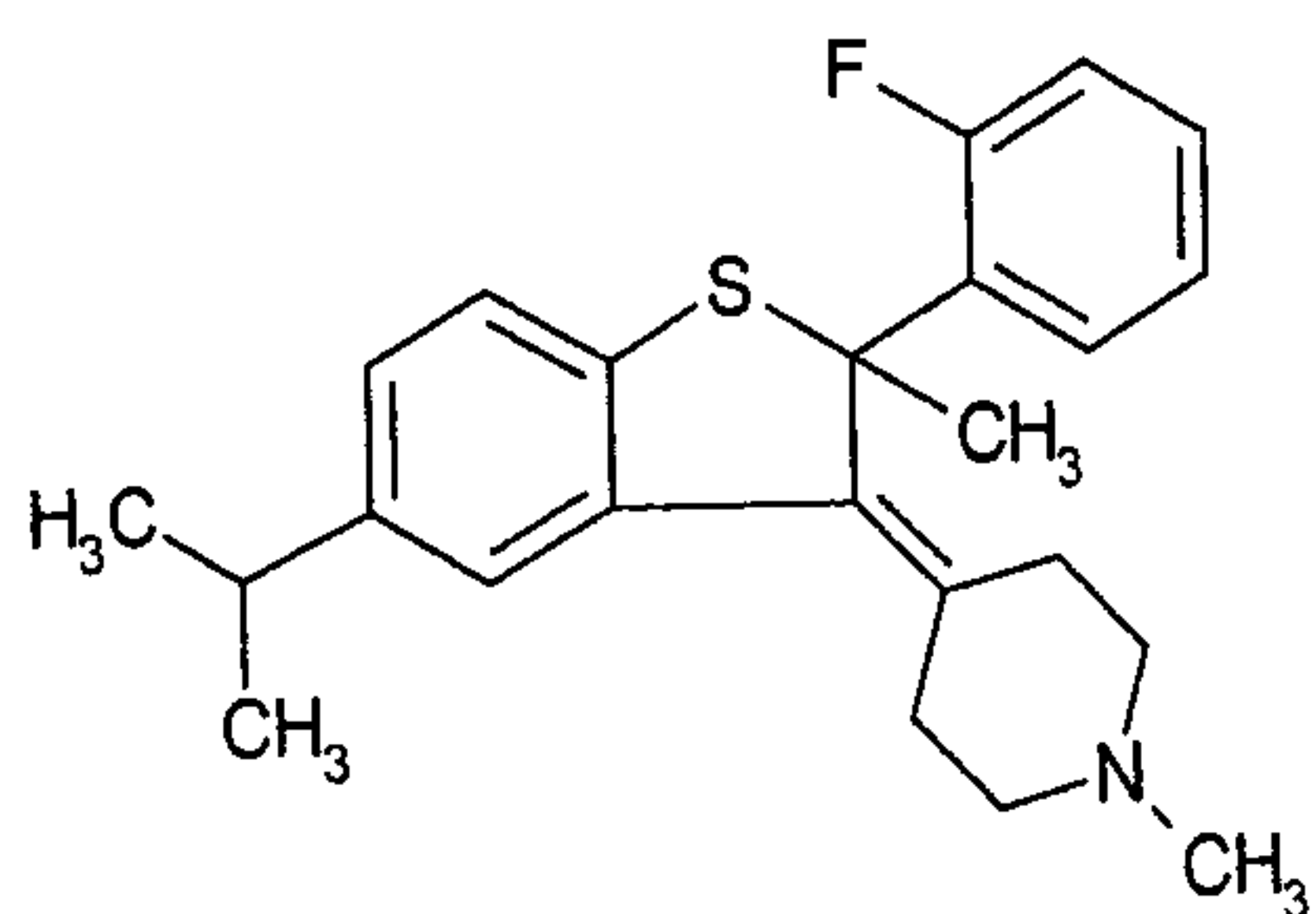
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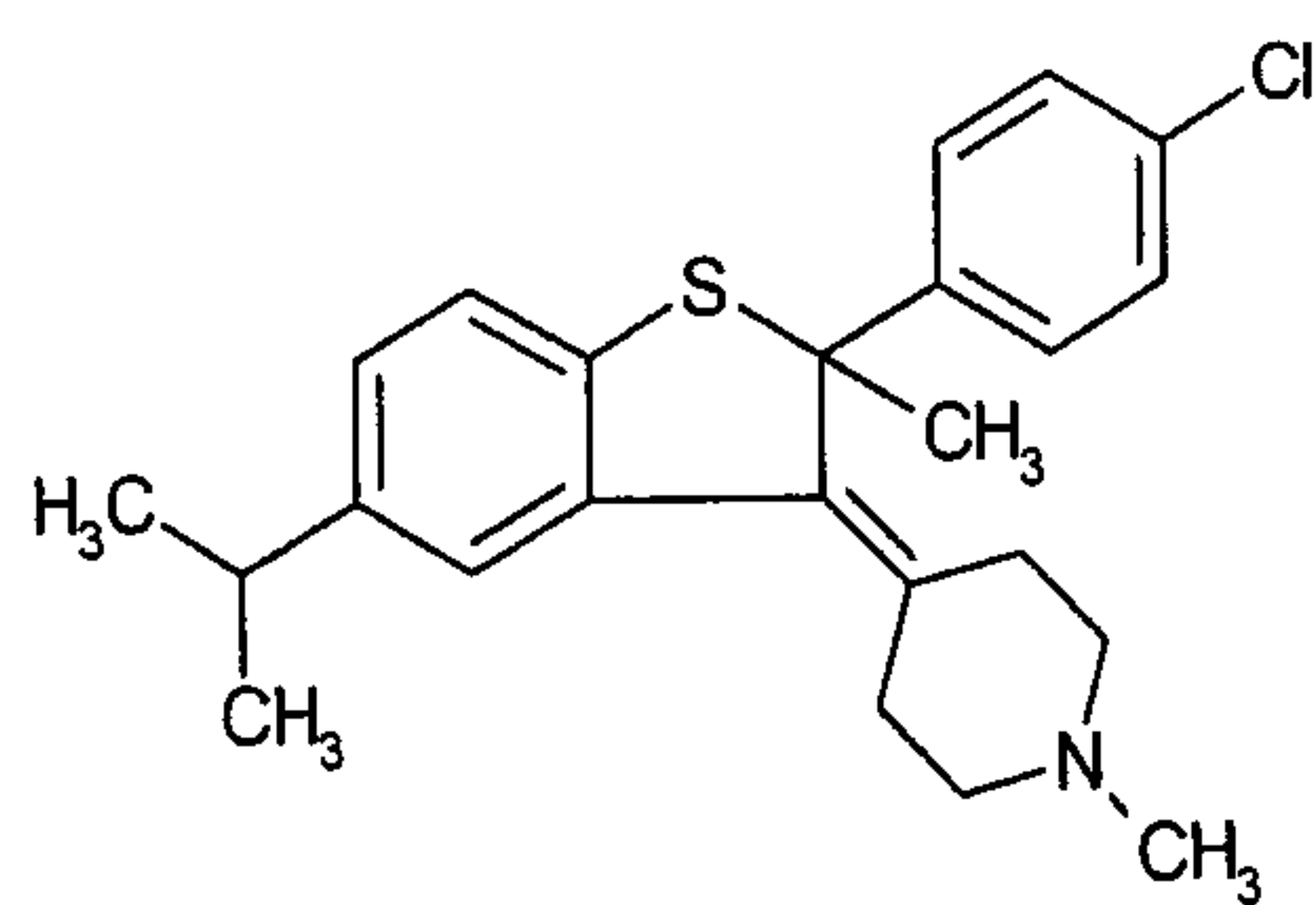
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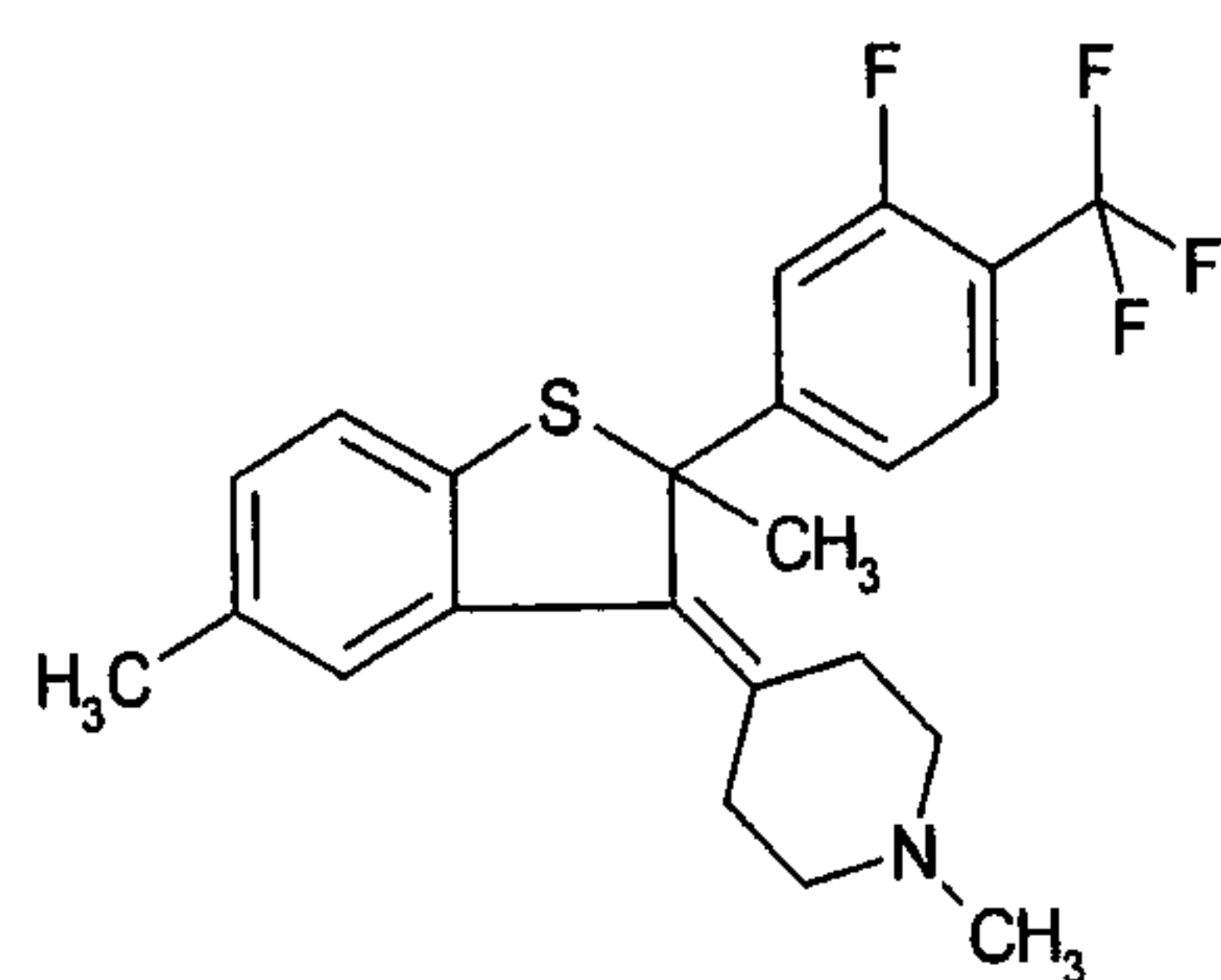
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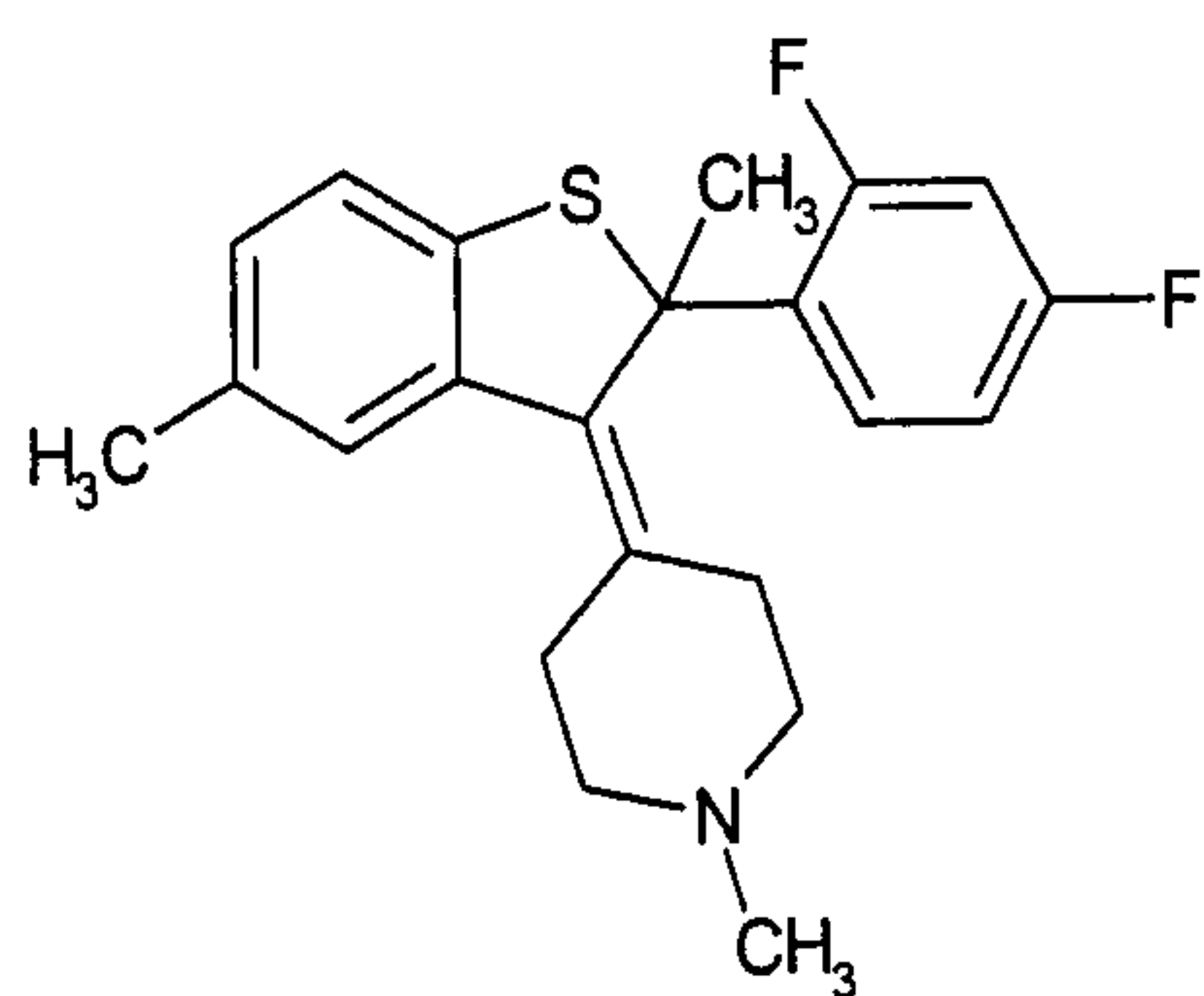
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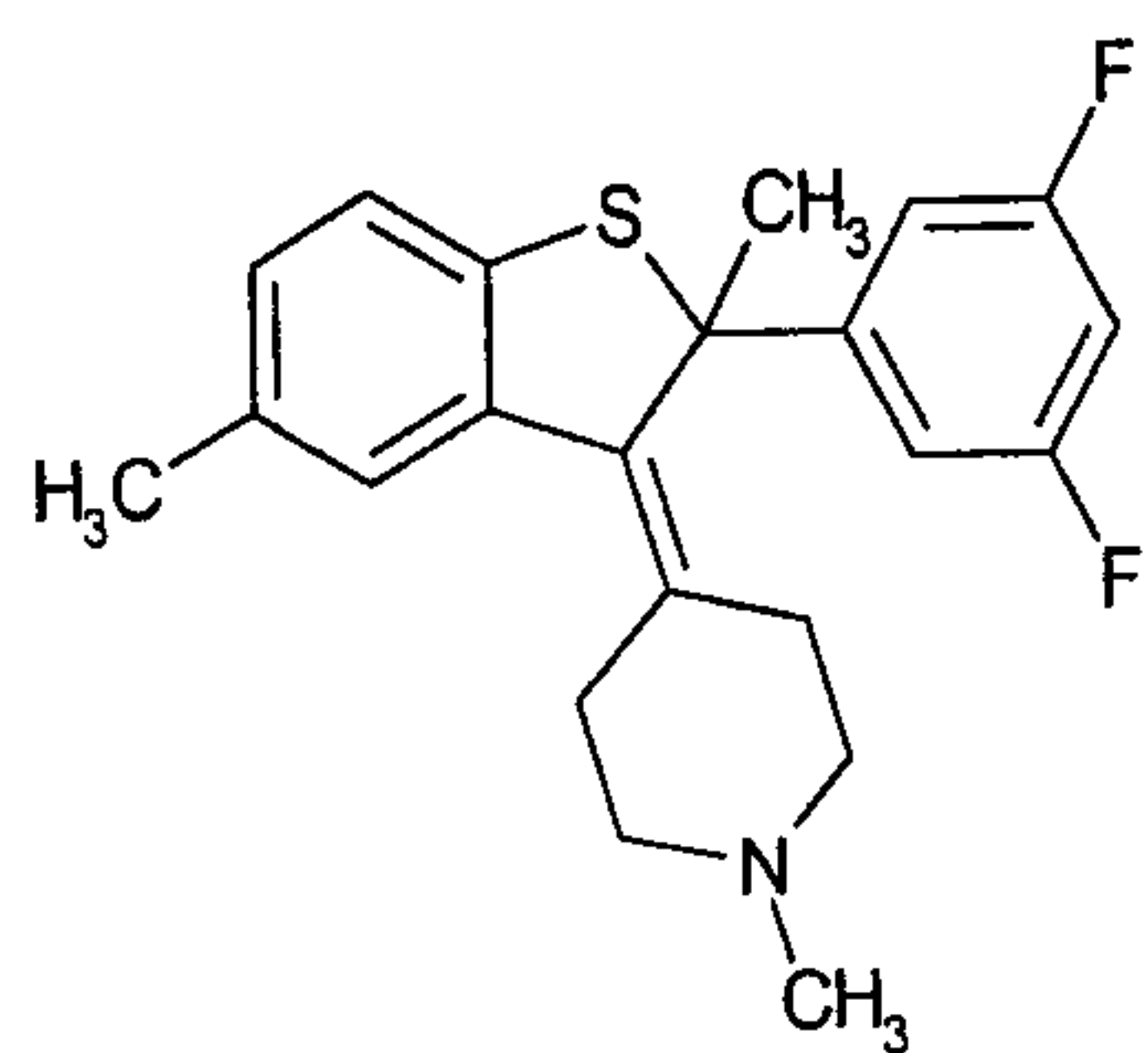
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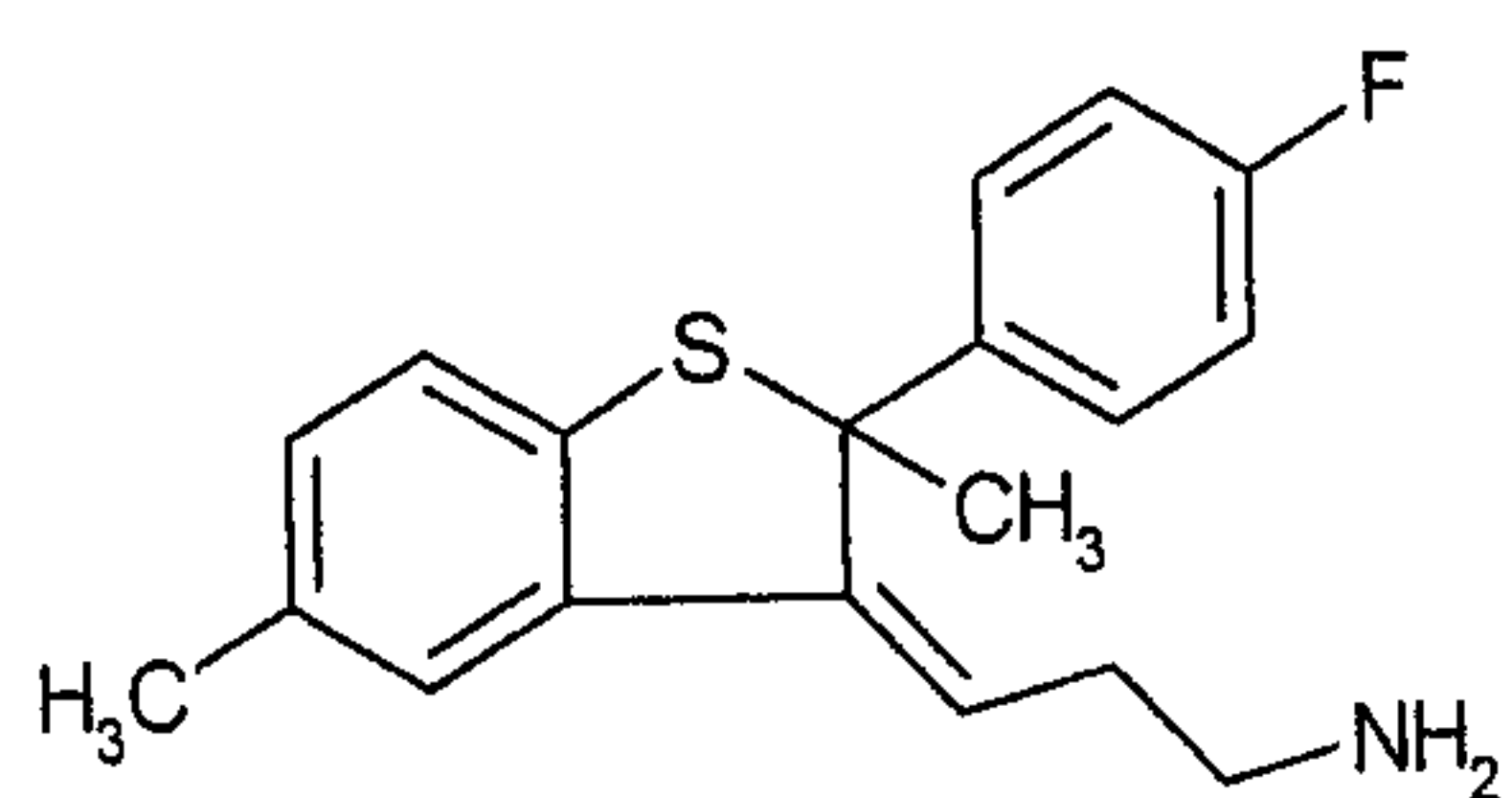
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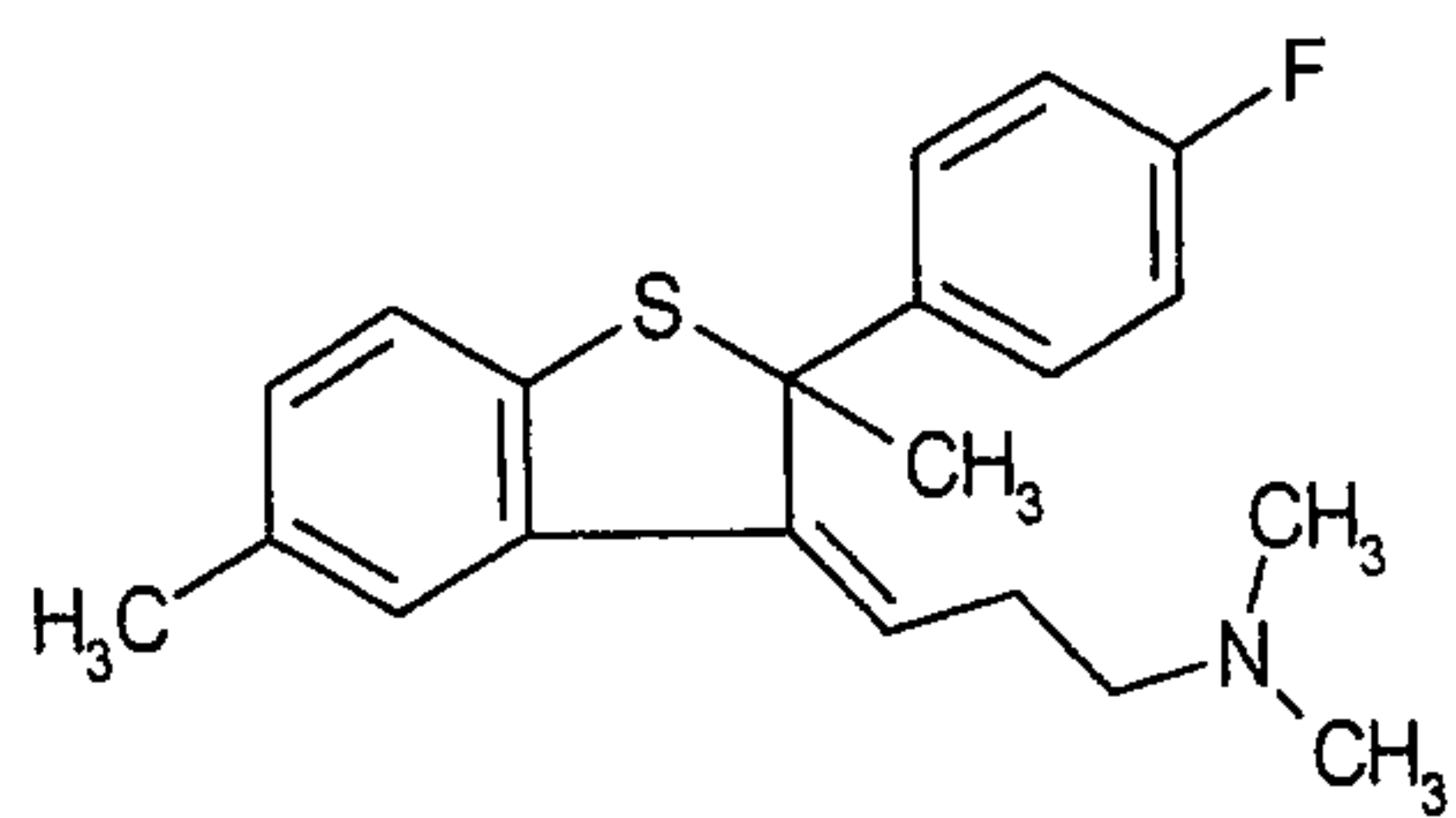
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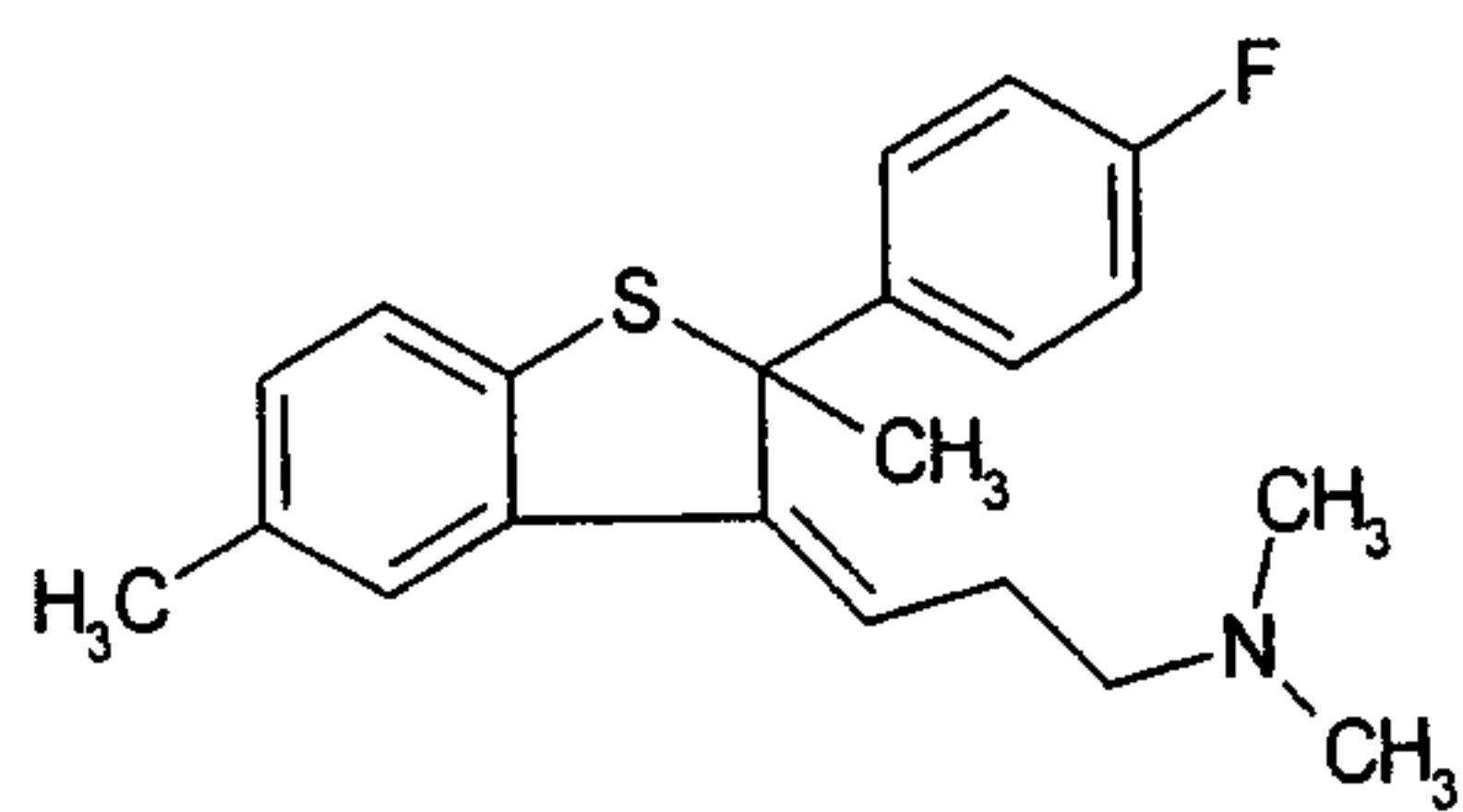
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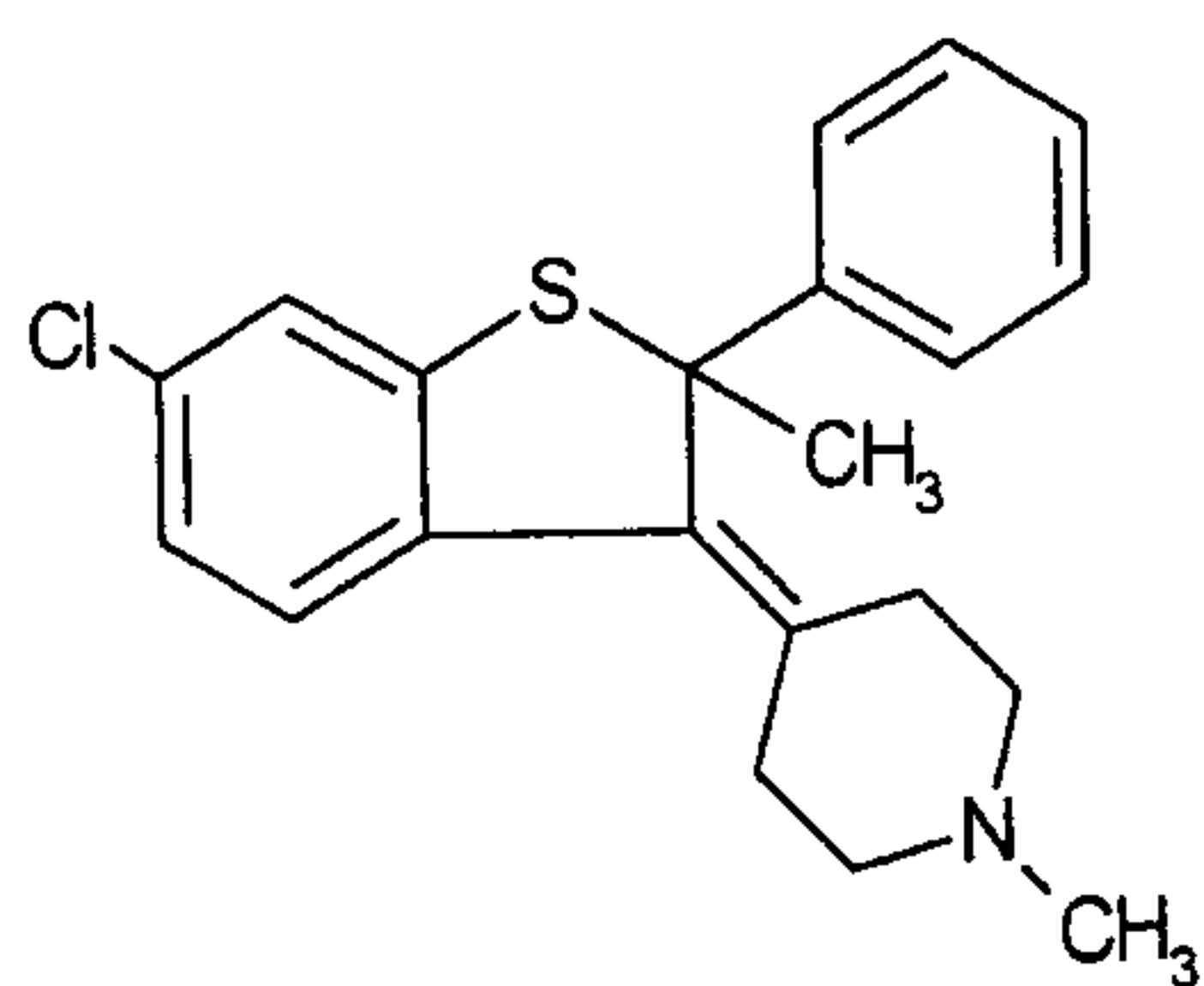
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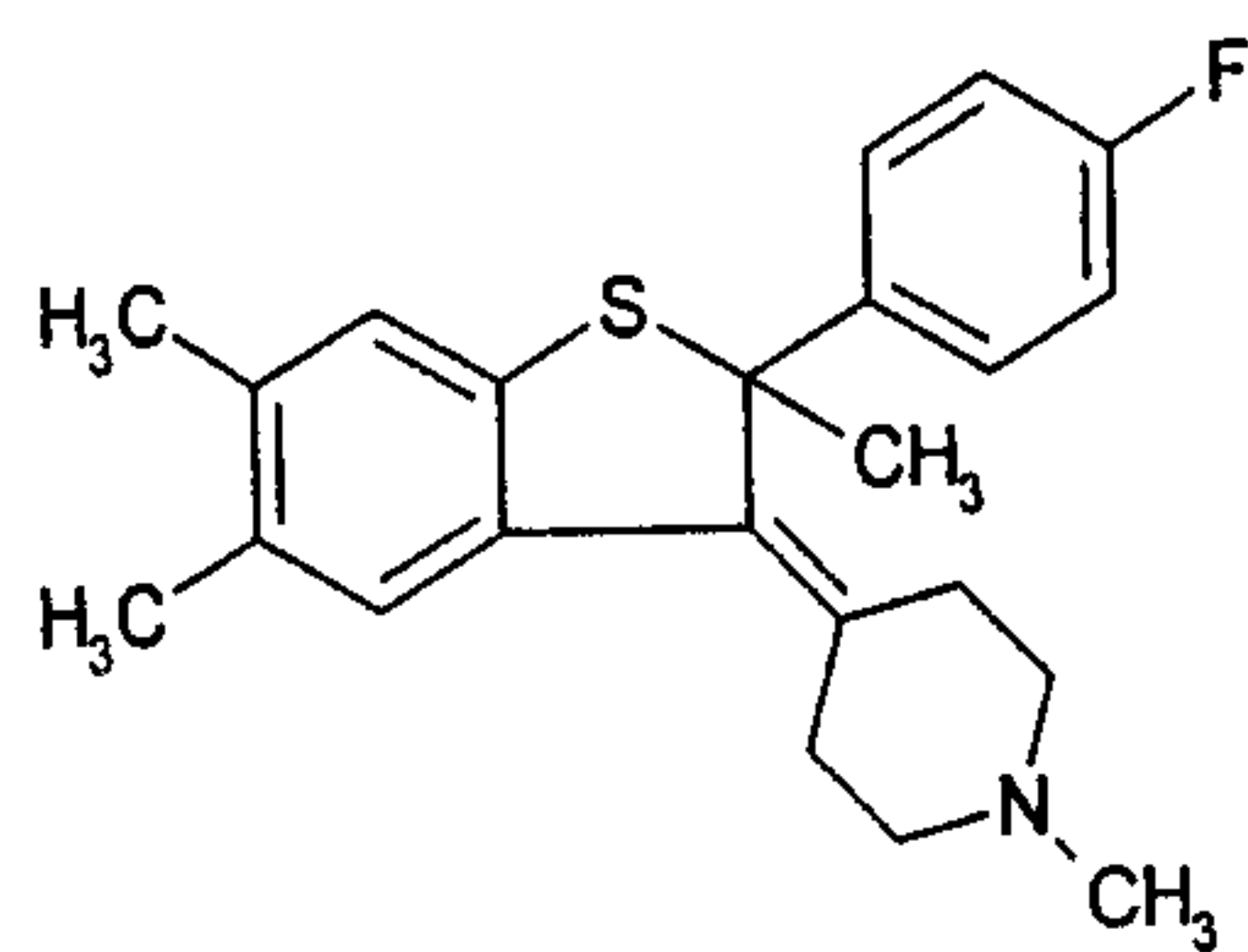
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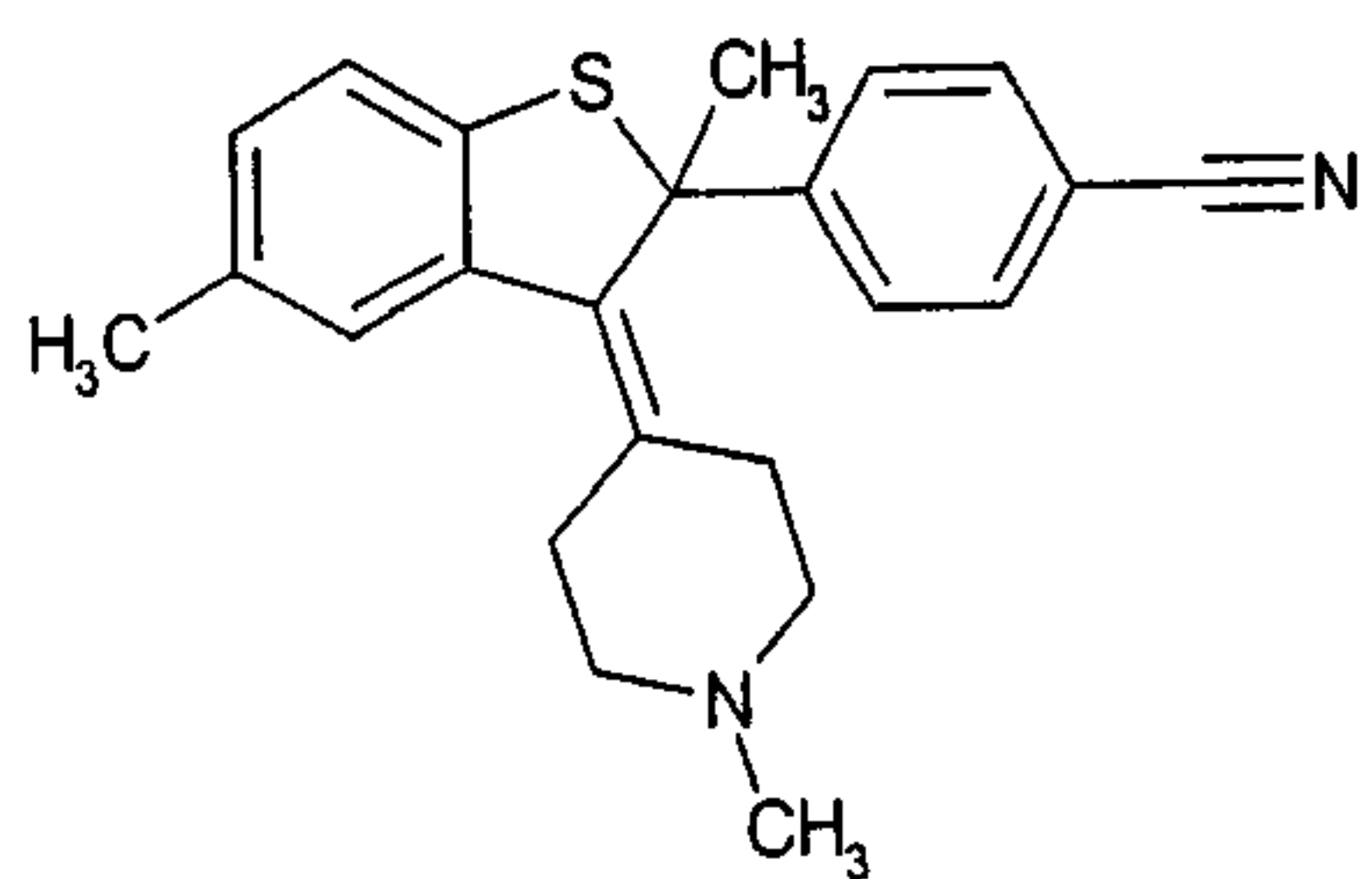
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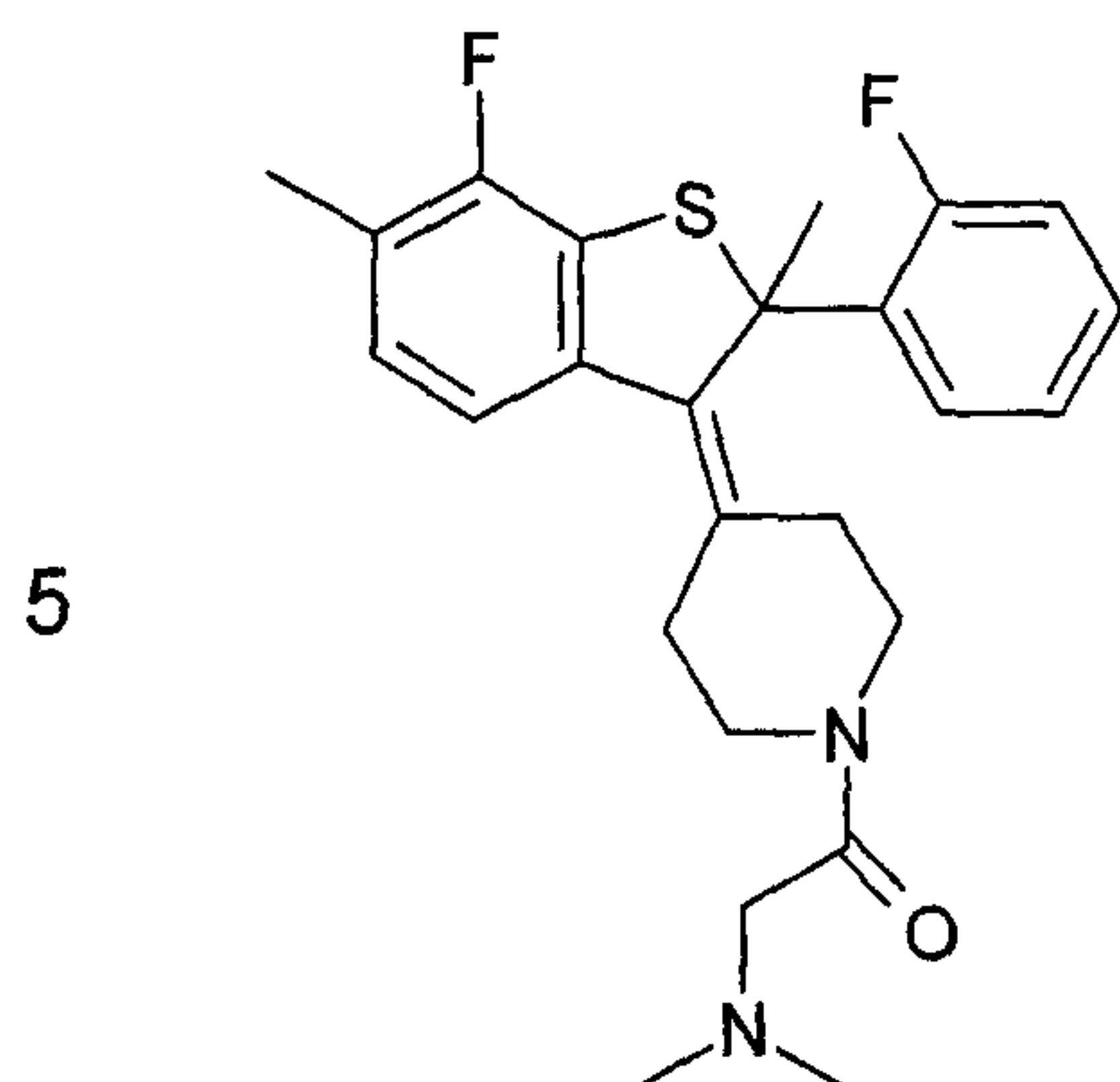
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The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use may also be made here of variants known per se which are not mentioned here in greater detail.

If desired, the starting materials may also be formed in situ so that they are not isolated from the reaction mixture, but instead are immediately converted further into the compounds of the formula I.

Suitable inert solvents are, for example, hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; nitriles, such as acetonitrile; carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene, or mixtures of the said solvents.

If desired, a functionally modified amino and/or hydroxyl group in a compound of the formula I can be liberated by solvolysis or hydrogenolysis by

conventional methods. This can be carried out, for example, using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°.

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The reduction of an ester to the aldehyde or alcohol or the reduction of a nitrile to the aldehyde or amine is carried out by methods as are known to the person skilled in the art and are described in standard works of organic chemistry.

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The said compounds according to the invention can be used in their final non-salt form. On the other hand, the present invention also relates to the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methyl-glutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other organic acids and corresponding salts thereof, such as acetate, trifluoro-

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acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

Furthermore, the base salts of the compounds according to the invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chlorprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine,

5 meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

10 Compounds of the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C₁-C₄)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C₁-C₄)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C₁₀-C₁₈)alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl(C₁-C₄)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds according to the invention can be prepared using such salts.

20 The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not intended to represent a restriction.

25 The acid-addition salts of basic compounds of the formula I are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner.

30 The free base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free base forms thereof.

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As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds according to the invention are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner.

The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

If a compound according to the invention contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the invention also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the term "pharmaceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmaco-

kinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

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The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

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Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit.

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Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

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Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

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Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medication after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture.

Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium

chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acacia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tableting machine, giving lumps of non-uniform shape which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The compounds according to the invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compound. Syrups can be prepared by dissolving the compound in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be for-

5 mulated by dispersion of the compound in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

10 The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

15 The compounds of the formula I and salts, solvates and physiologically functional derivatives thereof can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

20 The compounds of the formula I and the salts, solvates and physiologically functional derivatives thereof can also be delivered using monoclonal antibodies as individual carriers to which the compound molecules are coupled.

25 The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class

30 of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyranes, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

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Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active ingredient can be delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or suspended in a suitable carrier, in particular an aqueous solvent.

Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal pas-

sages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

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Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

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Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

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Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary.

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Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

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It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

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5 A therapeutically effective amount of a compound of the formula I depends on a number of factors, including, for example, the age and weight of the animal, the precise condition which requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound according to the invention for the treatment of neoplastic growth, for example colon or breast carcinoma, is generally in the range from 0.1 to 10 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as a single dose per day or usually in a series of part-doses (such as, for example, 15 two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the invention *per se*. It can be assumed that 20 similar doses are suitable for the treatment of other conditions mentioned above.

25 The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

30 The invention also relates to a set (kit) consisting of separate packs of
(a) an effective amount of a compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and
35 (b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound of the formula I and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

The medicaments from Table 1 are preferably, but not exclusively, combined with the compounds of the formula I. A combination of the formula I and medicaments from Table I can also be combined with compounds of the formula VI.

Table 1.		
Alkylating agents	Cyclophosphamide Busulfan Ifosfamide Melphalan Hexamethylmelamine Thiotepa Chloroambucil Dacarbazine Carmustine	Lomustine Procarbazine Altretamine Estramustine phosphate Mechloroethamine Streptozocin Temozolomide Semustine
Platinum agents	Cisplatin Oxaliplatin Spiroplatin Carboxyphthalatoplatinum Tetraplatin Ormiplatin Iproplatin	Carboplatin ZD-0473 (AnorMED) Lobaplatin (Aetema) Satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
Antimetabolites	Azacytidine Gemcitabine Capecitabine 5-Fluorouracil Floxuridine 2-Chlorodesoxyadenosine 6-Mercaptopurine 6-Thioguanine	Tomudex Trimetrexate Deoxycoformycin Fludarabine Pentostatin Raltitrexed Hydroxyurea Decitabine (SuperGen)

5		Cytarabine 2-Fluordesoxycytidine Methotrexate Idatrexate	Clofarabine (Bioenvision) Irofulven (MGI Pharrna) DMDC (Hoffmann-La Roche) Ethylnylcytidine (Taiho)
10	Topoisomerase inhibitors	Amsacrine Epirubicin Etoposide Teniposide or mitoxantrone Irinotecan (CPT-11) 7-Ethyl-10-hydroxycamptothecin Topotecan Dexrazoxanet (TopoTarget) Pixantrone (Novuspharrna) Rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharrna)	Rubitecan (SuperGen) Exatecan mesylate (Daiichi) Quinamed (ChemGenex) Gimatecan (Sigma- Tau) Diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) Elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)
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30	Antitumour antibiotics	Dactinomycin (Actinomycin D) Doxorubicin (Adriamycin) Deoxyrubicin Valrubicin Daunorubicin (Daunomycin) Epirubicin Therarubicin Idarubicin Rubidazon Plicamycinp Porfiromycin Cyanomorpholinodoxo-rubicin Mitoxantron (Novantron)	Amonafide Azonafide Anthrapyrazole Oxantrazole Losoantrone Bleomycin sulfate (Blenoxan) Bleomycinic acid Bleomycin A Bleomycin B Mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
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35	Antimitotic agents	Paclitaxel Docetaxel Colchicine Vinblastine Vincristine Vinorelbine Vindesine Dolastatin 10 (NCI)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott)
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5		Rhizoxin (Fujisawa) Mivobulin (Warner-Lambert) Cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) Vinflunine (Fabre) Auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexin (Protarga)	LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatin A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-Prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
15	Aromatase inhibitors	Aminoglutethimide Letrozole Anastrozole Formestan	Exemestan Atamestan (BioMedicines) YM-511 (Yamanouchi)
20	Thymidylate synthase inhibitors	Pemetrexed (Eli Lilly) ZD-9331 (BTG)	Nolatrexed (Eximias) CoFactor™ (BioKeys)
25	DNA antagonists	Trabectedin (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (Isotope Solutions) Thymectacin (NewBiotics) Edotreotid (Novartis)	Mafosfamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-Benzylguanine (Paligent)
30	Farnesyl transferase inhibitors	Arglabin (NuOncology Labs) Ionafernib (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnib (Johnson & Johnson) Perillyl alcohol (DOR BioPharma)
35	Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar trihydrochloride (Eli Lilly) Biricodar dicitrate (Vertex)

	Histone acetyl transferase inhibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethyl butyrate (Titan) Depsipeptide (Fujisawa)
5	Metalloproteinase inhibitors Ribonucleoside reductase inhibitors	Neovastat (Aeterna Laboratories) Marimastat (British Biotech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
10	TNF-alpha agonists/antagonists	Virulizin (Lorus Therapeutics) CDC-394 (Celgene)	Revimid (Celgene)
	Endothelin-A receptor antagonists	Atrasentan (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
15	Retinoic acid receptor agonists	Fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	Alitretinoin (Ligand)
20	Immunomodulators	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) Synchrovax vaccines (CTL Immuno) Melanoma vaccine (CTL Immuno) p21-RAS vaccine (Gem-Vax)	Dexosome therapy (Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) Cancer vaccine (Intercell) Norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) !3-Alethin (Dovetail) CLL-Thera (Vasogen)
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30	Hormonal and antihormonal agents	Oestrogens Conjugated oestrogens Ethynyloestradiol Chlorotrianisene Idenestrol Hydroxyprogesterone caproate Medroxyprogesterone Testosterone Testosterone propionate	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Bicalutamide Flutamide Octreotide
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5		Fluoxymesterone Methyltestosterone Diethylstilbestrol Megestrol Tamoxifen Toremofin Dexamethasone	Nilutamide Mitotan P-04 (Novogen) 2-Methoxyoestradiol (EntreMed) Arzoxifen (Eli Lilly)
10	Photodynamic agents	Talaporfin (Light Sciences) Theralux (Theratechnologies) Motexafin-Gadolinium (Pharmacyclics)	Pd-Bacteriopheophorbid (Yeda) Lutetium-Texaphyrin (Pharmacyclics) Hypericin
15	Tyrosine kinase inhibitors	Imatinib (Novartis) Leflunomide (Sugen/Pharmacia) ZD1839 (AstraZeneca) Erlotinib (Oncogene Science) Canertinib (Pfizer) Squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) Vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmith-Kline) EKB-509 (Wyeth) EKB-569 (Wyeth)	Kahalide F (PharmaMar) CEP-701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
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30	Various agents	SR-27897 (CCK-A inhibitor, Sanofi-Synthelabo) Tocladesine (cyclic AMP agonist, Ribapharm) Alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2 inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phytopharm) CapCell™ (CYP450 stimulant, Bavarian Nordic) GCS-100 (gal3 antagonist, GlycoGenesys) G17DT immunogen (gas-	BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (ribonuclease stimulant, Alfacell) Galarubicin (RNA synthesis inhibitor, Dong-A) Tirapazamine (reducing agent, SRI International) N-Acetylcysteine (reducing agent, Zambon) R-Flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech) Seocalcitol (vitamin D
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5	trin inhibitor, Aphton) Efaproxiral (oxygenator, Allos Therapeutics) PI-88 (heparanase inhibi- tor, Progen) Tesmilifen (histamine an- tagonist, YM BioSciences) Histamine (histamine H2 receptor agonist, Maxim) Tiazofurin (IMPDH inhibi- tor, Ribapharm)	receptor agonist, Leo) 131-I-TM-601 (DNA antagonist, TransMolecular) Eflornithin (ODC inhibitor, ILEX Oncology) Minodronic acid (osteoclast inhibitor, Yamanouchi) Indisulam (p53 stimulant, Eisai)
10	Cilengitide (integrin an- tagonist, Merck KGaA) SR-31747 (IL-1 antagonist, Sanofi-Synthelabo) CCI-779 (mTOR kinase inhibitor, Wyeth) Exisulind (PDE-V inhibitor, Cell Pathways)	Aplidin (PPT inhibitor, PharmaMar) Rituximab (CD20 antibody, Genentech) Gemtuzumab (CD33 antibody, Wyeth Ayerst) PG2 (haematopoiesis promoter, Pharmagenesis)
15	CP-461 (PDE-V inhibitor, Cell Pathways) AG-2037 (GART inhibitor, Pfizer)	Immunol™ (triclosan mouthwash, Endo) Triacetyluridine (uridine prodrug, Wellstat)
20	WX-UK1 (plasminogen activator inhibitor, Willex) PBI-1402 (PMN stimulant, ProMetic LifeSciences) Bortezomib (proteasome inhibitor, Millennium) SRL-172 (T-cell stimulant, SR Pharma)	SN-4071 (sarcoma agent, Signature BioScience) TransMID-107™ (immunotoxin, KS Biomedix) PCK-3145 (apoptosis promoter, Procyon)
25	TLK-286 (glutathione-S transferase inhibitor, Telik) PT-100 (growth factor agonist, Point Therapeu- tics)	Doranidazole (apoptosis promoter, Pola) CHS-828 (cytotoxic agent, Leo) Trans-retinic acid (differentiator, NIH)
30	Midostaurin (PKC inhibitor, Novartis) Bryostatin-1 (PKC stimu- lant, GPC Biotech) CDA-II (apoptosis pro- moter, Everlife)	MX6 (apoptosis promoter, MAXIA) Apomine (apoptosis promoter, ILEX Oncology) Urocidin (apoptosis promoter, Bioniche)
35	SDX-101 (apoptosis pro- moter, Salmedix) Ceflatonin (apoptosis pro- moter, ChemGenex)	Ro-31-7453 (apoptosis promoter, La Roche) Brostallicin (apoptosis promoter, Pharmacia)

5	Alkylating agents	Cyclophosphamide Busulfan Ifosfamide Melphalan Hexamethylmelamine Thiotepa Chloroambucil Dacarbazine Carmustine	Lomustine Procarbazine Altretamine Estramustine phosphate Mechloroethamine Streptozocin Temozolomide Semustine
10	Platinum agents	Cisplatin Oxaliplatin Spiroplatin Carboxyphthalatoplatinum Tetraplatin Ormiplatin Iproplatin	Carboplatin ZD-0473 (AnorMED) Lobaplatin (Aetema) Satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
20	Antimetabolites	Azacytidine Gemcitabine Capecitabine 5-Fluorouracil Floxuridine 2-Chlorodesoxyadenosine 6-Mercaptopurine 6-Thioguanine Cytarabine 2-Fluordesoxycytidine Methotrexate Idatrexate	Tomudex Trimetrexate Deoxycoformycin Fludarabine Pentostatin Raltitrexed Hydroxyurea Decitabine (SuperGen) Clofarabine (Bioenvision) Irofulven (MGI Pharma) DMDC (Hoffmann-La Roche) Ethinylcytidine (Taiho)
30	Topoisomerase inhibitors	Amsacrine Epirubicin Etoposide Teniposide or mitoxantrone Irinotecan (CPT-11) 7-Ethyl-10- hydroxycamptothecin Topotecan Dexrazoxanet (TopoTarget) Pixantrone (Novuspharma) Rebeccamycin analogue	Rubitecan (SuperGen) Exatecan mesylate (Daiichi) Quinamed (ChemGenex) Gimatecan (Sigma- Tau) Diflomotecan (Beaufour- Ipsen) TAS-103 (Taiho) Elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang)
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	(Exelixis) BBR-3576 (Novuspharma)	KW-2170 (Kyowa Hakko)
5	Antitumour antibiotics	Dactinomycin (Actinomycin D) Doxorubicin (Adriamycin) Deoxyrubicin Valrubicin Daunorubicin (Daunomycin) Epirubicin Therarubicin Idarubicin Rubidazon Plicamycin Porfiromycin Cyanomorpholinodoxo-rubicin Mitoxantron (Novantron)
10		Amonafide Azonafide Anthrapyrazole Oxantrazole Losoξανtrone Bleomycin sulfate (Blenoxan) Bleomycinic acid Bleomycin A Bleomycin B Mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
15		
20	Antimitotic agents	Paclitaxel Docetaxel Colchicine Vinblastine Vincristine Vinorelbine Vindesine Dolastatin 10 (NCI) Rhizoxin (Fujisawa) Mivobulin (Warner-Lambert) Cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) Vinflunine (Fabre) Auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexin (Protarga)
25		SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatin A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-Prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
30		
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	Aromatase	Aminoglutethimide Exemestan

	inhibitors	Letrozole Anastrozole Formestan	Atamestan (BioMedicines) YM-511 (Yamanouchi)
5	Thymidylate synthase inhibitors	Pemetrexed (Eli Lilly) ZD-9331 (BTG)	Nolatrexed (Eximias) CoFactor™ (BioKeys)
10	DNA antagonists	Trabectedin (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (Isotope Solutions) Thymectacin (NewBiotics) Edotreotid (Novartis)	Mafofosfamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-Benzylguanine (Paligent)
15	Farnesyl transferase inhibitors	Arglabin (NuOncology Labs) Ionafernib (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnib (Johnson & Johnson) Perillyl alcohol (DOR BioPharma)
20	Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar trihydrochloride (Eli Lilly) Biricodar dicitrate (Vertex)
	Histone acetyl transferase inhibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethyl butyrate (Titan) Depsipeptide (Fujisawa)
25	Metalloproteinase inhibitors Ribonucleoside reductase inhibitors	Neovastat (Aeterna Laboratories) Marimastat (British Biotech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
30	TNF-alpha agonists/ antagonists	Virulizin (Lorus Therapeutics) CDC-394 (Celgene)	Revimid (Celgene)
35	Endothelin-A receptor antagonists	Atrasentan (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
	Retinoic acid	Fenretinide (Johnson &	Alitretinoin (Ligand)

	receptor agonists	Johnson) LGD-1550 (Ligand)	
5	Immuno-modulators	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) Synchrovax vaccines (CTL Immuno) Melanoma vaccine (CTL Immuno) p21-RAS vaccine (GemVax)	Dexosome therapy (Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) Cancer vaccine (Intercell) Norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) !3-Alethin (Dovetail) CLL-Thera (Vasogen)
15	Hormonal and antihormonal agents	Oestrogens Conjugated oestrogens Ethinylloestradiol Chlorotrianisene Idenestrol Hydroxyprogesterone caproate Medroxyprogesterone Testosterone Testosterone propionate Fluoxymesterone Methyltestosterone Diethylstilbestrol Megestrol Tamoxifen Toremofin Dexamethasone	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Bicalutamide Flutamide Octreotide Nilutamide Mitotan P-04 (Novogen) 2-Methoxyoestradiol (EntreMed) Arzoxifen (Eli Lilly)
30	Photodynamic agents	Talaporfin (Light Sciences) Theralux (Theratechnologies) Motexafin-Gadolinium (Pharmacyclics)	Pd-Bacteriopheophorbid (Yeda) Lutetium-Texaphyrin (Pharmacyclics) Hypericin
35	Tyrosine kinase inhibitors	Imatinib (Novartis) Leflunomide(Sugen/Pharmacia) ZDI839 (AstraZeneca) Erlotinib (Oncogene	Kahalide F (PharmaMar) CEP- 701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis)

5	Science) Canertinib (Pfizer) Squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) Vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline)	Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
10	EKB-509 (Wyeth) EKB-569 (Wyeth)	
15	Various agents SR-27897 (CCK-A inhibitor, Sanofi- Synthelabo) Tocladesine (cyclic AMP agonist, Ribapharm) Alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2 inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phytopharm)	BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (ribonuclease stimulant, Alfacell) Galarubicin (RNA synthesis inhibitor, Dong- A)
20	CapCell™ (CYP450 stimulant, Bavarian Nordic) GCS-100 (gal3 antagonist, GlycoGenesys) G17DT immunogen (gastrin inhibitor, Aphton)	Tirapazamine (reducing agent, SRI International) N-Acetylcysteine (reducing agent, Zambon) R-Flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech)
25	Efaproxiral (oxygenator, Allos Therapeutics) PI-88 (heparanase inhibitor, Progen) Tesmifen (histamine antagonist, YM BioSciences)	Seocalcitol (vitamin D receptor agonist, Leo) 131-I-TM-601 (DNA antagonist, TransMolecular) Eflornithin (ODC inhibitor, ILEX Oncology)
30	Histamine (histamine H2 receptor agonist, Maxim) Tiazofurin (IMPDH inhibitor, Ribapharm) Cilengitide (integrin antagonist, Merck KGaA)	Minodronic acid (osteoclast inhibitor, Yamanouchi) Indisulam (p53 stimulant, Eisai) Aplidin (PPT inhibitor, PharmaMar)
35	SR-31747 (IL-1 antagonist, Sanofi-Synthelabo) CCI-779 (mTOR kinase inhibitor, Wyeth)	Rituximab (CD20 antibody, Genentech) Gemtuzumab (CD33 antibody, Wyeth Ayerst) PG2 (haematopoiesis

5	Exisulind (PDE-V inhibitor, Cell Pathways)	promoter, Pharmagenesis)
	CP-461 (PDE-V inhibitor, Cell Pathways)	Immunol™ (triclosan mouthwash, Endo)
	AG-2037 (GART inhibitor, Pfizer)	Triacetyluridine (uridine prodrug, Wellstat)
	WX-UK1 (plasminogen activator inhibitor, Willex)	SN-4071 (sarcoma agent, Signature BioScience)
	PBI-1402 (PMN stimulant, ProMetic LifeSciences)	TransMID-107™ (immunotoxin, KS Biomedix)
10	Bortezomib (proteasome inhibitor, Millennium)	PCK-3145 (apoptosis promoter, Procyon)
	SRL-172 (T-cell stimulant, SR Pharma)	Doranidazole (apoptosis promoter, Pola)
	TLK-286 (glutathione-S transferase inhibitor, Telik)	CHS-828 (cytotoxic agent, Leo)
	PT-100 (growth factor agonist, Point Therapeutics)	Trans-retinic acid (differentiator, NIH)
15	Midostaurin (PKC inhibitor, Novartis)	MX6 (apoptosis promoter, MAXIA)
	Bryostatin-1 (PKC stimulant, GPC Biotech)	Apomine (apoptosis promoter, ILEX Oncology)
	CDA-II (apoptosis promoter, Everlife)	Urocidin (apoptosis promoter, Bioniche)
20	SDX-101 (apoptosis promoter, Salmedix)	Ro-31-7453 (apoptosis promoter, La Roche)
	Ceflatonin (apoptosis promoter, ChemGenex)	Brostallicin (apoptosis promoter, Pharmacia)

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The compounds of the formula I are preferably combined with known anti-cancer agents:

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The present compounds are also suitable for combination with known anti-cancer agents. These known anti-cancer agents include the following: oestrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl- protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors and other angiogenesis inhibitors. The present compounds are particularly suitable for administration at the same

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time as radiotherapy. The synergistic effects of inhibition of VEGF in combination with radiotherapy have been described by specialists (see WO 00/61186).

5 "Oestrogen receptor modulators" refers to compounds which interfere with or inhibit the binding of oestrogen to the receptor, regardless of mechanism. Examples of oestrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY 117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]phenyl 2,2-dimethylpropanoate, 10 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone and SH646.

"Androgen receptor modulators" refers to compounds which interfere with or inhibit the binding of androgens to the receptor, regardless of mechanism. 15 Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere with or inhibit the binding of retinoids to the receptor, regardless of mechanism. 20 Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl)retinamide and N-4-carboxyphenylretinamide.

25 "Cytotoxic agents" refers to compounds which result in cell death primarily through direct action on the cellular function or inhibit or interfere with cell myosis, including alkylating agents, tumour necrosis factors, intercalators, microtubulin inhibitors and topoisomerase inhibitors.

30 Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosylate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, loba- 35 platin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-

aminedichloro(2-methylpyridine)platinum, benzylguanine, glufosfamide,
 GPX100, (trans,trans,trans)bis-mu-(hexane-1,6-diamine)mu-[diamine-
 platinum(II)]bis[diamine(chloro)platinum(II)] tetrachloride, diarisidinyl-
 spermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-
 5 dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxan-
 trone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplastone, 3'-de-
 amino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, gala-
 rubicin, elinafide, MEN10755 and 4-demethoxy-3-deamino-3-aziridinyl-4-
 10 methylsulfonyldaunorubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate,
 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin,
 dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881,
 15 BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-
 methoxyphenyl)benzenesulfonamide, anhydrovinblastine, N,N-dimethyl-L-
 valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258 and
 BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine,
 20 irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exobenzylidenechartreusin,
 9-methoxy-N,N-dimethyl-5-nitropyrzolo[3,4,5-kl]acridine-2- (6H)propan-
 amine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-
 benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione,
 25 lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350,
 BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobu-
 zoxane, 2'-dimethylamino-2'-deoxyetoposide, GL331, N-[2-(dimethylamino)-
 ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide,
 30 asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-
 methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexo-
 hydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-
 methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium, 6,9-bis[(2-amino-
 ethyl)amino]benzo[g]isoquinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-
 35 dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-
 one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-

ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one and dimesna.

5 "Antiproliferative agents" include antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231 and INX3001 and anti-metabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosphate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tia-

10 zofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-mannohepto-

15 pyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b]-1,4-thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo-

20 (7.4.1.0.0)tetradeca-2,4,6-trien-9-ylacetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabinofuranosyl cytosine and 3-aminopyridine-2-carboxaldehyde thio-semicarbazone. "Antiproliferative agents" also include monoclonal anti-

25 bodies to growth factors other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumour suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see US Patent No. 6,069,134, for example).

30 Particular preference is given to the use of the compound according to the invention for the treatment and prophylaxis of tumour diseases.

35 The tumour is preferably selected from the group of tumours of the squamous epithelium, of the bladder, of the stomach, of the kidneys, of head and neck, of the oesophagus, of the cervix, of the thyroid, of the intestine,

of the liver, of the brain, of the prostate, of the urogenital tract, of the lymphatic system, of the stomach, of the larynx and/or of the lung.

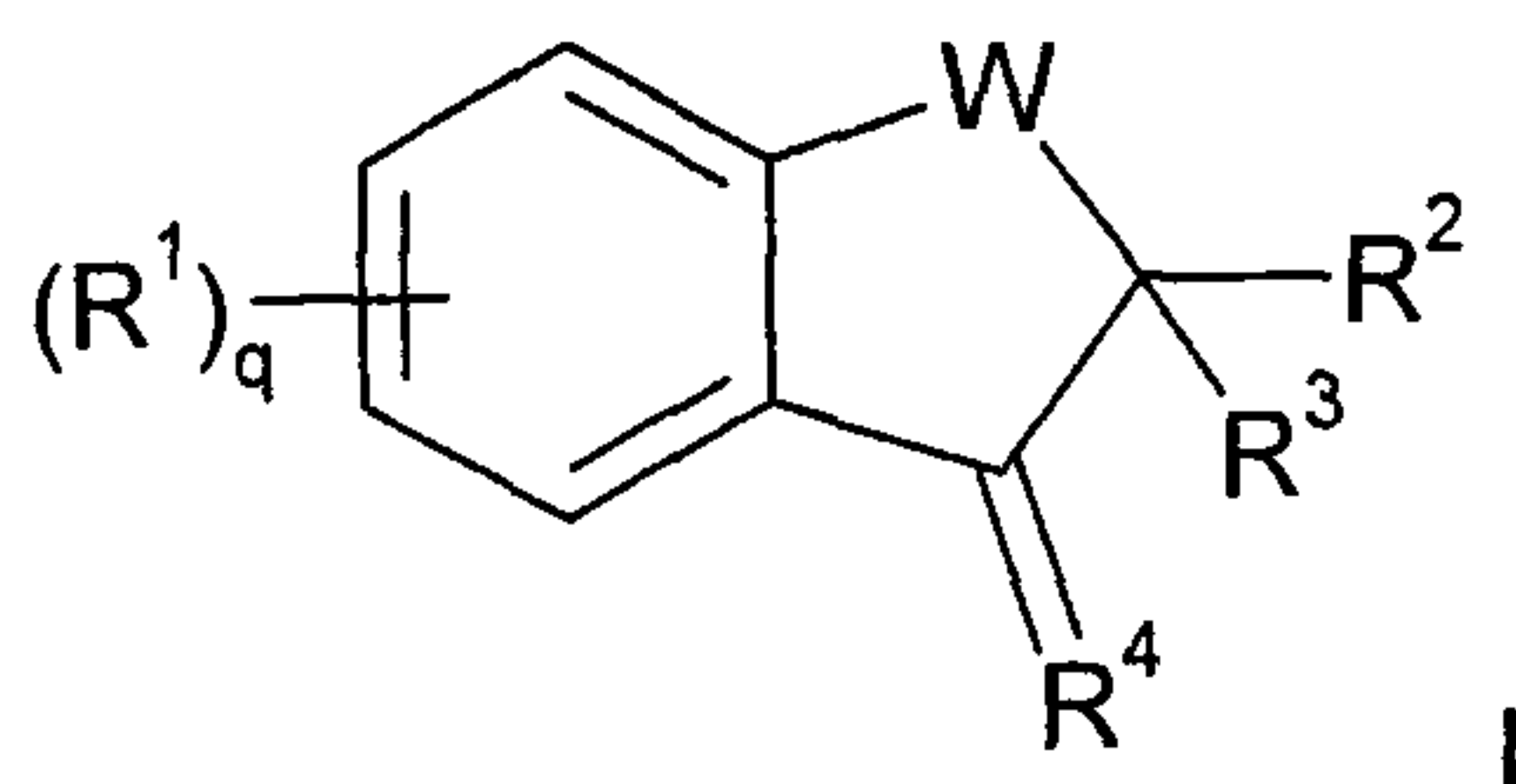
5 The tumour is furthermore preferably selected from the group lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, glioblastomas, colon carcinoma and breast carcinoma.

10 Preference is furthermore given to the use for the treatment of a tumour of the blood and immune system, preferably for the treatment of a tumour selected from the group of acute myelotic leukaemia, chronic myelotic leukaemia, acute lymphatic leukaemia and/or chronic lymphatic leukaemia.

15 The invention also encompasses a method for the treatment of a patient who has a neoplasm, such as a cancer, by administration of

a) one or more of the compound of the formula I:

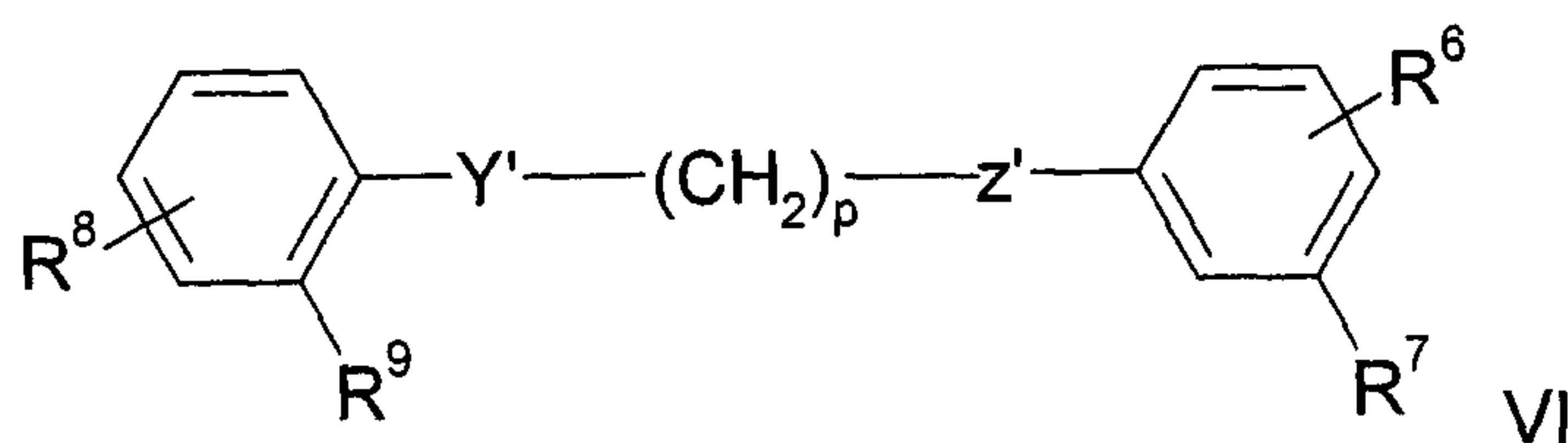
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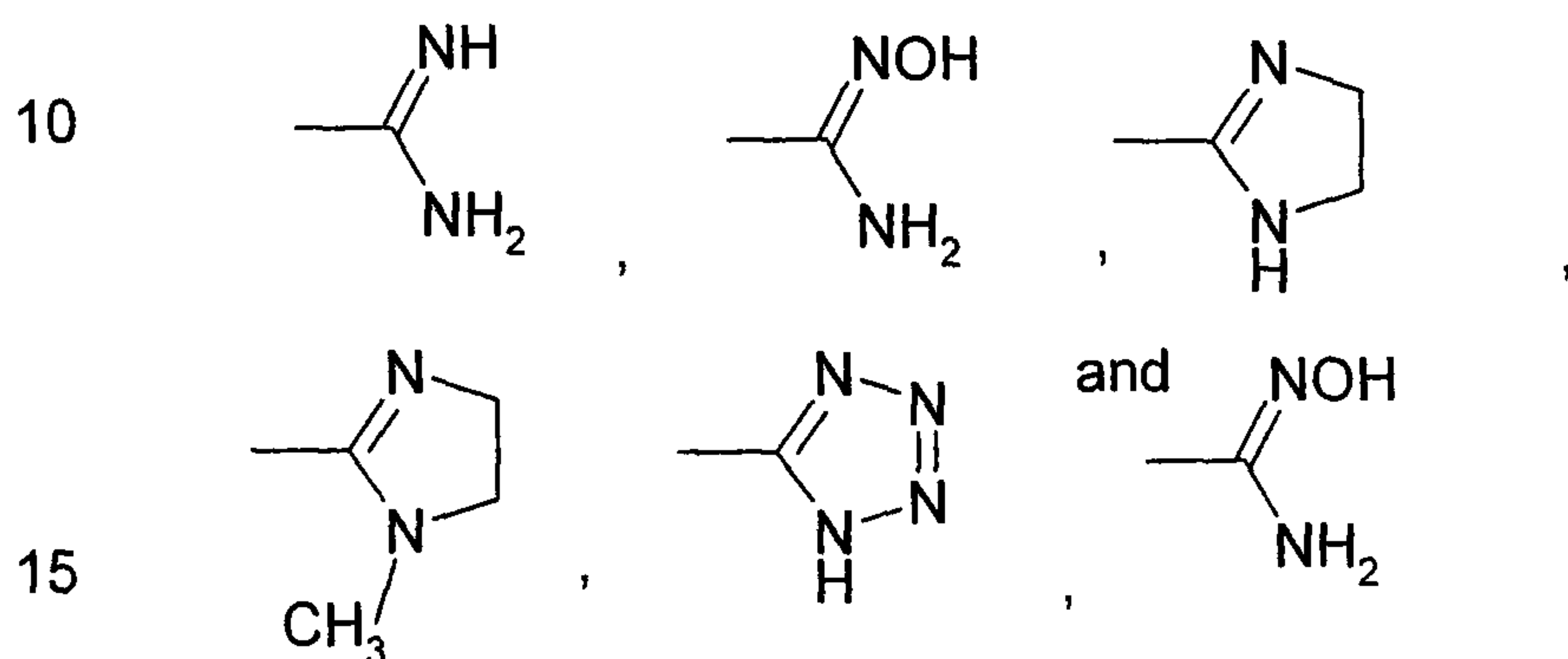
b) and at least one compound of the formula VI:

30



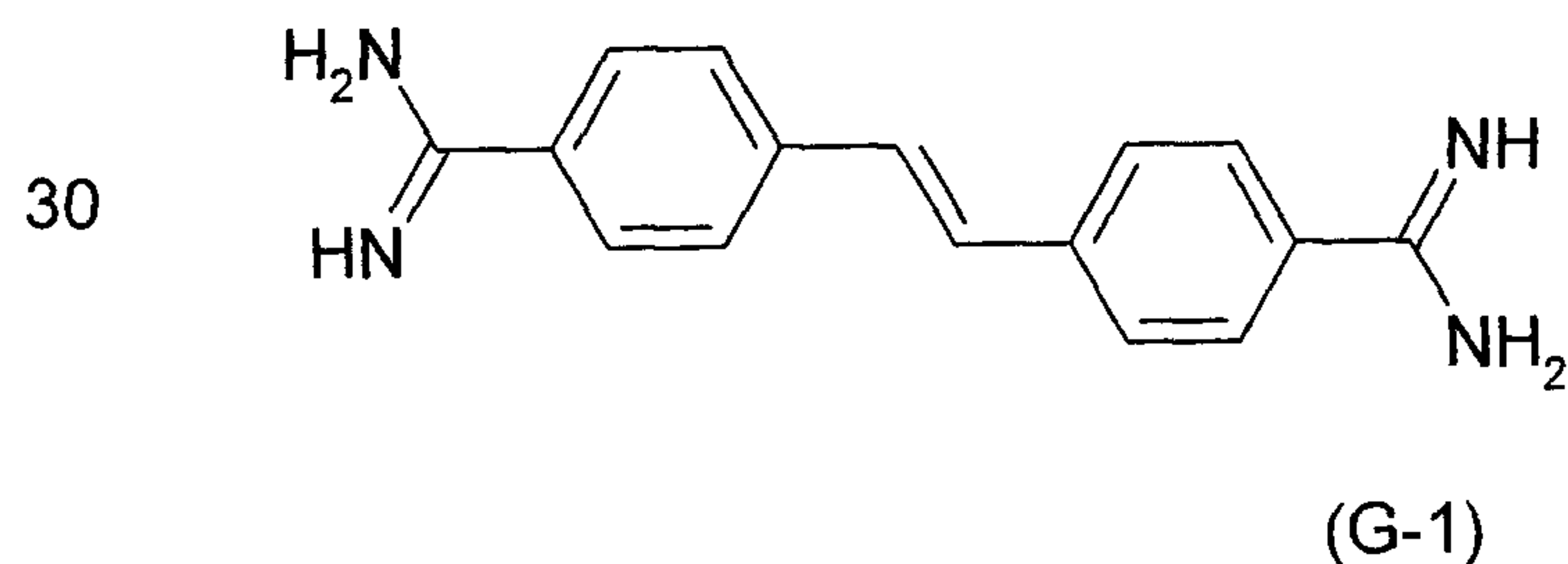
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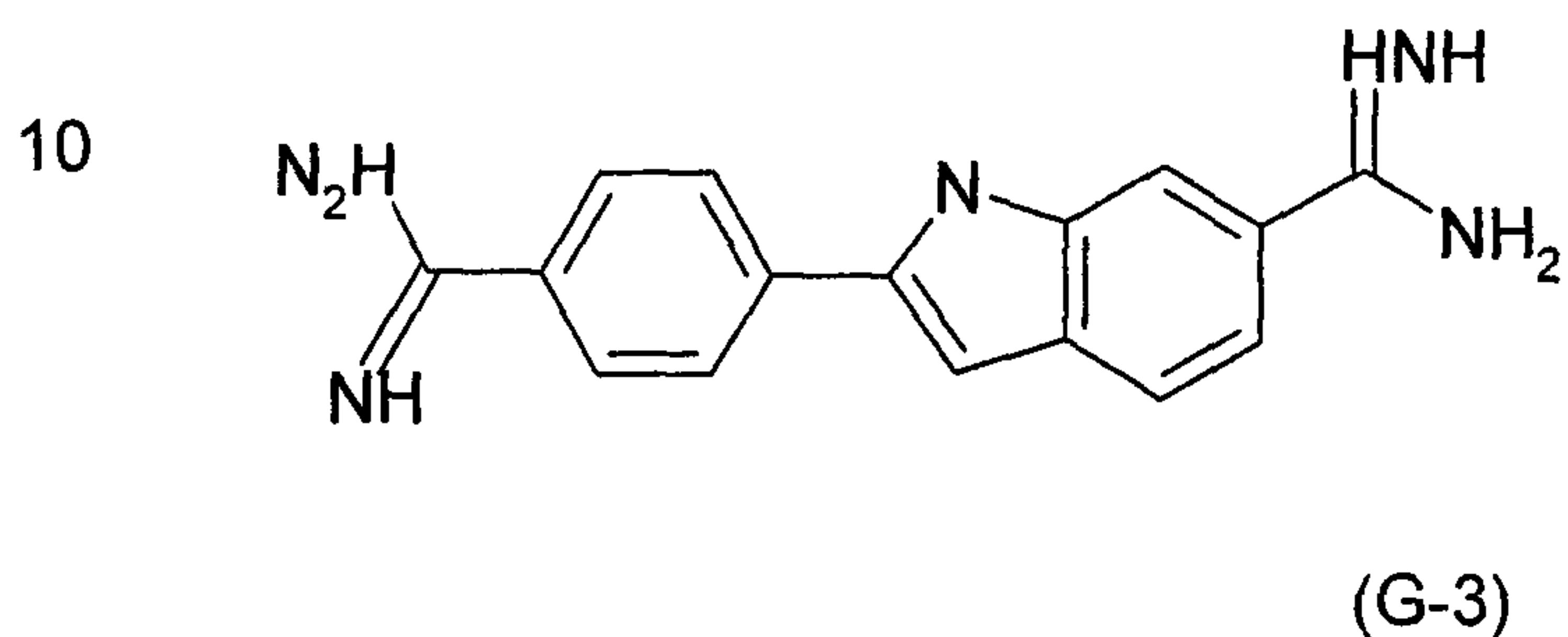
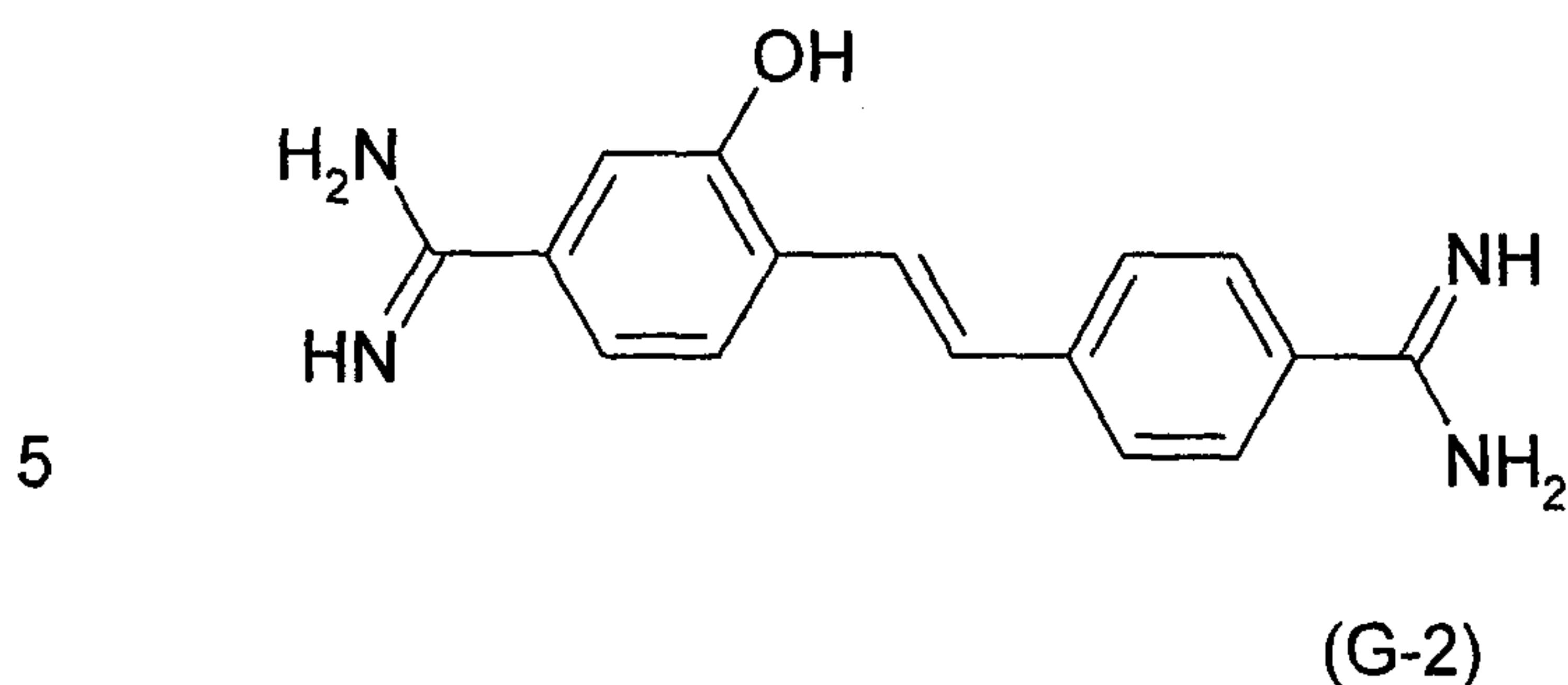
in which Y' and Z' each, independently of one another, denote O or N, R⁷ and R⁹ each, independently of one another, denote H, OH, halogen, OC1-10-alkyl, OCF₃, NO₂ or NH₂, n denotes an integer between 2 and 6 inclusive, and R⁶ and R⁸ are each, independently of one another, in the meta- or para-position and are selected from the group:



where the first and second compound are administered simultaneously or within 14 days of one another in amounts which are sufficient to inhibit the growth of the neoplasm.

Other suitable pentamidine analogues include stilbamidine (G-1) and hydroxystilbamidine (G-2) and indole analogues thereof (for example G-3):





Each amidine unit may be replaced, independently of one another, by one of the further total units As in the case of benzimidazoles and pentami-

20 dines, salts of stilbamidine, hydroxystilbamidine and indole derivatives thereof are also suitable in the process according to the invention. Preferred salts include, for example, dihydrochloride and methanesulfonate salts.

