

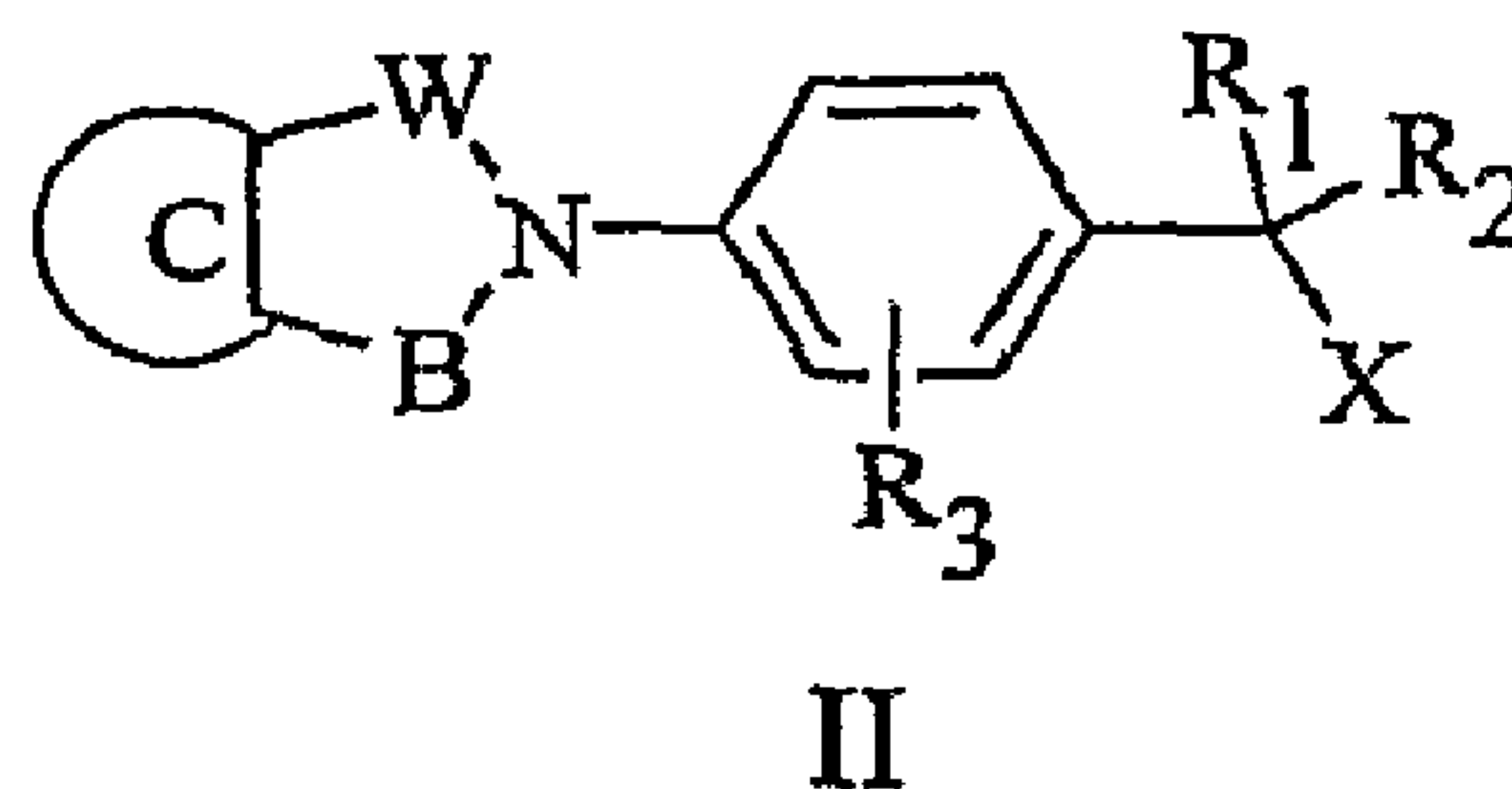
