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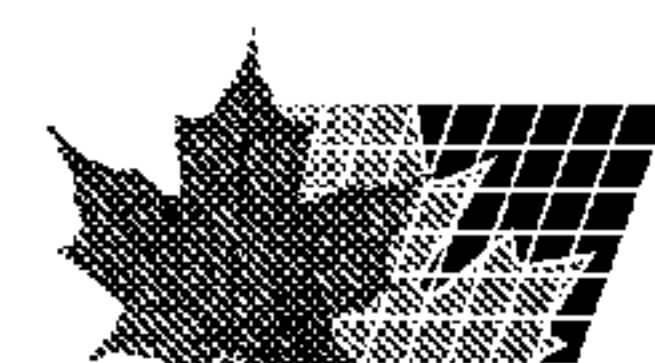
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(54) Titre : DERIVES D'ISOINDOLIN-1-ONE, D'ISOINDOLIN-3-ONE ET D'ISOINDOLIN-1,3-DIONE ET LEUR
UTILISATION

(54) Title: ISOINDOLIN-1-ONE, ISOINDOLIN-3-ONE AND ISOINDOLINE-1,3-DIONE-DERIVATIVES AND THEIR USE

(57) **Abrégé/Abstract:**

The invention relates to novel isoindolin-1-one-, isoindolin-3-one and isoindolin-1,3-dione-derivatives, to methods for the production thereof, to the use thereof for treating and/or preventing diseases, and to the use thereof for producing medicaments for treating and/or preventing diseases, in particular thromboembolic diseases.



Isoindolin-1-one, isoindolin-3-one and isoindoline-1,3-dione derivatives and their use

A b s t r a c t

The invention relates to novel isoindolin-1-one, isoindolin-3-one and isoindoline-1,3-dione derivatives, to processes for their preparation, to their use for the treatment and/or prophylaxis of diseases and to their use for preparing medicaments for the treatment and/or prophylaxis of diseases, in particular of thromboembolic disorders.

Isoindolin-1-one, isoindolin-3-one and isoindoline-1,3-dione derivatives and their use

The invention relates to novel isoindolin-1-one, isoindolin-3-one and isoindoline-1,3-dione derivatives, to processes for their preparation, to their use for the treatment and/or prophylaxis of diseases and to their use for preparing medicaments for the treatment and/or prophylaxis of
5 diseases, in particular of thromboembolic disorders.

Blood coagulation is a protective mechanism of the organism which helps to "seal" defects in the wall of the blood vessels quickly and reliably. Thus, loss of blood can be avoided or kept to a minimum. Haemostasis after injury of the blood vessels is effected mainly by the coagulation system in which an enzymatic cascade of complex reactions of plasma proteins is triggered.
10 Numerous blood coagulation factors are involved in this process, each of which factors converts, on activation, the respectively next inactive precursor into its active form. At the end of the cascade comes the conversion of soluble fibrinogen into insoluble fibrin, resulting in the formation of a blood clot. In blood coagulation, traditionally the intrinsic and the extrinsic system, which end in a joint reaction path, are distinguished. Here factor Xa, which is formed from the proenzyme
15 factor X, plays a key role, since it connects the two coagulation paths. The activated serine protease Xa cleaves prothrombin to thrombin. The resulting thrombin, in turn, cleaves fibrinogen to fibrin. Subsequent crosslinking of the fibrin monomers causes formation of blood clots and thus haemostasis. In addition, thrombin is a potent effector of platelet aggregation which likewise contributes significantly to haemostasis.

20

Haemostasis is subject to a complex regulatory mechanism. Uncontrolled activation of the coagulant system or defective inhibition of the activation processes may cause formation of local thrombi or embolisms in vessels (arteries, veins, lymph vessels) or in heart cavities. This may lead to serious thromboembolic disorders. In addition, in the case of consumption coagulopathy,
25 hypercoagulability may - systemically - result in disseminated intravascular coagulation. Thromboembolic complications furthermore occur in microangiopathic haemolytic anaemias, extracorporeal blood circulation, such as haemodialysis, and also in connection with prosthetic heart valves.

Thromboembolic disorders are the most frequent cause of morbidity and mortality in most
30 industrialized countries [Heart Disease: A Textbook of Cardiovascular Medicine, Eugene Braunwald, 5th edition, 1997, W.B. Saunders Company, Philadelphia].

The anticoagulants, i.e. substances for inhibiting or preventing blood coagulation, which are known from the prior art, have various, often grave disadvantages. Accordingly, in practice, an

efficient treatment method or prophylaxis of thromboembolic disorders is very difficult and unsatisfactory.

In the therapy and prophylaxis of thromboembolic disorders, use is firstly made of heparin, which is administered parenterally or subcutaneously. Owing to more favourable pharmacokinetic properties, preference is nowadays more and more given to low-molecular-weight heparin; however, even with low-molecular-weight heparin, it is not possible to avoid the known disadvantages described below, which are involved in heparin therapy. Thus, heparin is ineffective when administered orally and has a relatively short half-life. Since heparin inhibits a plurality of factors of the blood coagulation cascade at the same time, the action is non-selective. Moreover, there is a high risk of bleeding; in particular, brain haemorrhages and gastrointestinal bleeding may occur, which may result in thrombopenia, drug-induced alopecia or osteoporosis [Pschyrembel, Klinisches Wörterbuch, 257th edition, 1994, Walter de Gruyter Verlag, page 610, entry "Heparin"; Römpf Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Heparin"].

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A second class of anticoagulants are the vitamin K antagonists. These include, for example, 1,3-indanediones, and especially compounds such as warfarin, phenprocoumon, dicumarol and other coumarin derivatives which inhibit the synthesis of various products of certain vitamin K-dependent coagulation factors in the liver in a non-selective manner. Owing to the mechanism of action, however, the onset of the action is very slow (latency to the onset of action 36 to 48 hours). It is possible to administer the compounds orally; however, owing to the high risk of bleeding and the narrow therapeutic index, a time-consuming individual adjustment and monitoring of the patient are required [J. Hirsh, J. Dalen, D.R. Anderson *et al.*, "Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range" *Chest* **2001**, *119*, 8S-21S; J. Ansell, J. Hirsh, J. Dalen *et al.*, "Managing oral anticoagulant therapy" *Chest* **2001**, *119*, 22S-38S; P.S. Wells, A.M. Holbrook, N.R. Crowther *et al.*, "Interactions of warfarin with drugs and food" *Ann. Intern. Med.* **1994**, *121*, 676-683].

25

Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa. Because of the central role which factor Xa plays in the blood coagulation cascade, factor Xa is one of the most important targets for anticoagulants [J. Hauptmann, J. Stürzebecher, *Thrombosis Research* **1999**, *93*, 203; S.A.V. Raghavan, M. Dikshit, "Recent advances in the status and targets of antithrombotic agents" *Drugs Fut.* **2002**, *27*, 669-683; H.A. Wieland, V. Laux, D. Kozian, M. Lorenz, "Approaches in anticoagulation: Rationales for target positioning" *Curr. Opin. Investig. Drugs* **2003**, *4*, 264-271; U.J. Ries, W. Wienen, "Serine proteases as targets for

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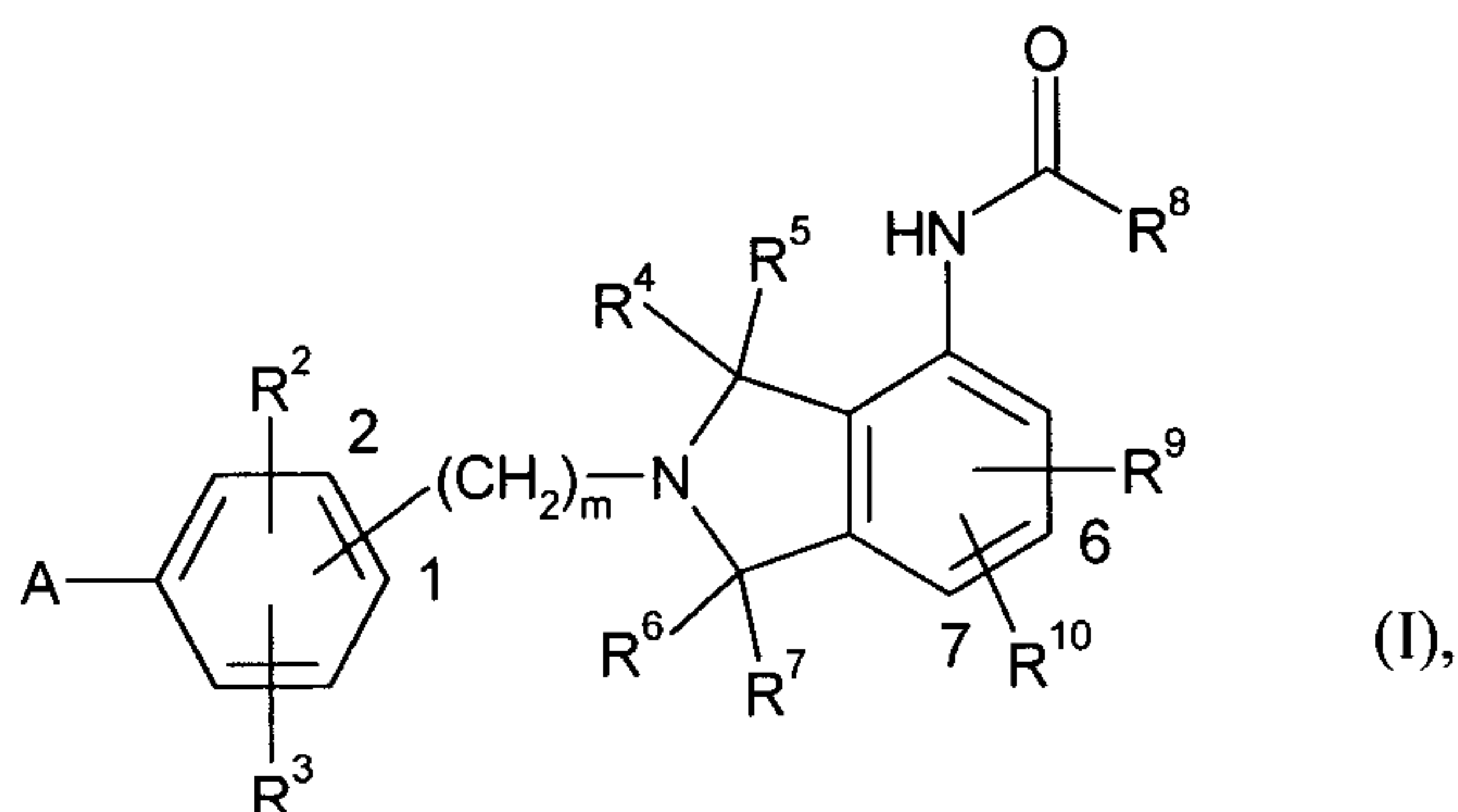
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antithrombotic therapy" *Drugs Fut.* **2003**, 28, 355-370; L.-A. Linkins, J.I. Weitz, "New anticoagulant therapy" *Annu. Rev. Med.* **2005**, 56, 63-77 ; A. Casimiro-Garcia *et al.*, "Progress in the discovery of Factor Xa inhibitors" *Expert Opin. Ther. Patents* **2006**, 15, 119-145].

- 5 It has been shown that, in animal models, various both peptidic and nonpeptidic compounds are effective as factor Xa inhibitors. A large number of direct factor Xa inhibitors is already known [J.M. Walenga, W.P. Jeske, D. Hoppensteadt, J. Fareed, "Factor Xa Inhibitors: Today and beyond" *Curr. Opin. Investig. Drugs* **2003**, 4, 272-281; J. Ruef, H.A. Katus, "New antithrombotic drugs on the horizon" *Expert Opin. Investig. Drugs* **2003**, 12, 781-797; M.L. Quan, J.M. Smallheer, "The race to
10 an orally active Factor Xa inhibitor: Recent advances" *Curr. Opin. Drug Discovery & Development* **2004**, 7, 460-469]. Nonpeptidic low-molecular-weight factor Xa inhibitors are also described, for example, in WO 03/099276, WO 03/011858 and WO 03/007942.

It is an object of the present invention to provide novel alternative compounds having a comparable or improved activity for controlling disorders, in particular thromboembolic disorders,
15 in humans and animals.

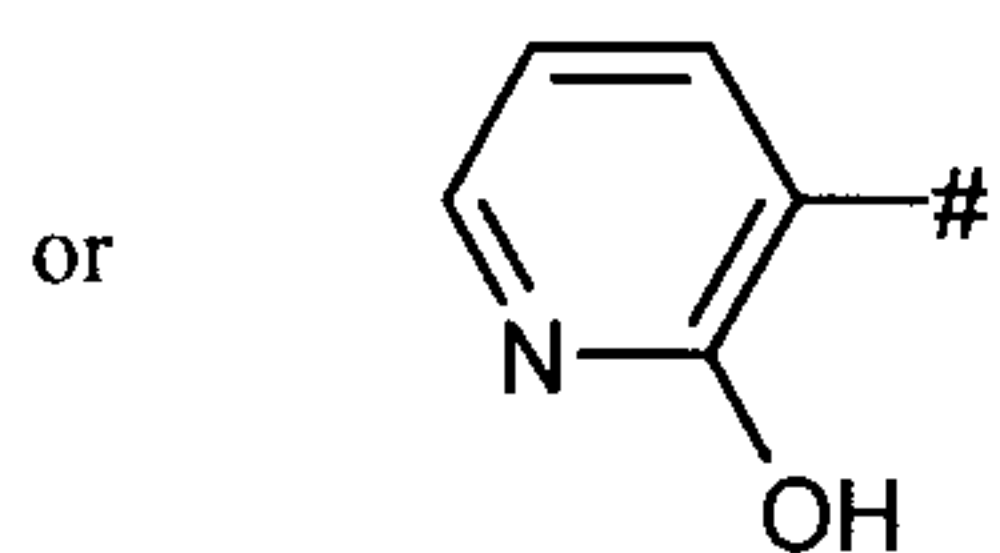
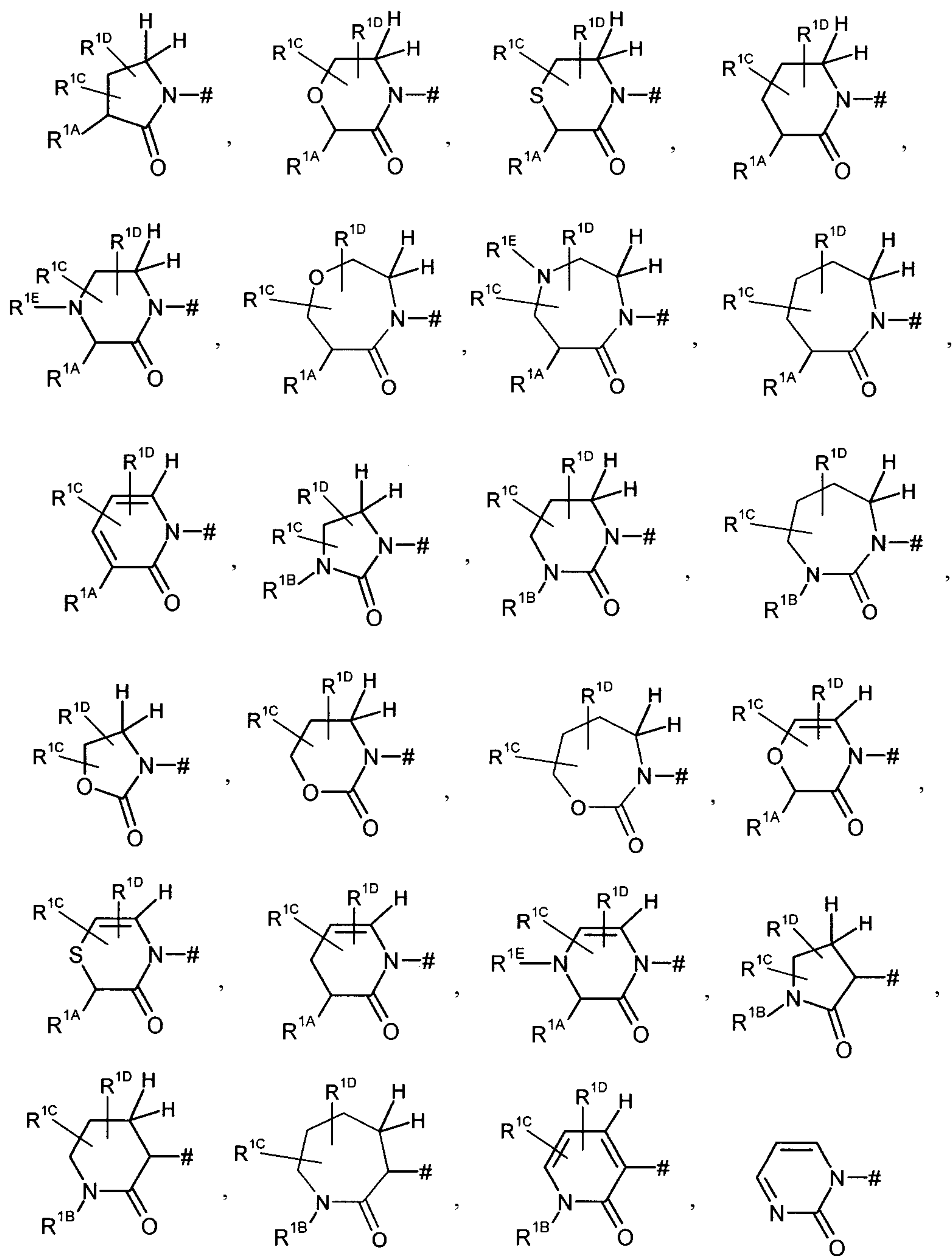
The invention provides compounds of the formula



in which

A represents a group of the formula

- 4 -



where

R^{1A} represents hydrogen, fluorine, trifluoromethyl, hydroxy, amino, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylamino, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyloxy or C₃-C₆-cycloalkylamino,

5 where alkyl, alkoxy, alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C₁-C₄-alkoxy, C₁-C₄-alkylamino, C₃-C₆-cycloalkyloxy, C₃-C₆-cycloalkylamino, (N-C₃-C₆-cycloalkyl)(N-C₁-C₄-alkyl)amino and a 4- to 7-membered saturated heterocycle which may contain a ring member from the group consisting of N-R²¹, S and O,

where

R²¹ represents hydrogen, C₁-C₄-alkyl or C₃-C₆-cycloalkyl,

and

10 the heterocycle may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C₁-C₄-alkyl and oxo,

15 R^{1B} represents hydrogen, hydroxy, amino, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylamino, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyloxy or C₃-C₆-cycloalkyl-amino,

20 where alkyl may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C₁-C₄-alkoxy, C₁-C₄-alkylamino, C₃-C₆-cycloalkyloxy, C₃-C₆-cycloalkylamino, (N-C₃-C₆-cycloalkyl)(N-C₁-C₄-alkyl)amino and a 4- to 7-membered saturated heterocycle which may contain a ring member from the group consisting of N-R²¹, S and O,

where

R²¹ represents hydrogen, C₁-C₄-alkyl or C₃-C₆-cycloalkyl,

and

25 the heterocycle may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C₁-C₄-alkyl and oxo,

R^{1C} represents hydrogen, fluorine, cyano, hydroxy, amino, oxo, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylamino or C₃-C₆-cycloalkyl,

- 6 -

R^{1D} represents hydrogen, fluorine, cyano, C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl,

R^{1E} represents hydrogen, C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl,

and # is the point of attachment to the phenyl ring,

m represents the number 0, 1 or 2,

5 and the $(CH_2)_m$ group is attached in the 1- or 2-position to the phenyl ring,

R^2 represents hydrogen, fluorine, chlorine, cyano, hydroxy, amino, trifluoromethyl, trifluoromethoxy, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkoxymethyl, C_1 - C_4 -alkylamino, C_3 - C_6 -cycloalkyl, aminocarbonyl, C_1 - C_4 -alkoxycarbonyl or C_1 - C_4 -alkylaminocarbonyl,

10 R^3 represents hydrogen, fluorine, chlorine, cyano, hydroxy, amino, trifluoromethyl, trifluoromethoxy, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkoxymethyl, C_1 - C_4 -alkylamino, C_3 - C_6 -cycloalkyl, aminocarbonyl, C_1 - C_4 -alkoxycarbonyl or C_1 - C_4 -alkylaminocarbonyl,

15 where alkyl, alkoxy and alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, C_1 - C_4 -alkoxy, C_3 - C_6 -cycloalkyloxy, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-tetrahydropyranyl and $-NR^{14}R^{15}$,

where piperazinyl and piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

and

20 R^{14} represents hydrogen, C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl,

and

R^{15} represents hydrogen or C_1 - C_4 -alkyl,

R^4 and R^5 represent hydrogen,

and

25 R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 represent hydrogen,

or

5 R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

R^8 represents phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl or thienyl,

10 where phenyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl are substituted by a
substituent R^{11} and/or a substituent R^{12} or by two different substituents R^{11} or by two
different substituents R^{12} ,

where

15 R^{11} is attached to a carbon atom which is not adjacent to a nitrogen atom in the
ring and represents hydrogen, fluorine, chlorine, cyano, ethynyl, C_1 - C_4 -
alkyl, C_1 - C_4 -alkoxy or C_3 - C_6 -cycloalkyl,

R^{12} is attached to a carbon atom which is adjacent to a nitrogen atom in the
ring and represents hydrogen, amino, C_1 - C_4 -alkyl, C_1 - C_4 -alkylamino or C_3 -
 C_6 -cycloalkyl,

and

20 where thienyl is substituted by a substituent R^{13} and a substituent R^{16} ,

where

R^{13} is attached to a carbon atom which is adjacent to the sulphur atom in the
ring and represents hydrogen, fluorine, chlorine, cyano, ethynyl, C_1 - C_4 -
alkyl, C_1 - C_4 -alkoxy or C_3 - C_6 -cycloalkyl,

25 R^{16} represents hydrogen, fluorine, chlorine, amino, C_1 - C_4 -alkyl, C_1 - C_4 -alkyl-
amino or C_3 - C_6 -cycloalkyl,

R⁹ represents hydrogen, fluorine, chlorine, cyano, hydroxy, amino, trifluoromethyl, trifluoromethoxy, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylamino, C₃-C₆-cycloalkyl, aminocarbonyl, C₁-C₄-alkoxycarbonyl or C₁-C₄-alkylaminocarbonyl,

5 where alkyl, alkoxy and alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, C₁-C₄-alkoxy, C₃-C₆-cycloalkyloxy, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-tetrahydropyranyl and -NR¹⁷R¹⁸,

10 where piperazinyl and piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

and

R¹⁷ represents hydrogen, C₁-C₄-alkyl or C₃-C₆-cycloalkyl,

and

R¹⁸ represents hydrogen or C₁-C₄-alkyl,

15 R¹⁰ represents hydrogen, fluorine, chlorine, cyano, trifluoromethyl, trifluoromethoxy, C₁-C₄-alkyl, C₁-C₄-alkoxy or C₃-C₆-cycloalkyl,

and

where R⁹ is attached to the 6-position and R¹⁰ is attached to the 7-position of the isoindoline ring,

or

20 where R⁹ is attached to the 7-position and R¹⁰ is attached to the 6-position of the isoindoline ring,
and their salts, their solvates and the solvates of their salts.

Compounds according to the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, the compounds, comprised by formula (I), of the formulae mentioned below and their salts, solvates and solvates of the salts and the compounds, comprised
25 by formula (I), mentioned below as embodiments and their salts, solvates and solvates of the salts if the compounds, comprised by formula (I), mentioned below are not already salts, solvates and solvates of the salts.

Depending on their structure, the compounds according to the invention can exist in stereoisomeric forms (enantiomers, diastereomers). Accordingly, the invention comprises the enantiomers or diastereomers and their respective mixtures. From such mixtures of enantiomers and/or
5 diastereomers, it is possible to isolate the stereoisomerically uniform components in a known manner.

If the compounds according to the invention can be present in tautomeric forms, the present invention comprises all tautomeric forms.

10

In the context of the present invention, preferred salts are physiologically acceptable salts of the compounds according to the invention. The invention also comprises salts which for their part are not suitable for pharmaceutical applications, but which can be used, for example, for isolating or purifying the compounds according to the invention.

15

Physiologically acceptable salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalene disulphonic acid, acetic acid,
20 trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds according to the invention also include salts of customary bases, such as, by way of example and by way of preference, alkali metal salts (for
25 example sodium salts and potassium salts), alkaline earth metal salts (for example calcium salts and magnesium salts) and ammonium salts, derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and by way of preference, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine,
30 arginine, lysine, ethylenediamine and N-methylpiperidine.

In the context of the invention, solvates are those forms of the compounds according to the invention which, in solid or liquid state, form a complex by coordination with solvent molecules. Hydrates are a specific form of the solvates where the coordination is with water. In the context of
35 the present invention, preferred solvates are hydrates.

Moreover, the present invention also comprises prodrugs of the compounds according to the invention. The term "prodrugs" includes compounds which for their part may be biologically active or inactive but which, during the time they spend in the body, are converted into compounds according to the invention (for example metabolically or hydrolytically).

5

In the context of the present invention, unless specified differently, the substituents have the following meanings:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkoxycarbonyl, alkylaminocarbonyl, alkylcarbonylamino and alkoxycarbonylamino represents a straight-chain or branched alkyl radical
10 having generally 1 to 4, preferably 1 or 2, carbon atoms, by way of example and by way of preference methyl, ethyl, n-propyl, isopropyl and *tert*-butyl.

By way of example and by way of preference, alkoxy represents methoxy, ethoxy, n-propoxy, isopropoxy and *tert*-butoxy.

Alkylamino represents an alkylamino radical having one or two alkyl substituents (selected
15 independently of one another), by way of example and by preference methylamino, ethylamino, n-propylamino, isopropylamino, *tert*-butylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino and *N-tert*-butyl-*N*-methylamino. By way of example, C₁-C₃-alkylamino represents a monoalkylamino radical having 1 to 3 carbon atoms or represents a dialkylamino radical having in each case 1 to 3 carbon atoms per
20 alkyl substituent.

By way of example and by way of preference alkoxycarbonyl represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and *tert*-butoxycarbonyl.

Alkylaminocarbonyl represents an alkylaminocarbonyl radical having one or two alkyl substituents (selected independently of one another), by way of example and by way of preference methyl-
25 aminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, *tert*-butylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl and *N-tert*-butyl-*N*-methylaminocarbonyl. By way of example, C₁-C₃-alkylaminocarbonyl represents a monoalkylaminocarbonyl radical having 1 to 3 carbon atoms or represents a
30 dialkylaminocarbonyl radical having in each case 1 to 3 carbon atoms per alkyl substituent.

By way of example and by way of preference, alkylcarbonylamino represents methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino and

tert-butylcarbonylamino.

By way of example and by way of preference, alkoxycarbonylamino represents methoxycarbonylamino, ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino and *tert*-butoxycarbonylamino.

- 5 Cycloalkyl represents a cycloalkyl group having generally 3 to 6 carbon atoms, preferably 3 to 5 carbon atoms, by way of example and by way of preference cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

- 10 Heterocyclyl represents a monocyclic heterocyclic radical having generally 4 to 7 ring atoms and up to 3, preferably up to 2, heteroatoms and/or heterogroups from the group consisting of N, O, S, SO, SO₂. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 7-membered monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the group consisting of O, N and S, such as, by way of example and by way of preference, tetrahydrofuranyl, pyrrolidinyl, pyrrolinyl, piperidinyl, tetrahydropyranyl, piperazinyl, morpholinyl and perhydroazepinyl.

- 15 Heteroaryl represents an aromatic monocyclic radical having 5 or 6 ring atoms and up to 4 heteroatoms from the group consisting of S, O and N, by way of example and by way of preference thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl and pyrazinyl.

- 20 If radicals in the compounds according to the invention are substituted, the radicals can, unless specified otherwise, be mono- or polysubstituted. In the context of the present invention, the meanings of all radicals which occur more than once are independent of one another. Substitution with one, two or three identical or different substituents is preferred. Very particular preference is given to substitution with one substituent.

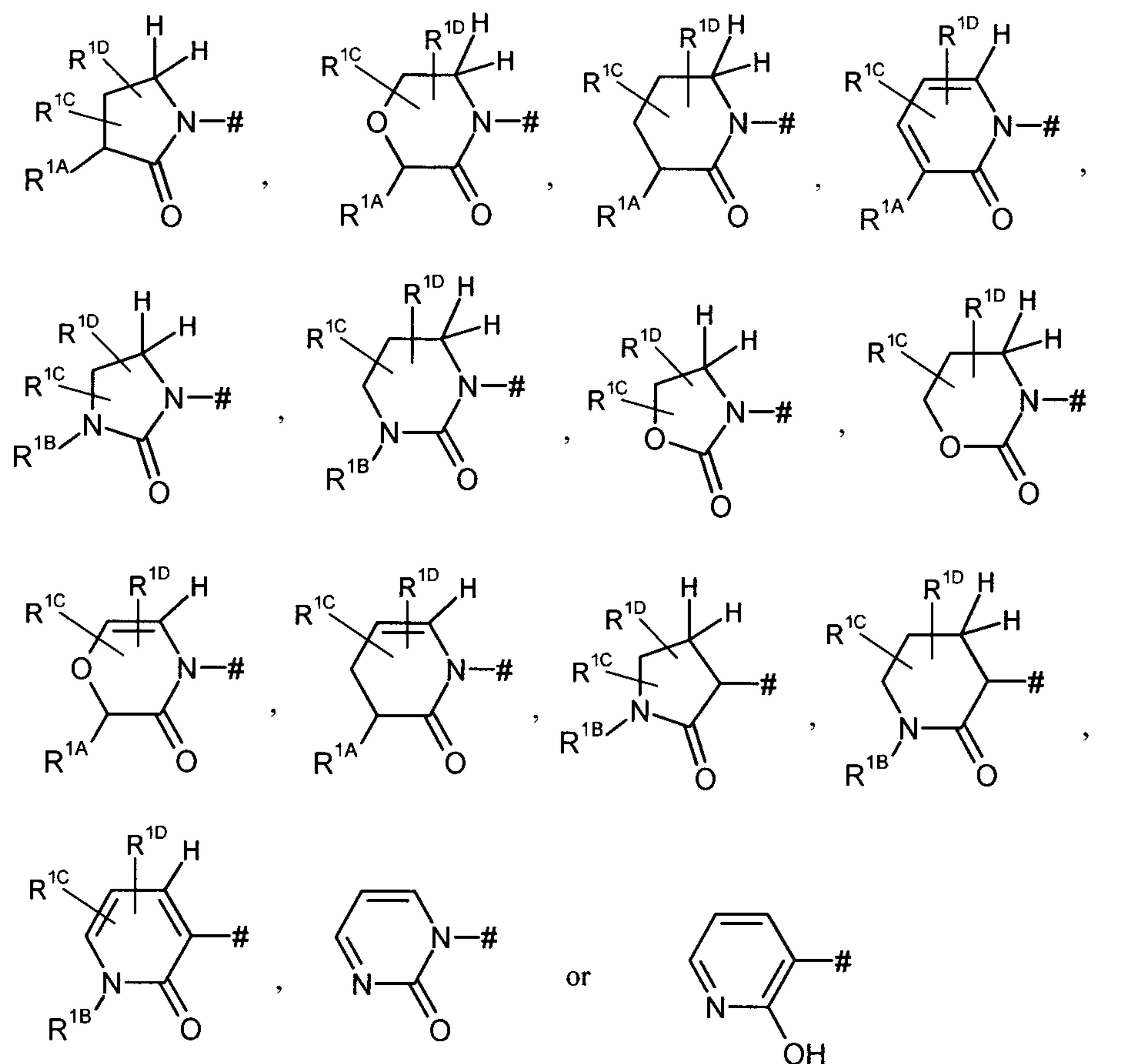
- 25 In the formulae of the group which may represent A, the end point of the line next to a # does not represent a carbon atom or a CH₂ group, but is part of the bond to the atom to which A is attached.

In the formulae of the group which may represent R⁸, the end point of the line next to a * does not represent a carbon atom or a CH₂ group, but is part of the bond to the atom to which R⁸ is attached.

Preference is given to compounds of the formula (I) in which

A represents a group of the formula

- 12 -



where

R^{1A} represents hydrogen, fluorine, hydroxy, amino, C_1 - C_4 -alkyl, methoxy, ethoxy, *tert*-butoxy, methylamino, dimethylamino, ethylamino, diethylamino, *tert*-butylamino, cyclopropyl, cyclopropylamino or cyclopropyloxy,

where alkyl, ethoxy, *tert*-butoxy, ethylamino, diethylamino and *tert*-butylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, methoxy, C_1 - C_4 -alkylamino, cyclopropyloxy, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-piperidinyl, 4-morpholinyl, 1-piperazinyl and 4-tetrahydropyranyl,

where 1-piperazinyl and 4-piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

R^{1B} represents hydrogen, hydroxy, amino, C_1 - C_4 -alkyl, methoxy, methylamino, dimethylamino or cyclopropyl,

5 where alkyl may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, methoxy, C₁-C₄-alkylamino, cyclopropyloxy, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-piperidinyl, 4-morpholinyl, 1-piperazinyl and 4-tetrahydropyranyl,

where 1-piperazinyl and 4-piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

10 R^{1C} represents hydrogen, fluorine, oxo or methyl,

R^{1D} represents hydrogen, fluorine or methyl,

and # is the point of attachment to the phenyl ring,

m represents the number 0, 1 or 2,

and the (CH₂)_m group is attached in the 1- or 2-position to the phenyl ring,

R² represents hydrogen, fluorine, chlorine, cyano, hydroxy, C₁-C₄-alkyl or C₁-C₄-alkoxy,

15 R³ represents hydrogen, fluorine, chlorine, cyano, hydroxy, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxymethyl, C₁-C₄-alkylamino, cyclopropyl, aminocarbonyl, C₁-C₄-alkoxycarbonyl or C₁-C₄-alkylaminocarbonyl,

20 where alkyl, alkoxy and alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, methoxy, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl and -NR¹⁴R¹⁵,

where 1-piperazinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

and

25 R¹⁴ represents hydrogen, methyl or cyclopropyl,

and

R¹⁵ represents hydrogen or methyl,

R^4 and R^5 represent hydrogen,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

or

5 R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 represent hydrogen,

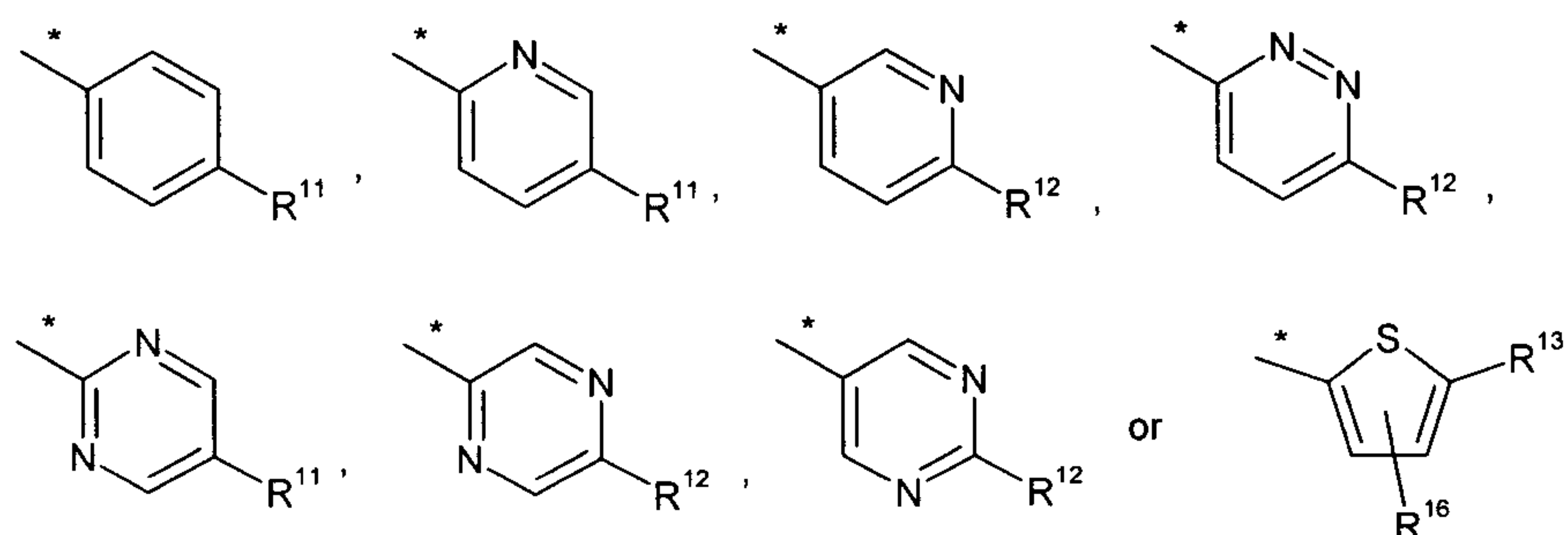
or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

10 and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

R^8 represents a group of the formula



where

15 * is the point of attachment to the carbonyl group,

R^{11} represents fluorine, chlorine, ethynyl, methyl, ethyl, methoxy or ethoxy,

R^{12} represents amino, methyl, methylamino or dimethylamino,

R^{13} represents fluorine, chlorine, ethynyl, methyl, ethyl, methoxy or ethoxy,

and

R^{16} represents hydrogen,

R^9 represents hydrogen, fluorine, chlorine, cyano, methyl, methoxy, aminocarbonyl, methyl-aminocarbonyl or dimethylaminocarbonyl,

5 where methyl and methoxy may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, methoxy, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl and $-NR^{17}R^{18}$,

where 1-piperazinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

10 and

R^{17} represents hydrogen, methyl or cyclopropyl,

and

R^{18} represents hydrogen or methyl,

15 R^{10} represents hydrogen, fluorine, chlorine, cyano, trifluoromethyl, trifluoromethoxy, methyl or methoxy,

and

where R^9 is attached to the 6-position and R^{10} to the 7-position of the isoindoline ring,

or

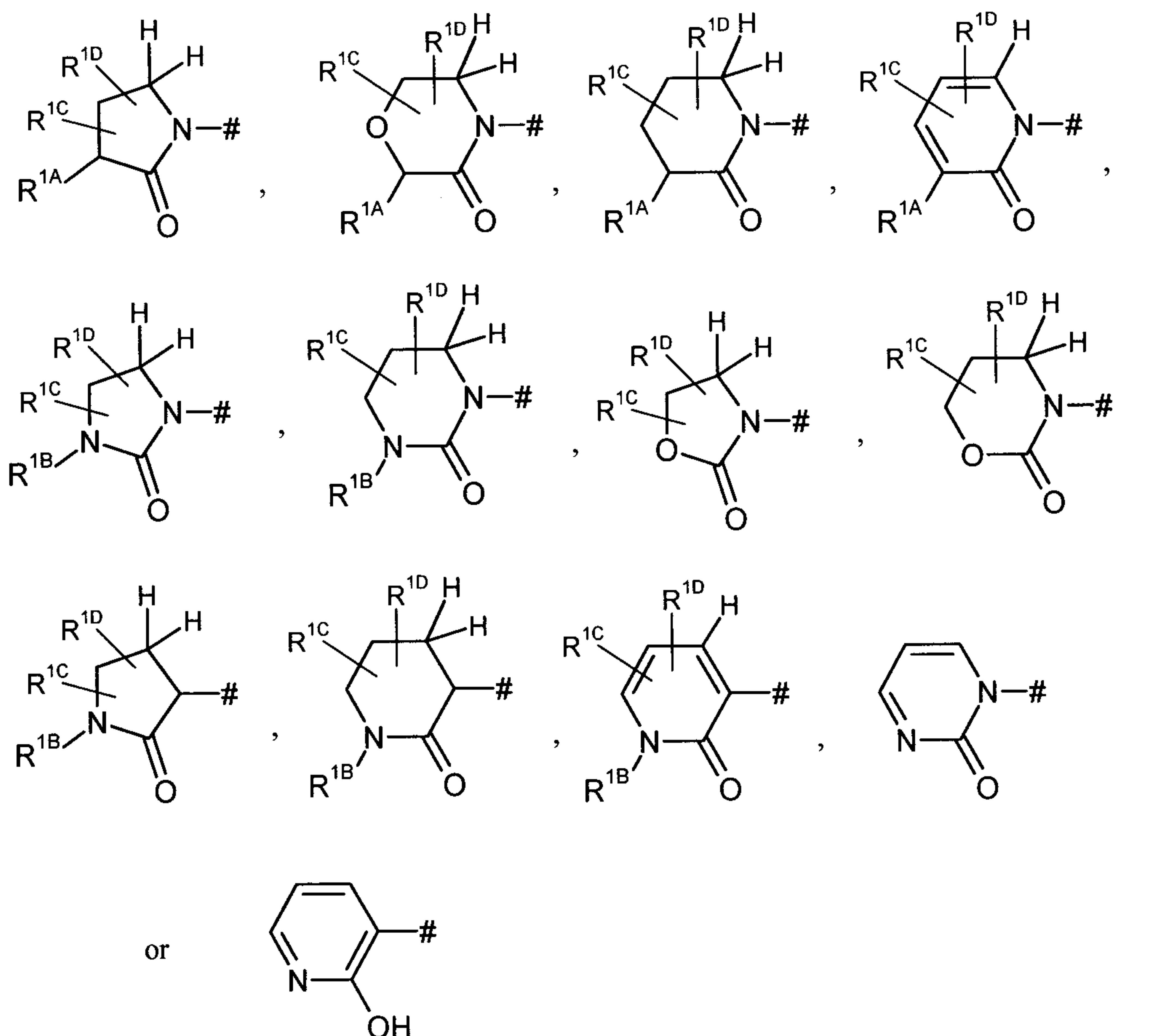
where R^9 is attached to the 7-position and R^{10} to the 6-position of the isoindoline ring,

20 and their salts, their solvates and the solvates of their salts.

Preference is also given to compounds of the formula (I) in which

A represents a group of the formula

- 16 -



where

5 R^{1A} represents hydrogen, fluorine, hydroxy, amino, methyl, ethyl, isopropyl, methoxy, ethoxy, methylamino, dimethylamino, ethylamino, diethylamino or cyclopropylamino,

10 where methyl, ethyl, isopropyl, ethoxy, ethylamino and diethylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, methoxy, methylamino, dimethylamino, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl and 1-piperazinyl,

where 1-piperazinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

15 R^{1B} represents hydrogen, hydroxy, amino, methyl, ethyl, isopropyl or cyclopropyl,

where ethyl and isopropyl may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, methoxy, methylamino, dimethylamino, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl and 1-piperazinyl,

5 where 1-piperazinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

R^{1C} represents hydrogen, fluorine, oxo or methyl,

R^{1D} represents hydrogen, fluorine or methyl,

10 and # is the point of attachment to the phenyl ring,

m represents the number 1,

and the $(CH_2)_m$ group is attached in the 1- or 2-position to the phenyl ring,

R^2 represents hydrogen,

R^3 represents hydrogen, fluorine, chlorine, cyano, methyl, ethyl, n-propyl, methoxy, ethoxy or
15 methoxymethyl,

R^4 and R^5 represent hydrogen,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

or

20 R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 represent hydrogen,

or

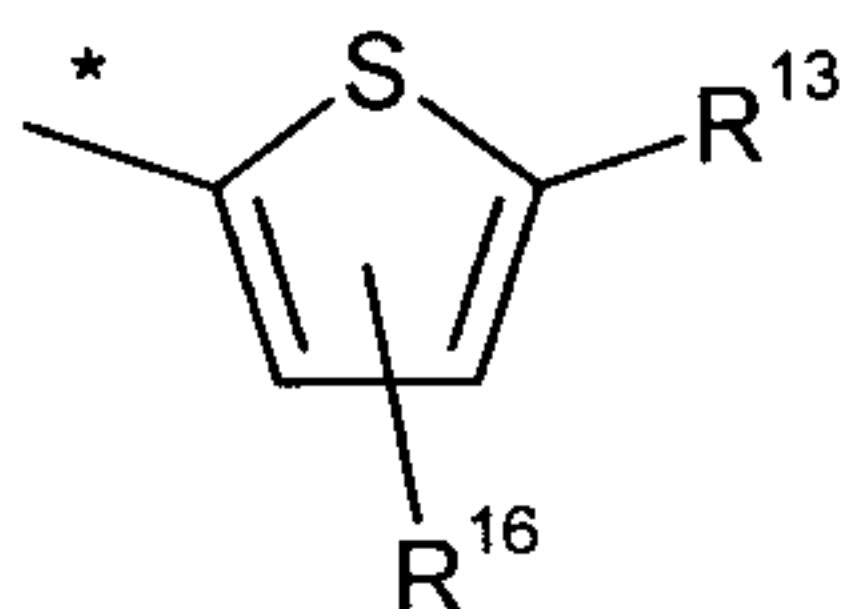
R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

25 and

- 18 -

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

R^8 represents a group of the formula



where

5 * is the point of attachment to the carbonyl group,

R^{13} represents fluorine, chlorine or methyl,

and

R^{16} represents hydrogen,

R^9 represents hydrogen,

10 R^{10} represents hydrogen,

and

where R^9 is attached to the 6-position and R^{10} to the 7-position of the isoindoline ring,

or

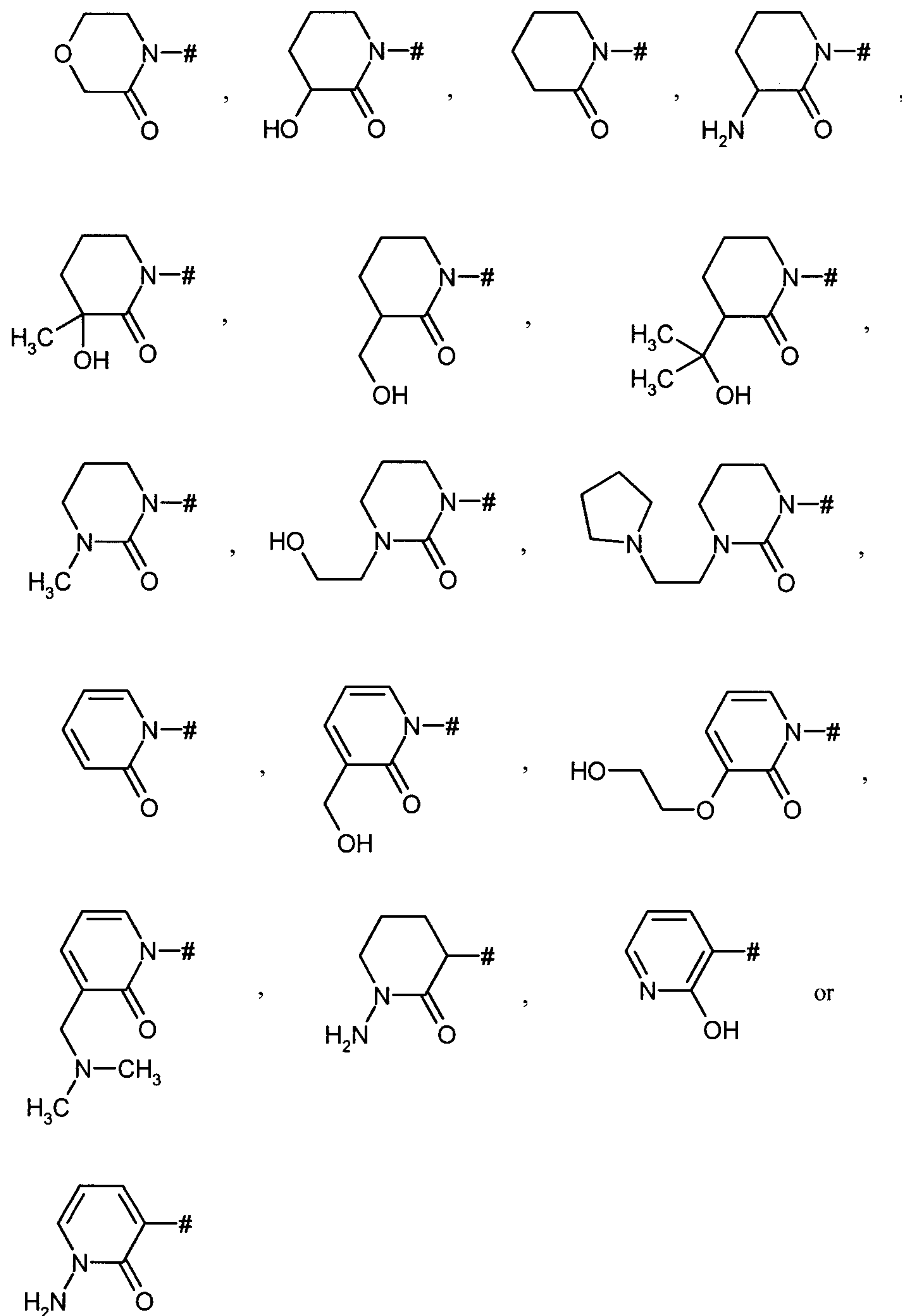
where R^9 is attached to the 7-position and R^{10} to the 6-position of the isoindoline ring,

15 and their salts, their solvates and the solvates of their salts.

Preference is also given to compounds of the formula (I) in which

A represents a group of the formula

- 19 -



where

is the point of attachment to the phenyl ring,

m represents the number 1,

5 and the (CH₂)_m group is attached in the 1- or 2-position to the phenyl ring,

R² represents hydrogen,

R^3 represents hydrogen, fluorine, chlorine, cyano or methyl,

R^4 and R^5 represent hydrogen,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

5 or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 represent hydrogen,

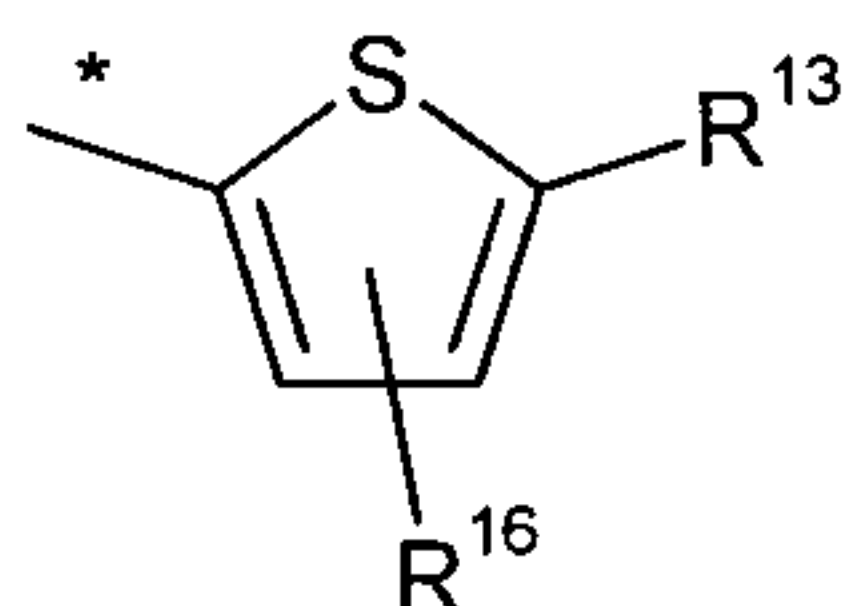
or

10 R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

R^8 represents a group of the formula



15 where

* is the point of attachment to the carbonyl group,

R^{13} represents chlorine,

and

R^{16} represents hydrogen,

20 R^9 represents hydrogen,

R^{10} represents hydrogen,

and

where R^9 is attached to the 6-position and R^{10} to the 7-position of the isoindoline ring,

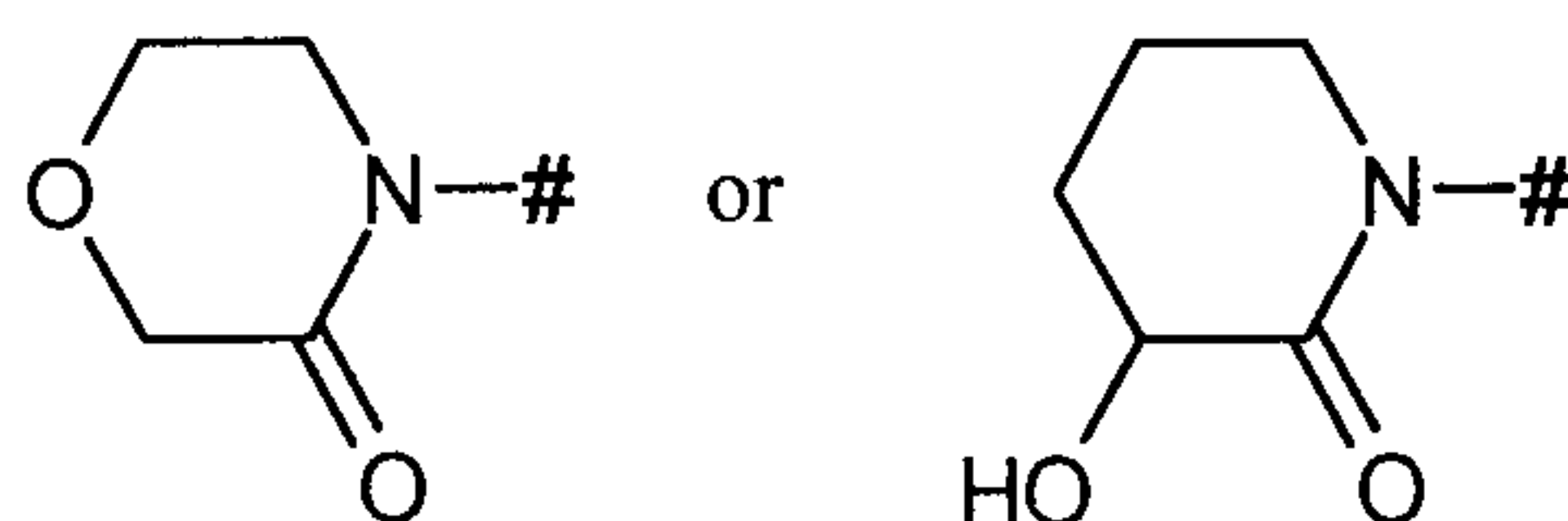
or

where R^9 is attached to the 7-position and R^{10} to the 6-position of the isoindoline ring,

5 and their salts, their solvates and the solvates of their salts.

Preference is also given to compounds of the formula (I) in which

A represents a group of the formula



where

10 # is the point of attachment to the phenyl ring,

m represents the number 1,

and the $(CH_2)_m$ group is attached in the 1- or 2-position to the phenyl ring,

R^2 represents hydrogen,

R^3 represents hydrogen, fluorine, chlorine, cyano or methyl,

15 R^4 and R^5 represent hydrogen,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

20 and

R^6 and R^7 represent hydrogen,

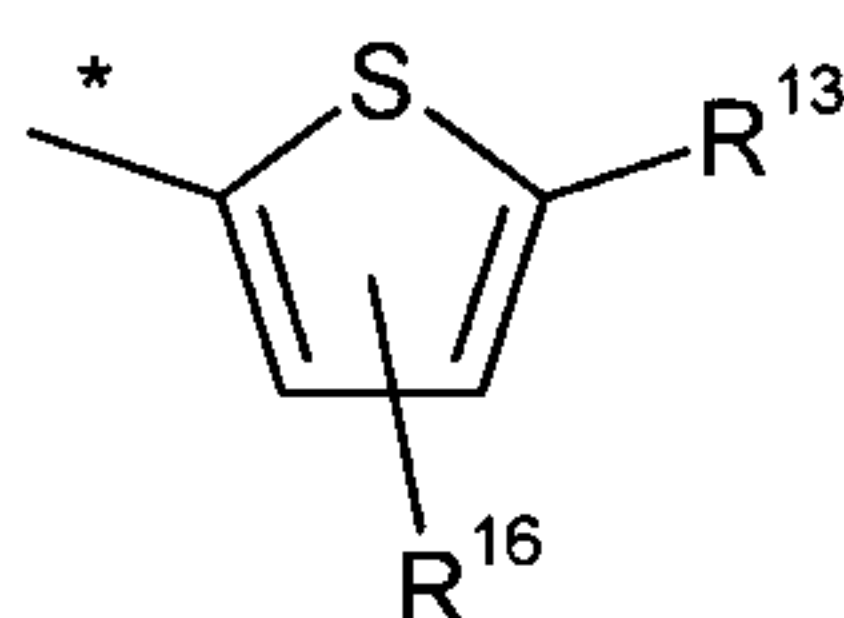
or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

5 R^8 represents a group of the formula



where

* is the point of attachment to the carbonyl group,

R^{13} represents chlorine,

10 and

R^{16} represents hydrogen,

R^9 represents hydrogen,

R^{10} represents hydrogen,

and

15 where R^9 is attached to the 6-position and R^{10} to the 7-position of the isoindoline ring,

or

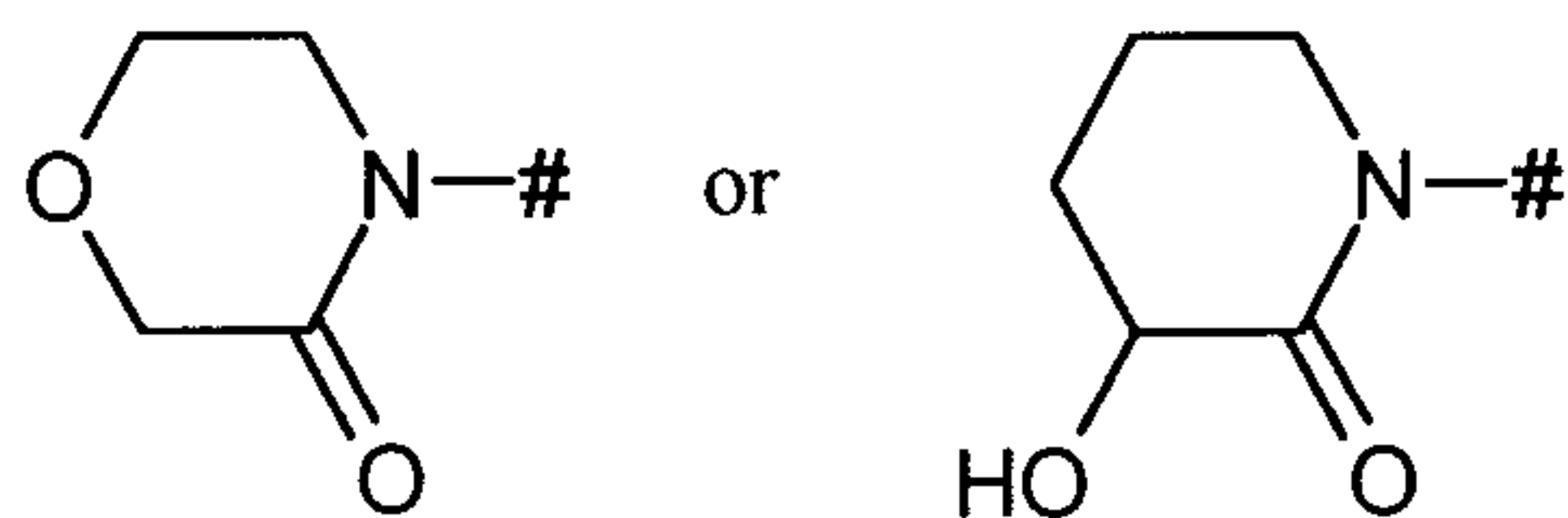
where R^9 is attached to the 7-position and R^{10} to the 6-position of the isoindoline ring,

and their salts, their solvates and the solvates of their salts.

Preference is also given to compounds of the formula (I) in which A represents a group of the

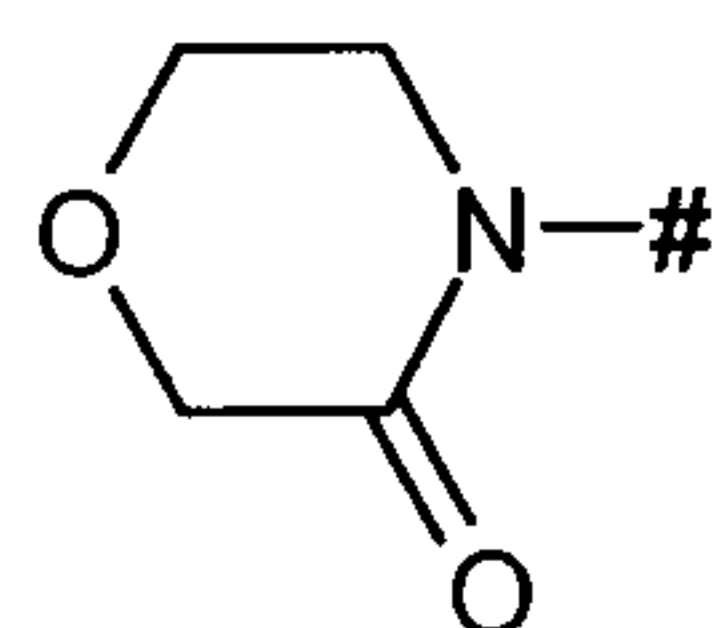
20 formula

- 23 -



where # is the point of attachment to the phenyl ring.

Preference is also given to compounds of the formula (I) in which A represents a group of the formula

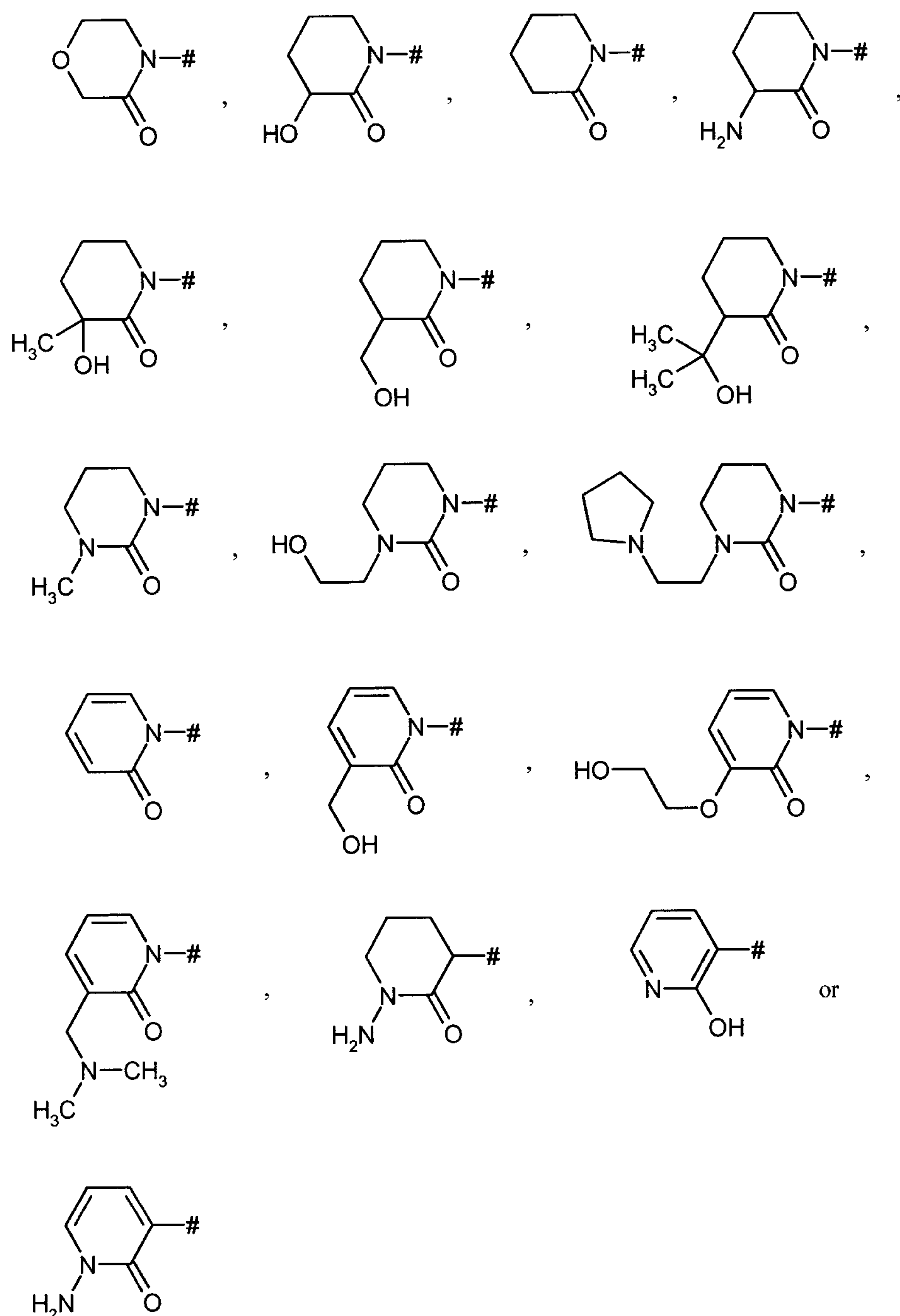


5

where # is the point of attachment to the phenyl ring.

Preference is also given to compounds of the formula (I) in which A represents a group of the formula

- 24 -



where # is the point of attachment to the phenyl ring.

Preference is also given to compounds of the formula (I) in which m represents the number 1.

Preference is also given to compounds of the formula (I) in which R^2 represents hydrogen.

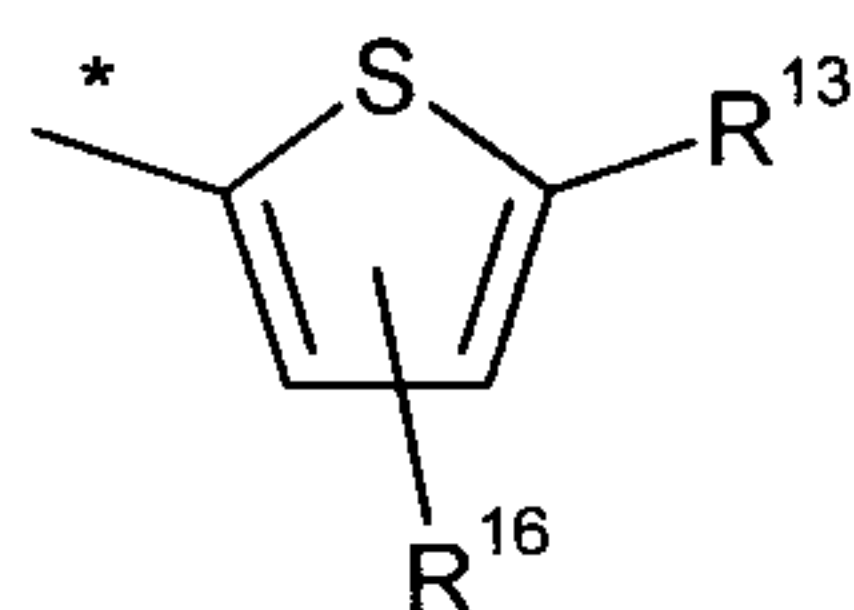
- 5 Preference is also given to compounds of the formula (I) in which R^3 represents hydrogen, fluorine, chlorine, cyano or methyl.

Preference is also given to compounds of the formula (I) in which R^3 represents hydrogen.

- 25 -

Preference is also given to compounds of the formula (I) in which R^2 and R^3 represent hydrogen.

Preference is also given to compounds of the formula (I) in which R^8 represents a group of the formula



- 5 where * is the point of attachment to the carbonyl group, R^{13} represents chlorine and R^{16} represents hydrogen.

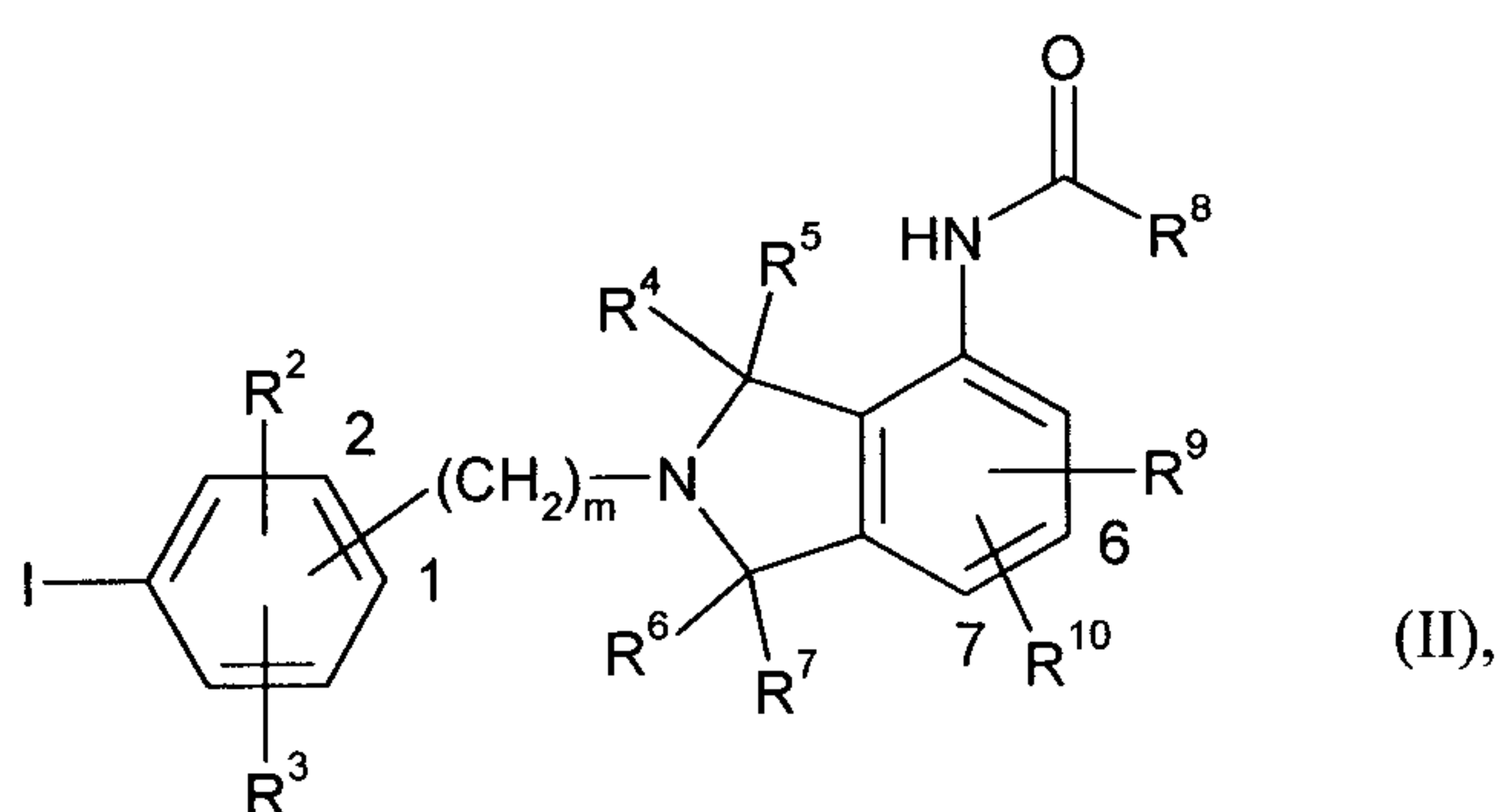
Preference is also given to compounds of the formula (I) in which R^9 and R^{10} represent hydrogen.

- The individual radical definitions given in the respective combinations or preferred combinations of radicals are, independently of the particular given combinations of radicals, also replaced by any
10 radical definitions of other combinations.

Very particular preference is given to combinations of two or more of the preferred ranges mentioned above.

The invention furthermore provides a process for preparing the compounds of the formula (I), or their salts, their solvates or the solvates of their salts, wherein

- 15 [A] the compounds of the formula



in which m , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} have the meaning given above, are reacted with compounds of the formula

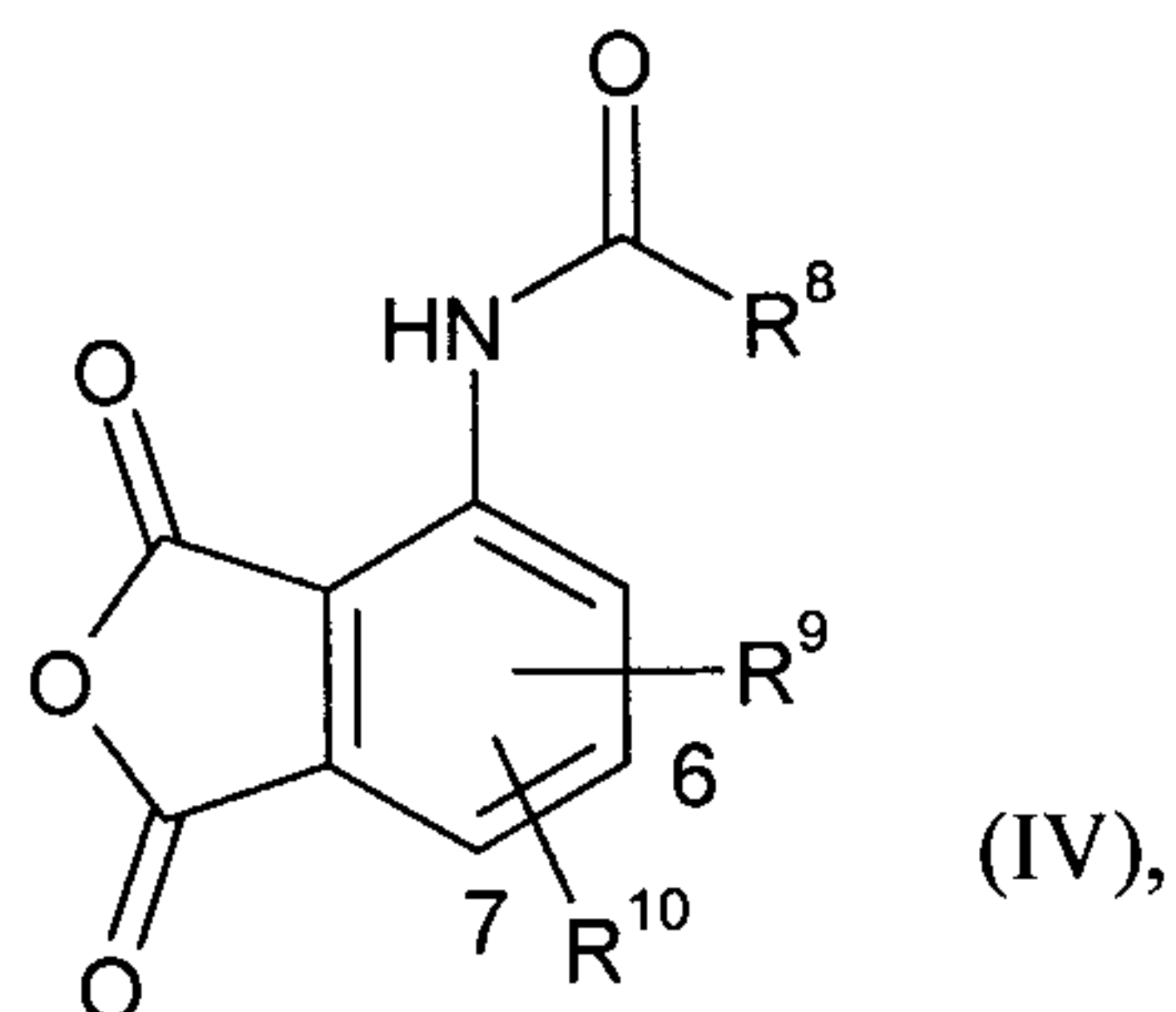
A-H (III),

- 20 in which A has the meaning given above,

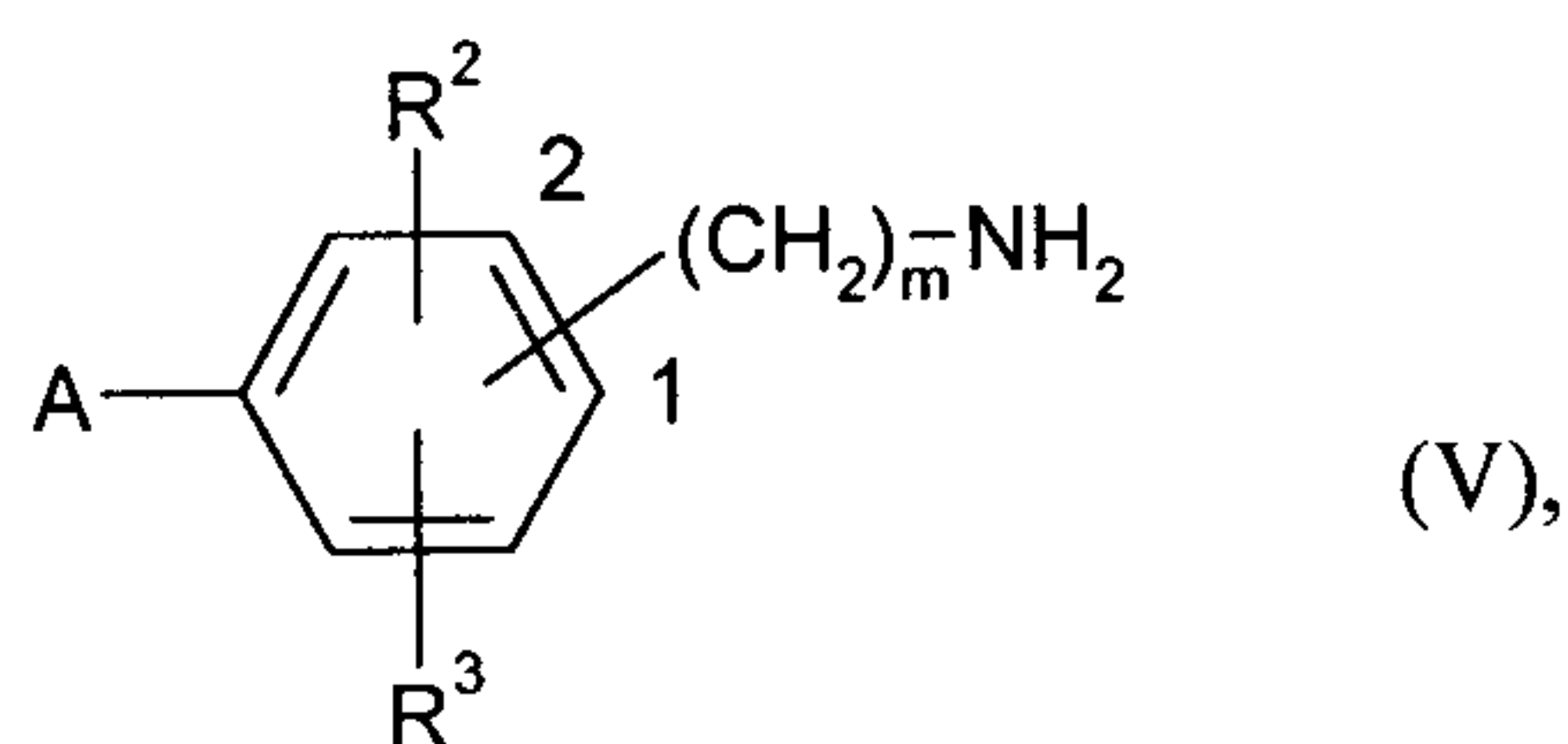
- 26 -

or

[B] the compounds of the formula



in which R^8 , R^9 and R^{10} have the meaning given above, are reacted with compounds of the formula

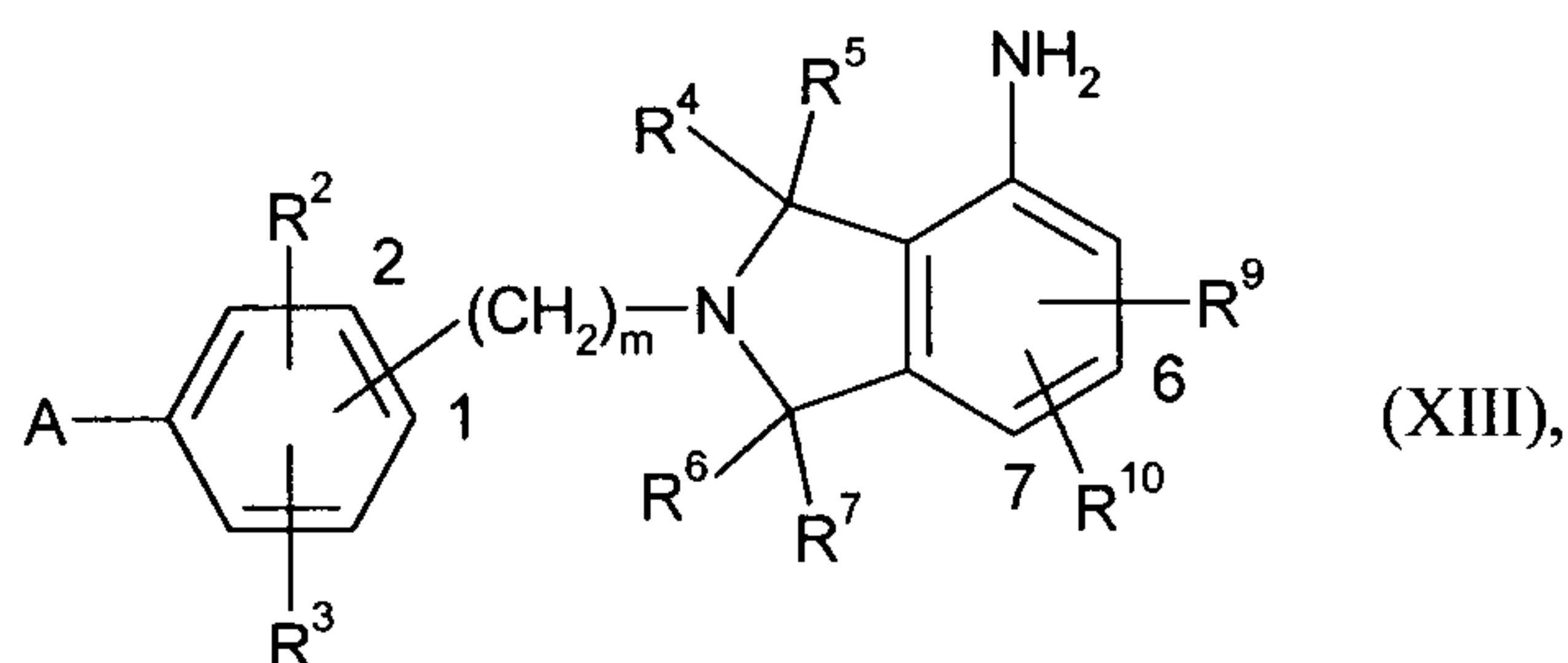


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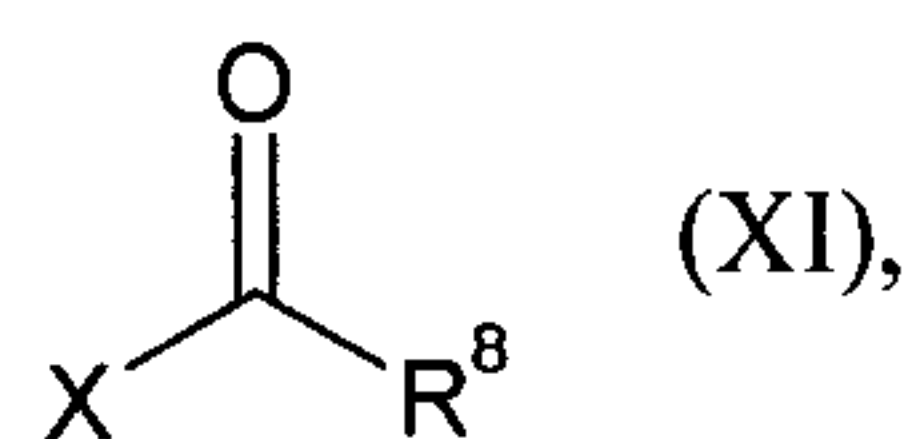
in which A, m, R^2 and R^3 have the meaning given above, to give compounds of the formula (I) in which R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group and R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

or

10 [C] the compounds of the formula



in which A, m, R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^9 and R^{10} have the meaning given above, are reacted with the compounds of the formula



in which R⁸ has the meaning given above, and

X represents halogen, preferably bromine or chlorine, or hydroxyl.