25 Still other analogues are those which fall under a formula which are provided in one of the US Patents No. 5,428,051, 5,521,189, 5,602,172, 5,643,935, 5,723,495, 5,843,980, 6,172,104 and 6,326,395 or the US patent application with the publication No. US 2002/0019437 A1, each of

30 which is incorporated in its entirety by way of reference. Illustrative analogues include 1,5-bis(4'-(N-hydroxyamidino)phenoxy)pentane, 1,3-bis(4'-(N-hydroxyamidino)phenoxy)propane, 1,3-bis(2'-methoxy-4'-(N-hydroxyamidino)phenoxy)propane, 1,4-bis(4'-(N-hydroxyamidino)phenoxy)butane,

35 1,5-bis(4'-(N-hydroxyamidino)phenoxy)pentane, 1,4-bis(4'-(N-hydroxyamidino)phenoxy)butane, 1,3-bis(4'-(4-hydroxyamidino)phenoxy)propane,

1,3-bis(2'-methoxy-4'-(N-hydroxyamidino)phenoxy)propane, 2,5-bis[4-
 amidinophenyl]furan, 2,5-bis[4-amidinophenyl]furan bisamide oxime, 2,5-
 bis[4-amidinophenyl]furan bis-O-methylamide oxime, 2,5-bis[4-amidino-
 phenyl]furan bis-O-ethylamide oxime, 2,8-diamidinodibenzothiophene, 2,8-
 bis(N-isopropylamidino)carbazole, 2,8-bis(N-hydroxyamidino)carbazole,
 2,8-bis(2-imidazoliny)ldibenzothiophene, 2,8-bis(2-imidazoliny)l-5,5-dioxo-
 dibenzothiophene, 3,7-diamidinodibenzothiophene, 3,7-bis(N-isopropyl-
 amidino)dibenzothiophene, 3,7-bis(N-hydroxyamidino)dibenzothiophene,
 3,7-diaminodibenzothiophene, 3,7-dibromodibenzothiophene, 3,7-dicyano-
 dibenzothiophene, 2,8-diamidinodibenzofuran, 2,8-di-(2-imidazoliny)l-
 dibenzofuran, 2,8-di-(N-isopropylamidino)dibenzofuran, 2,8-di-(N-hydroxyl-
 amidino)dibenzofuran, 3,7-di-(2-imidazoliny)ldibenzofuran, 3,7-di-(isopropyl-
 amidino)dibenzofuran, 3,7-di-(A-hydroxylamidino)dibenzofuran, 2,8-
 dicyanodibenzofuran, 4,4'-dibromo-2,2'-dinitrobiphenyl, 2-methoxy-2'-nitro-
 4,4'-dibromobiphenyl, 2-methoxy-2'-amino-4,4'-dibromobiphenyl, 3,7-di-
 bromodibenzofuran, 3,7-dicyanodibenzofuran, 2,5-bis(5-amidino-2-benz-
 imidazolyl)pyrrole, 2,5-bis[5-(2-imidazoliny)l-2-benzimidazolyl]pyrrole, 2,6-
 bis[5-(2-imidazoliny)l-2-benzimidazolyl]pyridine, 1-methyl-2,5-bis(5-amidino-
 2-benzimidazolyl)pyrrole, 1-methyl-2,5-bis[5-(2-imidazolyl)-2-benz-
 imidazolyl]pyrrole, 1-methyl-2,5-bis[5-(1,4,5,6-tetrahydro-2-pyrimidinyl)-2-
 benzimidazolyl]pyrrole, 2,6-bis(5-amidino-2-benzimidazolyl)pyridine, 2,6-bis-
 [5-(1,4,5,6-tetrahydro-2-pyrimidinyl)-2-benzimidazolyl]pyridine, 2,5-bis(5-
 amidino-2-benzimidazolyl)furan, 2,5-bis[5-(2-imidazoliny)l-2-benzimidazo-
 ly]furan, 2,5-bis(5-N-isopropylamidino-2-benzimidazolyl)furan, 2,5-bis(4-
 guanylphenyl)furan, 2,5-bis(4-guanylphenyl)-3,4-dimethylfuran, 2,5-di-p-[2-
 (3,4,5,6-tetrahydropyrimidyl)phenyl]furan, 2,5-bis[4-(2-imidazoliny)lphenyl]-
 furan, 2,5-[bis{4-(2-tetrahydropyrimidinyl)}phenyl]p-(tolylloxy)furan, 2,5-[bis-
 {4-(2-imidazoliny)l}phenyl]-3-p-(tolylloxy)furan, 2,5-bis{4-[5-(N-2-amino-
 ethylamido)benzimidazol-2-yl]phenyl}furan, 2,5-bis[4-(3a,4,5,6,7,7a-hexa-
 hydro-1H-benzimidazol-2-yl)phenyl]furan, 2,5-bis[4-(4,5,6,7-tetrahydro-1H-
 1,3-diazepin-2-yl)phenyl]furan, 2,5-bis(4-N,N-dimethylcarboxhydrazido-
 phenyl)furan, 2,5-bis{4-[2-(N-2-hydroxyethyl)imidazoliny]lphenyl}furan, 2,5-

bis[4-(N-isopropylamidino)phenyl]furan, 2,5-bis{4-[3-(dimethylaminopropyl)-
 amidino]phenyl}furan, 2,5-bis{4-[N-(3-aminopropyl)amidino]phenyl}furan,
 2,5-bis[2-(imidazolinyl)phenyl]-3,4-bis(methoxymethyl)furan, 2,5-bis[4-N-
 5 (dimethylaminoethyl)guanyl]phenylfuran, 2,5-bis{4-[(N-2-hydroxyethyl)-
 guanyl]phenyl}furan, 2,5-bis[4-N-(cyclopropylguanyl)phenyl]furan, 2,5-bis[4-
 (N,N-diethylaminopropyl)guanyl]phenylfuran, 2,5-bis{4-[2-(N-ethylimidazo-
 liny)]phenyl}furan, 2,5-bis{4-[N-(3-pentylguanyl)]}phenylfuran, 2,5-bis[4-(2-
 imidazolinyl)phenyl]-3-methoxyfuran, 2,5-bis[4-(N-isopropylamidino)phenyl]-
 10 3-methylfuran, bis[5-amidino-2-benzimidazolyl]methane, bis[5-(2-
 imidazolyl)-2-benzimidazolyl]methane, 1,2-bis[5-amidino-2-benzimidazolyl]-
 ethane, 1,2-bis[5-(2-imidazolyl)-2-benzimidazolyl]ethane, 1,3-bis[5-amidino-
 2-benzimidazolyl]propane, 1,3-bis[5-(2-imidazolyl)-2-benzimidazolyl]-
 15 propane, 1,4-bis[5-amidino-2-benzimidazolyl]propane, 1,4-bis[5-(2-imidazo-
 ly)-2-benzimidazolyl]butane, 1,8-bis[5-amidino-2-benzimidazolyl]octane,
 trans-1,2-bis[5-amidino-2-benzimidazolyl]ethene, 1,4-bis[5-(2-imidazolyl)-2-
 benzimidazolyl]-1-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-
 butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1-methylbutane, 1,4-bis-
 20 [5-(2-imidazolyl)-2-benzimidazolyl]-2-ethylbutane, 1,4-bis[5-(2-imidazolyl)-2-
 benzimidazolyl]-1-methyl-1-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimid-
 azolyl]-2,3-diethyl-2-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1,3-
 butadiene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-methyl-1,3-buta-
 25 diene, bis[5-(2-pyrimidyl)-2-benzimidazolyl]methane, 1,2-bis[5-(2-pyrimidyl)-
 2-benzimidazolyl]ethane, 1,3-bis[5-amidino-2-benzimidazolyl]propane, 1,3-
 bis[5-(2-pyrimidyl)-2-benzimidazolyl]propane, 1,4-bis[5-(2-pyrimidyl)-2-
 benzimidazolyl]butane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-butene,
 30 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-butene, 1,4-bis[5-(2-pyrimidyl)-2-
 benzimidazolyl]-1-methylbutane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-
 ethylbutane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-methyl-1-butene,
 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2,3-diethyl-2-butene, 1,4-bis[5-(2-
 pyrimidyl)-2-benzimidazolyl]-1,3-butadiene and 1,4-bis[5-(2-pyrimidyl)-2-
 35 benzimidazolyl]-2-methyl-1,3-butadiene, 2,4-bis(4-guanylphenyl)pyrimidine,
 2,4-bis(4-imidazolin-2-yl)pyrimidine, 2,4-bis[(tetrahydropyrimidinyl-2-

yl)phenyl]pyrimidine, 2-(4-[N-i-propylguanyl]phenyl)-4-(2-methoxy-4-[N-i-propylguanyl]phenyl)pyrimidine, 4-(N-cyclopentylamidino)-1,2-phenylene-diamine, 2,5-bis[2-(5-amidino)benzimidazolyl]furan, 2,5-bis[2-{5-(2-imidazolino)}benzimidazolyl]furan, 2,5-bis[2-(5-N-isopropylamidino)benzimidazolyl]furan, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazolyl]furan, 2,5-bis[2-(5-amidino)benzimidazolyl]pyrrole, 2,5-bis[2-{5-(2-imidazolino)}benzimidazolyl]pyrrole, 2,5-bis[2-(5-N-isopropylamidino)benzimidazolyl]pyrrole, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazolyl]pyrrole, 1-methyl-2,5-bis[2-(5-amidino)benzimidazolyl]pyrrole, 2,5-bis[2-{5-(2-imidazolino)}benzimidazolyl]-1-methylpyrrole, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazolyl]-1-methylpyrrole, 2,5-bis[2-(5-N-isopropylamidino)benzimidazolyl]thiophene, 2,6-bis[2-{5-(2-imidazolino)}benzimidazolyl]pyridine, 2,6-bis[2-(5-amidino)benzimidazolyl]pyridine, 4,4'-bis[2-(5-N-isopropylamidino)benzimidazolyl]-1,2-diphenylethane, 4,4'-bis[2-(5-N-cyclopentylamidino)benzimidazolyl]-2,5-diphenylfuran, 2,5-bis[2-(5-amidino)benzimidazolyl]benzo[b]furan, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazolyl]benzo[b]furan, 2,7-bis[2-(5-N-isopropylamidino)benzimidazolyl]fluorine, 2,5-bis[4-(3-(N-morpholinopropyl)-carbamoyl]phenyl]furan, 2,5-bis[4-(2-N,N-dimethylaminoethylcarbamoyl)-phenyl]furan, 2,5-bis[4-(3-N,N-dimethylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N-methyl-3-N-phenylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N,N8,N11-trimethylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[3-amidinophenyl]furan, 2,5-bis[3-(N-isopropylamidino)amidinophenyl]furan, 2,5-bis[3-[(N-(2-dimethylaminoethyl)amidino]phenyl]furan, 2,5-bis[4-(N-2,2,2-trichloroethoxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-thioethylcarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-benzyloxycarbonyl)-amidinophenyl]furan, 2,5-bis[4-(N-phenoxy carbonyl)amidinophenyl]furan, 2,5-bis[4-(N-(4-fluoro)phenoxy carbonyl)amidinophenyl]furan, 2,5-bis[4-(N-(4-methoxy)phenoxy carbonyl)amidinophenyl]furan, 2,5-bis[4-(1-acetoxyethoxycarbonyl)amidinophenyl]furan and 2,5-bis[4-(N-(3-fluoro)phenoxy carbonyl)amidinophenyl]furan. Processes for the preparation of one of the above compounds are described in US patents No. 5,428,051, 5,521,189,

5,602,172, 5,643,935, 5,723,495, 5,843,980, 6,172,104 and 6,326,395 or the US patent application with the publication No. US 2002/0019437 A1.

5 Pentamidine metabolites are likewise suitable in the antiproliferative combination according to the invention. Pentamidine is rapidly metabolised in the body to at least seven primary metabolites. Some of these metabolites have one or more actions in common with pentamidine. Some pentamidine
10 metabolites may exhibit an antiproliferative action when combined with a benzimidazole or an analogue thereof.

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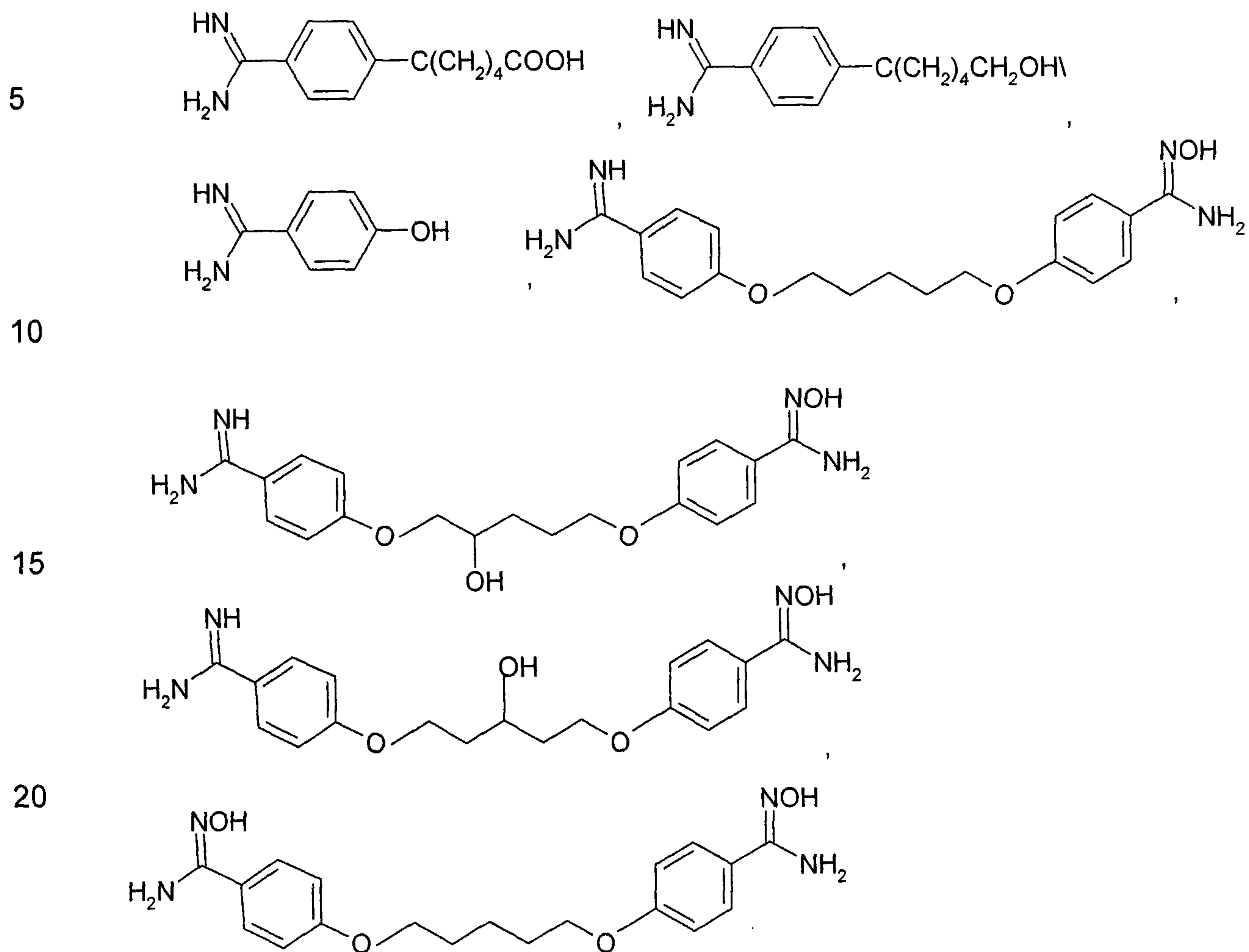
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Seven pentamidine analogues are shown below.



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5 The combinations according to the invention of compounds of the formula I and formula VI and metabolites thereof are suitable for the treatment of neoplasms. Combination therapy can be carried out alone or in combination with another therapy (for example operation, irradiation, chemotherapy, biological therapy). In addition, a person whose risk of developing a neoplasm is greater (for example someone who is genetically predisposed or someone who previously had a neoplasm) can be given prophylactic treatment in order to inhibit or delay neoplasm formation.

10 The dosage and frequency of administration of each compound in the combination can be controlled independently. For example, one compound may be administered orally three times daily, while the second compound may be administered intramuscularly once per day. The compounds may also be formulated together, leading to administration of both compounds.

20 The antiproliferative combinations according to the invention can also be provided as components of a pharmaceutical package. The two medicaments can be formulated together or separately and in individual dosage amounts.

25 In another aspect, the invention encompasses a method for the treatment of a patient who has a neoplasm, such as a cancer, by administration of a compound of the formula (I) and (VI) in combination with an antiproliferative agent. Suitable antiproliferative agents encompass those provided in Table 1.

30 Above and below, all temperatures are indicated in °C. In the following examples, "conventional work-up" means: if necessary, water is added, the pH is adjusted, if necessary, to values between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chro-

35

matography on silica gel and/or by crystallisation. R_f values on silica gel; eluent: ethyl acetate/methanol 9:1.

Mass spectrometry (MS): EI (electron impact ionisation) M⁺

5

FAB (fast atom bombardment) (M+H)⁺

ESI (electrospray ionisation) (M+H)⁺

APCI-MS (atmospheric pressure chemical ionisation – mass spectrometry) (M+H)⁺

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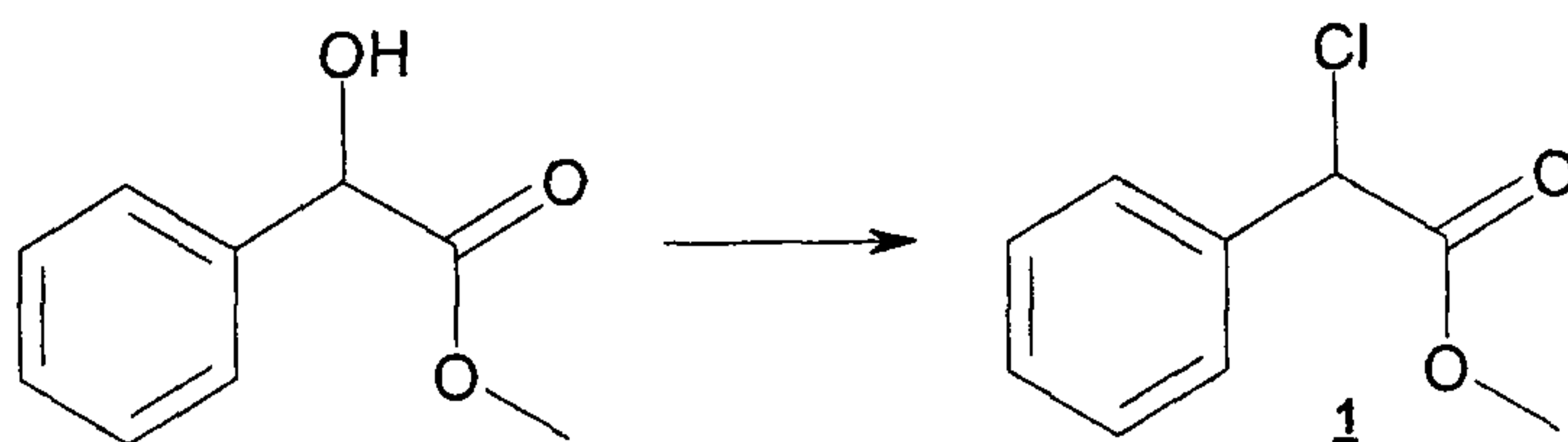
The mandelic acid derivatives employed below are accessible by syntheses described in the literature, for example from aromatic aldehydes.

15

Example 1

a) Synthesis of methyl chlorophenylacetate **1**

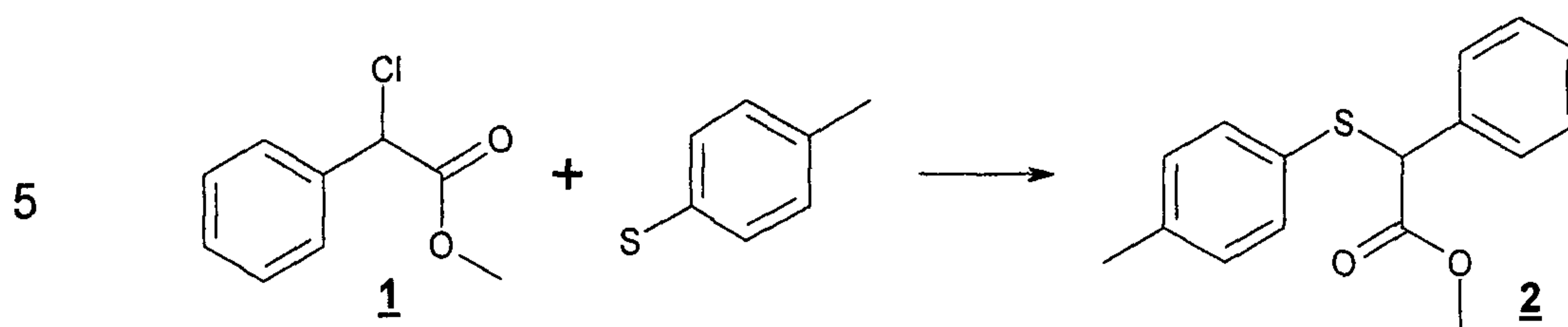
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For the synthesis of methyl chlorophenylacetate, 10.0 g (60 mmol) of methyl mandelate are dissolved in 10 ml of dichloromethane and, after addition of 4.79 ml (66 mmol, 1.1 equiv.) of thionyl chloride, warmed to 60°C. The mixture is stirred for 18 hours, the reaction solution is cooled to room temperature, a further 20 ml of dichloromethane are added, and the mixture is extracted twice each with 30 ml of water and saturated NaHCO₃ solution. The organic phase is dried over sodium sulfate, and the reaction product is obtained after filtration and removal of the solvent by distillation.

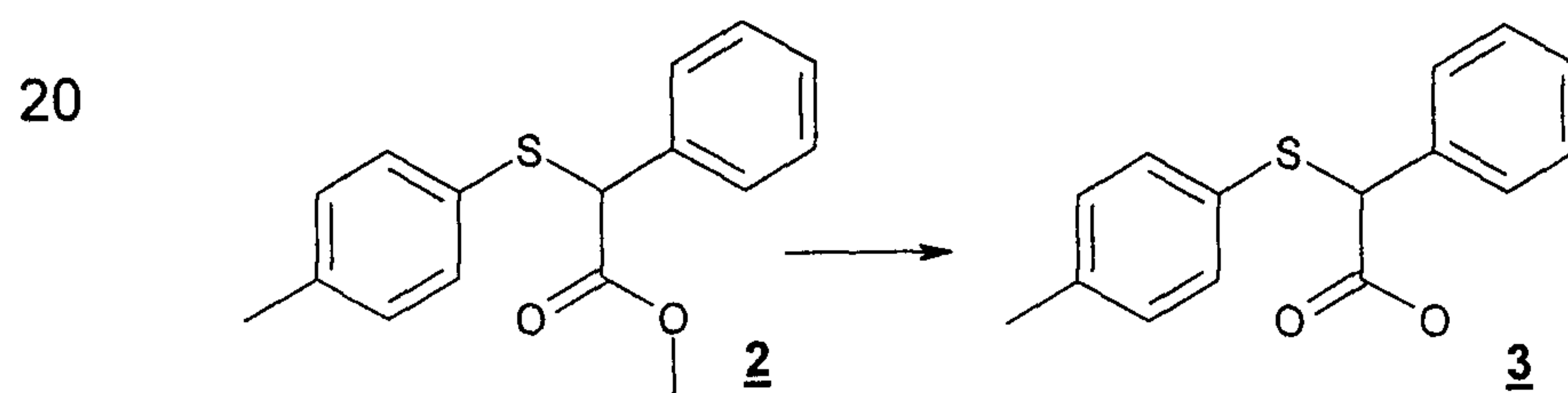
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b) Synthesis of methyl phenyl-p-tolylsulfanylacetate 2

For the synthesis of methyl phenyl-p-tolylsulfanylacetate, 2.0 g (7.9 mmol) of 1 are dissolved in 10 ml of dichloromethane, 1 equiv. of each of 4-methylthiophenol (7.9 mmol, 0.98 g) and sodium hydroxide (7.9 mmol, 0.32 g) are added, and the mixture is refluxed for 2 hours. The reaction mixture is cooled to room temperature and filtered, and the solvent is distilled off. Water is added to the residue, and the reaction product is extracted with ethyl acetate. The organic phase is dried using sodium sulfate, and the solvent is distilled off after filtration, giving the product 2.

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c) Synthesis of phenyl-p-tolylsulfanylacetic acid 3

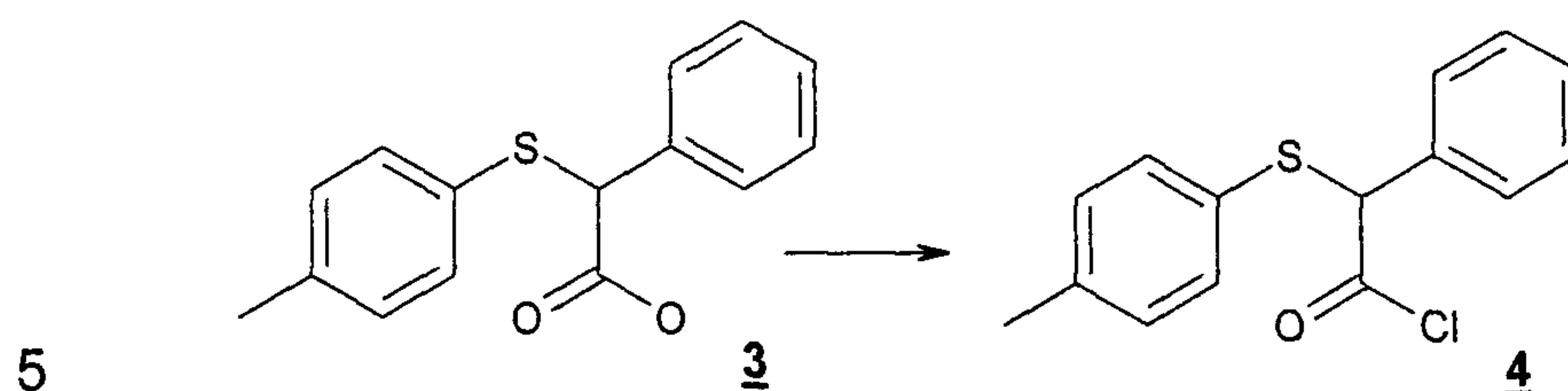
For the synthesis of phenyl-p-tolylsulfanylacetic acid, 2.2 g (6.4 mmol) of 2 are dissolved in 8 ml of methanol, and a solution of 1.32 g (9.57 mmol, 1.5 equiv.) of potassium carbonate in 1.5 ml of water is added. The mixture is refluxed for 15 hours. After the solvent has been removed by distillation, the residue is dissolved in water and extracted once with diethyl ether. 18 ml of 1N HCl are added to the aqueous phase with cooling, and the mixture is extracted with ethyl acetate. Drying over sodium sulfate, filtration and removal of the solvent by distillation gives the product 3.

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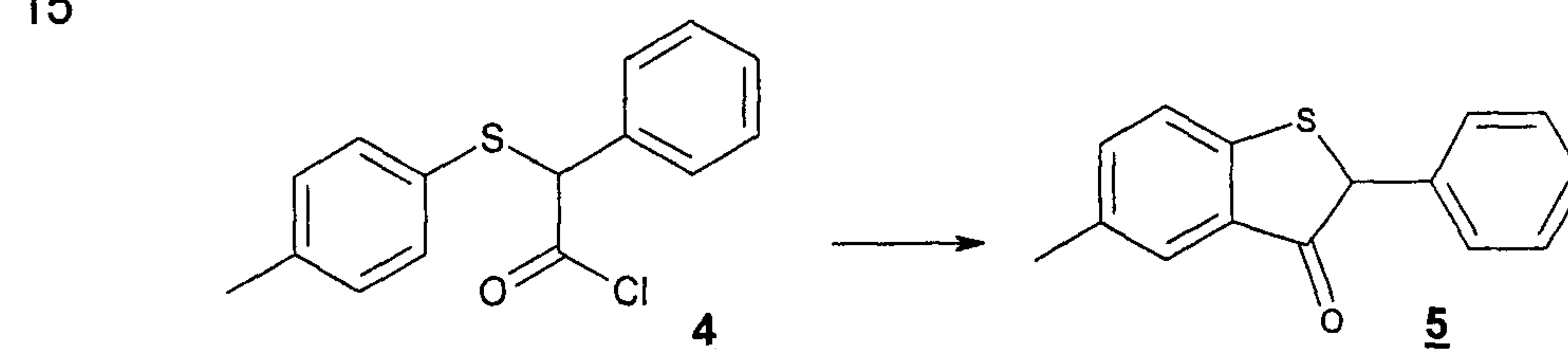
d) Synthesis of phenyl-p-tolylsulfanylacetyl chloride 4

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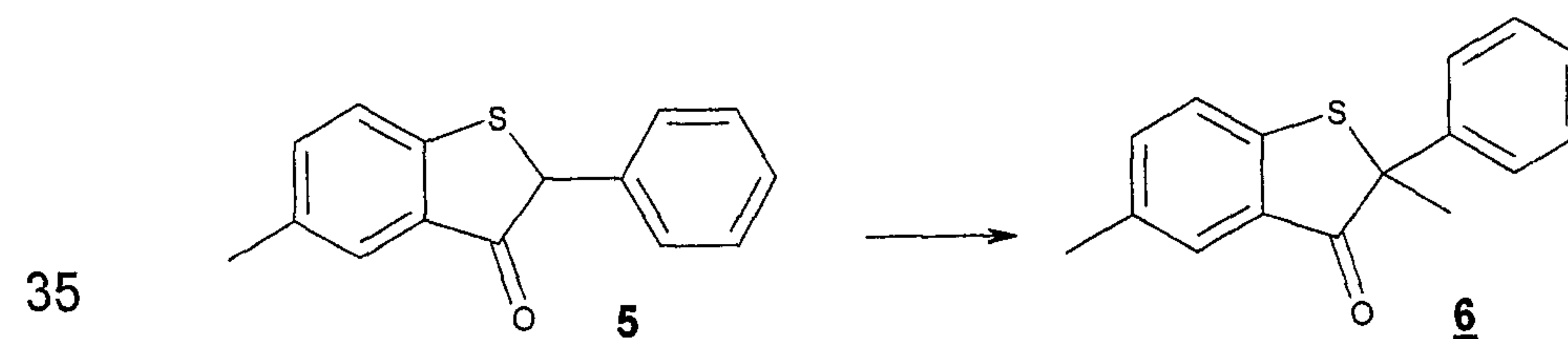
10 For the synthesis of phenyl-p-tolylsulfanylacetyl chloride, 1.7 g (5.5 mmol) of 3 are dissolved in 10 ml of dichloromethane, and 1.4 ml (3.5 equiv.) of thionyl chloride are added. Water is added to the residue, and the reaction product is extracted with ethyl acetate. The organic phase is dried using sodium sulfate, and the solvent is distilled off after filtration, giving the product 4.

15 e) Synthesis of 5-methyl-2-phenyl-2,3-dihydrobenzothiophen-3-one 5



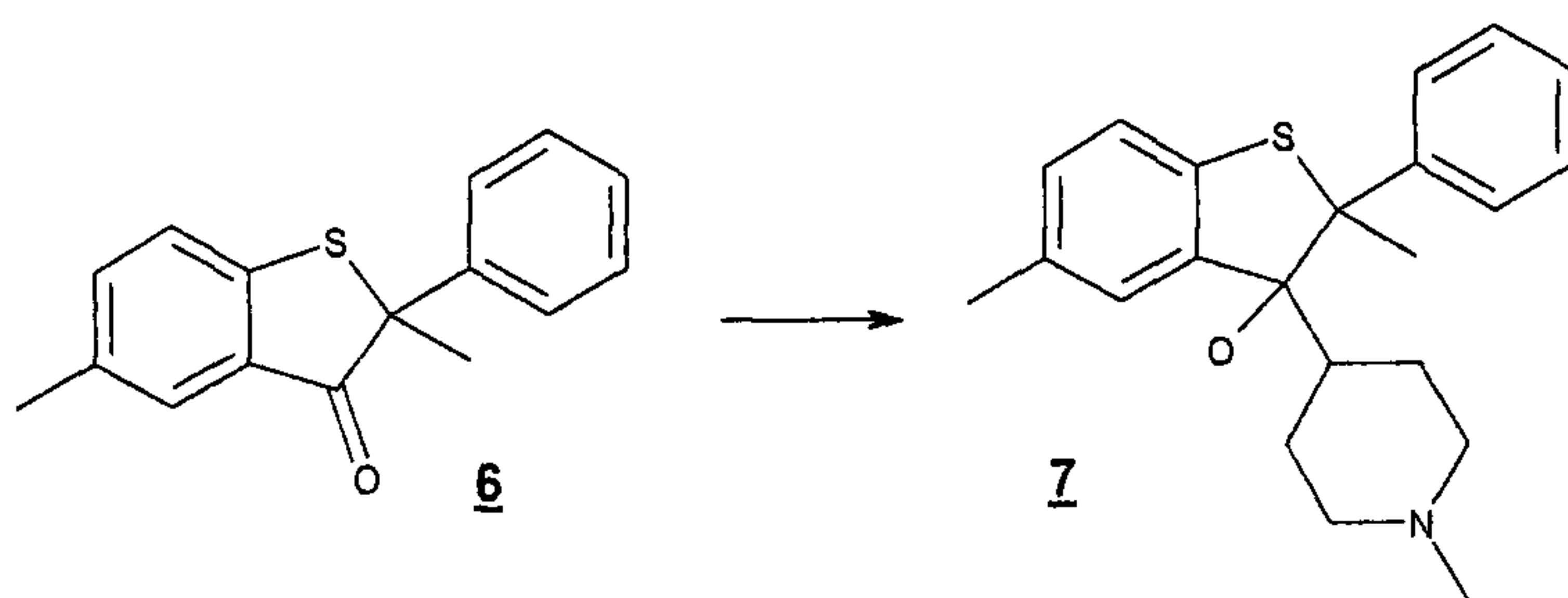
25 For the synthesis of 5-methyl-2-phenyl-2,3-dihydrobenzothiophen-3-one, 0.8 g (1.88 mmol) of 4 in 8 ml of dichloromethane are slowly added dropwise to 0.33 g (2.44 mmol, 1.3 equiv.) of AlCl₃ in 2 ml of dichloromethane, pre-cooled to -65°C. The reaction batch is stirred at room temperature for 15 hours and then poured onto ice, the organic phase is separated off and extracted twice against 1 N sodium hydroxide solution. The pH is adjusted to 6 using 50% acetic acid, and the precipitated reaction product is filtered off.

30 f) Synthesis of 2,5-dimethyl-2-phenyl-2,3-dihydrobenzothiophen-3-one 6



For the synthesis of 2,5-dimethyl-2-phenyl-2,3-dihydrobenzothiophen-3-one, 23.8 mg of sodium hydride (0.59 mmol, 60% in paraffin oil) are suspended in 10 ml of toluene. 122 μ l (1.27 mmol; 3 equiv.) of tert-butanol are added with stirring. After the mixture has been stirred at room temperature for one hour, 200 mg (0.42 mmol) of 5 are added, and the mixture is heated at 60°C for half an hour, and, after cooling to 40°C, 90.3 mg (0.63 mmol, 1.5 equiv.) of iodomethane are added. The mixture is stirred at 80°C for 3 hours. After cooling, ice-water is added, the organic phase is separated off, and the mixture is post-extracted with toluene. After drying over sodium sulfate, the mixture is filtered. The product 6 is obtained after filtration through silica gel and removal of the solvent by distillation.

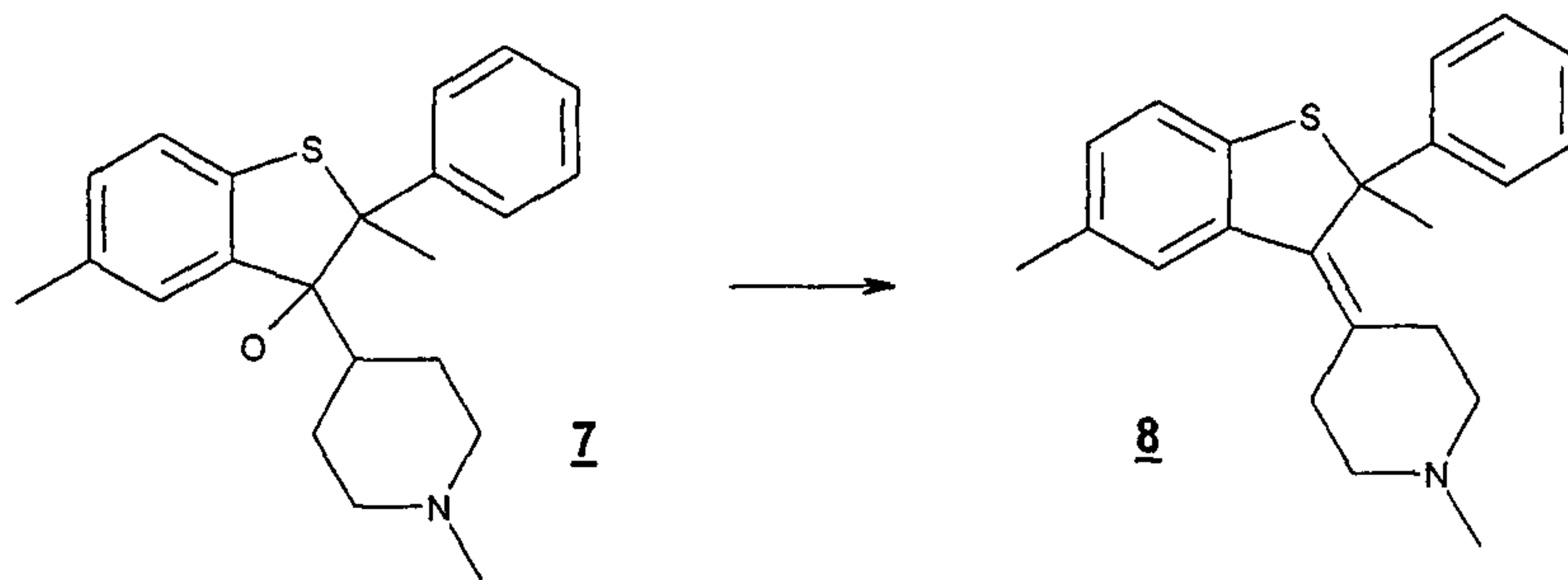
g) Synthesis of 2,5-dimethyl-3-(1-methylpiperidin-4-yl)-2-phenyl-2,3-dihydrobenzothiophen-3-ol 7



For the synthesis of 2,5-dimethyl-3-(1-methylpiperidin-4-yl)-2-phenyl-2,3-dihydrobenzothiophen-3-ol, 0.42 g of magnesium turnings in 5 ml of dried THF are initially introduced, and the Grignard reaction is initiated by addition of iodine and ethyl bromide. 2.3 g (17.2 mmol, 1.5 equiv.) of N-methyl-4-chloropiperidine (obtained from N-methylpiperidinol by reaction with thionyl chloride), dissolved in 5 ml of THF, are added with stirring, and the mixture is refluxed for one hour. After cooling to 10°C, 2.66 g (11.0 mmol) of 6, dissolved in 10 ml of THF, are added dropwise, and the mixture is stirred overnight. After addition of 2 ml of water, the precipitate is filtered off, the liquid phase is evaporated, and 1 N HCl is added, and the mixture is extracted with ethyl acetate. The separated-off aqueous phase is adjusted

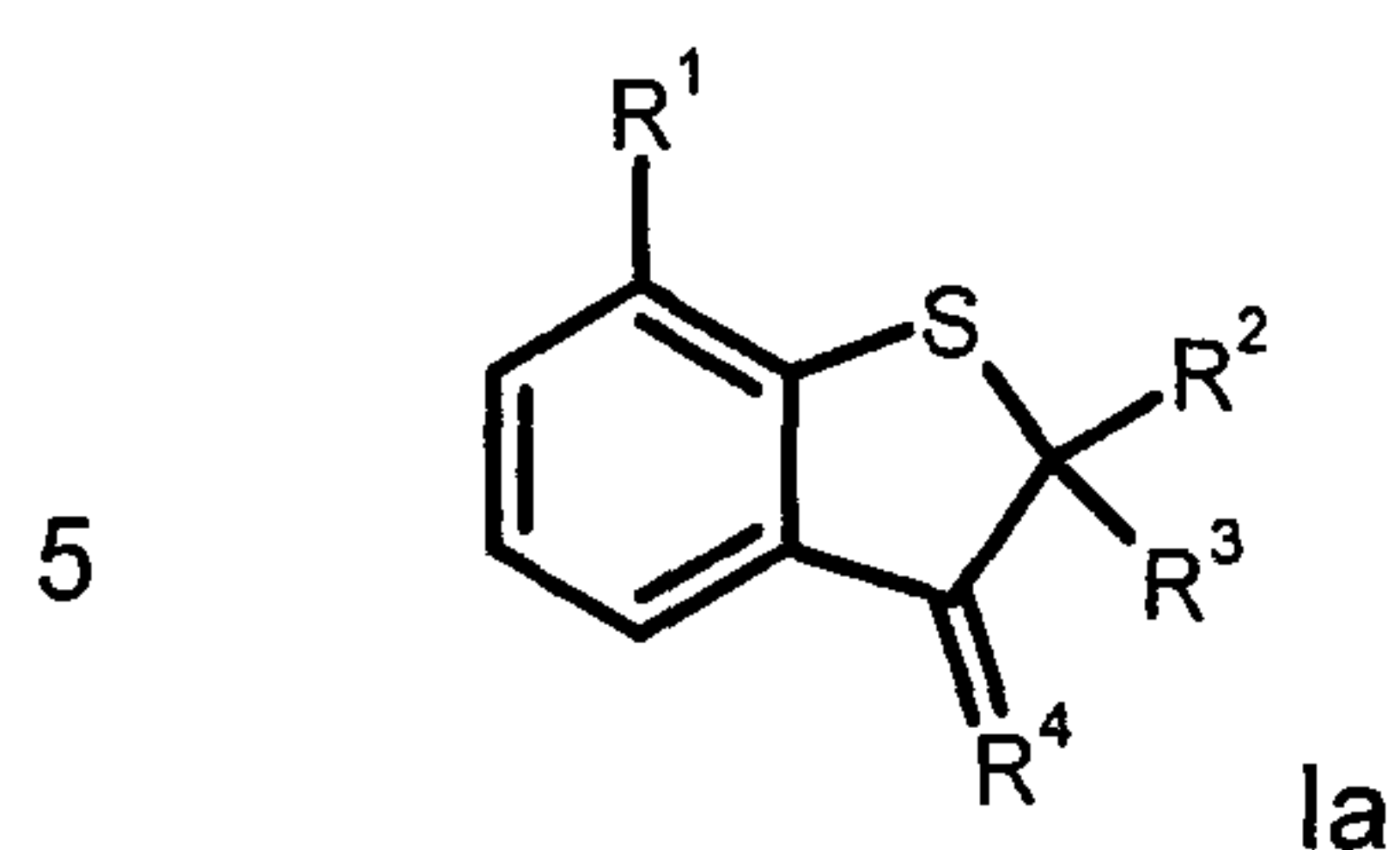
to pH 12 using NaOH solution, and the precipitated reaction product is filtered off.

h) Synthesis of 4-(2,5-dimethyl-2-phenyl-2,3-dihydrobenzothiophen-3-ylidene)-1-methylpiperidine 8



For the synthesis of 4-(2,5-dimethyl-2-phenyl-2,3-dihydro-benzothiophen-3-ylidene)-1-methylpiperidine, 1.9 g (5.4 mmol) of 7 are stirred at 60°C for 3 hours in 20 ml of HCl-saturated isopropanol. When the reaction is complete, the mixture is evaporated, and the crystalline residue is stirred with diethyl ether. The crystalline product 8 is dried.

The following compounds according to the invention are obtained analogously using or corresponding precursors:

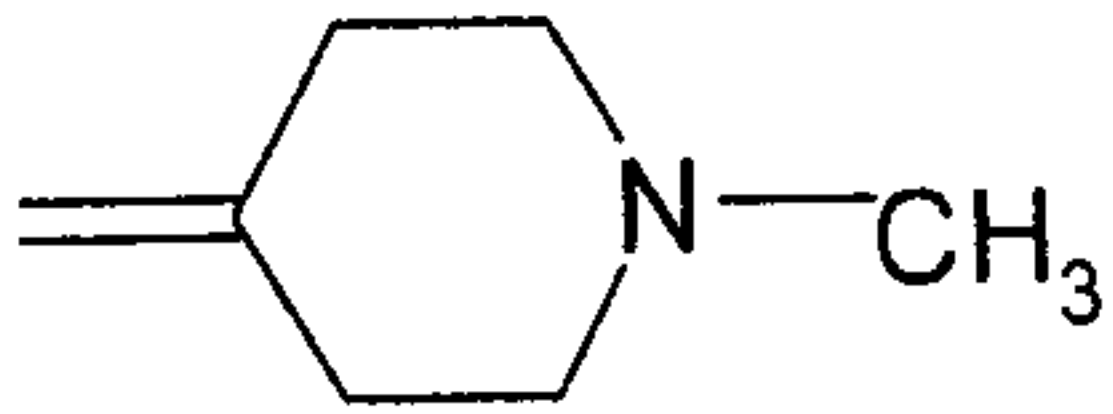
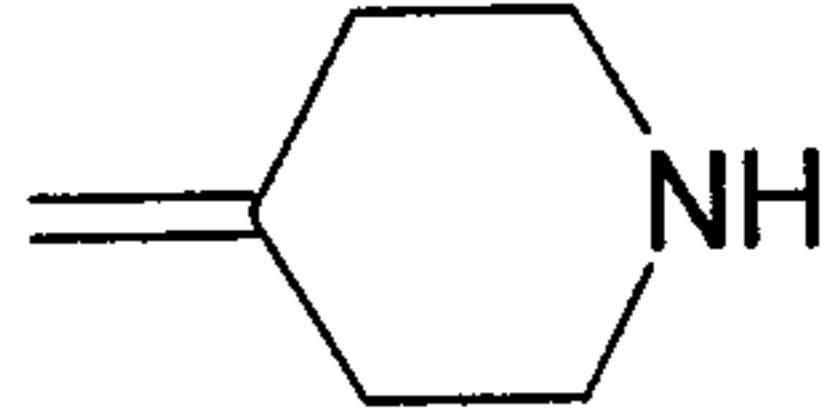
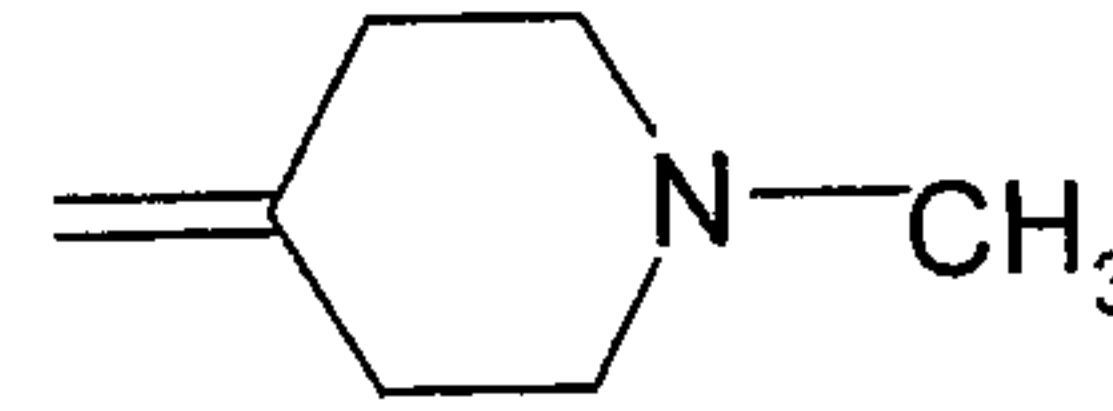
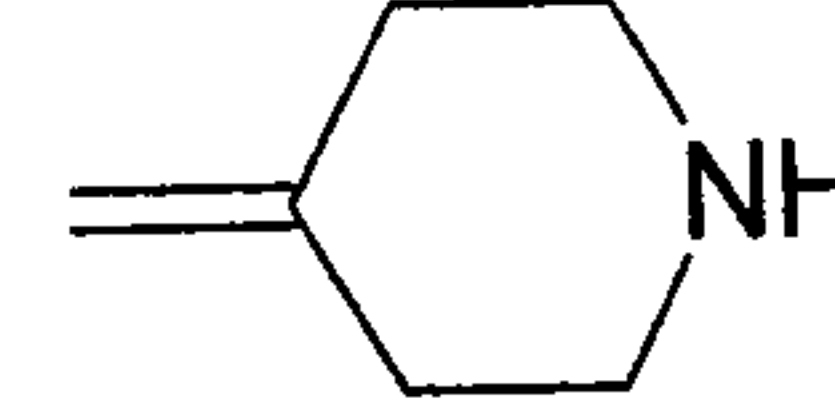
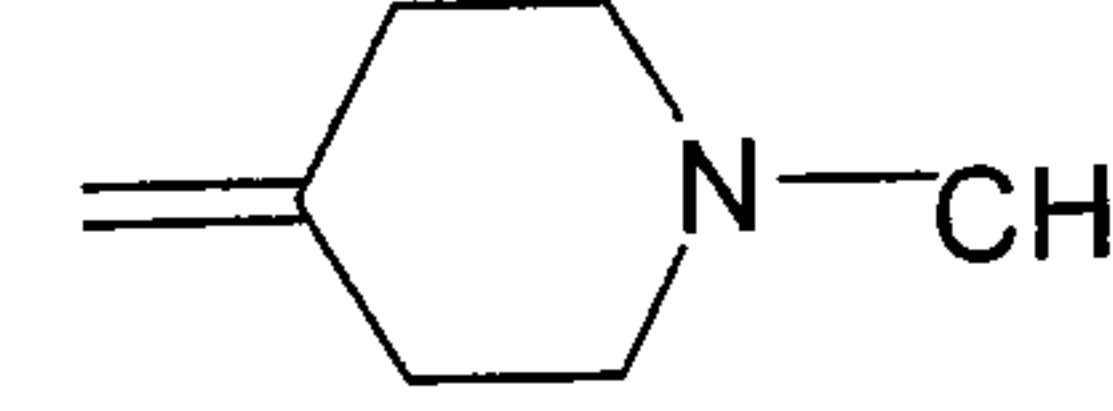
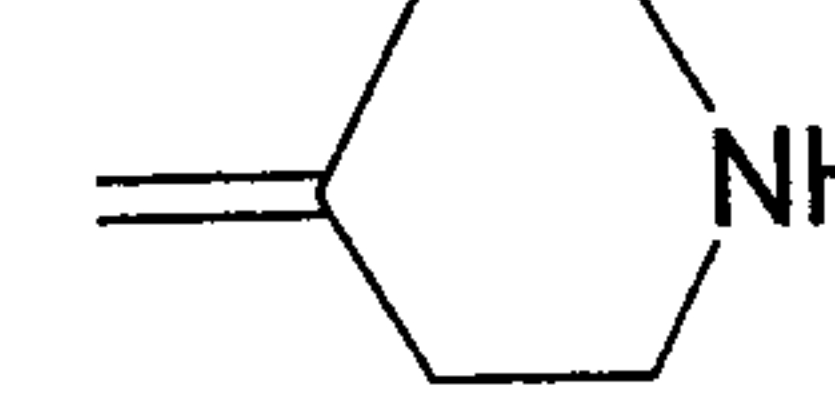
Example 2-41

	No.	R ¹	R ²	R ³	R ⁴
10	2.	Methyl	Methyl	H	O
	3.	Methyl	Phenyl	H	O
	4.	Methyl	Methyl	Methyl	O
	5.	Methyl	Phenyl	Methyl	O
	6.	Methyl	Methyl	H	
15					
	7.	Methyl	Phenyl	H	
20	8.	Methyl	Methyl	Methyl	
	9.	Methyl	Phenyl	Methyl	
25	10.	Phenyl	Methyl	H	O
	11.	Phenyl	Phenyl	H	O
	12.	Phenyl	Methyl	Methyl	O
	13.	Phenyl	Phenyl	Methyl	O
30	14.	Phenyl	Methyl	H	
	15.	Phenyl	Phenyl	H	
35					

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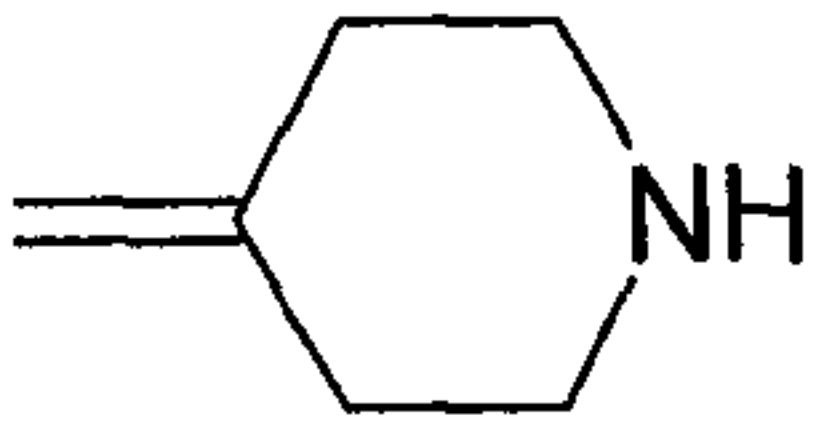
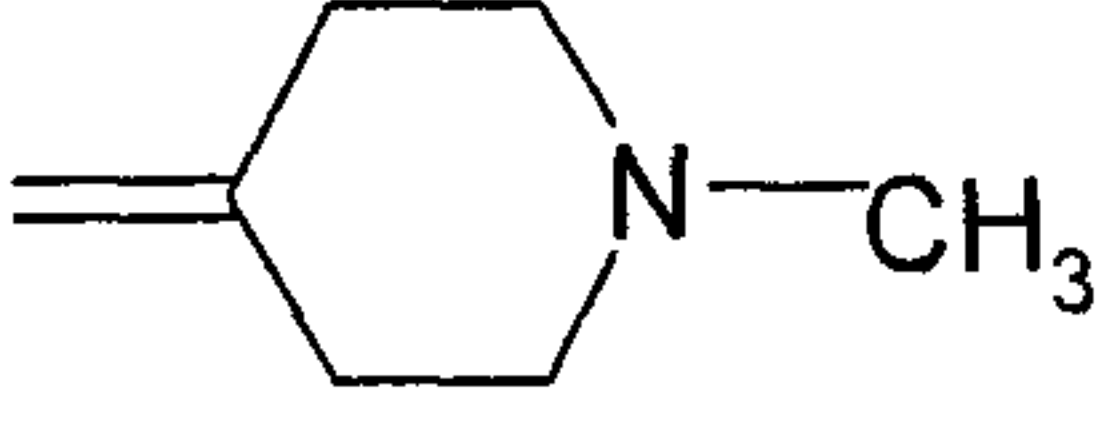
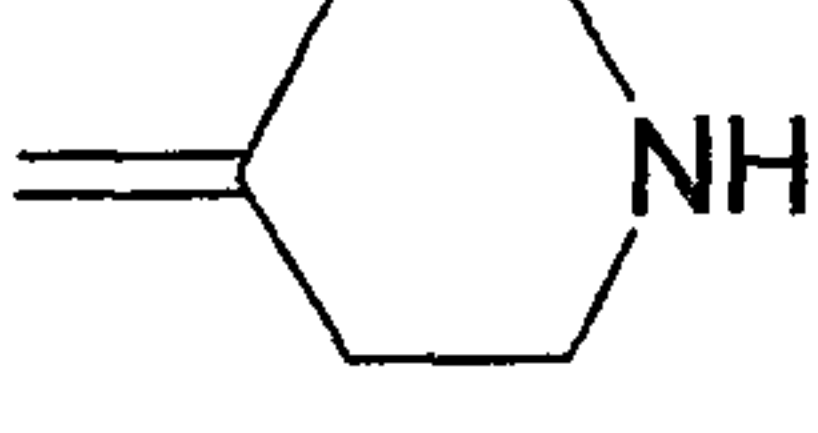
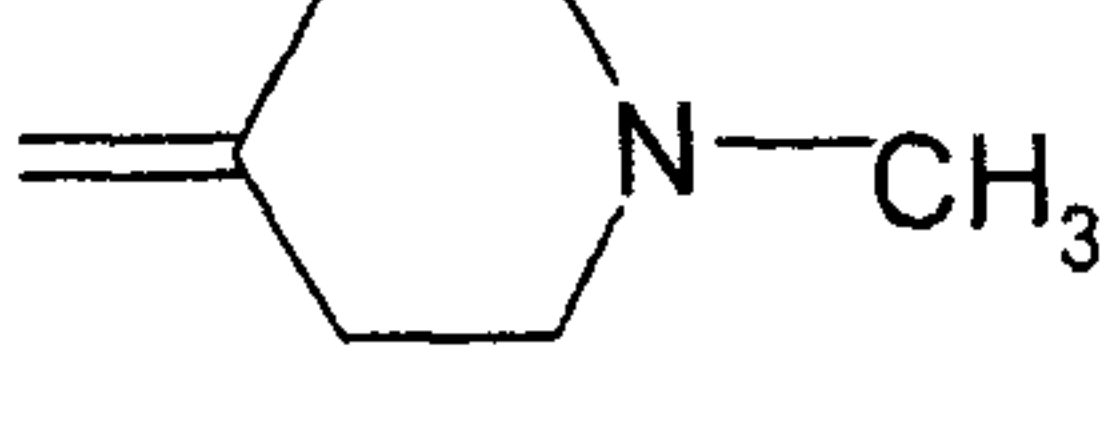
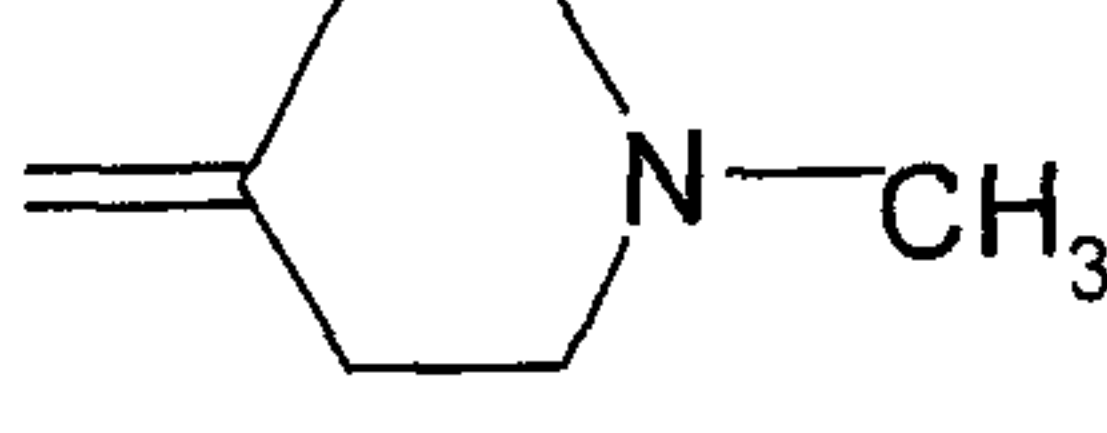
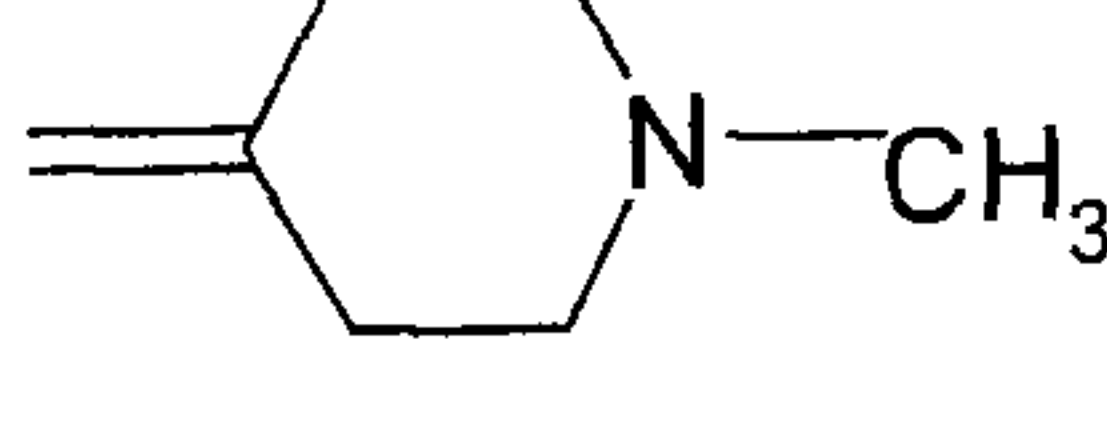
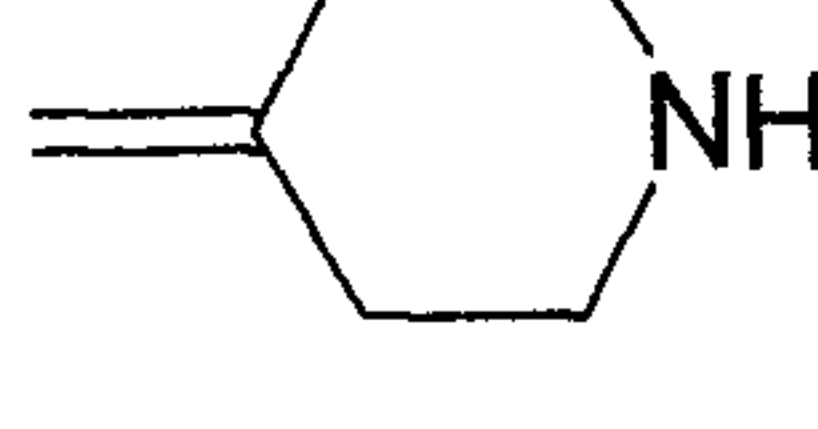
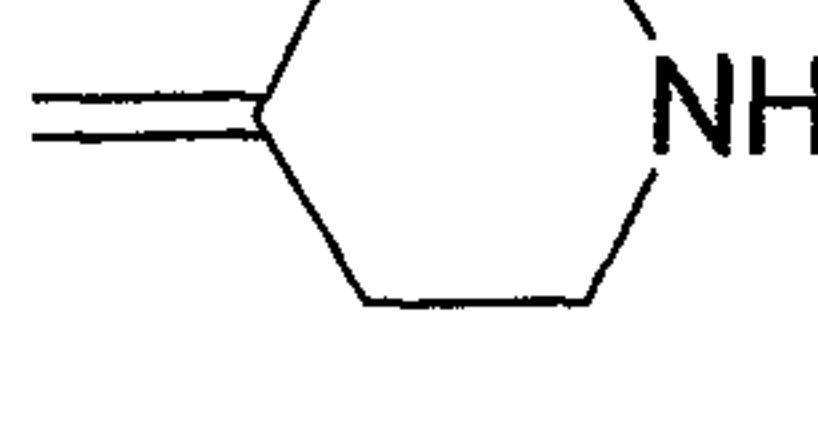
- 79 -

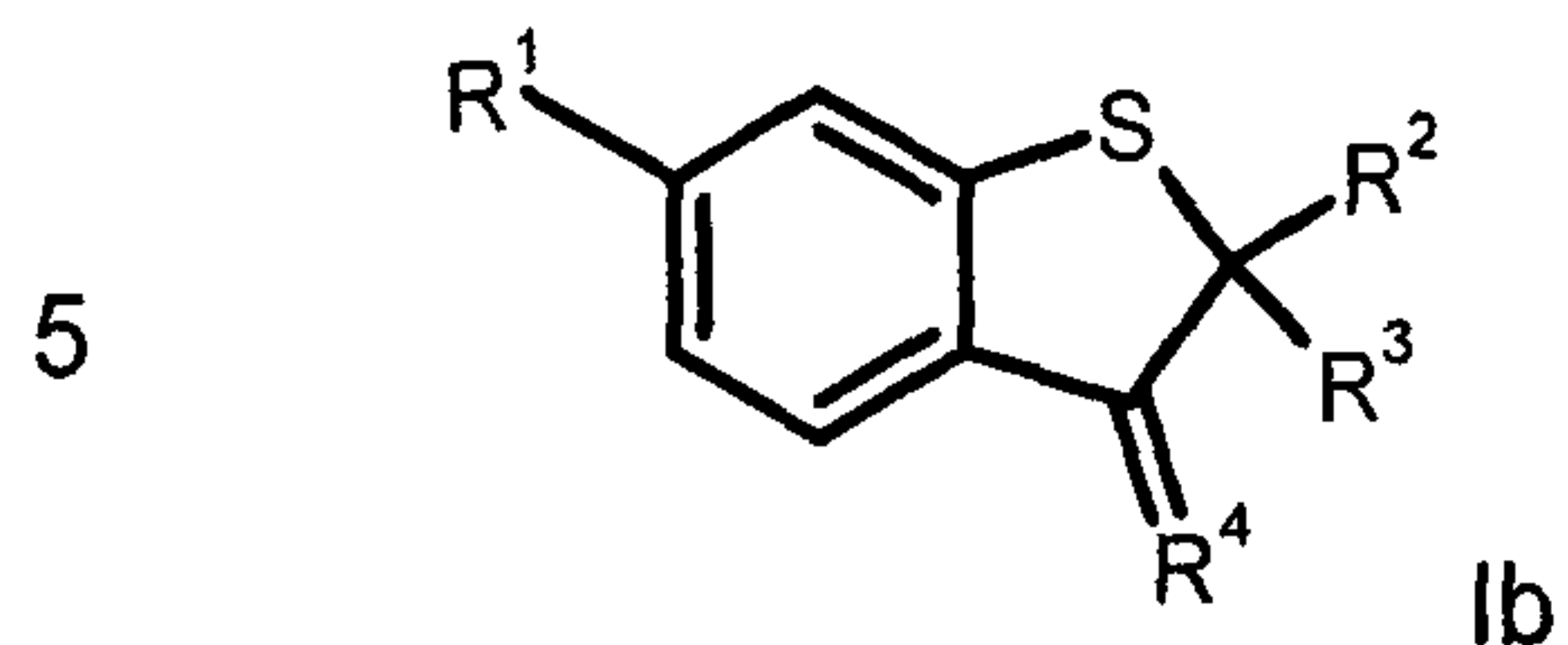
5	16.	Phenyl	Methyl	Methyl	
	17.	Phenyl	Phenyl	Methyl	
	18.	OH	Methyl	H	O
10	19.	OH	Phenyl	H	O
	20.	OH	Methyl	Methyl	O
	21.	OH	Phenyl	Methyl	O
	22.	OH	Methyl	H	
15	23.	OH	Phenyl	H	
20	24.	OH	Methyl	Methyl	
	25.	OH	Phenyl	Methyl	

25

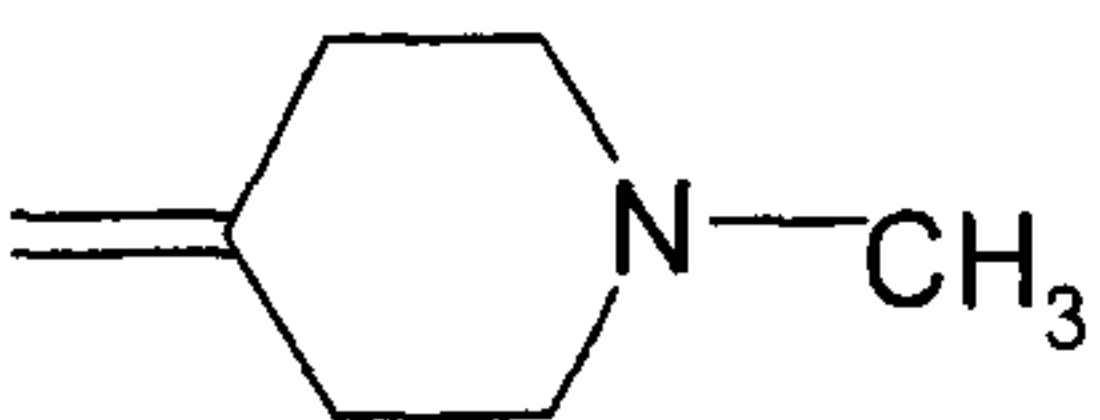
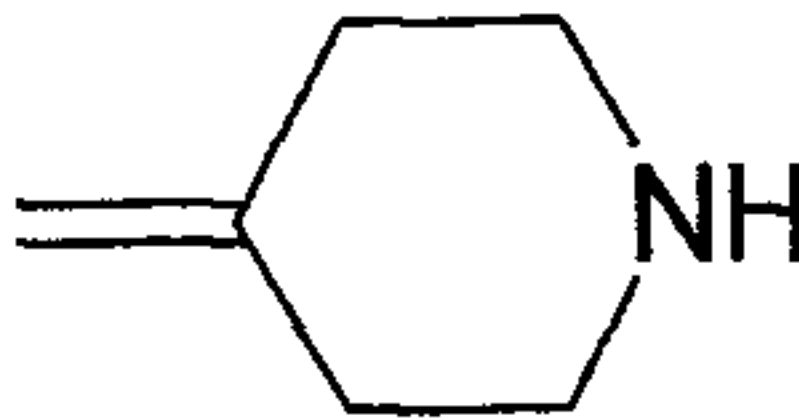
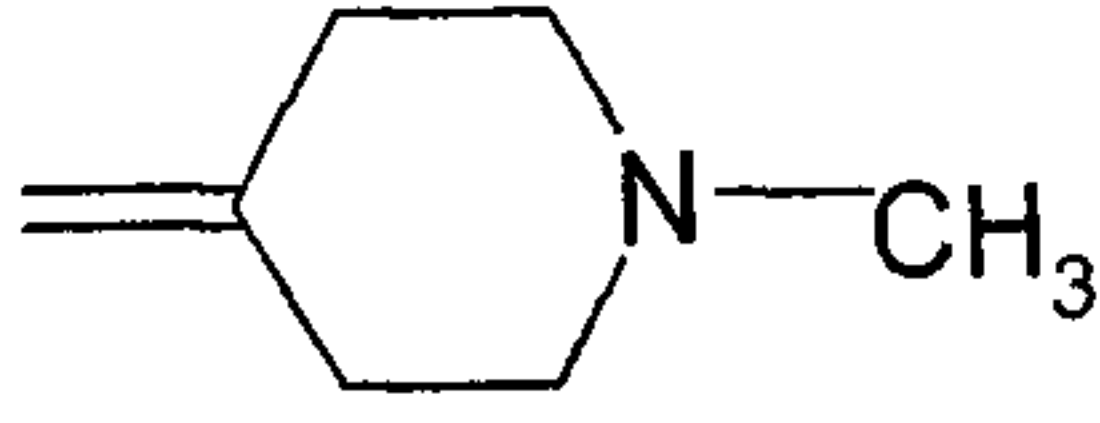
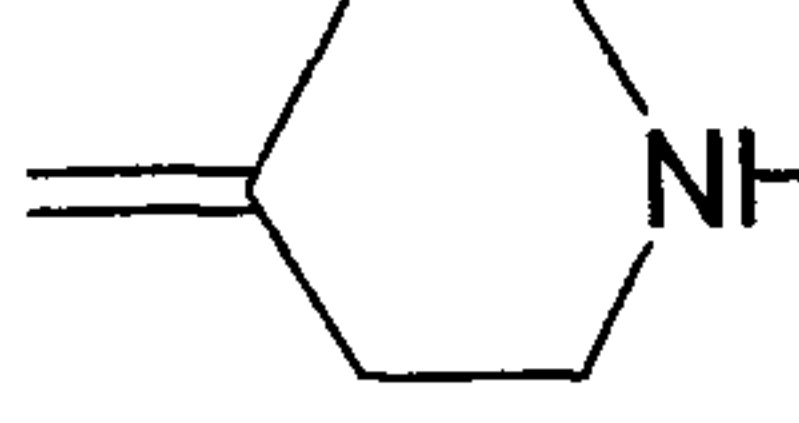
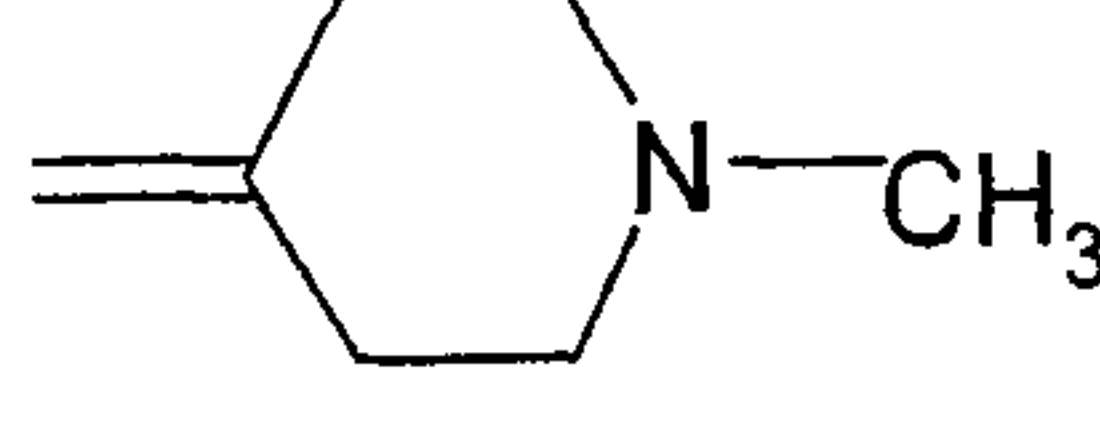
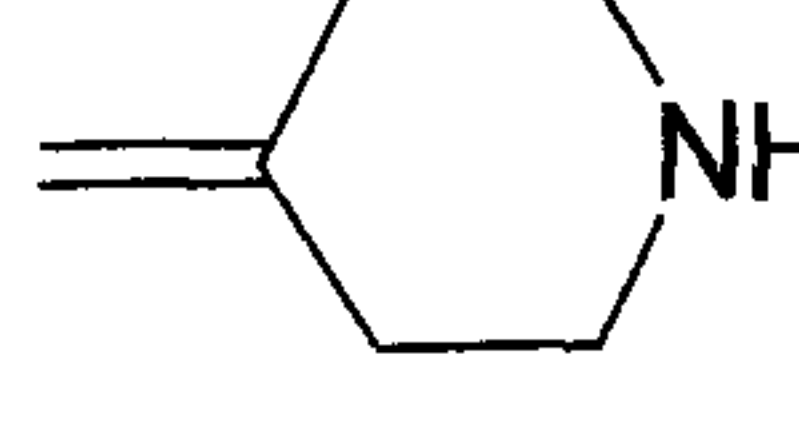
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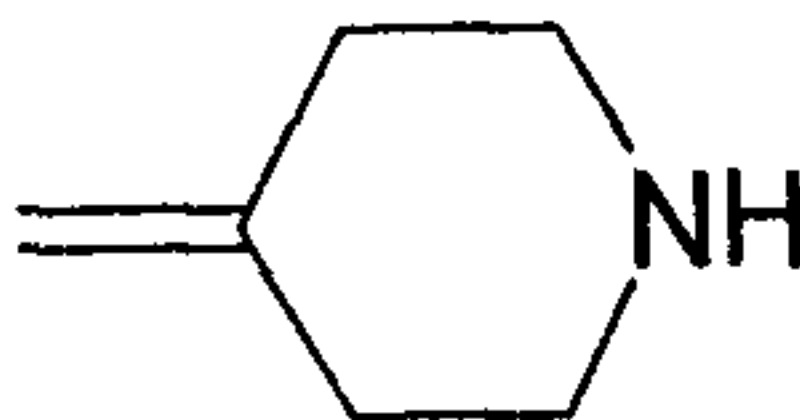
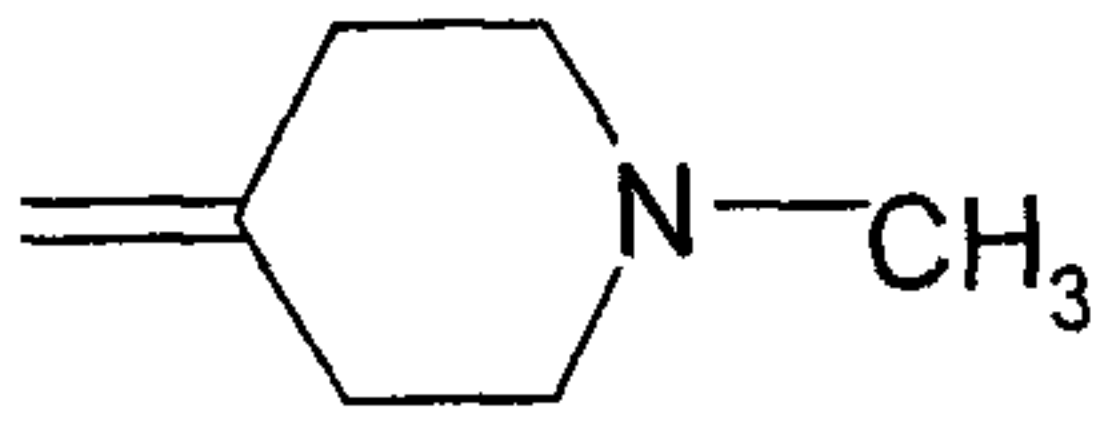
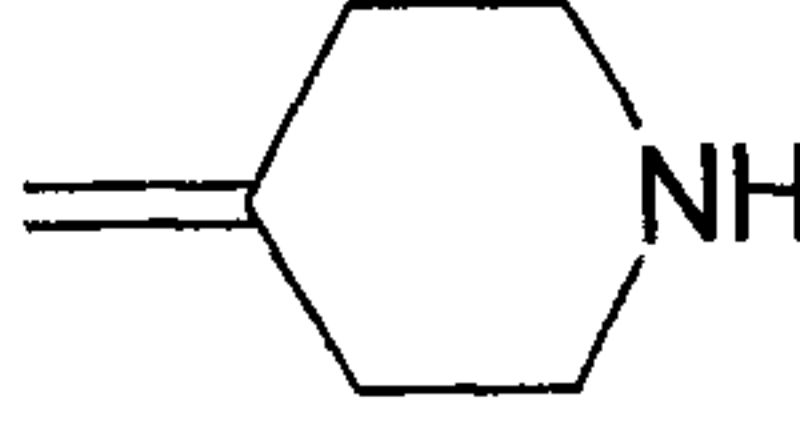
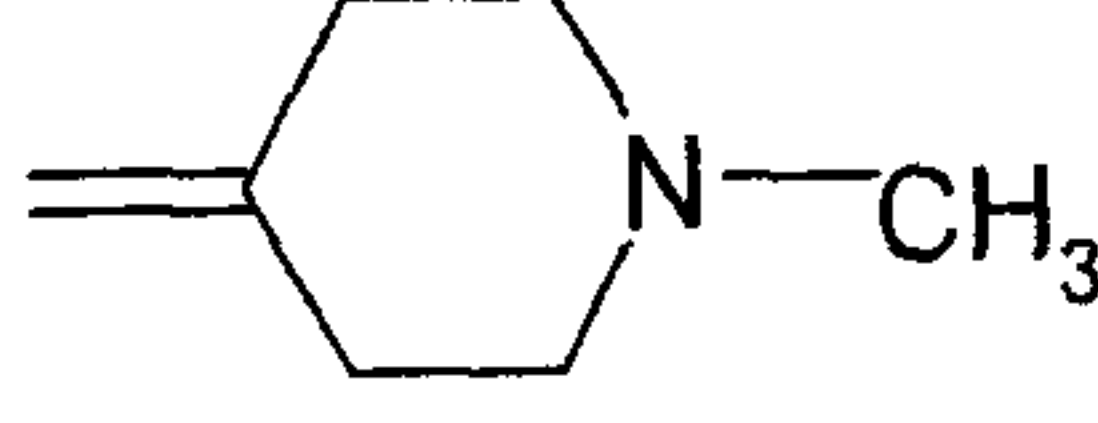
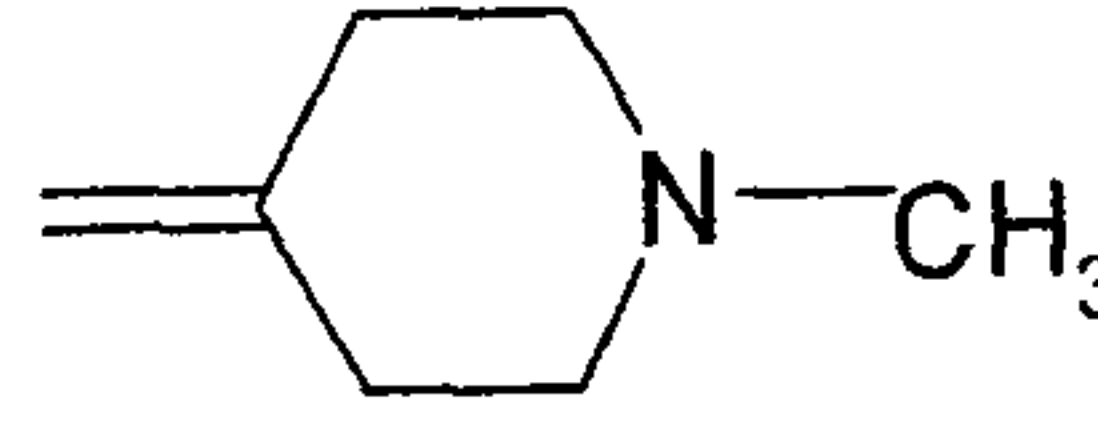
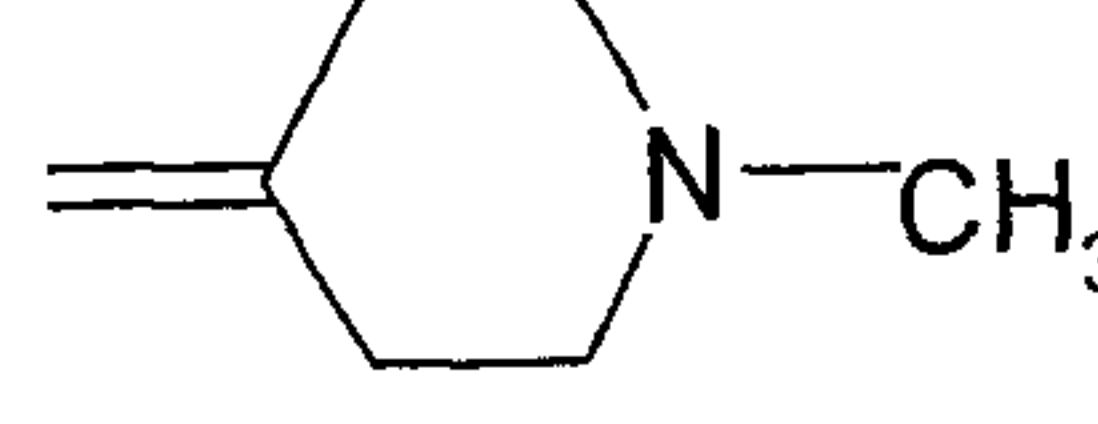
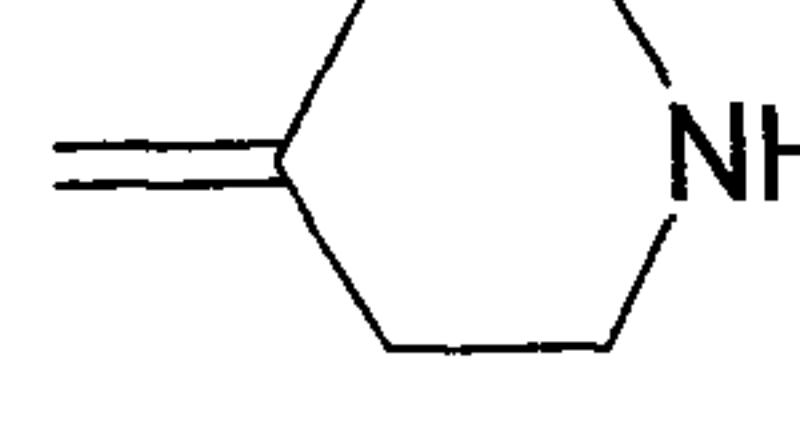
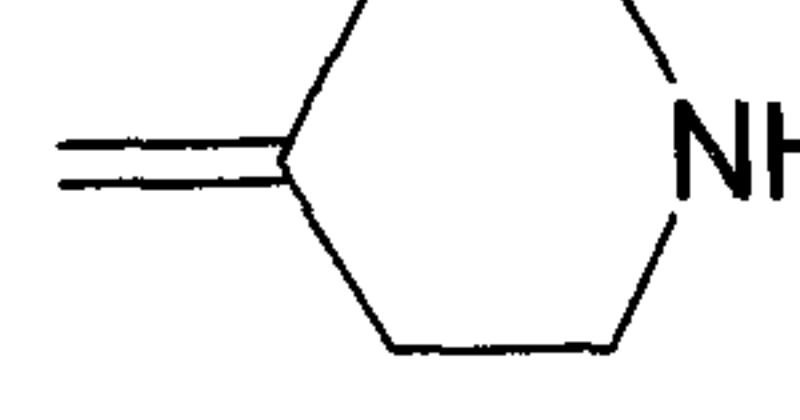
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	No.	R ¹	R ²	R ³	R ⁴
5	26.	NH ₂	Methyl	H	O
	27.	NH ₂	Phenyl	H	O
	28.	NH ₂	Methyl	Methyl	O
	29.	NH ₂	Phenyl	Methyl	O
	30.	NH ₂	Methyl	H	
10	31.	NH ₂	Phenyl	H	
	32.	NH ₂	Methyl	Methyl	
15	33.	NH ₂	Phenyl	Methyl	
	34.	CN	Methyl	H	O
20	35.	CN	Phenyl	H	O
	36.	CN	Methyl	Methyl	O
	37.	CN	Phenyl	Methyl	O
25	38.	CN	Methyl	H	
	39.	CN	Phenyl	H	
30	40.	CN	Methyl	Methyl	
	41.	CN	Phenyl	Methyl	
35					

Example 42-81

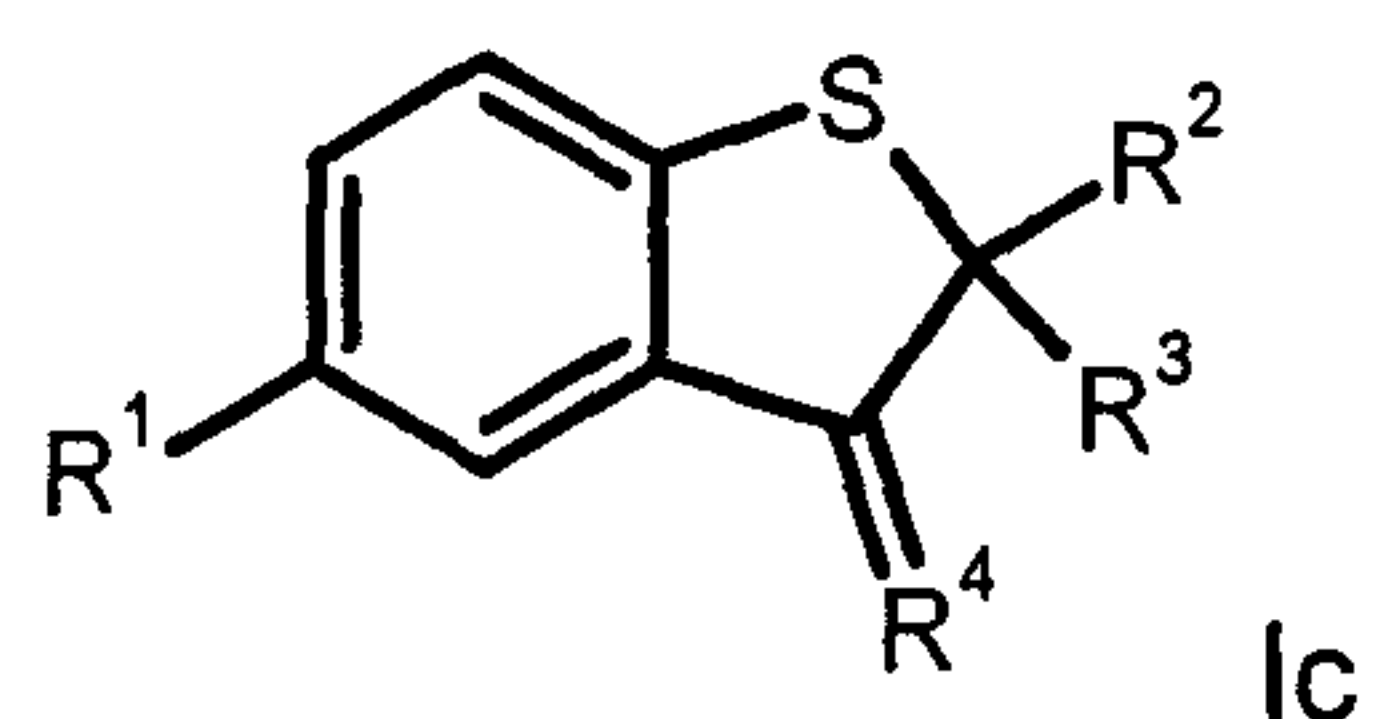
	No.	R ¹	R ²	R ³	R ⁴
10	42.	Methyl	Methyl	H	O
	43.	Methyl	Phenyl	H	O
	44.	Methyl	Methyl	Methyl	O
	45.	Methyl	Phenyl	Methyl	O
	46.	Methyl	Methyl	H	
20	47.	Methyl	Phenyl	H	
	48.	Methyl	Methyl	Methyl	
	49.	Methyl	Phenyl	Methyl	
30	50.	Phenyl	Methyl	H	O
	51.	Phenyl	Phenyl	H	O
	52.	Phenyl	Methyl	Methyl	O
	53.	Phenyl	Phenyl	Methyl	O
	54.	Phenyl	Methyl	H	
35	55.	Phenyl	Phenyl	H	

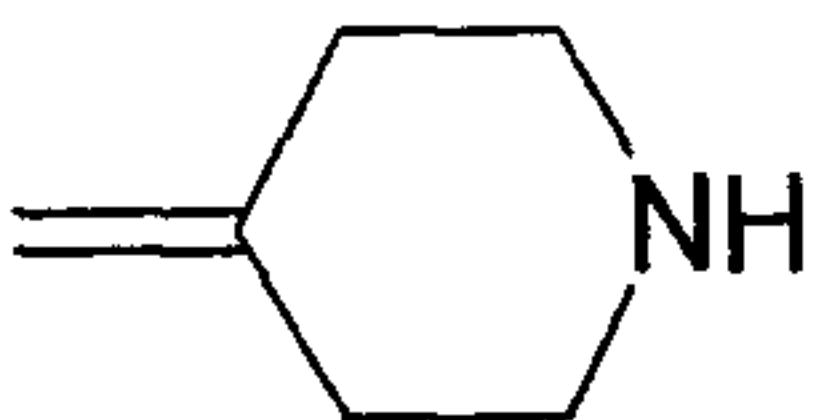
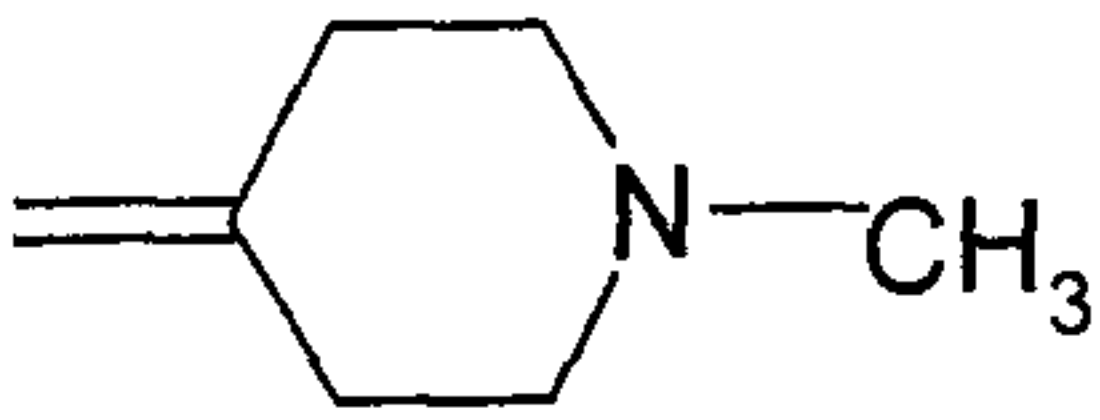
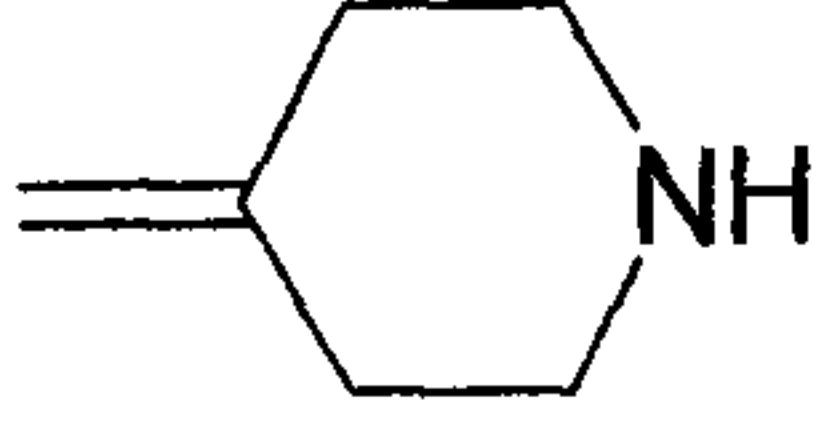
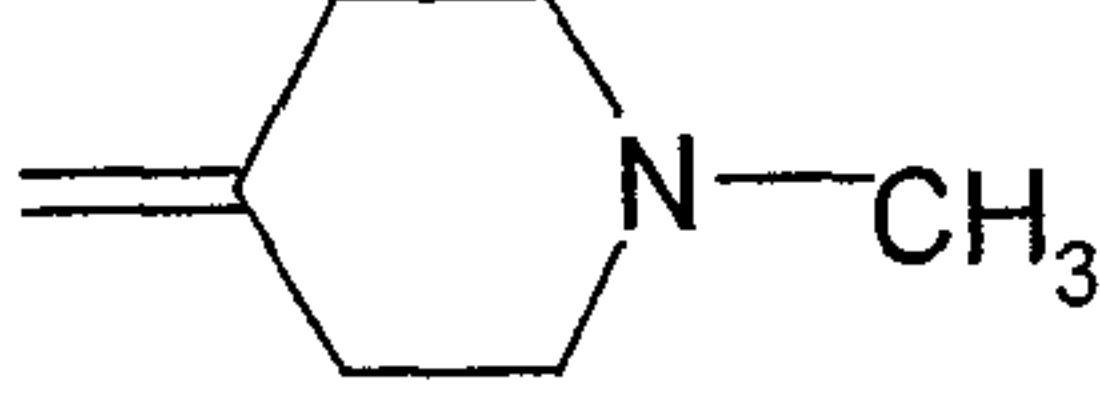
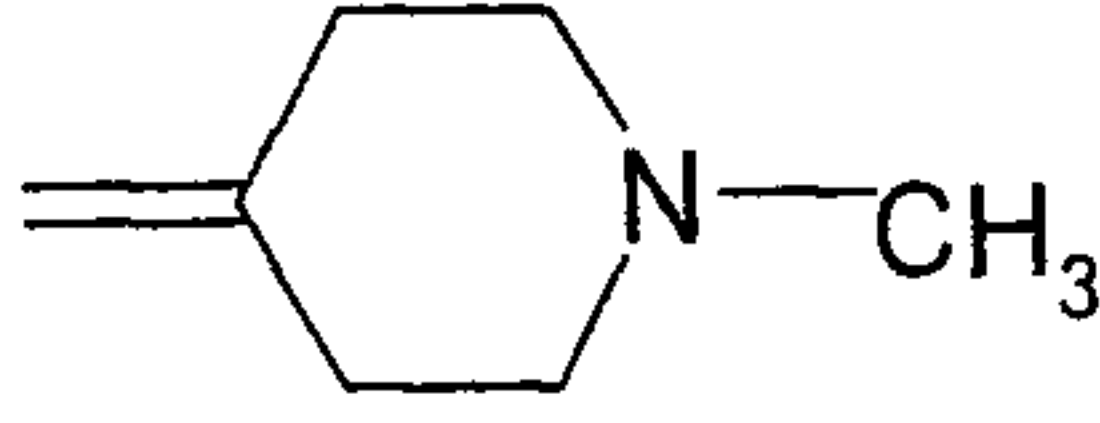
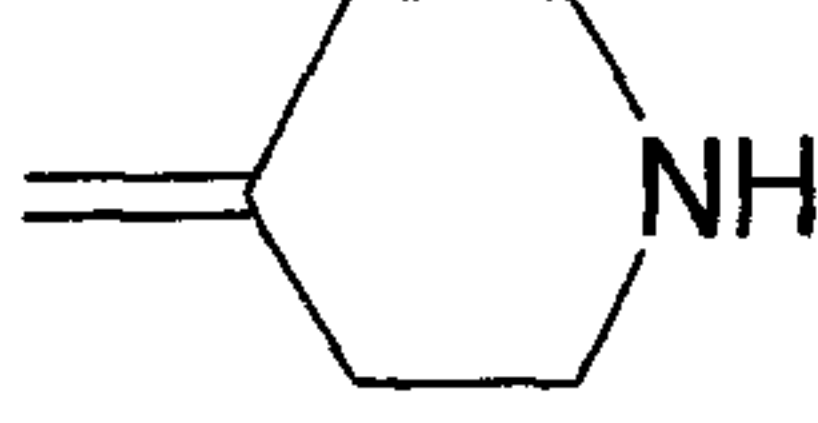
	No.	R ¹	R ²	R ³	R ⁴
5	56.	Phenyl	Methyl	Methyl	
	57.	Phenyl	Phenyl	Methyl	
10	58.	OH	Methyl	H	O
	59.	OH	Phenyl	H	O
	60.	OH	Methyl	Methyl	O
	61.	OH	Phenyl	Methyl	O
15	62.	OH	Methyl	H	
	63.	OH	Phenyl	H	
20	64.	OH	Methyl	Methyl	
	65.	OH	Phenyl	Methyl	
25					
30					
35					