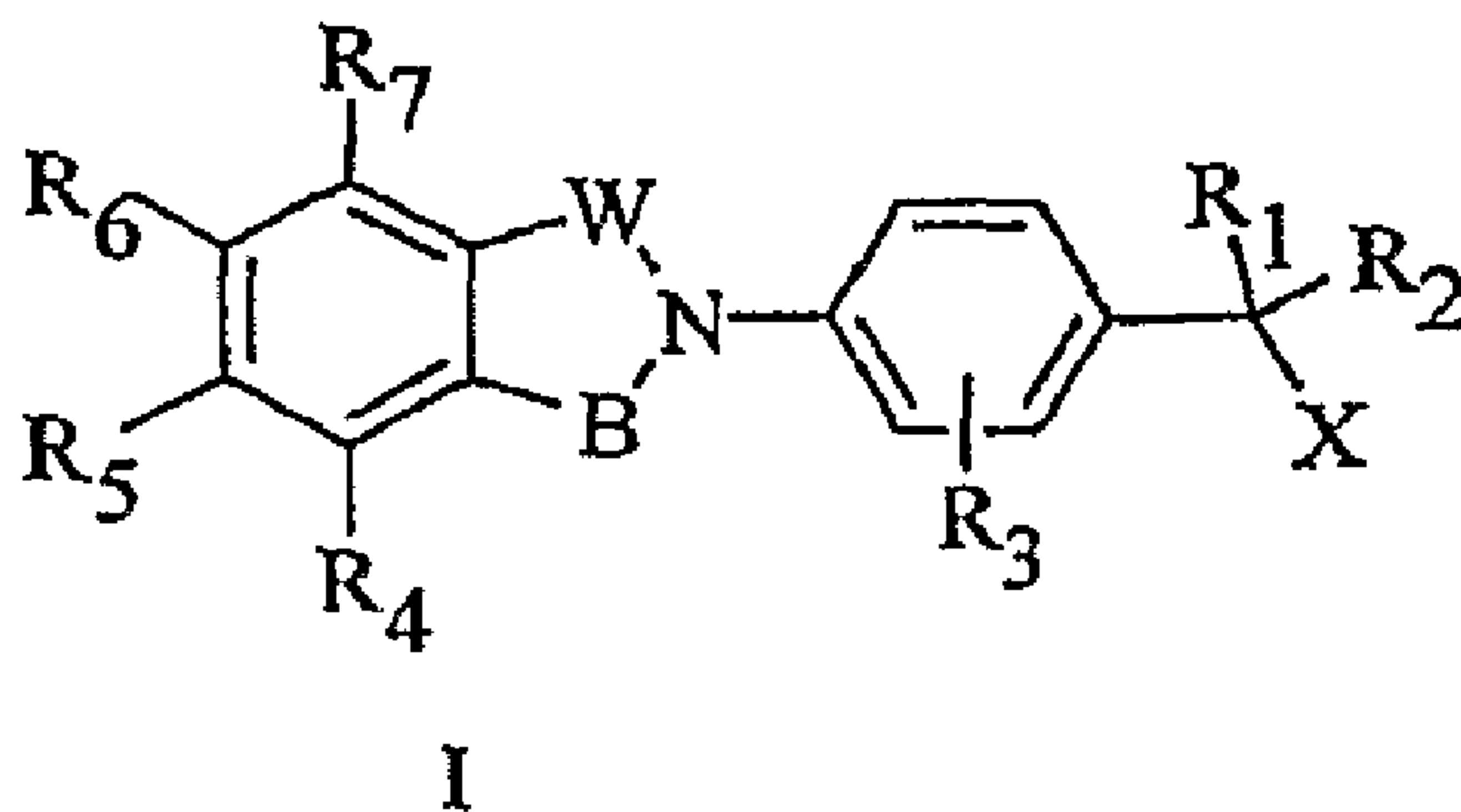