The free base of the salts can be obtained, for example, by chromatography on a reversed-phase column using an acetonitrile/water gradient with an added base, in particular by using an
5 RP18 Phenomenex Luna C18(2) column and diethylamine base, or by dissolving the salts in an organic solvent and extracting with aqueous solutions of basic salts such as sodium bicarbonate.

The invention furthermore provides a process for preparing the compounds of the formula (I) of their solvates wherein salts of the compounds or solvates of the salts of the compounds are converted into the compounds by chromatography with an added base.

10 The reaction according to process [A] is generally carried out in inert solvents with addition of a copper(I) salt, a base and a diamine ligand, preferably in a temperature range of from 60°C to reflux of the solvent at atmospheric pressure.

Inert solvents are, for example, aprotic solvents, such as toluene, dioxane, tetrahydrofuran or dimethylformamide; preference is given to dioxane.

15 Copper(I) salts are, for example, copper(I) iodide, copper(I) chloride or copper(I) oxide; preference is given to copper(I) iodide.

Bases are, for example, potassium phosphate, potassium carbonate or caesium carbonate; preference is given to potassium phosphate.

Diamine ligands are, for example, 1,2-diamines, such as *N,N'*-dimethylethylenediamine.

20 The reaction according to process [B] is generally carried out in inert solvents in the presence of a base, preferably in a temperature range of from 60°C to reflux of the solvent at atmospheric pressure.

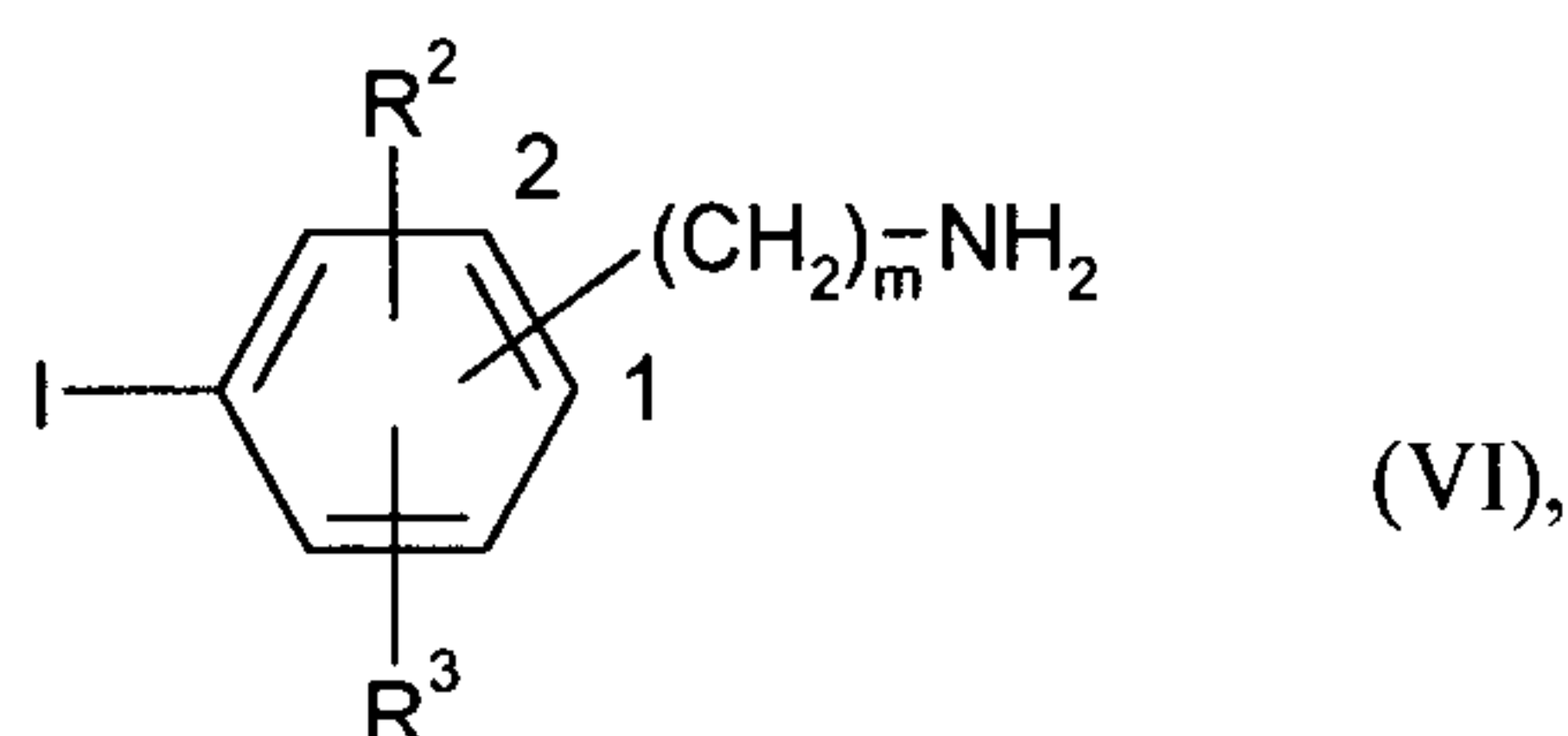
Inert solvents are, for example, ethers, such as dioxane or tetrahydrofuran; preference is given to dioxane.

25 Bases are, for example, amine bases, such as triethylamine or diisopropylethylamine; preference is given to diisopropylethylamine.

The reaction according to process [C] is carried out under the same reaction conditions as the third step of the reaction of the compounds of the formula (X) with compounds of the formula (XI).

The compounds of the formulae (III), (IV) and (V) are known or can be synthesized by known methods from the appropriate starting materials.

The compounds of the formula (IIa) in which R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group and R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group are known or can be prepared by reacting compounds of the formula (IV) with compounds of the formula

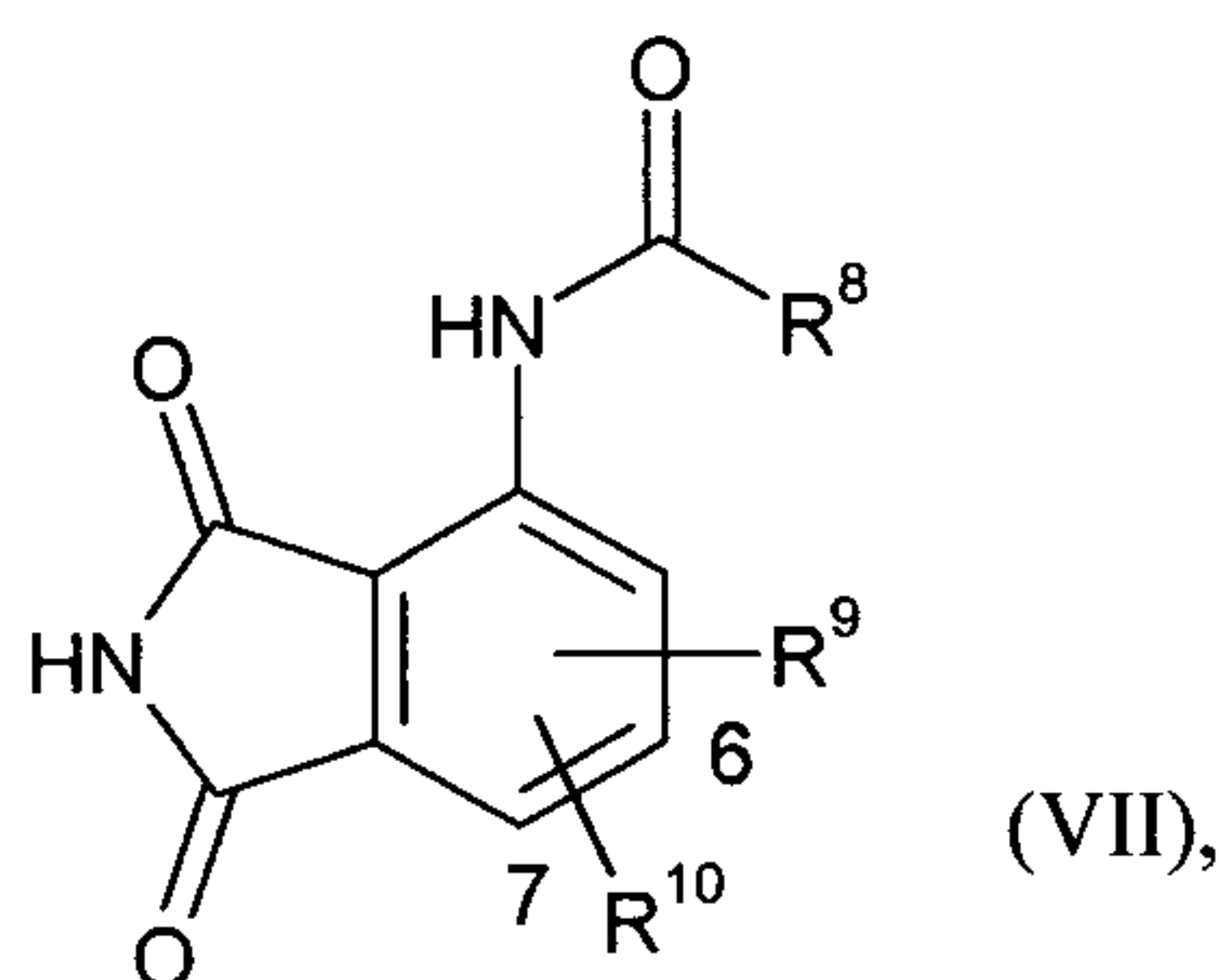


in which m , R^2 and R^3 have the meaning given above.

The reaction is carried out under the same reaction conditions as the reaction of the compounds of the formula (IV) with compounds of the formula (V) (process [B]).

The compounds of the formula (VI) are known or can be synthesized by known processes from the appropriate starting materials.

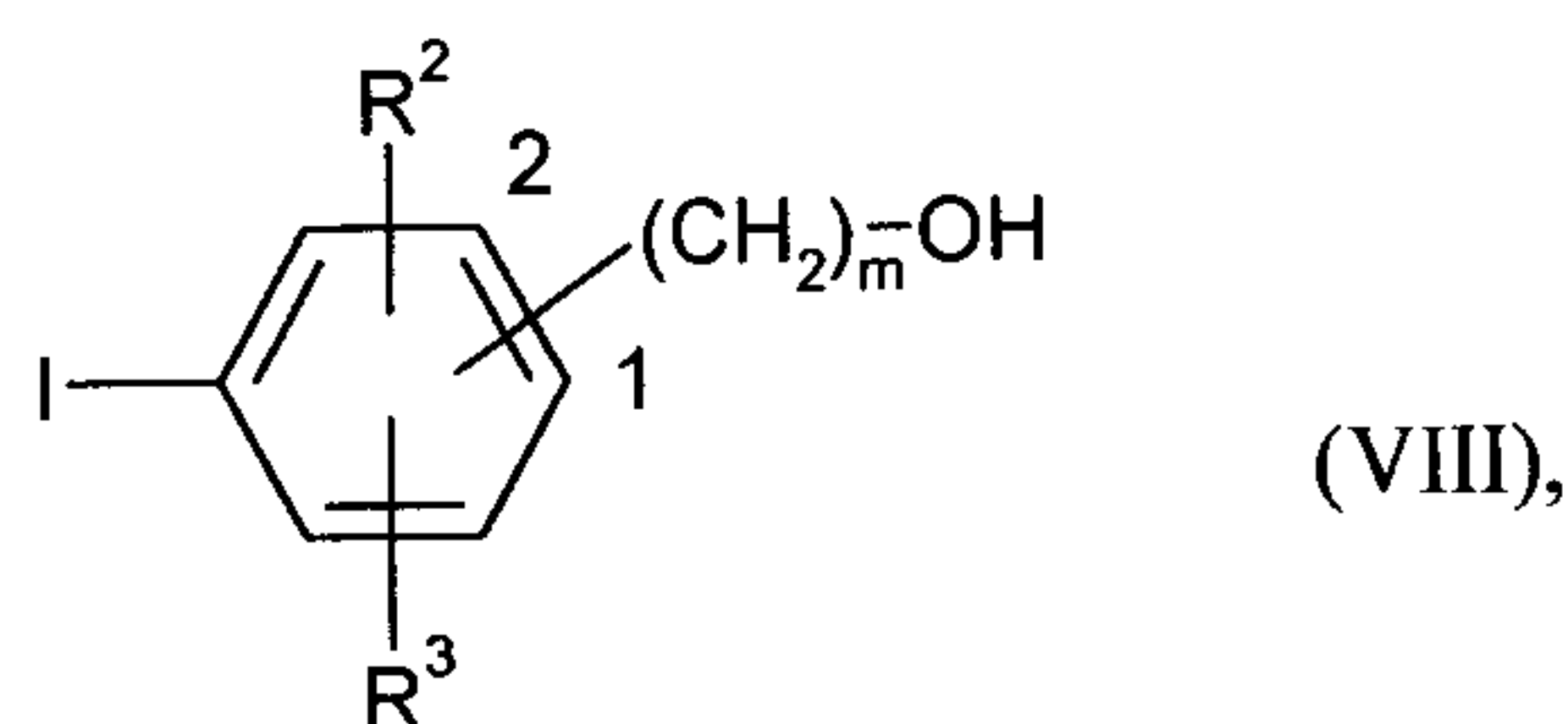
In an alternative process, the compounds of the formula (IIa) can be prepared by reacting compounds of the formula



in which R^8 , R^9 and R^{10} have the meaning given above,

with compounds of the formula

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in which m, R² and R³ have the meaning given above,

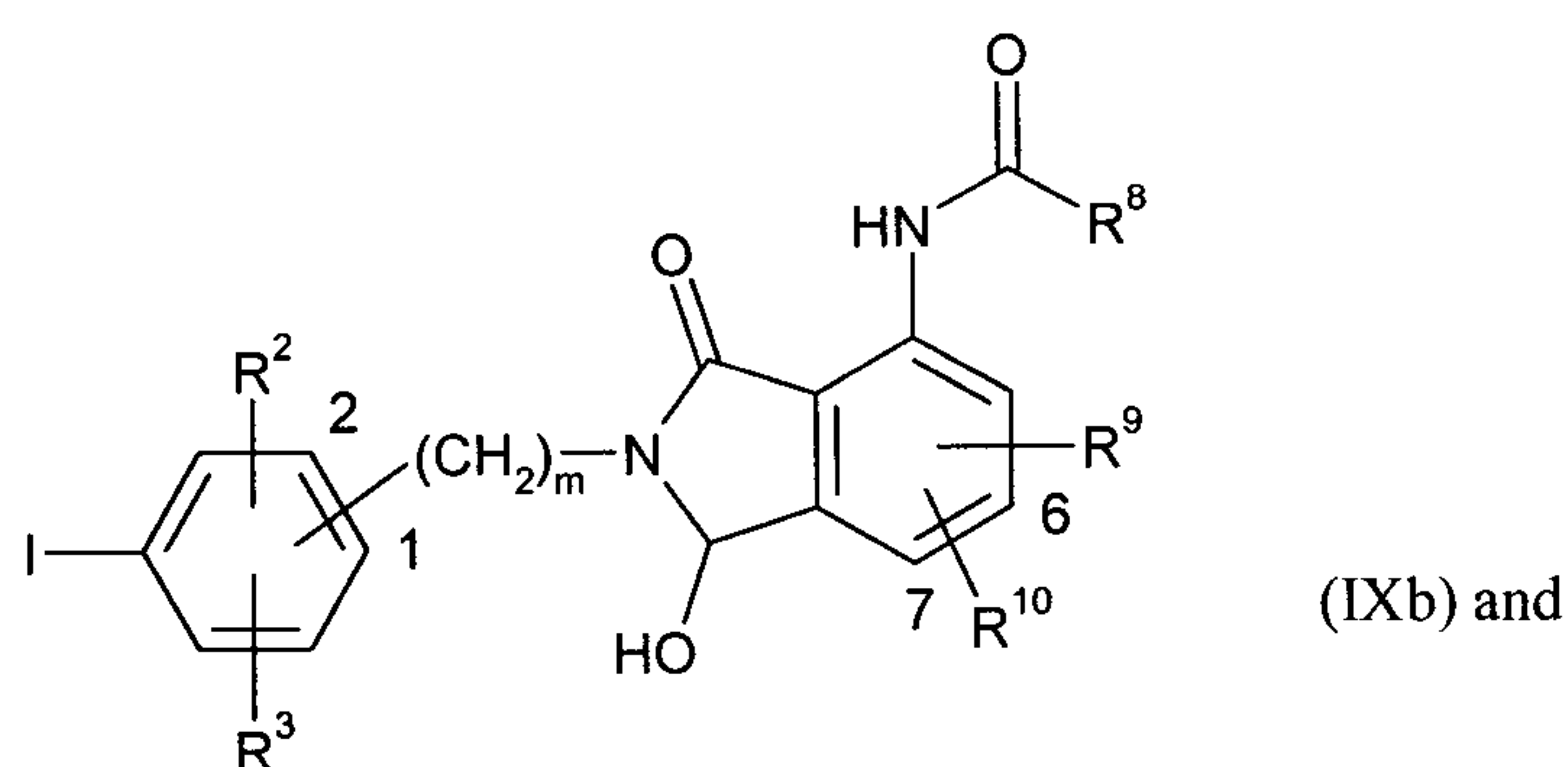
under Mitsunobu reaction conditions.

The reaction is generally carried out in inert solvents, preferably in a temperature range of from
5 -20°C to 40°C at atmospheric pressure.

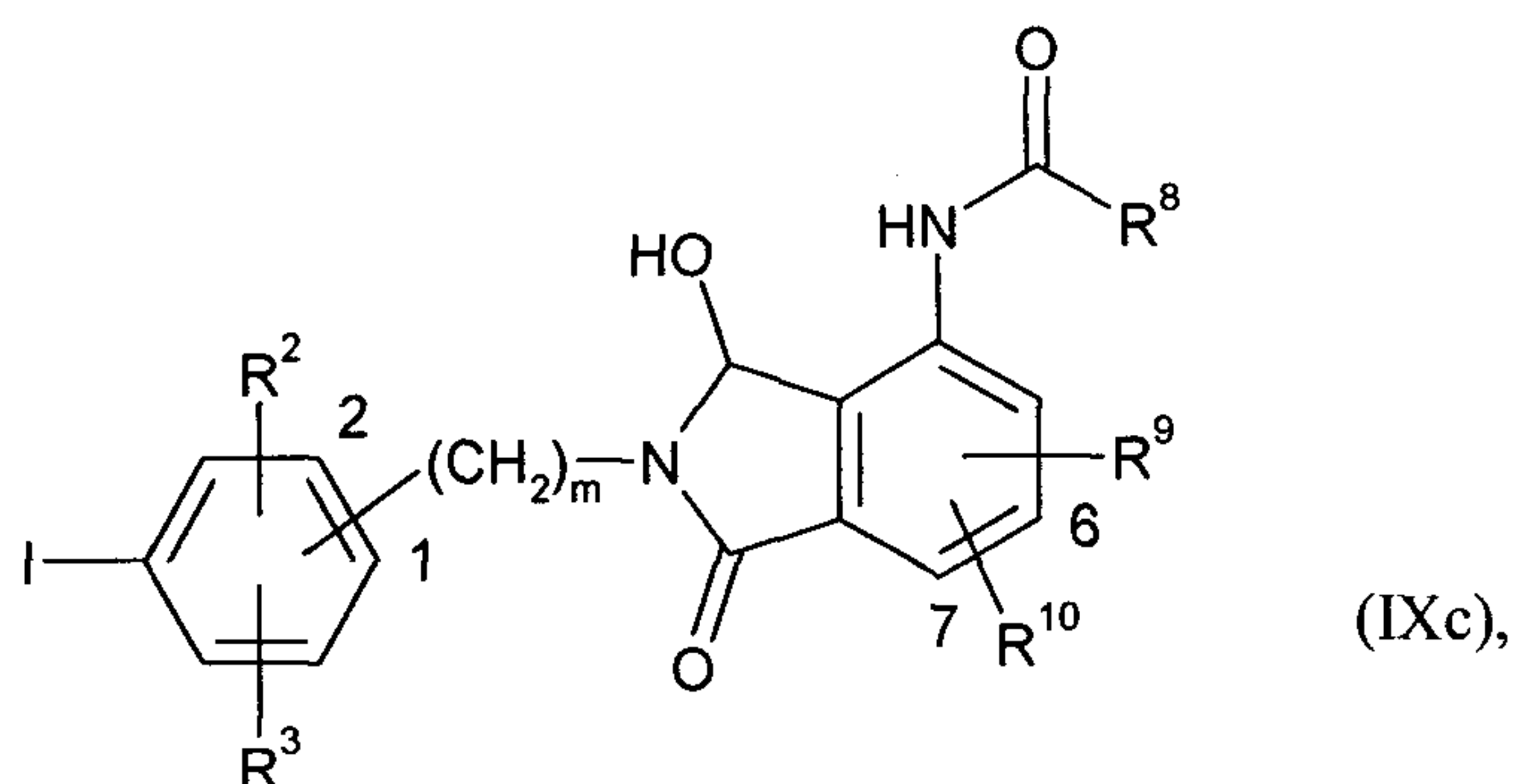
Inert solvents are, for example, tetrahydrofuran, methylene chloride, dioxane or dimethylformamide; preference is given to tetrahydrofuran.

The compounds of the formulae (VII) and (VIII) are known or can be synthesized by known processes from the appropriate starting materials.

- 10 The compounds of the formula (IIb) in which R⁴ and R⁵ together with the carbon atom to which they are attached form a carbonyl group and R⁶ and R⁷ represent hydrogen and the compounds of the formula (IIc) in which R⁴ and R⁵ represent hydrogen and R⁶ and R⁷ together with the carbon atom to which they are attached form a carbonyl group are known or can be prepared by converting, in the first step, compounds of the formula (IIa) with a borohydride into a mixture of
15 the compounds of the formulae



- 30 -



in which m , R^2 , R^3 , R^8 , R^9 and R^{10} have the meaning given above,

separating the isomers (IXb) and (IXc) by crystallization or chromatography and then reacting each isomer individually in the second step with trifluoroacetic acid and triethylsilane to give the compound of the formula (IIb) or the compound of the formula (IIc).

The reaction of the first step is generally carried out in inert solvents, preferably in a temperature range of from -20°C to 50°C at atmospheric pressure.

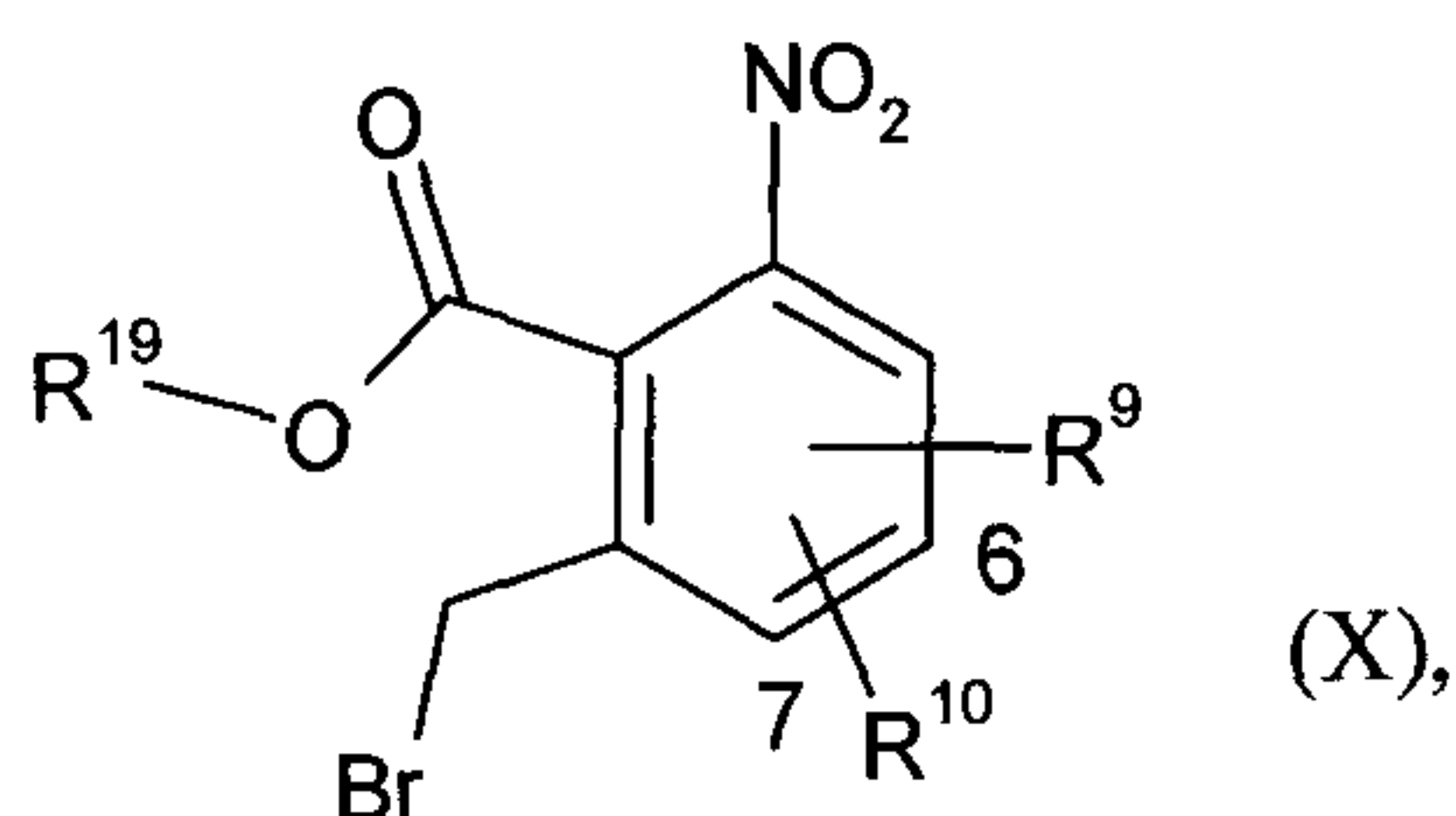
Borohydrides are, for example, sodium borohydride or lithium borohydride; preference is given to sodium borohydride.

Inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride or trichloromethane, alcohols, such as methanol, ethanol, n-propanol or isopropanol, or ethers, such as diethyl ether, dioxane or tetrahydrofuran, or mixtures of these solvents; preference is given to a mixture of methanol and methylene chloride.

The reaction of the second step is generally carried out in inert solvents, preferably in a temperature range of from -20°C to 50°C at atmospheric pressure.

Inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride or trichloromethane; preference is given to methylene chloride.

In an alternative process, the compounds of the formula (IIb) can be prepared by reacting compounds of the formula



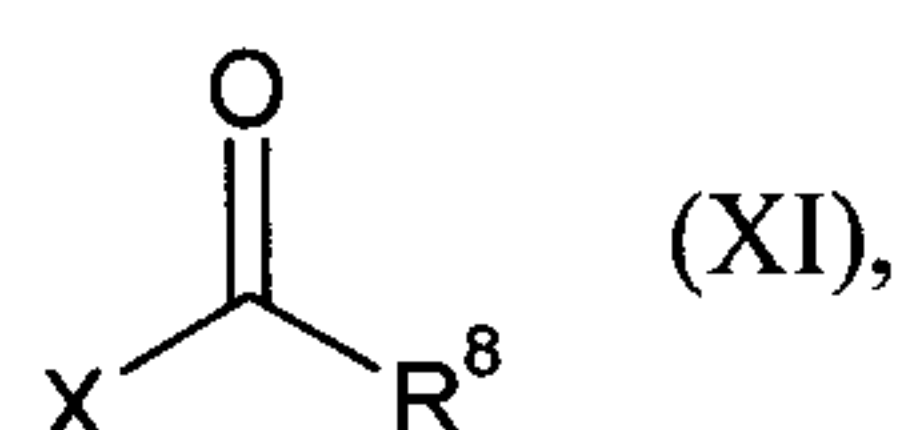
in which R^9 and R^{10} have the meaning given above and

R^{19} represents methyl or ethyl

in the first step with compounds of the formula (VI),

reducing the nitro group in the second step and

5 reacting, in the third step, with compounds of the formula



in which R^8 has the meaning given above and

X represents halogen, preferably bromine or chlorine, or hydroxyl.

The reaction is carried out under the same reaction conditions as the reaction of the compounds of
10 the formula (IV) with compounds of the formula (V) (process [B]).

The reduction of the nitro group in the second step is generally carried out using a reducing agent in inert solvents, preferably in a temperature range of from room temperature to reflux of the solvents at from atmospheric pressure to 3 bar.

Reducing agents are, for example, palladium on activated carbon and hydrogen, tin dichloride or
15 titanium trichloride; preference is given to palladium on activated carbon and hydrogen or tin chloride.

Inert solvents are, for example, ethers, such as diethyl ether, methyl-*tert*-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols, such as methanol, ethanol, n-propanol, isopropanol, n-butanol or *tert*-butanol,
20 hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as dimethylformamide, dimethylacetamide, acetonitrile or pyridine; preferred solvents are methanol, ethanol, isopropanol or, in the case of tin dichloride, dimethylformamide.

If, in the third step, X represents halogen, the reaction is generally carried out in inert solvents, if appropriate in the presence of a base, preferably in a temperature range of from -30°C to 50°C at
25 atmospheric pressure.

Inert solvents are, for example, tetrahydrofuran, methylene chloride, pyridine, dioxane or

dimethylformamide; preference is given to pyridine or dimethylformamide.

Preferred inert solvents are tetrahydrofuran and methylene chloride.

Bases are, for example, triethylamine, diisopropylethylamine or *N*-methylmorpholine; preference is given to diisopropylethylamine.

- 5 If, in the third step, X represents hydroxy, the reaction is generally carried out in inert solvents in the presence of a dehydrating agent, if appropriate in the presence of a base, preferably in a temperature range of from -30°C to 50°C at atmospheric pressure.

Inert solvents are, for example, halogenated hydrocarbons, such as dichloromethane or trichloromethane, hydrocarbons, such as benzene, nitromethane, dioxane, dimethylformamide or
10 acetonitrile. It is also possible to use mixtures of the solvents. Particular preference is given to dichloromethane or dimethylformamide.

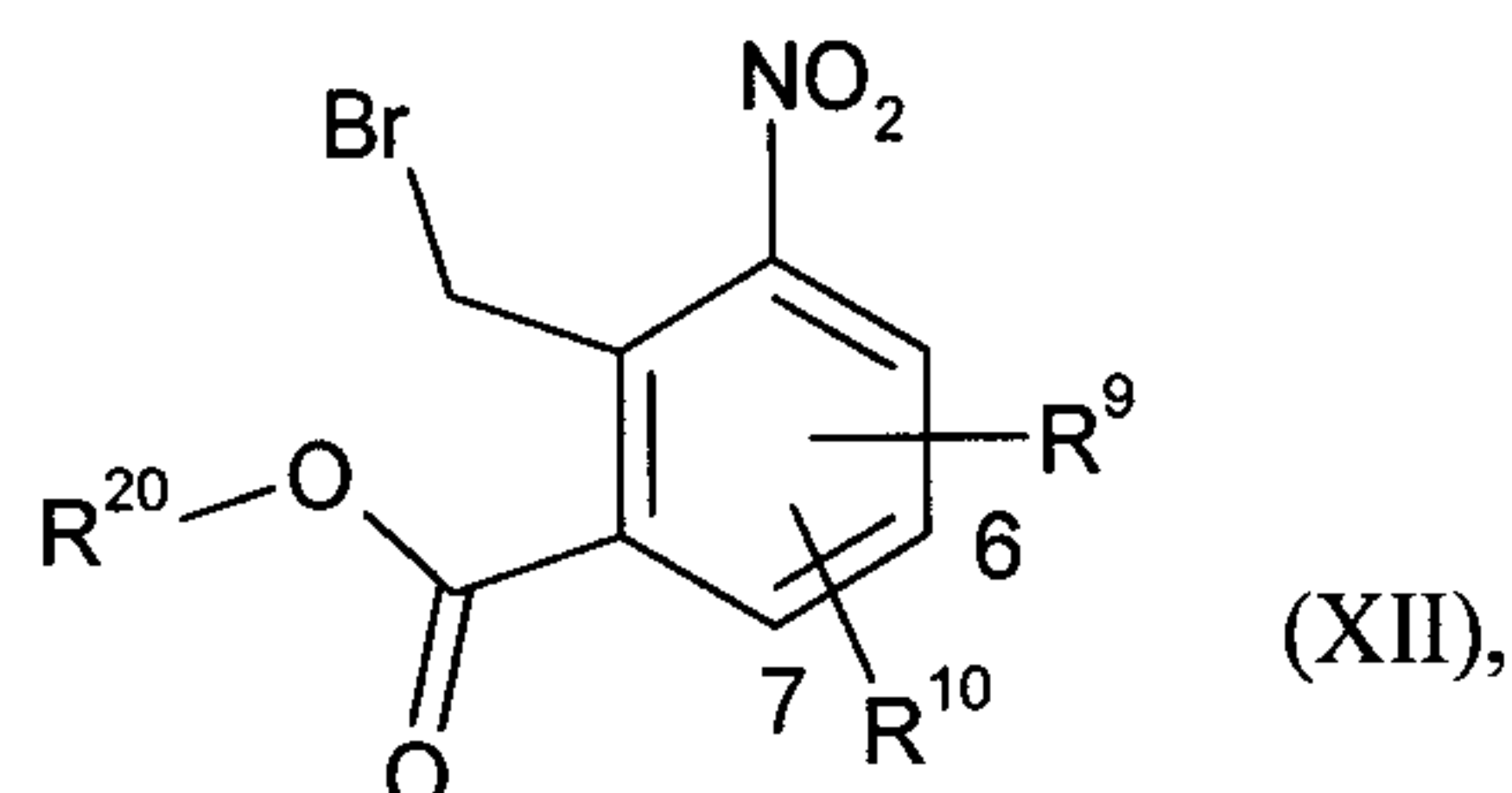
Here, suitable dehydrating agents are, for example, carbodiimides, such as, for example, *N,N'*-diethyl-, *N,N'*-dipropyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexylcarbodiimide, *N*-(3-dimethylamino-isopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), *N*-cyclohexylcarbodiimide-*N'*-
15 propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulphate or 2-*tert*-butyl-5-methyl-isoxazolium perchlorate, or acylamino compounds, such as 2-ethoxy-1-ethoxy-carbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis-(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium
20 hexafluorophosphate, or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxy-benzotriazole (HOBt), or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), or *N*-hydroxysuccinimide, or mixtures of these, with bases.

- 25 Bases are, for example, alkali metal carbonates, such as, for example, sodium carbonate or potassium carbonate or sodium bicarbonate or potassium bicarbonate, or organic bases, such as trialkylamines, for example triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine.

The condensation is preferably carried out with HATU or with EDC in the presence of HOBt.

- 30 The compounds of the formulae (X) and (XI) are known or can be synthesized according to known processes from the appropriate starting materials.

In an alternative process, the compounds of the formula (IIc) can be prepared as described in the alternative process for compounds of the formula (IIb). Starting materials are compounds of the formula

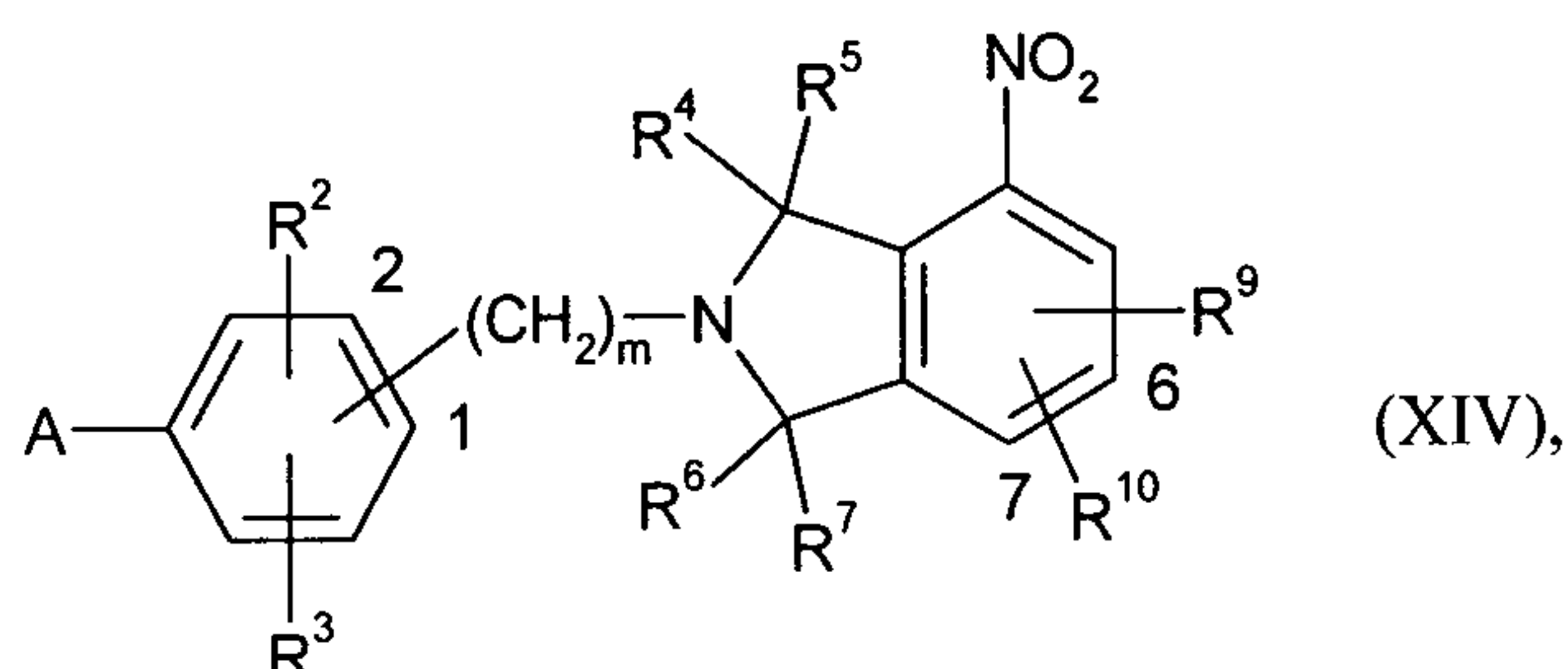


5 in which R^9 and R^{10} have the meaning given above and

R^{20} represents methyl or ethyl.

The compounds of the formula (XII) are known or can be synthesized according to known processes from the appropriate starting materials.

10 The compounds of the formula (XIII) are known or can be prepared by reducing the nitro group in compounds of the formula

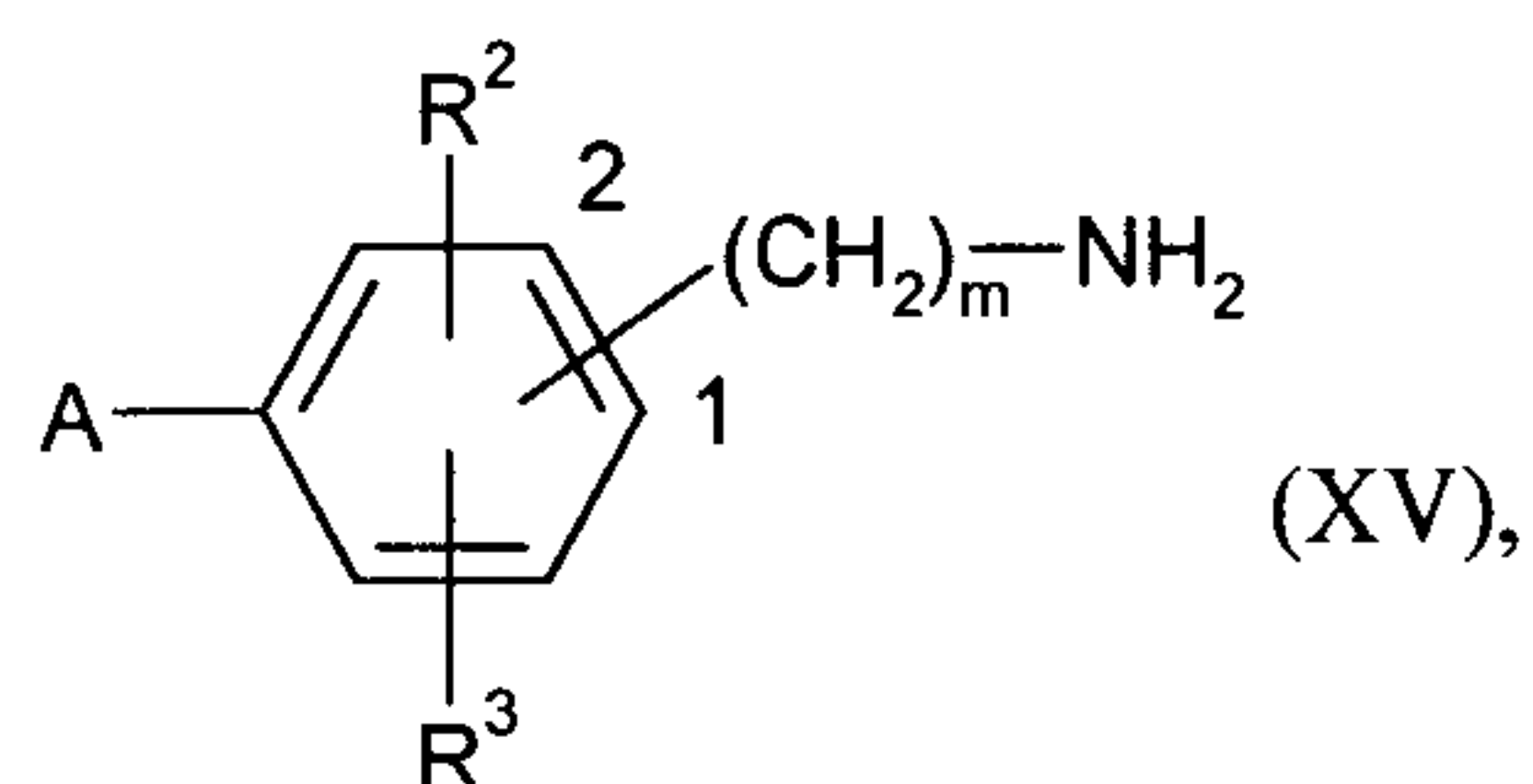


in which A, m, R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^9 and R^{10} have the meaning given above.

15 The compounds of the formula (XIVa) in which R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group and R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group are known or can be prepared analogously to process [B].

The compounds of the formula (XIVb) in which R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group and R^6 and R^7 represent hydrogen and the compounds of the formula (XIVc) in which R^4 and R^5 represent hydrogen and R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group are known or can be prepared by reacting
20 compounds of the formula

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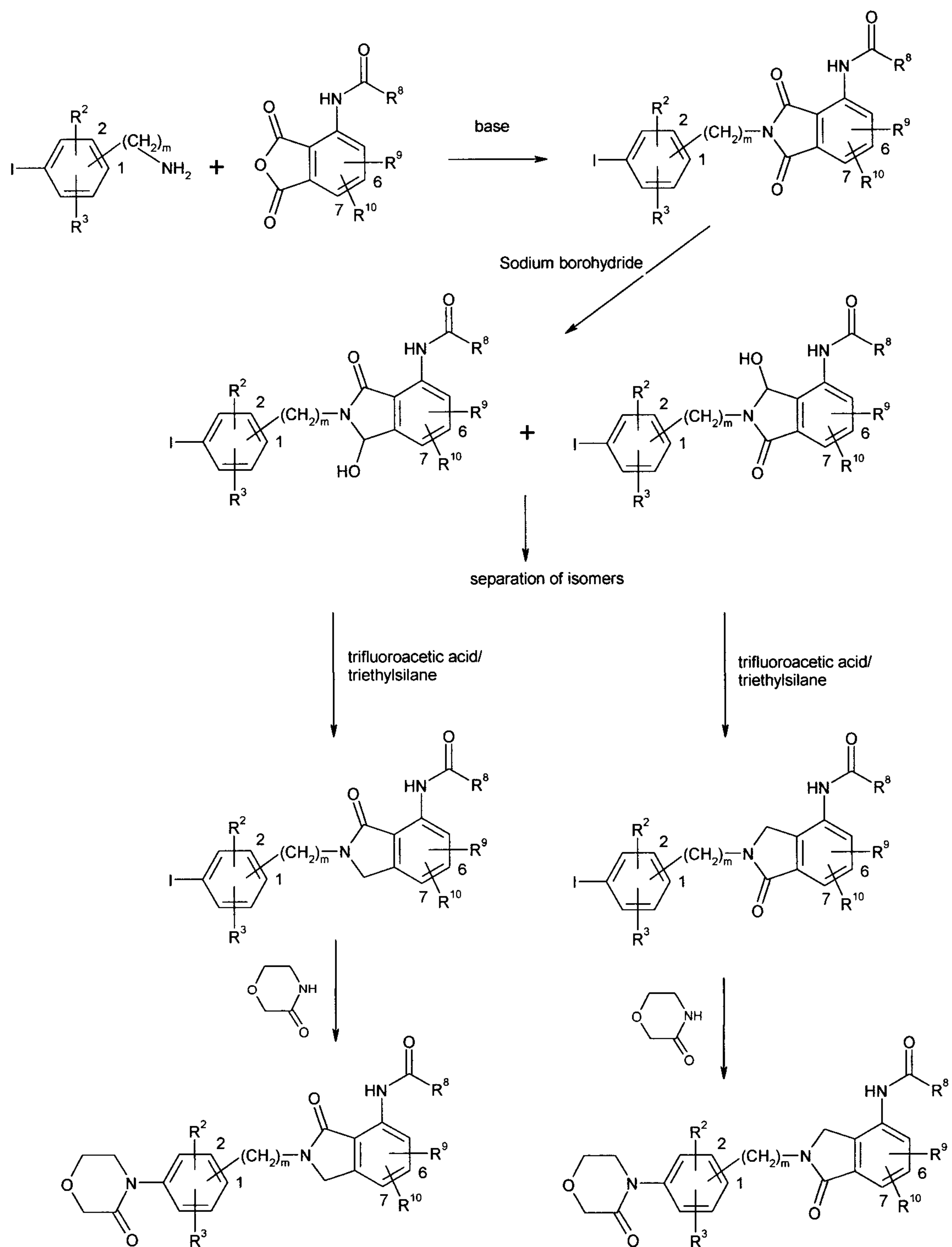
in which A, m, R² and R³ have the meaning given above with compounds of the formula (X) and (XII), respectively.

The reaction is carried out analogously to process [B].

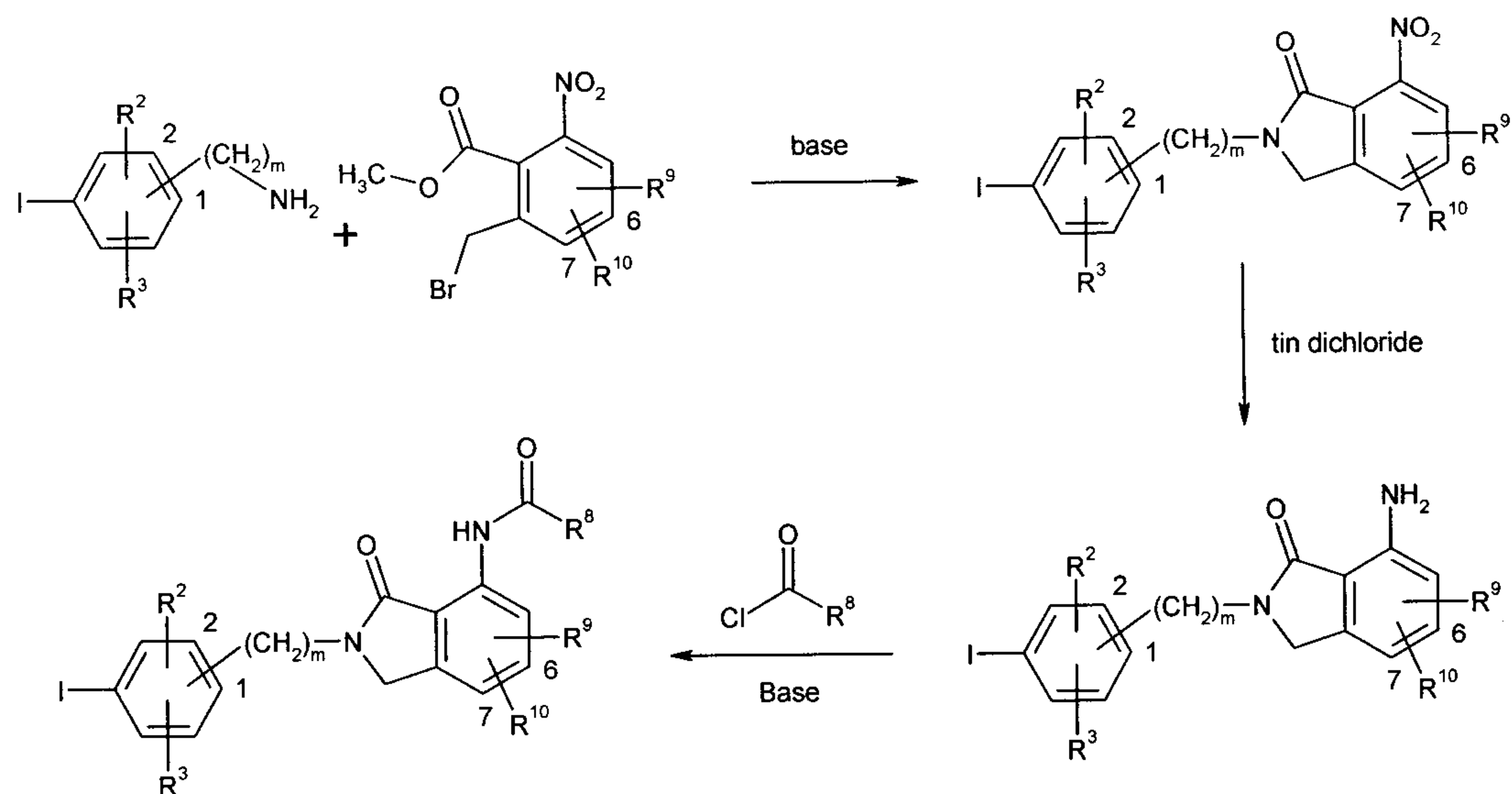
- 5 The compounds of the formula (XV) are known or can be synthesized according to known processes from the appropriate starting materials.

The preparation of the compounds according to the invention can be illustrated by the synthesis schemes below:

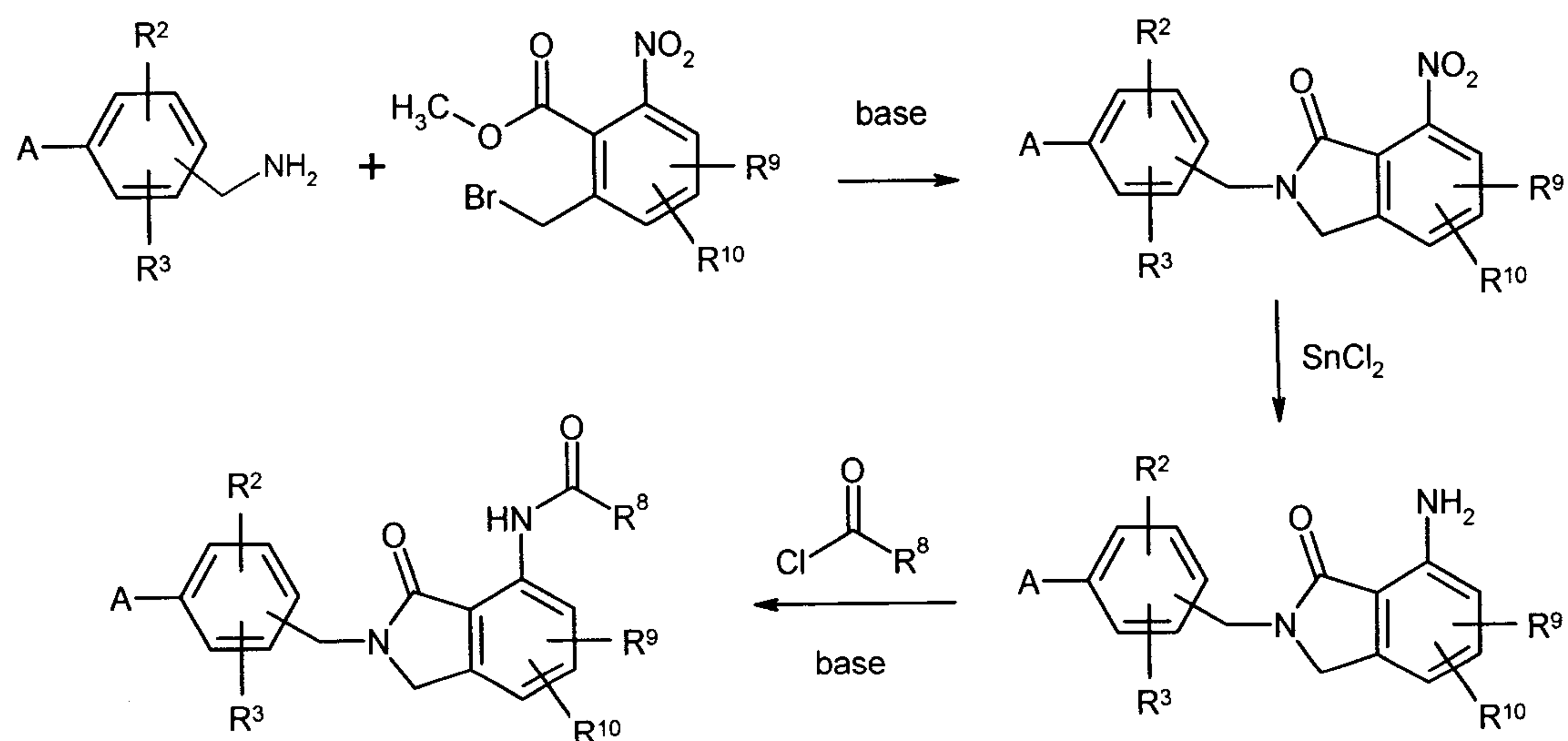
Scheme 1



Scheme 2



Scheme 3



- 5 The compounds according to the invention have an unforeseeable useful pharmacological activity spectrum.

Accordingly, they are suitable for use as medicaments for the treatment and/or prophylaxis of diseases in humans and animals.

10

The compounds according to the invention are selective inhibitors of blood coagulation factor Xa which act in particular as anticoagulants.

In addition, the compounds according to the invention have favourable physicochemical properties, such as, for example, good solubility in water and physiological media, which is advantageous for their therapeutic application.

- 5 The present invention furthermore provides the use of the compounds according to the invention for the treatment and/or prophylaxis of disorders, preferably thromboembolic disorders and/or thromboembolic complications.

10 For the purposes of the present invention, "thromboembolic disorders" include in particular disorders such as ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (non-STEMI), stable angina pectoris, unstable angina pectoris, reocclusions and restenoses after coronary interventions such as angioplasty or aortocoronary bypass, peripheral arterial occlusive diseases, pulmonary embolisms, deep vein thromboses and kidney vein thromboses, transitory ischaemic attacks and also thrombotic and thromboembolic stroke.

15

Accordingly, the substances are also suitable for preventing and treating cardiogenic thrombo-embolisms, such as, for example, brain ischaemias, stroke and systemic thromboembolisms and ischaemias, in patients having acute, intermittent or persistent cardioarrhythmias, such as, for example, atrial fibrillation, and those undergoing cardioversion, furthermore patients having heart
20 valve disorders or having artificial heart valves. In addition, the compounds according to the invention are suitable for treating disseminated intravascular coagulation (DIC).

Thromboembolic complications furthermore occur during microangiopathic haemolytic anaemias, extracorporeal blood circulation, such as haemodialysis, and in connection with heart valve
25 prostheses.

Moreover, the compounds according to the invention are also suitable for the prophylaxis and/or treatment of atherosclerotic vascular disorders and inflammatory disorders, such as rheumatic disorders of the locomotor apparatus, and in addition also for the prophylaxis and/or treatment of
30 Alzheimer's disease. Moreover, the compounds according to the invention can be used for inhibiting tumour growth and formation of metastases, for microangiopathies, age-related macular degeneration, diabetic retinopathy, diabetic nephropathy and other microvascular disorders, and also for the prevention and treatment of thromboembolic complications, such as, for example, venous thromboembolisms, in tumour patients, in particular patients undergoing major surgical
35 interventions or chemo- or radiotherapy.

The compounds according to the invention can additionally also be used for preventing coagulation *ex vivo*, for example for preserving blood and plasma products, for cleaning/pretreating catheters and other medical tools and instruments, for coating synthetic surfaces of medical tools and instruments used *in vivo* or *ex vivo* or for biological samples
5 comprising factor Xa.

The present invention furthermore provides the use of the compounds according to the invention for the treatment and/or prophylaxis of disorders, in particular the disorders mentioned above.

10 The present invention furthermore provides the use of the compounds according to the invention for preparing a medicament for the treatment and/or prophylaxis of disorders, in particular the disorders mentioned above.

The present invention furthermore provides a method for the treatment and/or prophylaxis of
15 disorders, in particular the disorders mentioned above, using an anticoagulatory effective amount of the compound according to the invention.

The present invention furthermore provides a method for preventing blood coagulation *in vitro*, in particular in banked blood or biological samples comprising factor Xa, which method is
20 characterized in that an anticoagulatory effective amount of the compound according to the invention is added.

The present invention furthermore provides medicaments comprising a compound according to the invention and one or more further active compounds, in particular for the treatment and/or
25 prophylaxis of the disorders mentioned above. The following compounds may be mentioned by way of example and by way of preference as active compounds suitable for combinations:

- lipid-lowering agents, in particular HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors;
30
- coronary therapeutics/vasodilators, in particular ACE (angiotensin converting enzyme) inhibitors; AII (angiotensin II) receptor antagonists; β -adrenoceptor antagonists; alpha-1-adrenoceptor antagonists; diuretics; calcium channel blockers; substances which cause an increase in the cyclic guanosine monophosphate (cGMP) concentration such as, for example,
35 stimulators of soluble guanylate cyclase;

- plasminogen activators (thrombolytics/fibrinolytics) and compounds enhancing thrombolysis/fibrinolysis, such as inhibitors of the plasminogen activator inhibitor (PAI inhibitors) or inhibitors of the thrombin-activated fibrinolysis inhibitor (TAFI inhibitors);
- 5 • anticoagulants;
- platelet aggregation inhibiting substances (platelet aggregation inhibitors, thrombocyte aggregation inhibitors);
- 10 • fibrinogen receptor antagonists (glycoprotein-IIb/IIIa antagonists);
- and also antiarrhythmics.

The present invention furthermore provides medicaments comprising at least one compound
15 according to the invention, usually together with one or more inert non-toxic pharmaceutically acceptable auxiliaries, and their use for the purposes mentioned above.

The compounds according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable way, such as, for example, by the oral, parenteral,
20 pulmonary, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival or otic route, or as implant or stent.

For these administration routes, it is possible to administer the compounds according to the invention in suitable administration forms.

25

Suitable for oral administration are administration forms which work as described in the prior art and deliver the compounds according to the invention rapidly and/or in modified form, which comprise the compounds according to the invention in crystalline and/or amorphous and/or dissolved form, such as, for example, tablets (uncoated and coated tablets, for example tablets
30 provided with enteric coatings or coatings whose dissolution is delayed or which are insoluble and which control the release of the compound according to the invention), tablets which rapidly decompose in the oral cavity, or films/wafers, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

35

Parenteral administration can take place with avoidance of an absorption step (for example

intravenously, intraarterially, intracardially, intraspinally or intralumbarily) or with inclusion of absorption (for example intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Administration forms suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions,
5 lyophilizates or sterile powders.

Examples suitable for other administration routes are pharmaceutical forms for inhalation (inter alia powder inhalers, nebulizers), nasal drops/solutions/sprays; tablets to be administered lingually, sublingually or buccally, films/wafers or capsules,
10 suppositories, preparations for the eyes or ears, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (e.g. patches), milk, pastes, foams, dusting powders, implants or stents.

Preference is given to oral or parenteral administration, in particular oral administration.
15

The compounds according to the invention can be converted into the stated administration forms. This can take place in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable auxiliaries. These auxiliaries include, inter alia, carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (for example liquid polyethylene glycols), emulsifiers and
20 dispersants or wetting agents (for example sodium dodecyl sulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (for example antioxidants, such as, for example, ascorbic acid), colorants (for example inorganic pigments, such as, for example, iron oxides) and flavour- and/or odour-masking agents.

25 In general, it has proved advantageous to administer on parenteral administration amounts of from about 0.001 to 1 mg/kg, preferably from about 0.01 to 0.5 mg/kg, of body weight to achieve effective results. The dosage on oral administration is from about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg, and very particularly preferably 0.1 to 10 mg/kg, of body weight.

30 It may nevertheless be necessary, where appropriate, to deviate from the amounts mentioned, depending on the body weight, the administration route, the individual response to the active compound, the mode of preparation and the time or interval over which administration takes place. Thus, in some cases it may be sufficient to make do with less than the aforementioned minimal amount, whereas in other cases the upper limit mentioned must be exceeded. In the event of
35 administration of larger amounts, it may be advisable to divide these into a plurality of individual doses over the day.

The invention is illustrated by the working examples below. The invention is not limited to the examples.

- 5 The percentage data in the following tests and examples are percentages by weight unless otherwise indicated; parts are parts by weight. Solvent ratios, dilution ratios and concentration data of liquid/liquid solutions are in each case based on volume.

A. Examples**Abbreviations**

TLC	Thin-Layer Chromatography
DCI	Direct Chemical Ionization (in MS)
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulphoxide
d	day(s)
ee	Enantiomeric excess
eq.	Equivalent(s)
ESI	Electrospray Ionization (in MS)
h	hour(s)
HPLC	High-Pressure, High-Performance Liquid Chromatography
LC-MS	Liquid Chromatography-coupled Mass Spectroscopy
min	minute(s)
MS	Mass Spectroscopy
NMR	Nuclear Magnetic Resonance spectroscopy
RP	Reversed Phase (in HPLC)
RT	Room Temperature
R _t	Retention time (in HPLC)
TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
THF	Tetrahydrofuran

LC-MS and HPLC methods

- 5 Method 1: MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2795; Column: Phenomenex Synergi 2 μ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water + 0.5 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; Gradient: 0.0 min 90% A $\rightarrow$ 2.5 min 30% A $\rightarrow$ 3.0 min 5% A $\rightarrow$ 4.5 min 5% A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV
10 detection: 210 nm.

Method 2: MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 Series; UV DAD; column: Phenomenex Synergi 2 μ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water + 0.5 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90% A $\rightarrow$ 2.5 min 30% A $\rightarrow$ 3.0 min 5% A $\rightarrow$ 4.5 min 5%

A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 3: Instrument: Micromass Quattro LCZ with HPLC Agilent Series 1100; column: Phenomenex Synergi 2 μ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water + 0.5 ml
5 of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90% A $\rightarrow$ 2.5 min 30% A $\rightarrow$ 3.0 min 5% A $\rightarrow$ 4.5 min 5% A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 208-400 nm.

Method 4: Instrument: Micromass Platform LCZ with HPLC Agilent Series 1100; column: Phenomenex Synergi 2 μ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water + 0.5 ml
10 of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90% A $\rightarrow$ 2.5 min 30% A $\rightarrow$ 3.0 min 5% A $\rightarrow$ 4.5 min 5% A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 5: Instrument: Micromass Platform LCZ with HPLC Agilent Series 1100; column: Thermo HyPURITY Aquastar 3 μ 50 mm x 2.1 mm; mobile phase A: 1 l of water + 0.5 ml of 50%
15 strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 100% A $\rightarrow$ 0.2 min 100% A $\rightarrow$ 2.9 min 30% A $\rightarrow$ 3.1 min 10% A $\rightarrow$ 5.5 min 10% A; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 6: MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2795; column: Merck Chromolith SpeedROD RP-18e 50 mm x 4.6 mm; mobile phase A: 1 l of
20 water + 0.5 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 10% B $\rightarrow$ 3.0 min 95% B $\rightarrow$ 4.0 min 95% B; oven: 35°C; flow rate: 0.0 min 1.0 ml/min $\rightarrow$ 3.0 min 3.0 ml/min $\rightarrow$ 4.0 min 3.0 ml/min; UV detection: 210 nm.

Method 7: MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 Series; UV DAD; column: Phenomenex Gemini 3 μ 30 mm x 3.00 mm; mobile phase A: 1 l of water + 0.5 ml
25 of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90%A $\rightarrow$ 2.5 min 30%A $\rightarrow$ 3.0 min 5%A $\rightarrow$ 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min. 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 8: Instrument: Micromass Quattro LCZ with HPLC Agilent Series 1100; column: Phenomenex Gemini 3 μ 30 mm x 3.00 mm; mobile phase A: 1 l of water + 0.5 ml of 50% strength
30 formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90%A $\rightarrow$ 2.5 min 30%A $\rightarrow$ 3.0 min 5%A $\rightarrow$ 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 208- 400 nm.

Method 9: Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm × 2.1 mm, 3.5 µm; mobile phase A: 5 ml of perchloric acid (70% strength) / 1 of water, mobile phase B: acetonitrile; gradient: 0 min 2% B → 0.5 min 2% B → 4.5 min 90% B → 9 min 0% B → 9.2 min 2% B → 10 min 2% B; flow rate: 0.75 ml/min; column temperature: 30°C; UV
5 detection: 210 nm.

Method 10: Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm × 2.1 mm, 3.5 µm; mobile phase A: 5 ml of perchloric acid (70 strength) / 1 of water, mobile phase B: acetonitrile; gradient: 0 min 2% B → 0.5 min 2% B → 4.5 min 90% B → 15 min 90% B → 15.2 min 2% B → 16 min 2% B; flow rate: 0.75 ml/min; column temperature: 30°C; UV
10 detection: 210 nm.

Method 11: Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm × 2.1 mm, 3.5 µm; mobile phase A: 5 ml of perchloric acid (70% strength) / 1 of water, mobile phase B: acetonitrile; gradient: 0 min 2% B → 0.5 min 2% B → 4.5 min 90% B → 6.5 min 90% B → 6.7 min 2% B → 7.5 min 2% B; flow rate: 0.75 ml/min; column temperature: 30°C; UV
15 detection: 210 nm.

Method 12: Instrument: HP 1100 with DAD detection; column: Kromasil C18 60*2; mobile phase A: 0.01 M phosphoric acid, mobile phase B: acetonitrile; gradient: 0 min 90% A → 0.5 min 90% A, → 4.5 min 10% A, → 6.5 min 10% A; flow rate: 0.75 ml/min; column temperature: 30°C; UV
detection: 210 nm.

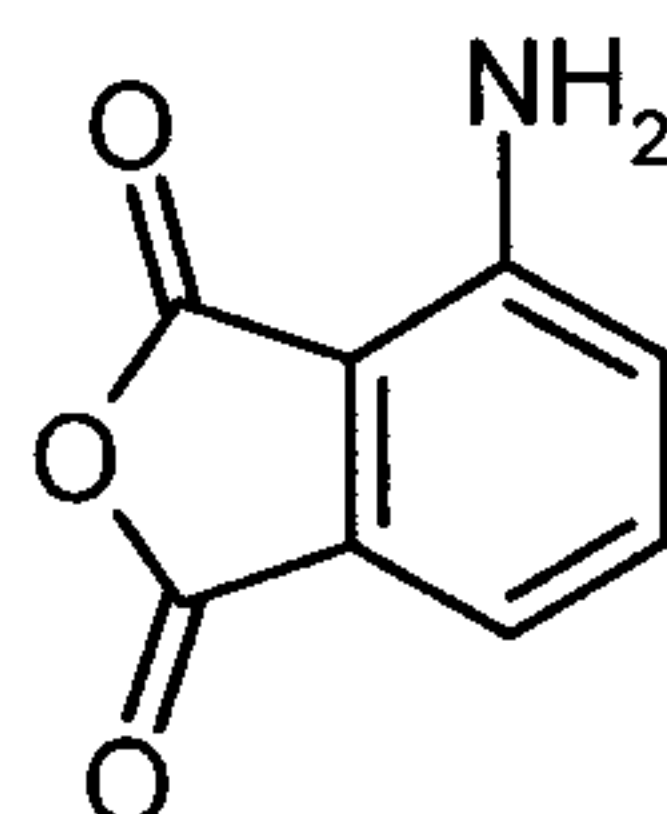
20 Method 13: Instrument: Micromass GCT, GC6890; column: Restek RTX-35, 15 m × 200 µm × 0.33 µm; constant helium flow: 0.88 ml/min; oven: 70°C; inlet: 250°C; gradient: 70°C, 30°C/min → 310°C (maintained for 3 min).

Method 14: Instrument: Micromass Platform LCZ with HPLC Agilent Series 1100; column: Thermo Hypersil GOLD 3µ 20 mm × 4 mm; mobile phase A: 1 l of water + 0.5 ml of 50%
25 strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 5.5 min 10% A; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

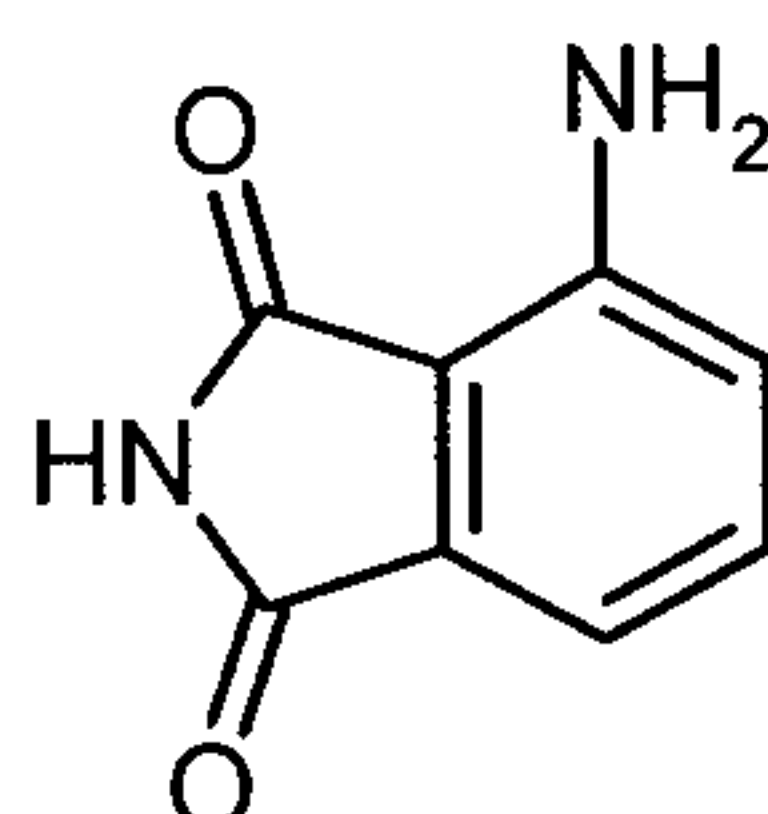
Method 15: Instrument: Micromass Quattro LCZ with HPLC Agilent Series 1100; column: Phenomenex Onyx Monolithic C18, 100 mm × 3 mm; mobile phase A: 1 l of water + 0.5 ml of
30 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90% A → 2 min 65% A → 4.5 min 5% A → 6 min 5% A; flow rate: 2 ml/min; oven: 40°C; UV detection: 208- 400 nm.

