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(72) Inventeurs/Inventors:
DAHNKE, KARL ROBERT, US;
GAJEWSKI, ROBERT PETER, US;
JONES, CHARLES DAVID, US;
LINEBARGER, JARED HARRIS, US;
...

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(54) Title: PHENYL-THIOPHENE TYPE VITAMIN D RECEPTOR MODULATORS

(57) **Abrégé/Abstract:**

The present invention relates to novel, non-secosteroidal, phenyl-thiophene compounds with vitamin D receptor (VDR) modulating activity that are less hypercalcemic than $1\alpha,25$ dihydroxy vitamin D₃. These compounds are useful for treating bone disease and psoriasis.



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(71) Applicant (*for all designated States except US*): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DAHNIKE, Karl, Robert** [US/US]; 5160 Rocky Cay Court, Carmel, IN 46033 (US). **GAJEWSKI, Robert, Peter** [US/US]; 1501 Friendship Drive, Indianapolis, IN 46217 (US). **JONES, Charles, David** [US/US]; 223 East Brunswick Avenue, Indianapolis, IN 46227 (US). **LINEBARGER, Jared, Harris** [US/US]; 5723 Kingsley Drive, Indianapolis, IN 46220 (US). **LU, Jianliang** [CN/US]; 11921 Castlestone Drive, Fishers, IN 46038 (US). **MA, Tianwei** [CN/US]; 5676 Sapphire Drive, Carmel, IN 46033 (US). **NAGPAL, Sunil** [US/US]; 5258 Comanche Trail, Carmel, IN 46033 (US). **SIMARD, Todd, Parker** [US/US]; 14375 Leland Muse, Fishers, IN 46038 (US). **YEE, Ying, Kwong** [US/US]; 5127 Briarstone Trace, Carmel, IN 46033 (US). **BUNEL, Emilio, Enrique** [CL/US]; 2991 Topaz Lane, Carmel, IN 46032 (US). **STITES, Ryan, Edward** [US/US]; 3406 H Admar Court, Indianapolis, IN 46205 (US).

(74) Agents: **BENJAMIN, Roger, S** et al.; Eli Lilly and Company, P. O. Box 6288, Indianapolis, IN 46206-6288 (US).

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(54) Title: PHENYL-THIOPHENE TYPE VITAMIN D RECEPTOR MODULATORS

(57) Abstract: The present invention relates to novel, non-secosteroidal, phenyl-thiophene compounds with vitamin D receptor (VDR) modulating activity that are less hypercalcemic than 1 α ,25 dihydroxy vitamin D₃. These compounds are useful for treating bone disease and psoriasis.



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DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

PHENYL-THIOPHENE TYPE VITAMIN D RECEPTOR MODULATORS

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BACKGROUND OF THE INVENTION

Vitamin D₃ Receptor (VDR) is a ligand dependent transcription factor that belongs to the superfamily of nuclear hormone receptors. The VDR protein is 427 amino acids, with a molecular weight of ~50 kDa. The VDR ligand, 1 α ,25-dihydroxyvitamin D₃ (the hormonally active form of Vitamin D) has its action mediated by its interaction with the nuclear receptor known as Vitamin D receptor ("VDR"). The VDR ligand, 1 α ,25-dihydroxyvitamin D₃ (1 α ,25(OH)₂D₃) acts upon a wide variety of tissues and cells both related to and unrelated to calcium and phosphate homeostasis.

The activity of 1 α ,25-dihydroxyvitamin D₃ (1 α ,25(OH)₂D₃) in various systems suggests wide clinical applications. However, use of conventional VDR ligands is hampered by their associated toxicity, namely hypercalcemia (elevated serum calcium). Currently, 1 α ,25(OH)₂D₃, marketed as Rocaltrol® pharmaceutical agent (product of Hoffmann-La Roche), is administered to kidney failure patients undergoing chronic kidney dialysis to treat hypocalcemia and the resultant metabolic bone disease. Other therapeutic agents, such as Calcipotriol® (synthetic analog of 1 α ,25(OH)₂D₃) show increased separation of binding affinity on VDR from hypercalcemic activity.

Recently, chemical modifications of 1 α ,25(OH)₂D₃ have yielded analogs with attenuated calcium mobilization effects (R. Bouillon et. al., Endocrine Rev. 1995, 16, 200-257). One such analog, Dovonex® pharmaceutical agent (product of Bristol-Meyers Squibb Co.), is currently used in Europe and the United States as a topical treatment for mild to moderate psoriasis (K. Kragballe et. al., Br. J. Dermatol. 1988, 119, 223-230).

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Other vitamin D₃ mimics have been described in the publication, Vitamin D Analogs: Mechanism of Action of Therapeutic Applications, by Nagpal, S.; Lu, J.; Boehm, M. F., Curr. Med. Chem. 2001, 8, 1661-1679.

Although some degree of separation between the beneficial action and calcium raising (calcemic) effects has been achieved with these VDR ligands, to date the separation has been insufficient to allow for oral administration to treat conditions such as osteoporosis, cancers, leukemias, and severe psoriasis.

One example of a major class of disorder that could benefit from VDR mediated biological efficacy in the absence of hypercalcemia is osteoporosis. Osteoporosis is a systemic disorder characterized by decreased bone mass and microarchitectural deterioration of bone tissue leading to bone fragility and increased susceptibility to fractures of the hip, spine, and wrist (World Health Organization WHO 1994). Osteoporosis affects an estimated 75 million people in the United States, Europe, and Japan.

Within the past few years, several antiresorptive therapies have been introduced. These include bisphosphonates, hormone replacement therapy (HRT), a selective estrogen receptor modulator (SERM), and calcitonins. These treatments reduce bone resorption, bone formation, and increase bone density. However, none of these treatments increase true bone volume nor can they restore lost bone architecture.

Synthetic vitamin D receptor (VDR) ligands with reduced calcemic potential have been synthesized. For example, a class of bis-phenyl compounds stated to mimic 1 α , 25-dihydroxyvitamin D₃ is described in US Patent No. 6,218,430 and the article; "Novel nonsecosteroidal vitamin D mimics exert VDR-modulating activities with less calcium mobilization than 1 α , 25-Dihydroxyvitamin D₃" by Marcus F. Boehm, et. al., Chemistry & Biology 1999, Vol 6, No. 5, pgs. 265-275.

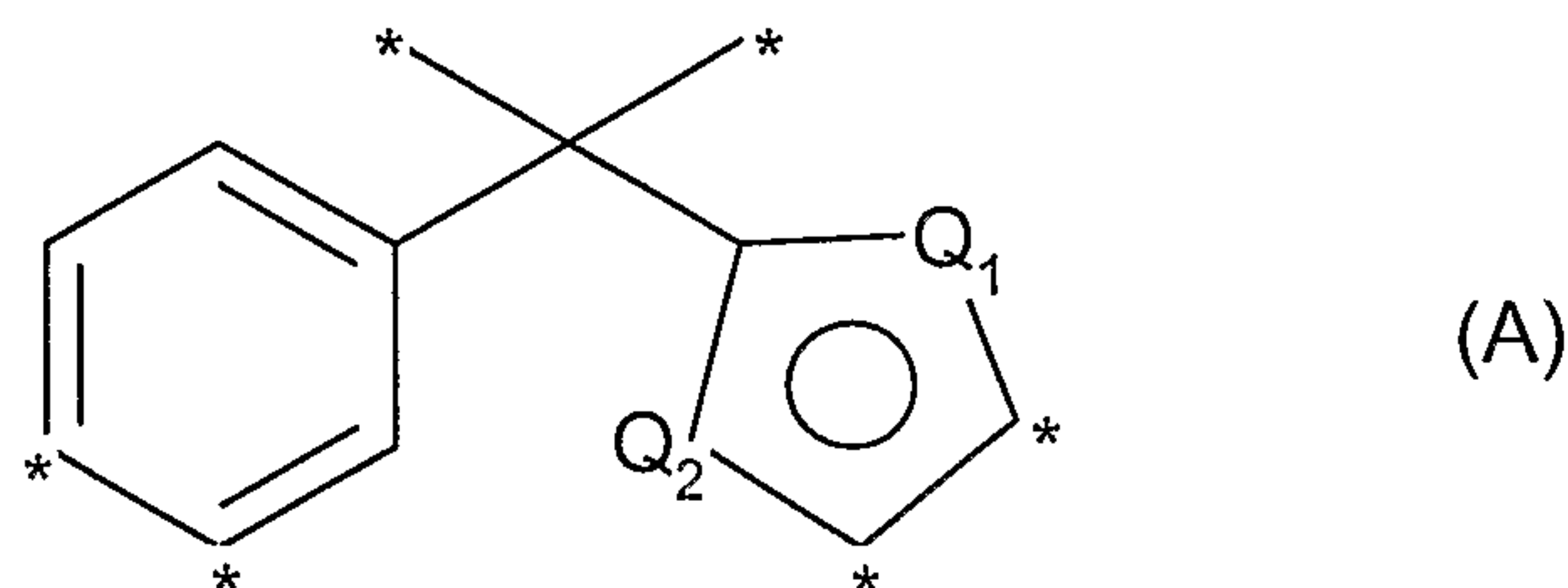
There remains a need for improved treatments using alternative or improved pharmaceutical agents that mimic 1 α , 25-dihydroxyvitamin D₃ to stimulate bone formation, restore bone quality, and treat other diseases without the attendant disadvantage of hypercalcemia.

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SUMMARY OF THE INVENTION

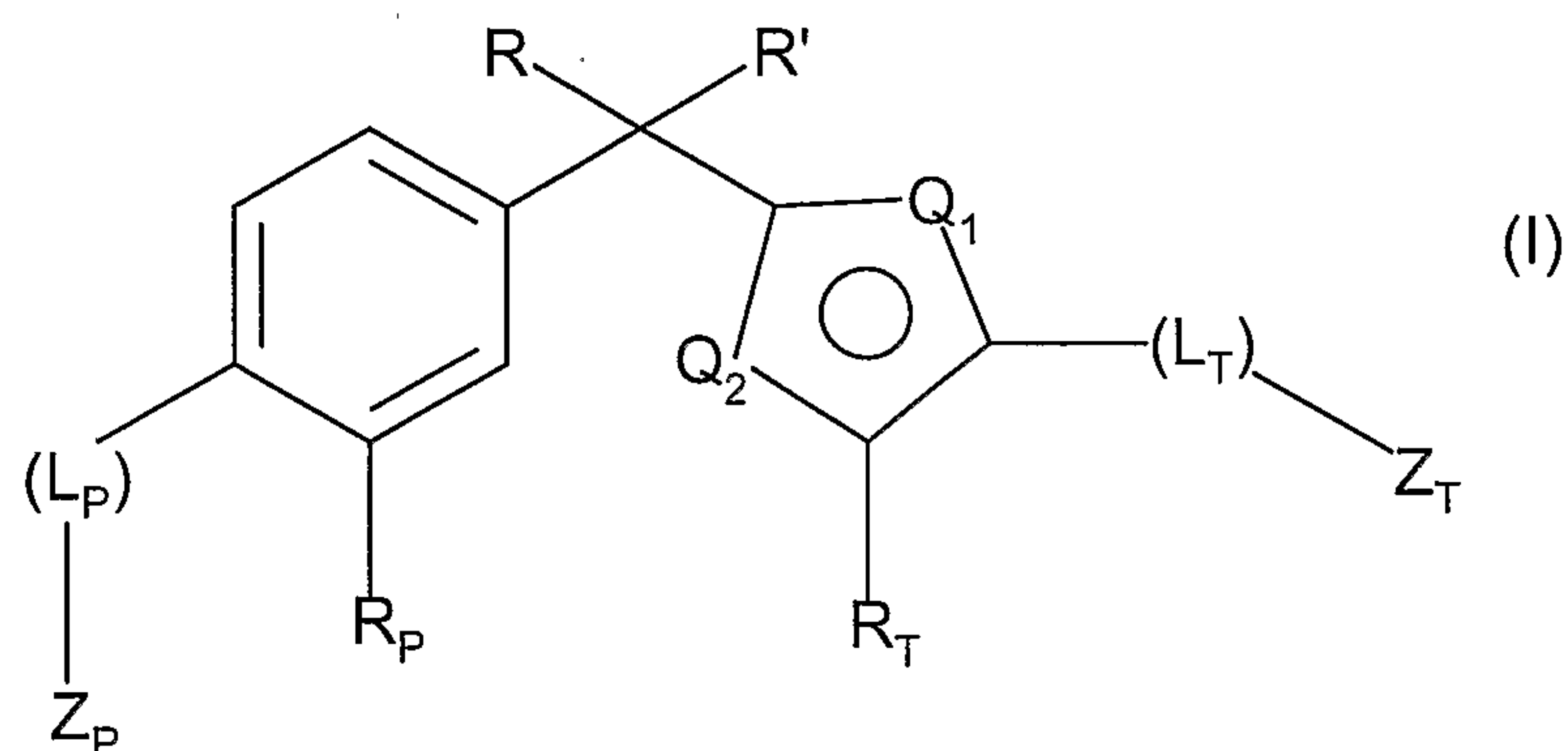
Novel compounds having a nucleus of formula “(A)” have been found effective as Vitamin D Receptor (VDR) modulators:

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where one of the pair of ring atoms (Q₁, Q₂) is sulfur and the other is carbon and each asterisk mark (“*”) is a point of substitution. Compounds of the present invention with VDR modulating activities are represented by formula (I)

10 formula I:



wherein the variables R, R', Q₁, Q₂, R_P, R_T, L_T, L_P, Z_T, and Z_P are as hereinafter defined. The inventors have discovered that compounds described herein display the desirable cell differentiation and antiproliferative effects of 1,25(OH)₂D₃ with reduced calcium mobilization (calcemic) effects.

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In another aspect, the present invention is directed towards pharmaceutical compositions containing pharmaceutically effective amounts of compounds of formulae I or a pharmaceutically acceptable salt or prodrug thereof, either singly or in combination, together with pharmaceutically acceptable carriers and/or auxiliary agents.

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Another aspect of the invention are novel chemical intermediates suitable for preparing the compounds of Formula I.

Another aspect of the invention is to use the compounds of the invention to treat

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or prevent disease states responsive to Vitamin D receptor ligands.

Another aspect of the invention is the prevention and treatment of abscess, acne, adhesion, actinic keratosis, alopecia, Alzheimer's disease, autoimmune induced diabetes, bone fracture healing, breast cancer, Crohn's disease, colon cancer, Type I diabetes, host-graft rejection, hypercalcemia, Type II diabetes, leukemia, multiple sclerosis, insufficient sebum secretion, osteomalacia, osteoporosis, insufficient dermal firmness, insufficient dermal hydration, myelodysplastic syndrome, psoriatic arthritis, prostate cancer, psoriasis, renal osteodystrophy, rheumatoid arthritis, scleroderma, seborrheic dermatitis, skin cancer, systemic lupus erythematosus, ulcerative colitis and wrinkles; by administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Formula I.

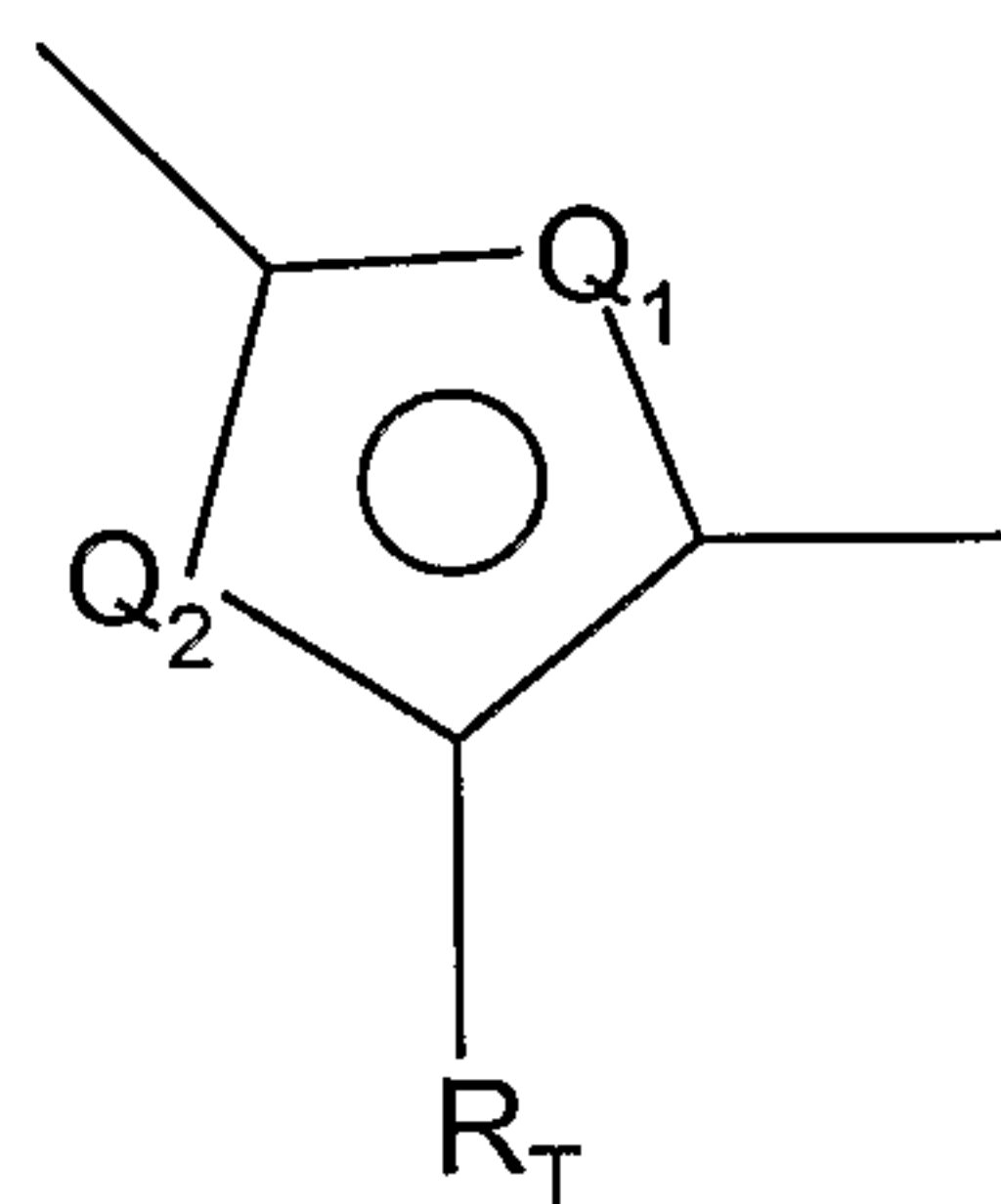
Another aspect of the invention is the use of the compounds of Formula I for treating or preventing disease states mediated by the Vitamin D receptor.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions:

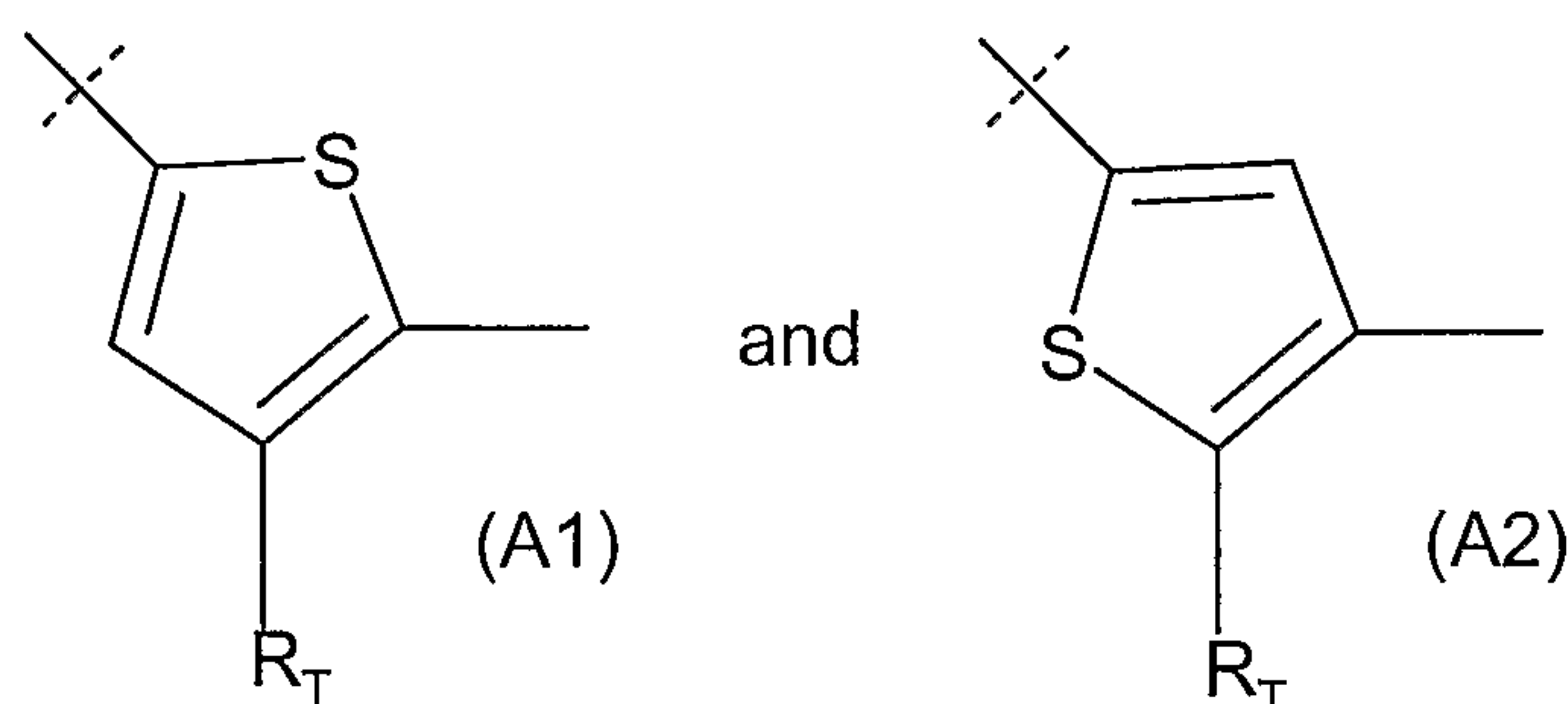
In accordance with the present invention and as used herein, the following terms are defined to have the following meanings, unless explicitly stated otherwise:

The structural formula:



is a substructure of Formula I and represents alternative thiophene substructures, namely;

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dependent on whether Q1 is sulfur when Q2 is carbon (A1) or Q1 is carbon when Q2 is sulfur (A2).

The term "alkenyl" refers to aliphatic groups wherein the point of attachment is a carbon-carbon double bond, for example vinyl, 1-propenyl, and 1-cyclohexenyl. Alkenyl groups may be straight-chain, branched-chain, cyclic, or combinations thereof, and may be optionally substituted. Suitable alkenyl groups have from 2 to about 20 carbon atoms.

The term "alkoxy" refers to -OR wherein R is an aliphatic or aromatic group which may be optionally substituted. Methoxy, ethoxy, propoxy, butoxy, and phenoxy are examples of alkoxy groups.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain, cyclic and any combinations thereof. Alkyl groups may further be divided into "primary", "secondary", and "tertiary" alkyl groups. In primary alkyl groups, the carbon atom of attachment is substituted with zero (methyl) or one organic radical. In secondary alkyl groups, the carbon atom of attachment is substituted with two organic radicals. In tertiary alkyl groups, the carbon atom of attachment is substituted with three organic radicals.

The term "cycloalkyl" includes organic radicals such as cyclopropanyl, cyclobutanyl, and cyclopentyl.

The term, "cycloalkenyl" includes organic radicals such as cyclopropenyl, cyclobutenyl, cyclopentenyl, and cyclohexenyl.

The term, "terminal hydroxyalkyl" is a group selected from 3-methyl-3-hydroxypentyl; 3-ethyl-3-hydroxypentyl; 3-ethyl-3-hydroxy-4-methylpentyl; 3-ethyl-3-hydroxy-4,4-dimethylpentyl; 3-methyl-3-hydroxy-4,4-dimethylpentyl; 1-hydroxycycloalkenyl; and 1-hydroxycycloalkyl.

The term, "C₁-C₅ fluoroalkyl" is an alkyl group containing fluorine and includes organic radicals such as -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, -CHF₂CF₃, -CH₂CF₃,

-CH₂CHF₂, and -CH₂CH₂F, with -CF₃ being preferred.

The term, "Active Ingredient" refers to a compound of the invention represented by any of (i) formulae I, II, III, IV, (ii) the product of any example set out herein, or (iii) a compound identified in any row of Tables 1, 2, 3, or 4; or a salt or prodrug derivative of
5 the preceding compound.

The abbreviation, "Me" means methyl.

The abbreviation, "Et" means ethyl.

The abbreviation, "iPr" means 1-methylethyl.

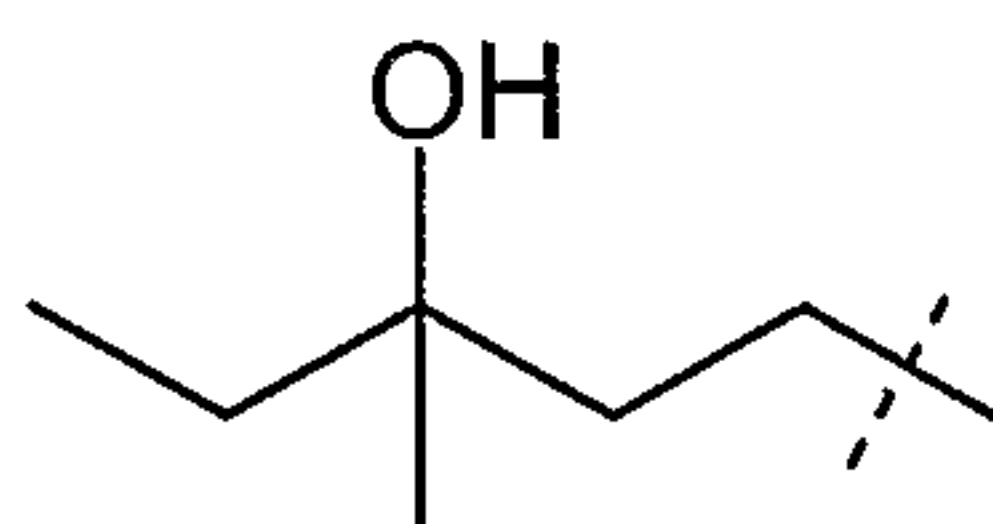
The abbreviation, "tBu" means 1,1-dimethylethyl.

10 The symbol "-(CH₂)₂- is equivalent to -CH₂-CH₂-.

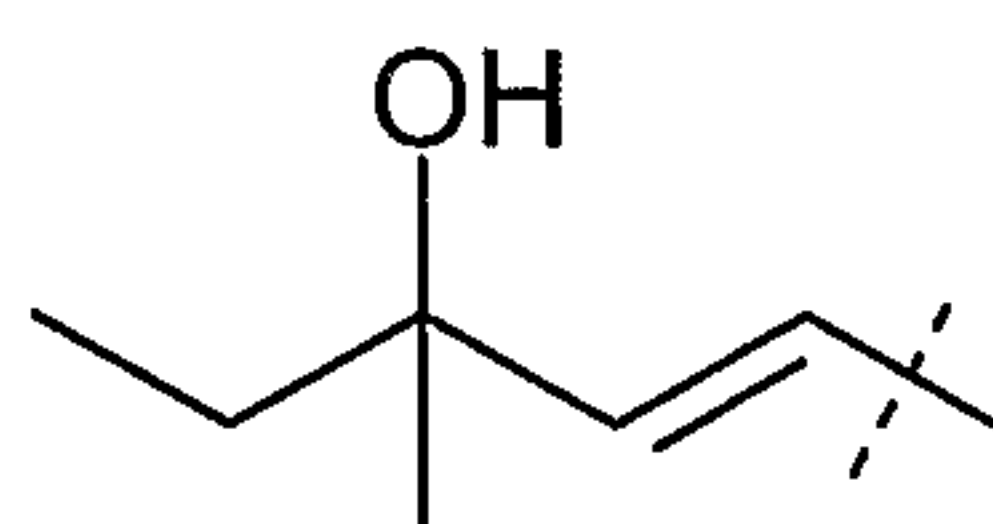
The symbol, "*" in a structural formula identifies a chiral center (except in formula "A" where it symbolizes substitution).

The univalent symbol "-O" in any structural formula is a hydroxyl group (-OH).

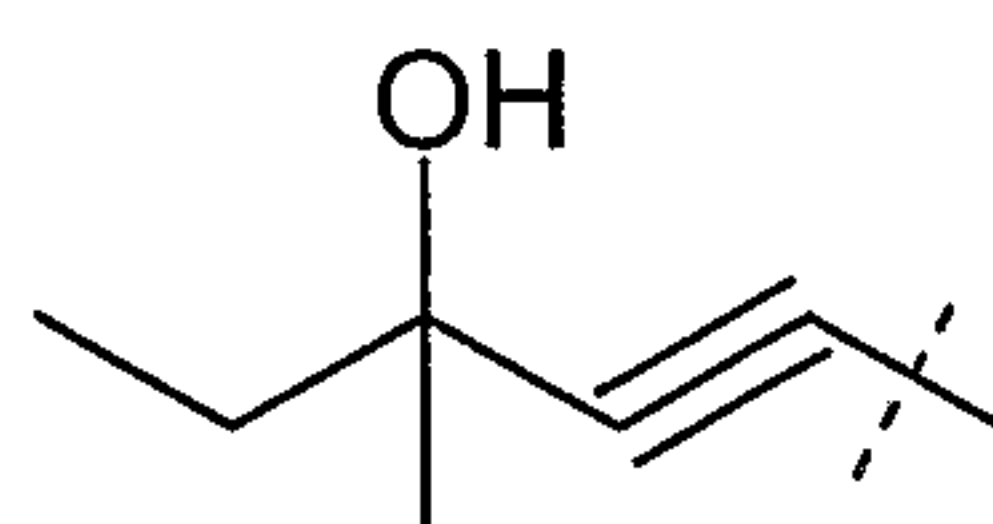
15 The term, "3-methyl-3-hydroxypentyl" refers to the radical having the structural formula:



The term, "3-methyl-3-hydroxypentenyl" refers to the radical having the structural formula:

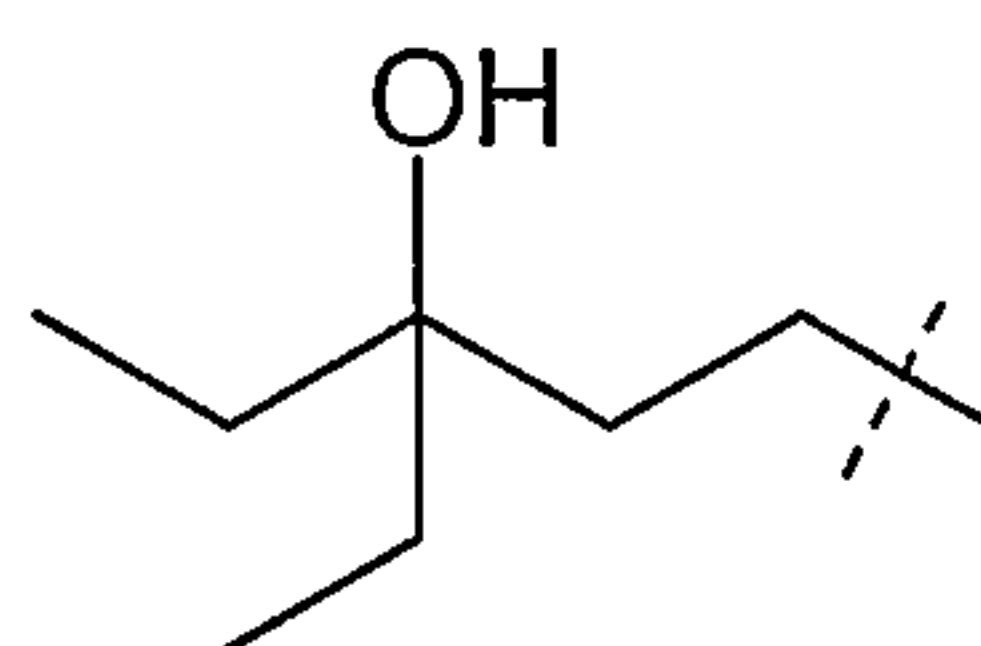


20 The term, "3-methyl-3-hydroxypentynyl" refers to the radical having the structural formula:

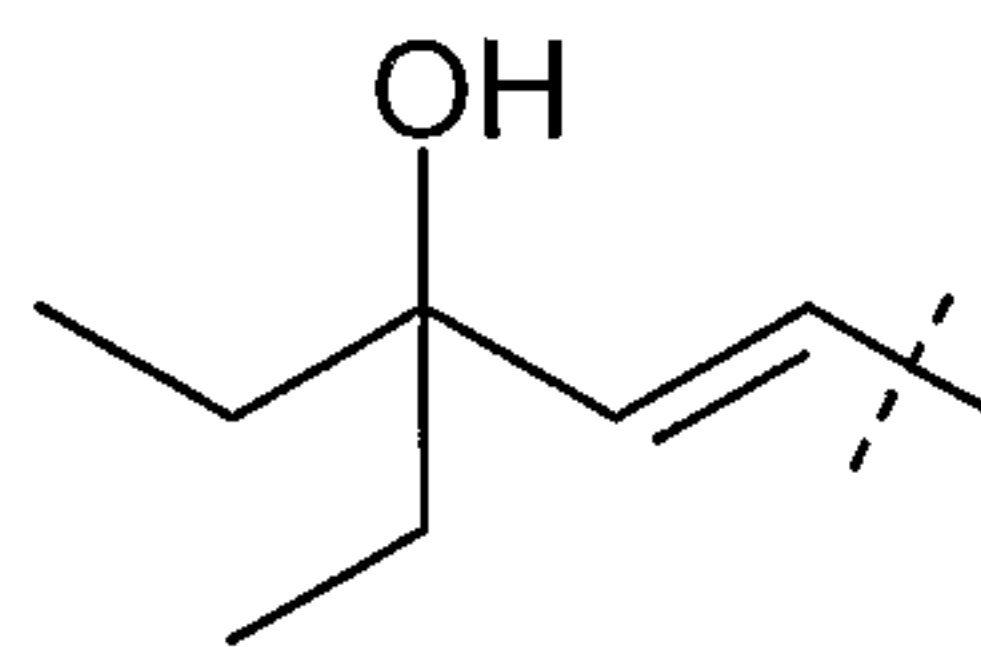


25 The term, "3-ethyl-3-hydroxypentyl" refers to the radical having the structural formula:

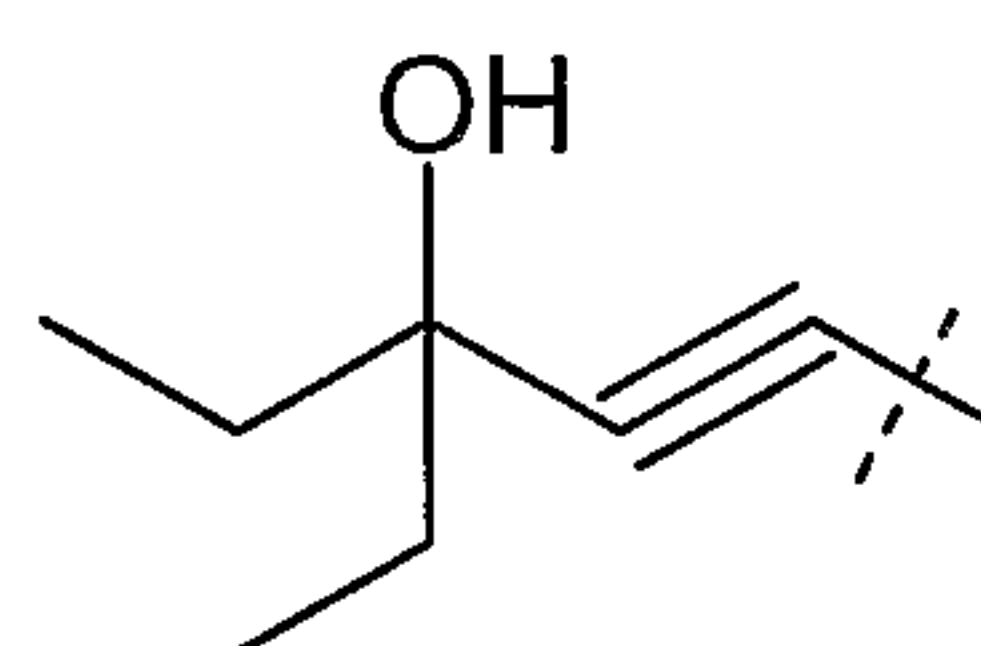
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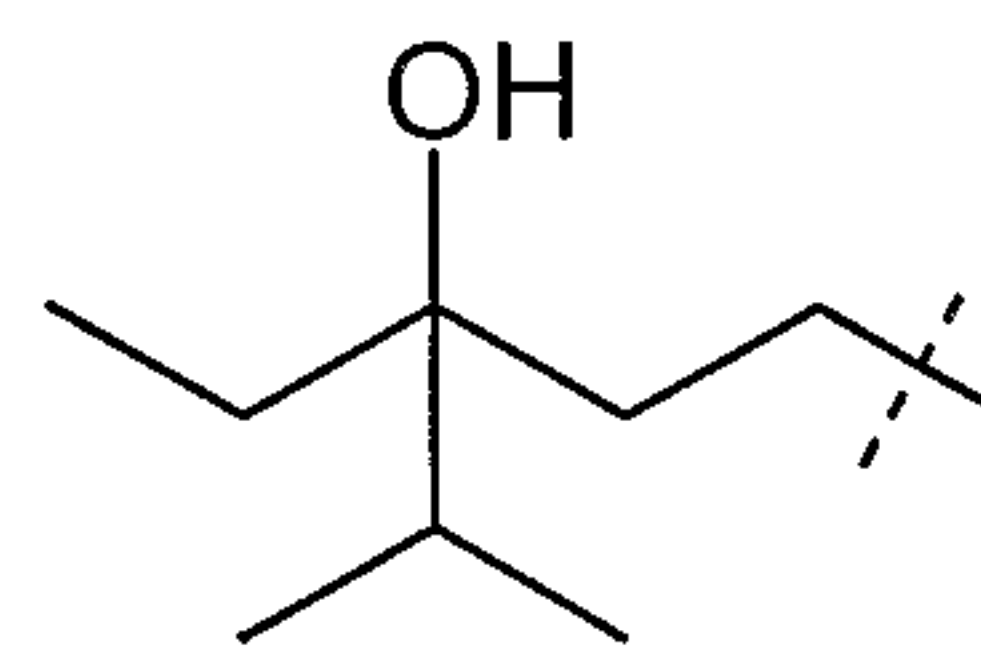
The term, “3-ethyl-3-hydroxypentenyl” refers to the radical having the structural formula:



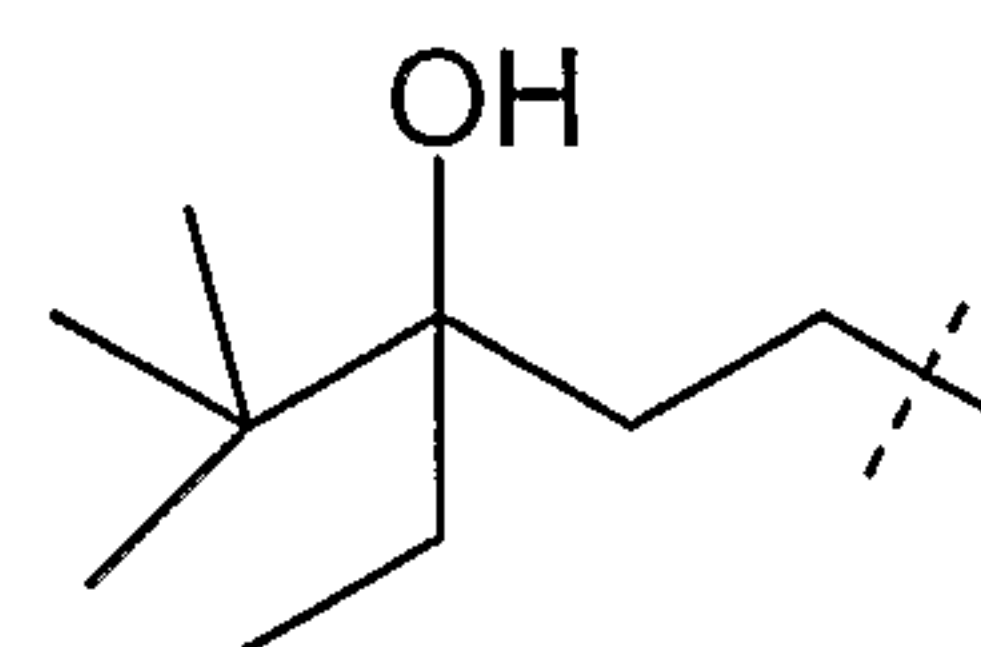
5 The term, “3-ethyl-3-hydroxypentynyl” refers to the radical having the structural formula:



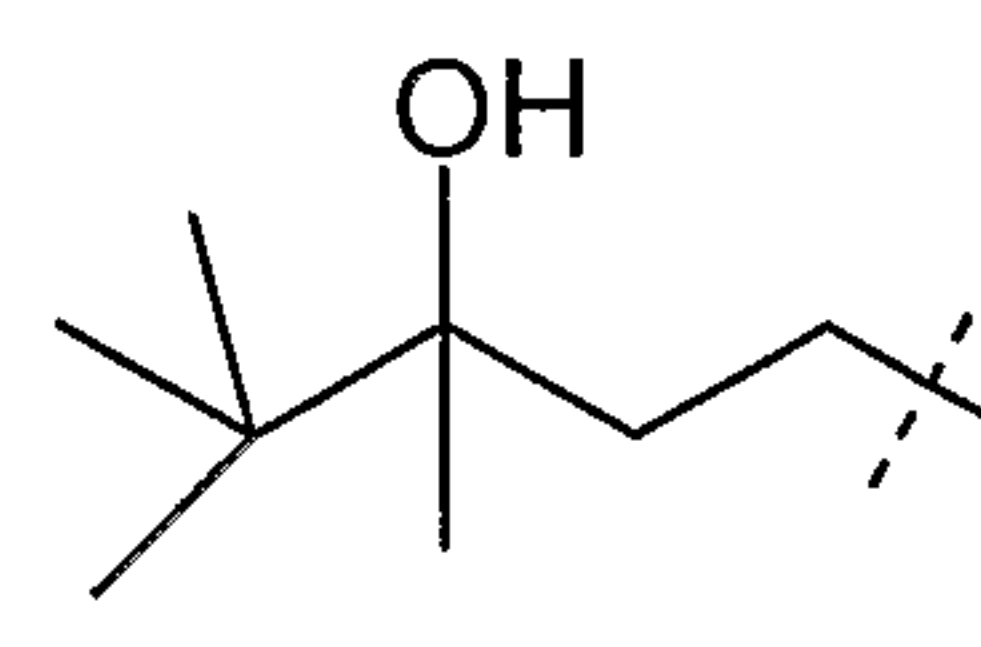
10 The term, “3-ethyl-3-hydroxy-4-methylpentyl” refers to the radical having the structural formula:



The term, “3-ethyl-3-hydroxy-4,4-dimethylpentyl” refers to the radical having the structural formula:

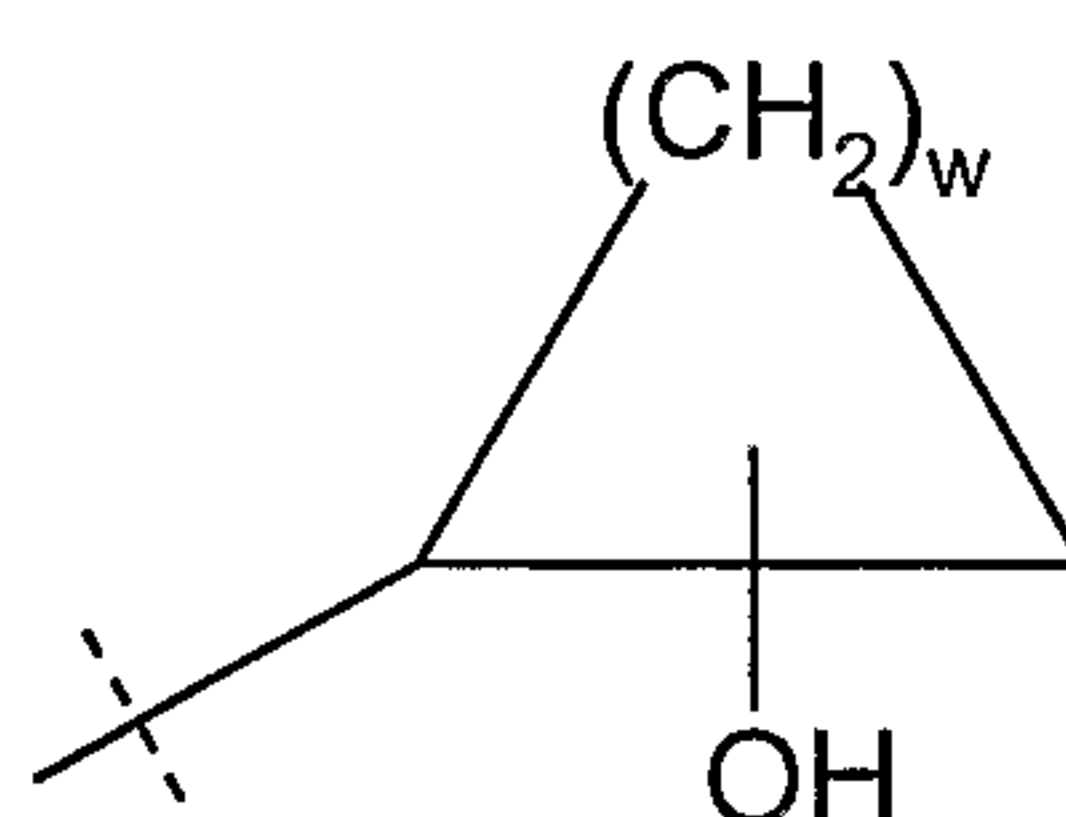


15 The term, “3-methyl-3-hydroxy-4,4-dimethylpentyl” refers to the radical having the structural formula:



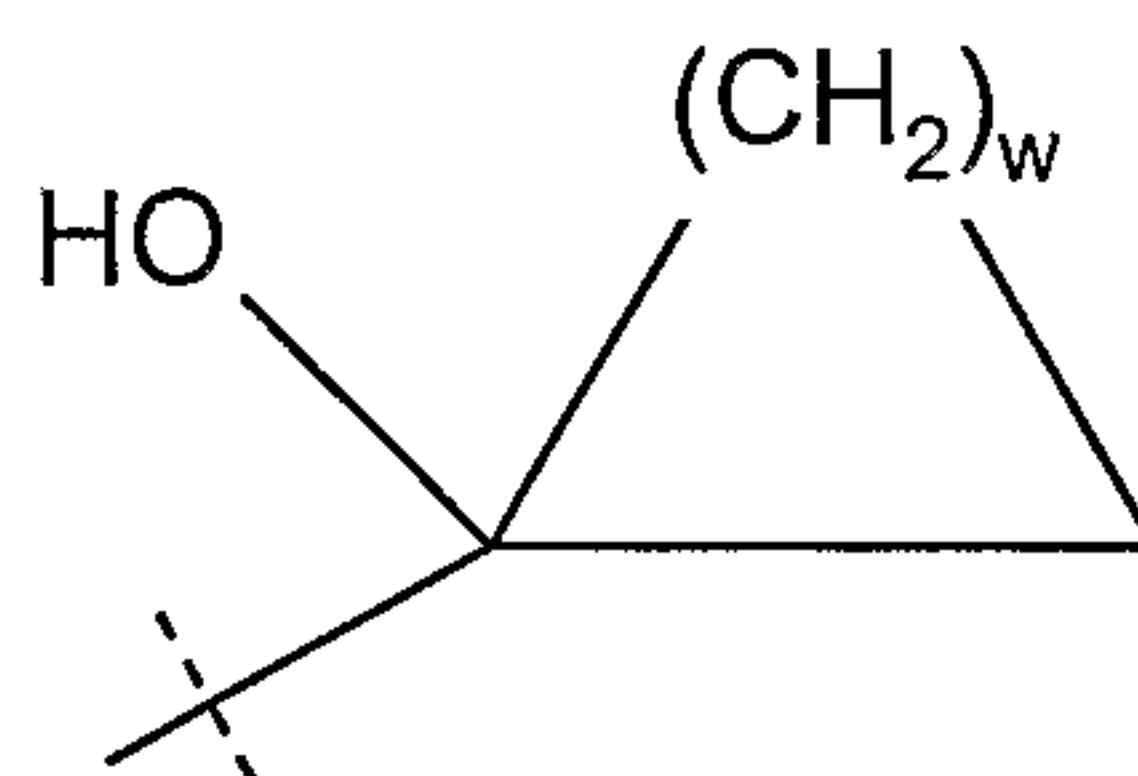
The term, "1-hydroxycycloalkenyl" refers to a radical selected from
 1-hydroxycyclopentenyl, 1-hydroxycyclohexenyl,
 5 1-hydroxycycloheptenyl, or 1-hydroxycyclooctenyl.

The term "hydroxycycloalkyl" refers to a radical having the general structural
 formula:



10 where w is an integer from 1 to 6 and the hydroxyl radical is substituted on any ring
 carbon atom.

The term "1-hydroxycycloalkyl" refers to a radical having the general structural
 formula:



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Examples of 1-hydroxycycloalkyl radicals are
 1-hydroxycyclopropyl, 1-hydroxycyclobutyl, 1-hydroxycyclopentyl,
 1-hydroxycyclohexyl, 1-hydroxycycloheptyl, and 1-hydroxycyclooctyl.

The abbreviation, "Me" means methyl.

20 The abbreviation, "Et" means ethyl.

The abbreviation, "iPr" means 1-methylethyl.

The abbreviation, "tBu" means 1,1-dimethylethyl.

The abbreviation, "3Me3OH-Pentyl" means 3-methyl-3-hydroxypentyl.

The abbreviation, "3Me3OH-Pentenyl" means 3-methyl-3-hydroxypentenyl

25 The abbreviation, "3Me3OH-Pentynyl" means 3-methyl-3-hydroxypentynyl

The abbreviation, "3Et3OH-Pentyl" means 3-ethyl-3-hydroxypentyl.

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The abbreviation, "3Et3OH-Pentenyl" means 3-ethyl-3-hydroxypentenyl

The abbreviation, "3Et3OH-Pentynyl" means 3-ethyl-3-hydroxypentynyl

The abbreviation, "3Et3OH4Me-Pentyl" means 3-ethyl-3-hydroxy-4-methylpentyl.

5 The abbreviation, "3Et3OH44DiMe-Pentyl" means 3-ethyl-3-hydroxy-4,4-dimethylpentyl.

The abbreviation, "3Me3OH44DiMe-Pentyl" means 3-methyl-3-hydroxy-4,4-dimethylpentyl.

The term "C₁-C₅ alkyl" is an alkyl substituent selected from the group consisting of : methyl; ethyl; propyl; 1-methylethyl; 1-methylpropyl; 2-methylpropyl; 1,1-
10 dimethylethyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; and 2,2-dimethylpropyl. The preferred groups are 2-methylpropyl and 1,1-dimethylethyl, with the 1,1-dimethylethyl group being most preferred.

The symbol "-(C₁-C₅ alkyl)₂" when included as part of a substituent group means two independently selected C₁-C₅ alkyl groups, for example, the generic formula:

15 $-(C_1-C_5 \text{ alkyl})-NH-(C_1-C_5 \text{ alkyl})_2$

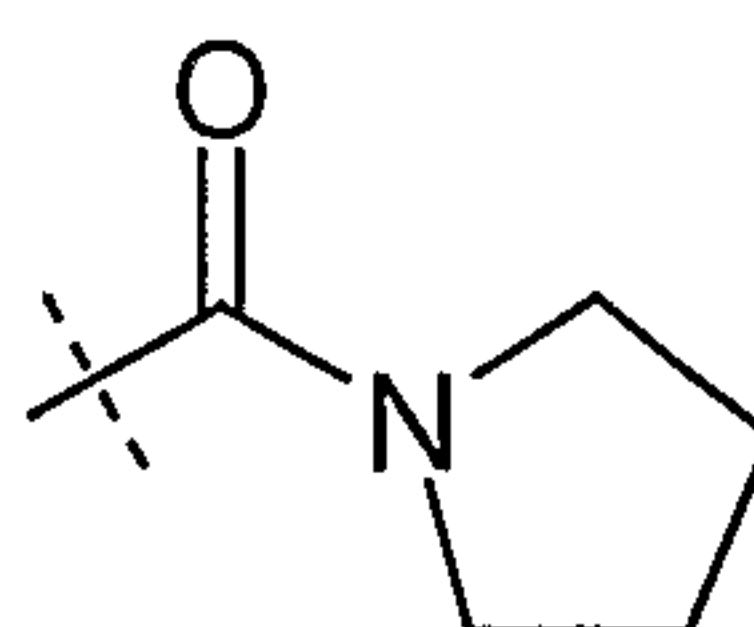
would be descriptive of species including;

$-(C_1-C_5 \text{ alkyl})-NH-(CH_3)_2$ or $-(C_1-C_5 \text{ alkyl})-NH-(CH_3)(C_2H_5)$

The term "amide" refers to derivatives of acids wherein one or more hydroxyl groups is replaced with a amino groups. The amino groups are optionally substituted with
20 one or two organic radicals which may be aliphatic or aromatic. Arnides may be cyclic. The term "carboxamide" refers to an amide of a carboxylic acid. The term "aminocarbonyl" refers to carboxamide radicals wherein the point of attachment is the carbonyl carbon. The term "acylamido" refers to carboxamide radicals wherein the point of attachment is the nitrogen atom.

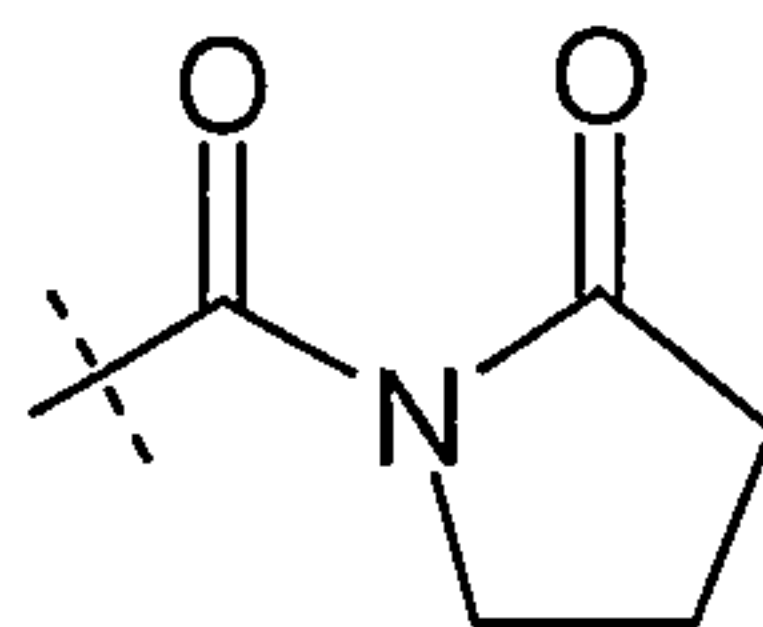
25 The term, "amine", includes primary, secondary and tertiary amines having respectively one, two, or three organic groups that are attached to the nitrogen atom.

The symbol, "-C(O)-N-pyrrolidine" refers to the radical represented by the formula:

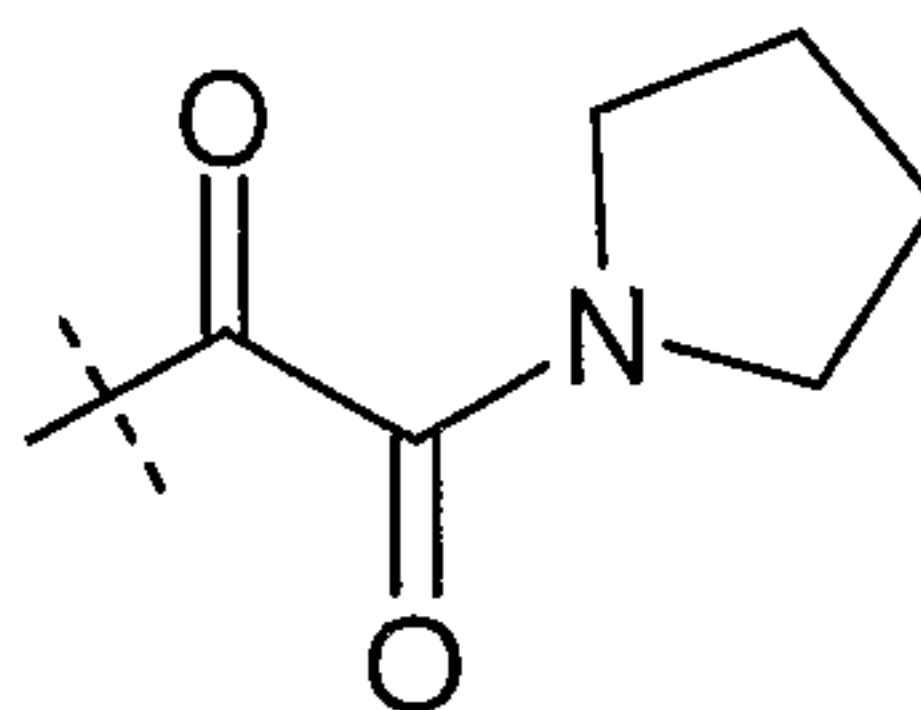


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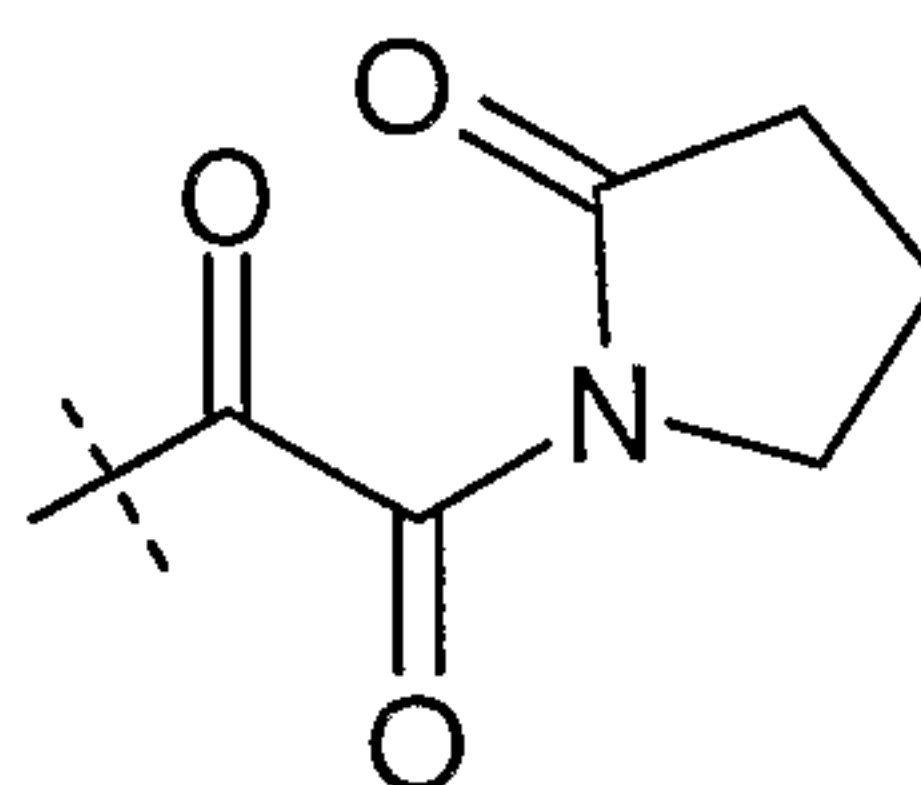
The symbol, “-C(O)-N-pyrrolidin-2-one” refers to the radical represented by the formula:



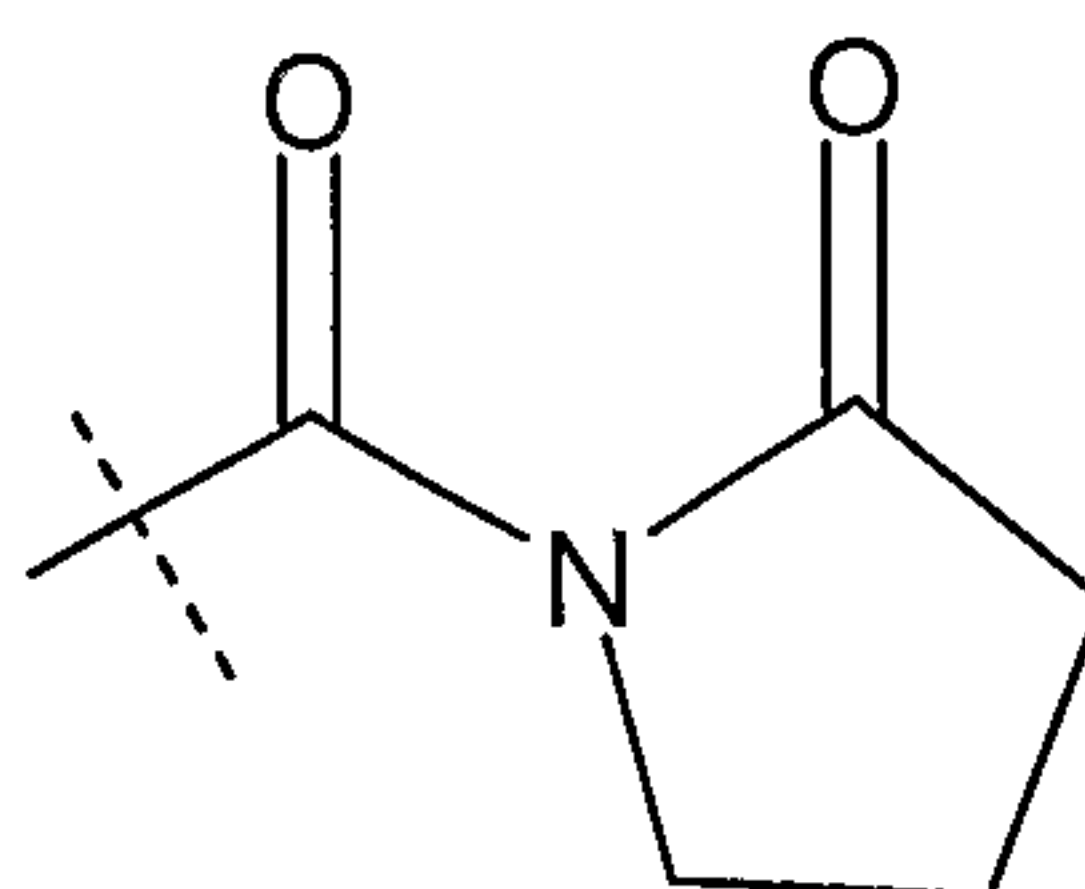
5 The symbol, “-C(O)-C(O)-N-pyrrolidine” refers to the radical represented by the formula:



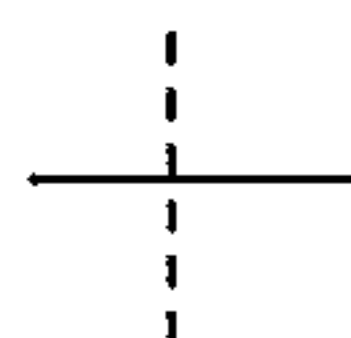
The symbol, “-C(O)-C(O)-N-pyrrolidin-2-one” refers to the radical represented by the formula:



10 The symbol, “-CH₂-C(O)-N-pyrrolidin-2-one is the organic radical represented by the structural formula:

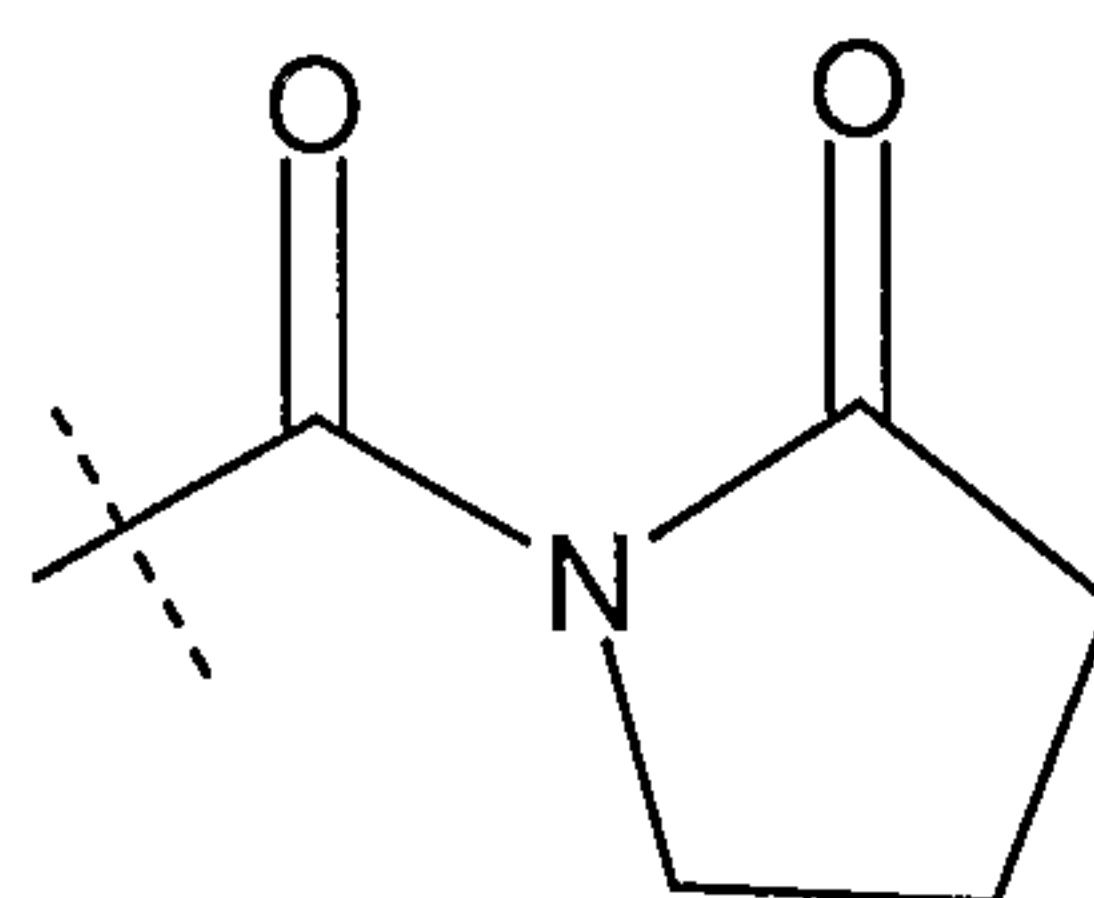


The dotted line symbol crossing a solid line representing a bond

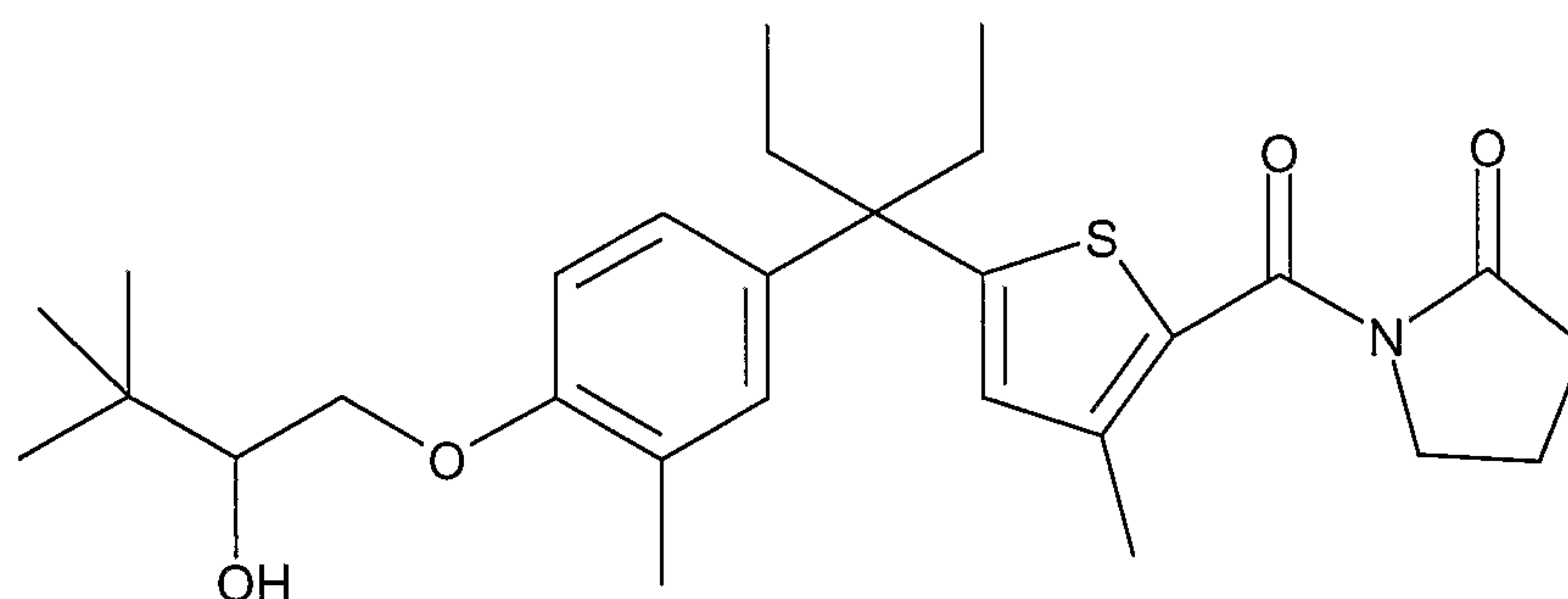


15 means that the bond so marked is the bond attached to the nucleus of formula “(A)” of the parent molecule or to a divalent linking group that is attached to the nucleus of the parent molecule. For example, the group;

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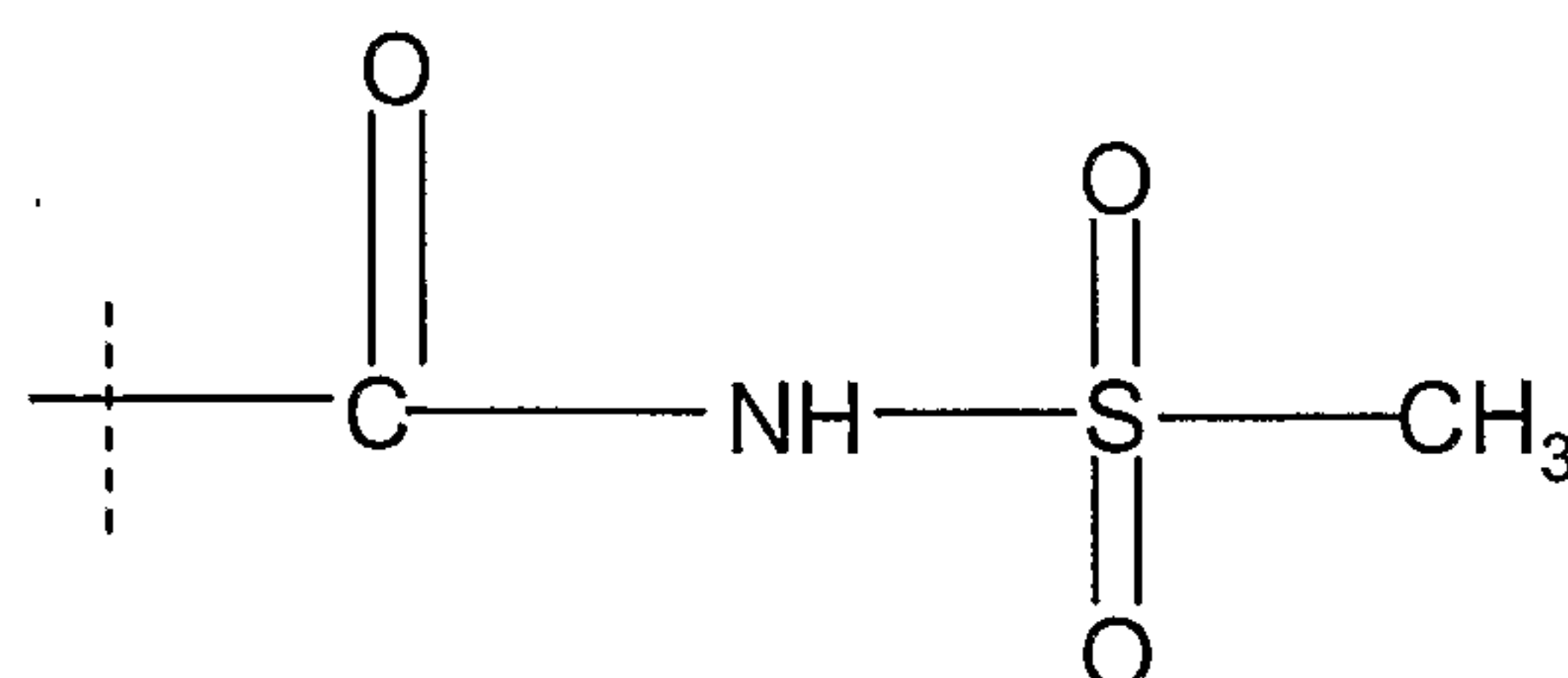


is attached to a parent aryl-thiophene nucleus to provide a compound of the invention as shown;

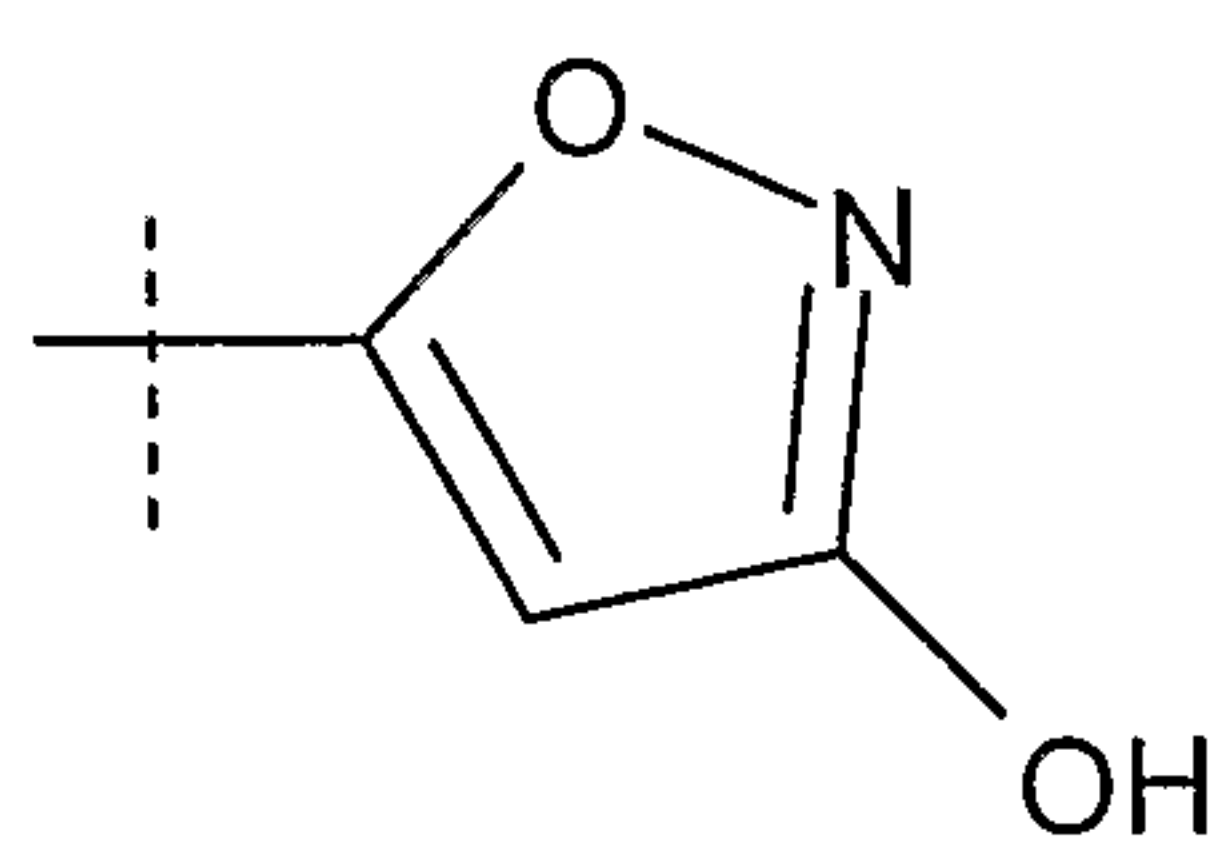


- 5 The term, “(Acidic Group)” means an organic group that acts as a proton donor capable of hydrogen bonding. Illustrative of an (Acidic Group) is a group selected from the following:

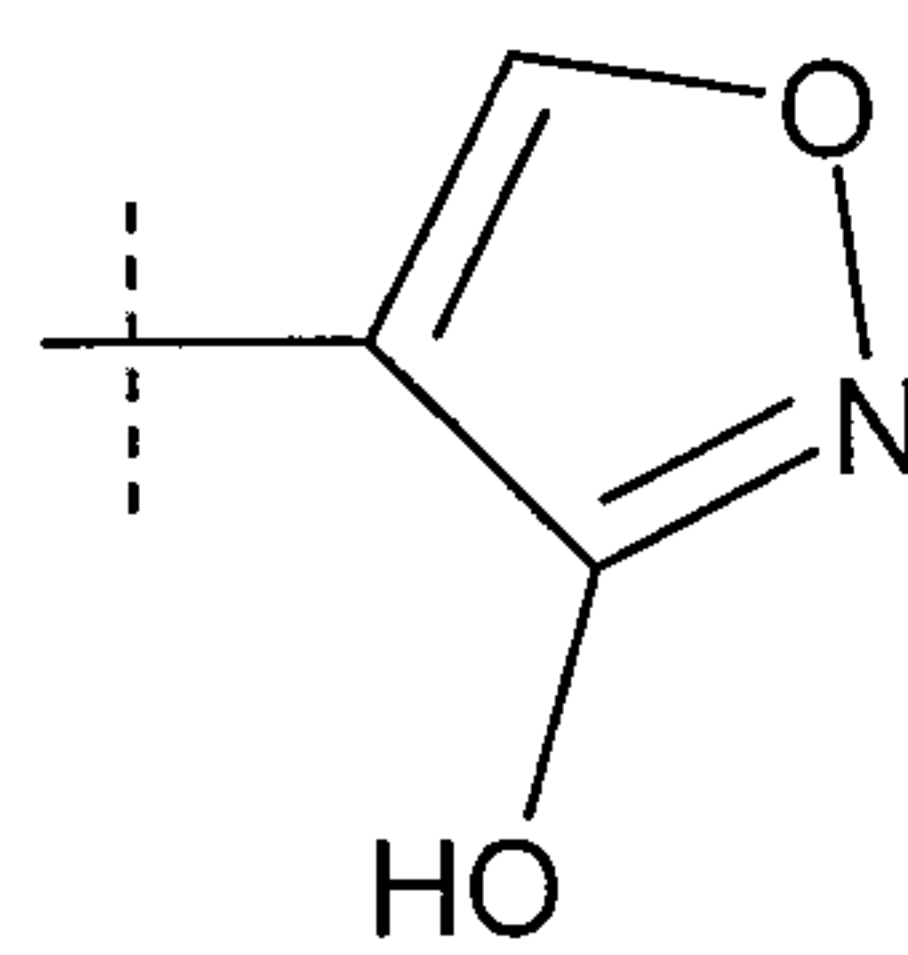
-C(O)OH,
-5-tetrazolyl,



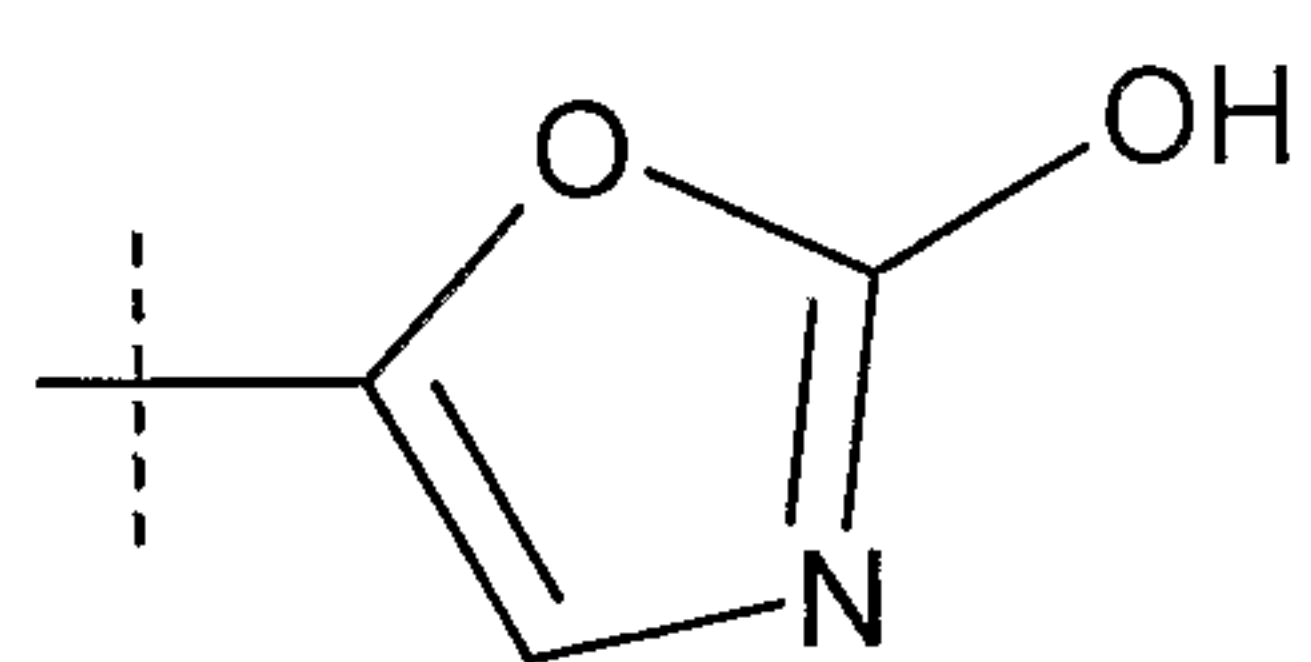
-12-



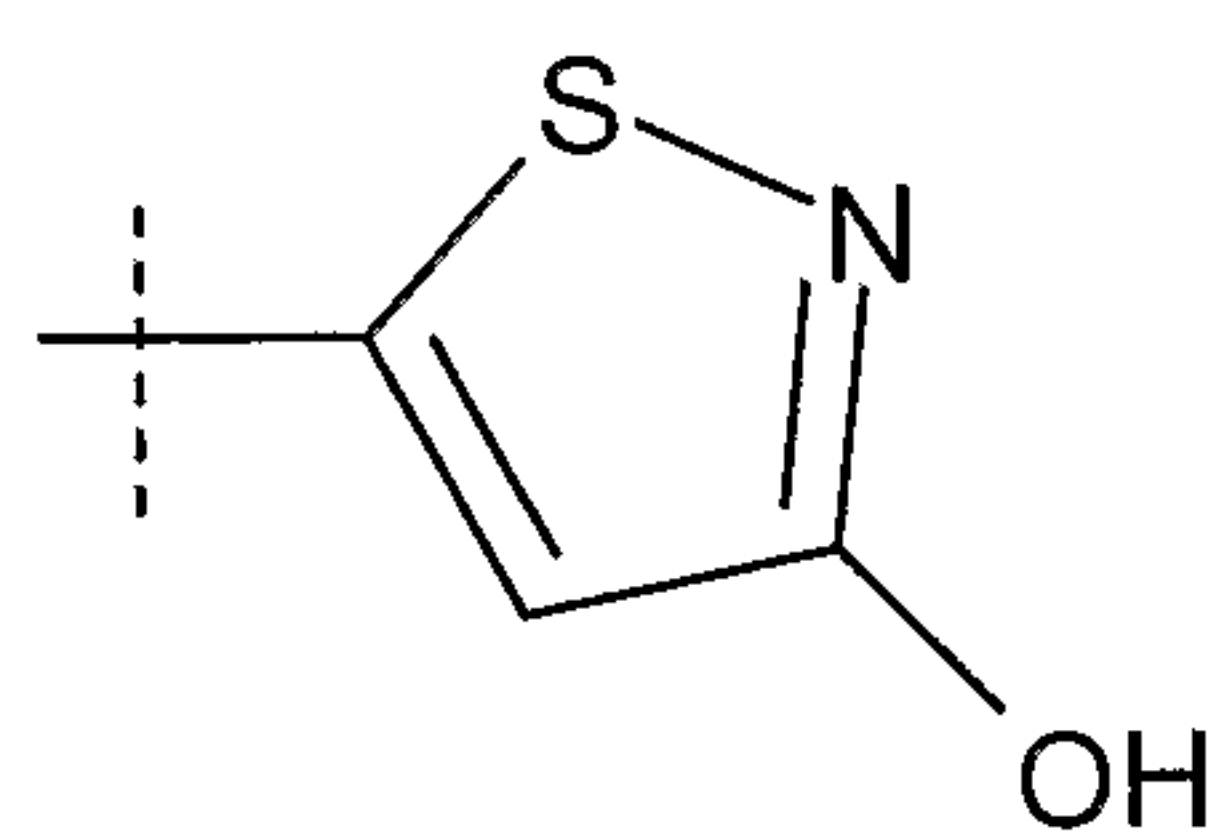
,



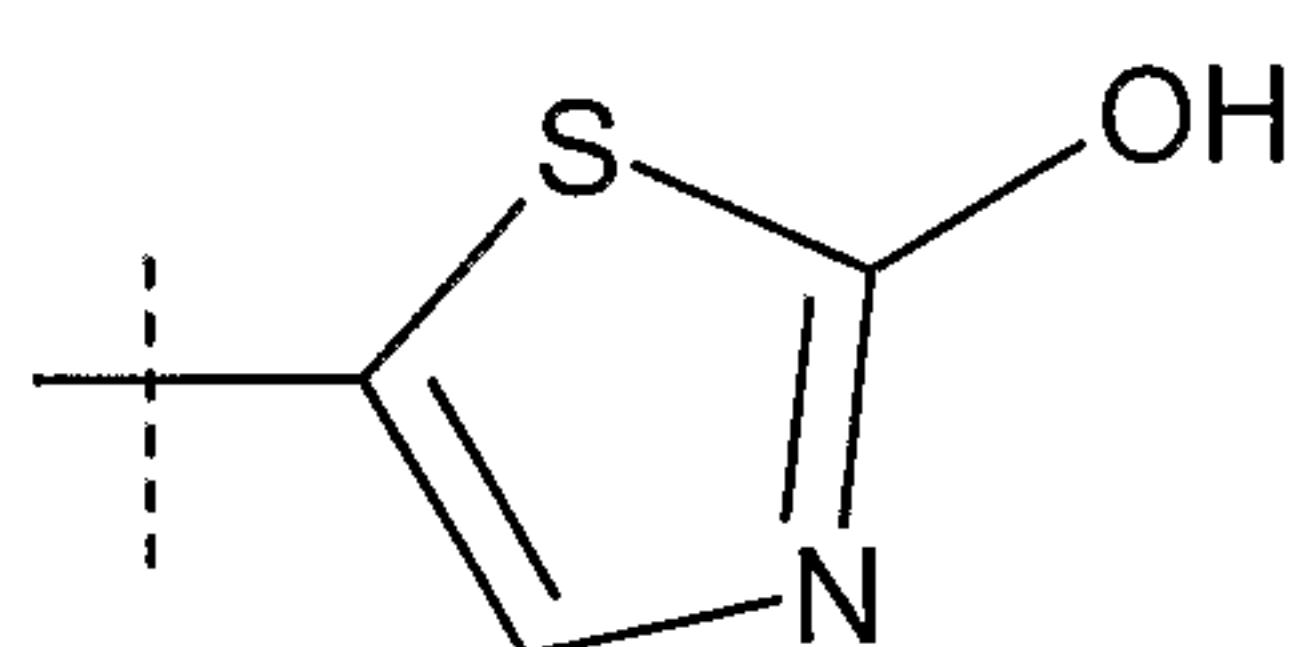
,



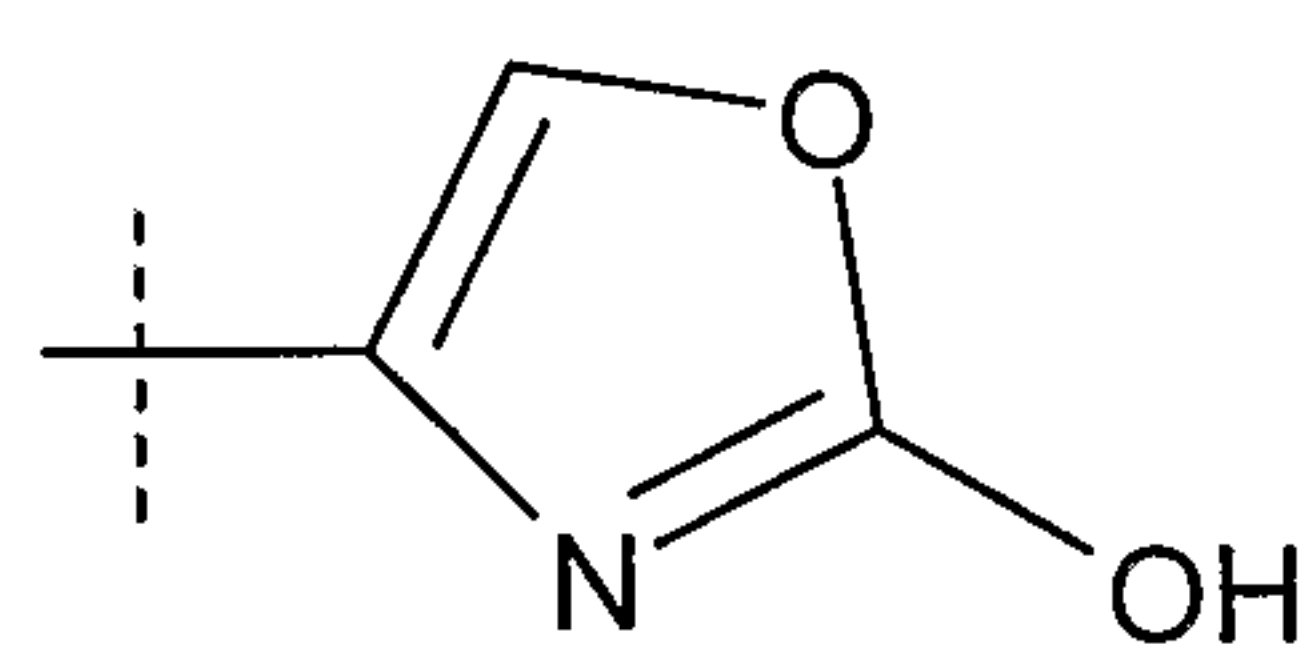
,



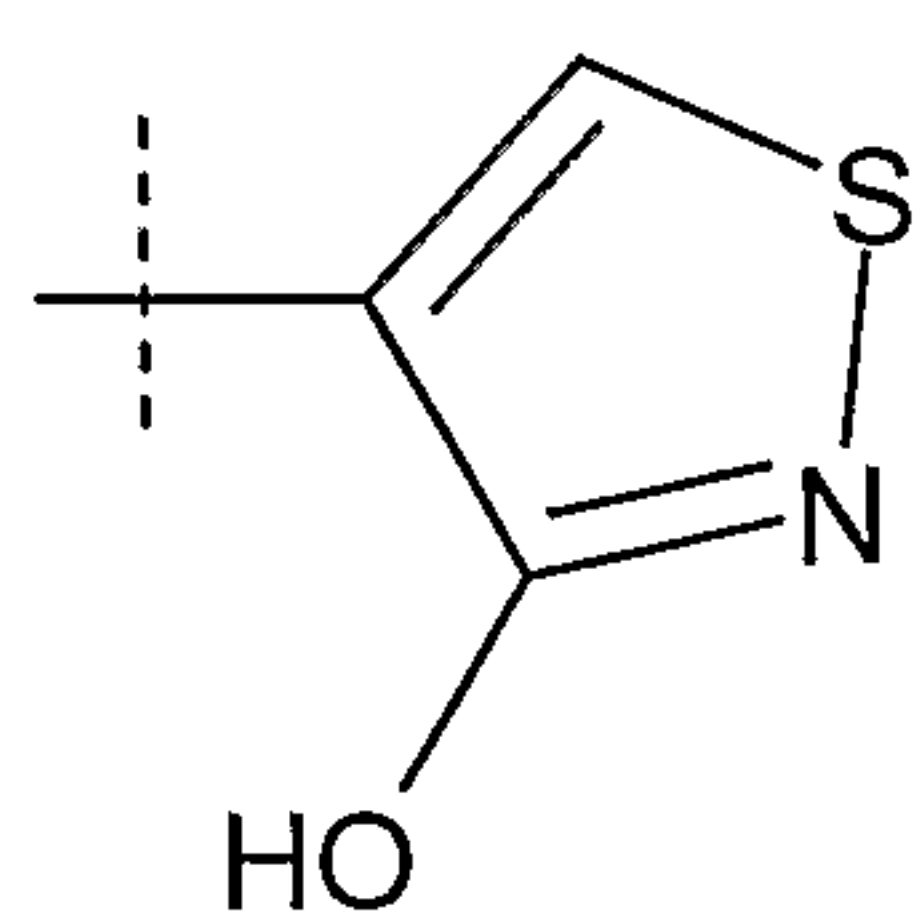
,



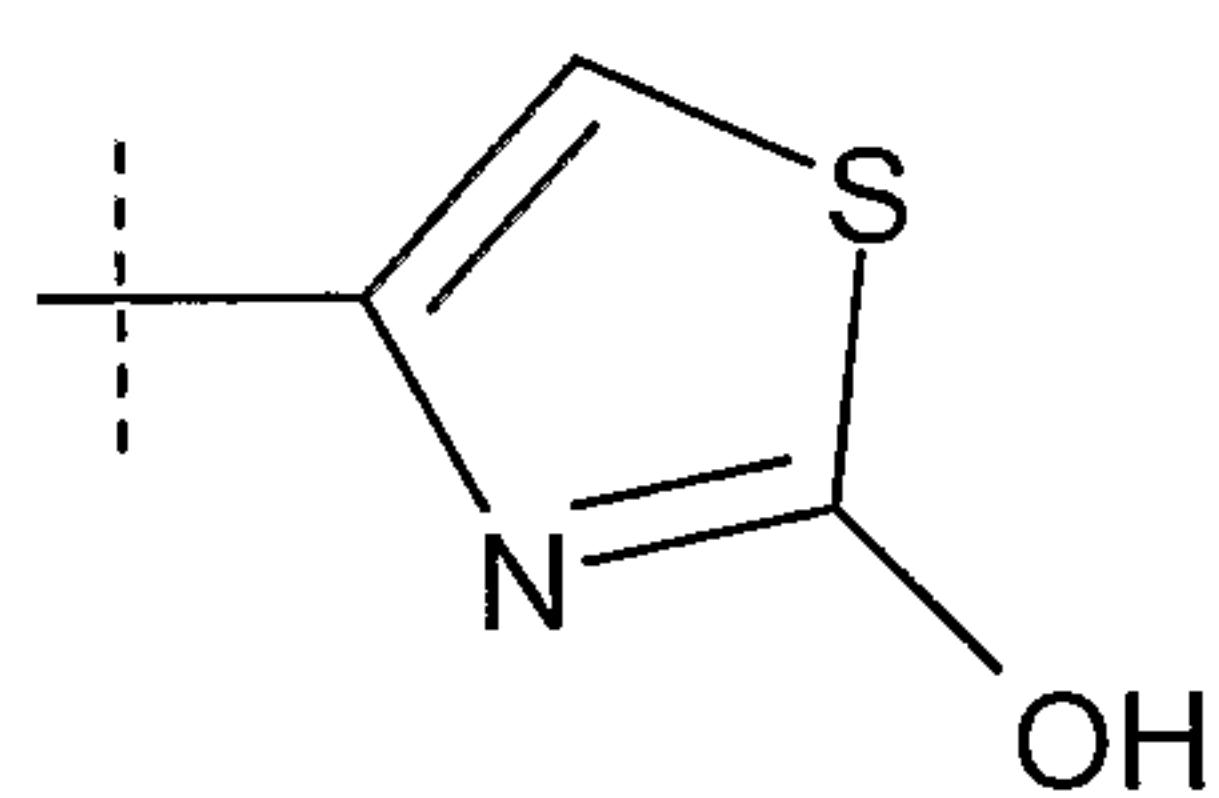
,



,

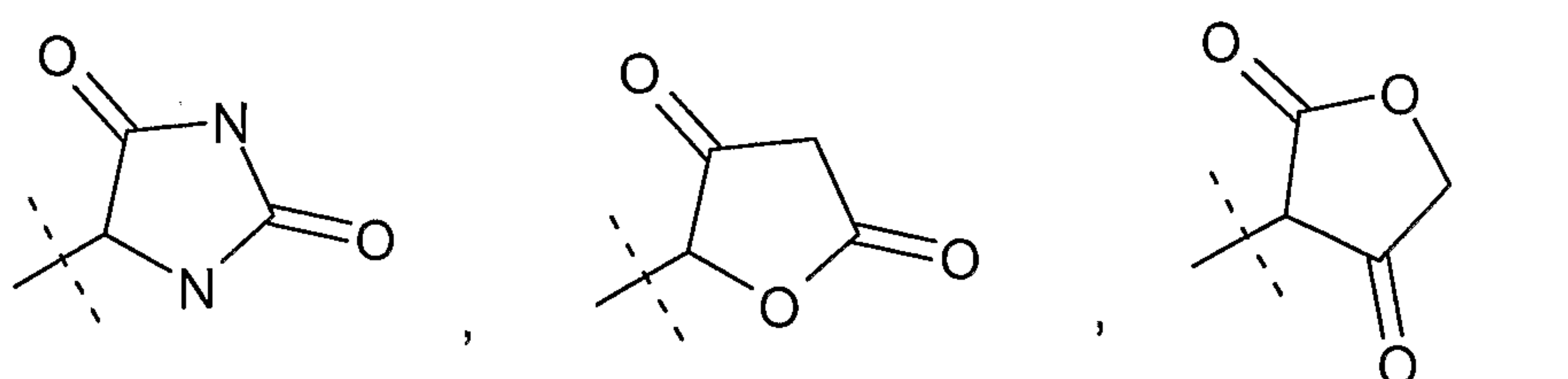
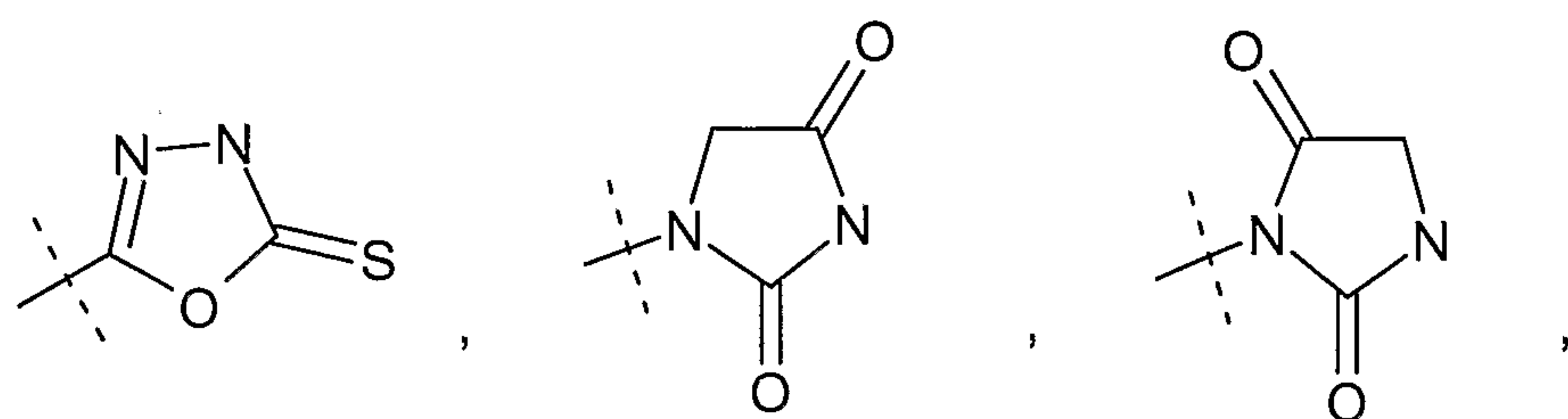
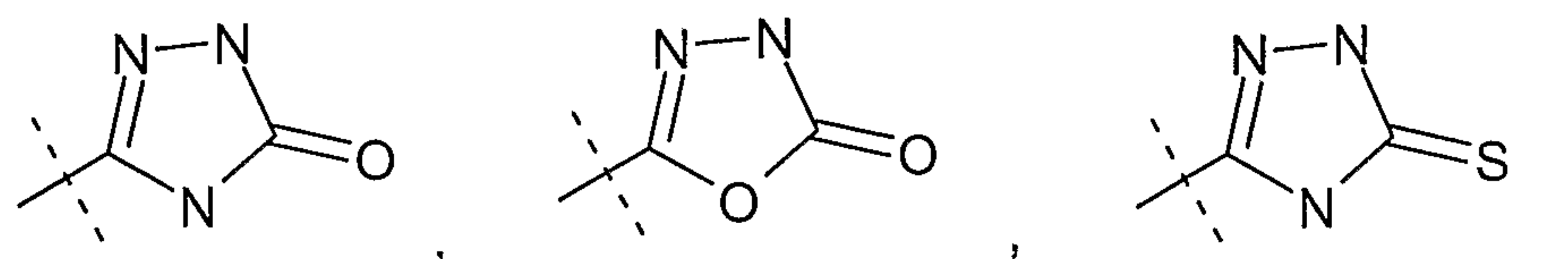
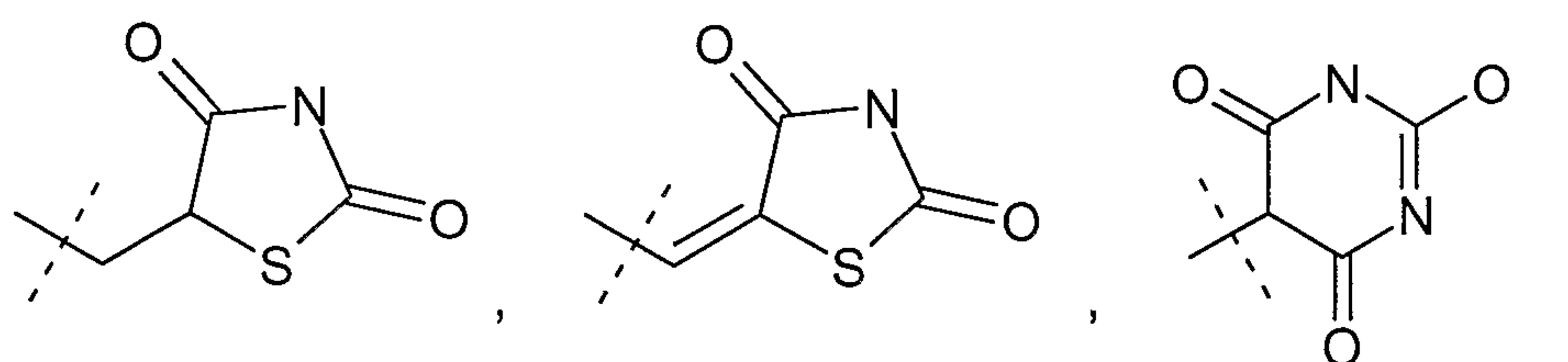


,

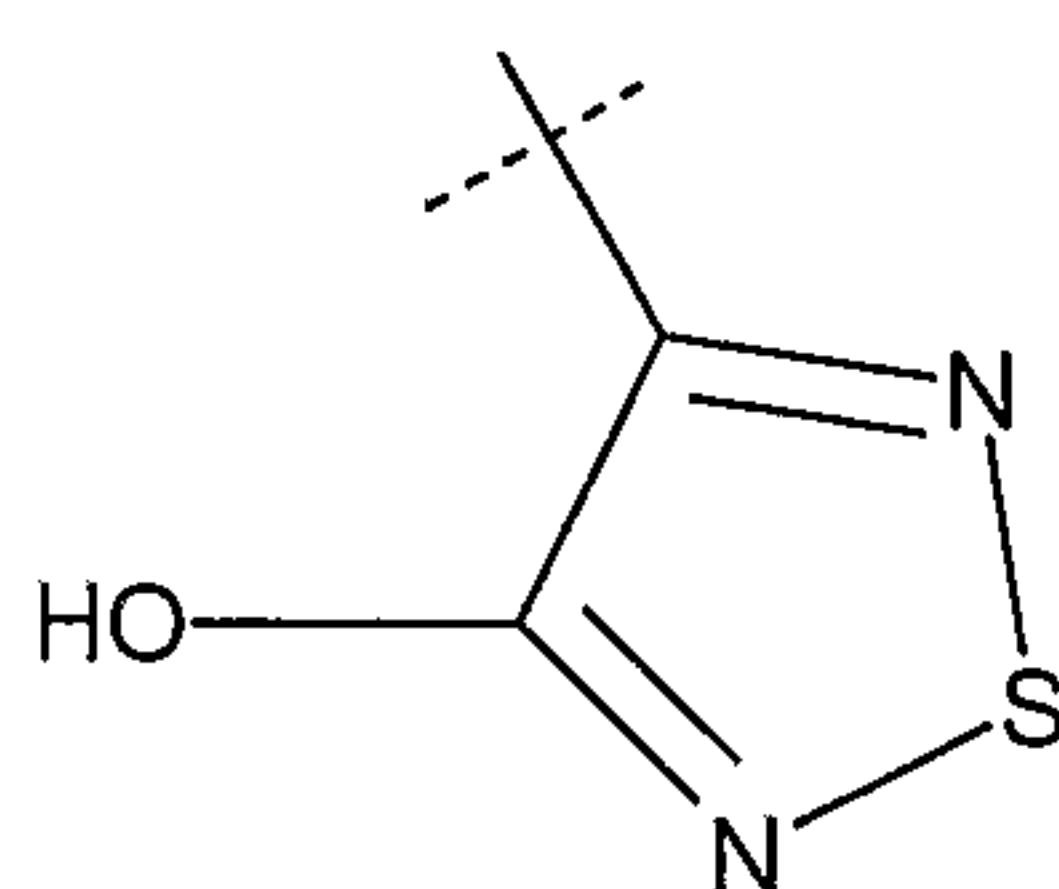


,

-13-



or

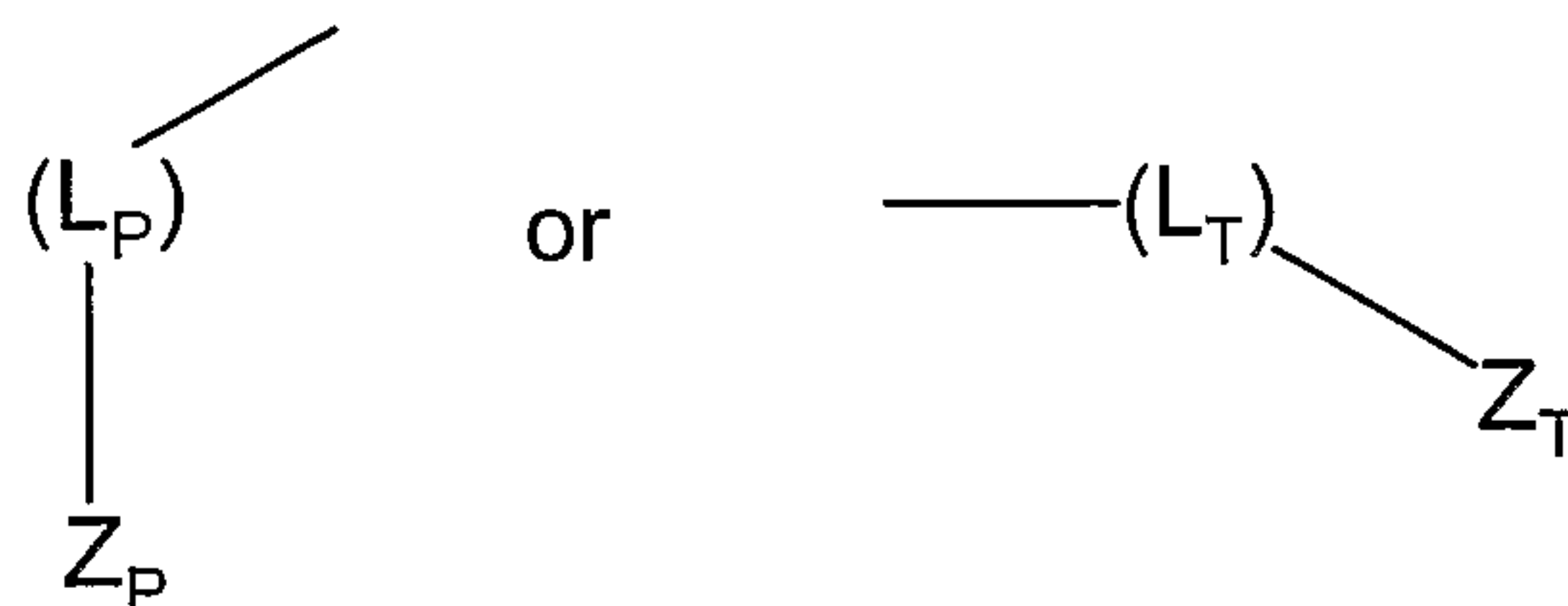


or corresponding salts of the above acids (e.g., Na, K, Ca, or Mg).

The term, "mammal" includes humans.

- 5 The term, "combined group" refers to the pendent binary groups of linkers, -(L)-, and Z substituents represented in formula I by either of:

-14-



The term "ester" refers to compounds wherein a hydroxy group of an acid is replaced with an alkoxide group. For example, a carboxylic ester is one in which the hydroxy group of a carboxylic acid is replaced with an alkoxide. Esters may derive from any acid comprising one or more hydroxy groups: for example, carbonic acid, carbamic acids, phosphonic acids, sulfonic acids, and boronic acids. The terms "alkoxycarbonyl" and "carboalkoxy" refer to carboxylic ester radicals wherein the point of attachment is the carbonyl carbon.

10 The term "halo" refer to fluorine, chlorine, bromine, and iodine.

The term "substituted" indicate that the group in question is substituted with from one or a plurality of independently selected conventional organic substituents such as acyl, acyloxy, alkenyl, alkoxy, alkyl, amino, aminocarbonyl, aryl, , carboxy, halo, hydroxy, oxa, oxo, perhaloalkyl, perhaloaryl, phosphino, phosphinyl, phosphonyl, sulfinyl, sulfonyl, thia, thio, and combinations and protected derivatives thereof.

15 The term "pharmaceutically acceptable salt" includes salts of the compounds of the present invention derived from the combination of the compound and an organic or inorganic acid or base. In practice, acidic members of the compounds of formulae I and II would be combined with a base or bases, basic members of the compounds of formulae I and II would be combined with an acid or acids, and members of the compounds of formulae I and II with both acid and base functionalities would be combined with one or more acids, bases or any combination thereof. Both the neutral and salt forms fall within the scope of the present invention. Examples of cationic salts are sodium, aluminum, zinc, potassium, calcium, magnesium and ammonium.

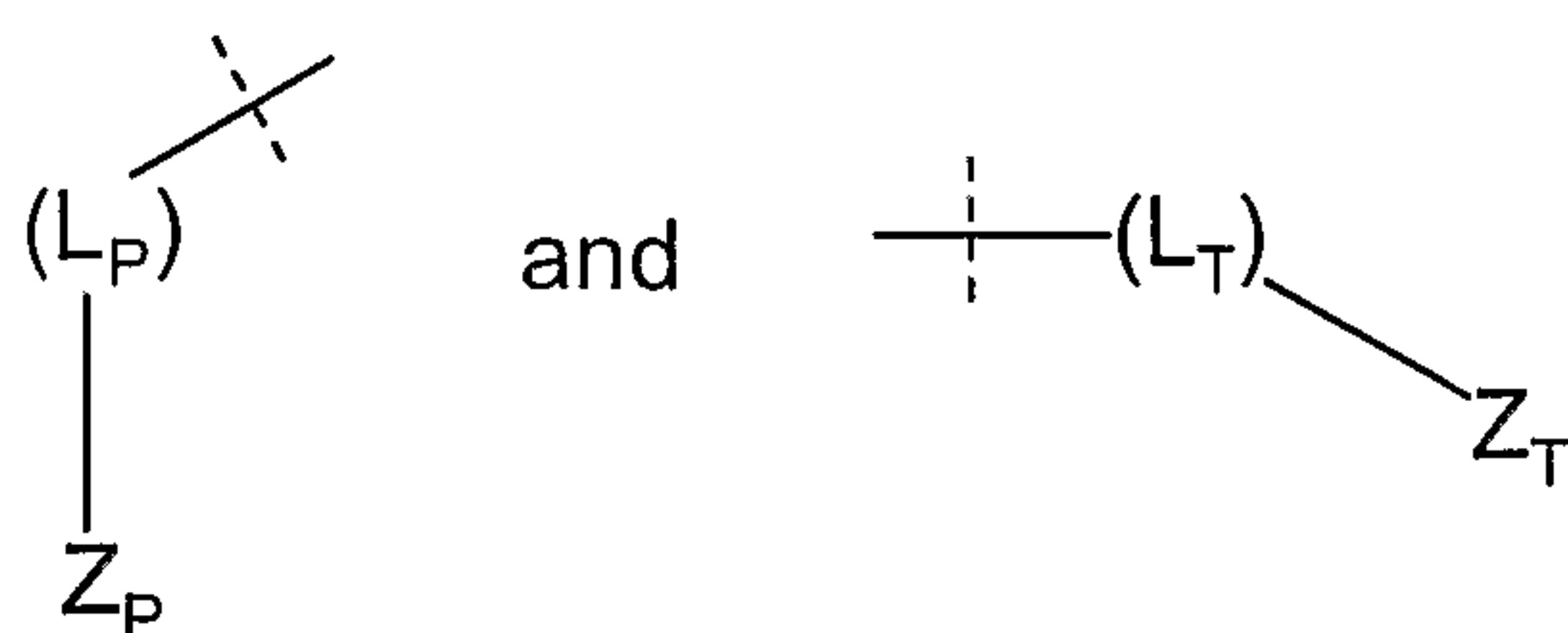
25 The word "abscess" is a complication often associated with surgery, trama, or diseases that predispose the host to abscess formation from encapsulated bacteria lymphocytes, macrophages, and etc.

The word "adhesion" refers to the abnormal union of surfaces normally separate by the formulation of new fibrous tissue resulting from an inflammatory

-15-

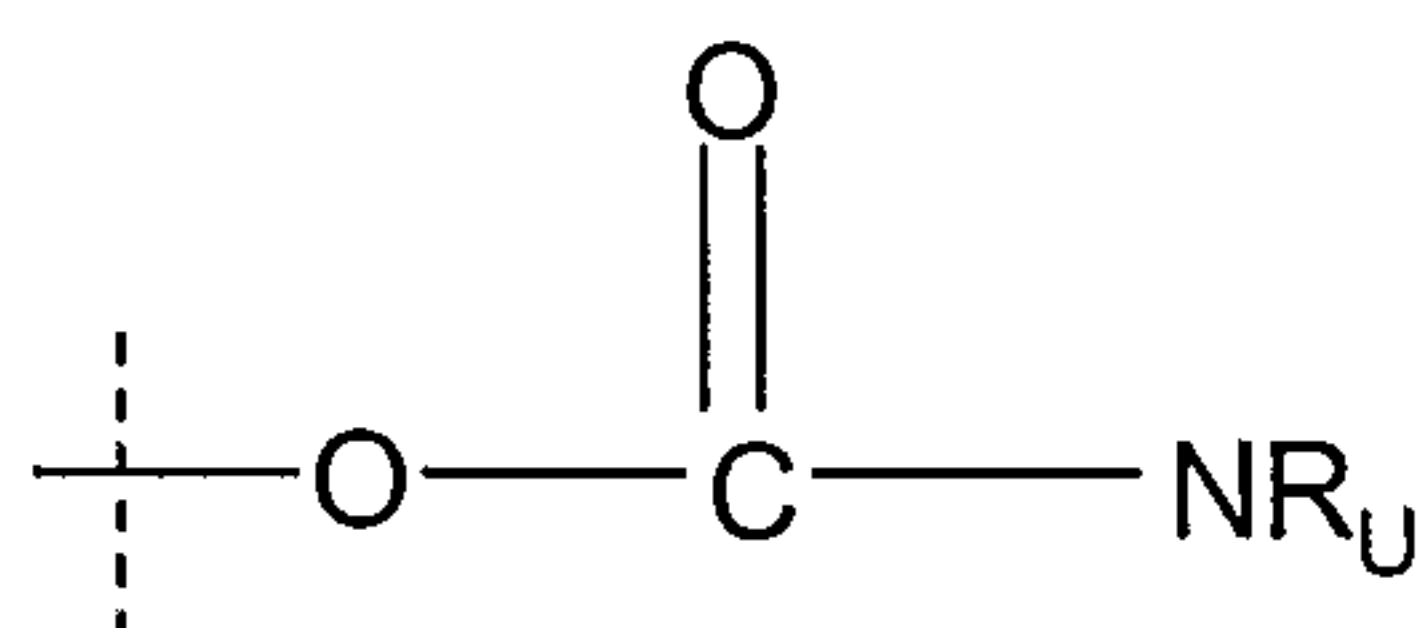
process.

The term, “combined groups” refers to the groups in Formula I represented by either of the groups



5

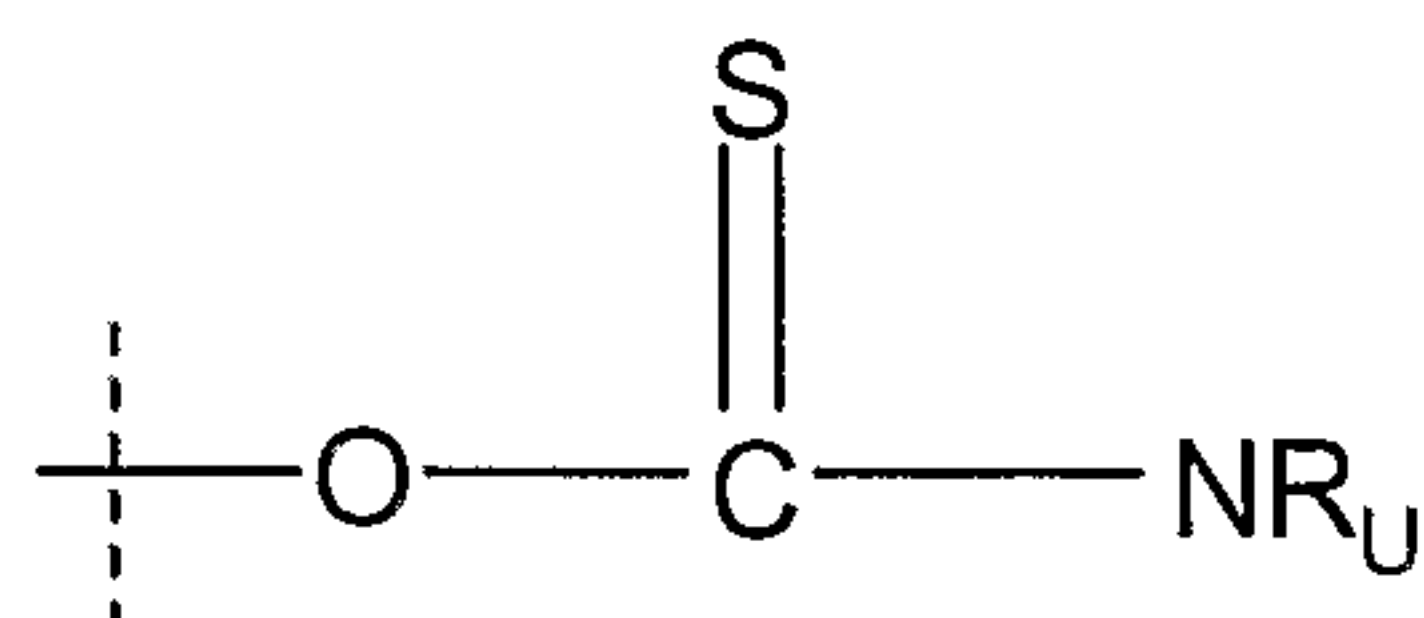
The term, “urethane” refers to the radical:



10

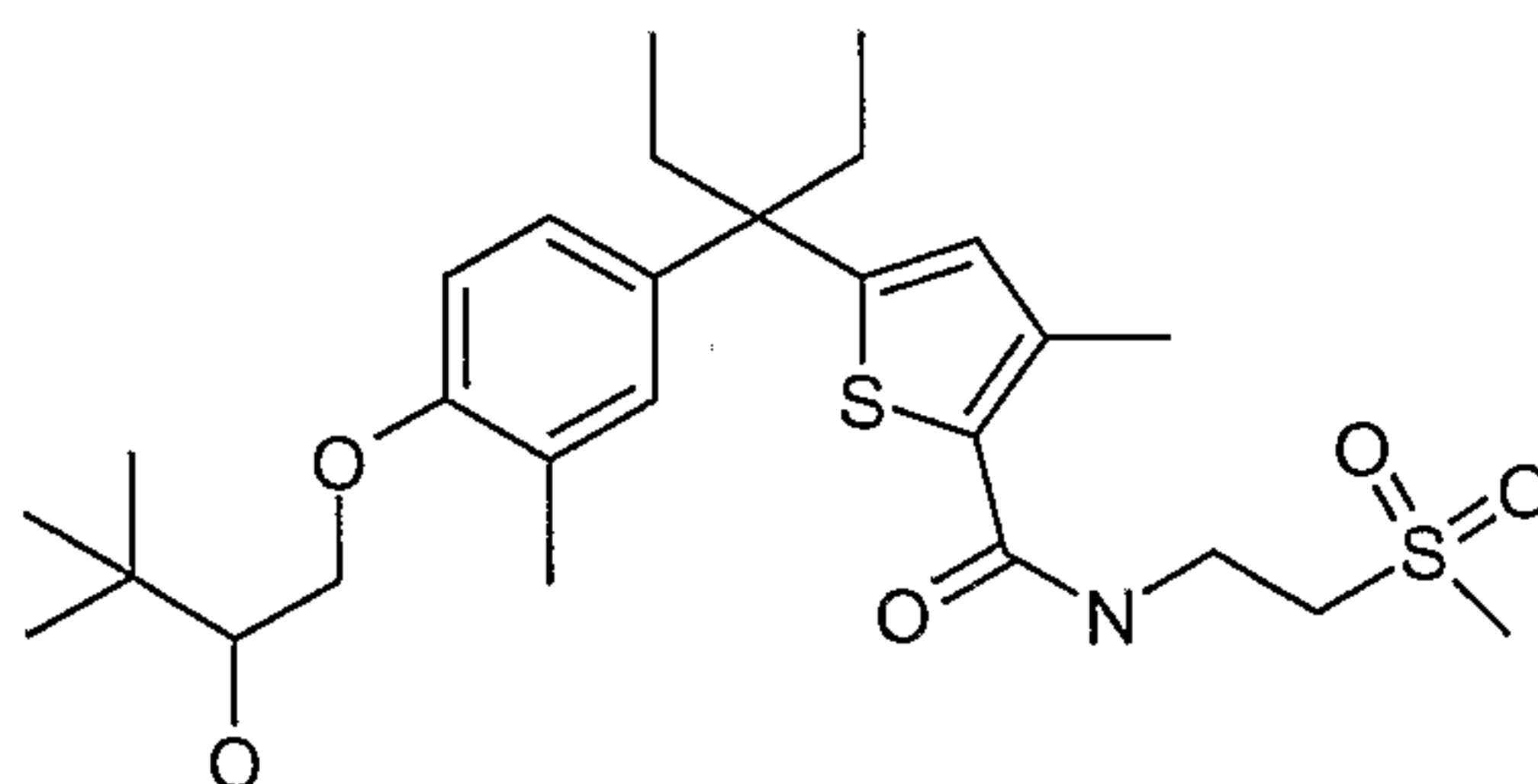
wherein each R_U is independently hydrogen or C_1 - C_8 alkyl, for example, methyl, ethyl, n-propyl, and isopropyl.

The term, “thiourethane” refers to the radical:



15 wherein R_U is hydrogen or C_1 - C_8 alkyl., for example, methyl, ethyl, n-propyl, and isopropyl.

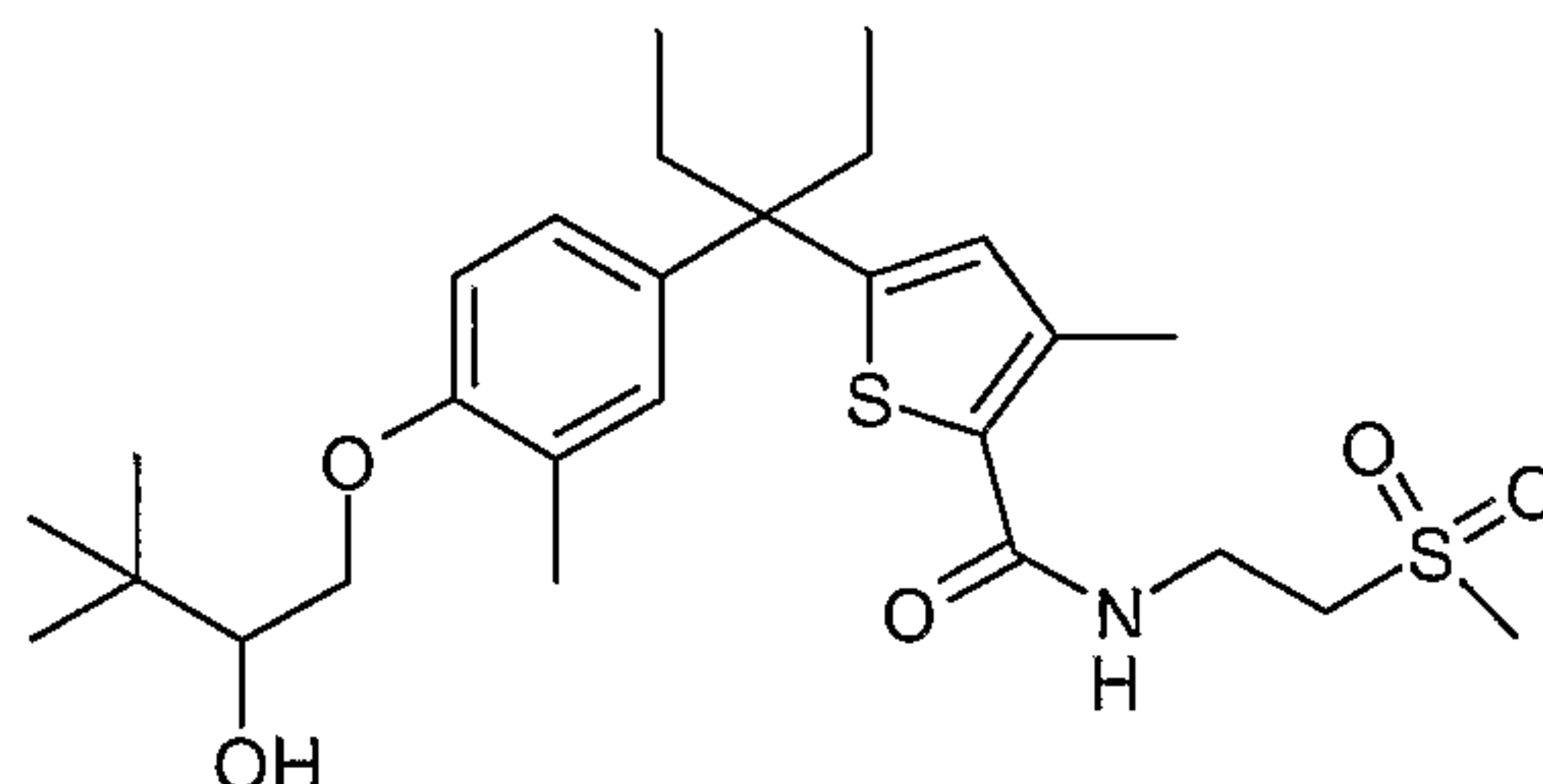
Some of the structural formulae used herein omit depiction of hydrogen atoms. For example, the formula:



20

-16-

is understood to be the equivalent of the formula:



The term, “urethane-type radical” refers to either urethane or thiourethane radicals.

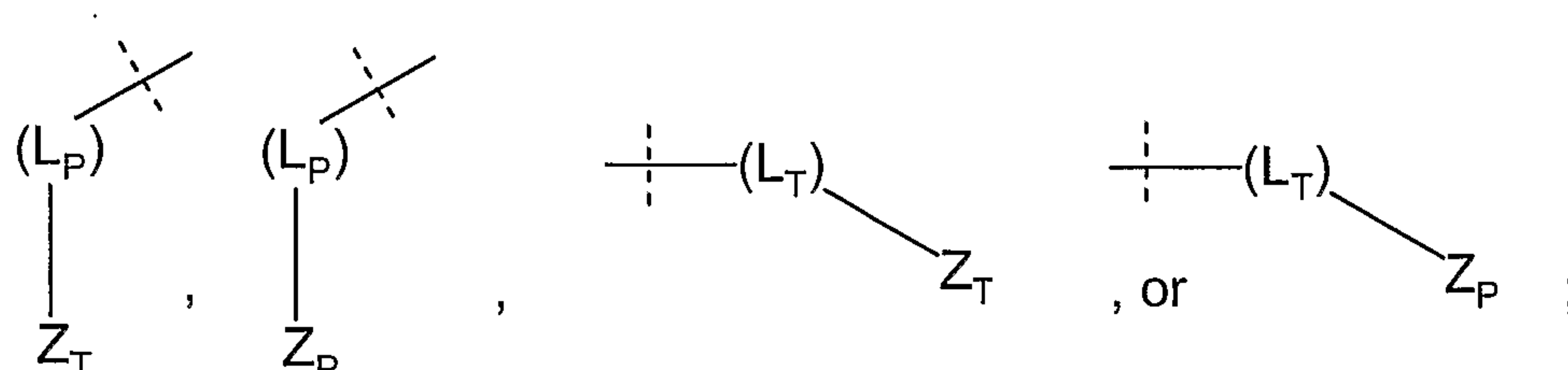
5

Definitions IA: Rule of Polarity and Lipophilicity for Substituents pendant on the compounds of the invention:

The substituents L_P , L_T , Z_P , and Z_T pendant on the compounds of the invention are constrained both by (i) the identity of each substituent, and (ii) the polar or lipophilic nature of each substituent. The occurrence of “polar” and “lipophilic” is to be done in accord with the following Rule:

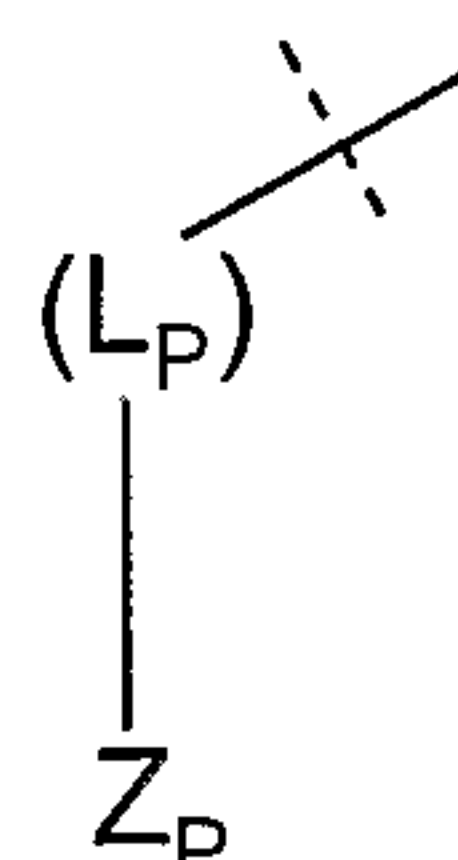
10

RULE: The combined groups in formula I, II, III, IV and V represented by



may all be lipophilic, or one may be lipophilic and the other one polar; but both combined groups may not be polar. If any part of a combined group is polar, then the “combined group” itself is deemed polar. For example, in the group

15

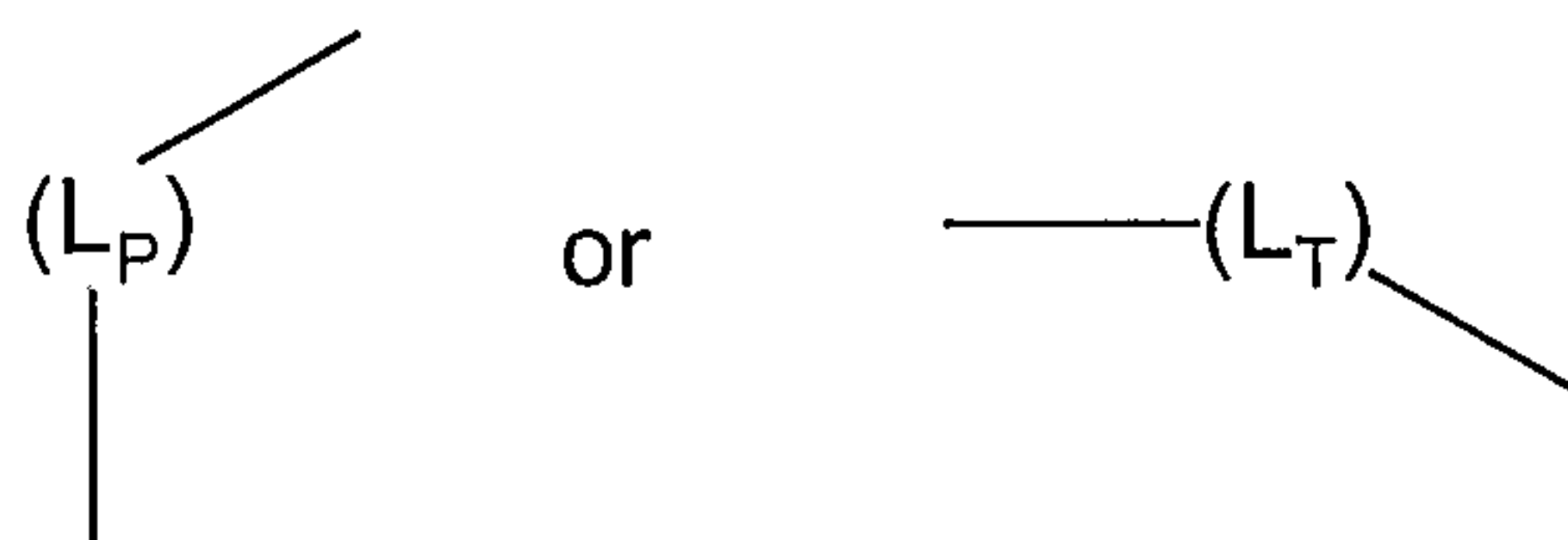


if the divalent linking group $-(L_P)-$ is the polar group, $-C(O)-NH-$ and Z_P is the lipophilic group, $-CH_2-CH_2-(t\text{-butyl})$; then the combined group is defined as “polar.”

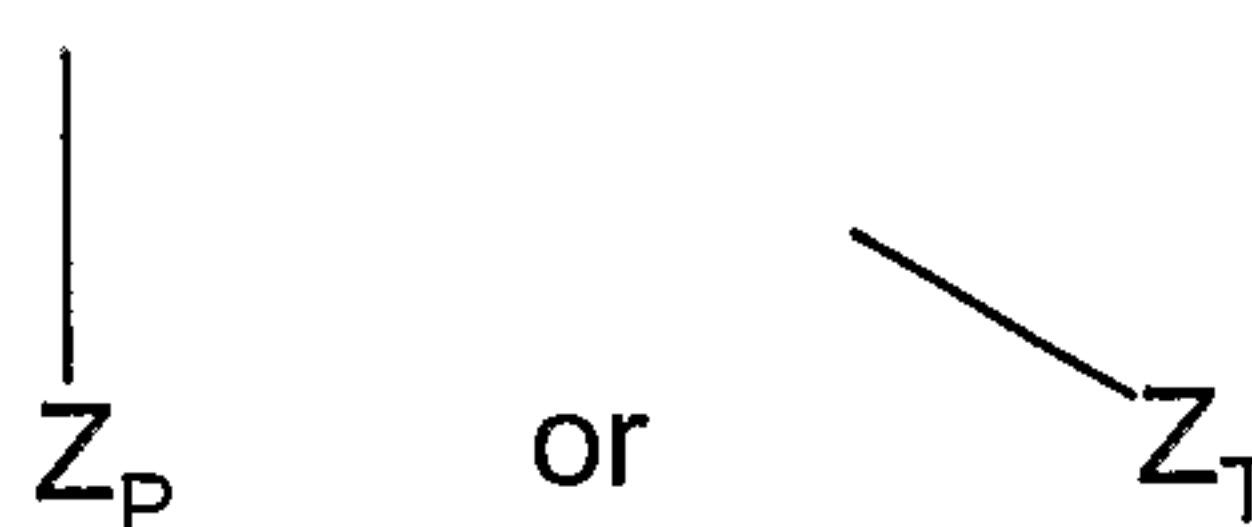
20

Definitions IB: Definition of "Polar" and "Lipophilic"

The term "lipophilic group" refers to any linking group

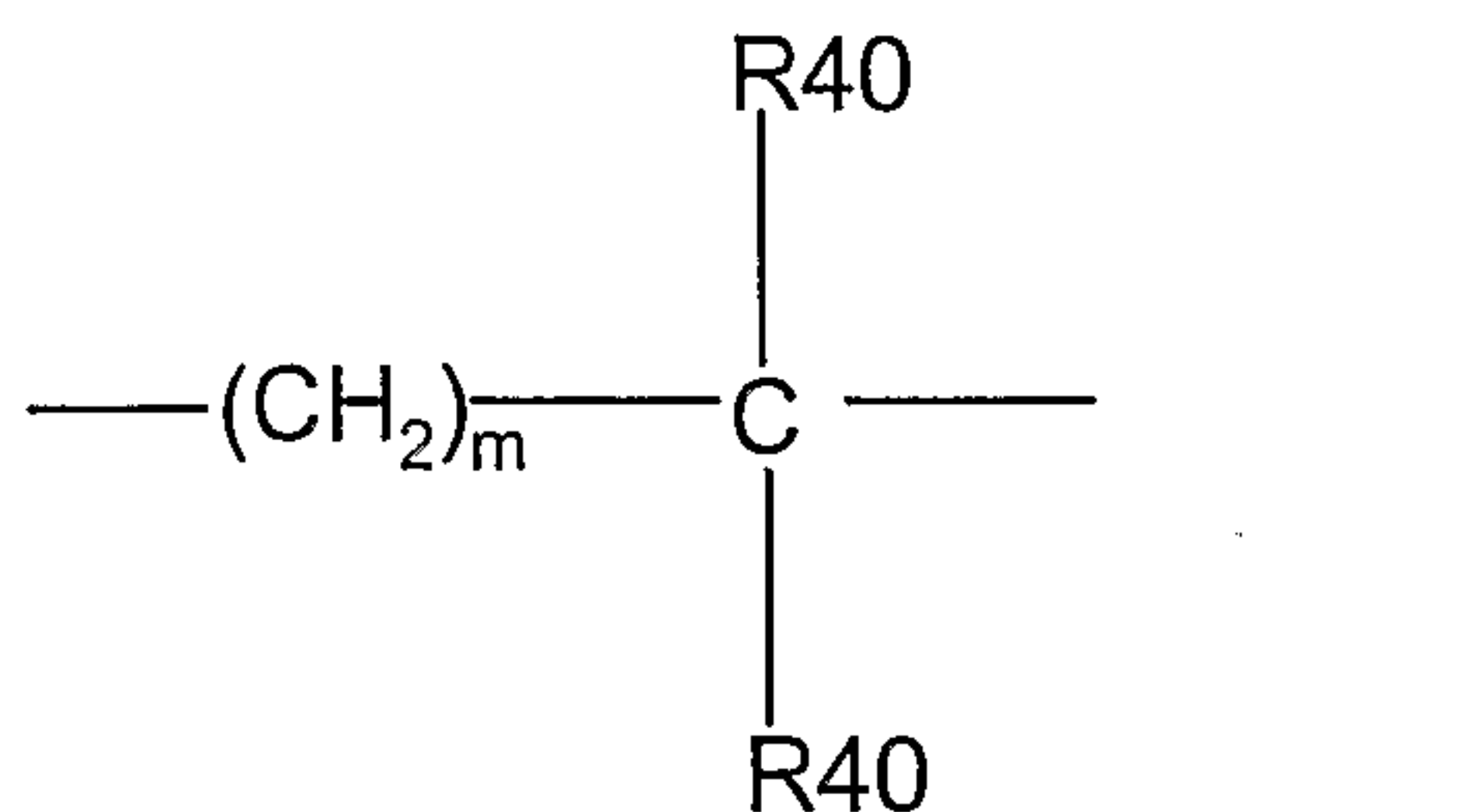
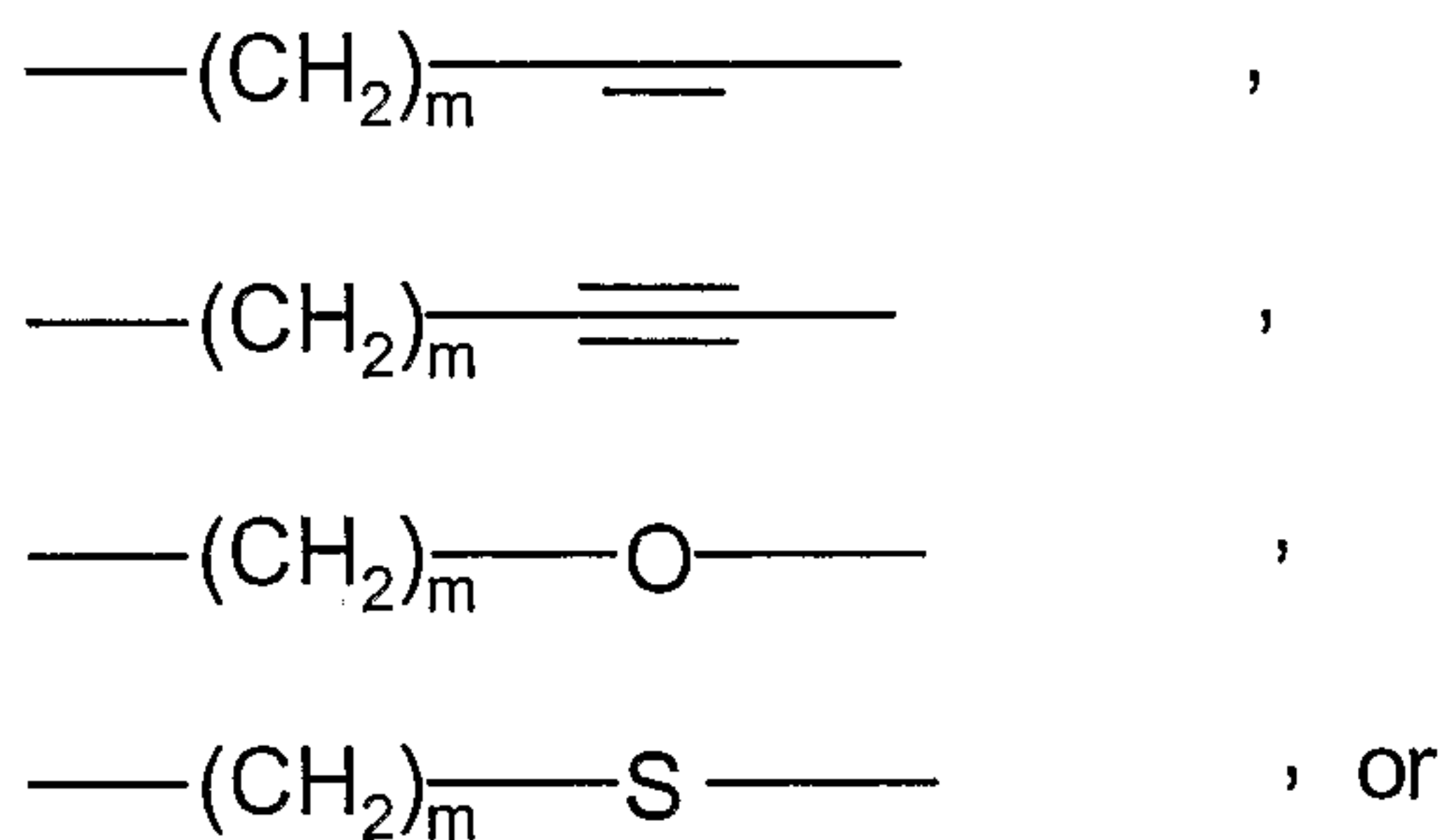


5 or any of the Z substituents



that is hydrophobic, preferring or attracted to a hydrocarbon loving, non-aqueous environment. Lipophilic linking groups in the practice of the invention are

a bond



10

where m is 0, 1, or 2, and each R₄₀ is independently hydrogen, -CH₃, -F, -CH₂F, -CHF₂, and -CF₃. All other exemplified linking groups are polar.

Generally all linking groups containing only hydrocarbon subunit groups or hydrocarbon subunit groups in combination with ether or thioether groups are lipophilic.

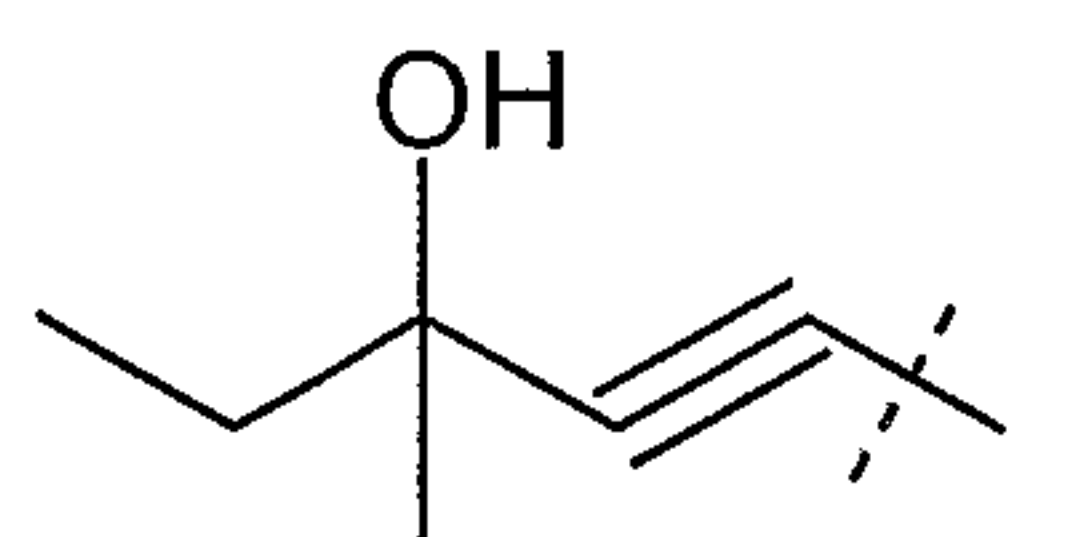
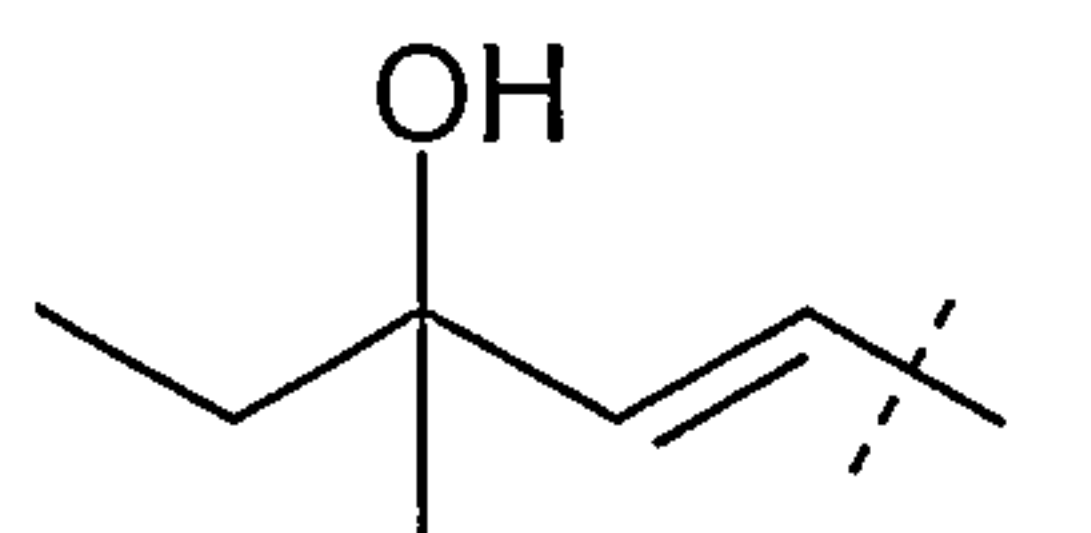
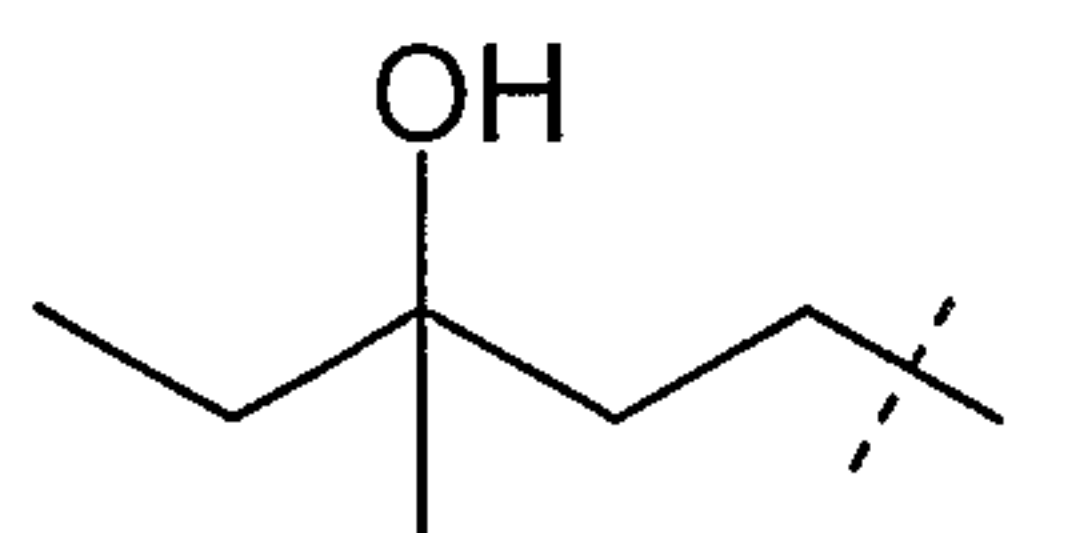
15 Moreover, fluorinated derivatives of such groups are considered lipophilic.

Lipophilic Z_T or Z_P groups in the practice of the invention are partially

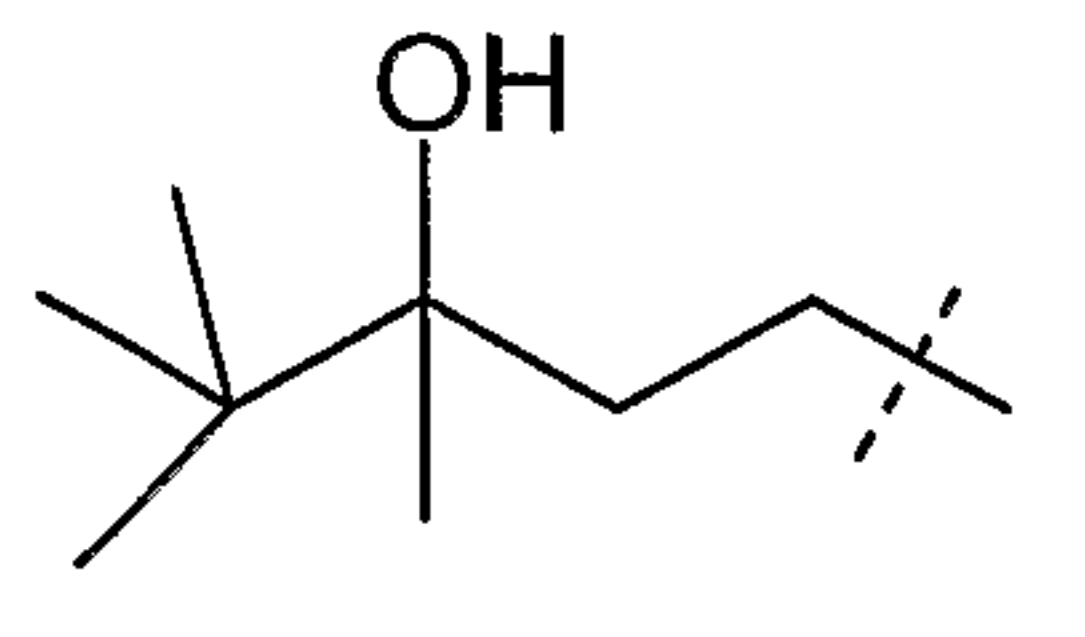
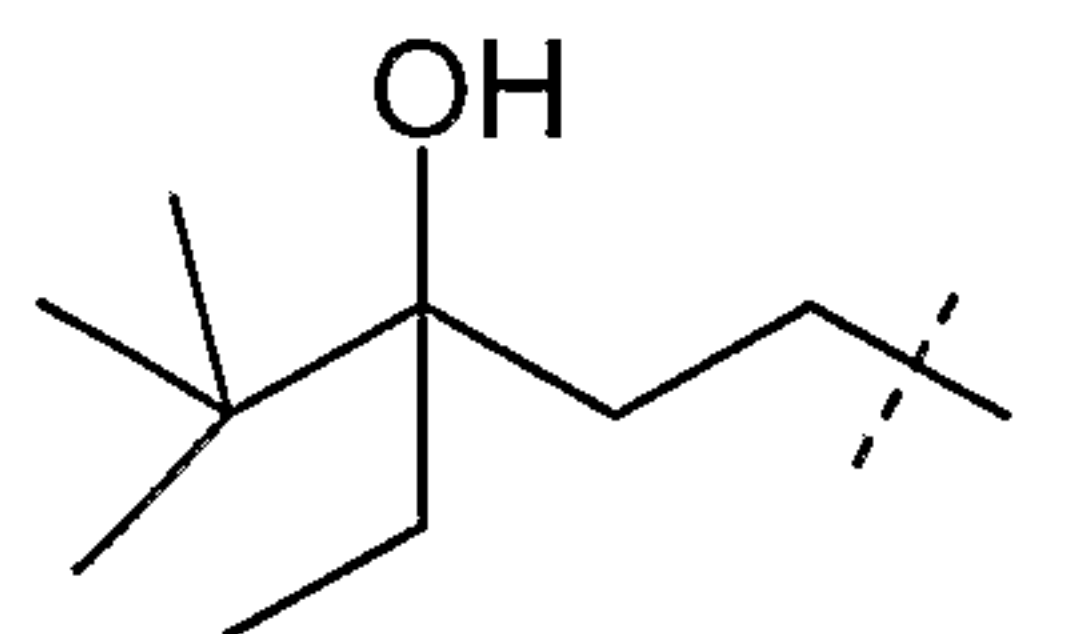
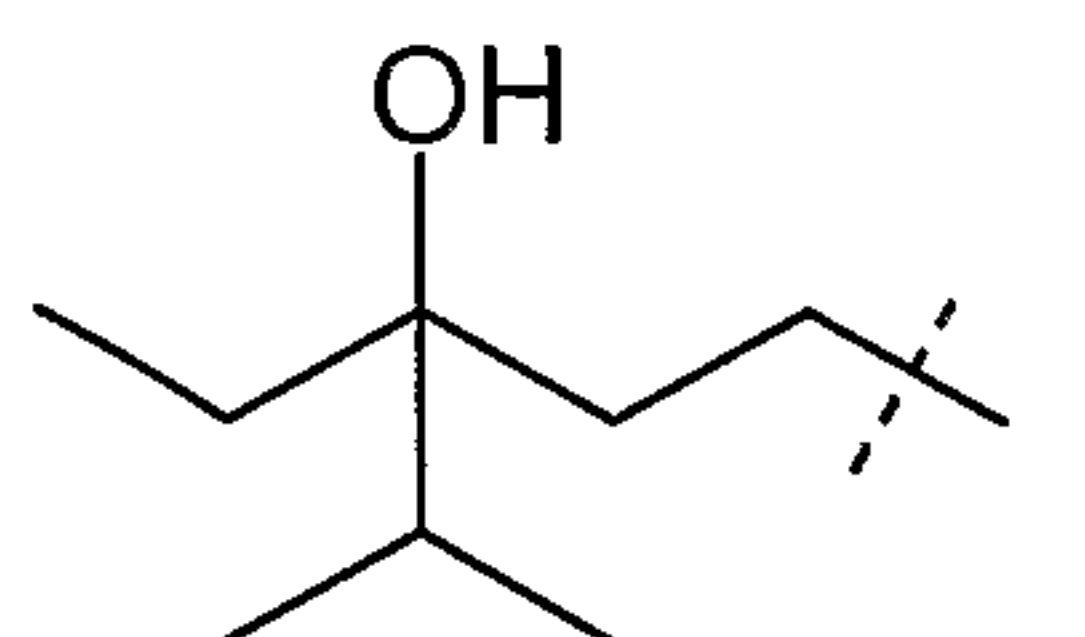
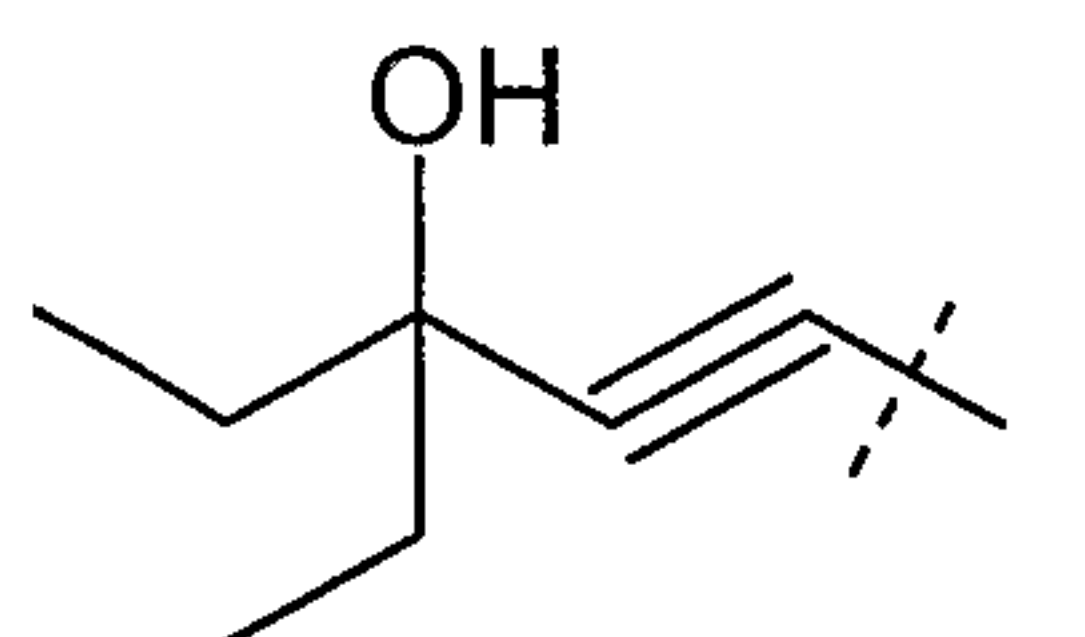
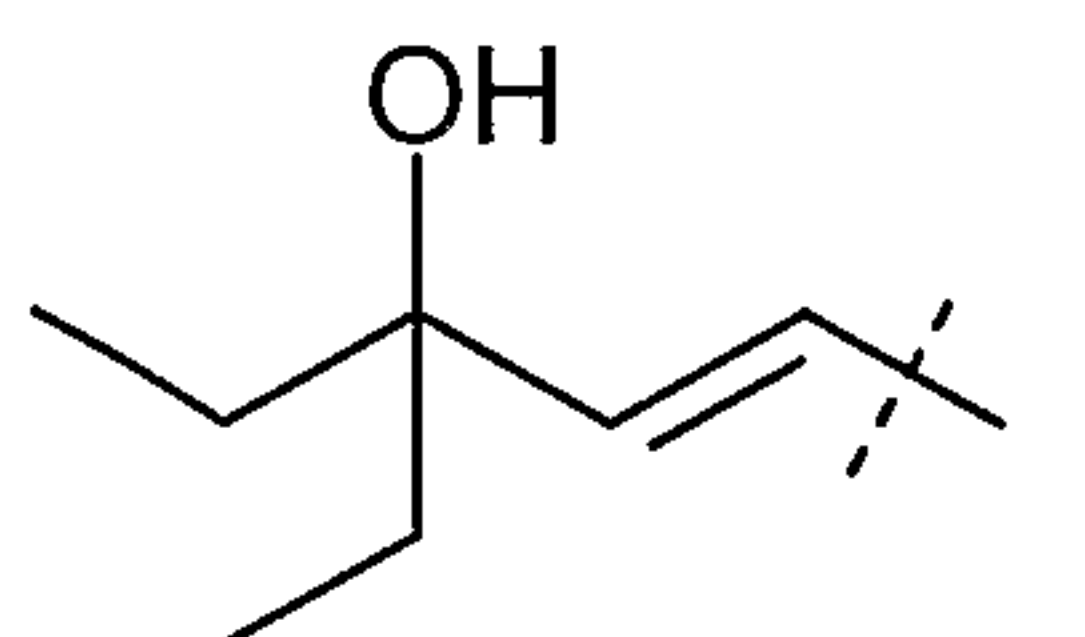
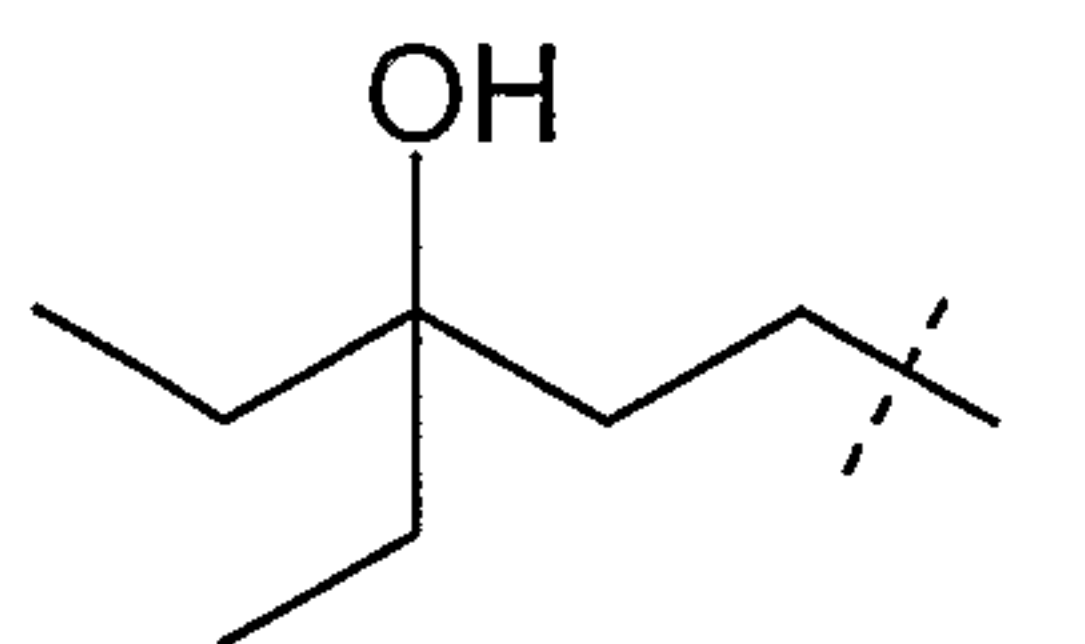
-18-

exemplified by

- 5
- O-CH₂-C(O)-C₁-C₅alkyl,
 - O-CH₂-CH(OH)-C₁-C₅alkyl,
 - O-CH₂-C(CH₃)(OH)-C₁-C₅alkyl,
 - O-CH₂-CH(OCH₃)-C₁-C₅alkyl,
 - O-CH(CH₃)-C(O)-C₁-C₅alkyl
 - O-CH(CH₃)-CH(OH)-C₁-C₅alkyl,
 - O-CH₂-C(O)-C(CH₃)₂-C₁-C₅alkyl,
 - O-CH₂-CH(OH)-C(CH₃)₂-C₁-C₅alkyl,
- 10
- O-CH₂-C(O)-C₁-C₅alkyl,
 - O-CH₂-CH(OH)-C₁-C₅alkyl,
 - O-CH₂-CH(OCH₃)-C₁-C₅alkyl,
 - CH₂-CH₂-C(O)-C₁-C₅alkyl,
 - CH₂-CH₂-CH(OH)-C₁-C₅alkyl,
- 15
- CH₂-CH₂-CH(OCH₃)-C₁-C₅alkyl,
 - CH₂-C(O)-C₁-C₅alkyl,
 - CH₂-CH(OH)-C₁-C₅alkyl,
 - CH₂-C(CH₃)(OH)-C₁-C₅alkyl,
 - CH(CH₃)-C(O)-C₁-C₅alkyl,
- 20
- CH(CH₃)-CH(OH)-C₁-C₅alkyl,
 - CH(CH₃)-C(CH₃)(OH)-C₁-C₅alkyl,



-19-



1-hydroxycyclopentenyl,

1-hydroxycyclohexenyl,

1-hydroxycycloheptenyl,

1-hydroxycyclooctenyl,

1-hydroxycyclopropyl,

1-hydroxycyclobutyl,

1-hydroxycyclopentyl,

1-hydroxycyclohexyl,

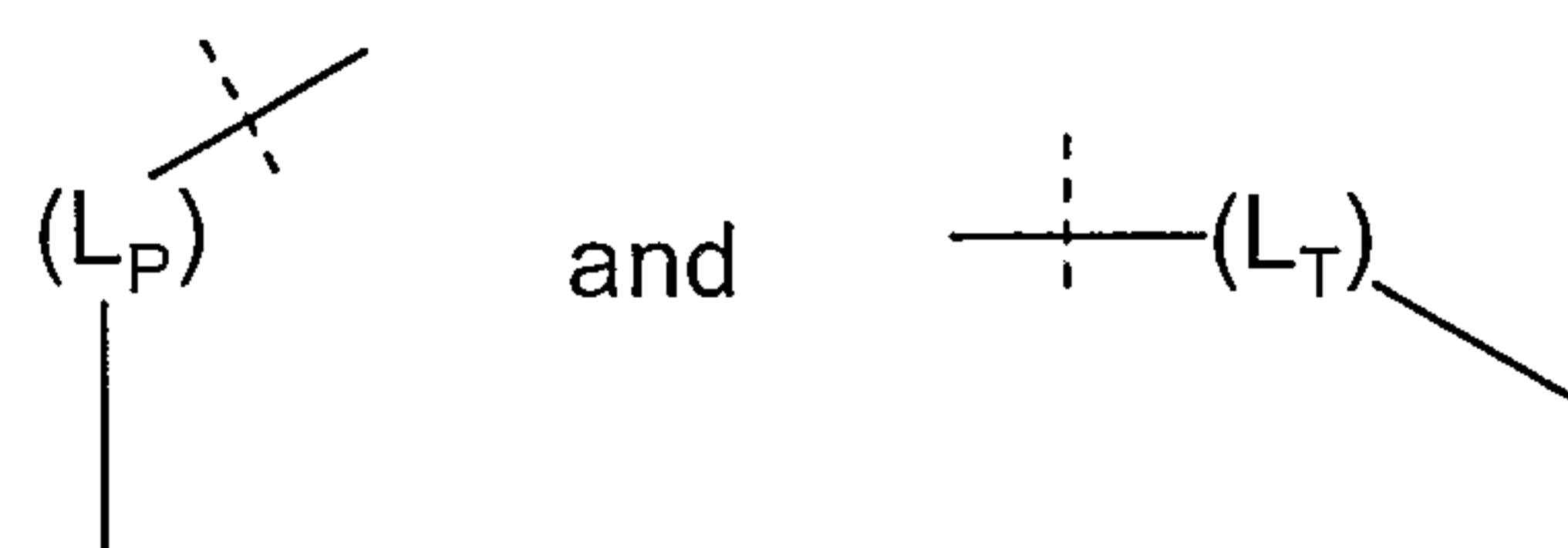
1-hydroxycycloheptyl,

and

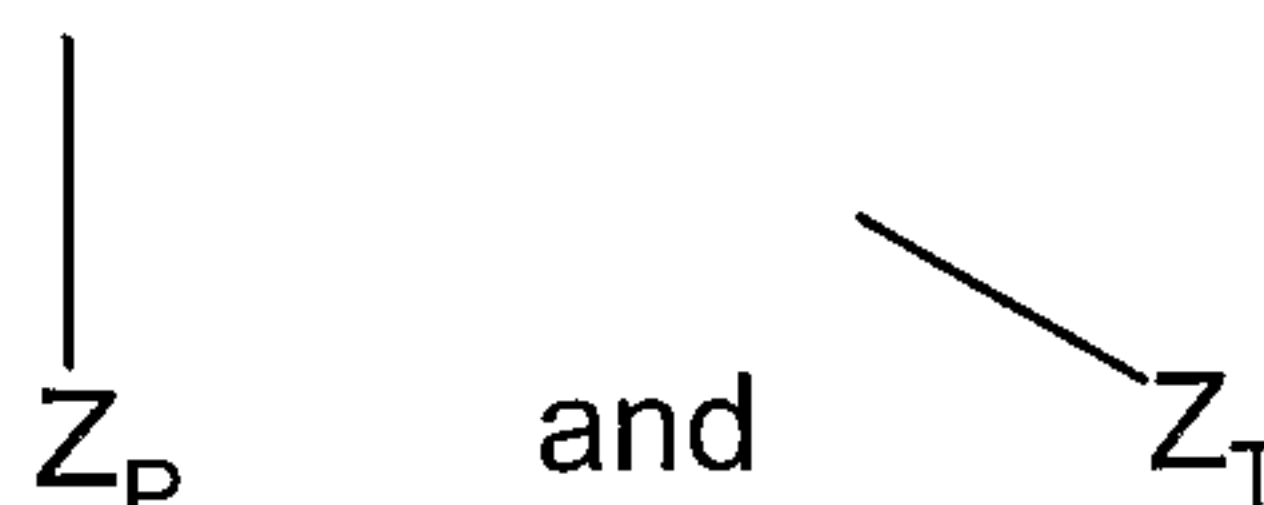
1-hydroxycyclooctyl.

-20-

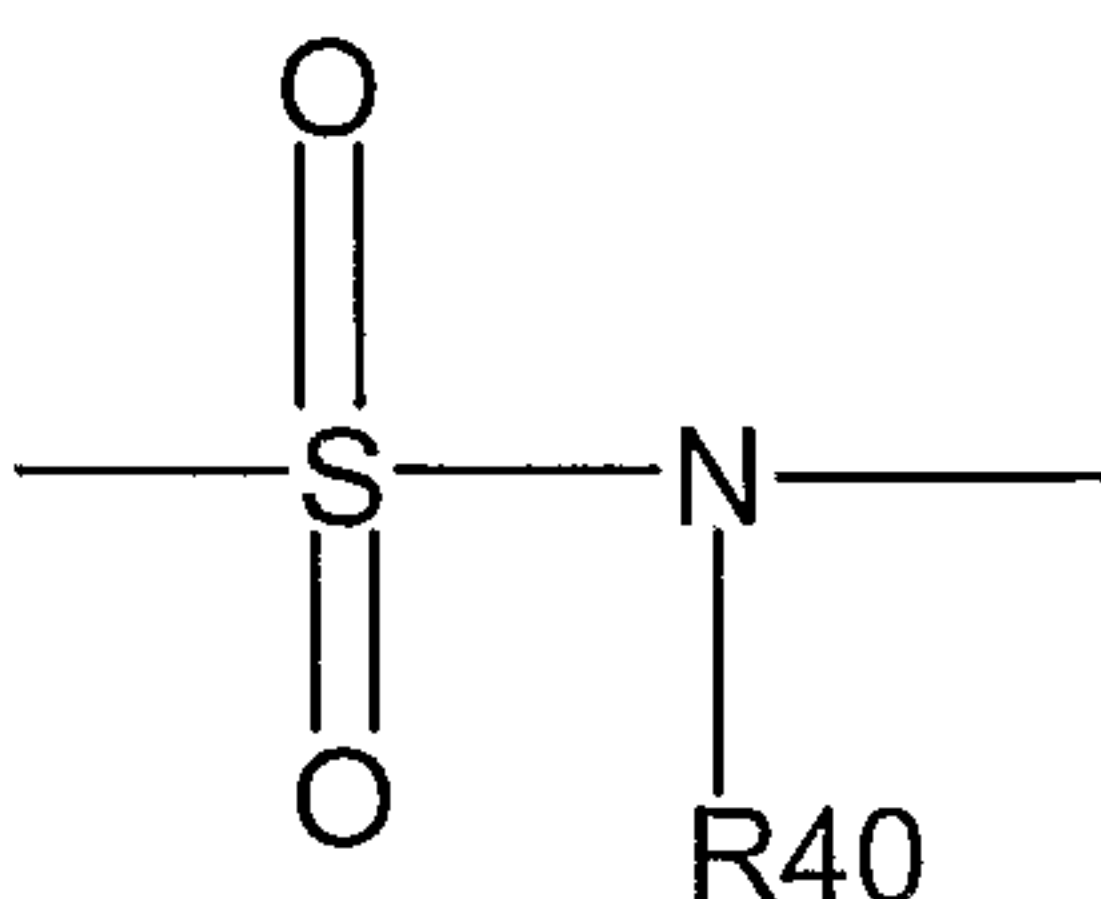
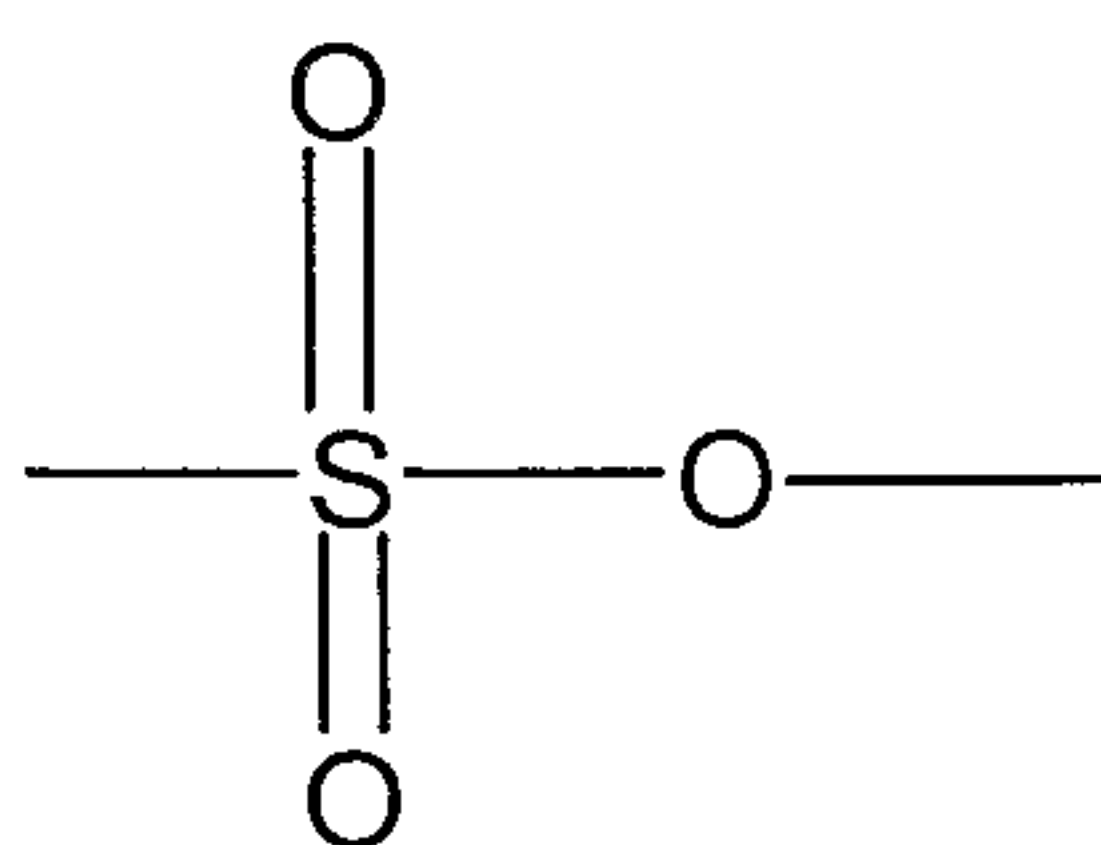
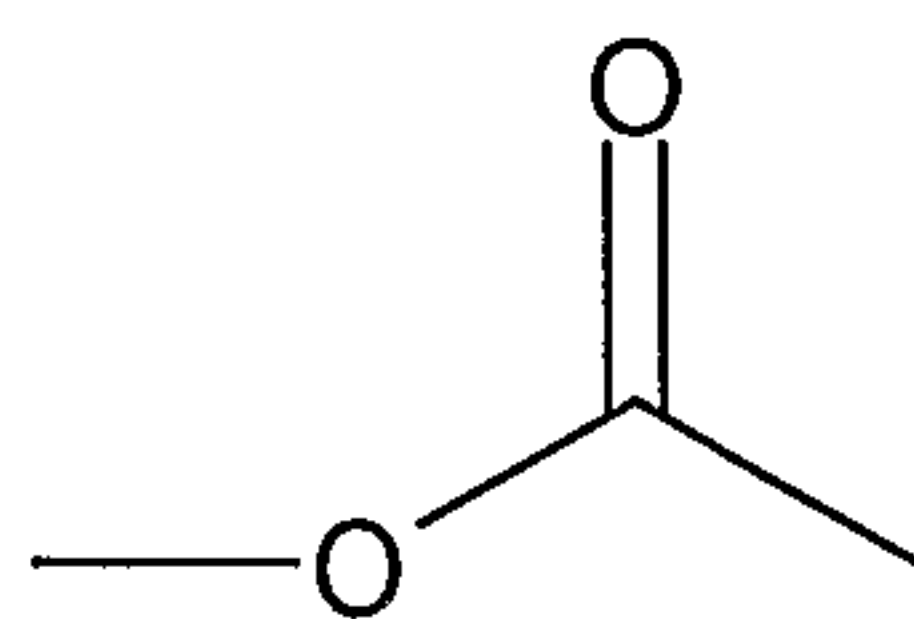
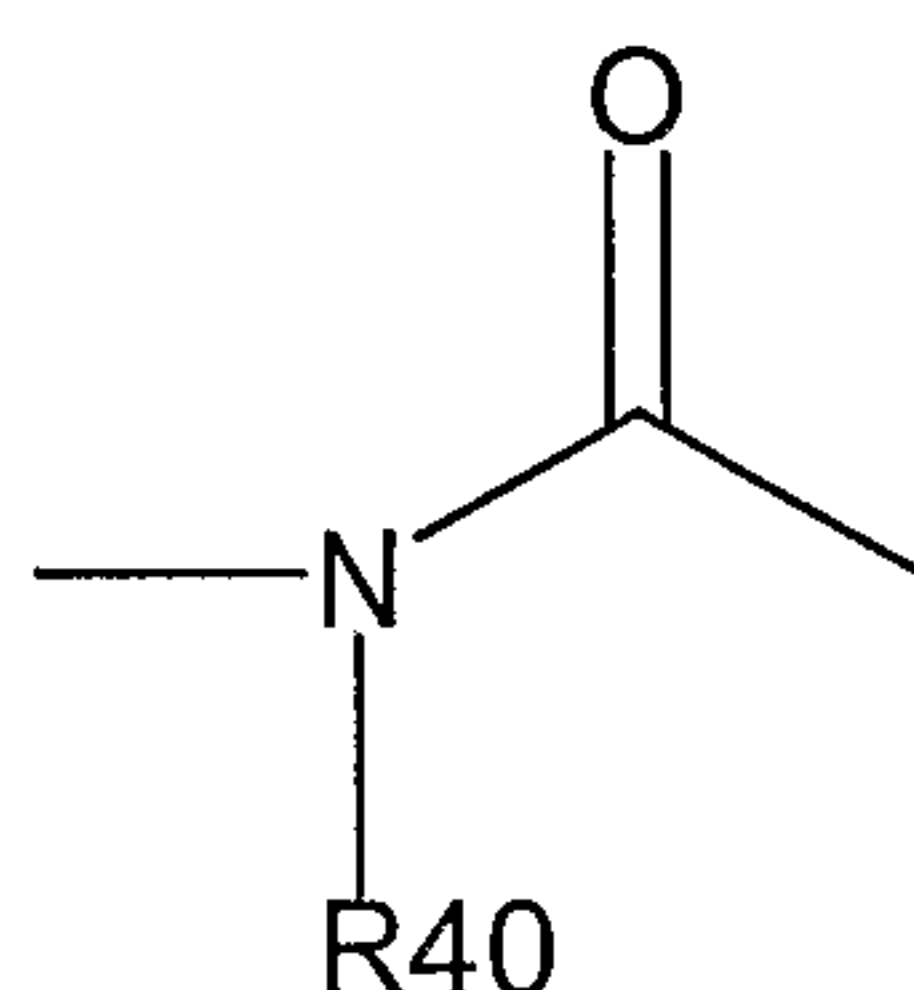
Conversely, the term “polar group” refers to any linking group



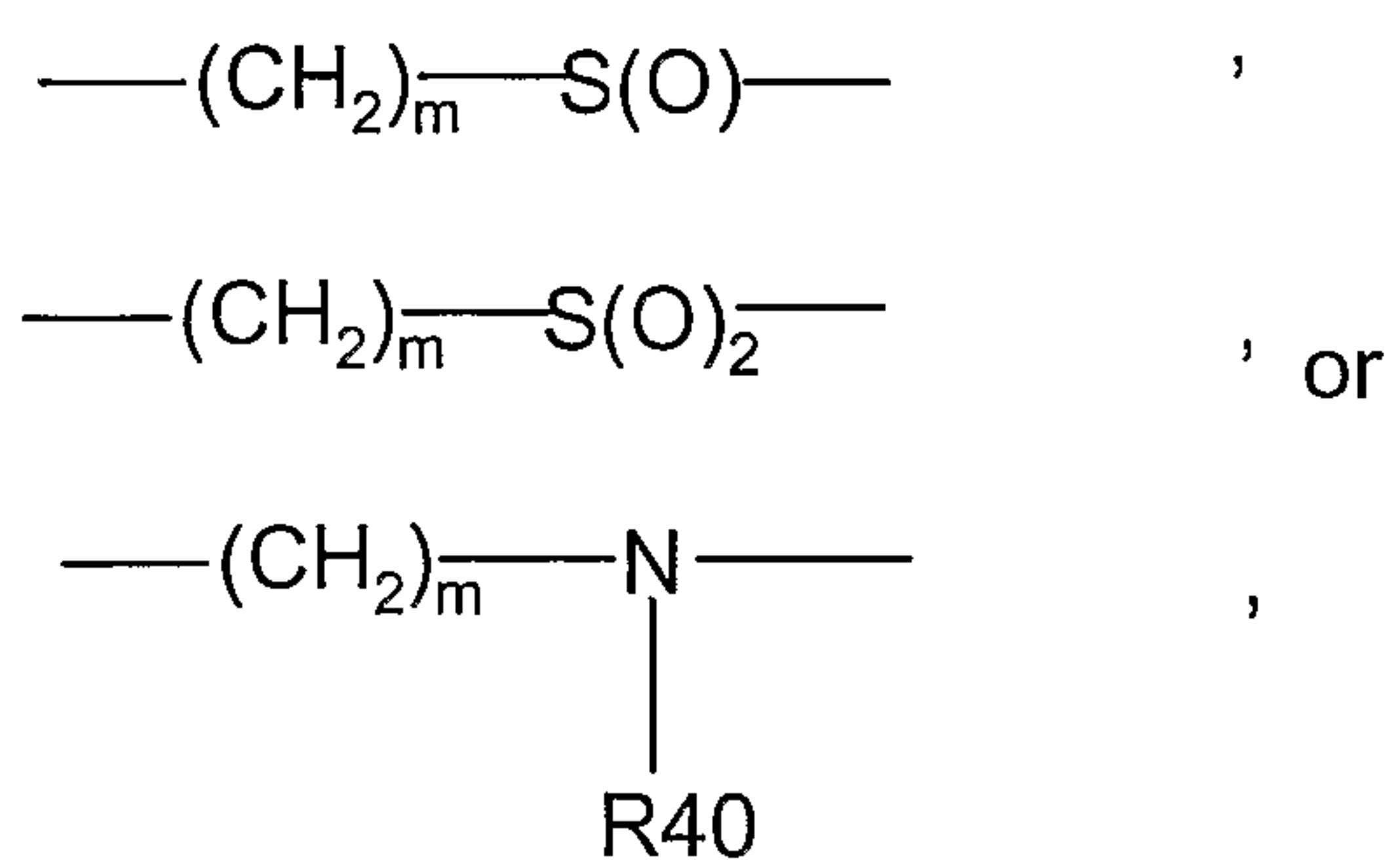
that is not a lipophilic group. The term “polar group” also refers to any Z substituent



- 5 that is not a lipophilic group. The term, “polar” as used herein generally refers to chemical substituents that are hydrophilic, preferring or attracted to an aqueous environment. An example of a polar linking group is a linking group selected from the following:



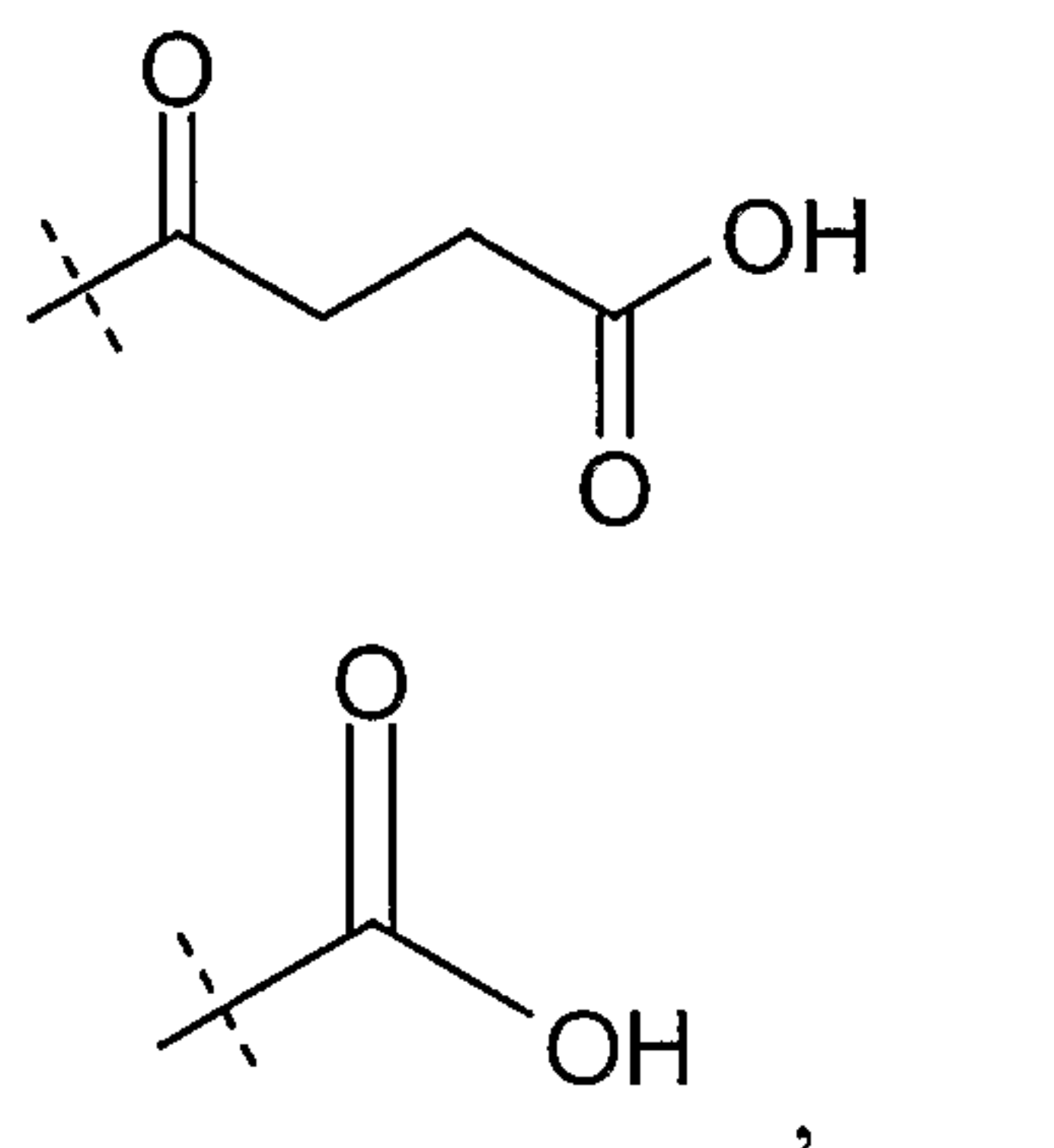
-21-



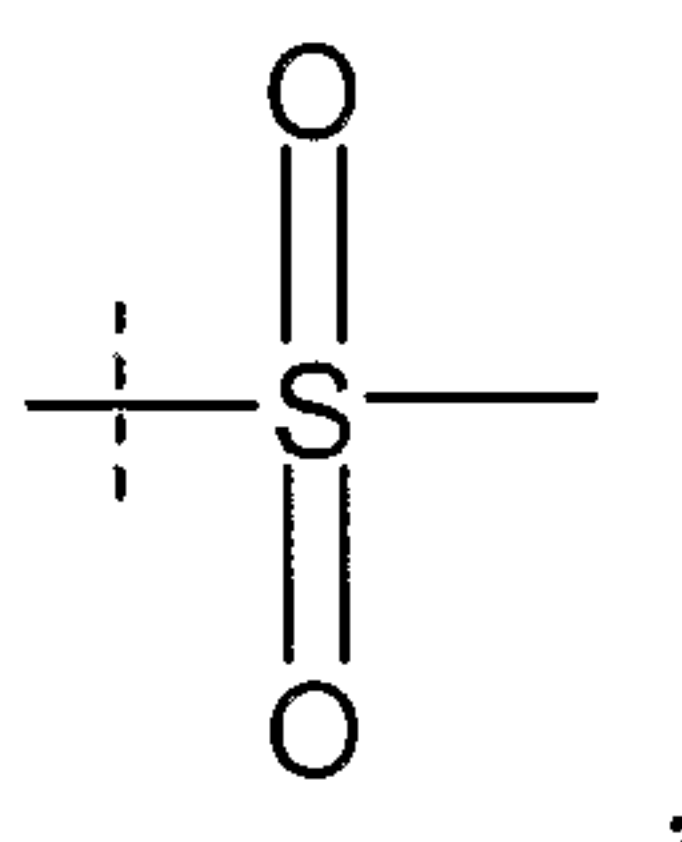
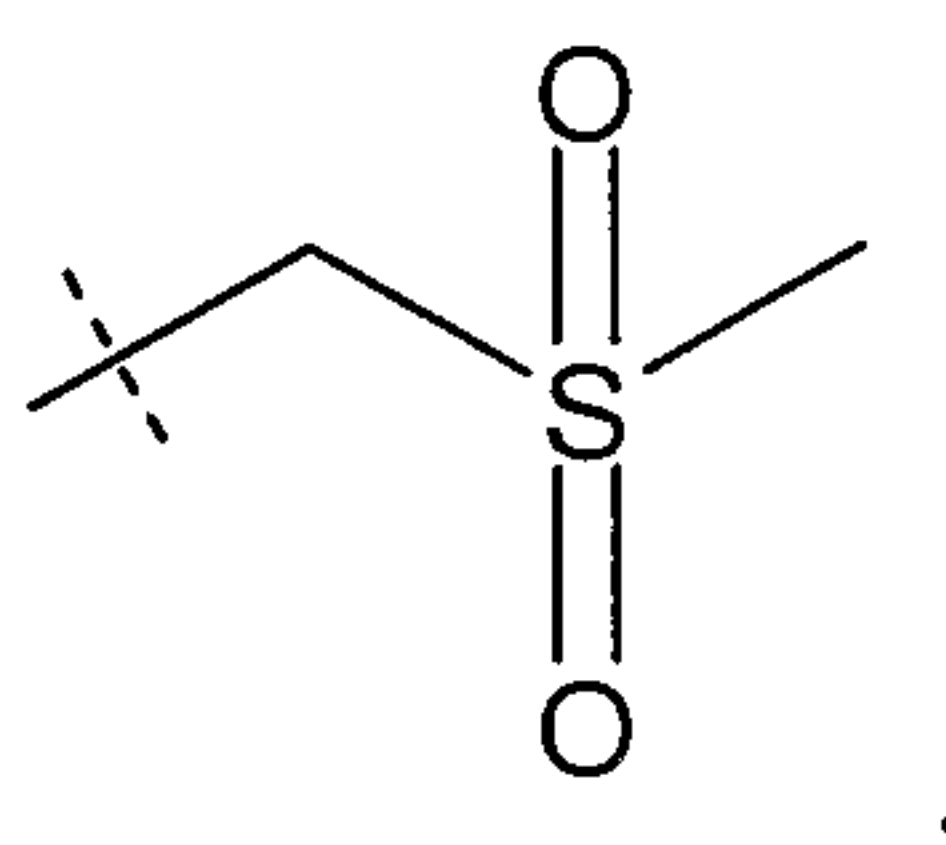
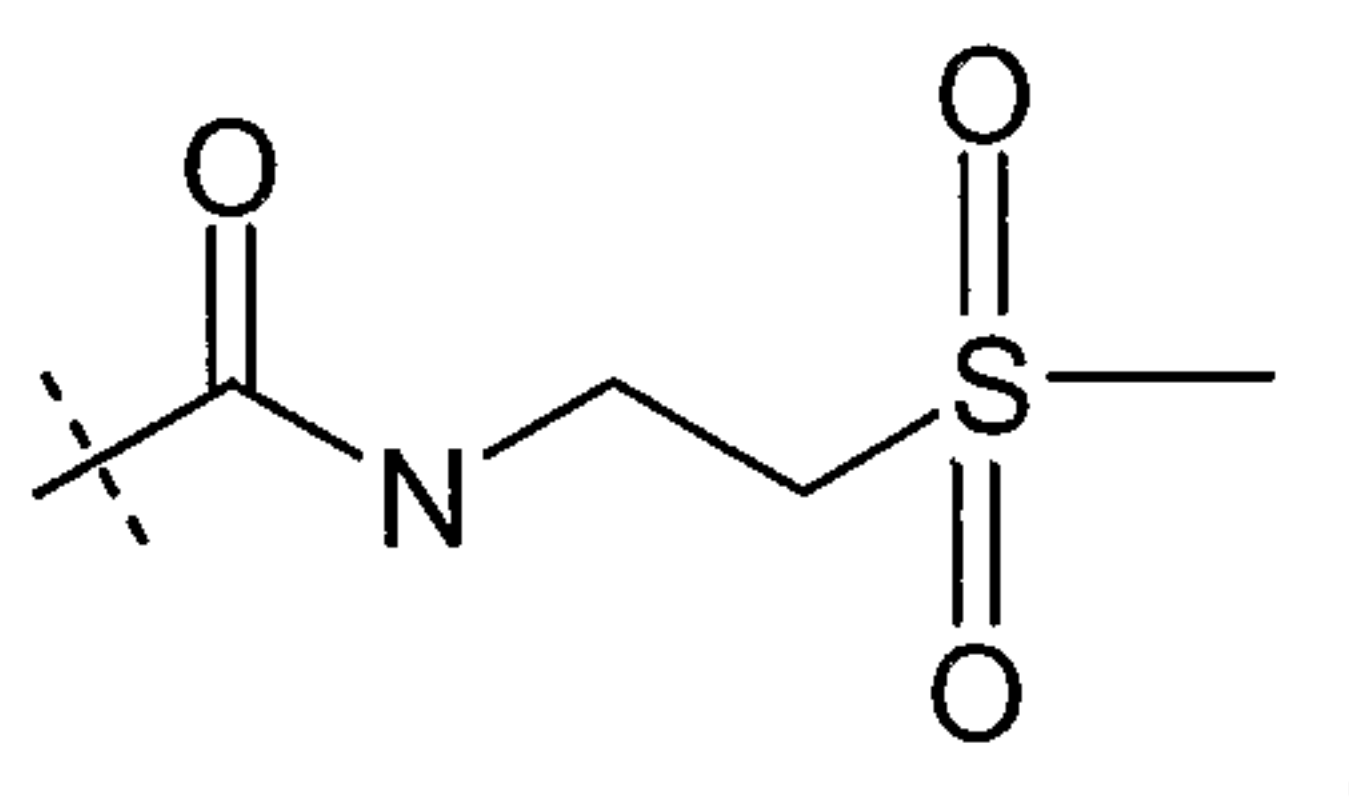
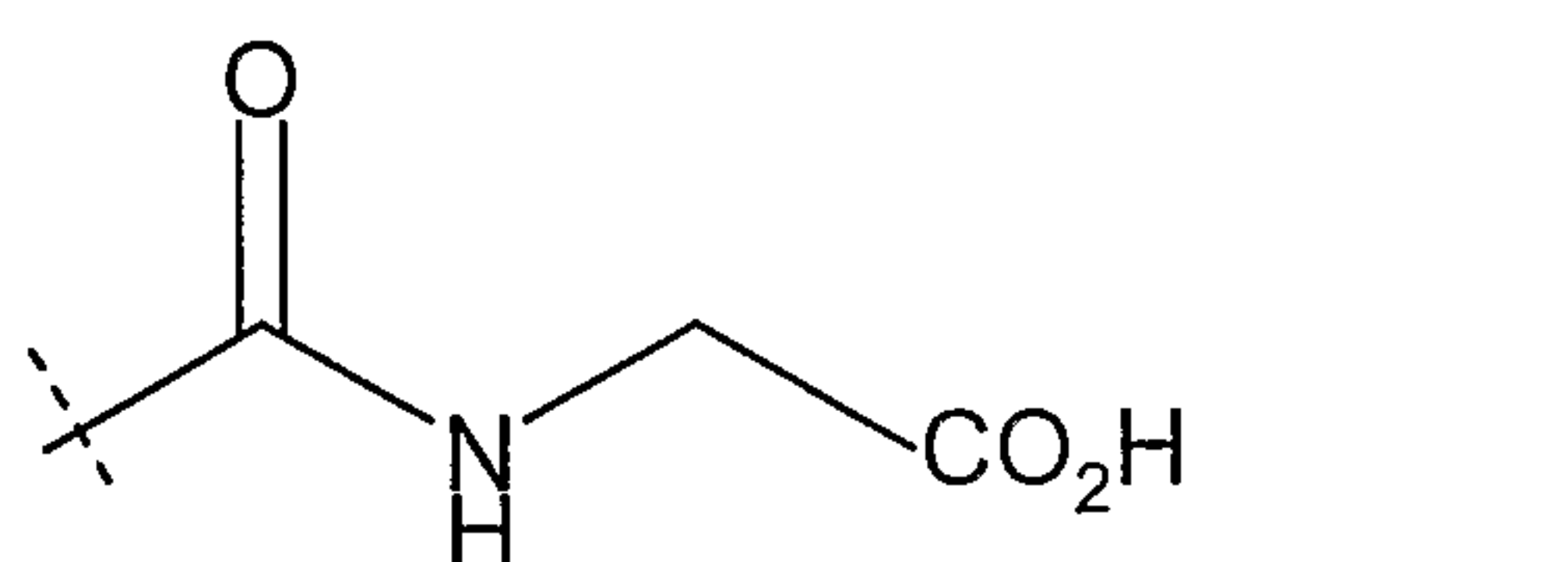
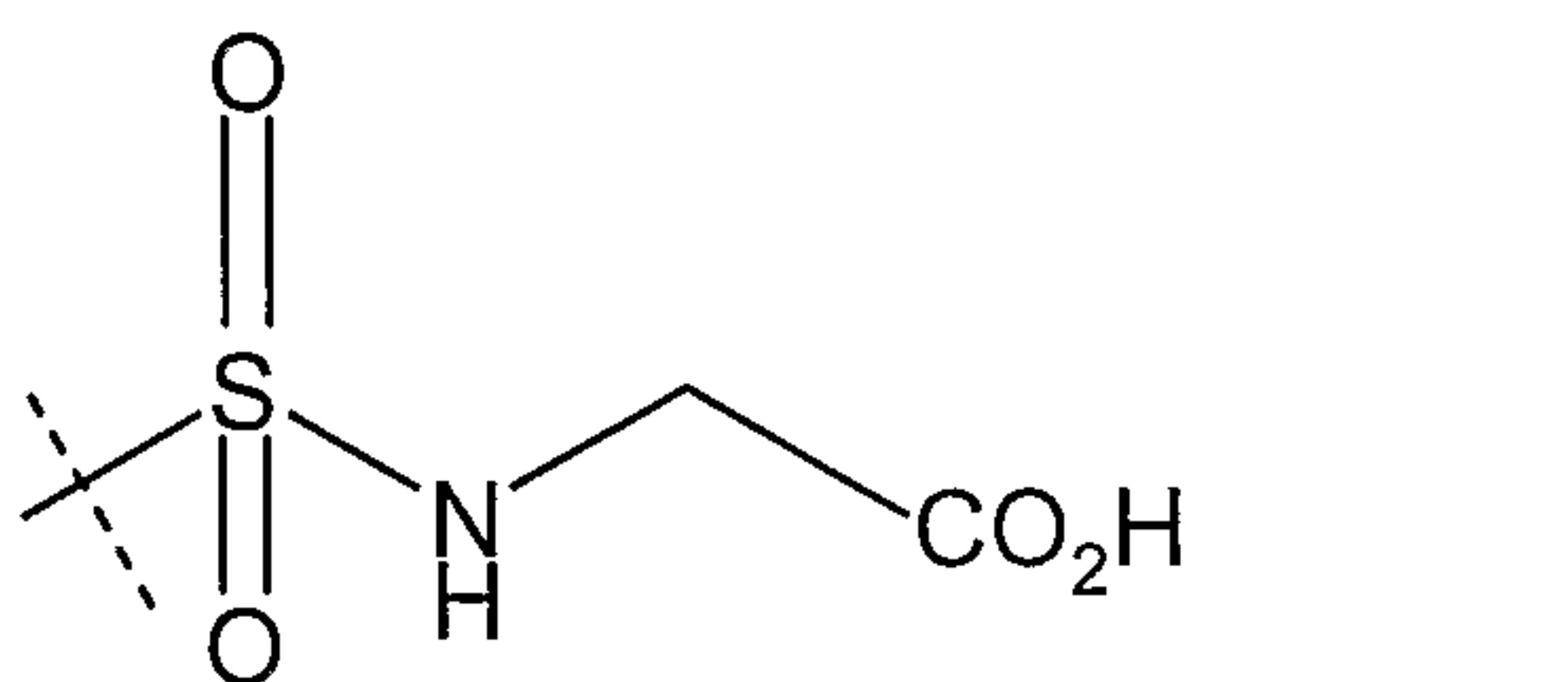
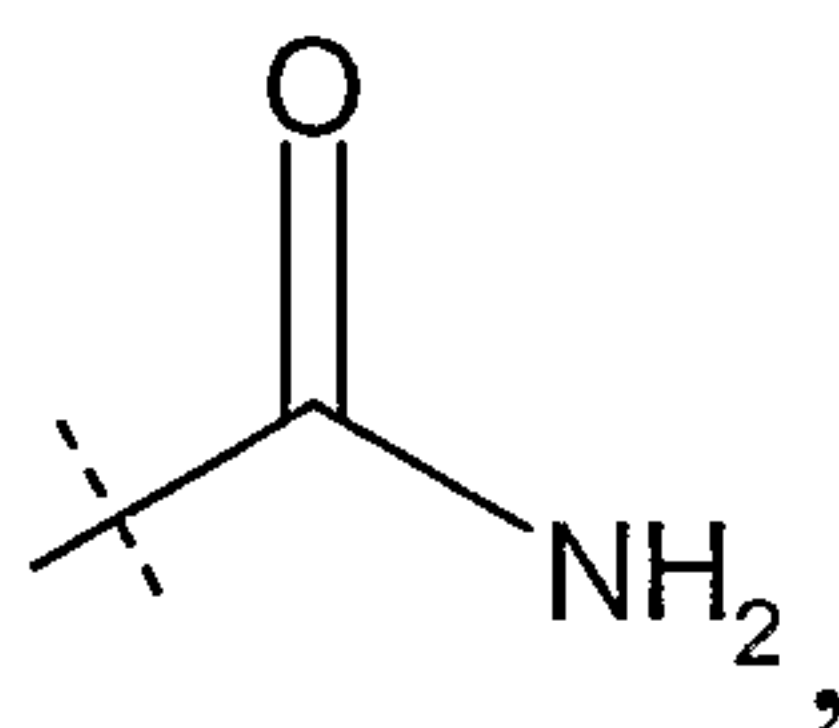
where m is 0, 1, or 2 and R40 is as previously defined.

Exemplary polar Z_T or Z_P groups in the practice of the invention are depicted by the following formulae:

5



-22-



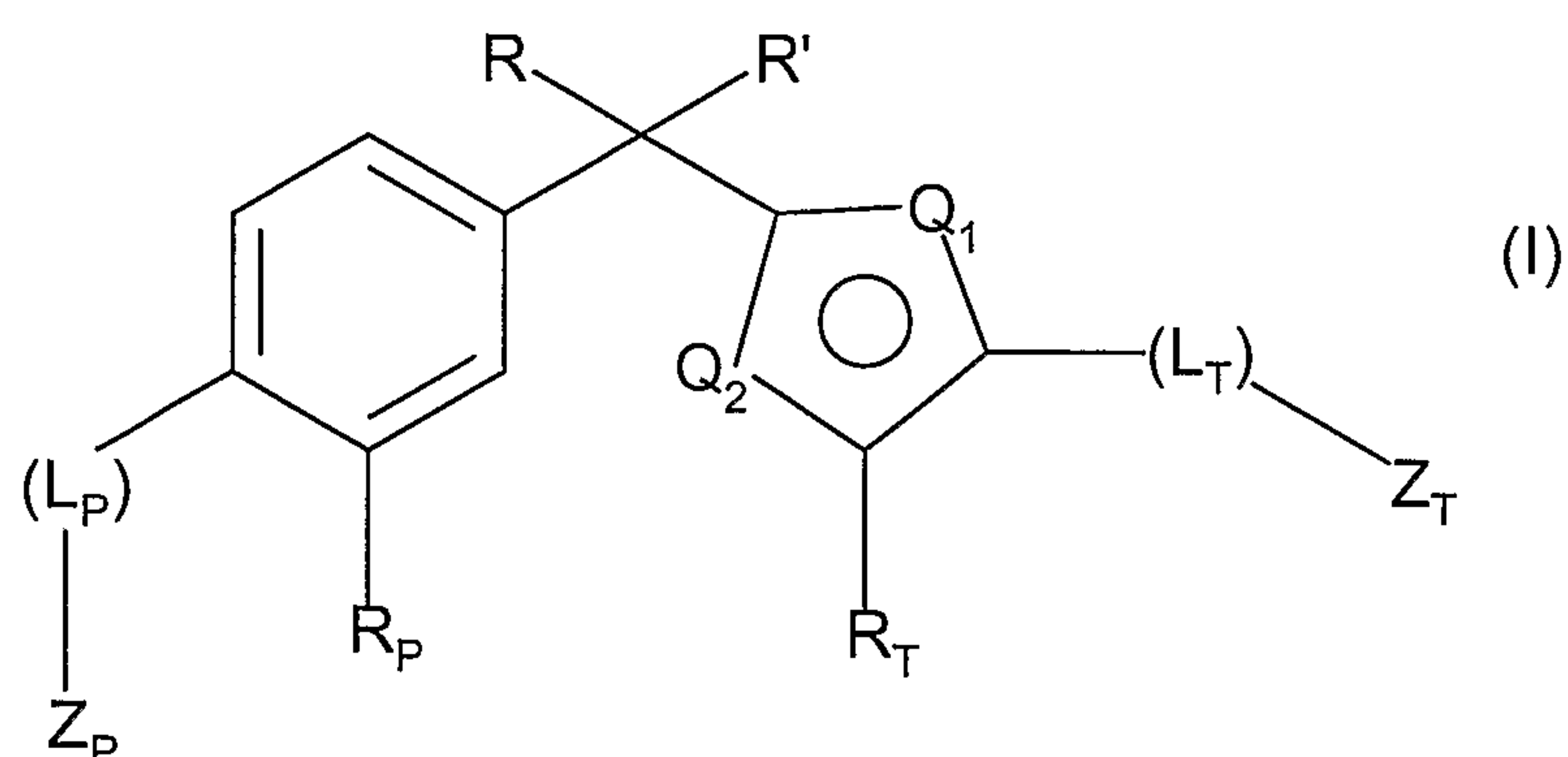
5

II. Compounds of the Invention:

The compounds of the invention are Vitamin D Receptor Modulators represented by formula I or a pharmaceutically acceptable salt or prodrug derivative thereof:

10

-23-



wherein;

R and R' are independently C₁-C₅ alkyl, C₁-C₅ fluoroalkyl, or together R and R' form a substituted or unsubstituted, saturated or unsaturated carbocyclic ring having from
5 3 to 8 carbon atoms;

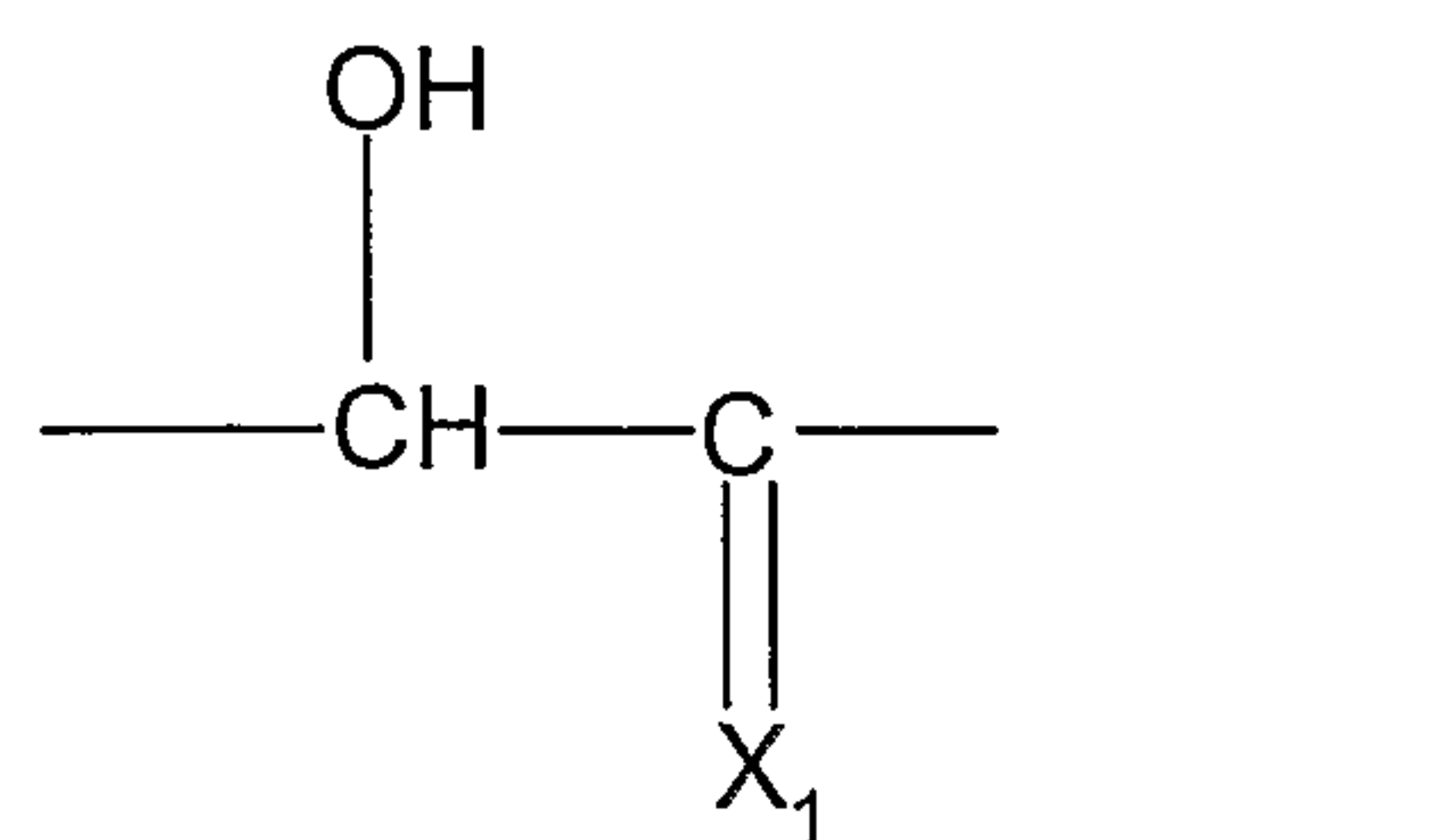
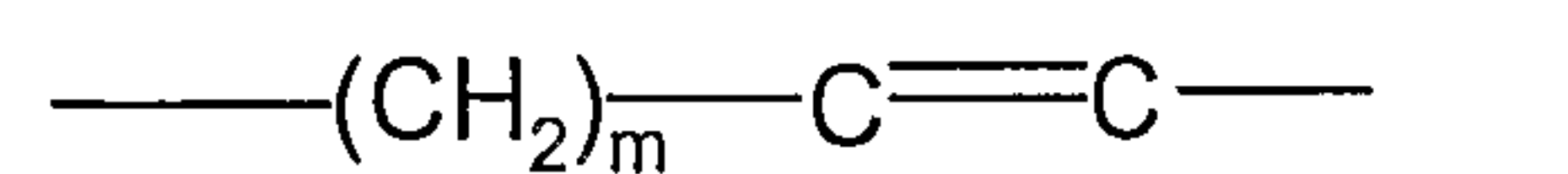
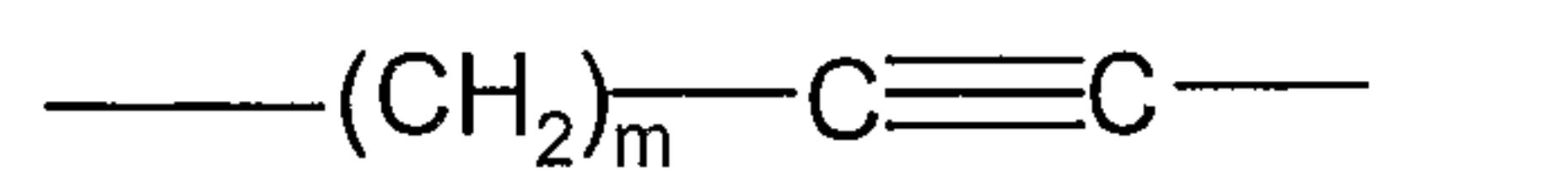
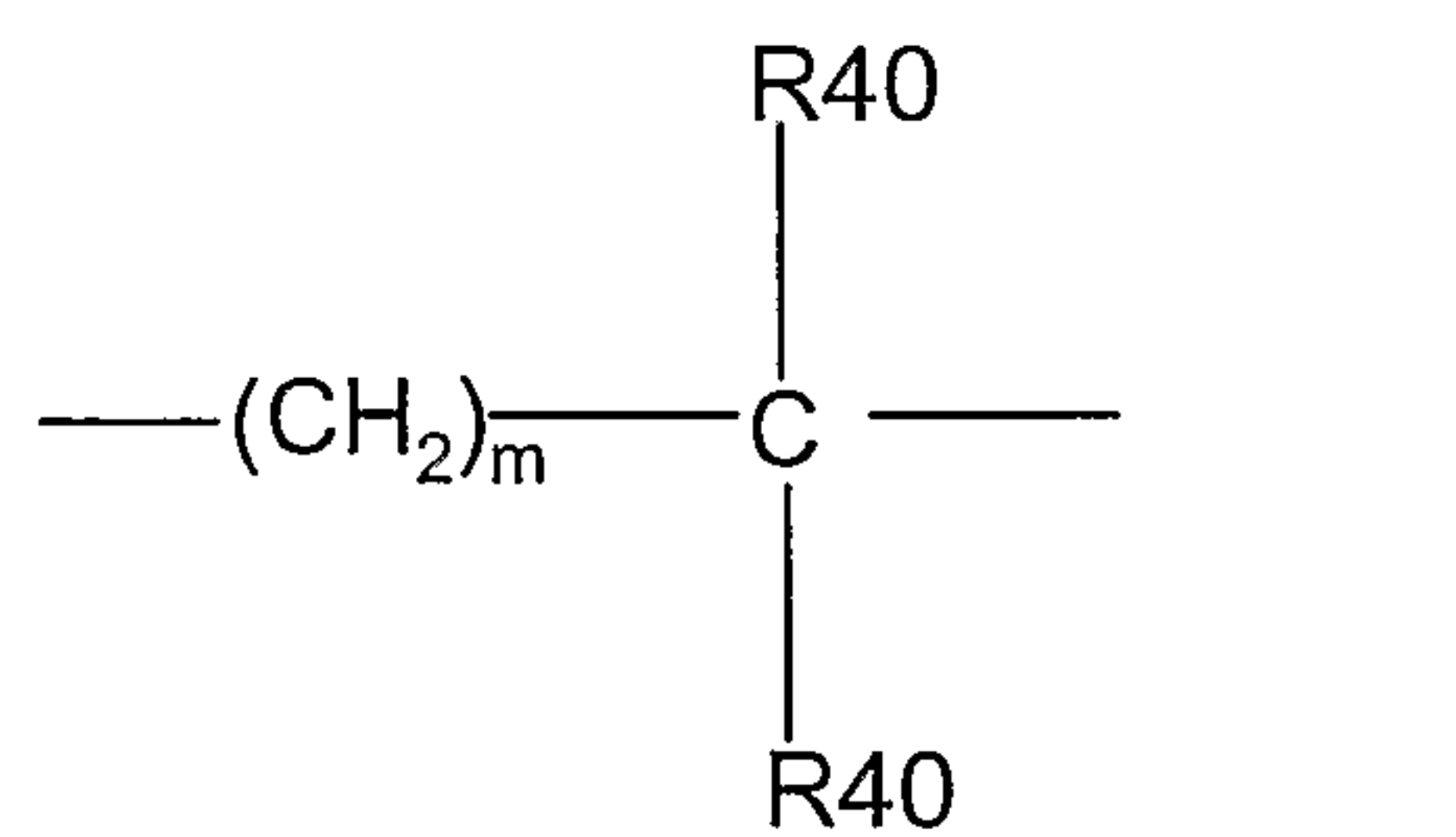
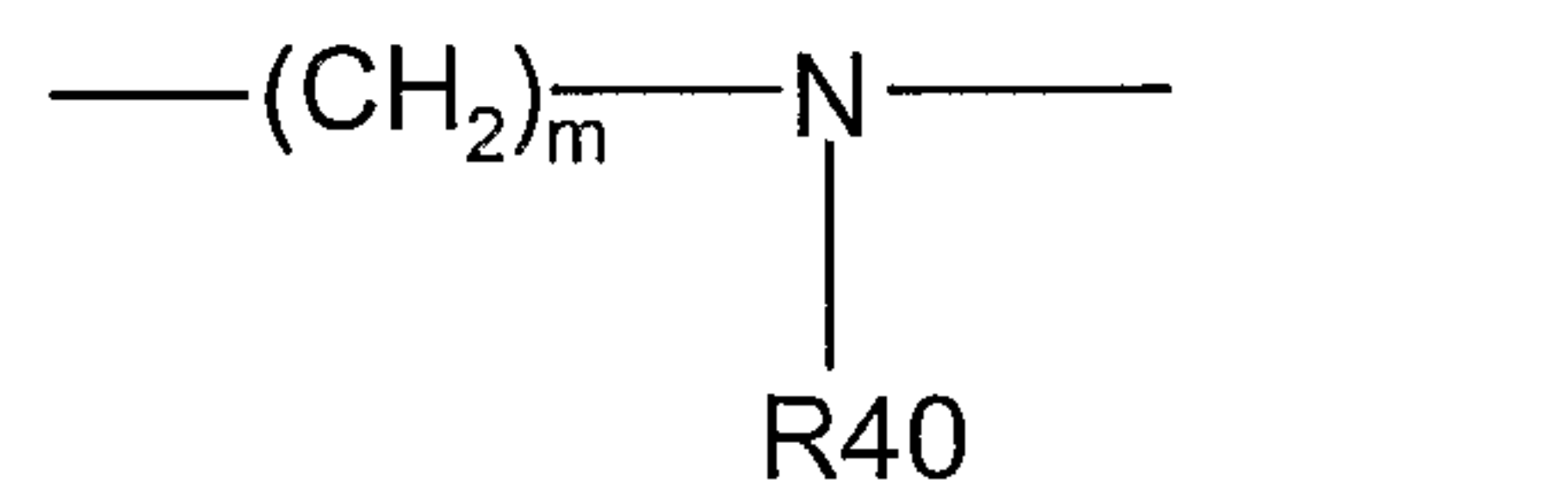
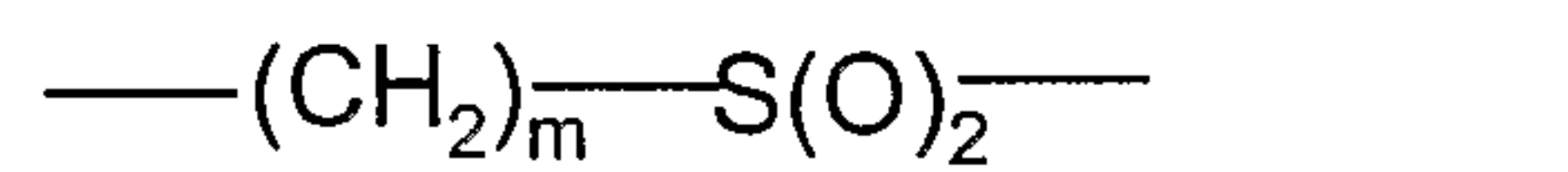
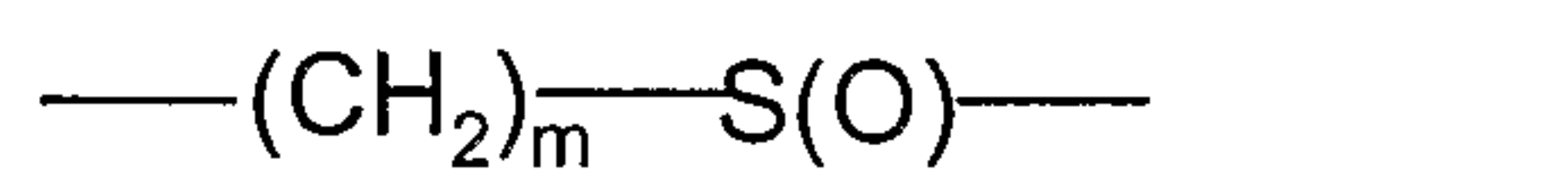
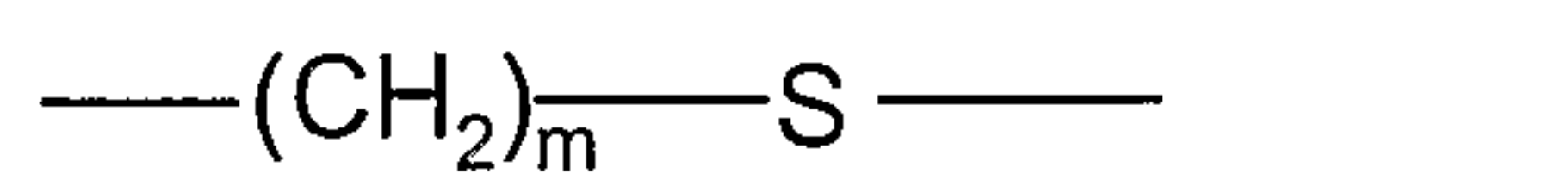
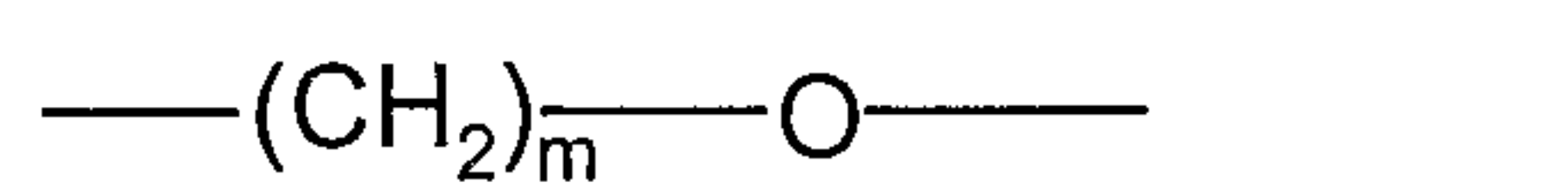
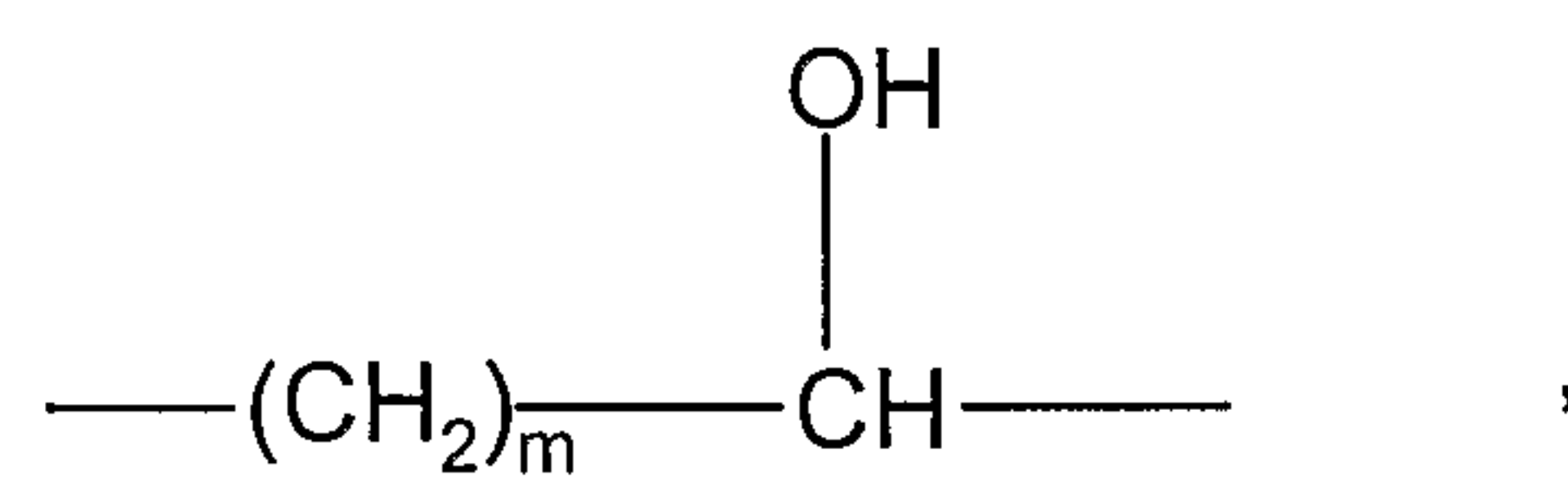
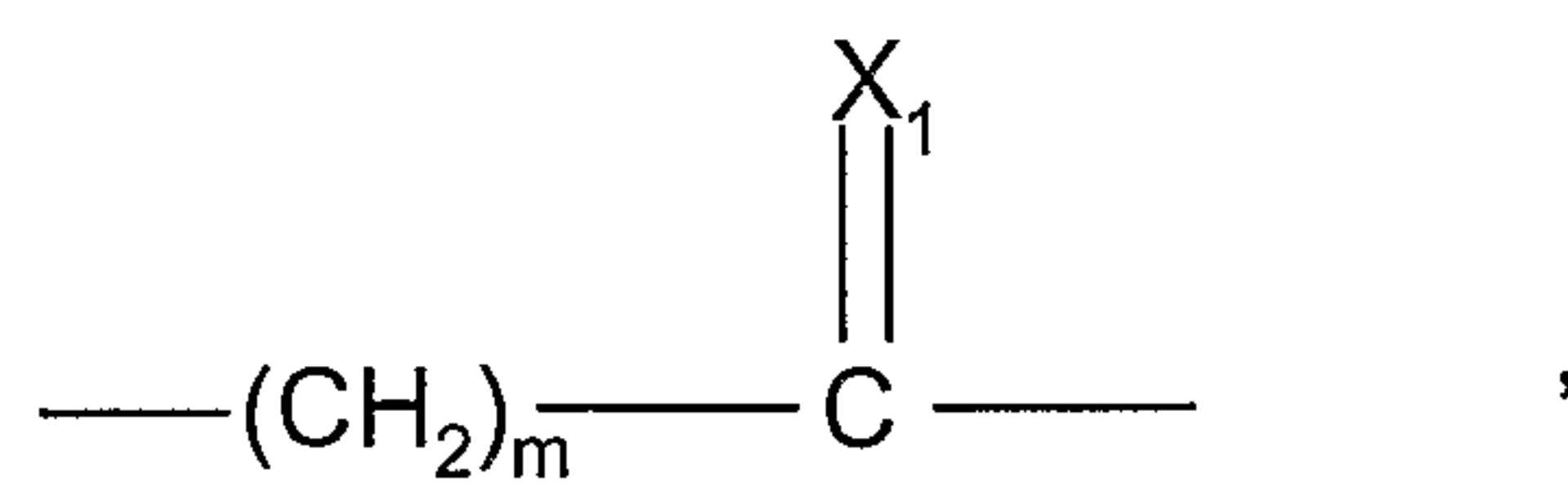
Ring atoms Q₁ and Q₂ are independently selected from carbon or sulfur, with the proviso that one atom is sulfur and the other atom is carbon;

R_P and R_T are independently selected from the group consisting of hydrogen, halo, C₁-C₅ alkyl, C₁-C₅ fluoroalkyl, -O-C₁-C₅ alkyl, -S-C₁-C₅ alkyl, -O-C₁-C₅
10 fluoroalkyl, -CN, -NO₂, acetyl, -S-C₁-C₅ fluoroalkyl, C₂-C₅ alkenyl, C₃-C₅ cycloalkyl, and C₃-C₅ cycloalkenyl;

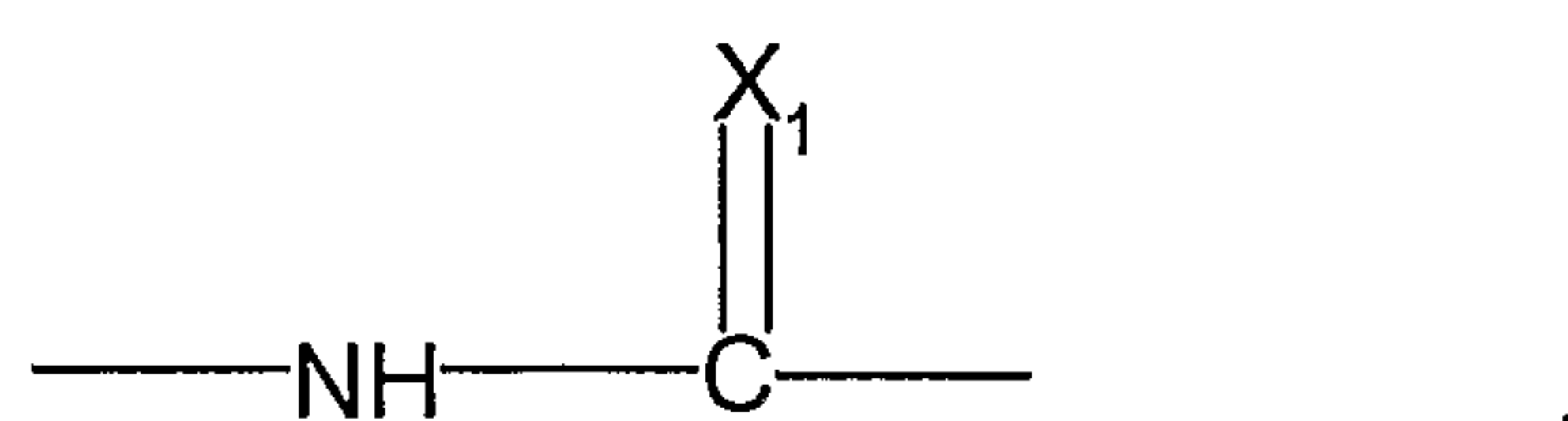
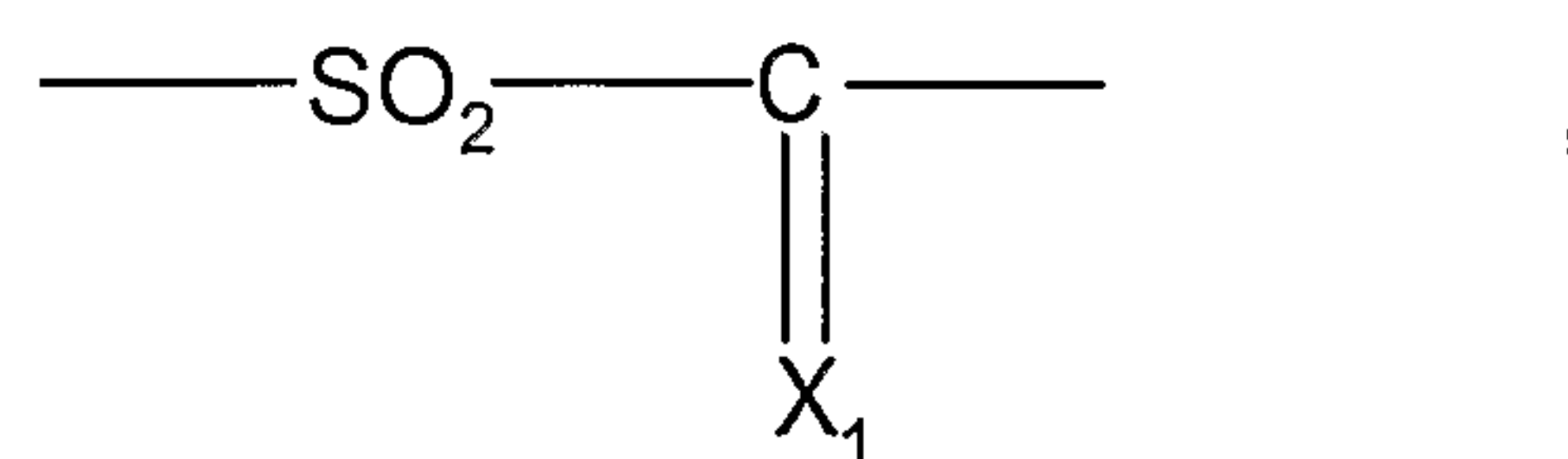
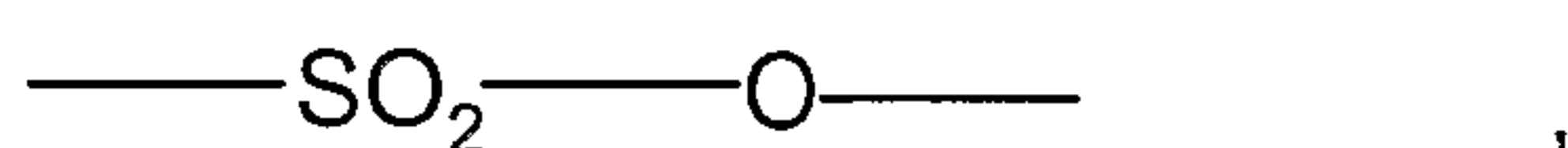
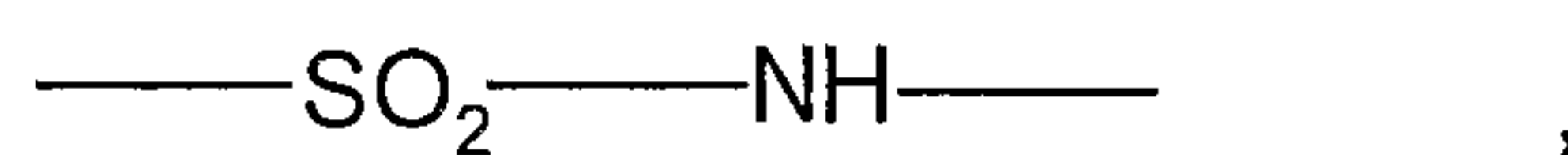
(L_P) and (L_T) are divalent linking groups independently selected from the group consisting of

-24-

a bond ,



-25-



5

where m is 0, 1 or 2, X₁ is oxygen or sulfur, and each R₄₀ is independently hydrogen or C₁-C₅ alkyl or C₁-C₅ fluoroalkyl;

Z_P and Z_T are independently selected from

10

-hydrogen,

-phenyl,

-benzyl,

-fluorophenyl,

-(C₁-C₅ alkyl),

-(C₂-C₅ alkenyl),

15

-(C₃-C₅ cycloalkyl),

-(C₃-C₅ cycloalkenyl),

-(C₁-C₅ hydroxyalkyl),

-(C₁-C₅ fluoroalkyl),

-(C₁-C₅ alkyl)-phenyl,

-26-

- 5
- (C₁-C₅ alkyl)-O-(C₁-C₅) alkyl,
 - (C₁-C₅ alkyl)-NH₂,
 - (C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,
 - (C₁-C₅ alkyl)-C(O)-NH₂,
 - (C₁-C₅ alkyl)-C(O)-NH-(C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-C(O)-N-(C₁-C₅ alkyl)₂,
 - (C₁-C₅ alkyl)-C(O)-(C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-NH-SO₂-(C₁-C₅ alkyl),

10

 - (C₁-C₅ alkyl)-N-pyrrolidin-2-one,
 - (C₁-C₅ alkyl)-N-pyrrolidine,
 - (C₁-C₅ alkyl)-(1-methylpyrrolidin-2-one-3-yl),
 - (C₁-C₅ alkyl)-C(O)-(O-C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-C(O)-OH,

15

 - (C₁-C₅ alkyl)-5-tetrazolyl,
 - (C₁-C₅ alkyl)-P(O)-(O-C₁-C₅ alkyl)₂,
 - (C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-SO₂-NH₂,
 - (C₁-C₅ alkyl)-SO₂-NH-(C₁-C₅ alkyl),

20

 - (C₁-C₅ alkyl)-SO₂-N-(C₁-C₅ alkyl)₂,
 - (C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-S(O)-NH₂,
 - (C₁-C₅ alkyl)-S(O)-NH-(C₁-C₅ alkyl),

25

 - (C₁-C₅ alkyl)-S(O)-N-(C₁-C₅ alkyl)₂,
 - (C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
 - (C₁-C₅ alkyl)-N(C(O)(C₁-C₅ alkyl)CH₂C(O)OH,
 - (C₁-C₅ alkyl)-N(C(O)(C₁-C₅ alkyl)CH₂C(O)-(C₁-C₅ alkyl),

30

 - (CH(OH)-(C₁-C₅ alkyl)
 - (CH(OH)-(C₂-C₅ alkenyl),

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- 5
- CH(OH)-(C₃-C₅ cycloalkyl),
 - CH(OH)-(C₃-C₅ cycloalkenyl),
 - CH(OH)-(C₁-C₅ hydroxyalkyl),
 - CH(OH)-(C₁-C₅ fluoroalkyl),
 - CH(OH)-phenyl
 - CH(OH)-5-tetrazolyl,
 - CH(OH)-(1-methylpyrrolidin-2-one-3-yl),
- 10
- C(O)-(C₁-C₅ alkyl),
 - C(O)-(C₁-C₅ alkyl)-C(O)OH,
 - C(O)-(C₁-C₅ alkyl)-C(O)(O-C₁-C₅ alkyl),
 - C(O)-(C₂-C₅ alkenyl),
 - C(O)-(C₃-C₅ cycloalkyl),
 - C(O)-(C₃-C₅ cycloalkenyl),
- 15
- C(O)-(C₁-C₅ hydroxyalkyl),
 - C(O)-(C₁-C₅ fluoroalkyl),
 - C(O)-(C₁-C₅ alkyl)-phenyl
 - C(O)-O-(C₁-C₅ alkyl),
 - C(O)-O-(C₂-C₅ alkenyl),
- 20
- C(O)-O-(C₃-C₅ cycloalkyl),
 - C(O)-O-(C₃-C₅ cycloalkenyl),
 - C(O)-O-(C₁-C₅ hydroxyalkyl),
 - C(O)-O-(C₁-C₅ fluoroalkyl),
 - C(O)-O-(C₁-C₅ alkyl)-phenyl,
- 25
- C(O)-NH₂,
 - C(O)-NH(OH),
 - C(O)-NH-(C₁-C₅ alkyl),
 - C(O)-N-(C₁-C₅ alkyl)₂,
 - C(O)-NH-(C₂-C₅ alkenyl),
- 30
- C(O)-NH-(C₃-C₅ cycloalkyl),
 - C(O)-NH-(C₃-C₅ cycloalkenyl),
 - C(O)-NH-(C₁-C₅ fluoroalkyl),

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- 5
- C(O)-NH-(C₁-C₅ alkyl)-phenyl,
 - C(O)-NH-SO₂-(C₁-C₅ alkyl),
 - C(O)-NH-SO₂-(C₂-C₅ alkenyl),
 - C(O)-NH-SO₂-(C₃-C₅ cycloalkyl),
 - C(O)-NH-SO₂-(C₃-C₅ cycloalkenyl),
 - C(O)-NH-S(O)-(C₁-C₅ alkyl),
 - C(O)-NH-S(O)-(C₂-C₅ alkenyl),
 - C(O)-NH-S(O)-(C₃-C₅ cycloalkyl),
 - C(O)-NH-S(O)-(C₃-C₅ cycloalkenyl),
- 10
- C(O)-NH-(C₁-C₅ fluoroalkyl),
 - C(O)-NH-(C₁-C₅ alkyl)-phenyl
 - C(O)-NH-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 - C(O)-NH-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
 - C(O)-NH-CH₂-C(O)OH
- 15
- C(O)-NH-CH₂-C(O)-(O-C₁-C₅ alkyl),
 - C(O)-N-(C₁-C₅ alkyl)(C(O)OH),
 - C(O)-N-(C₁-C₅ alkyl)(C(O)-(O-C₁-C₅ alkyl)),
 - C(O)-NH-CH((CH₂)(CO₂H))(CO₂H),
 - C(O)-NH-CH((CH₂)(C(O)-(C₁-C₅ alkyl)))(C(O)-(O-C₁-
- 20
- C₅ alkyl)),
 - C(O)-NH-CH((CH₂OH)(CO₂H)),
 - C(O)-NH-CH((CH₂OH)(C(O)(O-C₁-C₅ alkyl))),
 - C(O)-NH-C((C₁-C₅ alkyl)(C₁-C₅ alkyl))(CO₂H),
 - C(O)-NH-C((C₁-C₅ alkyl)(C₁-C₅ alkyl))(C(O)-(O-C₁-C₅
- 25
- alkyl)),
 - C(O)-NH-5-tetrazolyl,
 - C(O)-N-pyrrolidin-2-one,
 - C(O)-N-pyrrolidine,
 - C(O)-(1-methylpyrrolidin-2-one-3-yl),
- 30
- C(O)-(C₁-C₅ alkyl)-N-pyrrolidin-2-one,
 - C(O)-(C₁-C₅ alkyl)-N-pyrrolidine,
 - C(O)-(C₁-C₅ alkyl)-(1-methylpyrrolidin-2-one-3-yl),

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- C(O)-N-pyrrolidin-2-(CO₂H),
 -C(O)-N-pyrrolidin-2-(C(O)-(O-C₁-C₅ alkyl)),
 -C(O)-N-(C(O)-(C₁-C₅ alkyl))CH₂(CO₂H),
 -C(O)-N-(C(O)-(C₁-C₅ alkyl))CH₂(C(O)-(O-C₁-C₅ alkyl)),
 -C(O)-N-(C₁-C₅ alkyl)CH₂(CO₂H),
 -C(O)-C(O)-OH,
 -C(O)-C(O)-(C₁-C₅ alkyl),
 -C(O)-C(O)-(C₂-C₅ alkenyl),
 -C(O)-C(O)-(C₃-C₅ cycloalkyl),
 -C(O)-C(O)-(C₃-C₅ cycloalkenyl),
 -C(O)-C(O)-(C₁-C₅ hydroxyalkyl),
 -C(O)-C(O)-(C₁-C₅ fluoroalkyl),
 -C(O)-C(O)-(C₁-C₅ alkyl)-phenyl,
 -C(O)-C(O)-NH₂,
 -C(O)-C(O)-NH-(C₁-C₅ alkyl),
 -C(O)-C(O)-N-(C₁-C₅ alkyl)₂,
 -C(O)-C(O)-5-tetrazolyl,
 -C(O)-C(O)-N-pyrrolidin-2-one,
 -C(O)-C(O)-N-pyrrolidine,
 -C(O)-C(O)-(1-methylpyrrolidin-2-one-3-yl),
 -O-(C₁-C₅ alkyl),
 -O-(C₂-C₅ alkenyl),
 -O-(C₃-C₅ cycloalkyl),
 -O-(C₃-C₅ cycloalkenyl),
 -O-(C₁-C₅ hydroxyalkyl),
 -O-(C₁-C₅ fluoroalkyl),
 -O-(C₁-C₅ alkyl)-phenyl,
 -O-(C₁-C₅ alkyl)-(O)-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)NH₂,
 -O-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl)₂,

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-O-(C₁-C₅ alkyl)-C(O)-NH₂,
 -O-(C₁-C₅ alkyl)-C(O)-NH-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-C(O)-N-(C₁-C₅ alkyl)₂,
 -O-(C₁-C₅ alkyl)-C(O)-OH,
 5 -O-(C₁-C₅ alkyl)-C(O)-NH-5-tetrazolyl,
 -O-(C₁-C₅ alkyl)-C(O)-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-C(O)-(O-C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-NH₂,
 -O-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),
 10 -O-(C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,
 -O-(C₁-C₅ alkyl)-NH-SO₂-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-N-pyrrolidin-2-one,
 -O-(C₁-C₅ alkyl)-N-pyrrolidine,
 -O-(C₁-C₅ alkyl)-(1-methylpyrrolidin-2-one-3-yl),
 15 -O-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-SO₂-NH₂,
 -O-(C₁-C₅ alkyl)-SO₂-NH-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-SO₂-N-(C₁-C₅ alkyl)₂,
 -O-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 20 -O-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-S(O)-NH₂,
 -O-(C₁-C₅ alkyl)-S(O)-NH-(C₁-C₅ alkyl),
 -O-(C₁-C₅ alkyl)-S(O)-N-(C₁-C₅ alkyl)₂,
 -O-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
 25 -O-(C₁-C₅ alkyl)-P(O)-(O-C₁-C₅ alkyl)₂,
 -O-(C₁-C₅ alkyl)-5-tetrazolyl,
 -O-CH₂-CO₂H,
 -O-CH₂-5-tetrazolyl,
 -O-(C₁-C₅ alkyl),
 30 -O-C(O)-NH₂,
 -O-C(O)-N-(CH₃)₂,
 -O-C(S)-N-(CH₃)₂,

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- 5 -O-C(O)-O-(C₁-C₅ alkyl),
 -O-(5-tetrazolyl),
 -O-SO₂-(C₁-C₅ alkyl),
 -O-SO₂-NH₂,
 -O-SO₂-NH-(C₁-C₅ alkyl),
 -O-SO₂-N-(C₁-C₅ alkyl)₂,
 -O-S(O)-(C₁-C₅ alkyl),
 -O-S(O)-NH₂,
10 -O-S(O)-NH-(C₁-C₅ alkyl),
 -O-S(O)-N-(C₁-C₅ alkyl)₂,

 -S-(C₁-C₅ alkyl),
 -S-(C₂-C₅ alkenyl),
 -S-(C₃-C₅ cycloalkyl),
15 -S-(C₃-C₅ cycloalkenyl),
 -S-(C₁-C₅ fluoroalkyl),
 -S-(C₁-C₅ hydroxyalkyl),
 -S-(C₁-C₅ alkyl)-phenyl,
 -S-(C₁-C₅ alkyl)-O-(C₁-C₅ alkyl),
20 -S-(C₁-C₅ alkyl)-C(O)-OH,
 -S-(C₁-C₅ alkyl)-C(O)-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-C(O)-O-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-C(O)-NH₂,
 -S-(C₁-C₅ alkyl)-C(O)-NH-(C₁-C₅ alkyl),
25 -S-(C₁-C₅ alkyl)-C(O)-N-(C₁-C₅ alkyl)₂,
 -S-(C₁-C₅ alkyl) NH₂,
 -S-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,
 -S-(C₁-C₅ alkyl)-NH-SO₂-(C₁-C₅ alkyl),
30 -S-(C₁-C₅ alkyl)-N-pyrrolidin-2-one,
 -S-(C₁-C₅ alkyl)-N-pyrrolidine,
 -S-(C₁-C₅ alkyl)-(1-methylpyrrolidin-2-one-3-yl),

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- S-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-SO₂-NH₂,
 -S-(C₁-C₅ alkyl)-SO₂-NH-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-SO₂-N-(C₁-C₅ alkyl)₂,
 5 -S-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-P(O)-(O-C₁-C₅ alkyl)₂,
 -S-(C₁-C₅ alkyl)-5-tetrazolyl,
 -S-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-S(O)-NH₂,
 10 -S-(C₁-C₅ alkyl)-S(O)-NH-(C₁-C₅ alkyl),
 -S-(C₁-C₅ alkyl)-S(O)-N-(C₁-C₅ alkyl)₂,
 -S-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),

 -SO₂-(C₁-C₅ alkyl),
 15 -SO₂-(C₂-C₅ alkenyl),
 -SO₂-(C₃-C₅ cycloalkyl),
 -SO₂-(C₃-C₅ cycloalkenyl),
 -SO₂-(C₁-C₅ hydroxyalkyl),
 -SO₂-(C₁-C₅ fluoroalkyl),
 20 -SO₂-(C₁-C₅)-phenyl,

 -SO₂-NH₂,
 -SO₂-NH-(C₁-C₅ alkyl),
 -SO₂-NH-CH₂-C(O)OH,
 25 -SO₂-NH-CH₂-C(O)(O-C₁-C₅ alkyl),
 -SO₂-NH-(C₁-C₅ alkyl)-C(O)OH,
 -SO₂-NH-(C₁-C₅ alkyl)-C(O)(O-C₁-C₅ alkyl),
 -SO₂-NHC(O)-(C₃-C₆ cycloalkyl),

 30 -SO₂-NH-C(O)-(C₁-C₅ alkyl),
 -SO₂-N-(C₁-C₅ alkyl)₂,
 -SO₂-(C₁-C₅ alkyl)-O-(C₁-C₅ alkyl),

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- 5
- SO₂-(C₁-C₅ alkyl)-C(O)-(C₁-C₅ alkyl),
 - SO₂-(C₁-C₅ alkyl) NH₂,
 - SO₂-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),
 - SO₂-(C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,
 - SO₂-(C₁-C₅ alkyl)-C(O)-NH₂,
 - SO₂-(C₁-C₅ alkyl)-C(O)-NH-(C₁-C₅ alkyl),
 - SO₂-(C₁-C₅ alkyl)-C(O)-N-(C₁-C₅ alkyl)₂,
 - SO₂-(C₁-C₅ alkyl)-NH-SO₂-(C₁-C₅ alkyl),
 - SO₂-(C₁-C₅ alkyl)-N-pyrrolidin-2-one,

10

 - SO₂-(C₁-C₅ alkyl)-N-pyrrolidine,
 - SO₂-(C₁-C₅ alkyl)-(1-methylpyrrolidin-2-one-3-yl),
 - SO₂-(C₁-C₅ alkyl)-C(O)-O-(C₁-C₅ alkyl),
 - SO₂-(C₁-C₅ alkyl)-C(O)-OH,
 - SO₂-(C₁-C₅ alkyl)-5-tetrazolyl,

15

 - SO₂-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 - SO₂-(C₁-C₅ alkyl)-SO₂-NH₂,
 - SO₂-(C₁-C₅ alkyl)-SO₂-NH-(C₁-C₅ alkyl),
 - SO₂-(C₁-C₅ alkyl)-SO₂-N-(C₁-C₅ alkyl)₂,
 - SO₂-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),

20

 - SO₂-(C₁-C₅ alkyl)-P(O)-(O-C₁-C₅ alkyl)₂,
 - SO₂-(C₁-C₅ alkyl),
 - SO₂-(C₂-C₅ alkenyl),
 - SO₂-(C₃-C₅ cycloalkyl),
 - SO₂-(C₃-C₅ cycloalkenyl),

25

 - SO₂-(C₁-C₅ hydroxyalkyl),
 - SO₂-(C₁-C₅ fluoroalkyl),
 - SO₂-(C₁-C₅)-phenyl,
 - SO₂-N=CHN(C₁-C₅ alkyl)₂,

30

 - S(O)-NH₂,
 - S(O)-NH-(C₁-C₅ alkyl),
 - S(O)-NH-CH₂-C(O)OH

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5 -S(O)-NH-(C₁-C₅ alkyl)-C(O)OH,
-S(O)-NH-CH₂-C(O)(O-C₁-C₅ alkyl),
-S(O)-NH-(C₁-C₅ alkyl)-C(O)(O-C₁-C₅ alkyl),
-S(O)HC(O)-(C₃-C₆ cycloalkyl),
-S(O)-NH-C(O)-(C₁-C₅ alkyl),
-S(O)-N-(C₁-C₅ alkyl)₂,
-S(O)-(C₁-C₅ alkyl)-O-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-C(O)-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-C(O)-(O-C₁-C₅ alkyl),
10 -S(O)-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,
-S(O)-(C₁-C₅ alkyl)-C(O)-NH₂,
-S(O)-(C₁-C₅ alkyl)-C(O)-NH-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-C(O)-N-(C₁-C₅ alkyl)₂,
15 -S(O)-(C₁-C₅ alkyl)-NH-SO₂-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-NH-S(O)-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-N-pyrrolidin-2-one,
-S(O)-(C₁-C₅ alkyl)-N-pyrrolidine,
-S(O)-(C₁-C₅ alkyl)-(1-methylpyrrolidin-2-one-3-yl),
20 -S(O)-(C₁-C₅ alkyl)-C(O)-(O-C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-C(O)-OH,
-S(O)-(C₁-C₅ alkyl)-5-tetrazolyl,
-S(O)-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
25 -S(O)-(C₁-C₅ alkyl)-SO₂-NH₂,
-S(O)-(C₁-C₅ alkyl)-S(O)-NH₂,
-S(O)-(C₁-C₅ alkyl)-SO₂-NH-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-S(O)-NH-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-SO₂-N-(C₁-C₅ alkyl)₂,
30 -S(O)-(C₁-C₅ alkyl)-S(O)-N-(C₁-C₅ alkyl)₂,
-S(O)-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
-S(O)-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),

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-S(O)-(C₁-C₅ alkyl)-P(O)-(O-C₁-C₅ alkyl)₂,-S(O)-N=CHN(C₁-C₅ alkyl)₂,-NHC(S)NH₂,

5

-NHC(S)NH-(C₁-C₅ alkyl),-NHC(S)N-(C₁-C₅ alkyl)₂,-NHC(S)NH-(C₂-C₅ alkenyl),-NHC(S)NH-(C₃-C₅ cycloalkyl),-NHC(S)NH-(C₃-C₅ cycloalkenyl),

10

-NHC(S)NH-(C₁-C₅ fluoroalkyl),-NHC(S)NH-C₁-C₅ hydroxyalkyl,-NHC(S)NH-(C₁-C₅ fluoroalkyl)

-NHC(S)NH-phenyl,

-NHC(S)NH-(C₁-C₅ alkyl)-C(O)-OH,

15

-NHC(S)NH-(C₁-C₅ alkyl)-O-(C₁-C₅ alkyl),-NHC(S)NH-(C₁-C₅ alkyl)-C(O)-(C₁-C₅ alkyl),-NHC(S)NH-(C₁-C₅ alkyl)-C(O)-(O-C₁-C₅ alkyl),-NHC(S)NH-(C₁-C₅ alkyl)-NH₂,-NHC(S)NH-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),

20

-NHC(S)NH-(C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,-NHC(S)NH-(C₁-C₅ alkyl)-C(O)-NH₂,-NHC(S)NH-(C₁-C₅ alkyl)-C(O)-NH-(C₁-C₅ alkyl),-NHC(S)NH-(C₁-C₅ alkyl)-C(O)-N-(C₁-C₅ alkyl)₂,-NHC(S)NH-(C₁-C₅ alkyl)-NH-SO₂-(C₁-C₅ alkyl),

25

-NHC(S)NH-(C₁-C₅ alkyl)-NH-S(O)-(C₁-C₅ alkyl),-NHC(S)NH-(C₁-C₅ alkyl)-N-pyrrolidin-2-one,-NHC(S)NH-(C₁-C₅ alkyl)-N-pyrrolidine,-NHC(S)NH-(C₁-C₅ alkyl)-(1-methylpyrrolidin-2-one-3-yl),

30

-NHC(S)NH-(C₁-C₅ alkyl)-5-tetrazolyl,-NHC(S)NH-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),-NHC(S)NH-(C₁-C₅ alkyl)-SO₂-NH₂,

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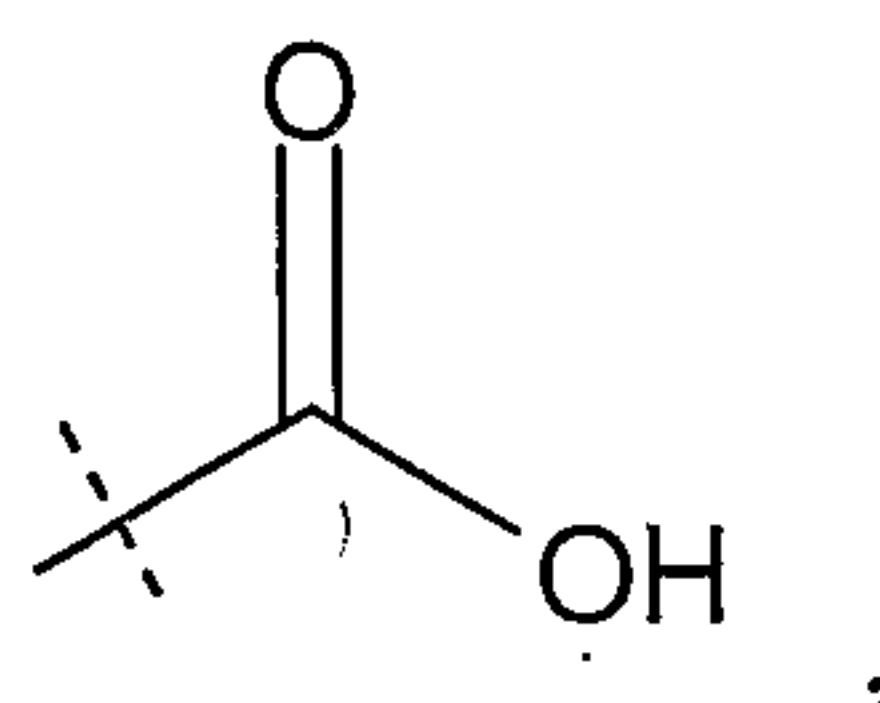
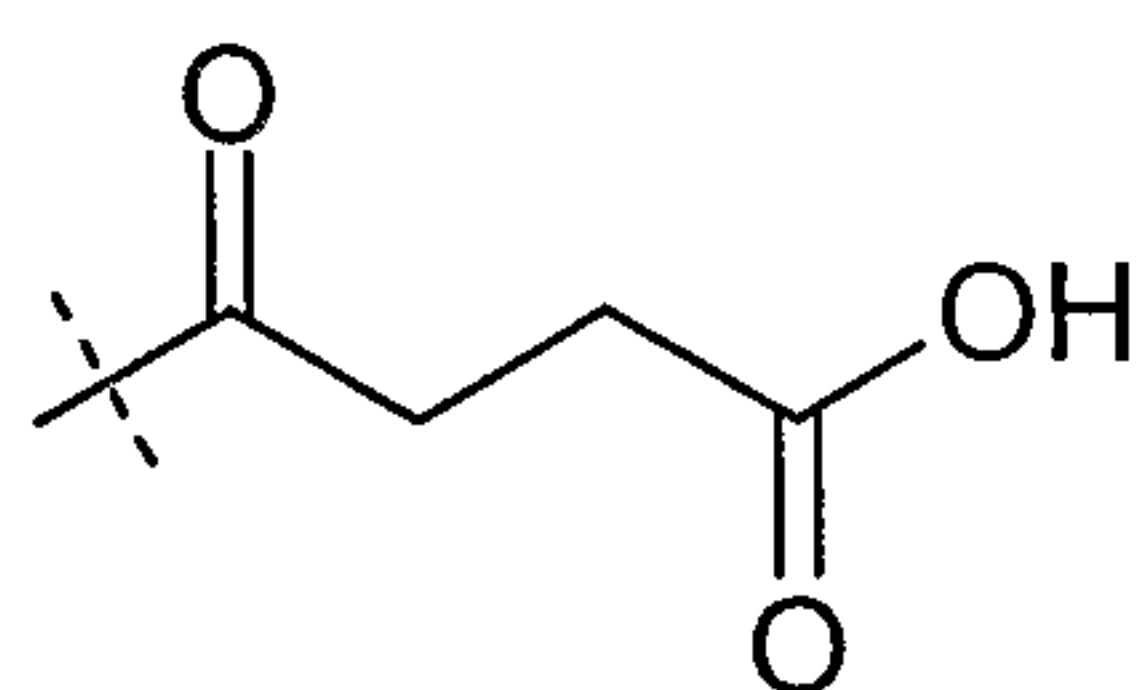
-NHC(S)NH-(C₁-C₅ alkyl)-SO₂-NH-(C₁-C₅ alkyl),
 -NHC(S)NH-(C₁-C₅ alkyl)-SO₂-N-(C₁-C₅ alkyl)₂,
 -NHC(S)NH-(C₁-C₅ alkyl)-S(O)-(C₁-C₅ alkyl),
 -NHC(S)NH-(C₁-C₅ alkyl)-S(O)-NH₂,
 5 -NHC(S)NH-(C₁-C₅ alkyl)-S(O)-NH-(C₁-C₅ alkyl),
 -NHC(S)NH-(C₁-C₅ alkyl)-S(O)-N-(C₁-C₅ alkyl)₂,
 -NHC(S)NH-(C₁-C₅ alkyl)-P(O)-(O-C₁-C₅ alkyl)₂,

 -NHC(O)NH₂,
 10 -NHC(O)NH-(C₁-C₅ alkyl),
 -NHC(O)N-(C₁-C₅ alkyl)₂,
 -NHC(O)NH-(C₂-C₅ alkenyl),
 -NHC(O)NH-(C₃-C₅ cycloalkyl),
 -NHC(O)NH-(C₃-C₅ cycloalkenyl),
 15 -NHC(O)NH-(C₁-C₅ hydroxyalkyl),
 -NHC(O)NH-(C₁-C₅ fluoroalkyl),
 -NHC(O)NH-phenyl,
 -NHC(O)NH-(C₁-C₅ alkyl)-NH₂,
 -NHC(O)NH-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),
 20 -NHC(O)NH-(C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,
 -NHC(O)NH-(C₁-C₅ alkyl)-O-(C₁-C₅ alkyl),
 -NHC(O)NH-(C₁-C₅ alkyl)-NH₂,
 -NHC(O)NH-(C₁-C₅ alkyl)-NH-(C₁-C₅ alkyl),
 -NHC(O)NH-(C₁-C₅ alkyl)-N-(C₁-C₅ alkyl)₂,
 25 -NHC(O)NH-(C₁-C₅ alkyl)-C(O)-NH₂,
 -NHC(O)NH-(C₁-C₅ alkyl)-C(O)-NH-(C₁-C₅ alkyl),
 -NHC(O)NH-(C₁-C₅ alkyl)-C(O)-N-(C₁-C₅ alkyl)₂,
 -NHC(O)NH-(C₁-C₅ alkyl)-C(O)-(C₁-C₅ alkyl),
 -NHC(O)NH-(C₁-C₅ alkyl)-NH-SO₂-(C₁-C₅ alkyl),
 30 -NHC(O)NH-(C₁-C₅ alkyl)-N-pyrrolidin-2-one,
 -NHC(O)NH-(C₁-C₅ alkyl)-N-pyrrolidine,
 -NHC(O)NH-(C₁-C₅ alkyl)-

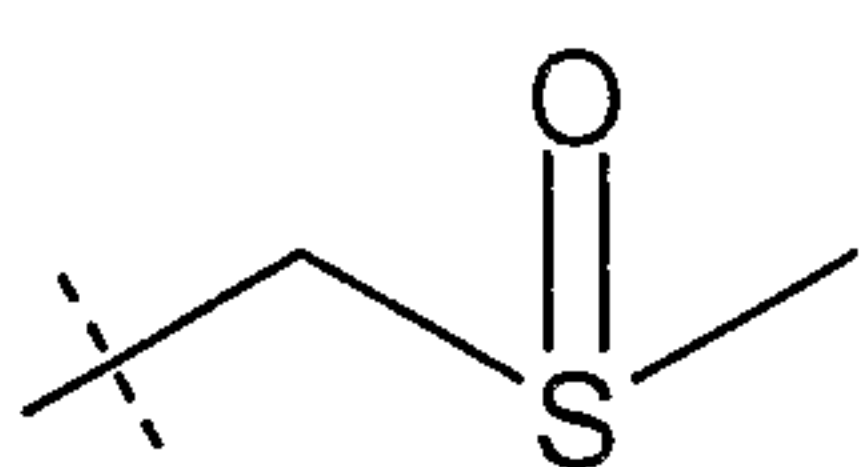
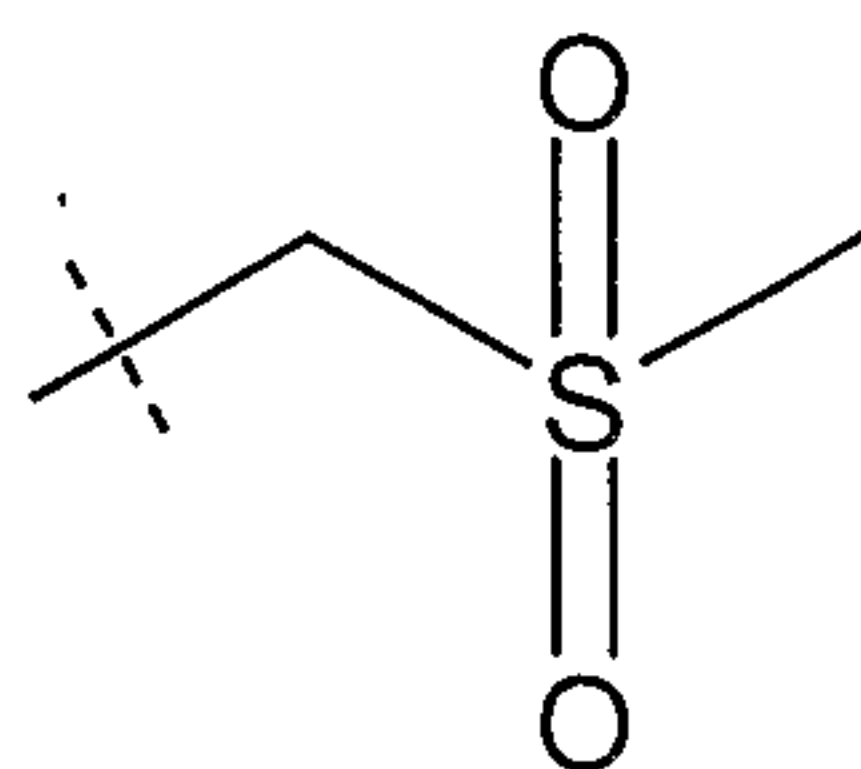
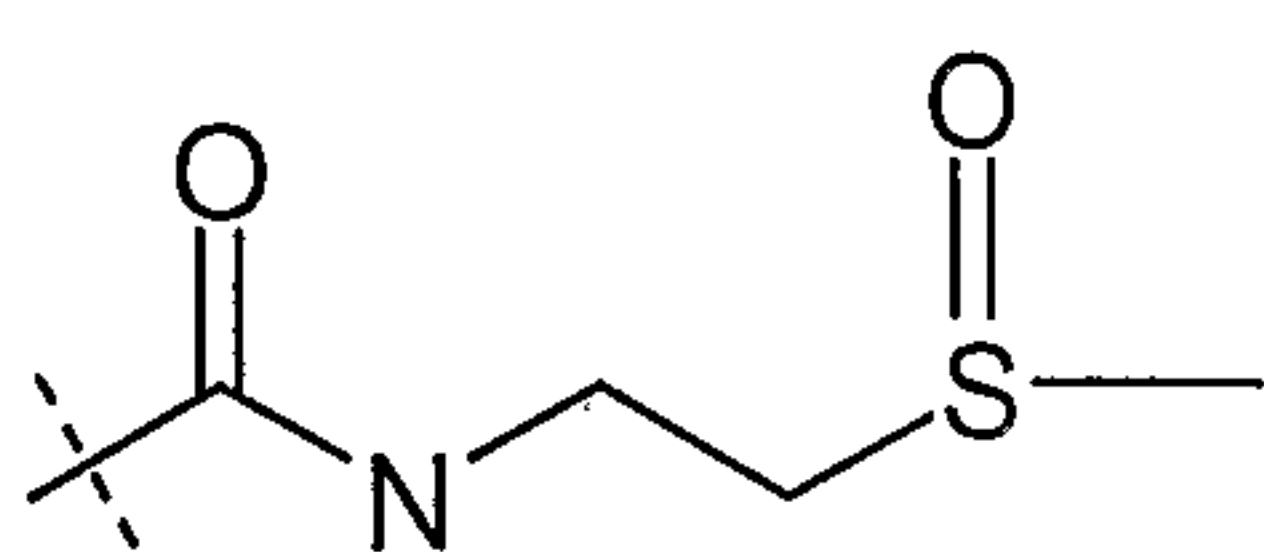
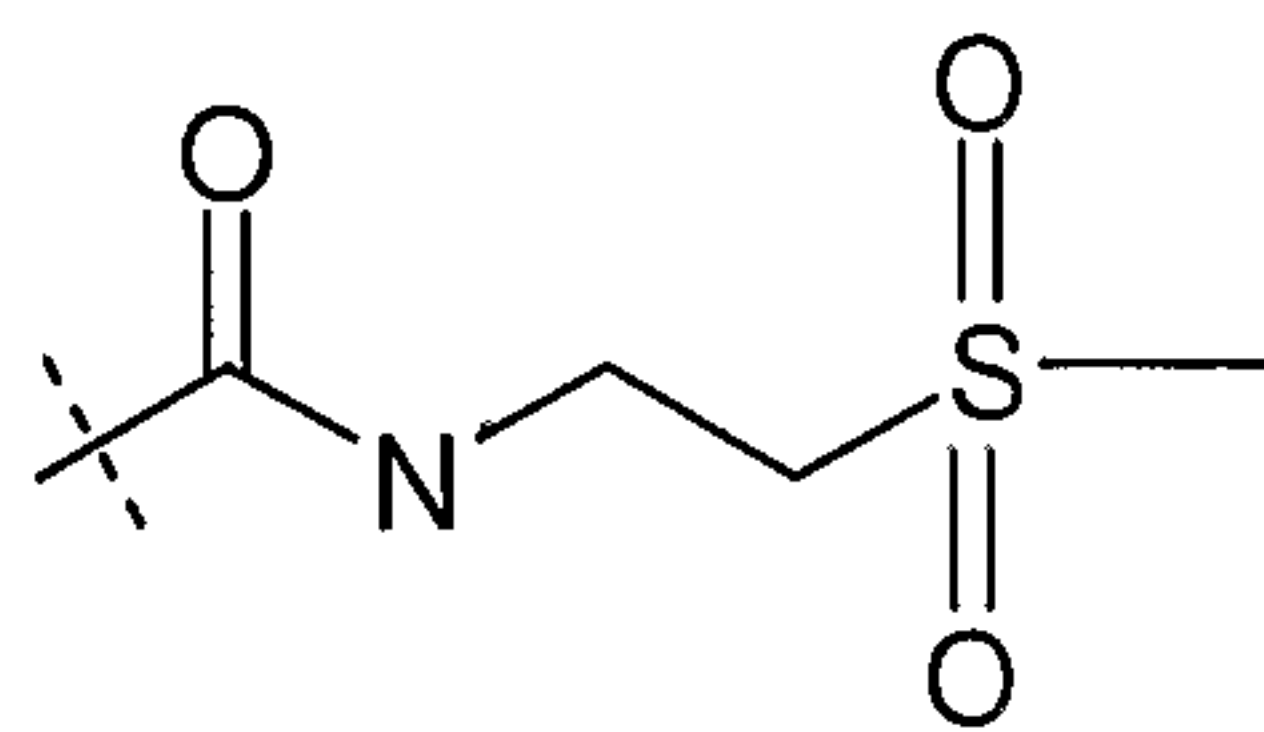
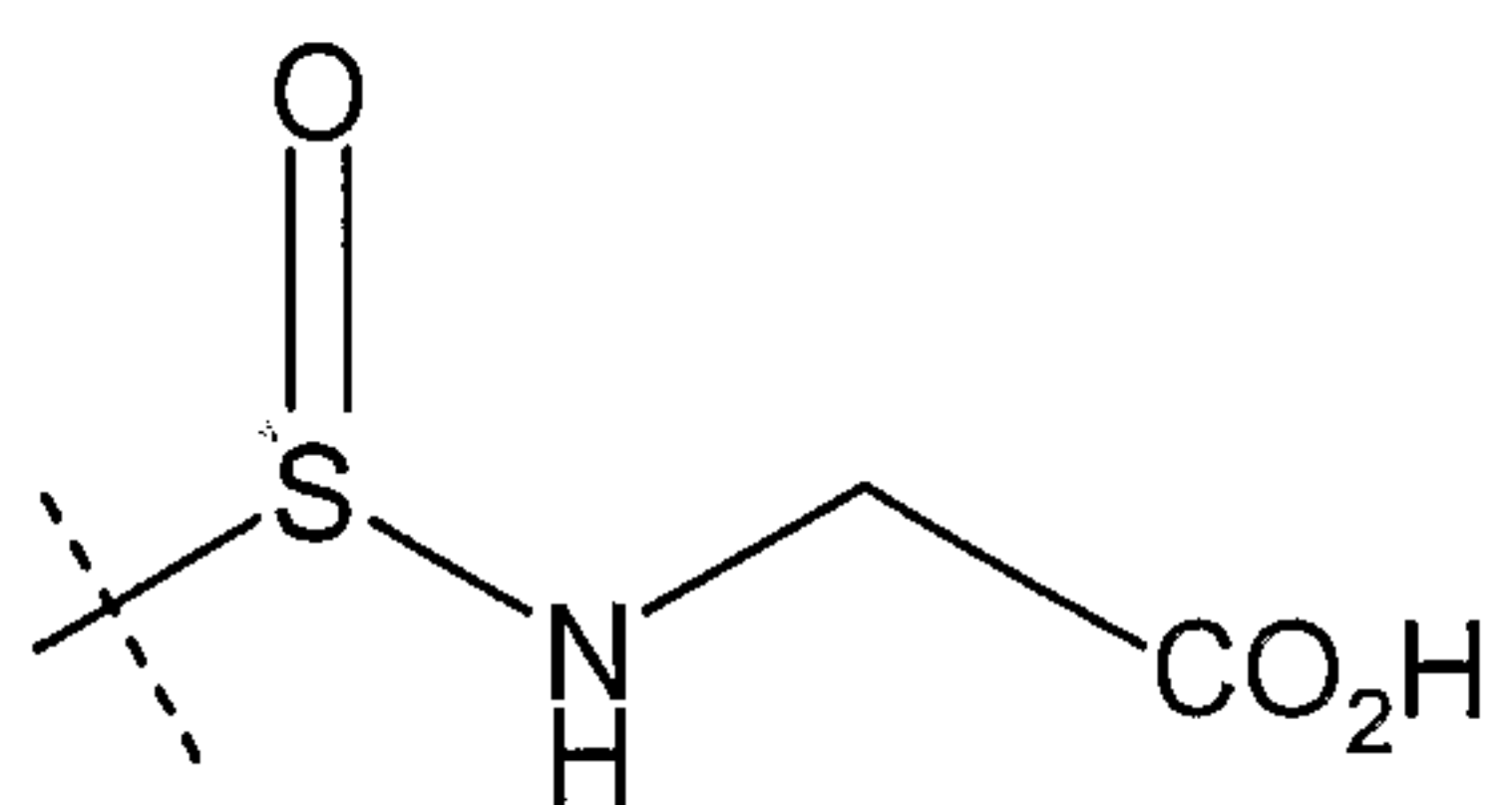
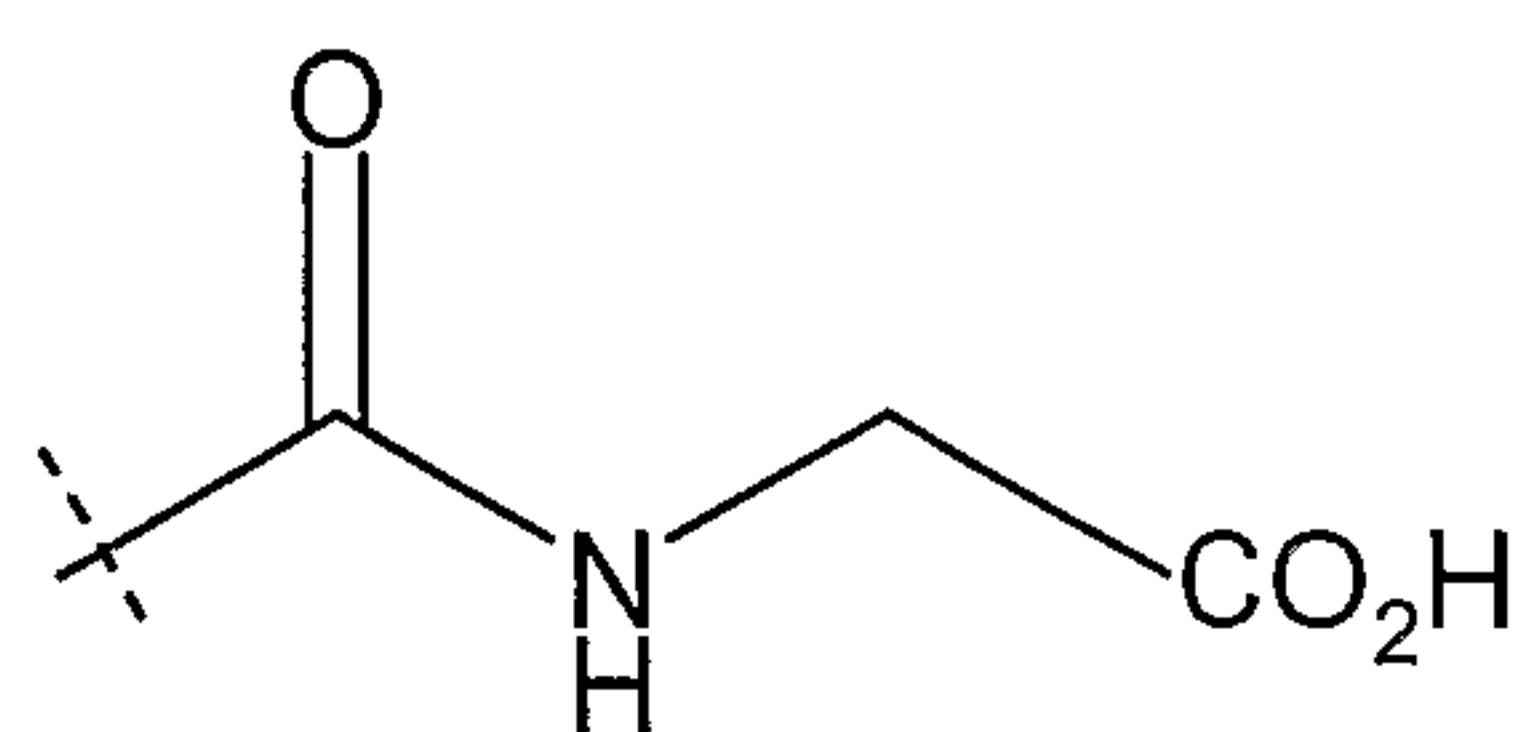
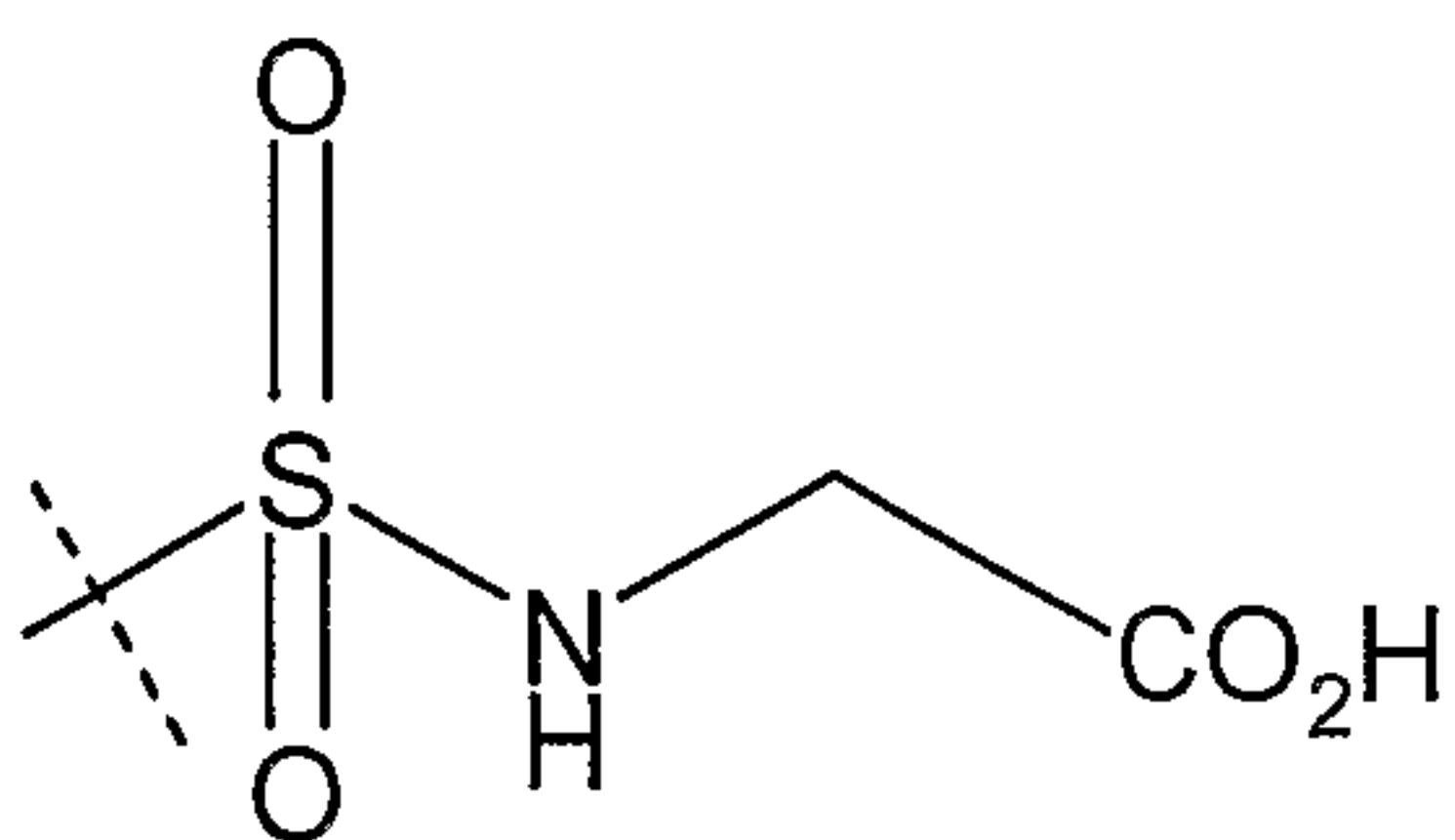
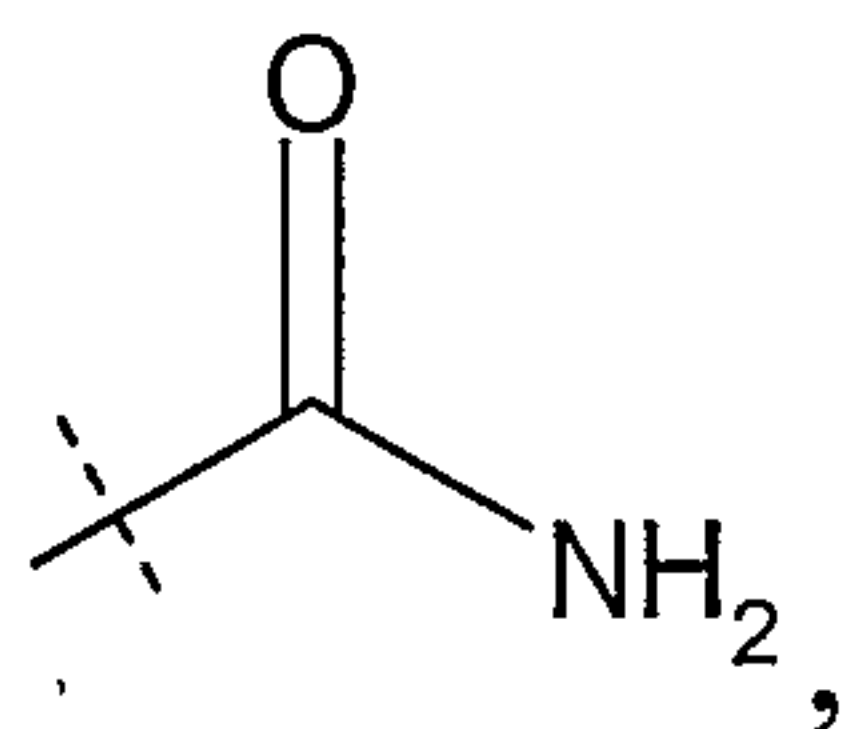
-37-

(1-methylpyrrolidin-2-one-3-yl),
 -NHC(O)NH-(C₁-C₅ alkyl)-C(O)-OH,
 -NHC(O)NH-(C₁-C₅ alkyl)-C(O)-O-(C₁-C₅ alkyl),
 -NHC(O)NH-(C₁-C₅ alkyl)-5-tetrazolyl,
 5 -NHC(O)NH-(C₁-C₅ alkyl)-SO₂-(C₁-C₅ alkyl),
 -NHC(O)NH-(C₁-C₅ alkyl)-SO₂-NH₂,
 -NHC(O)NH-(C₁-C₅ alkyl)-SO₂-NH-(C₁-C₅ alkyl),
 -NHC(O)NH-(C₁-C₅ alkyl)-SO₂-N-(C₁-C₅ alkyl)₂,
 -NHC(O)NH-(C₁-C₅ alkyl)-P(O)-O-(C₁-C₅ alkyl)₂ ,
 10 -NH₂,
 -NH-(C₁-C₅ alkyl),
 -NH-CH₂-C(O)OH,
 -N-(C₁-C₅ alkyl)₂,
 -NH-C(O)-NH₂,
 15 -NH-C(O)-NH-(C₁-C₅ alkyl),
 -NH-C(O)-N-(C₁-C₅ alkyl)₂,
 -NH-C(O)-(C₁-C₅ alkyl),
 -NH-SO₂-(C₁-C₅ alkyl),
 -NH-S(O)-(C₁-C₅ alkyl),
 20 -N(CH₃)(OCH₃),
 -N(OH)(CH₃),
 -N-pyrrolidin-2-one,
 -N-pyrrolidine,
 -(1-methylpyrrolidin-2-one-3-yl),

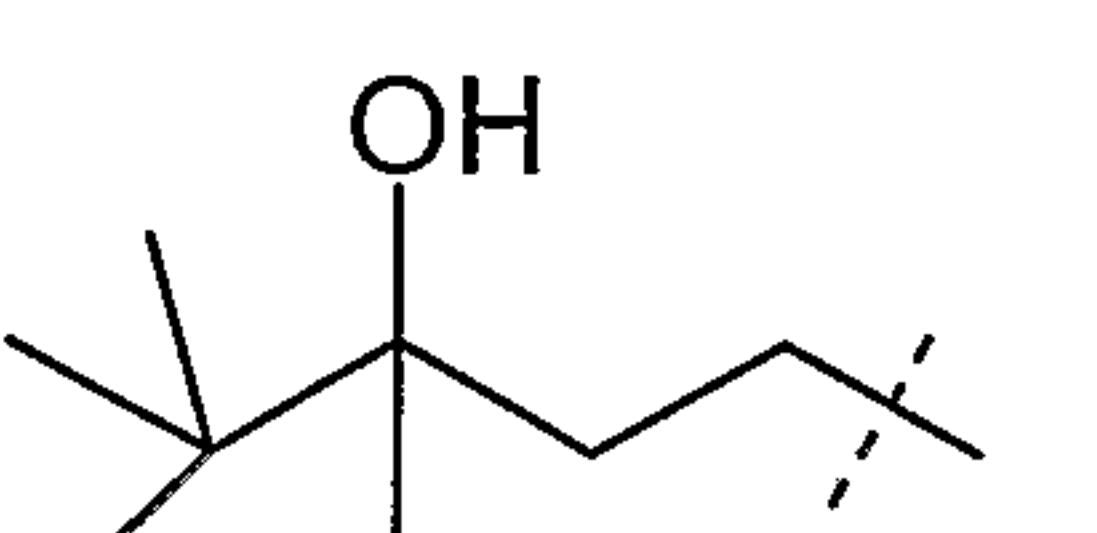
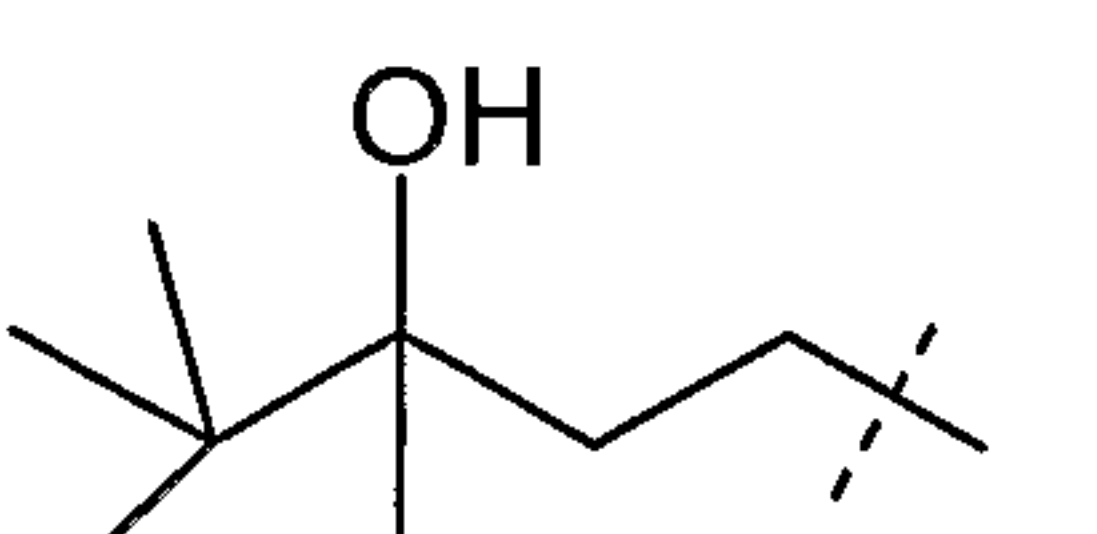
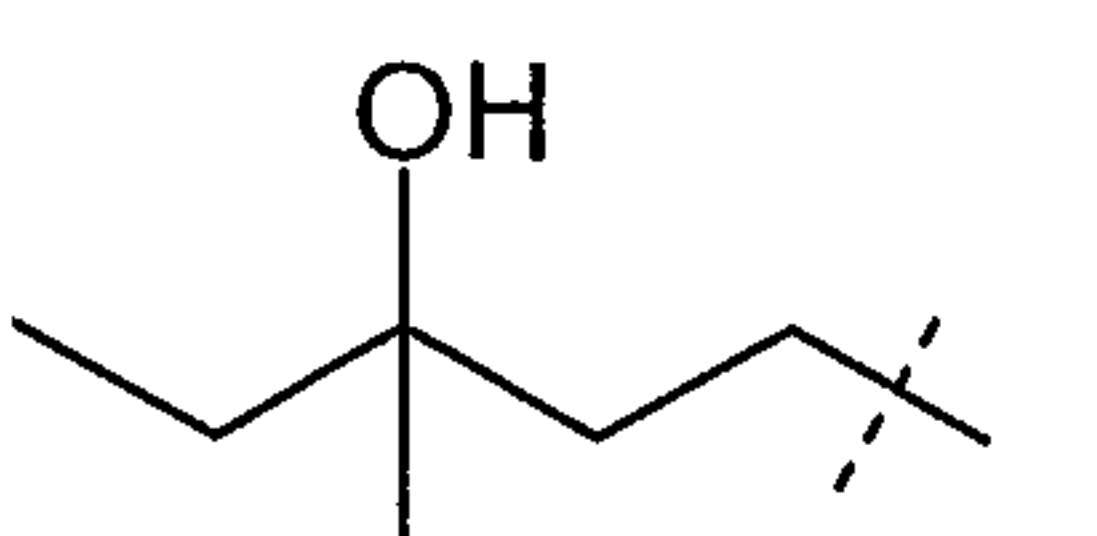
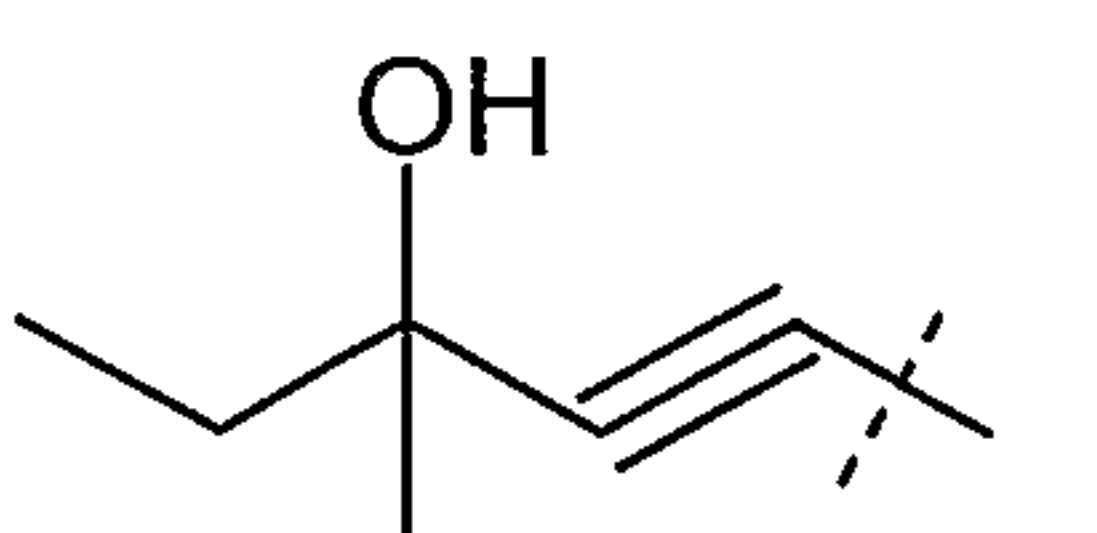
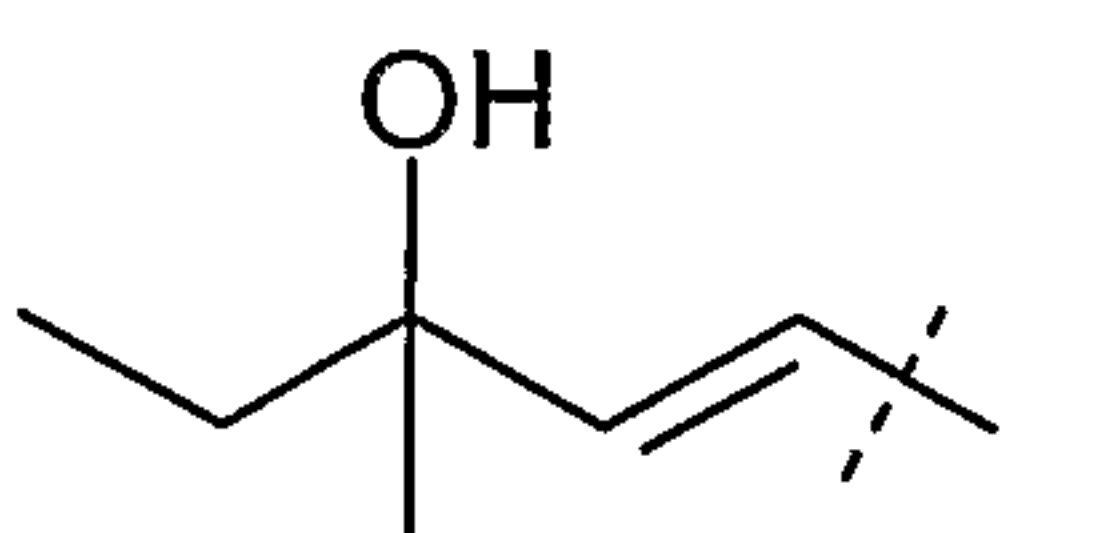
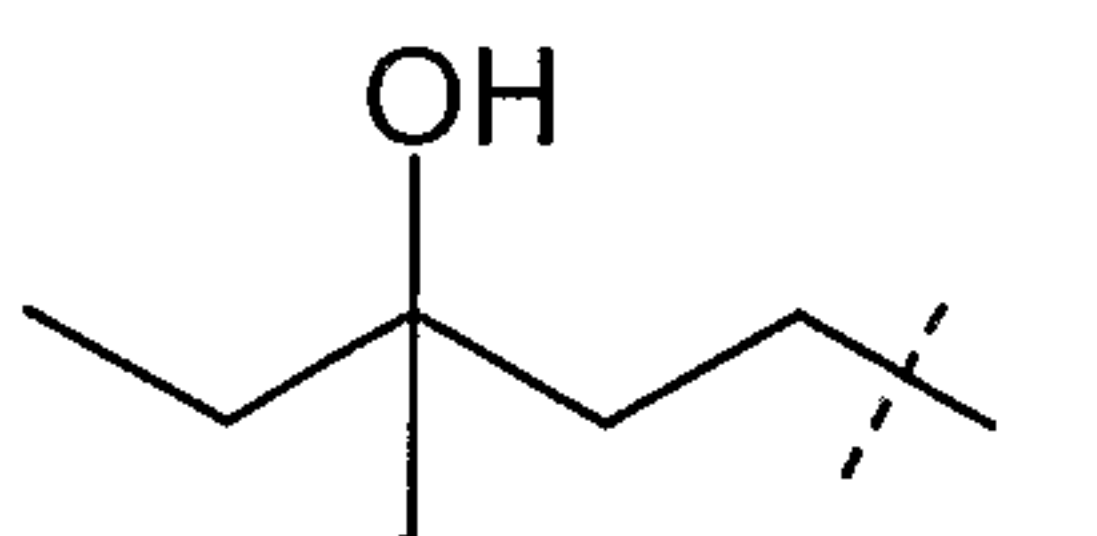
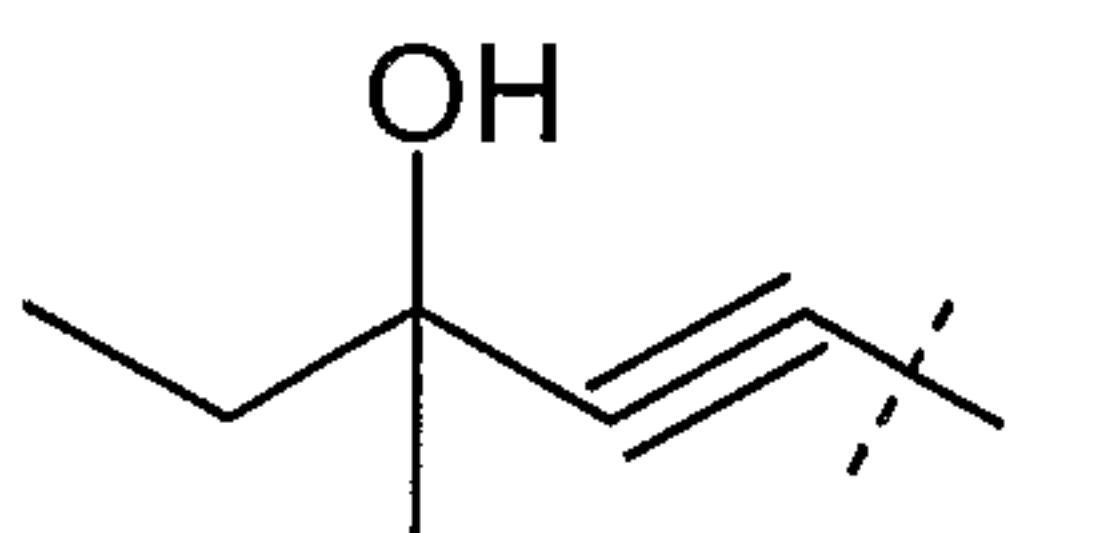
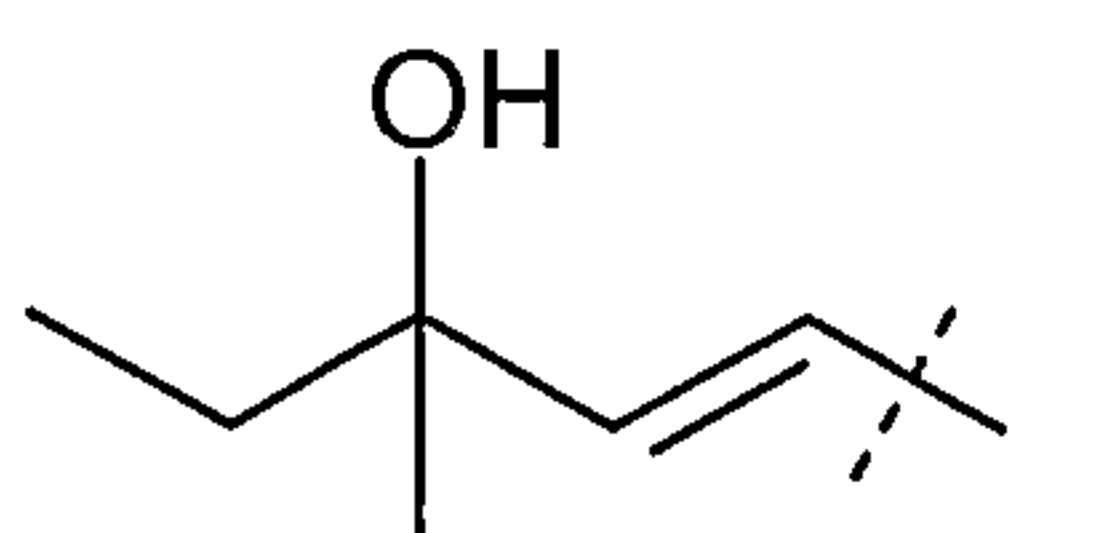
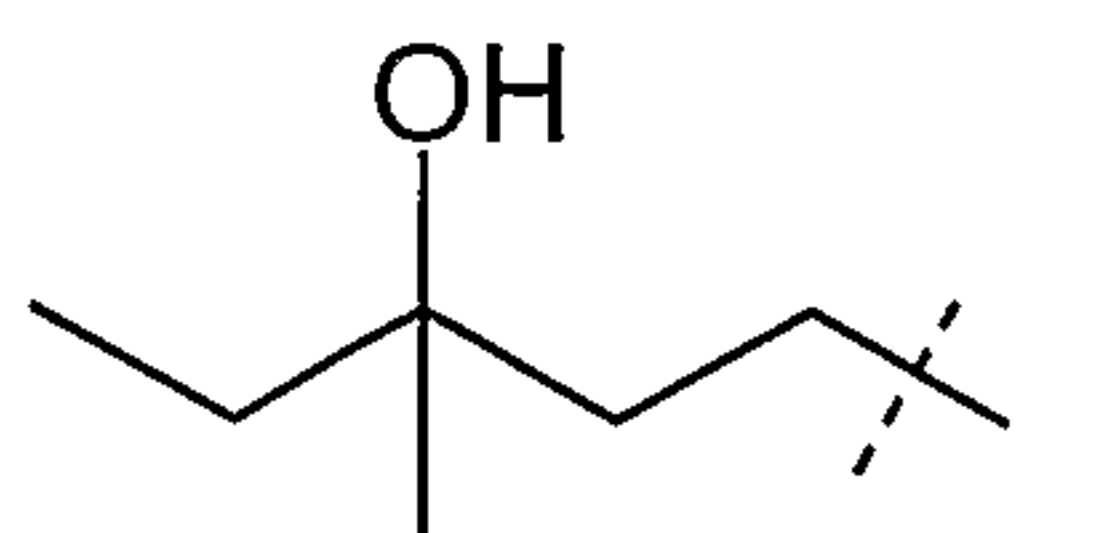
25



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1-hydroxycyclopentenyl,
1-hydroxycyclohexenyl,

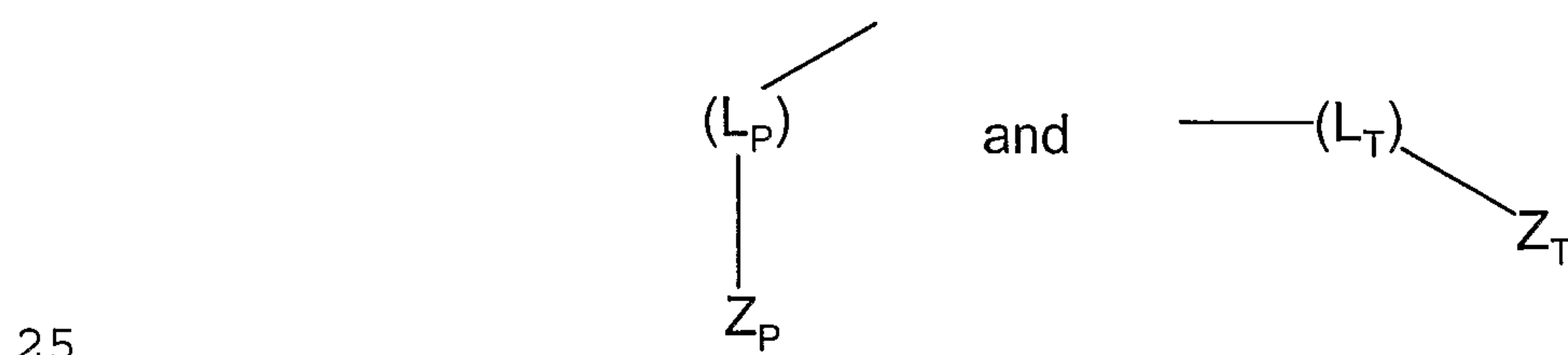
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10

-40-

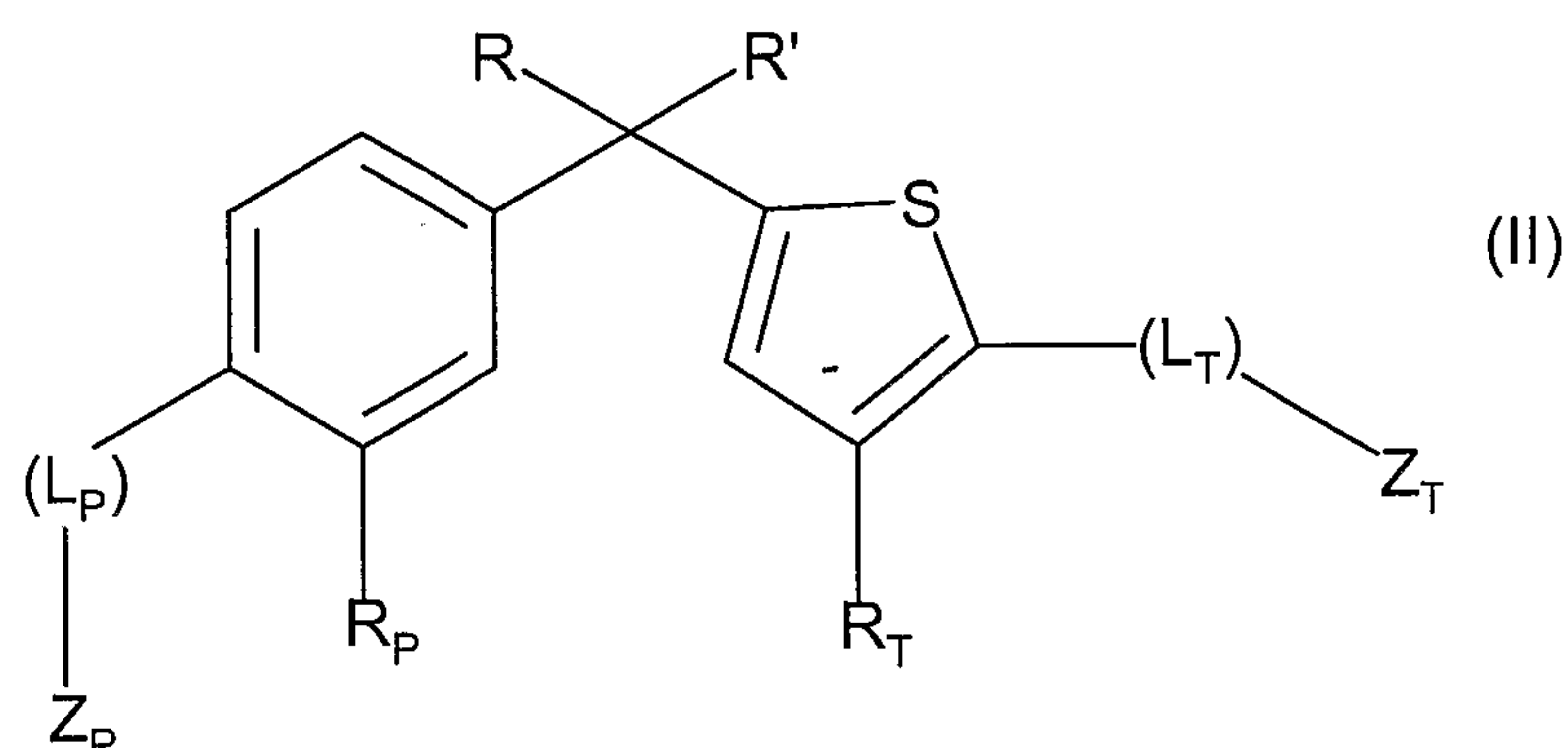
1-hydroxycycloheptenyl,
 1-hydroxycyclooctenyl,
 1-hydroxycyclopropyl,
 1-hydroxycyclobutyl,
 5 1-hydroxycyclopentyl,
 1-hydroxycyclohexyl,
 1-hydroxycycloheptyl,
 1-hydroxycyclooctyl,
 -5-tetrazolyl,
 10 -carboxyl,
 -OH,
 -I,
 -Br
 -Cl
 15 -F,
 -CHO,
 -NO₂,
 -CN,
 sulfonamide,
 20 sulfinamide,
 urethane-type radical, and
 (Acidic Group);

provided that the combined groups of formula I represented by



may both be lipophilic, or either one may be lipophilic and the other one polar; but both combined groups may not be polar.