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(54) Title: 1-OXO-ISOINDOLINE COMPOUNDS FOR THE TREATMENT OF SPINAL MUSCULAR ATROPHY AND OTHER USES



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Compounds of Formula (I) or (II) useful for the treatment of spinal muscular atrophy or other uses, as well as methods of using such compounds to increase SMN expression, increase EAAT2 expression, or increase the expression of a nucleic acid that encodes a translational stop codon introduced by mutation or frameshift.



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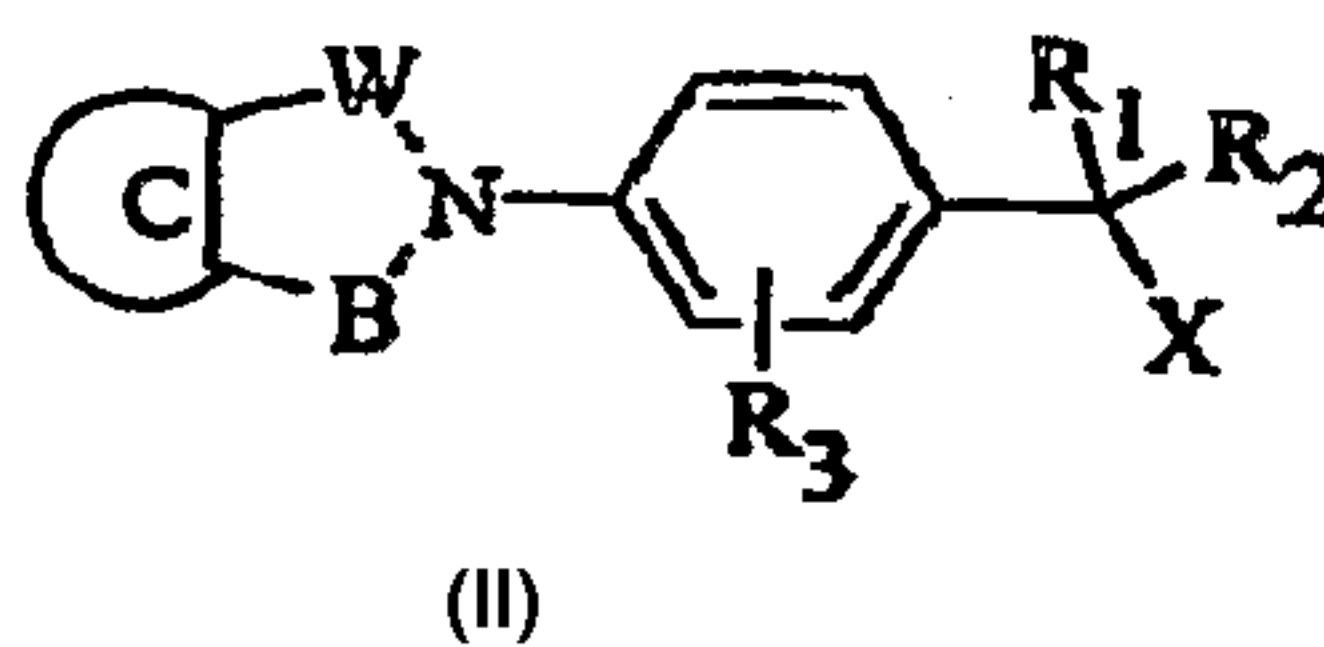
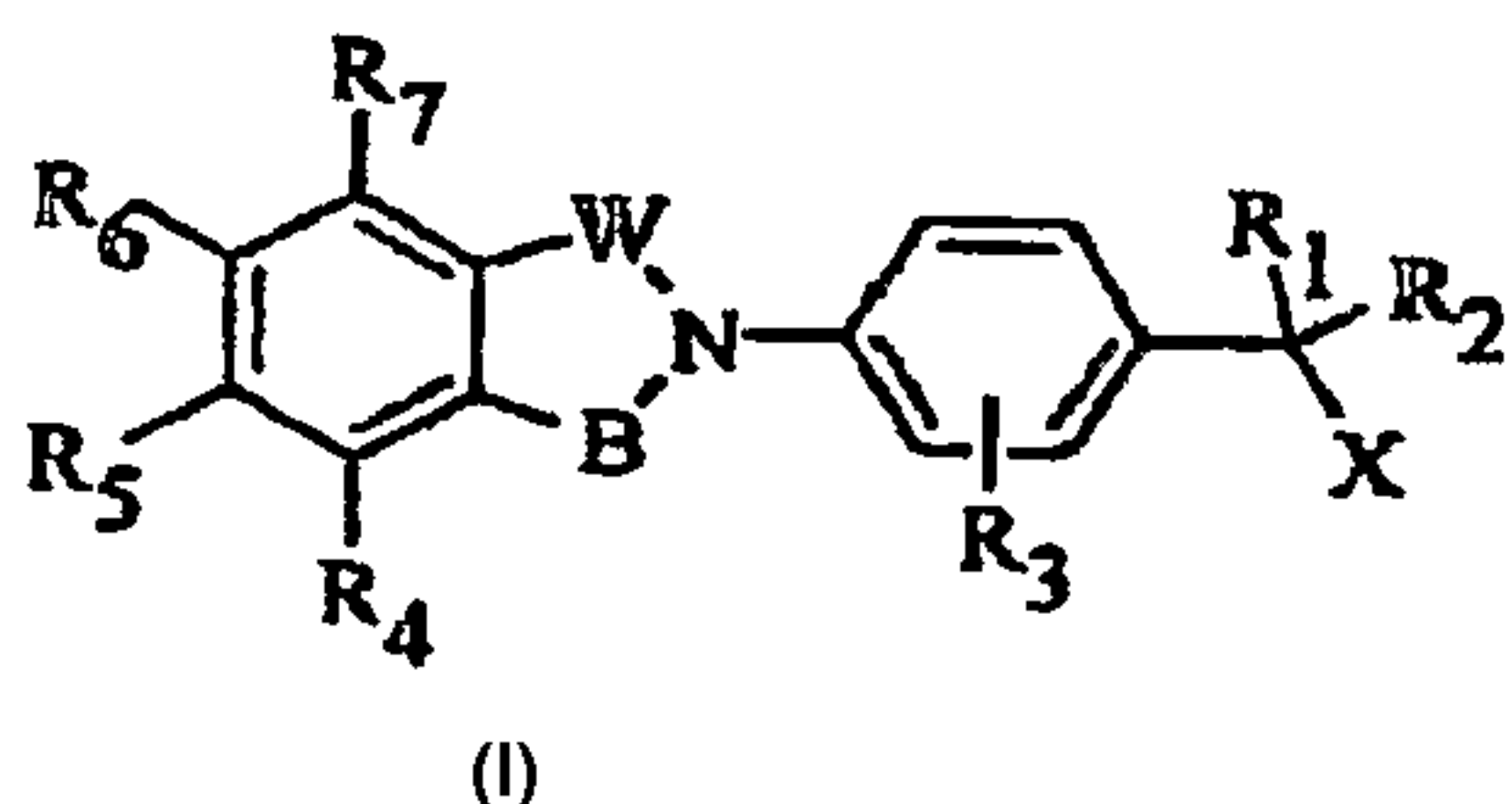
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(57) Abstract: Compounds of Formula (I) or (II) useful for the treatment of spinal muscular atrophy or other uses, as well as methods of using such compounds to increase SMN expression, increase EAAT2 expression, or increase the expression of a nucleic acid that encodes a translational stop codon introduced by mutation or frameshift.