Starting materials**Example 1A**

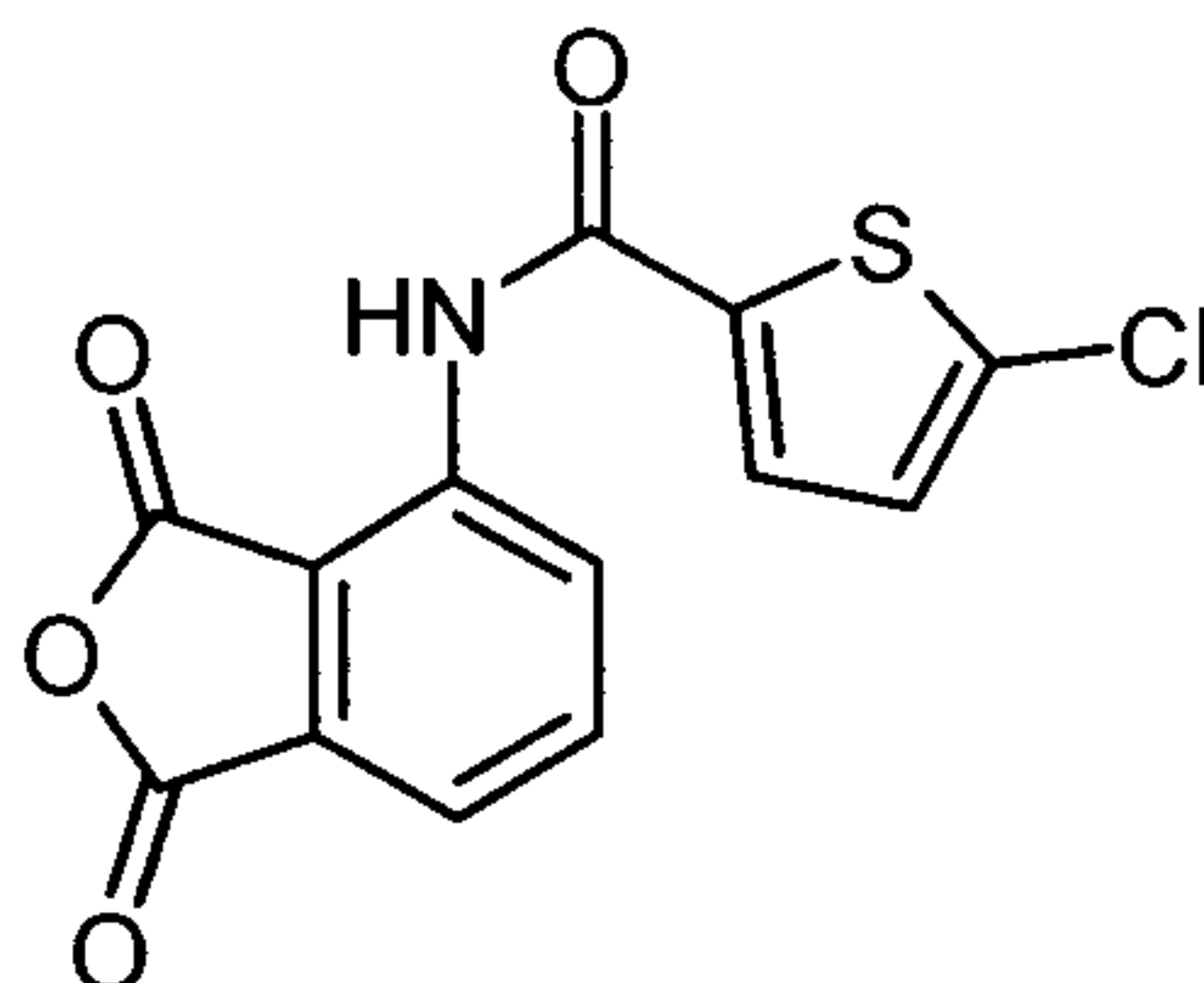
4-Amino-2-benzofuran-1,3-dione



- 5 The preparation of the title compound is carried out analogously to a process known from the literature [E.L. Eliel *et al.*, *J. Am. Chem. Soc.* **1955**, 77, 5092-5094].

Example 2A4-Amino-1*H*-isoindole-1,3(2*H*)-dione

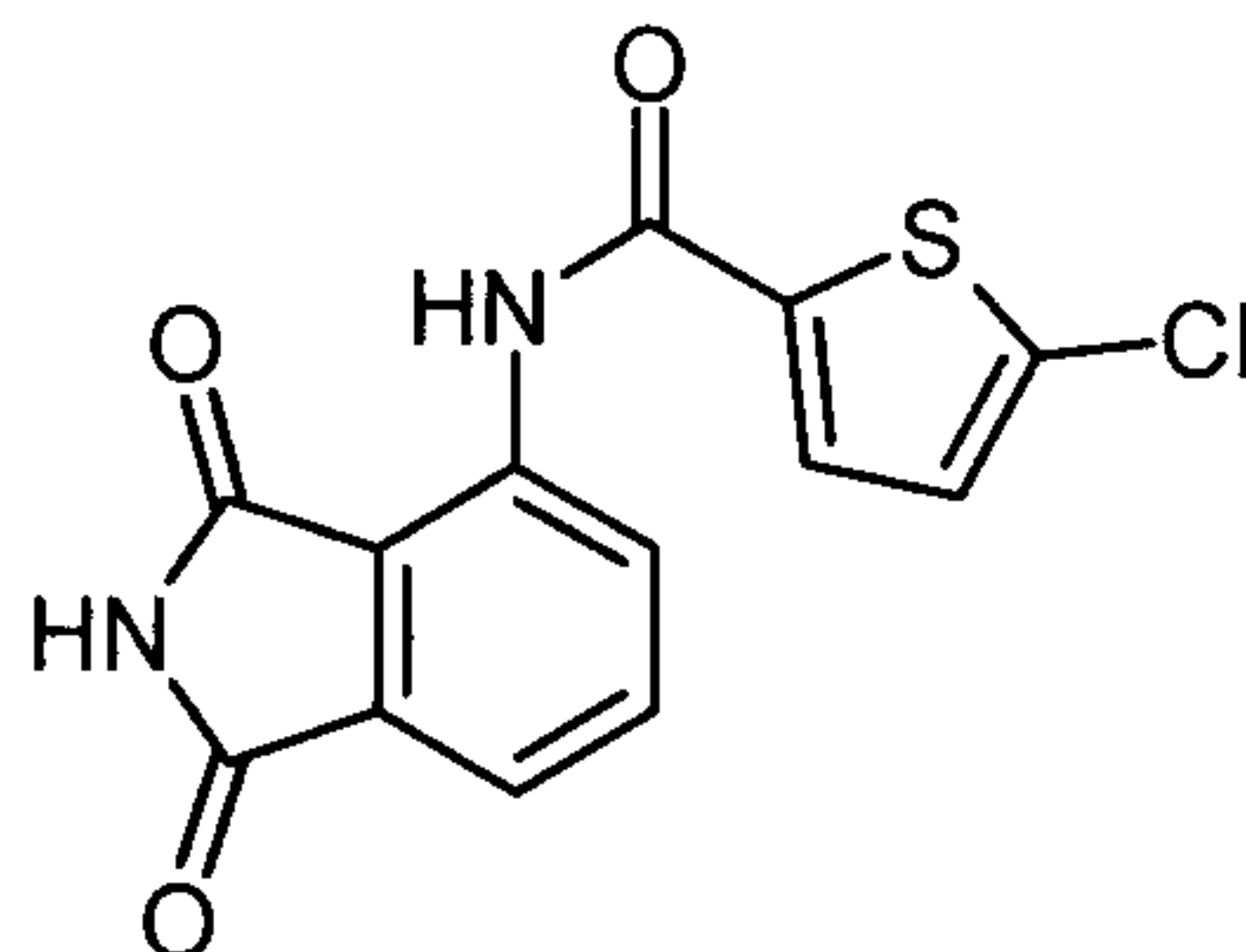
- 10 The preparation of the title compound is carried out analogously to a process known from the literature [H.D.K. Drew, F.H. Pearman, *J. Chem. Soc.* **1937**, 26-33].

Example 3A5-Chloro-*N*-(1,3-dioxo-1,3-dihydro-2-benzofuran-4-yl)thiophene-2-carboxamide

- 15 The preparation of the title compound is carried out analogously to the process described in WO 03/007942 (Example 1).

Example 4A

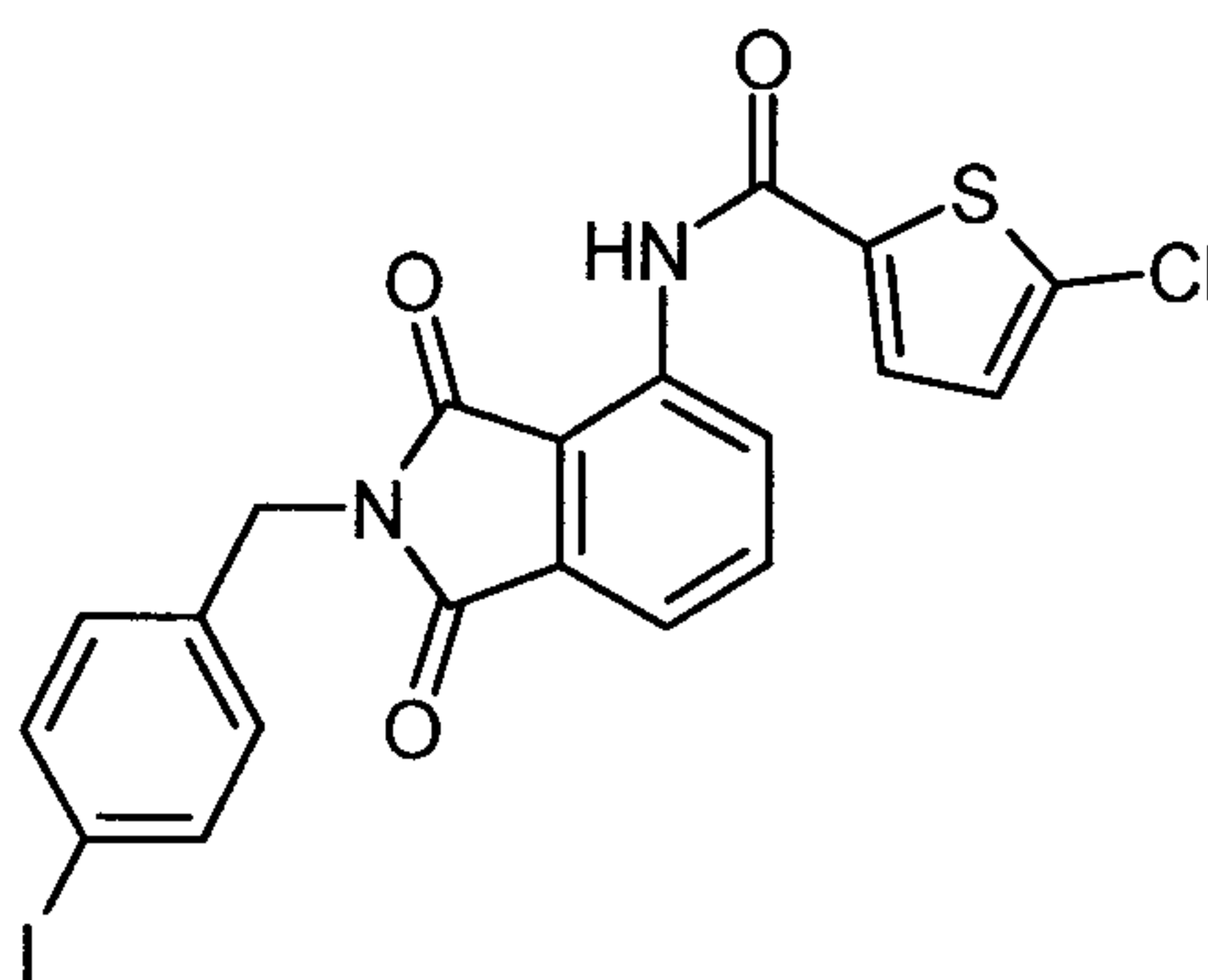
5-Chloro-*N*-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



The preparation of the title compound is carried out analogously to the process described in
 5 WO 03/011858 (Example 1).

Example 5A

5-Chloro-*N*-[2-(4-iodobenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



Under argon and at RT, a solution of 2.1 g (9.0 mmol, 1.3 eq.) of (4-iodophenyl)methanol in 10 ml
 10 of tetrahydrofuran and a solution of 2.3 g of (9.0 mmol, 1.3 eq.) of triphenylphosphine in 10 ml of
 tetrahydrofuran are added to a suspension of 2.1 g (6.9 mmol) of 5-chloro-*N*-(1,3-dioxo-2,3-
 dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide (Example 4A) in 20 ml of tetrahydrofuran.
 The reaction suspension is cooled to 0°C, a solution of 1.4 ml (9.0 mmol, 1.3 eq.) of diethyl
 azodicarboxylate in 10 ml of tetrahydrofuran is added (the suspension turning into a solution) and
 15 the reaction mixture is stirred at RT for 1 h. The reaction mixture is concentrated under reduced
 pressure and the residue is triturated with dichloromethane/water.

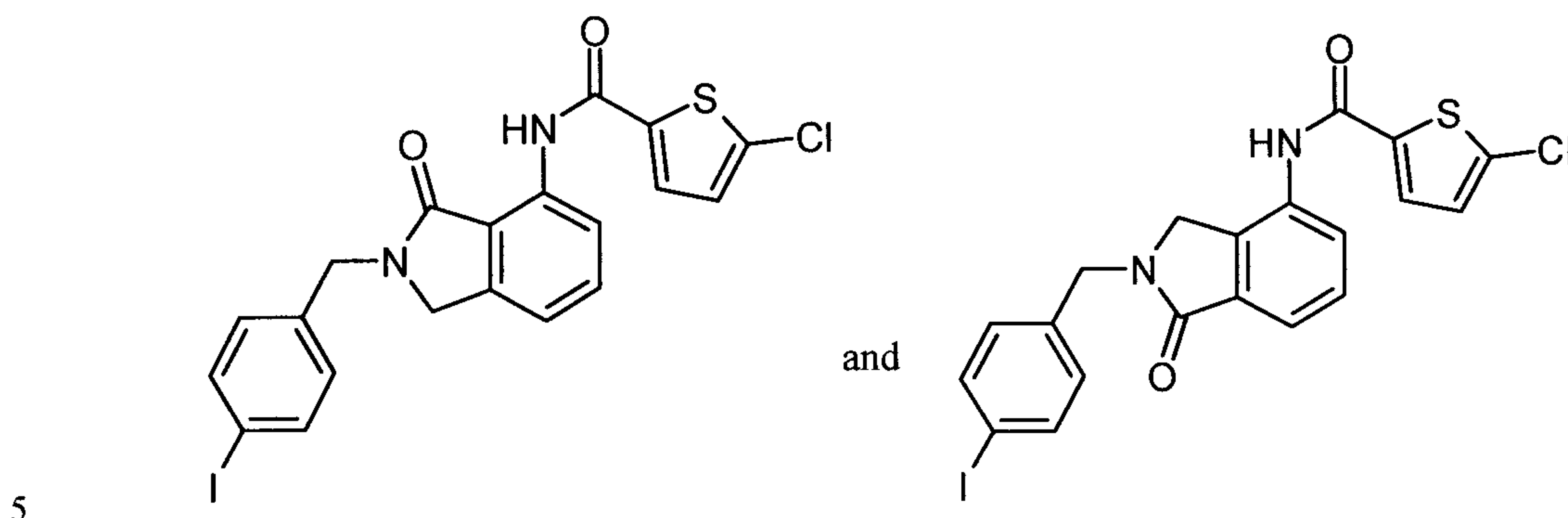
Yield: 2.5 g (70% pure, 49% of theory)

LC-MS (Method 1): $R_t = 3.22$ min;

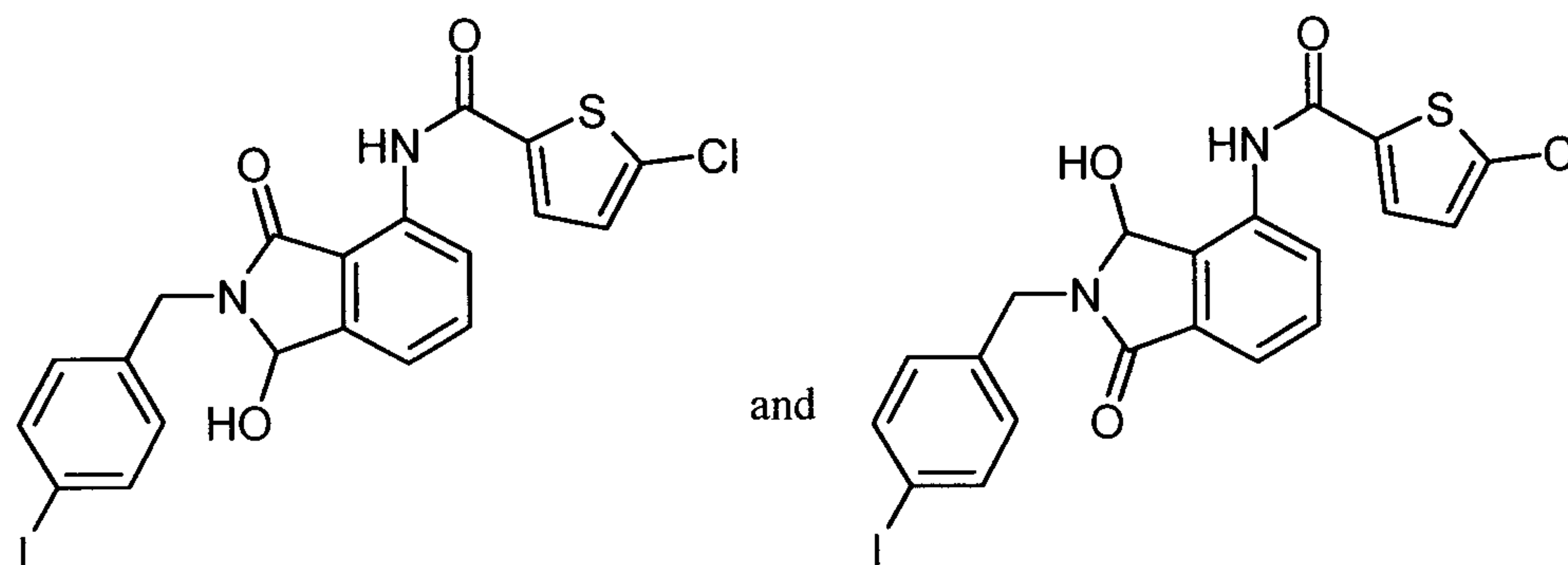
MS (ESIpos): $m/z = 521$ $[M+H]^+$.

Example 6A and Example 7A

5-Chloro-*N*-[2-(4-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 6A) and 5-chloro-*N*-[2-(4-iodobenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 7A)



Step a): Isomer mixture of 5-chloro-*N*-[1-hydroxy-2-(4-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide and 5-chloro-*N*-[3-hydroxy-2-(4-iodobenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



- 10 Under argon and at 0°C, 247 mg (6.5 mmol, 2.2 eq.) of sodium borohydride are added to a solution of 2.3 g (70% pure, 3.0 mmol) of 5-chloro-*N*-[2-(4-iodobenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 5A) in a mixture of 6 ml of methanol and 60 ml of dichloromethane. The reaction mixture is stirred at RT for 1.5 h and adjusted to pH 5 using hydrochloric acid (1 N). The resulting precipitate is filtered off, washed with water and
- 15 dichloromethane and dried under reduced pressure.

Isomer 1:

Yield: 1.5 g (88% pure, 57% of theory)

LC-MS (Method 1): $R_t = 2.93$ min;

MS (ESIpos): $m/z = 525 [M+H]^+$.

After addition of dichloromethane/water in phase separation, the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure.

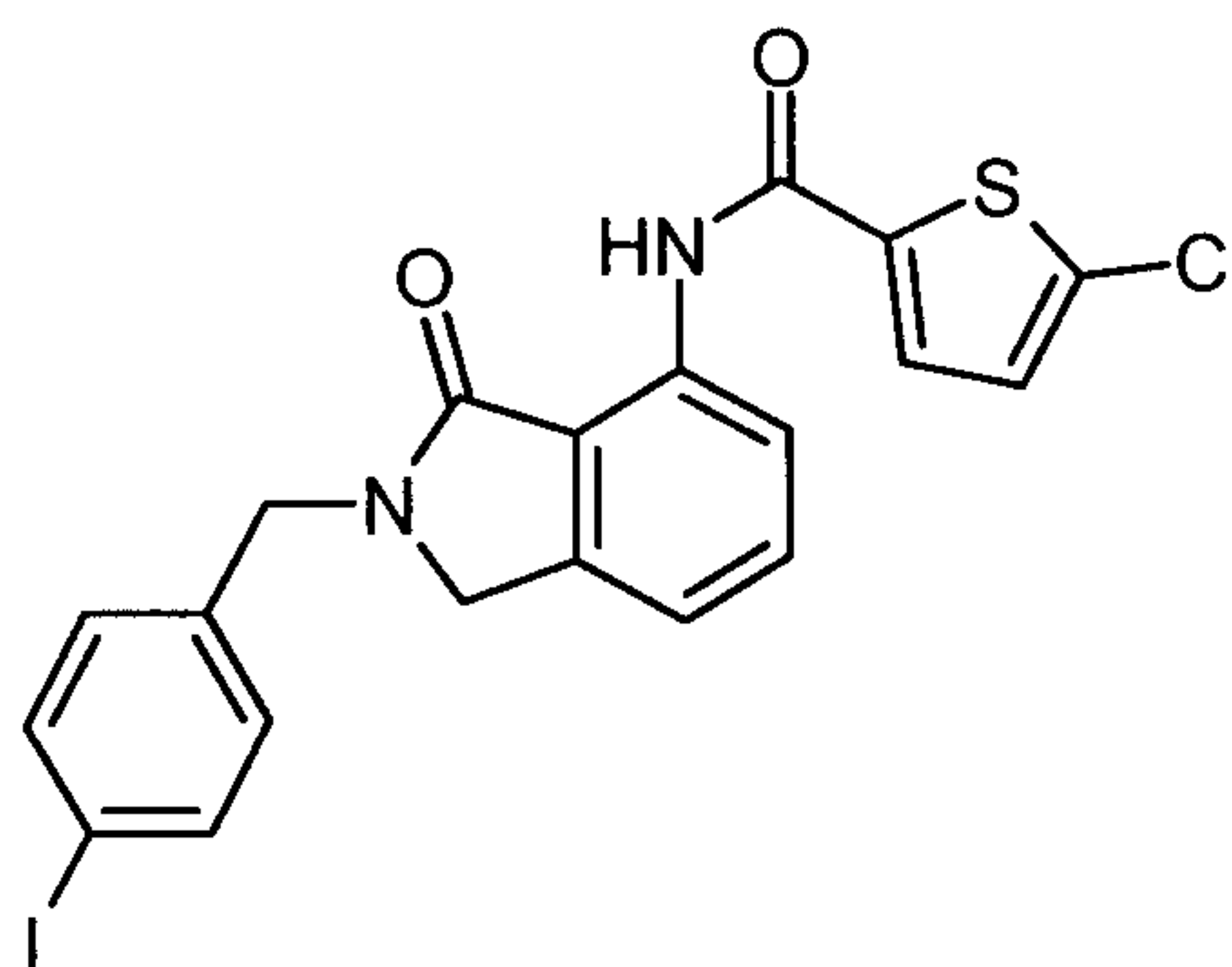
5 Isomer mixture:

Yield: 0.65 g (58% pure, 17% of theory)

LC-MS (Method 1): $R_t = 2.47$ min (Isomer 2) und 2.93 min (Isomer 1);

MS (ESIpos): $m/z = 525 [M+H]^+$.

10 Step b.1): 5-Chloro-*N*-[2-(4-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



Under argon and at RT, 2.7 ml (35.0 mmol, 13 eq.) of trifluoroacetic acid and 0.93 ml (5.8 mmol, 2.2 eq.) of triethylsilane are added dropwise to a suspension of 1.5 g (88% pure, 2.6 mmol) of 5-chloro-*N*-[1-hydroxy-2-(4-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide in 20 ml of dichloromethane. The reaction mixture is stirred at RT for 1 h, and a saturated aqueous sodium bicarbonate solution is added. After addition of dichloromethane and phase separation, the aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure.

Example 6A:

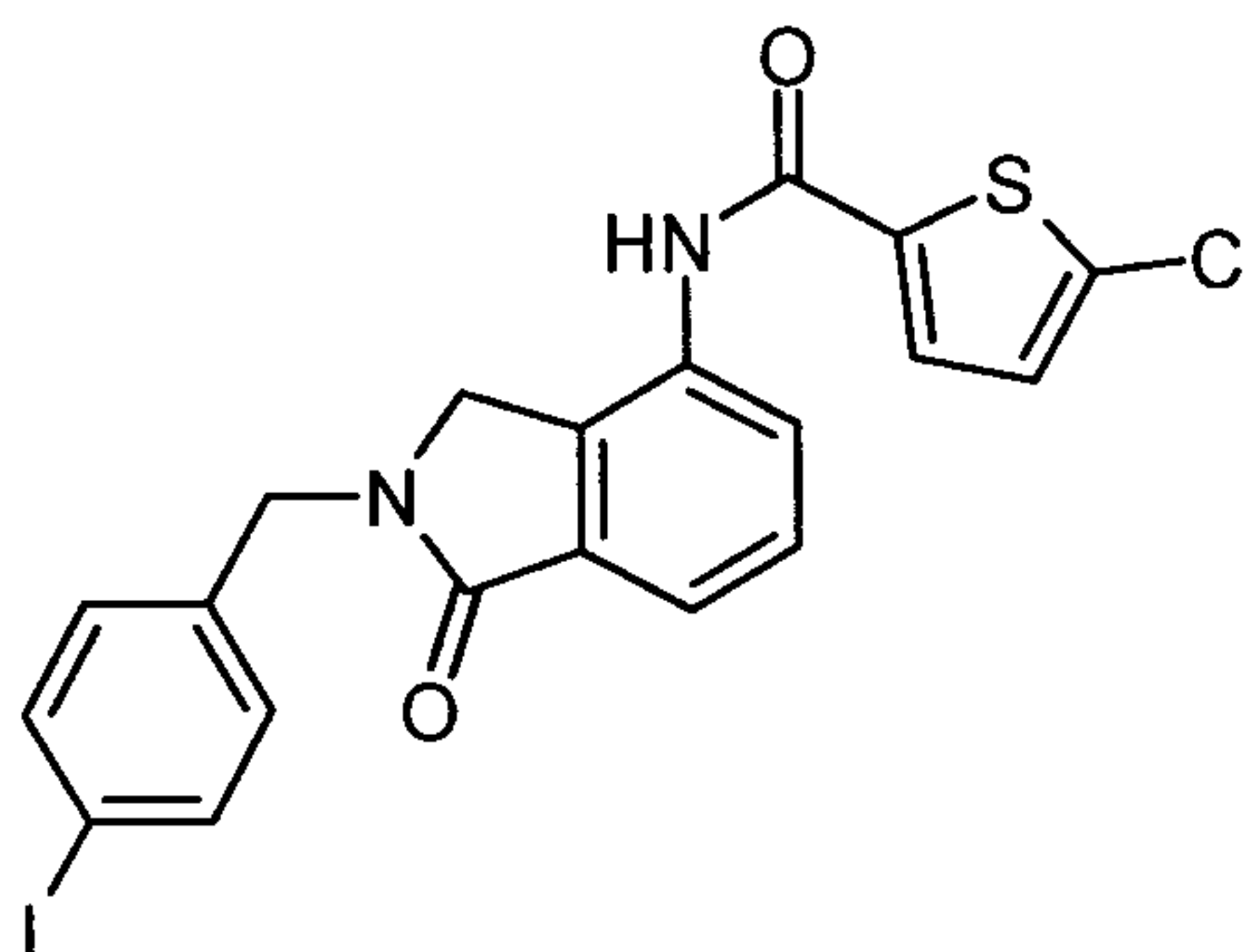
20 Yield: 1.4 g (95% of theory)

LC-MS (Method 3): $R_t = 3.32$ min;

MS (ESIpos): $m/z = 509 [M+H]^+$;

¹H-NMR (400 MHz, DMSO-d₆): δ = 11.27 (s, 1H), 8.25 (d, 1H), 7.72 (d, 2H), 7.64 (d, 1H), 7.59 (t, 1H), 7.33 (d, 1H), 7.28 (d, 1H), 7.13 (d, 2H), 4.71 (s, 2H), 4.43 (s, 2H).

Step b.2): 5-Chloro-*N*-[2-(4-iodobenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



5

Under argon at RT, 1.3 ml (17.0 mmol, 20 eq.) of trifluoroacetic acid and 0.46 ml (2.9 mmol, 3.5 eq.) of triethylsilane are added dropwise to a suspension of 0.75 g (58% pure, 0.83 mmol) of the isomer mixture in 10 ml of dichloromethane. The reaction mixture is stirred at RT for 1 h, and saturated aqueous sodium bicarbonate solution is added. After addition of dichloromethane and phase separation, the aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure. The title compound is isolated by triturating the crude product with dichloromethane/methanol.

10

Example 7A:

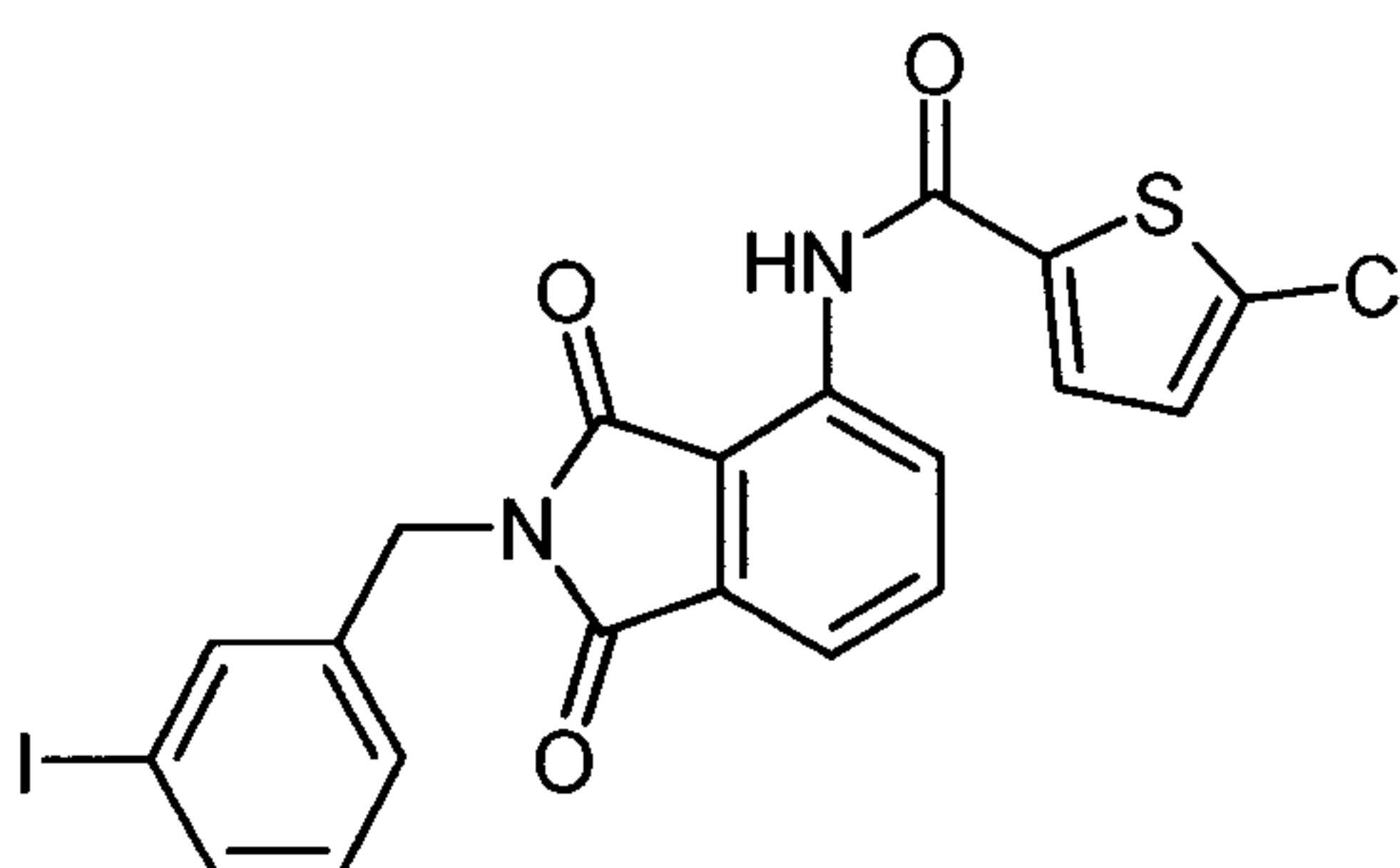
Yield: 149 mg (84% pure, 30% of theory)

15 LC-MS (Method 2): R_t = 2.83 min;

MS (ESIpos): m/z = 509 [M+H]⁺.

Example 8A

5-Chloro-*N*-[2-(3-iodobenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



At RT, 10.3 ml (59.0 mmol, 5 eq.) of *N,N*-diisopropylethylamine are added to a solution of 3.6 g (11.8 mmol) of 5-chloro-*N*-(1,3-dioxo-1,3-dihydro-2-benzofuran-4-yl)thiophene-2-carboxamide (Example 3A) and 2.7 g (11.8 mmol, 1 eq.) of 1-(3-iodophenyl)methanamine in 50 ml of dioxane. The reaction mixture is stirred under reflux for 9 h and cooled in an ice-bath. The resulting precipitate is filtered off, washed with dioxane and dried under reduced pressure. The combined mother liquors are concentrated under reduced pressure. The residue is triturated with acetone and the precipitate is filtered off, washed with acetone and dried under reduced pressure.

Yield: 3.9 g (62% of theory)

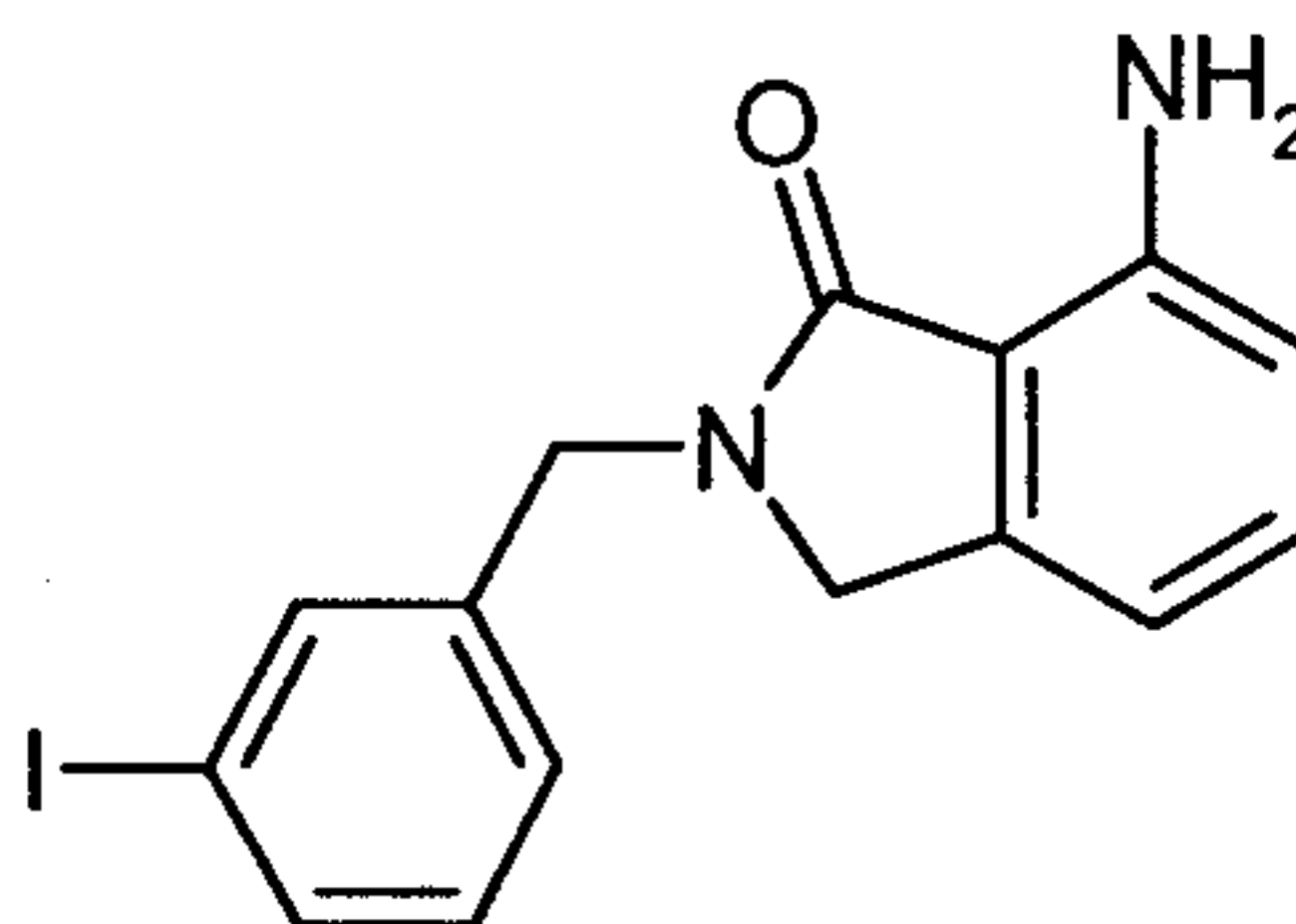
LC-MS (Method 3): $R_t = 3.36$ min;

10 MS (ESIpos): $m/z = 523$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 10.40$ (s, 1H), 8.33 (d, 1H), 7.87 (t, 1H), 7.80 (d, 1H), 7.72 (s, 1H), 7.67 (2xd, 2H), 7.37 (d, 1H), 7.34 (d, 1H), 7.15 (t, 1H), 4.73 (s, 2H).

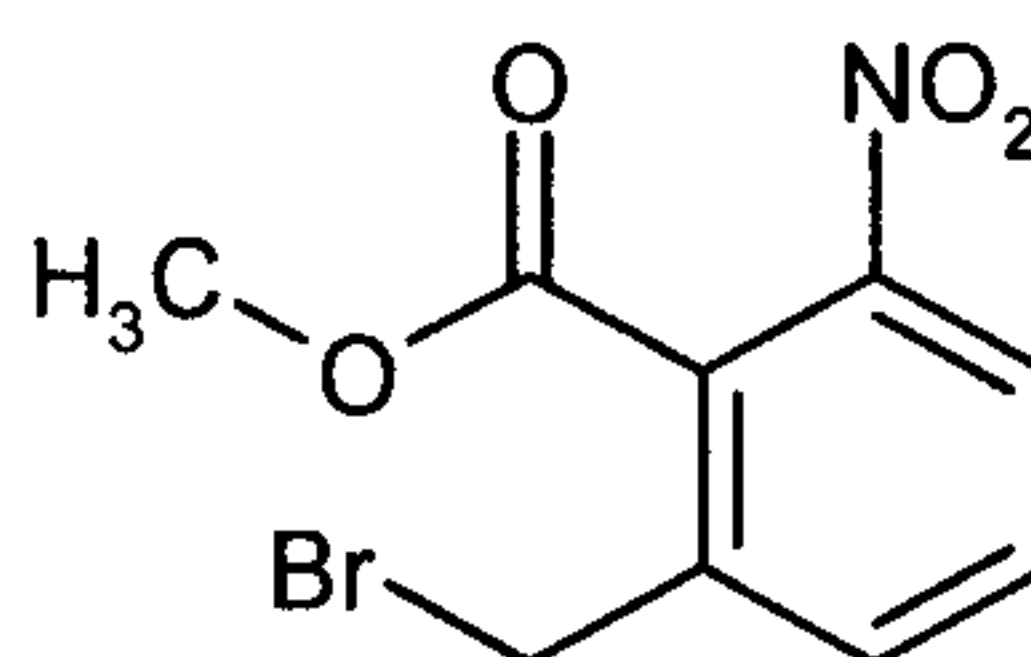
Example 9A

7-Amino-2-(3-iodobenzyl)isoindolin-1-one



15

Step a): Methyl 2-(bromomethyl)-6-nitrobenzoate



20

13.98 g (78.54 mmol) of *N*-bromosuccinimide (NBS) and 129 mg (0.79 mmol) of 2,2'-azobis-2-methylpropanenitrile (AIBN) are added to a solution of 15.33 g (78.54 mmol) of methyl 2-methyl-6-nitrobenzoate in 300 ml of carbon tetrachloride, and the mixture is heated at reflux. After 15 h and after a further 24 h of reaction time, in each case a further 13.98 g (78.54 mmol) of NBS are added. After a total reaction time of 111 h, the reaction mixture is allowed to cool to RT, insoluble material is filtered off and the solvent is removed on a rotary evaporator. The residue is purified by

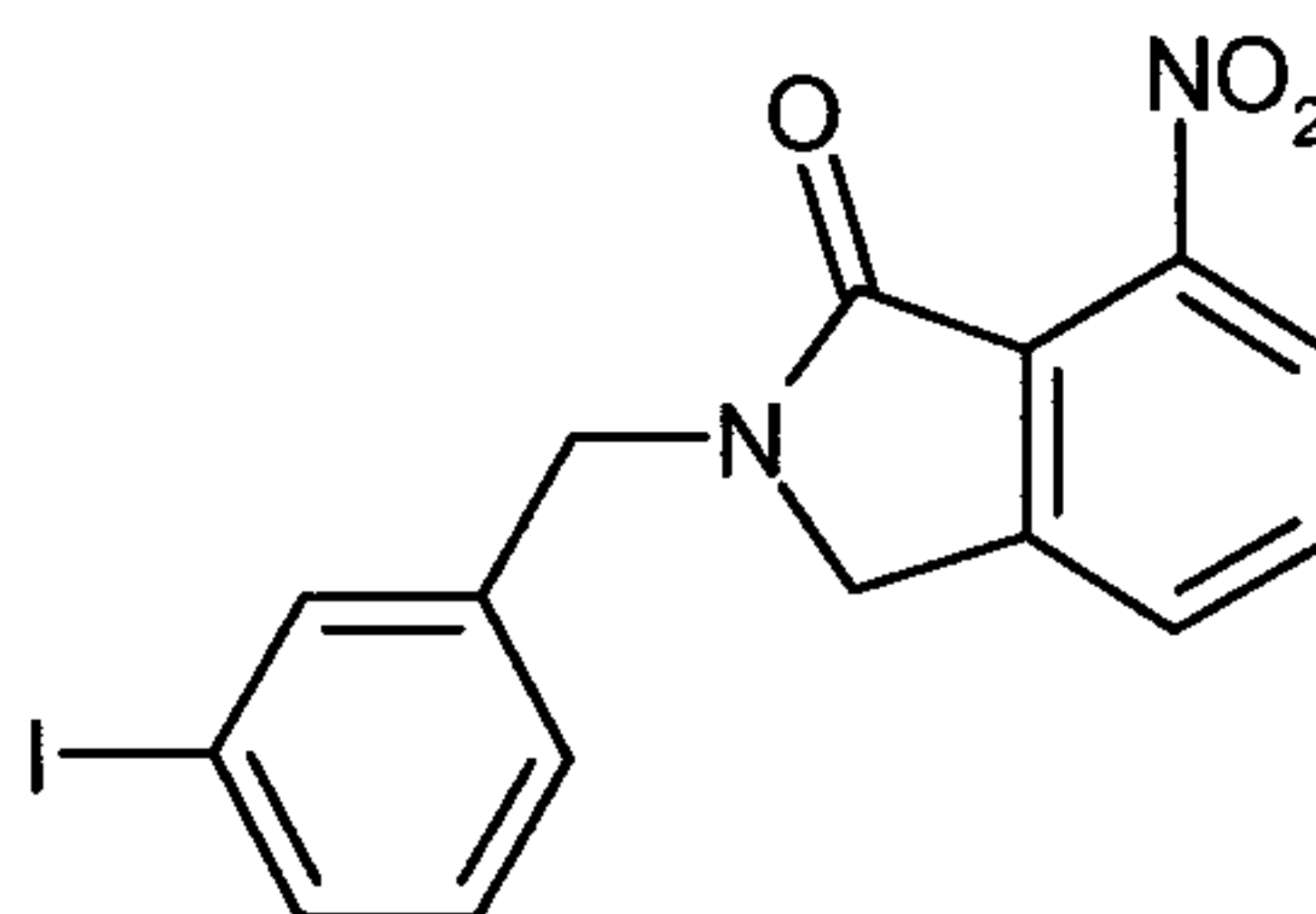
flash chromatography (silica gel, cyclohexane/dichloromethane 2:1). This gives two fractions. The first consists of 7.7 g (28% yield) of methyl 2-(dibromomethyl)-6-nitrobenzoate and the second of 12.82 g (60% yield) of the title compound.

GC/MS (Method 13): $R_t = 6.58$ min;

5 MS (TOF, EI): $m/z = 273/275$ ($^{79}\text{Br}/^{81}\text{Br}$, M^+);

$^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 8.08$ (d, 1H), 7.77 (d, 1H), 7.59 (dd, 1H), 4.58 (s, 2H), 3.99 (s, 3H).

Step b): 2-(3-Iodobenzyl)-7-nitroisindolin-1-one



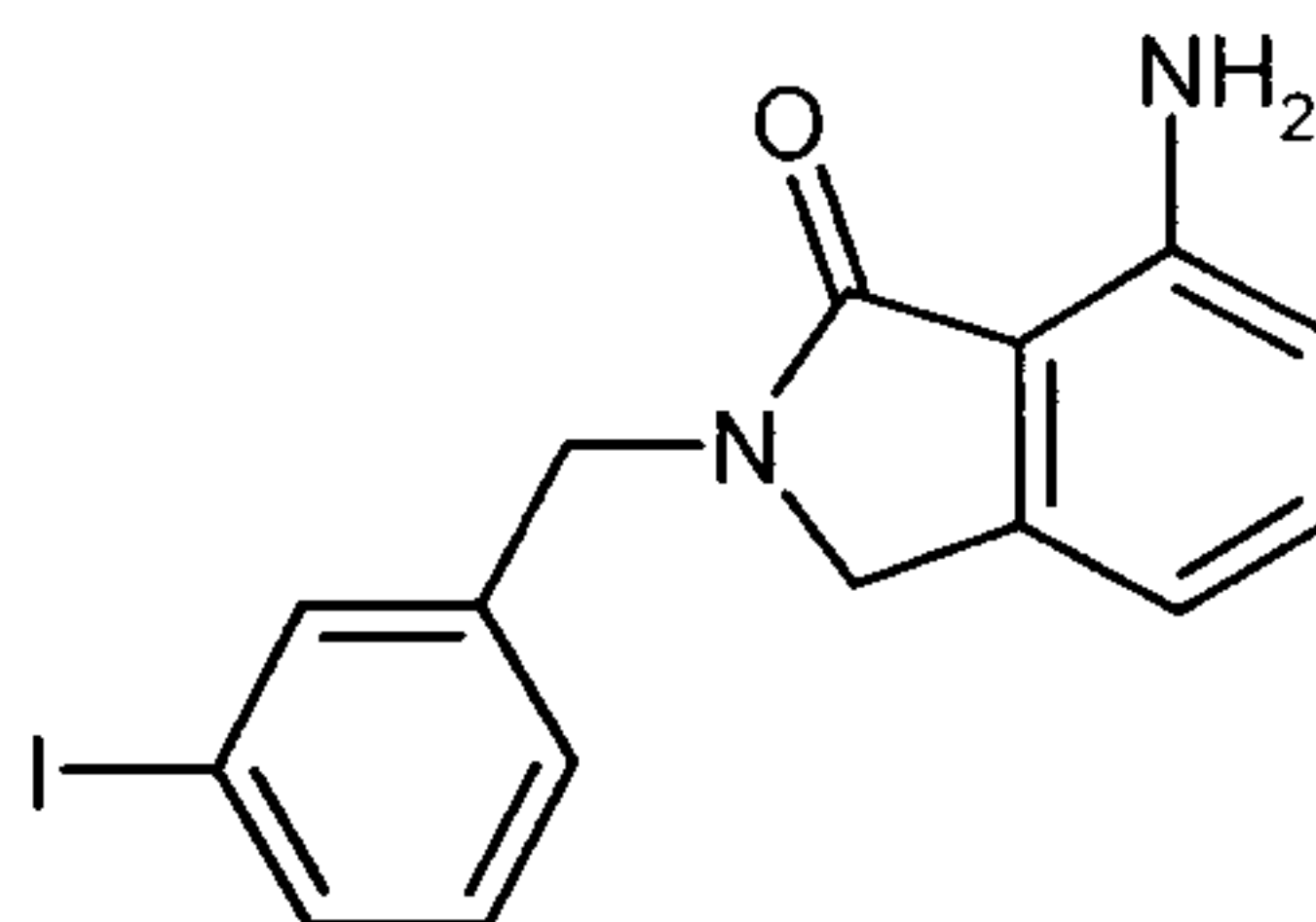
10 549 mg (2.36 mmol) of 1-(3-iodophenyl)methanamine and 630 μl (4.49 mmol) of triethylamine are added successively to a solution of 615 mg (2.24 mmol) of methyl 2-(bromomethyl)-6-nitrobenzoate in 5 ml of *N,N*-dimethylformamide. After 15 h of stirring at 80°C, about 25 ml of water are added and the mixture is extracted three times with dichloromethane. The combined organic extracts are washed successively with water and saturated sodium chloride solution. After
15 drying over anhydrous sodium sulphate, the mixture is filtered and the filtrate is freed from the solvent under reduced pressure. The residue obtained is purified by filtration with suction on silica gel using the mobile phase dichloromethane/methanol 100:0 $\rightarrow$ 100:1. This gives 0.83 g (84% yield, based on a purity of 90%) of the title compound.

HPLC (Method 8): $R_t = 2.79$ min;

20 MS (ESIpos): $m/z = 395$ ($\text{M}+\text{H}^+$);

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 7.91$ (d, 1H), 7.87 (d, 1H), 7.81 (dd, 1H), 7.70 (d, 1H), 7.67 (dd, 1H), 7.32 (d, 1H), 7.18 (dd, 1H), 4.68 (s, 2H), 4.50 (s, 2H).

Step c): 7-Amino-2-(3-iodobenzyl)isoindolin-1-one



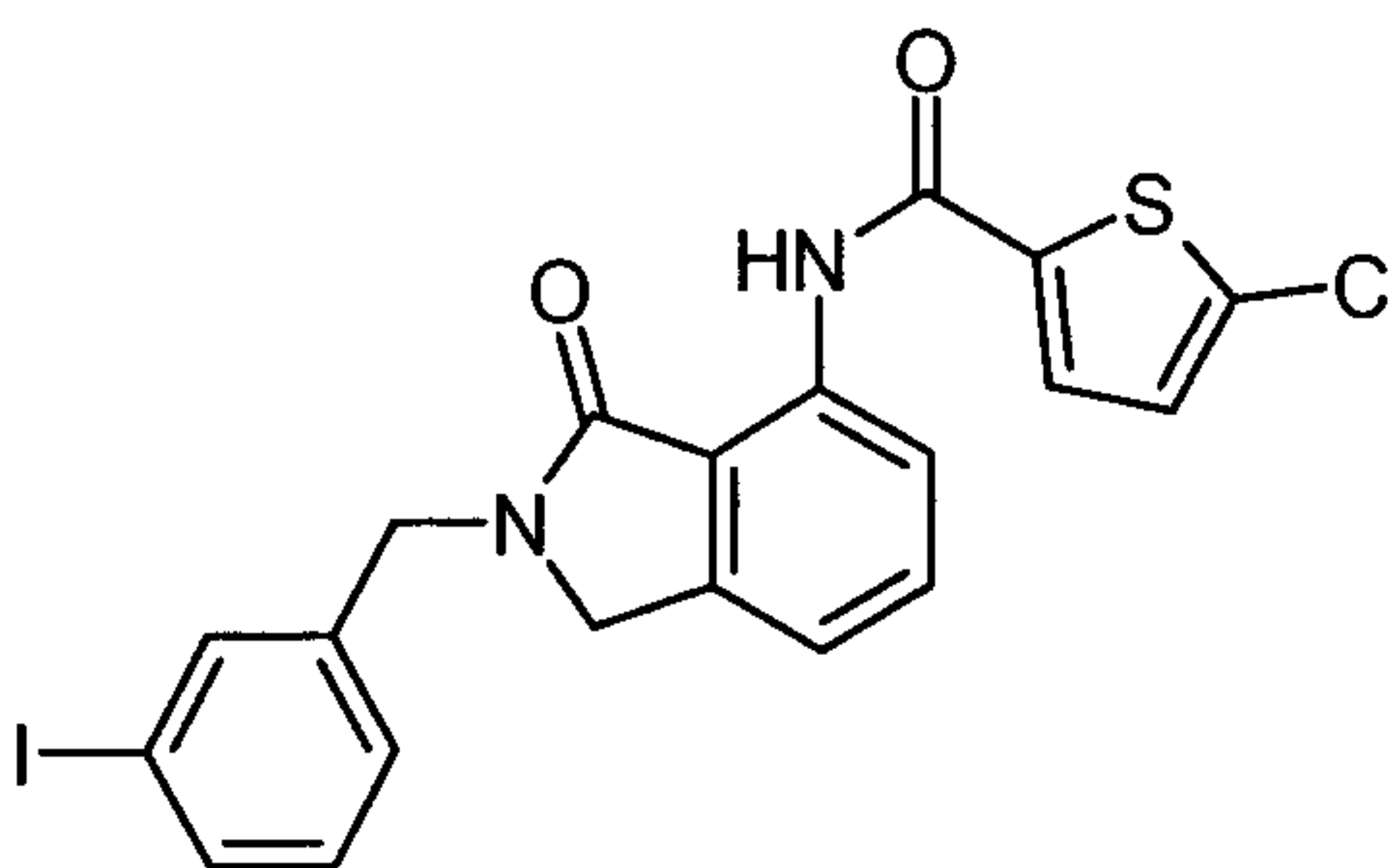
2.38 g (10.53 mmol) of tin(II)chloride dihydrate are added to a solution of 830 mg (2.11 mmol) of 2-(3-iodobenzyl)-7-nitroisoindolin-1-one in 15 ml of ethanol, and the mixture is heated at 70°C for 75 min. The reaction mixture is then poured into ice-water, adjusted to pH 8 using sodium bicarbonate solution and filtered through Celite. The filtercake is washed with ethyl acetate, the phases are separated and the aqueous phase is evaporated to dryness. The residue of the aqueous phase is combined with the Celite filter material and triturated with hot ethanol. After filtration, the ethanol is removed on a rotary evaporator. This gives 671 mg (87% yield) of the title compound which is reacted further without further purification.

HPLC (Method 7): $R_t = 2.71$ min;

MS (ESIpos): $m/z = 365$ (M+H)⁺.

Example 10A

5-Chloro-*N*-[2-(3-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide

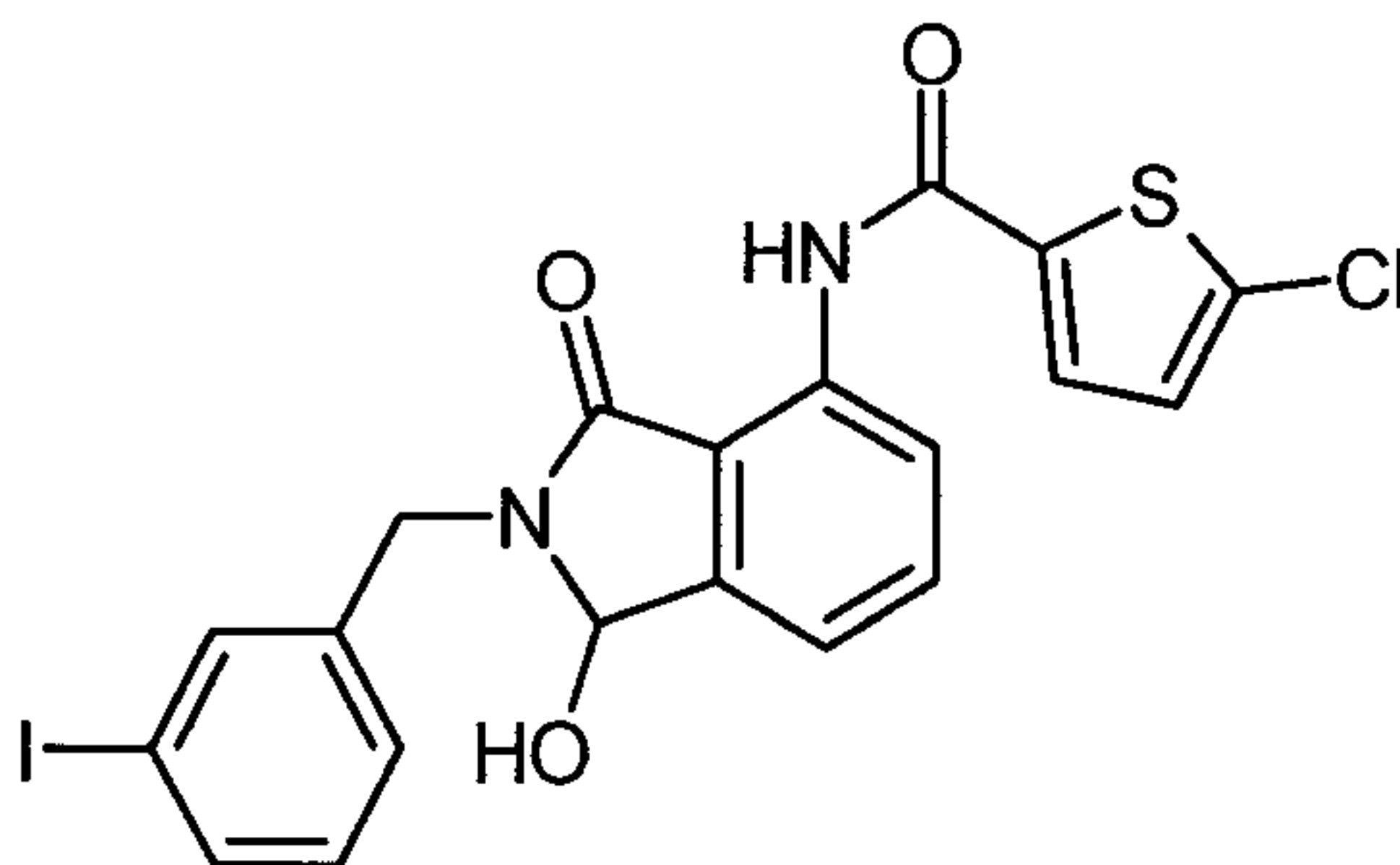


15

Method 1: Preparation from 5-chloro-*N*-[2-(3-iodobenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 8A)

Step a): 5-Chloro-*N*-[1-hydroxy-2-(3-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide

- 53 -



Under argon and at 0°C, 398 mg (10.5 mmol, 1.5 eq.) of sodium borohydride are added to a solution of 3.7 g (7.0 mmol) of 5-chloro-*N*-[2-(3-iodobenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 8A) in a mixture of 8 ml of methanol and 80 ml of dichloromethane. The reaction mixture is stirred at RT for 1 h and adjusted to pH 5 using hydrochloric acid (1 N). The resulting precipitate is filtered off, washed with water and dichloromethane and dried under reduced pressure.

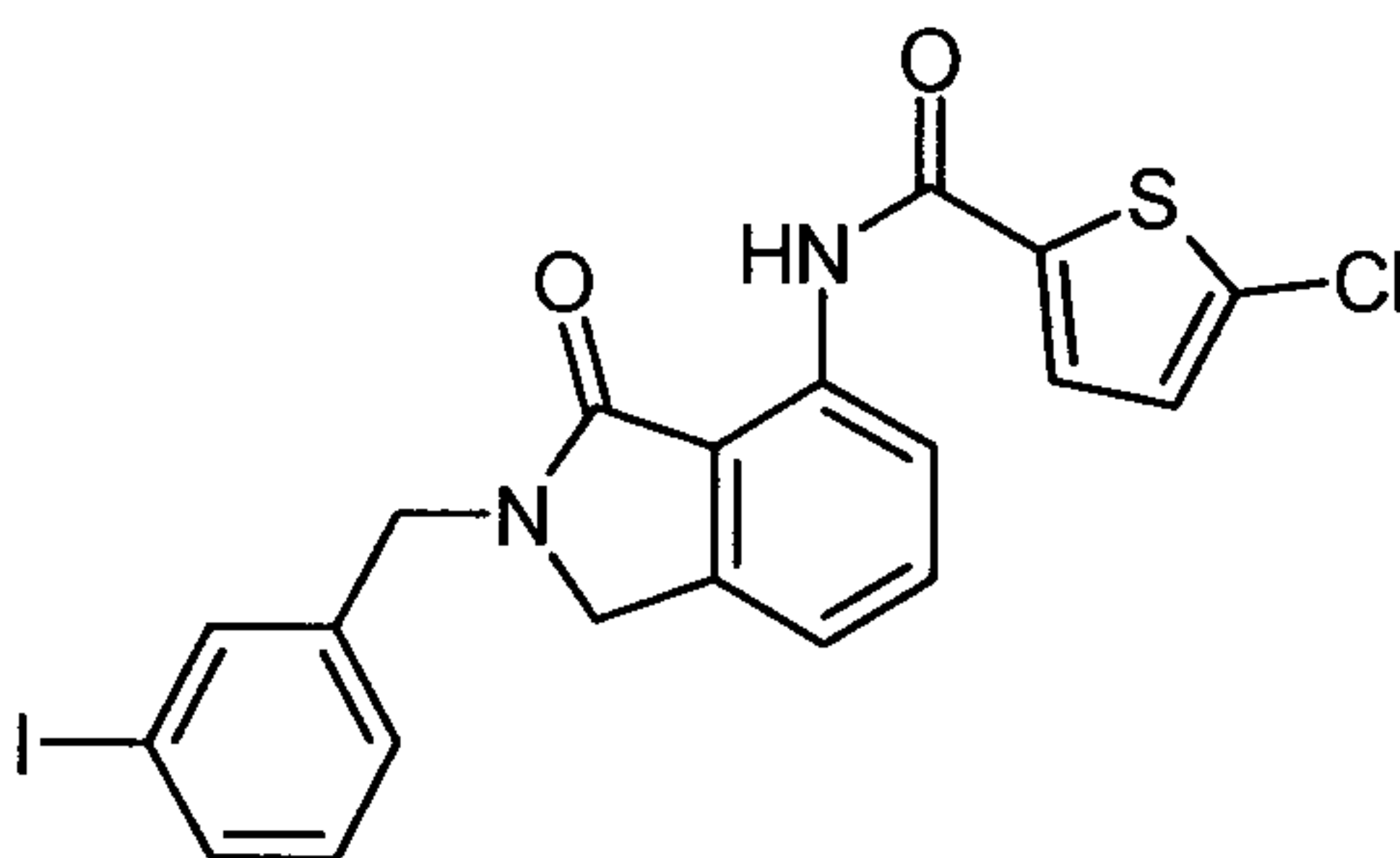
Yield: 2.3 g (61% of theory)

LC-MS (Method 3): $R_t = 3.10$ min;

10 MS (ESIpos): $m/z = 525$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.00$ (s, 1H), 8.30 (d, 1H), 7.74 (s, 1H), 7.69-7.61 (m, 3H), 7.37 (d, 1H), 7.35-7.30 (m, 2H), 7.15 (t, 1H), 7.00 (d, 1H), 5.80 (d, 1H), 4.80 (d, 1H), 4.43 (d, 1H).

Step b): 5-Chloro-*N*-[2-(3-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



15

Under argon and at RT, 4.0 ml (51.5 mmol, 12 eq.) of trifluoroacetic acid and 1.4 ml (8.6 mmol, 2 eq.) of triethylsilane are added dropwise to a suspension of 2.3 g (4.3 mmol) of 5-chloro-*N*-[1-hydroxy-2-(3-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide in 30 ml of dichloromethane. The reaction mixture is stirred at RT for 20 h, and saturated aqueous sodium bicarbonate solution is added. After addition of dichloromethane and phase separation, the

20

aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are washed with saturated aqueous sodium chloride solution, dried over sodium sulphate, filtered and concentrated under reduced pressure.

Yield: 1.5 g (97% of theory)

5 LC-MS (Method 3): $R_t = 3.33$ min;

MS (ESIpos): $m/z = 509$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.23$ (s, 1H), 8.27 (d, 1H), 7.71 (s, 1H), 7.68 (d, 1H), 7.65 (d, 1H), 7.61 (t, 1H), 7.33 (d, 2H), 7.29 (d, 1H), 7.19 (t, 1H), 4.73 (s, 2H), 4.46 (s, 2H).

Method 2: Preparation from 7-amino-2-(3-iodobenzyl)isoindolin-1-one (Example 9A)

10 352 μl (2.53 mmol) of triethylamine and a solution of 419 mg (2.32 mmol) of 5-chlorothiophenecarbonyl chloride are added to a solution of 767 mg (2.11 mmol) of 7-amino-2-(3-iodobenzyl)isoindolin-1-one (Example 9A) in 20 ml of anhydrous dichloromethane. The reaction mixture is stirred at RT for 15 h. The mixture is then diluted with further dichloromethane and washed successively with water and saturated sodium chloride solution. After drying over
15 anhydrous sodium sulphate, the mixture is filtered and the filtrate is freed from the solvent under reduced pressure. The residue obtained is purified by filtration with suction over silica gel using the mobile phase cyclohexane/ethyl acetate at 5:1. This gives 538 mg (50% yield) of the title compound.

HPLC (Method 1): $R_t = 3.18$ min;

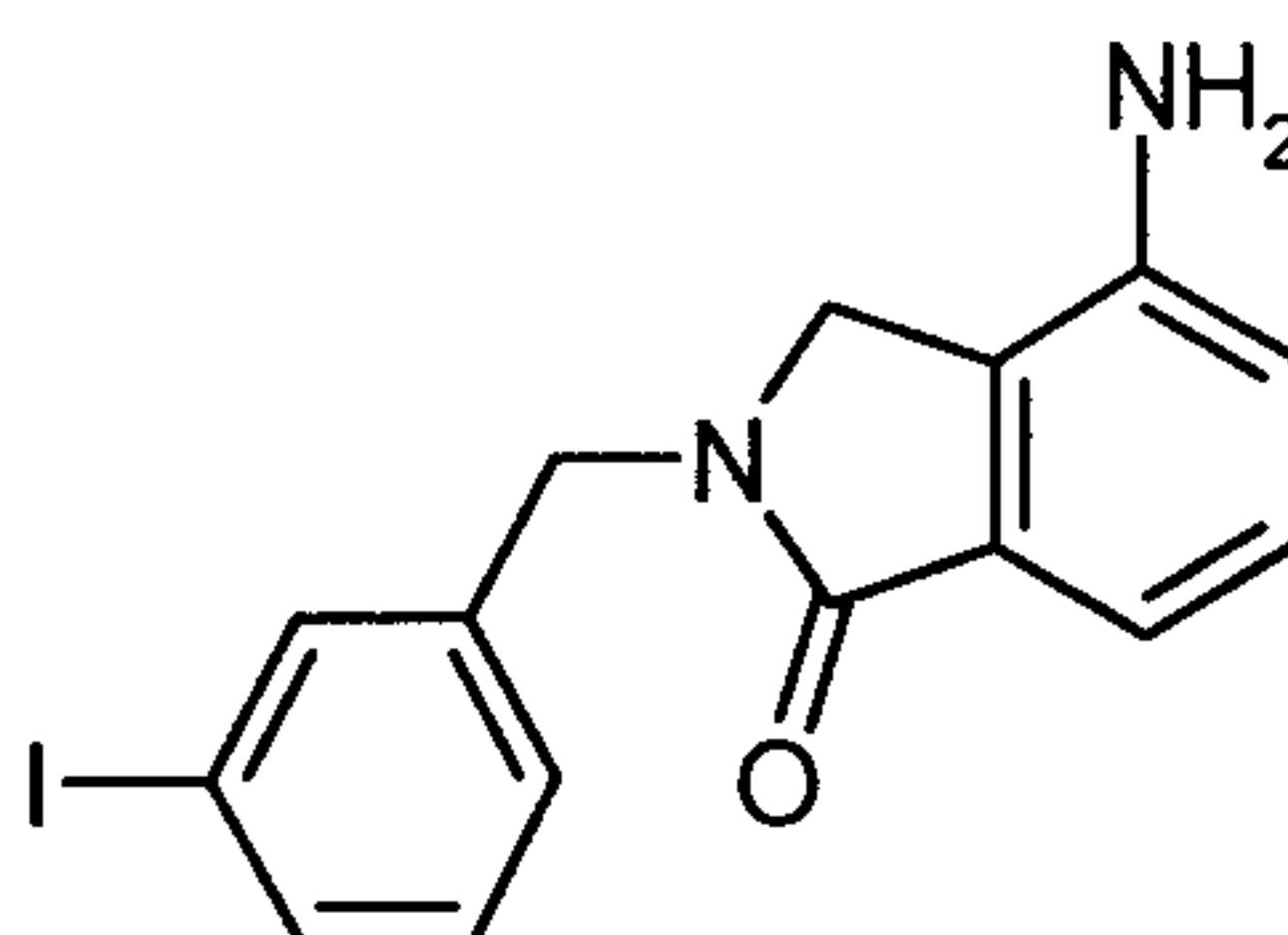
20 MS (ESIpos): $m/z = 509/511$ ($^{35}\text{Cl}/^{37}\text{Cl}$, $M+H$) $^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.25$ (s, 1H), 8.26 (d, 1H), 7.71 (s, 1H), 7.68 (d, 1H), 7.66 (d, 1H), 7.61 (dd, 1H), 7.33 (d, 1H), 7.32 (d, 1H), 7.29 (d, 1H), 7.18 (dd, 1H), 4.73 (s, 2H), 4.47 (s, 2H).

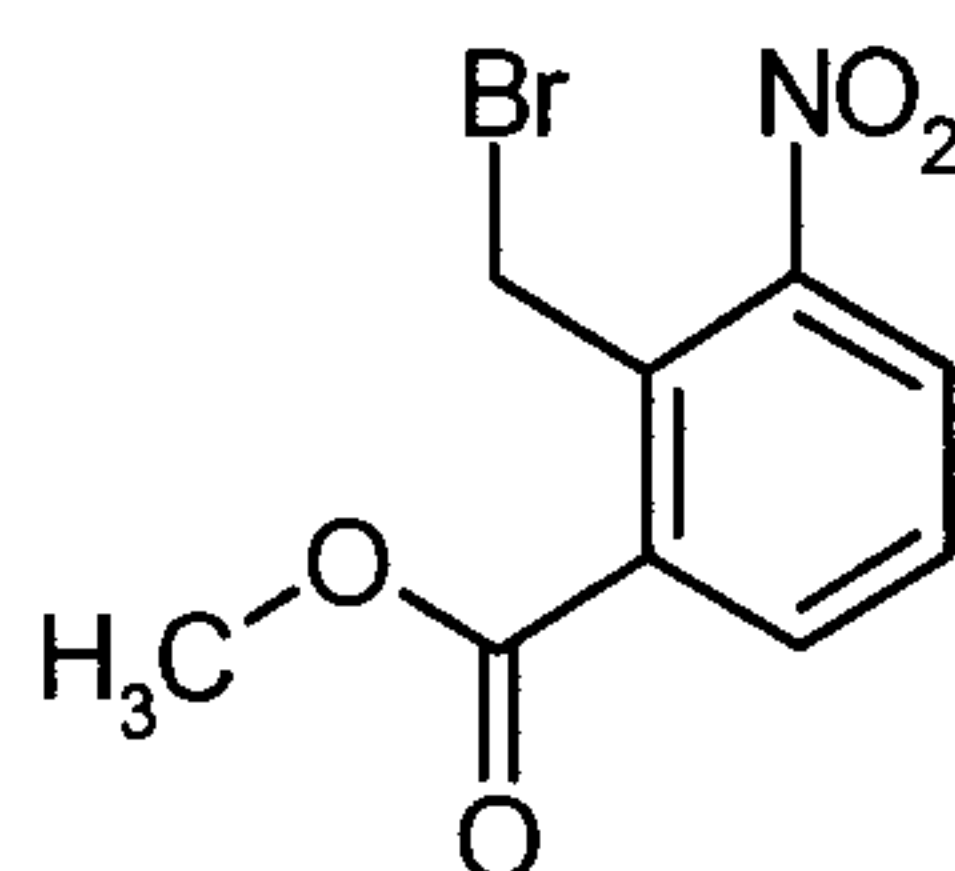
Example 11A

25 4-Amino-2-(3-iodobenzyl)isoindolin-1-one

- 55 -



Step a): Methyl 2-(bromomethyl)-3-nitrobenzoate



A solution of 21 g (109 mmol) of methyl 2-methyl-3-nitrobenzoate in 300 ml of carbon tetrachloride is stirred under reflux, 23 g (130 mmol, 1.2 eq.) of *N*-bromosuccinimide and 1.8 g (11 mmol, 0.1 eq.) of 2,2'-azobis-2-methylpropanenitrile are added and the mixture is stirred under reflux overnight. After cooling to RT, the reaction mixture is diluted with dichloromethane, washed repeatedly with water, dried over sodium sulphate, filtered and concentrated under reduced pressure.

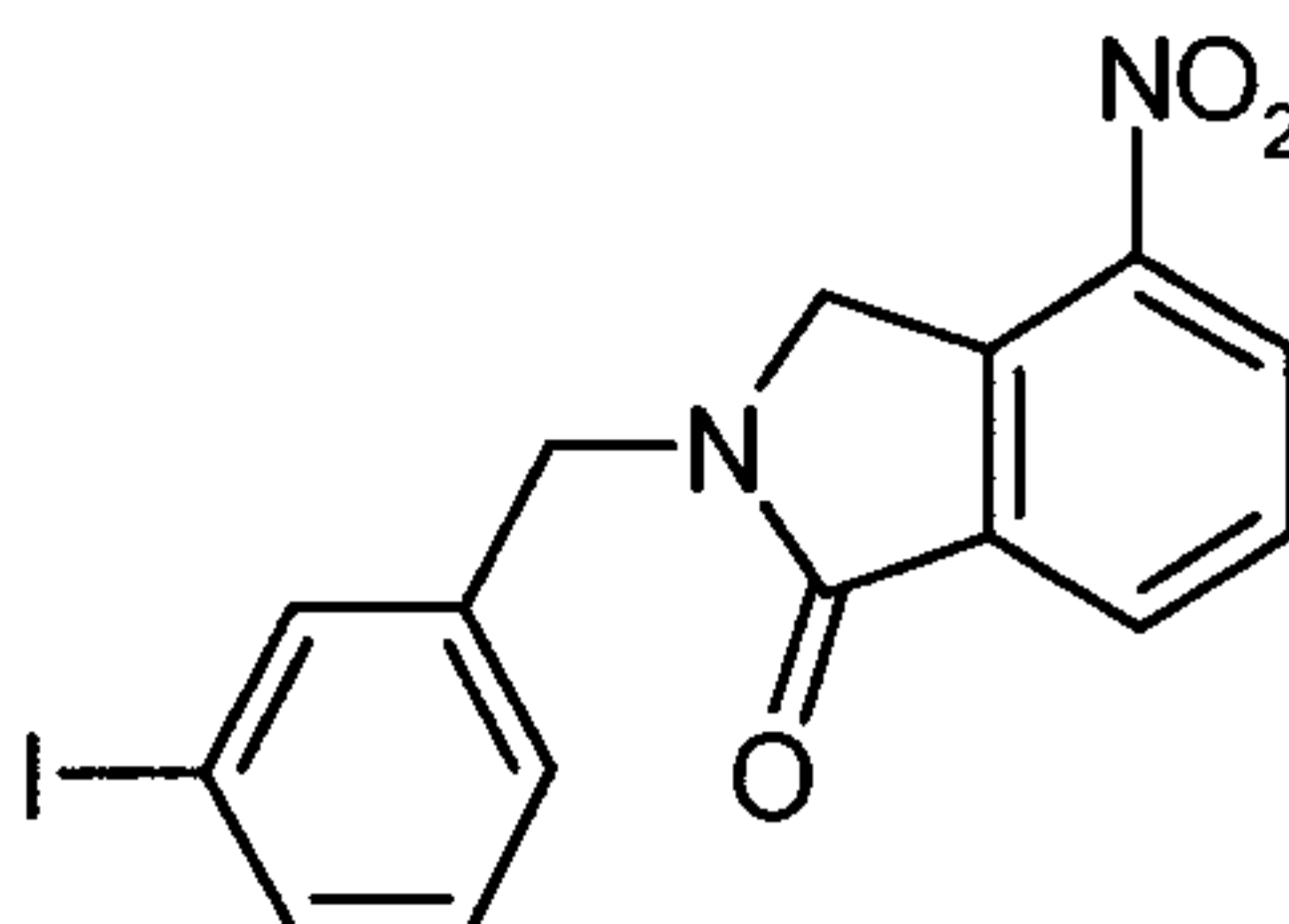
10 Yield: 31 g (quantitative)

HPLC (Method 12): $R_t = 4.33$ min;

MS (ESIpos): $m/z = 273$ $[M+H]^+$;

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 8.16$ (d, 1H), 8.11 (d, 1H), 7.74 (t, 1H), 5.03 (s, 2H), 3.92 (s, 3H).

15 Step b): 2-(3-Iodobenzyl)-4-nitroisoindolin-1-one



At RT, 1.3 ml (9.1 mmol, 1.1 eq.) of triethylamine are added to a solution of 2.3 g (8.2 mmol) of methyl 2-(bromomethyl)-3-nitrobenzoate and 1.9 g (8.2 mmol, 1 eq.) of 1-(3-

iodophenyl)methanamine in 40 ml of methanol. The reaction mixture is stirred under reflux for 3 h. After cooling to RT, saturated aqueous ammonium chloride solution is added to the reaction mixture. Following the addition of dichloromethane and phase separation, the aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are dried over magnesium sulphate, filtered and concentrated under reduced pressure. The title compound is isolated by flash chromatography (silica gel, dichloromethane/cyclohexane 2:1 → dichloromethane).