Preferred compounds of the invention are represented by formula (II) or a pharmaceutically acceptable salt or prodrug derivative thereof:



5 wherein;

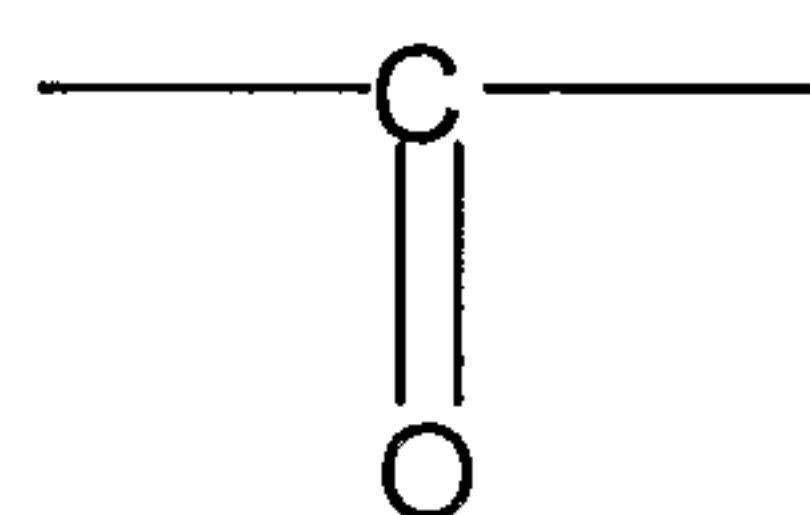
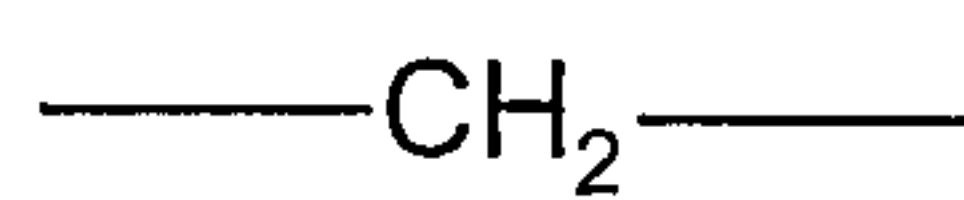
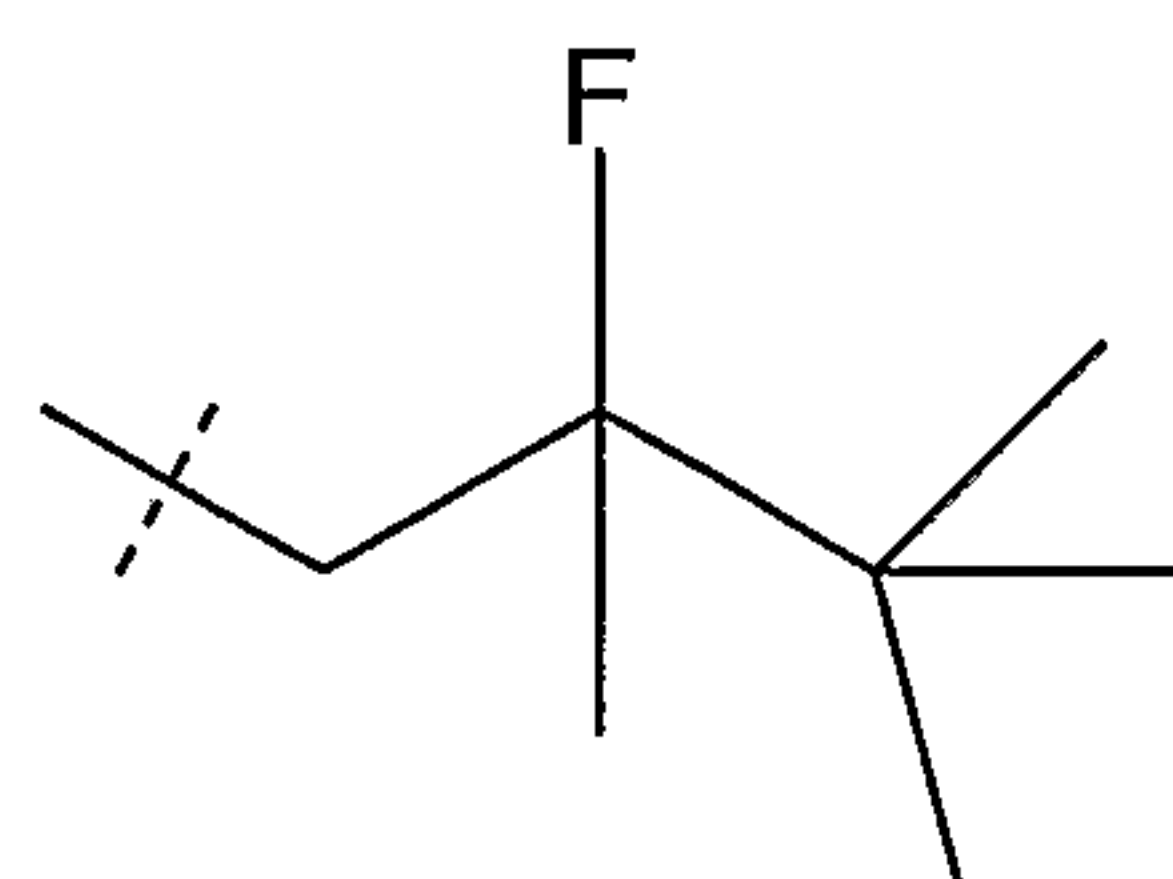
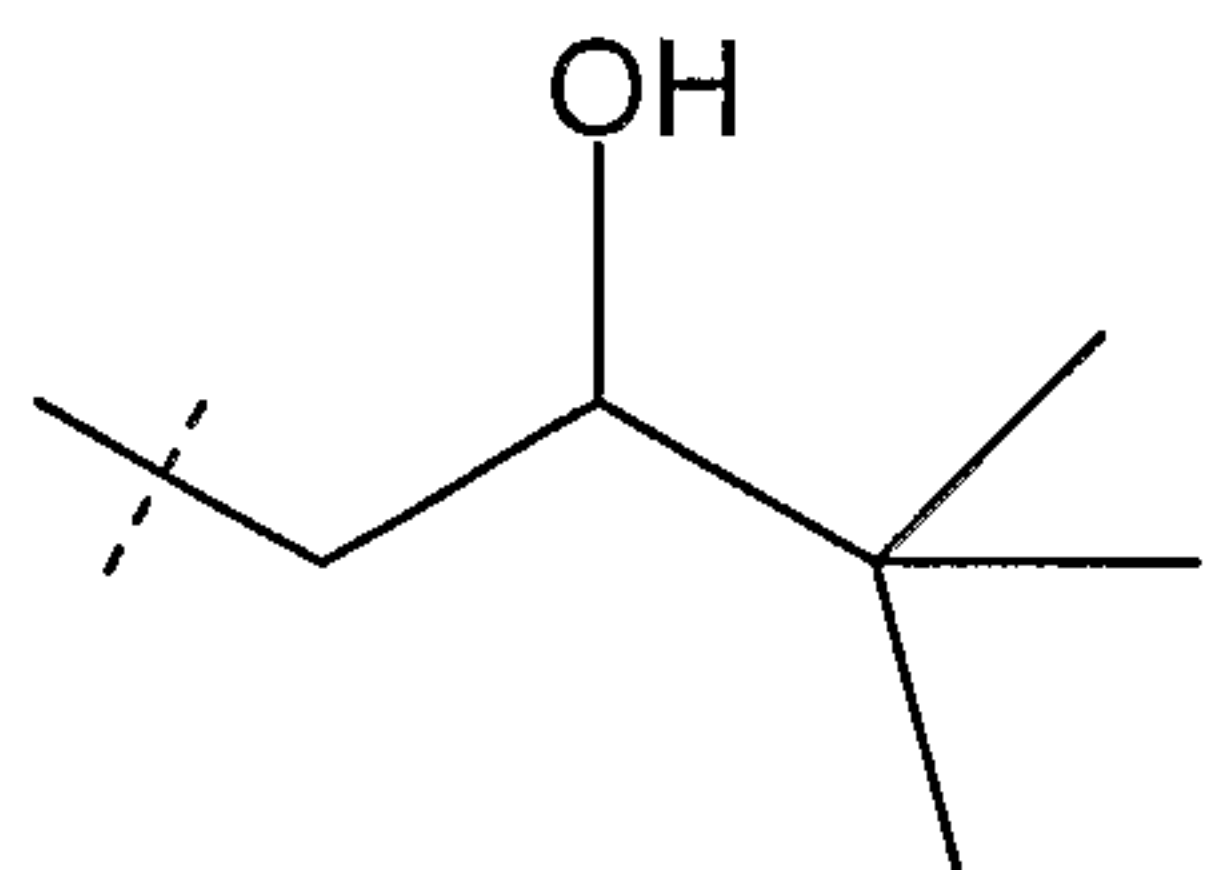
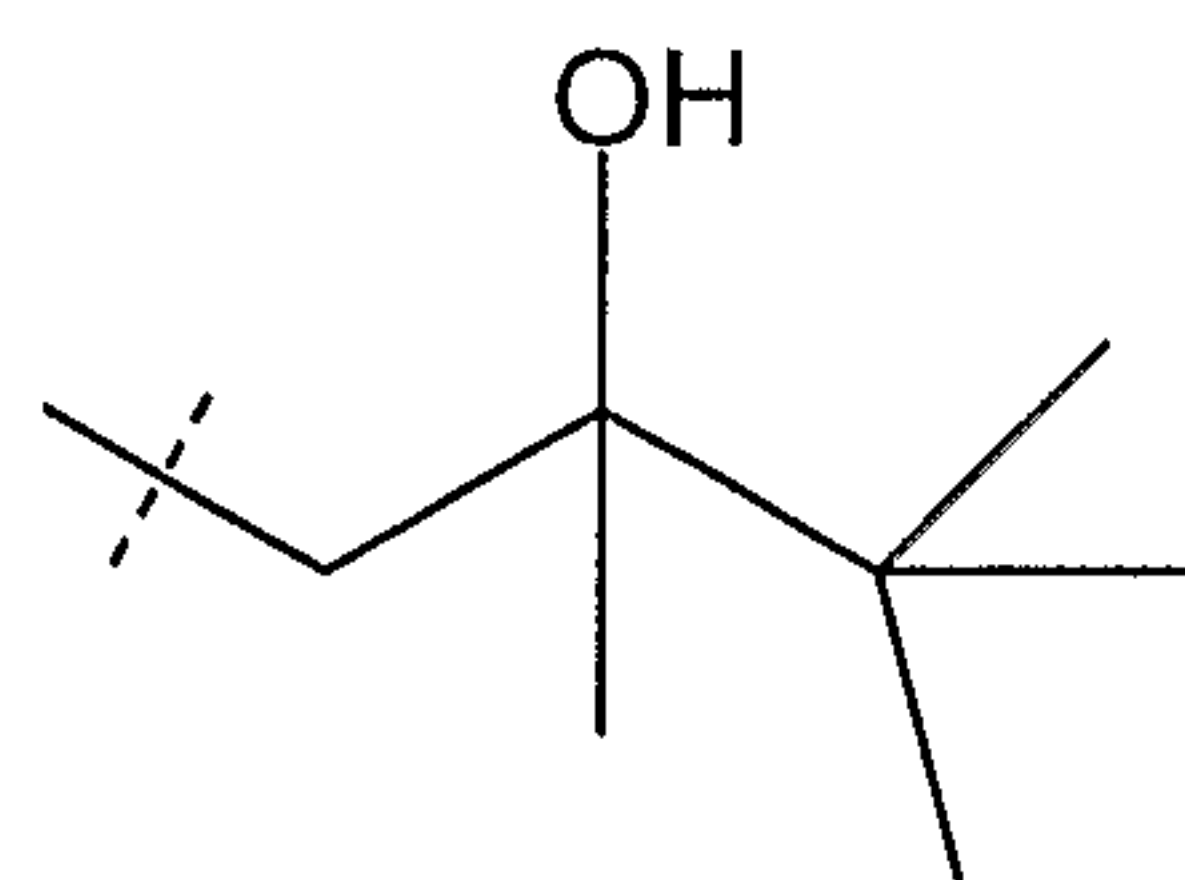
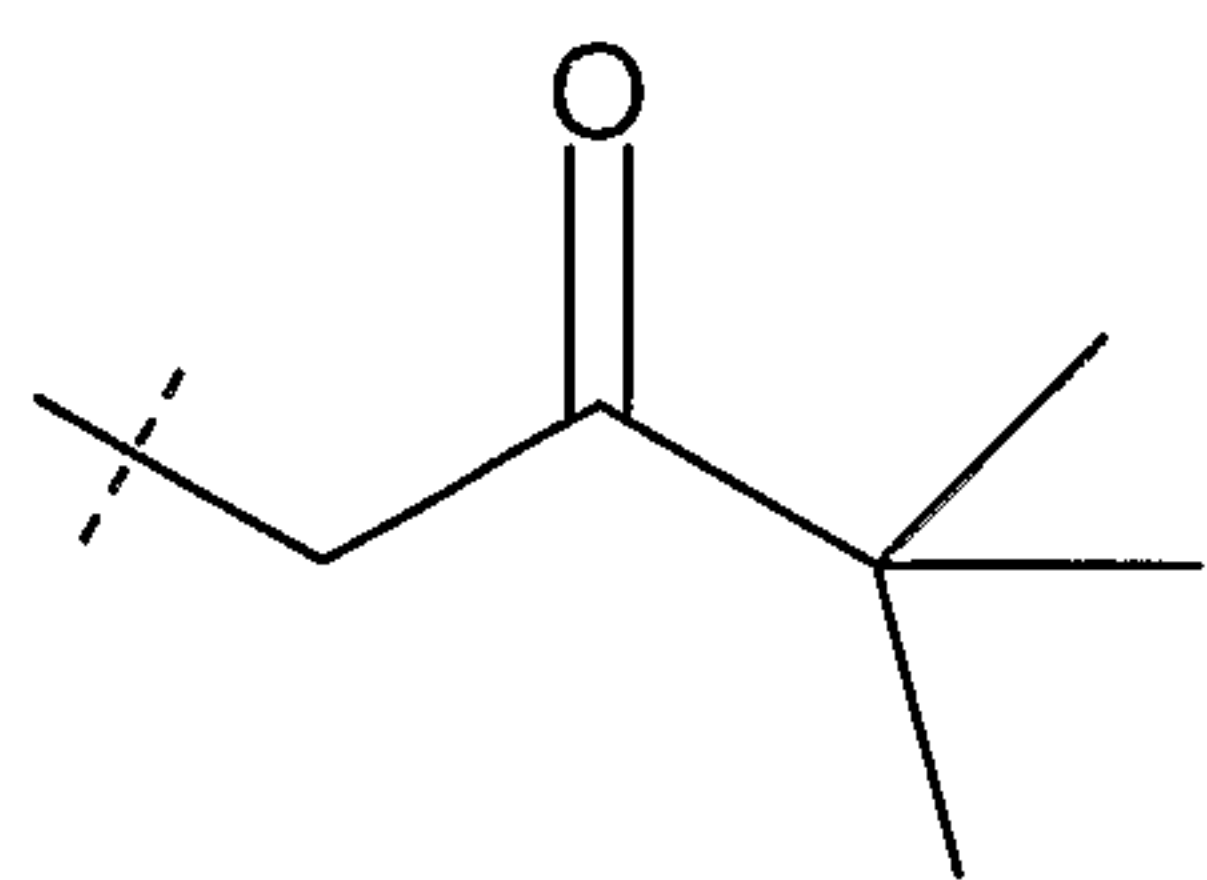
R and R' are independently methyl, ethyl, propyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, or 1,1-dimethylethyl;

R_P and R_T are independently selected from the group consisting of hydrogen, fluoro, -CF₃, -CH₂F, -CHF₂, -CH₂Cl, methoxy, ethoxy, vinyl, methyl, ethyl, propyl, cyclopropyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, or 1,1-dimethylethyl;

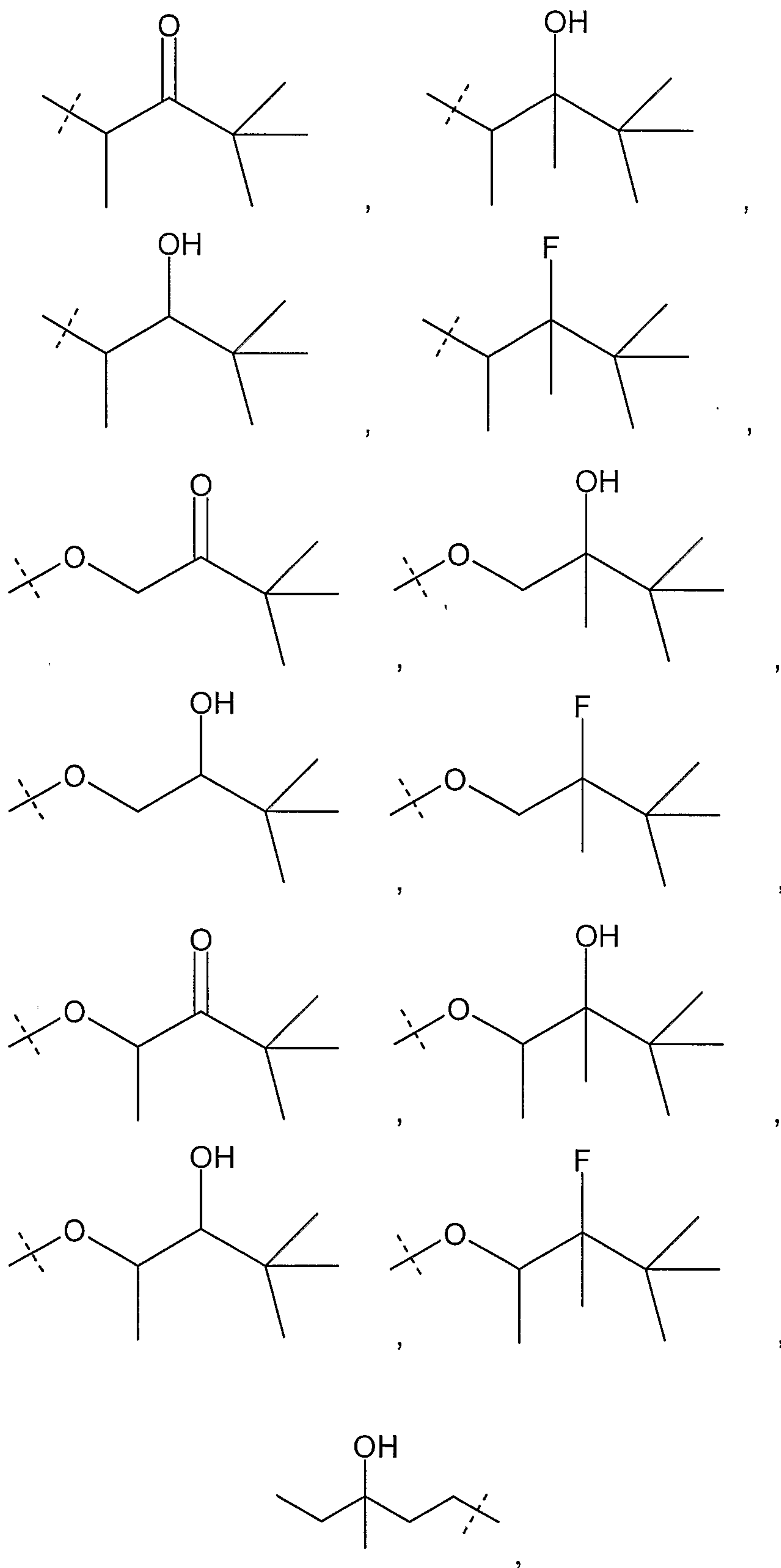
L_T and L_P are independently selected from one the following divalent linking group;

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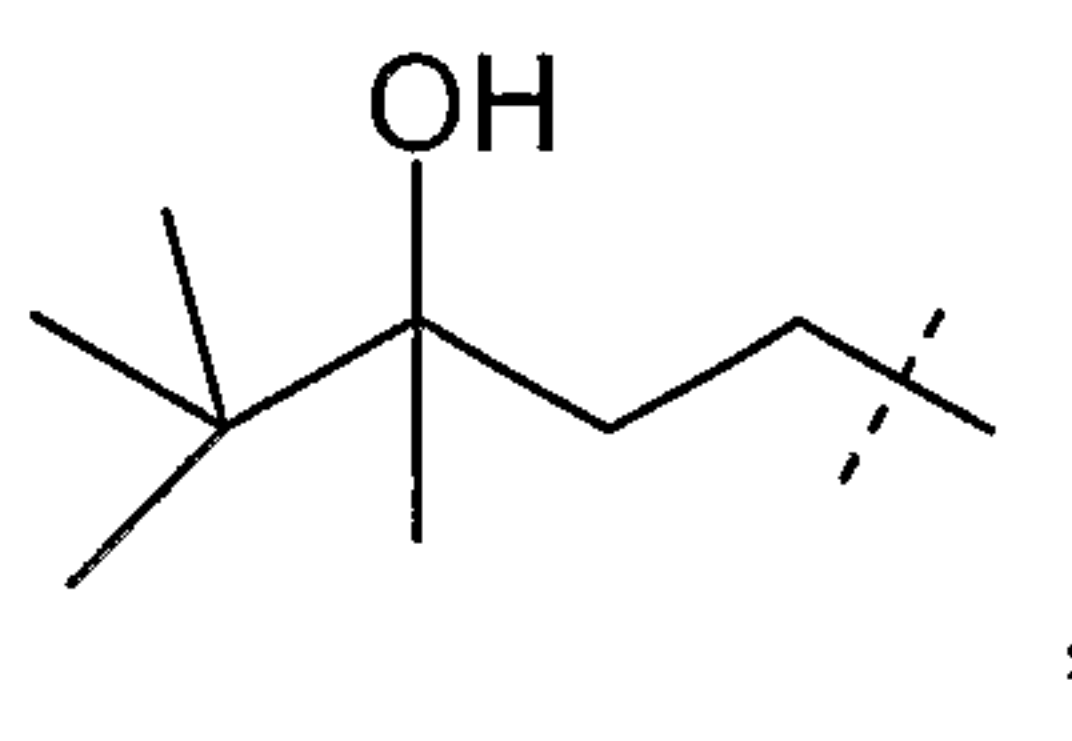
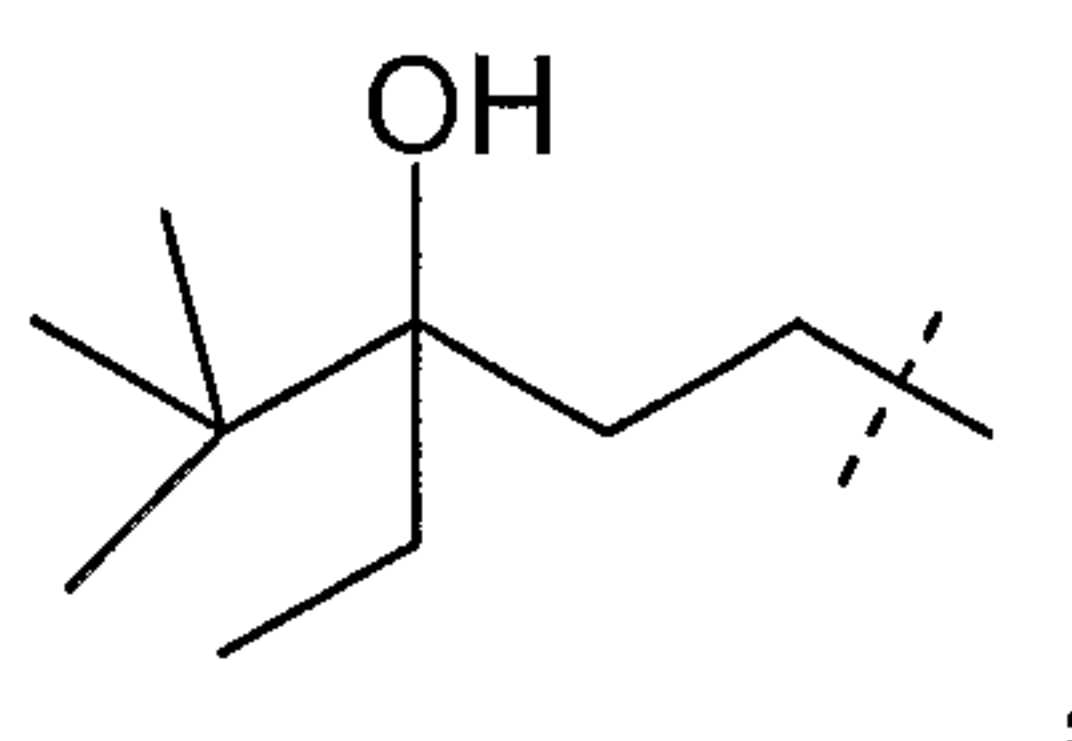
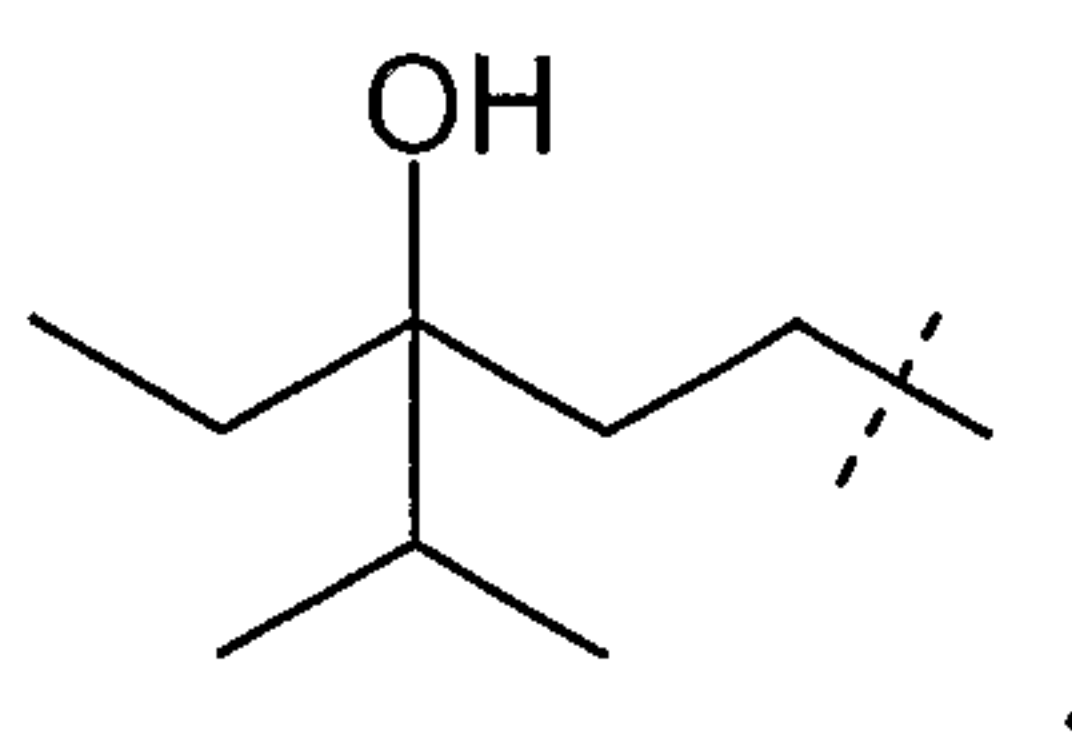
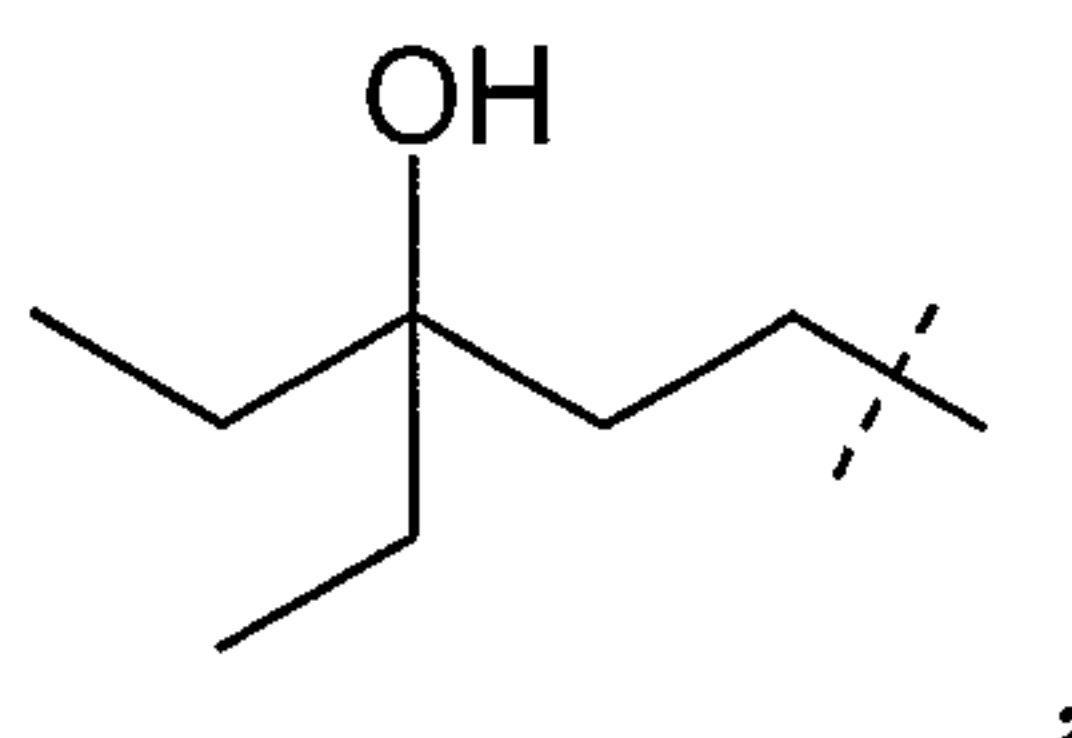
a bond

 Z_P is selected from

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5

1-hydroxycyclopentenyl,

1-hydroxycyclohexenyl,

1-hydroxycycloheptenyl,

1-hydroxycyclooctenyl,

10

1-hydroxycyclopropyl,

1-hydroxycyclobutyl,

1-hydroxycyclopentyl,

1-hydroxycyclohexyl,

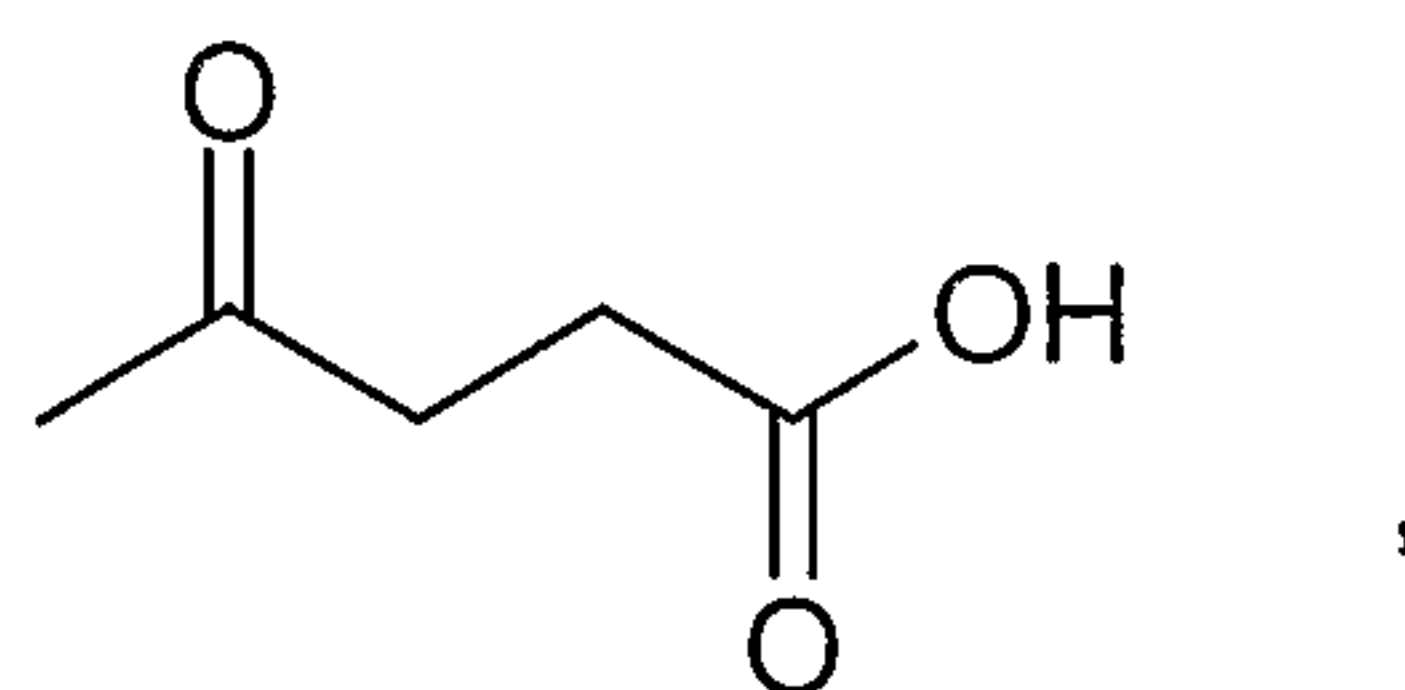
1-hydroxycycloheptyl,

15

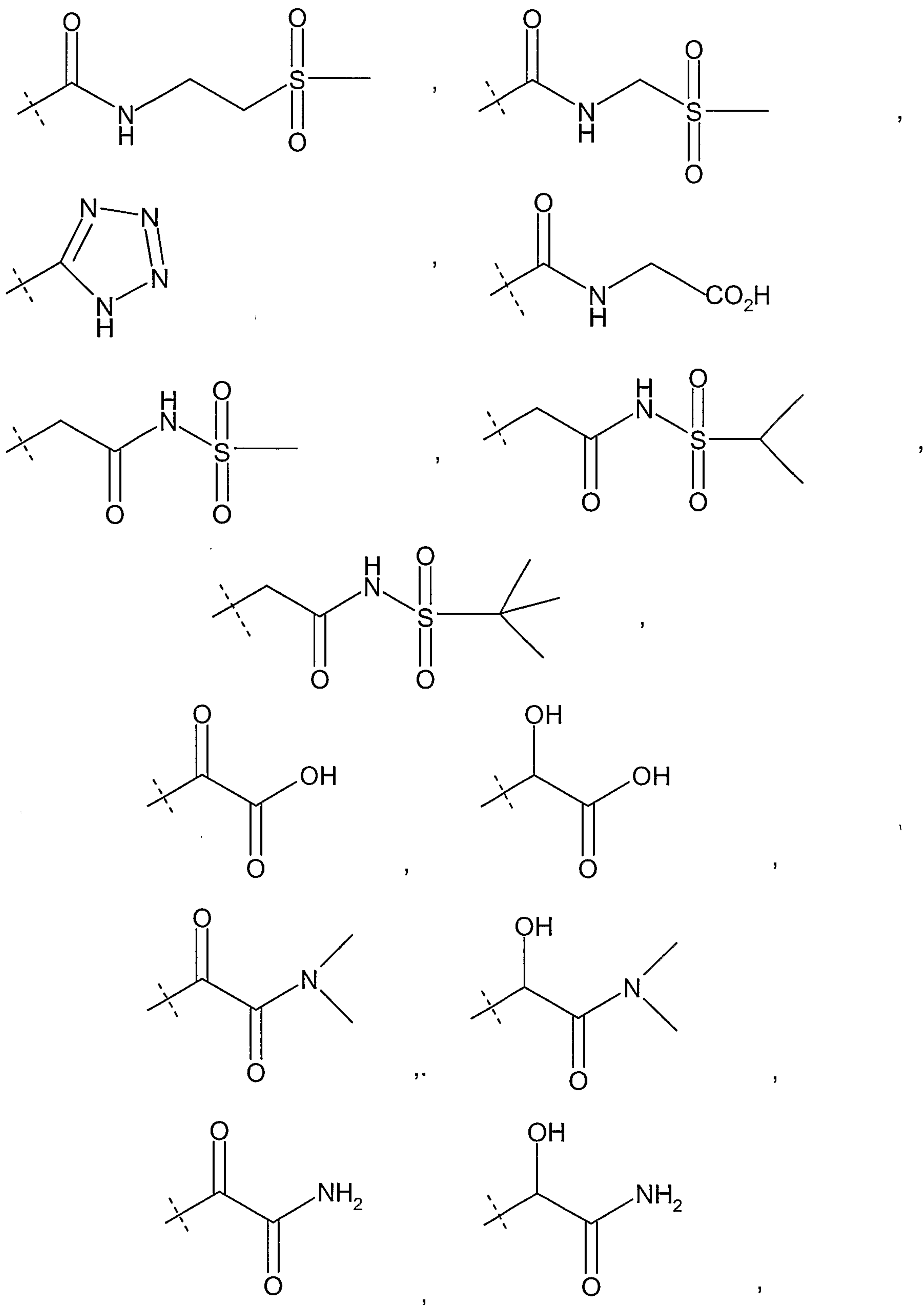
and

1-hydroxycyclooctyl.

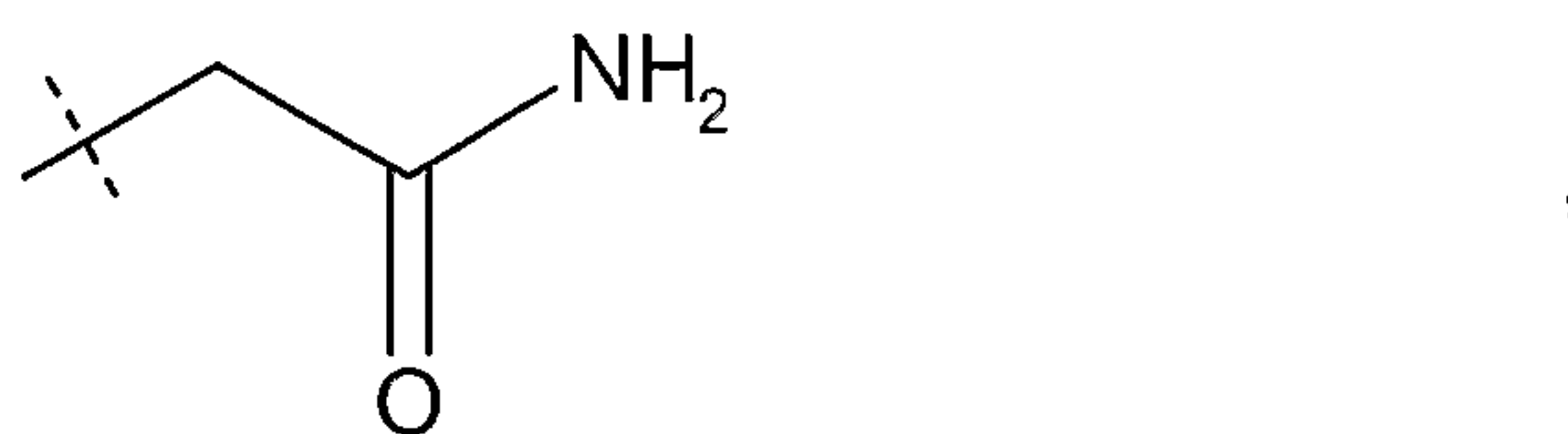
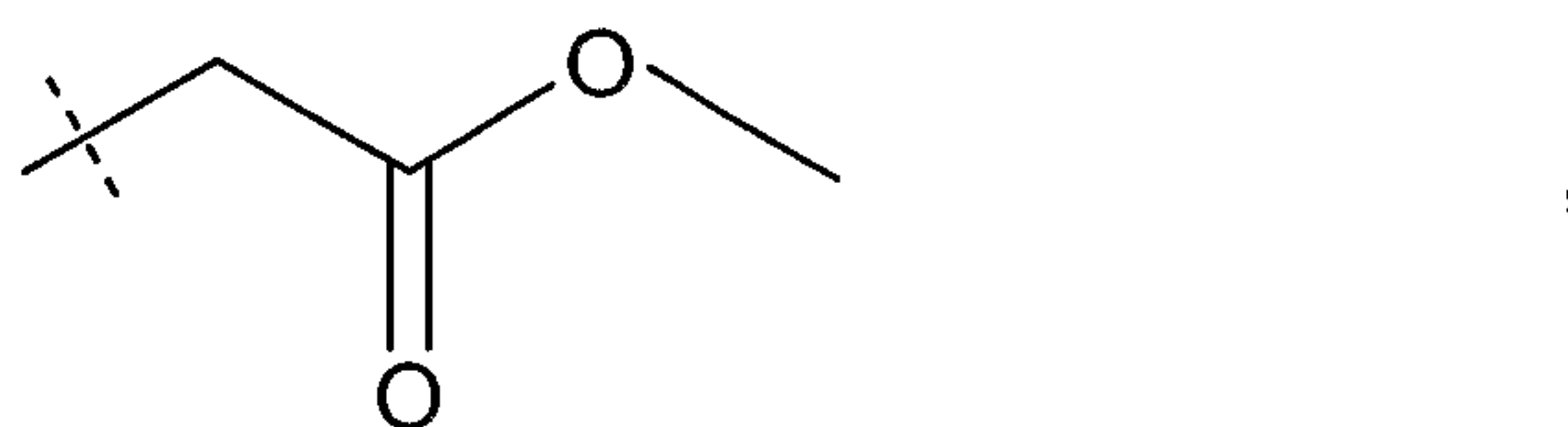
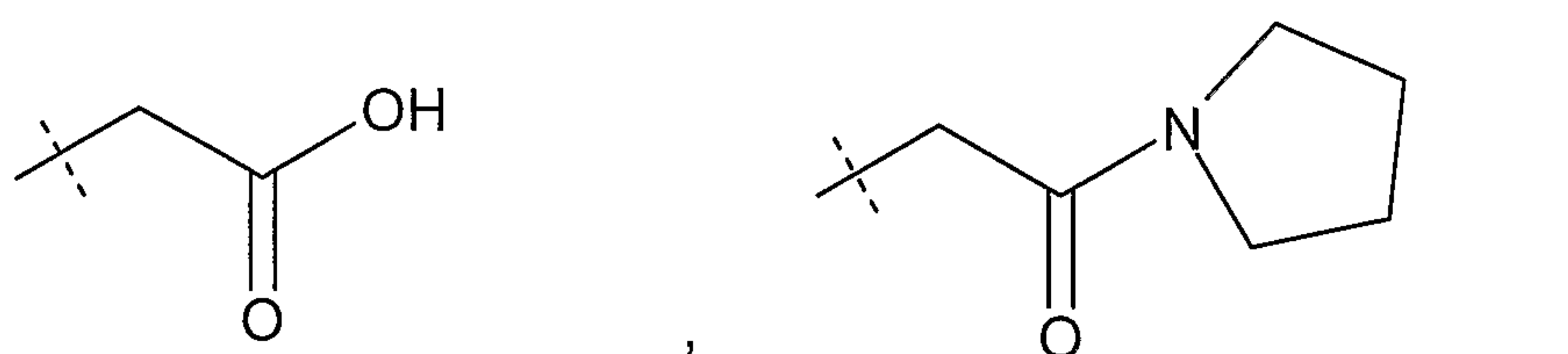
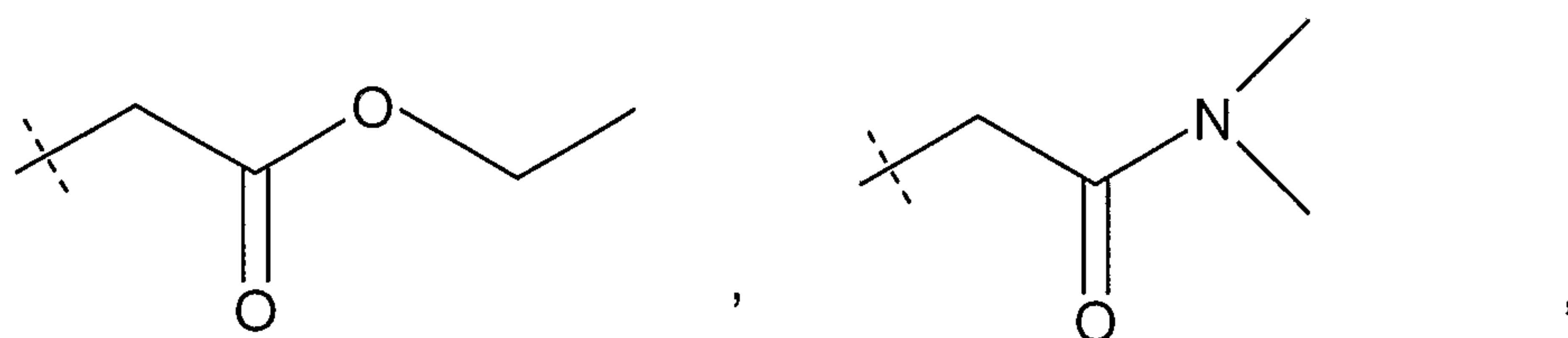
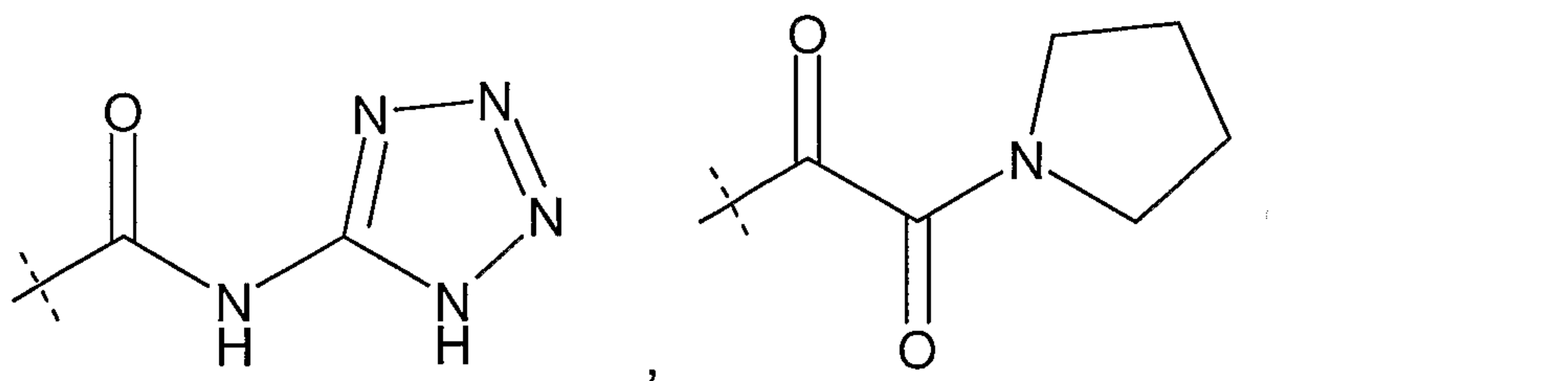
Z_T is a group represented by one of the structural formulae:



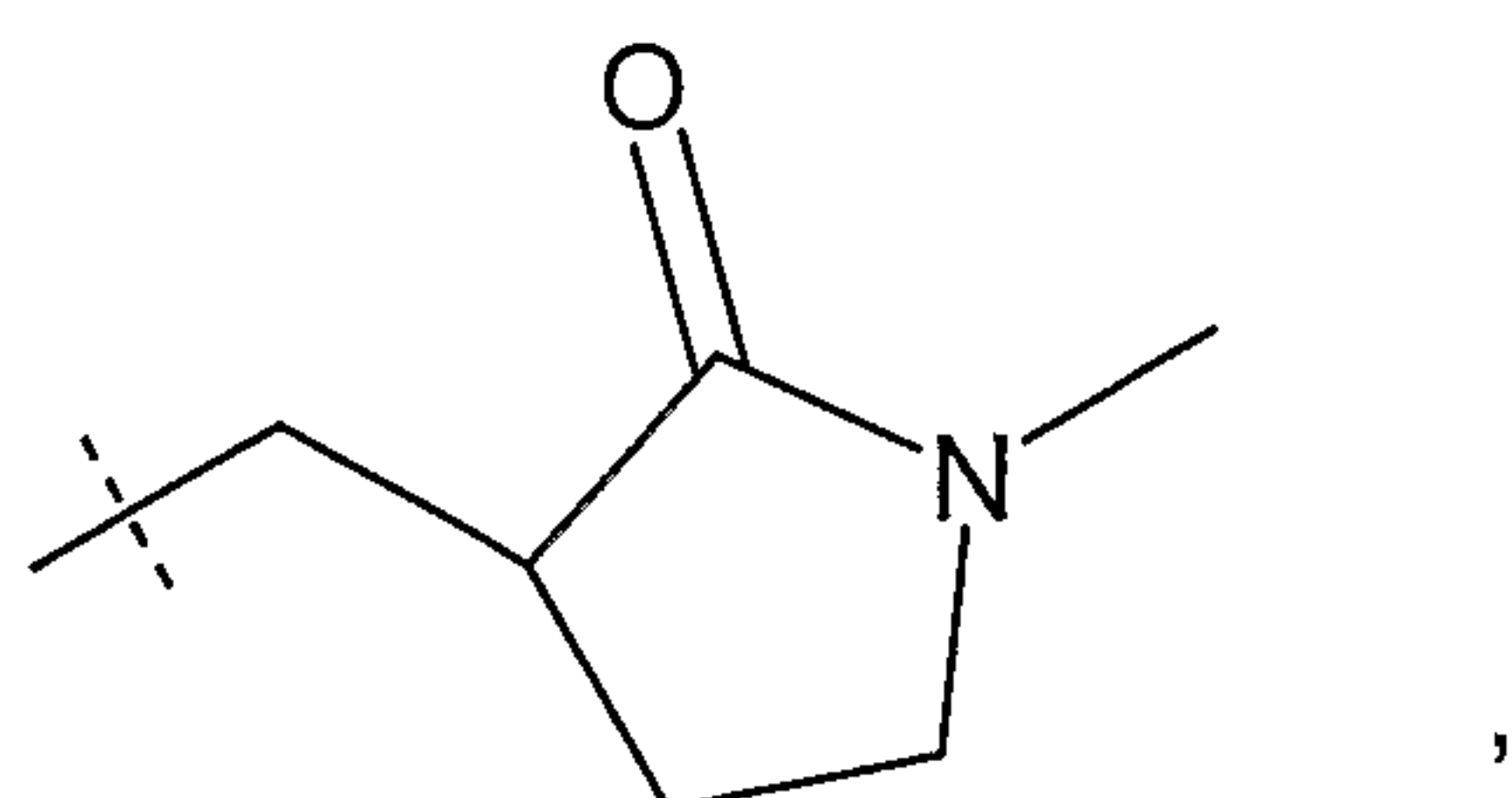
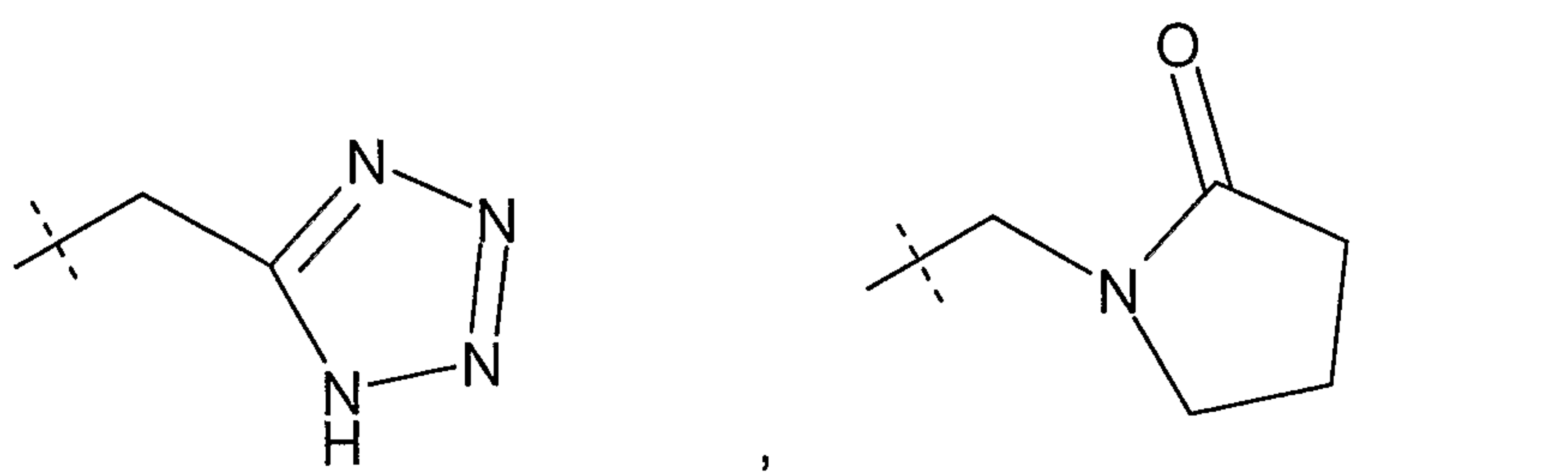
-45-



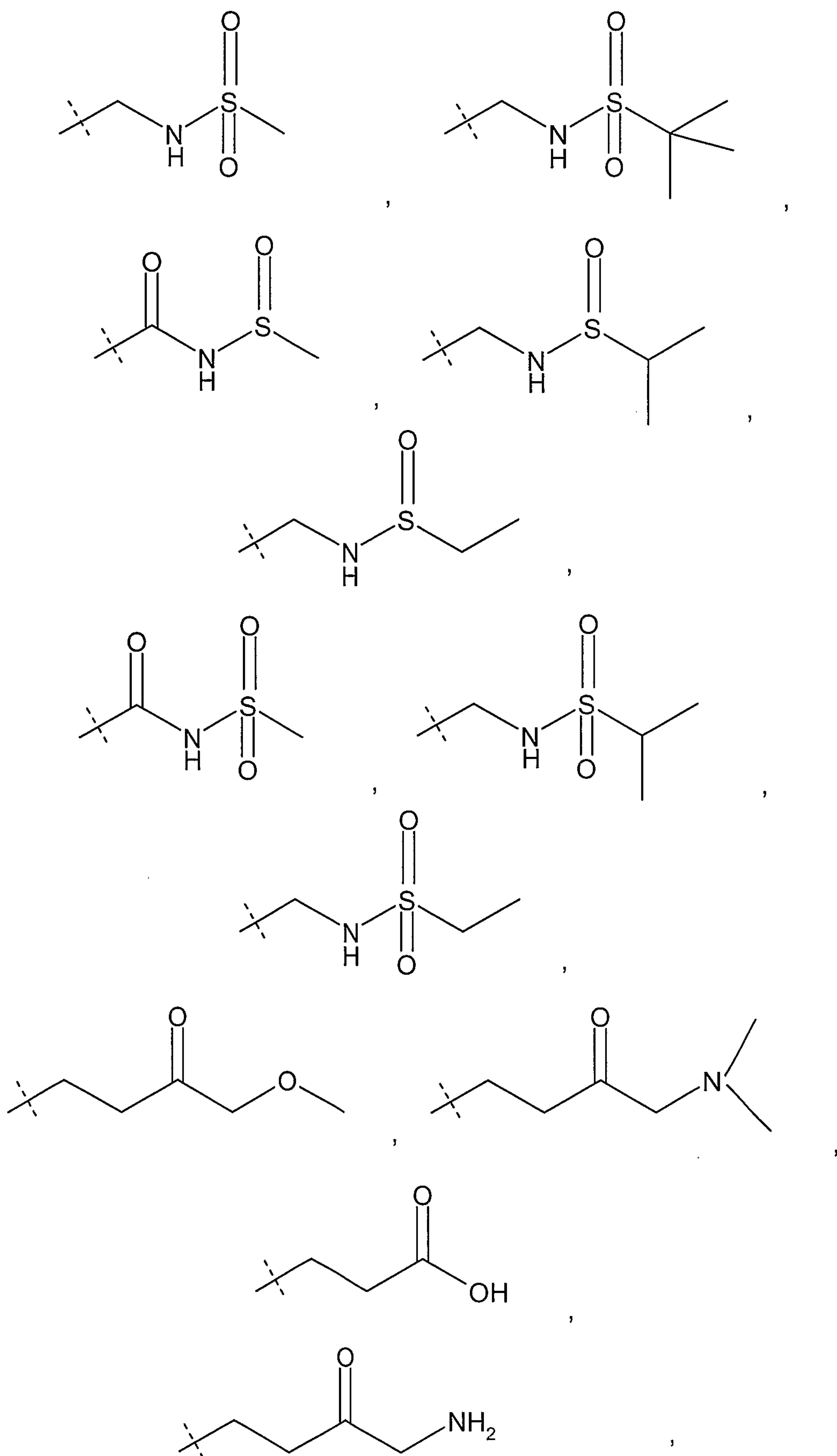
-46-



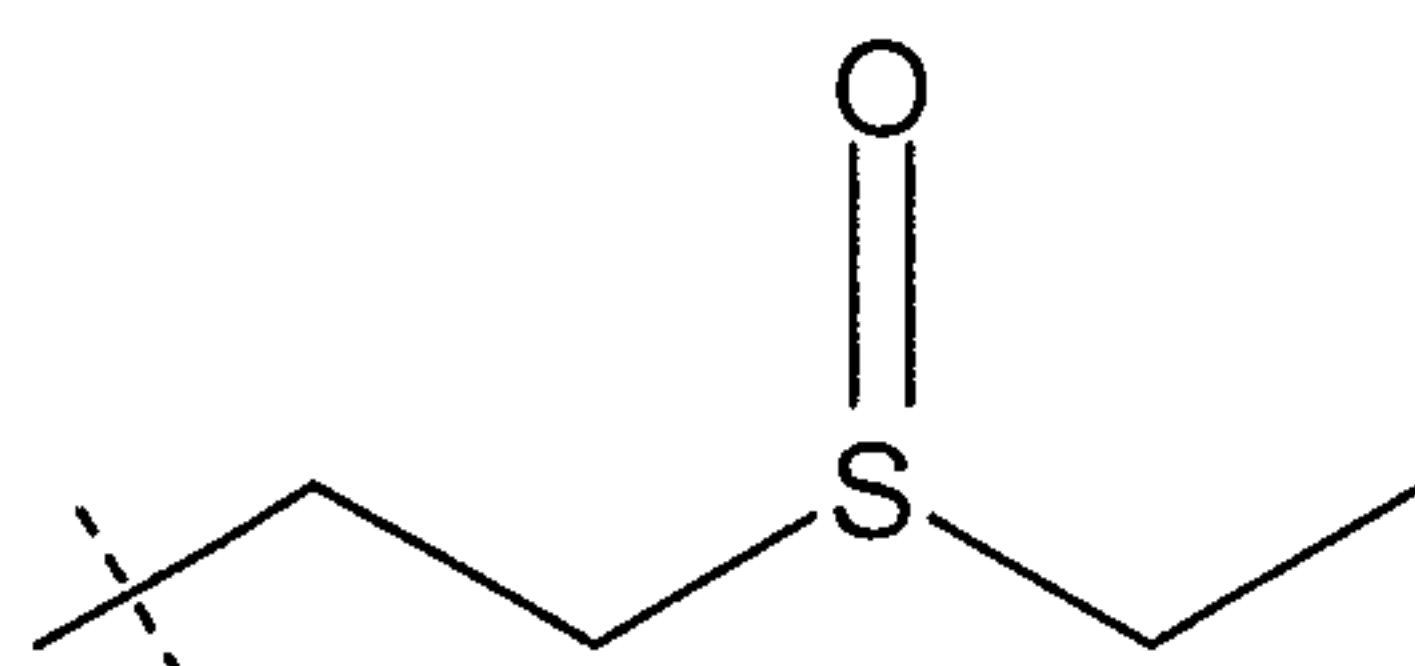
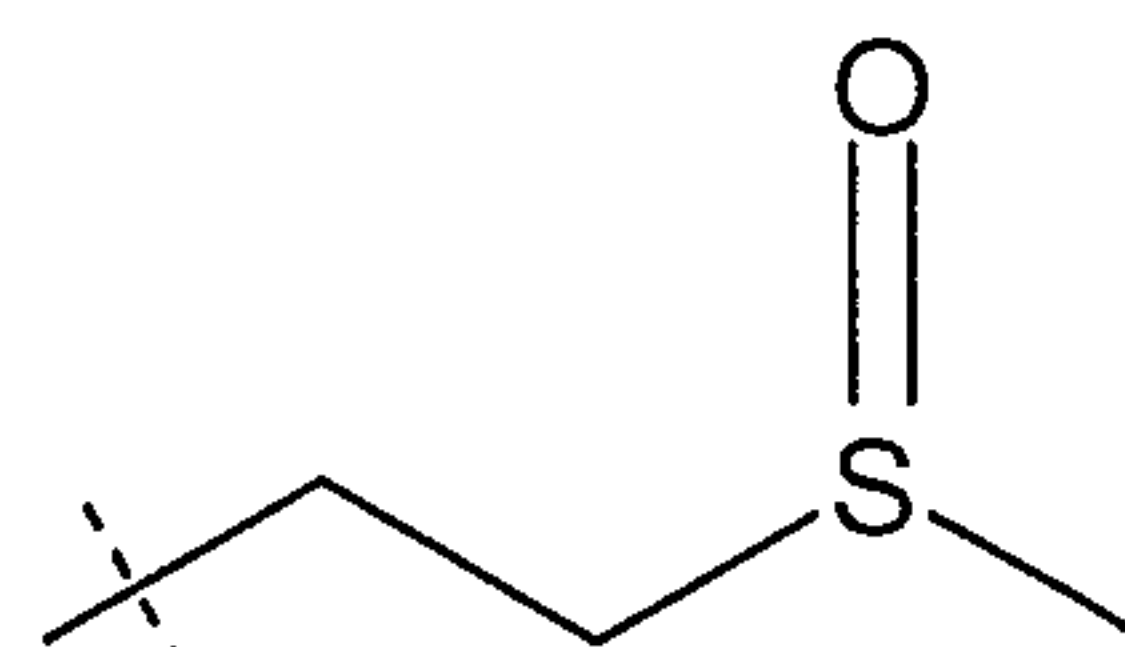
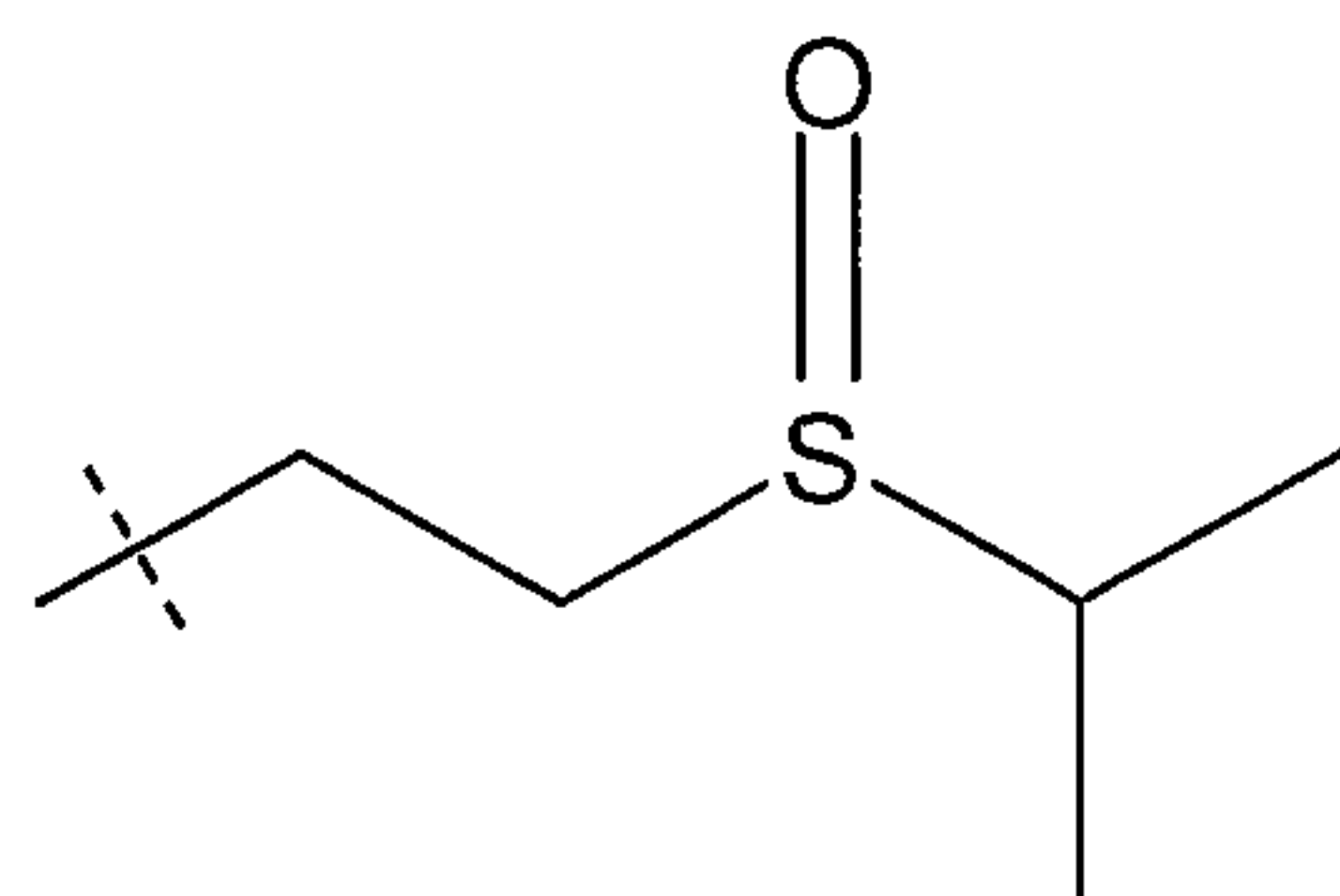
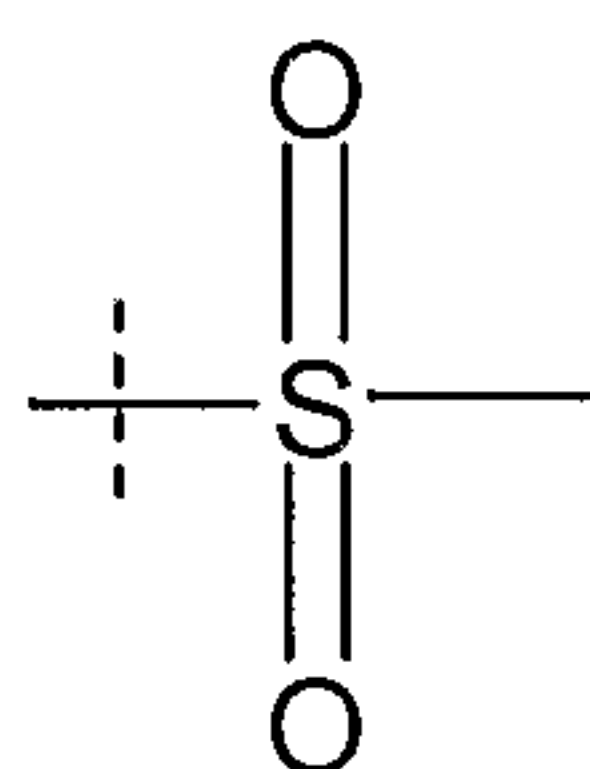
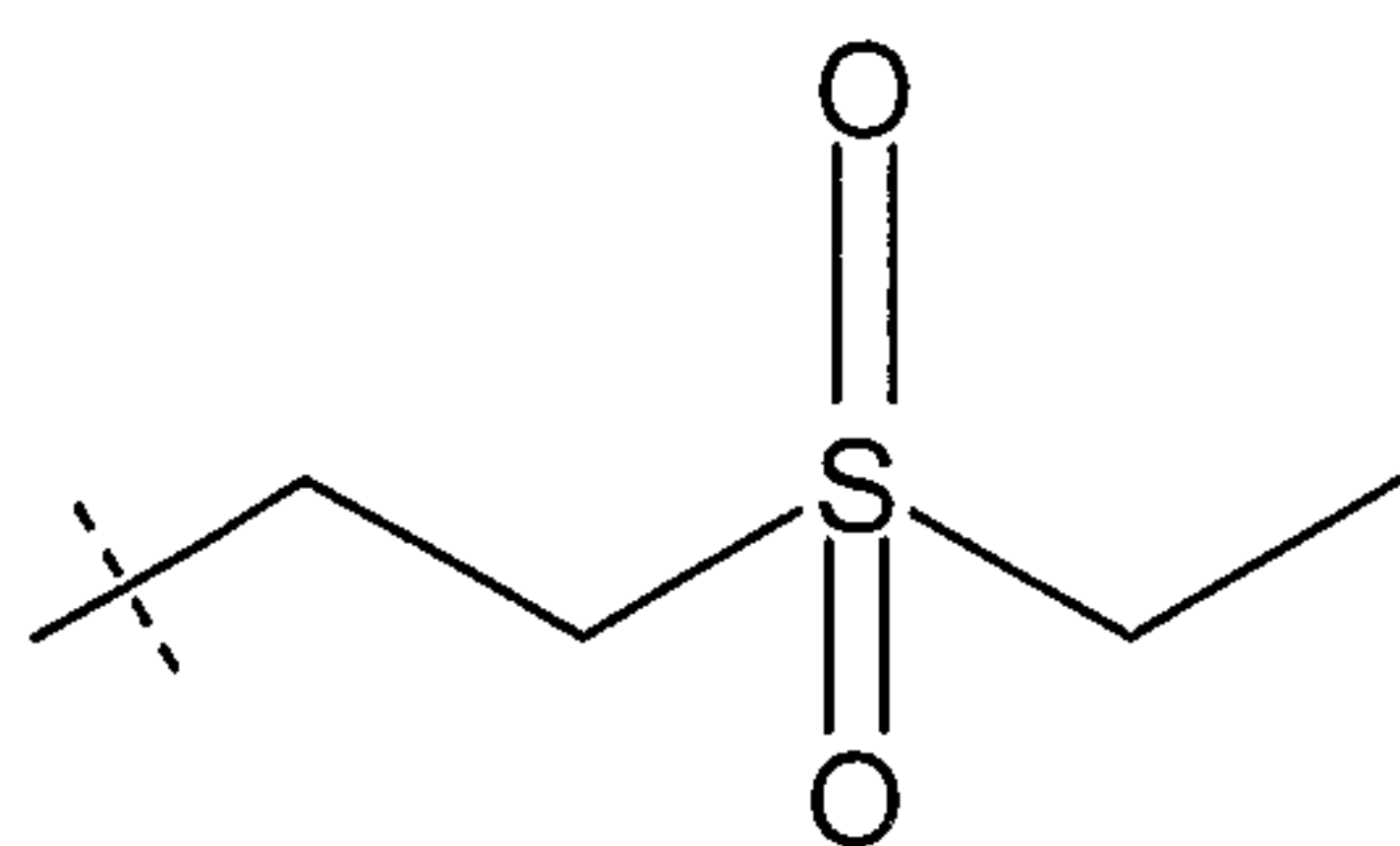
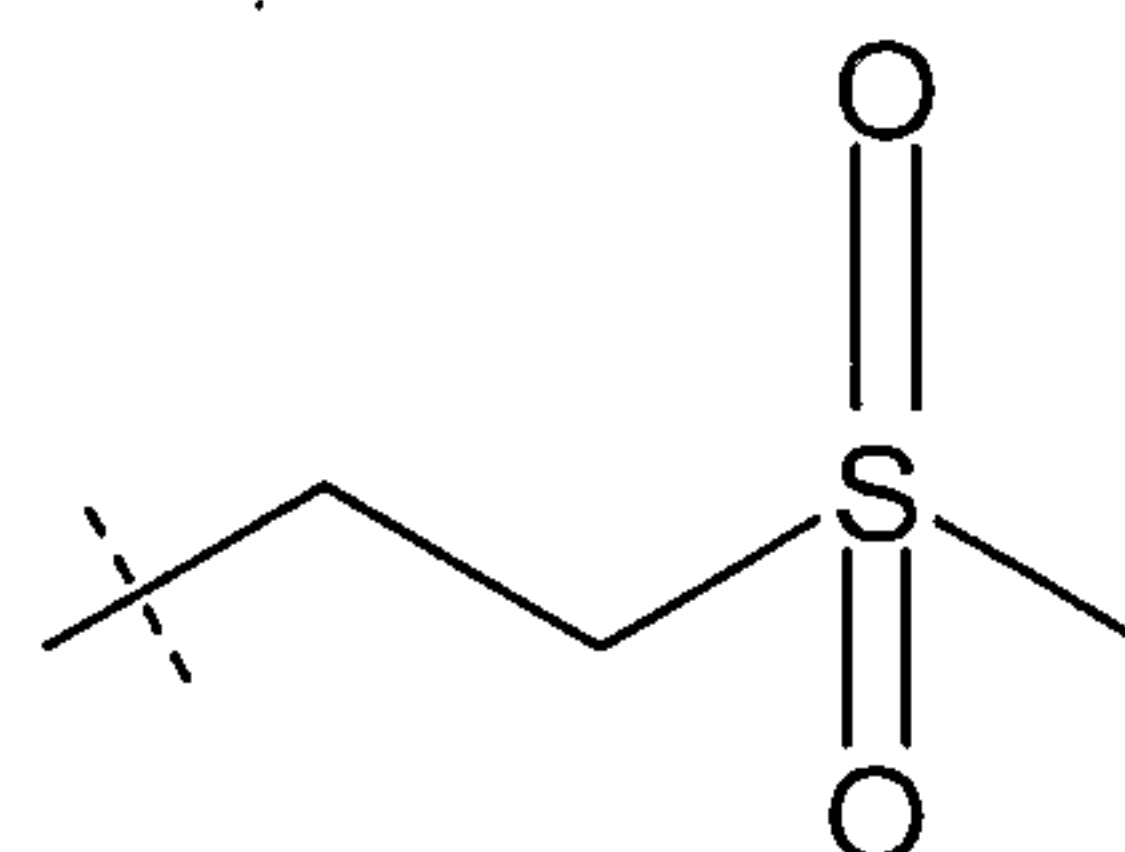
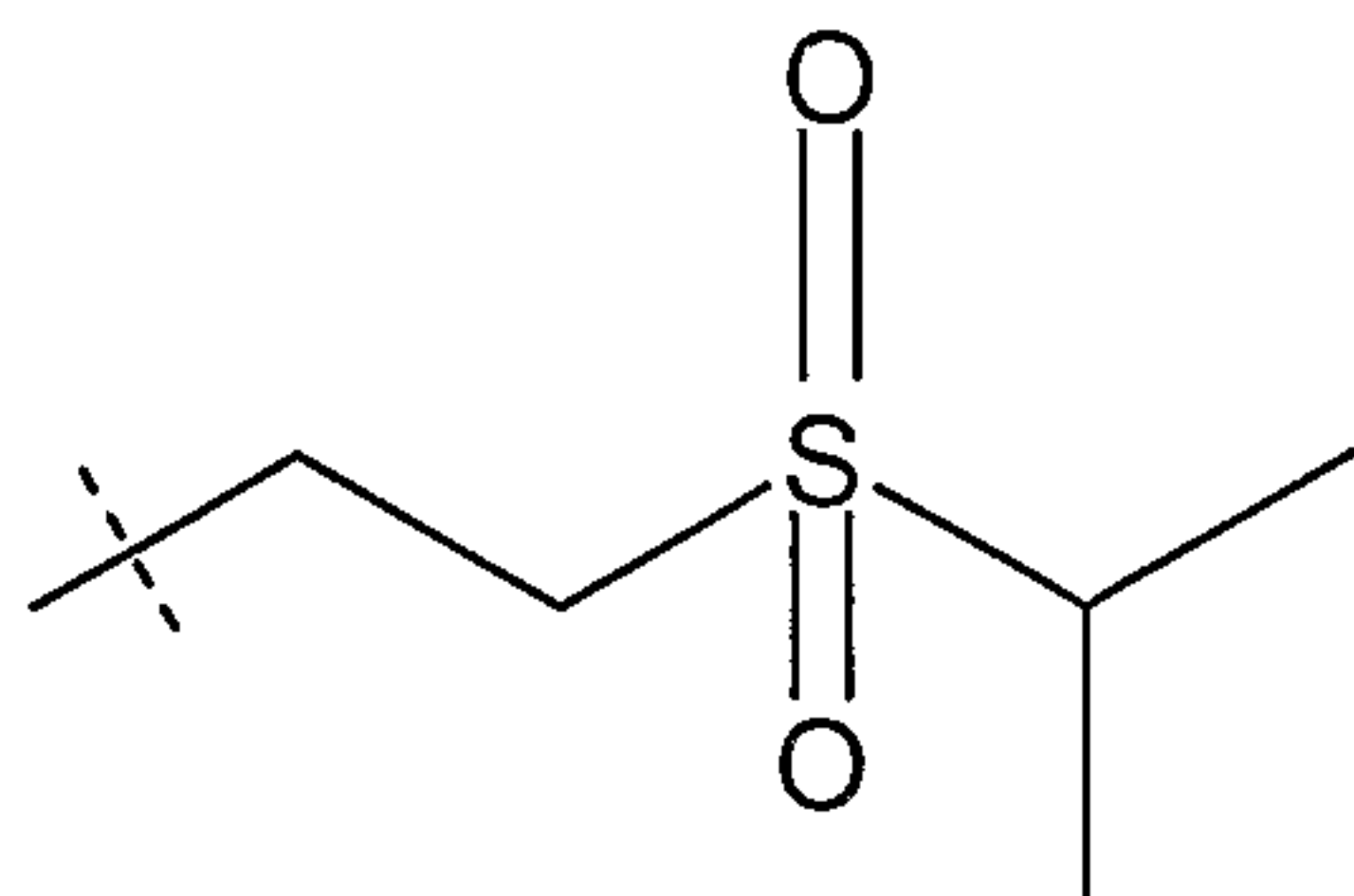
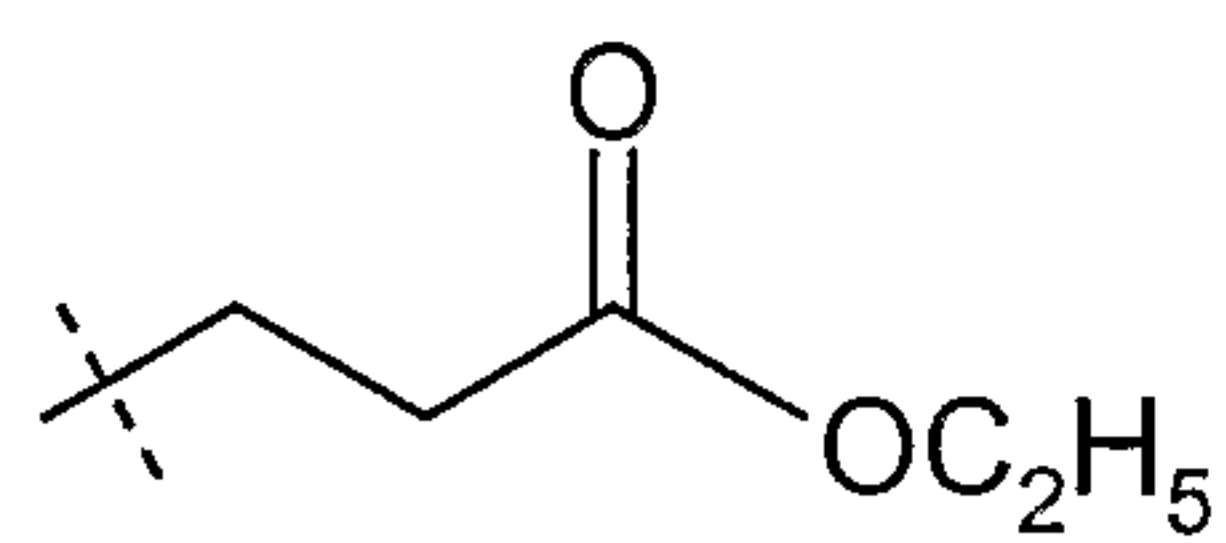
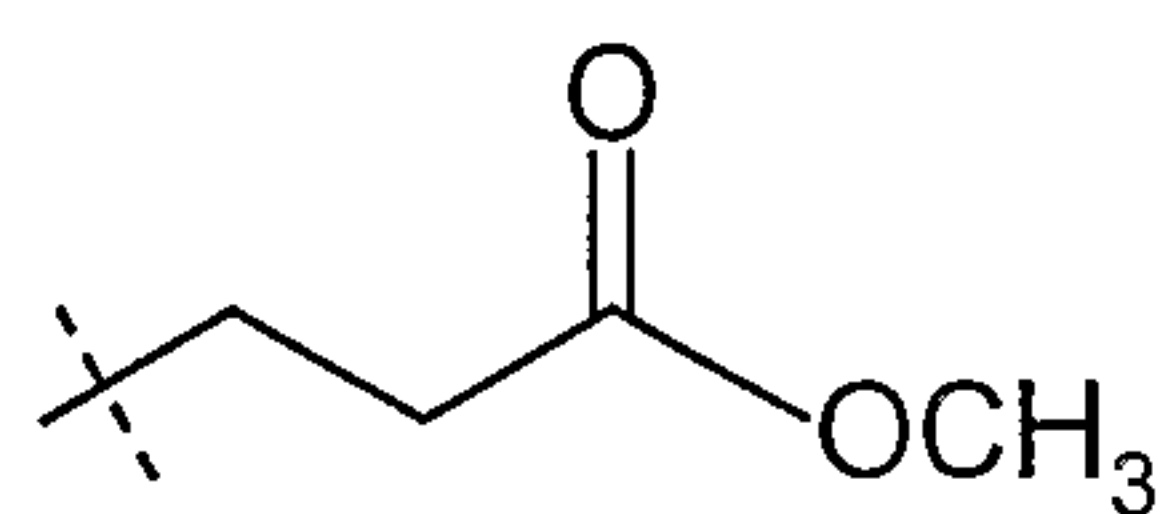
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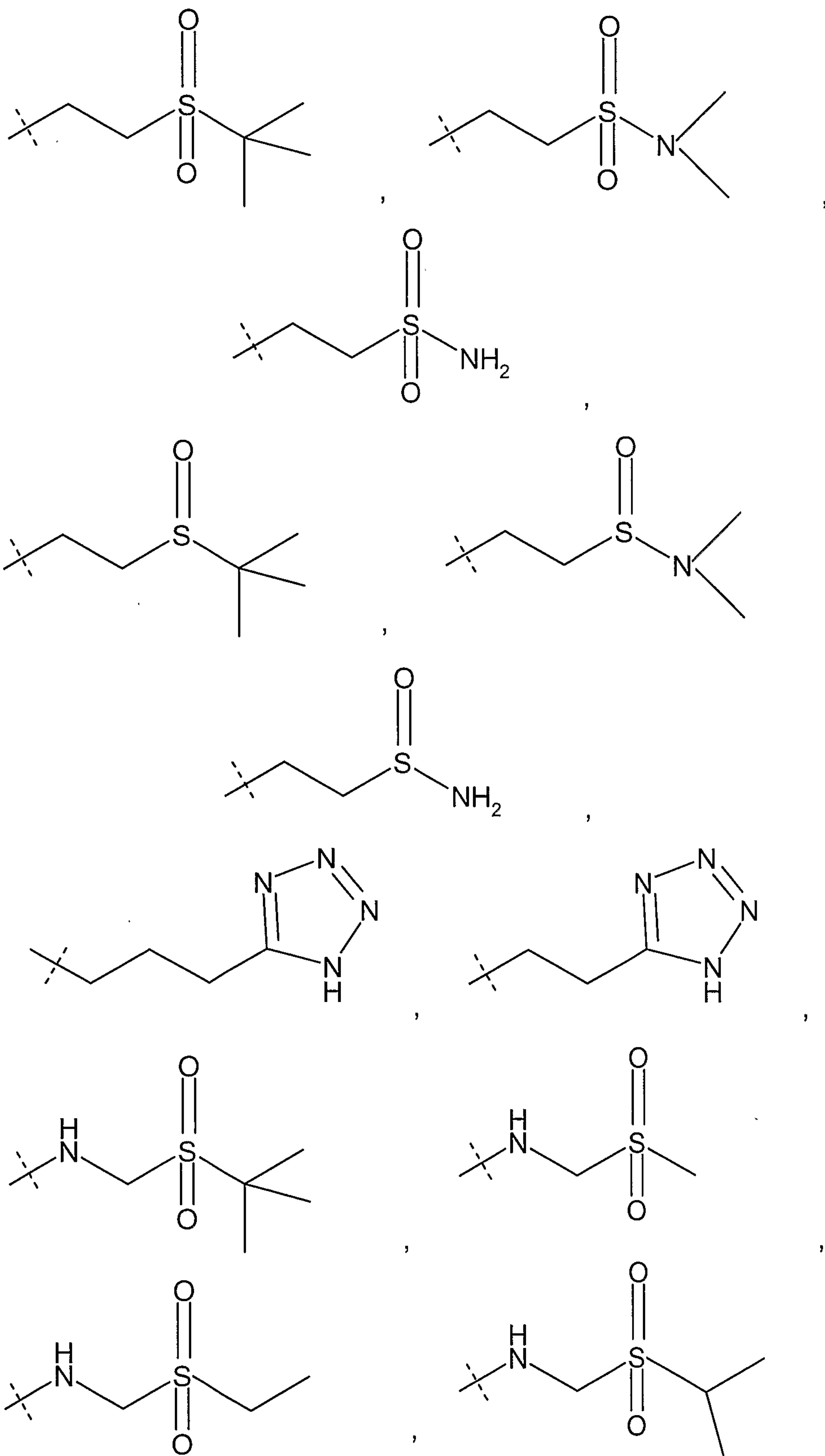
-47-



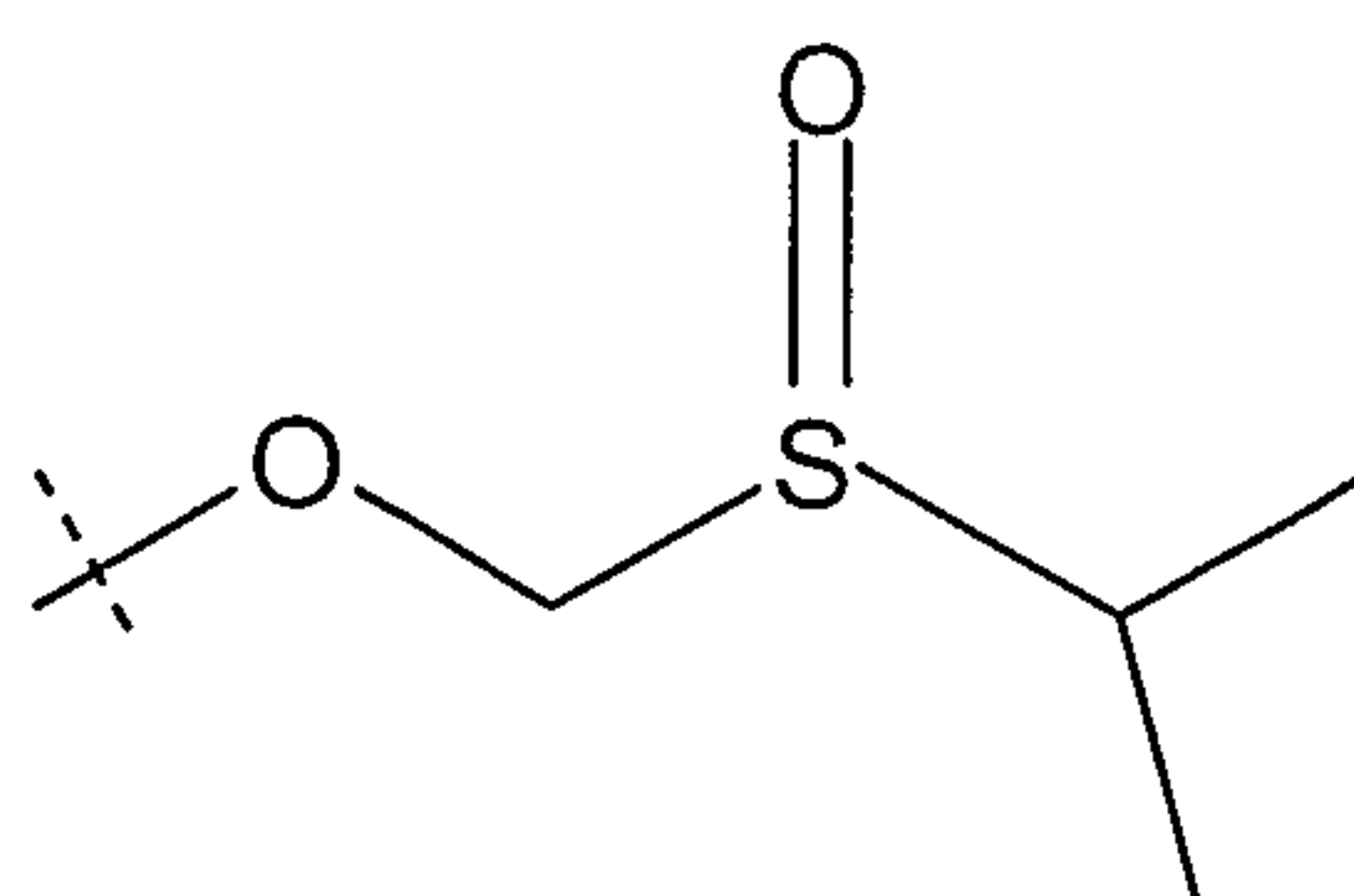
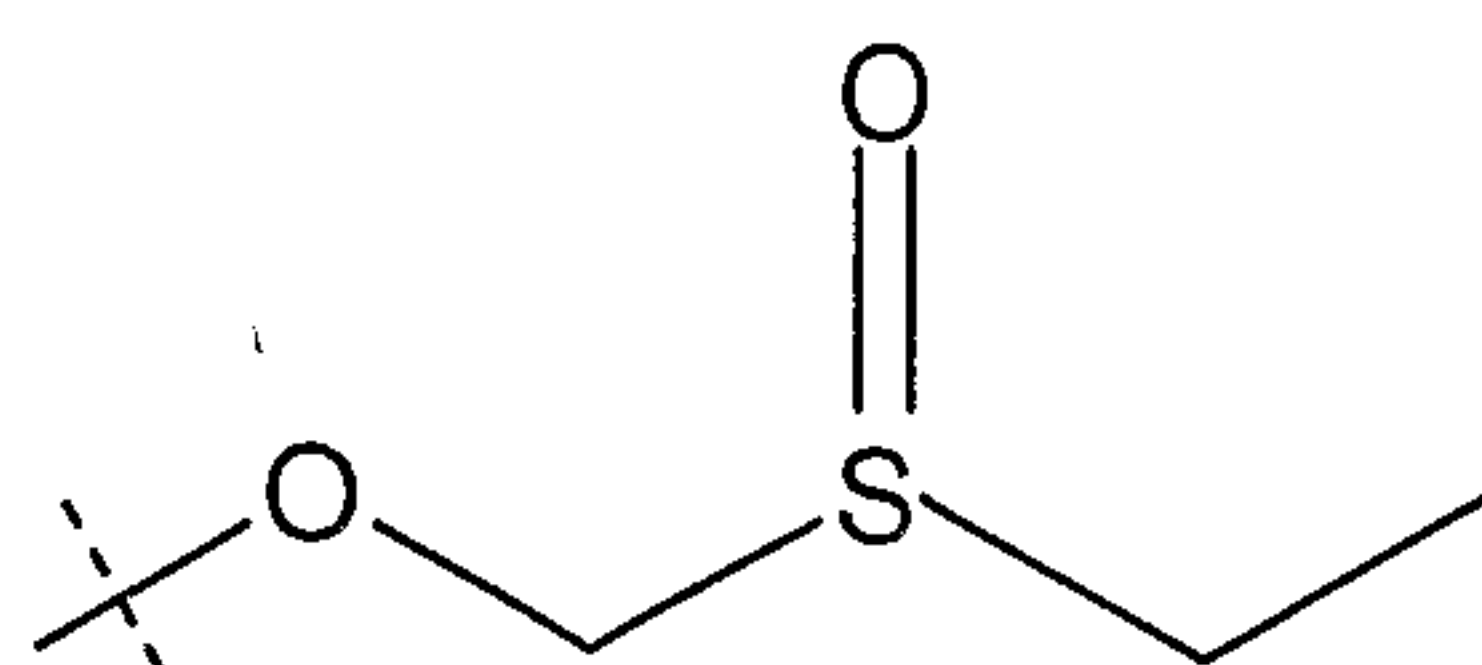
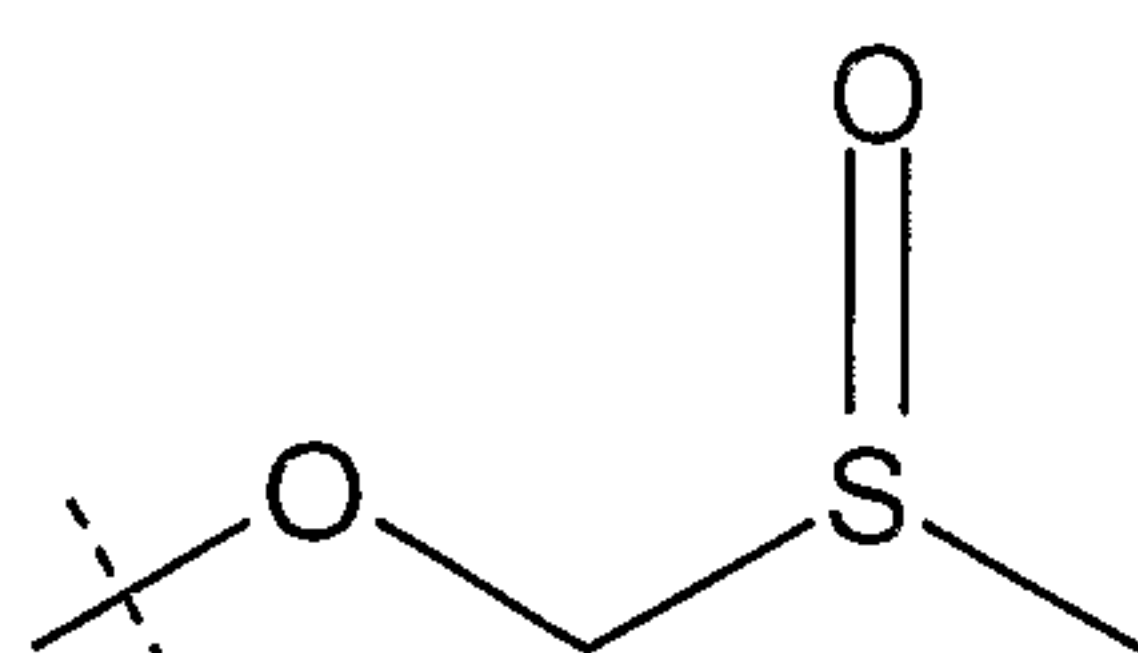
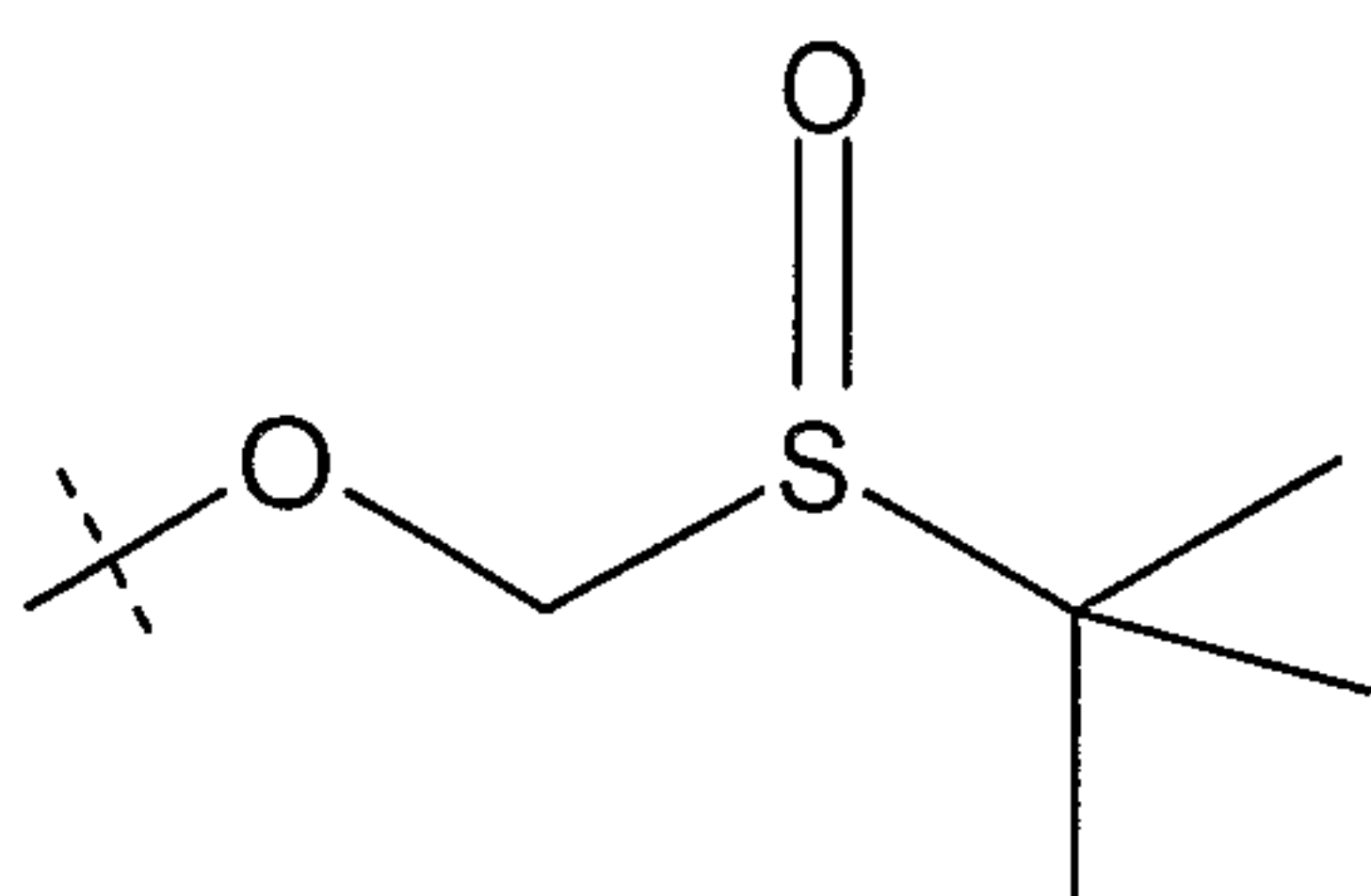
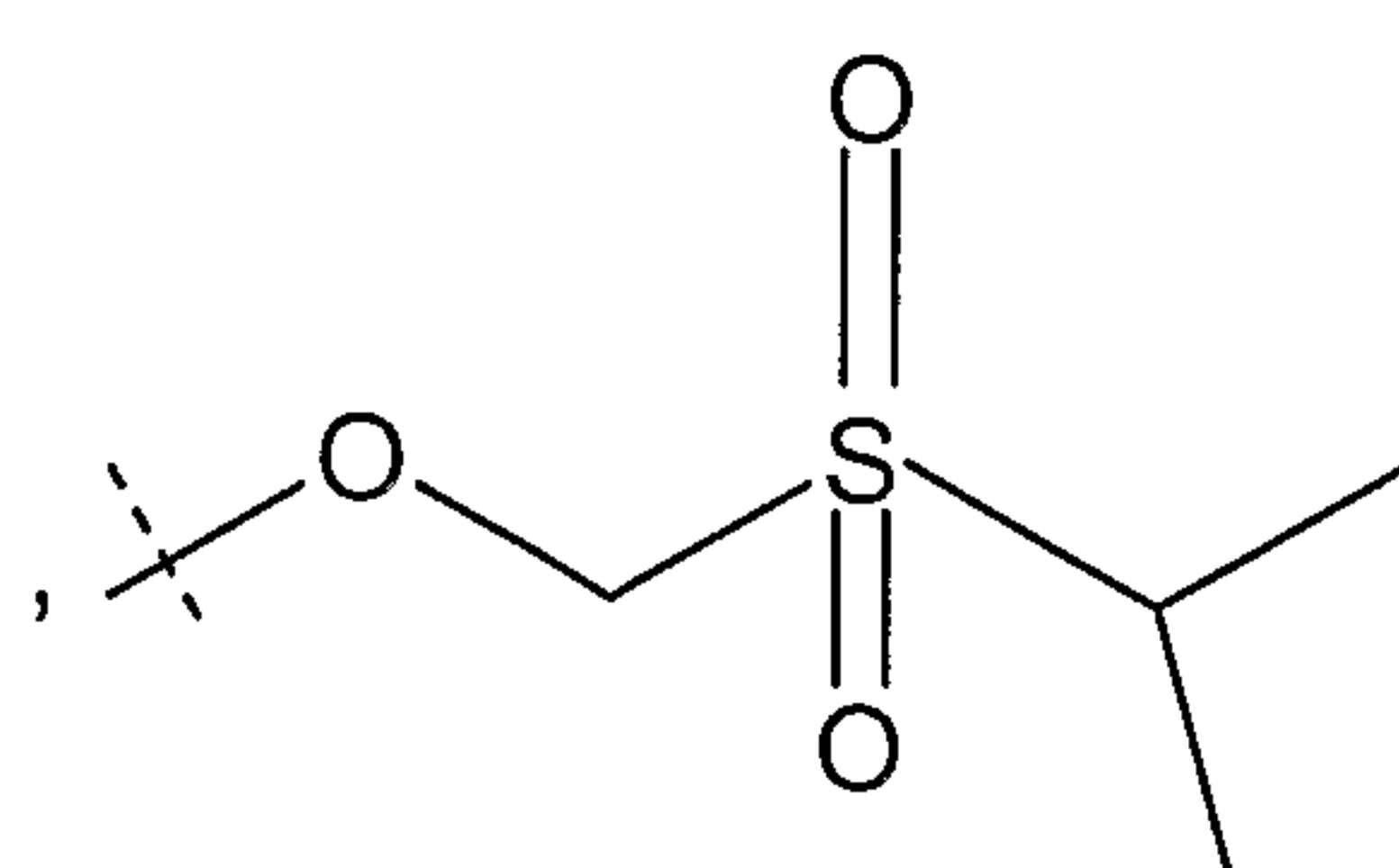
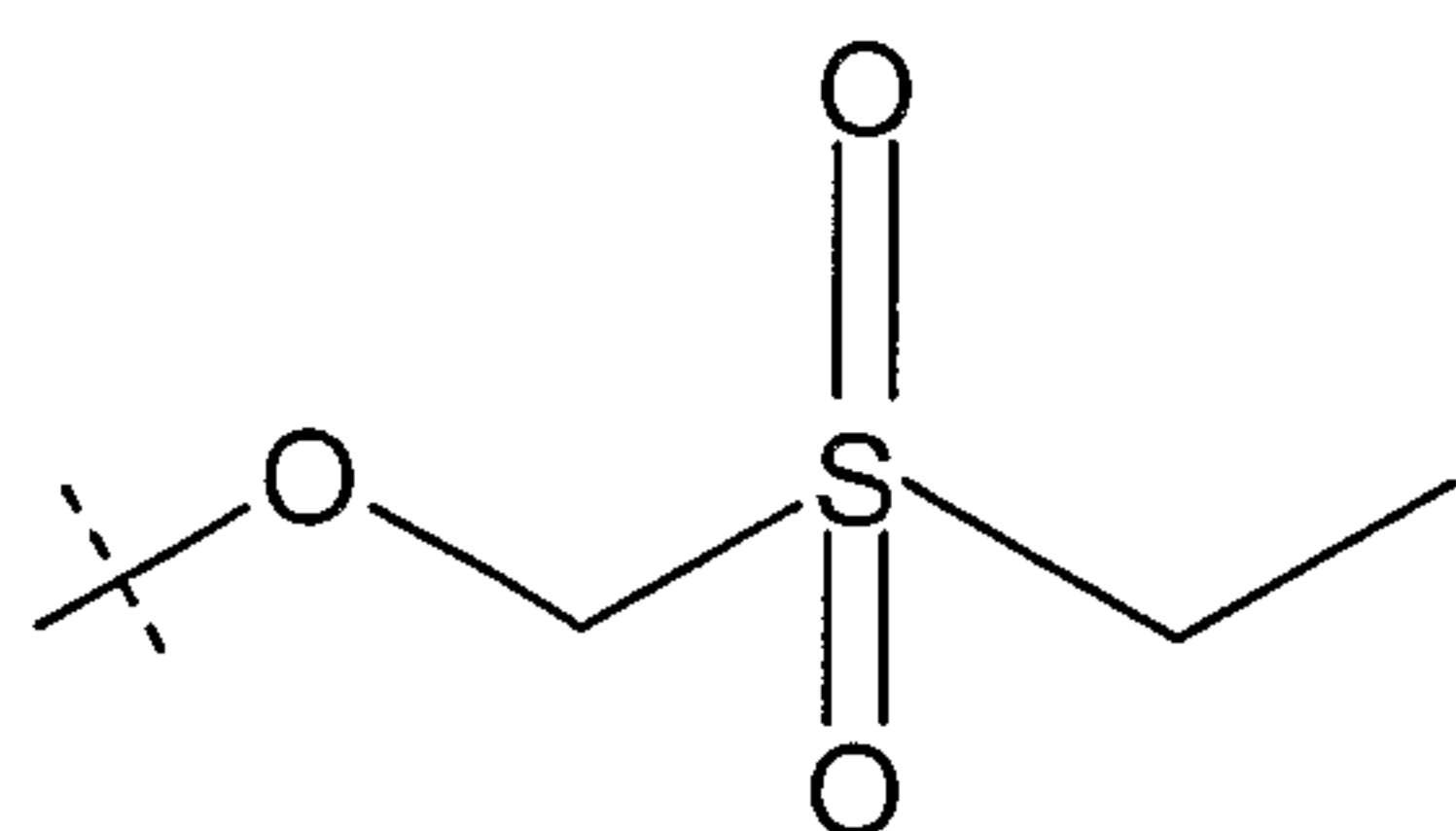
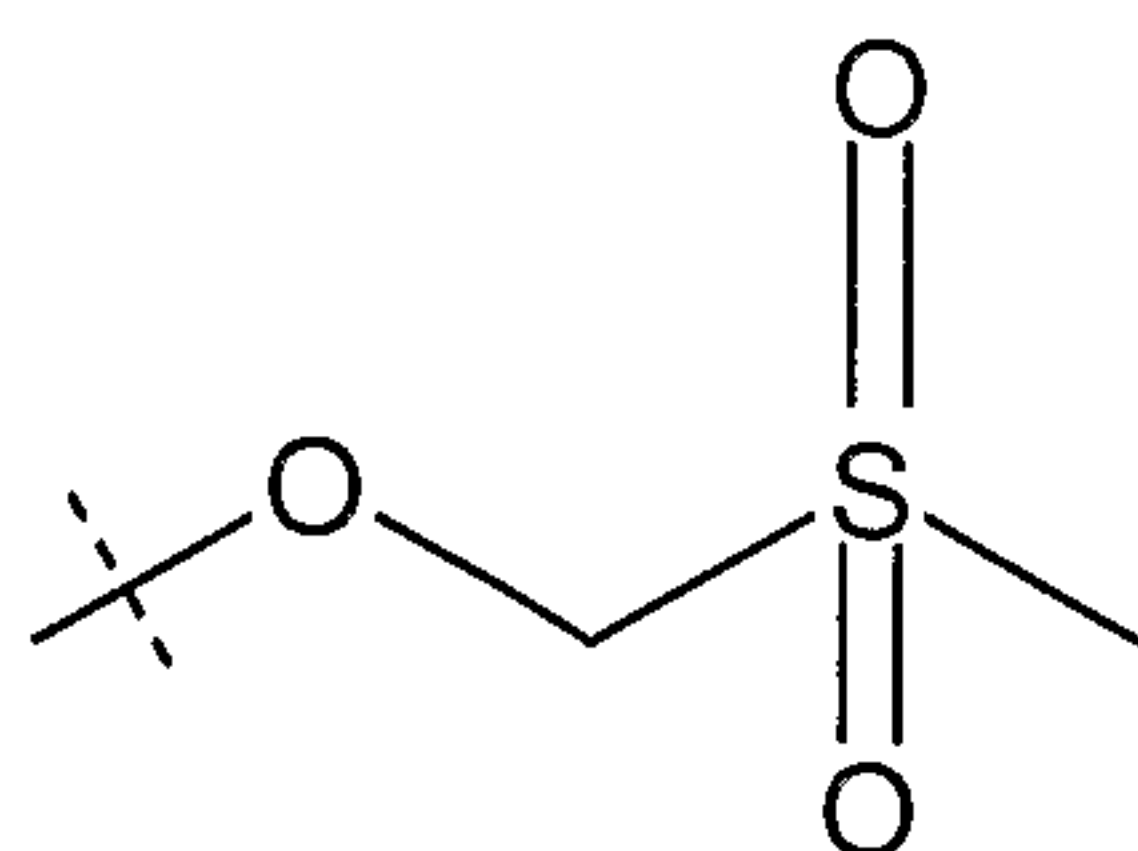
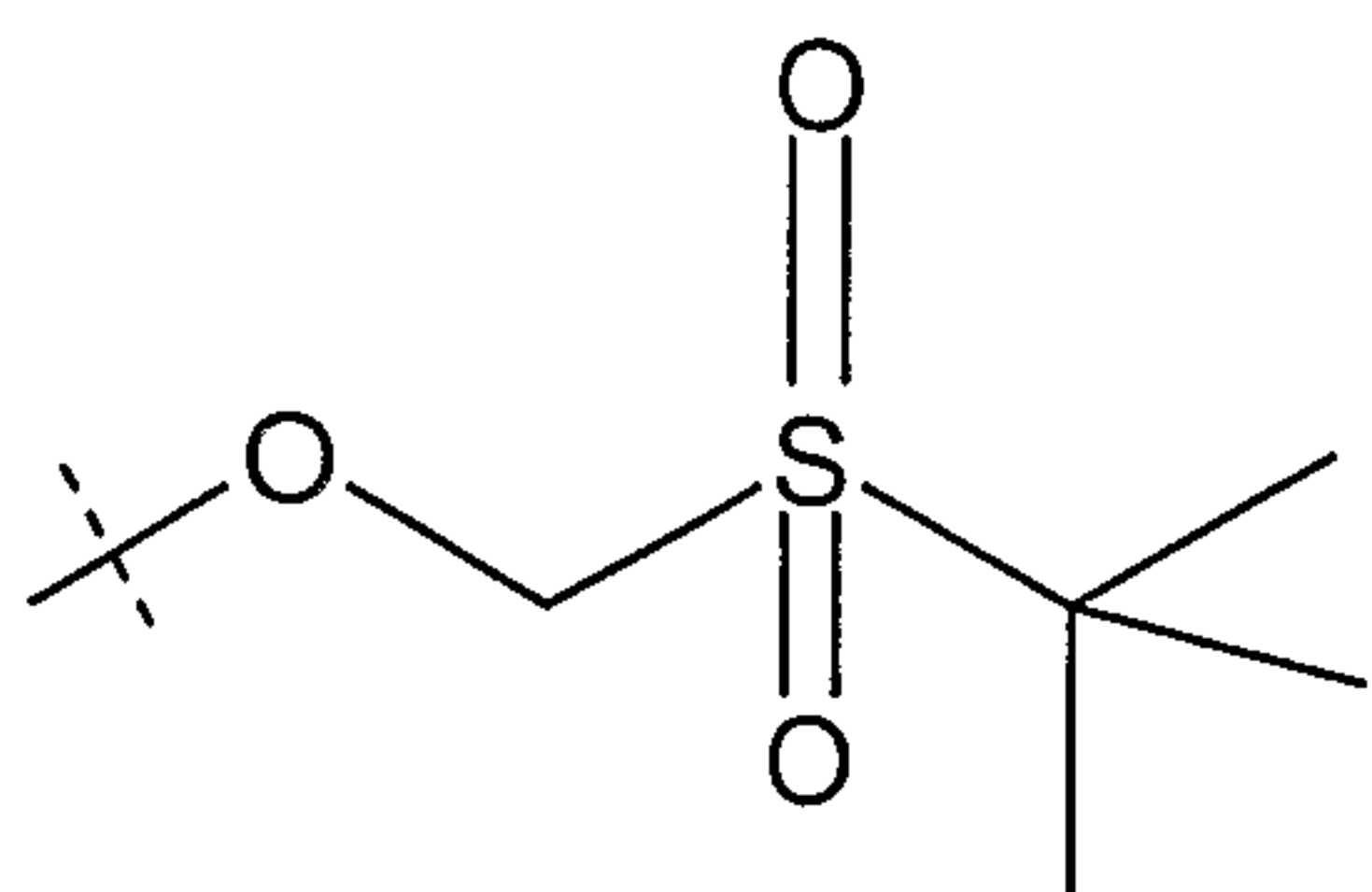
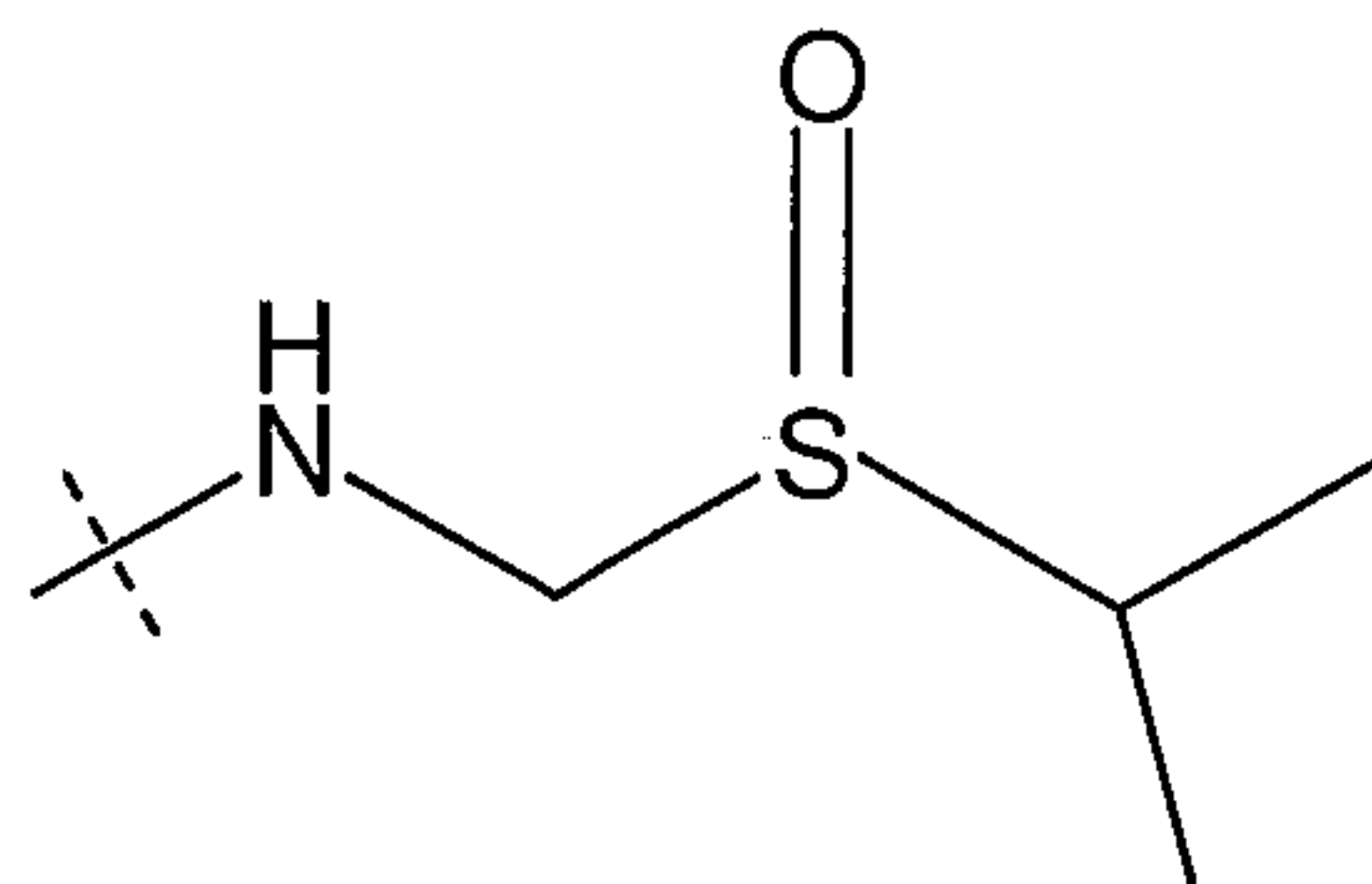
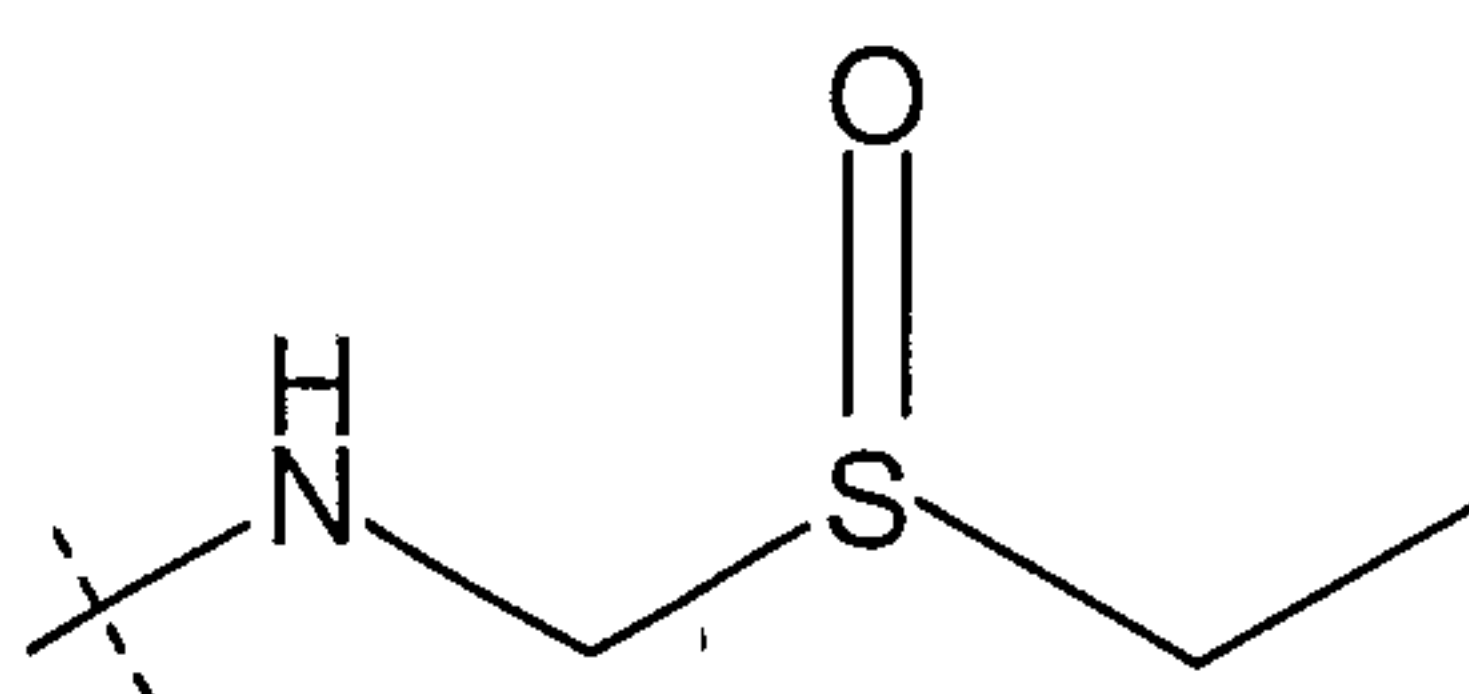
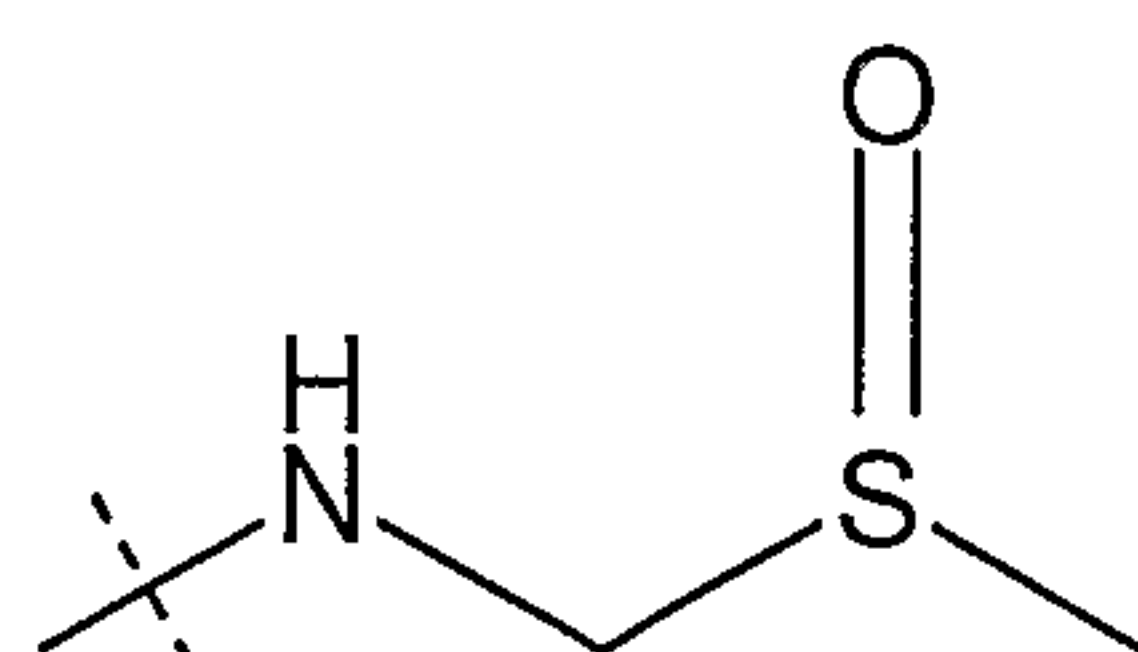
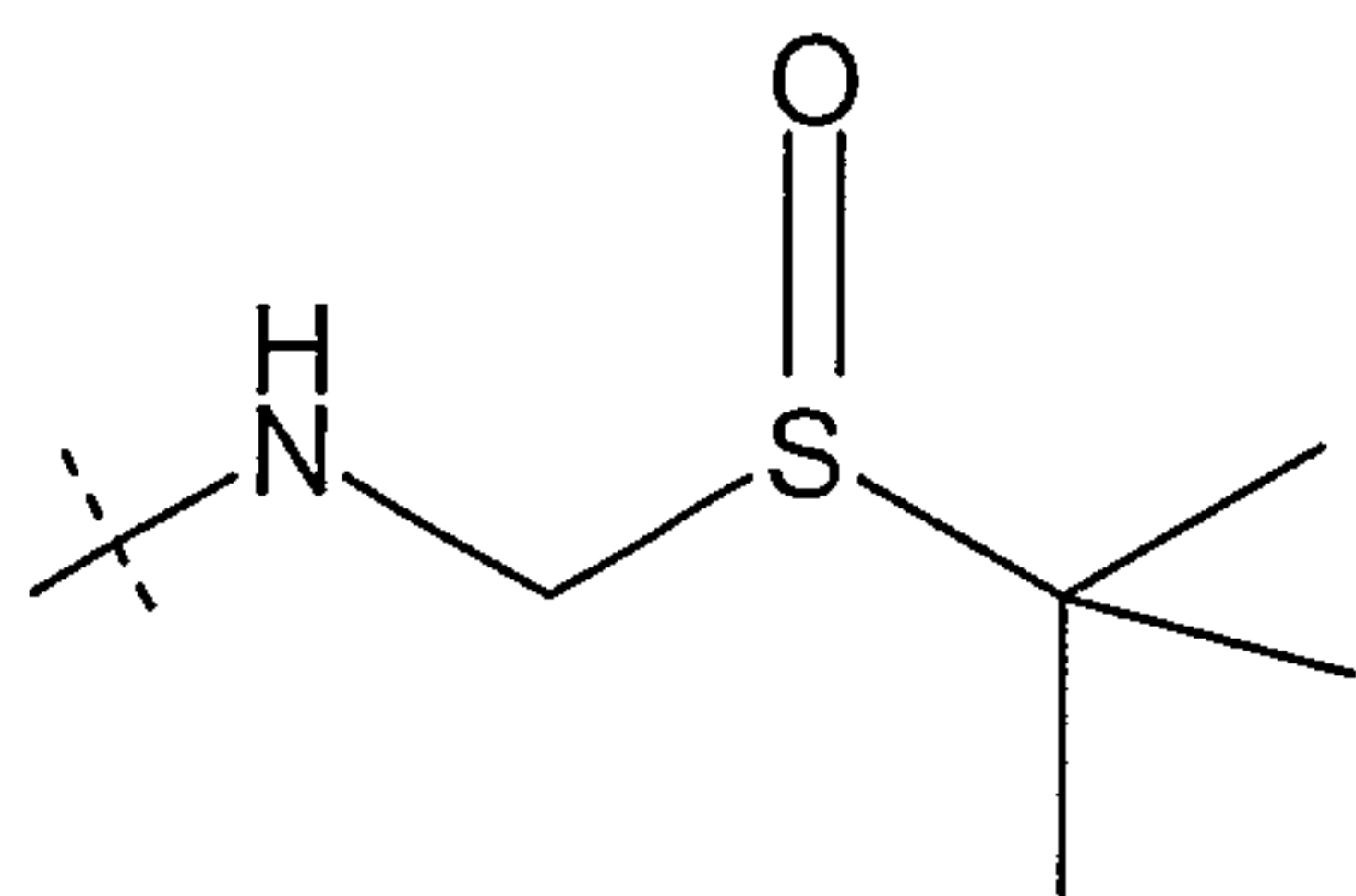
-48-



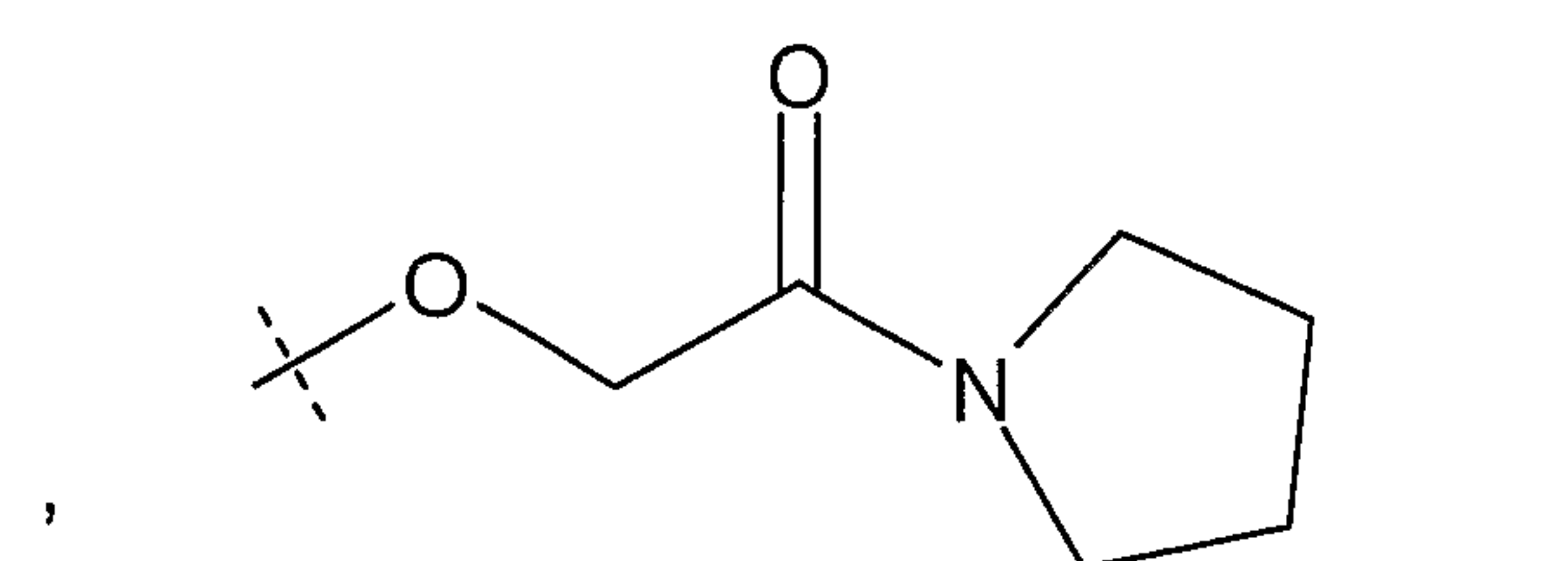
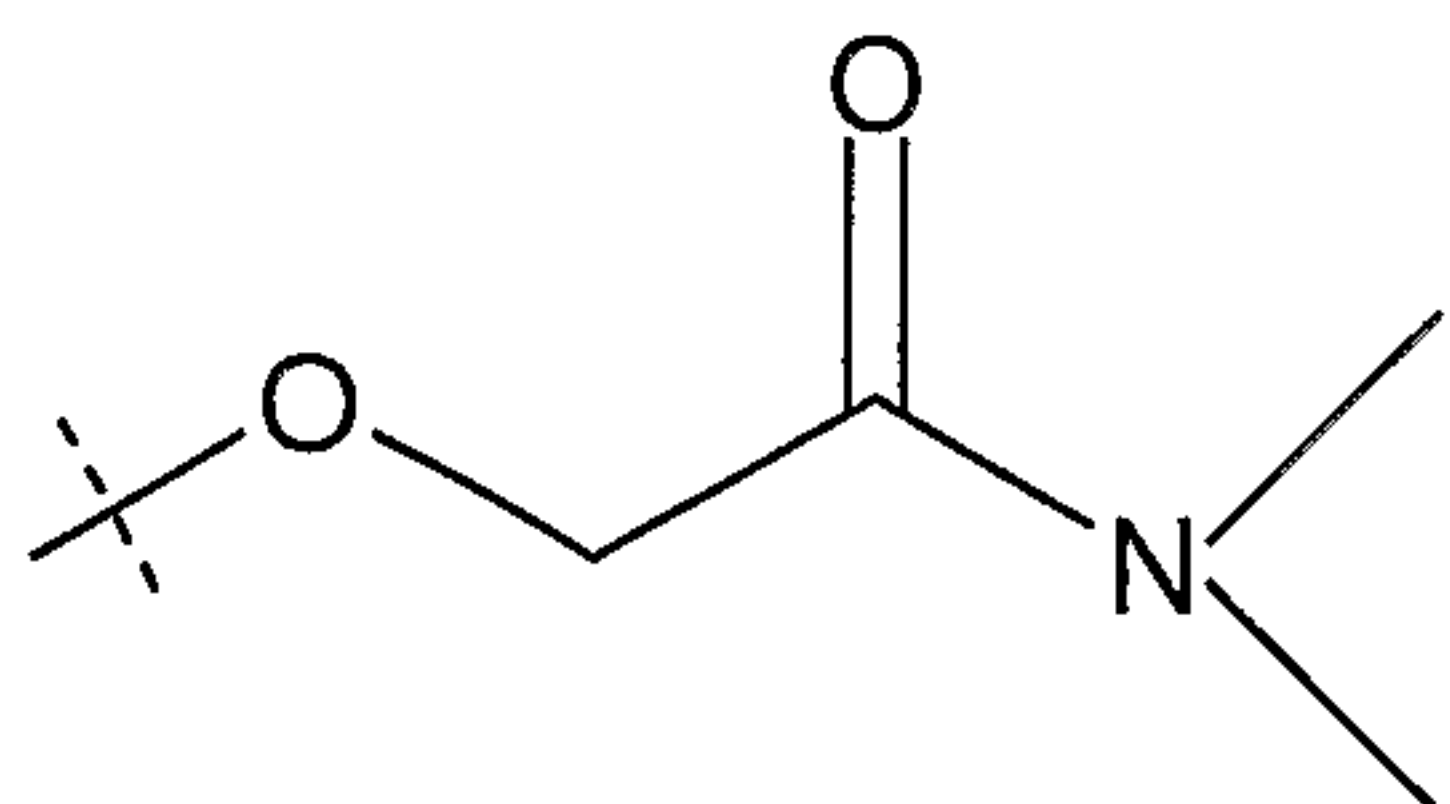
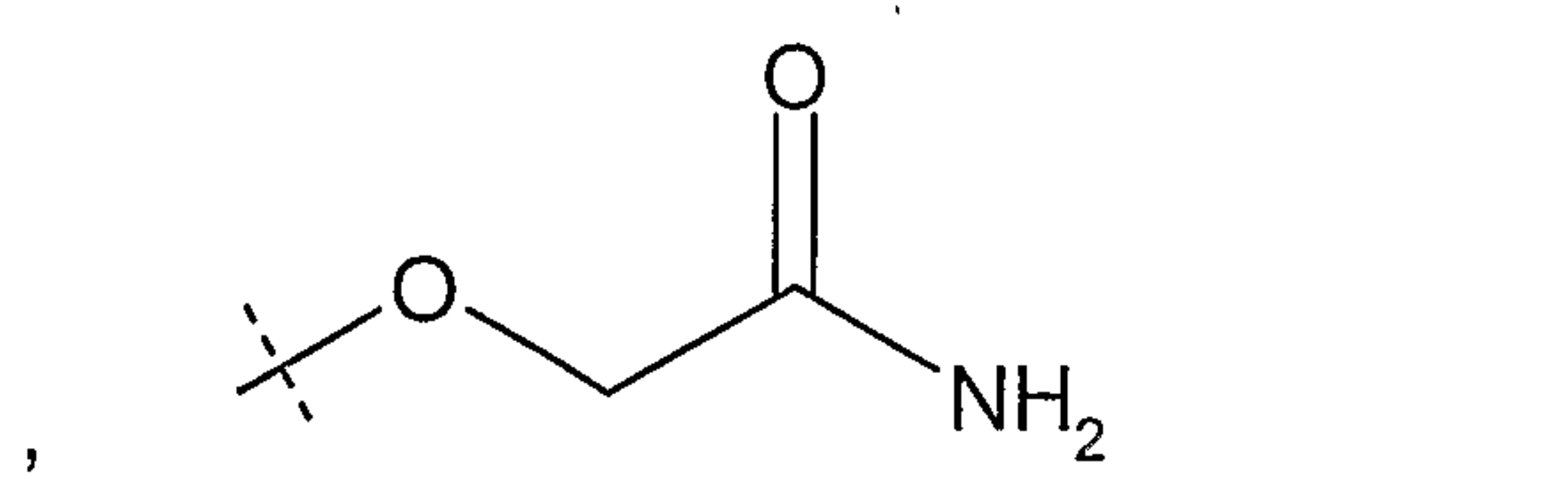
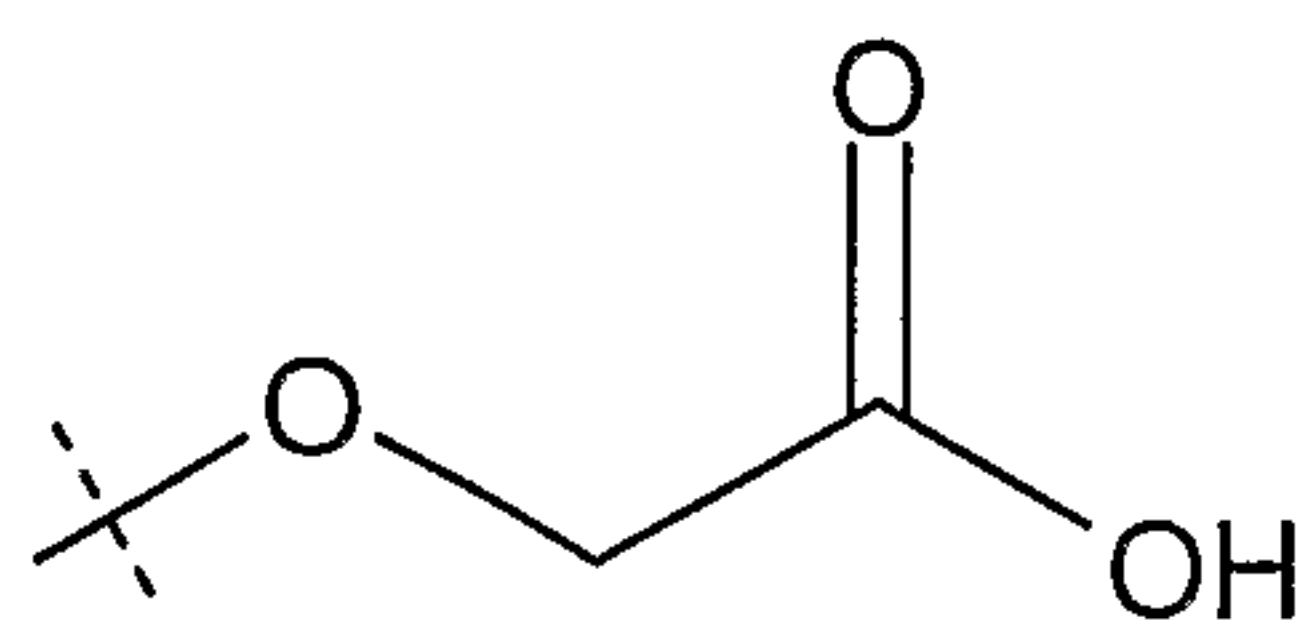
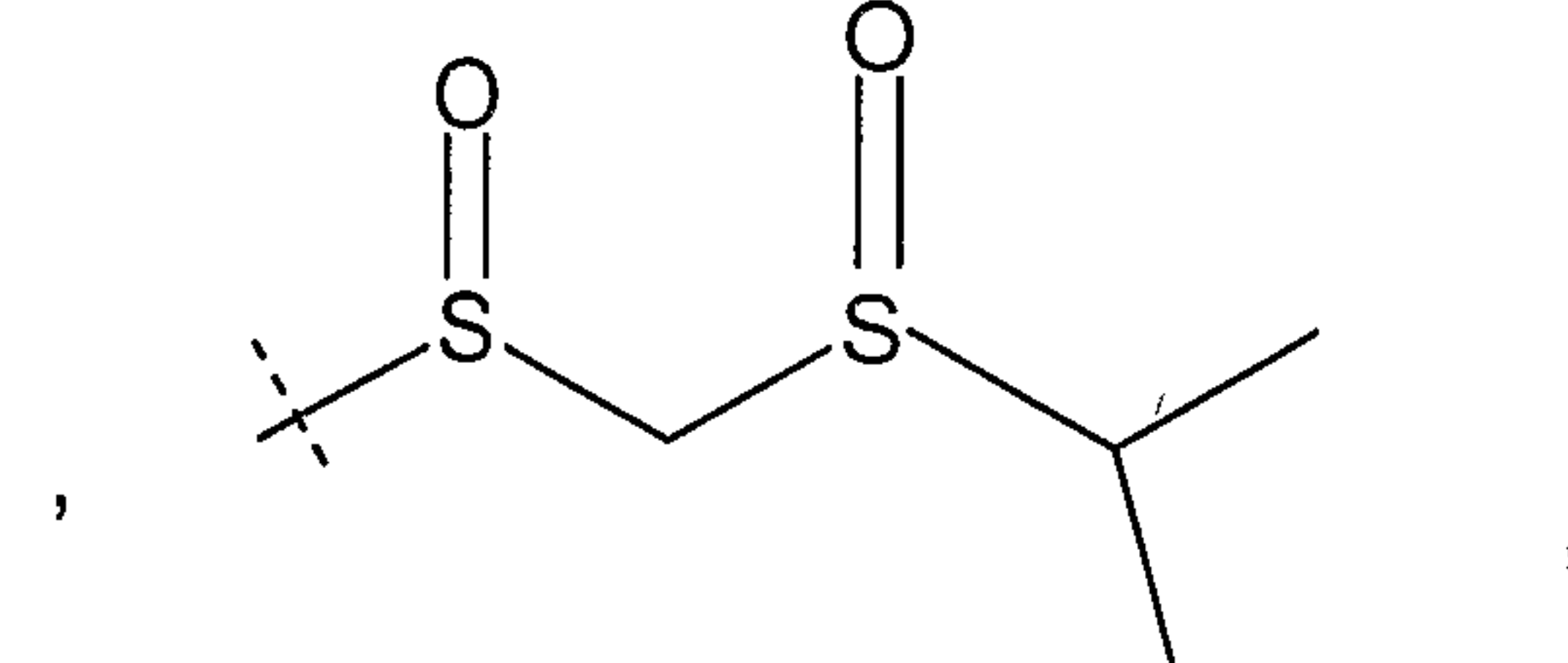
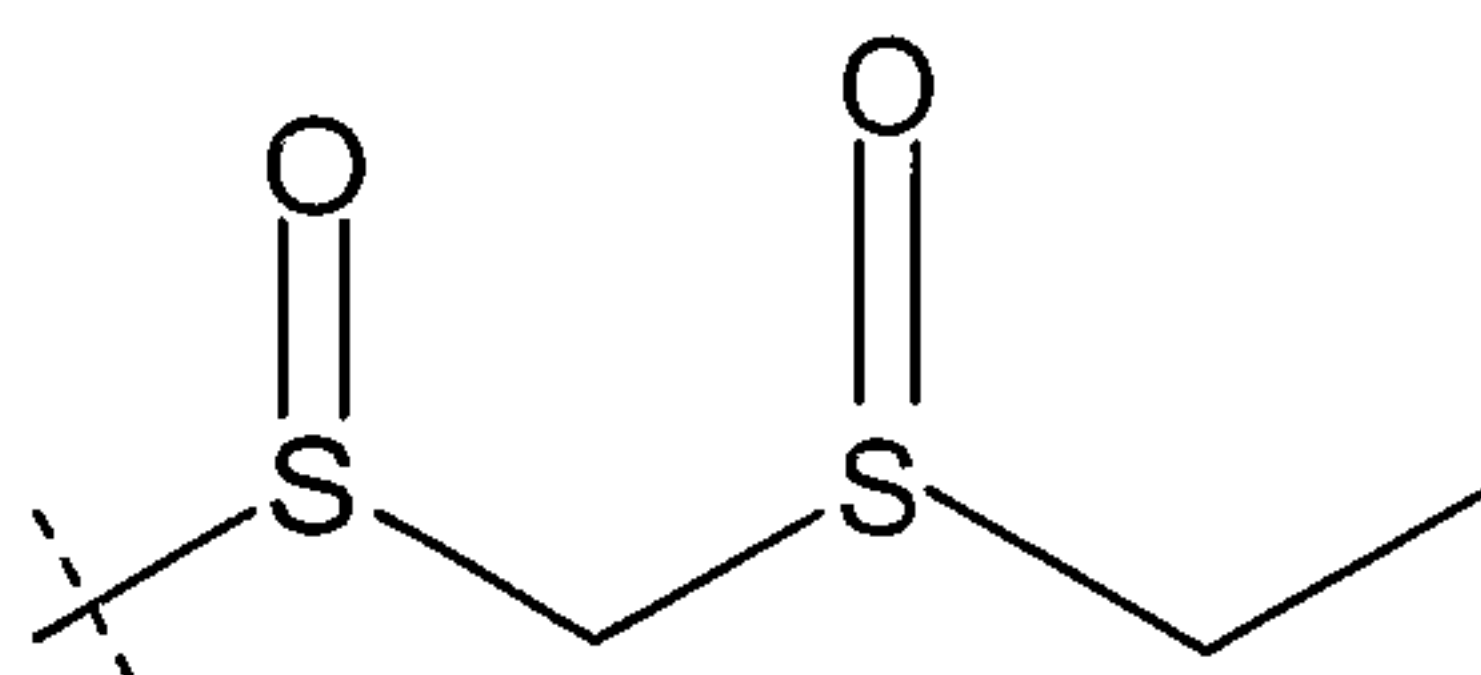
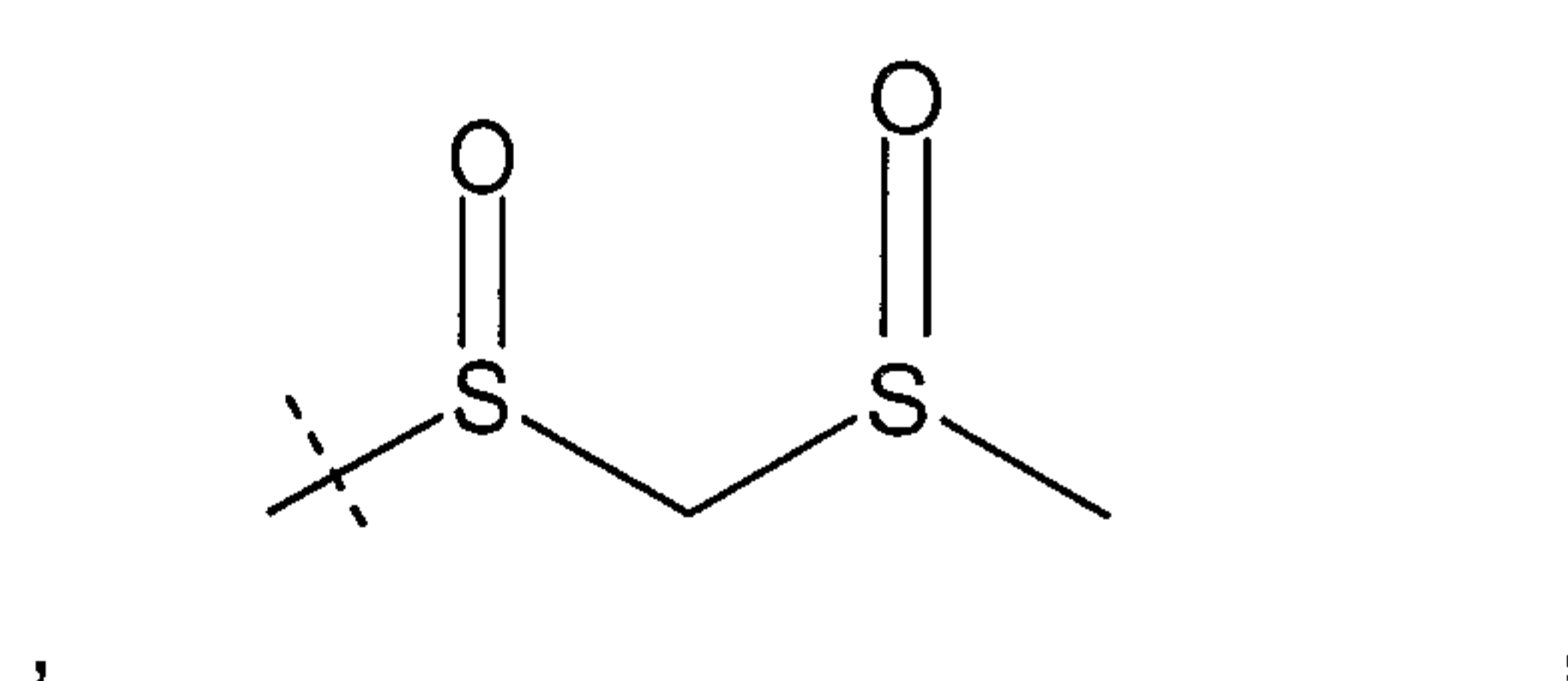
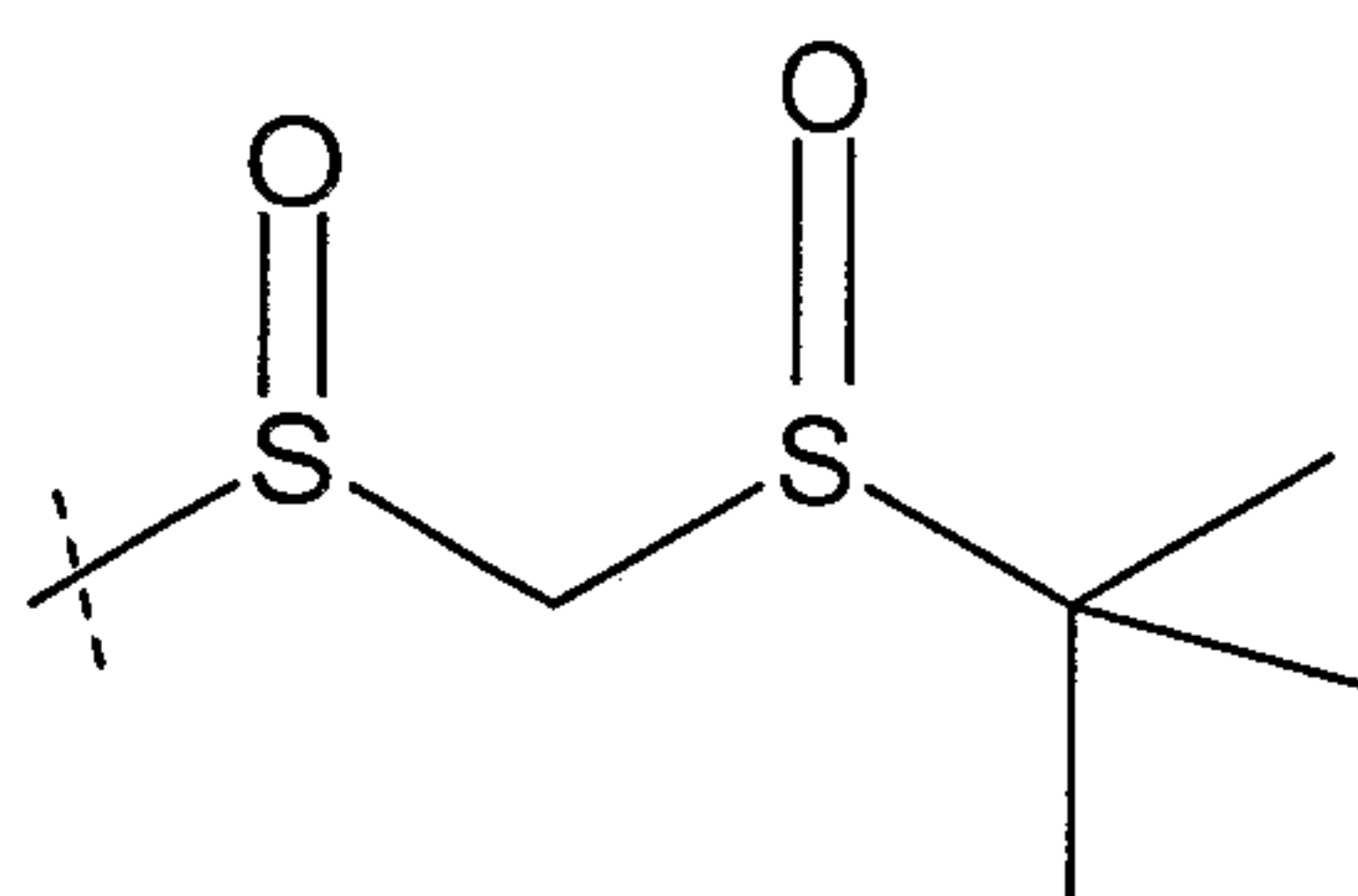
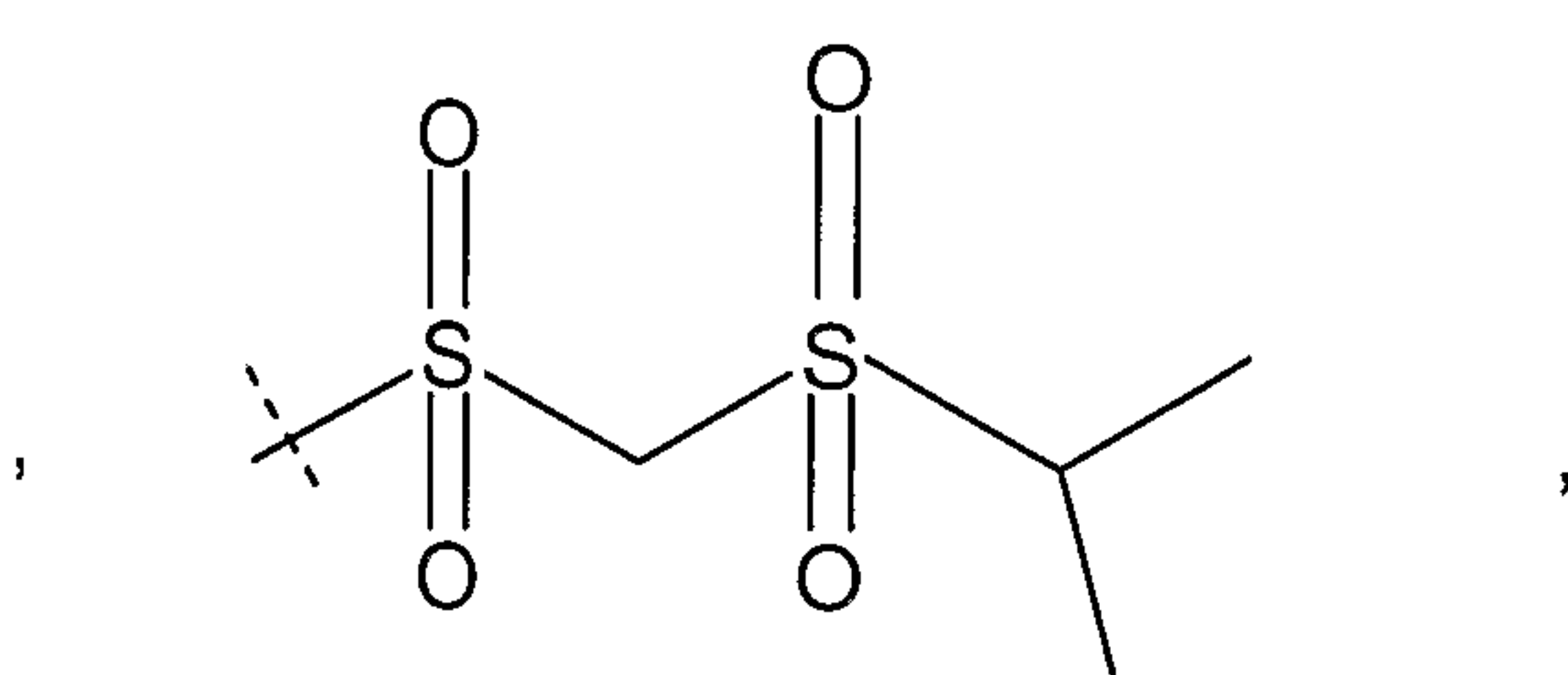
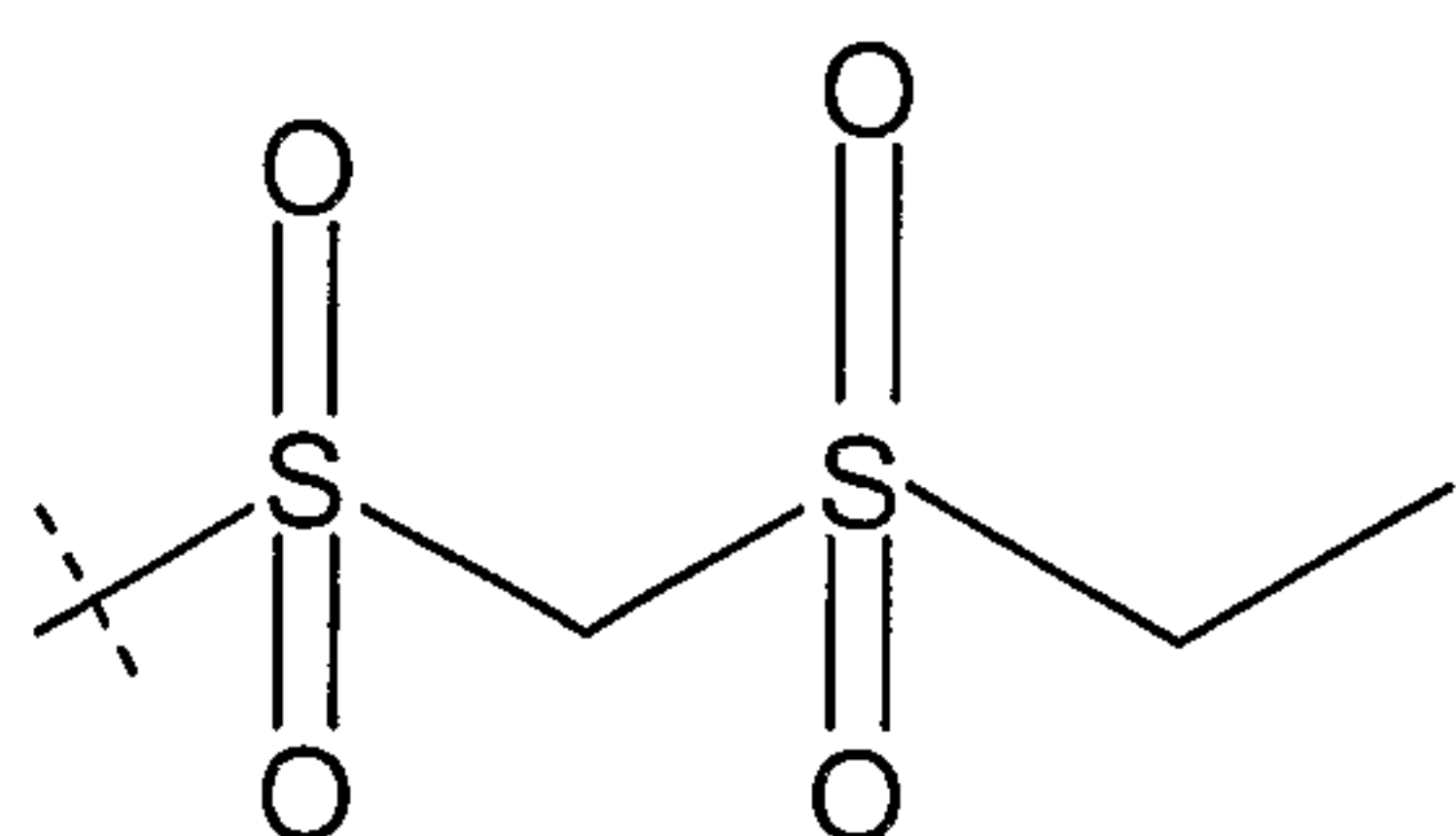
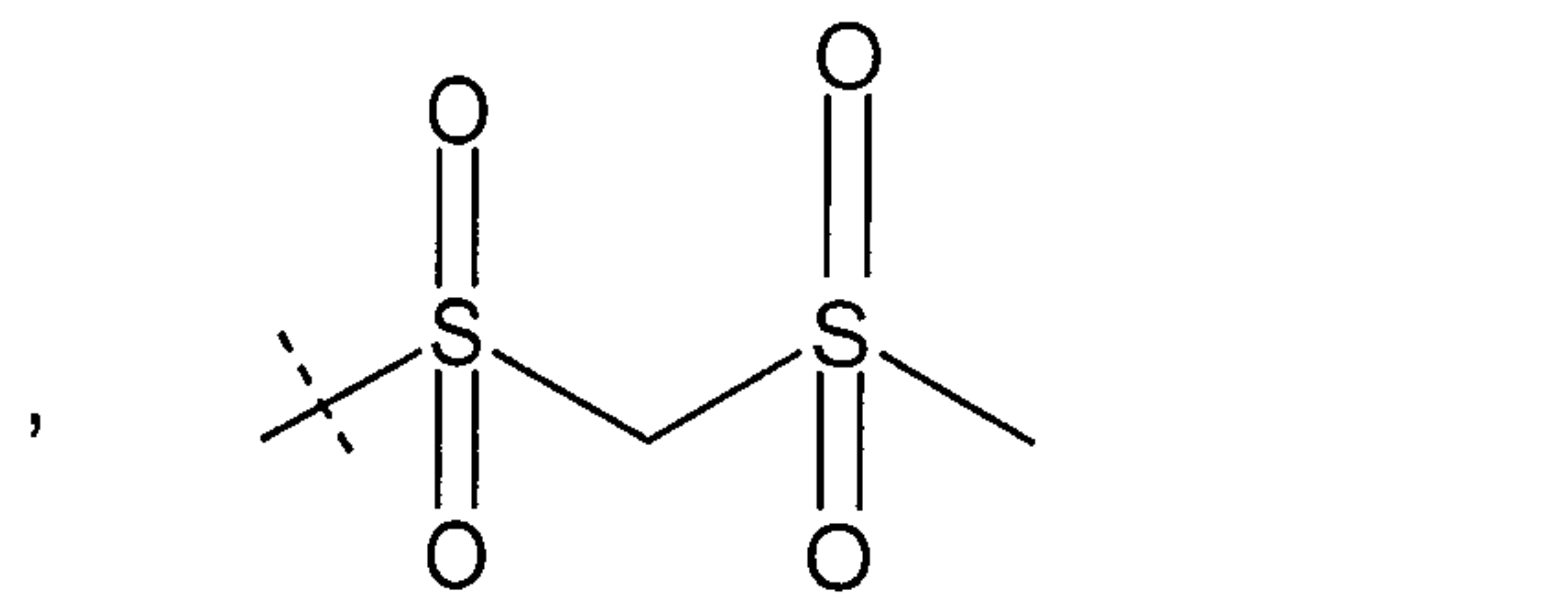
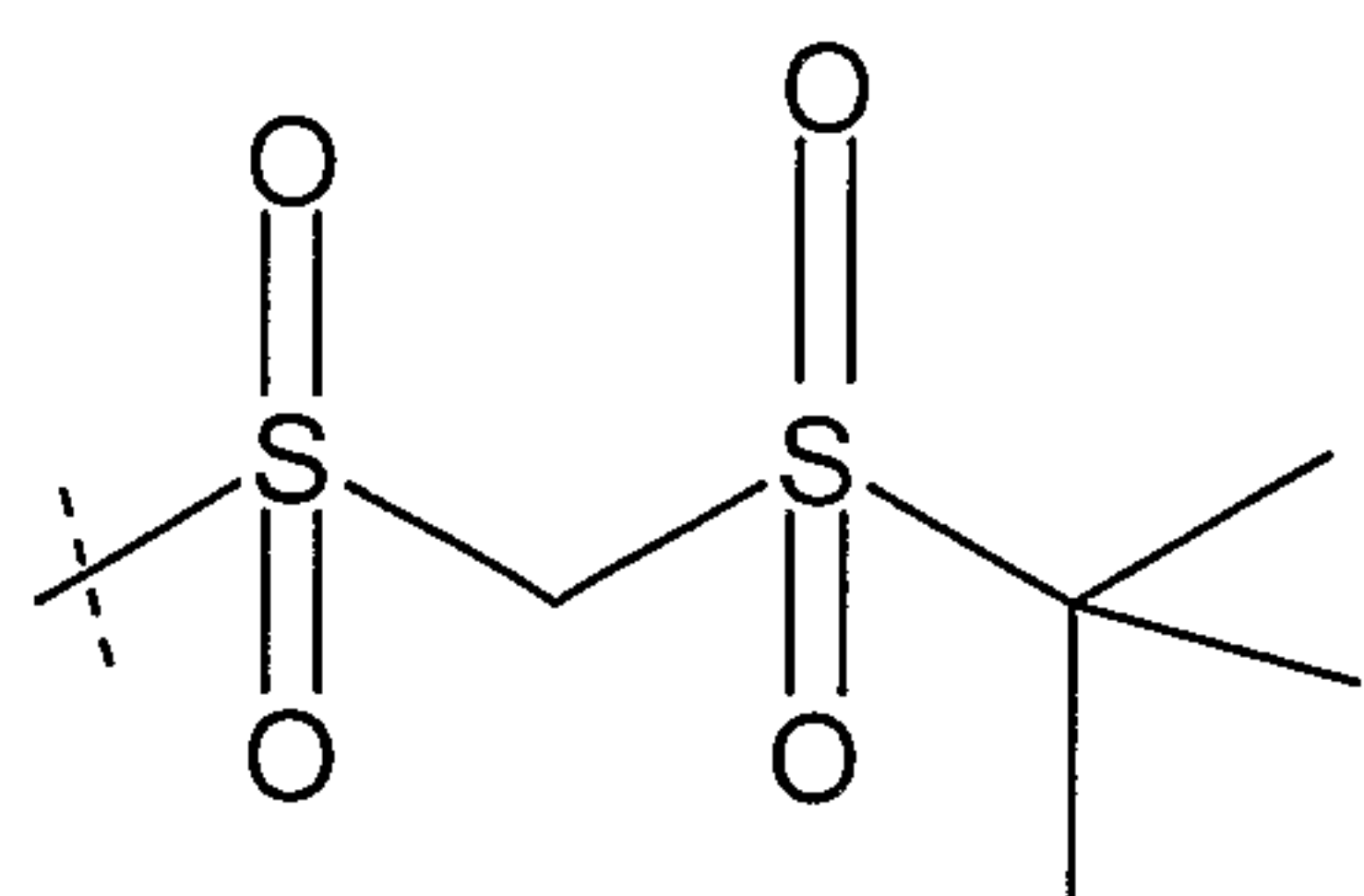
-49-



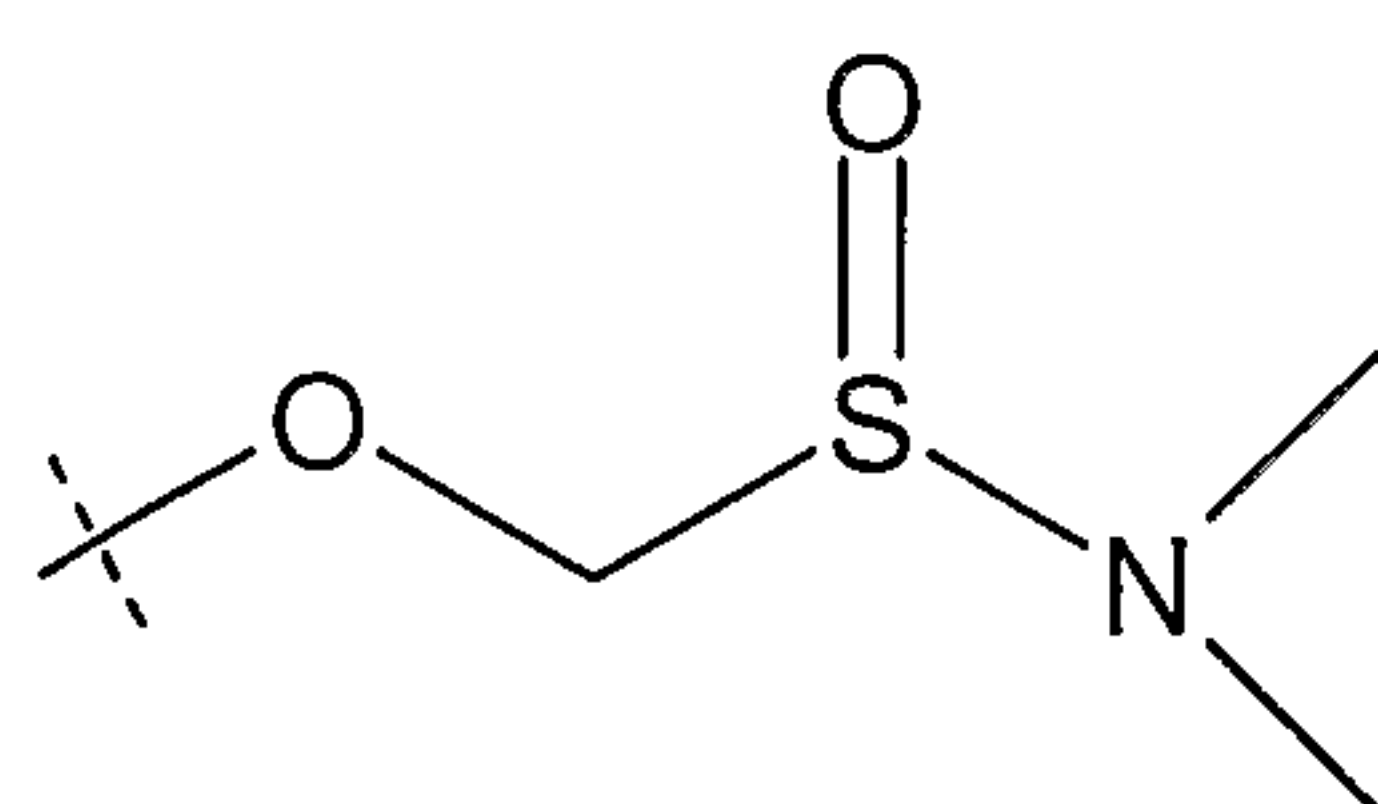
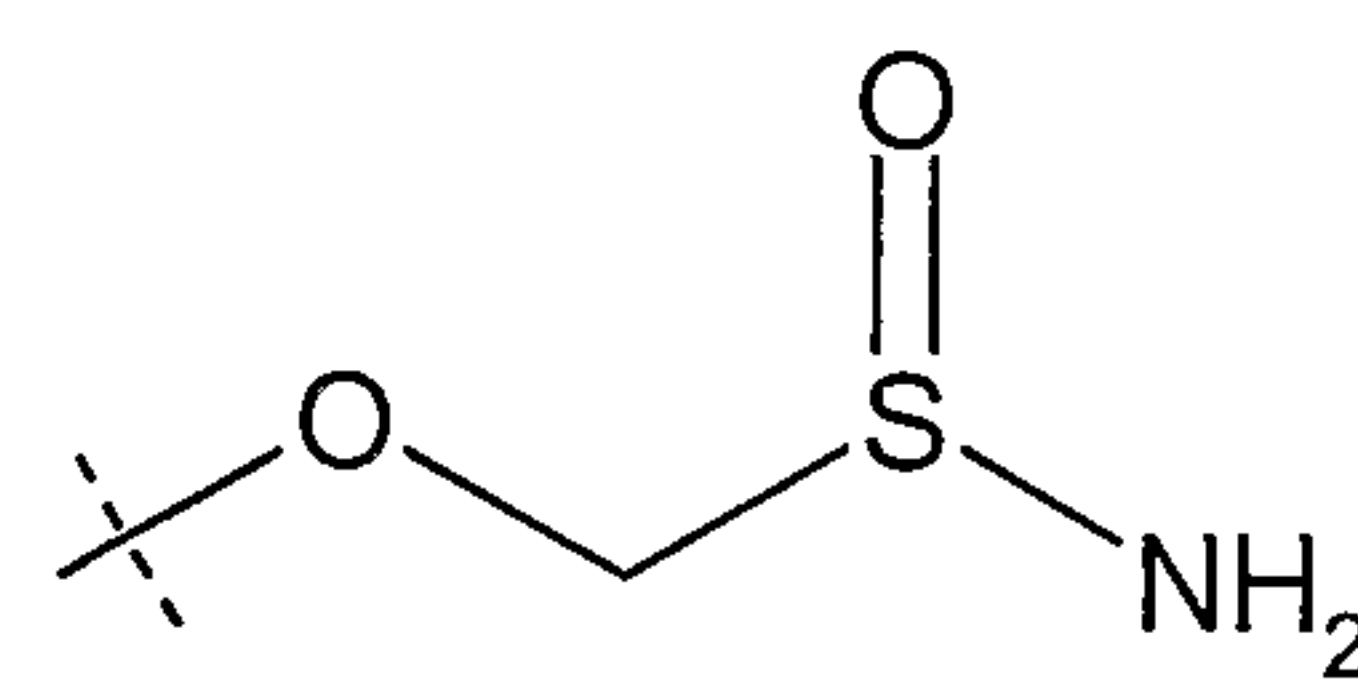
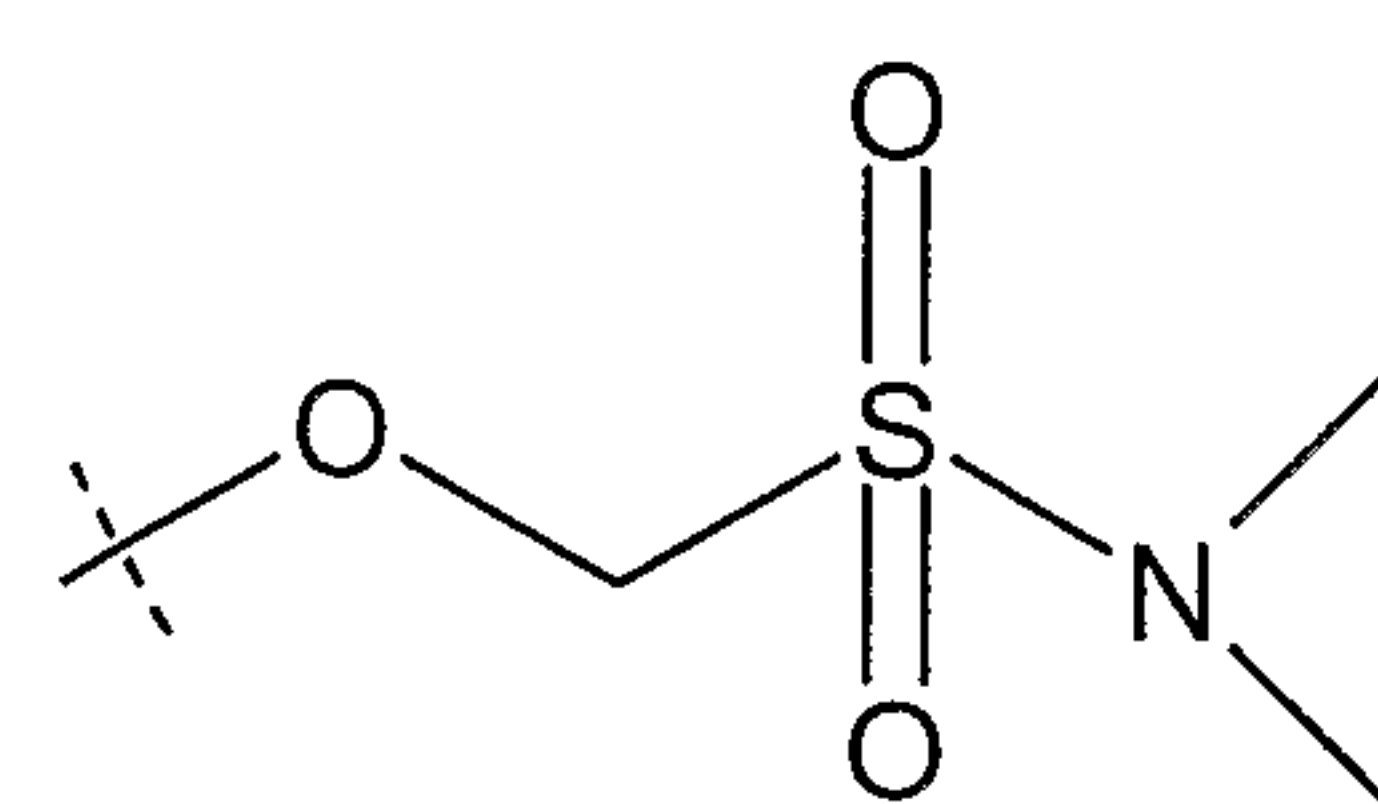
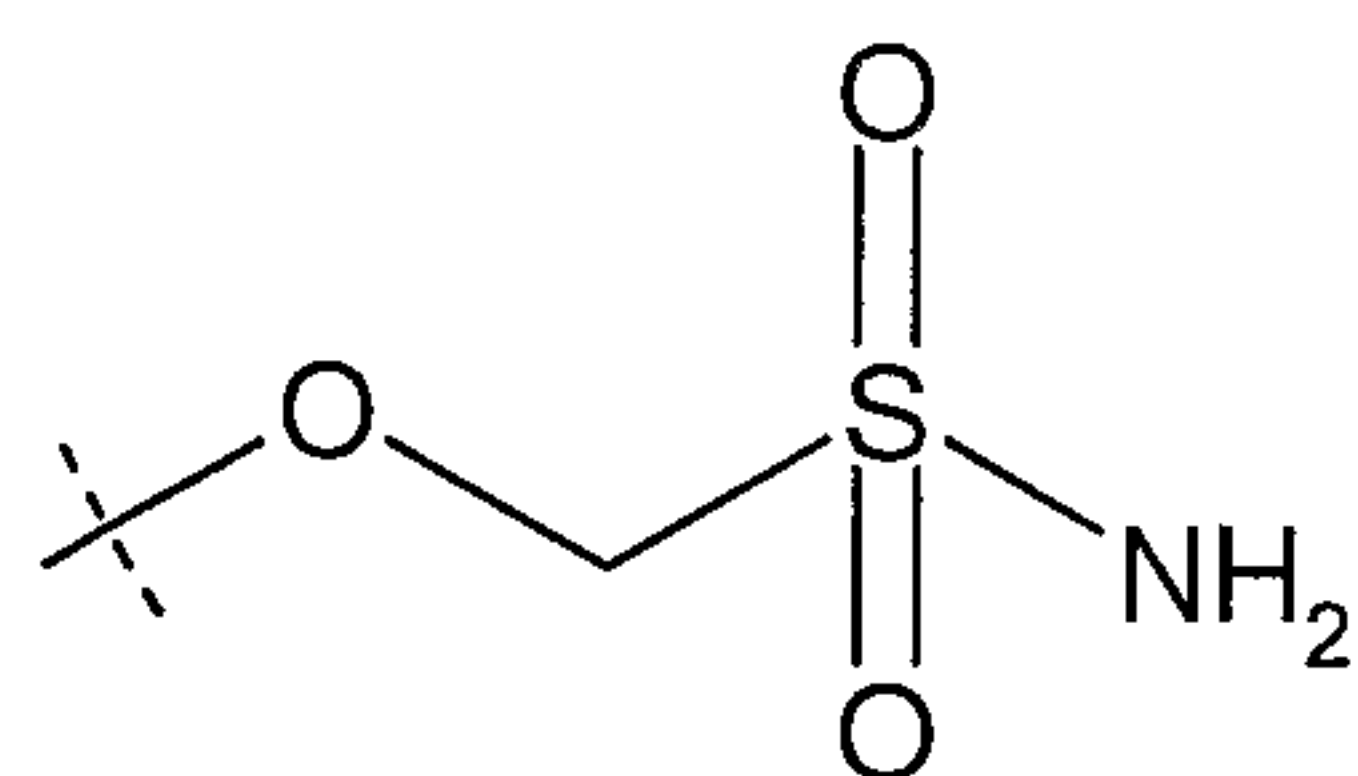
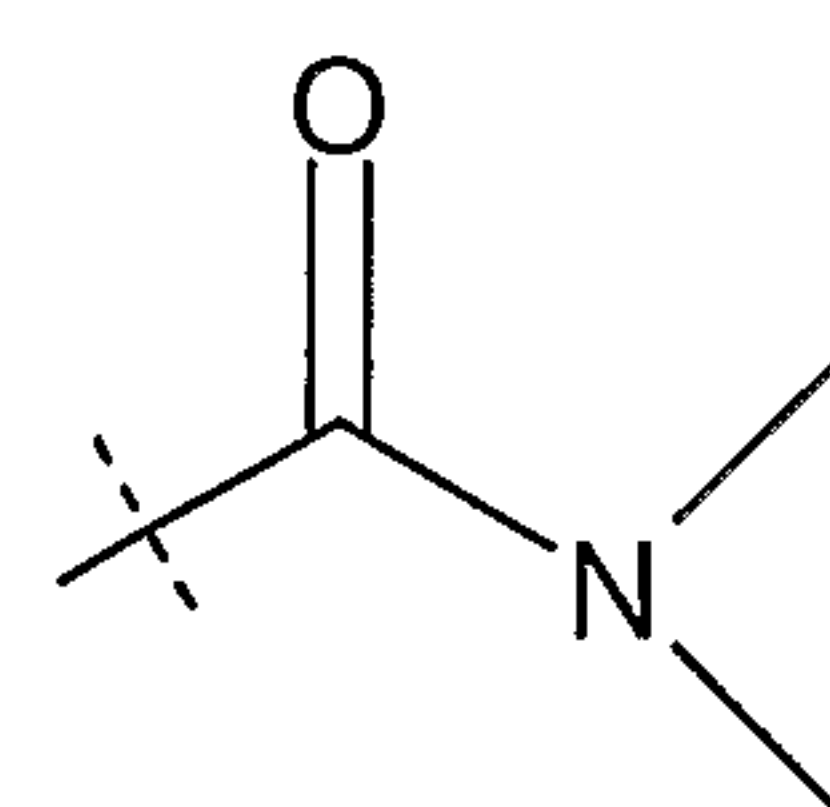
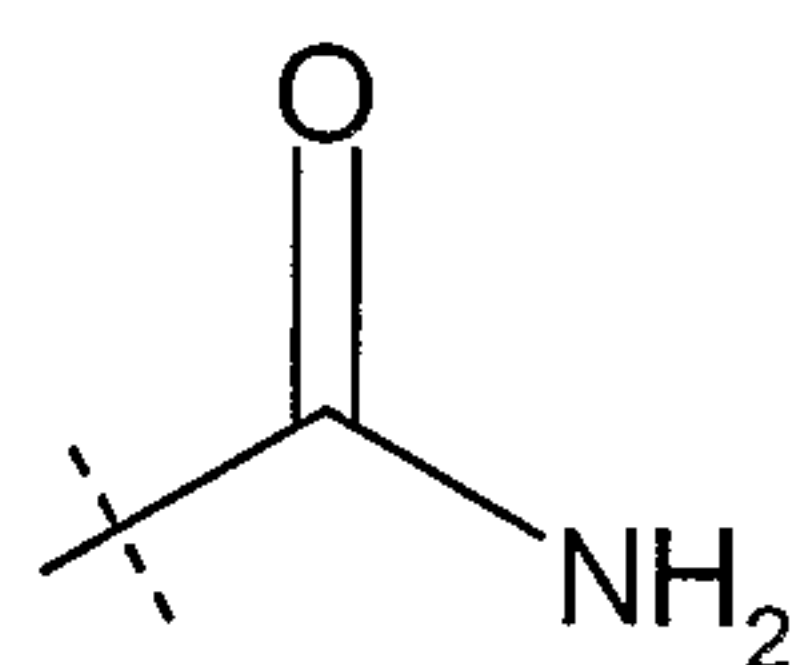
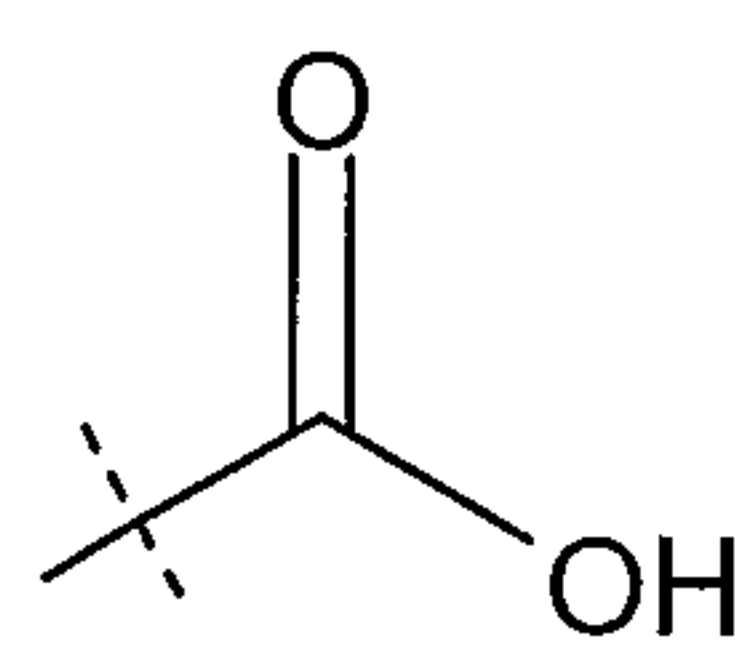
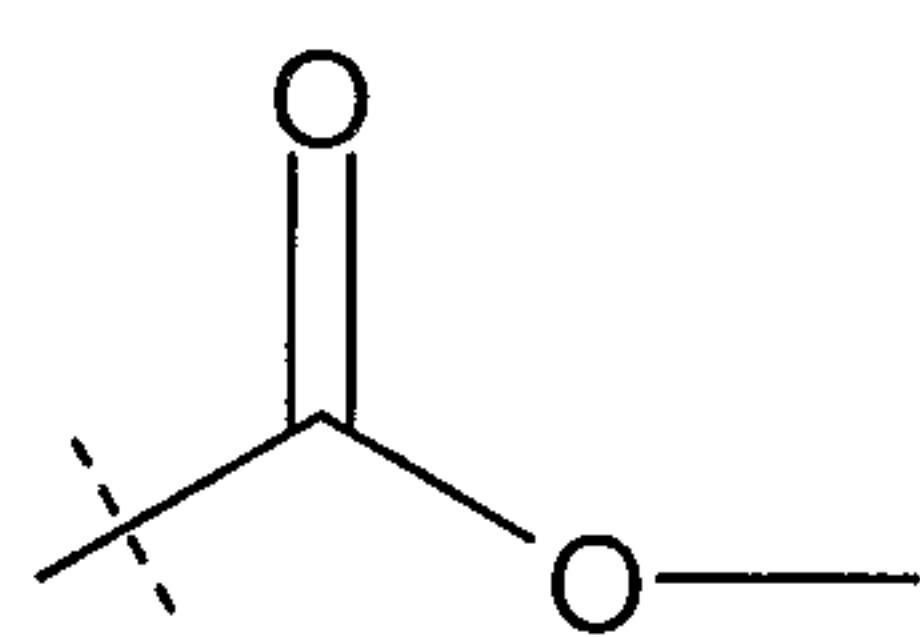
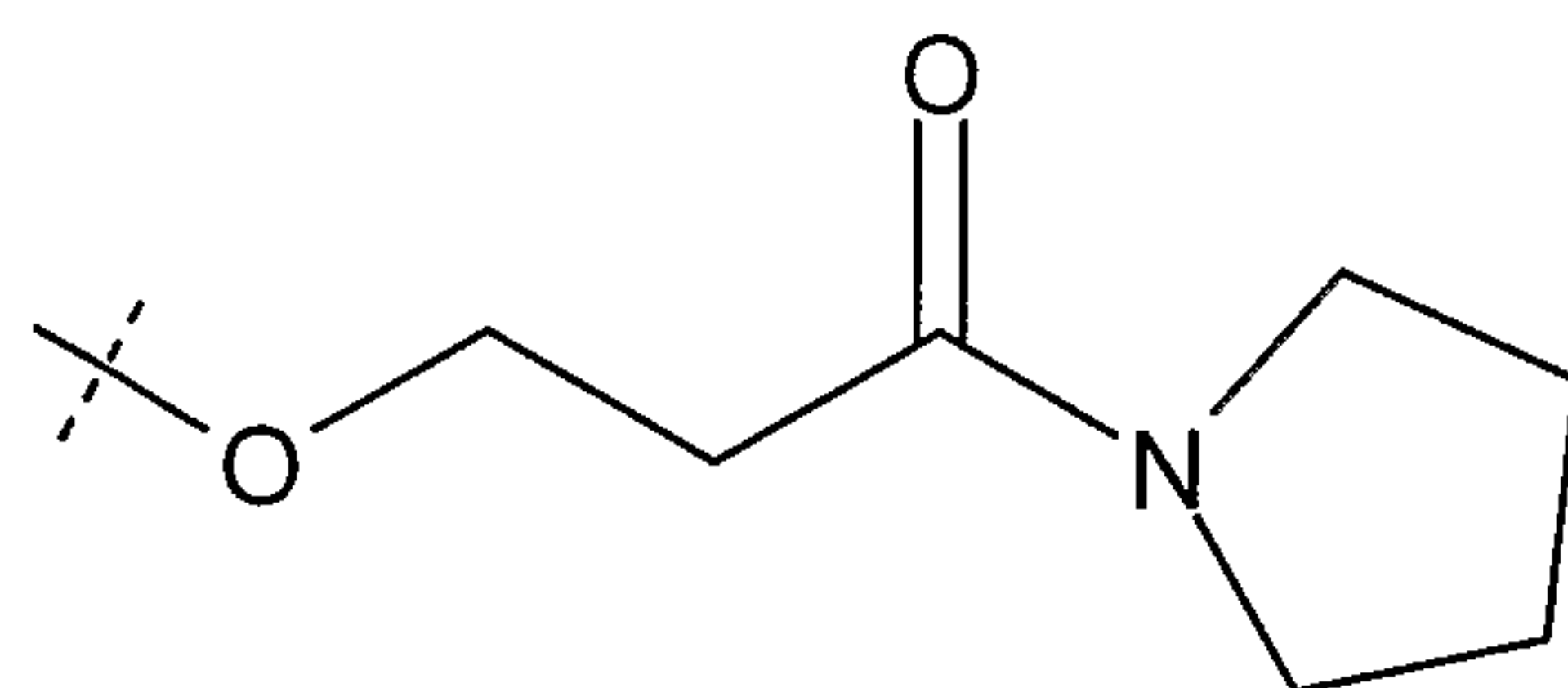
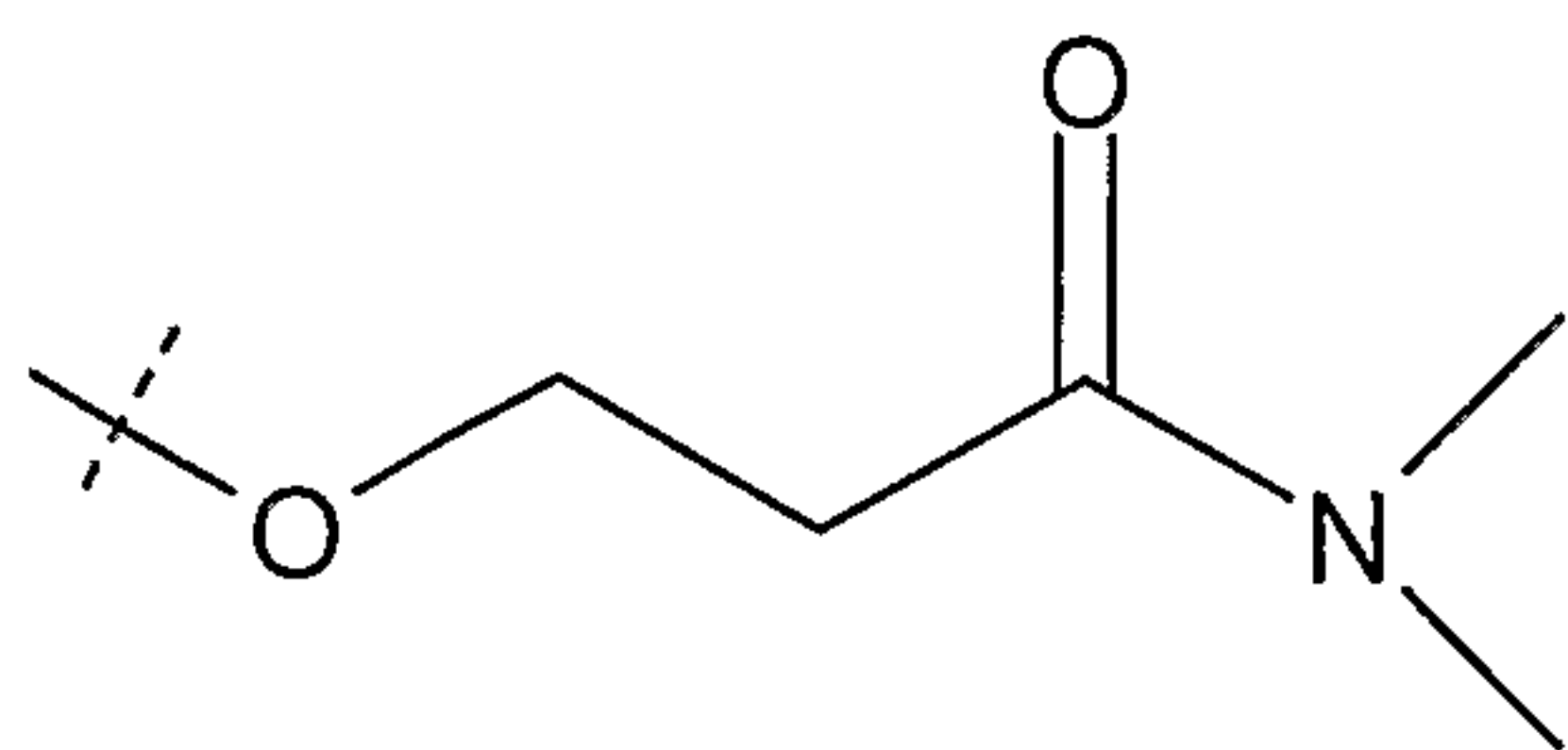
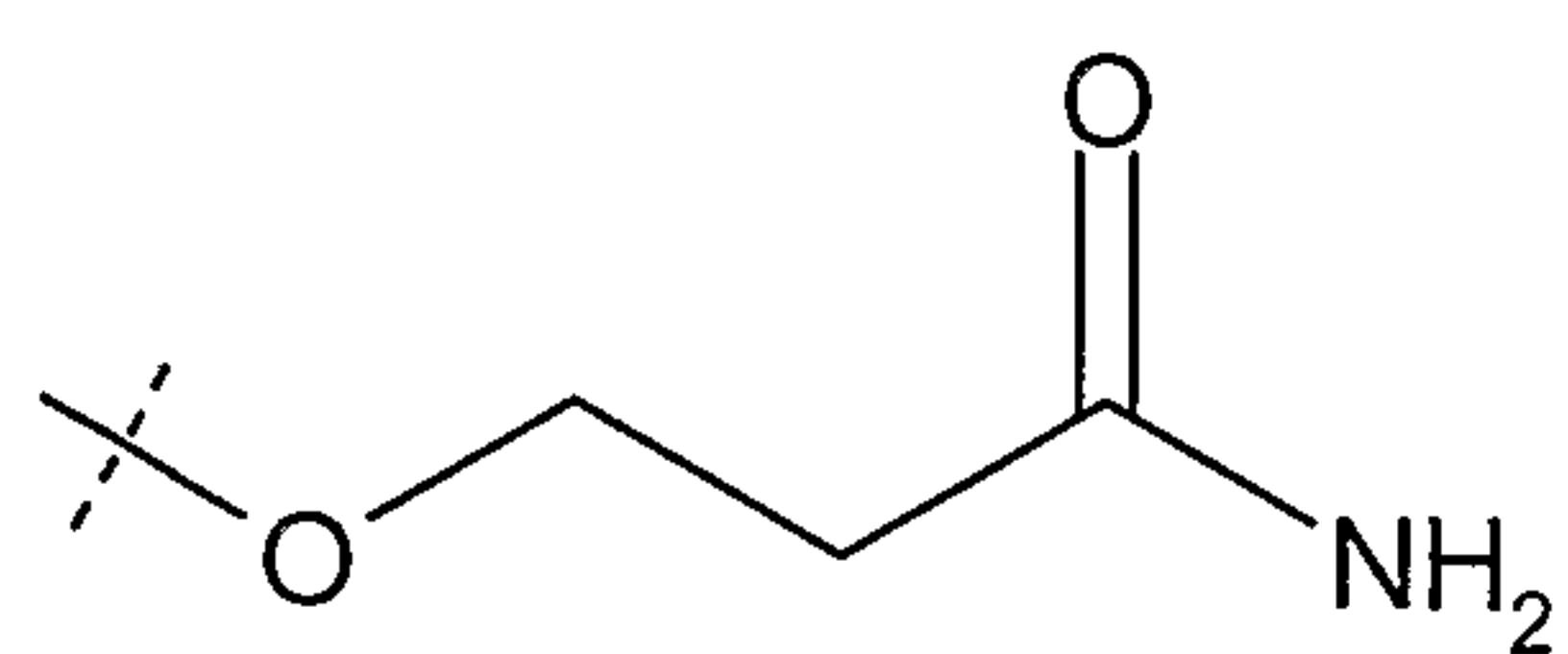
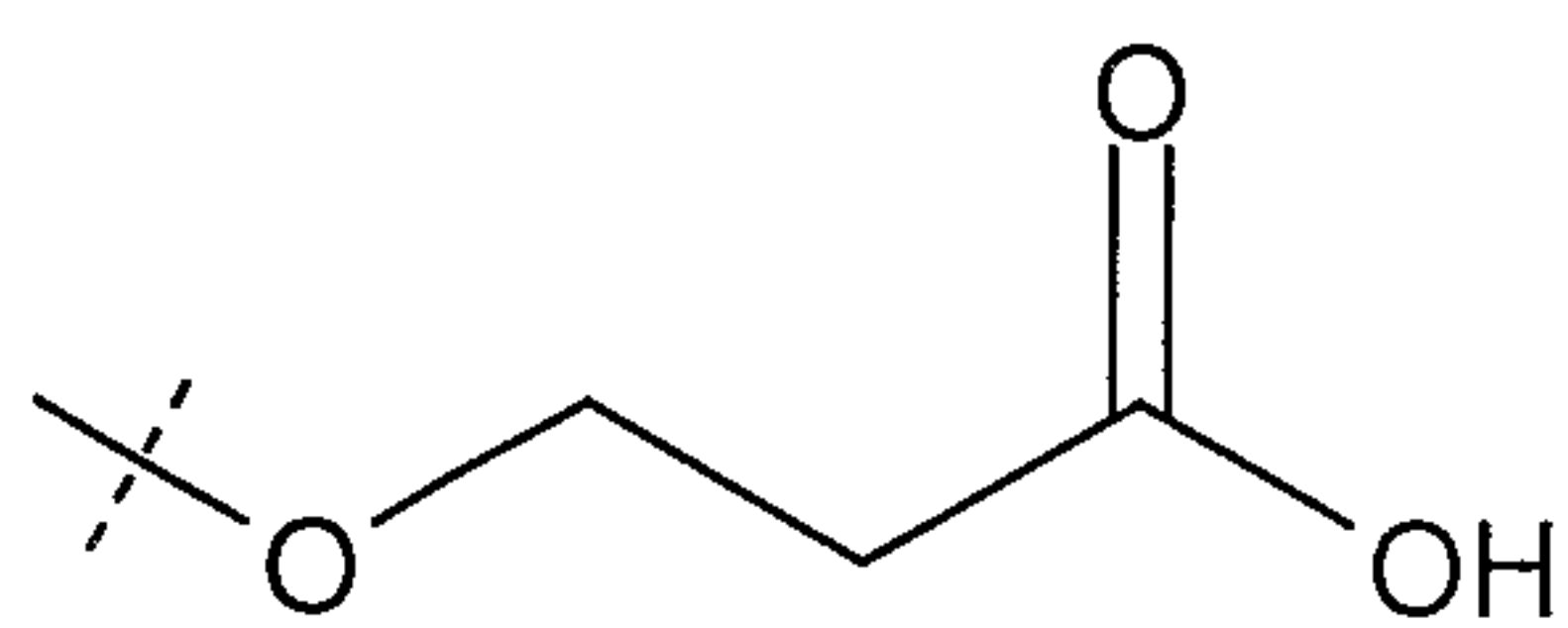
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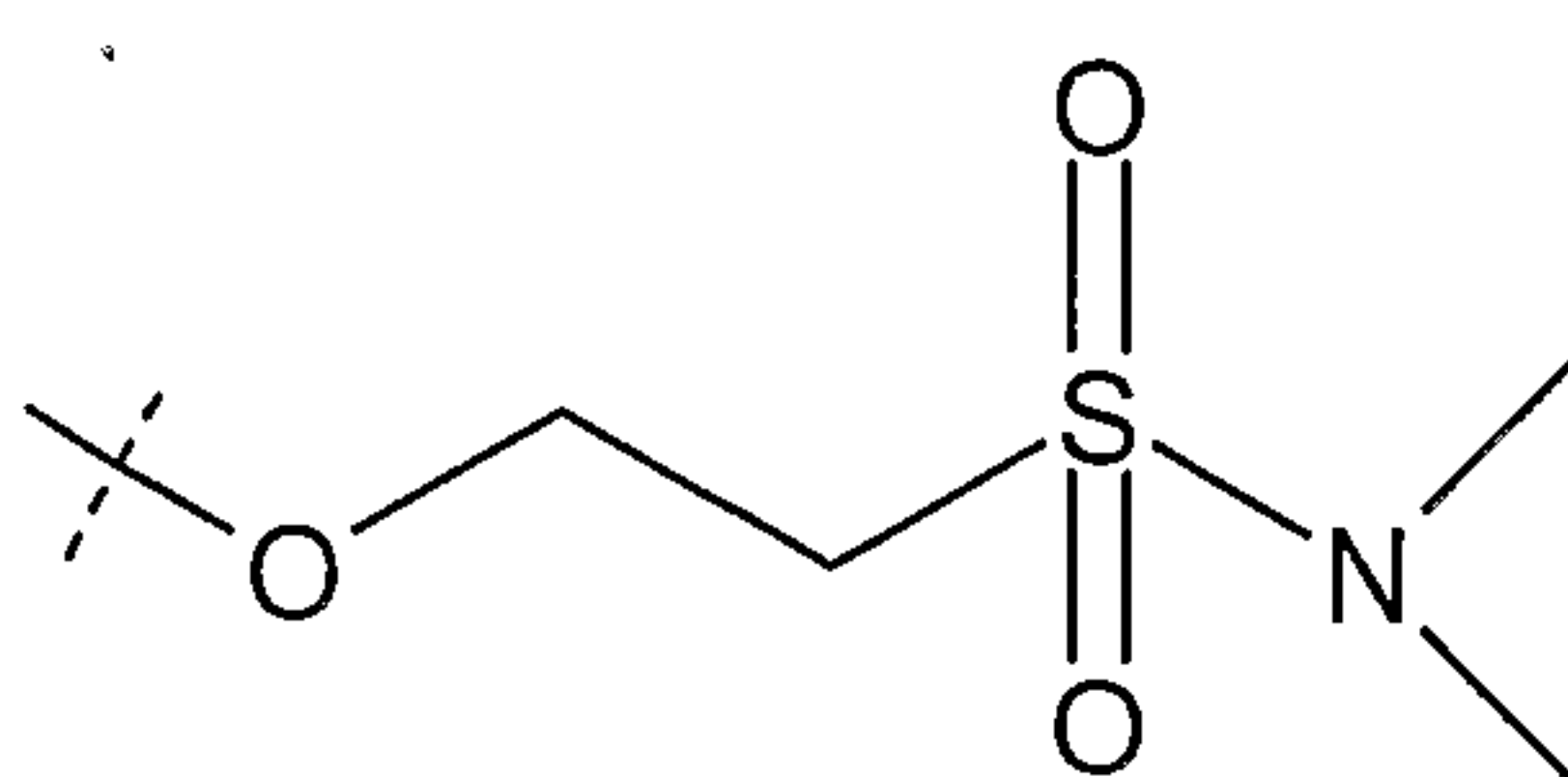
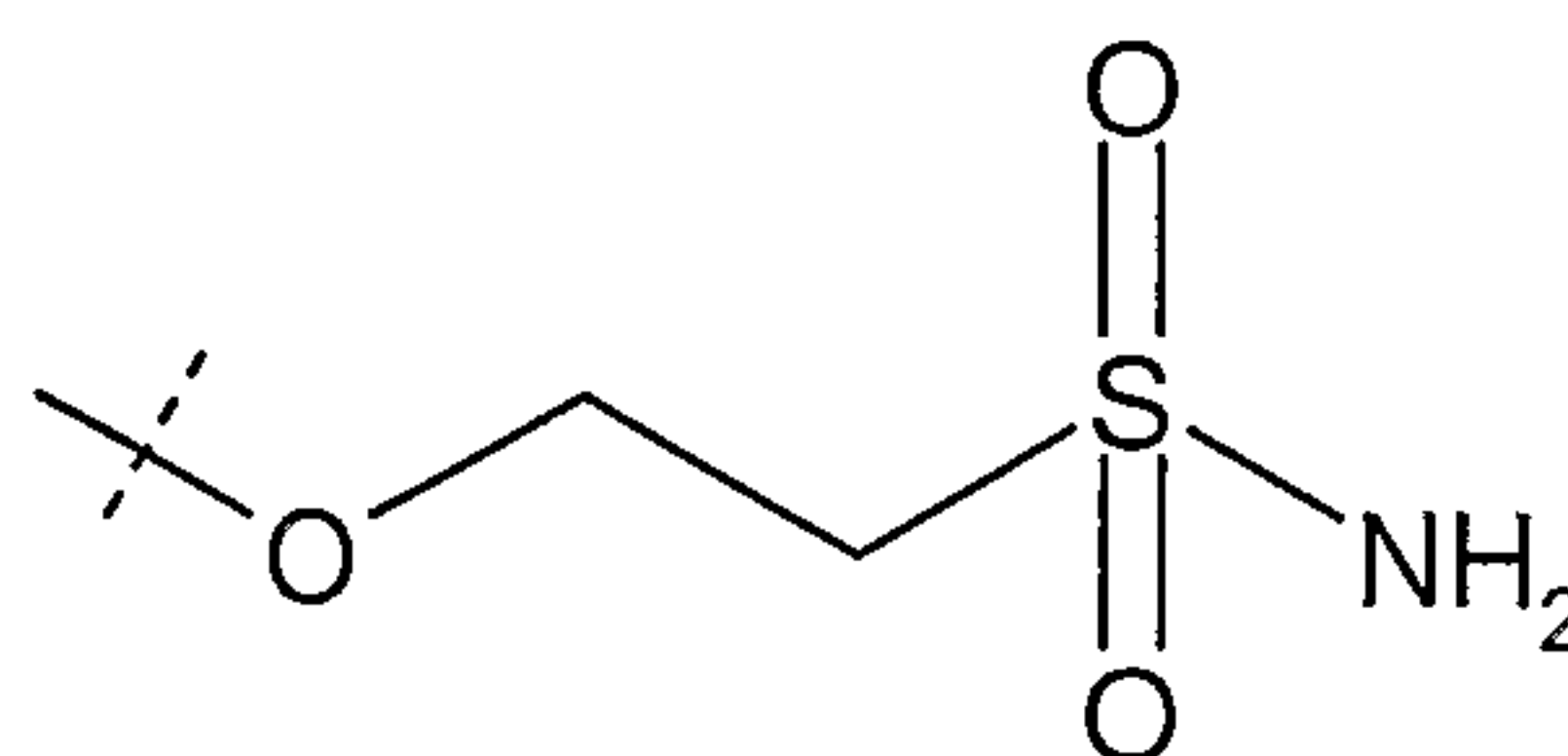
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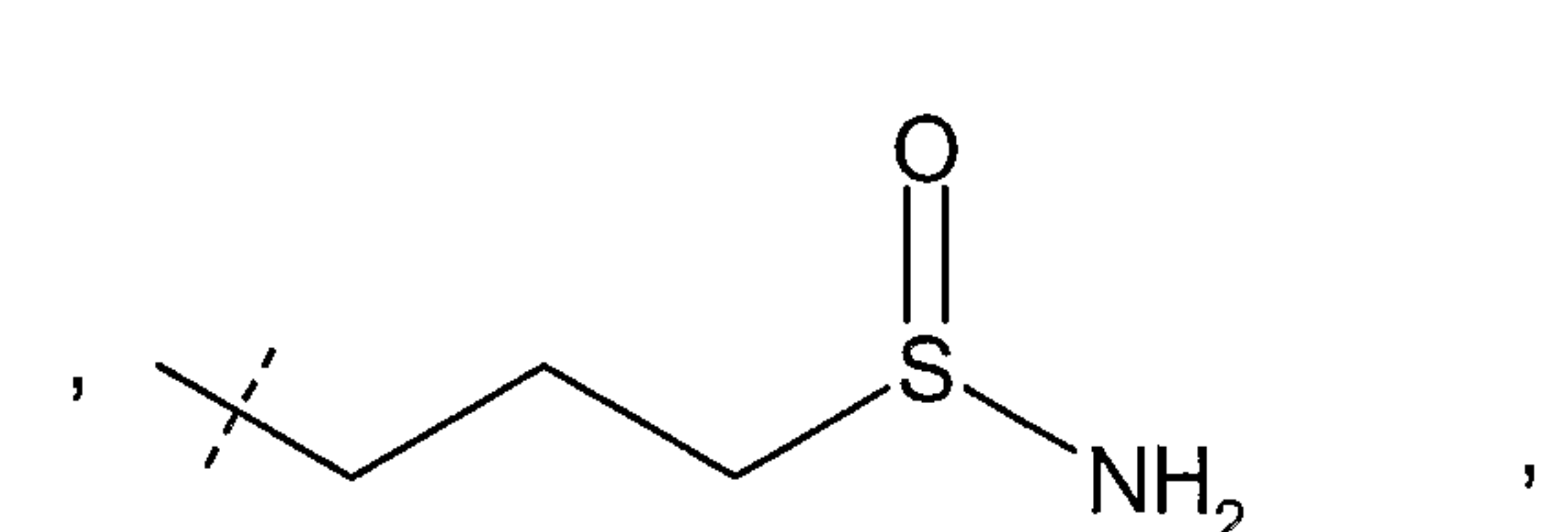
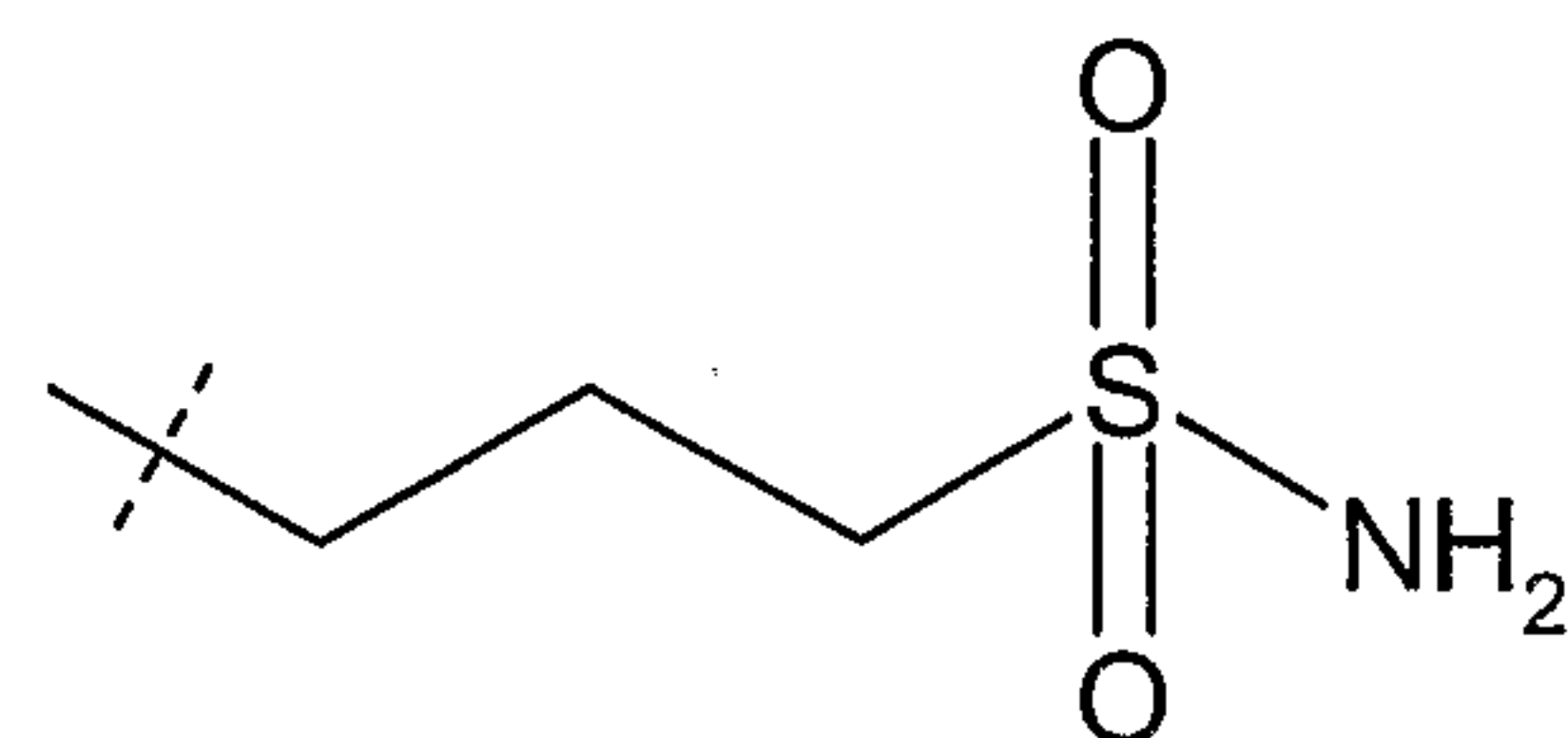
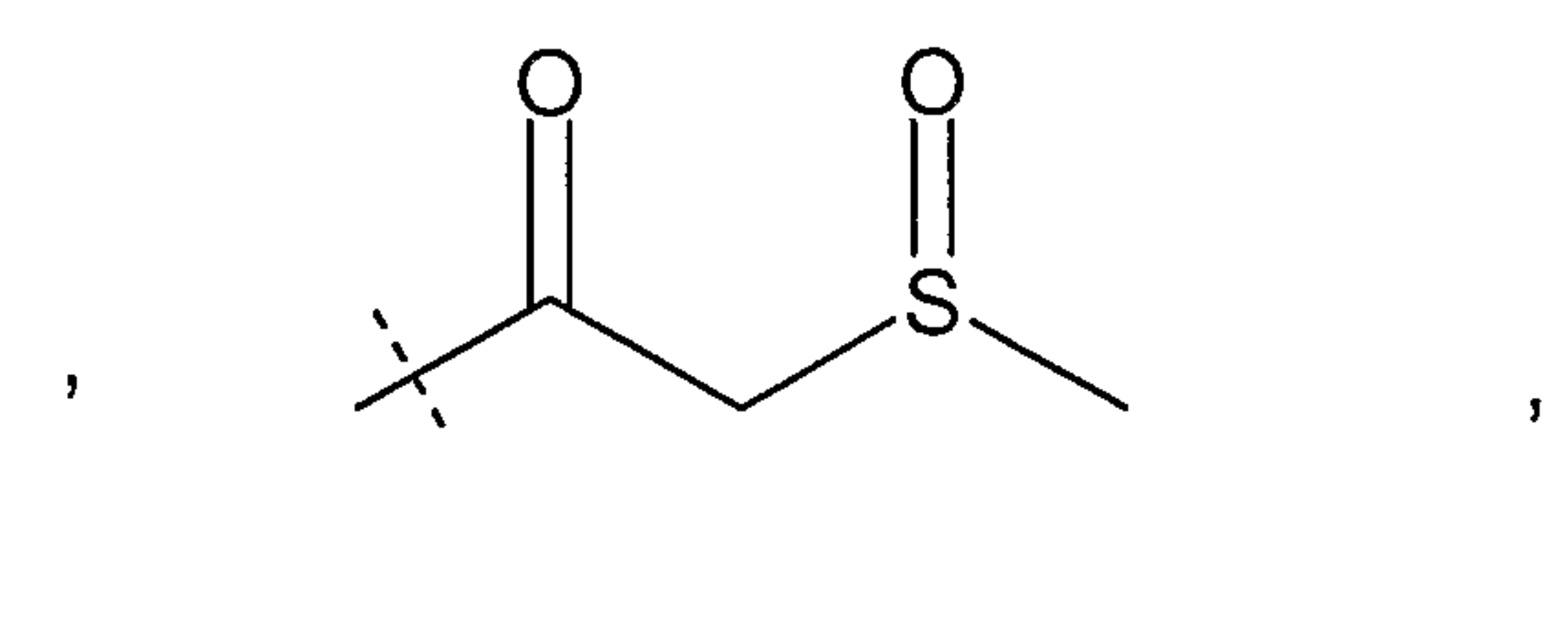
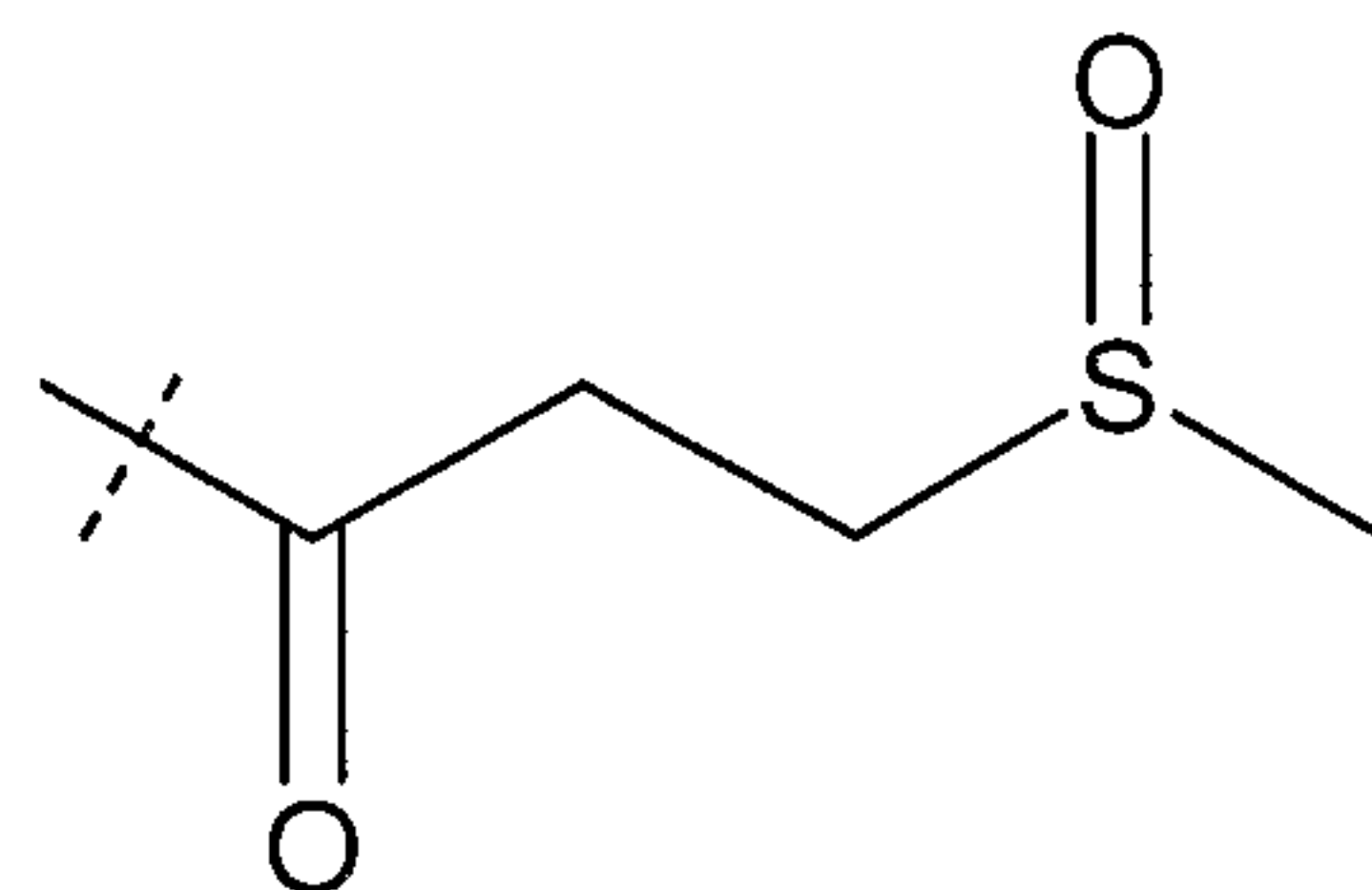
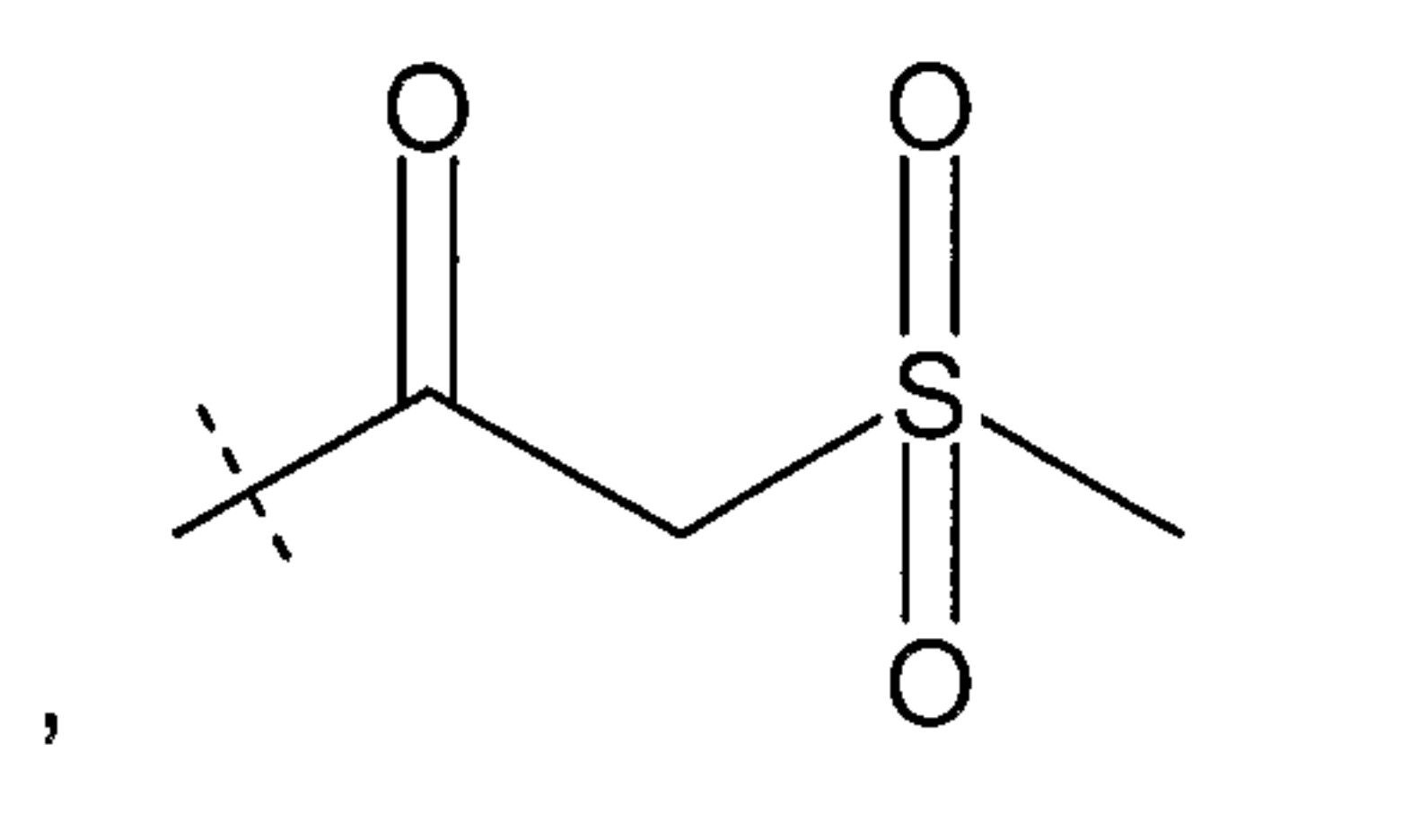
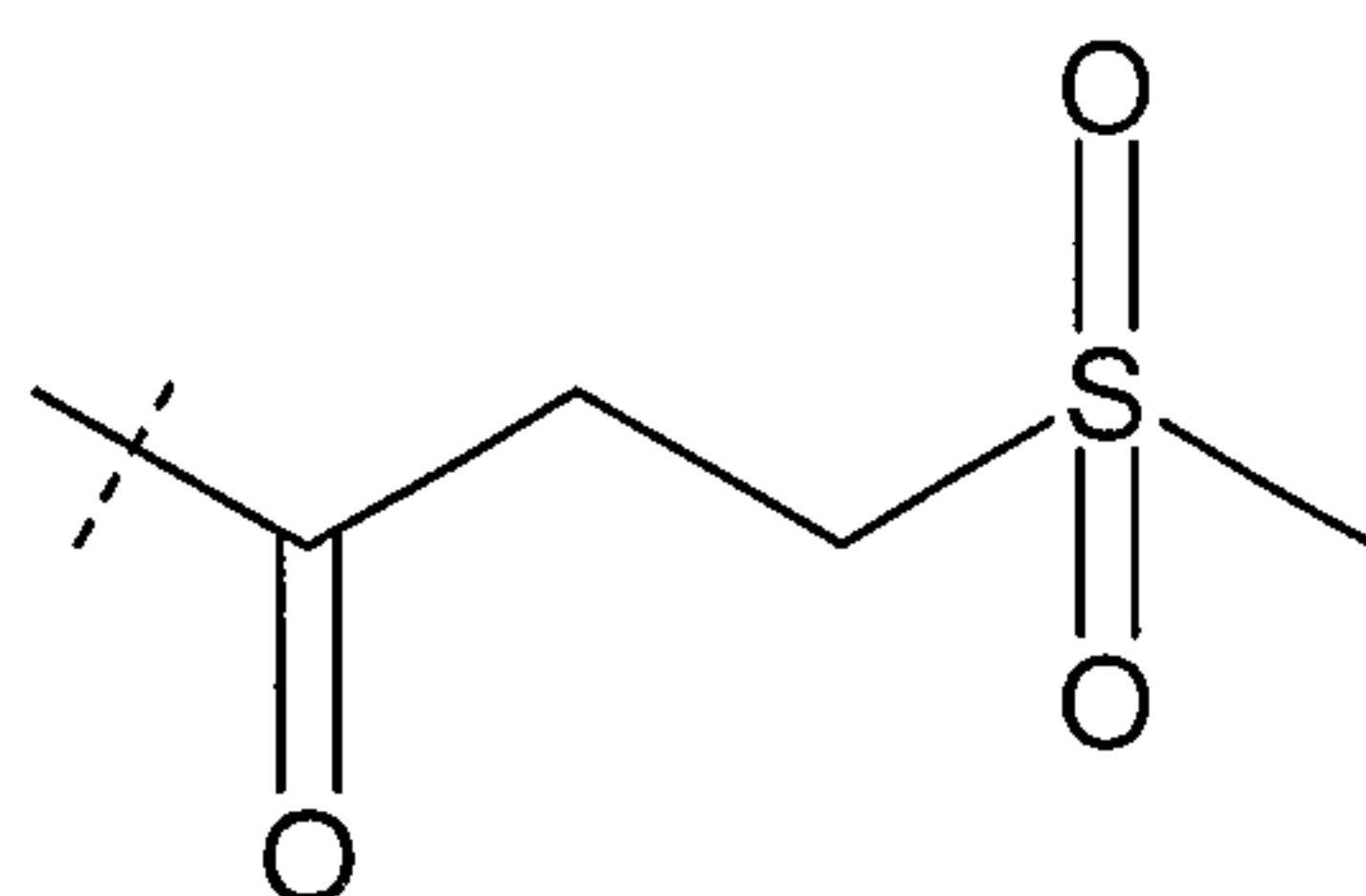
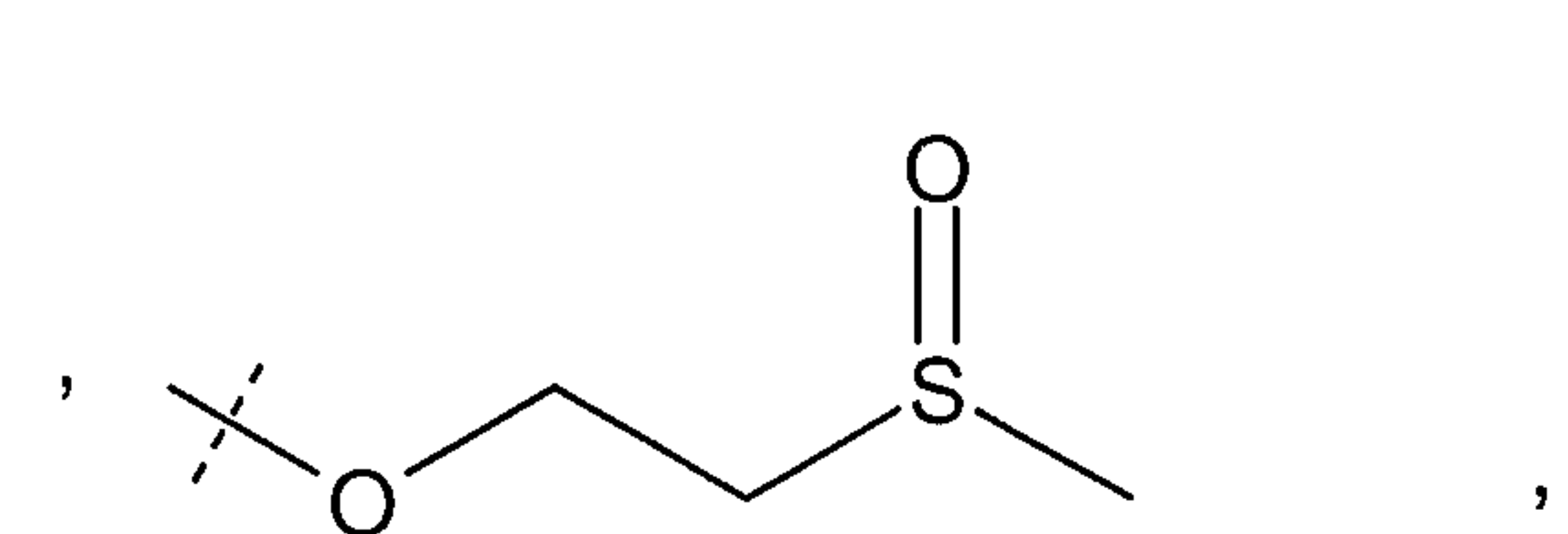
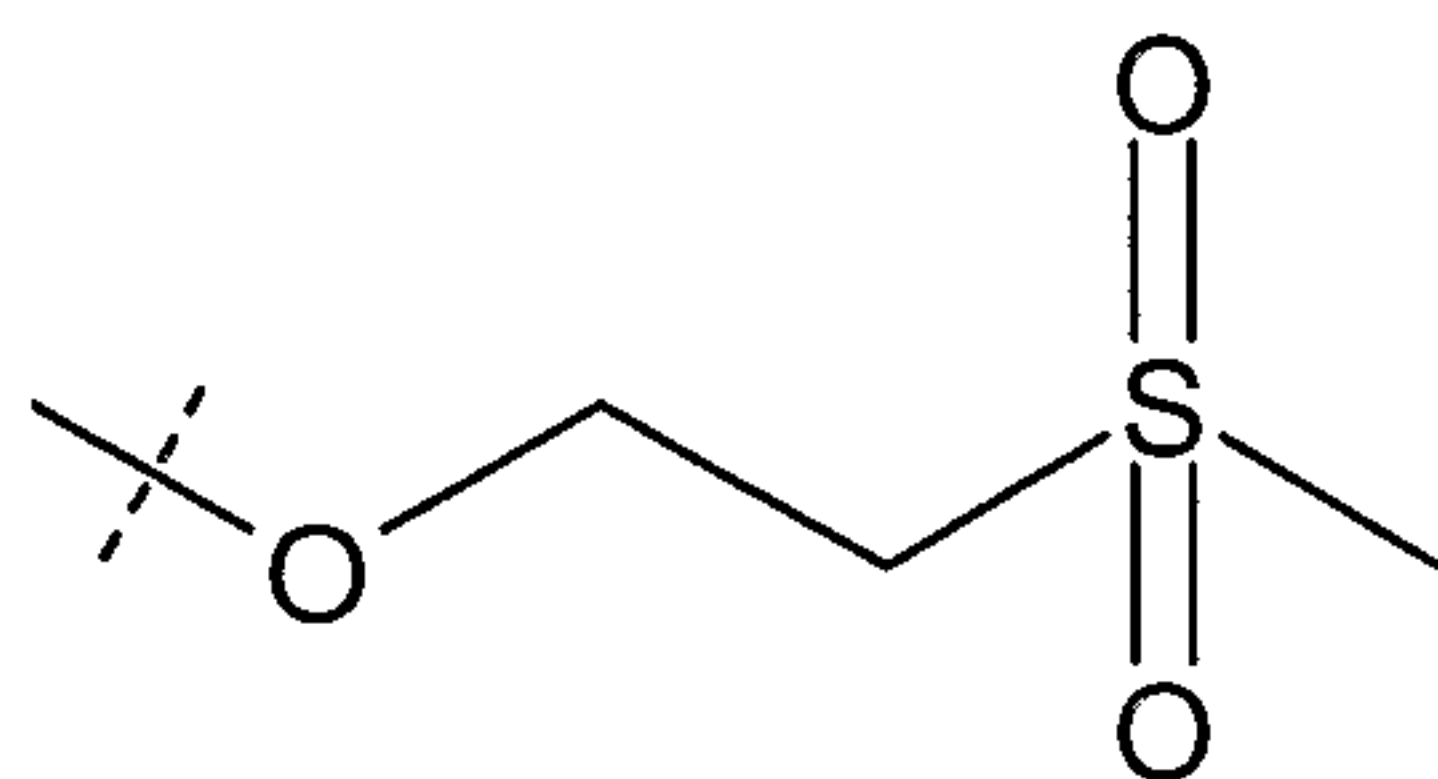
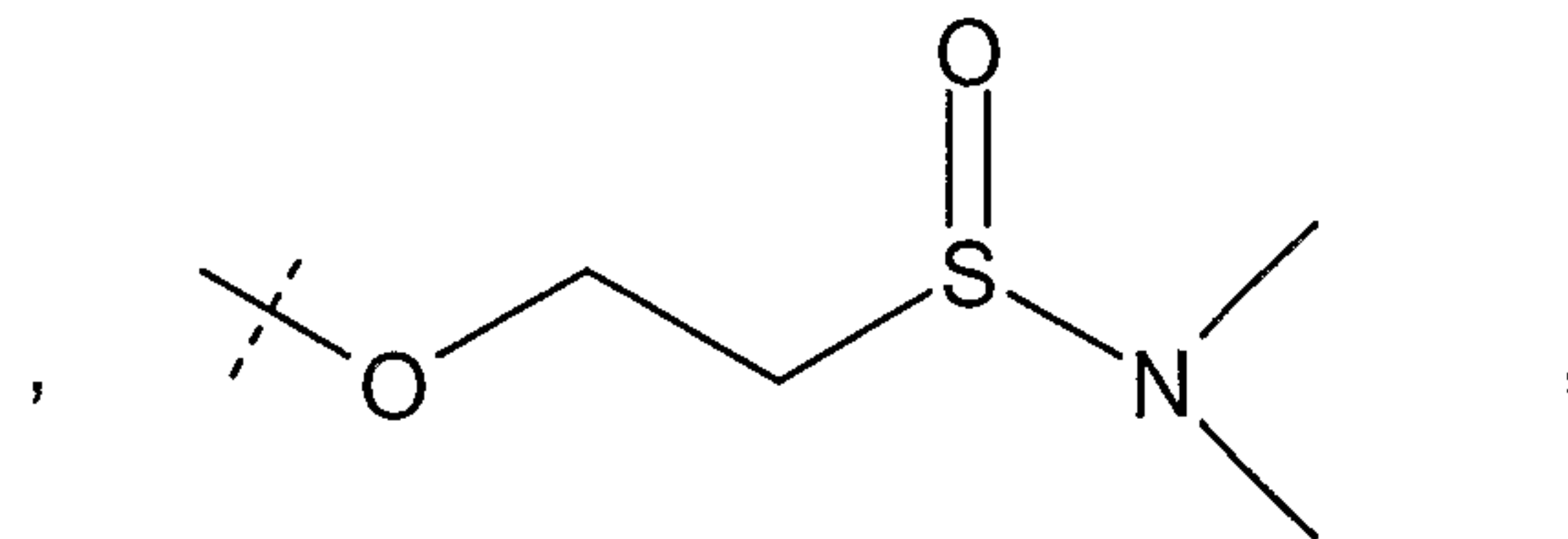
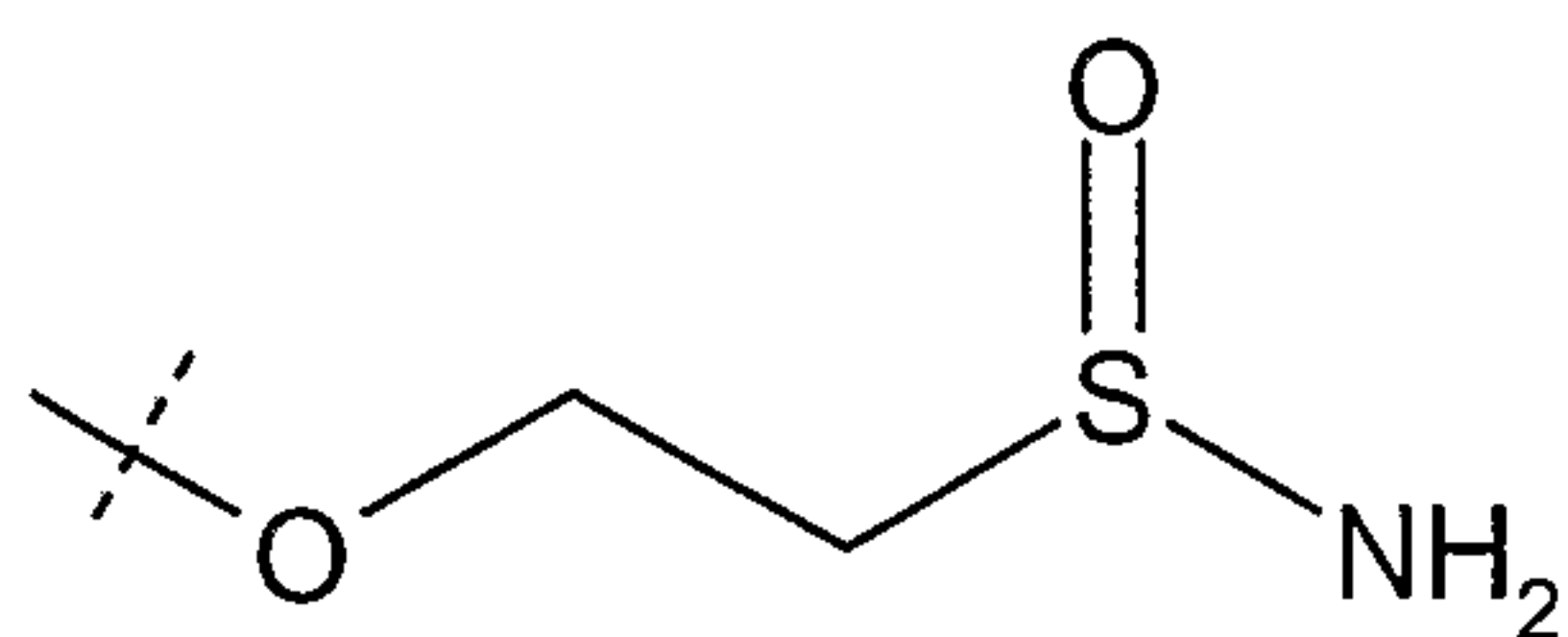
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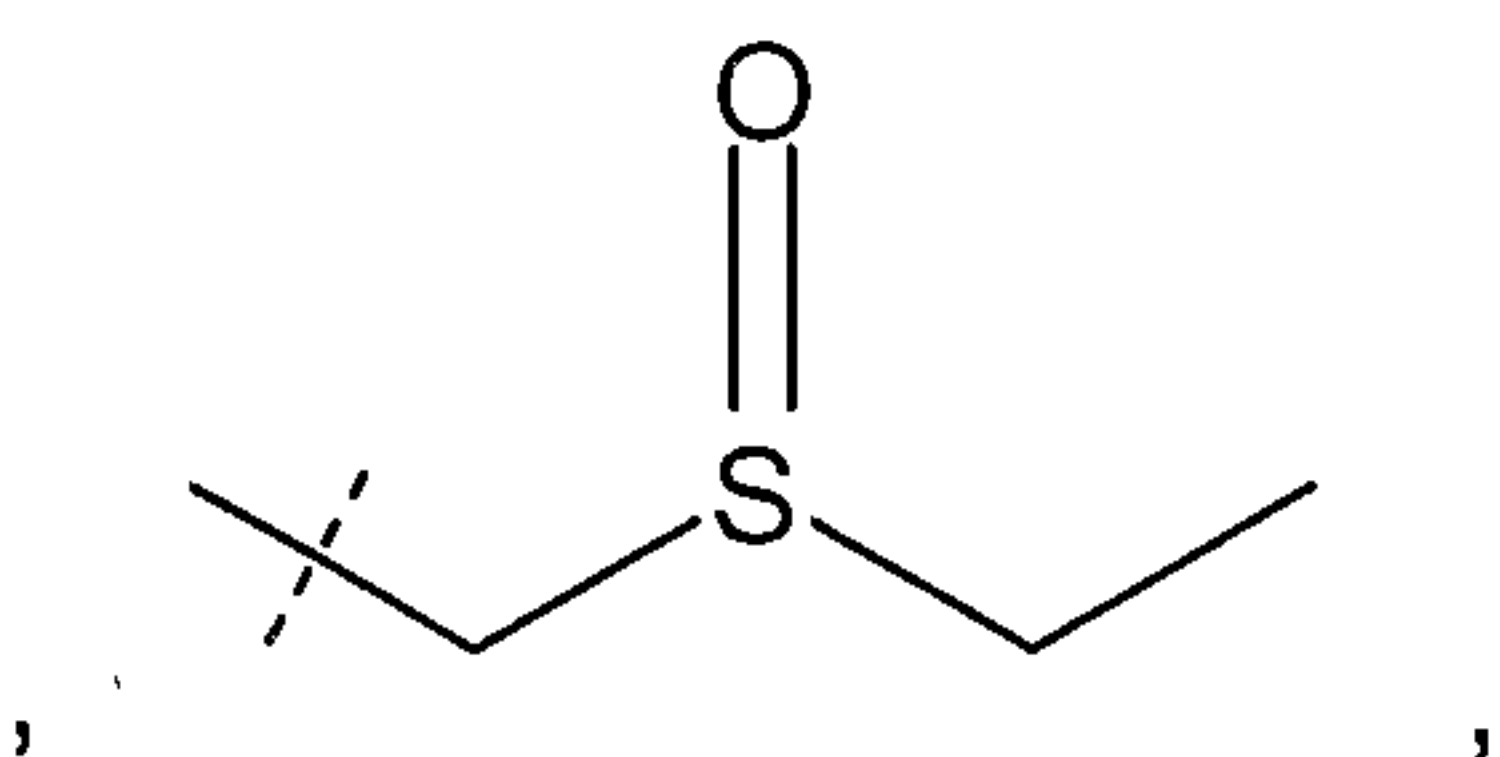
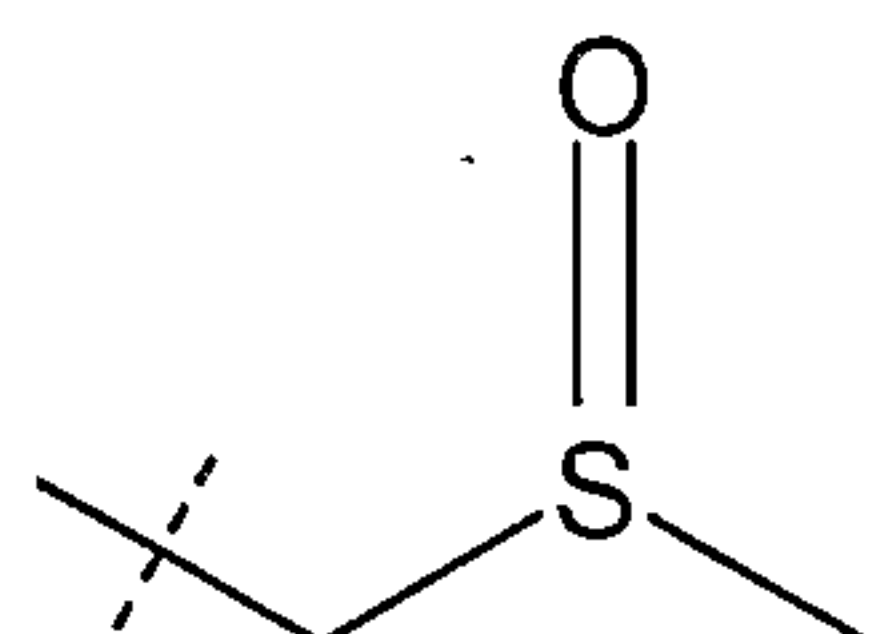
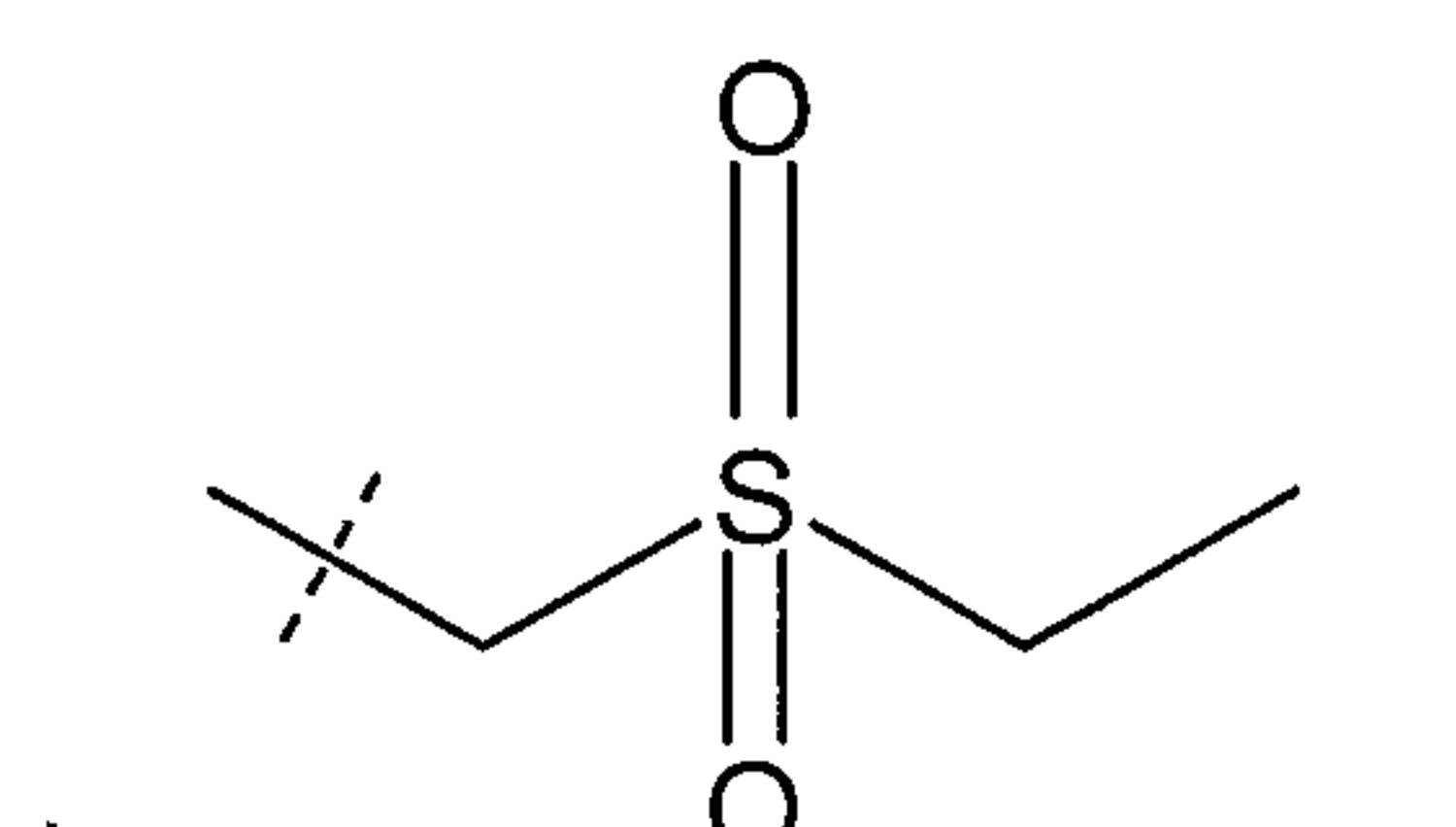
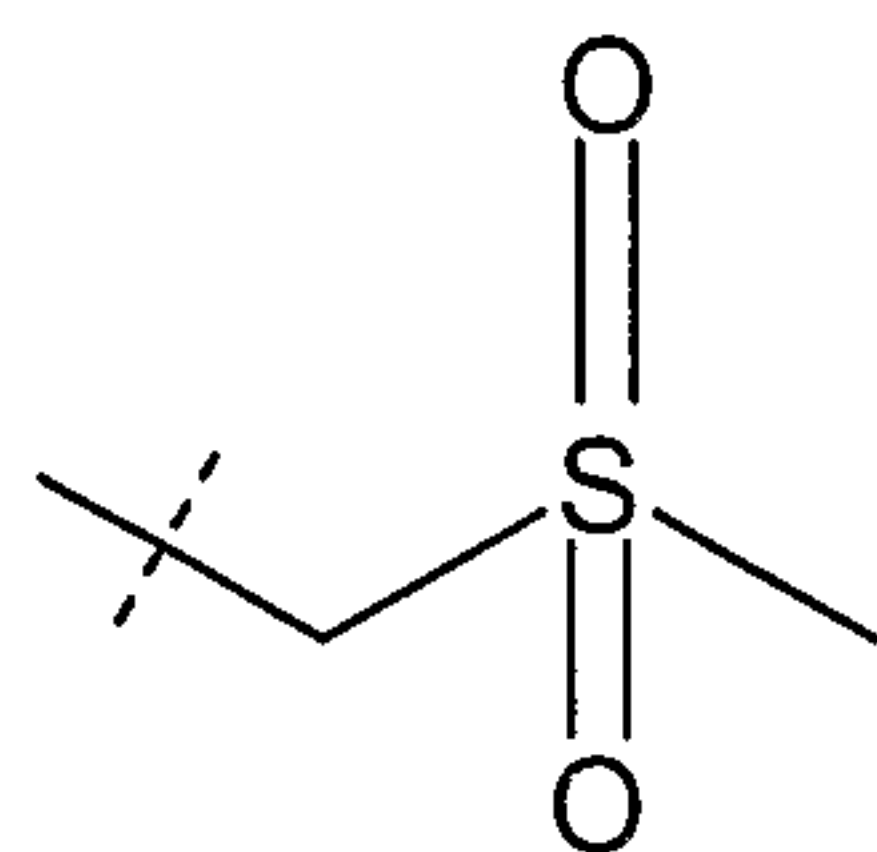
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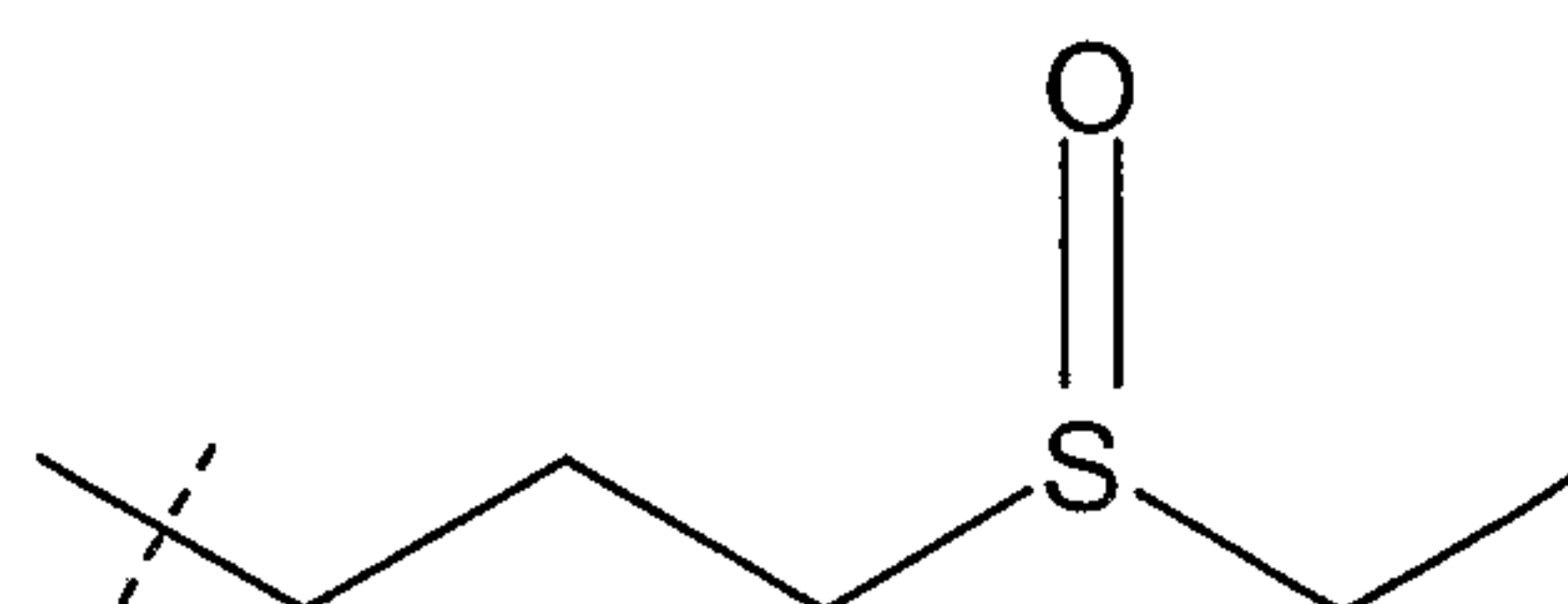
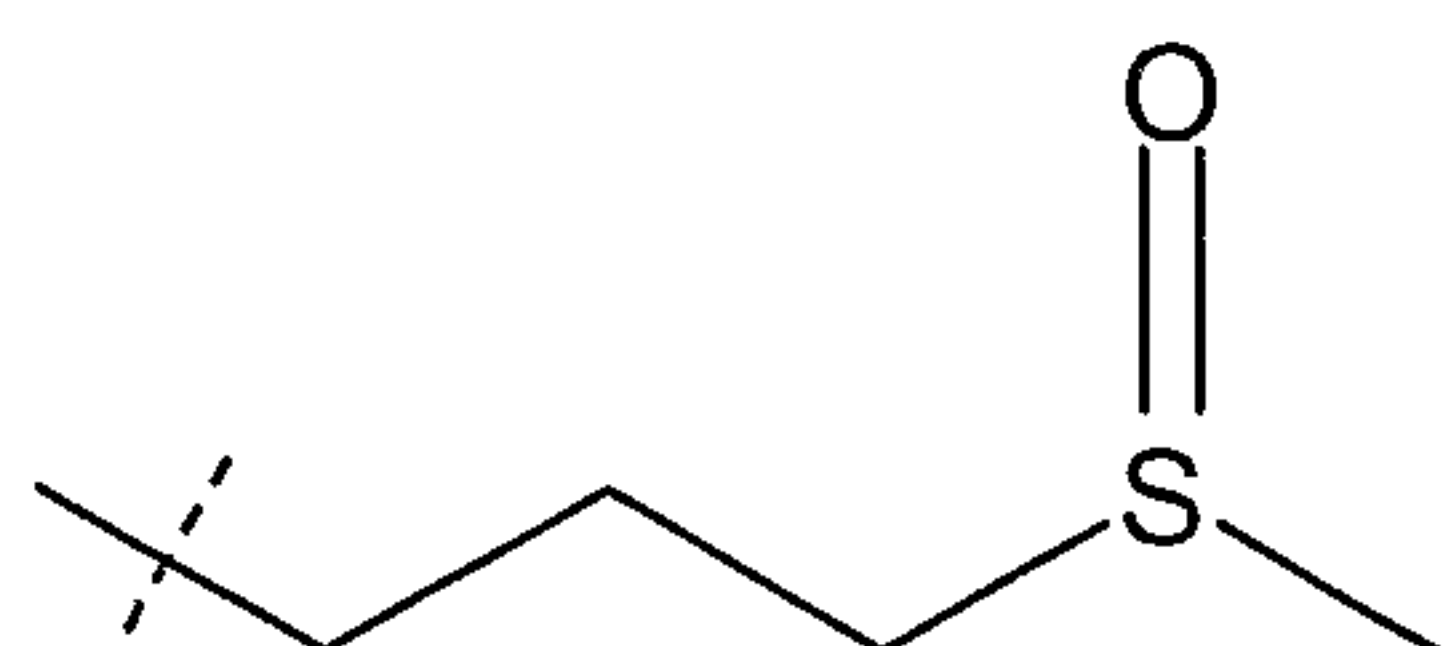
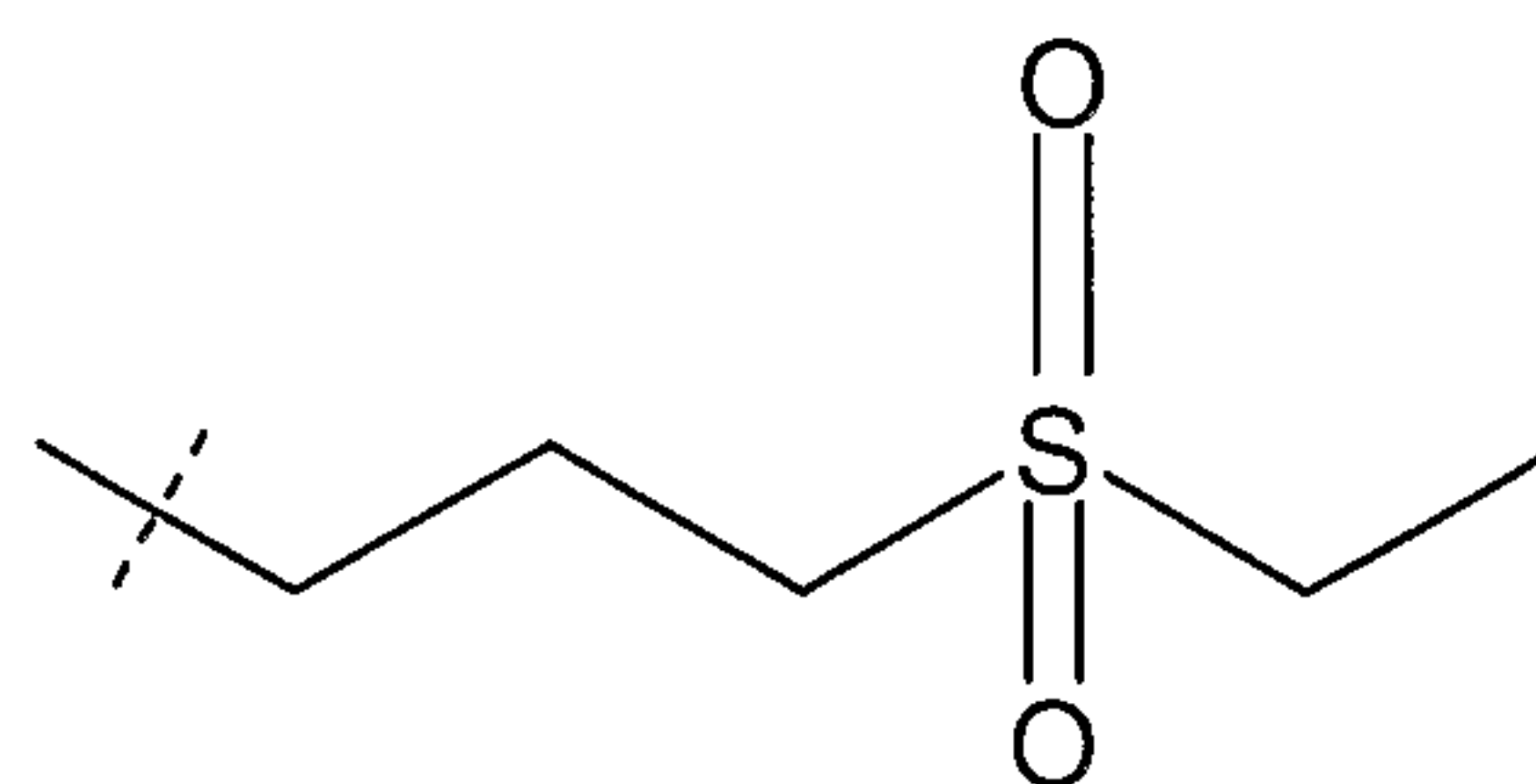
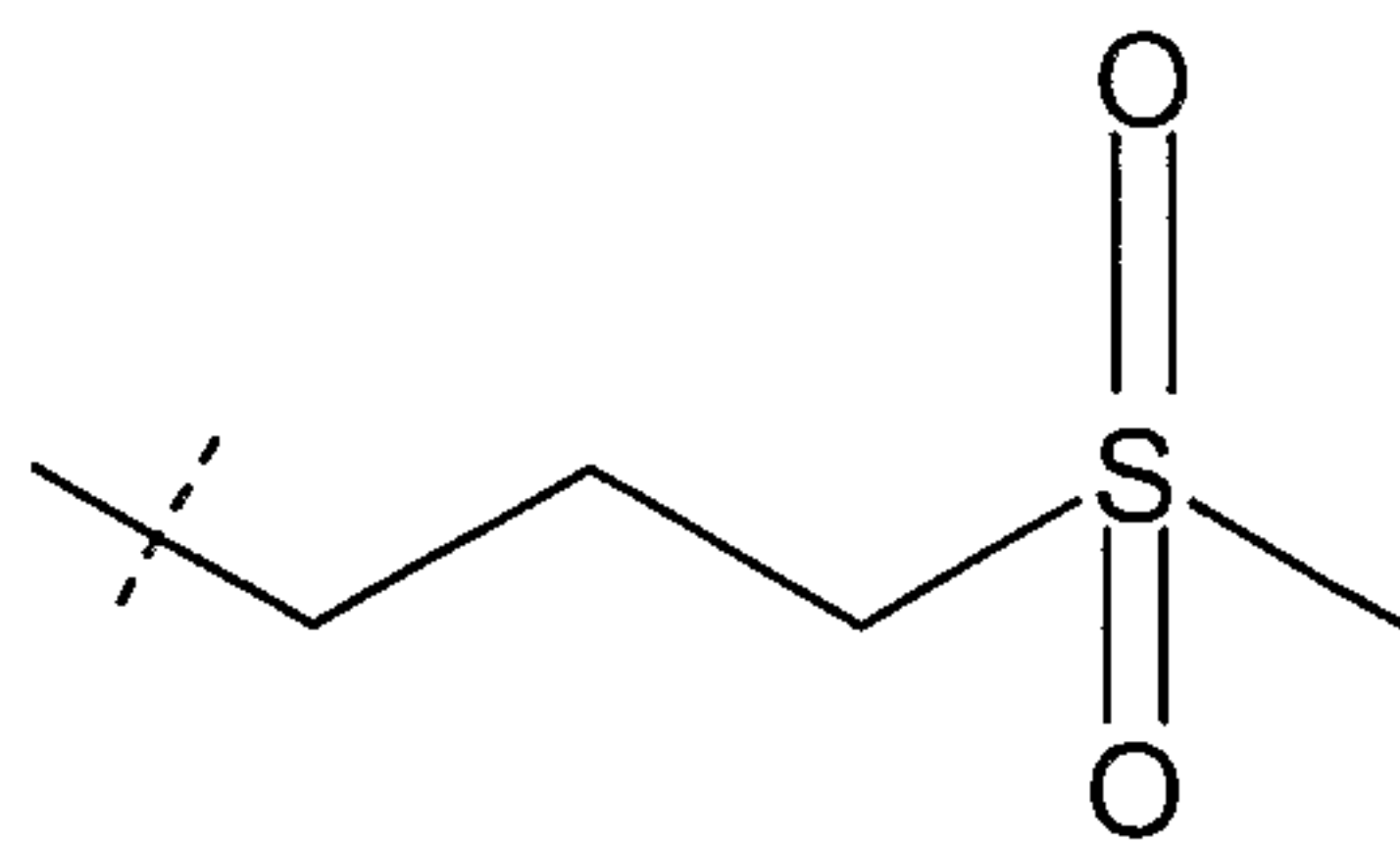
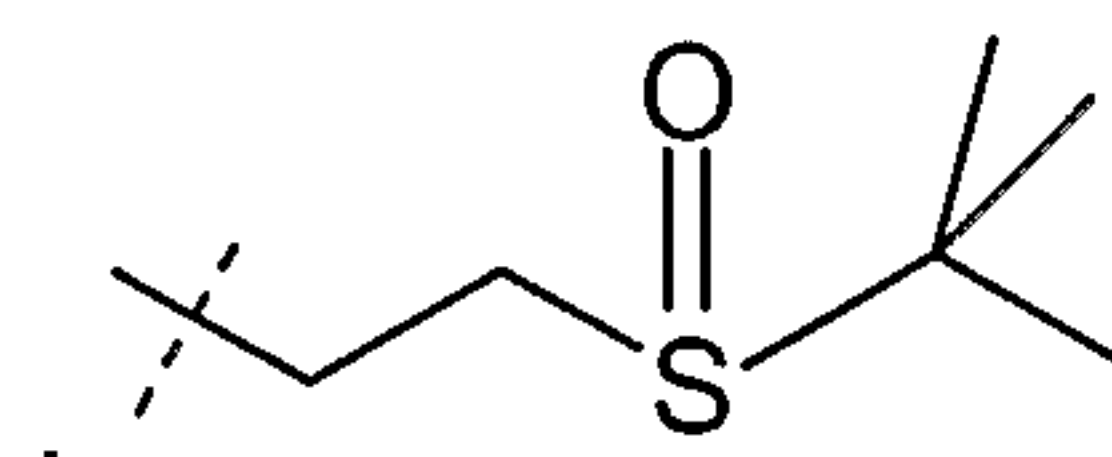
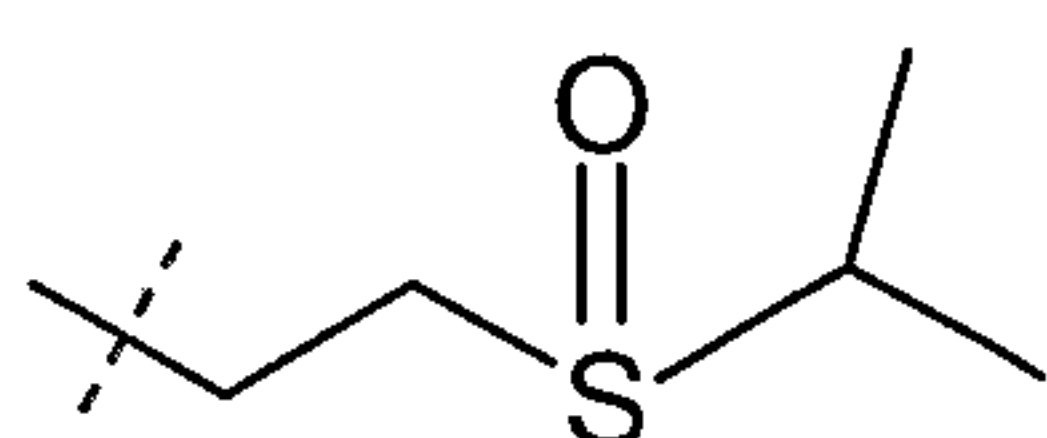
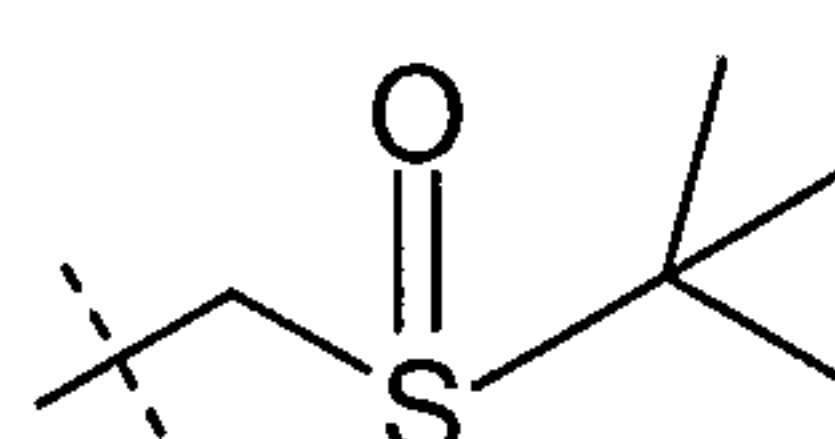
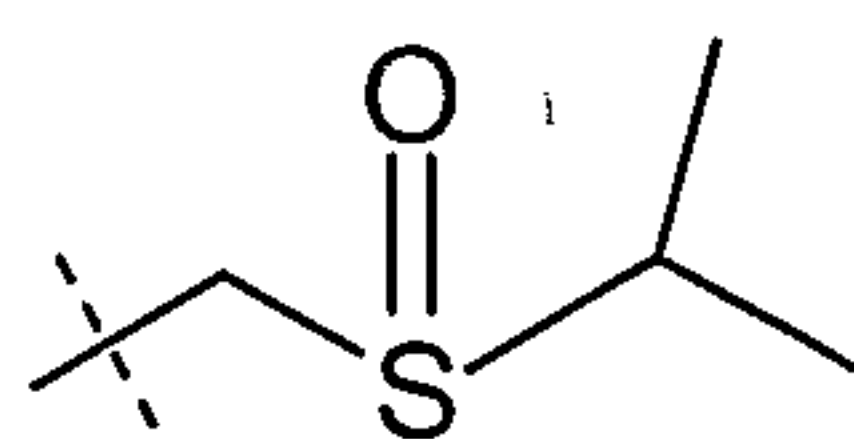
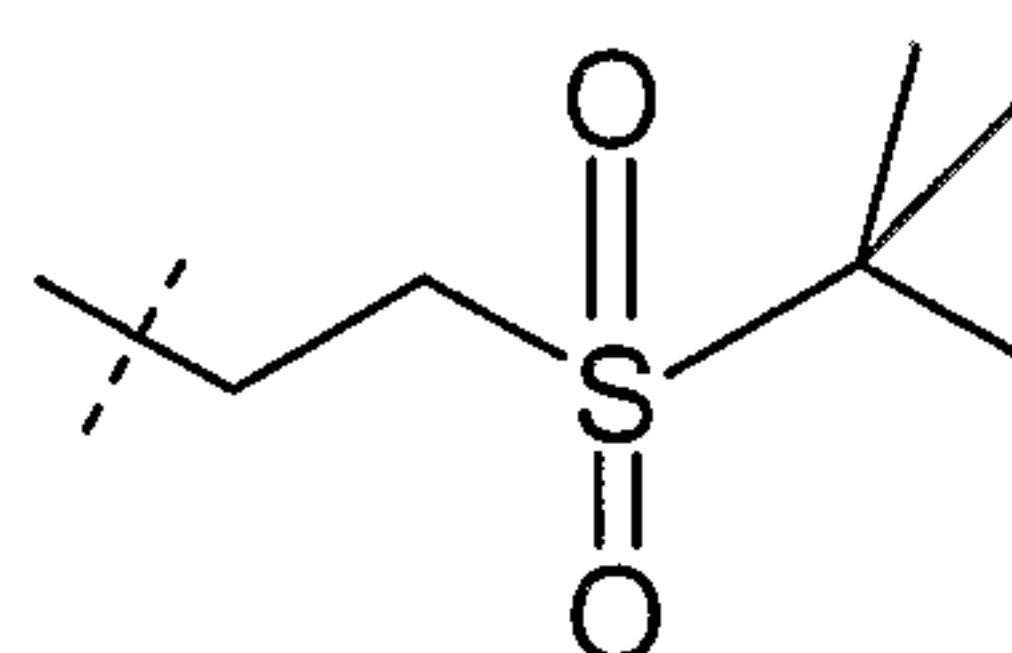
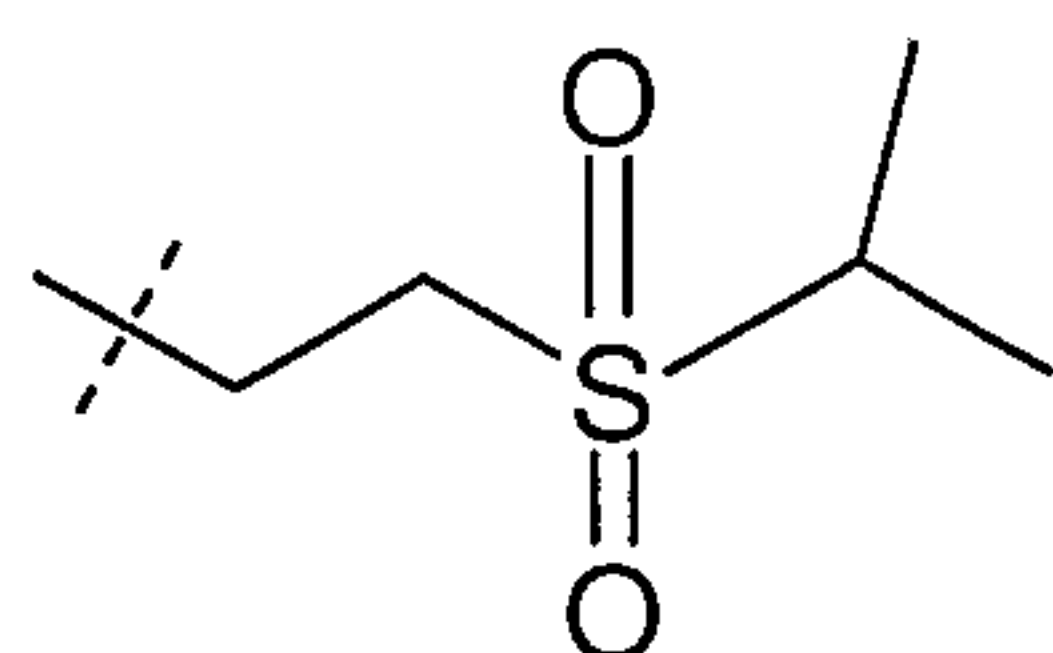
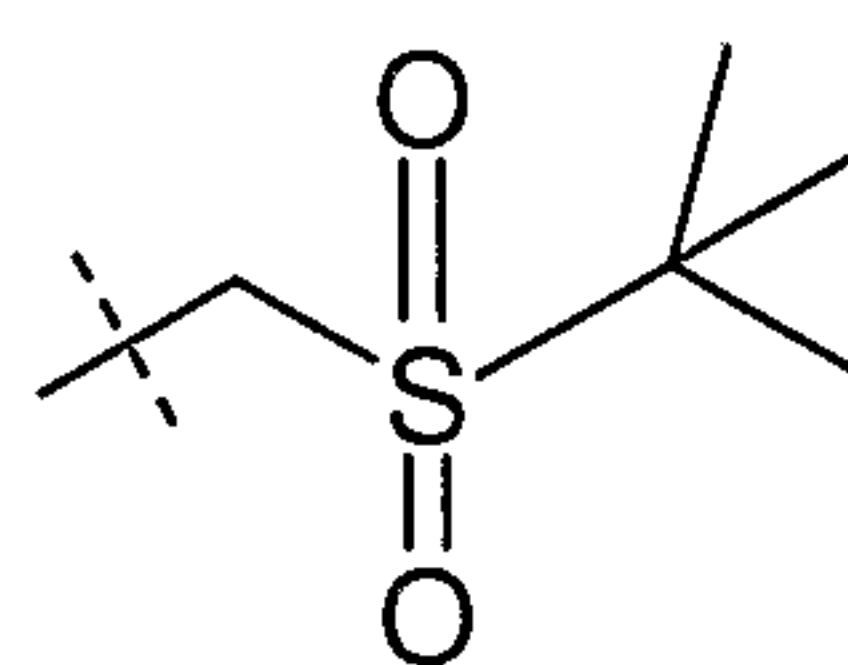
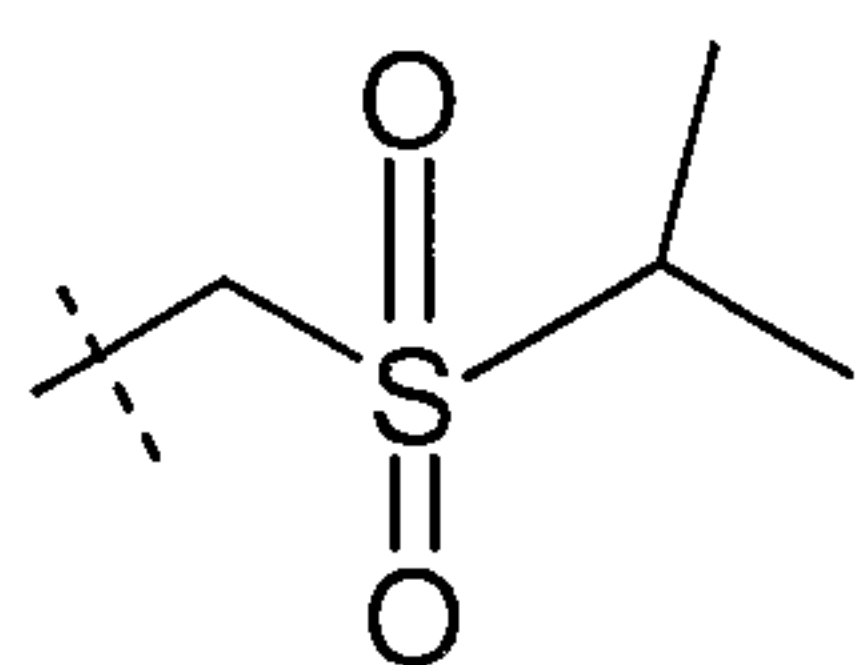
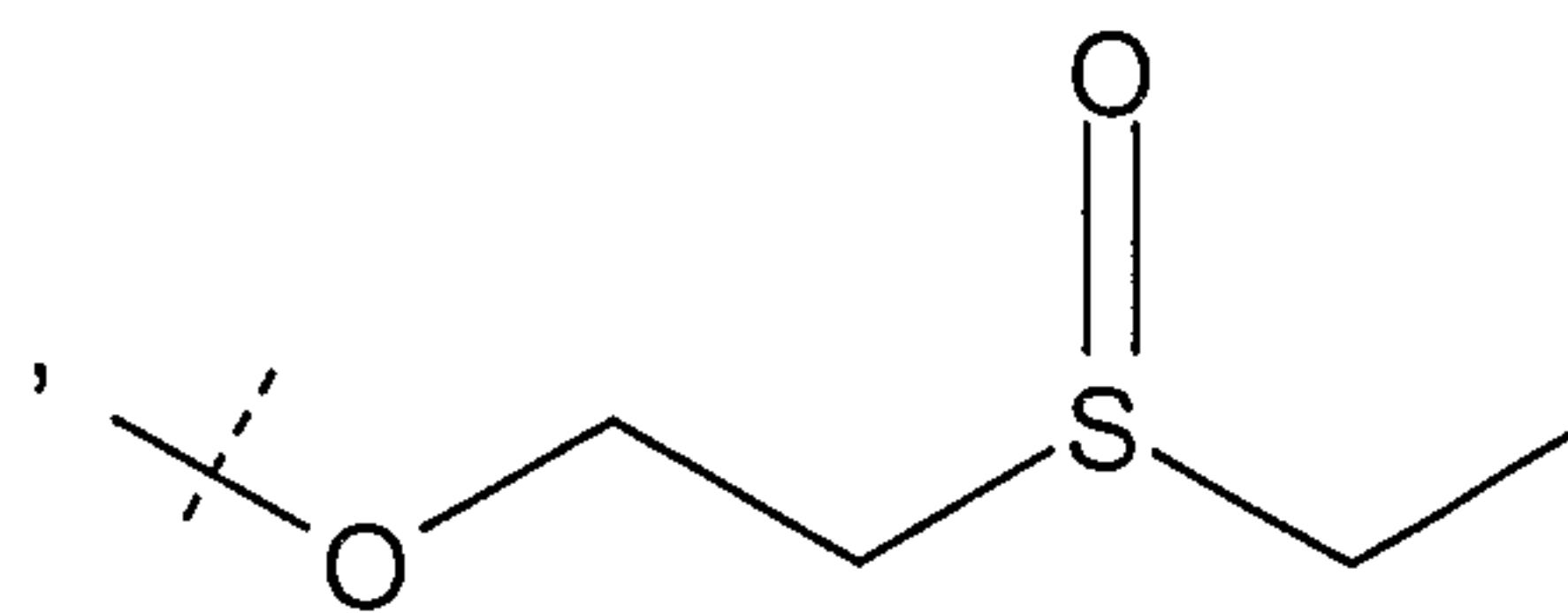
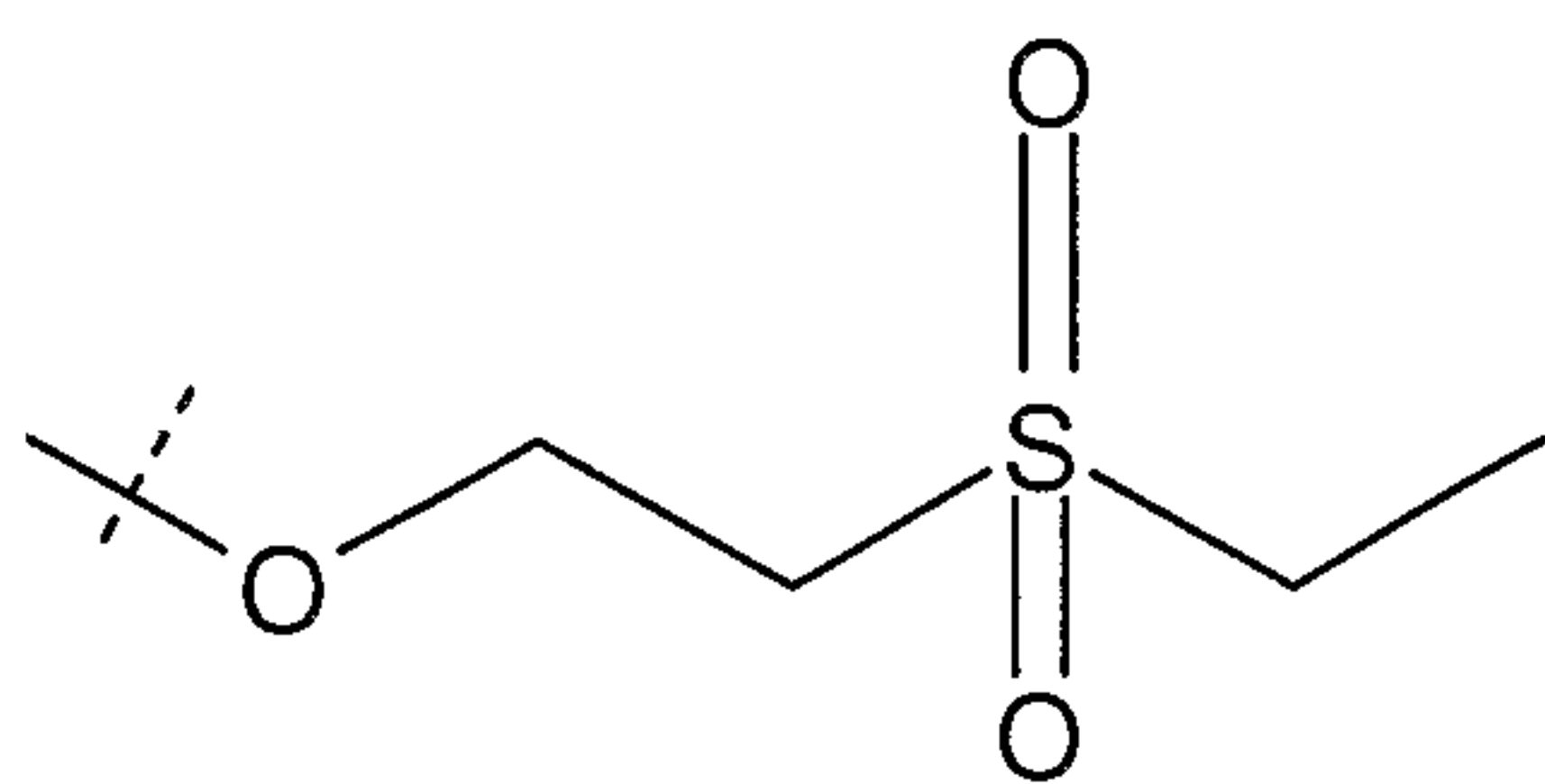
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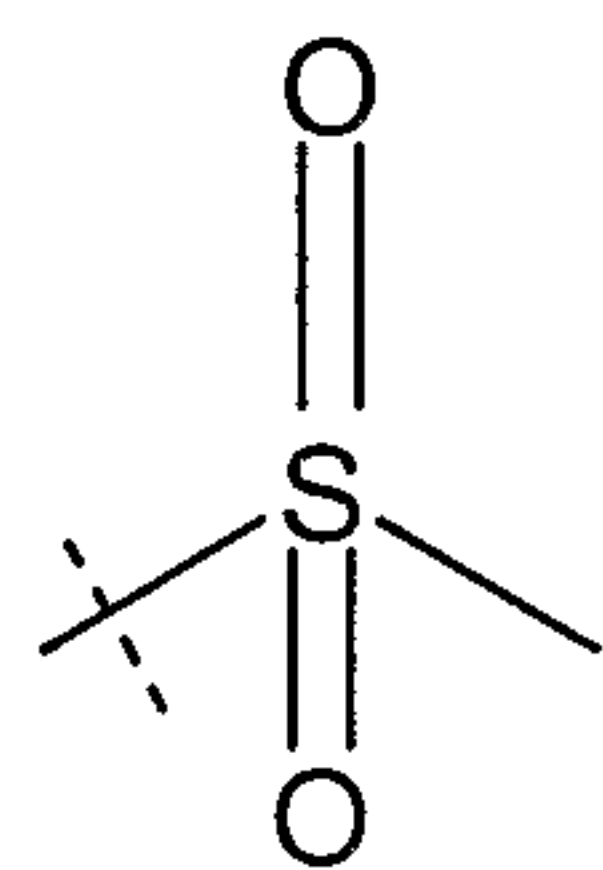
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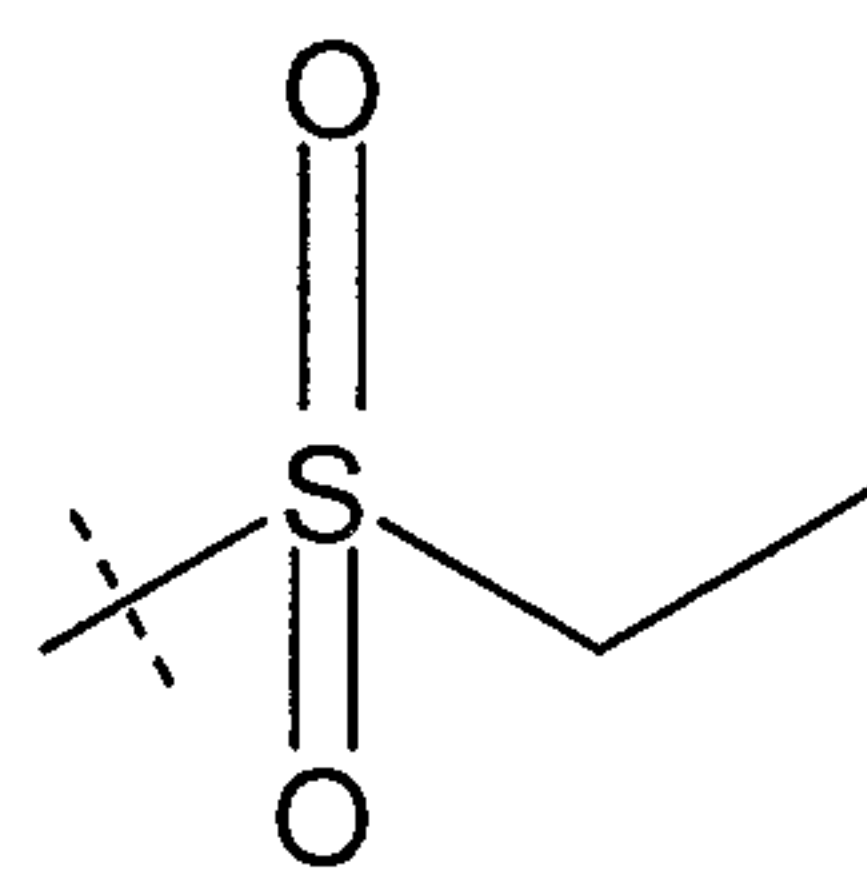
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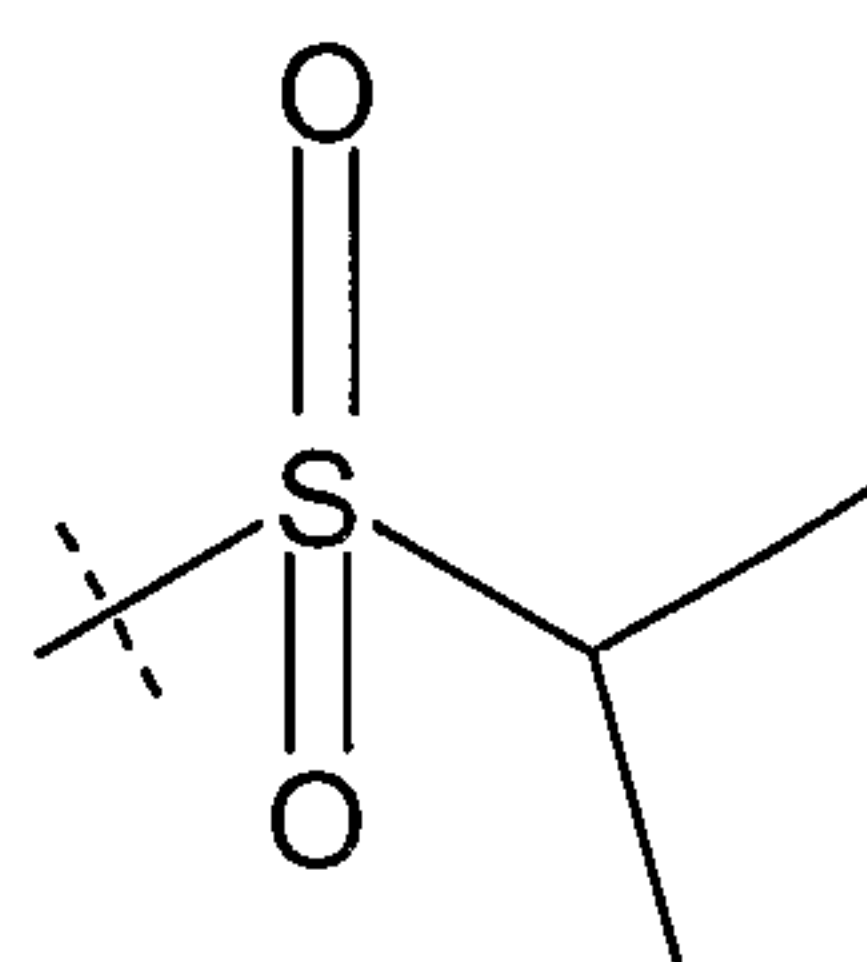
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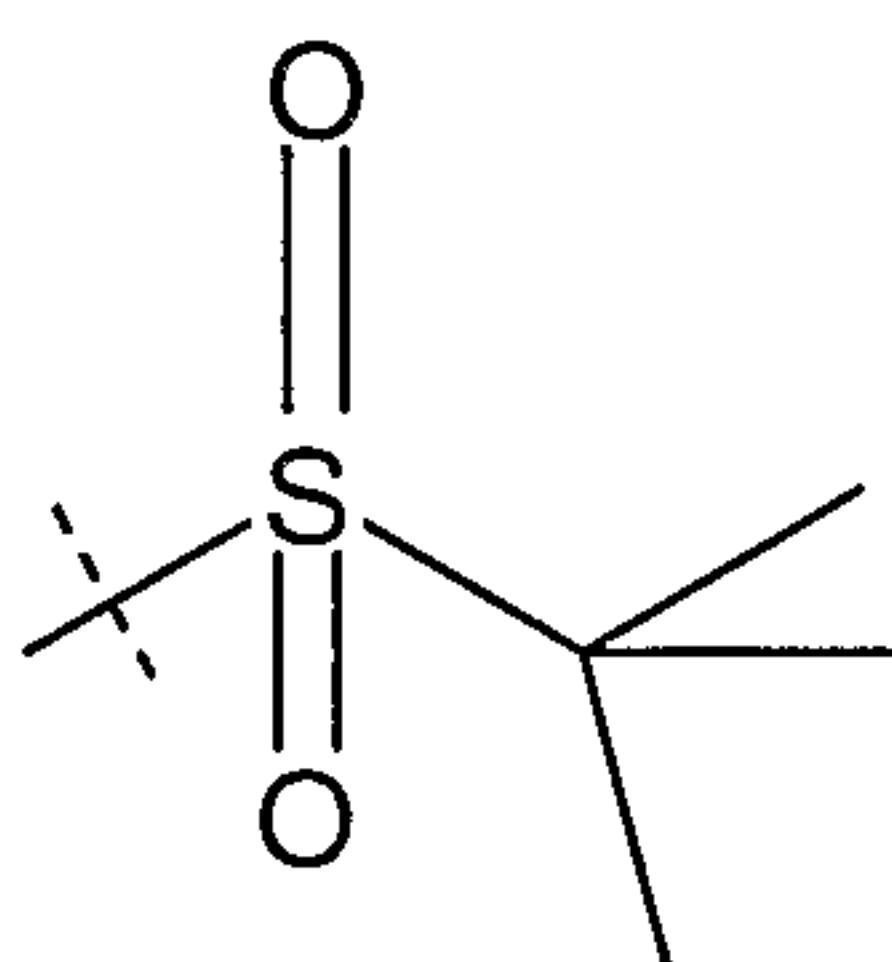
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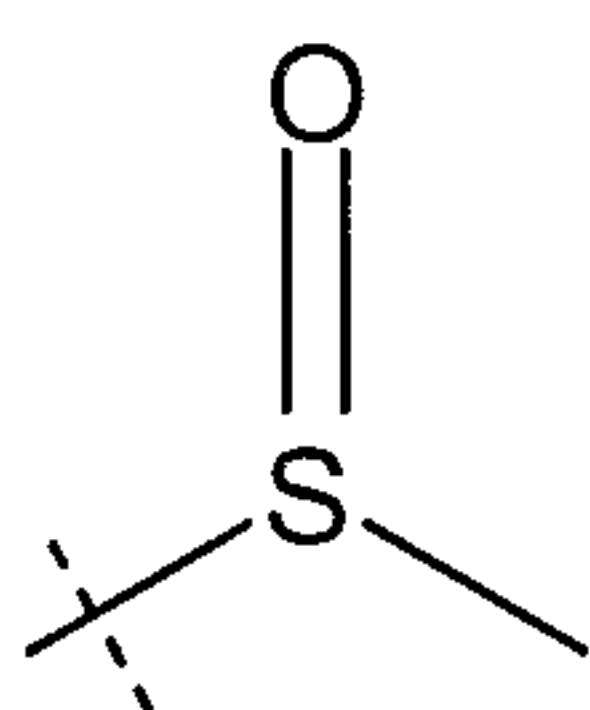
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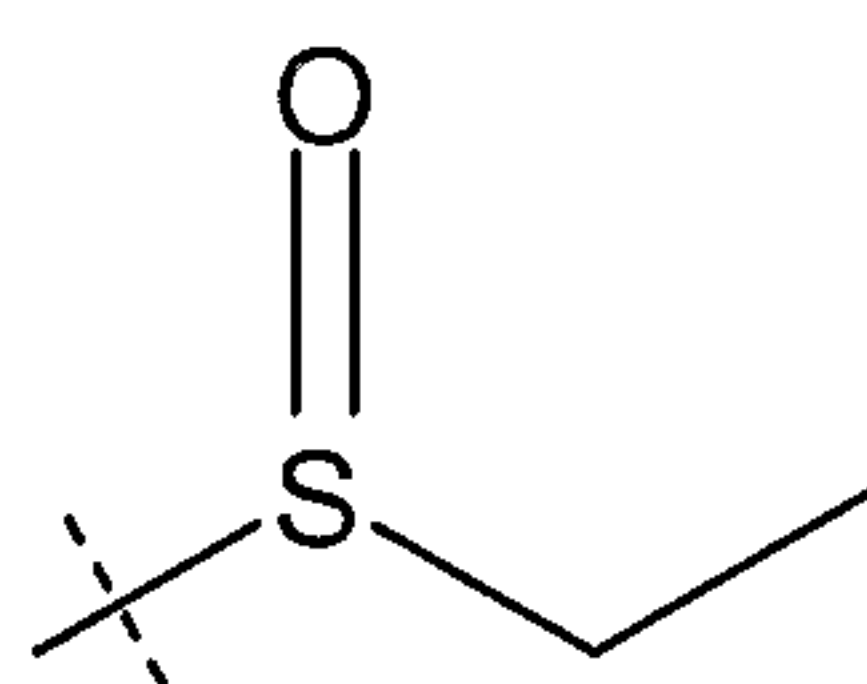
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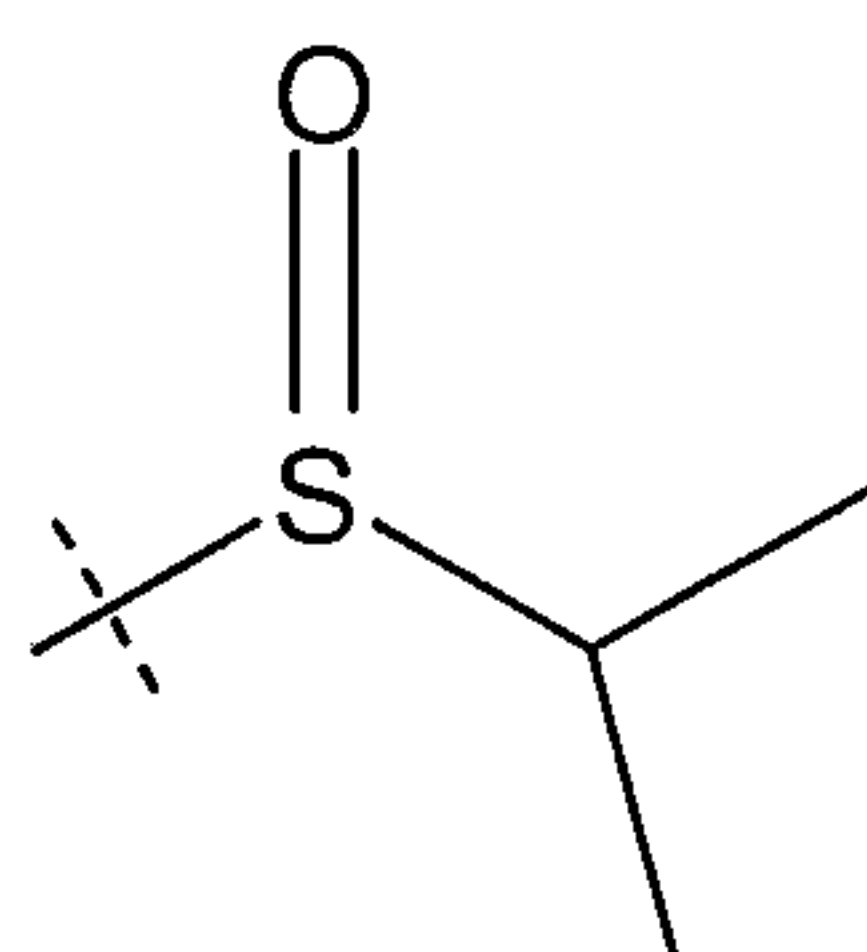
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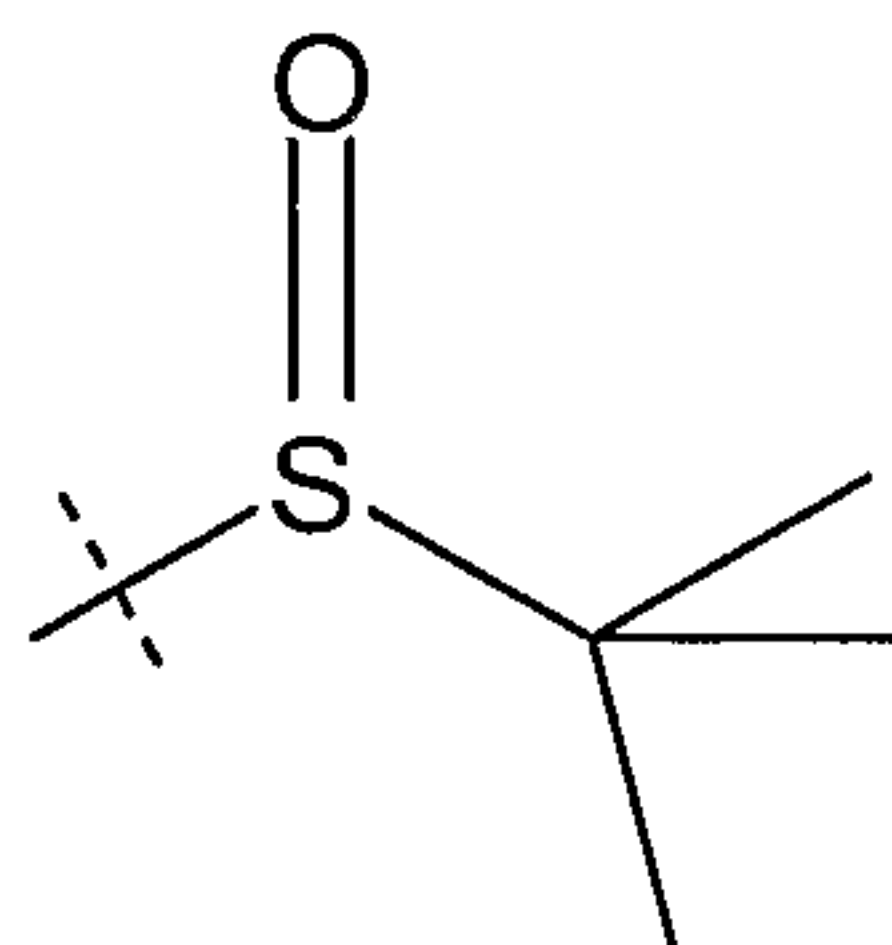
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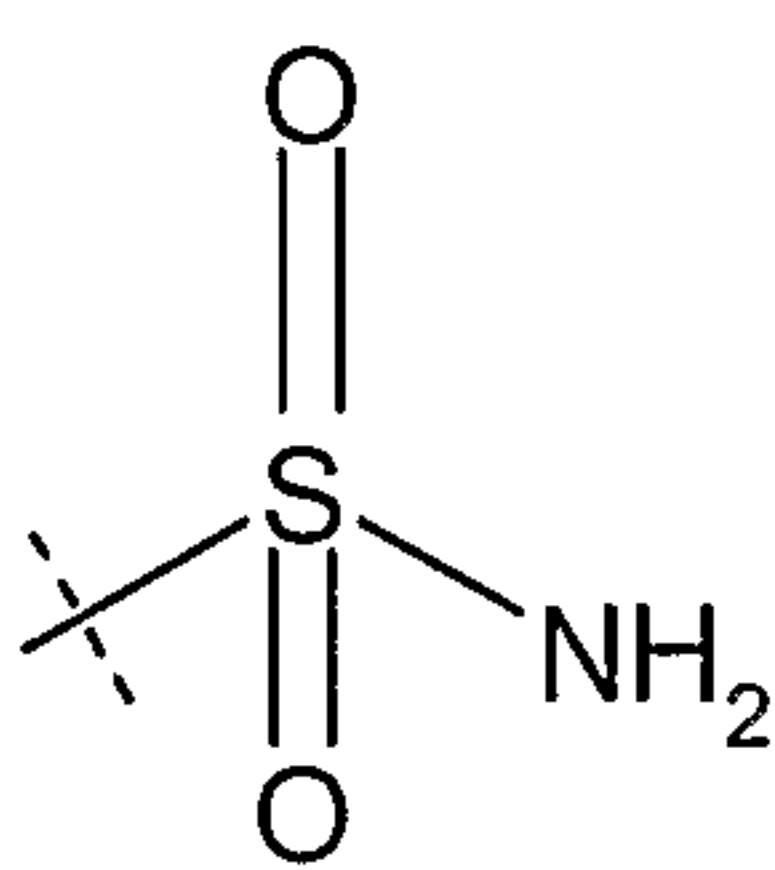
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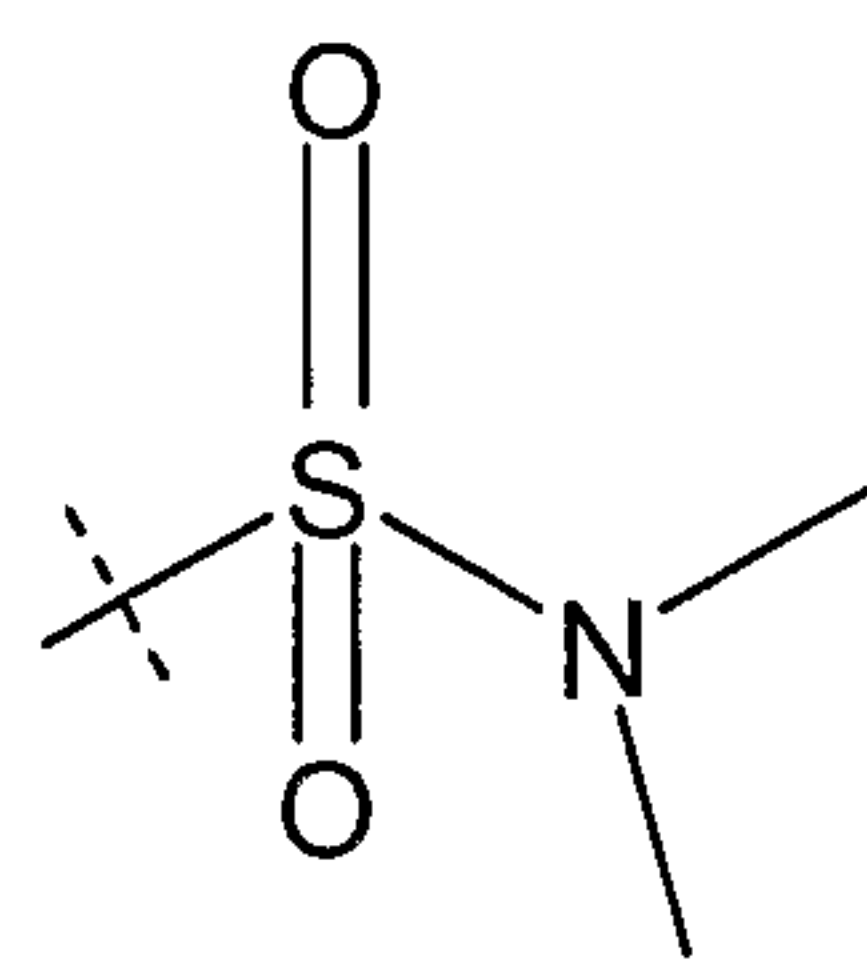
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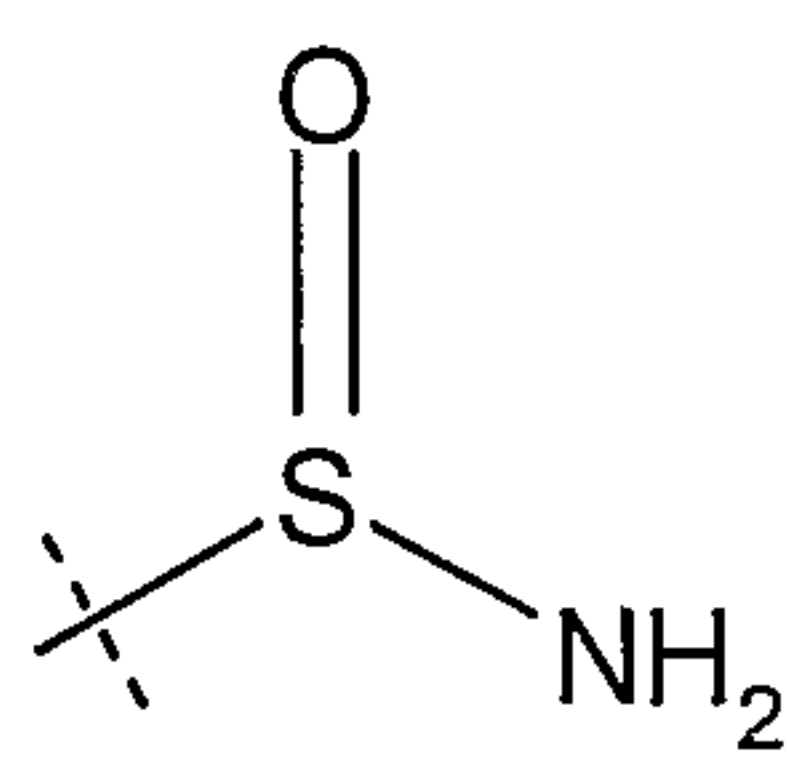
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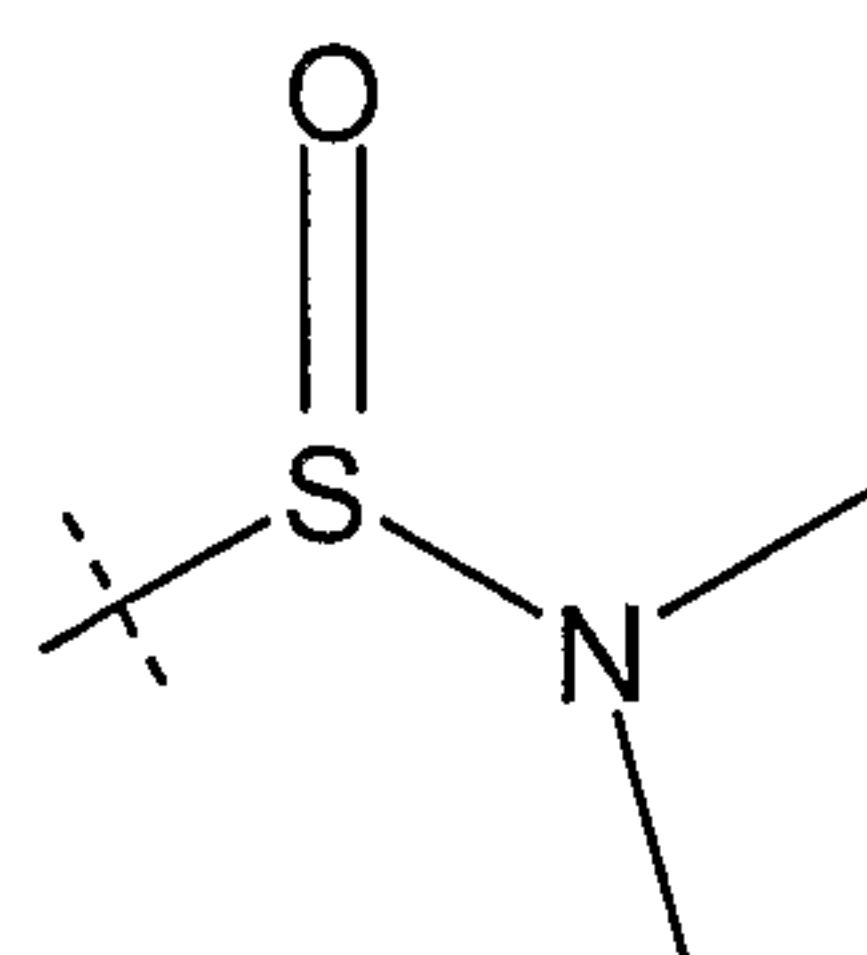
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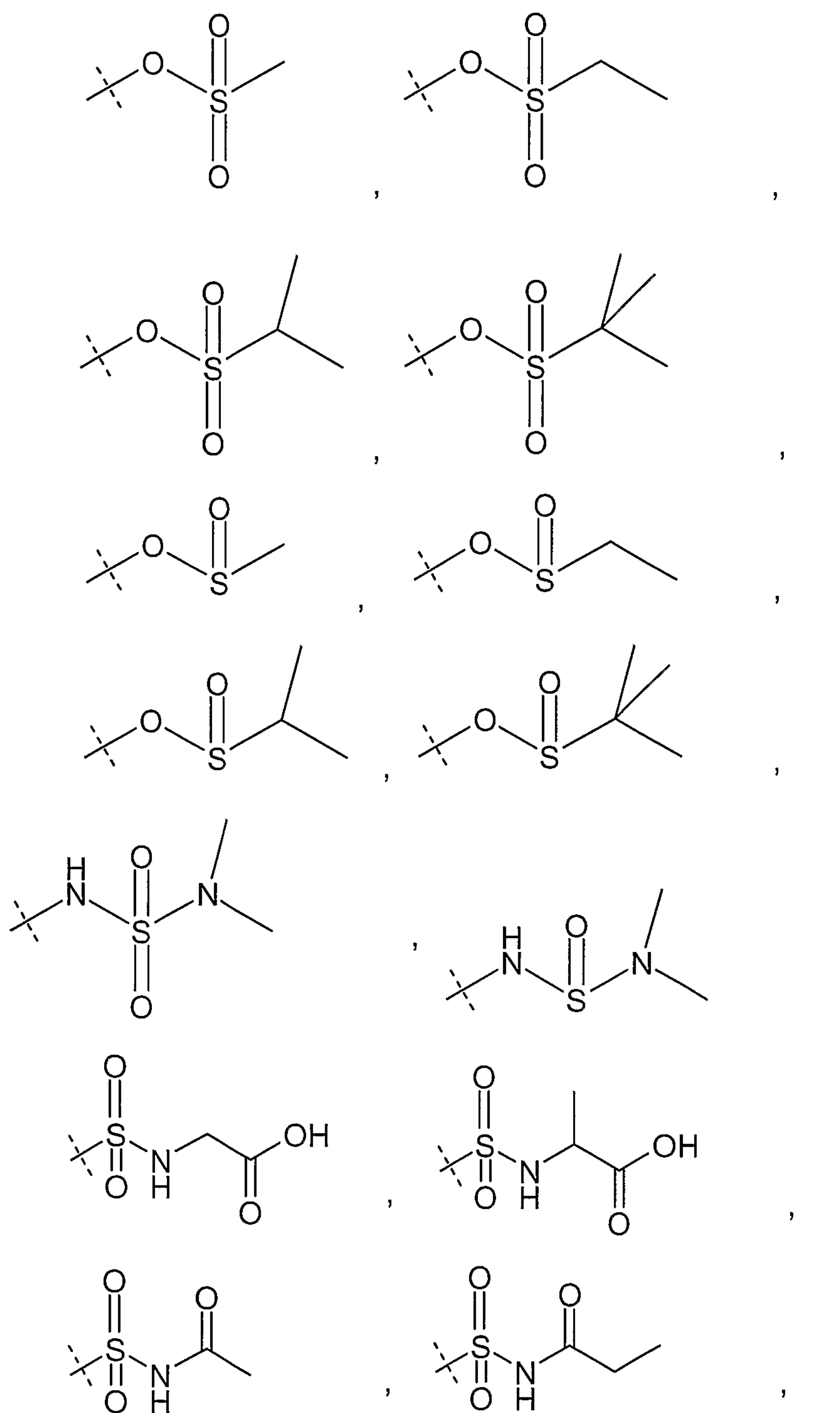