COMPOUNDS FOR THE TREATMENT OF SPINAL MUSCULAR ATROPHY AND OTHER USES

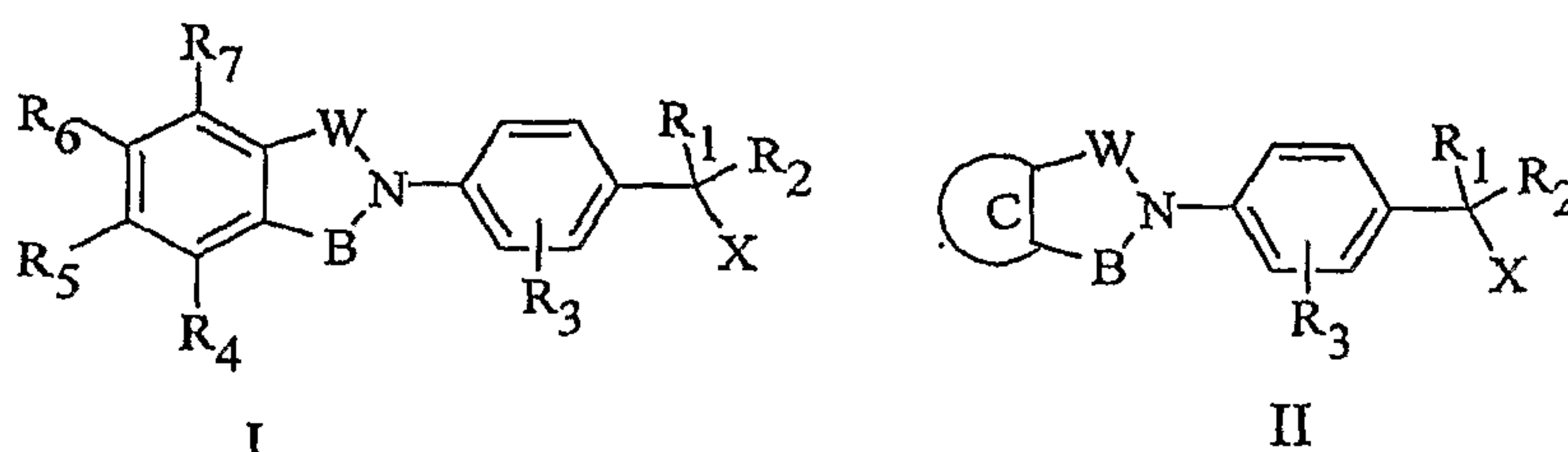
BACKGROUND OF THE INVENTION

[0001] Spinal Muscular Atrophy (SMA) is a paralyzing and often fatal disease of infants and children. To date there is no effective treatment for SMA. This disease is caused by mutations that reduce the level of survival motor neuron protein (SMN), resulting in the loss of motor neurons in the central nervous system. Drugs that increase SMN expression are expected to be useful in the prevention and treatment of SMA. Prior studies in cultured cells have shown that indoprofen, a previously marketed non-steroidal anti-inflammatory drug (NSAID), increases the level of expression of SMN protein via an unknown mechanism (Lunn et al., *Chem. & Biol.*, 11, 1489-1493(2004)). Indoprofen also was shown to increase survival of SMA model mouse fetuses when administered in utero. The mechanism of regulation of SMN expression is not thought to be related to indoprofen's NSAID activity since not all of the NSAIDs tested increase SMN expression. One possible mechanism of action is increased protein translation, as it has been shown that the level of the SMN protein can be improved by drugs that cause translational read-through of nonsense stop codons (Wolstencroft et al., *Hum. Mol. Genet.*, 14, 1199-210 (2005)). However, indoprofen is not a useful drug for SMA because it is only weakly active in increasing SMN expression, does not enter the brain at sufficient levels, and has lethal side effects due, at least in part, to its cyclooxygenase (Cox) inhibitory activity.

[0002] Accordingly, there is a need for new compounds, compositions, and methods that can address some of these problems.

BRIEF SUMMARY OF THE INVENTION

[0003] The invention provides compounds of Formula I or II:



[0004] The invention also provides related compounds, as well as methods for making the compounds of the invention, and compositions, especially pharmaceutical compositions, comprising one or more compounds of the invention and a carrier.

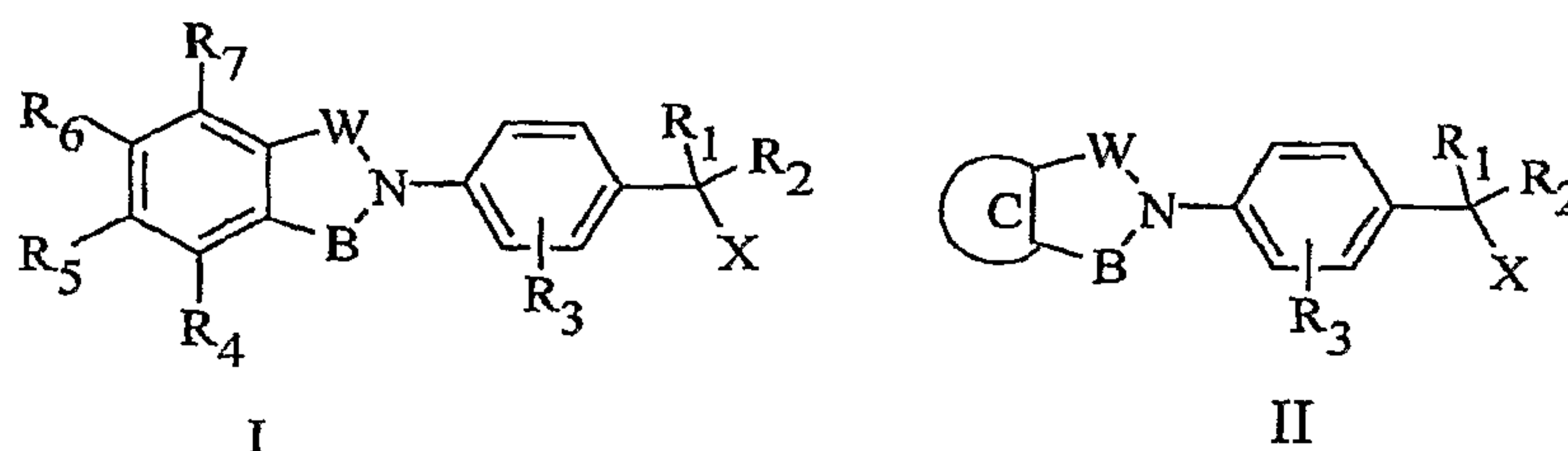
[0005] The invention further provides a method of increasing SMN expression in a cell comprising administering a compound of the invention to a cell comprising a nucleic acid encoding SMN2, whereby expression of SMN is increased.

[0006] The invention additionally provides a method of increasing the expression of excitatory amino acid transporter (EAAT2) in a cell comprising administering a compound of the invention to a cell comprising a nucleic acid that encodes EAAT2, whereby expression of EAAT2 is increased.