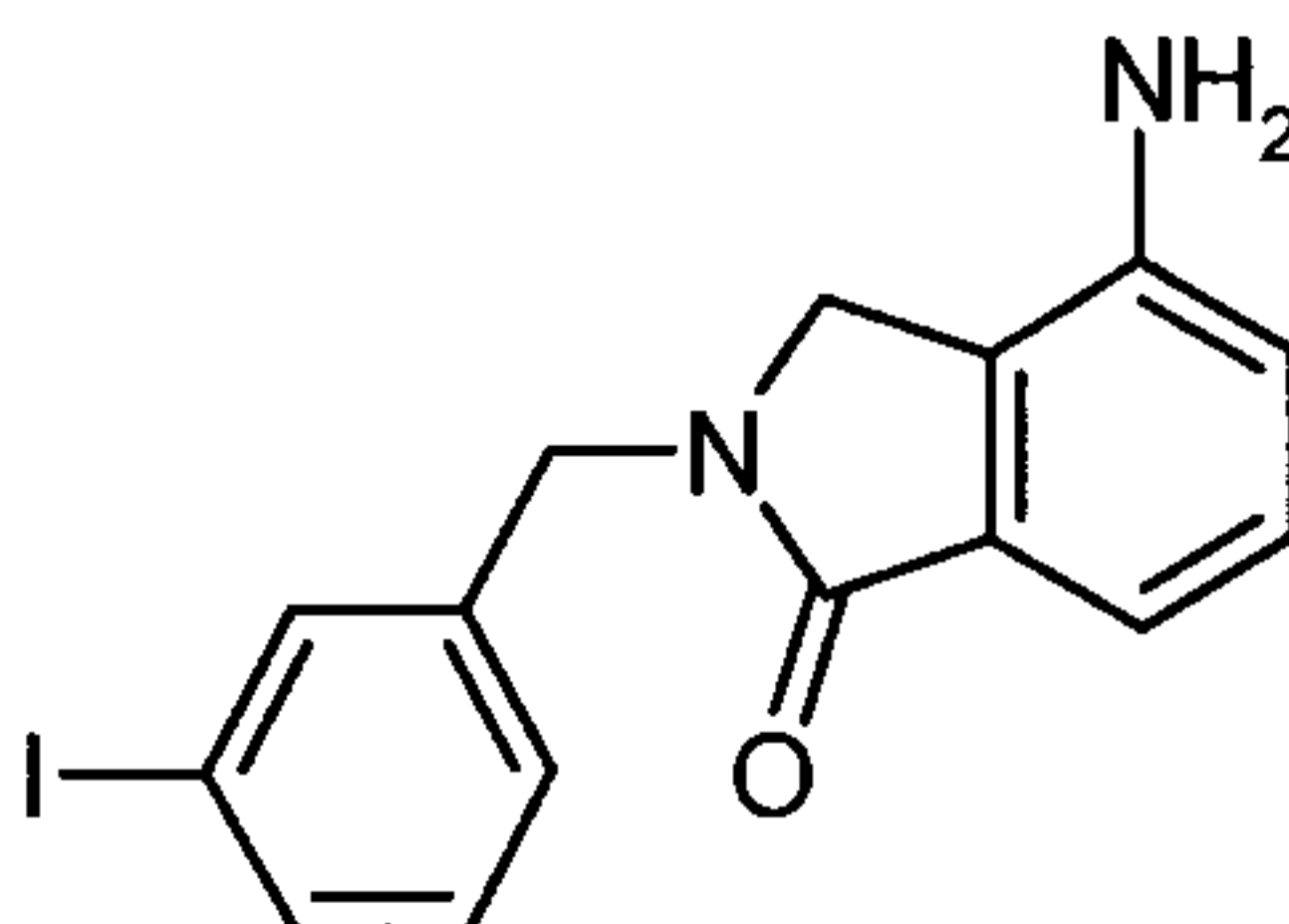
Yield: 2.8 g (87% of theory)

LC-MS (Method 1): $R_t = 2.29$ min;

10 MS (ESIpos): $m/z = 395$ $[M+H]^+$;

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 8.43$ (d, 1H), 8.18 (d, 1H), 7.82 (t, 1H), 7.73 (s, 1H), 7.68 (d, 1H), 7.35 (d, 1H), 7.18 (t, 1H), 4.84 (s, 2H), 4.77 (s, 2H).

Step c): 4-Amino-2-(3-iodobenzyl)isoindolin-1-one



15 At RT, 7.4 g (32.7 mmol, 5 eq.) of tin(II) chloride dihydrate are added to a suspension of 2.6 g (6.5 mmol) of 2-(3-iodobenzyl)-4-nitroisoindolin-1-one in 65 ml of ethanol, and the mixture is stirred at an oil bath temperature of 75°C for 2.5 h (formation of a solution). After cooling to RT, the reaction mixture is poured into ice-water, the mixture is adjusted to pH 8 using saturated aqueous sodium bicarbonate solution and filtered through Celite and the filtercake is washed repeatedly with ethyl acetate. After phase separation, the aqueous phase is extracted with ethyl acetate. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure. Without further purification, the title compound is used for the next reaction.

Yield: 2.0 g (93% of theory)

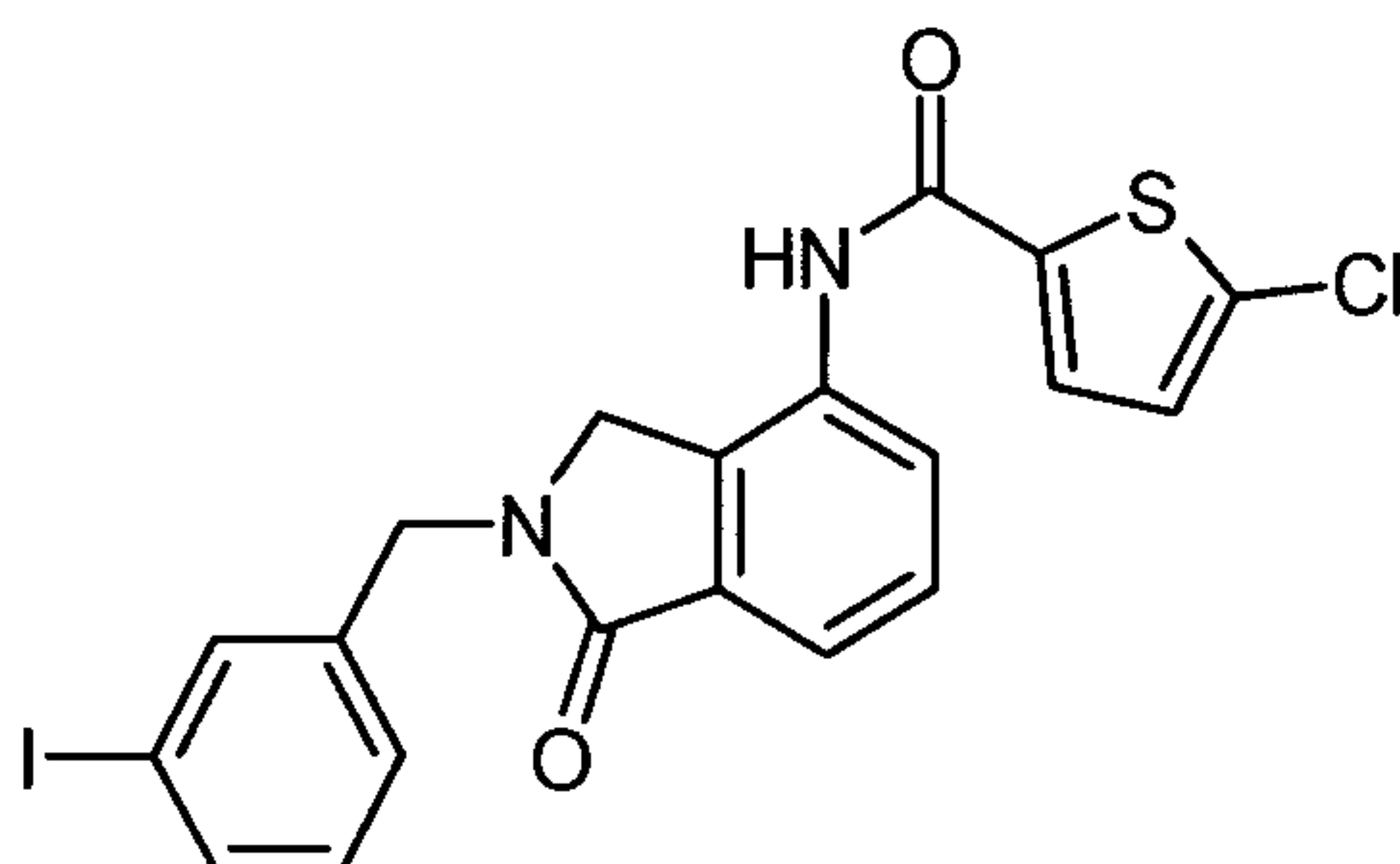
25 LC-MS (Method 8): $R_t = 2.05$ min;

MS (ESIpos): $m/z = 365$ $[M+H]^+$;

¹H-NMR (500 MHz, DMSO-d₆): δ = 7.70-7.62 (m, 2H), 7.26 (d, 1H), 7.22-7.15 (m, 2H), 6.91 (d, 1H), 6.76 (d, 1H), 5.40 (s, 2H), 4.69 (s, 2H), 4.11 (s, 2H).

Example 12A

5-Chloro-*N*-[2-(3-iodobenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



5

At RT, 335 mg (0.88 mmol, 1.1 eq.) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and 0.28 ml (1.6 mmol, 2 eq.) of *N,N*-diisopropylethylamine are added to a solution of 130 mg (0.80 mmol) of 5-chlorothiophenecarboxylic acid in 4 ml of dimethylformamide, the mixture is stirred for 30 min, 291 mg (0.80 mmol) of 4-amino-2-(3-iodobenzyl)isoindolin-1-one (Example 11A) are added and the mixture is stirred at RT overnight. The title compound is isolated by preparative RP-HPLC (CromSil C18, acetonitrile/water gradient).

10

Yield: 270 mg (66% of theory)

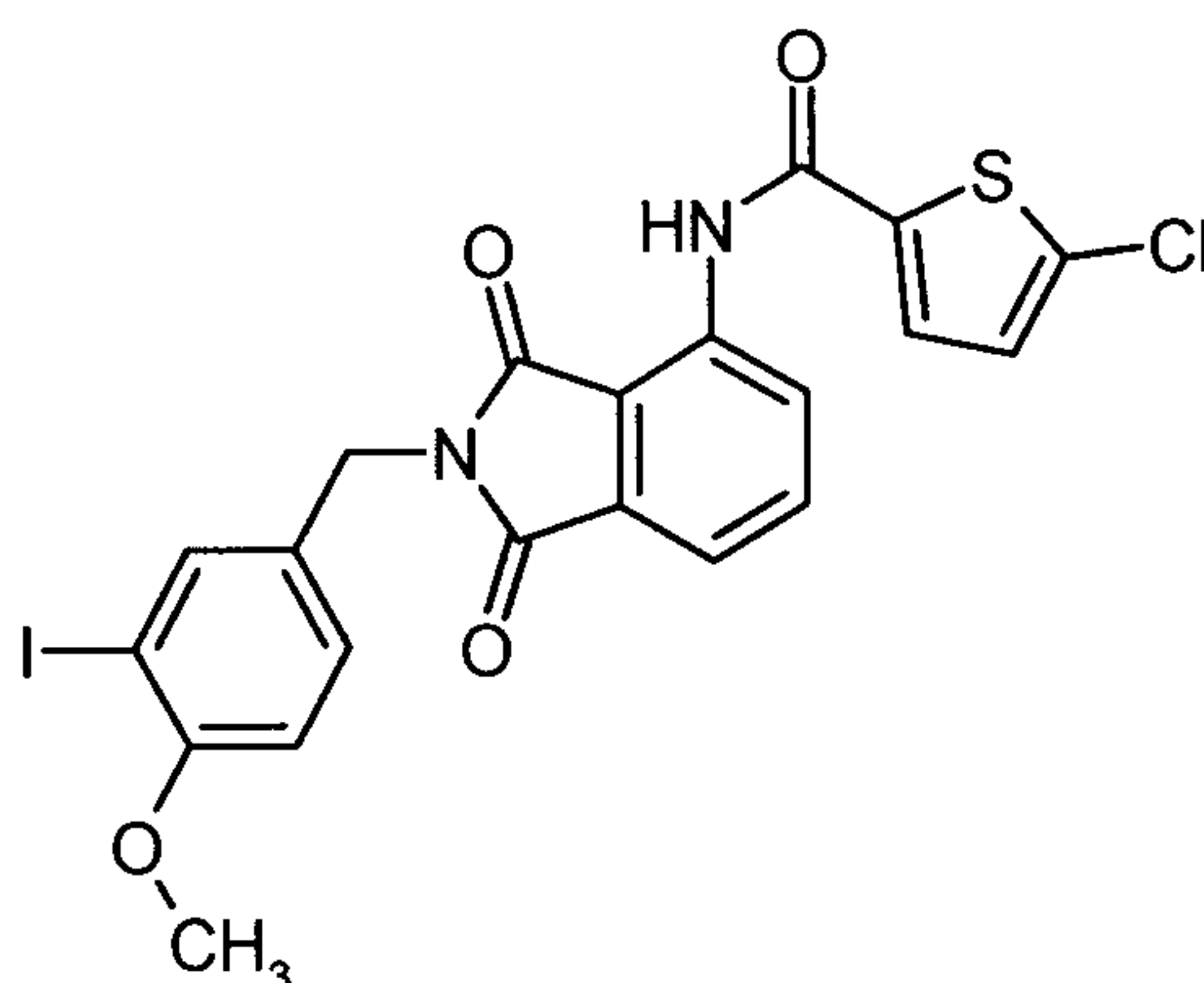
LC-MS (Method 8): *R*_t = 2.64 min;

15 MS (ESIpos): *m/z* = 509 [M+H]⁺;

¹H-NMR (500 MHz, DMSO-d₆): δ = 10.39 (s, 1H), 7.85 (d, 1H), 7.70-7.64 (m, 3H), 7.61 (d, 1H), 7.55 (t, 1H), 7.32-7.25 (m, 2H), 7.16 (t, 1H), 4.70 (s, 2H), 4.41 (s, 2H).

Example 13A

5-Chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



- 5 Under argon and at RT, a solution of 1.5 g (5.5 mol, 1.3 eq.) of (3-iodo-4-methoxyphenyl)methanol in 10 ml of tetrahydrofuran and a solution of 1.4 g (5.5 mmol, 1.3 eq.) of triphenylphosphine in 10 ml of tetrahydrofuran are added to a suspension of 1.3 g (4.2 mmol) of 5-chloro-*N*-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide (Example 4A) in 30 ml of tetrahydrofuran. The reaction suspension is cooled to 0°C, a solution of 1.1 ml (5.5 mmol, 1.3 eq.) of diisopropyl azodicarboxylate in 10 ml of tetrahydrofuran is added (the suspension turning into a solution) and
- 10 the mixture is stirred at RT for 2 h. The reaction mixture is concentrated under reduced pressure and the residue is triturated with dichloromethane/water.

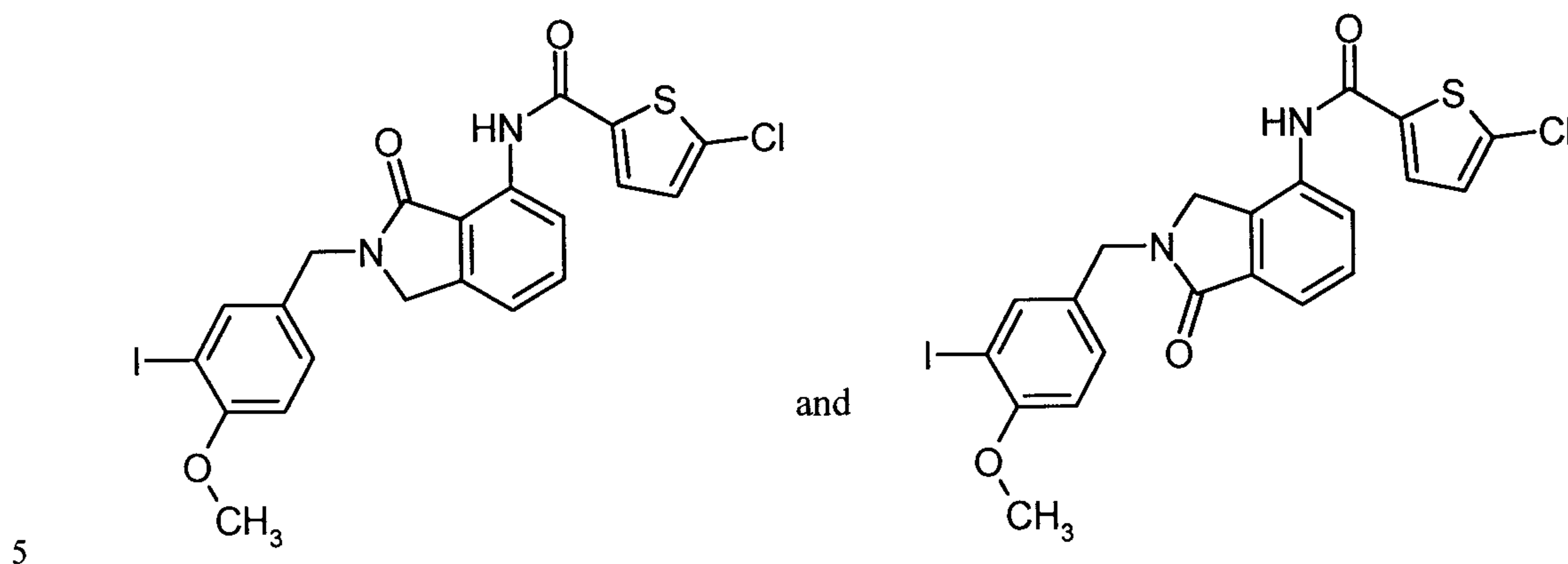
Yield: 2.0 g (87% of theory)

LC-MS (Method 7): $R_t = 3.18$ min;

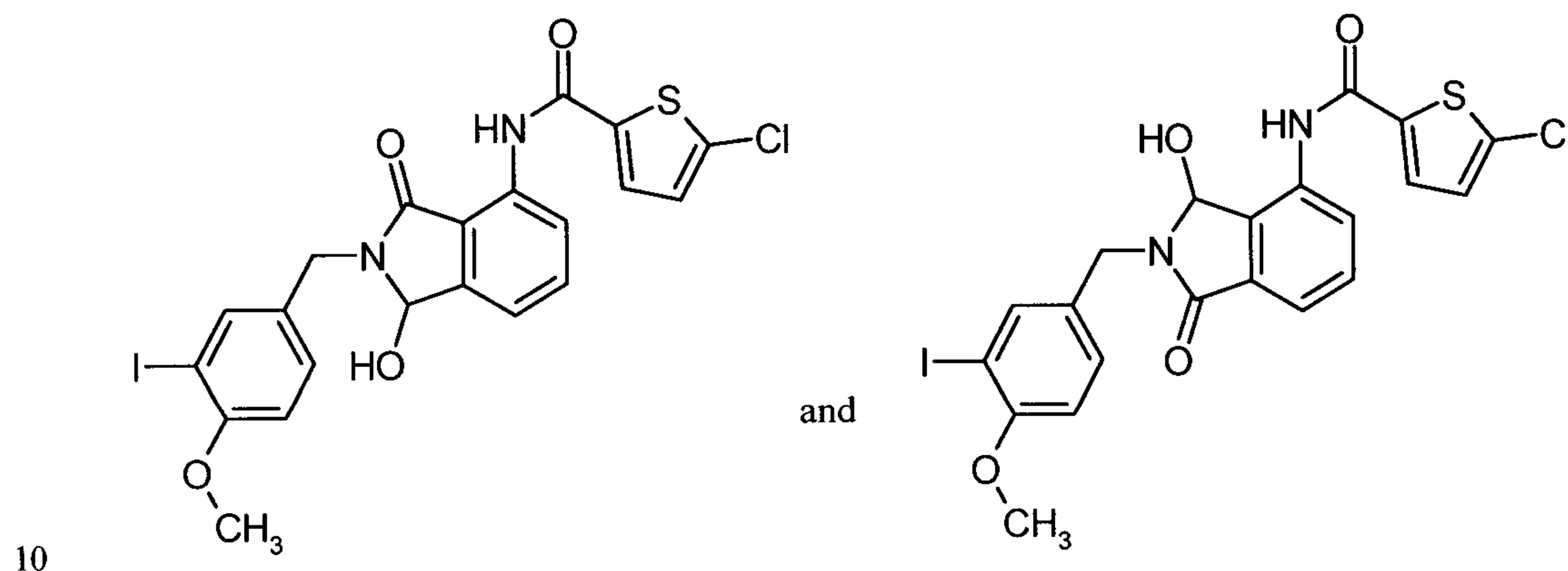
- 15 MS (ESIpos): $m/z = 553$ $[M+H]^+$.

Example 14A and Example 15A

5-Chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 14A) and 5-chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 15A)



Step a): 5-Chloro-*N*-[1-hydroxy-2-(3-iodo-4-methoxybenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (isomer 1) and 5-chloro-*N*-[3-hydroxy-2-(3-iodo-4-methoxybenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (isomer 2)



Under argon and at 0°C, 199 mg (5.3 mmol, 1.5 eq.) of sodium borohydride are added to a solution of 1.9 g (3.5 mmol) of 5-chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 13A) in a mixture of 10 ml of methanol and 100 ml of dichloromethane. The reaction mixture is stirred at RT overnight and adjusted to pH 5 using hydrochloric acid (1 N). The precipitate formed is filtered off, washed with water and dichloromethane and dried under reduced pressure (isomer 1).

After addition of dichloromethane/water and phase separation, the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and

concentrated under reduced pressure (isomer mixture, isomer 1/isomer 2 = 1:2).

Isomer 1:

Yield: 662 mg (34% of theory)

LC-MS (Method 8): $R_t = 2.95$ min;

5 MS (ESIpos): $m/z = 555$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.02$ (s, 1H), 8.29 (d, 1H), 7.77 (s, 1H), 7.68-7.60 (m, 2H), 7.39-7.29 (m, 3H), 7.01-6.93 (m, 2H), 5.74 (d, 1H), 4.78 (d, 1H), 4.34 (d, 1H), 3.80 (s, 3H).

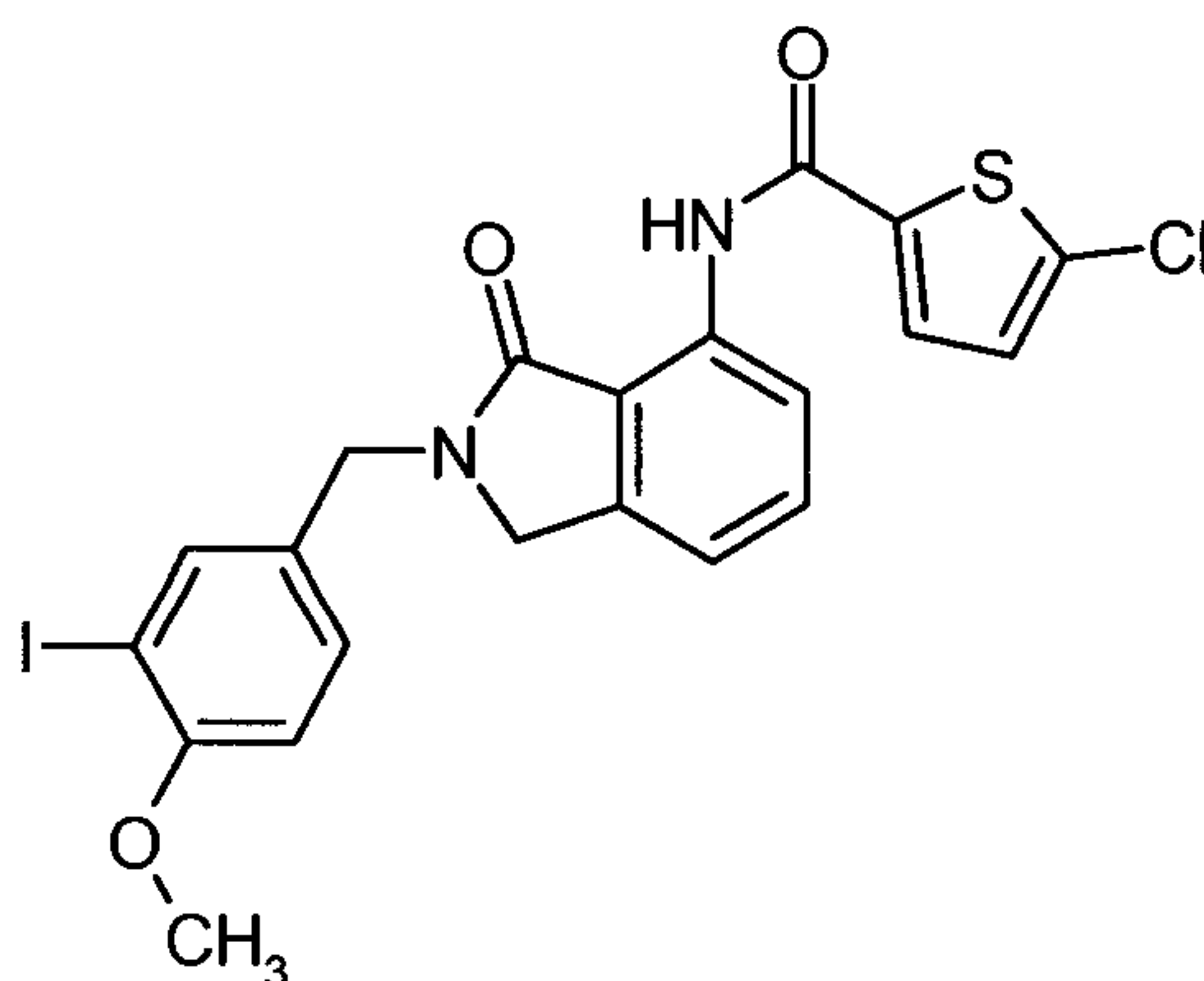
Isomer mixture:

Yield: 1.2 g (64% of theory)

10 LC-MS (Method 8): $R_t = 2.54$ min (Isomer 2) und 2.95 min (Isomer 1);

MS (ESIpos): $m/z = 555$ $[M+H]^+$.

Step b.1): 5-Chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



15 Under argon and at RT, 0.95 ml (12.0 mmol, 12 eq.) of trifluoroacetic acid and 0.32 ml (2.0 mmol, 2 eq.) of triethylsilane are added dropwise to a suspension of 568 mg (1.0 mmol) of isomer 1 in 20 ml of dichloromethane. The reaction mixture is stirred at RT for 1 h, and saturated aqueous sodium bicarbonate solution is added. After addition of dichloromethane and phase separation, the aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are
20 washed with saturated aqueous sodium chloride solution, dried over sodium sulphate, filtered and concentrated under reduced pressure.

Example 14A:

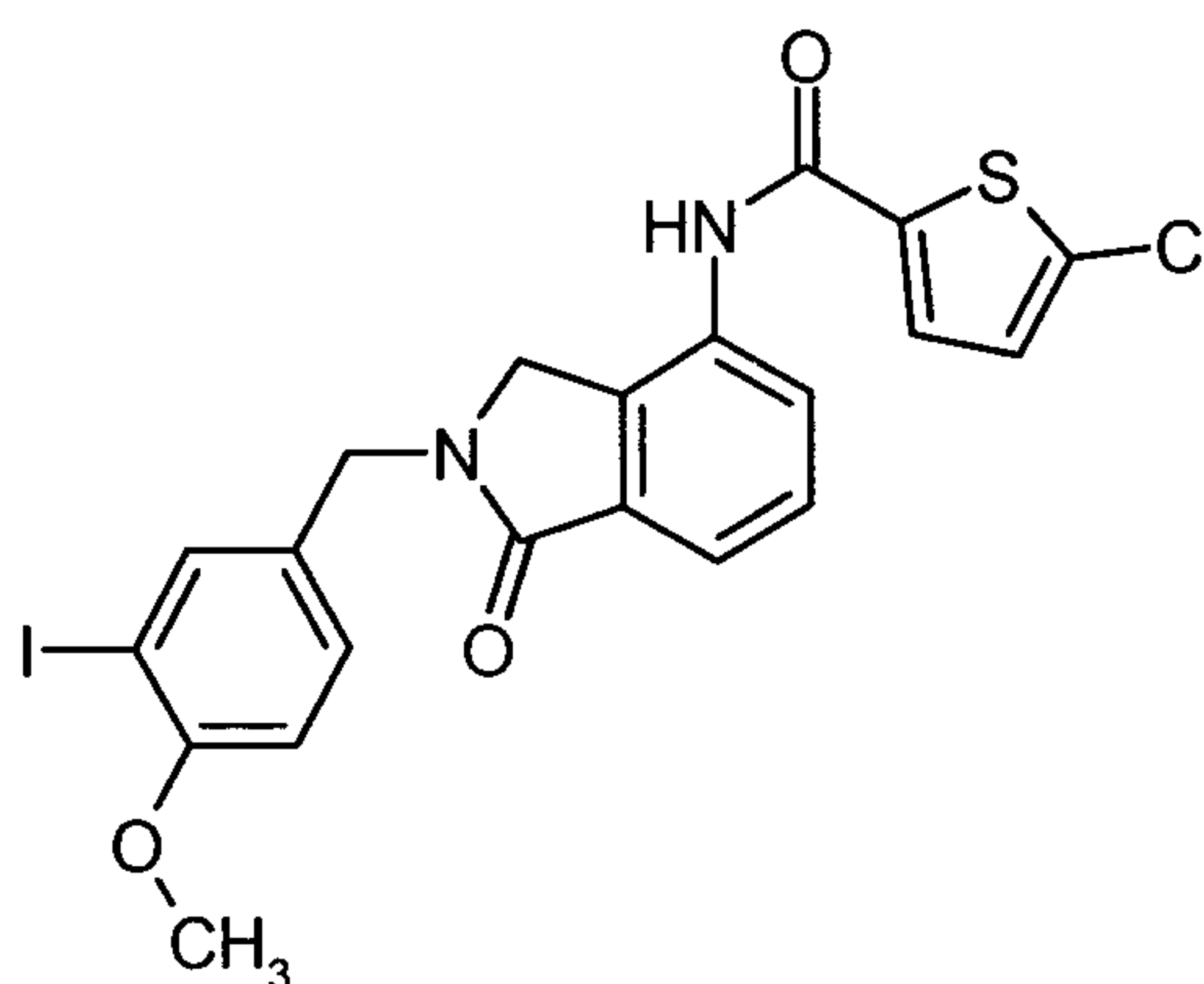
Yield: 535 mg (97% of theory)

LC-MS (Method 7): $R_t = 3.41$ min;

MS (ESIpos): $m/z = 539$ $[M+H]^+$;

- 5 $^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.29$ (s, 1H), 8.27 (d, 1H), 7.75 (s, 1H), 7.67 (d, 1H), 7.60 (t, 1H), 7.35 (d, 1H), 7.33 (d, 1H), 7.29 (d, 1H), 7.00 (d, 1H), 4.68 (s, 2H), 4.42 (s, 2H), 3.80 (s, 3H).

Step b.2): 5-Chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



- 10 Under argon and at RT, 2.3 ml (29.3 mmol, 12 eq.) of trifluoroacetic acid and 0.78 ml (4.9 mmol, 2 eq.) of triethylsilane are added dropwise to a suspension of 1.4 g (2.4 mmol) of isomer mixture in 20 ml of dichloromethane. The reaction mixture is stirred at RT for 1 h, and saturated aqueous sodium bicarbonate solution is added. After addition of dichloromethane and phase separation, the aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are
- 15 washed with saturated aqueous sodium chloride solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The isomers are separated by preparative RP-HPLC (CromSil C18, acetonitrile/water gradient).

Yield: 665 mg (51% of theory) of isomer 1 (Example 14A) and

160 mg (12% of theory) of isomer 2 (Example 15A)

Example 15A :

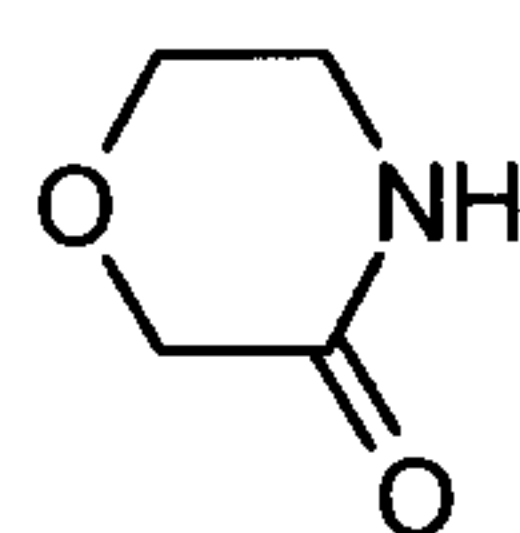
LC-MS (Method 1): $R_t = 2.45$ min;

MS (ESIpos): $m/z = 539$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 10.38$ (s, 1H), 7.86 (d, 1H), 7.70 (s, 1H), 7.65 (d, 1H), 7.61
5 (d, 1H), 7.56 (t, 1H), 7.31-7.25 (m, 2H), 6.99 (d, 1H), 4.64 (s, 2H), 4.38 (s, 2H), 3.80 (s, 3H).

Example 16A

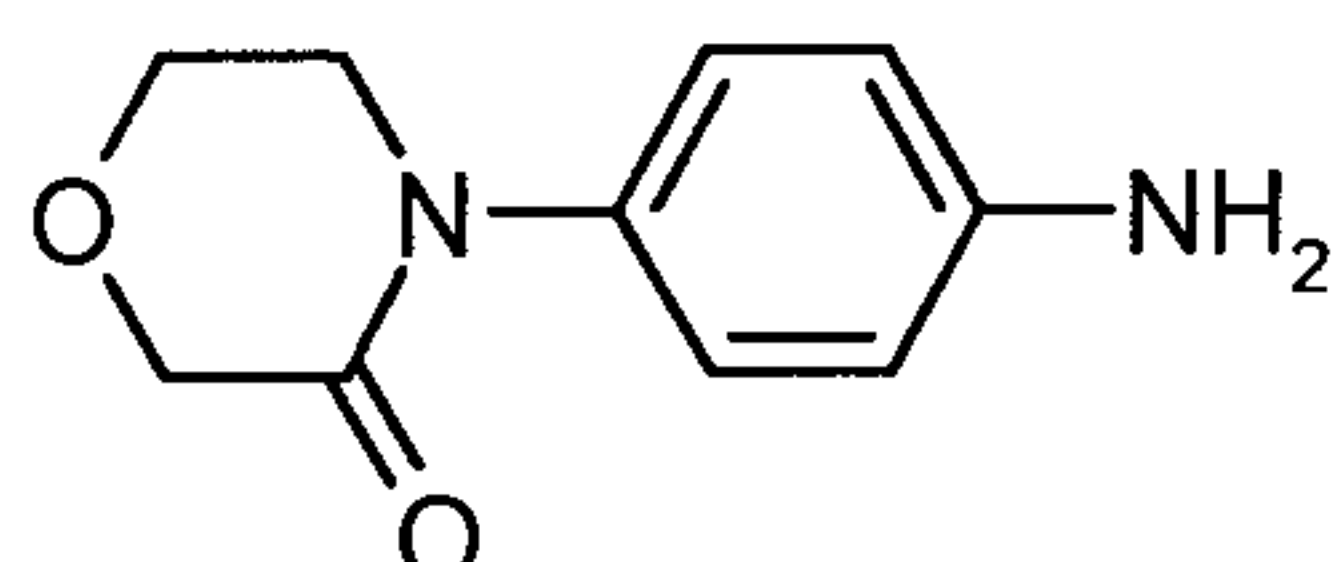
Morpholin-3-one



The preparation of the title compound is carried out analogously to a process known from the
10 literature [J.-M. Lehn, F. Montavon, *Helv. Chim. Acta* **1976**, 59, 1566-1583].

Example 17A

4-(4-Aminophenyl)morpholin-3-one



The preparation is carried out by substitution of 4-fluoronitrobenzene with morpholin-3-one
15 (Example 16A) and subsequent reduction of the 4-(4-nitrophenyl)morpholin-3-one (see
WO 01/47919, starting materials I and II, pp. 55-57).

Example 18A

3-Hydroxypiperidin-2-one

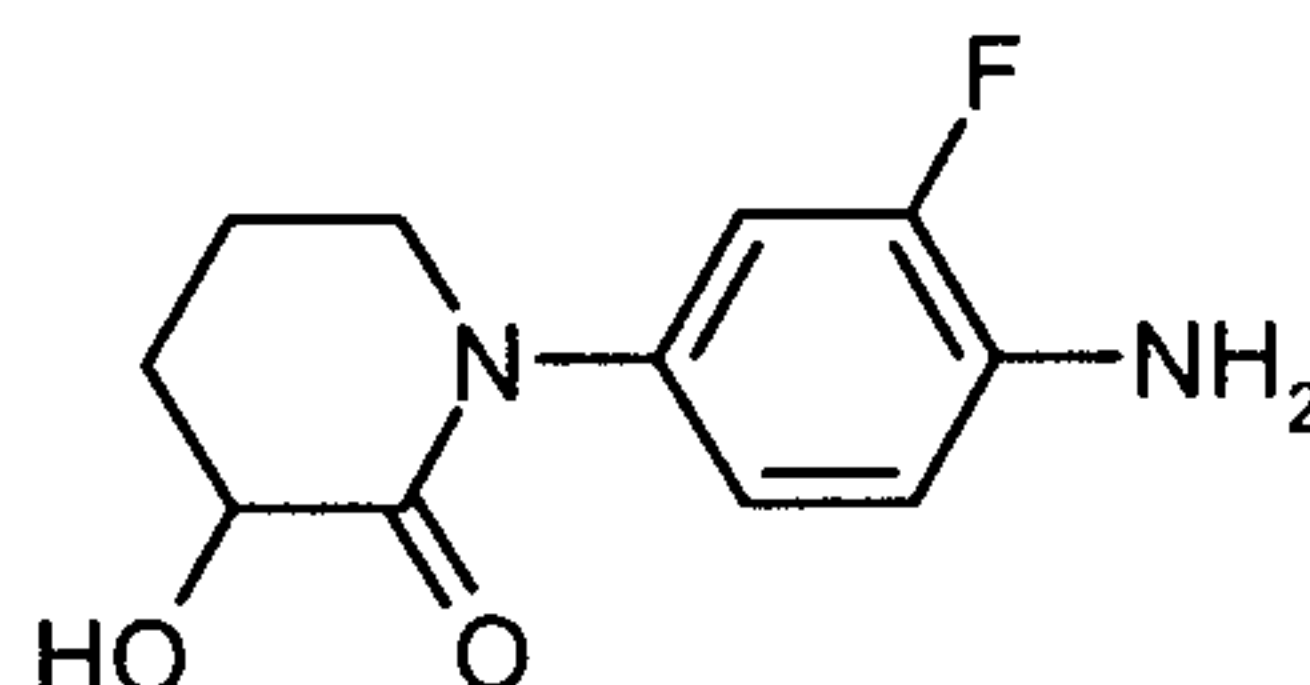


20 The preparation of the title compound is carried out analogously to a process known from the

literature [I.S. Hutchinson *et al.*, *Tetrahedron* **2002**, 58, 3137-3143].

Example 19A

1-(4-Amino-3-fluorophenyl)-3-hydroxypiperidin-2-one



- 5 The preparation of the title compound is carried out analogously to a method known from the literature [A. Klapers *et al.*, *J. Am. Chem. Soc.* **2002**, 124, 7421-7428] from 2-fluoro-4-iodoaniline and 3-hydroxypiperidin-2-one (Example 18A):

Under argon, a suspension of 6.45 g (27.2 mmol) of 2-fluoro-4-iodoaniline, 3.92 g (34.0 mmol, 1.25 eq.) of 3-hydroxypiperidin-2-one, 1.04 g (5.5 mmol, 0.2 eq.) of copper(I) iodide, 11.56 g
10 (54.5 mmol, 2 eq.) of potassium phosphate and 1.2 ml (10.9 mmol, 0.4 eq.) of *N,N'*-dimethylethylenediamine in 157 ml of dioxane is stirred under reflux overnight. A further 1.04 g (5.5 mmol, 0.2 eq.) of copper(I) iodide and 0.9 ml (8.2 mmol, 0.3 eq.) of *N,N'*-dimethylethylenediamine are added. The reaction mixture is stirred under reflux for a further 8 h and, after cooling to RT, filtered through a layer of kieselguhr, and the residue is washed with a
15 mixture of dichloromethane and methanol (1:1). The combined filtrates are concentrated under reduced pressure. The crude product is purified by flash chromatography (silica gel 60, dichloromethane/methanol 100:1 → 40:1).

Yield: 2.57 g (41% of theory)

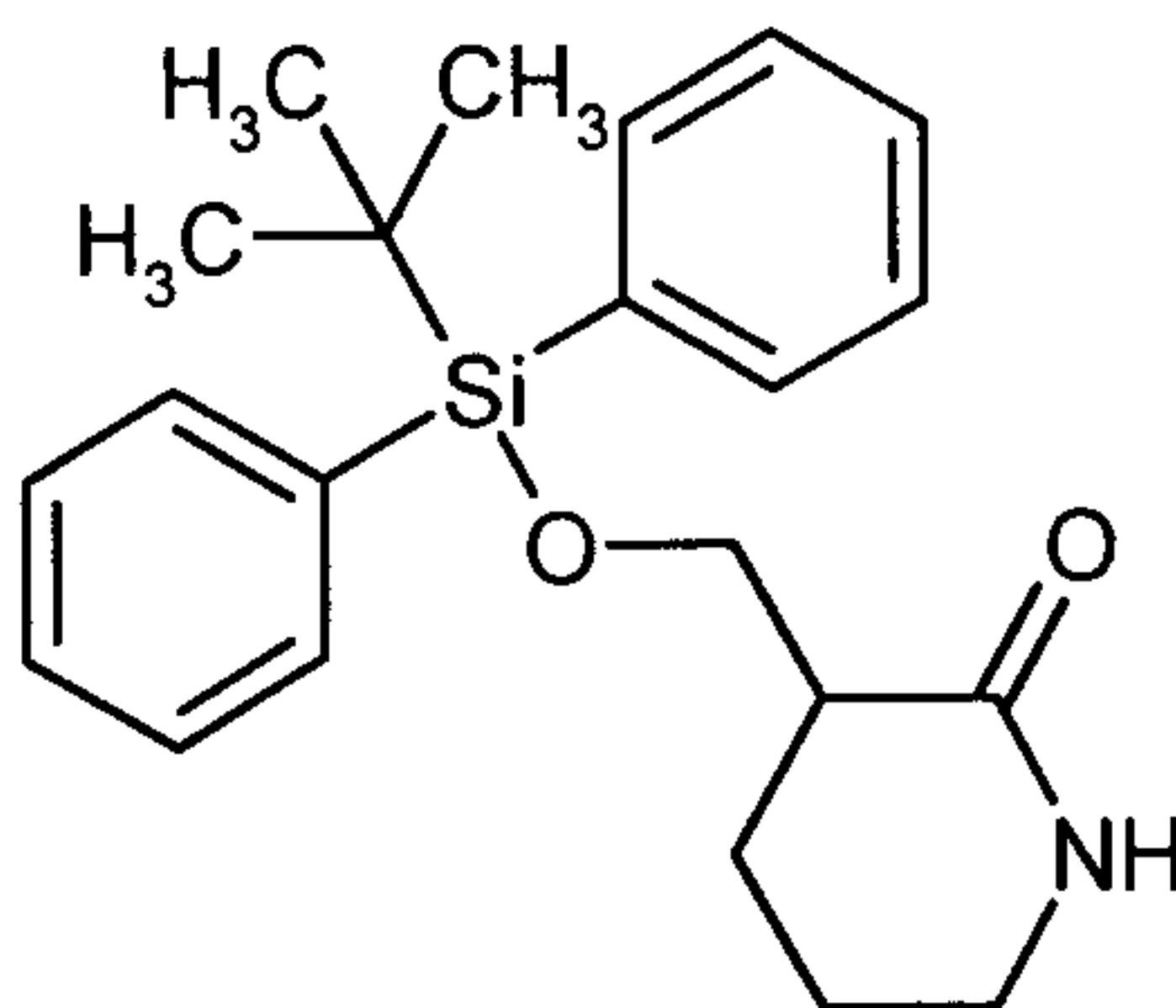
HPLC (Method 11): $R_t = 1.52$ min;

- 20 MS (DCI, NH_3): $m/z = 242$ $[\text{M}+\text{NH}_4]^+$;

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6): $\delta = 6.94$ (d, 1H), 6.81-6.65 (m, 2H), 5.12 (br. s, 2H), 3.99 (dt, 1H), 3.63-3.39 (m, 2H), 2.12-2.00 (m, 1H), 2.00-1.62 (m, 4H).

Example 20A

3-({*tert*-Butyl(diphenyl)silyl}oxy)methylpiperidin-2-one



3.16 g (46.5 mmol) of imidazole and, dropwise, 11 ml (42.6 mmol) of *tert*-butyl(diphenyl)silyl chloride are added successively to a solution of 5.0 g (38.7 mmol) of 3-hydroxymethylpiperidin-2-one [J. Yang *et al.*, *Org. Lett.* **2000**, 2, 763-766] in 40 ml of *N,N*-dimethylformamide. After 3 h at RT, about 400 ml of water are added and the mixture is extracted three times with ethyl acetate. The combined organic extracts are washed successively with saturated ammonium chloride solution, water and saturated sodium chloride solution. After drying over anhydrous magnesium sulphate, the mixture is filtered and the filtrate is freed from the solvent under reduced pressure. The residue obtained is purified by filtration with suction through silica gel using the mobile phase cyclohexane/ethyl acetate 20:1 → 1:1. This gives 9.43 g (66% of theory) of the title compound.

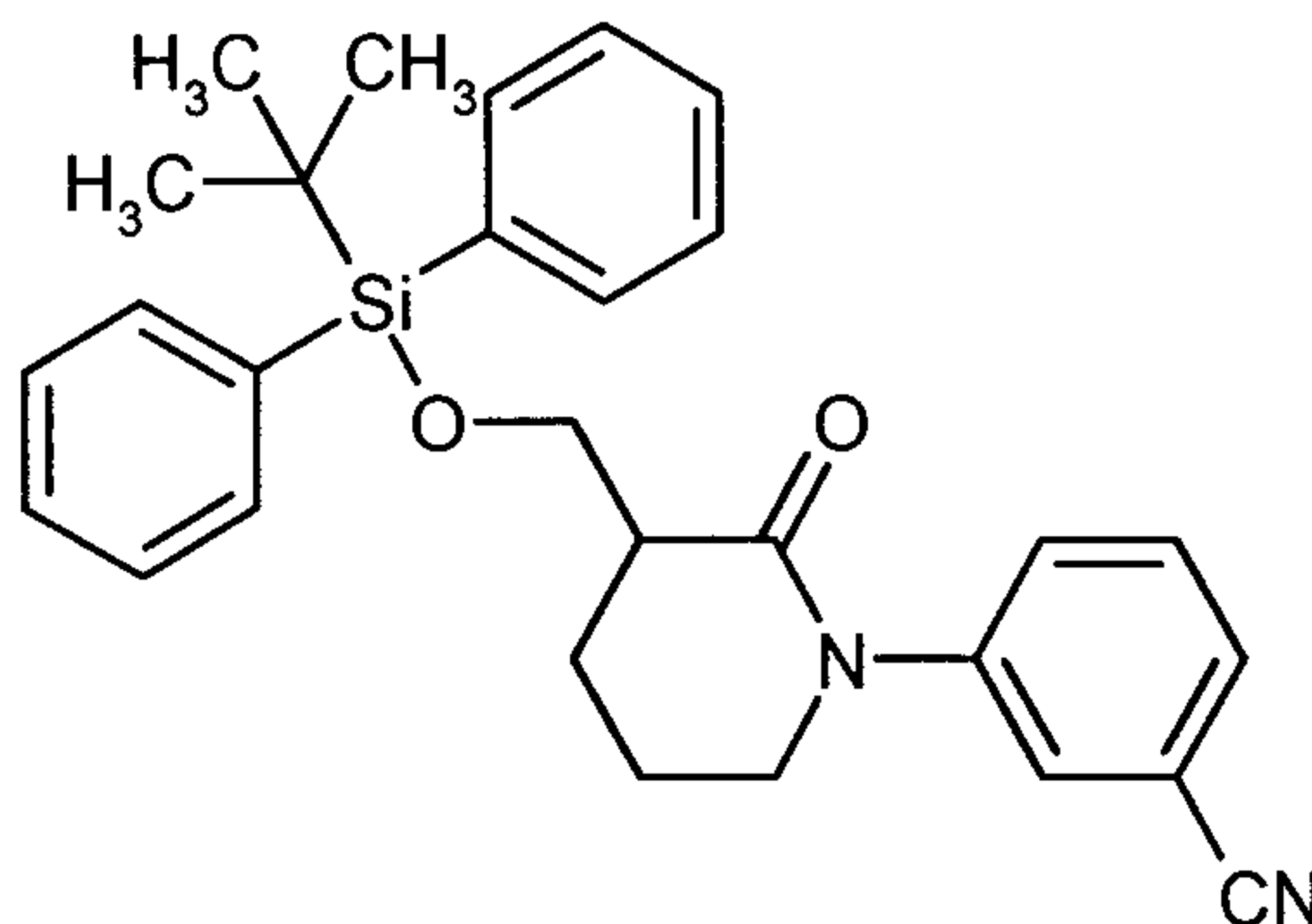
HPLC (Method 1): $R_t = 2.79$ min;

MS (ESIpos): $m/z = 368$ ($M+H$)⁺;

¹H-NMR (400 MHz, CDCl₃): $\delta = 7.69$ -7.65 (m, 4H), 7.42-7.34 (m, 6H), 5.82 (s, broad, 1H), 4.03 (dd, 1H), 3.93 (dd, 1H), 3.32-3.28 (m, 2H), 2.53-2.48 (m, 1H), 2.07-1.99 (m, 1H), 1.96-1.87 (m, 2H), 1.78-1.68 (m, 1H), 1.04 (s, 9H).

Example 21A

3-[3-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2-oxopiperidin-1-yl]benzonitrile



By repeatedly applying a weak vacuum and venting with argon, a suspension of 250 mg (1.09
5 mmol) of 3-iodobenzonitrile, 401 mg (1.09 mmol) of the compound from Example 20A, 1.85 g of
potassium phosphate (8.73 mmol), 139 μ l (1.31 mmol) of *N,N'*-dimethylethylenediamine and 166
mg (0.87 mmol) of copper(I) iodide in 10 ml of toluene is freed from oxygen, and then heated at
reflux for 8 days. After cooling to RT, insoluble material is filtered off and the product is isolated
from the concentrated filtrate by preparative HPLC. This gives 112 mg (22% of theory) of the title
10 compound.

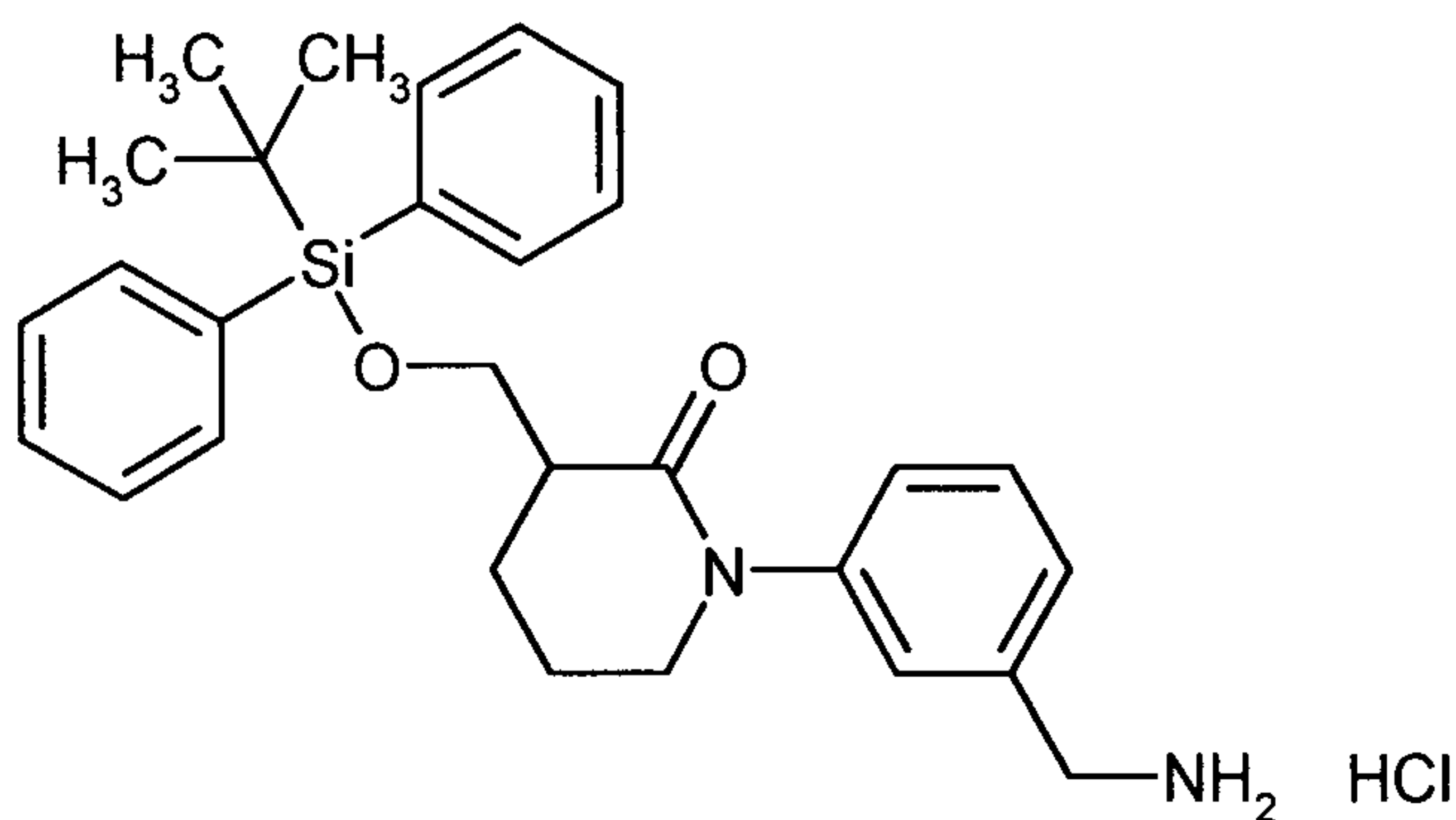
HPLC (Method 10): $R_t = 5.69$ min;

MS (ESIpos): $m/z = 469$ ($M+H$)⁺;

¹H-NMR (500 MHz, DMSO- d_6): $\delta = 7.77$ (d, 1H), 7.70 (dd, 1H), 7.63-7.57 (m, 6H), 7.49-7.40 (m,
6H), 4.07 (dd, 1H), 3.82 (dd, 1H), 3.71-3.65 (m, 2H), 2.68-2.63 (m, 1H), 2.13-2.08 (m, 1H), 2.06-
15 2.00 (m, 2H), 1.94-1.88 (m, 1H).

Example 22A

1-[3-(Aminomethyl)phenyl]-3-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)piperidin-2-one
hydrochloride



- 5 In the presence of 50 mg (0.22 mmol) of platinum(IV) oxide and at a hydrogen pressure of 3 bar, a solution of 110 mg (0.235 mmol) of the compound from Example 21A in 660 ml of ethanol and 0.5 ml of chloroform is hydrogenated at RT. After 2 hours, the mixture is filtered through Celite and the filtrate is concentrated to dryness. This gives 130 mg (97% of theory, based on a purity of 90%) of the title compound.

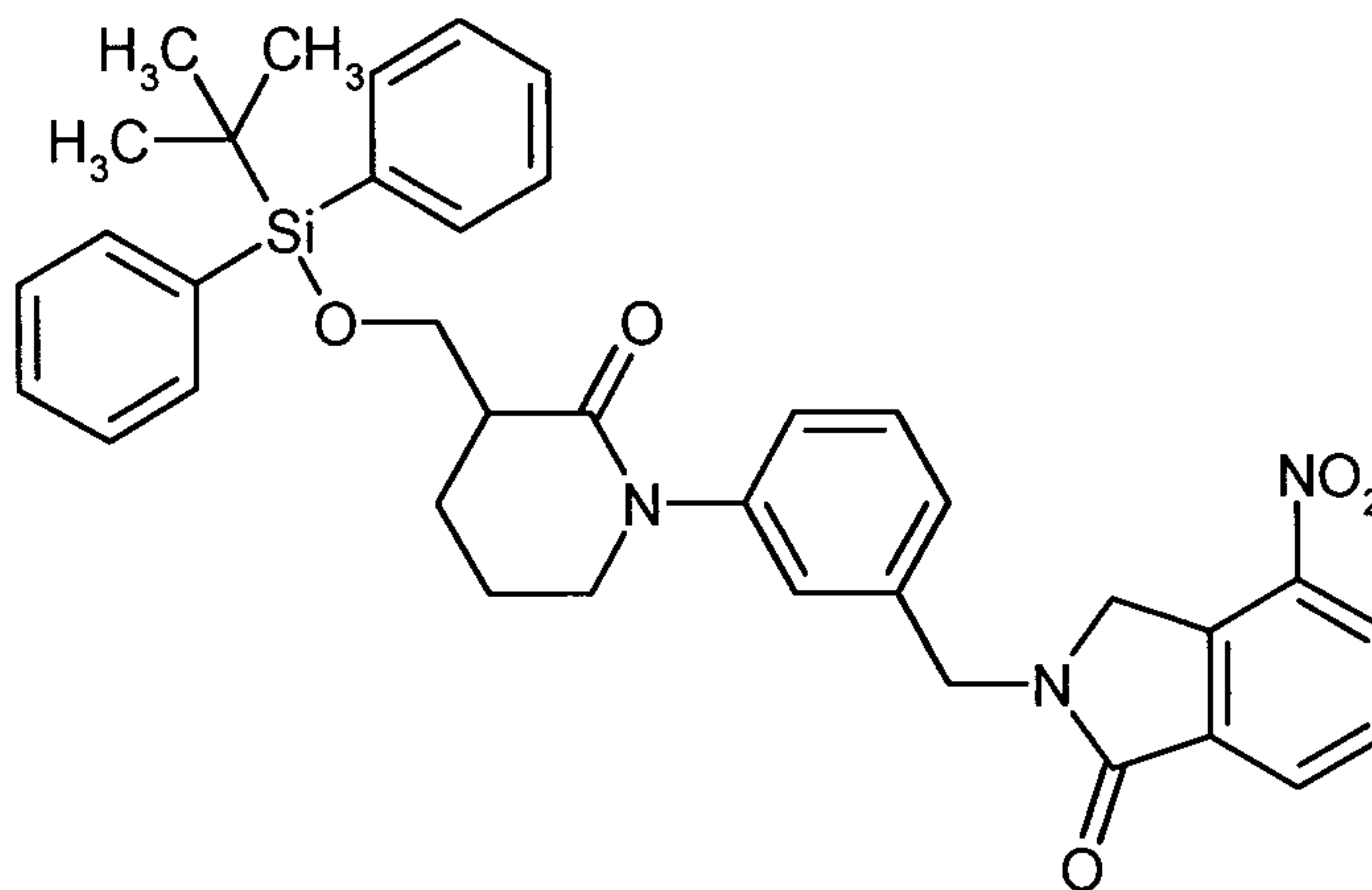
- 10 HPLC (Method 11): $R_t = 4.94$ min;

MS (ESIpos): $m/z = 473$ ($M+H$)⁺;

¹H-NMR (500 MHz, DMSO-*d*₆): $\delta = 8.27$ (broad, 3H), 7.65-7.60 (m, 4H), 7.48-7.41 (m, 7H), 7.37 (d, 1H), 7.33 (d, 1H), 7.26 (dd, 1H), 4.03 (dd, 1H), 4.01 (s, 2H), 3.86 (dd, 1H), 3.65-3.59 (m, 2H), 2.67-2.63 (m, 1H), 2.15-2.10 (m, 1H), 2.06-1.98 (m, 2H), 1.94-1.89 (m, 1H).

Example 23A

2-{3-[3-({*tert*-Butyl(diphenyl)silyl}oxy)methyl]-2-oxopiperidin-1-yl]benzyl}-4-nitroisindolin-1-one

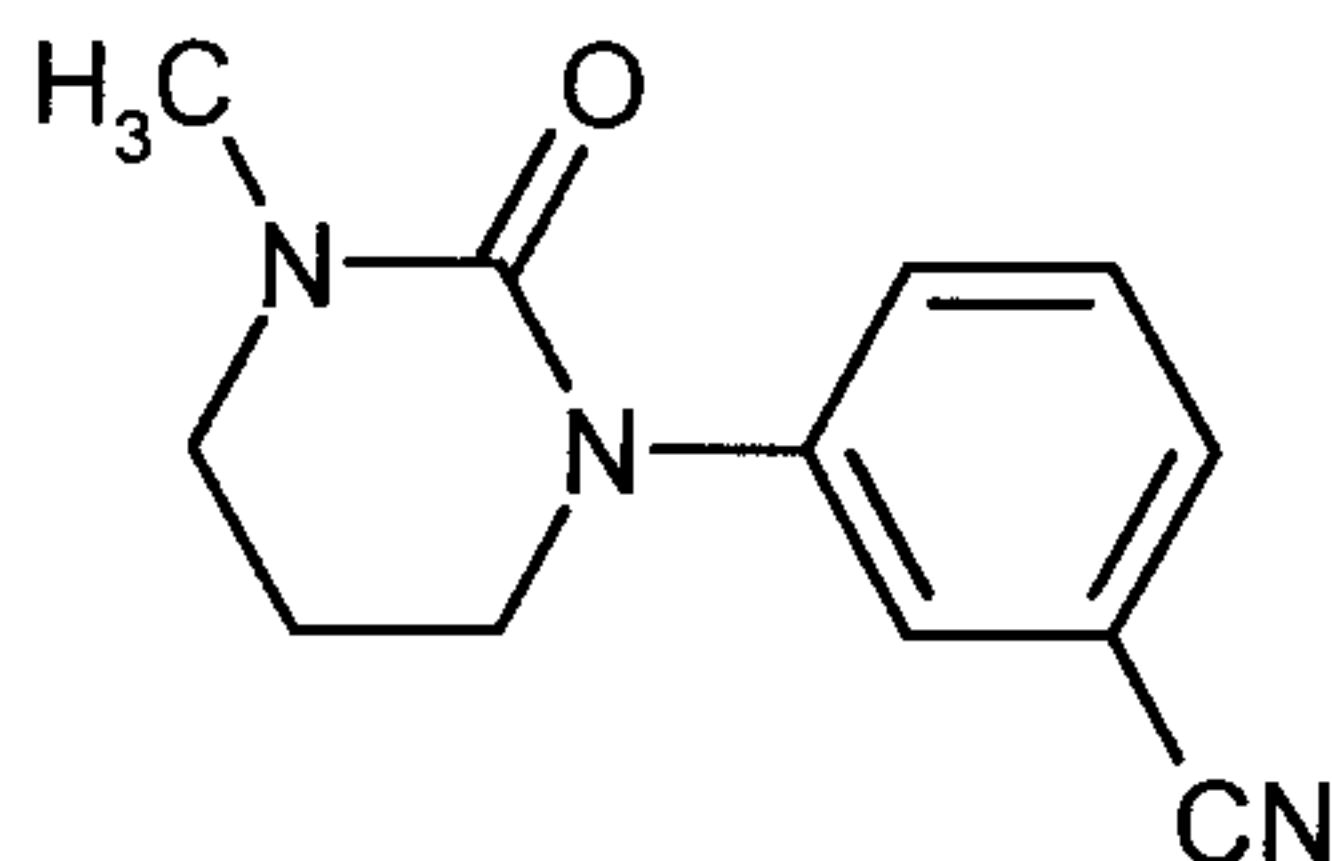


- 5 78 μ l (0.562 mmol) of triethylamine are added to a solution of 70 mg (0.255 mmol) of methyl 2-(bromomethyl)-3-nitrobenzoate (Example 11A, step a) and 130 mg (0.255 mmol) of the compound from Example 22A in 10 ml of methanol, and the mixture is heated at reflux for 18 hours. After cooling to RT, all volatile components are removed under reduced pressure and the product is isolated from the residue by preparative HPLC. This gives 65 mg (38% of theory) of the title compound.
- 10

HPLC (Method 11): R_t = 5.62 min;

MS (DCI, NH_3): m/z = 634 ($\text{M}+\text{H}$)⁺, 651 ($\text{M}+\text{NH}_4$)⁺;

- ¹H-NMR (500 MHz, $\text{DMSO}-d_6$): δ = 8.41 (d, 1H), 8.16 (d, 1H), 7.81 (t, 1H), 7.62-7.58 (m, 4H), 7.46-7.37 (m, 7H), 7.23-7.18 (m, 3H), 4.85-4.73 (m, 4H), 4.07 (dd, 1H), 3.78 (dd, 1H), 3.67-3.58 (m, 2H), 2.62-2.58 (m, 1H), 2.09-1.97 (m, 3H), 1.92-1.83 (m, 1H), 0.93 (s, 9H).
- 15

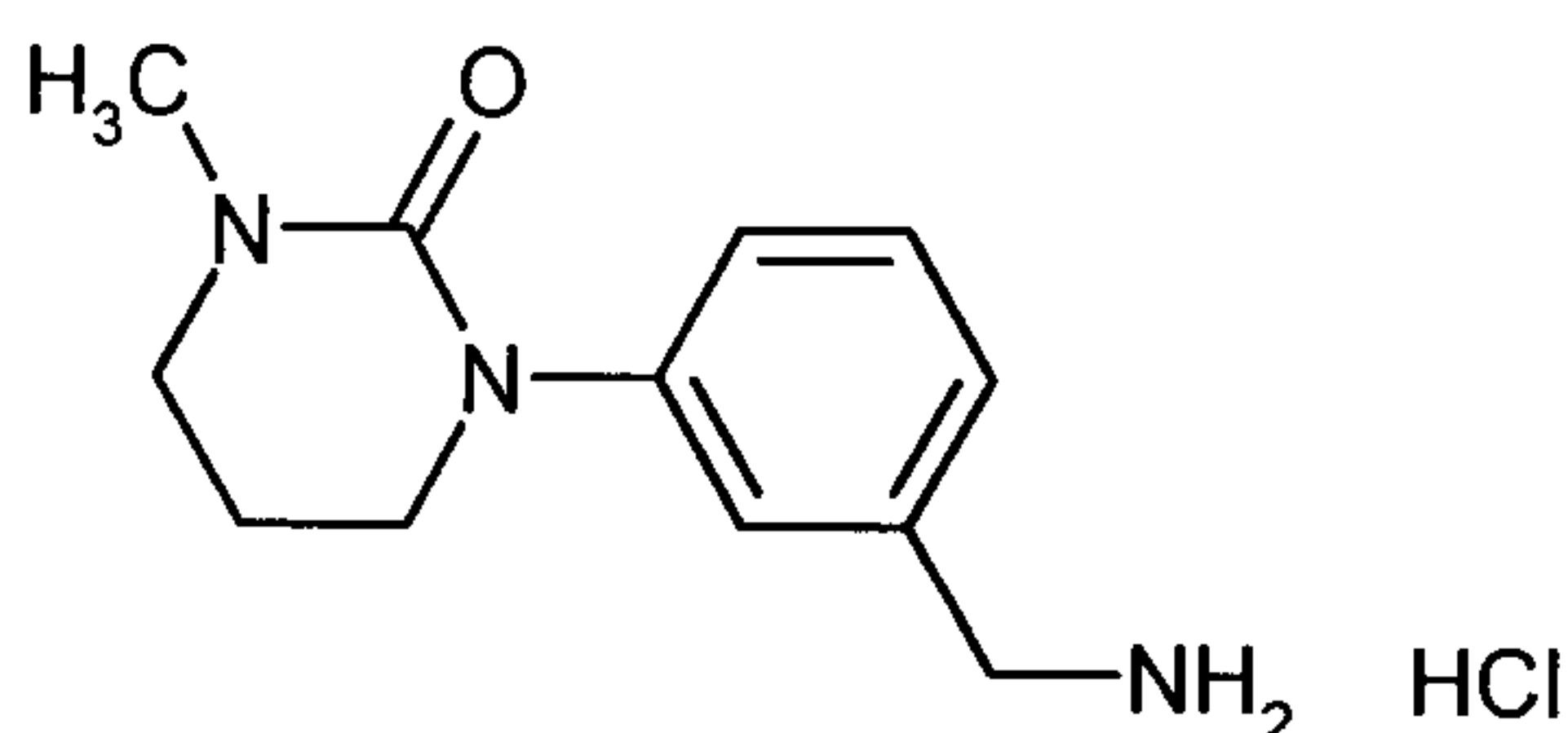
Example 24A3-(3-Methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)benzonitrile

Analogously to the process described in Example 21A, 500 mg (2.18 mmol) of 3-iodobenzonitrile
 5 and 249 mg (2.18 mmol) of 1-methyltetrahydropyrimidin-2(1*H*)-one give 227 mg (48% of theory)
 of the title compound. The reaction is carried out in dioxane as solvent.

HPLC (Method 11): $R_t = 3.36$ min;

MS (DCI, NH_3): $m/z = 216$ ($\text{M}+\text{H}^+$), 233 ($\text{M}+\text{NH}_4^+$);

^1H -NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 7.73$ (d, 1H), 7.62 (dd, 1H), 7.53-7.47 (m, 2H), 3.68 (t, 2H),
 10 3.34 (t, 2H), 2.86 (s, 3H), 2.06-2.00 (m, 2H).

Example 25A1-[3-(Aminomethyl)phenyl]-3-methyltetrahydropyrimidin-2(1*H*)-one hydrochloride

Analogously to the process described in Example 22A, 800 mg (3.72 mmol) of the compound from
 15 Example 24A give 829 mg (87% of theory) of the title compound.

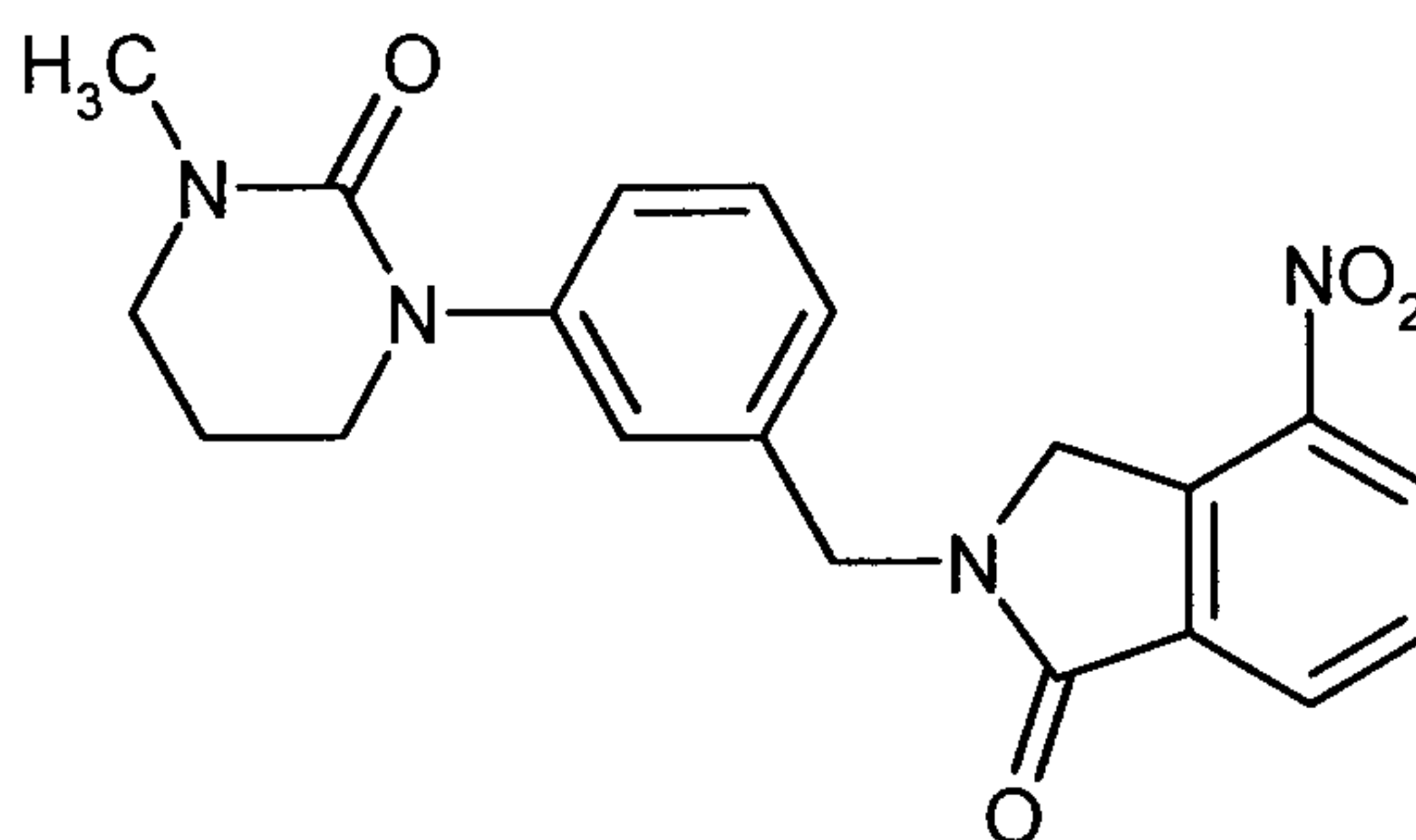
LC/MS (Method 14): $R_t = 1.99$ min;

MS (ESIpos): $m/z = 220$ ($\text{M}+\text{H}^+$);

^1H -NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 8.26$ (broad, 3H), 7.39 (s, 1H), 7.33 (dd, 1H), 7.27 (d, 1H),
 7.20 (d, 1H), 3.97 (s, 2H), 3.64 (t, 2H), 3.34 (t, 2H), 2.87 (s, 3H), 2.06-2.00 (m, 2H).

Example 26A

2-[3-(3-Methyl-2-oxotetrahydropyrimidin-1(2H)-yl)benzyl]-4-nitroisindolin-1-one



Analogously to the process described in Example 23A, 887 mg (3.24 mmol) of the compound from
5 Example 25A give 809 mg (66% of theory) of the title compound.

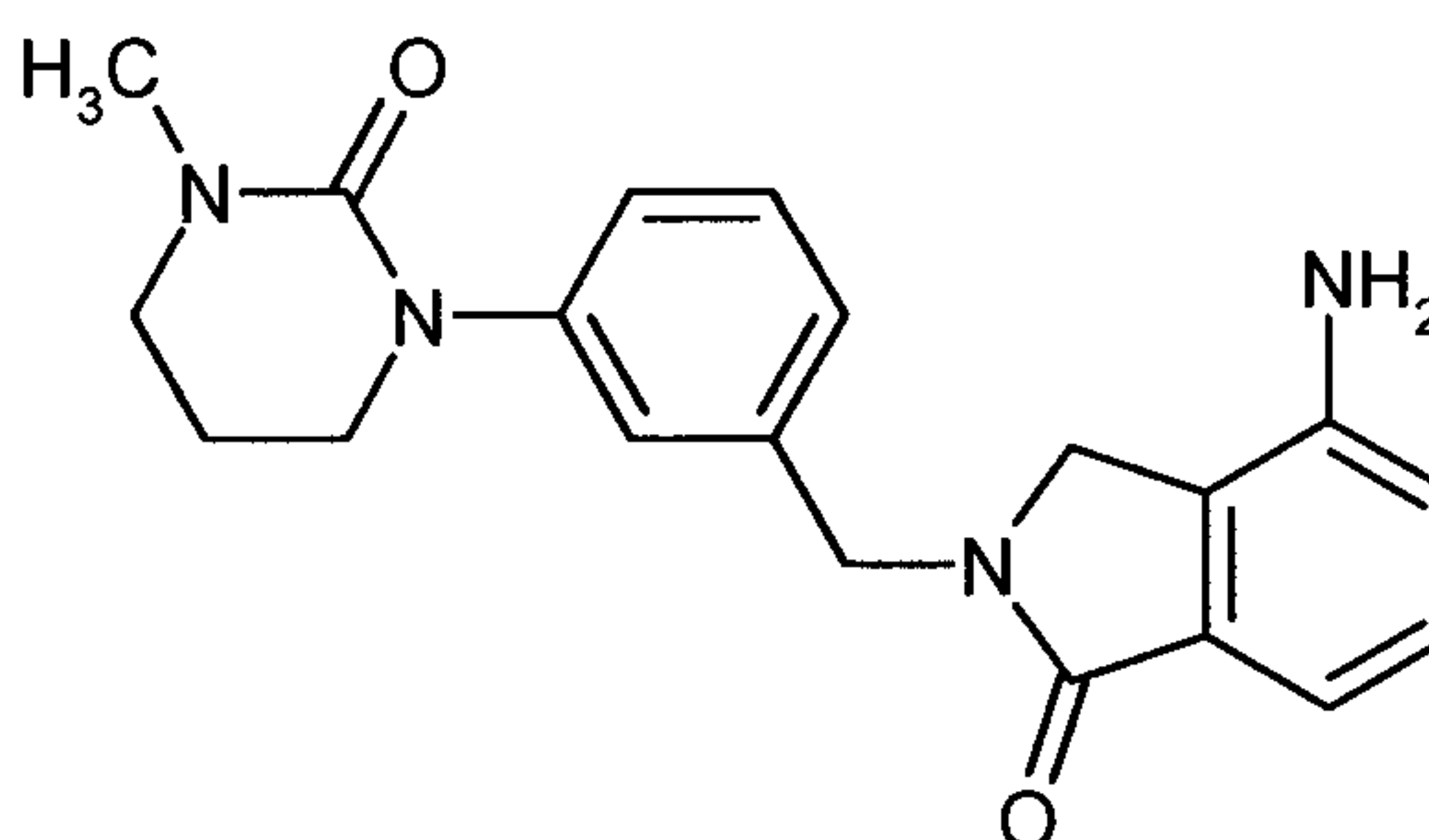
HPLC (Method 11): $R_t = 3.83$ min;

MS (DCI, NH_3): $m/z = 381$ ($\text{M}+\text{H}$)⁺, 398 ($\text{M}+\text{NH}_4$)⁺;

¹H-NMR (400 MHz, DMSO- d_6): $\delta = 8.42$ (d, 1H), 8.18 (d, 1H), 7.82 (dd, 1H), 7.28 (dd, 1H), 7.23
(dd, 1H), 7.17 (dd, 1H), 7.06 (dd, 1H), 4.81 (s, 2H), 4.75 (s, 2H), 3.62 (t, 2H), 3.32 (t, 2H,
10 obscured by the signal for water), 2.83 (s, 3H), 2.03-1.97 (m, 2H).