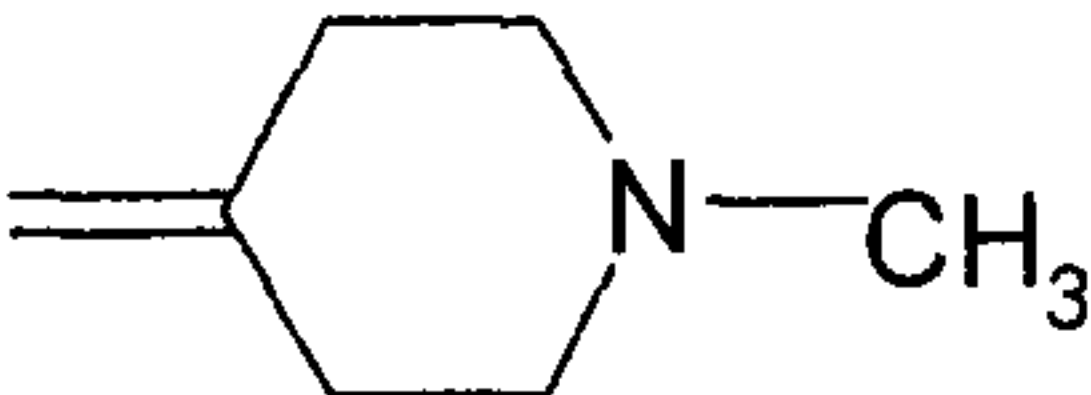
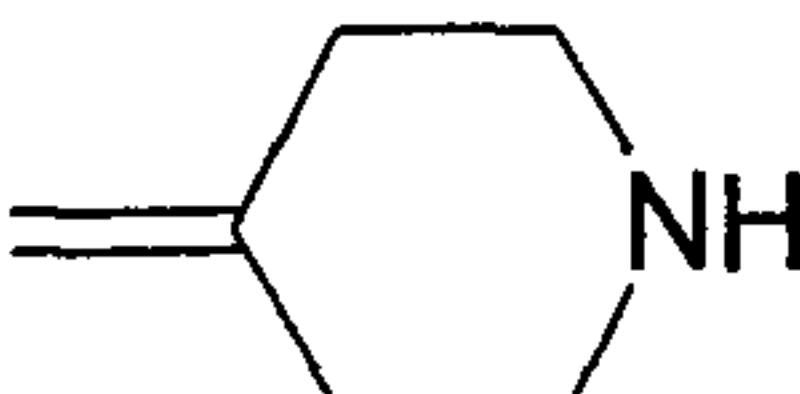
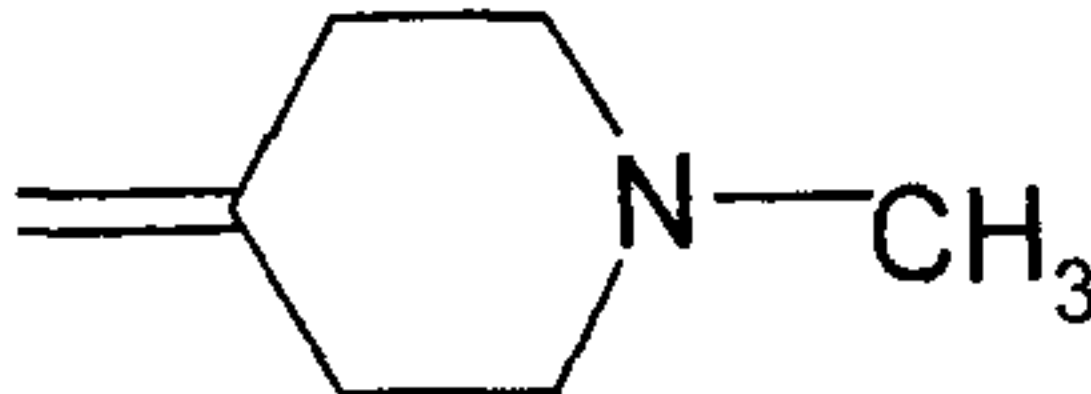
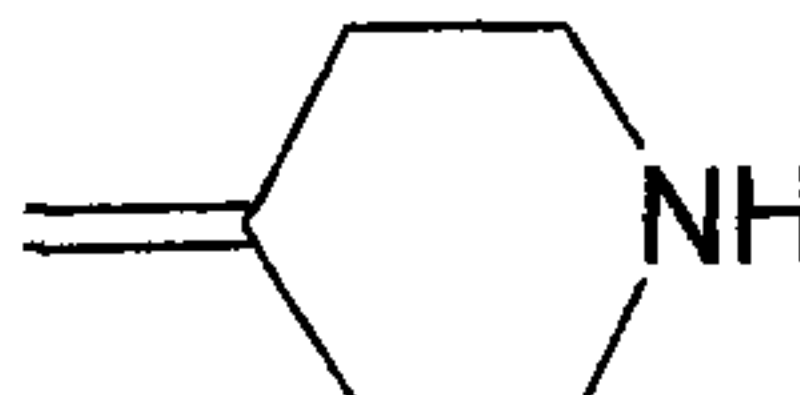
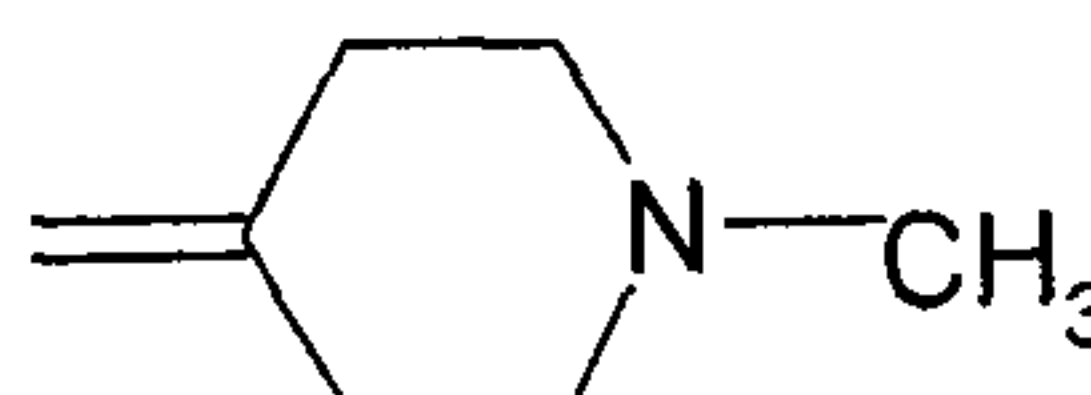
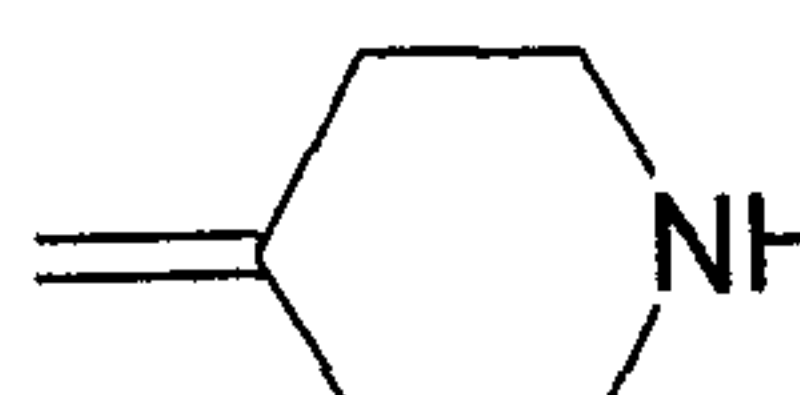
	No.	R ¹	R ²	R ³	R ⁴
5	66.	NH ₂	Methyl	H	O
	67.	NH ₂	Phenyl	H	O
	68.	NH ₂	Methyl	Methyl	O
	69.	NH ₂	Phenyl	Methyl	O
	70.	NH ₂	Methyl	H	
10	71.	NH ₂	Phenyl	H	
	72.	NH ₂	Methyl	Methyl	
15	73.	NH ₂	Phenyl	Methyl	
	74.	CN	Methyl	H	O
	75.	CN	Phenyl	H	O
	76.	CN	Methyl	Methyl	O
	77.	CN	Phenyl	Methyl	O
20	78.	CN	Methyl	H	
	79.	CN	Phenyl	H	
25	80.	CN	Methyl	Methyl	
	81.	CN	Phenyl	Methyl	
30					
35					

Example 82-121

5



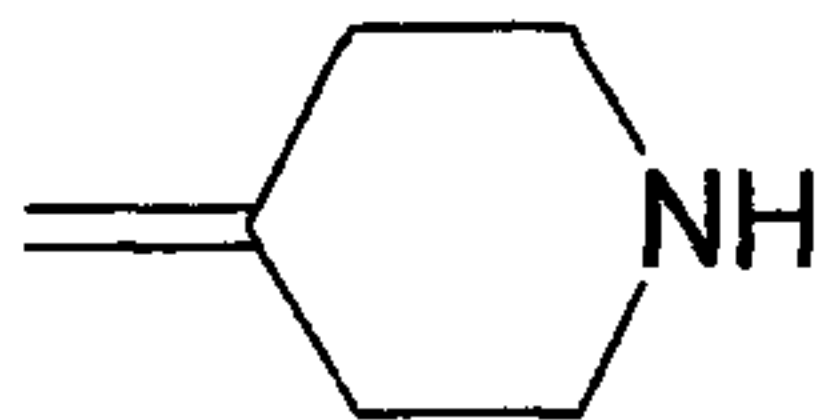
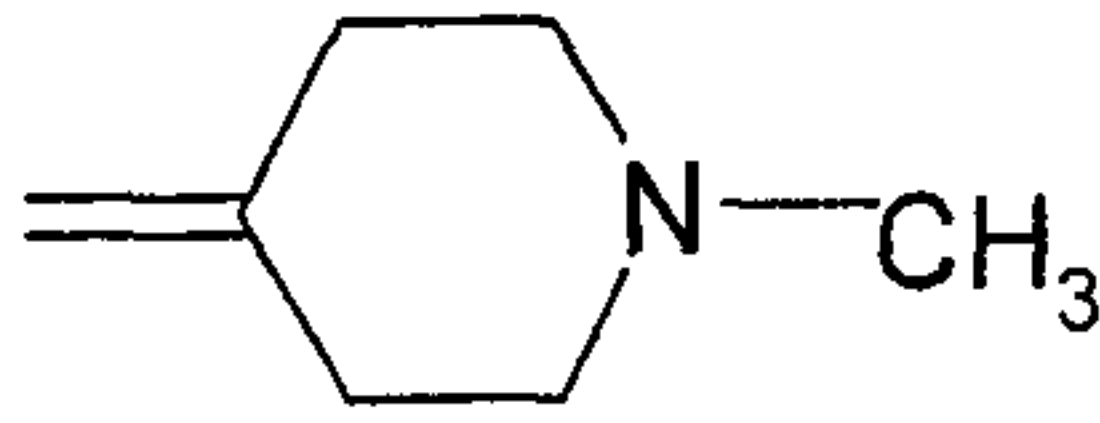
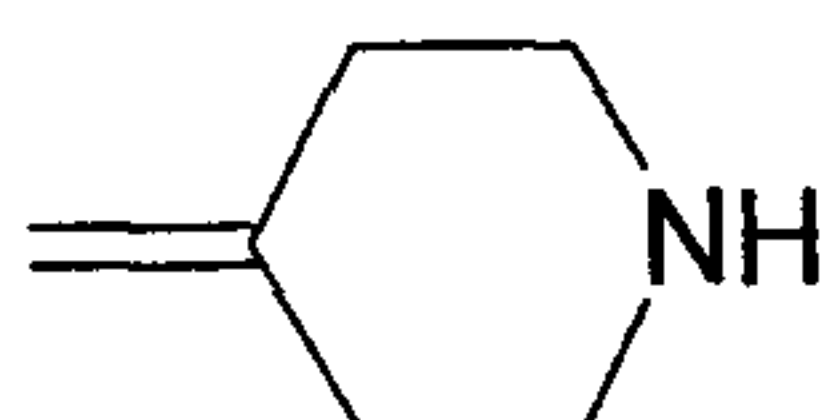
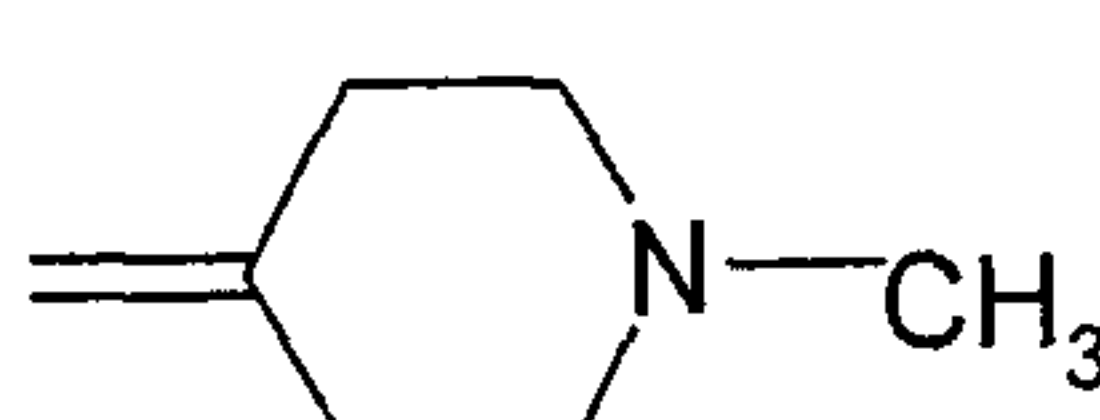
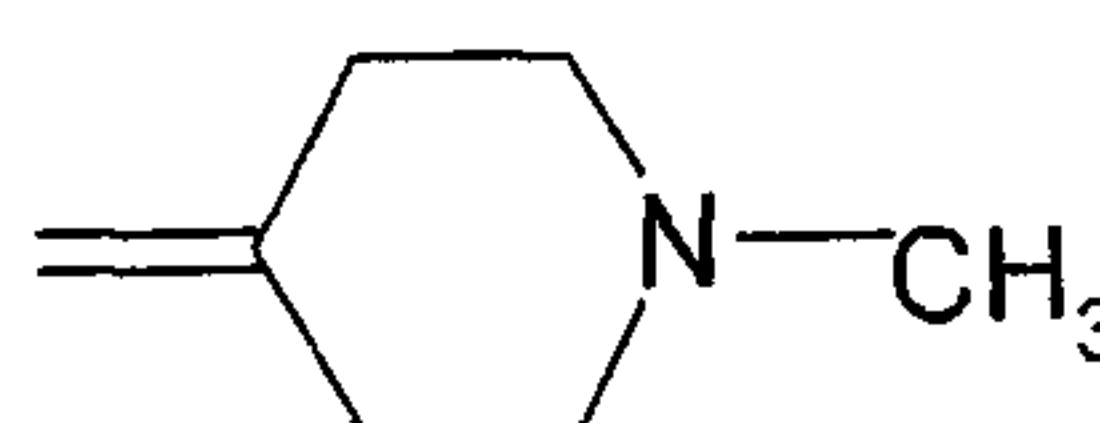
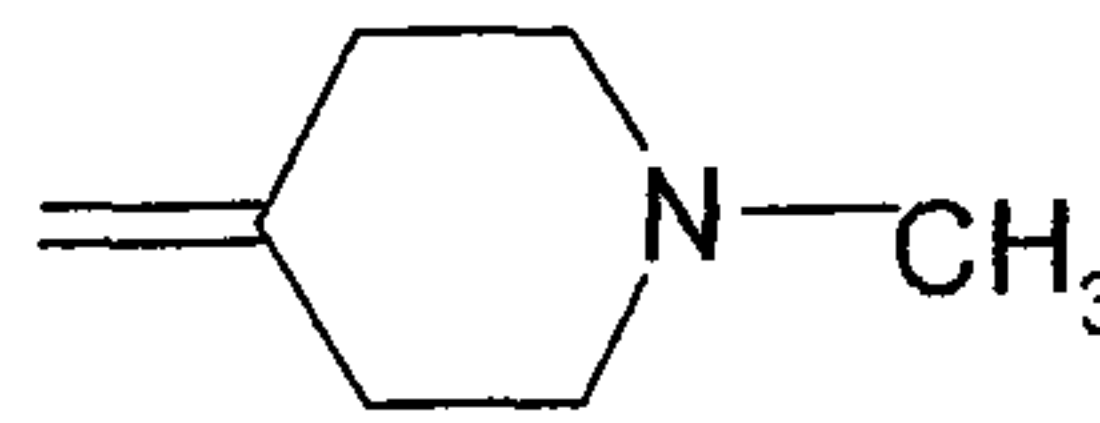
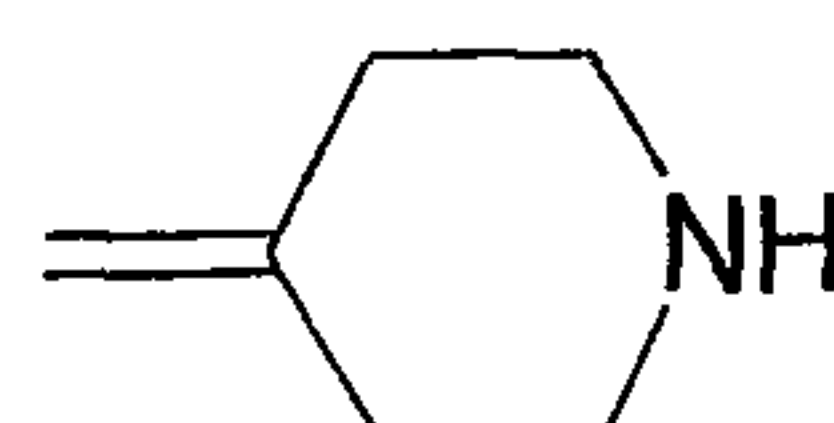
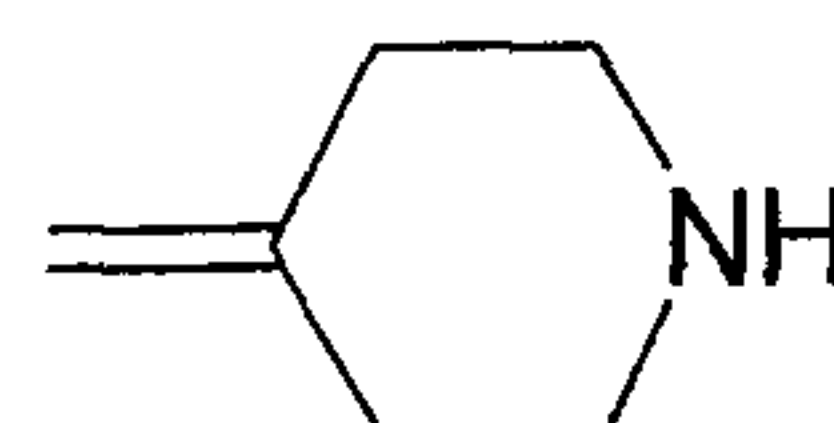
	No.	R ¹	R ²	R ³	R ⁴
10	82.	Methyl	Methyl	H	O
	83.	Methyl	Phenyl	H	O
	84.	Methyl	Methyl	Methyl	O
	85.	Methyl	Phenyl	Methyl	O
15	86.	Methyl	Methyl	H	
	87.	Methyl	Phenyl	H	
20	88.	Methyl	Methyl	Methyl	
	89.	Methyl	Phenyl	Methyl	
25	90.	Phenyl	Methyl	H	O
	91.	Phenyl	Phenyl	H	O
	92.	Phenyl	Methyl	Methyl	O
30	93.	Phenyl	Phenyl	Methyl	O
	94.	Phenyl	Methyl	H	
35	95.	Phenyl	Phenyl	H	

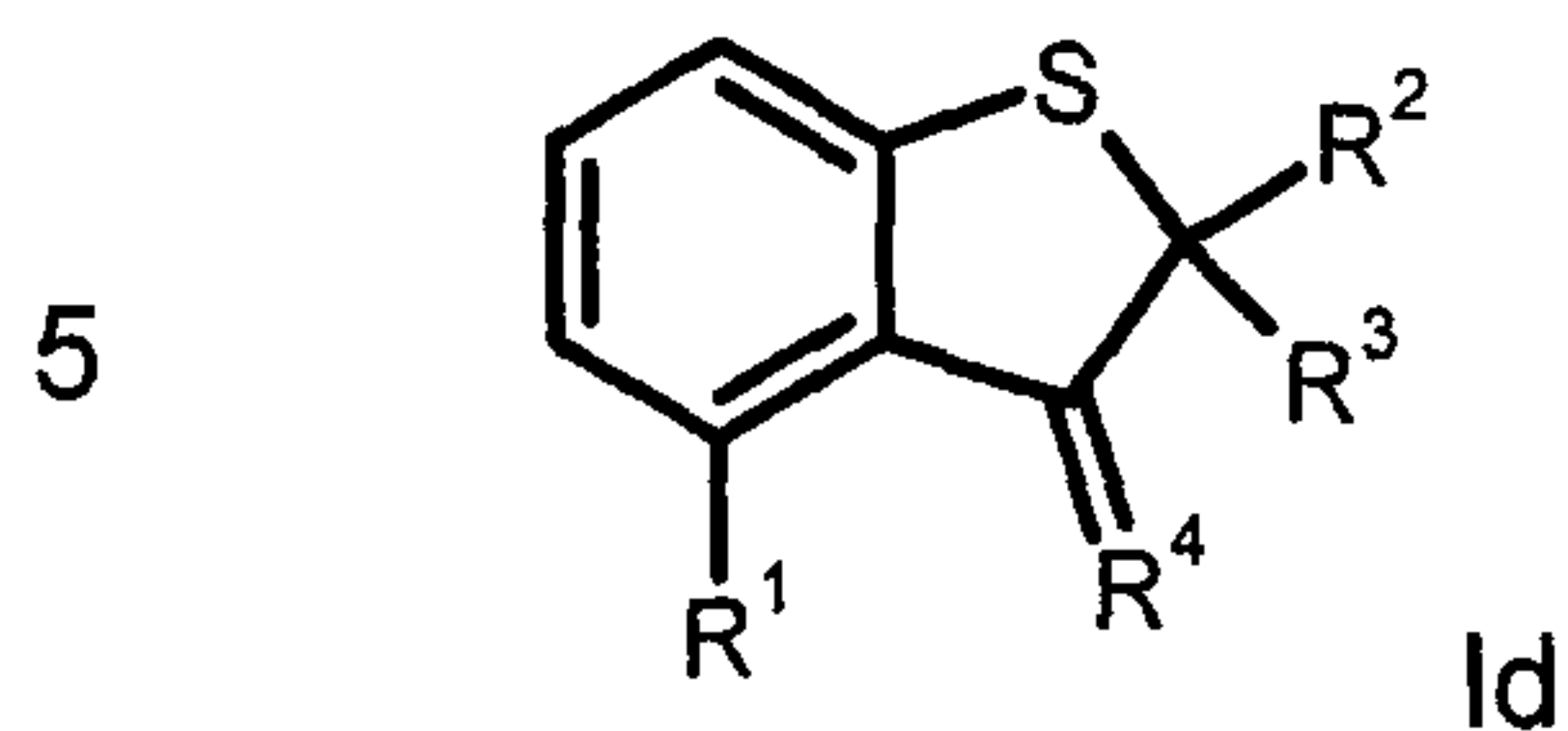
	No.	R ¹	R ²	R ³	R ⁴
	96.	Phenyl	Methyl	Methyl	
5	97.	Phenyl	Phenyl	Methyl	
	98.	OH	Methyl	H	O
	99.	OH	Phenyl	H	O
10	100.	OH	Methyl	Methyl	O
	101.	OH	Phenyl	Methyl	O
	102.	OH	Methyl	H	
15	103.	OH	Phenyl	H	
	104.	OH	Methyl	Methyl	
20	105.	OH	Phenyl	Methyl	

25

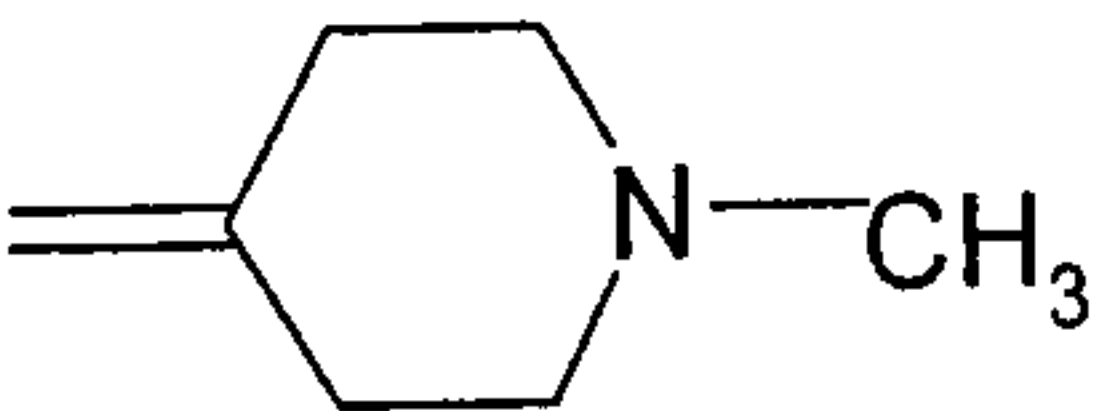
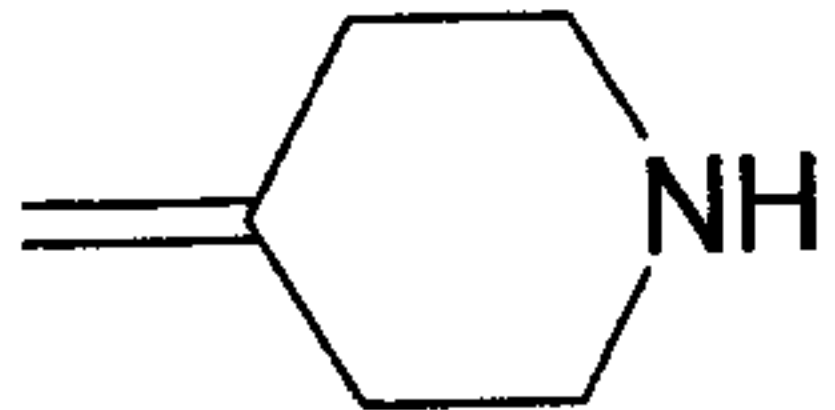
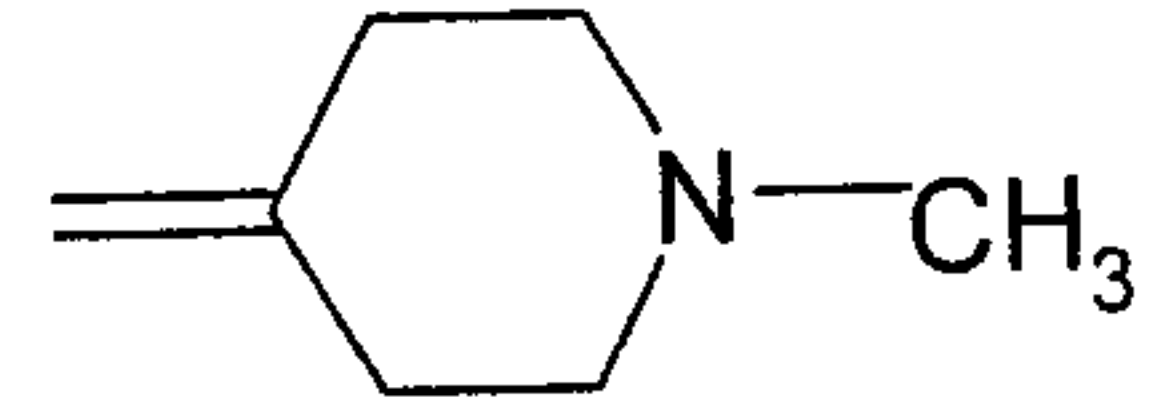
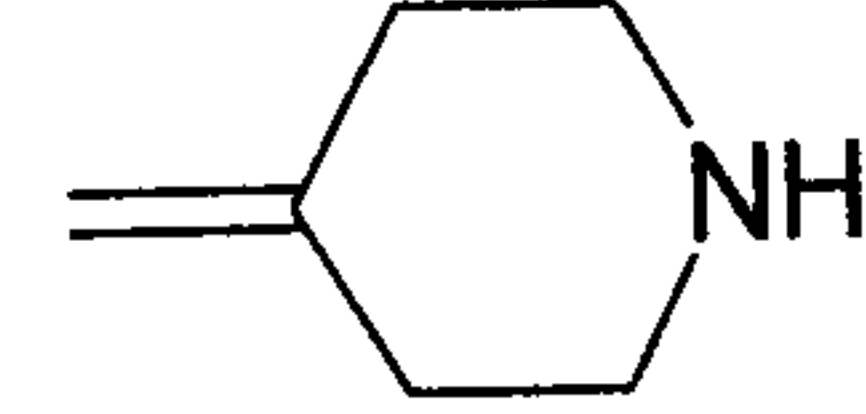
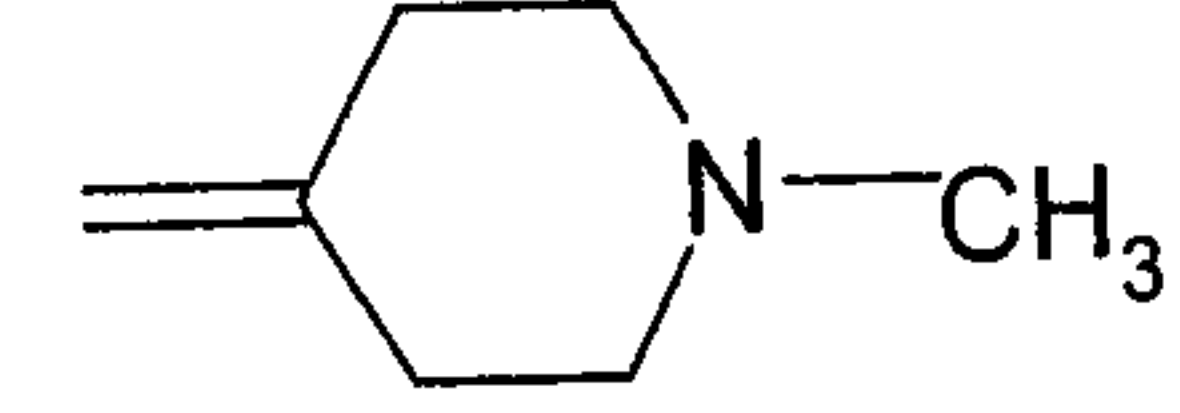
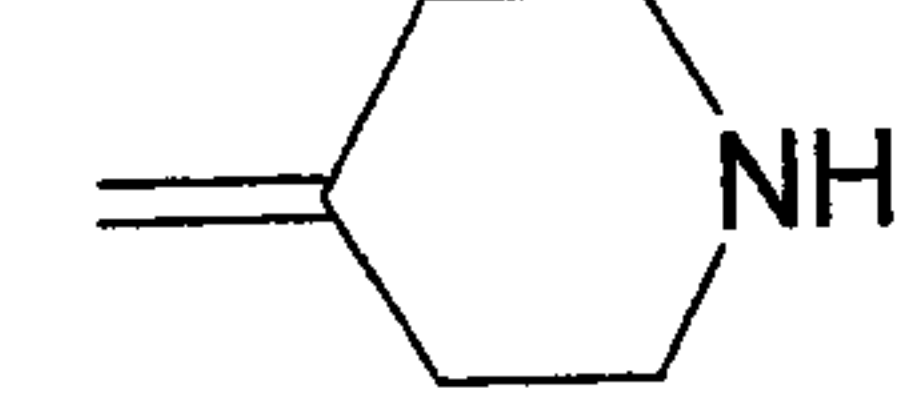
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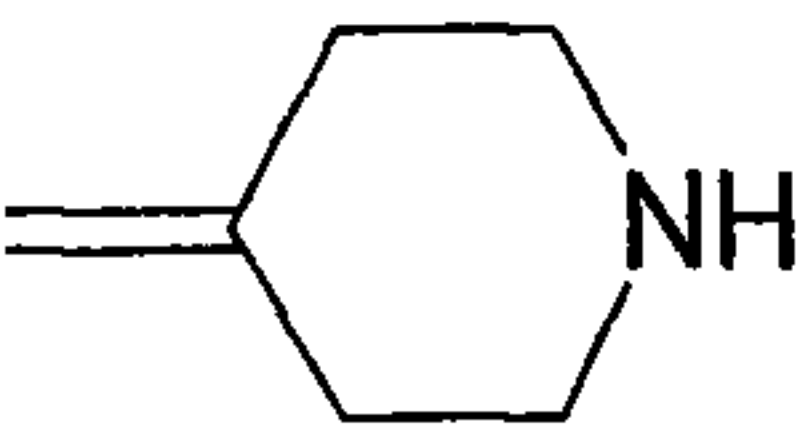
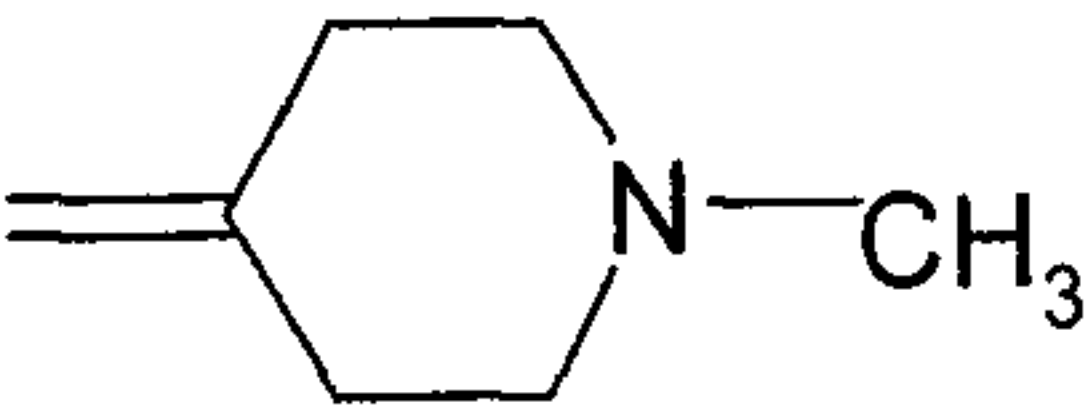
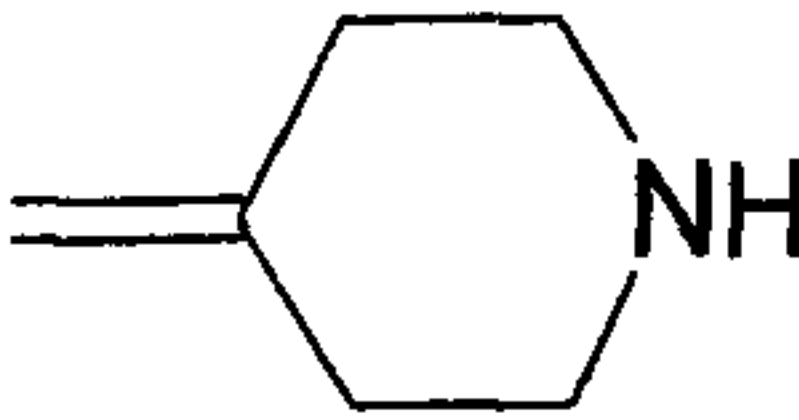
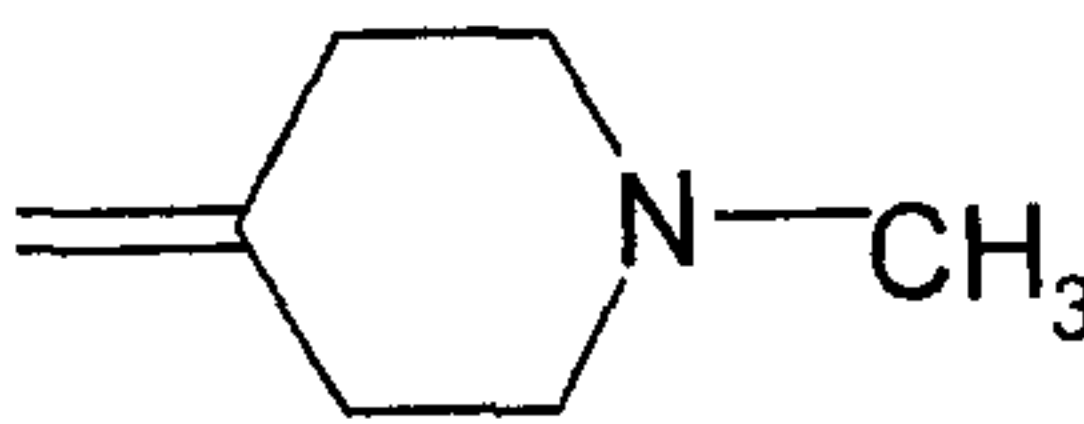
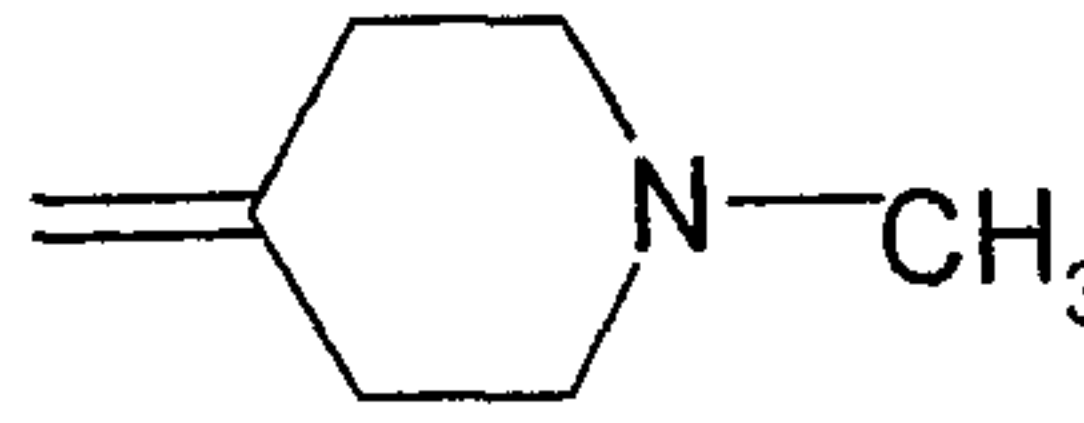
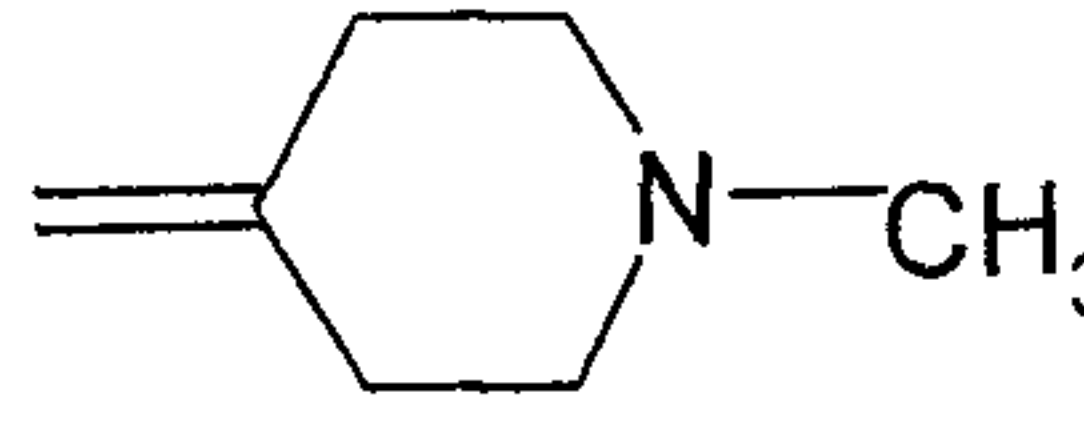
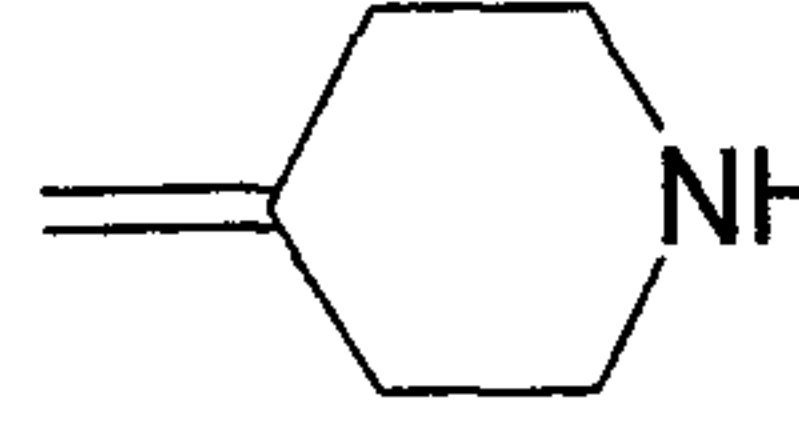
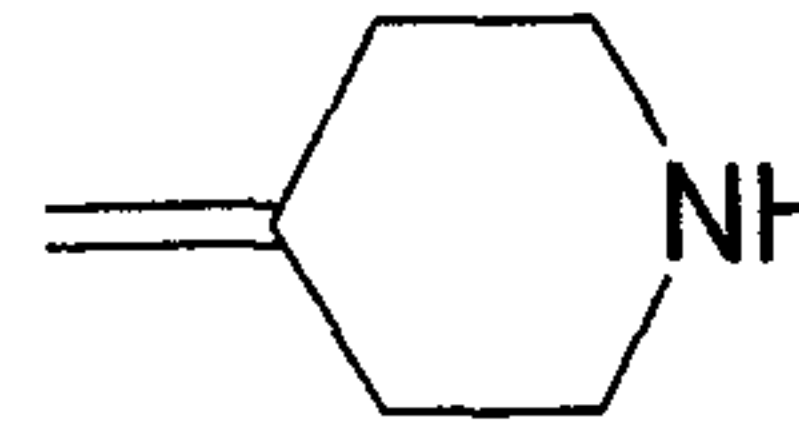
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	No.	R ¹	R ²	R ³	R ⁴
5	106.	NH ₂	Methyl	H	O
	107.	NH ₂	Phenyl	H	O
	108.	NH ₂	Methyl	Methyl	O
	109.	NH ₂	Phenyl	Methyl	O
	110.	NH ₂	Methyl	H	
10	111.	NH ₂	Phenyl	H	
	112.	NH ₂	Methyl	Methyl	
	113.	NH ₂	Phenyl	Methyl	
15	114.	CN	Methyl	H	O
	115.	CN	Phenyl	H	O
	116.	CN	Methyl	Methyl	O
	117.	CN	Phenyl	Methyl	O
	118.	CN	Methyl	H	
20	119.	CN	Phenyl	H	
	120.	CN	Methyl	Methyl	
25	121.	CN	Phenyl	Methyl	
30					
35					

Example 122- 161

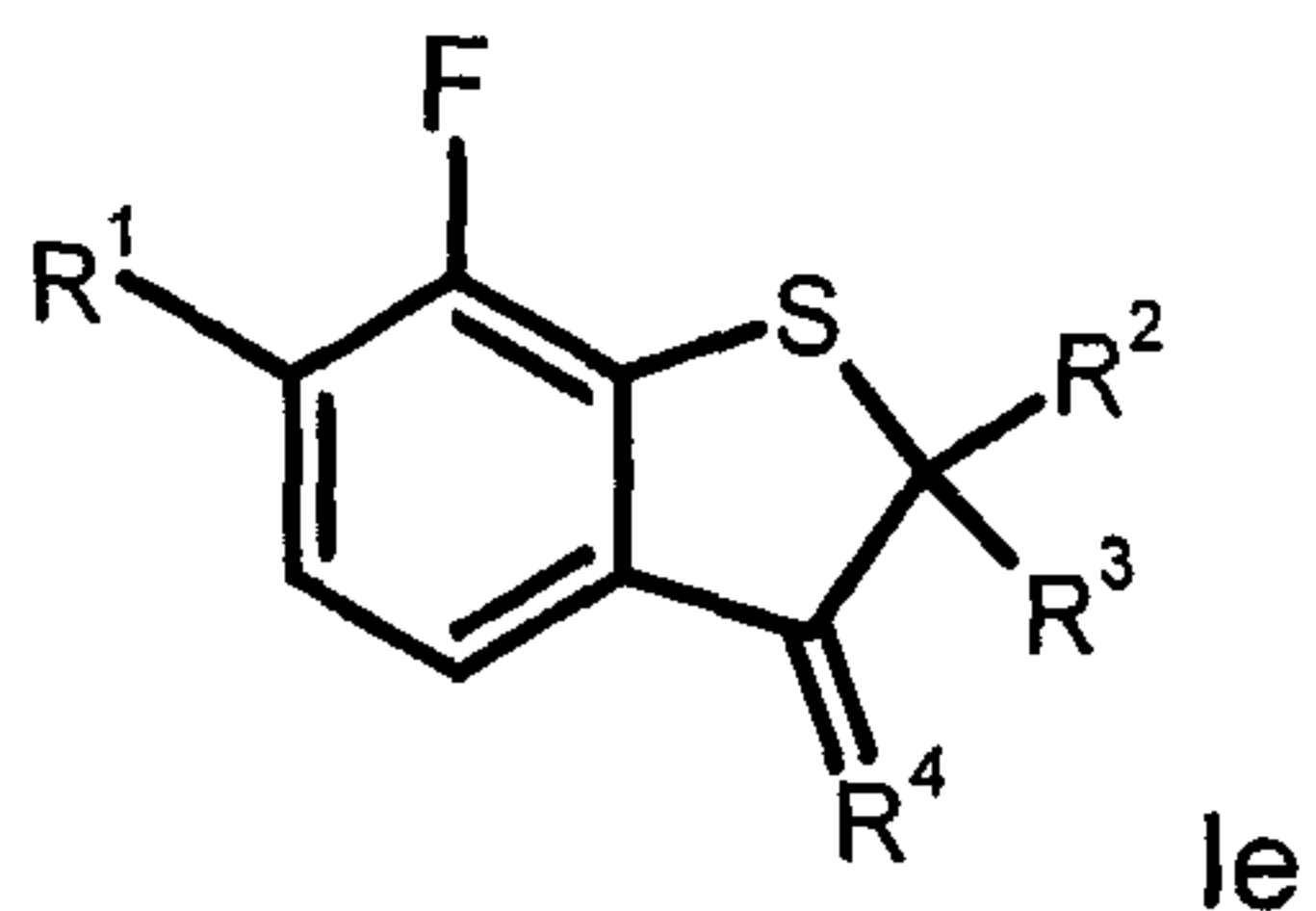
	No.	R ¹	R ²	R ³	R ⁴
10	122.	Methyl	Methyl	H	O
	123.	Methyl	Phenyl	H	O
	124.	Methyl	Methyl	Methyl	O
	125.	Methyl	Phenyl	Methyl	O
	126.	Methyl	Methyl	H	
20	127.	Methyl	Phenyl	H	
	128.	Methyl	Methyl	Methyl	
	129.	Methyl	Phenyl	Methyl	
30	130.	Phenyl	Methyl	H	O
	131.	Phenyl	Phenyl	H	O
	132.	Phenyl	Methyl	Methyl	O
	133.	Phenyl	Phenyl	Methyl	O
	134.	Phenyl	Methyl	H	
35	135.	Phenyl	Phenyl	H	

	No.	R ¹	R ²	R ³	R ⁴
5	136.	Phenyl	Methyl	Methyl	
	137.	Phenyl	Phenyl	Methyl	
10	138.	OH	Methyl	H	O
	139.	OH	Phenyl	H	O
	140.	OH	Methyl	Methyl	O
	141.	OH	Phenyl	Methyl	O
	142.	OH	Methyl	H	
15	143.	OH	Phenyl	H	
	144.	OH	Methyl	Methyl	
20	145.	OH	Phenyl	Methyl	
25					
30					
35					

	No.	R ¹	R ²	R ³	R ⁴
5	146.	NH ₂	Methyl	H	O
	147.	NH ₂	Phenyl	H	O
	148.	NH ₂	Methyl	Methyl	O
	149.	NH ₂	Phenyl	Methyl	O
	150.	NH ₂	Methyl	H	
10	151.	NH ₂	Phenyl	H	
	152.	NH ₂	Methyl	Methyl	
15	153.	NH ₂	Phenyl	Methyl	
	154.	CN	Methyl	H	O
20	155.	CN	Phenyl	H	O
	156.	CN	Methyl	Methyl	O
	157.	CN	Phenyl	Methyl	O
25	158.	CN	Methyl	H	
	159.	CN	Phenyl	H	
30	160.	CN	Methyl	Methyl	
	161.	CN	Phenyl	Methyl	
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Example 162-254

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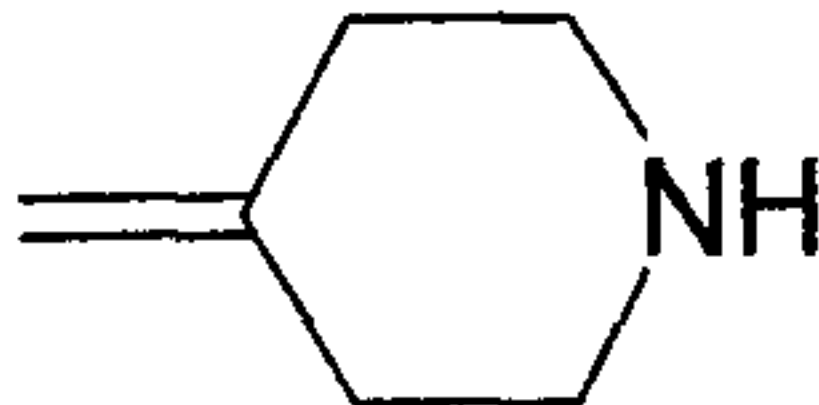
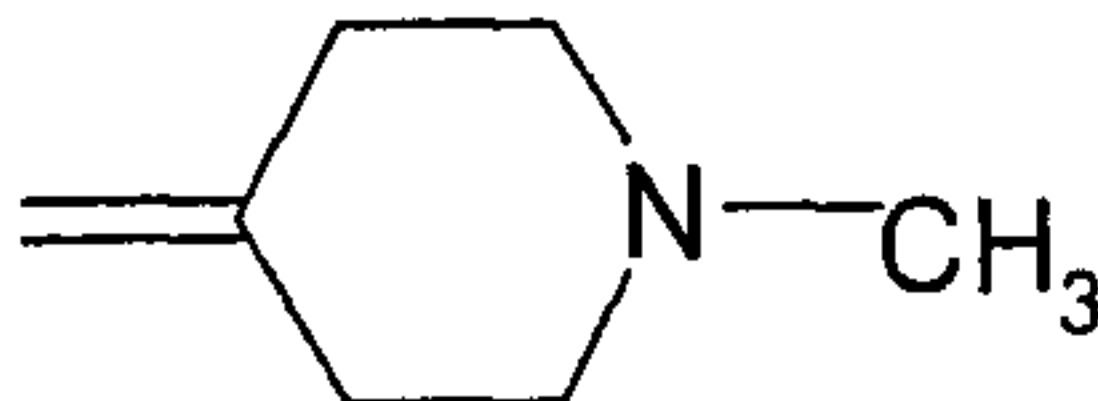
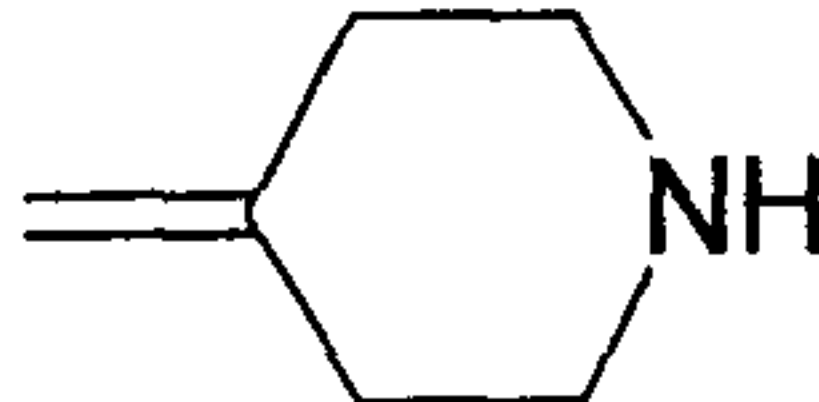
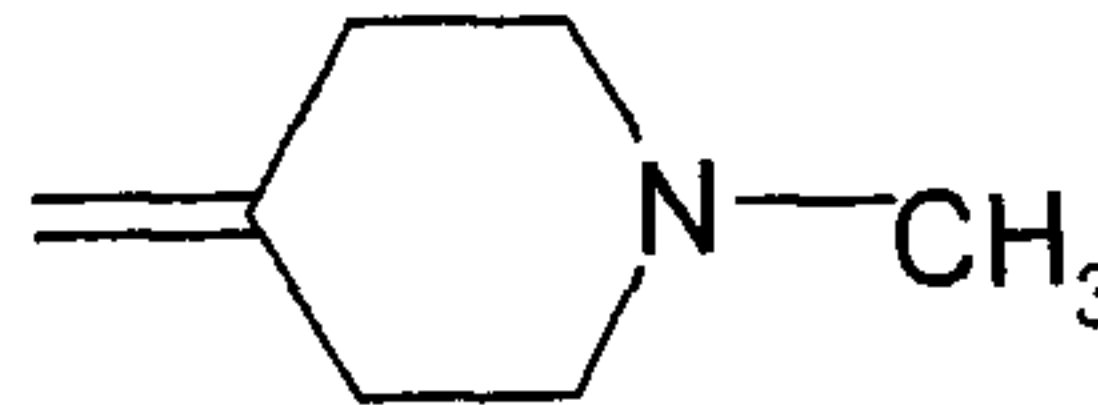
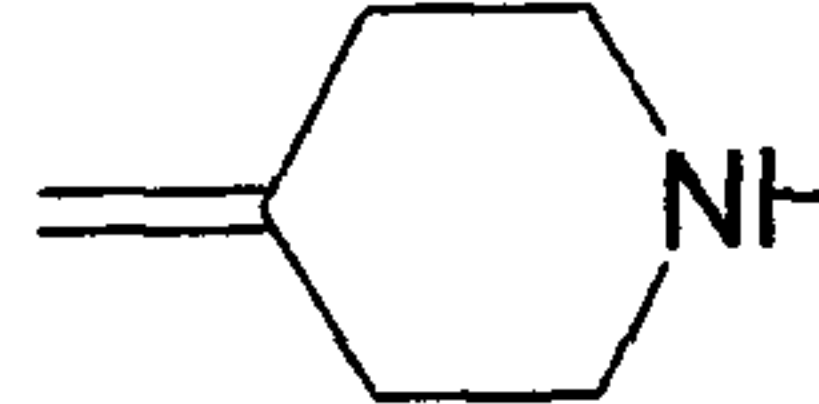
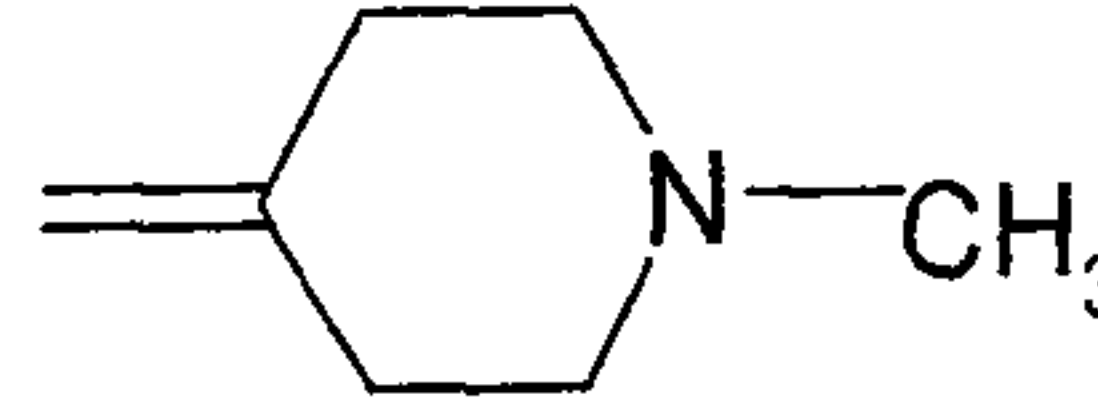
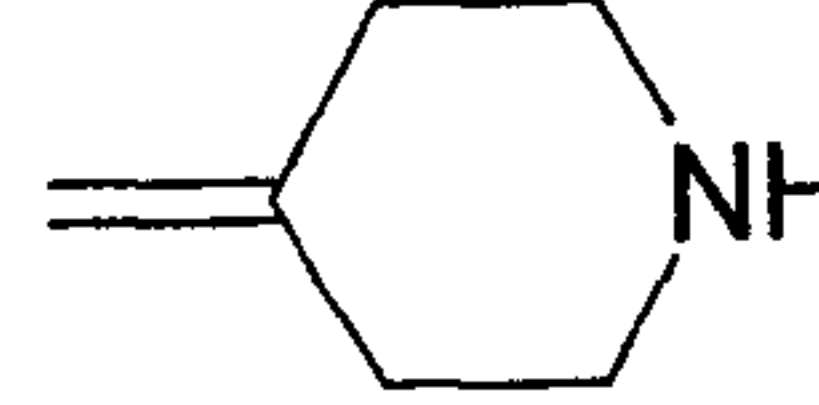
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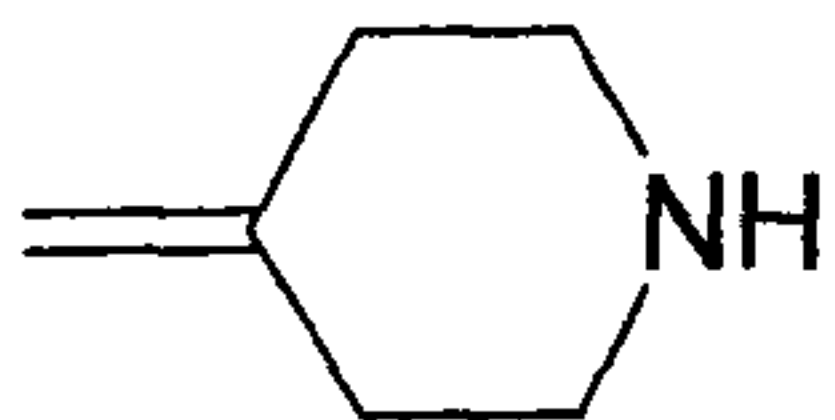
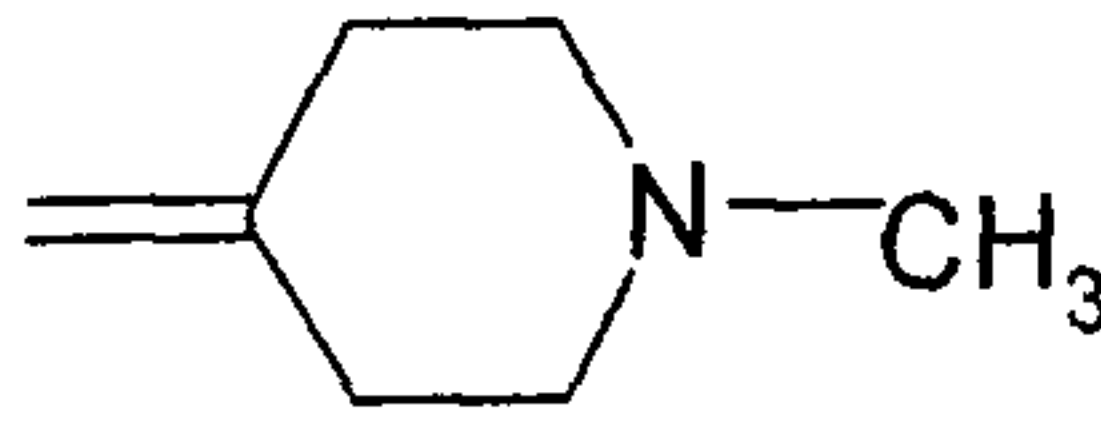
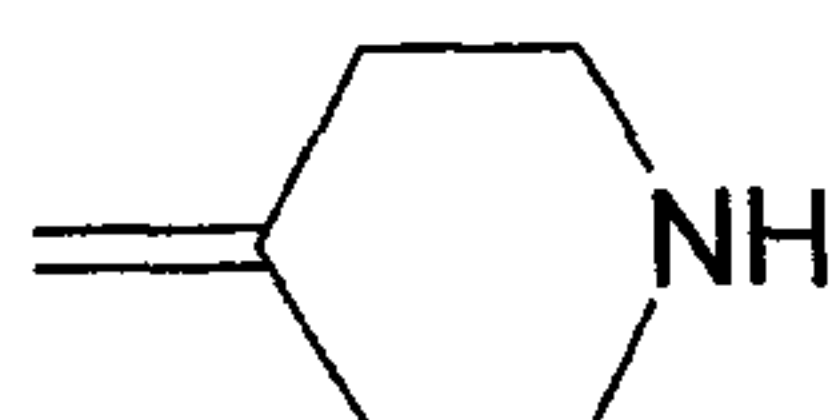
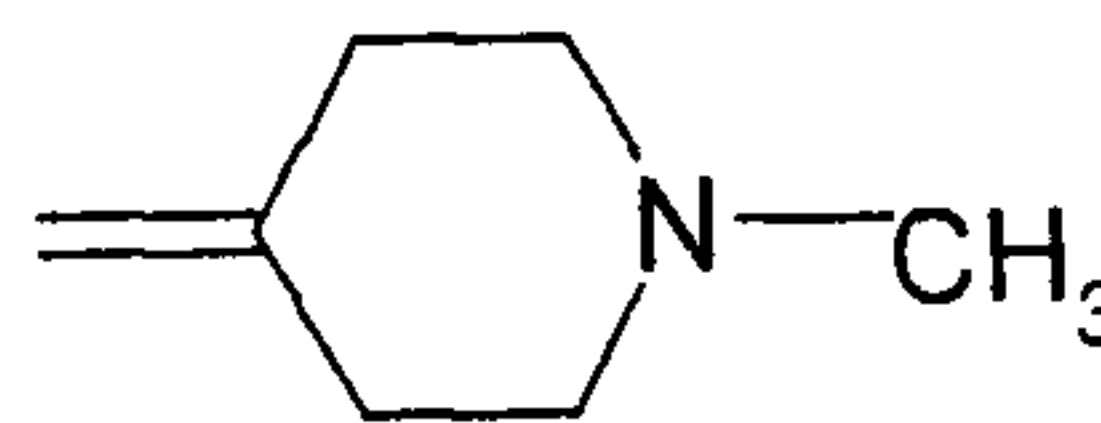
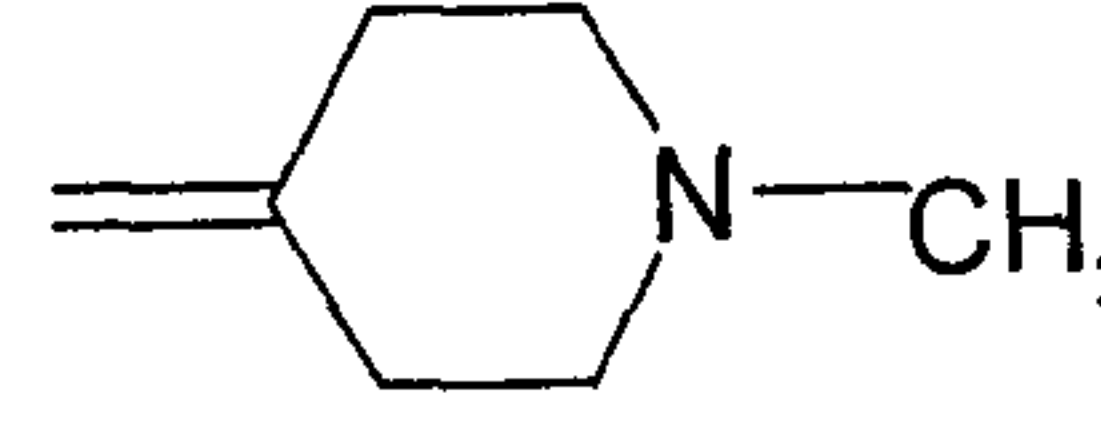
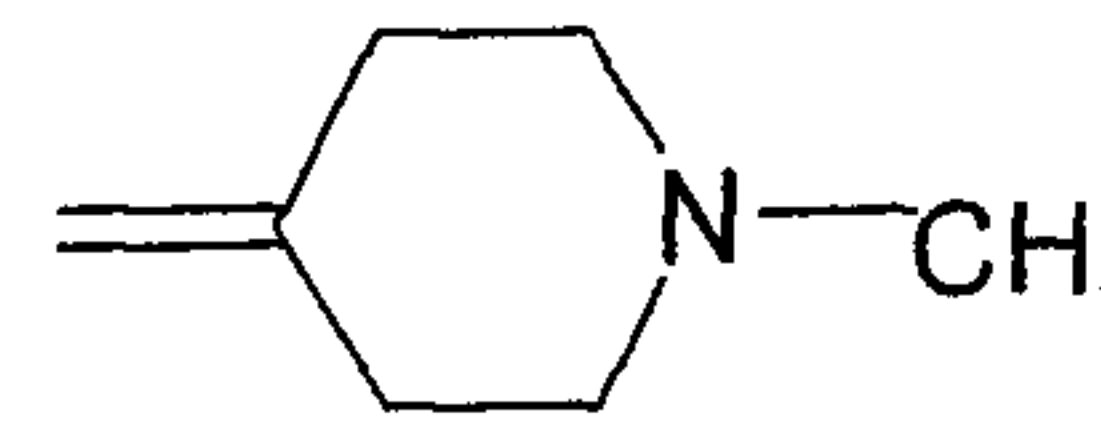
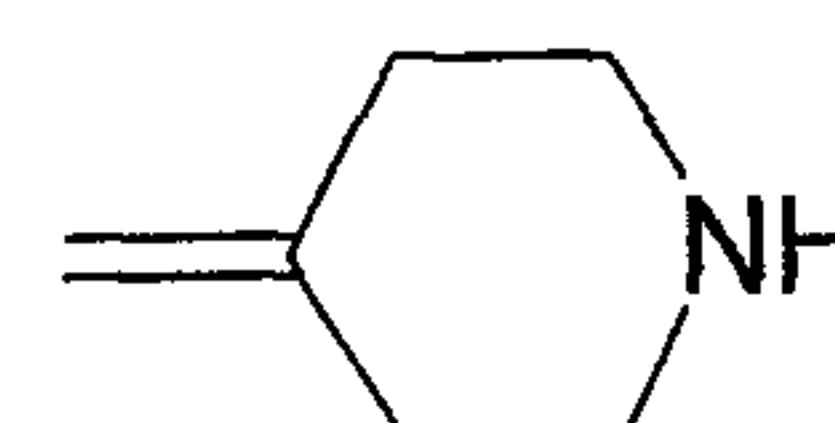
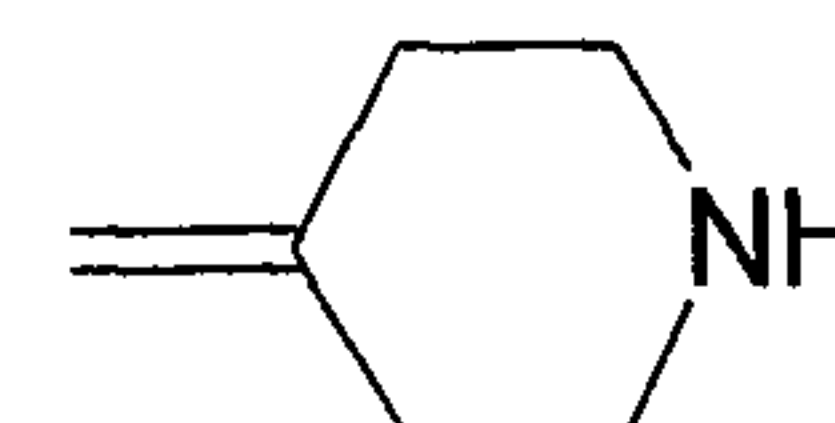
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No.	R ¹	R ²	R ³	R ⁴
162.	Methyl	Methyl	H	O
163.	Methyl	Phenyl	H	O
164.	Methyl	Methyl	Methyl	O
165.	Methyl	Phenyl	Methyl	O
166.	Methyl	Methyl	H	
167.	Methyl	Phenyl	H	
168.	Methyl	Methyl	Methyl	
169.	Methyl	Phenyl	Methyl	
170.	Phenyl	Methyl	H	O
171.	Phenyl	Phenyl	H	O
172.	Phenyl	Methyl	Methyl	O
173.	Phenyl	Phenyl	Methyl	O
174.	Phenyl	Methyl	H	

	175.	Phenyl	Phenyl	H	
5	No.	R ¹	R ²	R ³	R ⁴
	176.	Phenyl	Methyl	Methyl	
10	177.	Phenyl	Phenyl	Methyl	
	178.	OH	Methyl	H	O
	179.	OH	Phenyl	H	O
15	180.	OH	Methyl	Methyl	O
	181.	OH	Phenyl	Methyl	O
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20	183.	OH	Phenyl	H	
	184.	OH	Methyl	Methyl	
25	185.	OH	Phenyl	Methyl	

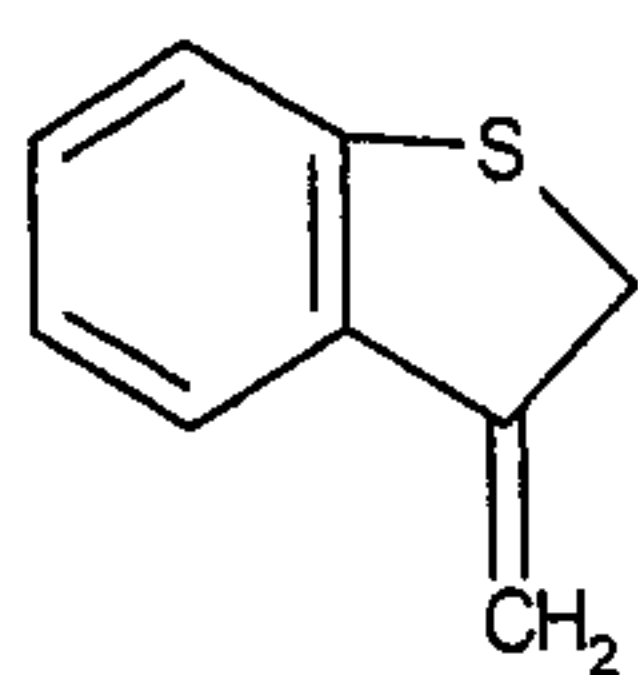
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	No.	R ¹	R ²	R ³	R ⁴
5	186.	NH ₂	Methyl	H	O
	187.	NH ₂	Phenyl	H	O
	188.	NH ₂	Methyl	Methyl	O
	189.	NH ₂	Phenyl	Methyl	O
	190.	NH ₂	Methyl	H	
10	191.	NH ₂	Phenyl	H	
	192.	NH ₂	Methyl	Methyl	
15	193.	NH ₂	Phenyl	Methyl	
20	194.	CN	Methyl	H	O
	195.	CN	Phenyl	H	O
	196.	CN	Methyl	Methyl	O
	197.	CN	Phenyl	Methyl	O
	198.	CN	Methyl	H	
25	199.	CN	Phenyl	H	
30	200.	CN	Methyl	Methyl	
	201.	CN	Phenyl	Methyl	
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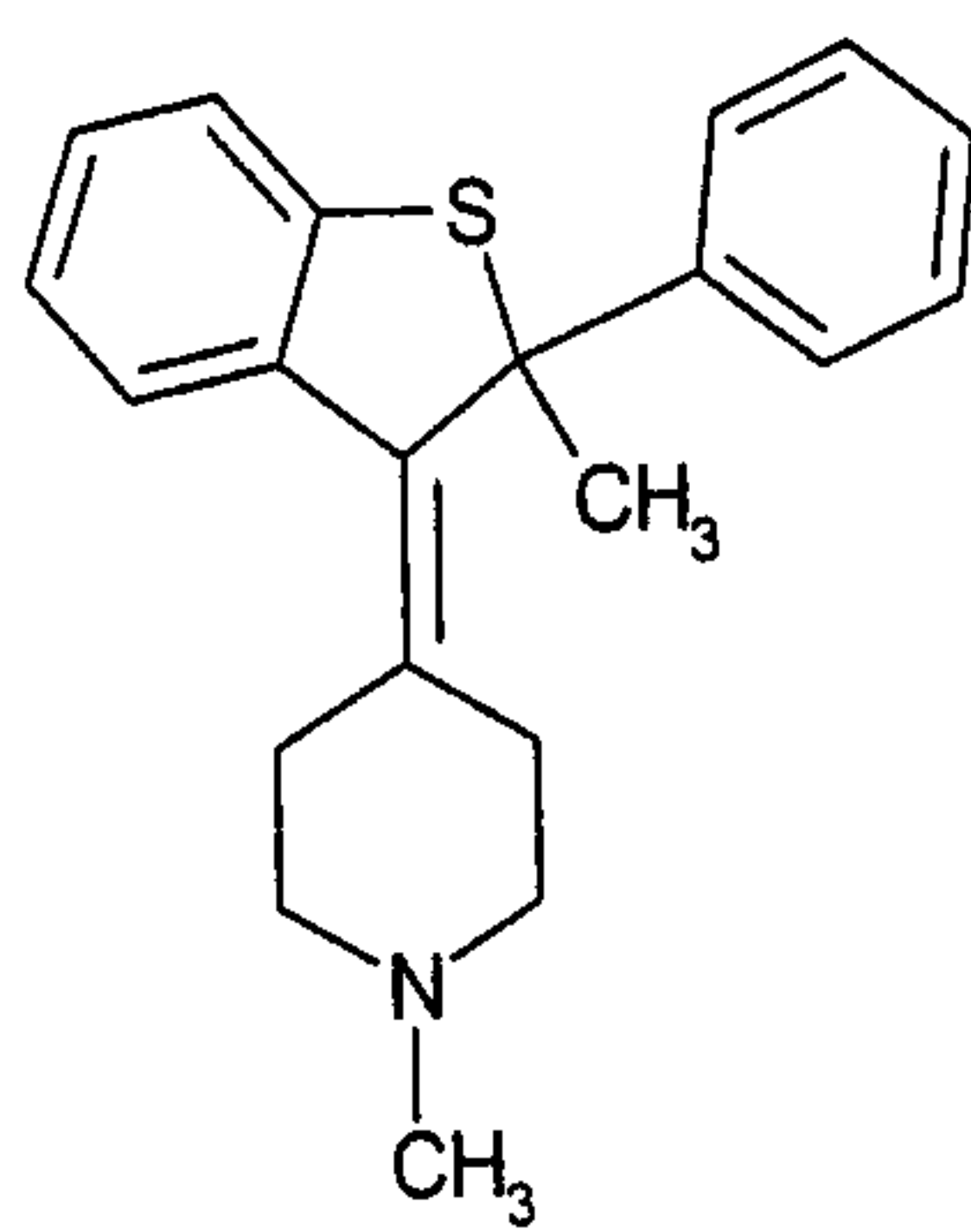
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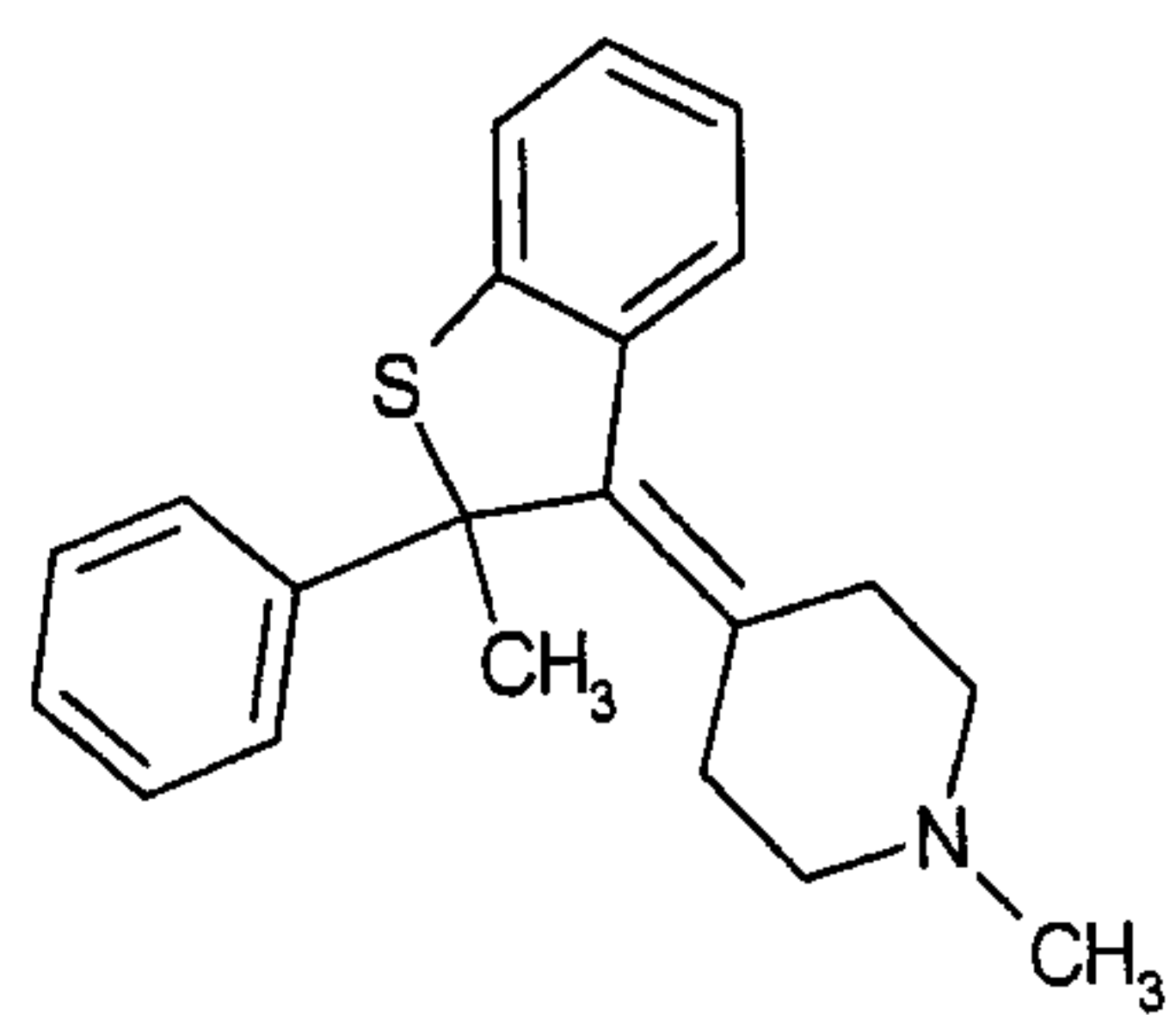
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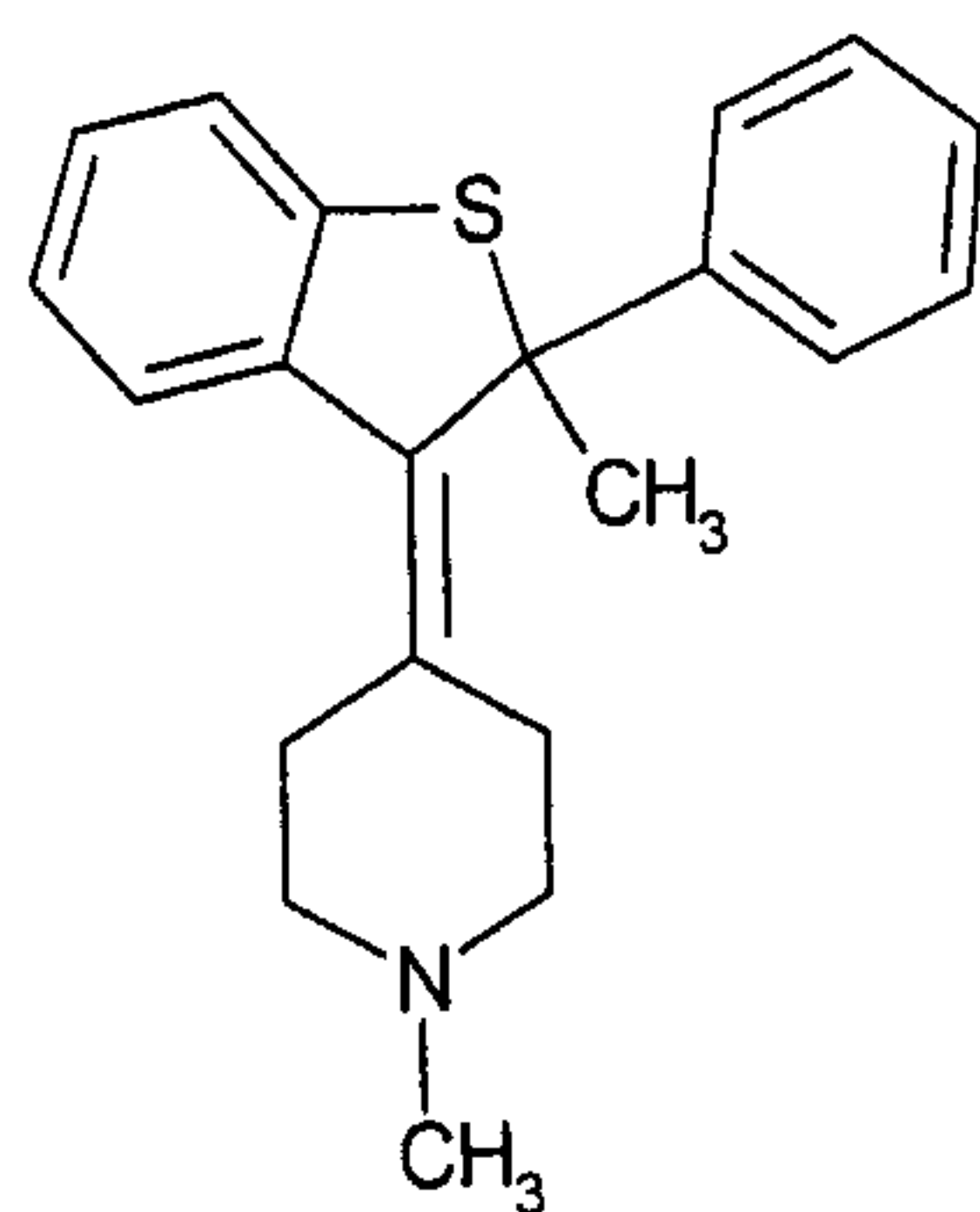
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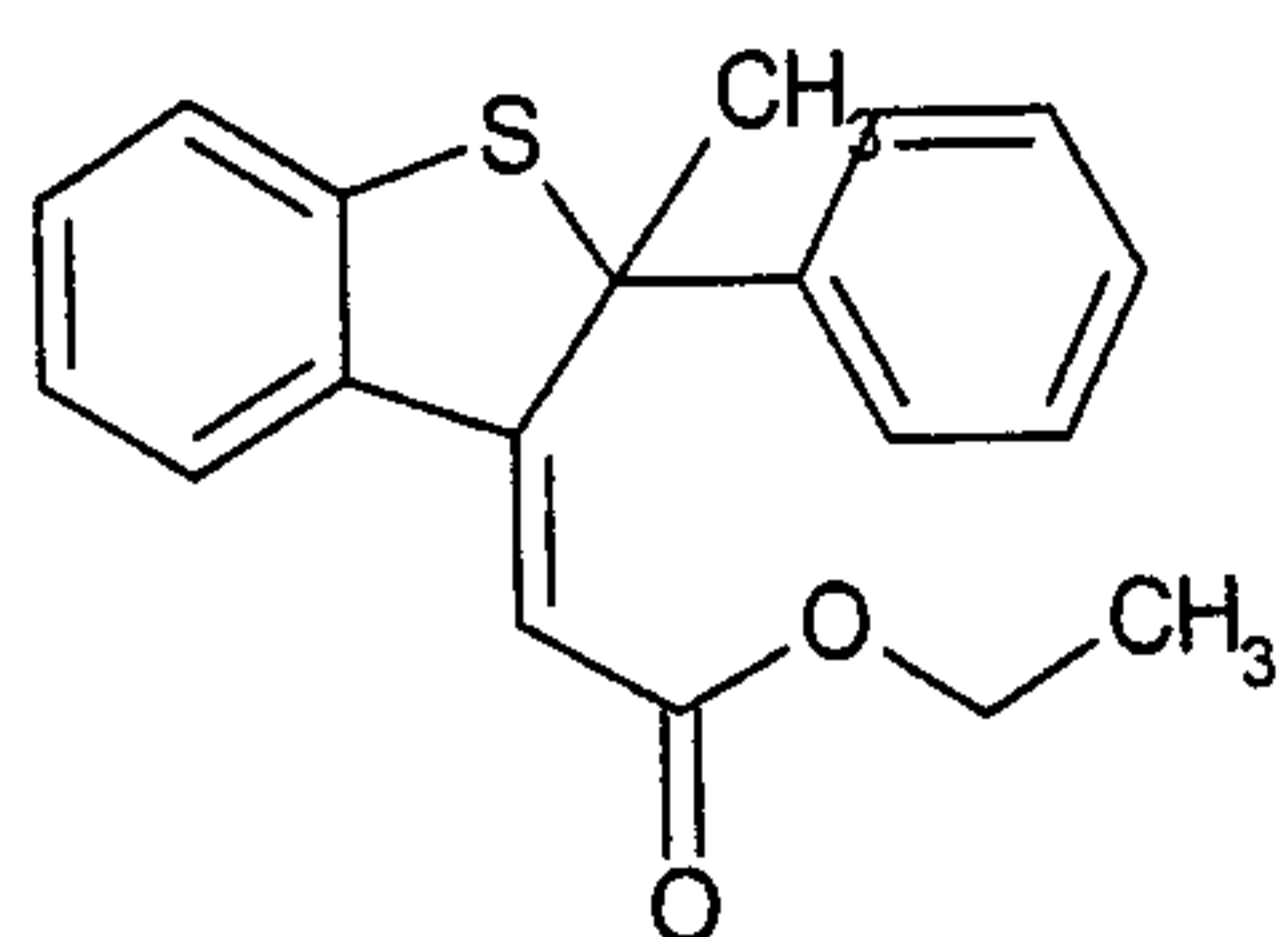