[0007] Also provided by the invention is a method of increasing in a cell the expression of a nucleic acid that encodes a translational stop codon, the method comprising administering a compound of the invention to a cell comprising a nucleic acid that encodes a translational stop codon, whereby expression of the nucleic acid is increased.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The invention provides compounds of Formula I or II:



wherein,

W is selected from the group consisting of C(O), C(S), and CH₂;

B is CH₂ or CH(C_nH_{2n+1}), wherein n is an integer of 1 to 8;

C is selected from the group consisting of a fused thiophene ring, a fused pyridine ring, and a cyclohexane ring, any of which can be saturated or contain one or two non-conjugated double bonds;

R₁ and R₂ are independently selected from the group consisting of H and C₁-C₃ alkyl, or R₁ and R₂ may be taken together with the carbon atom to which they are attached to form a C₃-C₆ cycloalkyl ring or a carbonyl group;

R₃ is selected from the group consisting of H, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, CN, NO₂, heteroaryl, and phenyl optionally substituted with any combination of one to five halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₁-C₄ alkoxy;

R₄, R₅, R₆ and R₇ are independently selected from the group consisting of H, hydroxyl, halogen, CN, NO₂, sulfonamide, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₄ haloalkyl, C₂-C₈ alkenyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, morpholine, heteroaryl (including without limitation thienyl, pyridyl and pyrimidinyl), arylamino, arylalkylamino, phenyl, C(O)R', NR'(COR''), NR'SO₂R'' and NR'(CONR'''R'''), wherein in R', R'' and R''' are independently H, C₁-C₆ alkyl, phenyl, or substituted phenyl, and wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine, and the phenyl is optionally substituted with one or more members selected from the group consisting of halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxy, or R₄ and R₅, R₅ and R₆, or R₆ and R₇, taken together with the carbon to which they are attached, form a ring;

X is selected from the group consisting of

H;

CN;

C(O)OR₈, wherein R₈ is H or C₁-C₆ alkyl, and the C₁-C₈ alkyl optionally is substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, phenyl, and morpholine;

C(O)NR₉R₁₀ or CH₂NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine;

$\text{CH}_2\text{OR}_{11}$, wherein R_{11} is H, $\text{C}_1\text{-C}_8$ alkyl, or $\text{C}_1\text{-C}_6$ cycloalkyl, wherein the $\text{C}_1\text{-C}_8$ alkyl optionally is substituted with one or members selected from the group consisting of $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_6$ dialkyl amino, $\text{C}_1\text{-C}_6$ alkylamino, cycloalkylamino, and morpholine;

CH_2Z , wherein Z is halogen;

$\text{C}(\text{O})\text{NHOH}$;

$\text{C}(\text{O})\text{NHCH}_3$;

$\text{C}(\text{O})\text{N}(\text{R}_1)\text{SO}_2\text{R}_{13}$, wherein R_{13} is $\text{C}_1\text{-C}_4$ alkyl, phenyl, or substituted phenyl;

$\text{C}_1\text{-C}_8$ alkyl, optionally substituted with one or more members selected from the group consisting of $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_6$ dialkylamino, and $\text{C}_1\text{-C}_6$ alkylamino; and

$\text{C}_2\text{-C}_8$ alkenyl, optionally substituted with one or more members selected from the group consisting of $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_6$ dialkylamino, and $\text{C}_1\text{-C}_6$ alkylamino;

provided that when the compound is a compound of Formula I, and each of R_4 , R_5 , R_6 and R_7 are H, then X is not $\text{C}(\text{O})\text{OH}$.

[0009] As used herein, unless otherwise specified, the term "alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having an indicated number of carbon atoms (e.g., $\text{C}_1\text{-C}_{20}$, $\text{C}_1\text{-C}_{10}$, $\text{C}_1\text{-C}_4$, etc.). Representative saturated straight chain alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl and -n-decyl; while representative saturated branched alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimethylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like. An alkyl group can be unsubstituted or substituted.

[0010] As used herein, unless otherwise specified, the term "cycloalkyl" means a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited

to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted. Preferably, the cycloalkyl group is a monocyclic ring or bicyclic ring.

[0011] As used herein, unless otherwise specified, the term "alkenyl group" means a straight chain or branched non-cyclic hydrocarbon having an indicated number of carbon atoms (e.g., C₂-C₂₀, C₂-C₁₀, C₂-C₄, etc.). Representative straight chain and branched alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. An alkenyl group can be unsubstituted or substituted.

[0012] As used herein, unless otherwise specified the term "alkynyl group" means a straight chain or branched non-cyclic hydrocarbon having an indicated number of carbon atoms (e.g., C₂-C₂₀, C₂-C₁₀, C₂-C₆, etc.), and including at least one carbon-carbon triple bond. Representative straight chain and branched alkynyls include -acetylenyl, -propynyl, -1-butyne, -2-butyne, -1-pentyne, -2-pentyne, -3-methyl-1-butyne, -4-pentyne, -1-hexyne, -2-hexyne, -5-hexyne, -1-heptyne, -2-heptyne, -6-heptyne, -1-octyne, -2-octyne, -7-octyne, -1-nonyne, -2-nonyne, -8-nonyne, -1-decynyl, -2-decynyl, -9-decynyl, and the like. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. An alkynyl group can be unsubstituted or substituted.

[0013] As used herein, unless otherwise specified, the term "halogen" or "halo" means fluorine, chlorine, bromine, or iodine. Furthermore, unless otherwise specified, the term "haloalkyl" means an alkyl substituted with one or more halogens, wherein alkyl and halogen are defined as above.