Example 27A

4-Amino-2-[3-(3-methyl-2-oxotetrahydropyrimidin-1(2H)-yl)benzyl]isindolin-1-one



1.89 g (8.37 mmol) of tin(II) chloride dihydrate are added to a solution of 796 mg (2.09 mmol) of
15 the compound from Example 26A in 15 ml of ethanol, and the mixture is heated at a bath
temperature of 70°C for 2 hours. The reaction mixture is then poured into ice-water, adjusted to
pH 8 using saturated sodium bicarbonate solution and filtered off with suction through Celite. The
filtrate is extracted with ethyl acetate. The organic extract is washed with saturated sodium
chloride solution. The mixture is dried over anhydrous sodium sulphate and then filtered, and the

filtrate is evaporated to dryness. This gives 678 mg (92% of theory) of the title compound.

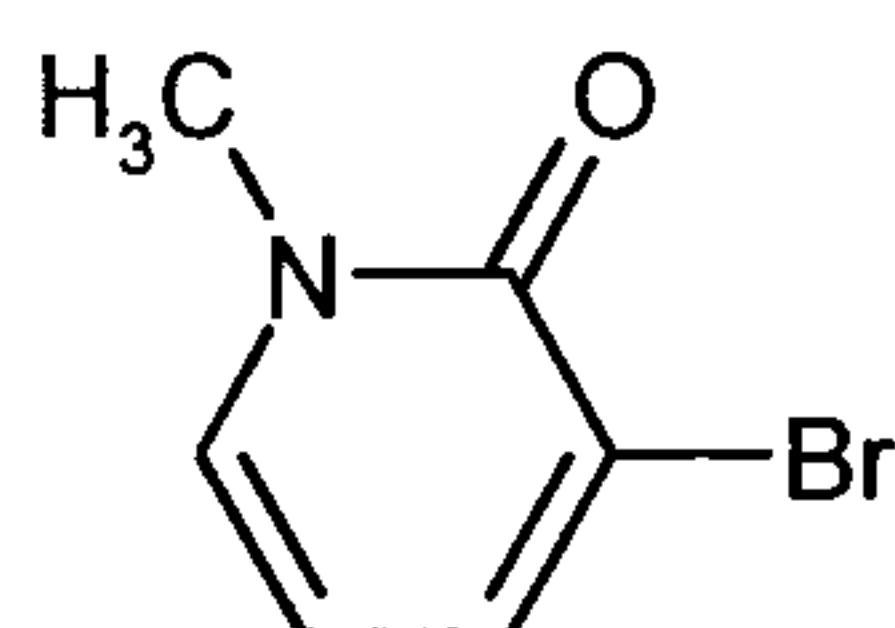
HPLC (Method 11): $R_t = 3.22$ min;

MS (ES⁺): $m/z = 351$ (M+H)⁺;

¹H-NMR (500 MHz, DMSO-*d*₆): $\delta = 7.28$ (dd, 1H), 7.19-7.13 (m, 3H), 6.97 (dd, 1H), 6.90 (d, 1H),
5 6.74 (d, 1H), 5.39 (s, 2H), 4.68 (s, 2H), 4.11 (s, 2H), 3.61 (t, 2H), 3.31 (t, 2H), 2.83 (s, 3H), 2.02-
1.98 (m, 2H).

Example 28A

3-Bromo-1-methylpyrid-2(1H)-one



- 10 A mixture of 5.0 g (28.7 mmol) of 3-bromo-2-hydroxypyridine, 17.9 ml (0.287 mol) of
iodomethane, 1.06 g (2.87 mmol) of tetra-*n*-butylammonium iodide and 19.9 g (0.144 mol) of
potassium carbonate in 60 ml of toluene is stirred at 40°C for 15 hours. 250 ml of water are then
added, and the reaction mixture is extracted with ethyl acetate. The organic extract is washed with
saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After filtration
15 and removal of the solvent on a rotary evaporator, the product is isolated by filtration with suction
through silica gel using the mobile phase cyclohexane/ethyl acetate 1:1 → 1:3. This gives 4.97 g
(92% of theory) of the title compound.

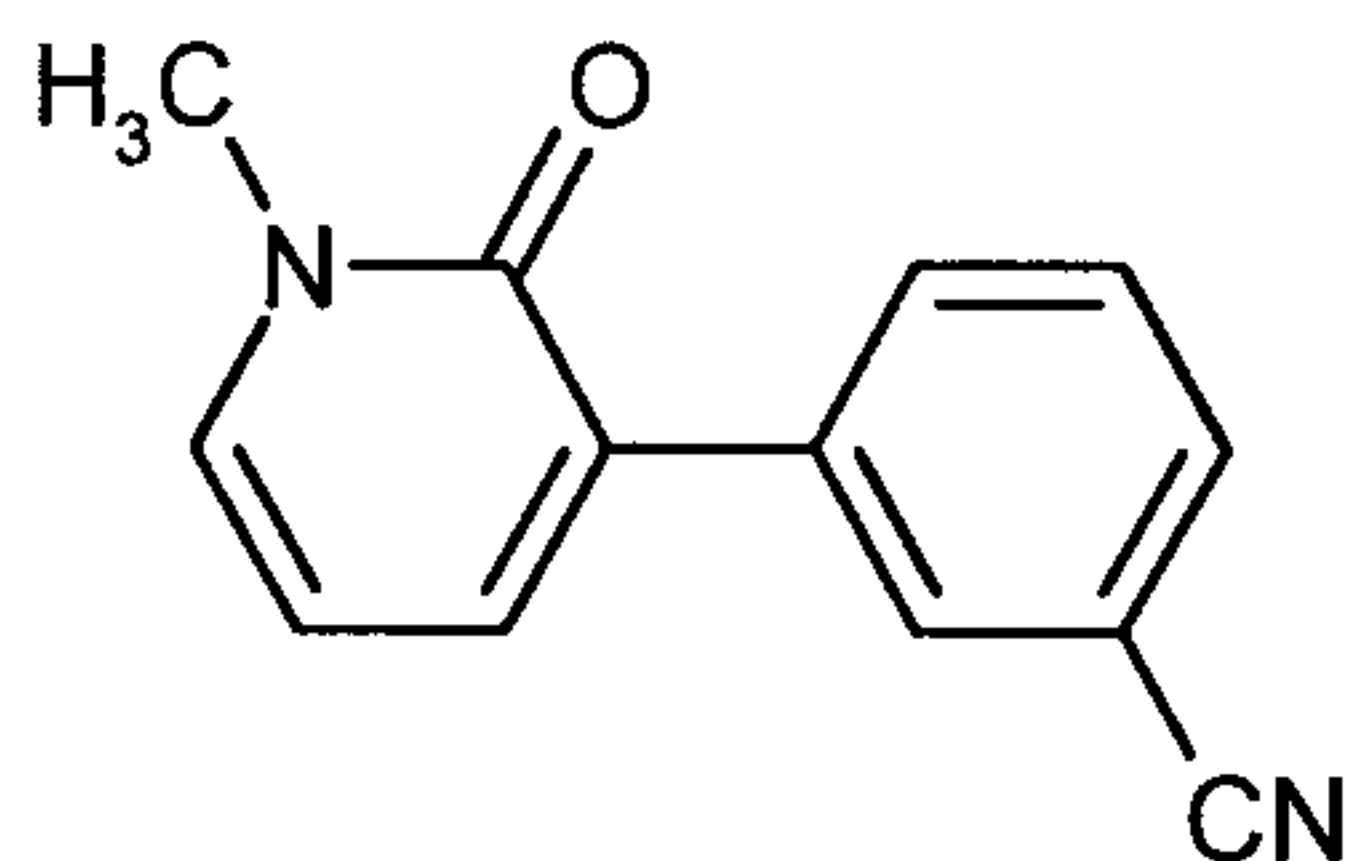
GC/MS (Method 13): $R_t = 5.62$ min;

MS (ES⁺): $m/z = 187/189$ (⁷⁹Br/⁸¹Br) (M)⁺;

- 20 ¹H-NMR (400 MHz, CDCl₃): $\delta = 7.73$ (dd, 1H), 7.30 (dd, 1H), 6.06 (dd, 1H), 3.61 (s, 3H).

Example 29A

3-(1-Methyl-2-oxo-1,2-dihydropyridin-3-yl)benzonitrile



33 ml of a 2 molar aqueous sodium carbonate solution and 1.51 g (1.31 mmol) of tetrakis
5 (triphenylphosphine)palladium(0) are added to a mixture of 4.92 g (26.2 mmol) of the compound
from Example 28A and 4.61 g (31.4 mmol) of 3-cyanophenylboronic acid in 90 ml of 1,4-dioxane.
The reaction mixture is heated at reflux for 15 hours. Water is then added, and the reaction mixture
is extracted with ethyl acetate. The organic extract is washed with saturated sodium chloride
solution and dried over anhydrous magnesium sulphate. After filtration and removal of the solvent
10 on a rotary evaporator, the product is isolated by filtration with suction through silica gel using the
mobile phase cyclohexane/ethyl acetate 5:1. The product fraction is purified by recrystallization
from diethyl ether. This gives 3.41 g (62% of theory) of the title compound.

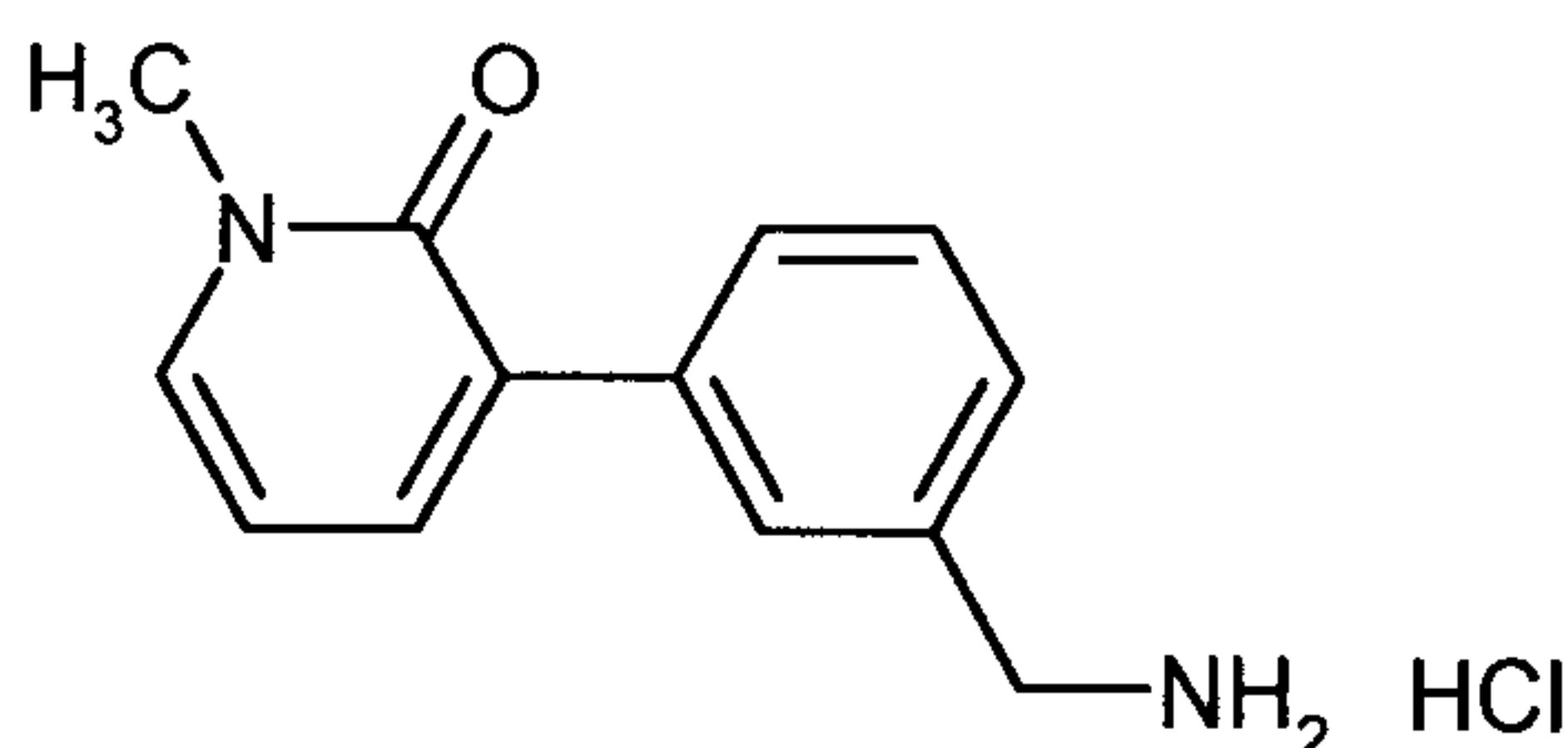
HPLC (Method 11): $R_t = 3.47$ min;

MS (DCI, NH_3): $m/z = 211$ ($\text{M}+\text{H}$)⁺, 228 ($\text{M}+\text{NH}_4$)⁺;

15 ¹H-NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 8.19$ (dd, 1H), 8.05 (dd, 1H), 7.82 (dd, 1H), 7.79-7.77 (m,
2H), 7.60 (dd, 1H), 6.37 (dd, 1H), 3.53 (s, 3H).

Example 30A

3-[3-(Aminomethyl)phenyl]-1-methylpyridin-2(1H)-one



20 11 ml of chloroform and 108 mg (0.476 mmol) of platinum(IV) oxide are added to a solution of
1.0 g (4.76 mmol) of the compound from Example 29A in 100 ml of ethanol. At a hydrogen
pressure of 3 bar, the mixture is hydrogenated at RT for 2 hours. The reaction mixture is then
filtered through Celite and freed from the solvent under reduced pressure. This gives 0.88 g (69%

of theory) of the title compound.

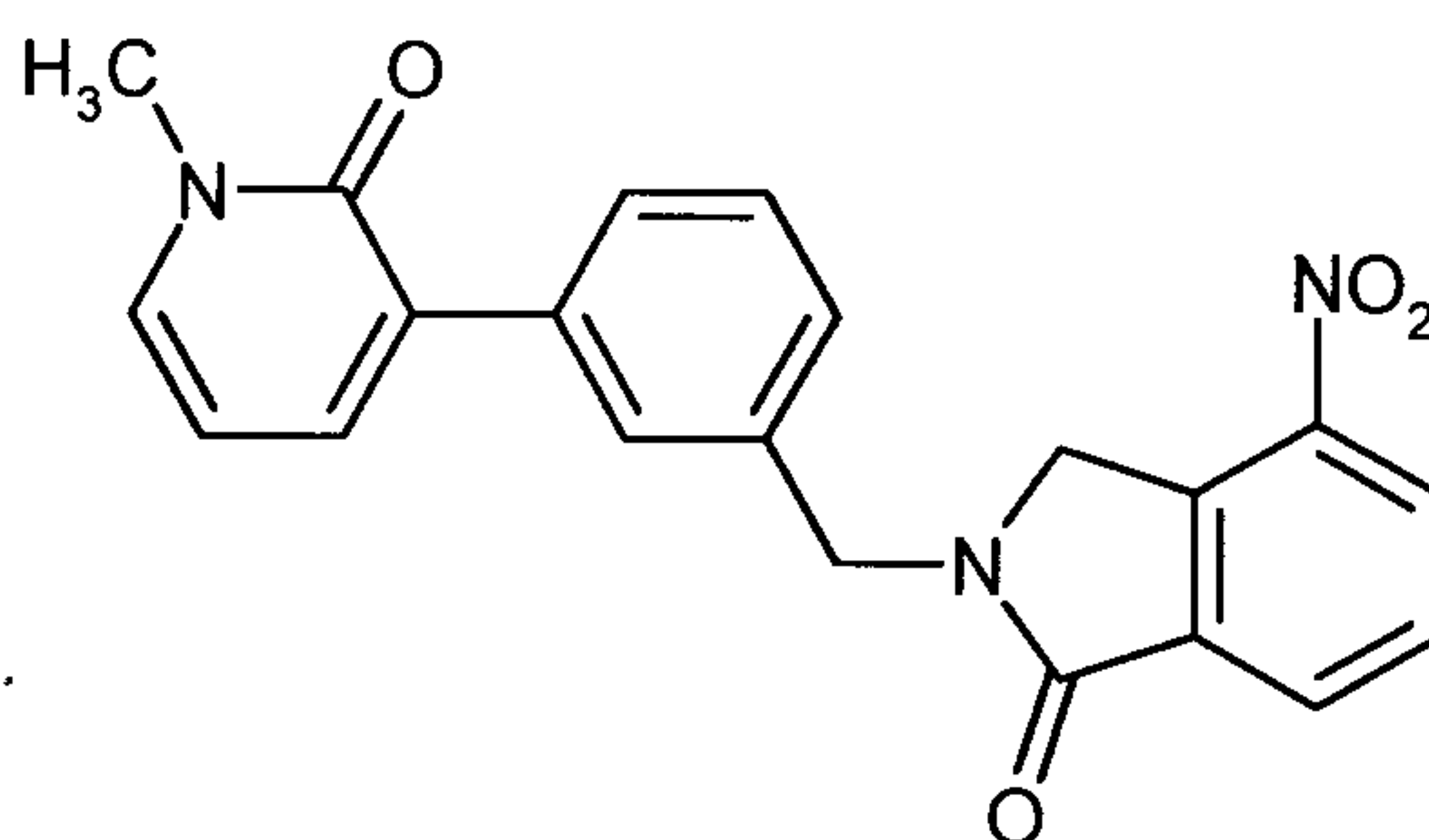
LC-MS (Method 14): $R_t = 2.05$ min;

MS (ESIpos): $m/z = 215$ ($M+H$)⁺;

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 8.47$ (broad, 3H), 7.80-7.74 (m, 3H), 7.67 (dd, 1H), 7.44-7.40
5 (m, 2H), 6.35 (dd, 1H), 4.03 (s, 2H), 3.52 (s, 3H).

Example 31A

2-[3-(1-Methyl-2-oxo-1,2-dihydropyridin-3-yl)benzyl]-4-nitroisindolin-1-one



At RT, 1 ml (7.43 mmol) of triethylamine is added to a solution of 926 mg (3.38 mmol) of the
10 compound from Example 11A (step A) and 847 mg (3.38 mmol) of the compound from
Example 30A in 20 ml of methanol. The reaction mixture is heated at reflux for 1.5 hours. On a
rotary evaporator, the reaction mixture is then concentrated to about half of its original volume.
The resulting precipitate is isolated and washed with a little methanol. This gives 866 mg (67% of
theory) of the title compound.

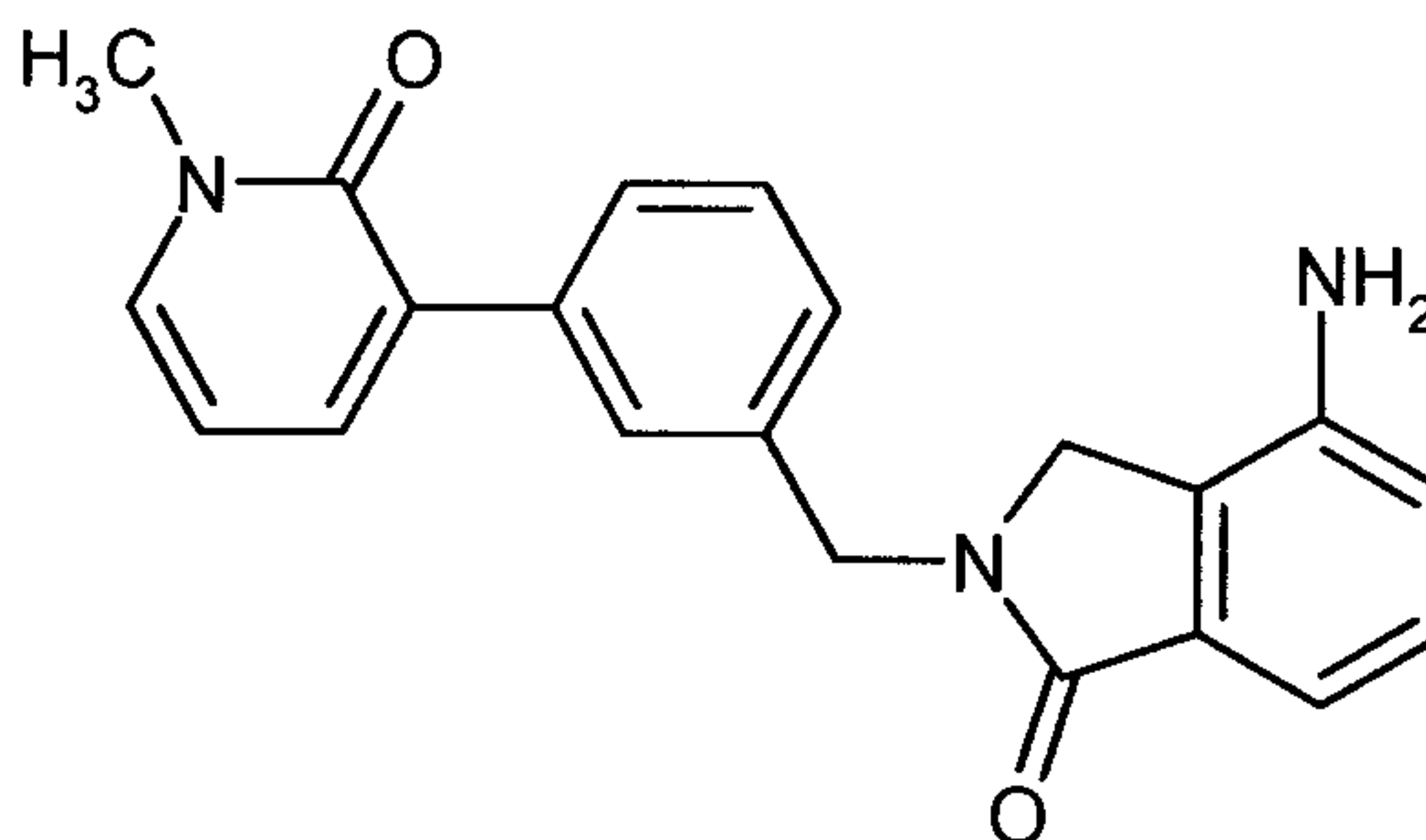
15 HPLC (Method 11): $R_t = 3.88$ min;

MS (DCI, NH₃): $m/z = 376$ ($M+H$)⁺, 393 ($M+NH_4$)⁺;

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 8.42$ (d, 2H), 8.17 (d, 1H), 7.82 (dd, 1H), 7.73 (dd, 1H), 7.68
(d, 1H), 7.63-7.59 (m, 2H), 7.38 (dd, 1H), 7.28 (dd, 1H), 6.31 (dd, 1H), 4.83 (s, 2H), 4.82 (s, 2H),
3.50 (s, 3H).

Example 32A

4-Amino-2-[3-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)benzyl]isoindolin-1-one



Analogously to the process described in Example 27A, 846 mg (2.25 mmol) of the compound from
5 Example 31A are converted into 658 mg (80% of theory) of the title compound.

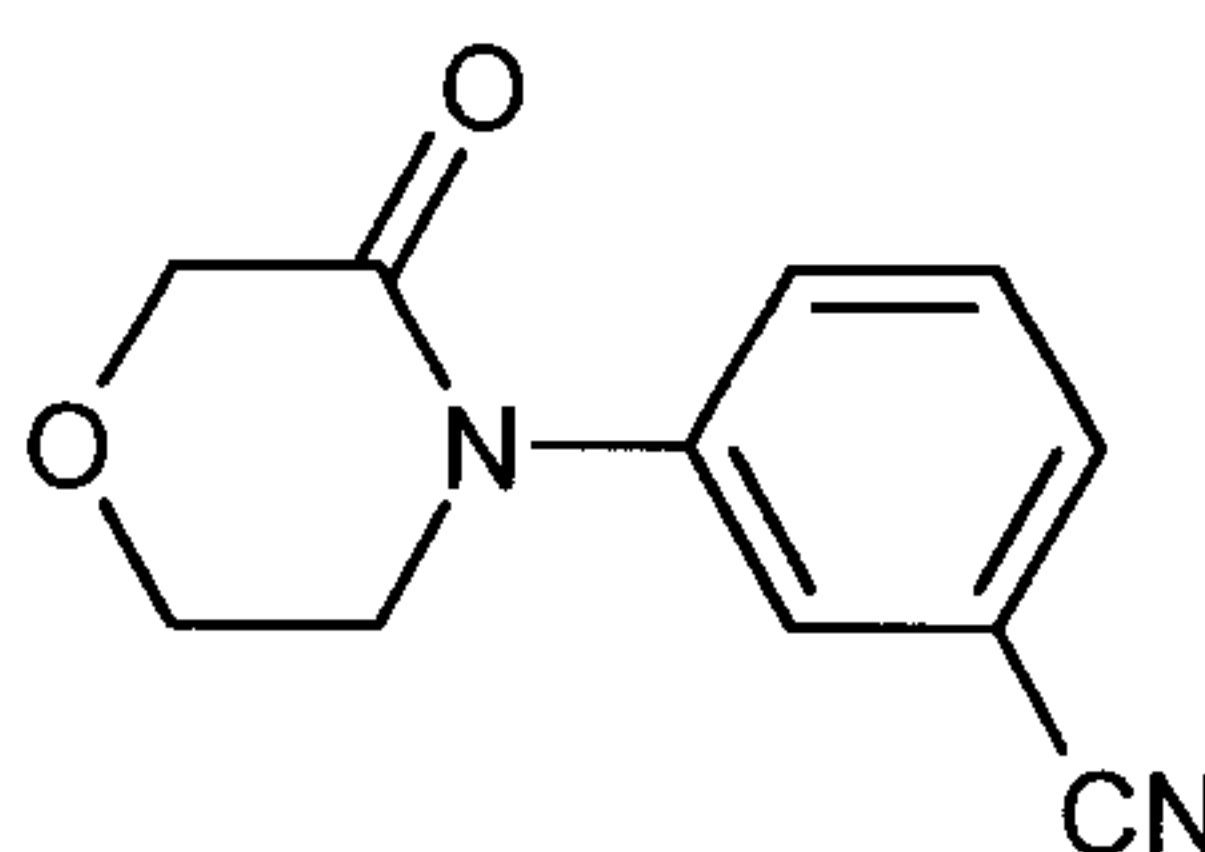
LC-MS (Method 15): $R_t = 2.09$ min;

MS (ES⁺): $m/z = 346$ (M+H)⁺;

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 7.73$ (dd, 1H), 7.62-7.58 (m, 3H), 7.37 (dd, 1H), 7.20-7.14
10 (m, 2H), 7.90 (d, 1H), 6.74 (d, 1H), 6.31 (dd, 1H), 5.37 (s, 2H), 4.74 (s, 2H), 4.12 (s, 2H), 3.49 (s,
3H).

Example 33A

3-(3-Oxomorpholin-4-yl)benzonitrile



Analogously to the process described in Example 21A, 6.5 g (28.4 mmol) of 3-iodobenzonitrile
15 and 3.44 g (34.1 mmol) of morpholinone give 5.35 g (91% of theory) of the title compound. The
reaction is carried out in dioxane as solvent.

HPLC (Method 11): $R_t = 2.91$ min;

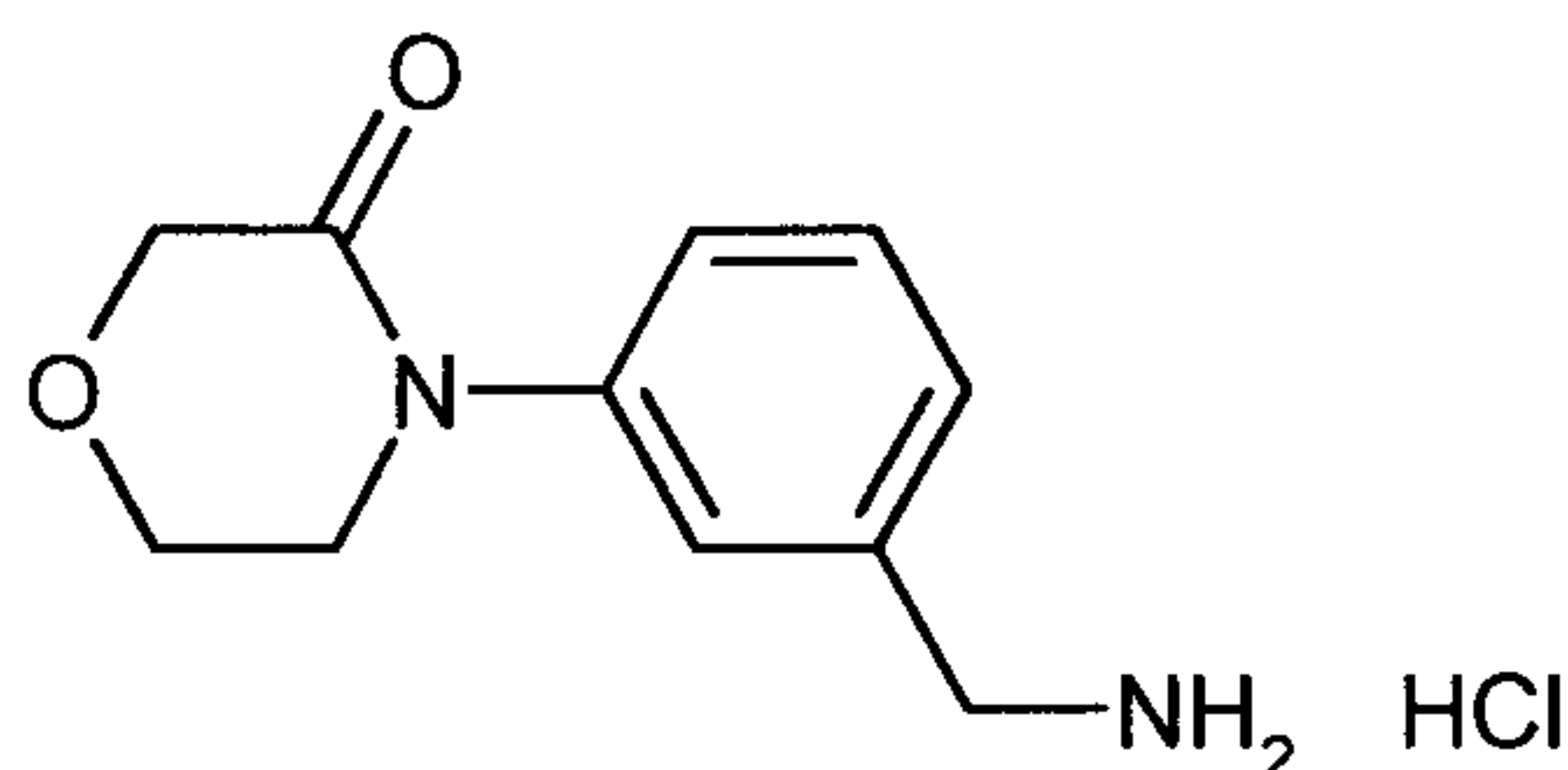
MS (DCI, NH₃): $m/z = 203$ (M+H)⁺, 220 (M+NH₄)⁺;

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 7.95$ (dd, 1H), 7.80 (ddd, 1H), 7.73 (ddd, 1H), 7.62 (dd, 1H),

4.23 (s, 2H), 3.99 (dd, 2H), 3.79 (dd, 2H).

Example 34A

4-[3-(Aminomethyl)phenyl]morpholin-3-one hydrochloride



- 5 Analogously to the process described in Example 30A, 5.30 g (26.2 mmol) of the compound from Example 33A give 5.96 g (91% of theory) of the title compound. The product is recrystallized from acetonitrile/diethyl ether 1:1.

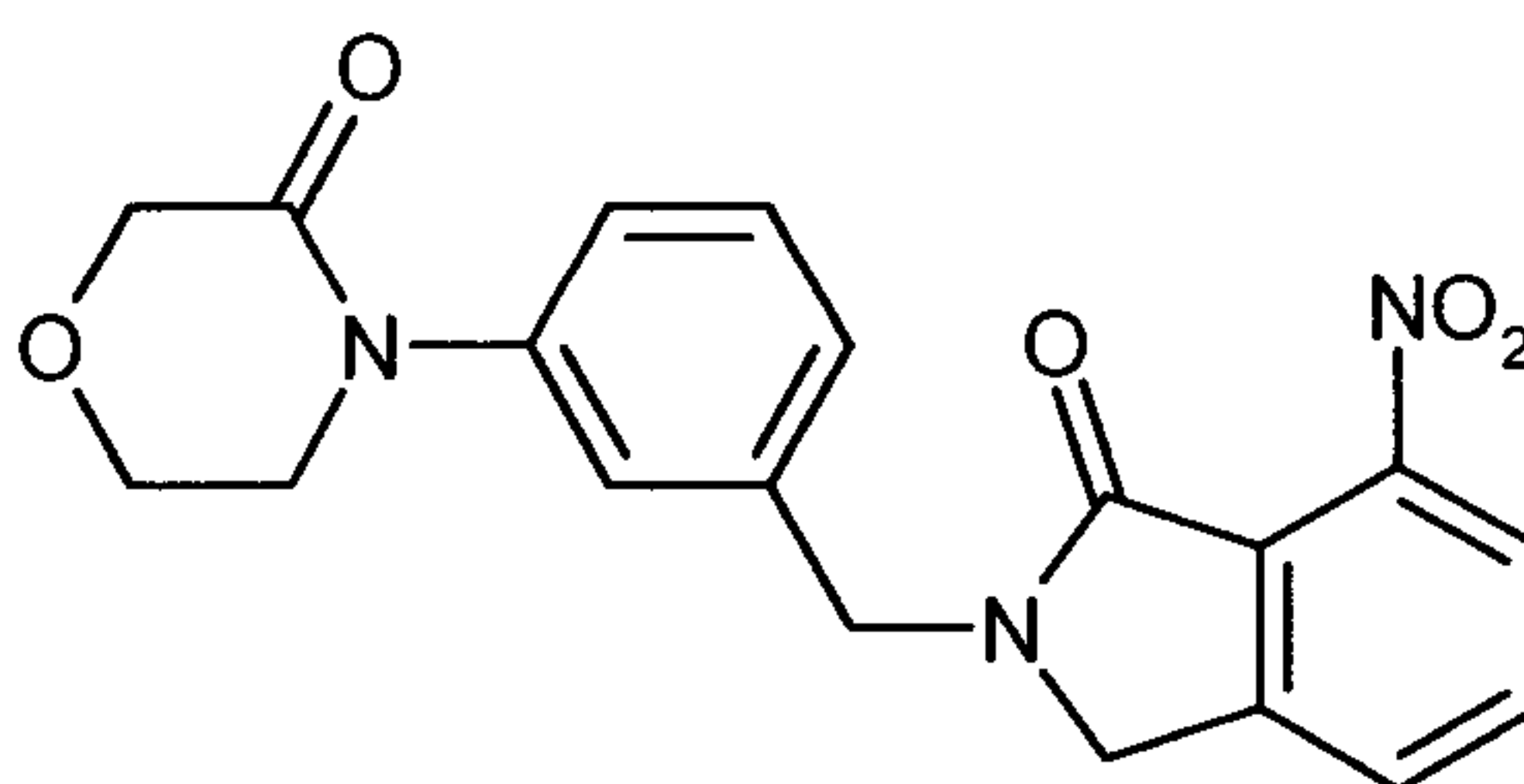
HPLC (Method 11): $R_t = 1.73$ min;

MS (DCI, NH_3): $m/z = 207$ ($\text{M}+\text{H}^+$), 224 ($\text{M}+\text{NH}_4^+$);

- 10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 8.20$ (broad, 3H), 7.52 (ddd, 1H), 7.47 (dd, 1H), 7.42 (ddd, 1H), 7.38 (ddd, 1H), 4.23 (s, 2H), 4.03 (s, 2H), 4.00 (dd, 2H), 3.72 (dd, 2H).

Example 35A

7-Nitro-2-[3-(3-oxomorpholin-4-yl)benzyl]isoindolin-1-one



- 15 Analogously to the process described in Example 31A, 2.97 g (10.8 mmol) of the compound from Example 9A (step A) and 2.63 g (10.8 mmol) of the compound from Example 34A are converted into 2.70 g (68% of theory) of the title compound. The product is chromatographed on silica gel using dichloromethane as solvent.

HPLC (Method 11): $R_t = 3.53$ min;

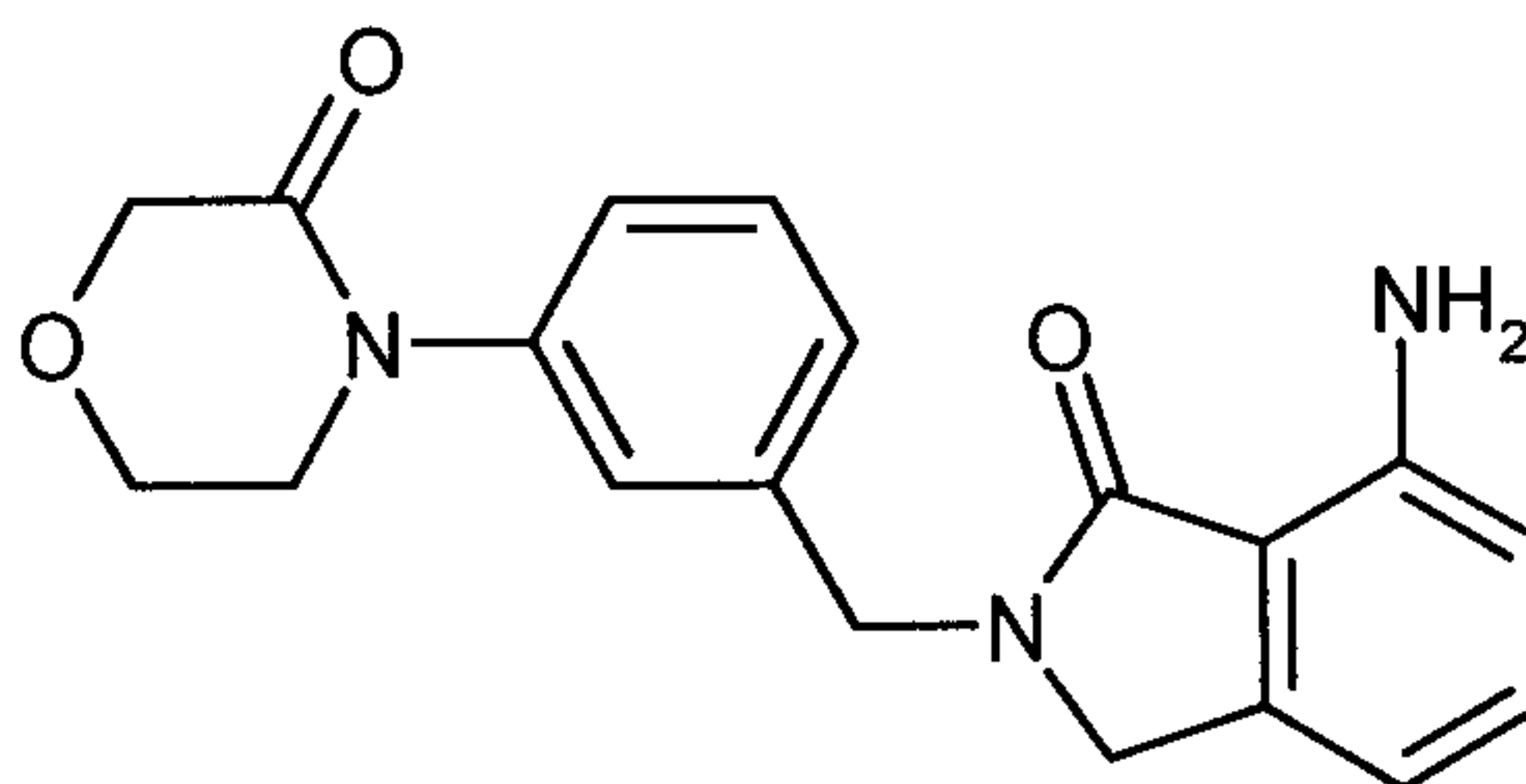
- 20 MS (DCI, NH_3): $m/z = 368$ ($\text{M}+\text{H}^+$), 385 ($\text{M}+\text{NH}_4^+$);

- 75 -

¹H-NMR (400 MHz, DMSO-d₆): δ = 7.90 (dd, 1H), 7.87 (dd, 1H), 7.81 (dd, 1H), 7.41 (dd, 1H), 7.37 (dd, 1H), 7.33 (ddd, 1H), 7.21 (ddd, 1H), 4.73 (s, 2H), 4.50 (s, 2H), 4.18 (s, 2H), 3.96 (dd, 2H), 3.72 (dd, 2H).

Example 36A

- 5 7-Amino-2-[3-(3-oxomorpholin-4-yl)benzyl]isoindolin-1-one



Analogously to the process described in Example 27A, 2.68 g (7.29 mmol) of the compound from Example 35A are converted into 2.42 g (91% of theory) of the title compound.

HPLC (Method 11): R_t = 3.32 min;

- 10 MS (DCI, NH₃): m/z = 338 (M+H)⁺, 355 (M+NH₄)⁺;

¹H-NMR (400 MHz, DMSO-d₆): δ = 7.40 (dd, 1H), 7.30 (s, 1H), 7.29 (d, 1H), 7.19 (dd, 1H), 7.17 (d, 1H), 6.60 (d, 1H), 6.57 (d, 1H), 6.08 (s, 2H), 4.64 (s, 2H), 4.24 (s, 2H), 4.18 (s, 2H), 3.95 (dd, 2H), 3.71 (dd, 2H).

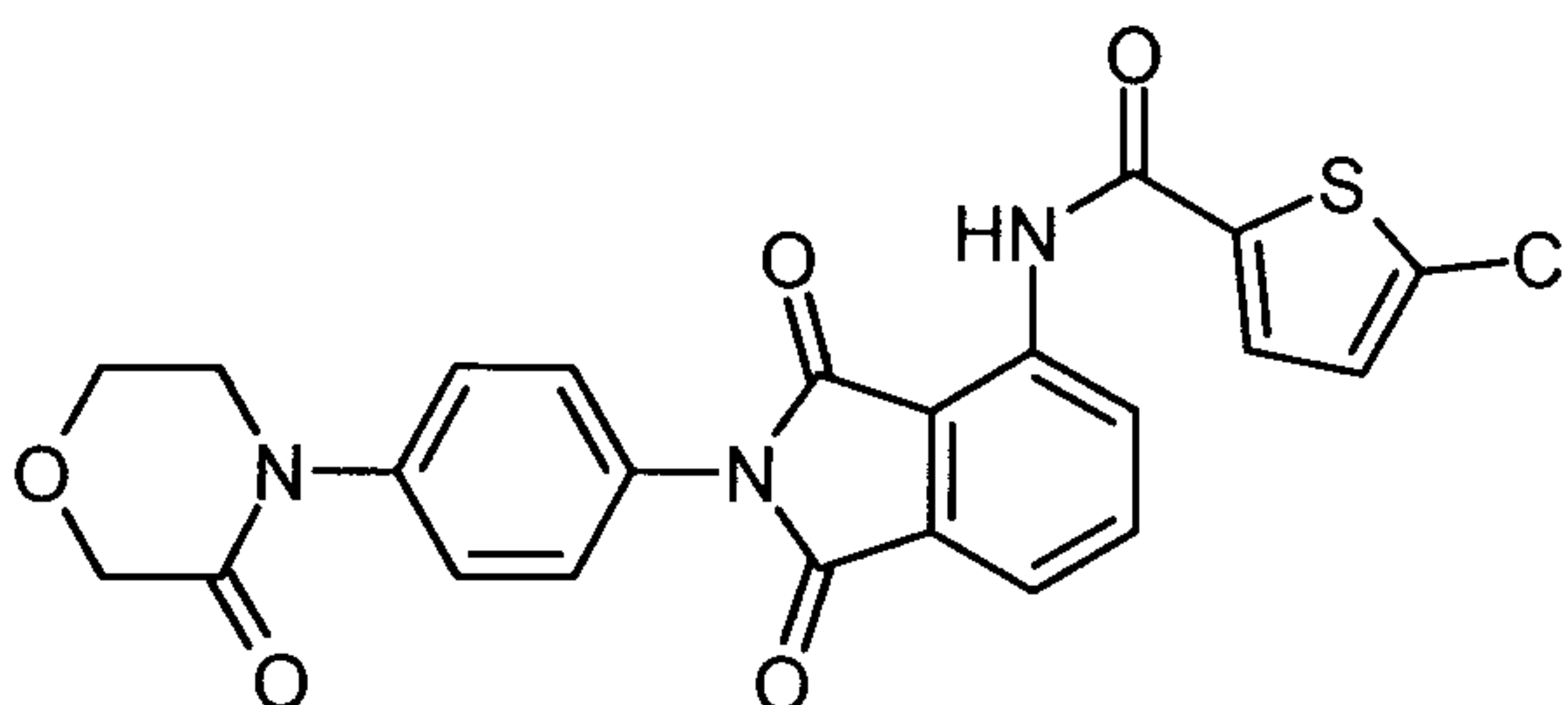
Working examples

General method 1 for coupling aryl iodides with lactams:

Under argon and at RT, the appropriate aryl iodide (1 eq.), lactam (1.5 eq.) and *N,N'*-dimethylethylenediamine (0.4 eq.) are added to a suspension of copper(I) iodide (0.2 eq.) and potassium phosphate (2 eq.) in dioxane (30 ml/mmol). The reaction mixture is stirred under reflux and, after cooling to RT, filtered, and the residue is washed with dioxane. The combined filtrates are concentrated under reduced pressure. The title compound is isolated by preparative RP-HPLC (CromSil C18, acetonitrile/water gradient).

Example 1

10 5-Chloro-*N*-{1,3-dioxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



At RT, 1.1 ml (7.8 mmol, 5 eq.) of triethylamine are added to a solution of 480 mg (1.56 mmol) of 5-chloro-*N*-(1,3-dioxo-1,3-dihydro-2-benzofuran-4-yl)thiophene-2-carboxamide (Example 3A) and 300 mg (1.56 mmol, 1 eq.) of 4-(4-aminophenyl)morpholin-3-one (Example 17A) in 7 ml of dioxane. The reaction mixture is stirred under reflux for 4 h and then cooled in an ice-bath. The precipitate formed is filtered off, washed with dioxane and dried under reduced pressure.

Yield: 633 mg (84% of theory)

HPLC (Method 11): $R_t = 4.54$ min;

20 MS (ESIpos): $m/z = 482$ $[M+H]^+$;

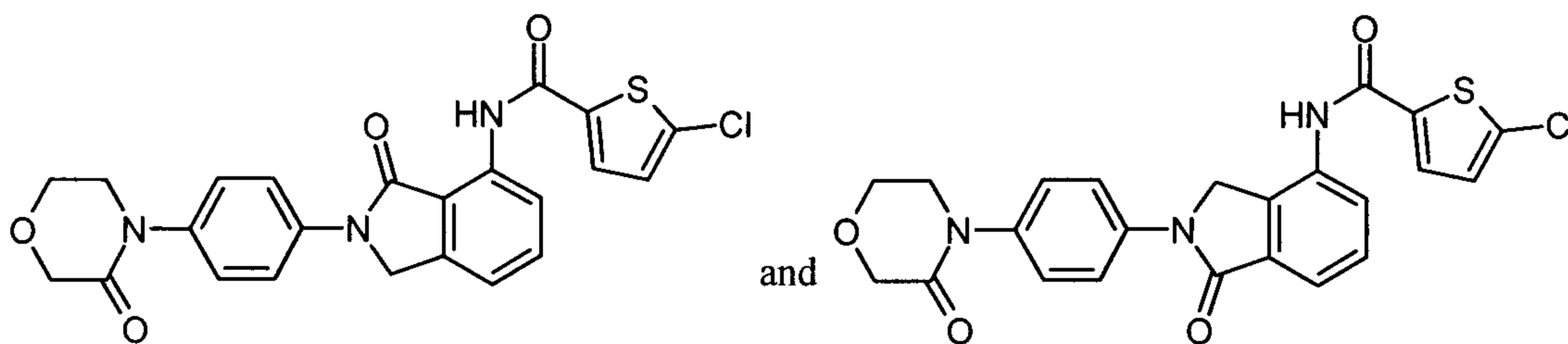
$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): $\delta = 10.50$ (s, 1H), 8.42 (d, 1H), 7.92 (t, 1H), 7.78 (d, 1H), 7.74 (d, 1H), 7.58 (d, 2H), 7.50 (d, 2H), 7.33 (d, 1H), 4.23 (s, 2H), 4.00 (t, 2H), 3.82 (t, 2H).

Example 2 and Example 3

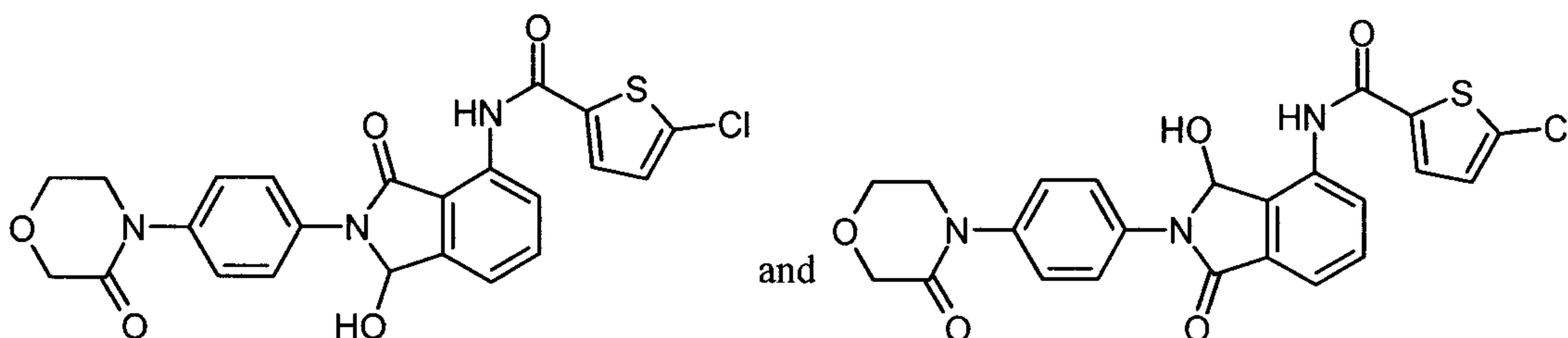
5-Chloro-*N*-{3-oxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-

- 77 -

carboxamide (Example 2) and 5-chloro-*N*-{1-oxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide (Example 3)



Step a): Isomer mixture of 5-chloro-*N*-{1-hydroxy-3-oxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide and 5-chloro-*N*-{3-hydroxy-1-oxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



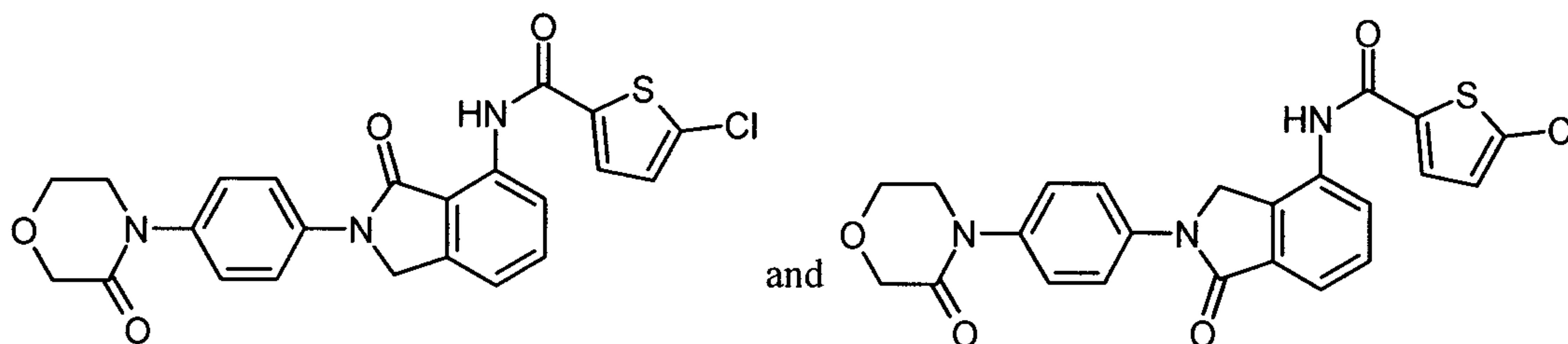
Under argon and at 0°C, 35 mg (0.93 mmol, 1.5 eq.) of sodium borohydride are added to a solution of 300 mg (0.62 mmol) of 5-chloro-*N*-{1,3-dioxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide (Example 1) in a mixture of 20 ml of methanol and 20 ml of dichloromethane. The reaction mixture is stirred at RT for 2 h and adjusted to pH 5 using hydrochloric acid (1 N). After addition of dichloromethane and phase separation, the aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are dried over magnesium sulphate, filtered and concentrated under reduced pressure. Without further purification, the crude product is used for the next step.

Yield: 240 mg (80% of theory)

LC-MS (Method 1): $R_t = 1.80$ min;

MS (ESIpos): $m/z = 483$ $[M+H]^+$.

Step b): 5-Chloro-*N*-{3-oxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide and 5-chloro-*N*-{1-oxo-2-[4-(3-oxomorpholin-4-yl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



- 5 Under argon and at RT, 0.23 ml (3.0 mmol, 6 eq.) of trifluoroacetic acid and 79 μ l (0.5 mmol, 1 eq.) of triethylsilane are added dropwise to a solution of 240 mg (0.5 mmol) of the isomer mixture from step a) in 3 ml of dichloromethane. The reaction mixture is stirred at RT for 2 d, and saturated aqueous sodium bicarbonate solution is added. After addition of dichloromethane and phase separation, the aqueous phase is extracted repeatedly with dichloromethane. The combined
- 10 organic phases are dried over magnesium sulphate, filtered and concentrated under reduced pressure. The isomers are isolated by preparative RP-HPLC (CromSil C18, acetonitrile/water gradient).

Example 2 (isomer 1):

Yield: 2 mg (2% of theory)

- 15 LC-MS (Method 1): $R_t = 2.43$ min;

MS (ESIpos): $m/z = 468$ $[M+H]^+$;

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 11.28$ (s, 1H), 8.31 (d, 1H), 7.93 (d, 2H), 7.69 (t, 1H), 7.67 (d, 1H), 7.50 (d, 2H), 7.40 (d, 1H), 7.36 (d, 1H), 5.10 (s, 2H), 4.22 (s, 2H), 4.00 (t, 2H), 3.78 (t, 2H).

Example 3 (isomer 2):

- 20 Yield: 44 mg (38% of theory)

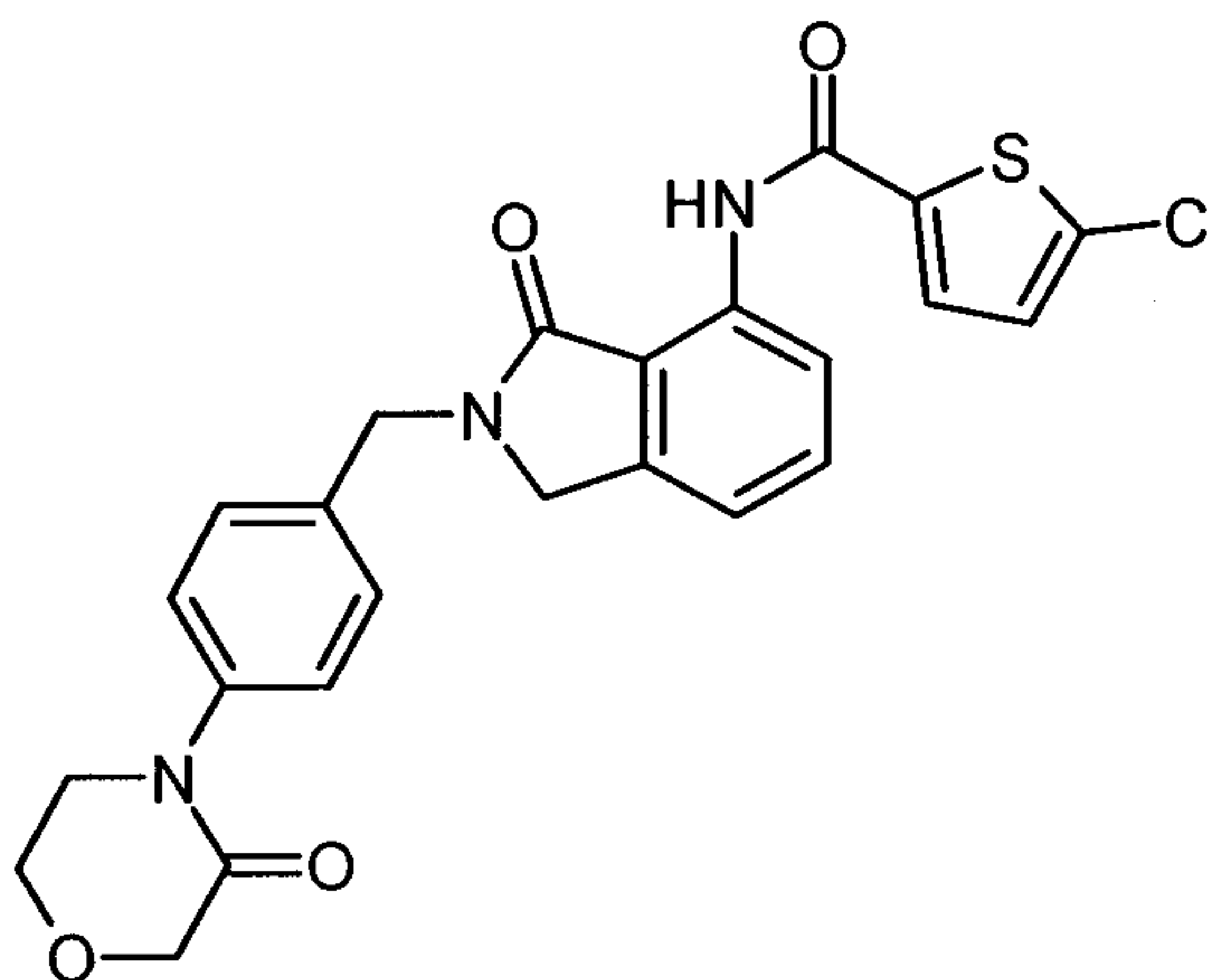
HPLC (Method 9): $R_t = 4.15$ min;

MS (ESIpos): $m/z = 468$ $[M+H]^+$;

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 10.50$ (s, 1H), 7.98-7.89 (m, 3H), 7.76 (d, 1H), 7.70 (d, 1H), 7.60 (t, 1H), 7.47 (d, 2H), 7.33 (d, 1H), 5.04 (s, 2H), 4.21 (s, 2H), 3.99 (t, 2H), 3.76 (t, 2H).

Example 4

5-Chloro-*N*-{3-oxo-2-[4-(3-oxomorpholin-4-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



- 5 According to the general method 1, 76 mg (0.15 mmol) of 5-chloro-*N*-[2-(4-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 6A) are reacted with 23 mg (0.23 mmol, 1.5 eq.) morpholin-3-one (Example 16A).

Yield: 58 mg (53% of theory)

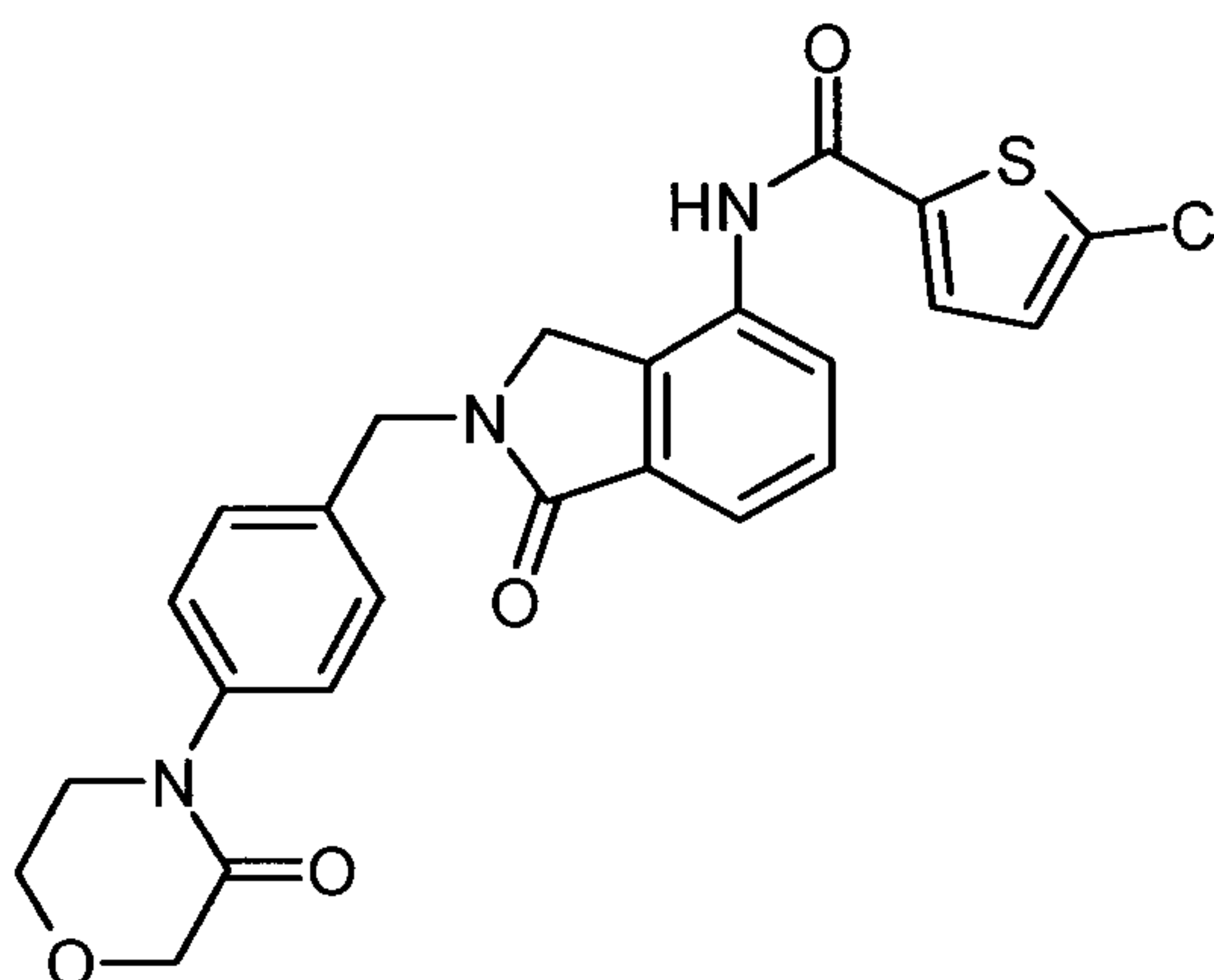
LC-MS (Method 1): $R_t = 2.34$ min;

- 10 MS (ESIpos): $m/z = 482$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 11.27$ (s, 1H), 8.24 (d, 1H), 7.63 (d, 1H), 7.58 (t, 1H), 7.35 (m, 4H), 7.31 (d, 1H), 7.28 (d, 1H), 4.74 (s, 2H), 4.46 (s, 2H), 4.17 (s, 2H), 3.93 (t, 2H), 3.69 (t, 2H).

Example 5

5-Chloro-*N*-{1-oxo-2-[4-(3-oxomorpholin-4-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



- 5 According to the general method 1, 91 mg (84% pure, 0.15 mmol) of 5-chloro-*N*-[2-(4-iodobenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 7A) are reacted with 23 mg (0.23 mmol, 1.5 eq.) of morpholin-3-one (Example 16A).

Yield: 15 mg (14% of theory)

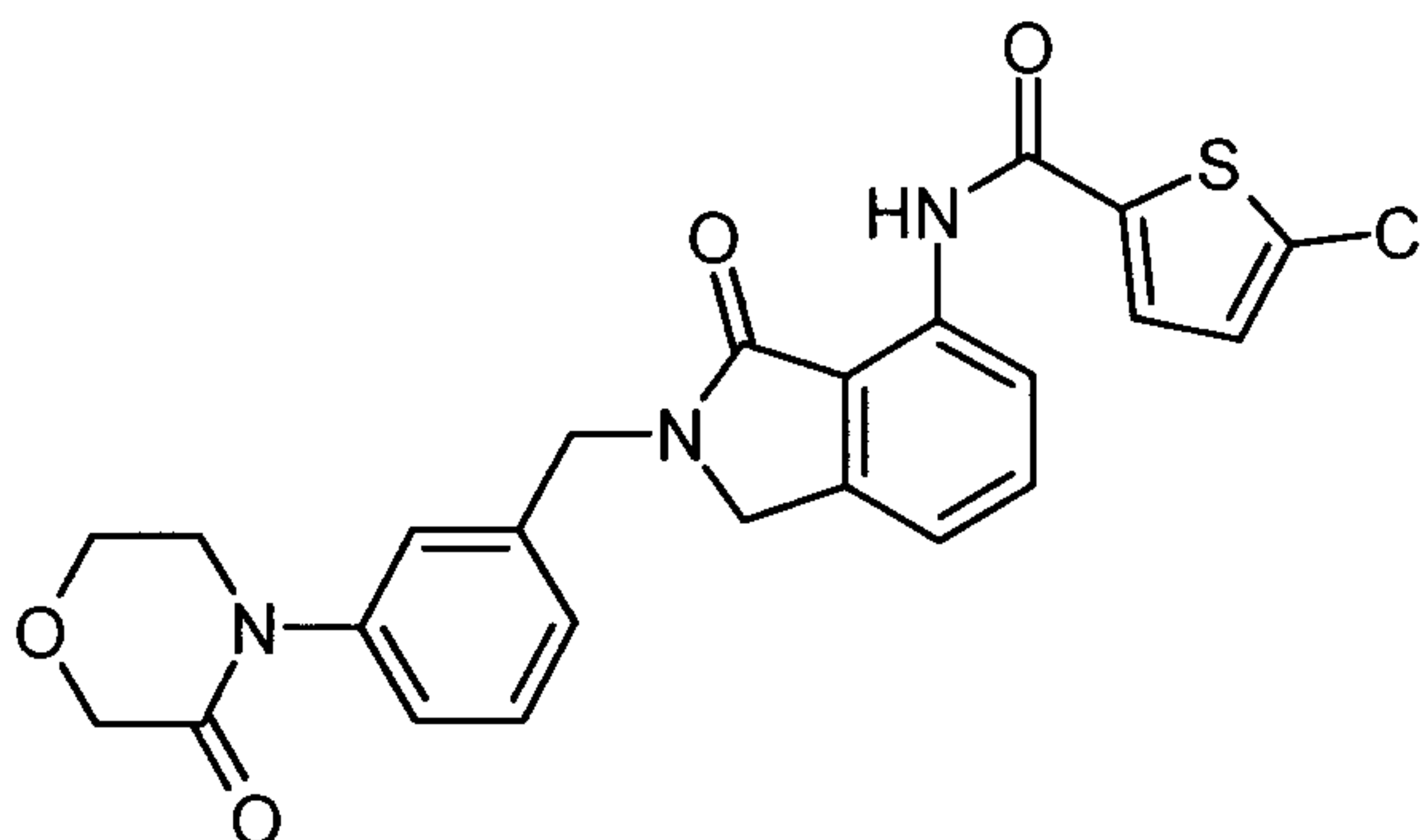
LC-MS (Method 1): $R_t = 1.86$ min;

- 10 MS (ESIpos): $m/z = 482$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 10.39$ (s, 1H), 7.87 (d, 1H), 7.67 (d, 1H), 7.63 (d, 1H), 7.55 (t, 1H), 7.38 (d, 2H), 7.31 (d, 2H), 7.28 (d, 1H), 4.74 (s, 2H), 4.43 (s, 2H), 4.19 (s, 2H), 3.95 (t, 2H), 3.71 (t, 2H).

Example 6

5-Chloro-*N*-{3-oxo-2-[3-(3-oxomorpholin-4-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



- 5 According to the general method 1, 100 mg (0.2 mmol) of 5-chloro-*N*-[2-(3-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 10A) are reacted with 30 mg (0.3 mmol, 1.5 eq.) of morpholin-3-one (Example 16A).

Yield: 34 mg (36% of theory)

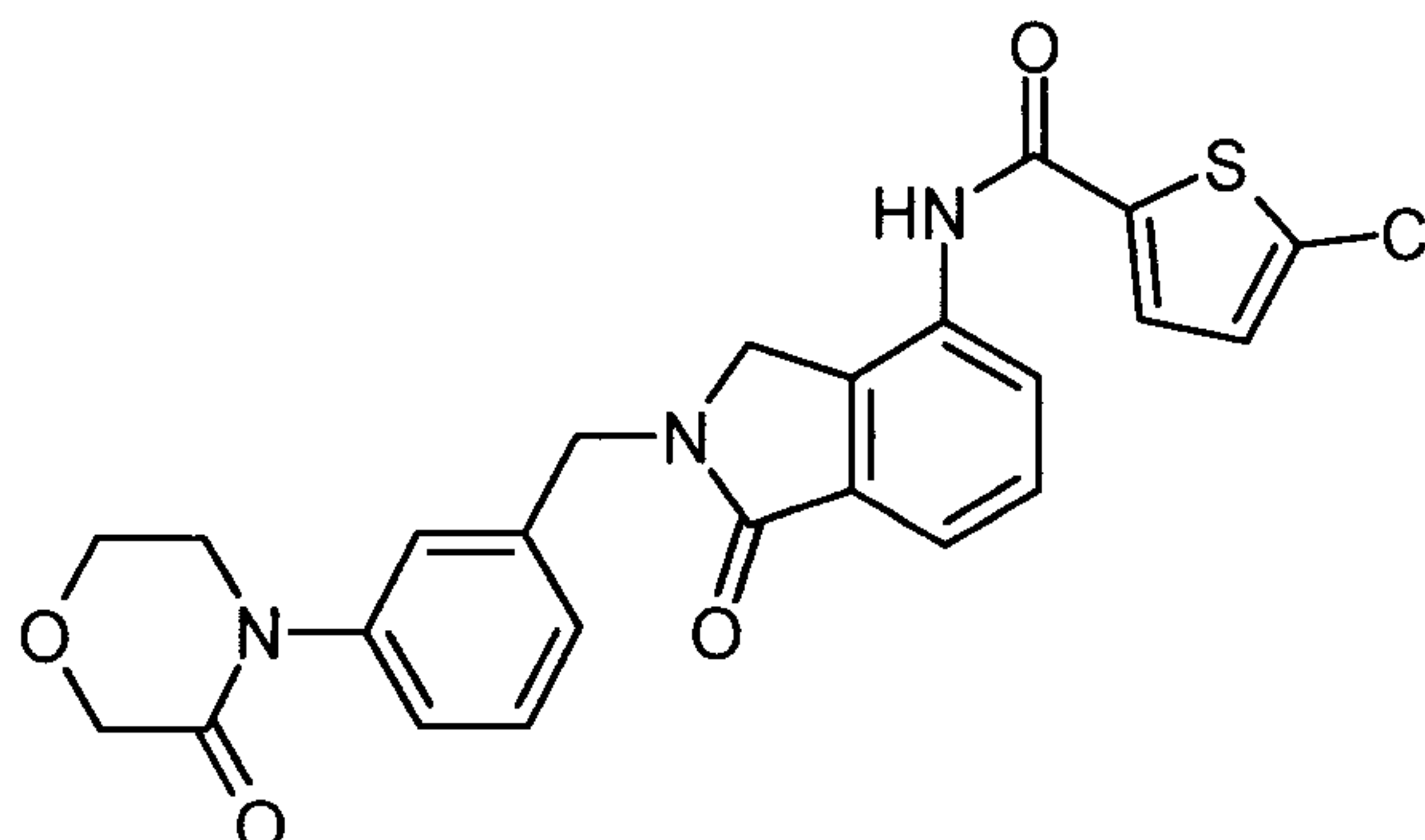
LC-MS (Method 1): $R_t = 2.35$ min;

- 10 MS (ESIpos): $m/z = 482$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 11.29$ (s, 1H), 8.28 (d, 1H), 7.67 (d, 1H), 7.60 (t, 1H), 7.42 (t, 1H), 7.38 (s, 1H), 7.35-7.28 (m, 3H), 7.24 (d, 1H), 4.78 (s, 2H), 4.48 (s, 2H), 4.19 (s, 2H), 3.97 (t, 2H), 3.73 (t, 2H).

Example 7

- 15 5-Chloro-*N*-{1-oxo-2-[3-(3-oxomorpholin-4-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



According to the general method 1, 76 mg (0.15 mmol) of 5-chloro-*N*-[2-(3-iodobenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 12A) are reacted with 23 mg (0.23 mmol, 1.5 eq.) of morpholin-3-one (Example 16A).

Yield: 40 mg (37% of theory)

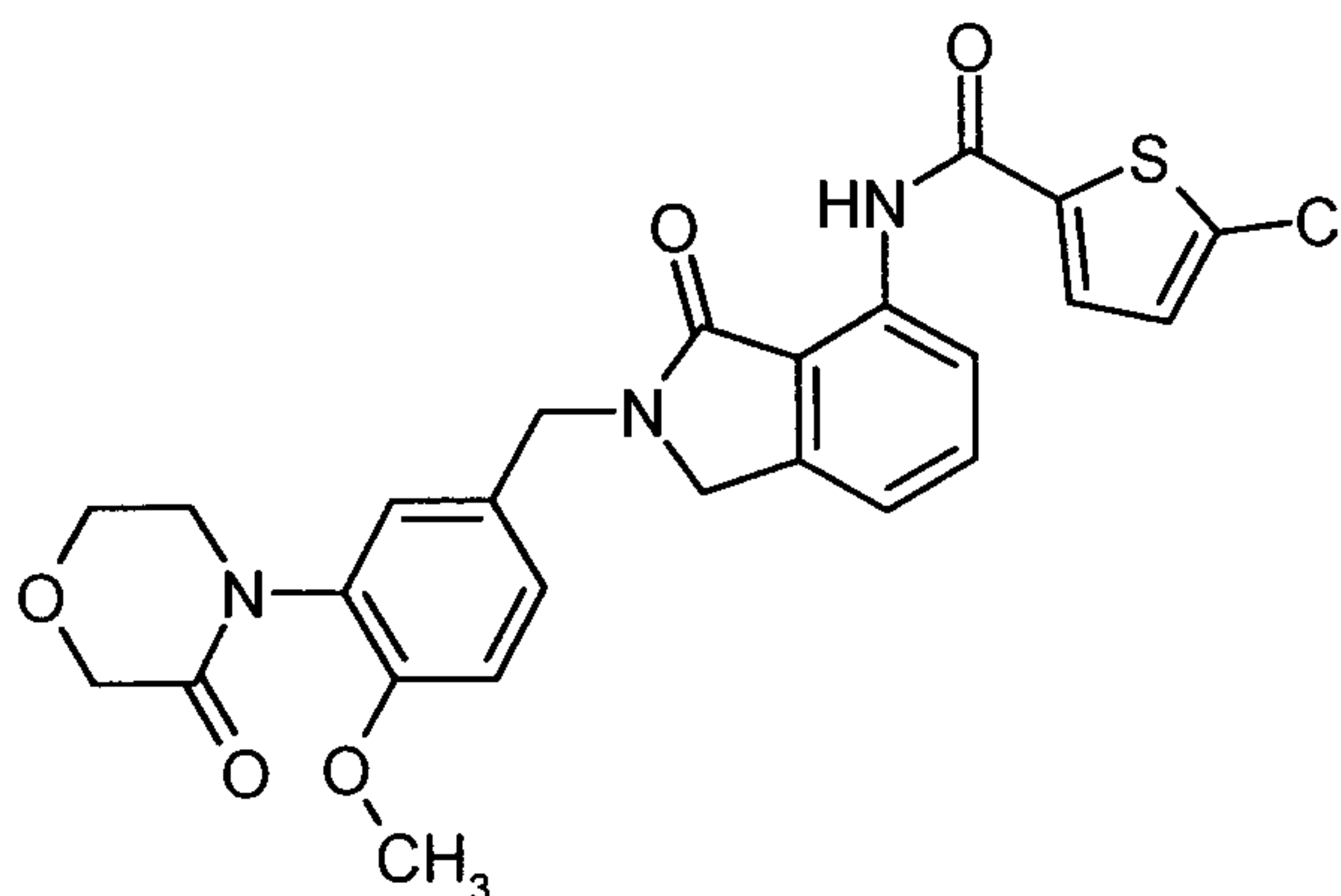
5 LC-MS (Method 1): $R_t = 1.88$ min;

MS (ESIpos): $m/z = 482$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 10.40$ (s, 1H), 7.85 (d, 1H), 7.67 (d, 1H), 7.61 (d, 1H), 7.55 (t, 1H), 7.40 (t, 1H), 7.34 (s, 1H), 7.31 (d, 1H), 7.28 (d, 1H), 7.18 (d, 1H), 4.75 (s, 2H), 4.42 (s, 2H), 4.18 (s, 2H), 3.95 (t, 2H), 3.71 (t, 2H).