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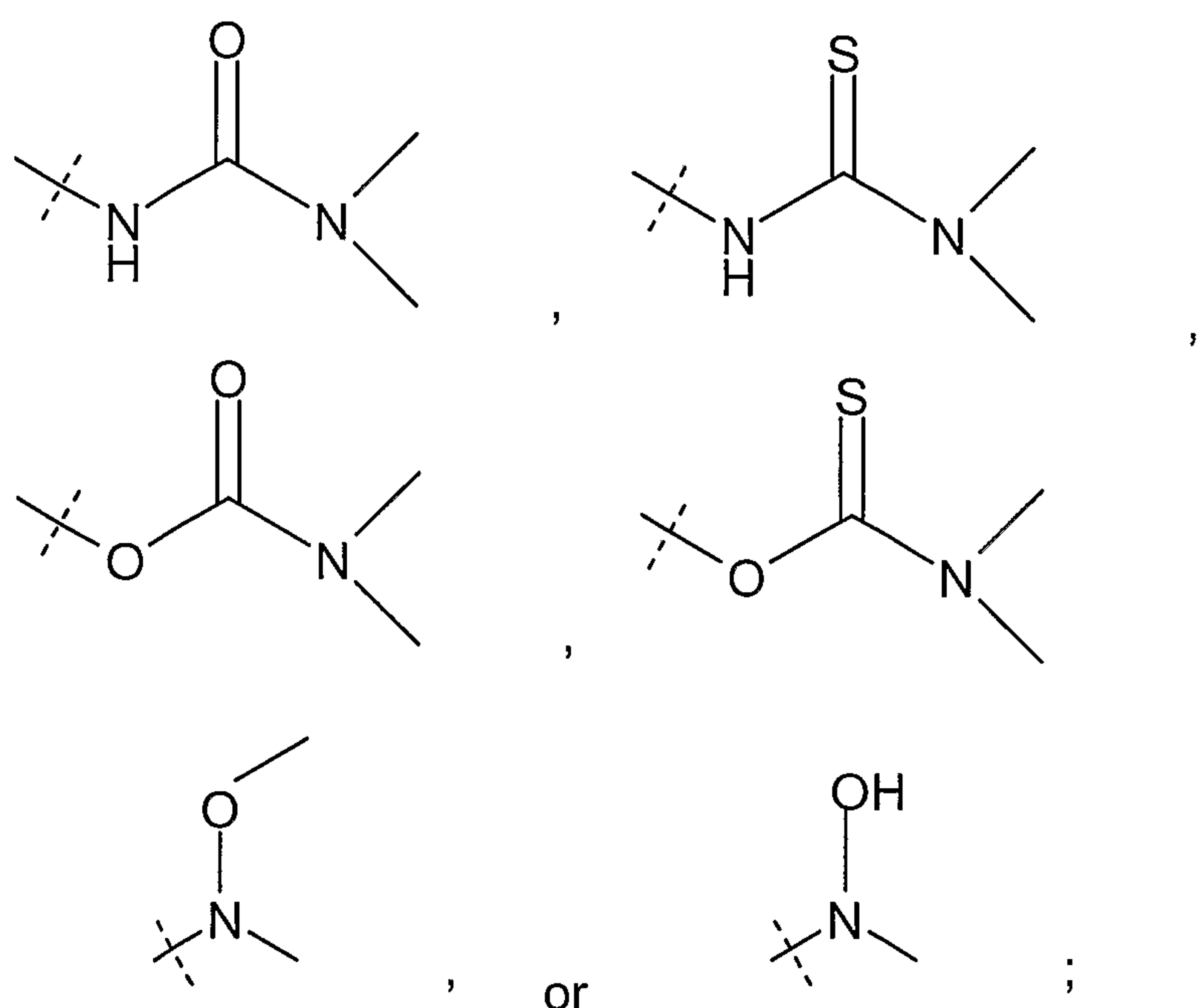


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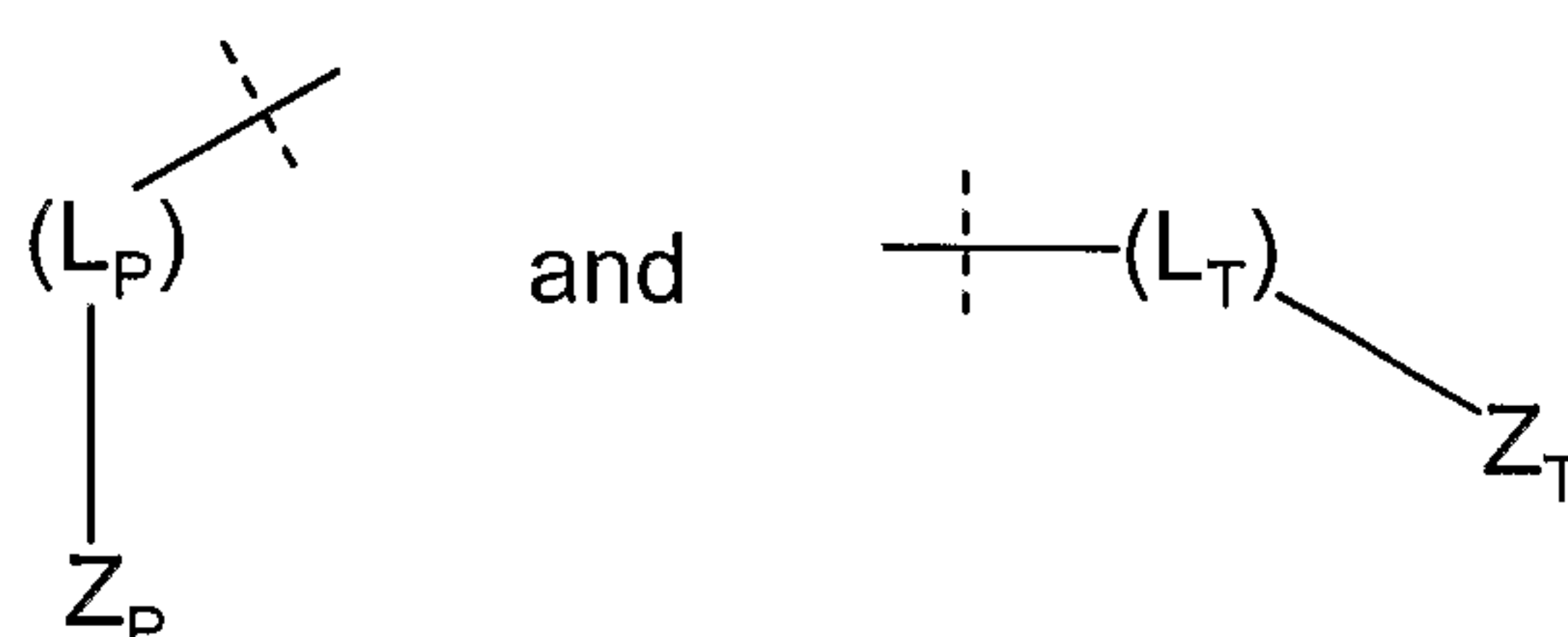
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-57-

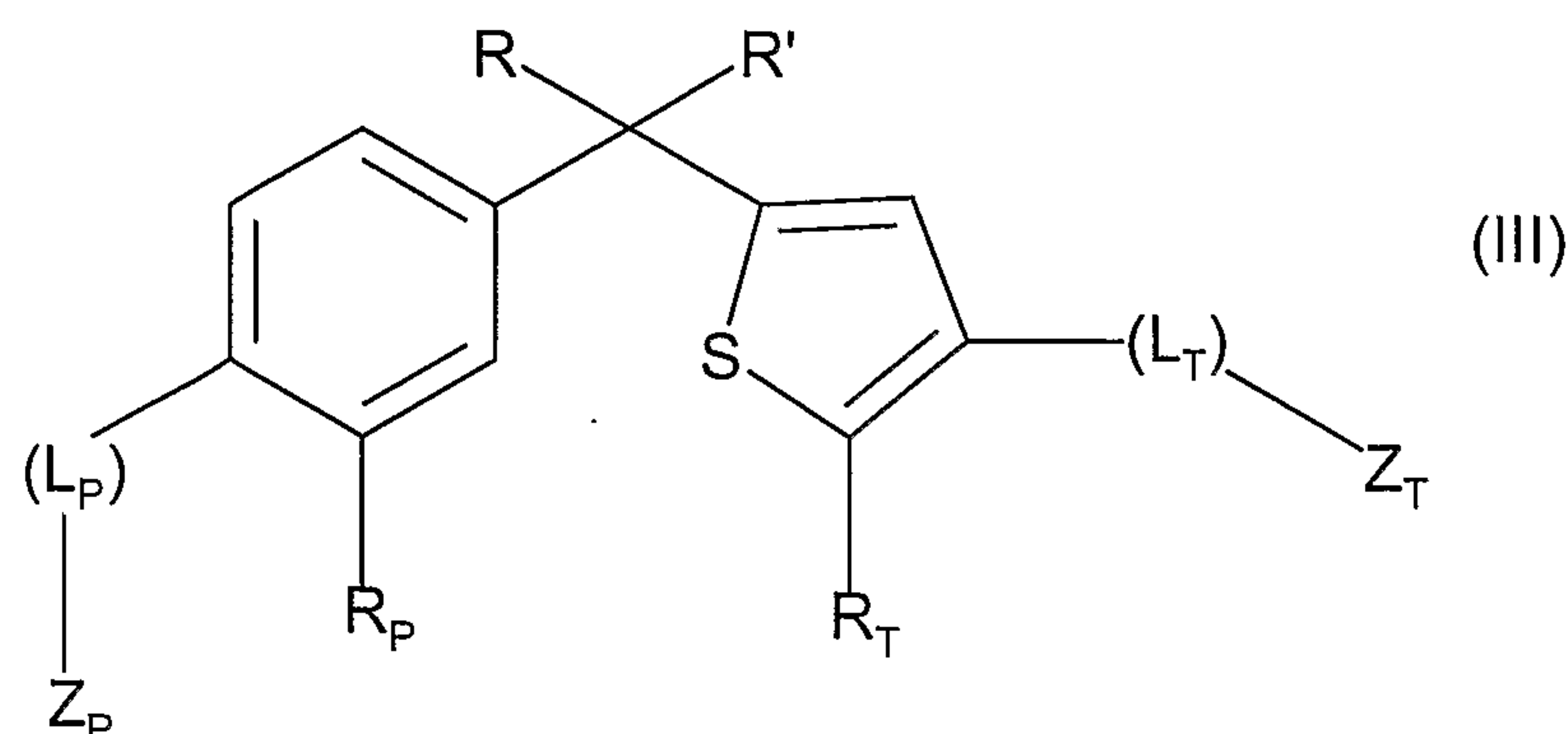


provided that the combined groups of formula I represented by



- 5 may both be lipophilic, or either one may be lipophilic and the other one polar; but both groups may not be polar.

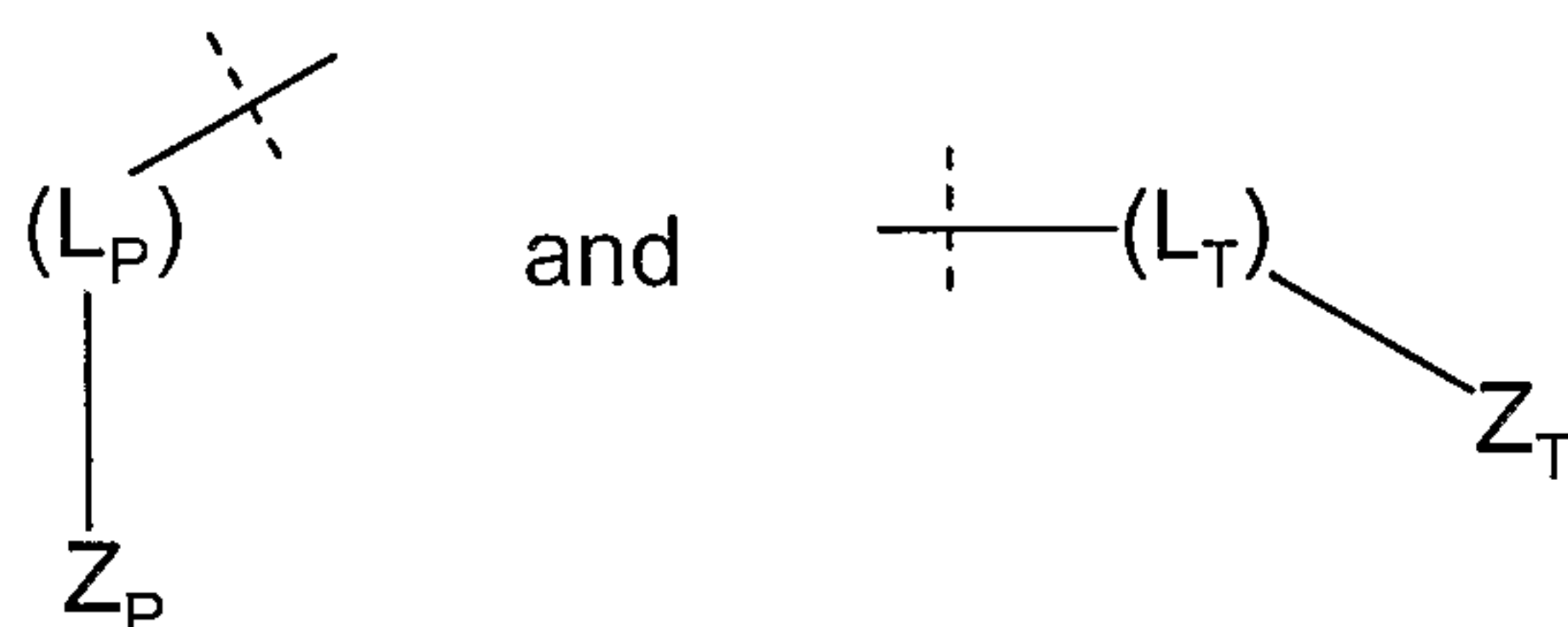
Preferred compounds of the invention are also those represented by the formula III or a pharmaceutically acceptable salt or prodrug derivative thereof:



10

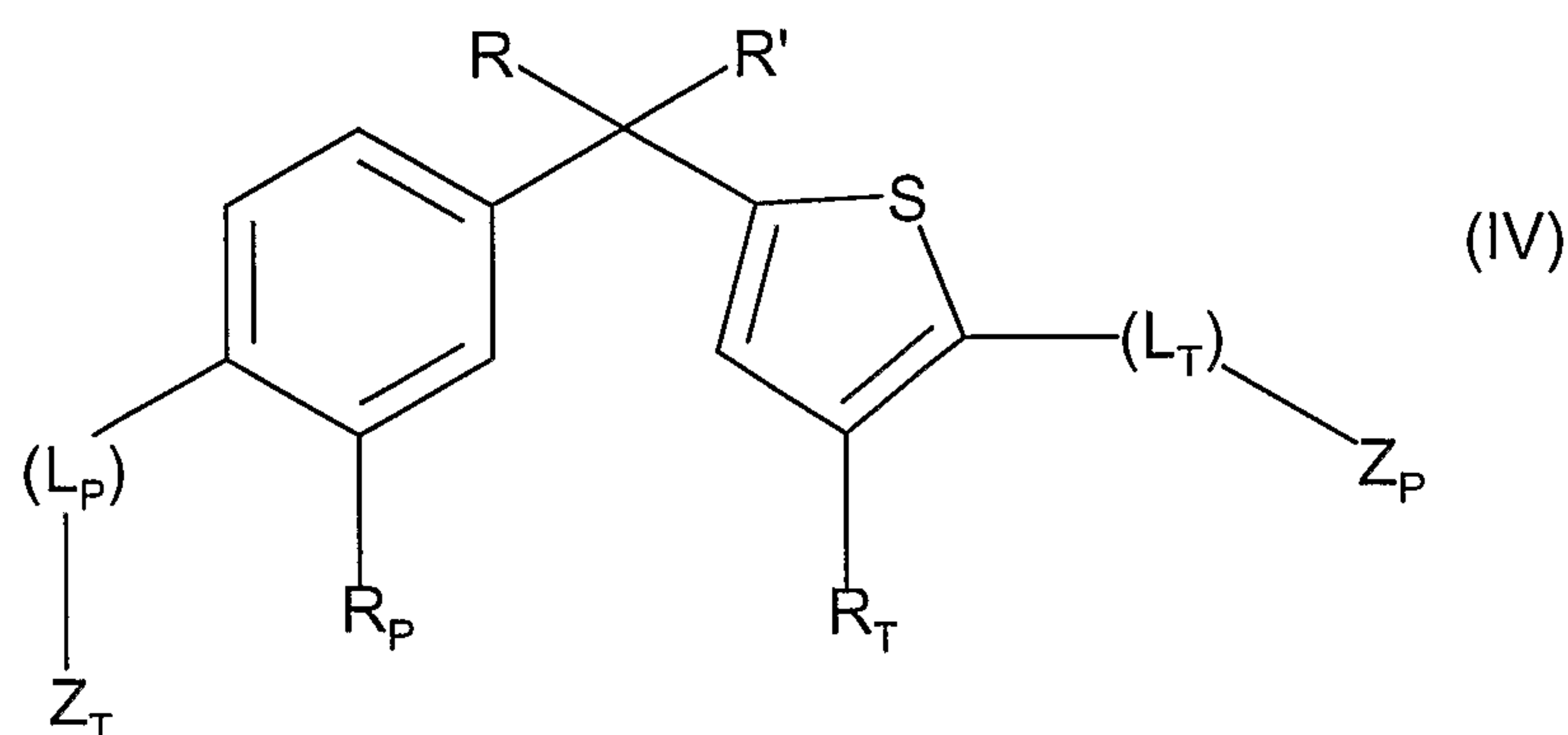
wherein the substituents R , R' , R_P , R_T , L_P , L_T , Z_P , and Z_T are the same as defined for formula II, supra., provided that the combined groups of formula I represented by

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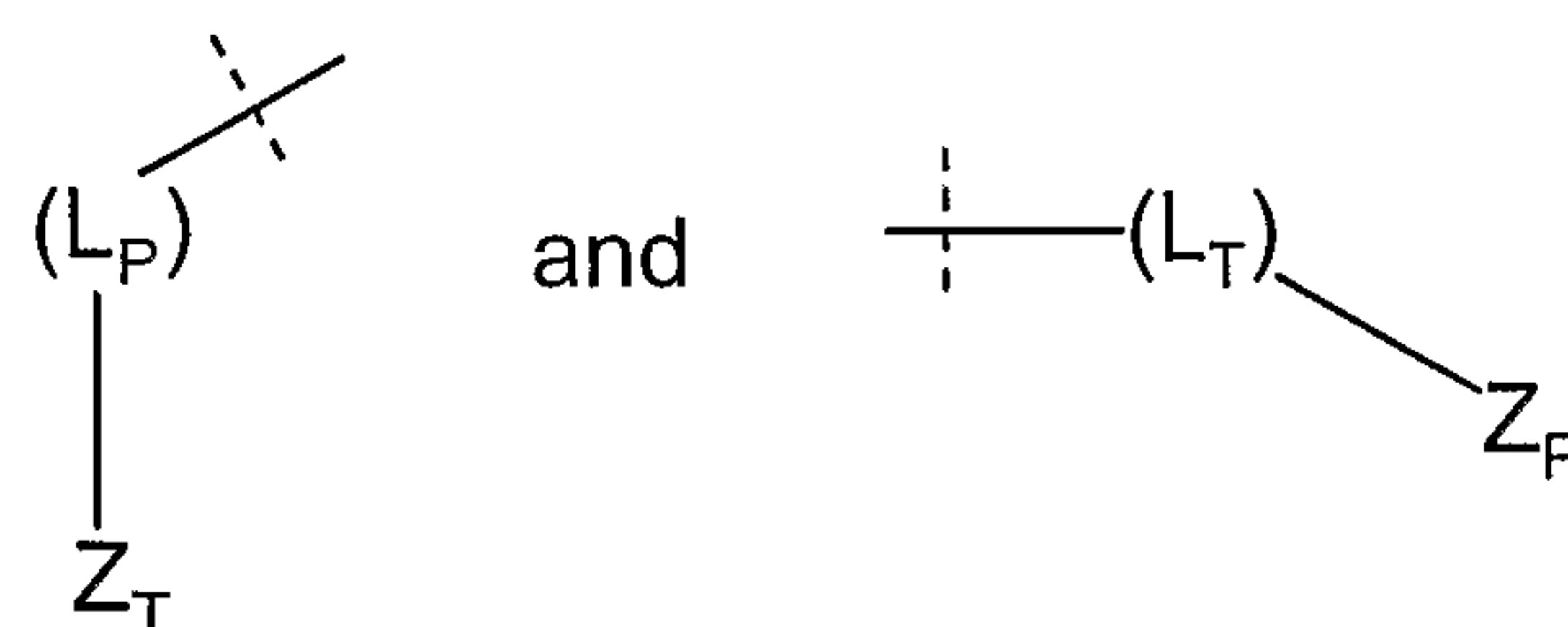


may both be lipophilic, or either one may be lipophilic and the other one polar; but both groups may not be polar.

Preferred compounds of the invention are also those represented by the formula IV
 5 or a pharmaceutically acceptable salt or prodrug derivative thereof:



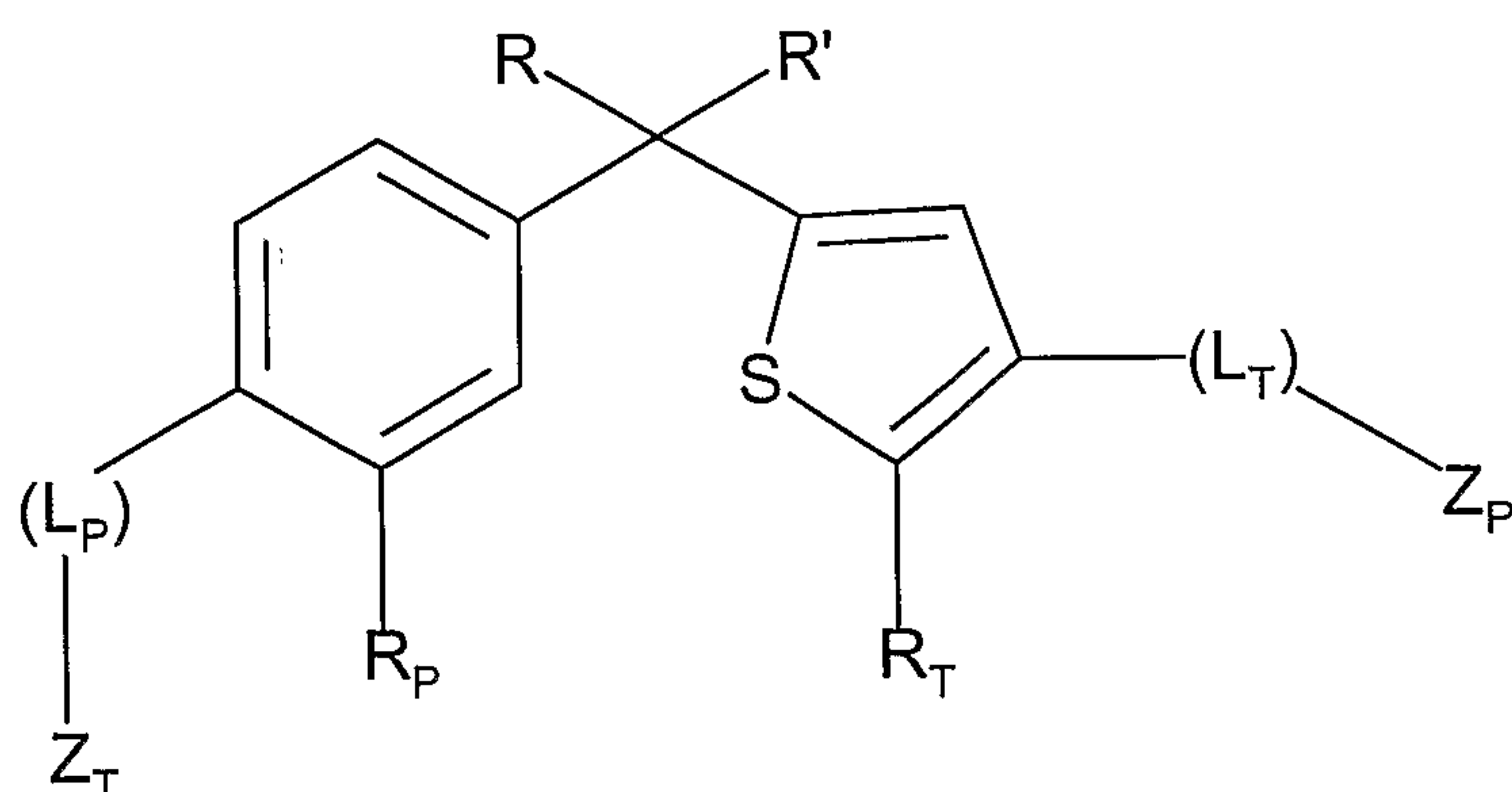
wherein the substituents R , R' , R_P , R_T , L_P , L_T , Z_P , and Z_T are the same as defined for
 10 formula II, supra., provided that the combined groups of formula I represented by



may both be lipophilic, or either one may be lipophilic and the other one polar; but both groups may not be polar.

Preferred compounds of the invention are also those represented by the formula V
 15 or a pharmaceutically acceptable salt or prodrug derivative thereof:

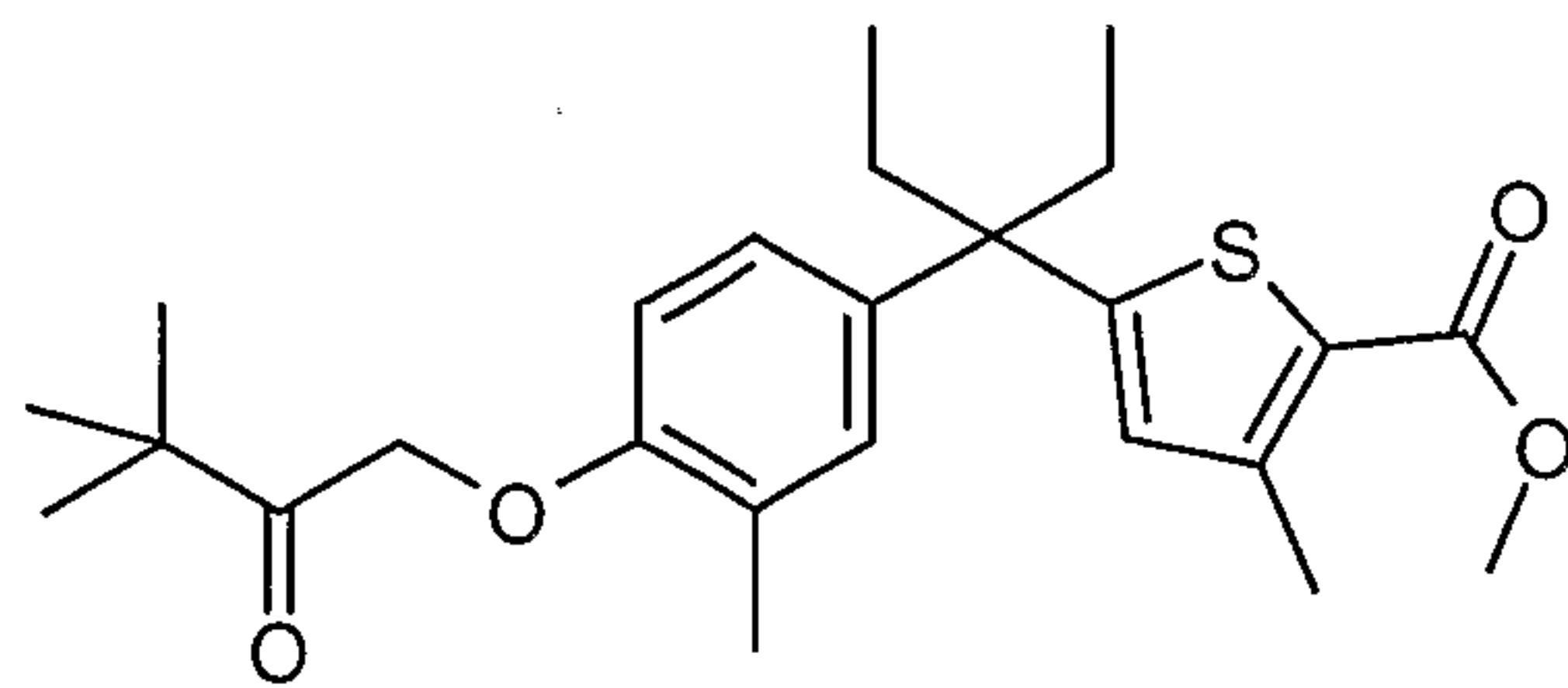
(V)



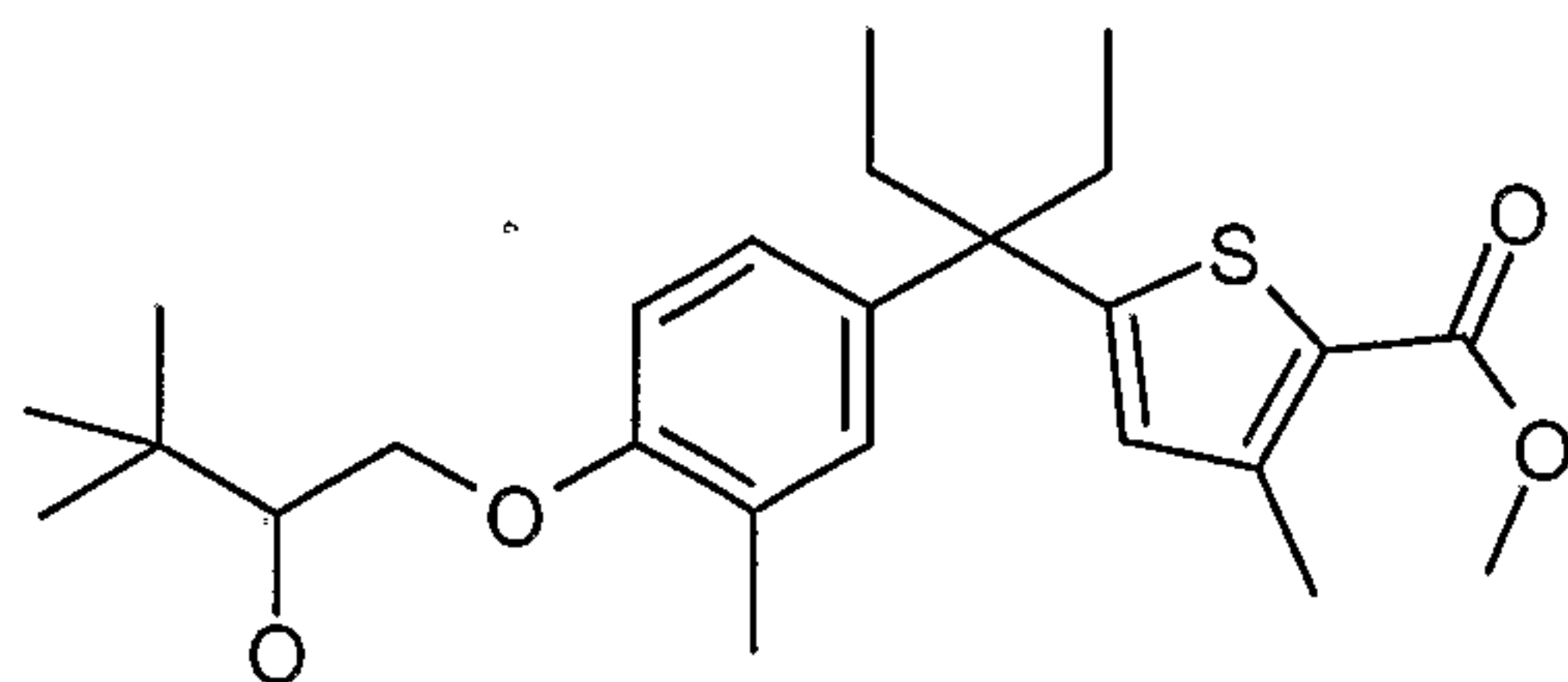
(L_P) and (L_T)

X1)

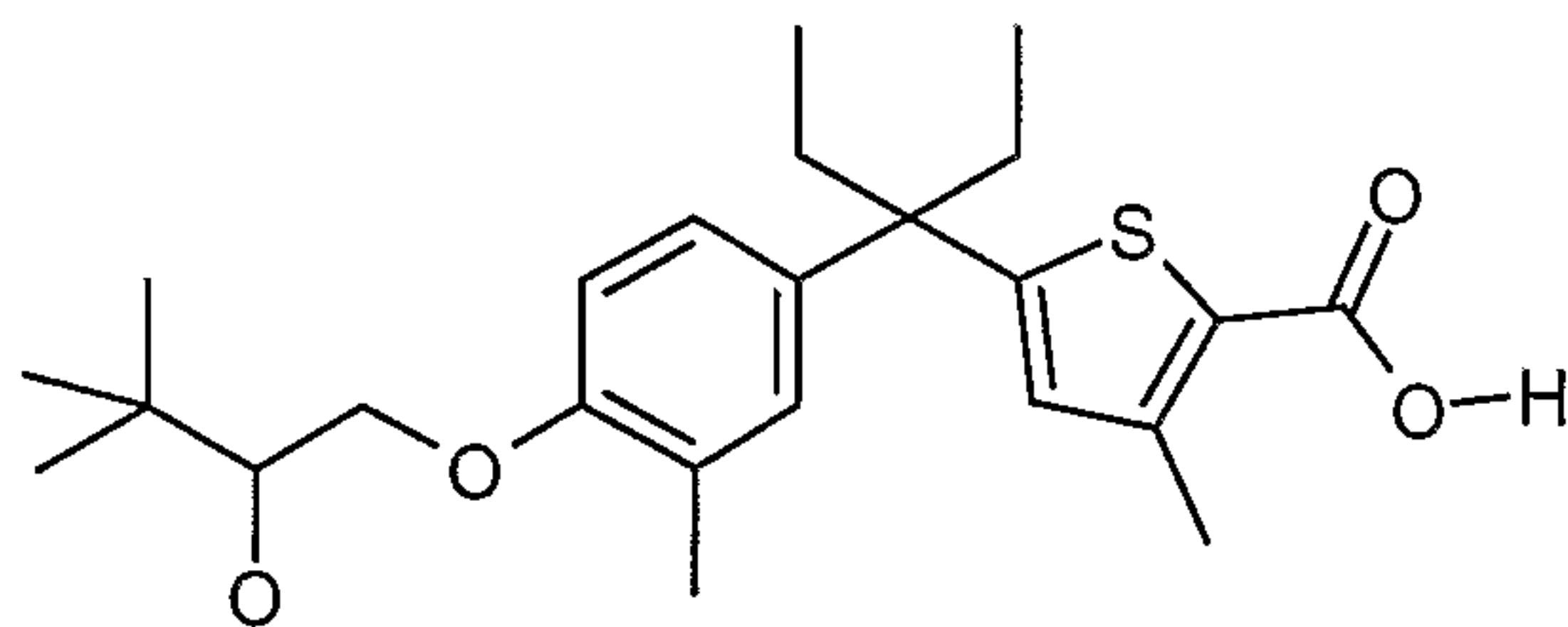
-60-



X2)

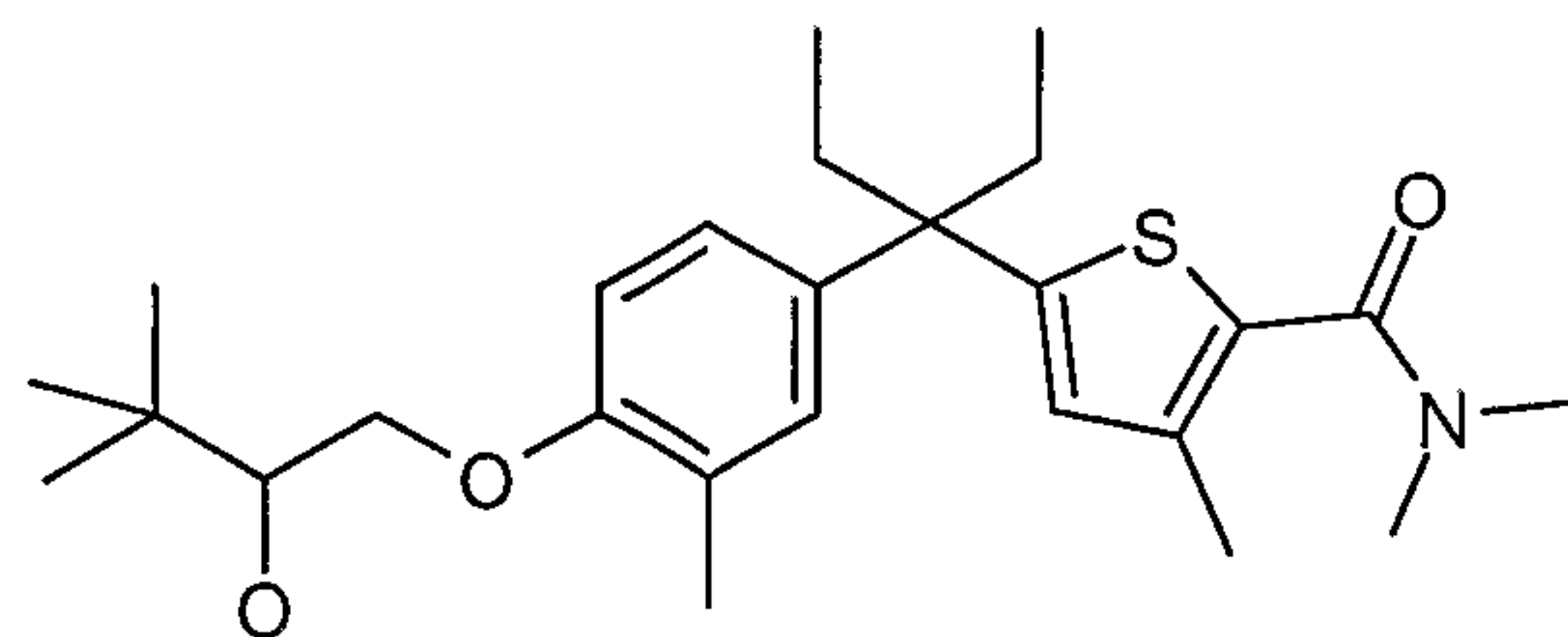


X3)

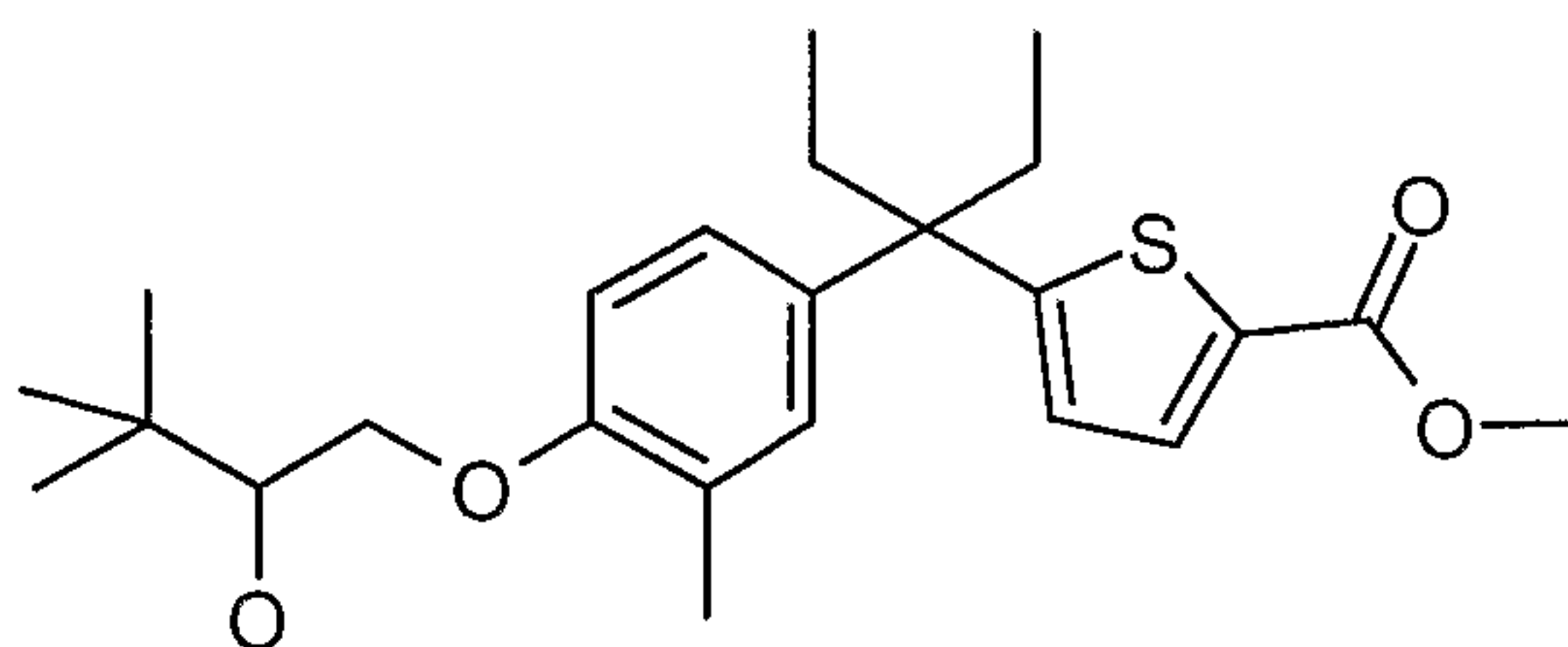


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X4)



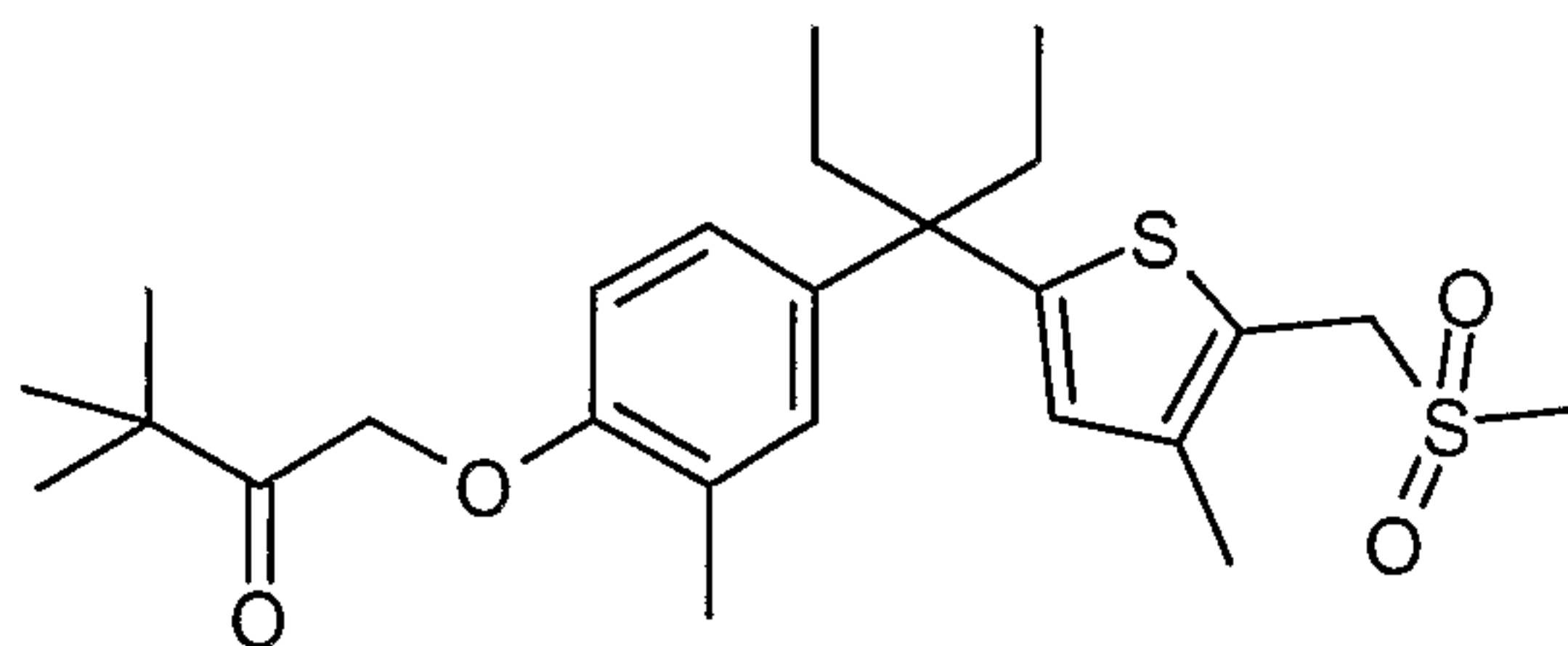
X5)



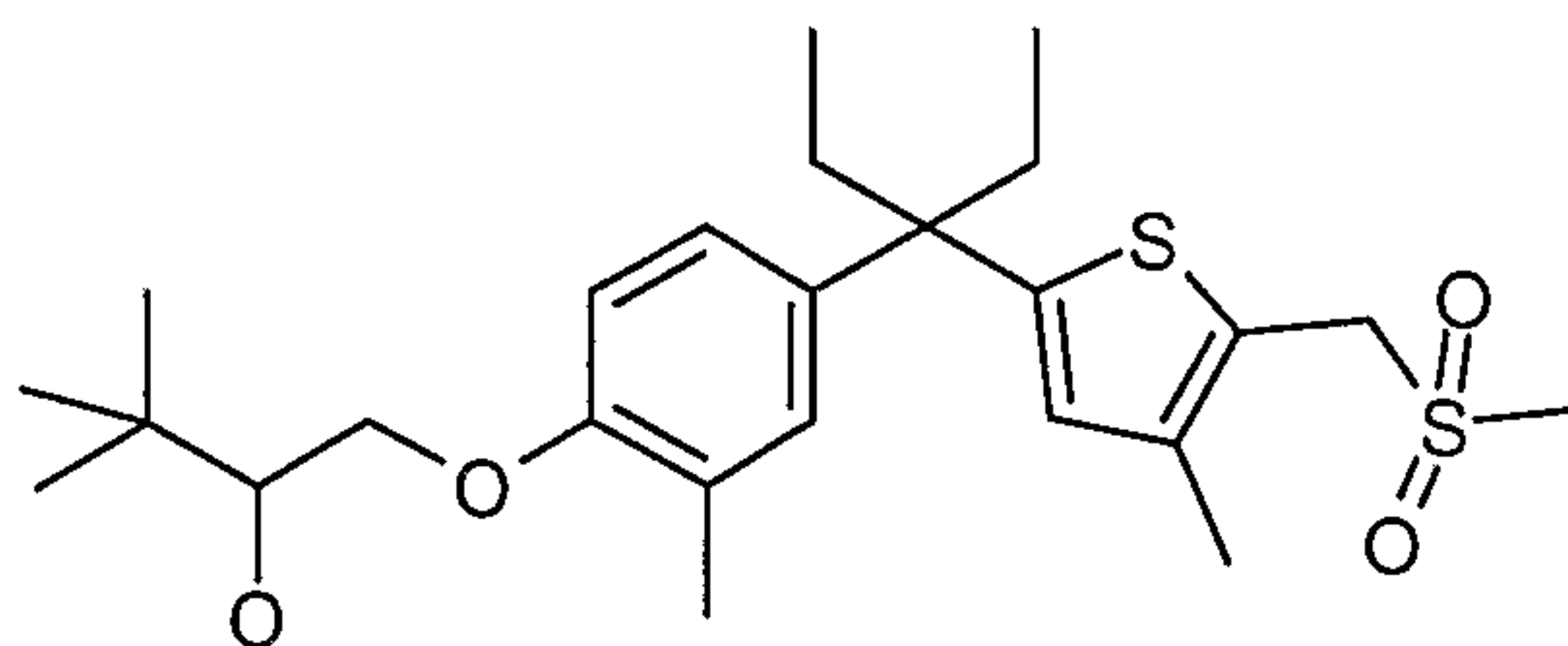
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X9)

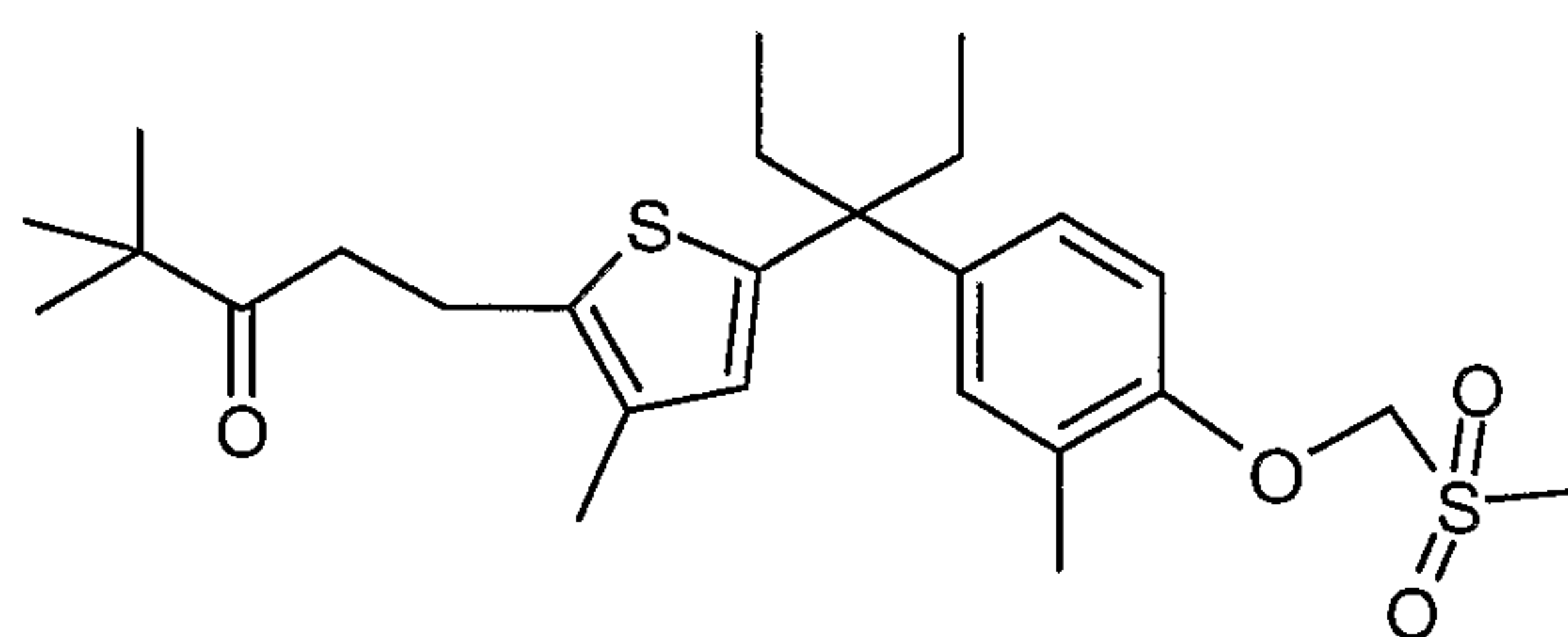


X10)

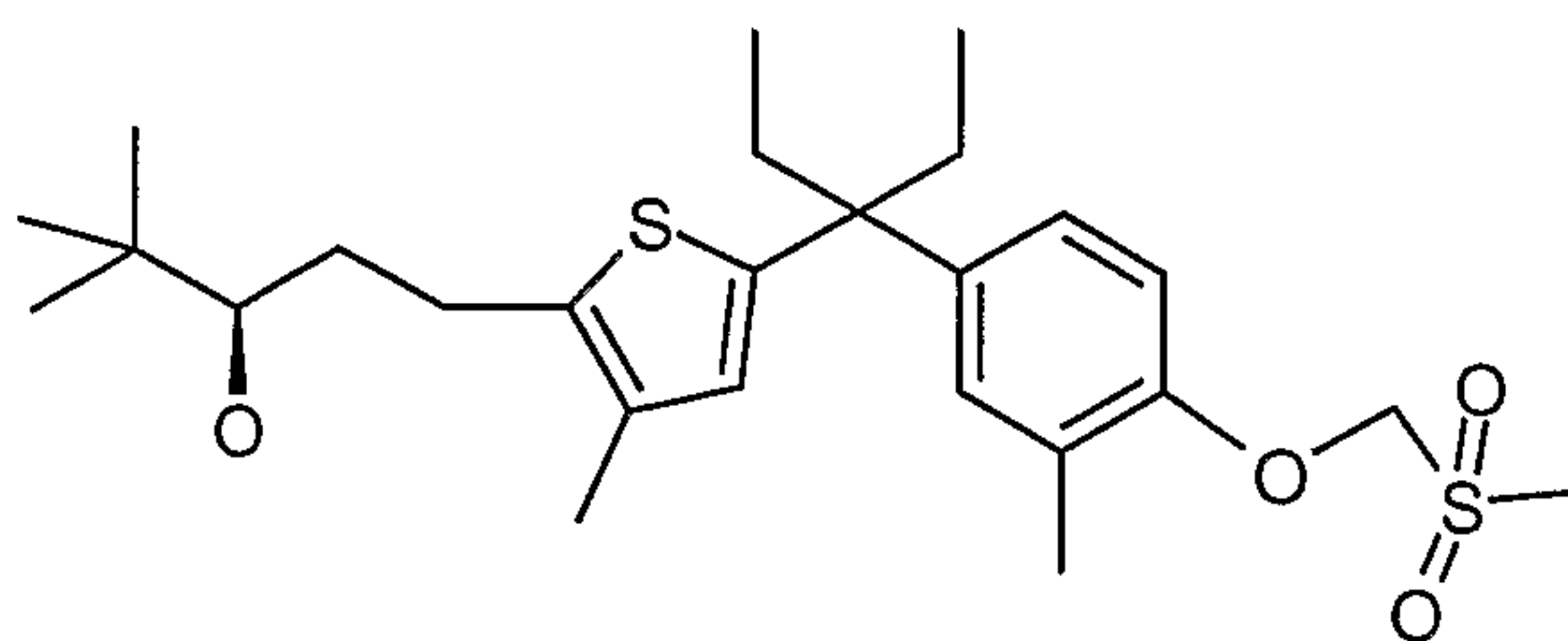


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10 X13)



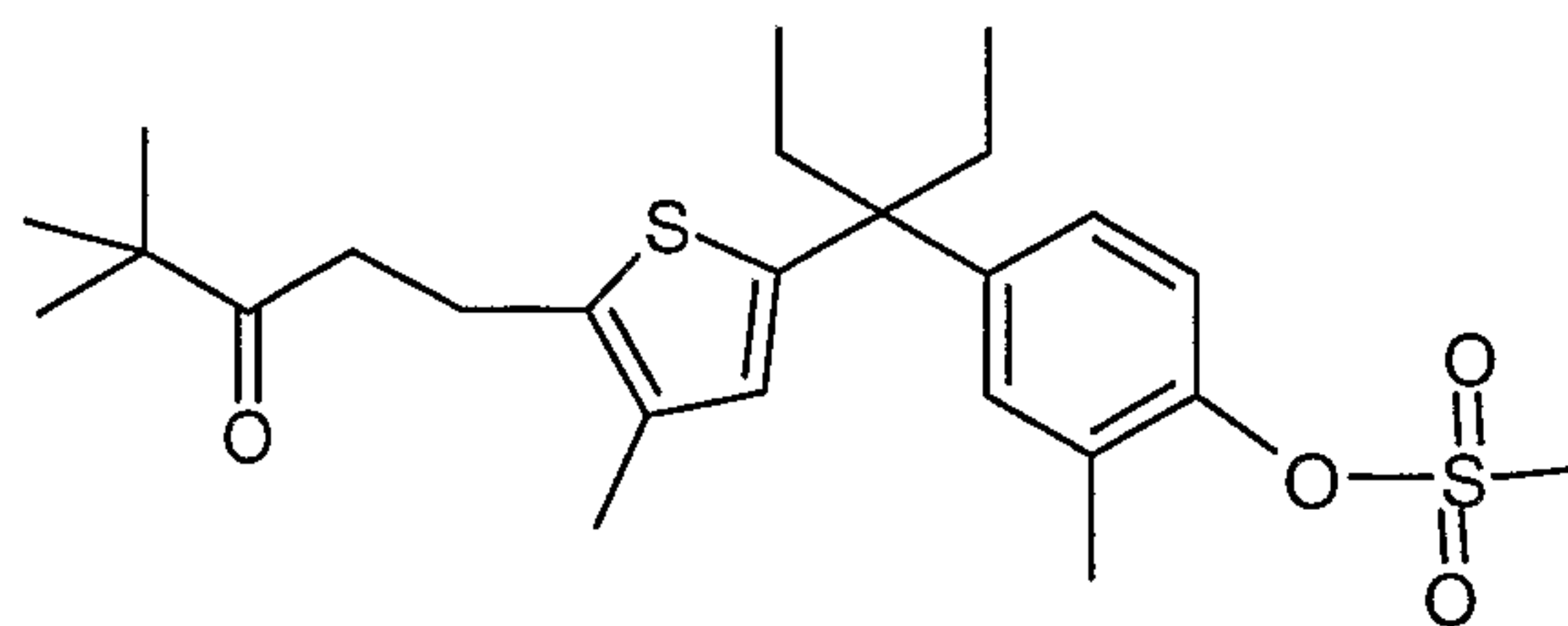
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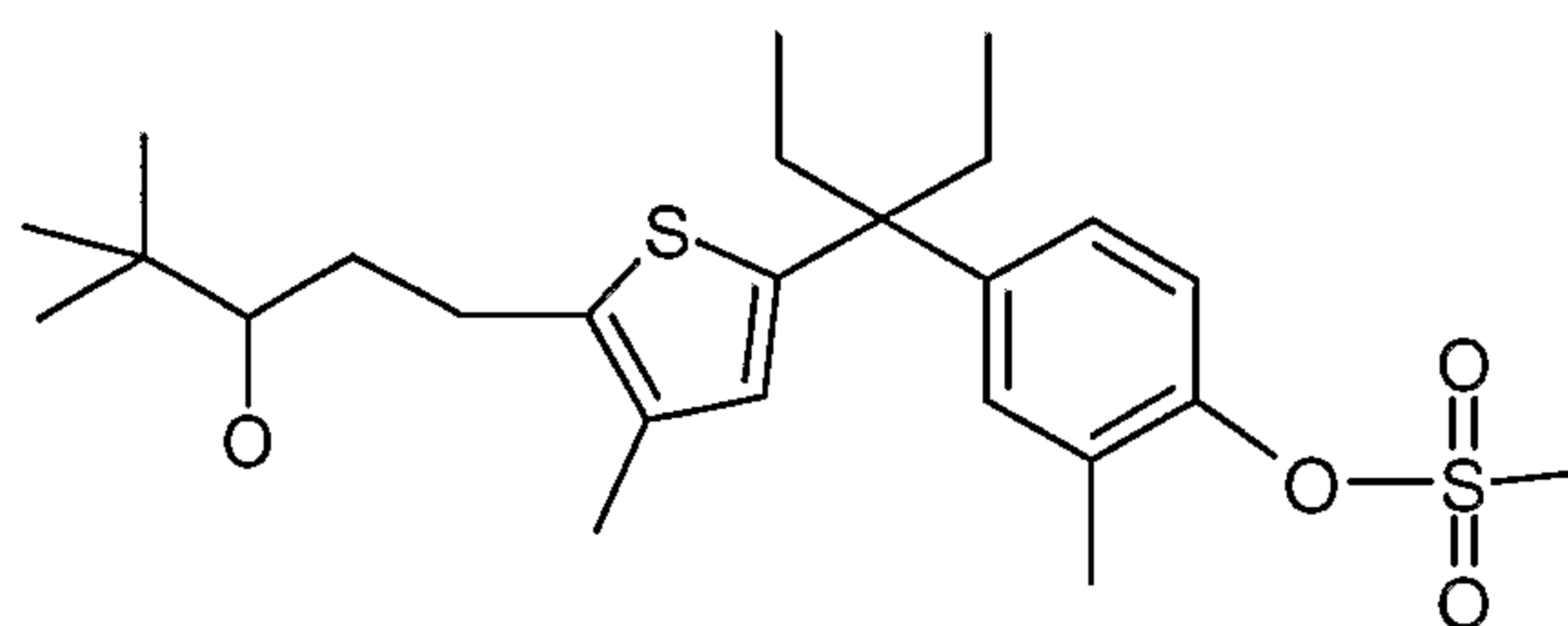
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X17)

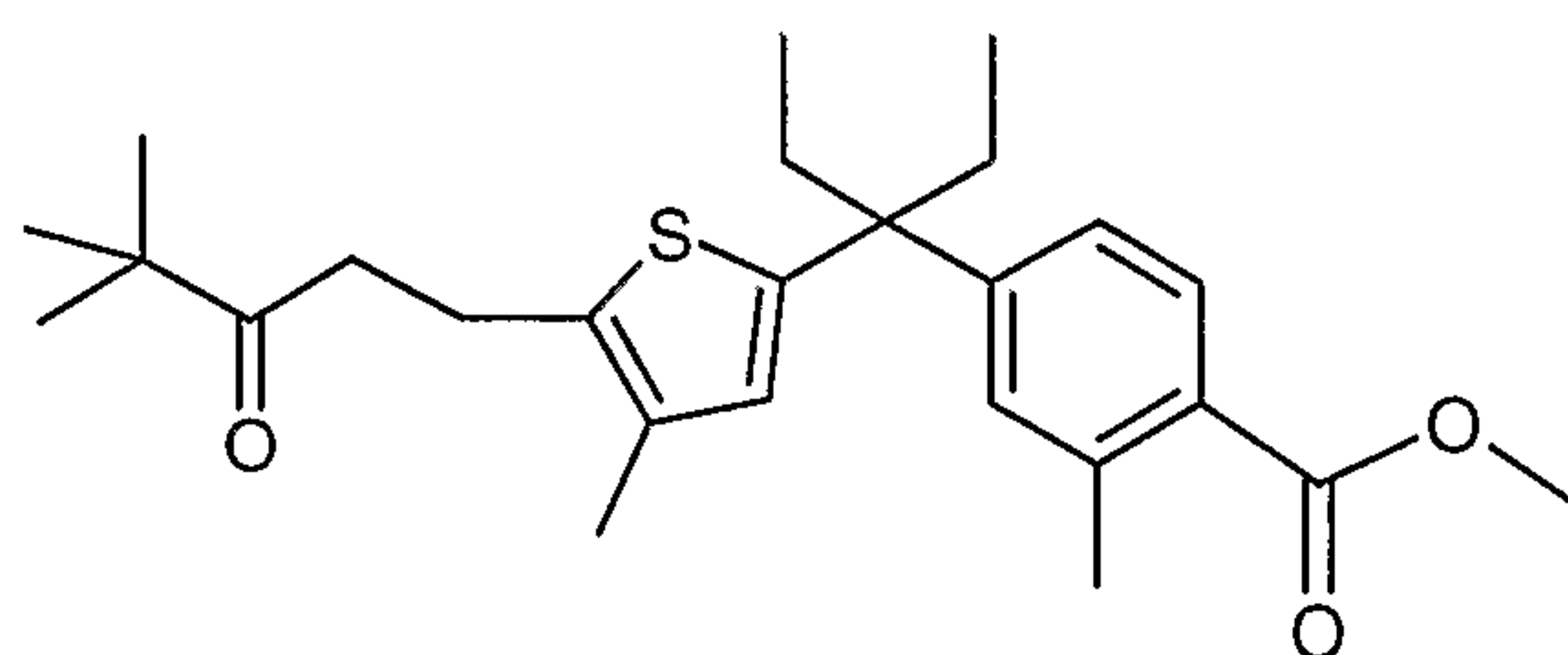


X19)

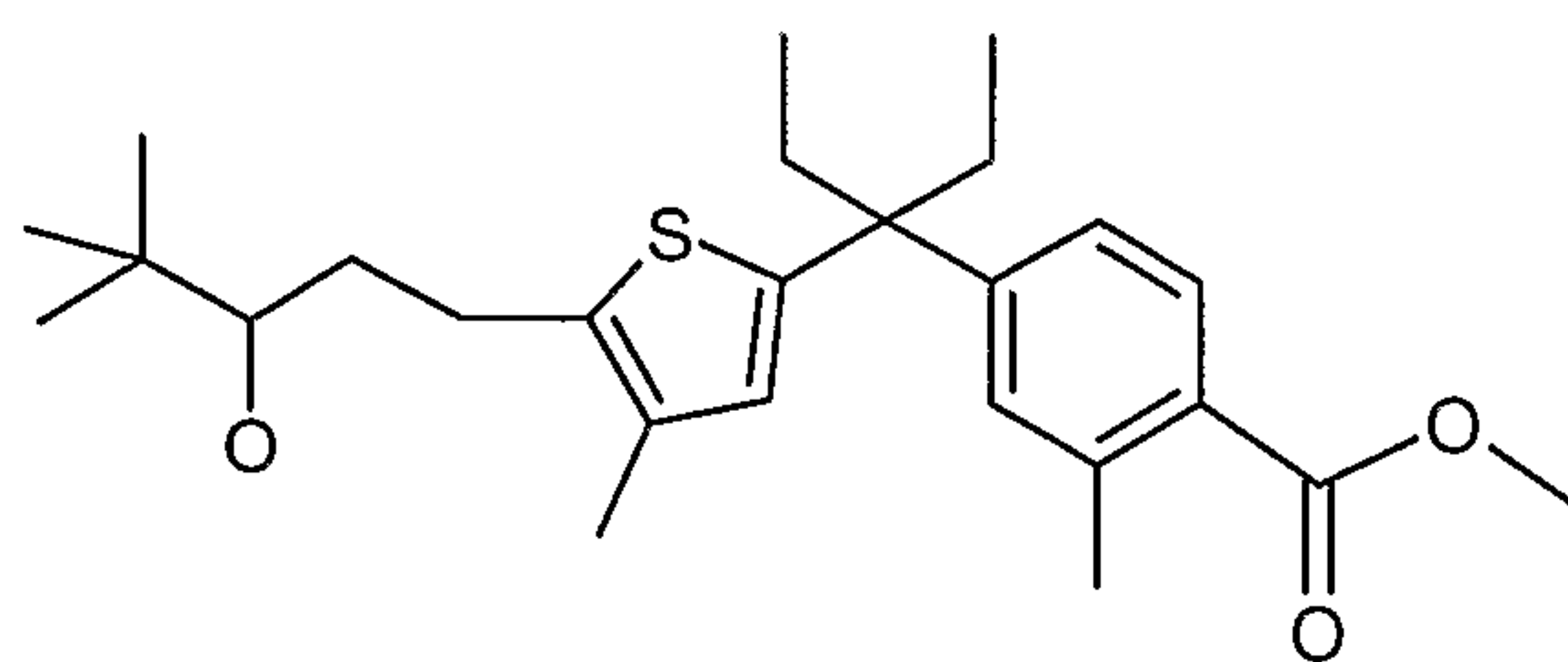


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X20)

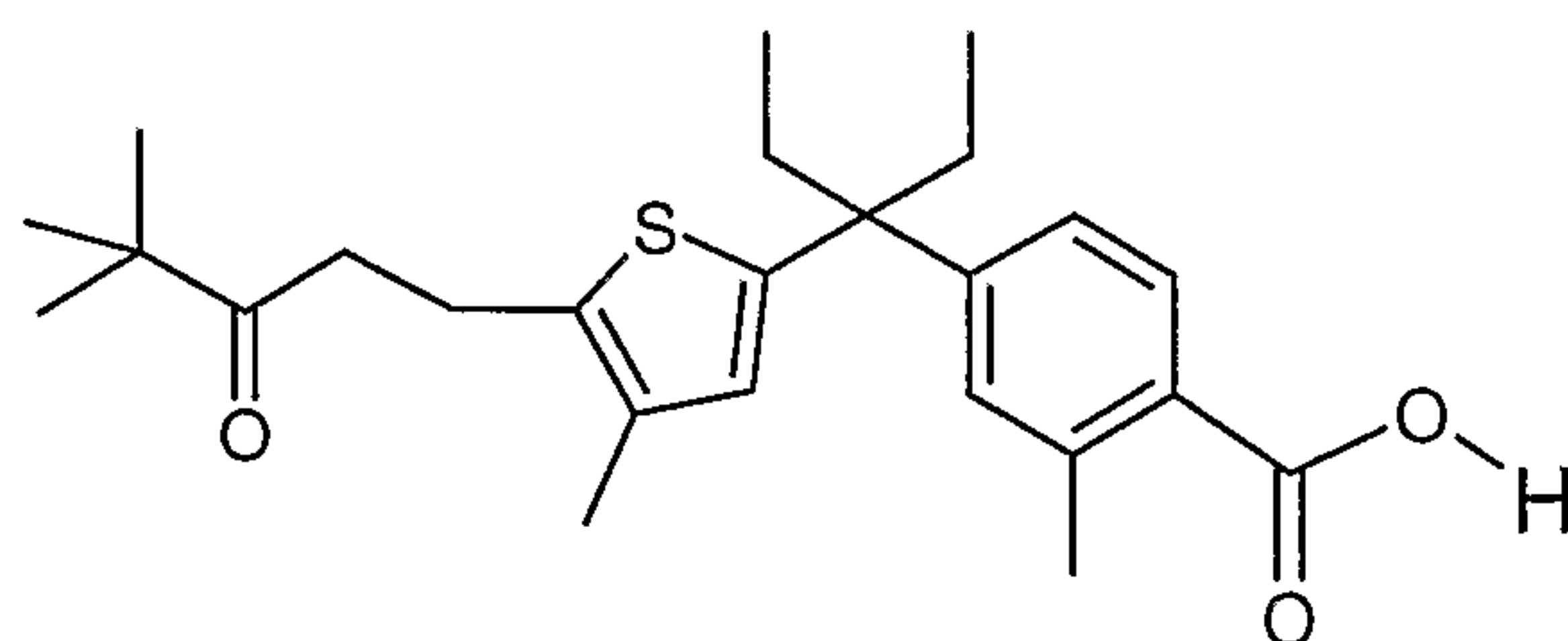


X21)



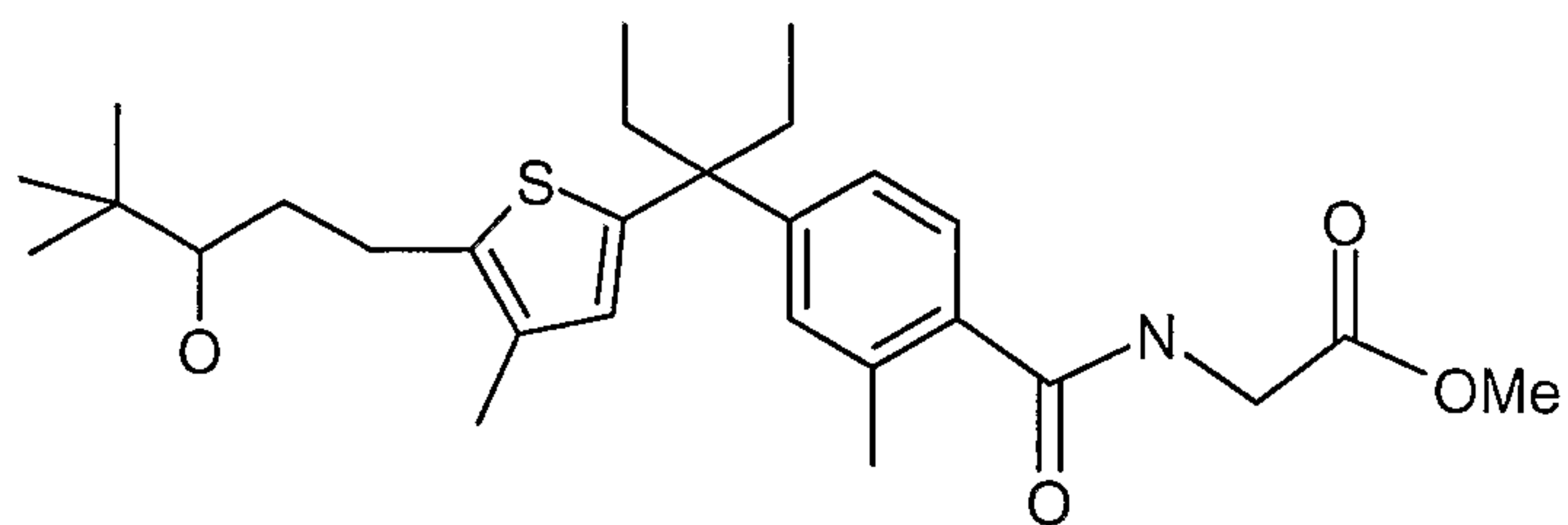
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X22)

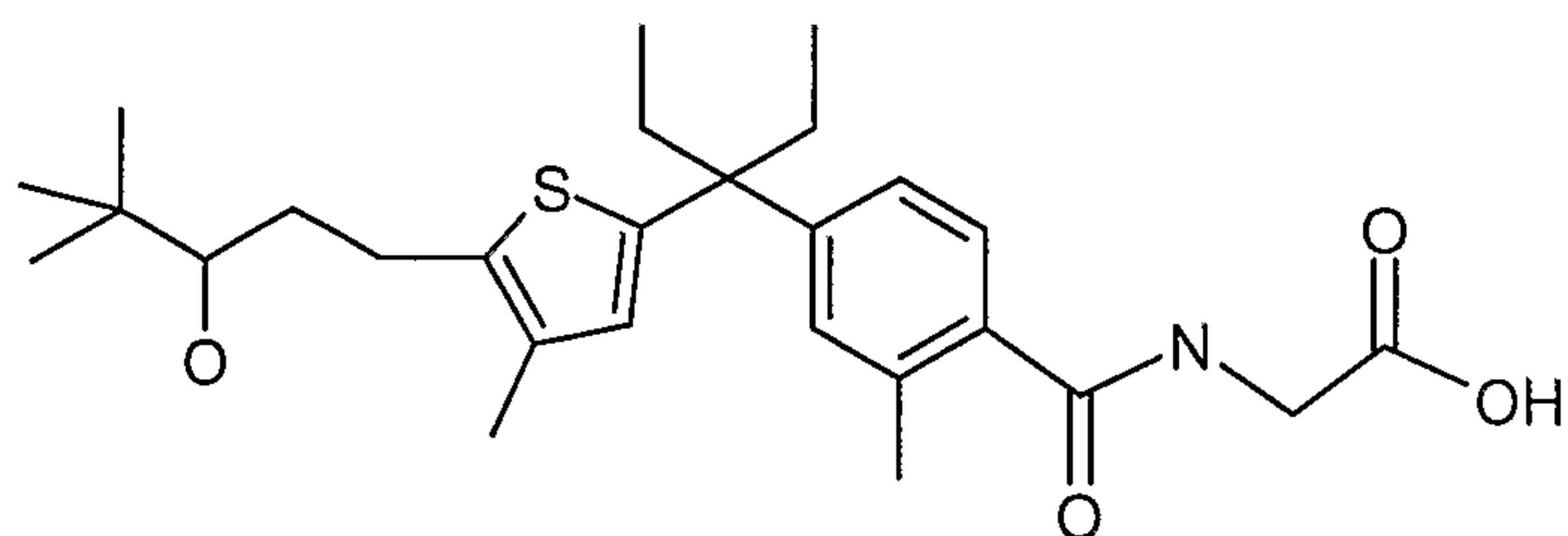


X24)

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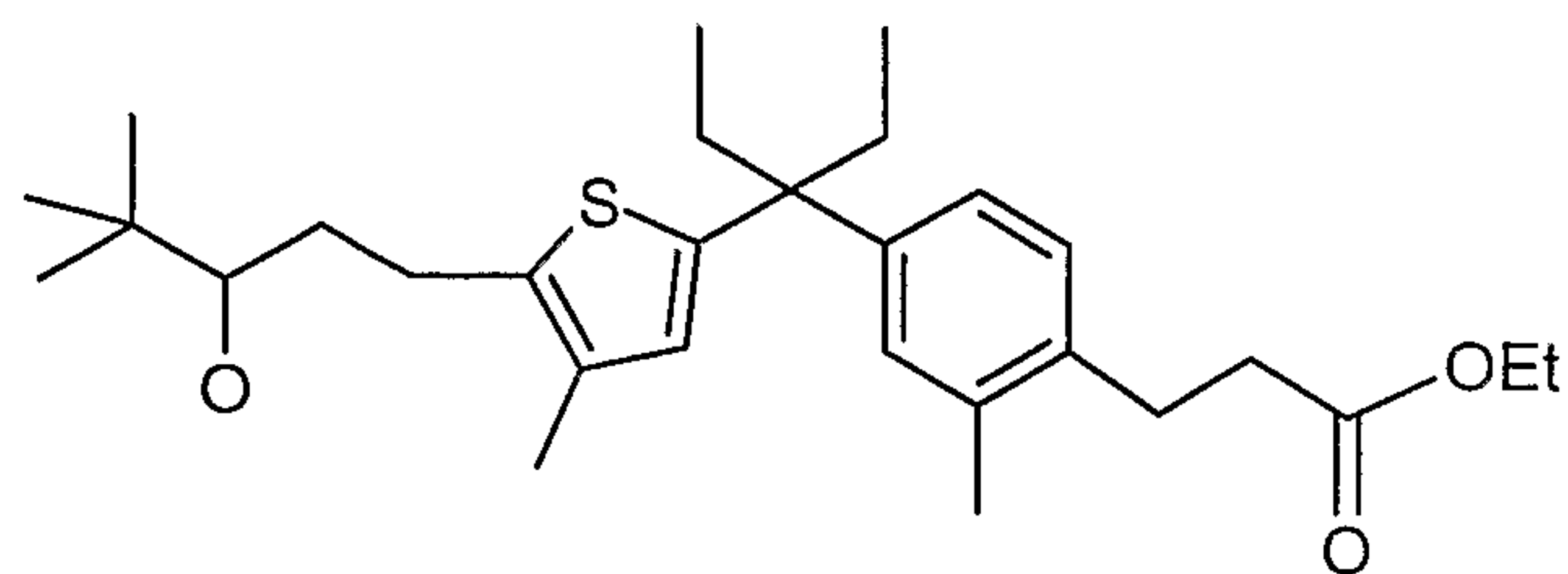


X26)

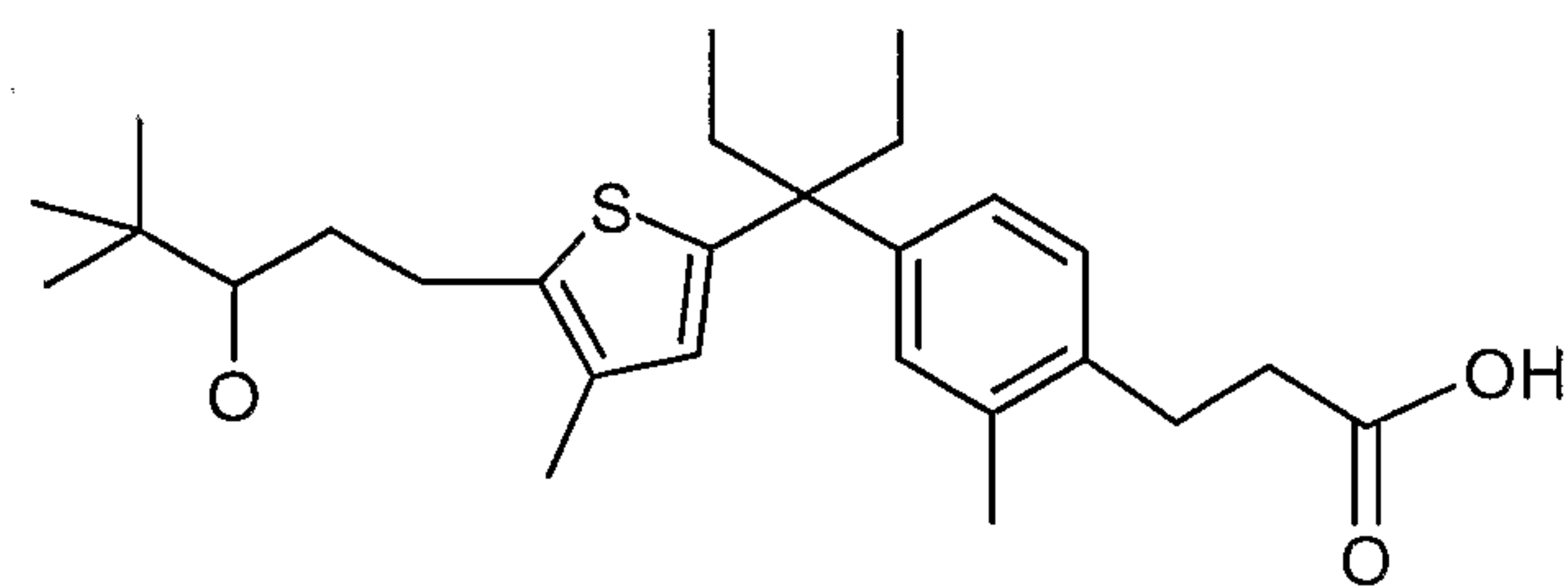


X28)

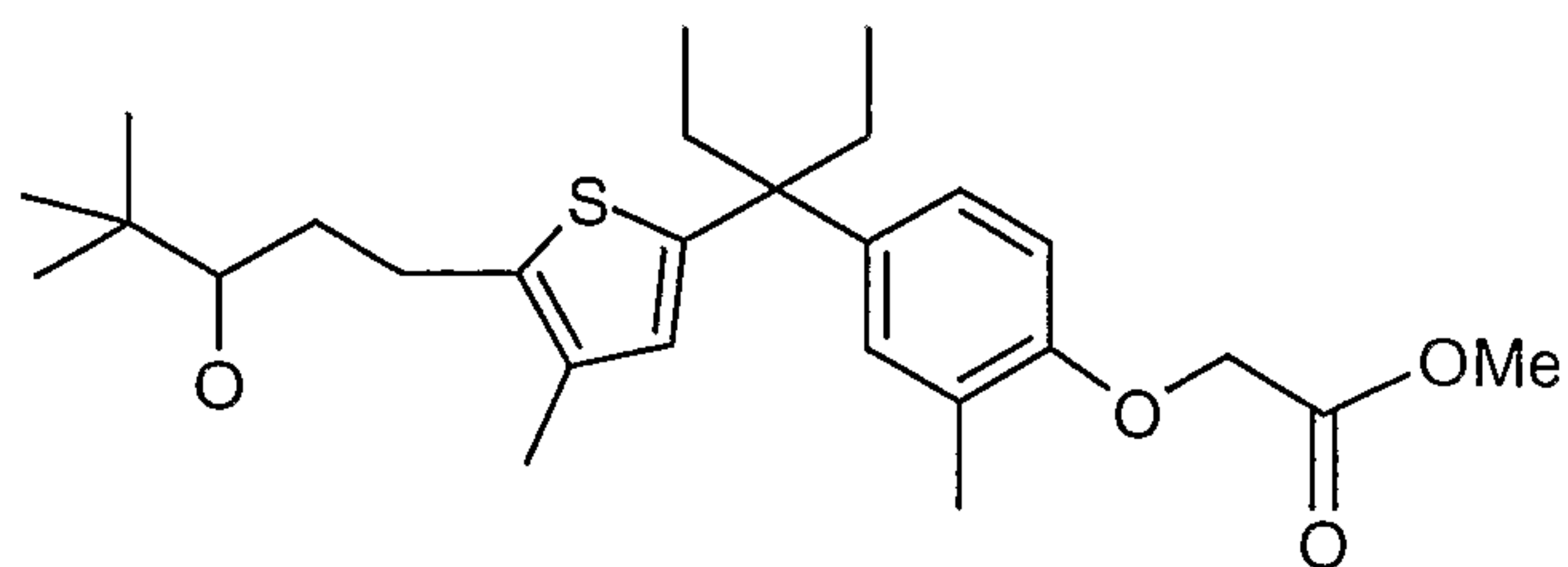
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X29)



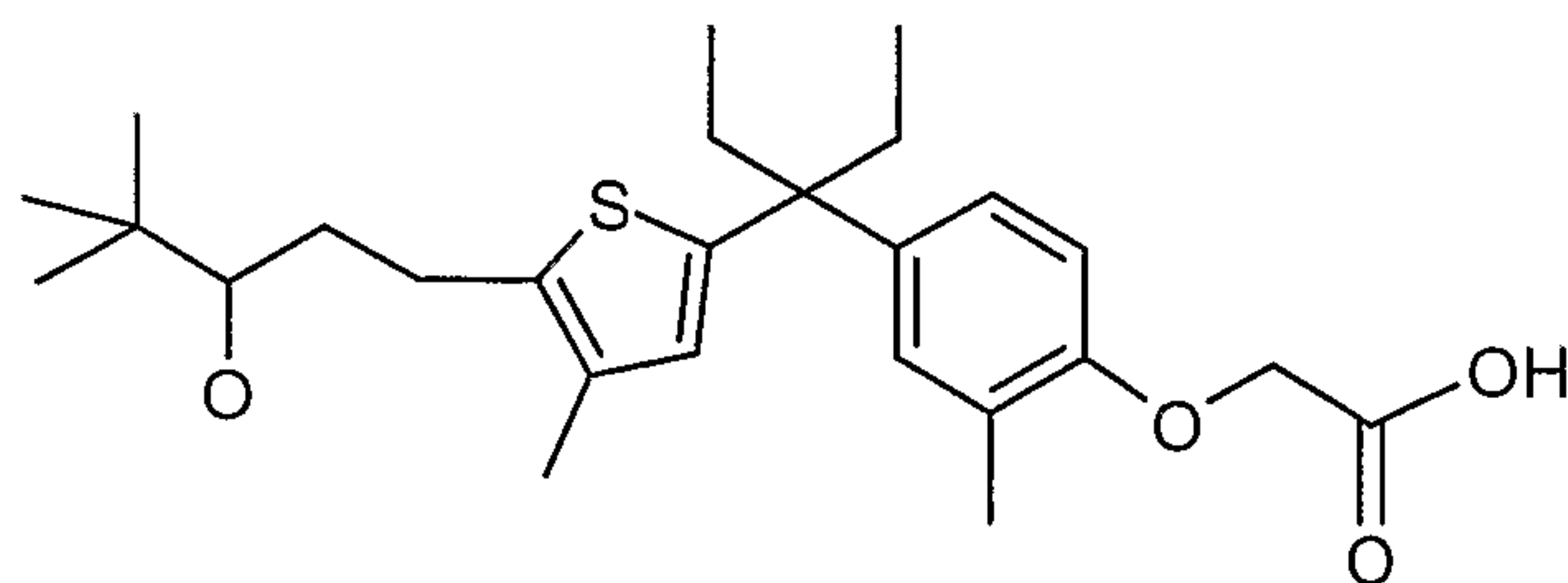
X31)



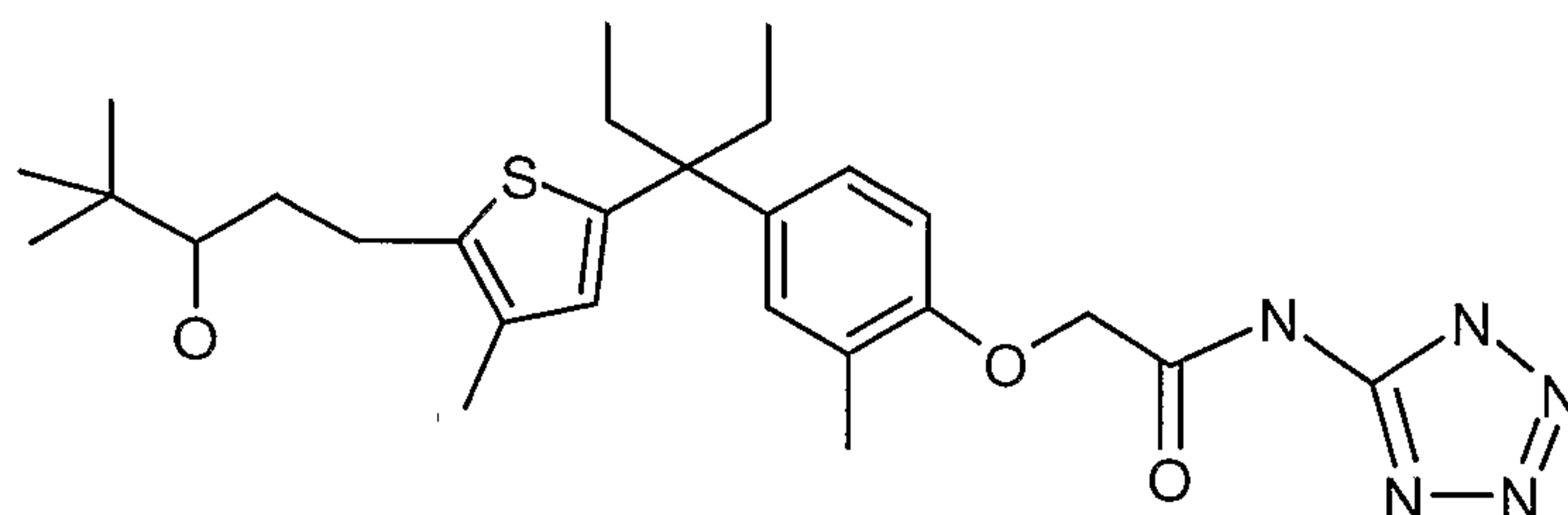
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X32)

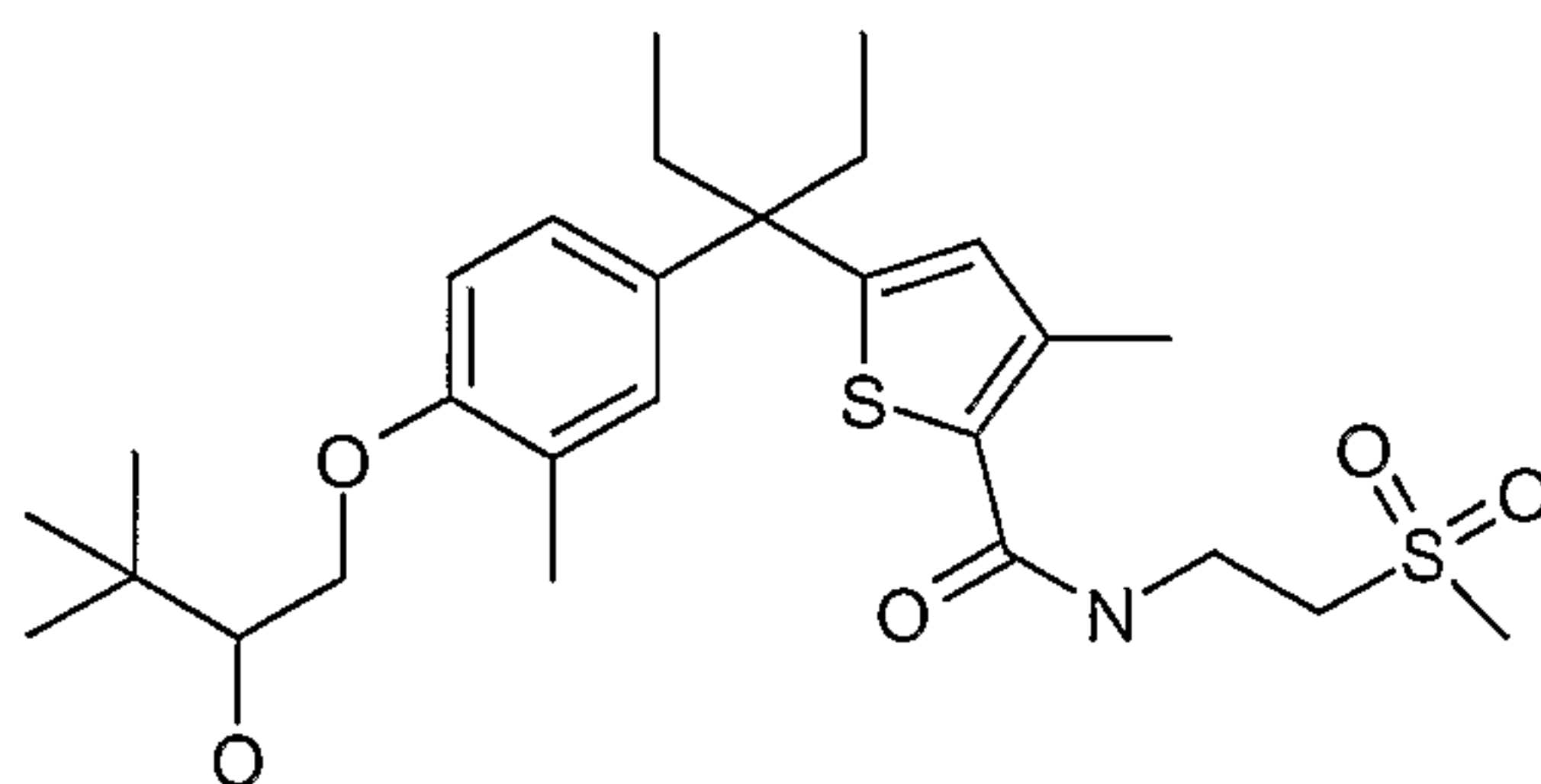


X34)

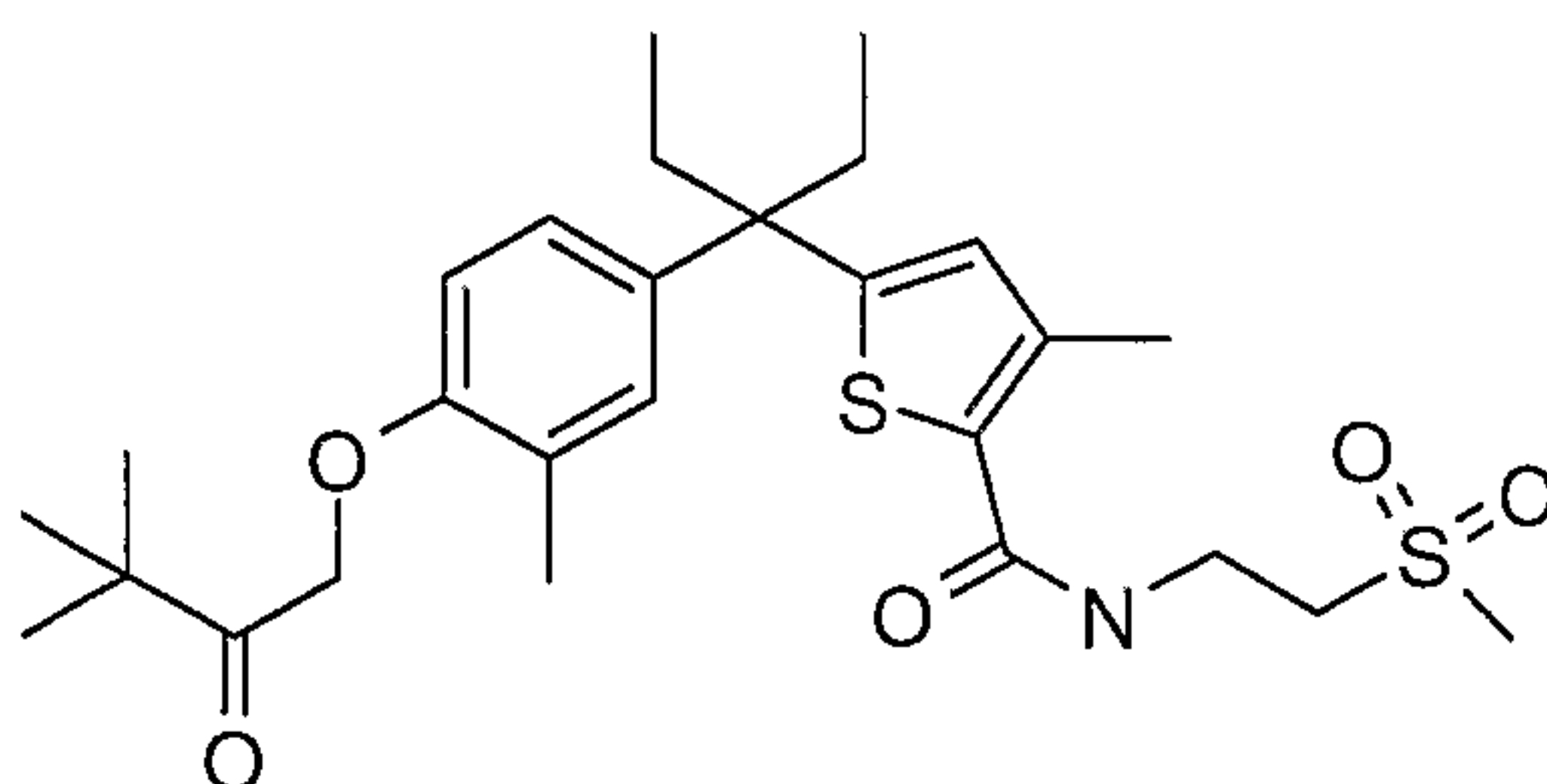


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X38)



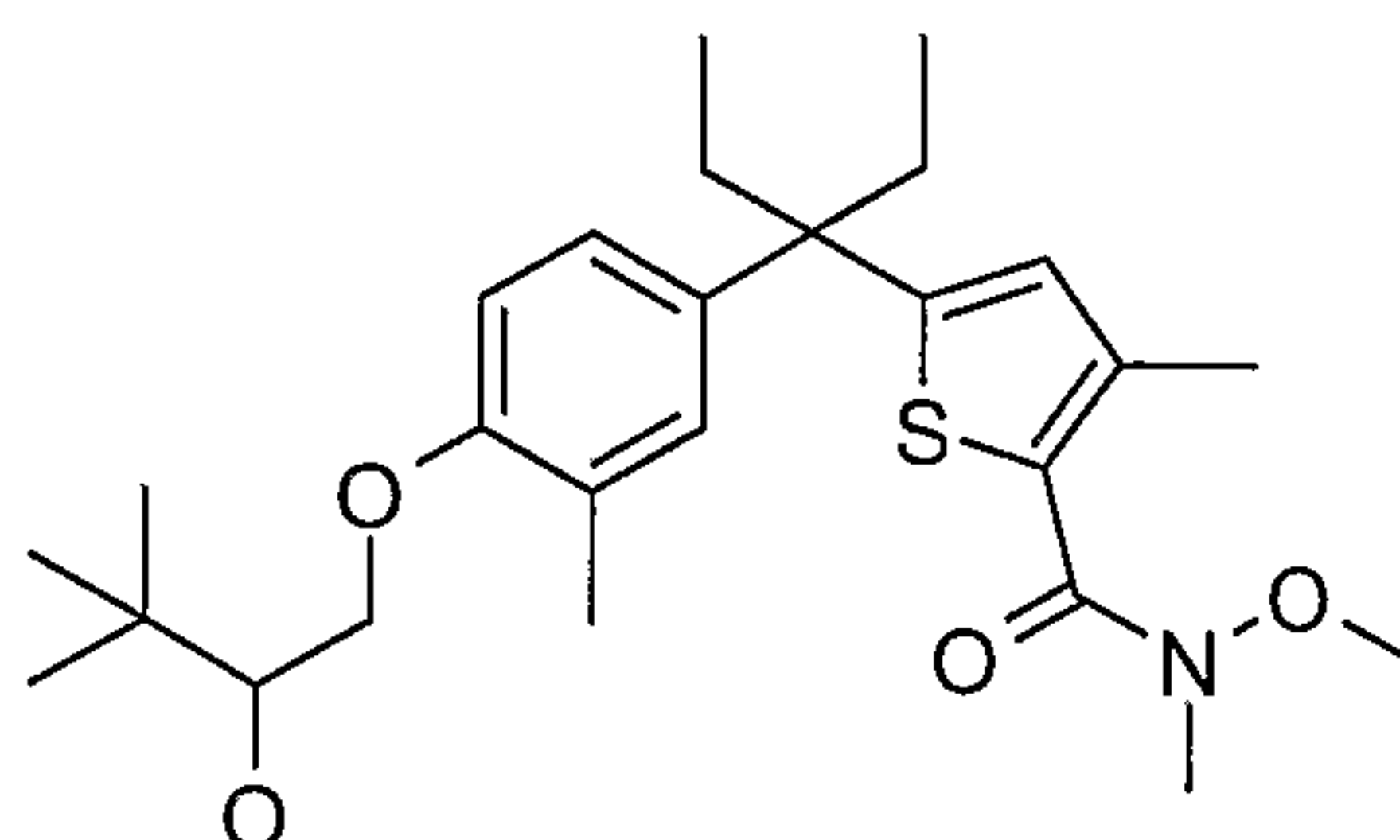
X41)



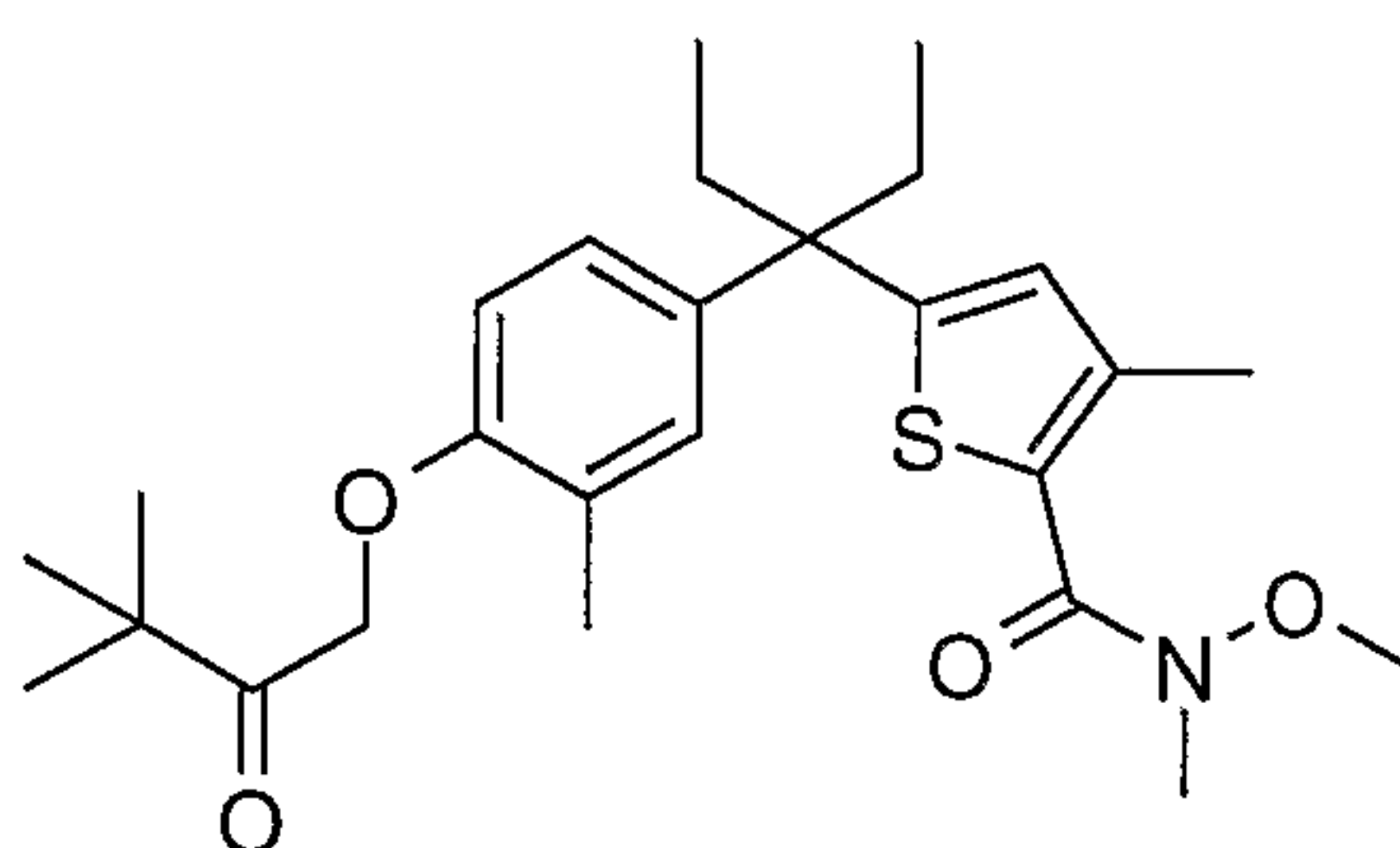
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X42)

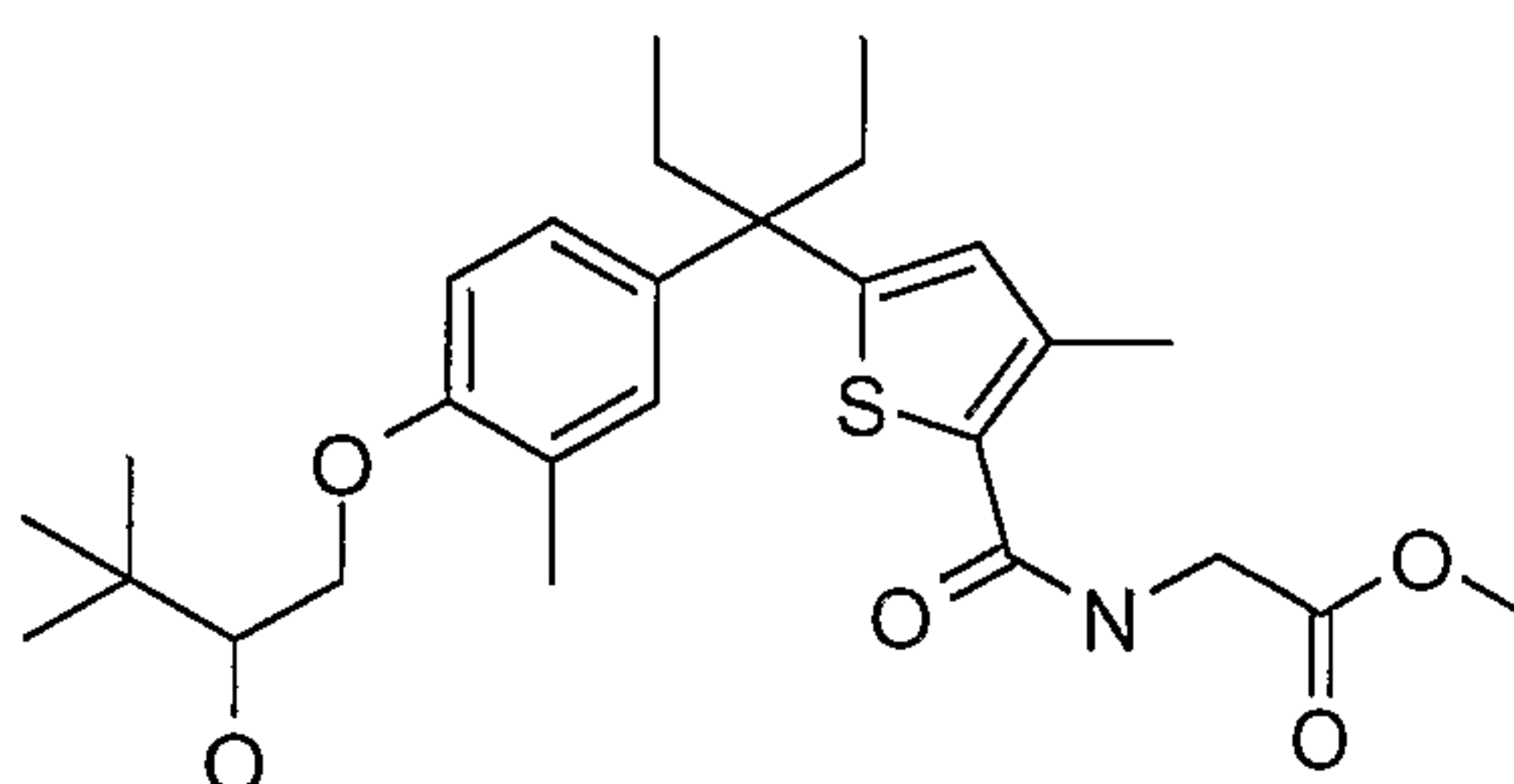
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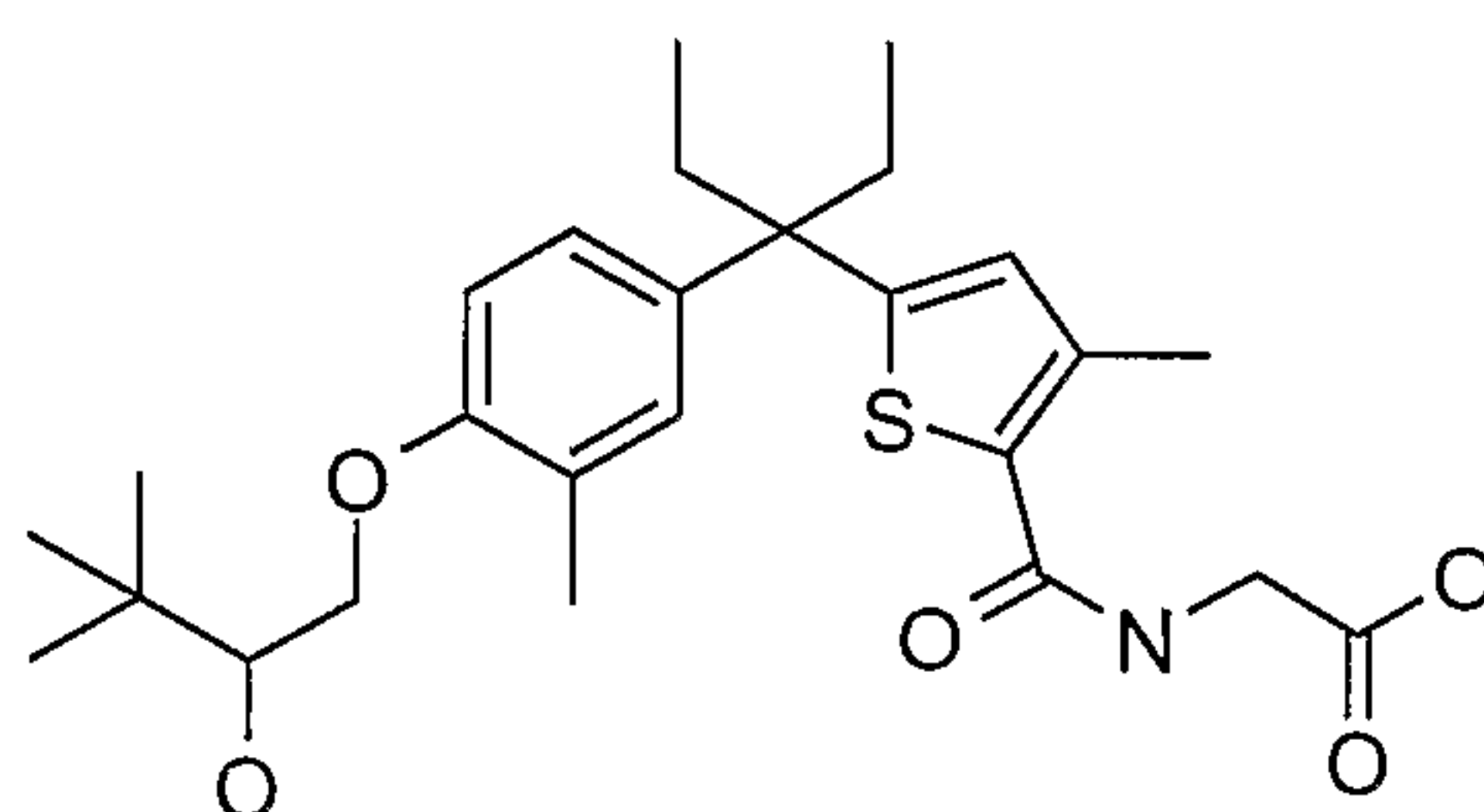
X45)



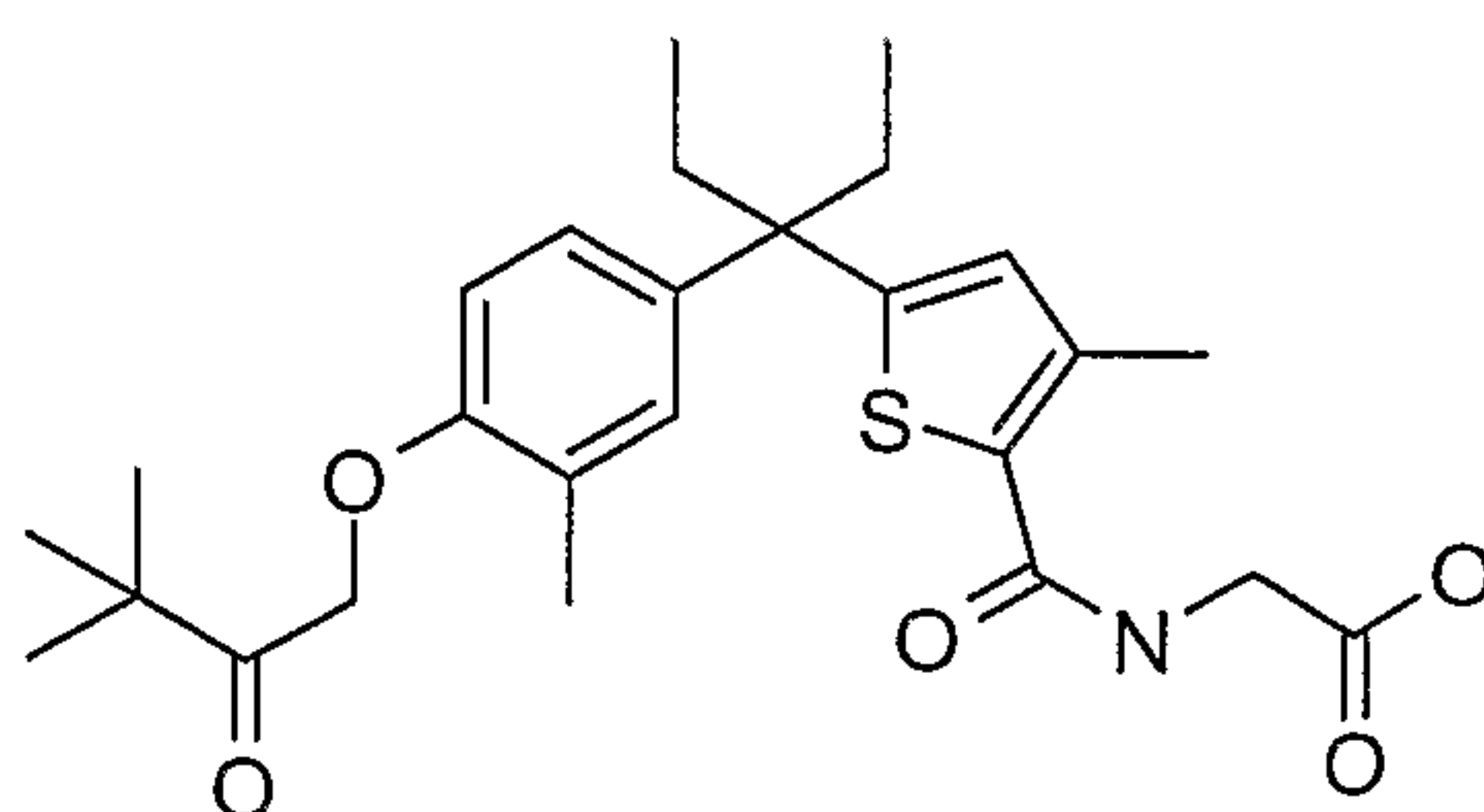
5 X46)



X47)

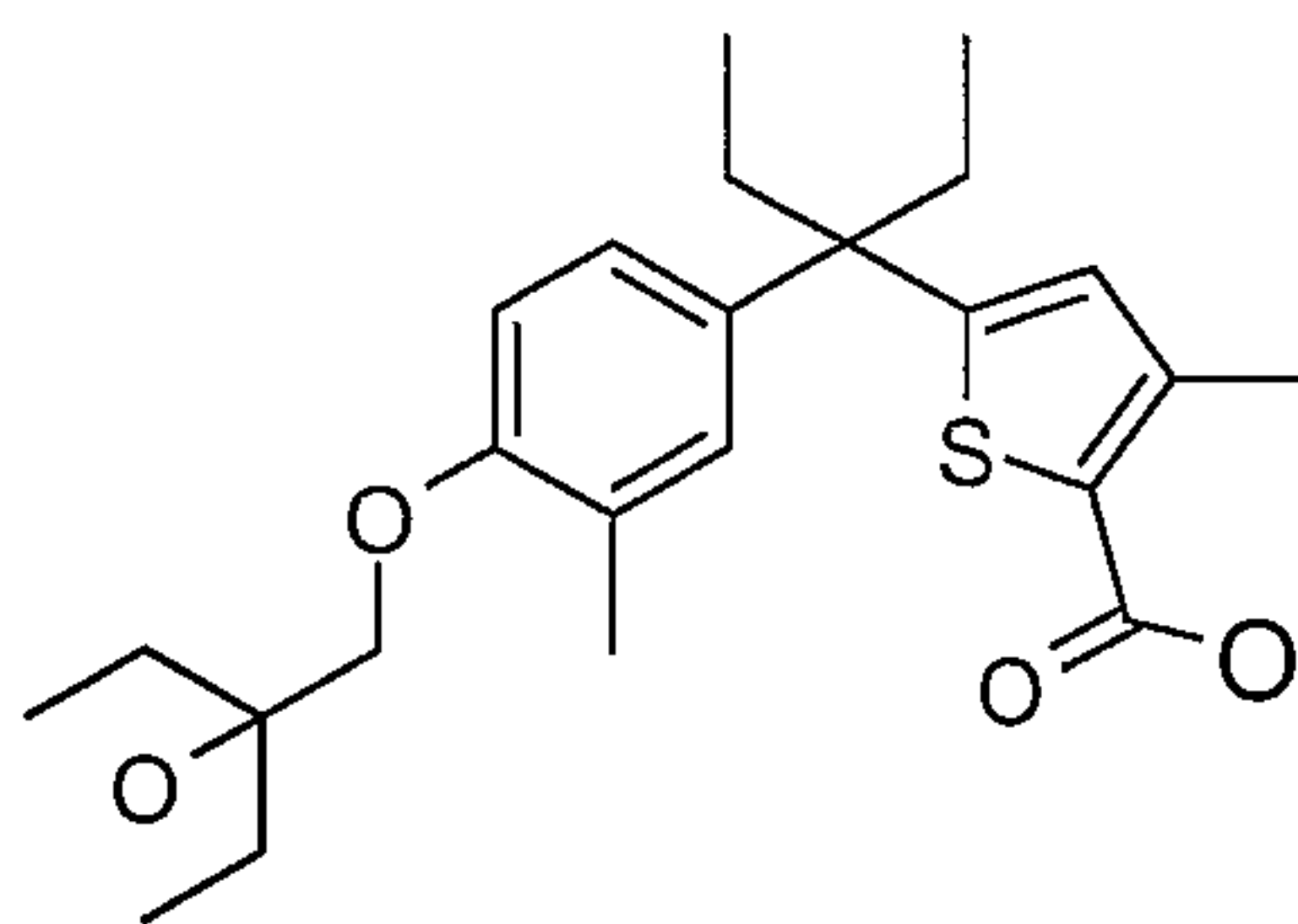


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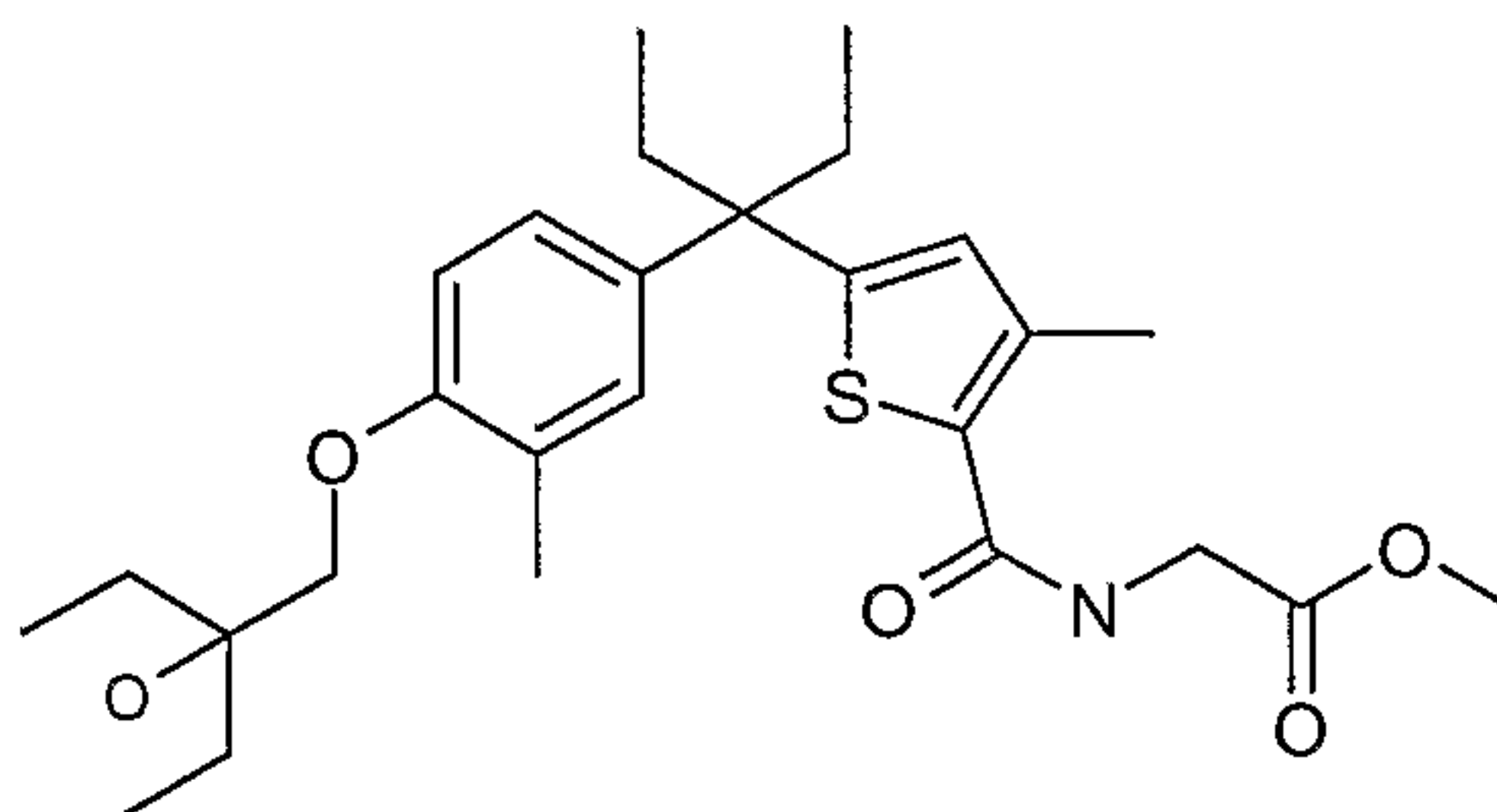


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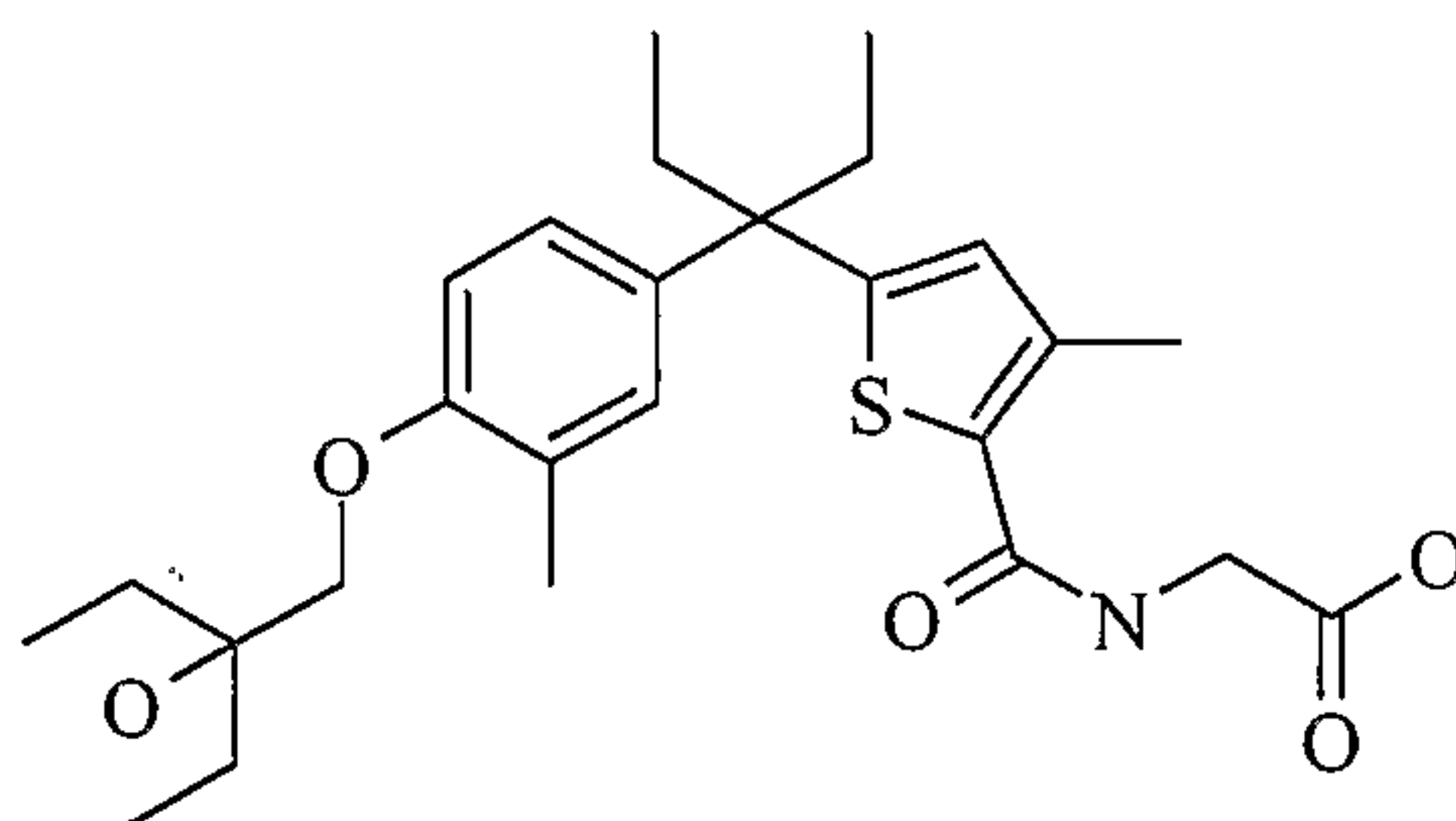
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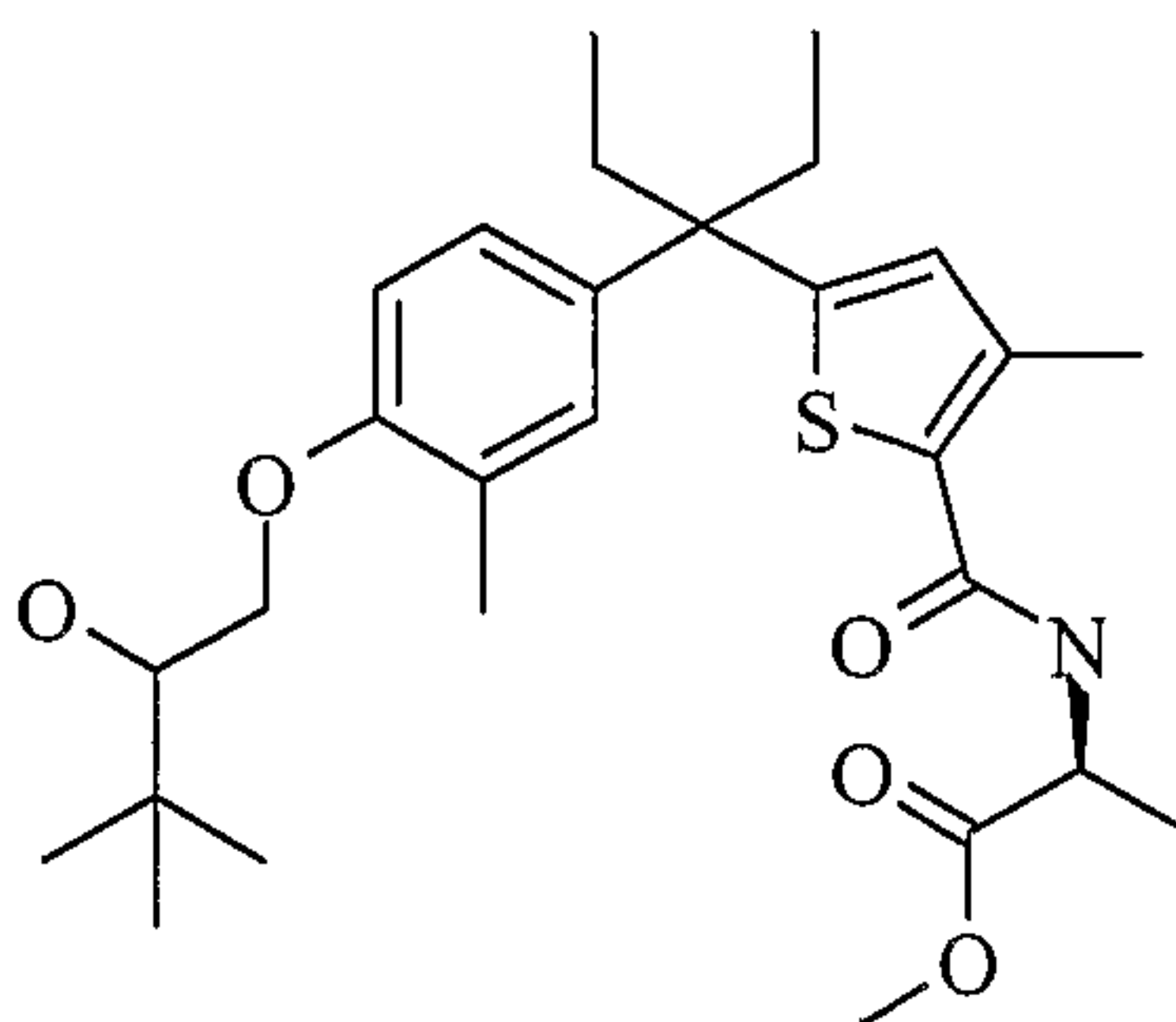
X52)



5 X53)

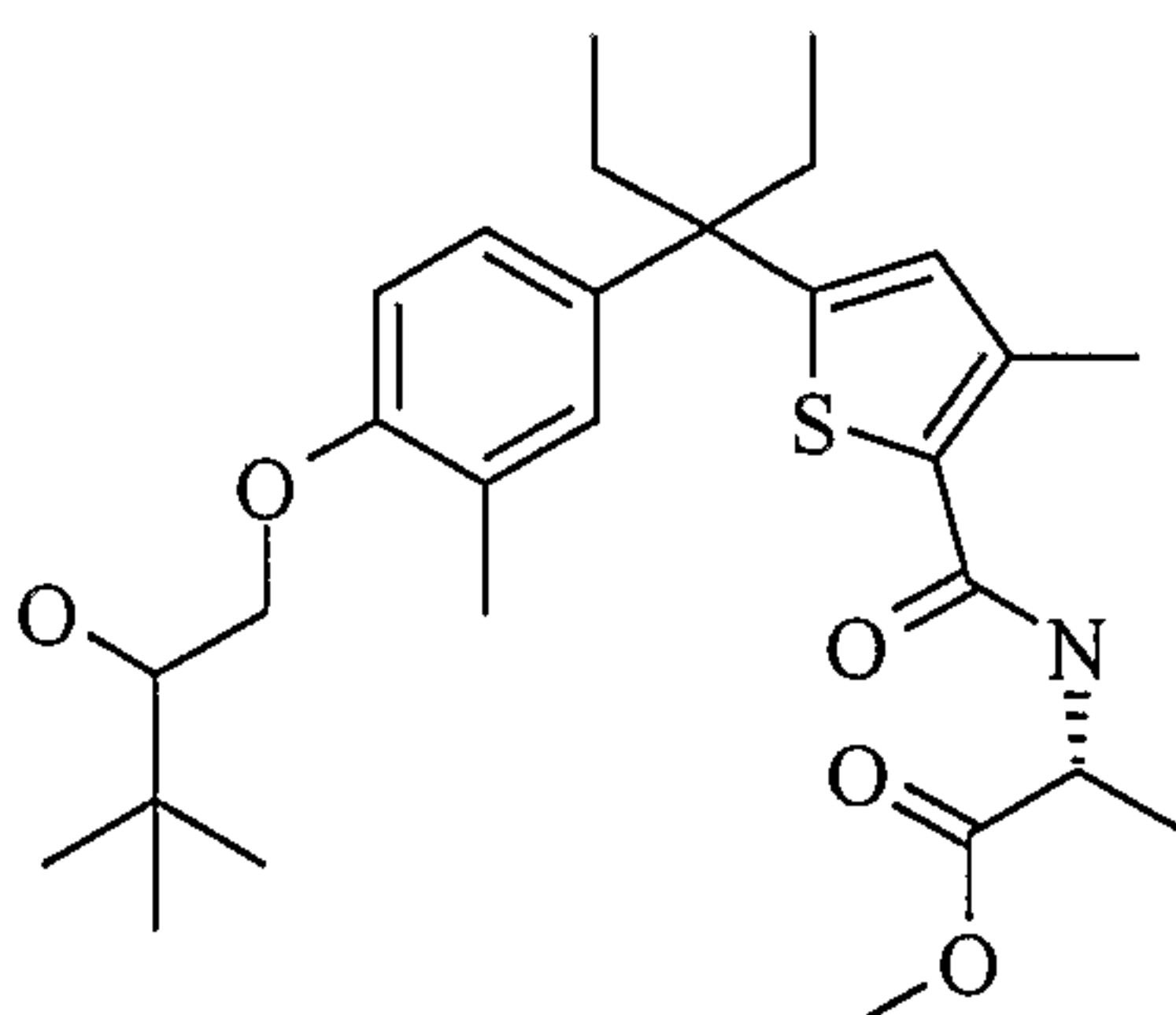


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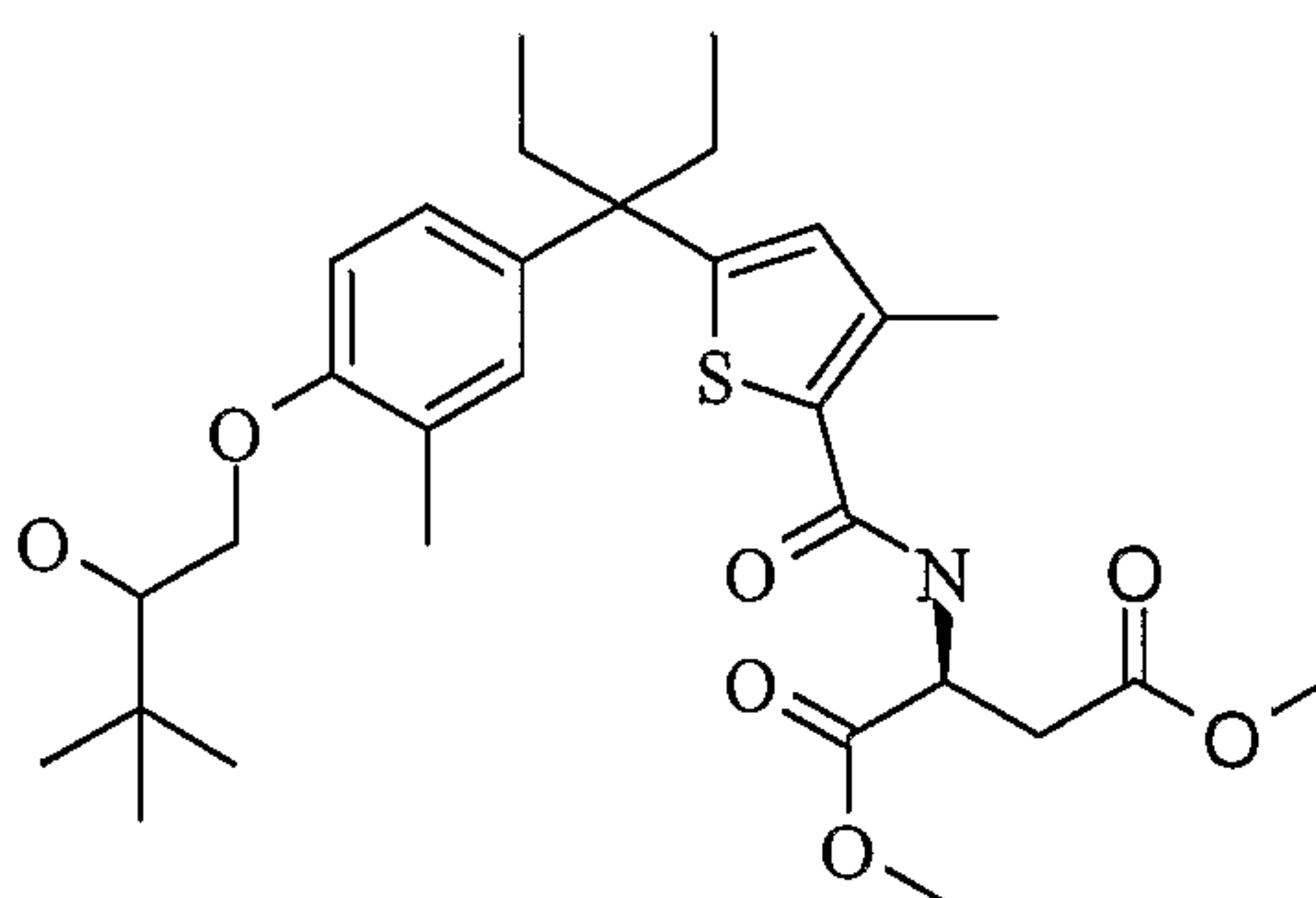


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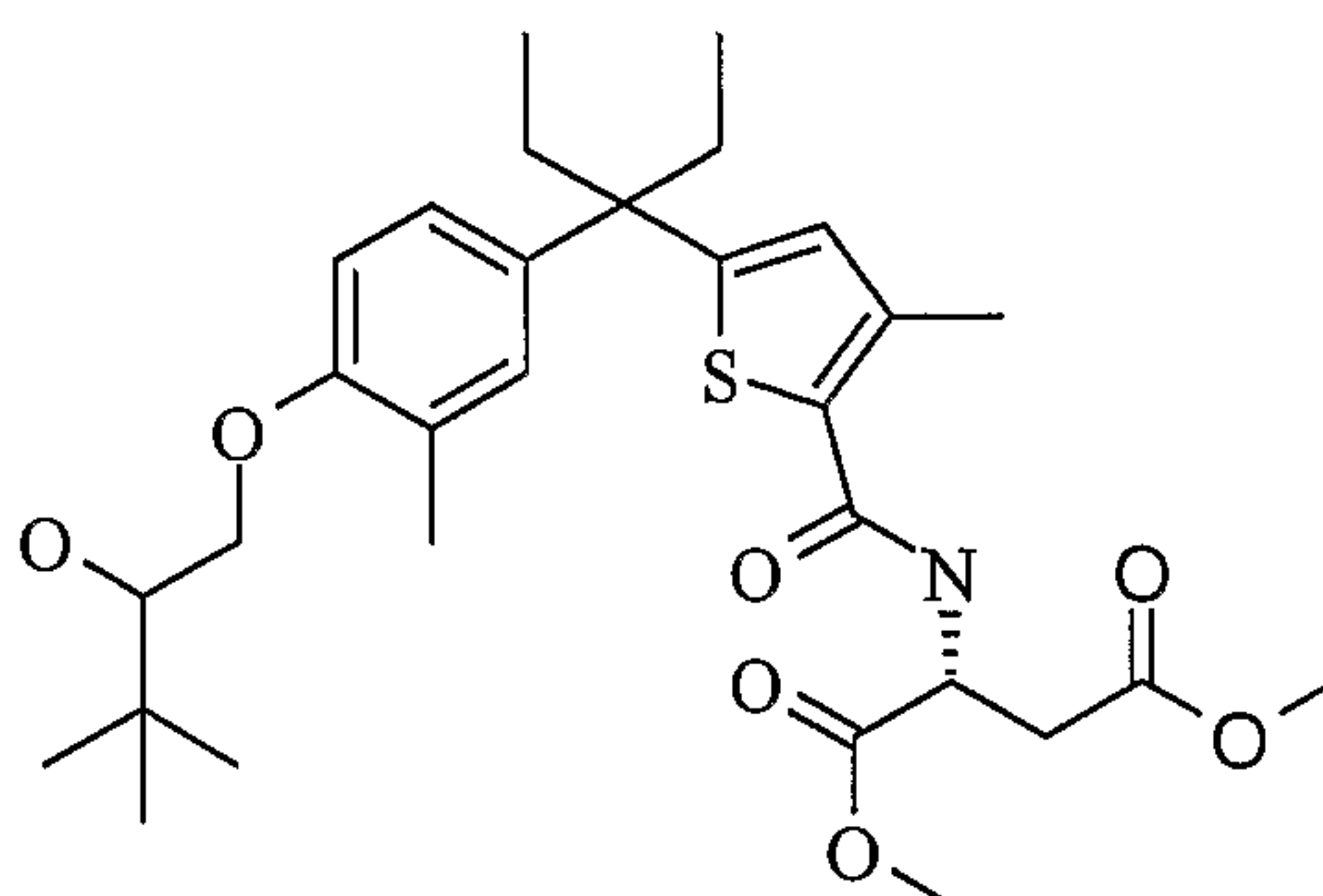
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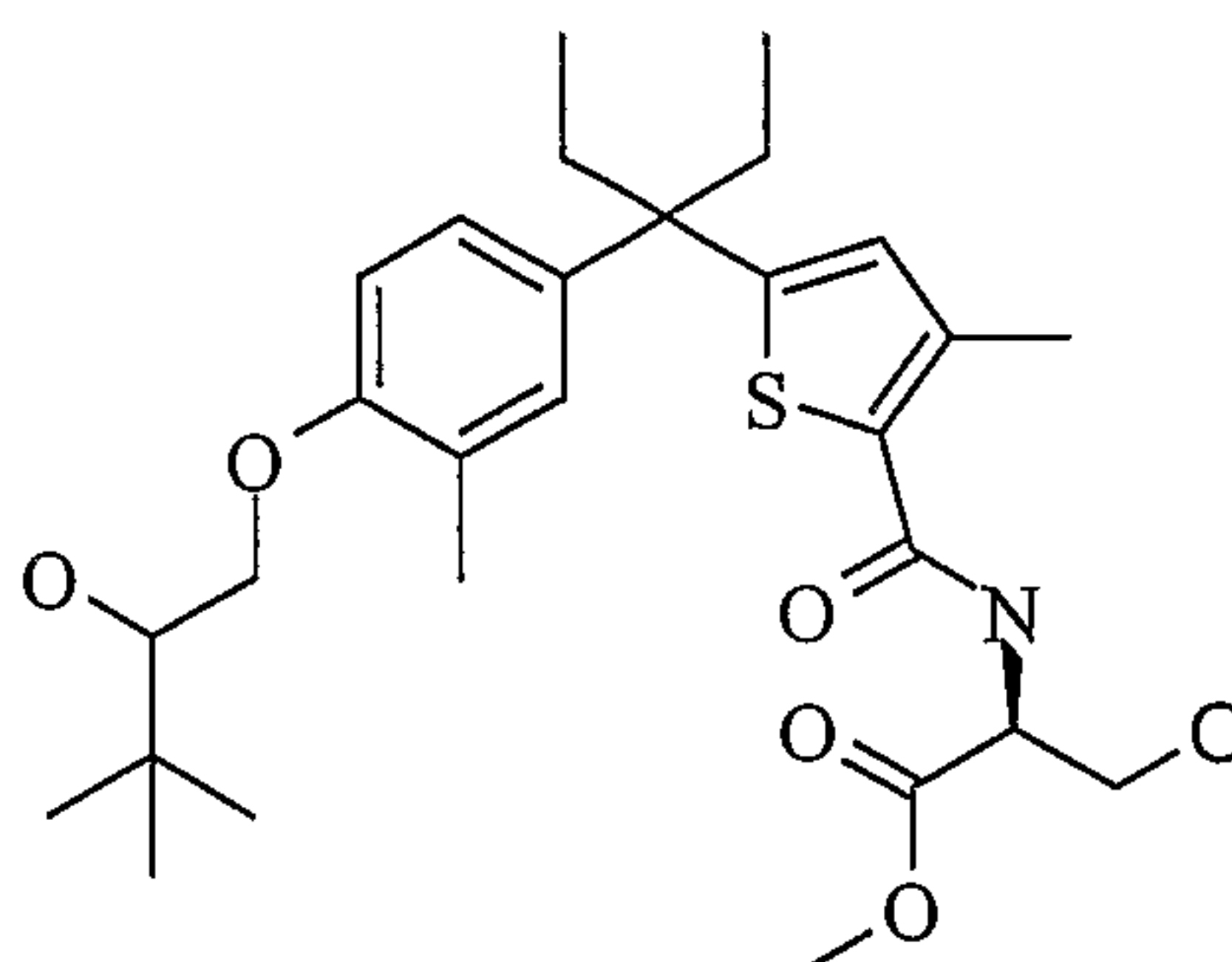
X58)



5 X60)

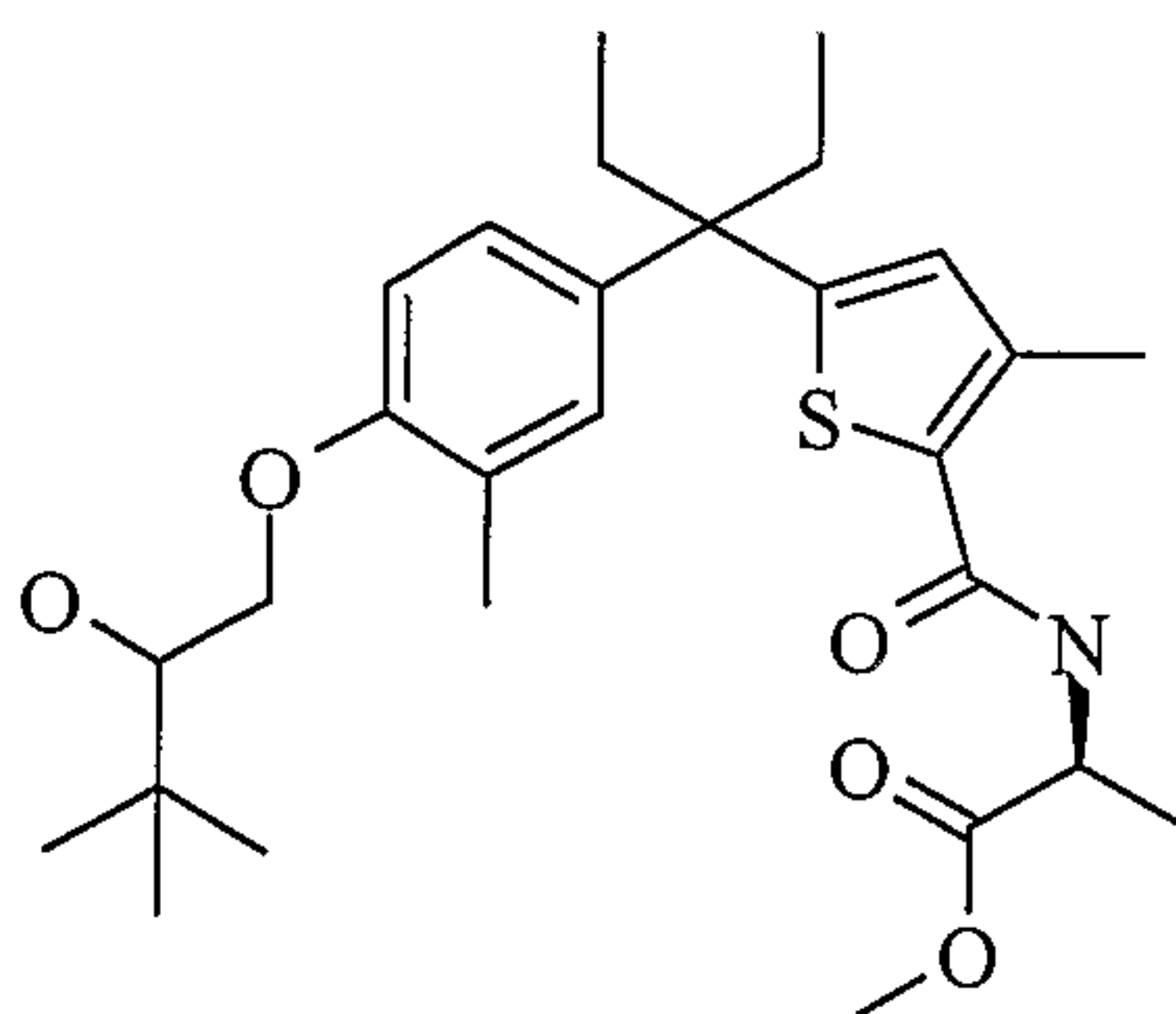


X62)

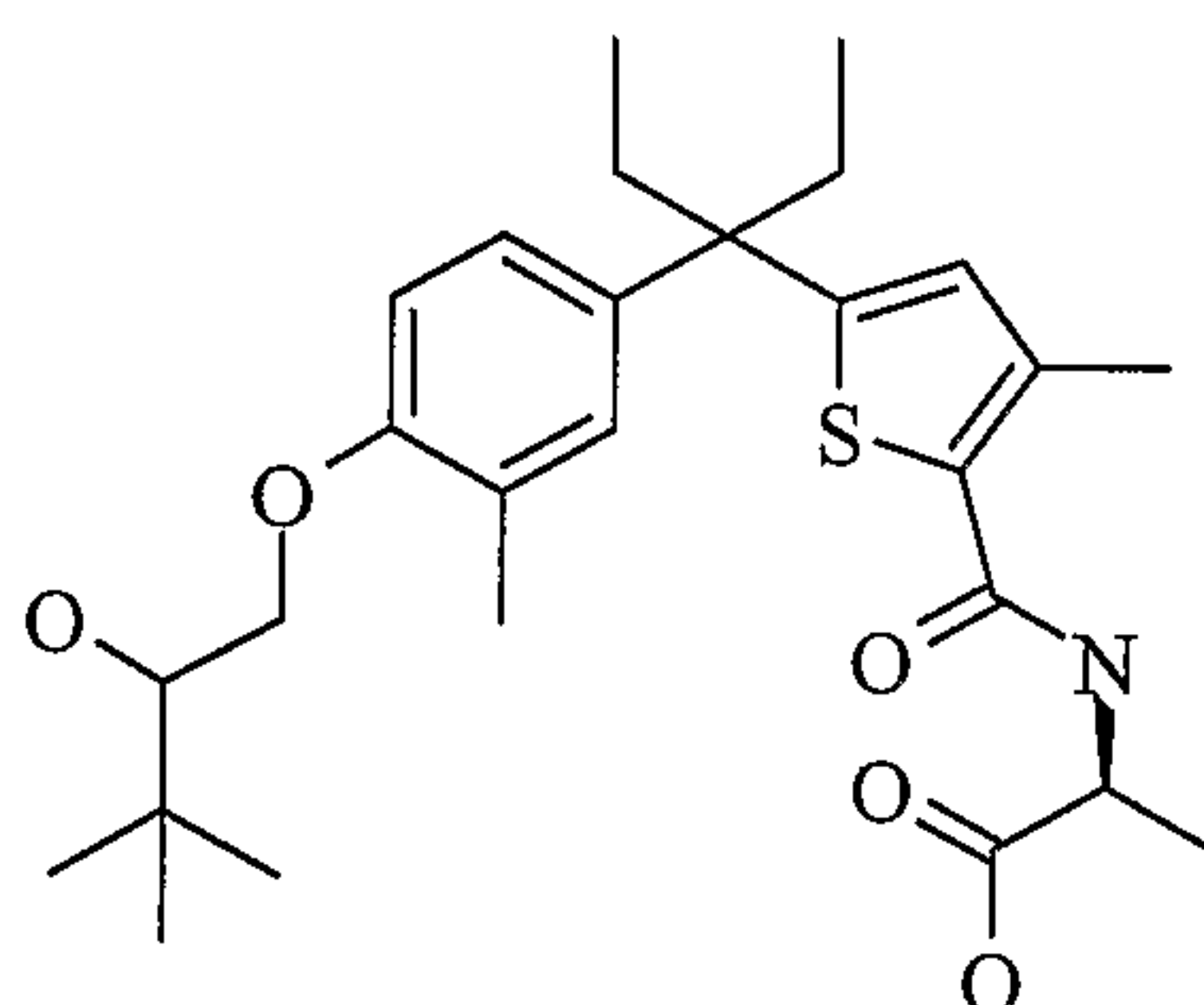


X64)

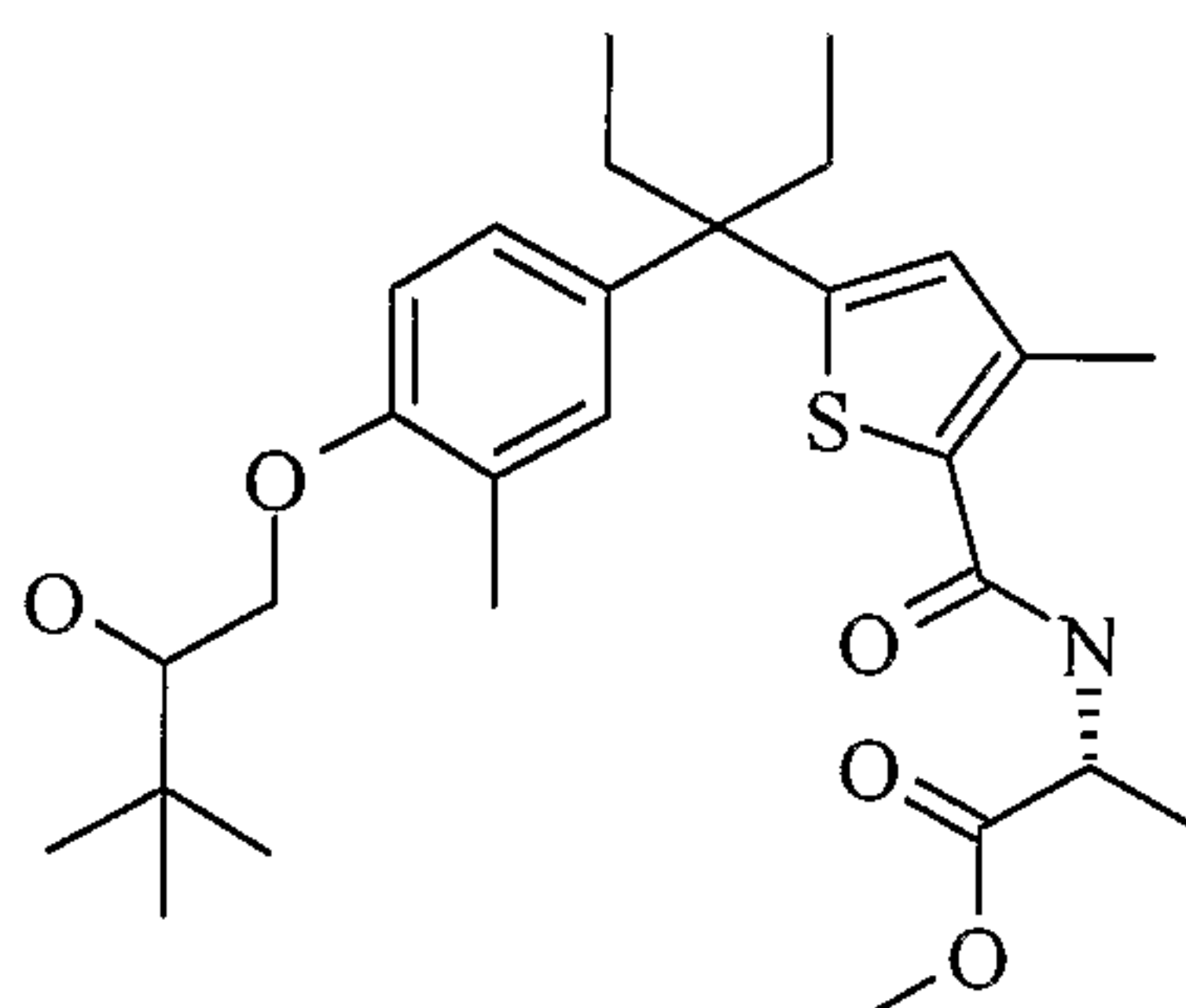
-68-



X65)

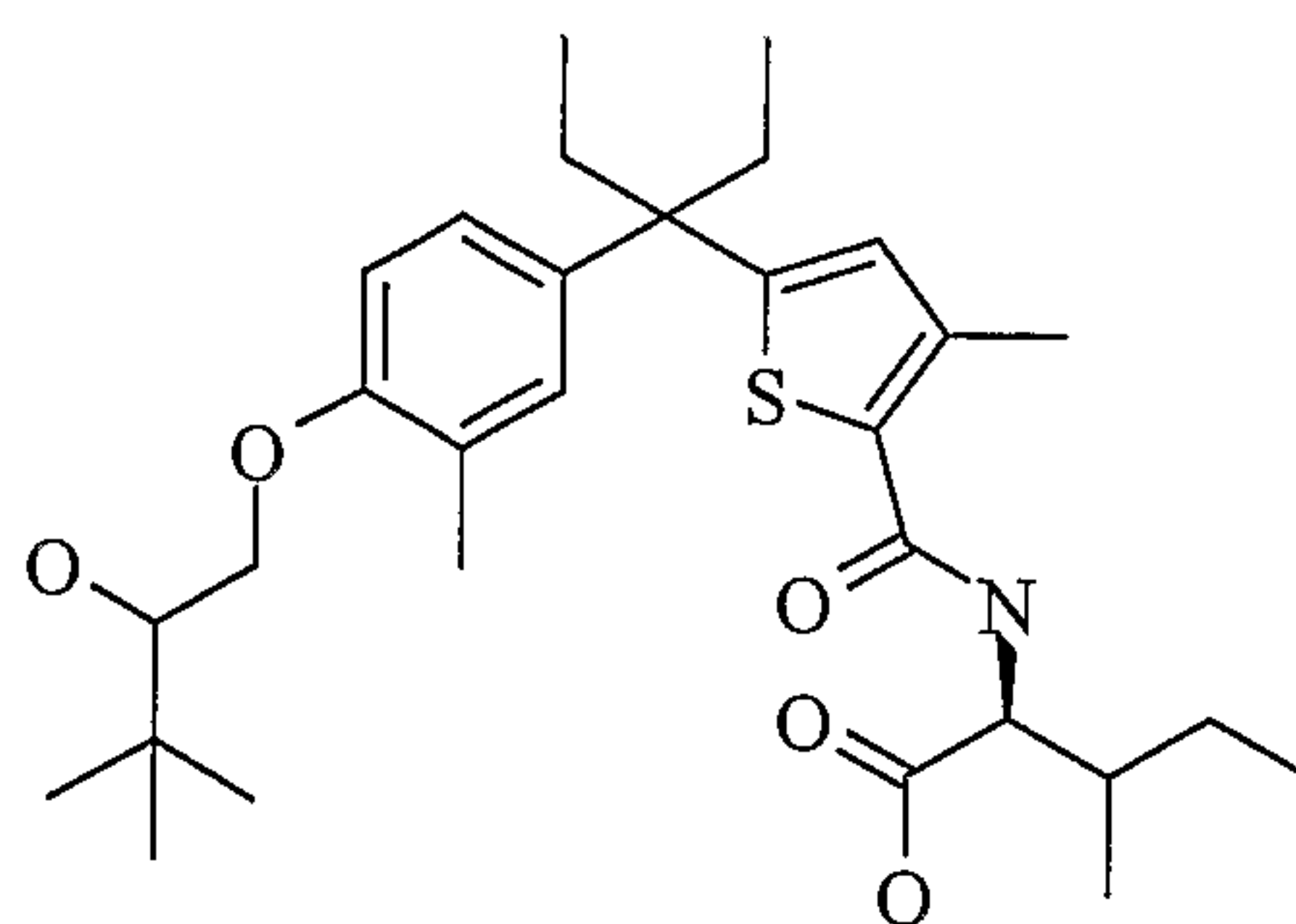


X66)



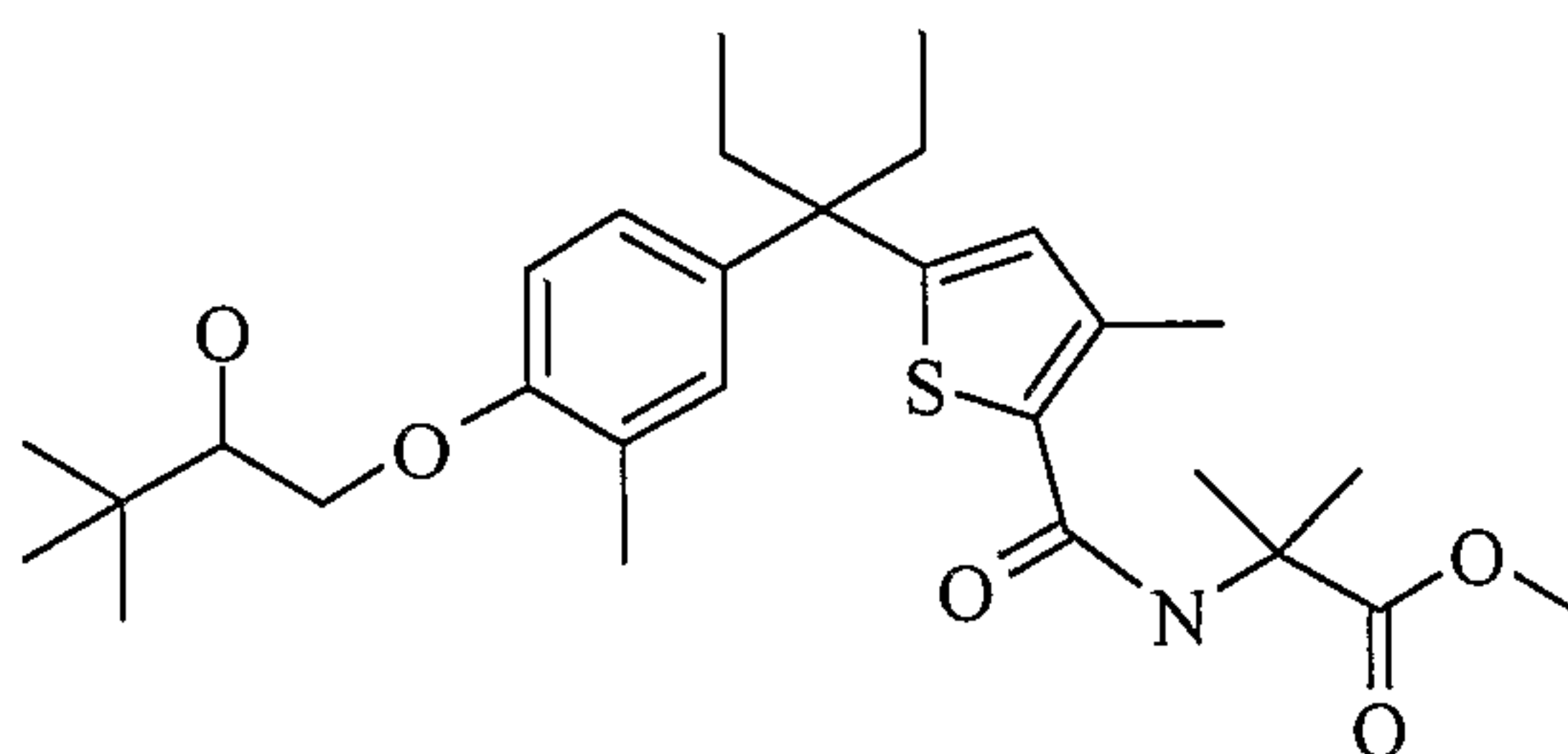
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X69)

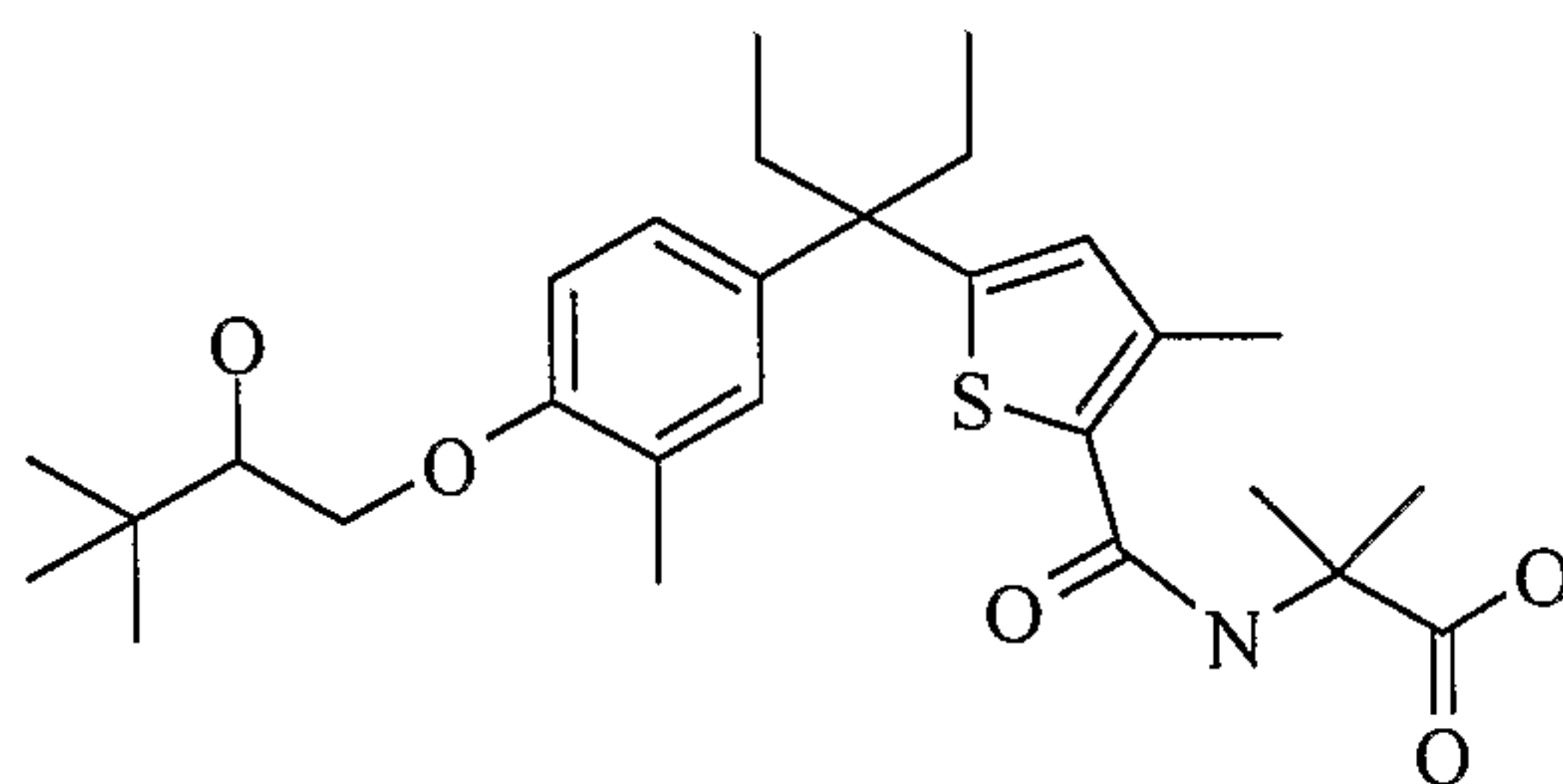


X70)

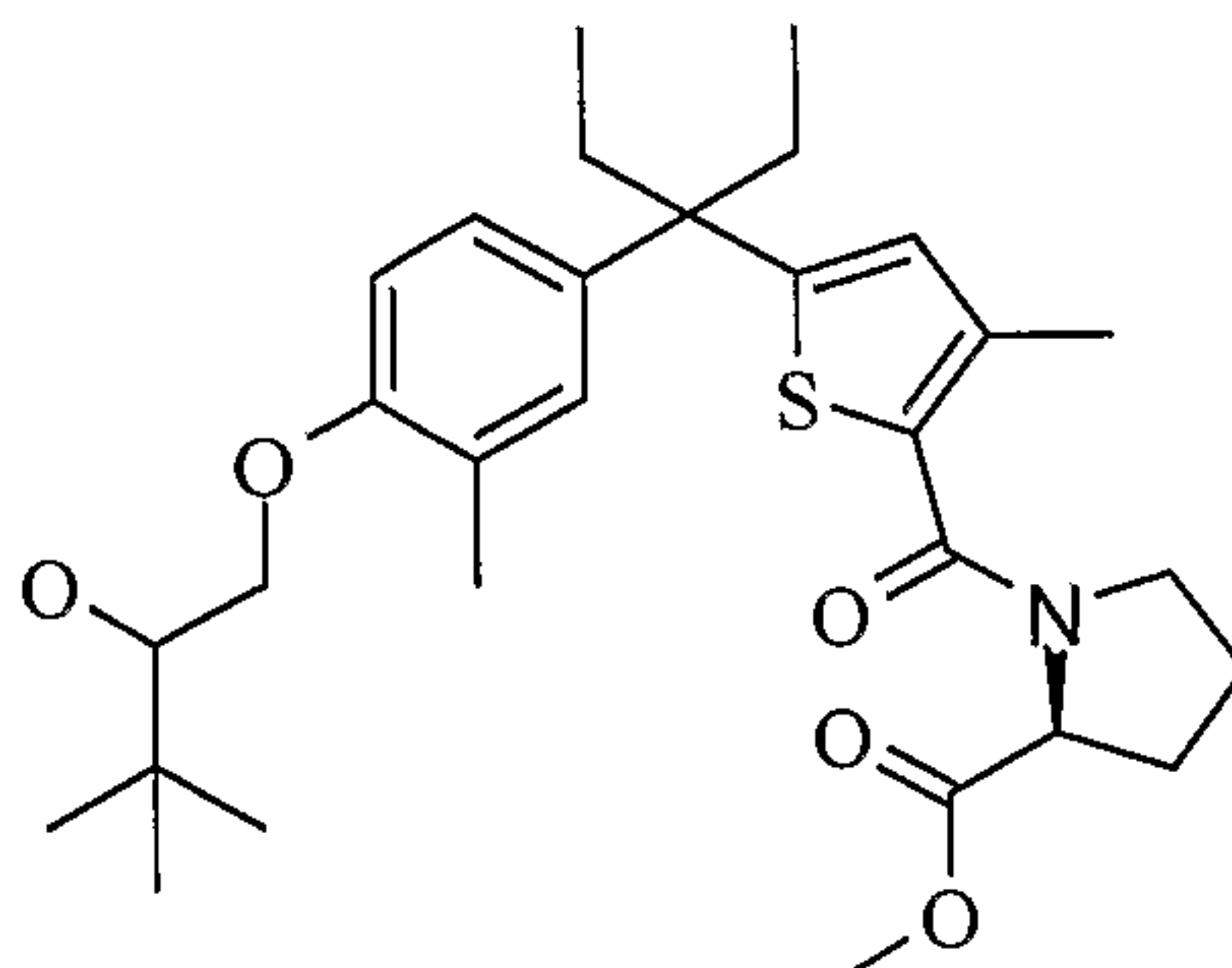
-69-



X71)

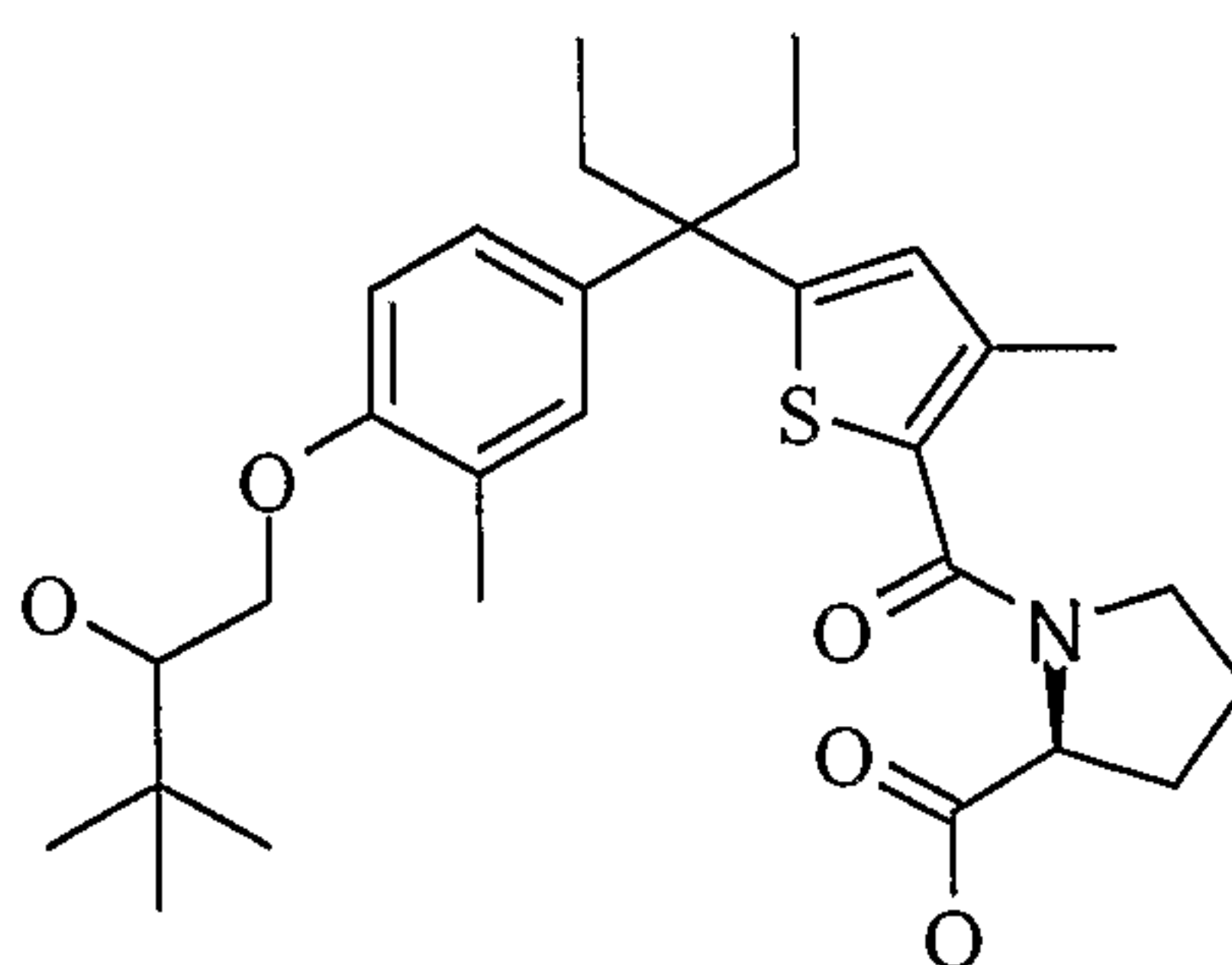


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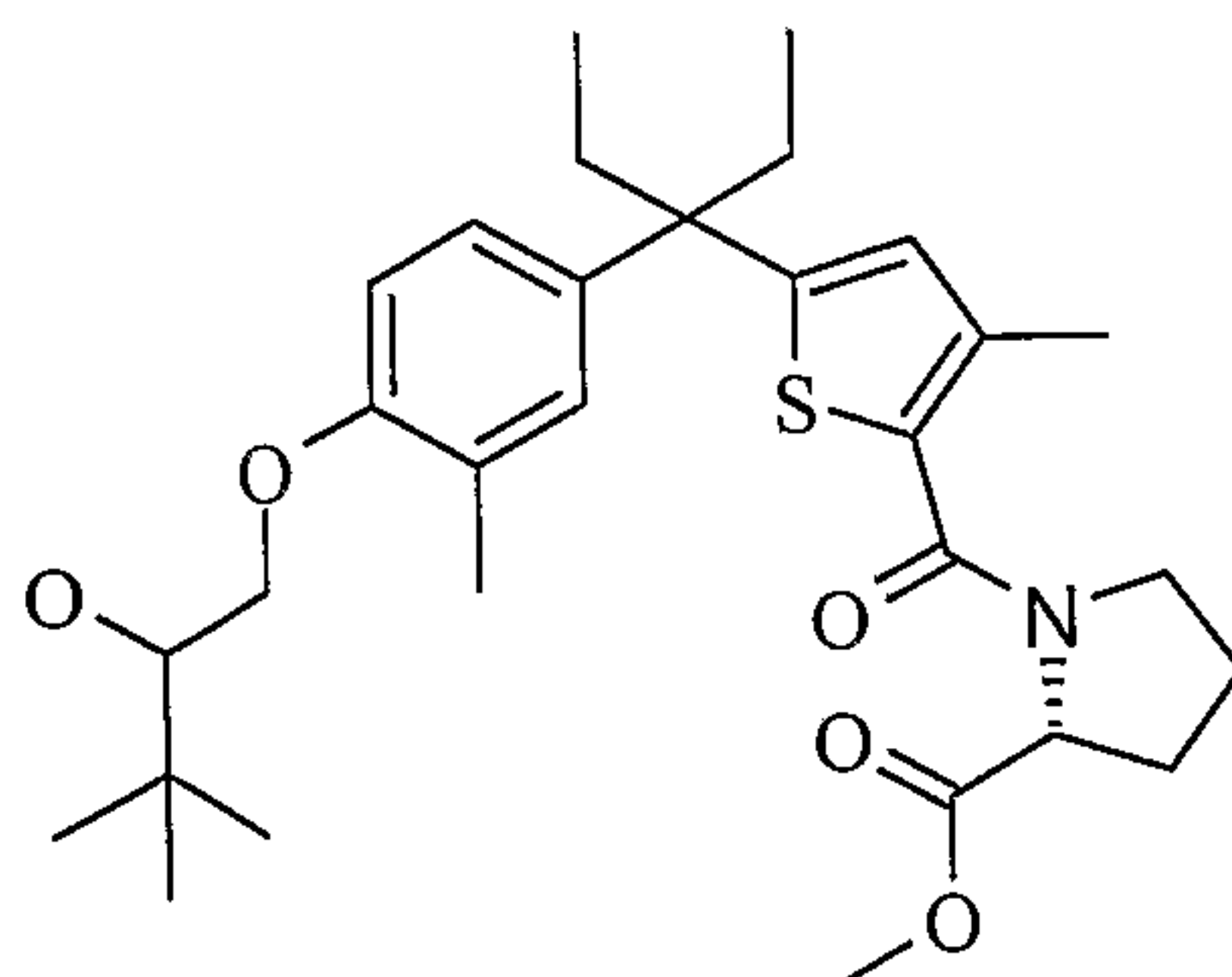
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X75)

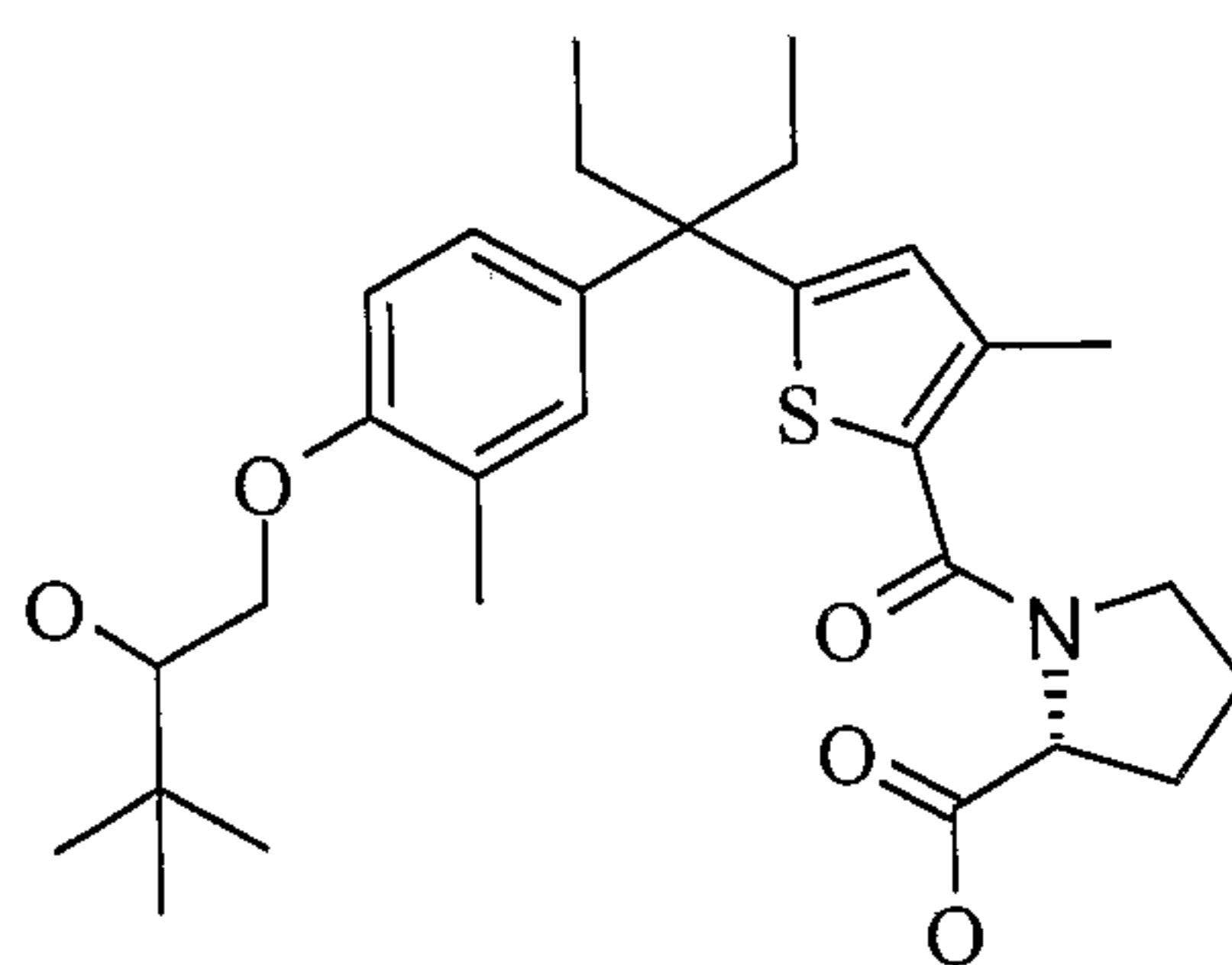


-70-

X78)

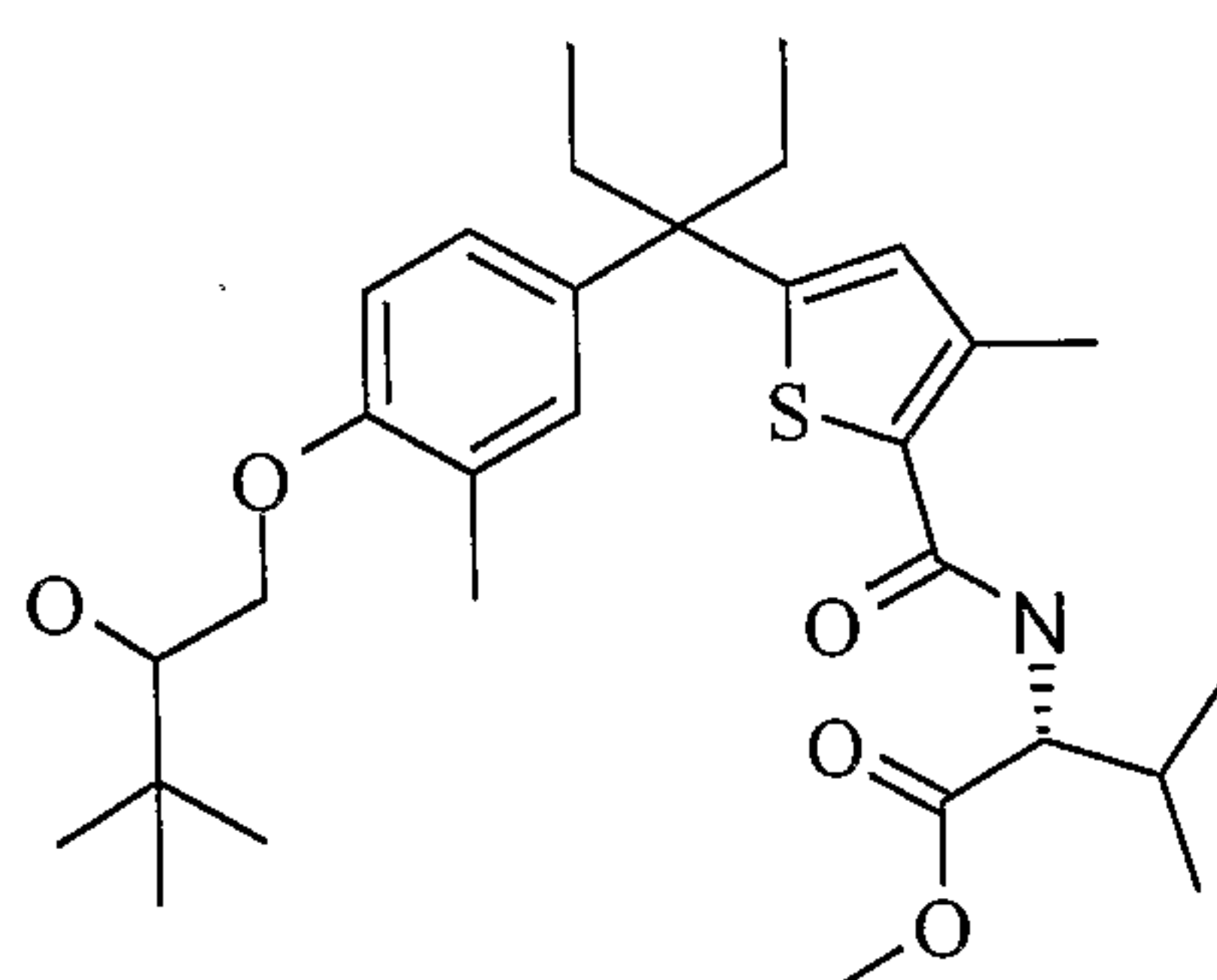


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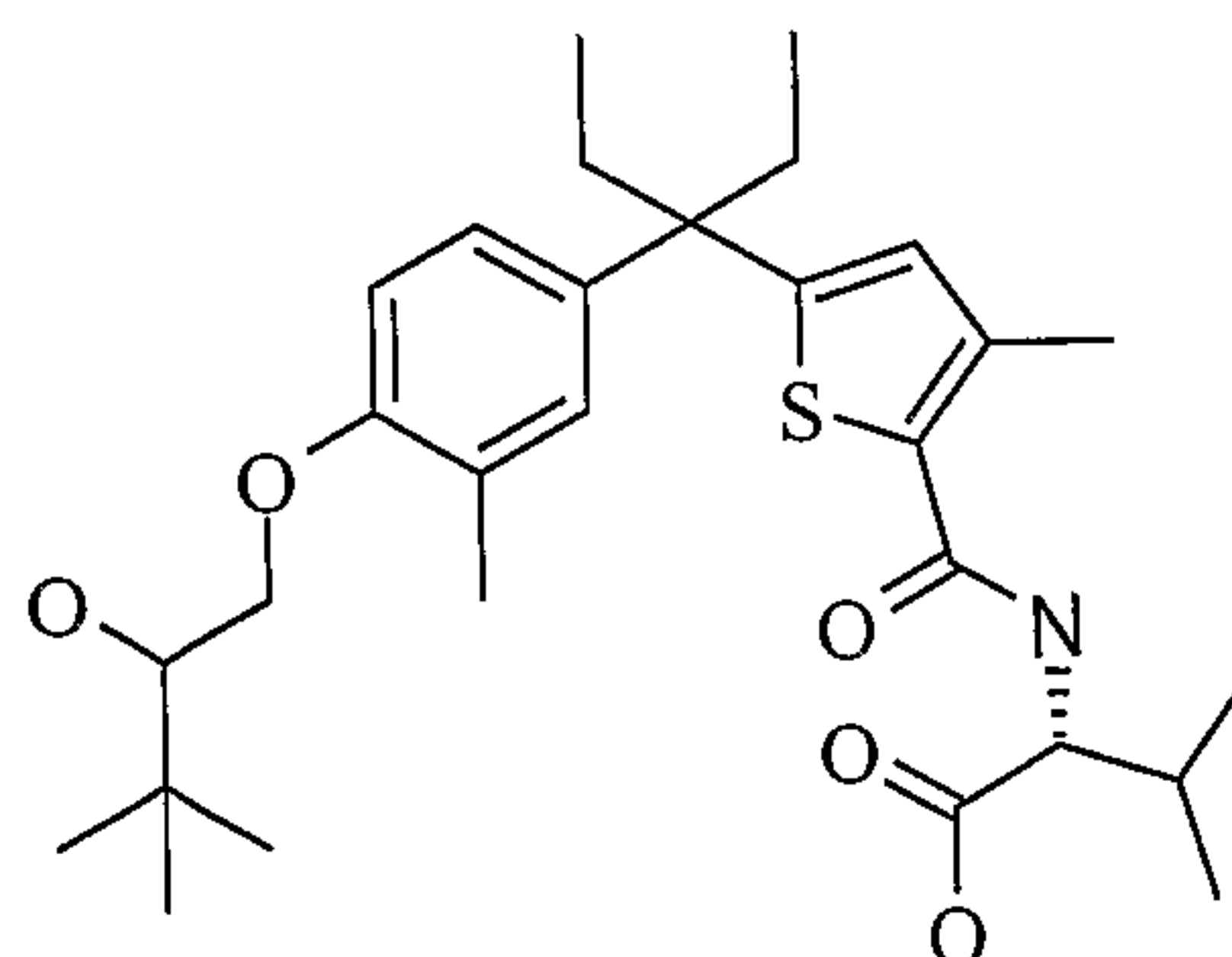


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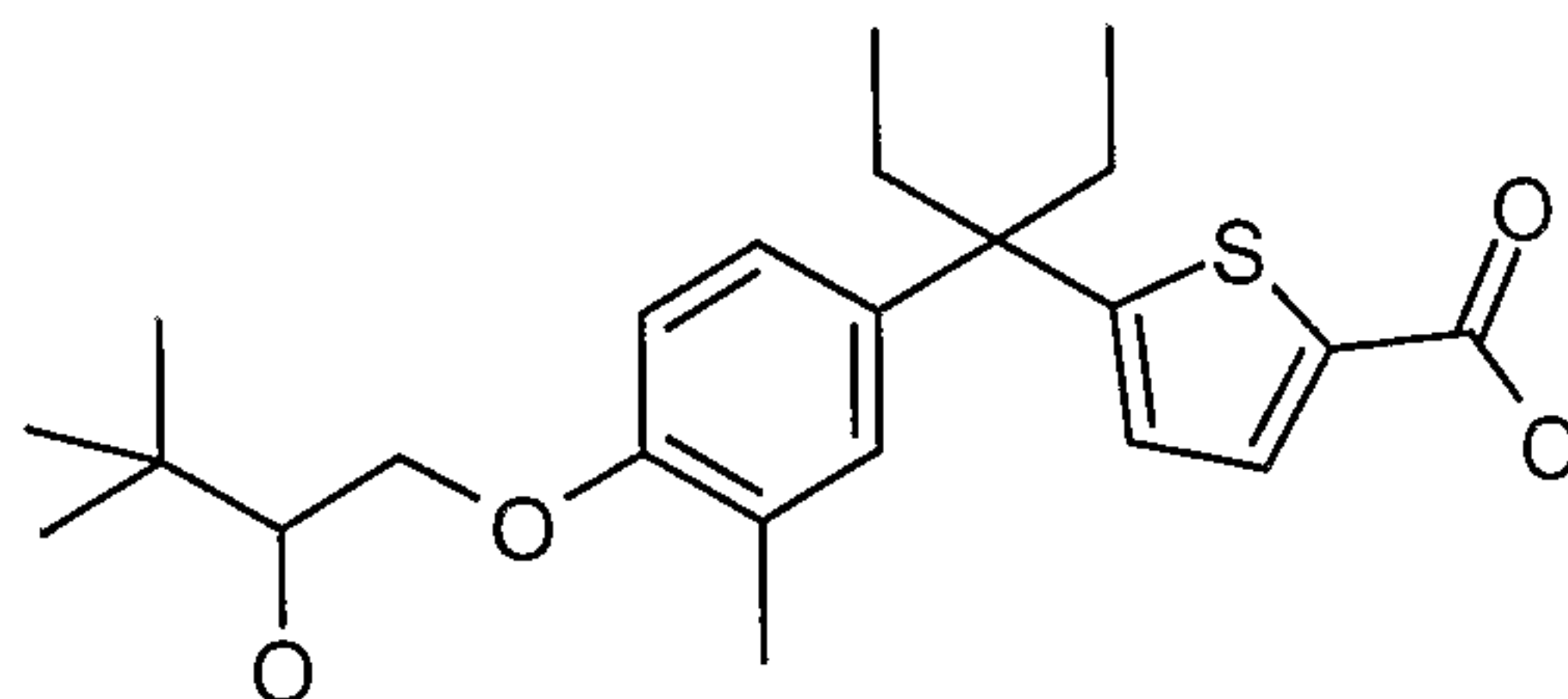
X83)



10 X86)

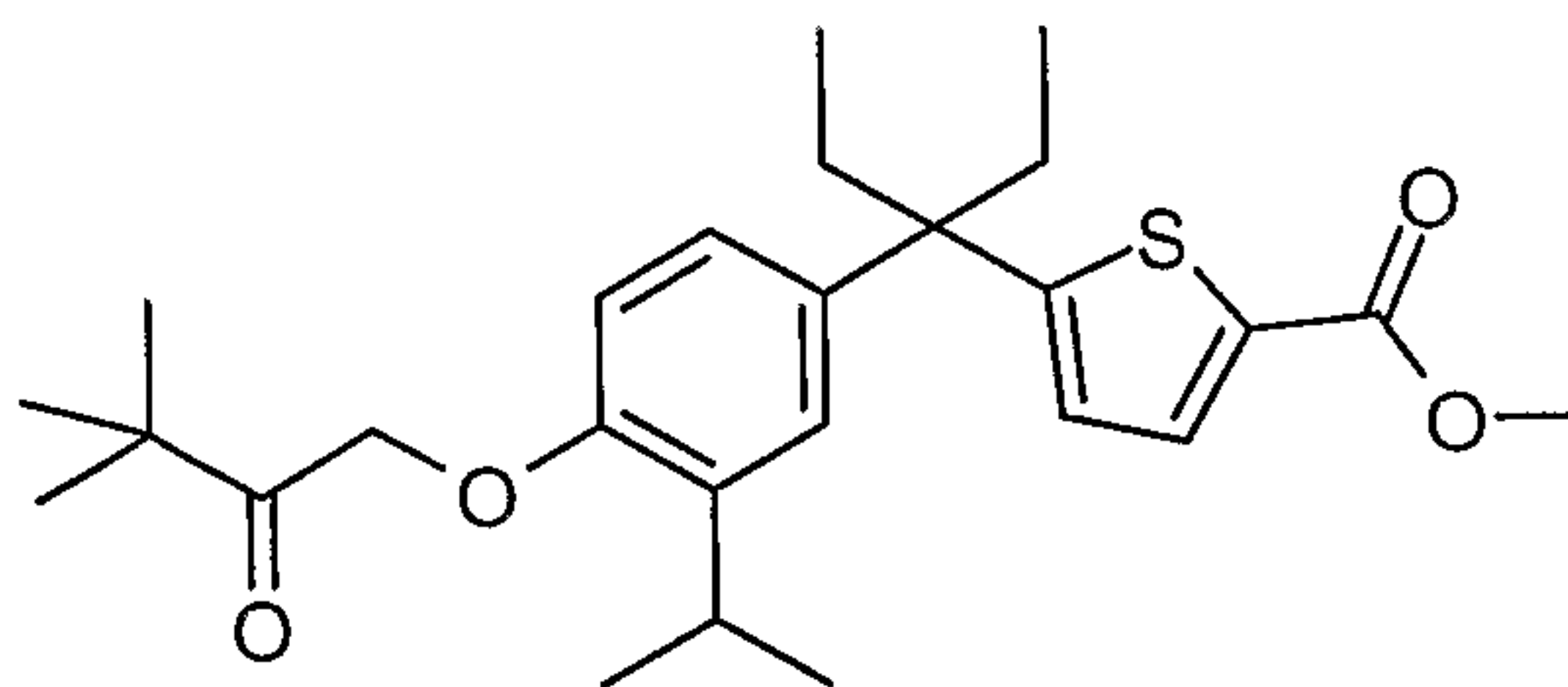


X88)

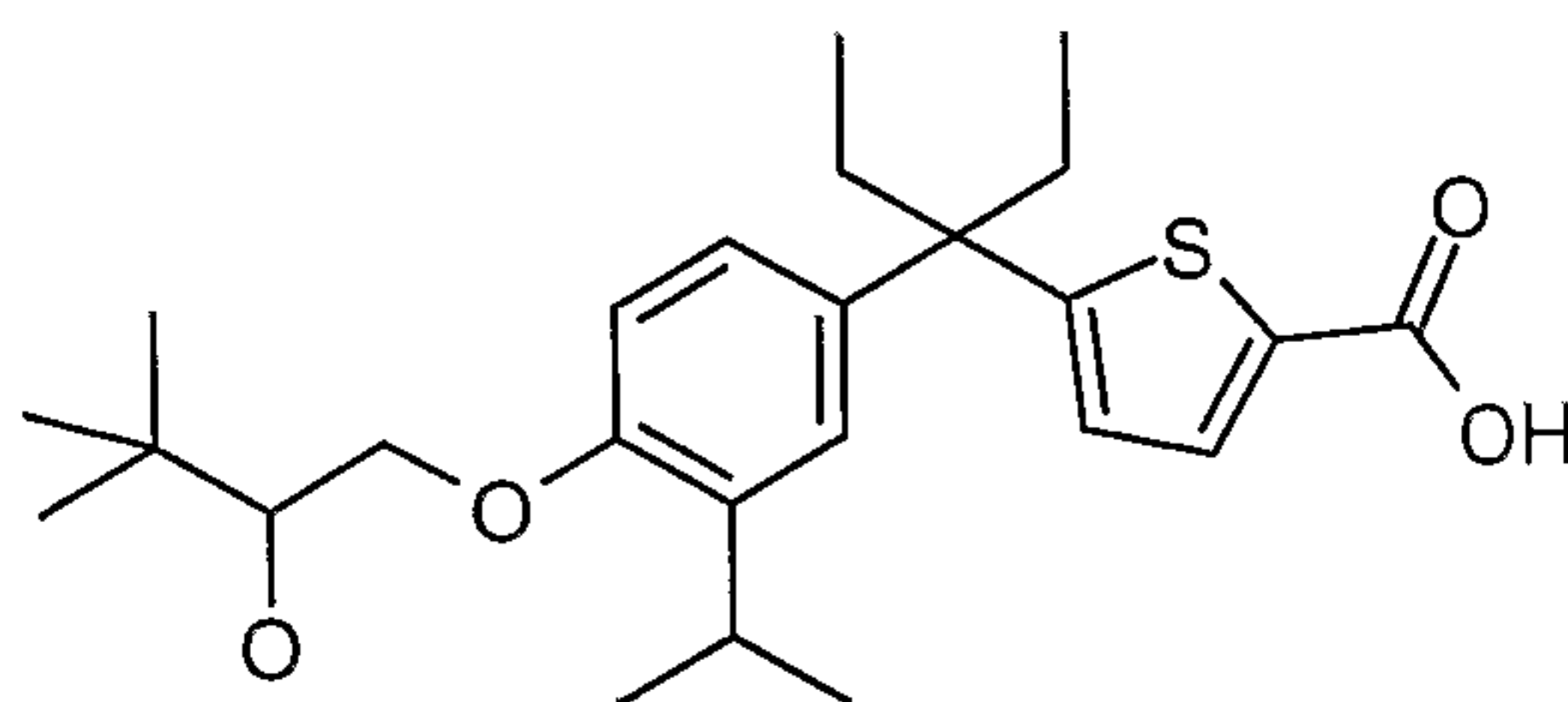


X91)

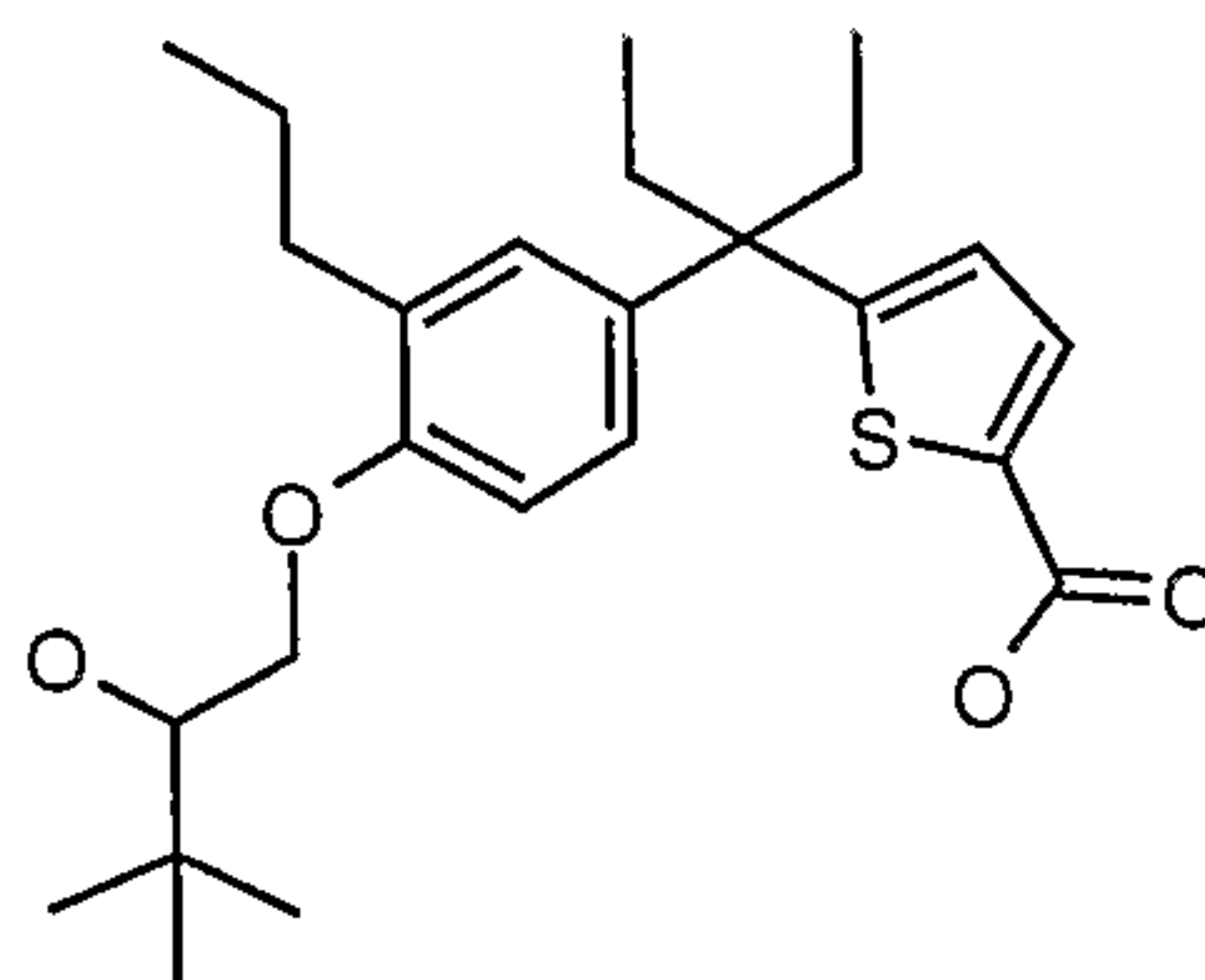
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X92)

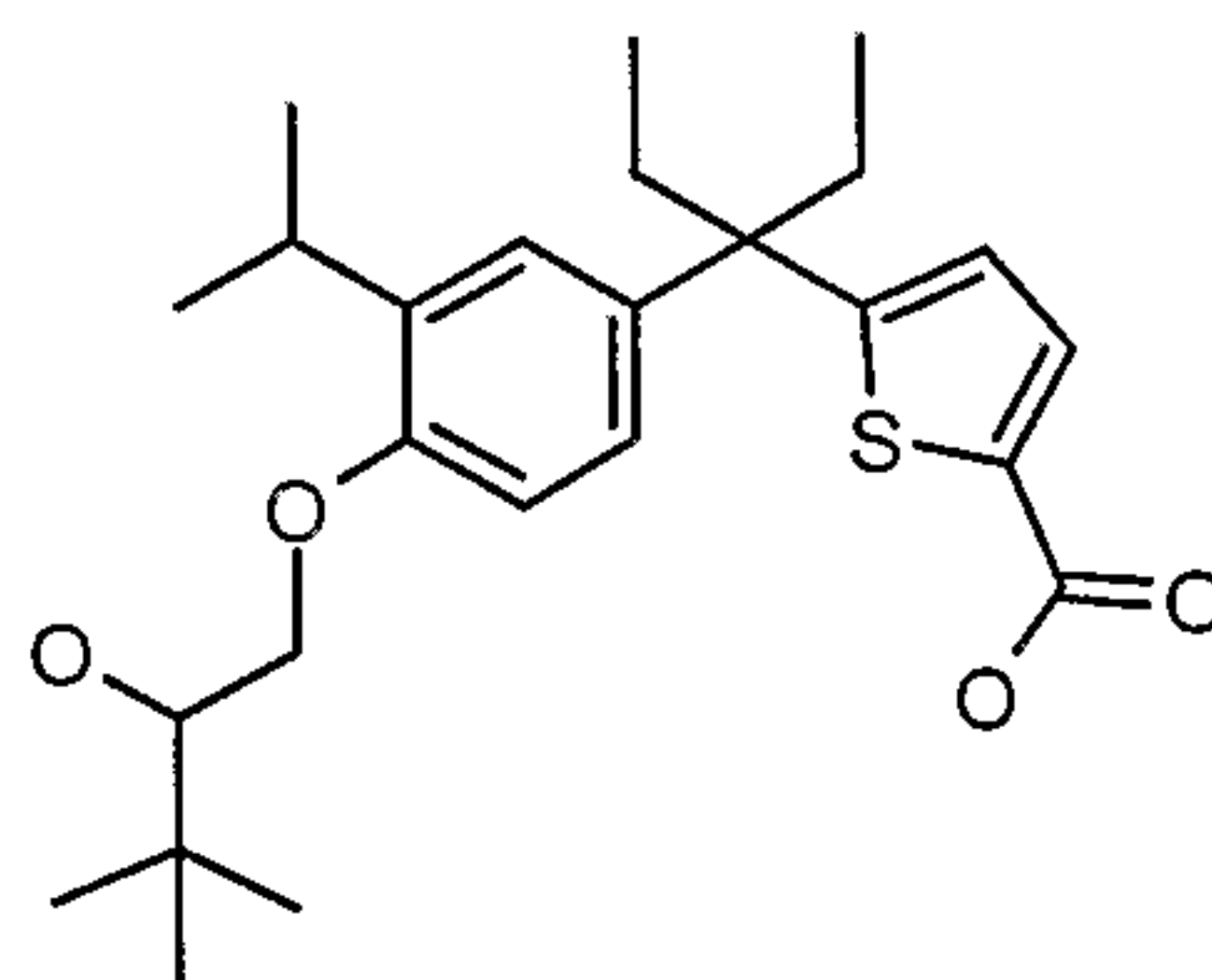


10 X93)

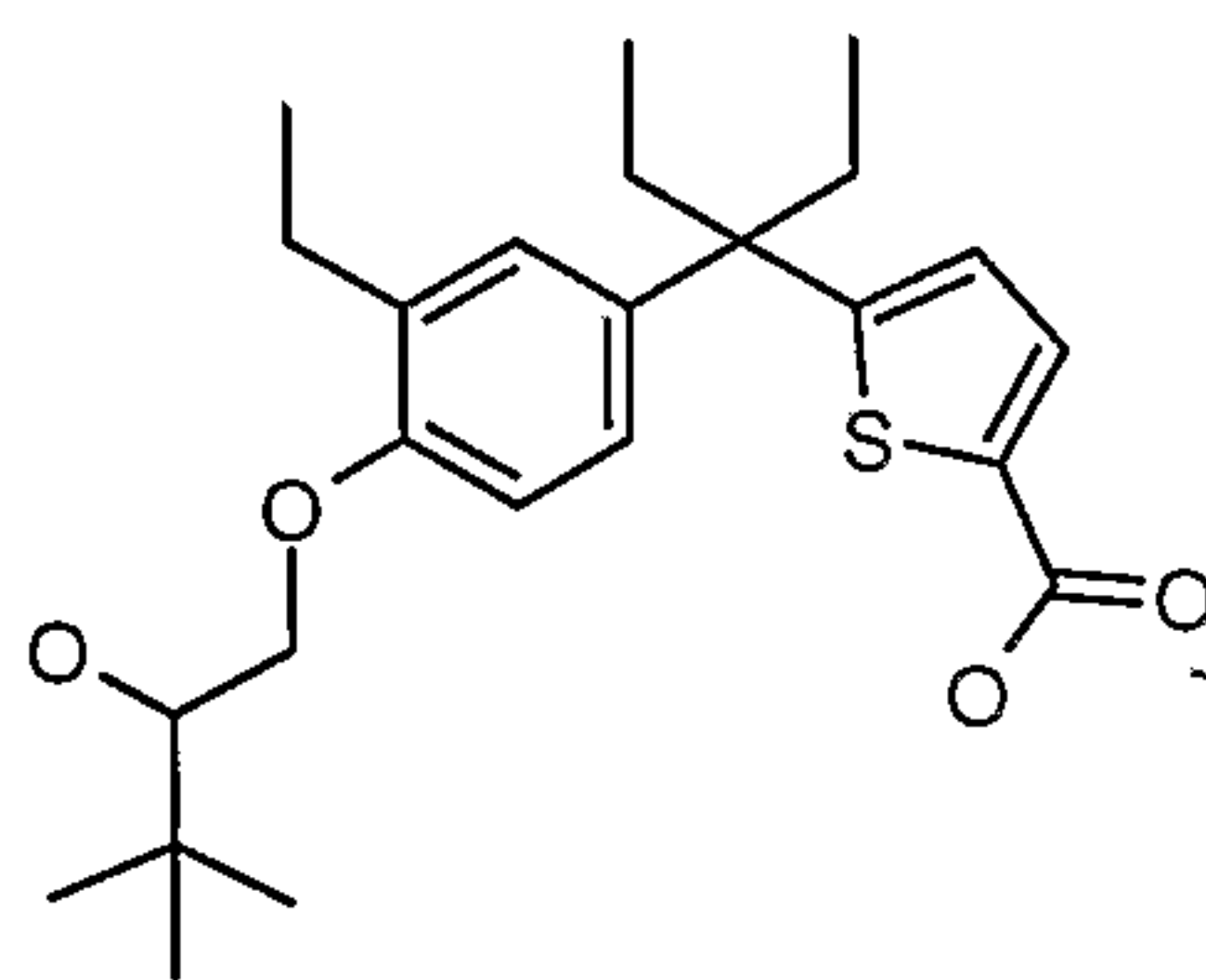


X96)

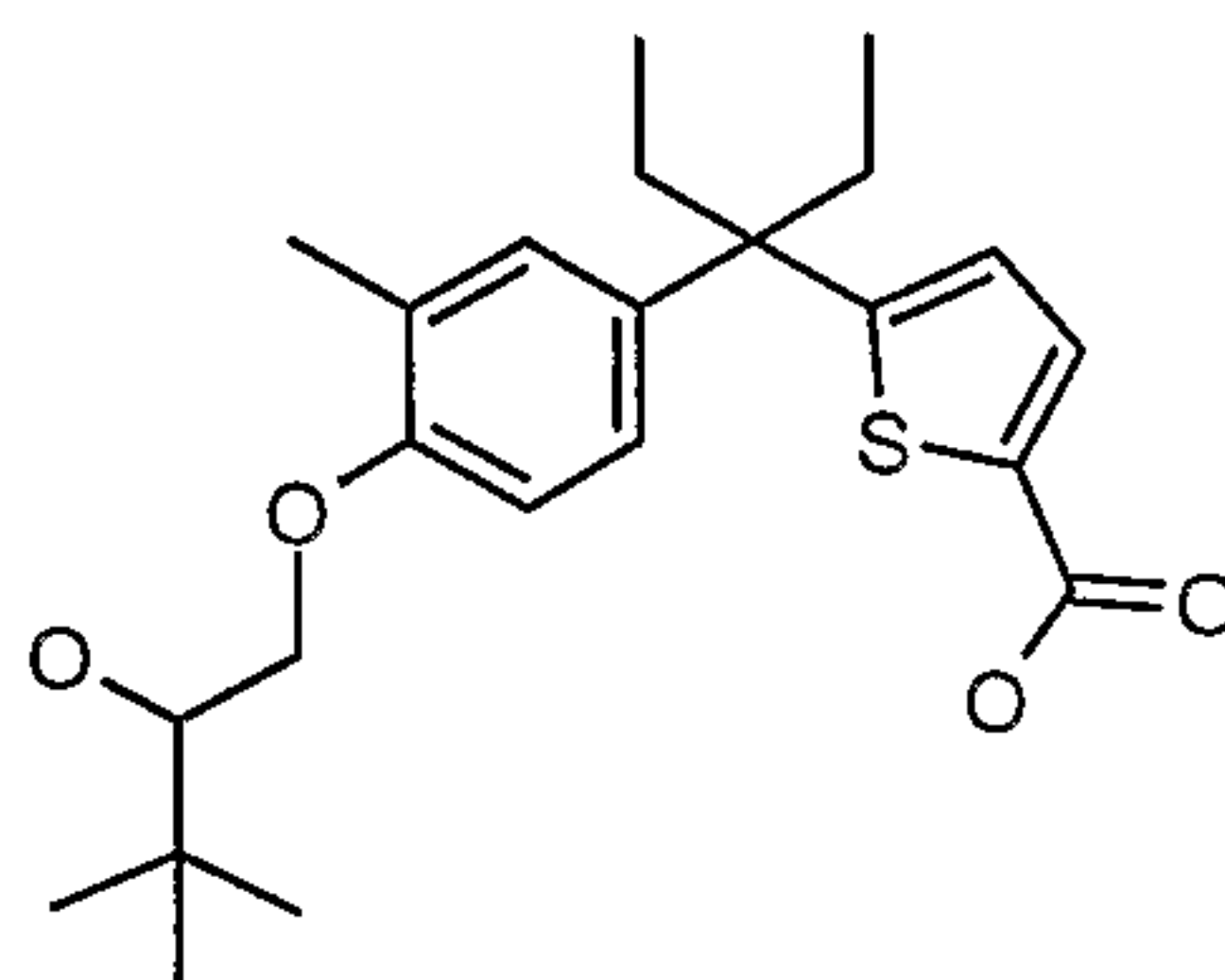
-72-



X99)

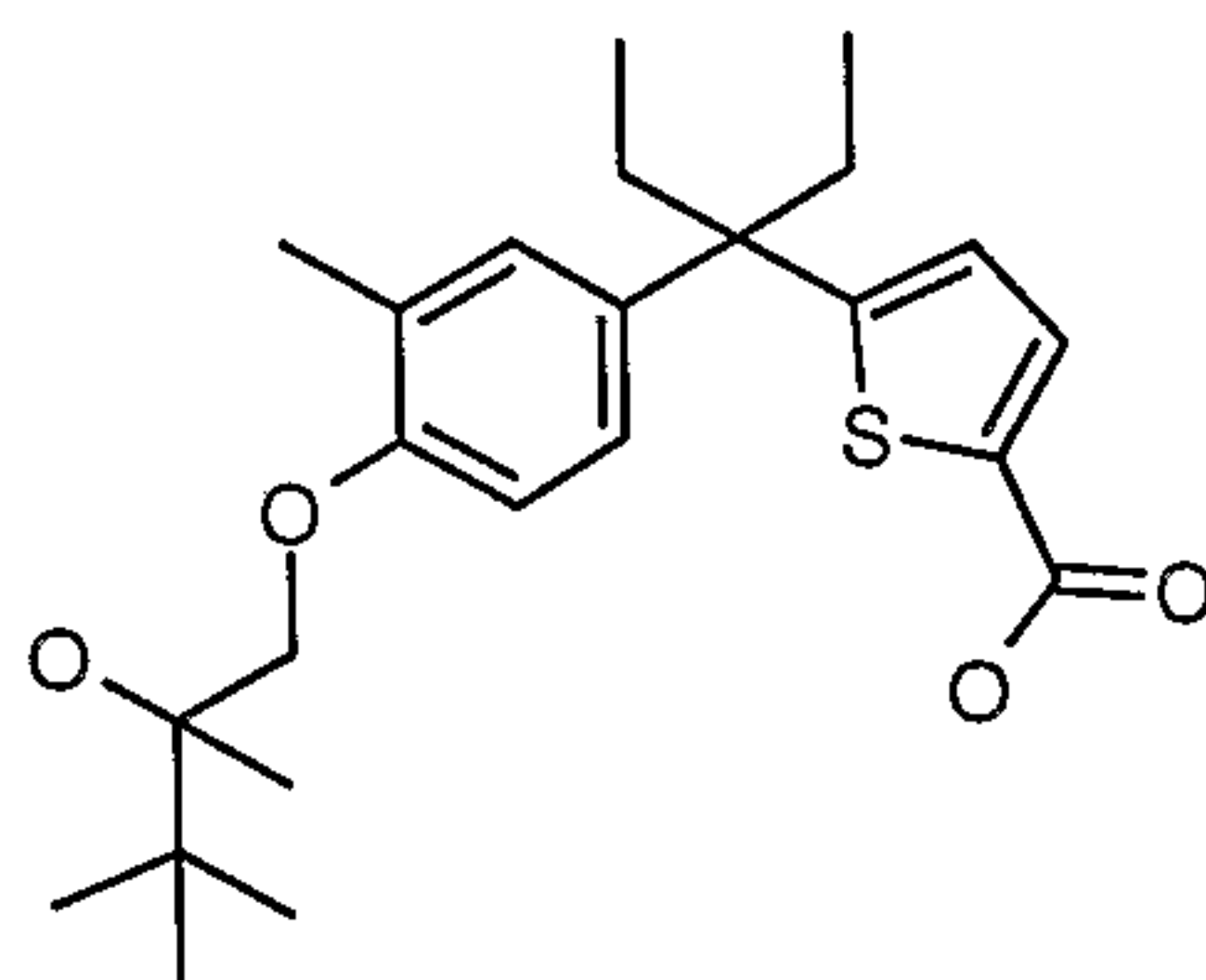


X102)

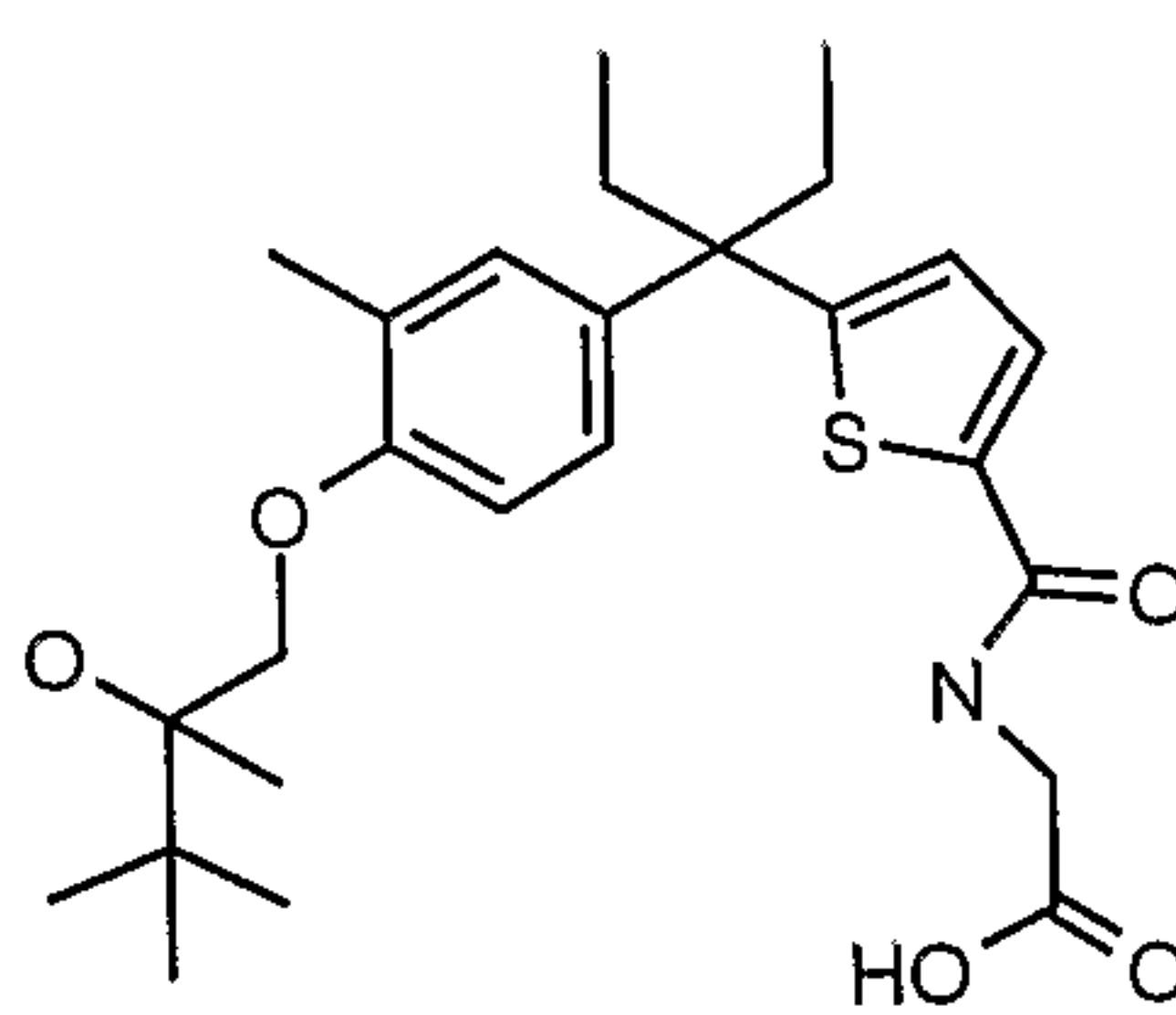


-73-

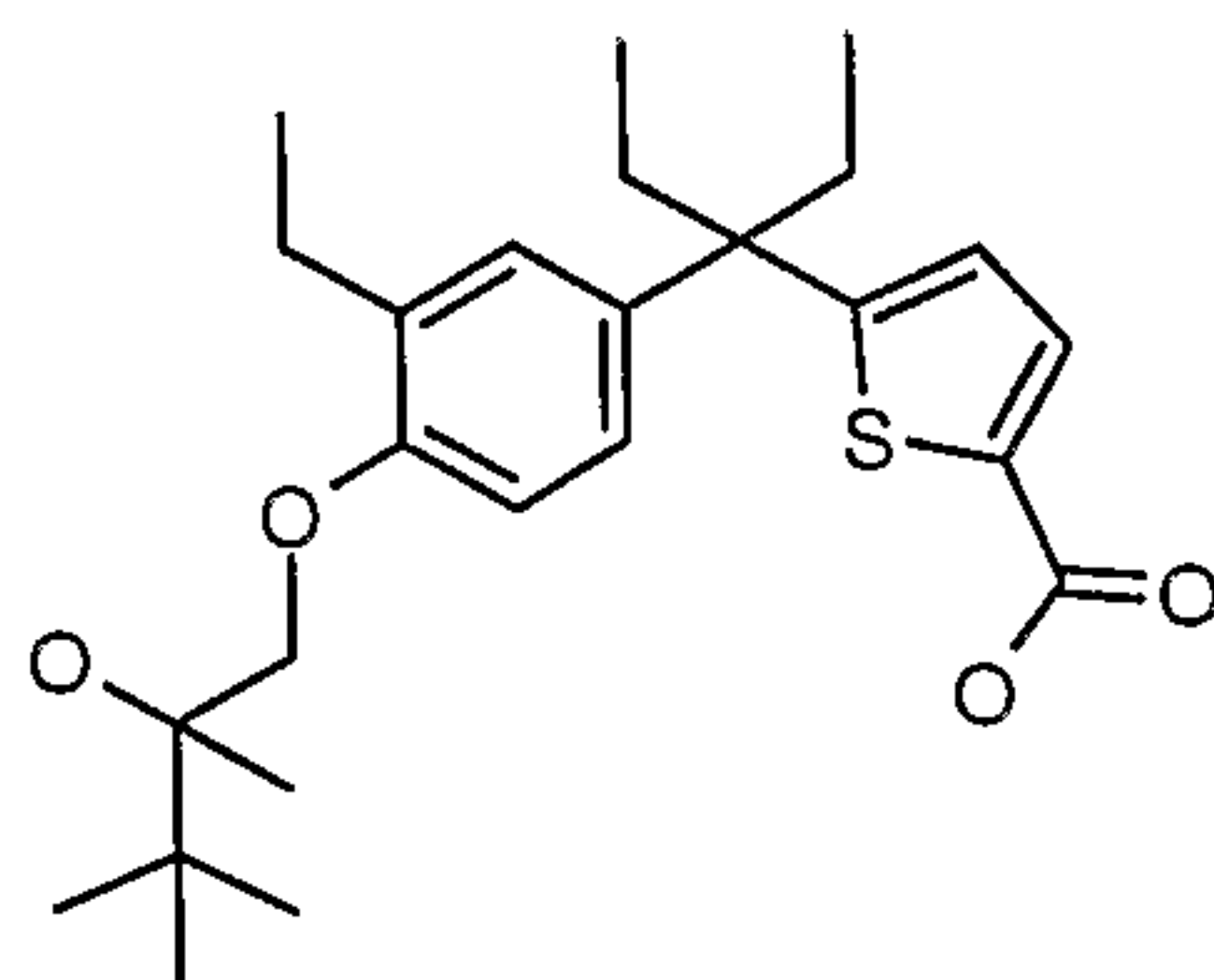
X103)



5 X106)

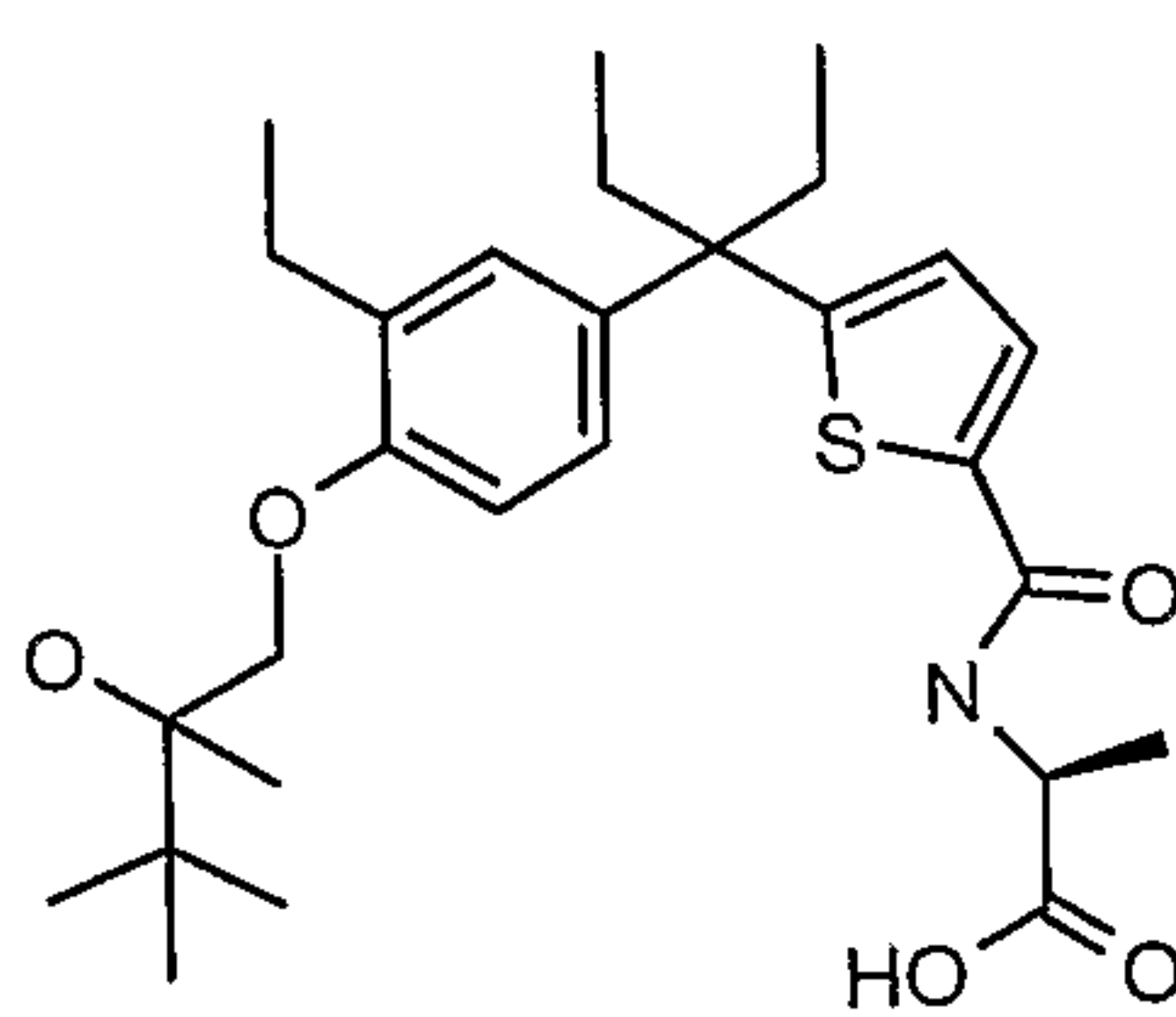


X107)