[0014] As used herein, unless otherwise specified, the term "alkoxy" means -O-(alkyl), wherein alkyl is defined above. Furthermore, as used herein, the term "haloalkoxy" means an alkoxy substituted with one or more halogens, wherein alkoxy and halogen are defined as above.

[0015] As used herein, unless otherwise specified, the term "heteroaryl" means a carbocyclic aromatic ring containing from 5 to 14 ring atoms comprising at least one heteroatom, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur. Heteroaryl ring structures include compounds having one or more ring structures,

such as mono-, bi-, or tricyclic compounds, as well as fused heterocyclic moities. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furanyl, benzofuranyl, thiophenyl, thiazolyl, benzothiophenyl, benzoisoxazolyl, benzoisothiazolyl, quinoliny, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnoliny, phthalazinyl, quinazolinyl, benzoquinazolinyl, acridinyl, pyrimidyl, oxazolyl, benzo[1,3]dioxole, and 2,3-dihydro-benzo[1,4]dioxine. A heteroaryl group can be unsubstituted or substituted.

[0016] As used herein, unless otherwise specified, the term "alkylamino" means -NH(alkyl) or -N(alkyl)(alkyl), wherein alkyl is defined above. As used herein, unless otherwise specified, the term "aminoalkyl" means -(alkyl)-NH₂, wherein alkyl is defined above.

[0017] As used herein, unless otherwise specified, the term "substituted" means a group substituted by one to four or more substituents, such as, alkyl, alkenyl, alkynyl, cycloalkyl, aroyl, halo, haloalkyl (e.g., trifluoromethyl), haloalkoxy (e.g., trifluoromethoxy), hydroxy, alkoxy, alkylthioether, cycloalkyloxy, heterocylooxy, oxo, alkanoyl, aryl, arylalkyl, alkylaryl, heteroaryl, heteroarylalkyl, alkylheteroaryl, heterocyclo, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, arylalkylamino, cycloalkylamino, heterocycloamino, mono- and di-substituted amino (in which the two substituents on the amino group are selected from alkyl, aryl or arylalkyl), alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, arylalkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, arylalkylthiono, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, sulfonamido (e.g., SO₂NH₂), substituted sulfonamido, nitro, cyano, carboxy, carbamyl (e.g., CONH₂), substituted carbamyl (e.g., CONH-alkyl, CONH-aryl, CONH-arylalkyl or instances where there are two substituents on the nitrogen selected from alkyl or arylalkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl (such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like).

[0018] Whenever a range of the number of atoms in a structure is indicated (e.g., a C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₃ alkyl, haloalkyl, alkylamino, alkenyl, etc.), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-8 carbon atoms (e.g., C₁-C₈), 1-6 carbon atoms (e.g., C₁-C₆), 1-4 carbon atoms (e.g., C₁-C₄), 1-3

carbon atoms (e.g., C₁-C₃), or 2-8 carbon atoms (e.g., C₂-C₈) as used with respect to any chemical group (e.g., alkyl, haloalkyl, alkylamino, alkenyl, etc.) referenced herein encompasses and specifically describes 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 2-7 carbon atoms, 2-8 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms, 4-7 carbon atoms, 4-8 carbon atoms, 5-6 carbon atoms, 5-7 carbon atoms, 5-8 carbon atoms, 6-7 carbon atoms, or 6-8 carbon atoms, as appropriate).

[0019] The invention encompasses all compounds described by Formulas I and II without limitation. However, for the purposes of further illustration, preferred aspects and elements of the invention are discussed herein.

[0020] With respect to Formulas I and II, W can be any member selected from the group consisting of C(O), C(S), and CH₂. According to certain preferred aspects of the invention, W is C(O), especially with respect to compounds of Formula I. B is CH₂ or CH(C_NH_{2N+1}), wherein n is an integer from 1 to 8.

[0021] R₁ and R₂ can be the same or different, and are selected from the group consisting of H and C₁-C₃ alkyl, or R₁ and R₂ may be taken together with the carbon atom to which they are attached to form a C₃-C₅ or C₃-C₆ cycloalkyl ring or a carbonyl group. Preferably, R₁ and R₂ are H or C₁-C₃ alkyl. More preferably, R₁ is H and R₂ is C₁-C₃ alkyl, such as CH₃.

[0022] R₃ can be any member selected from the group consisting of H, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, CN, NO₂, heteroaryl, and phenyl optionally substituted with any combination of one to five halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₁-C₄ alkoxy. However, R₃ preferably is H.

[0023] According to one preferred aspect of the invention, at least one of R₄, R₅, R₆ and R₇ is not H. Thus, according to this aspect of the invention, at least one of R₄, R₅, R₆ and R₇, preferably R₅, R₆, and/or R₇, is selected from the group consisting of hydroxyl, halogen, CN, NO₂, sulfonamide, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₄ haloalkyl, C₁-C₈ alkenyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, morpholine, heteroaryl, arylamino, arylalkylamino, phenyl, and C(O)R', NR'(COR''), NR'SO₂R'' and NR'(CONR''R'''), wherein in R', R'' and R''' are independently H, C₁-C₆ alkyl, phenyl or substituted phenyl, and phenyl, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy,

C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine, and the phenyl is optionally substituted with one or more members selected from the group consisting of halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxy, or any subgroup or sub-combination thereof.

[0024] It is further preferred according to this aspect of the invention that either R₅ or R₆, or both, are not H. Thus, either either R₅ or R₆, or both, are independently selected as above or from the group consisting of halogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, and morpholine, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine.