10 **Example 8**

5-Chloro-*N*-{2-[4-methoxy-3-(3-oxomorpholin-4-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



According to the general method 1, 162 mg (0.3 mmol) of 5-chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 14A) are reacted with 45 mg (0.45 mmol, 1.5 eq.) of morpholin-3-one (Example 16A).

Yield: 83 mg (35% of theory)

LC-MS (Method 7): $R_t = 2.61$ min;

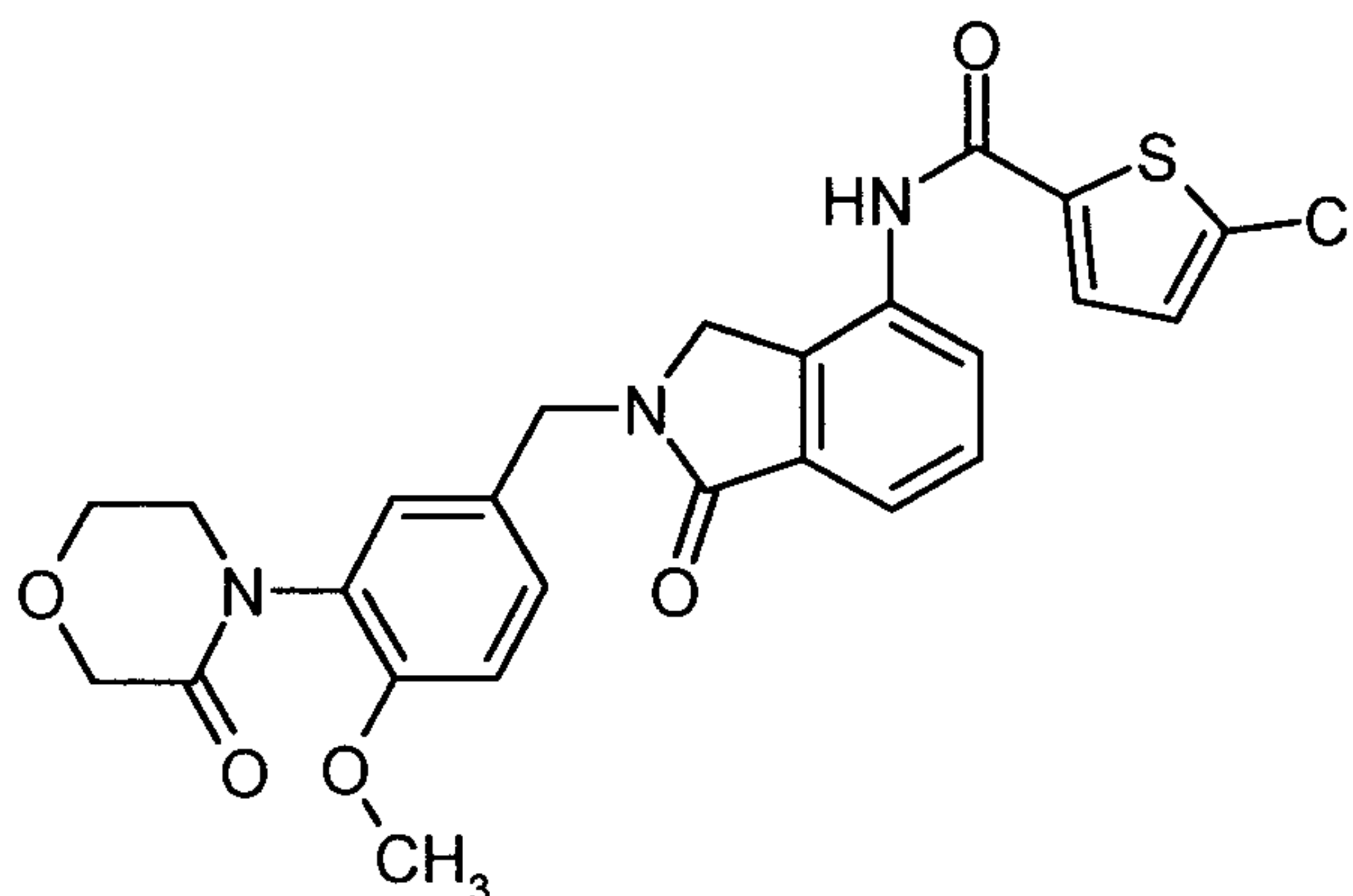
MS (ESIpos): $m/z = 512$ $[M+H]^+$;

20 $^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 11.30$ (s, 1H), 8.26 (d, 1H), 7.65 (d, 1H), 7.60 (t, 1H), 7.35 (d, 1H), 7.30 (t, 2H), 7.20 (s, 1H), 7.11 (d, 1H), 4.70 (s, 2H), 4.42 (s, 2H), 4.15 (s, 2H), 3.92 (t, 2H),

3.79 (s, 3H), 3.52 (t, 2H).

Example 9

5-Chloro-*N*-{2-[4-methoxy-3-(3-oxomorpholin-4-yl)benzyl]-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



5

According to the general method 1, 90 mg (0.17 mmol) of 5-chloro-*N*-[2-(3-iodo-4-methoxybenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 15A) are reacted with 25 mg (0.25 mmol, 1.5 eq.) of morpholin-3-one (Example 16A).

Yield: 13 mg (10% of theory)

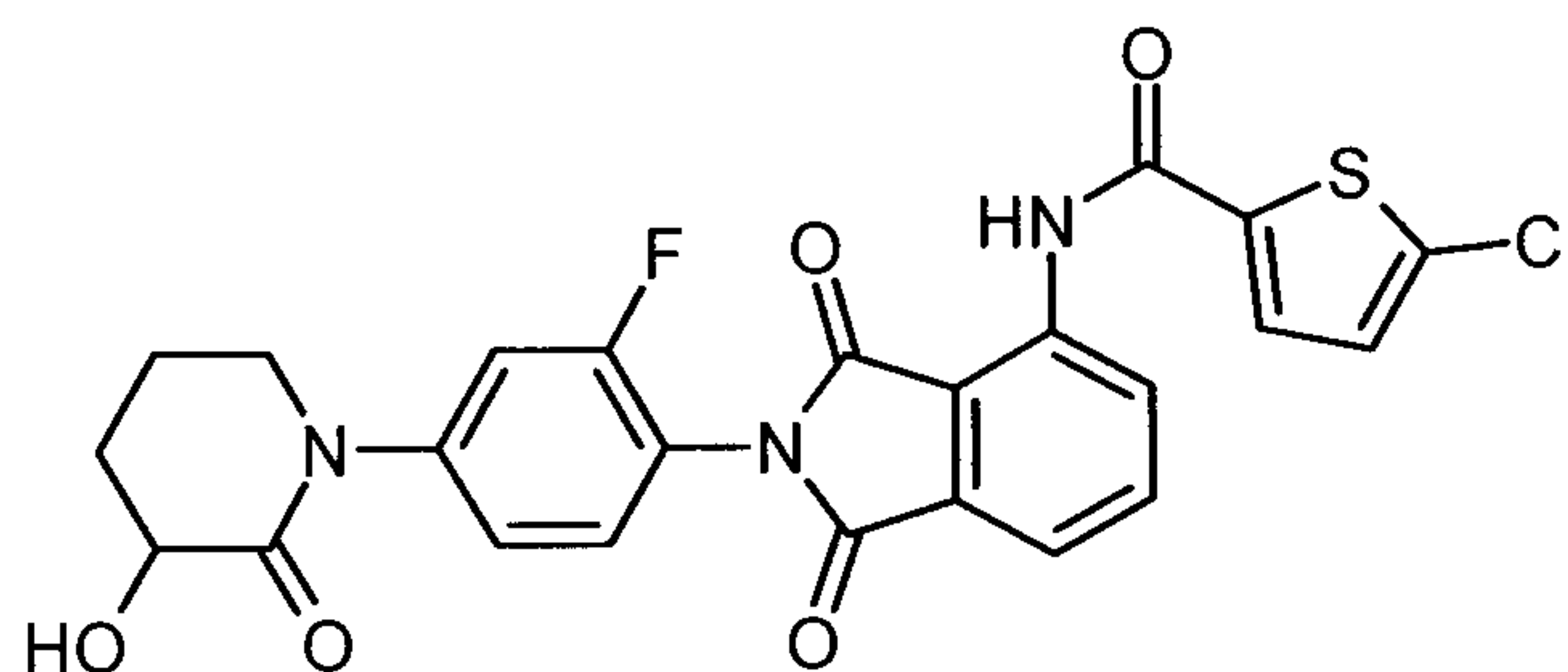
10 LC-MS (Method 8): $R_t = 2.05$ min;

MS (ESIpos): $m/z = 512$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 10.40$ (s, 1H), 7.87 (d, 1H), 7.64 (d, 1H), 7.61 (d, 1H), 7.54 (t, 1H), 7.29 (d, 1H), 7.26 (d, 1H), 7.16 (s, 1H), 7.10 (d, 1H), 4.68 (s, 2H), 4.40 (s, 2H), 4.15 (s, 2H), 3.92 (t, 2H), 3.78 (s, 3H), 5.51 (t, 2H).

Example 10

5-Chloro-*N*-{2-[2-fluoro-4-(3-hydroxy-2-oxopiperidin-1-yl)phenyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



- 5 At RT, 1.2 ml (6.7 mmol, 5 eq.) of *N,N*-diisopropylethylamine are added to a solution of 412 mg (1.34 mmol) of 5-chloro-*N*-(1,3-dioxo-1,3-dihydro-2-benzofuran-4-yl)thiophene-2-carboxamide (Example 3A) and 300 mg (1.34 mmol, 1 eq.) of 1-(4-amino-3-fluorophenyl)-3-hydroxypiperidin-2-one (Example 19A) in 5 ml of dioxane. The reaction mixture is stirred under reflux overnight and then cooled in an ice-bath. The precipitate formed is filtered off, washed with dioxane and
 10 dried under reduced pressure.

Yield: 459 mg (67% of theory)

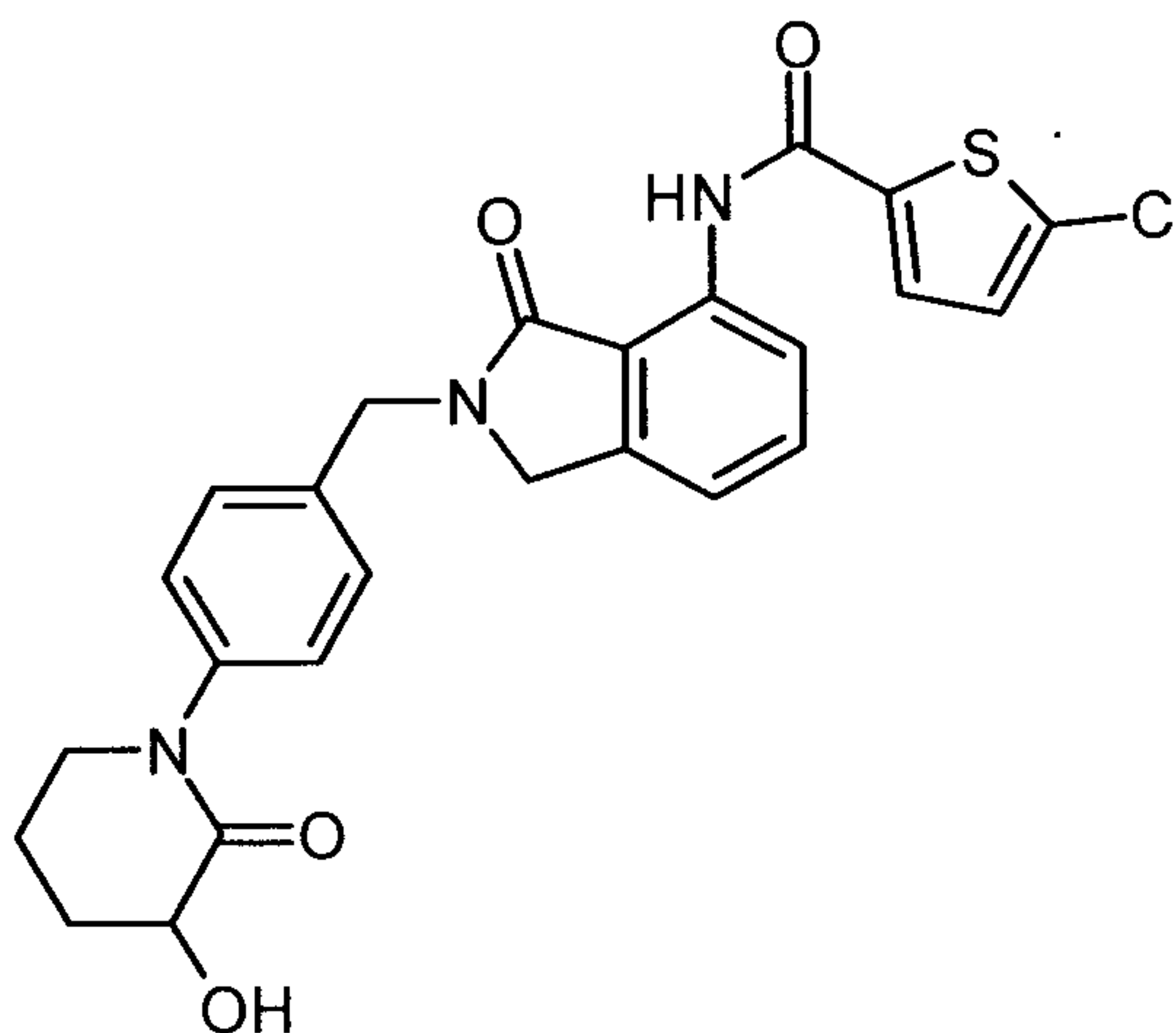
LC-MS (Method 3): $R_t = 2.61$ min;

MS (ESIpos): $m/z = 514$ $[M+H]^+$;

- $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 10.48$ (s, 1H), 8.40 (d, 1H), 7.95 (t, 1H), 7.87-7.71 (m, 2H),
 15 7.58 (t, 1H), 7.50 (d, 1H), 7.40-7.27 (m, 2H), 5.49 (s, 1H), 4.12 (m, 1H), 3.85-3.70 (m, 1H), 3.70-3.60 (m, 1H), 2.20-2.07 (m, 1H), 2.07-1.84 (m, 2H), 1.84-1.70 (m, 1H).

Example 11

5-Chloro-*N*-{2-[4-(3-hydroxy-2-oxopiperidin-1-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



- 5 According to the general method 1, 76 mg (0.15 mmol) of 5-chloro-*N*-[2-(4-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 6A) are reacted with 26 mg (0.23 mmol, 1.5 eq.) of 3-hydroxypiperidin-2-one (Example 18A).

Yield: 14 mg (12% of theory)

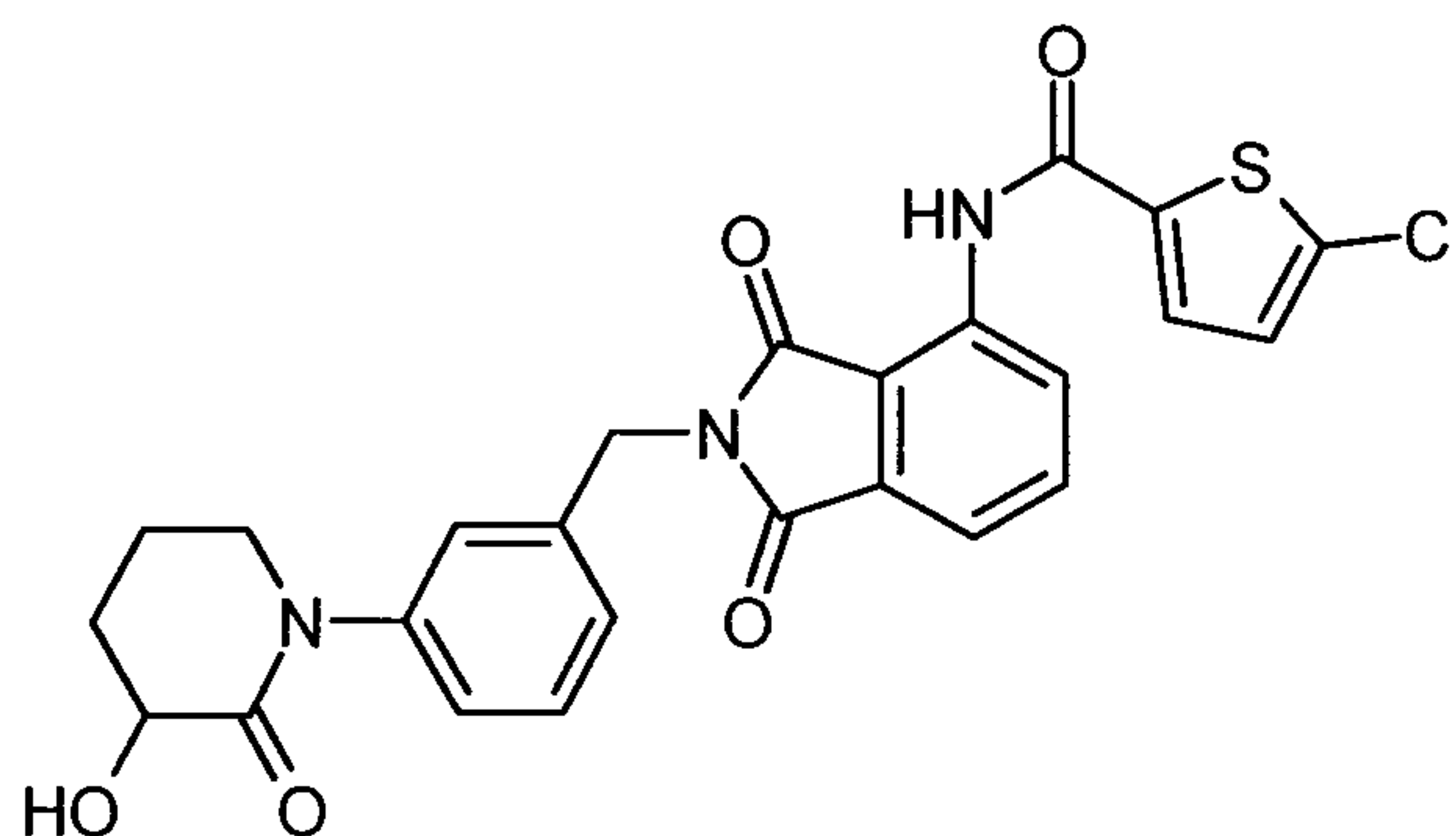
LC-MS (Method 8): $R_t = 2.47$ min;

- 10 MS (ESIpos): $m/z = 496$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 11.29$ (s, 1H), 8.26 (d, 1H), 7.66 (d, 1H), 7.60 (t, 1H), 7.38-7.30 (m, 3H), 7.30-7.22 (m, 3H), 5.26 (s, 1H), 4.76 (s, 2H), 4.49 (s, 2H), 4.10-4.00 (m, 1H), 3.70-3.60 (m, 1H), 3.57-3.47 (m, 1H), 2.13-2.03 (m, 1H), 2.00-1.81 (m, 2H), 1.79-1.68 (m, 1H).

Example 12

5-Chloro-*N*-{2-[3-(3-hydroxy-2-oxopiperidin-1-yl)benzyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



- 5 According to the general method 1, 76 mg (0.15 mmol) of 5-chloro-*N*-[2-(3-iodobenzyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 8A) are reacted with 26 mg (0.23 mmol, 1.5 eq.) of 3-hydroxypiperidin-2-one (Example 18A).

Yield: 13 mg (11% of theory)

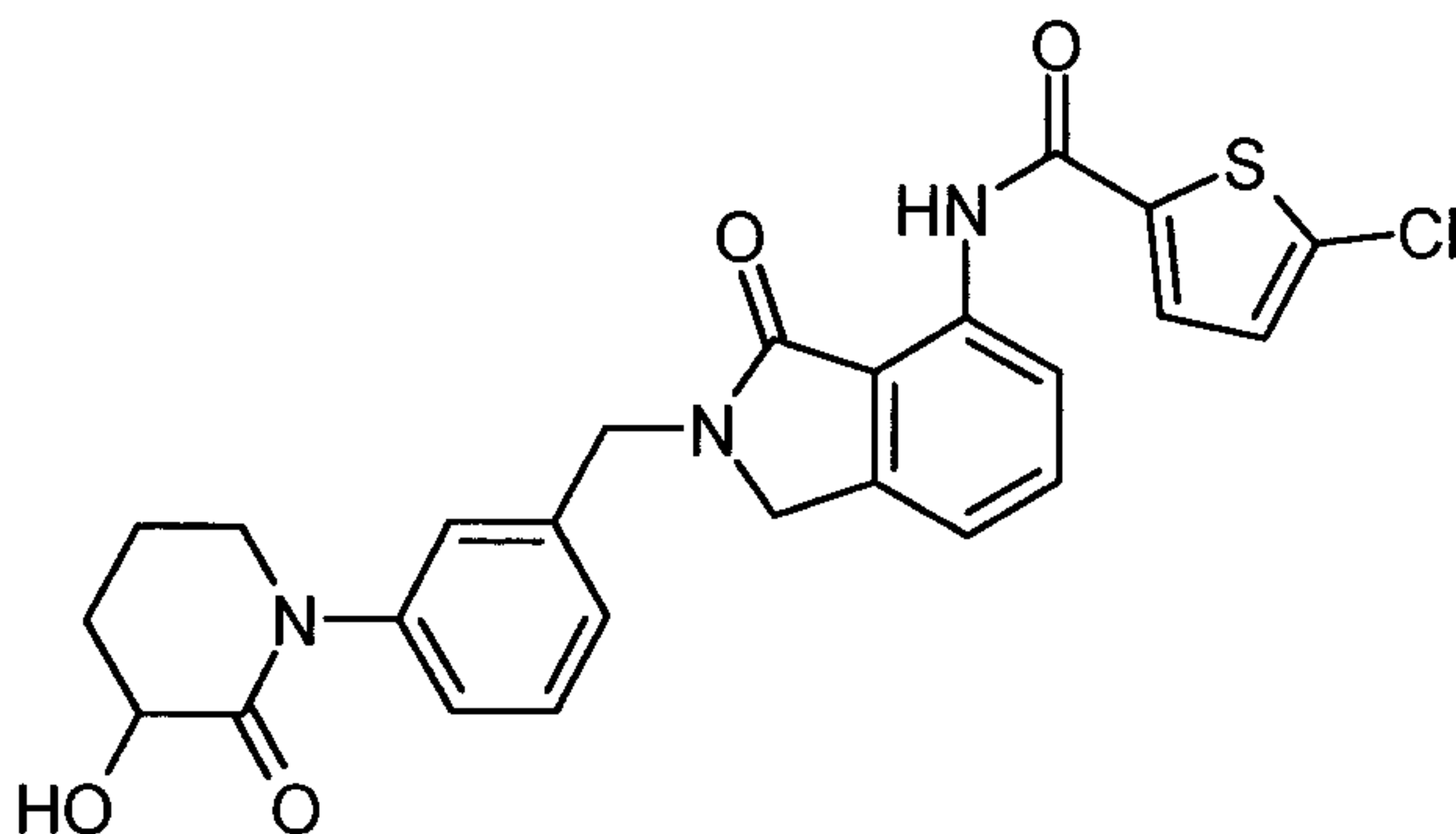
LC-MS (Method 1): $R_t = 2.40$ min;

- 10 MS (ESIpos): $m/z = 510$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 10.43$ (s, 1H), 8.31 (d, 1H), 7.87 (t, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.40-7.30 (m, 2H), 7.26 (s, 1H), 7.20 (t, 2H), 5.25 (d, 1H), 4.76 (s, 2H), 4.09-4.00 (m, 1H), 3.69-3.60 (m, 1H), 3.55-3.46 (m, 1H), 2.12-2.02 (m, 1H), 1.98-1.80 (m, 2H), 1.79-1.69 (m, 1H).

Example 13

- 15 5-Chloro-*N*-{2-[3-(3-hydroxy-2-oxopiperidin-1-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



According to the general method 1, 100 mg (0.2 mmol) of 5-chloro-*N*-[2-(3-iodobenzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 10A) are reacted with 34 mg (0.3 mmol, 1.5 eq.) of 3-hydroxypiperidin-2-one (Example 18A).

Yield: 24 mg (16% of theory)

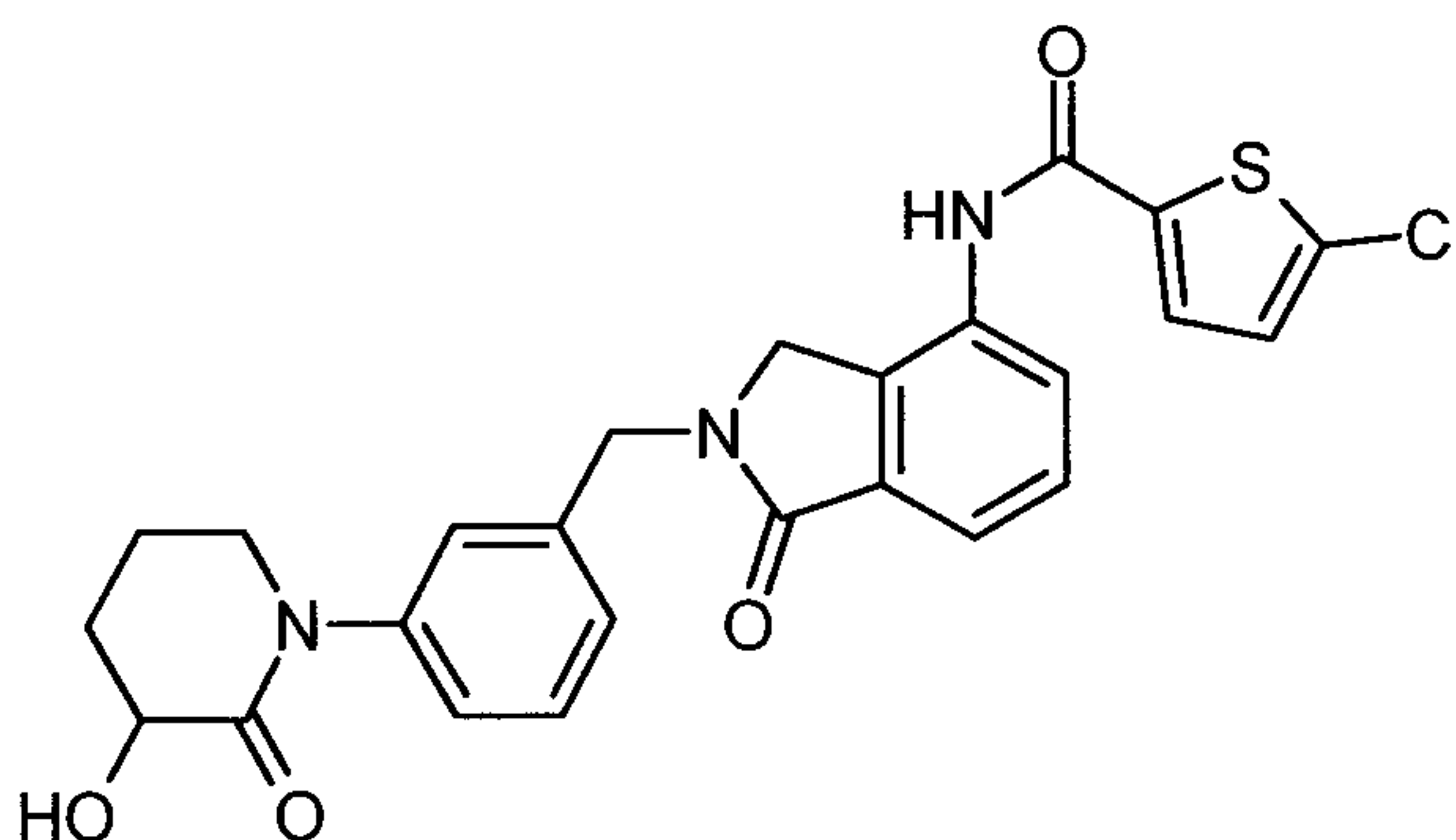
5 LC-MS (Method 7): $R_t = 2.68$ min;

MS (ESIpos): $m/z = 496$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.29$ (s, 1H), 8.27 (d, 1H), 7.66 (d, 1H), 7.60 (t, 1H), 7.39 (t, 1H), 7.34 (d, 1H), 7.30 (d, 1H), 7.25 (s, 1H), 7.21 (t, 2H), 5.23 (d, 1H), 4.77 (s, 2H), 4.47 (s, 2H), 4.08-4.00 (m, 1H), 3.70-3.61 (m, 1H), 3.59-3.50 (m, 1H), 2.12-2.03 (m, 1H), 2.00-1.80 (m, 2H), 1.79-1.69 (m, 1H).

Example 14

5-Chloro-*N*-{2-[3-(3-hydroxy-2-oxopiperidin-1-yl)benzyl]-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



15 According to the general method 1, 76 mg (0.15 mmol) of 5-chloro-*N*-[2-(3-iodobenzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide (Example 12A) are reacted with 26 mg (0.23 mmol, 1.5 eq.) of 3-hydroxypiperidin-2-one (Example 18A).

Yield: 12 mg (11% of theory)

LC-MS (Method 7): $R_t = 2.10$ min;

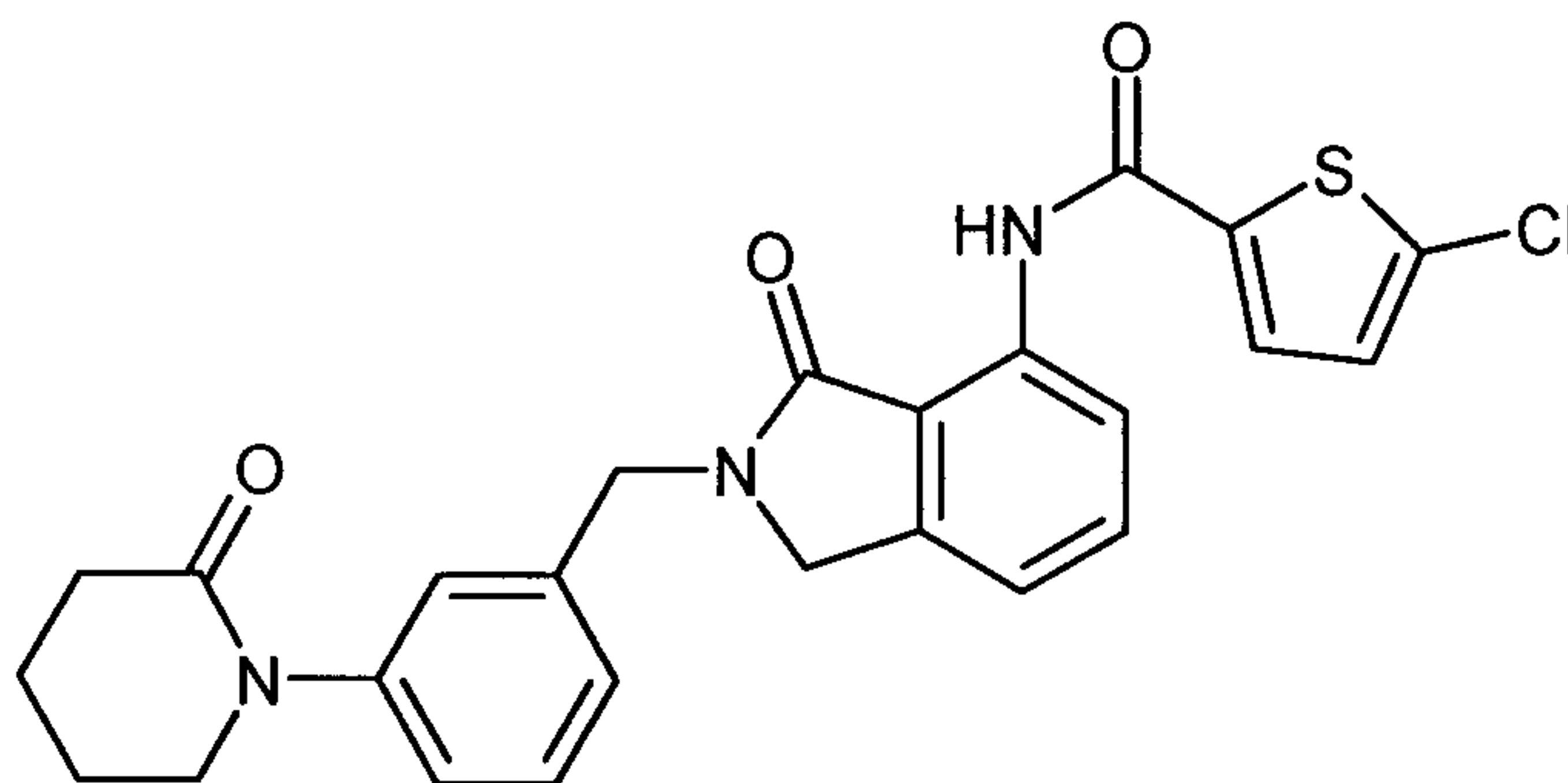
20 MS (ESIpos): $m/z = 496$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 10.40$ (s, 1H), 7.87 (d, 1H), 7.67 (d, 1H), 7.63 (d, 1H), 7.56 (t, 1H), 7.38 (t, 1H), 7.28 (d, 1H), 7.24-7.18 (m, 2H), 7.15 (d, 1H), 5.21 (d, 1H), 4.73 (s, 2H), 4.41 (s,

2H), 4.08-4.00 (m, 1H), 3.69-3.60 (m 1H), 3.57-3.48 (m, 1H), 2.12-2.02 (m, 1H), 1.98-1.80 (m, 2H), 1.78-1.68 (m, 1H).

Example 15

5-Chloro-*N*-{3-oxo-2-[3-(2-oxopiperidin-1-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



According to the general method 1, 150 mg (0.295 mmol) of the compound from Example 10A are reacted with 29 mg (0.295 mmol) of piperidin-2-one. Yield: 15 mg (11% of theory)

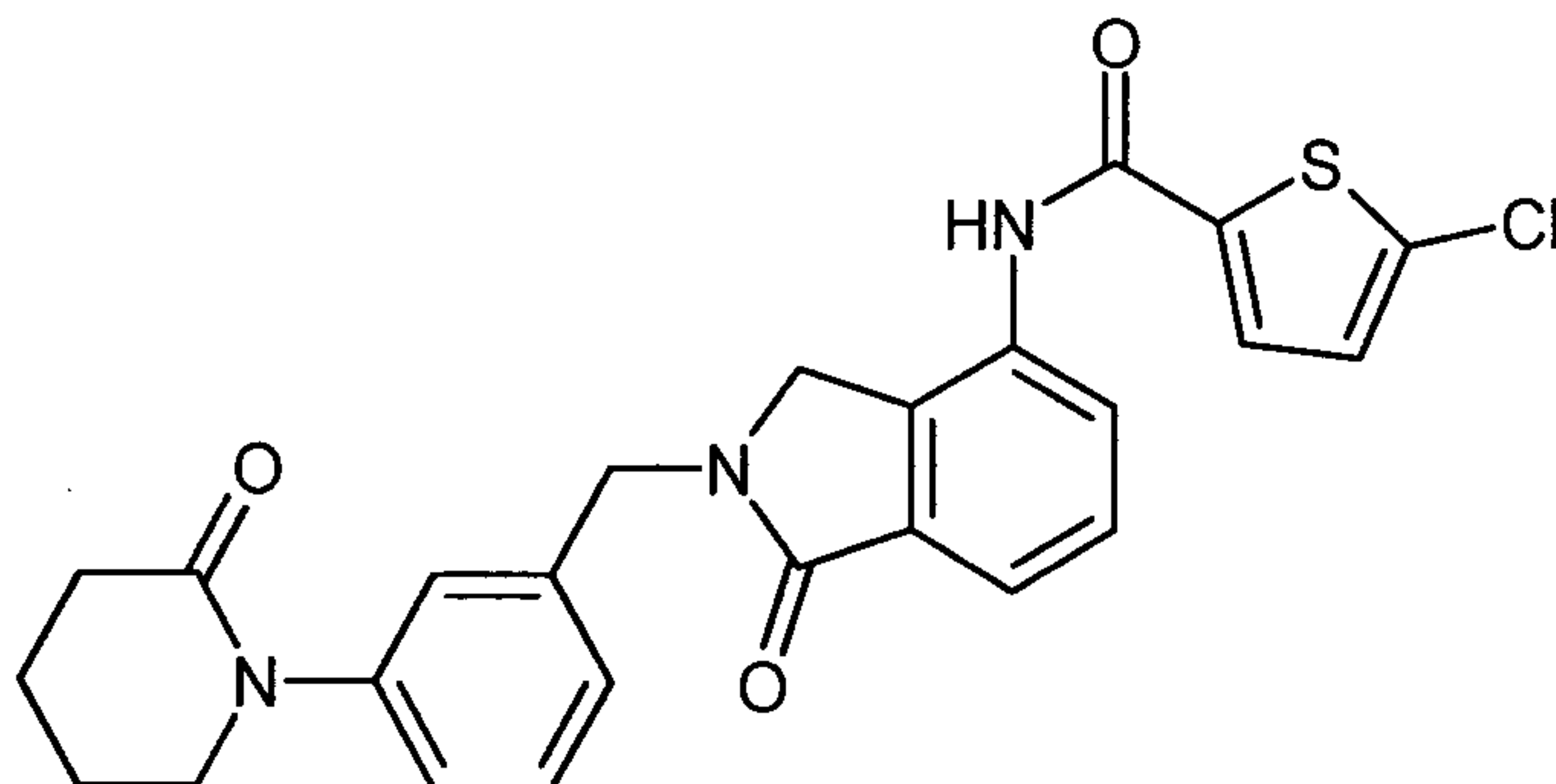
LC-MS (Method 1): $R_t = 2.50$ min;

10 MS (ESIpos): $m/z = 480$ $[M+H]^+$;

$^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 11.29$ (s, 1H), 8.26 (d, 1H), 7.66 (d, 1H), 7.60 (dd, 1H), 7.38 (dd, 1H), 7.33 (d, 1H), 7.30 (d, 1H), 7.23 (s, 1H), 7.21-7.18 (m, 2H), 4.75 (s, 2H), 4.44 (s, 2H), 3.60-3.57 (m, 2H), 2.36 (t, 2H), 1.87-1.79 (m, 4H).

Example 16

15 5-Chloro-*N*-{1-oxo-2-[3-(2-oxopiperidin-1-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



According to the general method 1, 150 mg (0.295 mmol) of the compound from Example 12A are reacted with 29 mg (0.295 mmol) of piperidin-2-one. Yield: 6 mg (4% of theory)

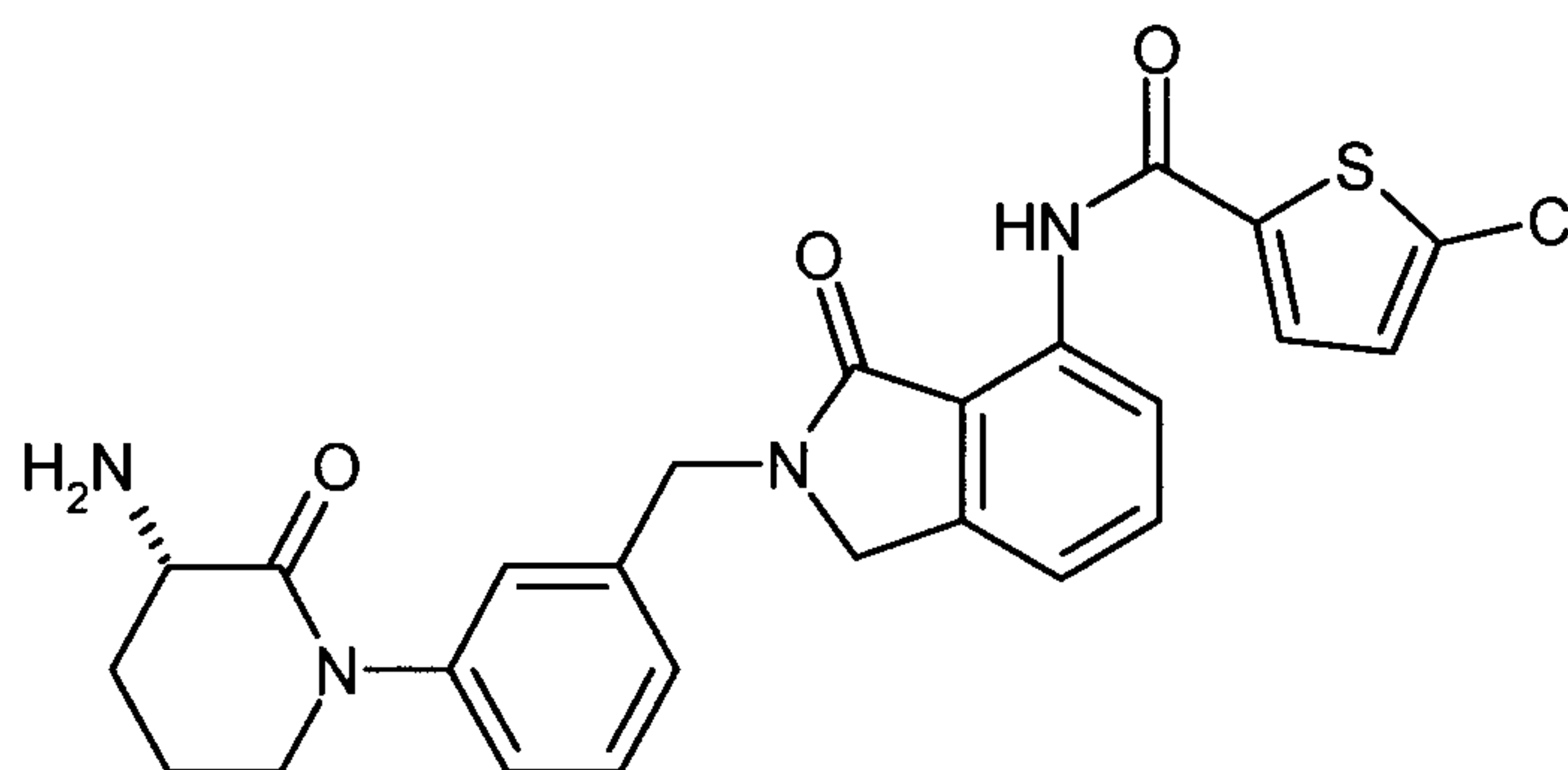
LC-MS (Method 7): $R_t = 2.27$ min;

MS (ESIpos): $m/z = 480$ $[M+H]^+$;

- 5 $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 8.48$ (s, 1H), 7.65 (d, 1H), 7.53 (d, 1H), 7.49 (d, 1H), 7.38 (dd, 1H), 7.23 (dd, 1H, partially obscured by the CHCl_3 signal), 7.13-7.07 (m, 3H), 6.88 (d, 1H), 4.70 (s, 2H), 4.21 (s, 2H), 3.62-3.58 (m, 2H), 2.47 (t, 2H), 1.95-1.87 (m, 4H).

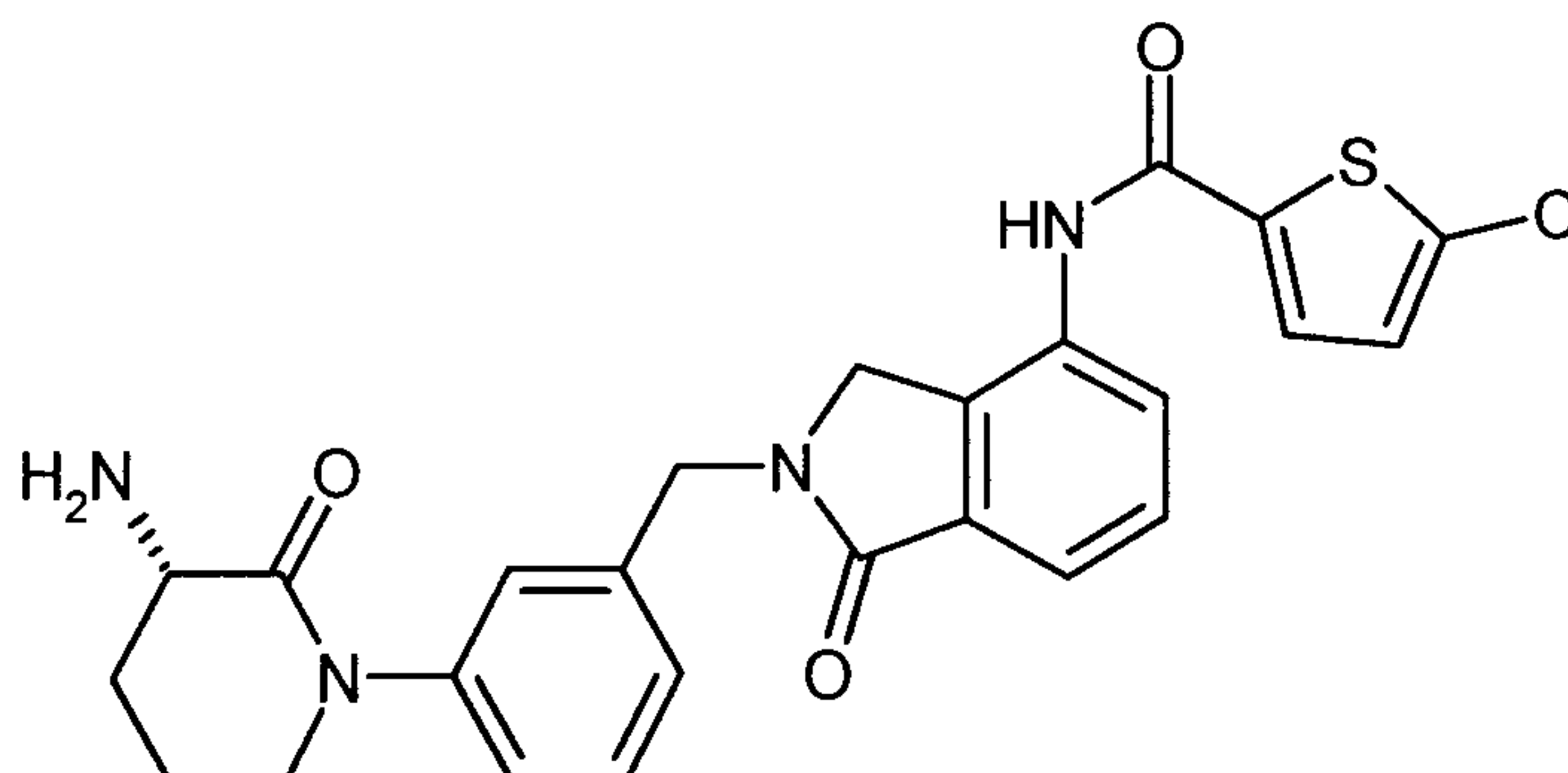
Example 17

- 10 *N*-(2-{3-[(3*S*)-3-Amino-2-oxopiperidin-1-yl]benzyl}-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl)-5-chlorothiophene-2-carboxamide



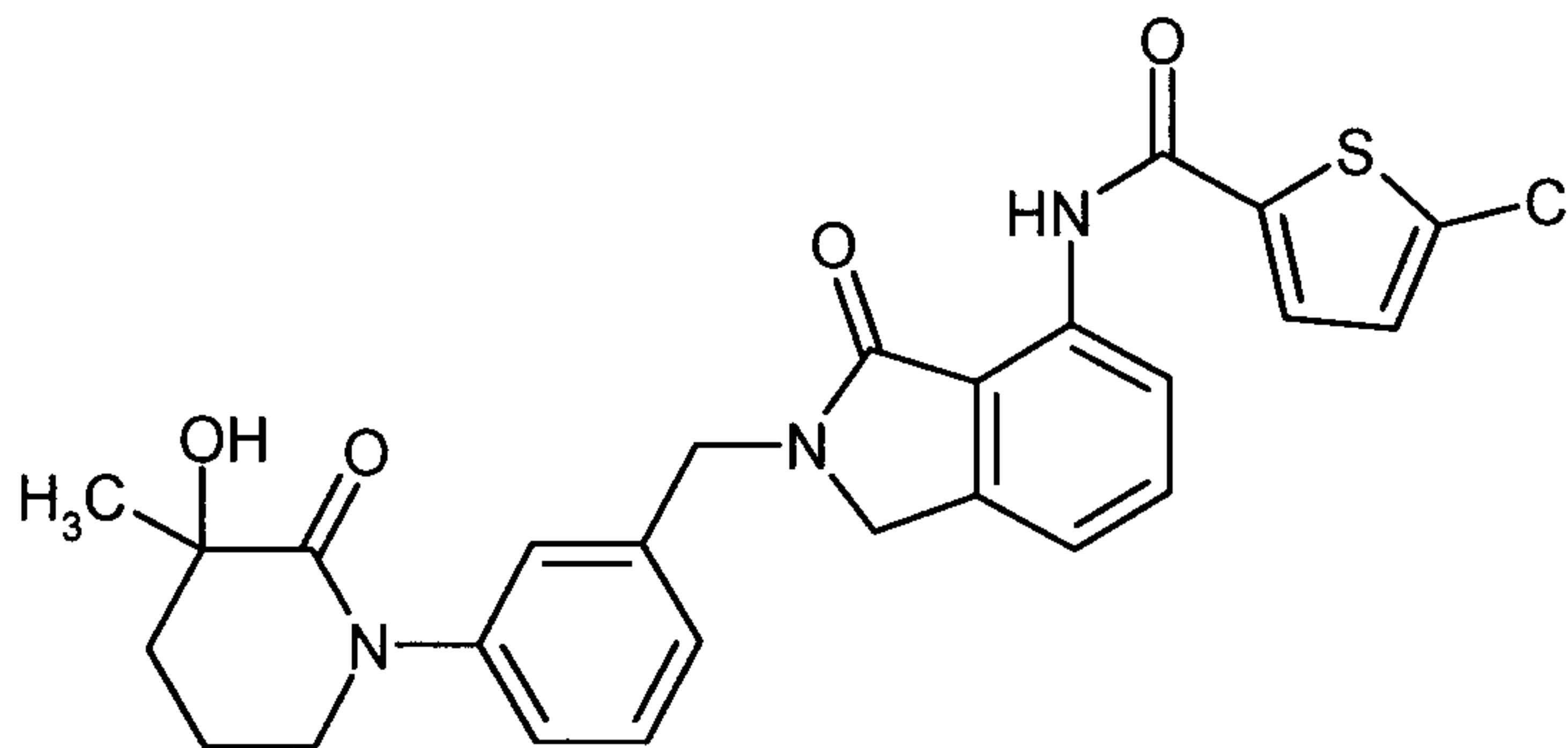
Example 18

- N*-(2-{3-[(3*S*)-3-Amino-2-oxopiperidin-1-yl]benzyl}-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl)-5-chlorothiophene-2-carboxamide

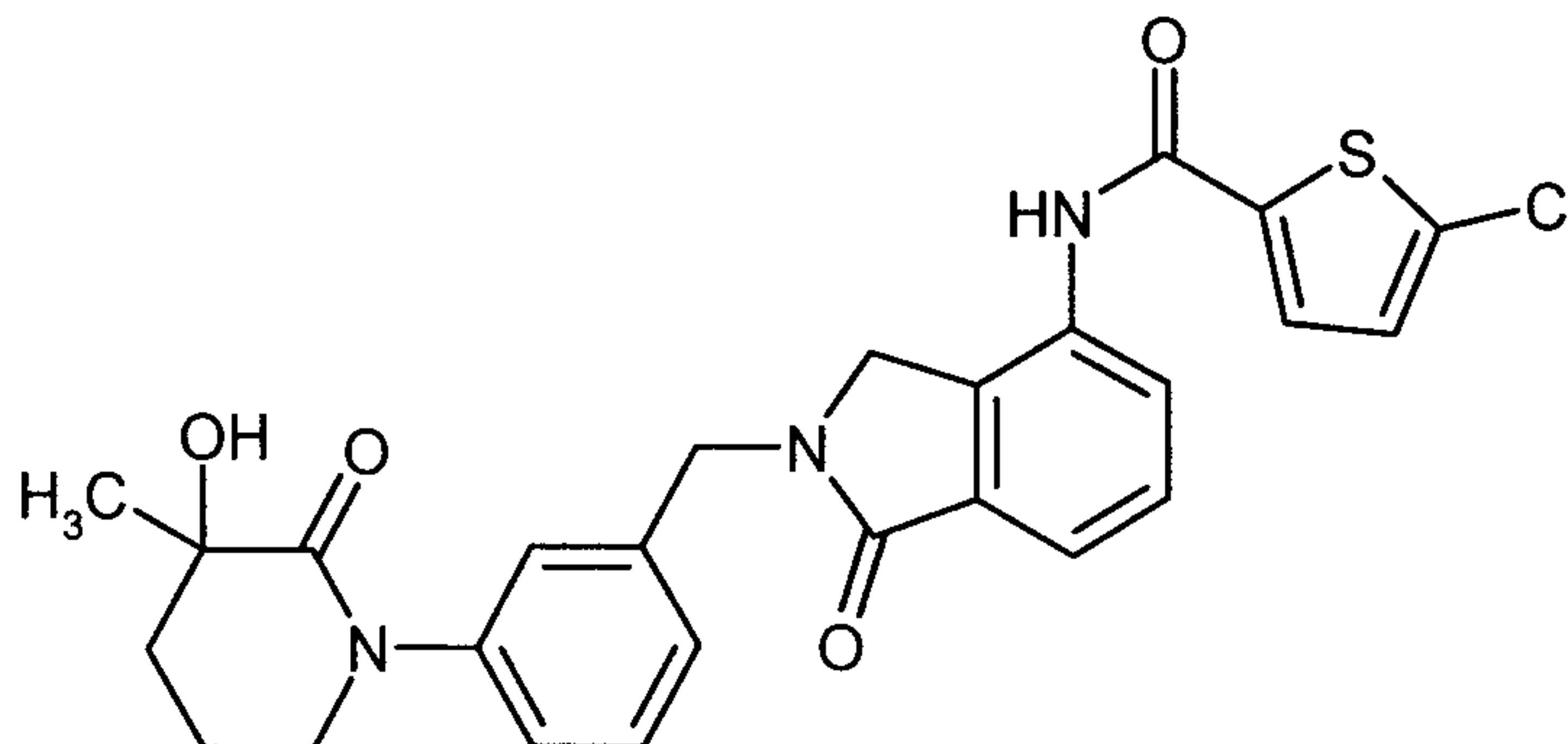


Example 19

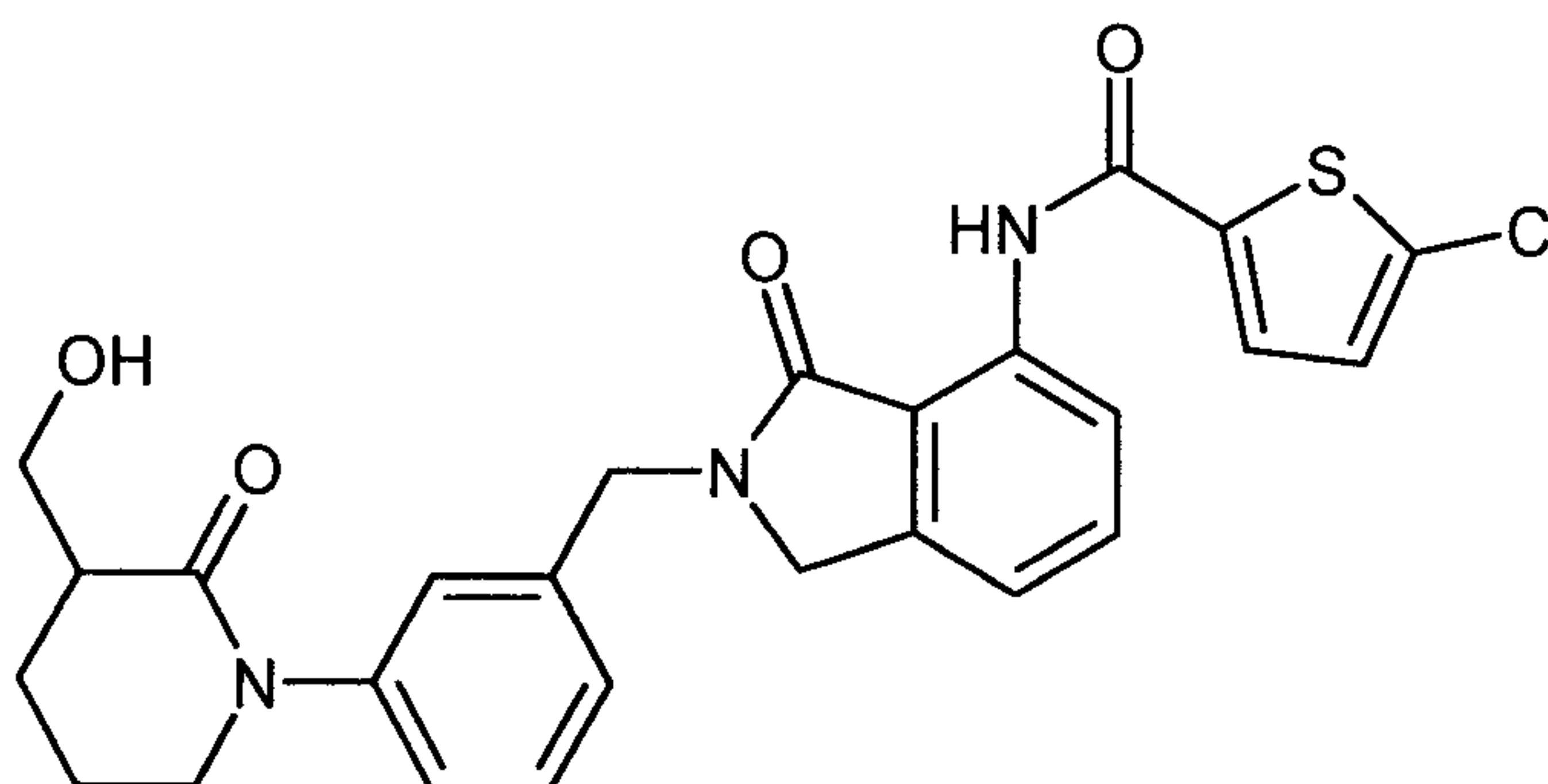
5-Chloro-*N*-{2-[3-(3-hydroxy-3-methyl-2-oxopiperidin-1-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide

5 **Example 20**

5-Chloro-*N*-{2-[3-(3-hydroxy-3-methyl-2-oxopiperidin-1-yl)benzyl]-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide

**Example 21**

10 5-Chloro-*N*-(2-{3-[3-(hydroxymethyl)-2-oxopiperidin-1-yl]benzyl}-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



According to the general method 1, 300 mg (0.59 mmol) of the compound from Example 10A are reacted with 217 mg (0.59 mmol) of the compound from Example 20A. Preparative HPLC gives 68 mg (15% of theory) of a silyl-protected compound which is dissolved in 5 ml of THF, and 93 μ l of a 1 molar solution of tetra-n-butylammonium fluoride are added at 0°C. After 10 minutes, the mixture is allowed to warm to RT. After 1 hour, the mixture is diluted with water and extracted with ethyl acetate. The organic extract is washed with saturated sodium chloride solution, dried over anhydrous sodium sulphate, filtered and freed from the solvent on a rotary evaporator. The crude product is purified by preparative HPLC. Yield: 34 mg (11% of theory, two steps)

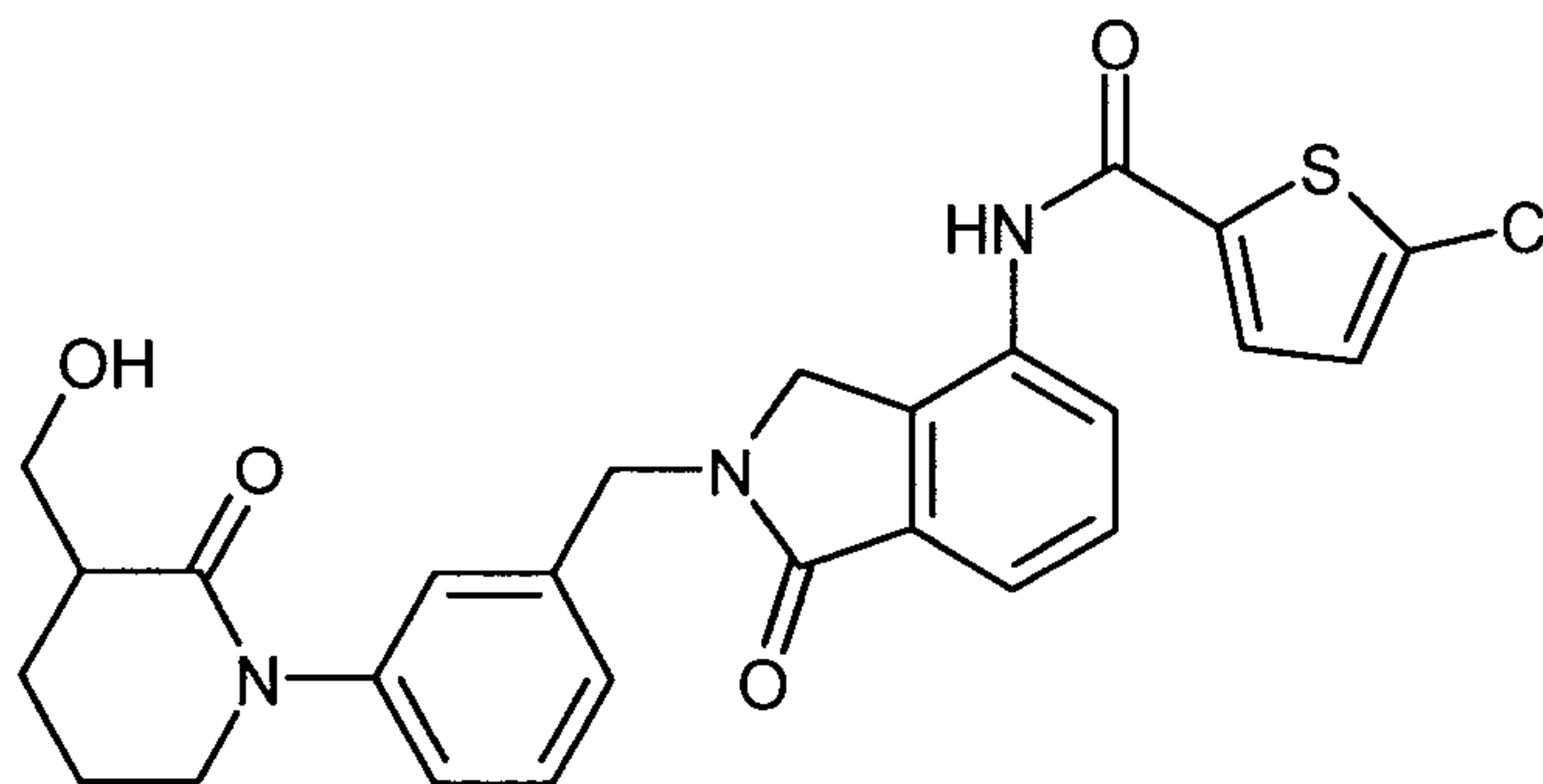
LC-MS (Method 7): R_t = 2.64 min;

MS (ESIpos): m/z = 510 $[M+H]^+$;

^1H -NMR (500 MHz, DMSO- d_6): δ = 11.29 (s, 1H), 8.27 (d, 1H), 7.65 (d, 1H), 7.60 (dd, 1H), 7.38 (dd, 1H), 7.34 (d, 1H), 7.30 (d, 1H), 7.23 (s, 1H), 7.20-7.17 (m, 2H), 4.75 (s, 2H), 4.64 (t, 1H), 4.45 (s, 2H), 3.70-3.53 (m, 4H), 2.48-2.42 (m, 2H, partially obscured by the DMSO signal), 1.97-1.92 (m, 2H), 1.84-1.78 (m, 2H).

15 **Example 22**

5-Chloro-*N*-(2-{3-[3-(hydroxymethyl)-2-oxopiperidin-1-yl]benzyl}-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



Step A: 4-amino-2-{3-[3-({[tert-butyl(diphenyl)silyl]oxy}methyl)-2-oxopiperidin-1-yl]benzyl}-isoindolin-1-one. 42 mg (0.186 mmol) of tin(II) chloride dihydrate are added to a solution of 59 mg (0.093 mmol) of the compound from Example 23A in 10 ml of ethanol, and the mixture is heated at a bath temperature of 70°C for nine hours. The reaction mixture is then poured into ice-water, the pH is adjusted to 8 using saturated sodium bicarbonate solution and the mixture is filtered off with suction through Celite. The filtrate is extracted with ethyl acetate. The organic extract is washed with saturated sodium chloride solution. After drying over anhydrous sodium sulphate, the mixture is filtered and the filtrate is evaporated to dryness. The residue obtained is reacted further

without purification.

Step B: N-(2-{3-[3-({[tert-butyl(diphenyl)silyl]oxy}methyl)-2-oxopiperidin-1-yl]benzyl}-1-oxo-2,3-dihydro-1H-isoindol-4-yl)-5-chlorothiophene-2-carboxamide. The crude product of step A is dissolved in 2.5 ml of THF, and 21 mg (0.166 mmol) of diisopropylethylamine and a solution of
5 15 mg (0.083 mmol) of 5-chlorothiophene-2-carbonyl chloride in 2.5 ml of THF are added successively. The reaction mixture is stirred at RT for one hour. The mixture is then diluted with dichloromethane and washed with water. The organic phase is separated off and dried over anhydrous sodium sulphate. The crude product obtained after removal of the solvent is reacted further without purification.

10 Step C: 5-chloro-N-(2-{3-[3-(hydroxymethyl)-2-oxopiperidin-1-yl]benzyl}-1-oxo-2,3-dihydro-1H-isoindol-4-yl)thiophene-2-carboxamide. 196 µl of a 1 molar solution of tetra-n-butylammonium fluoride in THF are added to a solution of the crude product from step B in 5 ml of THF, and the mixture is stirred at RT for 15 hours. Water is then added, and the mixture is extracted with ethyl acetate. The organic extract is washed with saturated sodium chloride solution and dried over
15 anhydrous sodium sulphate. After filtration and removal of the solvent under reduced pressure, the product is isolated by preparative HPLC. This gives 5 mg (10% of theory over 3 steps) of the title compound.

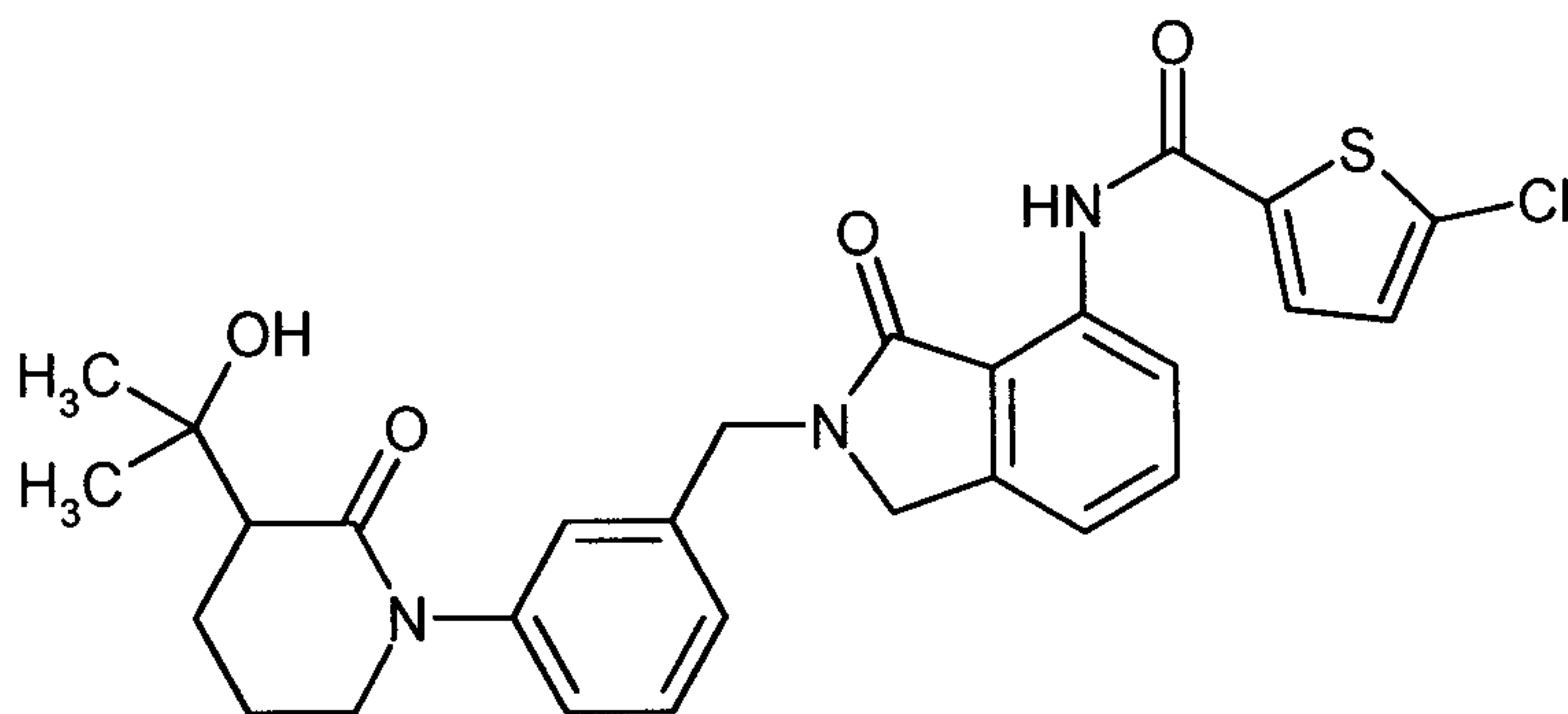
LC-MS (Method 15): $R_t = 2.84$ min;

MS (ESIpos): $m/z = 510$ $[M+H]^+$;

20 $^1\text{H-NMR}$ (500 MHz, DMSO-d_6): $\delta = 10.38$ (s, 1H), 7.86 (d, 1H), 7.67 (d, 1H), 7.62 (d, 1H), 7.54 (dd, 1H), 7.35 (dd, 1H), 7.27 (d, 1H), 7.20-7.16 (m, 2H), 7.12 (d, 1H), 4.72 (s, 2H), 4.61 (t, 1H), 4.41 (s, 2H), 3.70-3.52 (m, 4H), 2.48-2.42 (m, 2H, partially obscured by the DMSO signal), 1.97-1.91 (m, 2H), 1.87-1.77 (m, 2H).

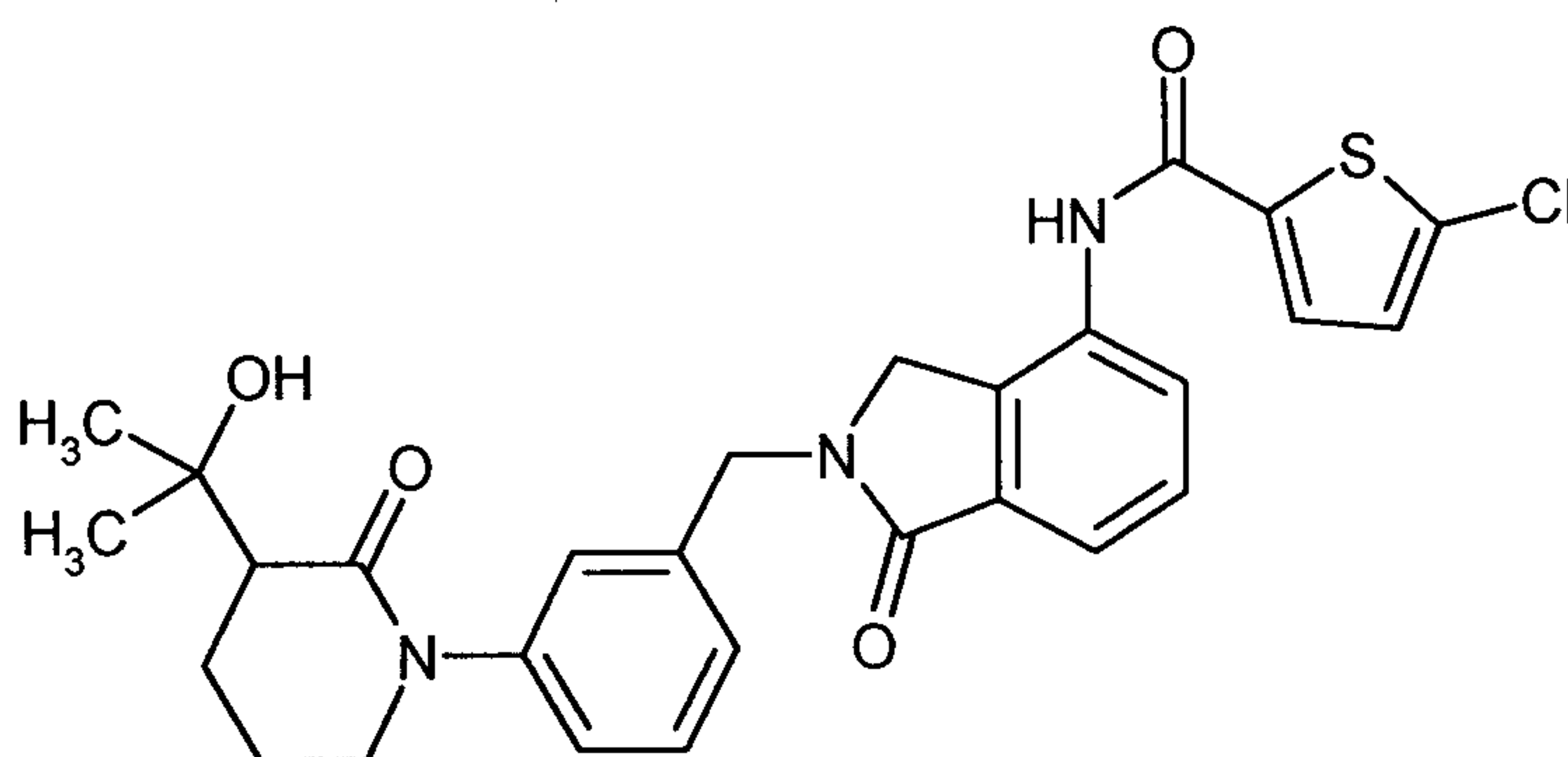
Example 23

25 5-Chloro-N-(2-{3-[3-(1-hydroxy-1-methylethyl)-2-oxopiperidin-1-yl]benzyl}-3-oxo-2,3-dihydro-1H-isoindol-4-yl)thiophene-2-carboxamide



Example 24

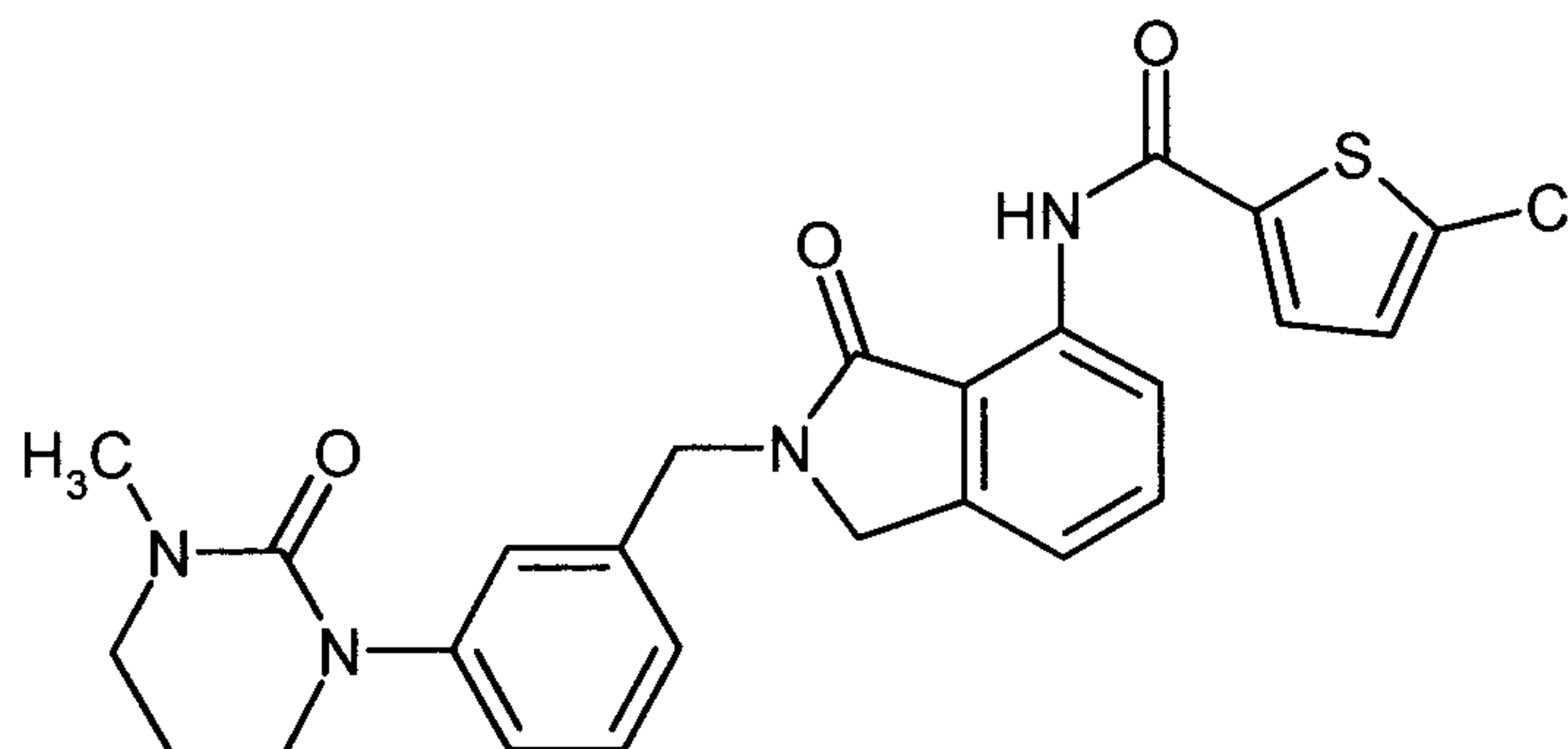
5-Chloro-*N*-(2-{3-[3-(1-hydroxy-1-methylethyl)-2-oxopiperidin-1-yl]benzyl}-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



5

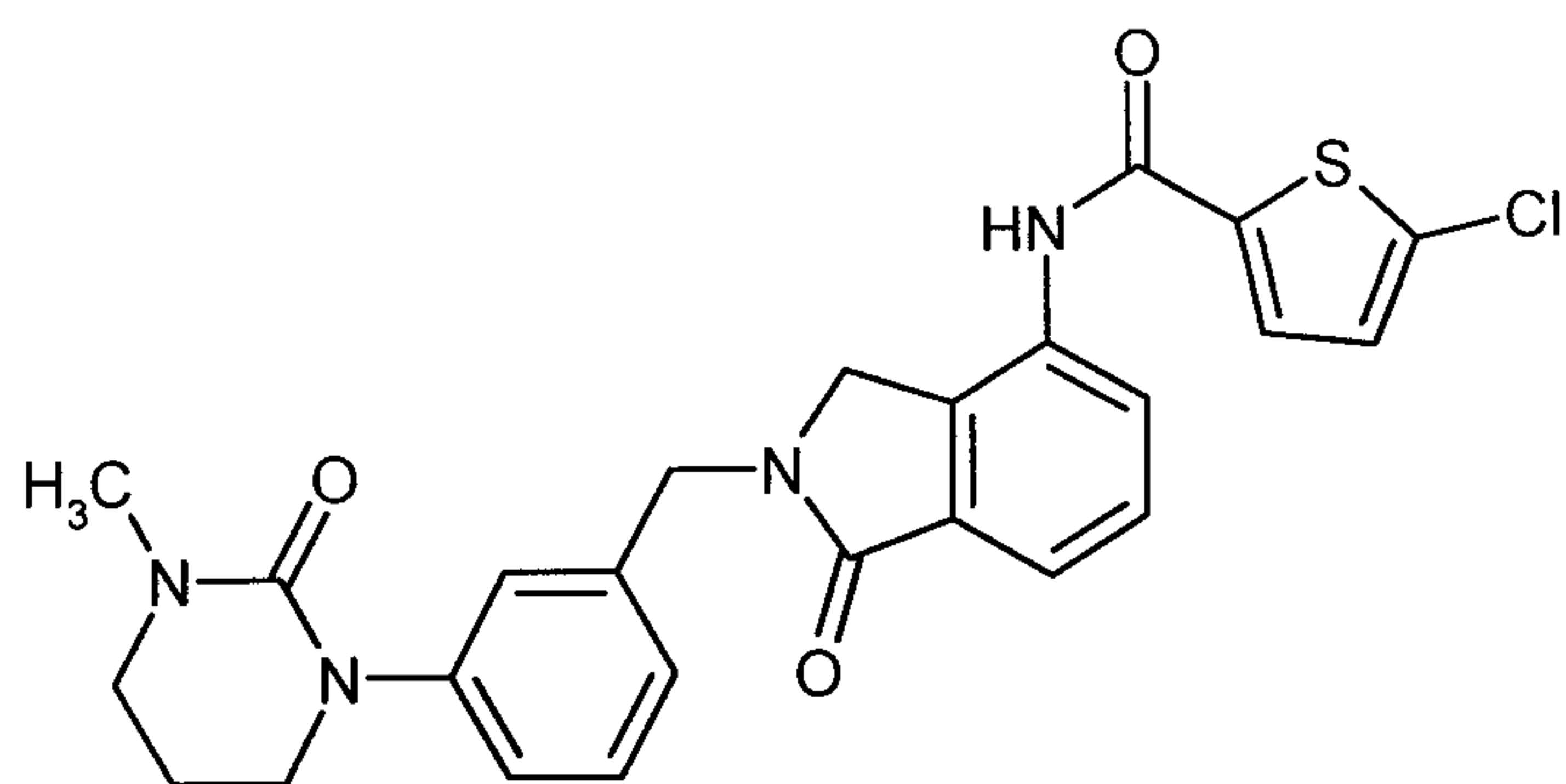
Example 25

5-Chloro-*N*-{2-[3-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



10 **Example 26**

5-Chloro-*N*-{2-[3-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)benzyl]-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



100 mg (0.285 mmol) of the product from Example 27A are dissolved in 2.5 ml of THF, and 65 μ l (0.371 mmol) of diisopropylethylamine and a solution of 62 mg (0.342 mmol) of 5-chlorothiophene-2-carbonyl chloride in 2.5 ml of THF are added successively. The reaction mixture is stirred at RT for one hour. The reaction mixture is then evaporated to complete dryness, and the product is isolated by preparative HPLC. This gives 69 mg (49% of theory) of the title compound.