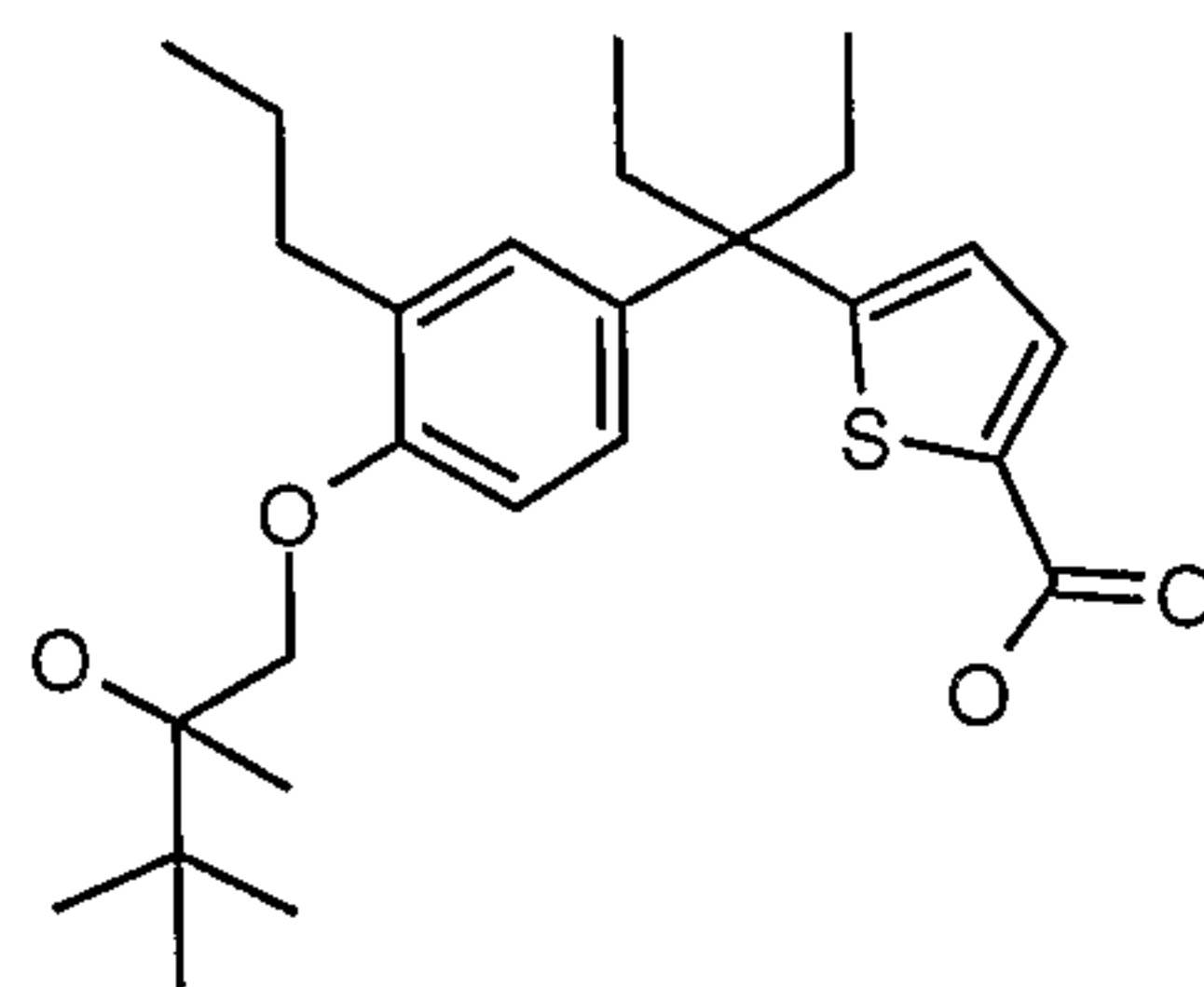
X110)

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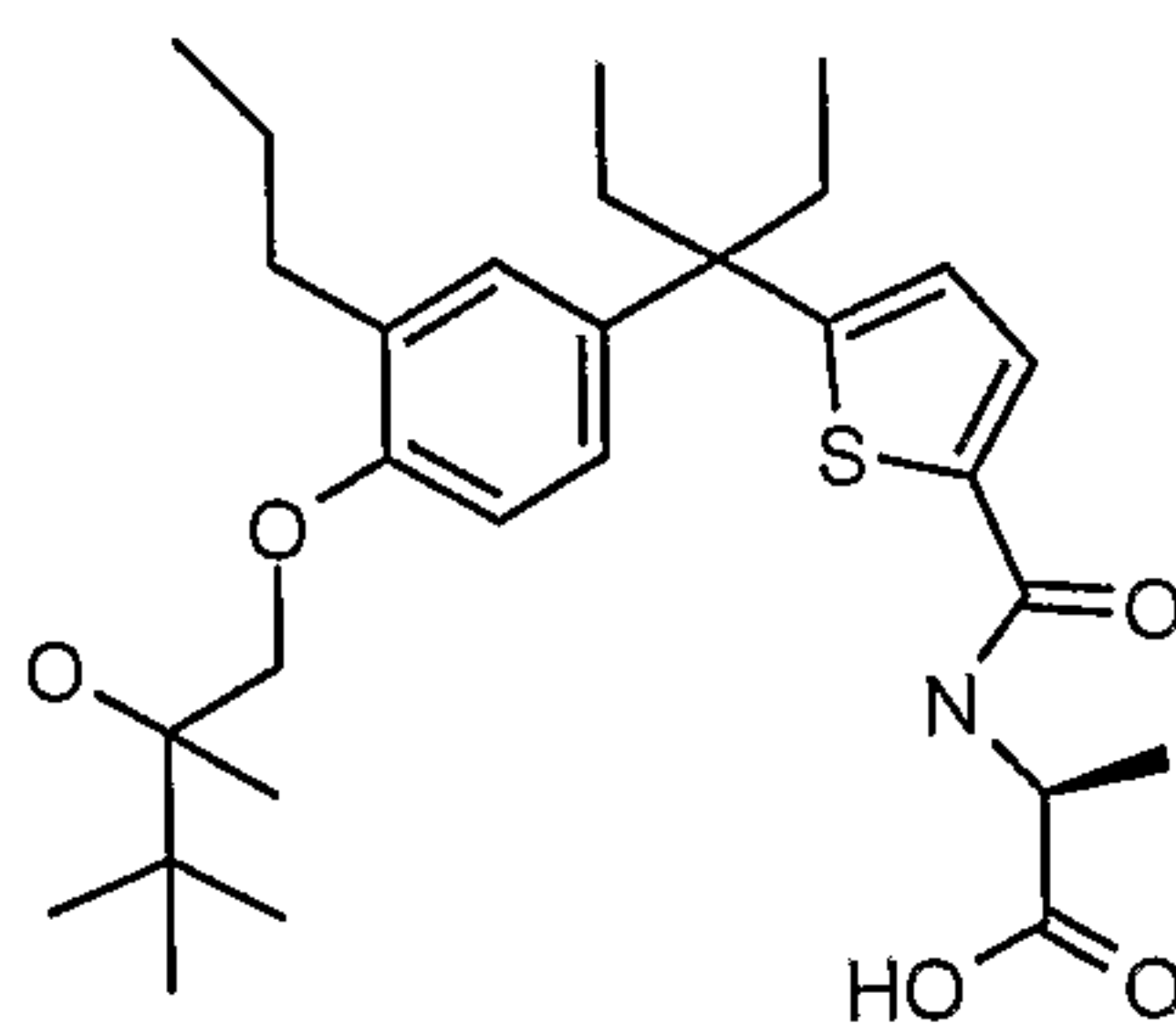


X111)

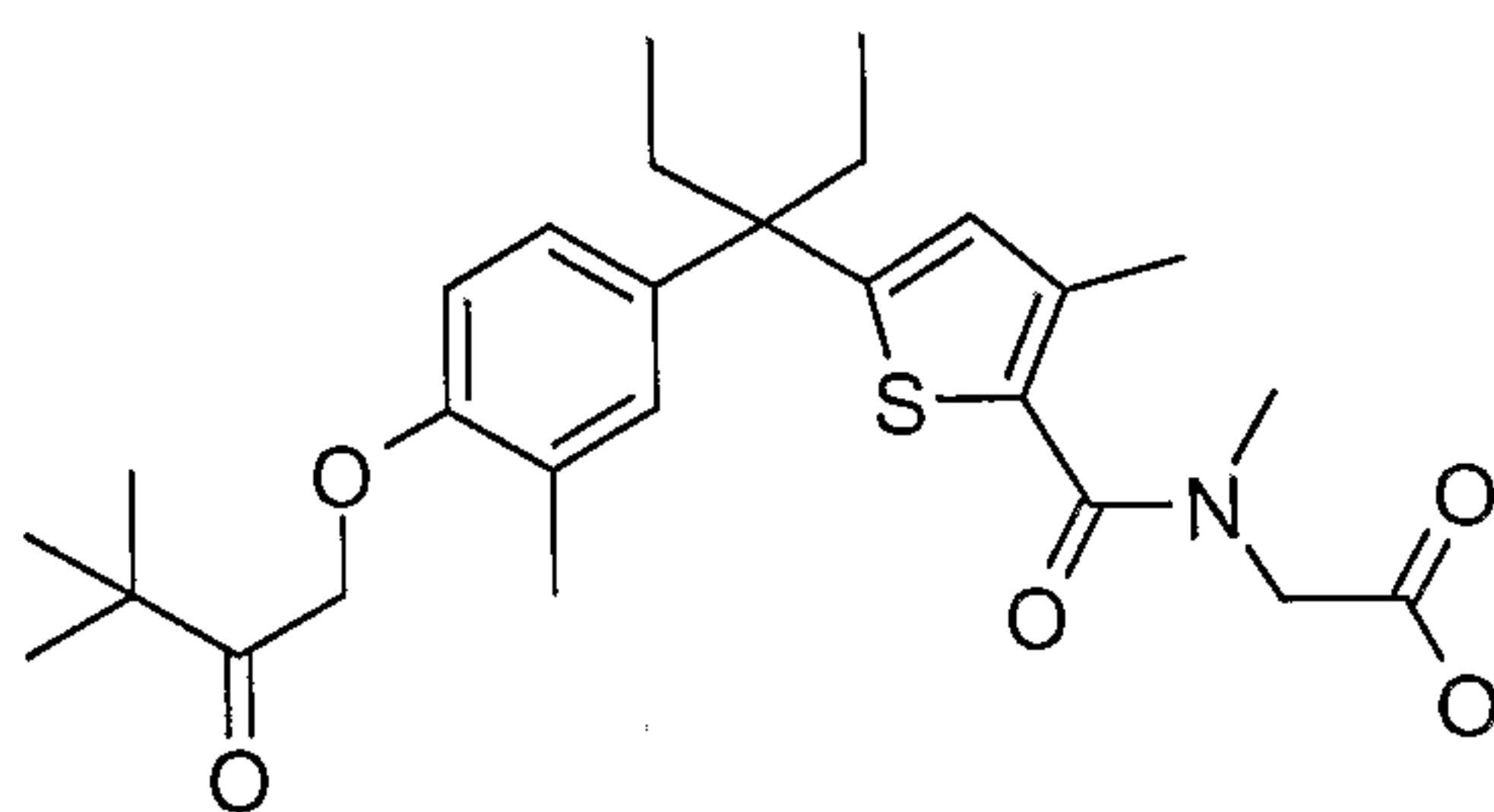
-74-



X114)

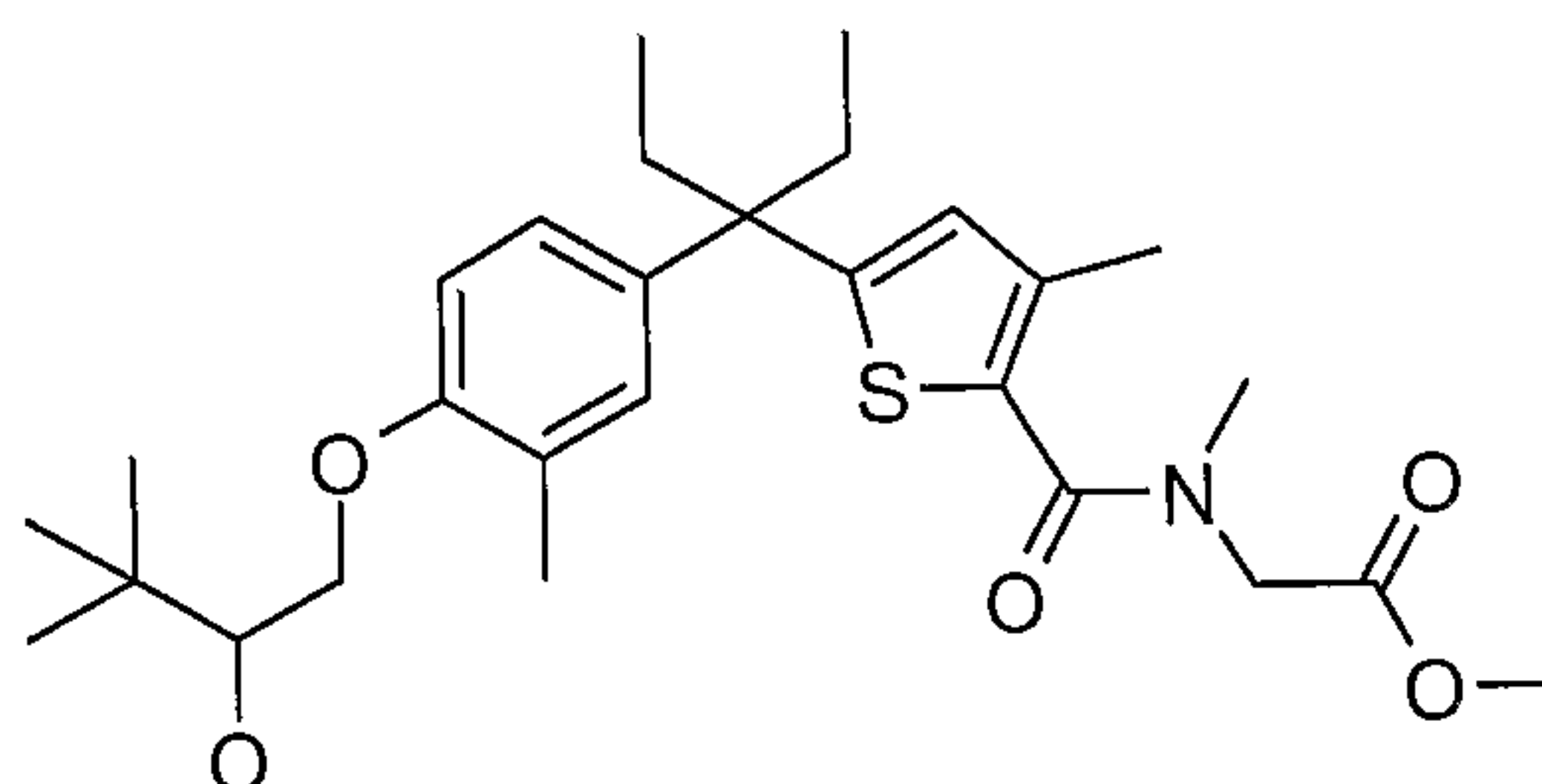


X118)

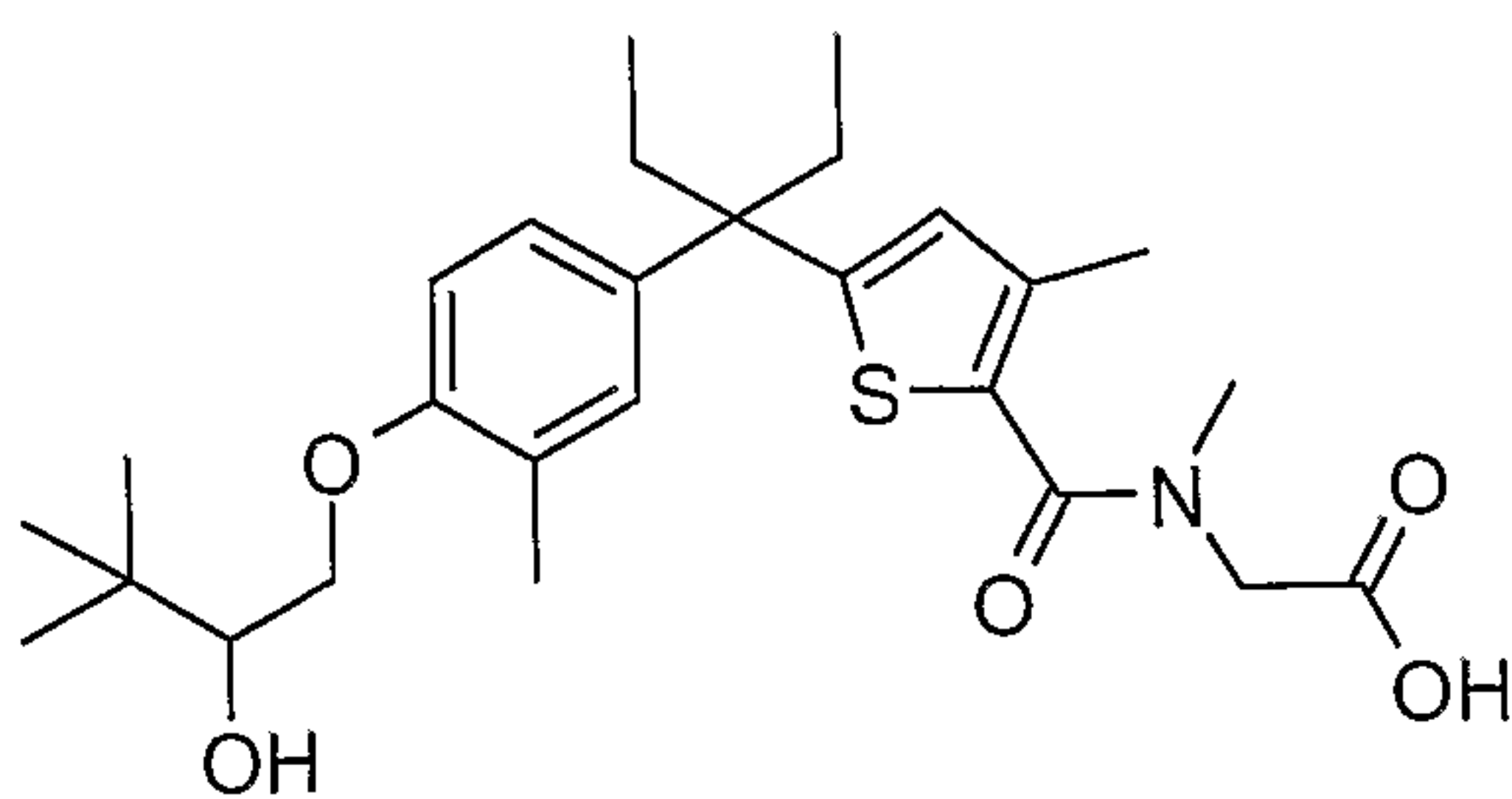


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X119)

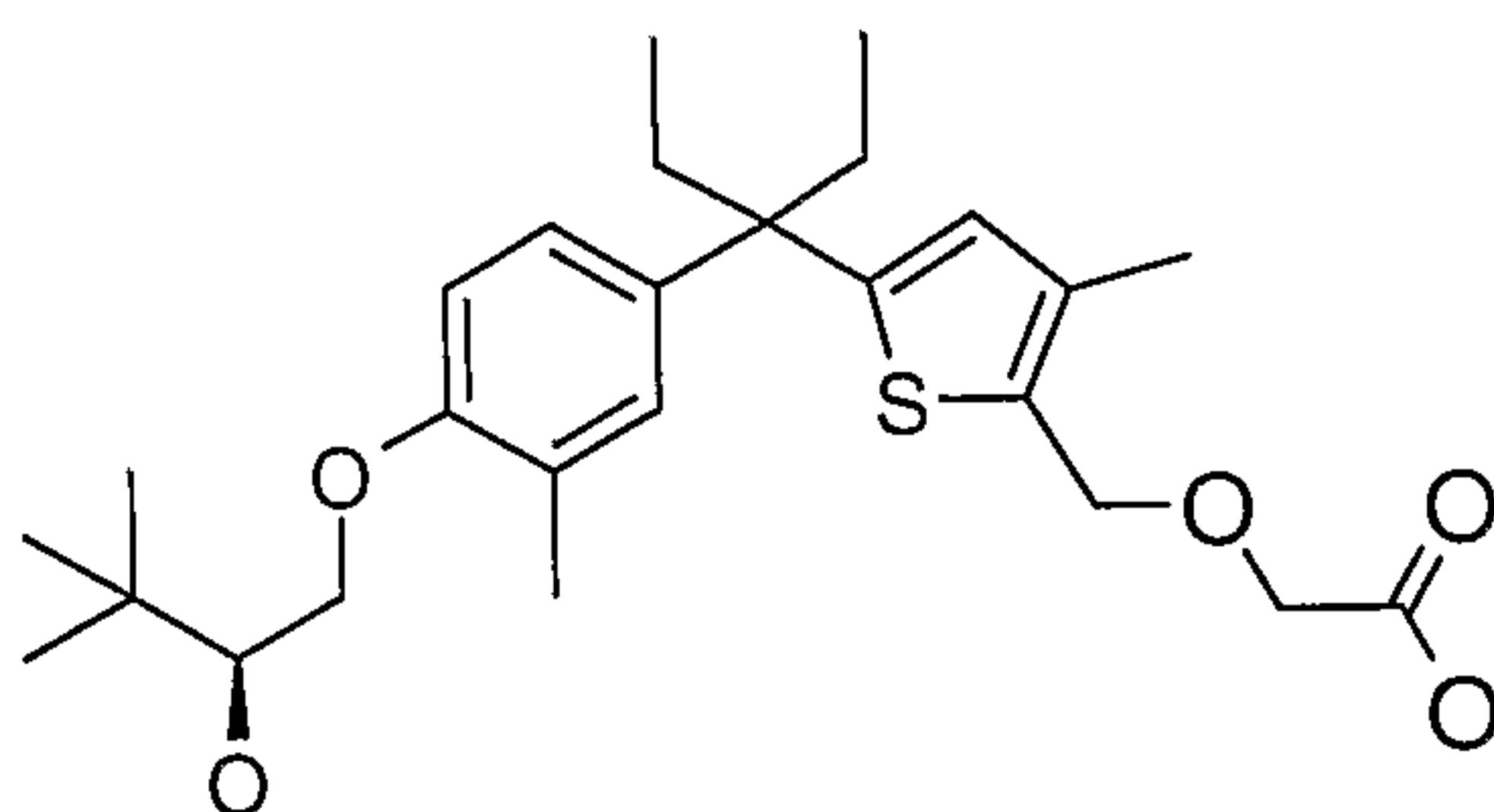


X122)

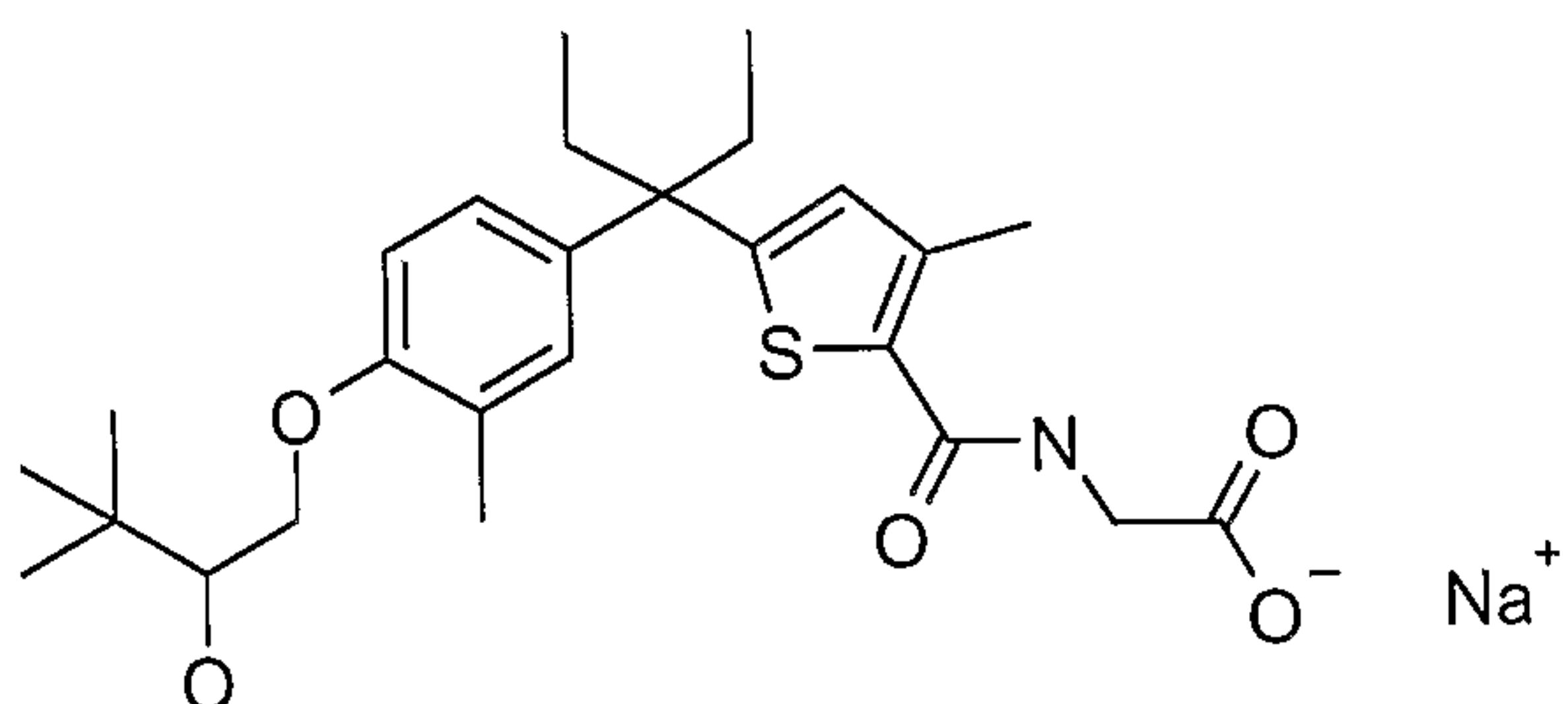


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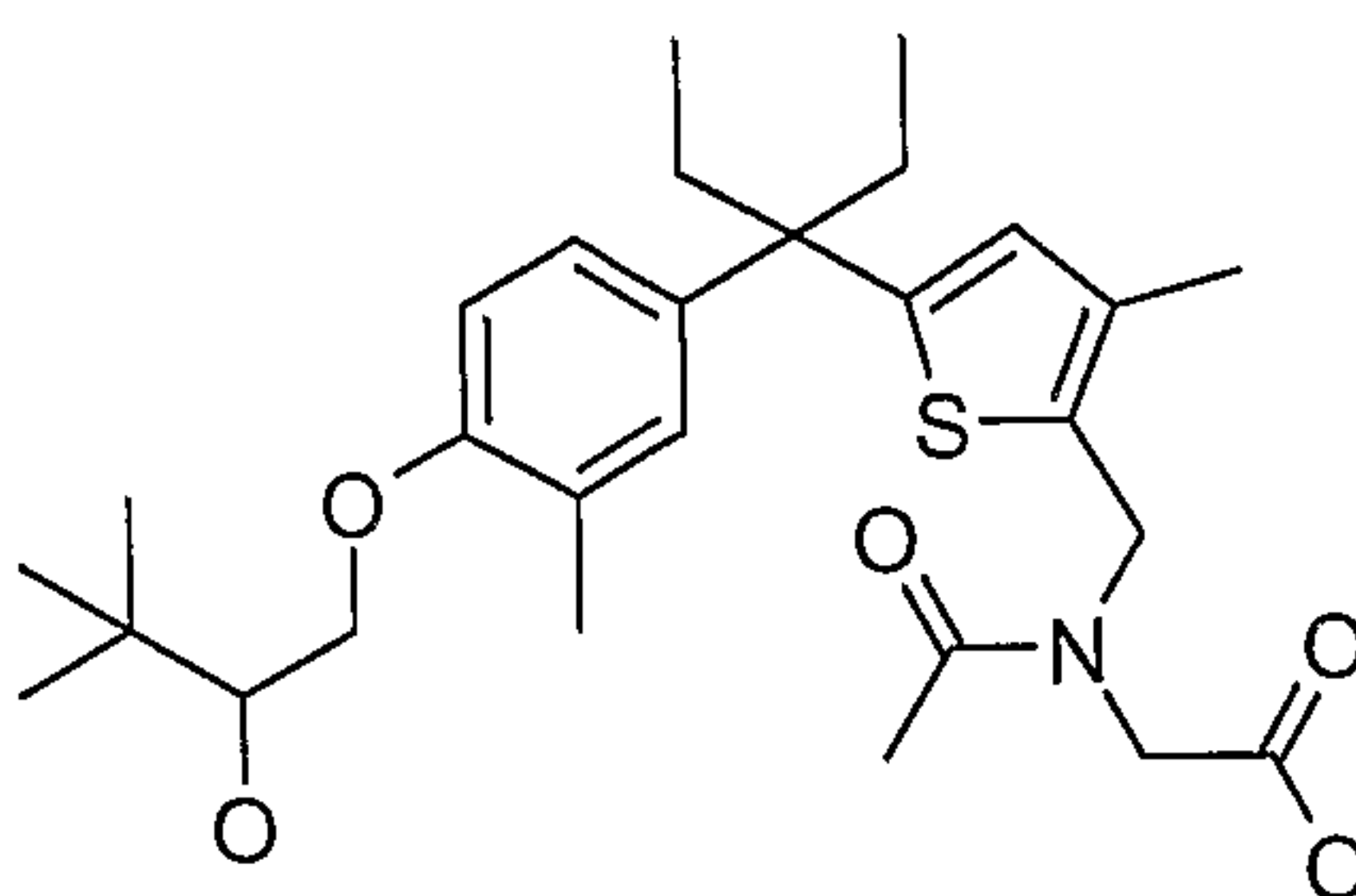
X124)

CC(C)(C)C(=O)OCCOc1ccc(Cc2cc(C)cc(COC)c2S)c(C)c1

X128)

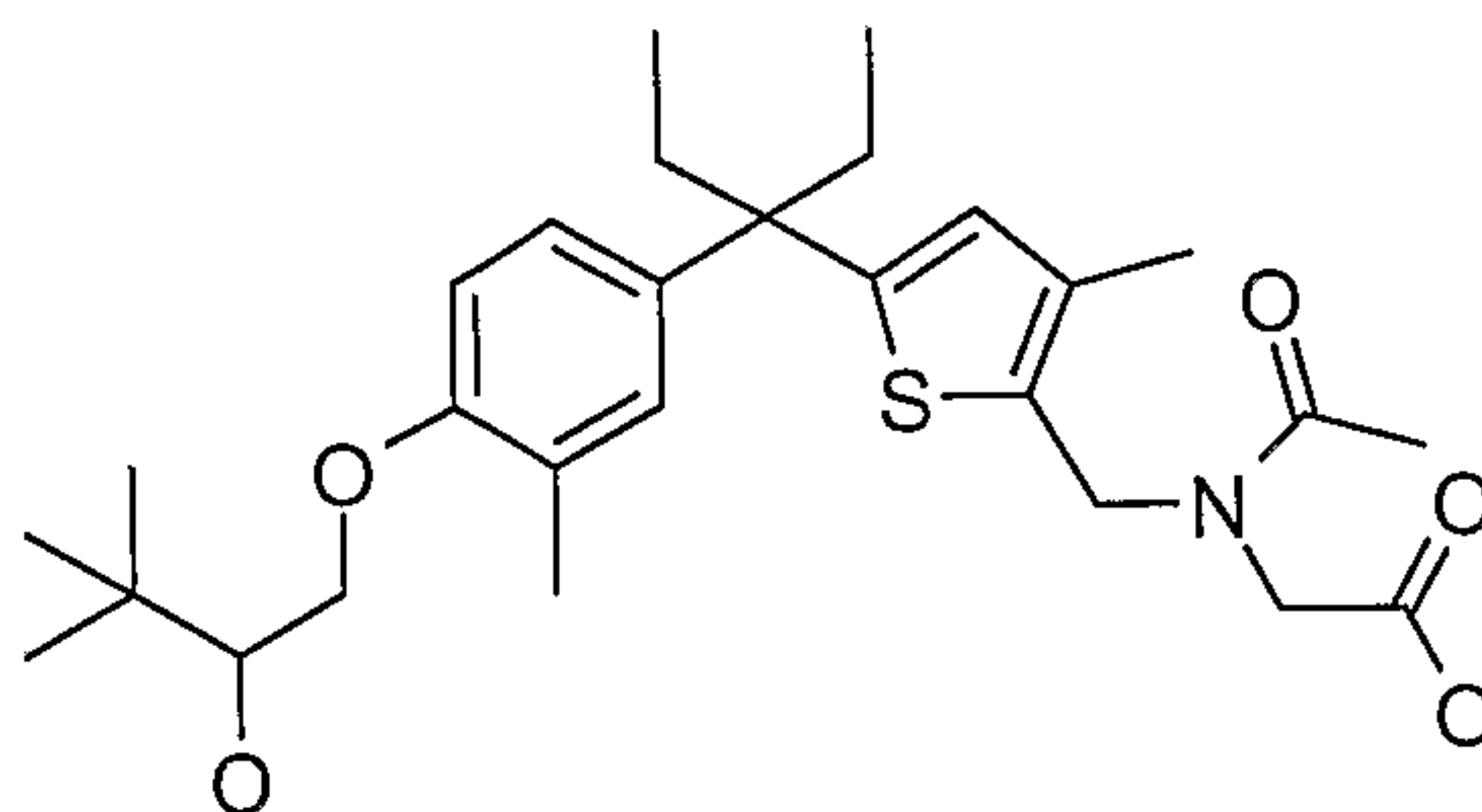


X130)

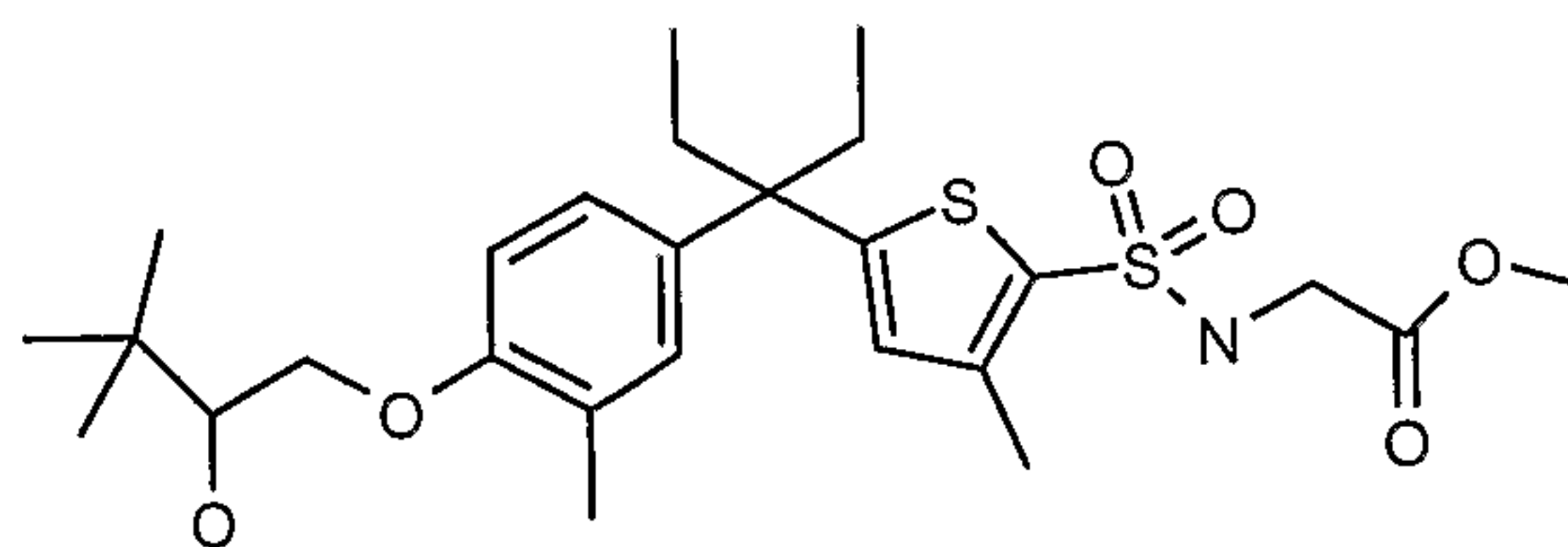


X131)

-76-

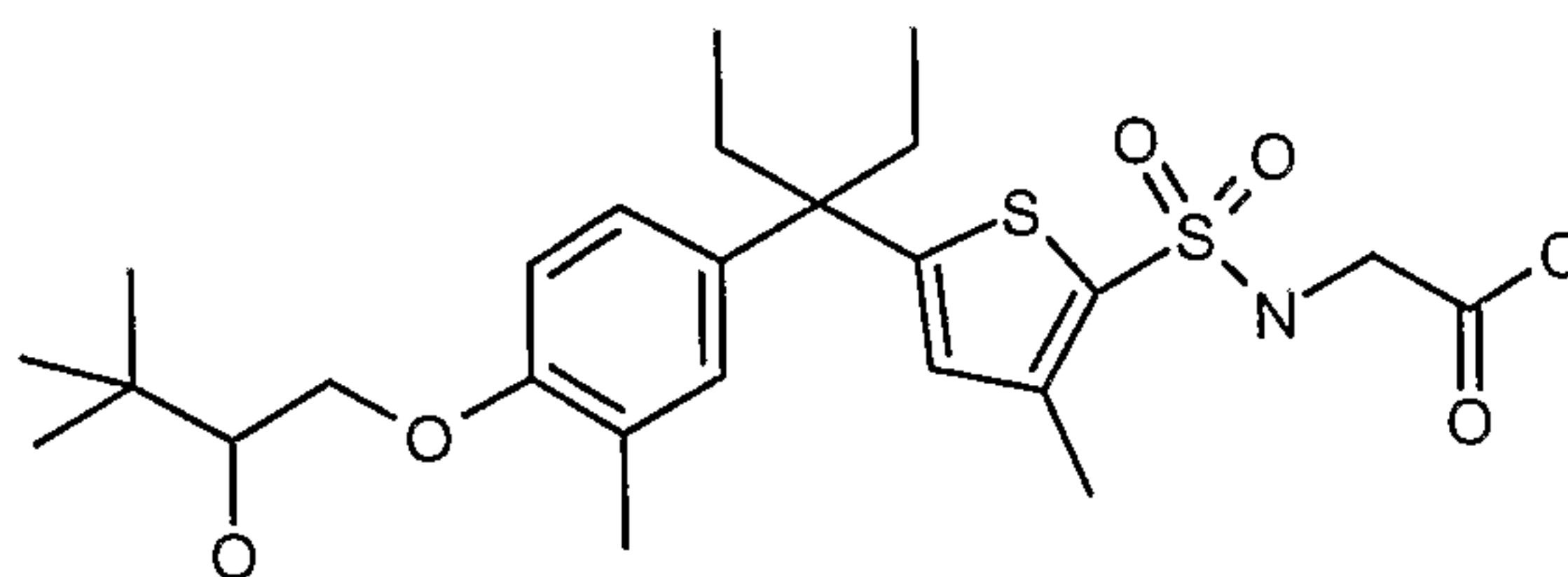


X134)



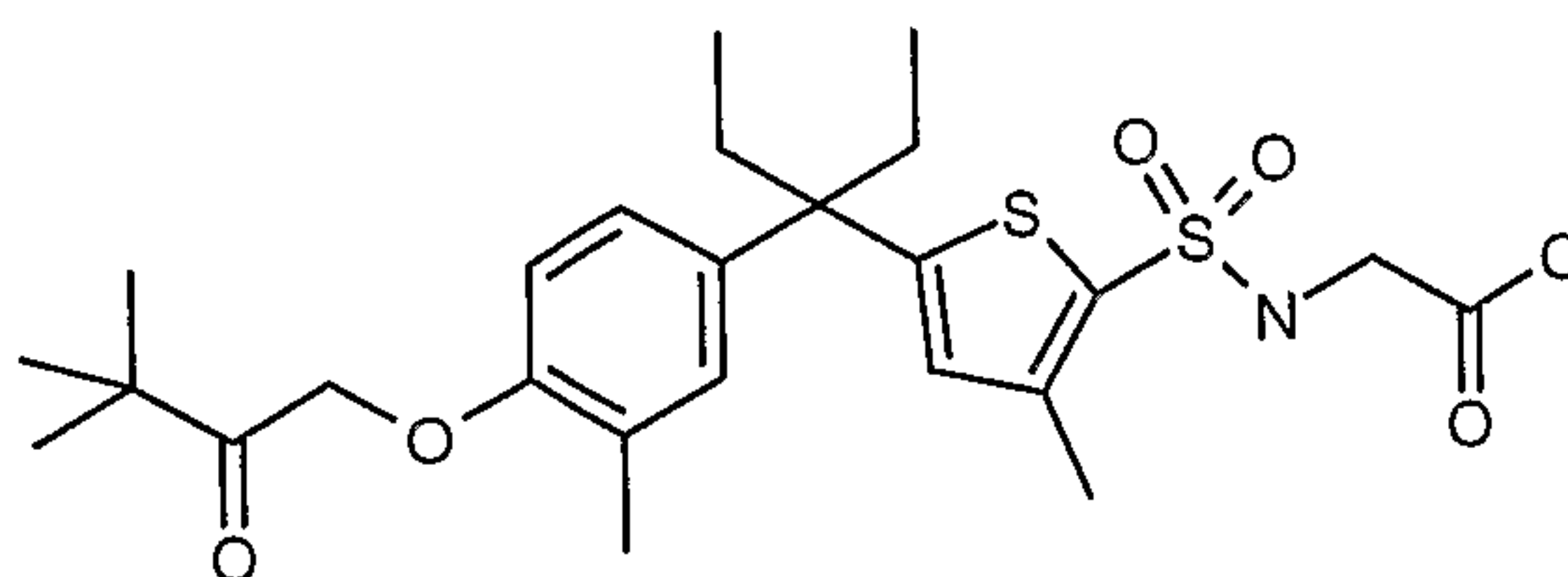
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X137)

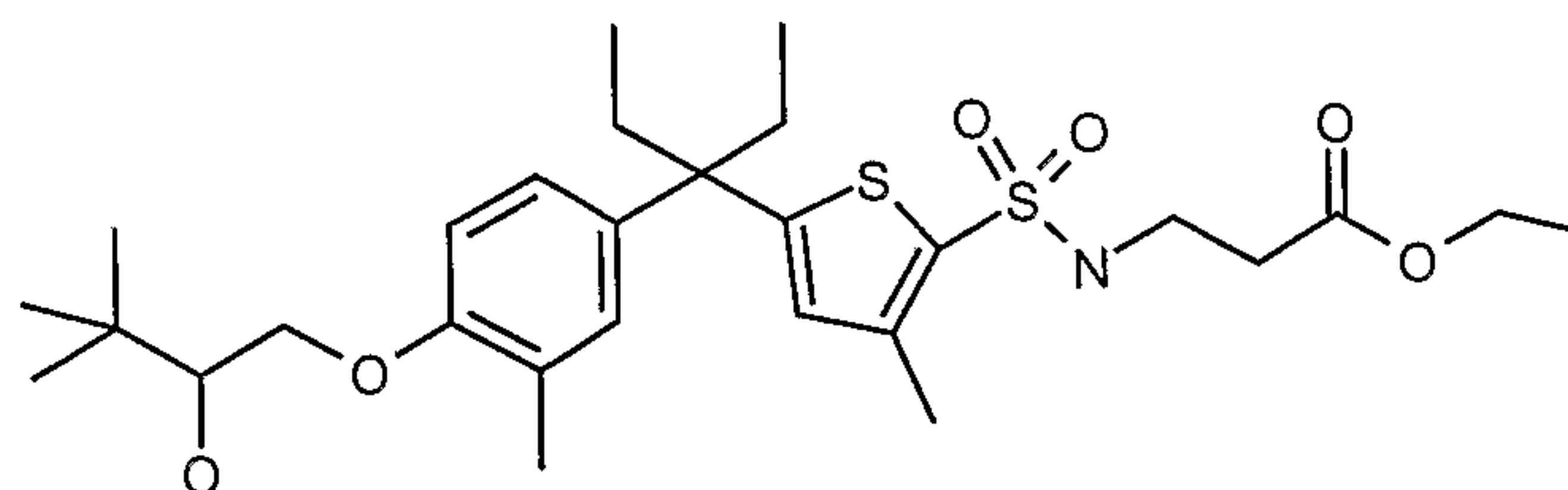


X139)

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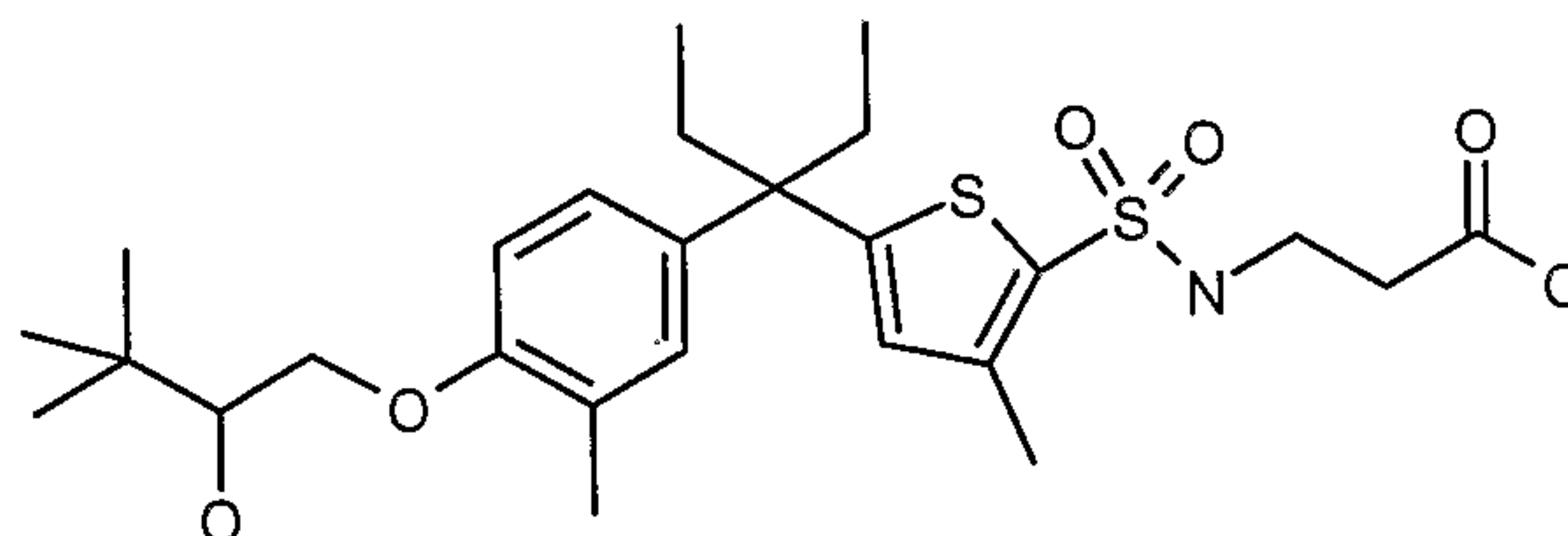
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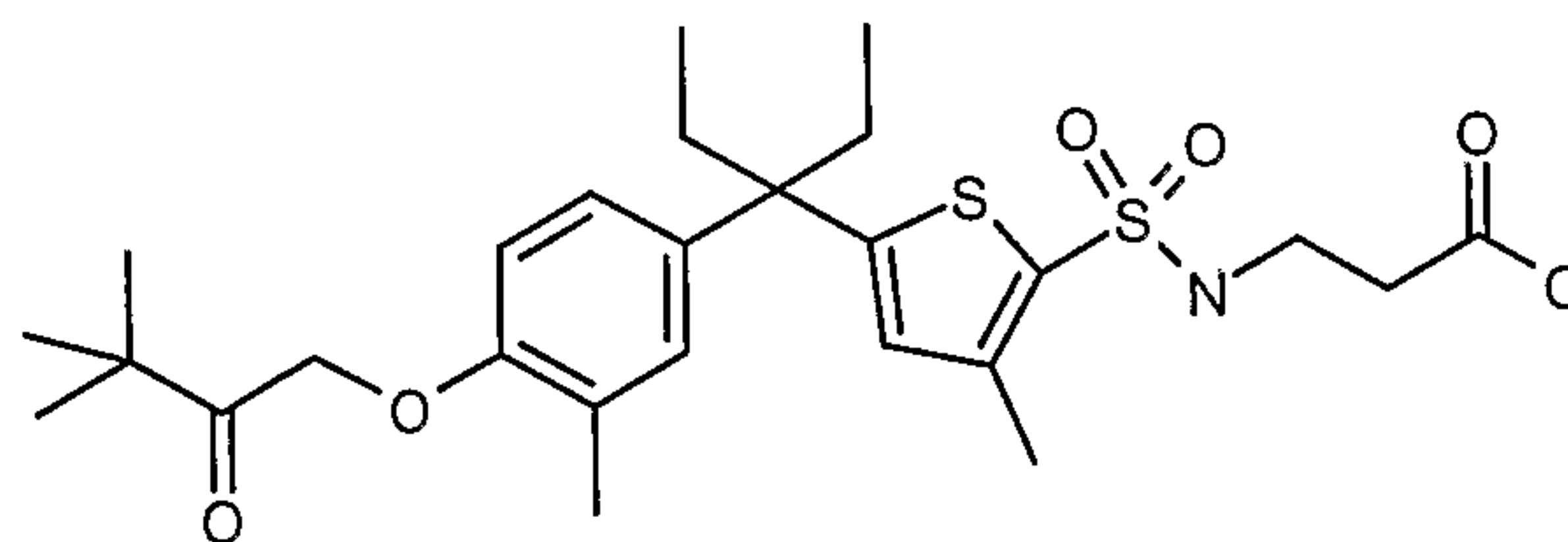
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-77-

X141)

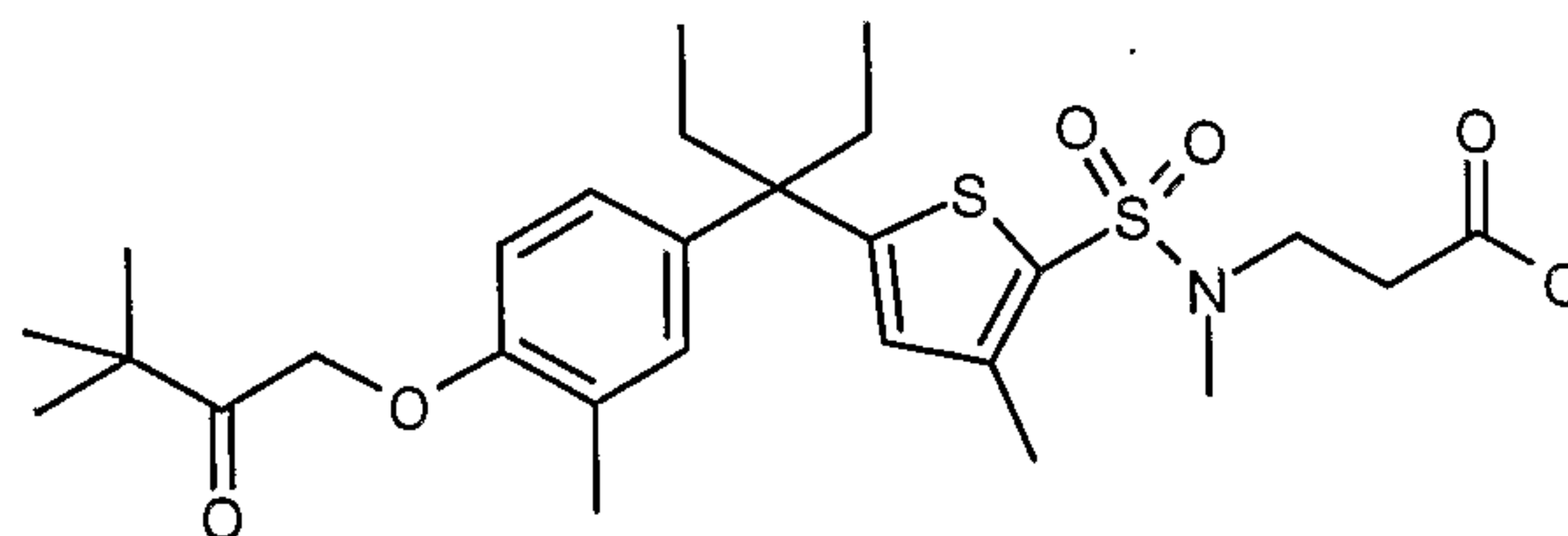


X144)

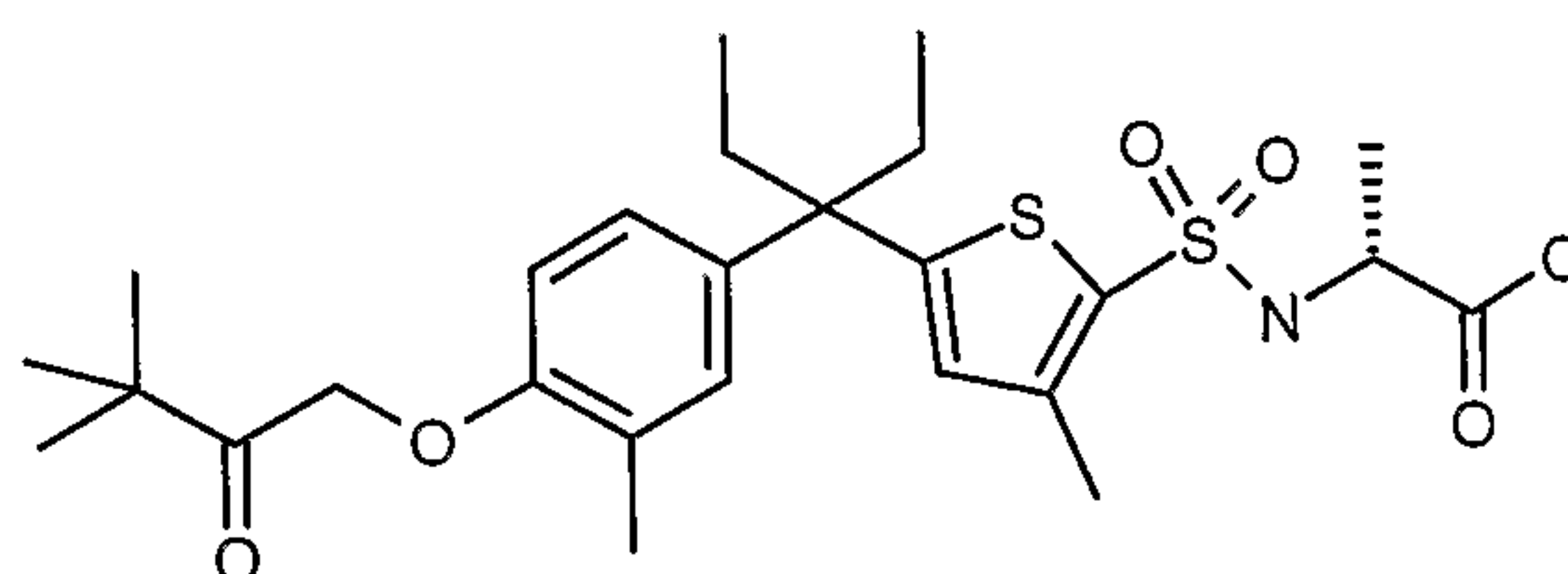


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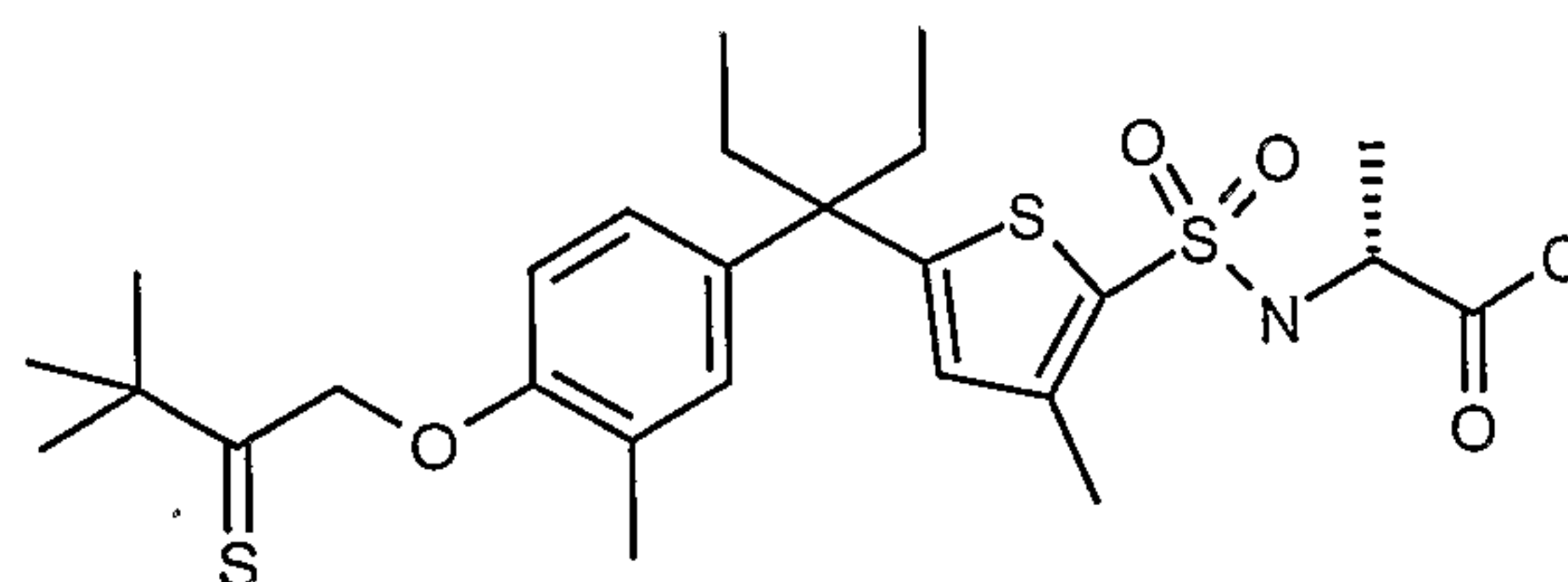
X145)



10 X146)

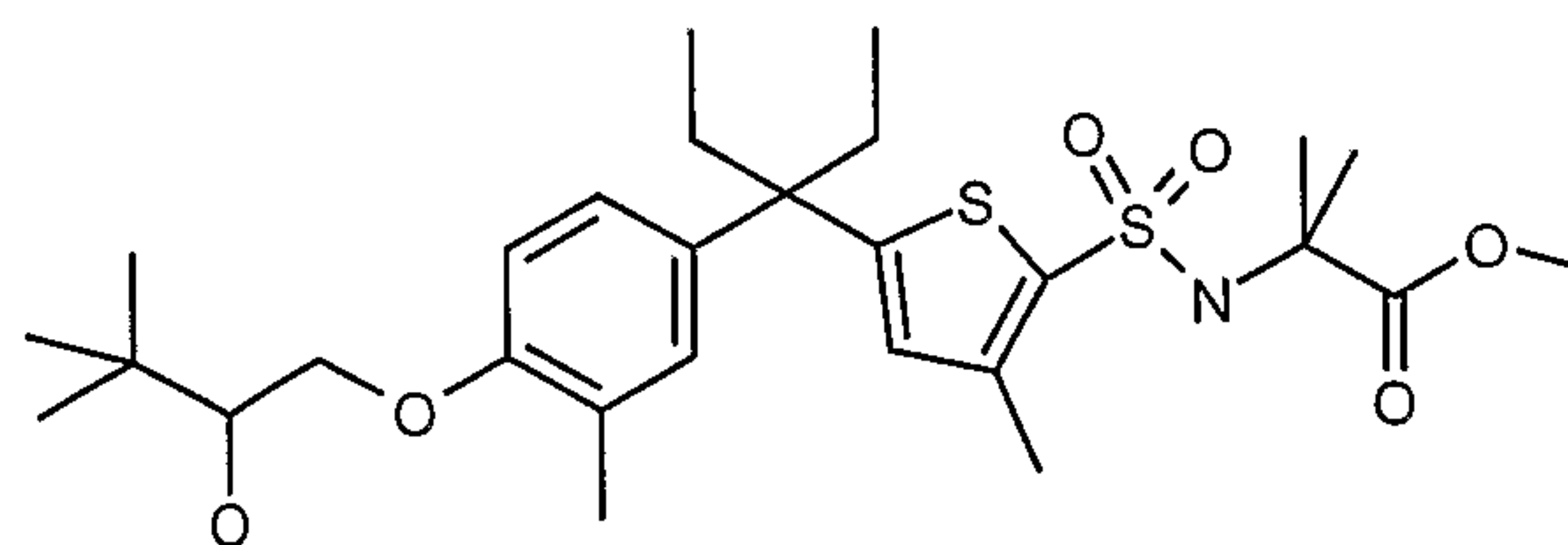


X147)

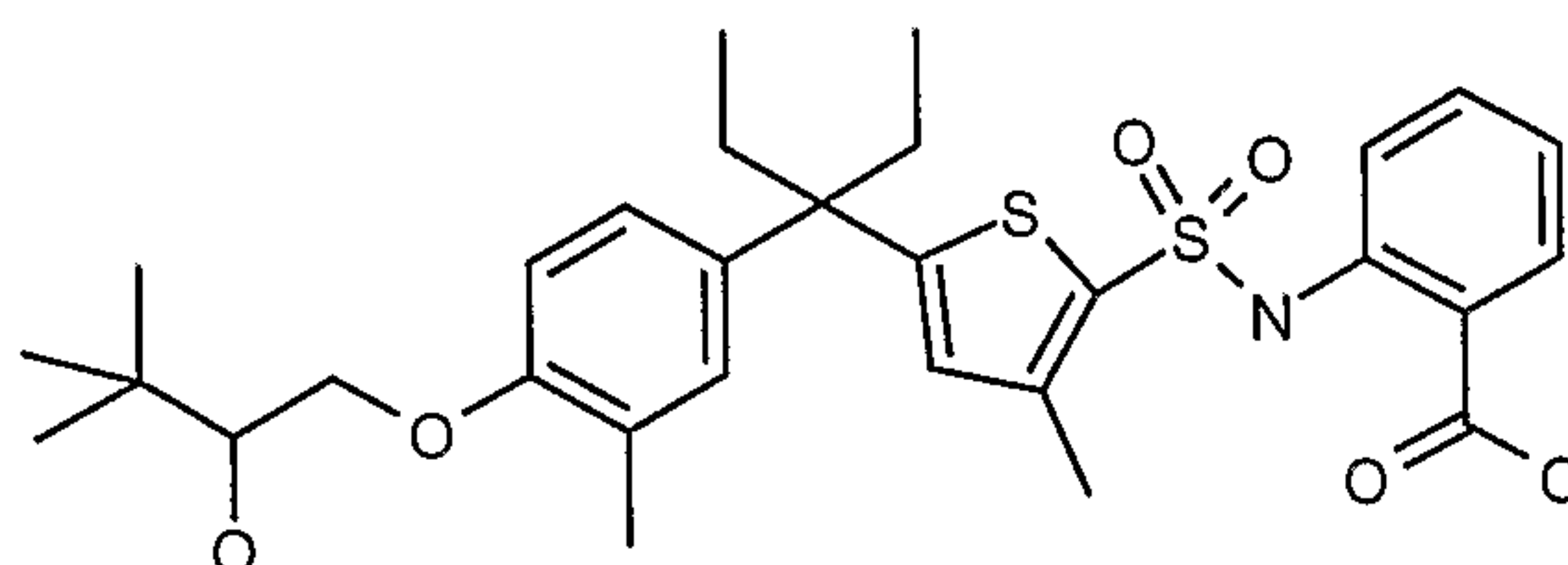


15 X148)

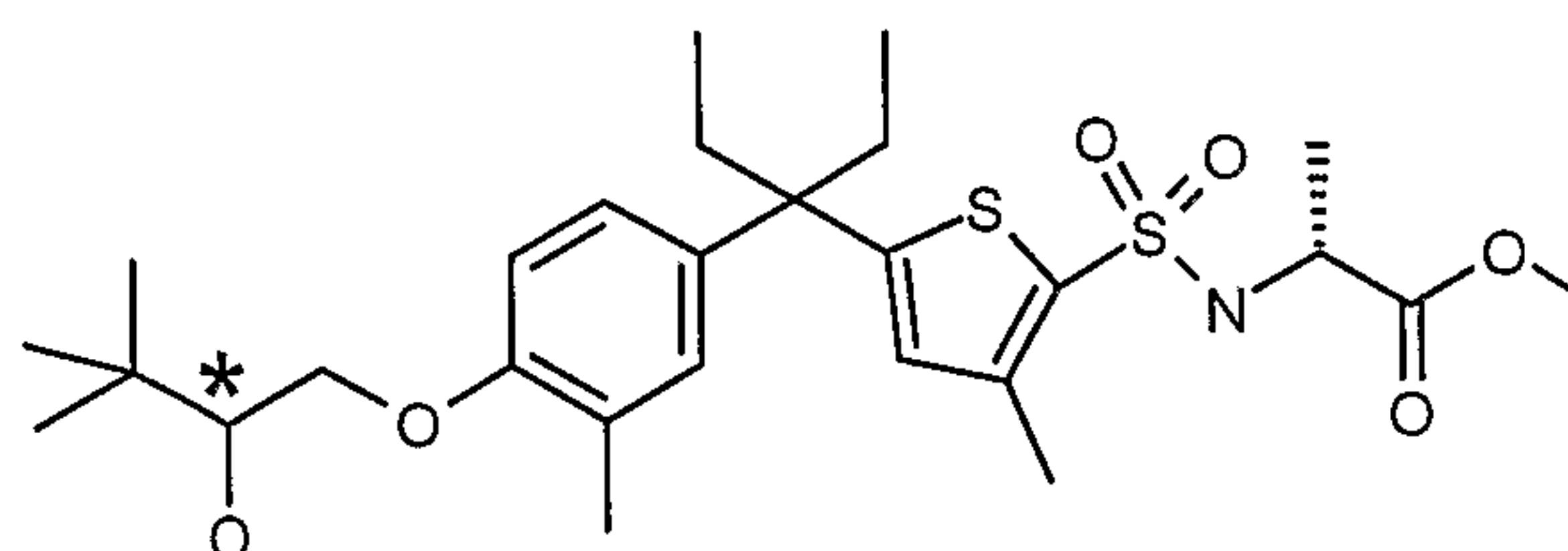
-78-



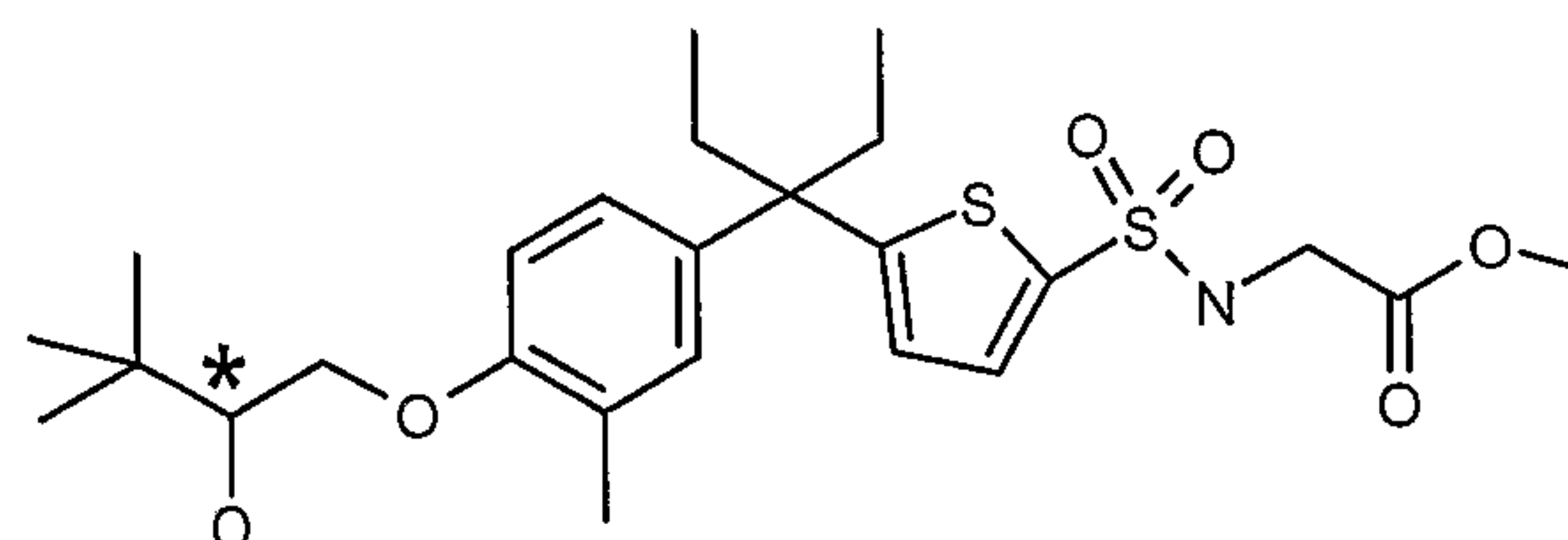
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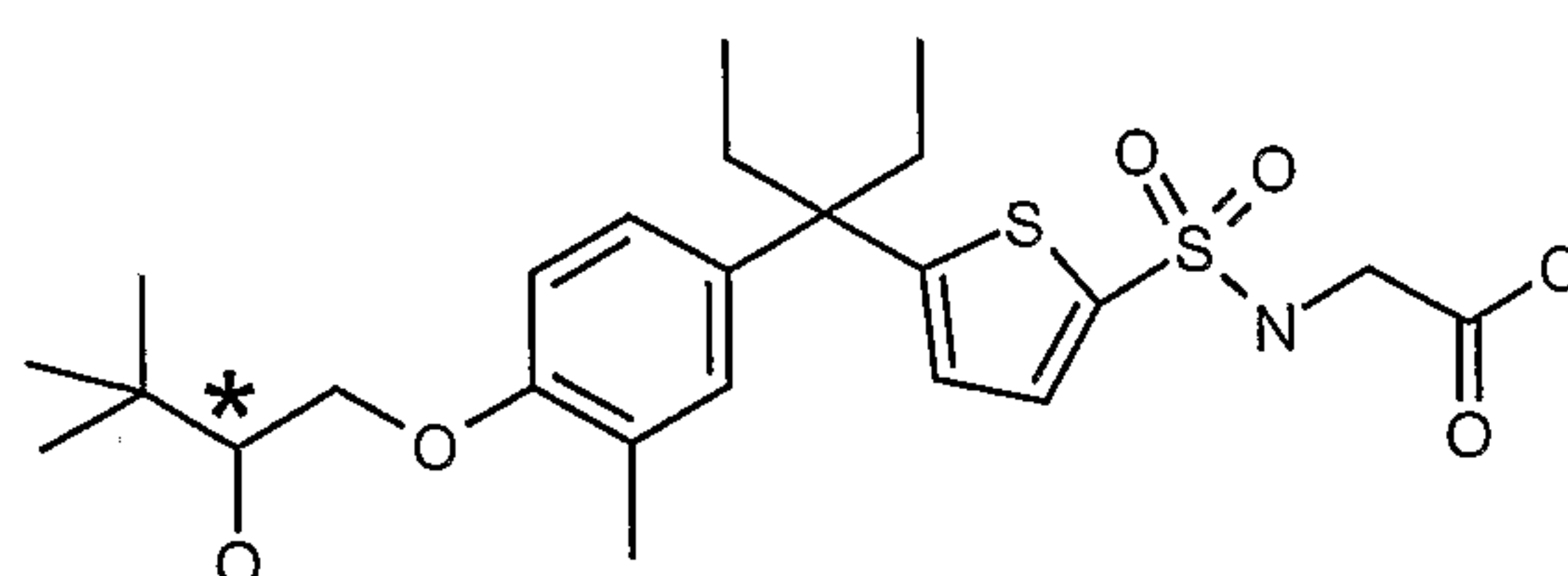
5 X150)



X152)

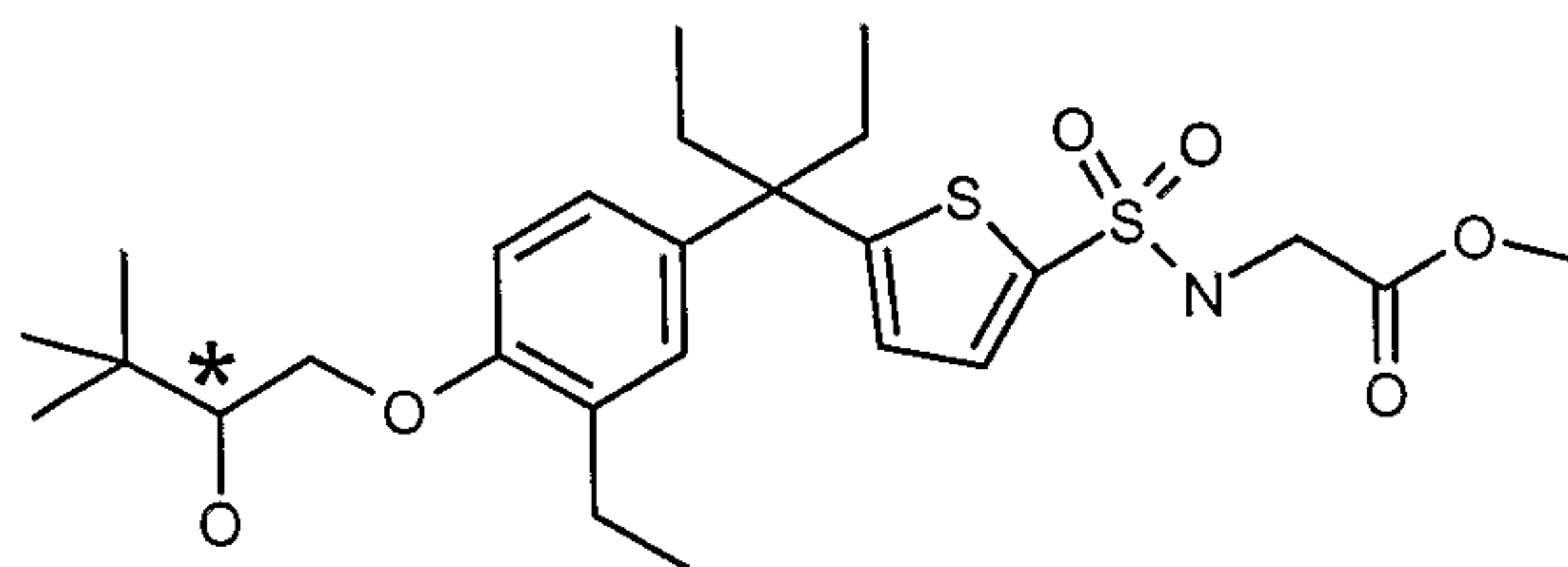


10 X153)

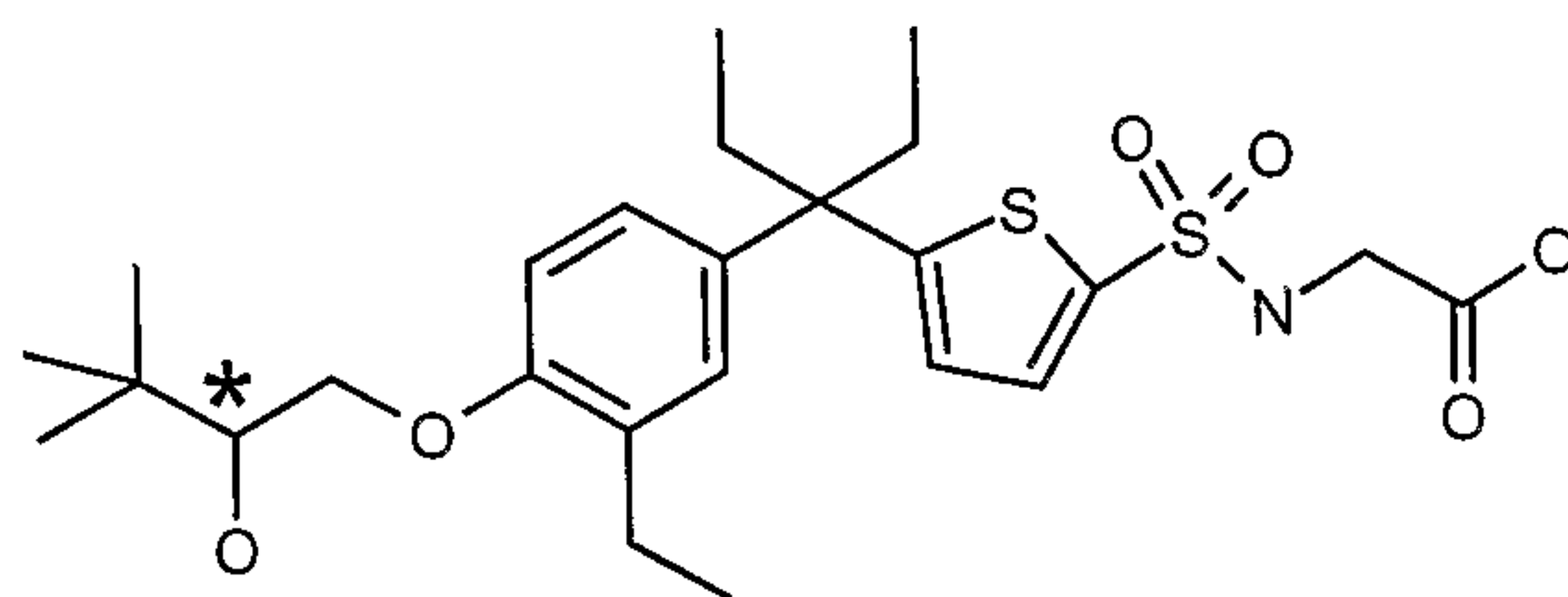


X154)

-79-

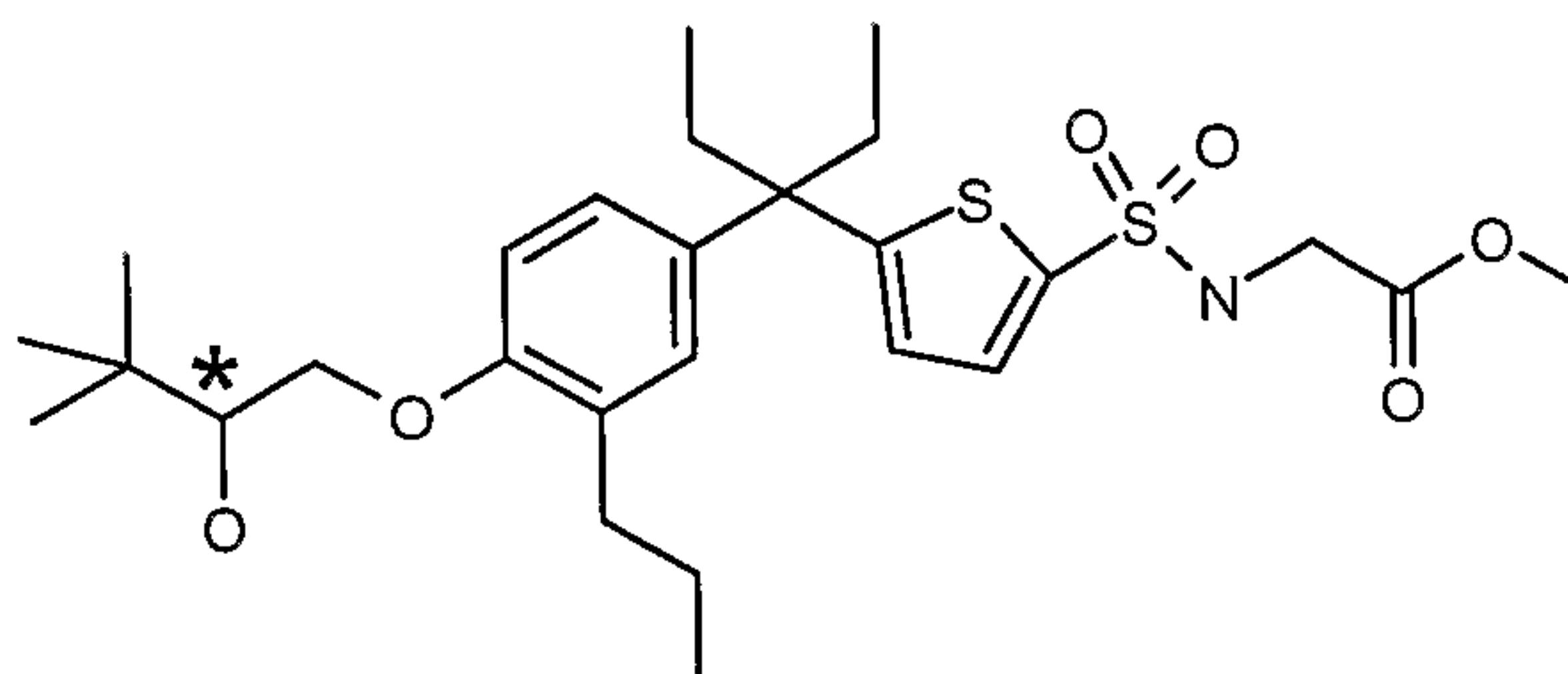


X155)

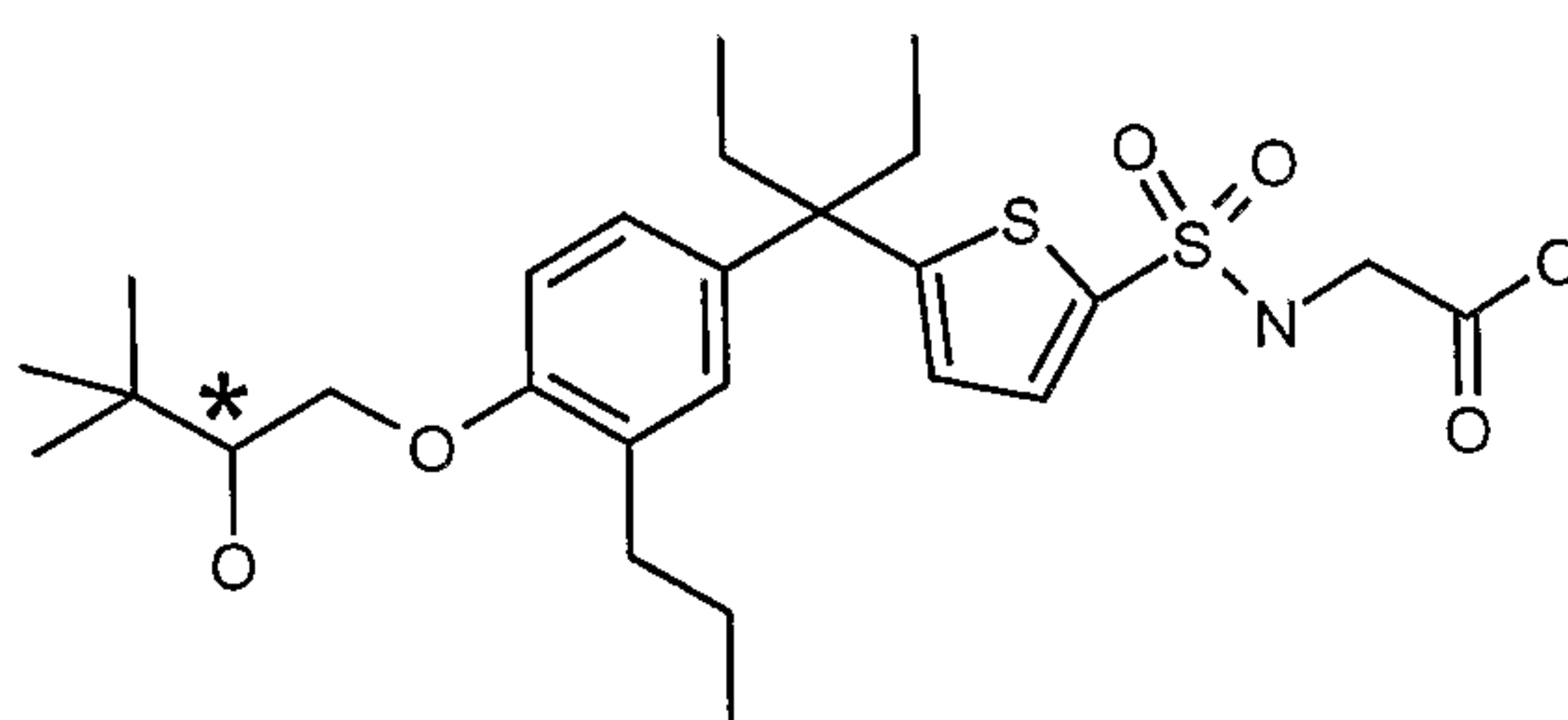


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X156)

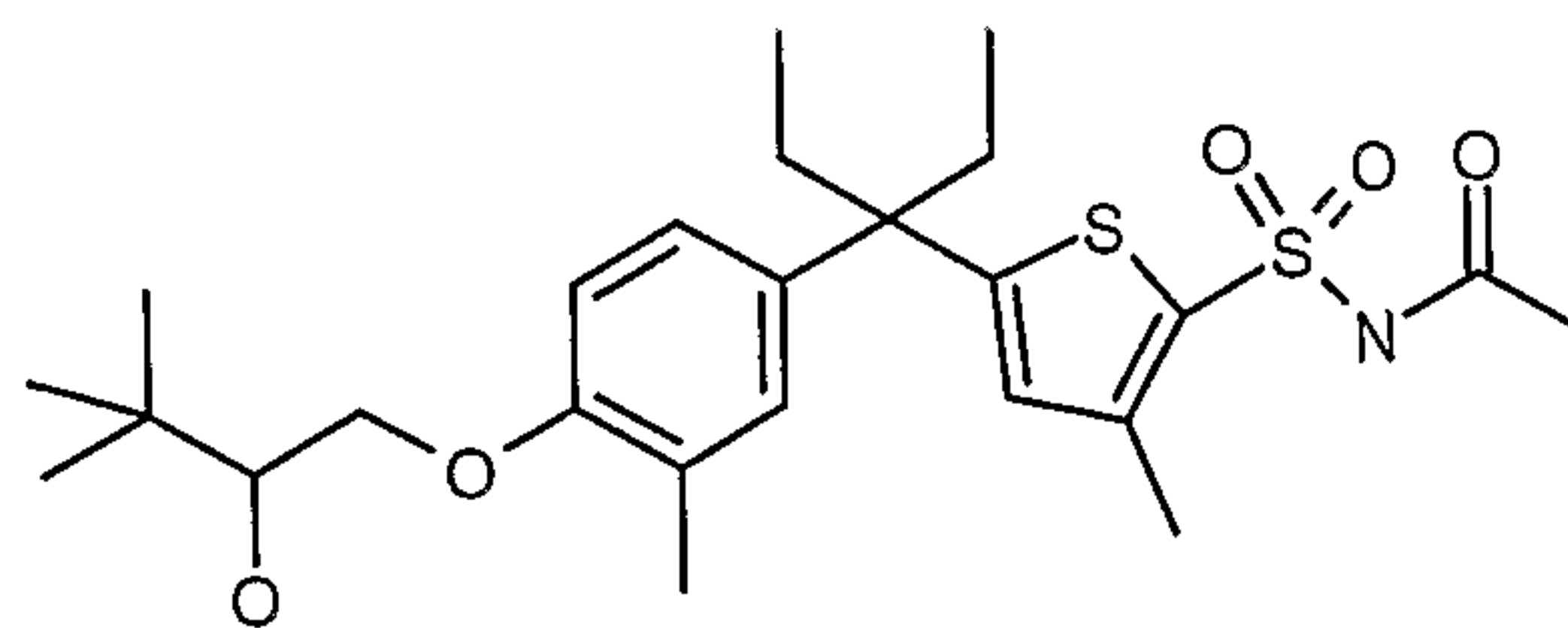


X157)



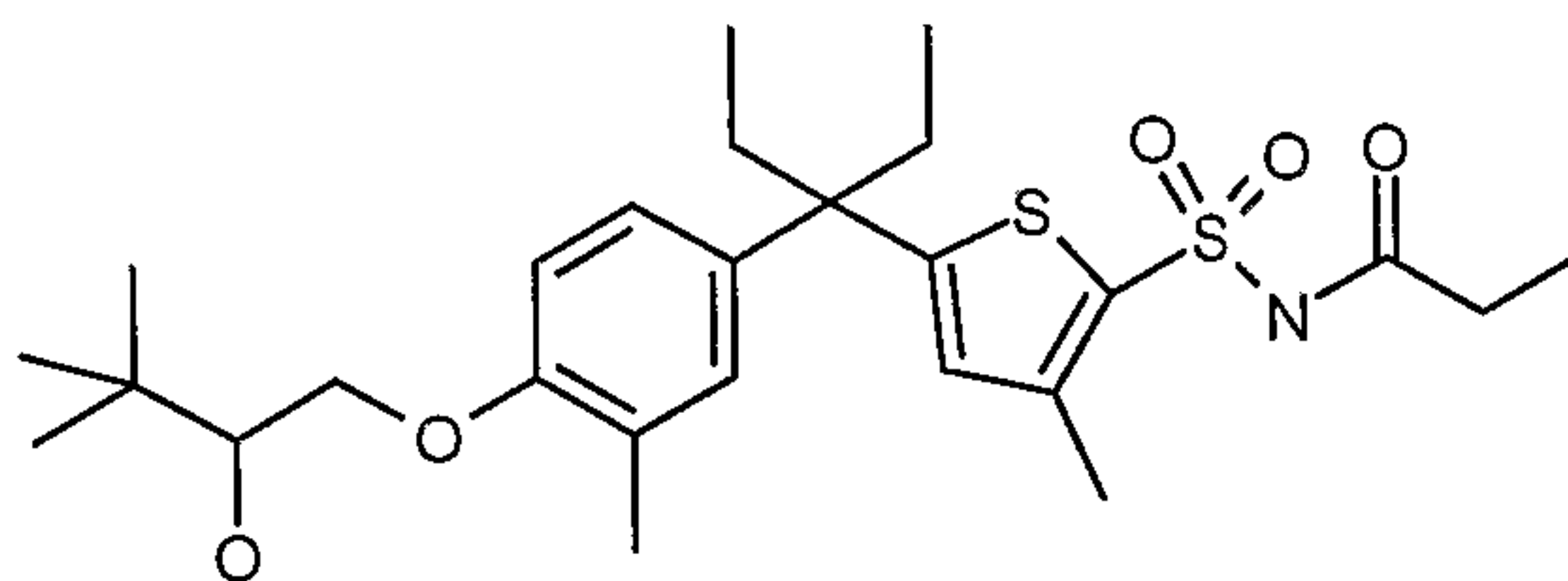
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X158)

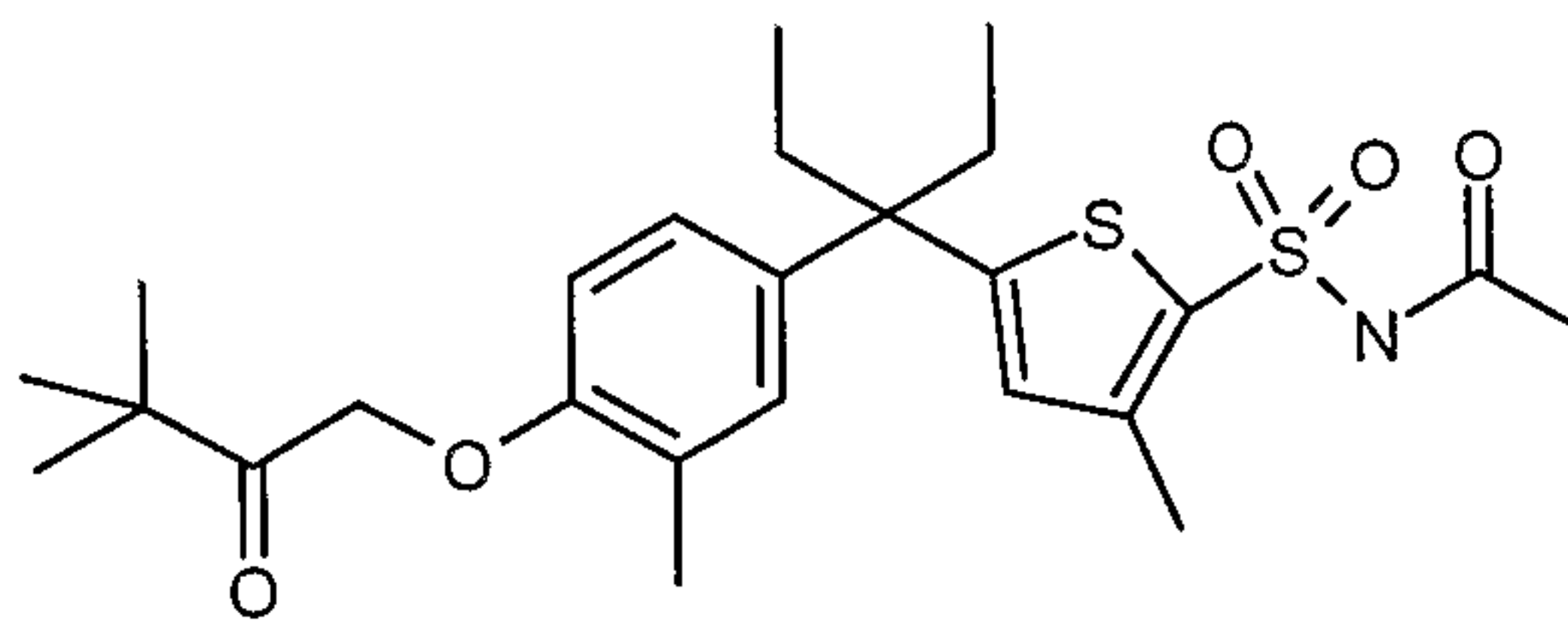


-80-

X159)

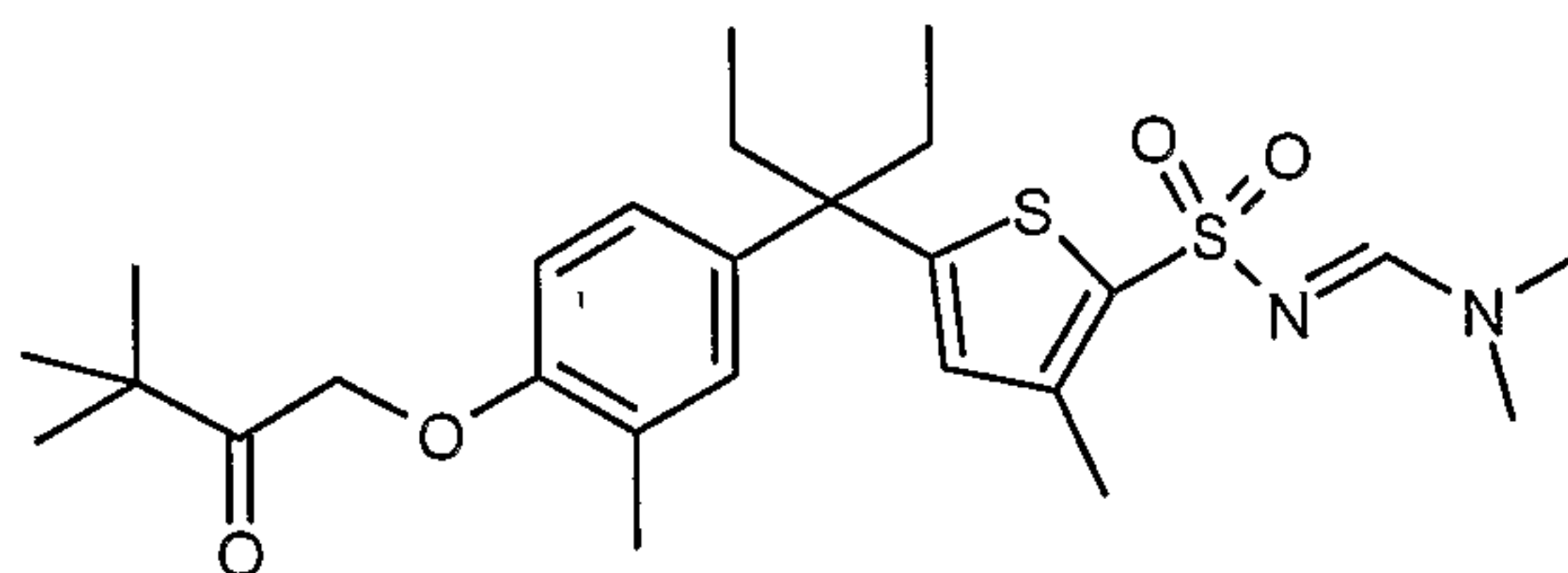


X160)

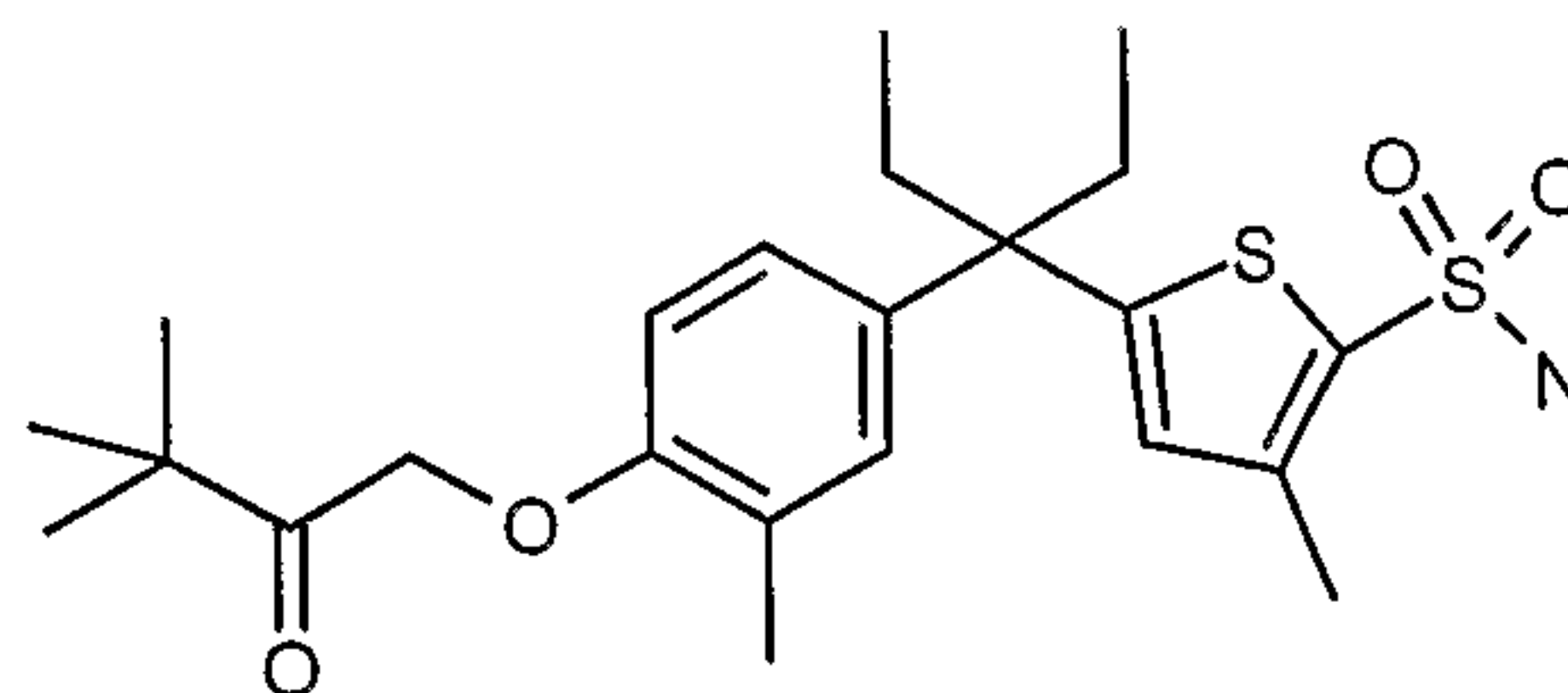


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X161)

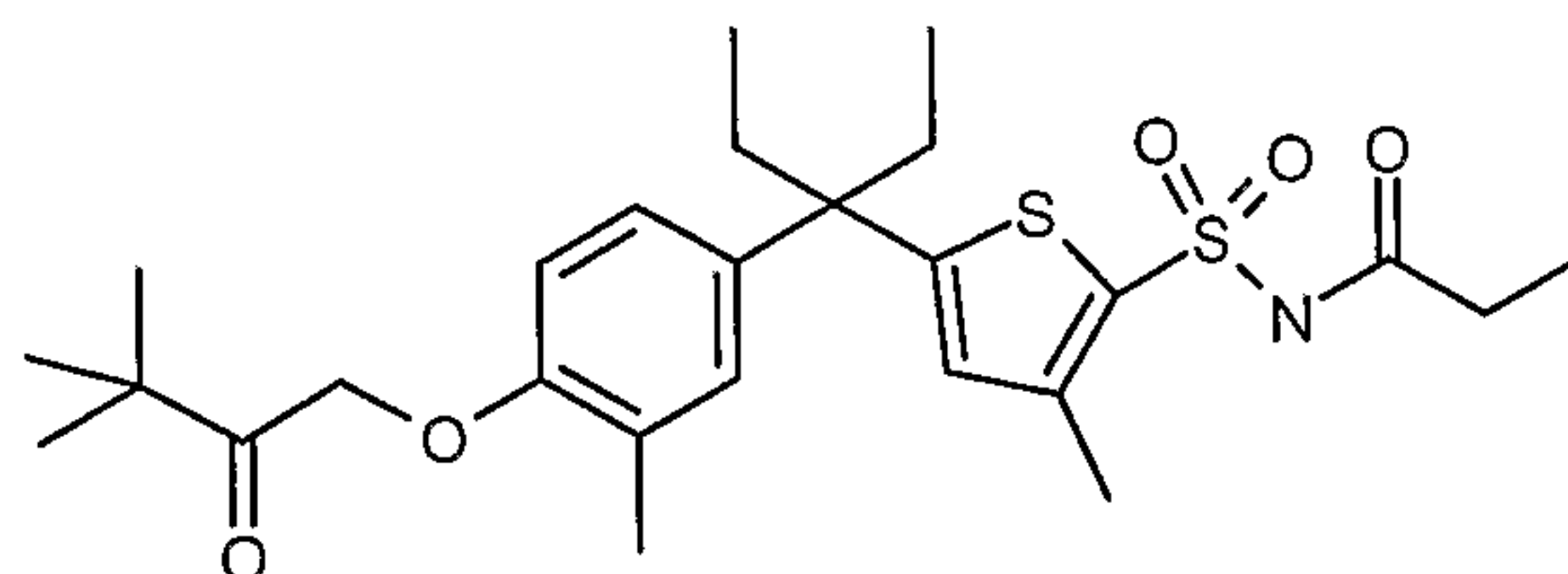


X162)

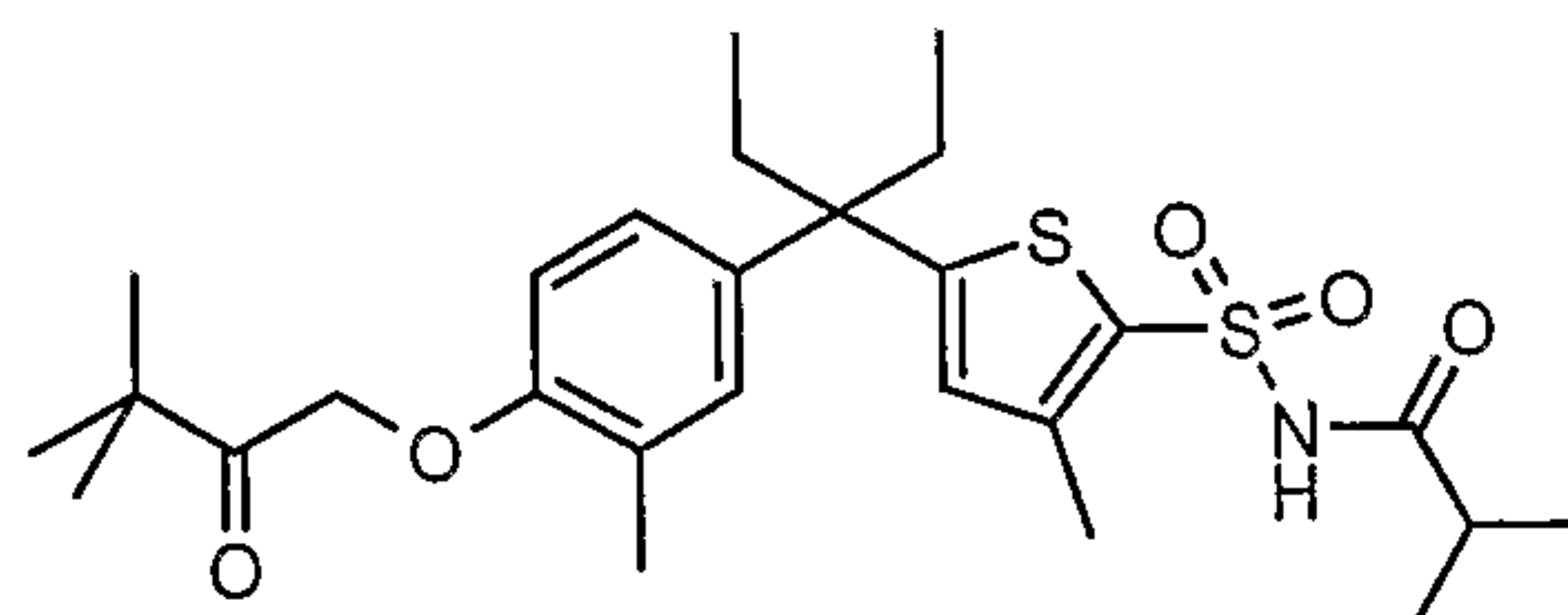


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X163)

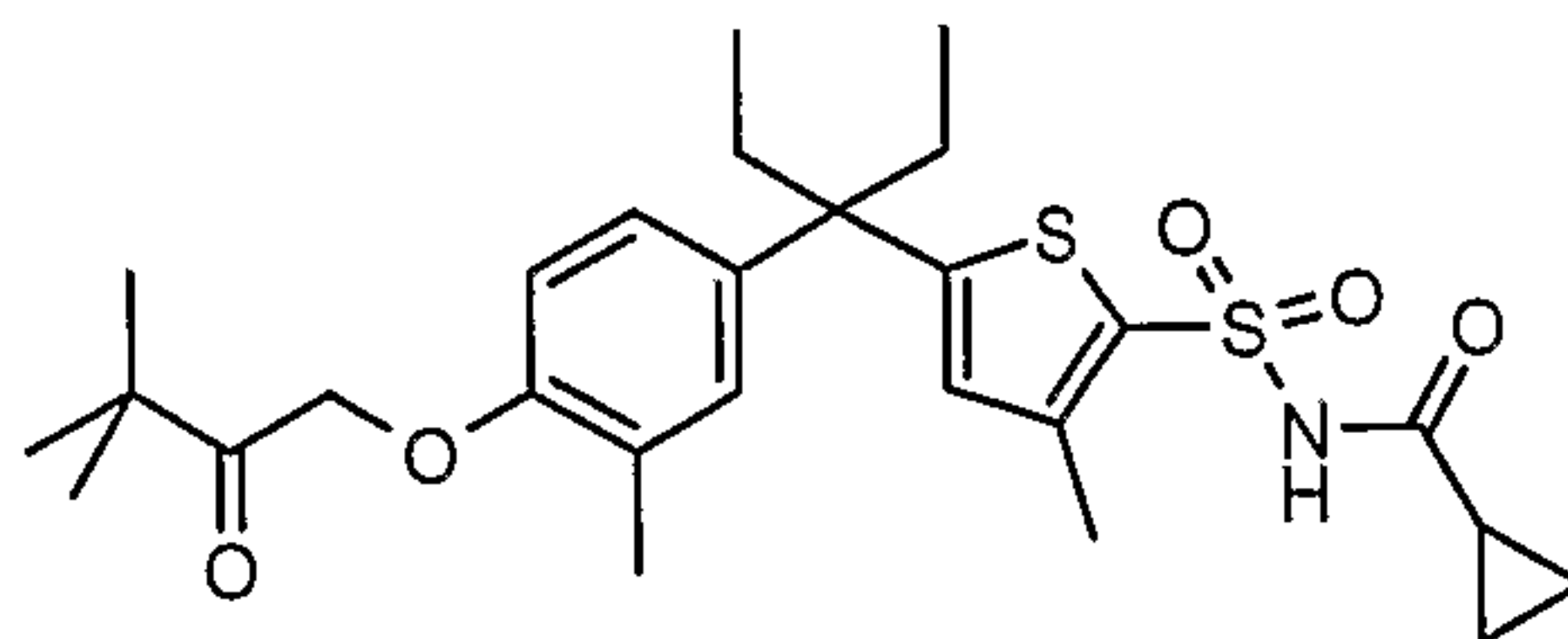


X164)

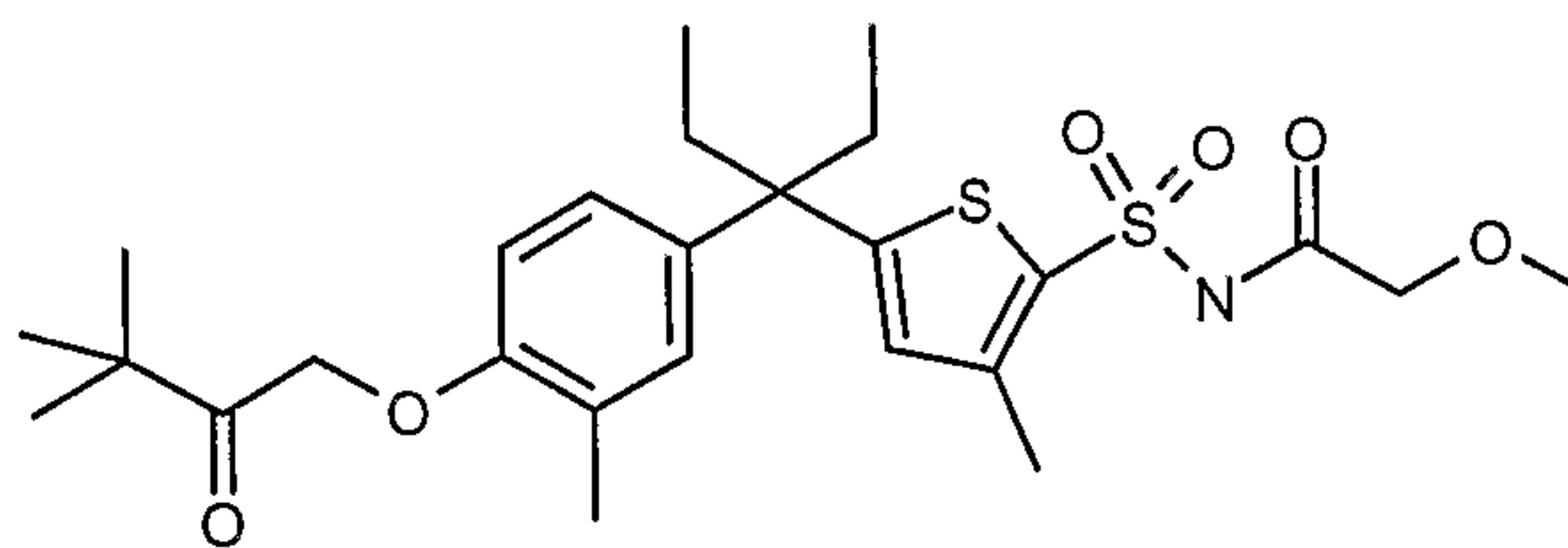


-81-

X165)

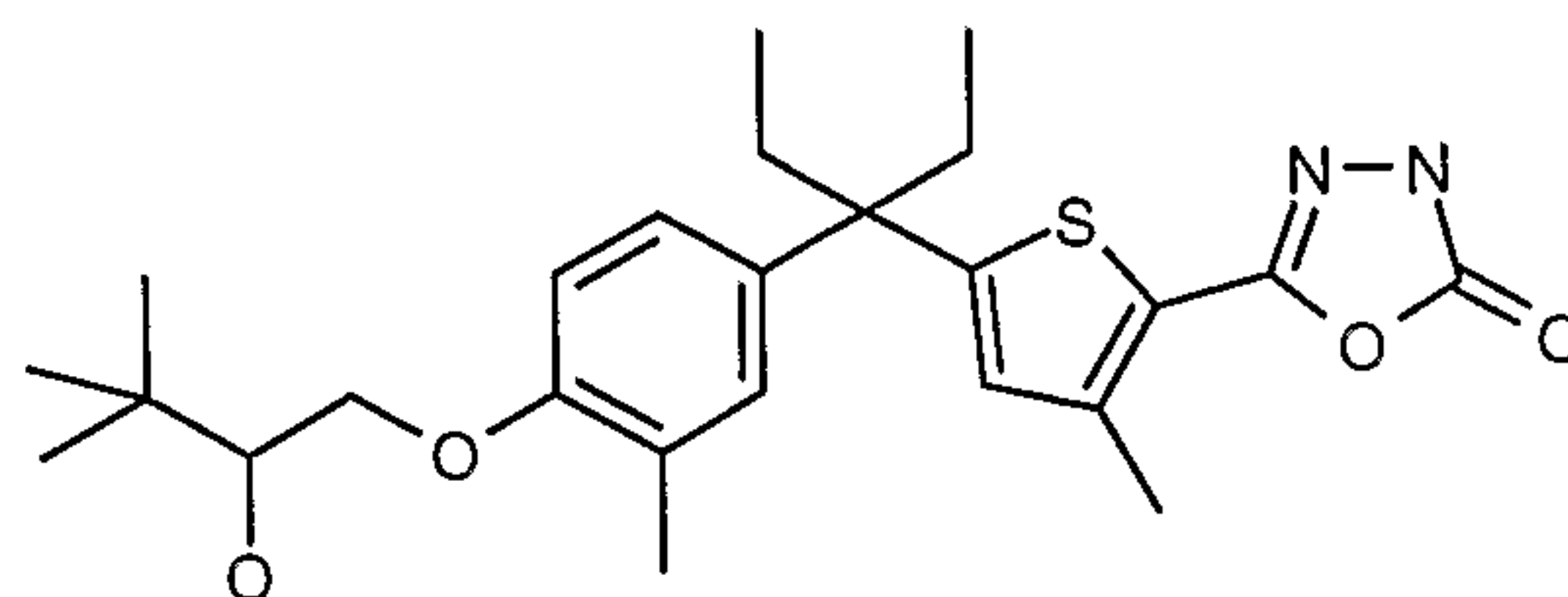


X166)

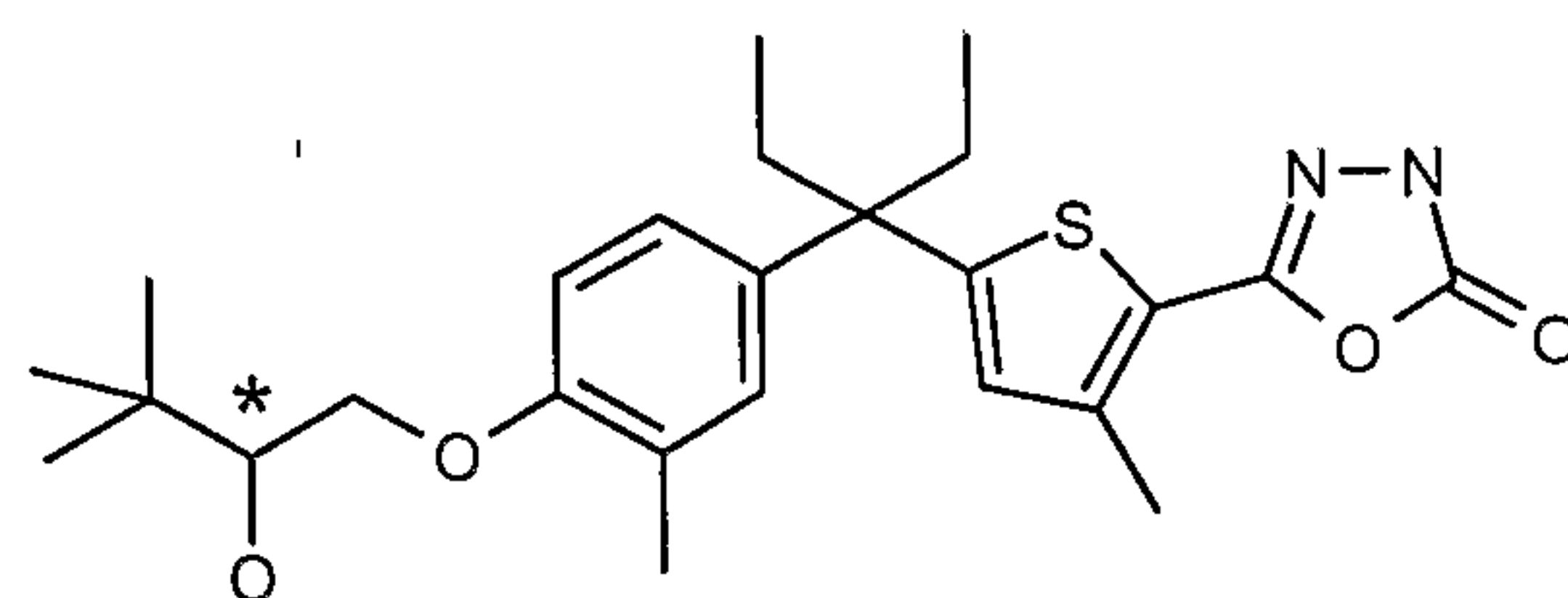


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X169)

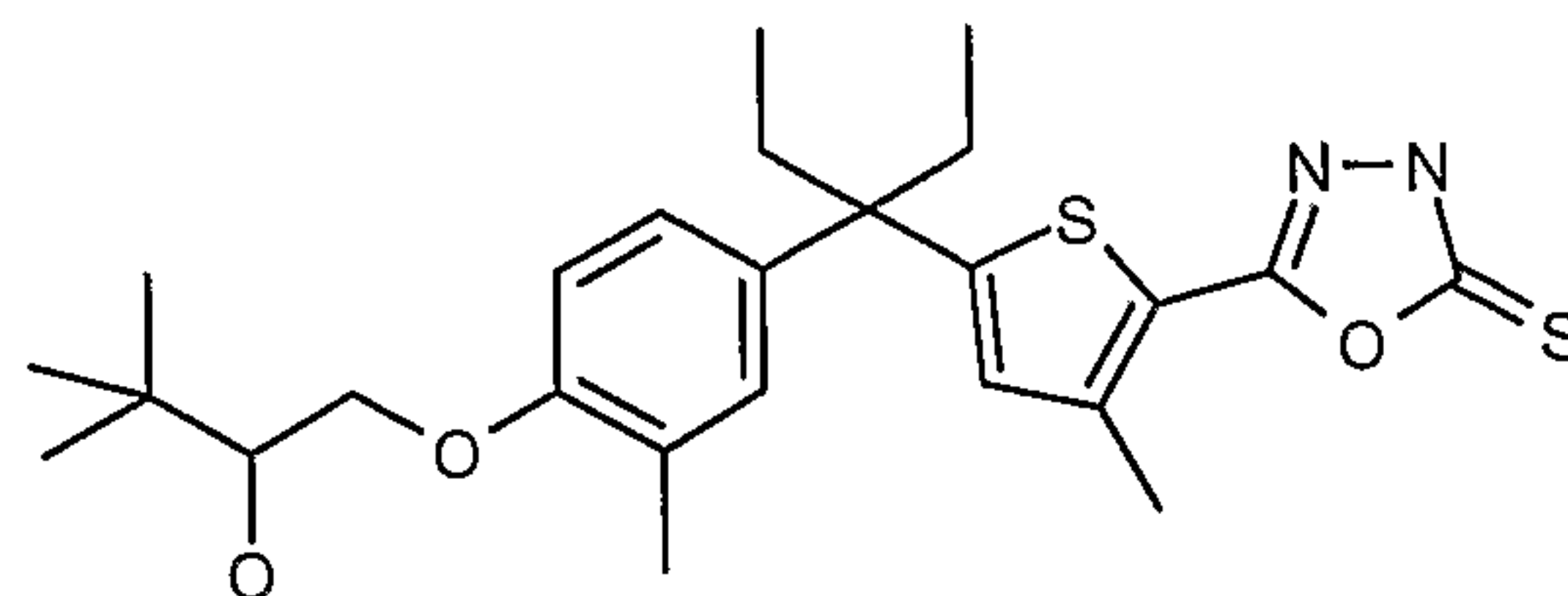


X171)

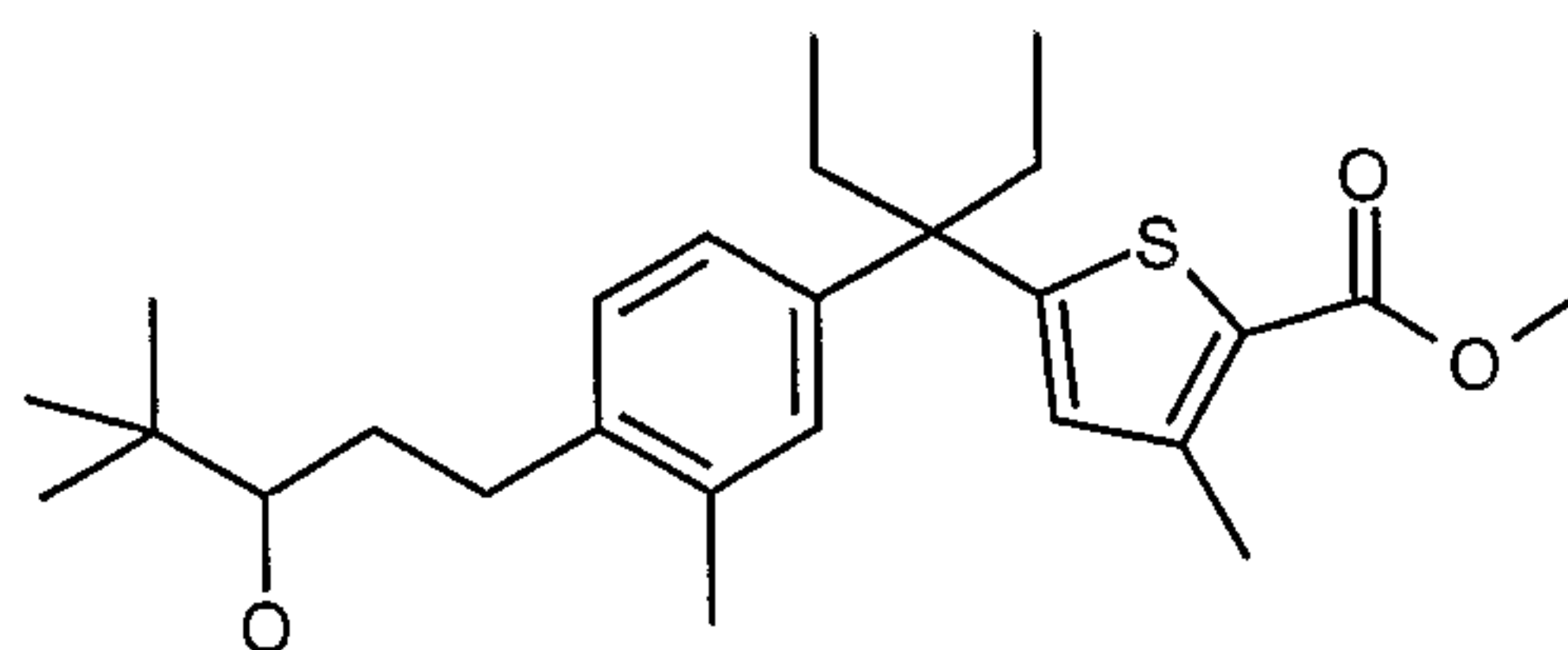


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X172)

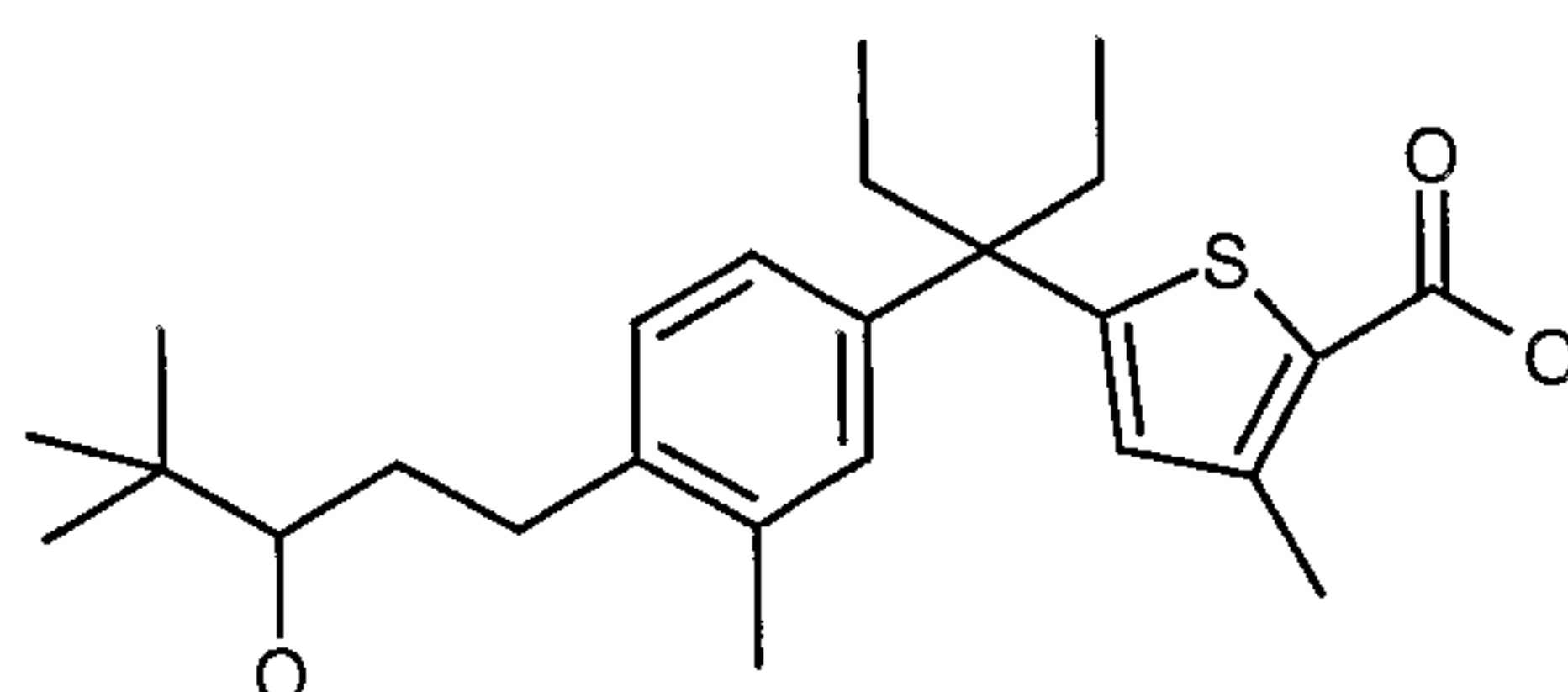


X174)

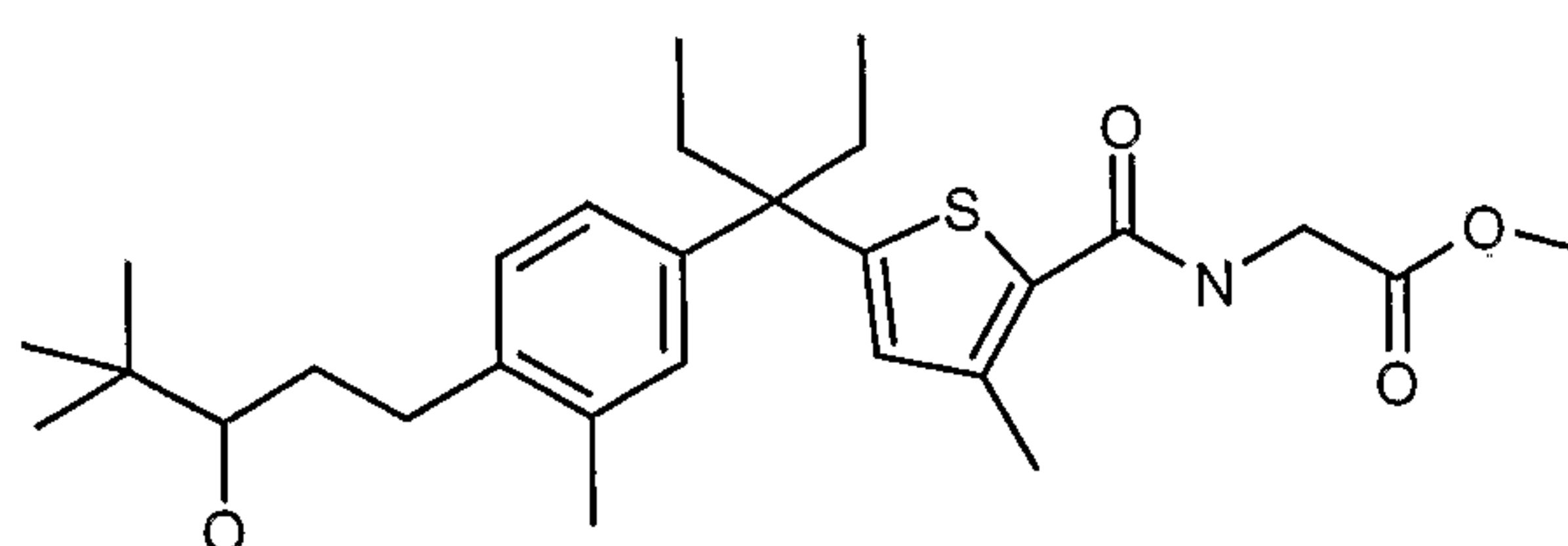


-82-

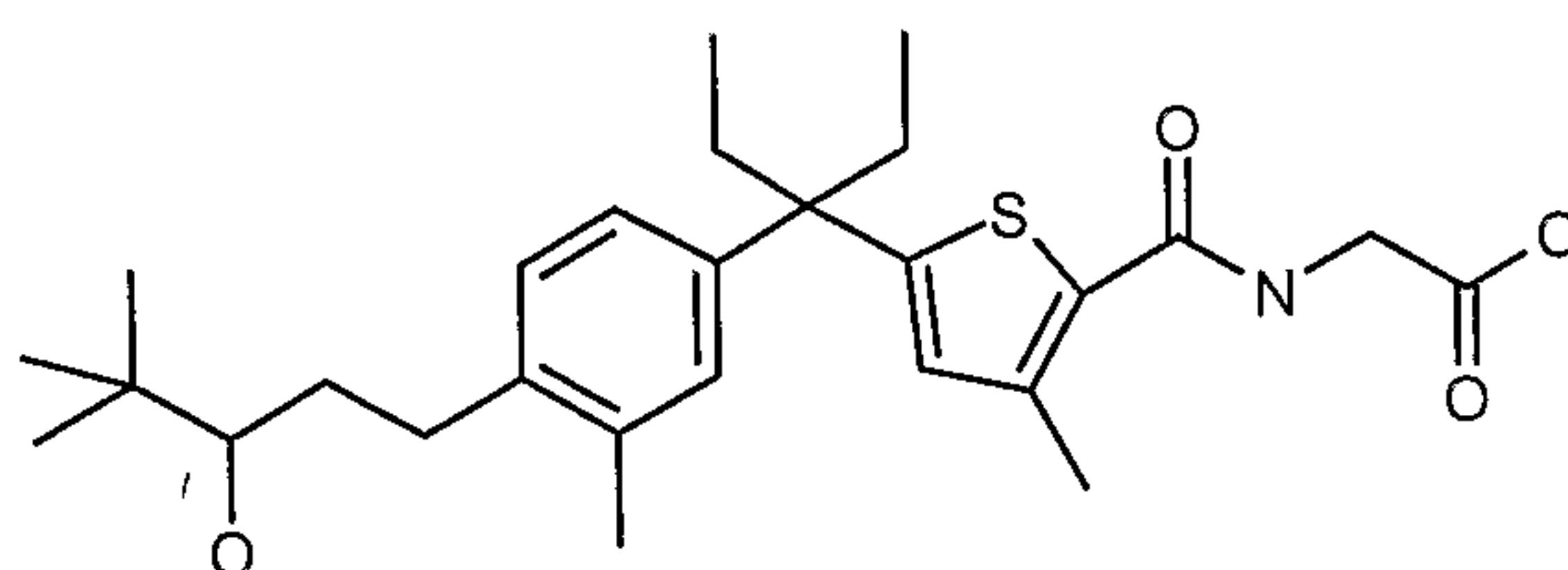
X175)



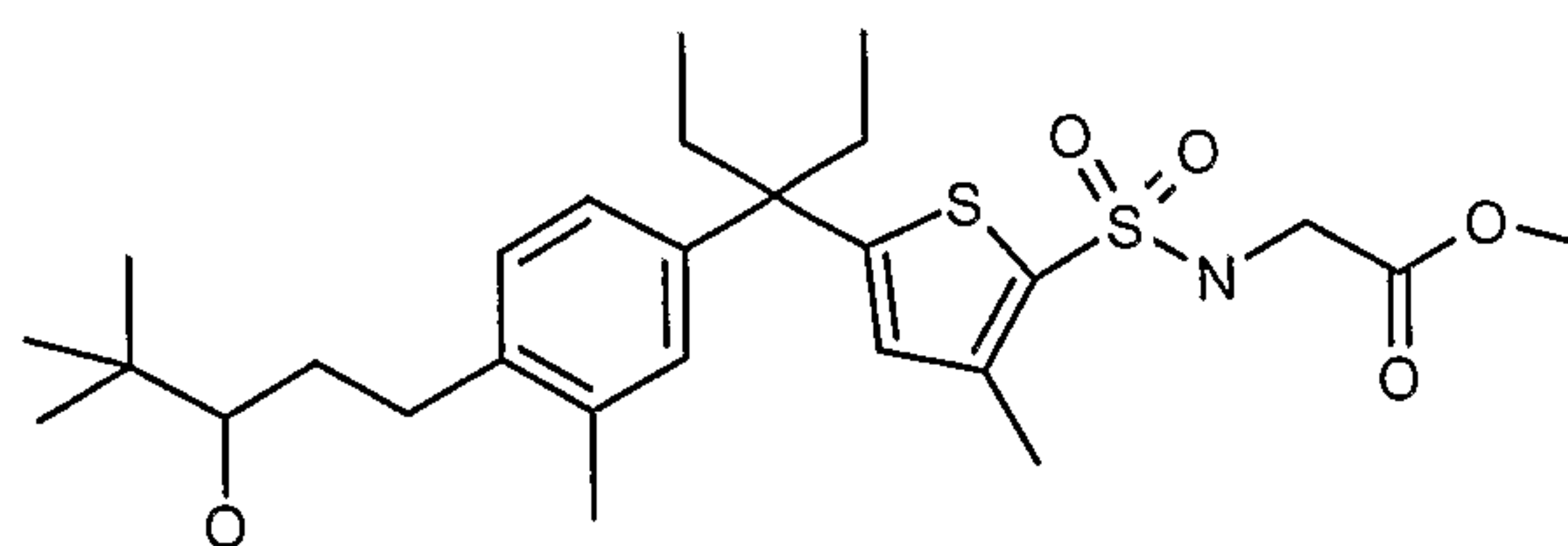
5 X176)



X177)

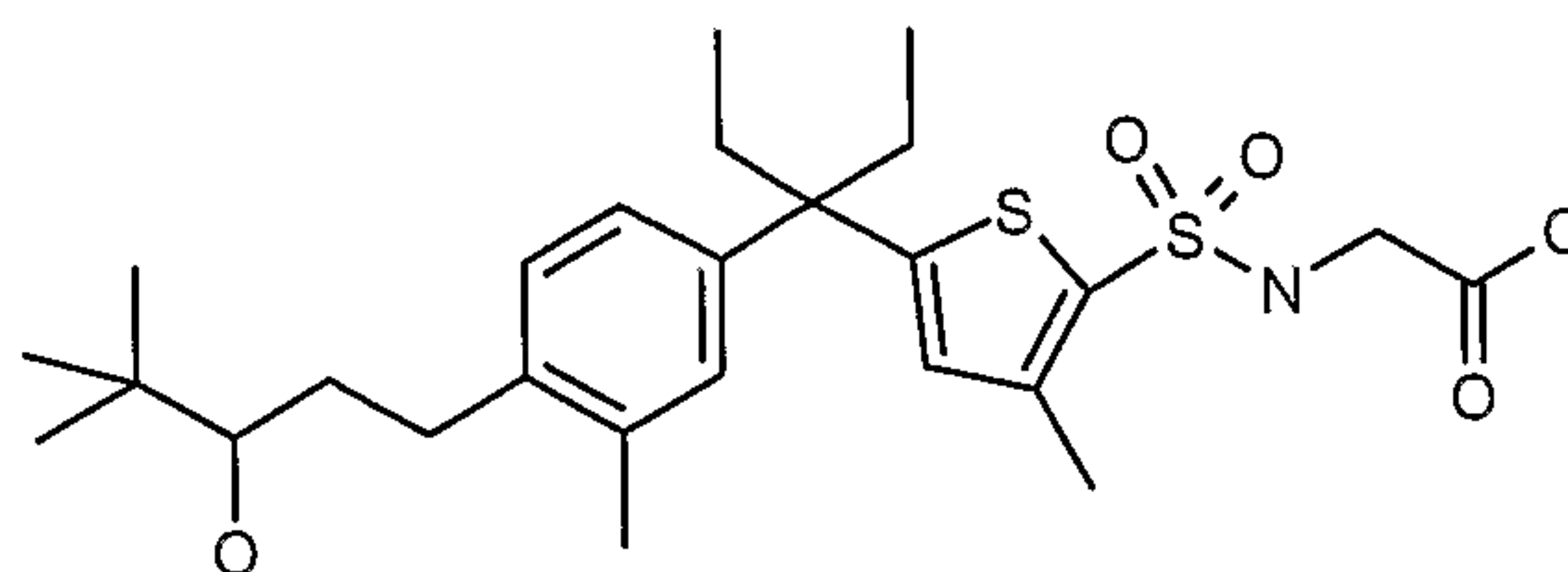


X178)



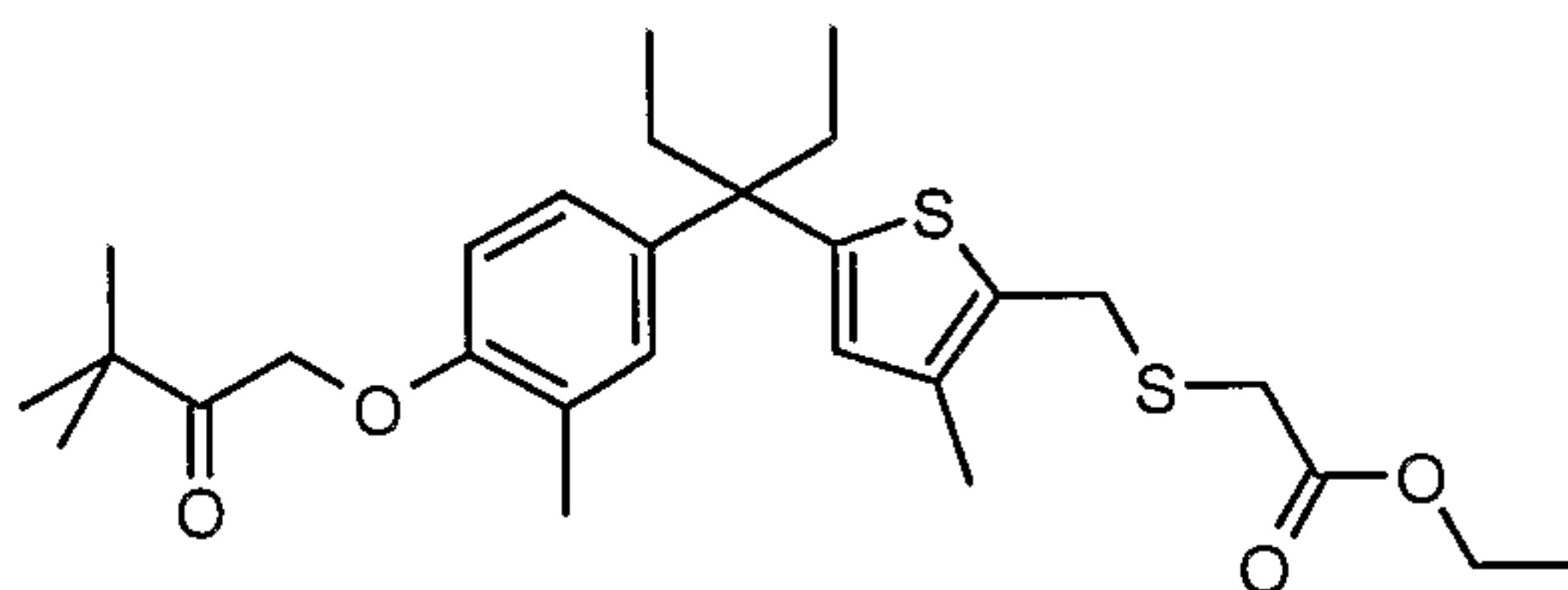
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X179)

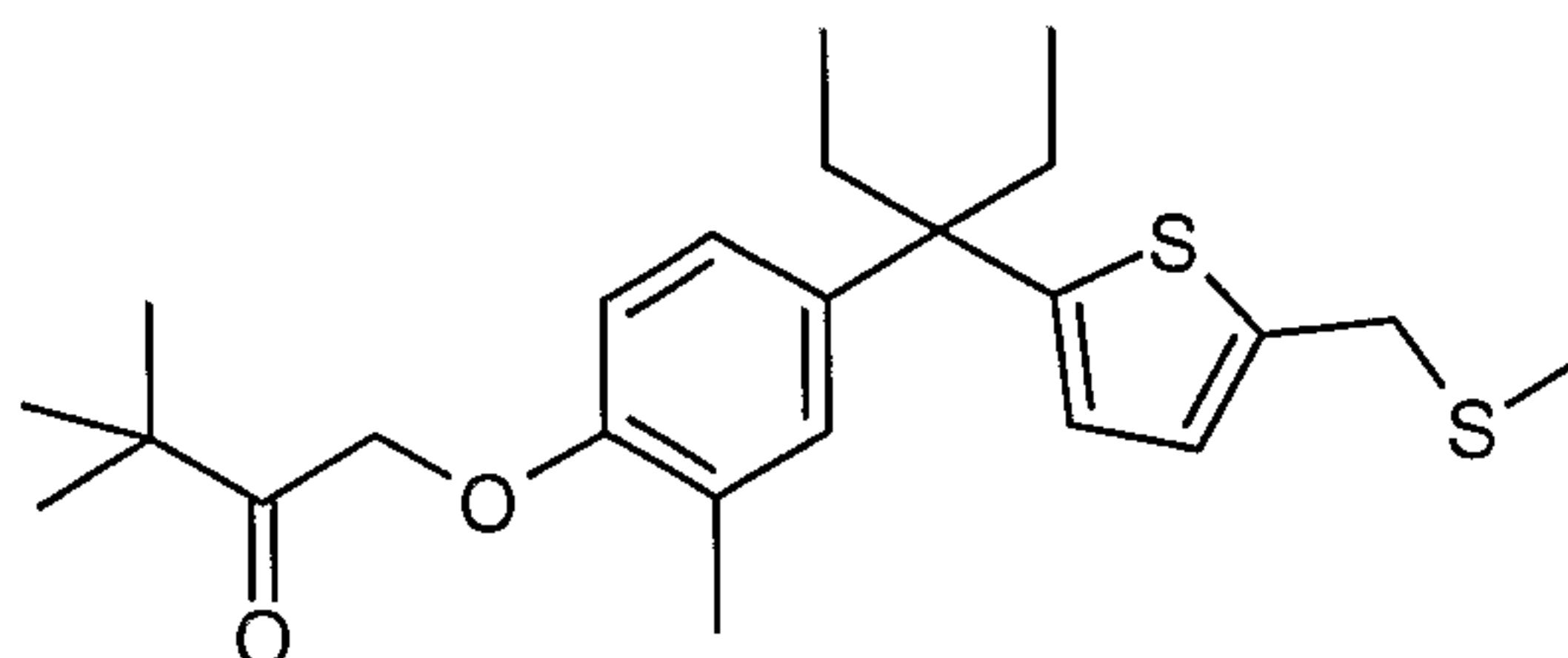


X183)

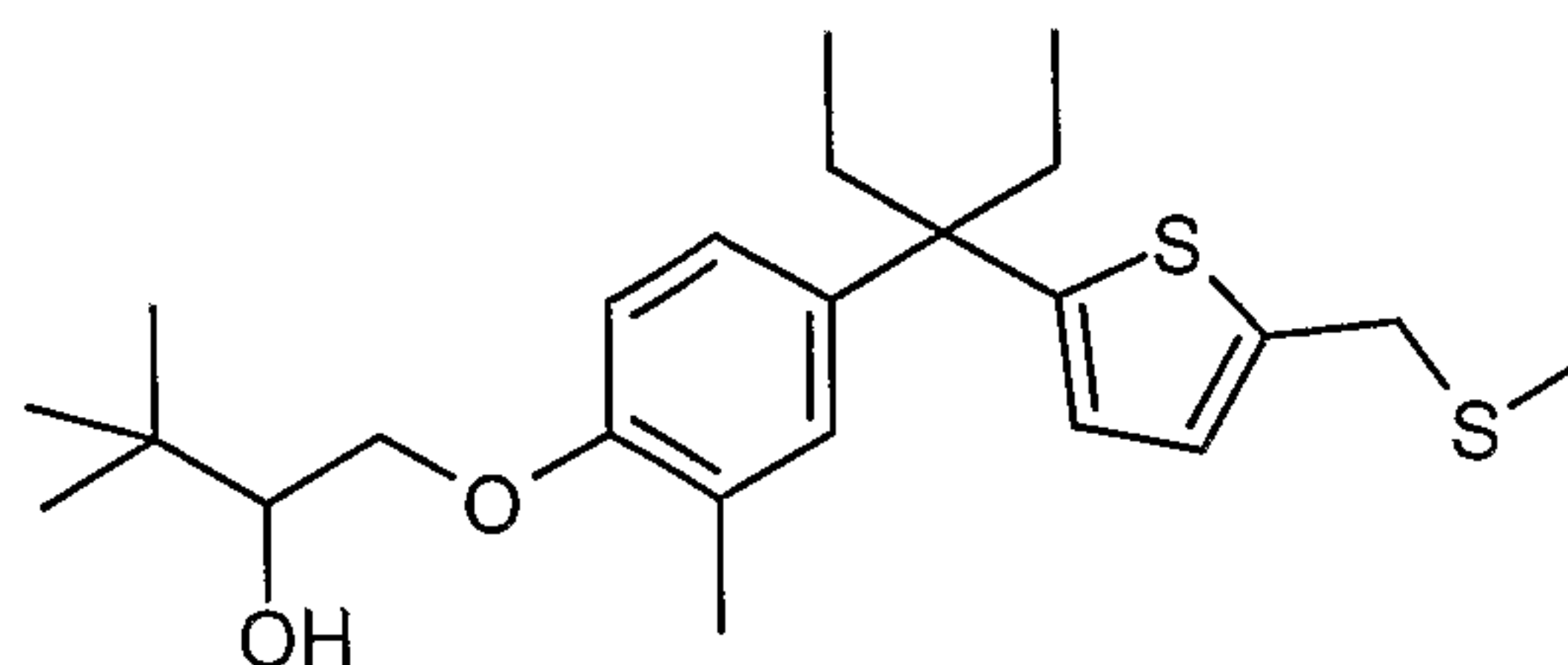
-83-



X184)

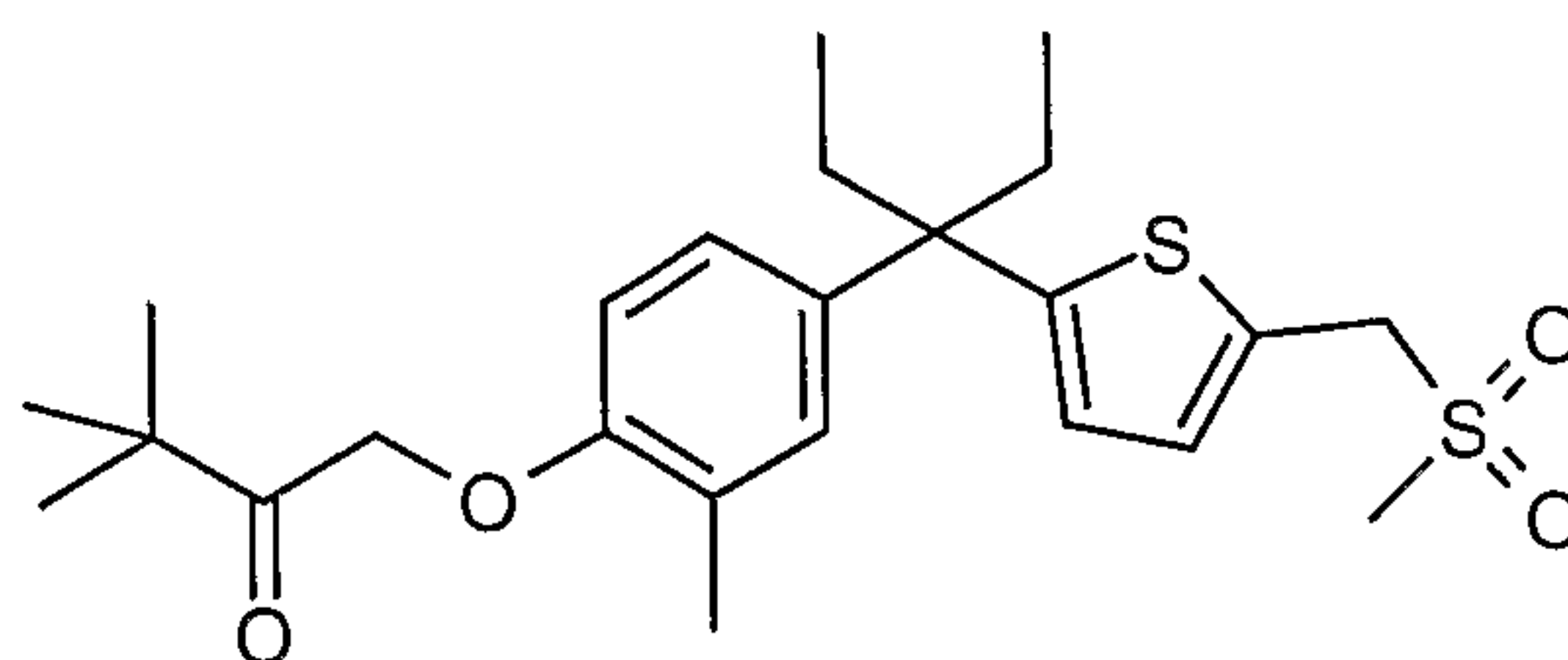


X185)

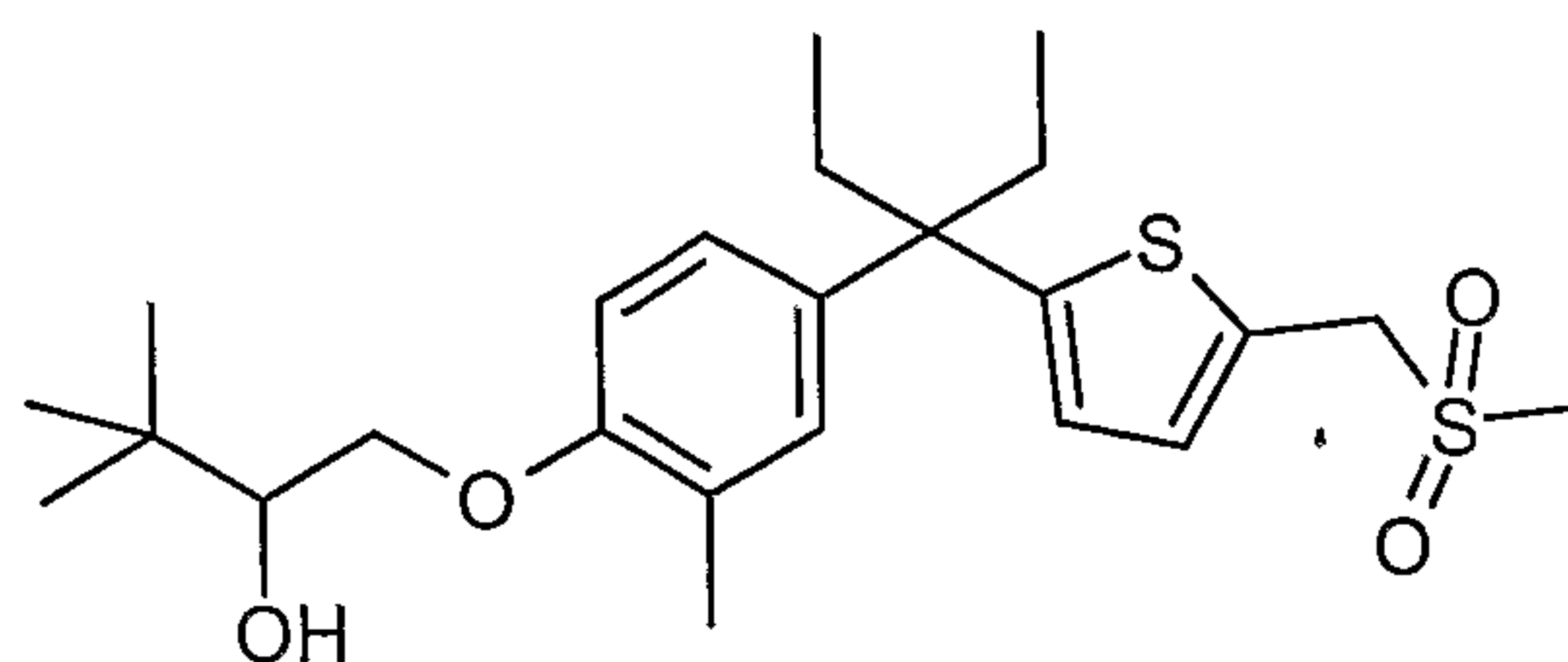


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X187)



X188)



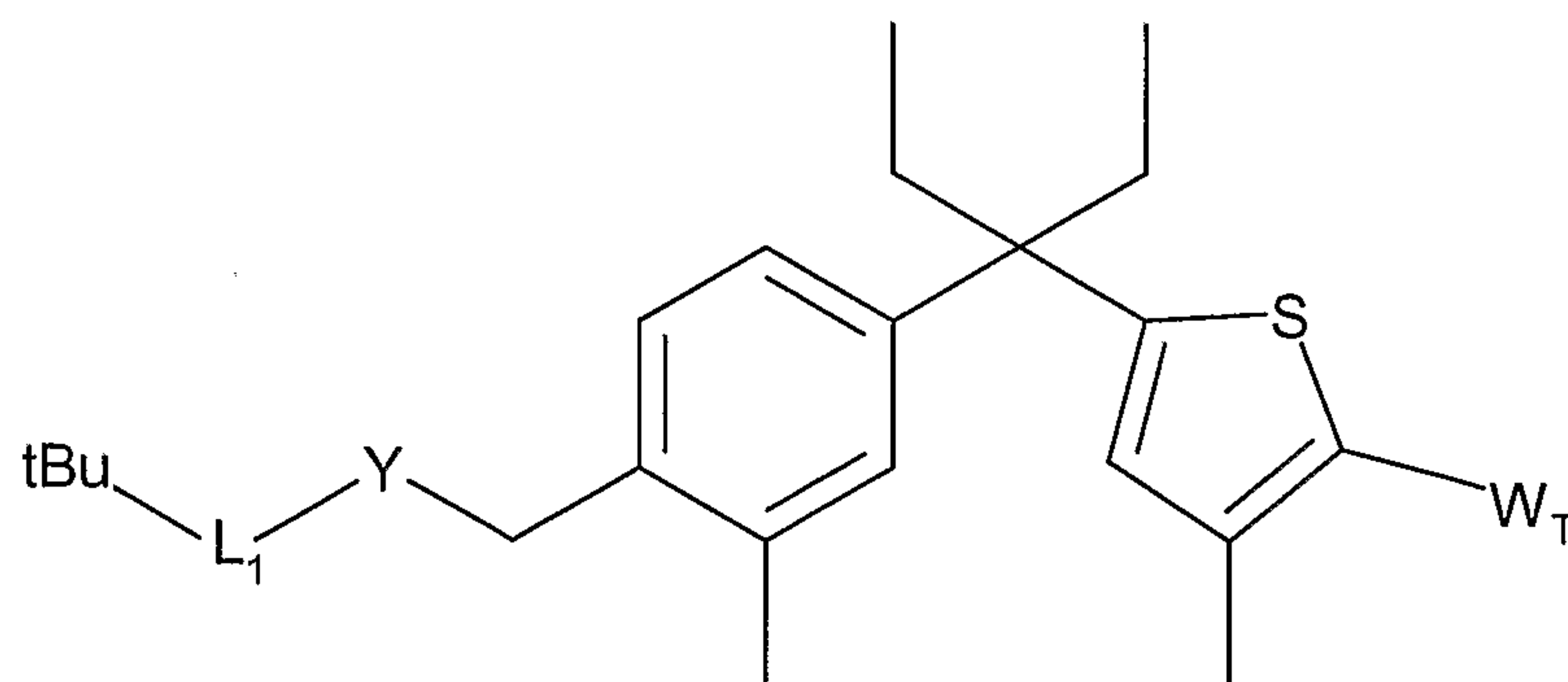
10

Other specific compounds that are preferred embodiments of this invention and are preferred for practicing the method of treatment of the invention are set out in the following four Tables. All numbers in the Tables cells reciting chemical species are subscripts, for example, in row, Code 11, Column, W_T, the symbol, "CO₂H" is to be understood as the conventional chemical nomenclature, -- CO₂H --. Each row of Tables

1, 2, 3, and 4 is a single compound having an identifying "Code" (e.g., "206", "318A") defining the specific substituents in the structural formula displayed above the Tables, as follows:

5

Table 1



Code	L ₁	Y	W _T
1	C(O)	CH ₂	-CO ₂ Me
2	CHOH	CH ₂	-CO ₂ Me
3	C(Me)OH	CH ₂	-CO ₂ Me
4	C(O)	CH(Me)	-CO ₂ Me
5	CHOH	CH(Me)	-CO ₂ Me
6	C(Me)OH	CH(Me)	-CO ₂ Me
7	C(O)	CH ₂	-CO ₂ H
8	CHOH	CH ₂	-CO ₂ H
9	C(Me)OH	CH ₂	-CO ₂ H
10	C(O)	CH(Me)	-CO ₂ H
11	CHOH	CH(Me)	-CO ₂ H
12	C(Me)OH	CH(Me)	-CO ₂ H
13	C(O)	CH ₂	-C(O)NH ₂
14	CHOH	CH ₂	-C(O)NH ₂
15	C(Me)OH	CH ₂	-C(O)NH ₂
16	C(O)	CH(Me)	-C(O)NH ₂
17	CHOH	CH(Me)	-C(O)NH ₂

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18	C(Me)OH	CH(Me)	-C(O)NH ₂
19	C(O)	CH ₂	-C(O)NMe ₂
20	CHOH	CH ₂	-C(O)NMe ₂
21	C(Me)OH	CH ₂	-C(O)NMe ₂
22	C(O)	CH(Me)	-C(O)NMe ₂
23	CHOH	CH(Me)	-C(O)NMe ₂
24	C(Me)OH	CH(Me)	-C(O)NMe ₂
25	C(O)	CH ₂	5-tetrazolyl
26	CHOH	CH ₂	5-tetrazolyl
27	C(Me)OH	CH ₂	5-tetrazolyl
28	C(O)	CH(Me)	5-tetrazolyl
29	CHOH	CH(Me)	5-tetrazolyl
30	C(Me)OH	CH(Me)	5-tetrazolyl
31	C(O)	CH ₂	-C(O)-NH-5-tetrazolyl
32	CHOH	CH ₂	-C(O)-NH-5-tetrazolyl
33	C(Me)OH	CH ₂	-C(O)-NH-5-tetrazolyl
34	C(O)	CH(Me)	-C(O)-NH-5-tetrazolyl
35	CHOH	CH(Me)	-C(O)-NH-5-tetrazolyl
36	C(Me)OH	CH(Me)	-C(O)-NH-5-tetrazolyl
37	C(O)	CH ₂	-C(O)NHCH ₂ SO ₂ Me
38	CHOH	CH ₂	-C(O)NHCH ₂ SO ₂ Me
39	C(Me)OH	CH ₂	-C(O)NHCH ₂ SO ₂ Me
40	C(O)	CH(Me)	-C(O)NHCH ₂ SO ₂ Me
41	CHOH	CH(Me)	-C(O)NHCH ₂ SO ₂ Me
42	C(Me)OH	CH(Me)	-C(O)NHCH ₂ SO ₂ Me
43	C(O)	CH ₂	-C(O)NHCH ₂ CH ₂ SO ₂ Me
44	CHOH	CH ₂	-C(O)NHCH ₂ CH ₂ SO ₂ Me
45	C(Me)OH	CH ₂	-C(O)NHCH ₂ CH ₂ SO ₂ Me
46	C(O)	CH(Me)	-C(O)NHCH ₂ CH ₂ SO ₂ Me
47	CHOH	CH(Me)	-C(O)NHCH ₂ CH ₂ SO ₂ Me
48	C(Me)OH	CH(Me)	-C(O)NHCH ₂ CH ₂ SO ₂ Me

49	C(O)	CH ₂	-C(O)NHSO ₂ Me
50	CHOH	CH ₂	-C(O)NHSO ₂ Me
51	C(Me)OH	CH ₂	-C(O)NHSO ₂ Me
52	C(O)	CH(Me)	-C(O)NHSO ₂ Me
53	CHOH	CH(Me)	-C(O)NHSO ₂ Me
54	C(Me)OH	CH(Me)	-C(O)NHSO ₂ Me
55	C(O)	CH ₂	-CH ₂ -C(O)NHSO ₂ Et
56	CHOH	CH ₂	-CH ₂ -C(O)NHSO ₂ Et
57	C(Me)OH	CH ₂	-CH ₂ -C(O)NHSO ₂ Et
58	C(O)	CH(Me)	-CH ₂ -C(O)NHSO ₂ Et
59	CHOH	CH(Me)	-CH ₂ -C(O)NHSO ₂ Et
60	C(Me)OH	CH(Me)	-CH ₂ -C(O)NHSO ₂ Et
61	C(O)	CH ₂	-CH ₂ -C(O)NHSO ₂ iPr
62	CHOH	CH ₂	-CH ₂ -C(O)NHSO ₂ iPr
63	C(Me)OH	CH ₂	-CH ₂ -C(O)NHSO ₂ iPr
64	C(O)	CH(Me)	-CH ₂ -C(O)NHSO ₂ iPr
65	CHOH	CH(Me)	-CH ₂ -C(O)NHSO ₂ iPr
66	C(Me)OH	CH(Me)	-CH ₂ -C(O)NHSO ₂ iPr
67	C(O)	CH ₂	-CH ₂ -C(O)NHSO ₂ tBu
68	CHOH	CH ₂	-CH ₂ -C(O)NHSO ₂ tBu
69	C(Me)OH	CH ₂	-CH ₂ -C(O)NHSO ₂ tBu
70	C(O)	CH(Me)	-CH ₂ -C(O)NHSO ₂ tBu
71	CHOH	CH(Me)	-CH ₂ -C(O)NHSO ₂ tBu
72	C(Me)OH	CH(Me)	-CH ₂ -C(O)NHSO ₂ tBu
73	C(O)	CH ₂	-CH ₂ NHSO ₂ Me
74	CHOH	CH ₂	-CH ₂ NHSO ₂ Me
75	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ Me
76	C(O)	CH(Me)	-CH ₂ NHSO ₂ Me
77	CHOH	CH(Me)	-CH ₂ NHSO ₂ Me
78	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ Me
79	C(O)	CH ₂	-CH ₂ NHSO ₂ Et

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80	CHOH	CH ₂	-CH ₂ NHSO ₂ Et
81	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ Et
82	C(O)	CH(Me)	-CH ₂ NHSO ₂ Et
83	CHOH	CH(Me)	-CH ₂ NHSO ₂ Et
84	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ Et
85	C(O)	CH ₂	-CH ₂ NHSO ₂ iPr
86	CHOH	CH ₂	-CH ₂ NHSO ₂ iPr
87	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ iPr
88	C(O)	CH(Me)	-CH ₂ NHSO ₂ iPr
89	CHOH	CH(Me)	-CH ₂ NHSO ₂ iPr
90	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ iPr
91	C(O)	CH ₂	-CH ₂ NHSO ₂ tBu
92	CHOH	CH ₂	-CH ₂ NHSO ₂ tBu
93	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ tBu
94	C(O)	CH(Me)	-CH ₂ NHSO ₂ tBu
95	CHOH	CH(Me)	-CH ₂ NHSO ₂ tBu
96	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ tBu
97	C(O)	CH ₂	-CH ₂ -N-pyrrolidin-2-one
98	CHOH	CH ₂	-CH ₂ -N-pyrrolidin-2-one
99	C(Me)OH	CH ₂	-CH ₂ -N-pyrrolidin-2-one
100	C(O)	CH(Me)	-CH ₂ -N-pyrrolidin-2-one
101	CHOH	CH(Me)	-CH ₂ -N-pyrrolidin-2-one
102	C(Me)OH	CH(Me)	-CH ₂ -N-pyrrolidin-2-one
103	C(O)	CH ₂	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
104	CHOH	CH ₂	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
105	C(Me)OH	CH ₂	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
106	C(O)	CH(Me)	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
107	CHOH	CH(Me)	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
108	C(Me)OH	CH(Me)	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
109	C(O)	CH ₂	-CH ₂ CO ₂ Me
110	CHOH	CH ₂	-CH ₂ CO ₂ Me

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111	C(Me)OH	CH ₂	-CH ₂ CO ₂ Me
112	C(O)	CH(Me)	-CH ₂ CO ₂ Me
113	CHOH	CH(Me)	-CH ₂ CO ₂ Me
114	C(Me)OH	CH(Me)	-CH ₂ CO ₂ Me
115	C(O)	CH ₂	-CH ₂ CO ₂ H
116	CHOH	CH ₂	-CH ₂ CO ₂ H
117	C(Me)OH	CH ₂	-CH ₂ CO ₂ H
118	C(O)	CH(Me)	-CH ₂ CO ₂ H
119	CHOH	CH(Me)	-CH ₂ CO ₂ H
120	C(Me)OH	CH(Me)	-CH ₂ CO ₂ H
121	C(O)	CH ₂	-CH ₂ C(O)NH ₂
122	CHOH	CH ₂	-CH ₂ C(O)NH ₂
123	C(Me)OH	CH ₂	-CH ₂ C(O)NH ₂
124	C(O)	CH(Me)	-CH ₂ C(O)NH ₂
125	CHOH	CH(Me)	-CH ₂ C(O)NH ₂
126	C(Me)OH	CH(Me)	-CH ₂ C(O)NH ₂
127	C(O)	CH ₂	-CH ₂ C(O)NMe ₂
128	CHOH	CH ₂	-CH ₂ C(O)NMe ₂
129	C(Me)OH	CH ₂	-CH ₂ C(O)NMe ₂
130	C(O)	CH(Me)	-CH ₂ C(O)NMe ₂
131	CHOH	CH(Me)	-CH ₂ C(O)NMe ₂
132	C(Me)OH	CH(Me)	-CH ₂ C(O)NMe ₂
133	C(O)	CH ₂	-CH ₂ C(O)-N-pyrrolidine
134	CHOH	CH ₂	-CH ₂ C(O)-N-pyrrolidine
135	C(Me)OH	CH ₂	-CH ₂ C(O)-N-pyrrolidine
136	C(O)	CH(Me)	-CH ₂ C(O)-N-pyrrolidine
137	CHOH	CH(Me)	-CH ₂ C(O)-N-pyrrolidine
138	C(Me)OH	CH(Me)	-CH ₂ C(O)-N-pyrrolidine
139	C(O)	CH ₂	-CH ₂ -5-tetrazolyl
140	CHOH	CH ₂	-CH ₂ -5-tetrazolyl
141	C(Me)OH	CH ₂	-CH ₂ -5-tetrazolyl

142	C(O)	CH(Me)	-CH ₂ -5-tetrazolyl
143	CHOH	CH(Me)	-CH ₂ -5-tetrazolyl
144	C(Me)OH	CH(Me)	-CH ₂ -5-tetrazolyl
145	C(O)	CH ₂	-C(O)C(O)OH
146	CHOH	CH ₂	-C(O)C(O)OH
147	C(Me)OH	CH ₂	-C(O)C(O)OH
148	C(O)	CH(Me)	-C(O)C(O)OH
149	CHOH	CH(Me)	-C(O)C(O)OH
150	C(Me)OH	CH(Me)	-C(O)C(O)OH
151	C(O)	CH ₂	-CH(OH)C(O)OH
152	CHOH	CH ₂	-CH(OH)C(O)OH
153	C(Me)OH	CH ₂	-CH(OH)C(O)OH
154	C(O)	CH(Me)	-CH(OH)C(O)OH
155	CHOH	CH(Me)	-CH(OH)C(O)OH
156	C(Me)OH	CH(Me)	-CH(OH)C(O)OH
157	C(O)	CH ₂	-C(O)C(O)NH ₂
158	CHOH	CH ₂	-C(O)C(O)NH ₂
159	C(Me)OH	CH ₂	-C(O)C(O)NH ₂
160	C(O)	CH(Me)	-C(O)C(O)NH ₂
161	CHOH	CH(Me)	-C(O)C(O)NH ₂
162	C(Me)OH	CH(Me)	-C(O)C(O)NH ₂
163	C(O)	CH ₂	-CH(OH)C(O)NH ₂
164	CHOH	CH ₂	-CH(OH)C(O)NH ₂
165	C(Me)OH	CH ₂	-CH(OH)C(O)NH ₂
166	C(O)	CH(Me)	-CH(OH)C(O)NH ₂
167	CHOH	CH(Me)	-CH(OH)C(O)NH ₂
168	C(Me)OH	CH(Me)	-CH(OH)C(O)NH ₂
169	C(O)	CH ₂	-C(O)C(O)NMe ₂
170	CHOH	CH ₂	-C(O)C(O)NMe ₂
171	C(Me)OH	CH ₂	-C(O)C(O)NMe ₂
172	C(O)	CH(Me)	-C(O)C(O)NMe ₂

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173	CHOH	CH(Me)	-C(O)C(O)NMe ₂
174	C(Me)OH	CH(Me)	-C(O)C(O)NMe ₂
175	C(O)	CH ₂	-CH(OH)C(O)NMe ₂
176	CHOH	CH ₂	-CH(OH)C(O)NMe ₂
177	C(Me)OH	CH ₂	-CH(OH)C(O)NMe ₂
178	C(O)	CH(Me)	-CH(OH)C(O)NMe ₂
179	CHOH	CH(Me)	-CH(OH)C(O)NMe ₂
180	C(Me)OH	CH(Me)	-CH(OH)C(O)NMe ₂
181	C(O)	CH ₂	-CH ₂ CH ₂ CO ₂ H
182	CHOH	CH ₂	-CH ₂ CH ₂ CO ₂ H
183	C(Me)OH	CH ₂	-CH ₂ CH ₂ CO ₂ H
184	C(O)	CH(Me)	-CH ₂ CH ₂ CO ₂ H
185	CHOH	CH(Me)	-CH ₂ CH ₂ CO ₂ H
186	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CO ₂ H
187	C(O)	CH ₂	-CH ₂ CH ₂ C(O)NH ₂
188	CHOH	CH ₂	-CH ₂ CH ₂ C(O)NH ₂
189	C(Me)OH	CH ₂	-CH ₂ CH ₂ C(O)NH ₂
190	C(O)	CH(Me)	-CH ₂ CH ₂ C(O)NH ₂
191	CHOH	CH(Me)	-CH ₂ CH ₂ C(O)NH ₂
192	C(Me)OH	CH(Me)	-CH ₂ CH ₂ C(O)NH ₂
193	C(O)	CH ₂	-CH ₂ CH ₂ C(O)NMe ₂
194	CHOH	CH ₂	-CH ₂ CH ₂ C(O)NMe ₂
195	C(Me)OH	CH ₂	-CH ₂ CH ₂ C(O)NMe ₂
196	C(O)	CH(Me)	-CH ₂ CH ₂ C(O)NMe ₂
197	CHOH	CH(Me)	-CH ₂ CH ₂ C(O)NMe ₂
198	C(Me)OH	CH(Me)	-CH ₂ CH ₂ C(O)NMe ₂
199	C(O)	CH ₂	-CH ₂ CH ₂ -5-tetrazolyl
200	CHOH	CH ₂	-CH ₂ CH ₂ -5-tetrazolyl
201	C(Me)OH	CH ₂	-CH ₂ CH ₂ -5-tetrazolyl
202	C(O)	CH(Me)	-CH ₂ CH ₂ -5-tetrazolyl
203	CHOH	CH(Me)	-CH ₂ CH ₂ -5-tetrazolyl

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204	C(Me)OH	CH(Me)	-CH ₂ CH ₂ -5-tetrazolyl
205	C(O)	CH ₂	-CH ₂ S(O) ₂ Me
206	CHOH	CH ₂	-CH ₂ S(O) ₂ Me
207	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ Me
208	C(O)	CH(Me)	-CH ₂ S(O) ₂ Me
209	CHOH	CH(Me)	-CH ₂ S(O) ₂ Me
210	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ Me
211	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ Me
212	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Me
213	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Me
214	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Me
215	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Me
216	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Me
217	C(O)	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
218	CHOH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
219	C(Me)OH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
220	C(O)	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
221	CHOH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
222	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
223	C(O)	CH ₂	-CH ₂ S(O) ₂ Et
224	CHOH	CH ₂	-CH ₂ S(O) ₂ Et
225	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ Et
226	C(O)	CH(Me)	-CH ₂ S(O) ₂ Et
227	CHOH	CH(Me)	-CH ₂ S(O) ₂ Et
228	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ Et
229	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ Et
230	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Et
231	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Et
232	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Et
233	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Et
234	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Et

235	C(O)	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
236	CHOH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
237	C(Me)OH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
238	C(O)	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
239	CHOH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
240	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
241	C(O)	CH ₂	-CH ₂ S(O) ₂ iPr
242	CHOH	CH ₂	-CH ₂ S(O) ₂ iPr
243	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ iPr
244	C(O)	CH(Me)	-CH ₂ S(O) ₂ iPr
245	CHOH	CH(Me)	-CH ₂ S(O) ₂ iPr
246	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ iPr
247	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ iPr
248	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ iPr
249	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ iPr
250	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ iPr
251	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ iPr
252	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ iPr
253	C(O)	CH ₂	-CH ₂ S(O) ₂ tBu
254	CHOH	CH ₂	-CH ₂ S(O) ₂ tBu
255	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ tBu
256	C(O)	CH(Me)	-CH ₂ S(O) ₂ tBu
257	CHOH	CH(Me)	-CH ₂ S(O) ₂ tBu
258	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ tBu
259	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ tBu
260	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ tBu
261	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ tBu
262	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ tBu
263	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ tBu
264	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ tBu
265	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ NH ₂

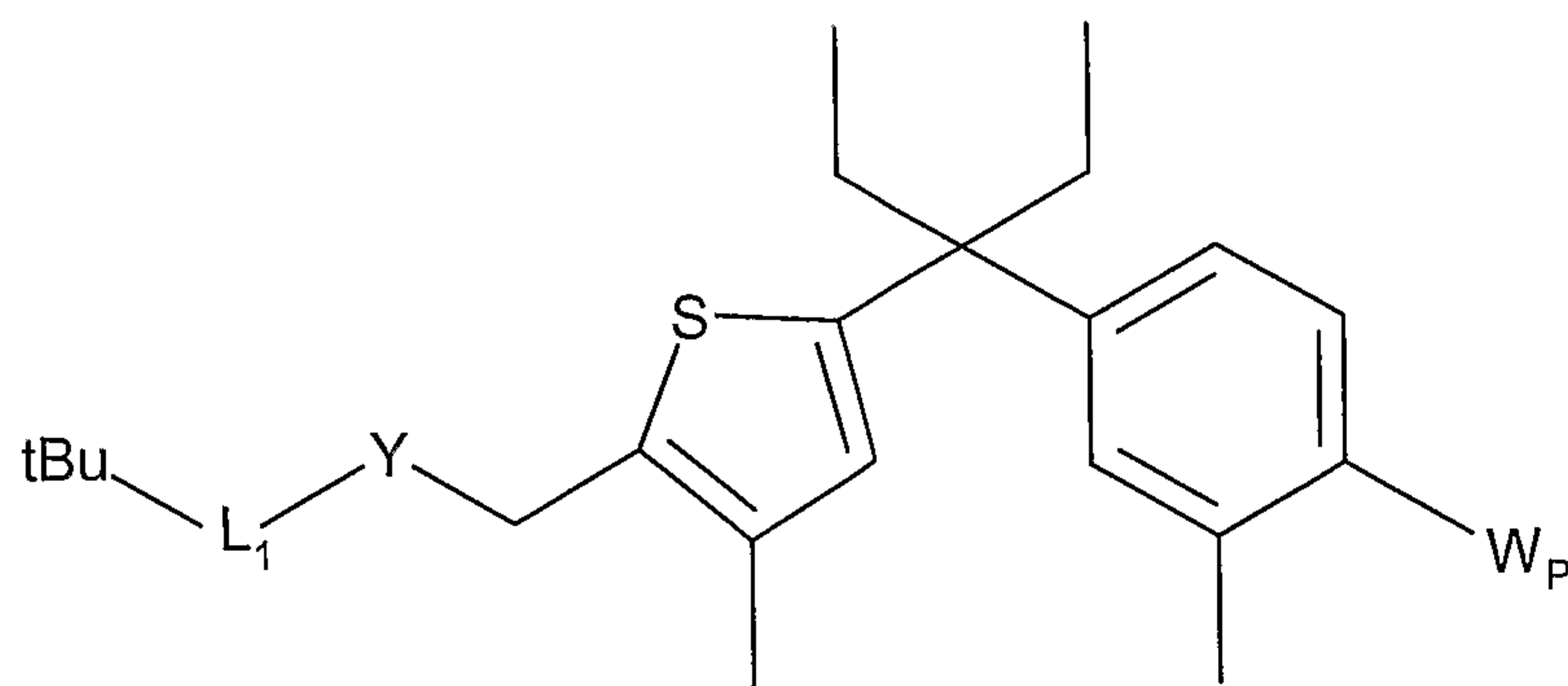
266	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NH ₂
267	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NH ₂
268	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NH ₂
269	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NH ₂
270	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NH ₂
271	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ NMe ₂
272	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NMe ₂
273	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NMe ₂
274	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NMe ₂
275	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NMe ₂
276	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NMe ₂
277	C(O)	CH ₂	-C(O)CH ₂ S(O) ₂ Me
278	CHOH	CH ₂	-C(O)CH ₂ S(O) ₂ Me
279	C(Me)OH	CH ₂	-C(O)CH ₂ S(O) ₂ Me
280	C(O)	CH(Me)	-C(O)CH ₂ S(O) ₂ Me
281	CHOH	CH(Me)	-C(O)CH ₂ S(O) ₂ Me
282	C(Me)OH	CH(Me)	-C(O)CH ₂ S(O) ₂ Me
283	C(O)	CH ₂	-C(O)CH ₂ CH ₂ S(O) ₂ Me
284	CHOH	CH ₂	-C(O)CH ₂ CH ₂ S(O) ₂ Me
285	C(Me)OH	CH ₂	-C(O)CH ₂ CH ₂ S(O) ₂ Me
286	C(O)	CH(Me)	-C(O)CH ₂ CH ₂ S(O) ₂ Me
287	CHOH	CH(Me)	-C(O)CH ₂ CH ₂ S(O) ₂ Me
288	C(Me)OH	CH(Me)	-C(O)CH ₂ CH ₂ S(O) ₂ Me
289	C(O)	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
290	CHOH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
291	C(Me)OH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
292	C(O)	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
293	CHOH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
294	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
295	C(O)	CH ₂	-S(O) ₂ Me
296	CHOH	CH ₂	-S(O) ₂ Me

297	C(Me)OH	CH ₂	-S(O) ₂ Me
298	C(O)	CH(Me)	-S(O) ₂ Me
299	CHOH	CH(Me)	-S(O) ₂ Me
300	C(Me)OH	CH(Me)	-S(O) ₂ Me
301	C(O)	CH ₂	-S(O) ₂ Et
302	CHOH	CH ₂	-S(O) ₂ Et
303	C(Me)OH	CH ₂	-S(O) ₂ Et
304	C(O)	CH(Me)	-S(O) ₂ Et
305	CHOH	CH(Me)	-S(O) ₂ Et
306	C(Me)OH	CH(Me)	-S(O) ₂ Et
307	C(O)	CH ₂	-S(O) ₂ iPr
308	CHOH	CH ₂	-S(O) ₂ iPr
309	C(Me)OH	CH ₂	-S(O) ₂ iPr
310	C(O)	CH(Me)	-S(O) ₂ iPr
311	CHOH	CH(Me)	-S(O) ₂ iPr
312	C(Me)OH	CH(Me)	-S(O) ₂ iPr
313	C(O)	CH ₂	-S(O) ₂ tBu
314	CHOH	CH ₂	-S(O) ₂ tBu
315	C(Me)OH	CH ₂	-S(O) ₂ tBu
316	C(O)	CH(Me)	-S(O) ₂ tBu
317	CHOH	CH(Me)	-S(O) ₂ tBu
318	C(Me)OH	CH(Me)	-S(O) ₂ tBu
319	C(O)	CH ₂	-S(O) ₂ NH ₂
320	CHOH	CH ₂	-S(O) ₂ NH ₂
321	C(Me)OH	CH ₂	-S(O) ₂ NH ₂
322	C(O)	CH(Me)	-S(O) ₂ NH ₂
323	CHOH	CH(Me)	-S(O) ₂ NH ₂
324	C(Me)OH	CH(Me)	-S(O) ₂ NH ₂
325	C(O)	CH ₂	-S(O) ₂ NMe ₂
326	CHOH	CH ₂	-S(O) ₂ NMe ₂
327	C(Me)OH	CH ₂	-S(O) ₂ NMe ₂

328	C(O)	CH(Me)	-S(O) ₂ NMe ₂
329	CHOH	CH(Me)	-S(O) ₂ NMe ₂
330	C(Me)OH	CH(Me)	-S(O) ₂ NMe ₂
331	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Me
332	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Me
333	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Me
334	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Me
335	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Me
336	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Me
337	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Et
338	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Et
339	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Et
340	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Et
341	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Et
342	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Et
343	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ iPr
344	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ iPr
345	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ iPr
346	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ iPr
347	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ iPr
348	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ iPr
349	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ tBu
350	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ tBu
351	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ tBu
352	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ tBu
353	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ tBu
354	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ tBu
355	C(O)	CH ₂	-C(O)NHCH ₂ CO ₂ H
356	CHOH	CH ₂	-C(O)NHCH ₂ CO ₂ H
357	C(Me)OH	CH ₂	-C(O)NHCH ₂ CO ₂ H
358	C(O)	CH(Me)	-C(O)NHCH ₂ CO ₂ H

359	CHOH	CH(Me)	-C(O)NHCH ₂ CO ₂ H
360	C(Me)OH	CH(Me)	-C(O)NHCH ₂ CO ₂ H
361	C(O)	CH ₂	-SO ₂ NHCH ₂ CO ₂ H
362	CHOH	CH ₂	-SO ₂ NHCH ₂ CO ₂ H
363	C(Me)OH	CH ₂	-SO ₂ NHCH ₂ CO ₂ H
364	C(O)	CH(Me)	-SO ₂ NHCH ₂ CO ₂ H
365	CHOH	CH(Me)	-SO ₂ NHCH ₂ CO ₂ H
366	C(Me)OH	CH(Me)	-SO ₂ NHCH ₂ CO ₂ H
367	C(O)	CH ₂	-CH ₂ -S-Me
368	CHOH	CH ₂	-CH ₂ -S-Me
369	C(Me)OH	CH ₂	-CH ₂ -S-Me
370	C(O)	CH(Me)	-CH ₂ -S-Me
371	CHOH	CH(Me)	-CH ₂ -S-Me
372	C(Me)OH	CH(Me)	-CH ₂ -S-Me

Table 2



Code	L ₁	Y	W _p
1A	C(O)	CH ₂	-CO ₂ Me
2A	CHOH	CH ₂	-CO ₂ Me
3A	C(Me)OH	CH ₂	-CO ₂ Me
4A	C(O)	CH(Me)	-CO ₂ Me
5A	CHOH	CH(Me)	-CO ₂ Me
6A	C(Me)OH	CH(Me)	-CO ₂ Me
7A	C(O)	CH ₂	-CO ₂ H

8A	CHOH	CH ₂	-CO ₂ H
9A	C(Me)OH	CH ₂	-CO ₂ H
10A	C(O)	CH(Me)	-CO ₂ H
11A	CHOH	CH(Me)	-CO ₂ H
12A	C(Me)OH	CH(Me)	-CO ₂ H
13A	C(O)	CH ₂	-C(O)NH ₂
14A	CHOH	CH ₂	-C(O)NH ₂
15A	C(Me)OH	CH ₂	-C(O)NH ₂
16A	C(O)	CH(Me)	-C(O)NH ₂
17A	CHOH	CH(Me)	-C(O)NH ₂
18A	C(Me)OH	CH(Me)	-C(O)NH ₂
19A	C(O)	CH ₂	-C(O)NMe ₂
20A	CHOH	CH ₂	-C(O)NMe ₂
21A	C(Me)OH	CH ₂	-C(O)NMe ₂
22A	C(O)	CH(Me)	-C(O)NMe ₂
23A	CHOH	CH(Me)	-C(O)NMe ₂
24A	C(Me)OH	CH(Me)	-C(O)NMe ₂
25A	C(O)	CH ₂	5-tetrazolyl
26A	CHOH	CH ₂	5-tetrazolyl
27A	C(Me)OH	CH ₂	5-tetrazolyl
28A	C(O)	CH(Me)	5-tetrazolyl
29A	CHOH	CH(Me)	5-tetrazolyl
30A	C(Me)OH	CH(Me)	5-tetrazolyl
31A	C(O)	CH ₂	-C(O)-NH-5-tetrazolyl
32A	CHOH	CH ₂	-C(O)-NH-5-tetrazolyl
33A	C(Me)OH	CH ₂	-C(O)-NH-5-tetrazolyl
34A	C(O)	CH(Me)	-C(O)-NH-5-tetrazolyl
35A	CHOH	CH(Me)	-C(O)-NH-5-tetrazolyl
36A	C(Me)OH	CH(Me)	-C(O)-NH-5-tetrazolyl
37A	C(O)	CH ₂	-C(O)NHCH ₂ SO ₂ Me
38A	CHOH	CH ₂	-C(O)NHCH ₂ SO ₂ Me

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39A	C(Me)OH	CH ₂	-C(O)NHCH ₂ SO ₂ Me
40A	C(O)	CH(Me)	-C(O)NHCH ₂ SO ₂ Me
41A	CHOH	CH(Me)	-C(O)NHCH ₂ SO ₂ Me
42A	C(Me)OH	CH(Me)	-C(O)NHCH ₂ SO ₂ Me
43A	C(O)	CH ₂	-C(O)NHCH ₂ CH ₂ SO ₂ Me
44A	CHOH	CH ₂	-C(O)NHCH ₂ CH ₂ SO ₂ Me
45A	C(Me)OH	CH ₂	-C(O)NHCH ₂ CH ₂ SO ₂ Me
46A	C(O)	CH(Me)	-C(O)NHCH ₂ CH ₂ SO ₂ Me
47A	CHOH	CH(Me)	-C(O)NHCH ₂ CH ₂ SO ₂ Me
48A	C(Me)OH	CH(Me)	-C(O)NHCH ₂ CH ₂ SO ₂ Me
49A	C(O)	CH ₂	-C(O)NHSO ₂ Me
50A	CHOH	CH ₂	-C(O)NHSO ₂ Me
51A	C(Me)OH	CH ₂	-C(O)NHSO ₂ Me
52A	C(O)	CH(Me)	-C(O)NHSO ₂ Me
53A	CHOH	CH(Me)	-C(O)NHSO ₂ Me
54A	C(Me)OH	CH(Me)	-C(O)NHSO ₂ Me
55A	C(O)	CH ₂	-CH ₂ -C(O)NHSO ₂ Et
56A	CHOH	CH ₂	-CH ₂ -C(O)NHSO ₂ Et
57A	C(Me)OH	CH ₂	-CH ₂ -C(O)NHSO ₂ Et
58A	C(O)	CH(Me)	-CH ₂ -C(O)NHSO ₂ Et
59A	CHOH	CH(Me)	-CH ₂ -C(O)NHSO ₂ Et
60A	C(Me)OH	CH(Me)	-CH ₂ -C(O)NHSO ₂ Et
61A	C(O)	CH ₂	-CH ₂ -C(O)NHSO ₂ iPr
62A	CHOH	CH ₂	-CH ₂ -C(O)NHSO ₂ iPr
63A	C(Me)OH	CH ₂	-CH ₂ -C(O)NHSO ₂ iPr
64A	C(O)	CH(Me)	-CH ₂ -C(O)NHSO ₂ iPr
65A	CHOH	CH(Me)	-CH ₂ -C(O)NHSO ₂ iPr
66A	C(Me)OH	CH(Me)	-CH ₂ -C(O)NHSO ₂ iPr
67A	C(O)	CH ₂	-CH ₂ -C(O)NHSO ₂ tBu
68A	CHOH	CH ₂	-CH ₂ -C(O)NHSO ₂ tBu
69A	C(Me)OH	CH ₂	-CH ₂ -C(O)NHSO ₂ tBu

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70A	C(O)	CH(Me)	-CH ₂ -C(O)NHSO ₂ tBu
71A	CHOH	CH(Me)	-CH ₂ -C(O)NHSO ₂ tBu
72A	C(Me)OH	CH(Me)	-CH ₂ -C(O)NHSO ₂ tBu
73A	C(O)	CH ₂	-CH ₂ NHSO ₂ Me
74A	CHOH	CH ₂	-CH ₂ NHSO ₂ Me
75A	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ Me
76A	C(O)	CH(Me)	-CH ₂ NHSO ₂ Me
77A	CHOH	CH(Me)	-CH ₂ NHSO ₂ Me
78A	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ Me
79A	C(O)	CH ₂	-CH ₂ NHSO ₂ Et
80A	CHOH	CH ₂	-CH ₂ NHSO ₂ Et
81A	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ Et
82A	C(O)	CH(Me)	-CH ₂ NHSO ₂ Et
83A	CHOH	CH(Me)	-CH ₂ NHSO ₂ Et
84A	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ Et
85A	C(O)	CH ₂	-CH ₂ NHSO ₂ iPr
86A	CHOH	CH ₂	-CH ₂ NHSO ₂ iPr
87A	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ iPr
88A	C(O)	CH(Me)	-CH ₂ NHSO ₂ iPr
89A	CHOH	CH(Me)	-CH ₂ NHSO ₂ iPr
90A	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ iPr
91A	C(O)	CH ₂	-CH ₂ NHSO ₂ tBu
92A	CHOH	CH ₂	-CH ₂ NHSO ₂ tBu
93A	C(Me)OH	CH ₂	-CH ₂ NHSO ₂ tBu
94A	C(O)	CH(Me)	-CH ₂ NHSO ₂ tBu
95A	CHOH	CH(Me)	-CH ₂ NHSO ₂ tBu
96A	C(Me)OH	CH(Me)	-CH ₂ NHSO ₂ tBu
97A	C(O)	CH ₂	-CH ₂ -N-pyrrolidin-2-one
98A	CHOH	CH ₂	-CH ₂ -N-pyrrolidin-2-one
99A	C(Me)OH	CH ₂	-CH ₂ -N-pyrrolidin-2-one
100A	C(O)	CH(Me)	-CH ₂ -N-pyrrolidin-2-one

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101A	CHOH	CH(Me)	-CH ₂ -N-pyrrolidin-2-one
102A	C(Me)OH	CH(Me)	-CH ₂ -N-pyrrolidin-2-one
103A	C(O)	CH ₂	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
104A	CHOH	CH ₂	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
105A	C(Me)OH	CH ₂	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
106A	C(O)	CH(Me)	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
107A	CHOH	CH(Me)	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
108A	C(Me)OH	CH(Me)	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
109A	C(O)	CH ₂	-CH ₂ CO ₂ Me
110A	CHOH	CH ₂	-CH ₂ CO ₂ Me
111A	C(Me)OH	CH ₂	-CH ₂ CO ₂ Me
112A	C(O)	CH(Me)	-CH ₂ CO ₂ Me
113A	CHOH	CH(Me)	-CH ₂ CO ₂ Me
114A	C(Me)OH	CH(Me)	-CH ₂ CO ₂ Me
115A	C(O)	CH ₂	-CH ₂ CO ₂ H
116A	CHOH	CH ₂	-CH ₂ CO ₂ H
117A	C(Me)OH	CH ₂	-CH ₂ CO ₂ H
118A	C(O)	CH(Me)	-CH ₂ CO ₂ H
119A	CHOH	CH(Me)	-CH ₂ CO ₂ H
120A	C(Me)OH	CH(Me)	-CH ₂ CO ₂ H
121A	C(O)	CH ₂	-CH ₂ C(O)NH ₂
122A	CHOH	CH ₂	-CH ₂ C(O)NH ₂
123A	C(Me)OH	CH ₂	-CH ₂ C(O)NH ₂
124A	C(O)	CH(Me)	-CH ₂ C(O)NH ₂
125A	CHOH	CH(Me)	-CH ₂ C(O)NH ₂
126A	C(Me)OH	CH(Me)	-CH ₂ C(O)NH ₂
127A	C(O)	CH ₂	-CH ₂ C(O)NMe ₂
128A	CHOH	CH ₂	-CH ₂ C(O)NMe ₂
129A	C(Me)OH	CH ₂	-CH ₂ C(O)NMe ₂
130A	C(O)	CH(Me)	-CH ₂ C(O)NMe ₂
131A	CHOH	CH(Me)	-CH ₂ C(O)NMe ₂

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132A	C(Me)OH	CH(Me)	-CH ₂ C(O)NMe ₂
133A	C(O)	CH ₂	-CH ₂ C(O)-N-pyrrolidine
134A	CHOH	CH ₂	-CH ₂ C(O)-N-pyrrolidine
135A	C(Me)OH	CH ₂	-CH ₂ C(O)-N-pyrrolidine
136A	C(O)	CH(Me)	-CH ₂ C(O)-N-pyrrolidine
137A	CHOH	CH(Me)	-CH ₂ C(O)-N-pyrrolidine
138A	C(Me)OH	CH(Me)	-CH ₂ C(O)-N-pyrrolidine
139A	C(O)	CH ₂	-CH ₂ -5-tetrazolyl
140A	CHOH	CH ₂	-CH ₂ -5-tetrazolyl
141A	C(Me)OH	CH ₂	-CH ₂ -5-tetrazolyl
142A	C(O)	CH(Me)	-CH ₂ -5-tetrazolyl
143A	CHOH	CH(Me)	-CH ₂ -5-tetrazolyl
144A	C(Me)OH	CH(Me)	-CH ₂ -5-tetrazolyl
145A	C(O)	CH ₂	-C(O)C(O)OH
146A	CHOH	CH ₂	-C(O)C(O)OH
147A	C(Me)OH	CH ₂	-C(O)C(O)OH
148A	C(O)	CH(Me)	-C(O)C(O)OH
149A	CHOH	CH(Me)	-C(O)C(O)OH
150A	C(Me)OH	CH(Me)	-C(O)C(O)OH
151A	C(O)	CH ₂	-CH(OH)C(O)OH
152A	CHOH	CH ₂	-CH(OH)C(O)OH
153A	C(Me)OH	CH ₂	-CH(OH)C(O)OH
154A	C(O)	CH(Me)	-CH(OH)C(O)OH
155A	CHOH	CH(Me)	-CH(OH)C(O)OH
156A	C(Me)OH	CH(Me)	-CH(OH)C(O)OH
157A	C(O)	CH ₂	-C(O)C(O)NH ₂
158A	CHOH	CH ₂	-C(O)C(O)NH ₂
159A	C(Me)OH	CH ₂	-C(O)C(O)NH ₂
160A	C(O)	CH(Me)	-C(O)C(O)NH ₂
161A	CHOH	CH(Me)	-C(O)C(O)NH ₂
162A	C(Me)OH	CH(Me)	-C(O)C(O)NH ₂

163A	C(O)	CH ₂	-CH(OH)C(O)NH ₂
164A	CHOH	CH ₂	-CH(OH)C(O)NH ₂
165A	C(Me)OH	CH ₂	-CH(OH)C(O)NH ₂
166A	C(O)	CH(Me)	-CH(OH)C(O)NH ₂
167A	CHOH	CH(Me)	-CH(OH)C(O)NH ₂
168A	C(Me)OH	CH(Me)	-CH(OH)C(O)NH ₂
169A	C(O)	CH ₂	-C(O)C(O)NMe ₂
170A	CHOH	CH ₂	-C(O)C(O)NMe ₂
171A	C(Me)OH	CH ₂	-C(O)C(O)NMe ₂
172A	C(O)	CH(Me)	-C(O)C(O)NMe ₂
173A	CHOH	CH(Me)	-C(O)C(O)NMe ₂
174A	C(Me)OH	CH(Me)	-C(O)C(O)NMe ₂
175A	C(O)	CH ₂	-CH(OH)C(O)NMe ₂
176A	CHOH	CH ₂	-CH(OH)C(O)NMe ₂
177A	C(Me)OH	CH ₂	-CH(OH)C(O)NMe ₂
178A	C(O)	CH(Me)	-CH(OH)C(O)NMe ₂
179A	CHOH	CH(Me)	-CH(OH)C(O)NMe ₂
180A	C(Me)OH	CH(Me)	-CH(OH)C(O)NMe ₂
181A	C(O)	CH ₂	-CH ₂ CH ₂ CO ₂ H
182A	CHOH	CH ₂	-CH ₂ CH ₂ CO ₂ H
183A	C(Me)OH	CH ₂	-CH ₂ CH ₂ CO ₂ H
184A	C(O)	CH(Me)	-CH ₂ CH ₂ CO ₂ H
185A	CHOH	CH(Me)	-CH ₂ CH ₂ CO ₂ H
186A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CO ₂ H
187A	C(O)	CH ₂	-CH ₂ CH ₂ C(O)NH ₂
188A	CHOH	CH ₂	-CH ₂ CH ₂ C(O)NH ₂
189A	C(Me)OH	CH ₂	-CH ₂ CH ₂ C(O)NH ₂
190A	C(O)	CH(Me)	-CH ₂ CH ₂ C(O)NH ₂
191A	CHOH	CH(Me)	-CH ₂ CH ₂ C(O)NH ₂
192A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ C(O)NH ₂
193A	C(O)	CH ₂	-CH ₂ CH ₂ C(O)NMe ₂

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194A	CHOH	CH ₂	-CH ₂ CH ₂ C(O)NMe ₂
195A	C(Me)OH	CH ₂	-CH ₂ CH ₂ C(O)NMe ₂
196A	C(O)	CH(Me)	-CH ₂ CH ₂ C(O)NMe ₂
197A	CHOH	CH(Me)	-CH ₂ CH ₂ C(O)NMe ₂
198A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ C(O)NMe ₂
199A	C(O)	CH ₂	-CH ₂ CH ₂ -5-tetrazolyl
200A	CHOH	CH ₂	-CH ₂ CH ₂ -5-tetrazolyl
201A	C(Me)OH	CH ₂	-CH ₂ CH ₂ -5-tetrazolyl
202A	C(O)	CH(Me)	-CH ₂ CH ₂ -5-tetrazolyl
203A	CHOH	CH(Me)	-CH ₂ CH ₂ -5-tetrazolyl
204A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ -5-tetrazolyl
205A	C(O)	CH ₂	-OCH ₂ S(O) ₂ Me
206A	CHOH	CH ₂	-OCH ₂ S(O) ₂ Me
207A	C(Me)OH	CH ₂	-OCH ₂ S(O) ₂ Me
208A	C(O)	CH(Me)	-OCH ₂ S(O) ₂ Me
209A	CHOH	CH(Me)	-OCH ₂ S(O) ₂ Me
210A	C(Me)OH	CH(Me)	-OCH ₂ S(O) ₂ Me
211A	C(O)	CH ₂	-OCH ₂ CH ₂ S(O) ₂ Me
212A	CHOH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ Me
213A	C(Me)OH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ Me
214A	C(O)	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ Me
215A	CHOH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ Me
216A	C(Me)OH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ Me
217A	C(O)	CH ₂	-CH ₂ S(O) ₂ Me
218A	CHOH	CH ₂	-CH ₂ S(O) ₂ Me
219A	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ Me
220A	C(O)	CH(Me)	-CH ₂ S(O) ₂ Me
221A	CHOH	CH(Me)	-CH ₂ S(O) ₂ Me
222A	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ Me
223A	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ Me
224A	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Me

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225A	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Me
226A	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Me
227A	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Me
228A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Me
229A	C(O)	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
230A	CHOH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
231A	C(Me)OH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
232A	C(O)	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
233A	CHOH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
234A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
235A	C(O)	CH ₂	-OCH ₂ S(O) ₂ Et
236A	CHOH	CH ₂	-OCH ₂ S(O) ₂ Et
237A	C(Me)OH	CH ₂	-OCH ₂ S(O) ₂ Et
238A	C(O)	CH(Me)	-OCH ₂ S(O) ₂ Et
239A	CHOH	CH(Me)	-OCH ₂ S(O) ₂ Et
240A	C(Me)OH	CH(Me)	-OCH ₂ S(O) ₂ Et
241A	C(O)	CH ₂	-OCH ₂ CH ₂ S(O) ₂ Et
242A	CHOH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ Et
243A	C(Me)OH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ Et
244A	C(O)	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ Et
245A	CHOH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ Et
246A	C(Me)OH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ Et
247A	C(O)	CH ₂	-CH ₂ S(O) ₂ Et
248A	CHOH	CH ₂	-CH ₂ S(O) ₂ Et
249A	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ Et
250A	C(O)	CH(Me)	-CH ₂ S(O) ₂ Et
251A	CHOH	CH(Me)	-CH ₂ S(O) ₂ Et
252A	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ Et
253A	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ Et
254A	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Et
255A	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ Et

256A	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Et
257A	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Et
258A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ Et
259A	C(O)	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
260A	CHOH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
261A	C(Me)OH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
262A	C(O)	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
263A	CHOH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
264A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
265A	C(O)	CH ₂	-OCH ₂ S(O) ₂ iPr
266A	CHOH	CH ₂	-OCH ₂ S(O) ₂ iPr
267A	C(Me)OH	CH ₂	-OCH ₂ S(O) ₂ iPr
268A	C(O)	CH(Me)	-OCH ₂ S(O) ₂ iPr
269A	CHOH	CH(Me)	-OCH ₂ S(O) ₂ iPr
270A	C(Me)OH	CH(Me)	-OCH ₂ S(O) ₂ iPr
271A	C(O)	CH ₂	-CH ₂ S(O) ₂ iPr
272A	CHOH	CH ₂	-CH ₂ S(O) ₂ iPr
273A	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ iPr
274A	C(O)	CH(Me)	-CH ₂ S(O) ₂ iPr
275A	CHOH	CH(Me)	-CH ₂ S(O) ₂ iPr
276A	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ iPr
277A	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ iPr
278A	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ iPr
279A	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ iPr
280A	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ iPr
281A	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ iPr
282A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ iPr
283A	C(O)	CH ₂	-OCH ₂ S(O) ₂ tBu
284A	CHOH	CH ₂	-OCH ₂ S(O) ₂ tBu
285A	C(Me)OH	CH ₂	-OCH ₂ S(O) ₂ tBu
286A	C(O)	CH(Me)	-OCH ₂ S(O) ₂ tBu

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287A	CHOH	CH(Me)	-OCH ₂ S(O) ₂ tBu
288A	C(Me)OH	CH(Me)	-OCH ₂ S(O) ₂ tBu
289A	C(O)	CH ₂	-CH ₂ S(O) ₂ tBu
290A	CHOH	CH ₂	-CH ₂ S(O) ₂ tBu
291A	C(Me)OH	CH ₂	-CH ₂ S(O) ₂ tBu
292A	C(O)	CH(Me)	-CH ₂ S(O) ₂ tBu
293A	CHOH	CH(Me)	-CH ₂ S(O) ₂ tBu
294A	C(Me)OH	CH(Me)	-CH ₂ S(O) ₂ tBu
295A	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ tBu
296A	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ tBu
297A	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ tBu
298A	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ tBu
299A	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ tBu
300A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ tBu
301A	C(O)	CH ₂	-OCH ₂ S(O) ₂ NH ₂
302A	CHOH	CH ₂	-OCH ₂ S(O) ₂ NH ₂
303A	C(Me)OH	CH ₂	-OCH ₂ S(O) ₂ NH ₂
304A	C(O)	CH(Me)	-OCH ₂ S(O) ₂ NH ₂
305A	CHOH	CH(Me)	-OCH ₂ S(O) ₂ NH ₂
306A	C(Me)OH	CH(Me)	-OCH ₂ S(O) ₂ NH ₂
307A	C(O)	CH ₂	-OCH ₂ S(O) ₂ NMe ₂
308A	CHOH	CH ₂	-OCH ₂ S(O) ₂ NMe ₂
309A	C(Me)OH	CH ₂	-OCH ₂ S(O) ₂ NMe ₂
310A	C(O)	CH(Me)	-OCH ₂ S(O) ₂ NMe ₂
311A	CHOH	CH(Me)	-OCH ₂ S(O) ₂ NMe ₂
312A	C(Me)OH	CH(Me)	-OCH ₂ S(O) ₂ NMe ₂
313A	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ NH ₂
314A	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NH ₂
315A	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NH ₂
316A	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NH ₂
317A	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NH ₂

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318A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NH ₂
319A	C(O)	CH ₂	-CH ₂ CH ₂ S(O) ₂ NMe ₂
320A	CHOH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NMe ₂
321A	C(Me)OH	CH ₂	-CH ₂ CH ₂ S(O) ₂ NMe ₂
322A	C(O)	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NMe ₂
323A	CHOH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NMe ₂
324A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ S(O) ₂ NMe ₂
325A	C(O)	CH ₂	-C(O)CH ₂ S(O) ₂ Me
326A	CHOH	CH ₂	-C(O)CH ₂ S(O) ₂ Me
327A	C(Me)OH	CH ₂	-C(O)CH ₂ S(O) ₂ Me
328A	C(O)	CH(Me)	-C(O)CH ₂ S(O) ₂ Me
329A	CHOH	CH(Me)	-C(O)CH ₂ S(O) ₂ Me
330A	C(Me)OH	CH(Me)	-C(O)CH ₂ S(O) ₂ Me
331A	C(O)	CH ₂	-C(O)CH ₂ CH ₂ S(O) ₂ Me
332A	CHOH	CH ₂	-C(O)CH ₂ CH ₂ S(O) ₂ Me
333A	C(Me)OH	CH ₂	-C(O)CH ₂ CH ₂ S(O) ₂ Me
334A	C(O)	CH(Me)	-C(O)CH ₂ CH ₂ S(O) ₂ Me
335A	CHOH	CH(Me)	-C(O)CH ₂ CH ₂ S(O) ₂ Me
336A	C(Me)OH	CH(Me)	-C(O)CH ₂ CH ₂ S(O) ₂ Me
337A	C(O)	CH ₂	-OCH ₂ CH ₂ S(O) ₂ NH ₂
338A	CHOH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ NH ₂
339A	C(Me)OH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ NH ₂
340A	C(O)	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ NH ₂
341A	CHOH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ NH ₂
342A	C(Me)OH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ NH ₂
343A	C(O)	CH ₂	-OCH ₂ CH ₂ S(O) ₂ NMe ₂
344A	CHOH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ NMe ₂
345A	C(Me)OH	CH ₂	-OCH ₂ CH ₂ S(O) ₂ NMe ₂
346A	C(O)	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ NMe ₂
347A	CHOH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ NMe ₂
348A	C(Me)OH	CH(Me)	-OCH ₂ CH ₂ S(O) ₂ NMe ₂

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349A	C(O)	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
350A	CHOH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
351A	C(Me)OH	CH ₂	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
352A	C(O)	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
353A	CHOH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
354A	C(Me)OH	CH(Me)	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
355A	C(O)	CH ₂	-S(O) ₂ Me
356A	CHOH	CH ₂	-S(O) ₂ Me
357A	C(Me)OH	CH ₂	-S(O) ₂ Me
358A	C(O)	CH(Me)	-S(O) ₂ Me
359A	CHOH	CH(Me)	-S(O) ₂ Me
360A	C(Me)OH	CH(Me)	-S(O) ₂ Me
361A	C(O)	CH ₂	-S(O) ₂ Et
362A	CHOH	CH ₂	-S(O) ₂ Et
363A	C(Me)OH	CH ₂	-S(O) ₂ Et
364A	C(O)	CH(Me)	-S(O) ₂ Et
365A	CHOH	CH(Me)	-S(O) ₂ Et
366A	C(Me)OH	CH(Me)	-S(O) ₂ Et
367A	C(O)	CH ₂	-S(O) ₂ iPr
368A	CHOH	CH ₂	-S(O) ₂ iPr
369A	C(Me)OH	CH ₂	-S(O) ₂ iPr
370A	C(O)	CH(Me)	-S(O) ₂ iPr
371A	CHOH	CH(Me)	-S(O) ₂ iPr
372A	C(Me)OH	CH(Me)	-S(O) ₂ iPr
373A	C(O)	CH ₂	-S(O) ₂ tBu
374A	CHOH	CH ₂	-S(O) ₂ tBu
375A	C(Me)OH	CH ₂	-S(O) ₂ tBu
376A	C(O)	CH(Me)	-S(O) ₂ tBu
377A	CHOH	CH(Me)	-S(O) ₂ tBu
378A	C(Me)OH	CH(Me)	-S(O) ₂ tBu
379A	C(O)	CH ₂	-OCH ₂ CO ₂ H

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380A	CHOH	CH ₂	-OCH ₂ CO ₂ H
381A	C(Me)OH	CH ₂	-OCH ₂ CO ₂ H
382A	C(O)	CH(Me)	-OCH ₂ CO ₂ H
383A	CHOH	CH(Me)	-OCH ₂ CO ₂ H
384A	C(Me)OH	CH(Me)	-OCH ₂ CO ₂ H
385A	C(O)	CH ₂	-OCH ₂ -5-tetrazolyl
386A	CHOH	CH ₂	-OCH ₂ -5-tetrazolyl
387A	C(Me)OH	CH ₂	-OCH ₂ -5-tetrazolyl
388A	C(O)	CH(Me)	-OCH ₂ -5-tetrazolyl
389A	CHOH	CH(Me)	-OCH ₂ -5-tetrazolyl
390A	C(Me)OH	CH(Me)	-OCH ₂ -5-tetrazolyl
391A	C(O)	CH ₂	-S(O) ₂ NH ₂
392A	CHOH	CH ₂	-S(O) ₂ NH ₂
393A	C(Me)OH	CH ₂	-S(O) ₂ NH ₂
394A	C(O)	CH(Me)	-S(O) ₂ NH ₂
395A	CHOH	CH(Me)	-S(O) ₂ NH ₂
396A	C(Me)OH	CH(Me)	-S(O) ₂ NH ₂
397A	C(O)	CH ₂	-S(O) ₂ NMe ₂
398A	CHOH	CH ₂	-S(O) ₂ NMe ₂
399A	C(Me)OH	CH ₂	-S(O) ₂ NMe ₂
400A	C(O)	CH(Me)	-S(O) ₂ NMe ₂
401A	CHOH	CH(Me)	-S(O) ₂ NMe ₂
402A	C(Me)OH	CH(Me)	-S(O) ₂ NMe ₂
403A	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Me
404A	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Me
405A	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Me
406A	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Me
407A	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Me
408A	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Me
409A	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Et
410A	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Et

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411A	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ Et
412A	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Et
413A	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Et
414A	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ Et
415A	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ iPr
416A	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ iPr
417A	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ iPr
418A	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ iPr
419A	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ iPr
420A	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ iPr
421A	C(O)	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ tBu
422A	CHOH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ tBu
423A	C(Me)OH	CH ₂	-S(O) ₂ CH ₂ S(O) ₂ tBu
424A	C(O)	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ tBu
425A	CHOH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ tBu
426A	C(Me)OH	CH(Me)	-S(O) ₂ CH ₂ S(O) ₂ tBu
427A	C(O)	CH ₂	-NHS(O) ₂ Me
428A	CHOH	CH ₂	-NHS(O) ₂ Me
429A	C(Me)OH	CH ₂	-NHS(O) ₂ Me
430A	C(O)	CH(Me)	-NHS(O) ₂ Me
431A	CHOH	CH(Me)	-NHS(O) ₂ Me
432A	C(Me)OH	CH(Me)	-NHS(O) ₂ Me
433A	C(O)	CH ₂	-NHS(O) ₂ Et
434A	CHOH	CH ₂	-NHS(O) ₂ Et
435A	C(Me)OH	CH ₂	-NHS(O) ₂ Et
436A	C(O)	CH(Me)	-NHS(O) ₂ Et
437A	CHOH	CH(Me)	-NHS(O) ₂ Et
438A	C(Me)OH	CH(Me)	-NHS(O) ₂ Et
439A	C(O)	CH ₂	-NHS(O) ₂ iPr
440A	CHOH	CH ₂	-NHS(O) ₂ iPr
441A	C(Me)OH	CH ₂	-NHS(O) ₂ iPr

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442A	C(O)	CH(Me)	-NHS(O)2iPr
443A	CHOH	CH(Me)	-NHS(O)2iPr
444A	C(Me)OH	CH(Me)	-NHS(O)2iPr
445A	C(O)	CH ₂	-NHS(O)2tBu
446A	CHOH	CH ₂	-NHS(O)2tBu
447A	C(Me)OH	CH ₂	-NHS(O)2tBu
448A	C(O)	CH(Me)	-NHS(O)2tBu
449A	CHOH	CH(Me)	-NHS(O)2tBu
450A	C(Me)OH	CH(Me)	-NHS(O)2tBu
451A	C(O)	CH ₂	-OS(O)2Me
452A	CHOH	CH ₂	-OS(O)2Me
453A	C(Me)OH	CH ₂	-OS(O)2Me
454A	C(O)	CH(Me)	-OS(O)2Me
455A	CHOH	CH(Me)	-OS(O)2Me
456A	C(Me)OH	CH(Me)	-OS(O)2Me
457A	C(O)	CH ₂	-OS(O)2Et
458A	CHOH	CH ₂	-OS(O)2Et
459A	C(Me)OH	CH ₂	-OS(O)2Et
460A	C(O)	CH(Me)	-OS(O)2Et
461A	CHOH	CH(Me)	-OS(O)2Et
462A	C(Me)OH	CH(Me)	-OS(O)2Et
463A	C(O)	CH ₂	-OS(O)2iPr
464A	CHOH	CH ₂	-OS(O)2iPr
465A	C(Me)OH	CH ₂	-OS(O)2iPr
466A	C(O)	CH(Me)	-OS(O)2iPr
467A	CHOH	CH(Me)	-OS(O)2iPr
468A	C(Me)OH	CH(Me)	-OS(O)2iPr
469A	C(O)	CH ₂	-OS(O)2tBu
470A	CHOH	CH ₂	-OS(O)2tBu
471A	C(Me)OH	CH ₂	-OS(O)2tBu
472A	C(O)	CH(Me)	-OS(O)2tBu

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473A	CHOH	CH(Me)	-OS(O)2tBu
474A	C(Me)OH	CH(Me)	-OS(O)2tBu
475A	C(O)	CH2	-NHC(O)NMe2
476A	CHOH	CH2	-NHC(O)NMe2
477A	C(Me)OH	CH2	-NHC(O)NMe2
478A	C(O)	CH(Me)	-NHC(O)NMe2
479A	CHOH	CH(Me)	-NHC(O)NMe2
480A	C(Me)OH	CH(Me)	-NHC(O)NMe2
481A	C(O)	CH2	-NHC(S)NMe2
482A	CHOH	CH2	-NHC(S)NMe2
483A	C(Me)OH	CH2	-NHC(S)NMe2
484A	C(O)	CH(Me)	-NHC(S)NMe2
485A	CHOH	CH(Me)	-NHC(S)NMe2
486A	C(Me)OH	CH(Me)	-NHC(S)NMe2
487A	C(O)	CH2	-OC(O)NMe2
488A	CHOH	CH2	-OC(O)NMe2
489A	C(Me)OH	CH2	-OC(O)NMe2
490A	C(O)	CH(Me)	-OC(O)NMe2
491A	CHOH	CH(Me)	-OC(O)NMe2
492A	C(Me)OH	CH(Me)	-OC(O)NMe2
493A	C(O)	CH2	-OC(S)NMe2
494A	CHOH	CH2	-OC(S)NMe2
495A	C(Me)OH	CH2	-OC(S)NMe2
496A	C(O)	CH(Me)	-OC(S)NMe2
497A	CHOH	CH(Me)	-OC(S)NMe2
498A	C(Me)OH	CH(Me)	-OC(S)NMe2
499A	C(O)	CH2	-NHS(O)2NMe2
500A	CHOH	CH2	-NHS(O)2NMe2
501A	C(Me)OH	CH2	-NHS(O)2NMe2
502A	C(O)	CH(Me)	-NHS(O)2NMe2
503A	CHOH	CH(Me)	-NHS(O)2NMe2

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504A	C(Me)OH	CH(Me)	-NHS(O)2NMe2
505A	C(O)	CH2	-C(O)NHCH2CO2H
506A	CHOH	CH2	-C(O)NHCH2CO2H
507A	C(Me)OH	CH2	-C(O)NHCH2CO2H
508A	C(O)	CH(Me)	-C(O)NHCH2CO2H
509A	CHOH	CH(Me)	-C(O)NHCH2CO2H
510A	C(Me)OH	CH(Me)	-C(O)NHCH2CO2H
511A	C(O)	CH2	-SO2NHCH2CO2H
512A	CHOH	CH2	-SO2NHCH2CO2H
513A	C(Me)OH	CH2	-SO2NHCH2CO2H
514A	C(O)	CH(Me)	-SO2NHCH2CO2H
515A	CHOH	CH(Me)	-SO2NHCH2CO2H
516A	C(Me)OH	CH(Me)	-SO2NHCH2CO2H
517A	C(O)	CH2	-CH2-S-Me
518A	CHOH	CH2	-CH2-S-Me
519A	C(Me)OH	CH2	-CH2-S-Me
520A	C(O)	CH(Me)	-CH2-S-Me
521A	CHOH	CH(Me)	-CH2-S-Me
522A	C(Me)OH	CH(Me)	-CH2-S-Me

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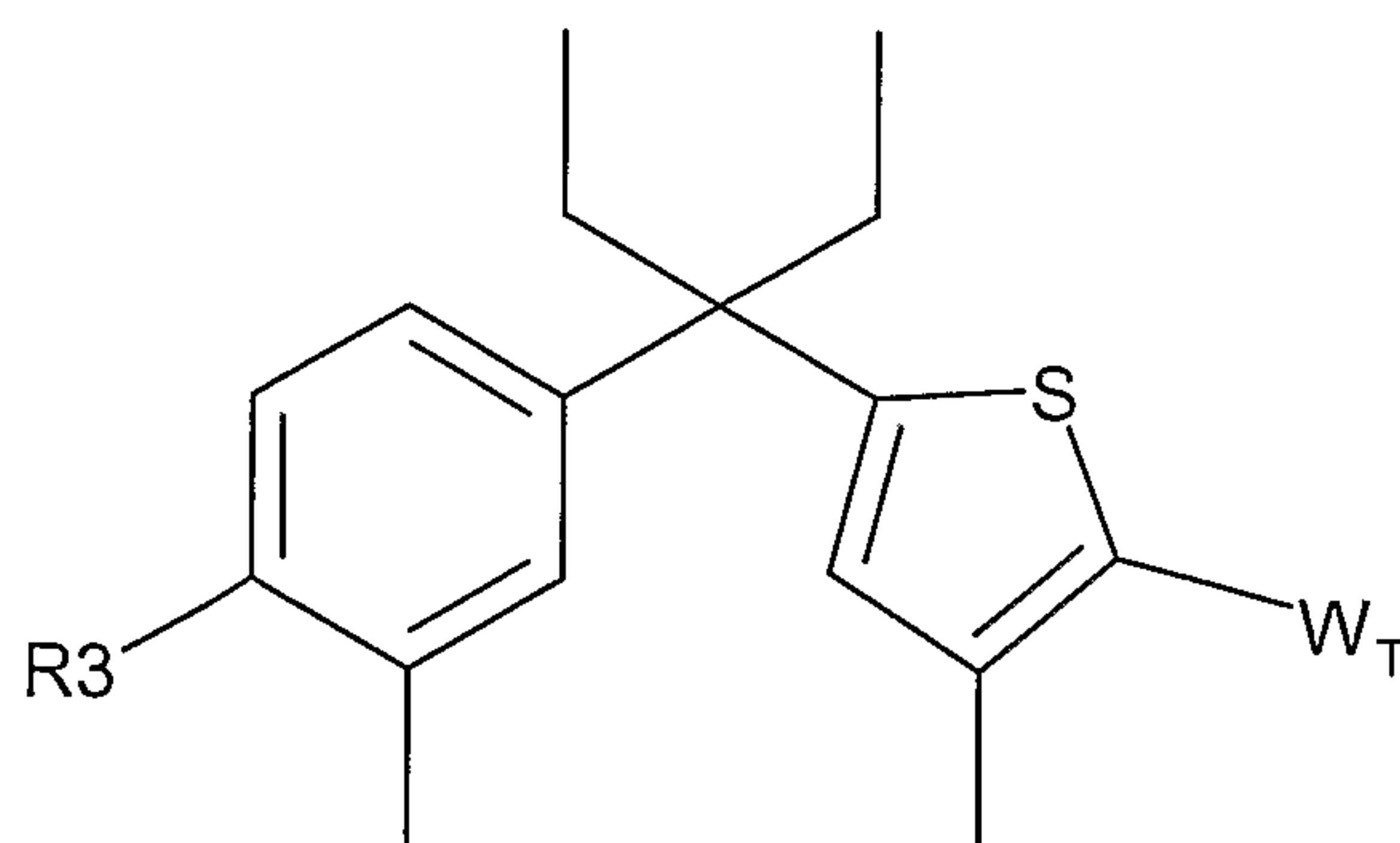


Table 3

Code	R ₃	W _T
1B	3Me3OH-Pentyl	-CO ₂ Me
2B	3Me3OH-Pentenyl	-CO ₂ Me
3B	3Me3OH-Pentynyl	-CO ₂ Me
4B	3Et3OH-Pentyl	-CO ₂ Me
5B	3Et3OH-Pentenyl	-CO ₂ Me
6B	3Et3OH-Pentynyl	-CO ₂ Me
7B	3Me3OH-Pentyl	-CO ₂ H
8B	3Me3OH-Pentenyl	-CO ₂ H
9B	3Me3OH-Pentynyl	-CO ₂ H
10B	3Et3OH-Pentyl	-CO ₂ H
11B	3Et3OH-Pentenyl	-CO ₂ H
12B	3Et3OH-Pentynyl	-CO ₂ H
13B	3Me3OH-Pentyl	-C(O)NH ₂
14B	3Me3OH-Pentenyl	-C(O)NH ₂
15B	3Me3OH-Pentynyl	-C(O)NH ₂
16B	3Et3OH-Pentyl	-C(O)NH ₂
17B	3Et3OH-Pentenyl	-C(O)NH ₂
18B	3Et3OH-Pentynyl	-C(O)NH ₂
19B	3Me3OH-Pentyl	-C(O)NMe ₂
20B	3Me3OH-Pentenyl	-C(O)NMe ₂
21B	3Me3OH-Pentynyl	-C(O)NMe ₂

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22B	3Et3OH-Pentyl	-C(O)NMe2
23B	3Et3OH-Pentenyl	-C(O)NMe2
24B	3Et3OH-Pentynyl	-C(O)NMe2
25B	3Me3OH-Pentyl	5-tetrazolyl
26B	3Me3OH-Pentenyl	5-tetrazolyl
27B	3Me3OH-Pentynyl	5-tetrazolyl
28B	3Et3OH-Pentyl	5-tetrazolyl
29B	3Et3OH-Pentenyl	5-tetrazolyl
30B	3Et3OH-Pentynyl	5-tetrazolyl
31B	3Me3OH-Pentyl	-C(O)-NH-5-tetrazolyl
32B	3Me3OH-Pentenyl	-C(O)-NH-5-tetrazolyl
33B	3Me3OH-Pentynyl	-C(O)-NH-5-tetrazolyl
34B	3Et3OH-Pentyl	-C(O)-NH-5-tetrazolyl
35B	3Et3OH-Pentenyl	-C(O)-NH-5-tetrazolyl
36B	3Et3OH-Pentynyl	-C(O)-NH-5-tetrazolyl
37B	3Me3OH-Pentyl	-C(O)NHCH2SO2Me
38B	3Me3OH-Pentenyl	-C(O)NHCH2SO2Me
39B	3Me3OH-Pentynyl	-C(O)NHCH2SO2Me
40B	3Et3OH-Pentyl	-C(O)NHCH2SO2Me
41B	3Et3OH-Pentenyl	-C(O)NHCH2SO2Me
42B	3Et3OH-Pentynyl	-C(O)NHCH2SO2Me
43B	3Me3OH-Pentyl	-C(O)NHCH2CH2SO2Me
44B	3Me3OH-Pentenyl	-C(O)NHCH2CH2SO2Me
45B	3Me3OH-Pentynyl	-C(O)NHCH2CH2SO2Me
46B	3Et3OH-Pentyl	-C(O)NHCH2CH2SO2Me
47B	3Et3OH-Pentenyl	-C(O)NHCH2CH2SO2Me
48B	3Et3OH-Pentynyl	-C(O)NHCH2CH2SO2Me
49B	3Me3OH-Pentyl	-C(O)NHSO2Me
50B	3Me3OH-Pentenyl	-C(O)NHSO2Me
51B	3Me3OH-Pentynyl	-C(O)NHSO2Me
52B	3Et3OH-Pentyl	-C(O)NHSO2Me

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53B	3Et3OH-Pentenyl	-C(O)NHSO ₂ Me
54B	3Et3OH-Pentynyl	-C(O)NHSO ₂ Me
55B	3Me3OH-Pentyl	-CH ₂ -C(O)NHSO ₂ Et
56B	3Me3OH-Pentenyl	-CH ₂ -C(O)NHSO ₂ Et
57B	3Me3OH-Pentynyl	-CH ₂ -C(O)NHSO ₂ Et
58B	3Et3OH-Pentyl	-CH ₂ -C(O)NHSO ₂ Et
59B	3Et3OH-Pentenyl	-CH ₂ -C(O)NHSO ₂ Et
60B	3Et3OH-Pentynyl	-CH ₂ -C(O)NHSO ₂ Et
61B	3Me3OH-Pentyl	-CH ₂ -C(O)NHSO ₂ iPr
62B	3Me3OH-Pentenyl	-CH ₂ -C(O)NHSO ₂ iPr
63B	3Me3OH-Pentynyl	-CH ₂ -C(O)NHSO ₂ iPr
64B	3Et3OH-Pentyl	-CH ₂ -C(O)NHSO ₂ iPr
65B	3Et3OH-Pentenyl	-CH ₂ -C(O)NHSO ₂ iPr
66B	3Et3OH-Pentynyl	-CH ₂ -C(O)NHSO ₂ iPr
67B	3Me3OH-Pentyl	-CH ₂ -C(O)NHSO ₂ tBu
68B	3Me3OH-Pentenyl	-CH ₂ -C(O)NHSO ₂ tBu
69B	3Me3OH-Pentynyl	-CH ₂ -C(O)NHSO ₂ tBu
70B	3Et3OH-Pentyl	-CH ₂ -C(O)NHSO ₂ tBu
71B	3Et3OH-Pentenyl	-CH ₂ -C(O)NHSO ₂ tBu
72B	3Et3OH-Pentynyl	-CH ₂ -C(O)NHSO ₂ tBu
73B	3Me3OH-Pentyl	-CH ₂ NHSO ₂ Me
74B	3Me3OH-Pentenyl	-CH ₂ NHSO ₂ Me
75B	3Me3OH-Pentynyl	-CH ₂ NHSO ₂ Me
76B	3Et3OH-Pentyl	-CH ₂ NHSO ₂ Me
77B	3Et3OH-Pentenyl	-CH ₂ NHSO ₂ Me
78B	3Et3OH-Pentynyl	-CH ₂ NHSO ₂ Me
79B	3Me3OH-Pentyl	-CH ₂ NHSO ₂ Et
80B	3Me3OH-Pentenyl	-CH ₂ NHSO ₂ Et
81B	3Me3OH-Pentynyl	-CH ₂ NHSO ₂ Et
82B	3Et3OH-Pentyl	-CH ₂ NHSO ₂ Et
83B	3Et3OH-Pentenyl	-CH ₂ NHSO ₂ Et

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84B	3Et3OH-Pentynyl	-CH ₂ NHSO ₂ Et
85B	3Me3OH-Pentyl	-CH ₂ NHSO ₂ iPr
86B	3Me3OH-Pentenyl	-CH ₂ NHSO ₂ iPr
87B	3Me3OH-Pentynyl	-CH ₂ NHSO ₂ iPr
88B	3Et3OH-Pentyl	-CH ₂ NHSO ₂ iPr
89B	3Et3OH-Pentenyl	-CH ₂ NHSO ₂ iPr
90B	3Et3OH-Pentynyl	-CH ₂ NHSO ₂ iPr
91B	3Me3OH-Pentyl	-CH ₂ NHSO ₂ tBu
92B	3Me3OH-Pentenyl	-CH ₂ NHSO ₂ tBu
93B	3Me3OH-Pentynyl	-CH ₂ NHSO ₂ tBu
94B	3Et3OH-Pentyl	-CH ₂ NHSO ₂ tBu
95B	3Et3OH-Pentenyl	-CH ₂ NHSO ₂ tBu
96B	3Et3OH-Pentynyl	-CH ₂ NHSO ₂ tBu
97B	3Me3OH-Pentyl	-CH ₂ -N-pyrrolidin-2-one
98B	3Me3OH-Pentenyl	-CH ₂ -N-pyrrolidin-2-one
99B	3Me3OH-Pentynyl	-CH ₂ -N-pyrrolidin-2-one
100B	3Et3OH-Pentyl	-CH ₂ -N-pyrrolidin-2-one
101B	3Et3OH-Pentenyl	-CH ₂ -N-pyrrolidin-2-one
102B	3Et3OH-Pentynyl	-CH ₂ -N-pyrrolidin-2-one
103B	3Me3OH-Pentyl	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
104B	3Me3OH-Pentenyl	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
105B	3Me3OH-Pentynyl	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
106B	3Et3OH-Pentyl	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
107B	3Et3OH-Pentenyl	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
108B	3Et3OH-Pentynyl	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
109B	3Me3OH-Pentyl	-CH ₂ CO ₂ Me

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110B	3Me3OH-Pentenyl	-CH ₂ CO ₂ Me
111B	3Me3OH-Pentynyl	-CH ₂ CO ₂ Me
112B	3Et3OH-Pentyl	-CH ₂ CO ₂ Me
113B	3Et3OH-Pentenyl	-CH ₂ CO ₂ Me
114B	3Et3OH-Pentynyl	-CH ₂ CO ₂ Me
115B	3Me3OH-Pentyl	-CH ₂ CO ₂ H
116B	3Me3OH-Pentenyl	-CH ₂ CO ₂ H
117B	3Me3OH-Pentynyl	-CH ₂ CO ₂ H
118B	3Et3OH-Pentyl	-CH ₂ CO ₂ H
119B	3Et3OH-Pentenyl	-CH ₂ CO ₂ H
120B	3Et3OH-Pentynyl	-CH ₂ CO ₂ H
121B	3Me3OH-Pentyl	-CH ₂ C(O)NH ₂
122B	3Me3OH-Pentenyl	-CH ₂ C(O)NH ₂
123B	3Me3OH-Pentynyl	-CH ₂ C(O)NH ₂
124B	3Et3OH-Pentyl	-CH ₂ C(O)NH ₂
125B	3Et3OH-Pentenyl	-CH ₂ C(O)NH ₂
126B	3Et3OH-Pentynyl	-CH ₂ C(O)NH ₂
127B	3Me3OH-Pentyl	-CH ₂ C(O)NMe ₂
128B	3Me3OH-Pentenyl	-CH ₂ C(O)NMe ₂
129B	3Me3OH-Pentynyl	-CH ₂ C(O)NMe ₂
130B	3Et3OH-Pentyl	-CH ₂ C(O)NMe ₂
131B	3Et3OH-Pentenyl	-CH ₂ C(O)NMe ₂
132B	3Et3OH-Pentynyl	-CH ₂ C(O)NMe ₂
133B	3Me3OH-Pentyl	-CH ₂ C(O)-N-pyrrolidine
134B	3Me3OH-Pentenyl	-CH ₂ C(O)-N-pyrrolidine
135B	3Me3OH-Pentynyl	-CH ₂ C(O)-N-pyrrolidine
136B	3Et3OH-Pentyl	-CH ₂ C(O)-N-pyrrolidine
137B	3Et3OH-Pentenyl	-CH ₂ C(O)-N-pyrrolidine
138B	3Et3OH-Pentynyl	-CH ₂ C(O)-N-pyrrolidine
139B	3Me3OH-Pentyl	-CH ₂ -5-tetrazolyl
140B	3Me3OH-Pentenyl	-CH ₂ -5-tetrazolyl

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141B	3Me3OH-Pentynyl	-CH2-5-tetrazolyl
142B	3Et3OH-Pentyl	-CH2-5-tetrazolyl
143B	3Et3OH-Pentenyl	-CH2-5-tetrazolyl
144B	3Et3OH-Pentynyl	-CH2-5-tetrazolyl
145B	3Me3OH-Pentyl	-C(O)C(O)OH
146B	3Me3OH-Pentenyl	-C(O)C(O)OH
147B	3Me3OH-Pentynyl	-C(O)C(O)OH
148B	3Et3OH-Pentyl	-C(O)C(O)OH
149B	3Et3OH-Pentenyl	-C(O)C(O)OH
150B	3Et3OH-Pentynyl	-C(O)C(O)OH
151B	3Me3OH-Pentyl	-CH(OH)C(O)OH
152B	3Me3OH-Pentenyl	-CH(OH)C(O)OH
153B	3Me3OH-Pentynyl	-CH(OH)C(O)OH
154B	3Et3OH-Pentyl	-CH(OH)C(O)OH
155B	3Et3OH-Pentenyl	-CH(OH)C(O)OH
156B	3Et3OH-Pentynyl	-CH(OH)C(O)OH
157B	3Me3OH-Pentyl	-C(O)C(O)NH2
158B	3Me3OH-Pentenyl	-C(O)C(O)NH2
159B	3Me3OH-Pentynyl	-C(O)C(O)NH2
160B	3Et3OH-Pentyl	-C(O)C(O)NH2
161B	3Et3OH-Pentenyl	-C(O)C(O)NH2
162B	3Et3OH-Pentynyl	-C(O)C(O)NH2
163B	3Me3OH-Pentyl	-CH(OH)C(O)NH2
164B	3Me3OH-Pentenyl	-CH(OH)C(O)NH2
165B	3Me3OH-Pentynyl	-CH(OH)C(O)NH2
166B	3Et3OH-Pentyl	-CH(OH)C(O)NH2
167B	3Et3OH-Pentenyl	-CH(OH)C(O)NH2
168B	3Et3OH-Pentynyl	-CH(OH)C(O)NH2
169B	3Me3OH-Pentyl	-C(O)C(O)NMe2
170B	3Me3OH-Pentenyl	-C(O)C(O)NMe2
171B	3Me3OH-Pentynyl	-C(O)C(O)NMe2

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172B	3Et3OH-Pentyl	-C(O)C(O)NMe2
173B	3Et3OH-Pentenyl	-C(O)C(O)NMe2
174B	3Et3OH-Pentynyl	-C(O)C(O)NMe2
175B	3Me3OH-Pentyl	-CH(OH)C(O)NMe2
176B	3Me3OH-Pentenyl	-CH(OH)C(O)NMe2
177B	3Me3OH-Pentynyl	-CH(OH)C(O)NMe2
178B	3Et3OH-Pentyl	-CH(OH)C(O)NMe2
179B	3Et3OH-Pentenyl	-CH(OH)C(O)NMe2
180B	3Et3OH-Pentynyl	-CH(OH)C(O)NMe2
181B	3Me3OH-Pentyl	-CH2CH2CO2H
182B	3Me3OH-Pentenyl	-CH2CH2CO2H
183B	3Me3OH-Pentynyl	-CH2CH2CO2H
184B	3Et3OH-Pentyl	-CH2CH2CO2H
185B	3Et3OH-Pentenyl	-CH2CH2CO2H
186B	3Et3OH-Pentynyl	-CH2CH2CO2H
187B	3Me3OH-Pentyl	-CH2CH2C(O)NH2
188B	3Me3OH-Pentenyl	-CH2CH2C(O)NH2
189B	3Me3OH-Pentynyl	-CH2CH2C(O)NH2
190B	3Et3OH-Pentyl	-CH2CH2C(O)NH2
191B	3Et3OH-Pentenyl	-CH2CH2C(O)NH2
192B	3Et3OH-Pentynyl	-CH2CH2C(O)NH2
193B	3Me3OH-Pentyl	-CH2CH2C(O)NMe2
194B	3Me3OH-Pentenyl	-CH2CH2C(O)NMe2
195B	3Me3OH-Pentynyl	-CH2CH2C(O)NMe2
196B	3Et3OH-Pentyl	-CH2CH2C(O)NMe2
197B	3Et3OH-Pentenyl	-CH2CH2C(O)NMe2
198B	3Et3OH-Pentynyl	-CH2CH2C(O)NMe2
199B	3Me3OH-Pentyl	-CH2CH2-5-tetrazolyl
200B	3Me3OH-Pentenyl	-CH2CH2-5-tetrazolyl
201B	3Me3OH-Pentynyl	-CH2CH2-5-tetrazolyl
202B	3Et3OH-Pentyl	-CH2CH2-5-tetrazolyl

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203B	3Et3OH-Pentenyl	-CH ₂ CH ₂ -5-tetrazolyl
204B	3Et3OH-Pentynyl	-CH ₂ CH ₂ -5-tetrazolyl
205B	3Me3OH-Pentyl	-CH ₂ S(O)2Me
206B	3Me3OH-Pentenyl	-CH ₂ S(O)2Me
207B	3Me3OH-Pentynyl	-CH ₂ S(O)2Me
208B	3Et3OH-Pentyl	-CH ₂ S(O)2Me
209B	3Et3OH-Pentenyl	-CH ₂ S(O)2Me
210B	3Et3OH-Pentynyl	-CH ₂ S(O)2Me
211B	3Me3OH-Pentyl	-CH ₂ CH ₂ S(O)2Me
212B	3Me3OH-Pentenyl	-CH ₂ CH ₂ S(O)2Me
213B	3Me3OH-Pentynyl	-CH ₂ CH ₂ S(O)2Me
214B	3Et3OH-Pentyl	-CH ₂ CH ₂ S(O)2Me
215B	3Et3OH-Pentenyl	-CH ₂ CH ₂ S(O)2Me
216B	3Et3OH-Pentynyl	-CH ₂ CH ₂ S(O)2Me
217B	3Me3OH-Pentyl	-CH ₂ CH ₂ CH ₂ S(O)2Me
218B	3Me3OH-Pentenyl	-CH ₂ CH ₂ CH ₂ S(O)2Me
219B	3Me3OH-Pentynyl	-CH ₂ CH ₂ CH ₂ S(O)2Me
220B	3Et3OH-Pentyl	-CH ₂ CH ₂ CH ₂ S(O)2Me
221B	3Et3OH-Pentenyl	-CH ₂ CH ₂ CH ₂ S(O)2Me
222B	3Et3OH-Pentynyl	-CH ₂ CH ₂ CH ₂ S(O)2Me
223B	3Me3OH-Pentyl	-CH ₂ S(O)2Et
224B	3Me3OH-Pentenyl	-CH ₂ S(O)2Et
225B	3Me3OH-Pentynyl	-CH ₂ S(O)2Et
226B	3Et3OH-Pentyl	-CH ₂ S(O)2Et
227B	3Et3OH-Pentenyl	-CH ₂ S(O)2Et
228B	3Et3OH-Pentynyl	-CH ₂ S(O)2Et
229B	3Me3OH-Pentyl	-CH ₂ CH ₂ S(O)2Et
230B	3Me3OH-Pentenyl	-CH ₂ CH ₂ S(O)2Et
231B	3Me3OH-Pentynyl	-CH ₂ CH ₂ S(O)2Et
232B	3Et3OH-Pentyl	-CH ₂ CH ₂ S(O)2Et
233B	3Et3OH-Pentenyl	-CH ₂ CH ₂ S(O)2Et

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234B	3Et3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ Et
235B	3Me3OH-Pentyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
236B	3Me3OH-Pentenyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
237B	3Me3OH-Pentynyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
238B	3Et3OH-Pentyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
239B	3Et3OH-Pentenyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
240B	3Et3OH-Pentynyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
241B	3Me3OH-Pentyl	-CH ₂ S(O) ₂ iPr
242B	3Me3OH-Pentenyl	-CH ₂ S(O) ₂ iPr
243B	3Me3OH-Pentynyl	-CH ₂ S(O) ₂ iPr
244B	3Et3OH-Pentyl	-CH ₂ S(O) ₂ iPr
245B	3Et3OH-Pentenyl	-CH ₂ S(O) ₂ iPr
246B	3Et3OH-Pentynyl	-CH ₂ S(O) ₂ iPr
247B	3Me3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ iPr
248B	3Me3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ iPr
249B	3Me3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ iPr
250B	3Et3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ iPr
251B	3Et3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ iPr
252B	3Et3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ iPr
253B	3Me3OH-Pentyl	-CH ₂ S(O) ₂ tBu
254B	3Me3OH-Pentenyl	-CH ₂ S(O) ₂ tBu
255B	3Me3OH-Pentynyl	-CH ₂ S(O) ₂ tBu
256B	3Et3OH-Pentyl	-CH ₂ S(O) ₂ tBu
257B	3Et3OH-Pentenyl	-CH ₂ S(O) ₂ tBu
258B	3Et3OH-Pentynyl	-CH ₂ S(O) ₂ tBu
259B	3Me3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ tBu
260B	3Me3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ tBu
261B	3Me3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ tBu
262B	3Et3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ tBu
263B	3Et3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ tBu
264B	3Et3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ tBu

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265B	3Me3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ NH ₂
266B	3Me3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ NH ₂
267B	3Me3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ NH ₂
268B	3Et3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ NH ₂
269B	3Et3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ NH ₂
270B	3Et3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ NH ₂
271B	3Me3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ NMe ₂
272B	3Me3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ NMe ₂
273B	3Me3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ NMe ₂
274B	3Et3OH-Pentyl	-CH ₂ CH ₂ S(O) ₂ NMe ₂
275B	3Et3OH-Pentenyl	-CH ₂ CH ₂ S(O) ₂ NMe ₂
276B	3Et3OH-Pentynyl	-CH ₂ CH ₂ S(O) ₂ NMe ₂
277B	3Me3OH-Pentyl	-C(O)CH ₂ S(O) ₂ Me
278B	3Me3OH-Pentenyl	-C(O)CH ₂ S(O) ₂ Me
279B	3Me3OH-Pentynyl	-C(O)CH ₂ S(O) ₂ Me
280B	3Et3OH-Pentyl	-C(O)CH ₂ S(O) ₂ Me
281B	3Et3OH-Pentenyl	-C(O)CH ₂ S(O) ₂ Me
282B	3Et3OH-Pentynyl	-C(O)CH ₂ S(O) ₂ Me
283B	3Me3OH-Pentyl	-C(O)CH ₂ CH ₂ S(O) ₂ Me
284B	3Me3OH-Pentenyl	-C(O)CH ₂ CH ₂ S(O) ₂ Me
285B	3Me3OH-Pentynyl	-C(O)CH ₂ CH ₂ S(O) ₂ Me
286B	3Et3OH-Pentyl	-C(O)CH ₂ CH ₂ S(O) ₂ Me
287B	3Et3OH-Pentenyl	-C(O)CH ₂ CH ₂ S(O) ₂ Me
288B	3Et3OH-Pentynyl	-C(O)CH ₂ CH ₂ S(O) ₂ Me
289B	3Me3OH-Pentyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
290B	3Me3OH-Pentenyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
291B	3Me3OH-Pentynyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
292B	3Et3OH-Pentyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
293B	3Et3OH-Pentenyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
294B	3Et3OH-Pentynyl	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
295B	3Me3OH-Pentyl	-S(O) ₂ Me

296B	3Me3OH-Pentenyl	-S(O)2Me
297B	3Me3OH-Pentynyl	-S(O)2Me
298B	3Et3OH-Pentyl	-S(O)2Me
299B	3Et3OH-Pentenyl	-S(O)2Me
300B	3Et3OH-Pentynyl	-S(O)2Me
301B	3Me3OH-Pentyl	-S(O)2Et
302B	3Me3OH-Pentenyl	-S(O)2Et
303B	3Me3OH-Pentynyl	-S(O)2Et
304B	3Et3OH-Pentyl	-S(O)2Et
305B	3Et3OH-Pentenyl	-S(O)2Et
306B	3Et3OH-Pentynyl	-S(O)2Et
307B	3Me3OH-Pentyl	-S(O)2iPr
308B	3Me3OH-Pentenyl	-S(O)2iPr
309B	3Me3OH-Pentynyl	-S(O)2iPr
310B	3Et3OH-Pentyl	-S(O)2iPr
311B	3Et3OH-Pentenyl	-S(O)2iPr
312B	3Et3OH-Pentynyl	-S(O)2iPr
313B	3Me3OH-Pentyl	-S(O)2tBu
314B	3Me3OH-Pentenyl	-S(O)2tBu
315B	3Me3OH-Pentynyl	-S(O)2tBu
316B	3Et3OH-Pentyl	-S(O)2tBu
317B	3Et3OH-Pentenyl	-S(O)2tBu
318B	3Et3OH-Pentynyl	-S(O)2tBu
319B	3Me3OH-Pentyl	-S(O)2NH2
320B	3Me3OH-Pentenyl	-S(O)2NH2
321B	3Me3OH-Pentynyl	-S(O)2NH2
322B	3Et3OH-Pentyl	-S(O)2NH2
323B	3Et3OH-Pentenyl	-S(O)2NH2
324B	3Et3OH-Pentynyl	-S(O)2NH2
325B	3Me3OH-Pentyl	-S(O)2NMe2
326B	3Me3OH-Pentenyl	-S(O)2NMe2

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327B	3Me3OH-Pentynyl	-S(O)2NMe2
328B	3Et3OH-Pentyl	-S(O)2NMe2
329B	3Et3OH-Pentenyl	-S(O)2NMe2
330B	3Et3OH-Pentynyl	-S(O)2NMe2
331B	3Me3OH-Pentyl	-S(O)2CH2S(O)2Me
332B	3Me3OH-Pentenyl	-S(O)2CH2S(O)2Me
333B	3Me3OH-Pentynyl	-S(O)2CH2S(O)2Me
334B	3Et3OH-Pentyl	-S(O)2CH2S(O)2Me
335B	3Et3OH-Pentenyl	-S(O)2CH2S(O)2Me
336B	3Et3OH-Pentynyl	-S(O)2CH2S(O)2Me
337B	3Me3OH-Pentyl	-S(O)2CH2S(O)2Et
338B	3Me3OH-Pentenyl	-S(O)2CH2S(O)2Et
339B	3Me3OH-Pentynyl	-S(O)2CH2S(O)2Et
340B	3Et3OH-Pentyl	-S(O)2CH2S(O)2Et
341B	3Et3OH-Pentenyl	-S(O)2CH2S(O)2Et
342B	3Et3OH-Pentynyl	-S(O)2CH2S(O)2Et
343B	3Me3OH-Pentyl	-S(O)2CH2S(O)2iPr
344B	3Me3OH-Pentenyl	-S(O)2CH2S(O)2iPr
345B	3Me3OH-Pentynyl	-S(O)2CH2S(O)2iPr
346B	3Et3OH-Pentyl	-S(O)2CH2S(O)2iPr
347B	3Et3OH-Pentenyl	-S(O)2CH2S(O)2iPr
348B	3Et3OH-Pentynyl	-S(O)2CH2S(O)2iPr
349B	3Me3OH-Pentyl	-S(O)2CH2S(O)2tBu
350B	3Me3OH-Pentenyl	-S(O)2CH2S(O)2tBu
351B	3Me3OH-Pentynyl	-S(O)2CH2S(O)2tBu
352B	3Et3OH-Pentyl	-S(O)2CH2S(O)2tBu
353B	3Et3OH-Pentenyl	-S(O)2CH2S(O)2tBu
354B	3Et3OH-Pentynyl	-S(O)2CH2S(O)2tBu
355B	3Me3OH-Pentyl	-C(O)NHCH2CO2H
356B	3Me3OH-Pentenyl	-C(O)NHCH2CO2H
357B	3Me3OH-Pentynyl	-C(O)NHCH2CO2H

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358B	3Et3OH-Pentyl	-C(O)NHCH ₂ CO ₂ H
359B	3Et3OH-Pentenyl	-C(O)NHCH ₂ CO ₂ H
360B	3Et3OH-Pentynyl	-C(O)NHCH ₂ CO ₂ H
361B	3Me3OH-Pentyl	-SO ₂ NHCH ₂ CO ₂ H
362B	3Me3OH-Pentenyl	-SO ₂ NHCH ₂ CO ₂ H
363B	3Me3OH-Pentynyl	-SO ₂ NHCH ₂ CO ₂ H
364B	3Et3OH-Pentyl	-SO ₂ NHCH ₂ CO ₂ H
365B	3Et3OH-Pentenyl	-SO ₂ NHCH ₂ CO ₂ H
366B	3Et3OH-Pentynyl	-SO ₂ NHCH ₂ CO ₂ H
367B	3Me3OH-Pentyl	-CH ₂ -S-Me
368B	3Me3OH-Pentenyl	-CH ₂ -S-Me
369B	3Me3OH-Pentynyl	-CH ₂ -S-Me
370B	3Et3OH-Pentyl	-CH ₂ -S-Me
371B	3Et3OH-Pentenyl	-CH ₂ -S-Me
372B	3Et3OH-Pentynyl	-CH ₂ -S-Me

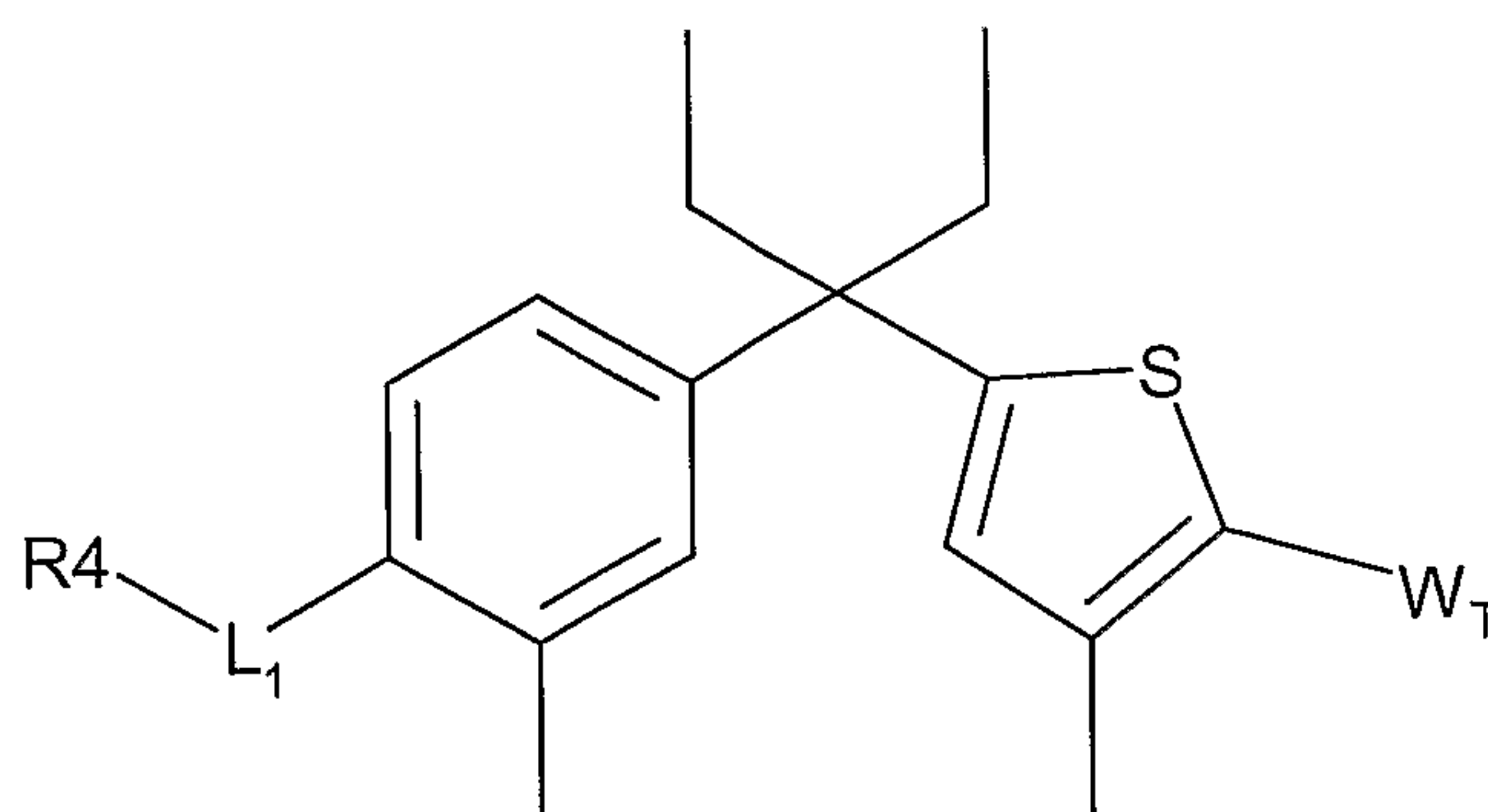


Table 4

Code	R ₄	L ₁	W _T
1C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CO ₂ Me
2C	1-hydroxycyclopentyl	-C≡C-	-CO ₂ Me
3C	1-hydroxycyclopentyl	-C=C-	-CO ₂ Me
4C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CO ₂ Me

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5C	1-hydroxycyclohexyl	-C≡C-	-CO ₂ Me
6C	1-hydroxycyclohexyl	-C=C-	-CO ₂ Me
7C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CO ₂ H
8C	1-hydroxycyclopentyl	-C≡C-	-CO ₂ H
9C	1-hydroxycyclopentyl	-C=C-	-CO ₂ H
10C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CO ₂ H
11C	1-hydroxycyclohexyl	-C≡C-	-CO ₂ H
12C	1-hydroxycyclohexyl	-C=C-	-CO ₂ H
13C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)NH ₂
14C	1-hydroxycyclopentyl	-C≡C-	-C(O)NH ₂
15C	1-hydroxycyclopentyl	-C=C-	-C(O)NH ₂
16C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)NH ₂
17C	1-hydroxycyclohexyl	-C≡C-	-C(O)NH ₂
18C	1-hydroxycyclohexyl	-C=C-	-C(O)NH ₂
19C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)NMe ₂
20C	1-hydroxycyclopentyl	-C≡C-	-C(O)NMe ₂
21C	1-hydroxycyclopentyl	-C=C-	-C(O)NMe ₂
22C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)NMe ₂
23C	1-hydroxycyclohexyl	-C≡C-	-C(O)NMe ₂
24C	1-hydroxycyclohexyl	-C=C-	-C(O)NMe ₂
25C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	5-tetrazolyl
26C	1-hydroxycyclopentyl	-C≡C-	5-tetrazolyl
27C	1-hydroxycyclopentyl	-C=C-	5-tetrazolyl
28C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	5-tetrazolyl
29C	1-hydroxycyclohexyl	-C≡C-	5-tetrazolyl
30C	1-hydroxycyclohexyl	-C=C-	5-tetrazolyl
31C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)-NH-5-tetrazolyl
32C	1-hydroxycyclopentyl	-C≡C-	-C(O)-NH-5-tetrazolyl
33C	1-hydroxycyclopentyl	-C=C-	-C(O)-NH-5-tetrazolyl
34C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)-NH-5-tetrazolyl
35C	1-hydroxycyclohexyl	-C≡C-	-C(O)-NH-5-tetrazolyl

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36C	1-hydroxycyclohexyl	-C=C-	-C(O)-NH-5-tetrazolyl
37C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)NHCH ₂ SO ₂ Me
38C	1-hydroxycyclopentyl	-C≡C-	-C(O)NHCH ₂ SO ₂ Me
39C	1-hydroxycyclopentyl	-C=C-	-C(O)NHCH ₂ SO ₂ Me
40C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)NHCH ₂ SO ₂ Me
41C	1-hydroxycyclohexyl	-C≡C-	-C(O)NHCH ₂ SO ₂ Me
42C	1-hydroxycyclohexyl	-C=C-	-C(O)NHCH ₂ SO ₂ Me
43C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)NHCH ₂ CH ₂ SO ₂ Me
44C	1-hydroxycyclopentyl	-C≡C-	-C(O)NHCH ₂ CH ₂ SO ₂ Me
45C	1-hydroxycyclopentyl	-C=C-	-C(O)NHCH ₂ CH ₂ SO ₂ Me
46C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)NHCH ₂ CH ₂ SO ₂ Me
47C	1-hydroxycyclohexyl	-C≡C-	-C(O)NHCH ₂ CH ₂ SO ₂ Me
48C	1-hydroxycyclohexyl	-C=C-	-C(O)NHCH ₂ CH ₂ SO ₂ Me
49C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)NHSO ₂ Me
50C	1-hydroxycyclopentyl	-C≡C-	-C(O)NHSO ₂ Me
51C	1-hydroxycyclopentyl	-C=C-	-C(O)NHSO ₂ Me
52C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)NHSO ₂ Me
53C	1-hydroxycyclohexyl	-C≡C-	-C(O)NHSO ₂ Me
54C	1-hydroxycyclohexyl	-C=C-	-C(O)NHSO ₂ Me
55C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ -C(O)NHSO ₂ Et
56C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ -C(O)NHSO ₂ Et
57C	1-hydroxycyclopentyl	-C=C-	-CH ₂ -C(O)NHSO ₂ Et
58C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ -C(O)NHSO ₂ Et
59C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ -C(O)NHSO ₂ Et
60C	1-hydroxycyclohexyl	-C=C-	-CH ₂ -C(O)NHSO ₂ Et
61C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ -C(O)NHSO ₂ iPr
62C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ -C(O)NHSO ₂ iPr
63C	1-hydroxycyclopentyl	-C=C-	-CH ₂ -C(O)NHSO ₂ iPr
64C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ -C(O)NHSO ₂ iPr
65C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ -C(O)NHSO ₂ iPr
66C	1-hydroxycyclohexyl	-C=C-	-CH ₂ -C(O)NHSO ₂ iPr

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67C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ -C(O)NHSO ₂ tBu
68C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ -C(O)NHSO ₂ tBu
69C	1-hydroxycyclopentyl	-C=C-	-CH ₂ -C(O)NHSO ₂ tBu
70C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ -C(O)NHSO ₂ tBu
71C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ -C(O)NHSO ₂ tBu
72C	1-hydroxycyclohexyl	-C=C-	-CH ₂ -C(O)NHSO ₂ tBu
73C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ Me
74C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ NHSO ₂ Me
75C	1-hydroxycyclopentyl	-C=C-	-CH ₂ NHSO ₂ Me
76C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ Me
77C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ NHSO ₂ Me
78C	1-hydroxycyclohexyl	-C=C-	-CH ₂ NHSO ₂ Me
79C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ Et
80C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ NHSO ₂ Et
81C	1-hydroxycyclopentyl	-C=C-	-CH ₂ NHSO ₂ Et
82C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ Et
83C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ NHSO ₂ Et
84C	1-hydroxycyclohexyl	-C=C-	-CH ₂ NHSO ₂ Et
85C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ iPr
86C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ NHSO ₂ iPr
87C	1-hydroxycyclopentyl	-C=C-	-CH ₂ NHSO ₂ iPr
88C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ iPr
89C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ NHSO ₂ iPr
90C	1-hydroxycyclohexyl	-C=C-	-CH ₂ NHSO ₂ iPr
91C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ tBu
92C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ NHSO ₂ tBu
93C	1-hydroxycyclopentyl	-C=C-	-CH ₂ NHSO ₂ tBu
94C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ NHSO ₂ tBu
95C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ NHSO ₂ tBu
96C	1-hydroxycyclohexyl	-C=C-	-CH ₂ NHSO ₂ tBu
97C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ -N-pyrrolidin-2-one

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98C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ -N-pyrrolidin-2-one
99C	1-hydroxycyclopentyl	-C=C-	-CH ₂ -N-pyrrolidin-2-one
100C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ -N-pyrrolidin-2-one
101C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ -N-pyrrolidin-2-one
102C	1-hydroxycyclohexyl	-C=C-	-CH ₂ -N-pyrrolidin-2-one
103C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
104C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
105C	1-hydroxycyclopentyl	-C=C-	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
106C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
107C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
108C	1-hydroxycyclohexyl	-C=C-	-CH ₂ -(1-methylpyrrolidin-2-one-3-yl)
109C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CO ₂ Me
110C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CO ₂ Me
111C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CO ₂ Me
112C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CO ₂ Me
113C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CO ₂ Me
114C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CO ₂ Me
115C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CO ₂ H
116C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CO ₂ H
117C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CO ₂ H
118C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CO ₂ H
119C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CO ₂ H
120C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CO ₂ H
121C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ C(O)NH ₂
122C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ C(O)NH ₂
123C	1-hydroxycyclopentyl	-C=C-	-CH ₂ C(O)NH ₂
124C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ C(O)NH ₂
125C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ C(O)NH ₂
126C	1-hydroxycyclohexyl	-C=C-	-CH ₂ C(O)NH ₂
127C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ C(O)NMe ₂
128C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ C(O)NMe ₂

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129C	1-hydroxycyclopentyl	-C=C-	-CH ₂ C(O)NMe ₂
130C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ C(O)NMe ₂
131C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ C(O)NMe ₂
132C	1-hydroxycyclohexyl	-C=C-	-CH ₂ C(O)NMe ₂
133C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ C(O)-N-pyrrolidine
134C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ C(O)-N-pyrrolidine
135C	1-hydroxycyclopentyl	-C=C-	-CH ₂ C(O)-N-pyrrolidine
136C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ C(O)-N-pyrrolidine
137C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ C(O)-N-pyrrolidine
138C	1-hydroxycyclohexyl	-C=C-	-CH ₂ C(O)-N-pyrrolidine
139C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ -5-tetrazolyl
140C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ -5-tetrazolyl
141C	1-hydroxycyclopentyl	-C=C-	-CH ₂ -5-tetrazolyl
142C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ -5-tetrazolyl
143C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ -5-tetrazolyl
144C	1-hydroxycyclohexyl	-C=C-	-CH ₂ -5-tetrazolyl
145C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)C(O)OH
146C	1-hydroxycyclopentyl	-C≡C-	-C(O)C(O)OH
147C	1-hydroxycyclopentyl	-C=C-	-C(O)C(O)OH
148C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)C(O)OH
149C	1-hydroxycyclohexyl	-C≡C-	-C(O)C(O)OH
150C	1-hydroxycyclohexyl	-C=C-	-C(O)C(O)OH
151C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH(OH)C(O)OH
152C	1-hydroxycyclopentyl	-C≡C-	-CH(OH)C(O)OH
153C	1-hydroxycyclopentyl	-C=C-	-CH(OH)C(O)OH
154C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH(OH)C(O)OH
155C	1-hydroxycyclohexyl	-C≡C-	-CH(OH)C(O)OH
156C	1-hydroxycyclohexyl	-C=C-	-CH(OH)C(O)OH
157C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)C(O)NH ₂
158C	1-hydroxycyclopentyl	-C≡C-	-C(O)C(O)NH ₂
159C	1-hydroxycyclopentyl	-C=C-	-C(O)C(O)NH ₂

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160C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)C(O)NH ₂
161C	1-hydroxycyclohexyl	-C≡C-	-C(O)C(O)NH ₂
162C	1-hydroxycyclohexyl	-C=C-	-C(O)C(O)NH ₂
163C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH(OH)C(O)NH ₂
164C	1-hydroxycyclopentyl	-C≡C-	-CH(OH)C(O)NH ₂
165C	1-hydroxycyclopentyl	-C=C-	-CH(OH)C(O)NH ₂
166C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH(OH)C(O)NH ₂
167C	1-hydroxycyclohexyl	-C≡C-	-CH(OH)C(O)NH ₂
168C	1-hydroxycyclohexyl	-C=C-	-CH(OH)C(O)NH ₂
169C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)C(O)NMe ₂
170C	1-hydroxycyclopentyl	-C≡C-	-C(O)C(O)NMe ₂
171C	1-hydroxycyclopentyl	-C=C-	-C(O)C(O)NMe ₂
172C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)C(O)NMe ₂
173C	1-hydroxycyclohexyl	-C≡C-	-C(O)C(O)NMe ₂
174C	1-hydroxycyclohexyl	-C=C-	-C(O)C(O)NMe ₂
175C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH(OH)C(O)NMe ₂
176C	1-hydroxycyclopentyl	-C≡C-	-CH(OH)C(O)NMe ₂
177C	1-hydroxycyclopentyl	-C=C-	-CH(OH)C(O)NMe ₂
178C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH(OH)C(O)NMe ₂
179C	1-hydroxycyclohexyl	-C≡C-	-CH(OH)C(O)NMe ₂
180C	1-hydroxycyclohexyl	-C=C-	-CH(OH)C(O)NMe ₂
181C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CO ₂ H
182C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ CO ₂ H
183C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ CO ₂ H
184C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CO ₂ H
185C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ CO ₂ H
186C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ CO ₂ H
187C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ C(O)NH ₂
188C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ C(O)NH ₂
189C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ C(O)NH ₂
190C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ C(O)NH ₂

191C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ C(O)NH ₂
192C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ C(O)NH ₂
193C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ C(O)NMe ₂
194C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ C(O)NMe ₂
195C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ C(O)NMe ₂
196C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ C(O)NMe ₂
197C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ C(O)NMe ₂
198C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ C(O)NMe ₂
199C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ -5-tetrazolyl
200C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ -5-tetrazolyl
201C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ -5-tetrazolyl
202C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ -5-tetrazolyl
203C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ -5-tetrazolyl
204C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ -5-tetrazolyl
205C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ Me
206C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ S(O) ₂ Me
207C	1-hydroxycyclopentyl	-C=C-	-CH ₂ S(O) ₂ Me
208C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ Me
209C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ S(O) ₂ Me
210C	1-hydroxycyclohexyl	-C=C-	-CH ₂ S(O) ₂ Me
211C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ Me
212C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ Me
213C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ Me
214C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ Me
215C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ Me
216C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ Me
217C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
218C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
219C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
220C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
221C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me

222C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Me
223C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ Et
224C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ S(O) ₂ Et
225C	1-hydroxycyclopentyl	-C=C-	-CH ₂ S(O) ₂ Et
226C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ Et
227C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ S(O) ₂ Et
228C	1-hydroxycyclohexyl	-C=C-	-CH ₂ S(O) ₂ Et
229C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ Et
230C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ Et
231C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ Et
232C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ Et
233C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ Et
234C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ Et
235C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
236C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
237C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
238C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
239C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
240C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ Et
241C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ iPr
242C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ S(O) ₂ iPr
243C	1-hydroxycyclopentyl	-C=C-	-CH ₂ S(O) ₂ iPr
244C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ iPr
245C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ S(O) ₂ iPr
246C	1-hydroxycyclohexyl	-C=C-	-CH ₂ S(O) ₂ iPr
247C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ iPr
248C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ iPr
249C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ iPr
250C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ iPr
251C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ iPr
252C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ iPr

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253C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ tBu
254C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ S(O) ₂ tBu
255C	1-hydroxycyclopentyl	-C=C-	-CH ₂ S(O) ₂ tBu
256C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ S(O) ₂ tBu
257C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ S(O) ₂ tBu
258C	1-hydroxycyclohexyl	-C=C-	-CH ₂ S(O) ₂ tBu
259C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ tBu
260C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ tBu
261C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ tBu
262C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ tBu
263C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ tBu
264C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ tBu
265C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ NH ₂
266C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ NH ₂
267C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ NH ₂
268C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ NH ₂
269C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ NH ₂
270C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ NH ₂
271C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ NMe ₂
272C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ NMe ₂
273C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ NMe ₂
274C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ S(O) ₂ NMe ₂
275C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ S(O) ₂ NMe ₂
276C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ S(O) ₂ NMe ₂
277C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)CH ₂ S(O) ₂ Me
278C	1-hydroxycyclopentyl	-C≡C-	-C(O)CH ₂ S(O) ₂ Me
279C	1-hydroxycyclopentyl	-C=C-	-C(O)CH ₂ S(O) ₂ Me
280C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)CH ₂ S(O) ₂ Me
281C	1-hydroxycyclohexyl	-C≡C-	-C(O)CH ₂ S(O) ₂ Me
282C	1-hydroxycyclohexyl	-C=C-	-C(O)CH ₂ S(O) ₂ Me
283C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)CH ₂ CH ₂ S(O) ₂ Me

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284C	1-hydroxycyclopentyl	-C≡C-	-C(O)CH ₂ CH ₂ S(O) ₂ Me
285C	1-hydroxycyclopentyl	-C=C-	-C(O)CH ₂ CH ₂ S(O) ₂ Me
286C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)CH ₂ CH ₂ S(O) ₂ Me
287C	1-hydroxycyclohexyl	-C≡C-	-C(O)CH ₂ CH ₂ S(O) ₂ Me
288C	1-hydroxycyclohexyl	-C=C-	-C(O)CH ₂ CH ₂ S(O) ₂ Me
289C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
290C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
291C	1-hydroxycyclopentyl	-C=C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
292C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
293C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
294C	1-hydroxycyclohexyl	-C=C-	-CH ₂ CH ₂ CH ₂ S(O) ₂ NH ₂
295C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-S(O) ₂ Me
296C	1-hydroxycyclopentyl	-C≡C-	-S(O) ₂ Me
297C	1-hydroxycyclopentyl	-C=C-	-S(O) ₂ Me
298C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-S(O) ₂ Me
299C	1-hydroxycyclohexyl	-C≡C-	-S(O) ₂ Me
300C	1-hydroxycyclohexyl	-C=C-	-S(O) ₂ Me
301C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-S(O) ₂ Et
302C	1-hydroxycyclopentyl	-C≡C-	-S(O) ₂ Et
303C	1-hydroxycyclopentyl	-C=C-	-S(O) ₂ Et
304C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-S(O) ₂ Et
305C	1-hydroxycyclohexyl	-C≡C-	-S(O) ₂ Et
306C	1-hydroxycyclohexyl	-C=C-	-S(O) ₂ Et
307C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-S(O) ₂ iPr
308C	1-hydroxycyclopentyl	-C≡C-	-S(O) ₂ iPr
309C	1-hydroxycyclopentyl	-C=C-	-S(O) ₂ iPr
310C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-S(O) ₂ iPr
311C	1-hydroxycyclohexyl	-C≡C-	-S(O) ₂ iPr
312C	1-hydroxycyclohexyl	-C=C-	-S(O) ₂ iPr
313C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-S(O) ₂ tBu
314C	1-hydroxycyclopentyl	-C≡C-	-S(O) ₂ tBu

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315C	1-hydroxycyclopentyl	-C=C-	-S(O)2tBu
316C	1-hydroxycyclohexyl	-(CH2)2-	-S(O)2tBu
317C	1-hydroxycyclohexyl	-C≡C-	-S(O)2tBu
318C	1-hydroxycyclohexyl	-C=C-	-S(O)2tBu
319C	1-hydroxycyclopentyl	-(CH2)2-	-S(O)2NH2
320C	1-hydroxycyclopentyl	-C≡C-	-S(O)2NH2
321C	1-hydroxycyclopentyl	-C=C-	-S(O)2NH2
322C	1-hydroxycyclohexyl	-(CH2)2-	-S(O)2NH2
323C	1-hydroxycyclohexyl	-C≡C-	-S(O)2NH2
324C	1-hydroxycyclohexyl	-C=C-	-S(O)2NH2
325C	1-hydroxycyclopentyl	-(CH2)2-	-S(O)2NMe2
326C	1-hydroxycyclopentyl	-C≡C-	-S(O)2NMe2
327C	1-hydroxycyclopentyl	-C=C-	-S(O)2NMe2
328C	1-hydroxycyclohexyl	-(CH2)2-	-S(O)2NMe2
329C	1-hydroxycyclohexyl	-C≡C-	-S(O)2NMe2
330C	1-hydroxycyclohexyl	-C=C-	-S(O)2NMe2
331C	1-hydroxycyclopentyl	-(CH2)2-	-S(O)2CH2S(O)2Me
332C	1-hydroxycyclopentyl	-C≡C-	-S(O)2CH2S(O)2Me
333C	1-hydroxycyclopentyl	-C=C-	-S(O)2CH2S(O)2Me
334C	1-hydroxycyclohexyl	-(CH2)2-	-S(O)2CH2S(O)2Me
335C	1-hydroxycyclohexyl	-C≡C-	-S(O)2CH2S(O)2Me
336C	1-hydroxycyclohexyl	-C=C-	-S(O)2CH2S(O)2Me
337C	1-hydroxycyclopentyl	-(CH2)2-	-S(O)2CH2S(O)2Et
338C	1-hydroxycyclopentyl	-C≡C-	-S(O)2CH2S(O)2Et
339C	1-hydroxycyclopentyl	-C=C-	-S(O)2CH2S(O)2Et
340C	1-hydroxycyclohexyl	-(CH2)2-	-S(O)2CH2S(O)2Et
341C	1-hydroxycyclohexyl	-C≡C-	-S(O)2CH2S(O)2Et
342C	1-hydroxycyclohexyl	-C=C-	-S(O)2CH2S(O)2Et
343C	1-hydroxycyclopentyl	-(CH2)2-	-S(O)2CH2S(O)2iPr
344C	1-hydroxycyclopentyl	-C≡C-	-S(O)2CH2S(O)2iPr
345C	1-hydroxycyclopentyl	-C=C-	-S(O)2CH2S(O)2iPr

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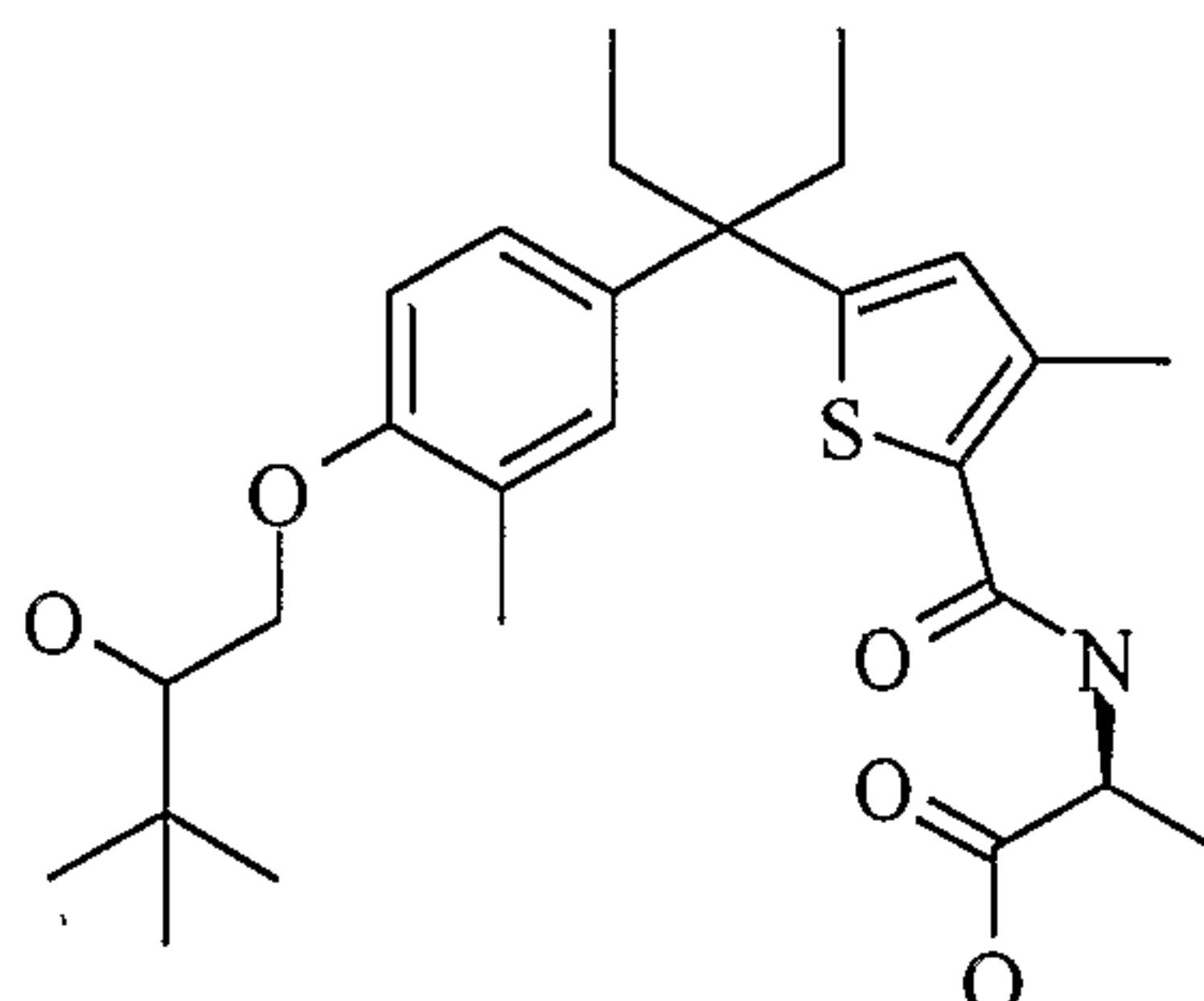
346C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-S(O) ₂ CH ₂ S(O) ₂ iPr
347C	1-hydroxycyclohexyl	-C≡C-	-S(O) ₂ CH ₂ S(O) ₂ iPr
348C	1-hydroxycyclohexyl	-C=C-	-S(O) ₂ CH ₂ S(O) ₂ iPr
349C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-S(O) ₂ CH ₂ S(O) ₂ tBu
350C	1-hydroxycyclopentyl	-C≡C-	-S(O) ₂ CH ₂ S(O) ₂ tBu
351C	1-hydroxycyclopentyl	-C=C-	-S(O) ₂ CH ₂ S(O) ₂ tBu
352C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-S(O) ₂ CH ₂ S(O) ₂ tBu
353C	1-hydroxycyclohexyl	-C≡C-	-S(O) ₂ CH ₂ S(O) ₂ tBu
354C	1-hydroxycyclohexyl	-C=C-	-S(O) ₂ CH ₂ S(O) ₂ tBu
355C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-C(O)NHCH ₂ CO ₂ H
356C	1-hydroxycyclopentyl	-C≡C-	-C(O)NHCH ₂ CO ₂ H
357C	1-hydroxycyclopentyl	-C=C-	-C(O)NHCH ₂ CO ₂ H
358C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-C(O)NHCH ₂ CO ₂ H
359C	1-hydroxycyclohexyl	-C≡C-	-C(O)NHCH ₂ CO ₂ H
360C	1-hydroxycyclohexyl	-C=C-	-C(O)NHCH ₂ CO ₂ H
361C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-SO ₂ NHCH ₂ CO ₂ H
362C	1-hydroxycyclopentyl	-C≡C-	-SO ₂ NHCH ₂ CO ₂ H
363C	1-hydroxycyclopentyl	-C=C-	-SO ₂ NHCH ₂ CO ₂ H
364C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-SO ₂ NHCH ₂ CO ₂ H
365C	1-hydroxycyclohexyl	-C≡C-	-SO ₂ NHCH ₂ CO ₂ H
366C	1-hydroxycyclohexyl	-C=C-	-SO ₂ NHCH ₂ CO ₂ H
367C	1-hydroxycyclopentyl	-(CH ₂) ₂ -	-CH ₂ -S-Me
368C	1-hydroxycyclopentyl	-C≡C-	-CH ₂ -S-Me
369C	1-hydroxycyclopentyl	-C=C-	-CH ₂ -S-Me
370C	1-hydroxycyclohexyl	-(CH ₂) ₂ -	-CH ₂ -S-Me
371C	1-hydroxycyclohexyl	-C≡C-	-CH ₂ -S-Me
372C	1-hydroxycyclohexyl	-C=C-	-CH ₂ -S-Me

Particularly preferred chemical species of the invention are represented by structural formulae P101 to P106 and P200 to P206 a pharmaceutically acceptable salt solvate or prodrug derivative thereof:

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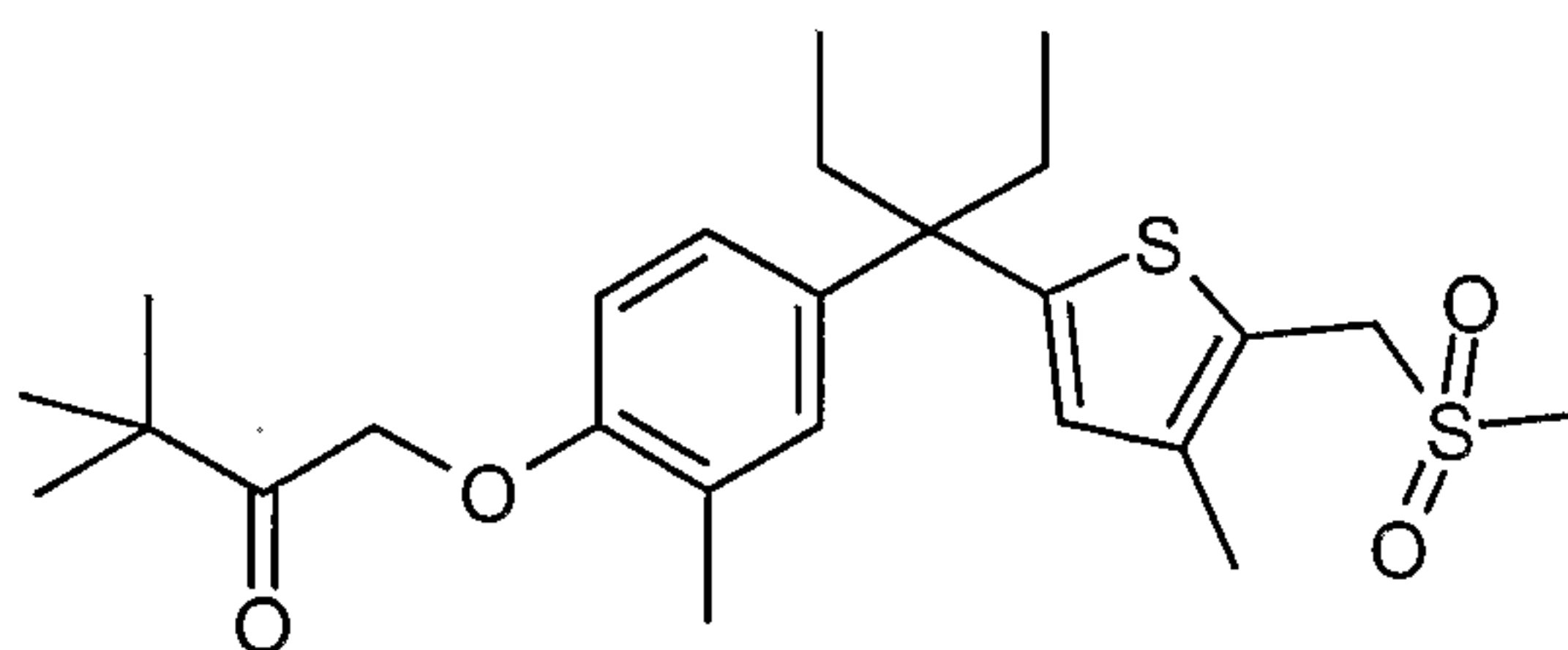
For treatment of psoriasis, preferred compounds are those defined by structural formulae P100 to P106 as follows:

P100

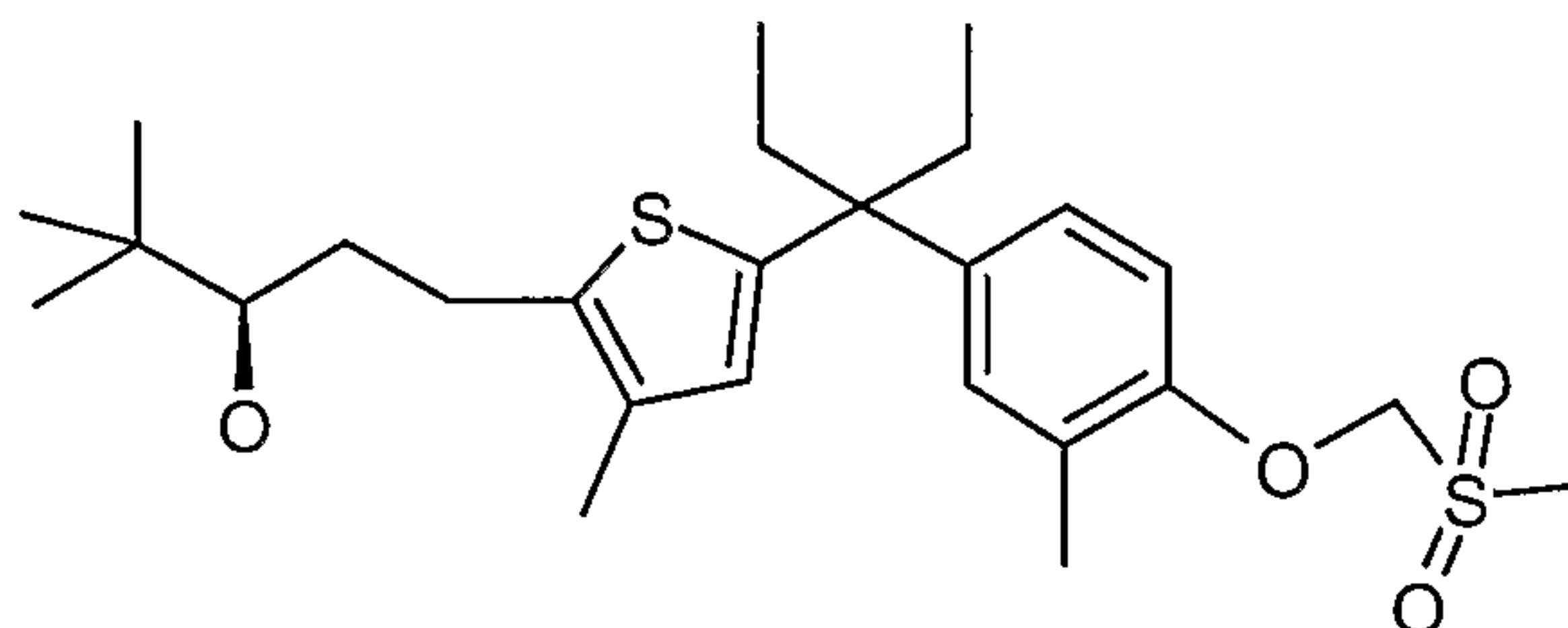


5

P101

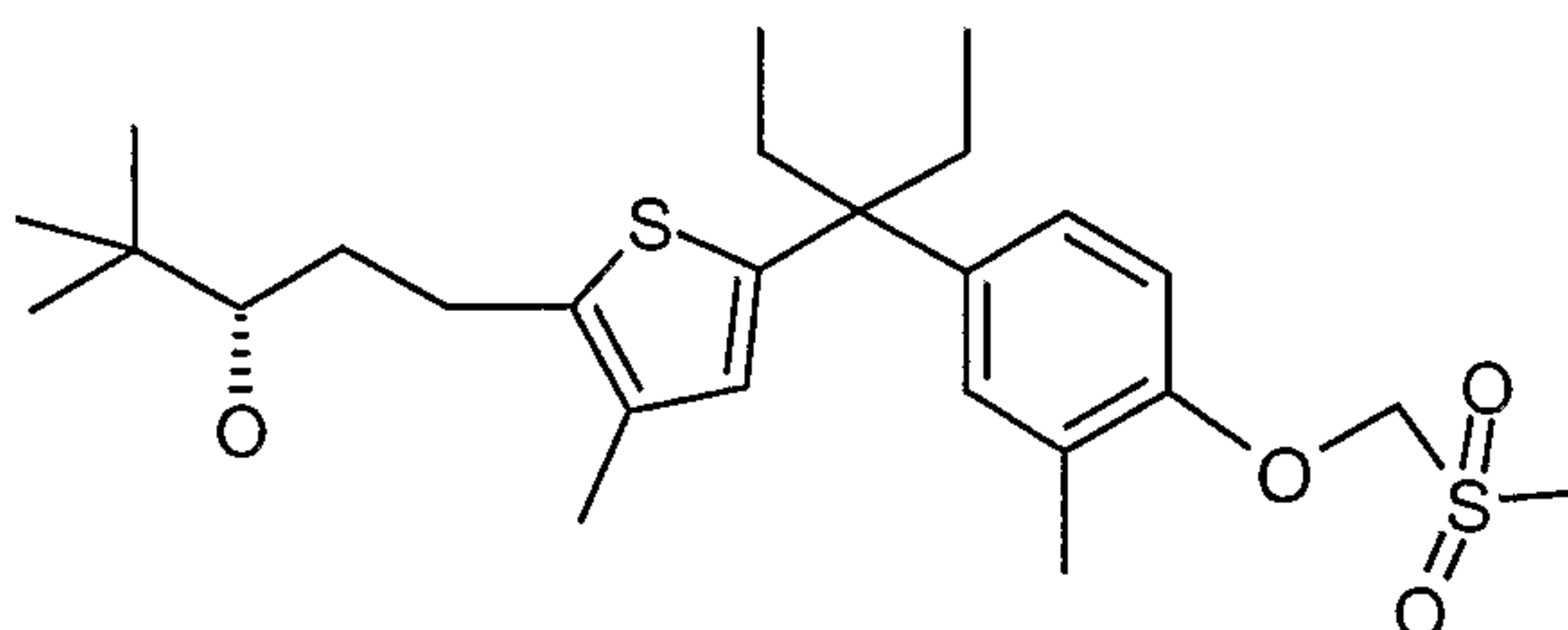


P102



10

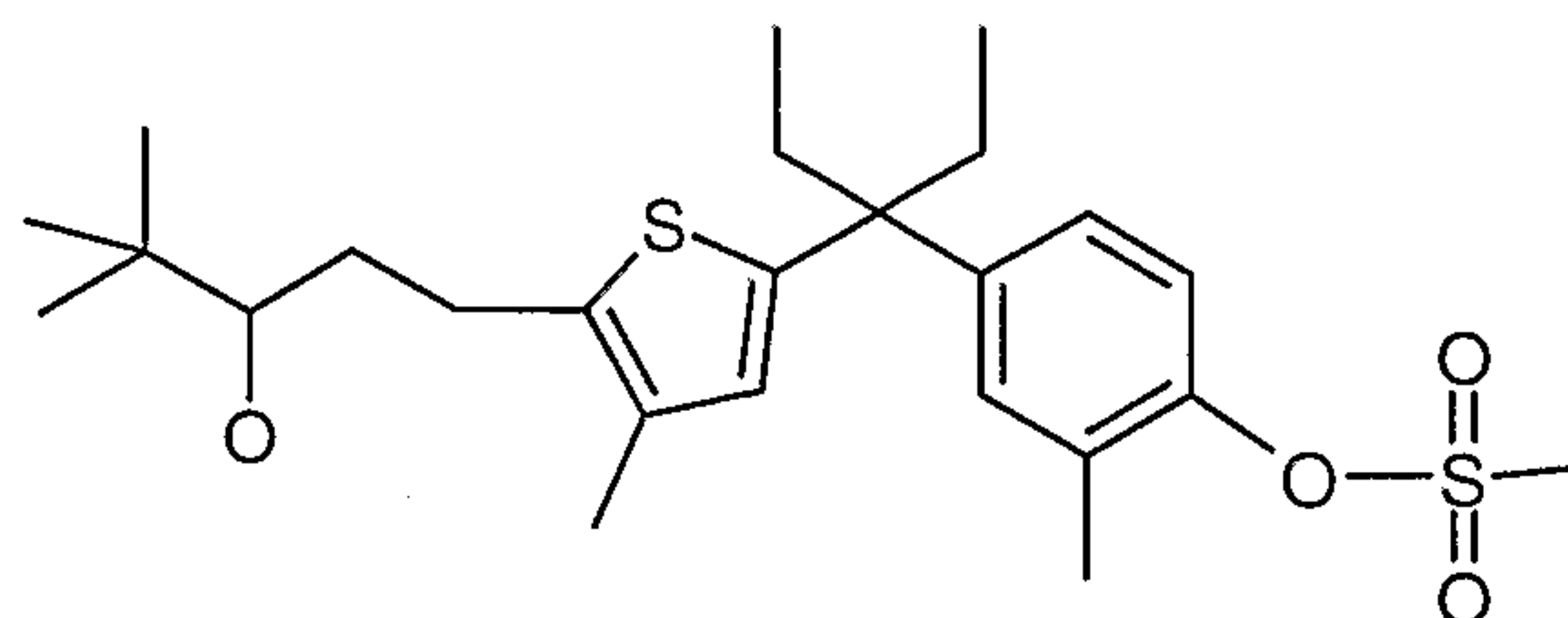
P103



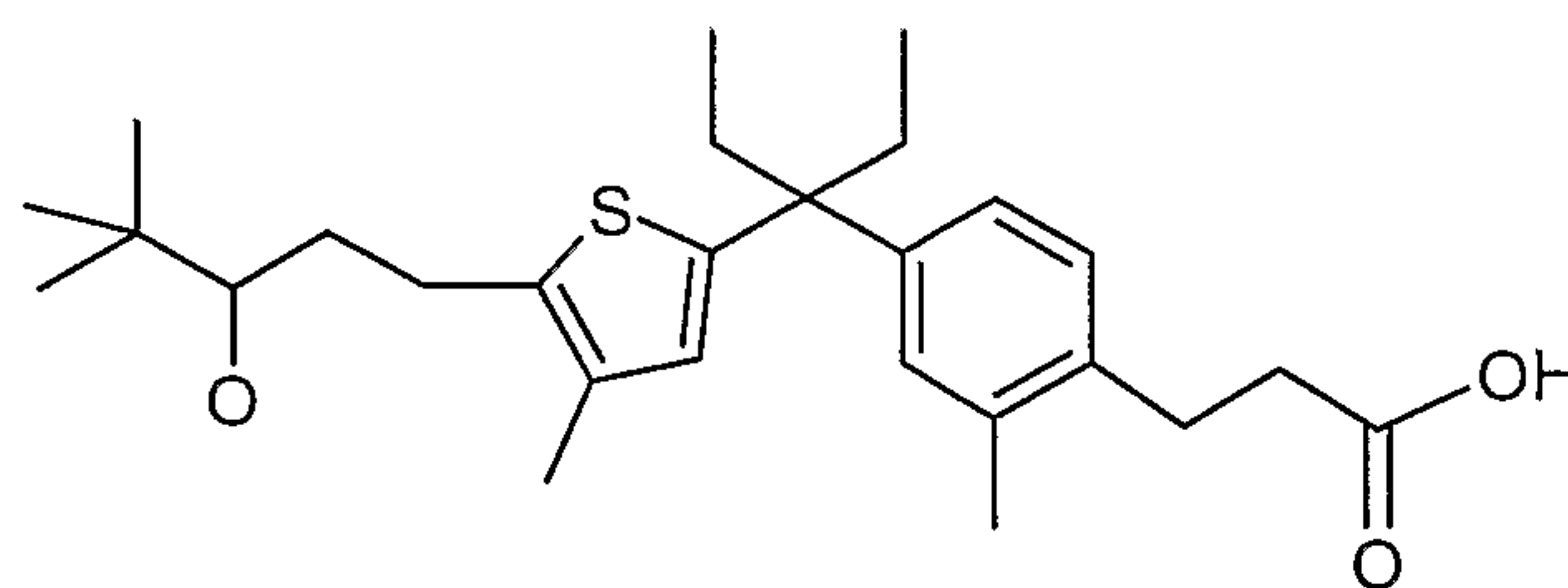
15

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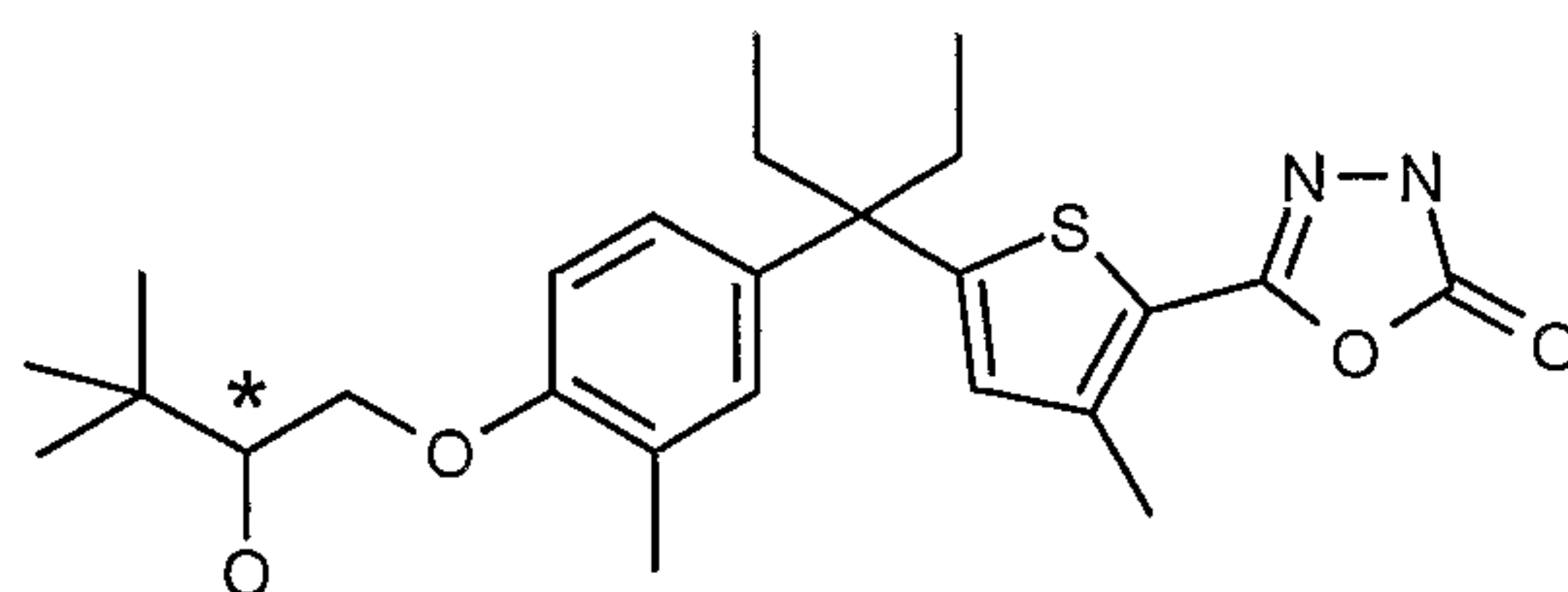
P104



P105

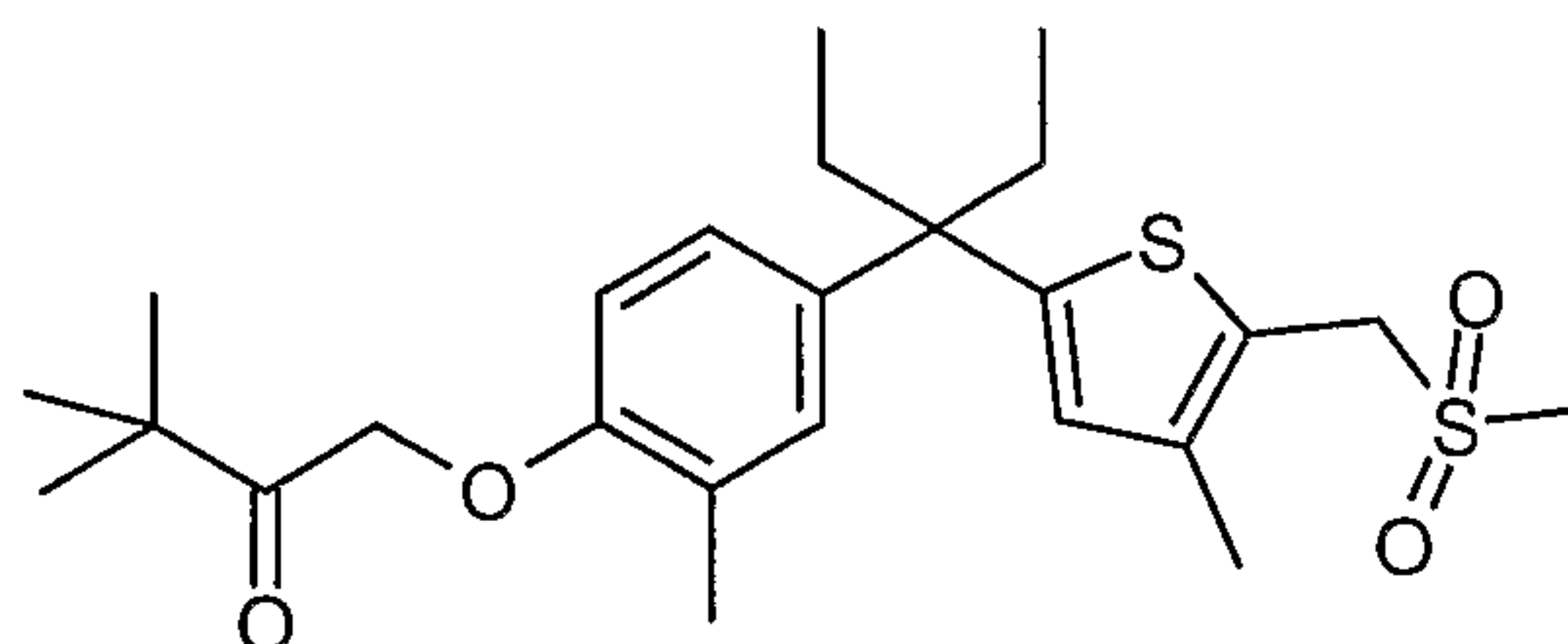


5 P106

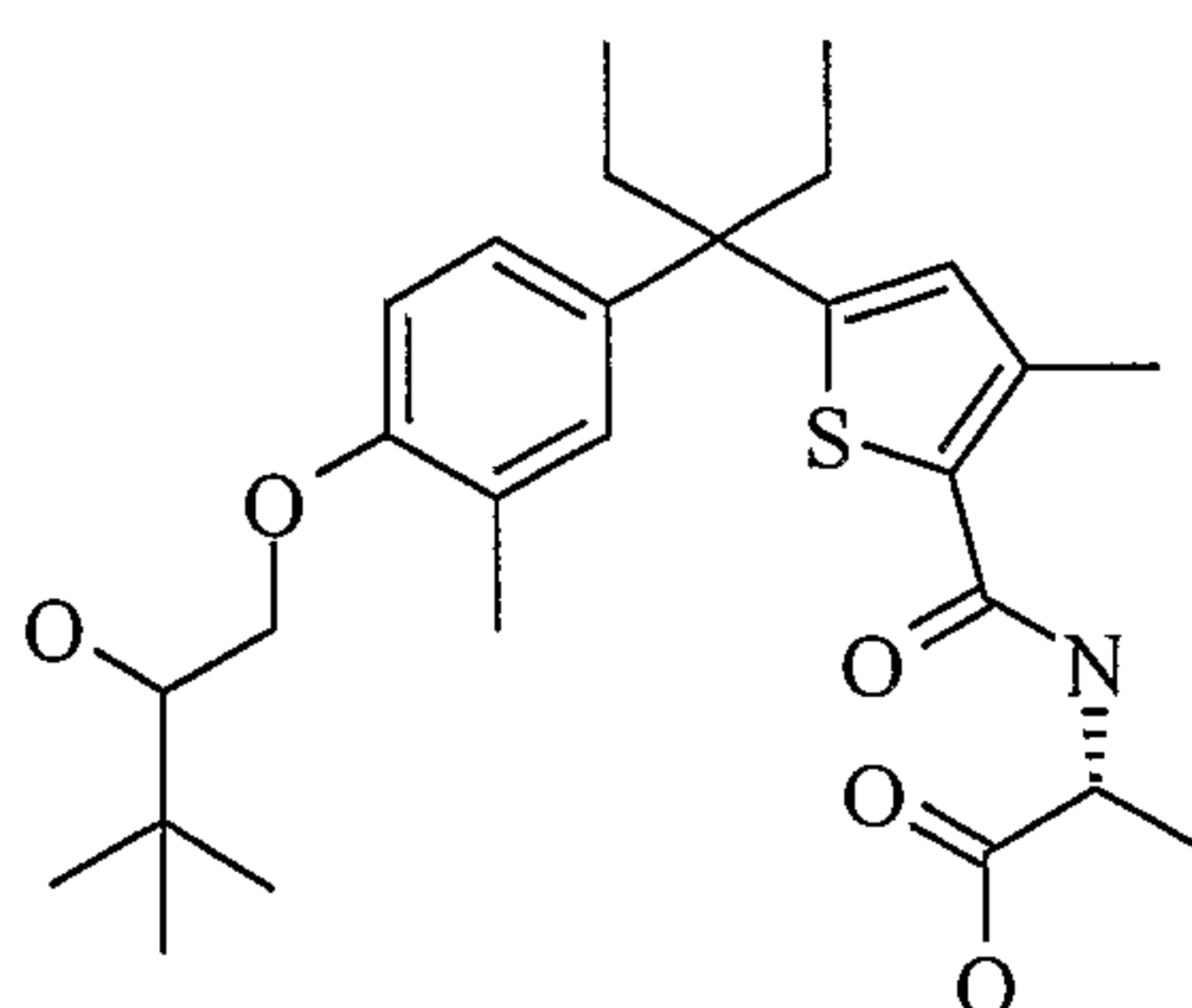


For treatment of osteoporosis, preferred compounds are those defined by structural formulae P101 and P200 to P206, as follows:

10 P101

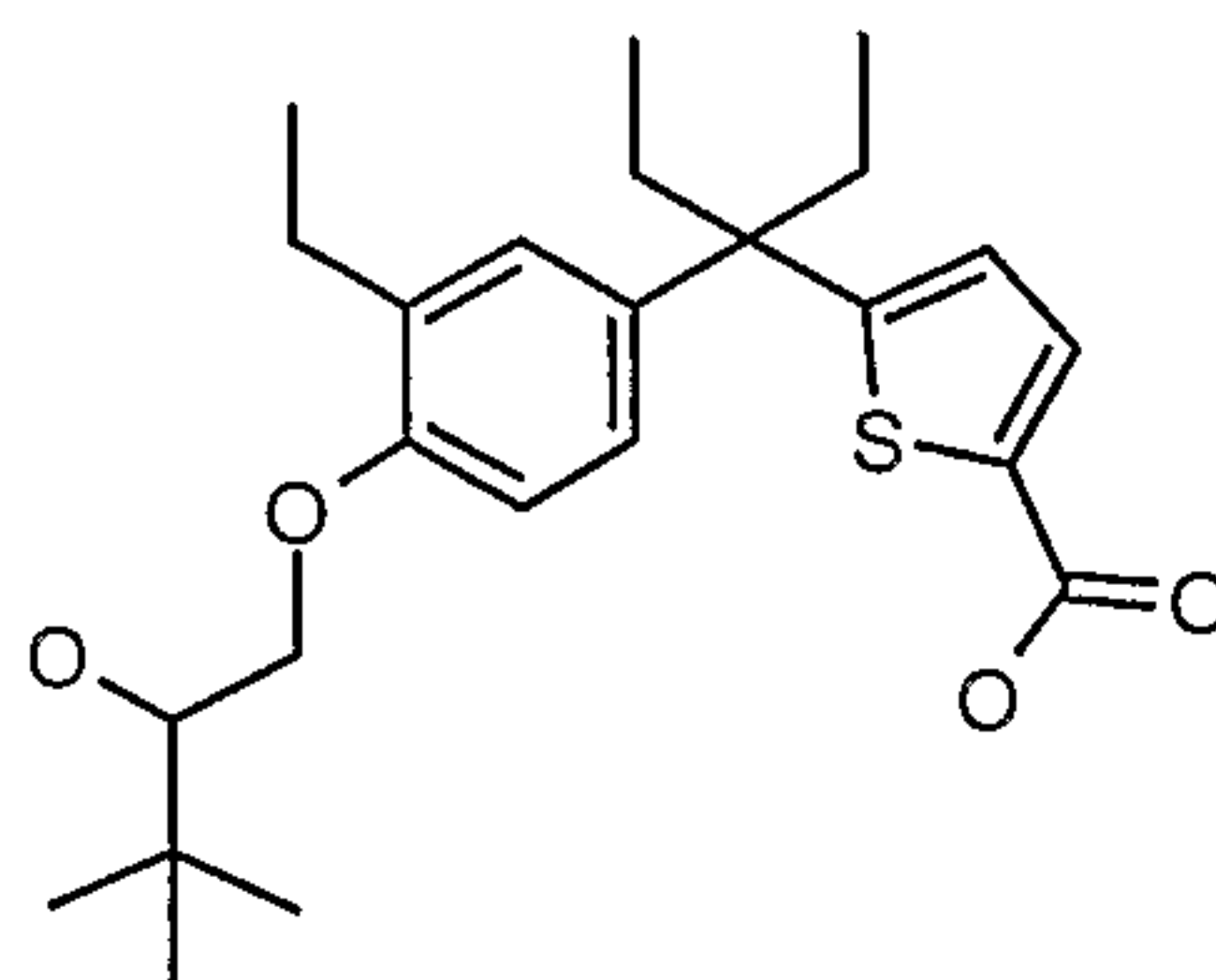


P200

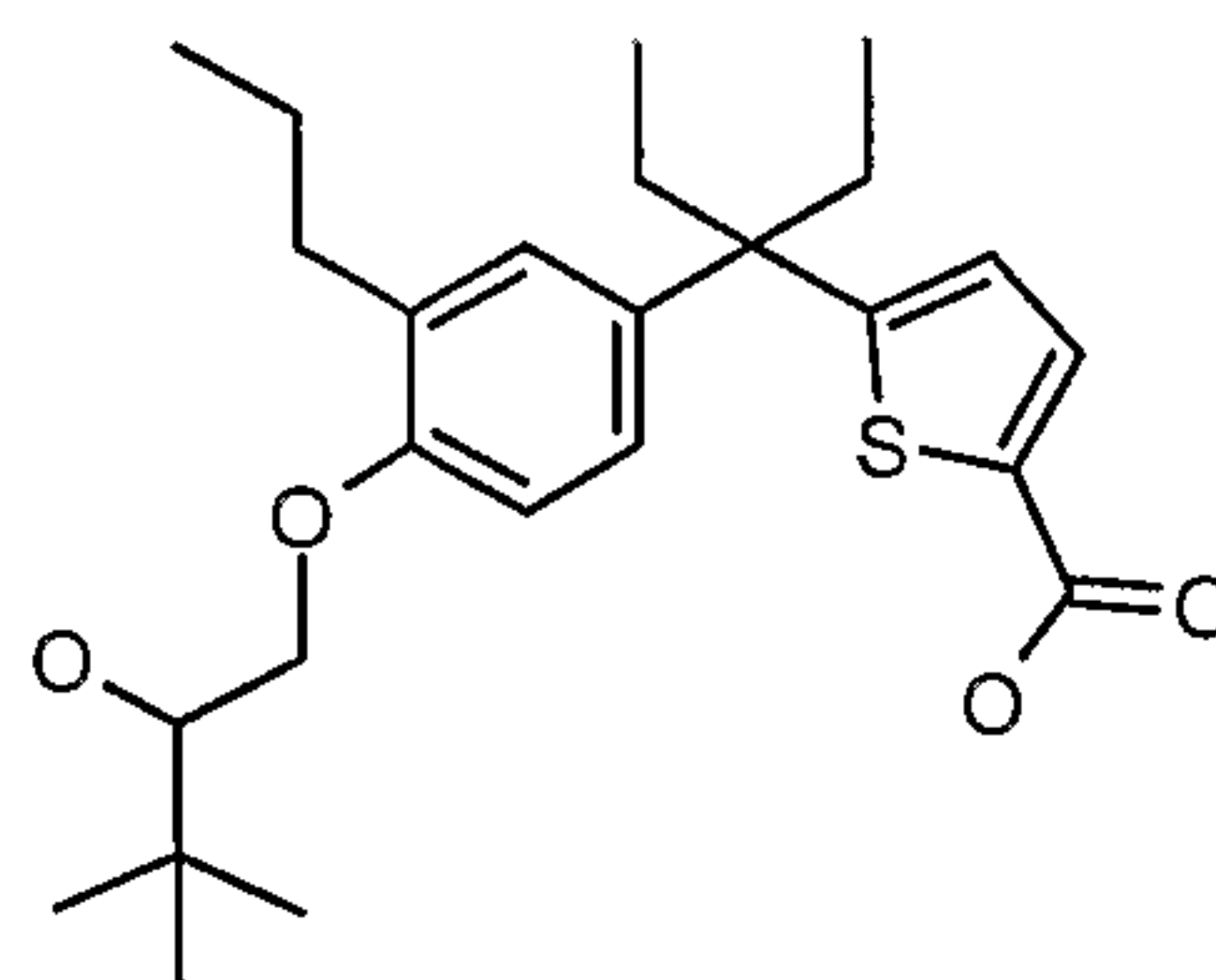


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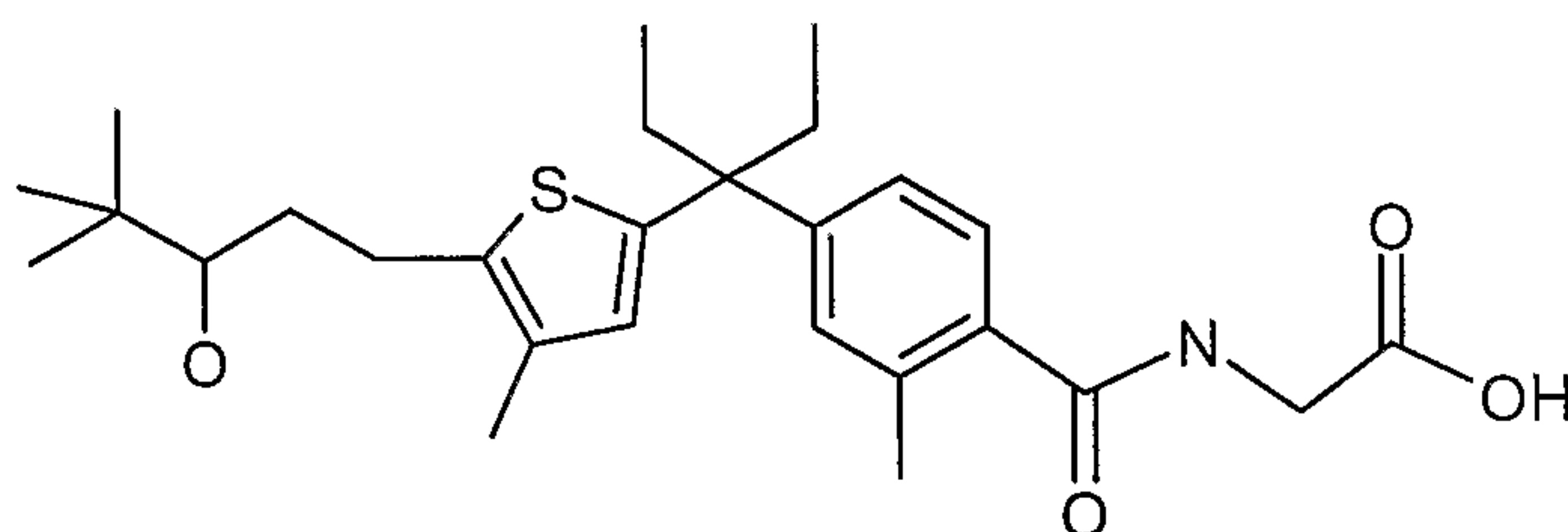
P201



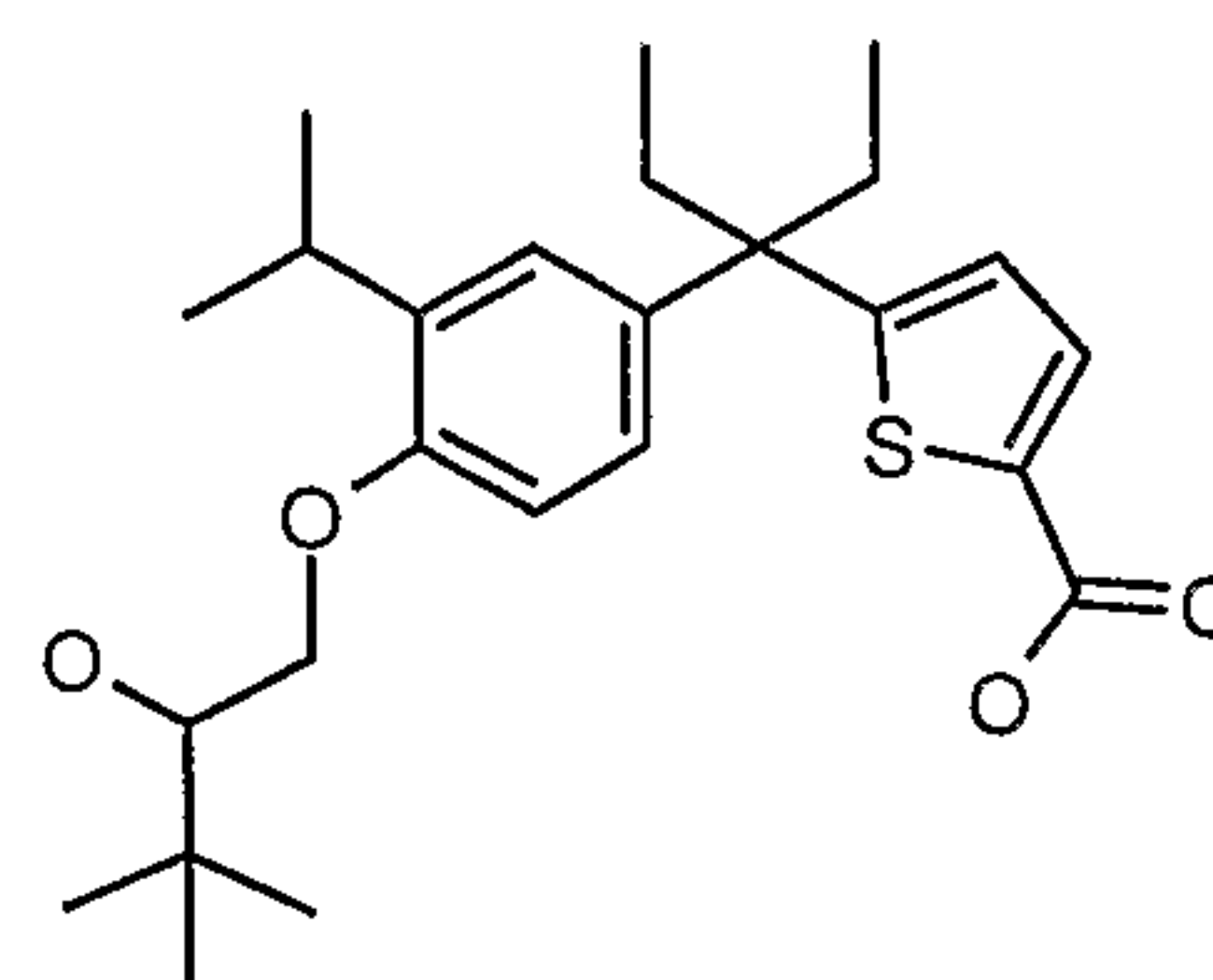
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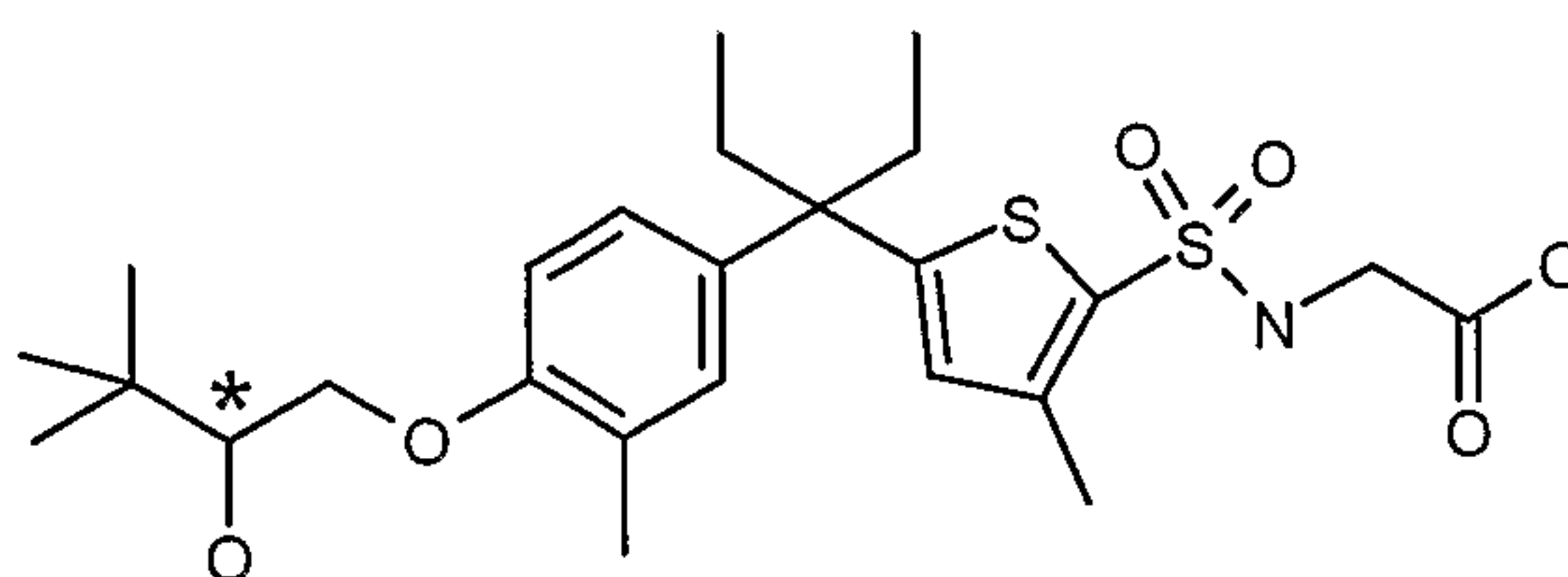
5 P203



P204



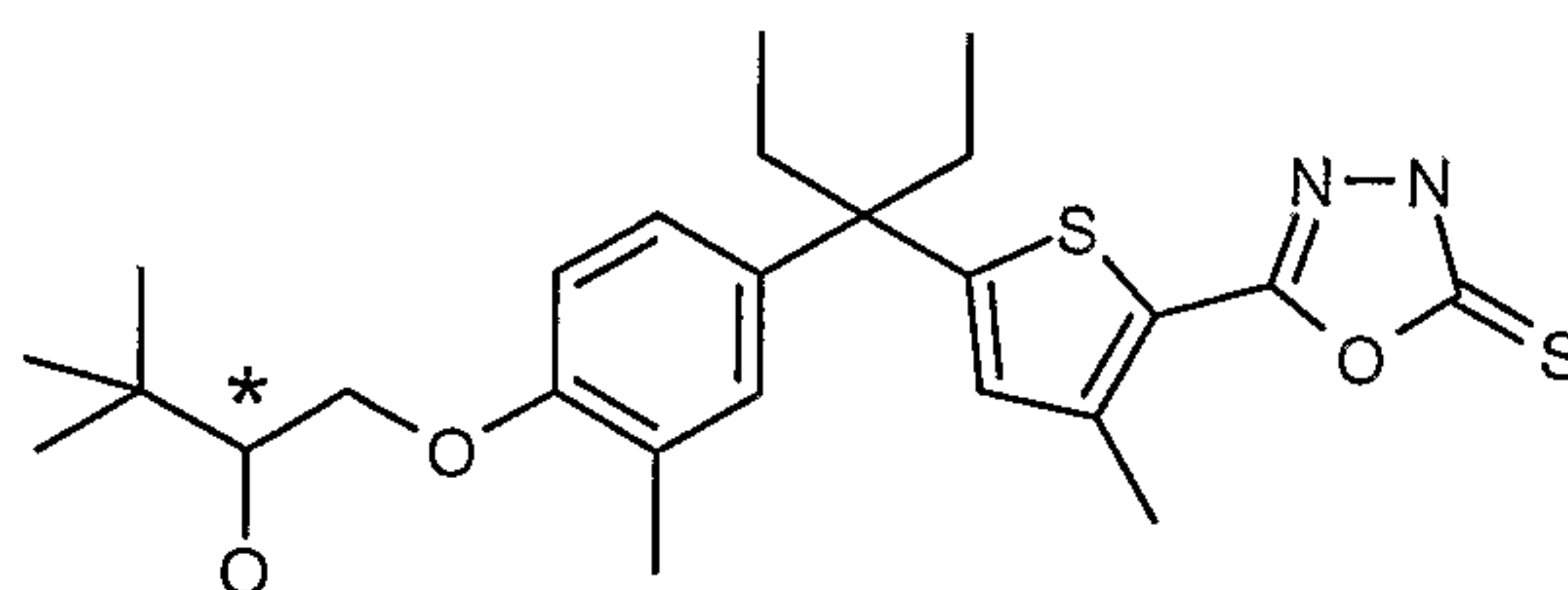
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The salts of the Active Ingredients are an additional aspect of the invention. The skilled artisan will also appreciate that the family of compounds include acidic and basic members and that the present invention includes pharmaceutically acceptable salts thereof.