[0025] Desirably, R₅ is H and R₆ is selected as described above, or R₆ is selected from the group consisting of halogen, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₁-C₄ dialkyl amino, and C₁-C₄ haloalkyl. More specific examples of suitable R₆ groups include chloro, bromo, methyl, ethyl, propyl, *i*-propyl, methoxy, ethoxy, propoxy, *i*-propoxy, cyclohexyloxy, dimethylamino, and CF₃. When R₆ is not H, it is suitable that each of R₄, R₅, and R₇ are H.

[0026] When R₅ is not H, R₅ advantageously can be selected as described above, or from the group consisting of CN, halogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, and morpholine, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine. Specific examples of suitable R₅ groups include methyl, ethyl, propyl, or CN. When R₅ is not H, it is suitable that each of R₄, R₆, and R₇ are H.

[0027] When R₇ is not H, R₇ can be selected as described above, or from the group consisting of halogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, and morpholine, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine. More specific examples of suitable R₇ groups include C₁-C₈ alkyl, amino, or C₁-C₄ alkylamino groups, such as methyl, ethyl, propyl, or amino. When R₇ is not H, it is suitable that R₄, R₅, and R₆ are H.

[0028] Alternatively, or in addition, R_4 and R_5 , R_5 and R_6 , or R_6 and R_7 , may be taken together with the carbon atoms to which they are attached to form a ring, preferably a 5 or 6 membered heterocyclic ring. Non-limiting examples of such rings include a dioxane or dioxolane ring.

[0029] Additional preferred compounds of Formula I are those in which wherein at least one of R_3 , R_4 , R_5 , R_6 , or R_7 is hydroxyl, C_1 - C_6 haloalkoxy, C_1 - C_6 alkenyl, or C_1 - C_8 alkyl substituted with an arylamino or arylalkylamino. Preferably, at least one of R_3 , R_4 , R_5 , R_6 , or R_7 is a C_1 - C_6 haloalkoxy. Non-limiting examples of haloalkoxy groups include $-OCHF_2$.

[0030] Alternatively, or in addition, at least one of R_3 , R_4 , R_5 , R_6 , or R_7 is $C(O)R'$, $NR'(COR'')$, $NR'SO_2R''$ and $NR'(CONR''R''')$, wherein in R' , R'' and R''' are independently H, C_1 - C_6 alkyl, phenyl or substituted phenyl. Non-limiting examples of such groups include urea (e.g., $NH(CO)NH_2$).

[0031] X can be any member selected from the group consisting of H, CN, $C(O)OR_8$, wherein R_8 is H or C_1 - C_8 alkyl, and the C_1 - C_8 alkyl optionally is substituted with one or more members selected from the group consisting of C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_6 dialkyl amino, C_1 - C_6 alkylamino, cycloalkylamino, phenyl, and morpholine; $C(O)NR_9R_{10}$, wherein R_9 and R_{10} are independently selected from the group consisting of H and C_1 - C_6 alkyl, or R_9 and R_{10} together with the nitrogen to which they are attached form a C_5 - C_6 cycloalkyl ring or a heteroring such as morpholine; CH_2OR_{11} , wherein R_{11} is H, C_1 - C_8 alkyl, or C_1 - C_6 cycloalkyl, wherein the C_1 - C_8 alkyl optionally is substituted with one or more members selected from the group consisting of C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_6 dialkyl amino, C_1 - C_6 alkylamino, cycloalkylamino, and morpholine; $CH_2NR_9R_{10}$, wherein R_9 and R_{10} are as defined above; CH_2Z , wherein Z is halogen; $C(O)NHOH$; $C(O)NH(CN)$; $C(O)N(R_1)SO_2R_{13}$, wherein in R_{13} is C_1 - C_4 alkyl, phenyl, or substituted phenyl; C_1 - C_8 alkyl, optionally substituted with one or more members selected from the group consisting of C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_6 dialkylamino, and C_1 - C_6 alkylamino; and C_1 - C_8 alkenyl, optionally substituted with one or more members selected from the group consisting of C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_6 dialkylamino, and C_1 - C_6 alkylamino; provided that when the compound is a compound of Formula I, and each of R_4 , R_5 , R_6 and R_7 are H, then X is not $C(O)OH$.

[0032] While X can be chosen as described above, X is more preferably selected from the group consisting of CN; $C(O)OR_8$, wherein R_8 is C_1 - C_6 alkyl, optionally substituted with a phenyl; $C(O)NR_9R_{10}$, wherein R_9 and R_{10} are independently selected from the group consisting of H and C_1 - C_6 alkyl, or R_9 and R_{10} together with the nitrogen to which they are

attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine; CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl optionally is substituted with one or members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine; CH₂NR₉R₁₀, wherein R₉ and R₁₀ are as defined above; and CH₂Z, wherein Z is halogen; C(O)NHOH; C(O)NHCN; C(O)N(R₁)SO₂R₁₃, wherein R₁₃ is C₁-C₄ alkyl, phenyl, or substituted phenyl..

[0033] According to another preferred aspect, X is selected from the group consisting of CN; C(O)OR₈, wherein R₈ is C₁-C₆ alkyl, optionally substituted with a phenyl; CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl is optionally substituted one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine; CH₂NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine; and CH₂Z, wherein Z is halogen. X can advantageously be selected as C(O)OR₈, wherein R₈ is C₁-C₆ alkyl, optionally substituted with a phenyl, or CH₂Z, wherein Z is halogen. More specific examples of suitable X groups include C(O)OR₈, wherein R₈ is methyl, ethyl, propyl, butyl, *t*-butyl, or benzyl.