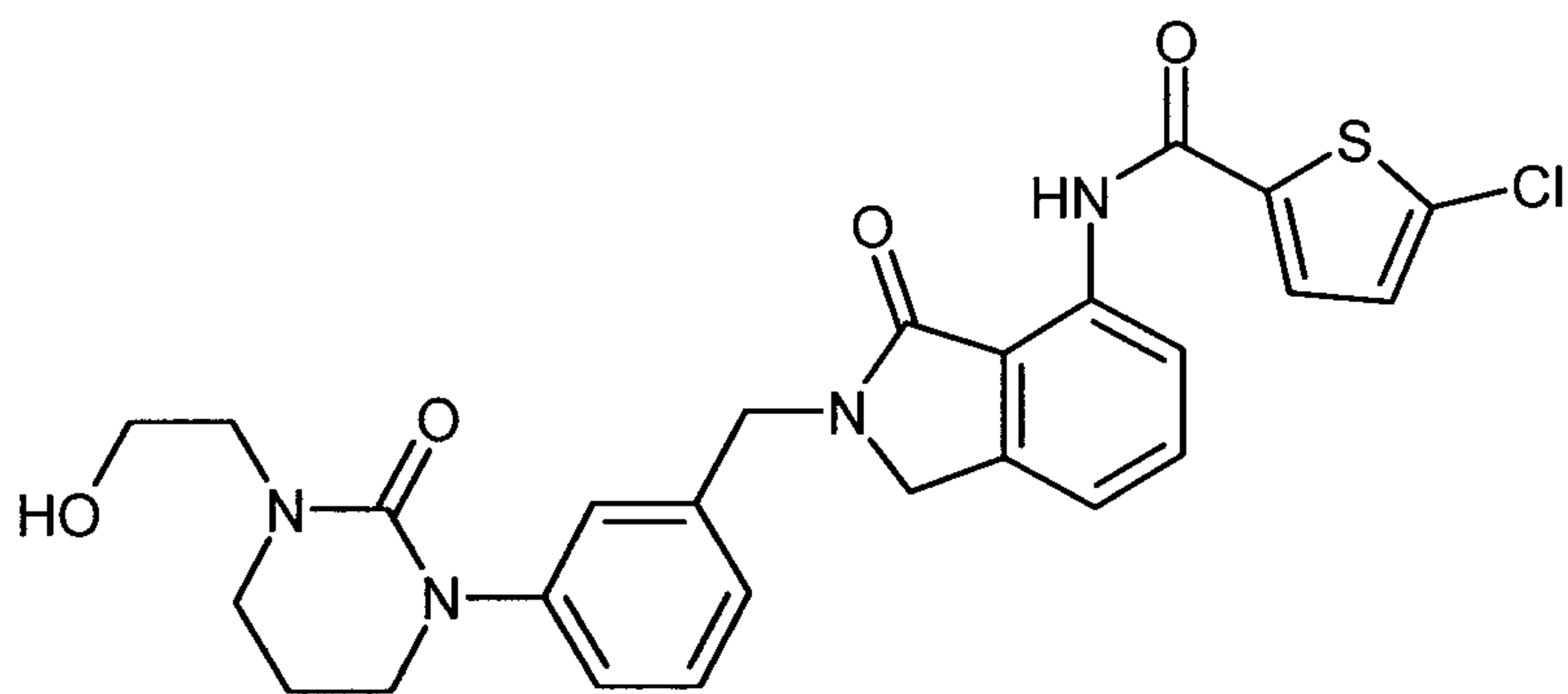
HPLC (Method 11): $R_t = 4.17$ min;

MS (DCI, NH_3): $m/z = 495$ $[\text{M}+\text{H}]^+$, 512 $[\text{M}+\text{NH}_4]^+$;

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 10.37$ (s, 1H), 7.86 (d, 1H), 7.67 (d, 1H), 7.62 (d, 1H), 7.54 (dd, 1H), 7.29-7.25 (m, 2H), 7.19 (dd, 1H), 7.15 (dd, 1H), 6.99 (d, 1H), 4.70 (s, 2H), 4.40 (s, 2H), 3.61 (t, 2H), 3.31 (t, 2H, partially obscured by the signal for water), 2.83 (s, 2H), 2.03-1.97 (m, 2H).

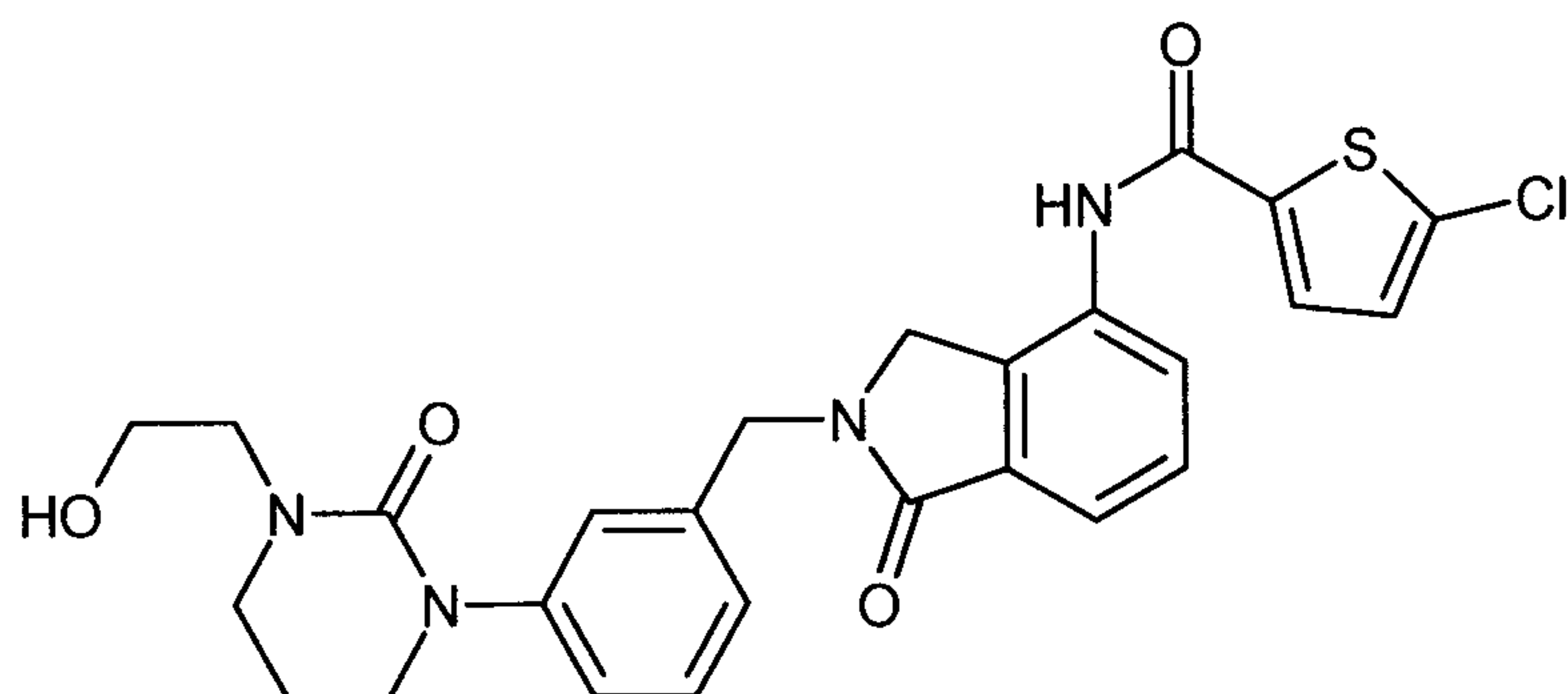
Example 27

15 5-Chloro-*N*-{2-[3-(3-(2-hydroxyethyl)-2-oxotetrahydropyrimidin-1(2*H*)-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



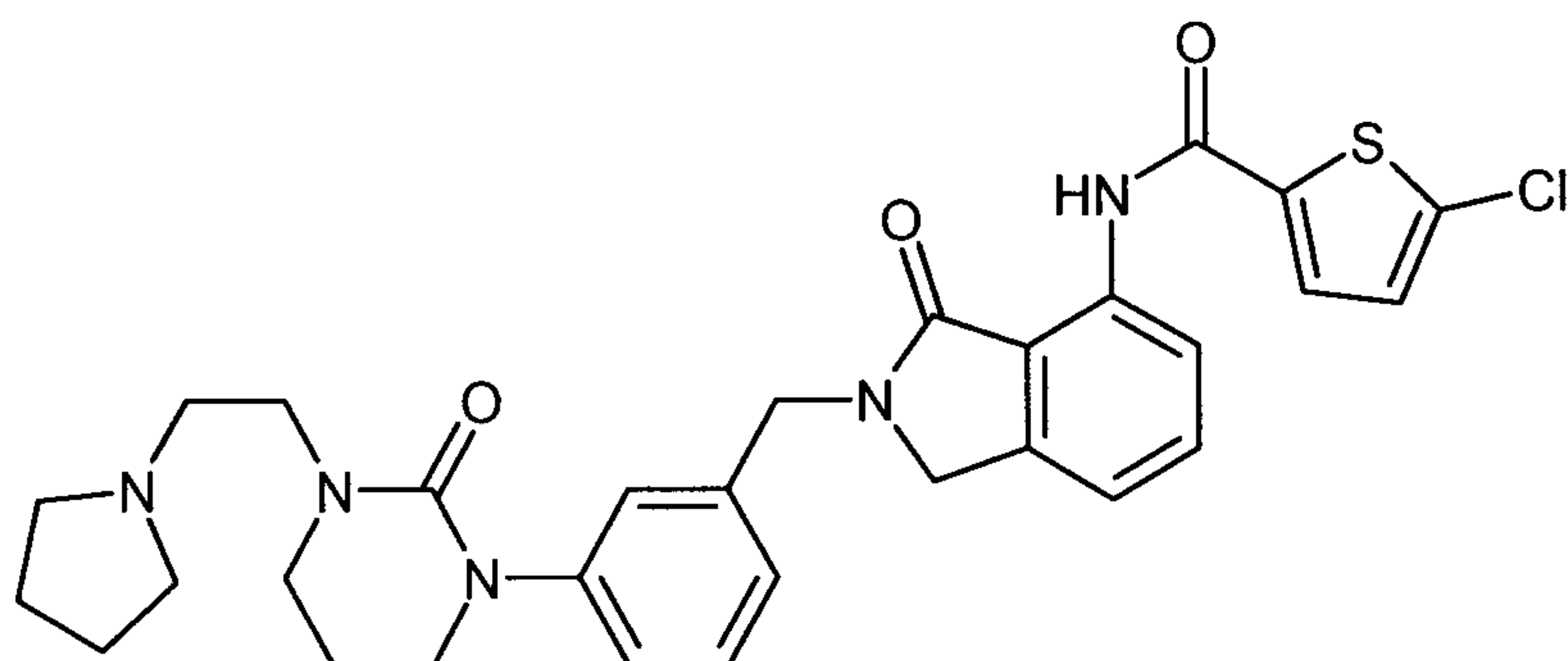
Example 28

5-Chloro-*N*-{2-[3-(3-(2-hydroxyethyl)-2-oxotetrahydropyrimidin-1(2*H*)-yl)benzyl]-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



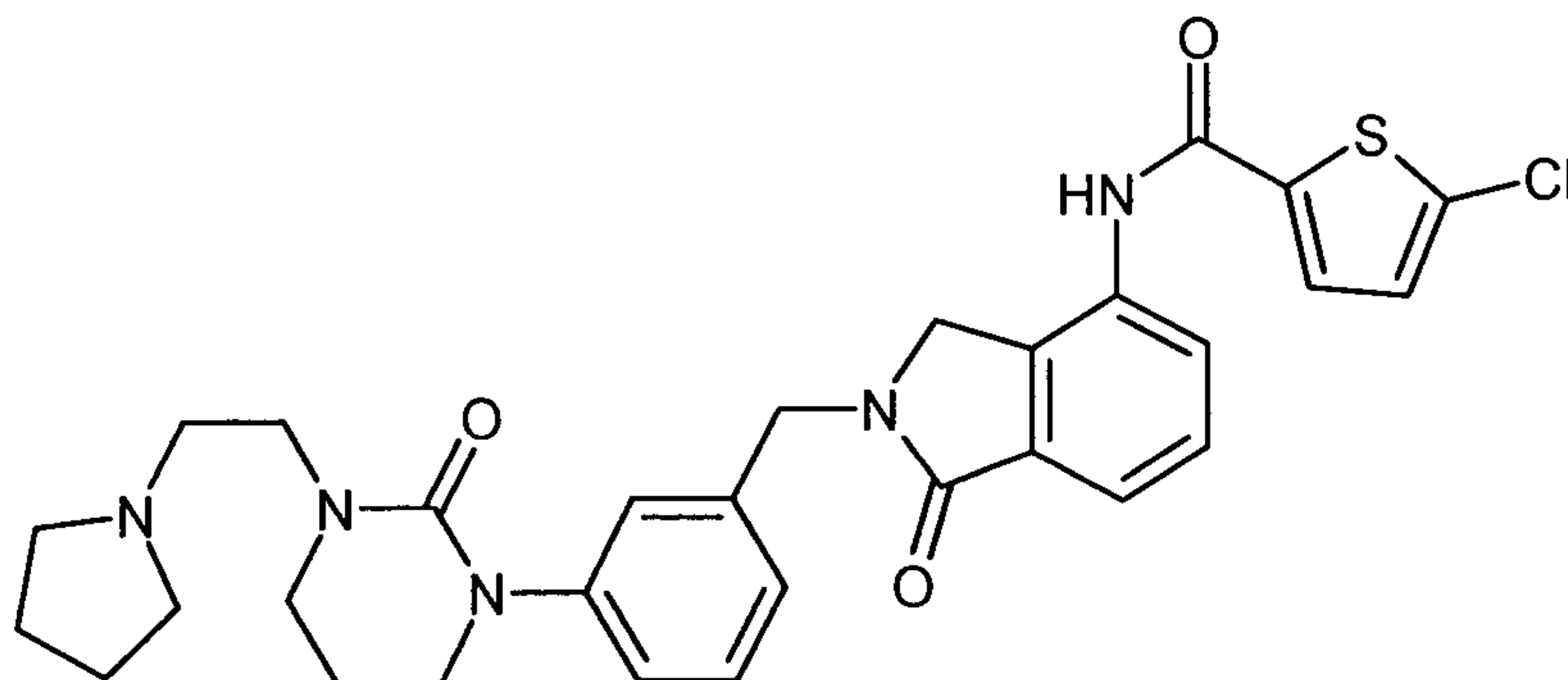
5 **Example 29**

5-Chloro-*N*-(3-oxo-2-{3-[2-oxo-3-(2-pyrrolidin-1-ylethyl)tetrahydropyrimidin-1(2*H*)-yl]benzyl}-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



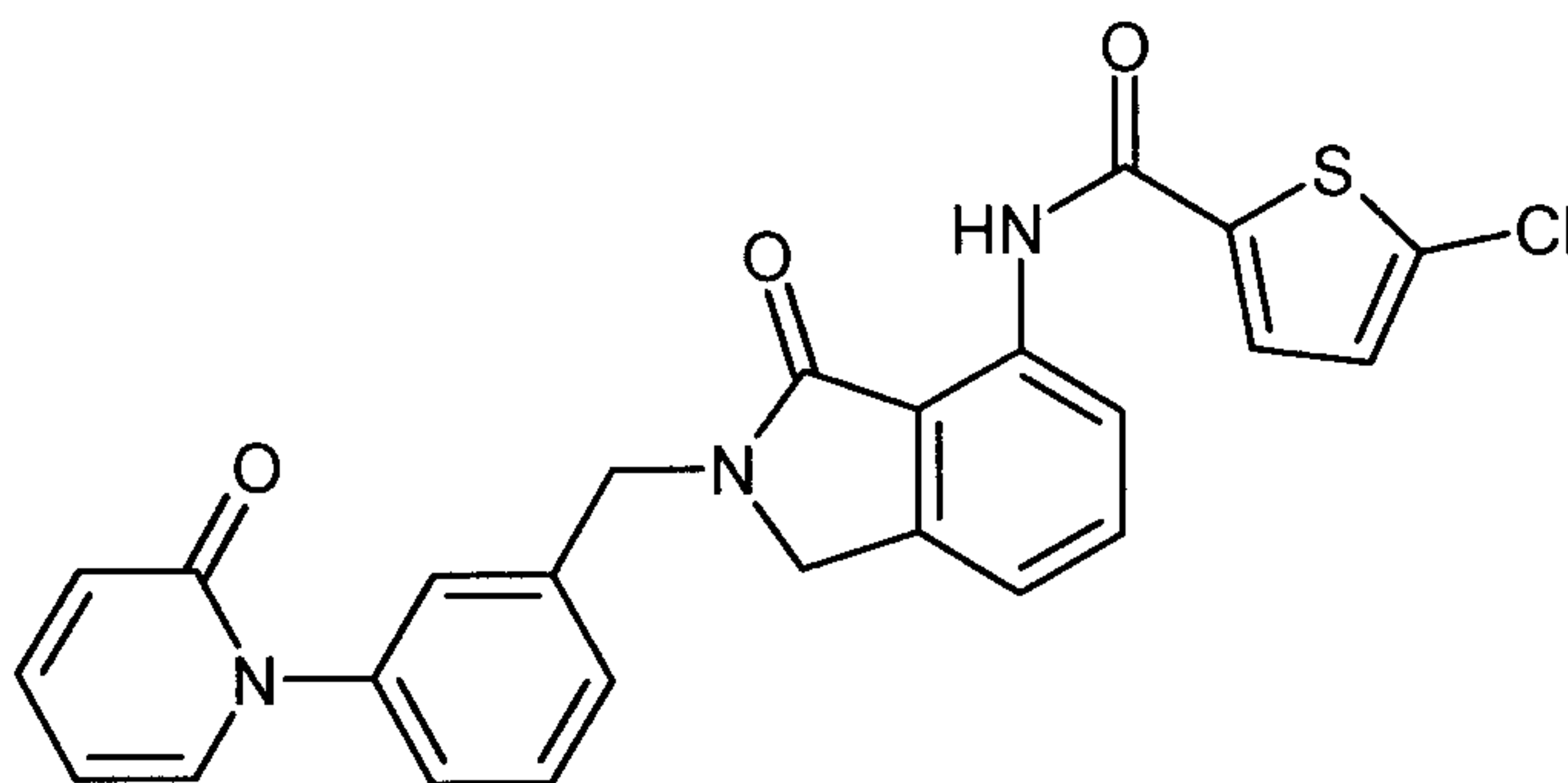
Example 30

10 5-Chloro-*N*-(1-oxo-2-{3-[2-oxo-3-(2-pyrrolidin-1-ylethyl)tetrahydropyrimidin-1(2*H*)-yl]benzyl}-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



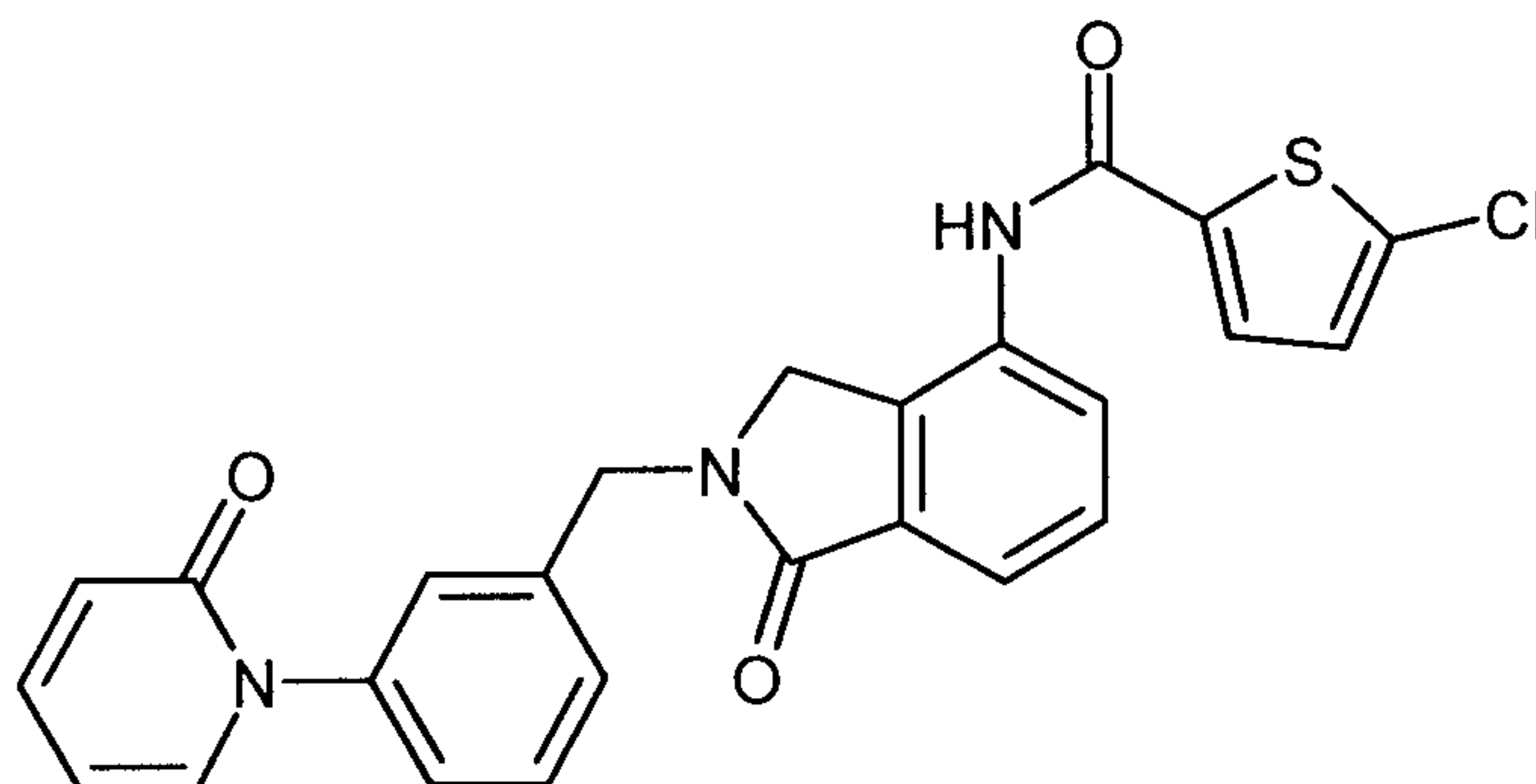
Example 31

5-Chloro-*N*-{3-oxo-2-[3-(2-oxopyridin-1(2*H*)-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



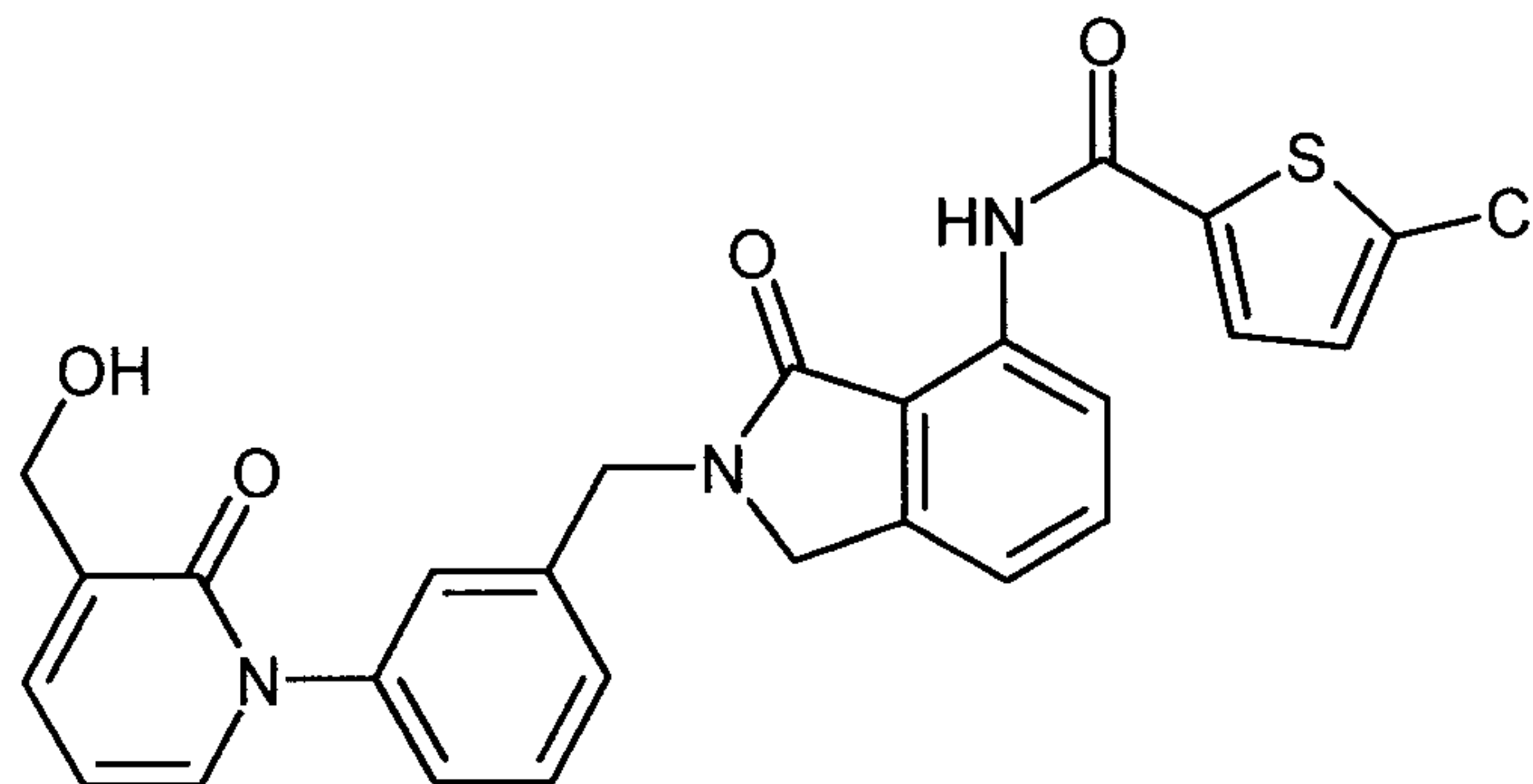
5 **Example 32**

5-Chloro-*N*-{1-oxo-2-[3-(2-oxopyridin-1(2*H*)-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



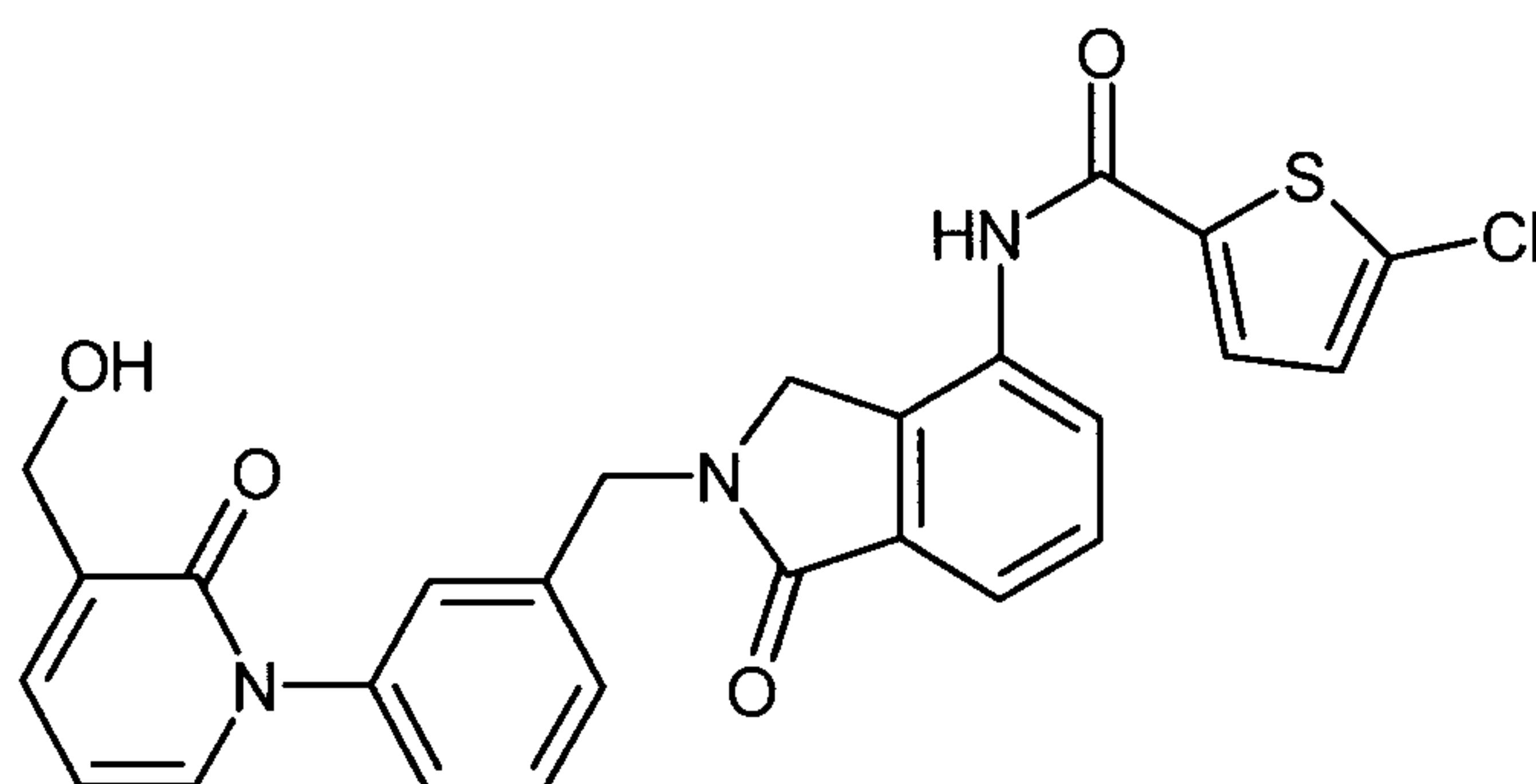
Example 33

10 5-Chloro-*N*-(2-{3-[3-(hydroxymethyl)-2-oxopyridin-1(2*H*)-yl]benzyl}-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



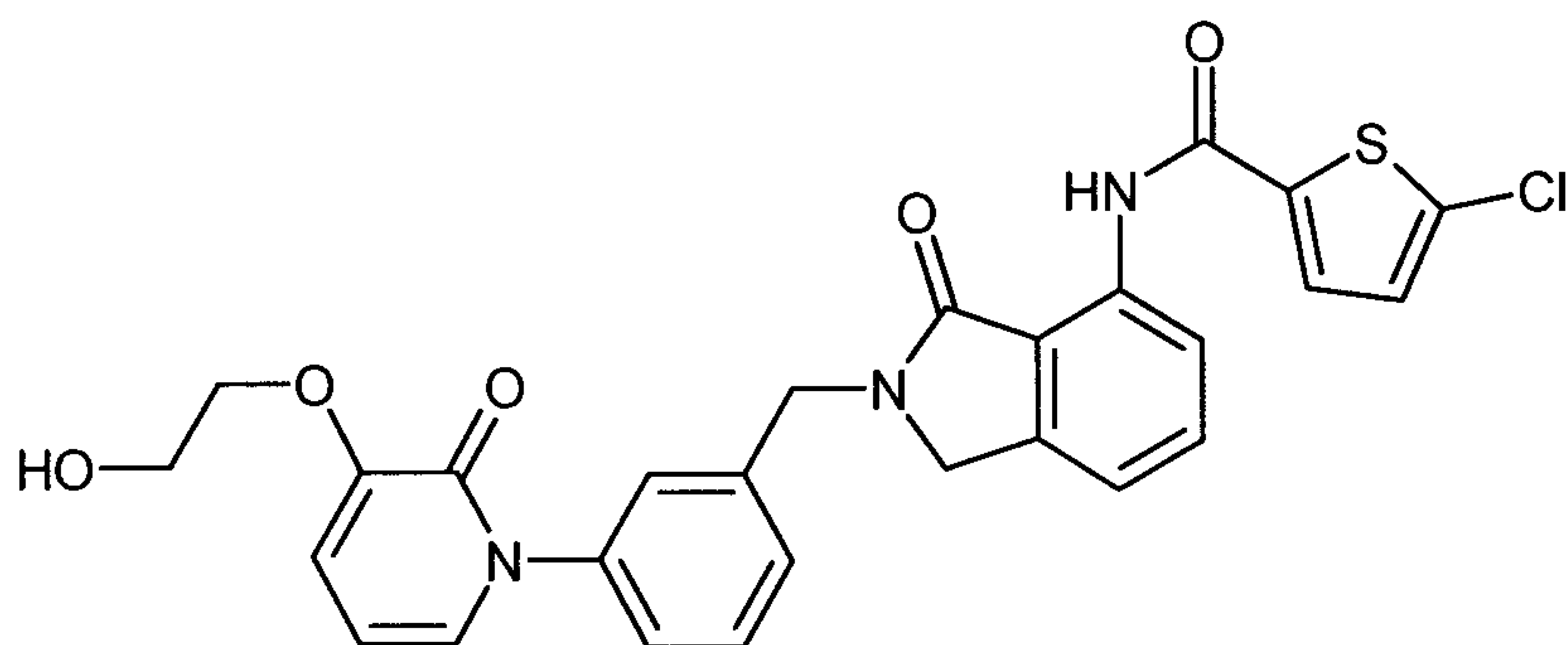
Example 34

5-Chloro-*N*-(2-{3-[3-(hydroxymethyl)-2-oxopyridin-1(2*H*)-yl]benzyl}-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



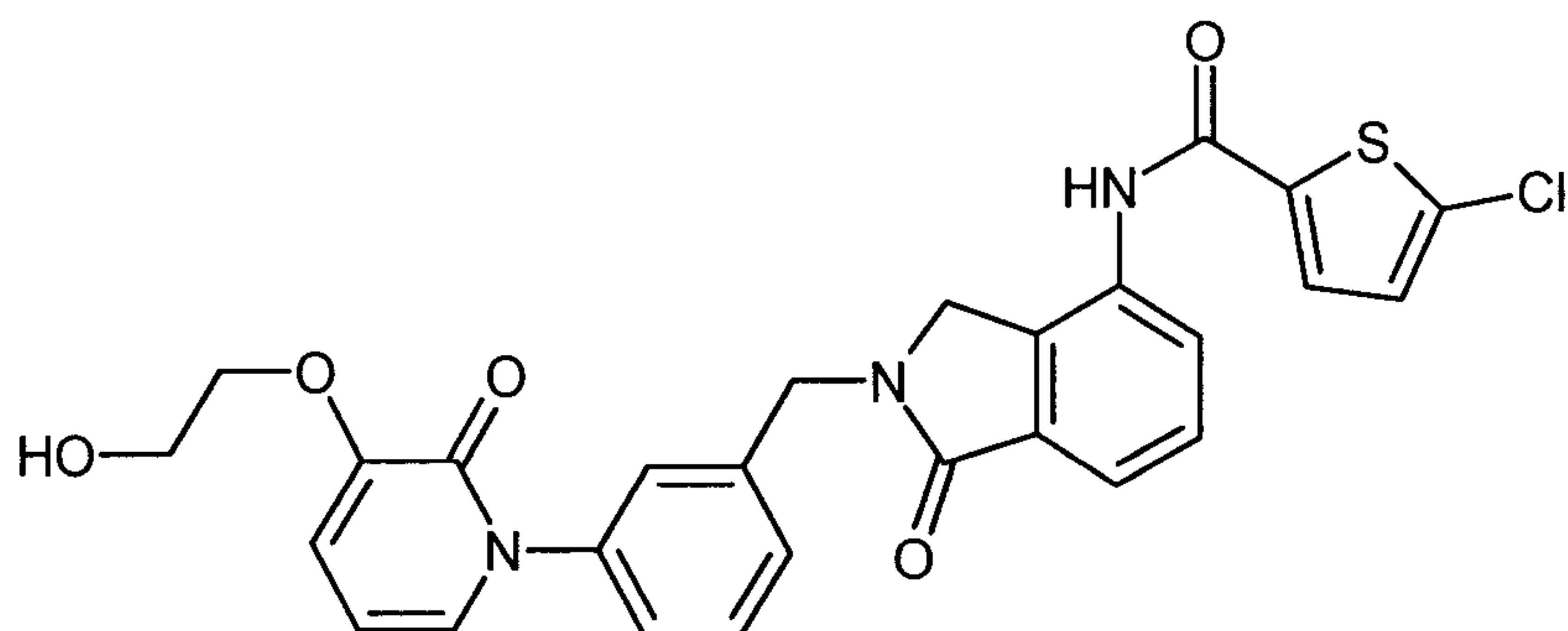
5 **Example 35**

5-Chloro-*N*-(2-{3-[3-(2-hydroxyethoxy)-2-oxopyridin-1(2*H*)-yl]benzyl}-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



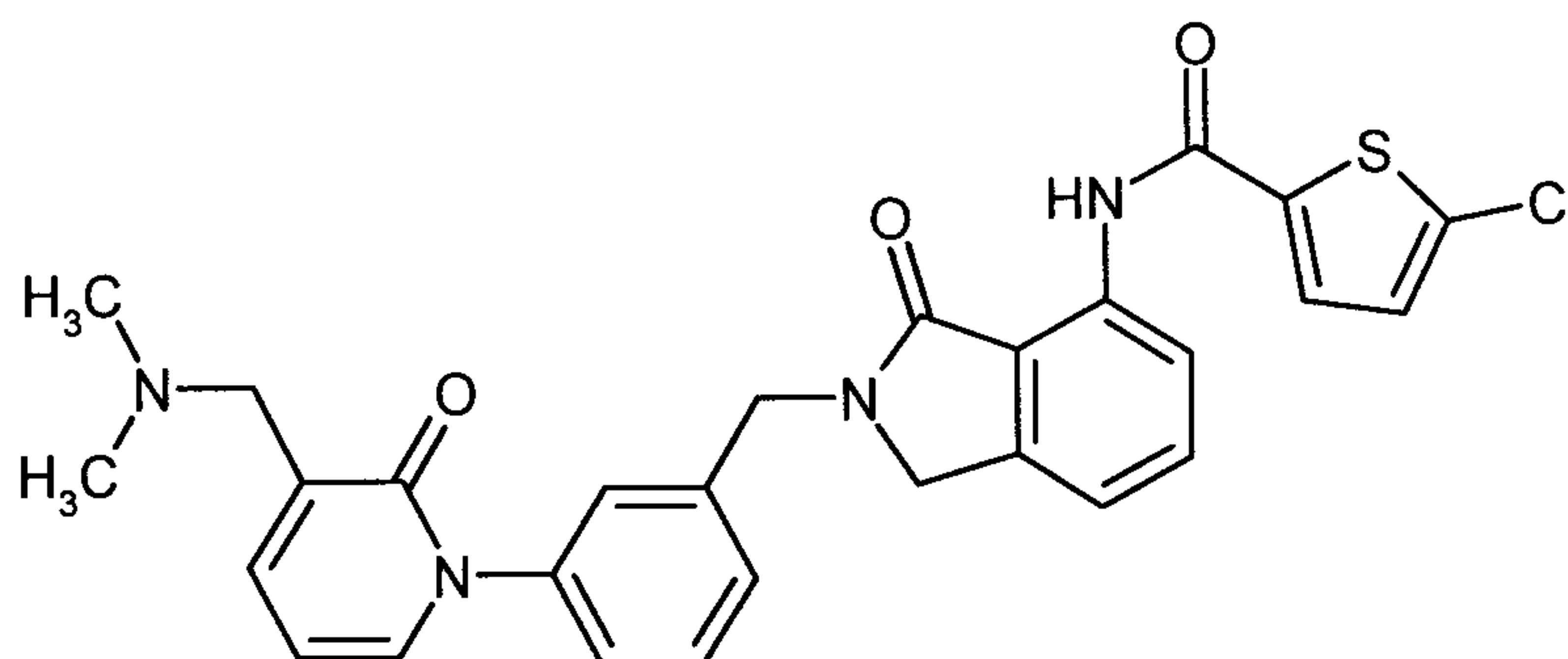
Example 36

10 5-Chloro-*N*-(2-{3-[3-(2-hydroxyethoxy)-2-oxopyridin-1(2*H*)-yl]benzyl}-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl)thiophene-2-carboxamide



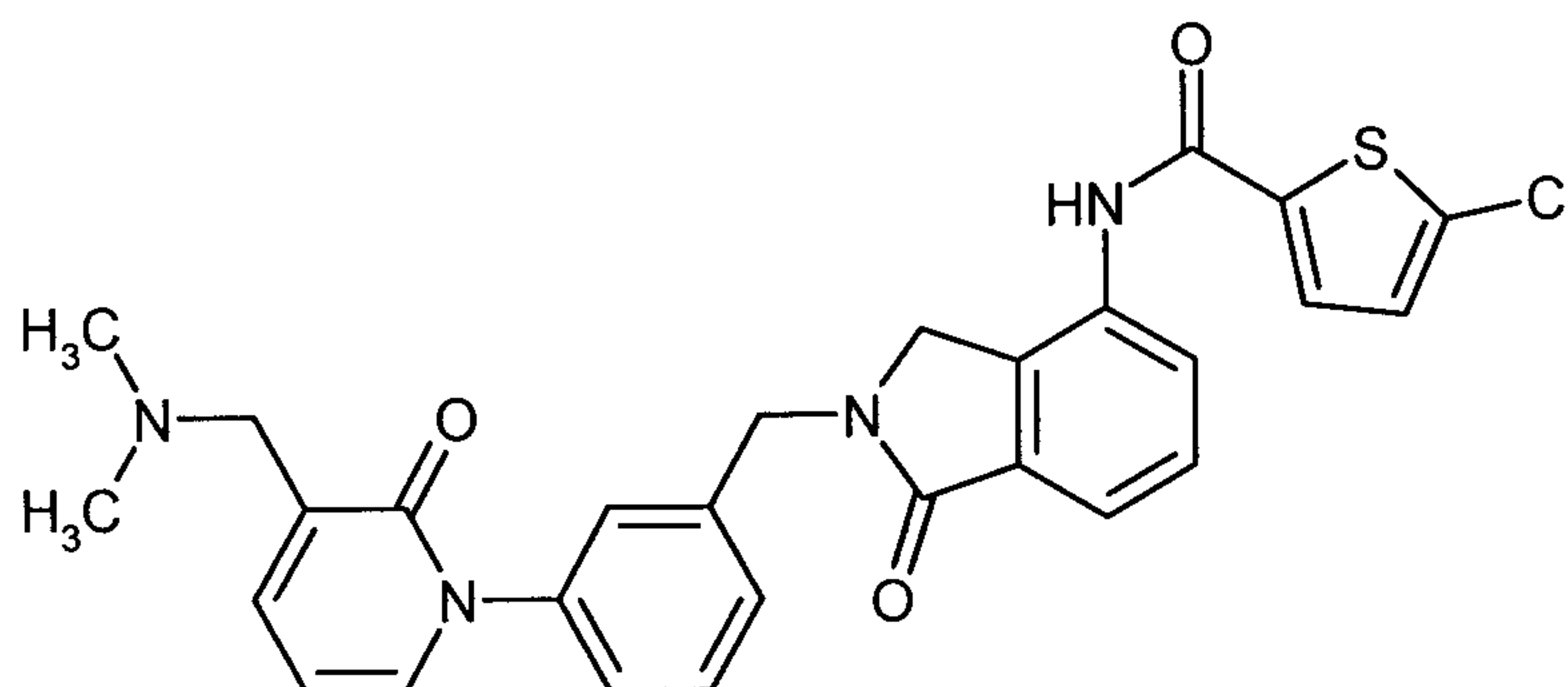
Example 37

5-Chloro-*N*-[2-(3-{3-[(dimethylamino)methyl]-2-oxopyridin-1(2*H*)-yl}benzyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



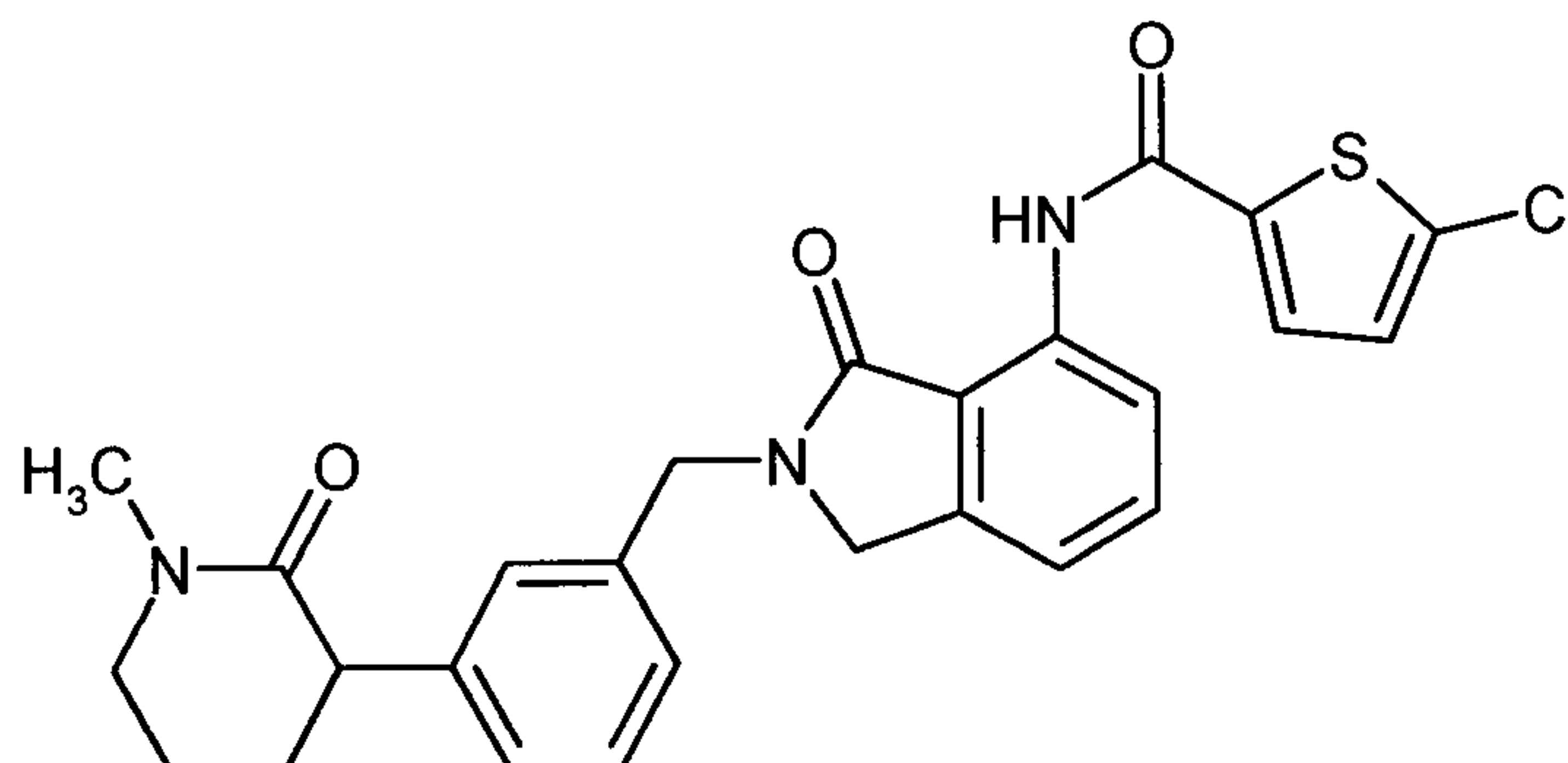
5 **Example 38**

5-Chloro-*N*-[2-(3-{3-[(dimethylamino)methyl]-2-oxopyridin-1(2*H*)-yl}benzyl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]thiophene-2-carboxamide



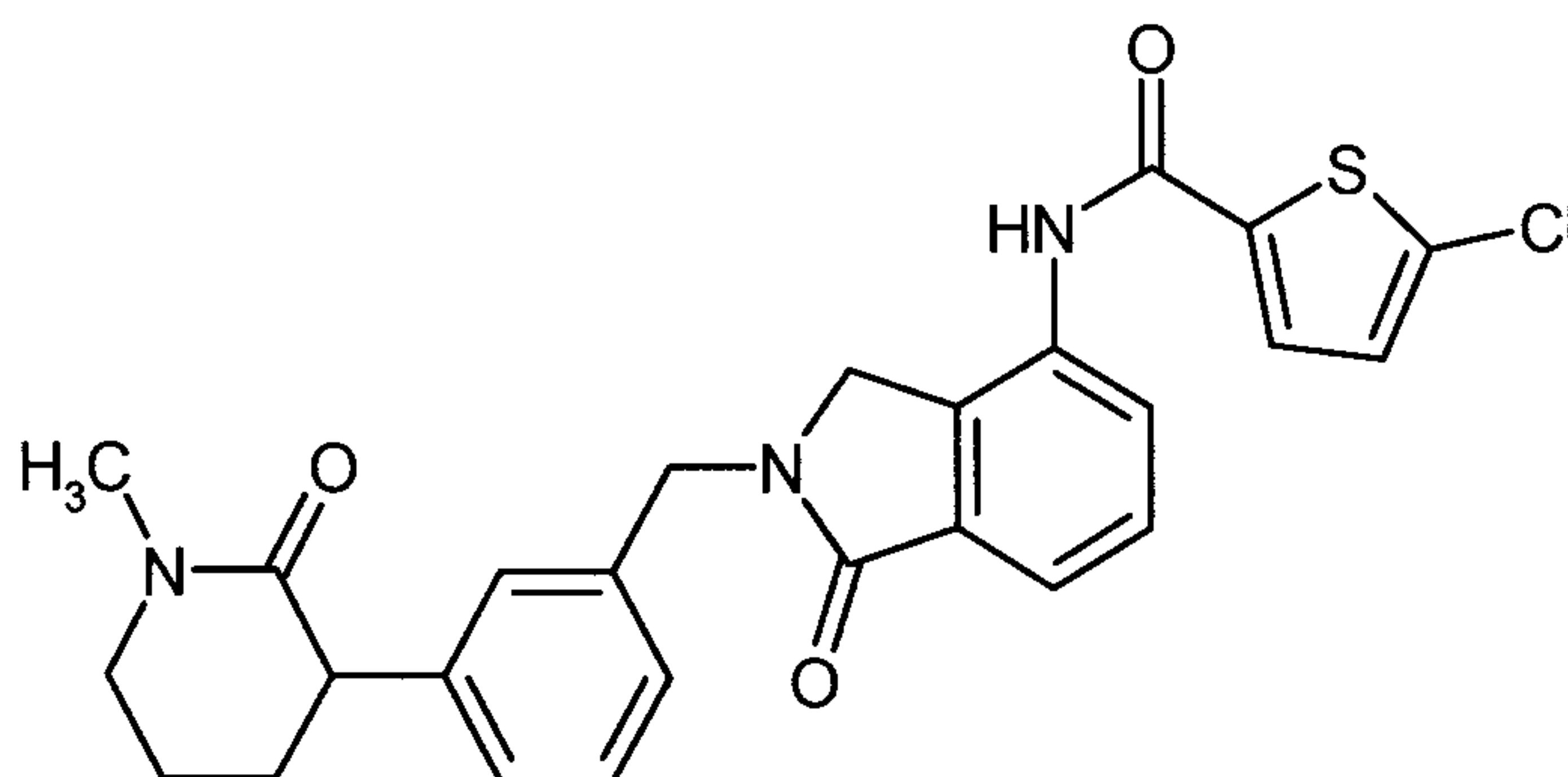
Example 39

10 5-Chloro-*N*-{2-[3-(1-methyl-2-oxopiperidin-3-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



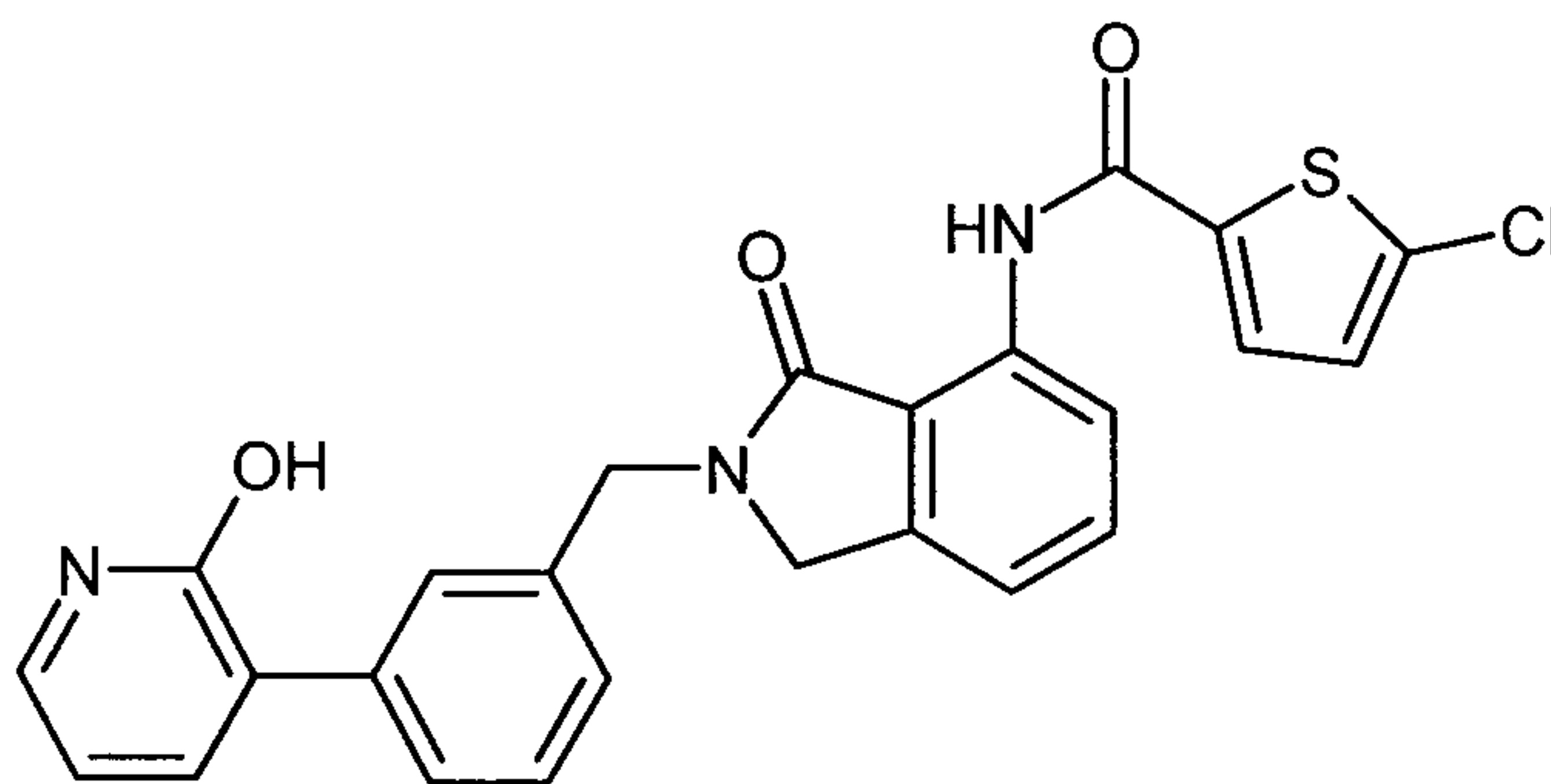
Example 40

5-Chloro-*N*-{2-[3-(1-methyl-2-oxopiperidin-3-yl)benzyl]-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



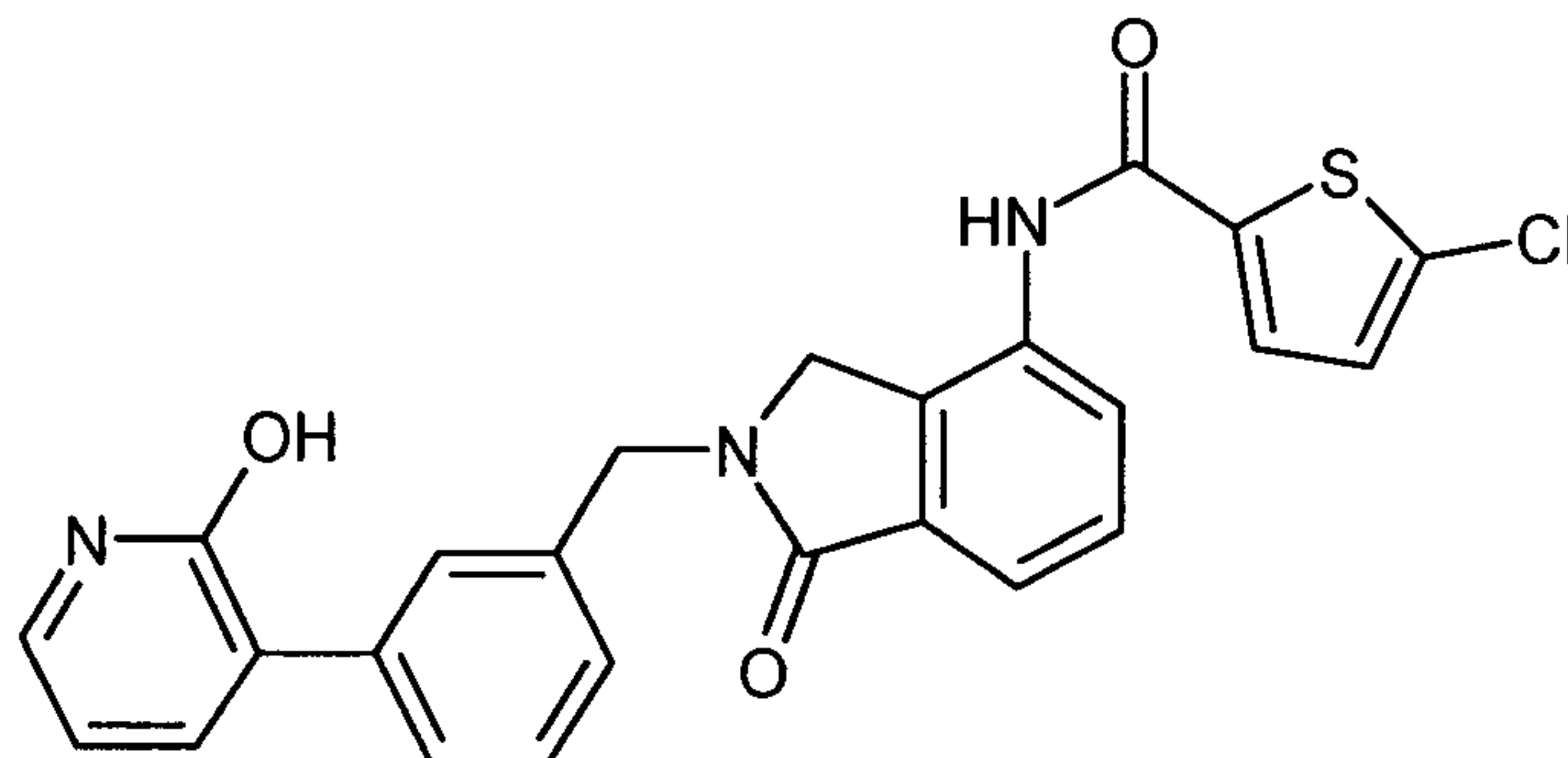
5 **Example 41**

5-Chloro-*N*-{2-[3-(2-hydroxypyridin-3-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



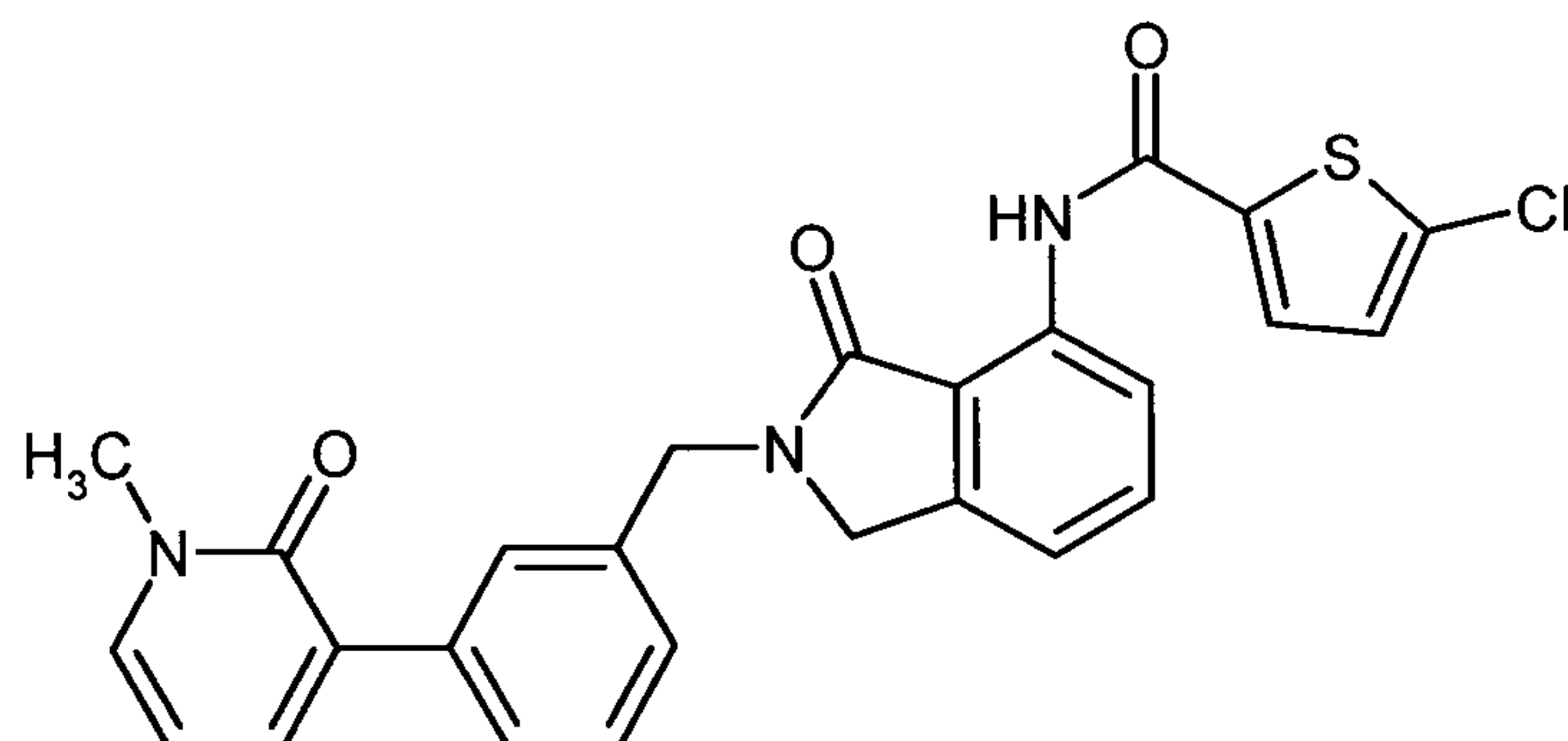
Example 42

10 5-Chloro-*N*-{2-[3-(2-hydroxypyridin-3-yl)benzyl]-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



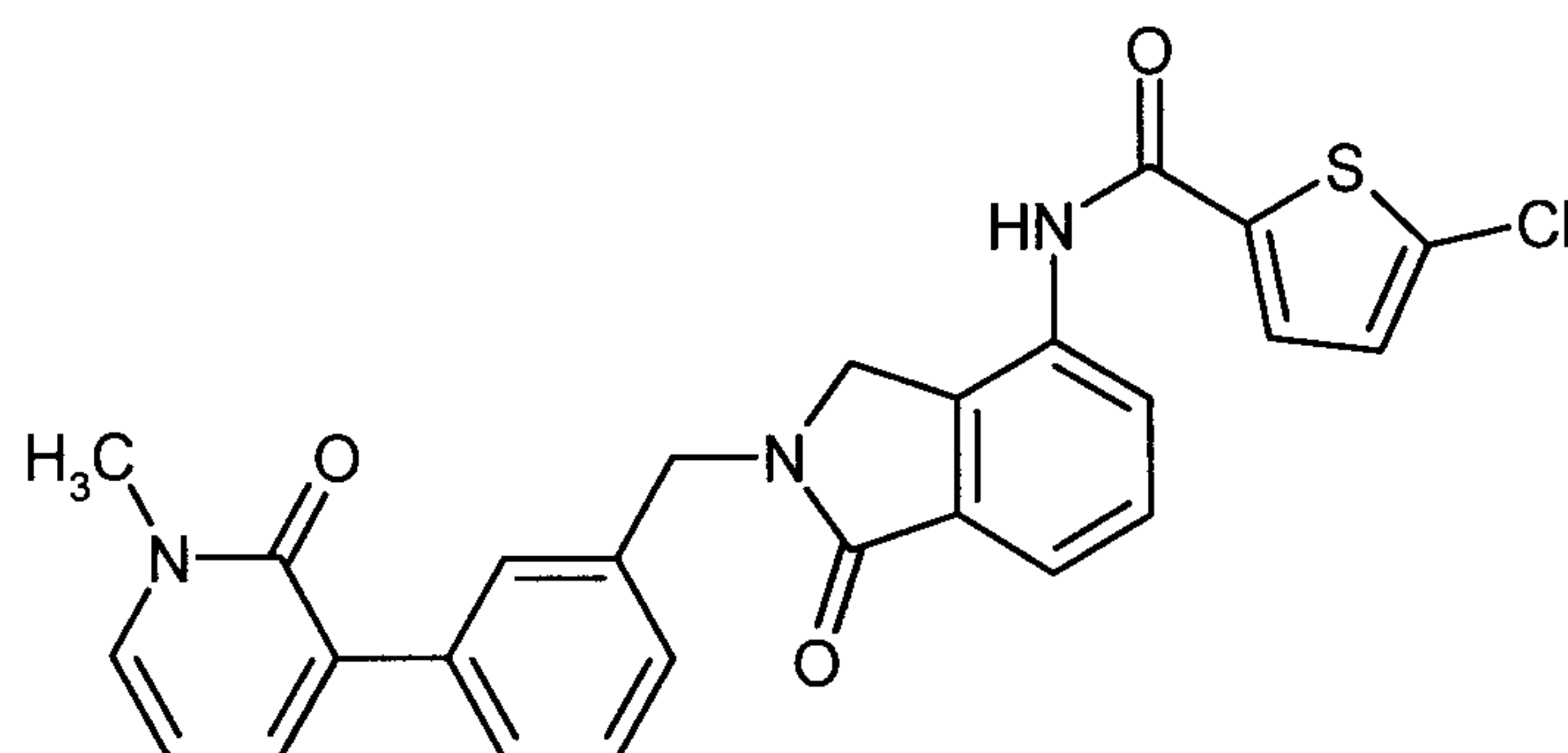
Example 43

5-Chloro-*N*-{2-[3-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



5 **Example 44**

5-Chloro-*N*-{2-[3-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)benzyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}thiophene-2-carboxamide



Analogously to the process described in Example 26, 100 mg (0.29 mmol) of the compound from
 10 Example 32A and 63 mg (0.347 mmol) of 5-chlorothiophene-2-carbonyl chloride give 100 mg
 (70% of theory) of the title compound.

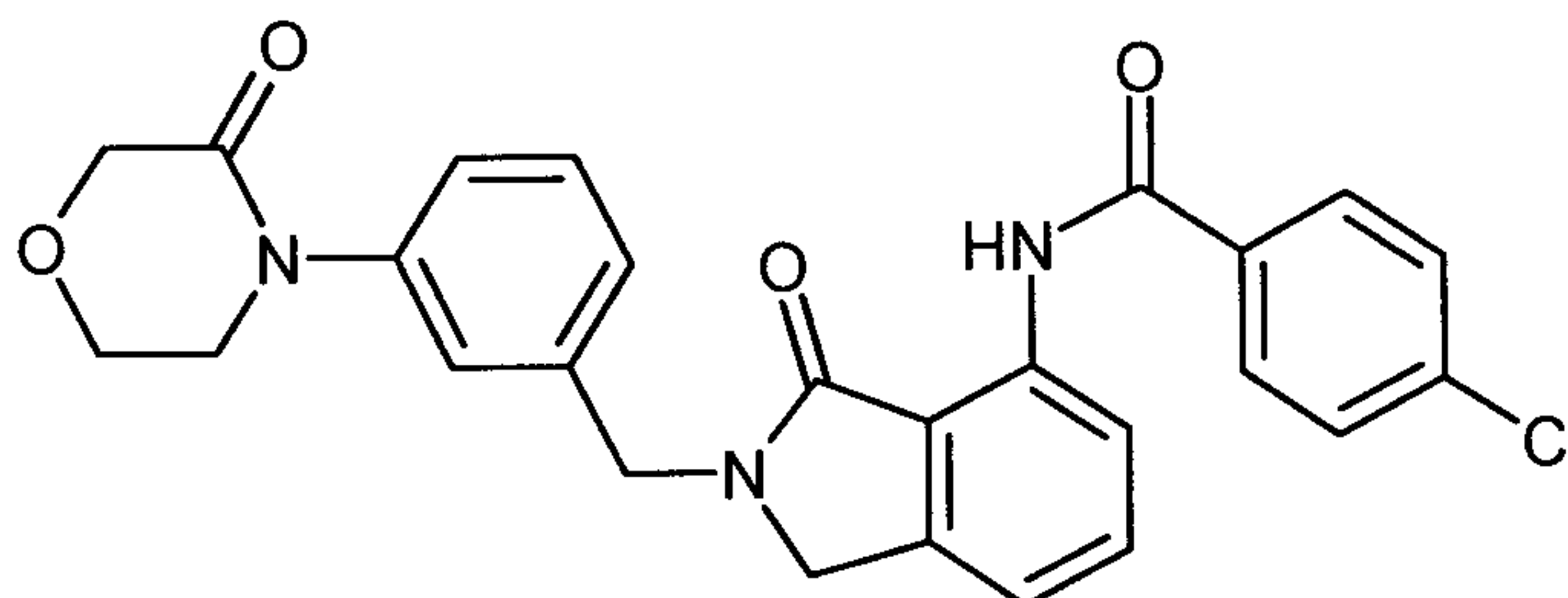
HPLC (Method 9): $R_t = 4.20$ min;

MS (ES⁺): $m/z = 490$ (M+H)⁺;

¹H-NMR (400 MHz, DMSO-*d*₆): $\delta = 10.37$ (s, 1H), 7.84 (d, 1H), 7.73 (dd, 1H), 7.68-7.53 (m, 6H),
 15 7.37 (dd, 1H), 7.26 (d, 1H), 7.23 (dd, 1H), 6.30 (dd, 1H), 4.77 (s, 2H), 4.42 (s, 2H), 3.49 (s, 3H).

Example 45

4-Chloro-*N*-{3-oxo-2-[3-(3-oxomorpholin-4-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}benzamide



Analogously to the process described in Example 26, 100 mg (0.296 mmol) of the compound from
5 Example 36A and 46 mg (0.356 mmol) of 4-chlorobenzoyl chloride give 111 mg (79% of theory)
of the title compound.