In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, ammonium, calcium, magnesium, aluminum, zinc, and the like. Sodium and potassium salts are particularly preferred. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin. For example, a carboxylic acid substituent on the compound of Formula I may be selected as $-CO_2H$ and salts may be formed by reaction with appropriate bases (e.g., NaOH, KOH) to yield the corresponding sodium and potassium salt.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, choline, clavulanate, citrate, chloride, chloroprocaine, choline, diethanolamine, dihydrochloride, diphosphate, edetate, edisylate, estolate, esylate, ethylenediamine, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, bromide, chloride, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate,

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malseate, mandelate, meglumine, mesylate, mesviate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pamoate, pantothenate, phosphate, polygalacturonate, procane, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, and all tautomers are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a chiral column may be used such as those sold by Daicel Chemical Industries identified by the trademarks: CHIRALPAK AD, CHIRALPAK AS, CHIRALPAK OD, CHIRALPAK OJ, CHIRALPAK OA, CHIRALPAK OB, CHIRALPAK OC, CHIRALPAK OF, CHIRALPAK OG, CHIRALPAK OK, and CHIRALPAK CA-1.

By another conventional method, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers. These diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

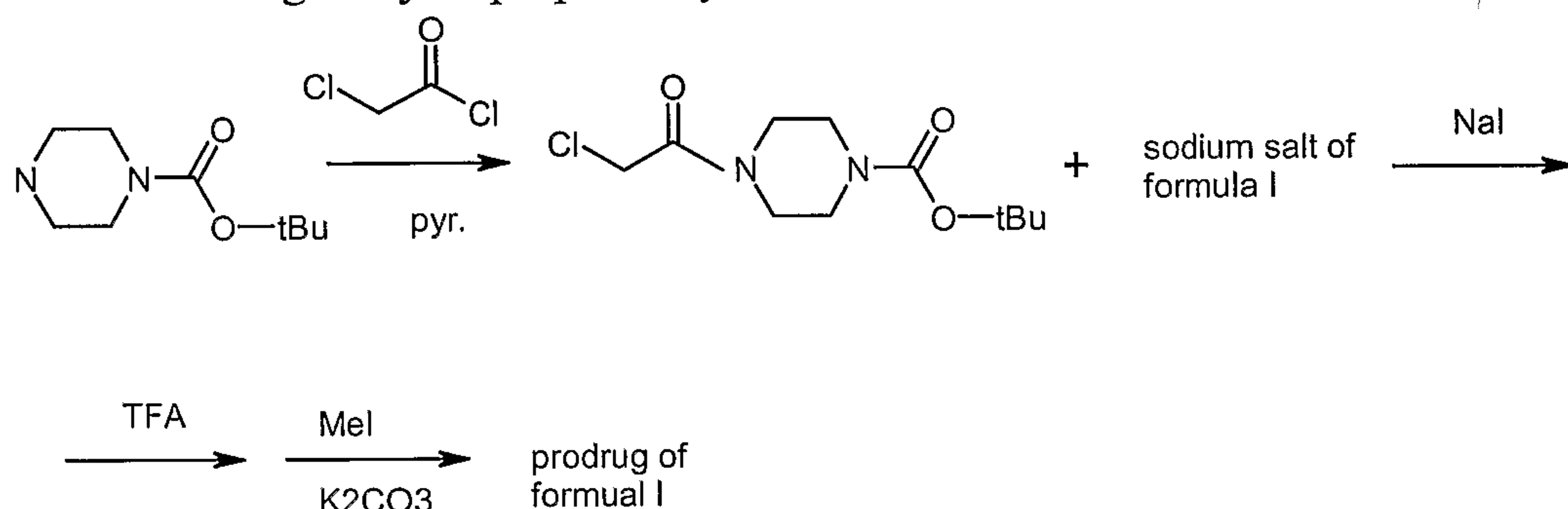
The present invention is also embodied in mixtures of Active Ingredients.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base

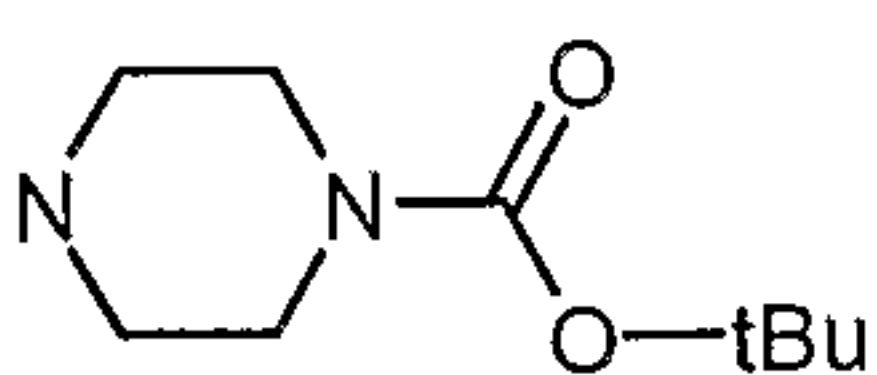
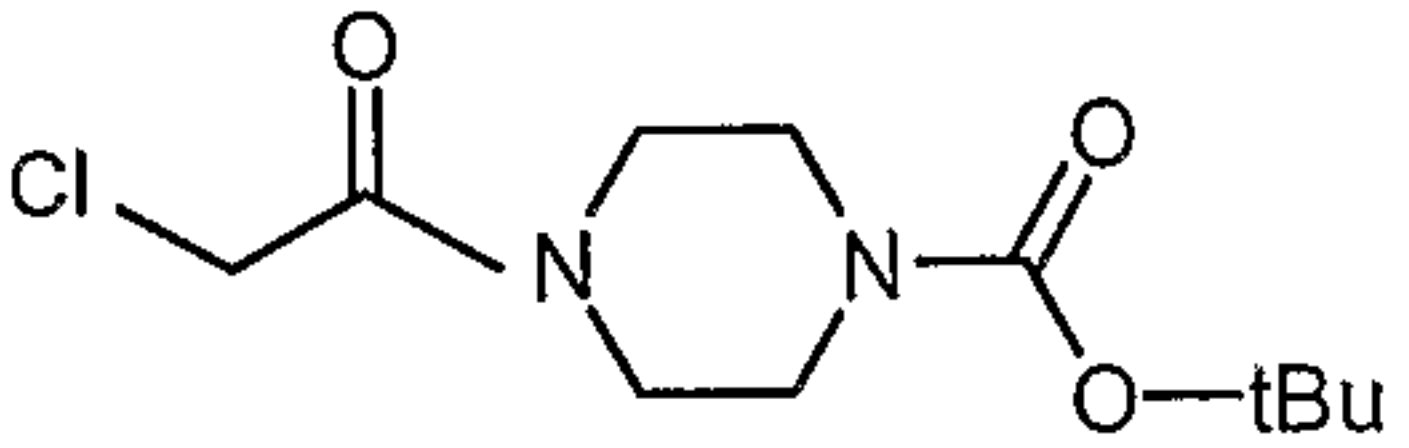
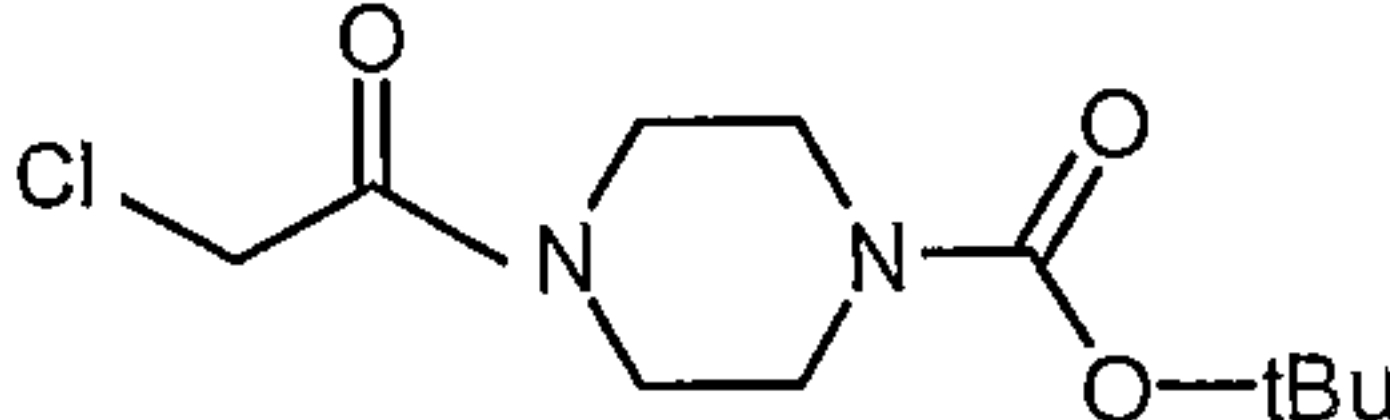
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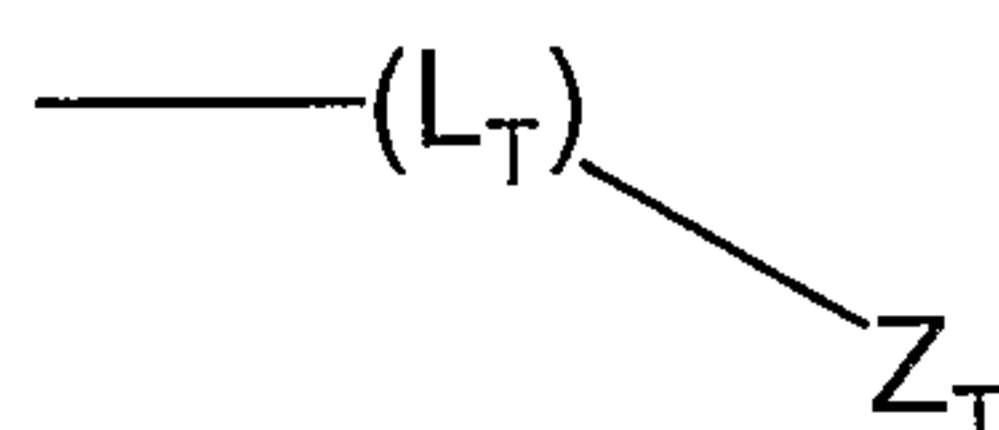
derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

Prodrugs may be prepared by methods as follows



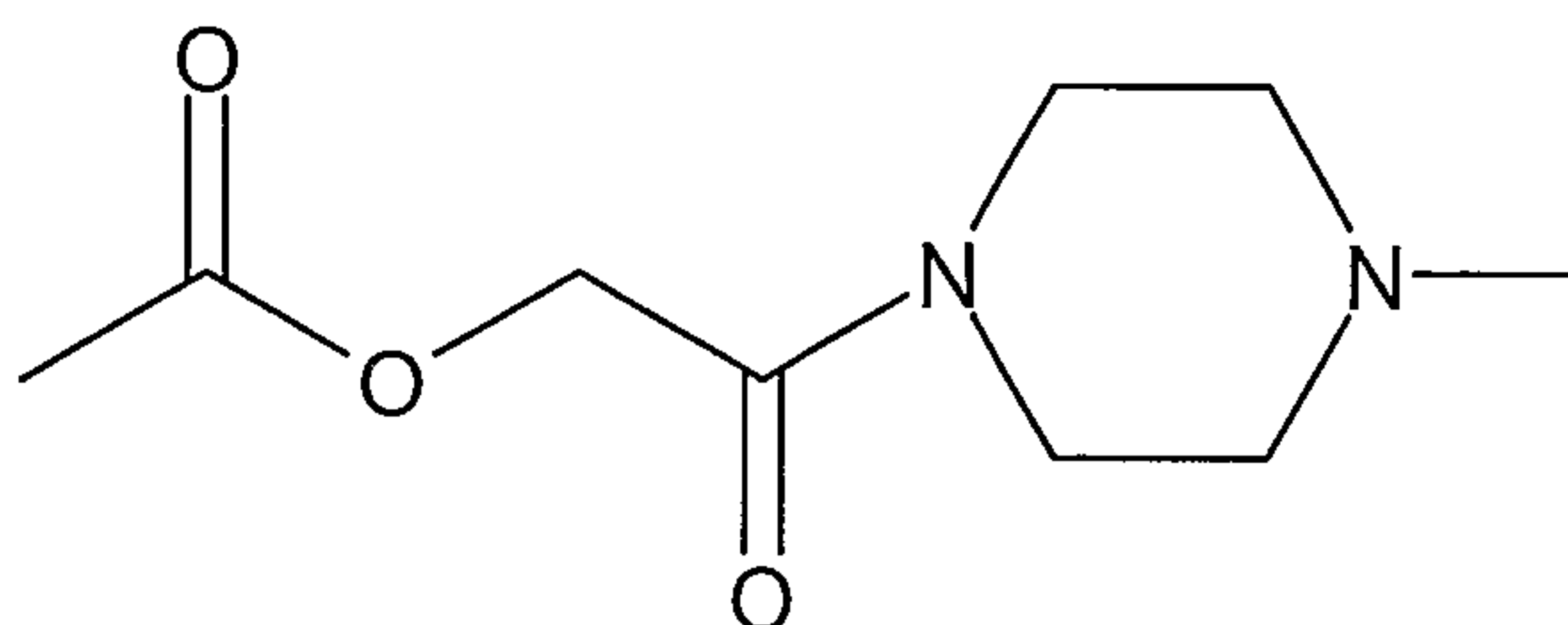
Prodrug of formula I is prepared by the following: treatment of

15  to give  . Reaction of the sodium salt of I with  and NaI; treatment with TFA; and methylation with MeI and K₂CO₃. for example, to provide a combined group



in Formula I typified by;

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Pharmaceutical Formulations containing the Novel Compounds of the Invention:

Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of Active Ingredient together with a pharmaceutically acceptable carrier or diluent. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients.

In making the compositions of the present invention, the Active Ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the compound. The Active Ingredient is preferably formulated prior to administration.

The Active Ingredient may also be delivered by suitable formulations contained in a transderm patch. Alternatively, the Active Ingredient may be delivered to a patient by sublingual administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

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In powders the carrier is a finely divided solid which is in admixture with finely divided Active ingredient. In tablets the Active Ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of Active Ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active Ingredient may be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active Ingredient may often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided Active Ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Ointment Formulation for Treatment of Psoriasis:

Treatment of psoriasis is preferably done with topical application by a formulation in the form of a cream, oil, emulsion, paste or ointment containing a therapeutically effective amount of Active Ingredient. The formulation for topical treatment contains from 0.5 to 0.00005 weight percent, preferably from .05 to 0.0005 weight percent, and most preferably from 0.025 to 0.001 of Active Ingredient.

For example, two semisolid topical preparations useful as vehicles for VDR modulators in treatment and prevention of psoriasis are as follows:

Polyethylene Glycol Ointment USP (p. 2495)

Prepare Polyethylene Glycol Ointment as follows:

Polyethylene Glycol 3350	400 g.
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Polyethylene Glycol 400	<u>600 g.</u>
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To make	1000 g.
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Heat the two ingredients on a water bath to 65C. Allow to cool, and stir until congealed. If a firmer preparation is desired, replace up to 100 g of the polyethylene glycol 400 with an equal amount of polyethylene glycol 3350.

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Hydrophilic Ointment USP (p. 1216)

Prepare Hydrophilic Ointment as follows:

	Methylparaben	0.25 g.
	Propylparaben	0.15 g.
5	Sodium Lauryl Sulfate	10 g.
	Propylene Glycol	120 g.
	Stearyl Alcohol	250 g.
	White Petrolatum	250 g.
	Purified Water	<u>370 g.</u>
10	To make about	1000 g.

The Stearyl Alcohol and White Petrolatum are melted on a steam bath, and warmed to about 75C. The other ingredients, previously dissolved in the water are added, warmed to 75C, and the mixture stirred until it congeals.

For each of the above formulations Active Ingredient is added during the heating
 15 step in an amount that is from 0.5 to 0.00005 weight percent, preferably from .05 to 0.0005 weight percent, and most preferably from 0.025 to 0.001 weight percent of the total ointment weight. (Source: - United States Pharmacopoeia 24, United States Pharmacopeial Convention, 1999)

Combination Therapy for Osteoporosis:

20 Conventional therapy for osteoporosis includes; (i) estrogens, (ii) androgens, (iii) calcium supplements, (iv) vitamin D metabolites, (v) thiazide diuretics, (vi) calcitonin, (vii) bisphosphonates, (viii) SERMS, and (ix) fluorides (see, Harrison's Principles of Internal Medicine, 13th edition, 1994, published by McGraw Hill Publ., ISBN 0-07-032370-4, pgs.2172-77; the disclosure of which is incorporated herein by reference.).
 25 Any one or combination of these conventional therapies may be used in combination with the method of treatment using Active Ingredient as taught herein. For example, in a method of treating osteoporosis, the vitamin D receptor modulator compounds of the invention may be administered separately or simultaneously with a conventional therapy. Alternatively, the Active Ingredient may be combined with conventional therapeutic
 30 agents in a formulation for treatment of osteoporosis such as set out below:

A formulation for treating osteoporosis comprising:

Ingredient (A1):

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Active Ingredient,

Ingredient (B1):

one or more co-agents that are conventional for treatment
osteoporosis selected from the group consisting of:

- 5 a. estrogens,
 b. androgens,
 c. calcium supplements,
 d. vitamin D metabolites,
 e. thiazide diuretics,
10 f. calcitonin,
 g. bisphosphonates,
 h. SERMS, and
 i. fluorides.

Ingredient (C1):

- 15 optionally, a carrier or diluent.

Typically useful formulations are those wherein the weight ratio of (A1) to (B1) is from
10:1 to 1:1000 and preferably from 1:1 to 1:100.

Combination Therapy for Psoriasis:

- 20 Conventional therapy for psoriasis includes topical glucocorticoids, salicylic acid,
crude coal tar, ultraviolet light, and methotrexate (see, Harrison's Principles of Internal
Medicine, 13th edition, 1994, published by McGraw Hill Publ., ISBN 0-07-032370-4,
pgs.2172-77). Any one or combination of these conventional therapies may be used in
combination with the method of treatment using Active Ingredient as taught herein. For
25 example, in a method of treating osteoporosis, the vitamin D receptor modulator
compounds of the invention may be topically administered separately or simultaneously
with a conventional therapy. Alternatively, the Active Ingredient may be combined with
conventional therapeutic agents in a topically applied formulation for treatment of
osteoporosis such as set out below:

- 30 A formulation for treating osteoporosis comprising:

Ingredient (A2):

Active Ingredient;

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Ingredient (B2):

one or more co-agents that are conventional for treatment psoriasis
selected from the group consisting of:

- a. topical glucocorticoids ,
- 5 b. salicylic acid, or
- c. crude coal tar.

Ingredient (C2):

optionally, a carrier or diluent.

Typically useful formulations are those wherein the weight ratio of (A2) to (B2) is from
10 1:10 to 1:100000 and preferably from 1:100 to 1:10000.

Methods of Using the Compounds of the Invention:

Generic disease states benefited by treatment with t Active Ingredient include, but are not
limited to:

- 15 disease states characterized by abnormal calcium regulation
- disease states characterized by abnormal cell proliferation
- disease states characterized by abnormal immune response
- disease states characterized by abnormal dermatological conditions
- disease states characterized by neurodegenerative condition
- 20 disease states characterized by inflammation
- disease states characterized by vitamin D sensitivity
- disease states characterized by hyperproliferative disorders

Specific disease states benefited by treatment with Active Ingredient include, but are not
limited to:

- 25 Abscess
- Acne
- Adhesion
- Actinic keratosis
- Alopecia
- 30 Alzheimer's disease
- Bone maintenance in zero gravity
- Bone fracture healing

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	Breast cancer
	Skin cancer
	Crohn's disease
	Colon cancer
5	Type I diabetes
	Host-graft rejection
	Hypercalcemia
	Type II diabetes
	Leukemia
10	Multiple sclerosis
	Myelodysplastic syndrome
	Insufficient sebum secretion
	Osteomalacia
	Osteoporosis
15	Insufficient dermal firmness
	Insufficient dermal hydration
	Psoriatic arthritis
	Prostate cancer
	Psoriasis
20	Renal osteodystrophy
	Rheumatoid arthritis
	Scleroderma
	Systemic lupus erythematosus
	Ulcerative colitis
25	Wrinkles

Particularly preferred is the treatment of psoriasis and osteoporosis by administration to a mammal (including a human) of a therapeutically effective amount of Active Ingredient. By "therapeutically effective amount" it is meant that quantity of a compound of the invention prevents, removes or significantly reduces the deleterious effects of a disease state in mammals, including humans.

The specific dose of Active Ingredient administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular

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circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a pharmaceutically effective amount typically in the range of from about 0.0001 mg/kg/day to about 50 mg/kg/day of body weight of an active compound of this invention. Preferably the dose of compounds of the invention will be from 0.0001 to 5 mg/kg/day of body weight.

Preferably the Active Ingredient or pharmaceutical formulations containing Active Ingredient are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active Ingredient in a unit dose of composition may be varied or adjusted from about 0.0001 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it is necessary to make routine variations to the dosage depending on the age and condition of the patient. The compounds of the invention may be administered by a variety of routes including oral, aerosol, rectal, transdermal, sublingual, subcutaneous, intravenous, intramuscular, and intranasal. The dosage will also depend on the route of administration.

Examples

General Experimental Conditions:

The starting material/intermediate is the compound from the immediate preceding experimental unless otherwise indicated.

All reactions are performed under nitrogen/argon atmosphere, in a stirred reaction vessel, and at room temperature unless indicated otherwise.

Unless otherwise indicated, the organic layer is MgSO₄/Na₂SO₄ dried is defined as stirring the solution with a dessicant for 5-15 m and filtering off the dessicant to give an anhydrous filtrate.

For analogous multi-step reaction procedures, the yield is given either for the ultimate step or overall multi-steps as indicated.

Solutions are "concentrated" at a range of 25-75 °C with reduced pressure.

in-vacuo – 25-75 °C; 0.05 to 1 mm

Unless otherwise indicated, "the residue is chromatographed" is defined as silica gel chromatography of residue with moderate nitrogen pressure (flash chromatography) or

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a medium pressure chromatography systems using a silica gel to crude product ratio of ~10-100.

Thin layer chromatography is performed with silica gel plates with UV and/or appropriate staining solution.

5 NMR spectra are obtained with either 300 or 400 mHz spectrometer.

NMR – denotes NMR spectrum is consistent with assigned structure.

HRMS – high resolution mass spectrum

ES-MS – electrospray mass spectrum

10

Abbreviations:

Aq - aqueous

d – day

15 eq - equivalent

h – hour

m – minute

satd – saturated

disp – dispersion

20 quant – quantitative

rt for retention time (both small caps to minimize confusion with RT)

RT – room temperature

25 Chemical Definitions:

BBr₃ – boron tribromide

BF₃-OEt₂ – boron trifluoride etherate

BnBr – benzyl bromide

CH₂Cl₂-dichloromethane

30 CH₃CN – acetonitrile

CO-carbon monoxide

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Dess-Martin reagent – 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one

DIBALH - Diisobutyl Aluminum Hydride

DMAP - 4-(dimethylamino)pyridine

5 DMF – N,N-dimethylformamide

DMSO – dimethylsulfoxide

DPPB – 1,4-bis(diphenylphosphino)butane

DPPF – dichloro[1,1'-bis(diphenylphosphino)ferrocene]

EDCI – 3-Ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride

10 Et₃N – triethylamine

EtMgBr- ethyl magnesium bromide

EtOAc – ethyl acetate

EtOH – ethanol

H₂NCH₂CO₂Me – methyl glycinate

15 Hept – heptane

Hex - hexanes

HN(OMe)Me – N-methyl-O-methyl hydroxylamine

HNMe₂ – dimethyl amine

HATU – O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

20 hexafluorophosphate

HOAT – 7-aza-1-hydroxybenzotriazole

HOBT – 1-hydroxybenzotriazole

K₂CO₃ – potassium carbonate

KOH – potassium hydroxide

25 LAH – lithium aluminum hydride

LiHMDS – lithium hexamethyldisilazide

mCPBA – meta-chloroperbenzoic acid

MeI – methyl iodide

MeOH – methanol

30 NaBH₄ – sodium borohydride

MgSO₄- magnesium sulfate

NaH – sodium hydride

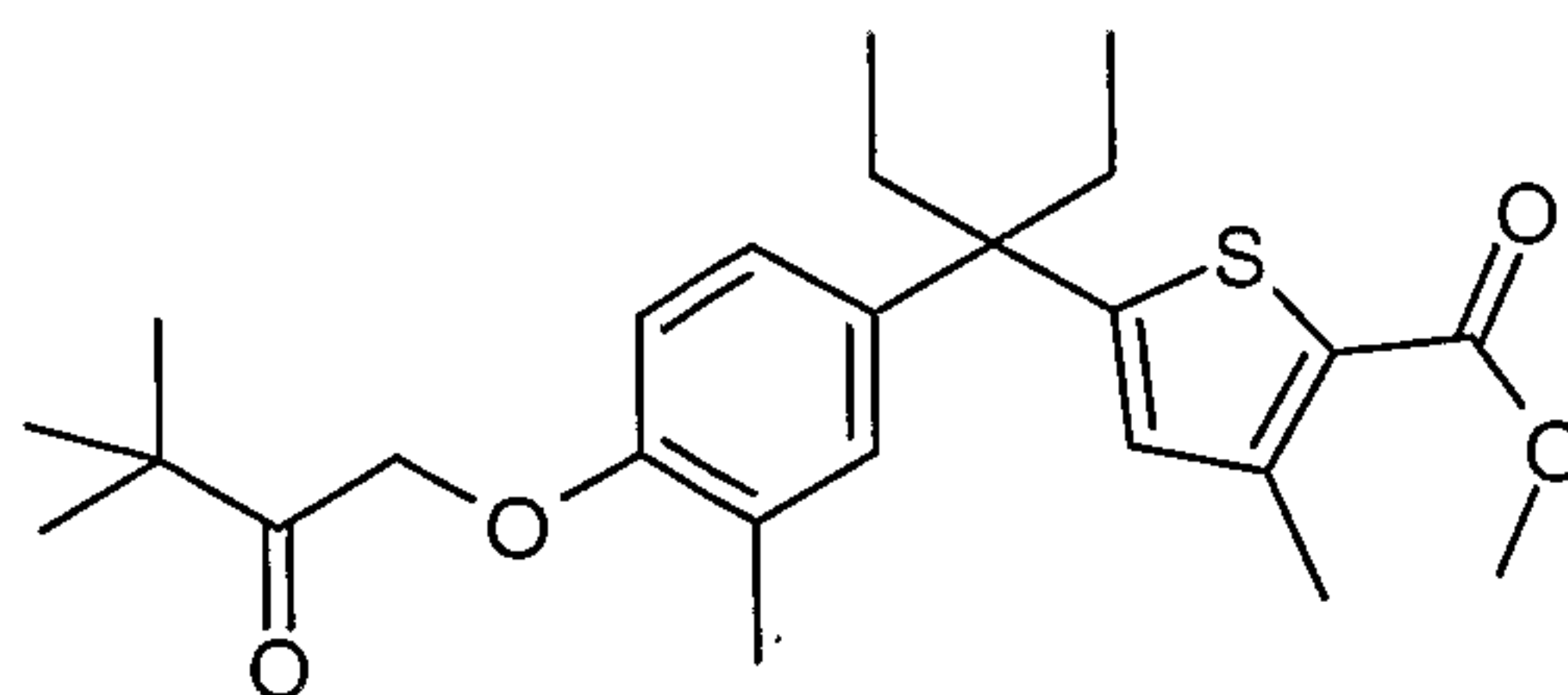
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- NaHCO₃-sodium bicarbonate
NaI – sodium iodide
Na₂SO₄- sodium sulfate
NH₄Cl- ammonium chloride
5 NMO – 4-methylmorpholine N-oxide
NMP - N-methylpyrrolidin-2-one
Na-S-R₃ – sodium alkylmercaptide
PBr₃ – phosphorus tribromide
Pd(DPPF) - palladium dichloro[1,1'-bis(diphenylphosphino)ferrocene
10 Pd(OAc)₂ – palladium (II) acetate
Pd(TPP)₄ – palladium tetrakis(triphenylphosphine)
Pd-C – palladium on carbon
(PhO)₂P(O)N₃ – diphenyl phosphorus azide
pTSA – para-toluenesulfonic acid
15 Pyr – pyridine
Red-Al – sodium bis(2-methoxyethoxy)aluminum hydride
R₂MgBr – alkyl magnesium bromide
R₃MgBr – alkyl magnesium bromide
R₅MgBr – alkyl magnesium bromide
20 R₂S(O)₂NH₂ – alkylsulfonamide
TBAF- tetrabutylammonium fluoride
TBSCl- *tert*-butyldimethylsilyl chloride
tBuC(O)CH₂Br – 1-bromopinacolone
Tf₂O – triflic anhydride
25 TFA – trifluoroacetic acid
THF – tetrahydrofuran
TPAP – tetrapropylammonium perruthenate
Zn(OTf)₂ – zinc trifluoromethane sulfonate.

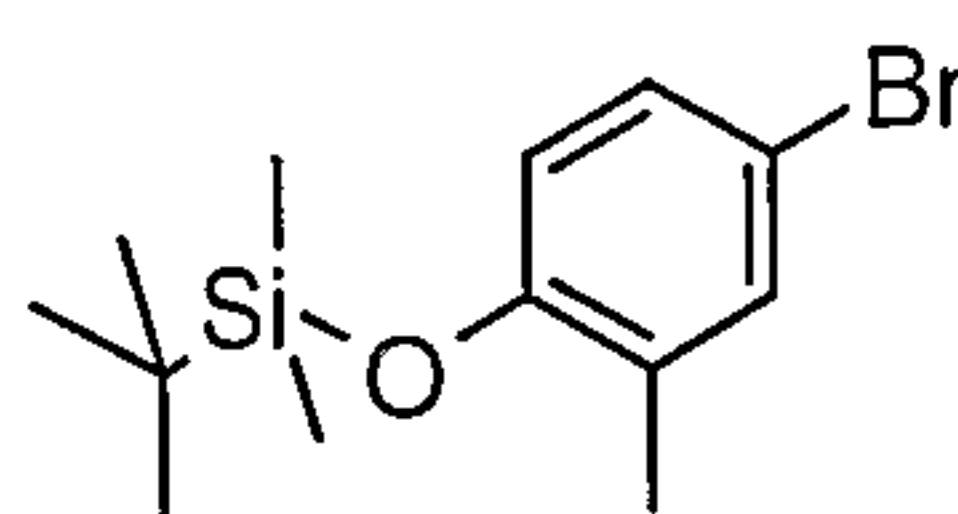
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Example 1

Preparation of 3'-[4-(2-Oxo-3,3-dimethylbutoxy-3-methylphenyl)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



5 A. 2-(t-Butyldimethylsilyloxy)-5-bromotoluene.

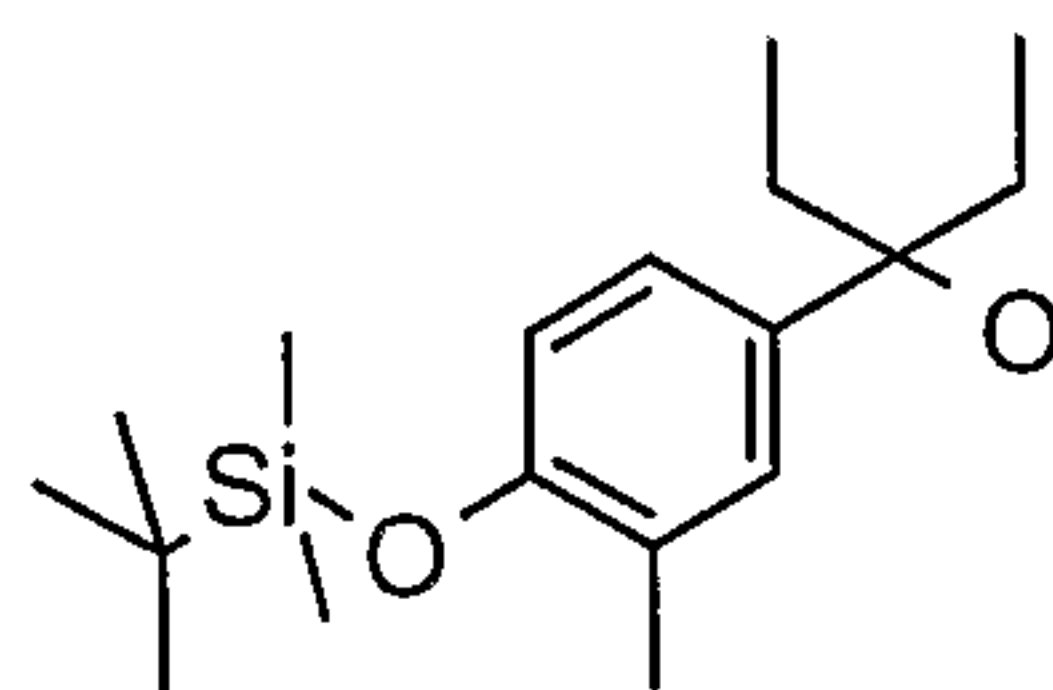


To a 0 °C mixture of 2-hydroxy-5-bromotoluene(48.63 g, 260 mmol), DMF (260 ml), imidazole (18.58 g, 273 mmol) is added t-butyldimethylsilyl chloride (41.15 g, 273 mol) in portions. After stirring for 30 m, the reaction is warmed to RT and stirred for 16 h. The reaction mixture is poured into ice/water (1.25 l) and extracted with Et₂O. The organic layer is washed with water (2X100 ml), 1N NaOH (2X5 ml), water, brine, MgSO₄ dried, concentrated, chromatographed (hex), and azeotroped with toluene to give the title compound as an oil (75.7 g, 97%)

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.21 (s, 6H), 0.99 (s, 9H), 2.15 (s, 3H), 6.77 (d, J = 8.3 Hz, 1H), 7.25 (dd, J = 6.8, 8.3 Hz, 1H), 7.37 (s, 1H).

EI-MS: 300, 302

B. 3'-[4-(t-Butyldimethylsilyloxy)-3-methylphenyl]pentan-3-ol.



20 Magnesium turnings (6 g, 248 mmol) is vigorously stirred under nitrogen for 18 h. To the magnesium turnings is added THF (600 ml) and I₂ (100 mg, 0.39 mmol). This is followed by dropwise addition of 2-(t-butyldimethylsilyloxy)-5-bromotoluene (60 g, 200 mmol) in THF (500 ml) and at the same time the reaction is gradually heated by setting the oil bath to 70 °C. After half of the addition of the 2-(t-

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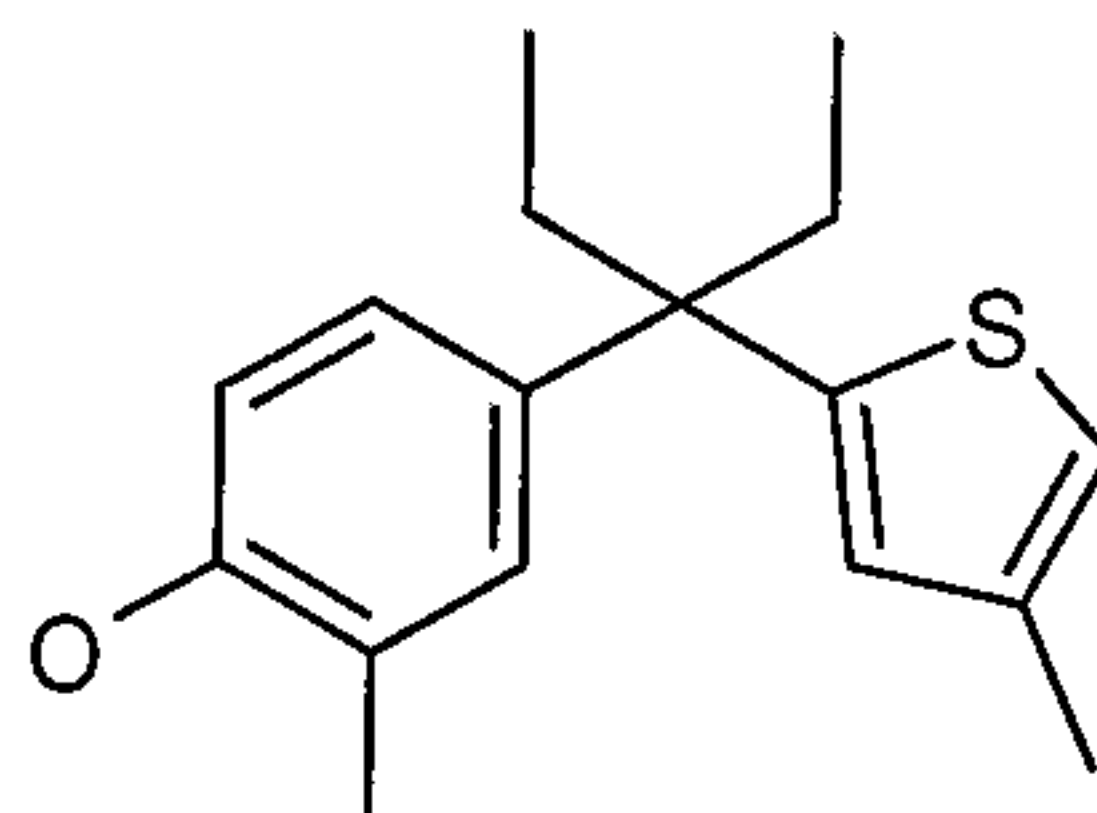
butyldimethylsilyloxy)-5-bromotoluene/THF is complete, the mixture is heated to 90 °C for 2.5 h. The mixture is allowed to cool to RT and then cooled to 0 °C. To this mixture is added 3-pentanone (21.2 ml, 200 mmol), warmed to RT, and then heated to 50 °C for 3 h. After cooling, the reaction is diluted with Et₂O and water, and

5 quenched with 1N HCl to pH 7. The mixture is partitioned and the organic layer is washed with water, Na₂SO₄ dried, concentrated, chromatographed (1.25 kg silica gel, 40% CH₂Cl₂/Hex to 70% CH₂Cl₂/Hex; rf: 0.3) to give the title compound as an oil (44.3 g, 72%).

10 ¹NMR (400MHz, DMSO-d₆) δ ppm: 0.20 (s, 6H), 0.64 (t, J = 7.8 Hz, 6H), 1.00 (s, 9H), 1.67 (m, 4H), 2.15 (s, 3H), 4.38 (s, 1H), 6.70 (d, J = 8.8 Hz, 1H), 7.04 (dd, J = 8.3, 2.0 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H).

EI-MS: 308.37

C. 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane.



15

To a -78 °C mixture of 3'-[4-(t-butyldimethylsilyloxy)-3-methylphenyl]pentan-3-ol (44 g, 142 mmol) and 3-methylthiophene (83 ml, 854 mmol) is added BF₃-Et₂O (180 ml, 1.42 mol). After stirring for 45 m, the reaction is placed in a 0 °C bath, allowed to warm to RT and stirred for 6 h. The reaction is

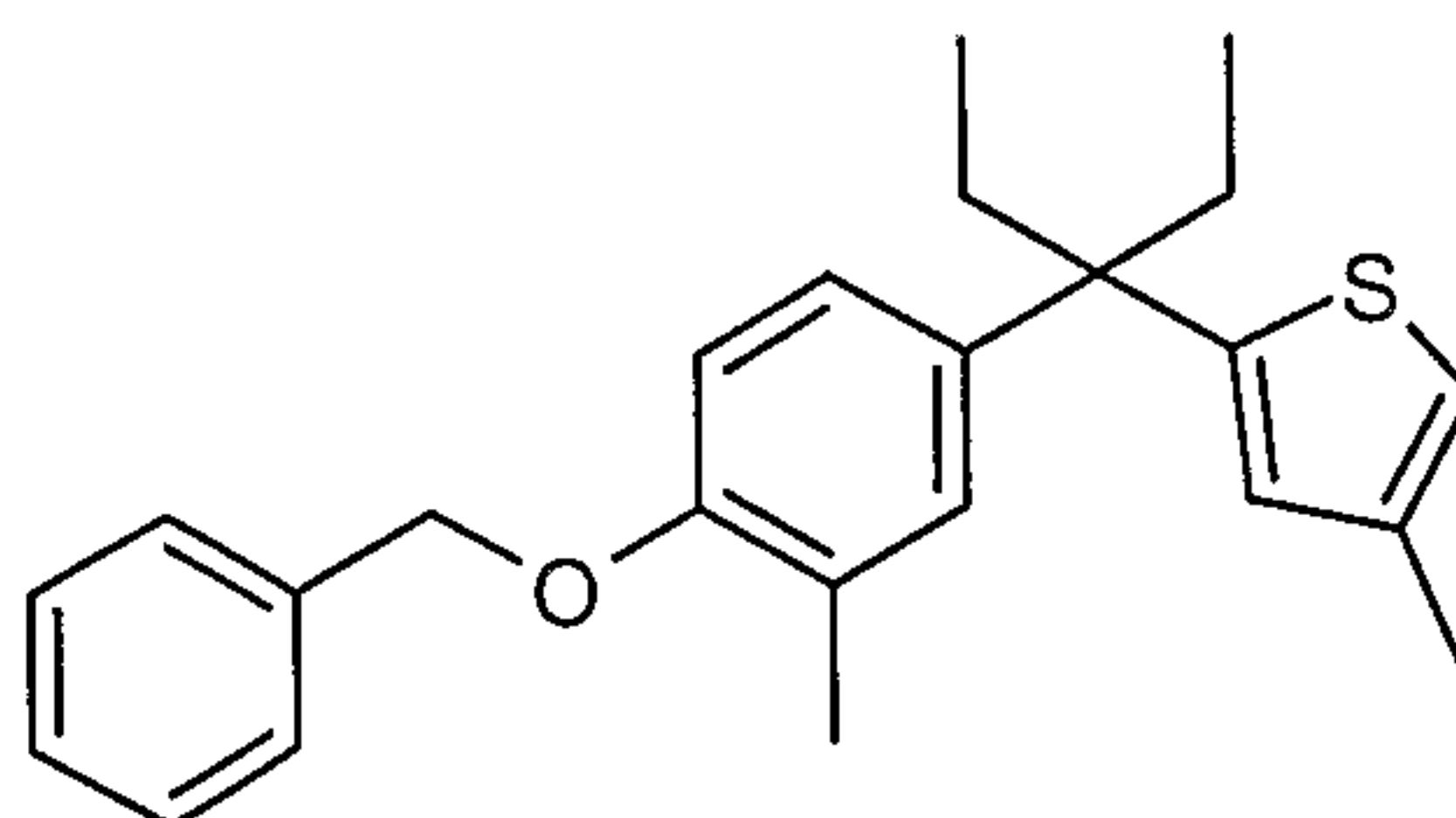
20 poured into Et₂O/water and washed with 5N HCl. The organic layer is washed with water, Na₂SO₄ dried, concentrated, and chromatographed (1.5 kg SiO₂, 70% CHCl₃/hex) to give the title compound (37 g, 95%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.63 (t, J = 7.3 Hz, 3H), 2.01 (m, 4H), 2.08 (s, 3H), 2.16 (s, 3H), 6.67 (m, 2H), 6.88 (m, 2H), 6.93 (d, J = 1.9 Hz, 1H), 9.10 (s, 1H).

25 High Res. EI-MS: 274.1389; calc. for C₁₇H₂₂OS: 274.1391

D. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane.

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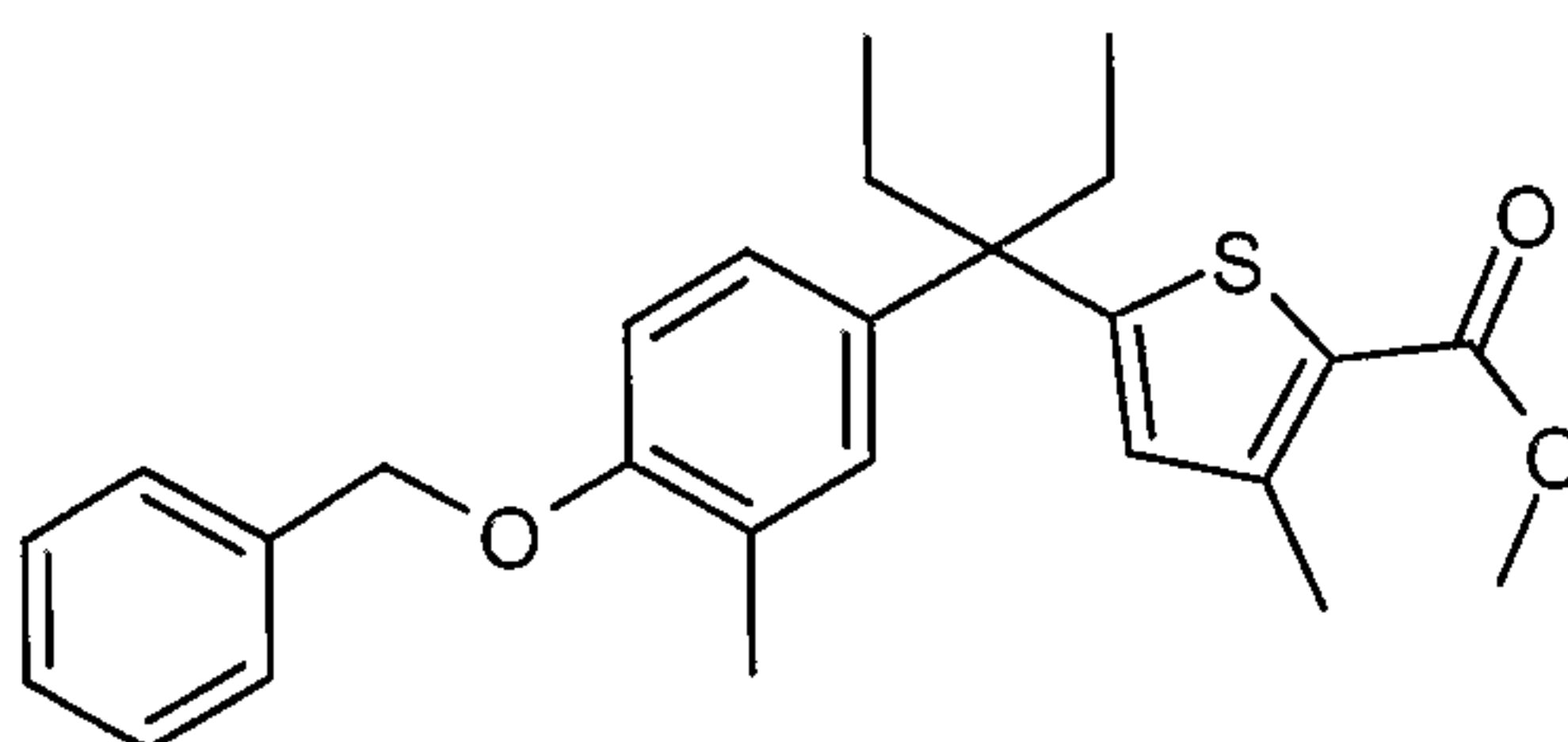


To a 0 °C mixture of 3'-[4-(hydroxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane (7.1 g, 25.9 mmol) and DMF (60 ml) is added 60% NaH disp (1.1 g, 28.5 mmol) and stirred for 15 m. The reaction is added benzyl bromide (3.4 ml, 28.5 mmol), warmed to RT and stirred overnight. The reaction is concentrated in-vacuo and partitioned between Et₂O/1N HCl. The organic layer is washed with water, dried with Na₂SO₄, concentrated, and chromatographed (20% CHCl₃/hex to 30% CHCl₃/hex) to give the title compound (8.7 g, 92%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.61 (t, J = 7.3 Hz, 6H), 1.95-2.07 (m, 4H), 2.13 (s, 6H), 5.05 (s, 2H), 6.65 (d, J = 1.5 Hz, 1H), 6.86 (m, 2H), 7.01 (m, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.38 (m, 2H), 7.44 (d, J = 6.8 Hz, 2H).

High Res. EI-MS: 364.1878; calc. for C₂₄H₂₈OS: 364.1861

E. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



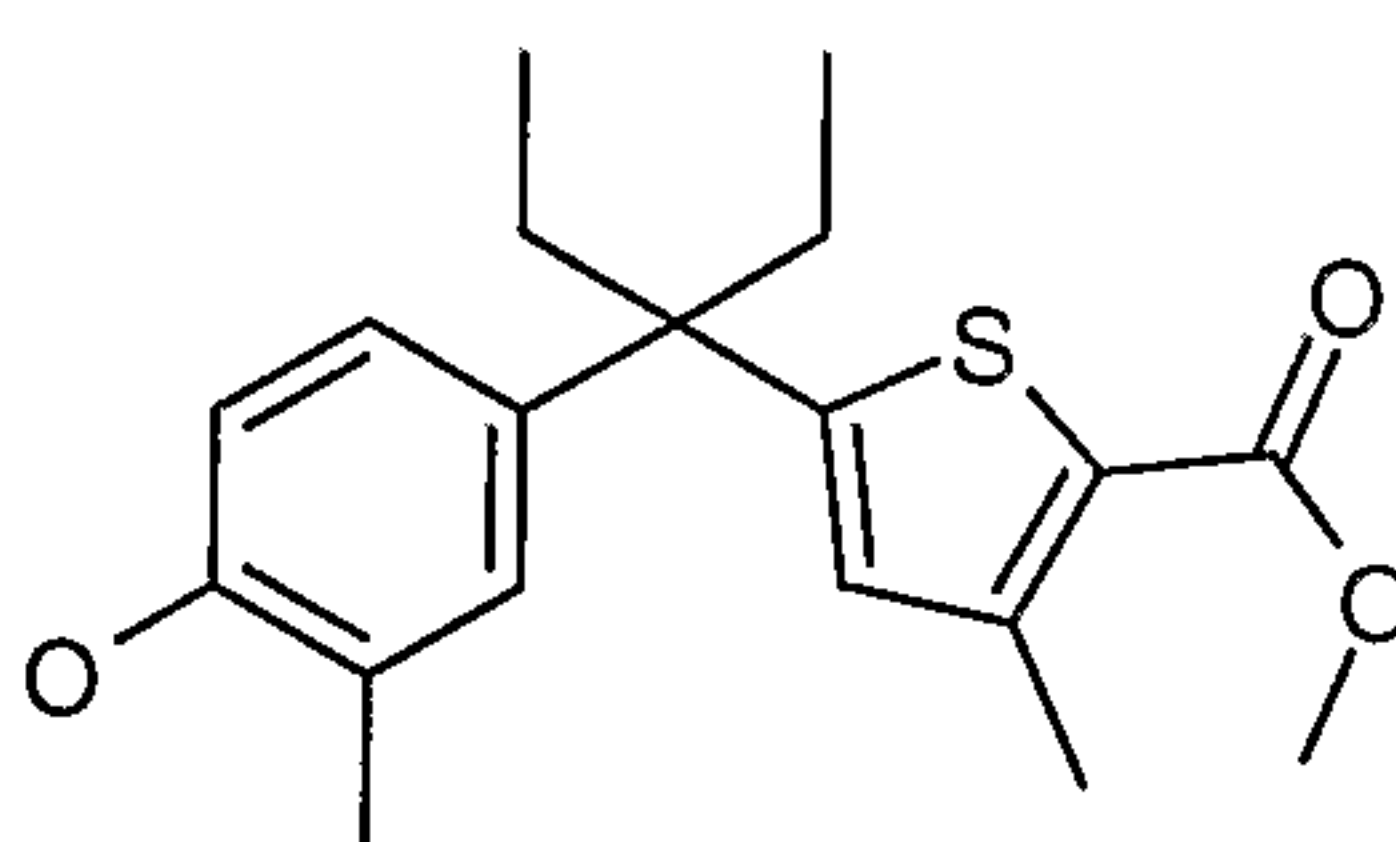
concentrated, and chromatographed (10% EtOAc/hex) to give the title compound. To a -78 °C mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane (7.7 g, 21 mmol) and THF (50 ml) is added 1.6 M n-BuLi/hex (1.6 ml, 25.3 mmol) and warmed to 0 °C for 2 m. The reaction is cooled to -78 °C, added methyl chloroformate (1.7 ml, 25 mmol) and warmed to RT over 2 h. The reaction is added Et₂O, quenched with 1N HCl, and partitioned. The organic layer is washed with brine, Na₂SO₄ dried, compound (4.8 g, 54%).

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¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 2.02-2.07 (m, 4H), 2.14 (s, 3H), 2.40 (s, 3H), 3.69 (s, 3H), 5.06 (s, 2H), 6.82 (s, 1H), 6.92 (d, J = 8.8 Hz, 1H), 7.03 (m, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.38 (t, J = 7.3 Hz, 2H), 7.44 (t, J = 7.3 Hz, 2H).

5 High Res. ES-MS: 423.2011; calc. for C₂₆H₃₀O₃S+H: 423.1994

F. 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



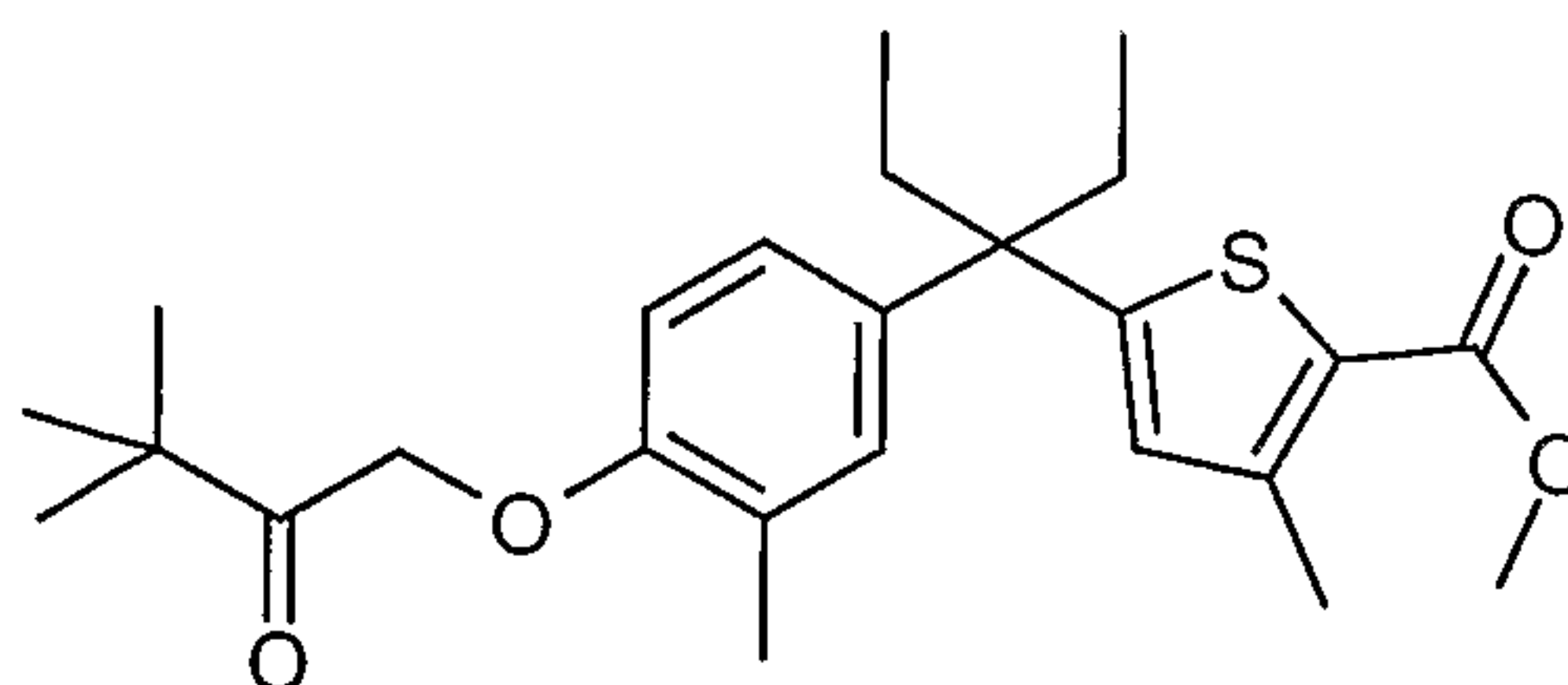
10 A mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (290 mg, 0.686 mmol), 10% Pd/C (1.6 g, 1.5 mmol), EtOH (3 ml), and EtOAc (3 ml) is hydrogenated overnight at atmospheric pressure. The reaction is filtered through diatomaceous earth with EtOH/EtOAc wash, concentrated, and chromatographed (CH₂Cl₂ to 10% EtOAc/CH₂Cl₂) to give the title
15 compound (220 mg, quant).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.61 (t, J = 7.3 Hz, 6H), 1.98-2.07 (m, 4H), 2.05 (s, 3H), 2.39 (s, 3H), 3.69 (s, 3H), 6.66 (d, J = 8.3 Hz, 1H), 6.79 (s, 1H), 6.86 (dd, J = 8.3, 2.4 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 9.15 (s, 1H).

High Res. ES-MS: 333.1528; calc. for C₁₉H₂₄O₃S+H: 333.1524

20

G. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



To a mixture of 3'-[4-(hydroxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (210 mg, 0.63 mmol) and DMF (2 ml) is added 60%
25

-159-

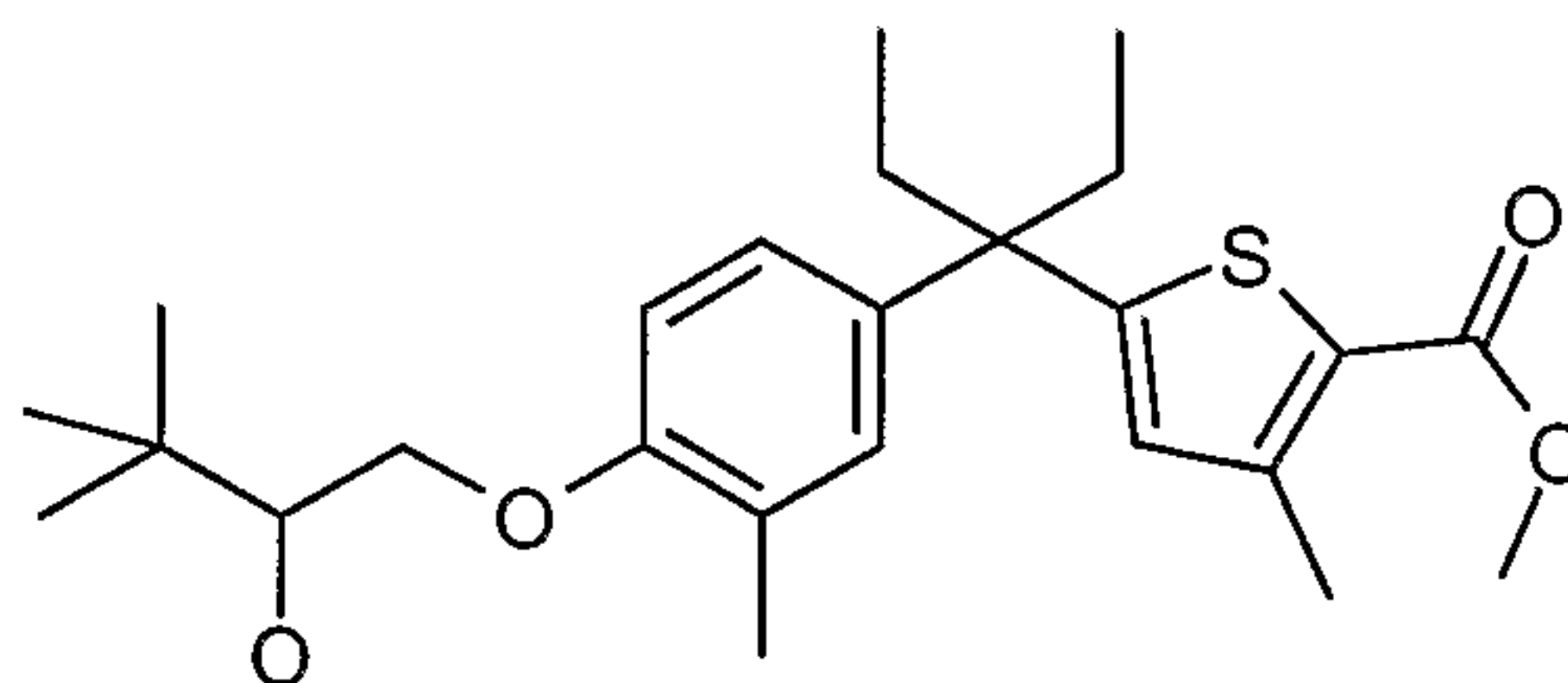
NaH disp (25 mg, 0.63 mmol) and warmed to RT. The reaction is cooled to 0 °C, added 3,3-dimethyl-1-bromo-2-butanone (85 ul, 0.63 mmol), warmed to RT, and stirred overnight. The mixture is concentrated and partitioned between Et₂O/1N HCl. The organic layer is washed with water, dried with Na₂SO₄, and chromatographed (10% EtOAc/hex to 20% EtOAc/hex) to give the title compound (230 mg, 85%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.61 (t, J = 7.3 Hz, 6H), 1.15 (s, 9H), 2.01-2.08 (m, 4H), 2.14 (s, 3H), 2.40 (s, 3H), 3.69 (s, 3H), 5.08 (s, 2H), 6.60 (d, J = 8.3 Hz, 1H), 6.82 (s, 1H), 6.97 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H).

High Res. ES-MS: 453.2072; calc. for C₂₅H₃₄O₄S+Na: 453.2076

Example 2

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



To a 0 °C mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (215 mg, 0.5 mmol) and MeOH (2 ml) is added NaBH₄ (28 mg, 0.75 mmol) and warmed to RT. The reaction is concentrated and partitioned between Et₂O/1N HCl. The organic layer is washed with water, dried with Na₂SO₄, and concentrated to give the title compound (220 mg, quant).

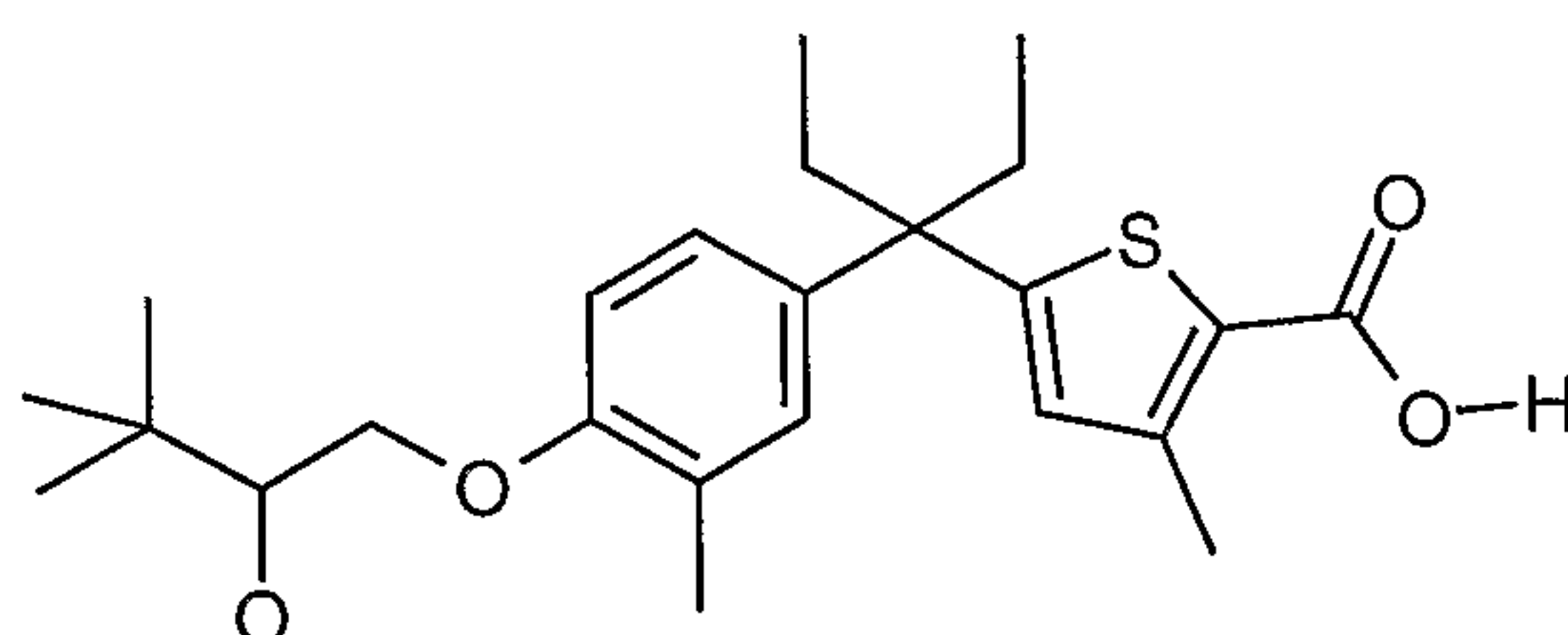
¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.90 (s, 9H), 1.99-2.08 (m, 4H), 2.11 (s, 3H), 2.40 (s, 3H), 3.44 (m, 1H), 3.69 (s, 3H), 3.75 (dd, J = 7.3, 10.2 Hz, 1H), 4.03 (dd, J = 3.4, 10.2 Hz, 1H), 4.79 (d, J = 5.4 Hz, 1H), 6.81 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.98 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H).

High Res. ES-MS: 450.2674; calc. for C₂₅H₃₆O₄S+NH₄: 450.2678

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Example 3

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxyl-4-methylthiophen-2-yl]pentane.



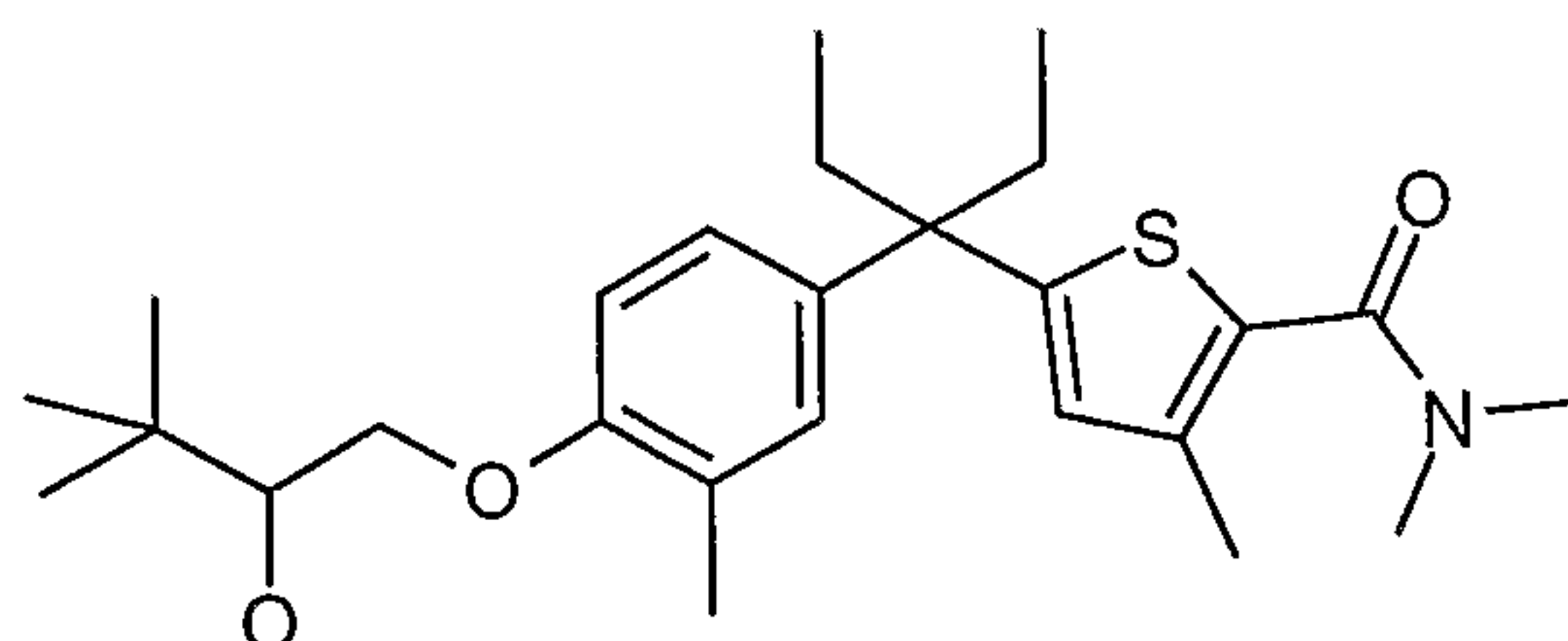
5 To a mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (200 mg, 0.46 mmol), EtOH (1.5 ml), and water (0.5 ml) is added KOH (200 mg, 3.56 mmol). The reaction is heated to 70 °C for 4 h. The mixture is concentrated, partitioned between 1:1 Et₂O:EtOAc and 1N HCl. The organic layer is washed with 1N HCl, Na₂SO₄ dried, and concentrated
10 to give the title compound (200 mg, quant).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.90 (s, 9H), 1.97-2.09 (m, 4H), 2.11 (s, 3H), 2.37 (s, 3H), 3.44 (m, 1H), 3.74 (dd, J = 7.3, 10.2 Hz, 1H), 4.01 (dd, J = 3.4, 10.2 Hz, 1H), 4.78 (d, J = 5.4 Hz, 1H), 6.76 (s, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.98 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H), 12.58 (br s, 1H).

15 High Res. ES-MS: 436.2518; calc. for C₂₅H₃₆O₄S+NH₄: 436.2521

Example 4

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-(dimethylaminocarbonyl)-4-methylthiophen-2-yl]pentane.



20

To a 0 °C mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxyl-4-methylthiophen-2-yl]pentane (175 mg, 0.42 mmol) and Et₃N (61 ul, 0.44 mmol) is added (PhO)₂P(O)N₃ (92 ul, 0.43 mmol). The reaction is warmed to RT and stirred for 30 m. After cooling to 0 °C, the reaction is added DMAP (56 mg,
25 0.46 mmol) and 2M HNMe₂/THF (0.46 ml, 0.92 mmol). The mixture is warmed to

-161-

RT and stirred for 2 h. The reaction is concentrated and partitioned between Et₂O/1N HCl. The organic layer is washed with 1N HCl, Na₂SO₄ dried, and chromatographed (CH₂Cl₂ to 15% EtOAc/CH₂Cl₂) to give the title compound (110 mg, 59%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 1.96-2.06 (m, 4H), 2.09 (s, 3H), 2.11 (s, 3H), 2.90 (s, 6H), 3.44 (m, 1H), 3.73 (dd, J = 7.3, 10.2 Hz, 1H), 4.01 (dd, J = 3.4, 10.2 Hz, 1H), 4.79 (br s, 1H), 6.65 (s, 1H), 6.82 (d, J = 8.8 Hz, 1H), 7.02 (m, 2H).

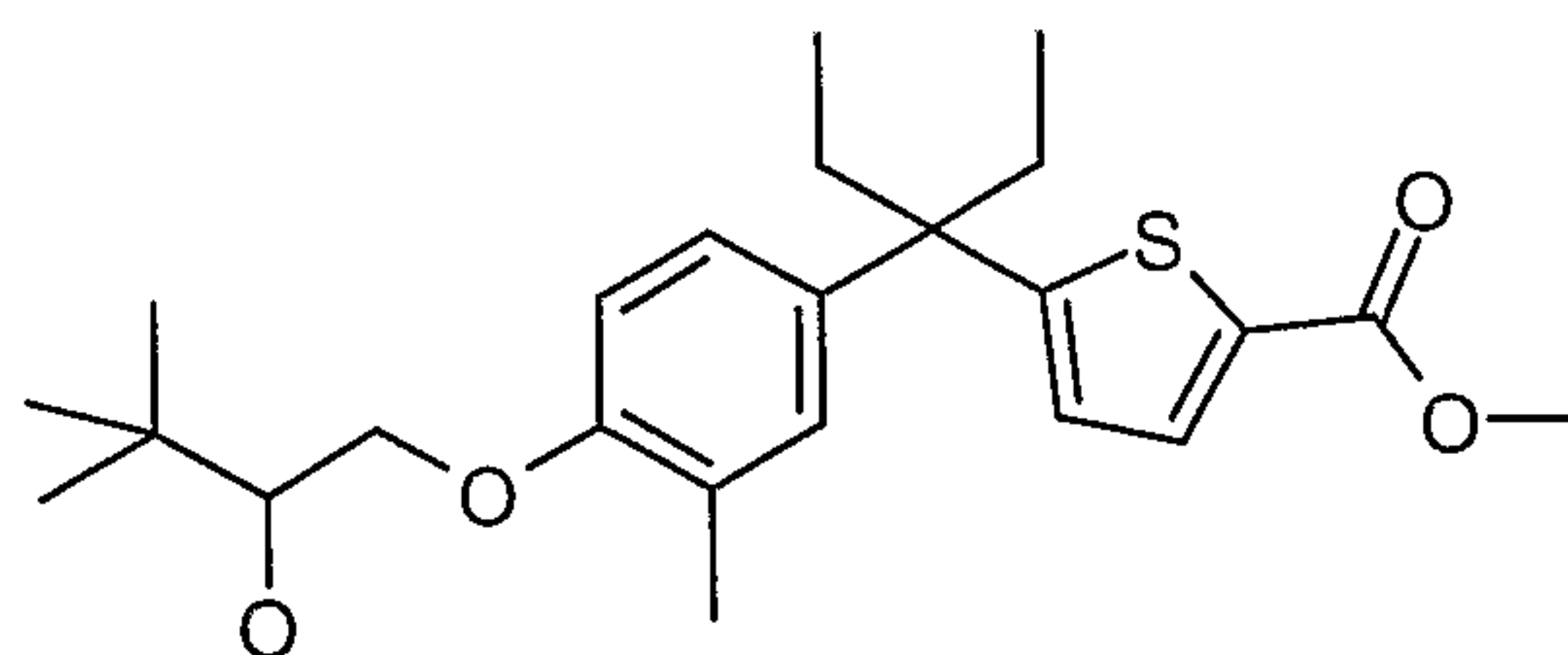
High Res. ES-MS: 446.2738; calc. for C₂₆H₃₉NO₃S+H: 446.2729

10

15

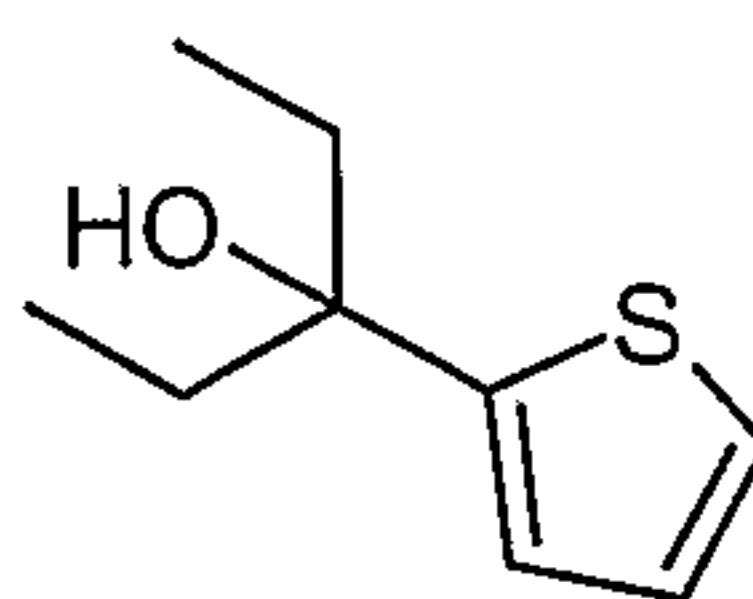
Example 5:

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl] pentane.



20

A. 2-(3-Hydroxy-3-pentyl)thiophene.



To a stirred 0 °C mixture of ethyl thiophene-2-carboxylate (3.12 g, 20.0 mmol) in diethyl ether (100 ml) is added 1M ethylmagnesium bromide (60 ml, 60 mmol). The reaction is allowed to warm to RT and stirred for 3 d. The reaction is partitioned between

25

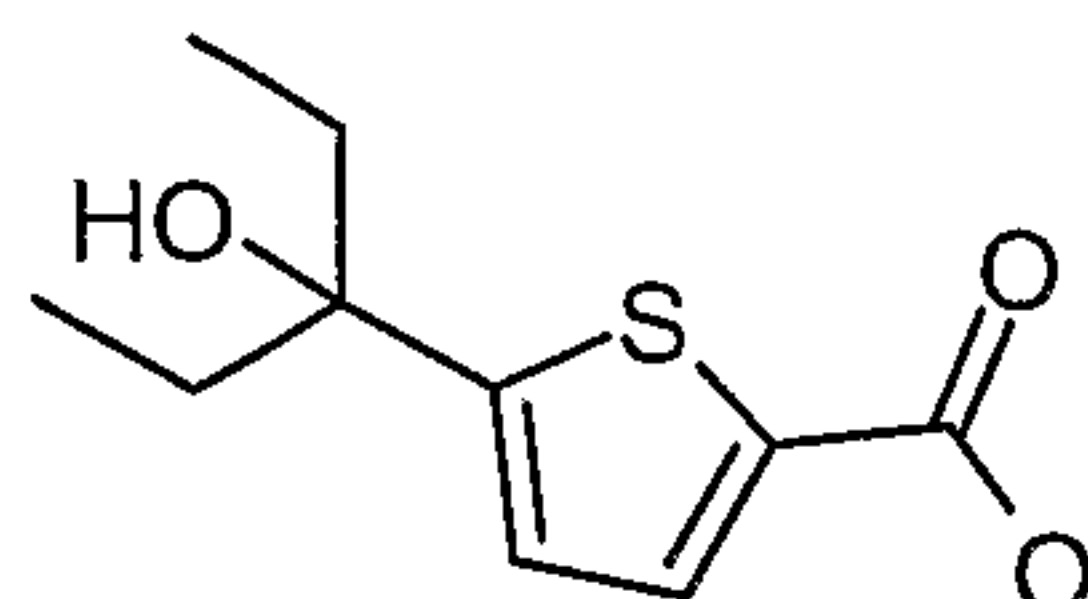
-162-

Et₂O and 1N NaHCO₃. The organic layer was Na₂SO₄ dried and concentrated to give the title compound (3.4 g, 99%).

H-NMR (ppm, CDCl₃): 7.98 (1H, d, 4.2 Hz), 6.95 (1H, m), 6.85 (1H, d, 3.0 Hz), 1.86 (4H, q, 7.5 Hz), 0.86 (6H, t, 7.5 Hz).

5

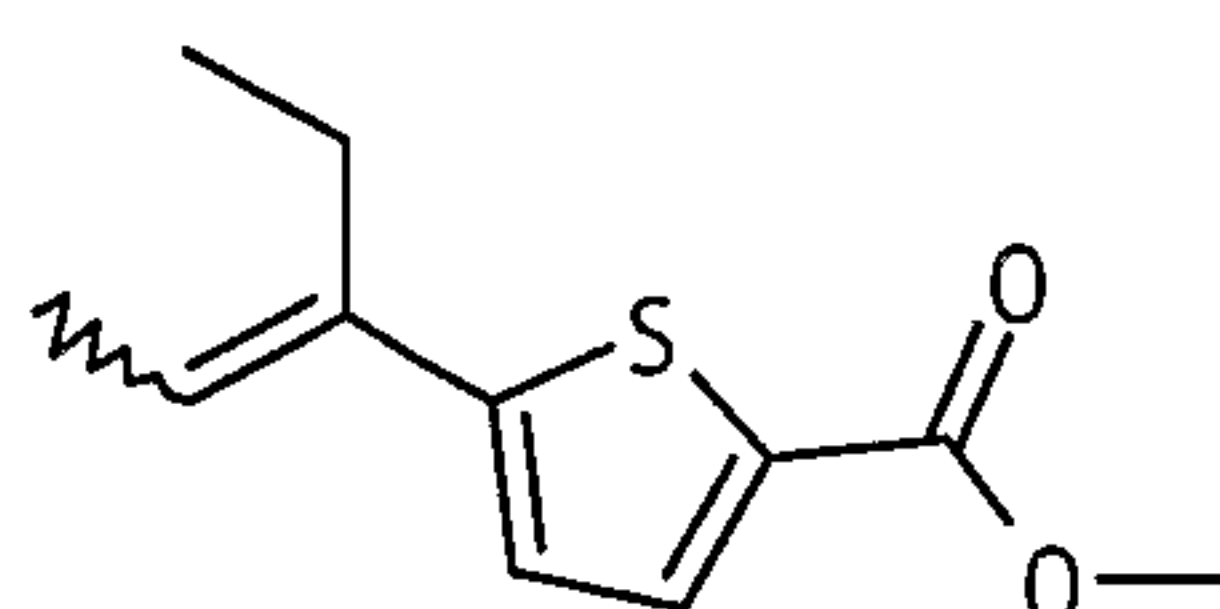
B. 5-(3-Hydroxy-3-pentyl)thiophene-2-carboxylic acid.



To a -78 °C mixture of 2-(3-hydroxy-3-pentyl)thiophene (0.34 g, 2.0 mmol) in THF (2 ml) is added of 1.6 M n-butyllithium in Hex (2.75 ml, 4.4 mmol). The mixture is allowed to warm to RT and powderized dry ice (CO₂) is added. After one h, the mixture is partitioned between diethyl ether and 1N NaHCO₃. The aqueous layer is washed with ether, acidified with conc. HCl and extracted with ether. The organic layer is Na₂SO₄ dried, filtered, and concentrated to give the title compound (0.236 g, 53%).

H-NMR (ppm, CDCl₃): 7.75 (1H, d, 3.0 Hz), 6.87 (1H, d, 3.0 Hz), 1.86 (4H, q, 5.7 Hz), 0.86 (6H, t, 5.7 Hz).

C. Methyl, 5-(E/Z-2-penten-3-yl)thiophene-2-carboxylate

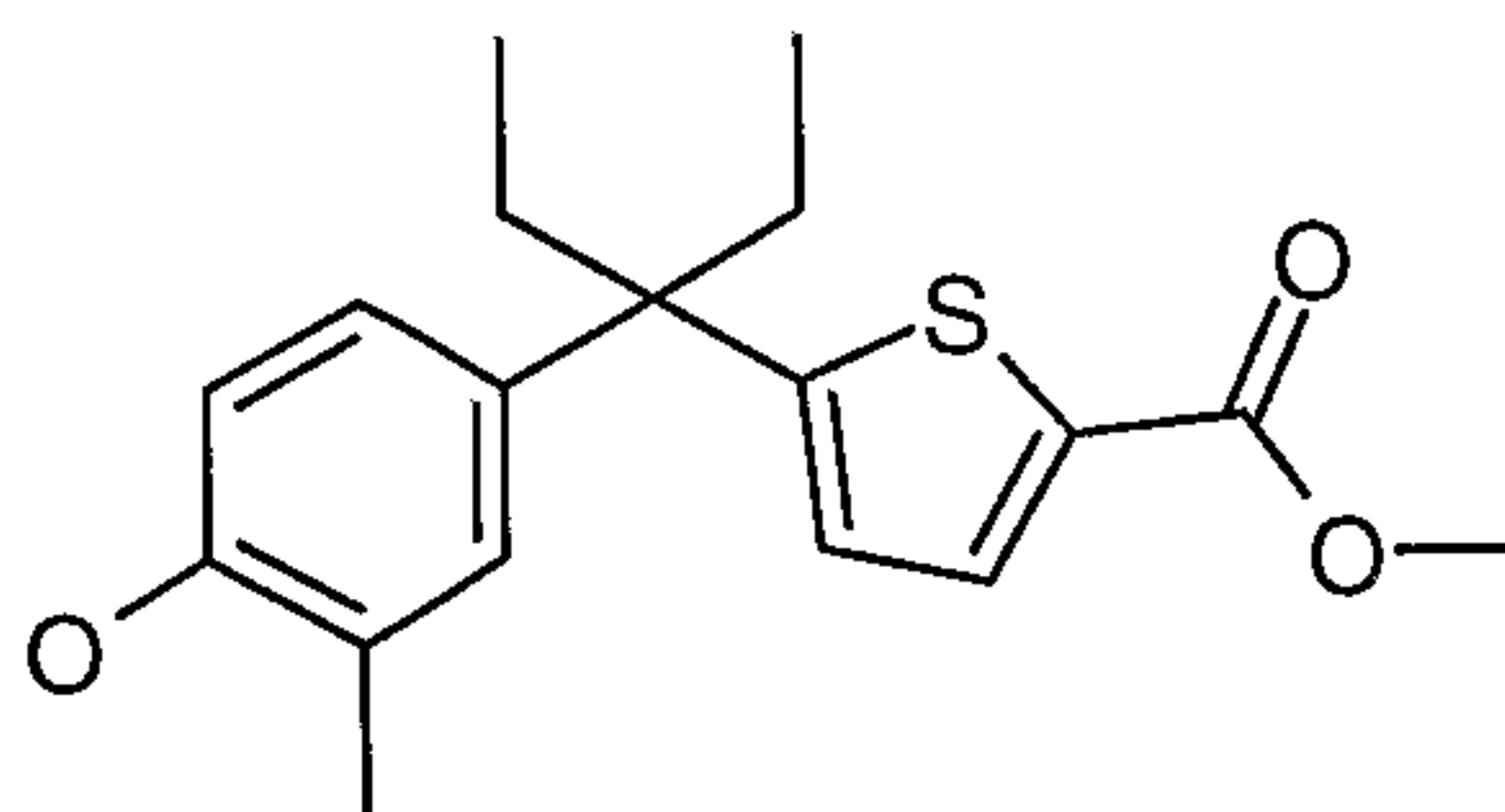


To a mixture of 5-(3-hydroxy-3-pentyl)thiophene-2-carboxylic acid 0.236 g (1.05 mmol) and methanol (15 ml) is bubbled HCl gas for a few minutes. The mixture is heated at reflux for 2 h and then concentrated under vacuum. The residue is partitioned between Et₂O and 1N NaHCO₃. The organic layer is Na₂SO₄ dried and concentrated to give the title compound (0.106 g, 62%).

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D. 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



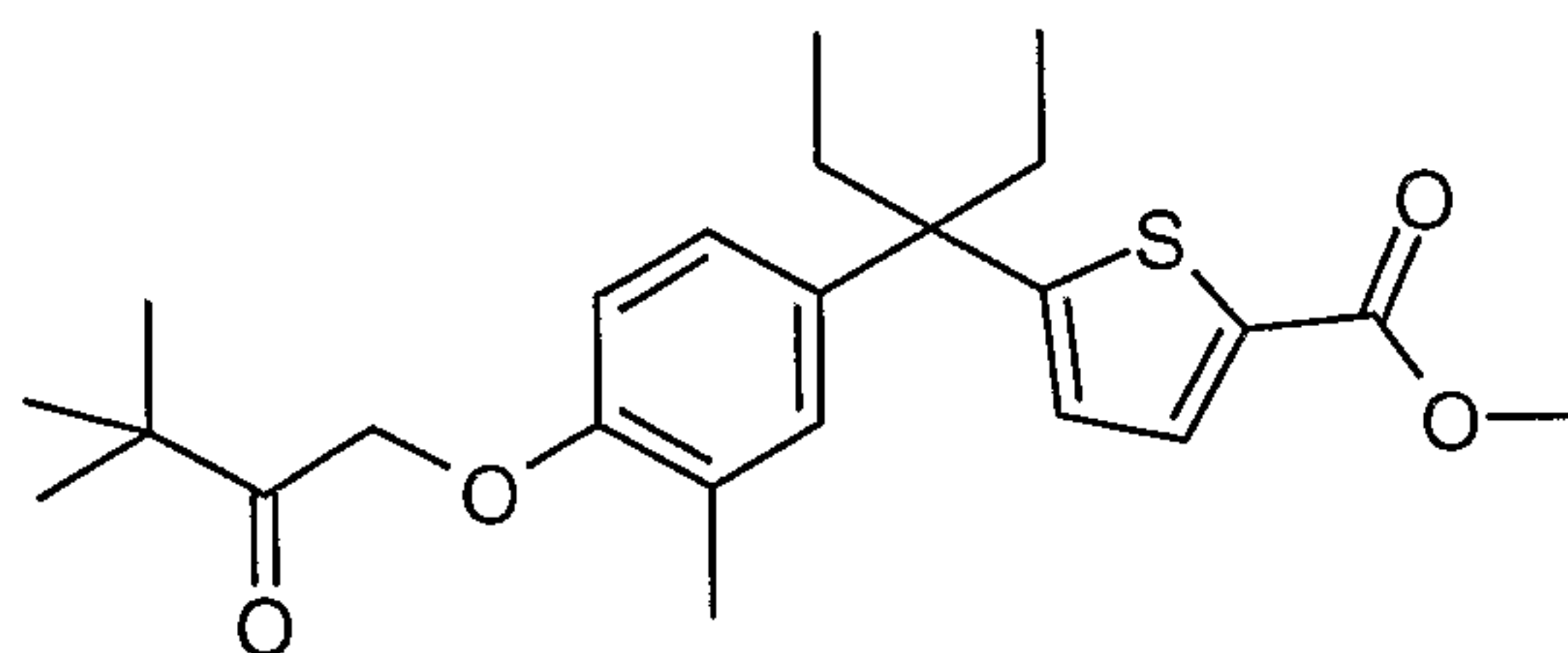
To a mixture of methyl 5-(E/Z-2-penten-3-yl)thiophene-2-carboxylate (0.106 g,
5 0.65 mmol) and o-cresol (0.282 g, 2.61 mmol) in a few drops of methylene chloride is added of BF₃ etherate (37 mg, 0.26 mmol). The mixture is stirred overnight and partitioned between Et₂O and 1N NaHCO₃. The organic layer is Na₂SO₄ dried, concentrated, and excess o-cresol is distilled off (73 °C/0.10 mm). The residue is

chromatographed (7.5% to 10% EtOAc/hex) to give the title compound (0.104 g, 50%).

10 H-NMR (ppm, CDCl₃): 7.62 (1H, d, 3.0 Hz), 6.96 (1H, s), 6.94 (1H, d, 6.0 Hz), 6.78 (1H, d, 3.0 Hz), 6.65 (1H, d, 6.0 Hz), 4.60 (1H, s), 3.82 (3H, s), 2.19 (3H, s), 2.10 (4H, q, 5.7 Hz), 0.69 (6H, t, 5.7 Hz).

LC/MS: 319.2 (M+1).

15 E. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.



To a stirred 0 °C mixture of 60% disp NaH (15.7 mg, 0.39 mmol, hex washed) is added 3'-[4-(hydroxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (100 mg, 0.31 mmol) in DMF (2.0 ml). The resulting mixture is added 1-chloropinacolone (46 mg, 0.34 mmol) with a crystal of KI. The reaction is allowed to warm to RT and stirred overnight. The mixture is partitioned between Et₂O and 1N NaHCO₃. The organic layer is Na₂SO₄ dried, filtered, concentrated, and chromatographed (on 4g of silica gel with 5% EtOAc/hex) to give the title compound

25 (0.114 g, 87%).

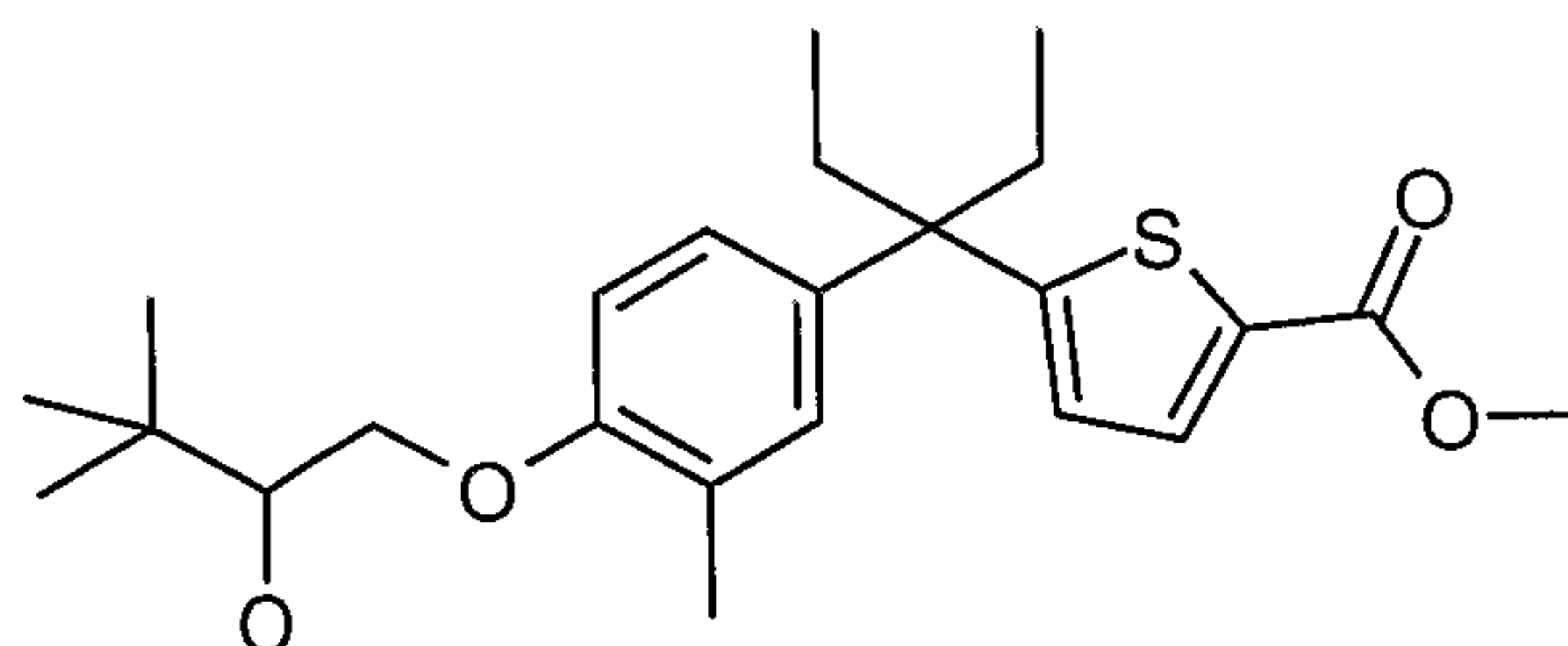
-164-

H-NMR (ppm, CDCl₃): 7.62 (1H, d, 3.0 Hz), 6.99 (1H, s), 6.97 (1H, d, 6.0 Hz), 6.77 (1H, d, 3.0 Hz), 6.50 (1H, d, 6.0 Hz), 4.83 (2H, s), 3.82 (3H, s), 2.24 (3H, s), 2.10 (4H, q, 5.7 Hz), 1.24 (9H, s), 0.68 (6H, t, 5.7 Hz).

LC/MS: 417.3 (M+1).

5

F. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.



To a mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (28 mg, 0.067 mmol) and 95% EtOH (1 ml) is added NaBH₄ (3.8 mg, 0.1 mmol). After stirring overnight, the reaction is added acetone (several drops) and partitioned between CH₂Cl₂ and 1N NaHCO₃. The organic layer is washed with water, Na₂SO₄ dried, and concentrated to give the title compound (23 mg, 82%).

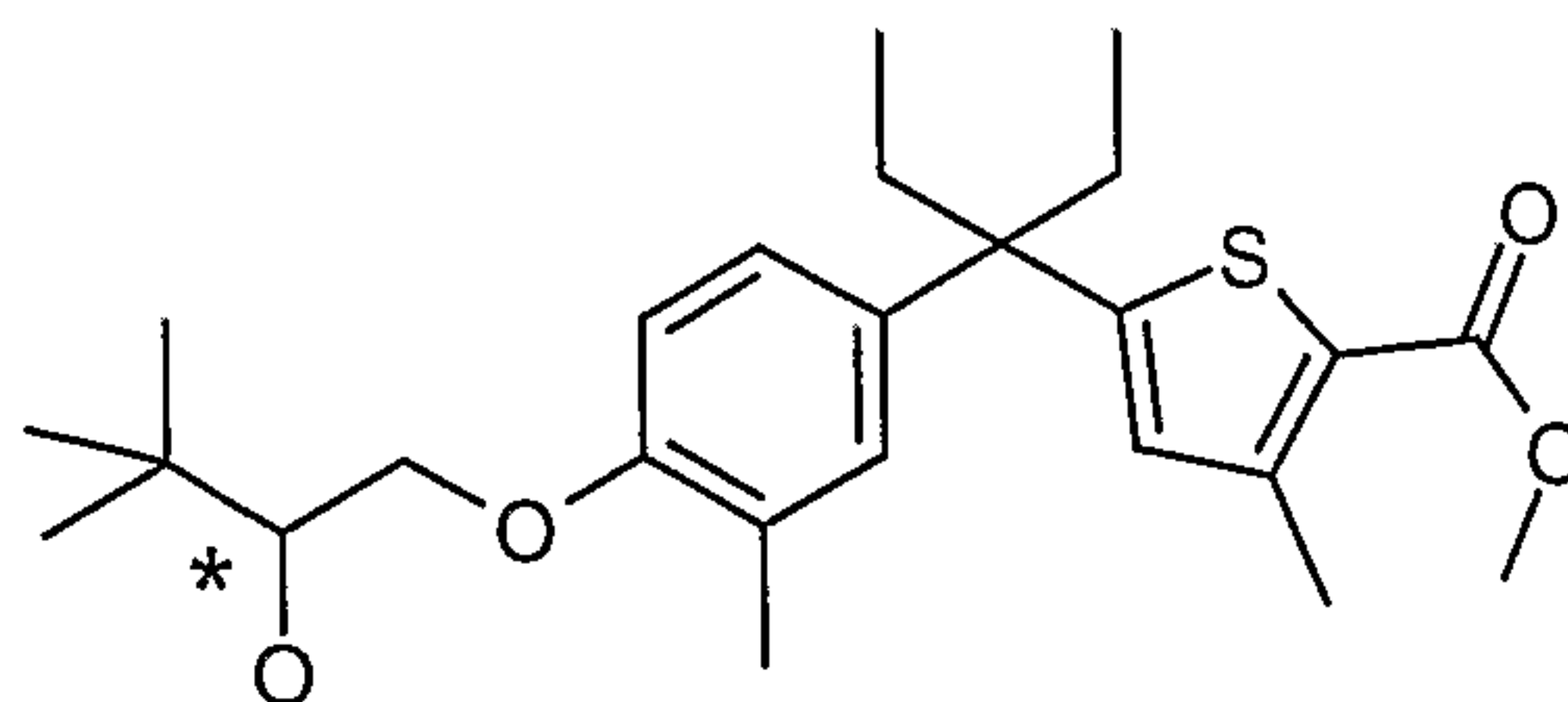
H-NMR (ppm, CDCl₃): 7.62 (1H, d, 2.7 Hz), 7.02 (1H, d, 6.0 Hz), 6.98 (1H, s), 6.78 (1H, d, 2.6 Hz), 6.71 (1H, d, 6.0 Hz), 4.06 (1H, d, 8.2 Hz), 3.86 (1H, d, 8.4 Hz), 3.82 (3H, s), 3.70 (1H, d, 8.2 Hz), 2.18 (3H, s), 2.10 (4H, q, 6.0 Hz), 1.00 (9H, s), 0.69 (6H, t, 5.8 Hz).

LC/MS: 418.2 (M+).

20

Example 6A and Example 6B:

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



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A mixture of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (1.4 g, 3.25 mmol) is chromatographed with a ChiralPak AD column to give enantiomer 1, Example 6A (666 mg, 48%) and enantiomer 2, Example 6B (686 mg, 49%).

5 Enantiomer 1, Example 6A

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate);
rt = 5.8 m

¹NMR (300MHz, DMSO-d₆) equivalent to Example 2.

High Res. ES-MS: 455.2231; calc. for C₂₅H₃₆O₄S+Na: 455.2232

10 Enantiomer 2, Example 6B

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate); rt =
9.8 m

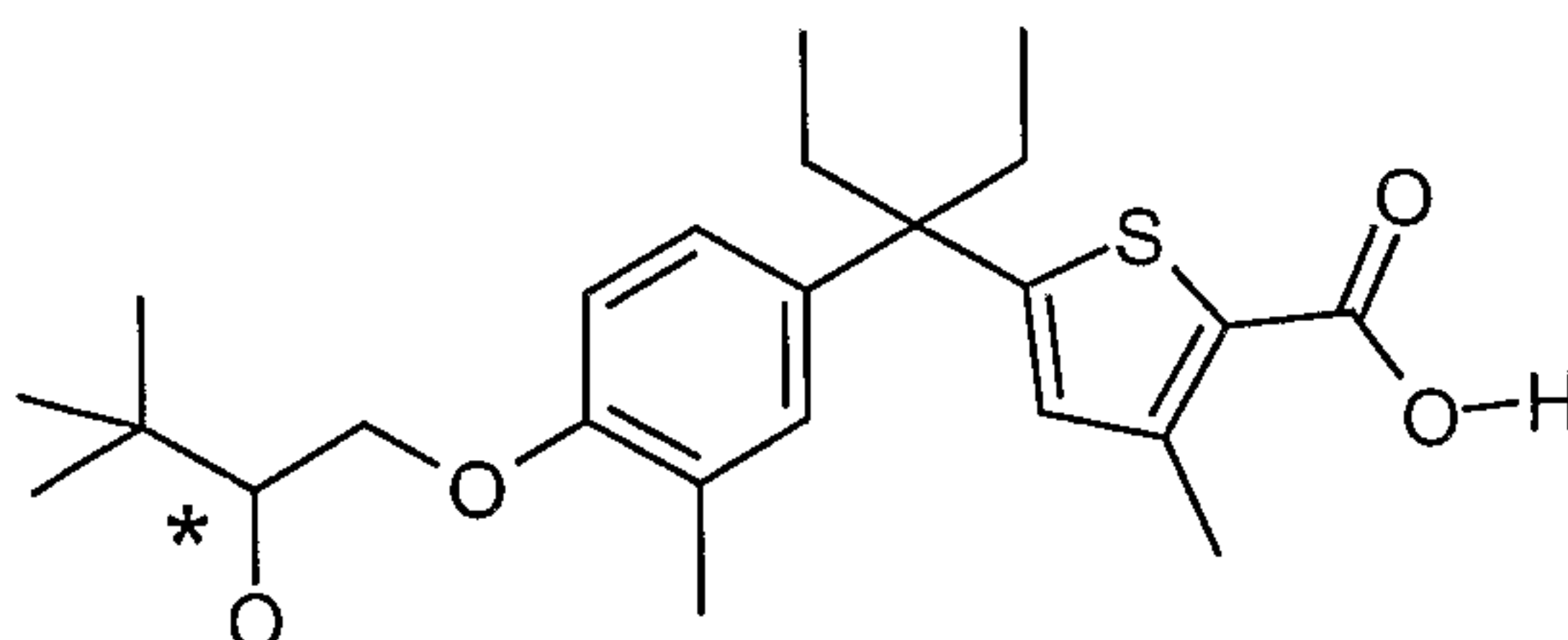
¹NMR (300MHz, DMSO-d₆) equivalent to Example 2.

High Res. ES-MS: 433.2427; calc. for C₂₅H₃₆O₄S+H: 433.2413

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Example 7:

Preparation of enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-4-methylthiophen-2-yl]pentane.



20 Using a procedure analogous to Example 3, enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (Example 6A) gives the title compound as a white foamy solid (440 mg, quant.).

¹NMR (300MHz, DMSO-d₆) equivalent to Example 3.

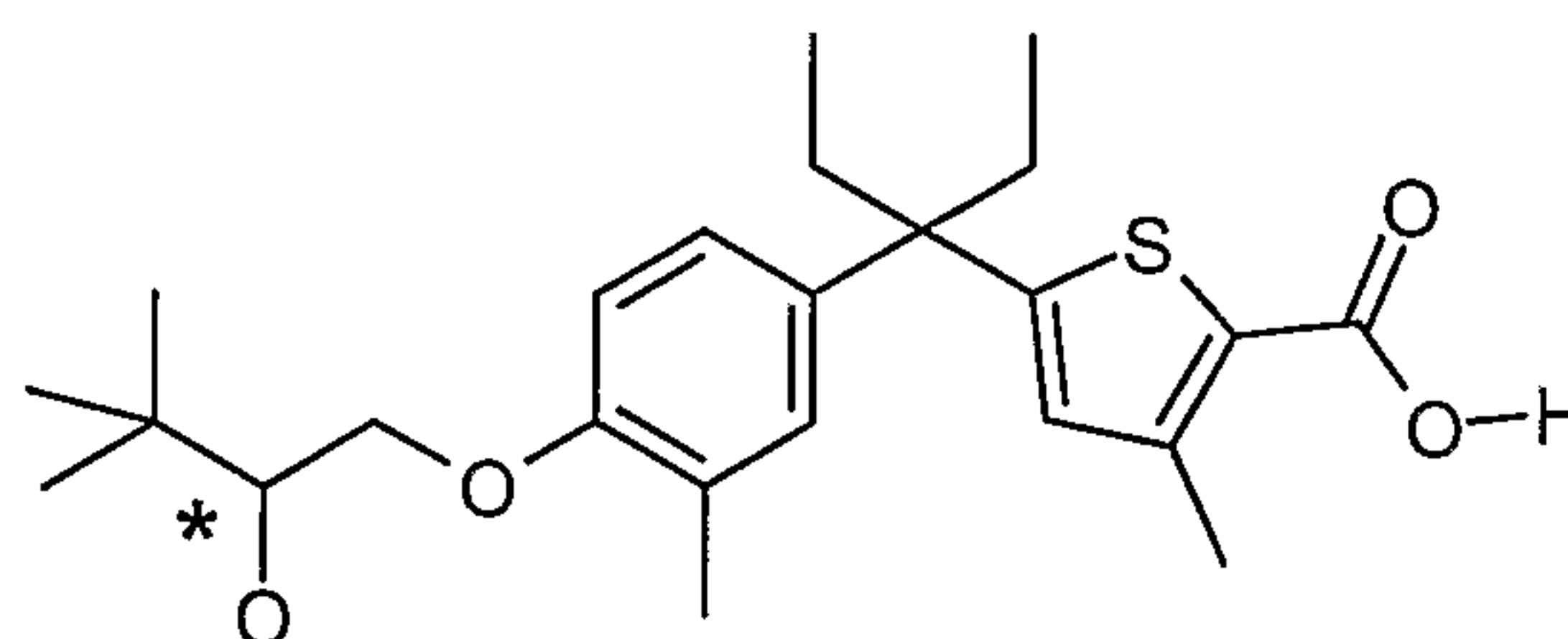
High Res. ES-MS: 441.2073; calc. for C₂₄H₃₄O₄S+Na: 441.2076

25

Example 8:

Preparation of enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-4-methylthiophen-2-yl]pentane.

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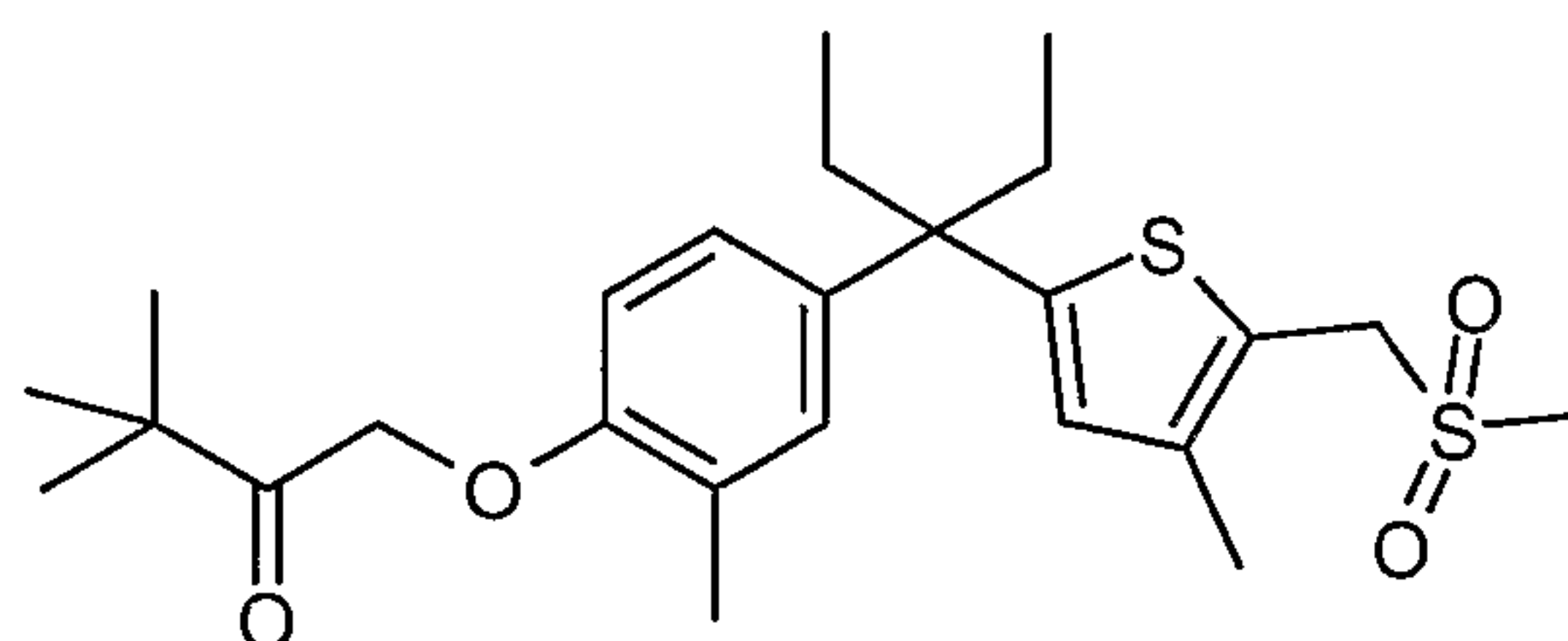
Using a procedure analogous to Example 3, enantiomer 2 (Example 6B) of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane gives the title compound as a white foamy solid (440 mg, quant.).

¹NMR (300MHz, DMSO-d₆) equivalent to Example 3.

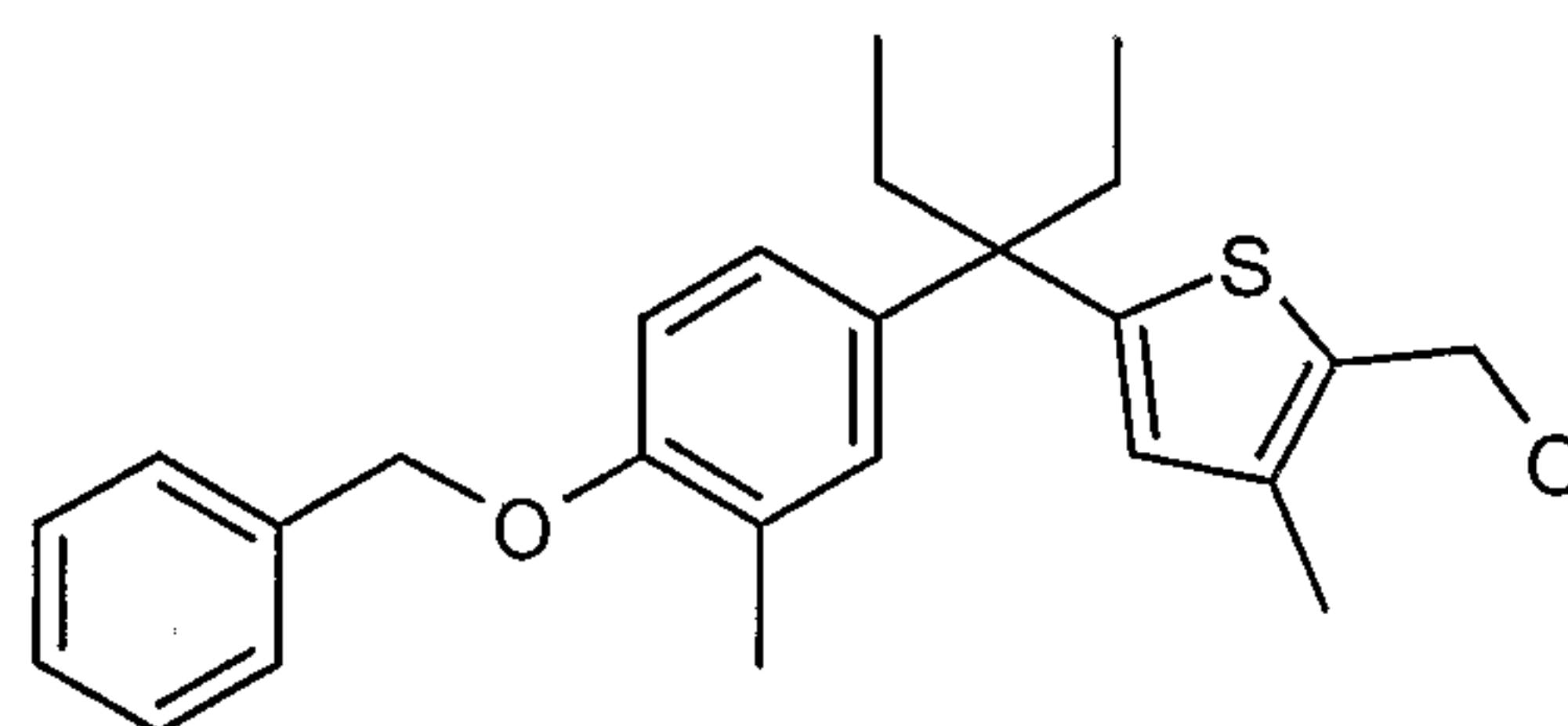
High Res. ES-MS: 441.2074; calc. for C₂₄H₃₄O₄S+Na: 441.2076

Example 9:

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methylsulfonylmethyl-4-methylthiophen-2-yl]pentane.



A. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-methyl-5-(hydroxymethyl)thiophen-2-yl]pentane.



To a 0 °C mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (1.55 g, 3.66 mmol) and THF (15 ml) is added LAH (417 mg, 11 mmol) and warmed to RT. The reaction is heated to 45 °C overnight and then cooled to 0 °C. The mixture is quenched with sat'd Na₂SO₄,

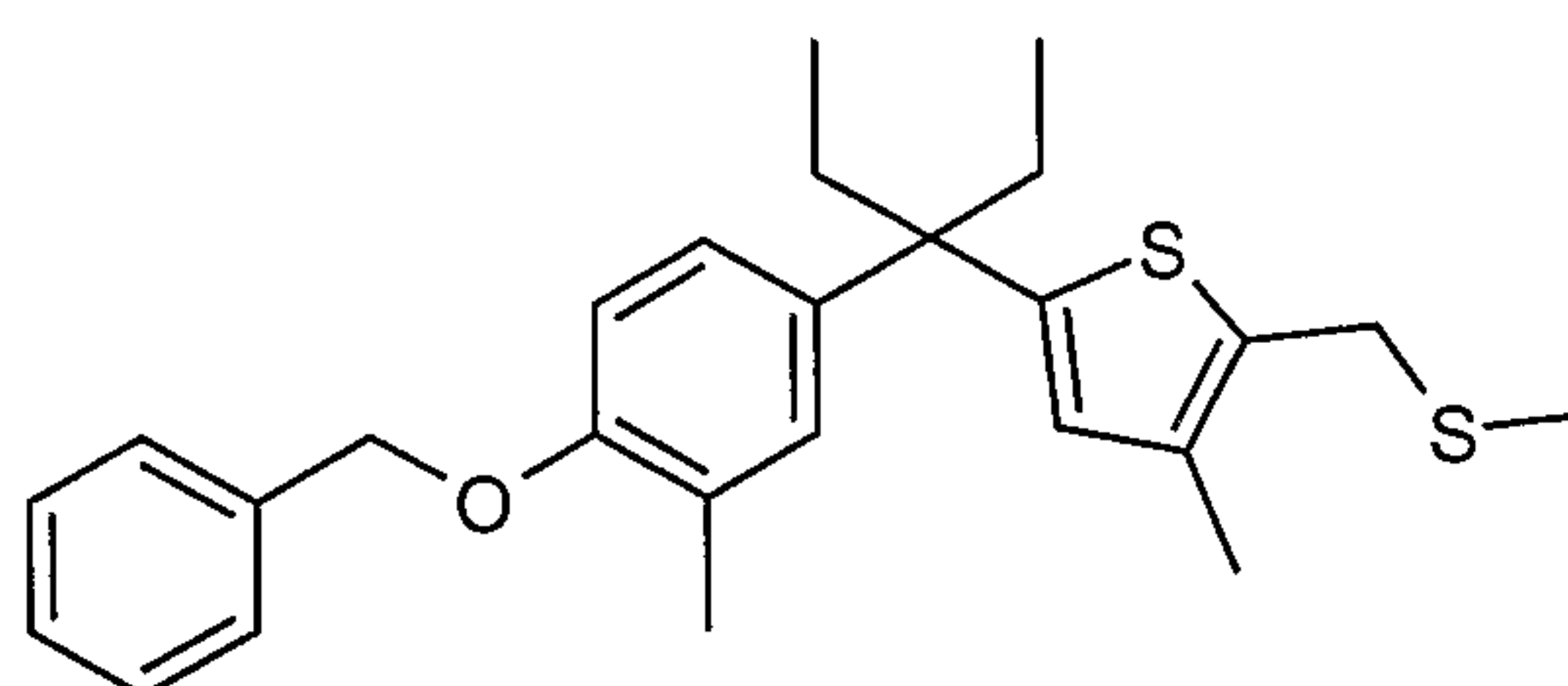
-167-

diluted with Et₂O, dried with Na₂SO₄ and filtered. After concentration, the residue is chromatographed (CHCl₃) to give the title compound (1.1 g, 76%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.64 (t, J = 7.3 Hz, 6H), 1.96-2.05 (m, 4H), 2.06 (s, 3H), 2.15 (s, 3H), 4.43 (s, 2H), 5.06 (m, 3H), 6.55 (s, 1H), 6.89 (d, J = 9.3 Hz, 1H),
 5 7.26 (br s, 2H), 7.31 (m, 1H), 7.37 (m, 2H), 7.44 (d, J = 7.8 Hz, 2H).

High Res. ES-MS: 377.1950; calc. for C₂₅H₃₀O₂S+H-H₂O: 377.1939

B. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-methyl-5-(methylmercaptylmethyl)thiophen-2-yl]pentane.



10

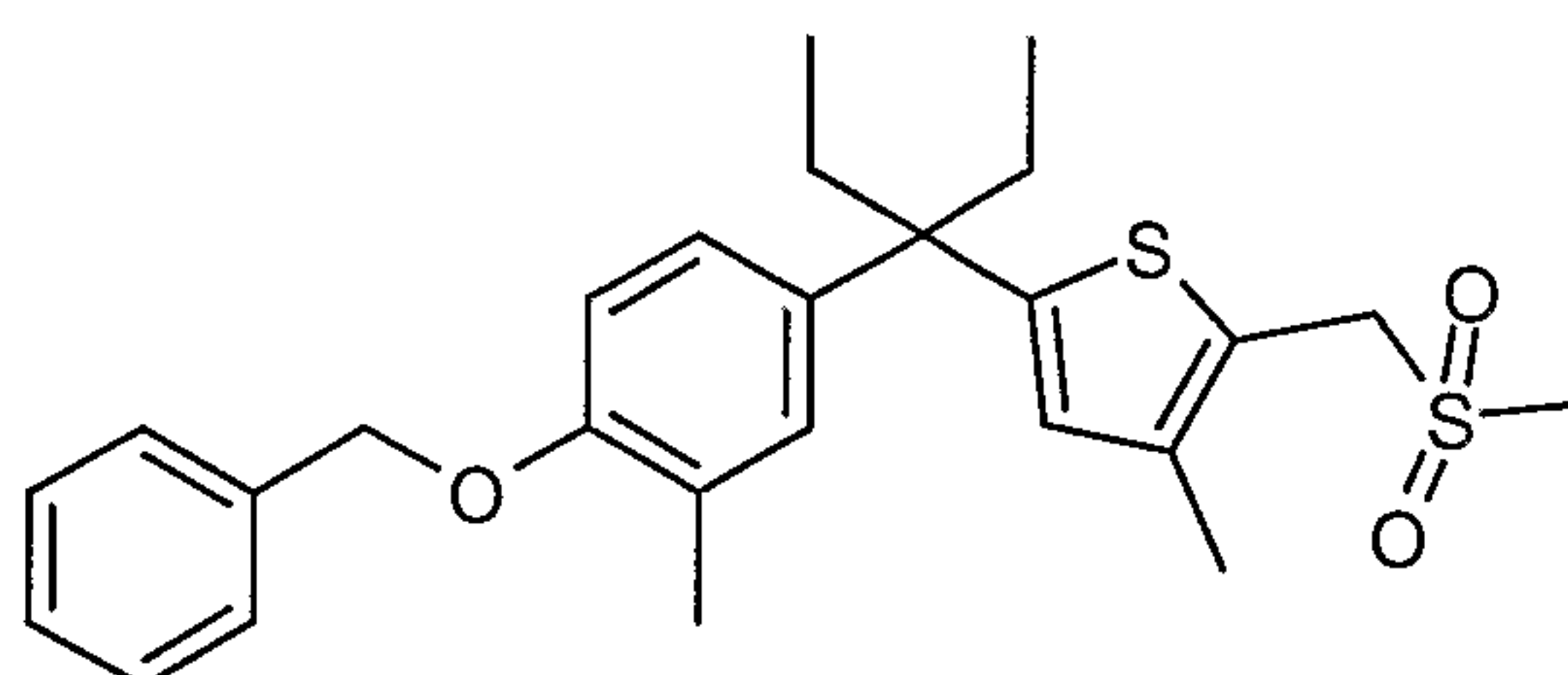
To a 0 °C mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[4-methyl-5-(hydroxymethyl)thiophen-2-yl]pentane (450 mg, 1.1 mmol) and Et₂O (3 ml) is added PBr₃ (113 ul, 1.2 mmol) and stirred for 1 h. The reaction is diluted with Et₂O, washed
 15 with water (1 X 5 ml), brine (1 X 5 ml), Na₂SO₄ dried, and concentrated. The resulting solid is dissolved in DMF, cooled to 0 °C, added NaSMe (330 mg, 4.8 mmol), and allowed to warmed RT. After stirring for 2 h, the reaction is concentrated and chromatographed (5% EtOAc/hex) to give the title compound (280 mg, 60%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.63 (t, J = 7.3 Hz, 6H), 1.94-2.05 (m, 4H), 1.97 (s, 3H), 2.07 (s, 3H), 2.15 (s, 3H), 3.75 (s, 2H), 5.06 (s, 2H), 6.56 (s, 1H), 6.90 (d, J =
 20 9.3 Hz, 1H), 7.01 (m, 2H), 7.31 (m, 1H), 7.38 (m, 2H), 7.44 (d, J = 6.8 Hz, 2H).

High Res. ES-MS: 425.1964; calc. for C₂₆H₃₂OS₂+H: 425.1973

C. 3'-[4-(Benzyloxy)-3-methylphenyl]-3'-[4-methyl-5-(methylsulfonylmethyl)thiophen-2-yl]pentane.
 25

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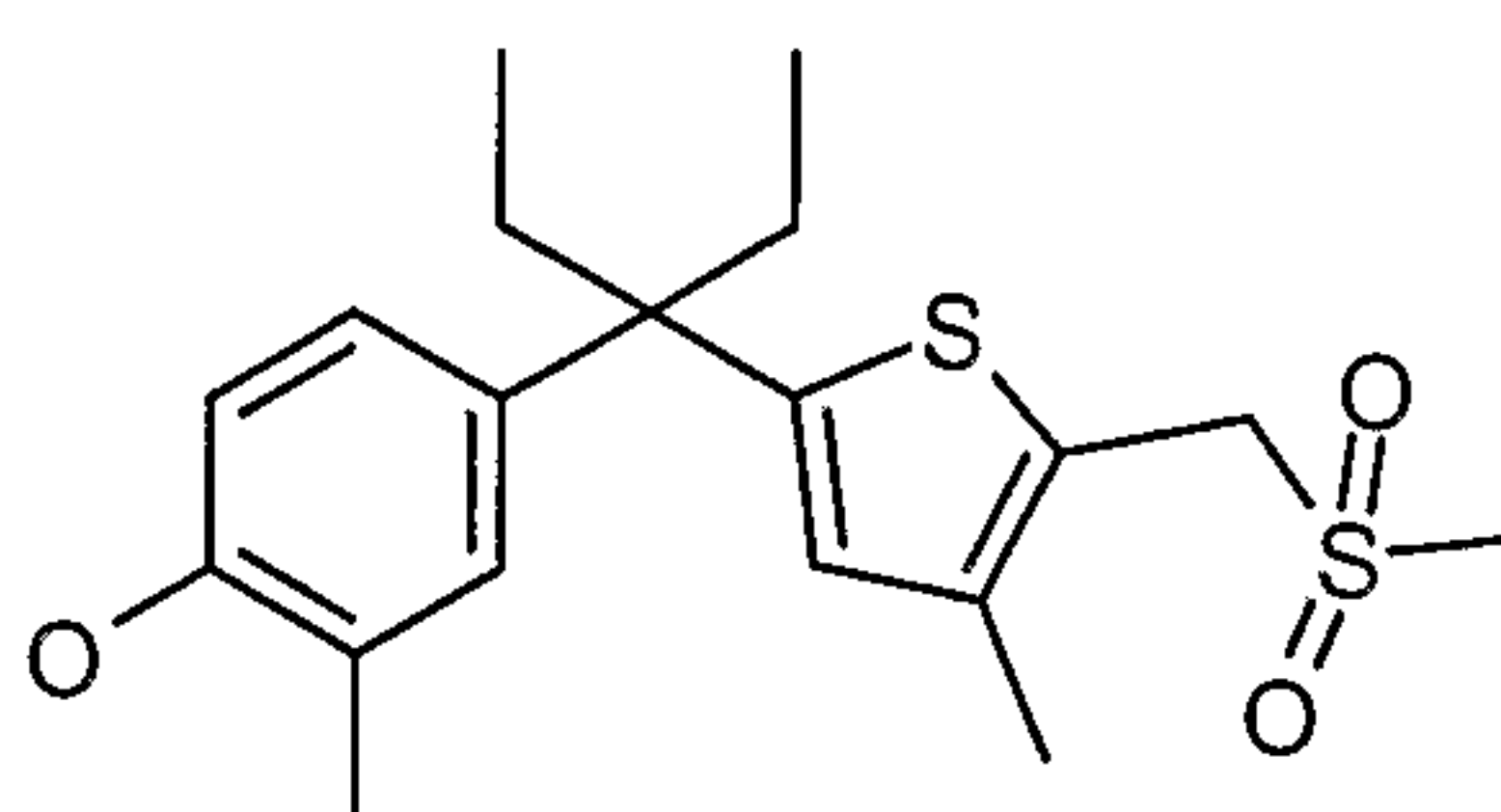


To a 0 °C mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[4-methyl-5-(methylmercaptylmethyl)thiophen-2-yl]pentane (260 mg, 0.611 mmol) and CHCl₃ (3 ml) is added 50% m-CPBA (465 mg, 1.35 mmol) and stirred for 1.5 h. The reaction is
 5 diluted with CHCl₃, washed with satd Na₂CO₃, Na₂SO₄ dried, concentrated, and chromatographed (CHCl₃ to 5% EtOAc/CHCl₃) to give the title compound as a white foamy solid (250 mg, 90%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.64 (t, J = 7.3 Hz, 6H), 1.99-2.07 (m, 4H), 2.14 (s, 3H), 2.15 (s, 3H), 2.90 (s, 3H), 4.53 (s, 2H), 5.06 (s, 2H), 6.67 (s, 1H), 6.91 (d, J =
 10 9.3 Hz, 1H), 7.03 (m, 2H), 7.31 (m, 1H), 7.38 (m, 2H), 7.44 (d, J = 7.3 Hz, 2H).

High Res. ES-MS: 474.2126; calc. for C₂₆H₃₂O₃S₂+NH₄: 474.2137

D. 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[4-methyl-5-(methylsulfonylmethyl)thiophen-2-yl]pentane.



15

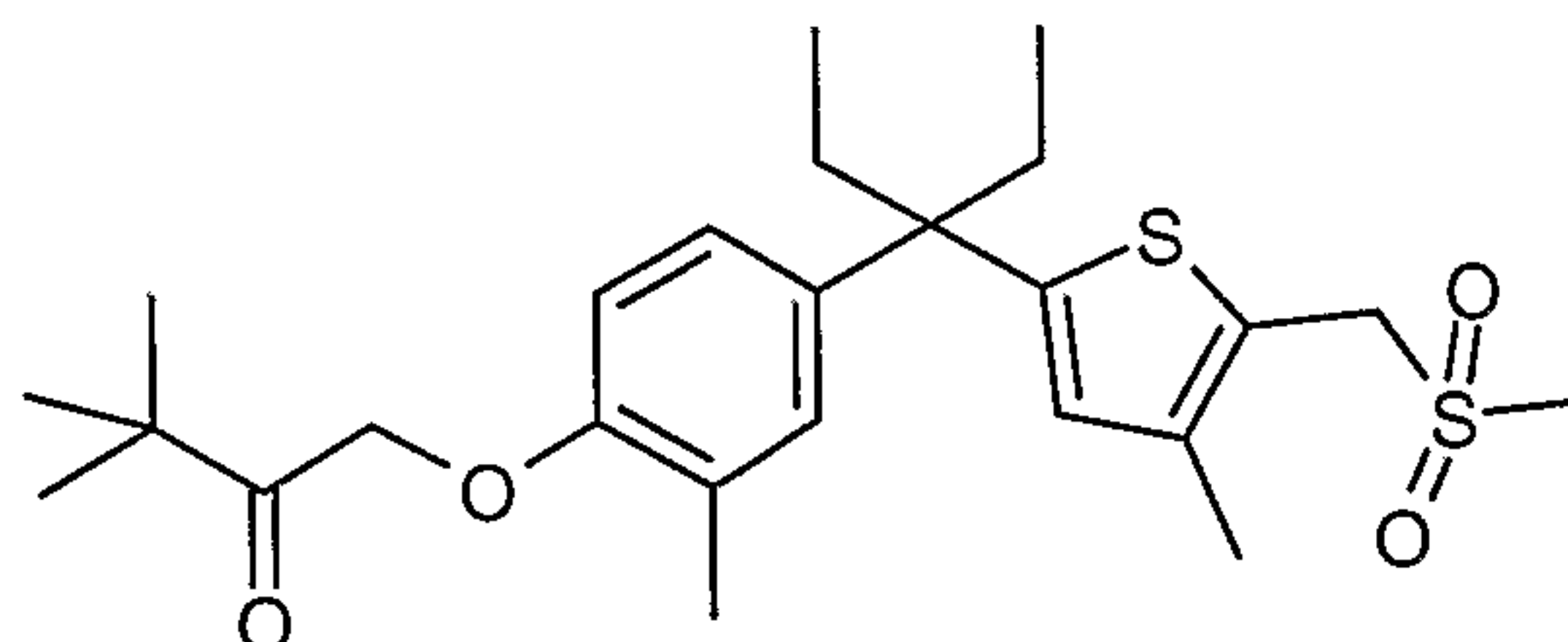
Using a procedure analogous to Example 1F, 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[4-methyl-5-(methylsulfonylmethyl)thiophen-2-yl]pentane gives the title compound as a white foamy solid (160 mg, 81%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.63 (t, J = 7.3 Hz, 6H), 1.94-2.03 (m, 4H), 2.06 (s, 3H), 2.14 (s, 3H), 2.89 (s, 3H), 4.52 (s, 2H), 6.65 (m, 2H), 6.85 (dd, J = 2.4, 8.3
 20 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 9.09 (s, 1H).

High Res. ES-MS: 384.1648; calc. for C₁₉H₂₆O₃S₂+NH₄: 384.1667

E. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methylsulfonylmethyl-4-methylthiophen-2-yl]pentane.
 25

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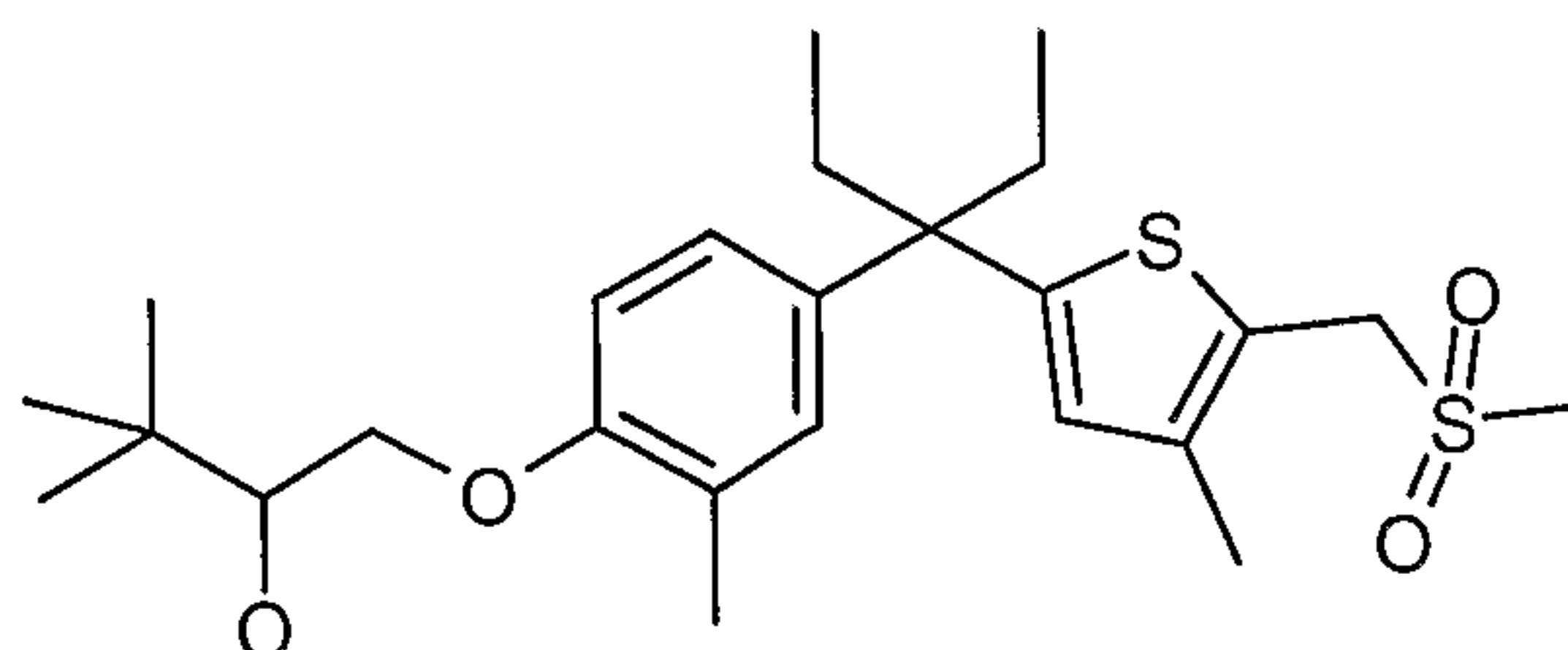
Using a procedure analogous to Example 1G, 3'-[4-(hydroxy)-3-methylphenyl]-3'-[4-methyl-5-(methylsulfonylmethyl)thiophen-2-yl]pentane gives the title compound (160 mg, 84%).

^1NMR (400MHz, DMSO- d_6) δ ppm: 0.63 (t, $J = 7.3$ Hz, 6H), 1.16 (s, 9H), 2.00-2.08 (m, 4H), 2.14 (s, 3H), 2.15 (s, 3H), 2.90 (s, 3H), 4.53 (s, 2H), 5.07 (s, 2H), 6.60 (d, $J = 8.3$ Hz, 1H), 6.67 (s, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 7.01 (s, 1H).

High Res. ES-MS: 482.2397; calc. for $\text{C}_{25}\text{H}_{26}\text{O}_4\text{S}_2 + \text{NH}_4$: 482.2399

Example 10:

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methylsulfonylmethyl-4-methylthiophen-2-yl]pentane.



Using a procedure analogous to Example 2, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methylsulfonylmethyl-4-methylthiophen-2-yl]pentane gives the title compound as a white foamy solid (440 mg, quant.).

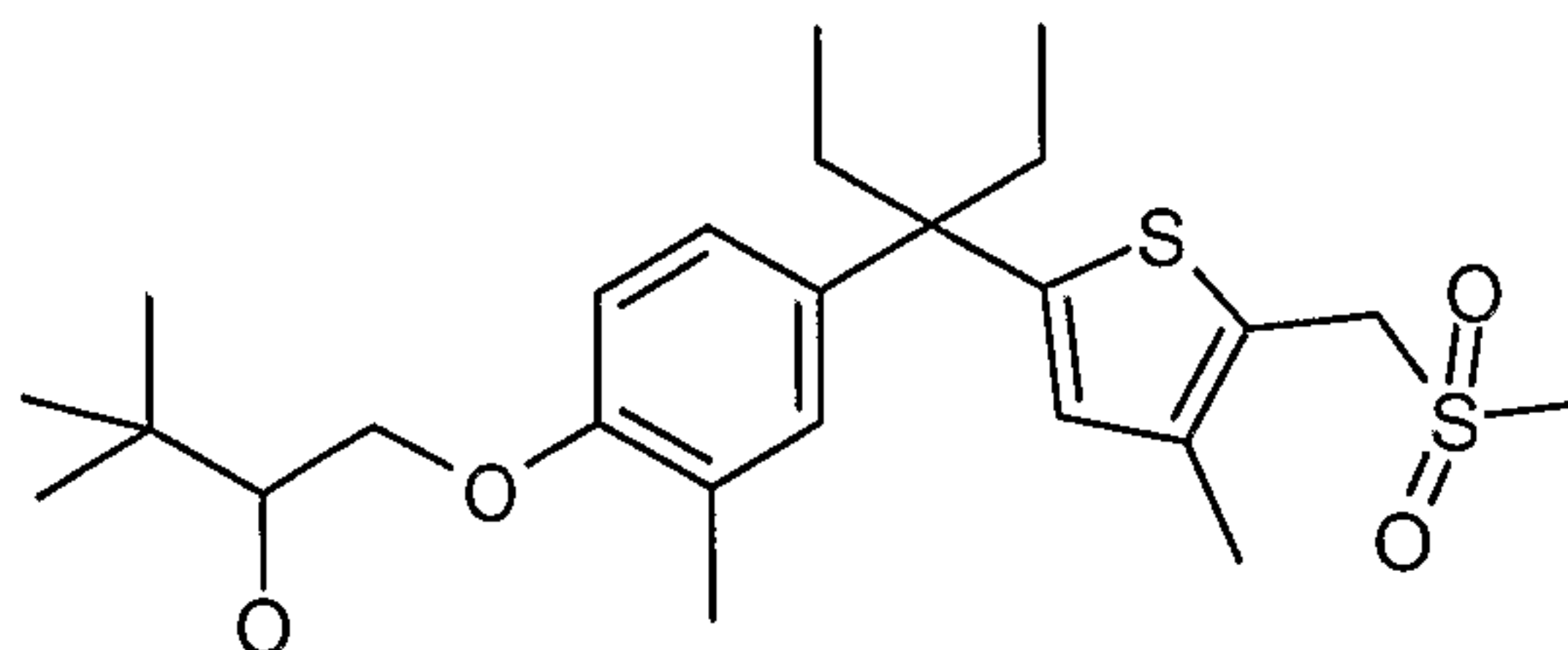
^1NMR (400MHz, DMSO- d_6) δ ppm: 0.62 (t, $J = 7.3$ Hz, 6H), 0.92 (s, 9H), 1.97-2.08 (m, 4H), 2.12 (s, 3H), 2.14 (s, 3H), 2.89 (s, 3H), 3.45 (m, 1H), 3.76 (dd, $J = 7.3, 9.8$ Hz, 1H), 4.02 (dd, $J = 2.9, 9.8$ Hz, 1H), 4.52 (s, 2H), 4.78 (d, $J = 5.4$ Hz, 1H), 6.66 (s, 1H), 6.82 (d, $J = 8.3$ Hz, 1H), 7.01 (m, 2H).

High Res. ES-MS: 484.2553; calc. for $\text{C}_{25}\text{H}_{38}\text{O}_4\text{S}_2 + \text{NH}_4$: 484.2555

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Example 11A and 11B

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methylsulfonylmethyl-4-methylthiophen-2-yl]pentane.



5

A racemic mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methylsulfonylmethyl-4-methylthiophen-2-yl]pentane is chromatographed with a Chiralcel AD column to give enantiomer 1, Example 11A (205 mg, ~50%) and enantiomer 2, Example 11B (150 mg, 38%) .

10 Enantiomer 1, Example 11A

HPLC: Chiralcel AD (4.6X250 mm); 40% IPA/60% hept; 1 ml/m (flow rate); rt = 9.86 m; 260 nm.

¹NMR equivalent to Example 10.

High Res. ES-MS: 489.2127; calc. for C₂₅H₃₈O₄S₂+Na: 489.2109.

15 Enantiomer 2, Example 11B

HPLC: Chiralcel AD (4.6X250 mm); 40% IPA/60% hept; 1 ml/m (flow rate); rt = 12.64 m; 260 nm.

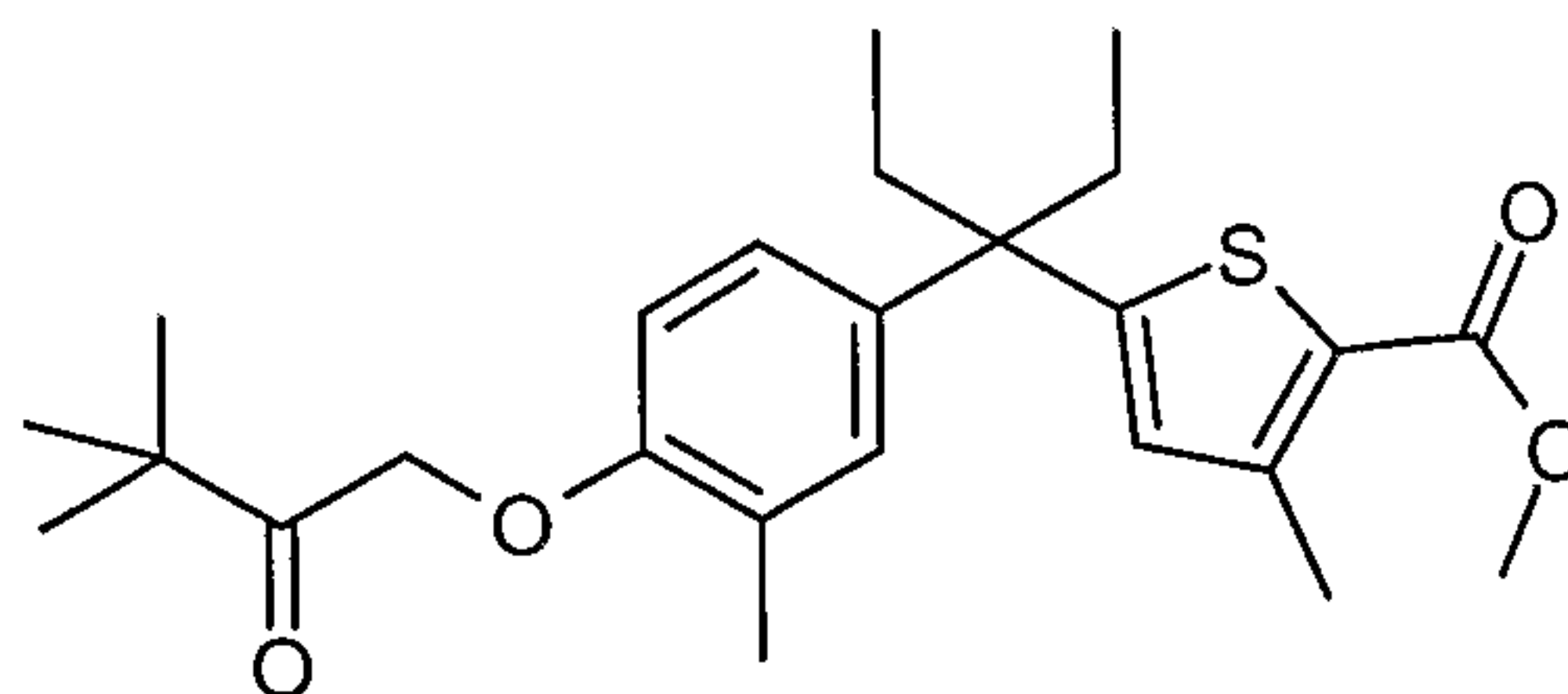
¹NMR equivalent to Example 10.

High Res. ES-MS: 489.2132; calc. for C₂₅H₃₈O₄S₂+Na: 489.2109.

20

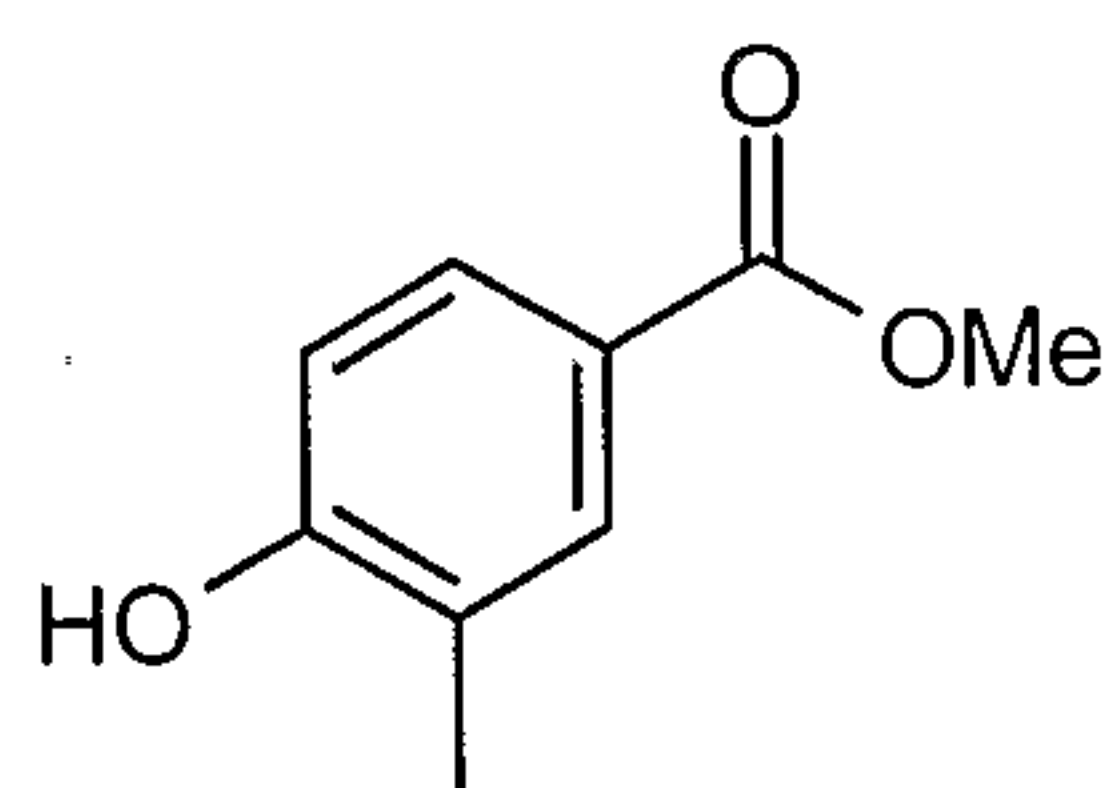
Example 12

Alternative preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonylmethyl-4-methylthiophen-2-yl]pentane (Example 1).



25 A. 4-Hydroxy-3-methylbenzoic acid methyl ester.

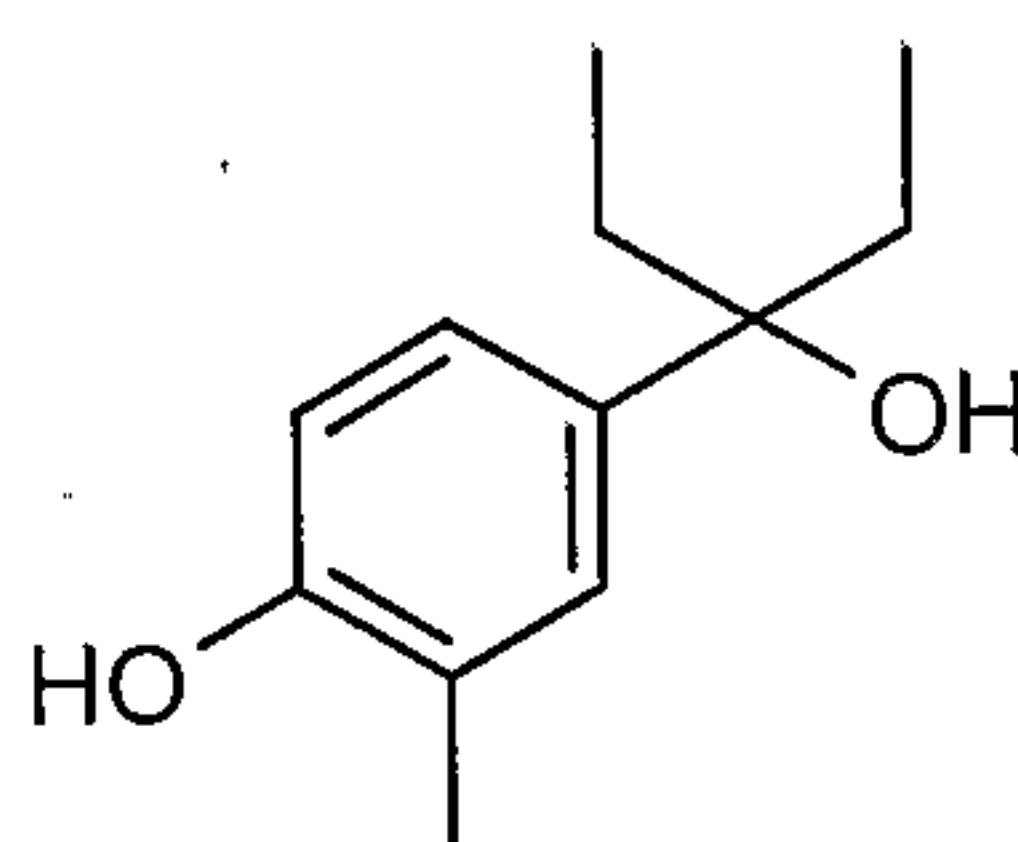
-171-



To a mixture of 3-methyl-4-hydroxybenzoic acid (342 g, 2.24 mol) in MeOH (3.5 l) is bubbled HCl (g) for 5 m. The mixture is stirred for 12 h at RT. The reaction is concentrated to give the title compound (372 g, quant).

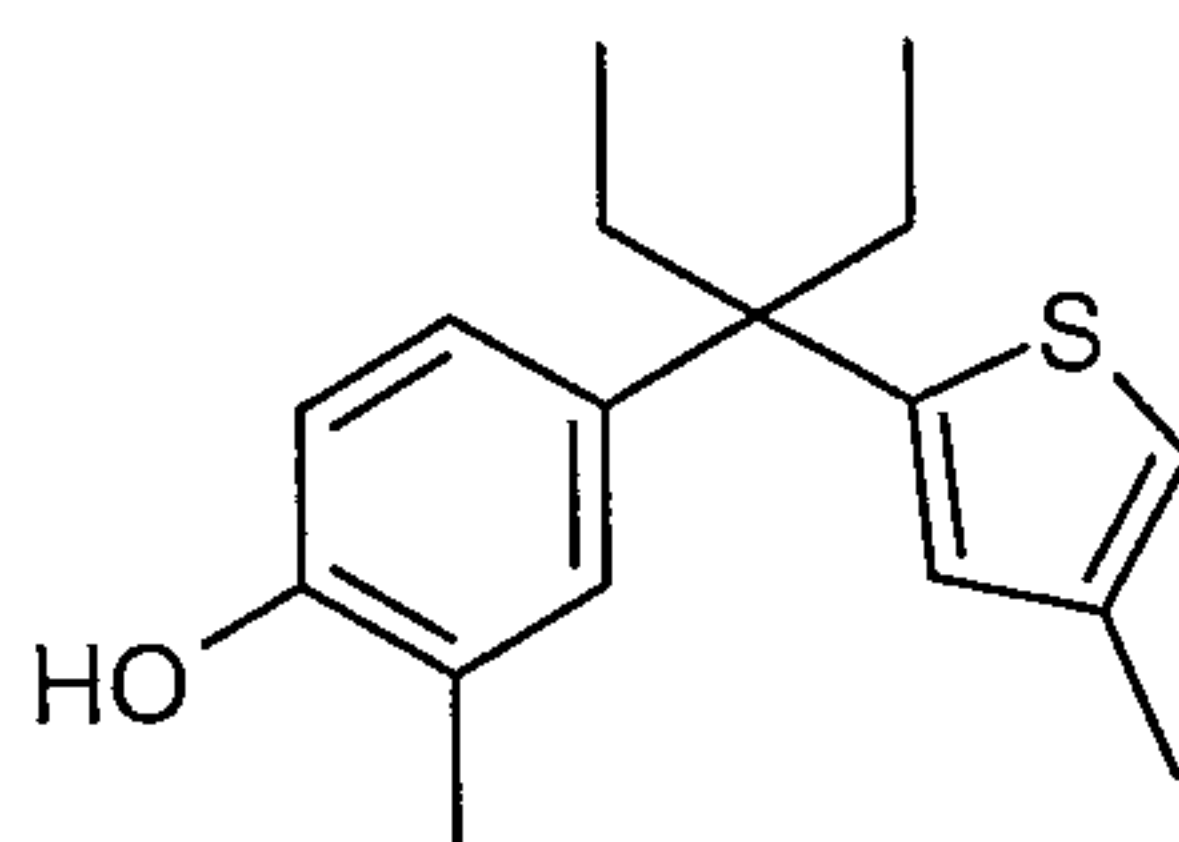
5 H-NMR (ppm, CDCl₃): 7.82 (1H, s), 7.78 (1H, dd,), 6.80 (1H, d), 3.86 (3H, s), 2.22 (3H, s).

B. 3'-[4-hydroxy-3-methylphenyl]pentan-3-ol].



10 To a 0 °C mixture of 4-hydroxy-3-methylbenzoic acid methyl ester (373 g, 2.24 mol) in THF (6 l) is added 3.0 M EtMgBr/Et₂O (2.3 l, 6.93 mol) over 3 h. The mixture is warmed to 40 °C for 2 h and cooled to 0 °C. Saturated NaHCO₃ is added slowly until gas evolution ceases and the reaction is partitioned between EtOAc/water. The organic layer is washed with brine, water, MgSO₄ dried and concentrated. The residue is dissolved in
15 CH₂Cl₂, dried with Na₂SO₄ and concentrated to give the title compound (440 g, quant).
H- NMR (ppm, CDCl₃): 7.06 (1H, s), 7.02 (1H, dd), 6.78 (1H, d), 4.60 (1H, s), 2.24 (3H, s), 1.80 (4H, m), 0.77 (6H, t).

C. 3'-[4-(Hydroxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane.



20

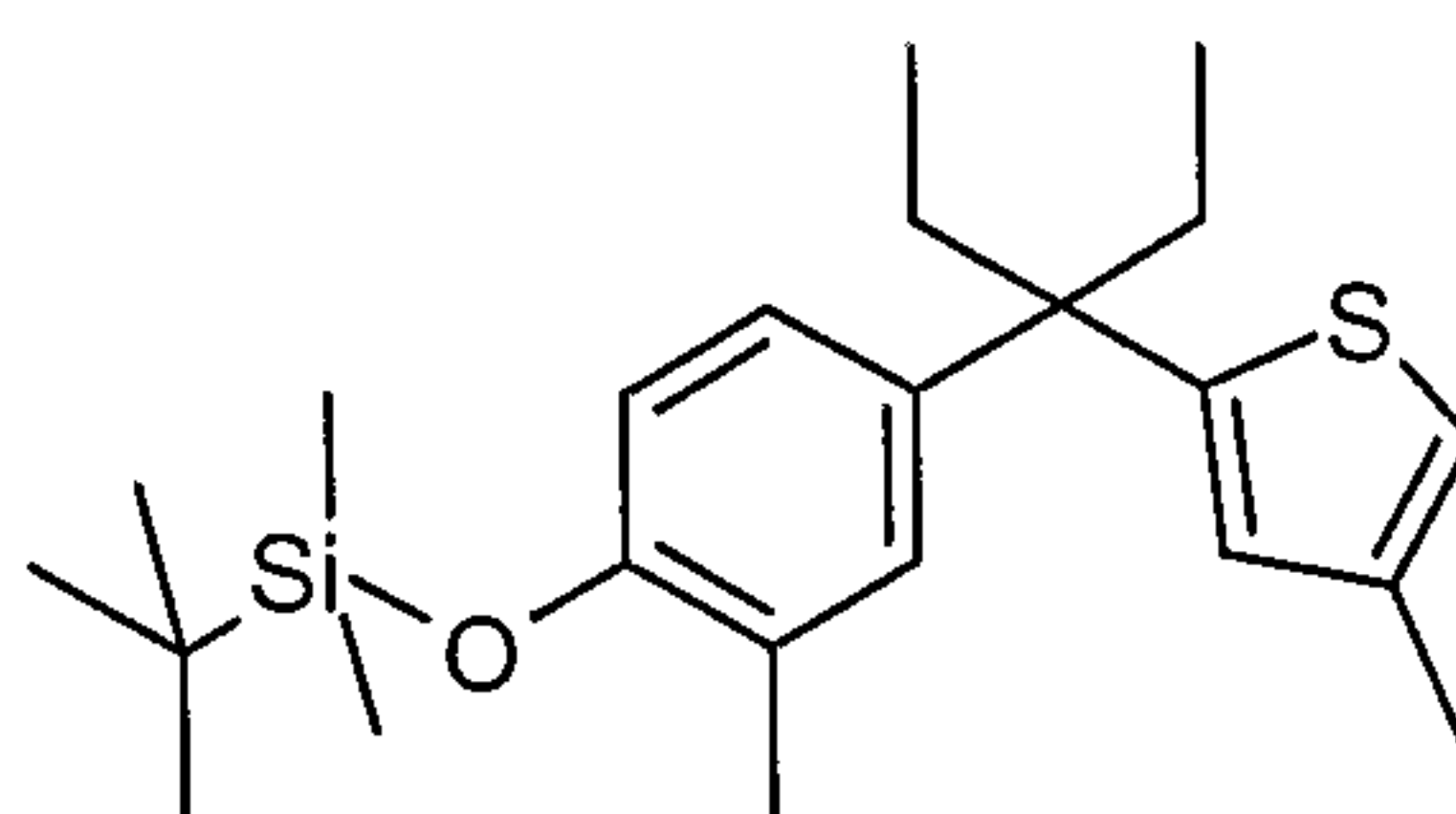
To a -78 °C mixture of 3'-[4-hydroxy-3-methylphenyl]pentan-3-ol] (415 g, 2.13 mol), 3-methylthiophene (627 g, 6.39 mol) and CH₂Cl₂ (6 l) is added BF₃·Et₂O (1.81 kg,

-172-

12.8 mol), maintaining the temperature below -75°C . The reaction is warmed to RT for 3 h and cooled to 0°C . Saturated NaHCO_3 is added until the gas evolution ceases and the mixture is partitioned with water. The organic layer is dried with Na_2SO_4 , concentrated and chromatographed (EtOAc/hex) to give the title compound (425 g, 73%).

^1NMR (400MHz, $\text{DMSO}-d_6$) δ ppm: 0.63 (t, $J = 7.3$ Hz, 3H), 2.01 (m, 4H), 2.08 (s, 3H), 2.16 (s, 3H), 6.67 (m, 2H), 6.88 (m, 2H), 6.93 (d, $J = 1.9$ Hz, 1H), 9.10 (s, 1H). High Res. EI-MS: 274.1389; calc. for $\text{C}_{17}\text{H}_{22}\text{OS}$: 274.1391

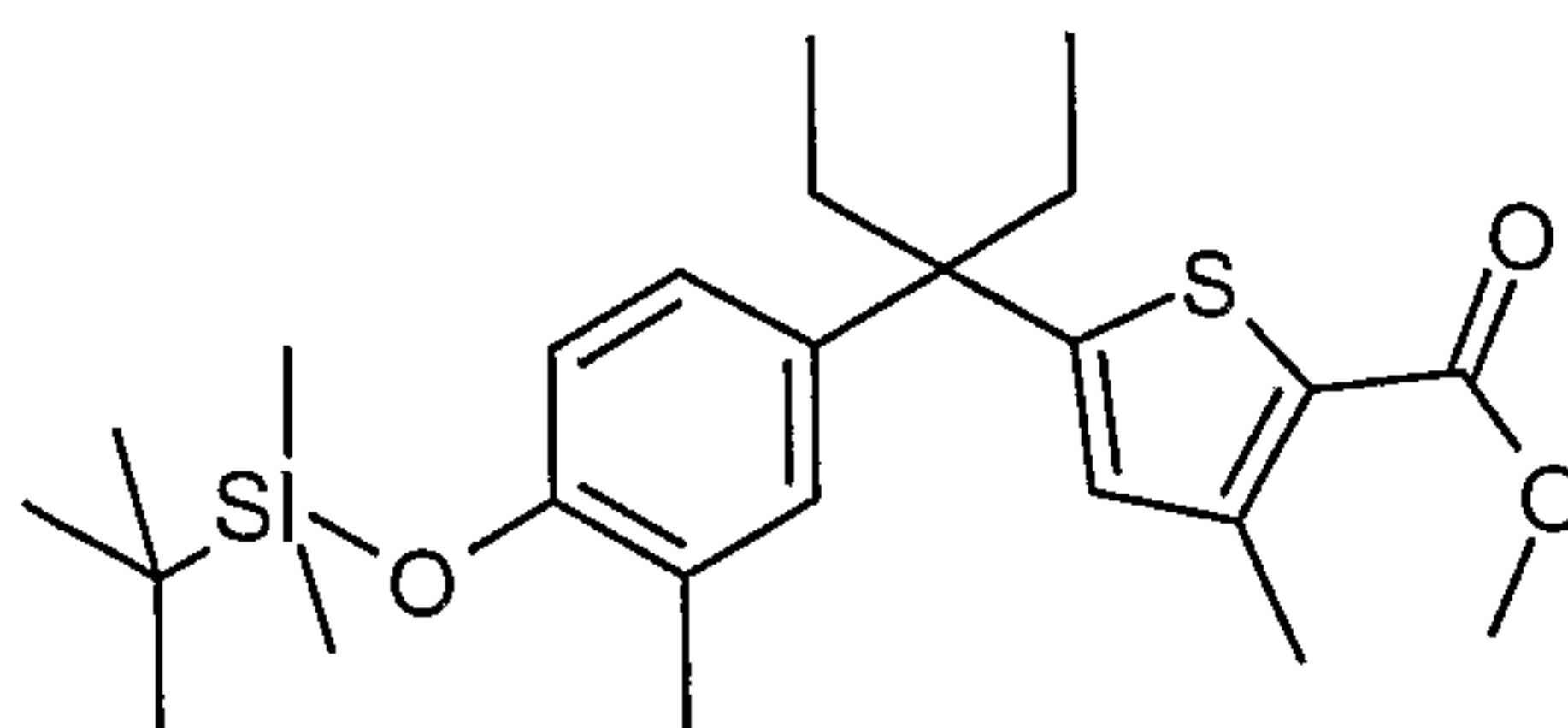
D. 3'-[4-(t-Butyldimethylsilyloxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane.



To a mixture of 3'-[4-(hydroxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane (5.00g, 187.2 mmol) and t-butyldimethylsilyl chloride (2.75g, 18.2 mmol) in CH_2Cl_2 (100 ml) is added imidazole (1.24g, 18.2 mmol). The reaction is stirred for 24 h at RT. The mixture is diluted with Hex (100 ml), filtered and concentrated. The concentrate is suspended in Hex (100 ml), filtered and concentrated to give the title compound as an oil (6.91 g, 98%).

H-NMR (ppm, CDCl_3): 7.05 (1H, d, 2.0 Hz), 6.97 (1H, d, 9.0 Hz), 6.72 (1H, d, 1.1 Hz), 6.68 (1H, d, 8.3 Hz), 6.62 (1H, d, 1.3 Hz), 2.23 (3H, s), 2.20 (3H, s), 2.10 (4H, m), 1.03 (9H, s), 0.72 (6H, t, 7.3 Hz), 0.23 (6H, s).

E. 3'-[4-(t-Butyldimethylsilyloxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.

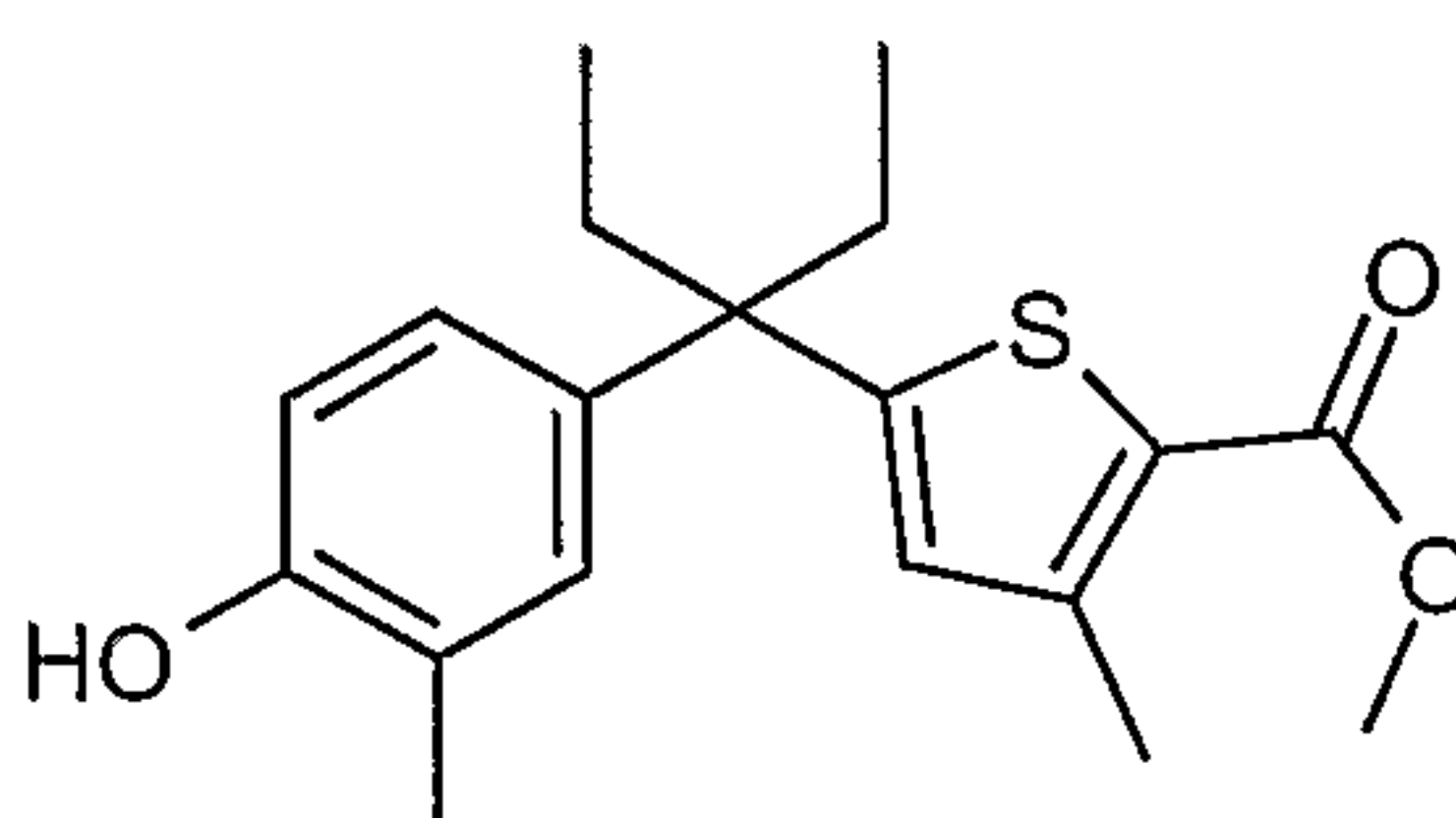


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To a -78°C mixture of 3'-[4-(t-butyldimethylsilyloxy)-3-methylphenyl]-3'-[4-methylthiophen-2-yl]pentane (6.75 g, 17.4 mmol) and THF (100 ml) is added 2.5 M n-BuLi/hex (7.64 ml, 19.1 mmol). The mixture is stirred for 25 m and warmed to 0°C over 15 m. The reaction is cooled to -78°C , added methyl chloroformate (1.48 ml, 19.1 mmol) and warmed to RT overnight. To the reaction is added water (25 ml). The mixture is concentrated and partitioned with CH_2Cl_2 / water. The organic layer is concentrated to yield the title compound (7.8g, quant.).

H-NMR (ppm, CDCl_3): 6.99 (1H, d, 2.0 Hz), 6.94 (1H, dd, 2.3, 8.5 Hz), 6.67 (1H, d, 8.5 Hz), 6.62 (1H, s), 3.77 (3H, s), 2.49 (3H, s), 2.17 (3H, s), 2.09 (4H, m), 1.01 (9H, s), 0.70 (6H, t, 7.3 Hz), 0.22 (6H, s).

F. 3'-[4-Hydroxy-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.

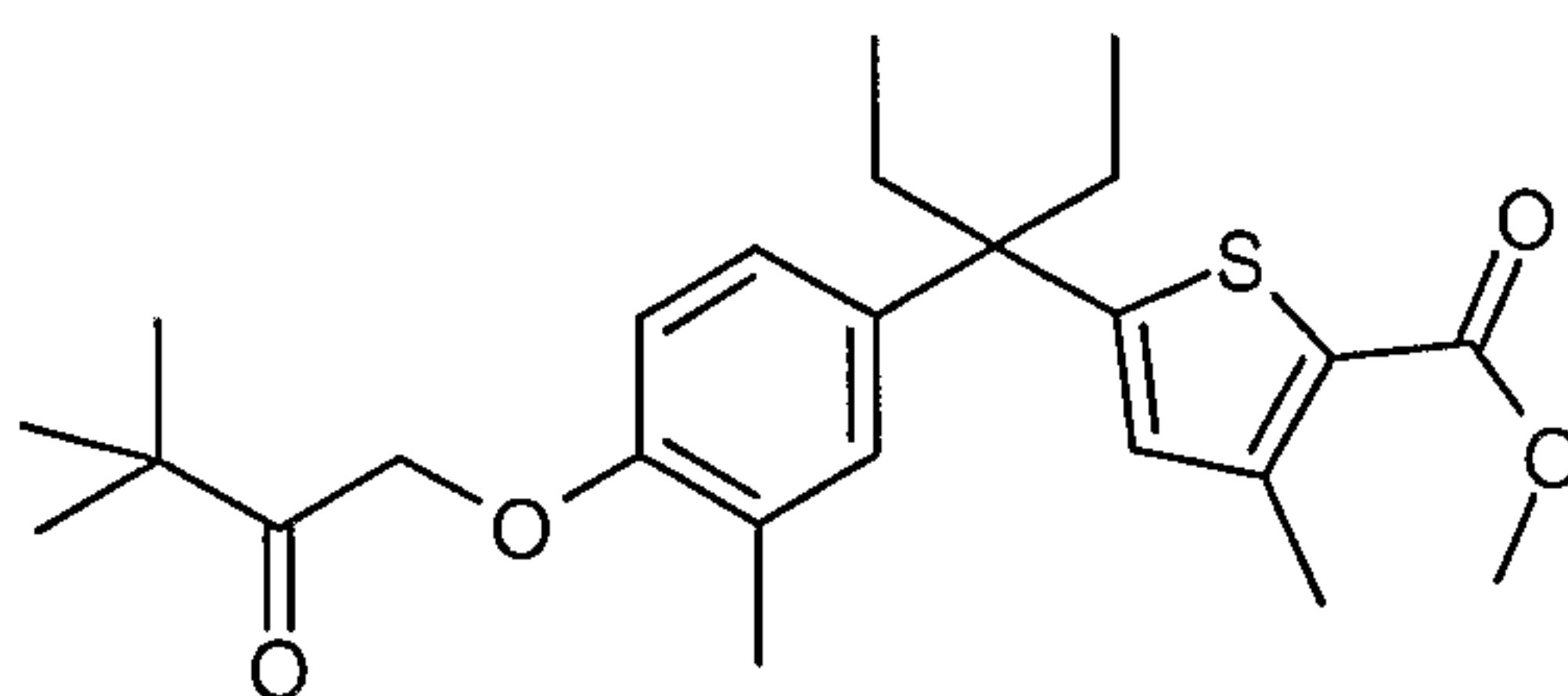


To a 0°C mixture of 3'-[4-(t-butyldimethylsilyloxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (130 g, 292 mmol) and THF (1 L) is added 1.0 M TBAF/THF (292 ml, 292 mmol) over 20 m. The reaction is warmed to RT and stirred for 1 d. The mixture is concentrated and partitioned with CH_2Cl_2 / water. The organic layer is concentrated and chromatographed (EtOAc/hex) to give the title compound (40.2 g, 41%).

H-NMR (ppm, CDCl_3): 6.97 (1H, s), 6.95 (1H, d, 7.5 Hz), 6.69 (1H, d, 8.2 Hz), 6.61 (1H, s), 4.95 (1H, br s), 3.80 (3H, s), 2.47 (3H, s), 2.21 (3H, s), 2.08 (4H, m), 0.91 (3H, s), 0.70 (6H, t, 7.3 Hz).

G. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.

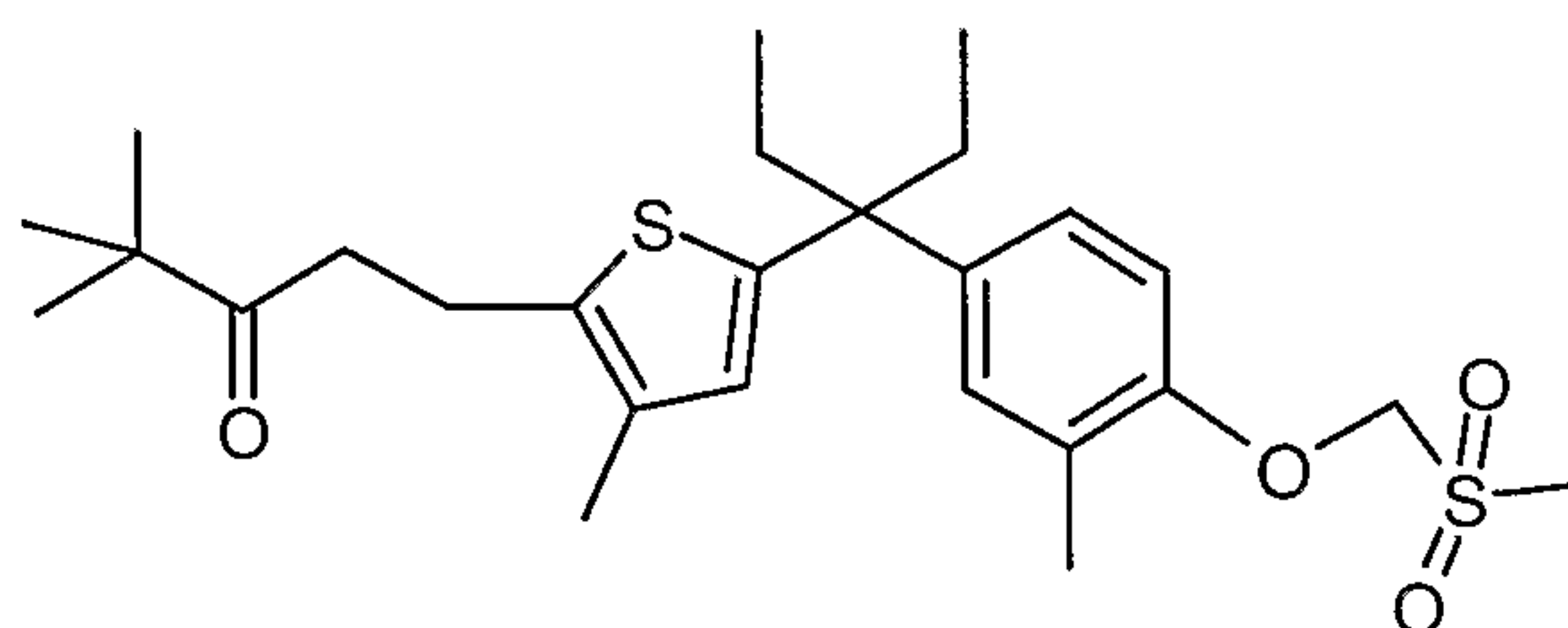
-174-



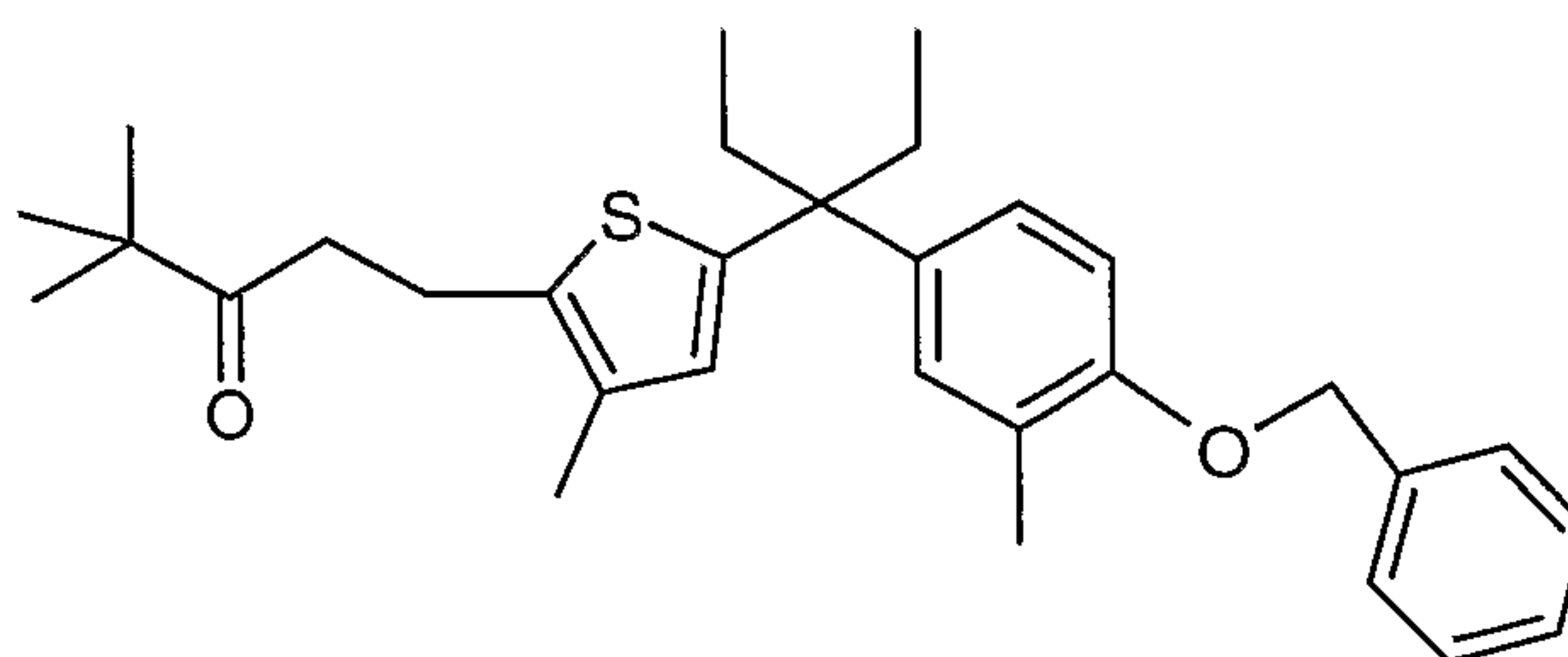
To a mixture of 3'-[4-hydroxy-3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (14.5 g, 43.6 mmol), acetone (200 ml) and K₂CO₃ (12.1 g, 87.2 mmol) is added 3,3-dimethyl-1-chloro-2-butanone (5.73 ml, 43.6 mmol). The mixture is stirred overnight, refluxed for 9 h and cooled to RT overnight. The reaction is filtered and concentrated to give the title compound (18.8 g, quant.).
 H-NMR (ppm, CDCl₃): 6.99 (2H, m), 6.60 (1H, s), 6.51 (1H, d, 8.5 Hz), 4.84 (2H, s), 3.79 (3H, s), 2.47 (3H, s), 2.25 (3H, s), 2.08 (4H, m), 1.25 (9H, s), 0.70 (6H, t, 7 Hz).

10 Example 13

Preparation of 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonylmethoxy)-3-methylphenyl]pentane.



15 H. 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-benzyloxy-3-methylphenyl]pentane.



To a 0 °C mixture of 3'-[4-(benzyloxy)-3-methylphenyl]-3'-[4-methyl-5-(hydroxymethyl)thiophen-2-yl]pentane (900 mg, 2.3 mmol) and Et₂O (7 ml) is added PBr₃ (240 ul, 2.5 mmol) and stirred for 1.5 h. The reaction is diluted with Et₂O, washed with water (10 ml), brine (10 ml), Na₂SO₄ dried, and concentrated. The

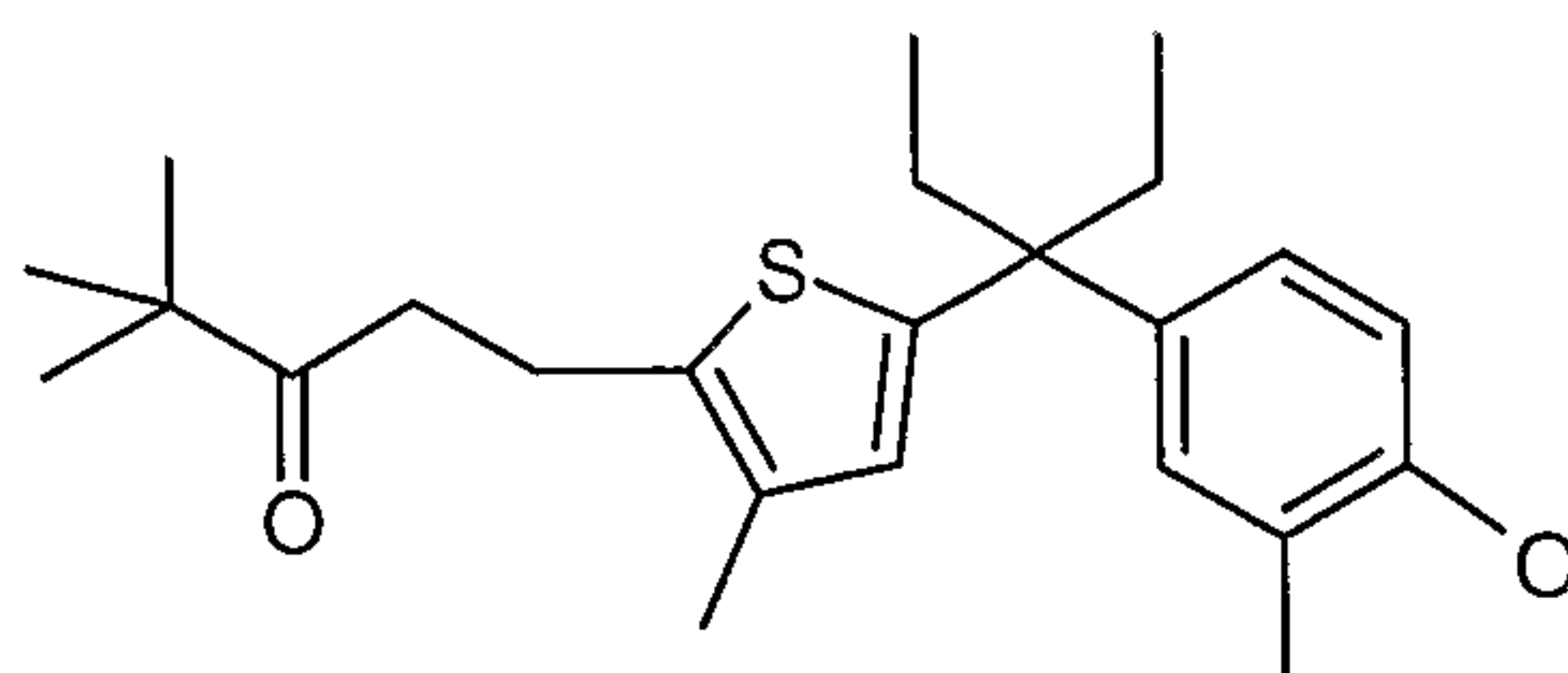
-175-

resulting residue is dissolved in THF (4 ml) and cooled to -78 °C to afford the bromide/THF solution. In a separate flask is charged with 1M LiHMDS (4.6 ml, 4.6 mmol), cooled to -78 °C, and added pinacolone (570 ul, 4.6 mmol). The reaction is stirred for 1.5 h, warmed to -50 °C and transferred (via syringe) to the -78 °C solution of bromide/THF. The reaction is warmed to RT with a cold water bath. After stirring for 15 m, the reaction is diluted with Et₂O and washed with 1N HCl. The organic layer is Na₂SO₄ dried and chromatographed (30% CHCl₃/hex to 80% CHCl₃/hex) to give the title compound (900 mg, 82%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 1.00 (s, 9H), 1.93-2.04 (m, 4H), 2.15 (s, 3H), 2.71 (m, 2H), 2.80 (m, 2H), 5.08 (s, 2H), 6.55 (s, 1H), 6.90 (d, J = 8.3 Hz, 1H), 7.01 (m, 2H), 7.34 (d, J = 7.3 Hz, 1H), 7.41 (m, 2H), 7.46 (d, J = 7.8 Hz, 2H).

High Res. ES-MS: 477.2830; calc. for C₃₁H₄₀O₂S+H: 477.2827.

I. 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-hydroxy-3-methylphenyl]pentane.



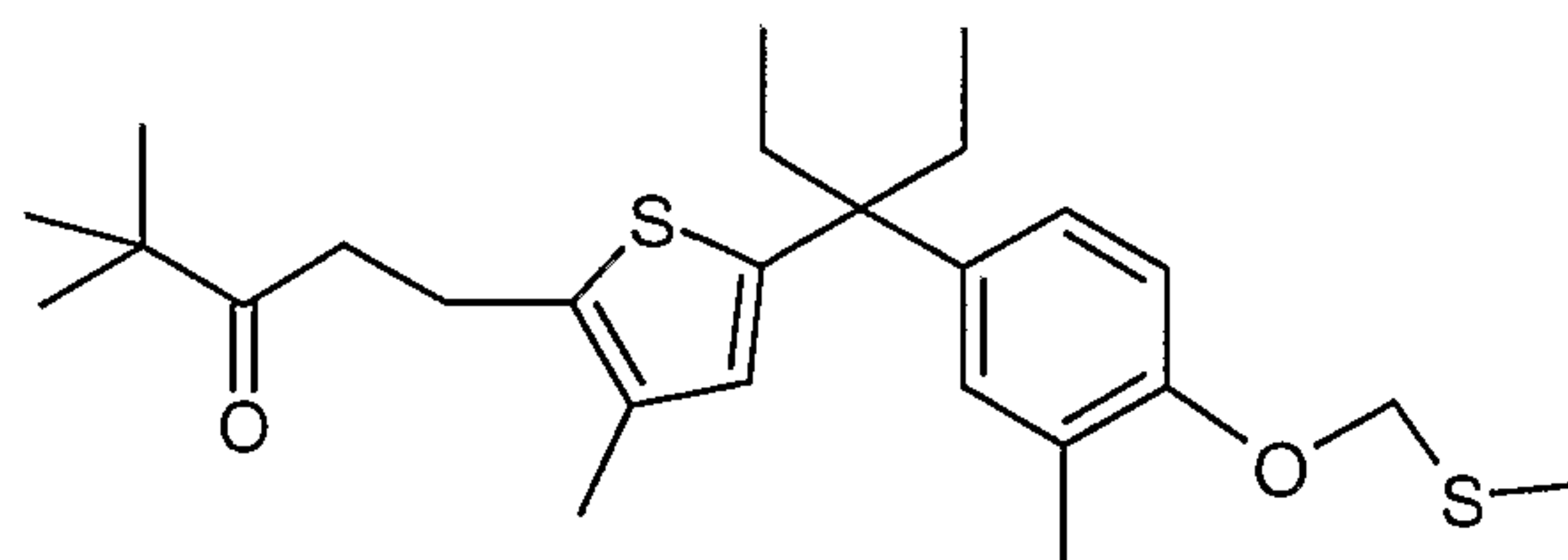
Using a procedure analogous to Example 1F, 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-benzyloxy-3-methylphenyl]pentane gives the title compound (600 mg, 97%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.59 (t, J = 7.3 Hz, 6H), 0.99 (s, 9H), 1.91-1.98 (m, 4H), 2.03 (s, 3H), 2.04 (s, 3H), 2.71 (m, 2H), 2.75 (m, 2H), 6.49 (s, 1H), 6.62 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.86 (s, 1H), 9.04 (s, 1H).

High Res. ES-MS: 409.2167; calc. for C₂₄H₃₄O₂S+Na: 409.2177.

J. 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylmercaptylmethoxy)-3-methylphenyl]pentane.

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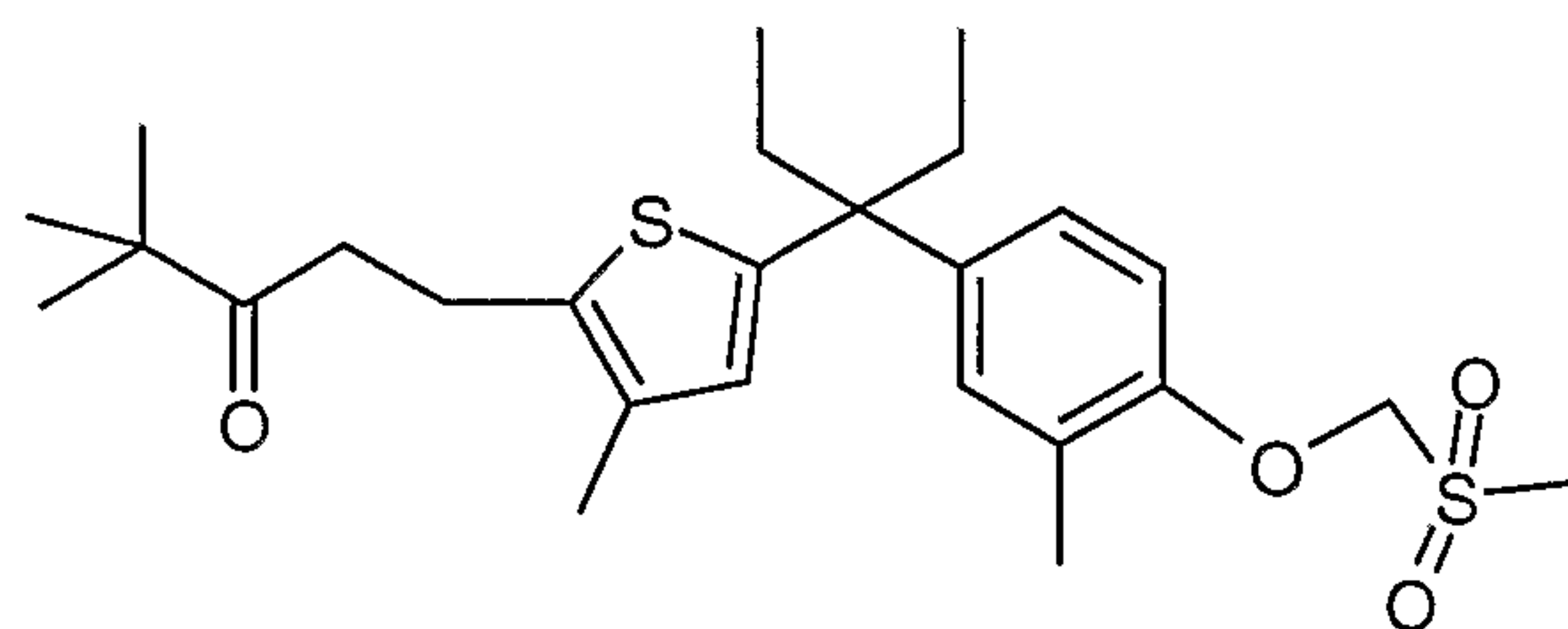


Using a procedure analogous to Example 1D, 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-hydroxy-3-methylphenyl]pentane and methylmercaptymethyl chloride give the title compound (440 mg, 73%).

- 5 ^1NMR (400MHz, DMSO- d_6) δ ppm: 0.61 (t, $J = 7.3$ Hz, 6H), 0.98 (s, 9H), 1.93-2.01 (m, 4H), 2.04 (s, 3H), 2.11 (s, 3H), 2.17 (s, 3H), 2.71 (m, 2H), 2.76 (m, 2H), 5.23 (s, 2H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.98 (m, 2H).

High Res. ES-MS: 469.2230; calc. for $\text{C}_{26}\text{H}_{38}\text{O}_2\text{S}_2 + \text{Na}$: 469.2211.

- 10 K. 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonylmethoxy)-3-methylphenyl]pentane.



Using a procedure analogous to Example 9C, 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylmercaptymethoxy)-3-methylphenyl]pentane gives the title compound (140 mg, 33%).

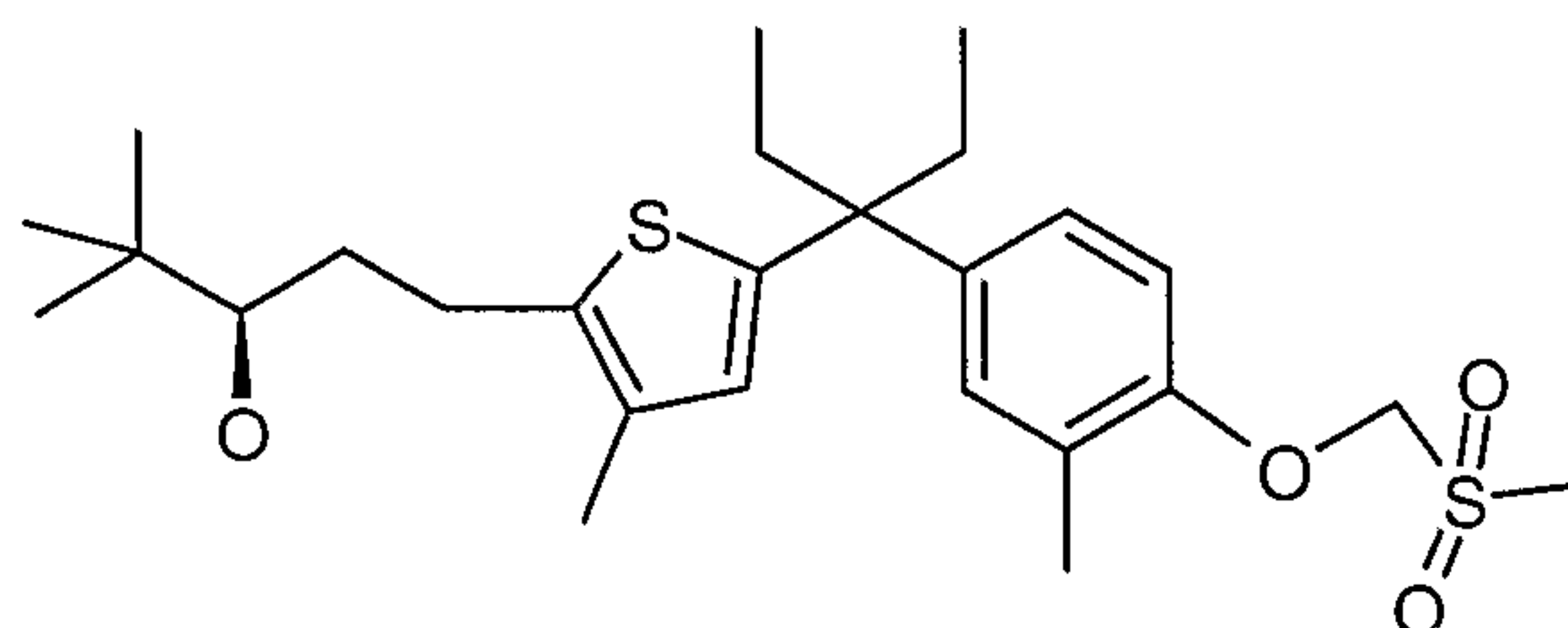
- 15 ^1NMR (400MHz, DMSO- d_6) δ ppm: 0.61 (t, $J = 7.3$ Hz, 6H), 0.99 (s, 9H), 1.95-2.02 (m, 4H), 2.04 (s, 3H), 2.17 (s, 3H), 2.71 (m, 2H), 2.76 (m, 2H), 3.04 (s, 3H), 5.24 (s, 2H), 6.53 (s, 1H), 7.01 (m, 3H).

High Res. ES-MS: 501.2129; calc. for $\text{C}_{26}\text{H}_{38}\text{O}_4\text{S}_2 + \text{Na}$: 501.2109.

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Example 14

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonylmethoxy)-3-methylphenyl]pentane.



5

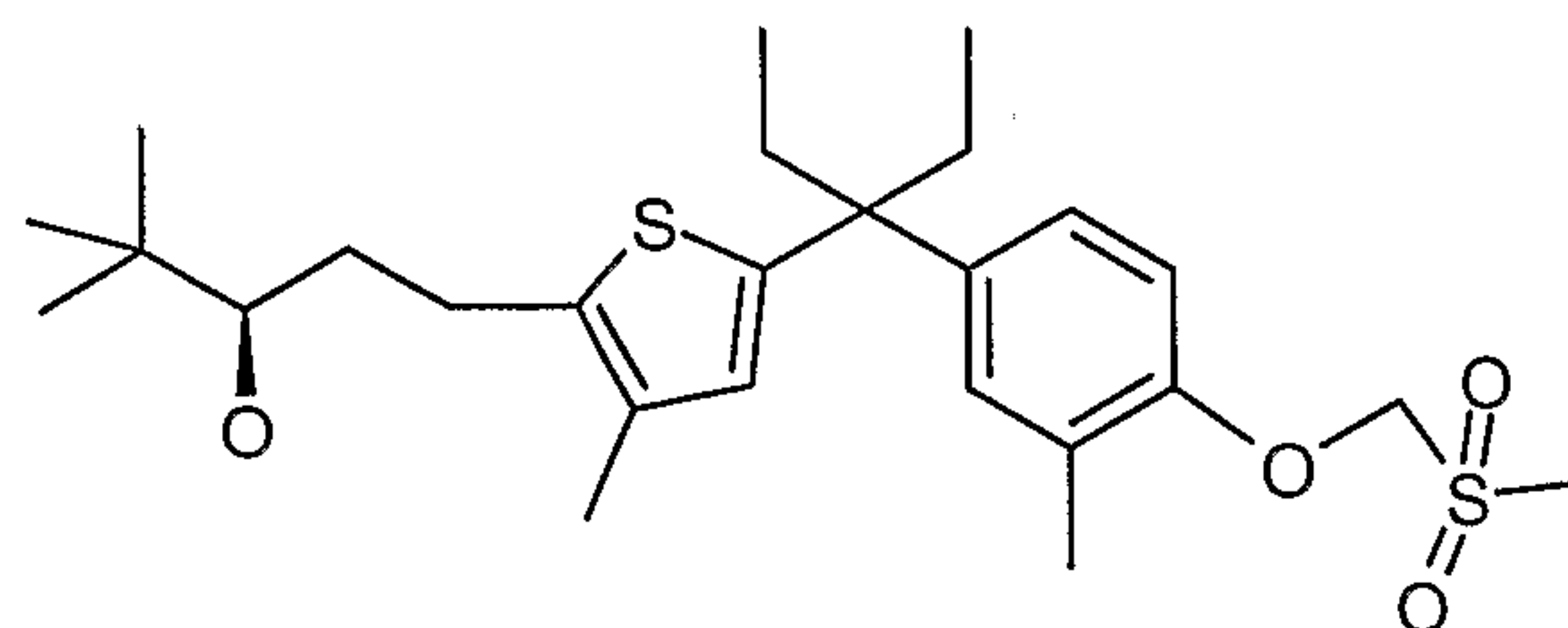
Using a procedure analogous to Example 2, 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonylmethoxy)-3-methylphenyl]pentane gives the title compound (100 mg, quant.).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.11-1.38 (m, 1H), 1.56-1.63 (m, 1H), 1.94-2.01 (m, 4H), 2.04 (s, 3H), 2.18 (s, 3H), 2.52-2.60 (m, 1H), 2.77-2.83 (m, 1H), 2.94-2.97 (m, 1H), 3.04 (s, 3H), 4.38 (d, J = 5.9, 1H), 5.25 (s, 2H), 6.53 (s, 1H), 7.01 (m, 3H).

High Res. ES-MS: 503.2268; calc. for C₂₆H₄₀O₄S₂+Na: 503.2266.

15 Example 15A and 15B

Preparation of enantiomers of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonylmethoxy)-3-methylphenyl]pentane.



20

A mixture of racemic 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonylmethoxy)-3-methylphenyl]pentane is chromatographed with a Chiralcel OD column to give enantiomer 1

Example 3A (54 mg, 43%) and enantiomer 2, Example 3B (55 mg, 44%) .

Enantiomer 1, Example 3A]

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HPLC: Chiralcel OD (4.6X250 mm); 40% IPA/60% heptane; 1 ml/m (flow rate); rt = 8.9 m; 225 nm.

¹NMR equivalent to Example Yee-2.

High Res. ES-MS: 503.2269; calc. for C₂₆H₄₀O₄S₂+Na: 503.2266.

5 Enantiomer 2, Example 3B

HPLC: Chiralcel OD (4.6X250 mm);); 40% IPA/60% heptane; 1 ml/m (flow rate); rt = 11.3 m; 225 nm.

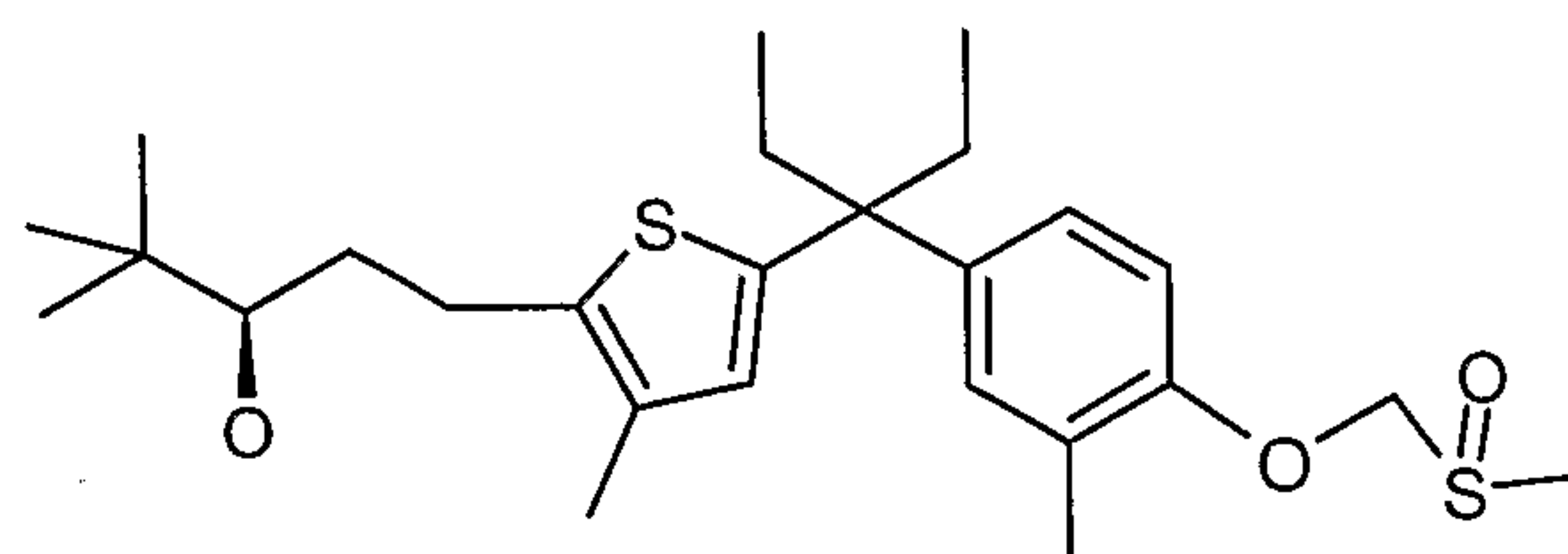
¹NMR equivalent to Example 2.

High Res. ES-MS: 503.2280; calc. for C₂₆H₄₀O₄S₂+Na: 503.2266.

10

Example 16

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfinylmethoxy)-3-methylphenyl]pentane.



15

To a 0 °C mixture of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylmercaptylmethoxy)-3-methylphenyl]pentane (725 mg, 1.67 mmol) and CHCl₃ (7 ml) is added 50% m-CPBA (1.3 g, 3.77 mmol). The stirred reaction is allowed to warm to RT over 1 h. The resulting suspension is added more CHCl₃ (7 ml) and stirred for 1 h. The mixture is diluted with CHCl₃ and washed with satd Na₂CO₃. The organic layer is concentrated and chromatographed (CHCl₃ to 50% EtOAc/ CHCl₃, TLC Rf: 0.05) to give the title compound (175 mg, 23%).

20

¹NMR (300MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.95-2.01 (m, 4H), 2.04 (s, 3H), 2.15 (s, 3H), 2.58 (m, 1H), 2.61 (s, 3H), 2.79 (m, 1H), 3.04 (m, 1H), 4.38 (m, 1H), 5.02 (d, J = 10.2 Hz, 1H), 5.20 (d, J = 10.7 Hz, 1H), 6.53 (s, 1H), 7.02 (m, 3H).

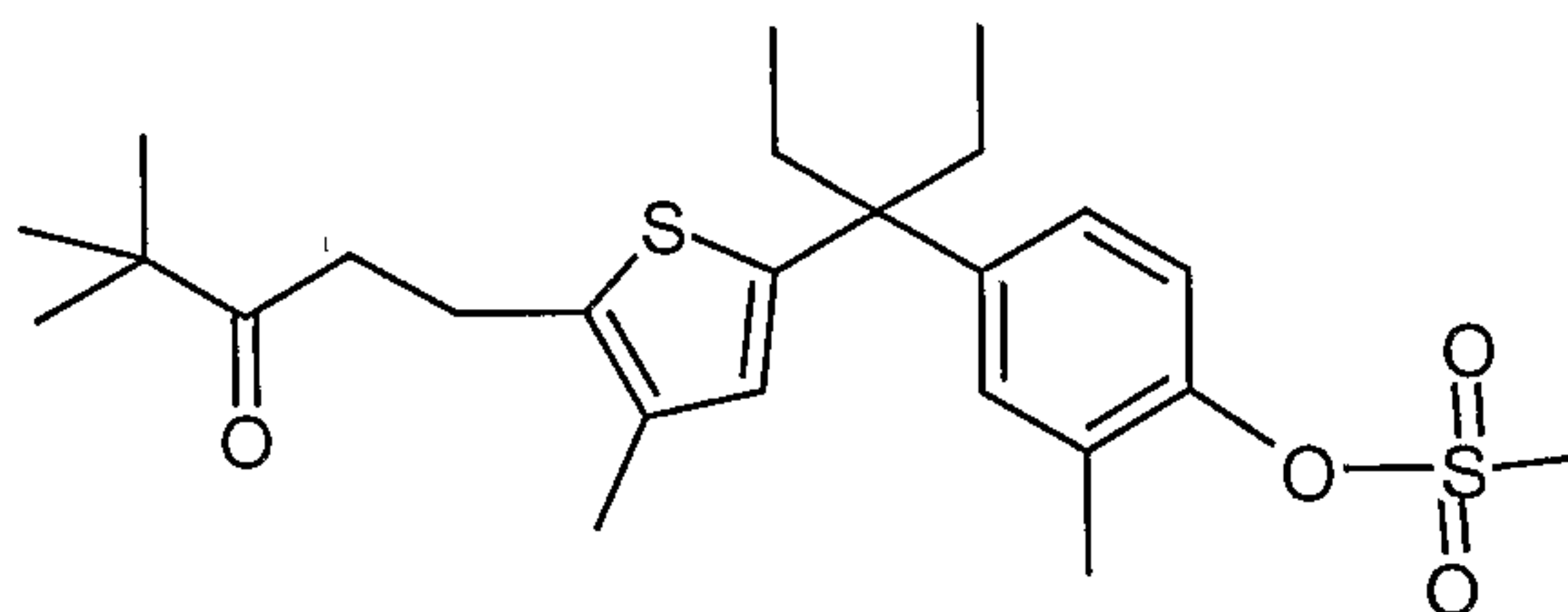
25

High Res. ES-MS: 465.2483; calc. for C₂₆H₄₀O₃S₂+H: 465.2497.

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Example 17

Preparation of 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonyloxy)-3-methylphenyl]pentane.



5

Using a procedure analogous to Example 1D, 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(hydroxy)-3-methylphenyl]pentane gives the title compound (425 mg, 65%).

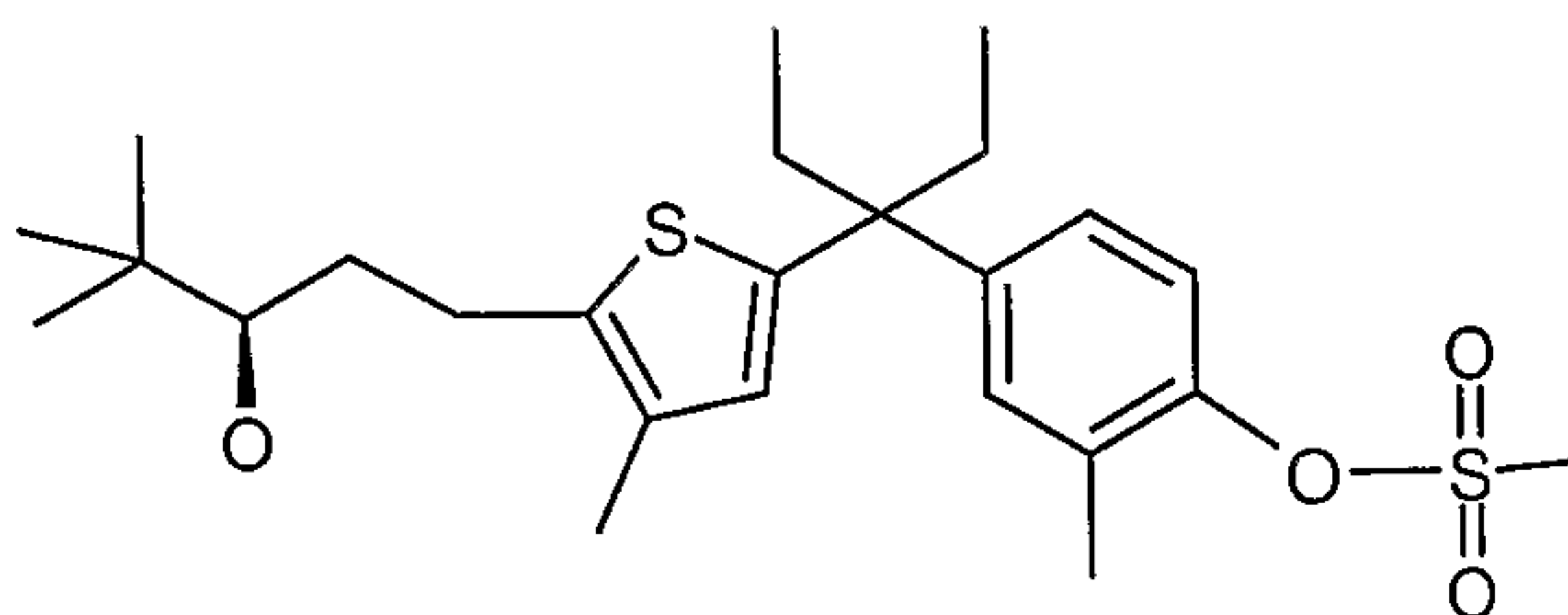
TLC: CHCl₃; R_f = 0.4.

10 ¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.98 (s, 9H), 1.93-2.15 (m, 4H), 2.05 (s, 3H), 2.24 (s, 3H), 2.72 (m, 2H), 2.77 (m, 2H), 3.40 (s, 3H), 6.57 (s, 1H), 7.11 (d, J = 2.5 Hz, 1H), 7.19 (m, 2H).

High Res. ES-MS: 487.1940; calc. for C₂₅H₃₆O₄S₂+Na: 487.1940.

15 Example 18

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonyloxy)-3-methylphenyl]pentane.



20 Using a procedure analogous to Example 2, 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methylsulfonyloxy)-3-methylphenyl]pentane gives the title compound (300 mg, 96%).

TLC: 5% EtOAc/CHCl₃; R_f = 0.35.

¹NMR (300MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.35 (m, 1H), 1.62 (m, 1H), 1.95-2.12 (m, 4H), 2.04 (s, 3H), 2.25 (s, 3H), 2.60 (m, 1H), 2.81

-180-

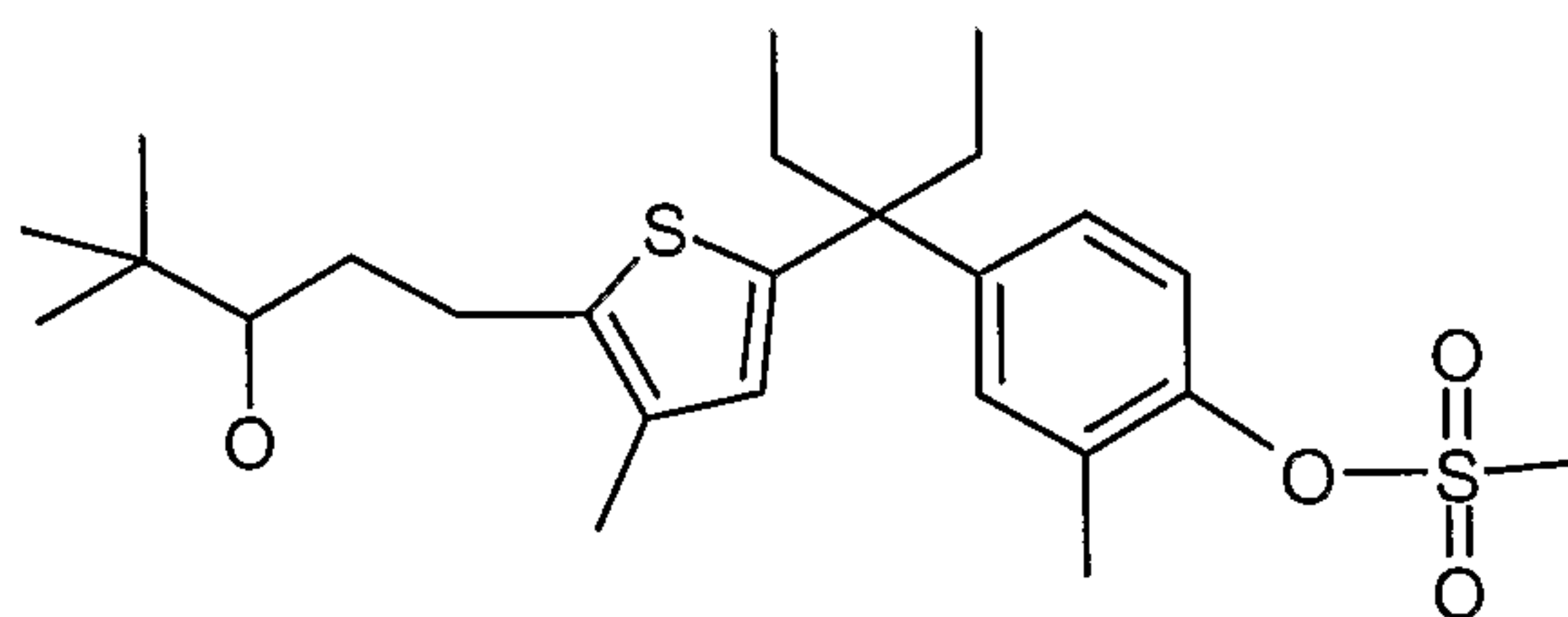
(m, 1H), 2.98 (m, 1H), 3.42 (s, 3H), 4.37 (d, J = 6.2 Hz, 1H), 6.59 (s, 1H), 7.13 (dd, J = 2.2, 8.8 Hz, 1H), 7.22 (m, 2H).

High Res. ES-MS: 484.2539; calc. for C₂₅H₃₈O₄S₂+NH₄: 484.2555.

5

Example 19A and 19B

Preparation of enantiomers of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]- 3'-[4-(methylsulfonyloxy)-3-methylphenyl]pentane.



10

A mixture of racemic 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]- 3'-[4-(methylsulfonyloxy)-3-methylphenyl]pentane is chromatographed with a Chiralcel AD column to give enantiomer 1, Example 19A (108 mg, 43%) and enantiomer 2, Example 19B (109 mg, 44%) .

15 Enantiomer 1, Example 19A

HPLC: Chiralcel AD (4.6X250 mm); 10% IPA/heptane; 1 ml/m (flow rate); rt = 6.85 m; 250 nm.

¹NMR equivalent to Example 18.

High Res. ES-MS: 489.2106; calc. for C₂₅H₃₈O₄S₂+Na: 489.2109.

20 Enantiomer 2, Example 19B.

HPLC: Chiralcel AD (4.6X250 mm); 10% IPA/heptane; 1 ml/m (flow rate); rt = 8.00 m; 250 nm.

¹NMR equivalent to Example 18..

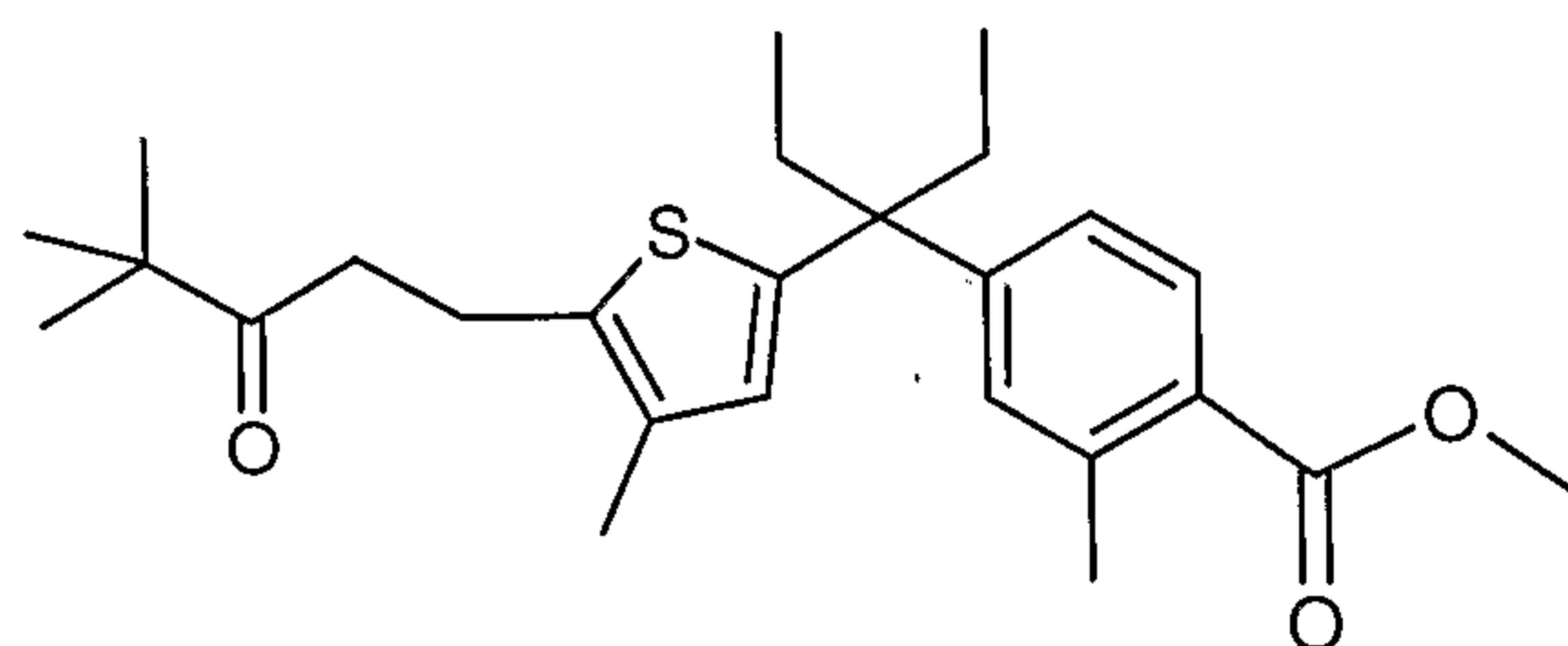
High Res. ES-MS: 489.2112; calc. for C₂₅H₃₈O₄S₂+Na: 489.2109.

25

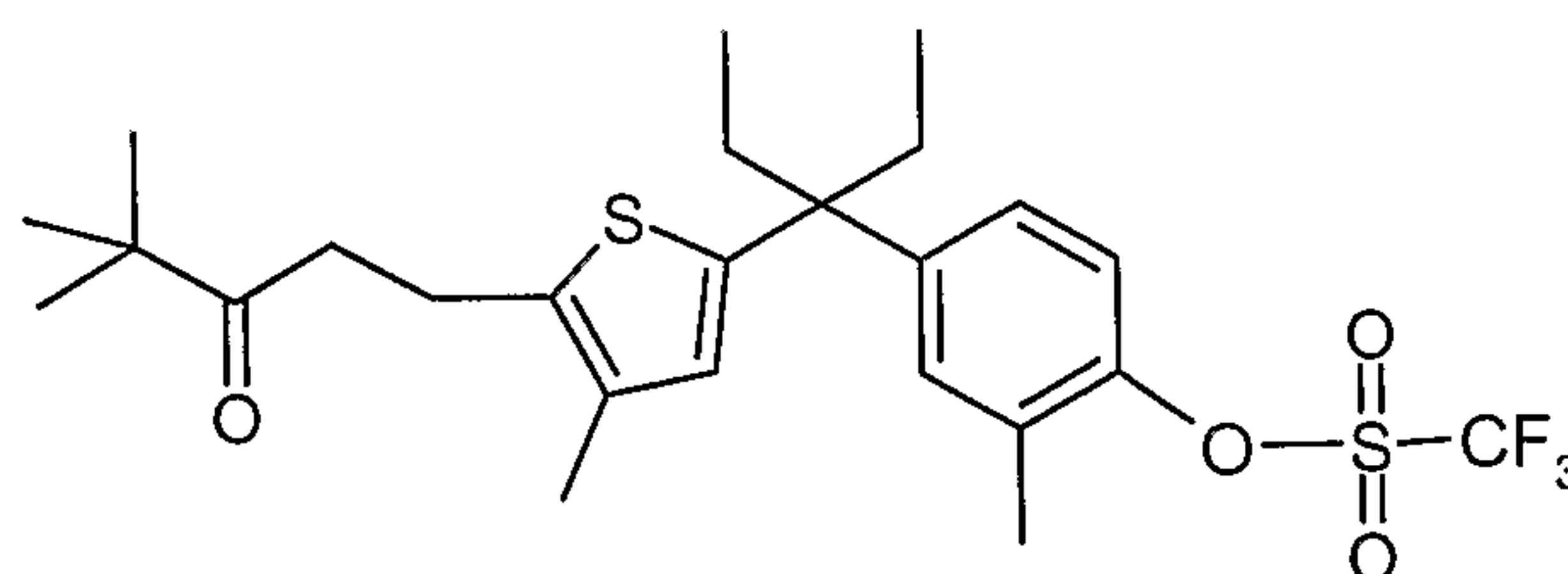
Example 20

Preparation of 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]- 3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

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- A. 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(trifluoromethylsulfonyloxy)-3-methylphenyl]pentane.



5 To a 0 °C mixture of 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-hydroxy-3-methylphenyl]pentane (2.7 g, 7.0 mmol) and pyridine (8 ml) is added Tf₂O (1.3 ml, 7.7 mmol). The reaction is warmed to RT and stirred overnight. The reaction is diluted with Et₂O, washed with 1N HCl and brine, Na₂SO₄ dried, and concentrated. The residue is chromatographed (30 /hex) to give the title compound
10 (2.9 g, 80%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.61 (t, J = 7.3 Hz, 6H), 0.97 (s, 9H), 1.95-2.11 (m, 4H), 2.04 (s, 3H), 2.28 (s, 3H), 2.70 (m, 2H), 2.77 (m, 2H), 6.59 (s, 1H), 7.19 (dd, J = 2.4, 8.8 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H).

High Res. ES-MS: 519.1838; calc. for C₂₅H₃₃F₃O₄S₂+H: 519.1851.

15

- B. 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

A mixture of 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(trifluoromethylsulfonyloxy)-3-methylphenyl]pentane (2.65 g, 5.1 mmol), DPPF (554
20 mg, 1.0 mmol), Pd(OAc)₂ (120 mg, 0.51 mmol), DMF (10 ml), MeOH (2.1 ml) and Et₃N (2.1 ml, 15.3 mmol) is heated in an autoclave at 110 °C under CO pressure (1000 psi). After 48 h, the reaction is cooled to RT and diluted with Et₂O. The mixture is washed with 5N HCl, water, and Na₂SO₄ dried and concentrated. The residue is
25 chromatographed (10% EtOAc/hex) to give the title compound (1.86 g, 85%).

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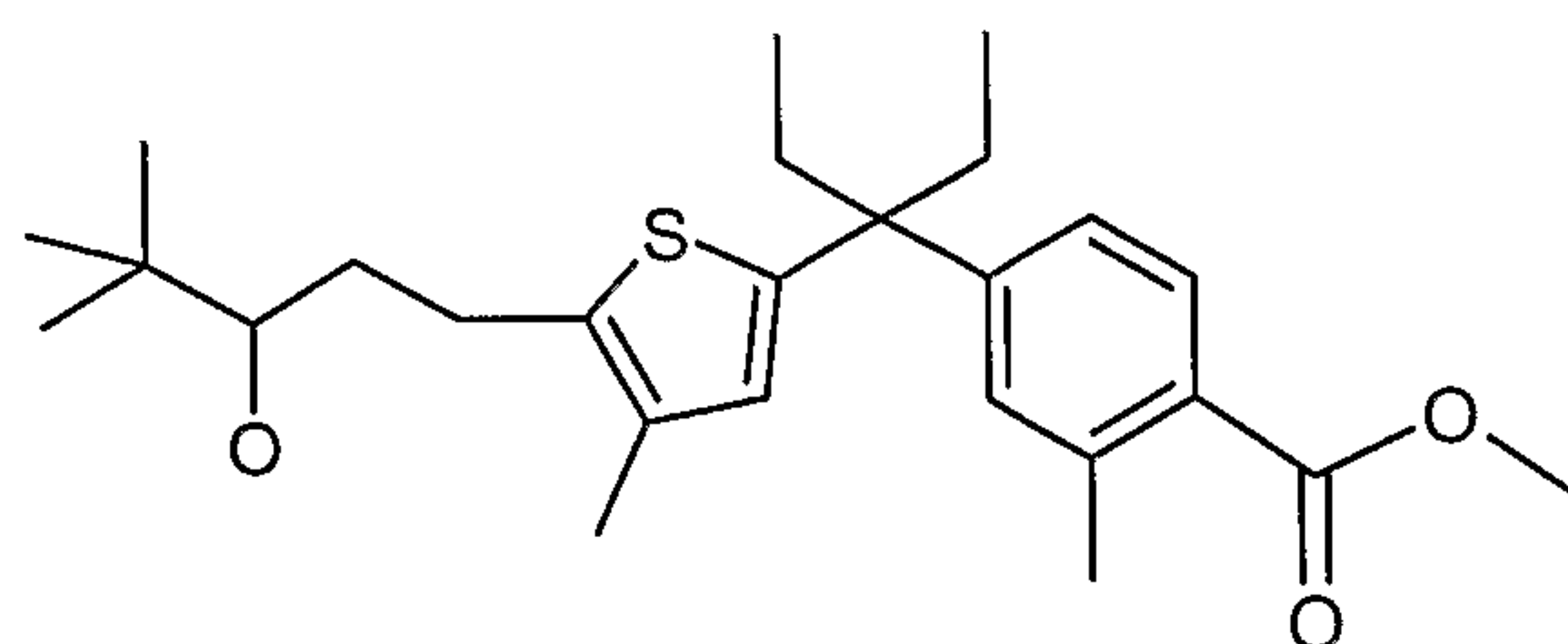
^1NMR (400MHz, DMSO- d_6) δ ppm: 0.61 (t, $J = 7.3$ Hz, 6H), 0.98 (s, 9H), 1.96-2.12 (m, 4H), 2.04 (s, 3H), 2.47 (s, 3H), 2.71 (m, 2H), 2.78 (m, 2H), 3.79 (s, 3H), 6.56 (s, 1H), 7.15 (m, 2H), 7.71 (d, $J = 7.8$ Hz, 1H).

High Res. ES-MS: 446.2741; calc. for $\text{C}_{26}\text{H}_{36}\text{O}_3\text{S}+\text{NH}_4$: 446.2729.

5

Example 21

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.



10

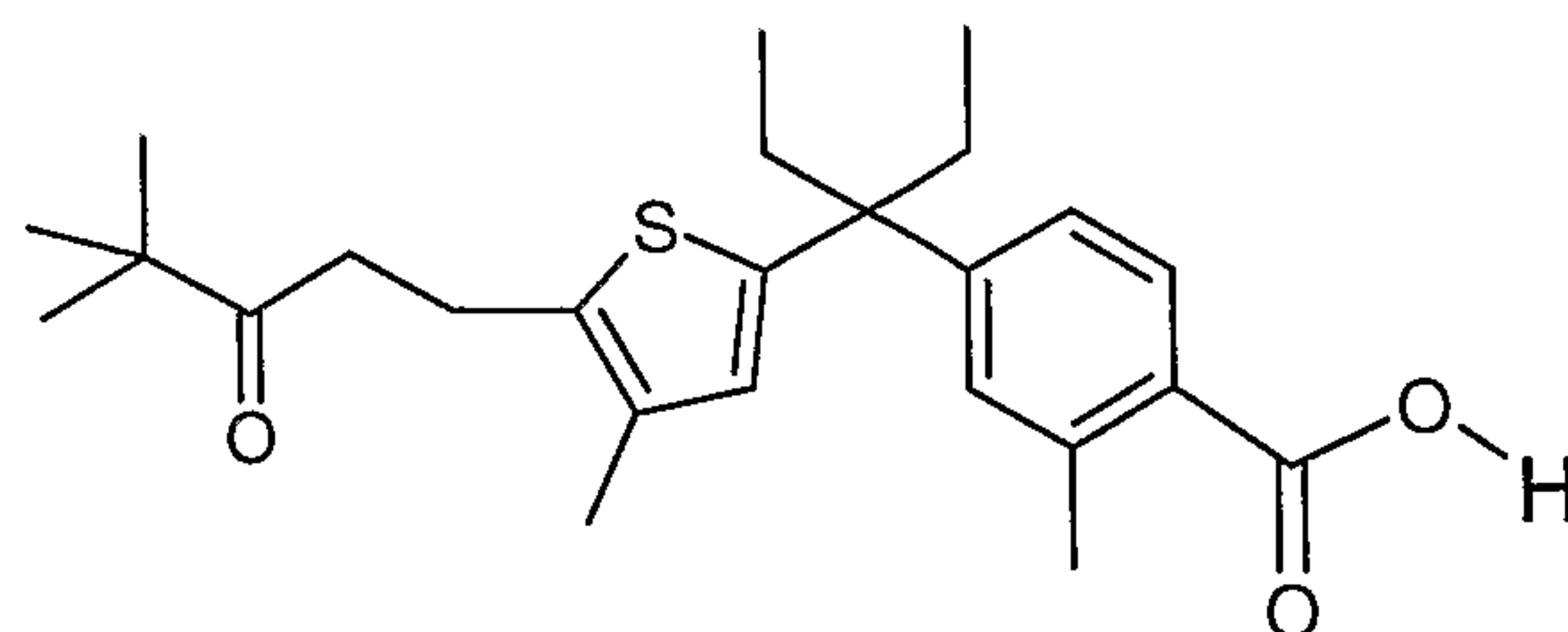
Using a procedure analogous to Example 2, 3'-[5-(3-Oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane gives the title compound (785 mg, 98%).

^1NMR (400MHz, DMSO- d_6) δ ppm: 0.63 (t, $J = 7.3$ Hz, 6H), 0.77 (s, 9H), 1.35 (m, 1H), 1.54 (m, 1H), 1.98-2.13 (m, 4H), 2.04 (s, 3H), 2.48 (s, 3H), 2.56 (m, 1H), 2.79 (m, 1H), 2.95 (m, 1H), 3.79 (s, 3H), 4.37 (br s, d, 1H), 6.57 (s, 1H), 7.17 (m, 2H), 7.72 (d, $J = 7.8$ Hz, 1H).

High Res. ES-MS: 431.2630; calc. for $\text{C}_{26}\text{H}_{38}\text{O}_3\text{S}+\text{H}$: 431.2620.

Example 22

Preparation of 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-carboxyl-3-methylphenyl]pentane.



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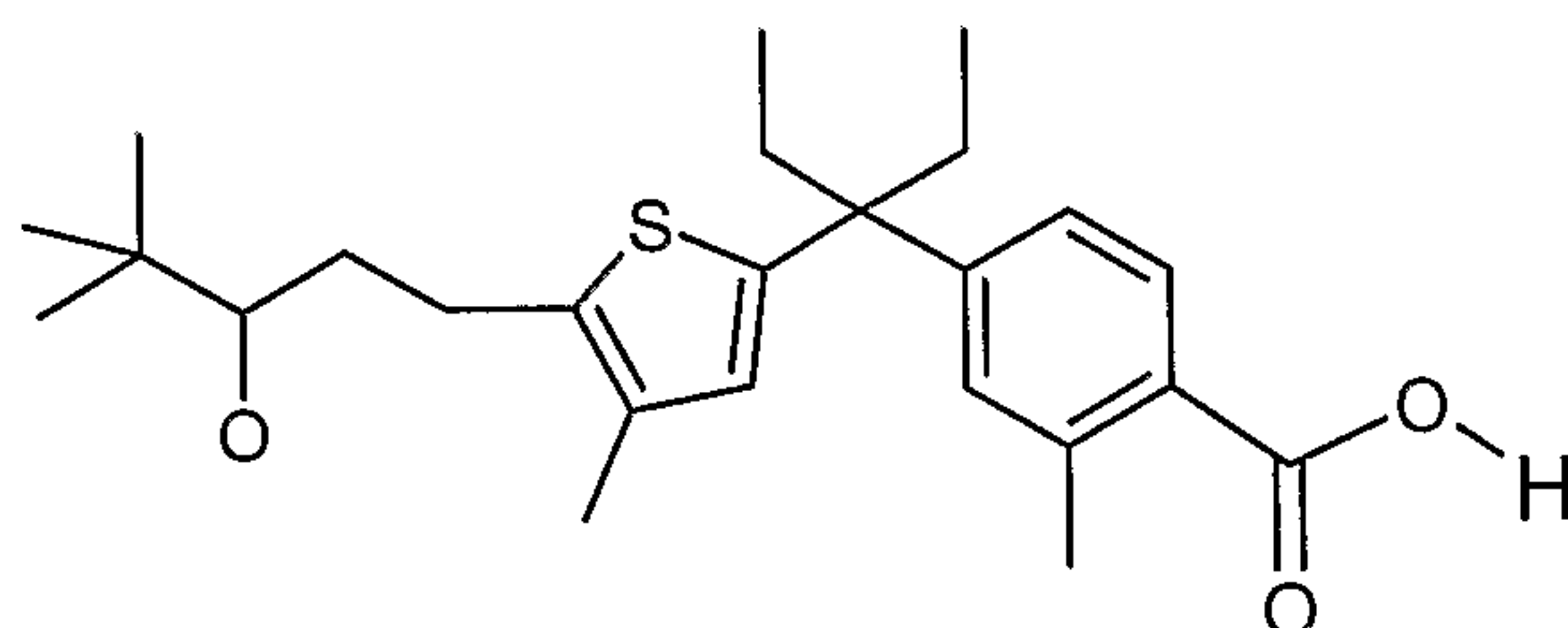
Using a procedure analogous to Example 3, 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane gives the title compound (800 mg, 92%).

5 ^1NMR (400MHz, DMSO-d_6) δ ppm: 0.62 (t, $J = 7.3$ Hz, 6H), 0.98 (s, 9H), 1.96-2.11 (m, 4H), 2.04 (s, 3H), 2.47 (s, 3H), 2.71 (m, 2H), 2.77 (m, 2H), 6.56 (s, 1H), 7.11 (m, 2H), 7.71 (d, $J = 8.3$ Hz, 1H), 12.64 (s, 1H).

High Res. ES-MS: 415.2297; calc. for $\text{C}_{25}\text{H}_{34}\text{O}_3\text{S}+\text{H}$: 415.2307.

10 Example 23

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-carboxyl-3-methylphenyl]pentane.



15 Using a procedure analogous to Example 3, 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane gives the title compound (700 mg, 99%).

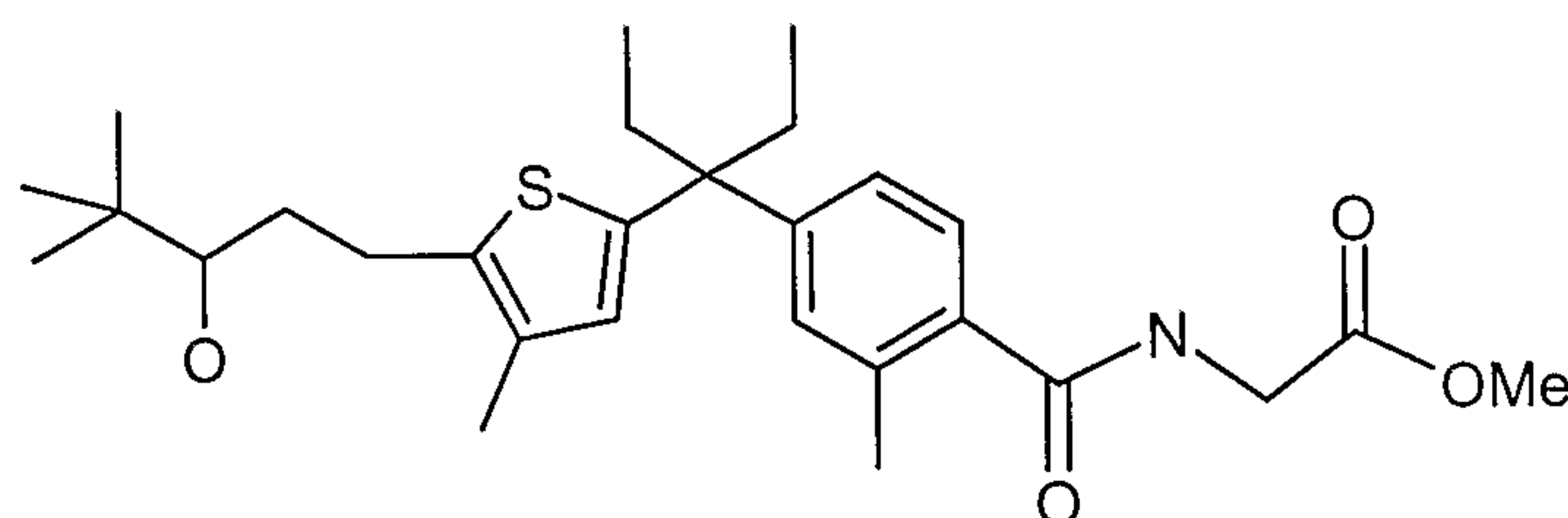
^1NMR (400MHz, DMSO-d_6) δ ppm: 0.62 (t, $J = 7.3$ Hz, 6H), 0.77 (s, 9H), 1.36 (m, 1H), 1.58 (m, 1H), 1.96-2.11 (m, 4H), 2.04 (s, 3H), 2.48 (s, 3H), 2.55 (m, 1H), 2.60 (m, 1H), 4.37 (d, $J = 6.2$ Hz, 1H), 6.58 (s, 1H), 7.17 (m, 2H), 7.73 (d, $J = 8.1$ Hz, 1H), 12.65 (br s, 1H).

High Res. ES-MS: 439.2322; calc. for $\text{C}_{25}\text{H}_{36}\text{O}_3\text{S}+\text{Na}$: 439.2283.

Example 24

25 Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane.

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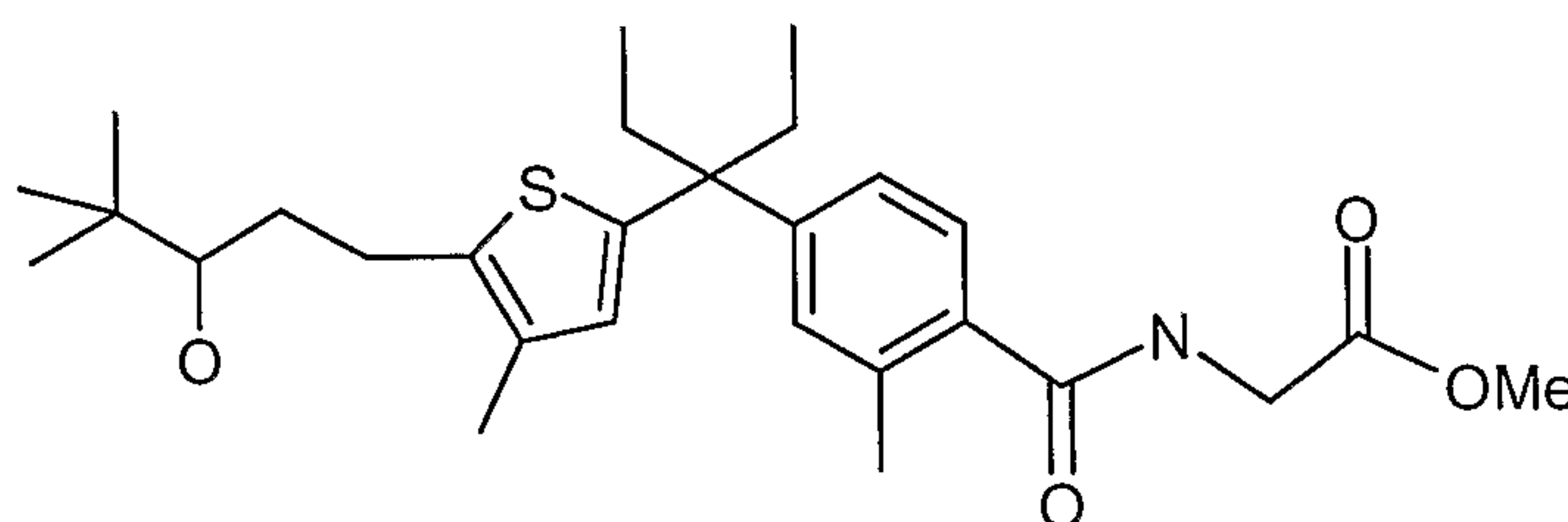


To a mixture of DMAP (256 mg, 2.1 mmol), methyl glycinate hydrochloride (123 mg, 1.01 mmol), EDCI (193 mg, 1.01 mmol) and CH₂Cl₂ (4 ml) is added 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-carboxyl-3-methylphenyl]pentane (350 mg, 0.84 mmol). The reaction is added CH₂Cl₂ (2 ml) and DMF (1 ml). The mixture is stirred for 16 h and concentrated. The residue is diluted with Et₂O, 1N HCl (3X), brine and Na₂SO₄ dried. The organic solution is concentrated and chromatographed (20% EtOAc/CHCl₃ to 50% EtOAc/CHCl₃) to give the title compound (320 mg, 78%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.64 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.35 (m, 1H), 1.57 (m, 1H), 1.98-2.12 (m, 4H), 2.32 (s, 3H), 2.53-2.61 (m, 1H), 2.77-2.84 (m, 1H), 2.95 (m, 1H), 3.65 (s, 3H), 3.94 (d, J = 5.9 Hz, 2H), 4.39 (br s, 1H), 6.56 (s, 1H), 7.11 (m, 2H), 7.26 (d, J = 8.3 Hz, 1H), 8.62 (t, J = 5.9 Hz, 1H).
ES-MS: 488.2 (M+H).

Example 25A and 25B

Preparation of enantiomers of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane.



20

A racemic mixture of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane is

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chromatographed with a Chiralcel AD column to give enantiomer 1, Example 25A (110 mg, 37%) and enantiomer 2, Example 25B (102 mg, 34%) .