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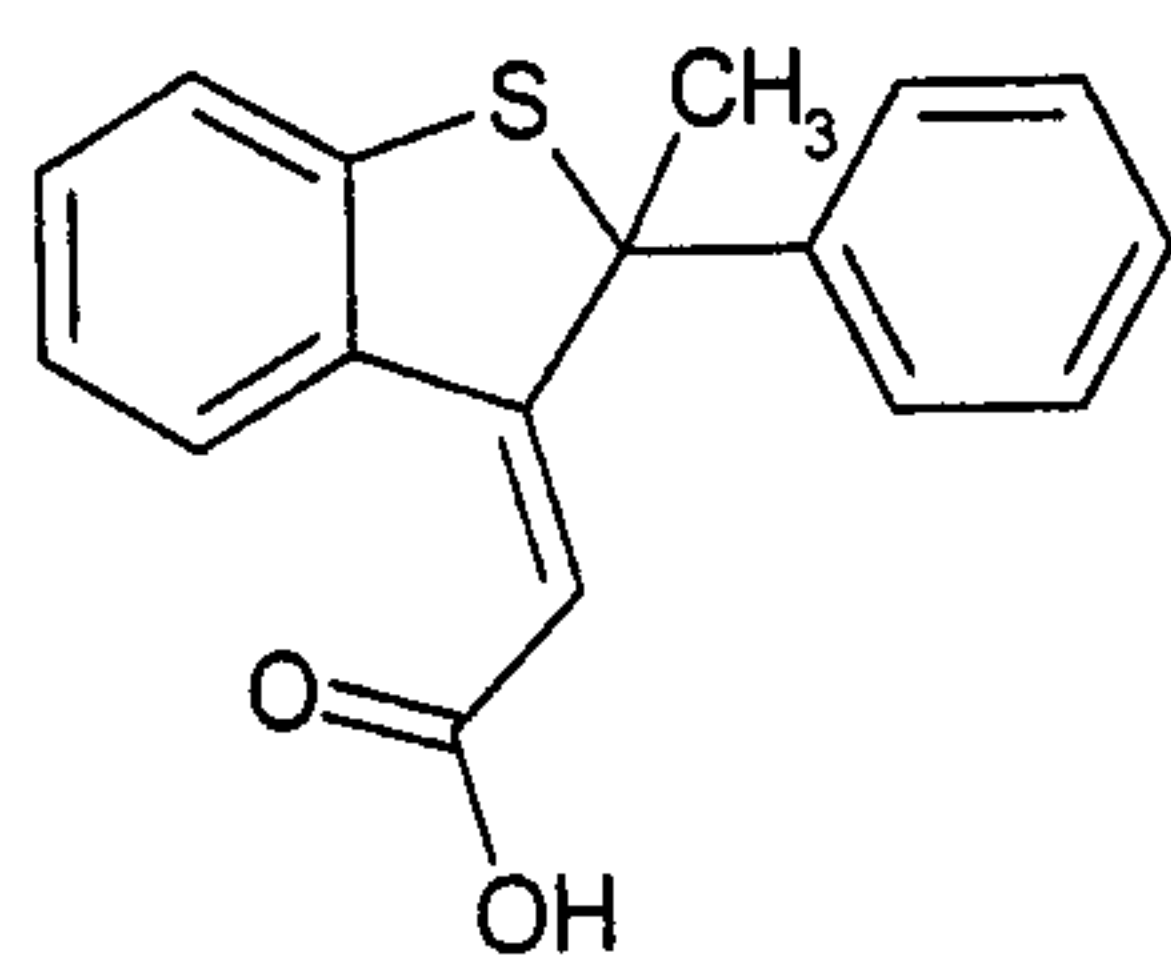
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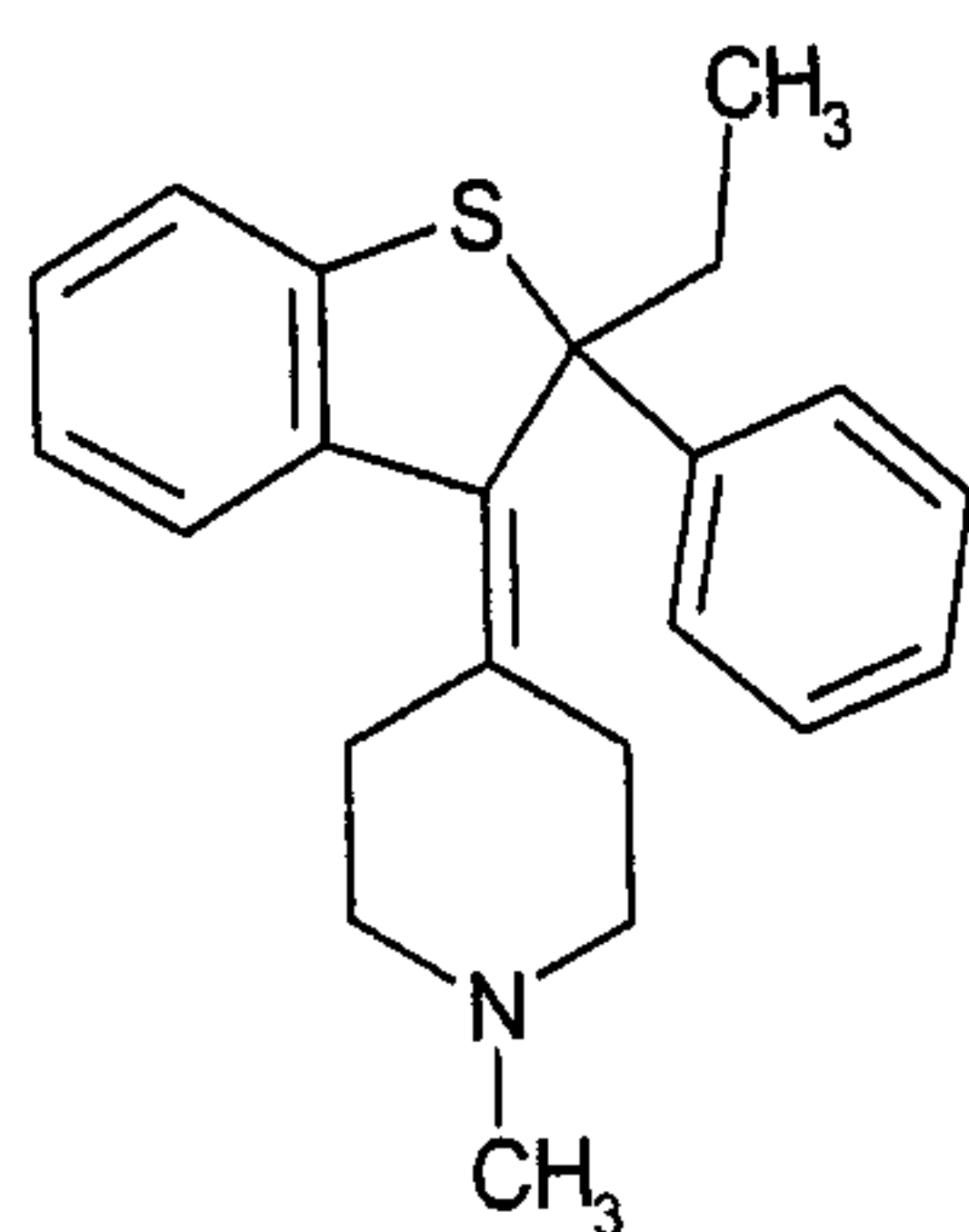
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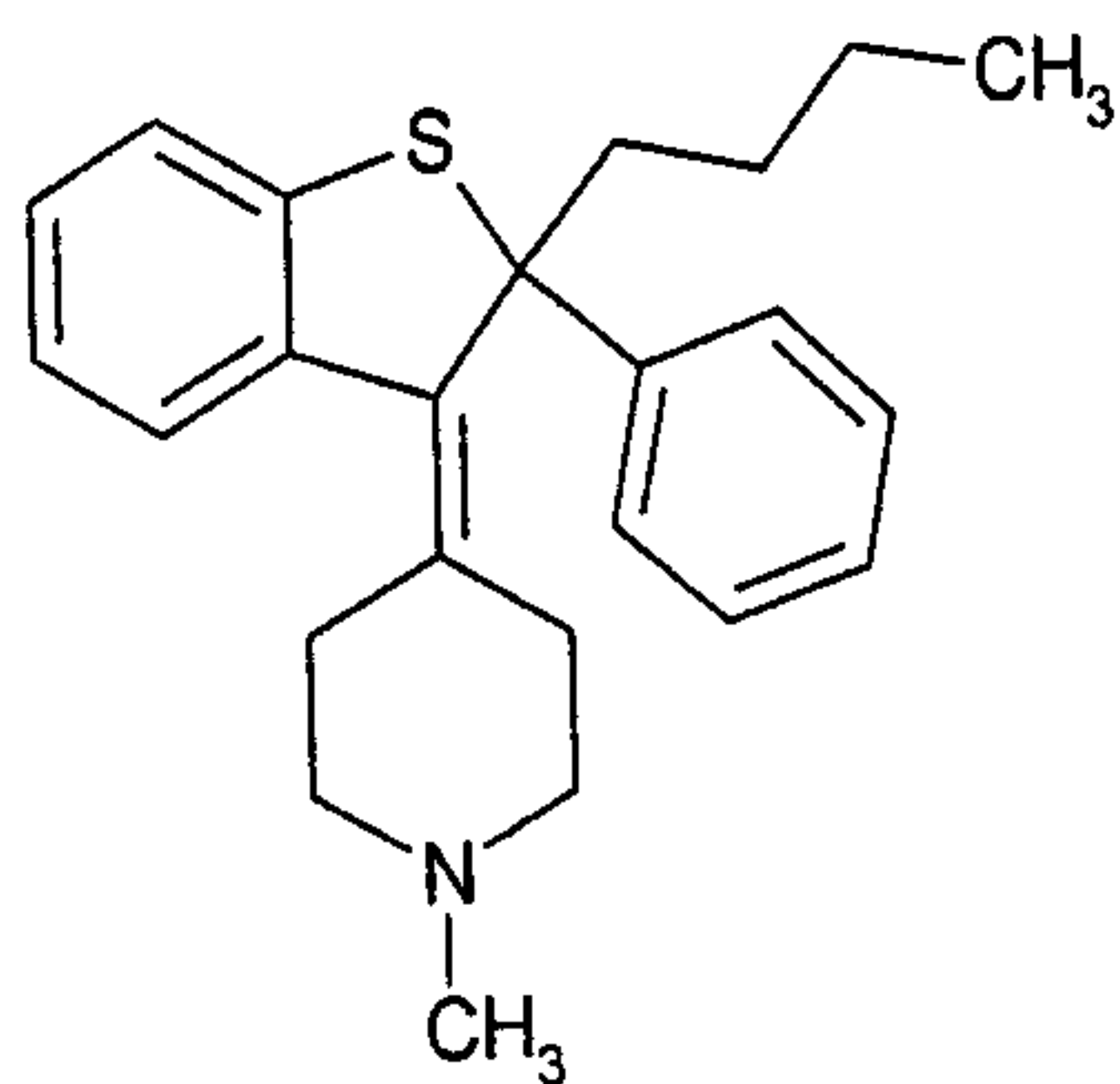
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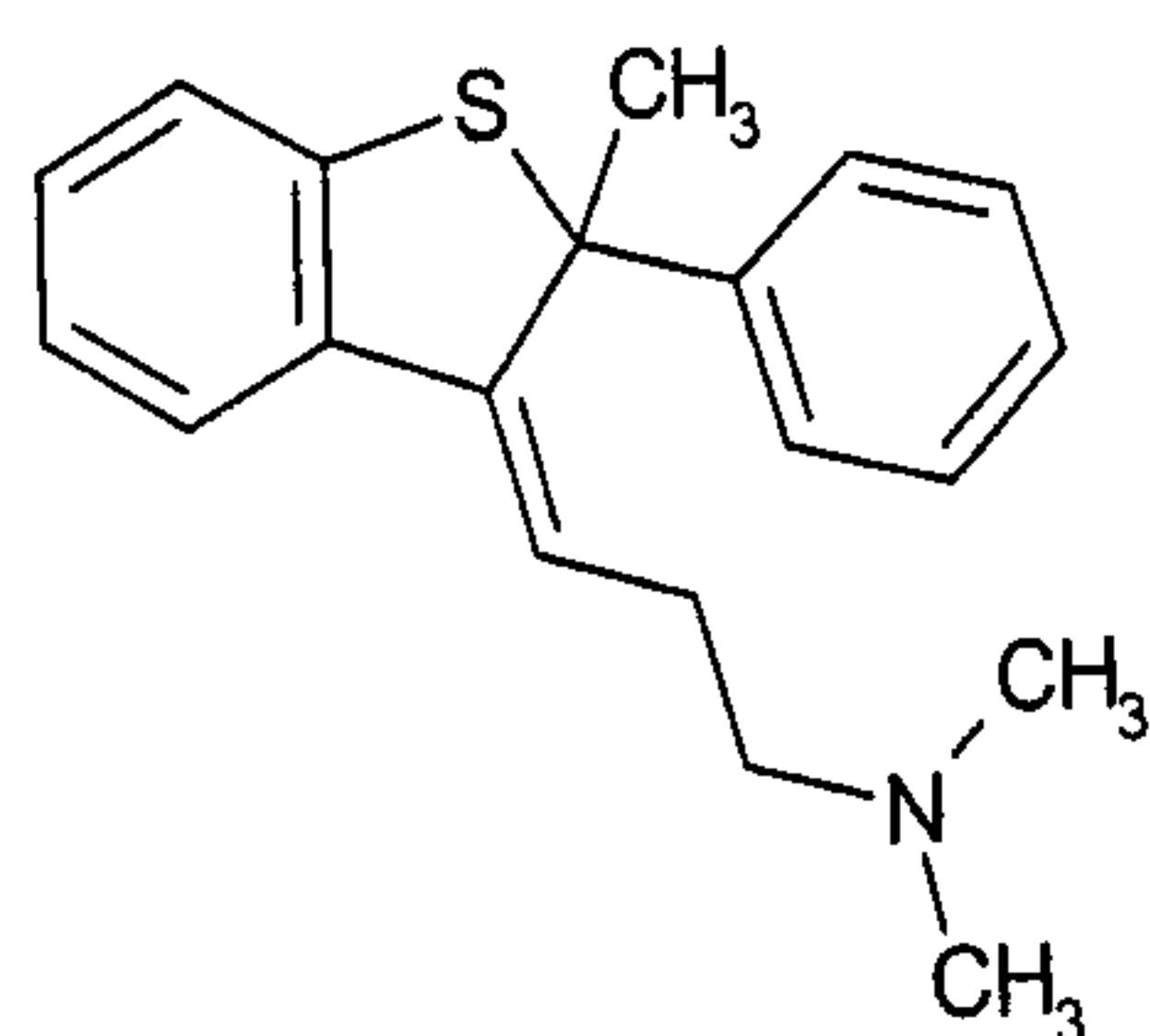
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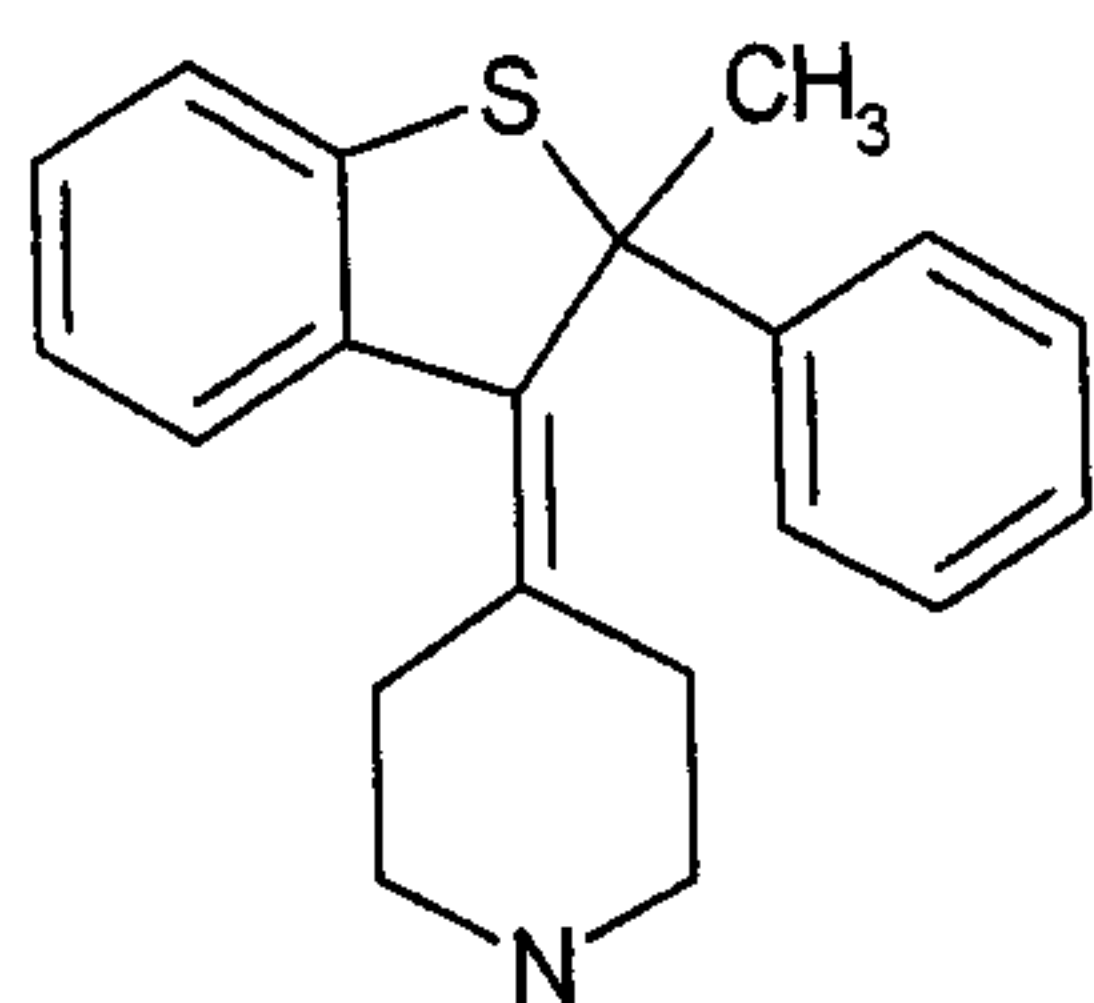
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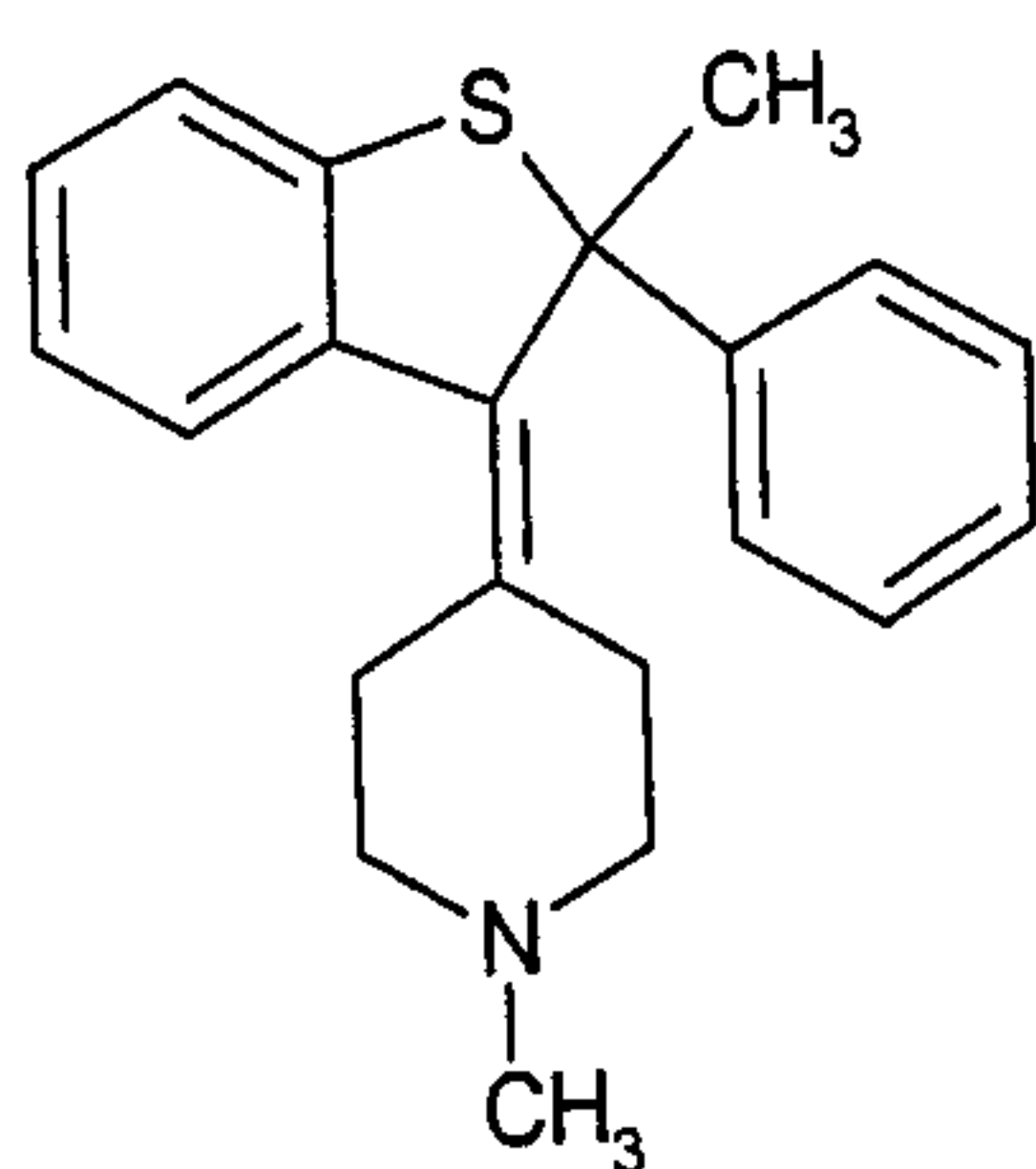
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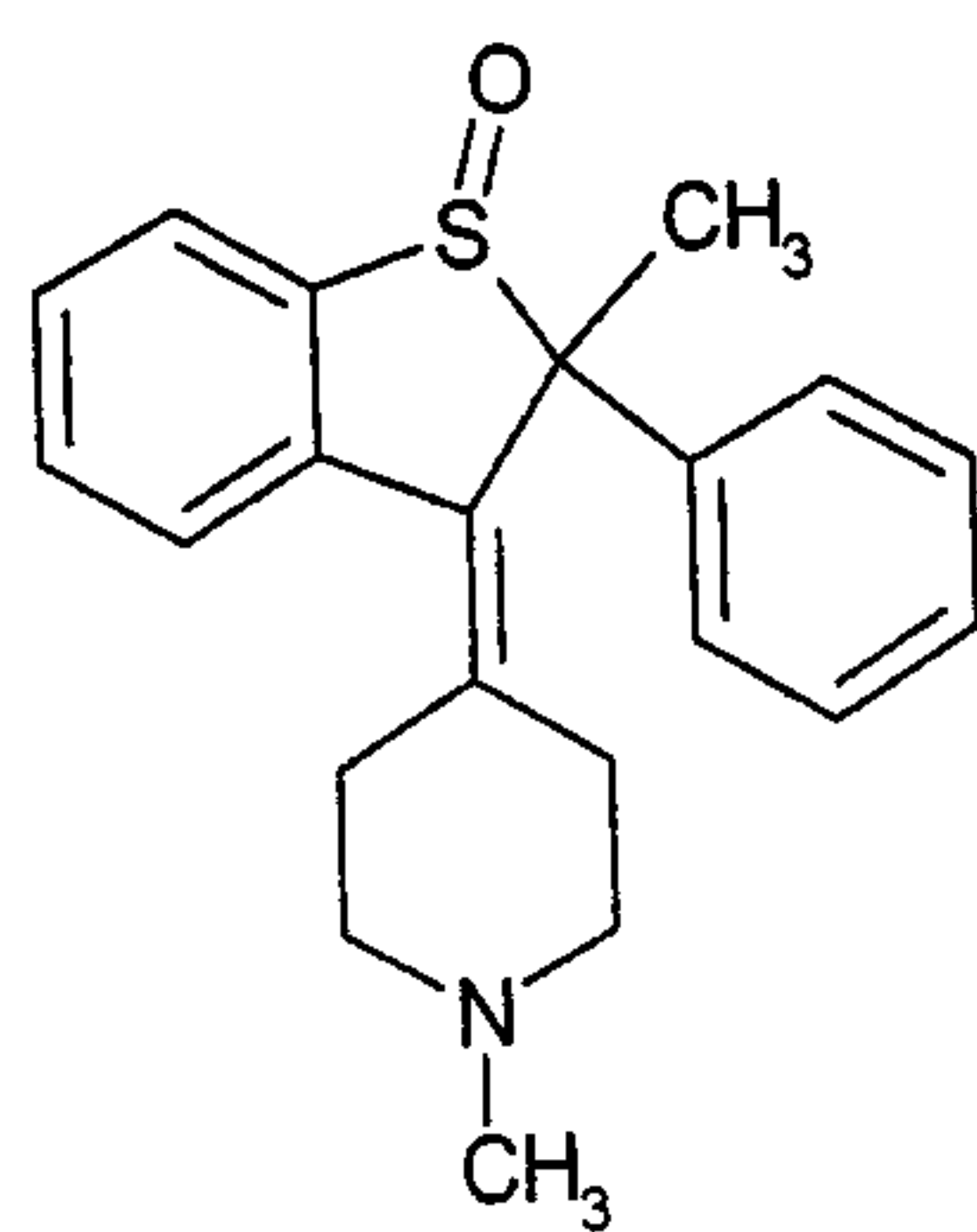
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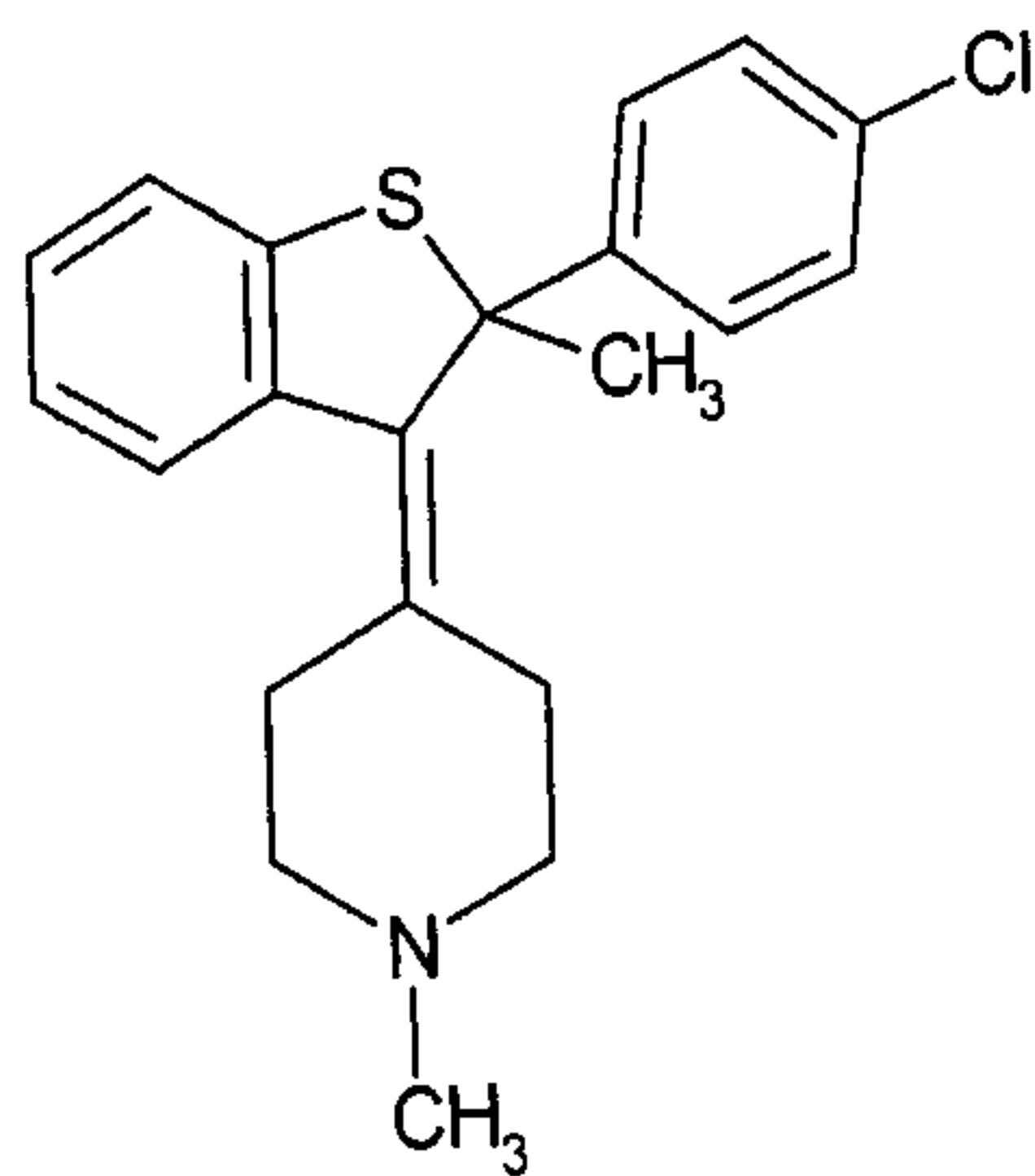
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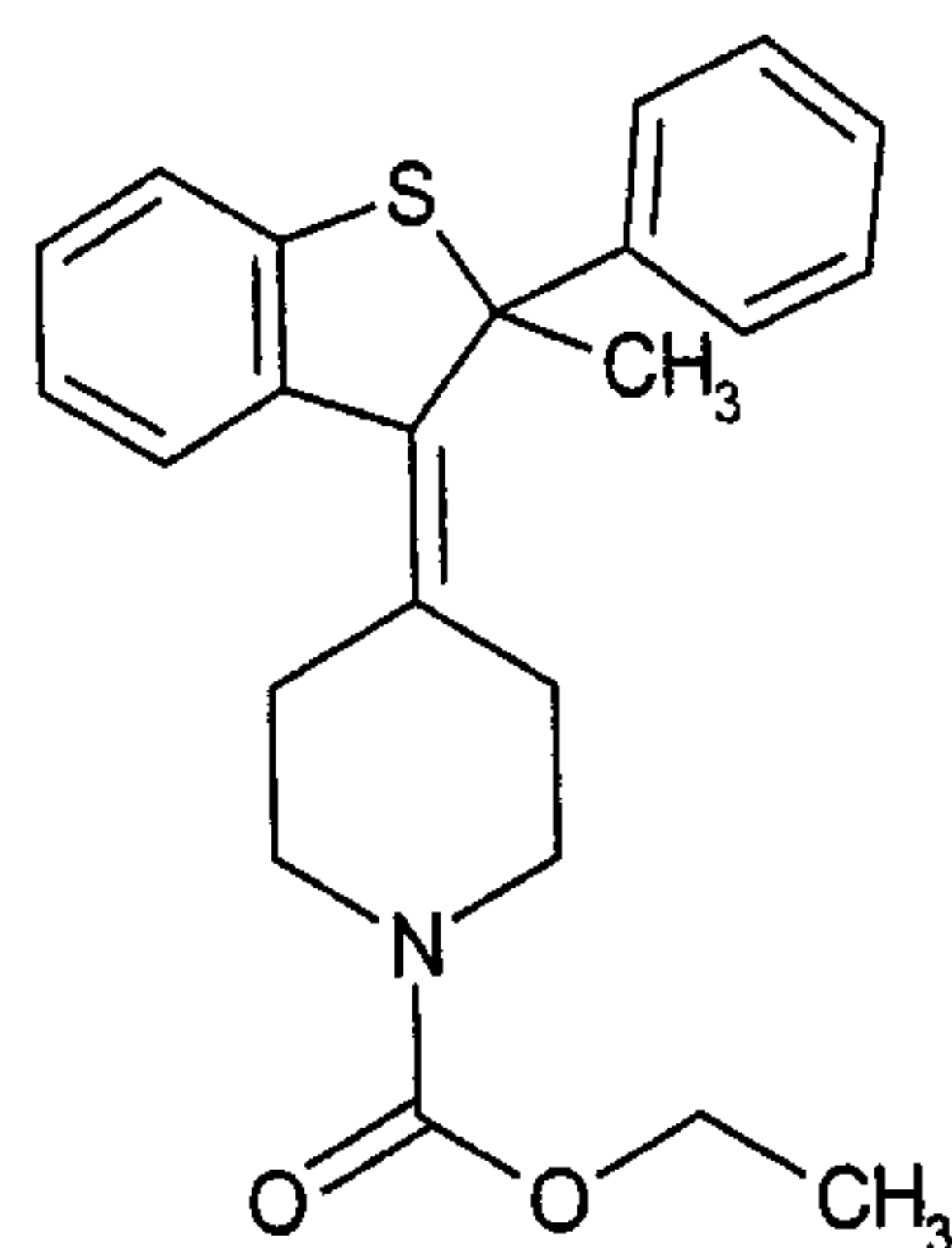
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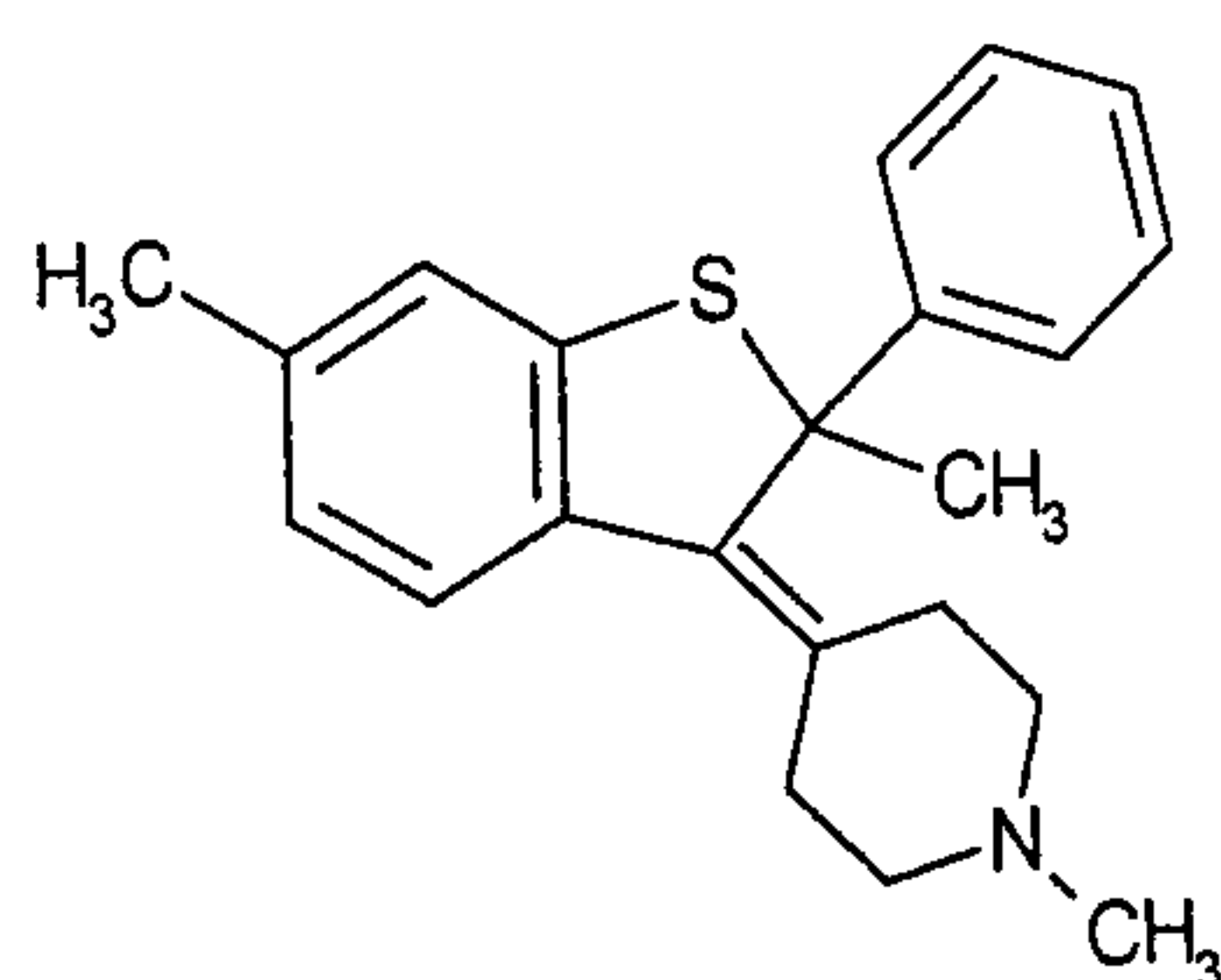
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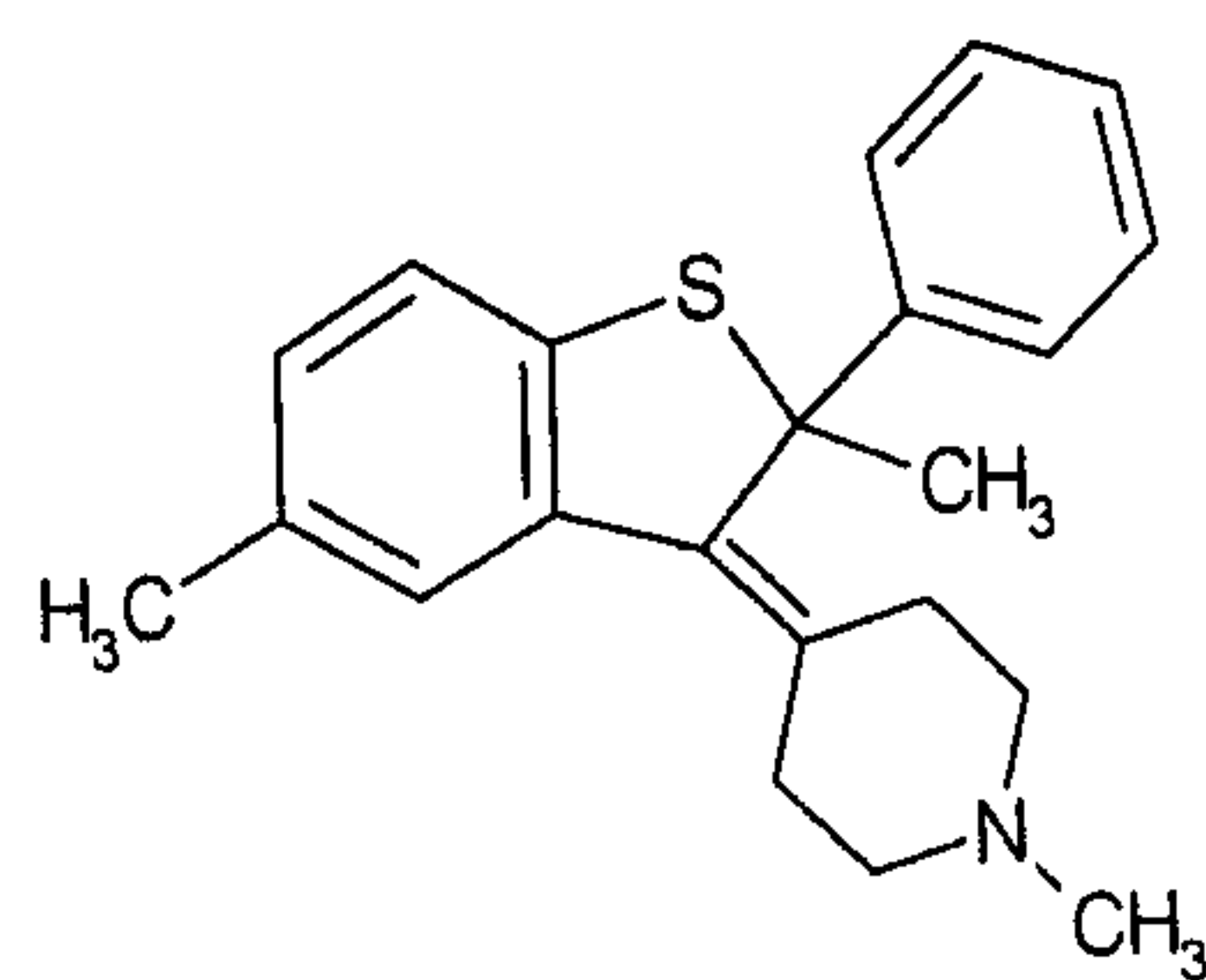
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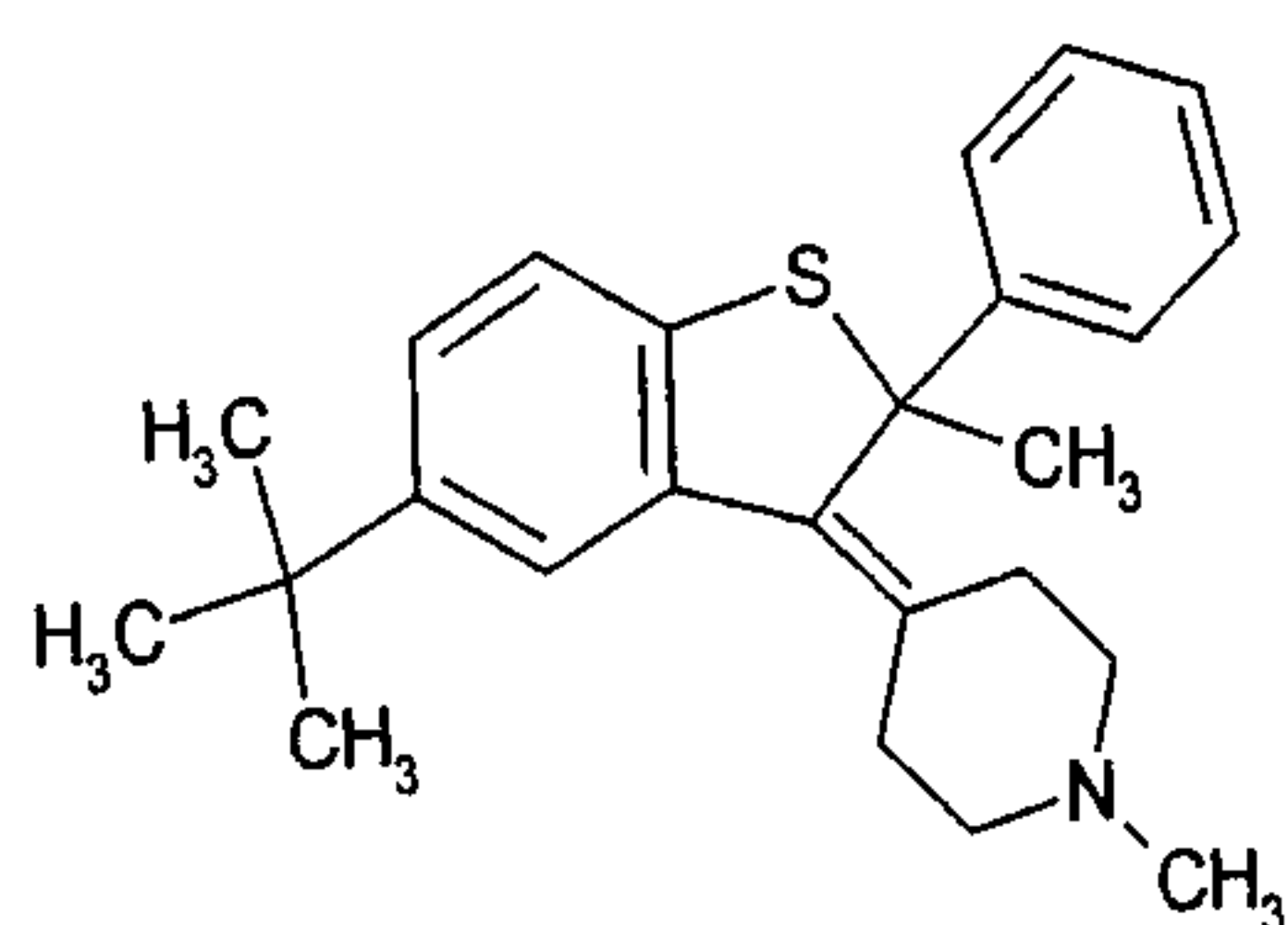
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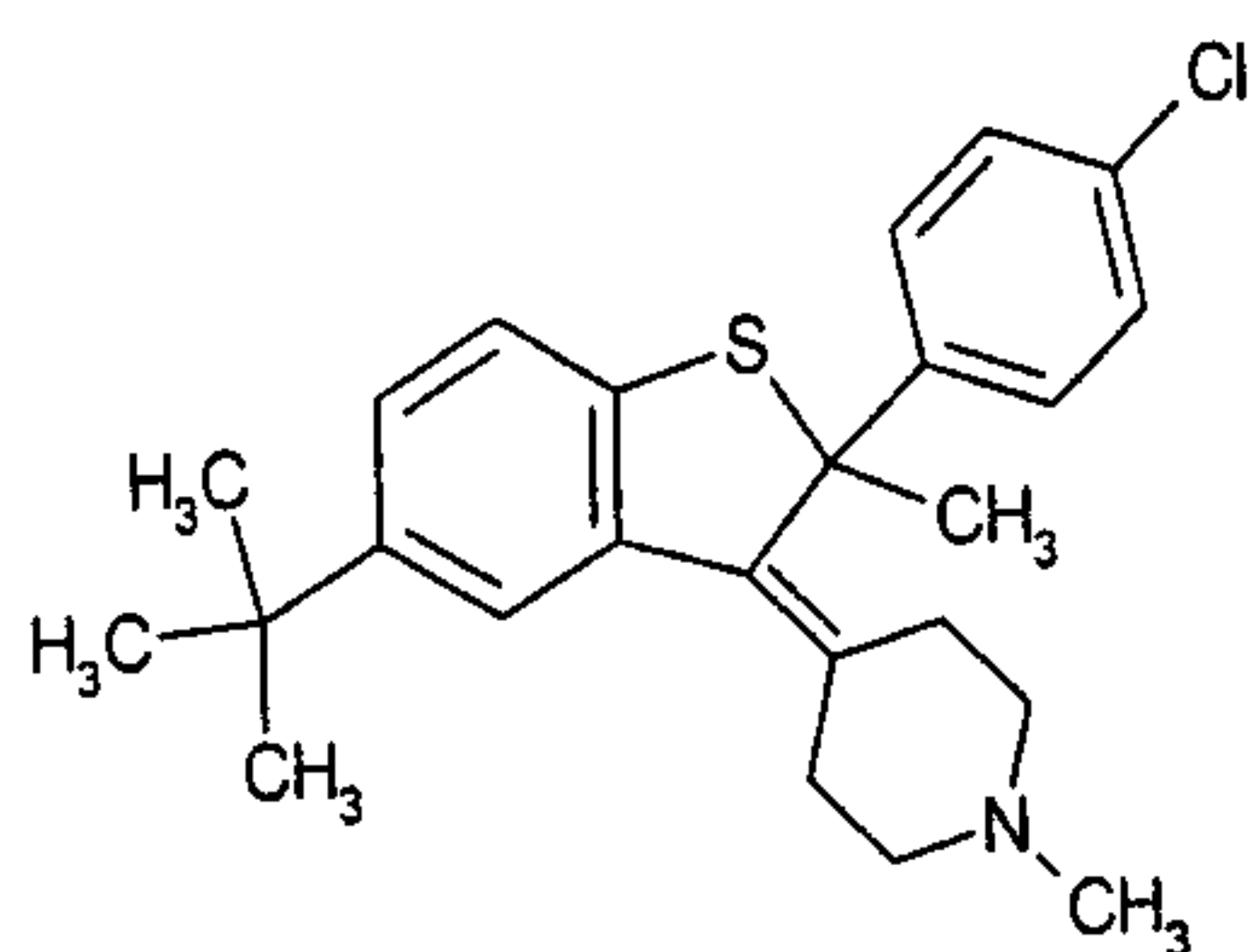
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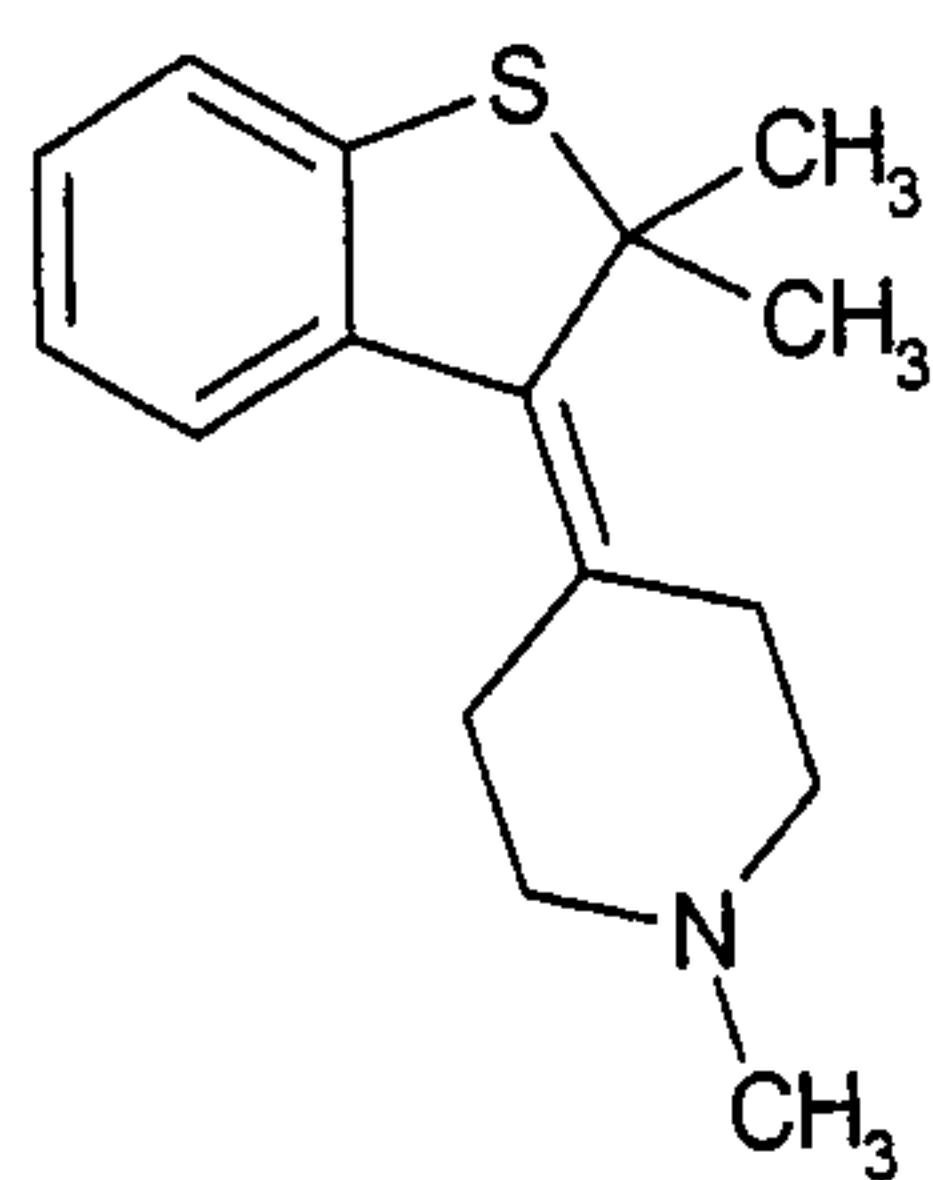
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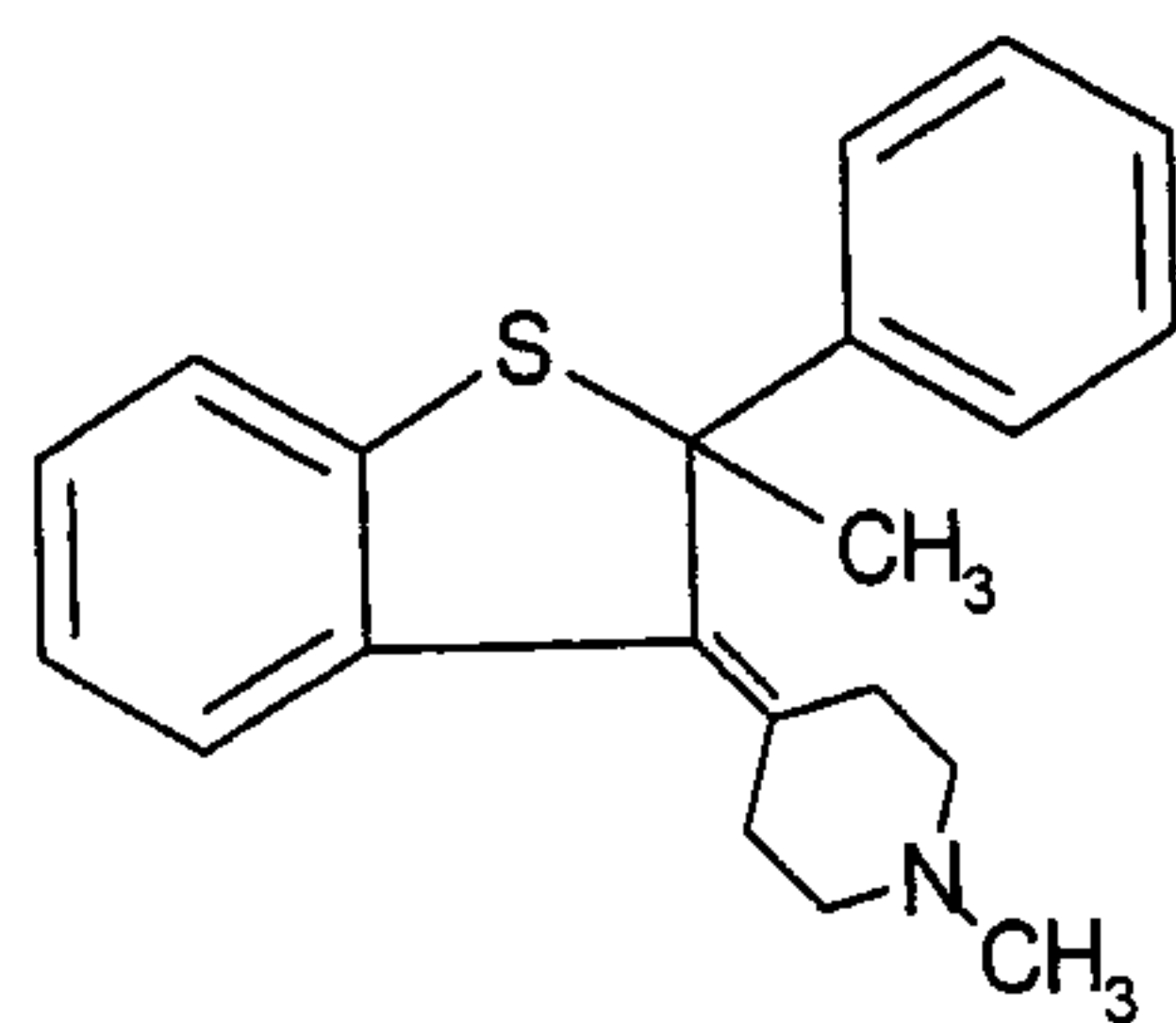
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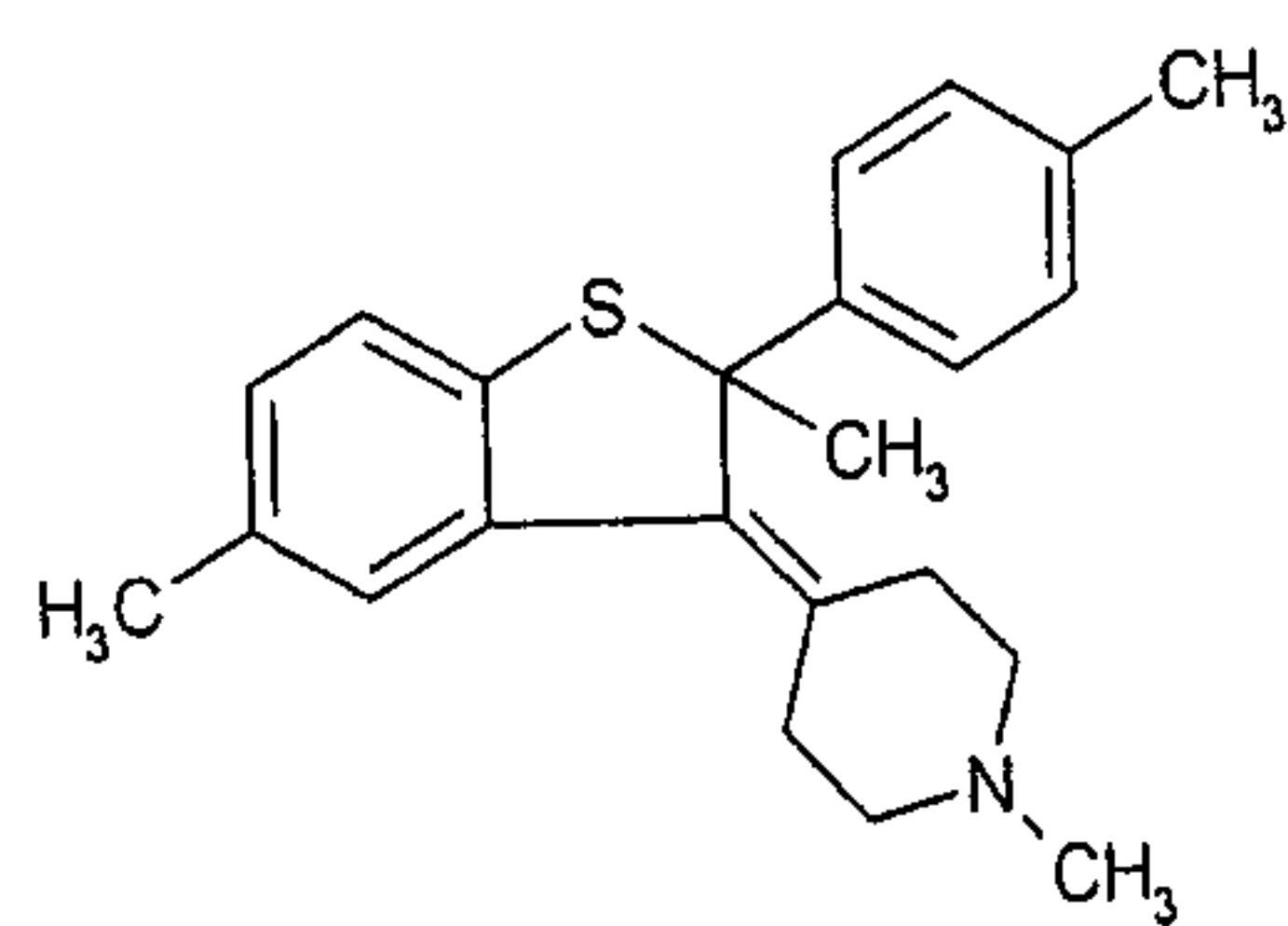