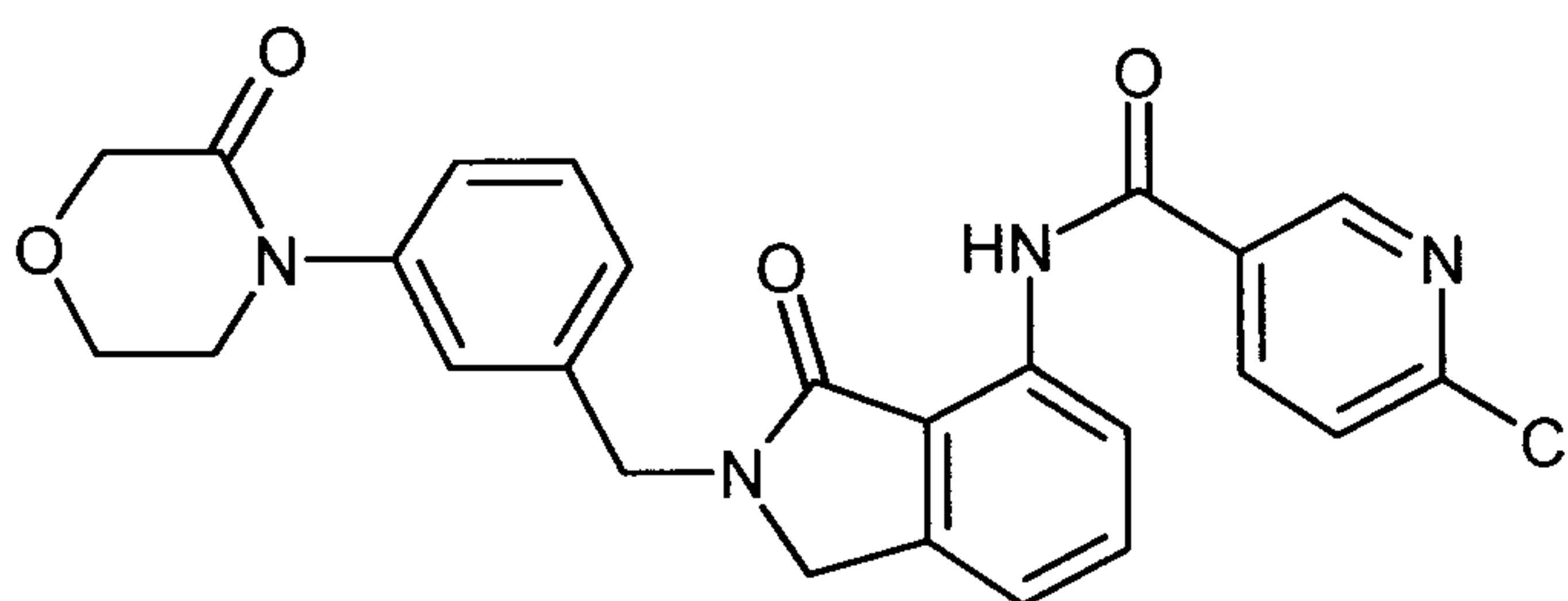
HPLC (Method 11): $R_t = 4.53$ min;

MS (DCI, NH_3): $m/z = 476$ ($\text{M}+\text{H}^+$), 493 ($\text{M}+\text{NH}_4^+$);

^1H -NMR (400 MHz, DMSO-d_6): $\delta = 11.42$ (s, 1H), 8.44 (d, 1H), 8.00 (d, 2H), 7.71 (d, 2H), 7.61
10 (dd, 1H), 7.41 (dd, 1H), 7.37 (dd, 1H), 7.32 (ddd, 1H), 7.30 (ddd, 1H), 7.23 (ddd, 1H), 4.77 (s,
2H), 4.47 (s, 2H), 4.18 (s, 2H), 3.94 (dd, 2H), 3.72 (dd, 2H).

Example 46

6-Chloro-*N*-{3-oxo-2-[3-(3-oxomorpholin-4-yl)benzyl]-2,3-dihydro-1*H*-isoindol-4-yl}nicotinamide



15 Analogously to the process described in Example 26, 100 mg (0.296 mmol) of the compound from
Example 36A and 46 mg (0.356 mmol) of 4-chloronicotinyl chloride give 26 mg (18% of theory)
of the title compound. The product is purified by preparative HPLC.

HPLC (Method 11): $R_t = 4.15$ min;

MS (ES^+): $m/z = 477$ ($\text{M}+\text{H}^+$);

- 102 -

¹H-NMR (400 MHz, DMSO-d₆): δ = 11.39 (s, 1H), 8.98 (d, 1H), 8.38 (d, 1H), 8.34 (dd, 1H), 7.80 (d, 1H), 7.63 (dd, 1H), 7.42 (dd, 1H), 7.37 (d, 1H), 7.33-7.30 (m, 2H), 7.22 (dd, 1H), 4.78 (s, 2H), 4.48 (s, 2H), 4.18 (s, 2H), 3.95 (dd, 2H), 3.72 (dd, 2H).

B. Evaluation of the pharmacological activity

The compounds according to the invention act in particular as selective inhibitors of blood coagulation factor Xa and do not, or only at significantly higher concentrations, inhibit other serine proteases, such as plasmin or trypsin.

- 5 “Selective” are those inhibitors of the blood coagulation factor Xa in which the IC_{50} values for the factor Xa inhibition are lower by a factor of at least 100 compared to the IC_{50} values for the inhibition of other serine proteases, in particular plasmin and trypsin, where, with respect to the test methods for the selectivity, reference is made to the test methods, described below, of Examples B.a.1) and B.a.2).
- 10 The advantageous pharmacological properties of the compounds according to the invention can be determined by the following methods:

a) Test descriptions (*in vitro*)

a.1) Determination of the factor Xa inhibition

a.1.1) Chromogenic assay:

- 15 The enzymatic activity of human factor Xa (FXa) is measured using the conversion of a chromogenic substrate specific for FXa. Factor Xa cleaves p-nitroaniline from the chromogenic substrate. The determinations are carried out in microtitre plates as follows:

The test substances, in various concentrations, are dissolved in DMSO and incubated for 10 minutes at 25°C with human FXa (0.5 nmol/l dissolved in 50 mmol/l of Tris buffer [C,C,C-
20 tris(hydroxymethyl)aminomethane], 150 mmol/l of NaCl, 0.1% BSA [bovine serum albumin], pH = 8.3). Pure DMSO is used as control. The chromogenic substrate (150 μ mol/l of Pefachrome® FXa from Pentapharm) is then added. After an incubation time of 20 minutes at 25°C, the extinction at 405 nm is determined. The extinctions of the test mixtures containing the test substance are compared with the control mixtures without test substance, and the IC_{50} values are
25 calculated from these data.

Representative activity data from this test are listed in Table 1 below:

Table 1

Example No.	IC ₅₀ [nM]
6	5.3
7	1.2

a.1.2) Fluorogenic assay:

The enzymatic activity of human factor Xa (FXa) is measured using the conversion of a
 5 fluorogenic substrate specific for FXa. FXa cleaves aminomethylcoumarin, whose fluorescence is measured, from the peptidic substrate. The determinations are carried out in microtitre plates.

Substances to be tested, in various concentrations, are dissolved in dimethyl sulphoxide and incubated for 15 min at 22°C with human FXa (1.3 nmol/l dissolved in 50 mmol/l of Tris buffer [C,C,C-tris(hydroxymethyl)aminomethane], 100 mmol/l NaCl, 0.1% BSA [bovine serum albumin],
 10 pH 7.4). The fluorogenic substrate (5 µmol/l of Boc-Ile-Glu-Gly-Arg-AMC from Bachem) is then added. After an incubation time of 30 min, the sample is excited at a wavelength of 360 nm, and the emission at 460 nm is measured. The measured emissions of the test batches with test substance are compared to the control batches without test substance (only dimethyl sulphoxide instead of test substance in dimethyl sulphoxide), and IC₅₀ values are calculated from the
 15 concentration/activity relationships.

a.2) Determination of the selectivity

a.2.1) Chromogenic assay:

To demonstrate the selective FXa inhibition, the test substances are examined for their inhibition of other human serine proteases, such as trypsin and plasmin. To determine the enzymatic activity
 20 of trypsin (500 mU/ml) and plasmin (3.2 nmol/l), these enzymes are dissolved in Tris buffer (100 mmol/l, 20 mmol/l of CaCl₂, pH = 8.0) and incubated with test substance or solvent for 10 minutes. The enzymatic reaction is then started by addition of the appropriate specific chromogenic substrates (Chromozym Trypsin® and Chromozym Plasmin®; from Roche Diagnostics), and after 20 minutes the extinction is determined at 405 nm. All determinations are
 25 carried out at 37°C. The extinctions of the test batches with test substance are compared to the control samples without test substance, and the IC₅₀ values are calculated from these data.

a.2.2) Fluorogenic assay:

To demonstrate the selectivity of the substances with respect to factor Xa inhibition, the test substances are examined for their inhibition of other human serine proteases, such as trypsin and plasmin. To determine the enzymatic activity of trypsin (83 mU/ml from Sigma) and plasmin (0.1 µg/ml from Kordia), these enzymes are dissolved (50 mmol/l of Tris buffer [C,C,C-
5 tris(hydroxymethyl)aminomethane], 100 mmol/l of NaCl, 0.1% BSA [bovine serum albumin], 5 mmol/l of calcium chloride, pH 7.4) and incubated for 15 min with various concentrations of test substance in dimethyl sulfoxide and also with dimethyl sulfoxide without test substance. The enzymatic reaction is then started by addition of the appropriate substrates (5 µmol/l of Boc-Ile-Glu-Gly-Arg-AMC from Bachem for trypsin and 50 µmol/l of MeOSuc-Ala-Phe-Lys-AMC from
10 Bachem for plasmin). After an incubation time of 30 min at 22°C, the fluorescence is measured (excitation: 360 nm, emission: 460 nm). The measured emissions of the test batches with test substance are compared to the control batches without test substance (only dimethyl sulfoxide instead of test substance in dimethyl sulfoxide), and IC₅₀ values are calculated from the concentration/activity relationships.

15 a.3) Determination of the anticoagulatory activity

The anticoagulatory activity of the test substances is determined *in vitro* in human and rabbit plasma. To this end, blood is drawn off in a mixing ratio of sodium citrate/blood of 1:9 using a 0.11 molar sodium citrate solution as receiver. Immediately after the blood has been drawn off, it is mixed thoroughly and centrifuged at about 2500 g for 10 minutes. The supernatant is pipetted
20 off. The prothrombin time (PT, synonyms: thromboplastin time, quick test) is determined in the presence of varying concentrations of test substance or the corresponding solvent using a commercial test kit (Hemoliance® RecombiPlastin, from Instrumentation Laboratory). The test compounds are incubated with the plasma at 37°C for 3 minutes. Coagulation is then started by addition of thromboplastin, and the time when coagulation occurs is determined. The concentration
25 of test substance which effects a doubling of the prothrombin time is determined.

b) Determination of the antithrombotic activity (*in vivo*)

b.1) Arteriovenous shunt model (rabbit)

Fasting rabbits (strain: Esd: NZW) are anaesthetized by intramuscular administration of Rompun/Ketavet solution (5 mg/kg and 40 mg/kg, respectively). Thrombus formation is initiated in an
30 arteriovenous shunt in accordance with the method described by C.N. Berry *et al.* [*Semin. Thromb. Hemost.* **1996**, 22, 233-241]. To this end, the left jugular vein and the right carotid artery are exposed. The two vessels are connected by an extracorporeal shunt using a vein catheter of a length of 10 cm. In the middle, this catheter is attached to a further polyethylene tube (PE 160,

Becton Dickenson) of a length of 4 cm which contains a roughened nylon thread which has been arranged to form a loop, to form a thrombogenic surface. The extracorporeal circulation is maintained for 15 minutes. The shunt is then removed and the nylon thread with the thrombus is weighed immediately. The weight of the nylon thread on its own was determined before the
5 experiment was started. Before extracorporeal circulation is set up, the test substances are administered either intravenously via an ear vein or orally using a pharyngeal tube.

c) Solubility assay

Reagents required:

- PBS buffer pH 7.4: 90.00 g of NaCl p.a. (for example Merck Art. No. 1.06404.1000), 13.61 g of
10 KH_2PO_4 p.a. (for example Merck Art. No. 1.04873.1000) and 83.35 g of 1N NaOH (for example Bernd Kraft GmbH Art. No. 01030.4000) are weighed into a 1 l measuring flask, the flask is filled with water and the mixture is stirred for about 1 hour.
- Acetate buffer pH 4.6: 5.4 g of sodium acetate x 3 H_2O p.a. (for example Merck Art. No. 1.06267.0500) are weighed into a 100 ml measuring flask and dissolved in 50 ml of water, 2.4 g of
15 glacial acetic acid are added, the mixture is made up to 100 ml with water, the pH is checked and, if required, adjusted to pH 4.6.
- Dimethyl sulphoxide (for example Baker Art. No. 7157.2500)
- Distilled water

Preparation of the calibration solutions:

- 20 *Preparation of the stock solution of calibration solutions:* About 0.5 mg of the active compound are weighed accurately into a 2 ml Eppendorf Safe-Lock tube (Eppendorf Art. No. 0030 120.094), DMSO is added to a concentration of 600 $\mu\text{g/ml}$ (for example 0.5 mg of active compound + 833 μl of DMSO) and the mixture is vortexed until everything has gone into solution.

Calibration solution 1 (20 $\mu\text{g/ml}$): 1000 μl of DMSO are added to 34.4 μl of the stock solution,
25 and the mixture is homogenized.

Calibration solution 2 (2.5 $\mu\text{g/ml}$): 700 μl of DMSO are added to 100 μl of calibration solution 1, and the mixture is homogenized.

Preparation of the sample solutions:

Sample solution for solubilities of up to 10 g/l in PBS buffer pH 7.4: About 5 mg of the active

compound are weighed accurately into a 2 ml Eppendorf Safe-Lock tube (Eppendorf Art. No. 0030 120.094), and PBS buffer pH 7.4 is added to a concentration of 5 g/l (for example 5 mg of active compound + 500 µl of PBS buffer pH 7.4).

Sample solution for solubilities of up to 10 g/l in acetate buffer pH 4.6: About 5 mg of the active compound are weighed accurately into a 2 ml Eppendorf Safe-Lock tube (Eppendorf Art. No. 0030 120.094), and acetate buffer pH 4.6 is added to a concentration of 5 g/l (for example 5 mg of active compound + 500 µl of acetate buffer pH 4.6).

Sample solution for solubilities of up to 10 g/l in water: About 5 mg of the active compound are weighed accurately into a 2 ml Eppendorf Safe-Lock tube (Eppendorf Art. No. 0030 120.094), and water is added to a concentration of 5 g/l (for example 5 mg of active compound + 500 µl of water).

Practice:

The sample solutions prepared in this manner are shaken at 1400 rpm in a temperature-adjustable shaker (for example Eppendorf Thermomixer comfort Art. No. 5355 000.011 with interchangeable block Art. No. 5362.000.019) at 20°C for 24 hours. In each case 180 µl are taken from these solutions and transferred into Beckman Polyallomer centrifuge tubes (Art. No. 343621). These solutions are centrifuged at about 223 000 *g for 1 hour (for example Beckman Optima L-90K ultracentrifuge with type 42.2 Ti rotor at 42 000 rpm). From each of the sample solutions, 100 µl of the supernatant are removed and diluted 1:5, 1:100 and 1:1000 with the respective solvent used (water, PBS buffer 7.4 or acetate buffer pH 4.6). From each dilution, a sample is transferred into a vessel suitable for HPLC analysis.

Analysis:

The samples are analyzed by RP-HPLC. Quantification is carried out using a two-point calibration curve of the test compound in DMSO. The solubility is expressed in mg/l.

25 Analysis sequence:

1. Calibration solution 2.5 mg/ml
2. Calibration solution 20 µg/ml
3. Sample solution 1:5
4. Sample solution 1:100

5. Sample solution 1:1000

HPLC method for acids:

Agilent 1100 with DAD (G1315A), quat. pump (G1311A), autosampler CTC HTS PAL, degasser (G1322A) and column thermostat (G1316A); column: Phenomenex Gemini C18, 50 x 2 mm, 5 µ;
5 temperature: 40°C; mobile phase A: water/phosphoric acid pH 2; mobile phase B: acetonitrile; flow rate: 0.7 ml/min; gradient: 0–0.5 min 85% A, 15% B; ramp: 0.5-3 min 10% A, 90% B; 3–3.5 min 10% A, 90% B; ramp: 3.5-4 min 85% A, 15% B; 4-5 min 85% A, 15% B.

HPLC method for bases:

Agilent 1100 with DAD (G1315A), quat. pump (G1311A), autosampler CTC HTS PAL, degasser
10 (G1322A) and column thermostat (G1316A); column: VDSoptilab Kromasil 100 C18, 60 x 2.1 mm, 3.5 µ; temperature: 30°C; mobile phase A: water + 5 ml perchloric acid/l; mobile phase B: acetonitrile; flow rate: 0.75 ml/min; gradient: 0–0.5 min 98% A, 2% B; ramp: 0.5-4.5 min 10% A, 90% B; 4.5–6 min 10% A, 90% B; ramp: 6.5-6.7 min 98% A, 2% B; 6.7-7.5 min 98% A, 2% B.

C. **Exemplary embodiments of pharmaceutical compositions**

The compounds according to the invention can be converted into pharmaceutical preparations in the following ways:

Tablet:

5 **Composition:**

100 mg of the compound according to the invention, 50 mg of lactose (monohydrate), 50 mg of corn starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

10 **Preparation:**

The mixture of the compound according to the invention, lactose and starch is granulated with a 5% strength solution (m/m) of PVP in water. The granules are dried and then mixed with the magnesium stearate for 5 minutes. This mixture is compressed using a conventional tablet press (see above for format of the tablet). As guideline, a compressive force of 15 kN is used for the

15 compression.

Oral suspension:

Composition:

1000 mg of the compound according to the invention, 1000 mg of ethanol (96%), 400 mg of Rhodigel® (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

20 10 ml of oral suspension are equivalent to a single dose of 100 mg of the compound according to the invention.

Preparation:

The Rhodigel is suspended in ethanol, and the compound according to the invention is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until the

25 swelling of the Rhodigel is complete.

Oral solution:**Composition:**

500 mg of the compound according to the invention, 2.5 g of polysorbate and 97 g of polyethylene glycol 400. 20 g of oral solution are equivalent to a single dose of 100 mg of the compound
5 according to the invention.

Production:

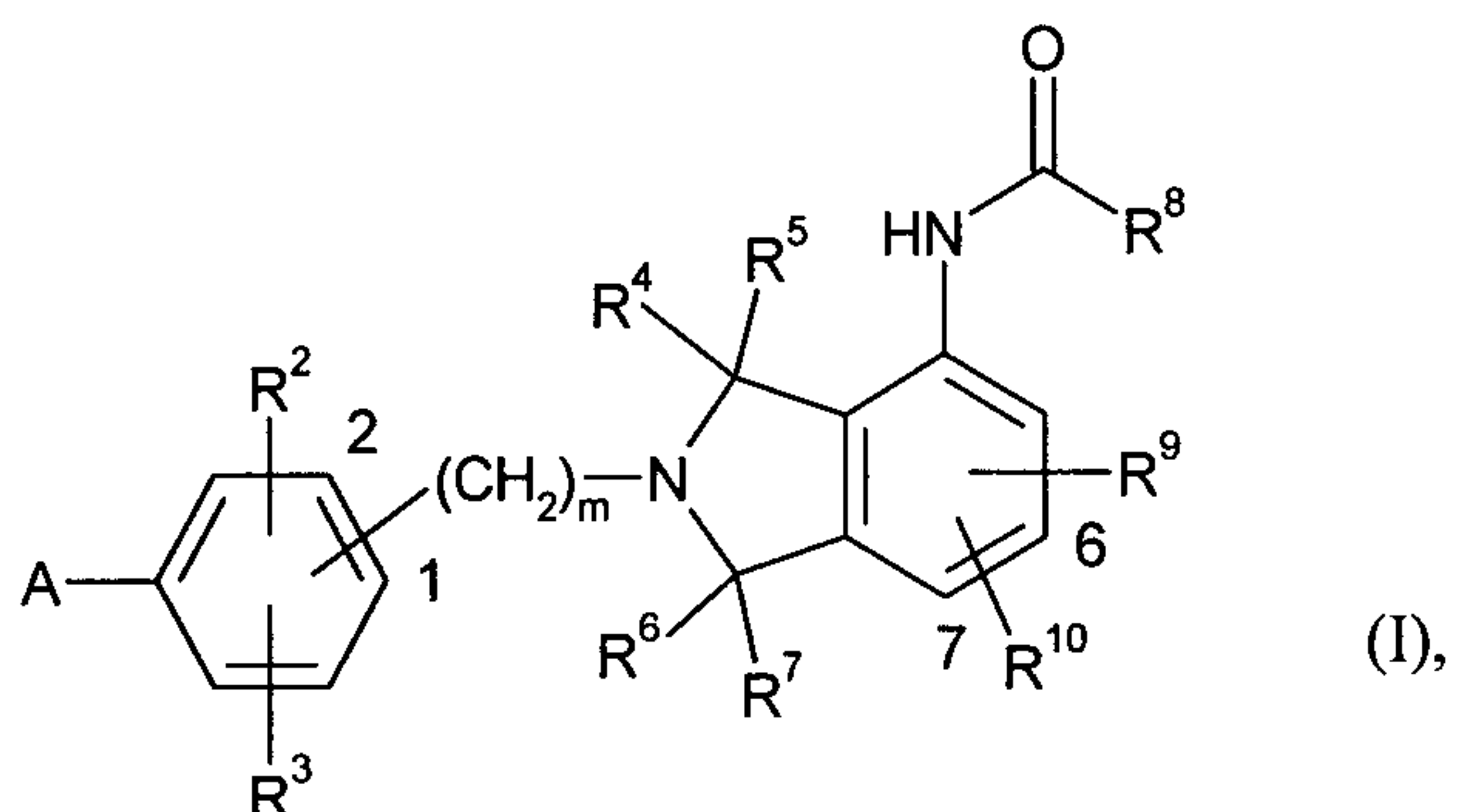
The compound according to the invention is suspended in the mixture of polyethylene glycol and polysorbate while stirring. Stirring is continued until the compound according to the invention is completely dissolved.

10 **i.v. solution:**

The compound according to the invention is dissolved at a concentration below saturation solubility in a physiologically acceptable solvent (for example isotonic sodium chloride solution, glucose solution 5% and/or PEG 400 solution 30%). The solution is sterilized by filtration and filled into sterile and pyrogen-free injection containers.

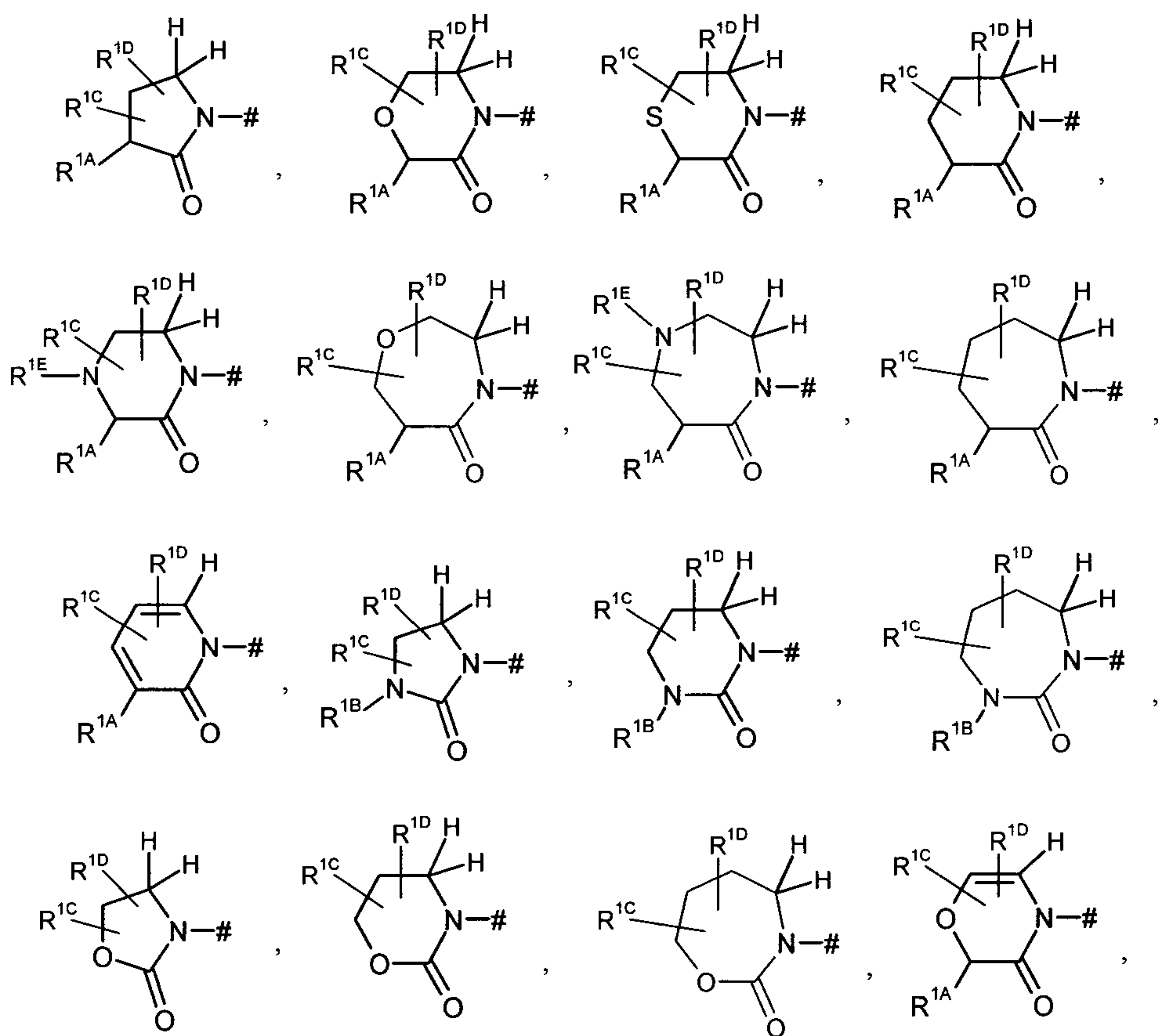
Patent Claims

1. Compound of the formula

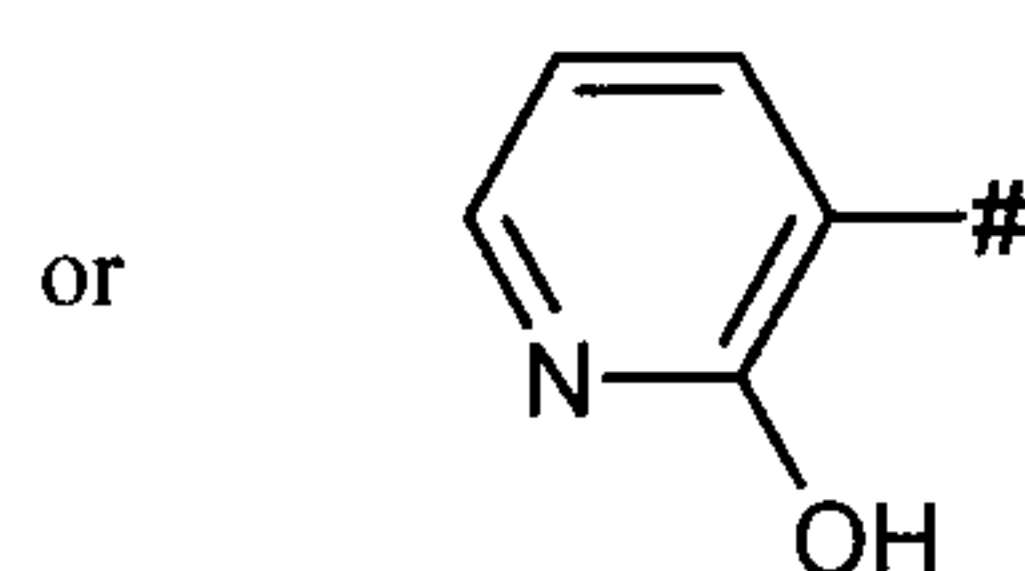
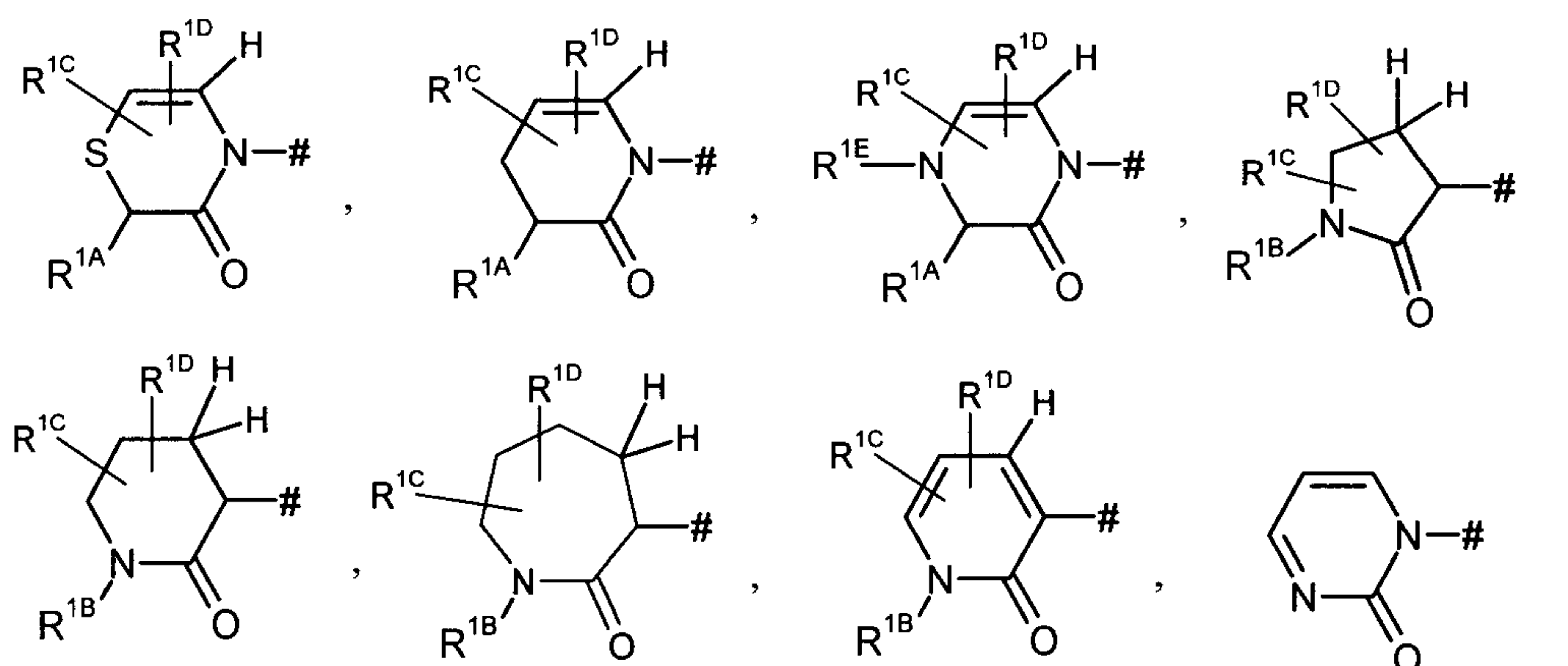


in which

5 A represents a group of the formula



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where

R^{1A} represents hydrogen, fluorine, trifluoromethyl, hydroxy, amino, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkylamino, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyloxy or C_3 - C_6 -cycloalkylamino,

where alkyl, alkoxy, alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C_1 - C_4 -alkoxy, C_1 - C_4 -alkylamino, C_3 - C_6 -cycloalkyloxy, C_3 - C_6 -cycloalkylamino, (N- C_3 - C_6 -cycloalkyl)(N- C_1 - C_4 -alkyl)amino and a 4- to 7-membered saturated heterocycle which may contain a ring member from the group consisting of N- R^{21} , S and O,

where

R^{21} represents hydrogen, C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl,

and

the heterocycle may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C_1 - C_4 -alkyl and oxo,

R^{1B} represents hydrogen, hydroxy, amino, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkylamino, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyloxy or C_3 - C_6 -cycloalkyl-

amino,

5 where alkyl may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C₁-C₄-alkoxy, C₁-C₄-alkylamino, C₃-C₆-cycloalkyloxy, C₃-C₆-cycloalkylamino, (N-C₃-C₆-cycloalkyl)(N-C₁-C₄-alkyl)amino and a 4- to 7-membered saturated heterocycle which may contain a ring member from the group consisting of N-R²¹, S and O,

where

R²¹ represents hydrogen, C₁-C₄-alkyl or C₃-C₆-cycloalkyl,

10 and

the heterocycle may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, C₁-C₄-alkyl and oxo,

15 R^{1C} represents hydrogen, fluorine, cyano, hydroxy, amino, oxo, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylamino or C₃-C₆-cycloalkyl,

R^{1D} represents hydrogen, fluorine, cyano, C₁-C₄-alkyl or C₃-C₆-cycloalkyl,

R^{1E} represents hydrogen, C₁-C₄-alkyl or C₃-C₆-cycloalkyl,

and # is the point of attachment to the phenyl ring,

m represents the number 0, 1 or 2,

20 and the (CH₂)_m group is attached in the 1- or 2-position to the phenyl ring,

R² represents hydrogen, fluorine, chlorine, cyano, hydroxy, amino, trifluoromethyl, trifluoromethoxy, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxymethyl, C₁-C₄-alkylamino, C₃-C₆-cycloalkyl, aminocarbonyl, C₁-C₄-alkoxycarbonyl or C₁-C₄-alkylaminocarbonyl,

25 R³ represents hydrogen, fluorine, chlorine, cyano, hydroxy, amino, trifluoromethyl, trifluoromethoxy, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxymethyl, C₁-C₄-alkylamino, C₃-C₆-cycloalkyl, aminocarbonyl, C₁-C₄-alkoxycarbonyl or C₁-C₄-alkylaminocarbonyl,

where alkyl, alkoxy and alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, C₁-C₄-alkoxy, C₃-C₆-cycloalkyloxy, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-tetrahydropyranyl and -NR¹⁴R¹⁵,

5 where piperazinyl and piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

and

R¹⁴ represents hydrogen, C₁-C₄-alkyl or C₃-C₆-cycloalkyl,

10 and

R¹⁵ represents hydrogen or C₁-C₄-alkyl,

R⁴ and R⁵ represent hydrogen,

and

15 R⁶ and R⁷ together with the carbon atom to which they are attached form a carbonyl group,

or

R⁴ and R⁵ together with the carbon atom to which they are attached form a carbonyl group,

and

20 R⁶ and R⁷ represent hydrogen,

or

R⁴ and R⁵ together with the carbon atom to which they are attached form a carbonyl group,

and

25 R⁶ and R⁷ together with the carbon atom to which they are attached form a carbonyl group,

R^8 represents phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl or thienyl,

where phenyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl are substituted by a substituent R^{11} and/or a substituent R^{12} or by two different substituents R^{11} or by two different substituents R^{12} ,

5 where

R^{11} is attached to a carbon atom which is not adjacent to a nitrogen atom in the ring and represents hydrogen, fluorine, chlorine, cyano, ethynyl, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or C_3 - C_6 -cycloalkyl,

10 R^{12} is attached to a carbon atom which is adjacent to a nitrogen atom in the ring and represents hydrogen, amino, C_1 - C_4 -alkyl, C_1 - C_4 -alkylamino or C_3 - C_6 -cycloalkyl,

and

where thienyl is substituted by a substituent R^{13} and a substituent R^{16} ,

where

15 R^{13} is attached to a carbon atom which is adjacent to the sulphur atom in the ring and represents hydrogen, fluorine, chlorine, cyano, ethynyl, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or C_3 - C_6 -cycloalkyl,

R^{16} represents hydrogen, fluorine, chlorine, amino, C_1 - C_4 -alkyl, C_1 - C_4 -alkylamino or C_3 - C_6 -cycloalkyl,

20 R^9 represents hydrogen, fluorine, chlorine, cyano, hydroxy, amino, trifluoromethyl, trifluoromethoxy, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkylamino, C_3 - C_6 -cycloalkyl, aminocarbonyl, C_1 - C_4 -alkoxycarbonyl or C_1 - C_4 -alkylaminocarbonyl,

25 where alkyl, alkoxy and alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, C_1 - C_4 -alkoxy, C_3 - C_6 -cycloalkyloxy, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-tetrahydropyranyl and $-NR^{17}R^{18}$,

where piperazinyl and piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

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and

R^{17} represents hydrogen, C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl,

and

R^{18} represents hydrogen or C_1 - C_4 -alkyl,

5 R^{10} represents hydrogen, fluorine, chlorine, cyano, trifluoromethyl, trifluoromethoxy,
 C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or C_3 - C_6 -cycloalkyl,

and

where R^9 is attached to the 6-position and R^{10} is attached to the 7-position of the isoindoline
ring,

10 or

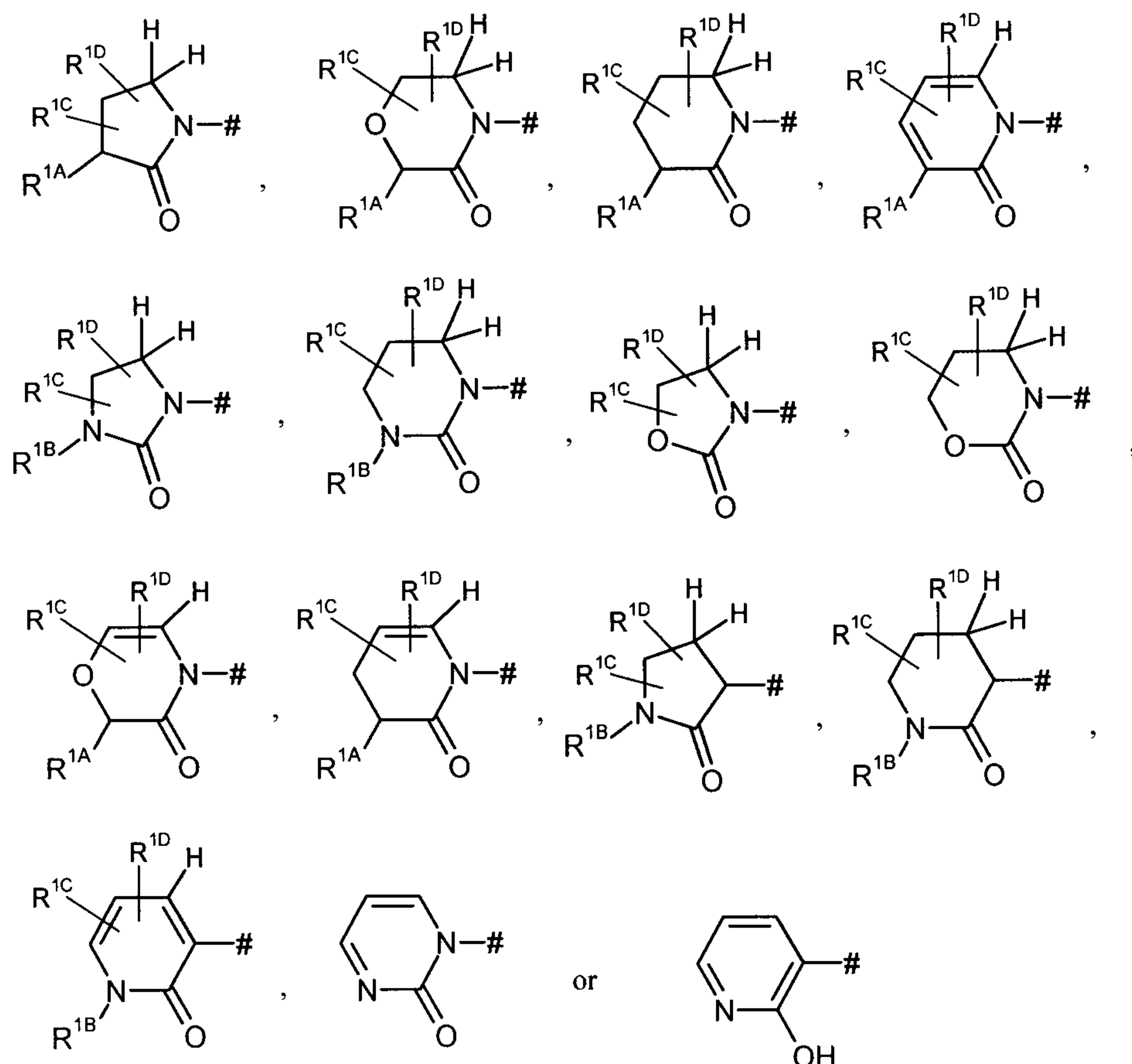
where R^9 is attached to the 7-position and R^{10} is attached to the 6-position of the
isoindoline ring,

or one of its salts, its solvates or the solvates of its salts.

2. Compound according to Claim 1, characterized in that

15 A represents a group of the formula

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where

R^{1A} represents hydrogen, fluorine, hydroxy, amino, C₁-C₄-alkyl, methoxy, ethoxy, *tert*-butoxy, methylamino, dimethylamino, ethylamino, diethylamino, *tert*-butylamino, cyclopropyl, cyclopropylamino or cyclopropyloxy,

where alkyl, ethoxy, *tert*-butoxy, ethylamino, diethylamino and *tert*-butylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, methoxy, C₁-C₄-alkylamino, cyclopropyloxy, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-piperidinyl, 4-morpholinyl, 1-piperazinyl and 4-tetrahydropyranyl,

where 1-piperazinyl and 4-piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

R^{1B} represents hydrogen, hydroxy, amino, C₁-C₄-alkyl, methoxy, methylamino,

dimethylamino or cyclopropyl,

where alkyl may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, methoxy, C₁-C₄-alkylamino, cyclopropyloxy, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-piperidinyl, 4-morpholinyl, 1-piperazinyl and 4-tetrahydropyranyl,

where 1-piperazinyl and 4-piperidinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

R^{1C} represents hydrogen, fluorine, oxo or methyl,

R^{1D} represents hydrogen, fluorine or methyl,

and # is the point of attachment to the phenyl ring,

m represents the number 0, 1 or 2,

and the (CH₂)_m group is attached in the 1- or 2-position to the phenyl ring,

R² represents hydrogen, fluorine, chlorine, cyano, hydroxy, C₁-C₄-alkyl or C₁-C₄-alkoxy,

R³ represents hydrogen, fluorine, chlorine, cyano, hydroxy, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxymethyl, C₁-C₄-alkylamino, cyclopropyl, aminocarbonyl, C₁-C₄-alkoxycarbonyl or C₁-C₄-alkylaminocarbonyl,

where alkyl, alkoxy and alkylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, methoxy, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl and -NR¹⁴R¹⁵,

where 1-piperazinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

and

R¹⁴ represents hydrogen, methyl or cyclopropyl,

and

R^{15} represents hydrogen or methyl,

R^4 and R^5 represent hydrogen,

and

5 R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

10 and

R^6 and R^7 represent hydrogen,

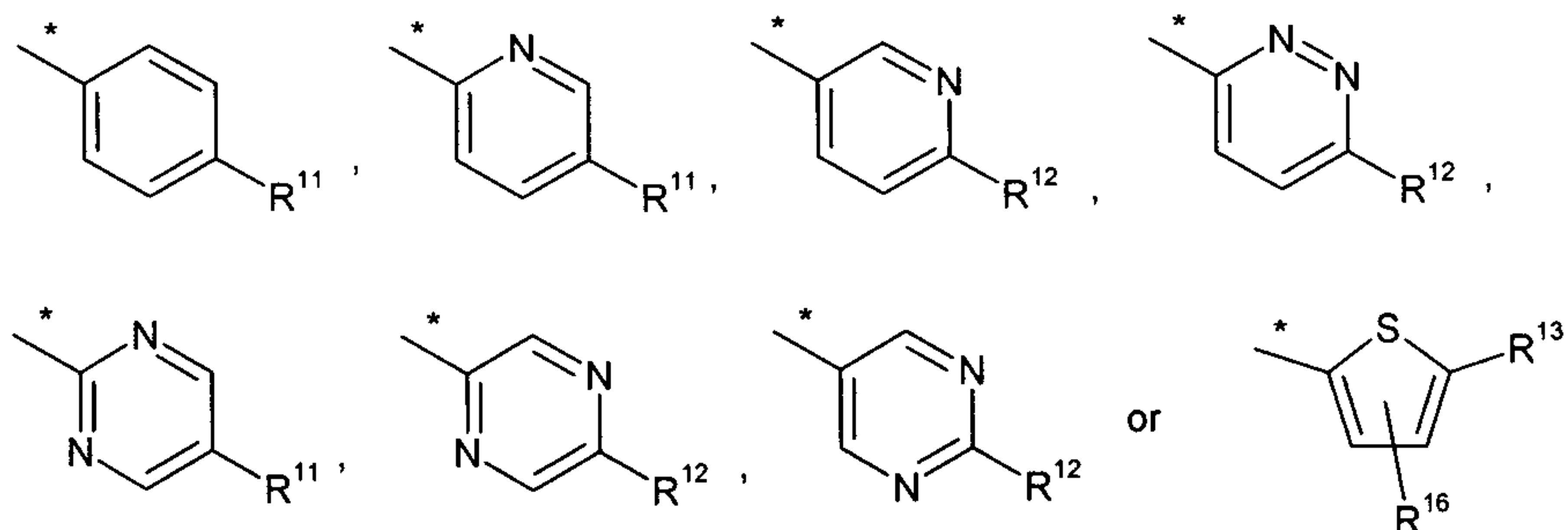
or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group,

15 and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

R^8 represents a group of the formula



20 where

* is the point of attachment to the carbonyl group,

R^{11} represents fluorine, chlorine, ethynyl, methyl, ethyl, methoxy or ethoxy,

R^{12} represents amino, methyl, methylamino or dimethylamino,

R^{13} represents fluorine, chlorine, ethynyl, methyl, ethyl, methoxy or ethoxy,

and

5 R^{16} represents hydrogen,

R^9 represents hydrogen, fluorine, chlorine, cyano, methyl, methoxy, aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl,

10 where methyl and methoxy may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, methoxy, 1-pyrrolidiny, 1-piperidiny, 4-morpholiny, 1-piperaziny and $-NR^{17}R^{18}$,

where 1-piperaziny may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

and

15 R^{17} represents hydrogen, methyl or cyclopropyl,

and

R^{18} represents hydrogen or methyl,

R^{10} represents hydrogen, fluorine, chlorine, cyano, trifluoromethyl, trifluoromethoxy, methyl or methoxy,

20 and

where R^9 is attached to the 6-position and R^{10} to the 7-position of the isoindoline ring,

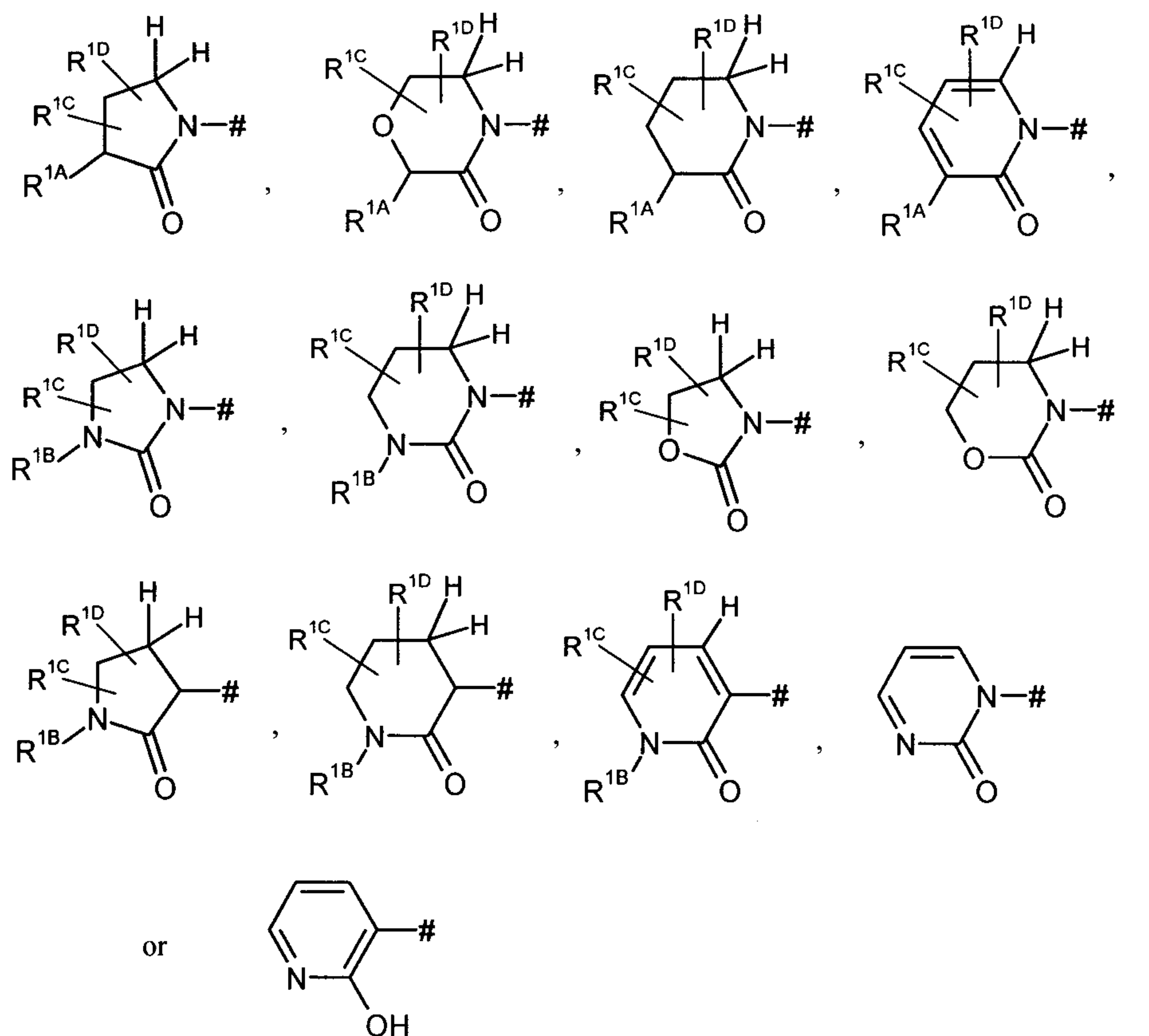
or

where R^9 is attached to the 7-position and R^{10} to the 6-position of the isoindoline ring.

3. Compound according to Claim 1 or 2, characterized in that

25 A represents a group of the formula

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where

R^{1A} represents hydrogen, fluorine, hydroxy, amino, methyl, ethyl, isopropyl, methoxy, ethoxy, methylamino, dimethylamino, ethylamino, diethylamino or cyclopropylamino,

where methyl, ethyl, isopropyl, ethoxy, ethylamino and diethylamino may be substituted by a substituent, the substituent being selected from the group consisting of hydroxy, amino, methoxy, methylamino, dimethylamino, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl and 1-piperazinyl,

where 1-piperazinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

R^{1B} represents hydrogen, hydroxy, amino, methyl, ethyl, isopropyl or cyclopropyl,

where ethyl and isopropyl may be substituted by a substituent, the

substituent being selected from the group consisting of hydroxy, amino, methoxy, methylamino, dimethylamino, cyclopropylamino, (N-cyclopropyl)(N-methyl)amino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl and 1-piperazinyl,

where 1-piperazinyl may be substituted at the nitrogen atom by a substituent, the substituent being selected from the group consisting of methyl and cyclopropyl,

R^{1C} represents hydrogen, fluorine, oxo or methyl,

R^{1D} represents hydrogen, fluorine or methyl,

10 and # is the point of attachment to the phenyl ring,

m represents the number 1,

and the $(\text{CH}_2)_m$ group is attached in the 1- or 2-position to the phenyl ring,

R^2 represents hydrogen,

15 R^3 represents hydrogen, fluorine, chlorine, cyano, methyl, ethyl, n-propyl, methoxy, ethoxy or methoxymethyl,

R^4 and R^5 represent hydrogen,

and

R⁶ and R⁷ together with the carbon atom to which they are attached form a carbonyl group,

20 or

R⁴ and R⁵ together with the carbon atom to which they are attached form a carbonyl group,

and

R^6 and R^7 represent hydrogen,

25 or

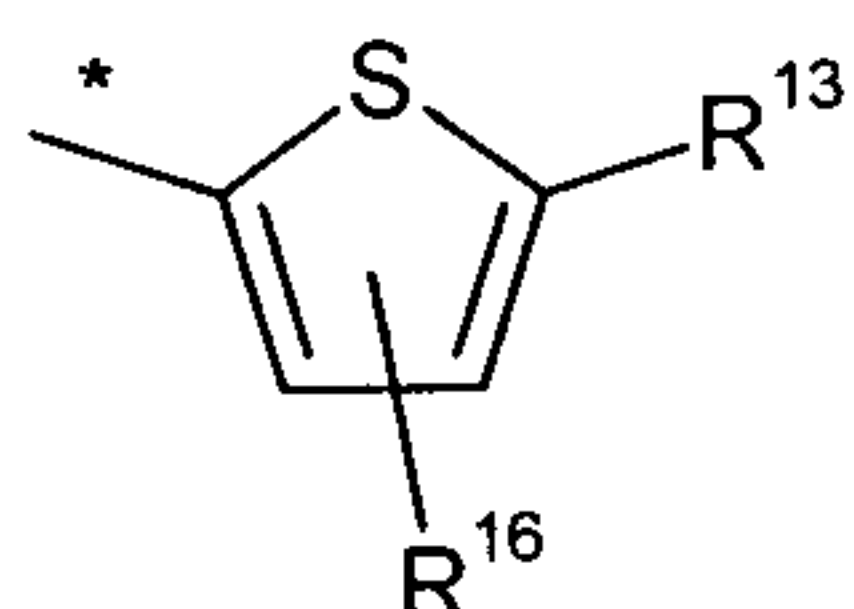
R⁴ and R⁵ together with the carbon atom to which they are attached form a carbonyl

group,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

5 R^8 represents a group of the formula



where

* is the point of attachment to the carbonyl group,

R^{13} represents fluorine, chlorine or methyl,

10 and

R^{16} represents hydrogen,

R^9 represents hydrogen,

R^{10} represents hydrogen,

and

15 where R^9 is attached to the 6-position and R^{10} to the 7-position of the isoindoline ring,

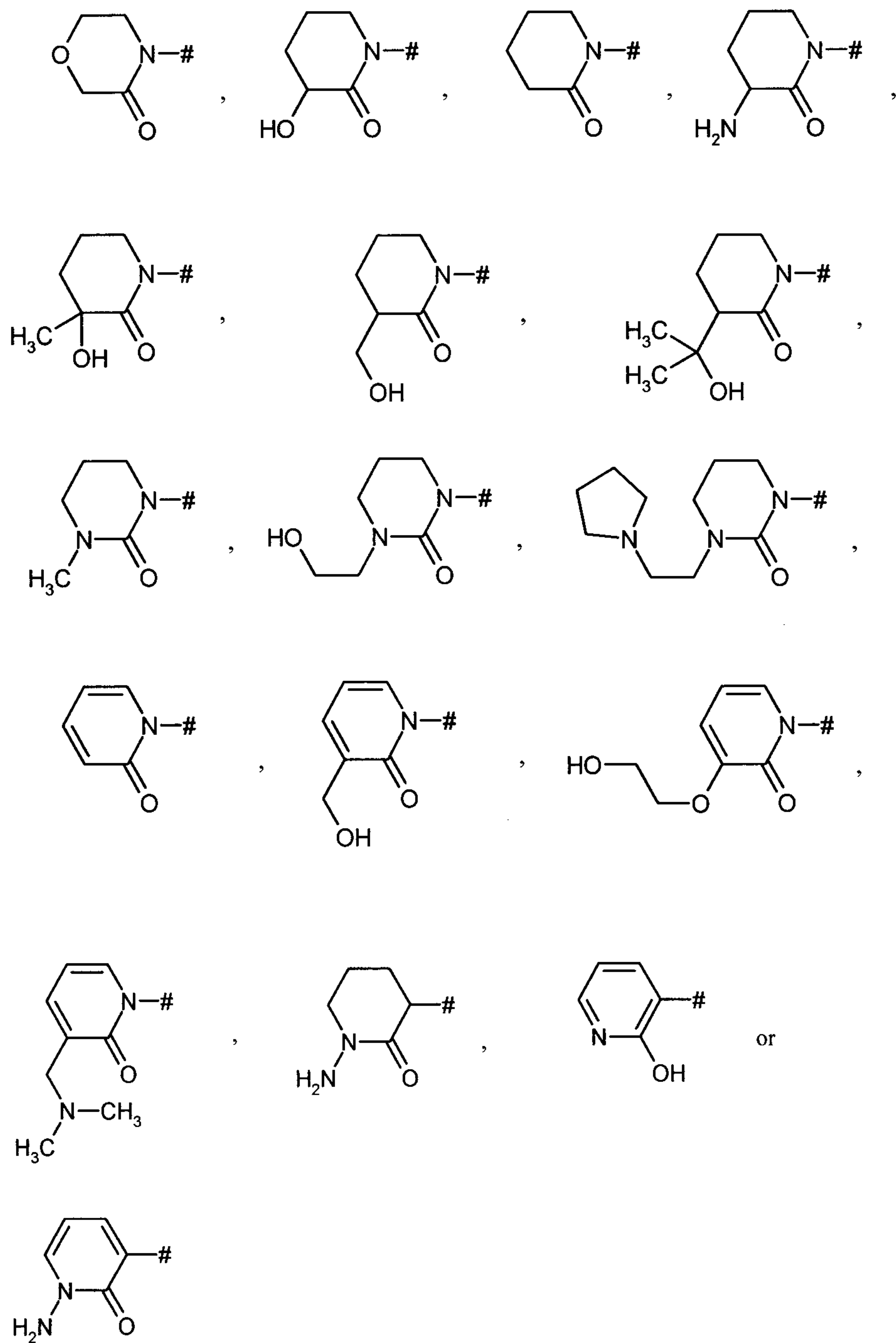
or

where R^9 is attached to the 7-position and R^{10} to the 6-position of the isoindoline ring.

4. Compound according to any of Claims 1 to 3, characterized in that

A represents a group of the formula

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where

5 # is the point of attachment to the phenyl ring,

m represents the number 1,

and the $(CH_2)_m$ group is attached in the 1- or 2-position to the phenyl ring,

R^2 represents hydrogen,

R^3 represents hydrogen, fluorine, chlorine, cyano or methyl,

R^4 and R^5 represent hydrogen,

and

R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl
5 group,

or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl
group,

and

10 R^6 and R^7 represent hydrogen,

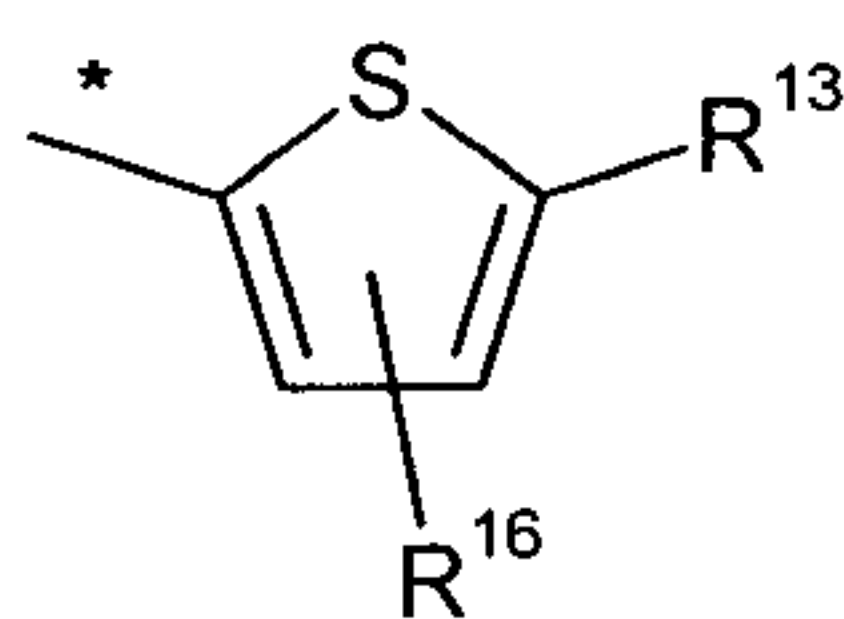
or

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl
group,

and

15 R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl
group,

R^8 represents a group of the formula



where

20 * is the point of attachment to the carbonyl group,

R^{13} represents chlorine,

and

R^{16} represents hydrogen,

R^9 represents hydrogen,

R^{10} represents hydrogen,

and

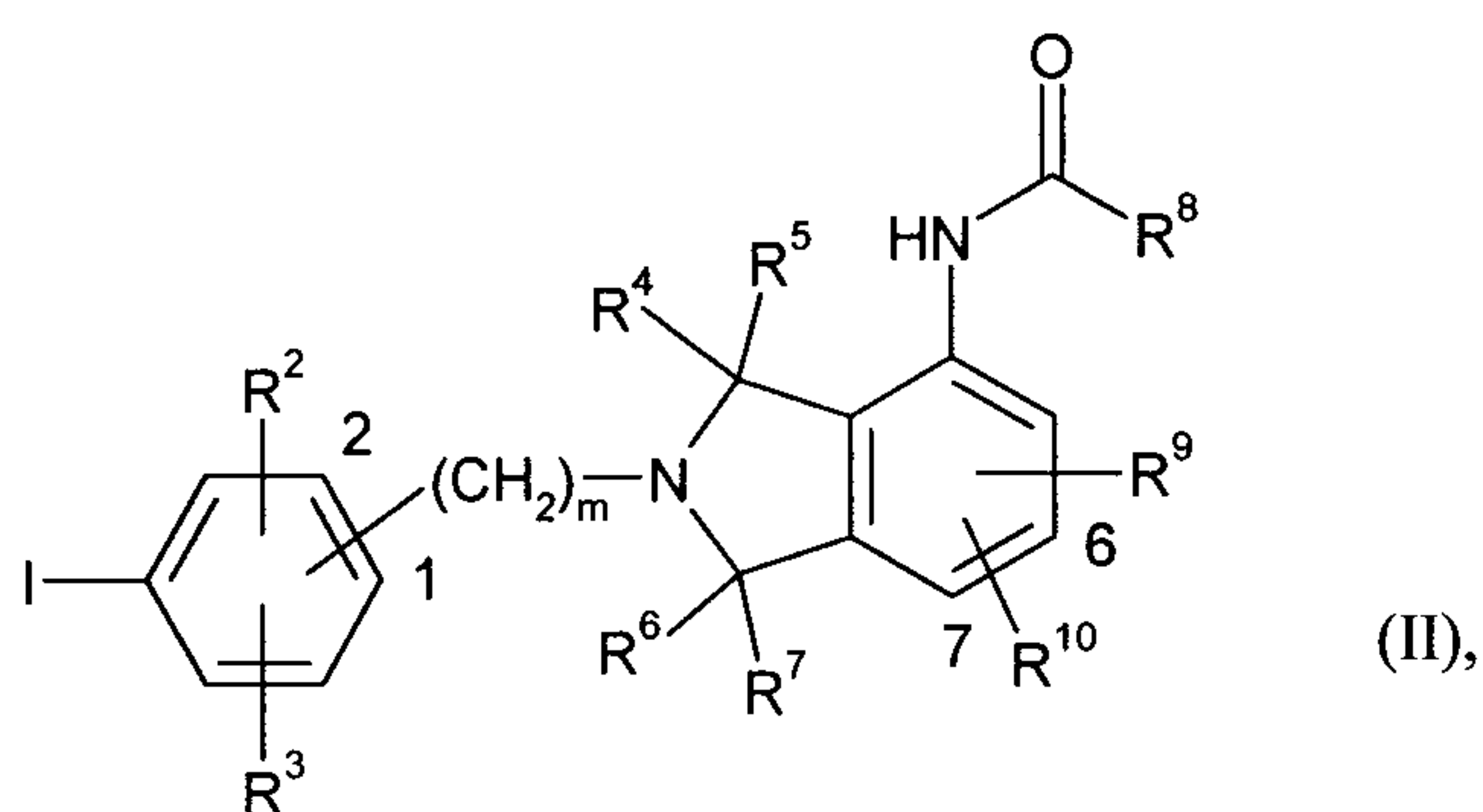
where R^9 is attached to the 6-position and R^{10} to the 7-position of the isoindoline ring,

5 or

where R^9 is attached to the 7-position and R^{10} to the 6-position of the isoindoline ring.

5. Process for preparing a compound of the formula (I) or one of its salts, its solvates or the solvates of its salts according to Claim 1, characterized in that

[A] a compound of the formula



10

in which m , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} have the meaning given in Claim 1,

is reacted with a compound of the formula

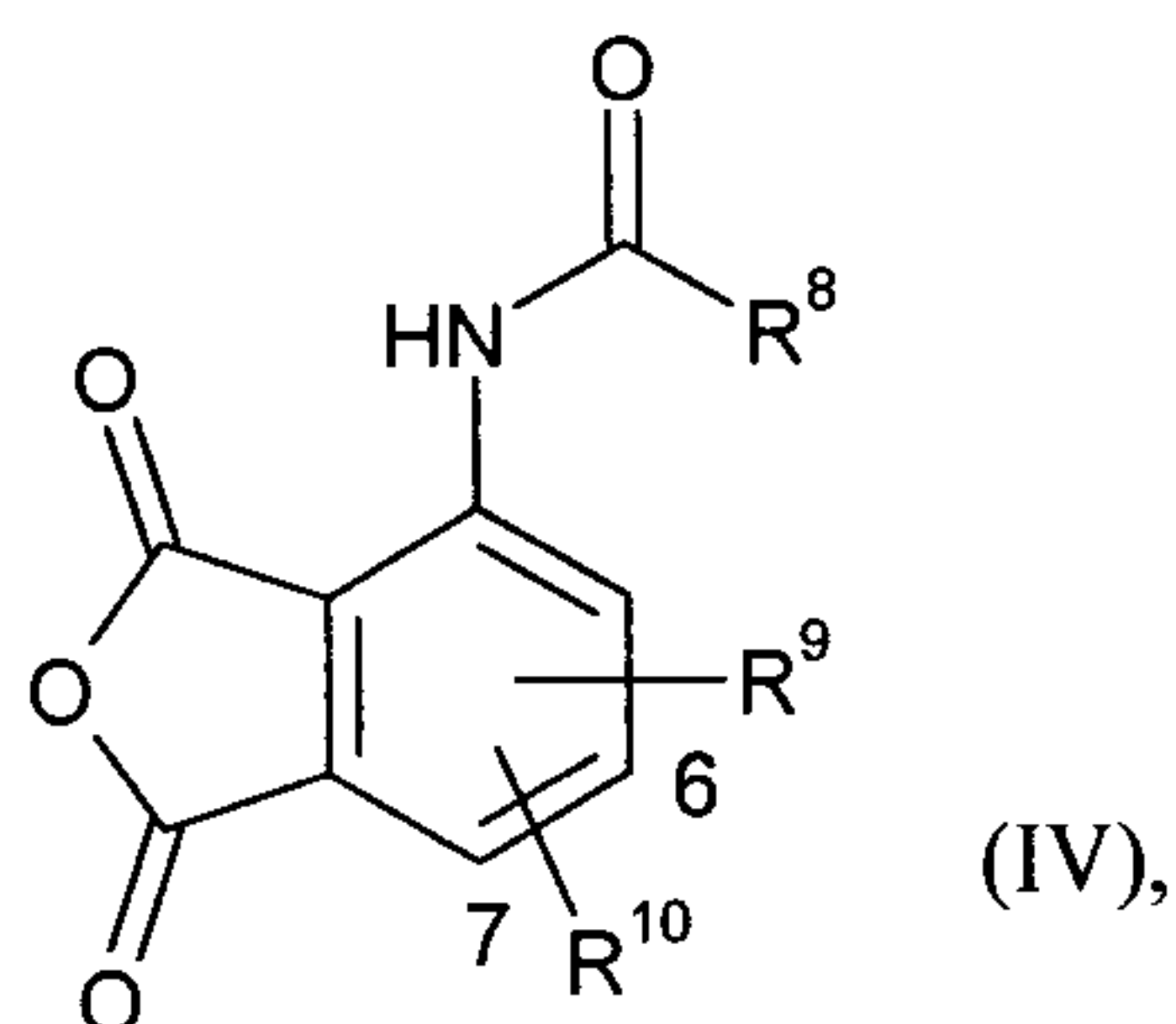
A-H (III),

in which A has the meaning given in Claim 1,

15 or

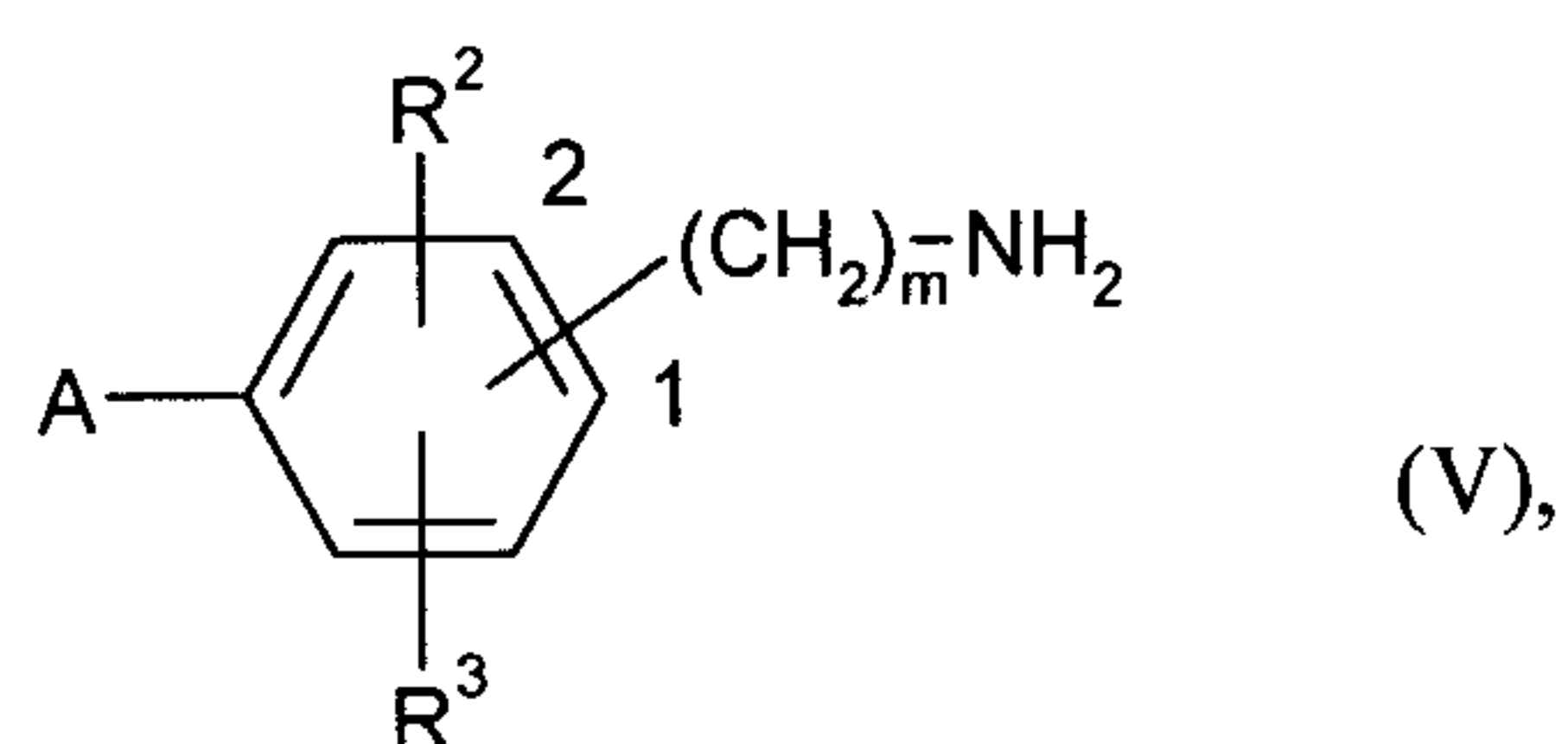
[B] a compound of the formula

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in which R^8 , R^9 and R^{10} have the meaning given in Claim 1,

is reacted with a compound of the formula

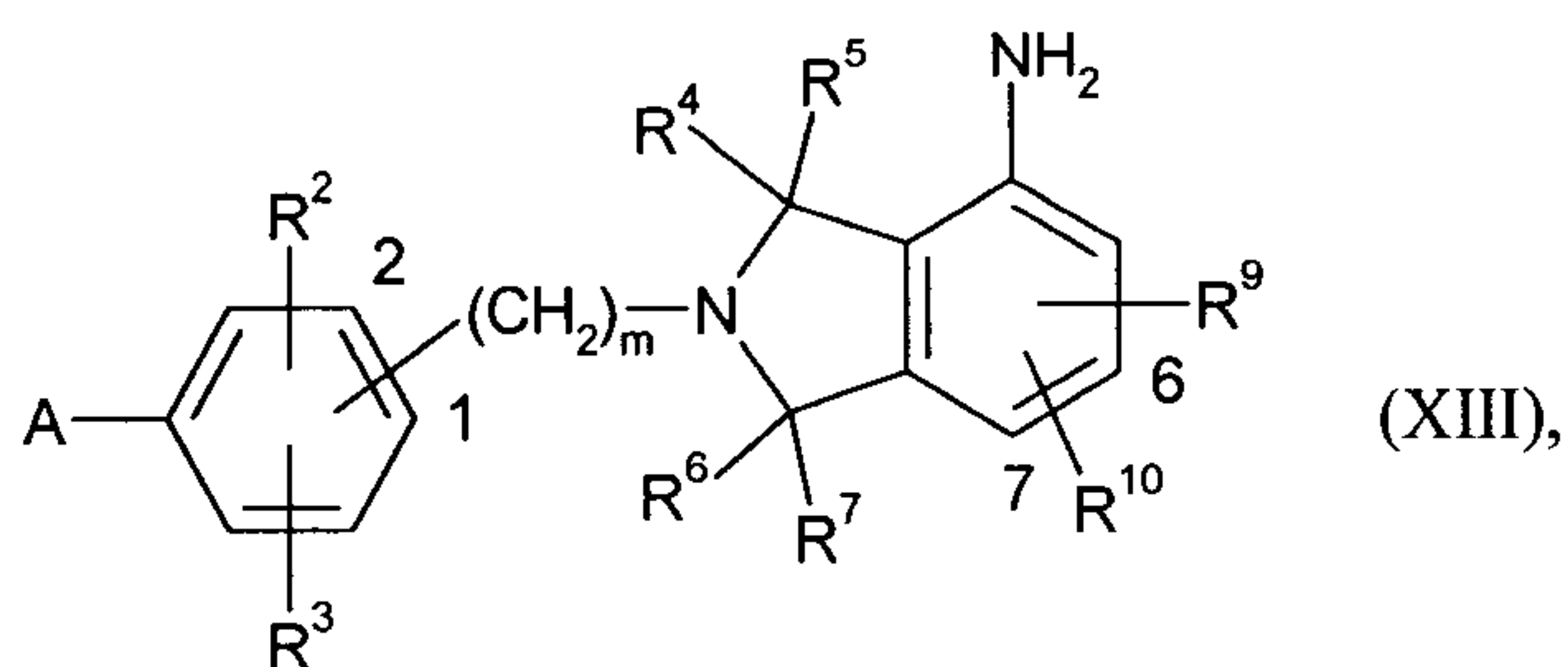


5 in which A, m, R^2 and R^3 have the meaning given in Claim 1,

to give a compound of the formula (I) in which R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group and R^6 and R^7 together with the carbon atom to which they are attached form a carbonyl group,

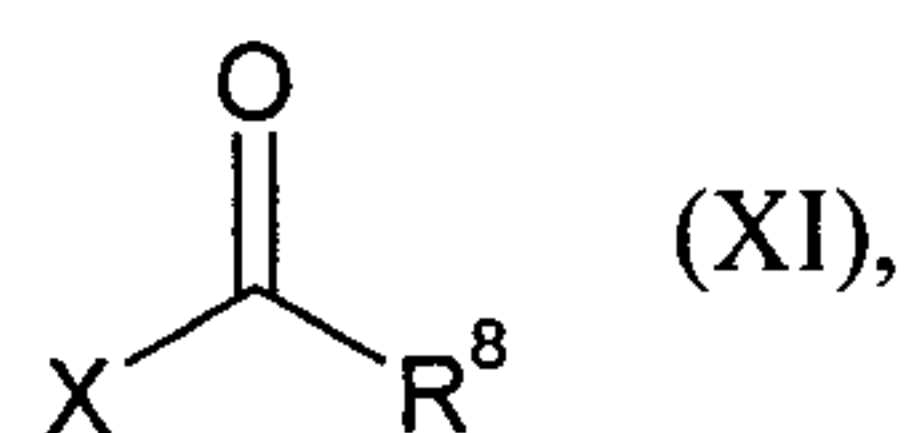
or

10 [C] a compound of the formula



in which A, m, R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^9 and R^{10} have the meaning given in Claim 1,

is reacted with a compound of the formula



in which R⁸ has the meaning given in Claim 1, and

X represents halogen, preferably bromine or chlorine, or hydroxy.

6. Compound according to any of Claims 1 to 4 for the treatment and/or prophylaxis of diseases.
- 5 7. Use of a compound according to any of Claims 1 to 4 for preparing a medicament for the treatment and/or prophylaxis of diseases.
8. Use of a compound according to any of Claims 1 to 4 for preparing a medicament for the treatment and/or prophylaxis of thromboembolic disorders.
9. Use of a compound according to any of Claims 1 to 4 for preventing blood coagulation in
10 vitro.
10. Medicament, comprising a compound according to any of Claims 1 to 4 in combination with an inert non-toxic pharmaceutically acceptable auxiliary.
11. Medicament comprising a compound according to any of Claims 1 to 4 in combination with a further active compound.
- 15 12. Medicament according to Claim 10 or 11 for the treatment and/or prophylaxis of thromboembolic disorders.
13. Method for the treatment and/or prophylaxis of thromboembolic disorders in humans and animals using an anticoagulatory effective amount of at least one compound according to any of Claims 1 to 4, a medicament according to any of Claims 10 to 12 or a medicament
20 obtained according to Claim 7 or 8.
14. Method for preventing blood coagulation in vitro, characterized in that an anticoagulatory effective amount of a compound according to any of Claims 1 to 4 is added.

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