Enantiomer 1, Example 25A

HPLC: Chiralcel AD (4.6X250 mm); 10% IPA/heptane; 1 ml/m (flow rate); rt = 16.90 m; 240 nm.

¹NMR equivalent to Example 24.

High Res. ES-MS: 488.2812; calc. for C₂₈H₄₁NO₄S+H: 488.2835.

Enantiomer 2, Example 25B.

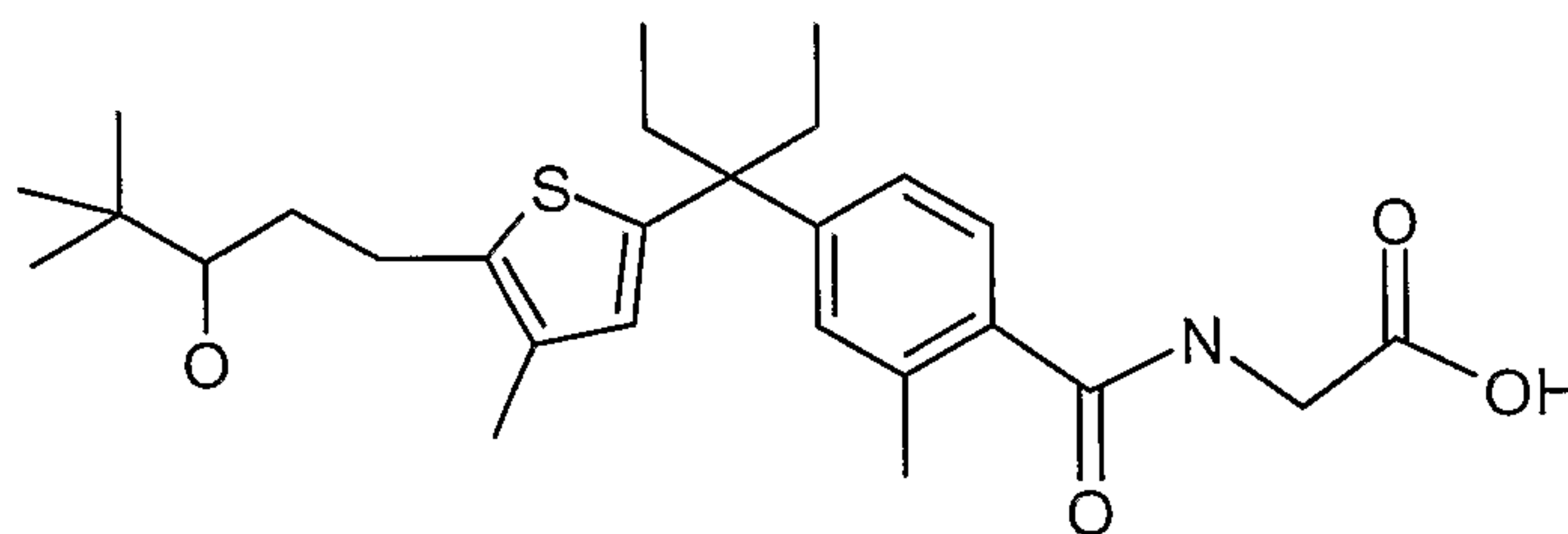
HPLC: Chiralcel AD (4.6X250 mm); 10% IPA/heptane; 1 ml/m (flow rate); rt = 20.00 m; 240 nm.

¹NMR equivalent to Example 24.

High Res. ES-MS: 488.2831; calc. for C₂₈H₄₁NO₄S+H: 488.2835.

Example 26

Preparation of isomer 1 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(carboxymethylaminocarbonyl)-3-methylphenyl]pentane.



Using a procedure analogous to Example 3 but reacted at 50 °C, isomer 1 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane (Example 13A) gives the title compound (95 mg, 98%).

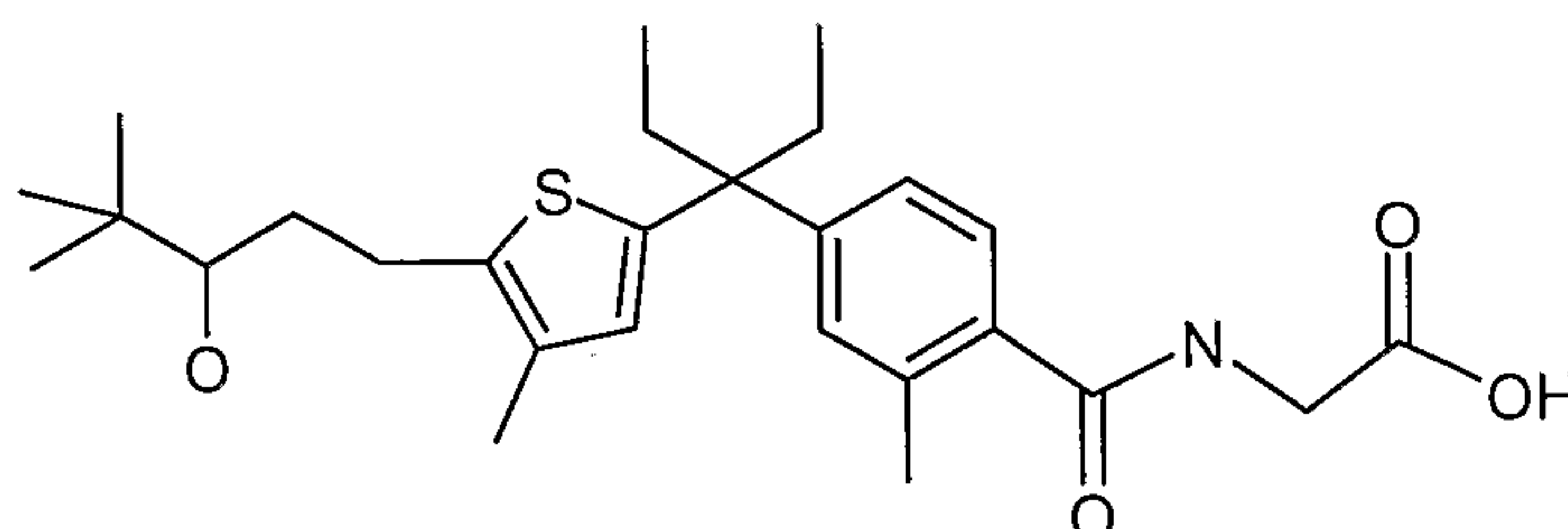
¹NMR (400MHz, DMSO-d₆) δ ppm: 0.64 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.34 (m, 1H), 1.58 (m, 1H), 1.97-2.12 (m, 4H), 2.04 (s, 3H), 2.32 (s, 3H), 2.57 (m, 1H), 2.80 (m, 1H), 2.95 (m, 1H), 3.84 (d, J = 6.3 Hz, 1H), 4.38 (br s, 1H), 6.56 (s, 1H), 7.10 (m, 2H), 7.26 (d, J = 8.8 Hz, 1H), 8.48 (t, J = 6.3 Hz, 1H), 12.47 (br s, 1H).

High Res. ES-MS: 474.2689; calc. for C₂₇H₃₉NO₄S+H: 474.2678.

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Example 27

Preparation of isomer 2 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(carboxymethylaminocarbonyl)-3-methylphenyl]pentane.



5

Using a procedure analogous to Example 3 except using LiOH at 60 °C, isomer 2 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane gives the title compound (79 mg, 94%).

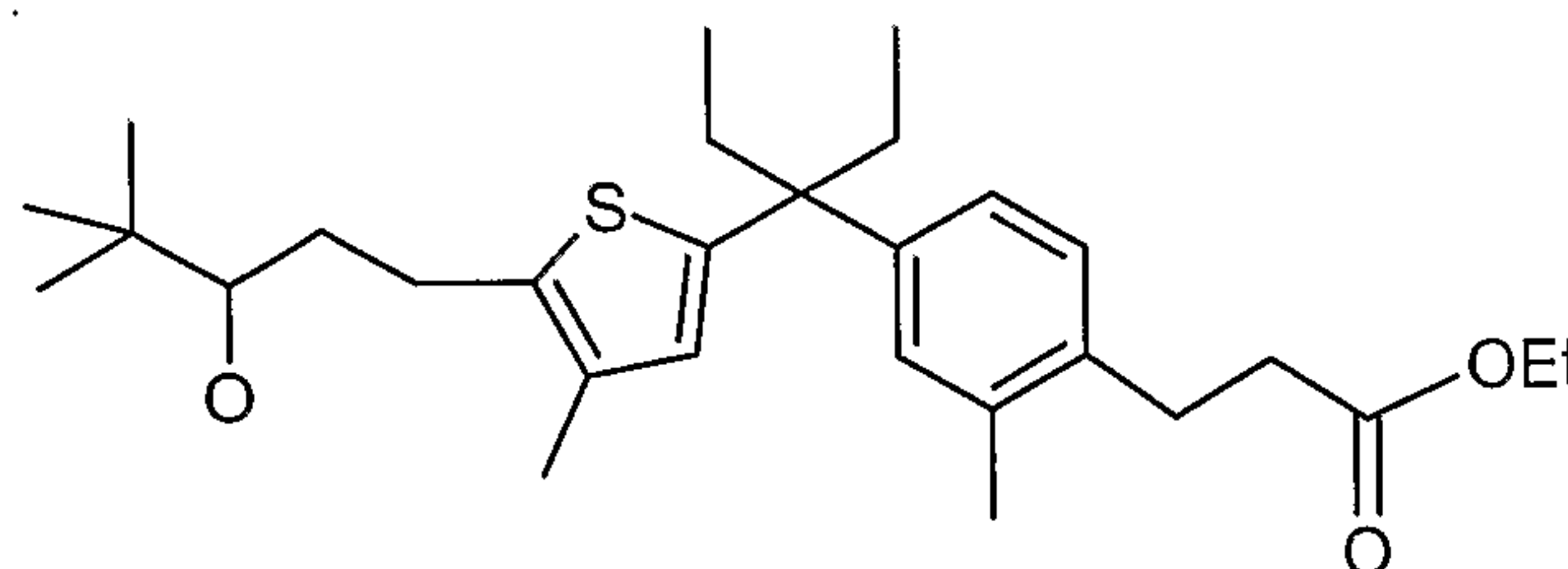
10 ^1NMR equivalent to Example 26.

High Res. ES-MS: 474.2672; calc. for $\text{C}_{27}\text{H}_{39}\text{NO}_4\text{S}+\text{H}$: 474.2678.

Example 28

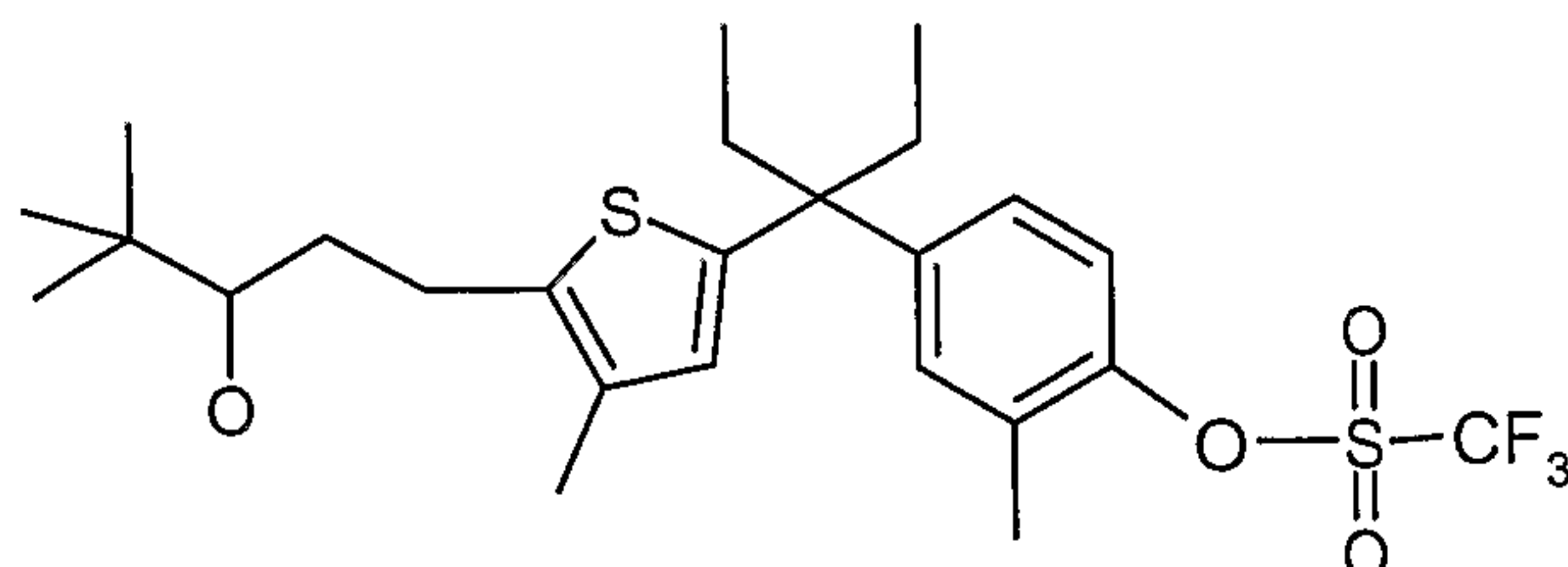
Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(ethoxycarbonyl-ethyl)-3-methylphenyl]pentane.

15



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3'-[5-(3-Hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]- 3'-[4-(trifluoromethylsulfonyloxy)-3-methylphenyl]pentane.



Using a procedure analogous to Example 8A, isomer 1 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]- 3'-[4-hydroxy-3-methylphenyl]pentane gives the title compound (1.1 g, 64%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.63 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.35 (m, 1H), 1.59 (m, 1H), 1.97-2.12 (m, 4H), 2.04 (s, 3H), 2.29 (s, 3H), 2.58 (m, 1H), 2.80 (m, 1H), 2.94 (m, 1H), 4.38 (br s, 1H), 6.59 (s, 1H), 7.21 (dd, J = 2.4, 8.8 Hz, 1H), 7.26 (m, 2H), 7.33 (d, J = 2.0 Hz, 1H).

High Res. EI-MS: 520.1927; calc. for C₂₅H₃₅F₃O₄S₂: 520.1929.

A. 3'-[5-(3-Hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]- 3'-[4-(ethoxycarbonyl)ethyl]-3-methylphenyl]pentane.

To a 0 °C mixture of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]- 3'-[4-(trifluoromethylsulfonyloxy)-3-methylphenyl]pentane (1.08 g, 2.07 mmol), Pd(Dppf)₂Cl₂ (170 mg, 0.207 mmol), LiCl (350 mg, 8.3 mmol) and THF (1 ml) is added 0.5M of 2-(ethoxycarbonyl)ethylzinc bromide/THF (12.4 ml, 6.21 mmol). The reaction is heated to 60 °C for 1 h and concentrated (to ~8 ml of volume) with a stream of nitrogen. The reaction is heated under nitrogen for another 15 h. After cooling, the reaction is diluted with Et₂O, quenched with 2.5N HCl, washed with water, Na₂SO₄ dried, and concentrated. The residue is chromatographed (70% CHCl₃/hex to 100% CHCl₃) to give the title compound (550 mg, 56%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.61 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.14 (t, J = 6.8 Hz, 3H), 1.33 (m, 1H), 1.58 (m, 1H), 1.93-2.19 (m, 4H), 2.04 (s, 3H), 2.22 (s, 3H),

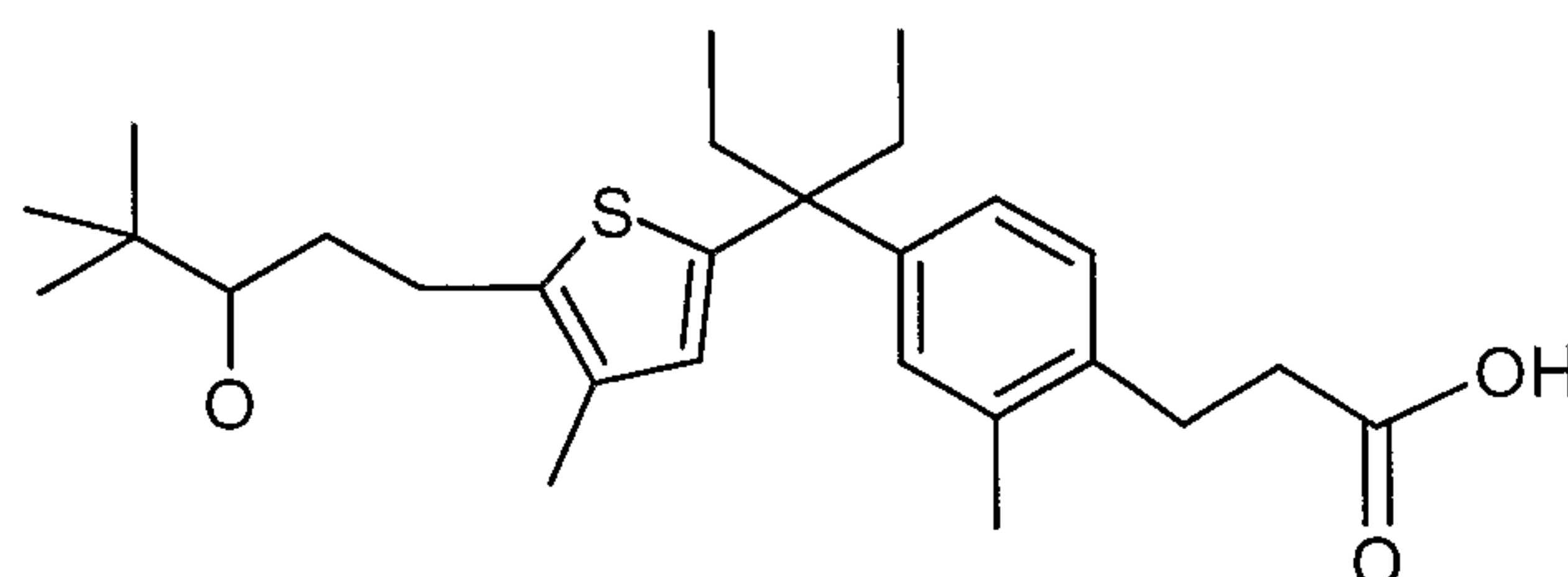
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2.51-2.59 (m, 3H), 2.75-2.83 (m, 3H), 2.95 (m, 1H), 4.02 (q, J = 7.3 Hz, 2H), 4.38 (br s, 1H), 6.53 (s, 1H), 6.98 (m, 3H).

High Res. ES-MS: 495.2926; calc. for C₂₉H₄₄O₃S+Na: 495.2909.

5 Example 29

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(2-carboxylethyl)-3-methylphenyl]pentane.



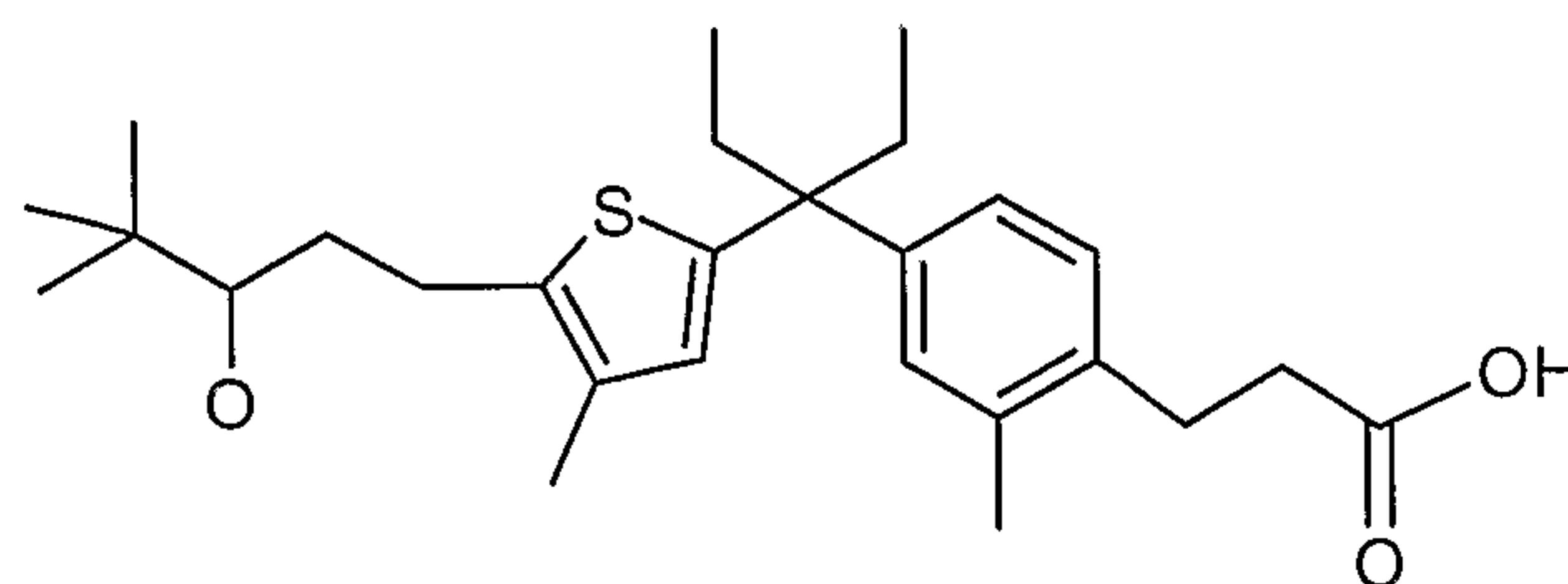
Using a procedure analogous to Example 3 but reacted at RT for 45 m, 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(2-ethoxycarbonylethyl)-3-methylphenyl]pentane gives the title compound (450 mg, 95%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.34 (m, 1H), 1.59 (m, 1H), 1.97-2.19 (m, 4H), 2.04 (s, 3H), 2.21 (s, 3H), 2.45 (t, J = 7.3 Hz, 2H), 2.54 (m, 1H), 2.74 (t, J = 8.3 Hz, 2H), 2.79 (m, 1H), 2.96 (m, 1H), 4.38 (br s, 1H), 6.53 (s, 1H), 6.99 (m, 3H), 12.09 (br s, 1H).

ES-MS: 445.3 (M+H).

Example 30A and 30B

Preparation of enantiomers of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(2-carboxylethyl)-3-methylphenyl]pentane.



A racemic mixture of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(2-carboxylethyl)-3-methylphenyl]pentane is chromatographed with a Chiralcel

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AD column to give enantiomer 1, Example 30A (108 mg, 43%) and enantiomer 2, Example 30B (109 mg, 44%) .

Enantiomer 1, Example 30A

HPLC: Chiralcel AD (4.6X250 mm); 0.1% TFA in 5% EtOH/hept; 1 ml/m (flow
5 rate); rt = 8.20 m; 210 nm.

¹NMR (300MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.35 (m, 1H), 1.61 (m, 1H), 1.97-2.10 (m, 4H), 2.04 (s, 3H), 2.22 (s, 3H), 2.47 (m, 2H), 2.56 (m, 1H), 2.77 (m, 3H), 2.95 (m, 1H), 4.37 (d, J = 6.2 Hz, 1H), 6.54 (s, 1H), 7.02 (m, 3H), 12.12 (br s, 1H).

10 High Res. ES-MS: 462.3054; calc. for C₂₇H₄₀NO₃S+NH₄: 462.3042.

Enantiomer 2, Example 30B.

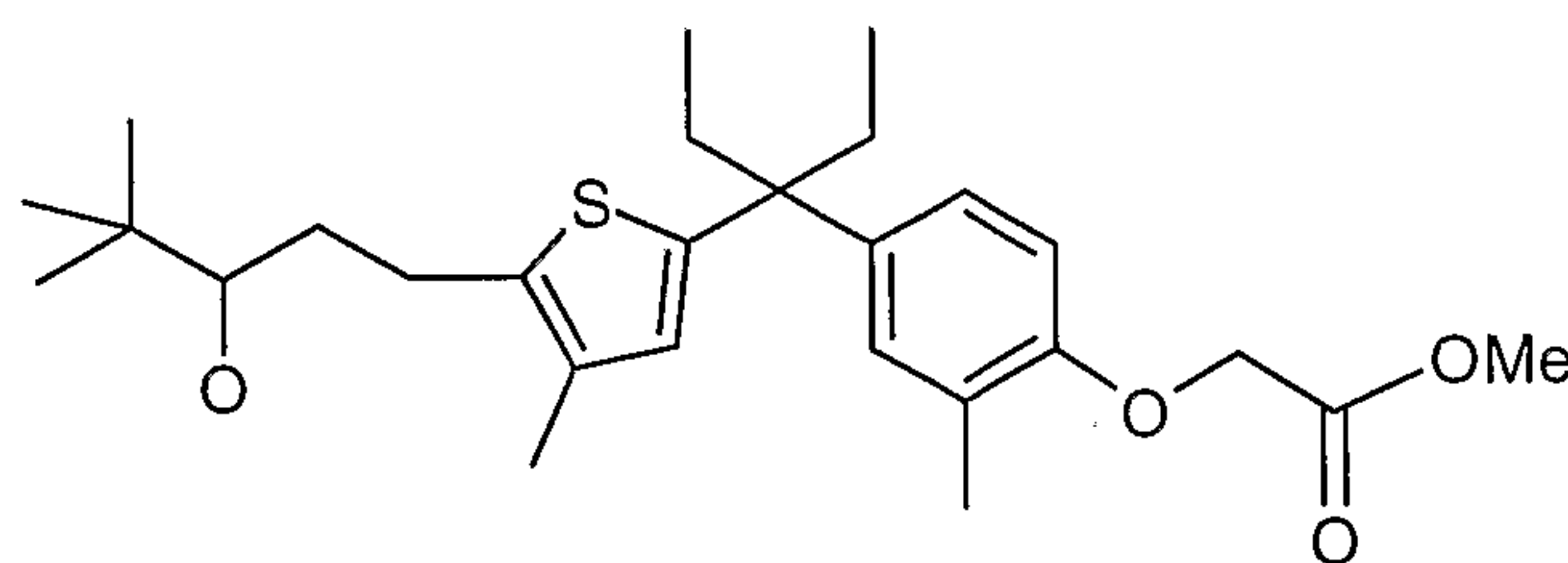
HPLC: Chiralcel AD (4.6X250 mm); 0.1% TFA in 5% EtOH/hept; 1 ml/m (flow
rate); rt = 10.09 m; 210 nm.

¹NMR equivalent to Example 29.

15 High Res. ES-MS: 462.3057; calc. for C₂₇H₄₀NO₃S+NH₄: 462.3042.

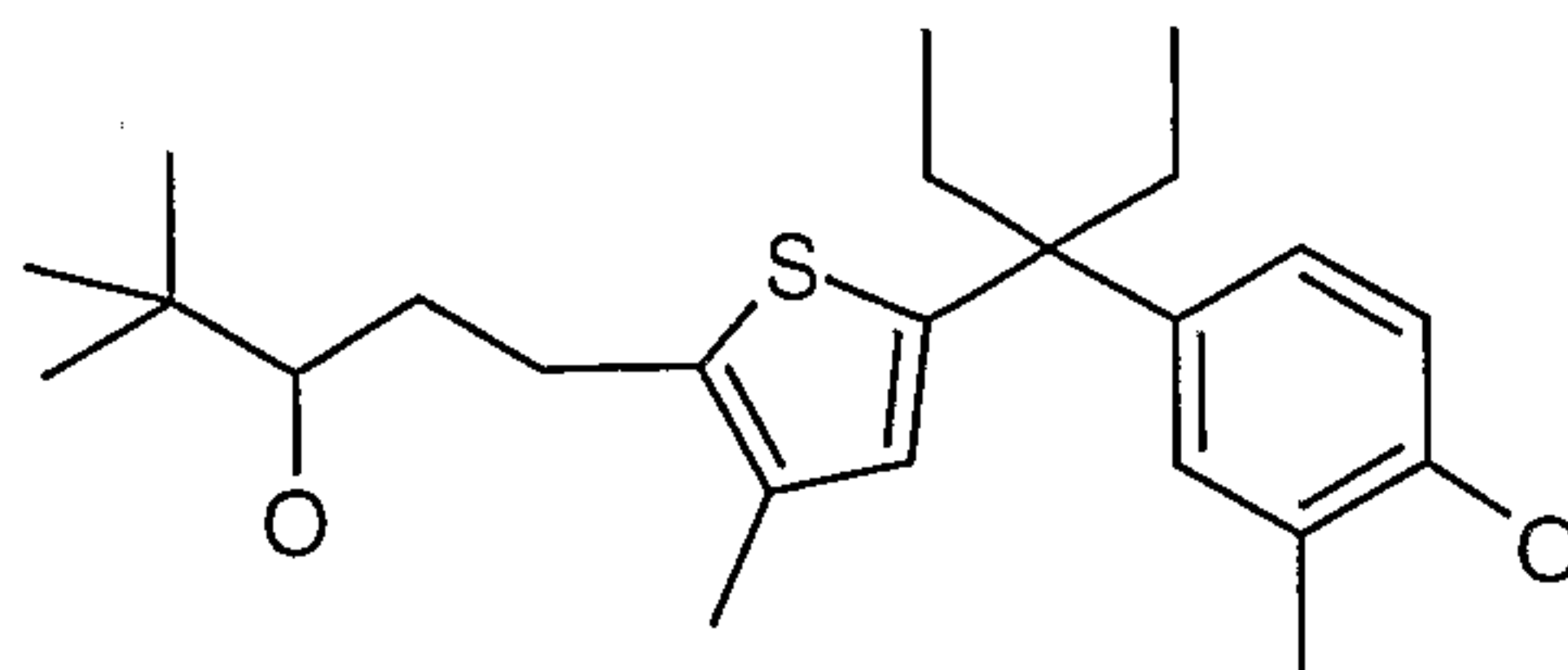
Example 31

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethoxy)-3-methylphenyl]pentane.



20

A. 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-hydroxy-3-methylphenyl]pentane.



25

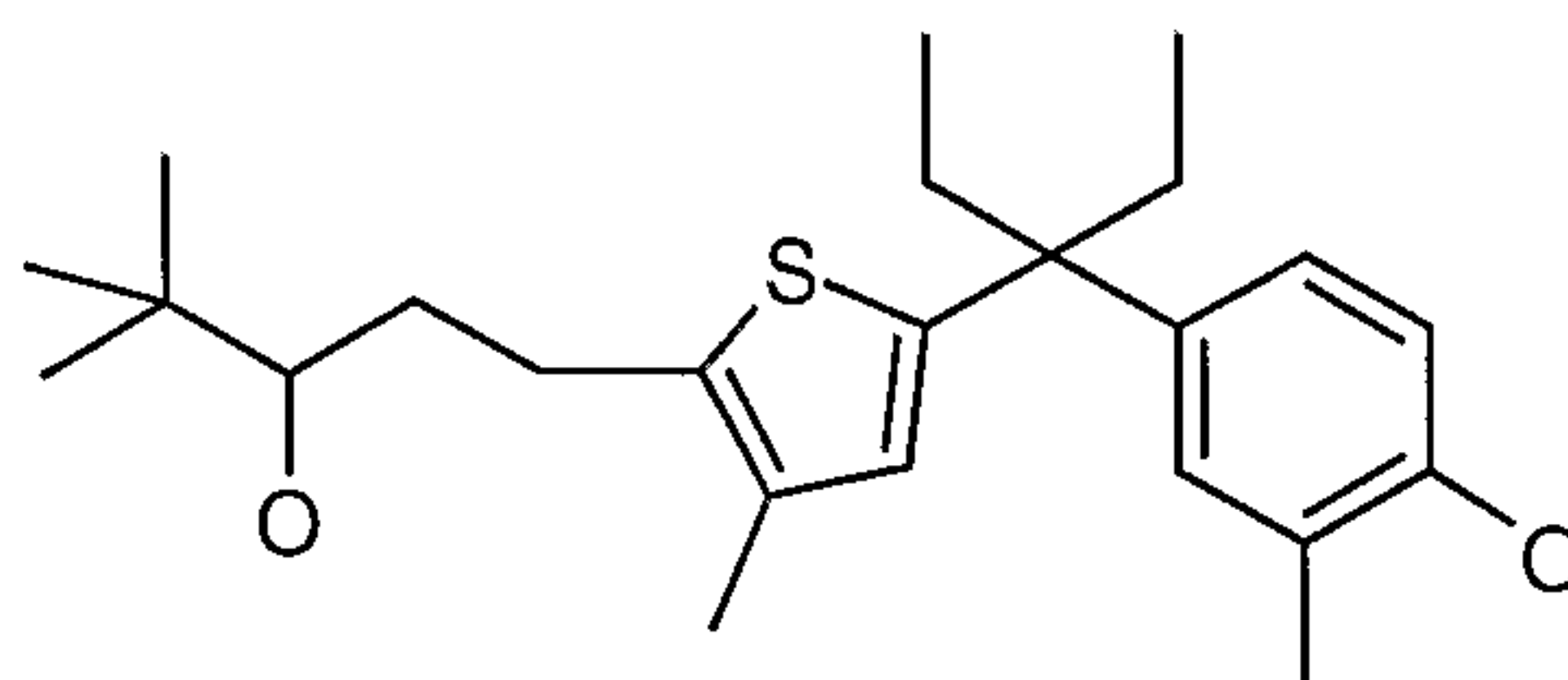
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Using a procedure analogous to Example 2, 3'-[5-(3-oxo-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-hydroxy-3-methylphenyl]pentane gives the title compound (4.6 g, 98%).

¹NMR (300MHz, DMSO-d₆) δ ppm: 0.61 (t, J = 7.3 Hz, 6H), 0.78 (s, 9H), 1.35 (m, 1H), 1.57 (m, 1H), 1.87-2.11 (m, 4H), 2.04 (s, 3H), 2.06 (s, 3H), 2.58 (m, 1H), 2.96 (dd, J = 6.2, 9.1 Hz, 1H), 4.36 (d, J = 6.2 Hz, 1H), 6.51 (s, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.85 (dd, J = 2.2, 8.4 Hz, 1H), 6.90 (s, 1H), 9.03 (s, 1H).

High Res. ES-MS: 389.2502; calc. for C₂₄H₃₆O₂S+H: 389.2514.

10 B. 3'-[5-(3-Hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethoxy)-3-methylphenyl]pentane.



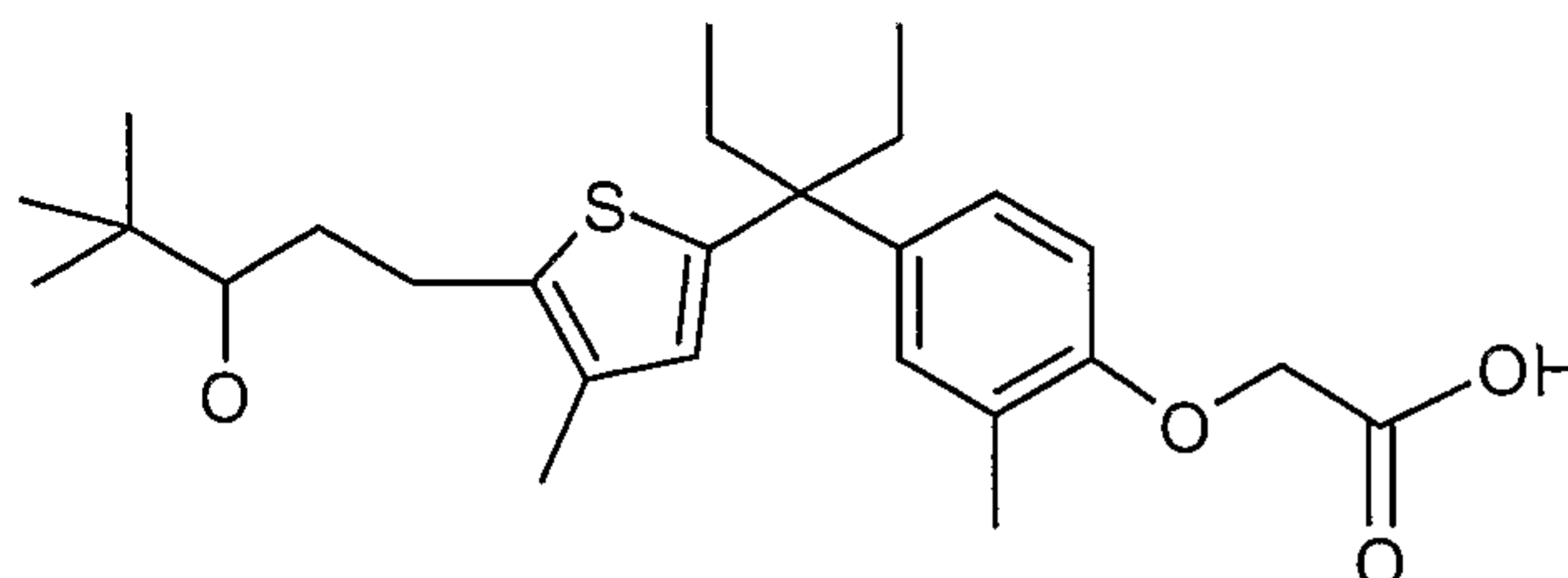
Using a procedure analogous to Example 1D, 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-hydroxy-3-methylphenyl]pentane is reacted with NaH and methyl chloroacetate to give the title compound (1.85 g, 92%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.78 (s, 9H), 1.35 (m, 1H), 1.58 (m, 1H), 1.92-2.02 (m, 4H), 2.04 (s, 3H), 2.14 (s, 3H), 2.55 (m, 1H), 2.78 (m, 1H), 2.95 (m, 1H), 3.69 (s, 3H), 4.38 (br s, 1H), 4.78 (s, 2H), 6.53 (s, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.98 (m, 2H).

20 High Res. ES-MS: 461.2738; calc. for C₂₇H₄₀O₄S+H: 461.2726.

Example 32

Preparation of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(carboxymethoxy)-3-methylphenyl]pentane.



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Using a procedure analogous to Example 3, 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(methoxycarbonylmethoxy)-3-methylphenyl]pentane gives the title compound (1.4 g, 80%).

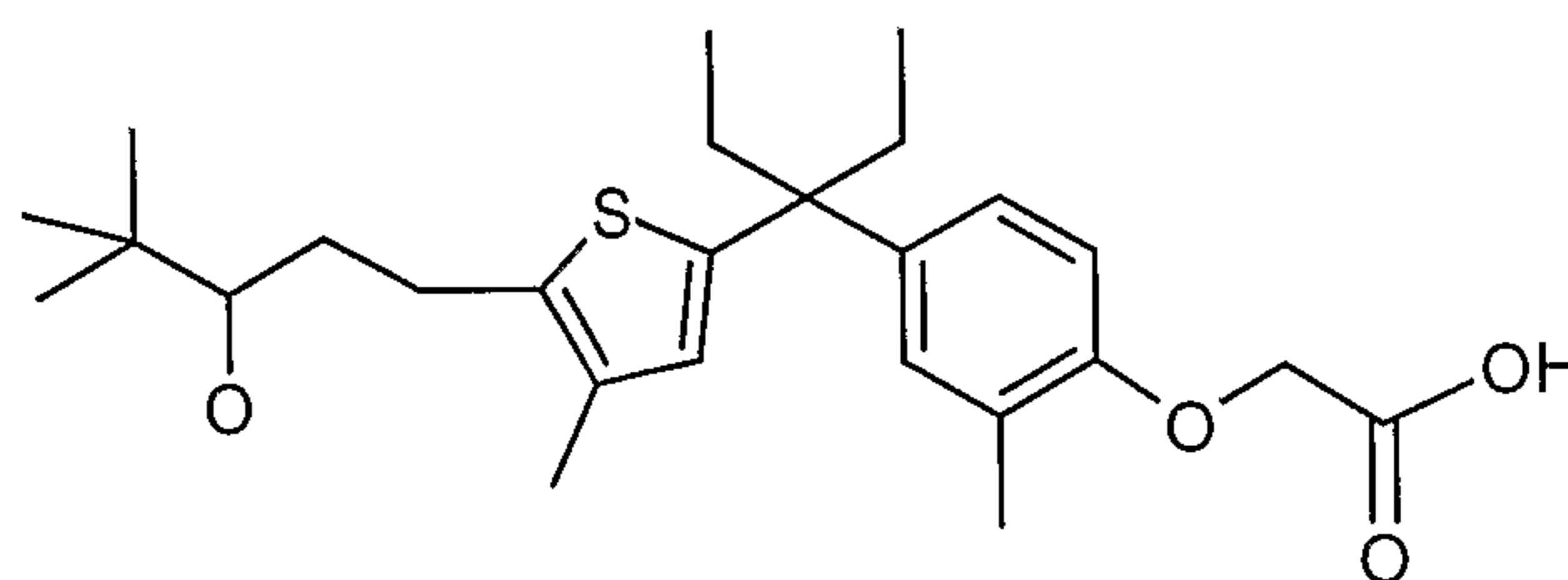
5 ¹NMR (300MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.78 (s, 9H), 1.59 (m, 1H), 1.61 (m, 1H), 1.90-2.07 (m, 4H), 2.04 (s, 3H), 2.14 (s, 3H), 2.58 (m, 1H), 2.78 (m, 1H), 2.96 (m, 1H), 4.37 (d, J = 6.2 Hz, 1H), 4.64 (s, 2H), 6.53 (s, 1H), 6.68 (d, J = 9.1 Hz, 1H), 7.00 (m, 2H), 12.92 (br s, 1H).

High Res. ES-MS: 469.2392; calc. for C₂₆H₃₈O₄S+Na: 469.2389.

10

Example 33A & 33B

Preparation of enantiomers of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(carboxylmethoxy)-3-methylphenyl]pentane.



15

A racemic mixture of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(carboxylmethoxy)-3-methylphenyl]pentane is chromatographed with a Chiralcel OJ column to give enantiomer 1, Example 33A (600 mg, 46%) and enantiomer 2, Example 33B (600 mg, 46%).

20 Enantiomer 1, Example 33A

HPLC: Chiralcel OJ (4.6X250 mm); 0.1% TFA in (2% MeOH and 5% EtOH in hept); 0.6 ml/m (flow rate); rt = 7.10 m; 240 nm.

¹NMR equivalent to Example 32.

High Res. ES-MS: 469.2393; calc. for C₂₆H₃₈O₄S+Na: 469.2389.

25 Enantiomer 2, Example 33B.

HPLC: Chiralcel OJ (4.6X250 mm); 0.1% TFA in (2% MeOH and 5% EtOH in hept); 0.6 ml/m (flow rate); rt = 10.50 m; 240 nm.

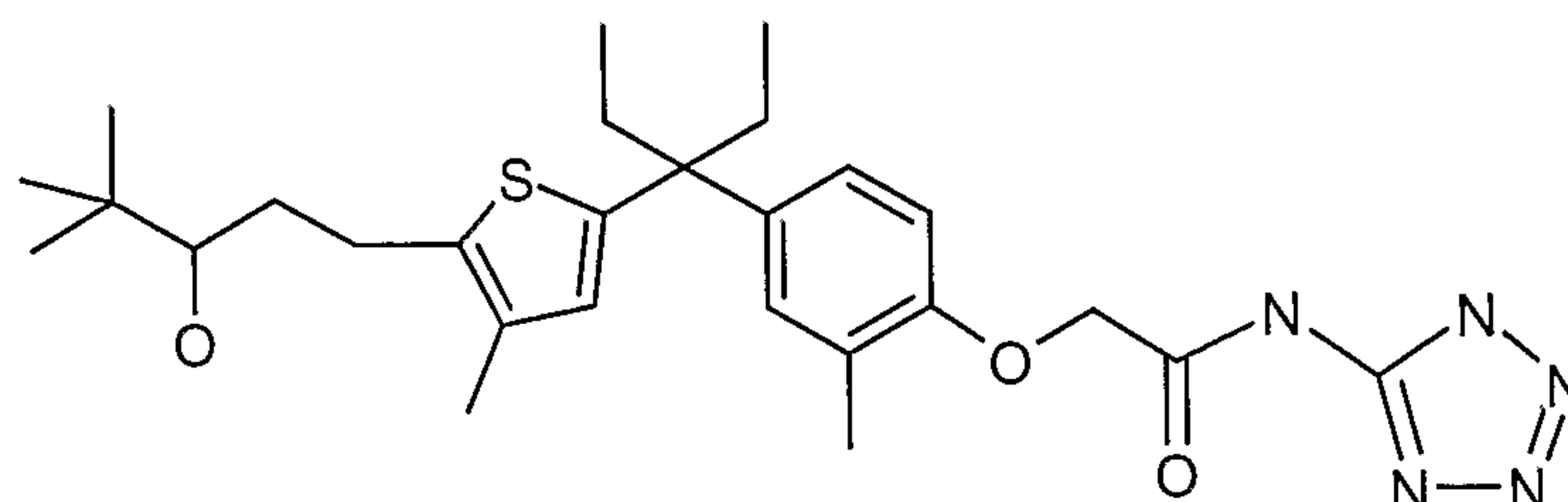
¹NMR equivalent to Example 32.

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High Res. ES-MS: 469.2385; calc. for $C_{26}H_{38}O_4S+Na$: 469.2389.

Example 34

Preparation of isomer 1 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(tetrazol-5-yl-aminocarbonylmethoxy)-3-methylphenyl]pentane.



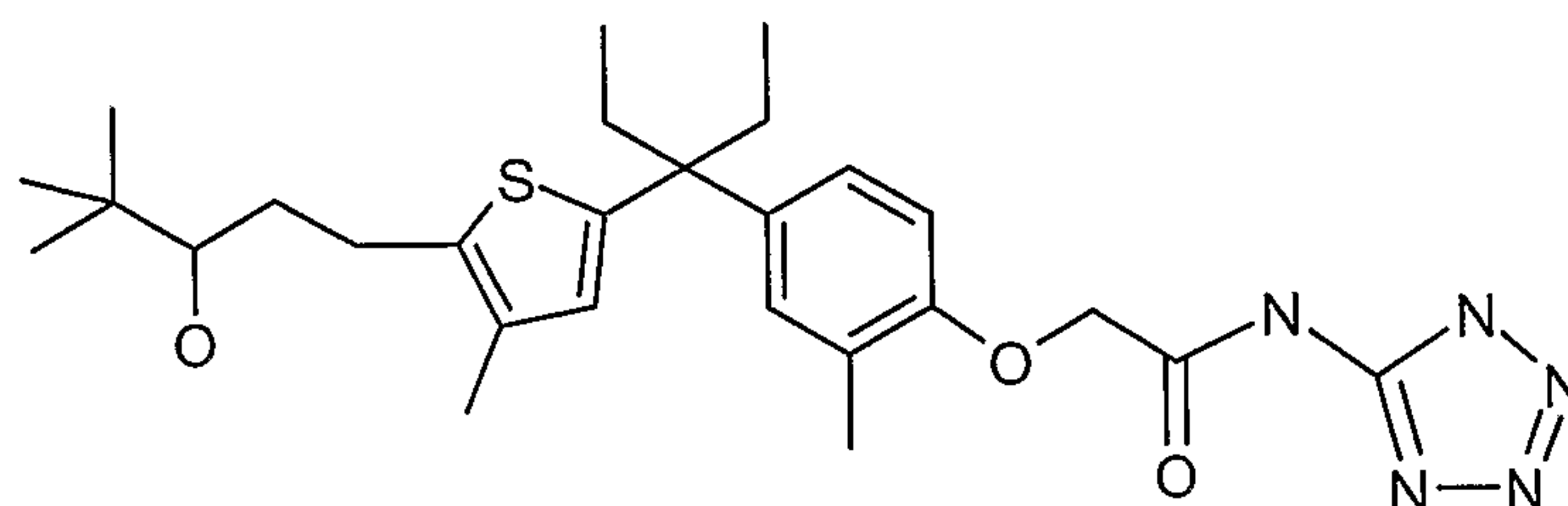
Using a procedure analogous to Example 24 and crystallization from Et₂O/hex, enantiomer 1 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(carboxylmethoxy)-3-methylphenyl]pentane (Example 33A) and 5-aminotetrazole give the title compound as a white solid (45 mg, 20%).

¹NMR (400MHz, DMSO-d₆) δ ppm: 0.62 (t, J = 7.3 Hz, 6H), 0.77 (s, 9H), 1.33 (m, 1H), 1.57 (m, 1H), 1.92-2.00 (m, 4H), 2.04 (s, 3H), 2.19 (s, 3H), 2.56 (m, 1H), 2.78 (m, 1H), 2.95 (m, 1H), 4.38 (d, J = 6.3 Hz, 1H), 4.86 (s, 2H), 6.52 (s, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.99 (m, 2H), 12.21 (br s, 1H), 15.97 (br s, 1H).

High Res. ES-MS: 536.2677; calc. for $C_{27}H_{39}O_3N_5S+Na$: 536.2671.

Example 35

Preparation of isomer 2 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(tetrazol-5-yl-aminocarbonylmethoxy)-3-methylphenyl]pentane.



Using a procedure analogous to Example 24 with crystallization from Et₂O/hex, enantiomer 2 of 3'-[5-(3-hydroxy-4,4-dimethylpentyl)-4-methylthiophen-2-yl]-3'-[4-(carboxylmethoxy)-3-methylphenyl]pentane (Example 33B) and 5-aminotetrazole give the title compound as a white solid (70 mg, 32%).

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¹NMR equivalent to Example 34.

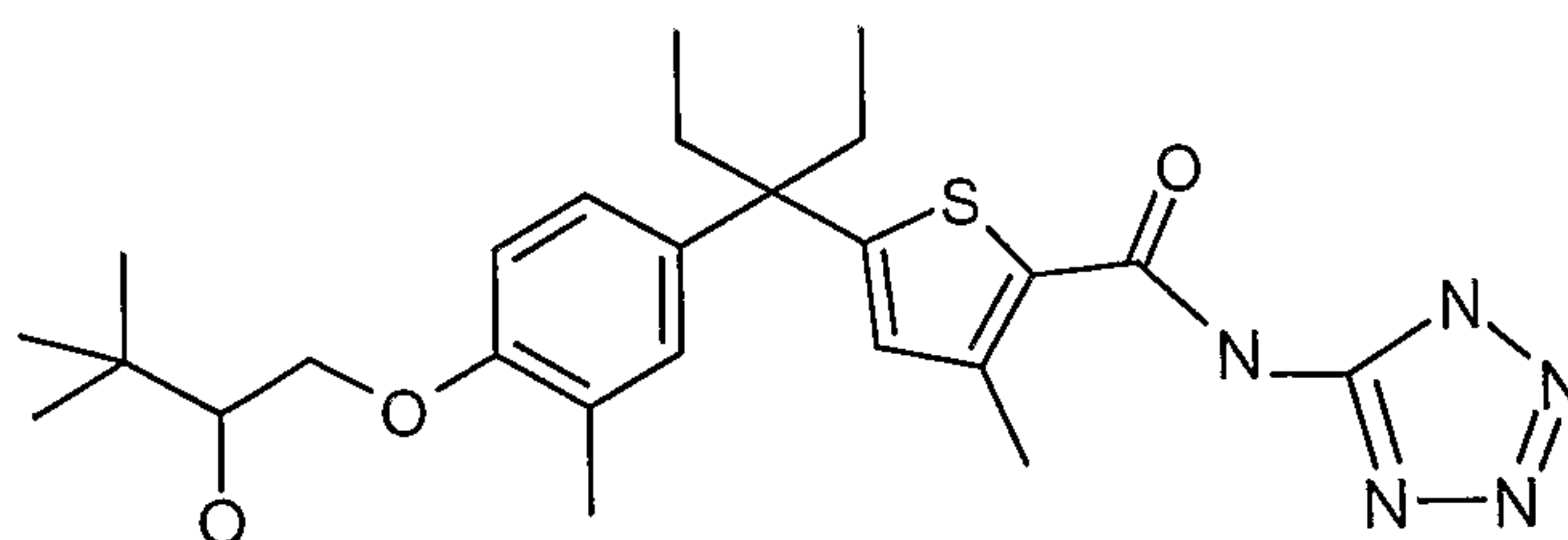
High Res. ES-MS: 536.2690; calc. for C₂₇H₃₉O₃N₅S+Na: 536.2671.

Add Preparation of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-

5 3'-[5-(tetrazol-5-yl-aminocarbonyl)- 4-methylthiophen-2-yl]pentane.

Example 36

Preparation of isomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-
3'-[5-(tetrazol-5-yl-aminocarbonyl)- 4-methylthiophen-2-yl]pentane.



10

Using a procedure analogous to Example 24 and crystallization from CH₂Cl₂, enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxyl-4-methylthiophen-2-yl]pentane (Example 7) and 5-aminotetrazole give the title compound as a white solid (335 mg, 77%).

15

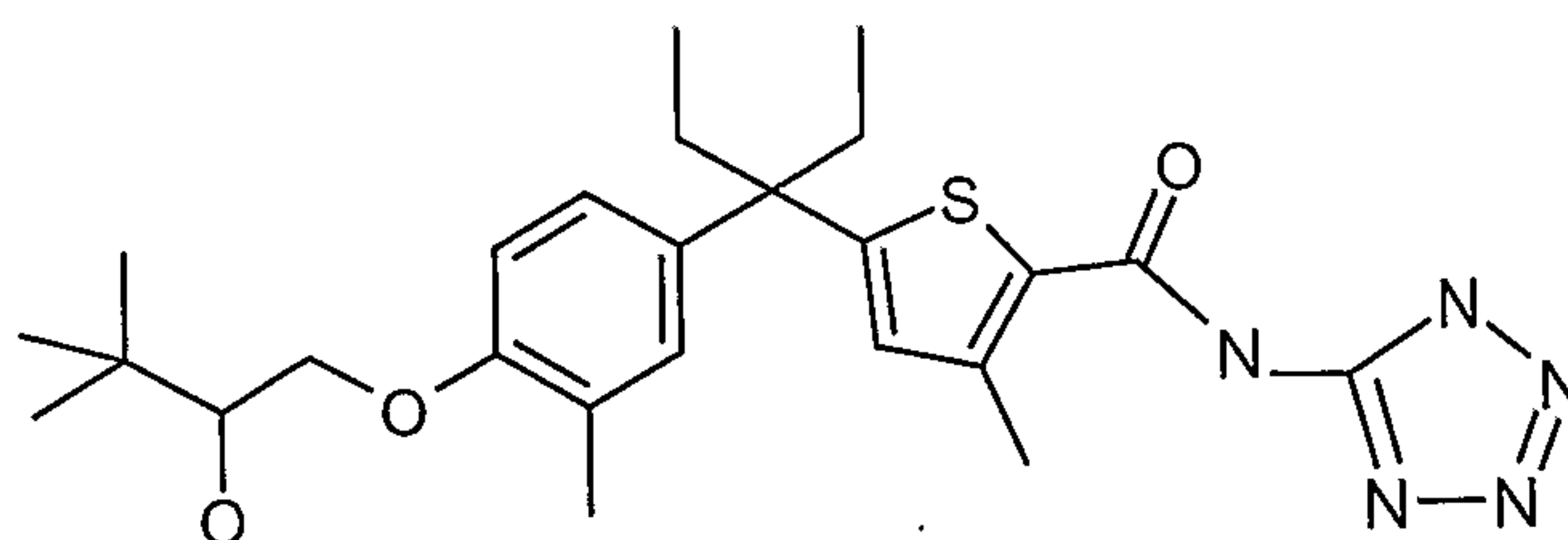
¹NMR (300MHz, DMSO-d₆) δ ppm: 0.67 (t, J = 7.3 Hz, 6H), 0.93 (s, 9H), 2.00-2.15 (m, 4H), 2.13 (s, 3H), 2.46 (s, 3H), 3.46 (m, 1H), 3.77 (dd, J = 7.3, 9.9 Hz, 1H), 4.04 (dd, J = 2.9, 10.2 Hz, 1H), 4.80 (d, J = 5.5 Hz, 1H), 6.87 (m, 2H), 7.04 (m, 2H), 11.80 (s, 1H), 15.92 (br s, 1H).

High Res. ES-MS: 486.2556; calc. for C₂₅H₃₅O₃N₅S+H: 486.2539.

20

Example 37

Preparation of isomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-
3'-[5-(tetrazol-5-yl-aminocarbonyl)- 4-methylthiophen-2-yl]pentane.



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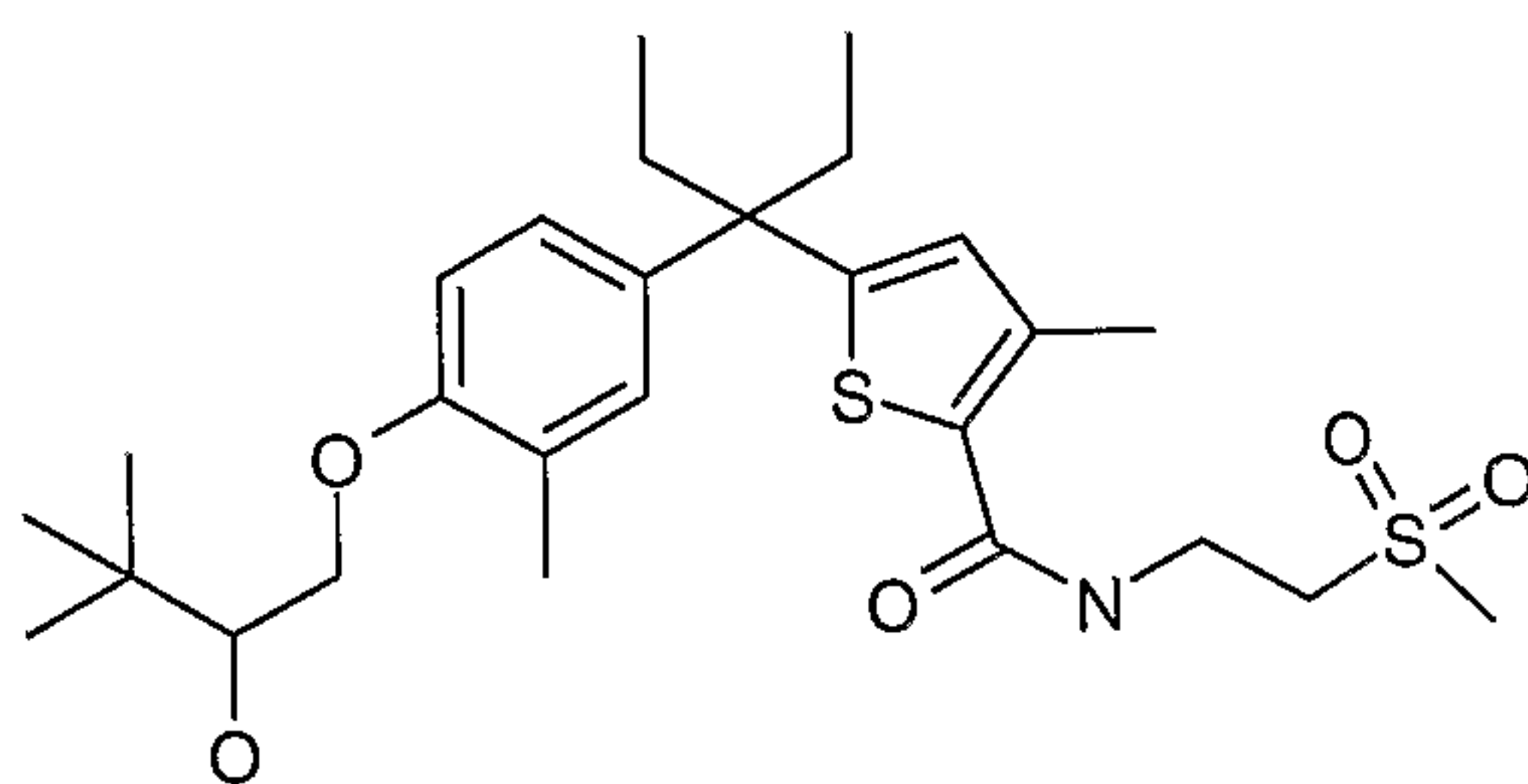
Using a procedure analogous to Example 24 and crystallization from CH₂Cl₂, enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxyl-4-methylthiophen-2-yl]pentane (Example 8) and 5-aminotetrazole give the title compound as a white solid (335 mg, 77%).

¹NMR (300MHz, DMSO-d₆) δ ppm: 0.67 (t, J = 7.3 Hz, 6H), 0.93 (s, 9H), 2.00-2.15 (m, 4H), 2.13 (s, 3H), 2.46 (s, 3H), 3.46 (m, 1H), 3.77 (dd, J = 7.3, 9.9 Hz, 1H), 4.04 (dd, J = 2.9, 10.2 Hz, 1H), 4.80 (d, J = 5.1 Hz, 1H), 6.87 (m, 2H), 7.04 (m, 2H), 11.80 (s, 1H), 15.92 (br s, 1H).

High Res. ES-MS: 486.2545; calc. for C₂₅H₃₅O₃N₅S+H: 486.2539.

Example 38

Preparation of 5-[1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methylphenyl]propyl]-3-methylthiophene-2-carboxylic acid (2-methylsulfonyl-ethyl) amide.



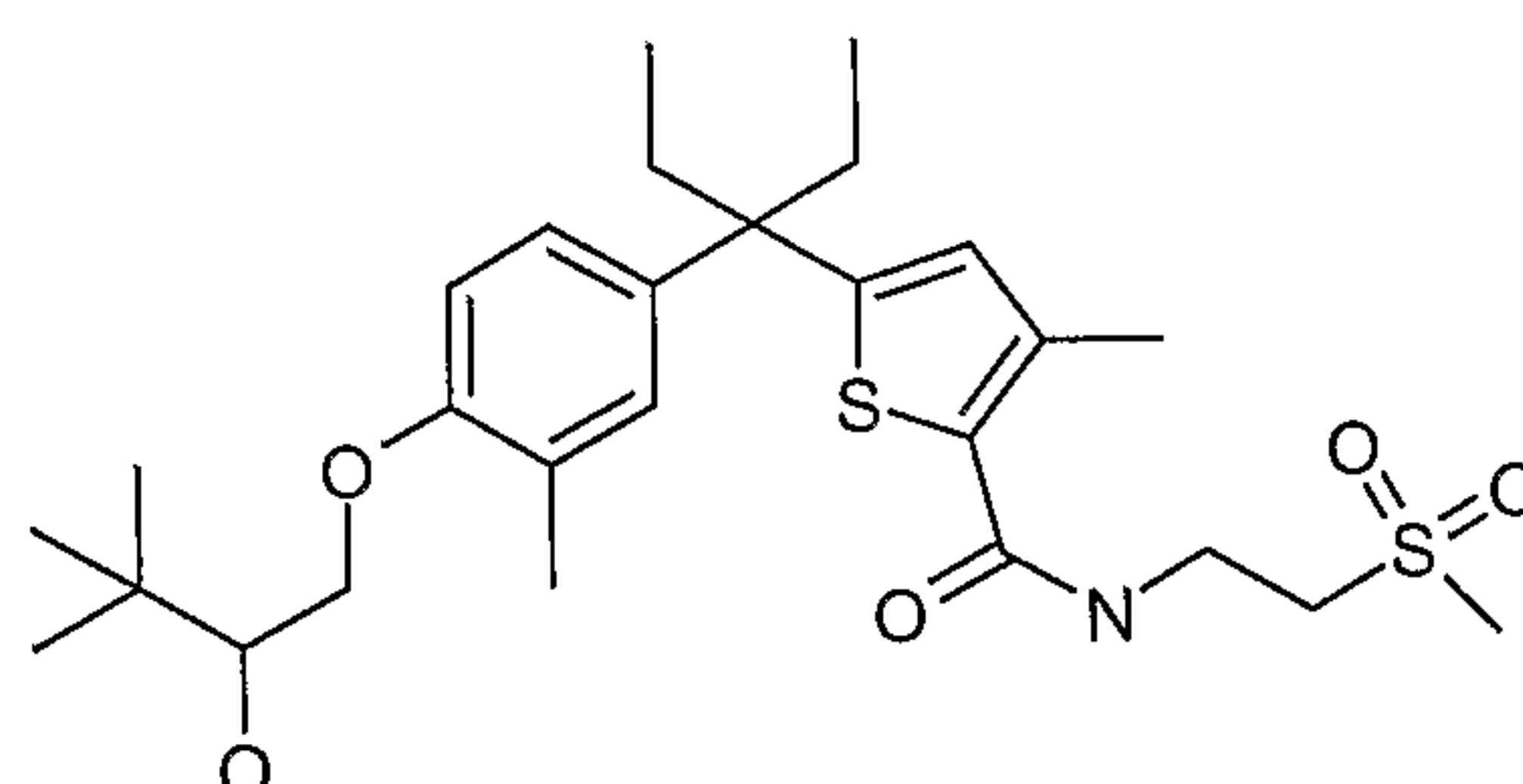
To a mixture of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methylphenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (0.6344 g, 1.52 mmol) and CH₂Cl₂ (10 mL) is added Et₃N (0.85 mL, 6.07 mmol), followed by hydrochloride salt of 2-aminoethylmethylsulfone (0.2416 g, 1.52 mmol), EDCI (0.320 g, 1.67 mmol), and HOBt (0.226 g, 1.67 mmol). The resulting solution is stirred at RT overnight, diluted with CH₂Cl₂ (30 mL), washed with 1.0 M HCl (3 x 20 mL), brine (20 mL), dried over MgSO₄, and concentrated. The resulting residue is purified by chromatography (50% EtOAc/Hex) to give the titled compound (0.4042 g, 0.77 mmol, 51%). ¹H NMR (CDCl₃), δ 0.71 (t, J = 7.3 Hz, 6H), 1.03 (s, 9H), 2.09 (q, J = 7.3 Hz, 4H), 2.21 (s, 3H), 2.42 (d, J = 3.0 Hz, 1H), 2.46 (s, 3H), 2.98 (s, 3H), 3.32 (t, J = 6.4 Hz, 2H), 3.71 (dt, J = 8.9, 2.9 Hz, 1H), 3.84-3.94 (m, 3H), 4.10 (dd, J = 9.3, 2.5 Hz, 1H), 6.44 (t, J = 5.8 Hz, 1H), 6.59 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 1.7

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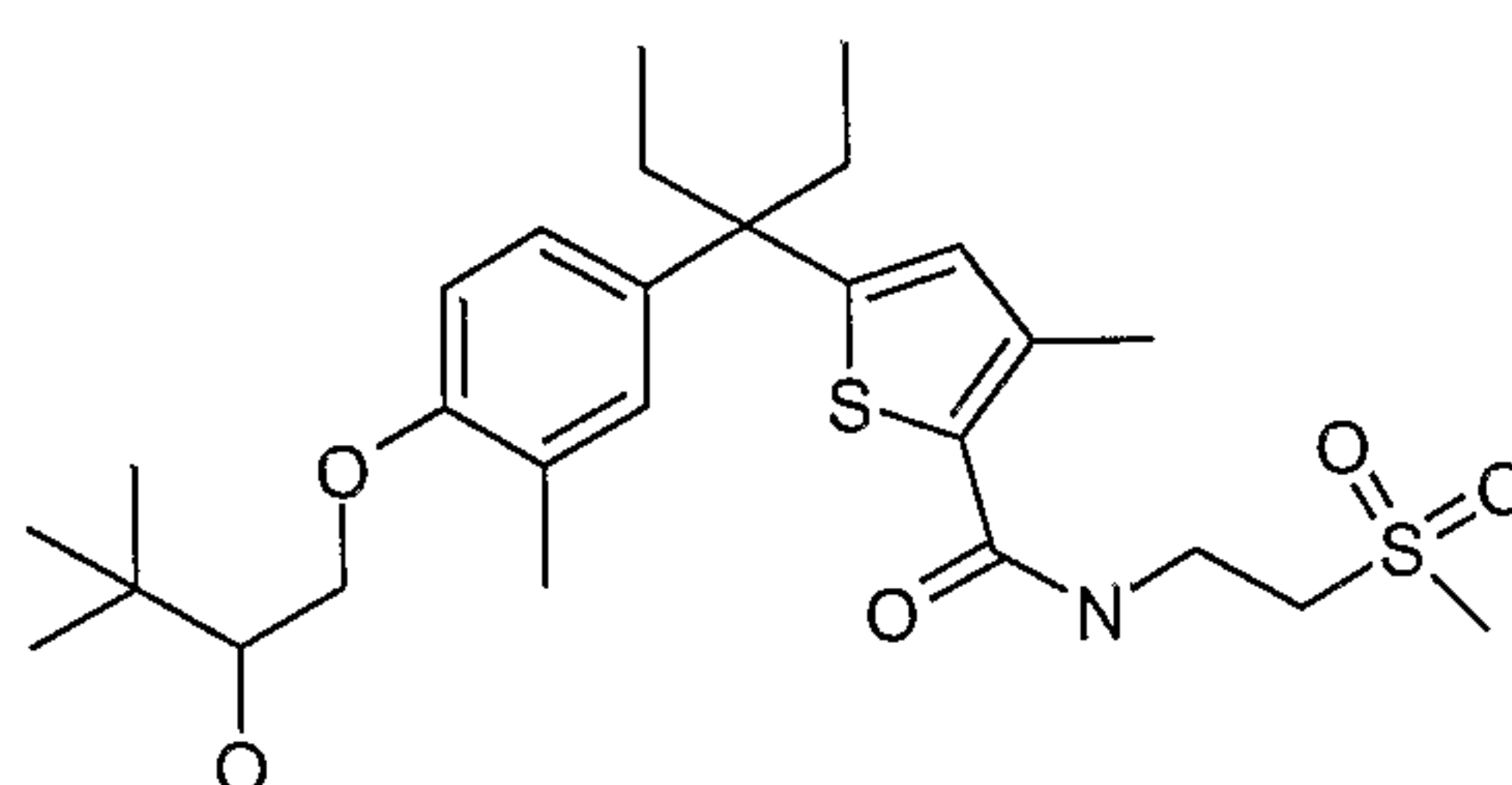
Hz, 1H), 7.03 (dd, $J = 8.7, 2.5$ Hz, 1H). LC/MS (m/z): calcd for $C_{27}H_{42}NO_5S_2$ ($M+H$)⁺: 524.8; found: 524.2.

Example 39 and Example 40

- 5 Preparation of enantiomers of 5-[1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methylphenyl]propyl]-3-methylthiophene-2-carboxylic acid (2-methylsulfonyl-ethyl) amide.



Enantiomer 1



Enantiomer 2

10

- A racemic mixture of 5-[1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methylphenyl]propyl]-3-methylthiophene-2-carboxylic acid (2-methylsulfonyl-ethyl) amide (247mg) is chromatographed (CHIRALPAK AD column, 40% *i*-PrOH/Hept) to give enantiomer 1, Example 39 (100 mg, 40 %) and enantiomer 2, Example 40 (80 mg, 32%).

15

Example 39, Enantiomer 1 :

rt = 6.0 m

- 20 NMR & LC/MS: Identical to the racemic material, Example 38.

Example 40, Enantiomer 2 :

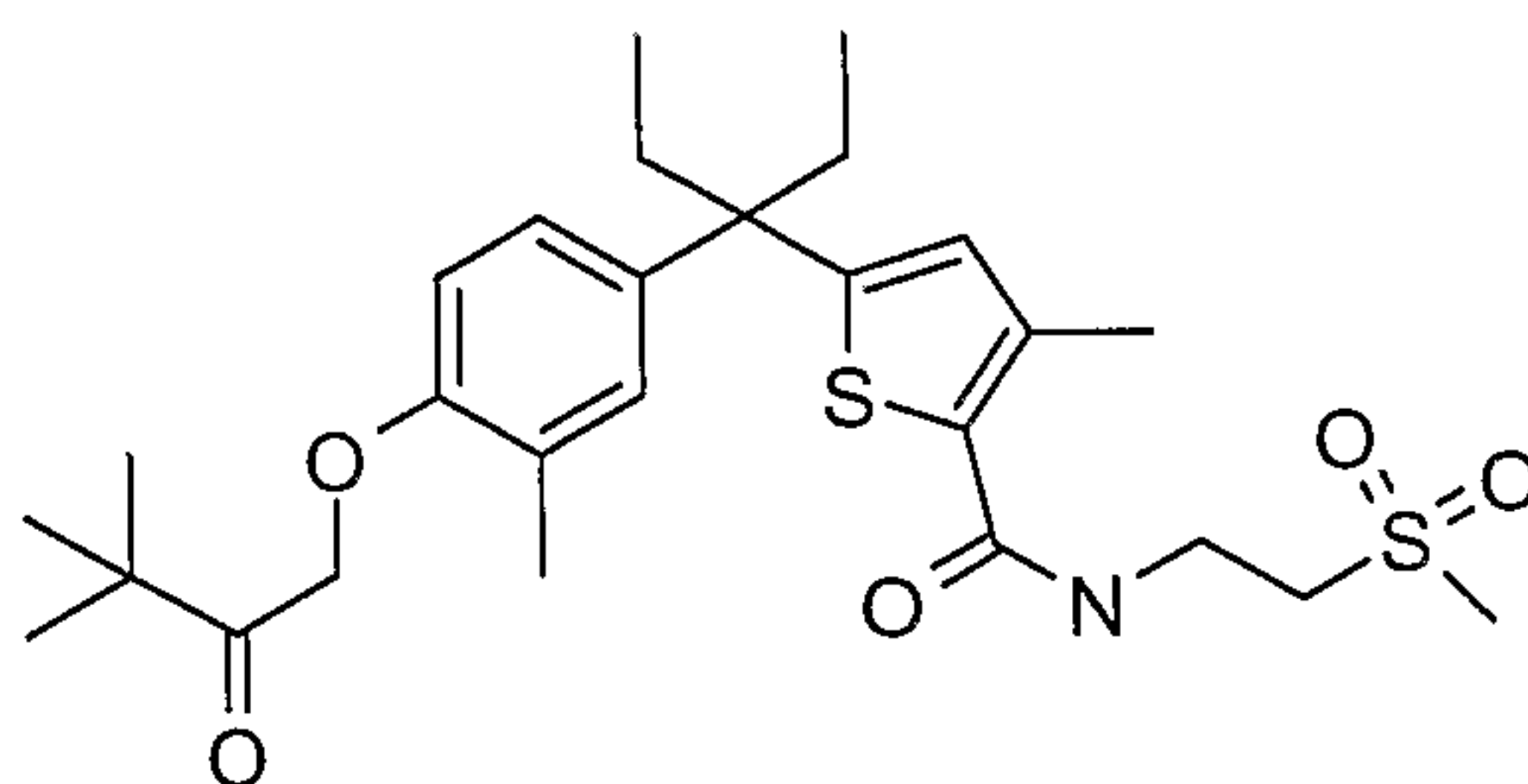
rt = 10.2 m

NMR & LC/MS: Identical to the racemic material, Example 38.

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Example 41

Preparation of 5-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-3-methyl-thiophene-2-carboxylic acid (2-methanesulfonyl-ethyl)-amide.



To a solution of 5-[1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methylphenyl]propyl]-3-methylthiophene-2-carboxylic acid (2-methylsulfonyl-ethyl) amide, Example 38 (0.1096 g, 0.21 mmol) in CH_2Cl_2 (10 mL) is added NMO (37 mg, 0.31 mmol), and TPAP (3.7 mg, 0.01 mmol). The resulting solution is stirred at RT for 5 m, then it is filtered through a silica gel column, and washed with excess amount of EtOAc. Concentration of the solvent resulted in the title compound (62 mg, 0.12 mmol, 57%).

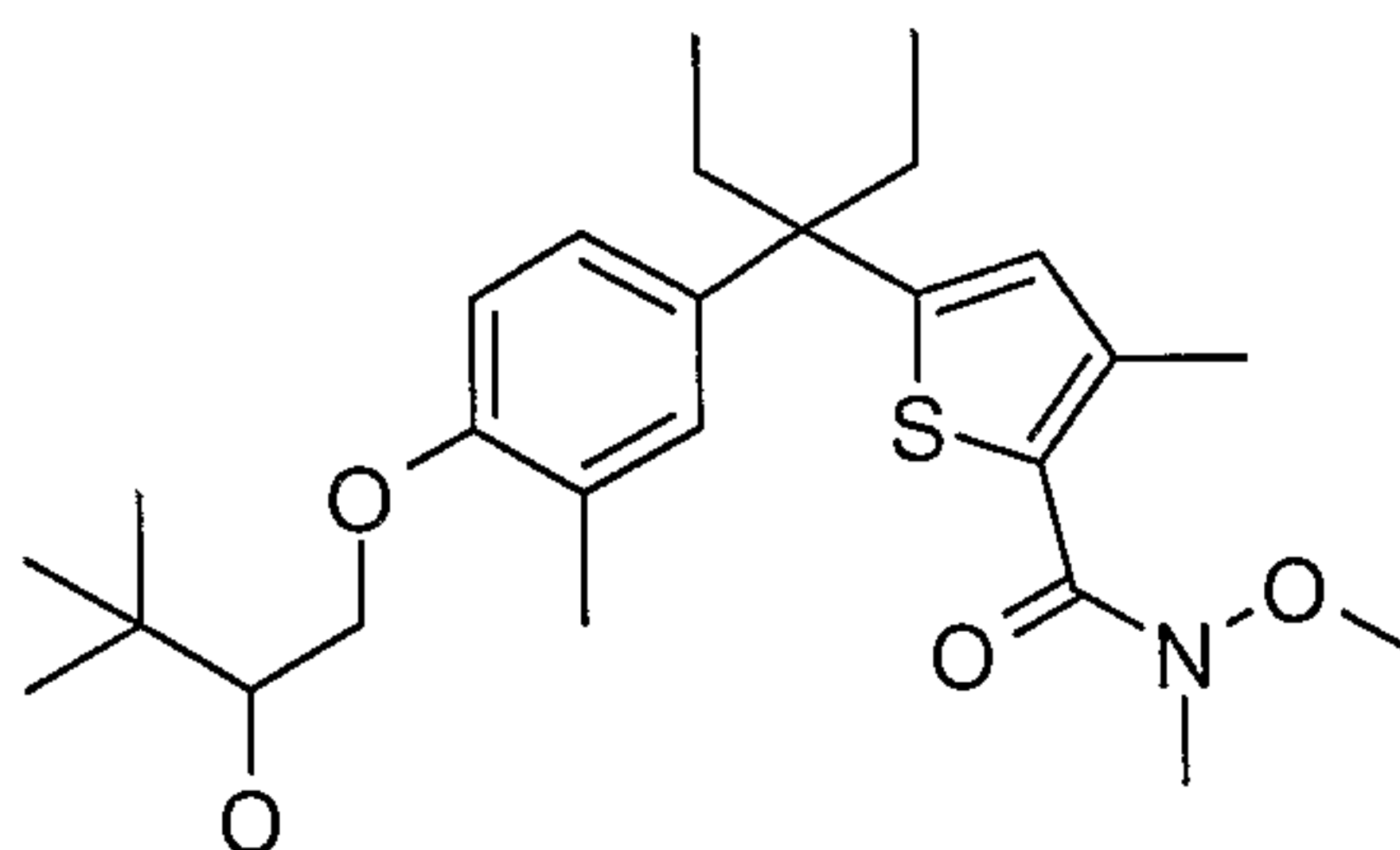
^1H NMR (CDCl_3), δ 0.70 (t, $J = 8.0$ Hz, 6H), 1.27 (s, 9H), 1.99 (m, 4H), 2.18 (s, 3H), 2.38 (s, 3H), 2.90 (s, 3H), 3.24 (t, $J = 6.0$ Hz, 2H), 3.82 (m, 2H), 6.36 (t, $J = 5.8$ Hz, 1H), 6.42 (d, $J = 8.4$ Hz, 1H), 6.50 (s, 1H), 6.85-6.95 (m, 2H).

LC/MS (m/z): 522.1 ($\text{M}+\text{H}$) $^+$.

Example 42

Preparation of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid methoxy-methyl-amide.

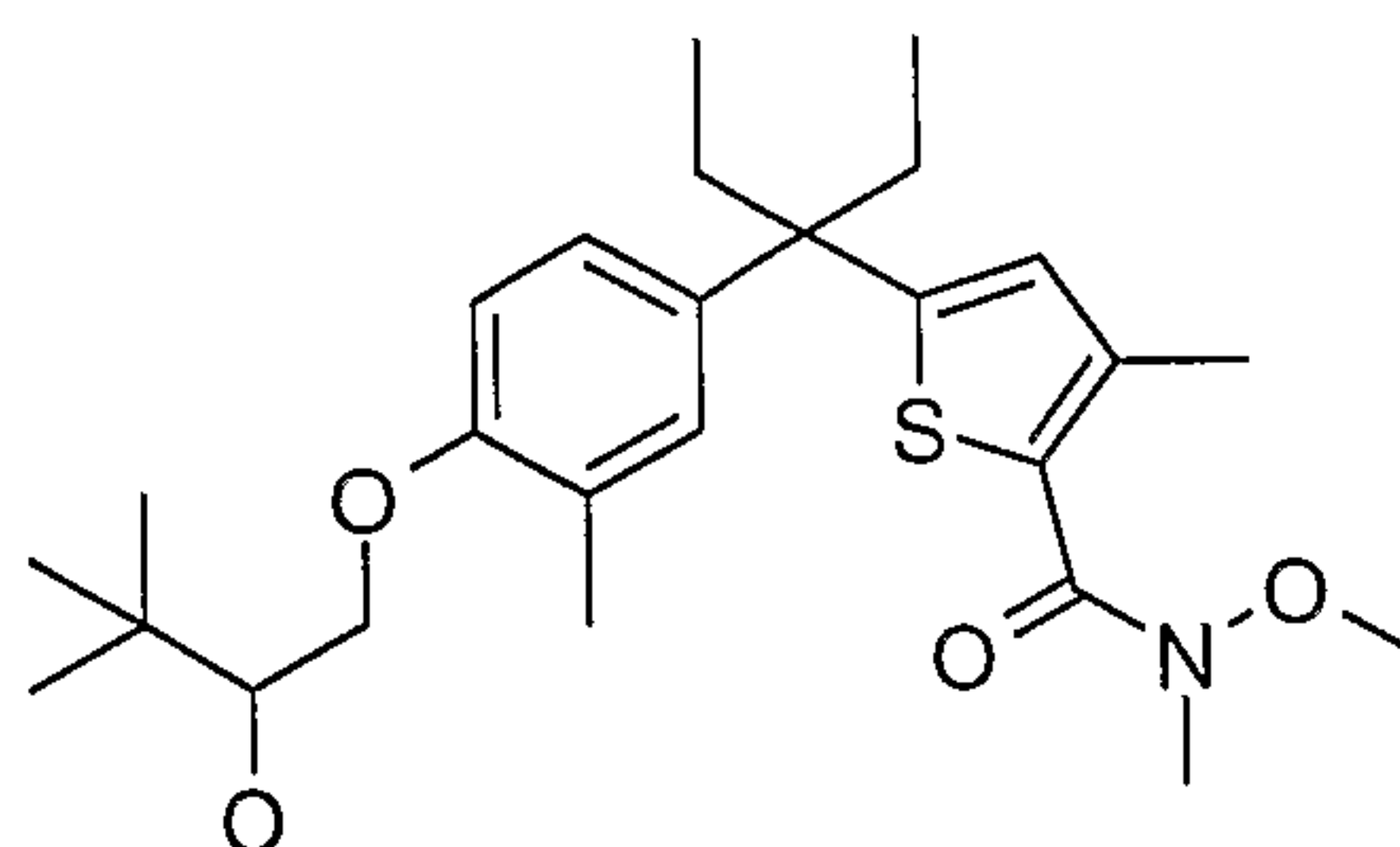
-197-



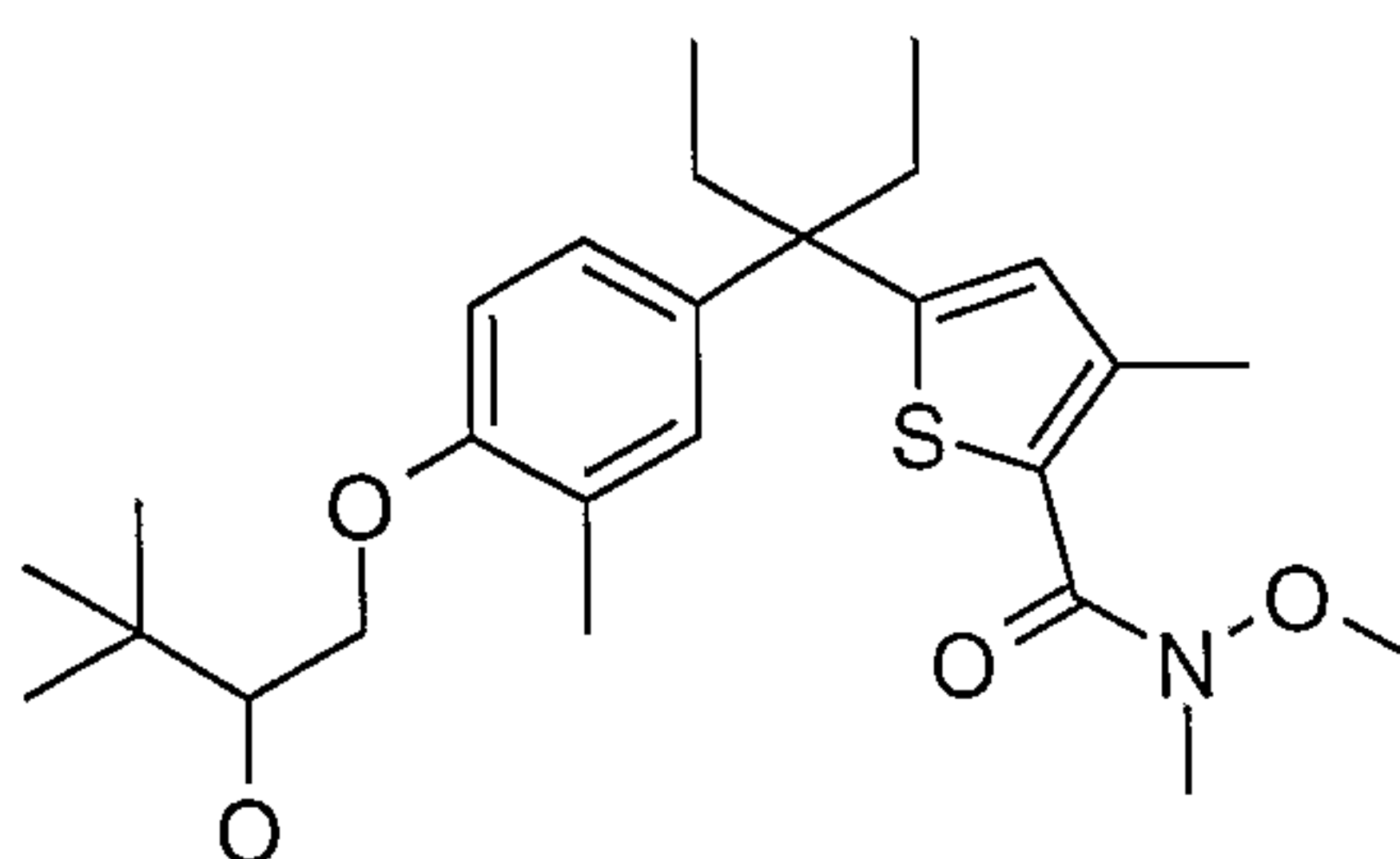
Using the procedure analogous to Example 38, from 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (0.34 g, 0.81 mmol) and *N*-methoxy-*N*-methylamine hydrochloride salt (0.087 g, 0.89 mmol) furnished the titled compound (0.2083 g, 0.45 mmol, 56%).
¹H NMR (CD₃OD), δ 0.65 (t, *J* = 7.4 Hz, 6H), 0.95 (s, 9H), 2.07 (q, *J* = 7.4 Hz, 4H), 2.14 (s, 3H), 2.35 (s, 3H), 3.25 (s, 3H), 3.57 (dd, *J* = 7.8, 2.9 Hz, 1H), 3.58 (s, 3H), 3.82 (dd, *J* = 9.7, 7.8 Hz, 1H), 4.07 (dd, *J* = 9.7, 2.9 Hz, 1H), 6.62 (s, 1H), 6.73 (d, *J* = 8.9 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J* = 8.9, 2.4 Hz, 1H). LC/MS (*m/z*):
 calcd for C₂₆H₄₀NO₄S (M+H)⁺: 462.2; found: 462.2.

Example 43 and Example 44

Preparation of enantiomers of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid methoxy-methyl-amide.



Enantiomer 1



Enantiomer 2

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A racemic mixture of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid methoxy-methyl-amide (92 mg) is chromatographed (CHIRALPAK AD column, 40% *i*-PrOH/Hept) to give enantiomer 1, Example 43 (42 mg, 46 %) and enantiomer 2, Example 44 (34.5 mg, 38 %).

5

Example 43, Enantiomer 1 :

rt = 4.4 m

NMR & LC/MS: Identical to the racemic material, Example 42.

Example 44, Enantiomer 2 :

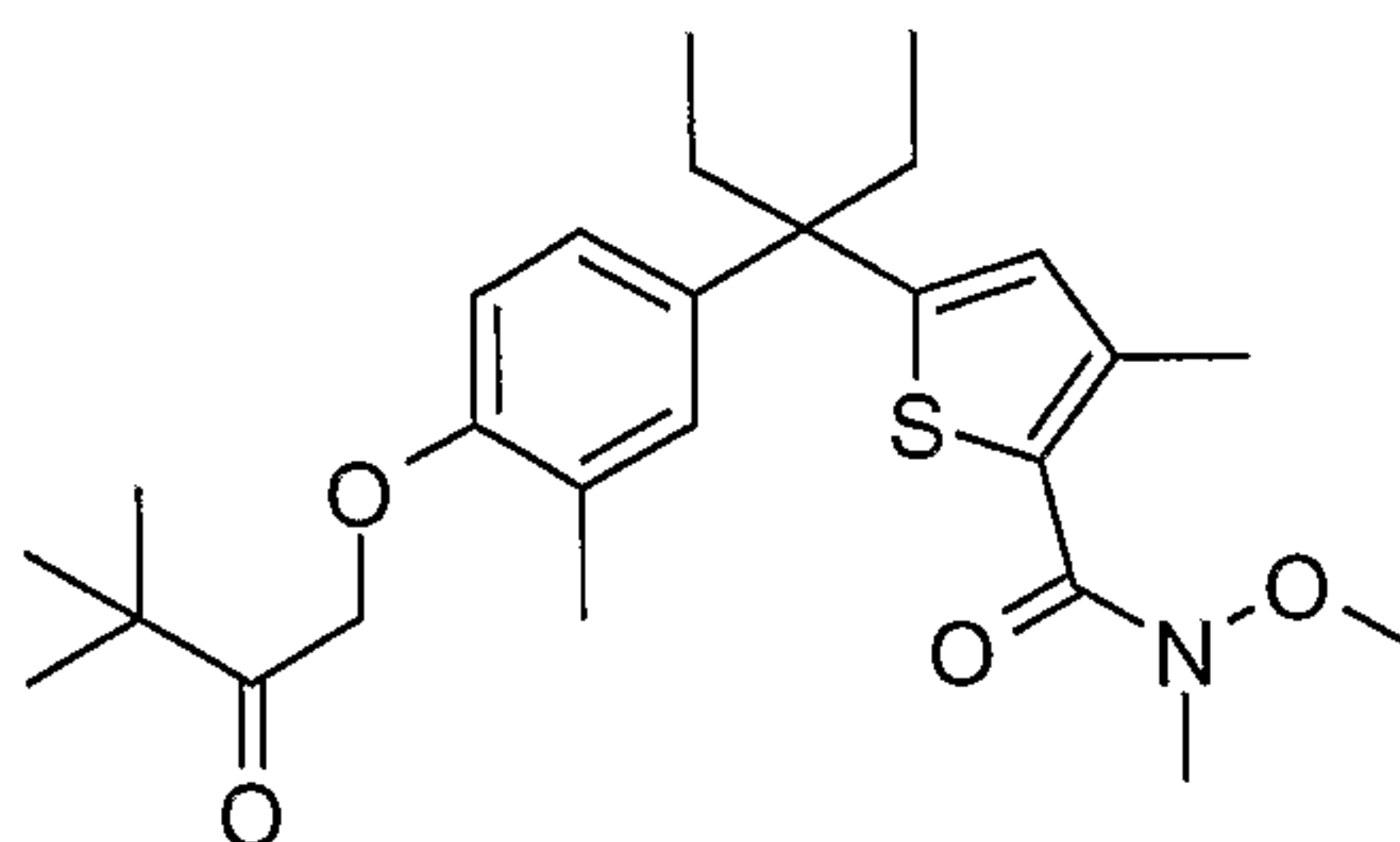
10 rt = 7.3 m

NMR & LC/MS: Identical to the racemic material, Example 42.

Example 45

Preparation of 5-{1-[4-(3,3-dimethyl-2-oxo-butyloxy)-3-methyl-phenyl]-1-ethyl-propyl}-3-methyl-thiophene-2-carboxylic acid methoxy-methyl-amide.

15



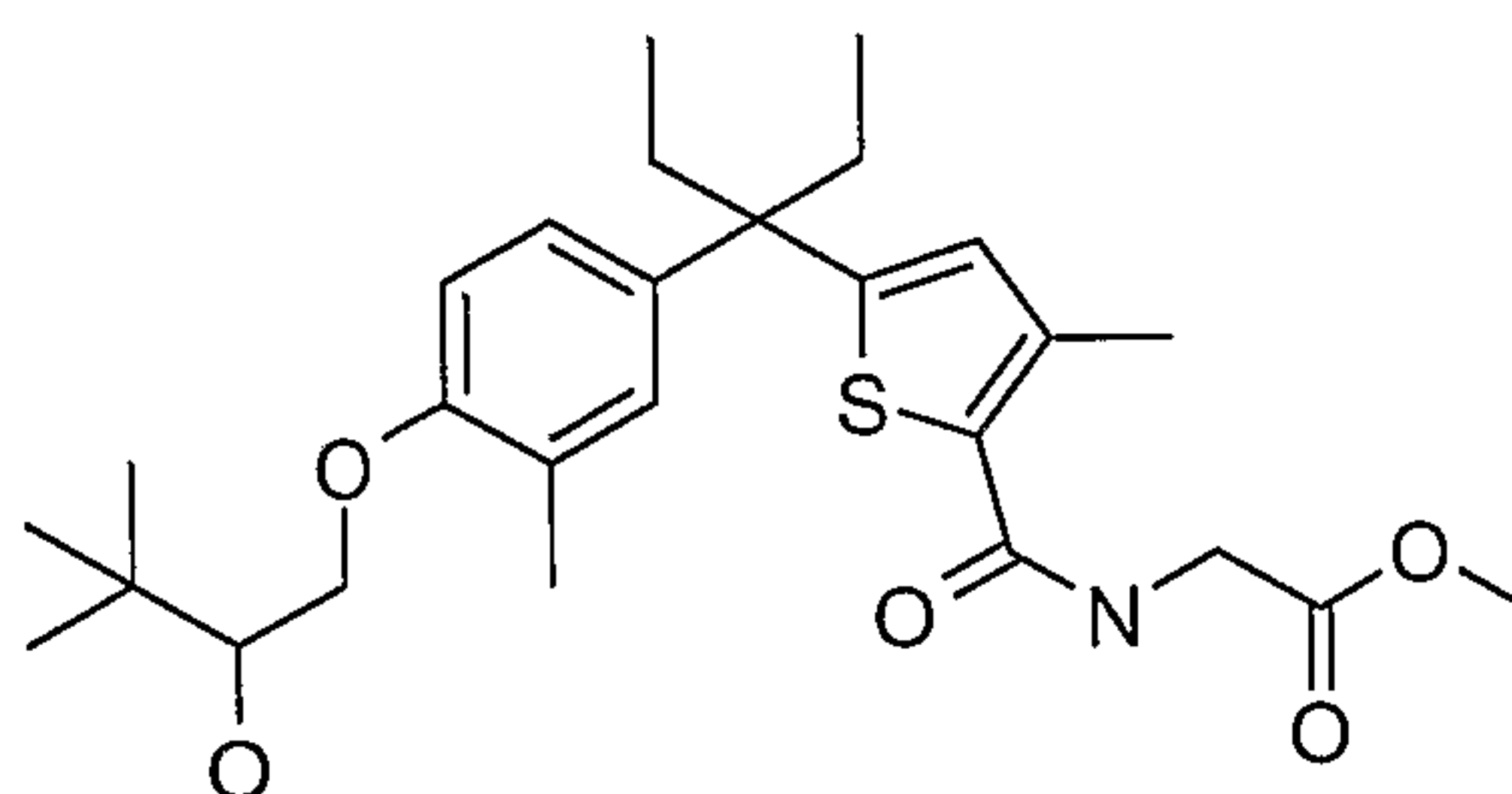
Using a procedure analogous to Example 41, from 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid methoxy-methyl-amide (Example 42) (110 mg, 0.245 mmol) yielded the titled compound (107.9 mg, 98%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 6.4 Hz, 6H), 1.27 (s, 9H), 2.09 (q, *J* = 6.4 Hz, 4H), 2.27 (s, 3H), 2.48 (s, 3H), 3.30 (s, 3H), 3.67 (s, 3H), 4.85 (s, 2H), 6.52 (d, *J* = 8.6 Hz, 1H), 6.57 (s, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.02 (s, 1H). LC/MS (*m/z*): calcd for C₂₆H₃₈NO₄S (M+H)⁺: 460.2; found: 460.2.

25

Example 46

Preparation of 2-[5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl-propyl]-3-methyl-thiophene-2-carbonyl]-amino]-acetic acid methyl ester.

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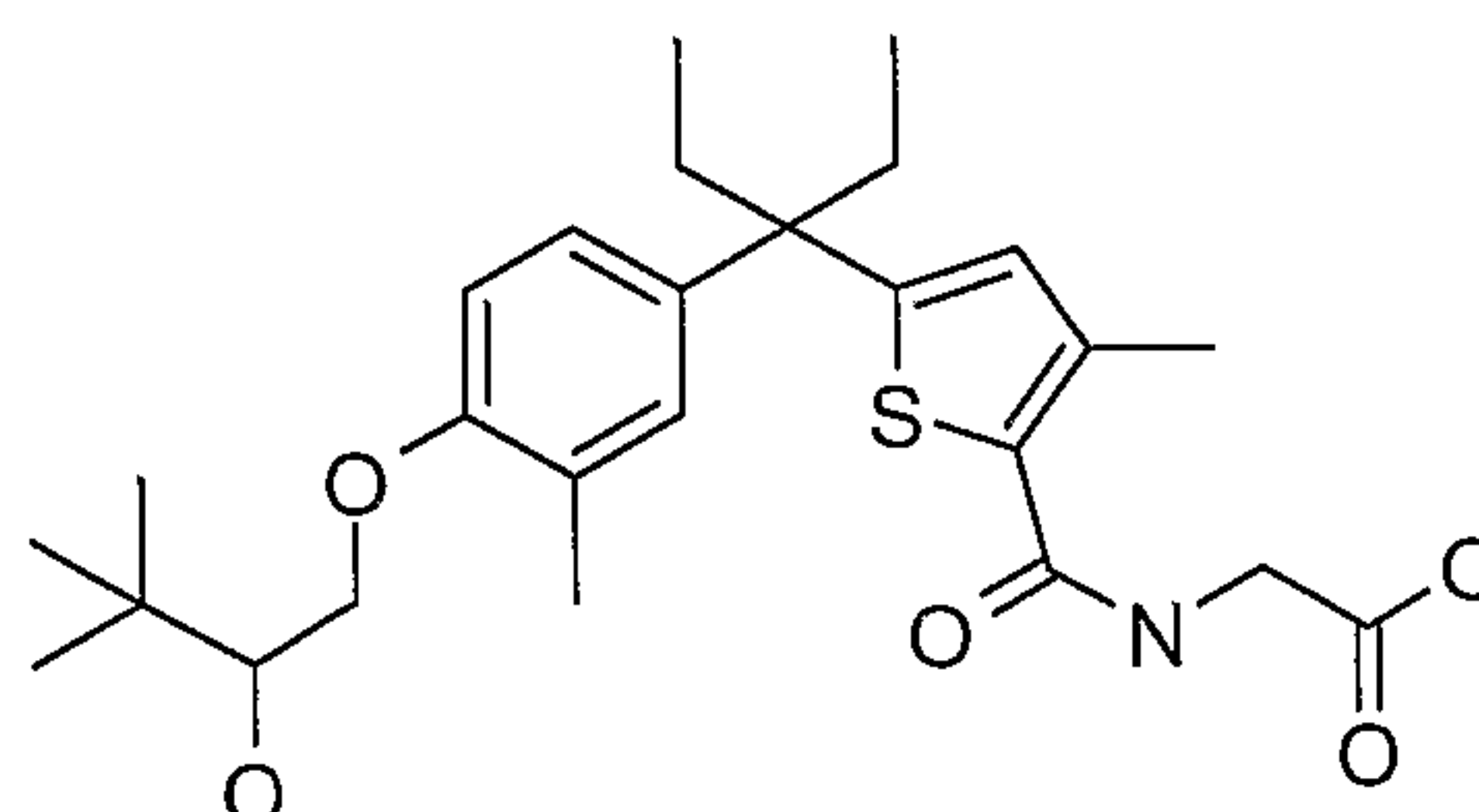


5 Using the procedure analogous to Example 38, from 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butyoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (0.4307 g, 1.03 mmol) and glycine methyl ester hydrochloride (0.129 g, 1.03 mmol) furnished the titled compound (0.2535 g, 50%). ¹H NMR (CDCl₃), δ

10 0.71 (t, *J* = 6.8 Hz, 6H), 1.03 (s, 9H), 2.09 (q, *J* = 6.8 Hz, 4H), 2.21 (s, 3H), 2.44 (d, *J* = 2.5 Hz, 1H), 2.48 (s, 3H), 3.72 (dt, *J* = 8.3, 2.5 Hz, 1H), 3.78 (s, 3H), 3.87 (t, *J* = 8.8 Hz, 1H), 4.11 (dd, *J* = 9.2, 2.5 Hz, 1H), 4.17 (d, *J* = 5.4 Hz, 2H), 6.20 (s, 1H), 6.61 (s, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.99-7.01 (m, 1H), 7.04 (dd, *J* = 8.8, 2.4 Hz, 1H). LC/MS (*m/z*): 490.2 (M+H)⁺.

15 Example 47

Preparation of 2-[5-{1-Ethyl-1-{4-(2-hydroxy-3,3-dimethyl-butyoxy)-3-methyl-phenyl-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid.



20

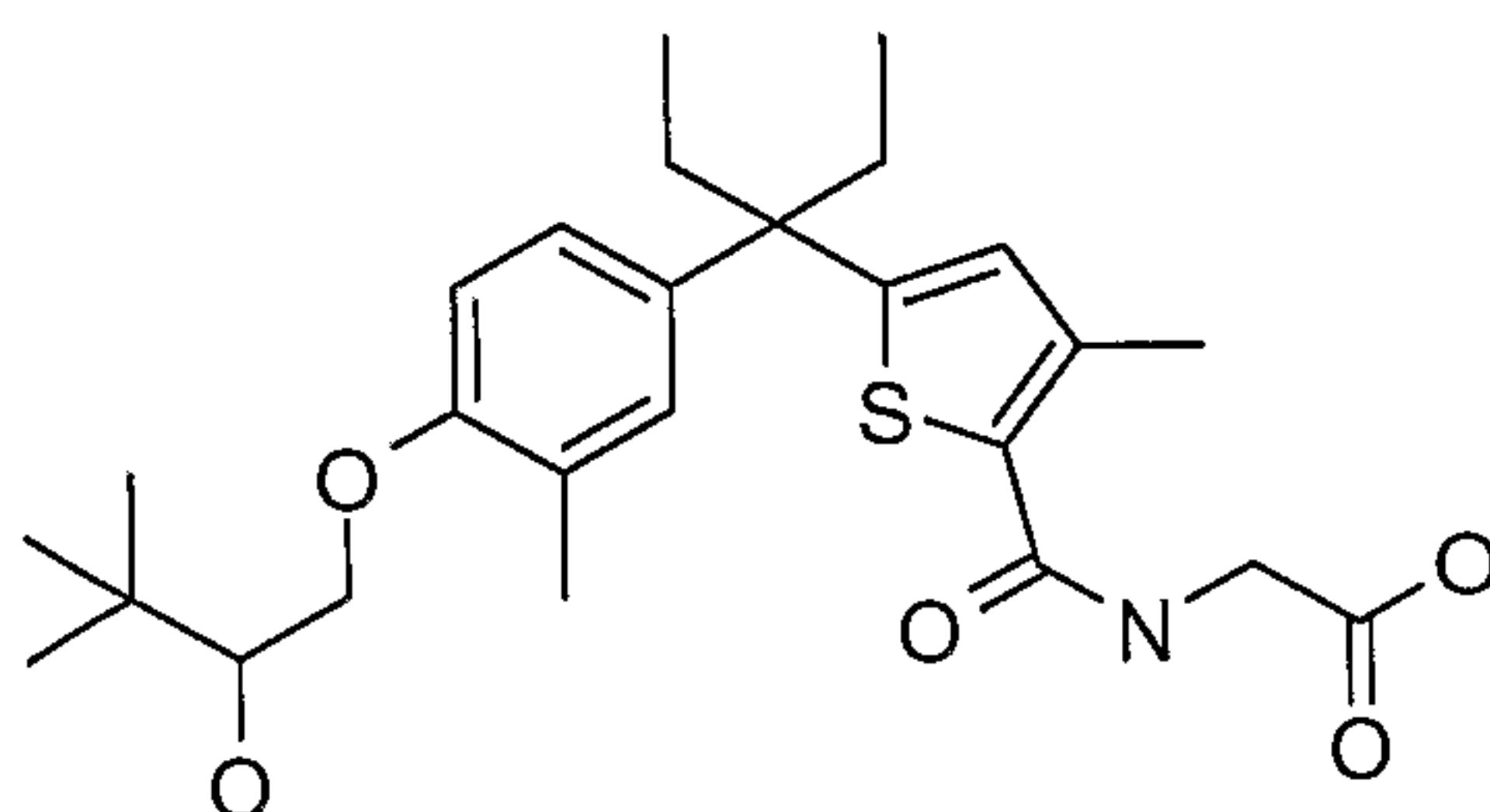
2-[5-{1-Ethyl-1-{4-(2-hydroxy-3,3-dimethyl-butyoxy)-3-methyl-phenyl-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid methyl ester (Example 46) (0.24 g, 0.49 mmol) is dissolved in THF (5 mL), treated with H₂O (1 mL) and LiOH (59 mg, 2.46 mmol) and the resulting mixture is stirred at RT overnight. The

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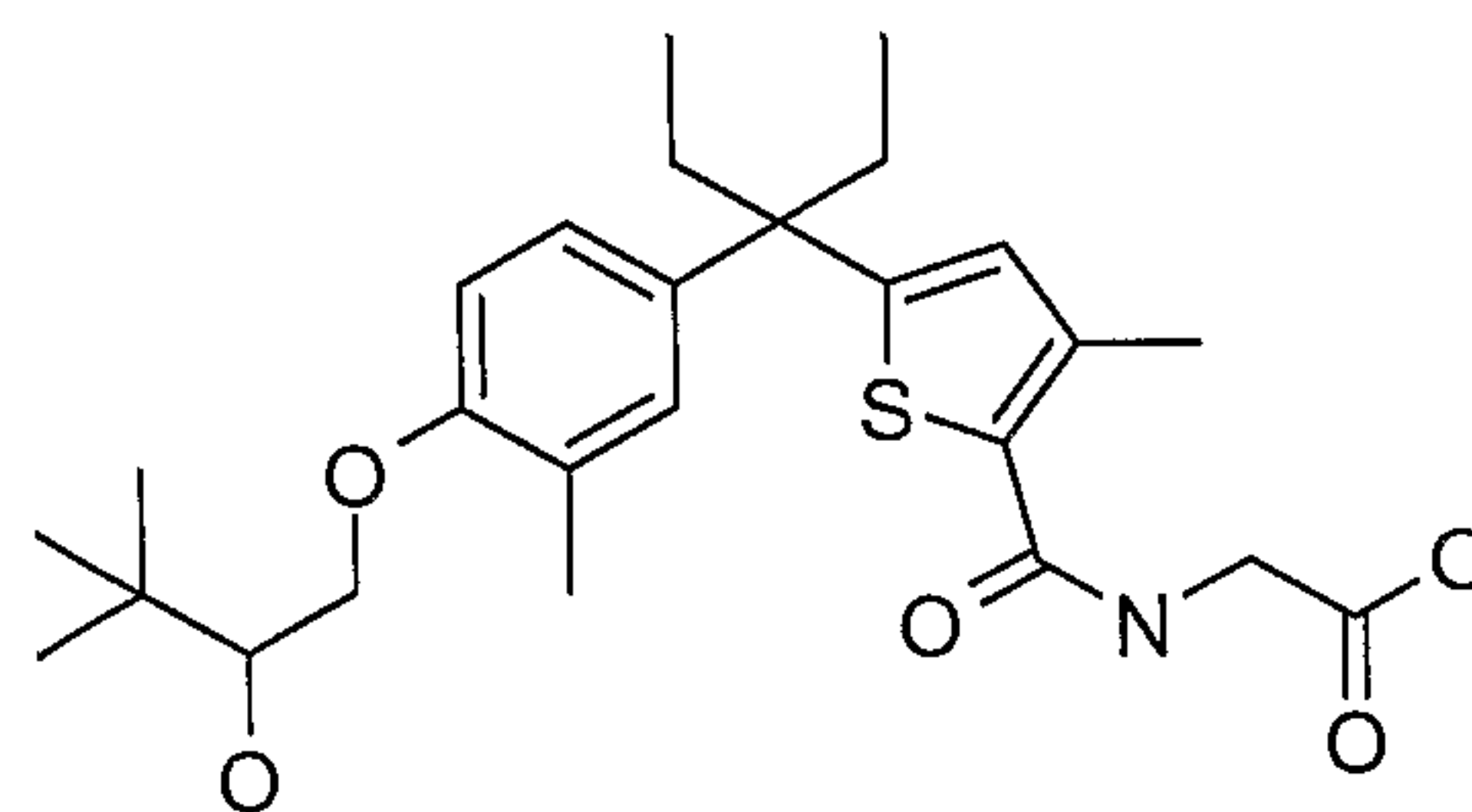
solution is diluted with H₂O (10 mL), the pH value is adjusted to *ca.* 3-4 using 1 M HCl, it is extracted with EtOAc (2 x 40 mL), dried with MgSO₄, filtered and concentrated to yield the titled compound (0.233 g, 0.49 mmol, 99%). ¹H NMR (CD₃OD), δ 0.75 (t, *J* = 7.4 Hz, 6H), 1.05 (s, 9H), 2.17 (q, *J* = 7.4 Hz, 4H), 2.23 (s, 3H), 2.48 (s, 3H), 3.66 (dd, *J* = 7.8 2.9 Hz, 1H), 3.91 (dd, *J* = 9.6, 7.8 Hz, 1H), 4.01 (s, 2H), 4.16 (dd, *J* = 9.6, 2.9 Hz, 1H), 6.74 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 7.03-7.06 (m, 1H), 7.11 (dd, *J* = 8.2, 2.5 Hz, 1H). LC/MS (*m/z*): calcd for C₂₆H₃₈NO₅S (M+H)⁺: 476.2; found: 476.2.

10 Example 48 and Example 49

Preparation of enantiomers of 2-[5-{1-Ethyl-1-{4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid.



Enantiomer 1



Enantiomer 2

A racemic mixture of 2-[5-{1-Ethyl-1-{4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid, Example 47 (130 mg) is chromatographed (CHIRALPAK AD column, 20% *i*-PrOH/Hept, 0.2%TFA) to give enantiomer 1, Example 48 (47.9 mg, 37%) and enantiomer 2, Example 49 (39 mg, 30%).

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Example 48, Enantiomer 1 :

rt = 6.5 m

NMR & LC/MS: Identical to the racemic material, Example 47.

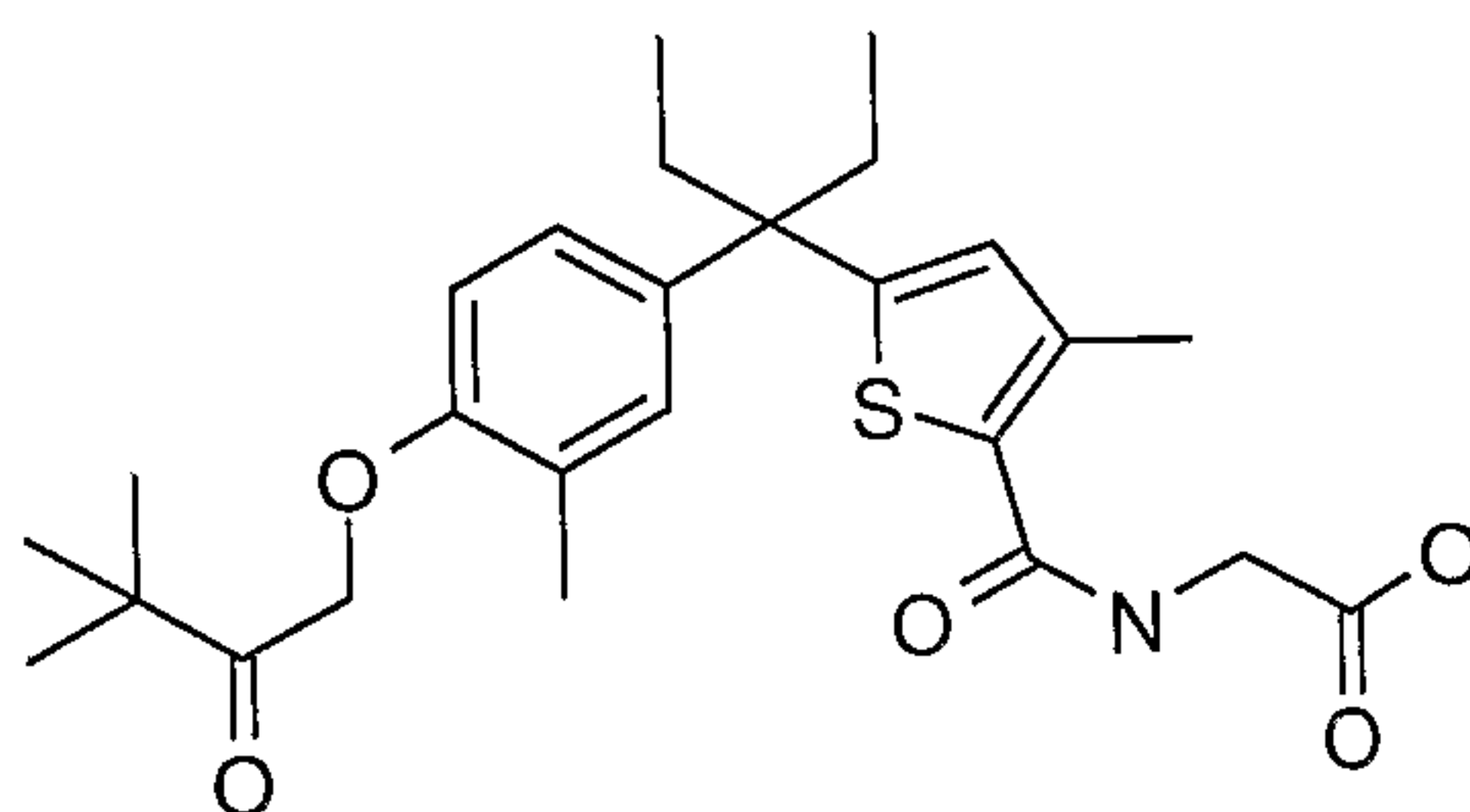
Example 49, Enantiomer 2 :

5 rt = 15.2 m

NMR & LC/MS: Identical to the racemic material, Example 47.

Example 50

Preparation of 2-[5-{1-[4-(3,3-Dimethyl-2-oxo-butyloxy)-3-methyl-phenyl]-1-ethyl-
 10 propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid.

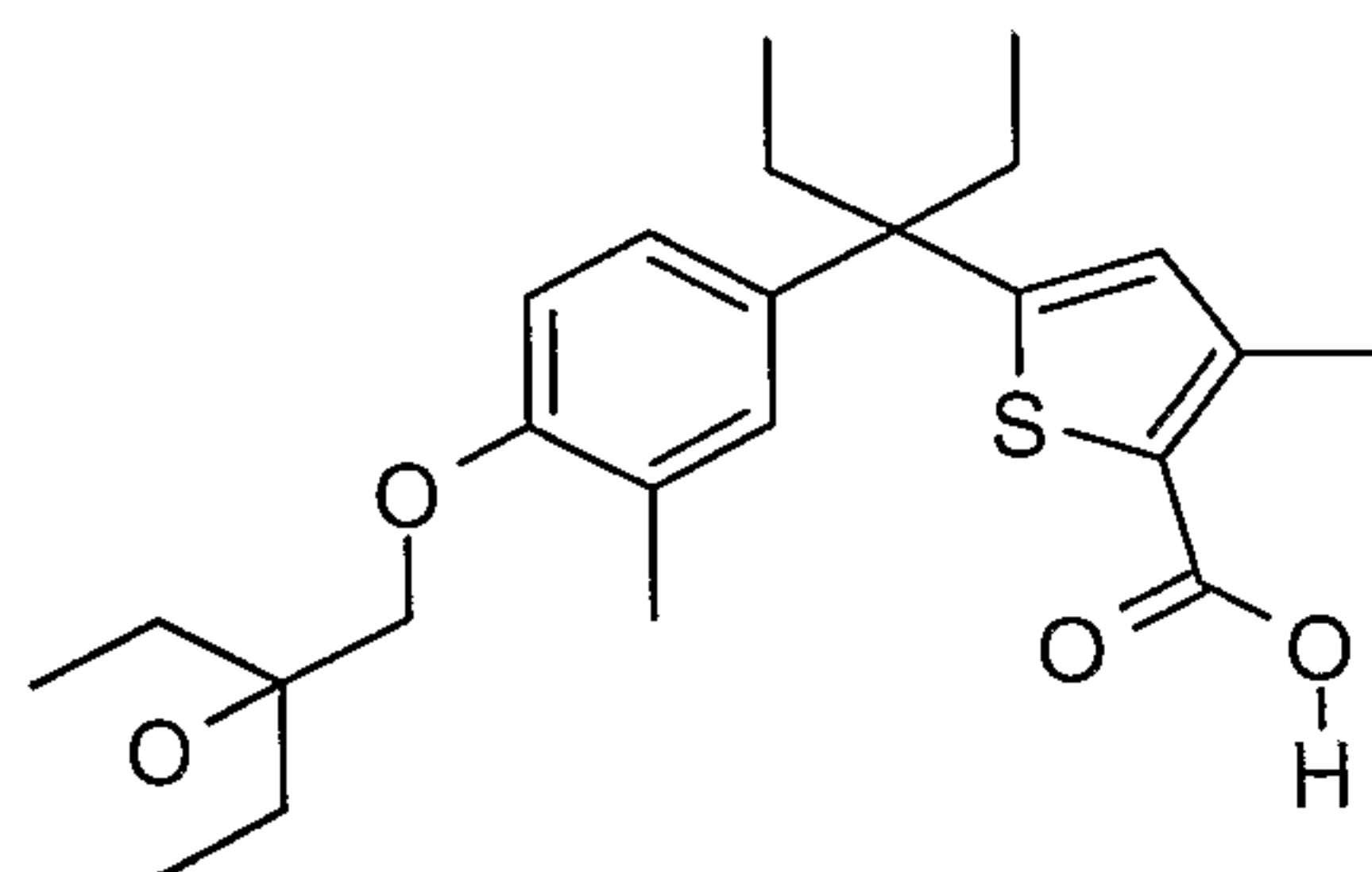


2-[5-{1-Ethyl-1-{4-(2-hydroxy-3,3-dimethyl-butyloxy)-3-methyl-phenyl-
 propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid (Example 47) (99 mg,
 15 0.21 mmol) is dissolved in CH₂Cl₂ (4 mL), treated with Dess-Martin reagent (97 mg,
 0.23 mmol). The resulting mixture is stirred at RT 2h. It is diluted with EtOAc (25
 mL), washed with 10% Na₂SO₃ (2 x 20 mL) along with 0.1 M HCl (20 mL); dried
 with MgSO₄, filtered and concentrated. Purification of the resulting crude product by
 flash chromatography, eluted with 15% CH₃OH/EtOAc with 0.5%HOAc yielded the
 20 titled compound (56.2 mg, 0.11mmol, 53%). ¹H NMR (CD₃OD), δ 0.75 (t, J = 7.2
 Hz, 6H), 1.29 (s, 9H), 2.19 (q, J = 7.2 Hz, 4H), 2.25 (s, 3H), 2.47 (s, 3H), 4.02 (s, 2H),
 5.05 (s, 2H), 6.66 (d, J = 7.6 Hz, 1H), 6.74 (s, 1H), 7.00-7.11 (m, 2H), 7.96 (bs, 1H).
 LC/MS (m/z): calcd for C₂₆H₃₆NO₅S (M+H)⁺: 474.2; found: 474.2.

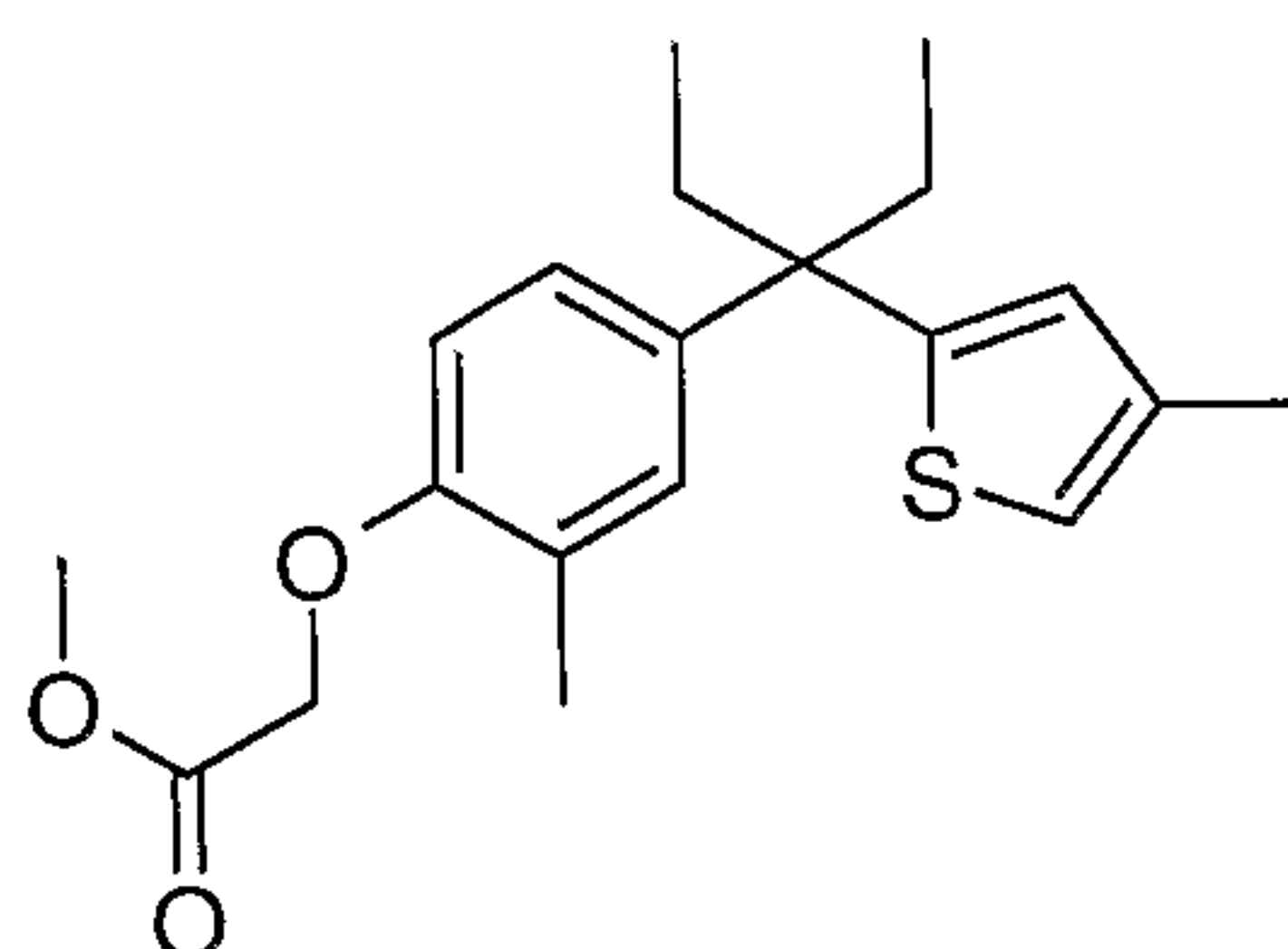
25 Example 51

Preparation of (5-{1-ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-
 propyl}-3-methyl-thiophene-2-carboxylic acid.

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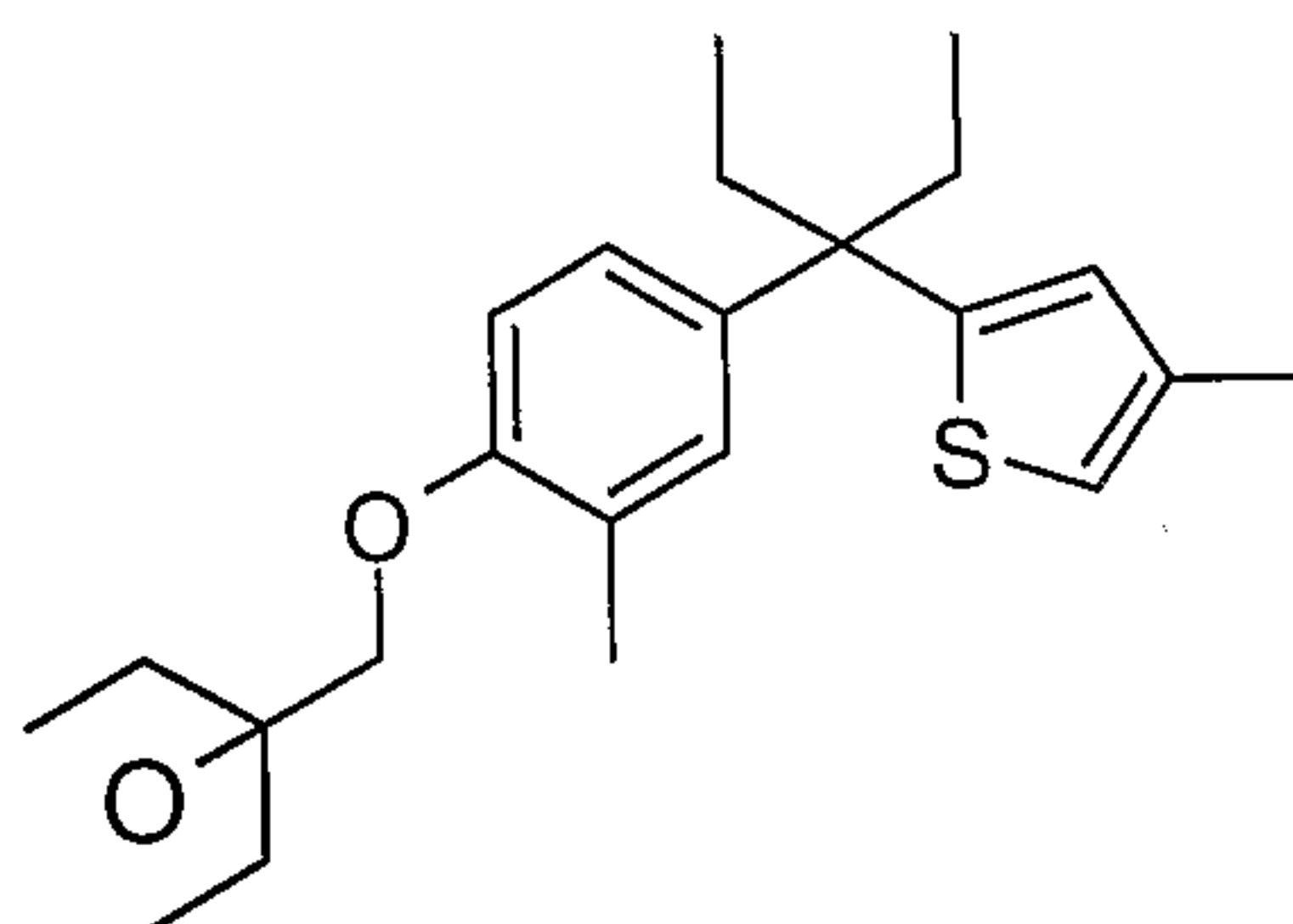
A. 2-{4-[1-Ethyl-1-(4-methyl-thiophen-2-yl)-propyl]-2-methyl-phenoxy}-acetic acid methyl ester.



5

4-[1-Ethyl-1-(4-methyl-thiophen-2-yl)-propyl]-2-methyl-phenol (10.66g, 38.9 mmol) is reacted with methyl bromoacetate (4.4 ml, 46.7 mmol) and K_2CO_3 (10.70 g, 77.81 mmol) in acetone (100 m) at refluxing temperature overnight. The reaction is cooled to RT, filtered and washed with Et_2O and concentrated. The crude product is purified by chromatography to give the titled compound (12.15 g, 35.1 mmol, 90%). ^1H NMR (CD_3Cl_3), δ 0.70 (t, $J = 7.2$ Hz, 6H), 2.04-2.12 (m, 4H), 2.21 (s, 3H), 2.26 (s, 3H), 3.81 (s, 3H), 4.63 (s, 2H), 6.57-6.61 (m, 2H), 6.69-6.71 (m, 1H), 7.02-7.06 (m, 2H). LC/MS (m/z): calcd for $C_{20}H_{27}O_3S$ ($M+H$) $^+$: 347.5; found: 347.1.

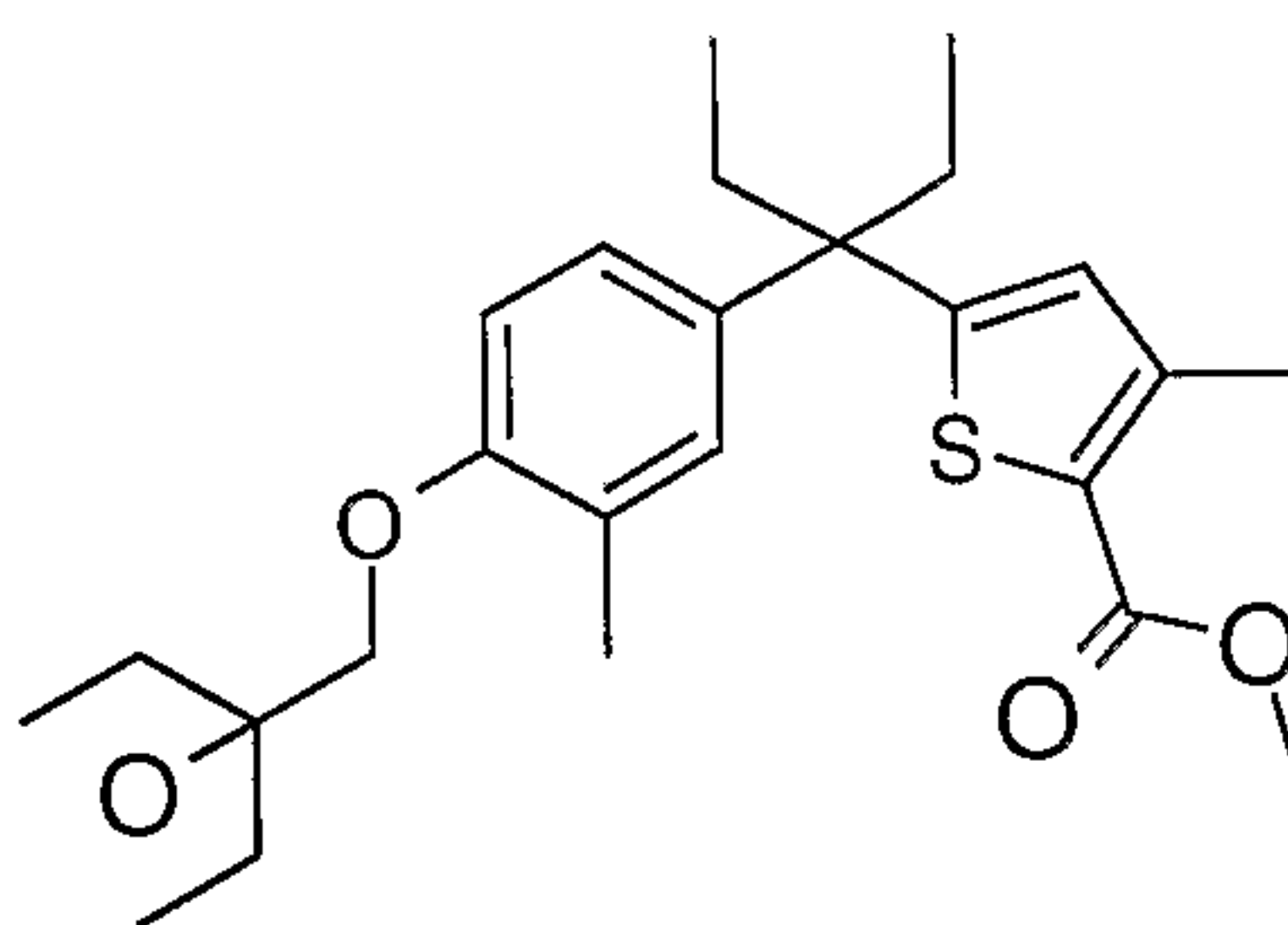
B. 3-{4-[1-Ethyl-1-(4-methyl-thiophen-2-yl)-propyl]-2-methyl-phenoxyethyl}-pentan-3-ol.



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{4-[1-Ethyl-1-(4-methyl-thiophen-2-yl)-propyl]-2-methyl-phenoxy}acetic acid methyl ester (5.52 g, 15.95 mmol) is dissolved in THF (50 mL). The solution is cooled to 0 °C, and treated with Ethyl magnesiumbromide (3.0 M, 13.3 mL) in a dropwise fashion. The reaction is stirred at 0 °C for 10 m, and refluxed for 3 h. It is cooled to 0 °C, quenched with sat. NH₄Cl (50 mL), then 1.0 M HCl (30 mL) is added. It is extracted with EtOAc (2 x 100 mL), dried and concentrated. The crude product is purified by chromatography to give the titled compound (5.22 g, 13.96 mmol, 87%).
¹H NMR (CD₃Cl₃), δ 0.71 (t, *J* = 7.4 Hz, 6H), 0.95 (t, *J* = 7.1 Hz, 6H), 1.62-1.73 (m, 4H), 2.04-2.14 (m, 4H), 2.21 (s, 6H), 3.81 (s, 2H), 6.59-6.61 (m, 1H), 6.69-6.74 (m, 2H), 7.02-7.08 (m, 2H). LC/MS (*m/z*): calcd for C₂₃H₃₅O₂S (M+H)⁺: 375.6; found: 375.3.

C. 5-{1-Ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid methyl ester.

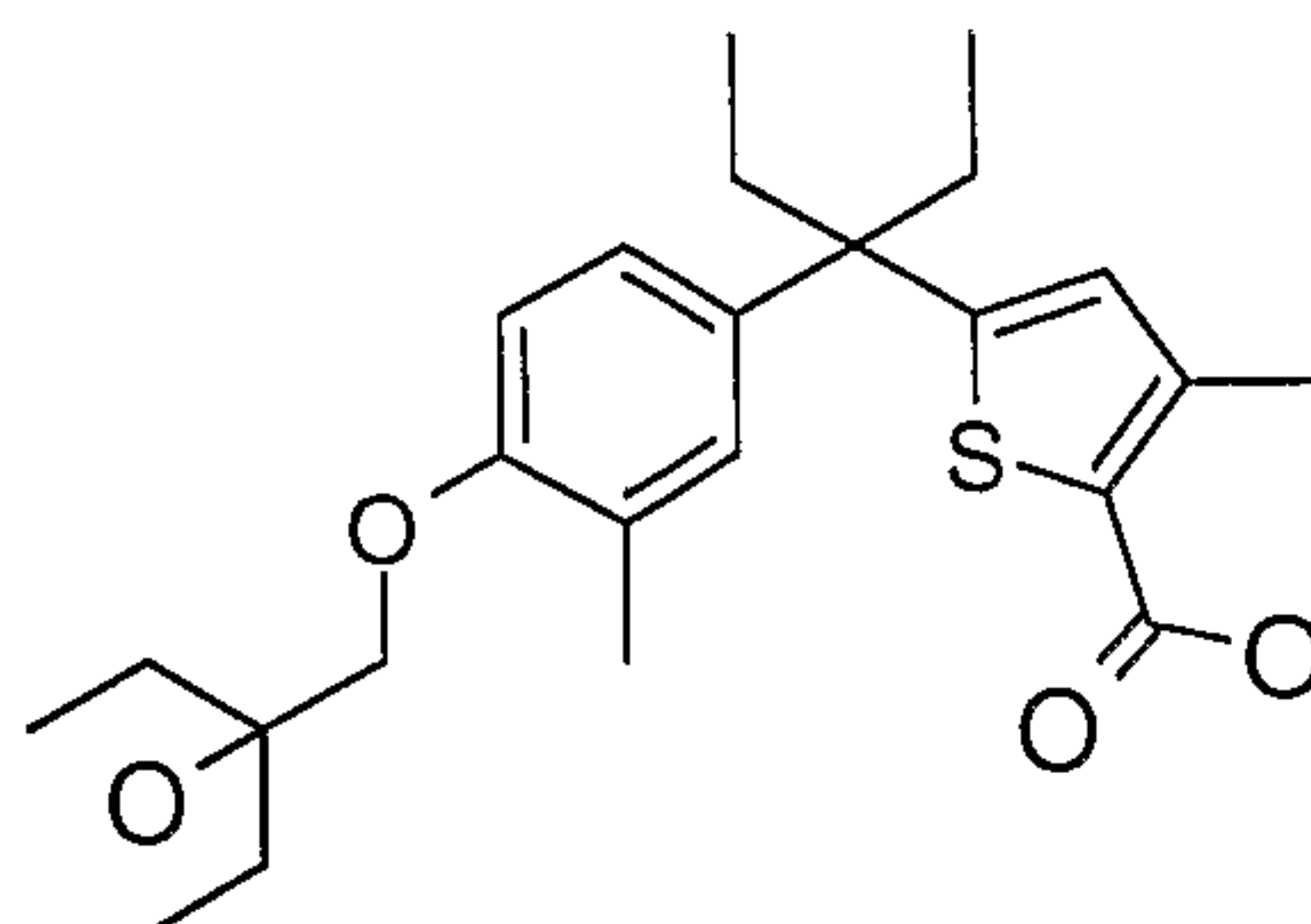


3-{4-[1-Ethyl-1-(4-methyl-thiophen-2-yl)-propyl]-2-methyl-phenoxy}pentan-3-ol, Example 51B (0.50g, 1.34 mmol) is dissolved in THF (10 mL). The solution is cooled to 0 °C, treated with *n*BuLi (1.6 M, 1.8 mL, 2.95 mmol). It is stirred at 0 °C for 20 min, and methyl chloroformate (113 μL, 1.47 mmol) is added. The reaction is stirred at 0 °C for 10 min and RT for 20 m before it is quenched with satd NH₄Cl (5 mL). It is diluted with H₂O (10 mL), treated with 0.1 M HCl (10 mL) and extracted with EtOAc (3 x 15 mL), dried and concentrated. The crude product is purified by chromatography to give the titled compound (0.24 g, 0.56 mmol, 41%).
¹H NMR (CD₃Cl₃), δ 0.71 (t, *J* = 7.1 Hz, 6H), 0.95 (t, *J* = 7.9 Hz, 6H), 1.64-1.72 (m, 4H), 2.11 (q, *J* = 7.1 Hz, 4H), 2.21 (s, 3H), 2.49 (s, 3H), 3.81 (s, 3H), 6.61 (s, 1H),

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6.72 (d, $J = 8.4$ Hz, 1H), 6.85-7.01 (m, 2H). LC/MS (m/z): calcd for $C_{25}H_{40}NO_4S$ ($M+NH_4$)⁺: 450.3; found: 450.3.

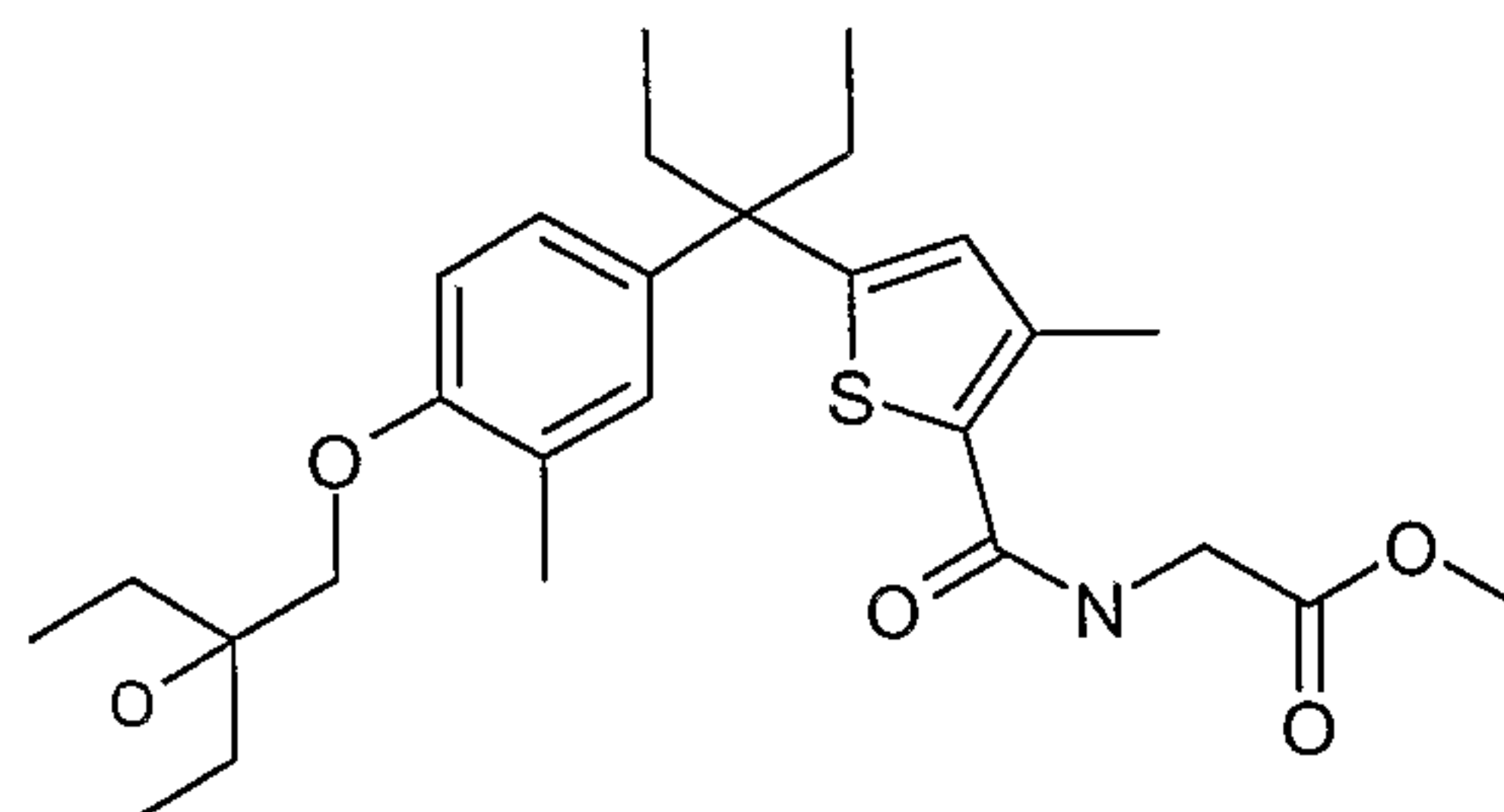
D. 5-{1-Ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid.



Using a procedure analogous to Example 47, 5-{1-Ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid methyl ester (0.23 g, 0.53 mmol) gives the title compound (0.20 g, 0.48 mmol, 91%). ¹H NMR (CD_3Cl_3), δ 0.72 (t, $J = 7.6$ Hz, 6H), 0.95 (t, $J = 7.1$ Hz, 6H), 1.64-1.72 (m, 4H), 2.11 (q, $J = 7.6$ Hz, 4H), 2.22 (s, 3H), 2.49 (s, 3H), 3.82 (s, 3H), 6.62 (s, 1H), 6.73 (d, $J = 8.3$ Hz, 1H), 6.99-7.06 (m, 2H). LC/MS (m/z): calcd for $C_{24}H_{33}O_4S$ ($M-H$)⁺: 417.6; found: 417.2.

Example 52

Preparation of 2-[(5-{1-Ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid methyl ester.

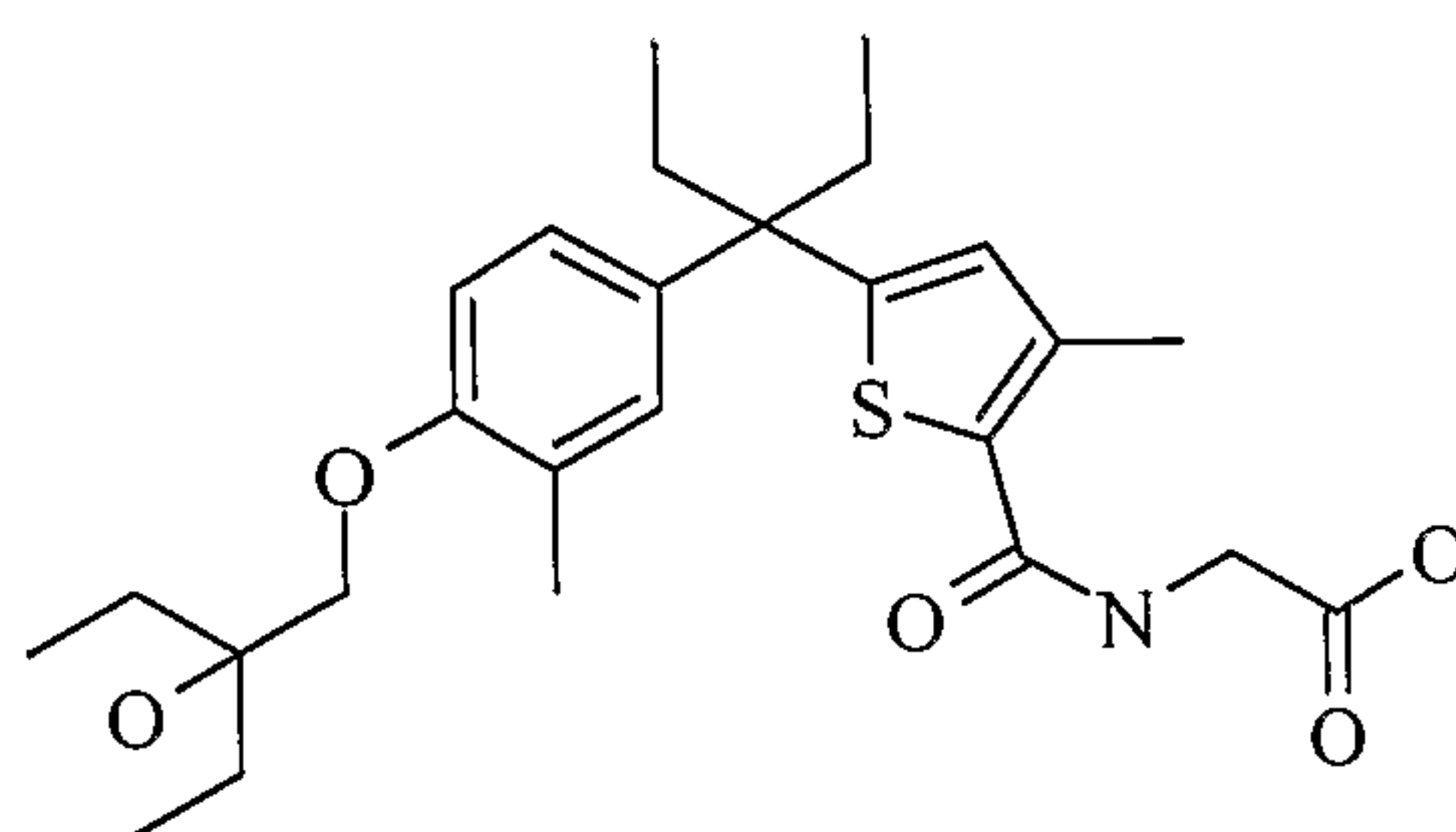


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Using a procedure analogous to Example 38, 5-{1-Ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 51) (0.3 g, 0.72 mmol), glycine methyl ester hydrochloride, and DMF (2 mL) as reaction solvent to give the title compound (0.34 g, 0.69 mmol, 97%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.1 Hz, 6H), 0.95 (t, *J* = 7.1 Hz, 6H), 1.63-1.72 (m, 4H), 2.04-2.14 (m, 4H), 2.21 (s, 3H), 2.48 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.15 (d, *J* = 5.2 Hz, 2H), 6.20 (t, *J* = 5.2 Hz, 1H), 6.63 (s, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.98-7.01 (m, 1H), 7.01-7.06 (m, 1H). LC/MS (*m/z*): calcd. for C₂₇H₃₈NO₅S (M-H)⁻: 488.7; found: 488.5.

10 Example 53

Preparation of 2-[(5-{1-Ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid.

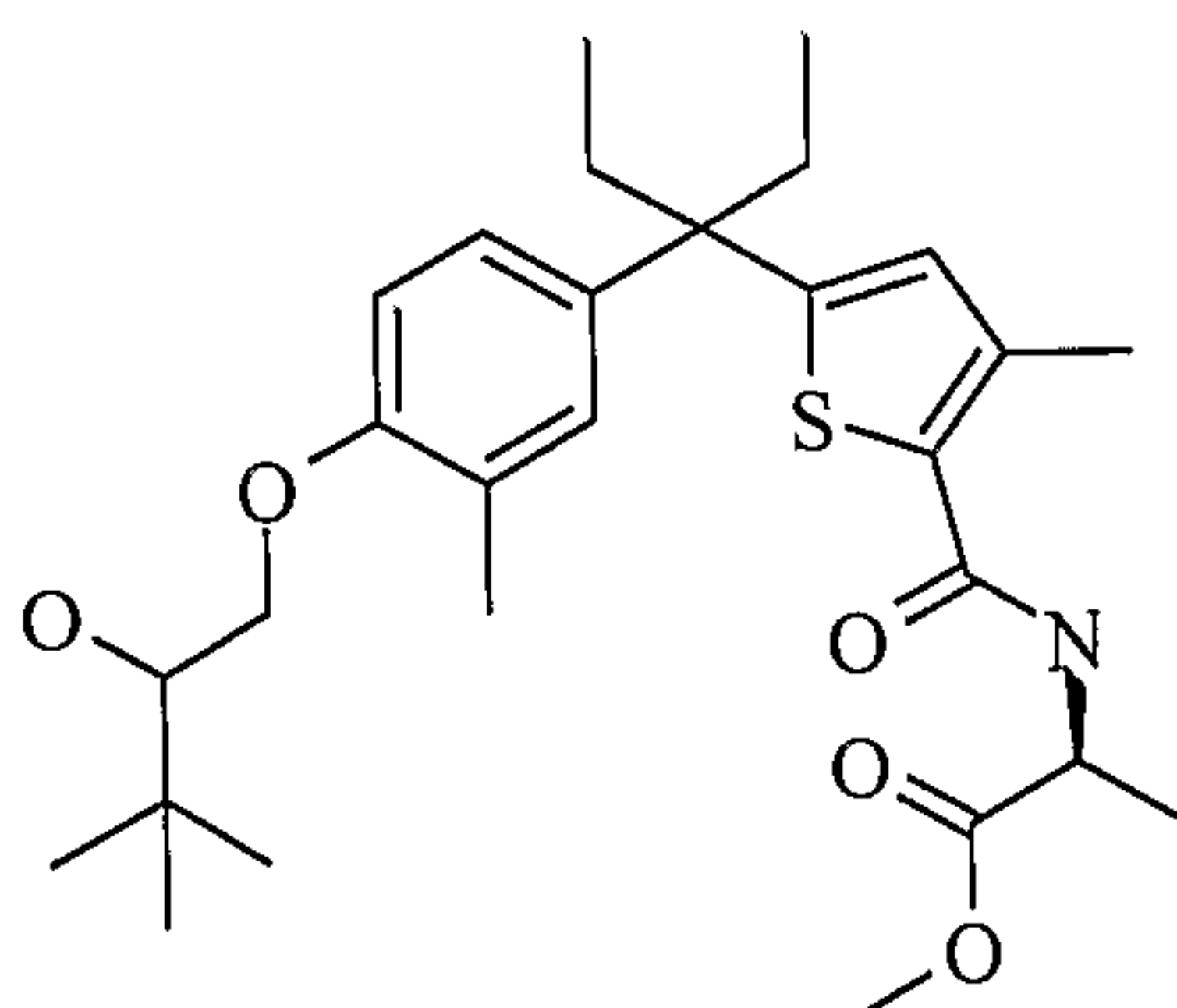


15 2-[(5-{1-Ethyl-1-[4-(2-ethyl-2-hydroxy-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-acetic acid methyl ester (Example 52) (0.34 g, 0.69 mmol) is dissolved in MeOH (2 mL), treated with H₂O (0.5 mL) and NaOH (0.14 g, 3.47 mmol) and the resulting mixture is heated at a reflux for two hours cooled to at ambient temperature and stirred overnight. The solution is diluted with
20 H₂O (10 mL), the pH value is adjusted to about 3-4 using 1 M HCl, it is extracted with EtOAc (40 mL). The EtOAc layer is washed with brine (20 mL), dried with MgSO₄, filtered and concentrated to yield the titled compound (0.244 g, 0.51 mmol, 74%). ¹H NMR (CD₃OD), δ 0.72 (t, *J* = 7.4 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 6H), 1.64-1.74 (m, 4H), 2.03-2.20 (m, 4H), 2.18 (s, 3H), 2.44 (s, 3H), 3.79 (s, 2H), 3.97-3.99 (m, 2H), 6.71 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.99-7.02 (m, 1H), 7.06-7.10 (m, 1H),
25 7.88-7.94 (t, *J* = 5.7 Hz, 1H). LC/MS (*m/z*): calcd. for C₂₆H₃₆NO₅S (M-H)⁻: 475.6; found: 474.3

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Example 54

Preparation of epimer 2 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)amino]propionic acid methyl ester.



5

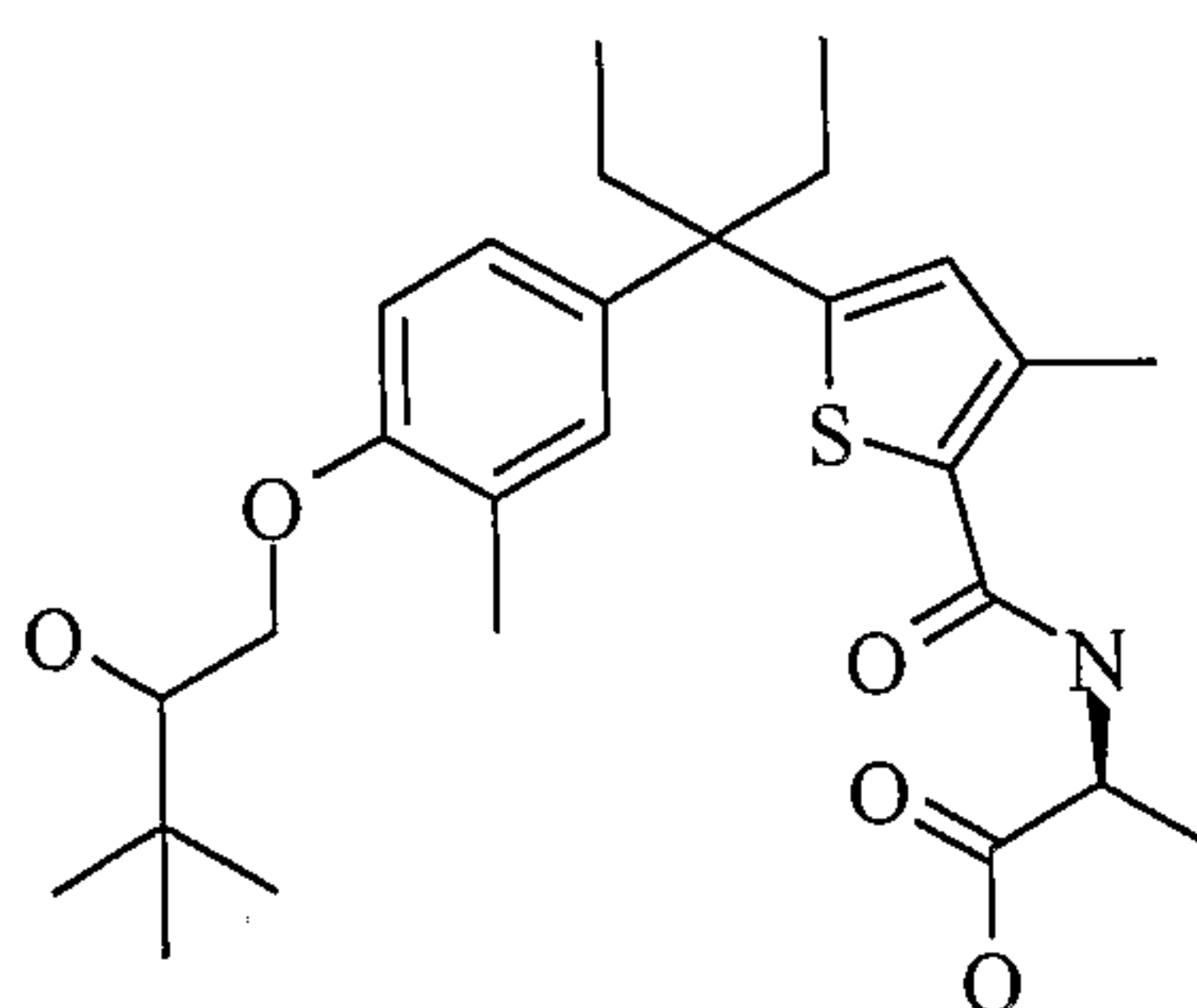
L-Epimer-2

Using a procedure analogous to Example 52, enantiomer 2 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 8) (0.50 g, 1.2 mmol) and *L*-alanine methyl ester

- hydrochloride salt (0.18 g, 1.3 mmol) to give the titled compound (0.44 g, 0.87 mmol, 73%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.2 Hz, 6H), 1.02 (s, 9H), 1.47 (d, *J* = 7.2 Hz, 3H), 2.04-2.14 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 3.71 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.77 (s, 3H), 3.88 (t, *J* = 8.6 Hz, 1H), 4.10 (dd, *J* = 9.2, 2.5 Hz, 1H), 4.67-4.75 (m, 1H), 6.26 (d, *J* = 7.1 Hz, 1H), 6.60 (s, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.97-7.06 (m, 2H).
- LC/MS (*m/z*): calcd. for C₂₈H₄₂NO₅S (*M*+H)⁺: 504.7; found: 504.4.

Example 55

Preparation of epimer 2 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid.



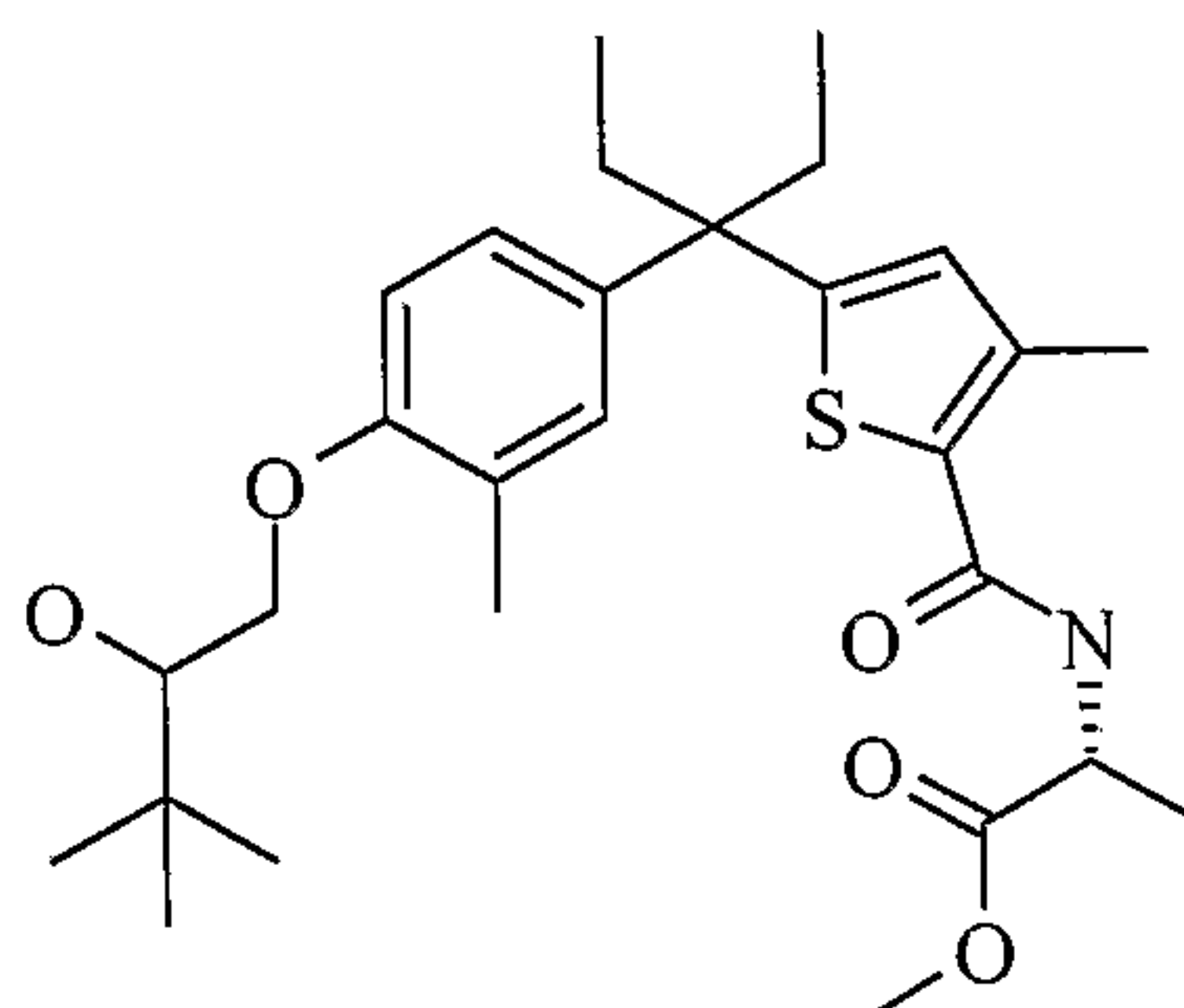
20

L-Epimer 2

Using a procedure analogous to Example 53, epimer 2 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid methyl ester (0.42g, 1.0mmol) gives the title compound (0.37 g, 0.76 mmol, 73%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.4 Hz, 6H), 1.02 (s, 9H), 1.51 (d, *J* = 7.7 Hz, 3H), 2.04-2.14 (m, 4H), 2.20 (s, 3H), 2.47 (s, 3H), 3.72 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.87 (t, *J* = 8.7, 1H), 4.10 (dd, *J* = 9.3, 2.8 Hz, 1H), 4.64-4.72 (m, 1H), 6.22 (d, *J* = 7.4, 1H), 6.62 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.97-7.06 (m, 2H). LC/MS (*m/z*): calcd. for C₂₇H₄₀NO₅S (M+H)⁺: 490.7; found: 490.4.

10 Example 56

Preparation of epimer 2 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid methyl ester.



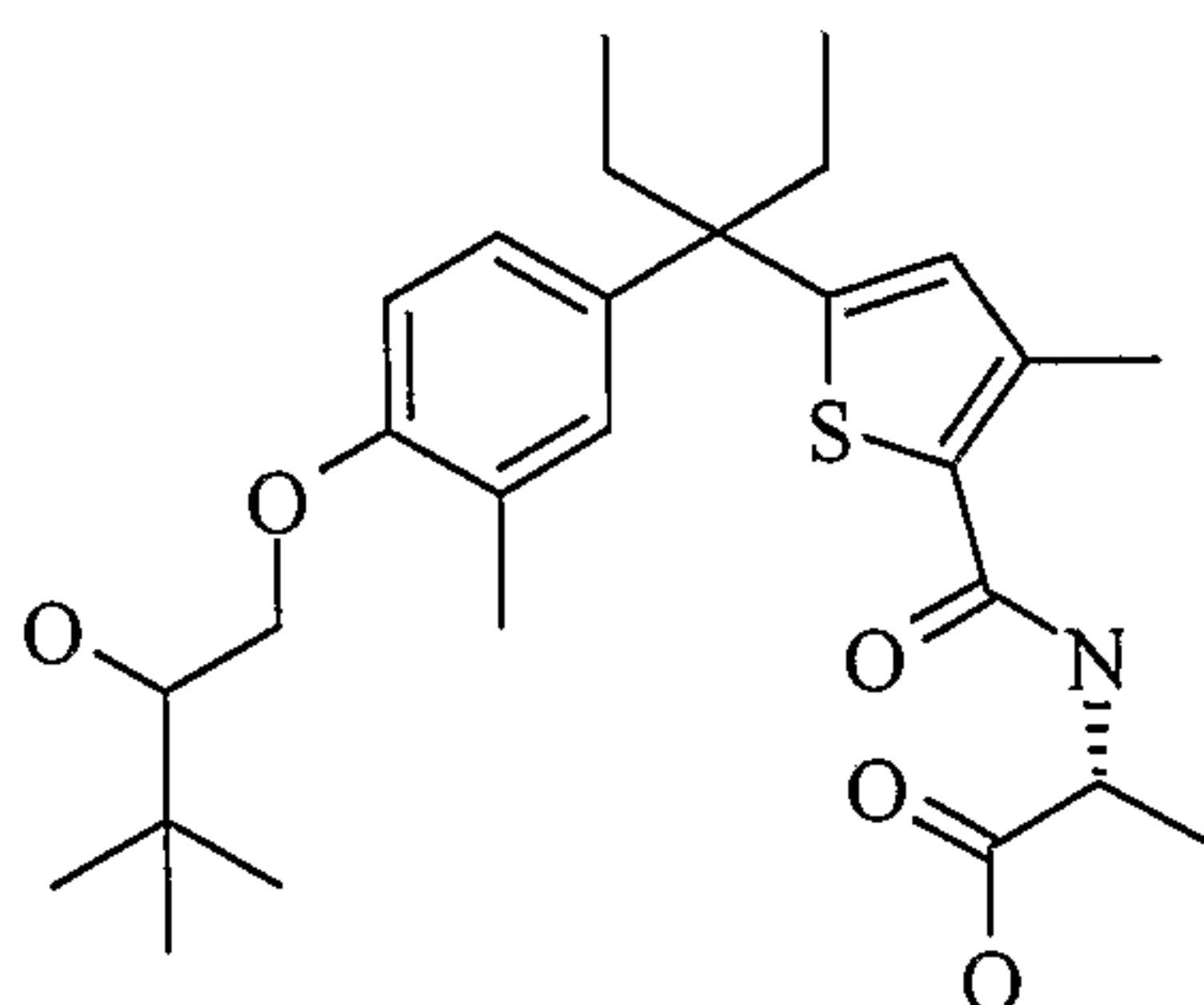
D-Epimer 2

Using a procedure analogous to Example 52, enantiomer 2 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 8) (0.40 g, 0.96 mmol) and *D*-alanine methyl ester hydrochloride salt (0.15 g, 1.05 mmol) to give the title compound (0.48 g, 0.95 mmol, 71%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.5 Hz, 6H), 1.02 (s, 9H), 1.47 (d, *J* = 7.0 Hz, 3H), 2.04-2.15 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 3.71 (d, *J* = 8.6 Hz, 1H), 3.77 (s, 3H), 3.87 (t, *J* = 9.2, 1H) 4.10 (dd, *J* = 9.1, 2.7 Hz, 1H), 4.66-4.76 (m, 1H), 6.26 (d, *J* = 7.6, 1H), 6.60 (s, 1H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.98-7.07 (m, 2H). LC/MS (*m/z*): calcd. for C₂₈H₄₂NO₅S (M+H)⁺: 504.7; found: 504.4.

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Example 57

Preparation of epimer 2 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid.



5

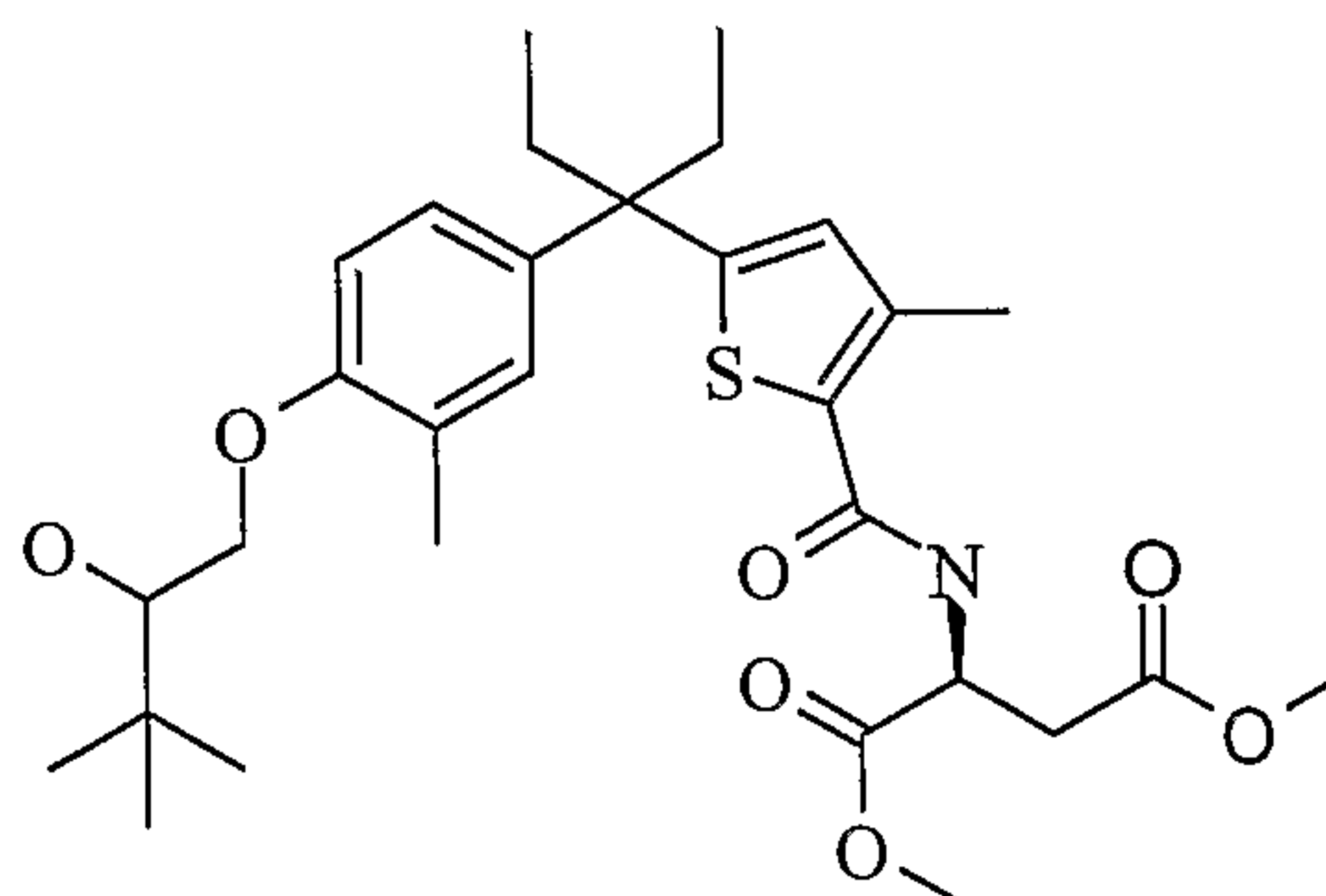
D-Epimer 2

Using a procedure analogous to Example 53, epimer 2 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid methyl ester (0.34g, 0.68 mmol) gives the title compound (0.33 g, 0.66 mmol, 79%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.5 Hz, 6H), 1.02 (s, 9H), 1.52 (d, *J* = 7.1 Hz, 3H), 2.04-2.14 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 3.71 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.88 (t, *J* = 8.8, 1H), 4.10 (dd, *J* = 9.2, 2.7 Hz, 1H), 4.64-4.73 (m, 1H), 6.21 (d, *J* = 6.9, 1H), 6.62 (s, 1H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.98-7.06 (m, 2H). LC/MS (*m/z*): calcd. for C₂₇H₄₀NO₅S (M+H)⁺: 490.7; found: 490.2.

15

Example 58

Preparation of *L*-2-[(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-succinic acid dimethyl ester.

*L*-Epimer 2

20

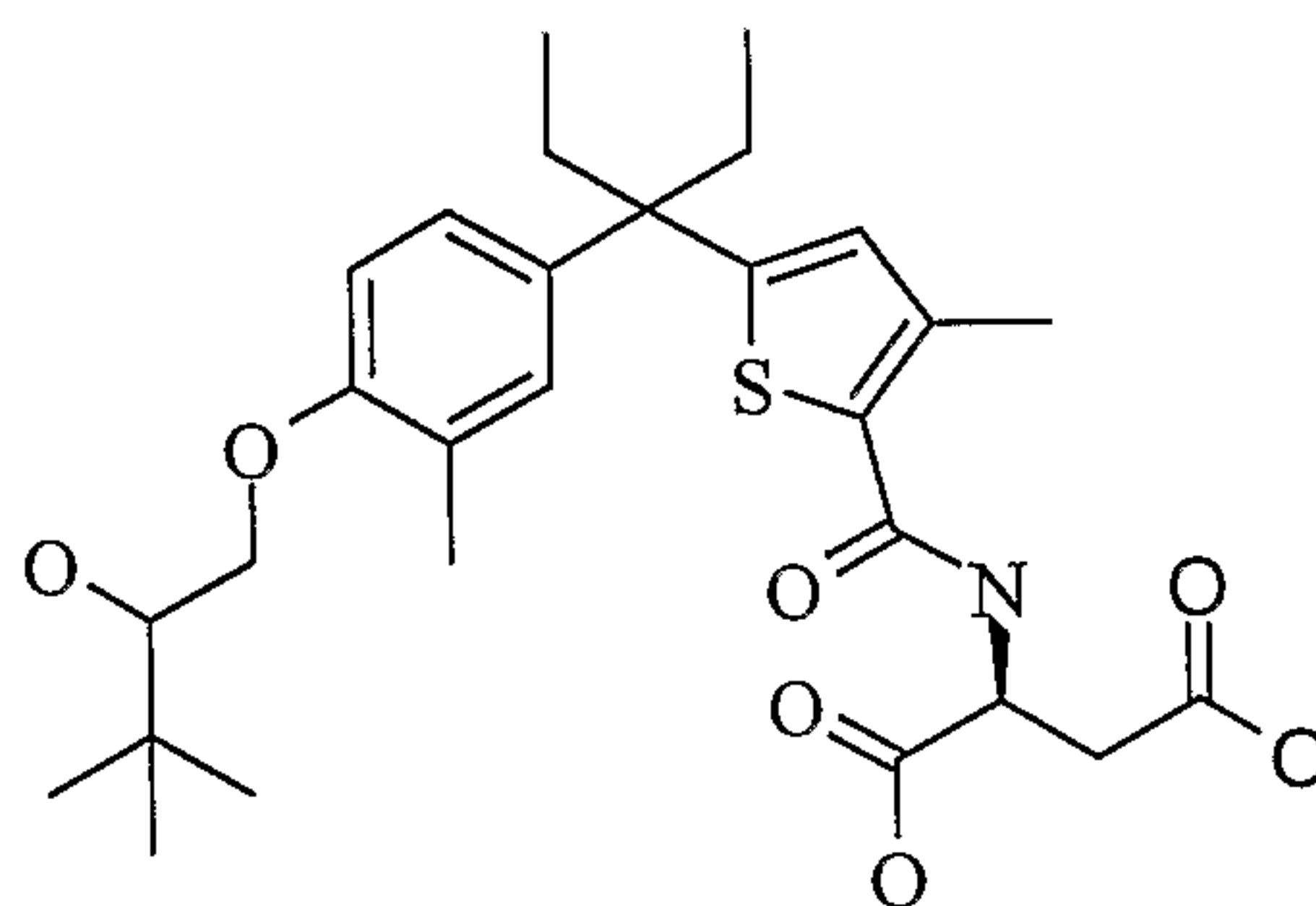
Using a procedure analogous to Example 52, enantiomer 2 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-

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carboxylic acid (Example 8) (0.4 g, 0.96 mmol) and *L*-aspartic acid dimethyl ester hydrochloride salt (0.21 g, 1.05 mmol) to give the title compound (0.42 g, 0.758 mmol, 78%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.7 Hz, 6H), 1.02 (s, 9H), 2.04-2.14 (m, 4H), 2.20 (s, 3H), 2.47 (s, 3H), 2.93 (dd, *J* = 17.2, 4.5 Hz, 1H), 3.10 (dd, *J* = 17.2, 4.3 Hz, 1H), 3.69-3.73 (m, 4H), 3.78 (s, 3H), 3.87 (t, *J* = 9.1, 1H), 4.10 (dd, *J* = 9.1, 2.6, 1H), 4.96-5.01 (m, 1H), 6.58 (s, 1H), 6.72 (d, *J* = 7.7, 1H), 6.78 (d, *J* = 7.8, 1H), 7.00 (d, *J* = 1.7, 1H), 7.04 (dd, *J* = 2.7, 8.5, 1H). LC/MS (*m/z*): calcd. for C₃₀H₄₄NO₇S (M+H)⁺: 562.7; found: 562.4.

10 Example 59

Preparation of epimer 2 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-succinic acid.



L-Epimer 2

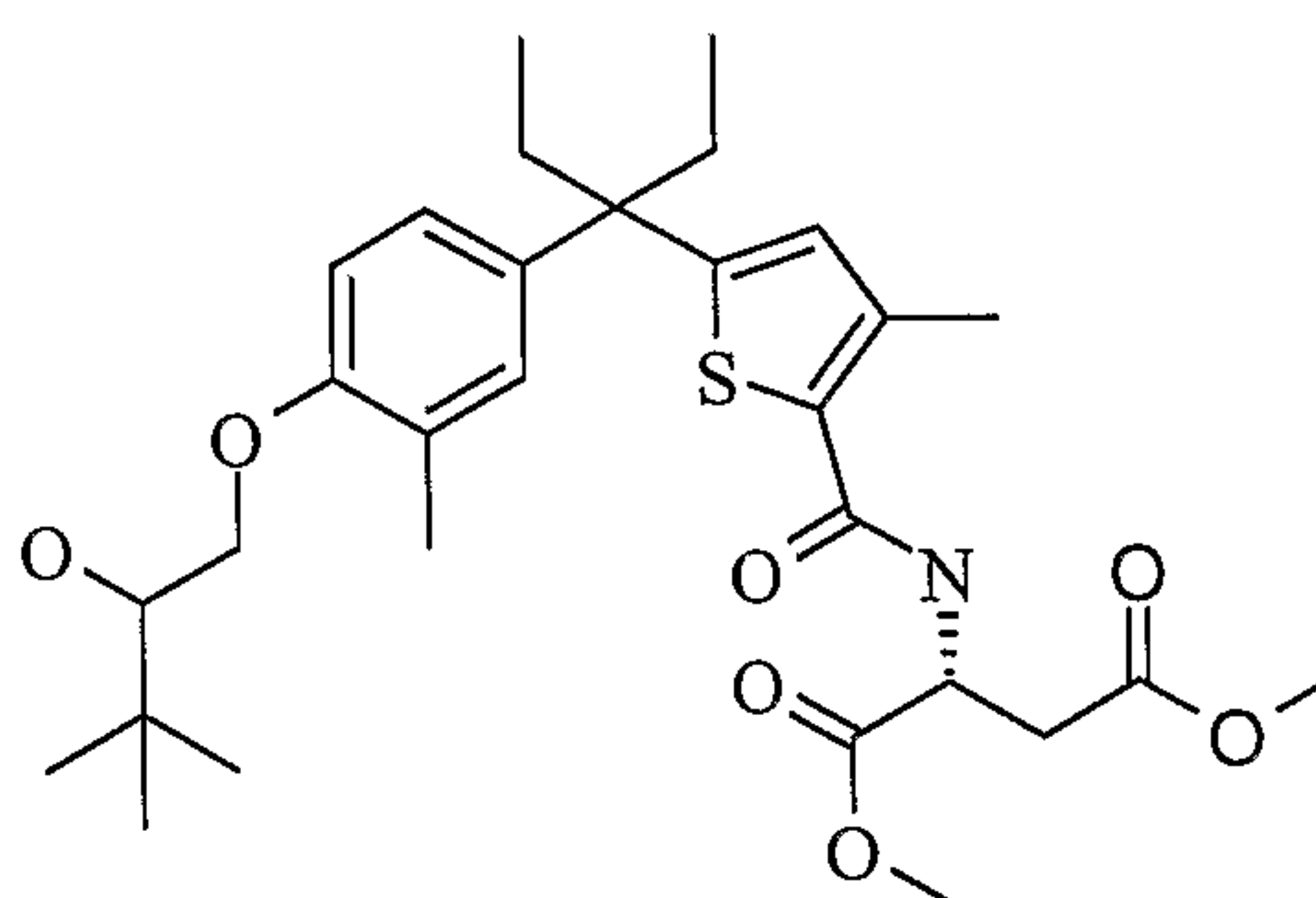
15

Using a procedure analogous to Example 53, *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-succinic acid dimethyl ester, gives to the title compound (0.29 g, 0.54 mmol, 78%). ¹H NMR (CDCl₃), δ 0.70 (t, *J* = 7.4 Hz, 6H), 1.01 (s, 9H), 2.04-2.14 (m, 4H), 2.19 (s, 3H), 2.45 (s, 3H), 2.89-3.01 (m, 1H), 3.09-3.19 (m, 1H), 3.72 (d, *J* = 8.0 Hz, 1H), 3.87 (t, *J* = 8.8 Hz, 1H), 4.09 (d, *J* = 8.2 Hz, 1H), 4.98-5.05 (m, 1H), 6.60 (s, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.98-7.05 (m, 2H), 7.30-7.60 (bs, 2H). LC/MS (*m/z*): calcd. for C₂₈H₄₀NO₇S (M+H)⁺: 534.7; found: 534.4.

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Example 60

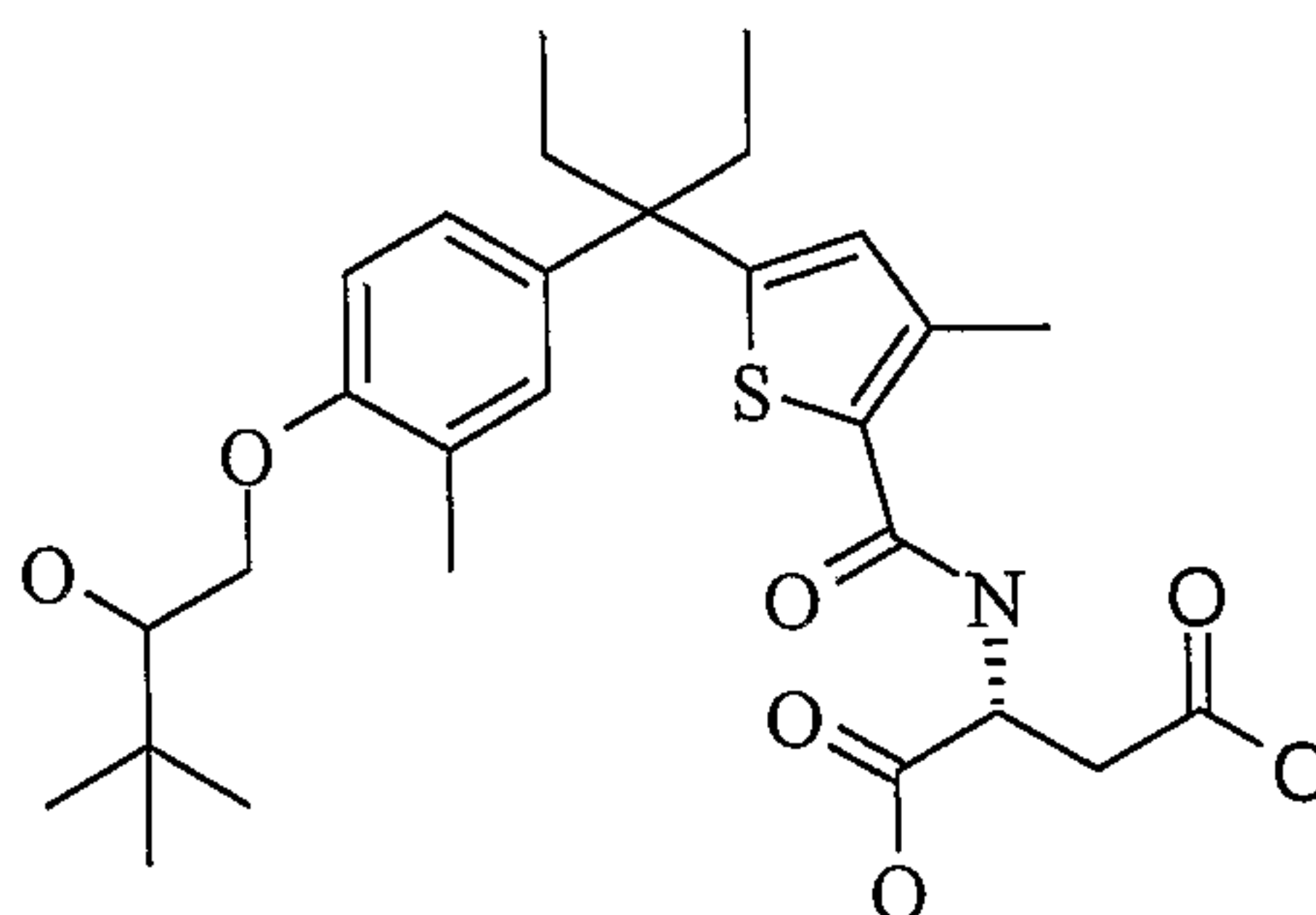
Preparation of epimer 2 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-succinic acid dimethyl ester.

*D*-Epimer 2

Using a procedure analogous to Example 52, enantiomer 2 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 8) (0.4 g, 0.96 mmol) and *D*-aspartic acid dimethyl ester hydrochloride salt (0.21 g, 1.05 mmol) to give the title compound (0.42 g, 0.75 mmol, 78%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.4 Hz, 6H), 1.02 (s, 9H), 2.04-2.14 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.94 (dd, *J* = 17.0, 4.6 Hz, 1H), 3.10 (dd, *J* = 17.0, 4.6 Hz, 1H), 3.69-3.74 (m, 4H), 3.78 (s, 3H), 3.87 (t, *J* = 9.1 Hz, 1H), 4.10 (dd, *J* = 9.1, 3.0 Hz, 1H), 4.96-5.02 (m, 1H), 6.59 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 7.04 (dd, *J* = 2.7, 8.4 Hz, 1H). LC/MS (*m/z*): calcd. for C₃₀H₄₄NO₇S (M+H)⁺: 562.7; found: 562.4.

Example 61:

Preparation of epimer 2 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-succinic acid.



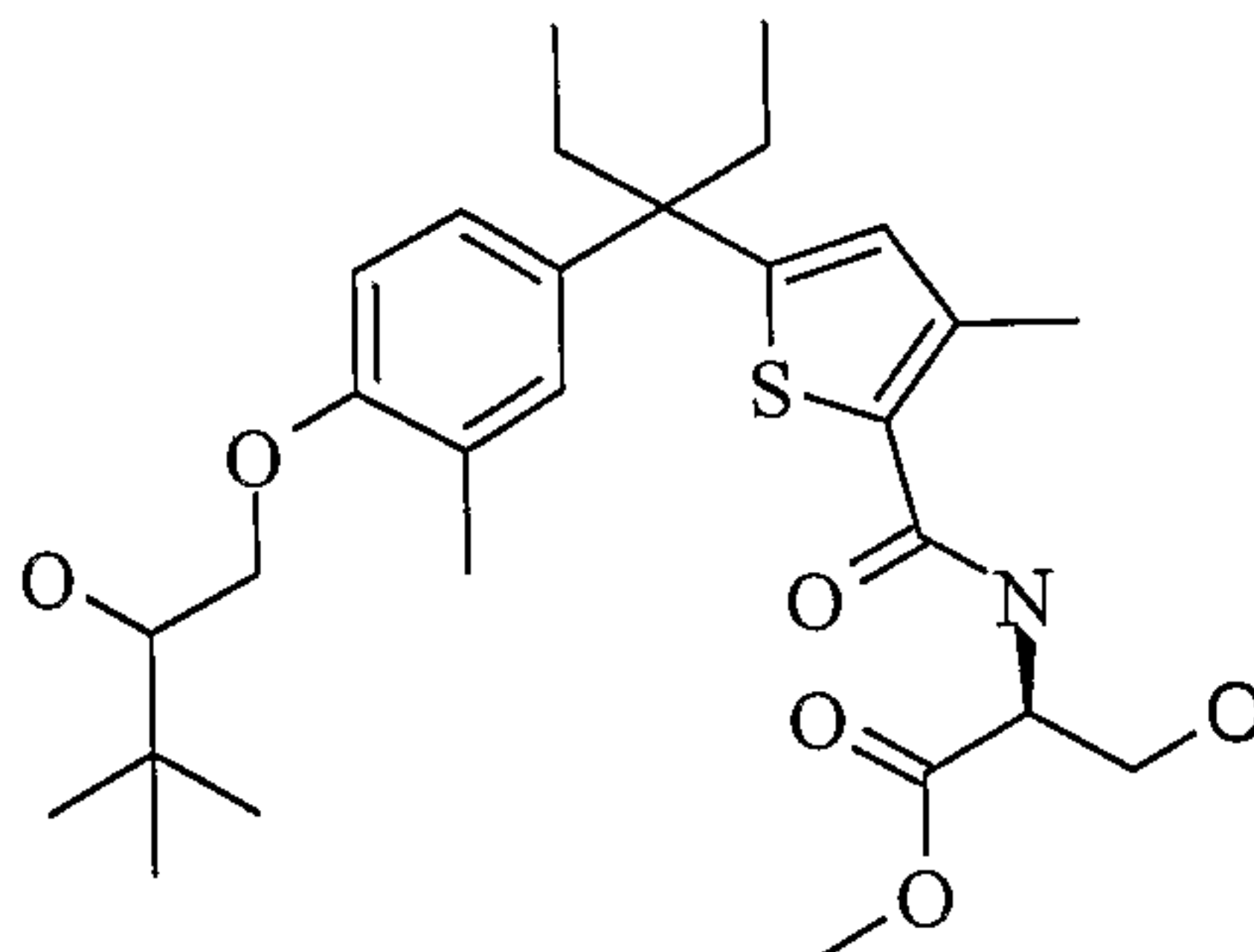
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D-Epimer 2

Using the procedure analogous to Example 53, epimer 2 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-succinic acid dimethyl ester (0.40g, 0.71 mmol) gives the titled compound (0.30 g, 0.56 mmol, 79%). ¹H NMR (CDCl₃), δ 0.70 (t, *J* = 7.4 Hz, 6H), 1.01 (s, 9H), 2.04-2.14 (m, 4H), 2.19 (s, 3H), 2.45 (s, 3H), 2.89-3.01 (m, 1H), 3.09-3.19 (m, 1H), 3.72 (d, *J* = 8.0 Hz, 1H), 3.87 (t, *J* = 8.8 Hz, 1H), 4.09 (d, *J* = 8.2 Hz, 1H), 4.98-5.05 (m, 1H), 6.60 (s, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.98-7.05 (m, 2H), 7.30-7.60 (bs, 2H). LC/MS (*m/z*): calcd. for C₂₈H₄₀NO₇S (*M*+H)⁺: 534.7; found: 534.4.

Example 62:

Preparation of epimer 2 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-hydroxy-propionic acid methyl ester.

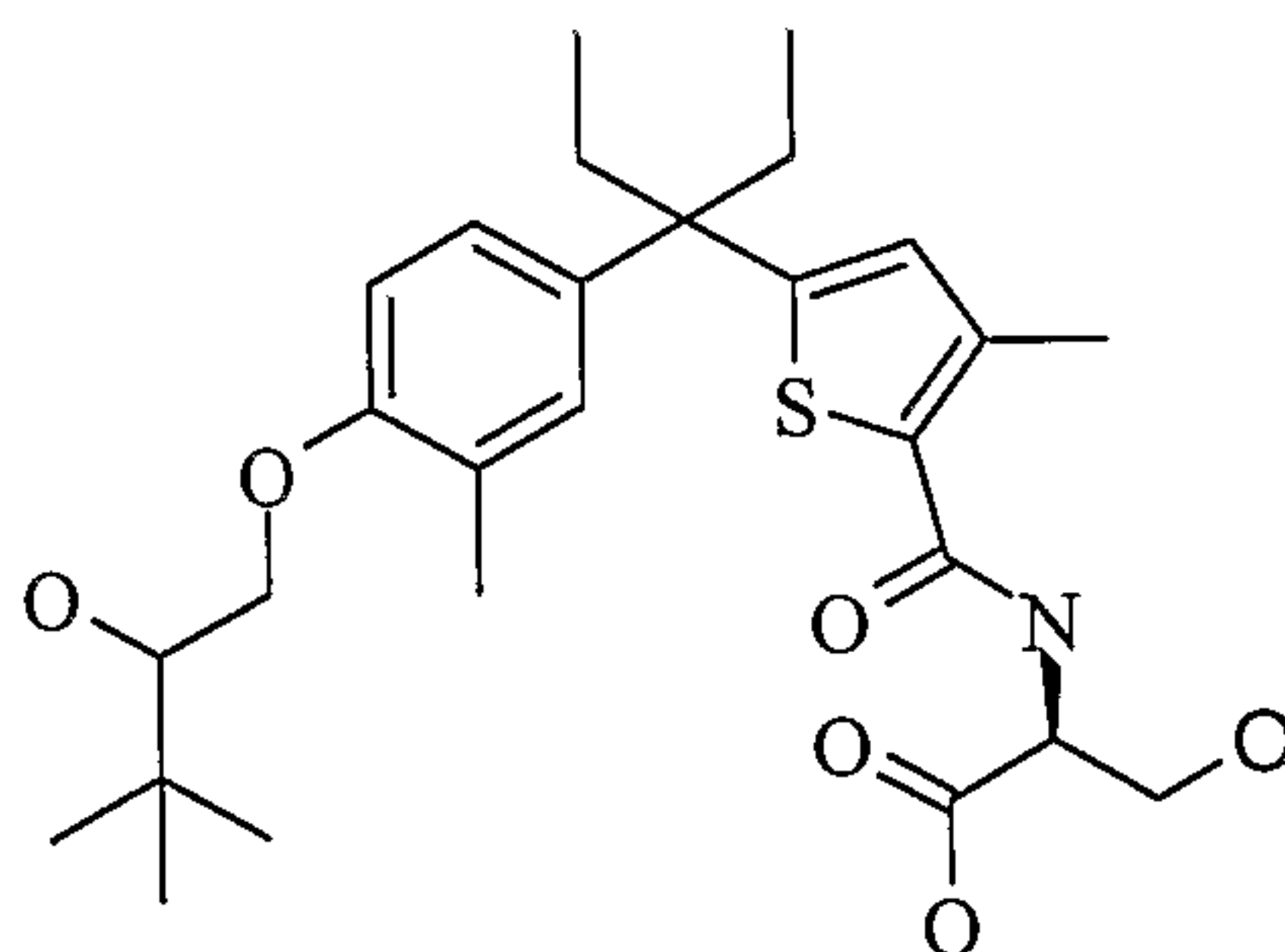
*L*-Epimer 2

Using a procedure analogous to Example 52, enantiomer 2 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 8) (0.4 g, 0.96 mmol) and *L*-serine methyl ester hydrochloride salt (0.16 g, 1.05 mmol) to give the title compound (0.41 g, 0.79 mmol, 82%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.7 Hz, 6H), 1.02 (s, 9H), 2.04-2.14 (m, 4H), 2.21 (s, 3H), 2.49 (s, 3H), 3.71 (dd, *J* = 8.6, 2.6 Hz, 2H), 3.81 (s, 3H), 3.87 (t, *J* = 8.7 Hz, 1H), 4.01 (d, *J* = 3.5 Hz, 2H), 4.09 (dd, *J* = 5.0, 2.7 Hz, 1H), 4.77-4.81 (m, 1H), 6.61 (s, 1H), 6.65 (d, *J* = 6.6 Hz, 1H), 6.73 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 7.04 (dd, *J* = 8.9, 2.6 Hz, 1H). LC/MS (*m/z*): calcd. for C₂₈H₄₂NO₆S (*M*+H)⁺: 520.7; found: 520.2.

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Example 63:

Preparation of epimer 2 of *L*-2-[(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-hydroxy-propionic acid.

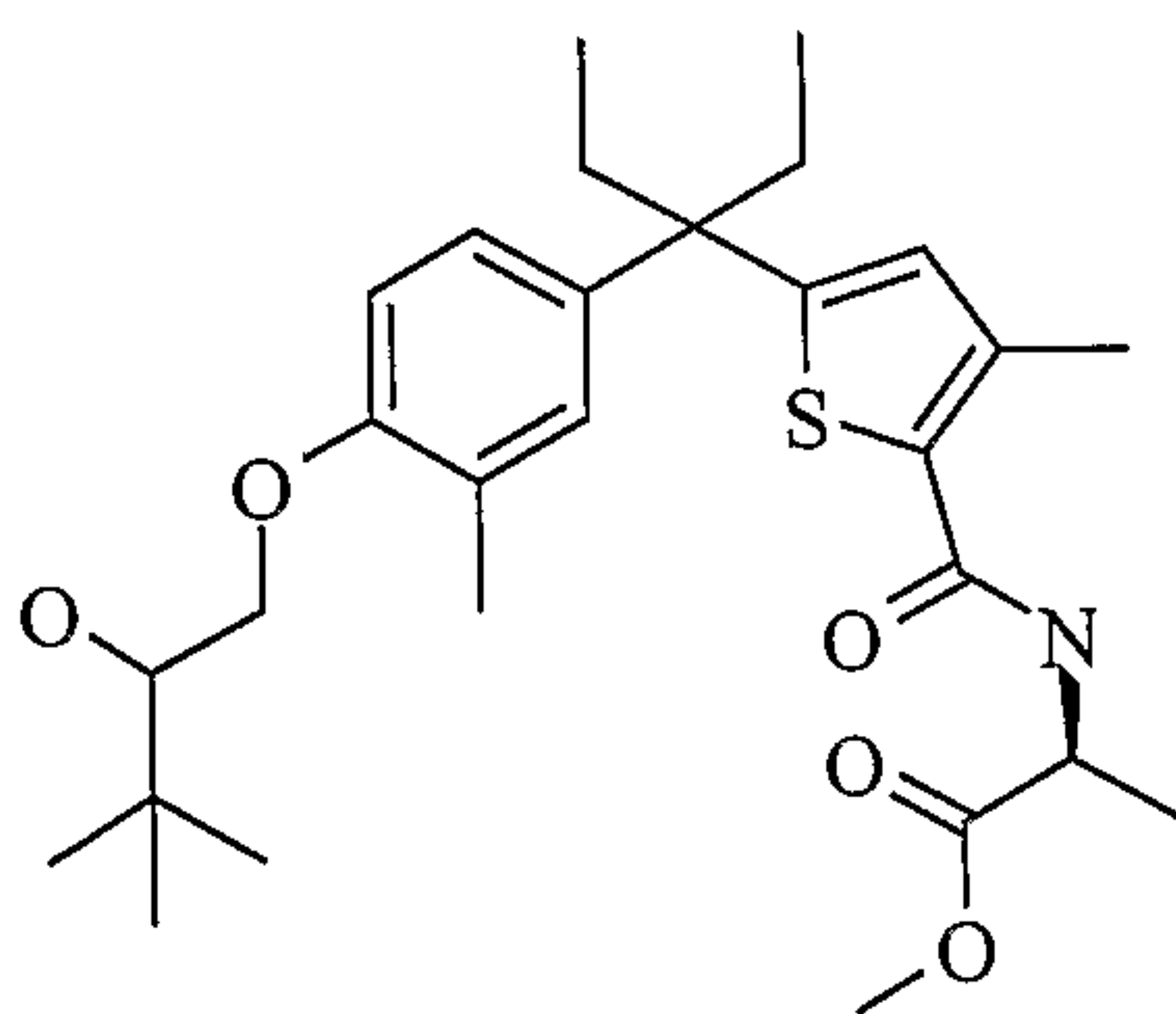
*L*-Epimer 2

Using a procedure analogous to Example 53, epimer 2 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-hydroxy-propionic acid methyl ester (0.40g, 0.77 mmol) gives the titled compound (0.33 g, 0.66 mmol, 85%). ¹H NMR (CDCl₃) δ 0.69 (t, *J* = 7.2 Hz, 6H), 1.01 (s, 9H), 2.00-2.14 (m, 4H), 2.18 (s, 3H), 2.44 (s, 3H), 3.50 (dd, *J* = 13.9, 6.8 Hz, 1H), 3.71 (d, *J* = 8.0 Hz, 1H), 3.88 (t, *J* = 8.6 Hz, 1H), 4.02 (d, *J* = 9.2 Hz, 1H), 4.06-4.12 (m, 1H), 4.62-4.71 (m, 1H), 5.53 (bs, 2H), 6.60 (s, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.79 (d, *J* = 6.6 Hz, 1H), 6.95-7.05 (m, 2H). LC/MS (*m/z*): calcd. for C₂₇H₄₀NO₆S (M+H)⁺: 506.7; found: 506.2.

Example 64:

Preparation of epimer 1 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid methyl ester.

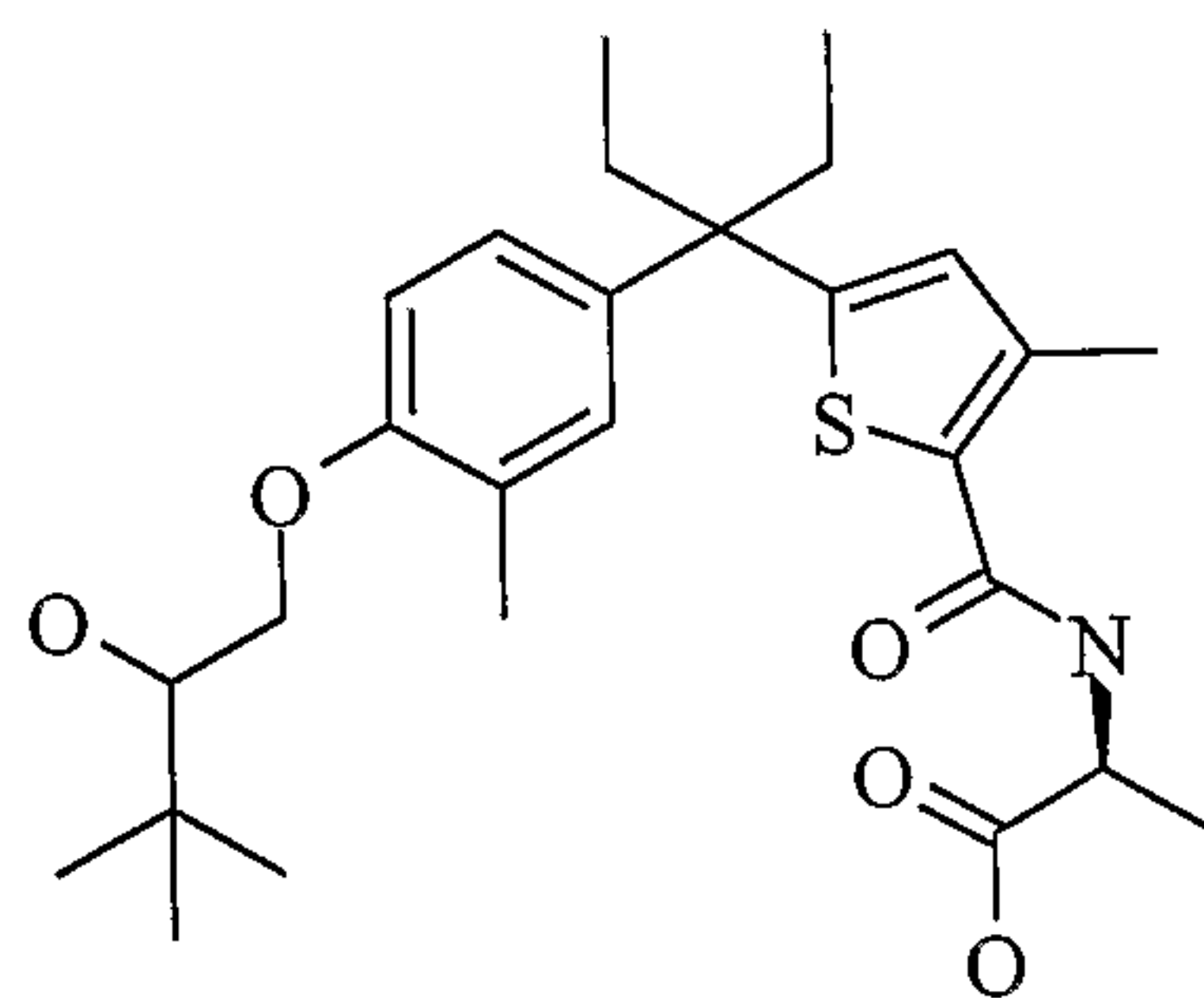
-213-

*L*-Epimer 1

Using a procedure analogous to Example 52, enantiomer 1 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 1) (0.50 g, 1.19 mmol) and *L*-alanine methyl ester hydrochloride salt (0.18 g, 1.31 mmol) to give the title compound (0.3 g, 0.60 mmol, 50%). ¹H NMR and LC/MS: identical to (*D*-epimer-2), Example 56.

Example 65:

- Preparation of epimer 1 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid.

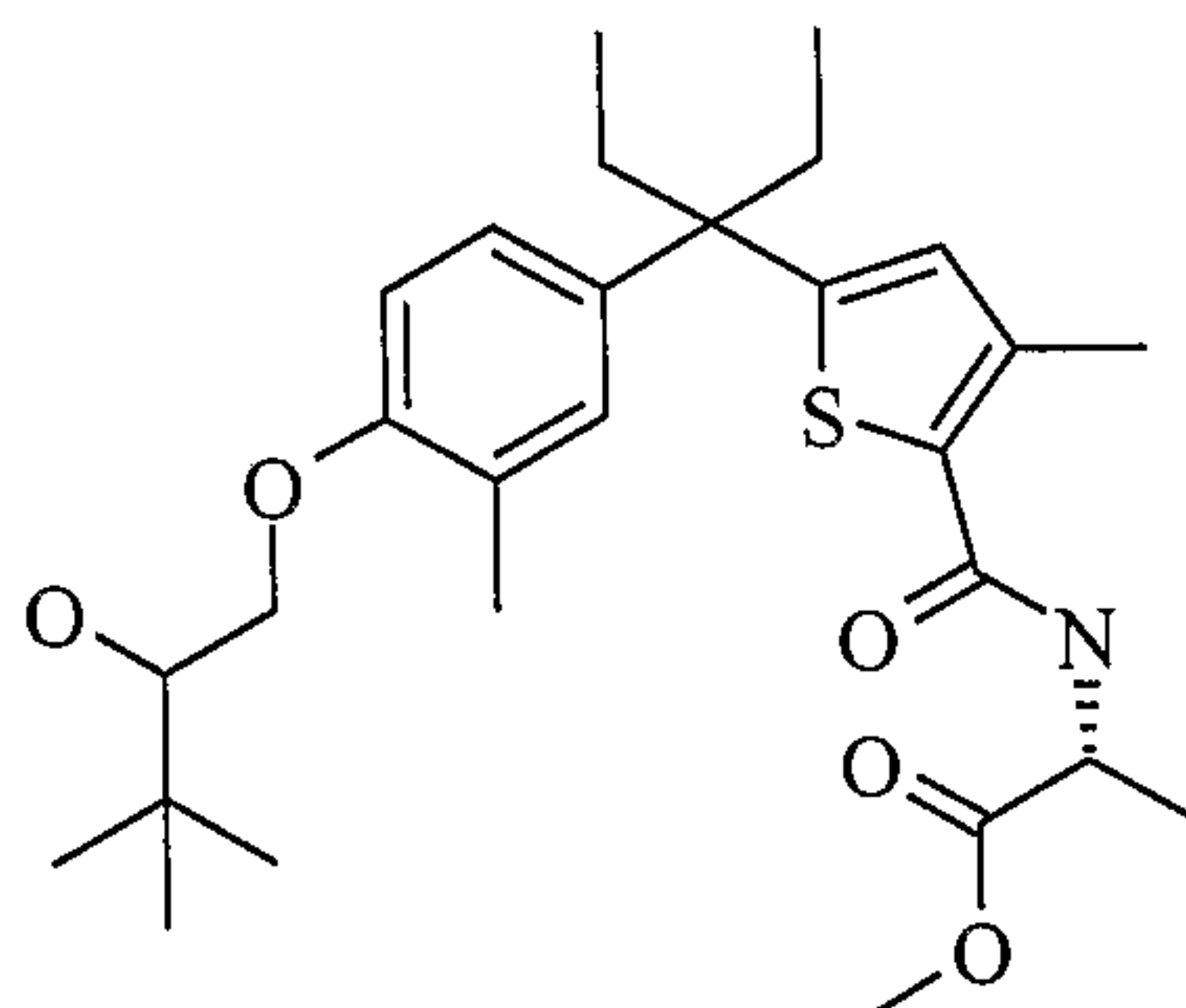
*L*-Epimer 1

- Using a procedure analogous to 53, epimer 1 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid methyl ester (0.3g, 0.60 mmol) gives the title compound (0.27 g, 0.55 mmol, 93%). ¹H NMR and LC/MS: identical to (*D*-epimer-2), Example 57.

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Example 66

Preparation of epimer 1 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid methyl ester.



5

D-Epimer 1

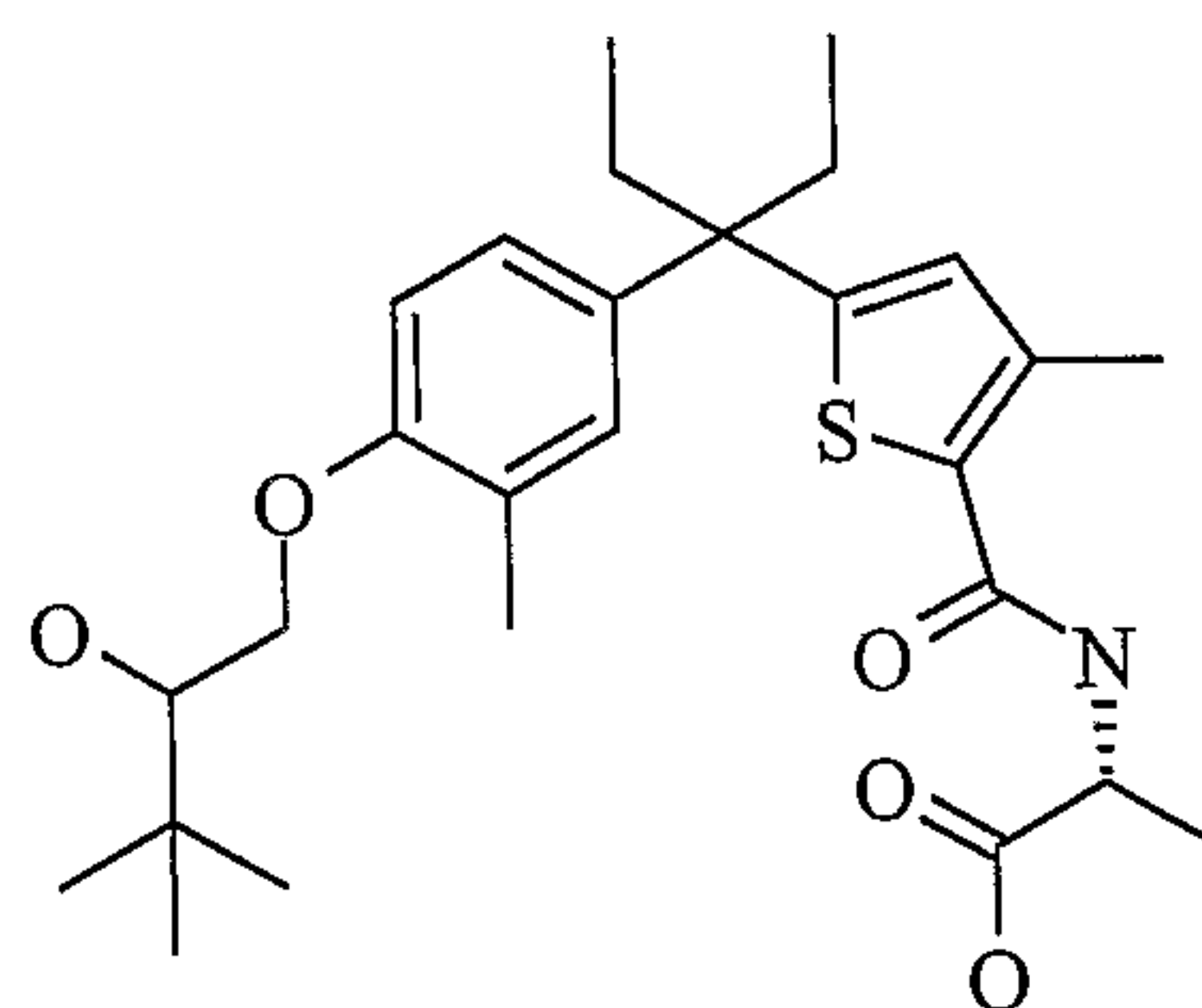
Using a procedure analogous to Example 52, enantiomer 1 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 7) (0.5 g, 1.19 mmol) and *D*-alanine methyl ester hydrochloride salt (0.18 g, 1.31 mmol) to give the title compound (0.4 g, 0.79 mmol, 66%). ¹H NMR and LC/MS: identical to 2133006 (*L*-Epimer-2), Example 54.

10

Example 67

Preparation of epimer 1 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-propionic acid.

15

*D*-Epimer 1

20

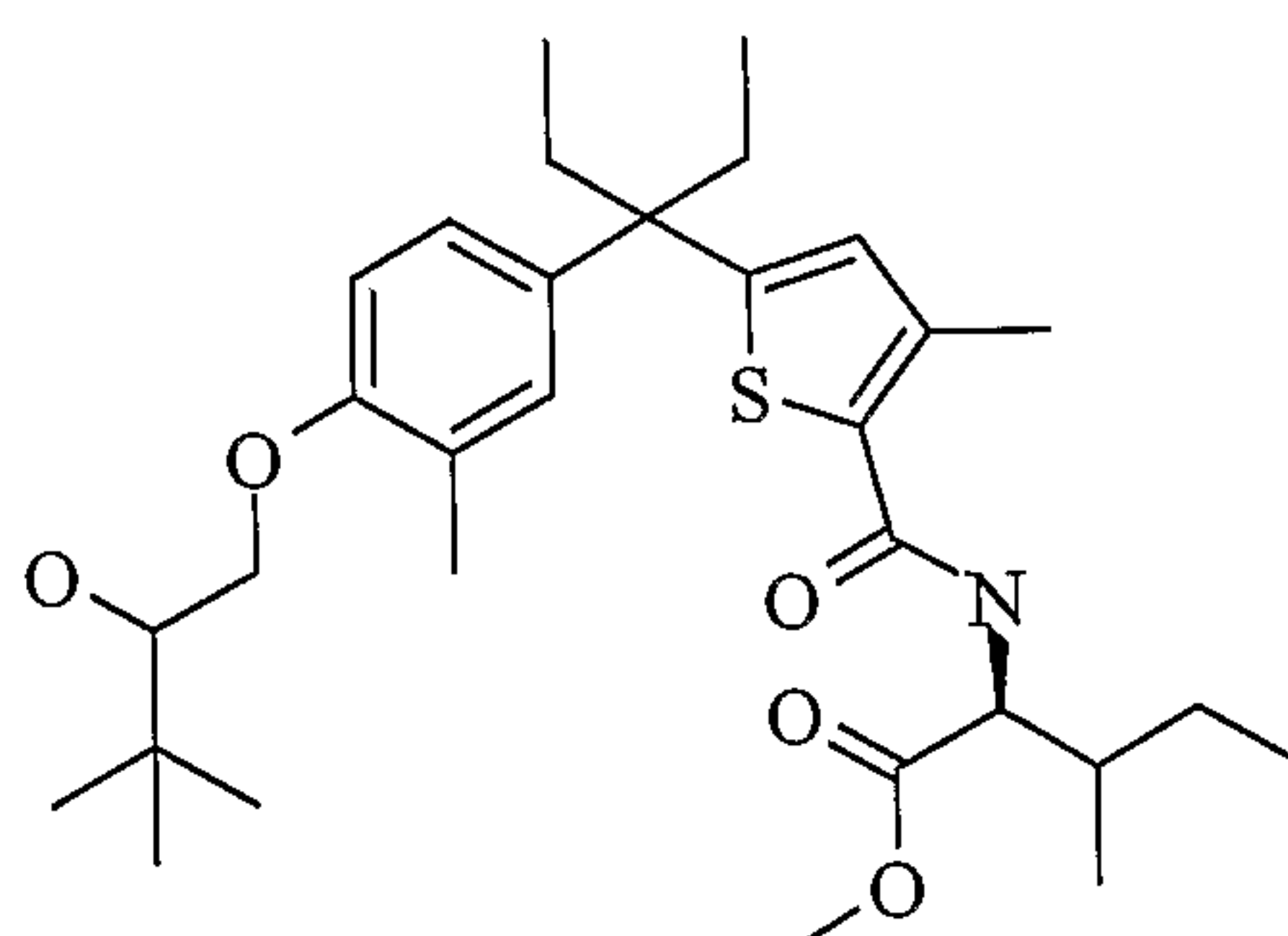
Using a procedure analogous to Example 53, epimer 1 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-

-215-

carbonyl)-amino]-propionic acid methyl ester (0.4 g, 0.79 mmol) gives the title compound (0.33 g, 0.67 mmol, 85%). ¹H NMR and LC/MS: identical to (*L*-epimer-2), Example 55.

Example 68:

- 5 Preparation of epimer 1 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-pentanoic acid methyl ester.



L-Epimer 1

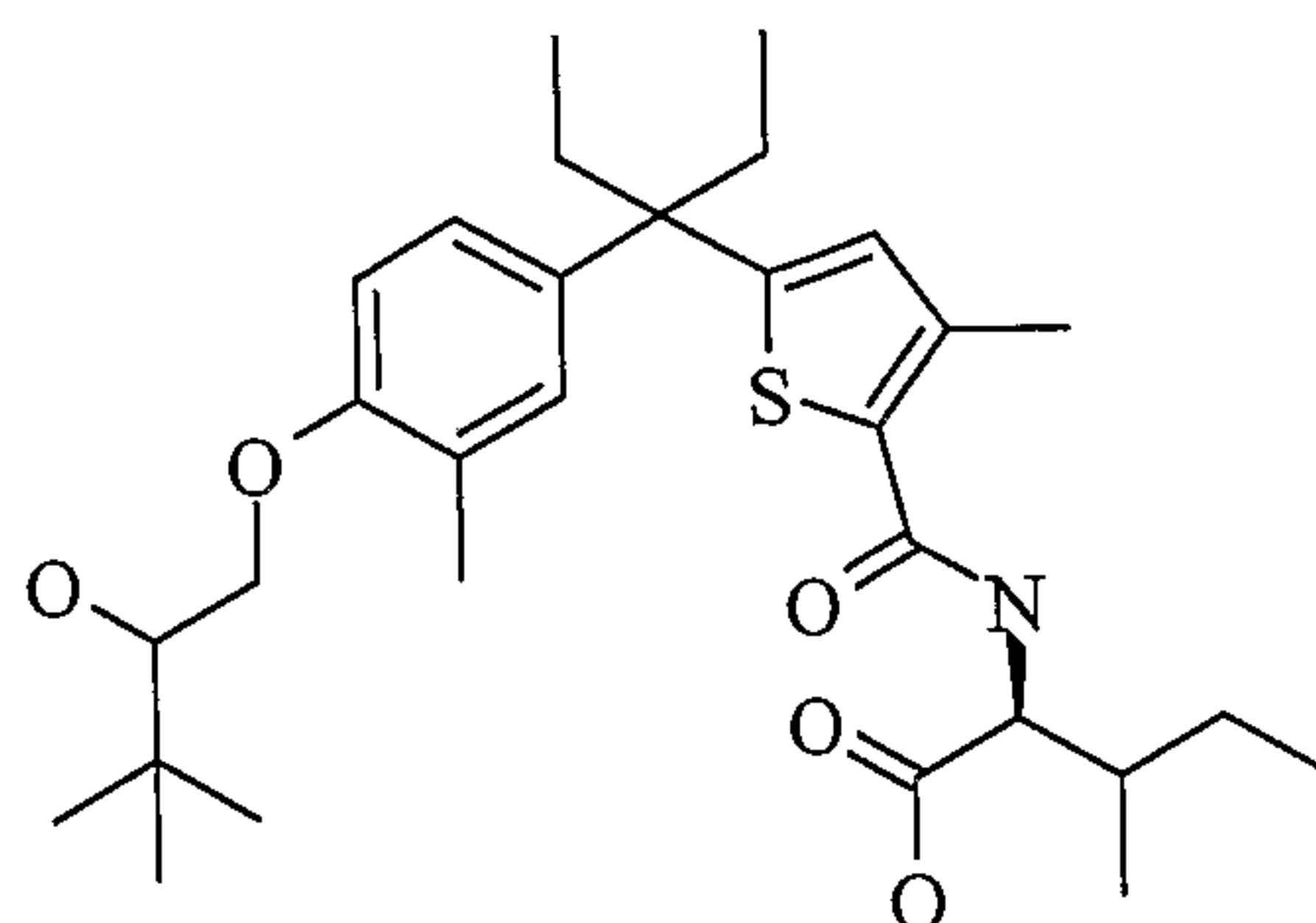
10

- Using a procedure analogous to Example 52, enantiomer 1 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 7) (0.20 g, 0.48 mmol) and *L*-isoleucine methyl ester hydrochloride salt (0.095 g, 0.53 mmol) to give the title compound (0.20 g, 0.37 mmol, 76%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.4 Hz, 6H), 0.91-0.98 (m, 6H), 1.02 (s, 9H), 1.16-1.29 (m, 1H), 1.43-1.55 (m, 1H), 1.90-2.00 (m, 1H), 2.02-2.16 (m, 4H), 2.21 (s, 3H), 2.49 (s, 3H), 3.71 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.74 (s, 3H), 3.87 (t, *J* = 8.7 Hz, 1H), 4.10 (dd, *J* = 9.2, 2.6 Hz, 1H), 4.74 (dd, *J* = 8.4, 4.9 Hz, 1H), 6.21 (d, *J* = 8.4, 1H), 6.59 (s, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 7.04 (dd, *J* = 8.6, 2.3 Hz, 1H).
 15 LC/MS (*m/z*): calcd. for C₃₁H₄₈NO₅S (*M*+H)⁺: 546.8; found: 546.2.
 20

Example 69

Preparation of epimer 1 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-pentanoic acid.

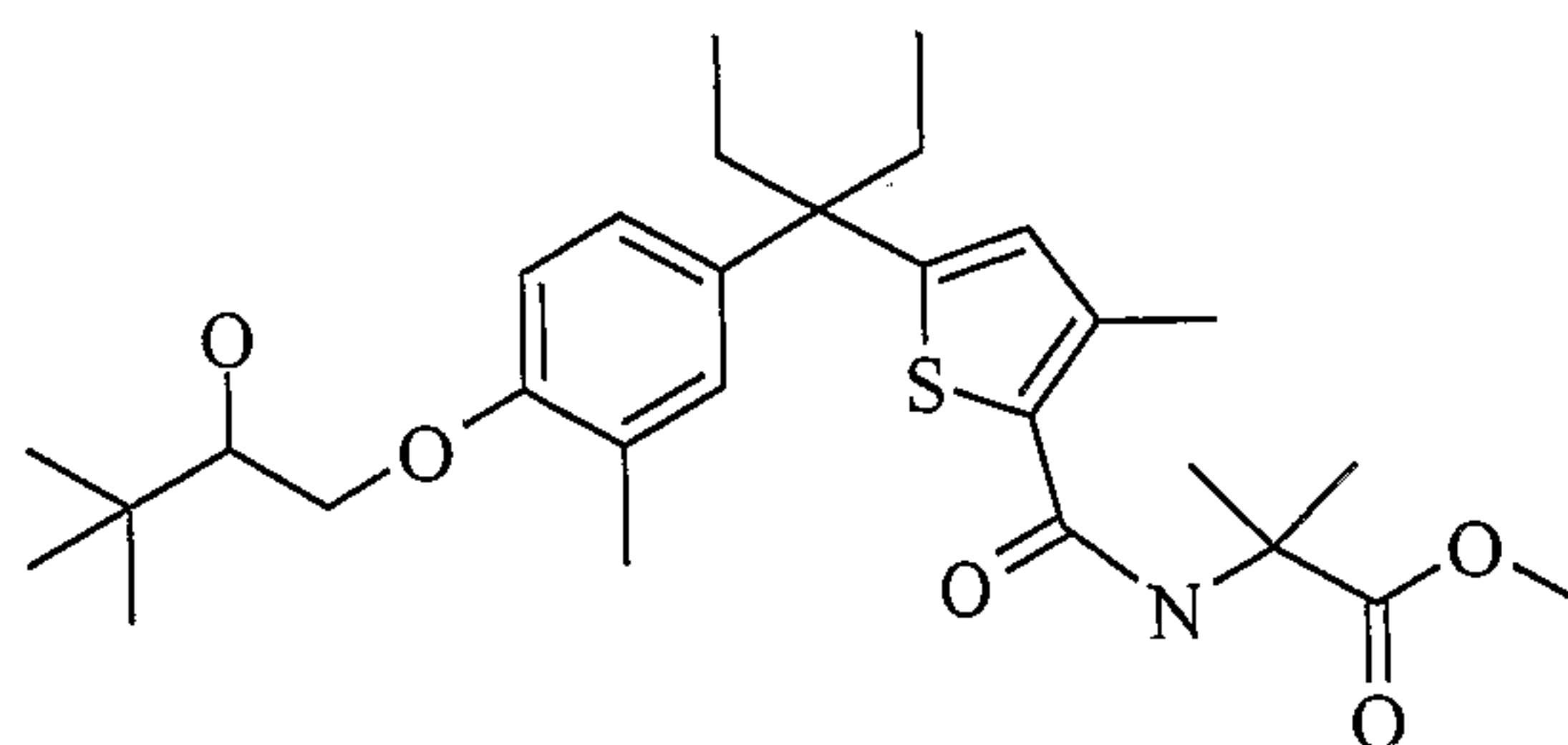
-216-

*L*-Epimer 1

Using a procedure analogous to Example 53, epimer 1 of *L*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-pentanoic acid methyl ester (0.2g, 0.37 mmol) gives the title compound (0.16 g, 0.30 mmol, 84%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.5 Hz, 6H), 0.94-1.02 (m, 6H), 1.03 (s, 9H), 1.21-1.32 (m, 1H), 1.48-1.62 (m, 1H), 1.98-2.16 (m, 5H), 2.21 (s, 3H), 2.47 (s, 3H), 3.72 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.88 (t, *J* = 8.5 Hz, 1H), 4.10 (dd, *J* = 9.3, 2.7 Hz, 1H), 4.73 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.18 (d, *J* = 8.7, 1H), 6.60 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.2 Hz, 1H). LC/MS (m/z): calcd. for C₃₀H₄₆NO₅S (M+H)⁺: 531.8; found: 532.1.

Example 70

Preparation of enantiomer 1 of 2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester.



Enantiomer 1

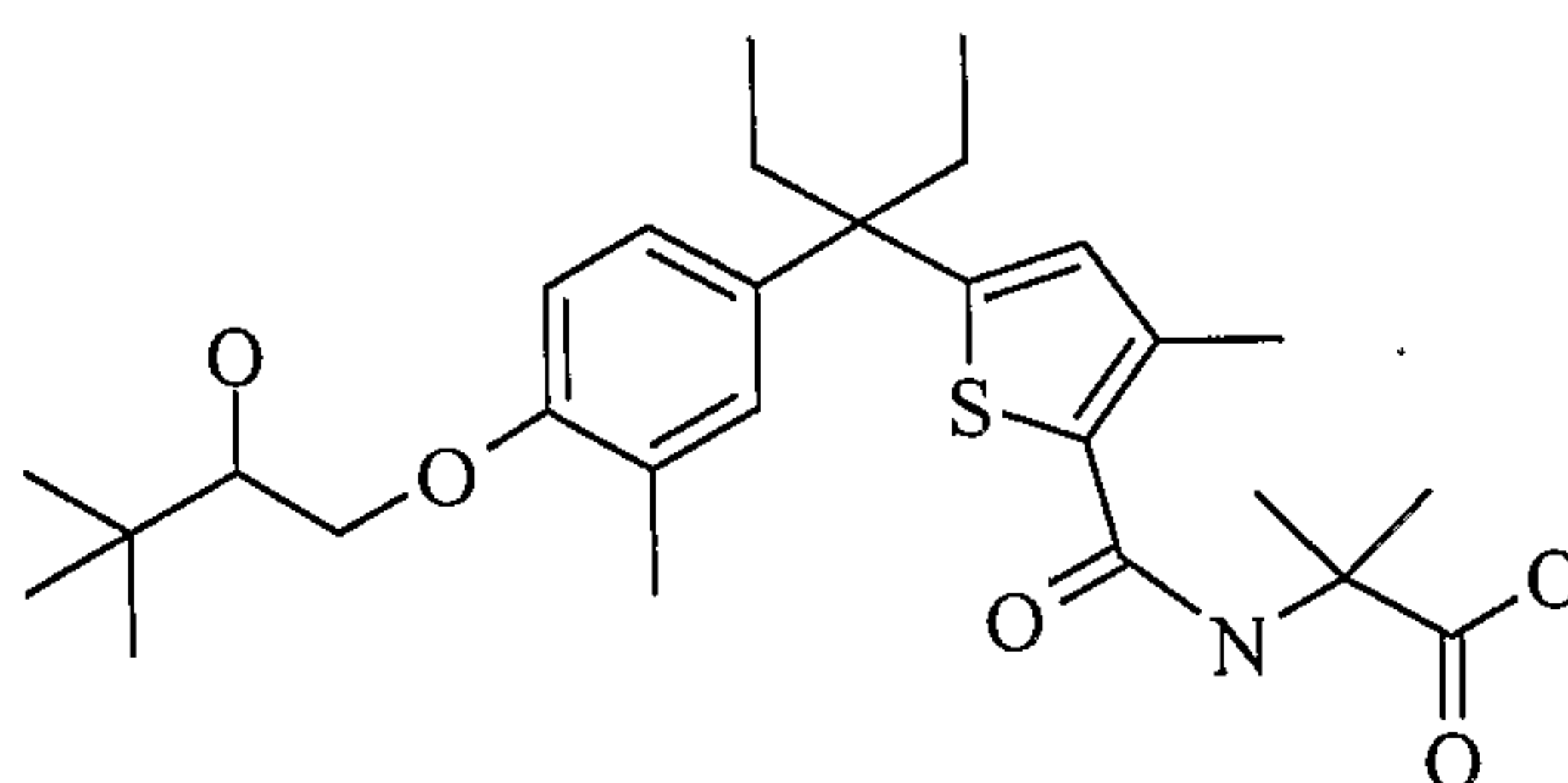
Using the procedure analogous to Example 52, enantiomer 1 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 7) (0.2 g, 0.48 mmol) and 2-amino-2-methyl-propionic acid

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methyl ester hydrochloride salt (0.018 g, 0.53 mmol) to give the title compound (0.20 g, 0.39 mmol, 71%). ^1H NMR (CDCl_3), δ 0.69 (t, $J = 7.0$ Hz, 6H), 1.01 (s, 9H), 1.60 (s, 6H), 2.02-2.13 (m, 4H), 2.19 (s, 3H), 2.44 (s, 3H), 3.70 (dd, $J = 8.9, 2.6$ Hz, 1H), 3.76 (s, 3H), 3.86 (t, $J = 8.7$, 1H), 4.09 (dd, $J = 9.4, 2.6$ Hz, 1H), 6.28 (s, 1H), 6.59 (s, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 6.99 (d, $J = 2.2$ Hz, 1H), 7.04 (dd, $J = 8.4, 2.2$ Hz, 1H). LC/MS (m/z): calcd. for $\text{C}_{29}\text{H}_{44}\text{NO}_5\text{S}$ ($\text{M}+\text{H}$) $^+$: 518.7; found: 518.2.

Example 71

Preparation of enantiomer 1 of 2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid.



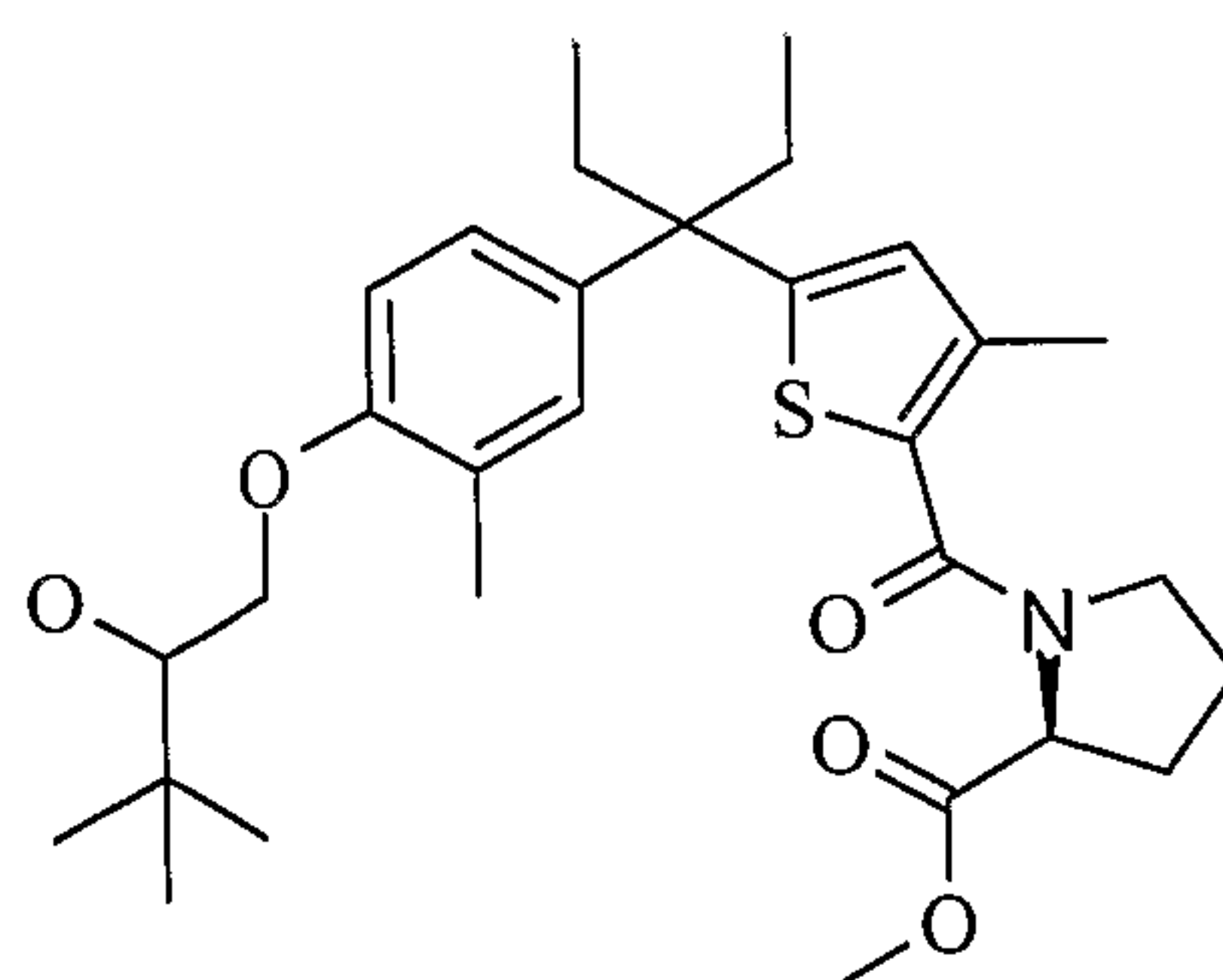
Enantiomer 1

Using a procedure analogous to Example 53, enantiomer 1 of 2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester (0.20 g, 0.39 mmol) gives the title compound (0.17 g, 0.34 mmol, 84%). ^1H NMR (CDCl_3), δ 0.71 (t, $J = 7.5$ Hz, 6H), 1.02 (s, 9H), 1.65 (s, 6H), 2.03-2.14 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 3.71 (dd, $J = 8.6, 2.5$ Hz, 1H), 3.87 (t, $J = 8.6$, 1H), 4.09 (dd, $J = 9.2, 2.5$ Hz, 1H), 6.11 (s, 1H), 6.63 (s, 1H), 6.73 (d, $J = 8.3$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 6.98 (d, $J = 2.2$ Hz, 1H), 7.04 (dd, $J = 8.4, 2.2$ Hz, 1H). LC/MS (m/z): calcd. for $\text{C}_{28}\text{H}_{42}\text{NO}_5\text{S}$ ($\text{M}+\text{H}$) $^+$: 504.7; found: 504.2.

Example 72

Preparation of epimer 1 of L-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)pyrrolidine-2-carboxylic acid methyl ester.

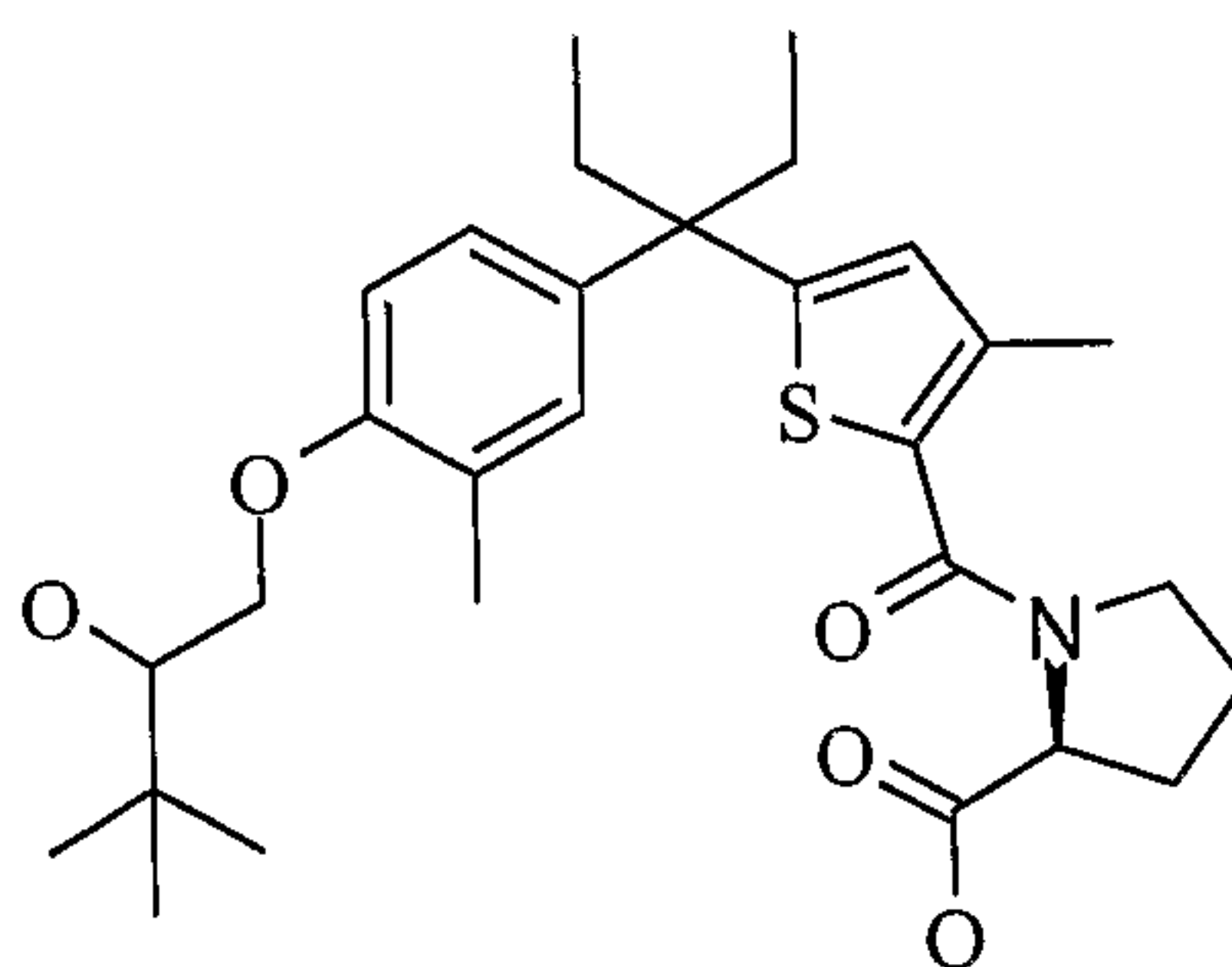
-218-

*L*-Epimer 1

Using a procedure analogous to Example 52, enantiomer 1 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 7) (0.20 g, 0.4778 mmol) and *L*-proline methyl ester hydrochloride salt (0.09 g, 0.53 mmol) to give the title compound (0.14 g, 0.26 mmol, 56%). ¹H NMR (CDCl₃), δ 0.69 (t, *J* = 7.4 Hz, 3H), 0.70 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 9H), 1.85-2.14 (m, 7H), 2.19 (s, 3H), 2.21-2.36 (m, 4H), 3.60-3.78 (m, 6H), 3.86 (t, *J* = 9.3, 1H), 4.09 (dd, *J* = 9.3, 2.8 Hz, 1H), , 4.53-4.65 (m, 1 H), 6.53 (s, 1H), 6.71 (d, *J* = 8.9 Hz, 1H), 6.96-7.06 (m, 2H). LC/MS (*m/z*): calcd. for C₃₀H₄₄NO₅S (M+H)⁺: 530.8; found: 530.2.

Example 73

Preparation of epimer 1 of *L*-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)pyrrolidine-2-carboxylic acid.

*L*-Enantiomer 1

Using a procedure analogous to Example 53, epimer 1 of *L*-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)pyrrolidine-2-carboxylic acid methyl ester (0.20g, 0.39 mmol) gives the title compound (0.17 g, 0.34 mmol, 84%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.5 Hz, 6H),

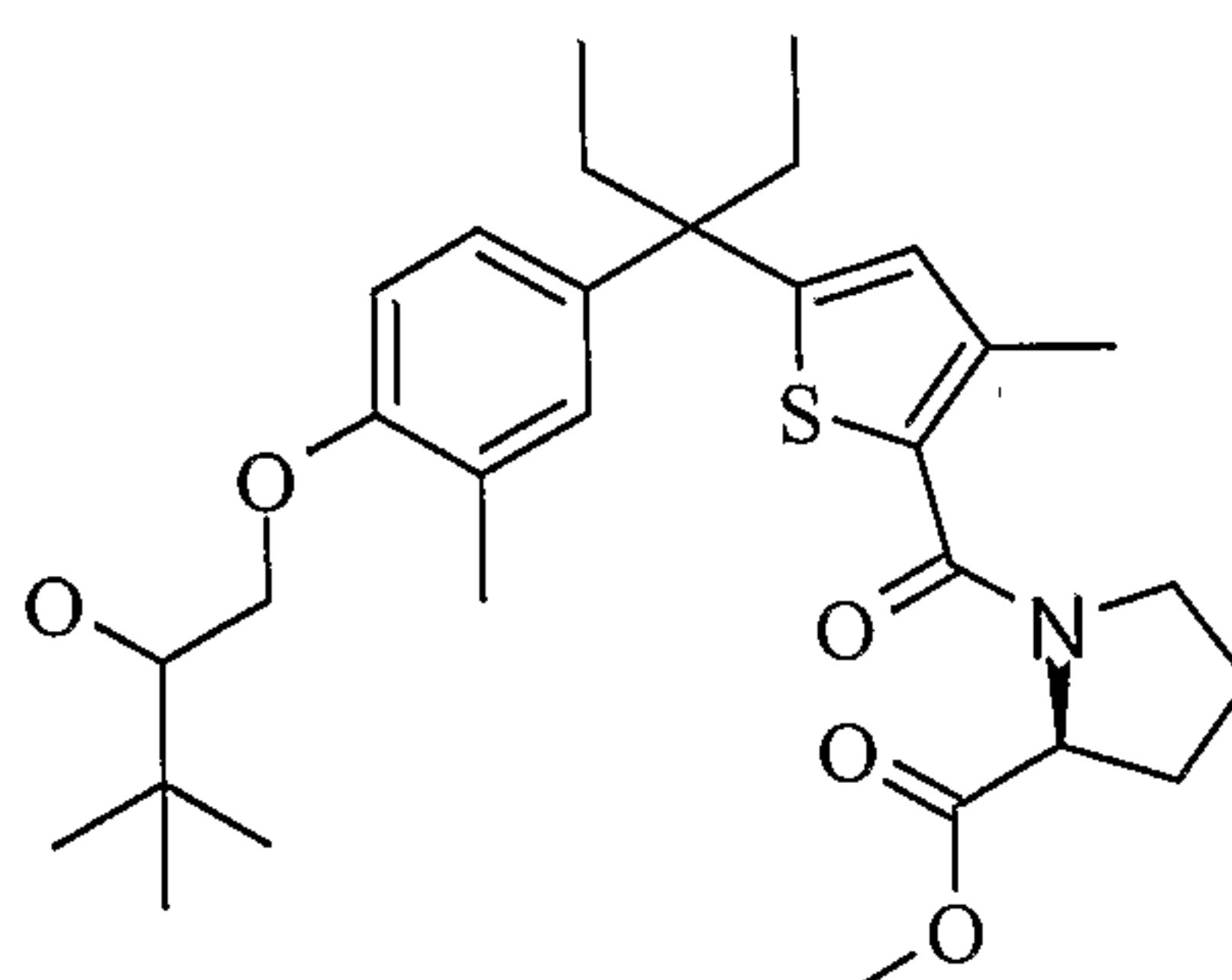
-219-

1.02 (s, 9H), 1.91-2.15 (m, 8H), 2.20 (s, 3H), 2.36 (s, 3H), 2.42 (bs, 1H), 3.63-3.76 (m, 3H), 3.87 (t, $J = 9.2$, 1H), 4.09 (dd, $J = 9.2$, 2.6 Hz, 1H), 4.68-4.75 (m, 1H), 6.60 (s, 1H), 6.72 (d, $J = 8.3$ Hz, 1H), 6.99 (d, $J = 2.2$ Hz, 1H), 7.03 (dd, $J = 8.3$, 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{29}H_{42}NO_5S$ ($M+H$)⁺: 516.7; found: 516.2.

5

Example 74

Preparation of epimer 2 of *L*-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid methyl ester.



10

L-Epimer 2

Using the procedure analogous to Example 52, enantiomer 2 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 8) (0.50 g, 1.19 mmol) and *L*-proline methyl ester hydrochloride salt (0.22 g, 1.3 mmol) to give the title compound (0.31 g, 0.59 mmol, 49%). ¹H NMR (CDCl₃), δ 0.70 (t, $J = 7.1$ Hz, 3H), 0.71 (t, $J = 7.5$ Hz, 1H), 1.02 (s, 9H), 1.87-2.15 (m, 7H), 2.20 (s, 3H), 2.22-2.38 (m, 4H), 3.60-3.78 (m, 6H), 3.87 (t, $J = 9.3$, 1H), 4.09 (dd, $J = 9.3$, 2.7 Hz, 1H), 4.53-4.65 (m, 1H), 6.54 (s, 1H), 6.71 (d, $J = 8.9$ Hz, 1H), 6.96-7.06 (m, 2H). LC/MS (m/z): calcd. for $C_{30}H_{44}NO_5S$ ($M+H$)⁺: 530.8; found: 530.2.

15

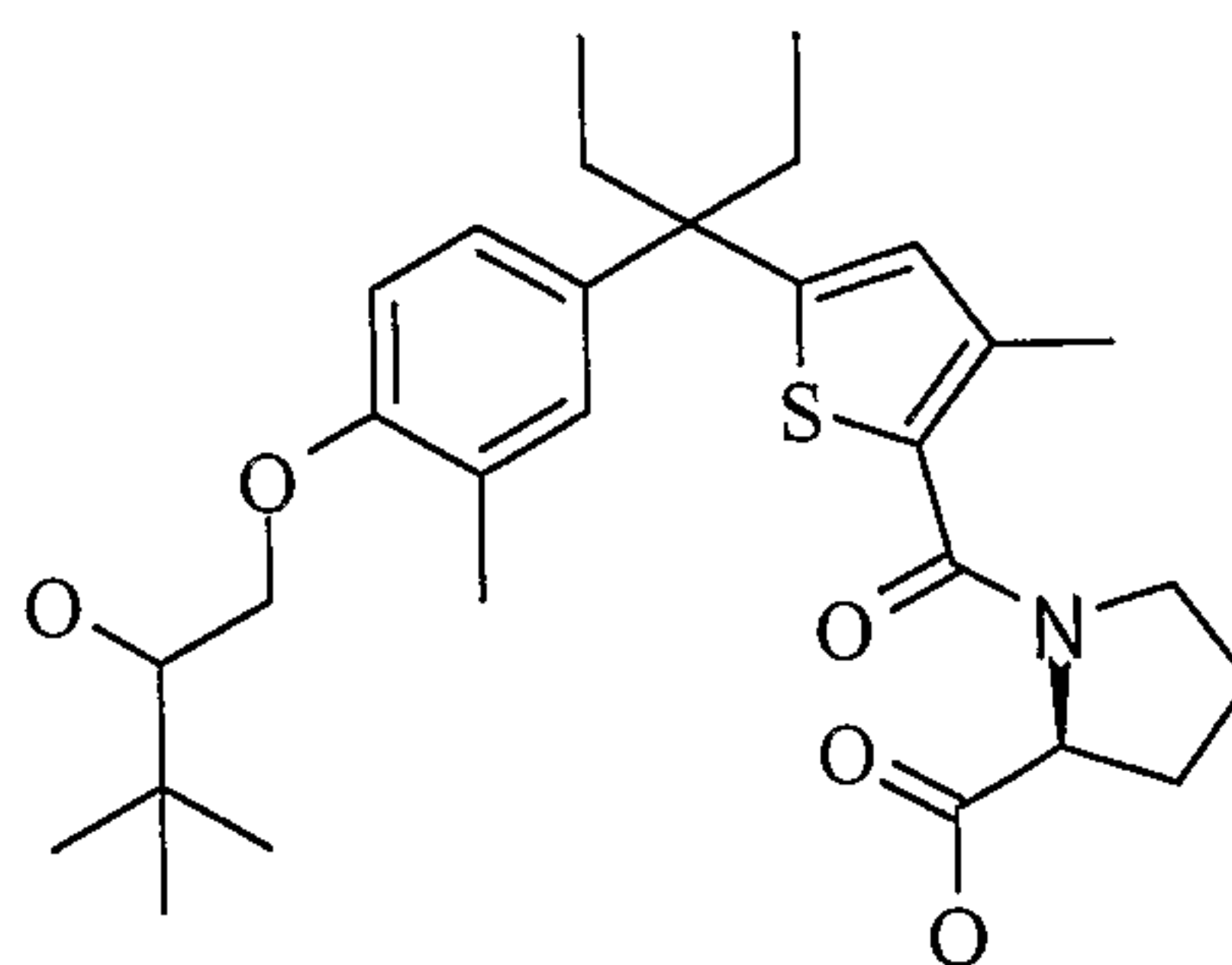
20

Example 75

Preparation of epimer 2 of *L*-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid.

25

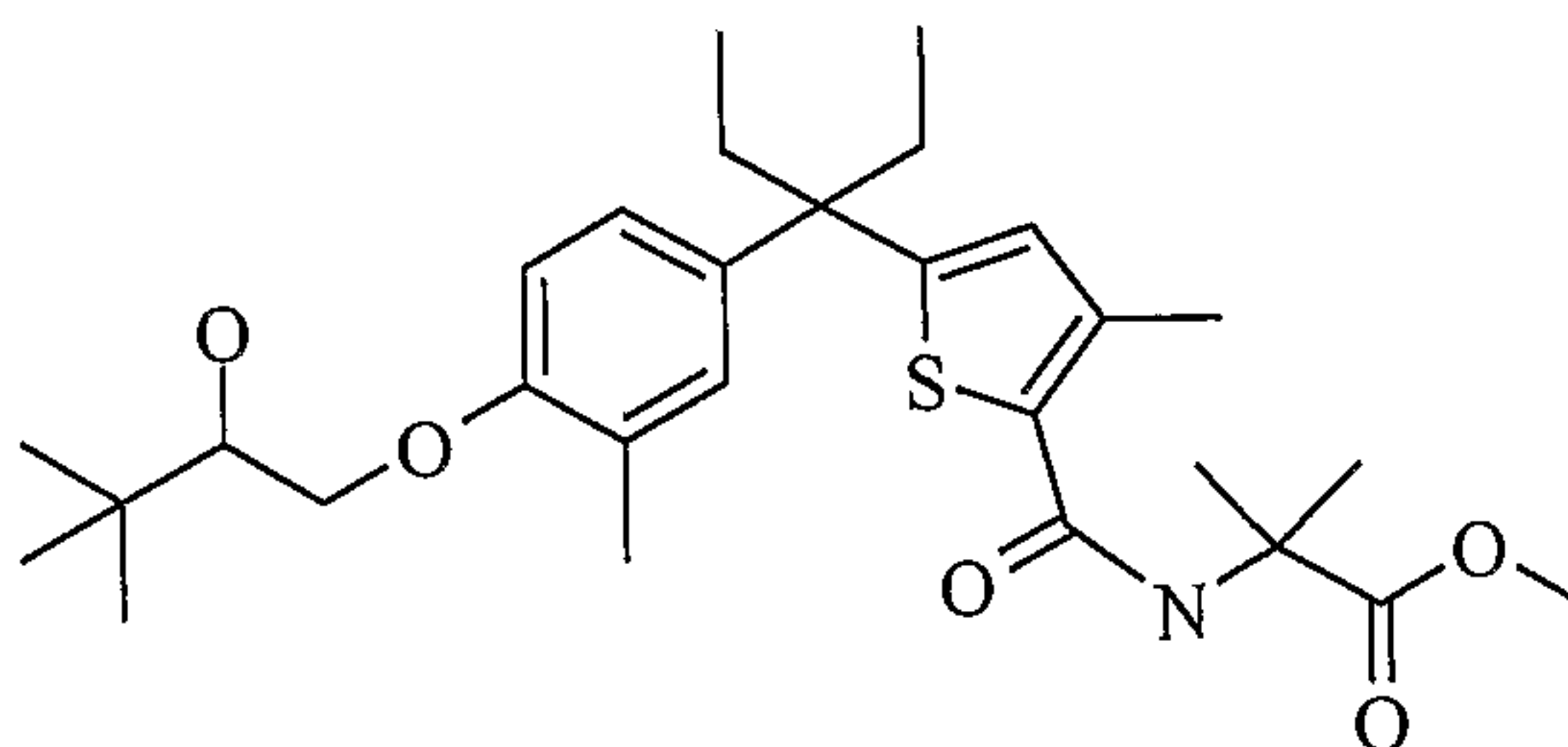
-220-

*L*-Epimer 2

Using the procedure analogous to Example 53, epimer 2 of 2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester, (0.31 g, 0.59 mmol) gives the title compound (0.29 g, 0.56 mmol, 97%). ¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.5 Hz, 6H), 1.02 (s, 9H), 1.92-2.15 (m, 8H), 2.20 (s, 3H), 2.36 (s, 3H), 2.41 (bs, 1H), 3.63-3.76 (m, 3H), 3.90 (t, *J* = 8.9, 1H), 4.10 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.68-4.75 (m, 1H), 6.60 (s, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 7.03 (dd, *J* = 8.5, 2.3 Hz, 1H). LC/MS (m/z): calcd. for C₂₉H₄₂NO₅S (M+H)⁺: 516.7; found: 516.3.

Example 76

Preparation of enantiomer 2 of 2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester.



Enantiomer 2

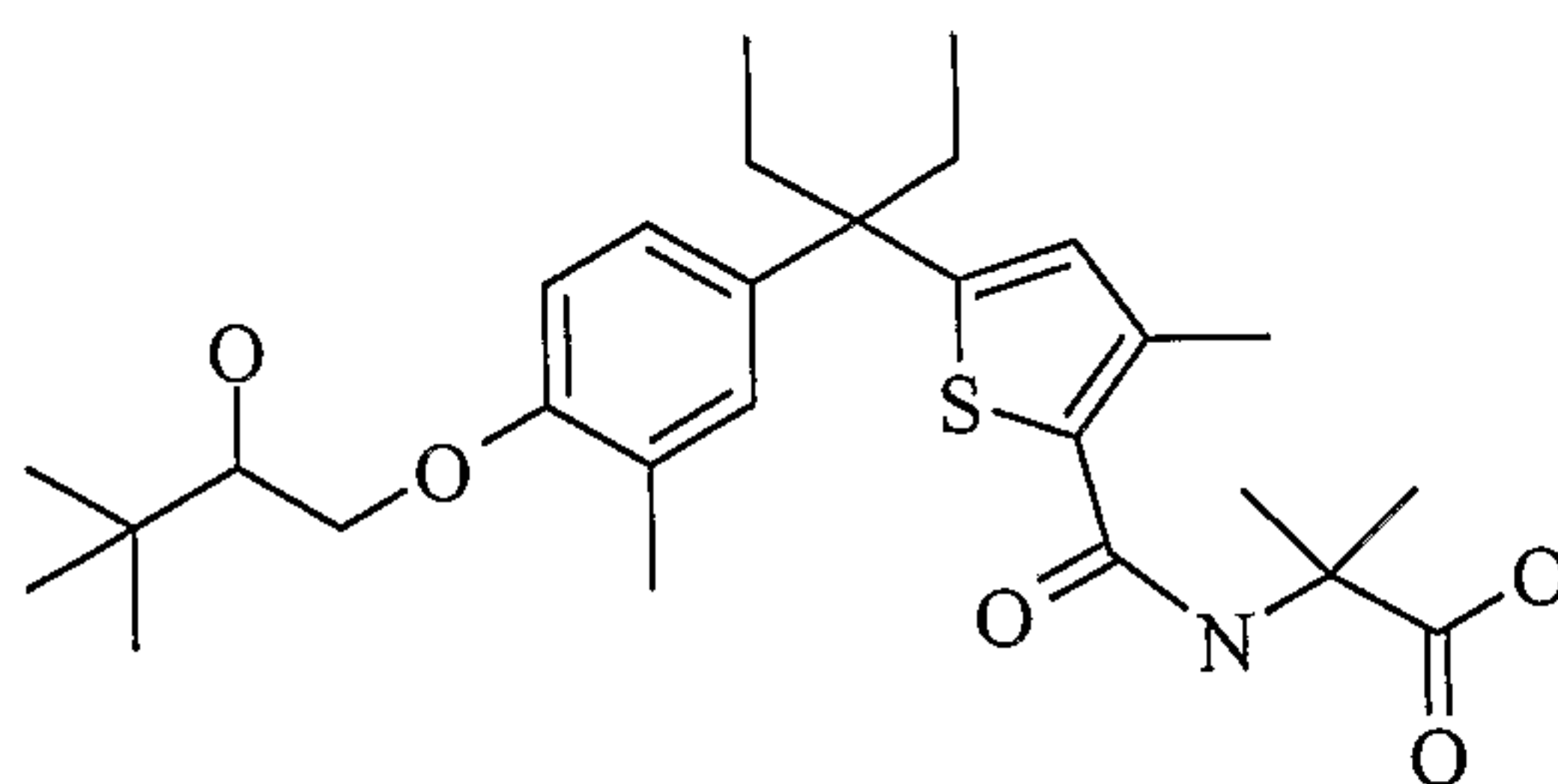
Using the procedure analogous to Example 52, enantiomer 2 of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 8) (0.5 g, 1.19 mmol) and 2-amino-2-methyl-propionic acid

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methyl ester hydrochloride salt (0.2 g, 1.31 mmol) to give the title compound (0.44 g, 0.85 mmol, 71%). ^1H NMR and LC/MS: identical to (enantiomer-1), Example 70.

Example 77

- 5 Preparation of enantiomer of 2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid.



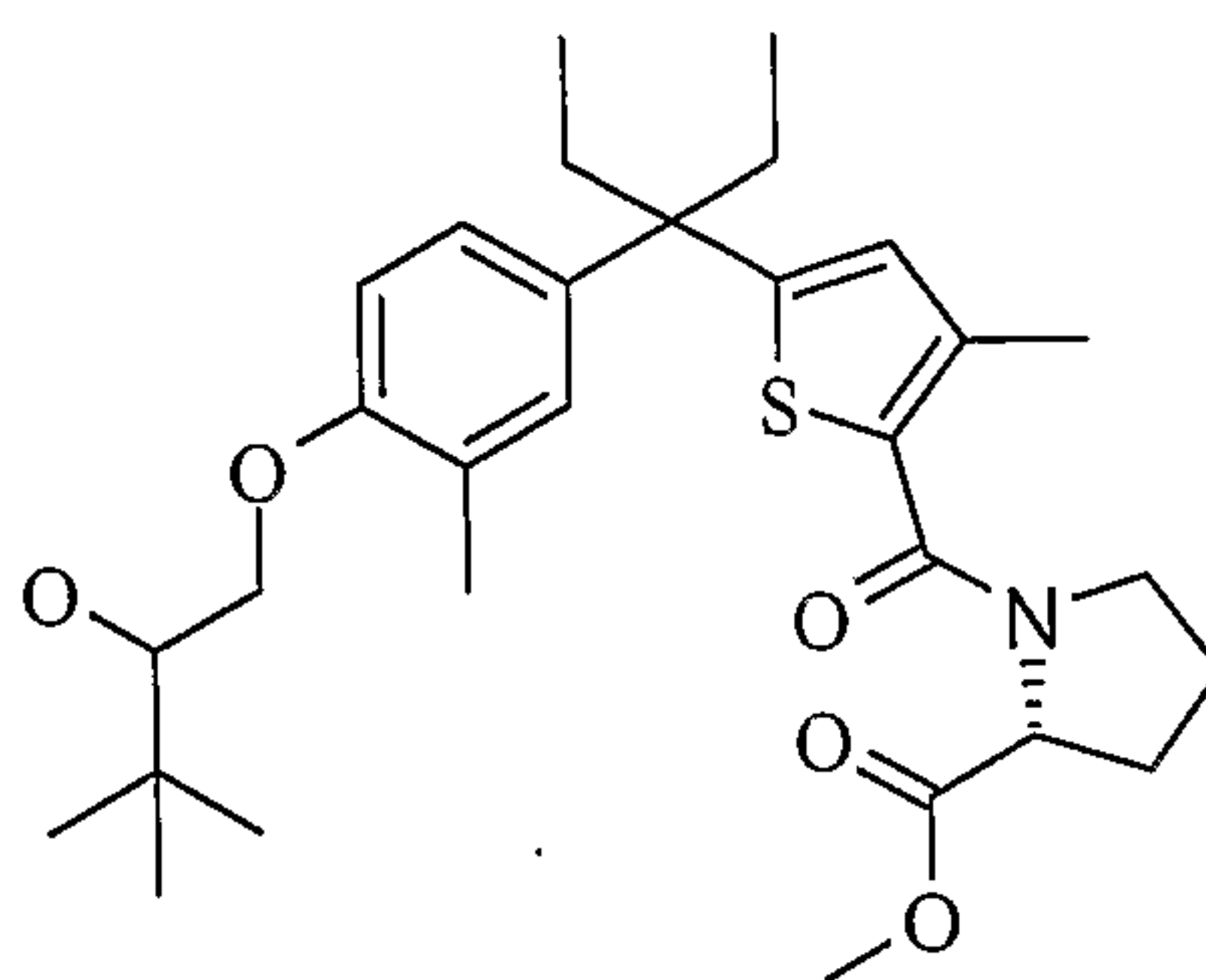
Enantiomer 2

- 10 Using the procedure analogous to Example 53, enantiomer 2 of 2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester (0.44g, 0.85 mmol) gives the title compound (0.35 g, 0.69 mmol, 81%). ^1H NMR and LC/MS: identical to (enantiomer-1), Example 71.

15

Example 78

Preparation of *D*-1-(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid methyl ester



D-Racemic

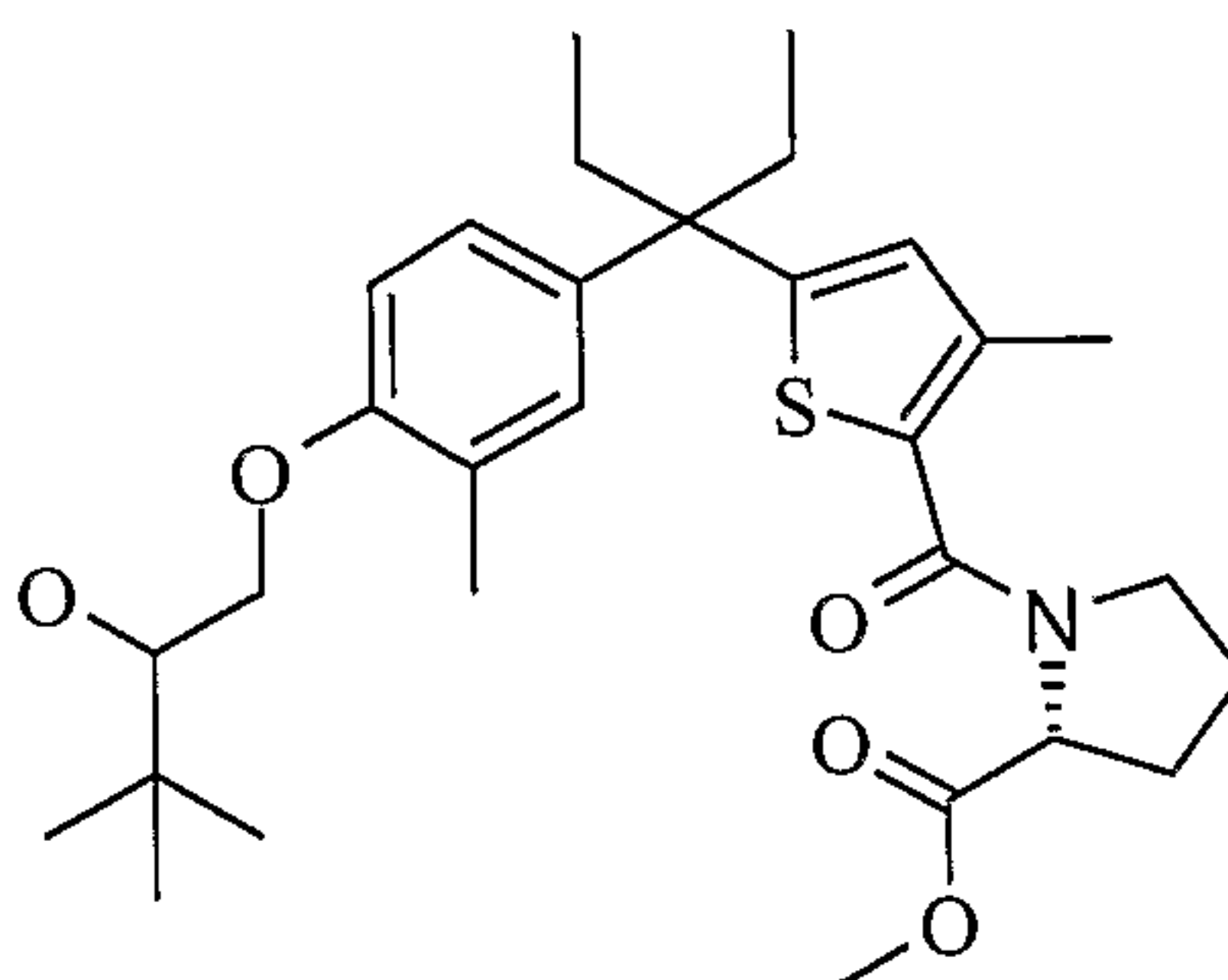
20

-222-

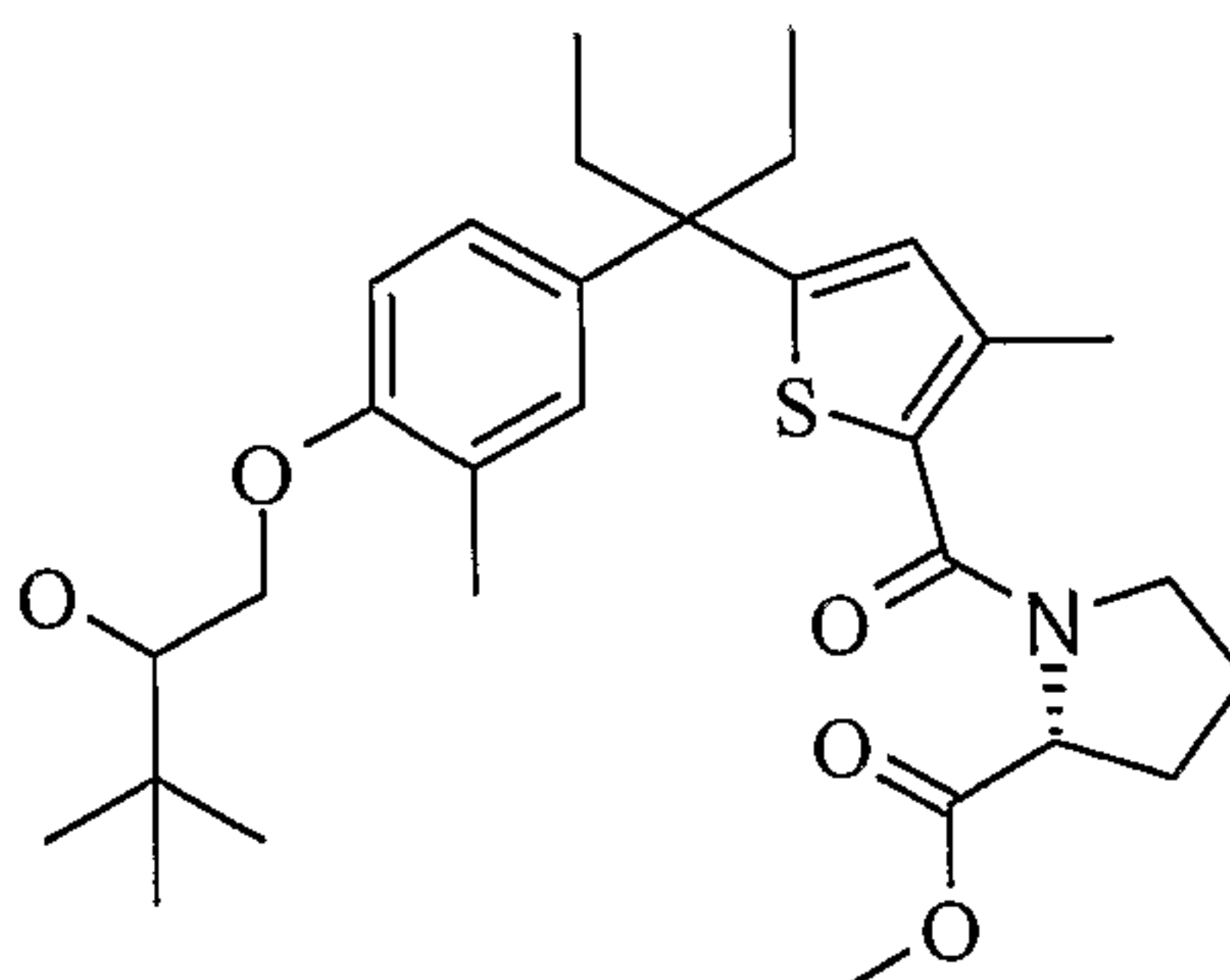
Using a procedure analogous to Example 52, a racemic mixture of 5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (0.6 g, 1.39 mmol) and *D*-proline methyl ester hydrochloride salt (0.28 g, 1.53 mmol) give the title compound (0.54 g, 1.02 mmol, 73%). ¹H NMR (CDCl₃), δ 0.70 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.5 Hz, 3H) 1.02 (s, 9H), 1.88-2.16 (m, 7H), 2.20 (s, 3H), 2.22-2.38 (m, 4H), 3.61-3.79 (m, 6H), 3.87 (t, *J* = 8.8, 1H), 4.09 (dd, *J* = 9.1, 2.6 Hz, 1H), 4.56-4.65 (m, 1 H), 6.54 (s, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.98-7.06 (m, 2H). LC/MS (m/z): calcd. for C₃₀H₄₄NO₅S (M+H)⁺: 530.8; found: 530.2.

10 Example 79 and 80

Preparation of epimers of *D*-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid methyl ester.



15 *D*-Epimer 1



D-Epimer 2

20 A racemic mixture of *D*-1-(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid

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methyl ester (0.54 g) is chromatographed (CHIRALPAK AD column, 40% *i*-PrOH/Hept) to give epimer1, Example 79 (0.244 g, 45 %) and epimer 2, Example 80 (0.283 g, 52%).

Example 79, Epimer1 rt = 10.2 m

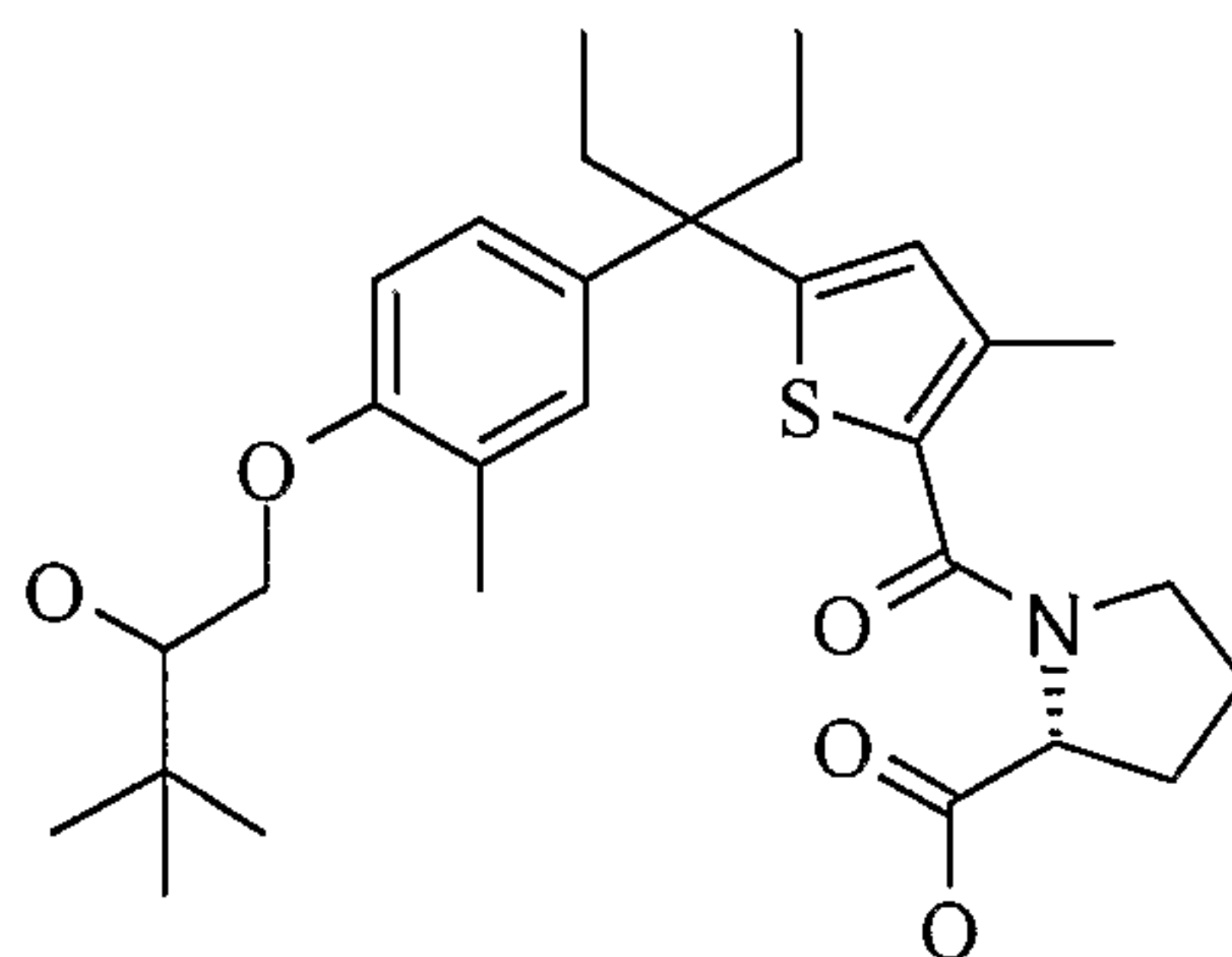
5 NMR & LC/MS: identical to 2158904 (*L*-epimer-2), Example 78.

Example 80, Epimer 2 rt = 18.1 m

NMR & LC/MS: identical to (*L*-epimer-1), Example 78.

10 Example 81

Preparation of epimer 1 of *D*-1-(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid.



15 *D*-Epimer 1

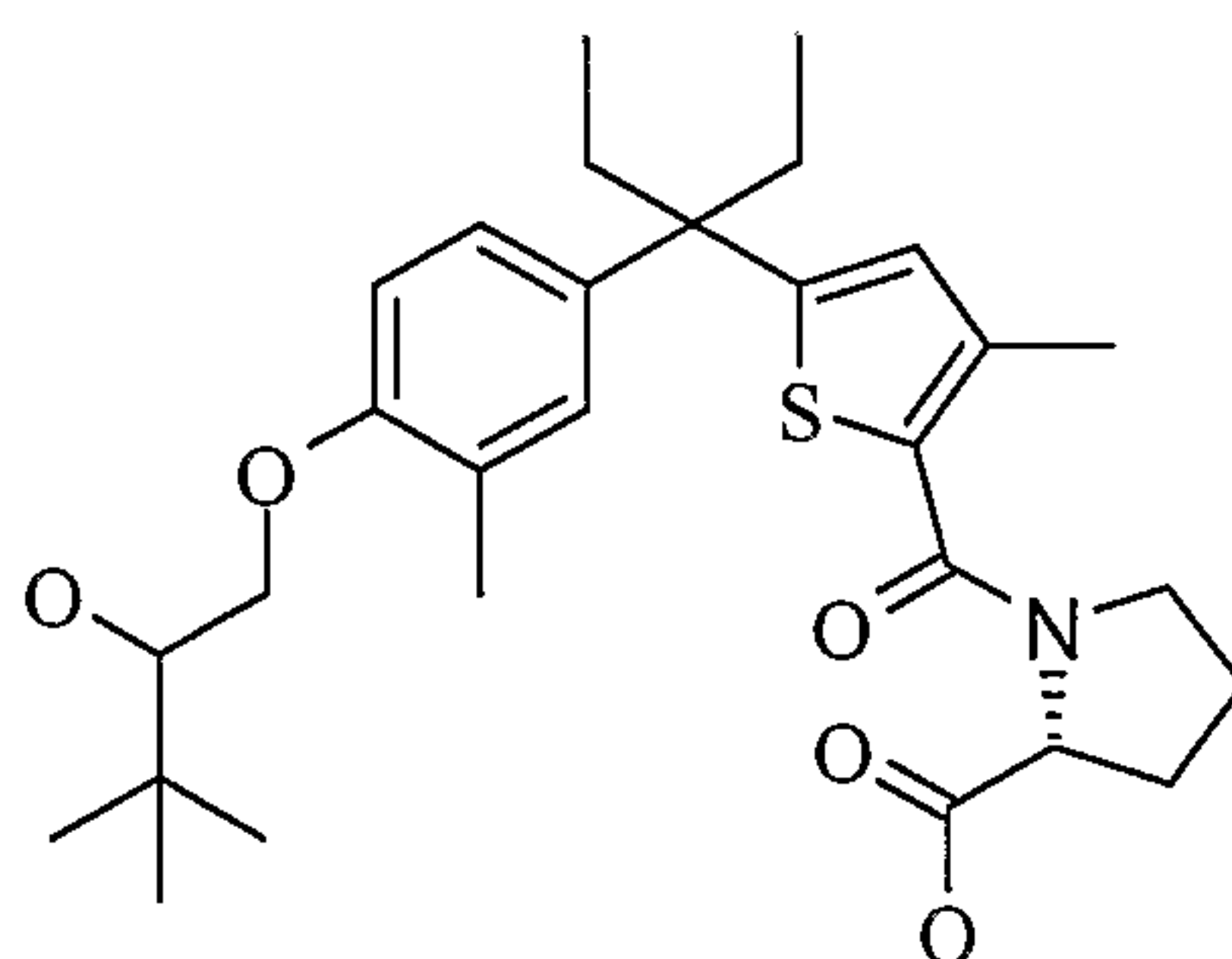
Using the procedure analogous to Example 53, epimer 1 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester (Example 79) (0.24g, 0.46 mmol) gives the title compound (0.15 g, 0.29 mmol, 63%). ¹H NMR and LC/MS:

20 identical to (*L*-enantiomer-2), Example 75.

Example 82

Preparation of epimer 2 of *D*-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid.

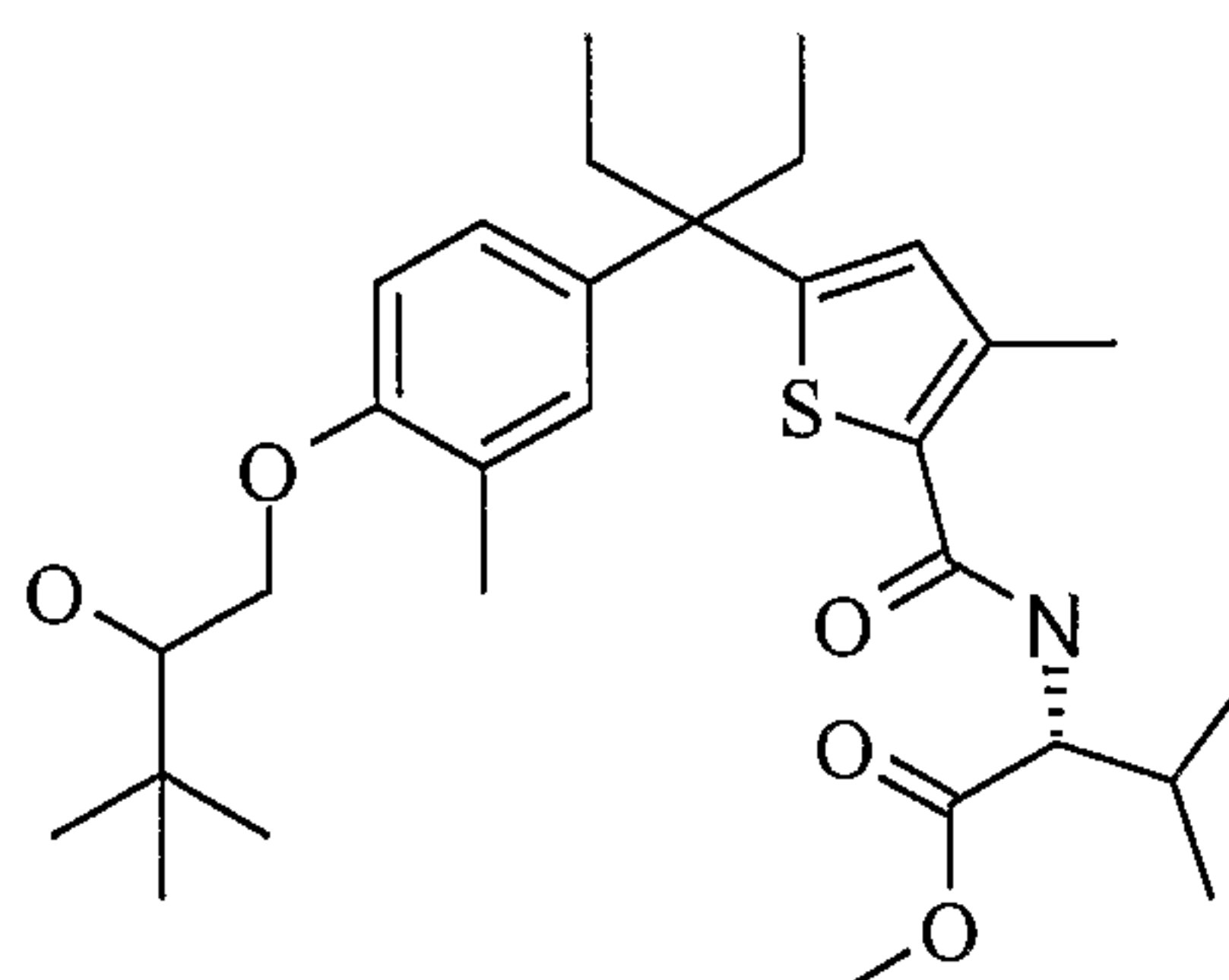
-224-

*D*-Enantiomer 2

Using a procedure analogous to Example 53, epimer-2 of *D*-1-(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-pyrrolidine-2-carboxylic acid methyl ester (Example 80) (0.28 g, 0.53 mmol) gives the title compound (0.22 g, 0.43 mmol, 79%). ¹H NMR and LC/MS: identical to (*L*-epimer-1), Example 73.