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ClH

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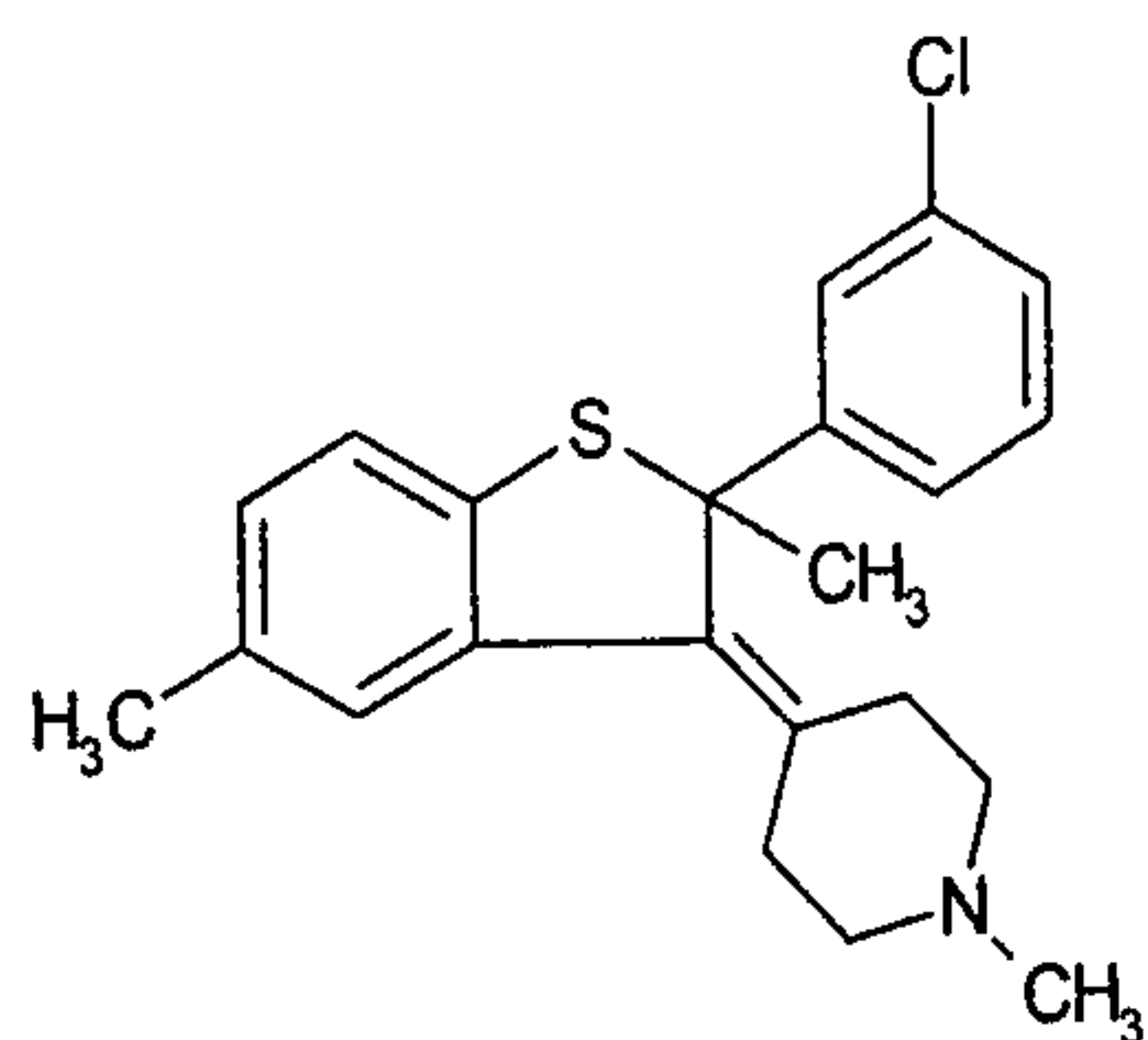
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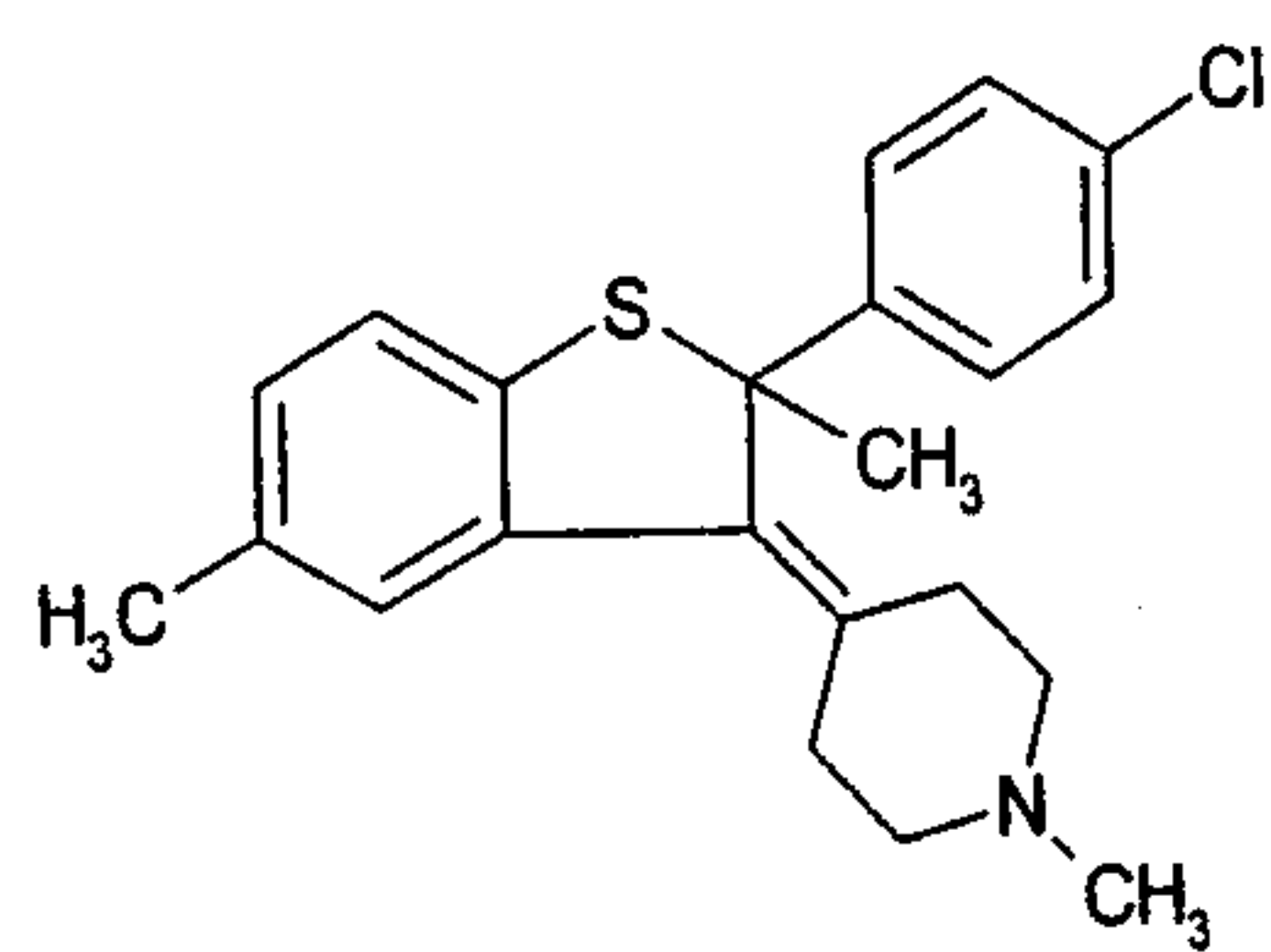
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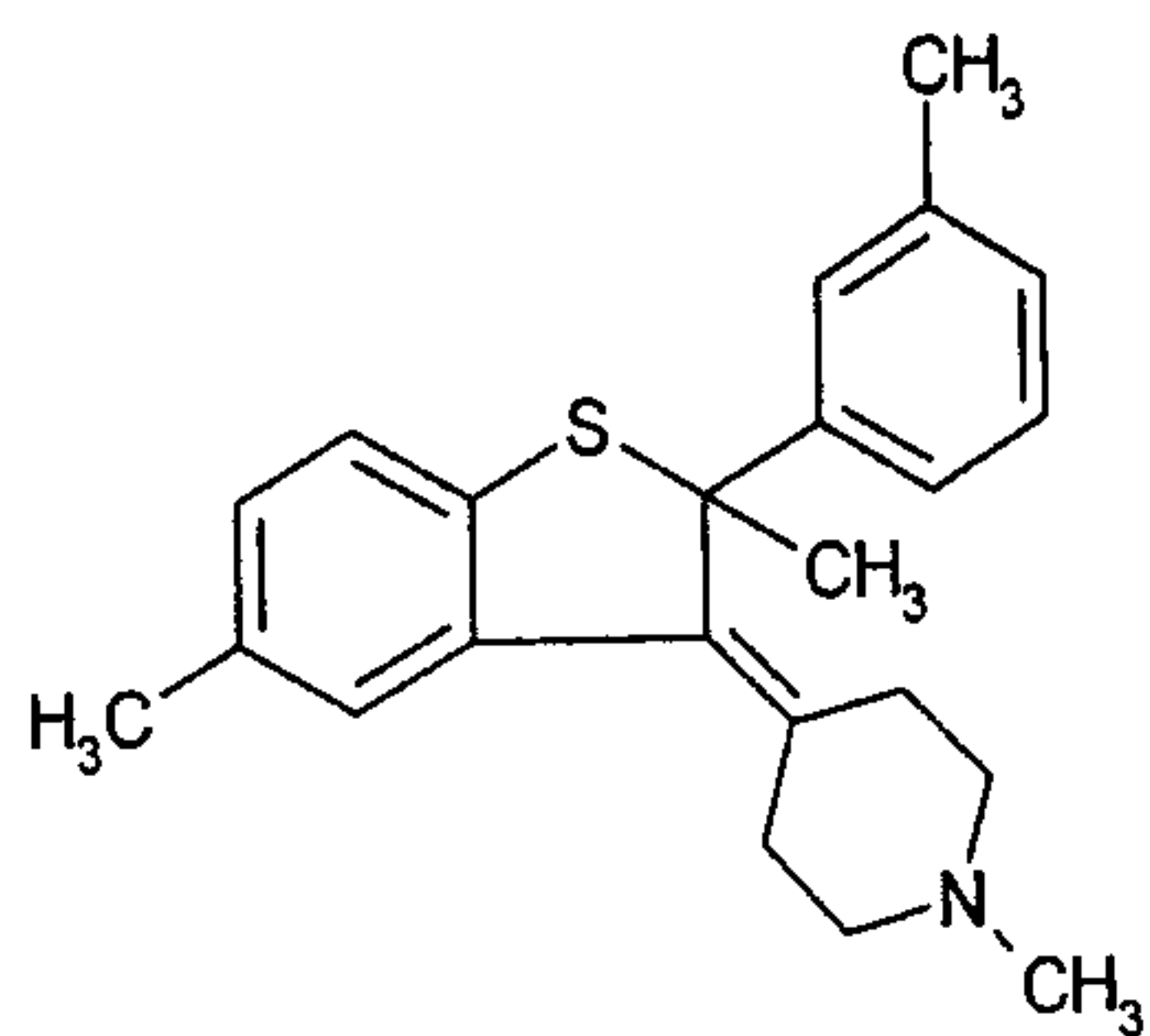
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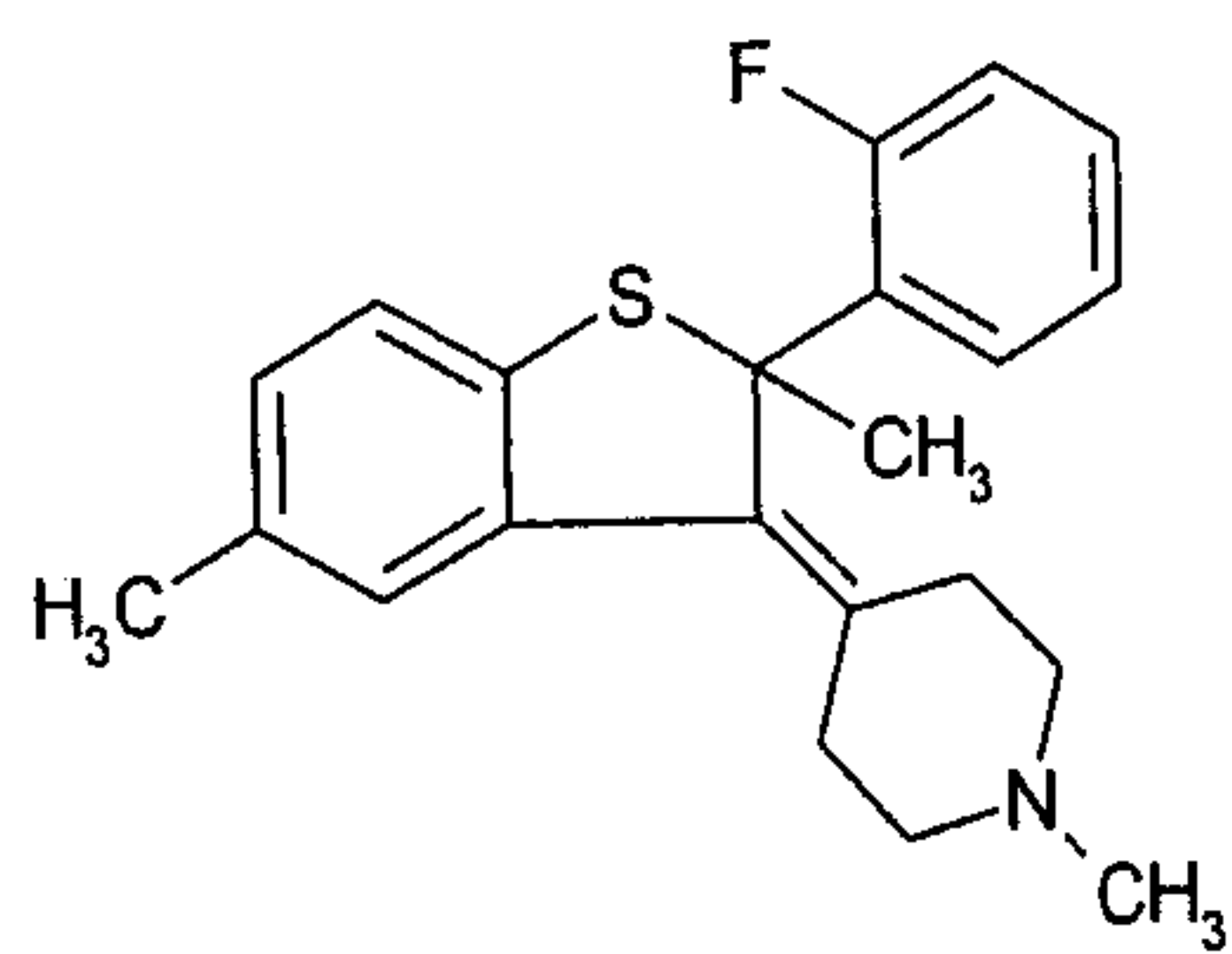
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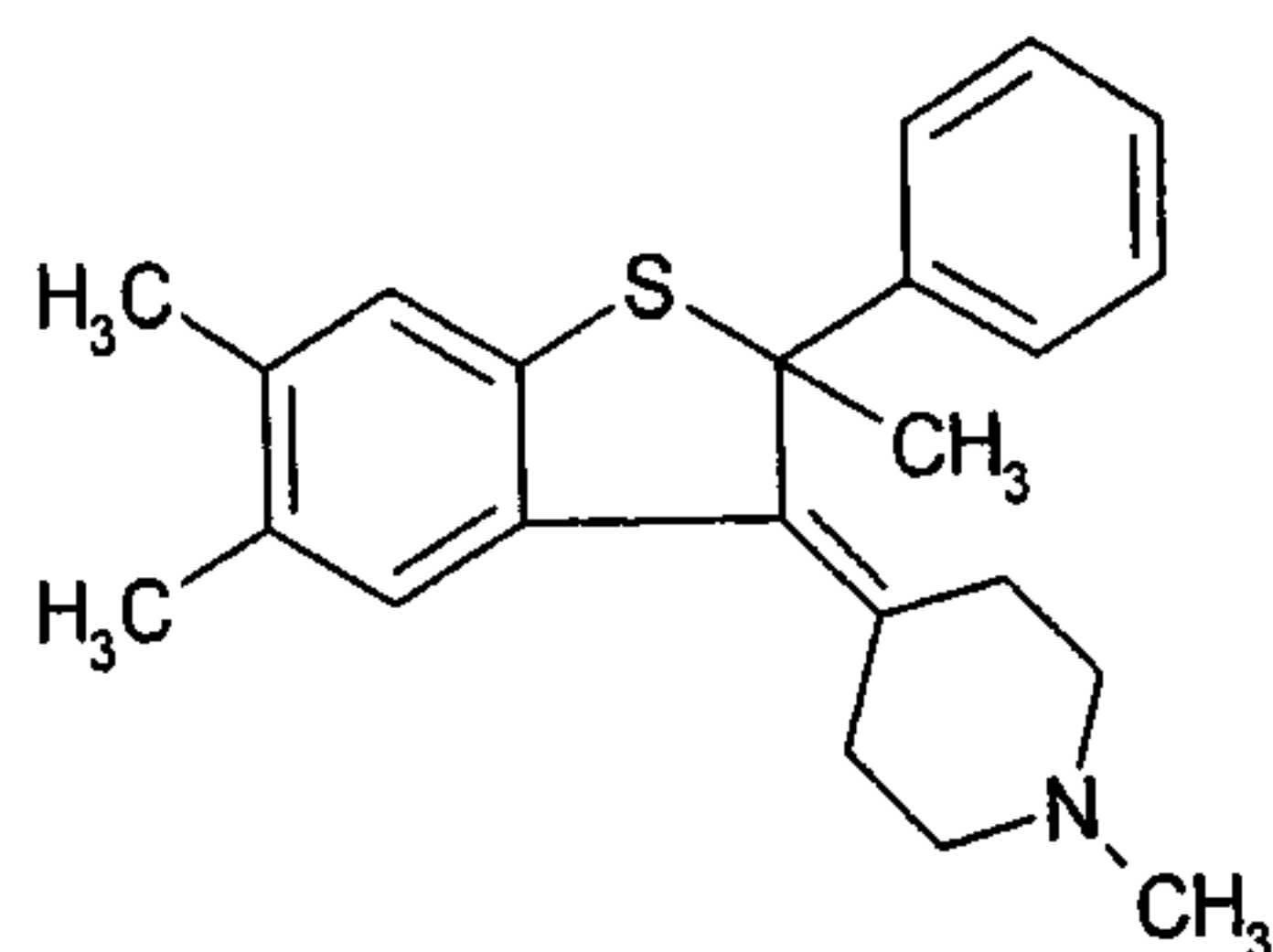
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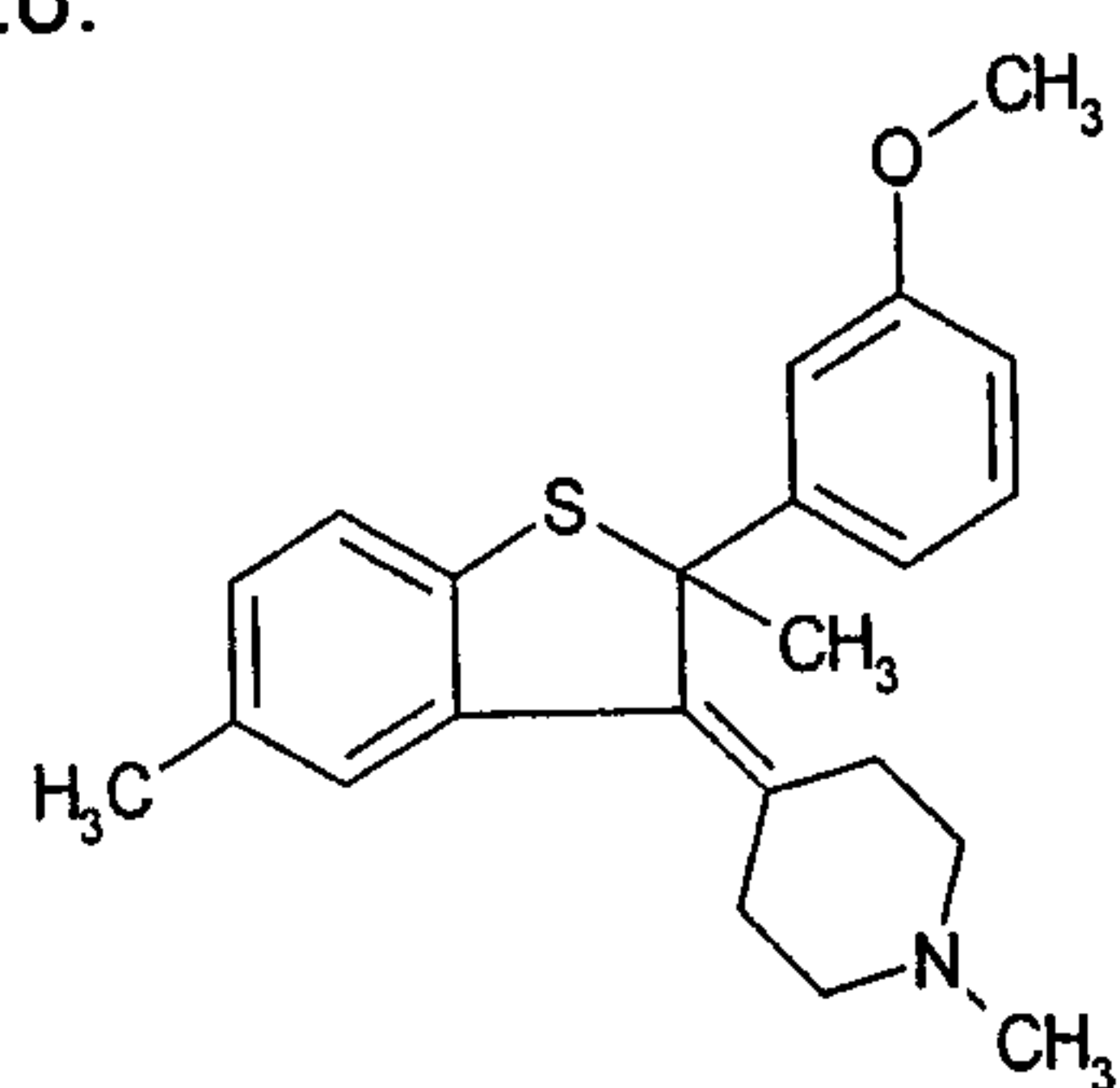
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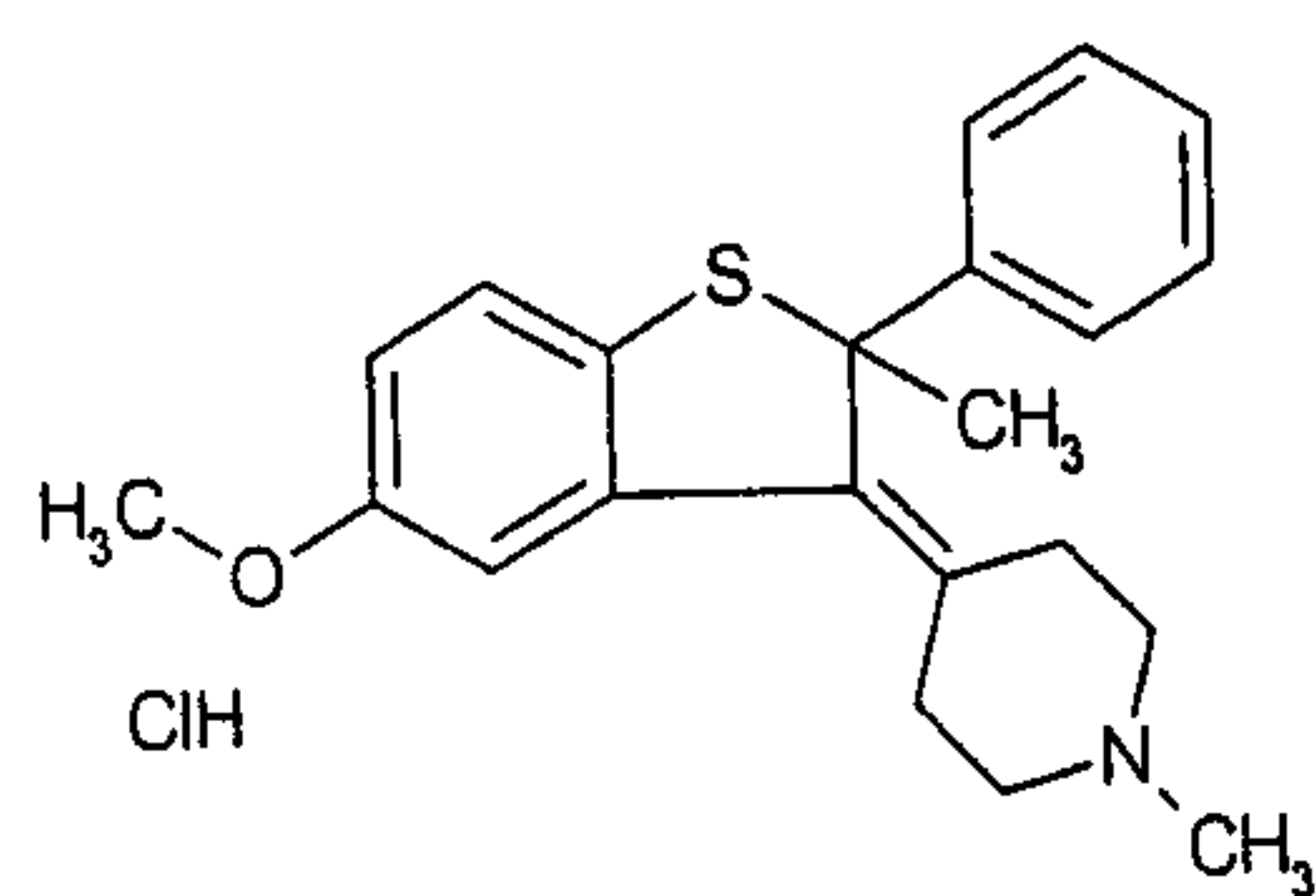
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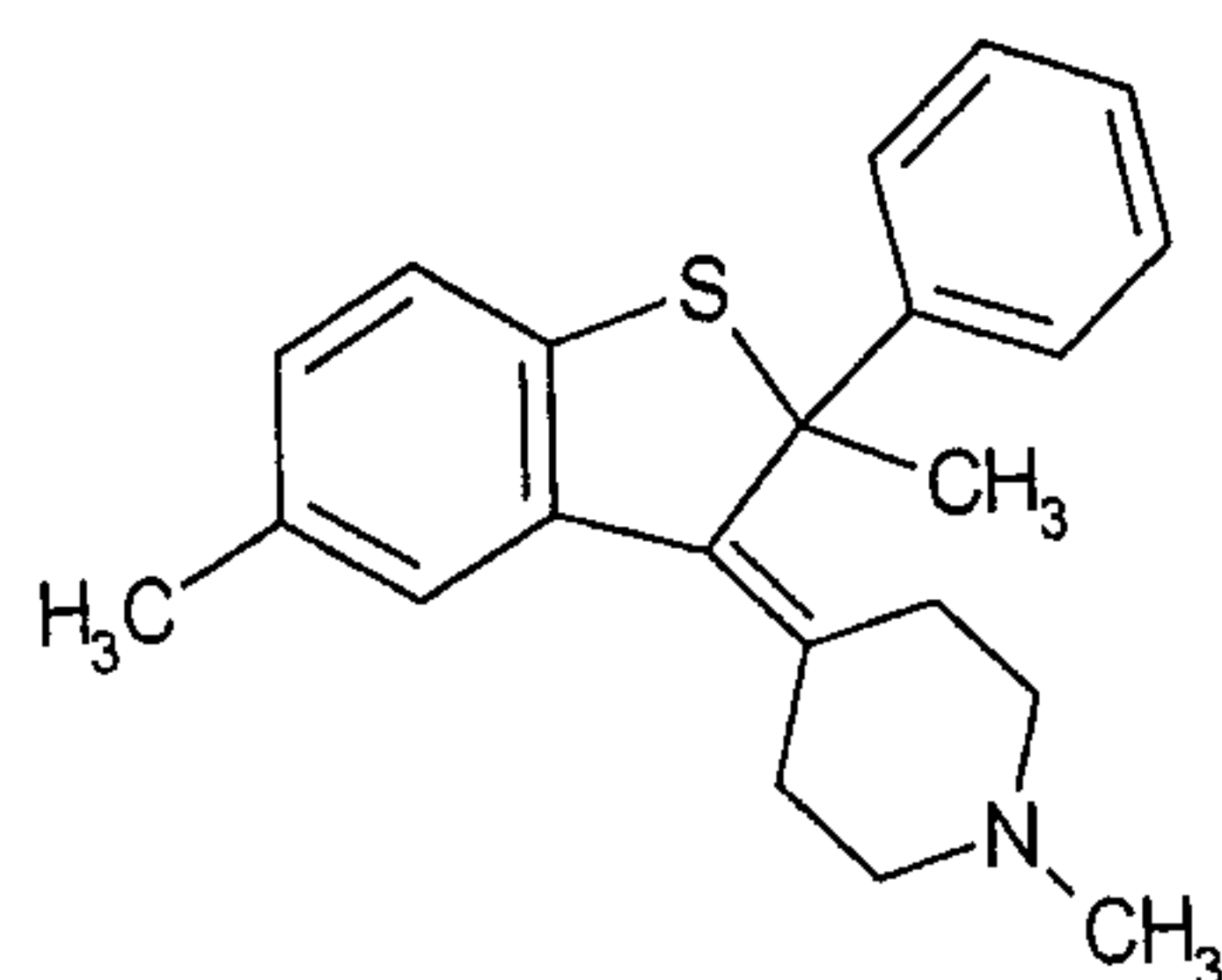
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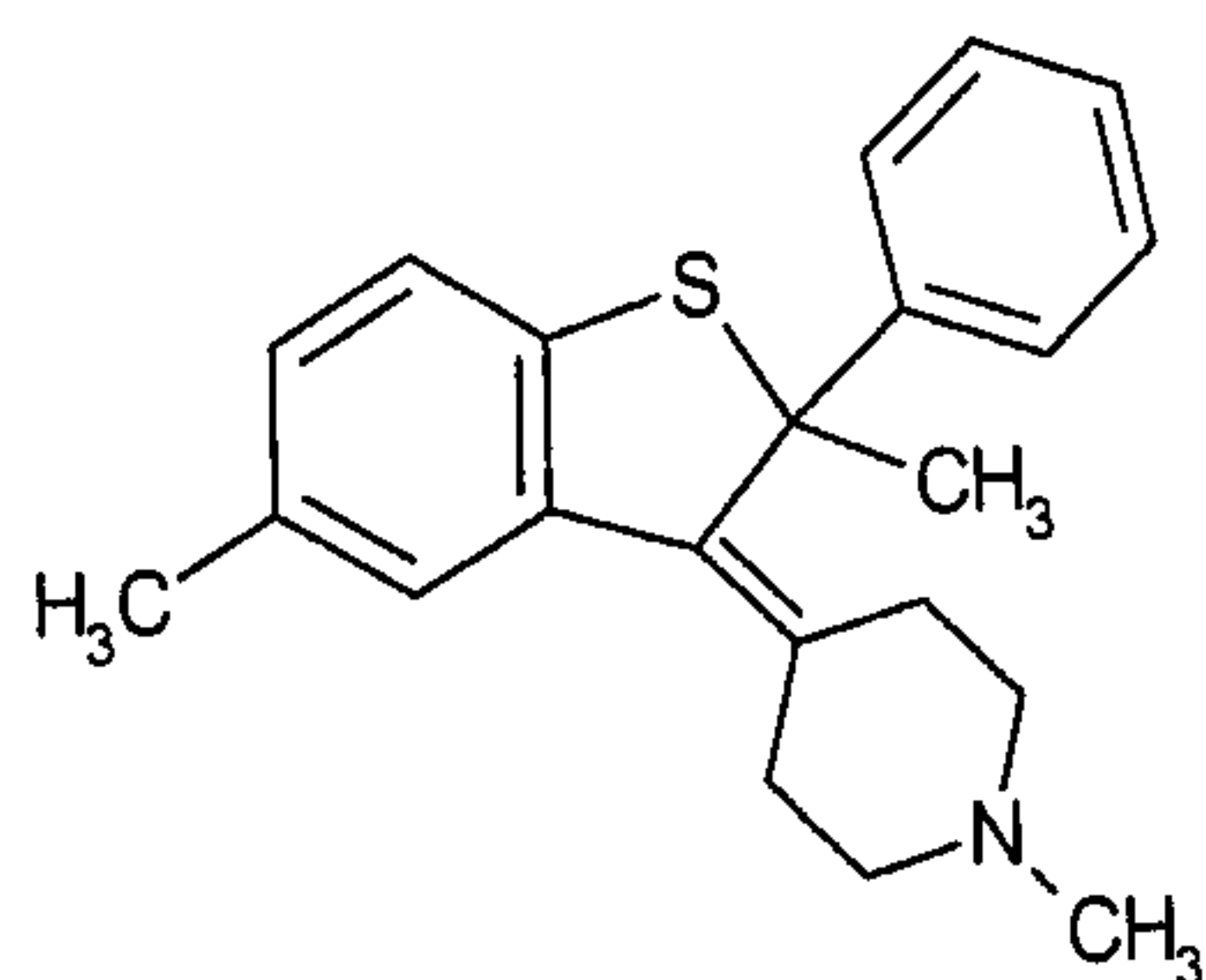
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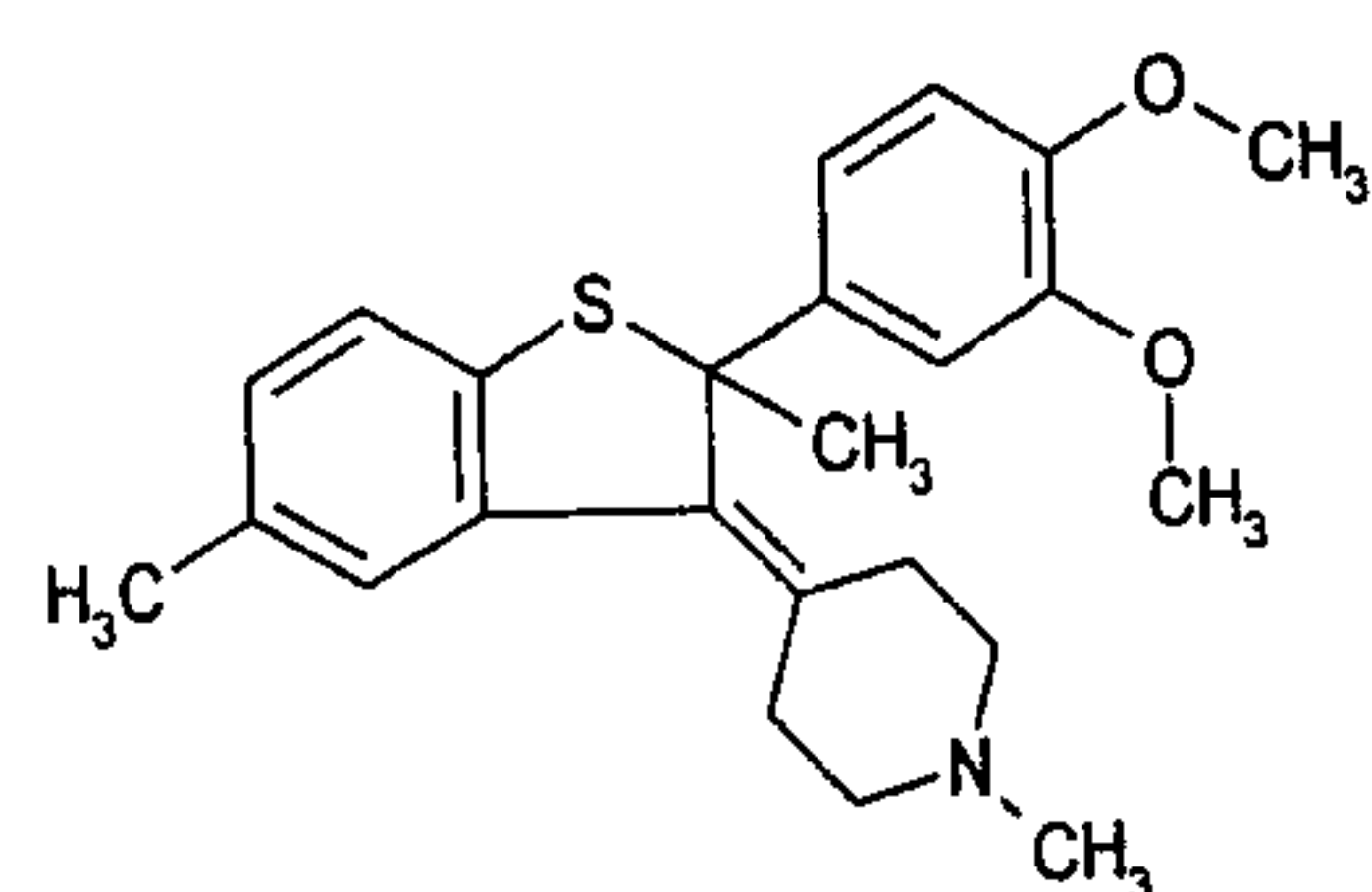
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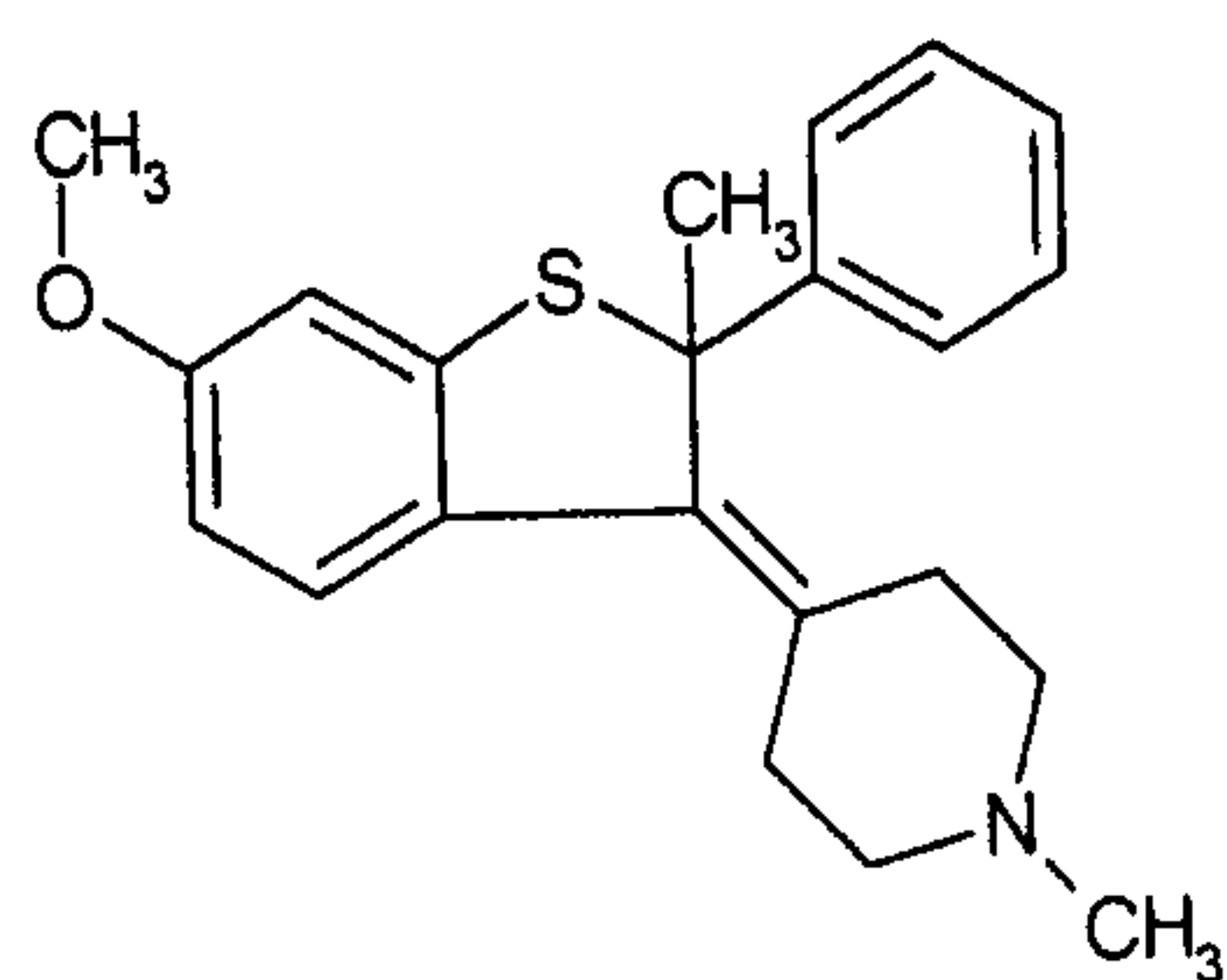
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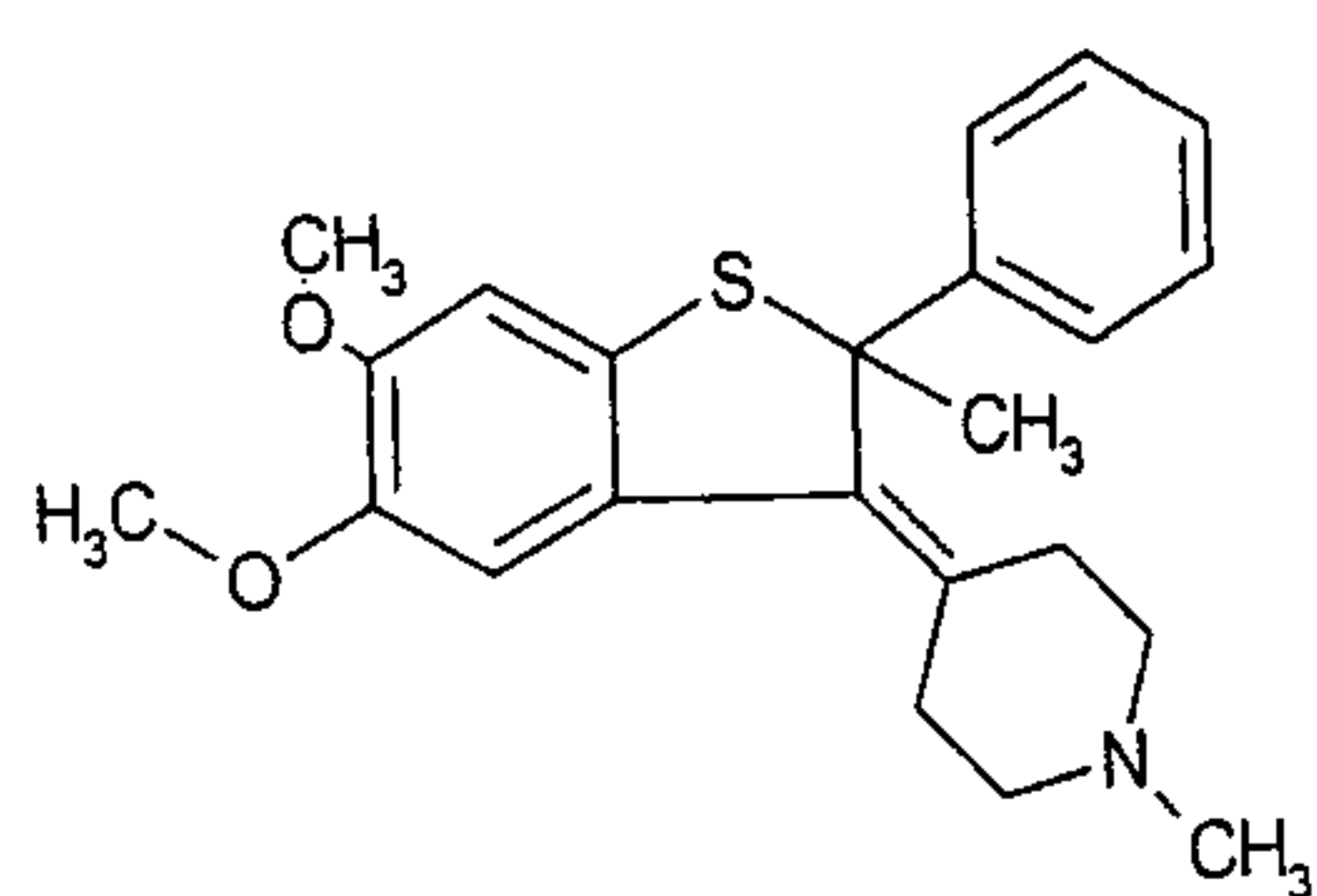
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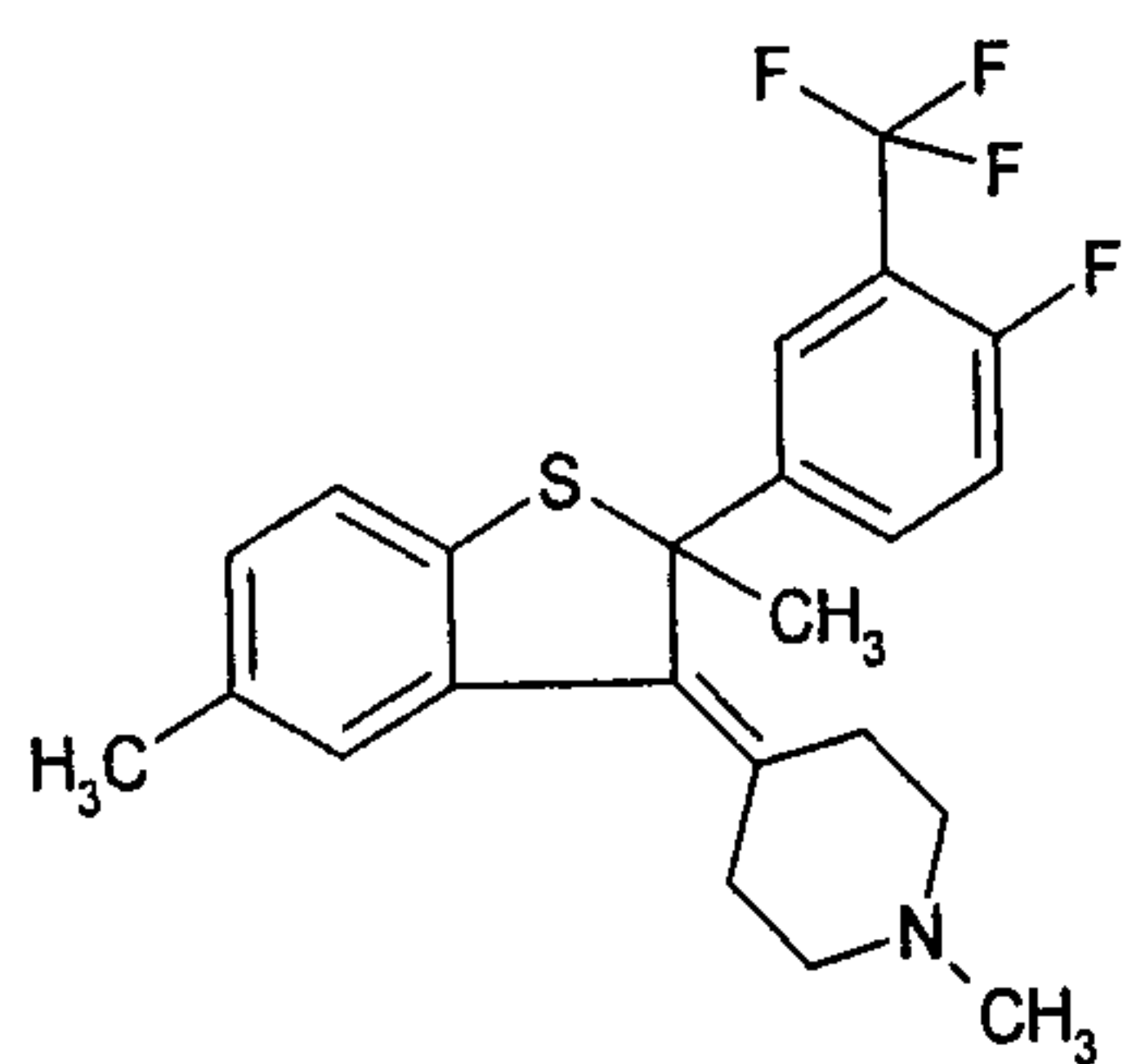
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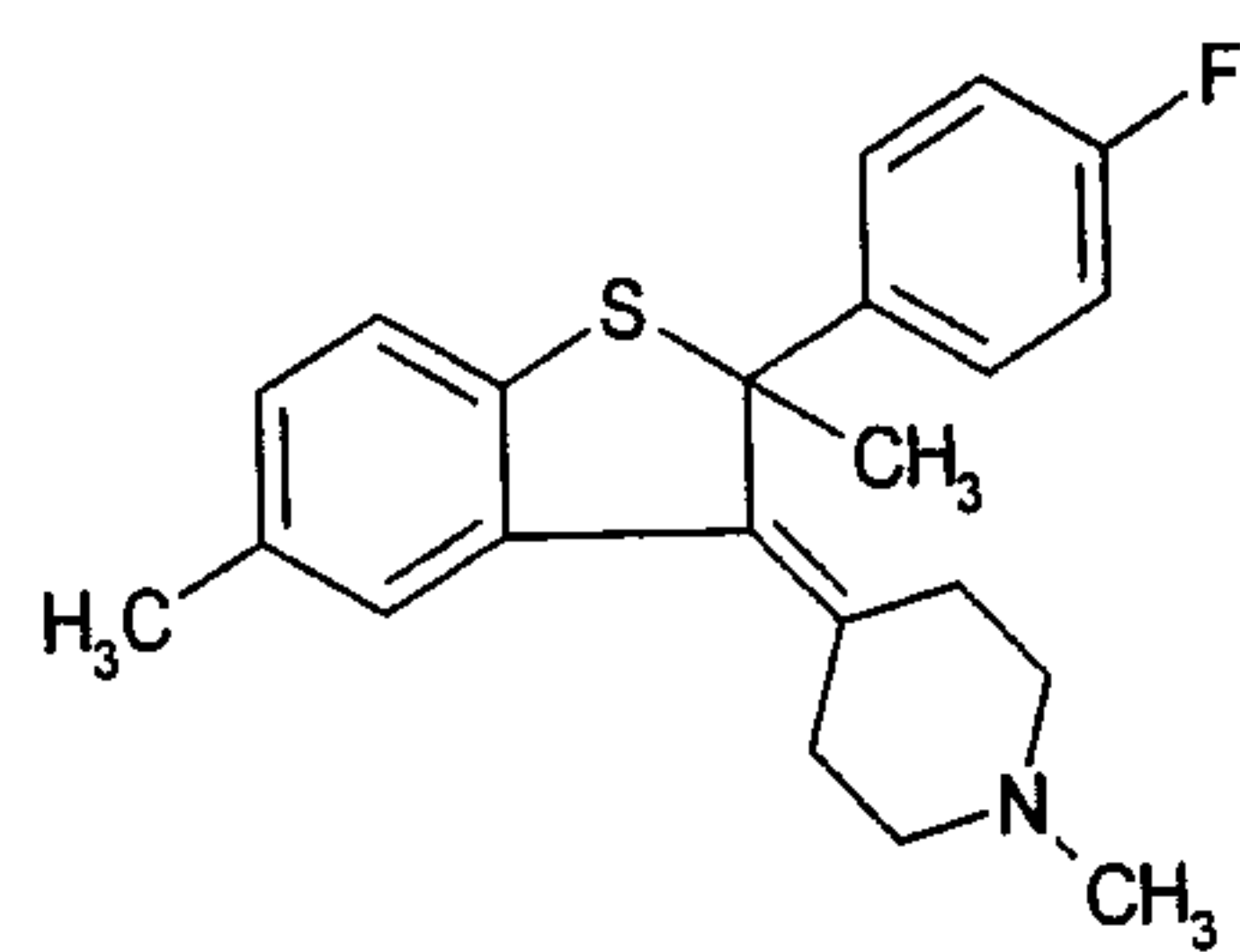
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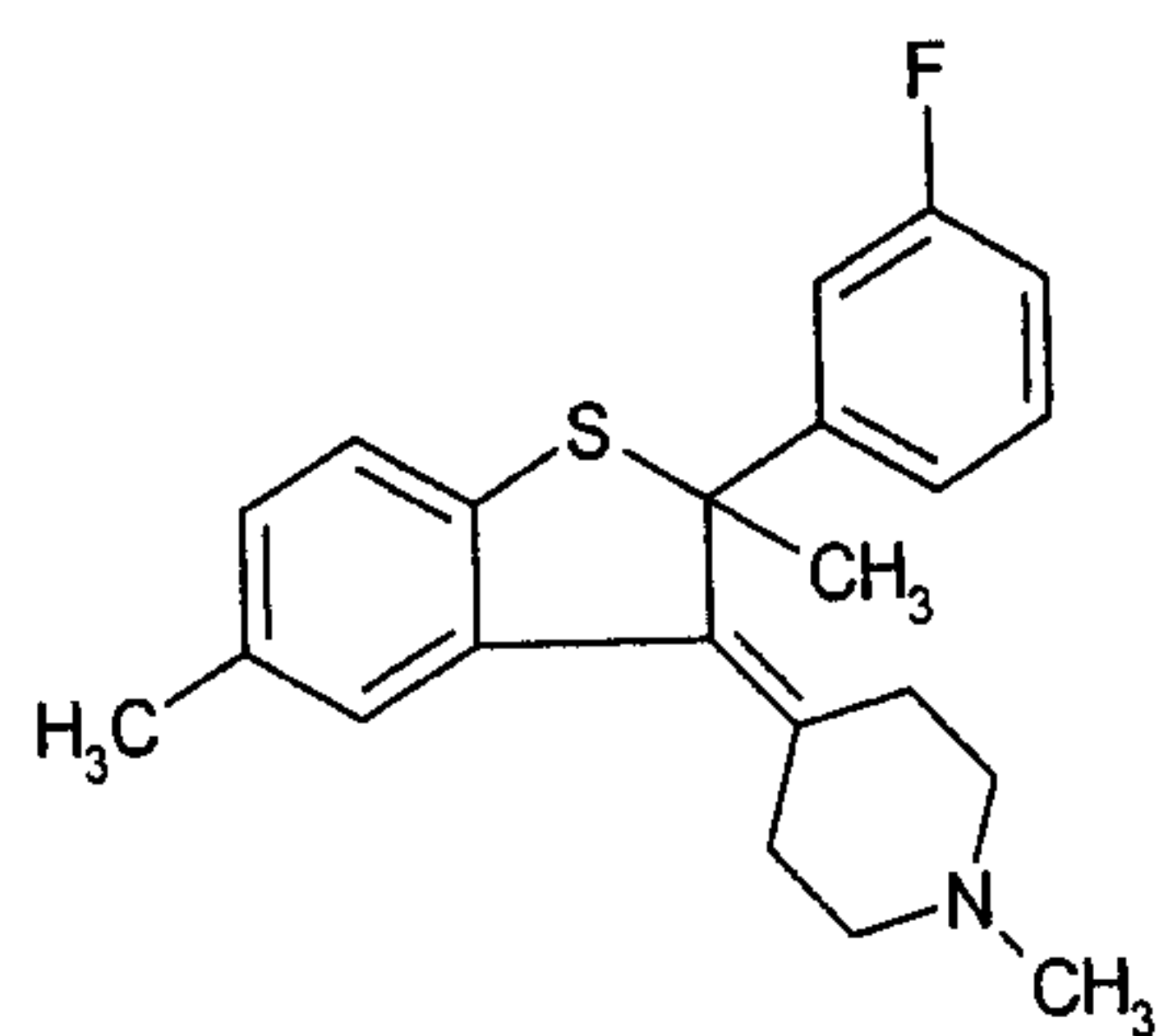
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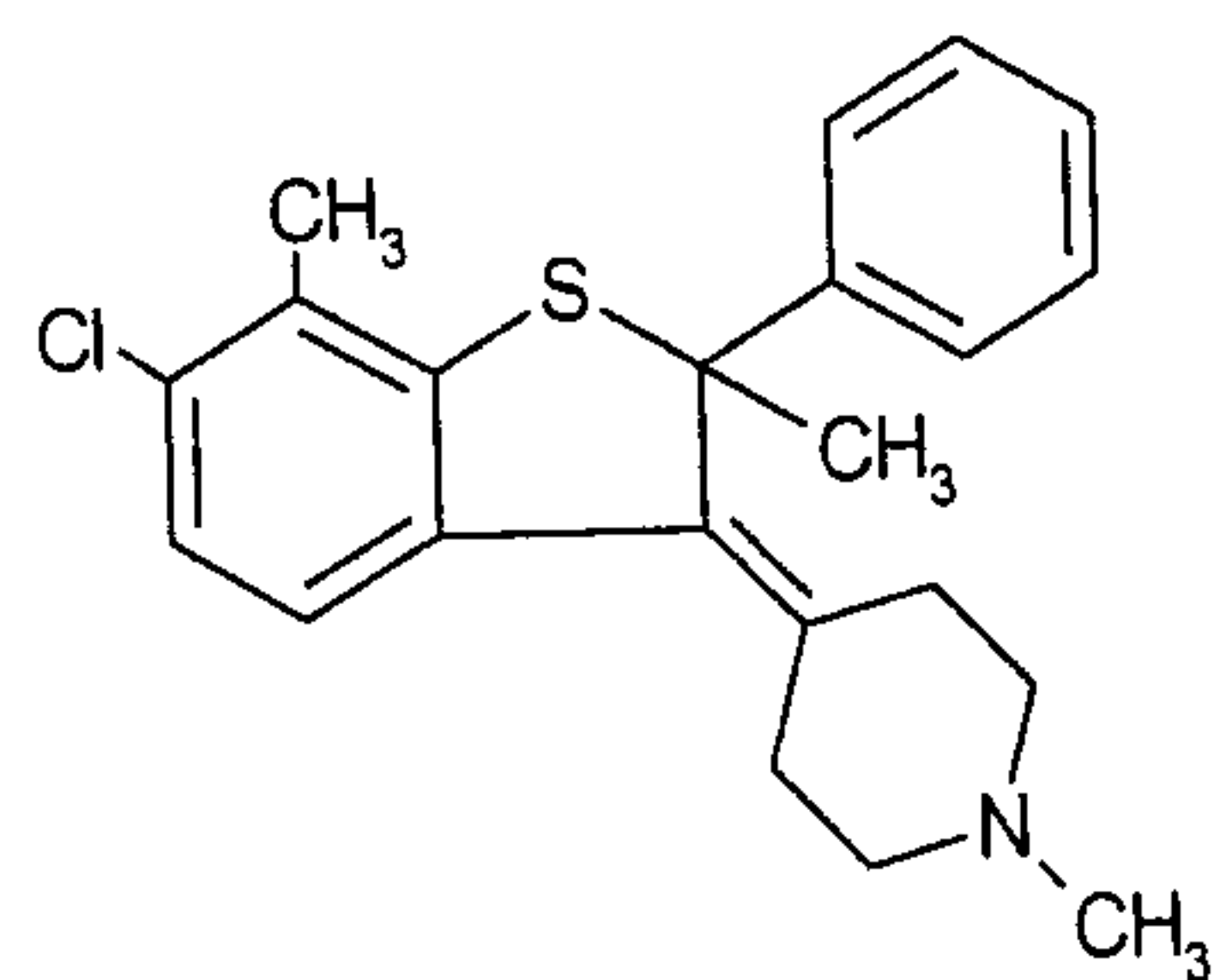
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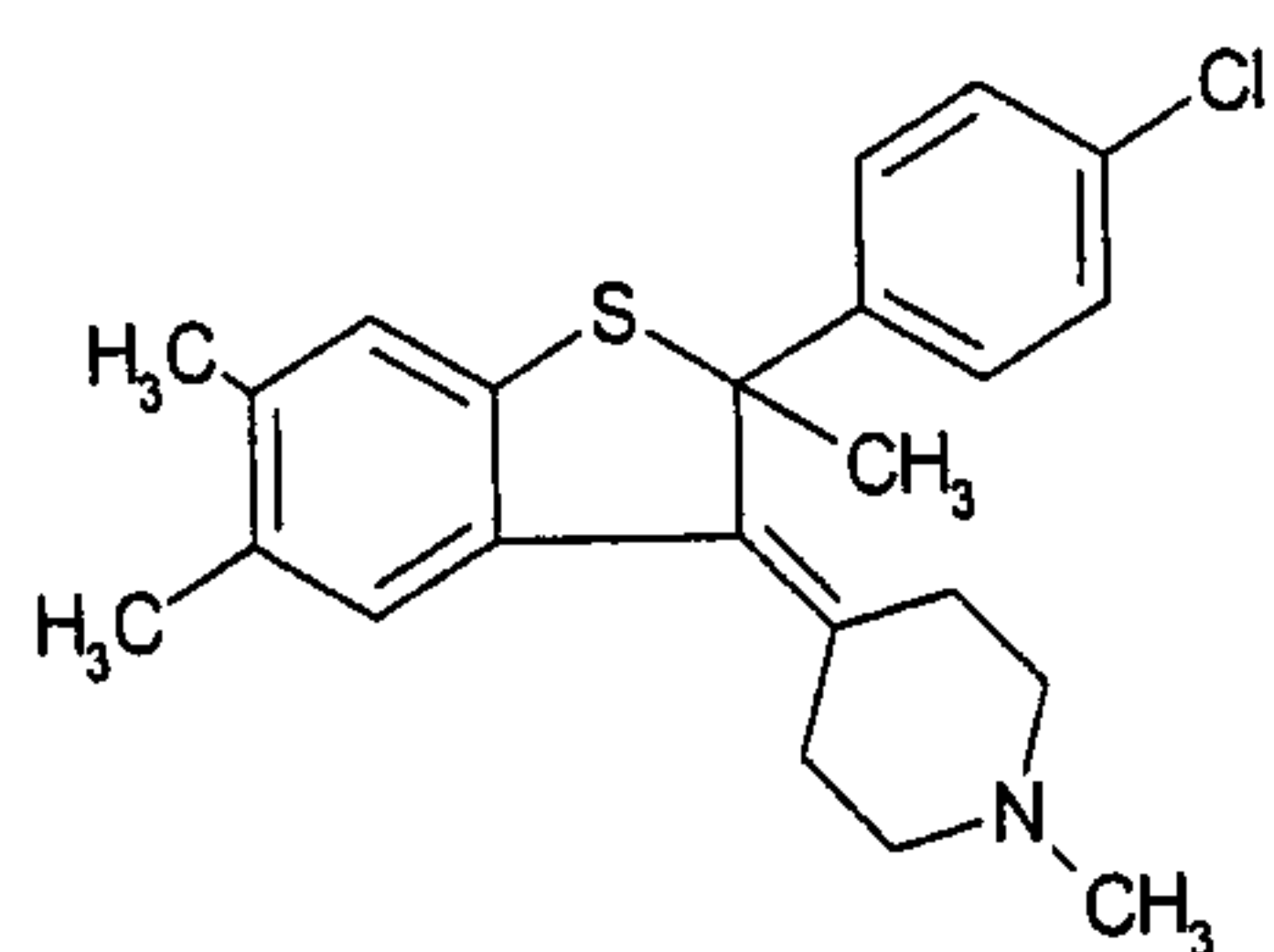
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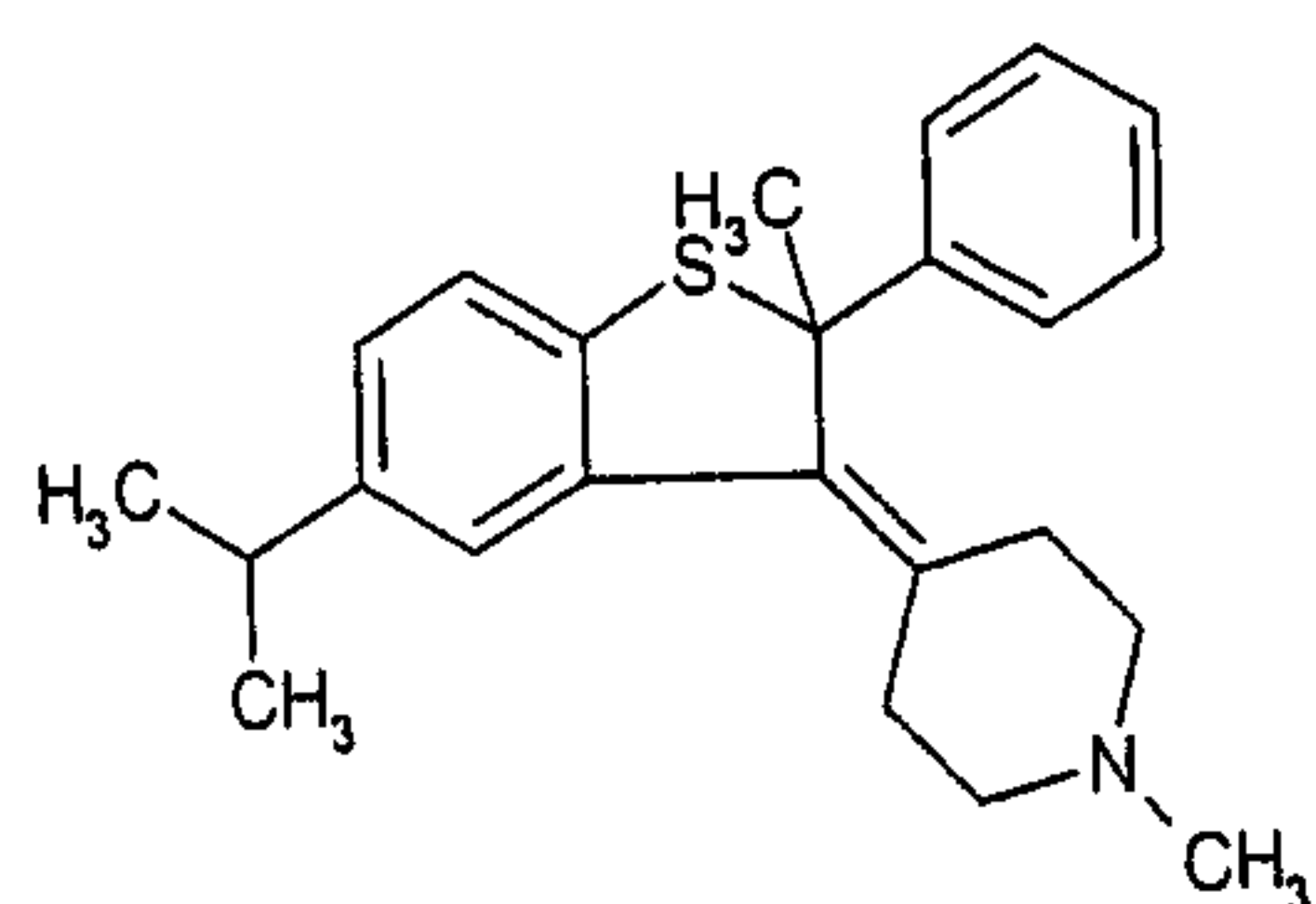
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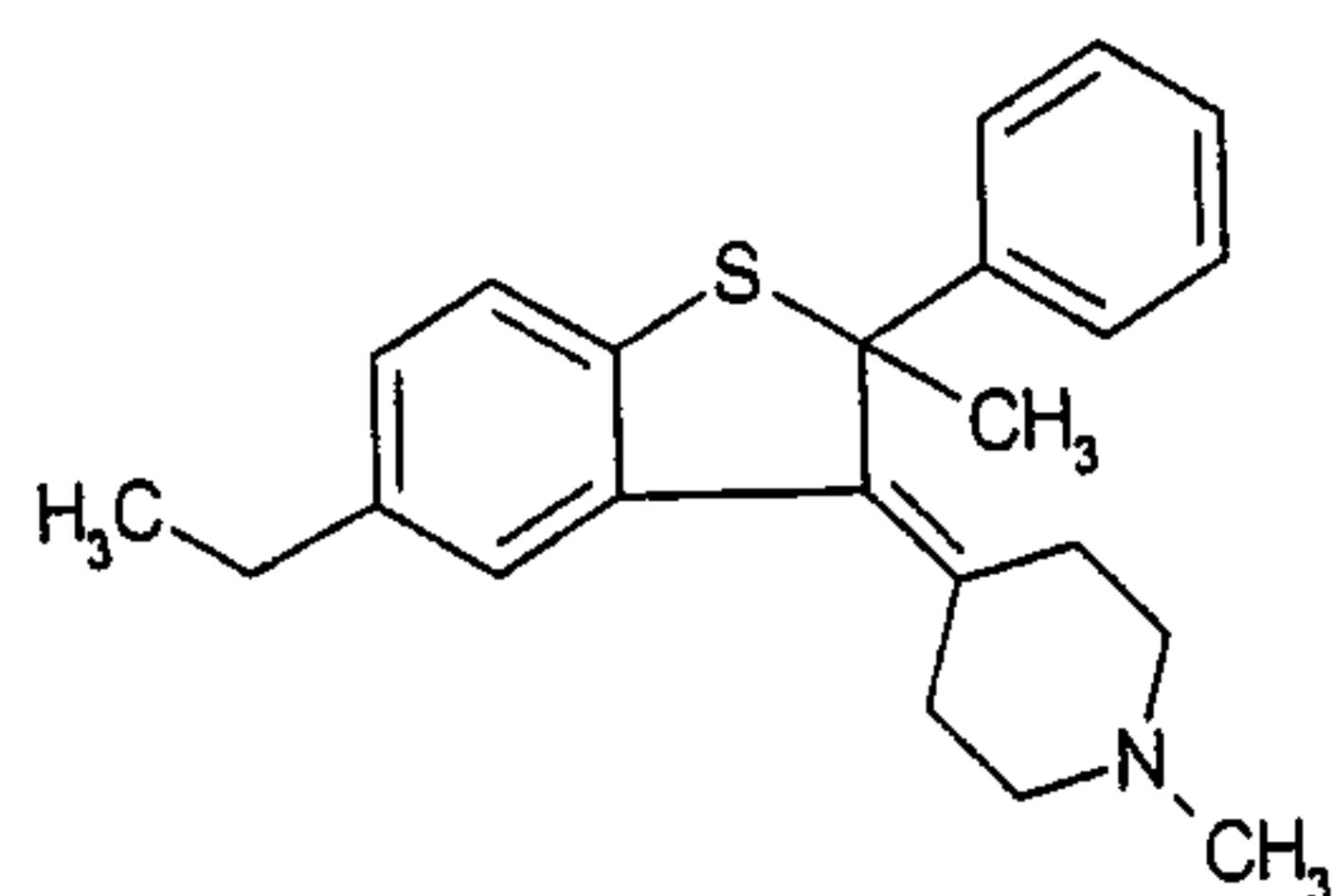
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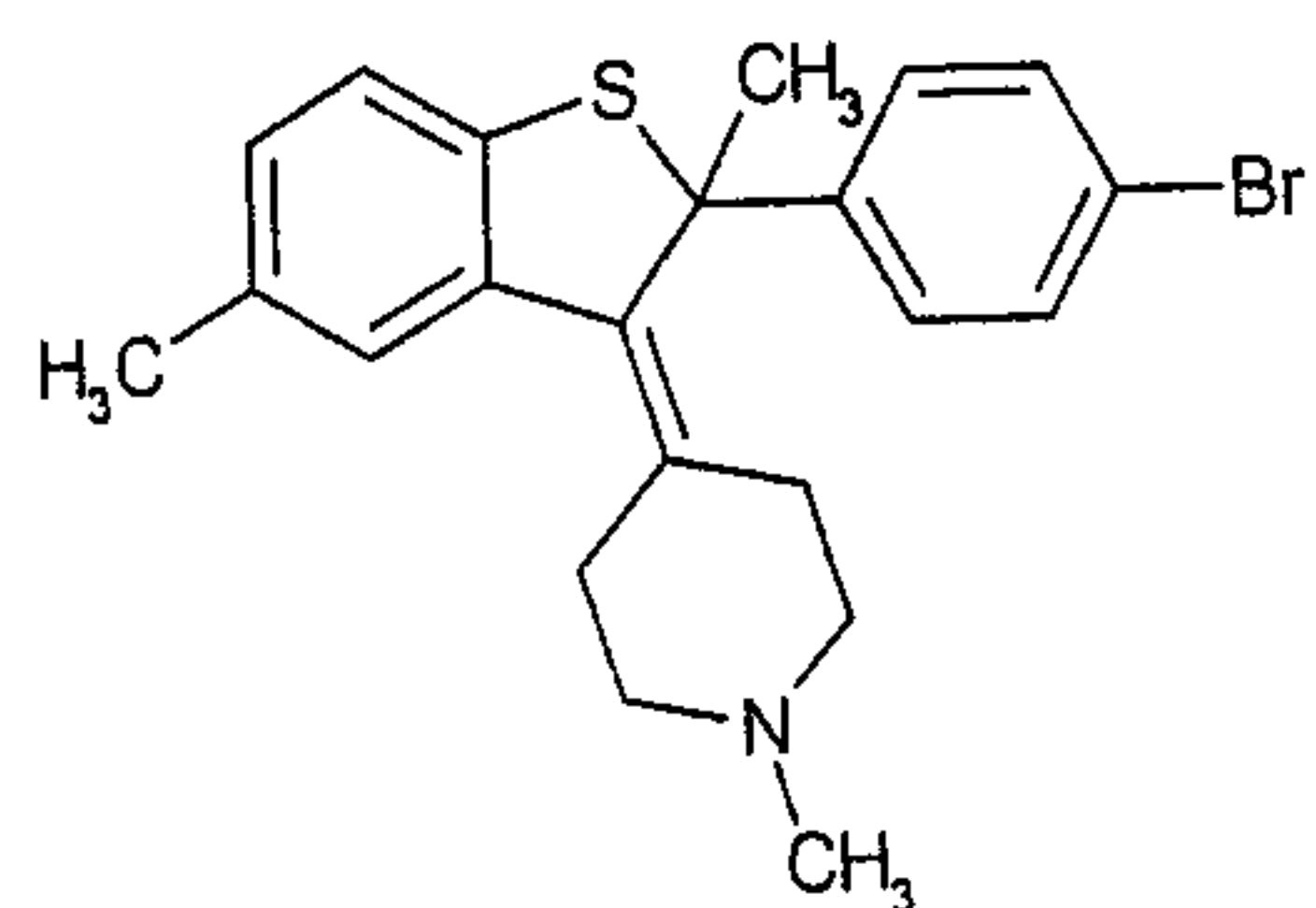
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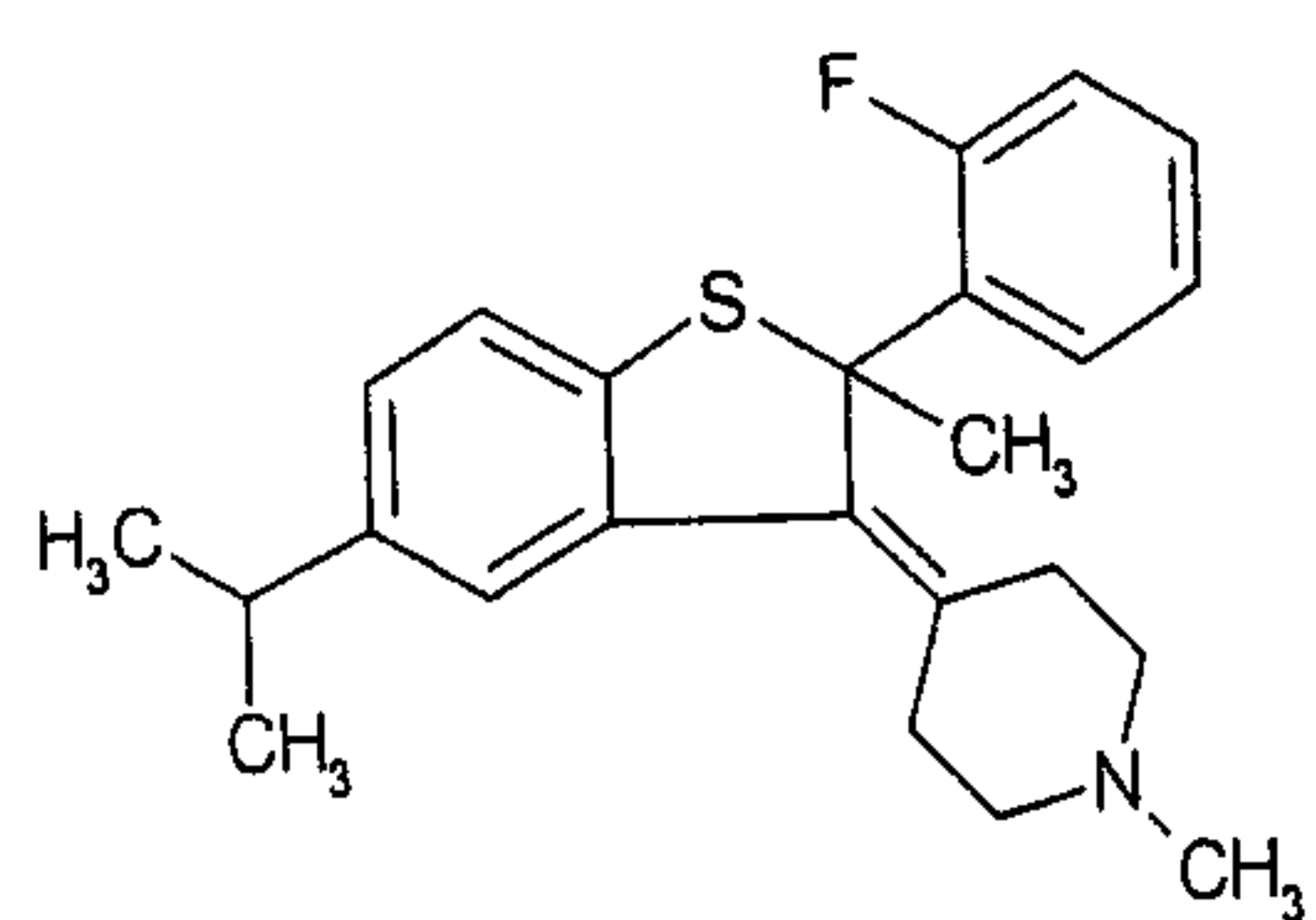
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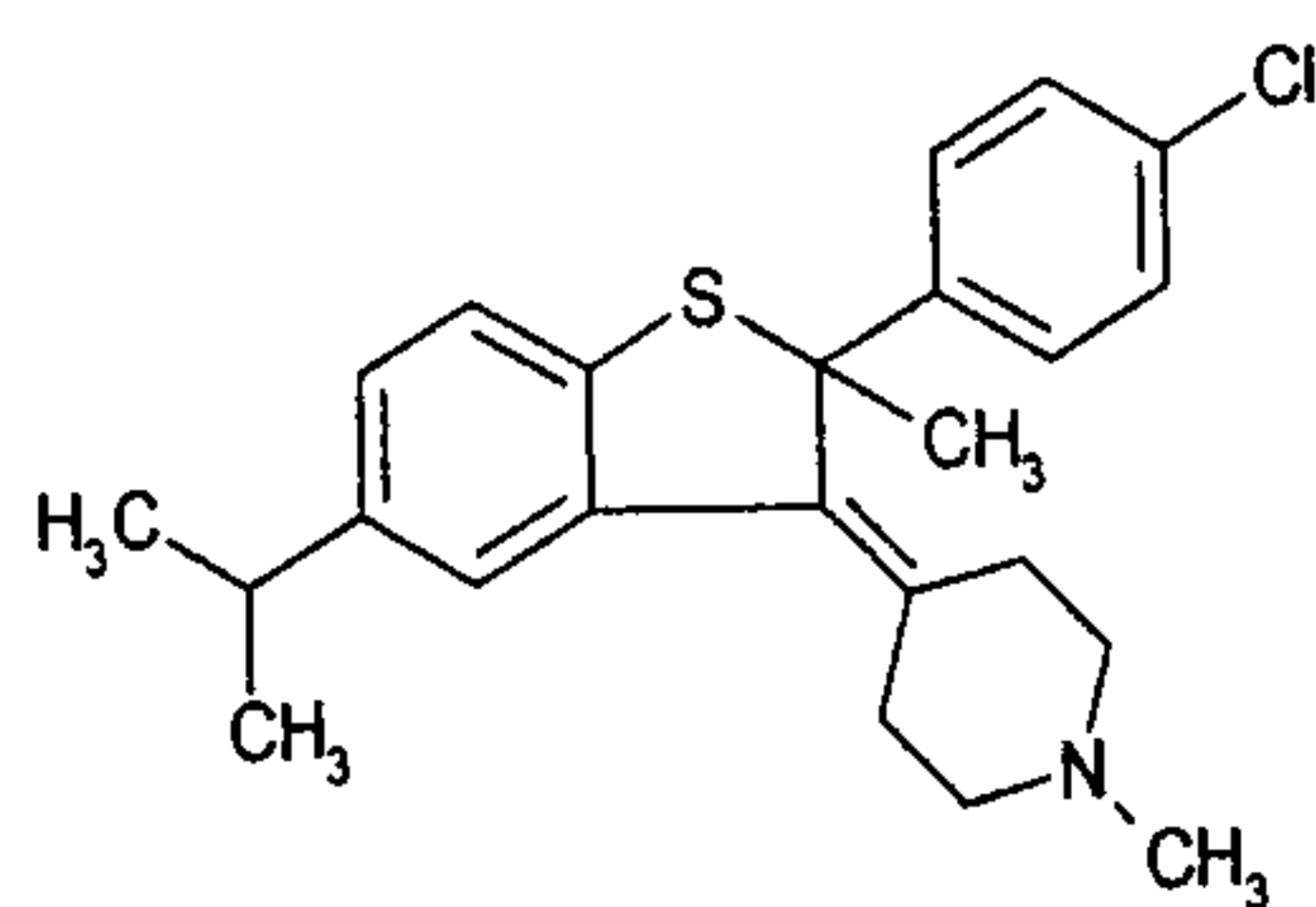
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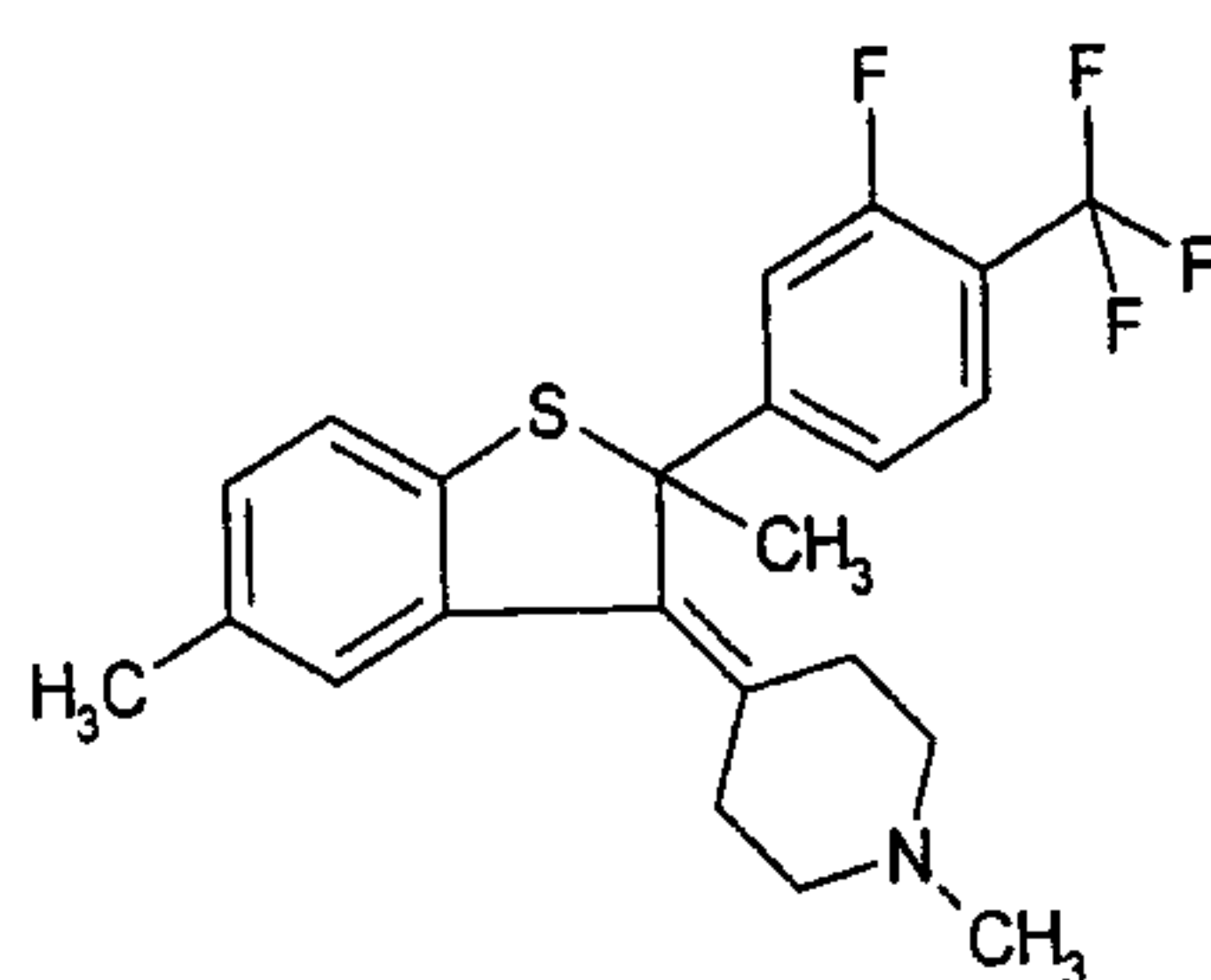
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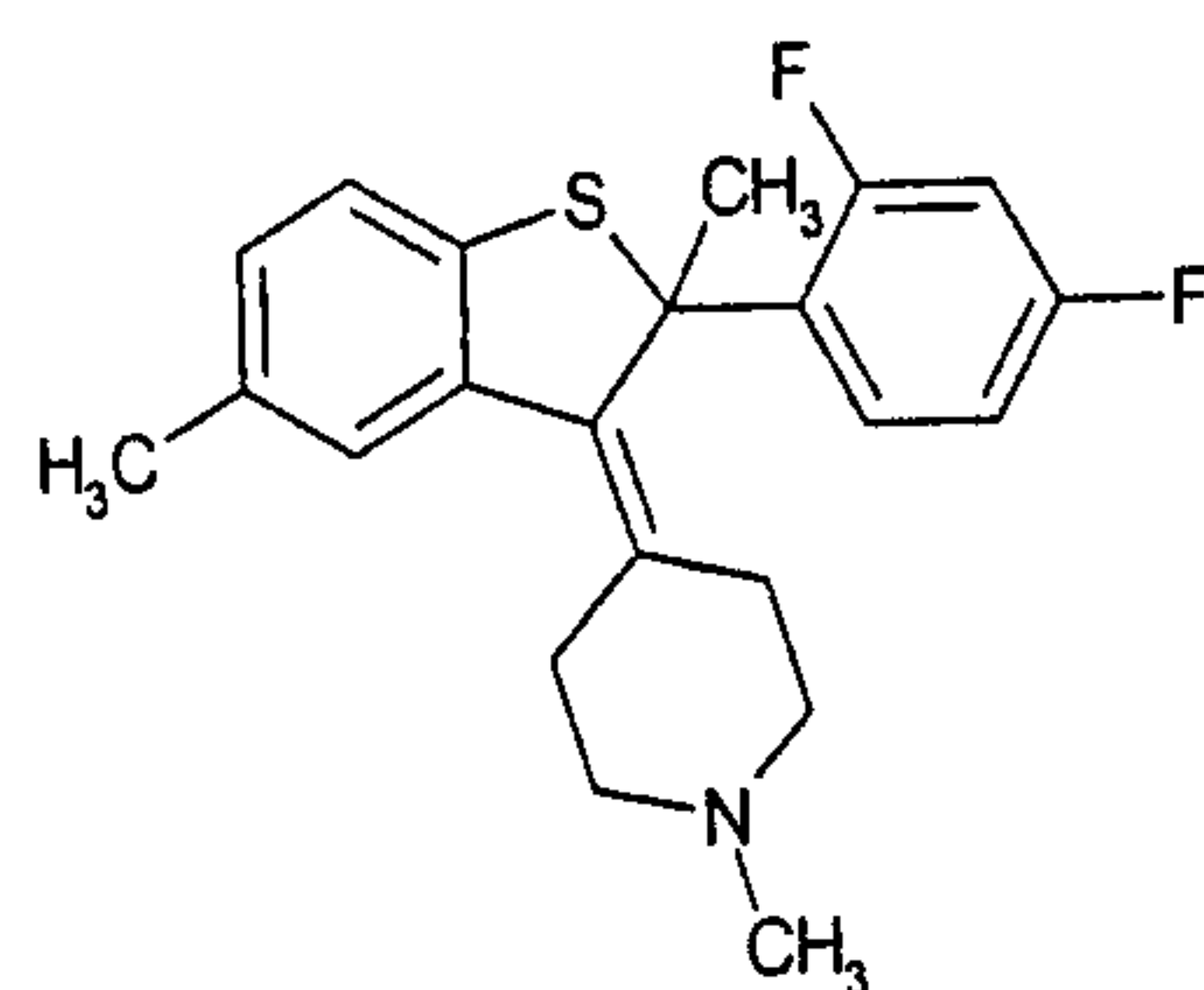
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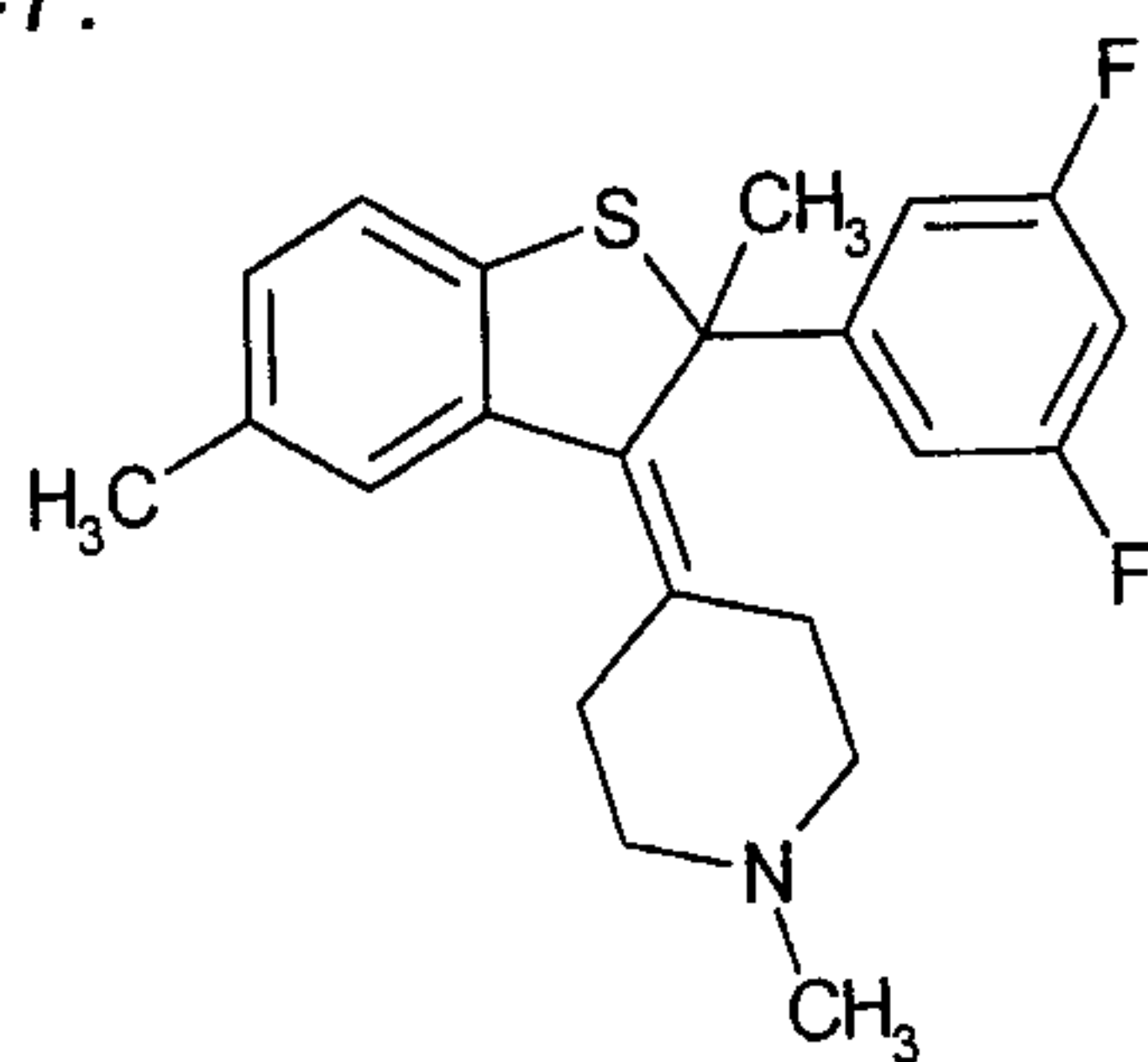
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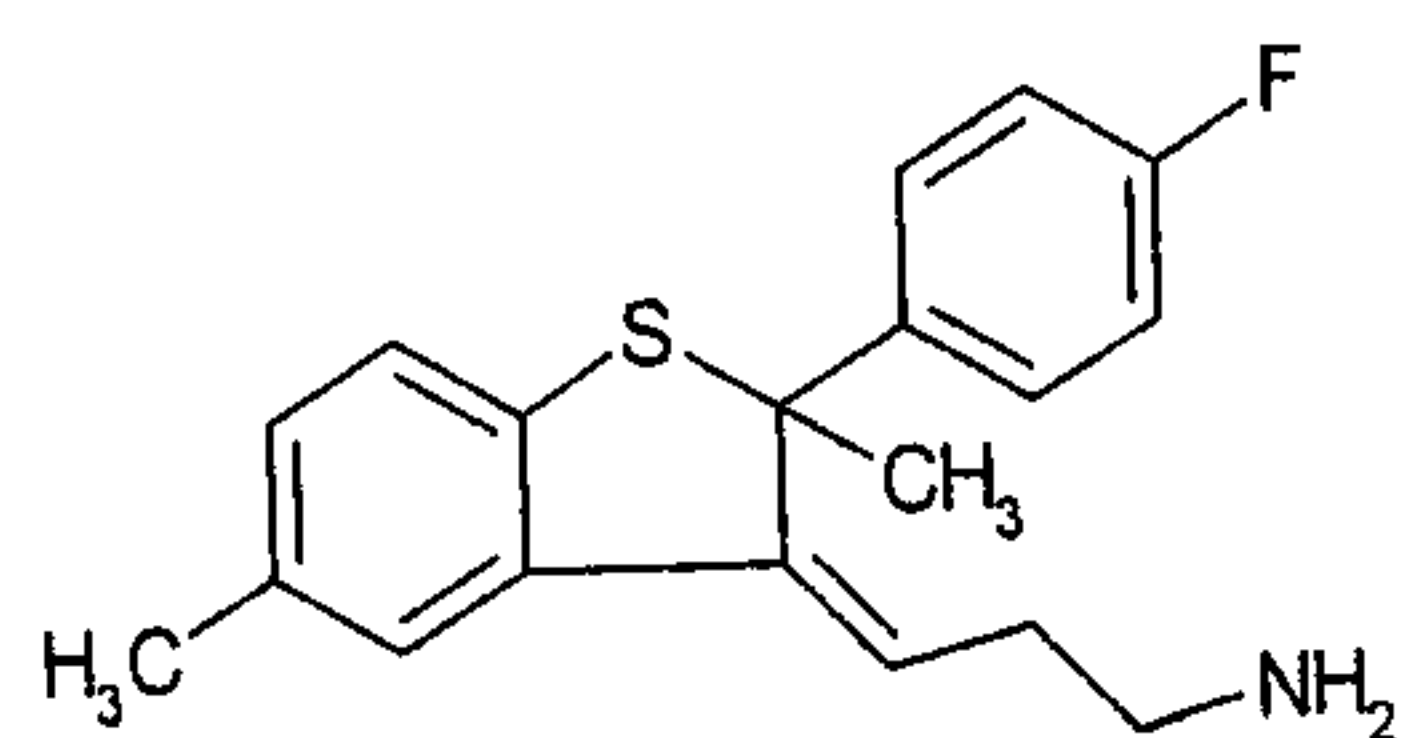
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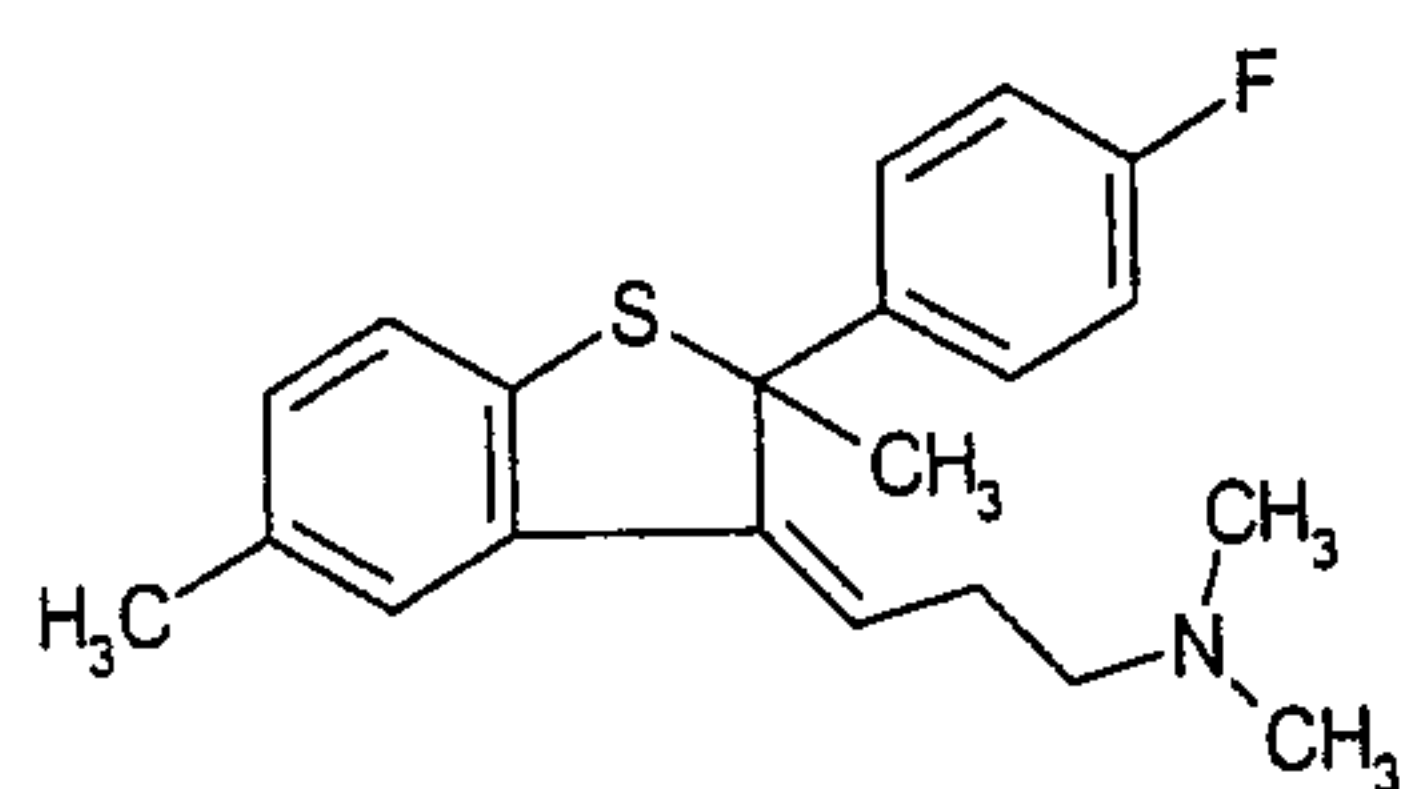
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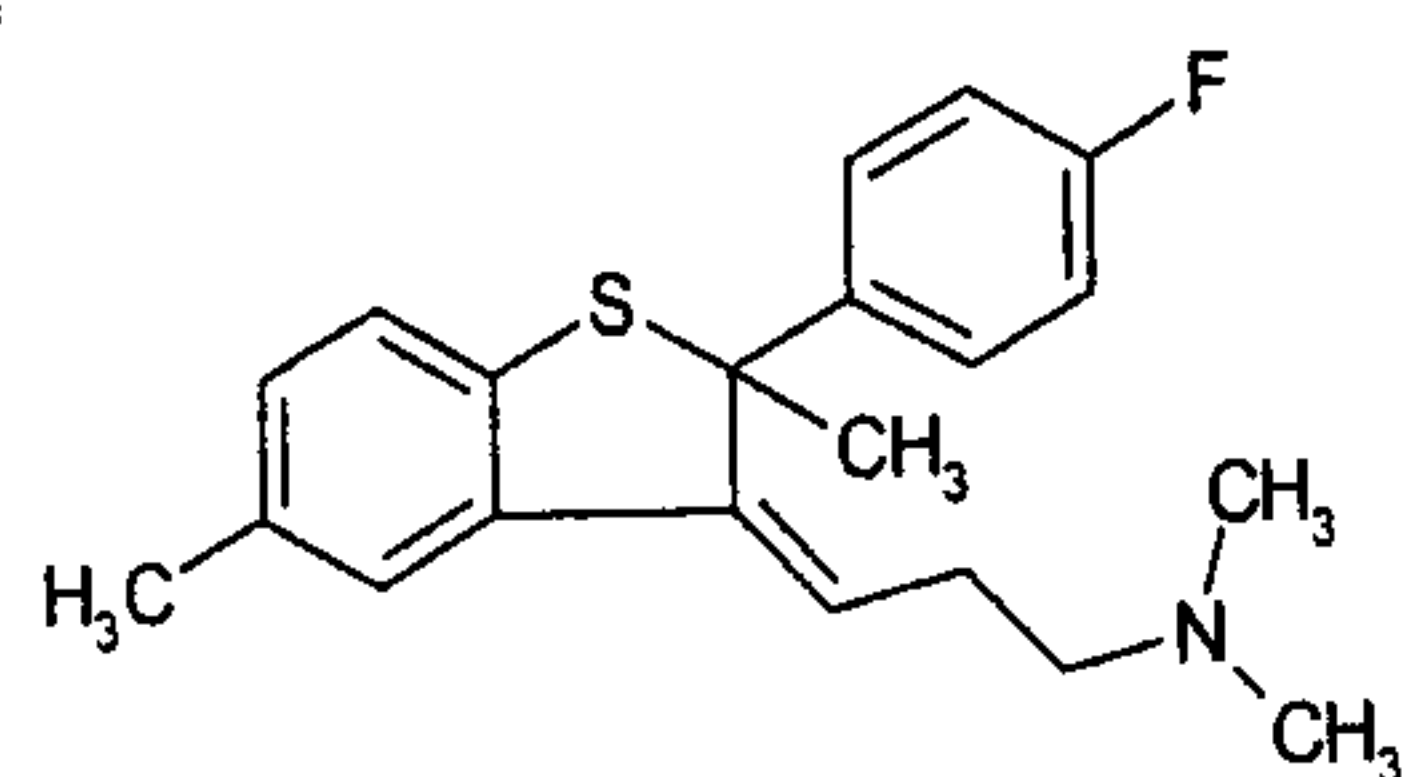
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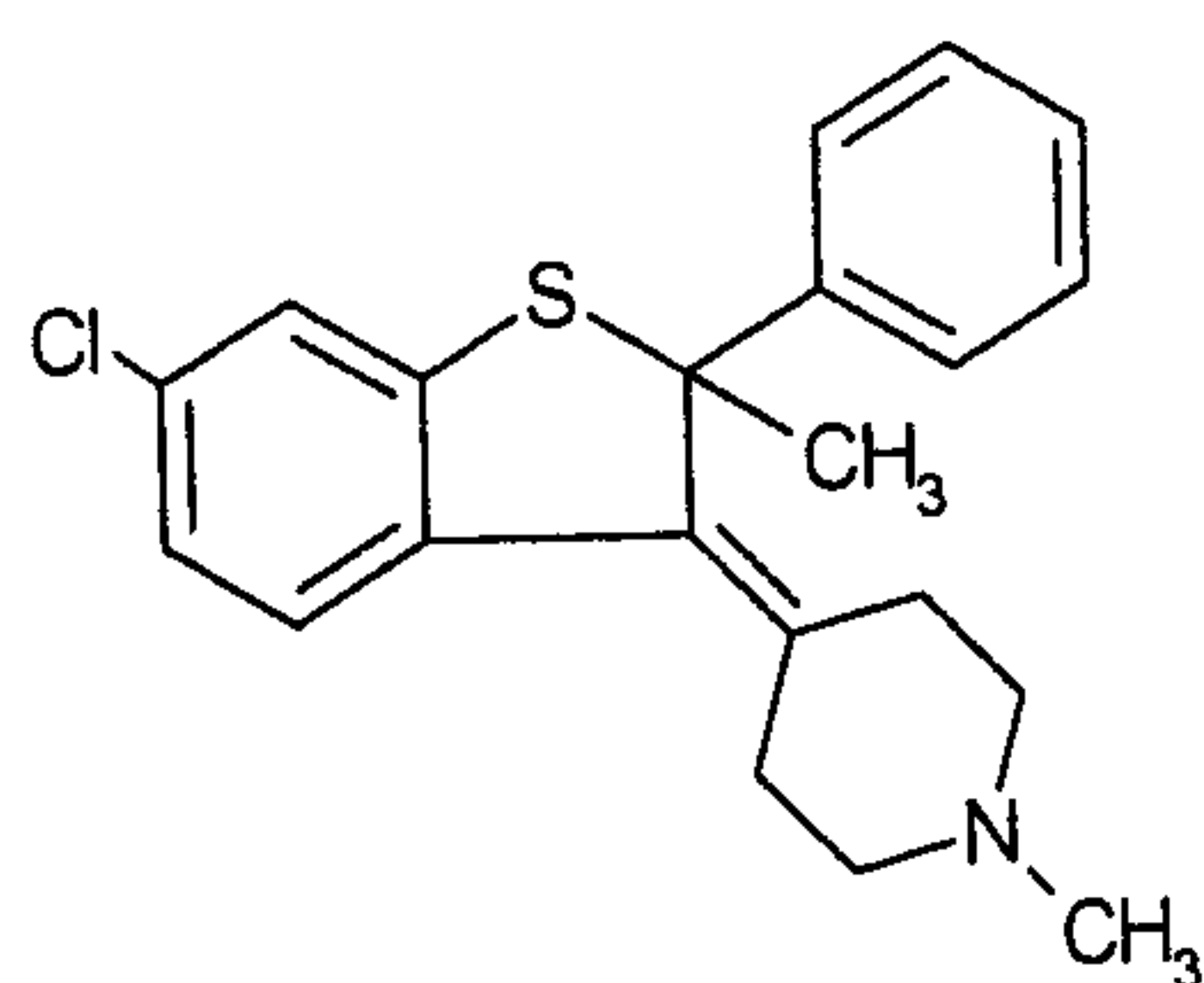
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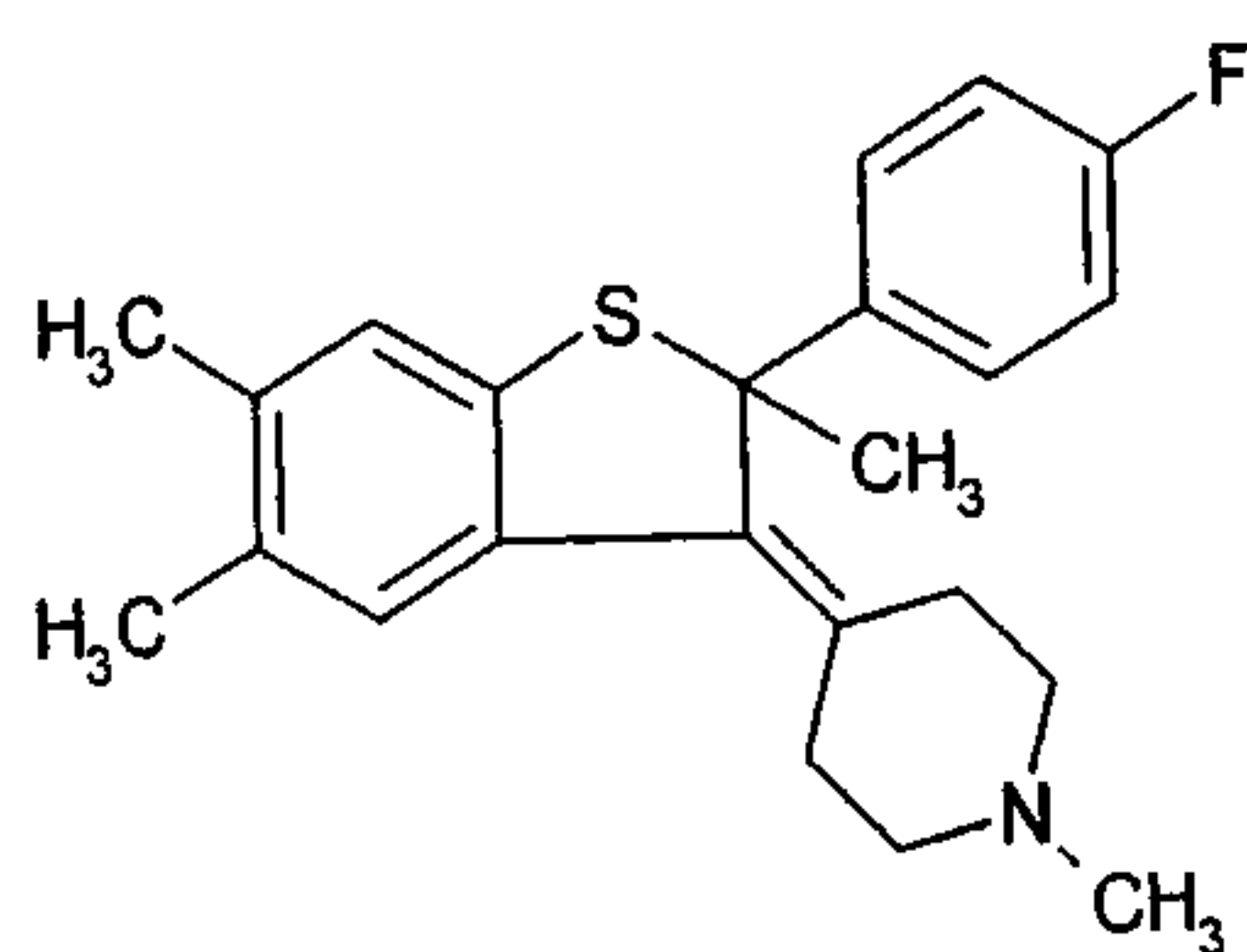
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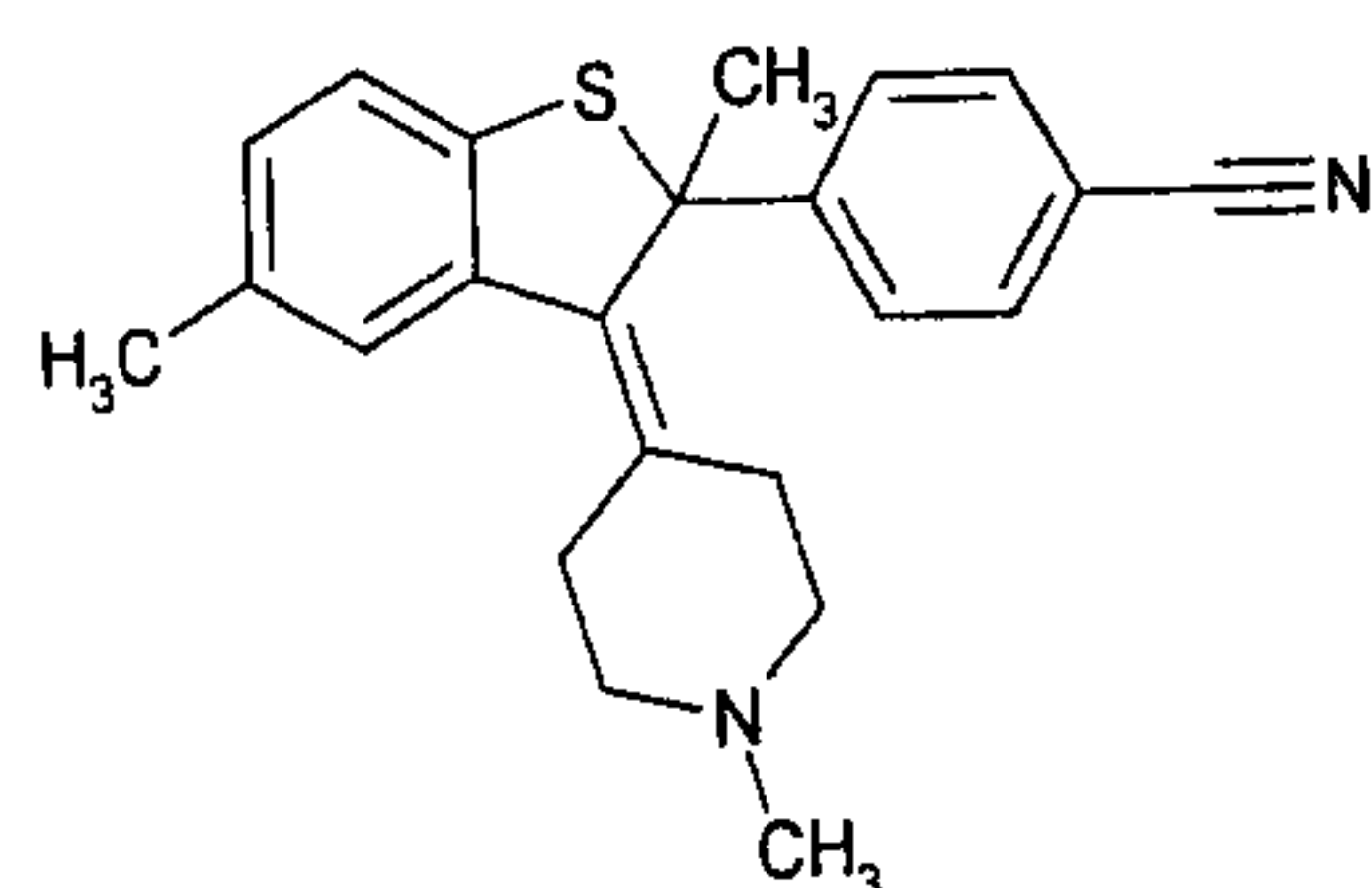
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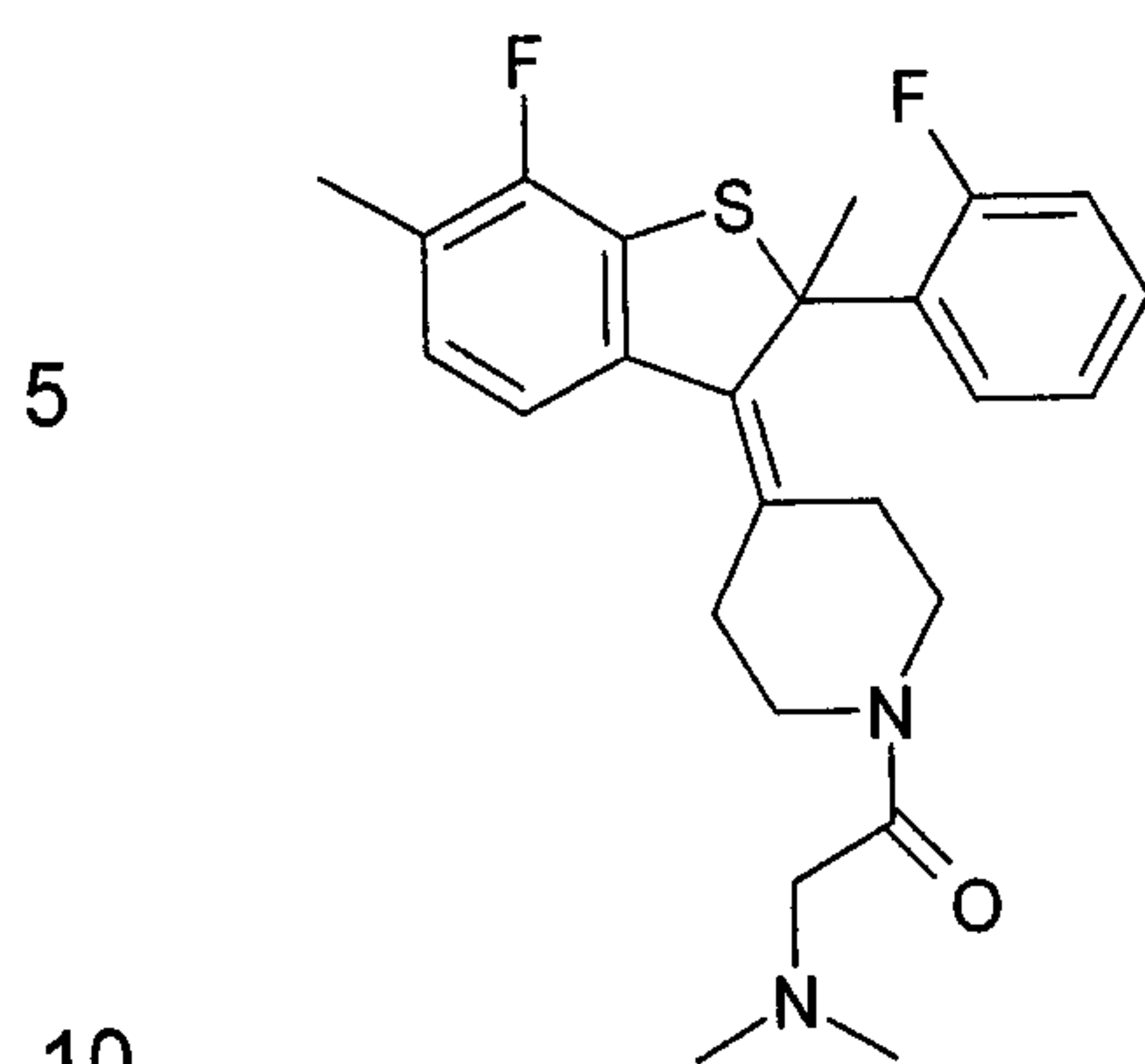
253.

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254.



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Example A: Assay I

5 The efficacy of the compounds of the formula I according to the invention can be determined, for example, via the Eg5 ATPase activity, which is measured via an enzymatic regeneration of the product ADP to ATP by means of pyruvate kinase (PK) and subsequent coupling to an NADH-
10 dependent lactate dehydrogenase (LDH) reaction. The reaction can be monitored via the change in absorbance at 340 nm by coupling to the NADH-dependent LDH. The regeneration of the ATP simultaneously ensures that the substrate concentration remains constant. The change in absorbance per time unit are analysed graphically and a linear regression
15 carried out in the visually linear region of the reaction.

Example B: Assay II

20 The determination of the efficacy of the compounds of the formula I according to the invention in combination with compounds of the formula VI and/or medicaments from Table I can be demonstrated as follows in combination assays:

25 10^3 to 10^4 cells of a defined cell line (HCT116, Colo 205, MDA-MB 231, etc.) are sown into each well of a 96-well microtitre plate and cultivated overnight under standard conditions. For the substances of the combination to be tested, 10-50 mM stock solutions in DMSO were prepared. Dilution
30 series (generally 3-fold dilution steps) of the individual substances were combined with one another in the form of a pipetting scheme (see scheme below), while maintaining a DMSO final concentration of 0.5% (v/v). Next morning, the substance mixtures were added to the cells, which were
35 incubated under culture conditions for a further 48 hours. At the end of the cultivation, Crystal Violet staining of the cells was carried out. After

extraction of the Crystal Violet from the fixed cells, the absorption at 550 nm was measured spectrophotometrically. It can be used as a quantitative measure of the adherent cells present.

5

Scheme

Substance 1 (Eq5)

←

10		1	2	3	4	5	6	7	8	9	10	11	12
	A		81 y	27 y	9 y	3 y	y	0					
	B	81 x								empty	empty	empty	
	C	27 x								0.5% DMS O	0.5% DMS O	0.5% DMS O	
15	D	9 x											
	E	3 x											
	F	x											
	G	0											
20	H												

↑

Substance 2

25

The following examples relate to medicaments:

Example C: Injection vials

30

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions.

35

Each injection vial contains 5 mg of active ingredient.

Example D: Suppositories

5 A mixture of 20 g of an active ingredient of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example E: Solution

10 A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This so-
15 lution can be used in the form of eye drops.

Example F: Ointment

20 500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example G: Tablets

25 A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

Example H: Dragees

30 Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example I: Capsules

5 2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example J: Ampoules

10 A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains
15 10 mg of active ingredient.

20

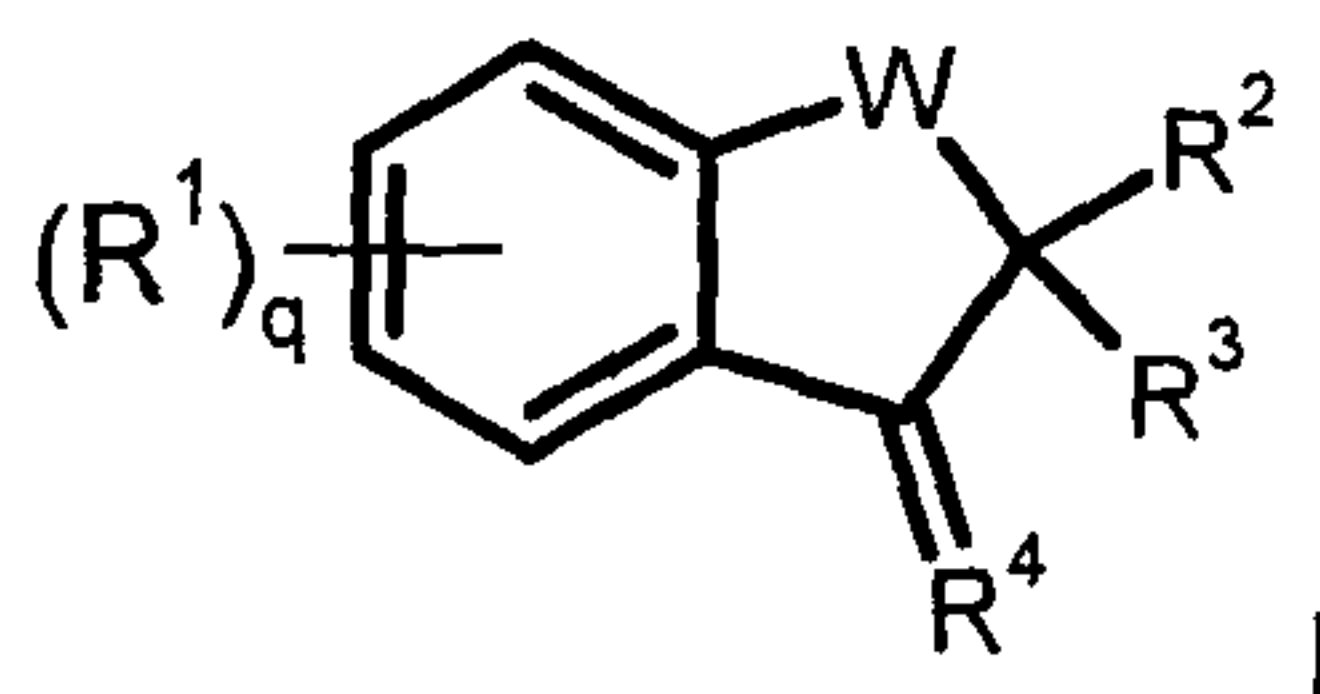
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Patent Claims

1. Compounds of the formula I:



where

W denotes S, SO or SO₂,

R¹ denotes H, A, Ar, Het, phenyl, methyl, OR⁵, SR⁵, OAr, SAr, N(R⁵)₂, N R⁵Ar, Hal, NO₂, CN, (CH₂)_mCOOR⁵, (CH₂)_mCOOAr, (CH₂)_mCON(R⁵)₂, (CH₂)_mCONHAr, COR⁵, COAr, S(O)_mA, S(O)_mAr, NHCOA, NHCOAr, NHSO₂A, NHSO₂Ar or SO₂N(R⁵)₂, heteroaryl, Hal, -(CY₂)_n-SA, -(CY₂)_n-SCF₃, -(CY₂)_n-SCN, -(CY₂)_n-CF₃, -(CY₂)_n-OCF₃, cycloalkyl, -SCH₃, -SCN, -CF₃, -OCF₃, -OA, -(CY₂)_n-OH, -(CY₂)_n-CO₂R⁵, -(CY₂)_n-CN, -(CY₂)_n-Hal, -(CY₂)_n-N(R⁵)₂, (CY₂)_n-OA, (CY₂)_n-OCOA, -SCF₃, (CY₂)_n-CON(R⁵)₂, -(CY₂)_n-NHCOA, -(CY₂)_n-NHSO₂A, SF₅, Si(CH₃)₃, CO-(CY₂)_n-CH₃, -(CY₂)_n-(N-pyrrolidone), and, if the R¹ occurs twice and vicinally on the aromatic ring, together also denote -N-C(CF₃)=N-, -N-CR=N-, -N-N=N-,

R², R³, independently of one another, denote A, Het, H, -OH, -OA, -OAr, Ar, -O-CO-A, -OSO₃R⁵, -OSO₂R⁵, -OAr₂R⁵, SO₂R⁵, Hal, COOR⁵, CON(R⁵)₂, NHSO₂A, COA, CHO or SO₂N(R⁵)₂, -(CH₂)_o-Ar, -(CH₂)_o-cycloalkyl, -(CH₂)_o-OH, -(CH₂)_o-N(R⁵)₂, NO₂, CN, -(CH₂)_o-COOR⁵, -(CH₂)_o-CON(R⁵)₂, -(CH₂)_o-NHCOA, NHCON(R⁵)₂, -(CH₂)_o-NHSO₂A, -(C(R⁵)₂)_o-Ar, or aryl or heteroaryl, each of which is unsubstituted or mono- or polysubstituted

by aryl or heteroaryl, which may be substituted by Hal, NO₂, CN, A, OR, OCOR, COR, NR₂, CF₃, OCF₃, OCH(CF₃)₂, or Hal, NO₂, CN, OR, A, -(CY₂)_n-OR, -OCO R⁵, -(CY₂)_n-CO₂ R⁵,
 5 -(CY₂)_n-CN, -NCO R⁵, -CO R⁵ or -(CY₂)_n-N(R⁵)₂,
 N[(CH₂)_nXCOOR⁵]CO(CH₂)_naryl, N[(CH₂)_nXR⁵]CO(CH₂)_naryl,
 N[(CH₂)_nXR⁵]CO(CH₂)_nXaryl, N[(CH₂)_nXR⁵]SO₂(CH₂)_naryl,
 N[(CH₂)_nNR⁵COOR⁵]CO(CH₂)_naryl, N[(CH₂)_nN(R⁵)₂]CO(CH₂)_n-
 10 aryl, N[(CH₂)_nN(R⁵)₂]CO(CH₂)_nNR⁵aryl,
 N[(CH₂)_nN(R⁵)₂]SO₂(CH₂)_naryl, N[(CH₂)_nXR⁵]CO(CH₂)Het,
 N[(CH₂)_nXR⁵]CO(CH₂)nHet, N[(CH₂)_nXR⁵]SO₂(CH₂)nHet I,
 N[(CH₂)_nNR⁵COOR⁵] CO(CH₂)nHet,
 N[(CH₂)_nN(R⁵)₂]CO(CH₂)nHet or N[(CH₂)_n-
 15 N(R⁵)₂]CO(CH₂)nNR⁵Het,

R⁴ denotes O, =CH-(CH₂)_nN(R⁵)₂, or cyclo[C(CH₂)_k (NY¹)-(CH₂)_p-] ,
 cyclo[C(CH₂)_k (CHY¹)-(CH₂)_p-] or E or Z - =CH(CH₂)_nX(CH₂)_l-
 20 Q(CH₂)_sT

R⁵ denotes H or A, in the case of geminal radicals R⁵ together
 also denote -(CH₂)₅-, -(CH₂)₄- or -(CH₂)_n-Q-(CH₂)_n,

25 Y denotes H, A, Hal

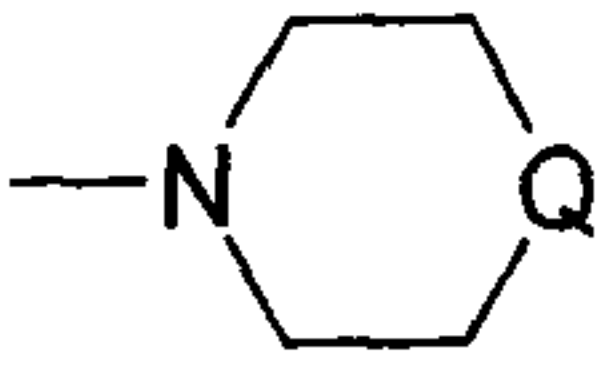
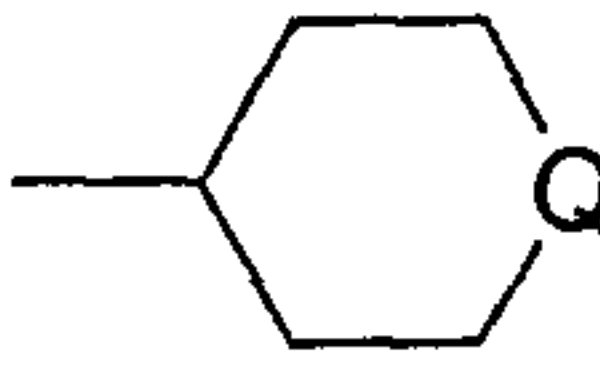
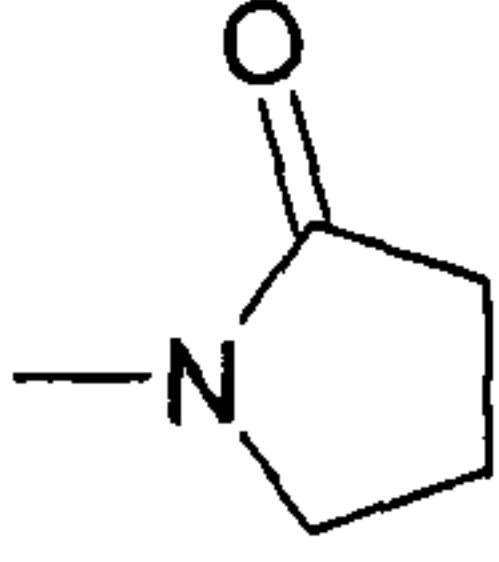
Y¹ denotes R², R⁵, Ar, -(C(R⁵)₂)₀-Ar or -(C(R⁵)₂)₀-Het,
 X(CH₂)_lQ(CH₂)_sT, XCH₂T or T,

30 X denotes NR⁵, CH₂, CO or SO₂ or a single bond

Q denotes CH₂, NR⁵, O, S, CO, SO₂, C(R⁵)₂ or a single bond,
 35 CH(CH₂)_nNR⁵COOR⁵, CHNR⁵COOR⁵, NCO, CH(CH₂)_nCOOR⁵,
 NCOOR⁵, CHX(CH₂)_nOH, N(CH₂)_nOH, CHNH₂, CH(CH₂)_nN(R⁵)₂,
 CHX(CH₂)_nN(R⁵)₂, C(OH)R⁵, CHNCOR⁵, CH(CH₂)_naryl,

CH(CH₂)_nheteroaryl, CH(CH₂)_nR¹, N(CH₂)_nCOOR⁵,
 CH(CH₂)_nX(CH₂)_naryl, CH(CH₂)_nX(CH₂)_nheteroaryl,
 N(CH₂)_nCON(R⁵)₂, CHCONR⁵(CH₂)_nN(R⁵)₂,

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T denotes R², Het, ,  or ,

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Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by Hal, A, -(CH₂)_o-Ar, -(CH₂)_o-cycloalkyl, -(CH₂)_o-OH, -(CH₂)_o-N(R⁵)₂, NO₂, CN, -(CH₂)_o-COOR⁵, -(CH₂)_o-CONR⁵, -(CH₂)_o-NHCOA, NHCONR⁵, -(CH₂)_o-NHSO₂A, CHO, COA, SO₂NH₂ and/or S(O)_oA,

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Ar denotes aryl, or phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR⁵, N(R⁵)₂, NO₂, CN, COOR⁵, CON(R⁵)₂, NHCOA, NHCON(R⁵)₂, NHSO₂A, CHO, COA, SO₂N(R⁵)₂ or S(O)_oA,

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A denotes unbranched or branched alkyl having 1-10 C atoms, in which one or more H atoms may be replaced by Hal or Ar,

Hal denotes F, Cl, Br or I,

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o denotes 0, 1, 2 or 3,

m denotes 0, 1, 2 or 3,

n denotes 0, 1, 2, 3 or 4,

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k, p, l, s denote 1, 2, 3, 4 or 5,

where

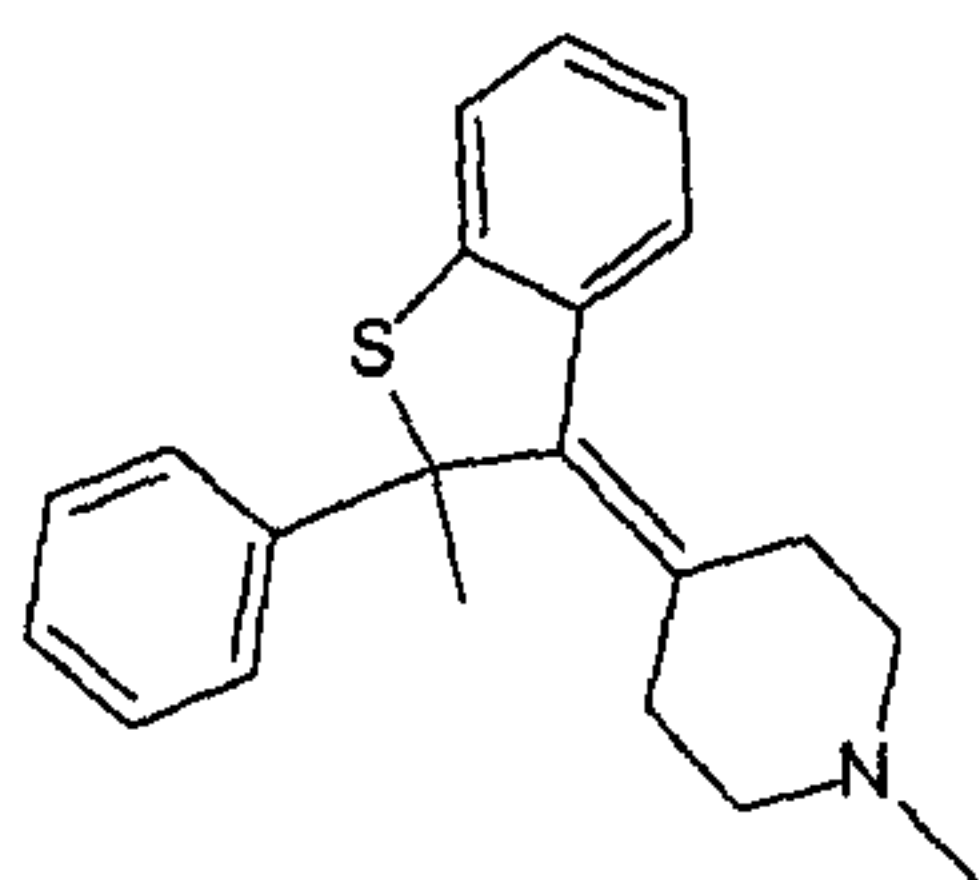
$k + p$ denotes 2, 3, 4 or 5

and

q denotes 1, 2, 3 or 4,

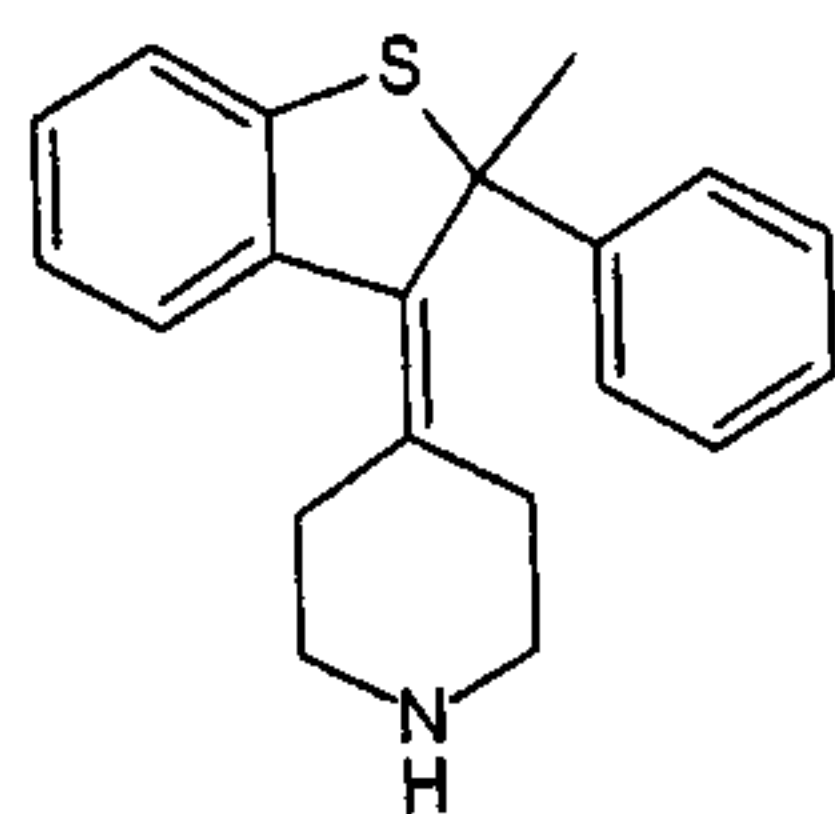
and pharmaceutically usable derivatives, solvates, tautomers, salts and stereoisomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1 in which R^1 denotes A, SR^5 , OR^5 , Hal, CN, NO_2 , $N(R^5)_2$ and q denotes 1 or 2 and R^5 has the meaning indicated in Claim 1.
3. Compounds according to Claim 1 or 2 in which R^2 denotes H, A, Ar or methyl and R^3 denotes H, Ar or $-(C(R^5)_2)_oAr$.
4. Compounds according to one or more of Claims 1-3 in which W has the meaning S for a sulfur atom.
5. Compounds according to one or more of Claims 1-4 in which R^4 denotes cyclo $[-C(CH_2)_k(NY)-(CH_2)_p-]$ or $=CH(CH_2)_nX(CH_2)_lQ(CH_2)_sT$.
6. Compounds of the sub-formulae I1 to I64:



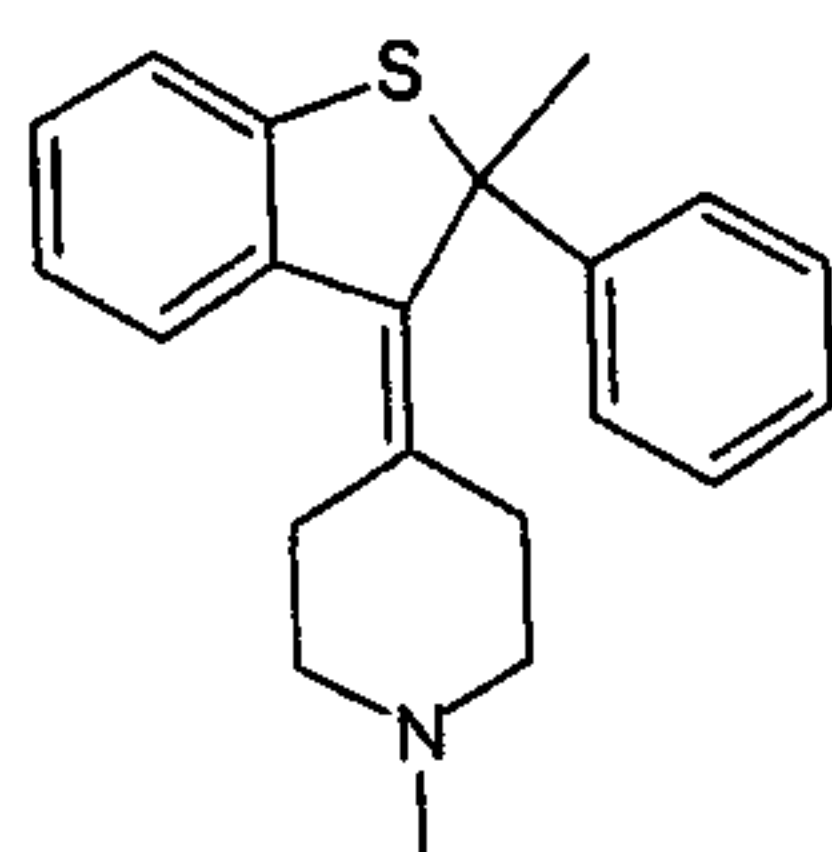
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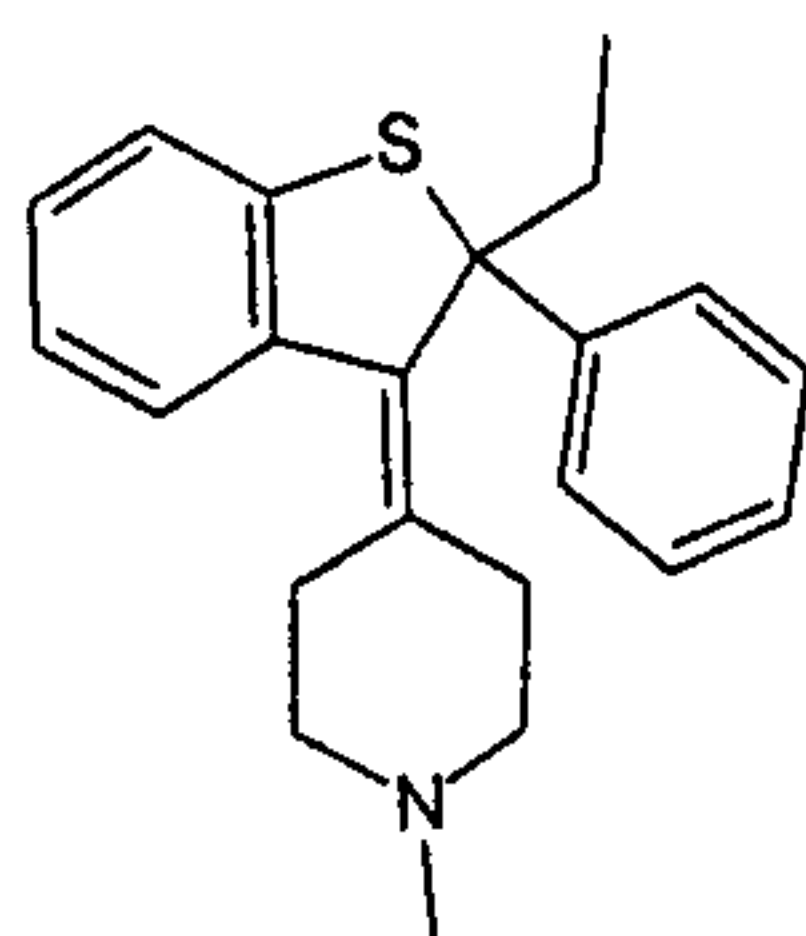
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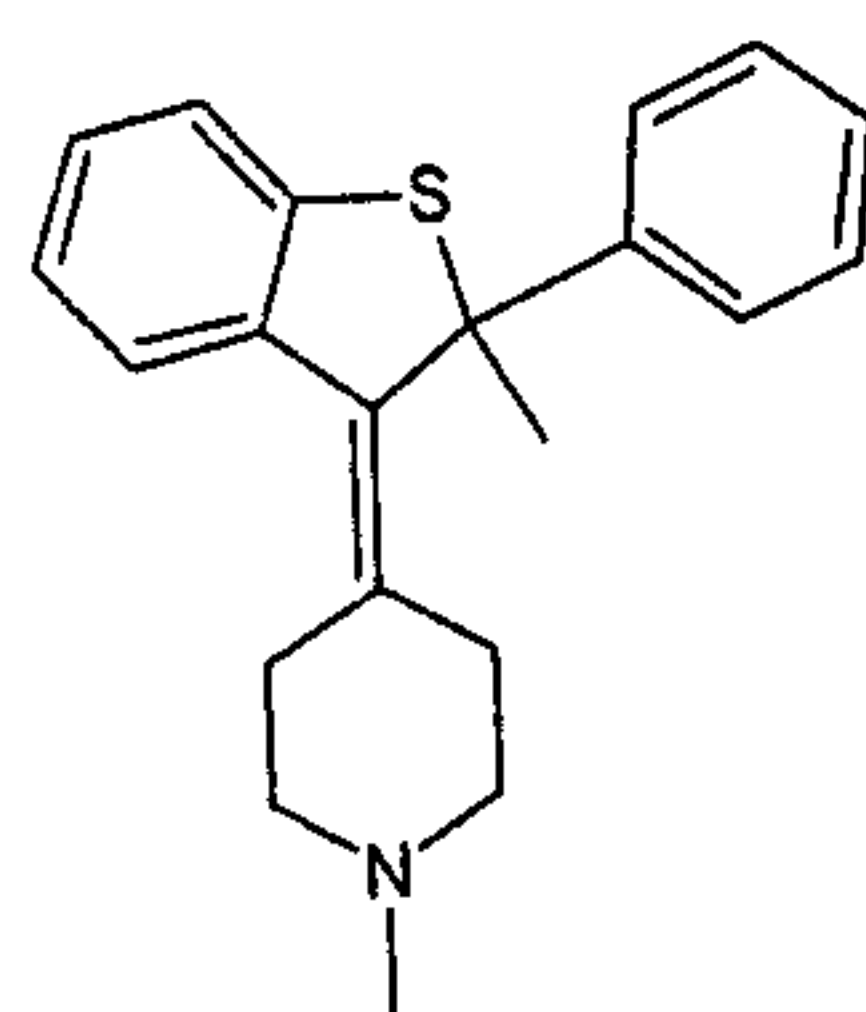
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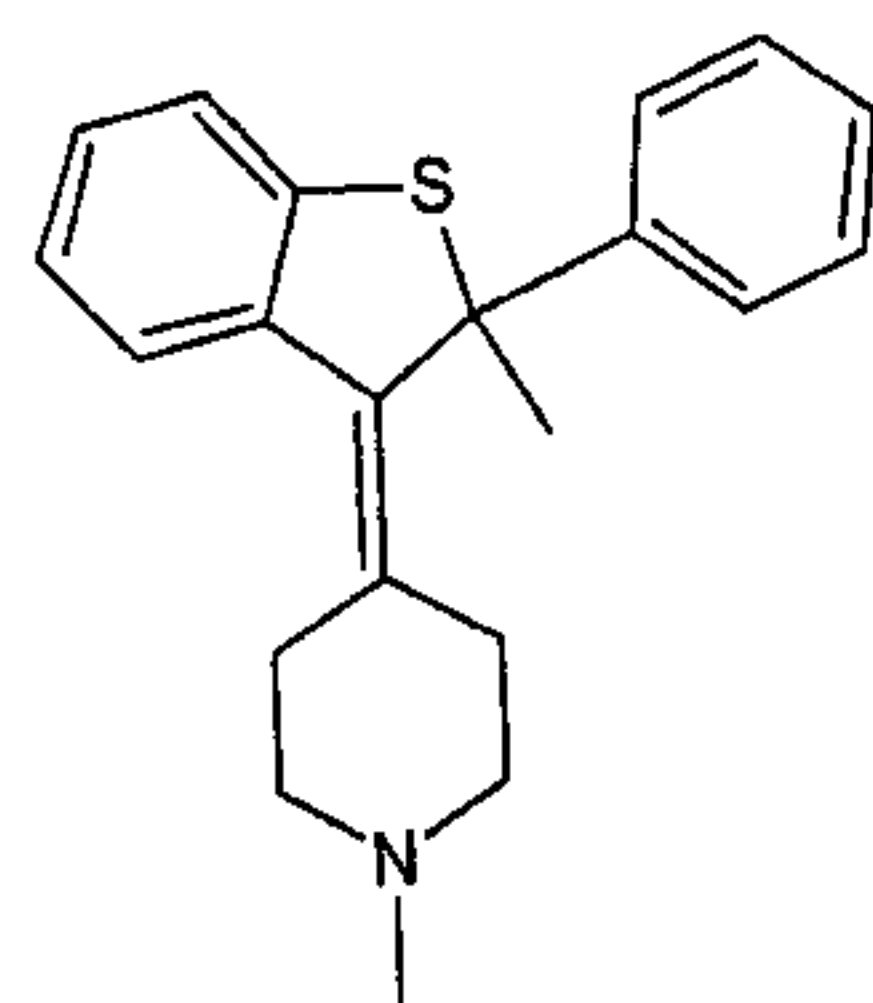
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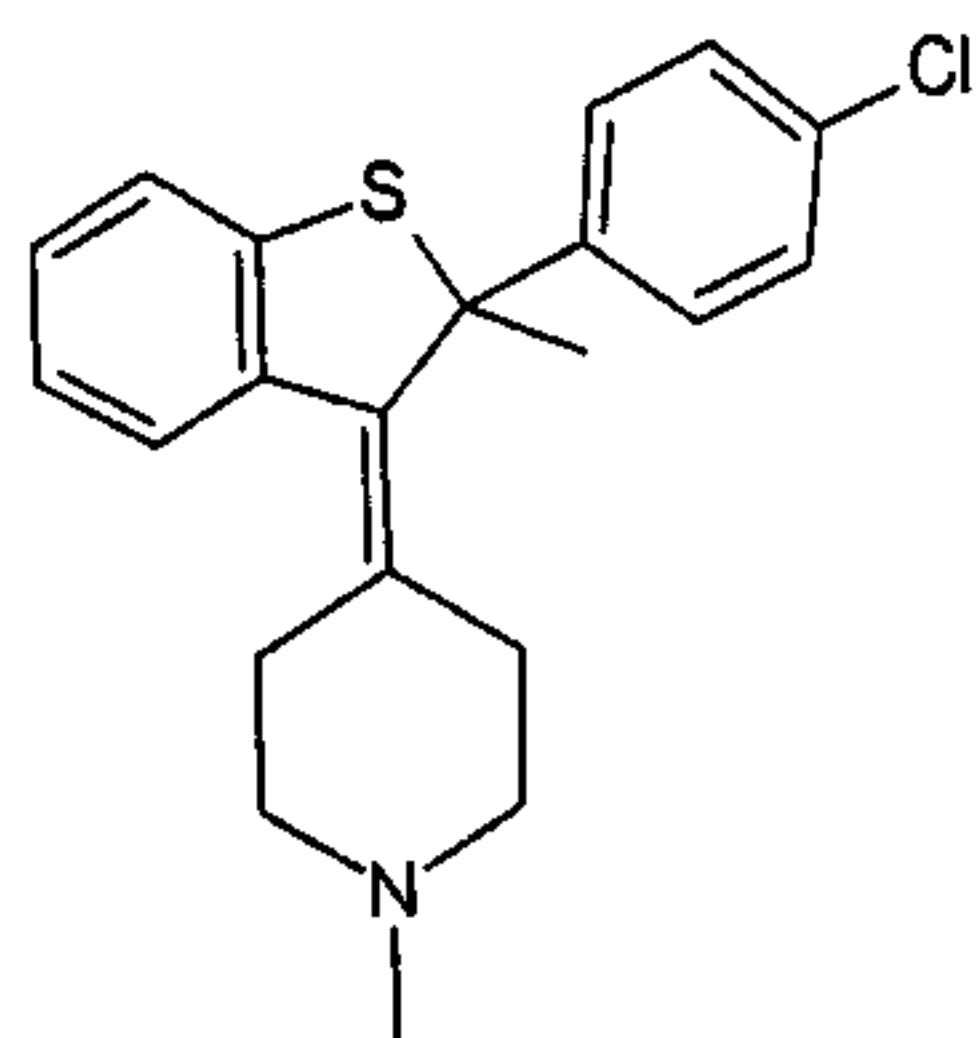
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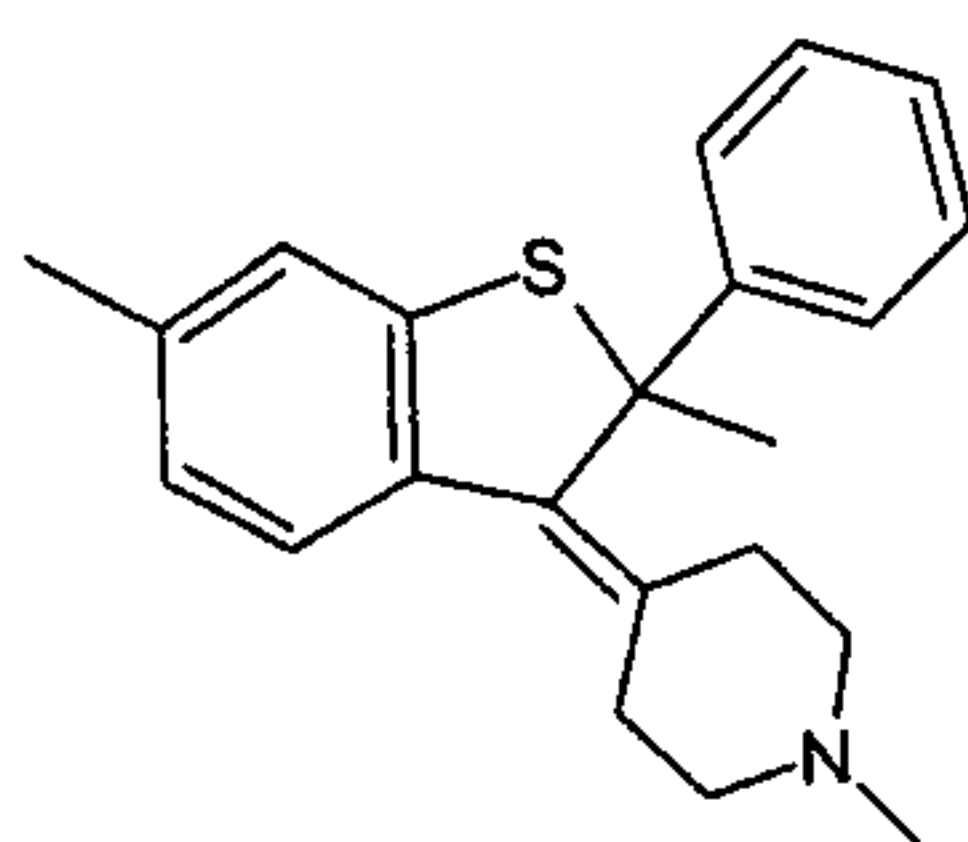
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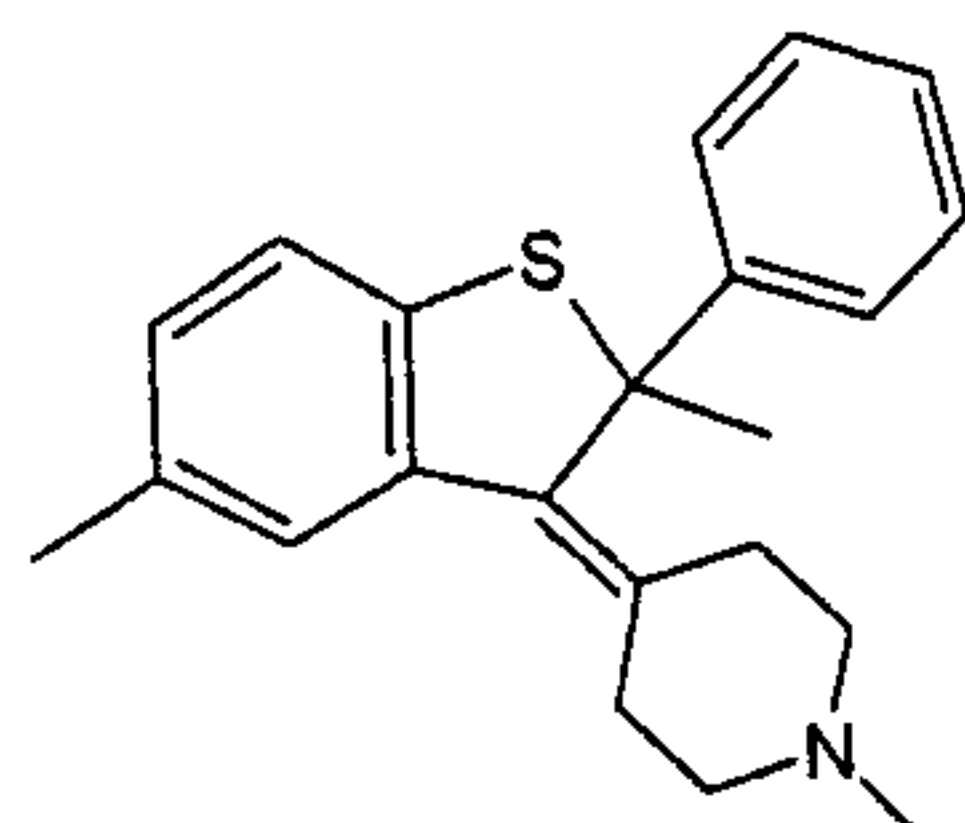
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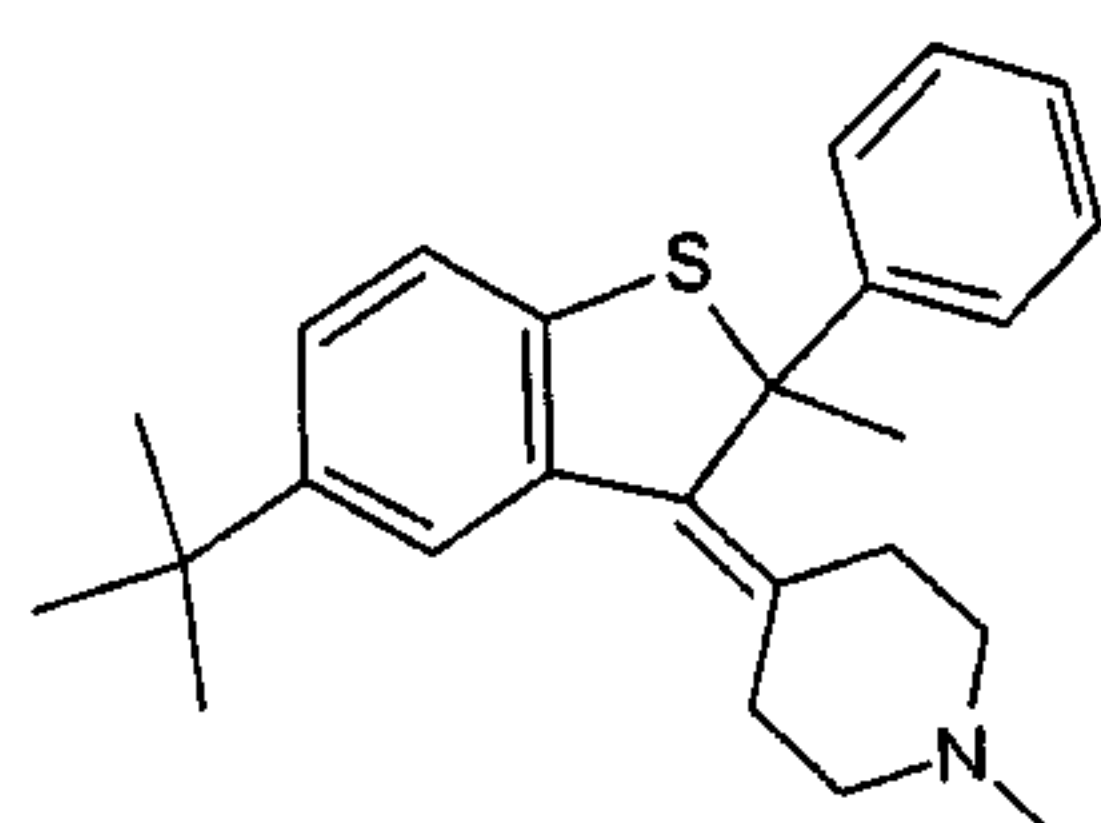
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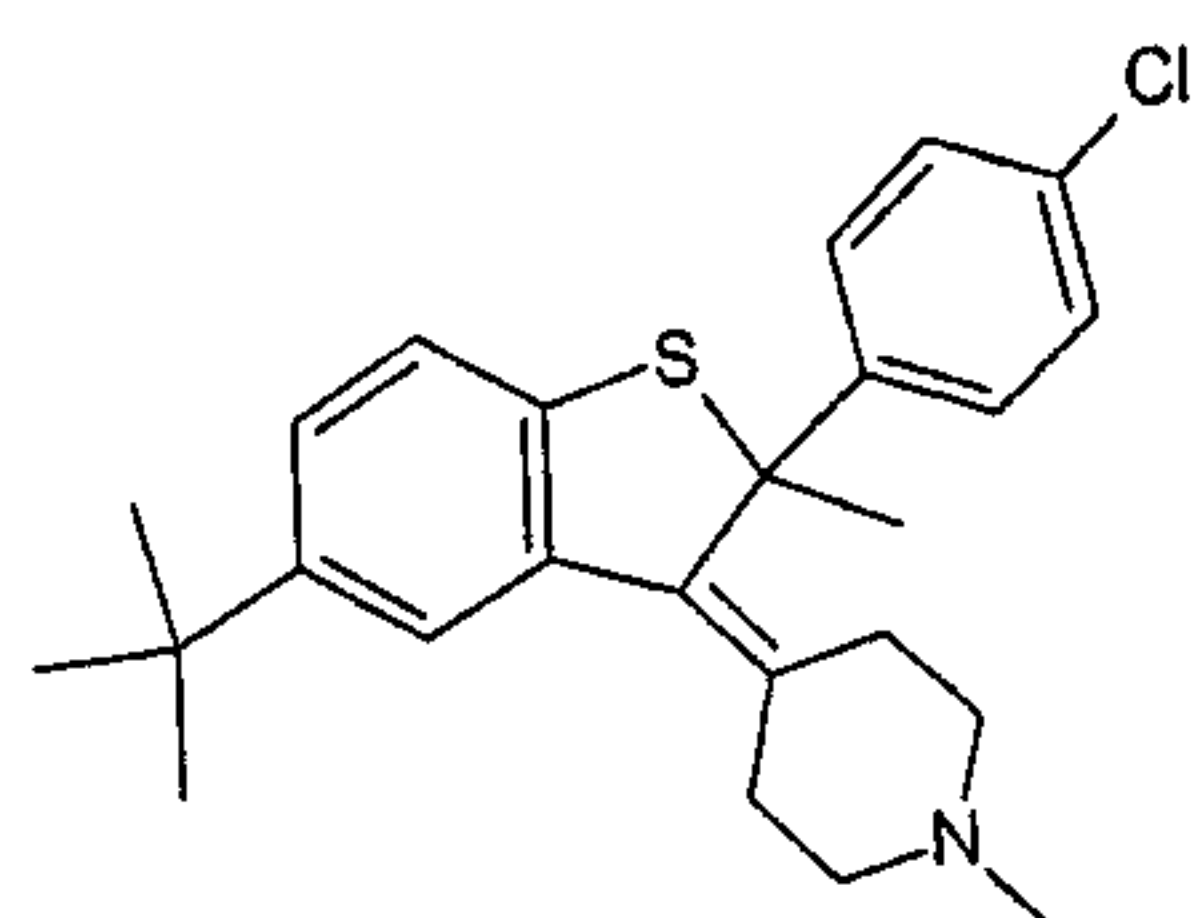
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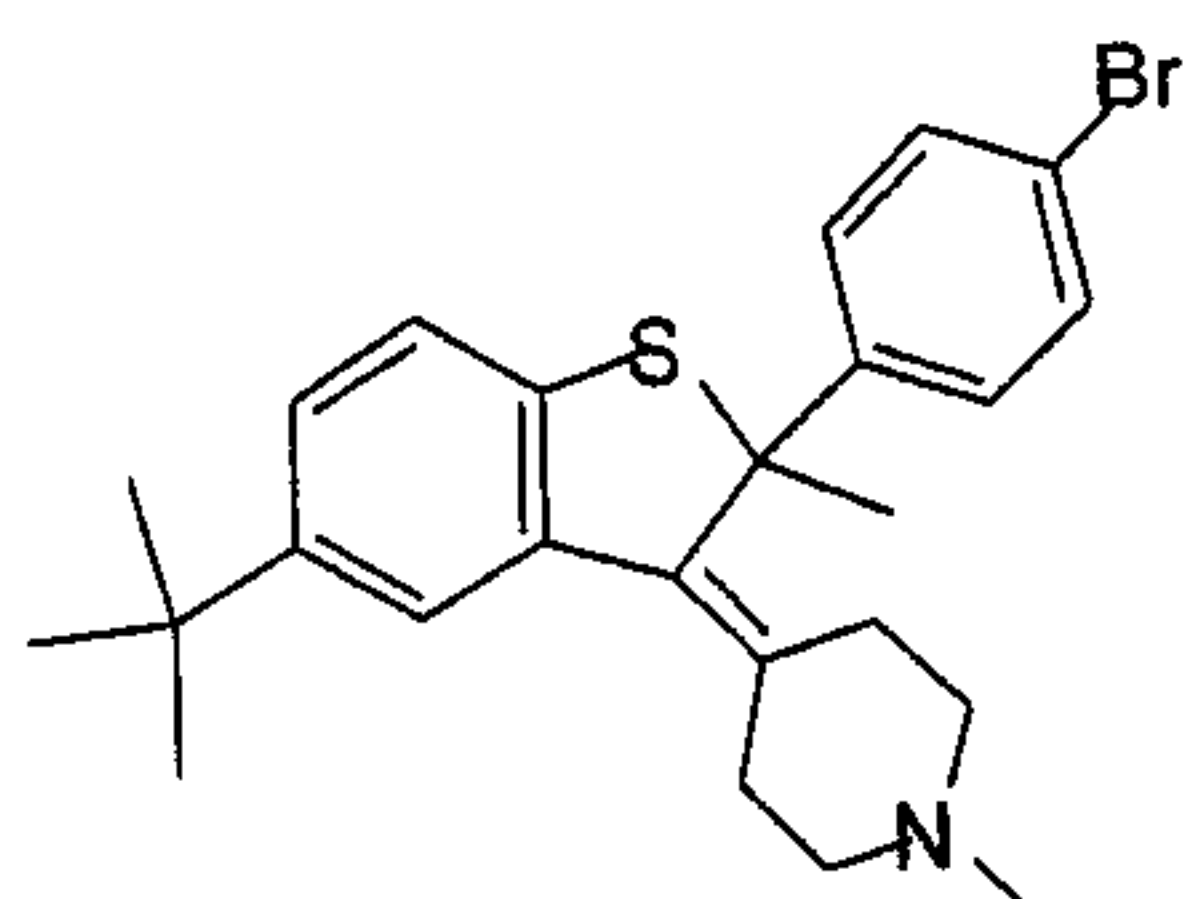
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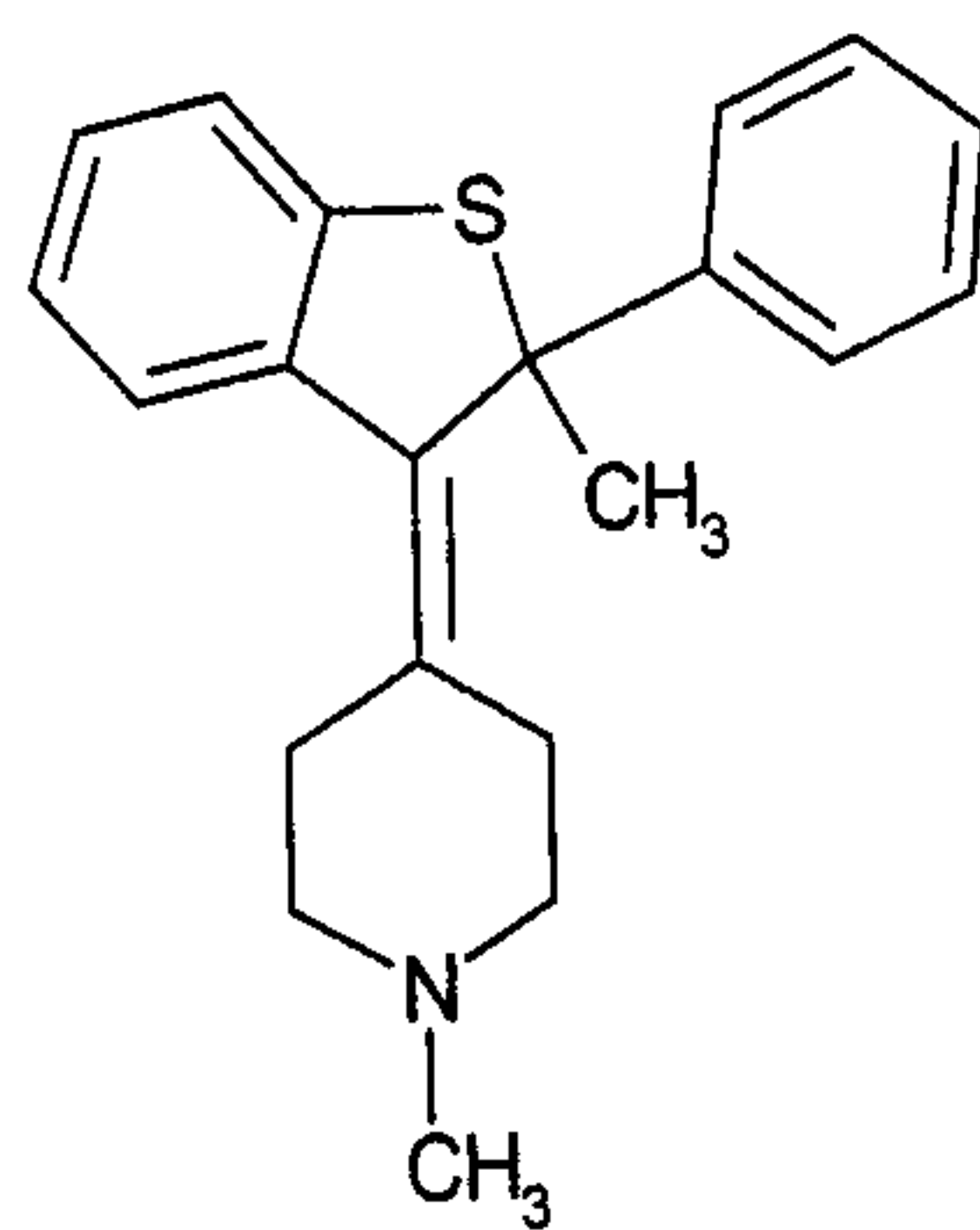
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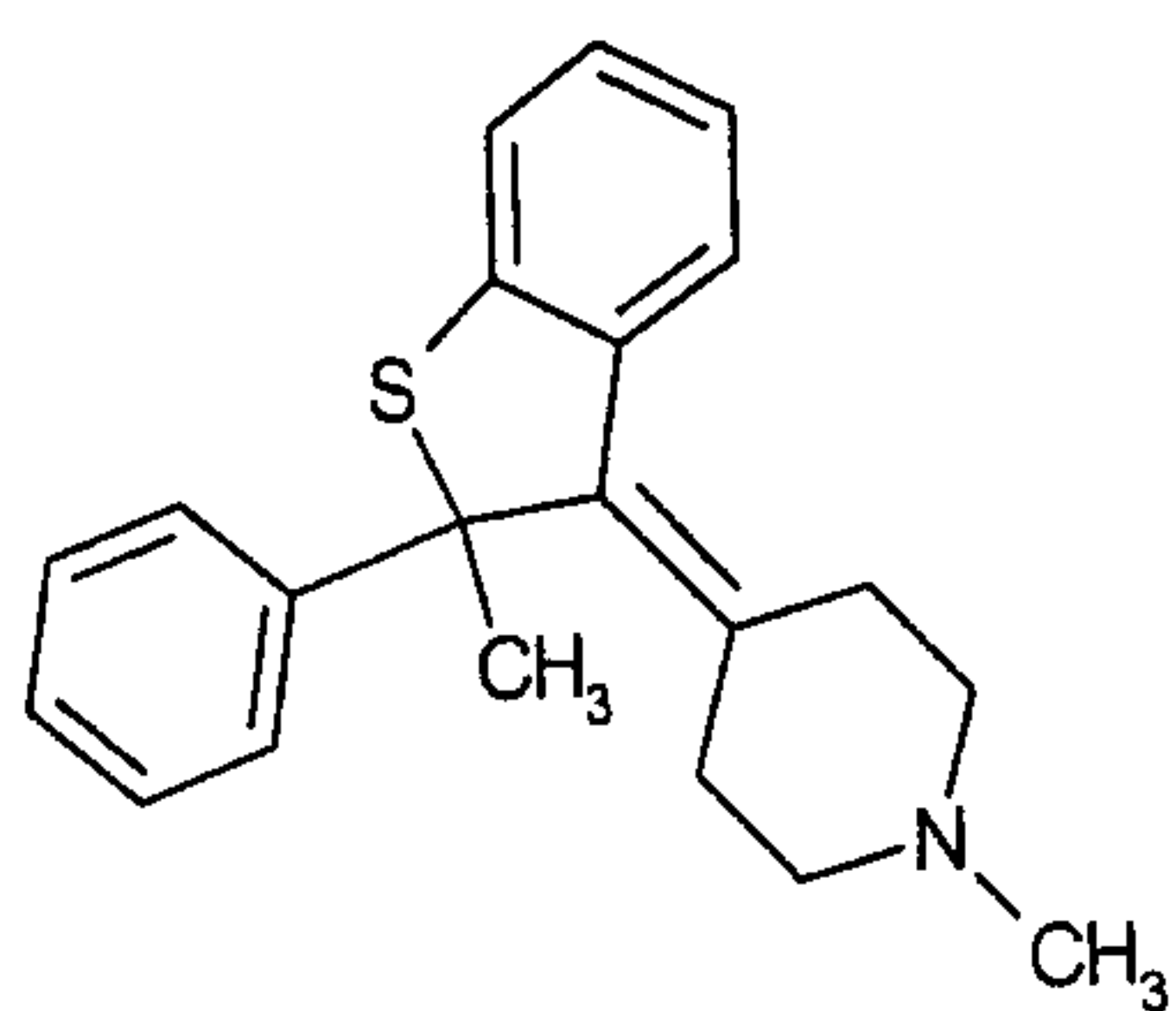
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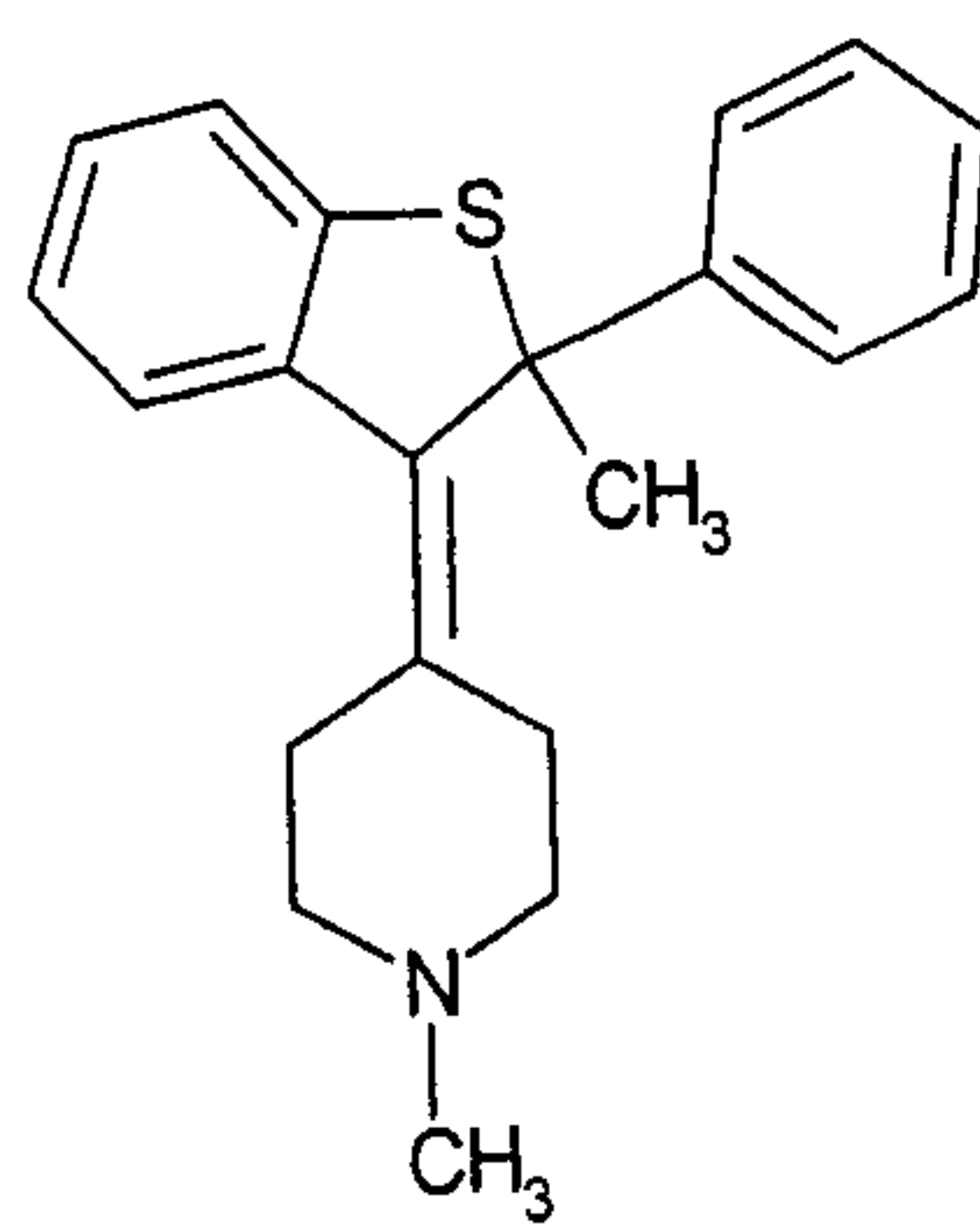
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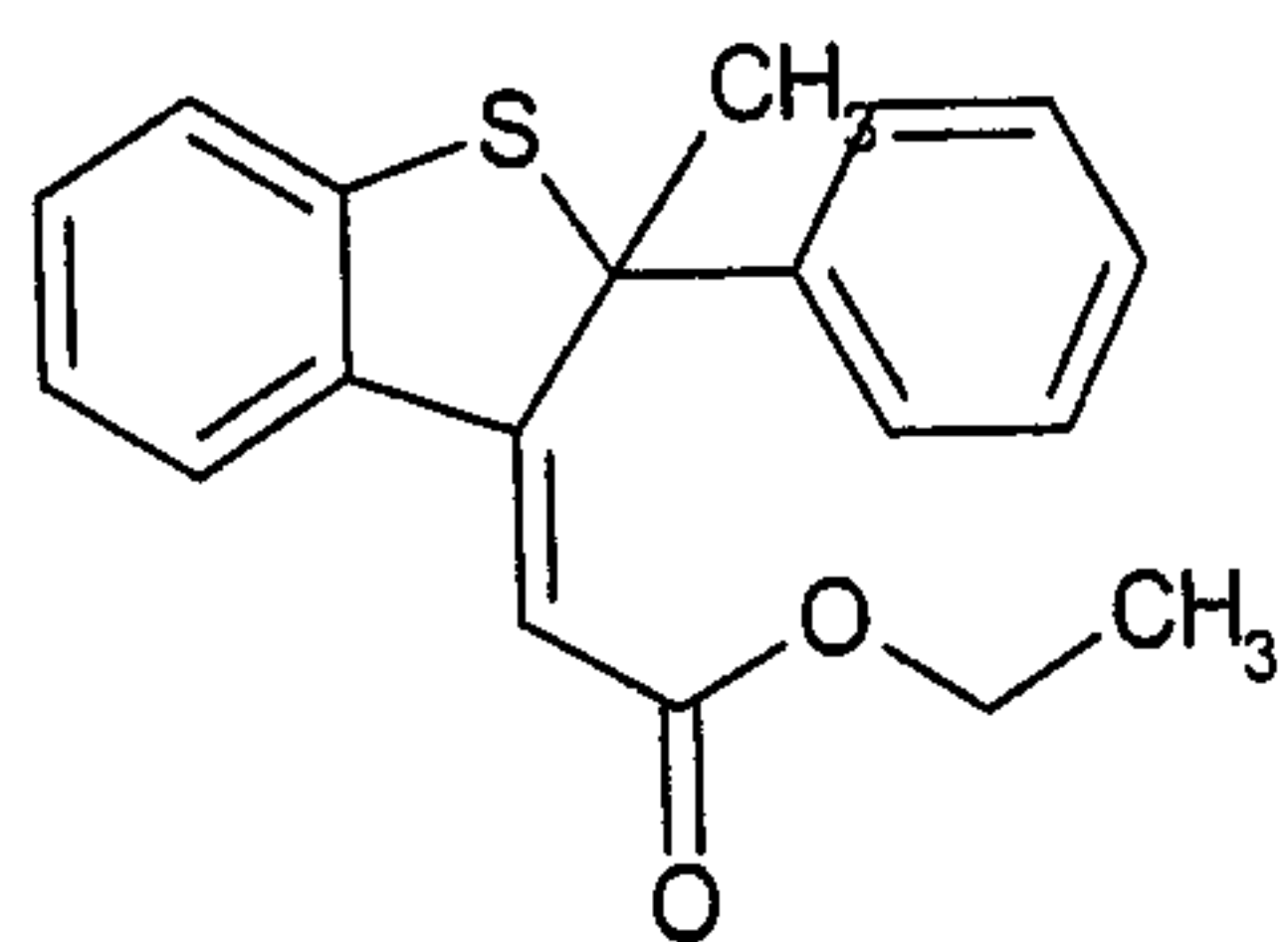


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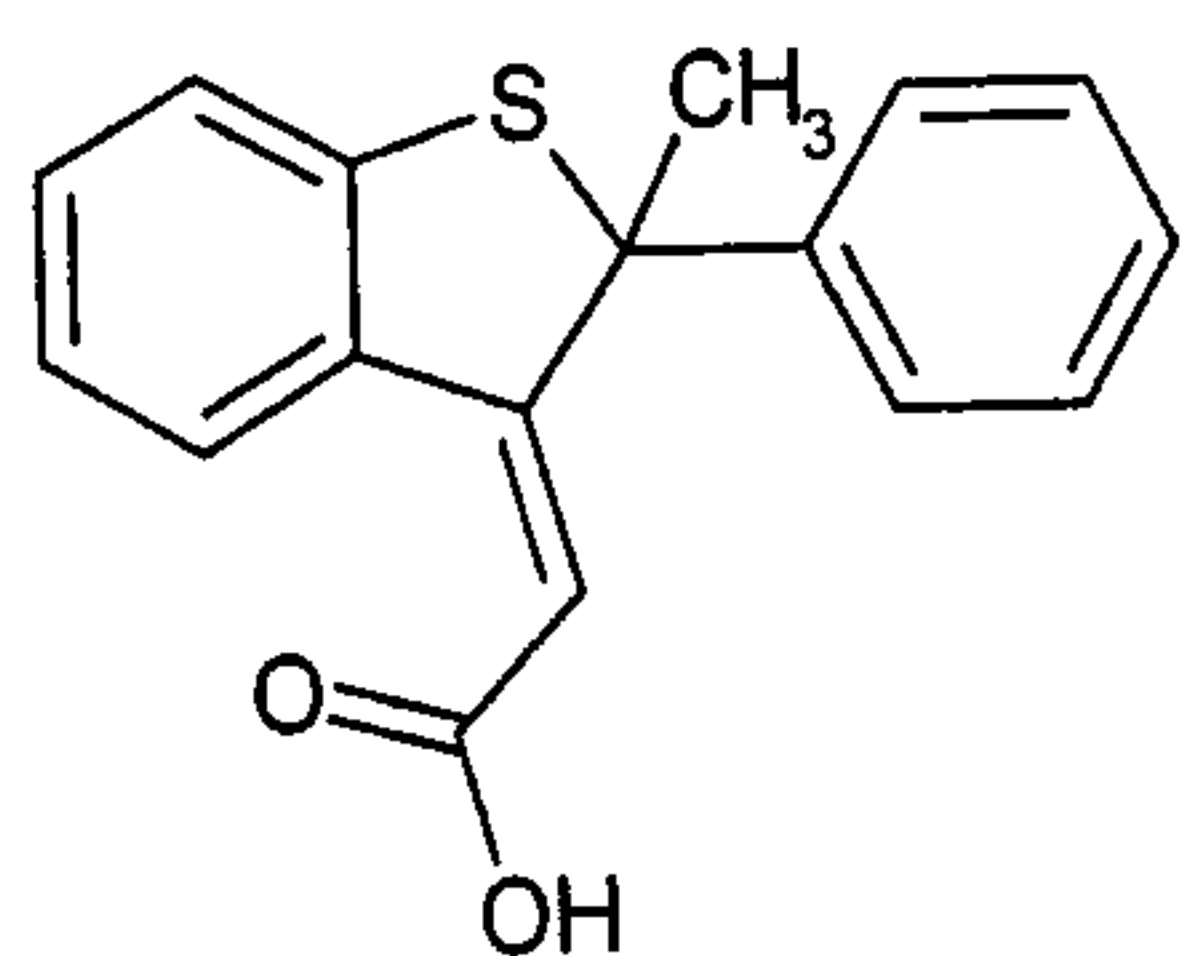
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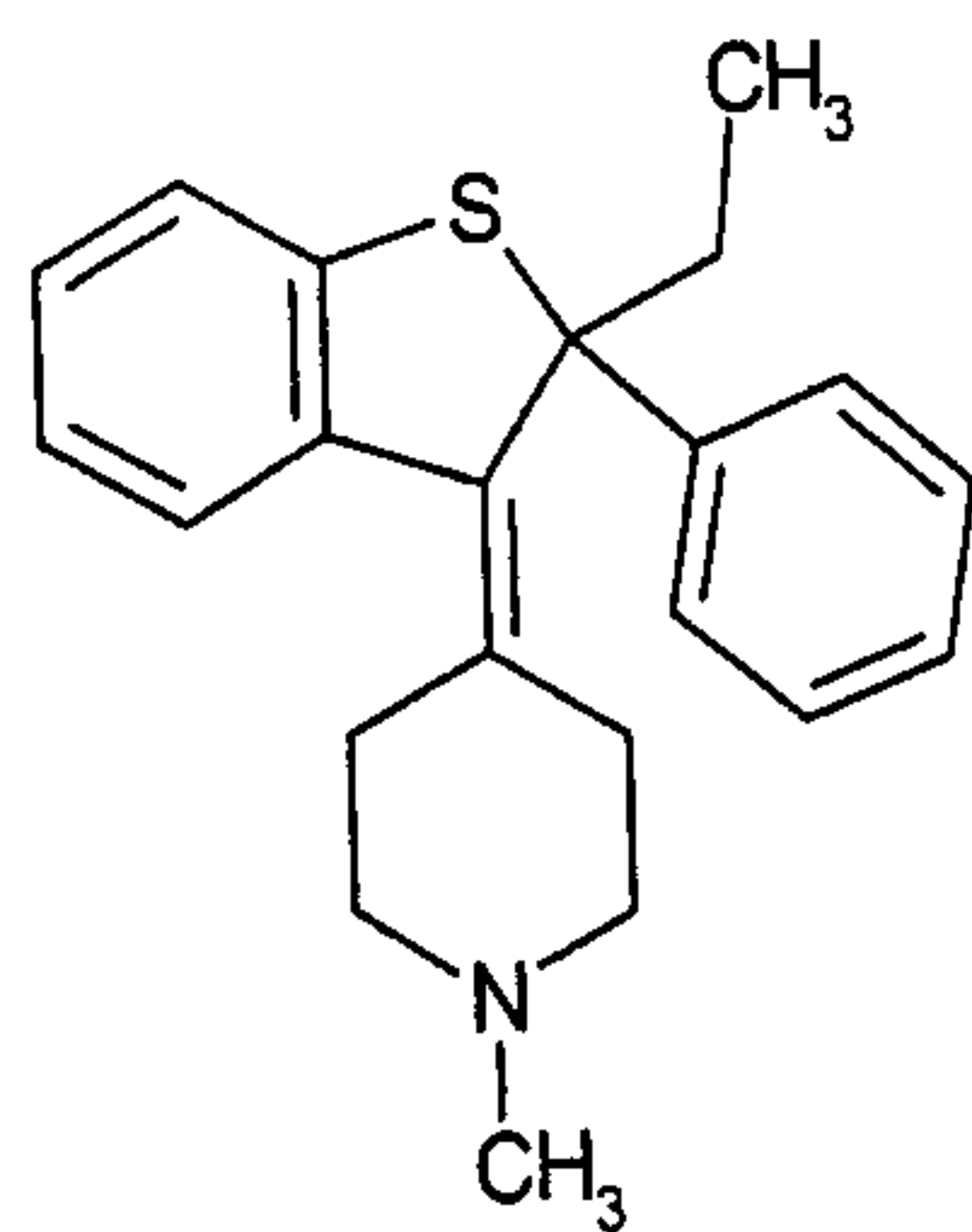
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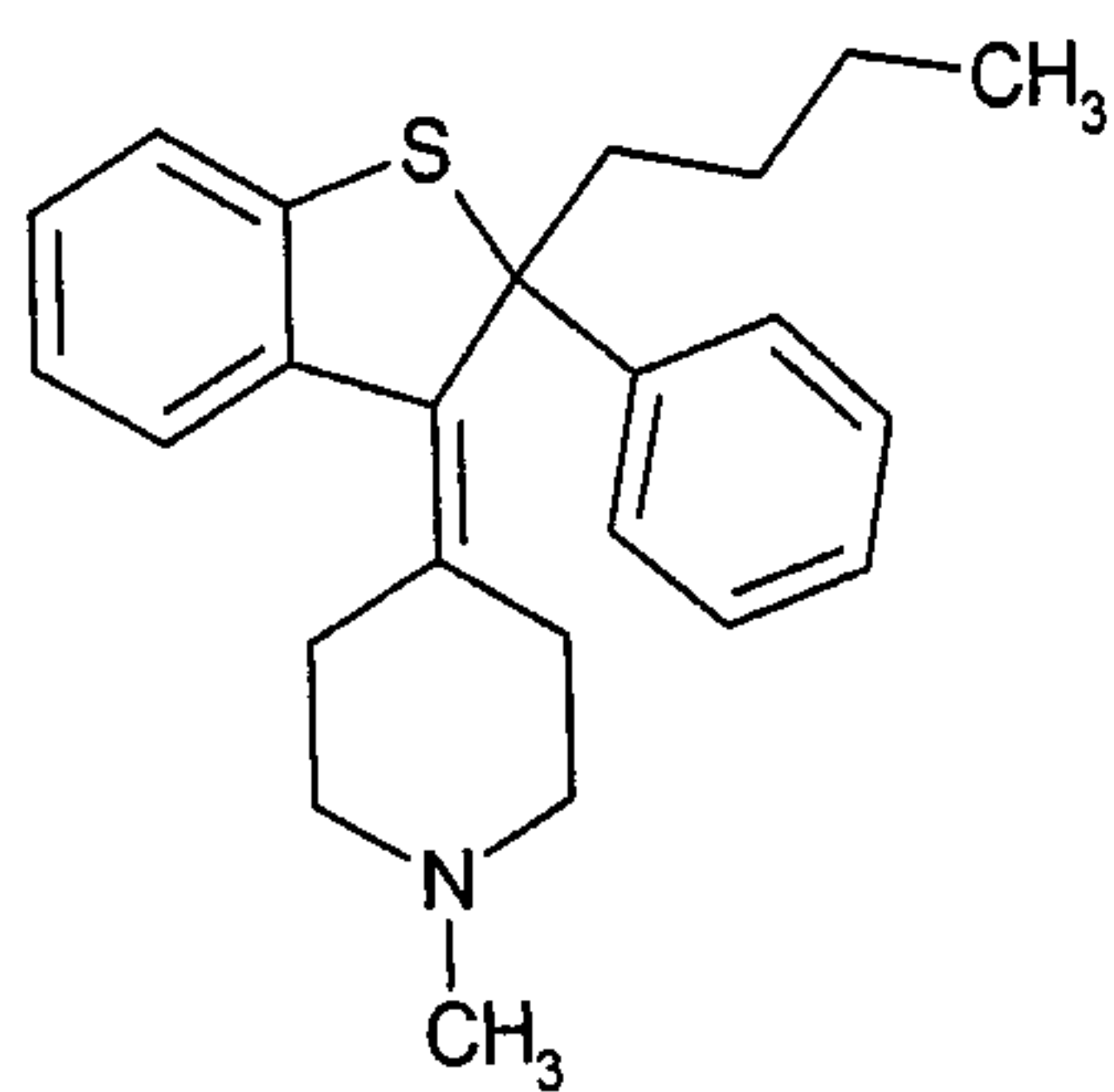
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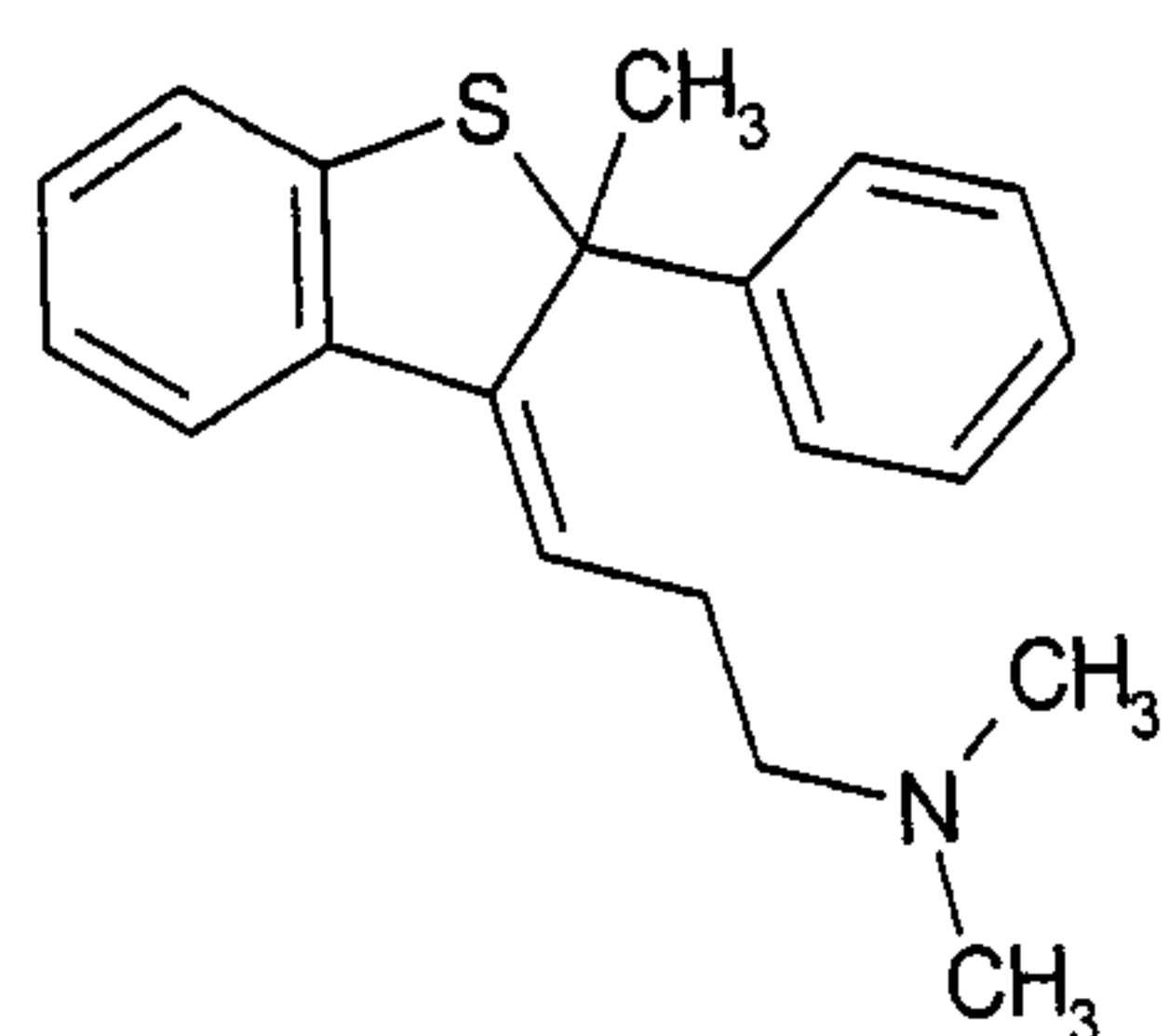
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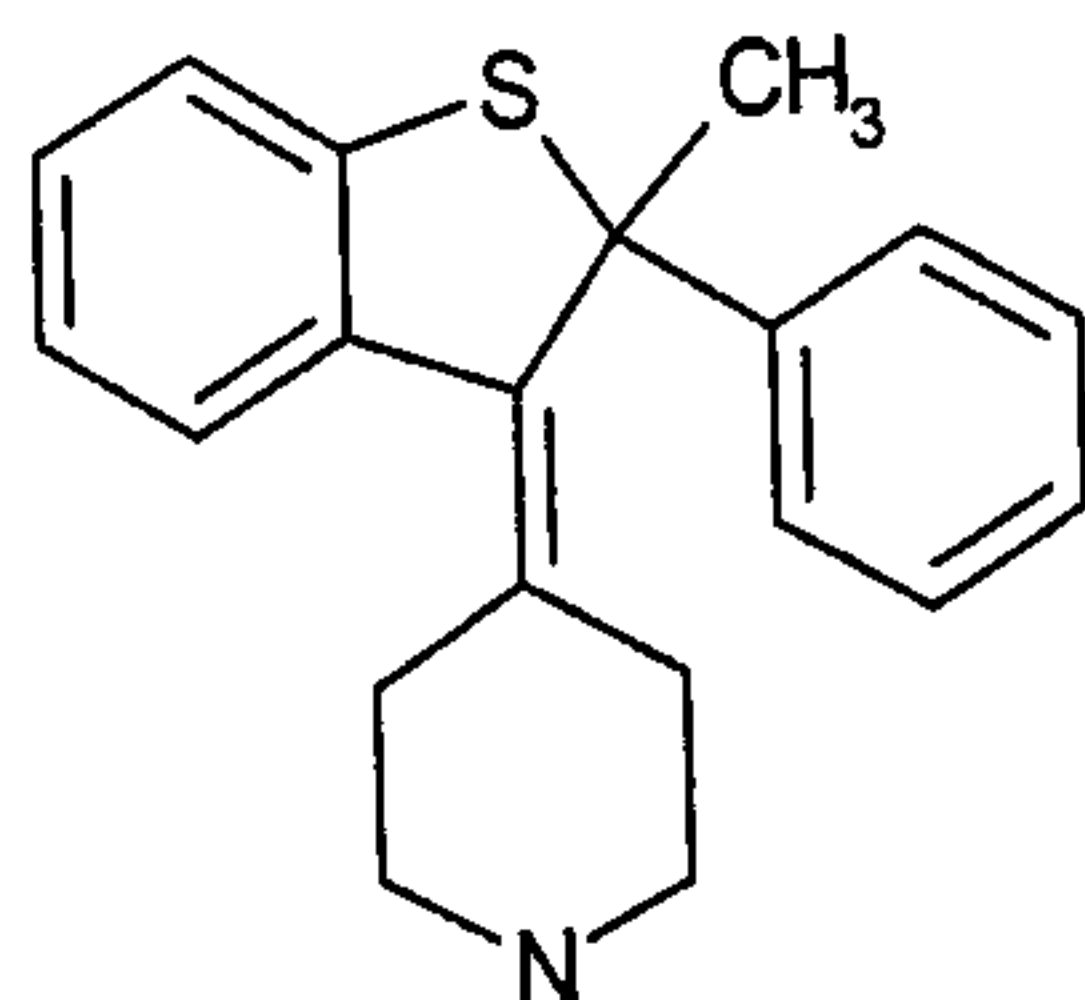


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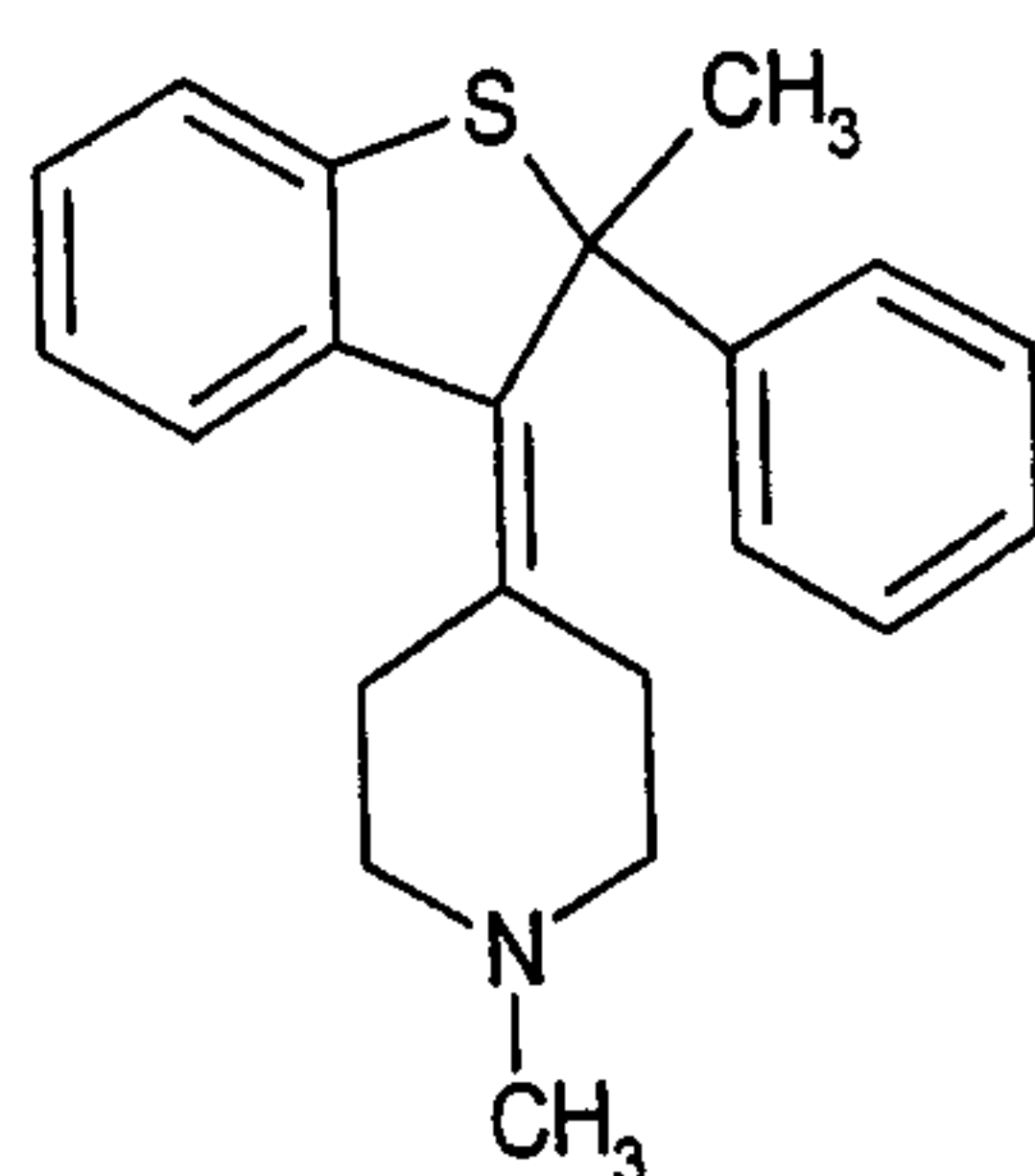
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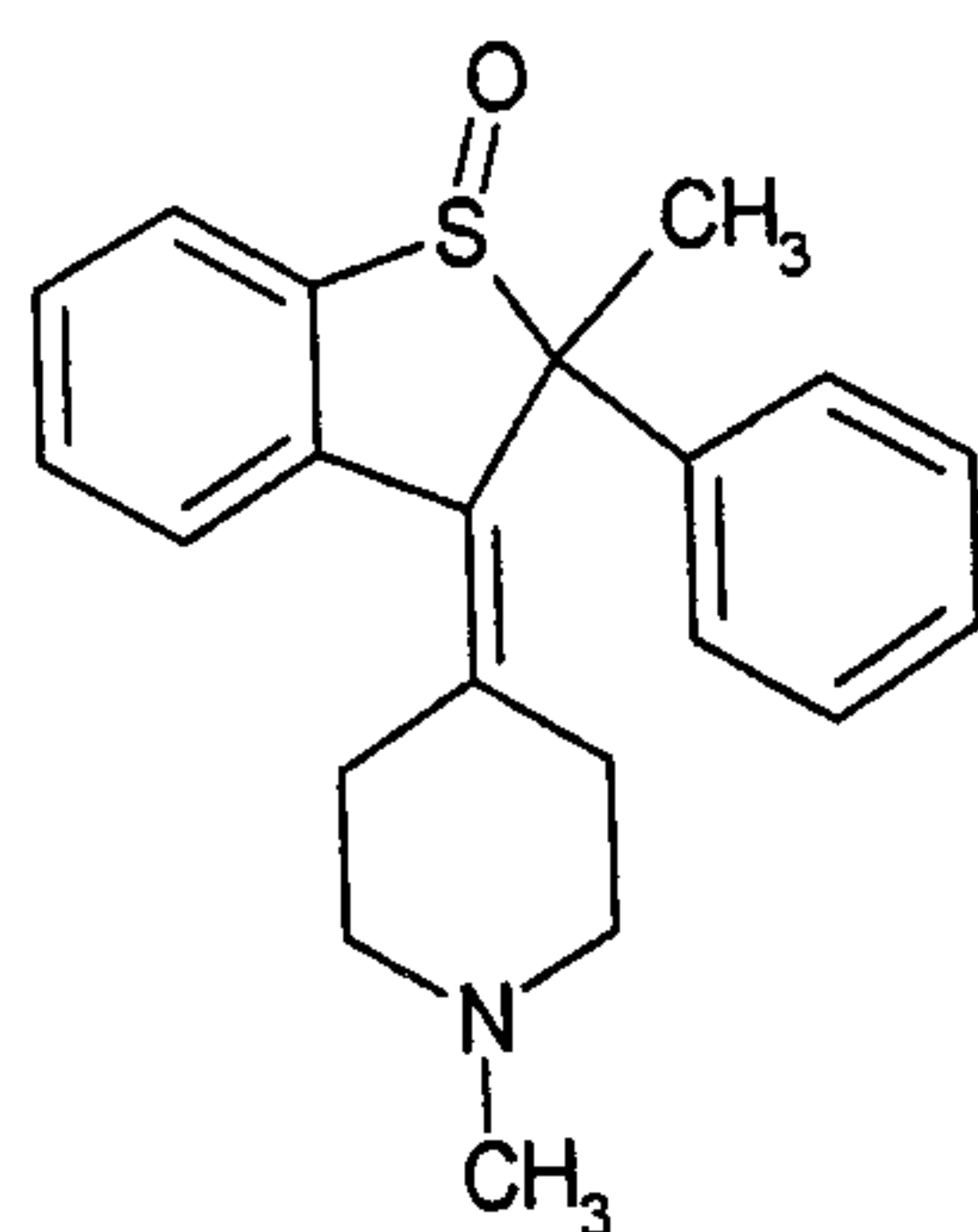
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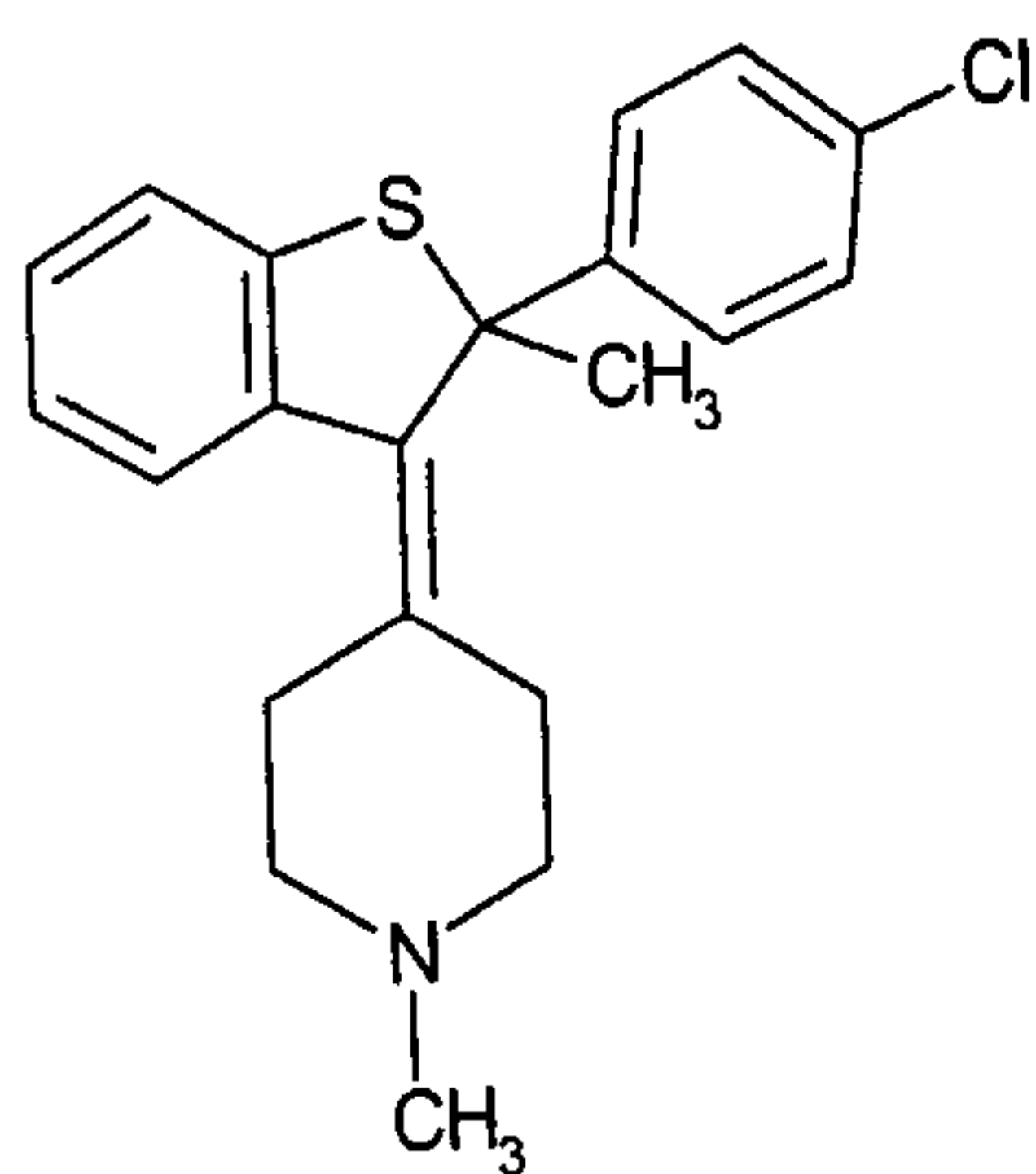
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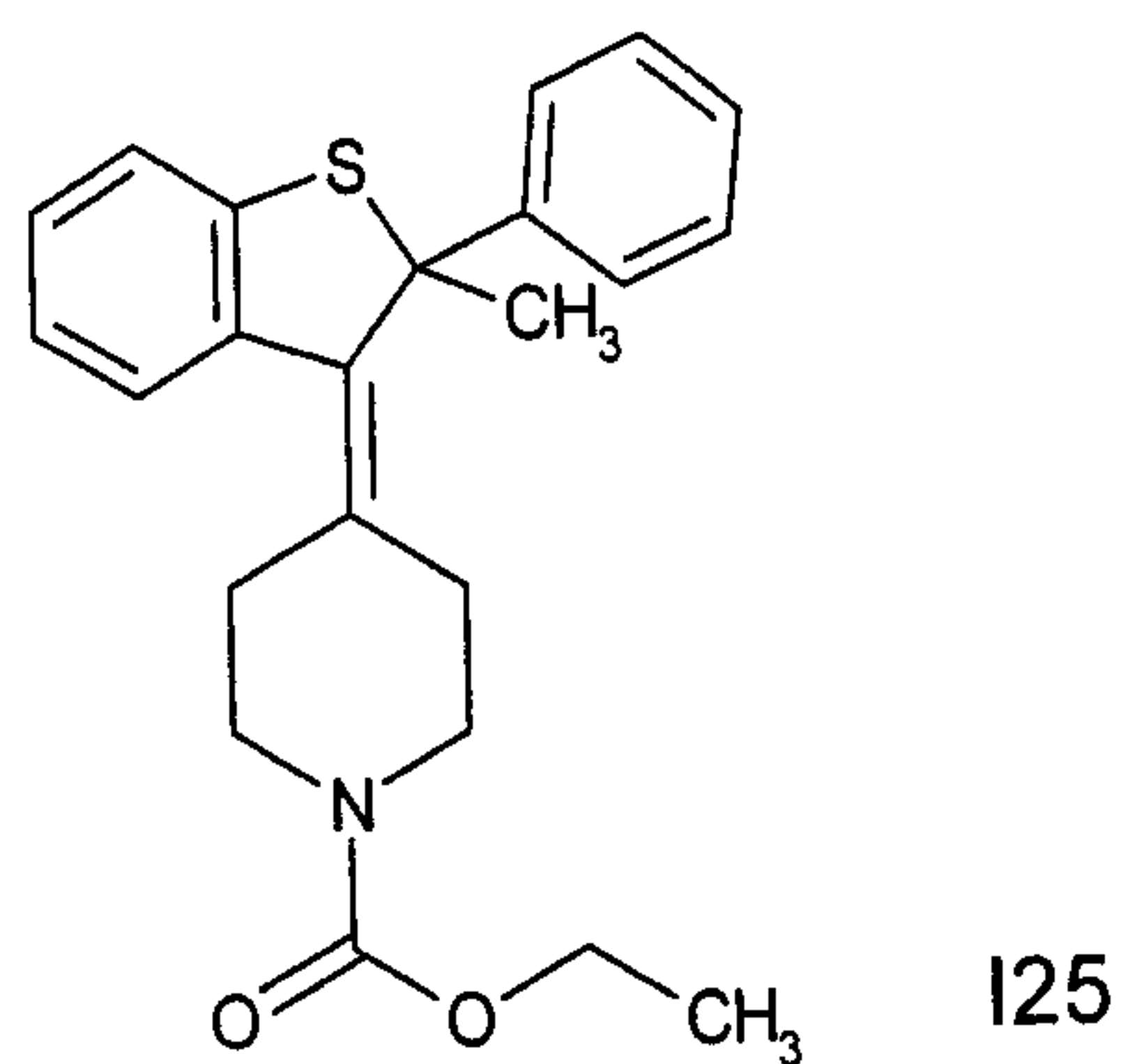