Example 83

Preparation of *D*-2-[(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-butyric acid methyl ester

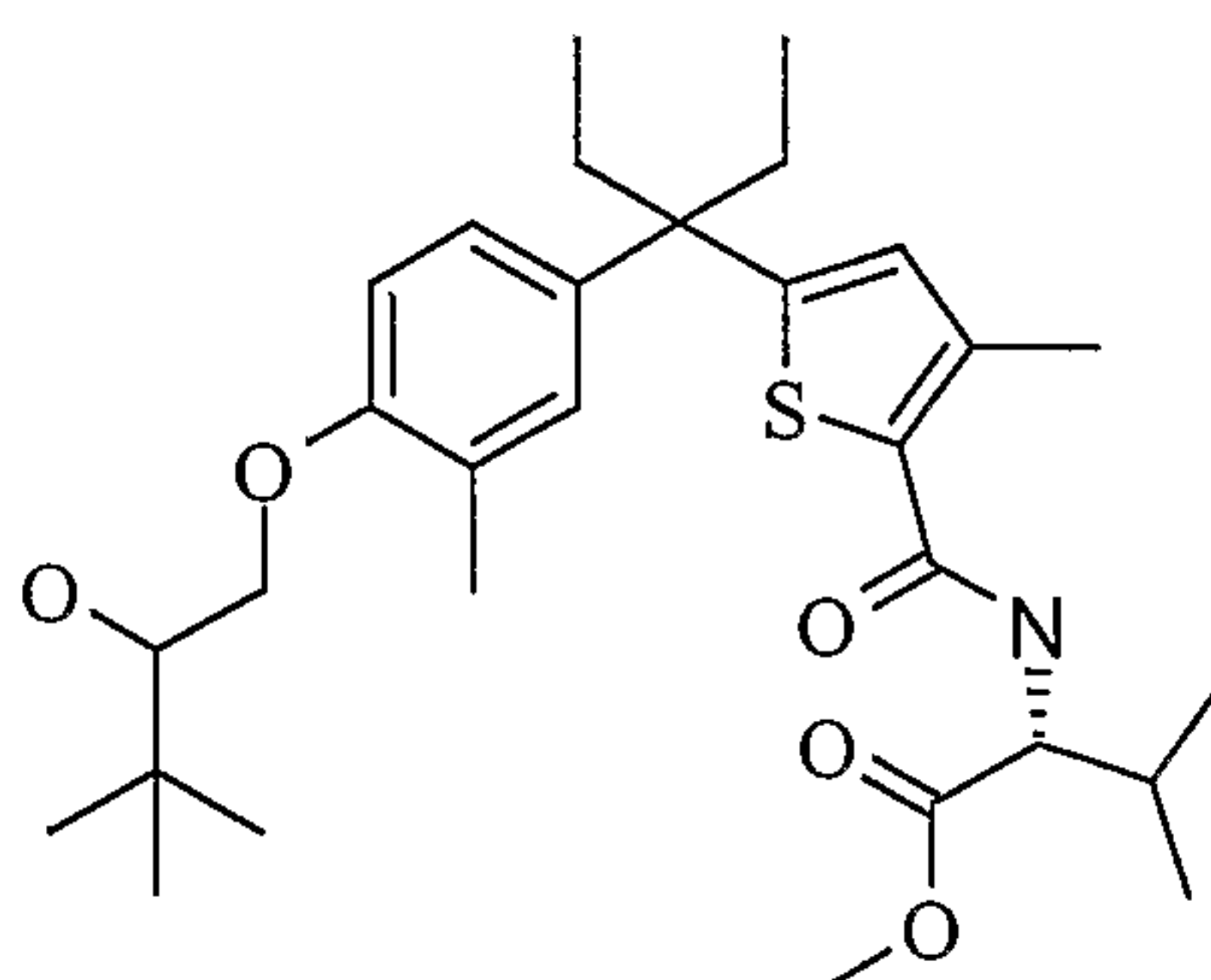
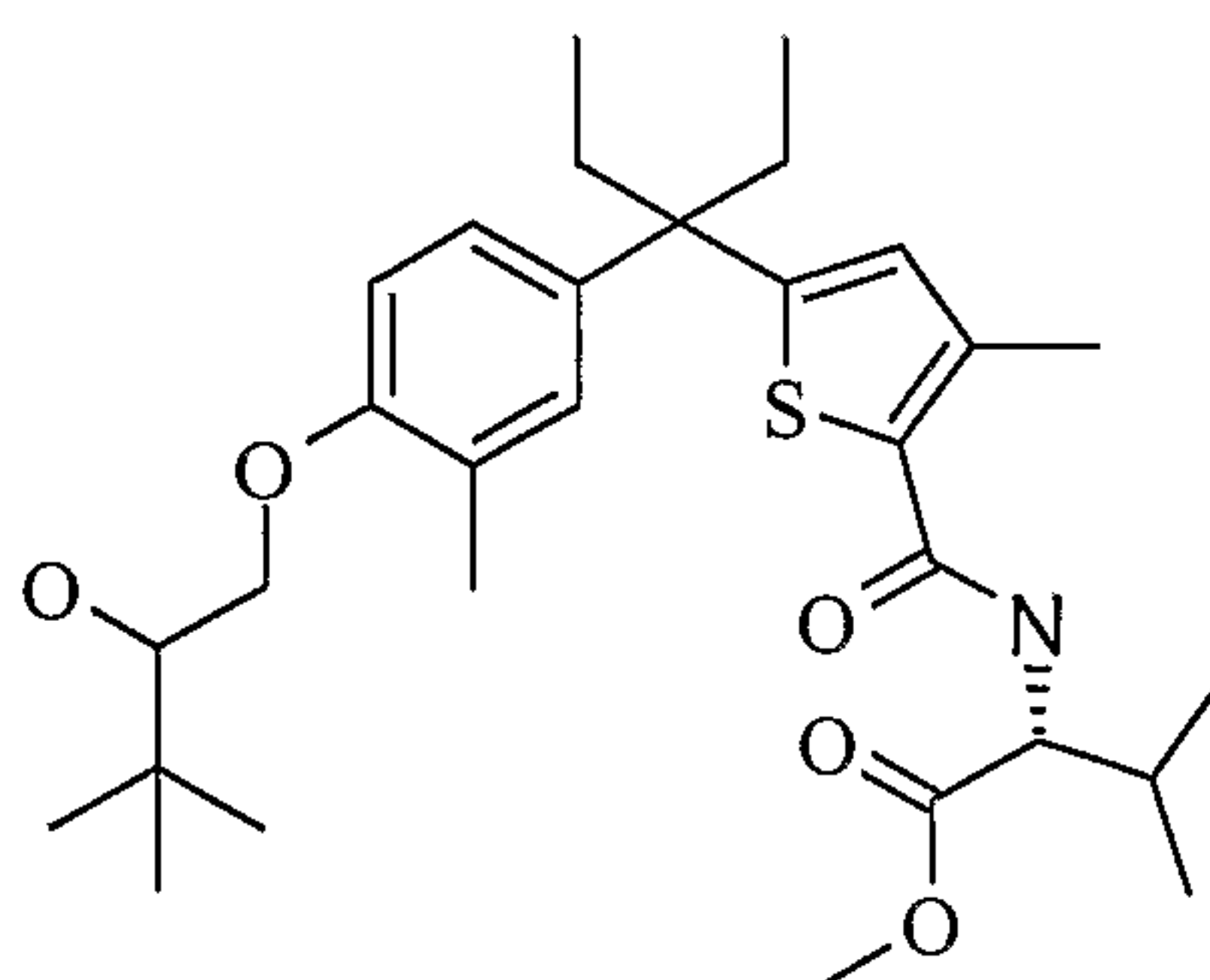
*D*-Racemic

Using a procedure analogous to Example 52, a racemic mixture of 5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carboxylic acid (Example 3) (0.60 g, 1.39 mmol) and *D*-valine methyl ester hydrochloride salt (0.29 g, 1.53 mmol) to give the title compound (0.54 g, 1.02mmol, 73%). LC/MS (*m/z*): calcd. for C₃₀H₄₆NO₅S (M+H)⁺: 532.8; found: 532.2.

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Example 84 and 85

Preparation of epimers of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-butyric acid methyl ester.

*D*-Epimer 1*D*-Epimer 2

A racemic mixture of *D*-2-[(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-butyric acid methyl ester (Example 83) (0.54 g) is chromatographed (CHIRALPAK AD column, 40% *i*-PrOH/Hept) to give epimer 1, Example 84 (0.36 g, 48 %) and epimer 2, Example 85 (0.33 g, 45%).

Example 84, Epimer 1

rt = 6.8 m

¹H NMR (CDCl₃), δ 0.71 (t, *J* = 7.2 Hz, 6H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 7.1 H, 3H), 1.02 (s, 9H), 2.04-2.15 (m, 4H), 2.18 (s, 3H), 2.20-2.21 (m, 2H), 2.47 (s, 3H), 3.71 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.76 (s, 3H), 3.88 (t, *J* = 8.8 Hz, 1H), 4.11 (dd, *J* = 9.2,

-226-

2.6 Hz, 1H), 4.69 (dd, $J = 8.4, 4.9$ Hz, 1 H), 6.19 (d, $J = 8.4$ Hz, 1H), 6.60 (s, 1H), 6.73 (d, $J = 8.3$ Hz, 1H), 6.90-7.06 (m, 2H). LC/MS (m/z): calcd. for $C_{30}H_{46}NO_5S$ ($M+H$)⁺: 532.8; found: 532.2.

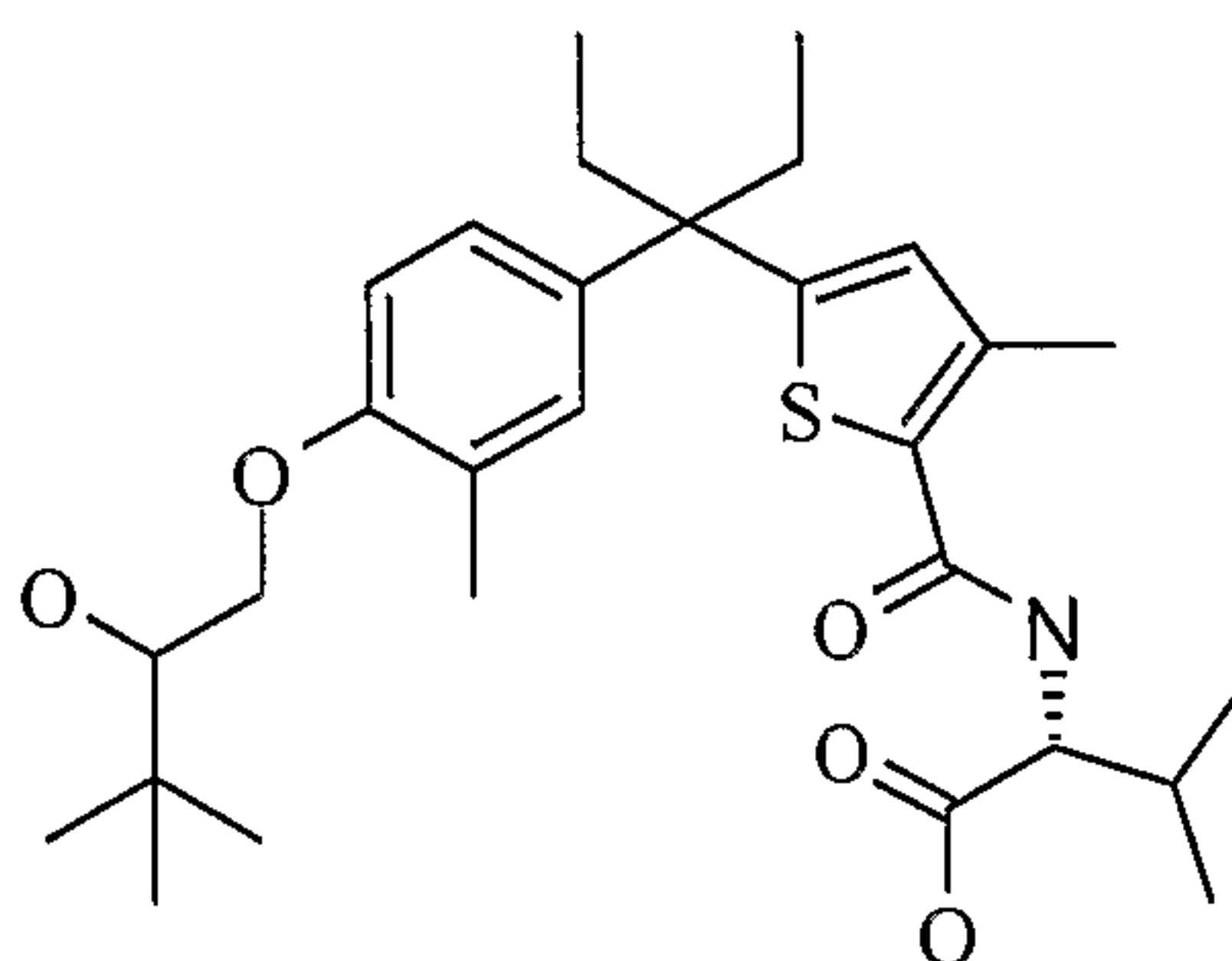
5 Example 85, Epimer 2

rt = 10.6 m

¹H NMR and LC/MS: identical to (*D*-enantiomer-1), example 33.

Example 86:

- 10 Preparation of epimer 1 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-butyric acid



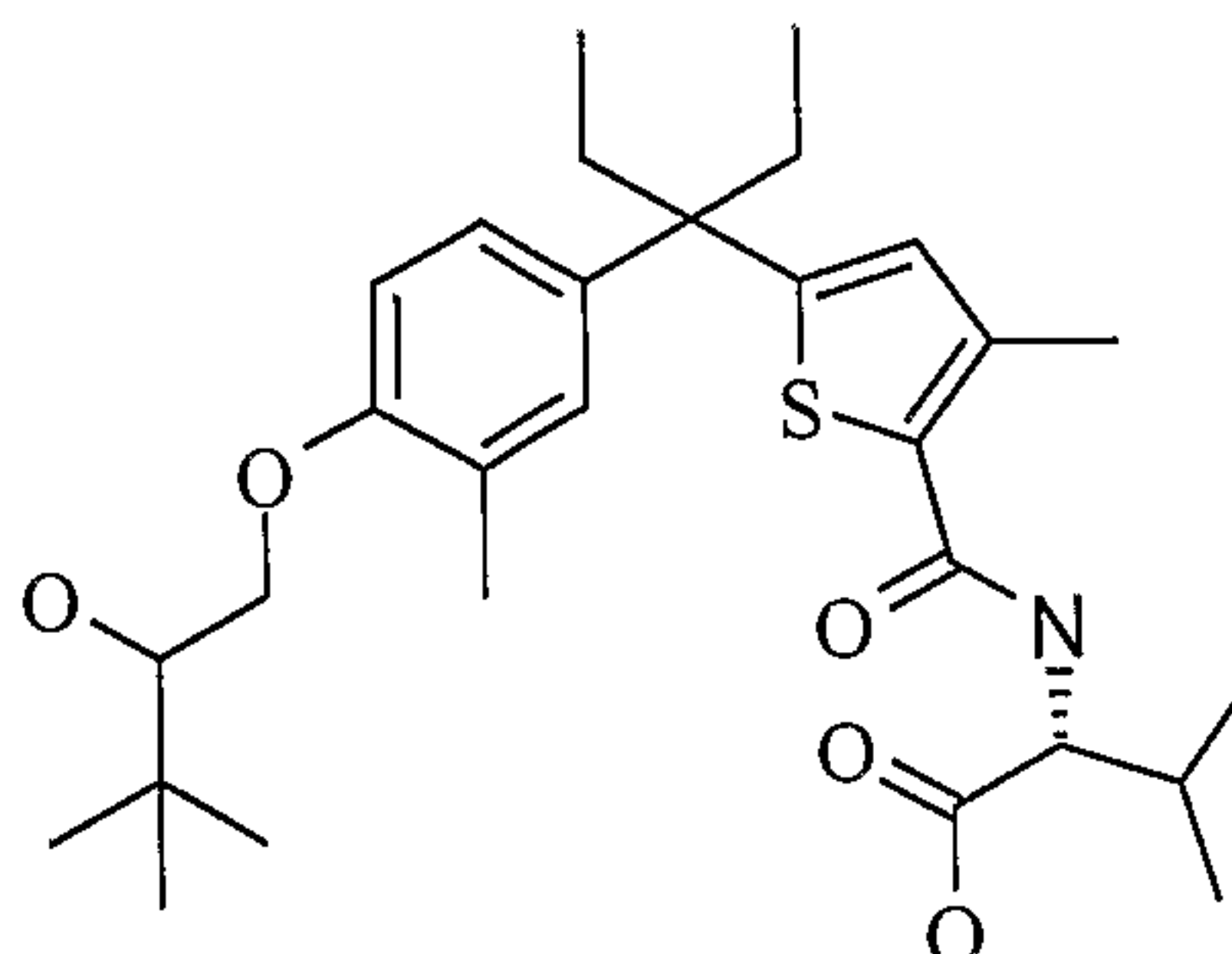
D-Epimer 1

- 15 Using the procedure analogous to Example 53, epimer 1 of *D*-2-[(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester (Example 84) (0.28g, 0.53 mmol) gives the title compound (0.22 g, 0.43 mmol, 79%). ¹H NMR (CDCl₃), δ 0.71 (t, $J = 7.4$ Hz, 6H), 1.00 (d, $J = 6.6$ Hz, 3H), 1.03 (s, 9H), 1.04 (d, $J = 6.6$ Hz, 3H), 2.04-2.14 (m, 4H), 2.21 (s, 3H), 2.25-2.35 (m, 1H), 2.47 (s, 3H), 3.72 (dd, $J = 8.4, 2.6$ Hz, 1H), 3.88 (t, $J = 9.2$ Hz, 1H), 4.10 (dd, $J = 9.2, 2.6$ Hz, 1H), 4.69 (dd, $J = 8.0, 4.4$ Hz, 1 H), 6.19 (d, $J = 8.0$ Hz), 6.60 (s, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 7.00 (dd, $J = 2.2$ Hz, 1H), 7.04 (dd, $J = 8.4, 2.6$ Hz, 1H). LC/MS (m/z): calcd. for $C_{29}H_{44}NO_5S$ ($M+H$)⁺: 518.7; found: 518.2.
- 20

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Example 87

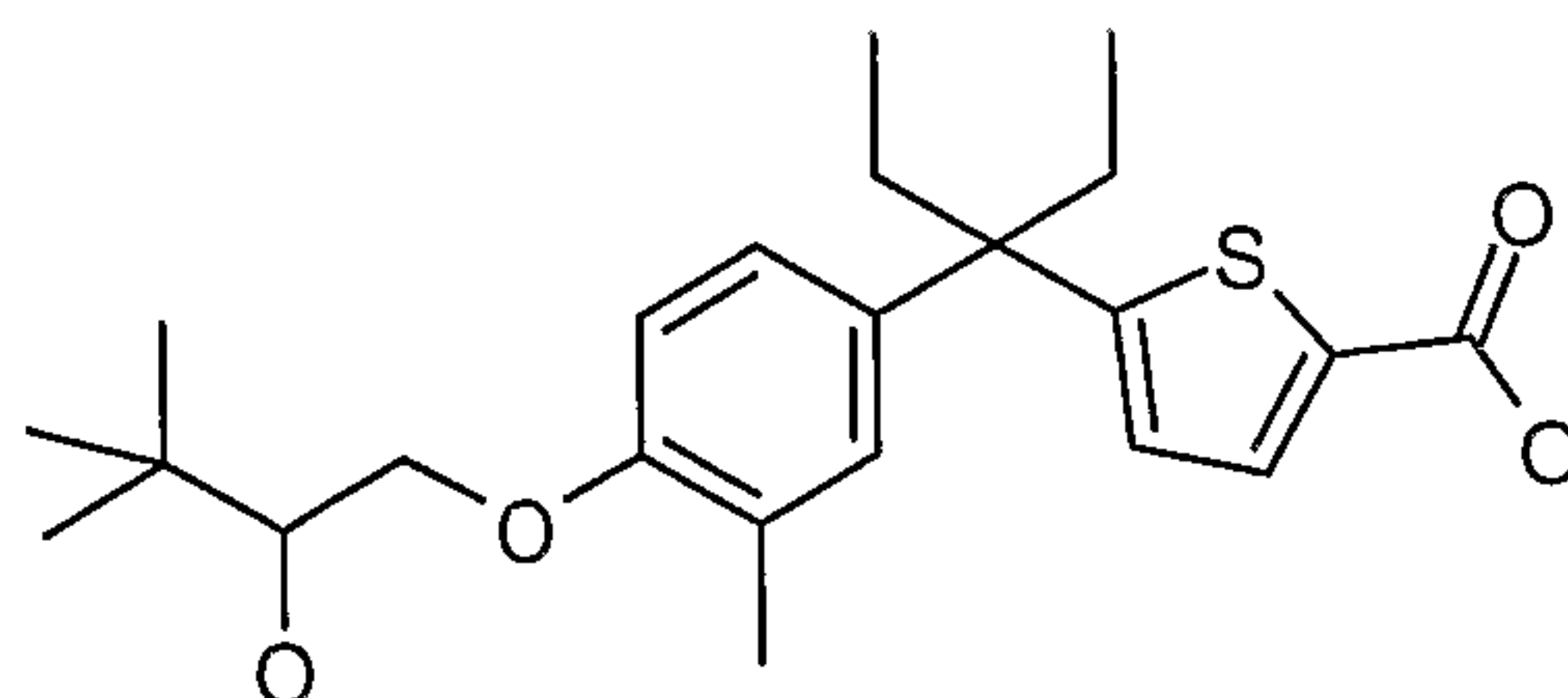
Preparation of epimer 2 of *D*-2-[(5-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-3-methyl-butyric acid.

*D*-Epimer 2

Using a procedure analogous to Example 53, epimer 2 of *D*-2-[(5-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-3-methyl-thiophene-2-carbonyl)-amino]-2-methyl-propionic acid methyl ester (Example 85) (0.33g, 0.62 mmol) gives the title compound (0.23 g, 0.44 mmol, 79%). ¹H NMR and LC/MS: equivalent to (*D*-epimer-1), Example 86.

Example 88

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxythiophen-2-yl]pentane.



Using a procedure analogous to Example 3, 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (0.23 g,

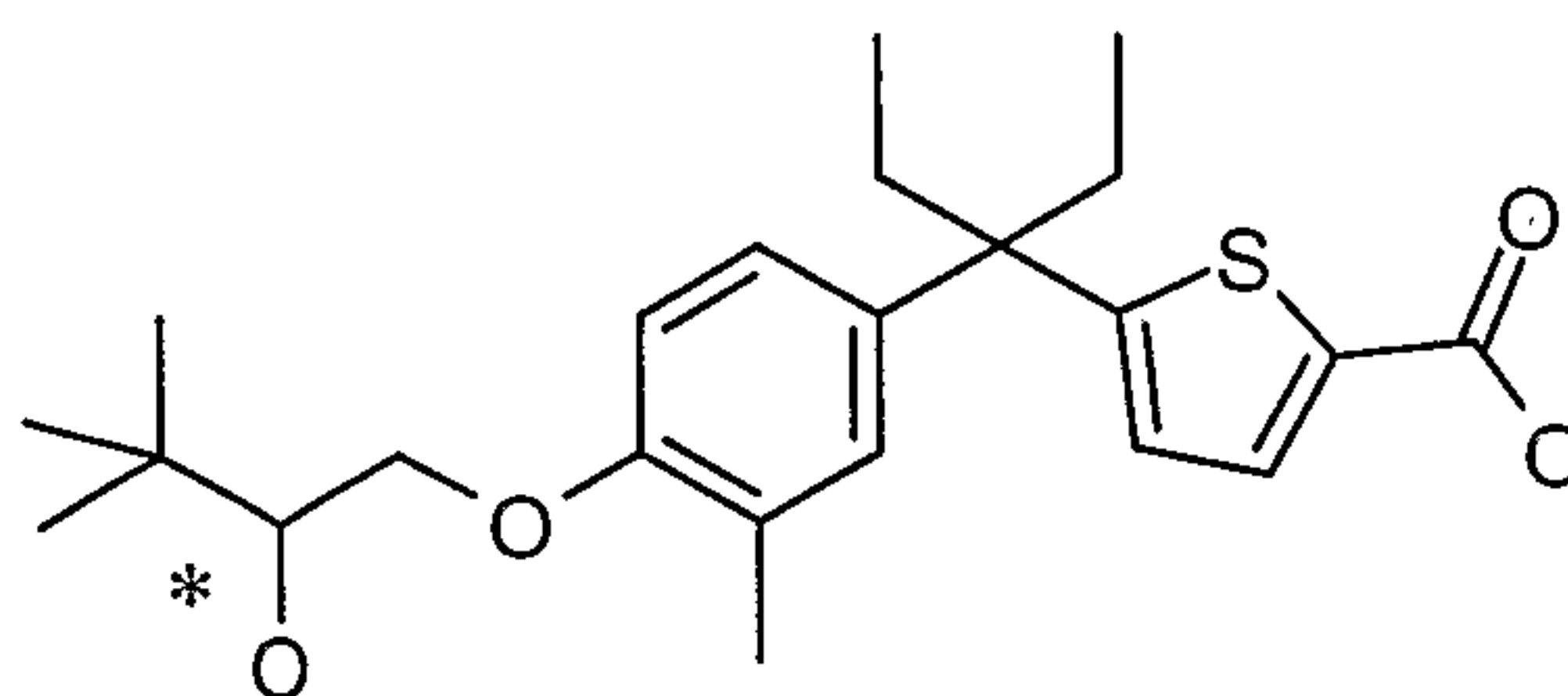
-228-

0.55 mmol) and 5N sodium hydroxide (220 ul, 1.1 mmol) give the title compound (0.18 g, 81%).

H-NMR (ppm, CDCl₃): 7.68 (1H, d, 4.0 Hz), 7.03 (1H, d, 8.2 Hz), 6.98 (1H, s), 6.79 (1H, d, 4.0 Hz), 6.72 (1H, d, 8.2 Hz), 4.09 (1H, d, 9.3 Hz), 3.85 (1H, t, 9.3 Hz), 3.73 (1H, d, 9.3 Hz), 2.19 (3H, s), 2.13 (4H, q, 7.0 Hz), 1.02 (9H, s), 0.71 (6H, t, 7.0 Hz).
ES/MS: 403.2 (M+1) 422.2 (M + NH₄).

Example 89 and 90

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



A mixture of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane (166 mg) is chromatographed with a ChiralPak AD column (10% IPA/hept to 15% IPA/hept) to give enantiomer 1 (63 mg), Example 89 and enantiomer 2 (67 mg), Example 90.

Enantiomer 1, Example 89

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate); rt = 4.9 m; 225 nm.

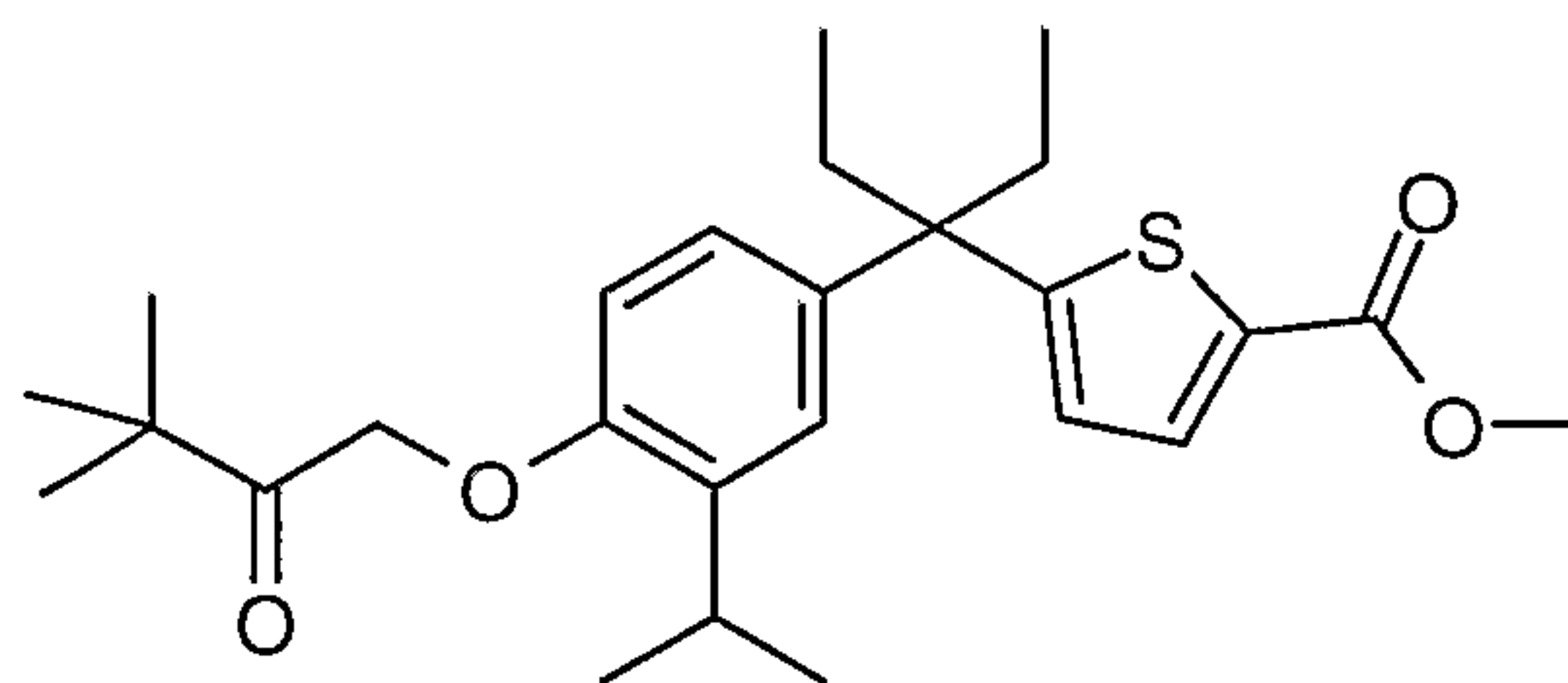
Enantiomer 2, Example 90

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate); rt = 6.9 m; 225 nm.

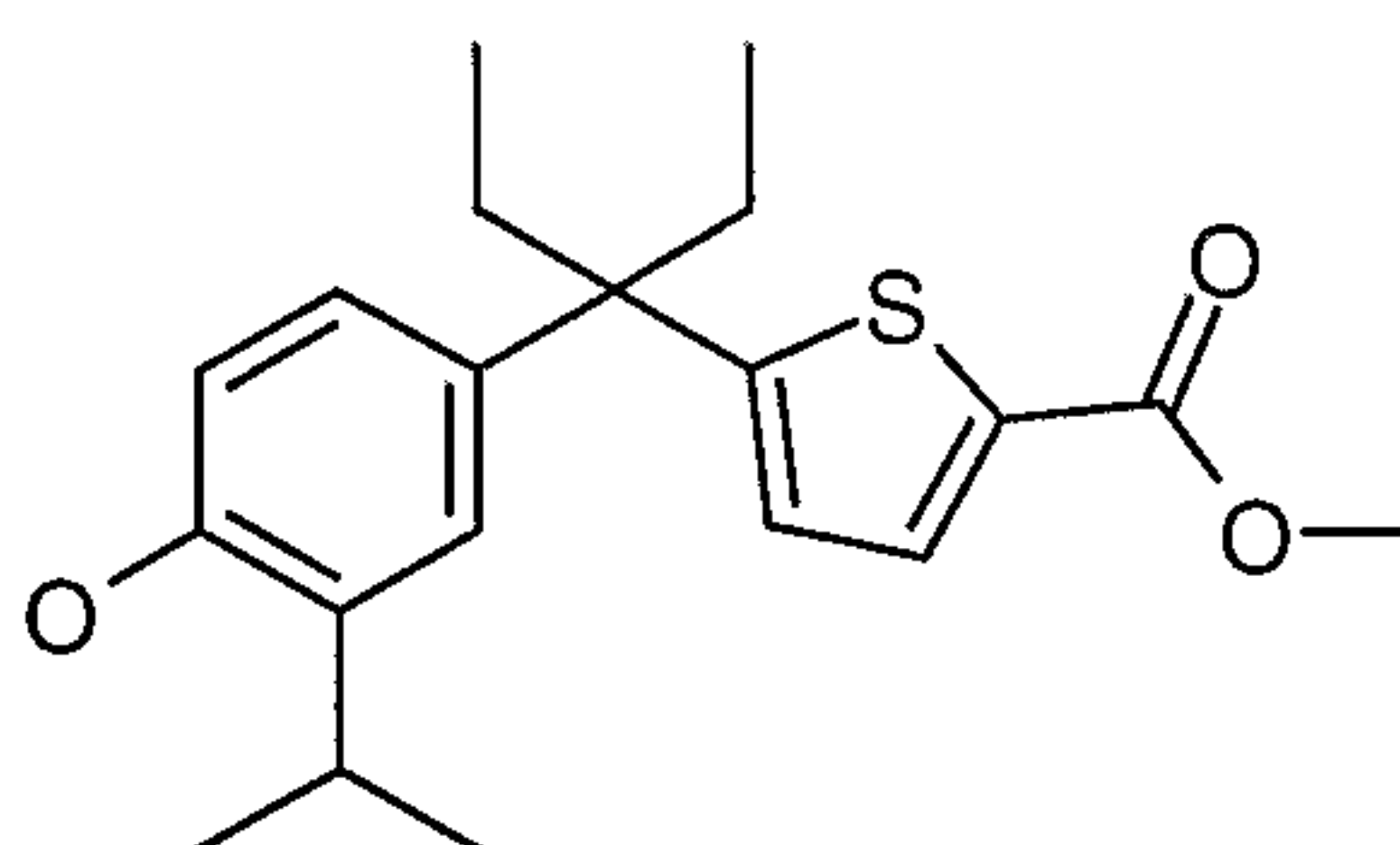
Example 91

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-(1-methylethyl)phenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.

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A. 3'-[4-(Hydroxy)-3-(1-methylethyl)phenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane.



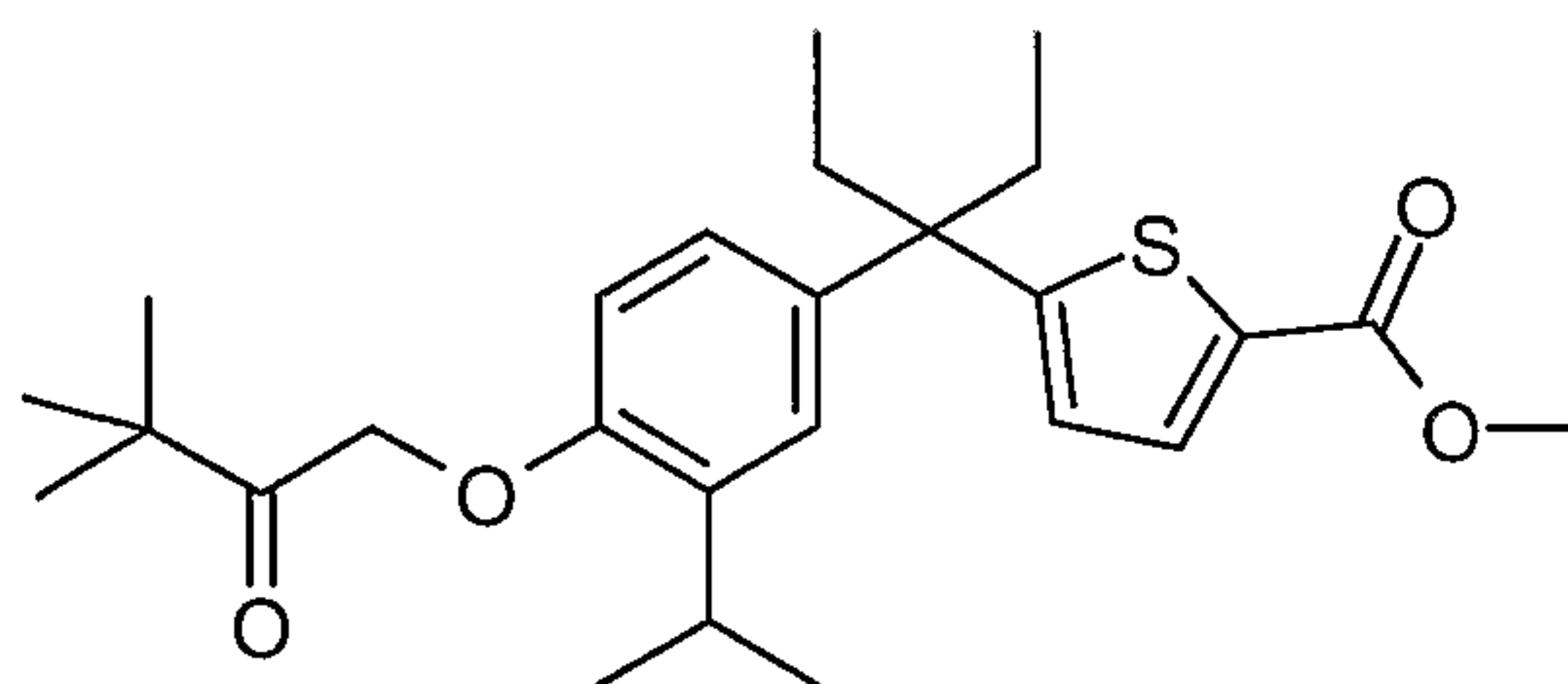
5

Methyl, 5-(E/Z-2-penten-3-yl)thiophene-2-carboxylate (Example 5C) (0.21 g, 1.0 mmol), o-isopropylphenol (1.09 g, 4.0 mmol), and BF₃-etherate (58 mg, 0.2 mmol) are reacted and purified as described in Example 5D to give the title compound (0.28 g, 81%).

10 H-NMR (ppm, CDCl₃): 7.62 (1H, d, 4.0 Hz), 7.05 (1H, s), 6.90 (1H, d, 8.8 Hz), 6.78 (1H, d, 4.0 Hz), 6.63 (1H, d, 8.8 Hz), 4.58 (1H, s), 3.83 (3H, s), 3.15 (1H, m), 2.11 (4H, q, 7.2 Hz), 1.21 (6H, d, 6.8 Hz), 0.71 (6H, t, 7.4 Hz).

ES/MS: 347.2 (M+1).

15 B. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-(1-methylethyl)phenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.



20 3'-[4-(Hydroxy)-3-(1-methylethyl)phenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane (0.18 g, 0.52 mmol), sodium hydride 60% (23 mg, 0.56 mmol), and 1-chloropinacolone (71 mg, 0.52 mmol) with a catalytic amount of

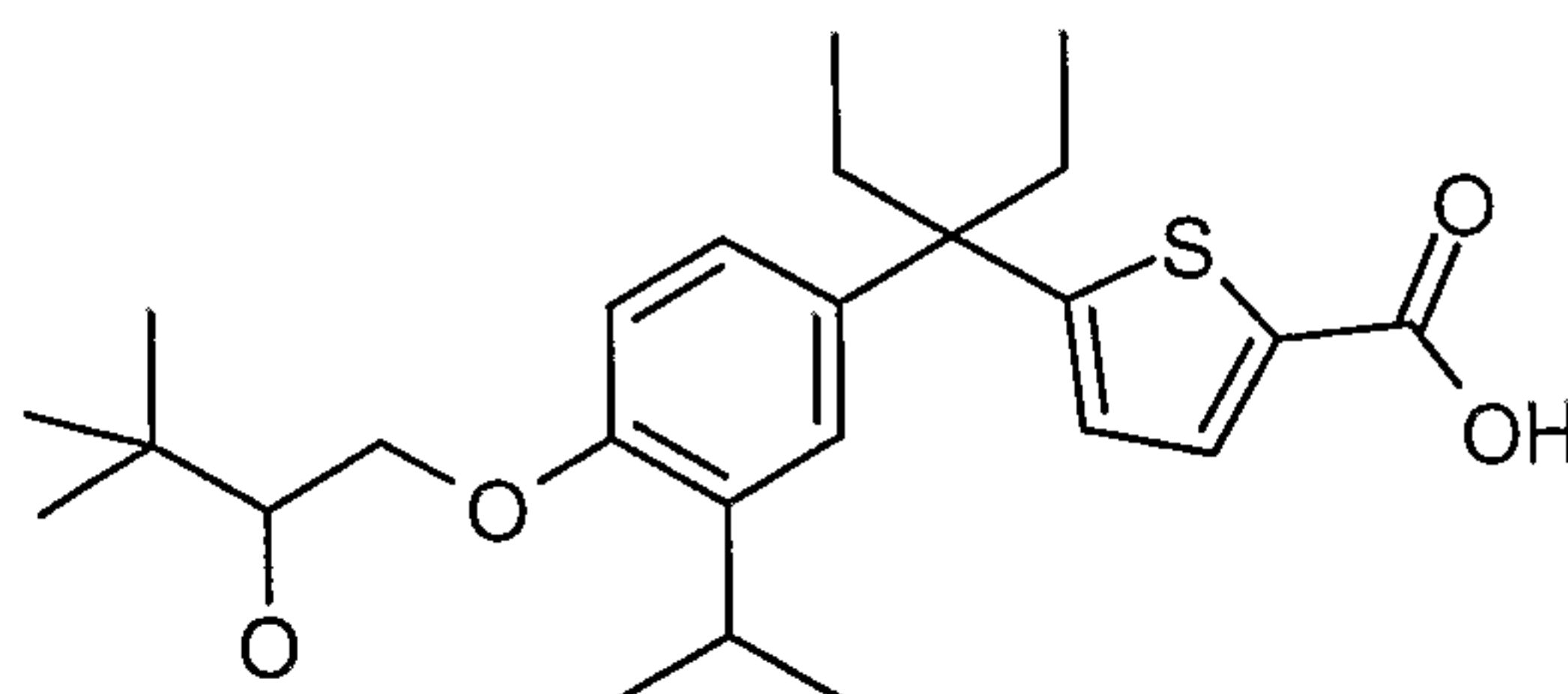
-230-

potassium iodide (7 mg, 0.04 mmol) are reacted and purified as described in Example 5E to give the title compound (0.13 g, 56%).

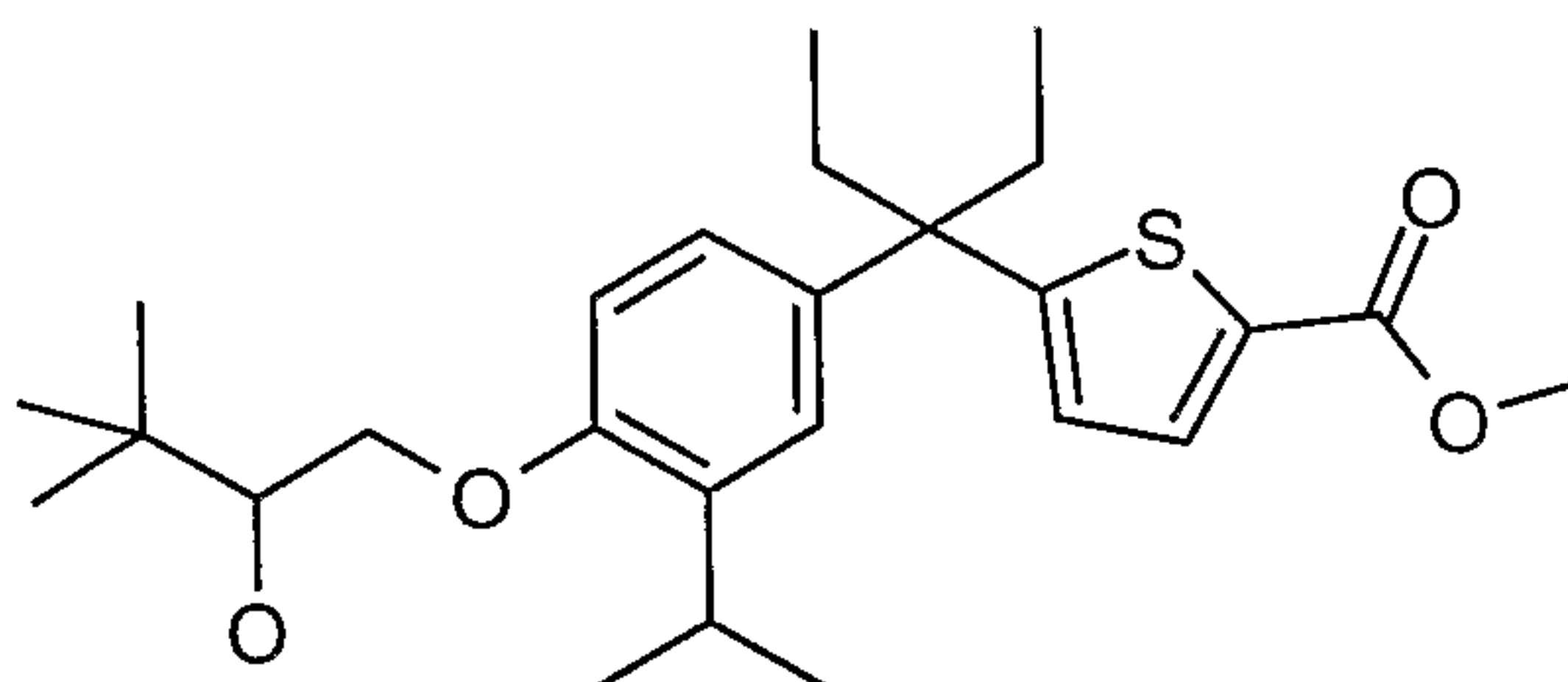
H-NMR (ppm, CDCl₃): 7.61 (1H, d, 4.0 Hz), 7.08 (1H, s), 6.93 (1H, d, 6.0 Hz), 6.77 (1H, d, 4.0 Hz), 6.52 (1H, d, 6.0 Hz), 4.84 (2H, s), 3.83 (3H, s), 3.38 (1H, m), 2.11 (4H, q, 7.2 Hz), 1.26 (9H, s), 1.19 (6H, d, 7.2 Hz), 0.71 (6H, t, 7.4 Hz).
ES/MS: 445.2 (M+H) 462.2 (M + NH₄).

Example 92

3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-(1-methylethyl)phenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



A. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-(1-methylethyl)phenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.

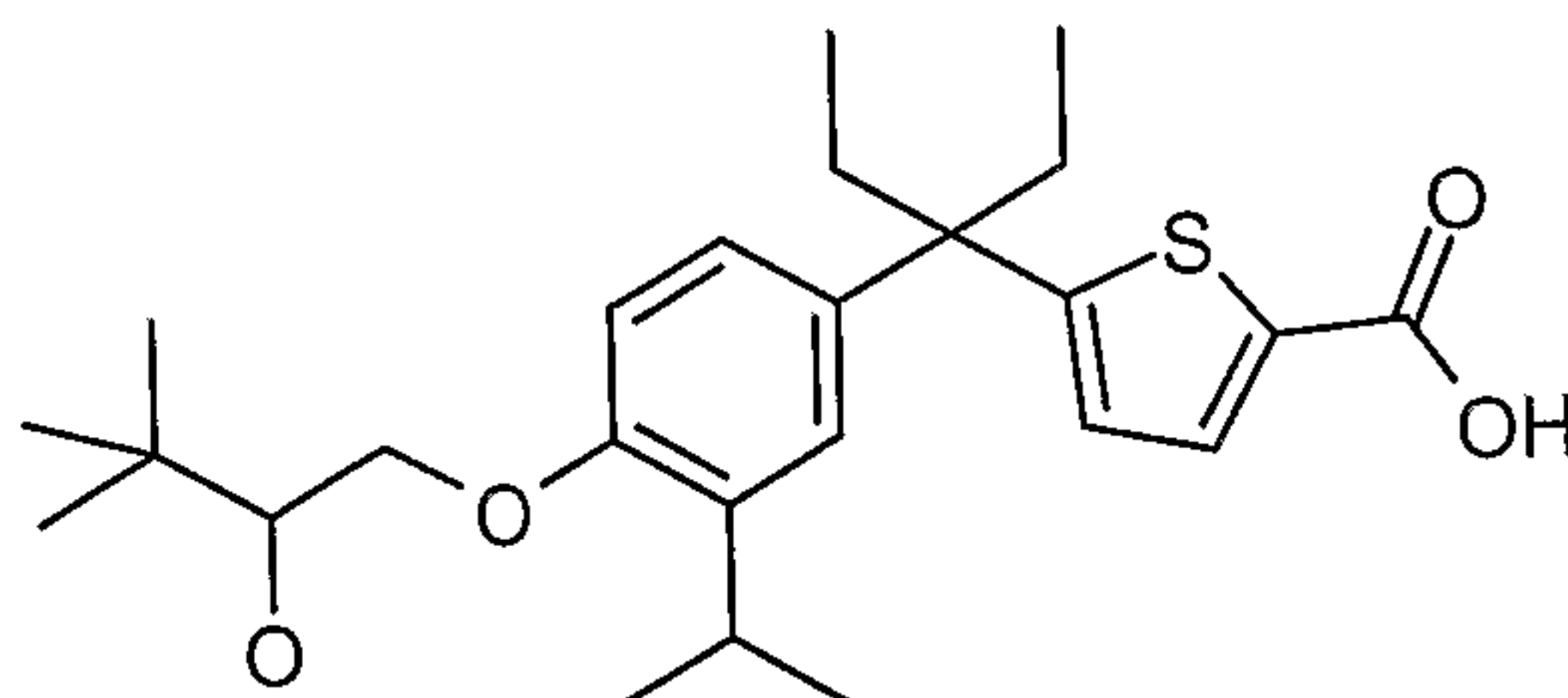


3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-(1-methylethyl)phenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (16 mg 0.26mmol) and sodium borohydride (9.8 mg, 0.26 mmol) are reacted in methanol and purified as described in Example 5F to give the title compound (93 mg, 80%).

H-NMR (ppm, CDCl₃): 7.63 (1H, d, 4.0 Hz), 7.08 (1H, s), 6.99 (1H, d, 9.0 Hz), 6.78 (1H, d, 4.0 Hz), 6.74 (1H, d, 9.0 Hz), 4.09 (1H, d, 8.2 Hz), 3.85 (1H, t, 8.2 Hz), 3.83 (3H, s), 3.72 (1H, d, 8.2 Hz), 3.25 (1H, m), 2.40 (1H, s), 2.12 (4H, q, 7.2 Hz), 1.17 (6H, d, 6.8 Hz), 1.02 (9H, s), 0.71 (6H, t, 7.2 Hz).
ES/MS: 447.2 (M+1).

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B. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-(1-methylethyl)phenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



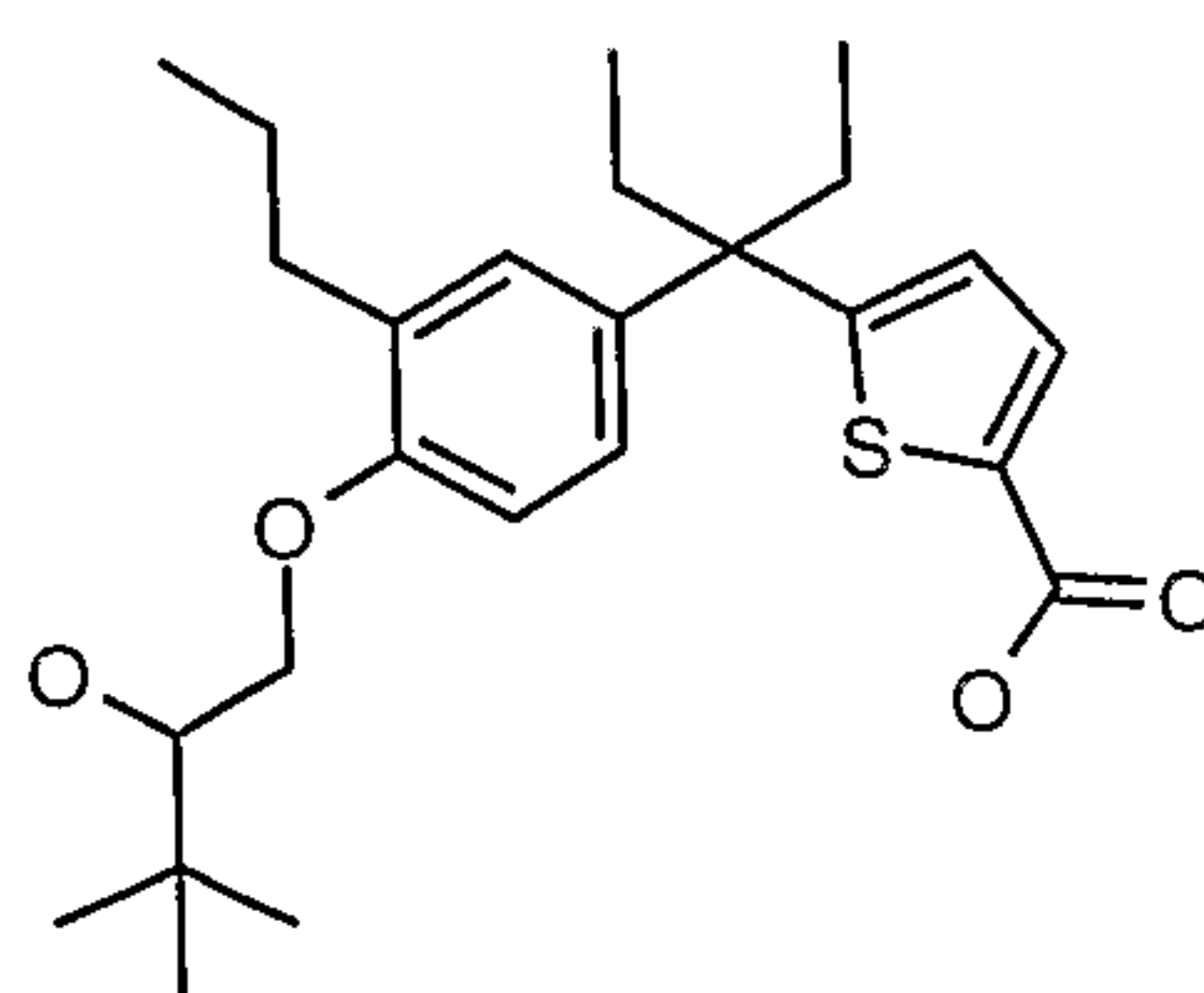
Using a procedure analogous to Example 3, 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-(1-methylethyl)phenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (93 mg, 0.21 mmol) and 5N sodium hydroxide (1 ml, 5 mmol) are reacted and purified to give the title compound (66 mg, 73%).

H-NMR (ppm, CDCl₃): 7.69 (1H, d, 4.0 Hz), 7.08 (1H, s), 6.99 (1H, d, 6.0 Hz), 6.80 (1H, d, 4.0 Hz), 6.74 (1H, d, 6.0 Hz), 4.08 (1H, d, 8.0 Hz), 3.84 (1H, t, 8.0 Hz), 3.73 (1H, d, 8.0 Hz), 3.25 (1H, m), 2.13 (4H, q, 6.8 Hz), 1.17 (6H, d, 6.0 Hz), 1.02 (9H, s), 0.72 (6H, t, 7.0 Hz).

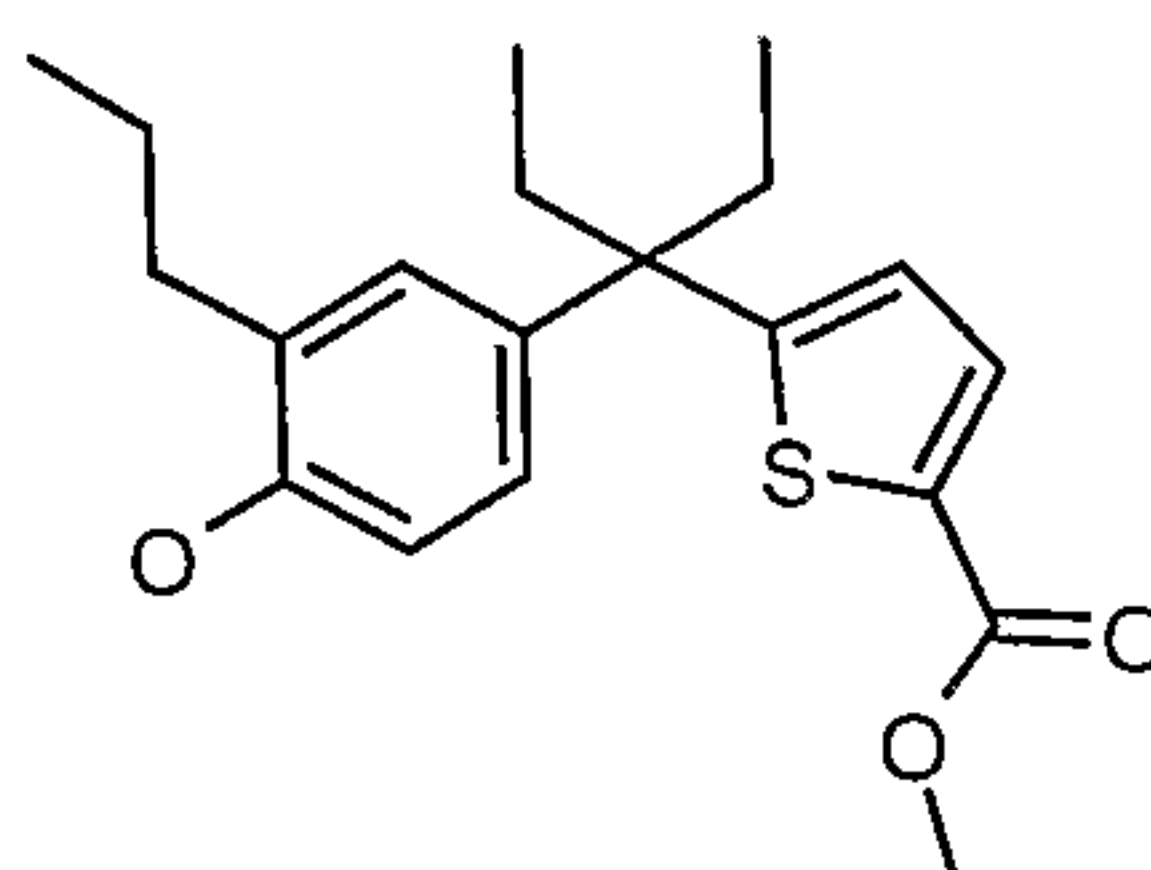
ES/MS: 431.2 (M-1) 450.2 (M + NH₄).

Example 93

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



A. 3'-(4-hydroxy-3-n-propylphenyl)-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.

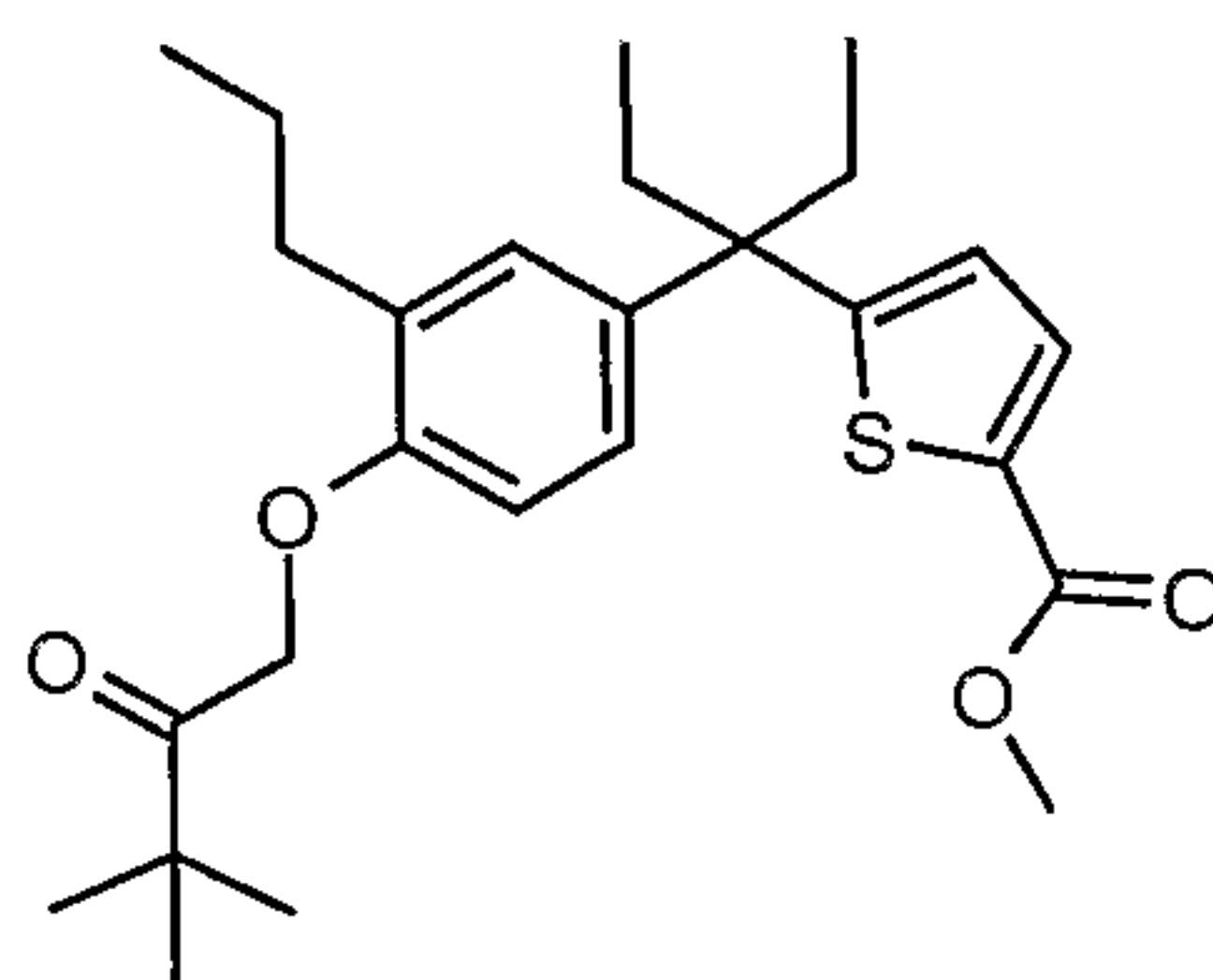


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To a mixture of o-propylphenol (1.09 g, 8.0 mol) and methyl, 5-(z/e-2-penten-3-yl)thiophene-2-carboxylate (0.21 g, 1.0 mmol) in methylene chloride (1 ml) is added BF₃-etherate (56 mg, 0.2 mmol) under nitrogen and stirred for 16 h. The mixture is partitioned between satd NaHCO₃ and diethylether. The organic layer is washed with water, Na₂SO₄ dried, and concentrated. The excess phenol is removed from the residue by vacuum distillation at 70 °C/0.04 mm. The residue is chromatographed (4% EtOAc/hex) to give the title compound as an oil (0.27 g, 78%).

NMR (CDCl₃): 7.62 (d, 1H, J = 3.6 Hz); 6.96 (s, 1H); 6.94 (d, 1H, J = 7.3 Hz); 6.77 (d, 1H, J = 3.6 Hz); 6.66 (d, 1H, J = 8.0 Hz); 4.61 (s, 1H); 3.83 (s, 3H); 2.55 (t, 2H, J = 7.3 Hz); 2.11 (q, 4H, J = 7.2 Hz); 1.60 (m, 2H); 0.93 (t, 3H, J = 7.3 Hz); 0.71 (t, 6H, J = 7.2 Hz). FAB/MS: 347 M+1.

B. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-methoxycarbonylthiophen-2-yl]pentane.



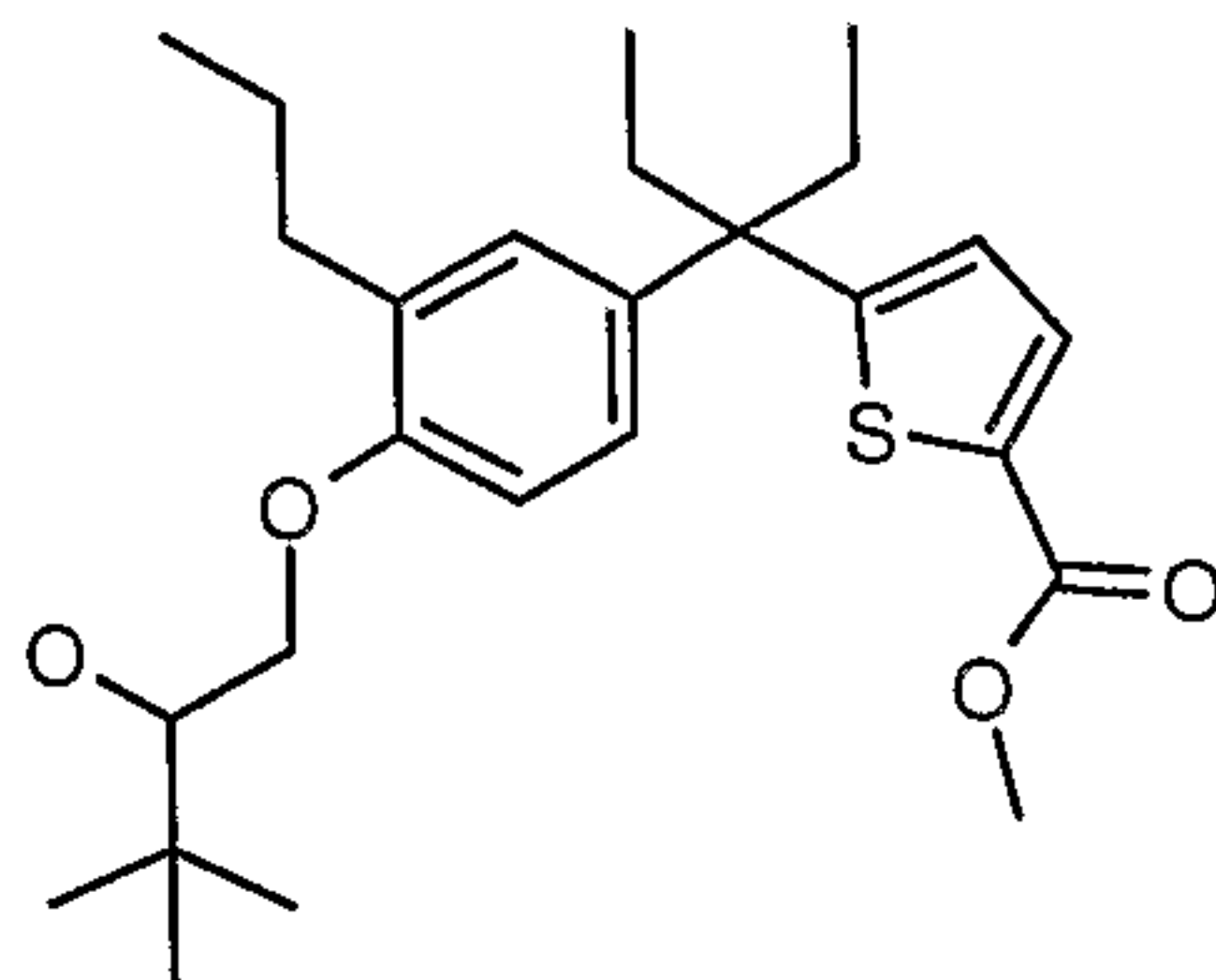
Using a procedure analogous to Example 91B, 3'-(4-hydroxy-3-n-propylphenyl)-3'-[5-methoxycarbonylthiophen-2-yl]pentane (0.27 g, 0.78 mmol) give the title compound as an oil (0.21 g, 60%).

NMR (CDCl₃): 7.61 (d, 1H, J = 4.4 Hz); 6.97 (s, 1H); 6.95 (d, 1H, J = 7.3 Hz); 6.77 (d, 1H, J = 4.4 Hz); 6.50 (d, 1H, J = 7.3 Hz); 4.83 (s, 2H); 3.83 (s, 3H); 2.61 (t, 2H, J = 7.3 Hz); 2.10 (q, 4H, J = 7.3 Hz); 1.59 (m, 2H); 1.26 (s, 9H); 0.90 (t, 3H, 7.3 Hz); 0.70 (t, 6H, 7.3 Hz).

FAB-MS: 444.3 molecular ion.

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C. 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-methoxycarbonyl-



thiophen-2-yl]pentane.

To a mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (0.199 g, 0.45 mmol) and MeOH (5 ml) is added NaBH₄ (17 mg, 0.45 mmol) in portions. After stirring for 4.5 h at room temperature, the reaction is concentrated and partitioned between satd NaHCO₃ and diethylether. The organic layer is washed with water, Na₂SO₄ dried, and concentrated to give the title compound as an oil (0.18 g, 90%).

NMR(CDCl₃): 7.62 (d, 1H, J = 3.6 Hz); 7.02 (1H, d, J = 7.5 Hz); 6.98 (s, 1H); 6.78 (d, 1H, 3.6 Hz); 6.73 (d, 1H, 7.5 Hz); 4.08 (1H, d, J = 9.0); 3.85 (t, 1H, J = 9.0); 3.83 (s, 3H); 3.71 (d, 1H, J = 9.0 Hz); 2.55 (t, 2H, 7.5 Hz); 2.40 (s, 1H); 2.12 (q, 4H, J = 7.6 Hz); 1.55 (m, 2H); 1.02 (s, 9H); 0.90 (t, 3H, J = 7.6 Hz); 0.71 (t, 6H, J = 7.2 Hz). LC/MS: 447.2 M+1.

D. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.

A mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (0.18 g, 0.4 mmol), methanol (3 ml) and 5N NaOH (161 uL, 0.8 mmol) is heated to 50°C for 16 h. The reaction mixture is concentrated and the residue dissolved in water (4 mL). The solution is added conc. HCl, filtered with water wash, and air dried to give the title compound (0.16 g, 92%).

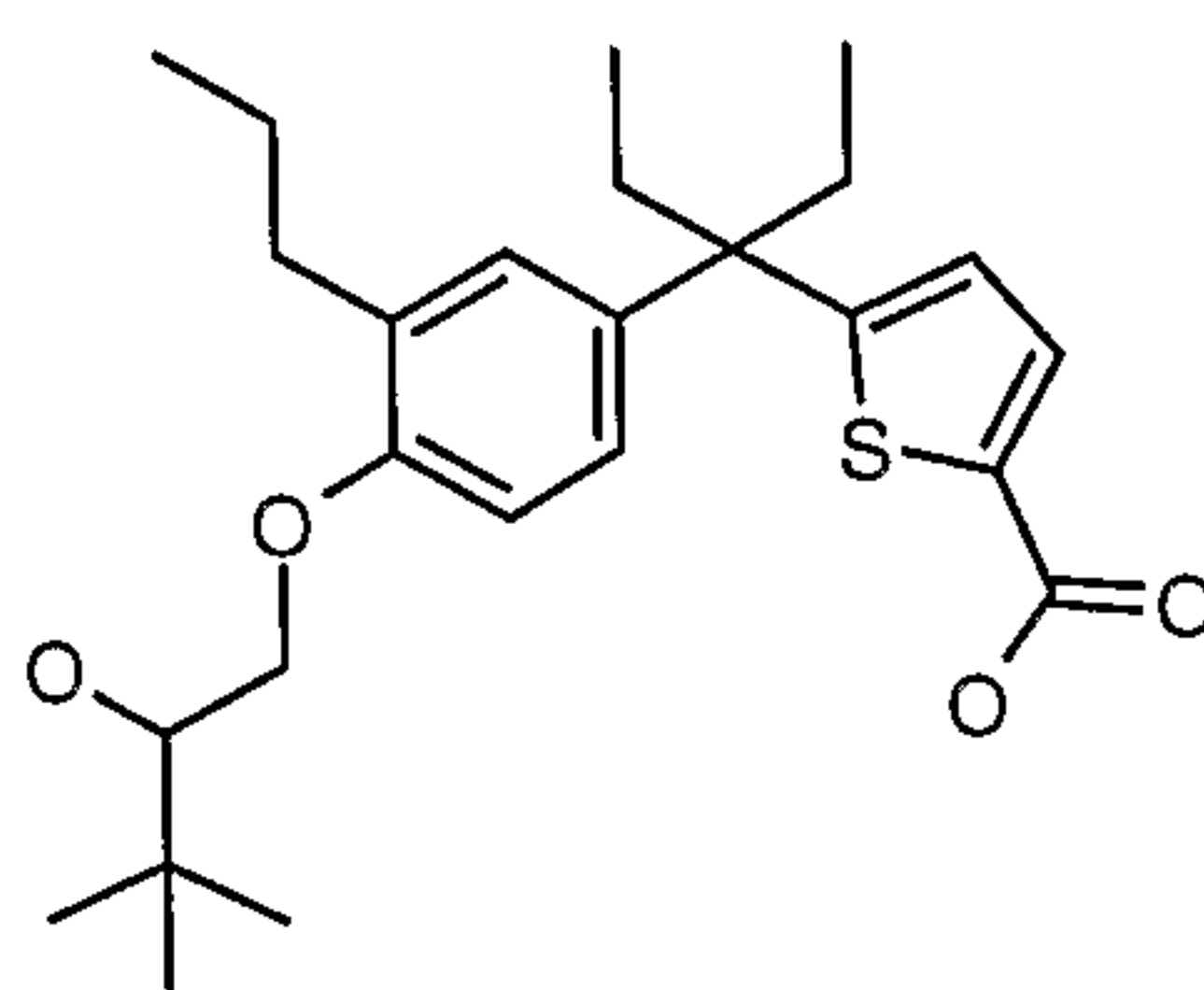
NMR(CDCl₃): 7.69 (d, 1H, J = 4.0 Hz); 7.02 (d, 1H, J = 7.5 Hz); 6.98 (s, 1H); 6.79 (d, 1H, J = 4.0 Hz); 6.75 (d, 1H, J = 7.5 Hz); 5.29 (s, 1H); 4.08 (d, 1H, J = 9.0); 3.85 (t, 1H, J = 9.0 Hz); 3.70 (d, 1H, J = 9.0 Hz); 2.55 (t, 2H, J = 7.5 Hz); 2.13 (q, 4H, J = 7.2 Hz); 1.55 (m, 1H); 1.02 (s, 9H); 0.90 (t, 3H, H = 7.4 Hz); 0.72 (t, 6H, J = 7.4 Hz).

LC/MS: 413.2 M-1.

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Example 94 and 95

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



5

A mixture of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-n-propylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane (200 mg) is chromatographed on a ChiralPak AD column with IPA/heptane. Enantiomer 1 is further chromatographed on 4g of Silica Gel from 0% EtOAc/Hex to 50% EtOAc/Hex over 38 min at 12 ml/min to give pure enantiomer 1 (66 mg), Example 94. Enantiomer 2 from ChiralPak is further chromatographed on 4g of Silica Gel from 0% EtOAc/Hex to 50% EtOAc/Hex over 38 min at 12 ml/min. to give pure enantiomer 2 (66 mg), Example 95.

10

Enantiomer 1, Example 94

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/min (flow rate);

15

rt = 6.22 min; 225 nm.

Enantiomer 2, Example 95

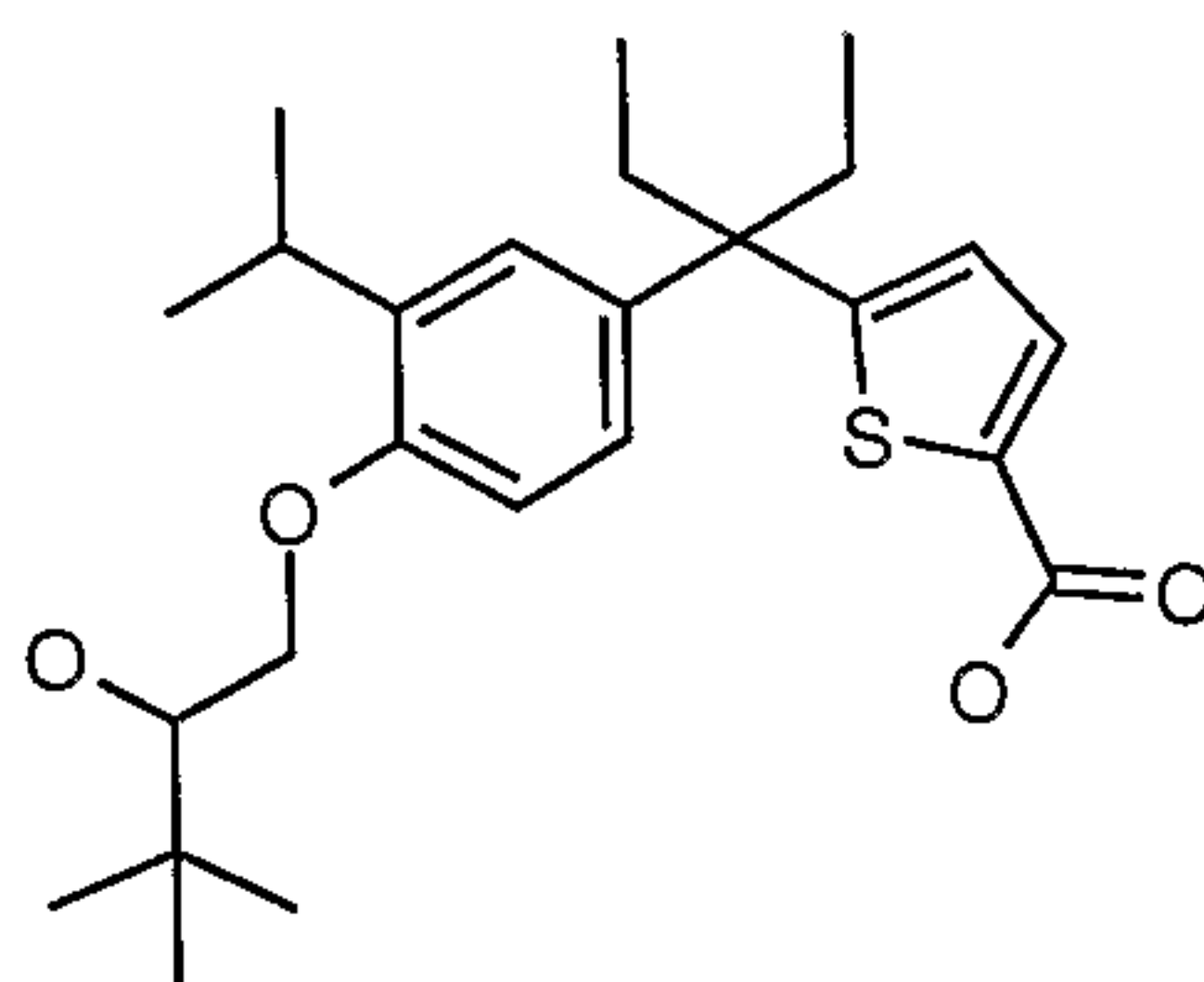
HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/min (flow rate); rt = 9.0 min; 225 nm.

20

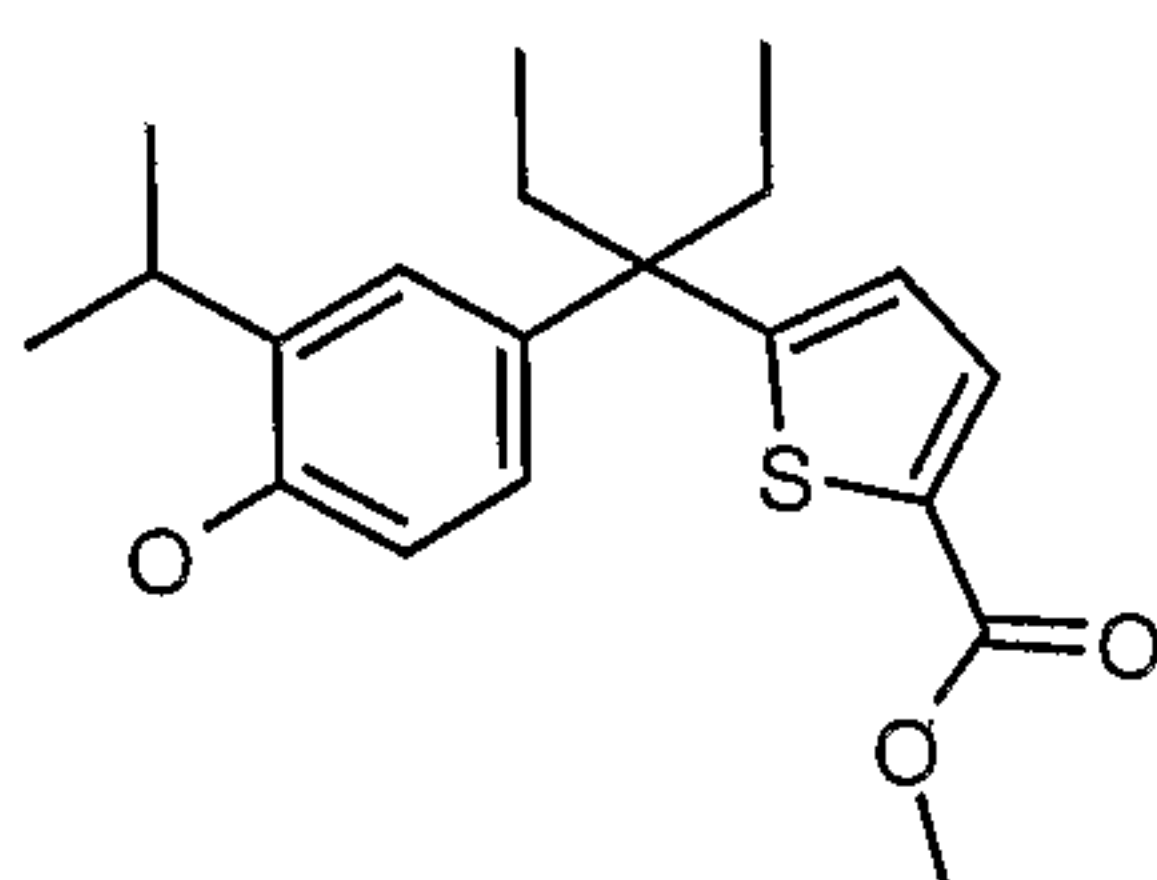
Example 96

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-i-propylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.

-235-



A. 3'-(4-hydroxy-3-i-propylphenyl)-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.

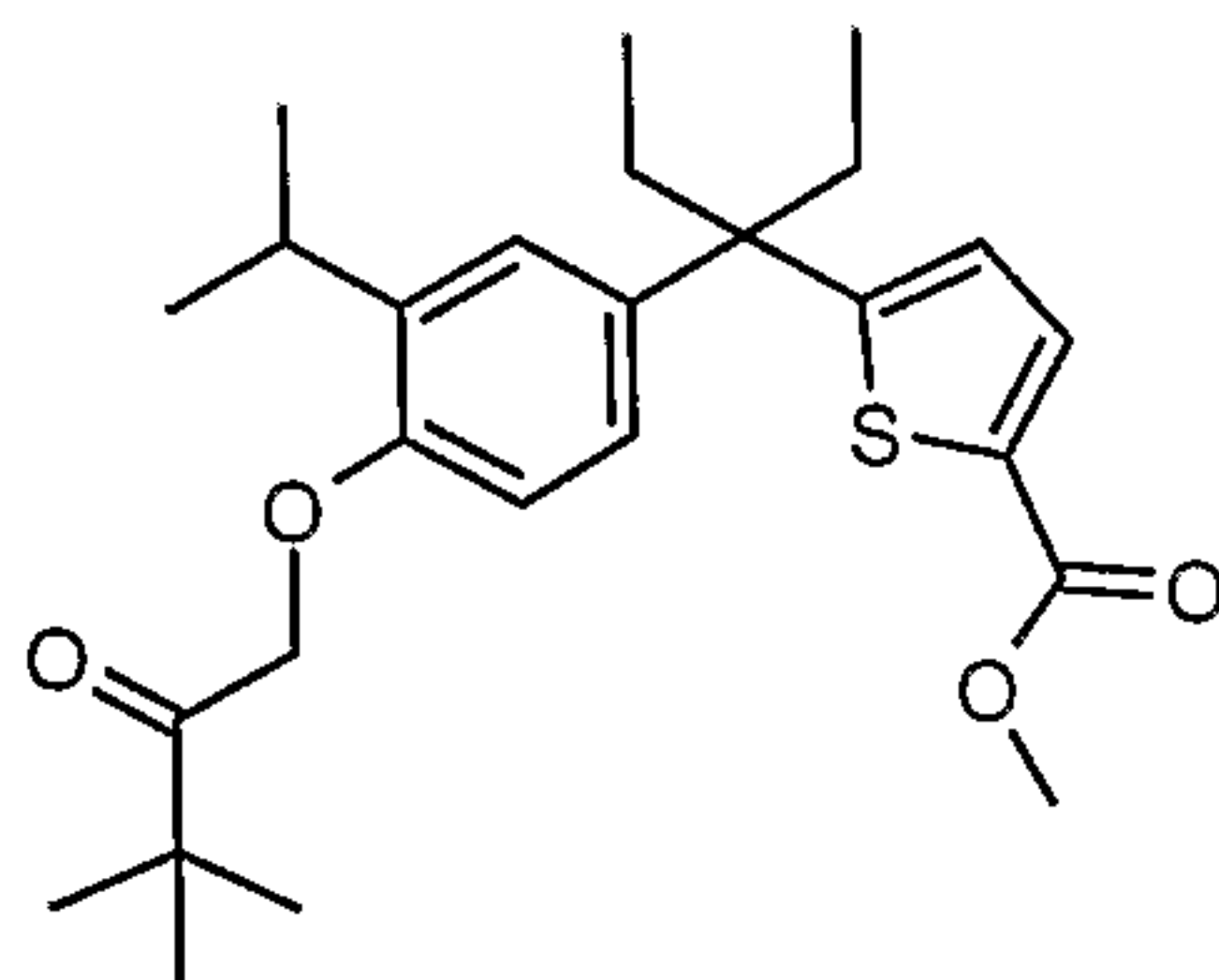


Using a procedure analogous to Example 93A, o-isopropylphenol (1.09 g, 8 mol) and methyl, 5-(E/Z-2-penten-3-yl)thiophene-2-carboxylate (0.21 g, 1.0 mol) give the title compound as an oil (0.28 g, 81%).

NMR (CDCl₃): 7.62 (d, 1H, J = 4.0 Hz); 7.05 (s, 1H); 6.90 (d, 1H, J = 8.4 Hz); 6.78 (d, 1H, J = 4.0 Hz); 6.63 (d, 1H, J = 8.8 Hz); 4.58 (s, 1H); 3.83 (s, 3H); 3.15 (m, 1H); 2.11 (q, 4H, J = 7.2 Hz); 1.21 (d, 6H, J = 6.1 Hz); 0.71 (t, 6H, J = 7.4 Hz).

LC/MS: 347.2 M+1.

B. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-isopropylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.



Using a procedure analogous to Example 91B, 3'-(4-hydroxy-3-isopropylphenyl)-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (0.28 g, 0.81 mmol) gives the title compound as an oil (0.13 g, 56%).

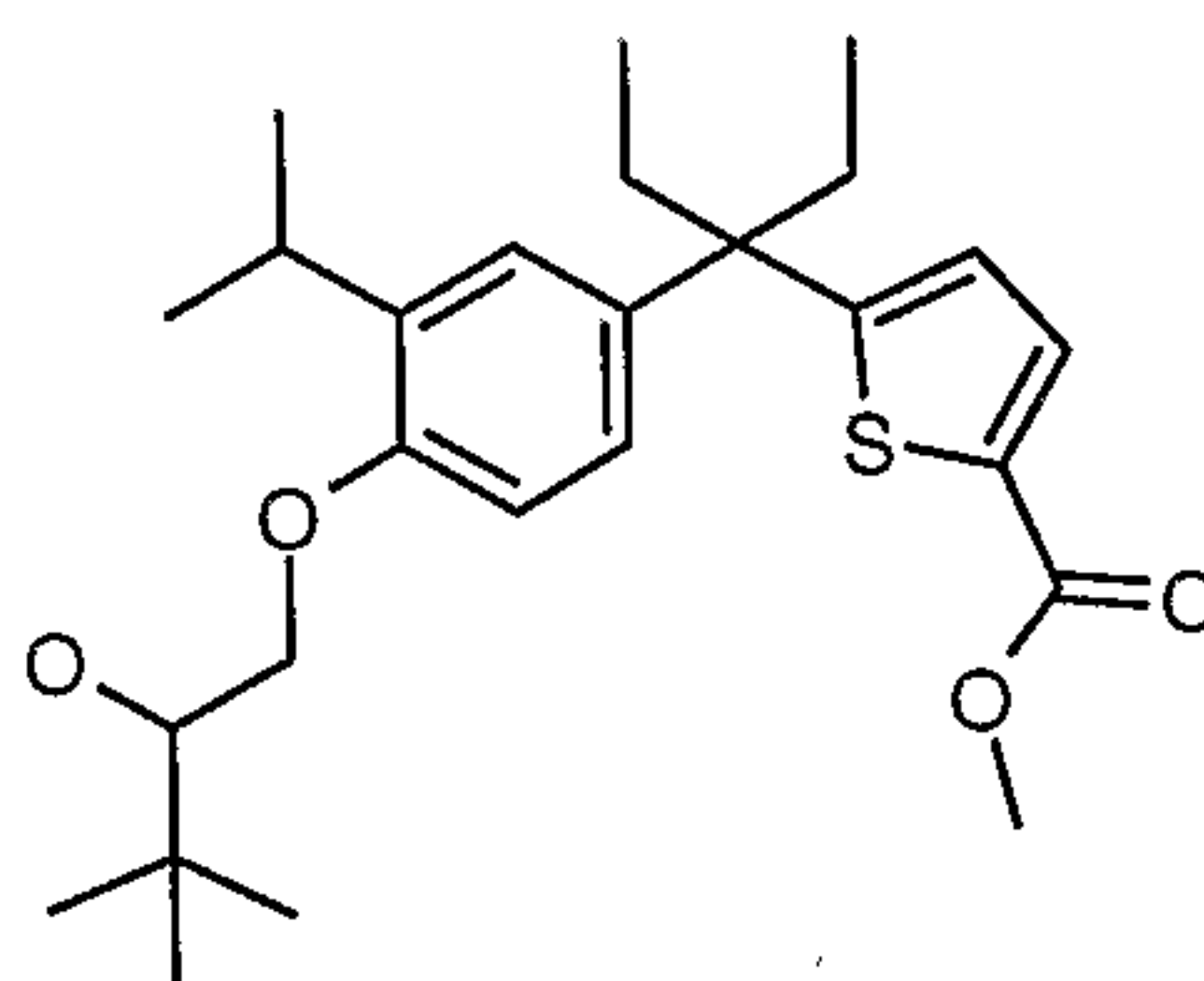
NMR (CDCl₃): 7.61 (d, 1H, J = 4.4 Hz); 7.09 (s, 1H); 6.94 (d, 1H, J = 8.4 Hz); 6.77 (d, 1H, J = 4.4 Hz); 6.53 (d, 1H, J = 8.4 Hz); 4.84 (s, 2H); 3.83 (s, 3H); 3.38 (m, 2H); 2.11 (q, 4H, J = 7.2 Hz); 1.26 (s, 9H); 1.19 (d, 6H, J = 7.2 Hz); 0.70 (t, 6H, 7.2 Hz).

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FAB-MS: 444.3 molecular ion.

LC/MS: 445.2 M+1 and 462.2 M+NH₄.

C. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-i-propylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.



Using a procedure analogous to Example 2, 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-i-propylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane gives the title compound as an oil (0.09 g, 80%).

10 NMR(CDCl₃): 7.62 (d, 1H, J = 3.6 Hz); 7.08 (s, 1H); 6.99 (1H, d, J = 8.8 Hz); 6.78 (d, 1H, 3.6 Hz); 6.73 (d, 1H, 8.8 Hz); 4.08 (1H, d, J = 8.8); 3.85 (t, 1H, J = 8.8); 3.83 (s, 3H); 3.71 (d, 1H, J = 8.8 Hz); 3.28 (m, 1H); 2.12 (q, 4H, J = 7.2 Hz); 1.17 (d, 6H, J = 6.8 Hz); 1.02 (s, 9H); 0.71 (t, 6H, J = 7.2 Hz).

LC/MS: 447.2 M+1.

15

D. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-i-propylphenyl]-3'-[5-carboxyl-thiophen-2-yl]pentane.

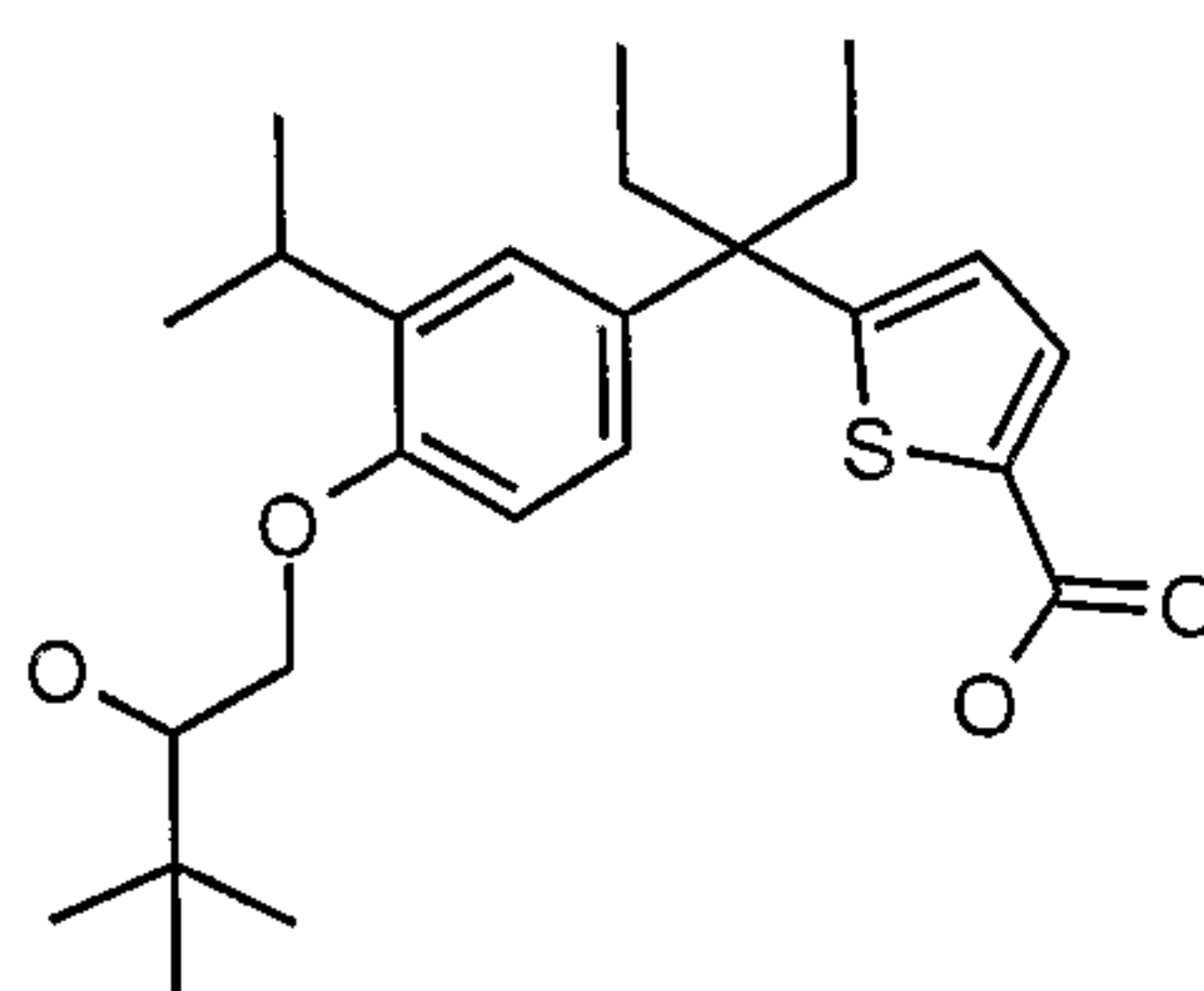
Using a procedure analogous to Example 3, 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-i-propylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (0.93 g, 0.21 mmol) and 5N NaOH aq (1 mL, 5 mmol) give the title compound as an oil (66 mg, 73%).

20 NMR(CDCl₃): 7.69 (d, 1H, J = 3.6 Hz); 7.08 (s, 1H); 6.98 (d, 1H, J = 8.1 Hz); 6.79 (d, 1H, J = 3.6 Hz); 6.74 (d, 1H, J = 8.1 Hz); 4.08 (d, 1H, J = 7.4); 3.85 (t, 1H, J = 7.4 Hz); 3.72 (d, 1H, J = 7.4 Hz); 3.25 (m, 1H); 2.13 (q, 4H, J = 6.8 Hz); 1.17 (d, 6H, J = 6.0 Hz);
25 1.02 (s, 9H); 0.72 (t, 6H, J = 6.8 Hz).

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LC/MS: 450.2 M+NH₄.Example 97 and Example 98

- 5 Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-i-propylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



- 10 A mixture of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-i-propylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane (22 mg) is chromatographed on a ChiralPak AD column with IPA/heptane) to give enantiomer 1 (8 mg), Example 97 and enantiomer 2 (7 mg), Example 98.

Enantiomer 1, Example 97

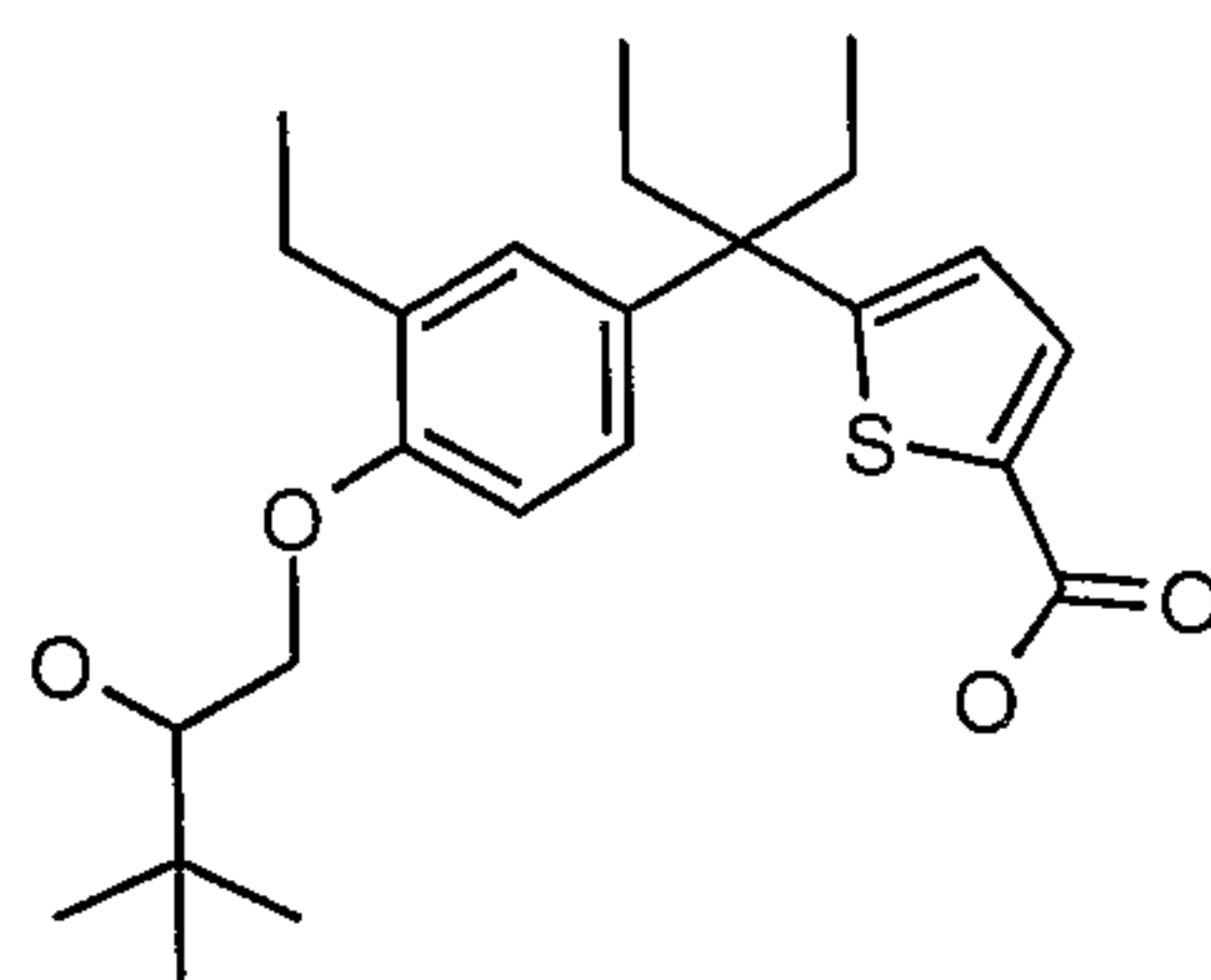
HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate); rt

- 15 Enantiomer 2, Example 98

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate); rt = 6.53 m; 225 nm.

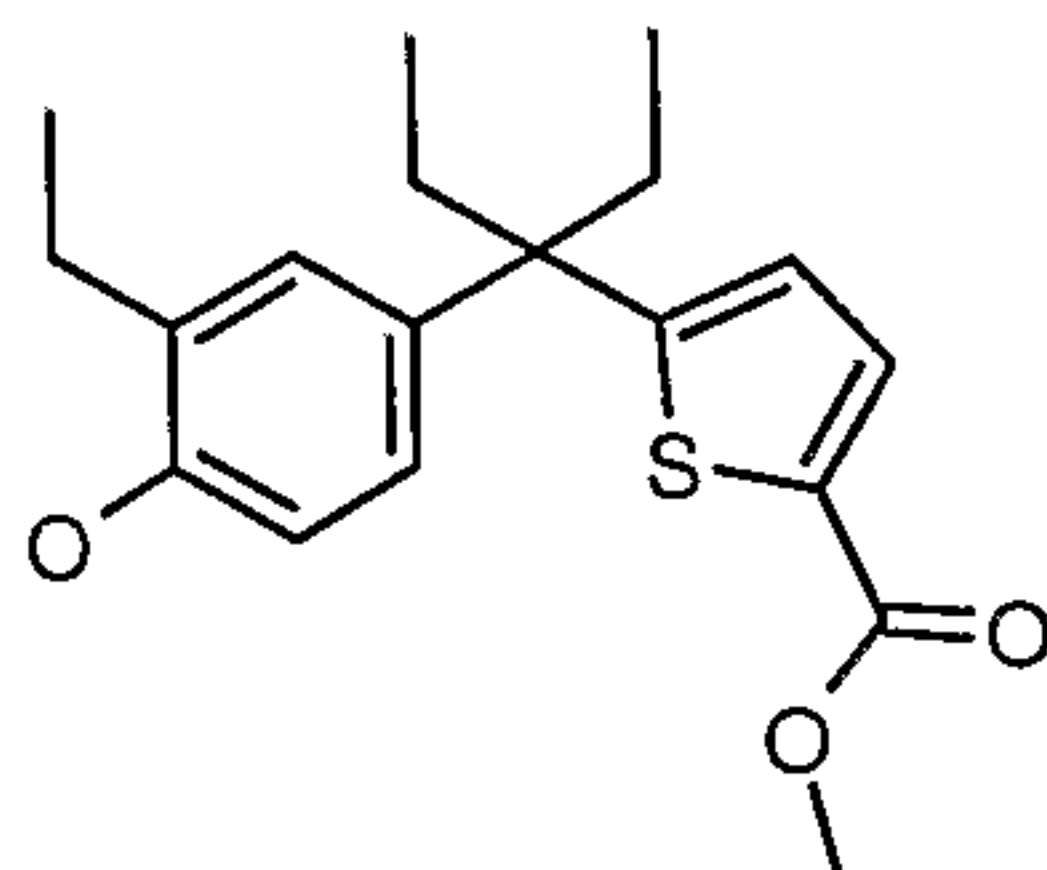
Example 99

- 20 Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



-238-

A. 3'-(4-hydroxy-3-ethylphenyl)-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane.

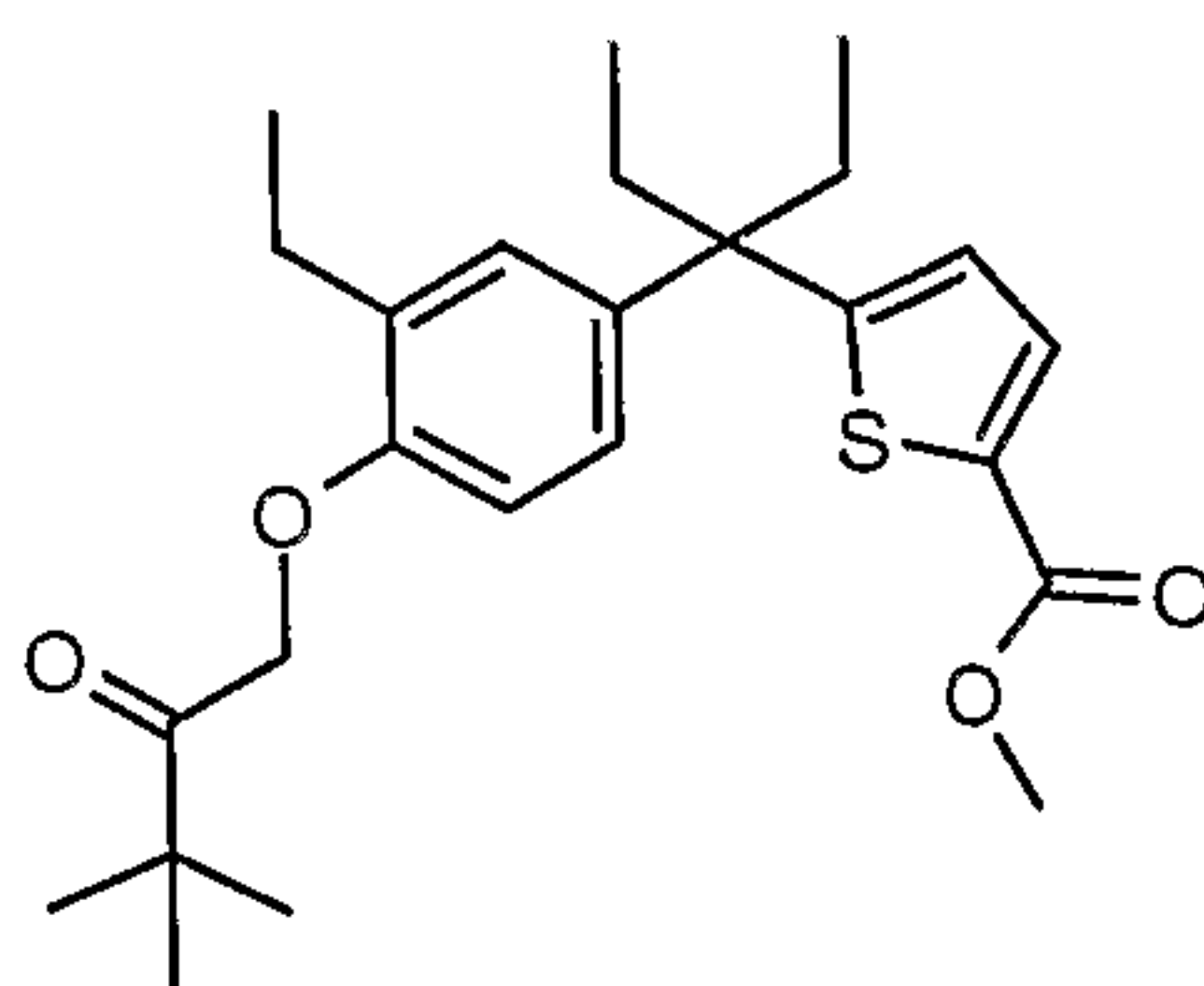


Using a procedure analogous to Example 93A, o-ethylphenol (0.98 g, 8.0 mol) and methyl, 5-(E/Z-2-penten-3-yl)thiophene-2-carboxylate (0.21 g, 1.0 mol) give the title compound as an oil (0.26 g, 78%).

NMR (CDCl₃): 7.62 (d, 1H, J = 4.0 Hz); 6.98 (s, 1H); 6.94 (d, 1H, J = 7.2 Hz); 6.78 (d, 1H, J = 4.0 Hz); 6.66 (d, 1H, J = 7.2 Hz); 4.60 (s, 1H); 3.83 (s, 3H); 2.59 (q, 2H, J = 7.7 Hz); 2.11 (q, 4H, J = 7.2 Hz); 1.19 (t, 3H, J = 7.6 Hz); 0.71 (t, 6H, J = 7.2 Hz).

FAB/MS: 333 M+1.

B. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-methoxycarbonyl-



thiophen-2-yl]pentane.

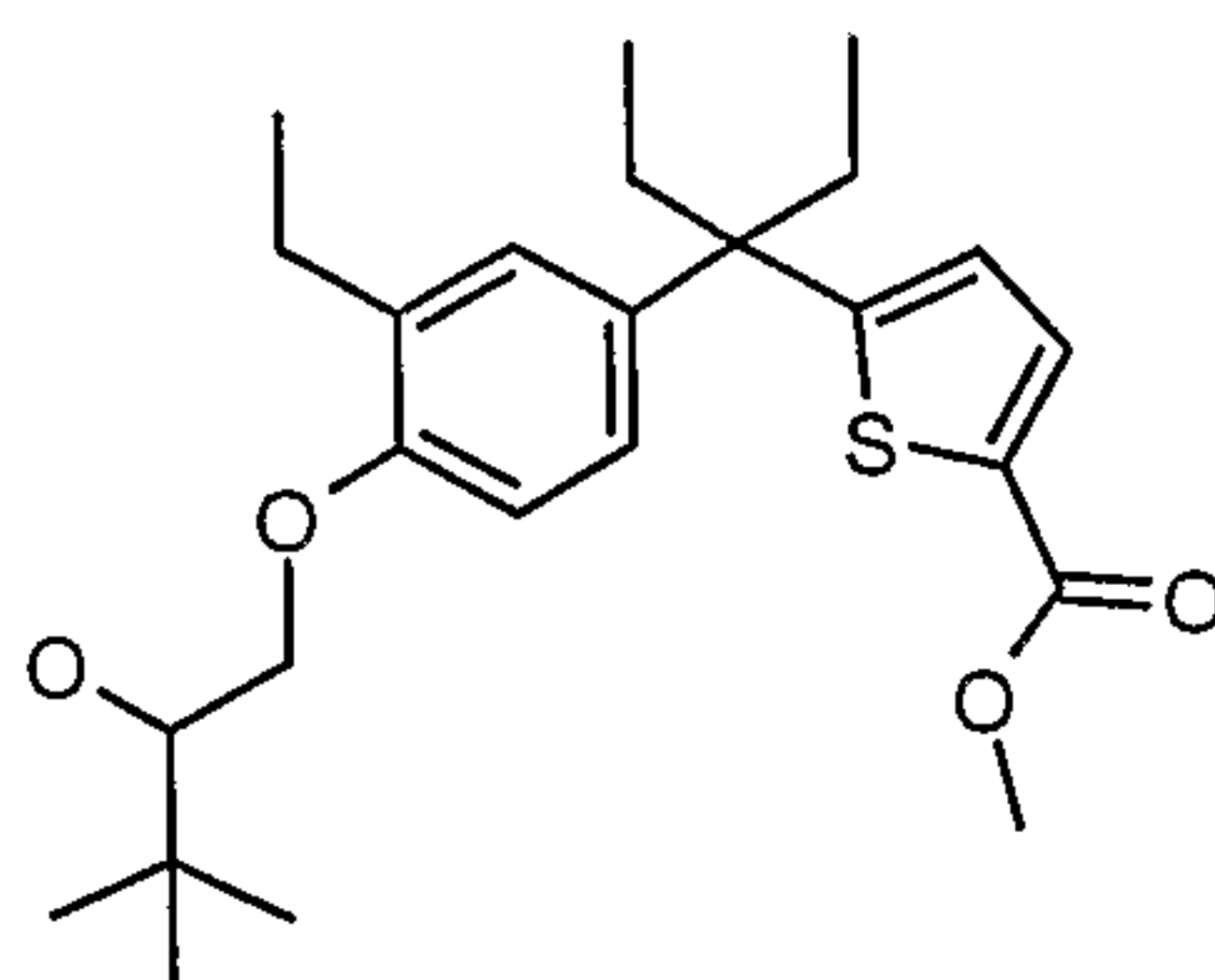
Using a procedure analogous to Example 91B, 3'-(4-hydroxy-3-ethylphenyl)-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (0.26 g, 0.78 mmol) gives the title compound as an oil (0.24 g, 71%).

NMR (CDCl₃): 7.61 (d, 1H, J = 3.6 Hz); 7.02 (s, 1H); 6.96 (d, 1H, J = 7.3 Hz); 6.77 (d, 1H, J = 3.6 Hz); 6.52 (d, 1H, J = 7.3 Hz); 4.83 (s, 2H); 3.83, (s, 3H); 2.66 (q, 2H, J = 7.3 Hz); 2.12 (q, 4H, J = 7.6 Hz); 1.21 (s, 9H); 1.18 (t, 3H, 7.3 Hz); 0.70 (t, 6H, 7.6 Hz).

LC/MS: 431.2 M+1.

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C. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-methoxycarbonyl-



thiophen-2-yl]pentane.

Using a procedure analogous to Example 2, 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane (0.22 g, 0.5 mmol) gives the title compound as an oil (0.16 g, 75%).

NMR(CDCl₃): 7.62 (d, 1H, J = 3.2 Hz); 7.01 (1H, d, J = 7.4 Hz); 7.00 (s, 1H); 6.78 (d, 1H, J = 3.2 Hz); 6.73 (d, 1H, J = 7.4 Hz); 4.08 (1H, d, J = 8.1); 3.85 (t, 1H, J = 8.1); 3.83 (s, 3H); 3.70 (d, 1H, J = 8.1 Hz); 2.60 (t, 2H, J = 7.6 Hz); 2.40 (s, 1H); 2.12 (q, 4H, J = 7.2 Hz); 1.49 (t, 3H, J = 7.2 Hz); 1.02 (s, 9H); 0.71 (t, 6H, J = 7.2 Hz).

LC/MS showed a 433.2 M+1.

D. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxyl-thiophen-2-yl]pentane.

Using a procedure analogous to Example 3, 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-methoxycarbonyl-thiophen-2-yl]pentane, methanol, and 5N NaOH at 50 °C for 16 h to give the title compound (0.15 g, 94%).

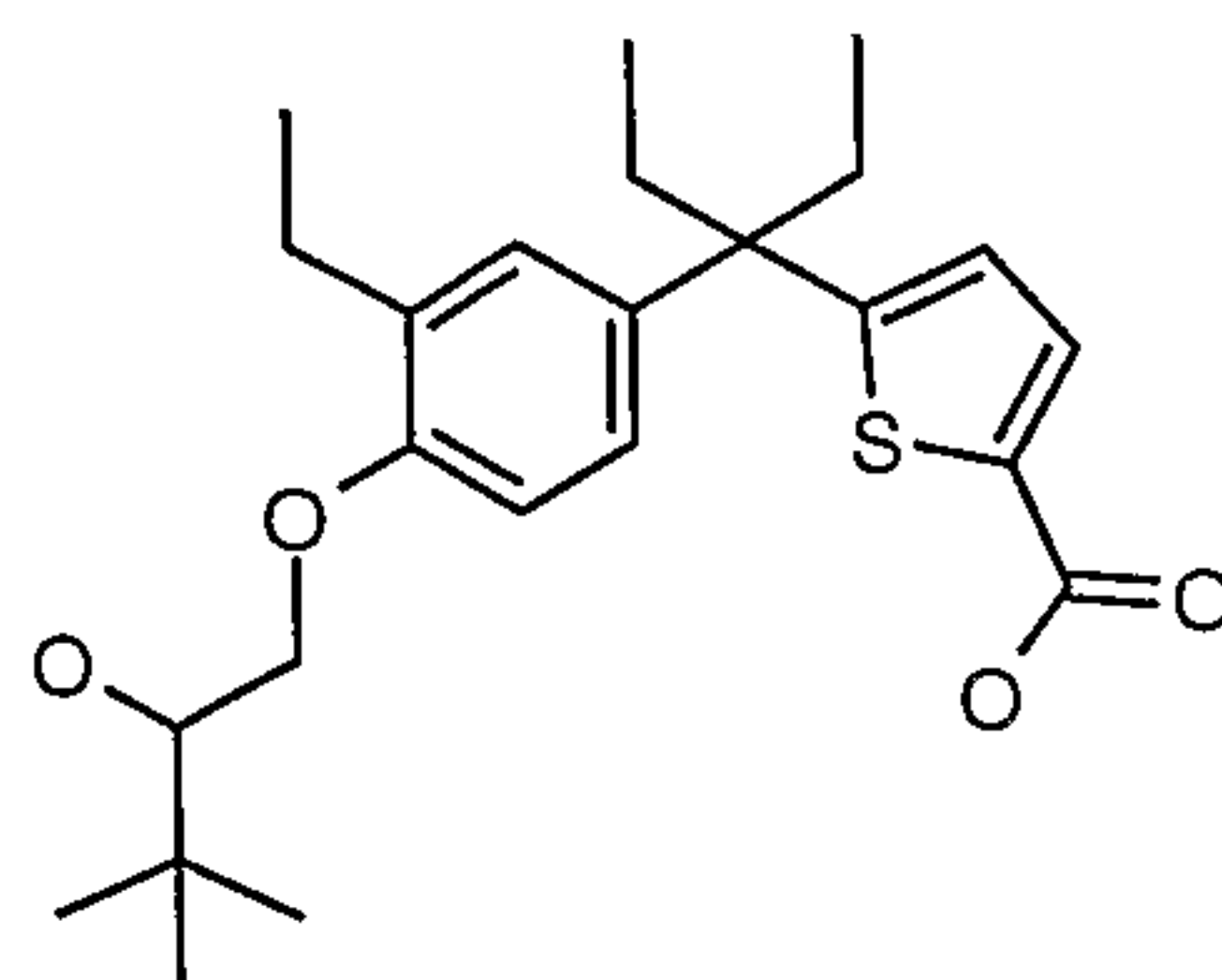
NMR(DMSO-D₆): 7.53 (d, 1H, J = 3.6 Hz); 7.01 (d, 1H, J = 8.8 Hz); 7.00 (s, 1H); 6.90 (d, 1H, J = 3.6 Hz); 6.85 (d, 1H, J = 8.8 Hz); 4.04 (d, 1H, J = 9.4); 3.86 (t, 1H, J = 9.4 Hz); 3.44 (d, 1H, J = 9.4 Hz); 2.56 (m, 2H); 2.09 (m, 4H); 1.08 (t, 3H, J = 8.0 Hz); 0.93 (s, 9H); 0.65 (t, 6H, J = 7.4 Hz).

LC/MS: 417.2 M-1.

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Example 100 and Example 101

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



5 A mixture of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane (140 mg) is chromatographed on a ChiralPak AD column with IPA/heptane to give enantiomer 1 (59 mg), Example 100 and enantiomer 2 (51 mg), Example 101.

Enantiomer 1, Example 100

10 HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate);
rt = 4.42 m; 225 nm..

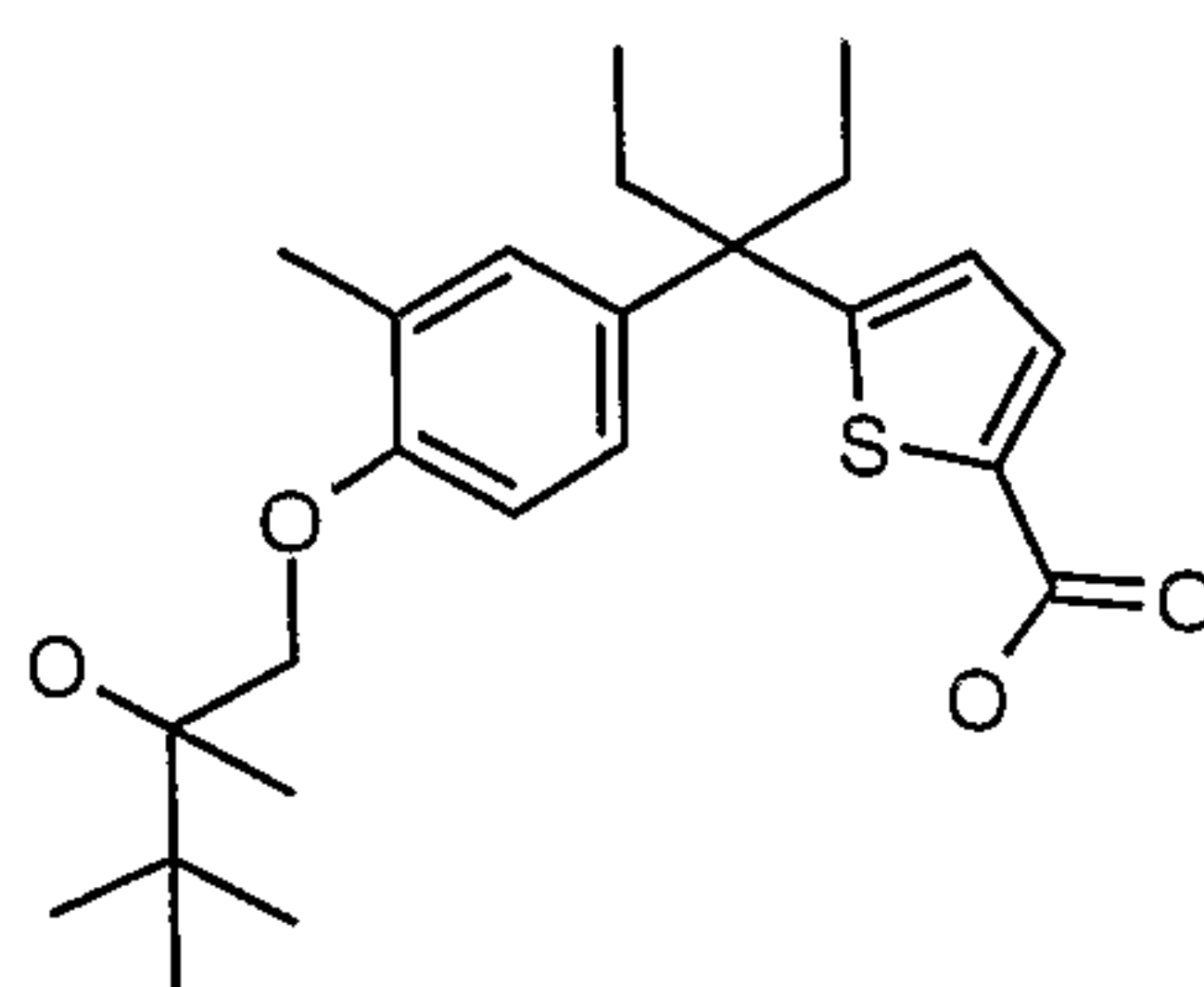
Enantiomer 2, Example 101

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/85% heptane; 1 ml/m (flow rate);
rt = 6.61 m; 225 nm.

15

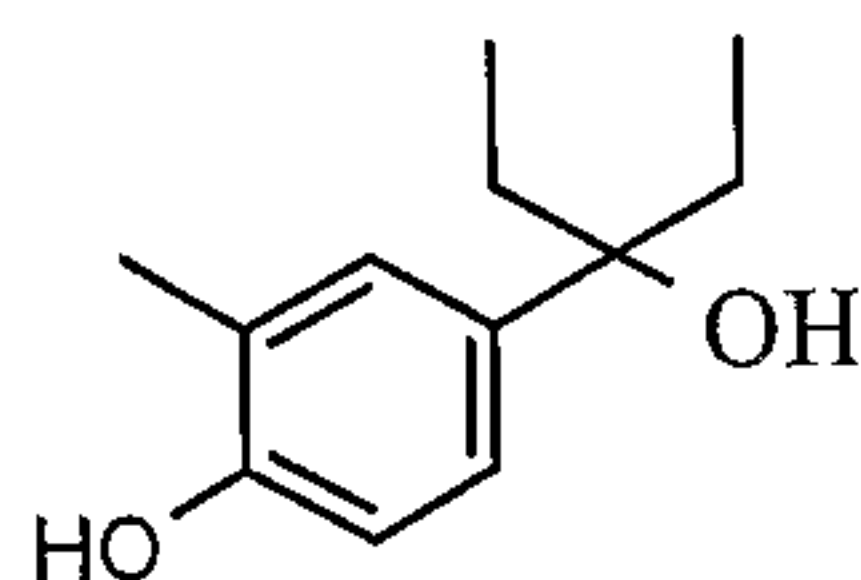
Example 103

20 Preparation of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



A. 3'-[4-Hydroxy-3-methylphenyl]pentan-3-ol.

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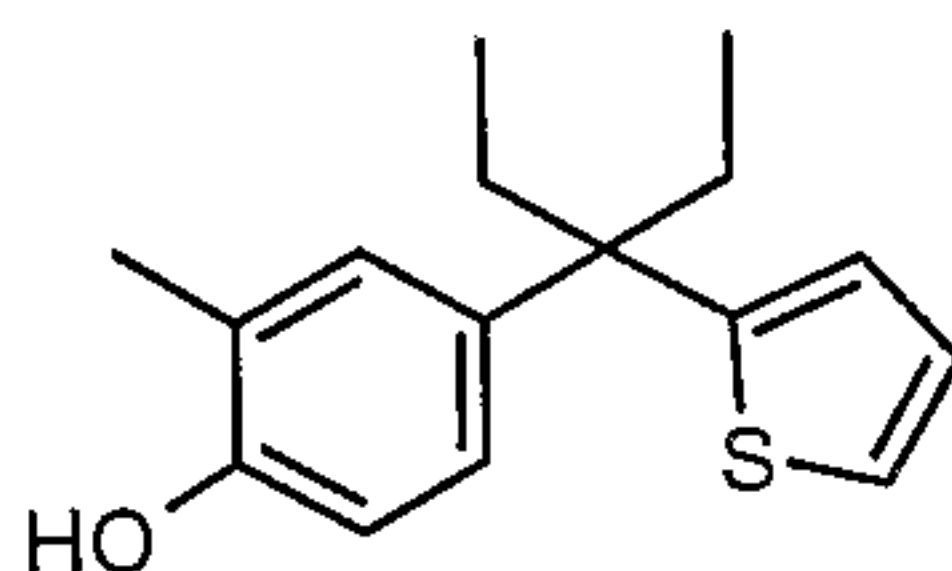


To a mixture of methyl, 4-hydroxy-3-methylbenzoate (21.8 g (0.13 mol) and 200 ml of THF is added 1 M ethylmagnesium bromide/THF (432 mL (0.43 mol) under nitrogen. The mixture is stirred for 60 h and quenched with satd NaHCO₃. The mixture is triturated five times with ether and the combined organic layers is washed with satd NaHCO₃ and brine. The organic layer is Na₂SO₄ dried, filtered, and concentrated to give 27 g (99%) of the title compound.

NMR (CDCl₃): 7.12 (s, 1H); 7.03 (d, 1H, 8.0 Hz); 6.72 (d, 1H, J = 8.0 Hz); 4.69 (s, 1H); 2.26 (s, 3H); 1.80 (m, 4H); 0.79 (t, 6H, 7.4 Hz).

ES/MS: 193 (M-1).

B. 3'-[4-Hydroxy-3-methylphenyl]-3'-(thiophen-2-yl)pentane.

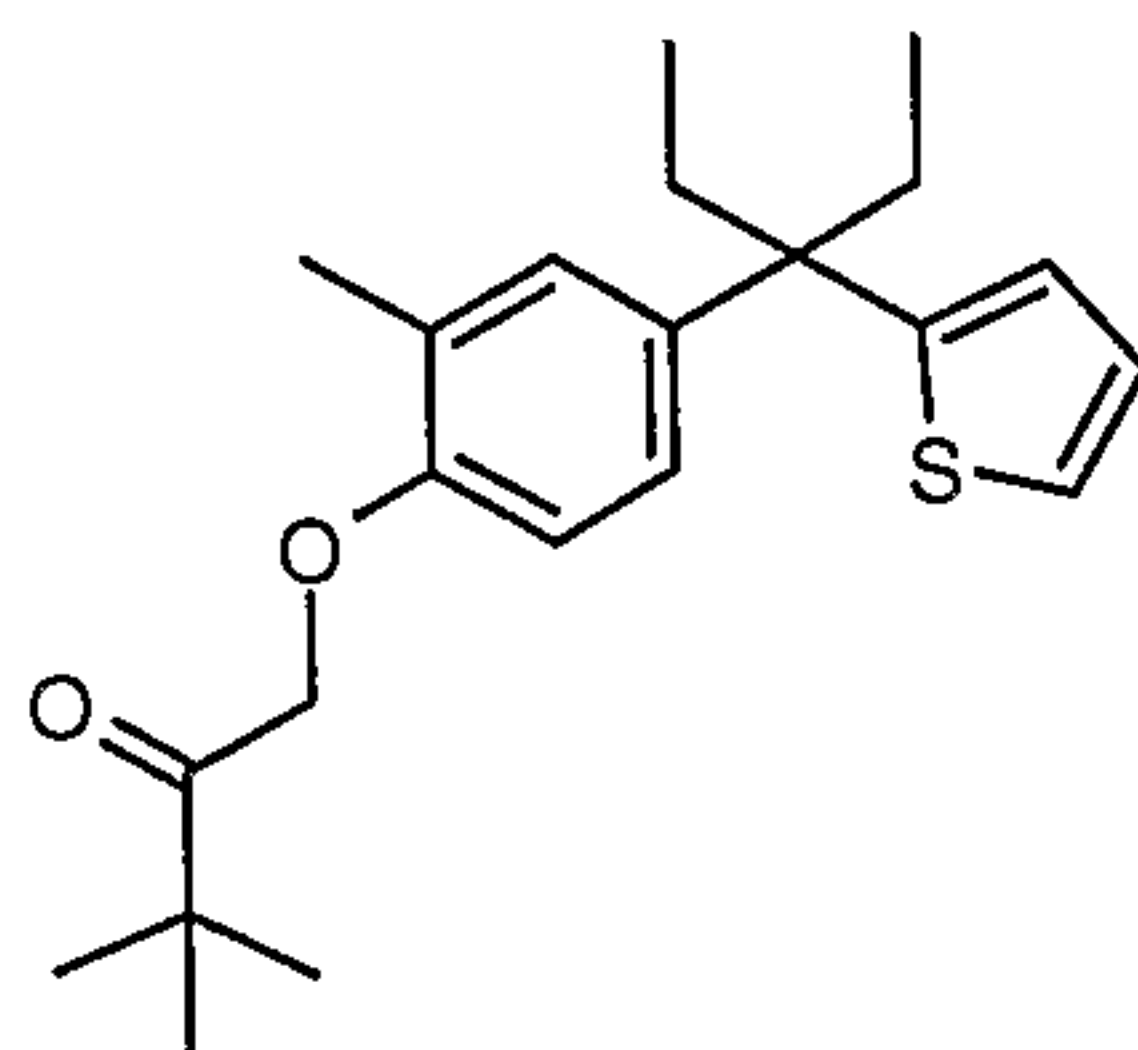


To a mixture of thiophene (6 mL) and 3'-[4-hydroxy-3-methylphenyl]pentan-3-ol (0.92 g, 5 mmol) is added boron trifluoride etherate (100 ul, 0.8 mmol). The mixture is stirred for 96 h and partitioned between diethyl ether and satd NaHCO₃. The organic layer is washed with satd NaHCO₃, brine, Na₂SO₄ dried, and concentrated. The residue is chromatographed (12 g of SiO₂, Hex to 8% EtOAc/Hex) to give the title compound (0.53 g (41%).

[ES/MS 259.1 (M-1)].

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C. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-(thiophen-2-yl)pentane.

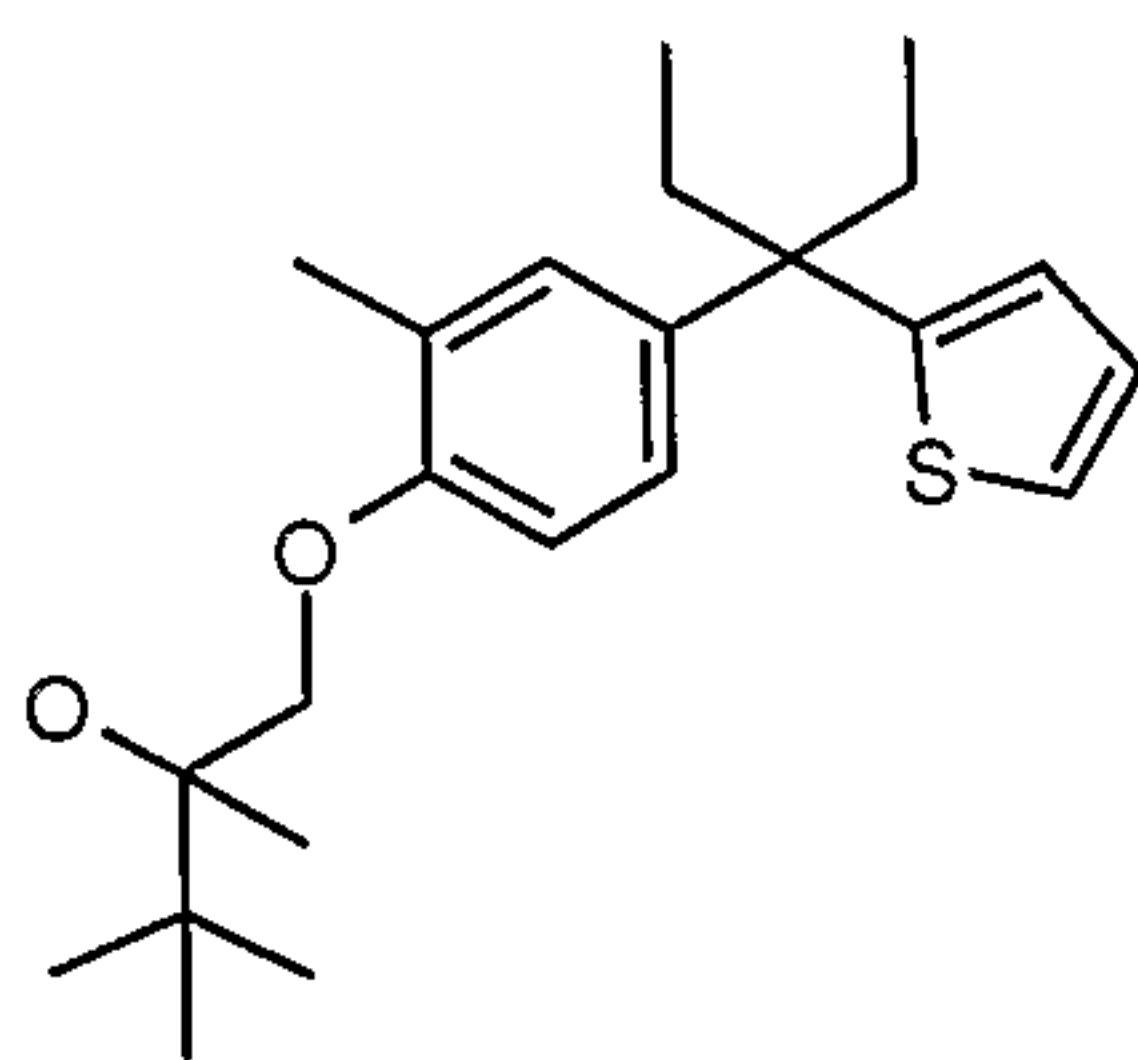


Using a procedure analogous to Example 91B, 3'-[4-hydroxy-3-methylphenyl]-3'-(thiophen-2-yl)pentane (0.53 g, 2.2 mmol) gives the title compound as an oil (0.47 g, 64%).

NMR (CDCl₃): 7.14 (d, 1H, J = 6.3 Hz); 7.03 (s, 1H); 6.98 (d, 1H, J = 9.0 Hz); 6.90 (m, 1H), 6.79 (d, 1H, J = 6.3 Hz), 6.52 (d, 1H, J = 9.0 Hz), 4.83 (s, 2H); 2.26 (s, 3H); 2.09 (m, 4H); 1.24 (s, 9H), 0.68 (t, 6H, 7.0 Hz).

ES/MS: 359.2 (M+1) 376.2 (M+NH₄).

D. 3'-[4-(2-Hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-(thiophen-2-yl)pentane.



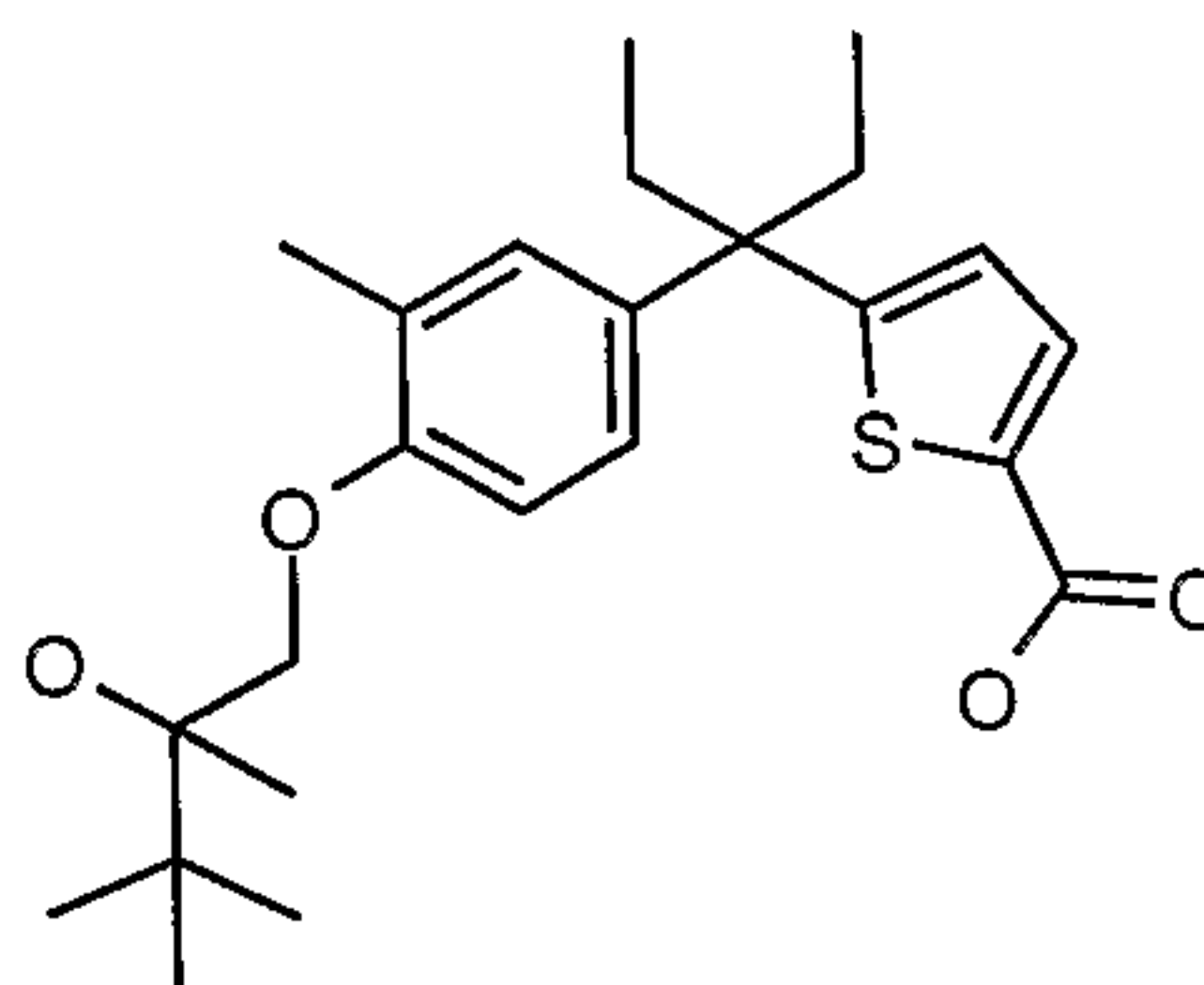
To a mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-(thiophen-2-yl)pentane (0.47 g (1.3 mmol) and diethyl ether (15 mL) is added 3 M methylmagnesium iodide/THF (1.3 ml, 3.9 mmol). After stirring for 2 h, the mixture is quenched with satd NaHCO₃ and triturated five times with diethyl ether. The combined organic layers is washed with water, brine, Na₂SO₄ dried, and concentrated to give the title compound (0.6 g, 99%).

NMR (CDCl₃): 7.13 (d, 1H, J = 5.0 Hz); 7.02 (s, 1H); 7.03 (d, 1H, J = 8.4 Hz); 6.90 (m, 1H), 6.80 (d, 1H, J = 5.0 Hz), 6.70 (d, 1H, J = 8.4 Hz), 4.00 (d, 1H, J = 8.8 Hz); 3.83 (d, 1H, J = 8.8 Hz); 2.27 (s, 1H); 2.21 (s, 3H); 2.11 (m, 4H); 1.32 (s, 3H); 1.05 (s, 9H), 0.70 (t, 6H, 7.2 Hz).

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ES-MS: 375.2 (M+1) 357.2 (M-H₂O).

E. 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



5

To a 0 °C mixture of 3'-[4-(2-Hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-(thiophen-2-yl)pentane (0.6 g, 1.3 mmol) and cycloHex (20 ml) and ether (2 ml) is added 1.4 M sec-butyl lithium/cycloHex (2.85 ml, 3.2 mmol). The mixture is allowed to warm to RT and excess CO₂ gas is bubbled in. After two h, the mixture is partitioned between satd NaHCO₃ and diethyl ether. The aq phase is acidified with conc. perchloric acid and extracted into diethyl ether. The organic phase is washed with water, brine, Na₂SO₄ dried and concentrated. The residue is chromatographed (2% EtOAc/Hex to 50% EtOAc/Hex) to give of the title compound (0.3 g (44%).

10

NMR (CDCl₃): 7.69 (d, 1H, J = 3.6 Hz); 6.99 (s, 1H); 7.03 (d, 1H, J = 8.4 Hz); 6.80 (d, 1H, J = 3.6 Hz), 6.72 (d, 1H, J = 8.4 Hz), 4.00 (d, 1H, J = 8.8 Hz); 3.83 (d, 1H, J = 8.8 Hz); 2.22 (s, 3H); 2.13 (q, 4H, J = 7.2 Hz); 1.33 (s, 3H); 1.04 (s, 9H), 0.72 (t, 6H, 7.2 Hz).

15

ES-MS: 417.3 (M-1) 436.3 (M+NH₄).

20

Example 104 and Example 105

Preparation of enantiomers of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.

25

A mixture of racemic 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane (~290 mg) is chromatographed on a ChiralPak AD column with IPA/heptane to give enantiomer 1 (125 mg, 43%), Example 104 and enantiomer 2 (140 mg, 48%), Example 105.

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Enantiomer 1, Example 104

HPLC: ChiralPak AD (4.6X250 mm); 20% IPA/80% heptane; 1 ml/m (flow rate);

rt = 6.09 m; 225 nm..

Enantiomer 2, Example 105

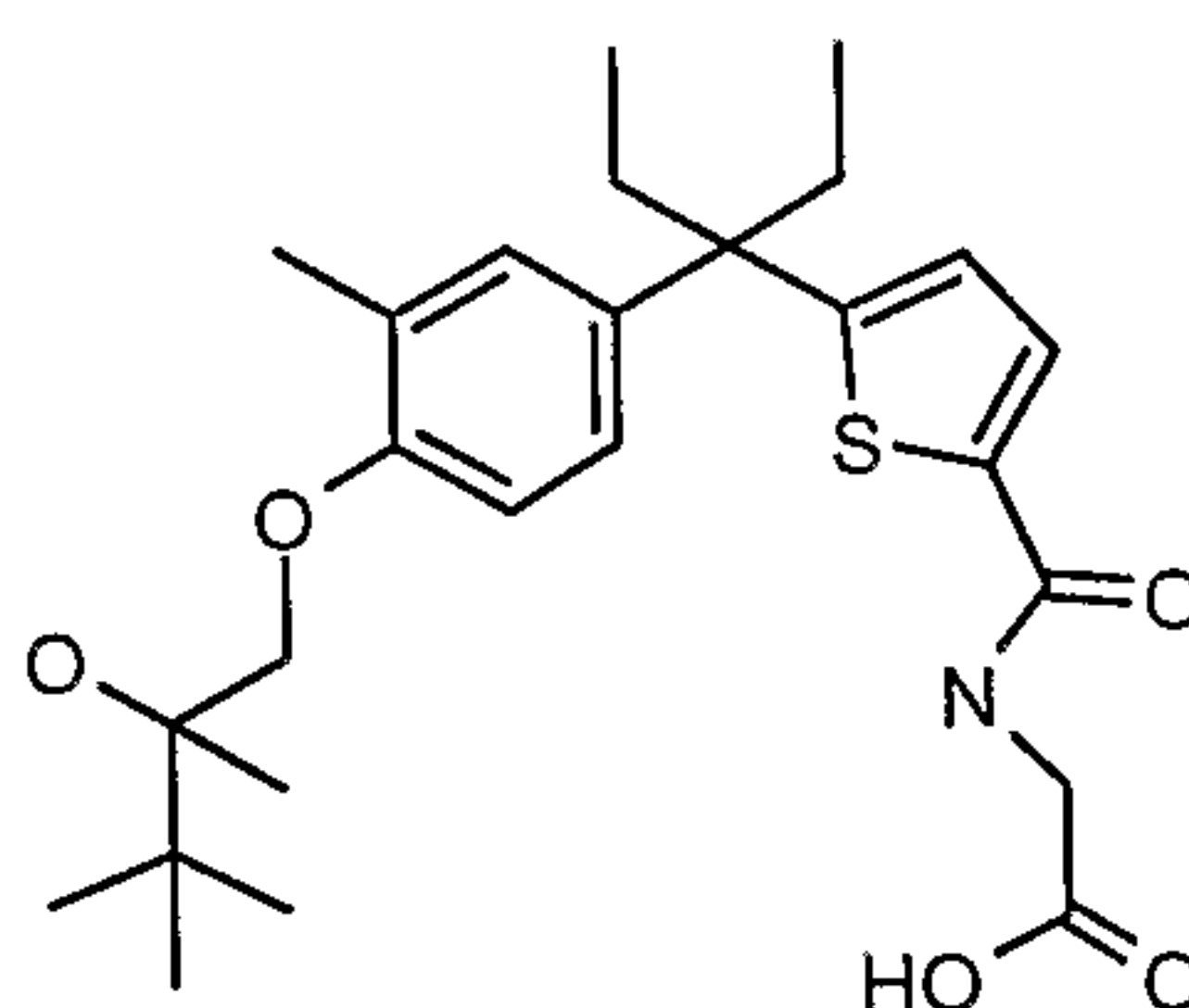
5 HPLC: ChiralPak AD (4.6X250 mm); 20% IPA/80% heptane; 1 ml/m (flow rate);

rt = 8.00 m; 225 nm.

Example 106

Preparation of enantiomer 1 of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-

10 3'-[5-(carboxymethylamino)carbonyl-thiophen-2-yl]pentane.



A. of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-(methylcarbonyl-methylamino)carbonyl-thiophen-2-yl]pentane.

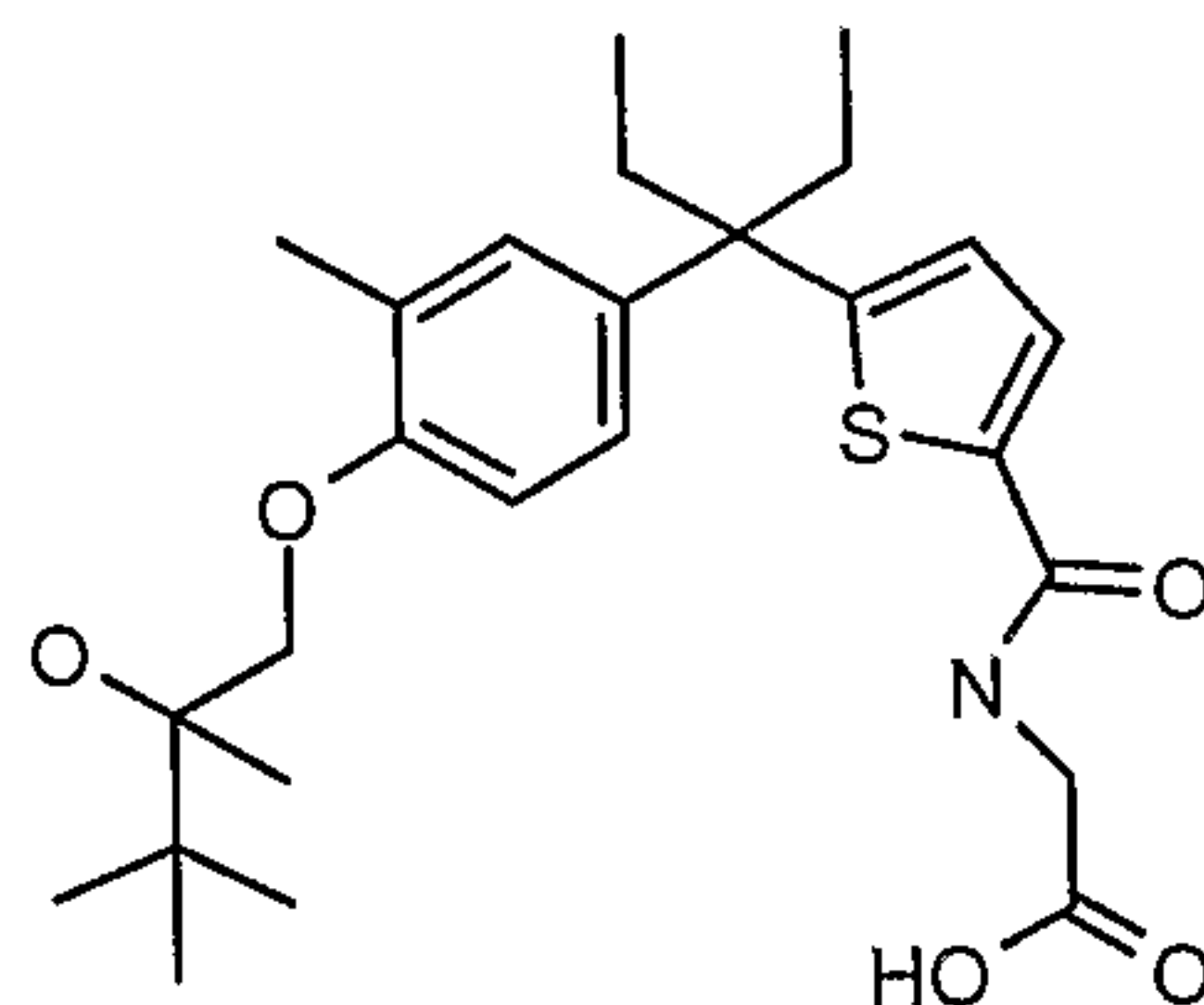
To a mixture of enantiomer 1 of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane and DMSO (1 ml) is added EDCI (55
15 mg, 0.29 mmol), 0.5 M HOAT (523 uL, 0.26 mmol), methyl, aminoacetic acid hydrochloride (33 mg, 0.26 mmol), and triethylamine (136 uL, 1 mmol). The mixture is stirred for 72 h at RT, partitioned between diethyl ether and satd NaHCO₃. The organic layer is washed with water, 2M HCl, water, satd NaHCO₃, then Na₂SO₄ dried, and
20 concentrated. The residue is chromatographed (Hex to 30% EtOAc/Hex) to give the title compound (60 mg, 51%).

NMR (CDCl₃): 7.40 (d, 1H, J = 3.6 Hz); 7.04 (d, 1H, J = 8.8 Hz); 6.98 (s, 1H); 6.77 (d, 1H, J = 3.6 Hz), 6.71 (d, 1H, J = 8.8 Hz), 4.00 (d, 1H, J = 8.8 Hz); 6.53 (m, 1H); 4.18 (d, 1H, J = 4.8 Hz); 4.00 (d, 1H, J = 8.8 Hz); 3.84 (d, 1H, J = 8.8 Hz); 3.78 (s, 3H); 2.21 (s, 3H); 2.11 (q, 4H, J = 7.2 Hz); 1.33 (s, 3H); 1.04 (s, 9H), 0.70 (t, 6H, 7.2
25 Hz).

ES-MS: 490.4 (M+1) 488.4 (M-1).

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B. 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-(carboxymethyl-amino)carbonyl-thiophen-2-yl]pentane, enantiomer 1.

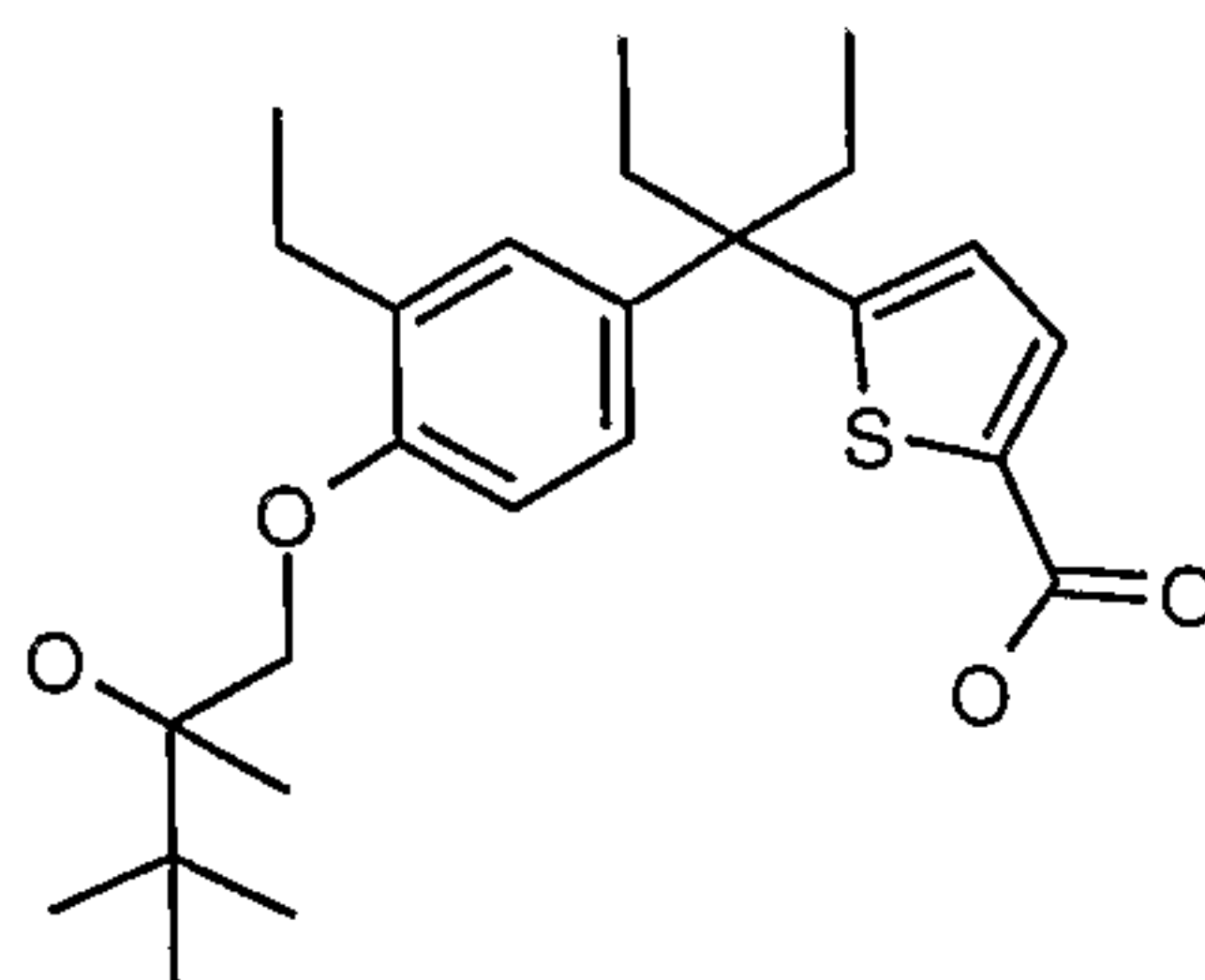


To a mixture of enantiomer 1 of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[5-(methylcarbonyl-methylamino)carbonyl-thiophen-2-yl]pentane (60 mg, 0.12 mmol) and 50% methanol/water (0.5 ml) is added lithium hydroxide (6 mg, 0.24 mmol). The mixture is heated to 40 °C for one h and concentrated. The residue is added ice and acidified with conc. HCl (pH~1). The suspension is filtered, washed with water, and air dried to give the title compound as a solid (50 mg, 86%).

NMR (CDCl₃): 7.45 (d, 1H, J = 4.0 Hz); 7.04 (d, 1H, J = 8.4 Hz); 6.97 (s, 1H); 6.79 (d, 1H, J = 4.0 Hz), 6.70 (d, 1H, J = 8.4 Hz), 4.00 (d, 1H, J = 8.8 Hz); 6.59 (m, 1H); 4.17 (s, 1H); 4.00 (d, 1H, J = 8.8 Hz); 3.83 (d, 1H, J = 8.8 Hz); 3.02 (m, 1H); 2.20 (s, 3H); 2.11 (q, 4H, J = 7.2 Hz); 1.33 (s, 3H); 1.01 (s, 9H), 0.70 (t, 6H, 7.2 Hz). ES/MS: 476.3 (M+1) 474.3 (M-1).

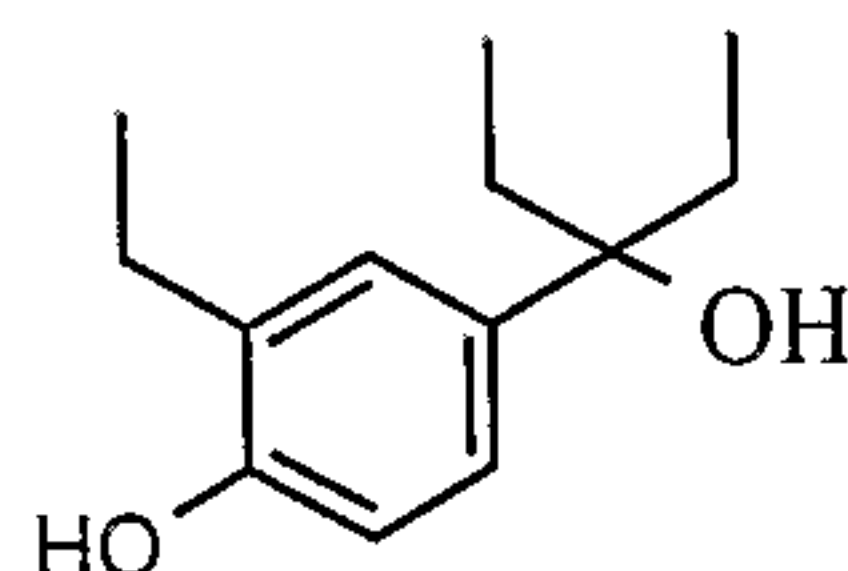
Example 107

Preparation of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



A. 3'-[4-Hydroxy-3-ethylphenyl]pentan-3-ol.

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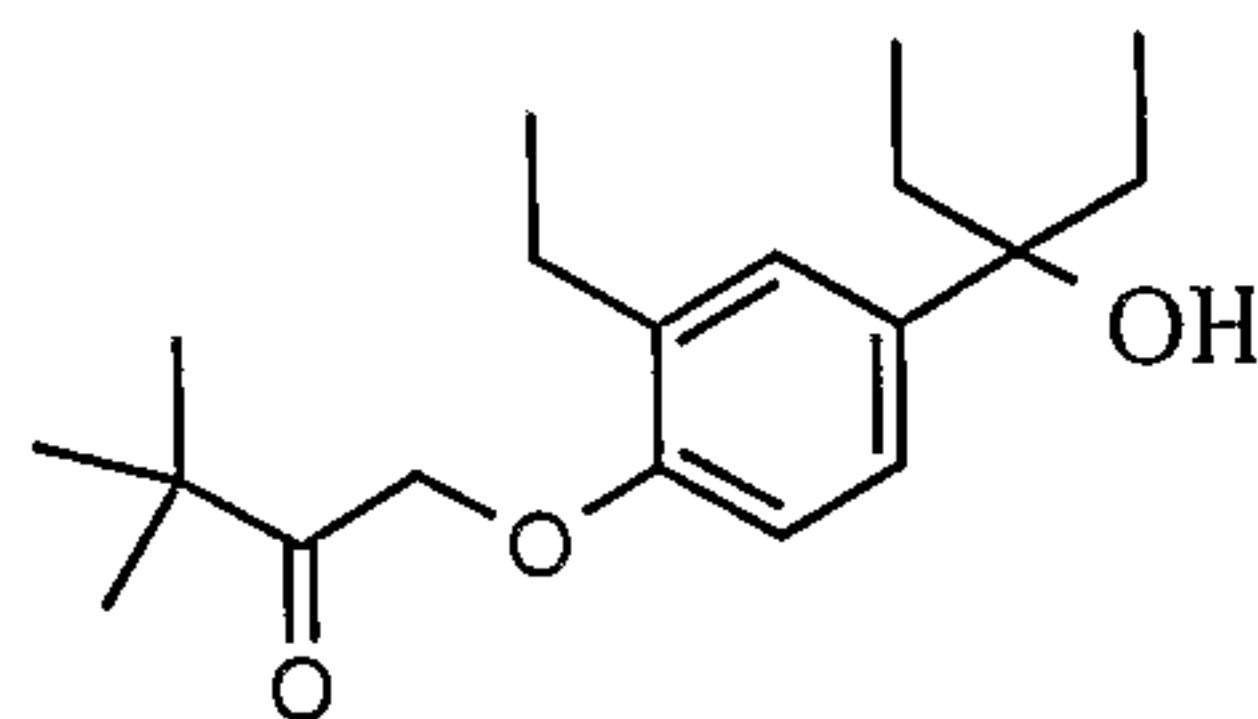
Using a procedure analogous to Example 103A, methyl, 4-hydroxy-3-ethylbenzoate (7.7g, 43 mmol) gives the title compound as an oil (9.2 g, 99%).

5 NMR (CDCl₃): 7.13 (s, 1H); 7.04 (d, 1H, 8.0 Hz); 6.71 (d, 1H, J = 8.0 Hz); 4.65 (s, 1H); 2.64 (q, 2H, J = 7.2 Hz); 1.81 (m, 4H); 1.23 (m, 3H); 0.77 (t, 6H, 7.2 Hz).

ES/MS: 207.1 (M-1).

B. 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-ethylphenyl]pentan-3-ol.

10

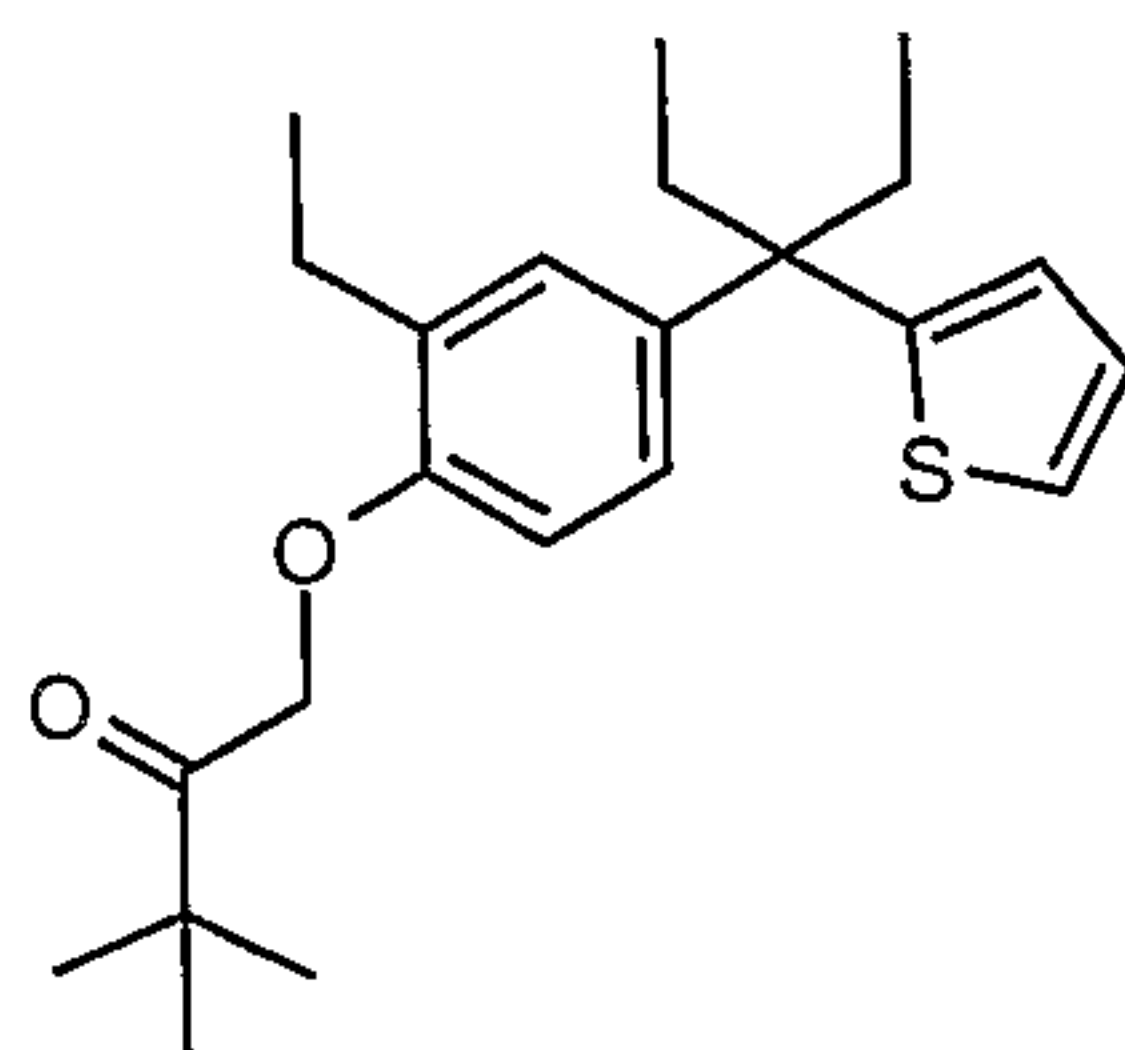


Using a procedure analogous to Example 91B, 3'-[4-hydroxy-3-ethylphenyl]pentan-3-ol (9.2 g, 43 mmol) gives the title compound (11.9 g, 91%).

15 NMR (CDCl₃): 7.14 (s, 1H); 7.10 (d, 1H, J = 8.0 Hz); 6.58 (d, 1H, J = 8.0 Hz); 4.85 (s, 2H); 2.71 (q, 2H, J = 7.6 Hz); 1.80 (m, 4H); 1.25 (s, 9H); 1.23 (t, 3H, J = 7.6 Hz); 0.76 (t, 6H, 7.2 Hz).

ES/MS: 289.1 (M+H-H₂O).

C. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-(thiophen-2-yl)pentane.



20

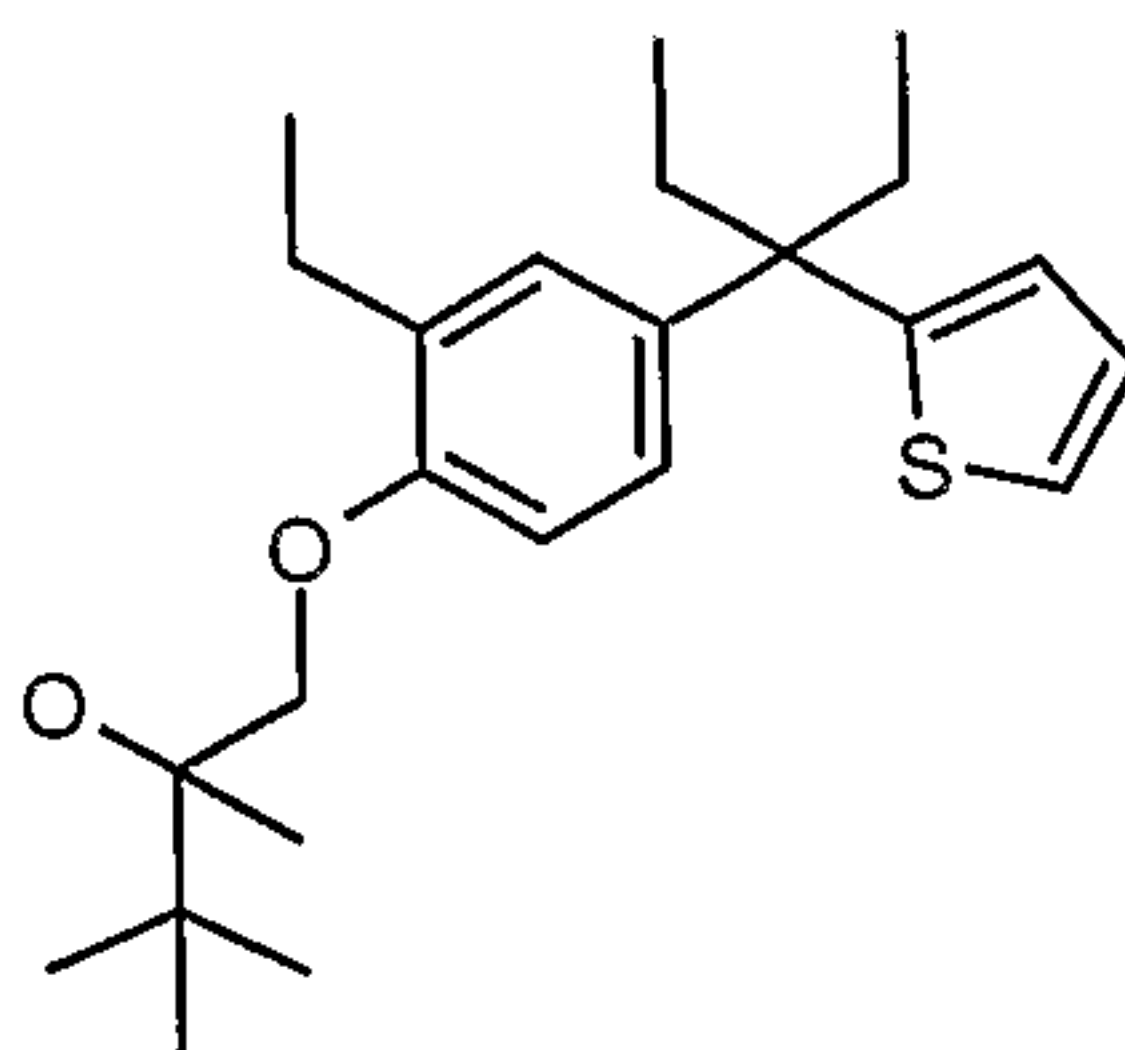
-247-

Using a procedure analogous to Example 103B, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-ethylphenyl]pentan-3-ol (10.9 g, 36 mmol) gives the title compound (6.1 g, 46%).

NMR (CDCl₃): 7.14 (d, 1H, J = 1.2 Hz); 7.06 (s, 1H); 6.96 (d, 1H, J = 8.4 Hz); 6.90 (t, 1H, J = 5.2 Hz); 6.80 (d, 1H, J = 1.2 Hz); 6.52 (d, 1H, J = 8.4 Hz); 4.83 (s, 2H); 2.67 (q, 2H, J = 7.2 Hz); 2.10 (q, 4H, J = 7.4); 1.25 (s, 9H); 1.20 (t, 3H, J = 7.2 Hz); 0.70 (t, 6H, 7.4 Hz).

ES/MS: 373.2 (M+1) 390.2 (M+NH₄).

10 D. 3'-[4-(2-Hydroxy-2,3,3-trimethylbutoxy)-3-ethylphenyl]-3'-(thiophen-2-yl)pentane.



Using a procedure analogous to Example 103D, 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-ethylphenyl]-3'-(thiophen-2-yl)pentane (3.7 g, 10 mmol) gives the title compound after silica gel chromatography (1.8 g, 46%).

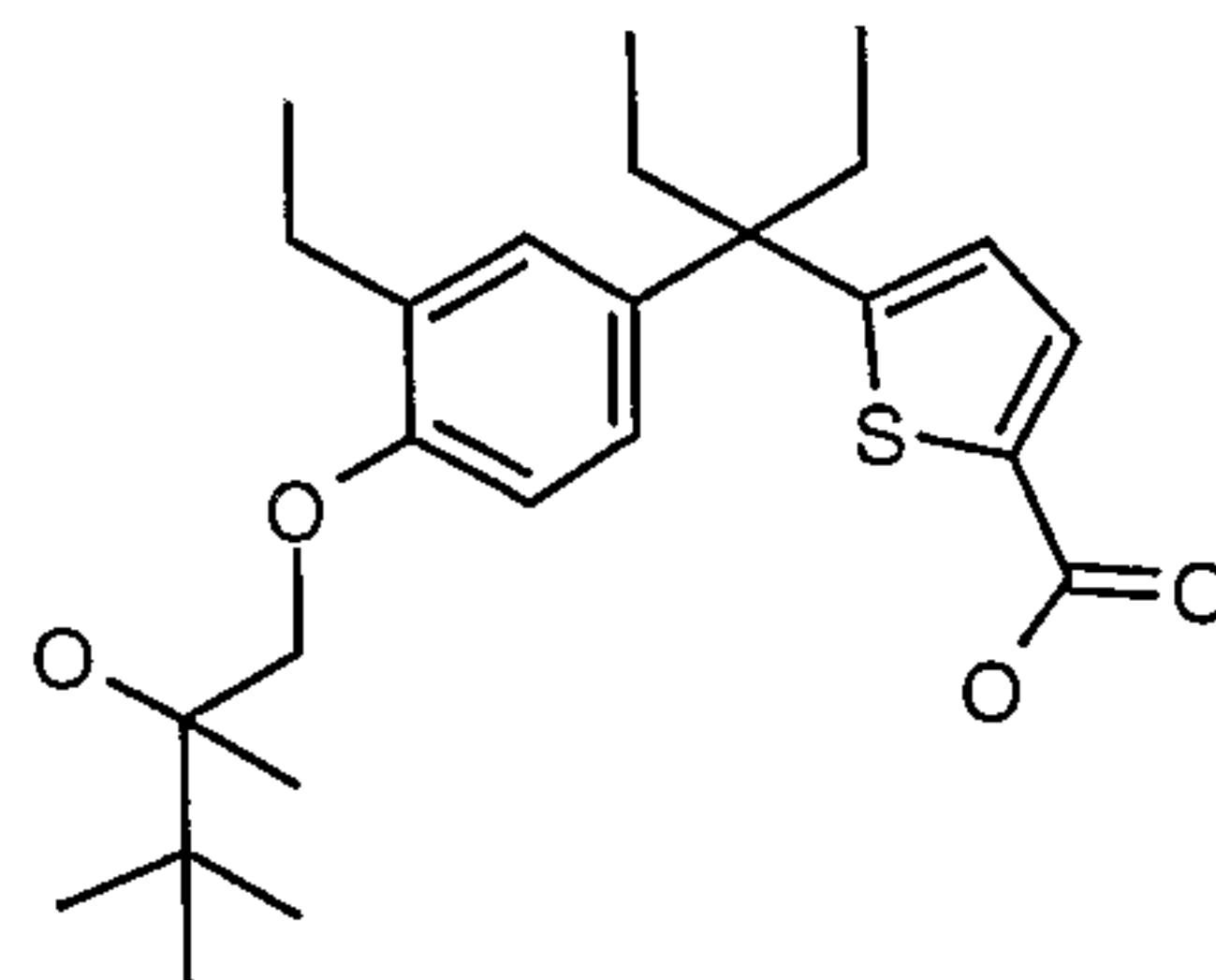
15 NMR (CDCl₃): 7.15 (d, 1H, J = 6.3 Hz); 7.04 (s, 1H); 7.03 (d, 1H, underlying); 6.90 (t, 1H, J = 5.2 Hz); 6.81 (m, 1H); 6.53 (d, 1H, J = 8.4 Hz); 4.00 (d, 1H, J = 8.4 Hz); 3.84 (d, 1H, J = 8.4 Hz); 2.62 (q, 2H, J = 7.6 Hz); 2.11 (q, 4H, J = 7.6); 1.33 (s, 3H); 1.16 (t, 3H, J = 7.6 Hz); 1.04 (s, 9H); 0.71 (t, 6H, 7.6 Hz).

ES/MS: 371.2 (M-H₂O+1) 389.2 (M+1).

20

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E. 3'-[4-(2-Hydroxy-2,3,3-trimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.



Using a procedure analogous to Example 103E, 3'-[4-(2-Hydroxy-2,3,3-trimethylbutoxy)-3-ethylphenyl]-3'-(thiophen-2-yl)pentane (1.45 g, 3.7 mmol) gives the title compound (0.75 g, 46%).

NMR (CDCl₃): 7.70 (d, 1H, J = 3.6 Hz); 7.02 (s, 1H); 7.03 (d, 1H, underlying); 6.80 (d, 1H, J = 3.6 Hz); 6.73 (d, 1H, J = 8.4 Hz); 4.00 (d, 1H, J = 8.8 Hz); 3.85 (d, 1H, J = 8.8 Hz); 2.62 (q, 2H, J = 7.6 Hz); 2.14 (q, 4H, J = 7.2); 1.33 (s, 3H); 1.17 (t, 3H, J = 7.6 Hz); 1.04 (s, 9H); 0.72 (t, 6H, 7.2 Hz).

ES/MS: 431.5 (M-1).

Example 108 and Example 109

Preparation of enantiomers of 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane.

enantiomer 1

enantiomer 2

A mixture of racemic 3'-[4-(2-hydroxy-2,3,3-trimethylbutoxy)-3-ethylphenyl]-3'-[5-carboxy-thiophen-2-yl]pentane (0.93 g) is chromatographed (ChiralPak AD column; 5% ethyl alcohol/95% Hept to give enantiomer 1 (453 mg), Example 108 and enantiomer 2 (438 mg), Example 109.

Enantiomer 1, Example 108

HPLC: ChiralPak AD (4.6X250 mm); 5% IPA/95% heptane; 1 ml/m (flow rate); rt = 10.2 m; 225 nm..

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

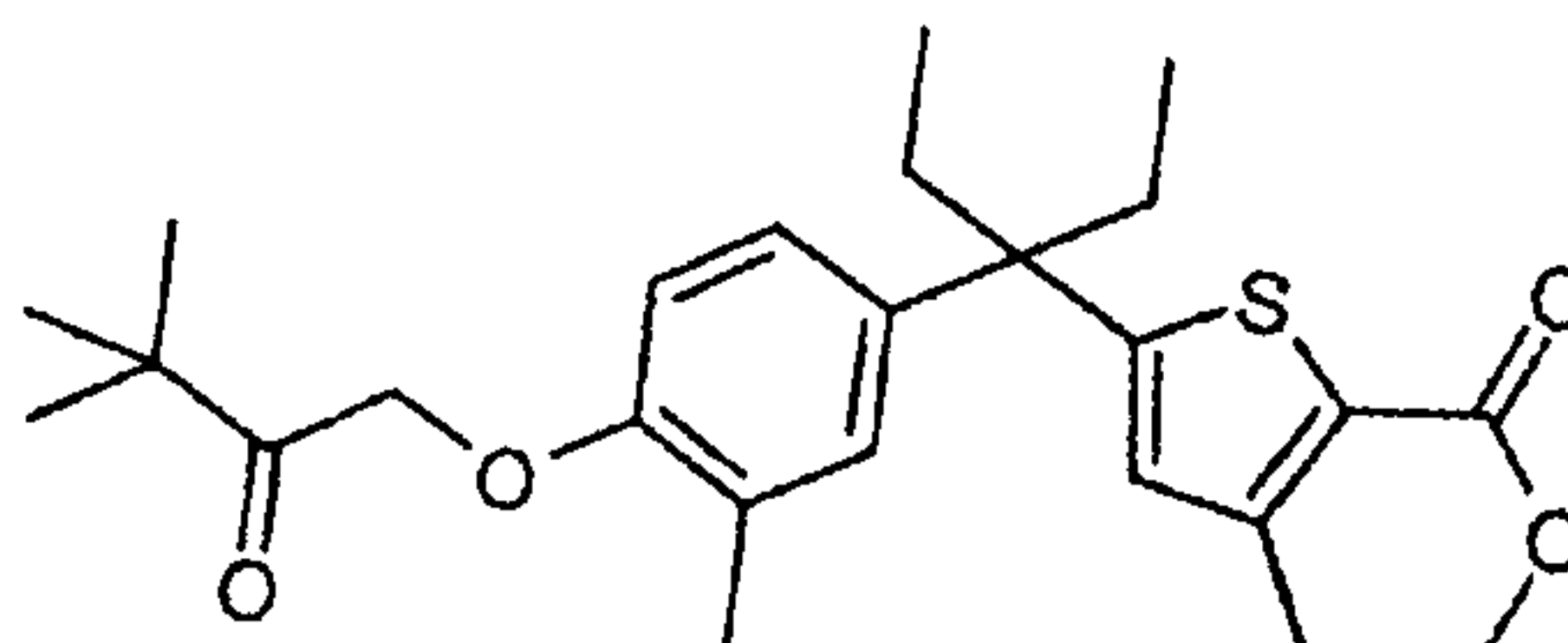
THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

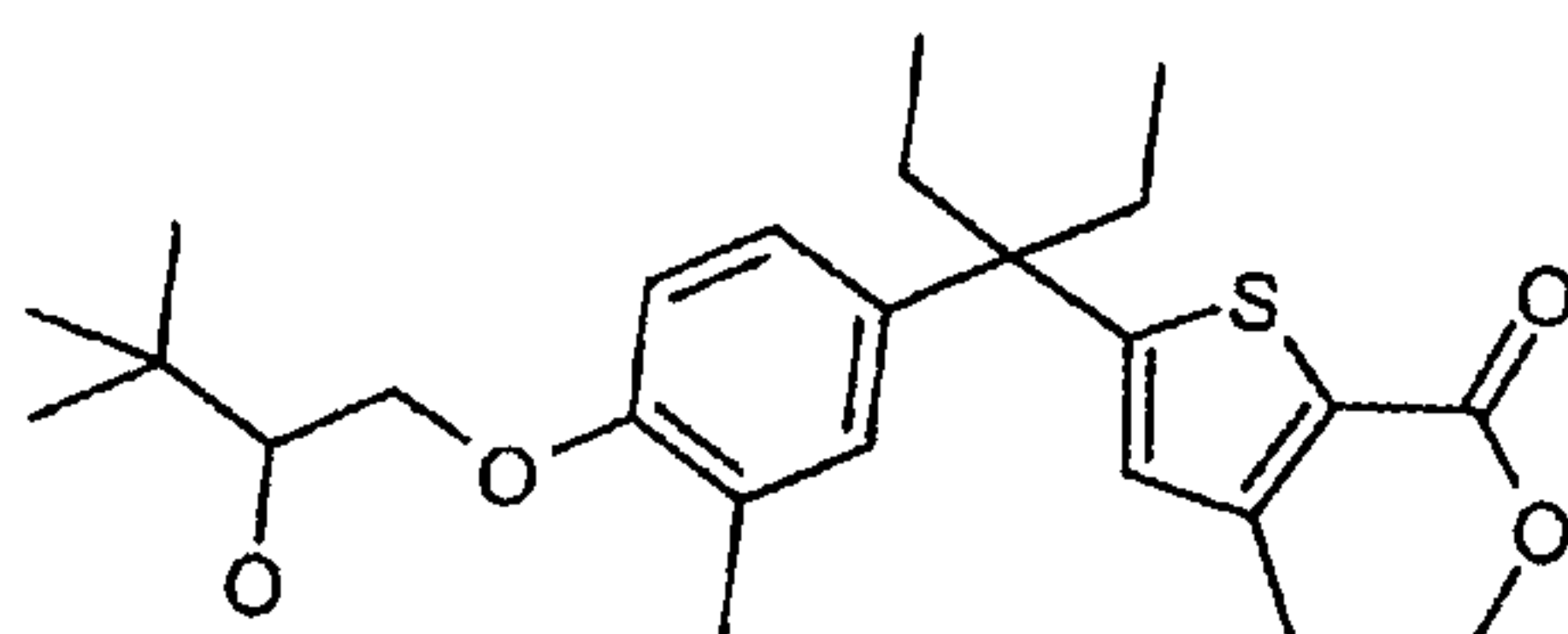
CLAIMS:

1. A compound represented by any one of the formulae below, or a pharmaceutically acceptable salt or solvate thereof:

X1)

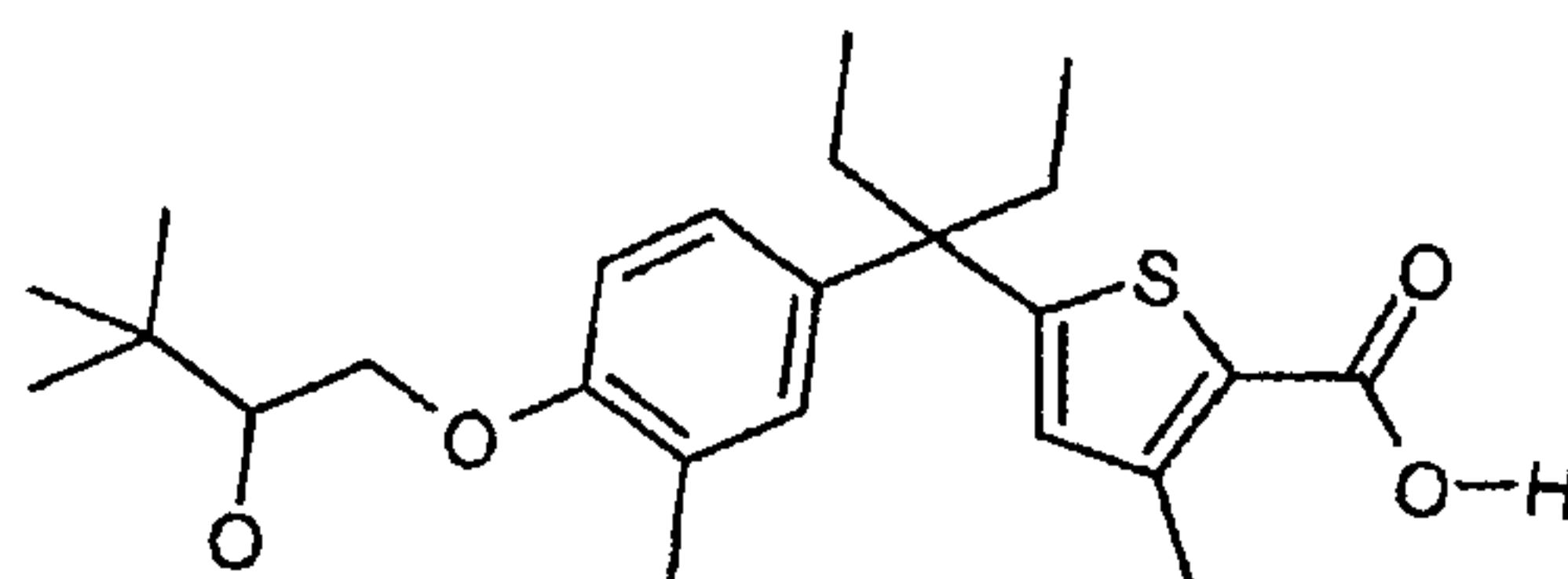


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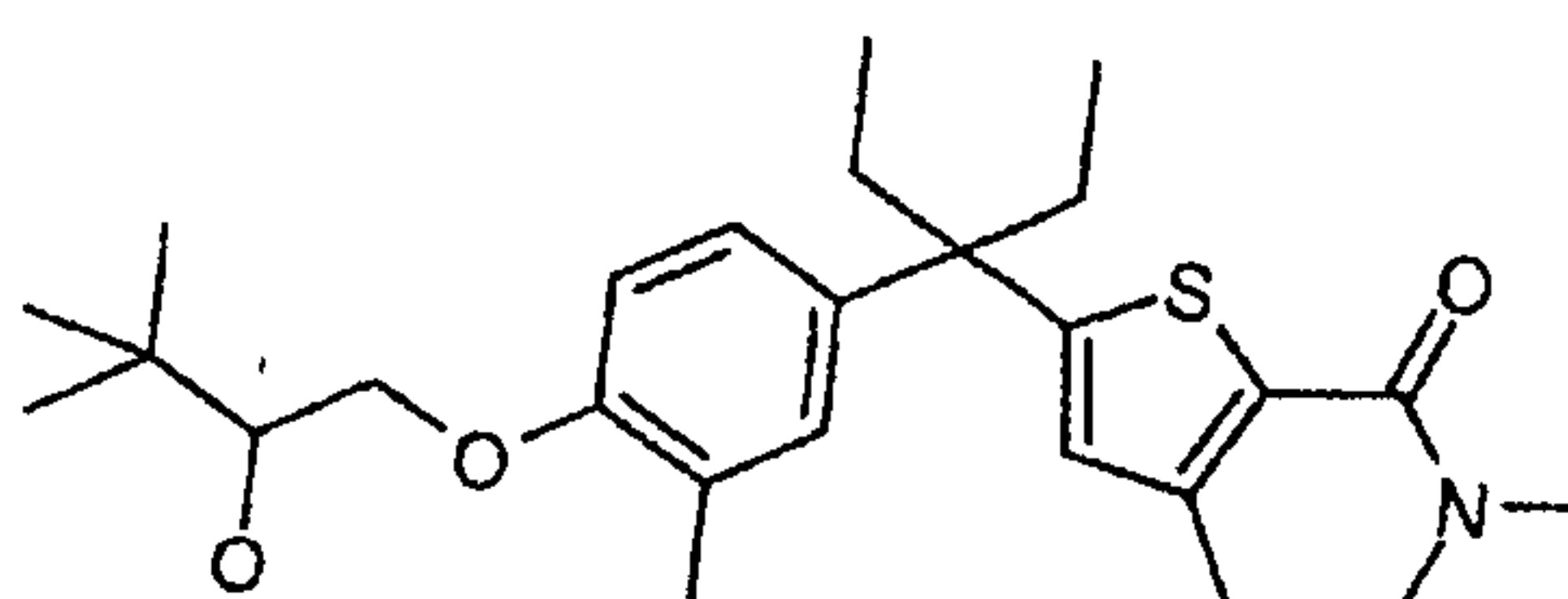
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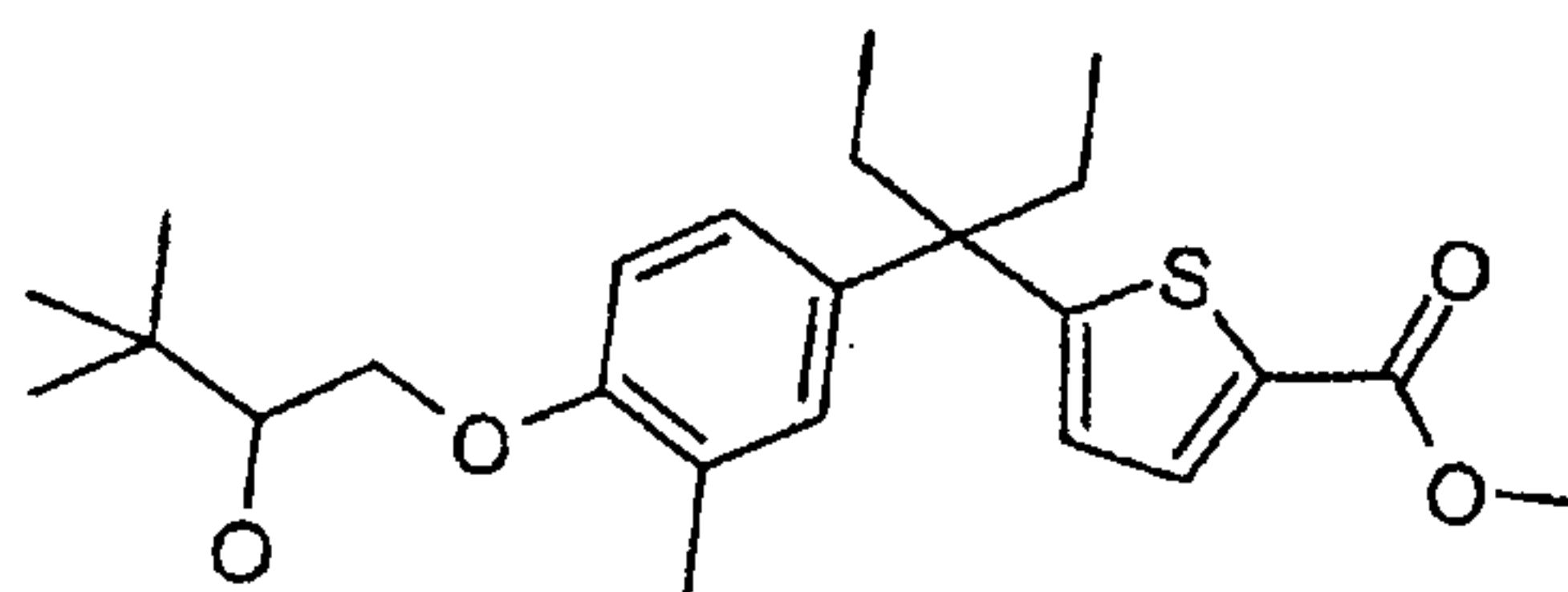


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X4)

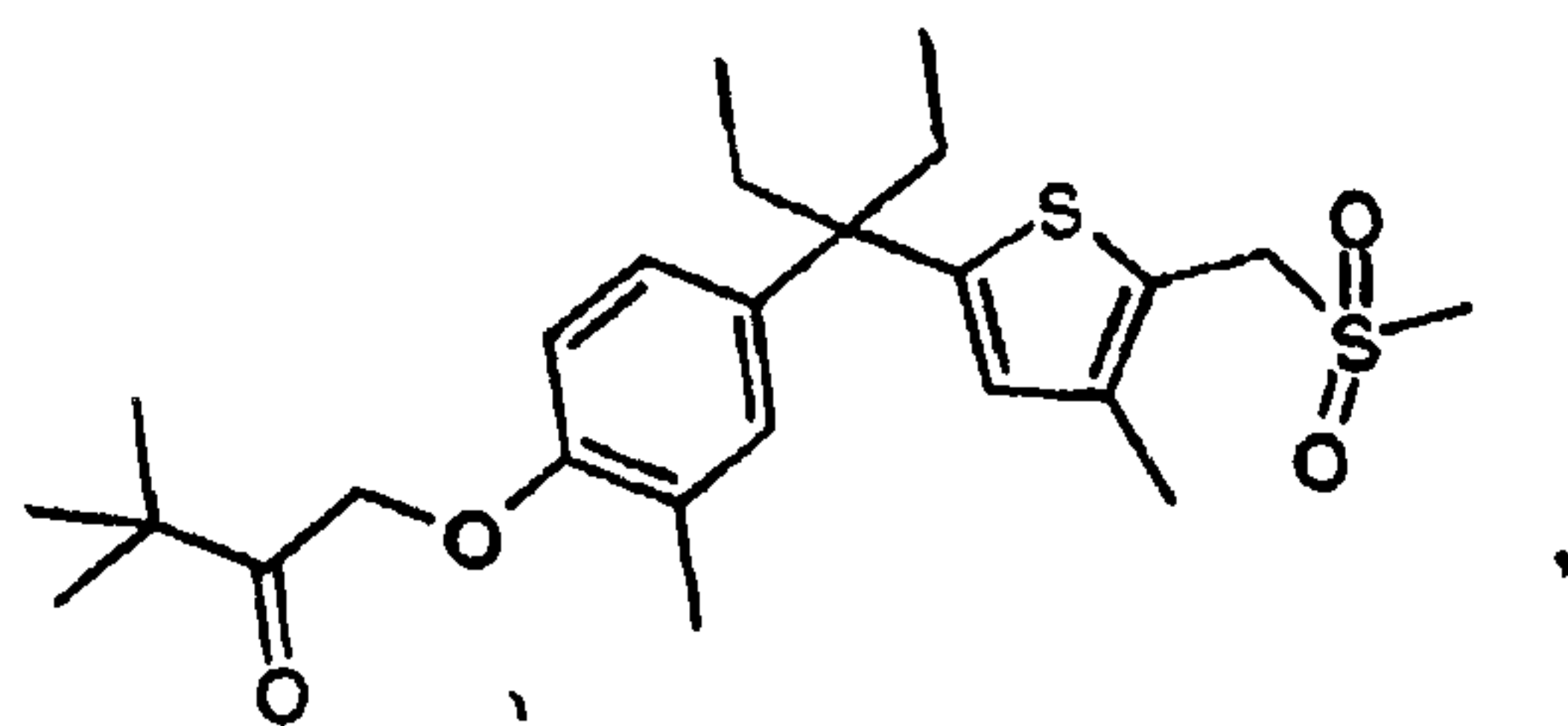


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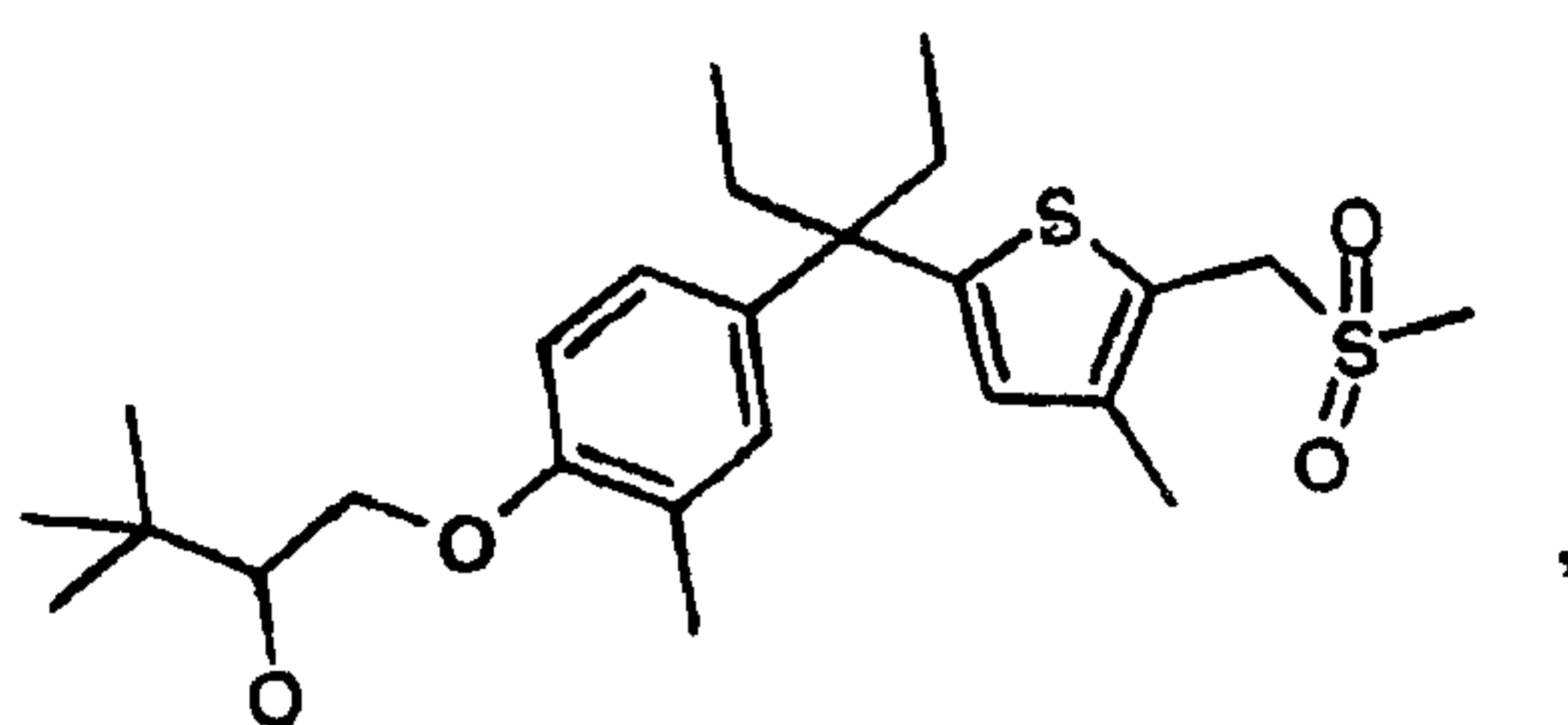


-378-

X9)

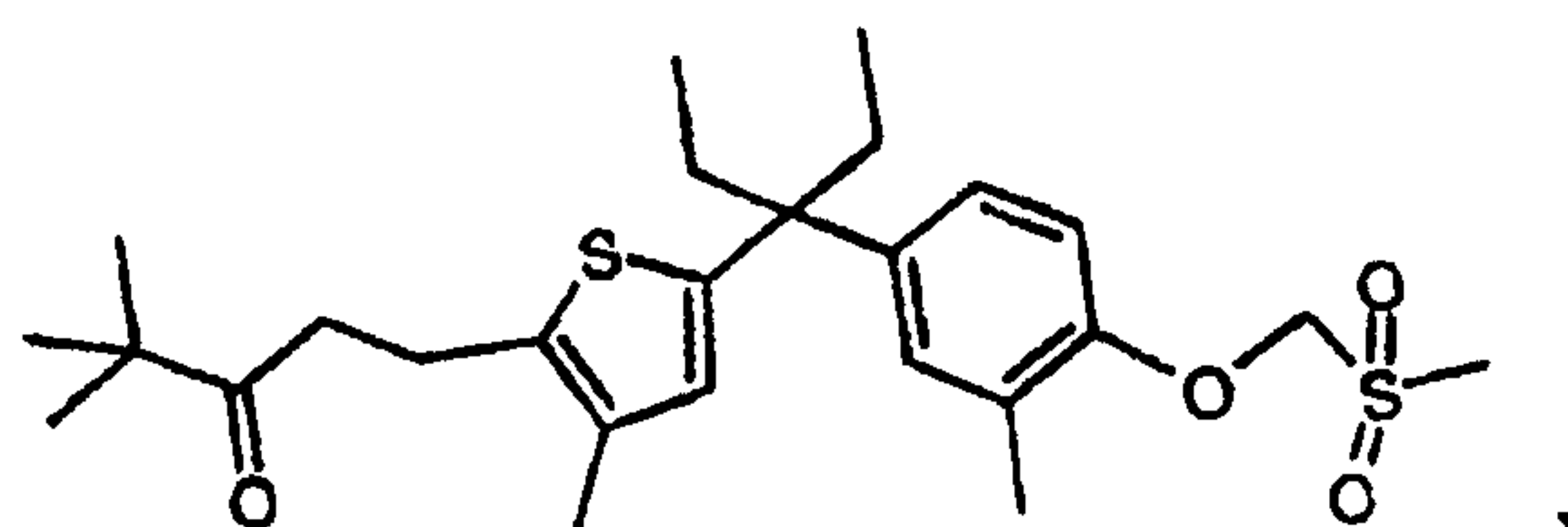


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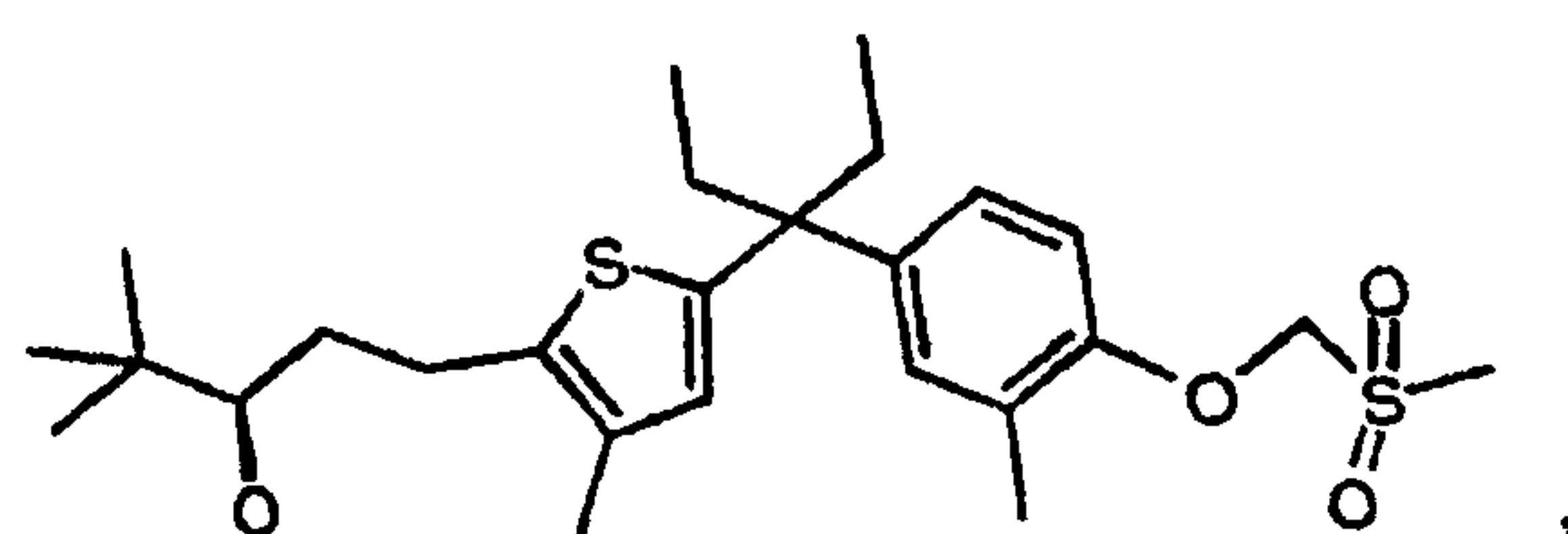


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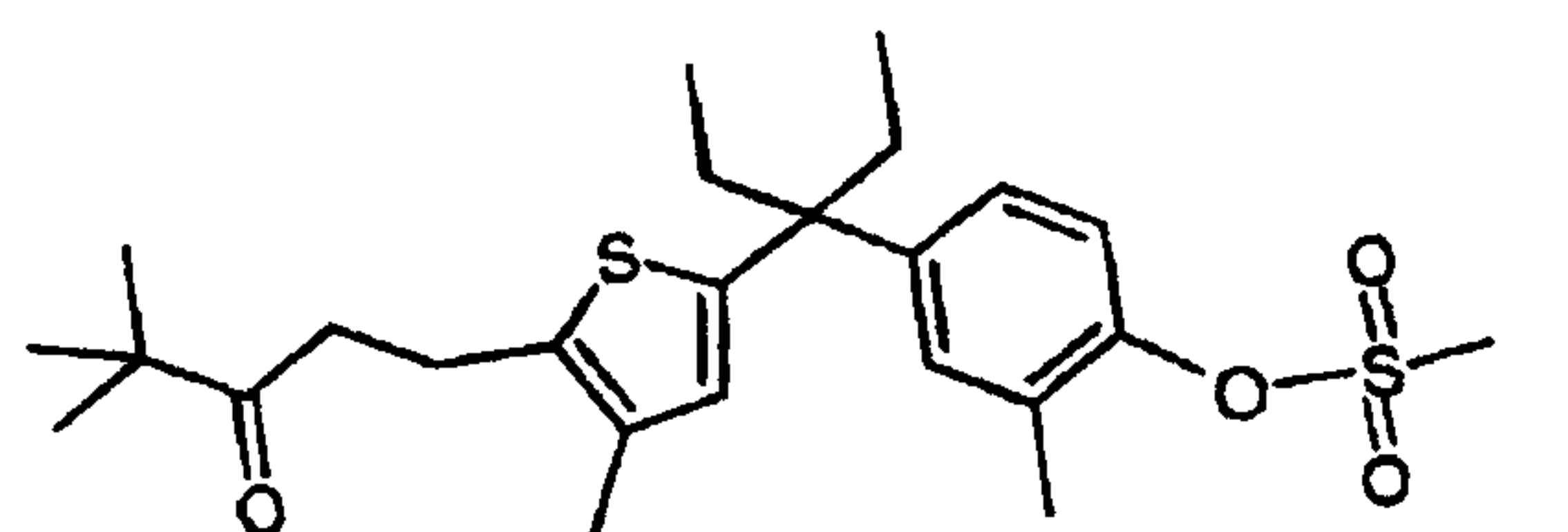


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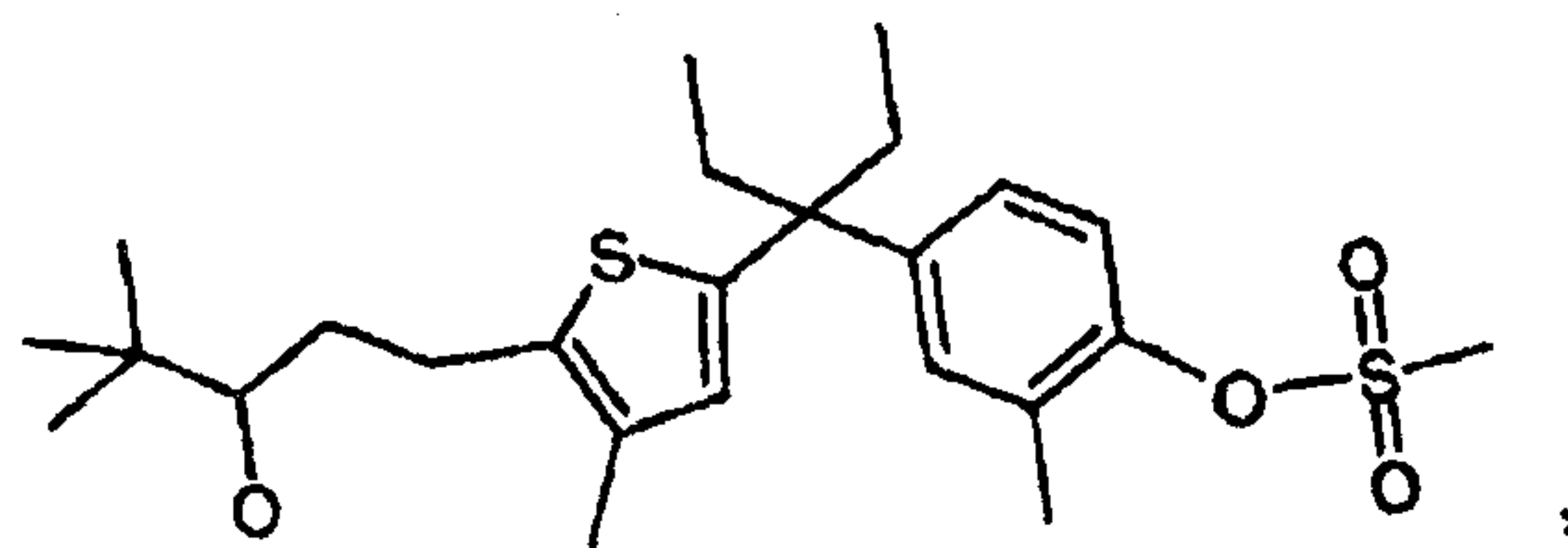
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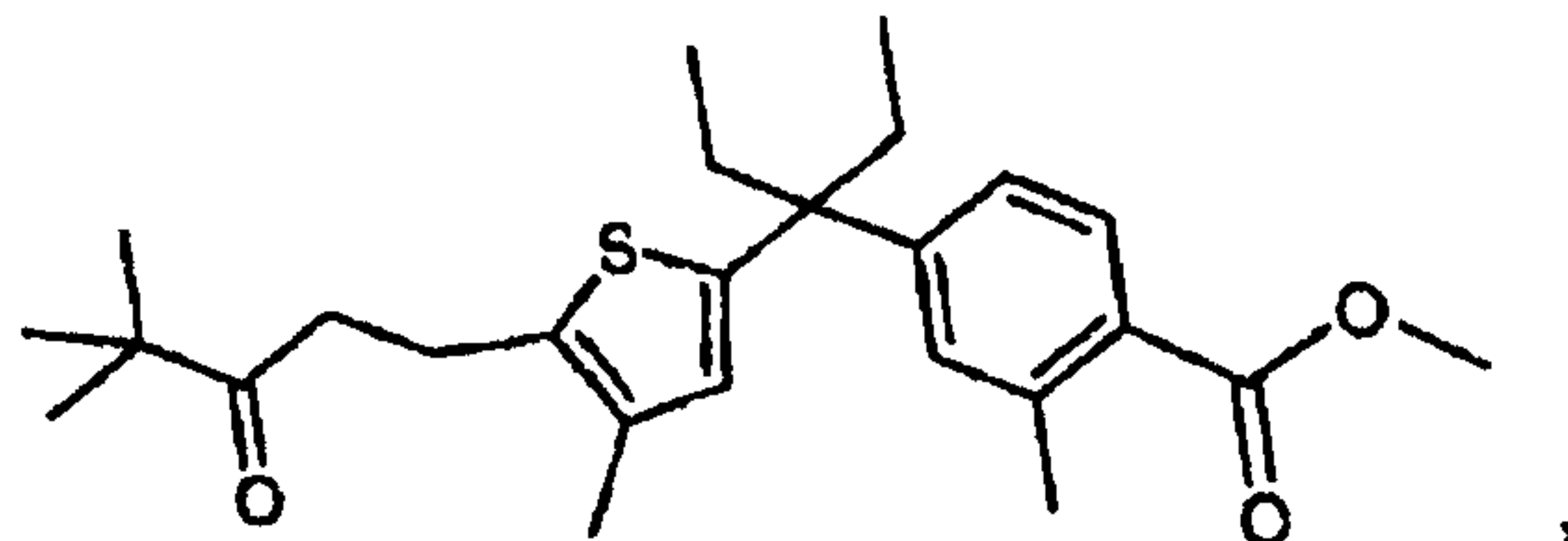


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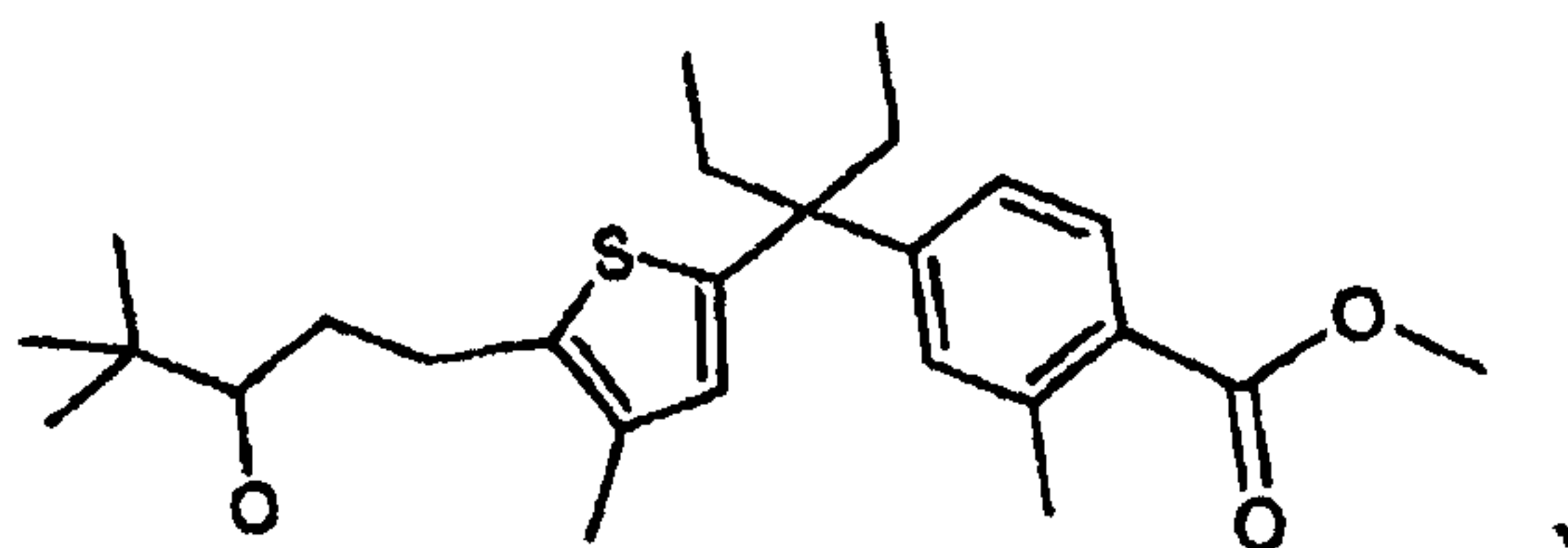
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X20)

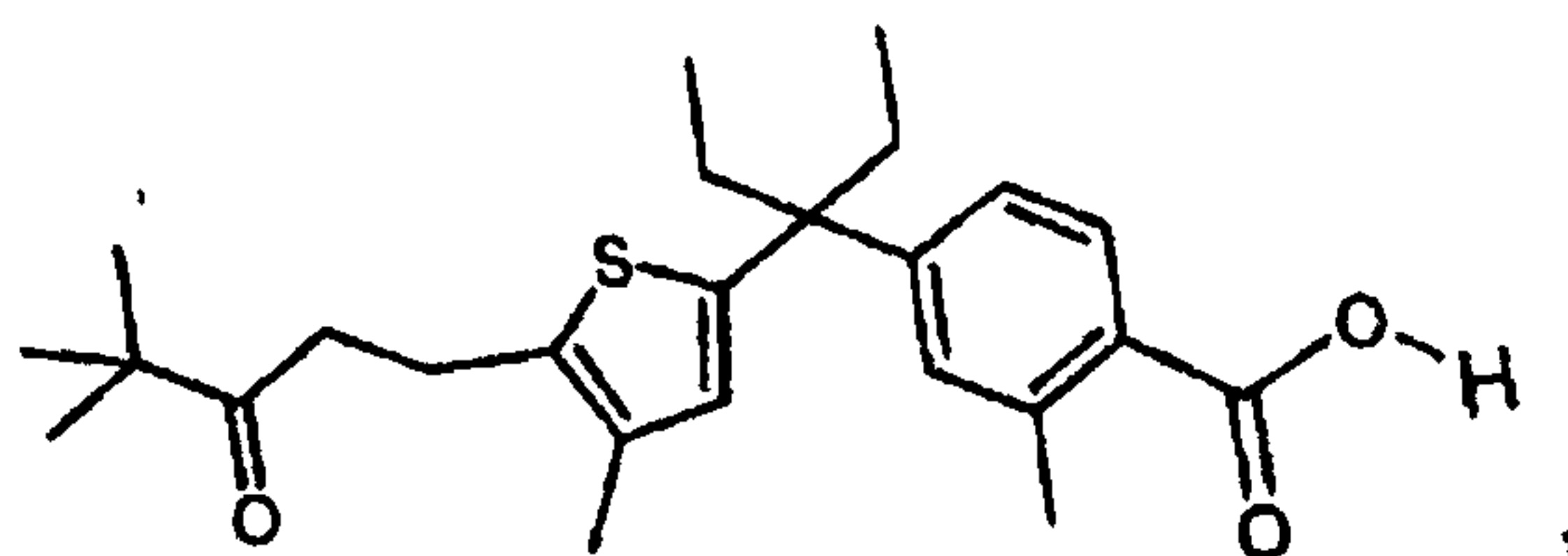


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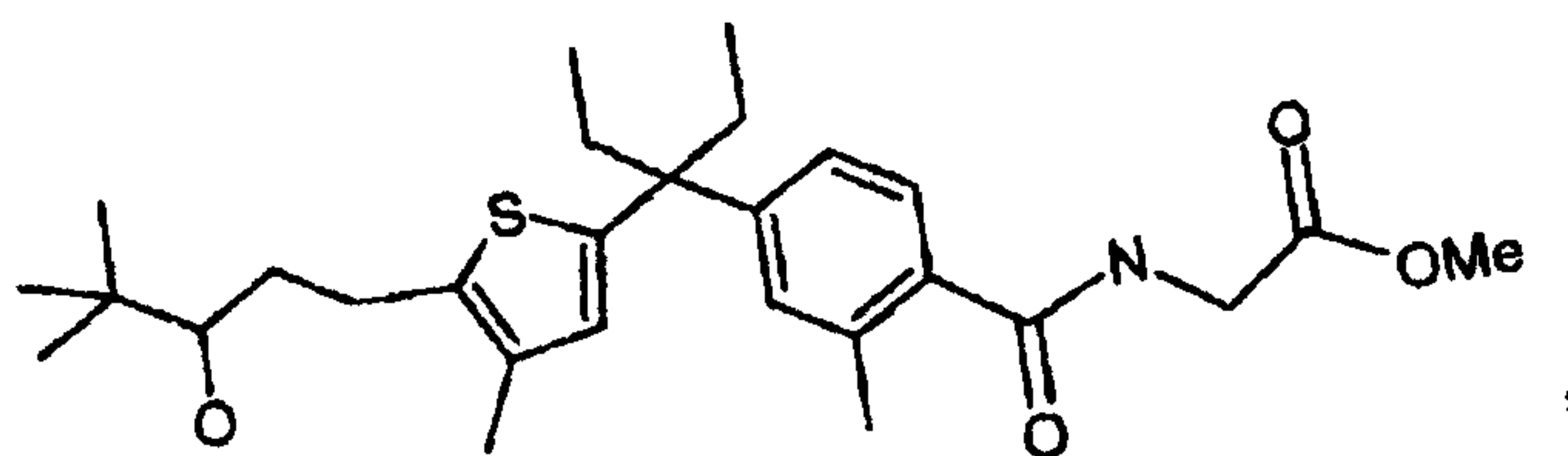


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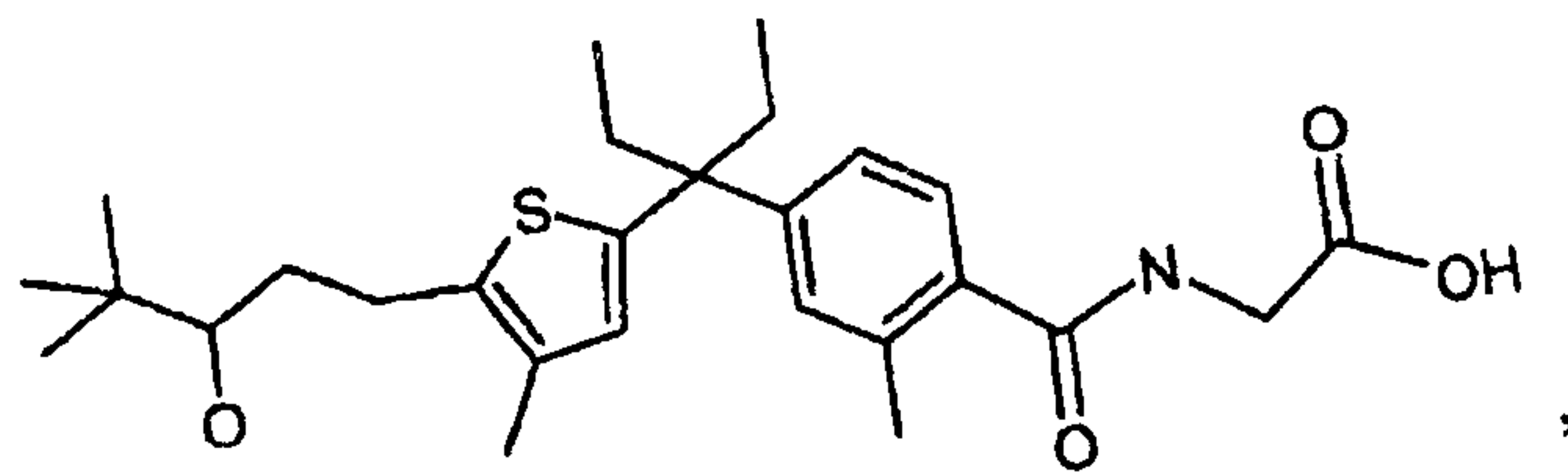


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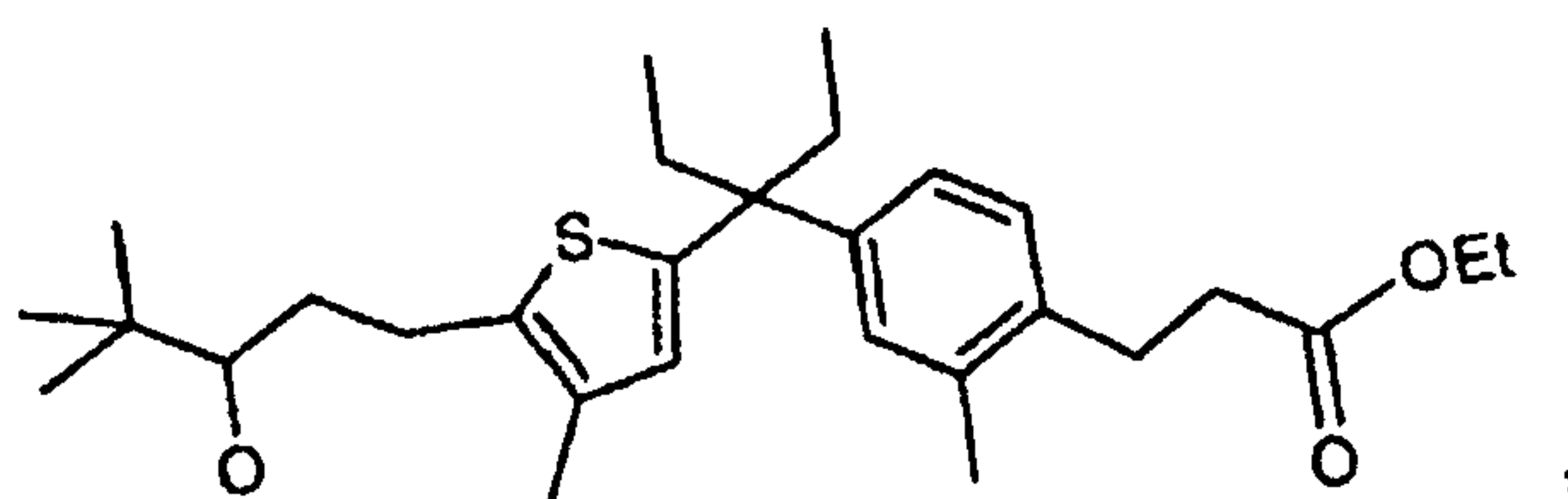


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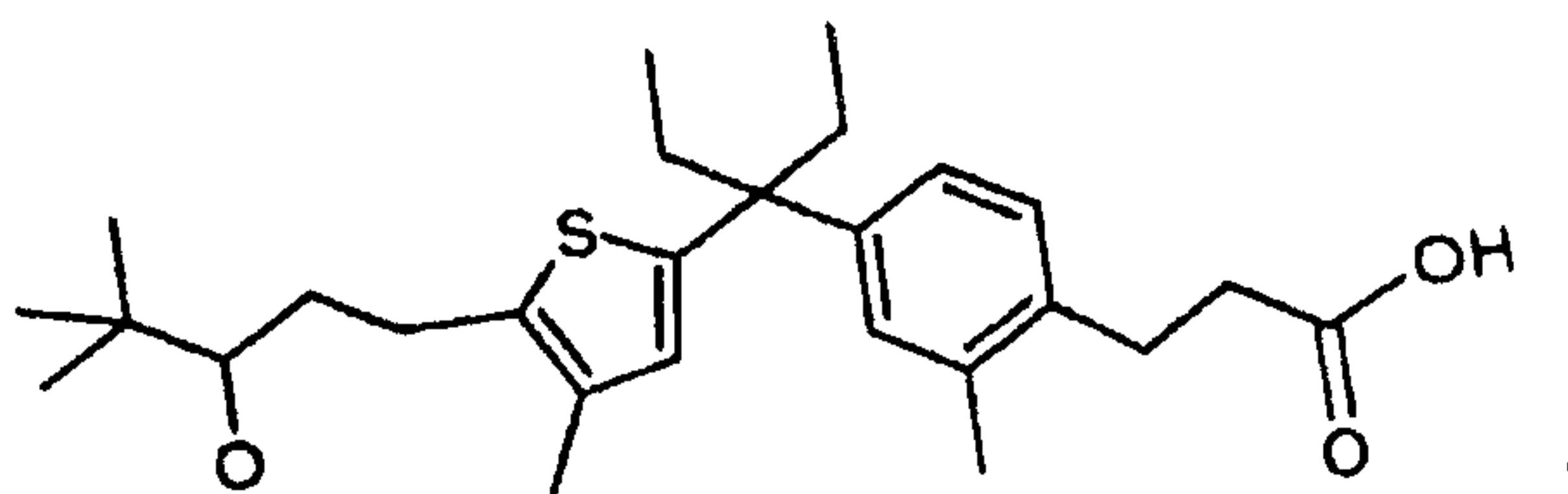


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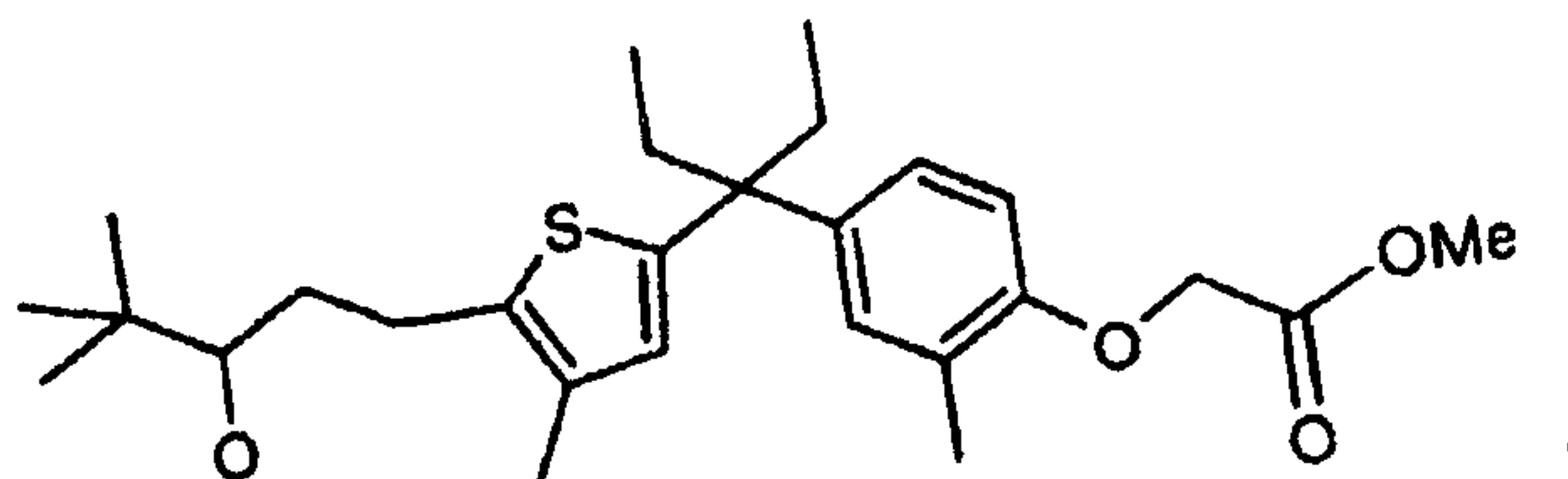


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X29)

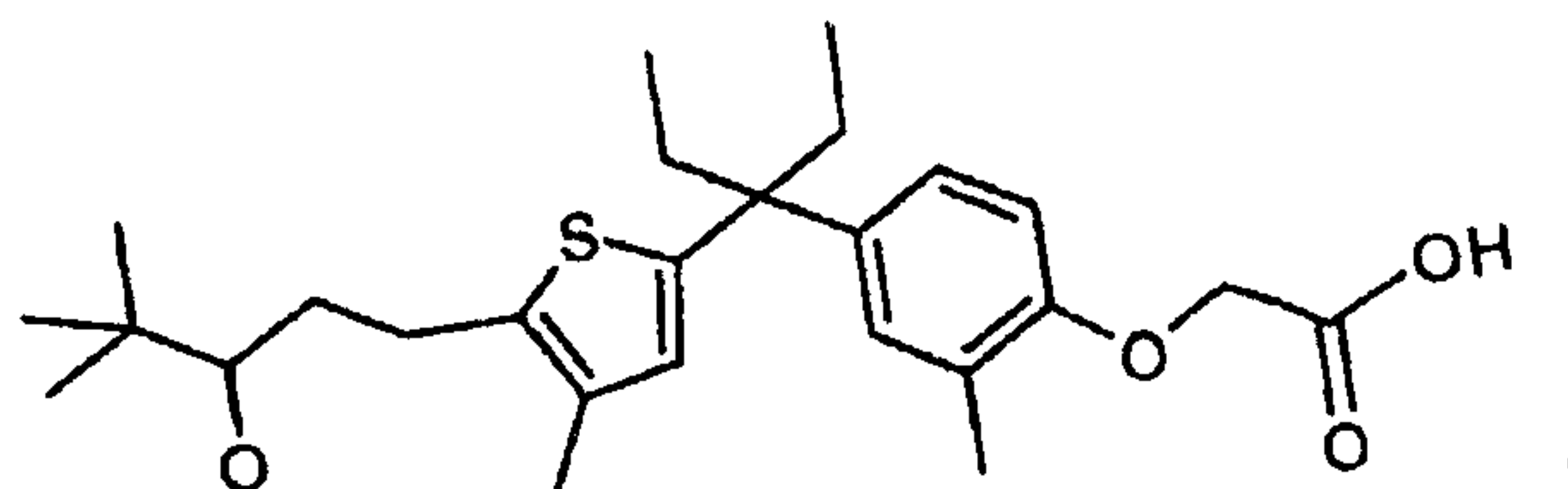


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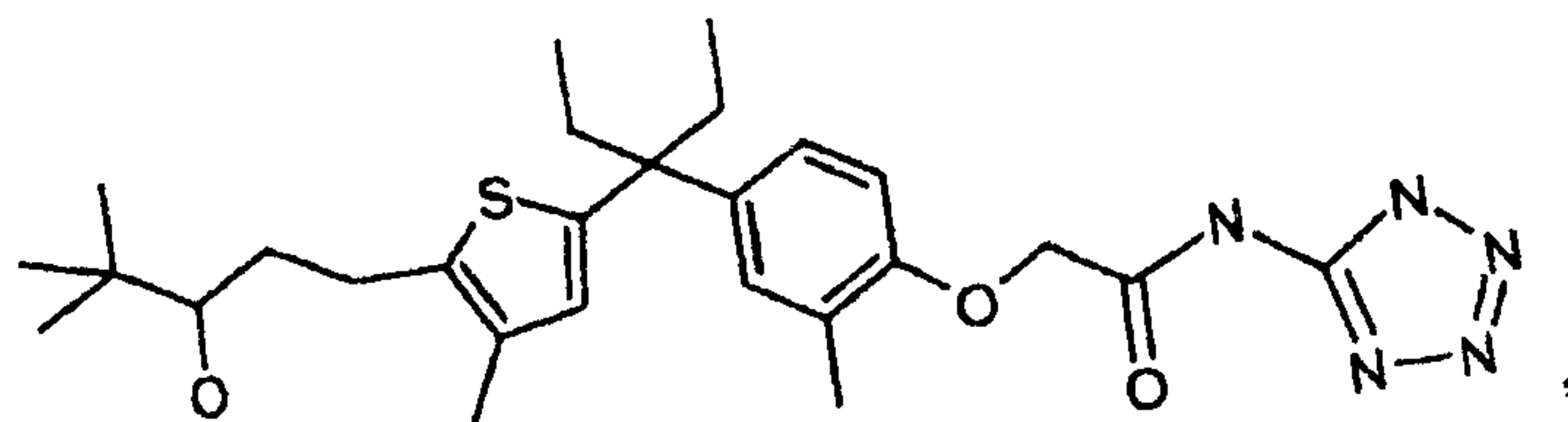
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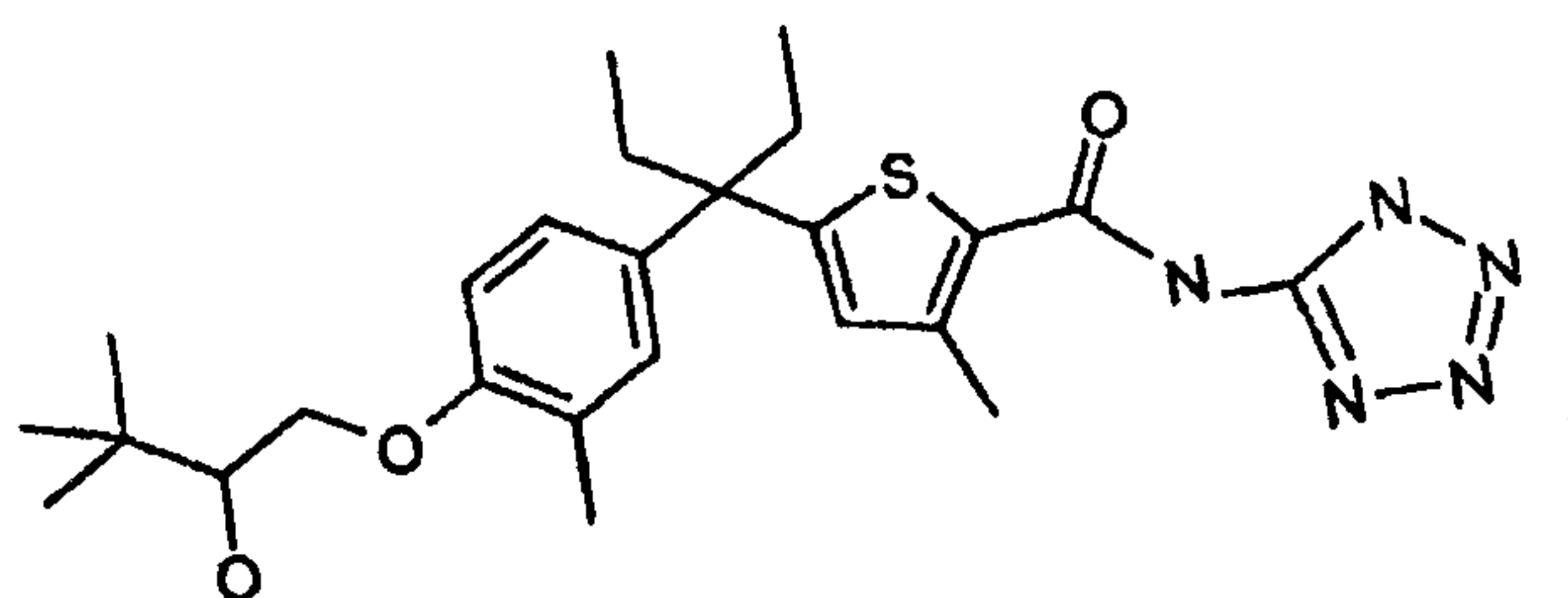


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X34)

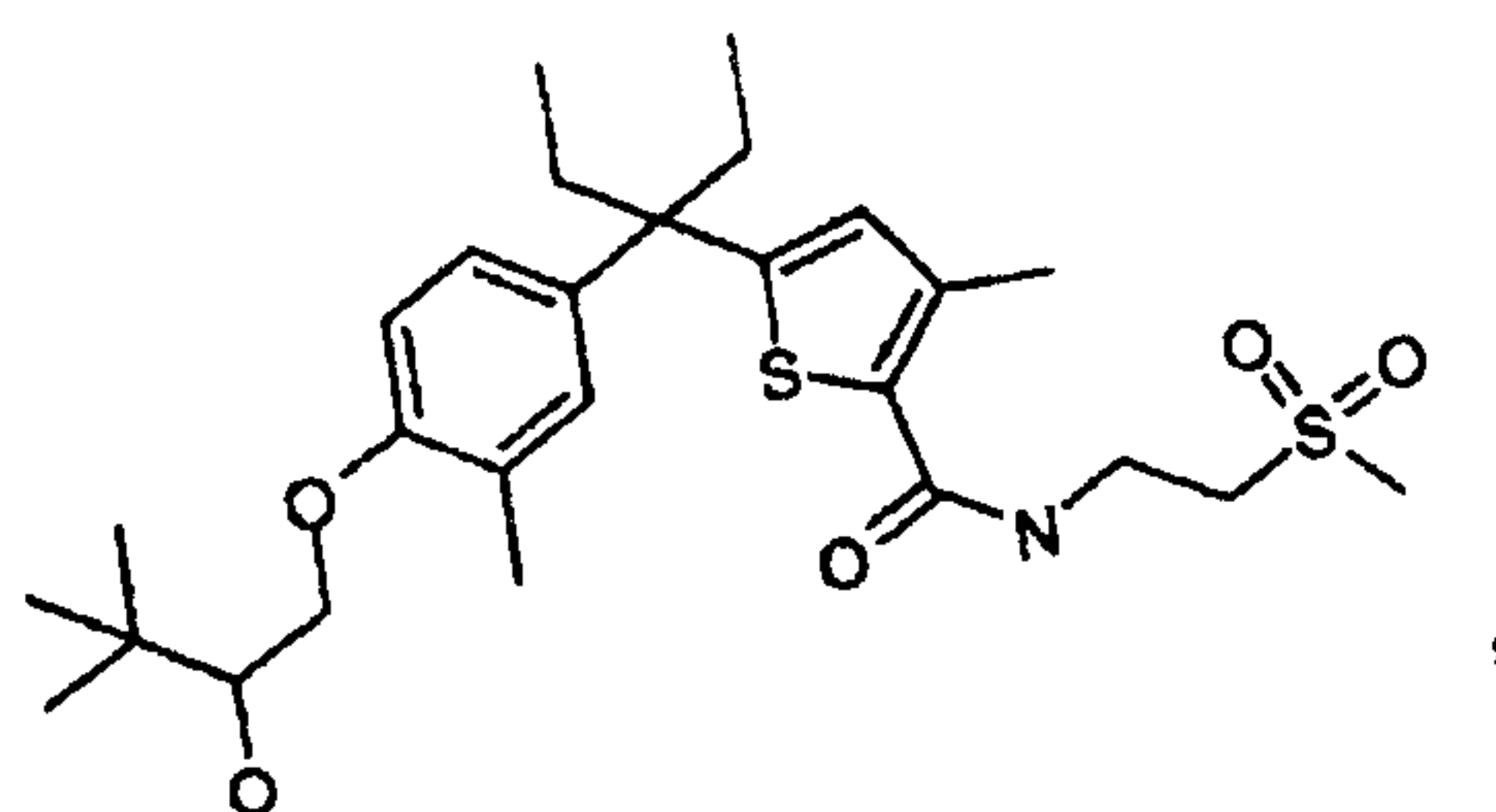


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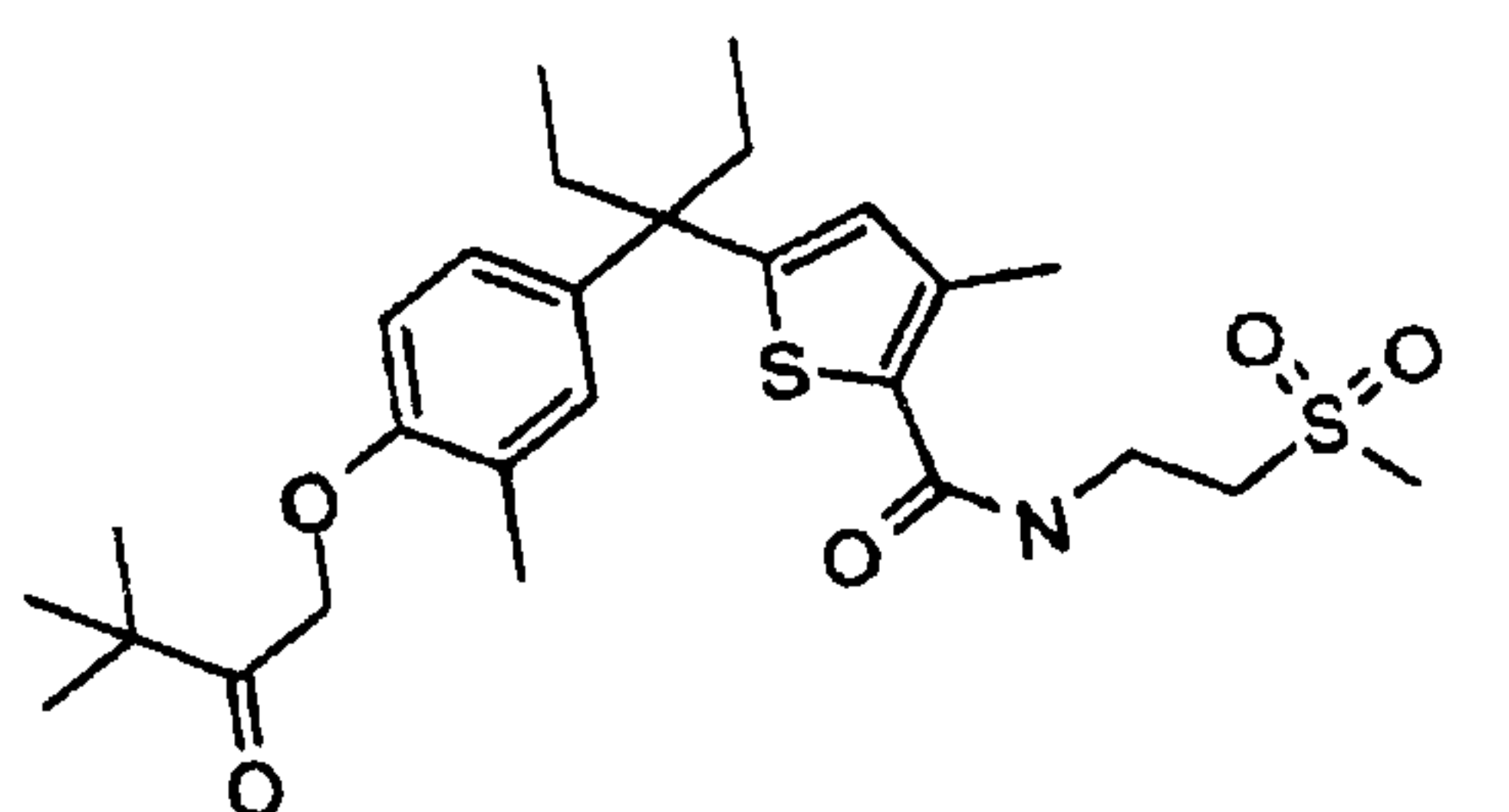


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X38)

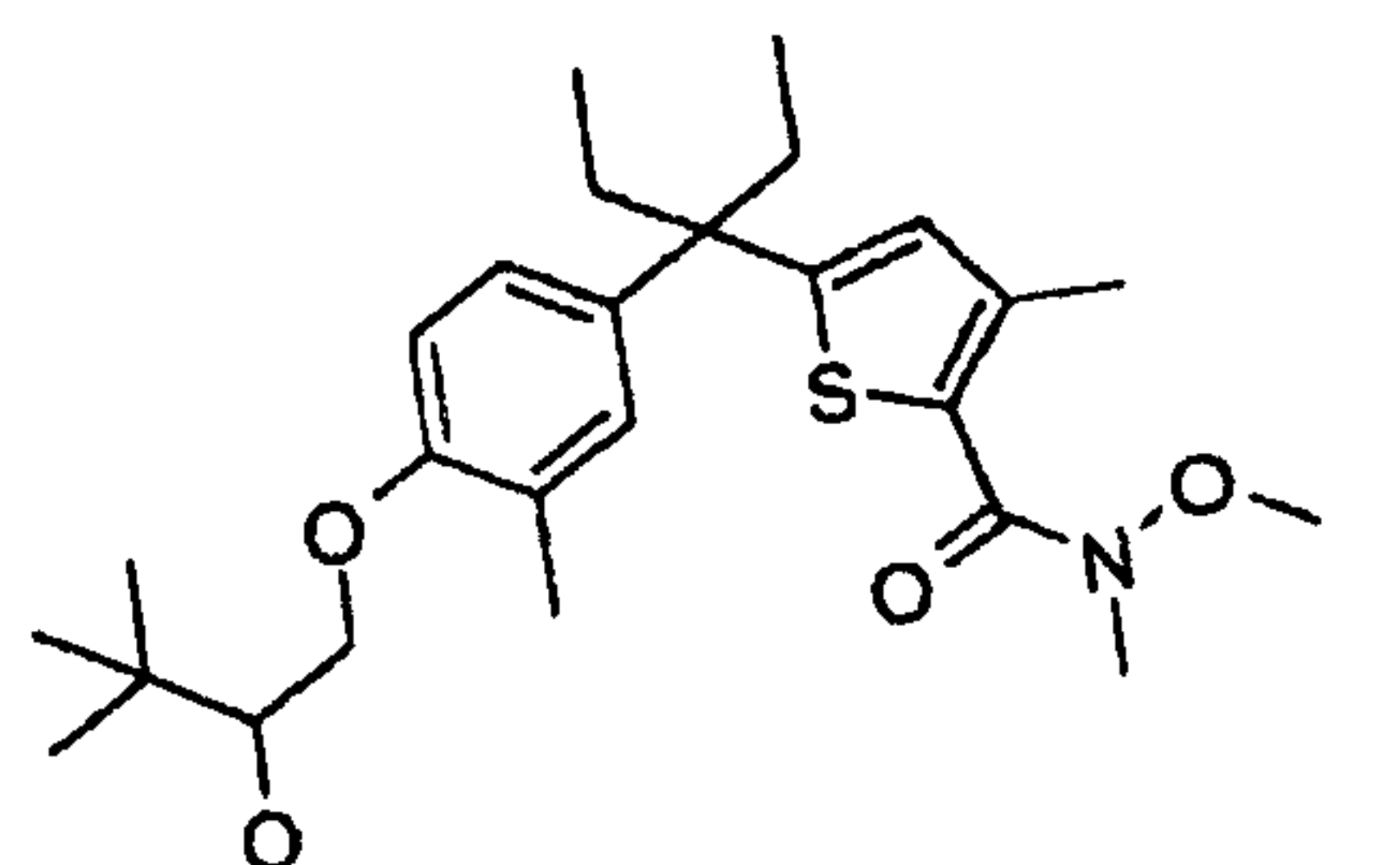


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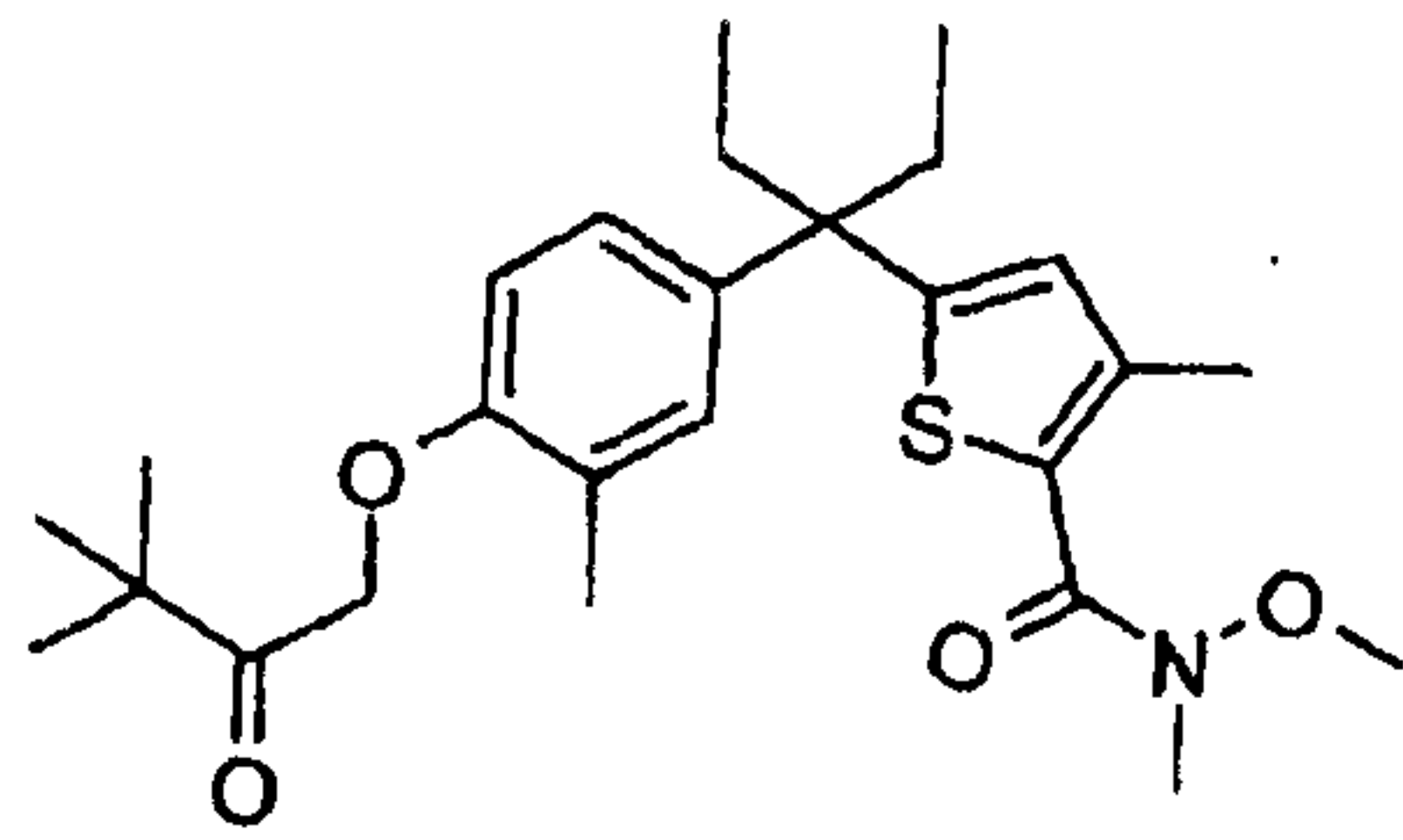
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X42)

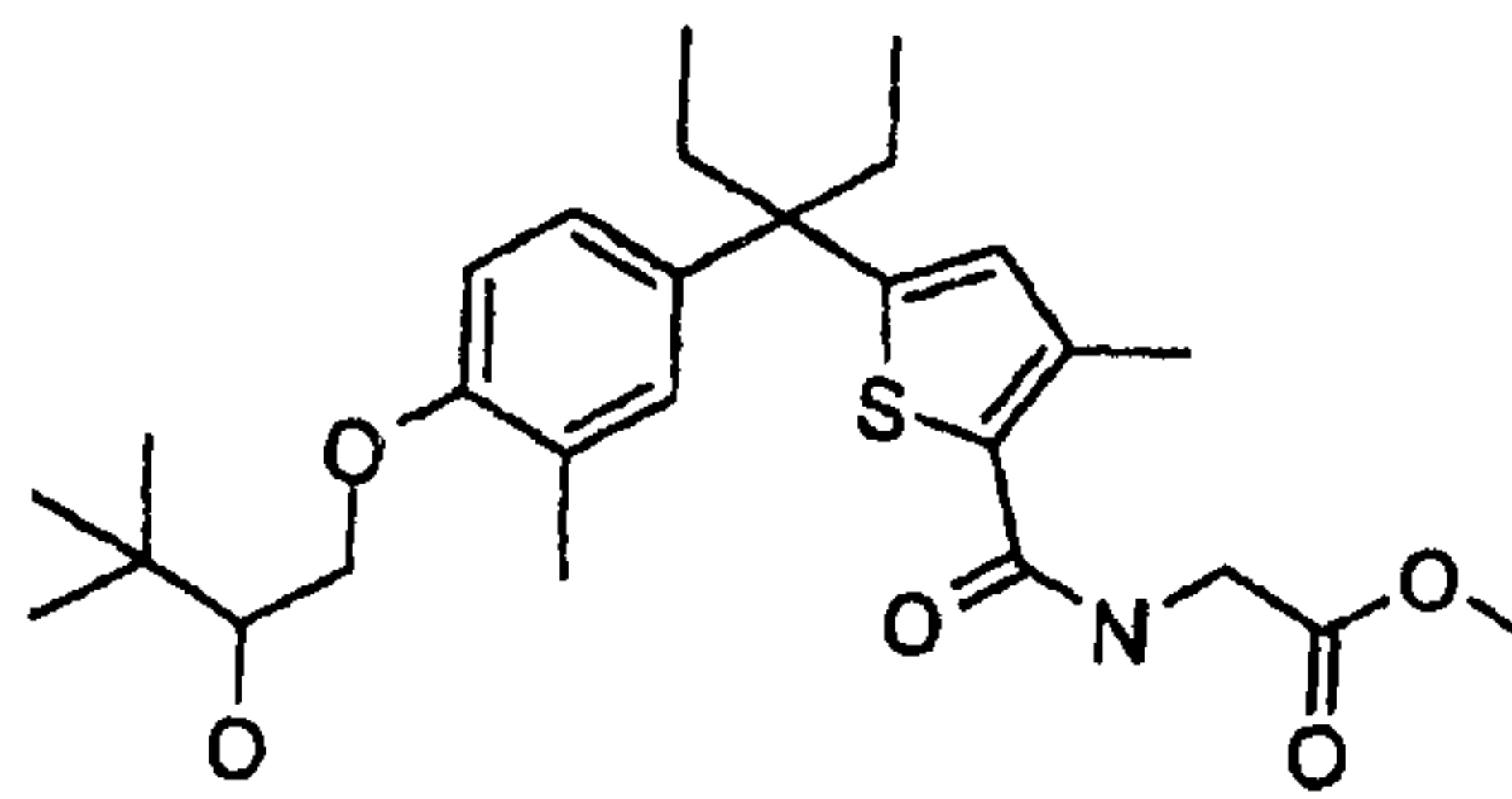


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X45)

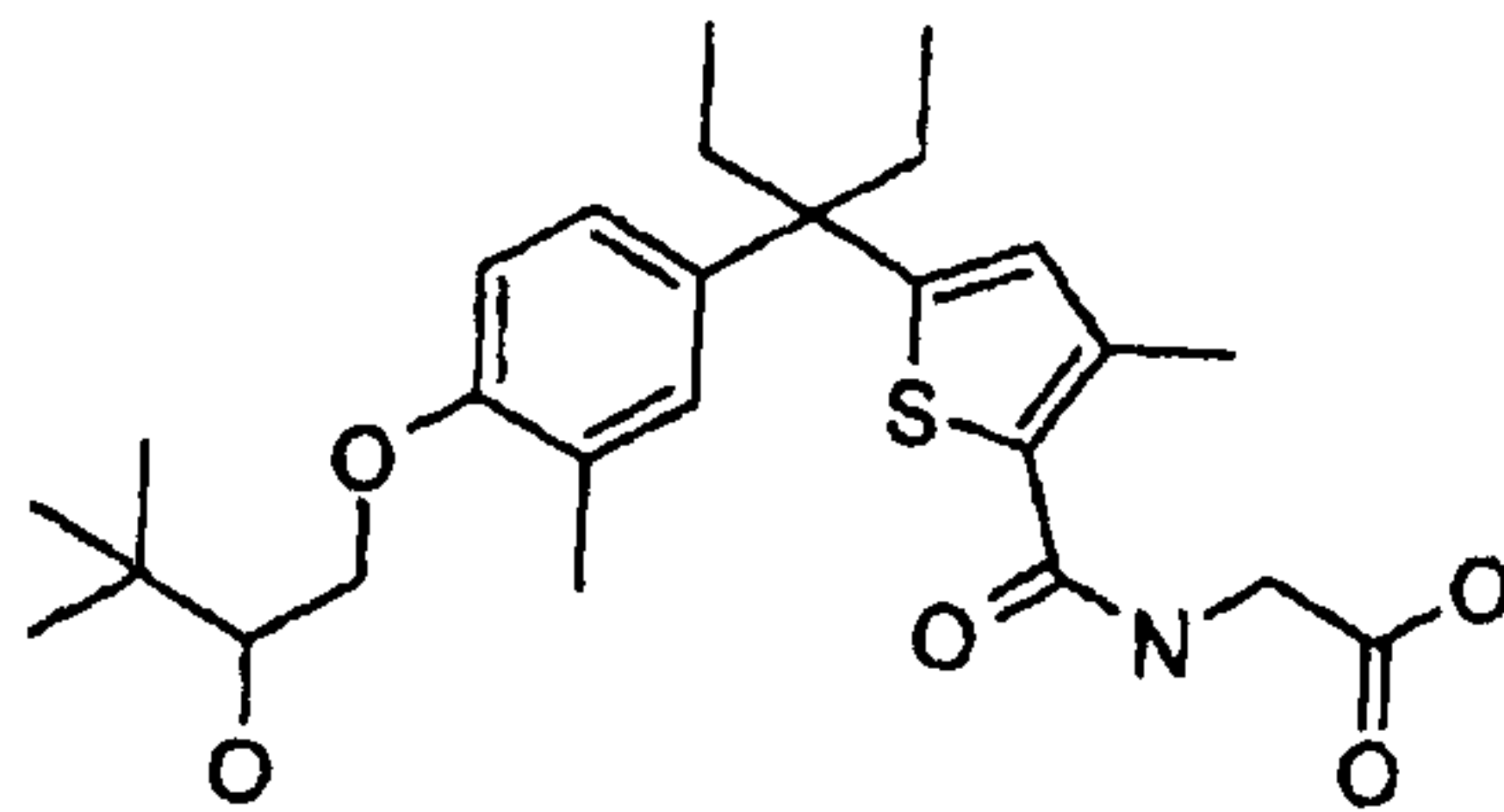


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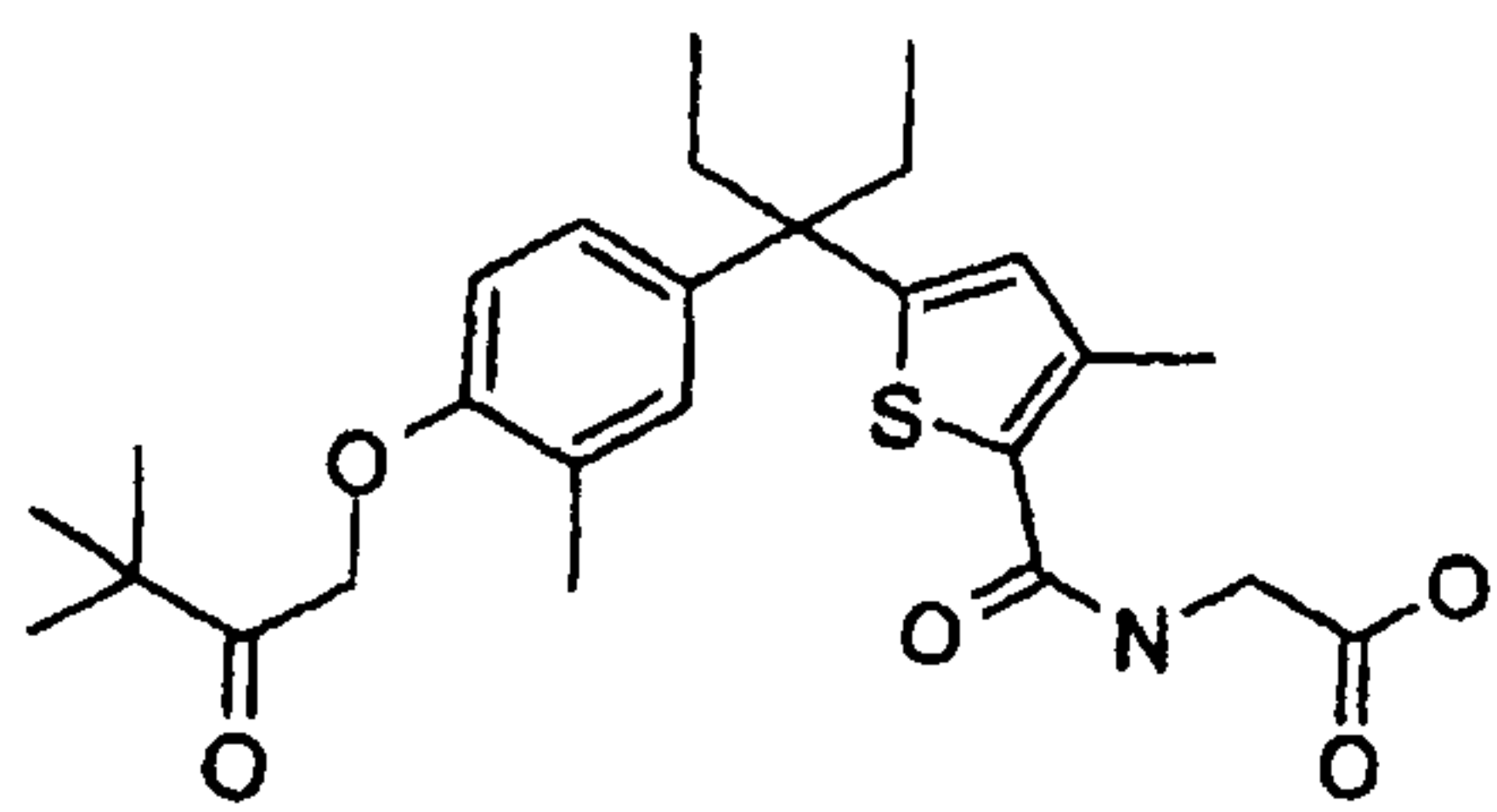


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X47)



X50)



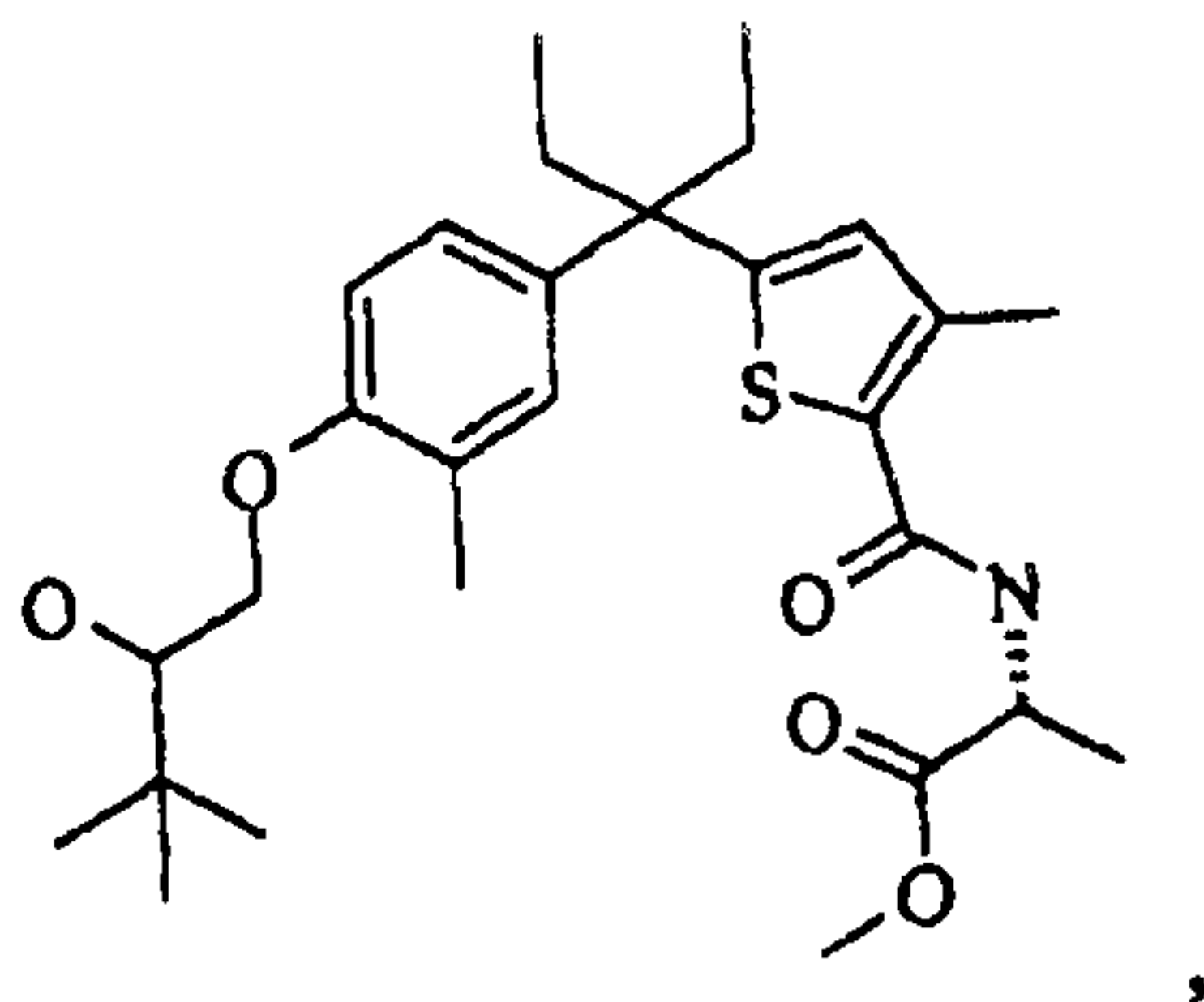
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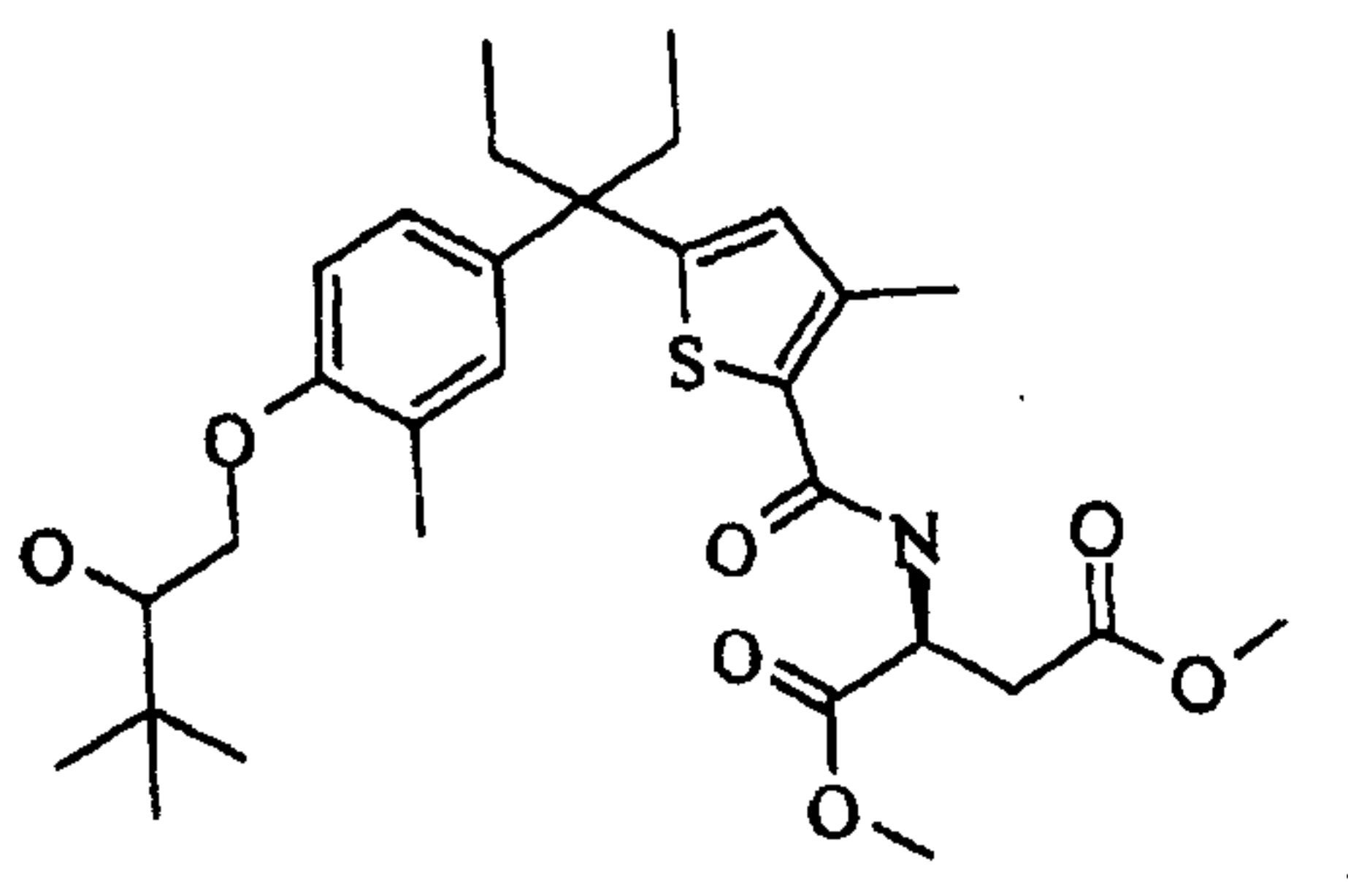
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-384-

X56)

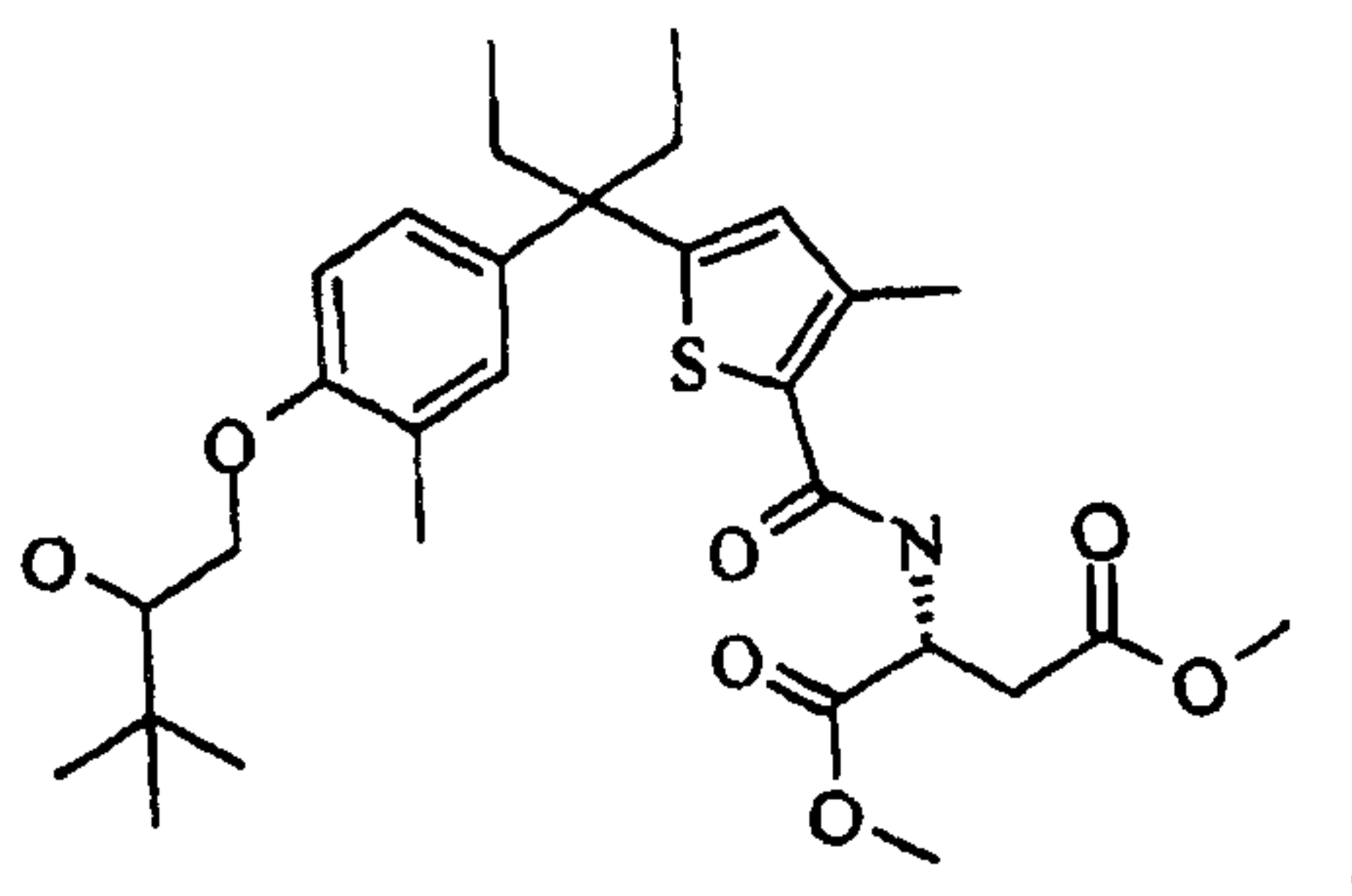


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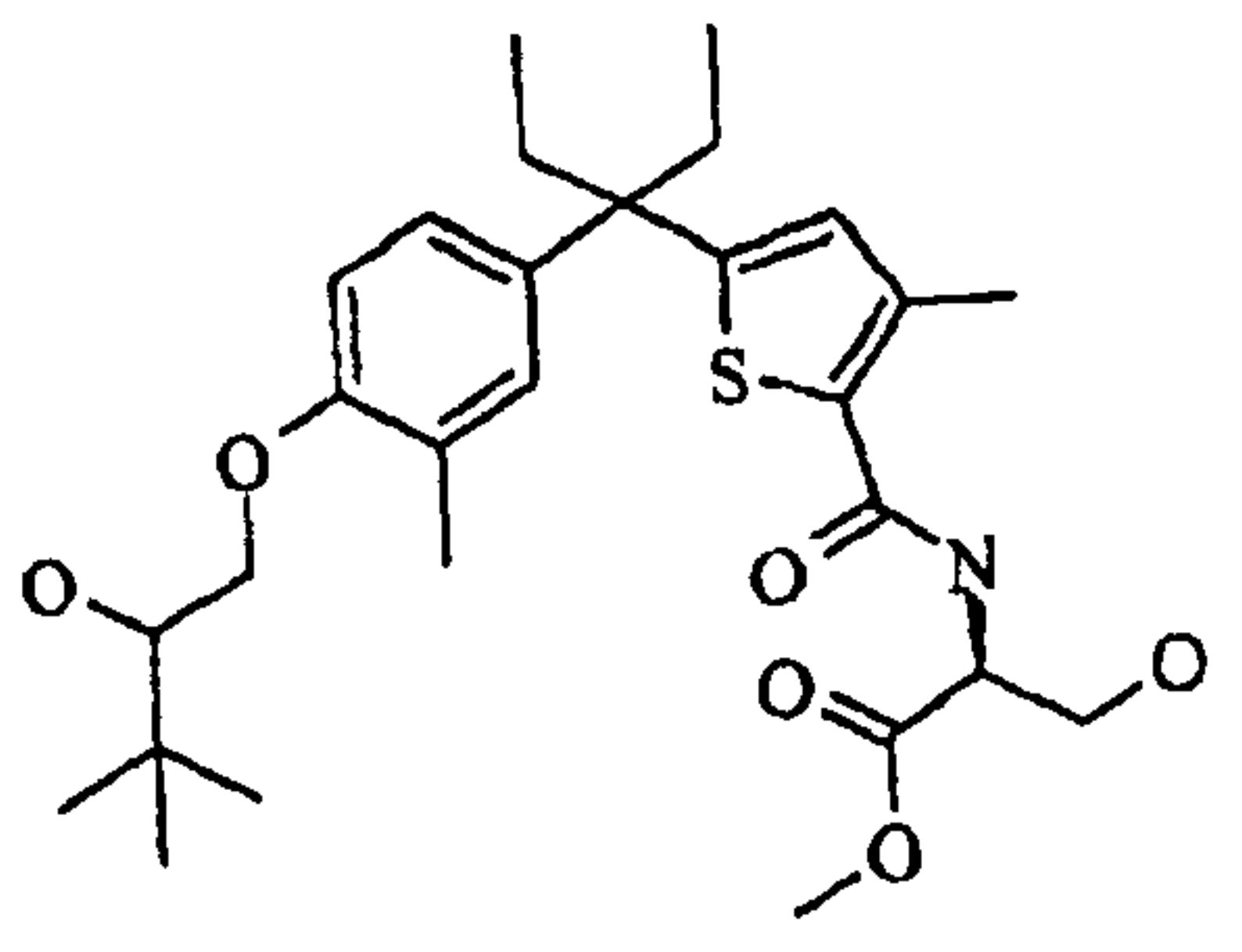


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X60)



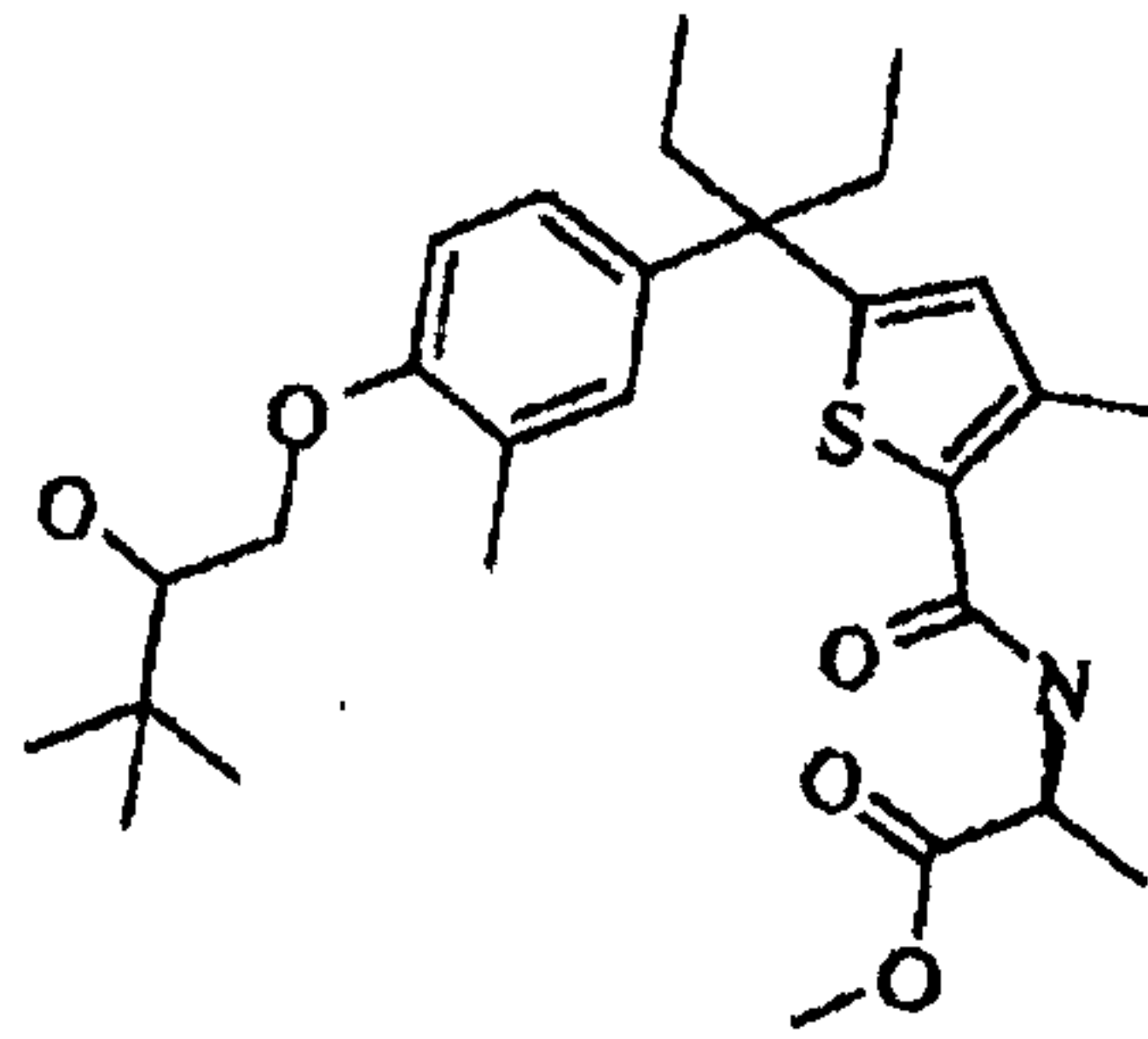
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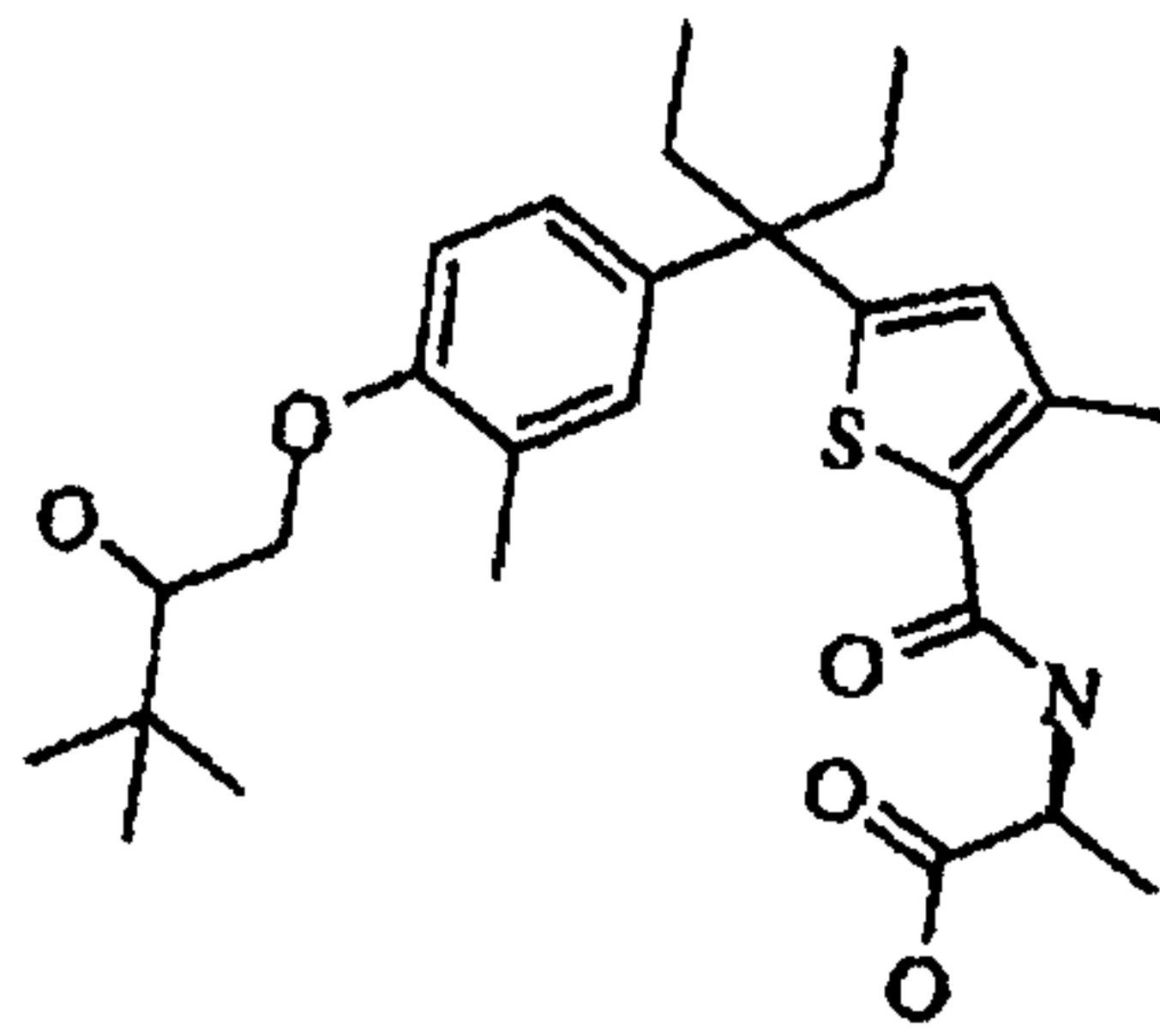
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X64)