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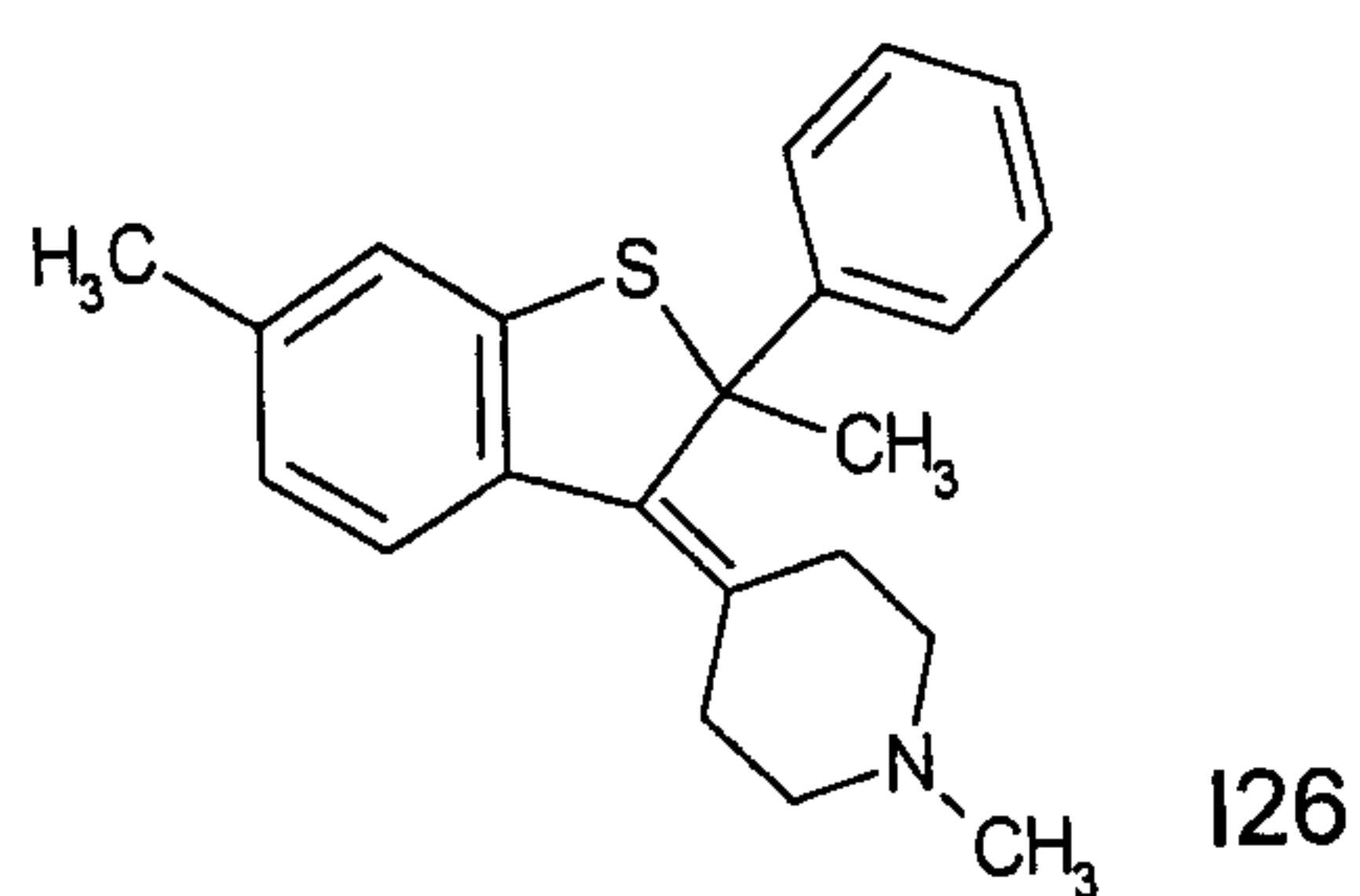
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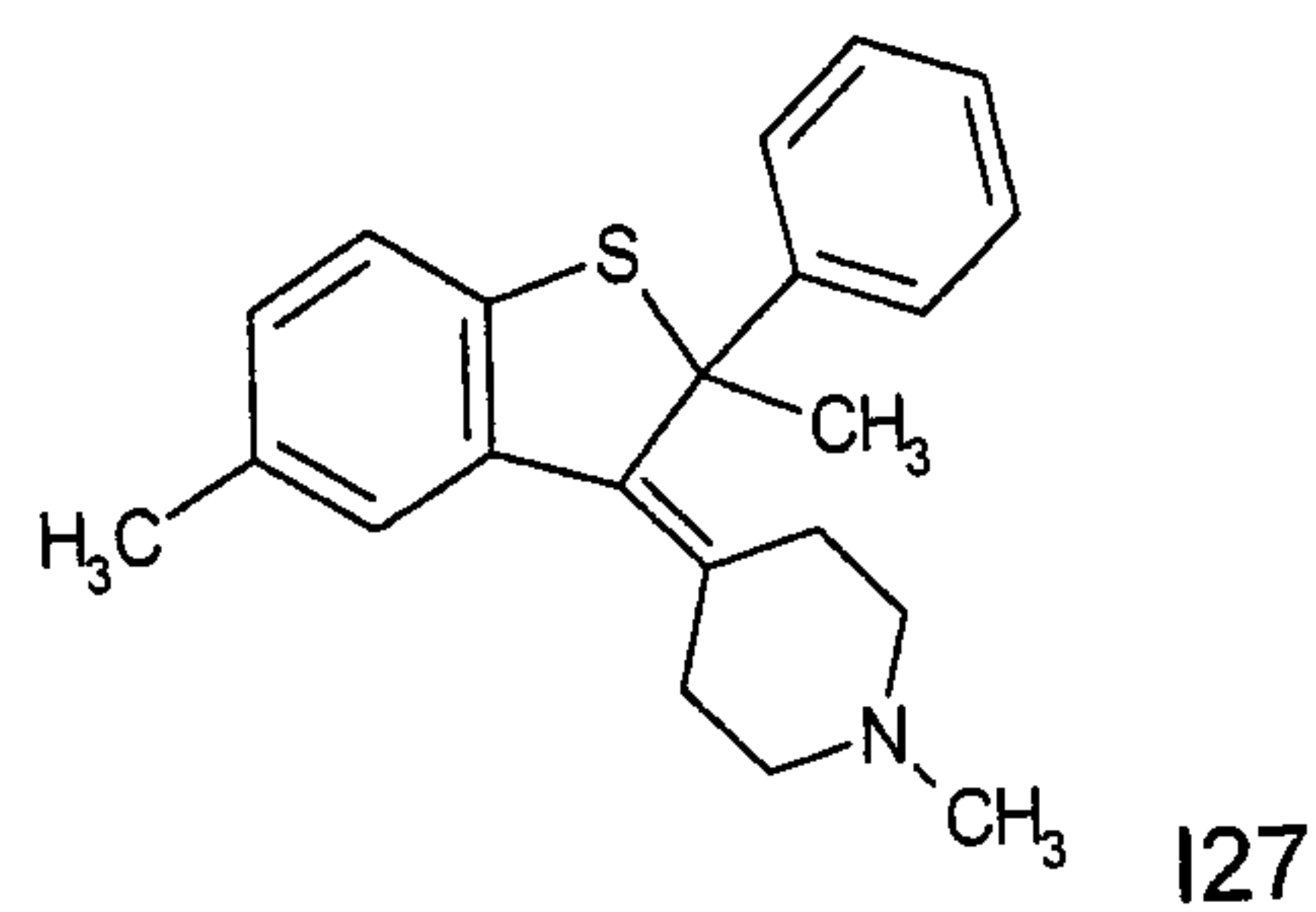
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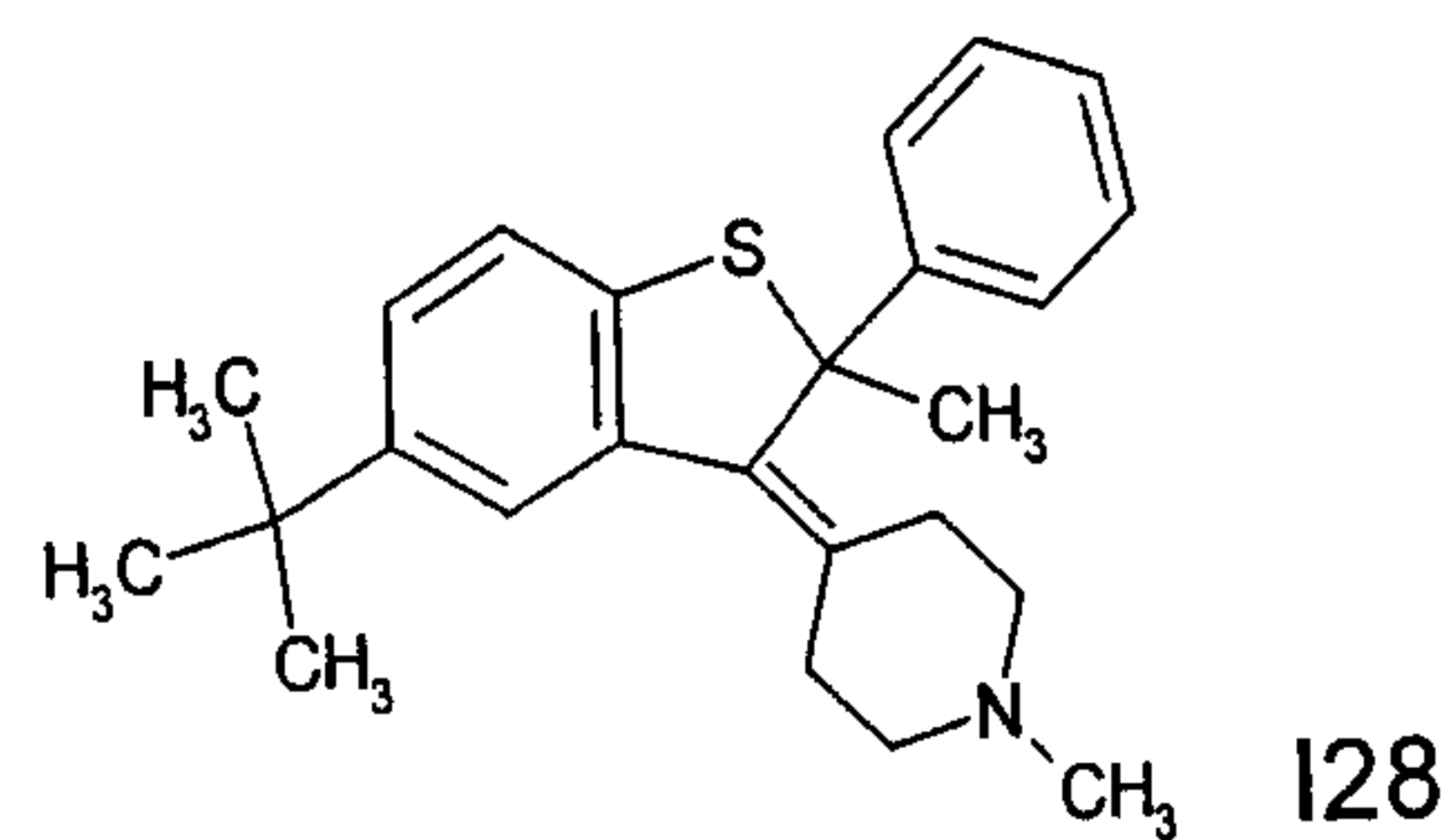
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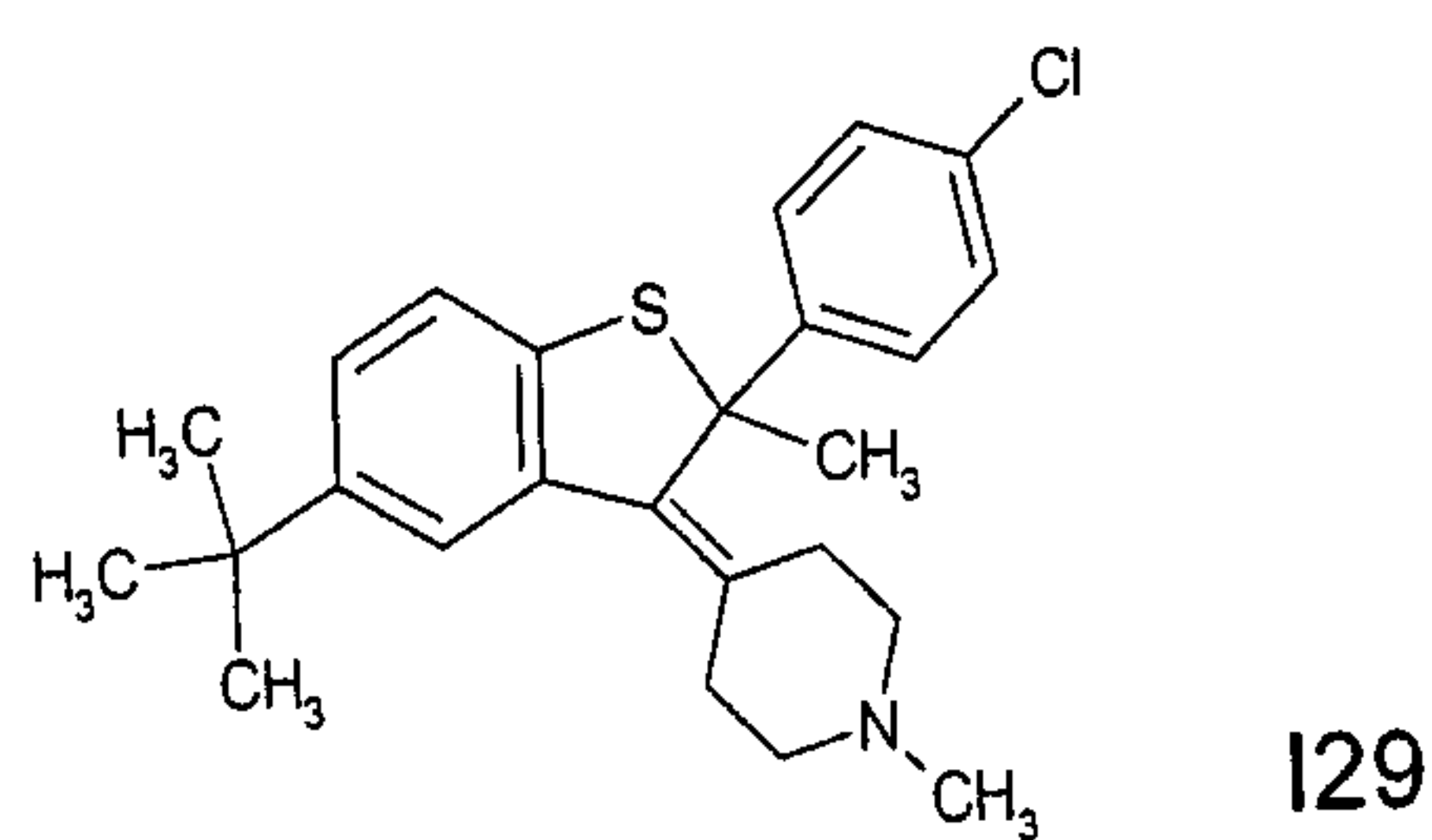
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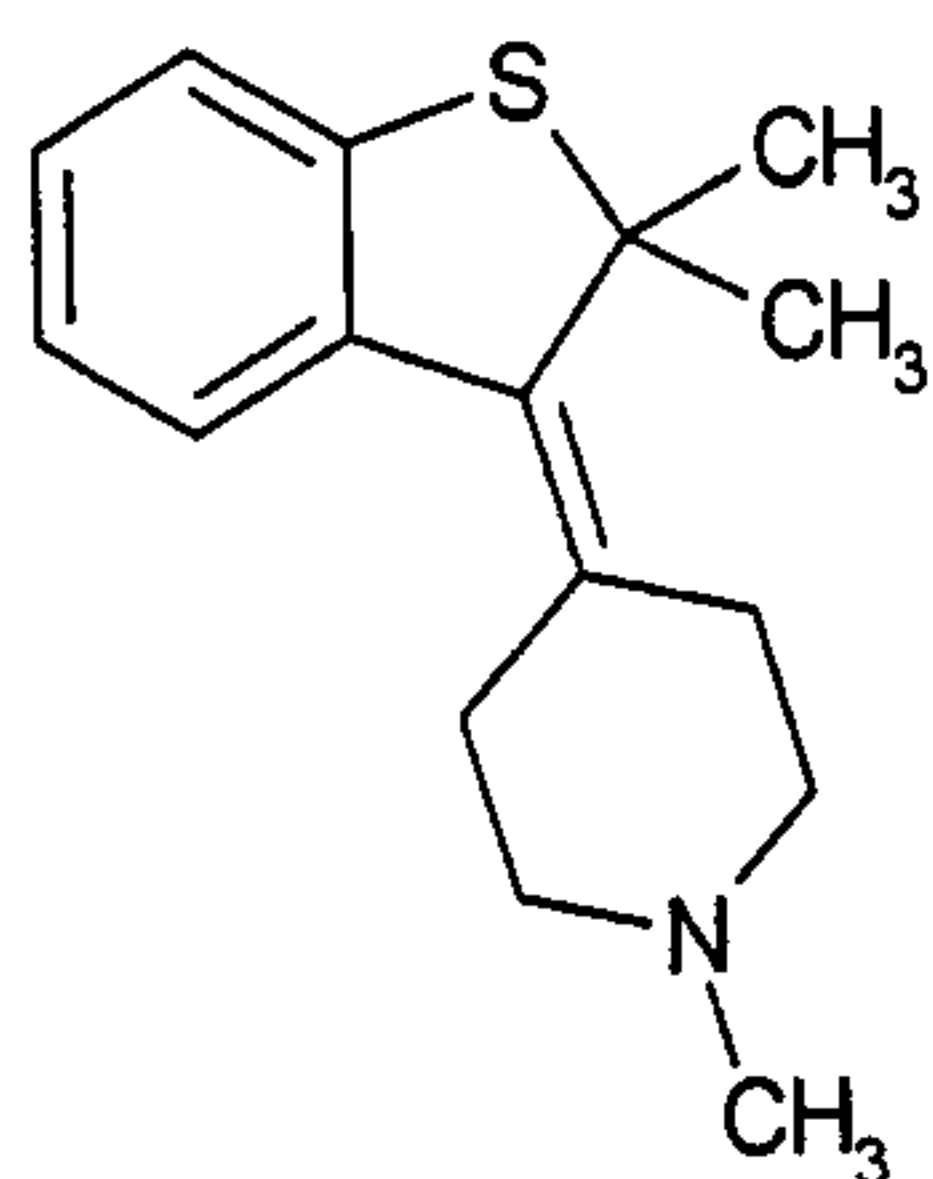
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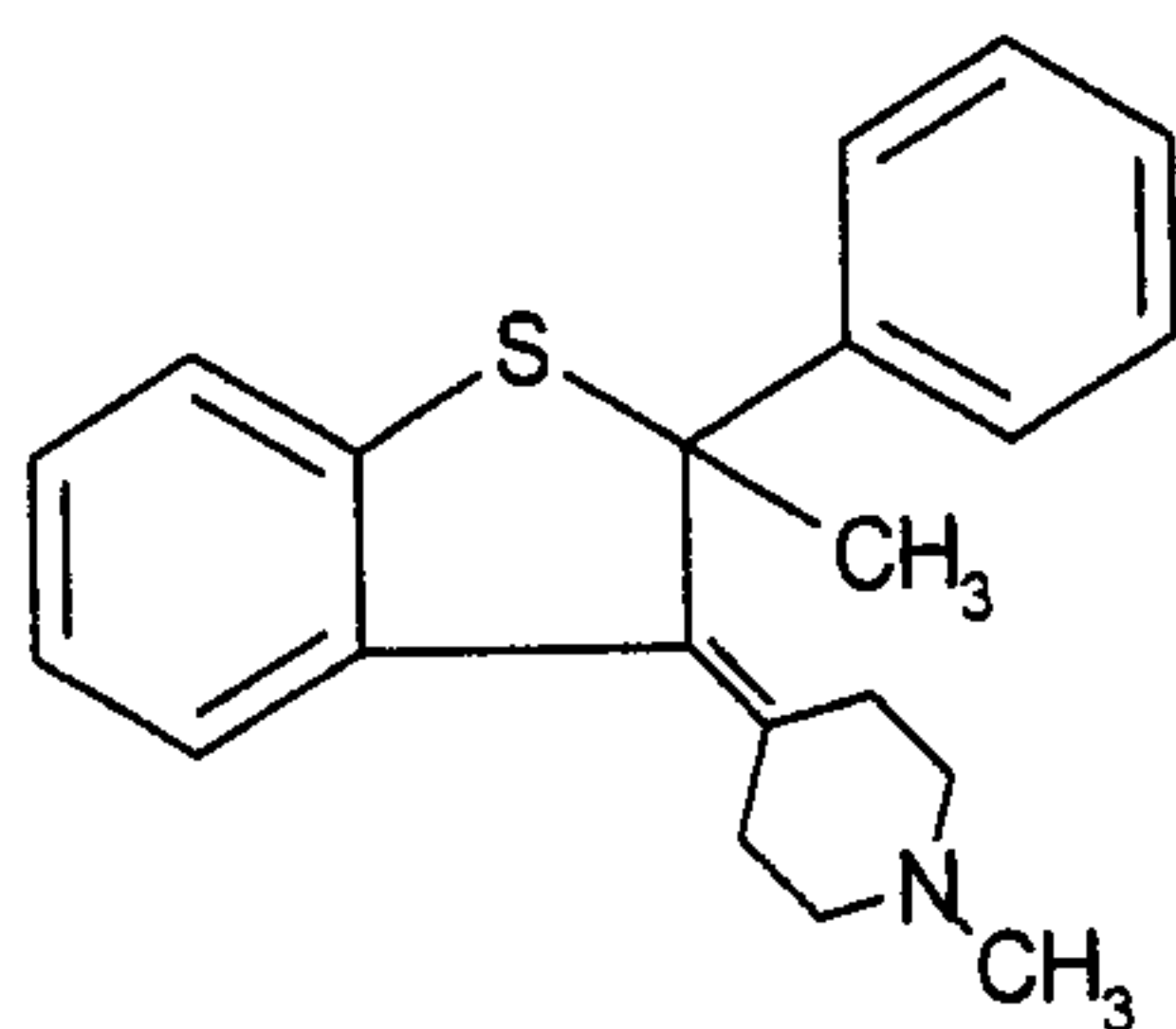
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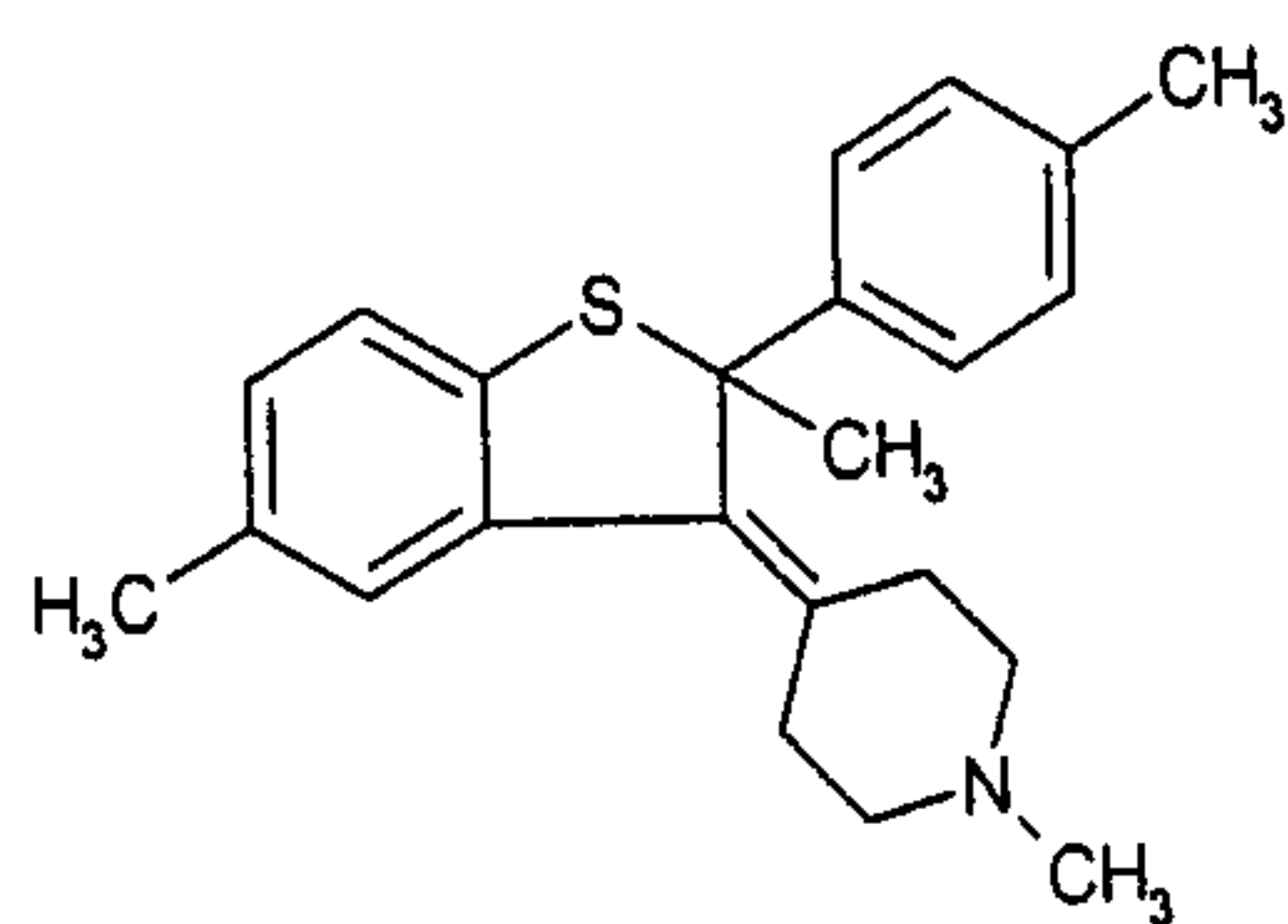


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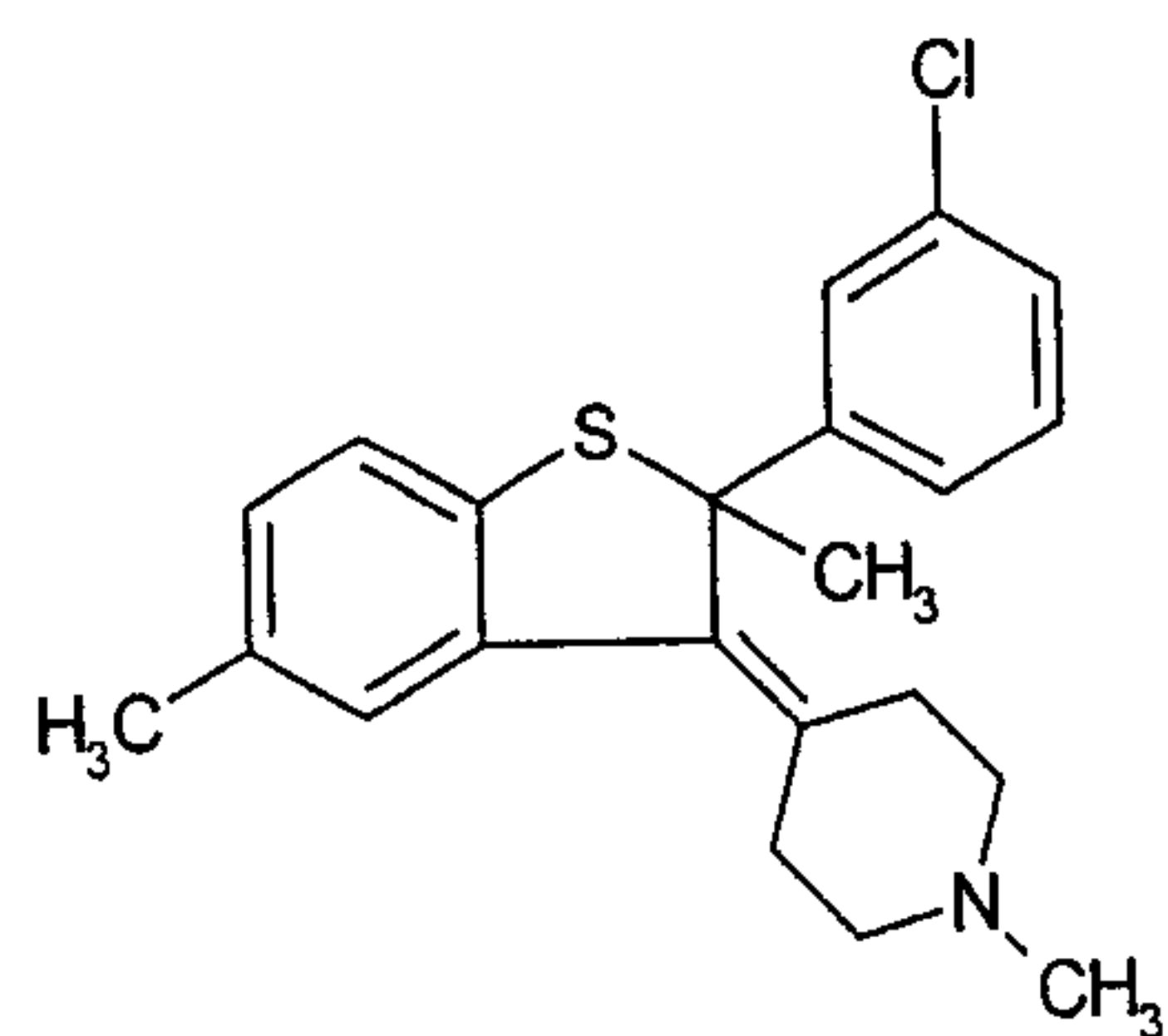
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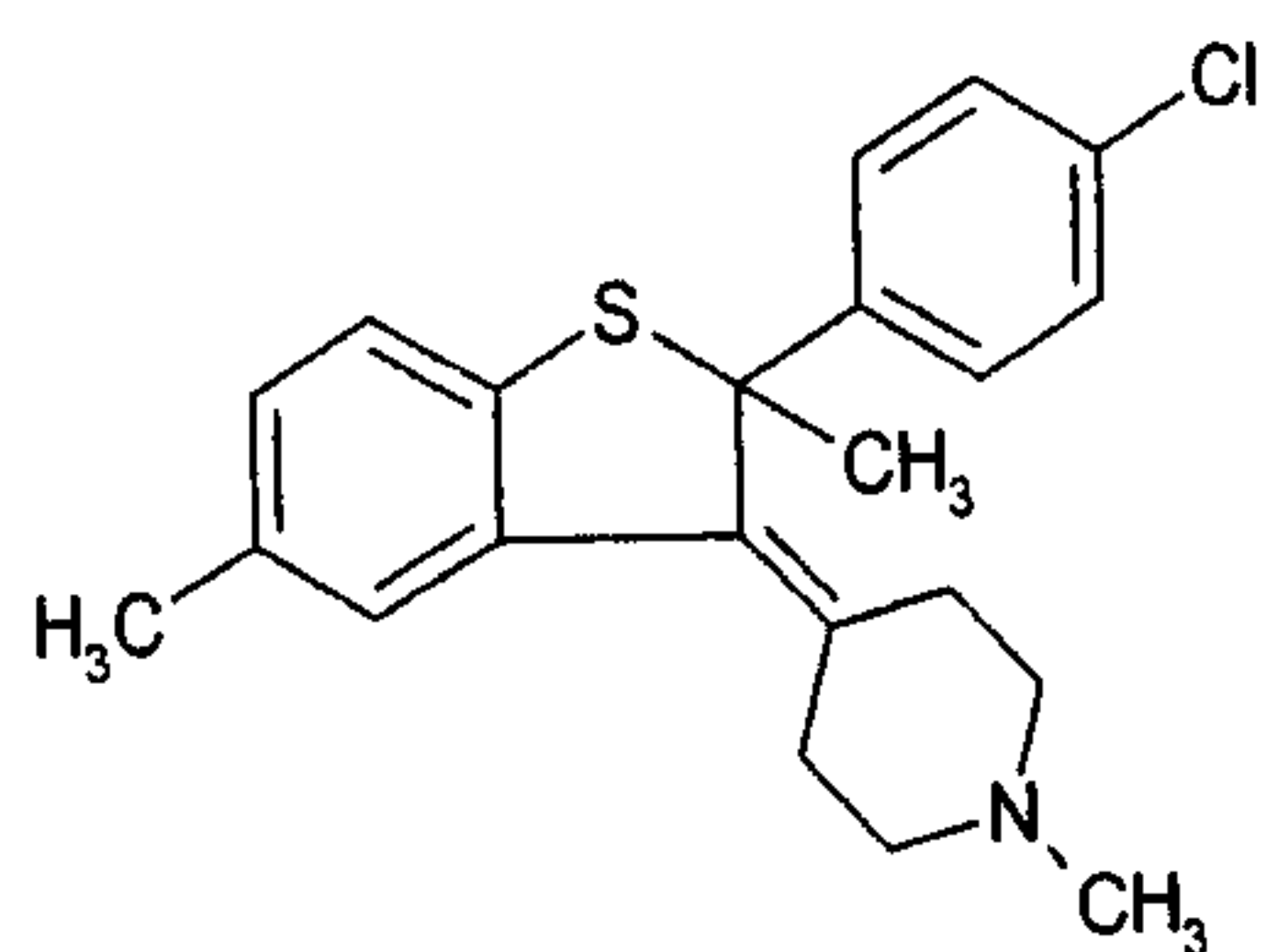
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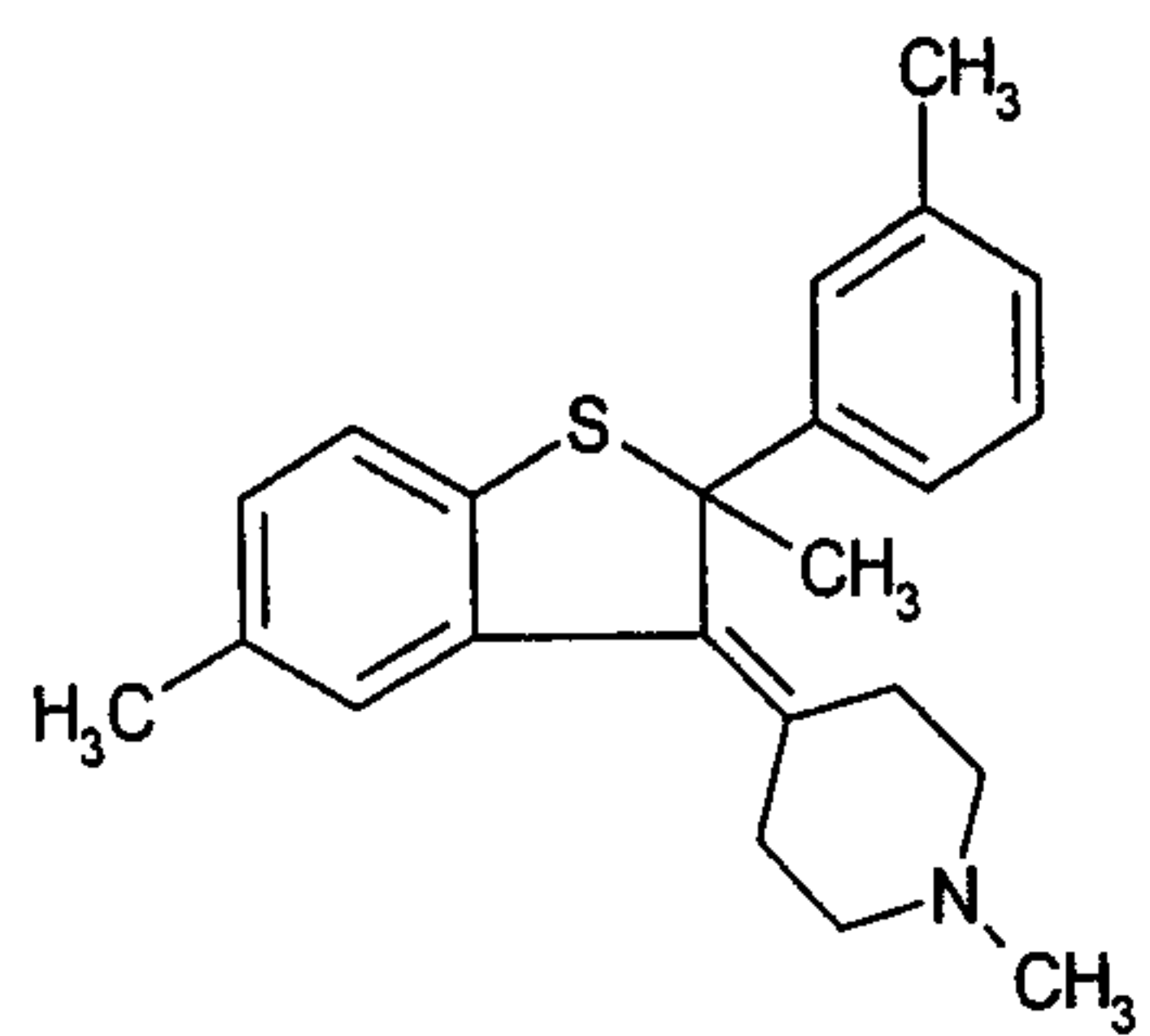


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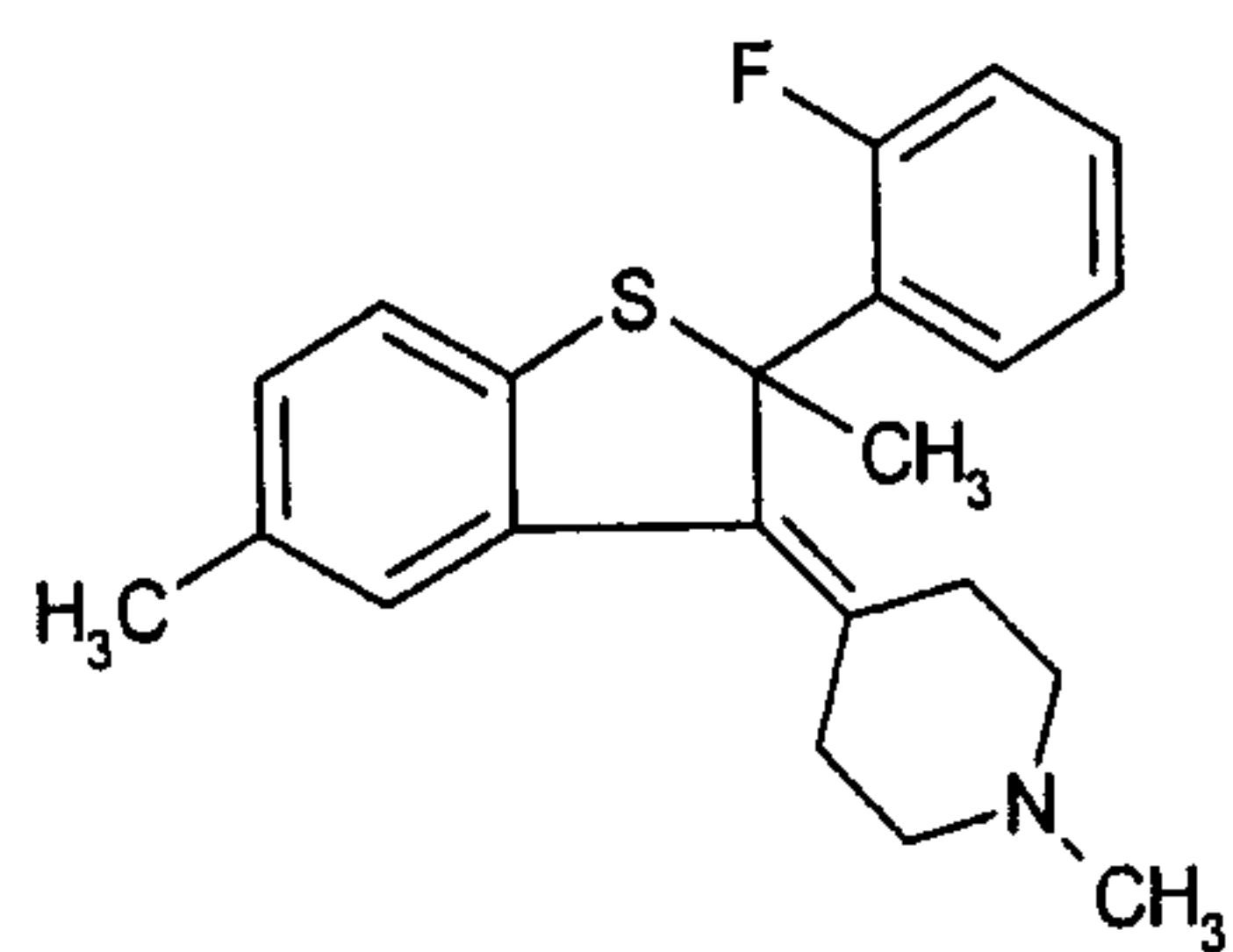
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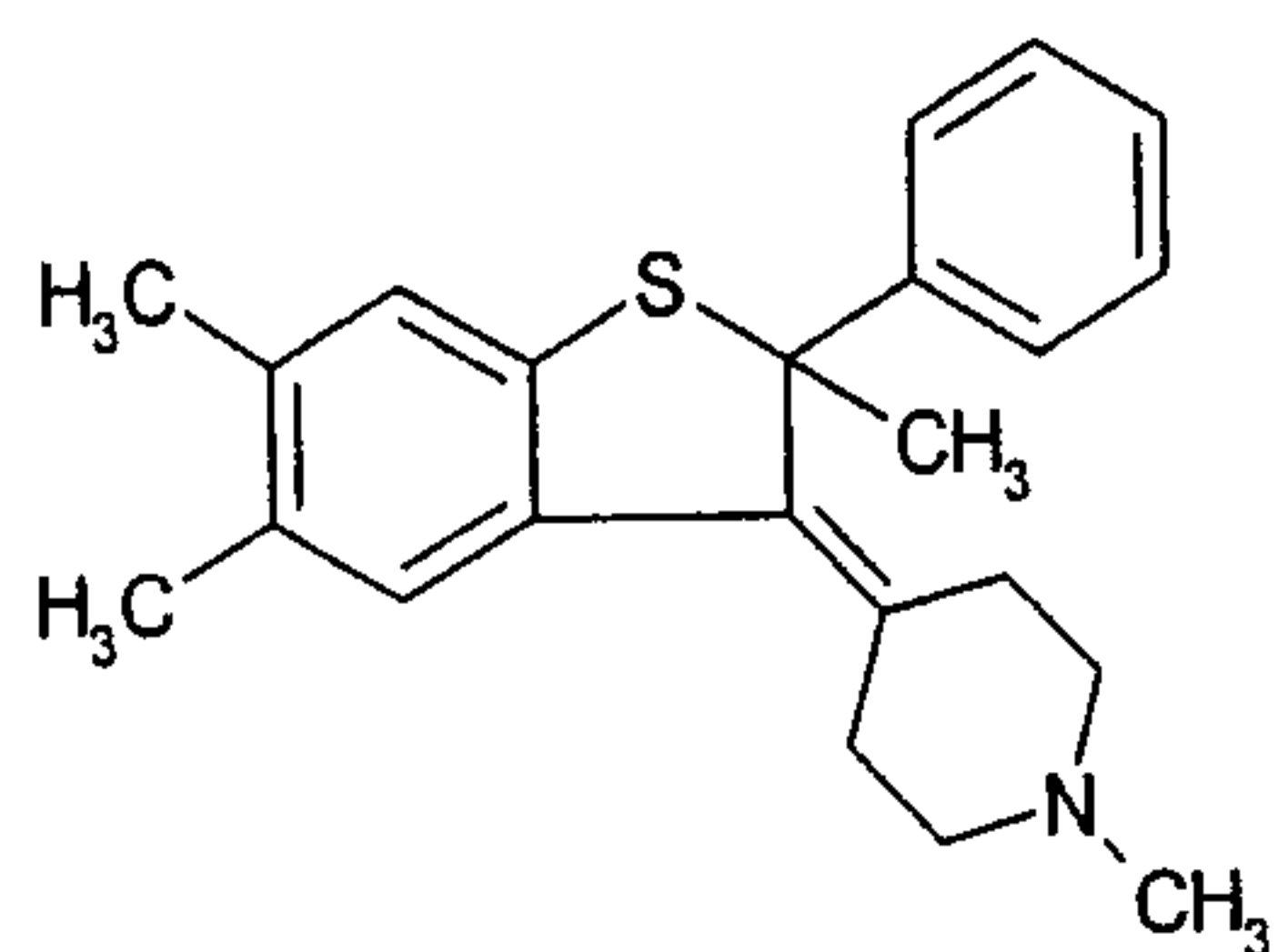
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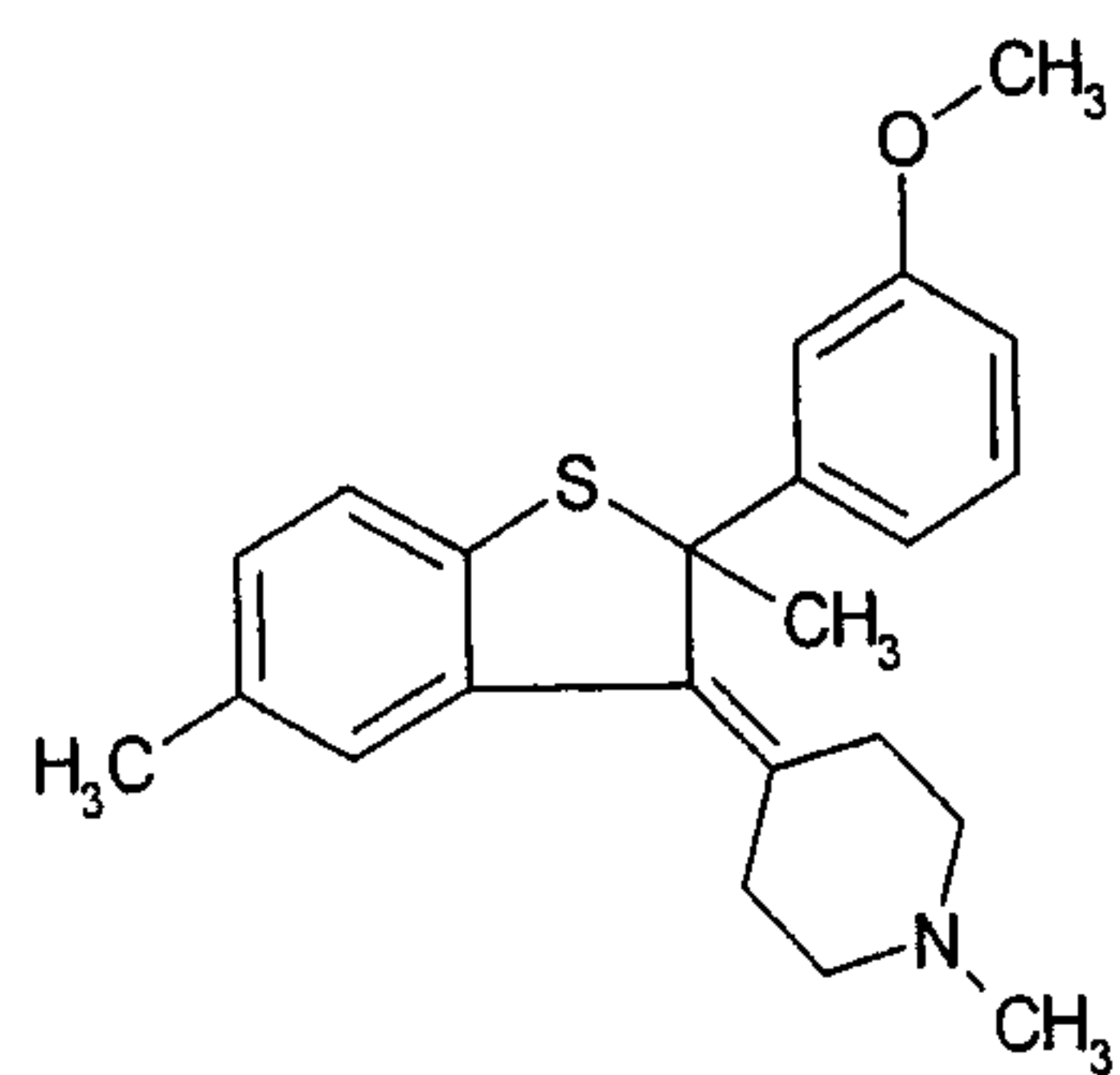
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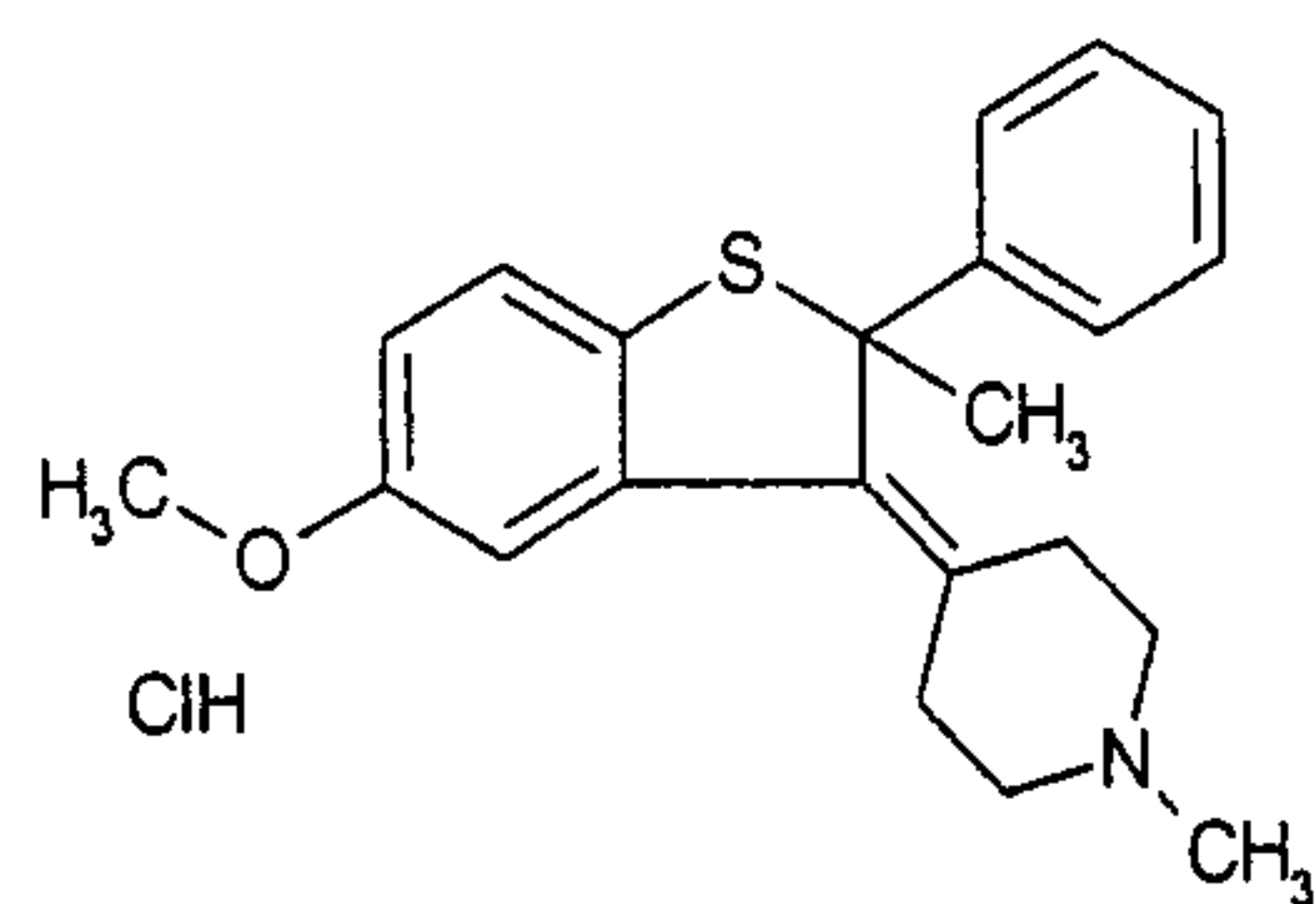
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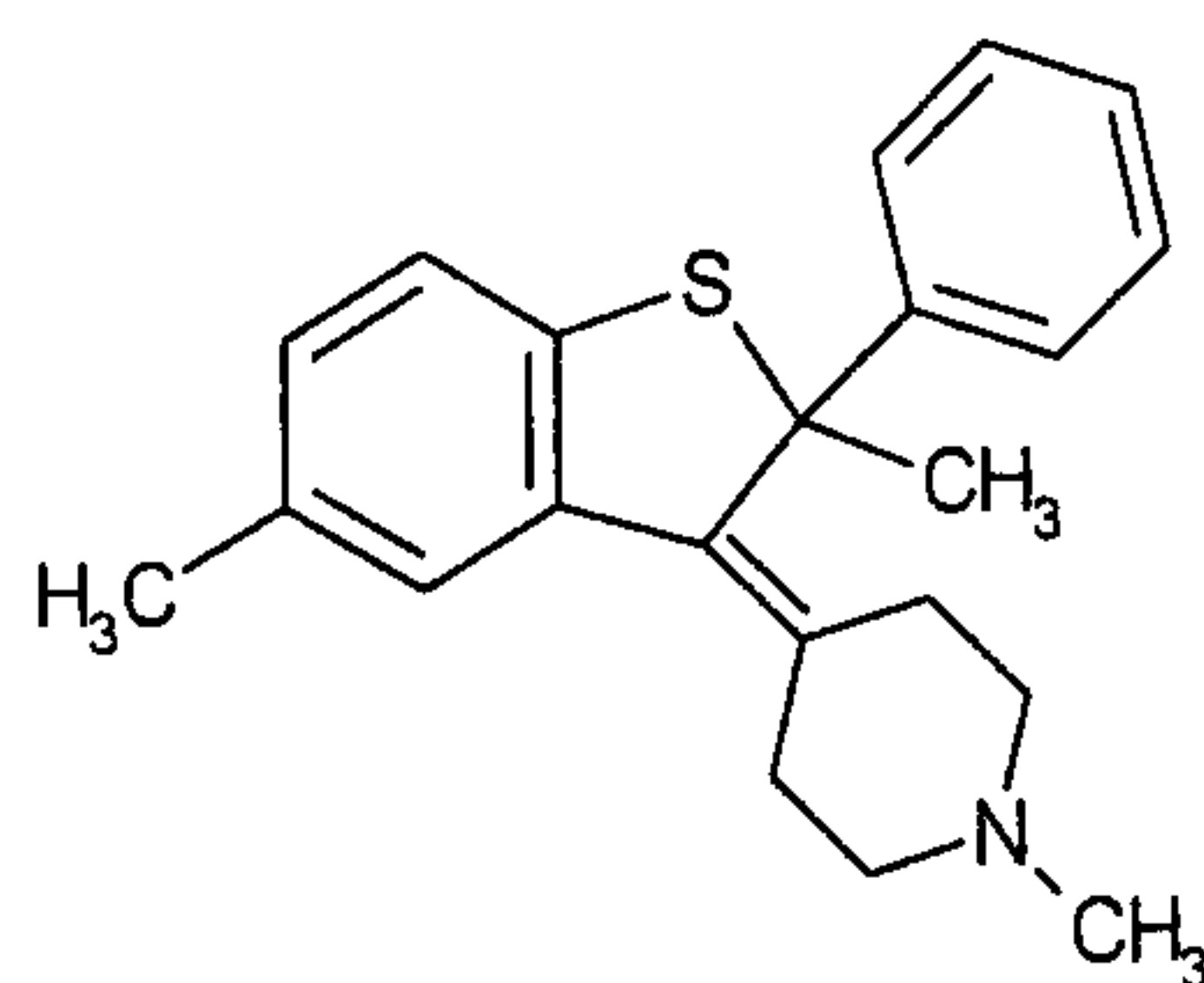
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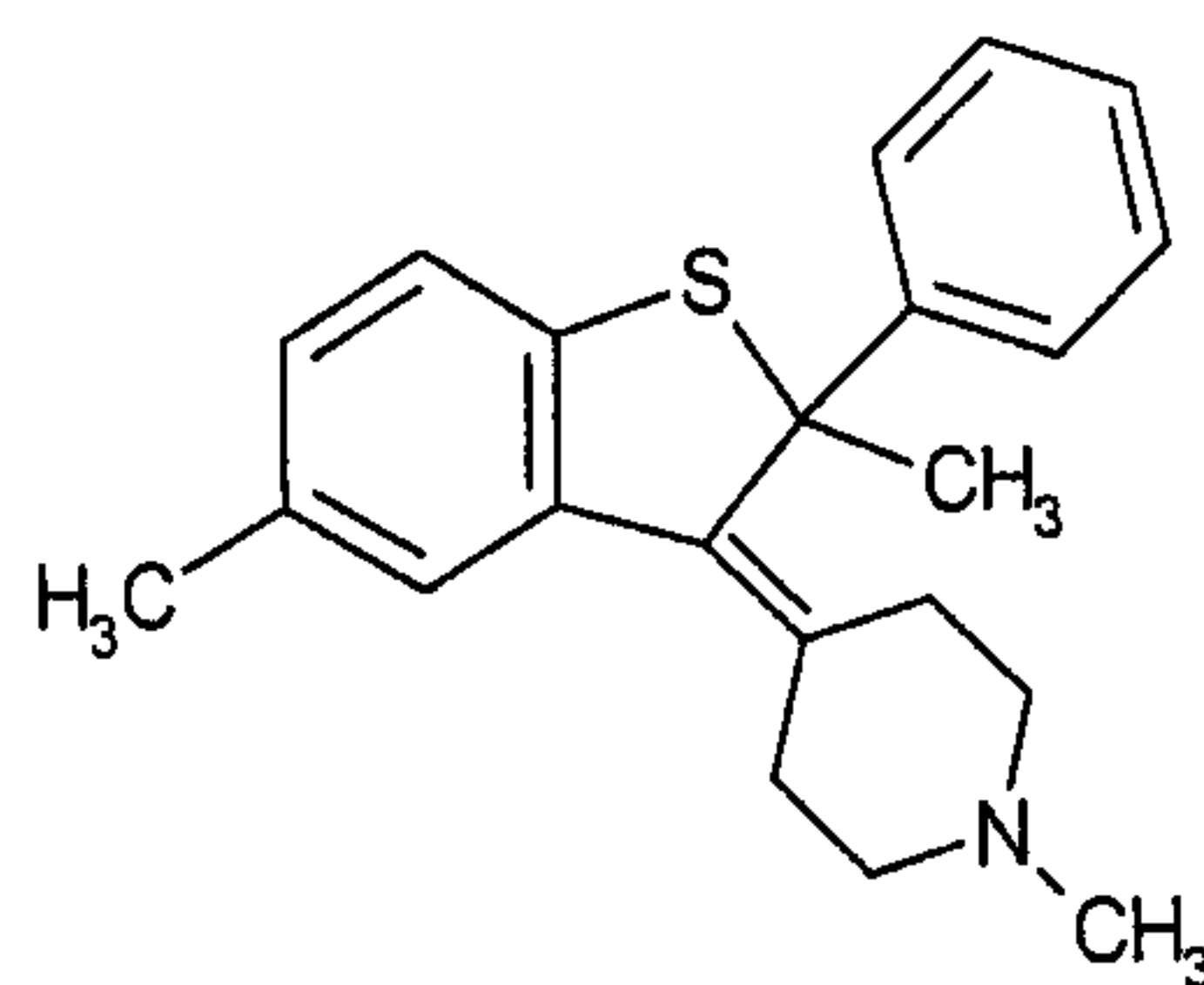
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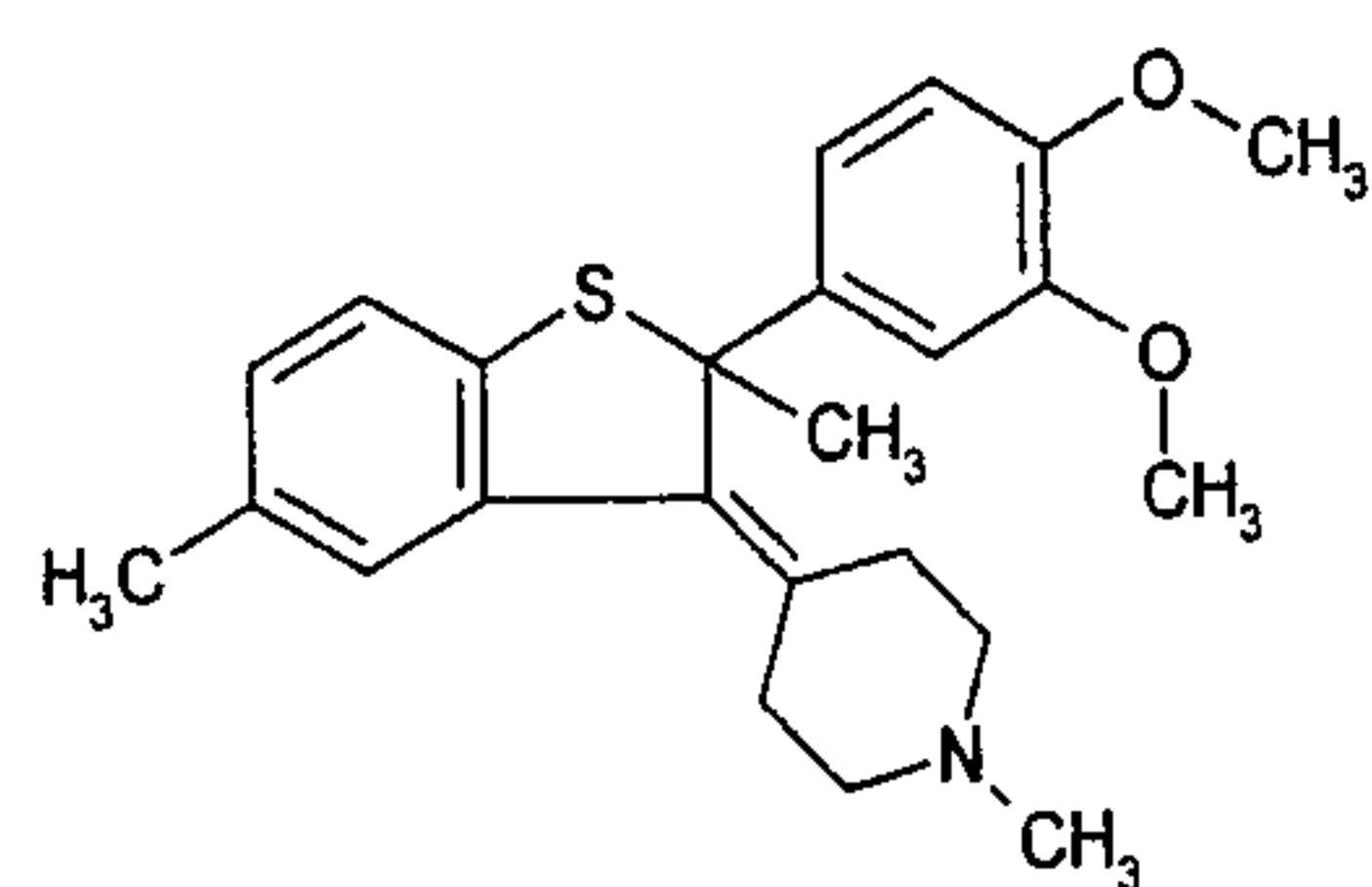
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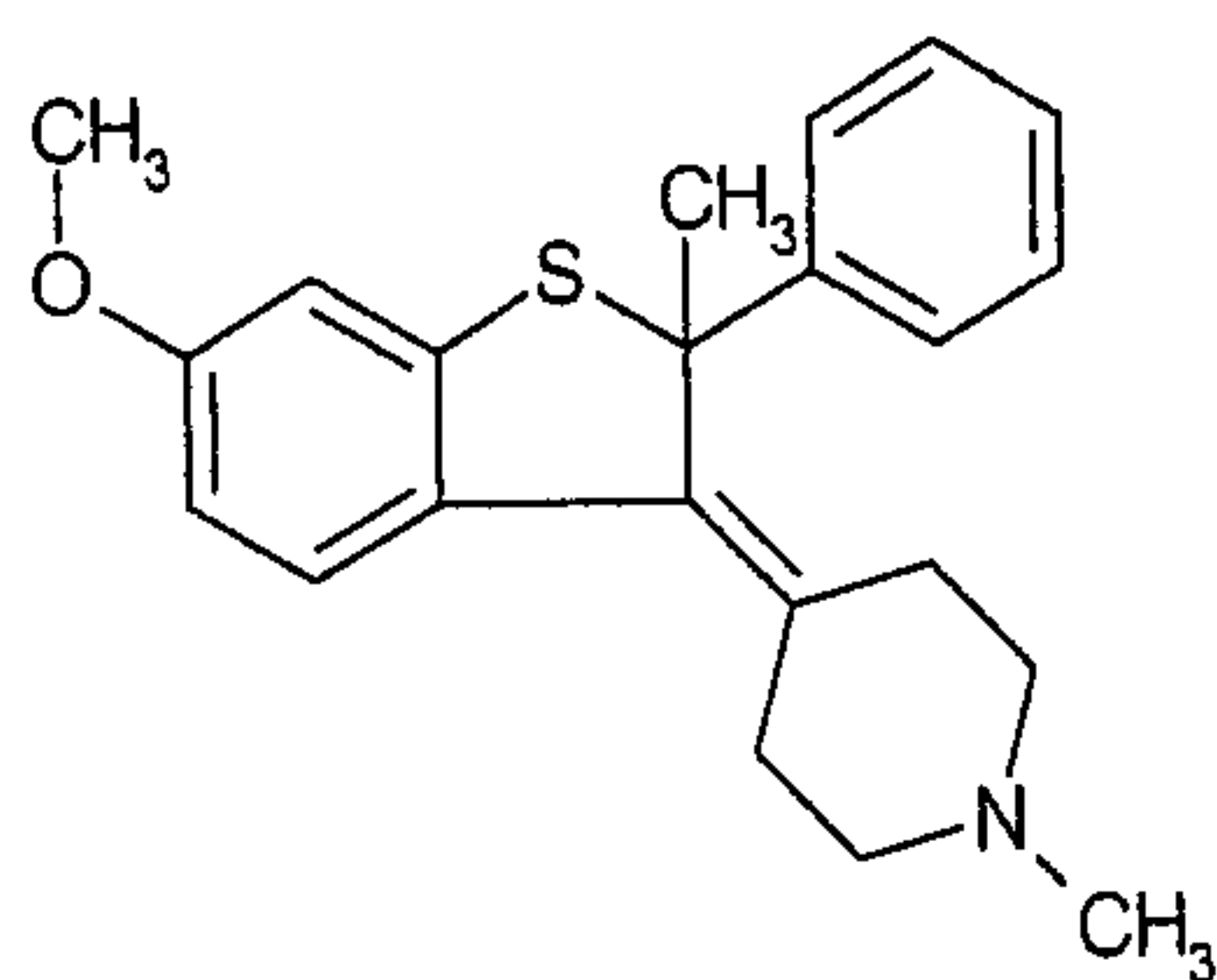
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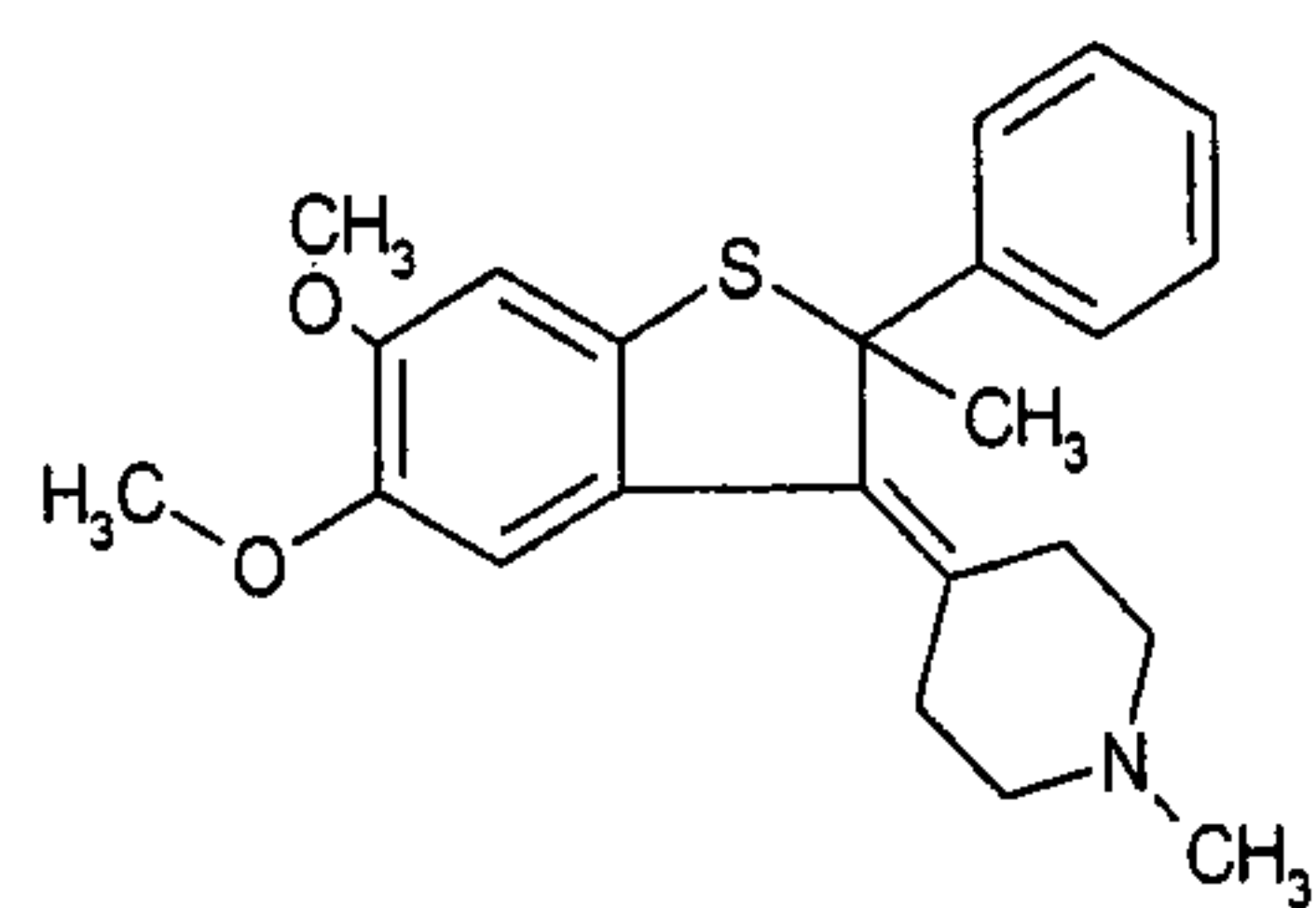
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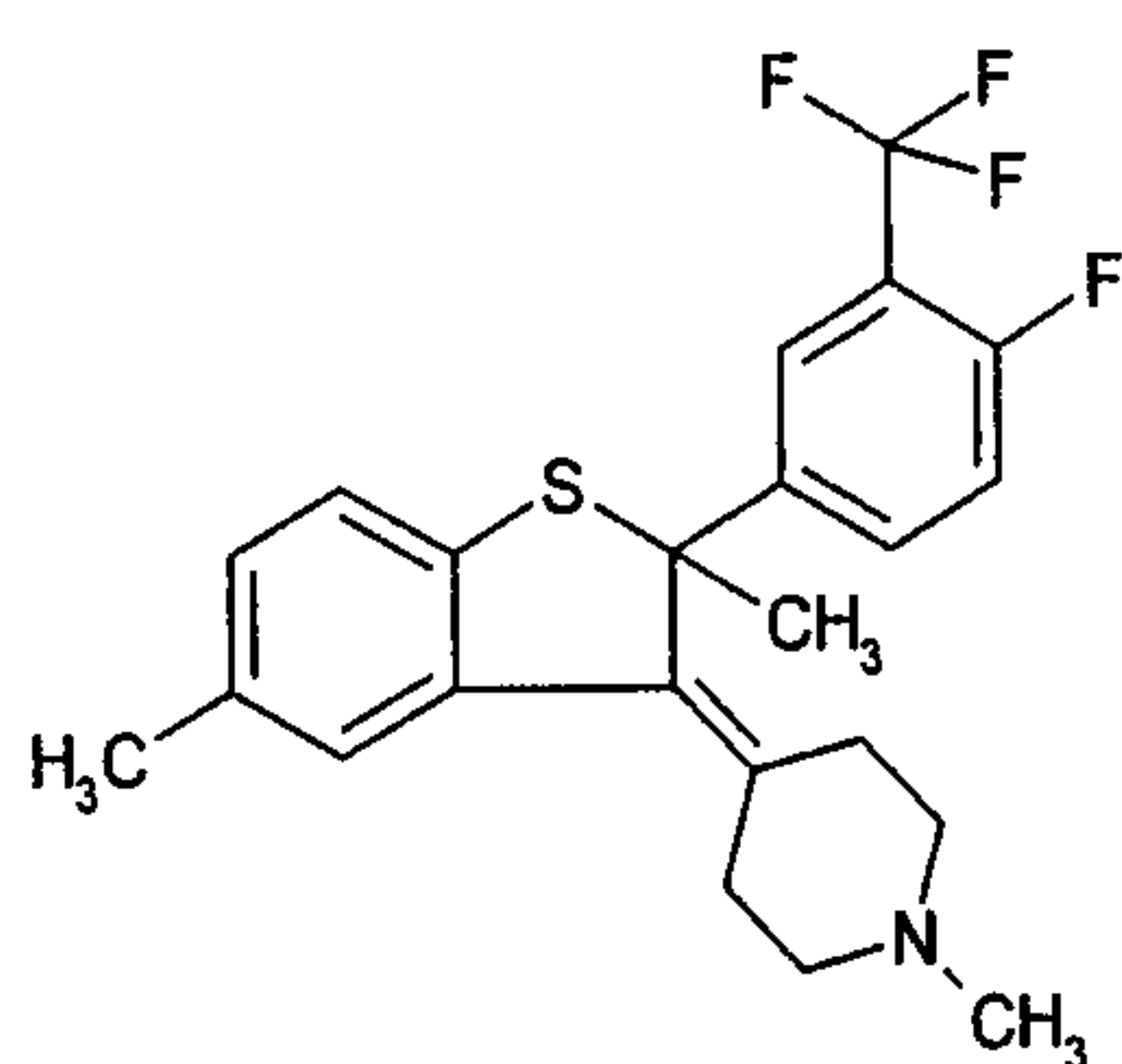
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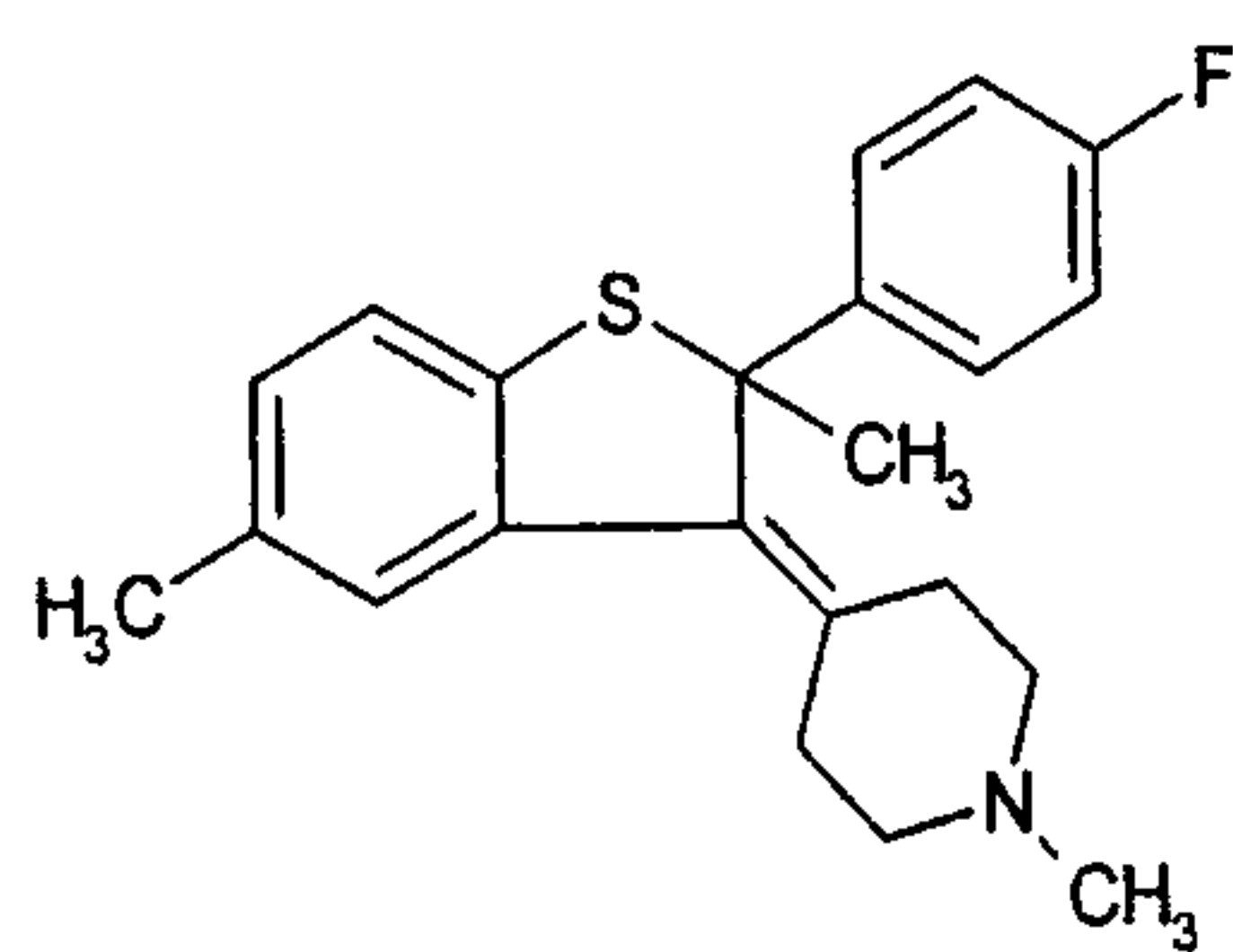
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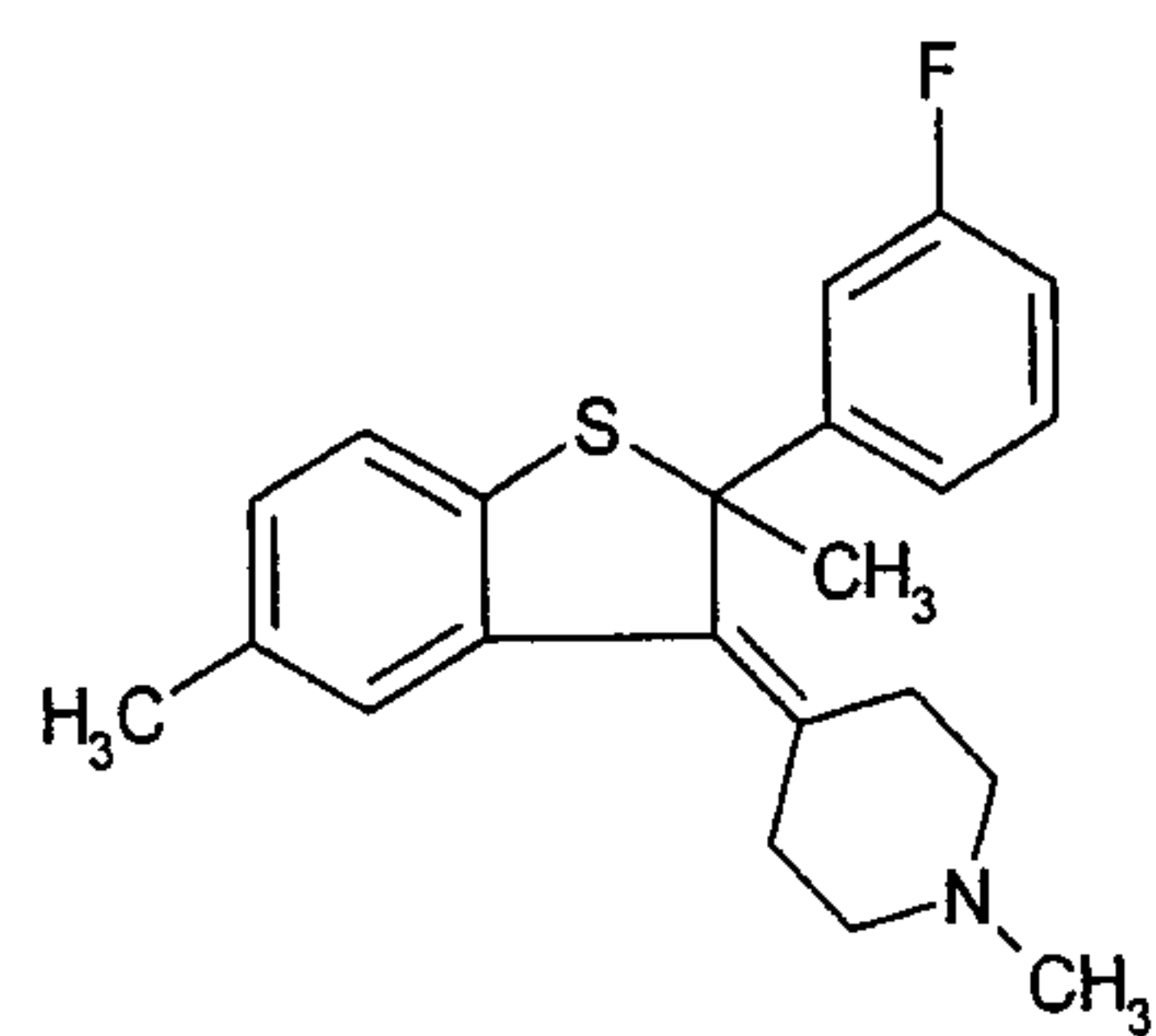
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I46

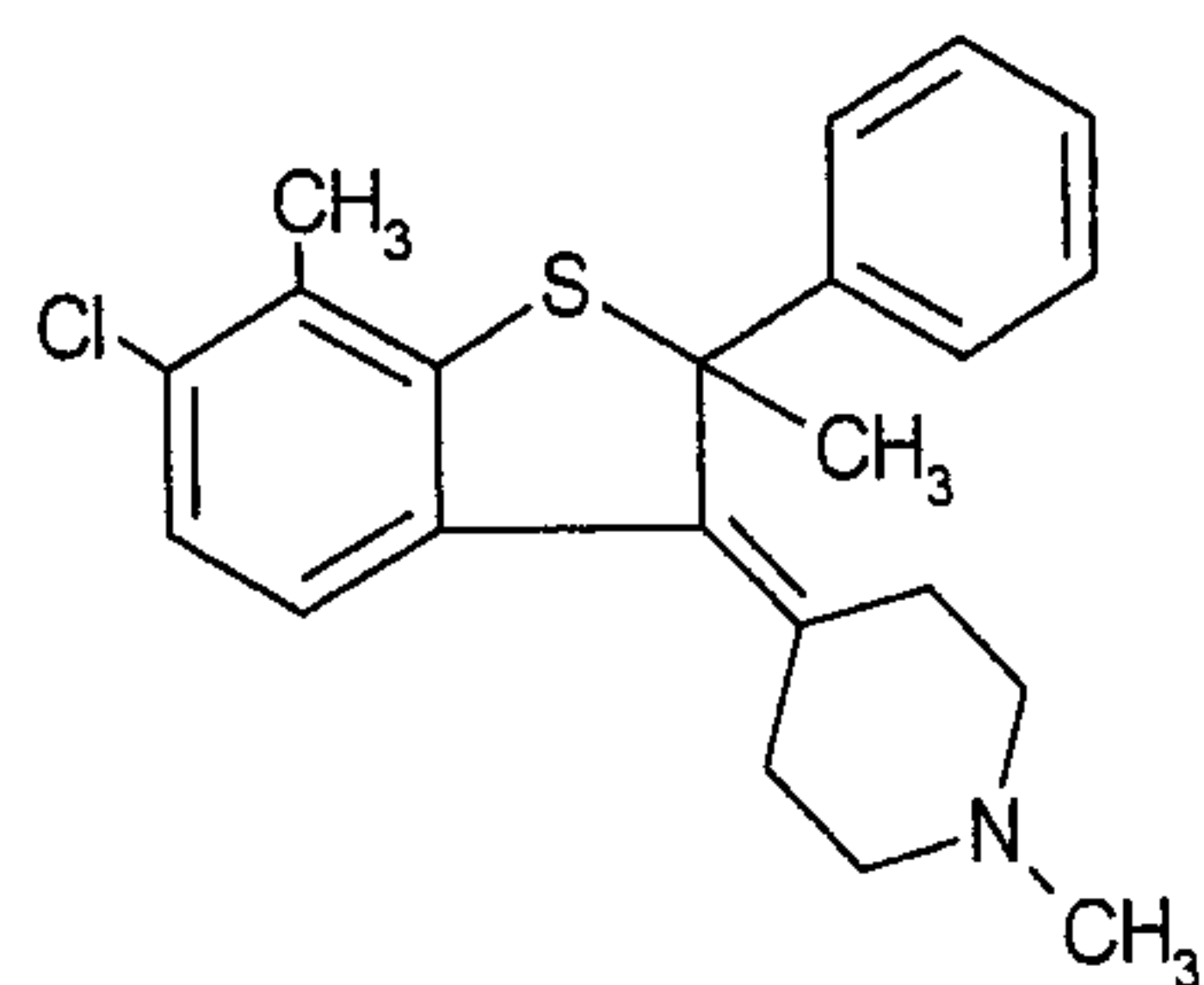
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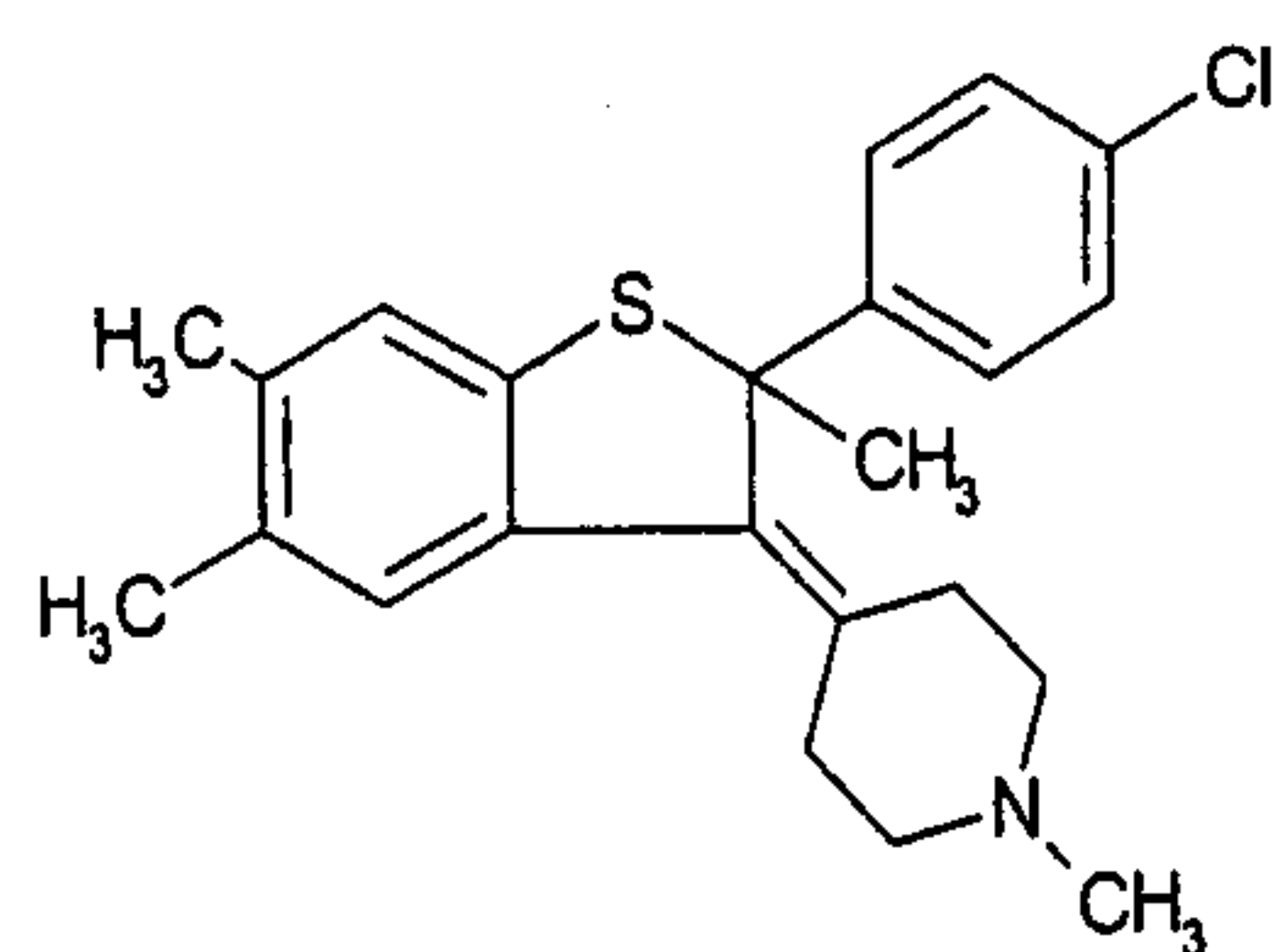
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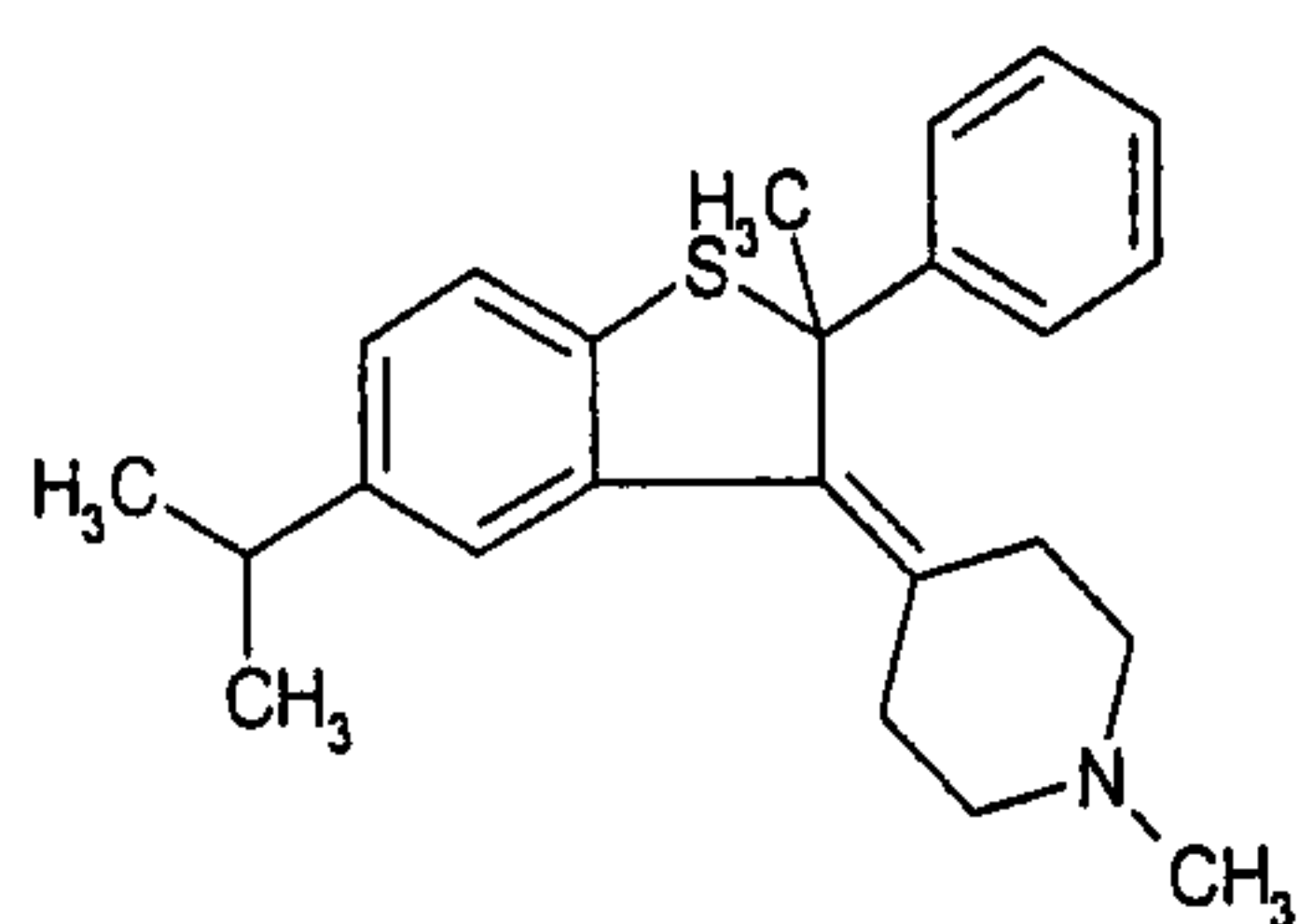
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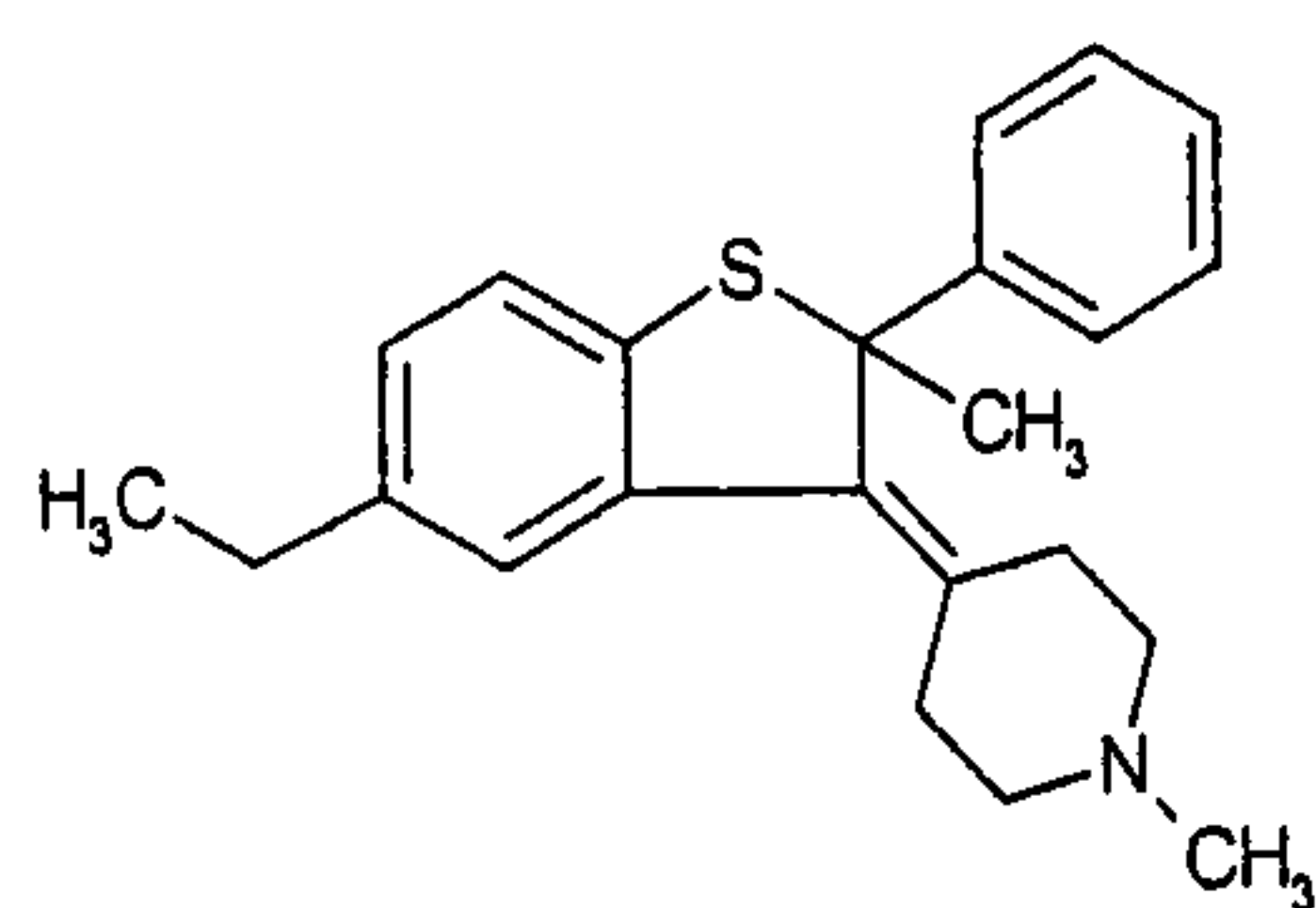
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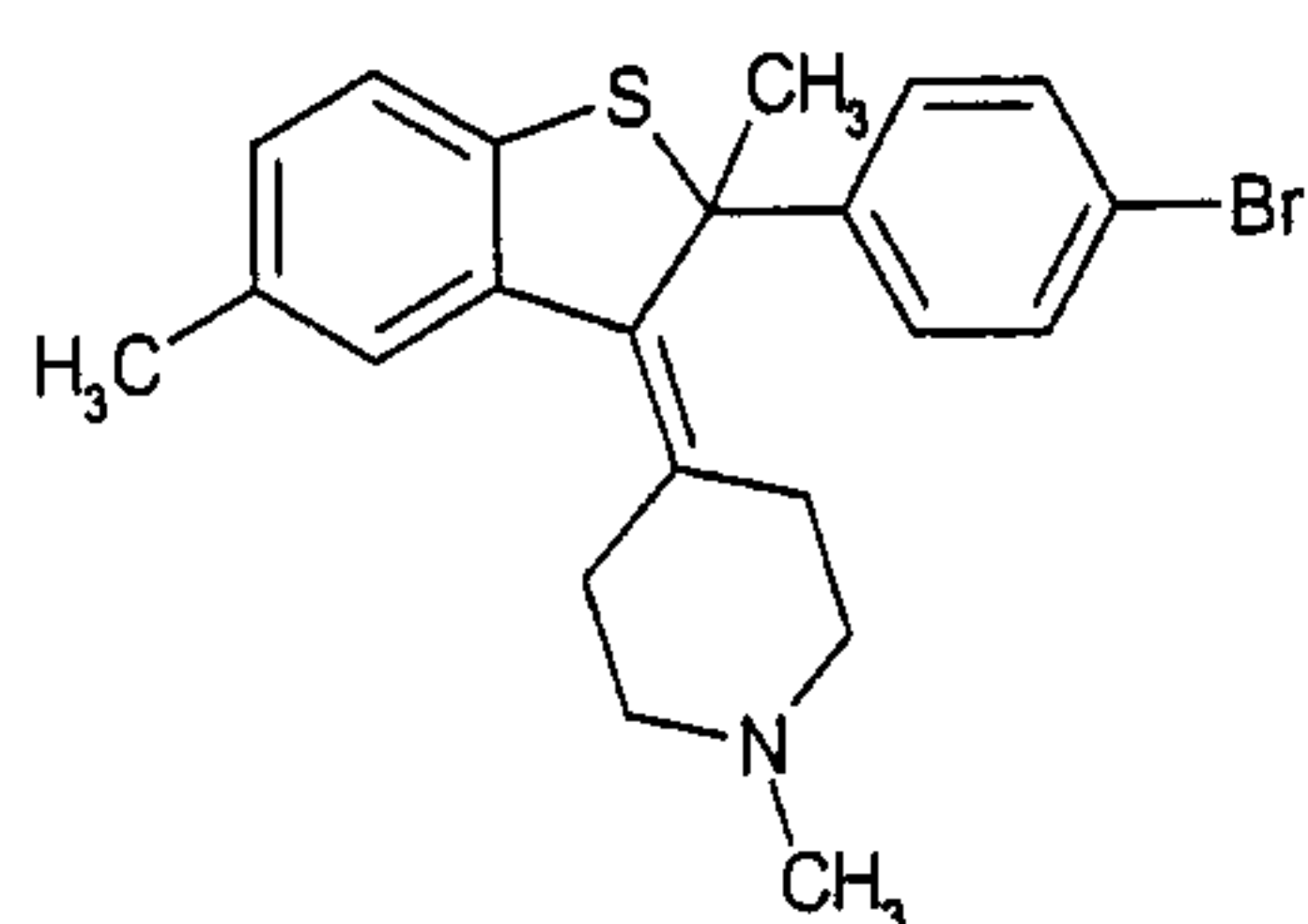
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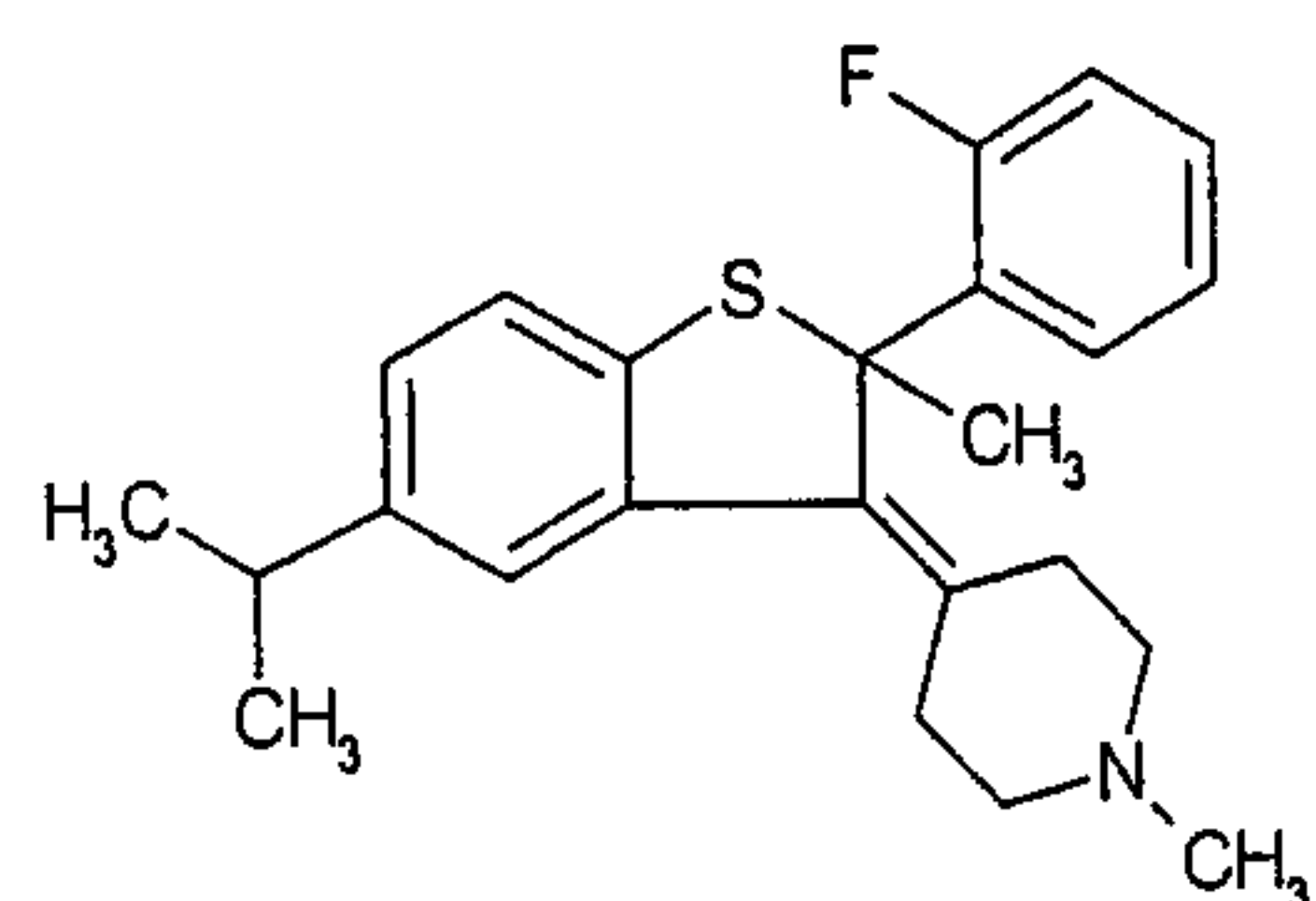
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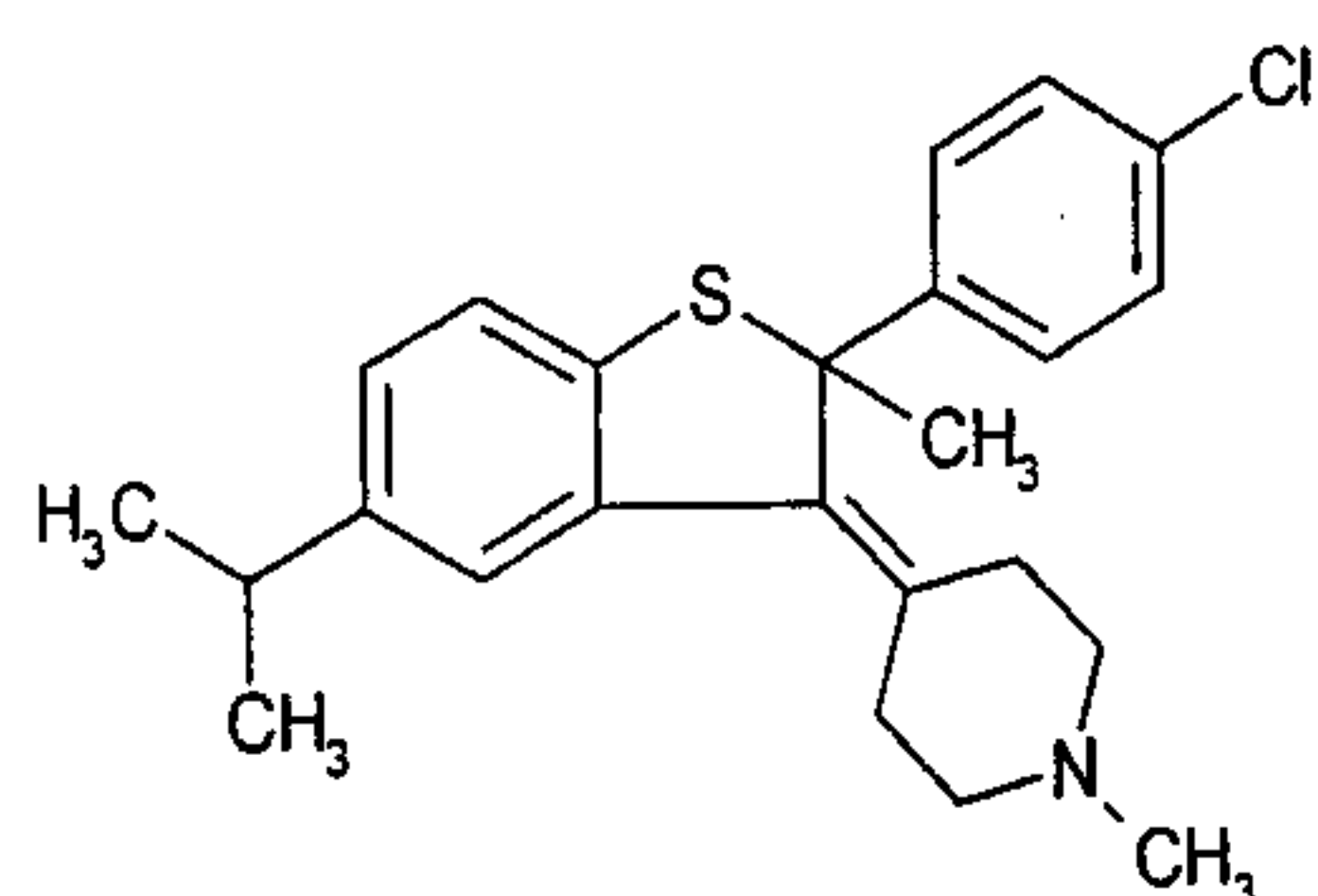
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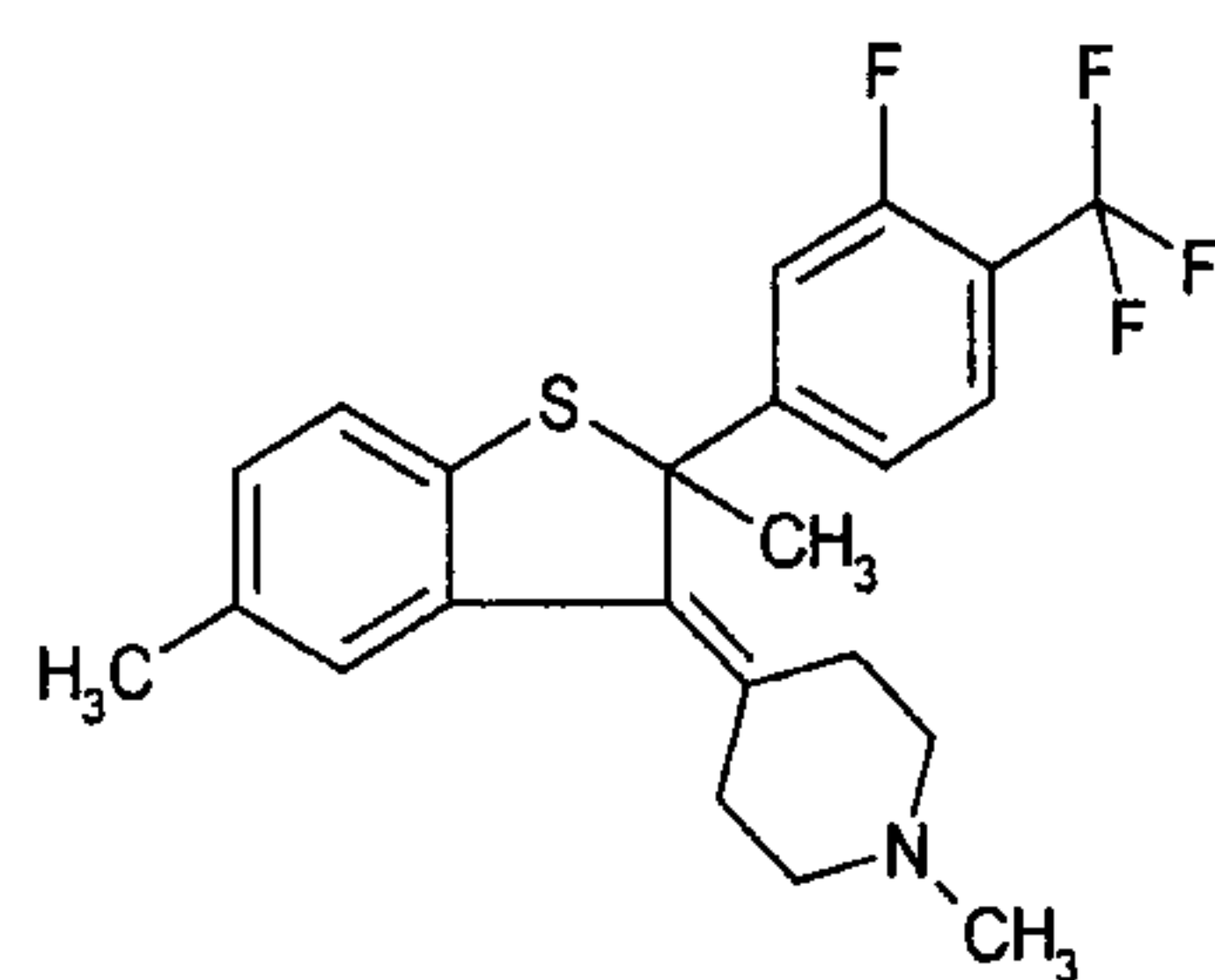
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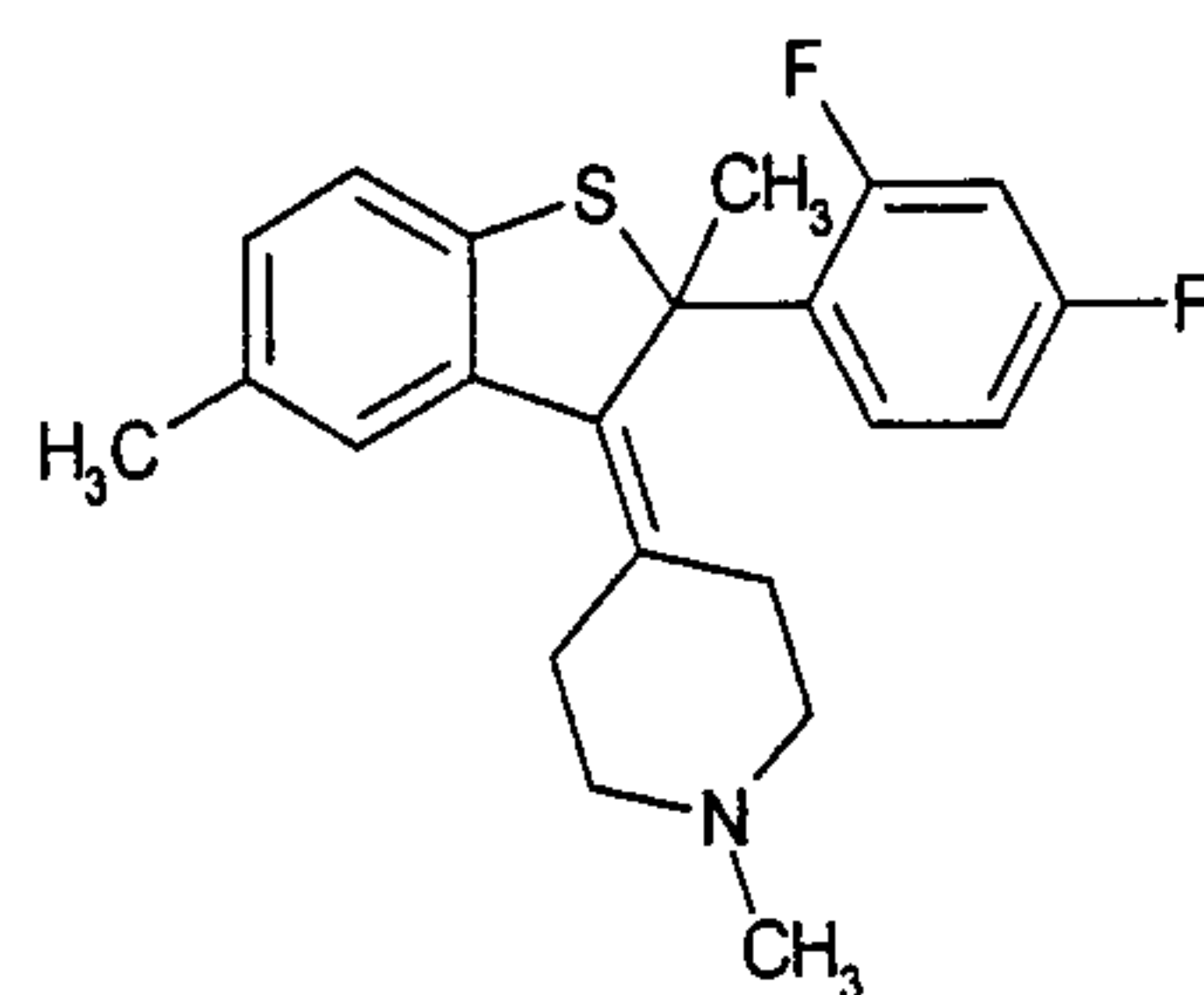
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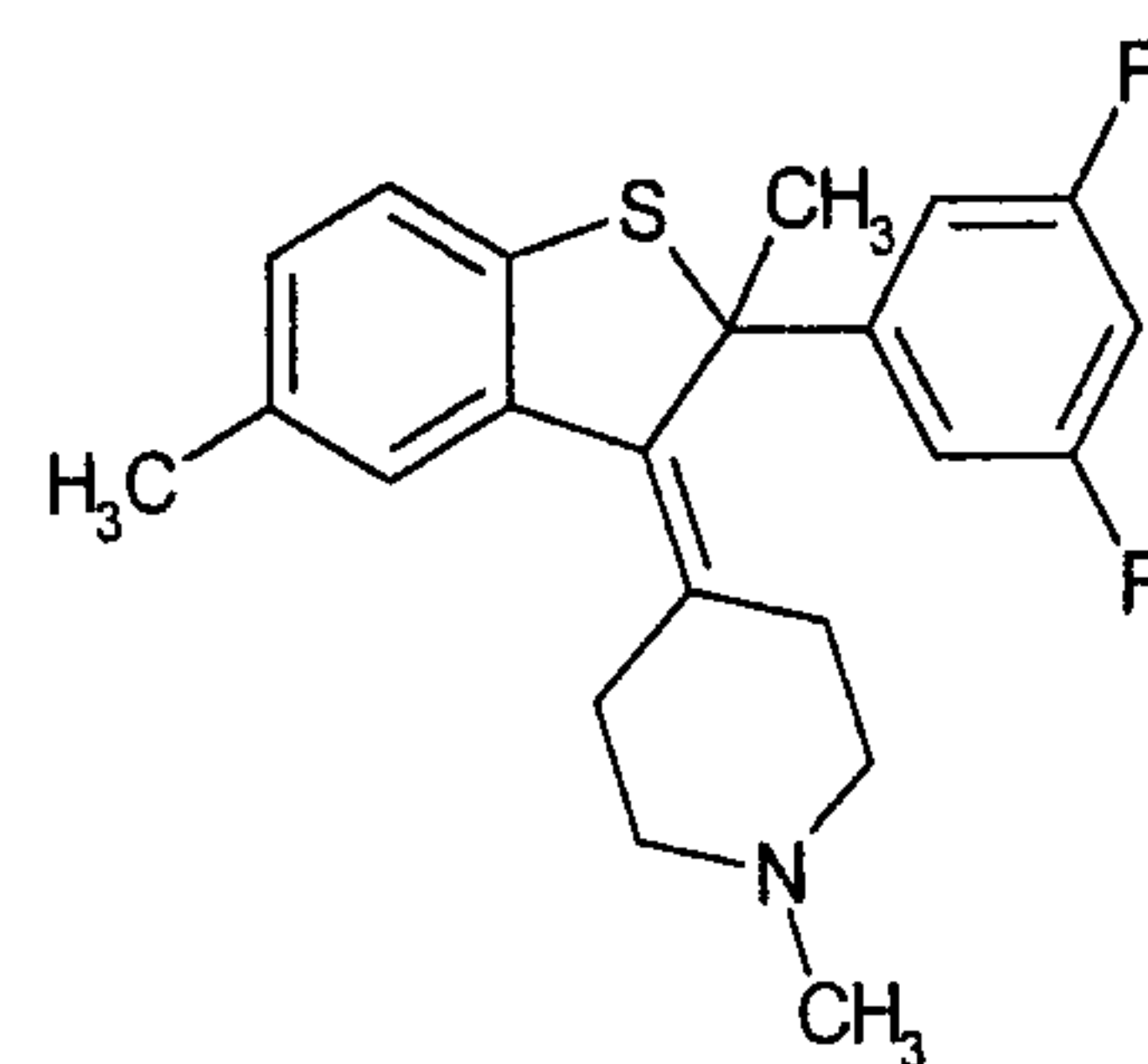
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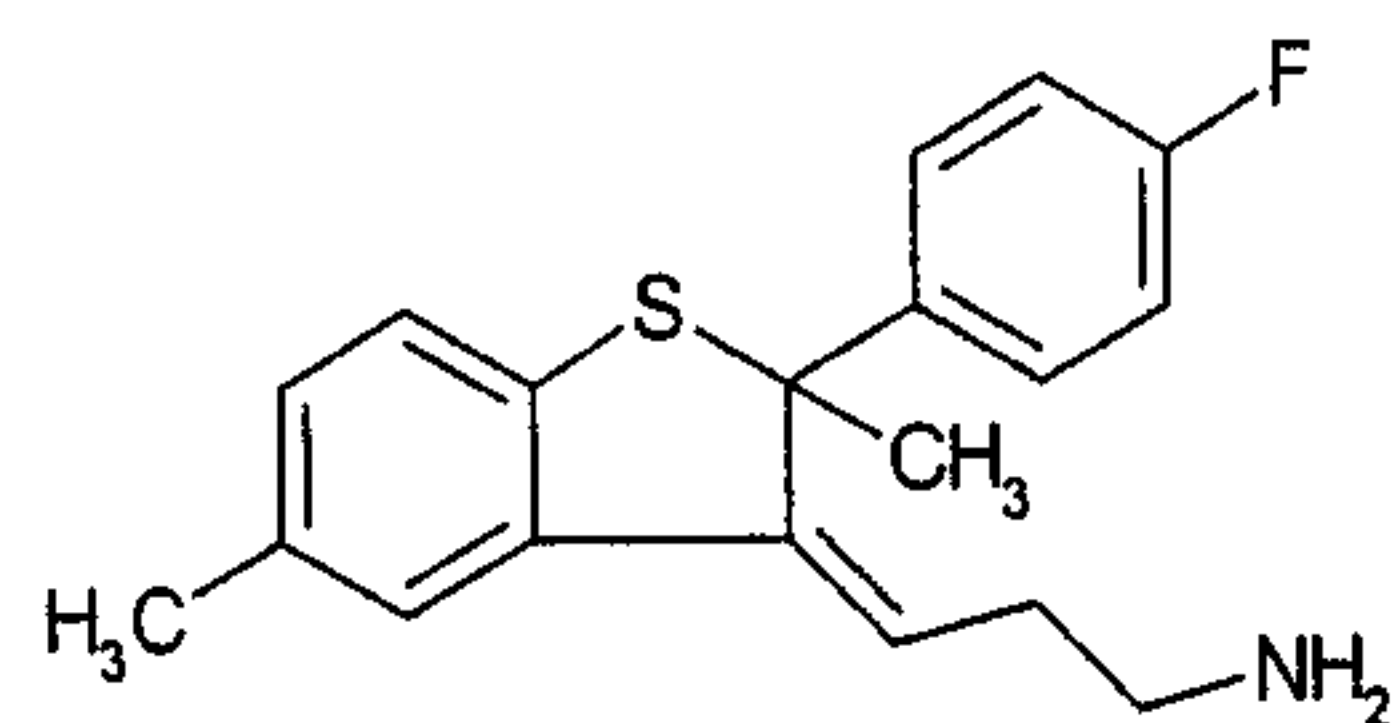
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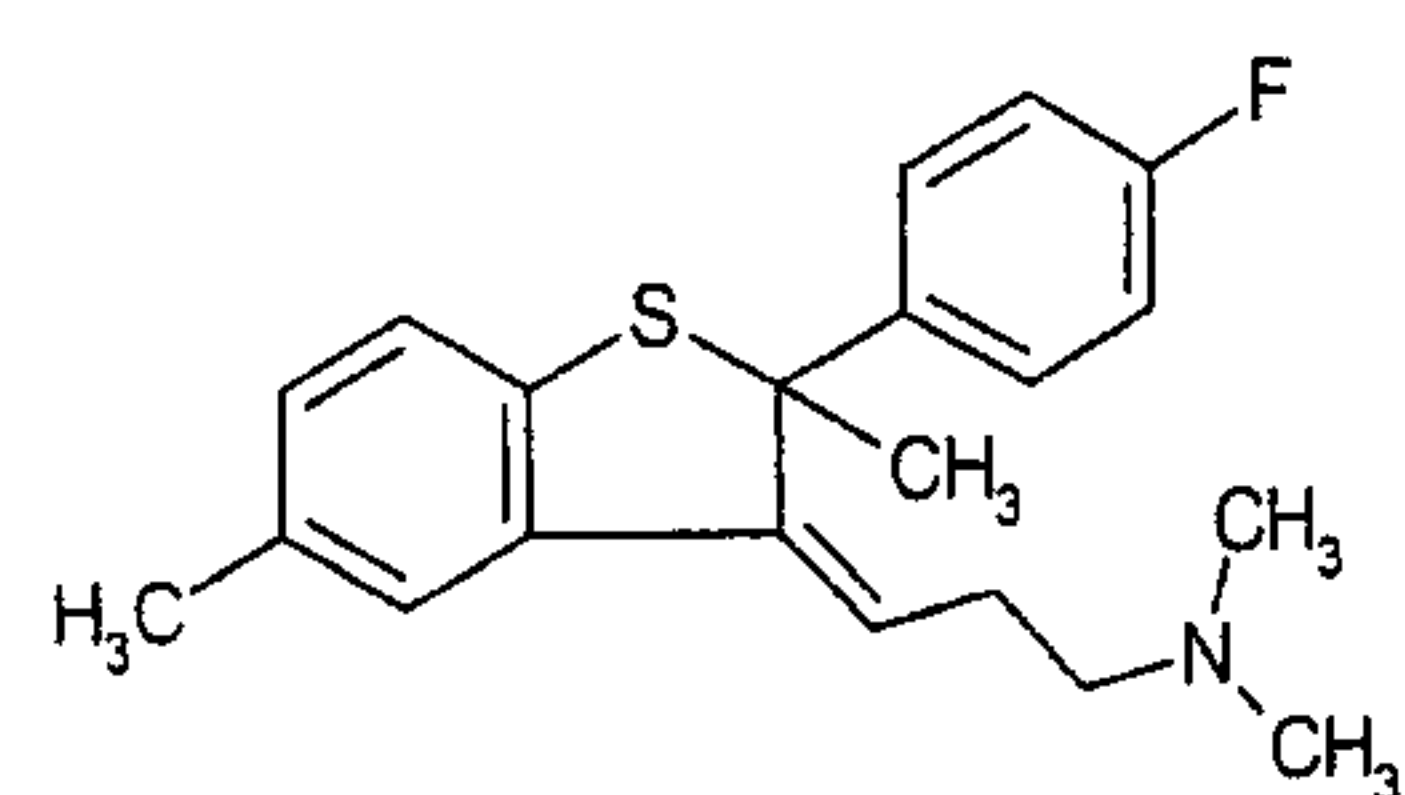
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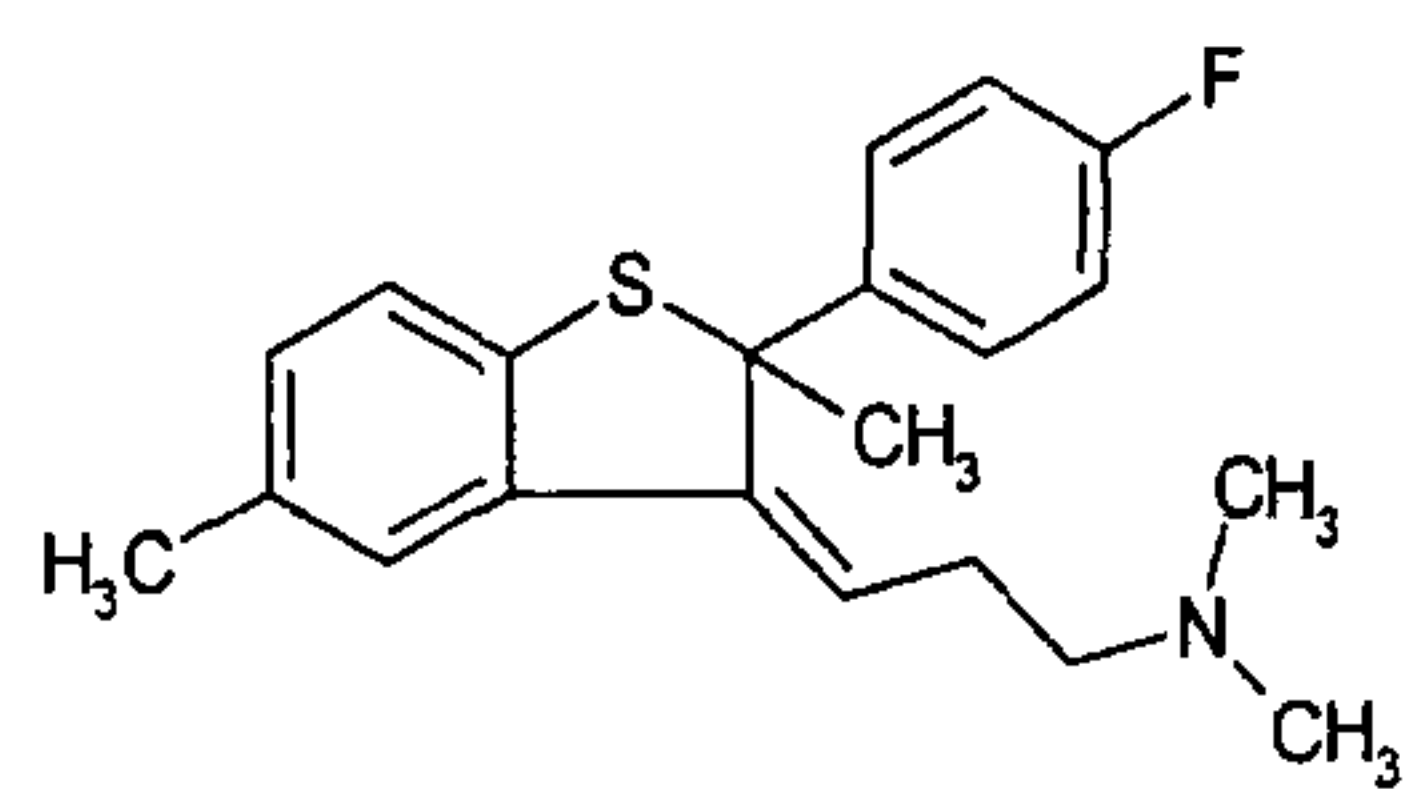
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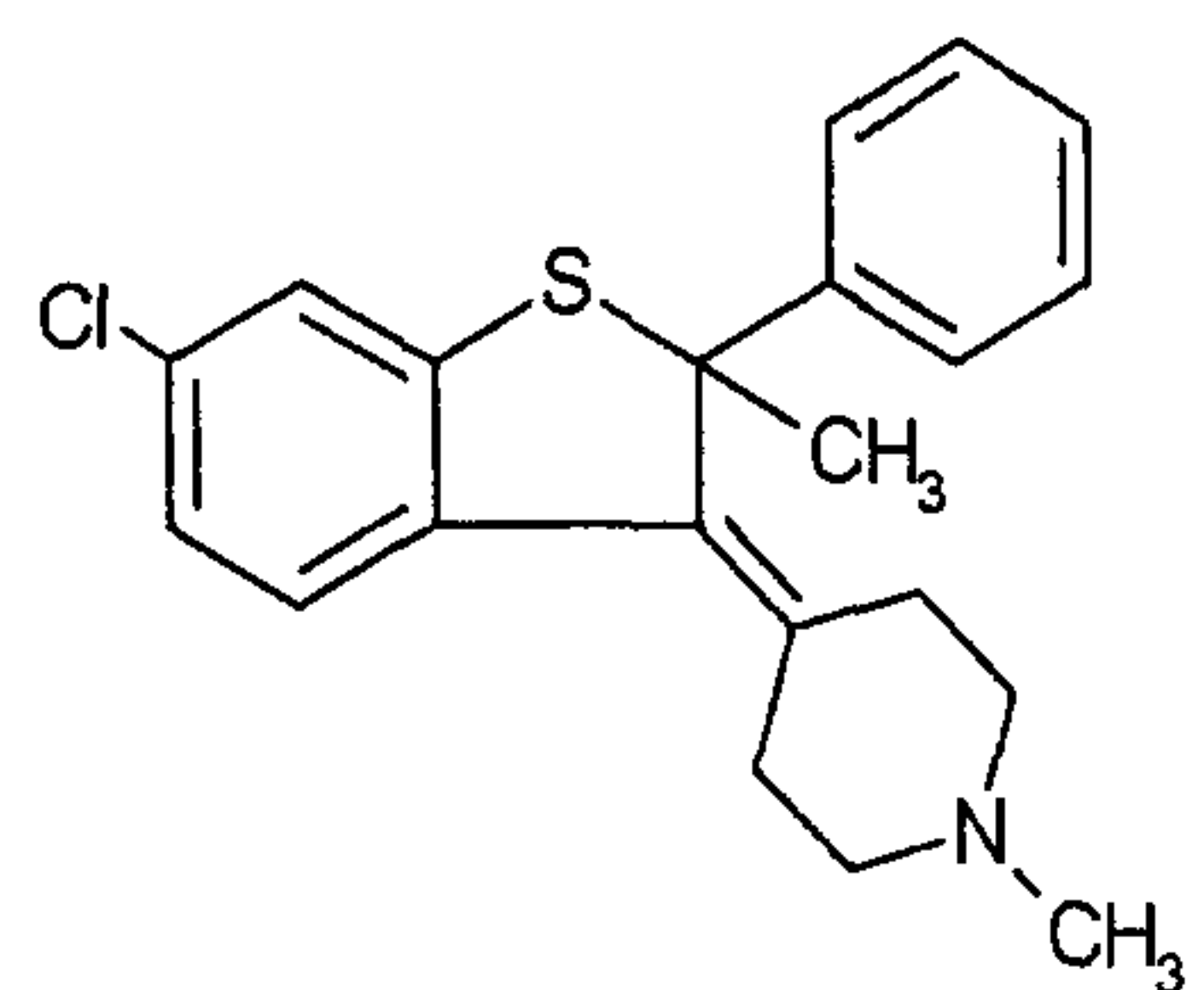
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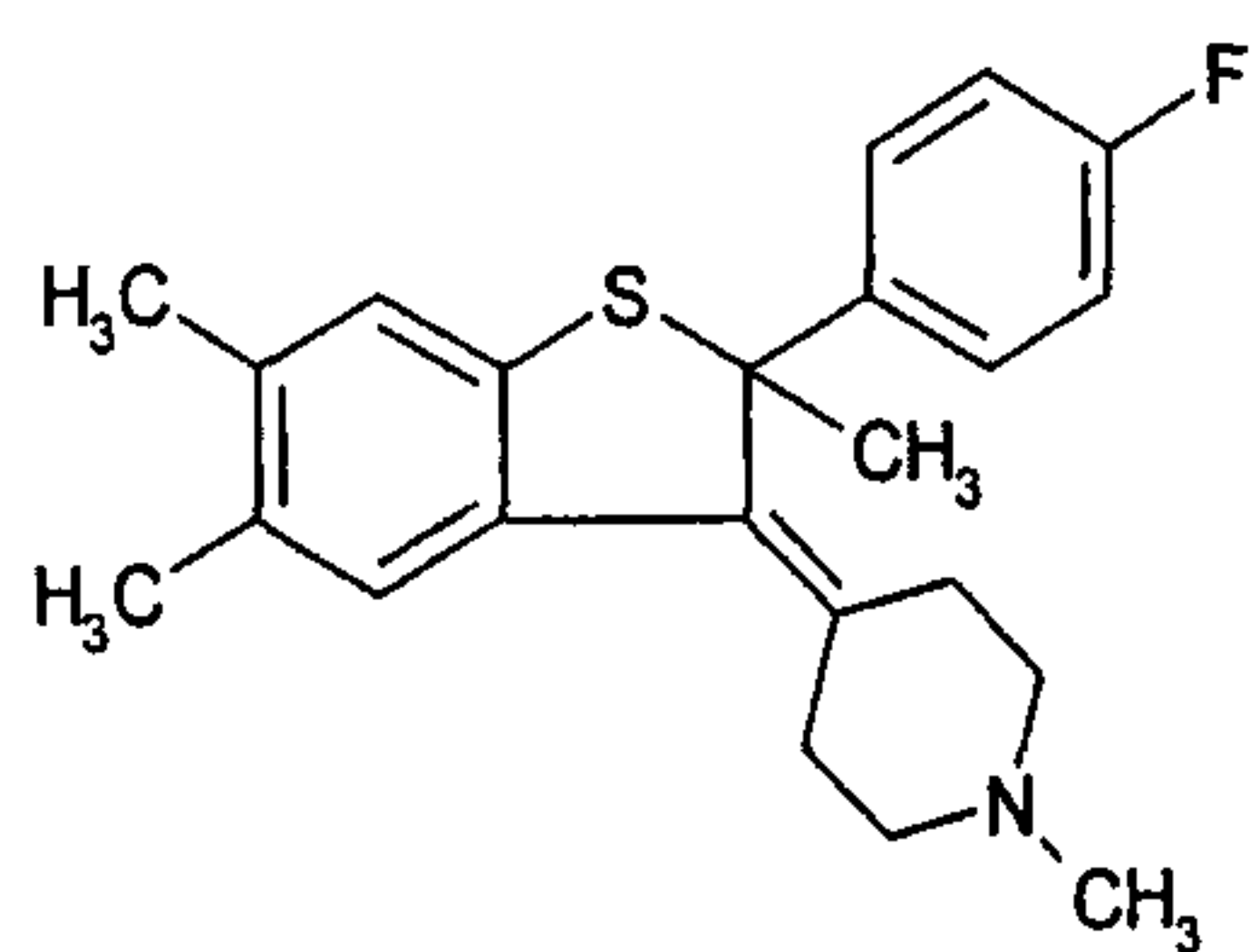
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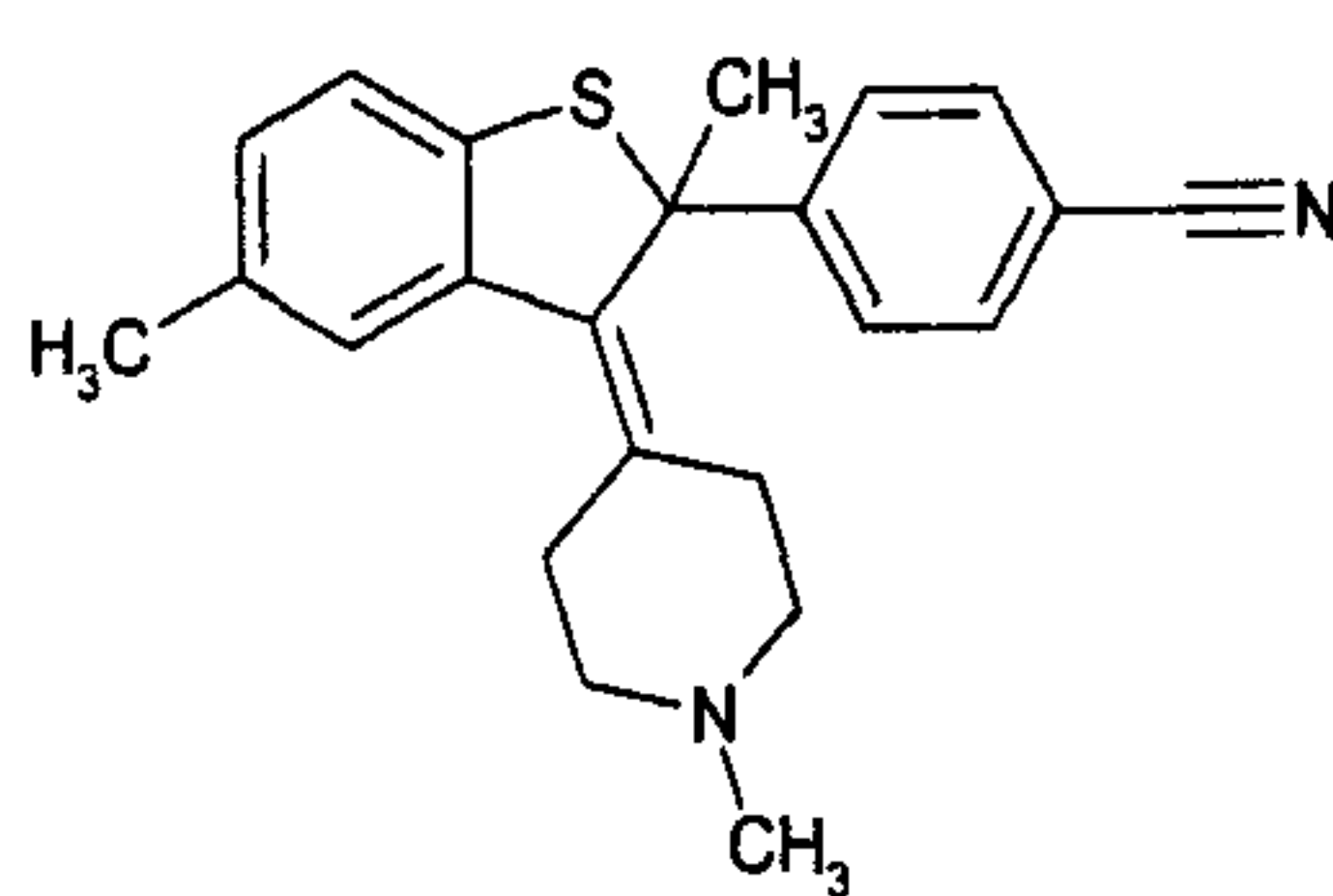
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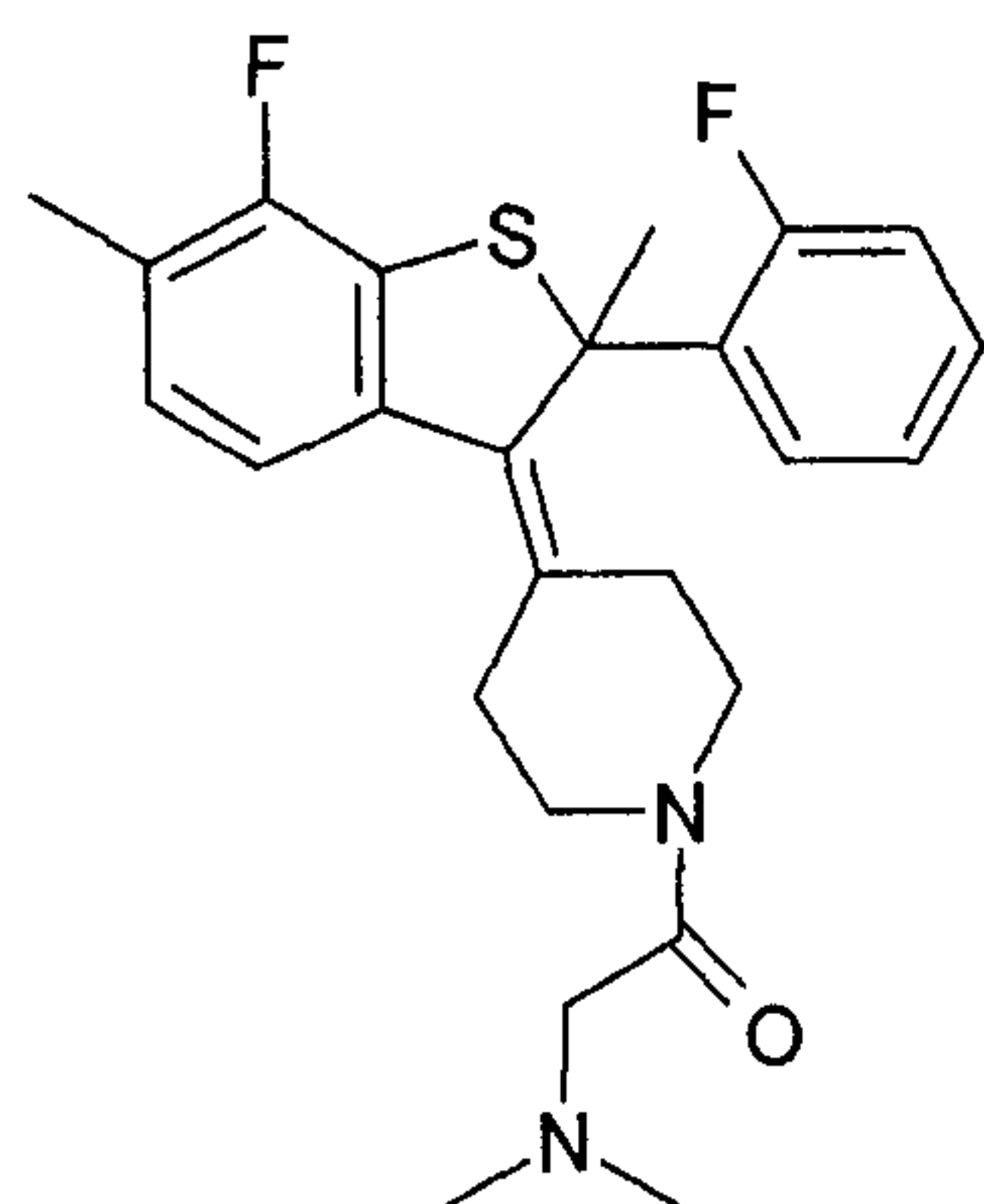
I62

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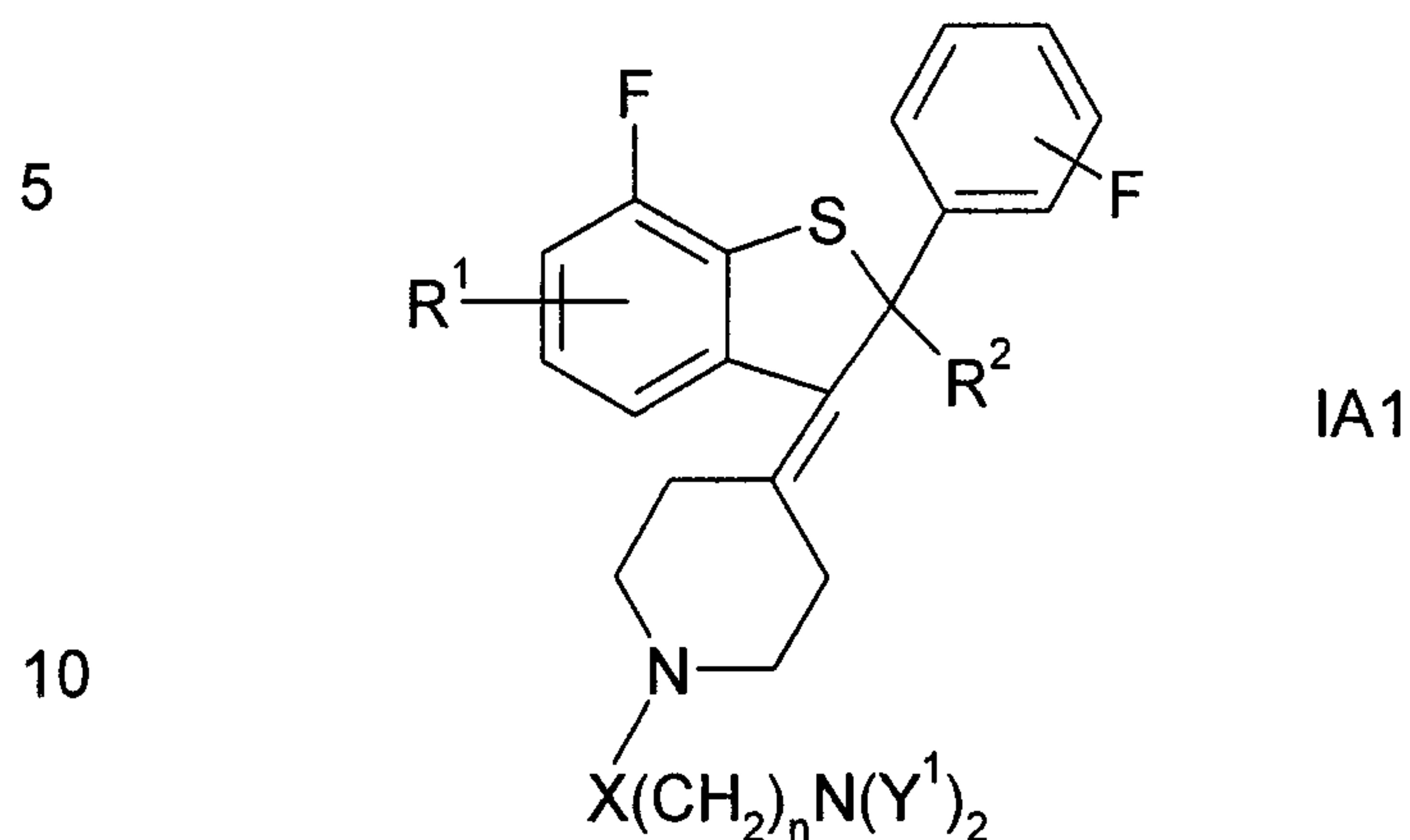
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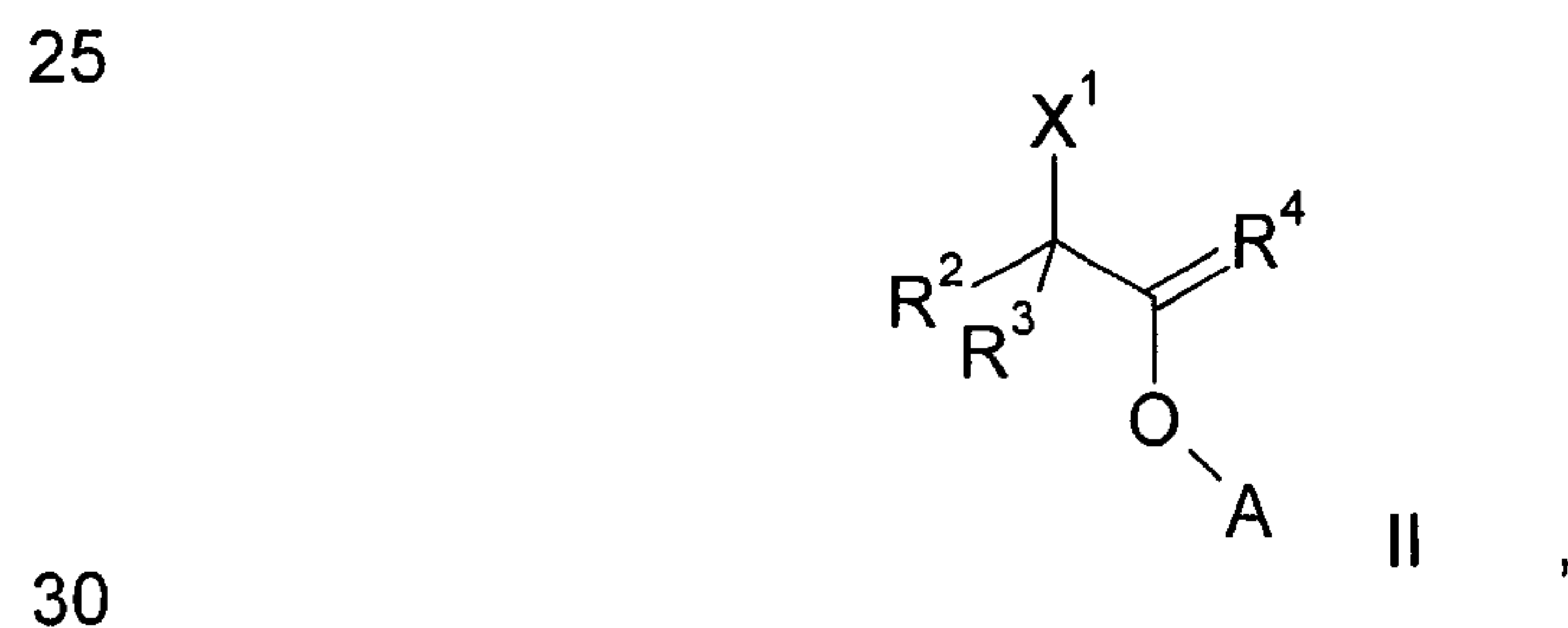
and pharmaceutically usable derivatives, solvates, tautomers, salts
and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compounds of the formula IA1:



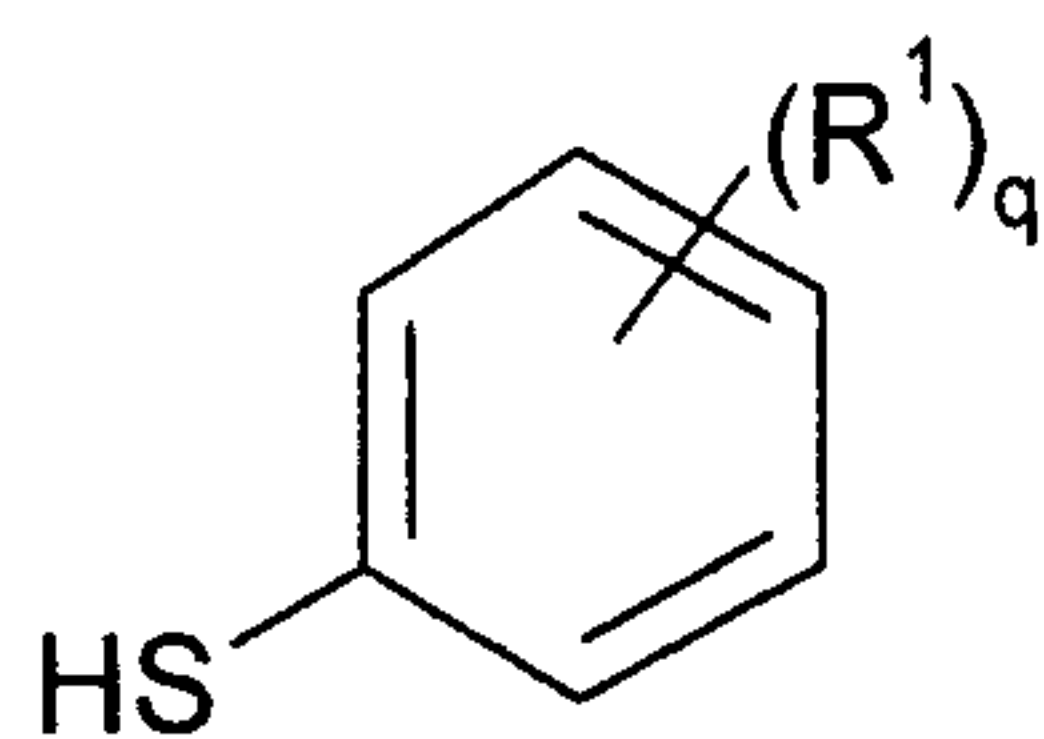
15 in which R^1 , R^2 , X , Y^1 and n have the meaning indicate in Claim 1, and pharmaceutically usable derivatives, solvates, tautomers, salts and stereoisomers thereof, including mixtures thereof in all ratios.

20 8. Process for the preparation of compounds of the formula I according to Claims 1-7 and pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, characterised in that a compound of the formula II



35 in which R^2 , R^3 and R^4 have the meanings indicated in Claim 1 and X^1 can be a leaving group and preferably Hal or a reactive modified OH group, in particular tosyl or mesyl,

is reacted with a compound of the formula III

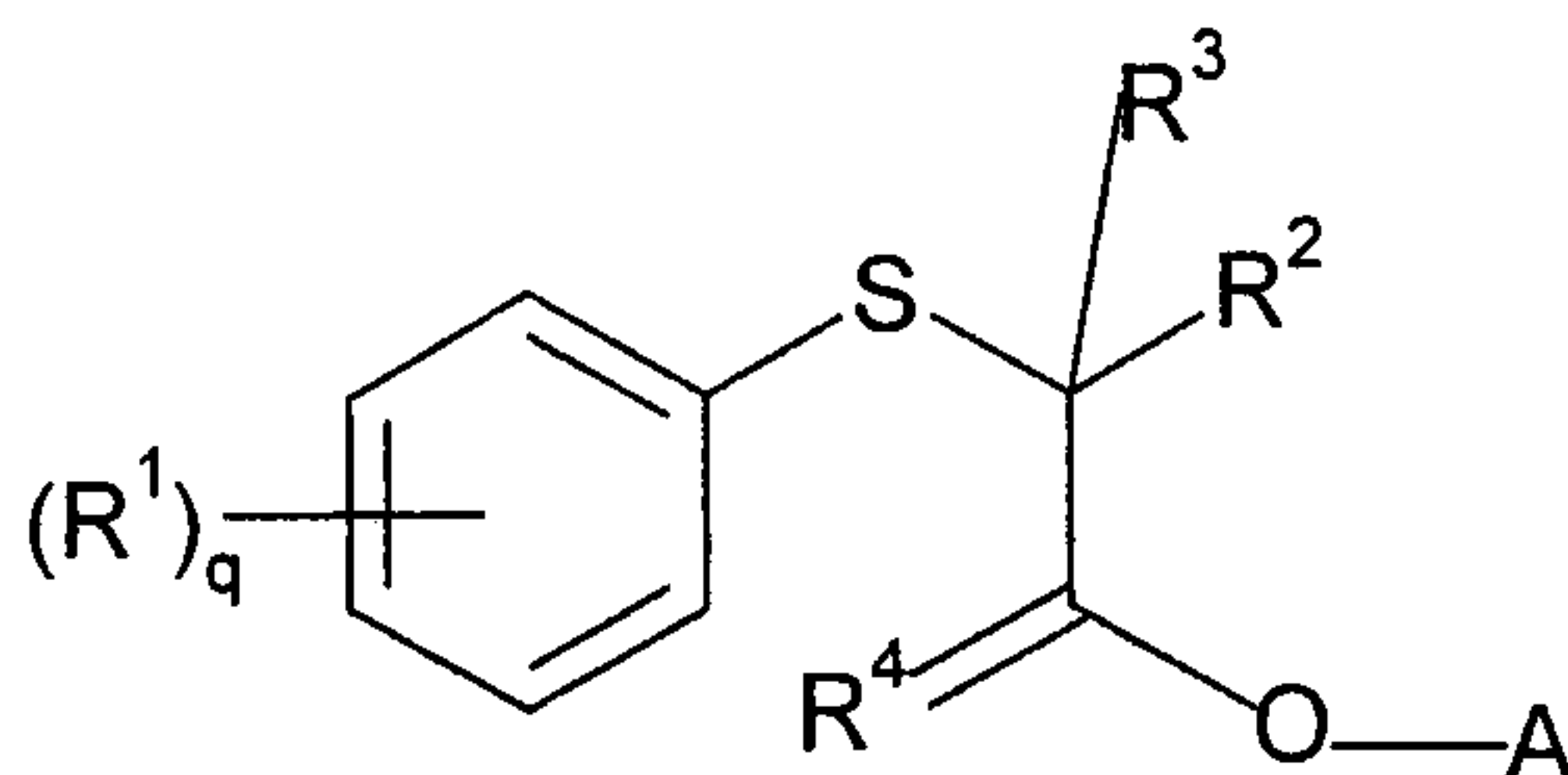


III,

in which

R^1 and y have the meanings indicated in Claim 1,

and the resultant compound of the formula IV

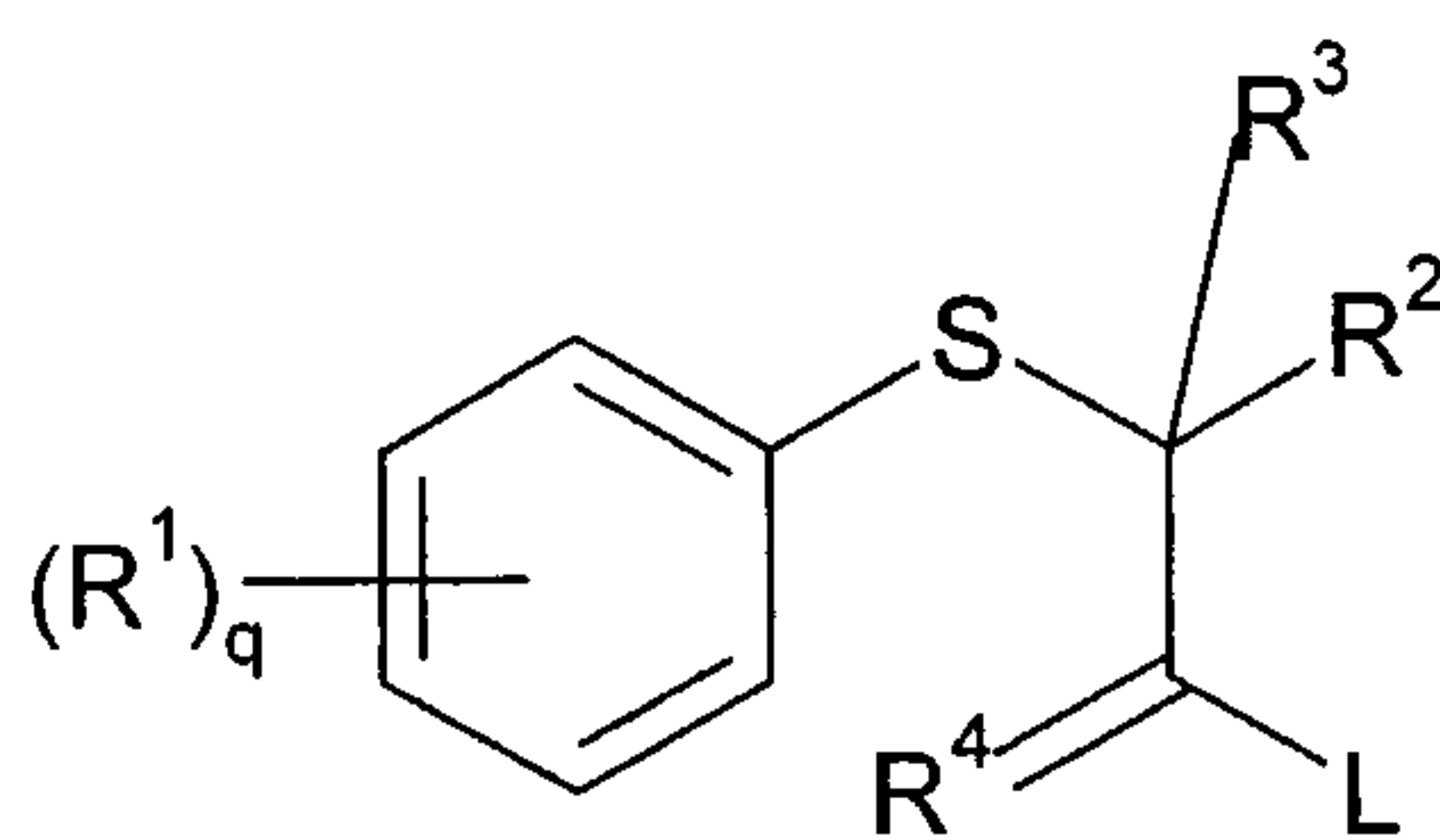


IV,

in which

R^1, R^2, R^3, R^4 and q have the meanings indicated in Claim 1,

is converted into the free acid by saponification, and this is subsequently converted by conventional methods into the corresponding formula V

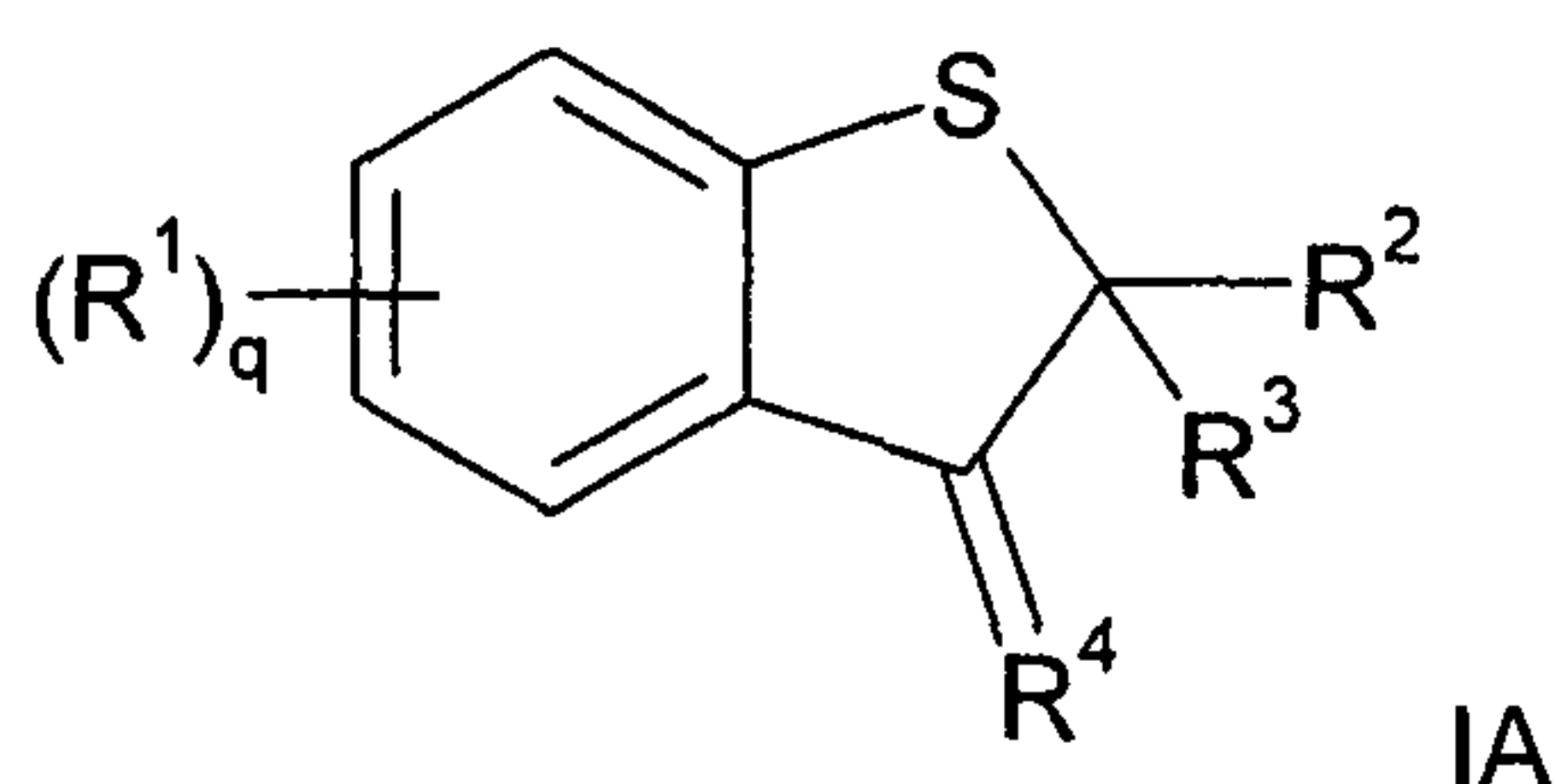


V,

in which

L denotes Hal or a reactive modified OH group, such as, for example, triflate, nonaflate, tosylate, mesylate or benzenesulfonate, and R^1, R^2, R^3, R^4 and q have the meanings indicated in Claim 1, and

the compound of the formula V is then converted in the presence of a suitable catalyst into formula IA

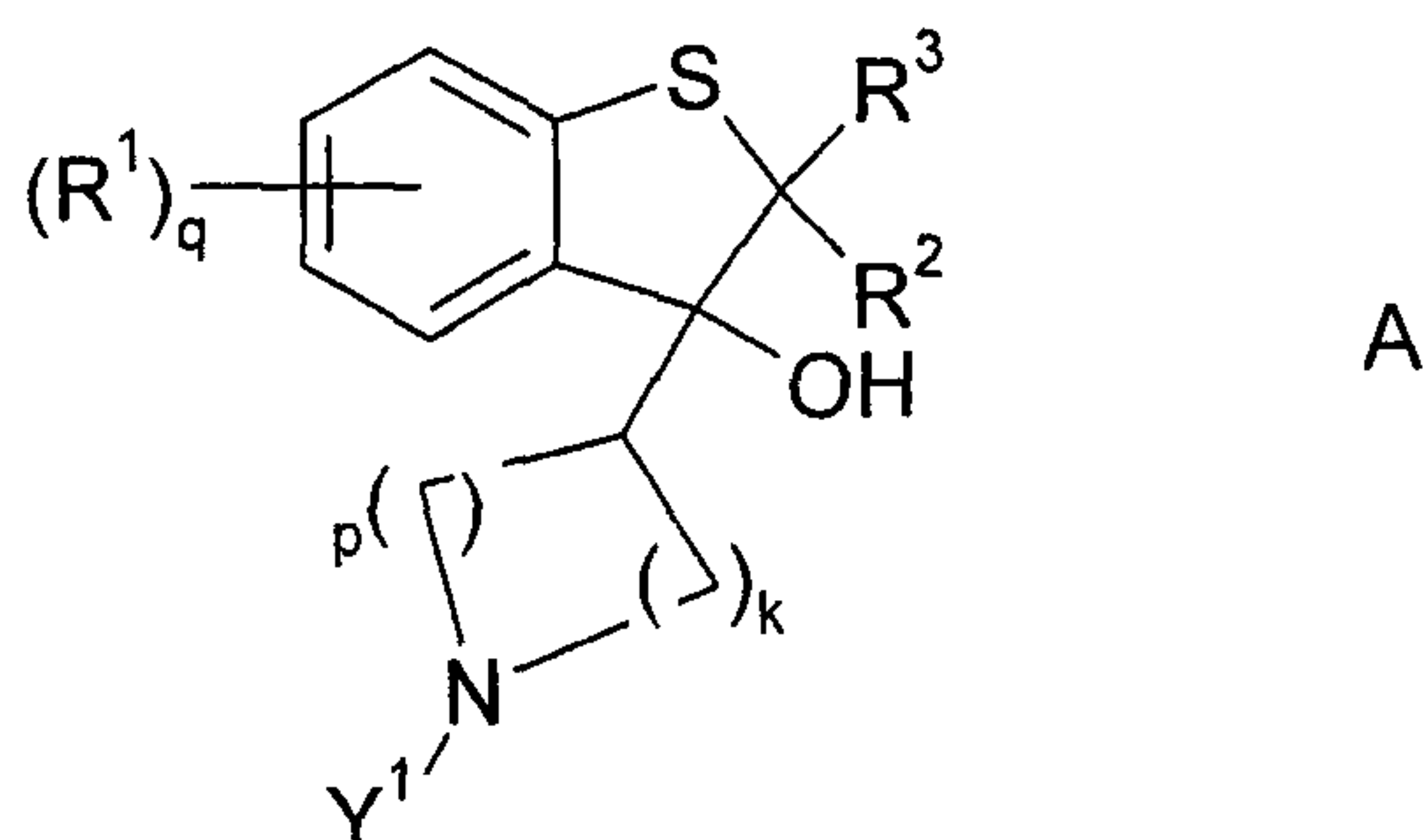


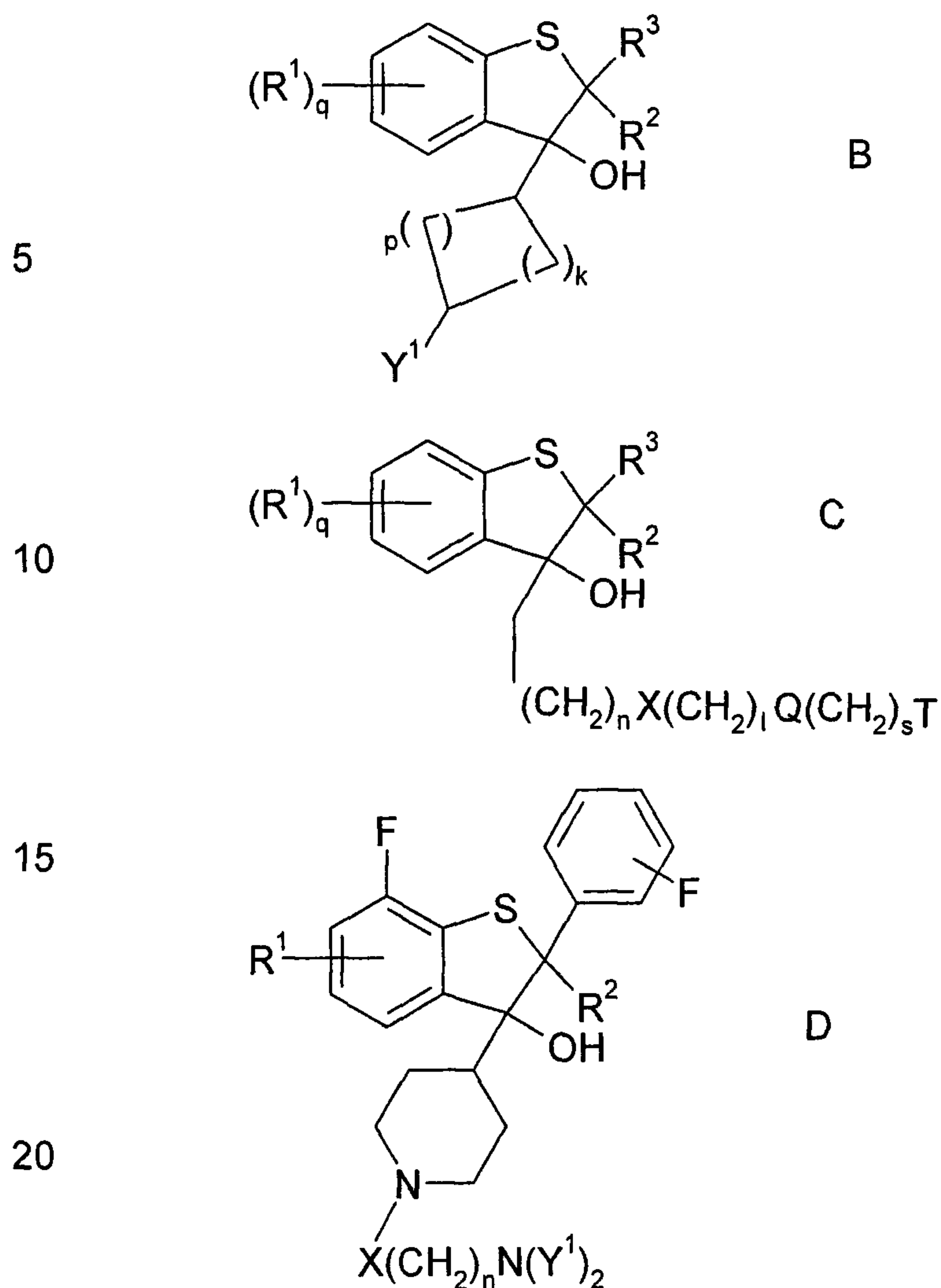
in which

R^1 , R^2 , R^3 , R^4 and q have the meanings indicated in Claim 1, and optionally compounds of the formula I in which R^2 and/or R^3 denote H are converted into further compounds of the formula I in which R^2 and/or R^3 have a meaning other than H by reaction in a base and an alkylating reagent, and optionally compounds of the formula I in which R^4 denotes O are converted into the further compounds of the formula I in which R^4 has the meaning indicated in Claim 1 by reaction with corresponding organometallic reagents and subsequent elimination, and optionally compounds of the formula I in which W denotes SO or SO₂ are obtained by reaction with suitable oxidants.

9. Process according to Claim 8, characterised in that the catalyst used is a Friedel-Crafts catalyst.

10. Compounds of the formulae A, B, C and D:





in which R^1 , R^2 , R^3 , Y^1 , X , Q , T , n , l , p , k , q and s have the meaning indicated in Claim 1, and the sulfoxides and sulfones obtainable by oxidation of the ring sulfur atom of compounds A to D.

11. Medicaments comprising at least one compound of the formula I according to Claim 1 to 7 and/or pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.
12. Use of compounds according to Claim 1 to 7 and pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for the preparation of a

medicament for the treatment of diseases in which the inhibition, regulation and/or modulation of the mitotic motor protein Eg5 plays a role.

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13. Use of compounds according to Claim 1 to 7 for the preparation of a medicament for the treatment and prophylaxis of cancer diseases.

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14. Use according to Claim 13, where the cancer diseases are associated with a tumour from the group of tumours of the squamous epithelium, the bladder, the stomach, the kidneys, of head and neck, the oesophagus, the cervix, the thyroid, the intestine, the liver, the brain, the prostate, the urogenital tract, the lymphatic system, the stomach, the larynx and/or the lung.

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15. Use according to Claim 14, where the tumour originates from the group monocytic leukaemia, lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, glioblastomas and breast carcinoma and colocal carcinoma.

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16. Use according to Claim 15, where the disease to be treated is a tumour of the blood and immune system.

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17. Use according to Claim 16, where the tumour originates from the group of acute myelotic leukaemia, chronic myelotic leukaemia, acute lymphatic leukaemia and/or chronic lymphatic leukaemia.

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18. Use of compounds of the formula I according to Claim 1 to 7 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of tumours, where a therapeutically effective amount of a compound of the formula I is administered in combination with radiotherapy and a compound from the group 1) oestrogen receptor modulator, 2) androgen receptor modulator, 3)

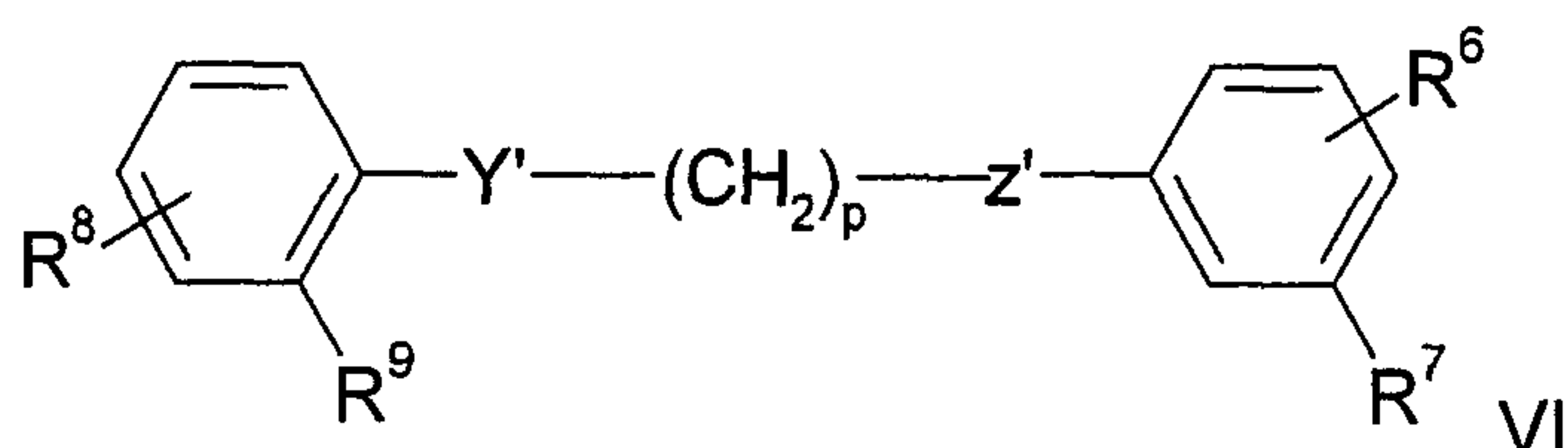
retinoid receptor modulator, 4) cytotoxic agent, 5) antiproliferative agent, 6) prenyl protein transferase inhibitor, 7) HMG-CoA reductase inhibitor, 8) HIV protease inhibitor, 9) reverse transcriptase inhibitor and 10) further angiogenesis inhibitors.

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19. Use of compounds of the formula I according to Claim 1 to 7 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of tumours in combination with a therapeutically effective amount of one or more compounds of the formula VI

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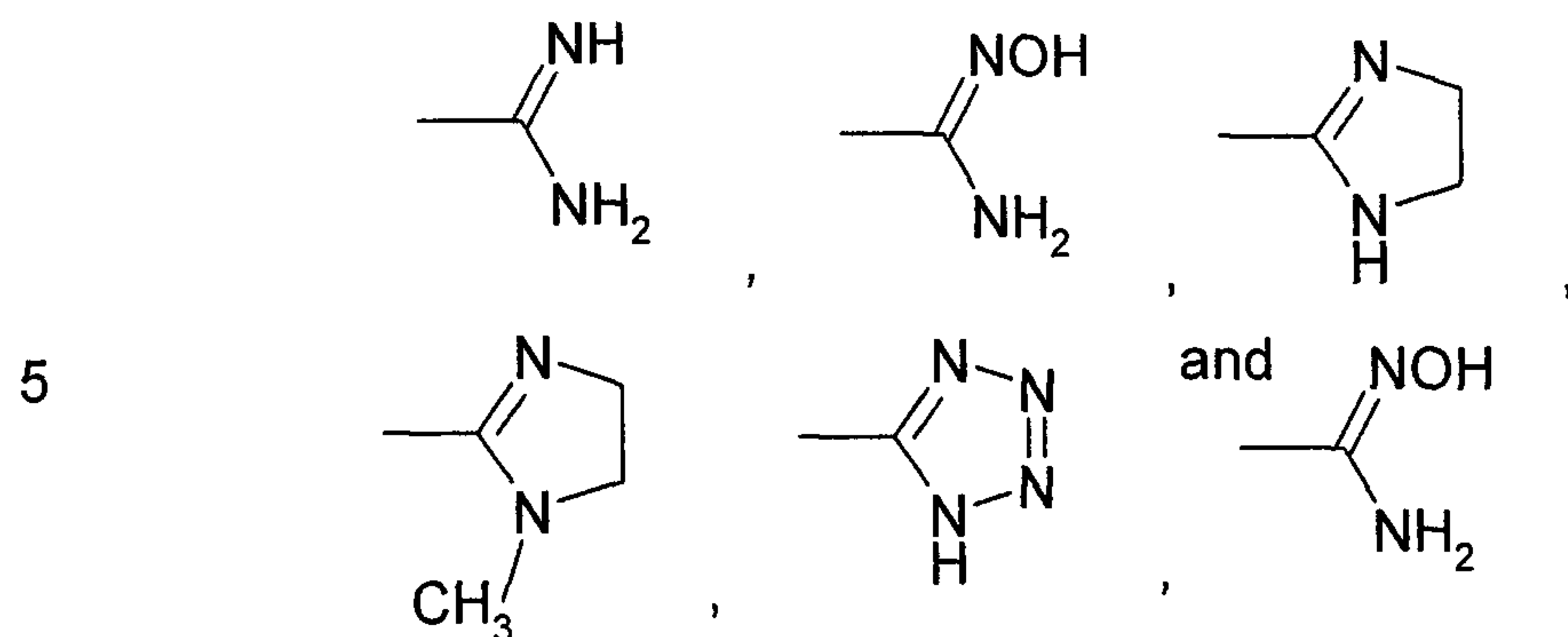
in which

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Y' and Z' each, independently of one another, denote O or N, R⁷ and R⁹ each, independently of one another, denote H, OH, halogen, OC1-10-alkyl, OCF₃, NO₂ or NH₂, n denotes an integer between 2 and 6, in each case inclusive, and R⁶ and R⁸ are each, independently of one another, in the meta- or para-position and are selected from the group:

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where

the first and second compounds are administered simultaneously or within 14 days of one another in amounts which are sufficient to inhibit the growth of a tumour.

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20. Process for the preparation of the compounds according to Claim 8 or 9, characterised in that the compounds of the formula I in which R⁴ denotes O are reacted with suitable organometallic reagents and subjected to aqueous work-up.

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