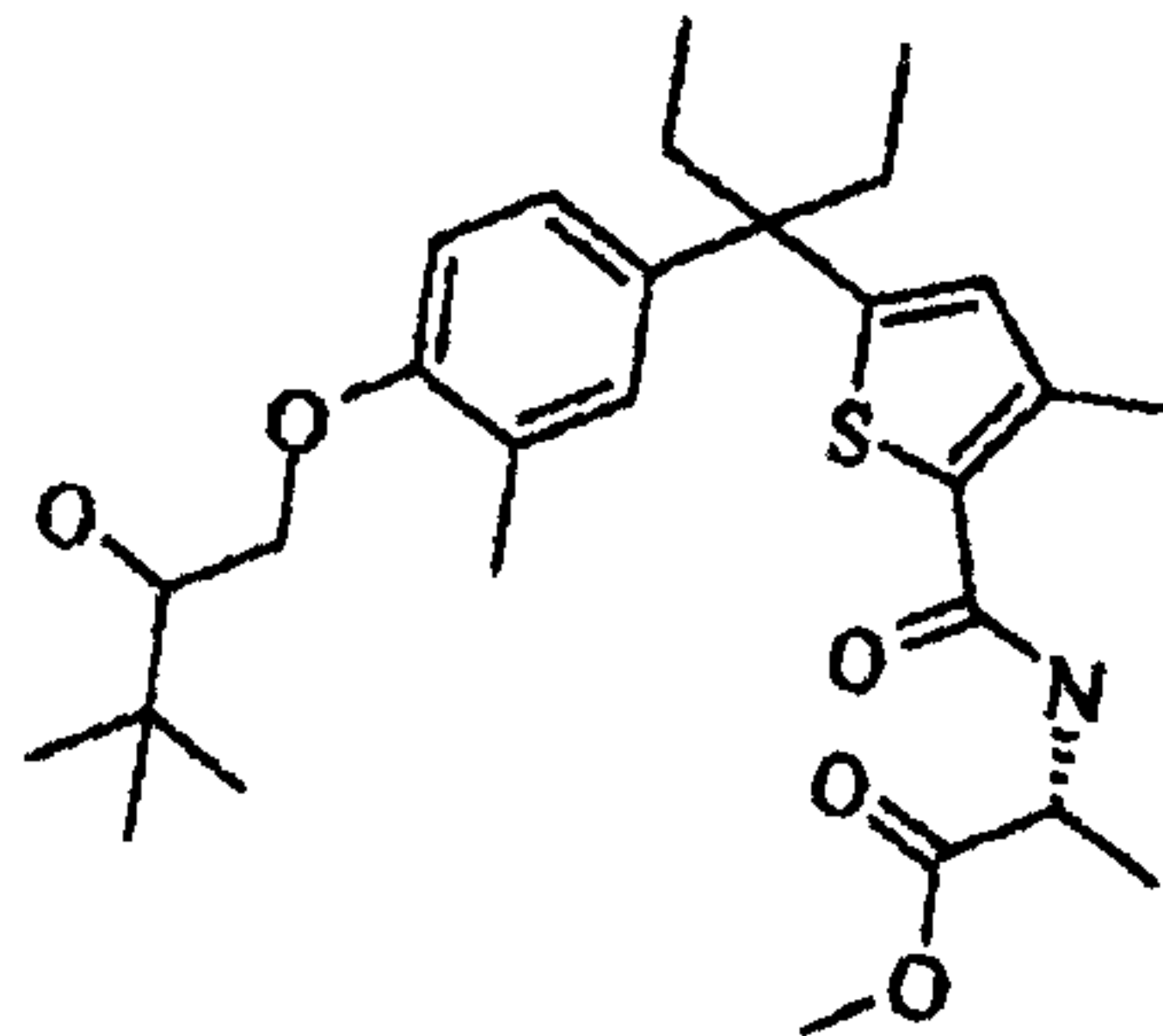
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X65)

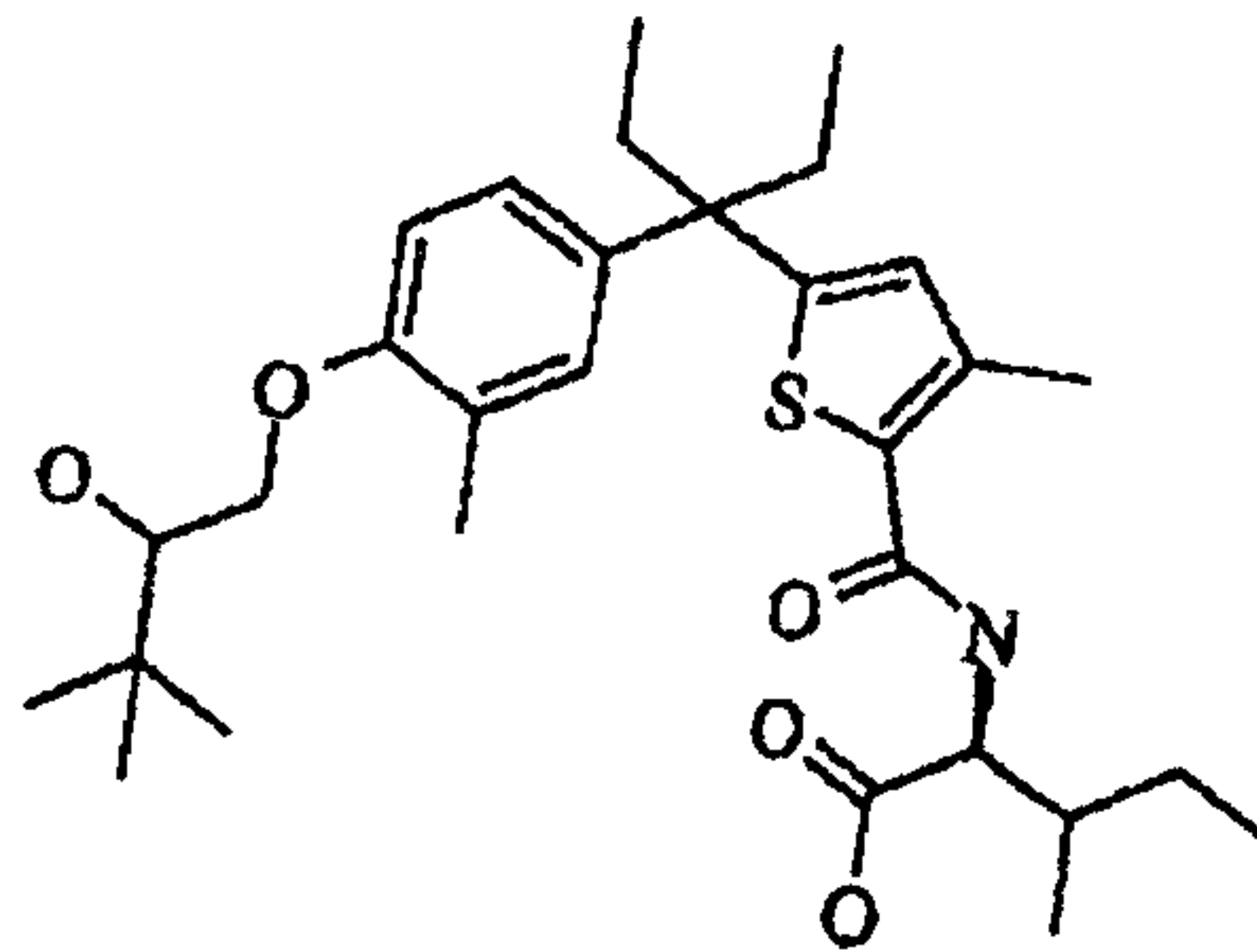


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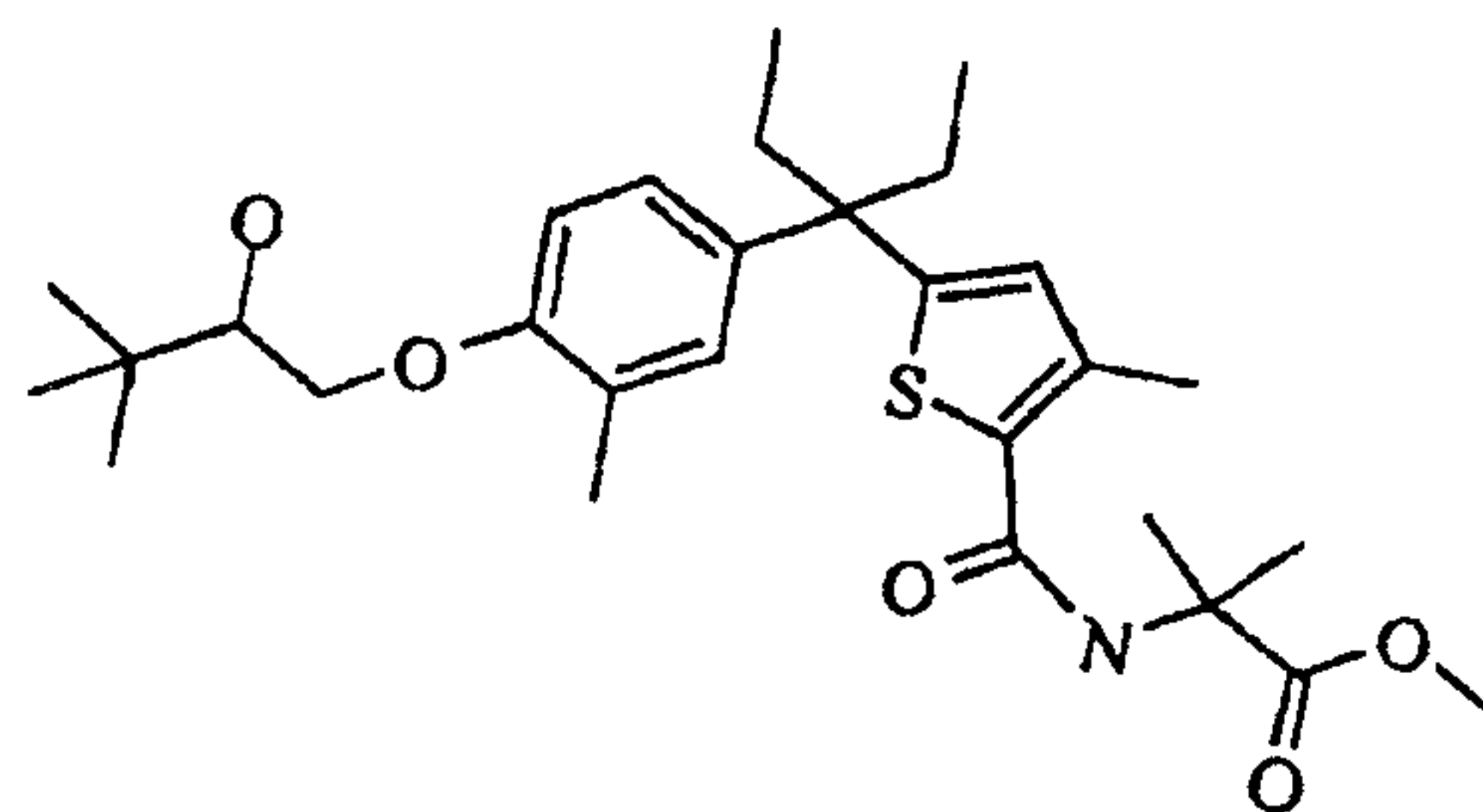
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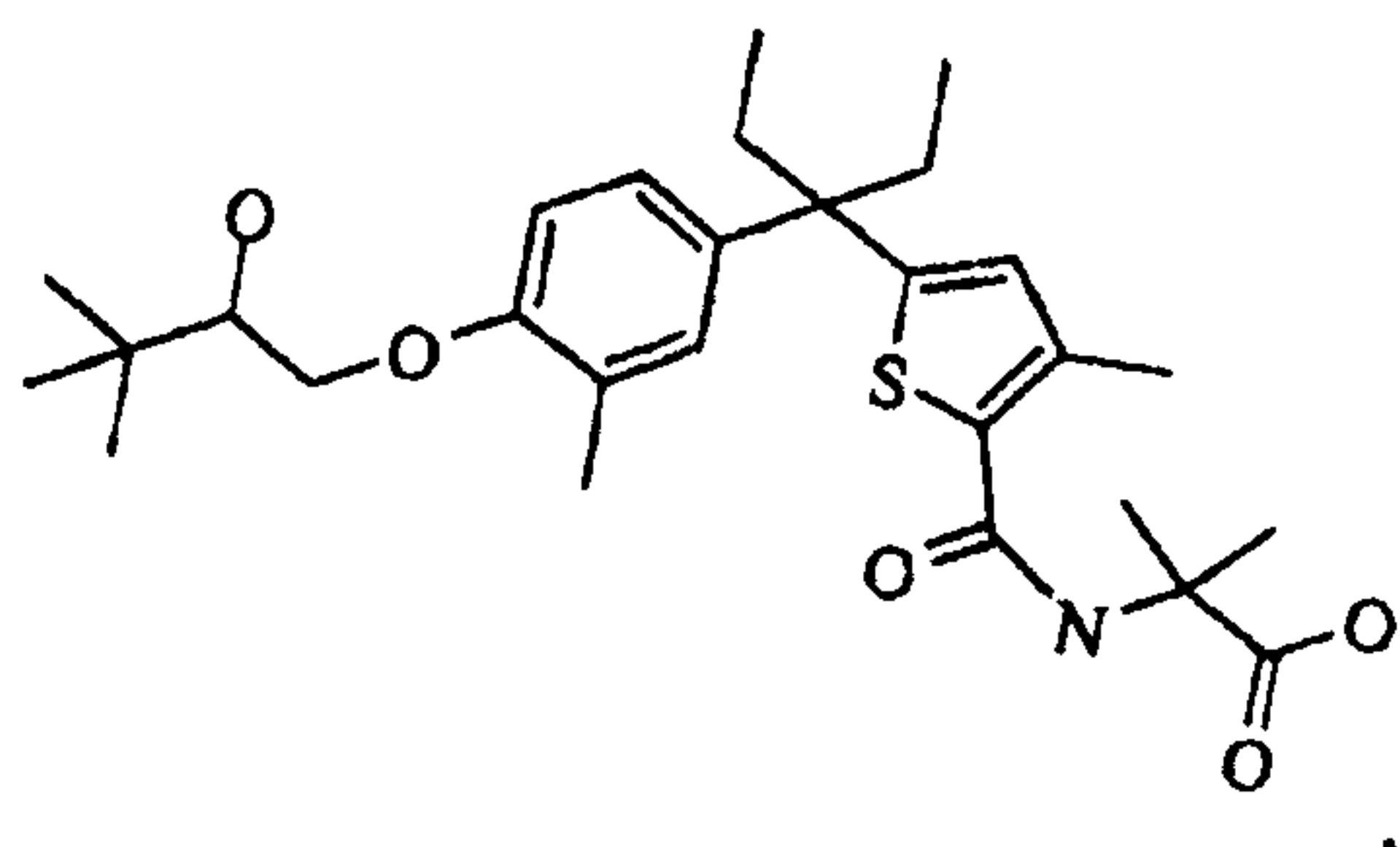


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X70)

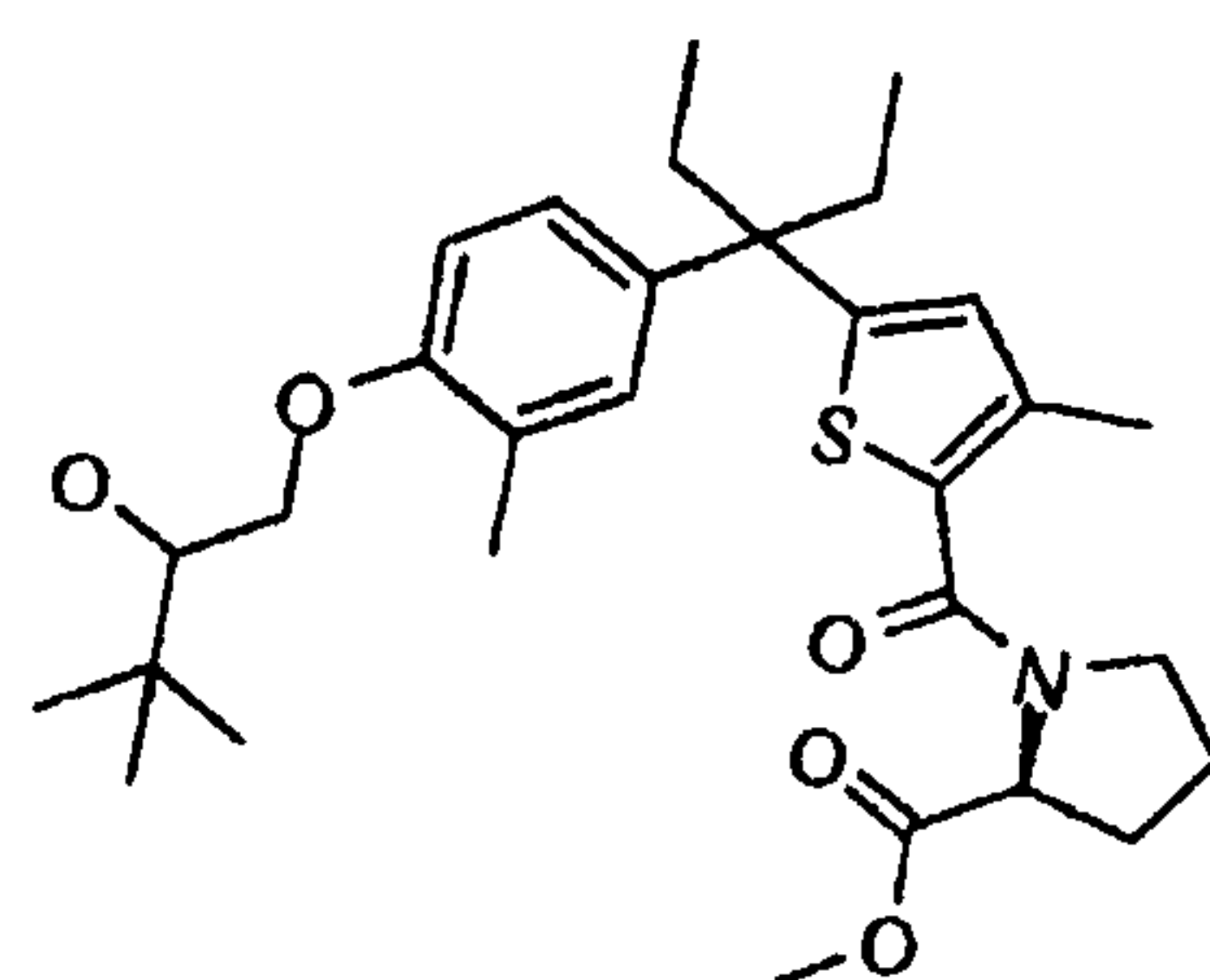


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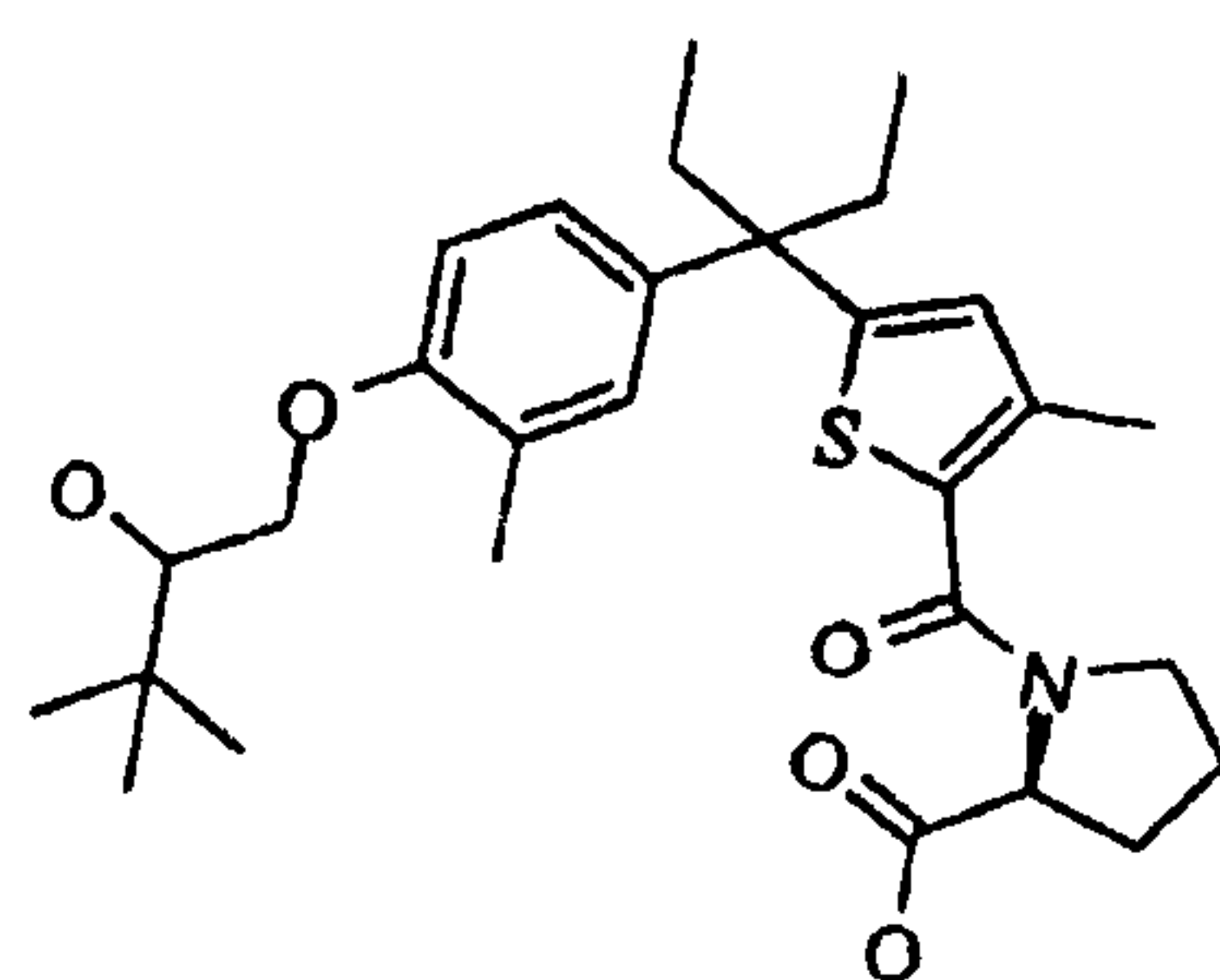


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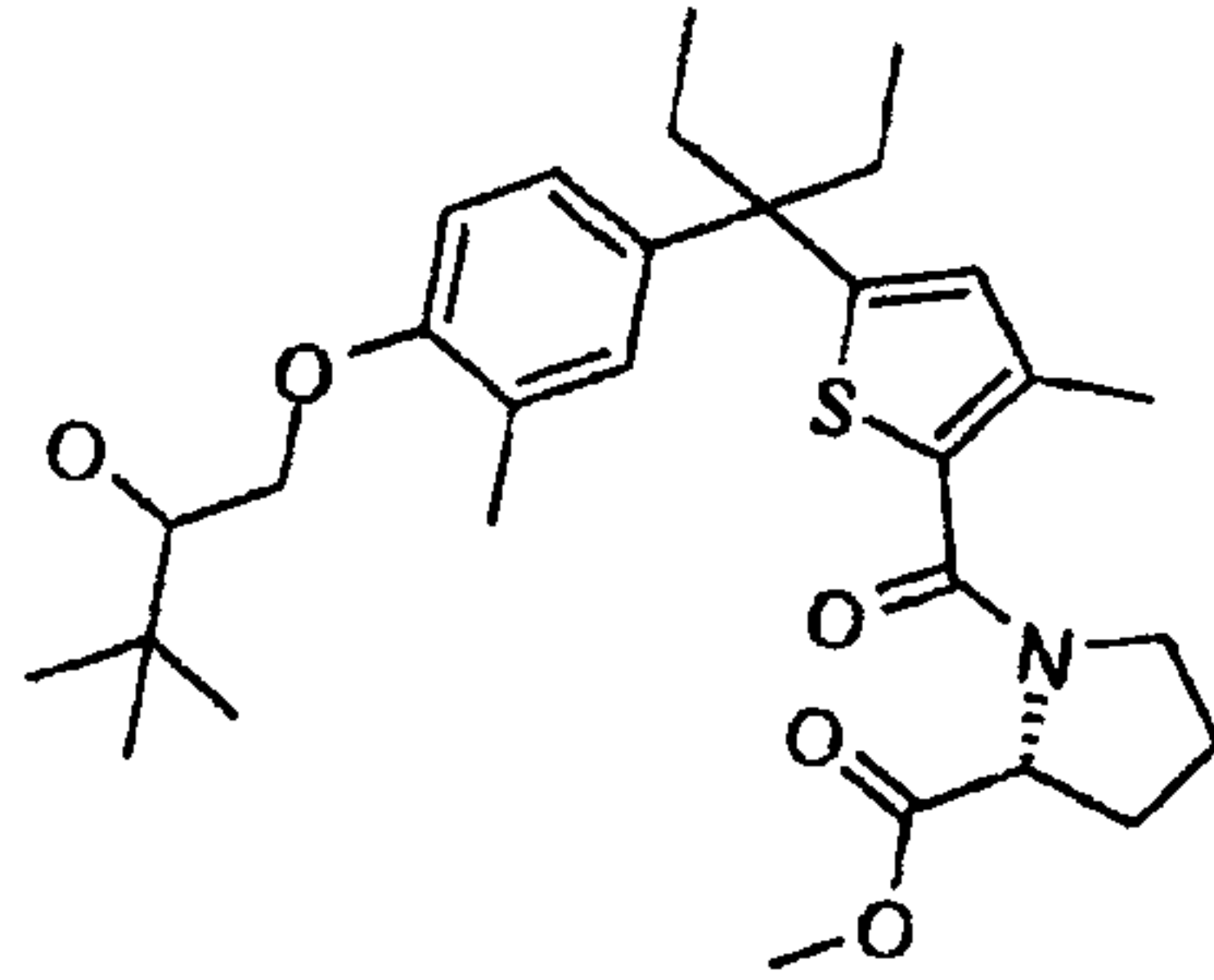


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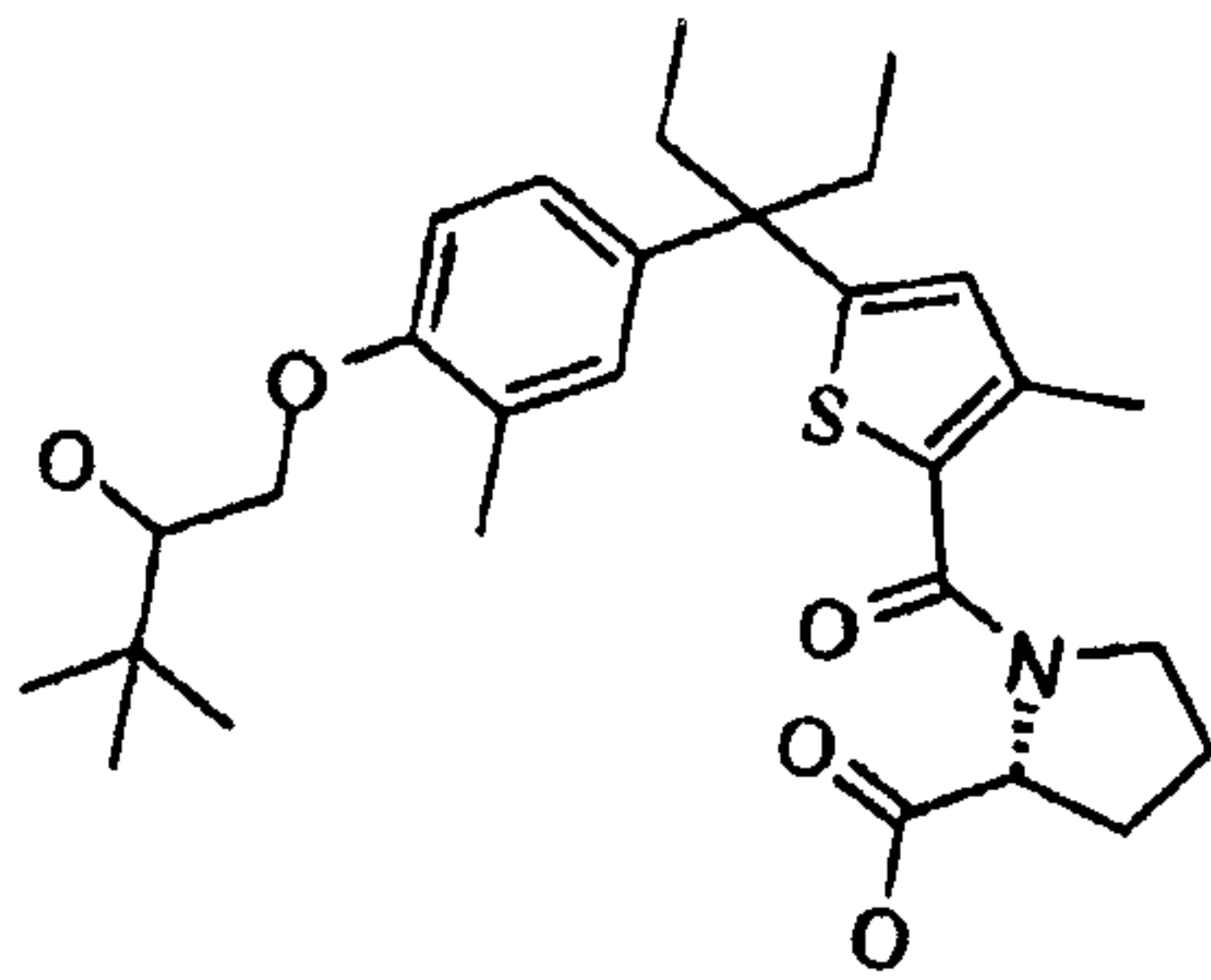


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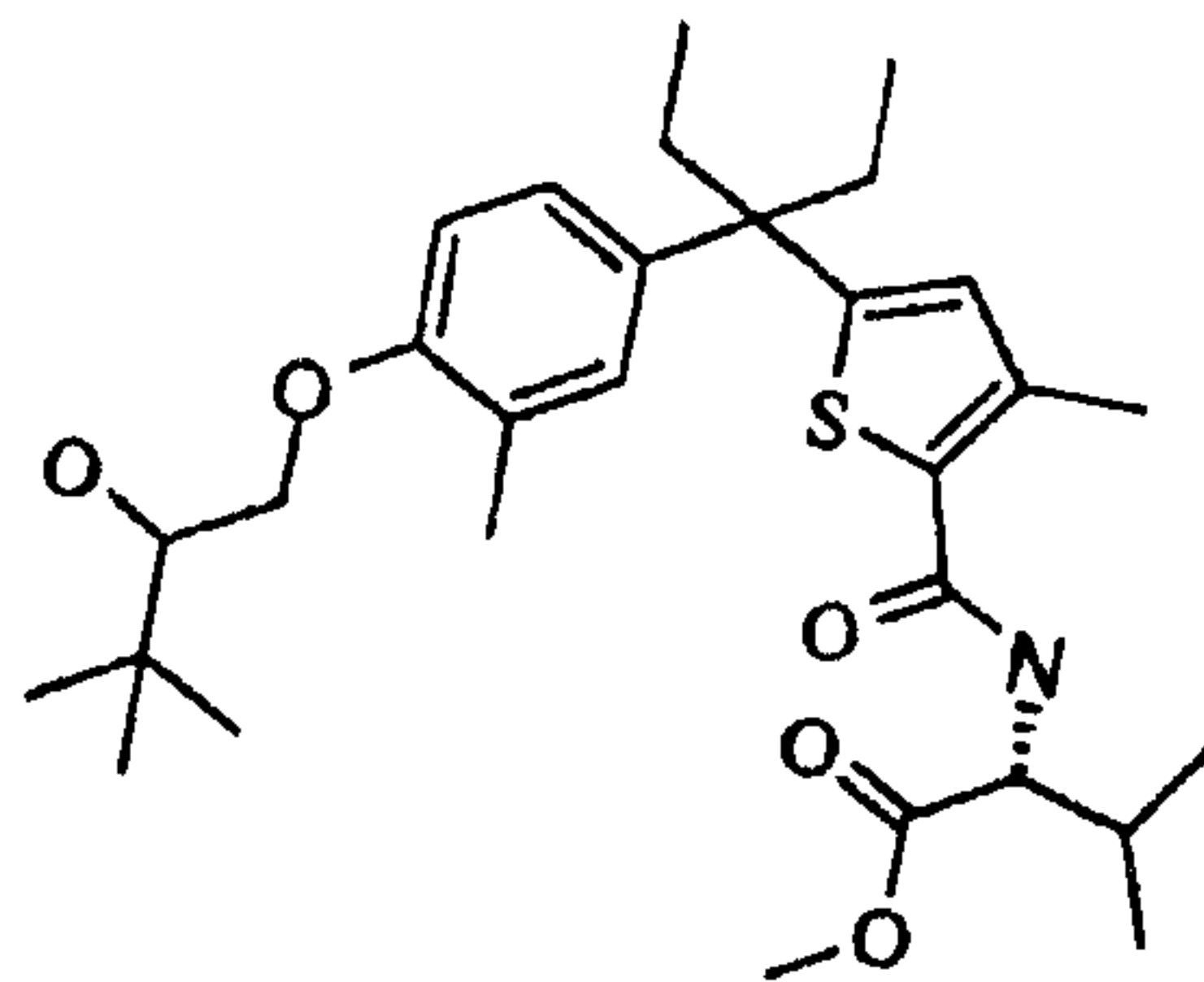


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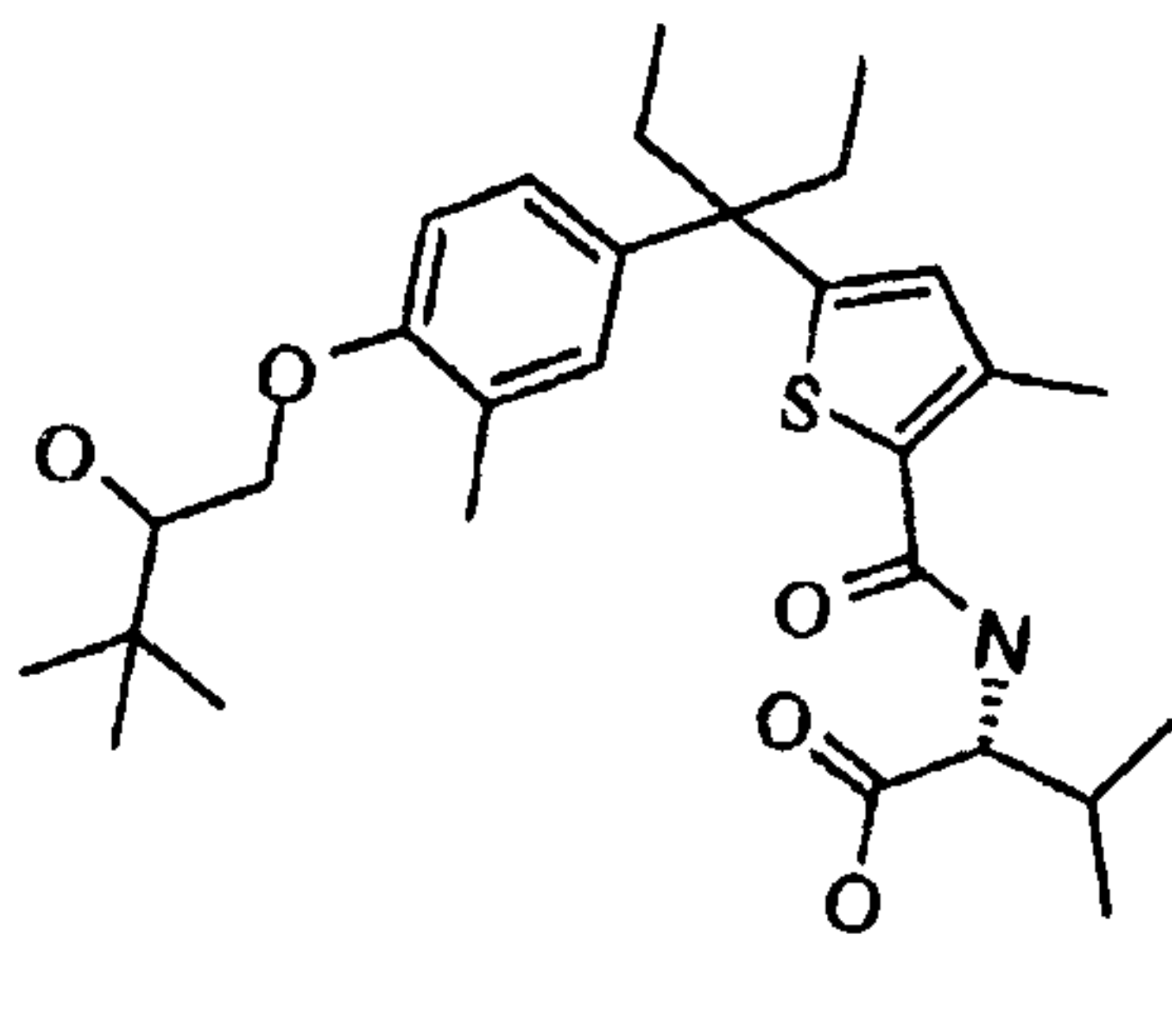


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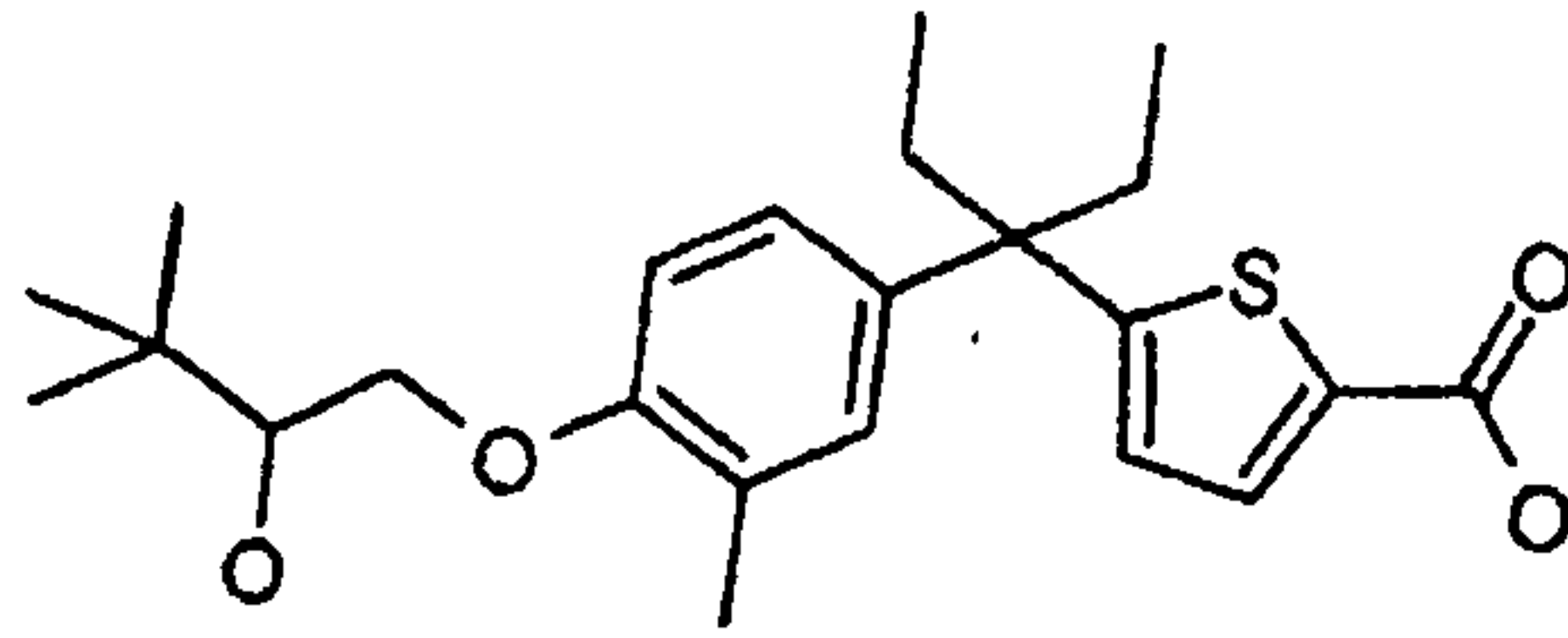


X86)

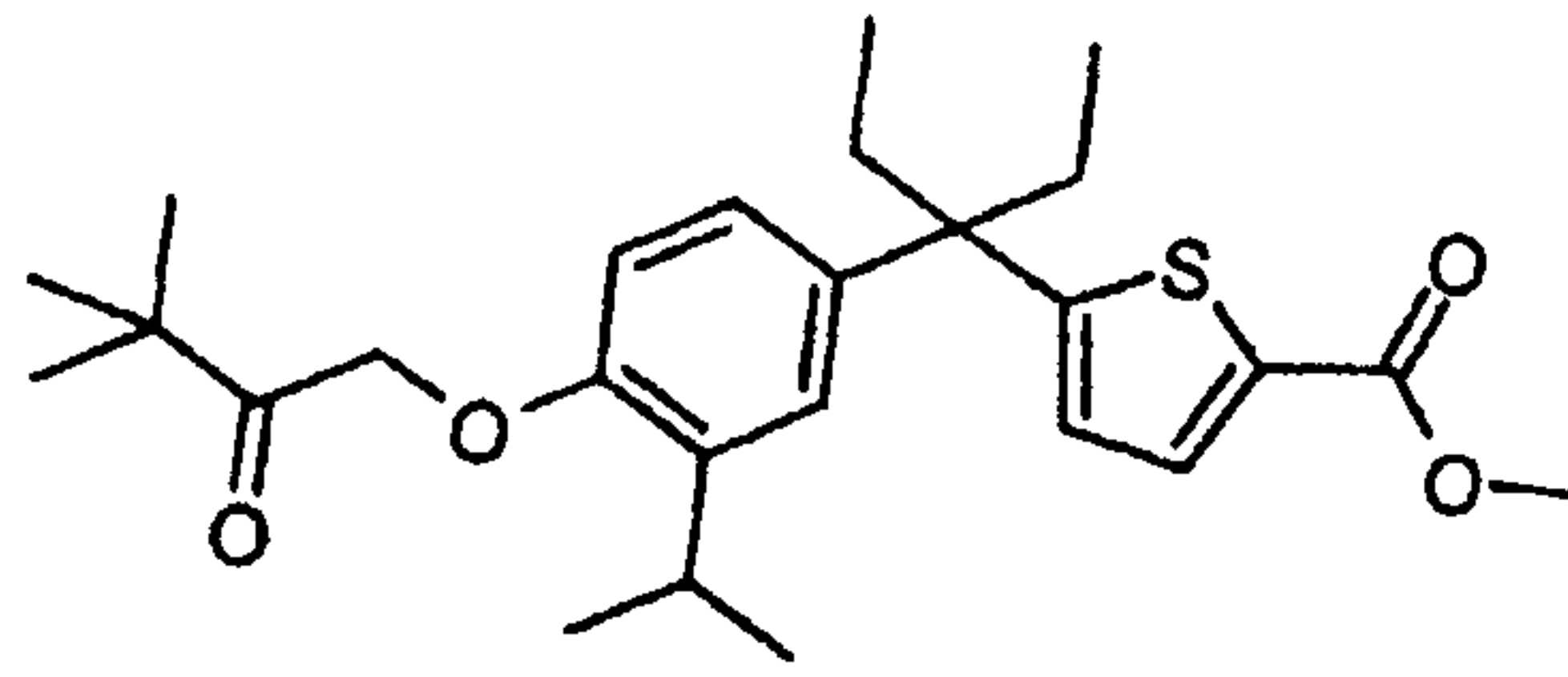


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X88)

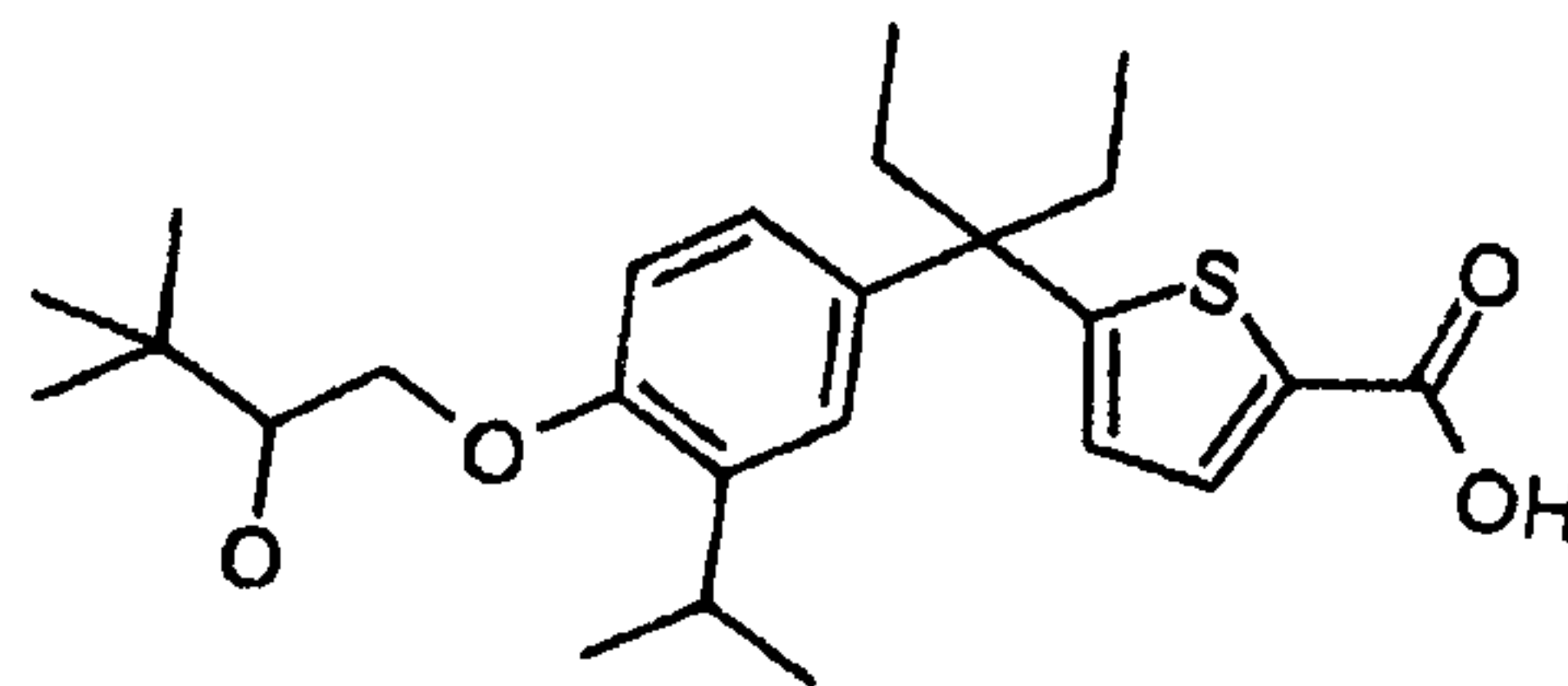


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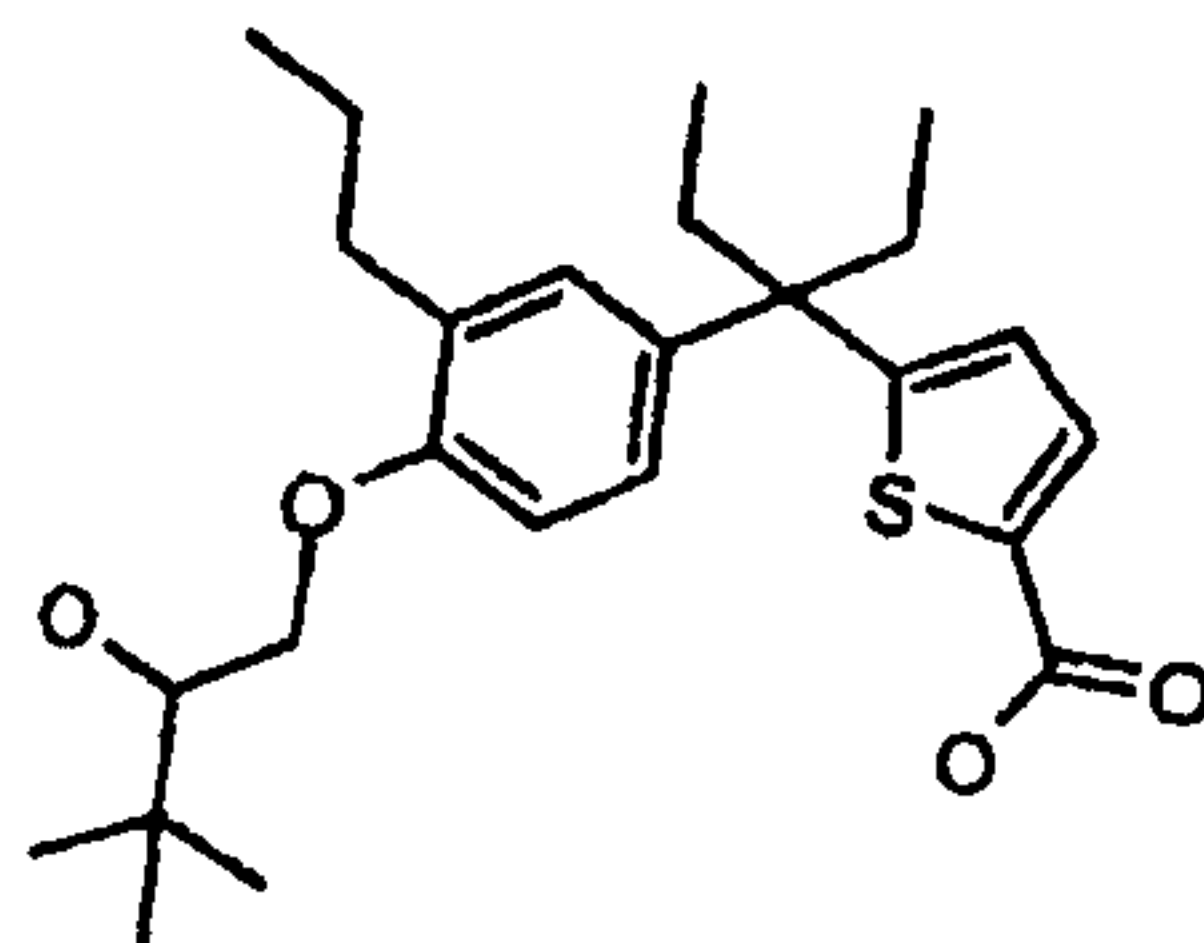


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X92)

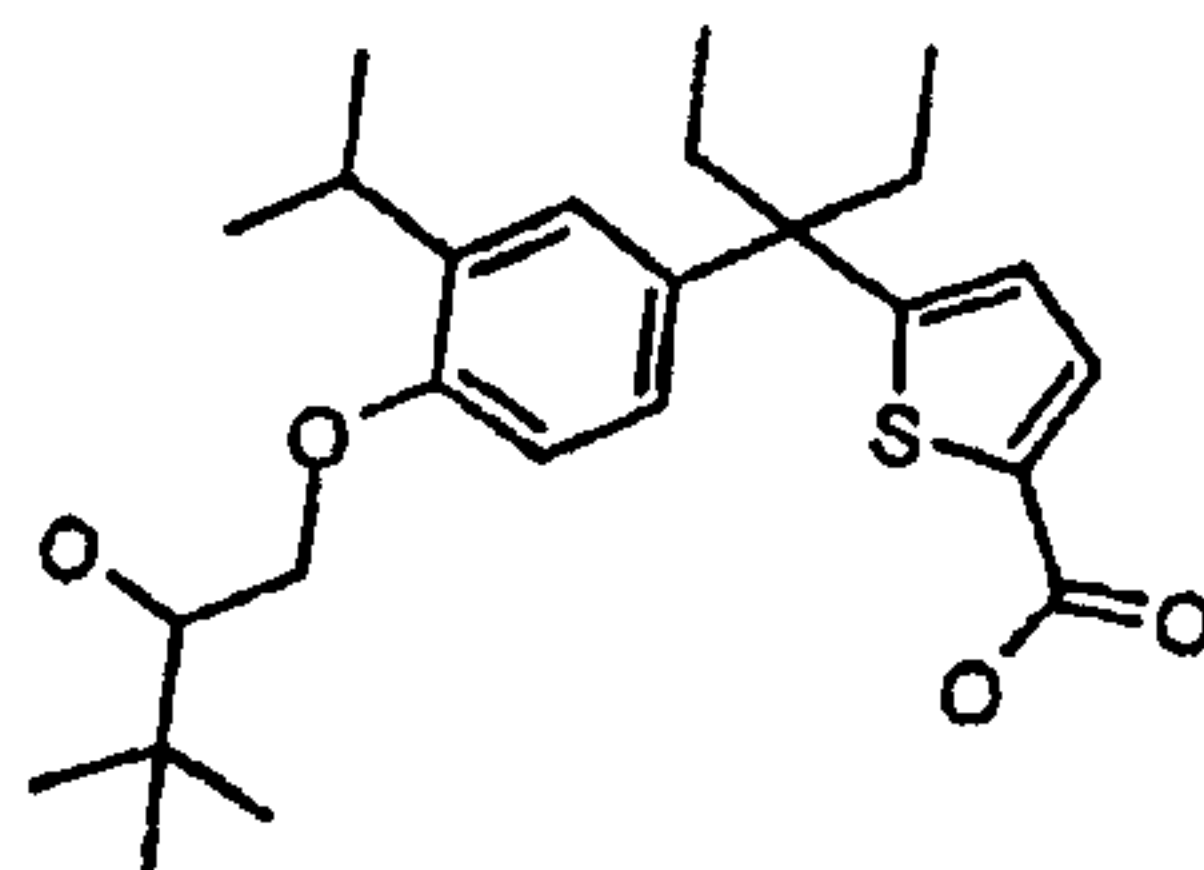


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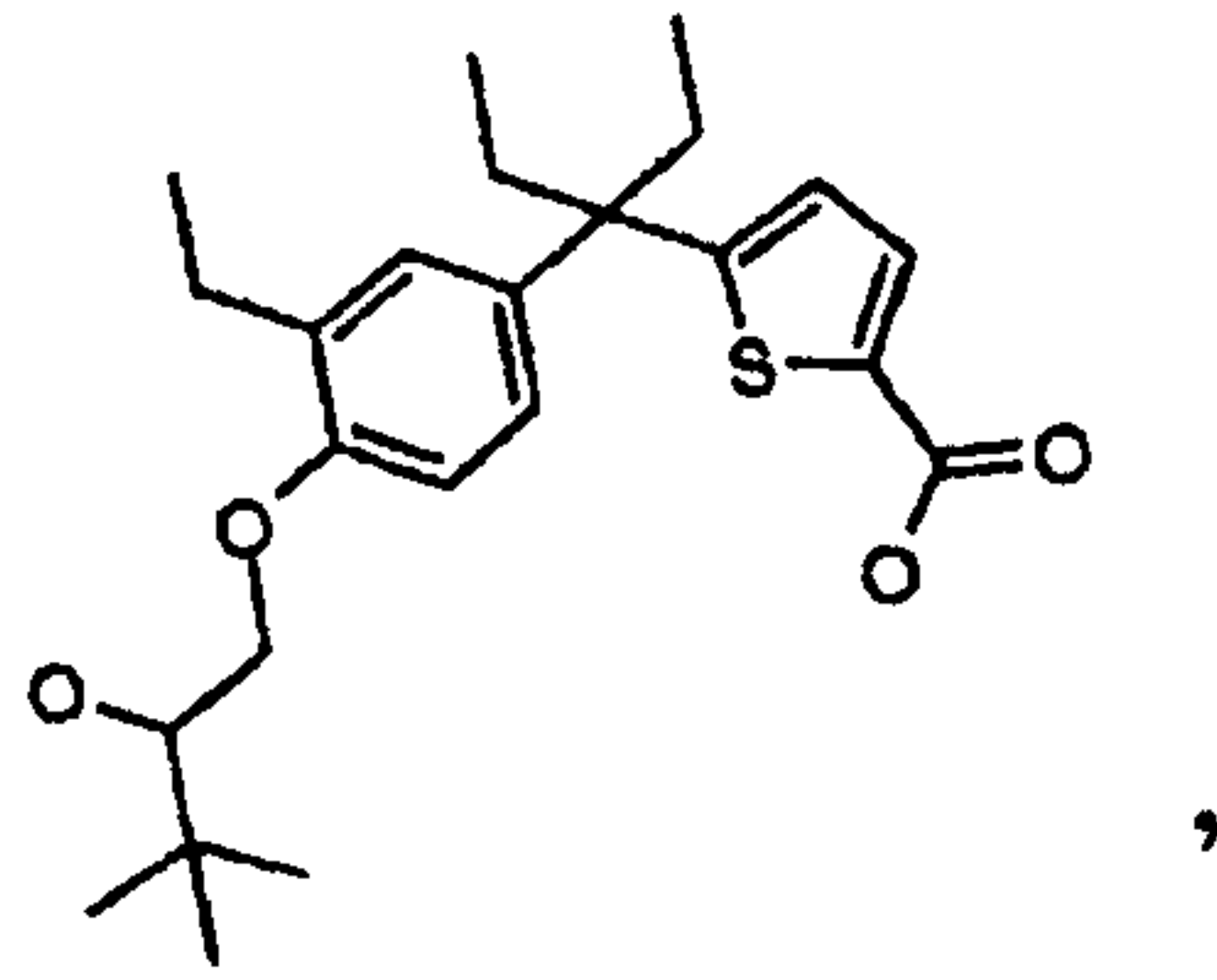
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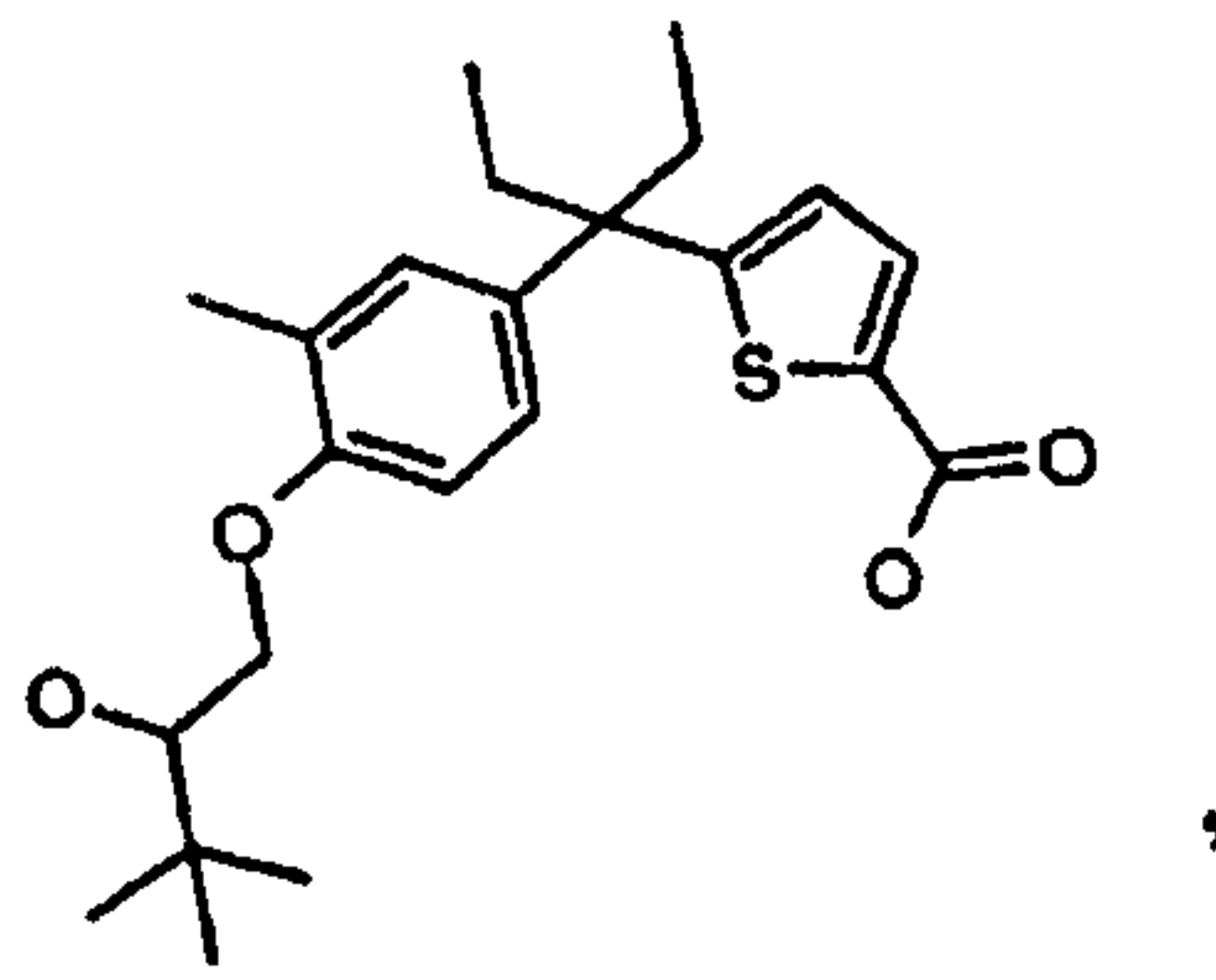


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X99)

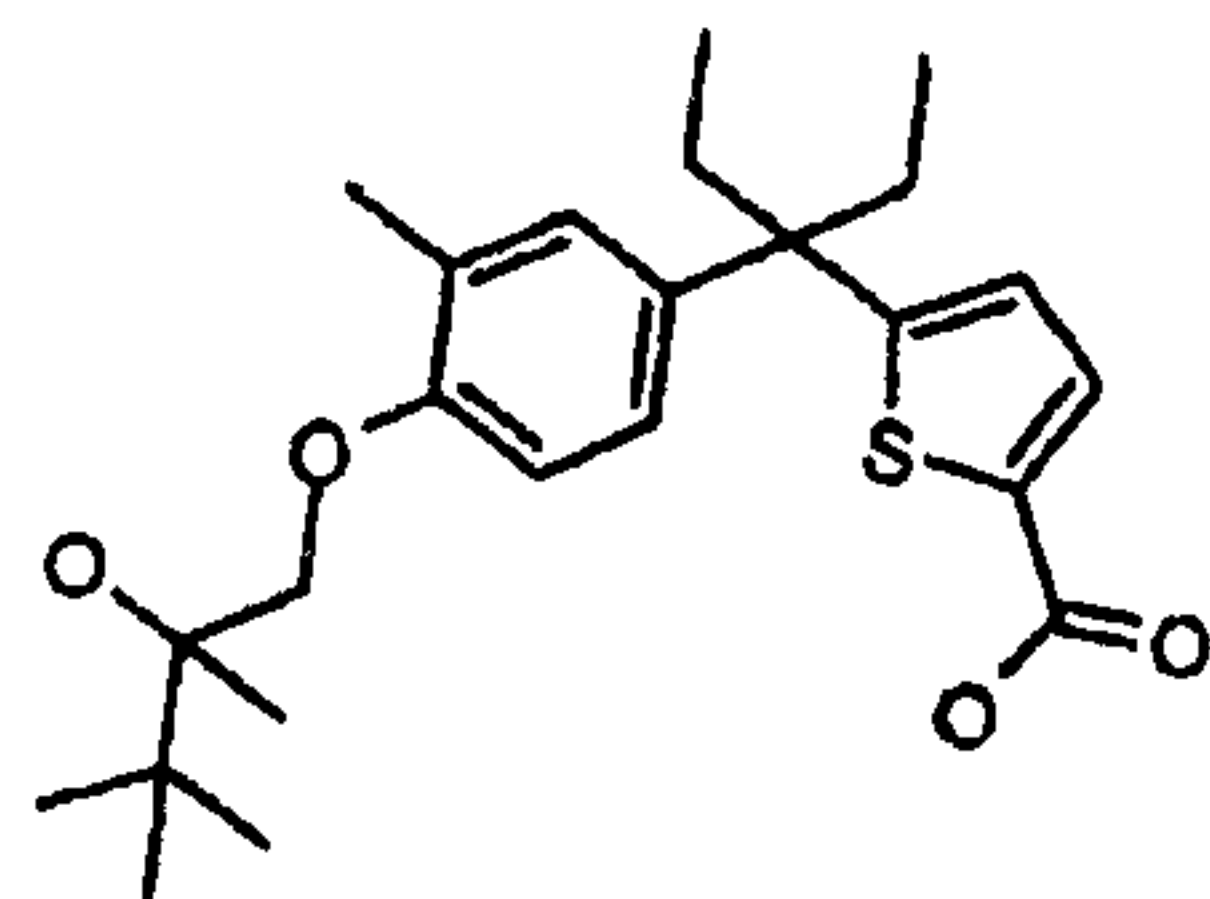


X102)



-390-

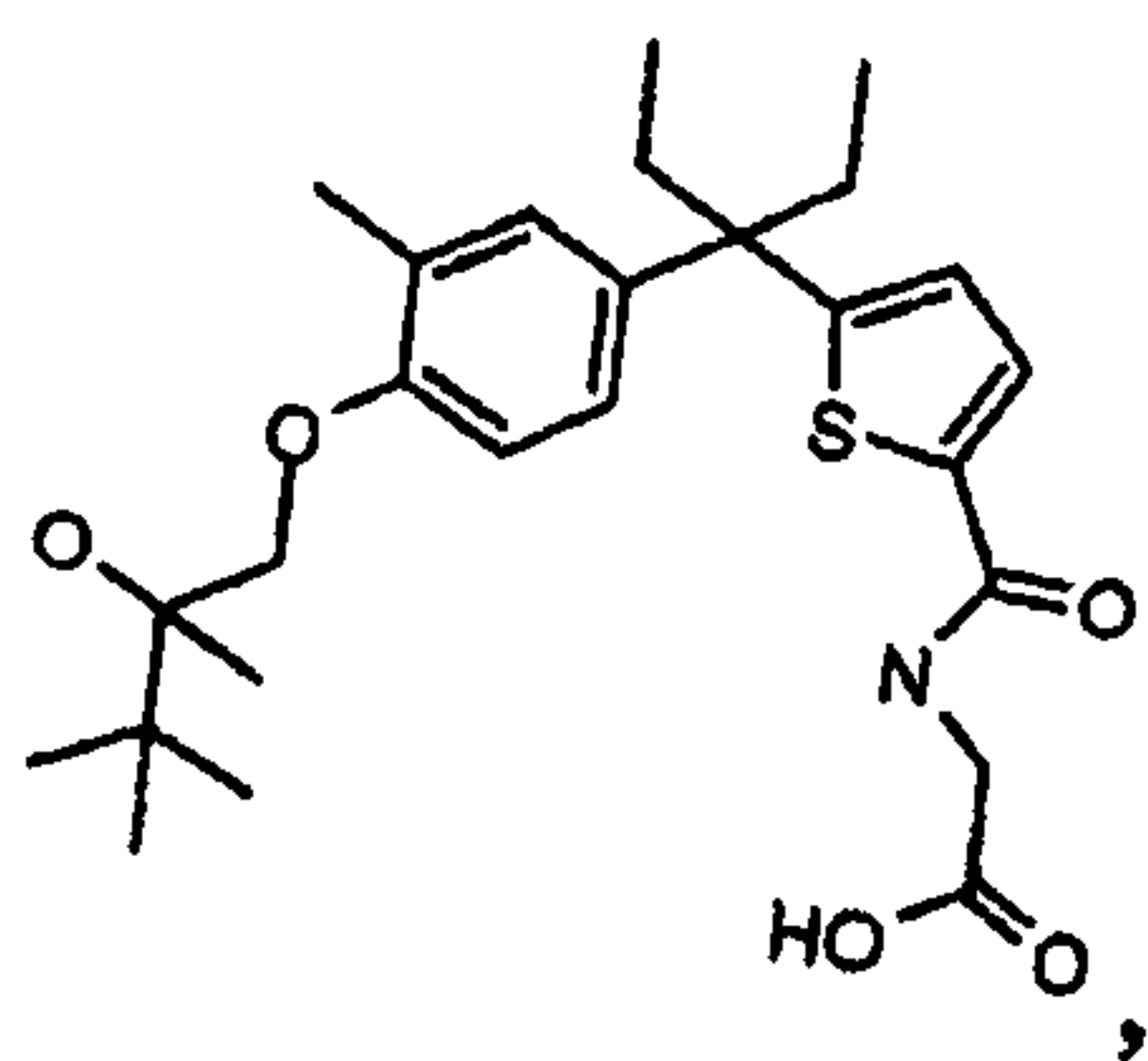
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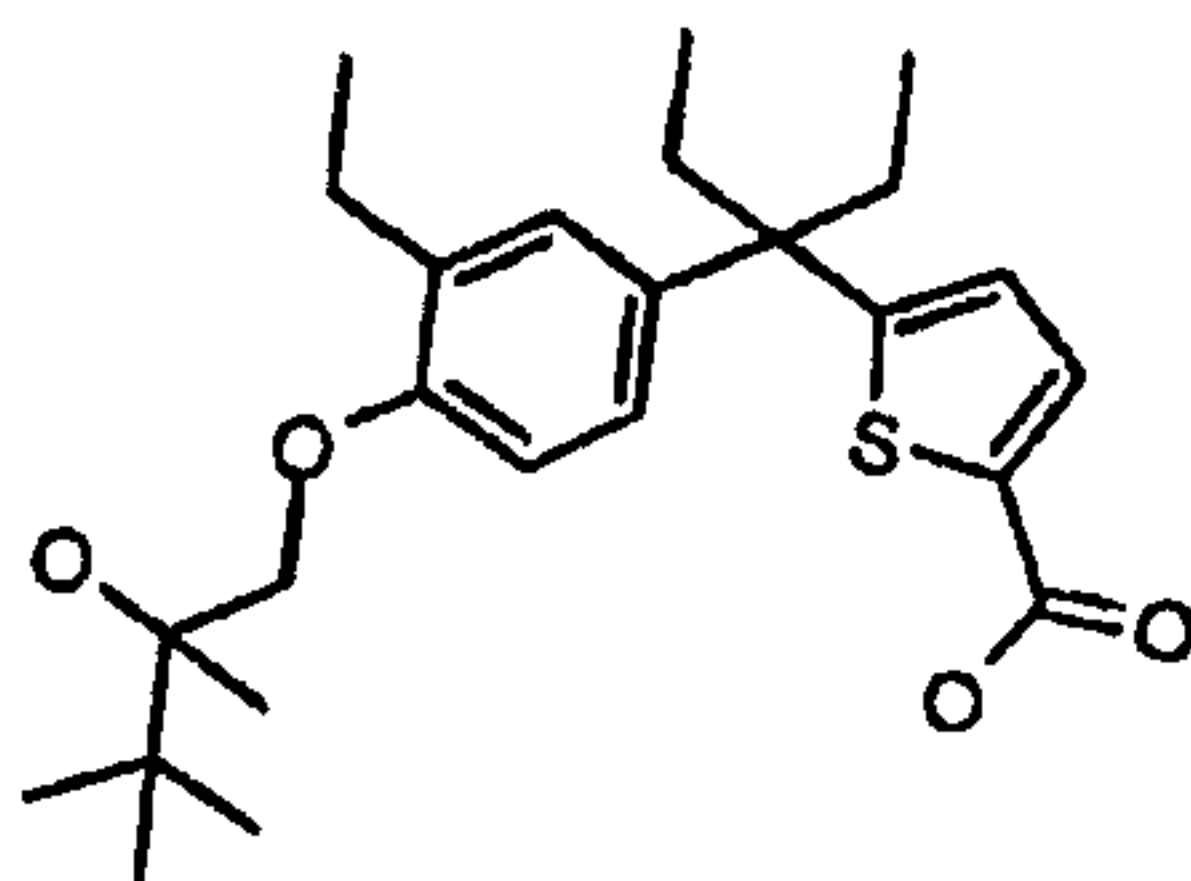
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X106)



X107)

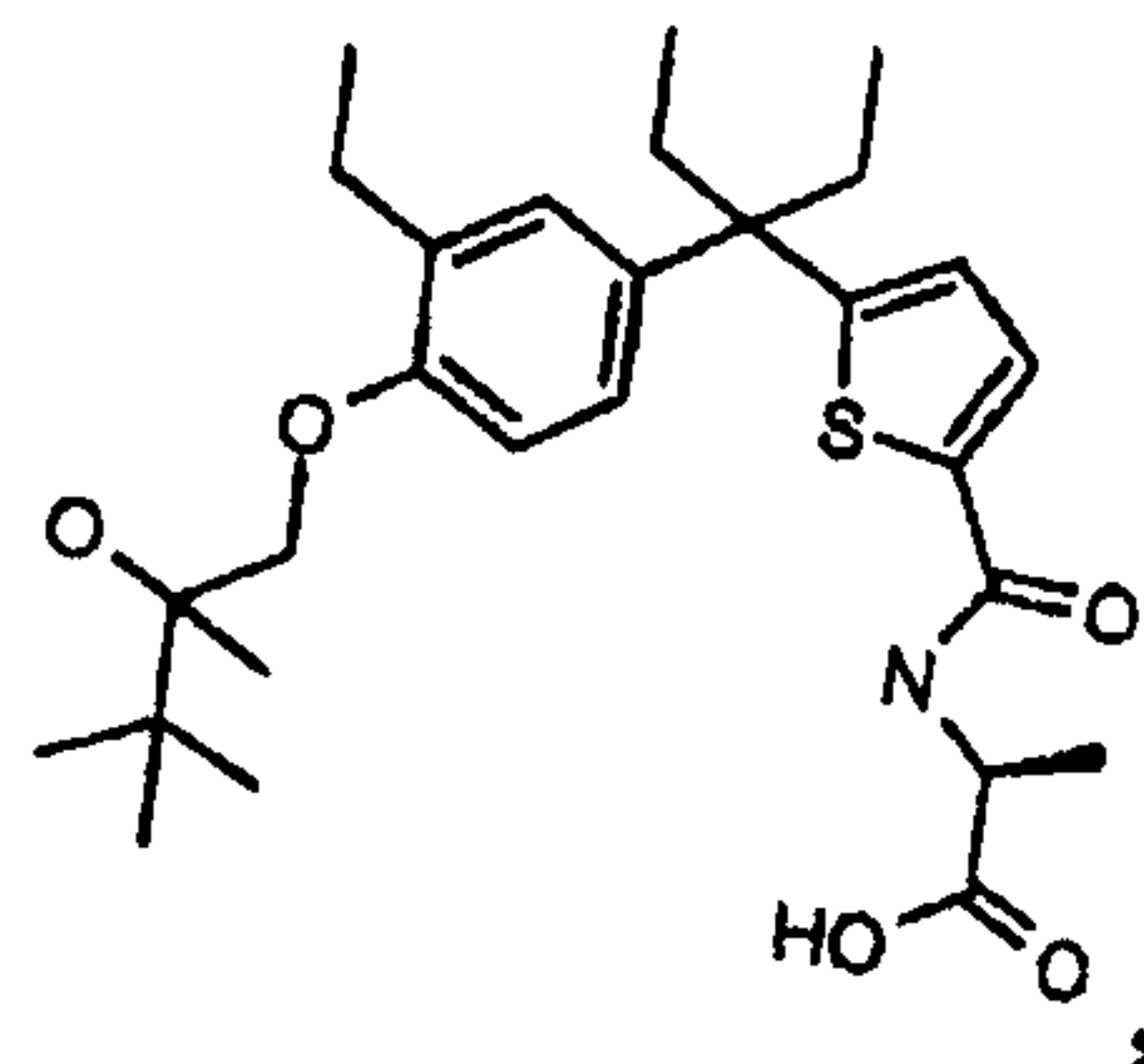


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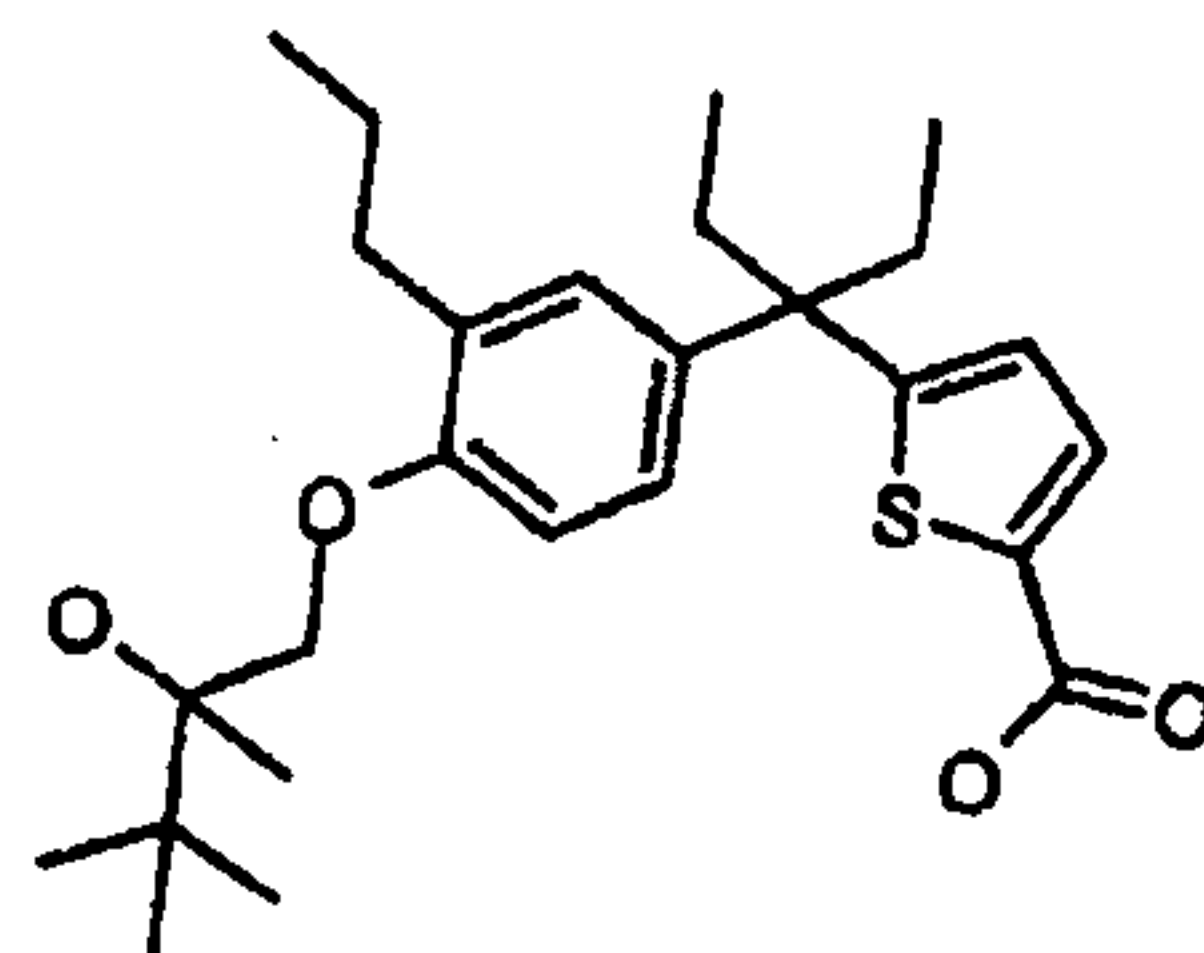
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-391-

X110)

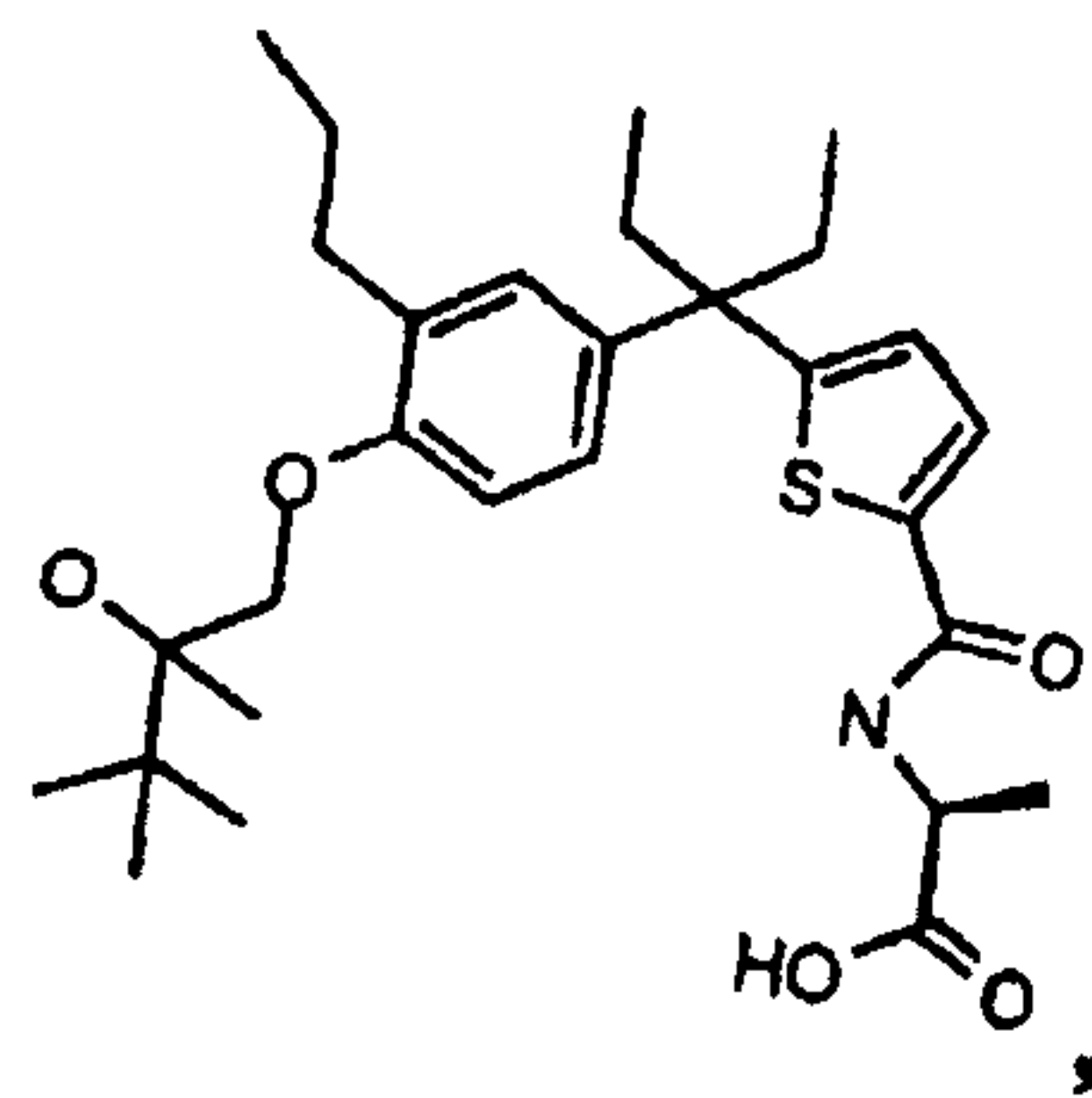


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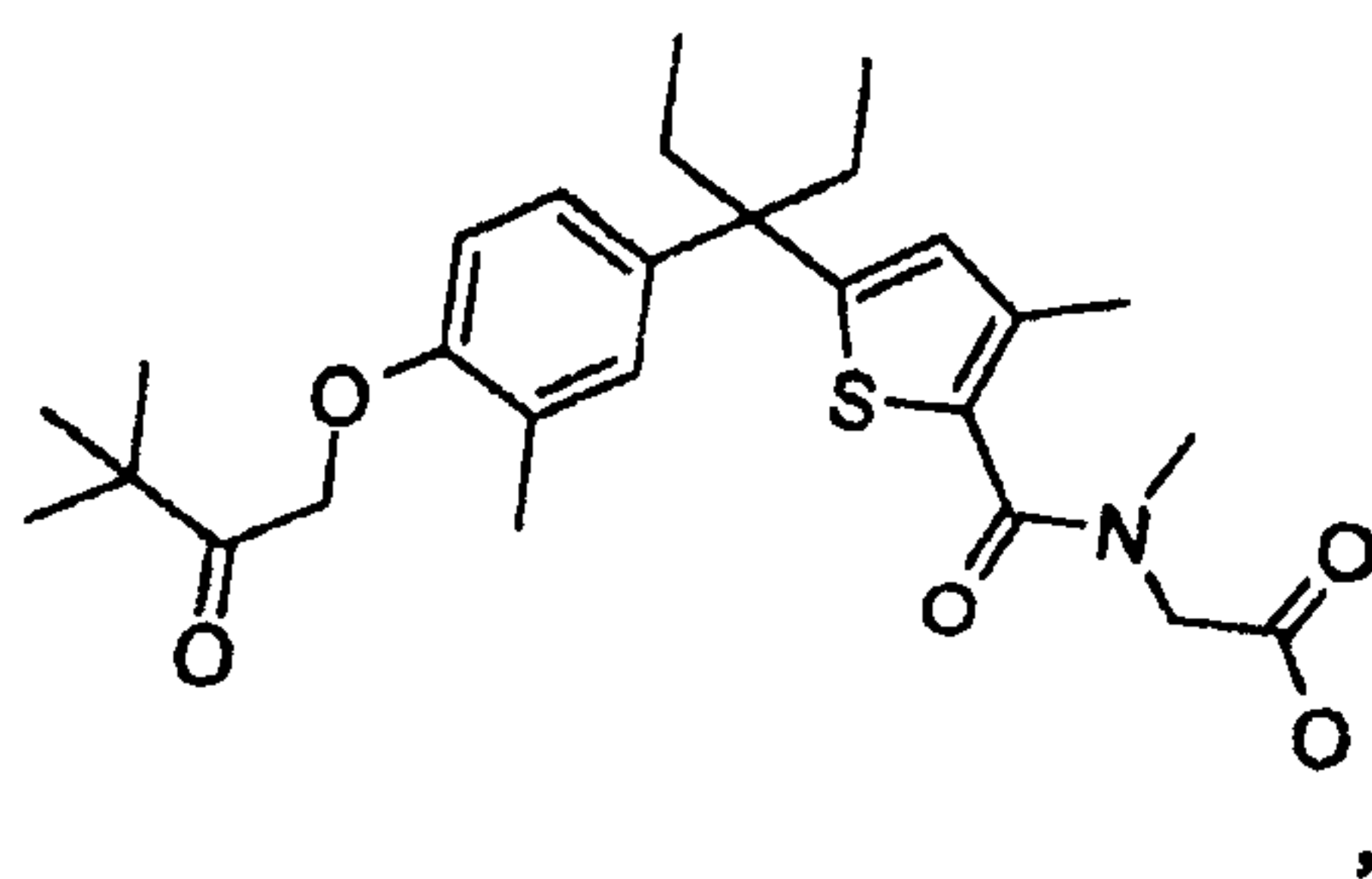


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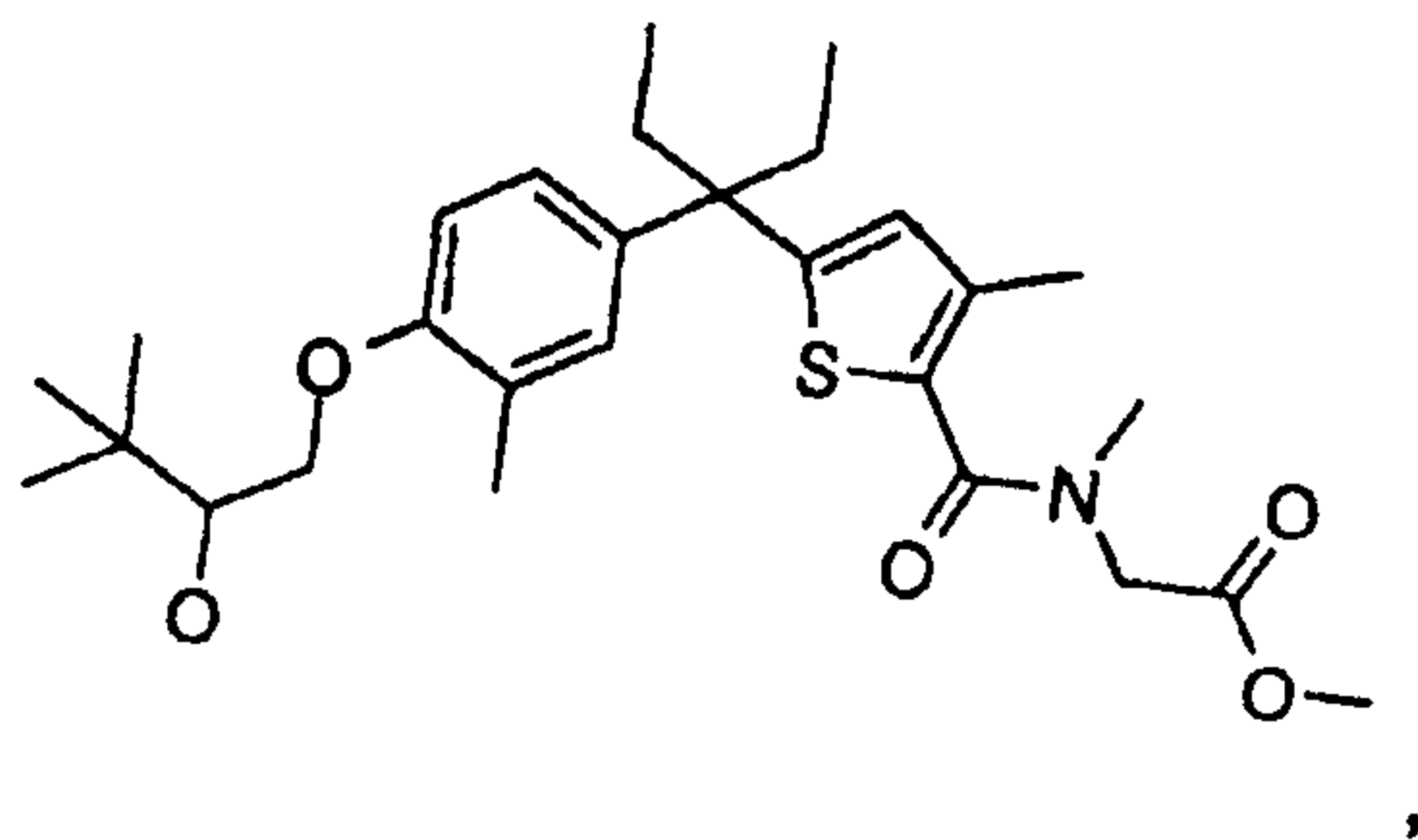
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X118)



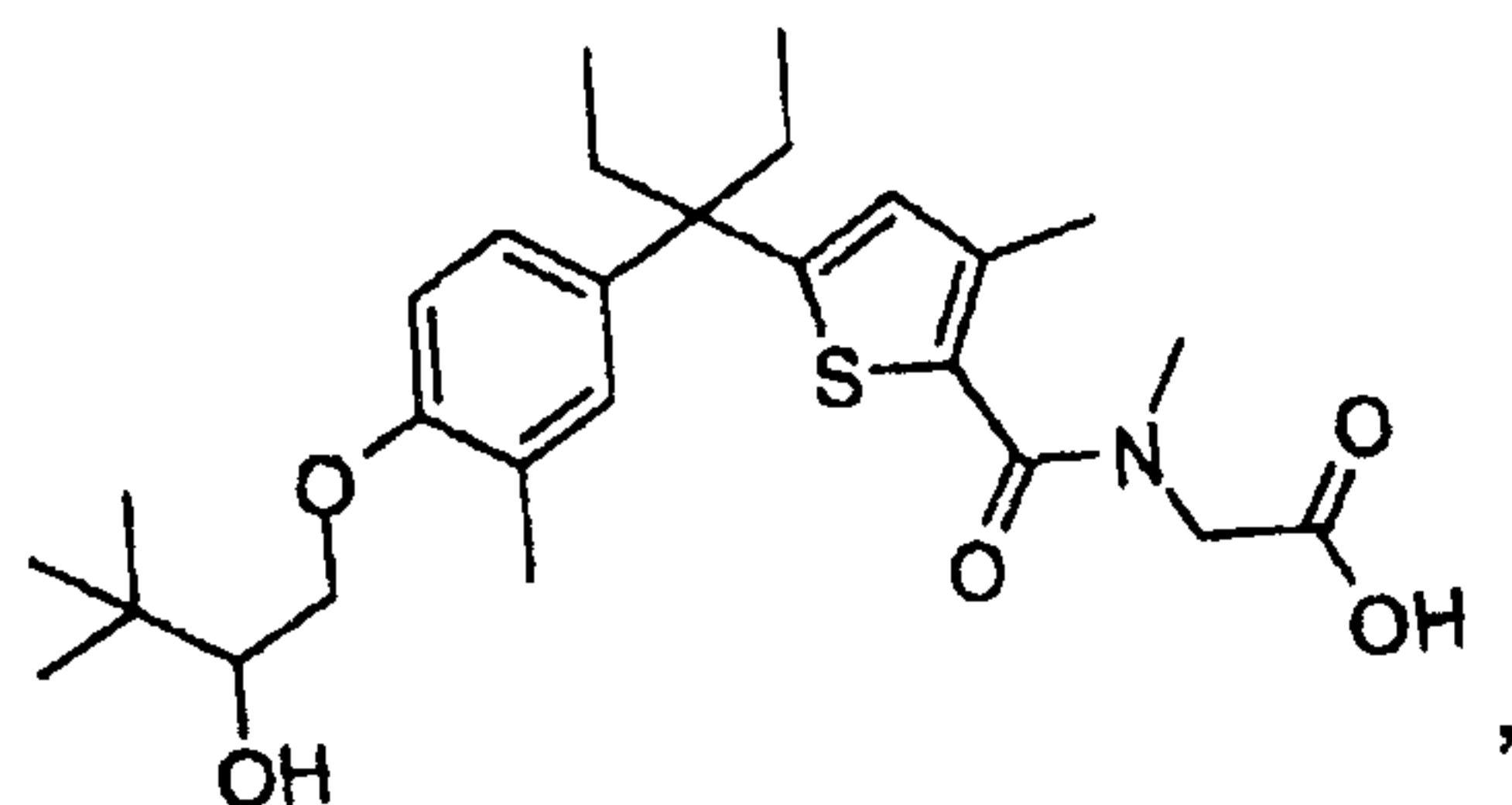
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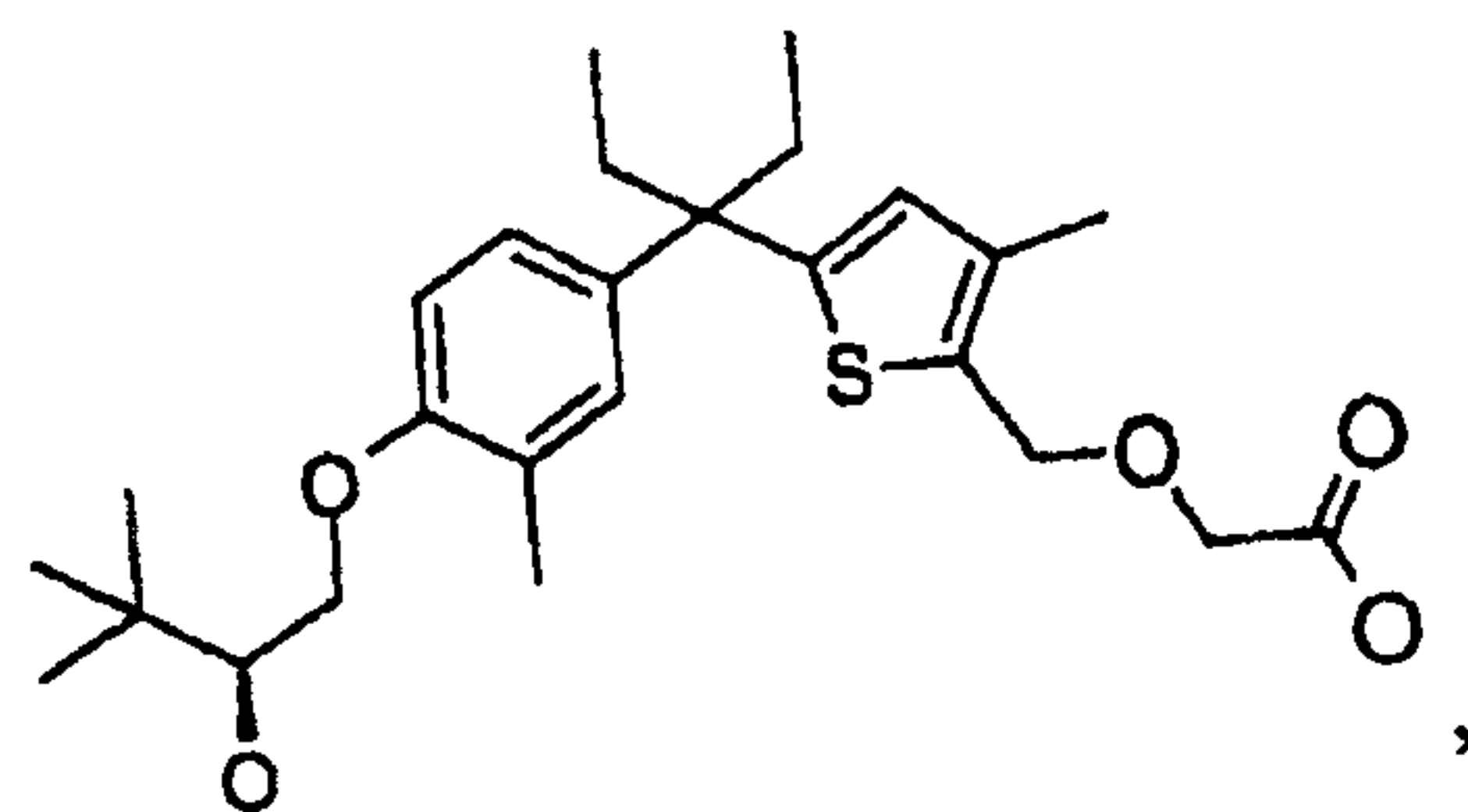
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-392-

X122)

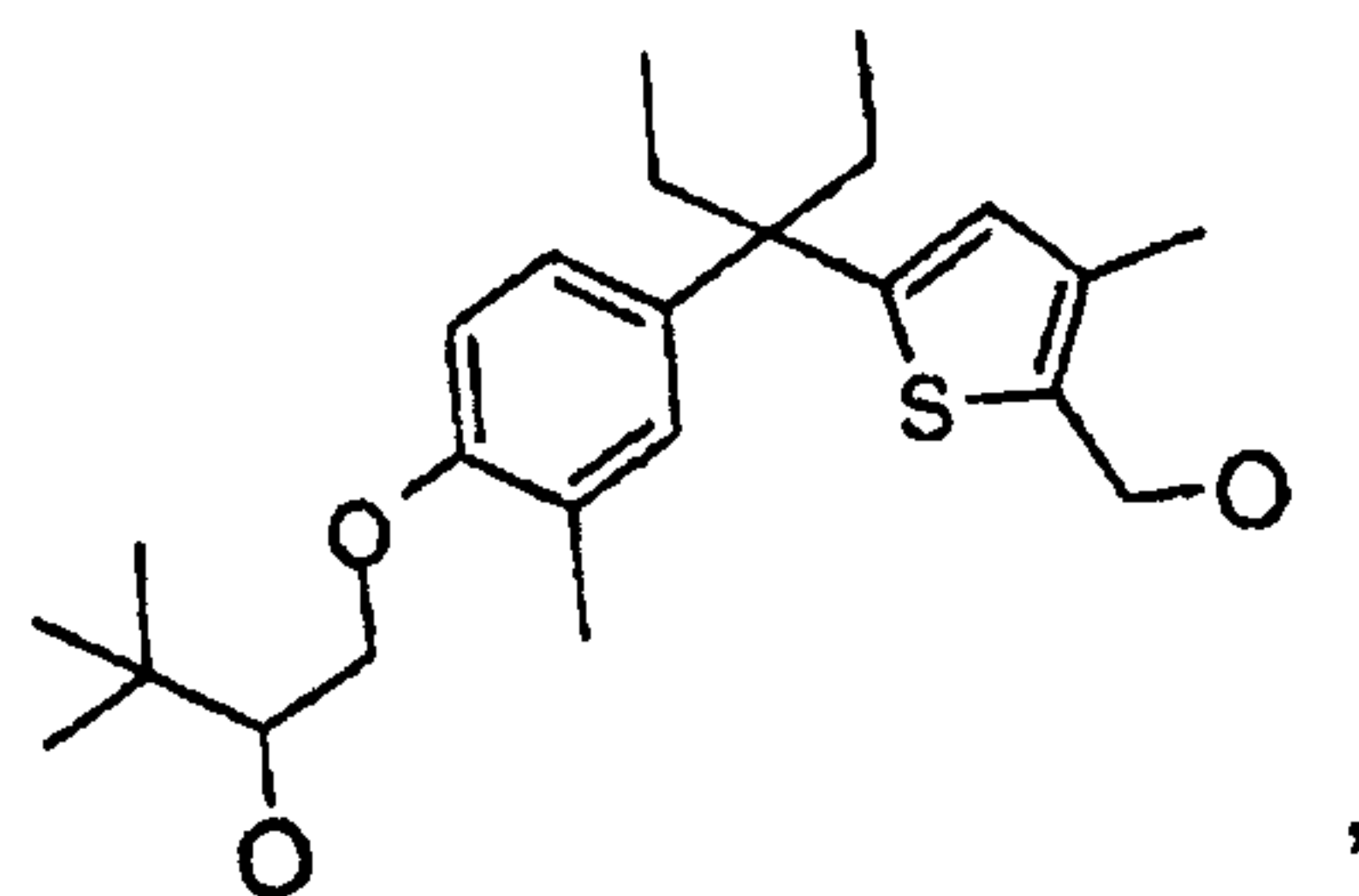


X124)

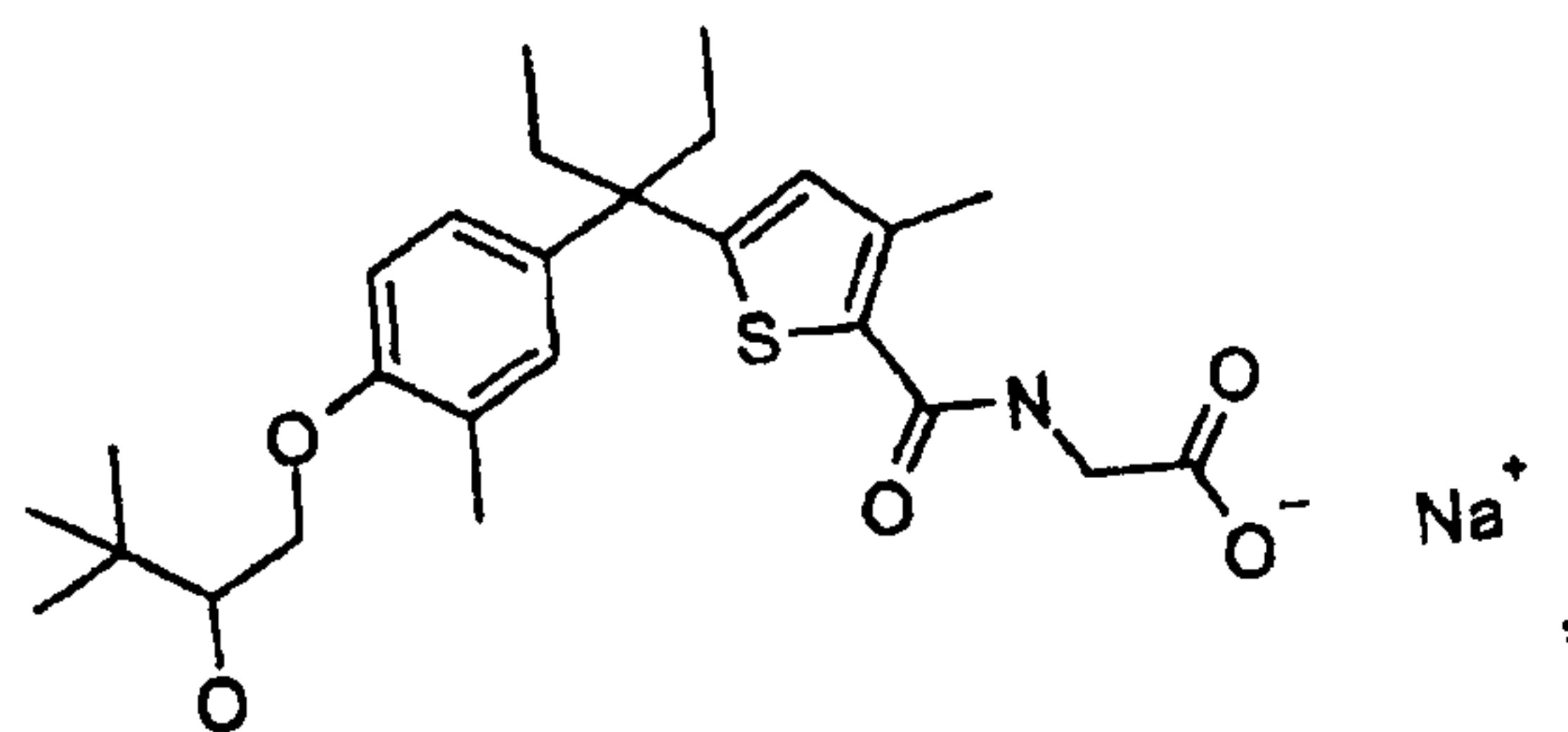


5

X125)



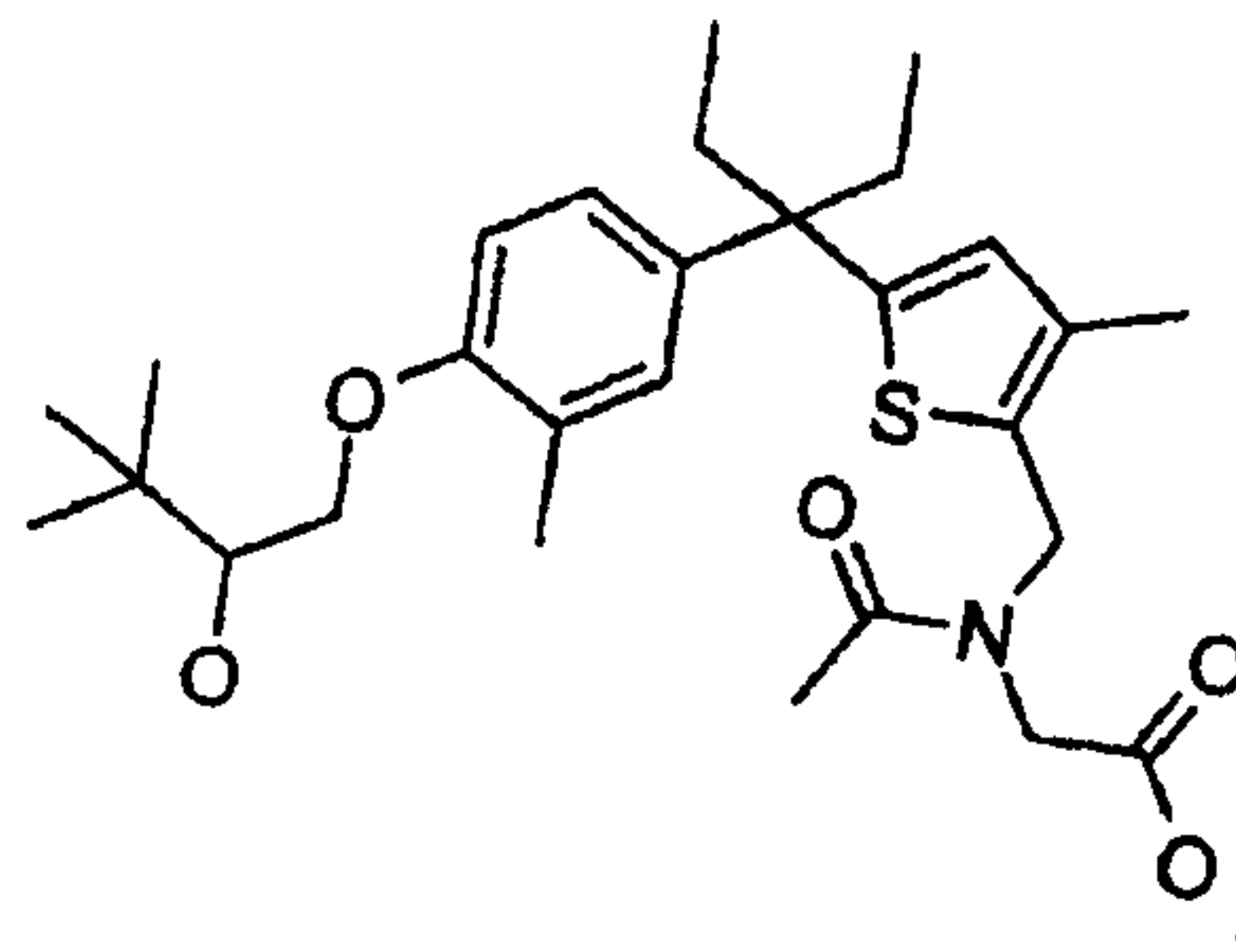
X128)



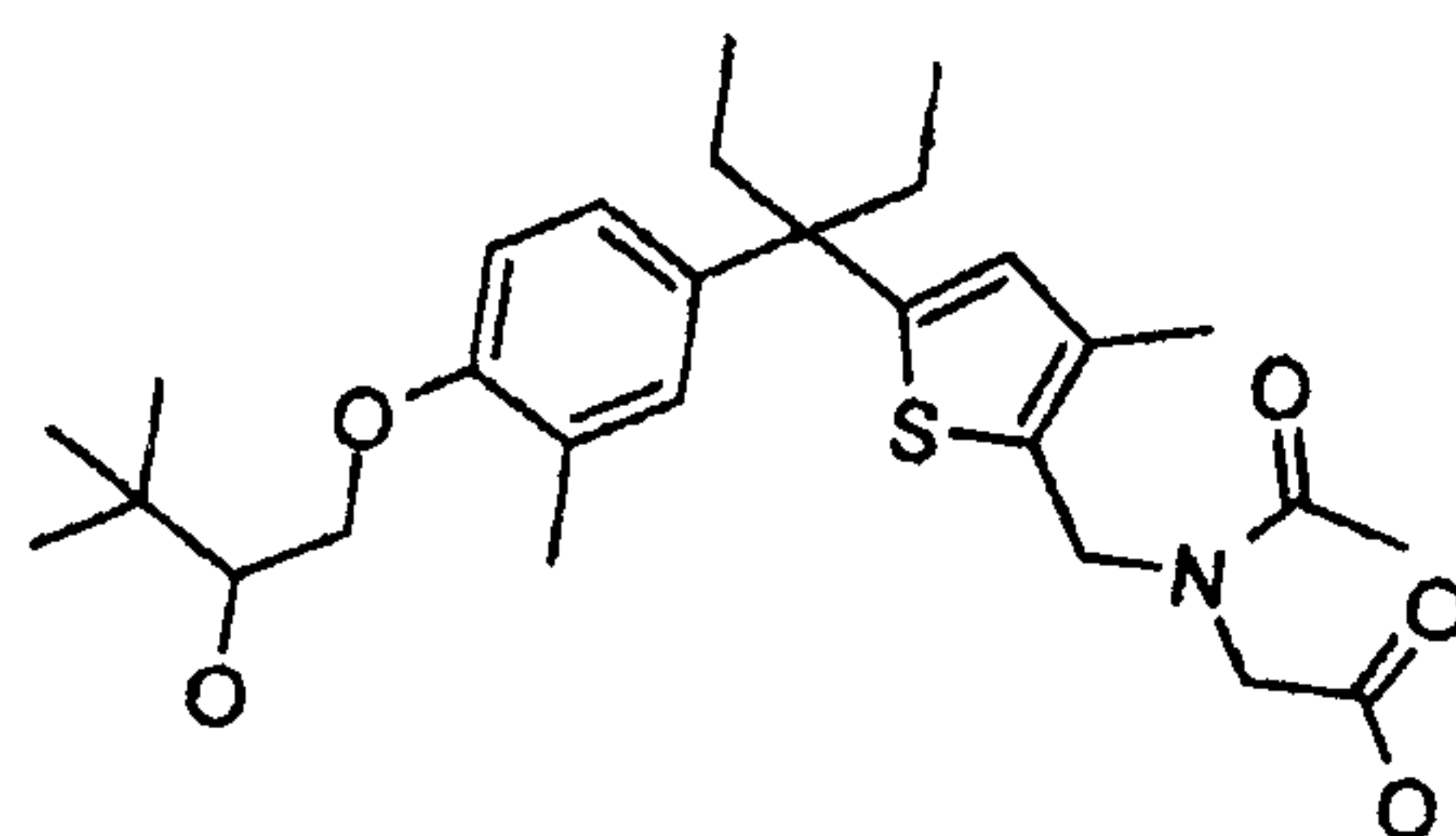
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-393-

X130)

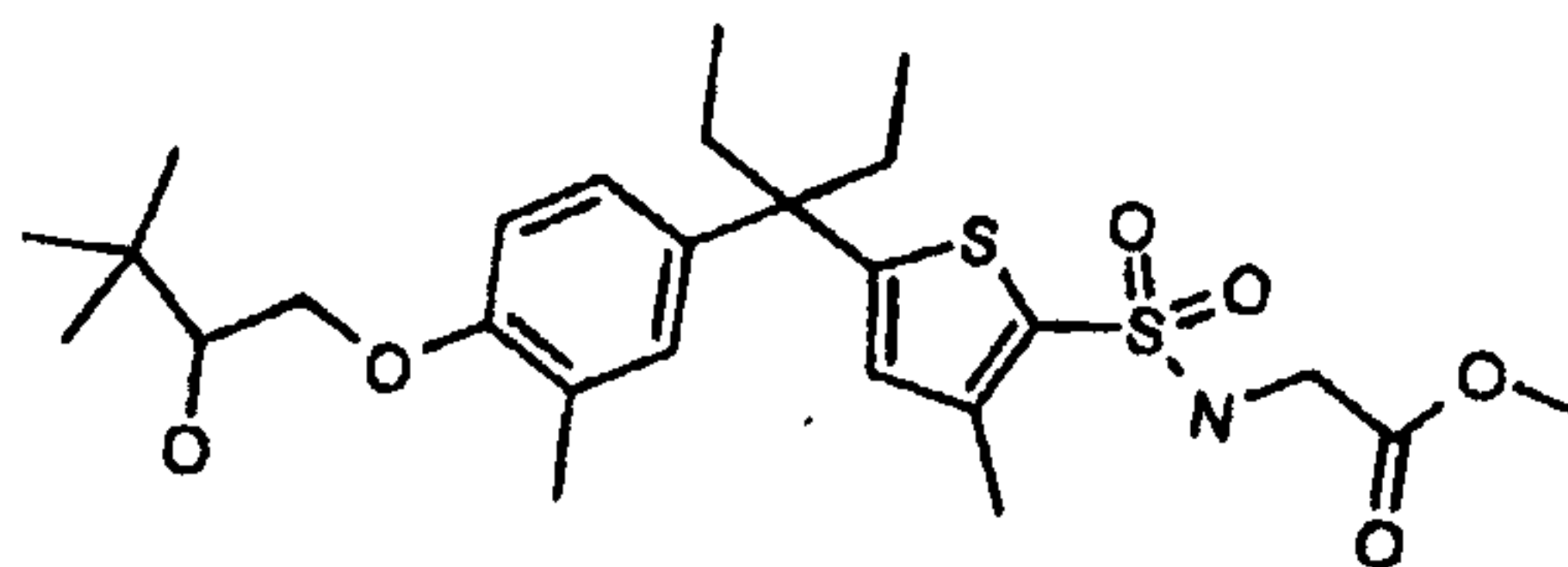


X131)

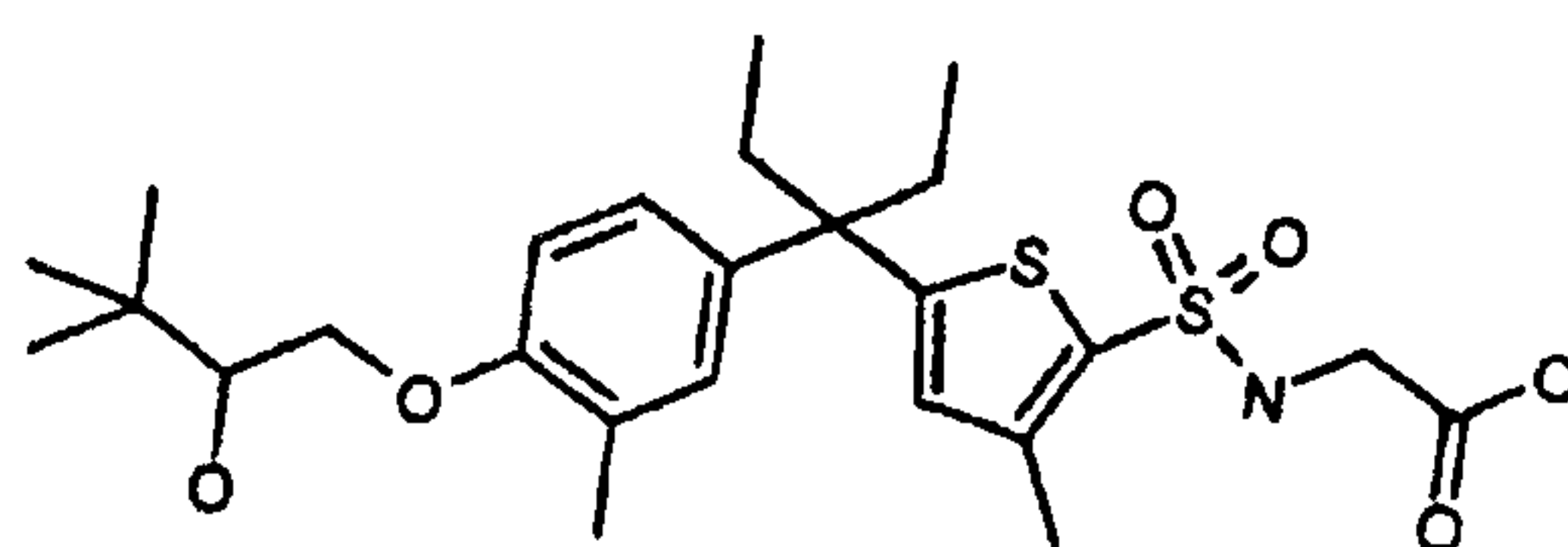


5

X134)

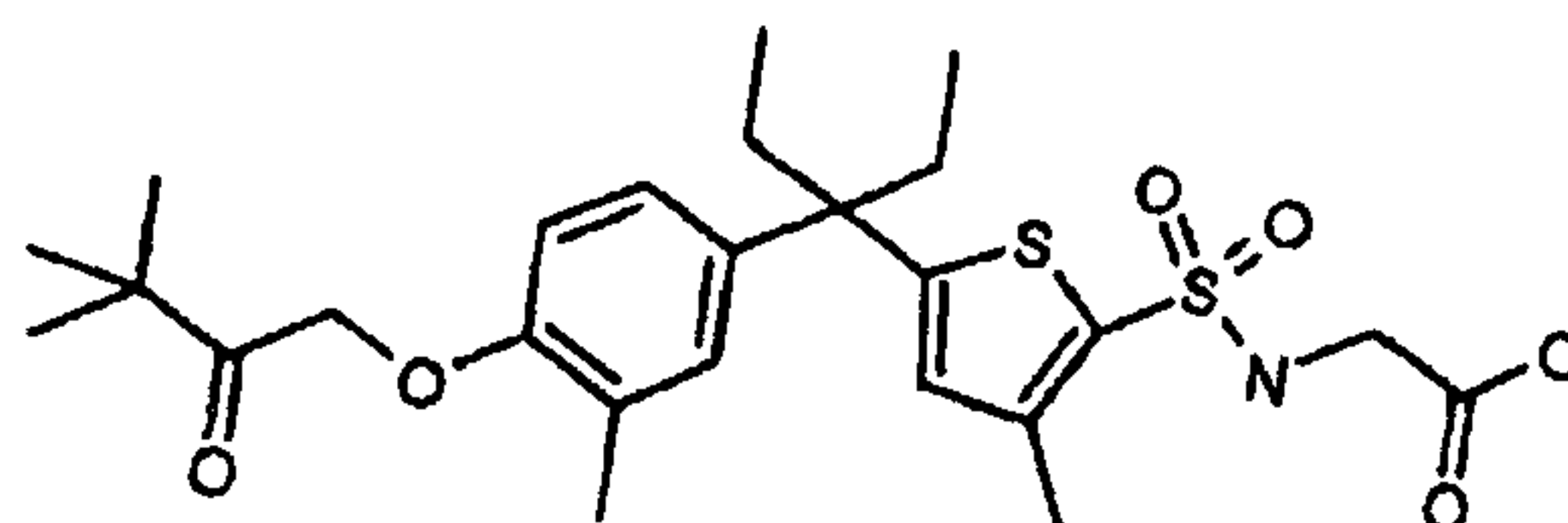


X137)



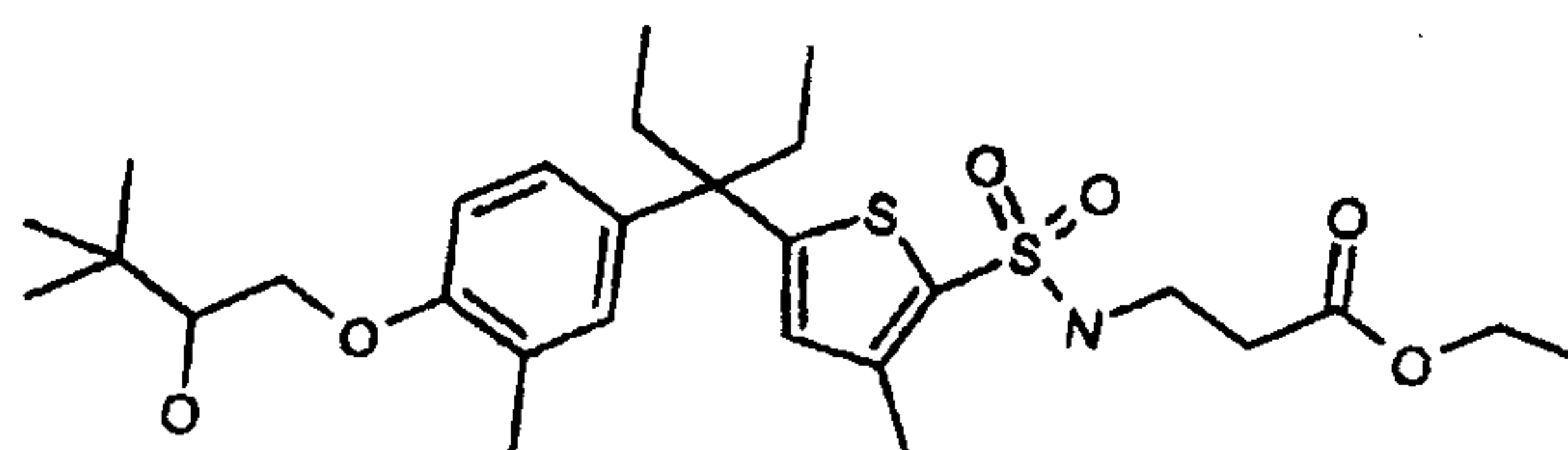
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X139)

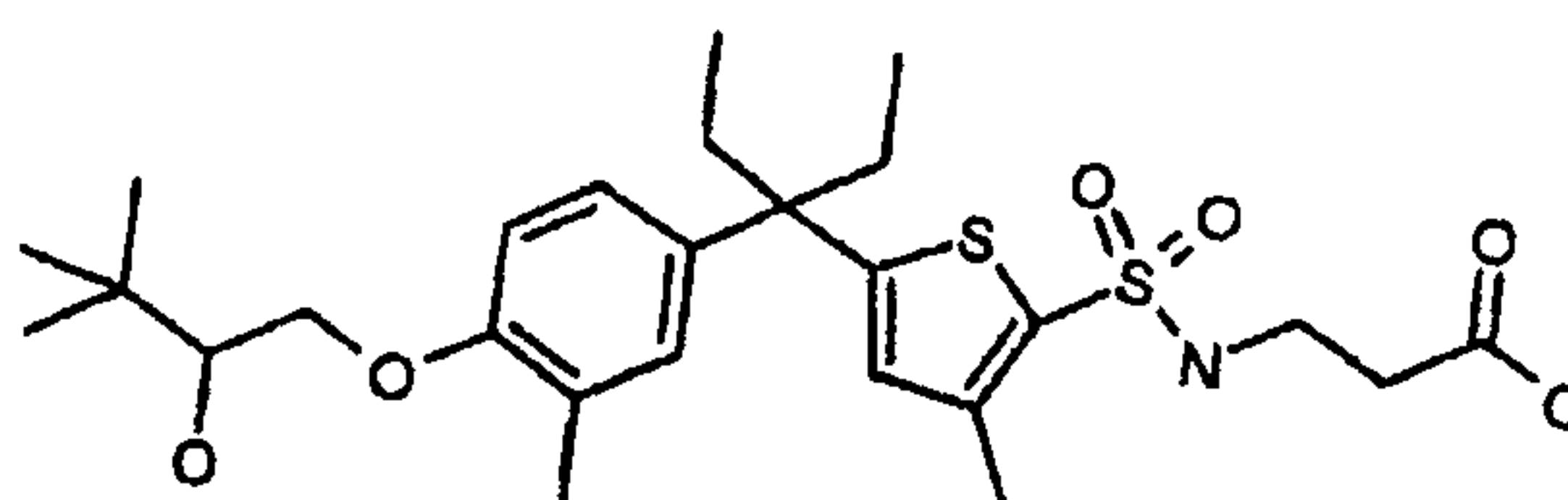


-394-

X140)

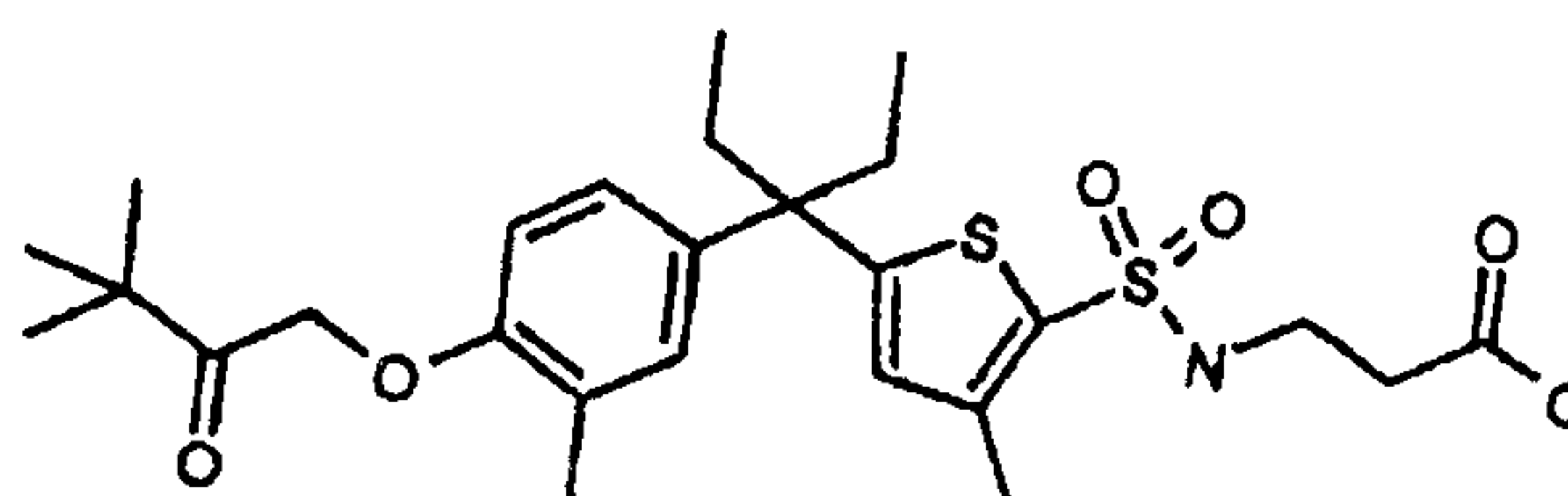


X141)

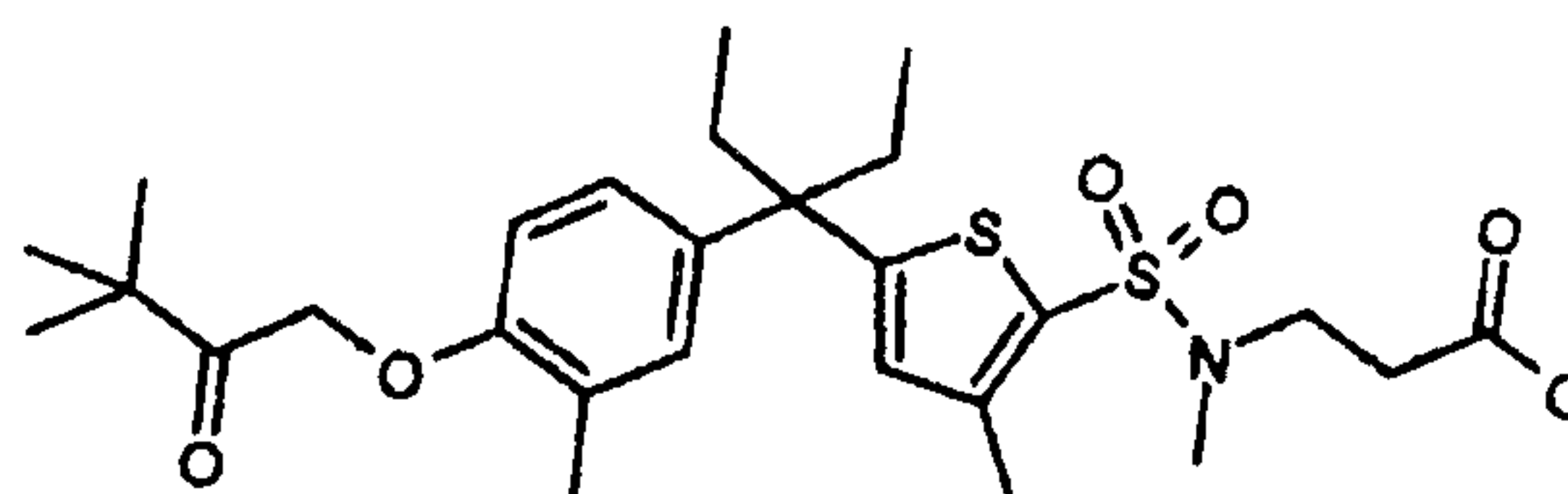


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X144)

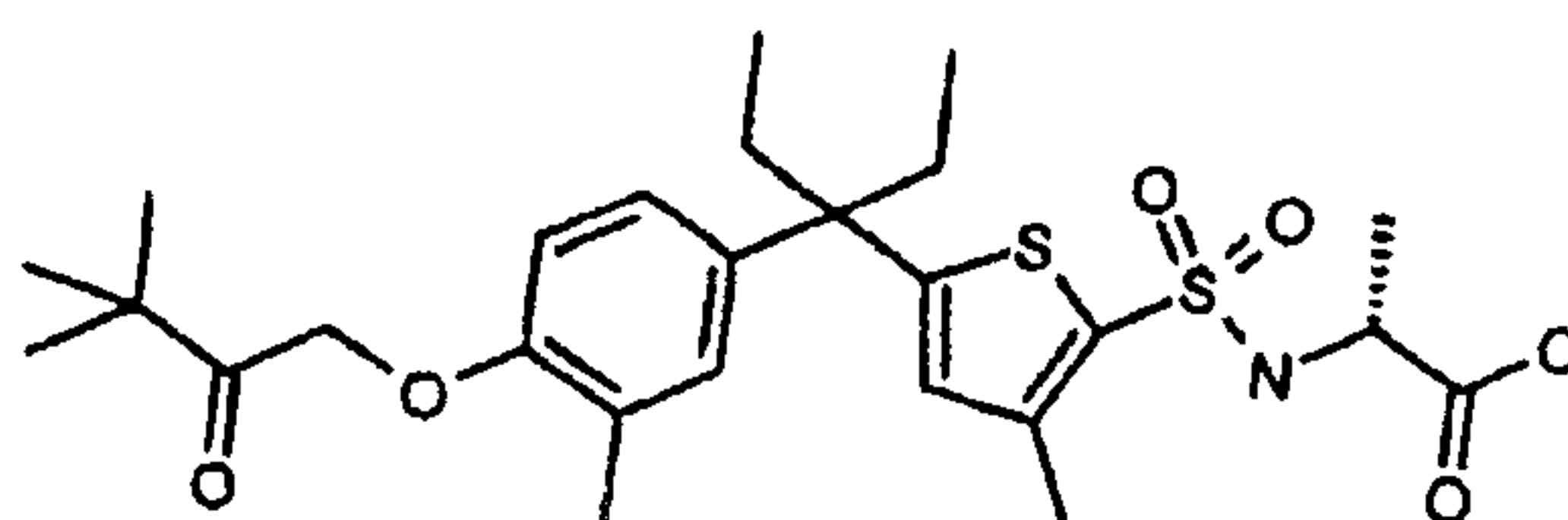


X145)



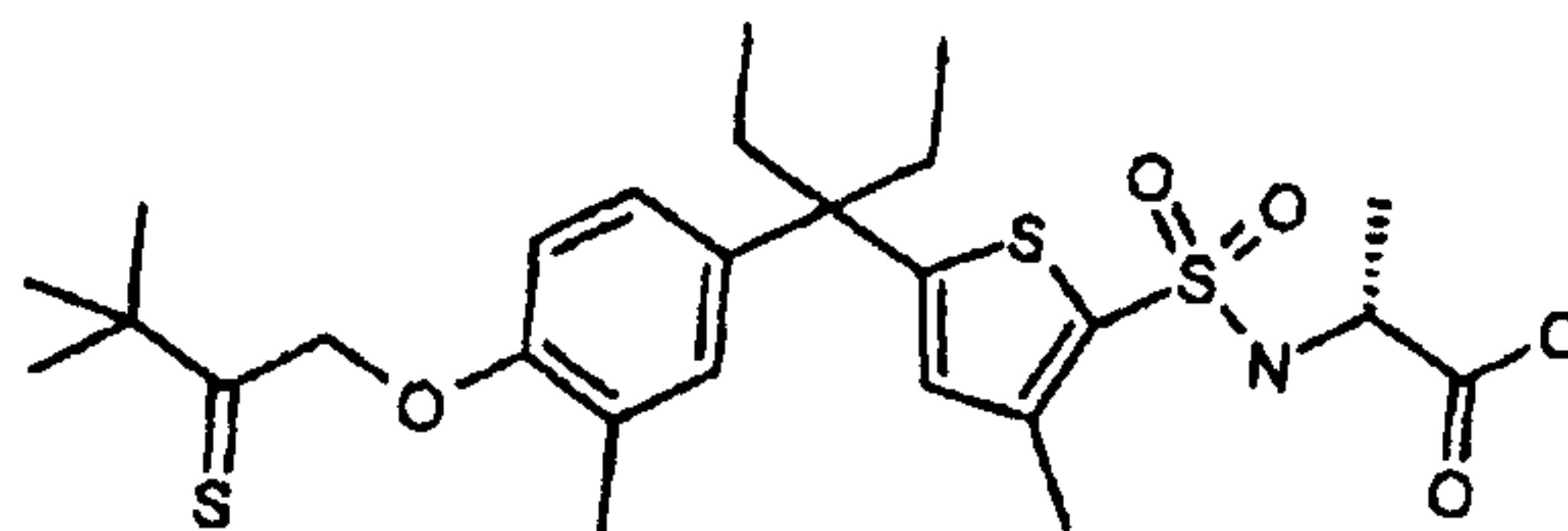
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X146)



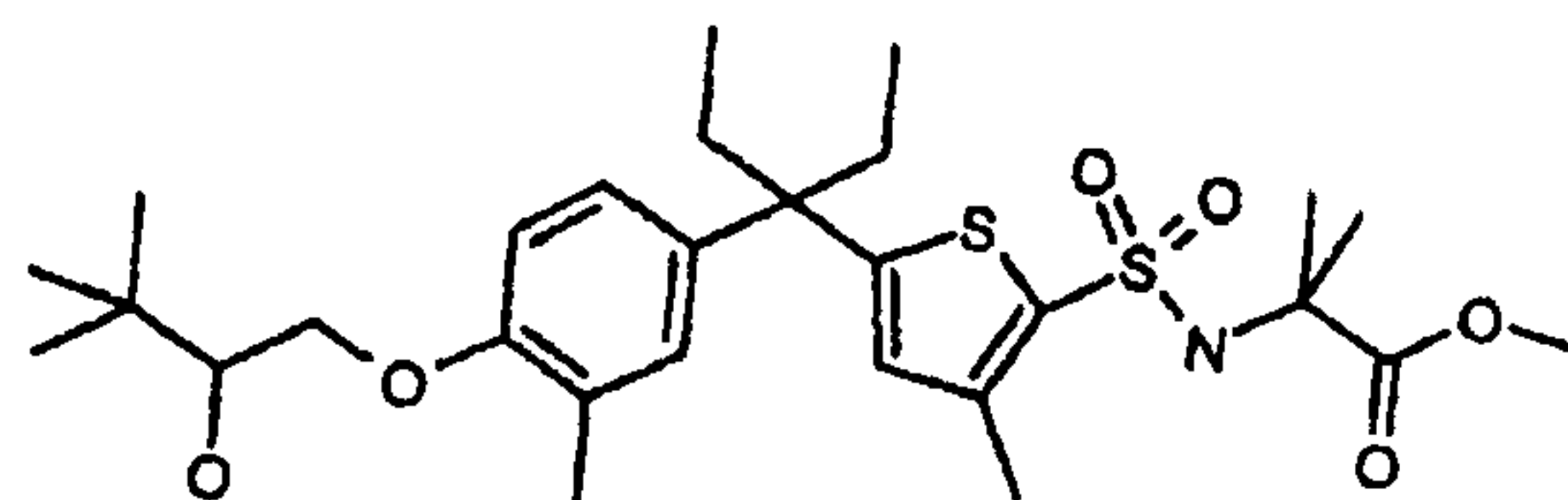
-395-

X147)

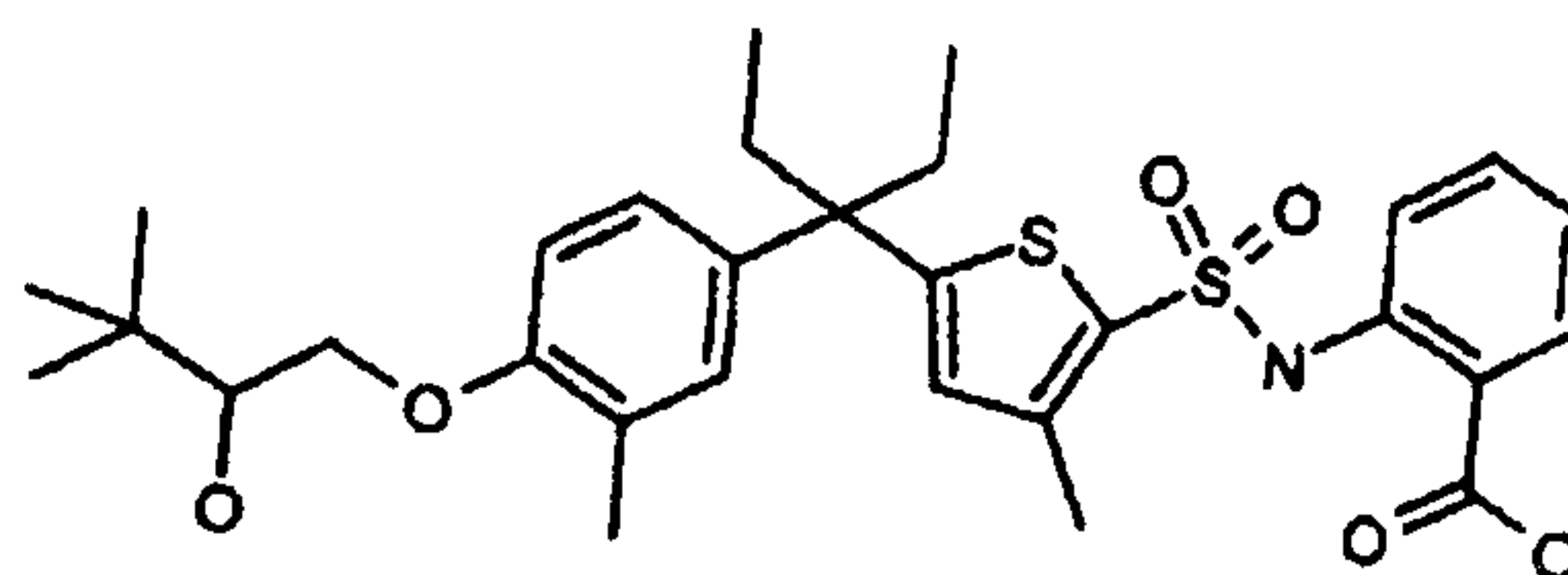


5

X148)

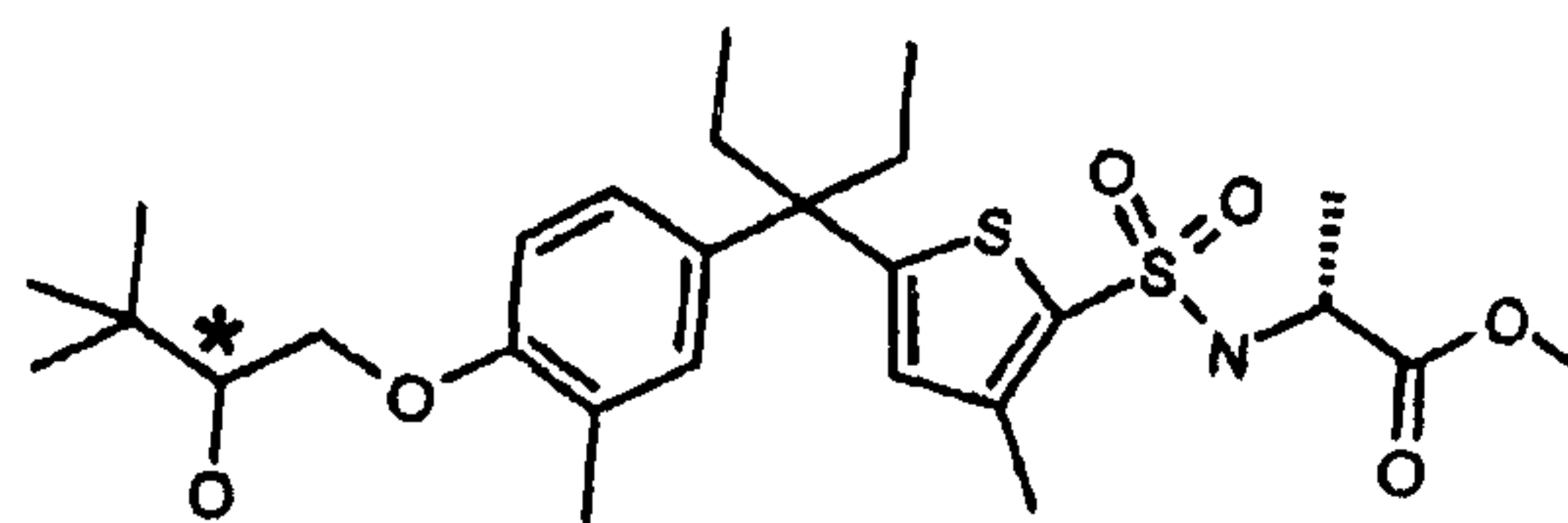


X149)

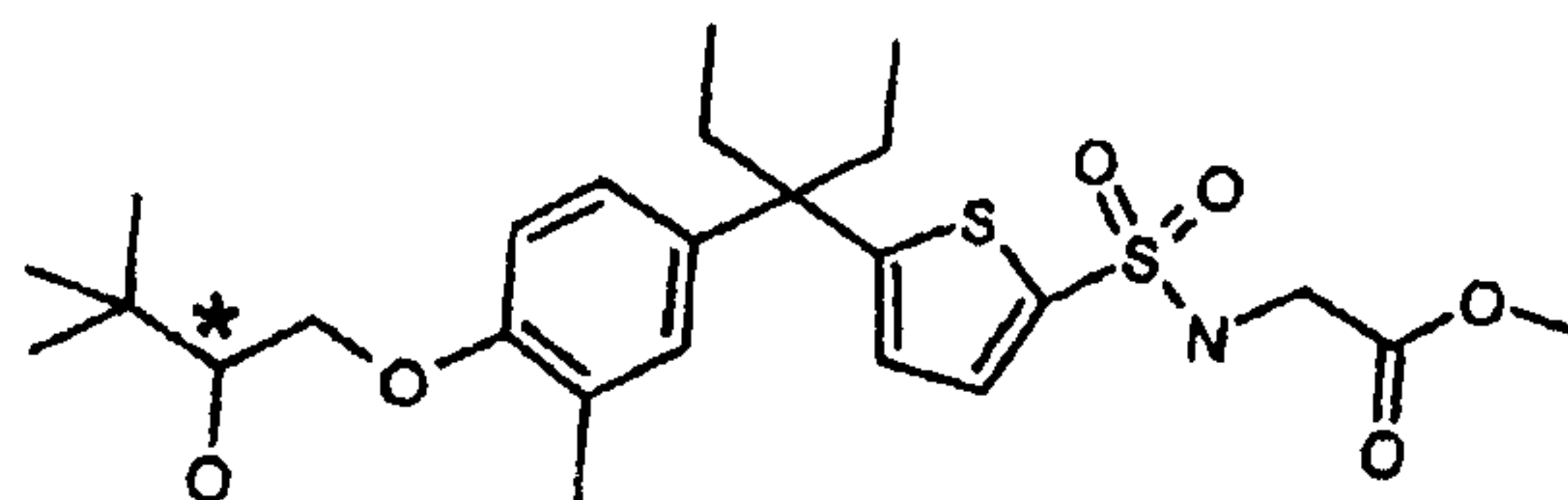


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X150)



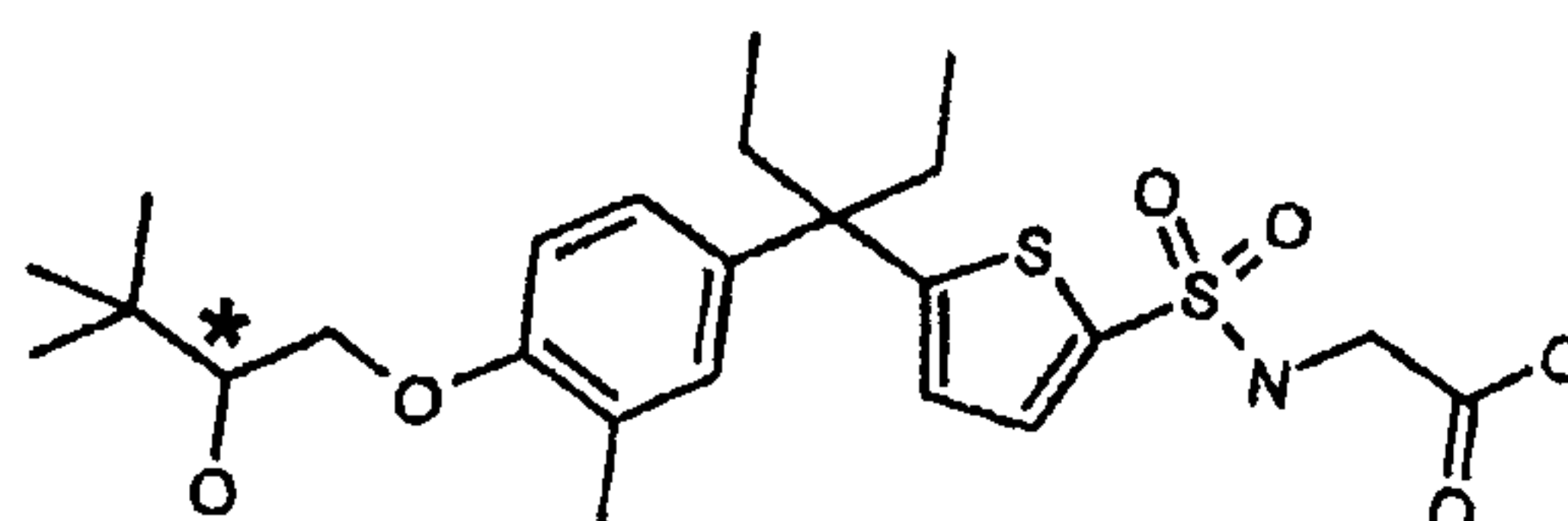
X152)



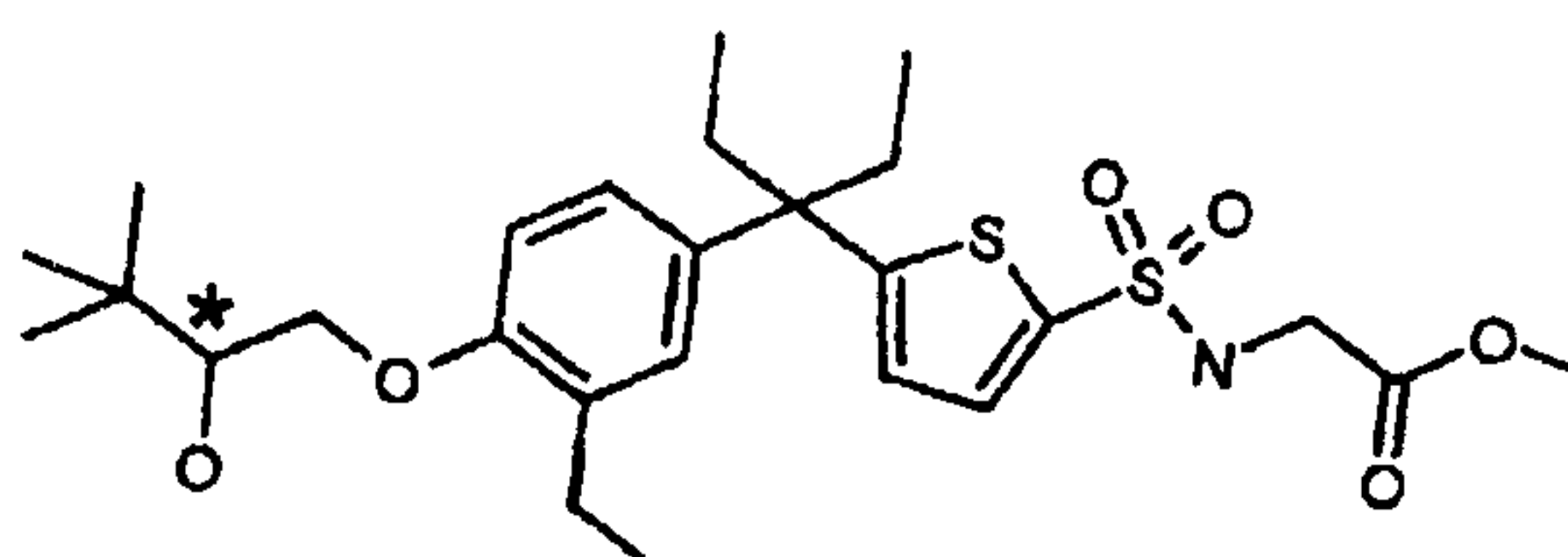
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-396-

X153)

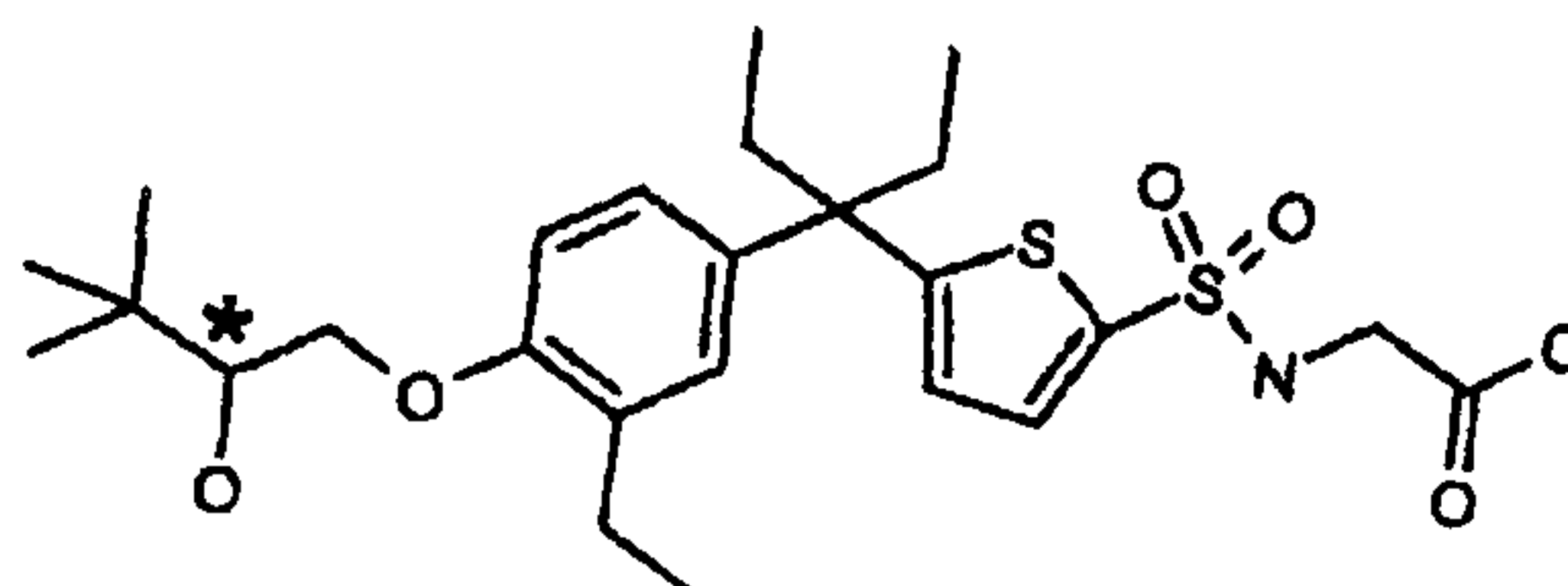


X154)

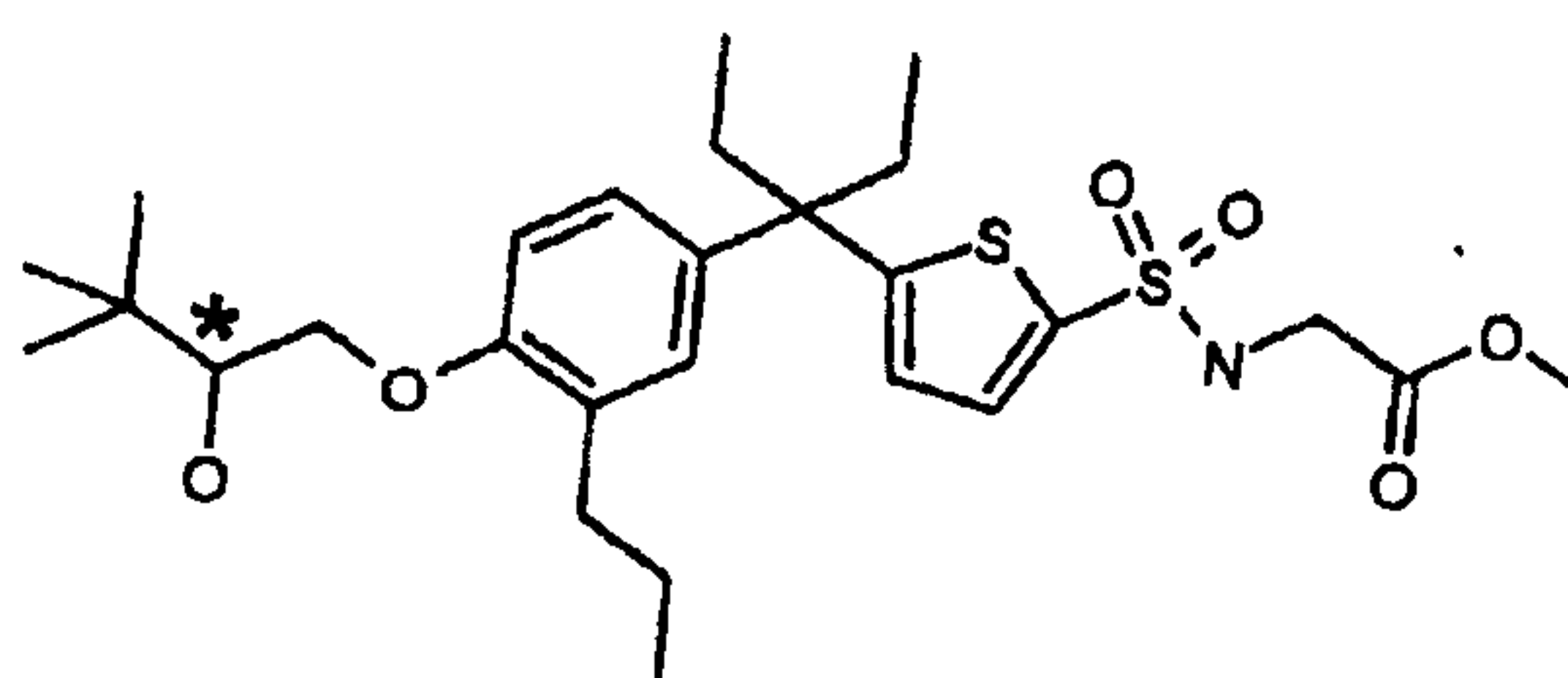


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X155)

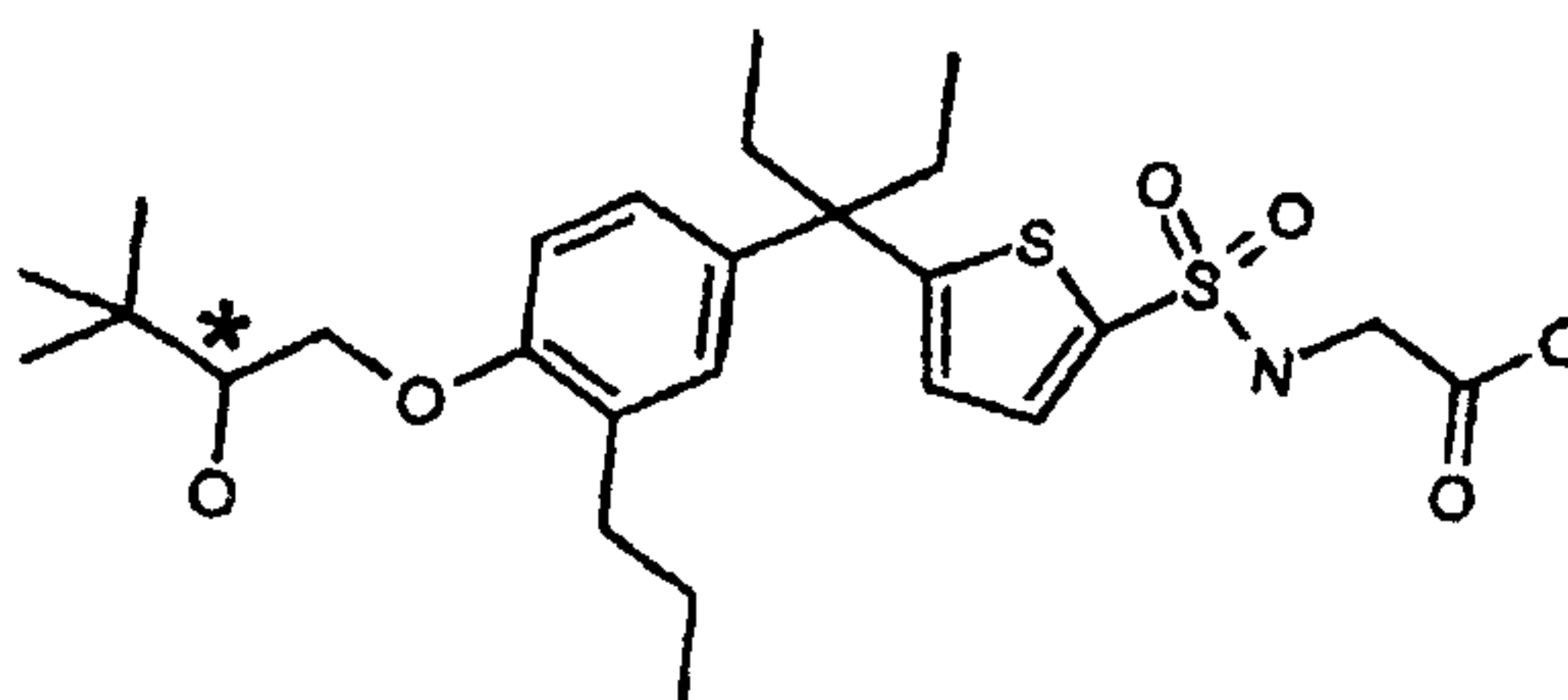


X156)



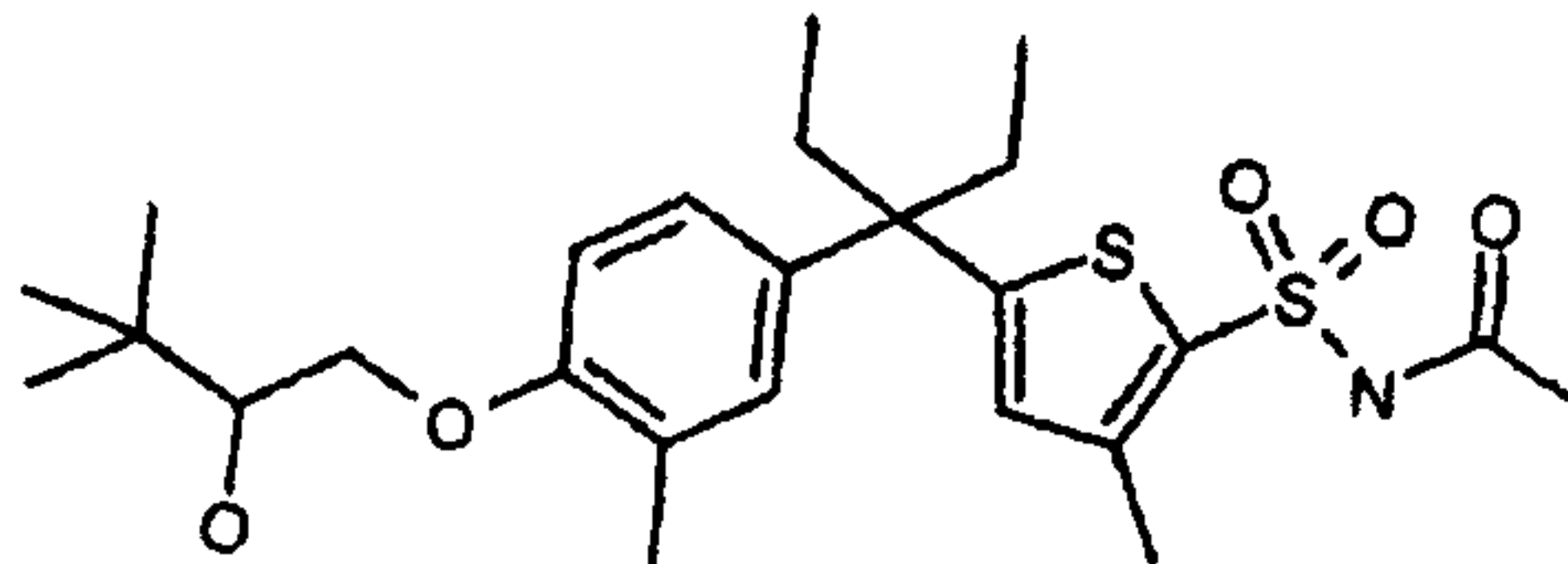
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X157)

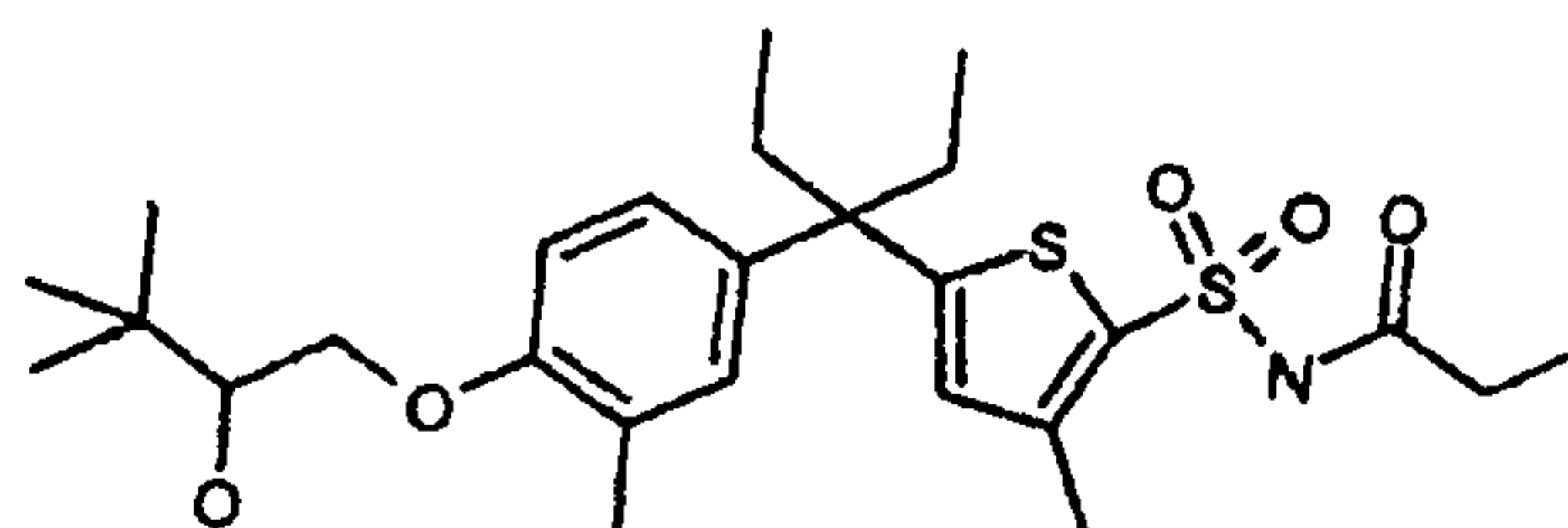


-397-

X158)

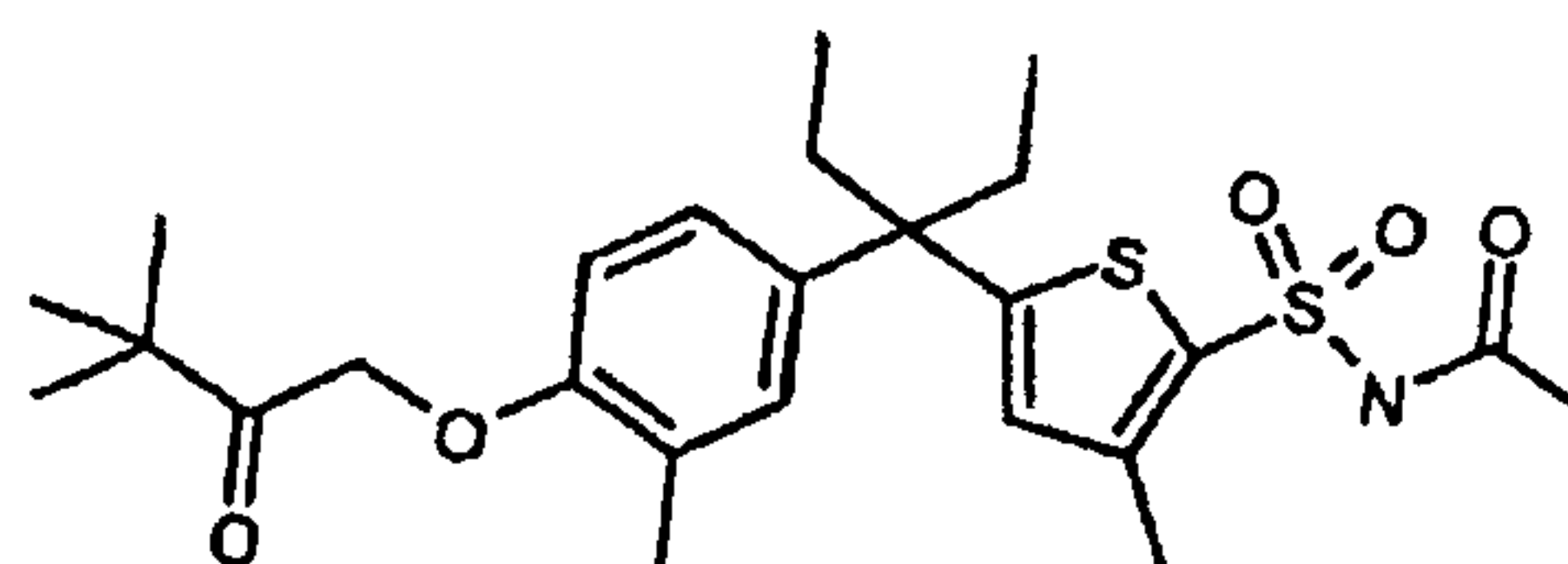


X159)

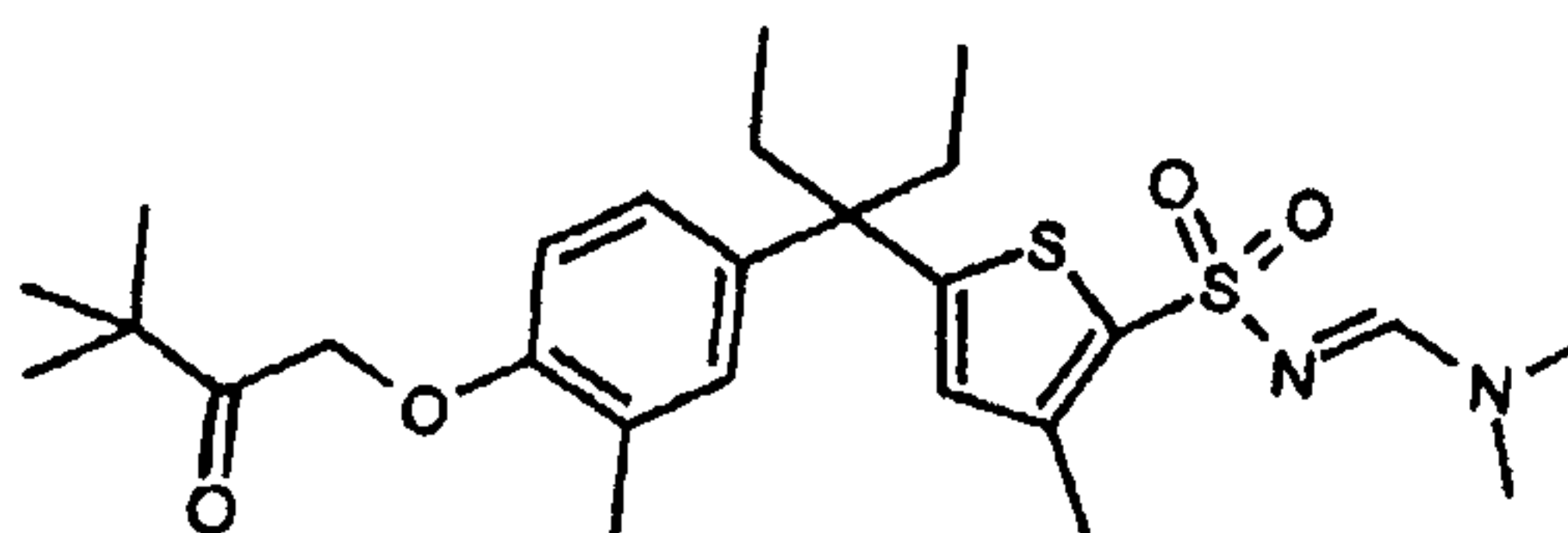


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X160)

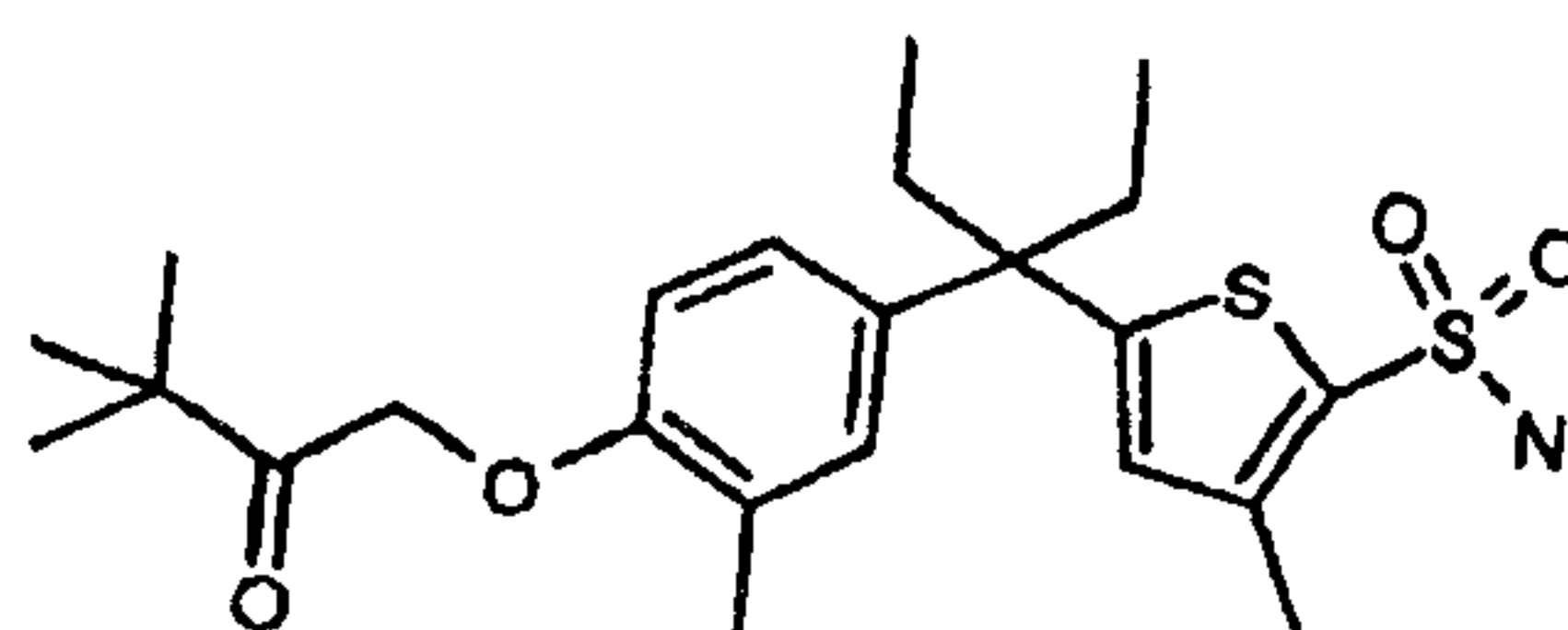


X161)



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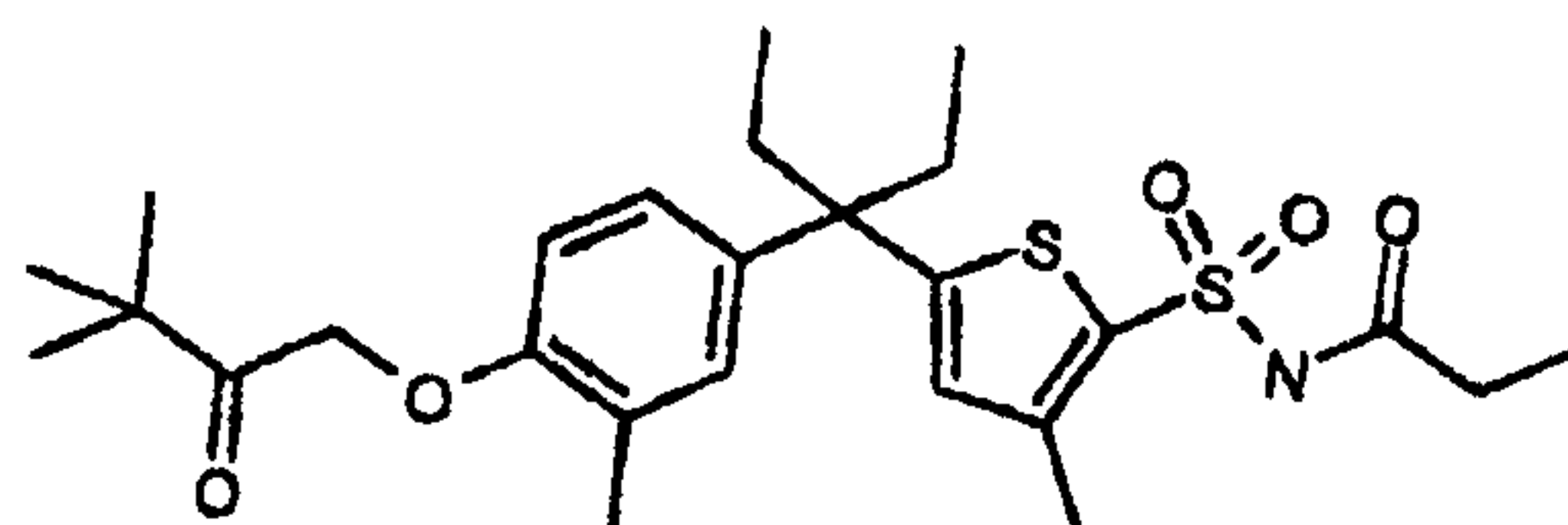
X162)



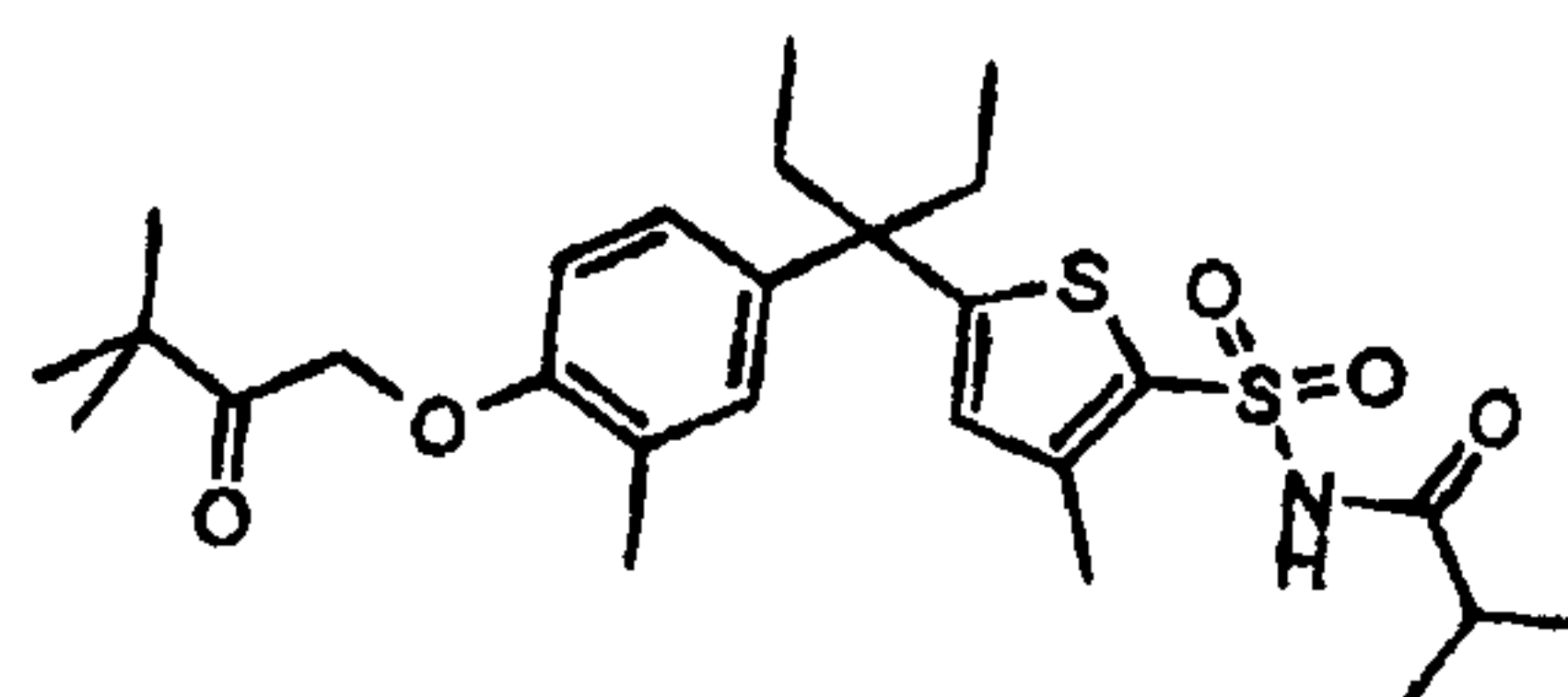
-398-

5

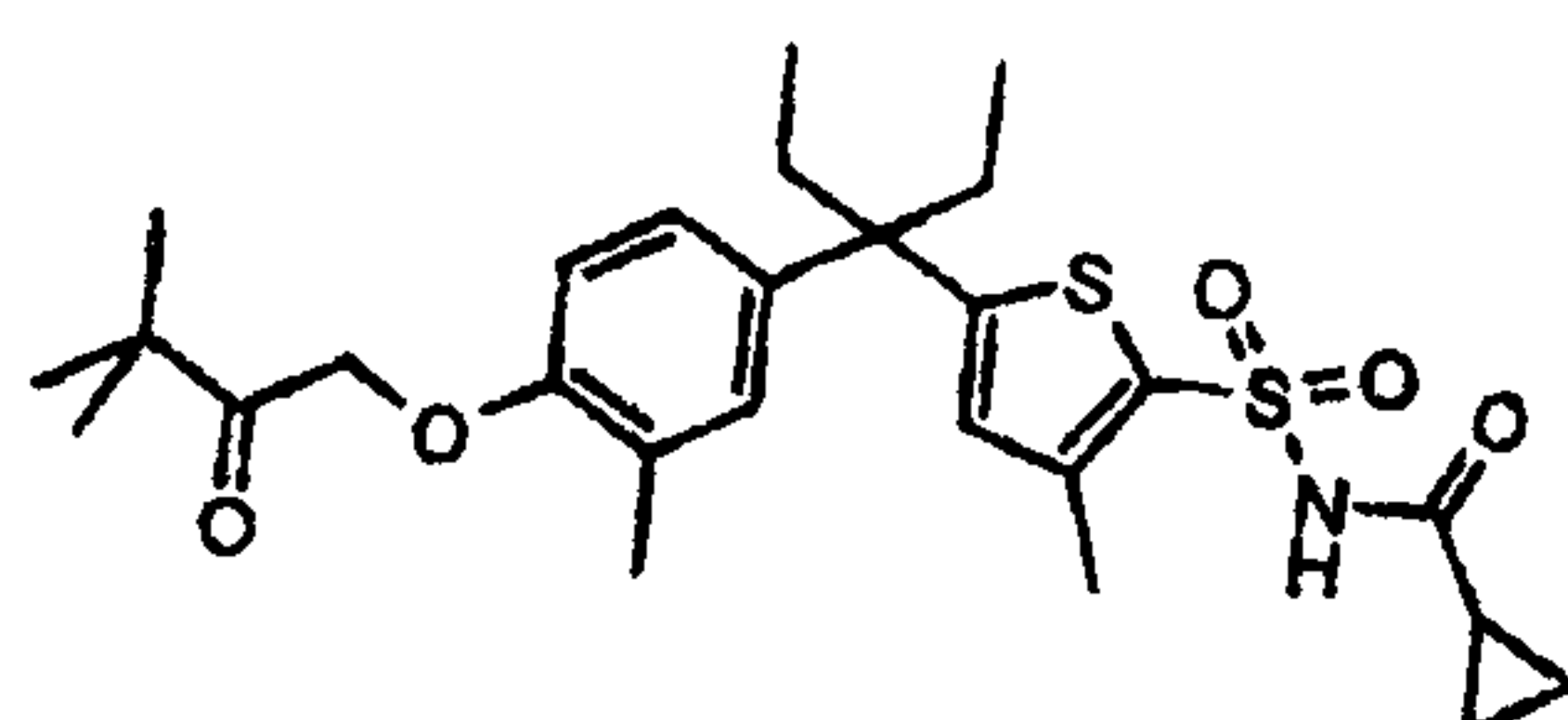
X163)



X164)

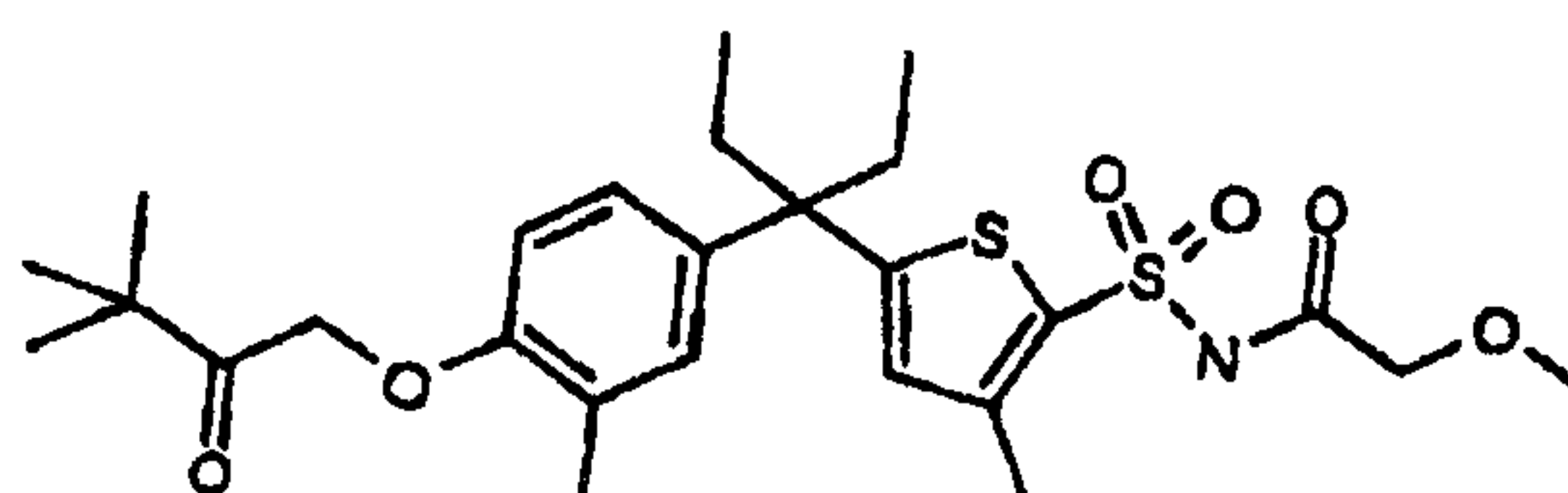


X165)

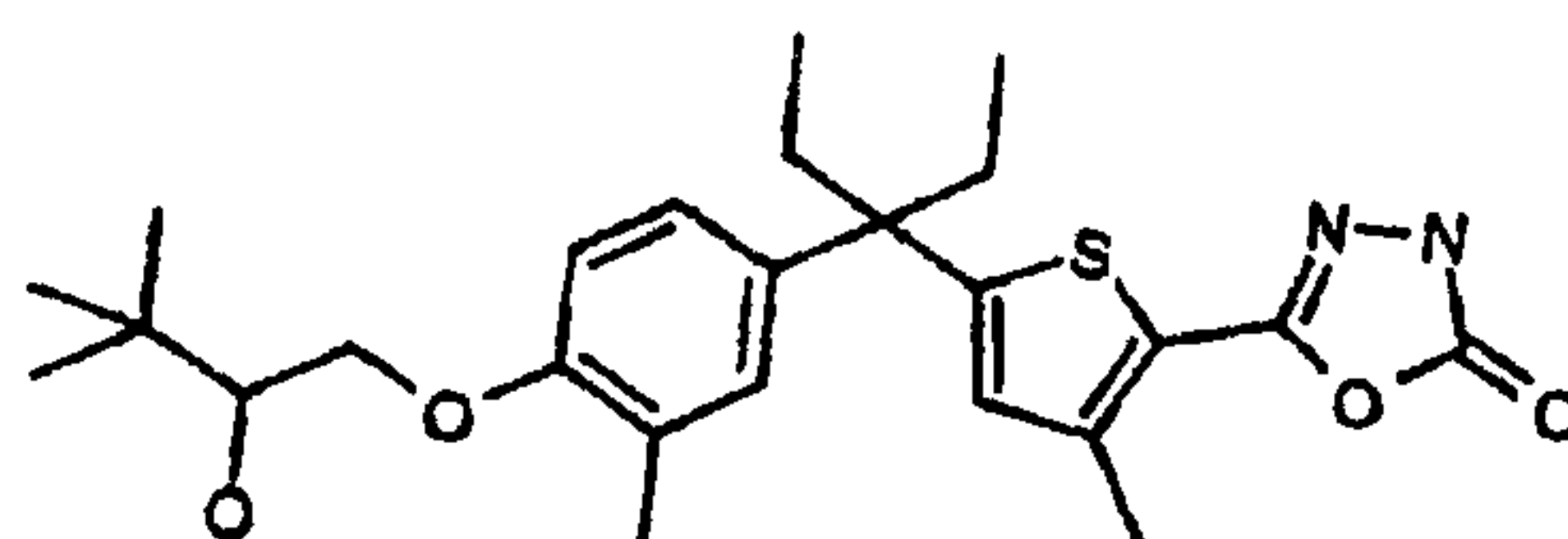


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X166)



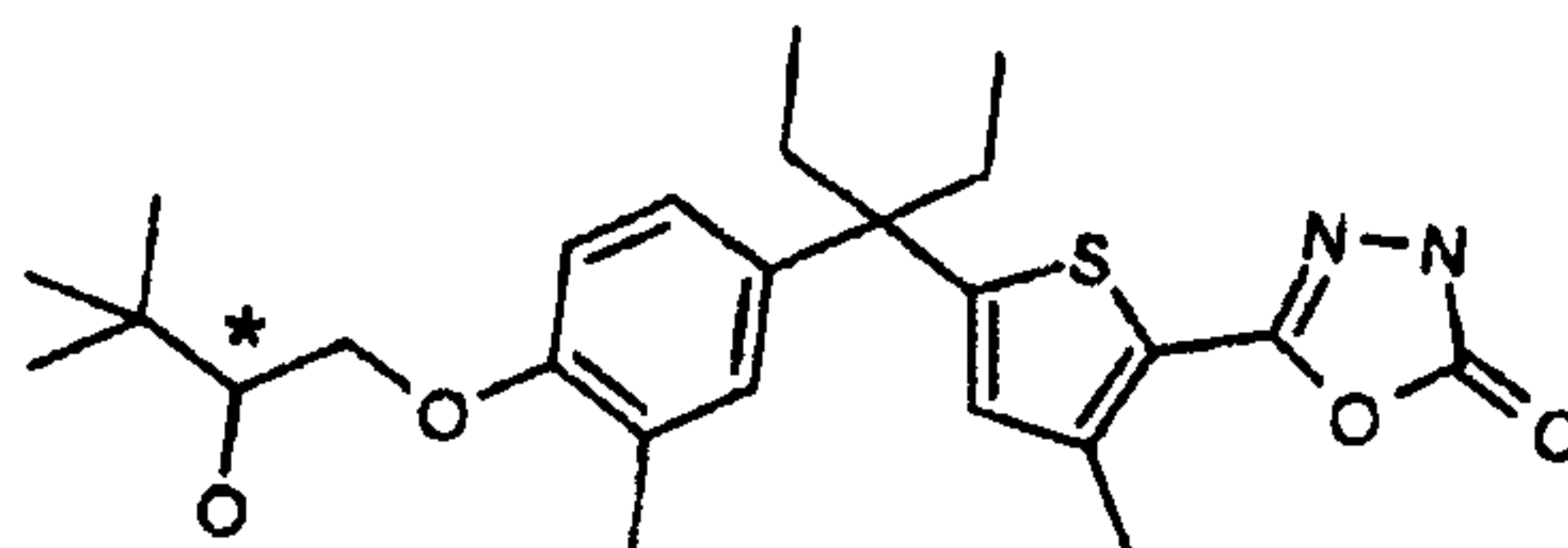
X169)



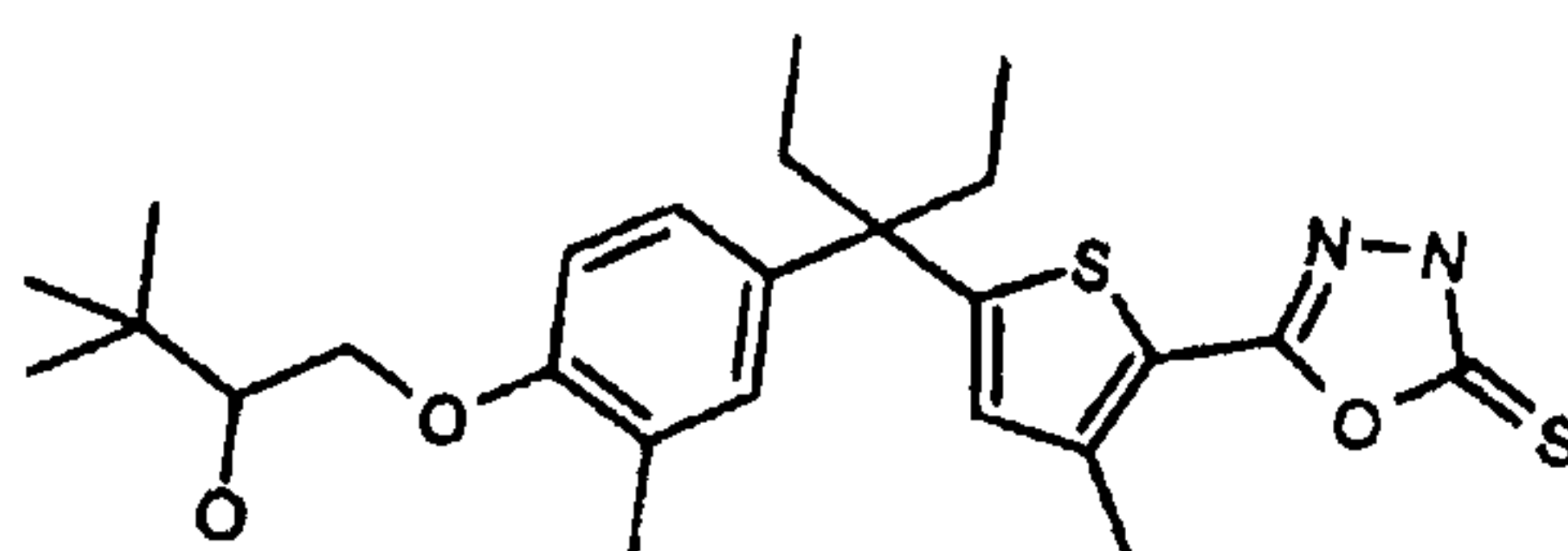
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-399-

X171)

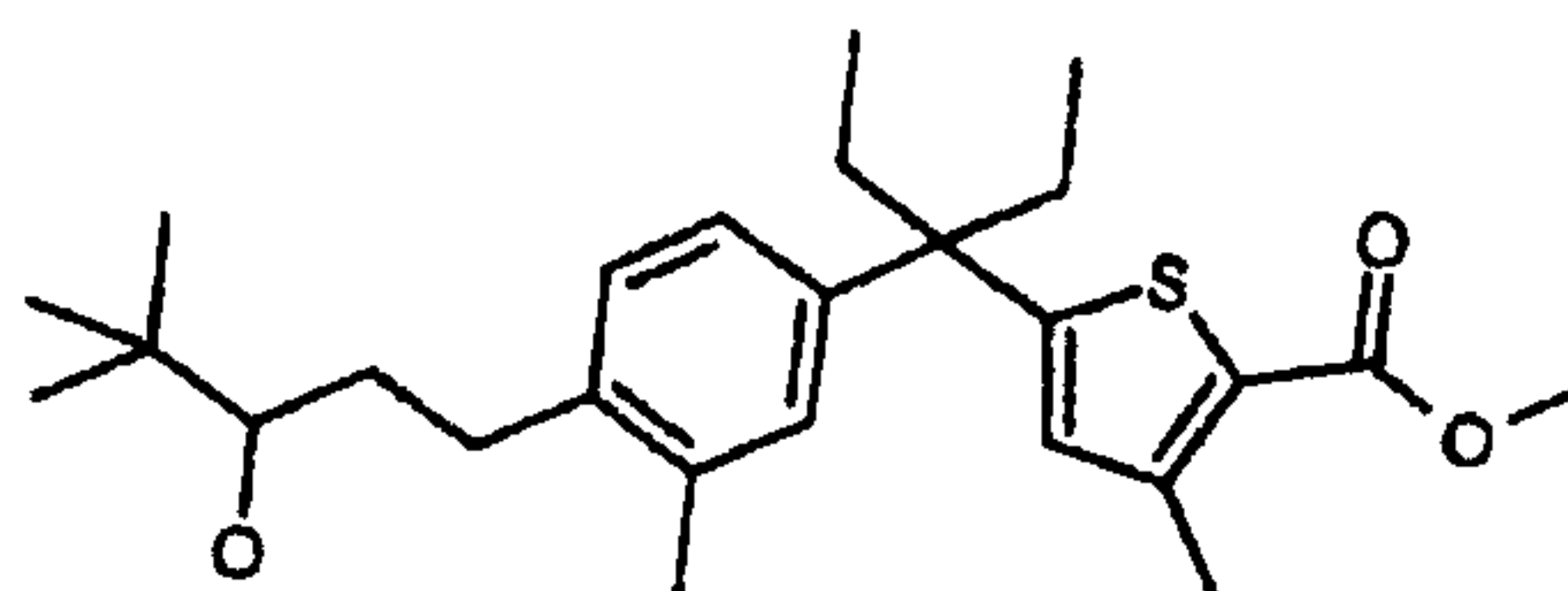


X172)

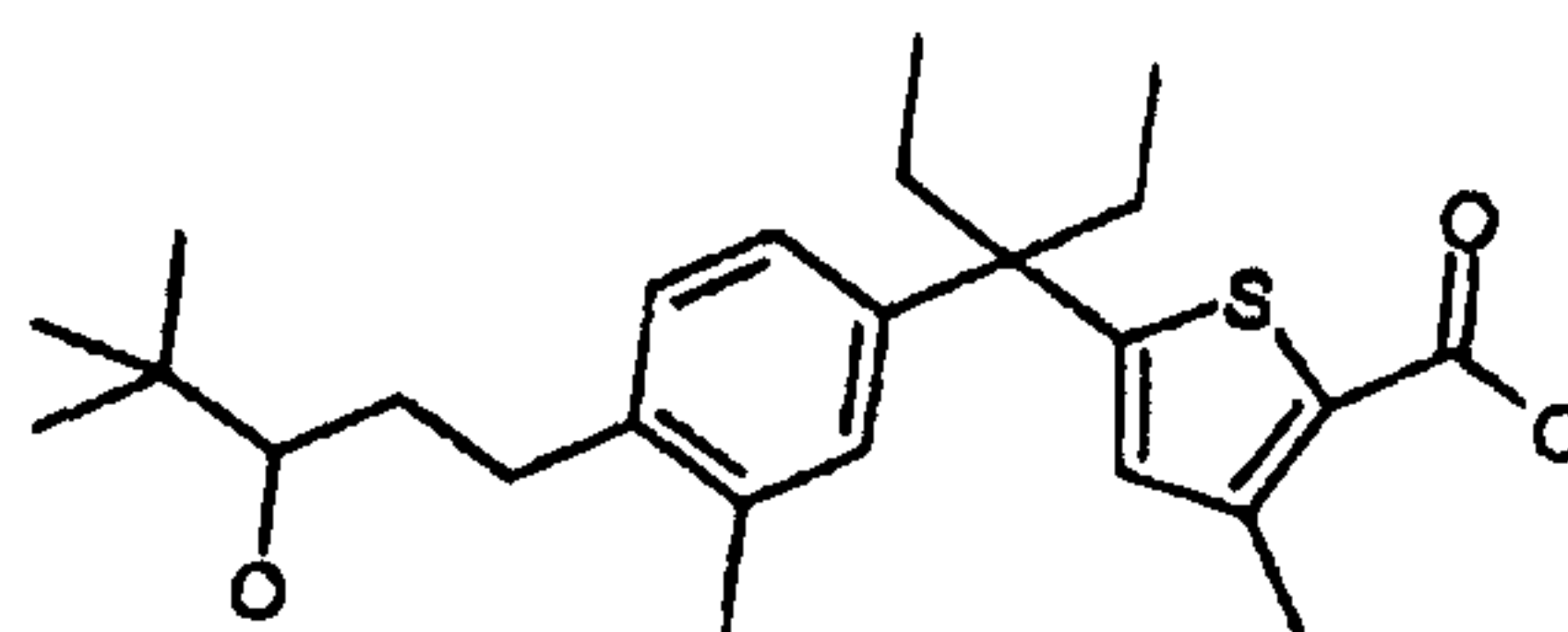


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X174)

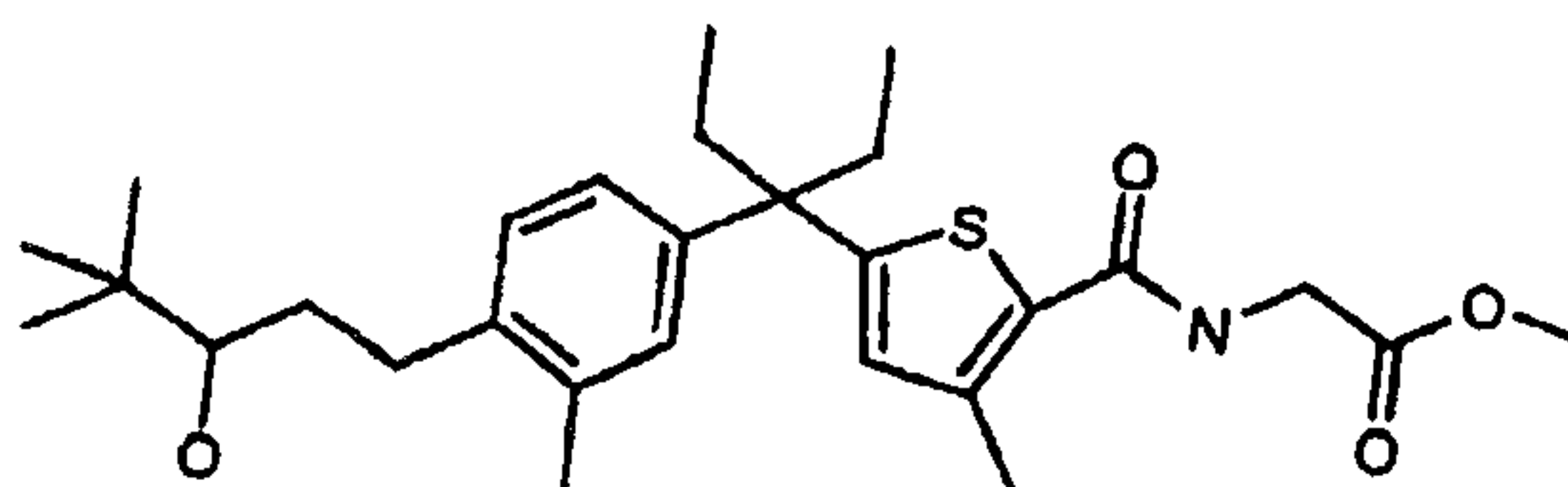


X175)



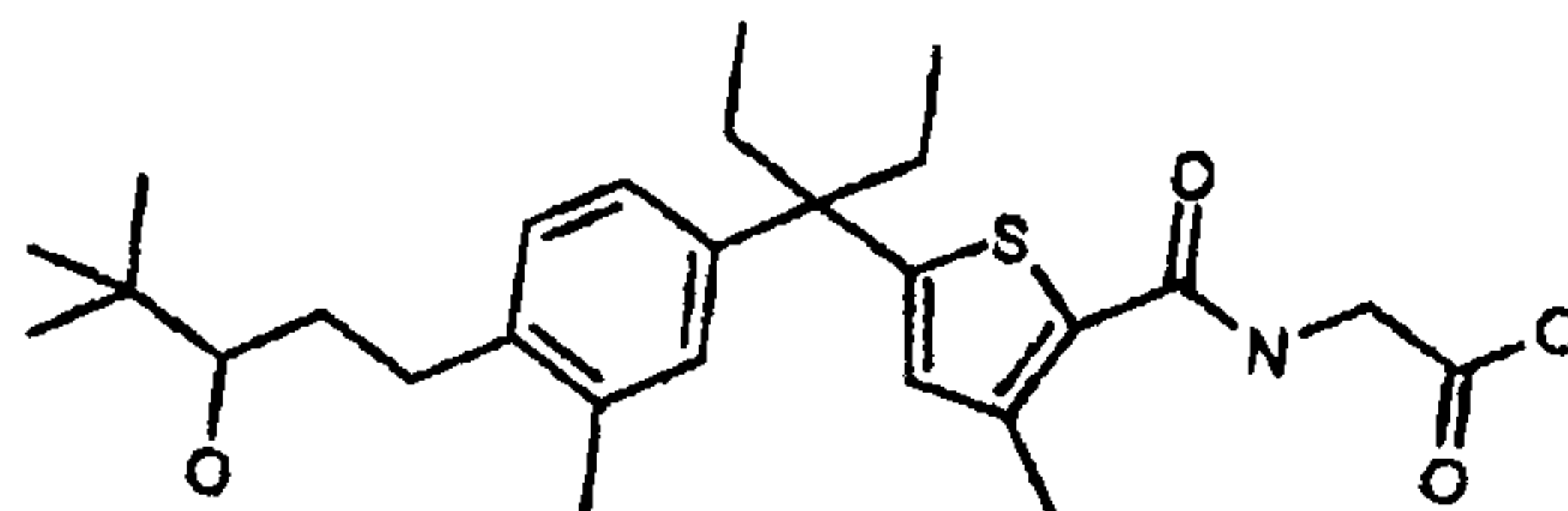
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X176)

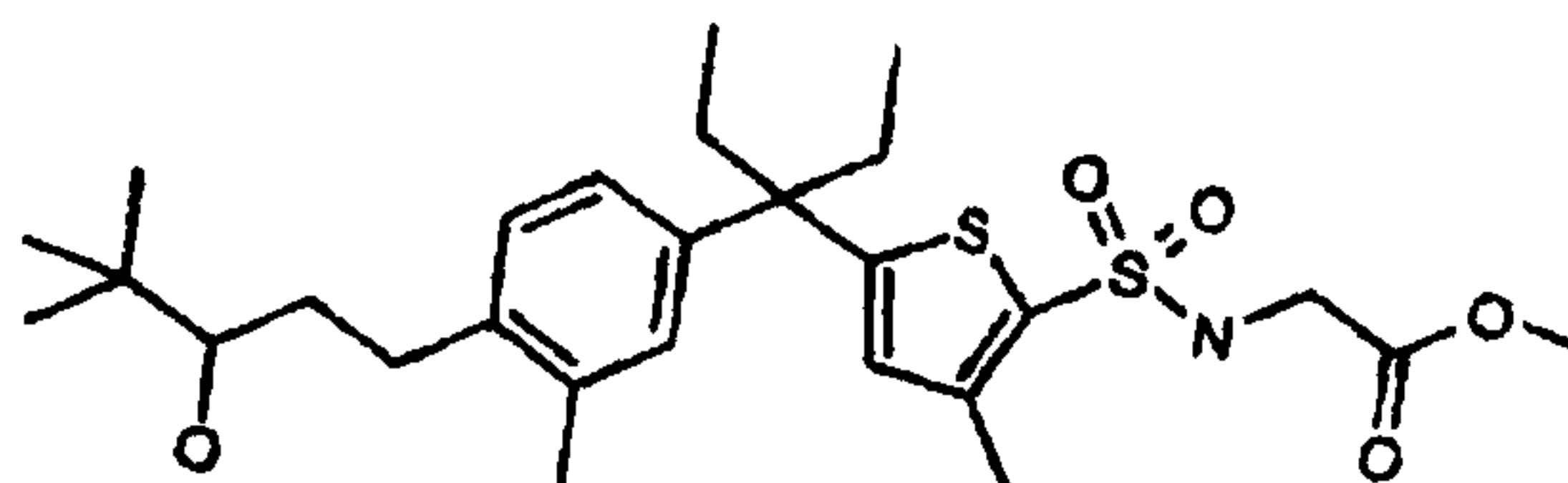


-400-

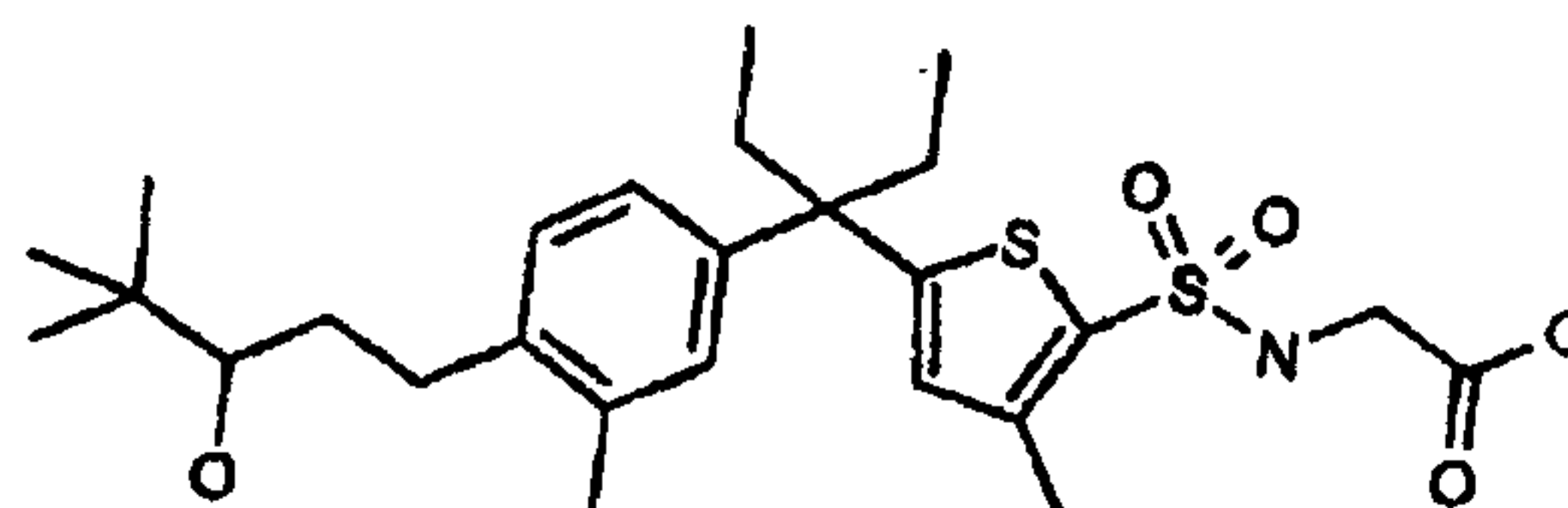
X177)



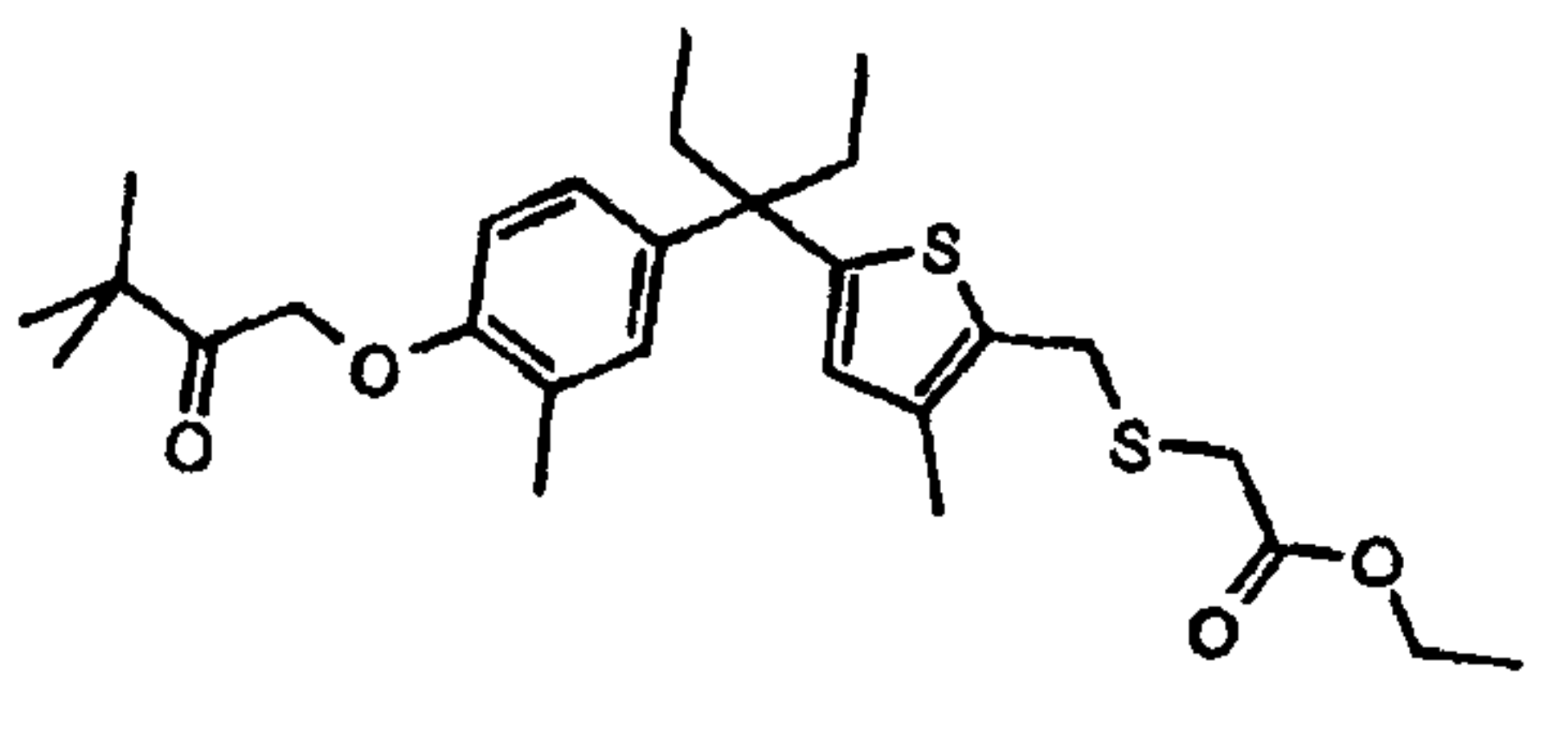
X178)



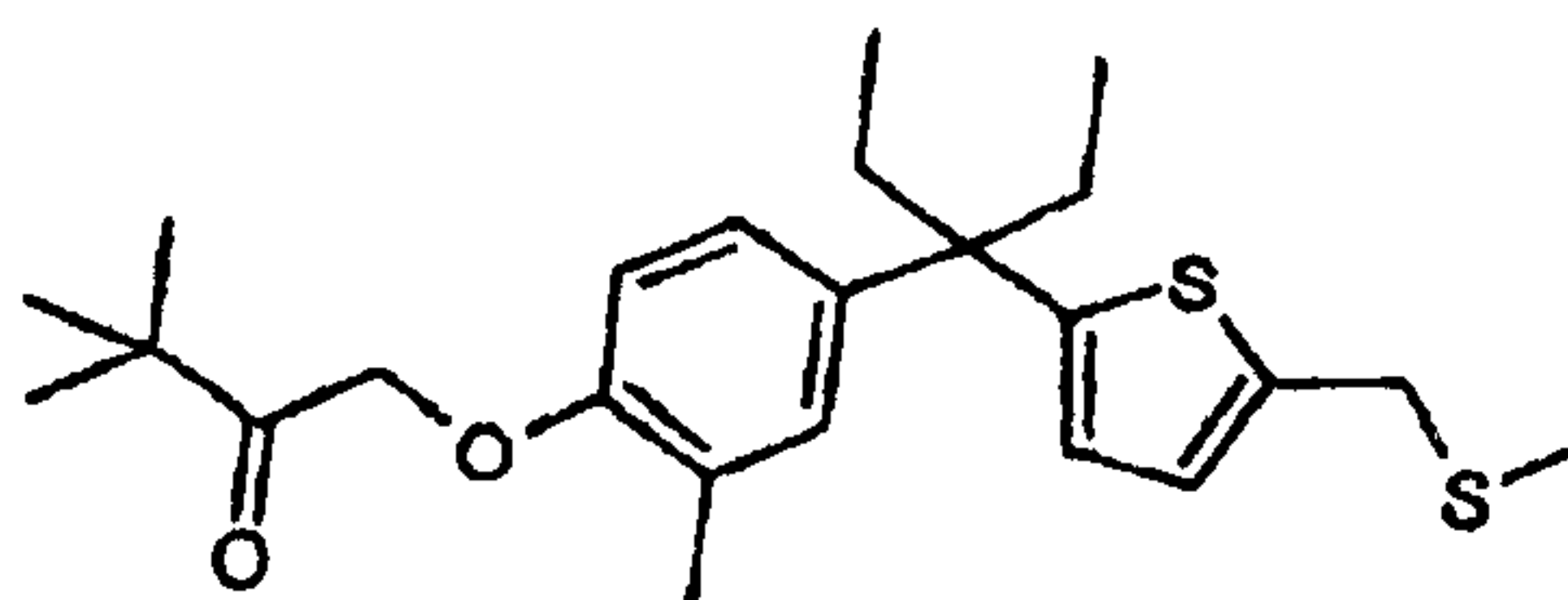
X179)



X183)

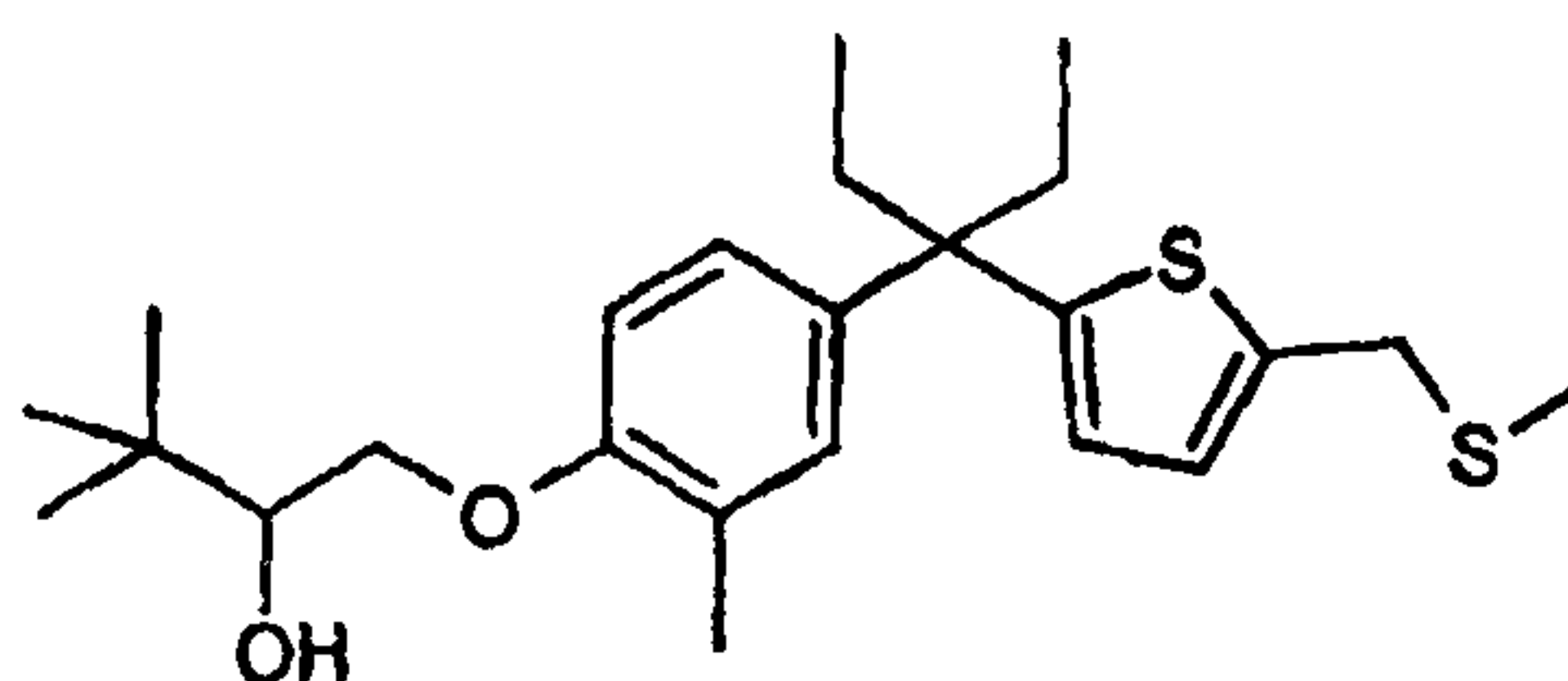


X184)

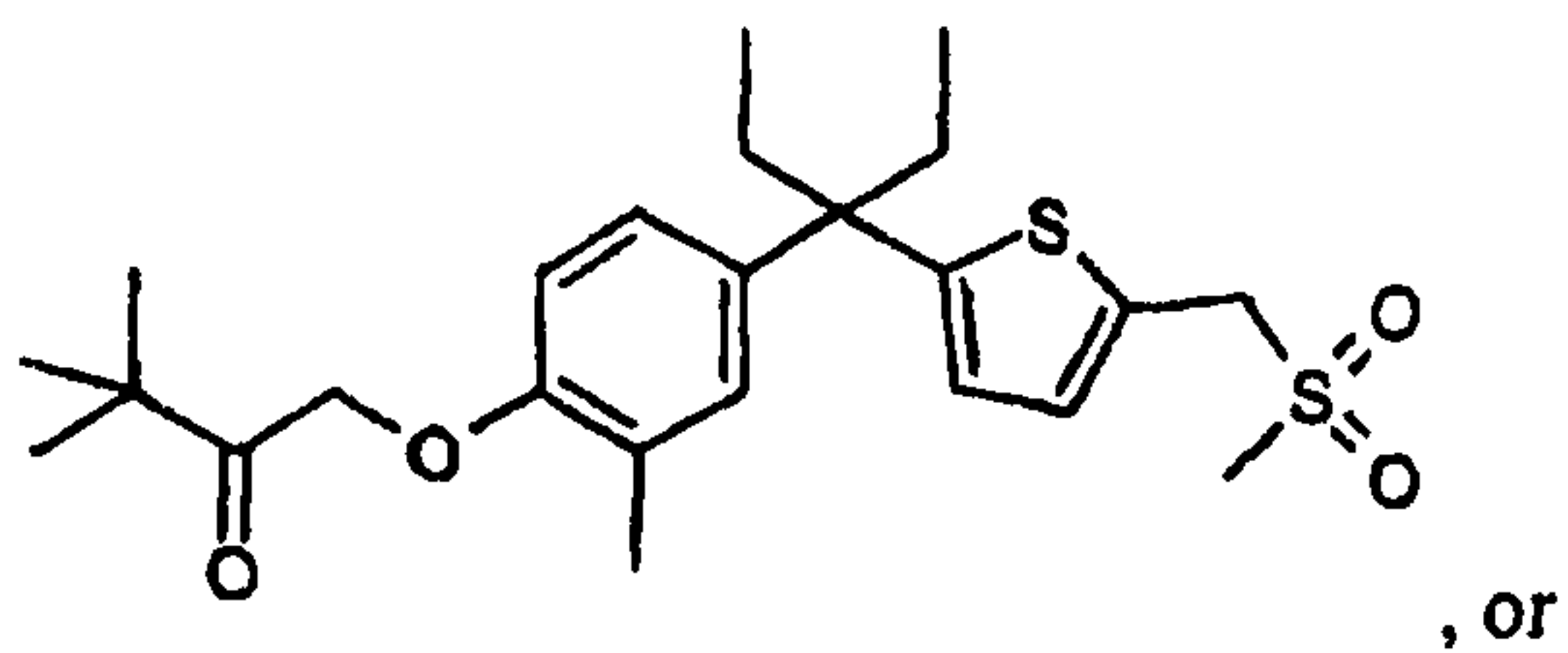


-401-

X185)

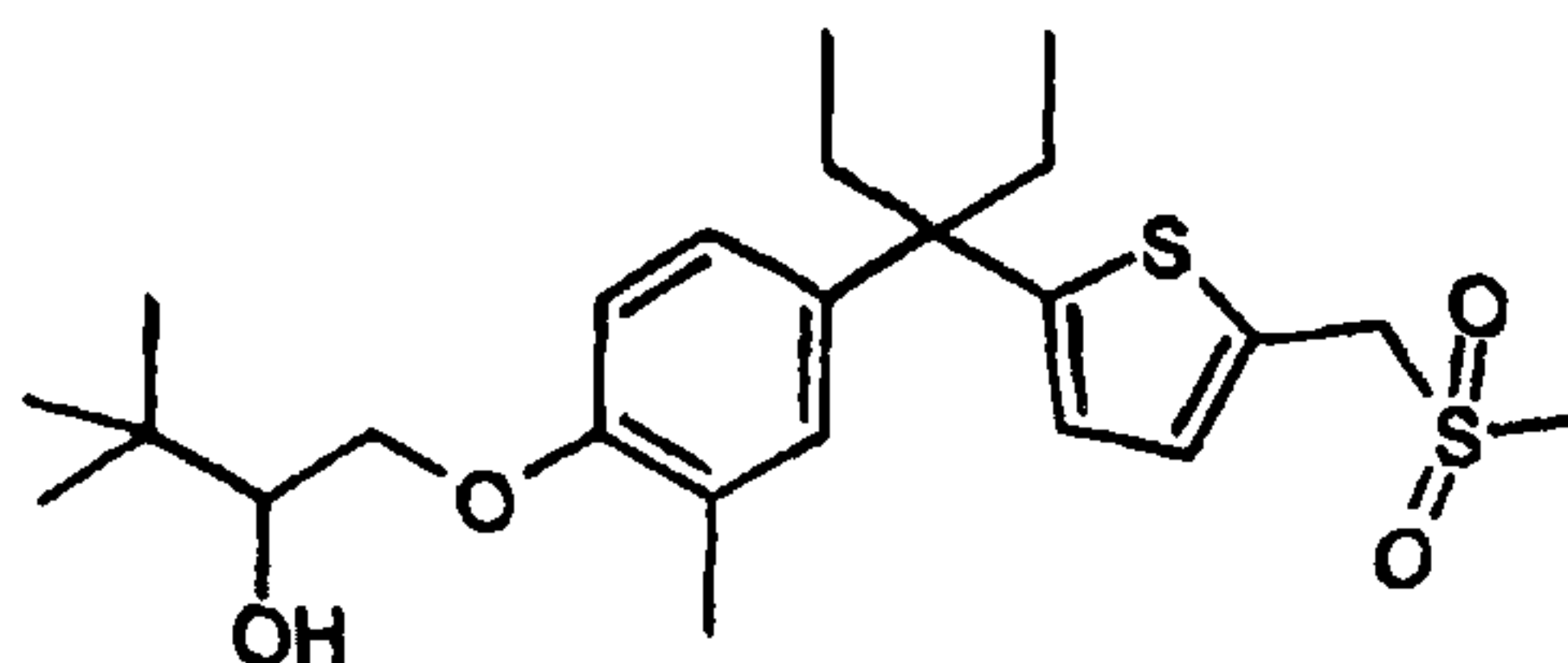


X187)



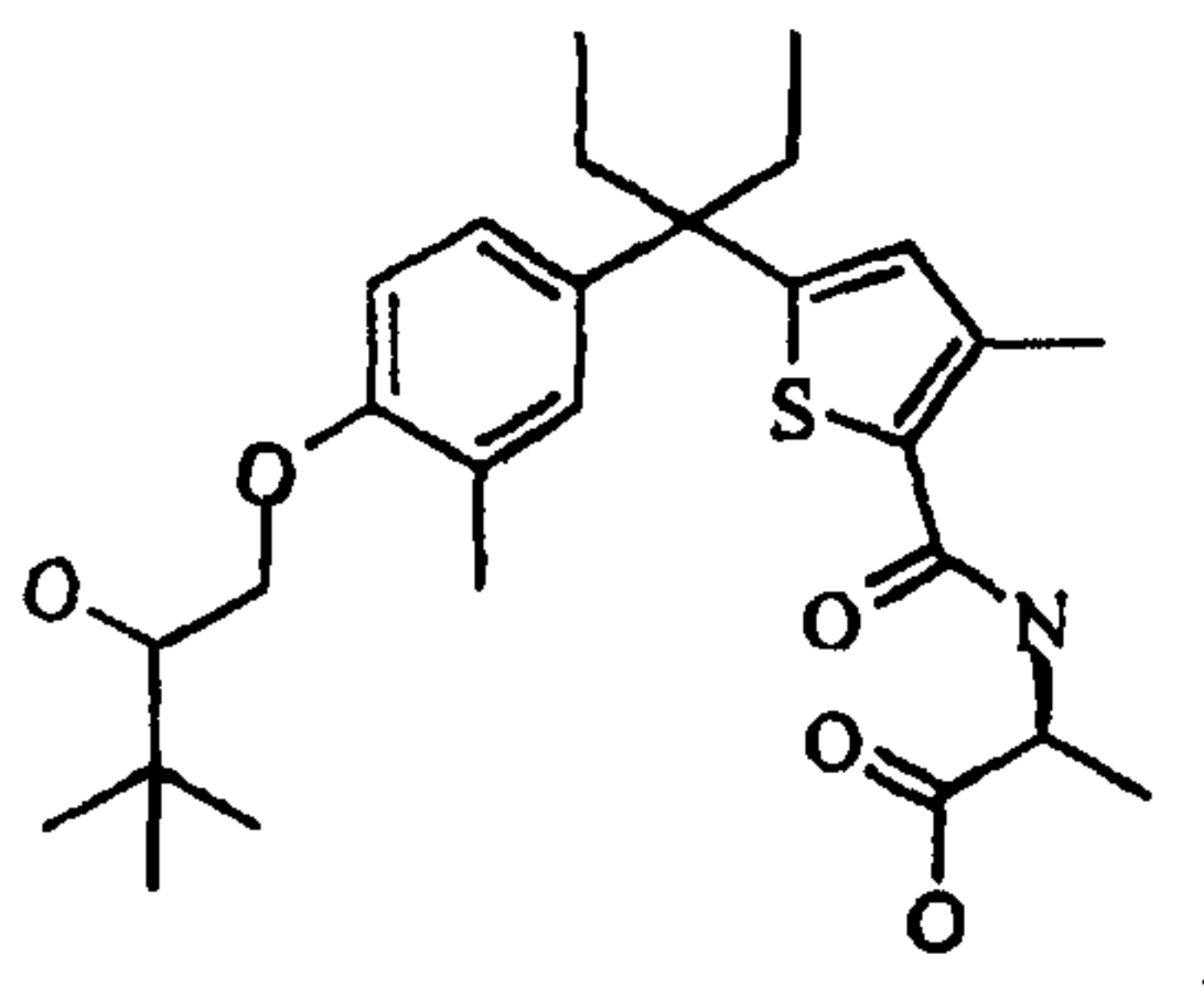
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X188)



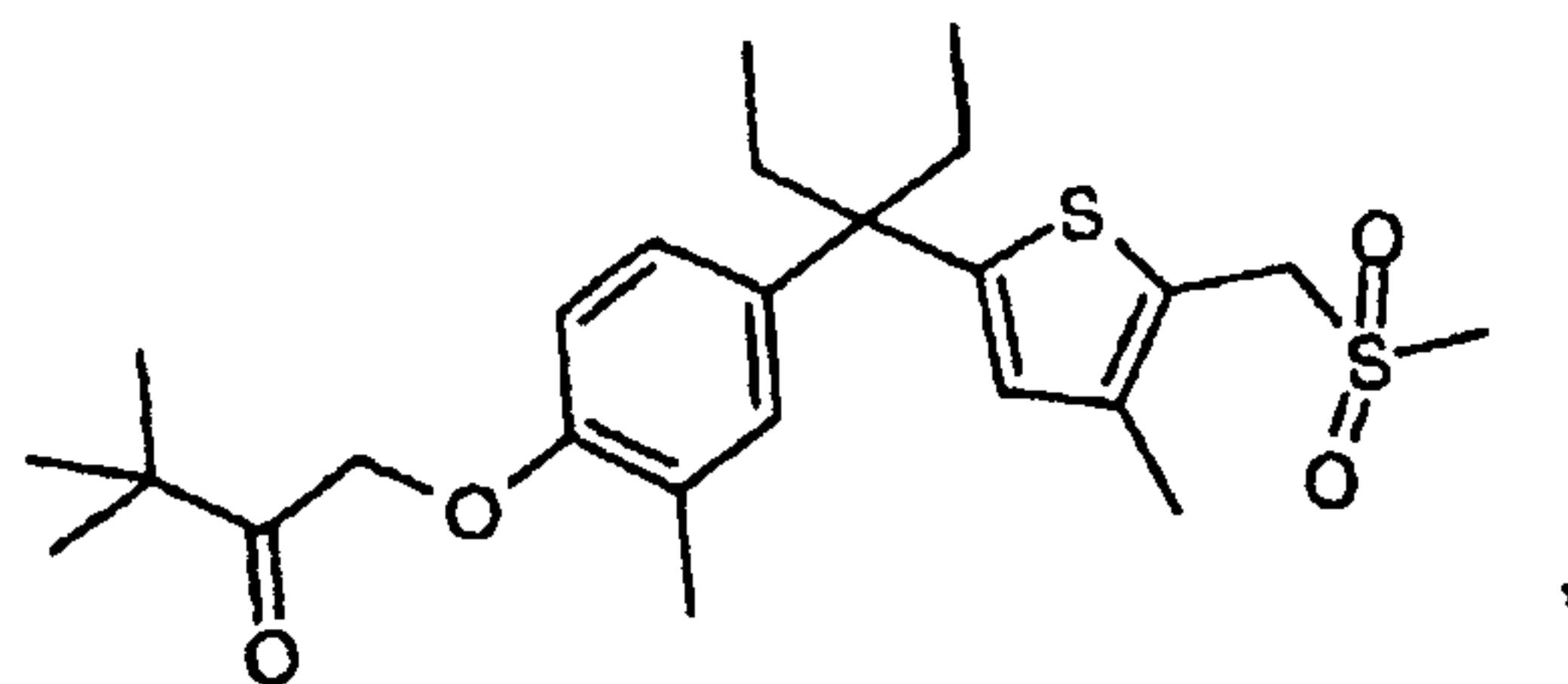
2. A compound selected from the group consisting of compounds represented by
 10 the formula:

P100



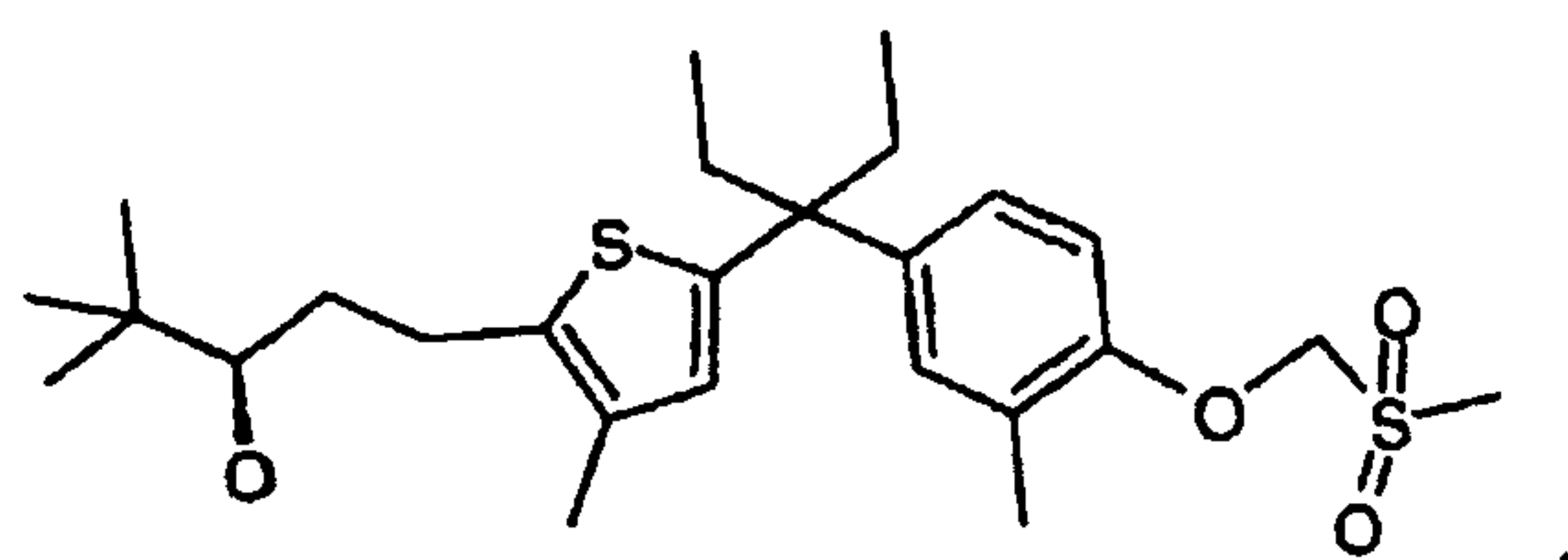
-402-

P101

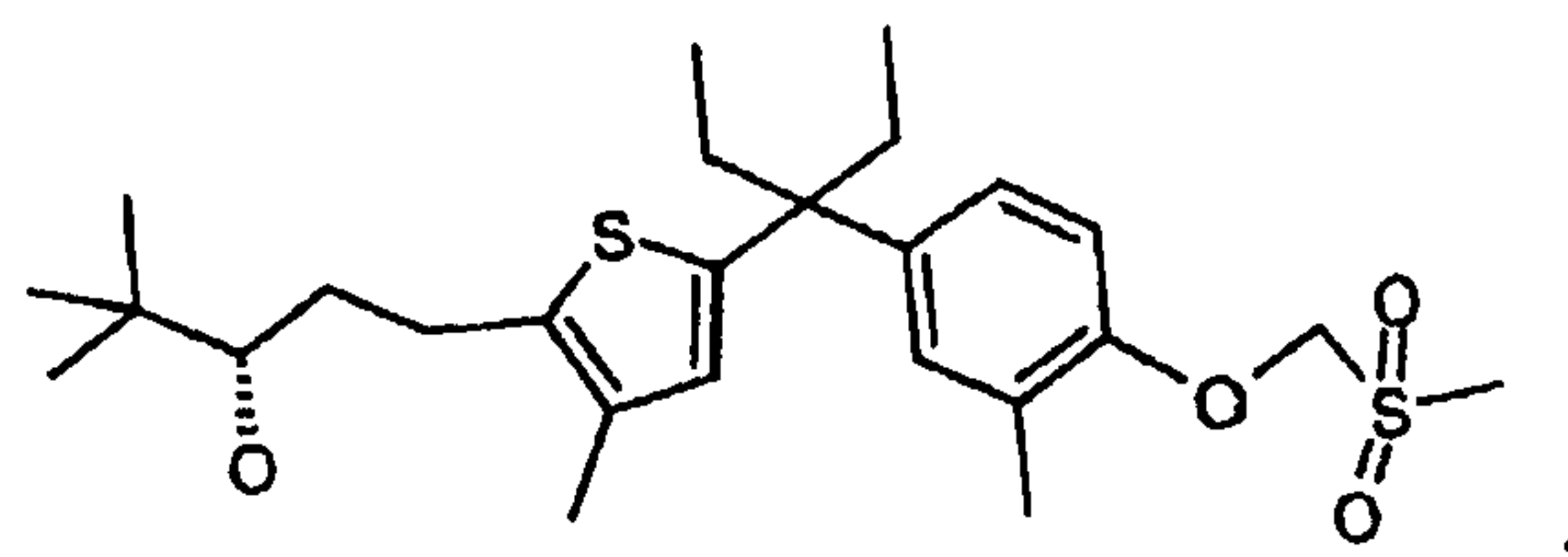


P102

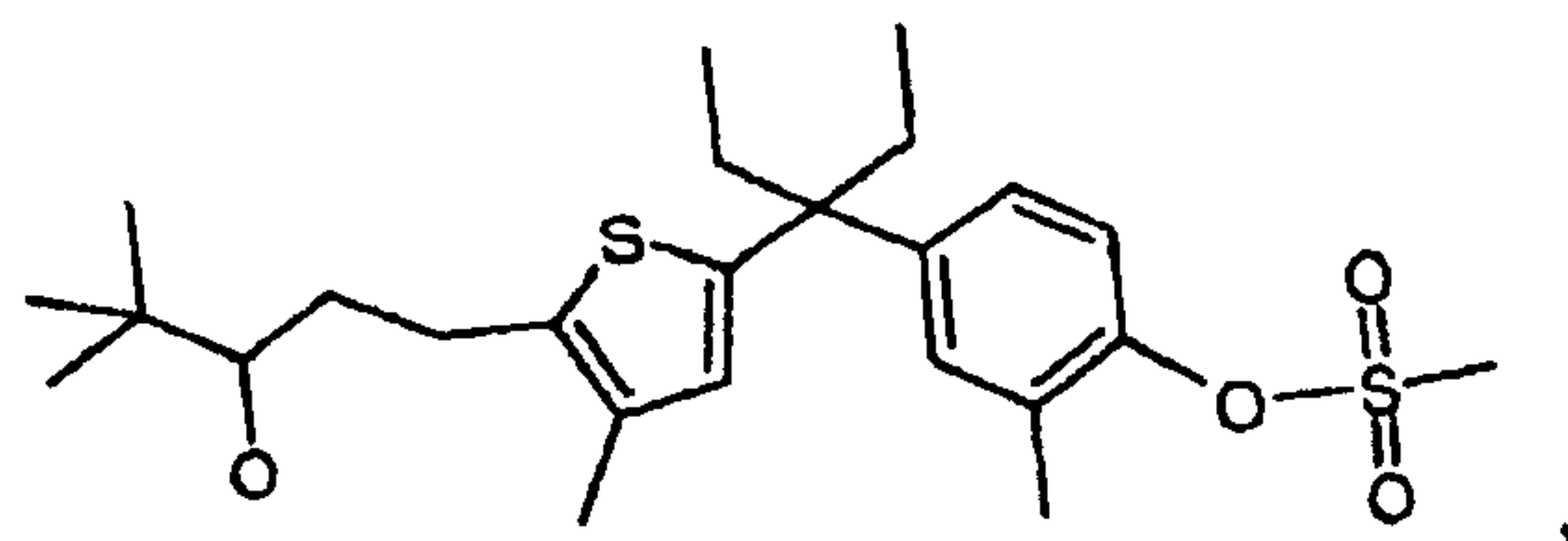
5



P103

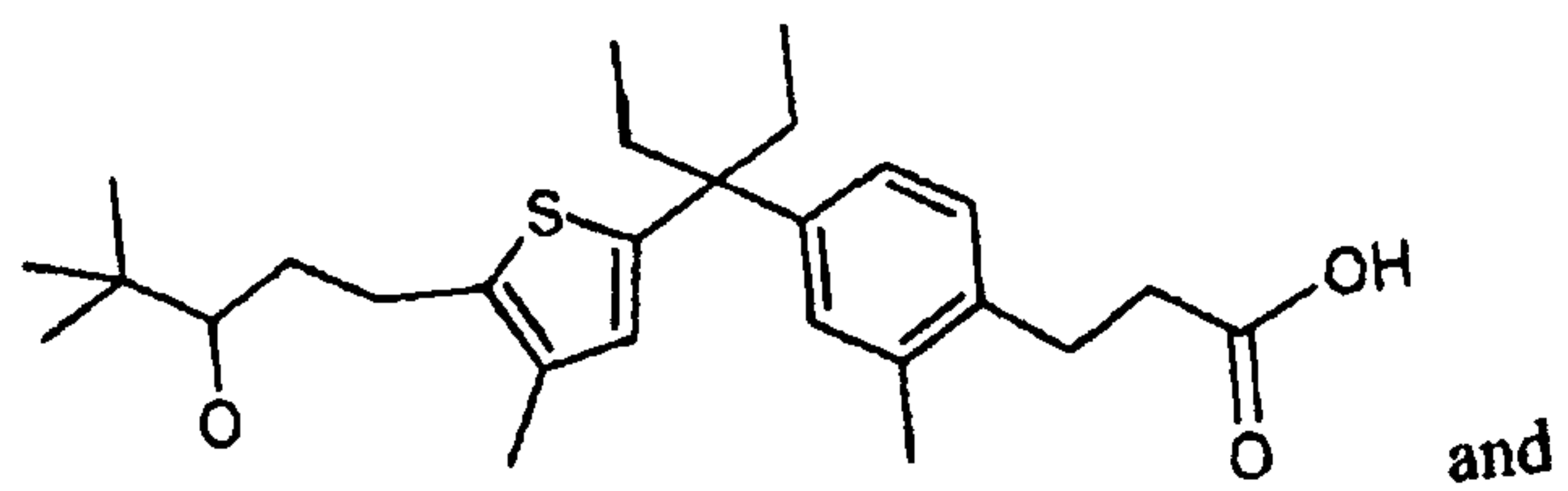


P104



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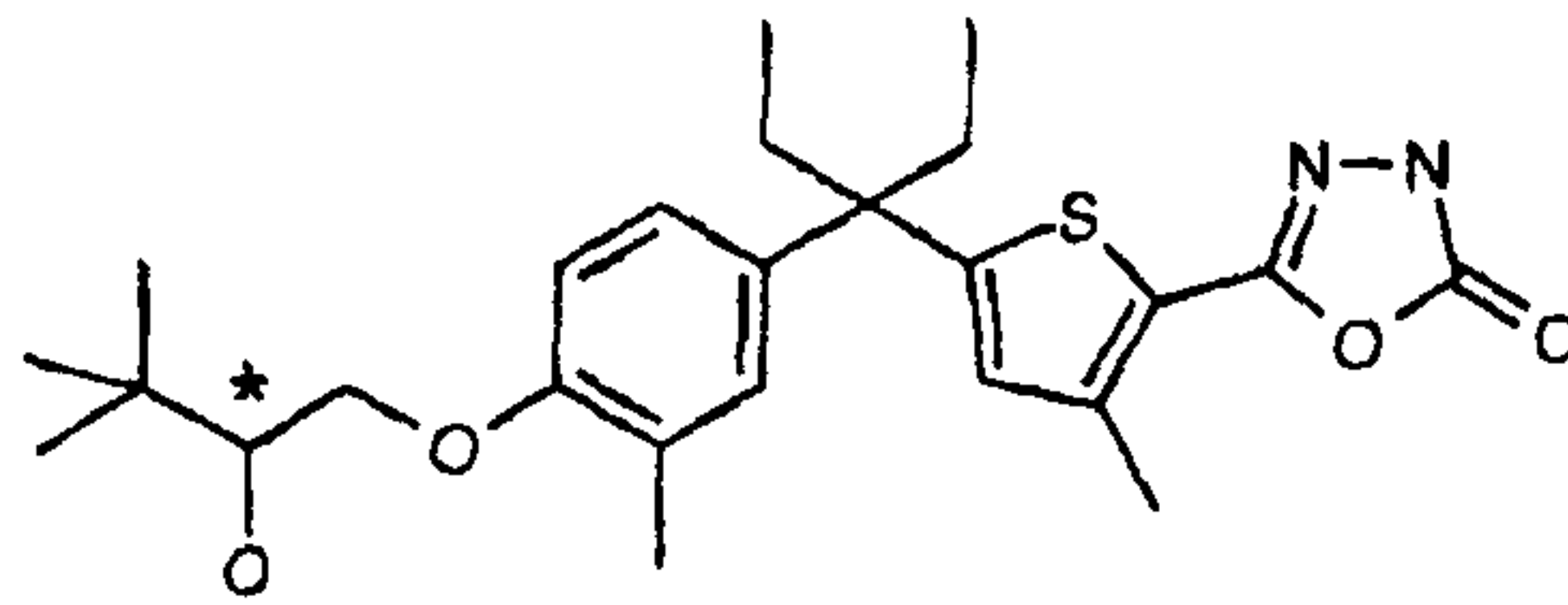
P105



and

-403-

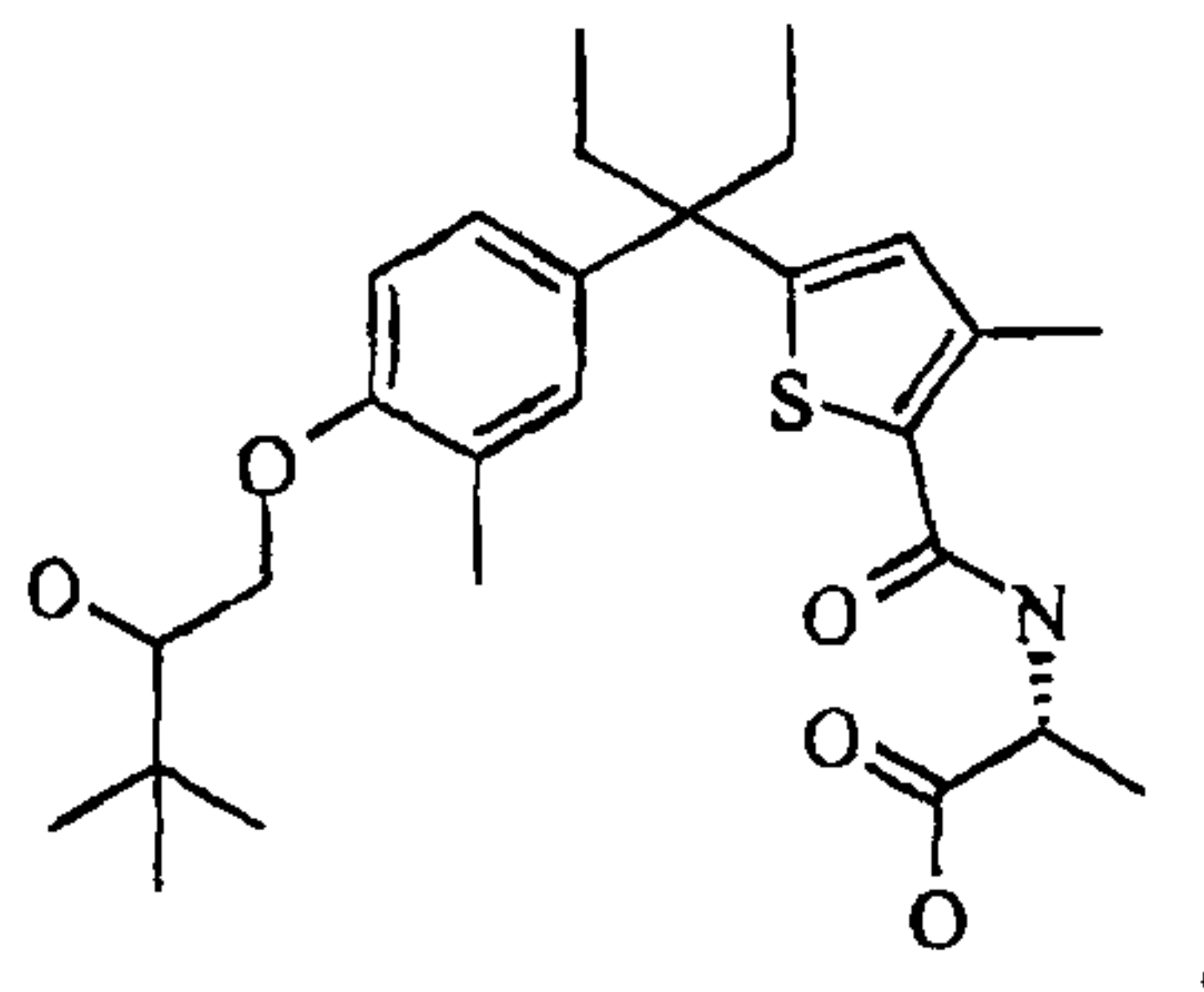
P106



or a pharmaceutically suitable salt or solvate thereof.

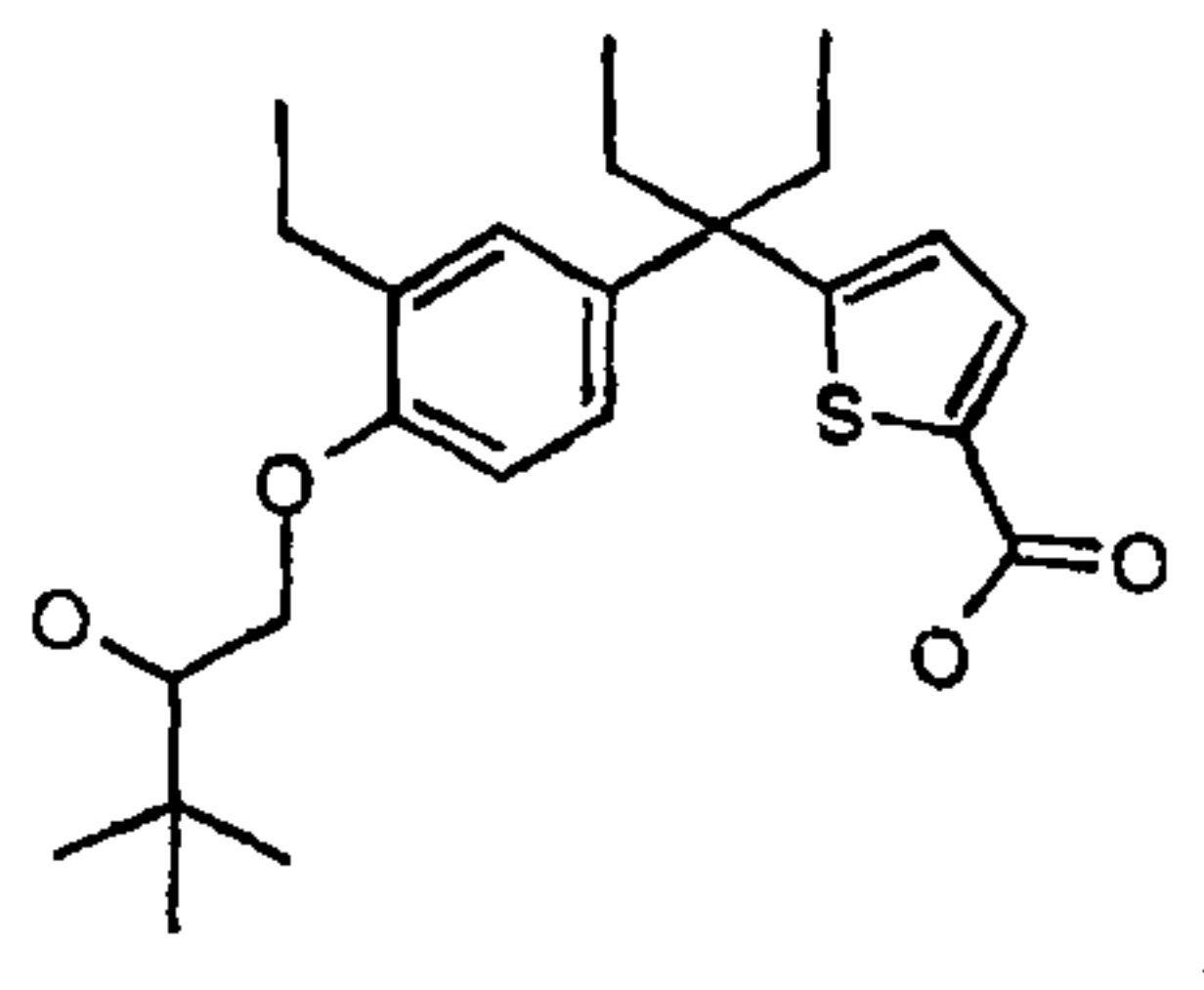
- 5 3. A compound selected from the group consisting of compounds represented by the formula:

P200



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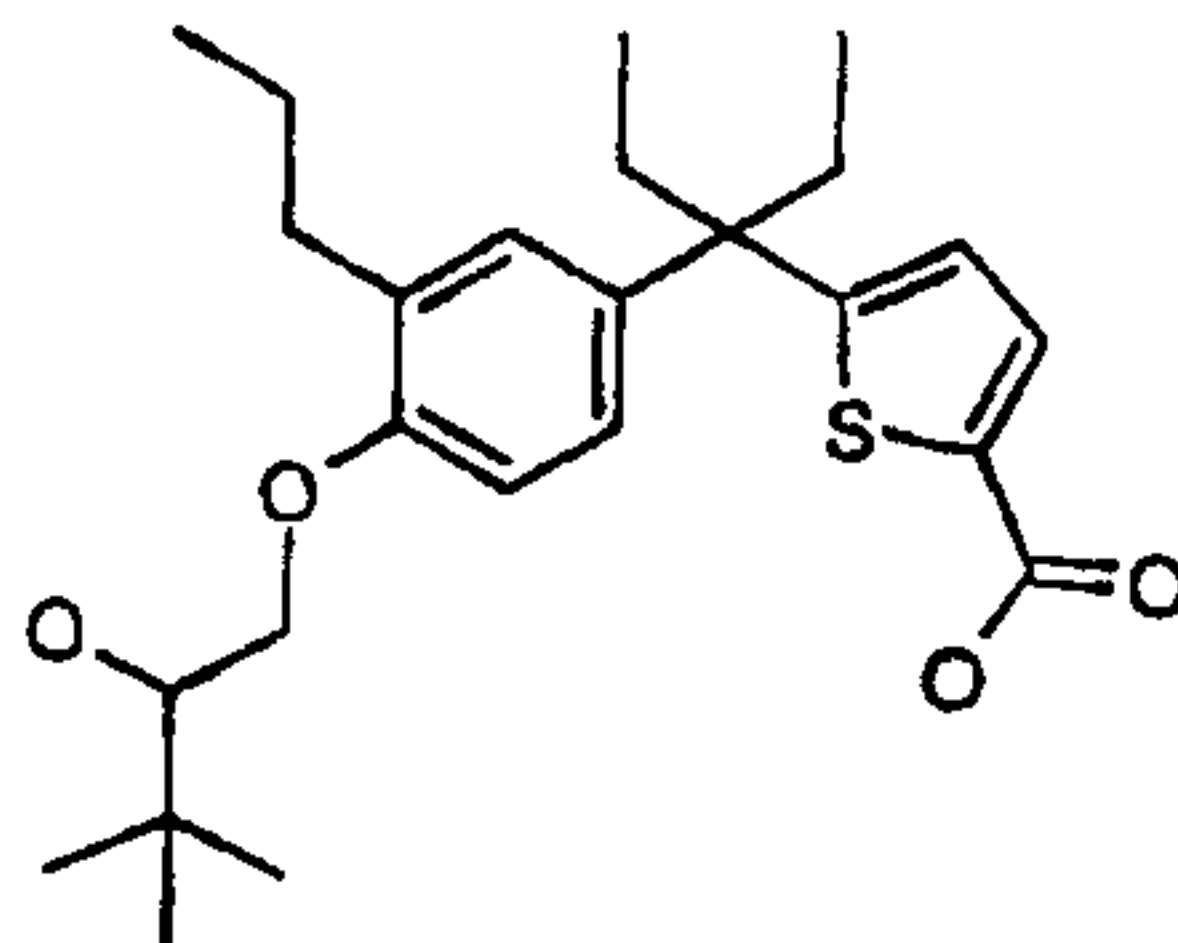
P201



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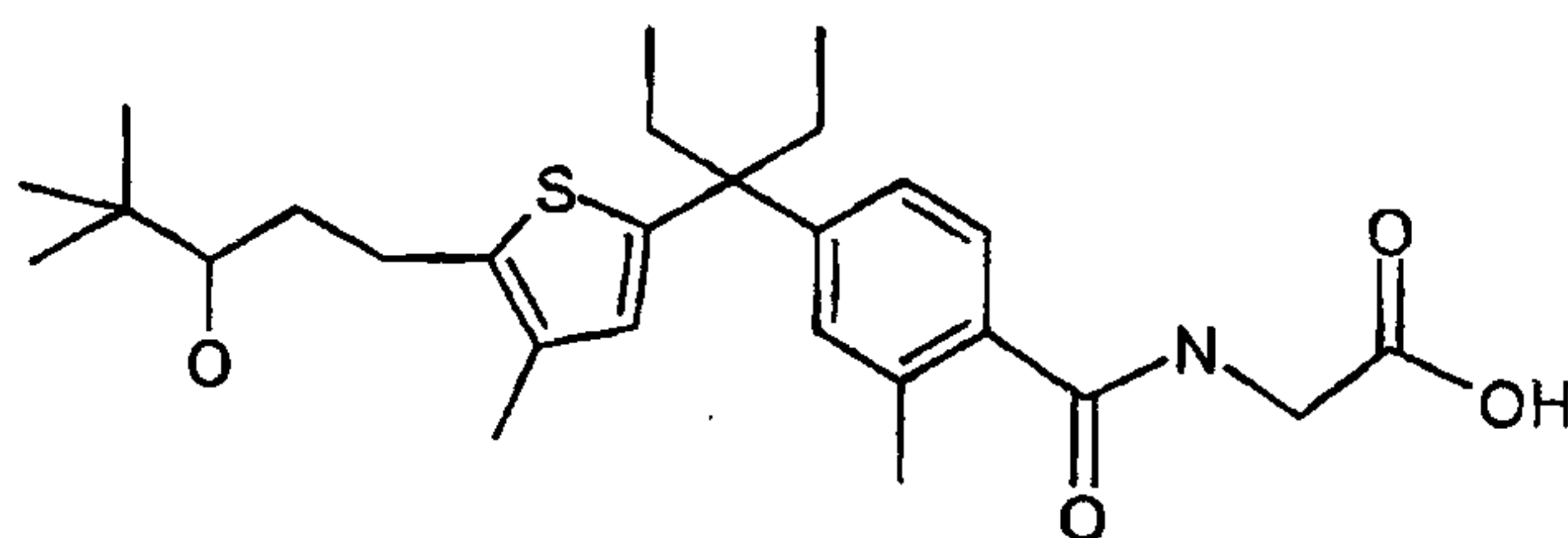
-404-

P202



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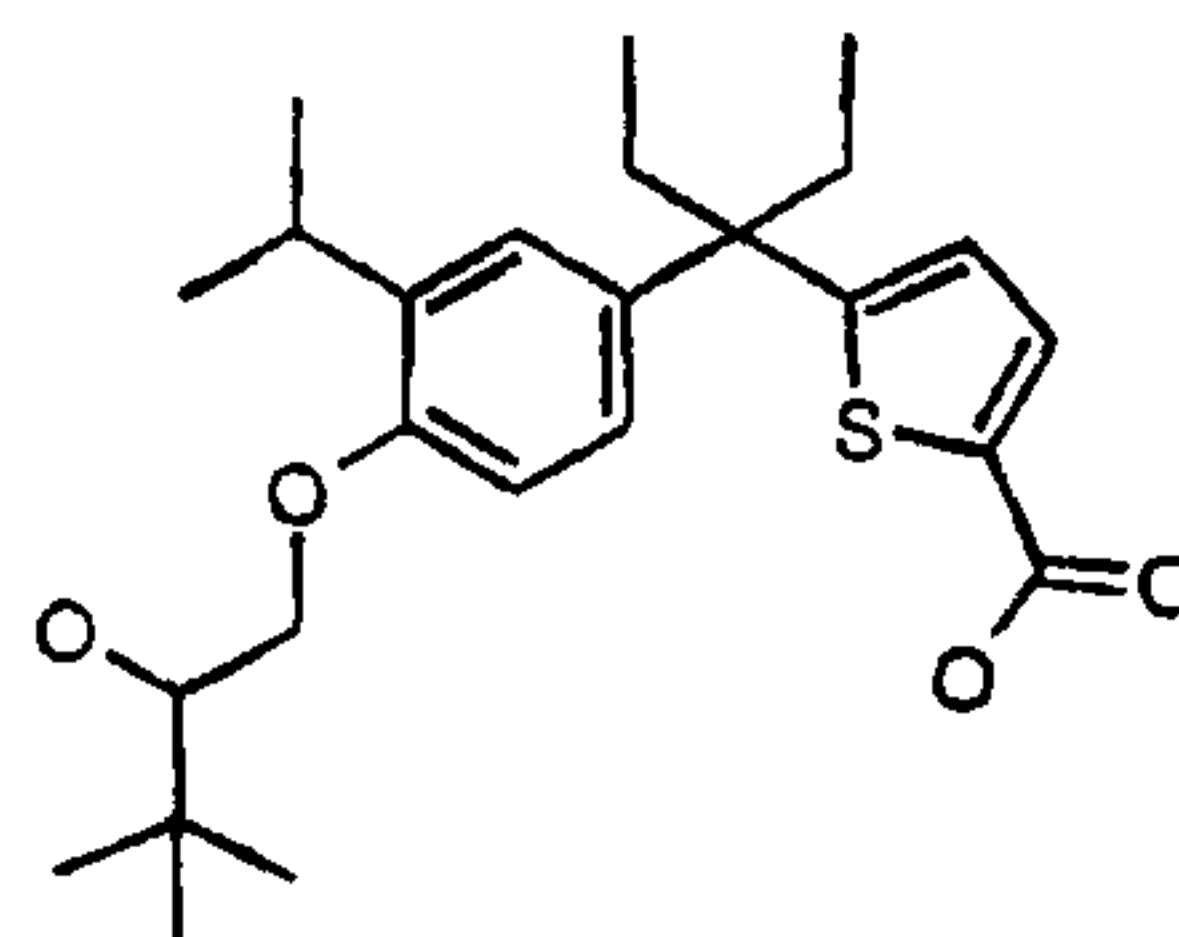
P203



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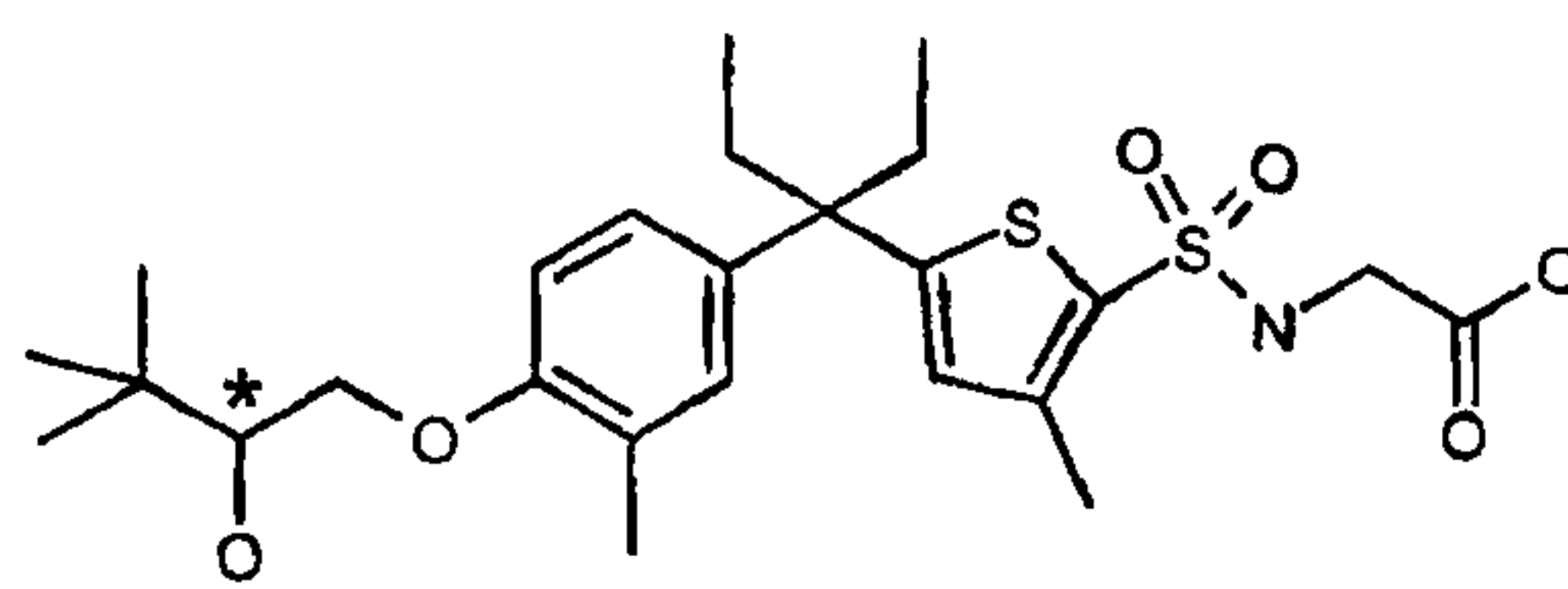
5

P204



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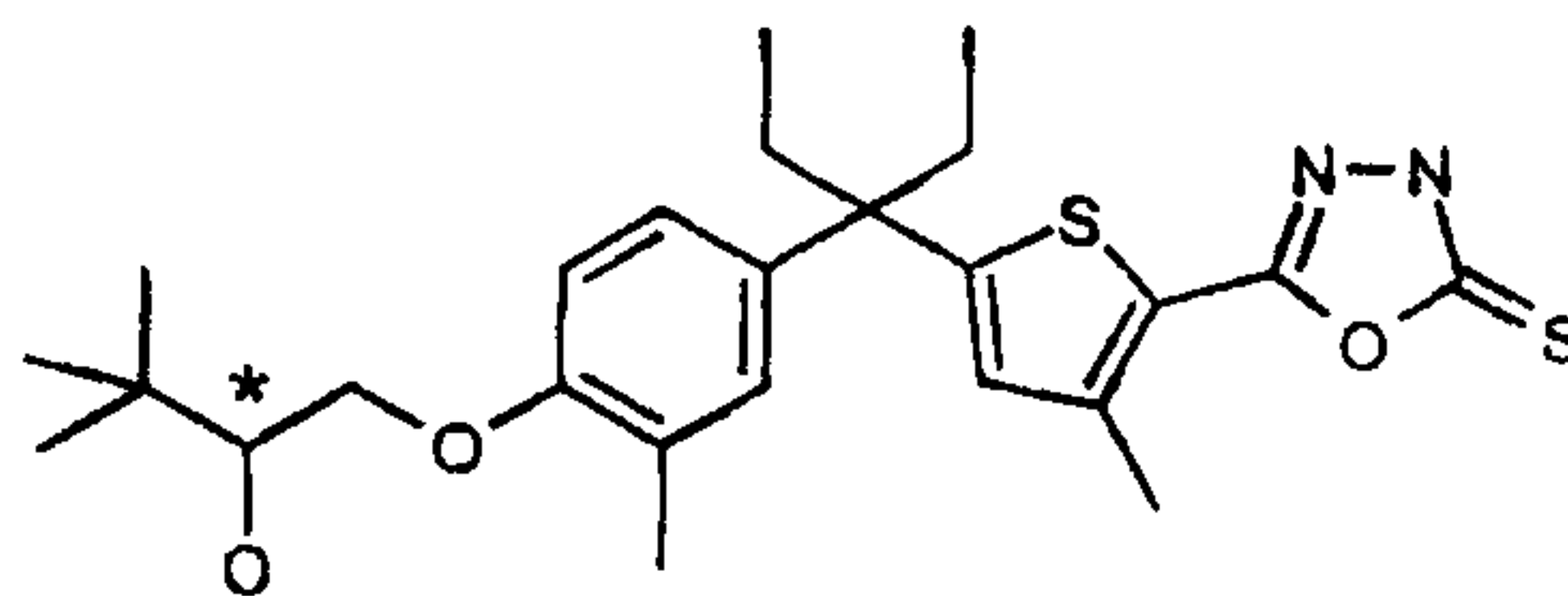
P205



or

10

P206

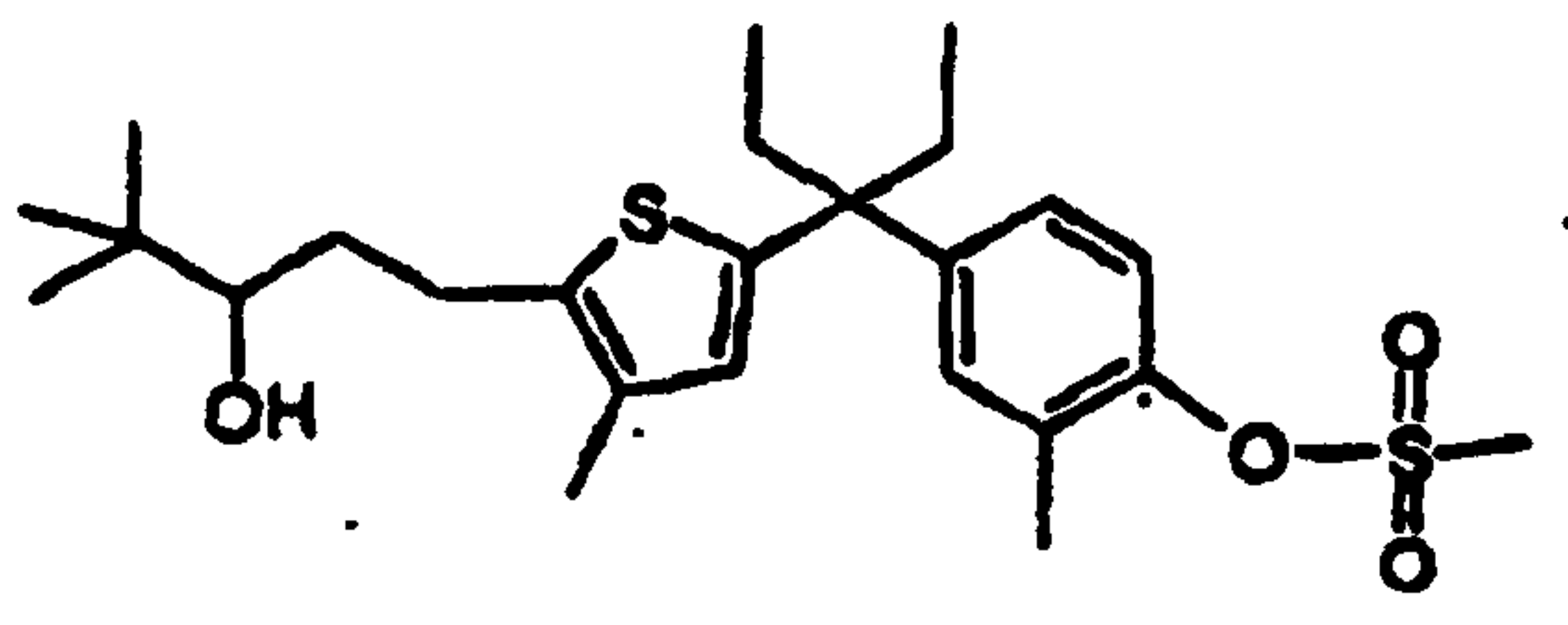


,

or a pharmaceutically suitable salt or solvate thereof.

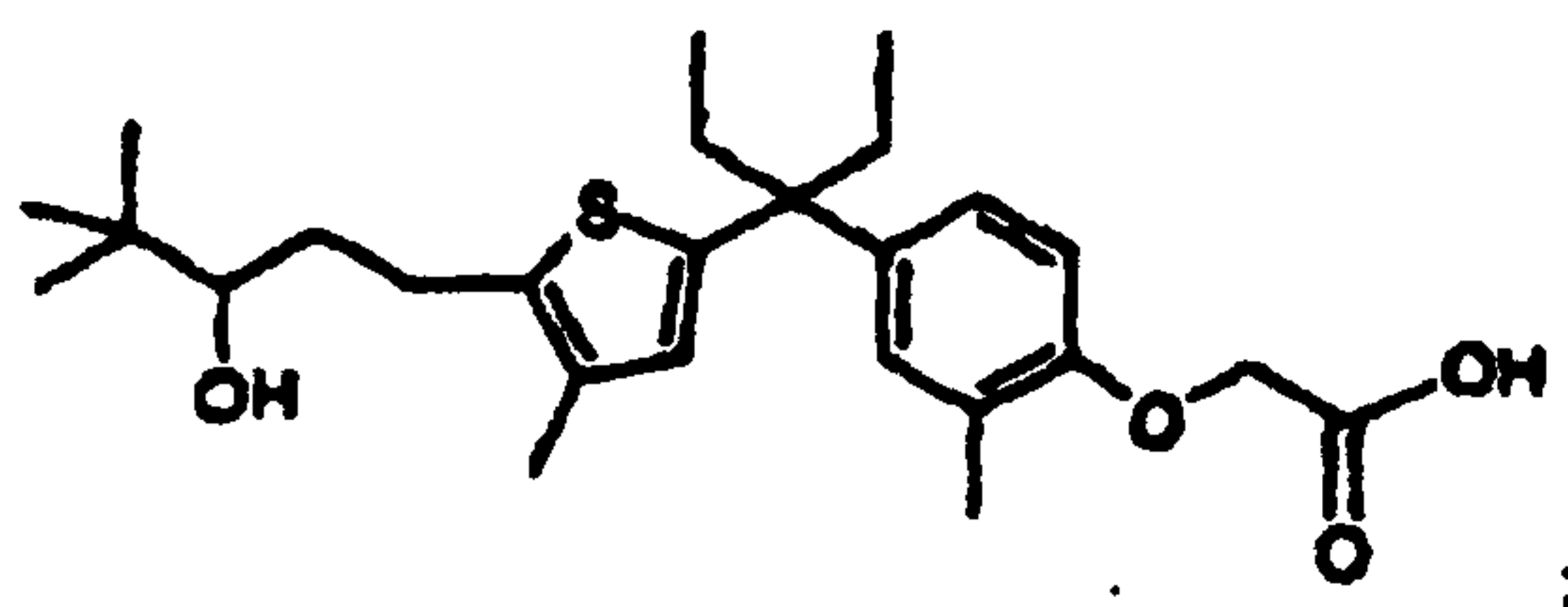
-405-

4. A compound according to Claim 1 of the formula:



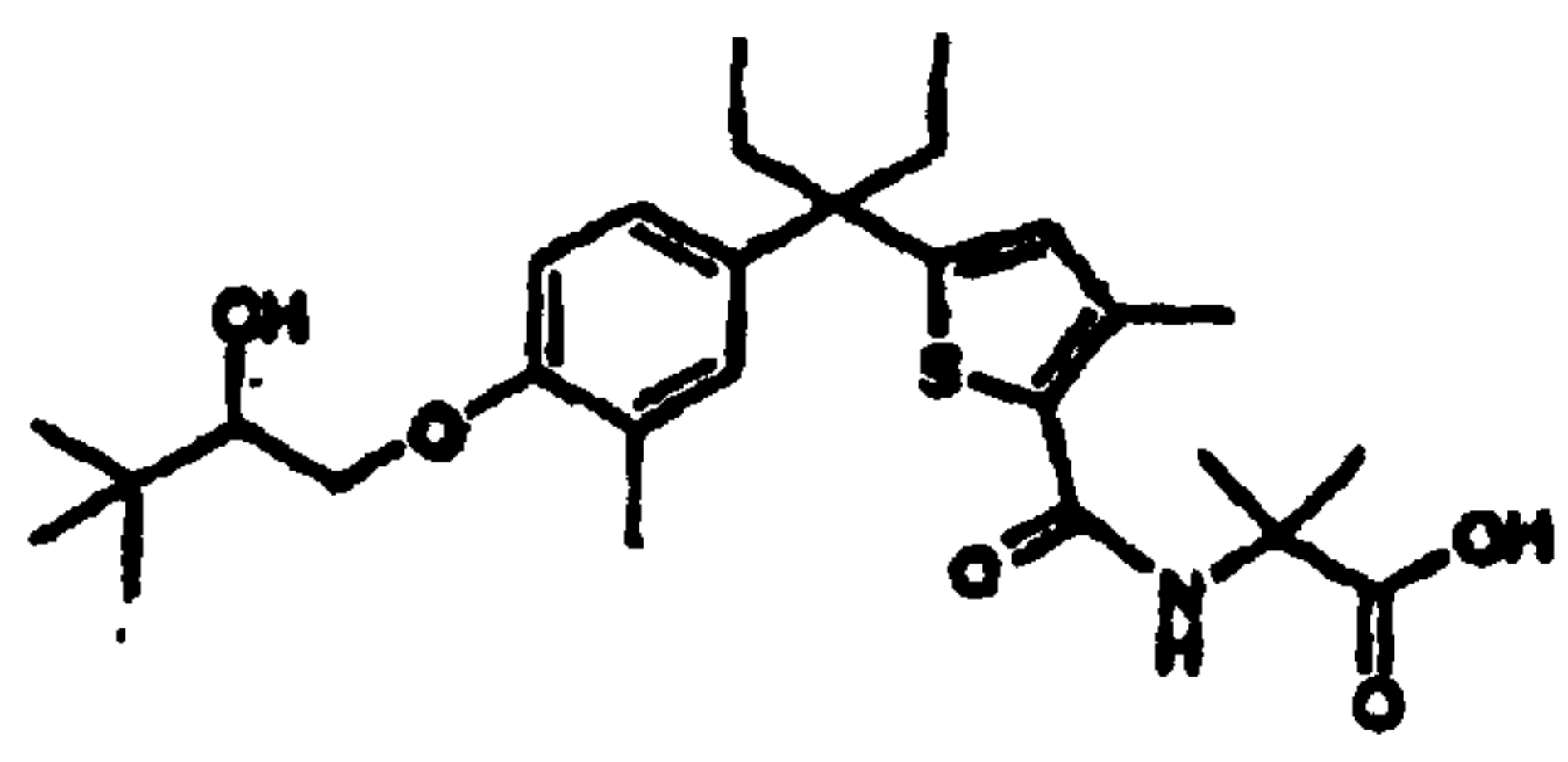
or a pharmaceutically suitable salt thereof.

5. A compound according to Claim 1 of formula:



or a pharmaceutically suitable salt thereof.

6. A compound according to Claim 1 of the formula:



or a pharmaceutically suitable salt thereof.

-406-

7. A pharmaceutical formulation comprising a compound of any one of claims 1 to 6, together with a pharmaceutically acceptable carrier or diluent therefor.

5 8. Use of a pharmaceutically effective amount of at least one compound of claims 1 to 6 for treating a mammal to prevent or alleviate the pathological effects of abscess, acne, adhesion, alopecia, Alzheimer's disease, autoimmune induced diabetes, bone fracture healing, breast cancer, cancer, colon cancer, Type I diabetes, host- graft rejection, hypercalcemia, leukemia,
10 multiple sclerosis, insufficient sebum secretion, osteomalacia, osteoporosis, insufficient dermal firmness, insufficient dermal hydration, psoriatic arthritis, prostate cancer, psoriasis, renal osteodystrophy, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, actinic keratosis, Crohns disease, type II diabetes, myelodysplastic syndrome, seboroderma, dermatitis, skin cancer, ulcerative colitis, and wrinkles.

15

9. A compound as claimed in any one of Claims 1 to 8 for use in treating a mammal to prevent or alleviate the pathological effects of abscess, acne, adhesion, alopecia, Alzheimer's disease, autoimmune induced diabetes,
20 bone fracture healing, breast cancer, cancer, colon cancer, Type I diabetes, host-graft rejection, hypercalcemia, leukemia, lupus, multiple sclerosis, insufficient sebum secretion, osteomalacia, osteoporosis, insufficient dermal firmness, insufficient dermal hydration, psoriatic arthritis, prostate cancer, psoriasis, renal osteodystrophy, rheumatoid
25 arthritis, scleroderma, systemic lupus erythematosus, actinic keratosis, Crohns disease, type II diabetes, myelodysplastic syndrome, seboroderma, dermatitis, skin cancer, ulcerative colitis, and wrinkles.

10. A compound according to claim 9 for use in treating psoriasis.

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