[0034] According to another preferred aspect of the invention, when X is selected as described above, and is not C(O)OH, each of R₄, R₅, R₆ and R₇ can be H. Also, when at least one of R₄, R₅, R₆ and R₇ is not H, and is instead selected as described above, X can advantageously be chosen as C(O)OH. This aspect of the invention is especially applicable to Formula I compounds.

[0035] According to another aspect of the invention, compounds of Formula I are selected such that W is C(S) or CH₂, B is CH₂, and R₁-R₇ are selected as described above.

[0036] Specific examples of compounds of the invention are provided in Table 1. Accordingly, the invention encompasses each of the compounds provided in Table 1. To the extent any of the compounds provided in Table 1 fall outside the scope of Formula I or II, such compounds are considered additional aspects of the invention. Preferred compounds of Table 1 include those identified as ALB-116244, ALB-115069, ALB1113310, and ALB 112355.

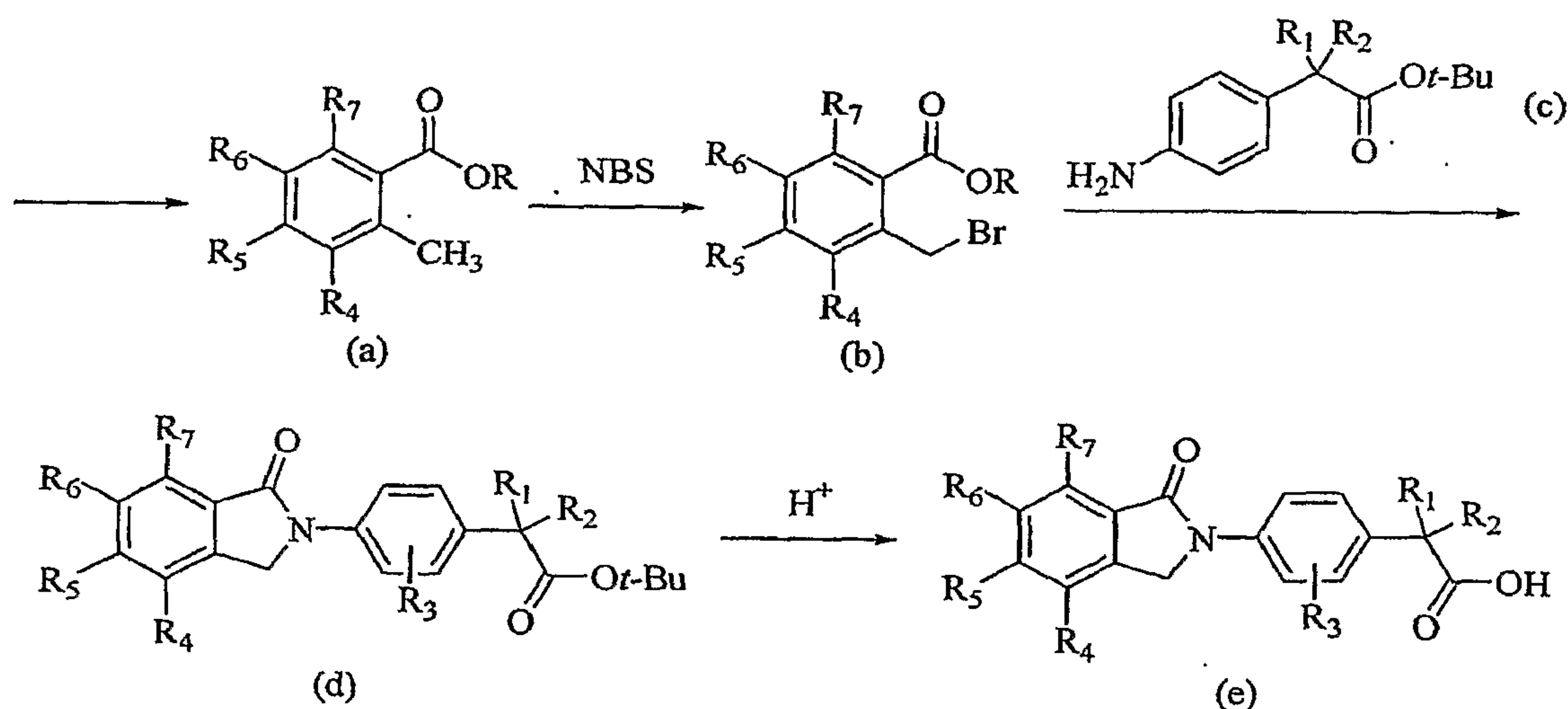
[0037] As those of ordinary skill in the art will appreciate, many of the molecules described herein may contain chiral centers and have more than one stereoisomer (e.g., diastereomer or enantiomer) of the molecule exists. If the stereochemistry of a structure or a

portion of a structure is not indicated, for example, with bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. The invention specifically contemplates any individual stereoisomers (e.g., diastereomers or enantiomers) of the compounds described herein, as well as mixtures thereof (e.g., racemic mixtures).

[0038] The compounds of the invention described herein can be prepared by any of several techniques. By way of a non-limiting example, the compounds can be prepared in accordance with Flow Diagrams 1-5 or as set forth in the Examples.

[0039] With respect to Flow Diagram 1, compounds of Formula (a) are commercially available or can be readily prepared using routine techniques. A compound of Formula (b) can be prepared by reacting the Formula (a) ester (R = lower alkyl) with a halogenating agent, such as *N*-bromosuccinimide (NBS), as illustrated in Flow Diagram 1. The Formula (b) compound (benzyl bromide) is then reacted with a compound of Formula (c) (e.g., aniline) to provide the cyclized product of Formula (d). Formula (e) compounds of the invention can then be prepared by hydrolysis of the ester of Formula (d) under basic or acidic conditions.

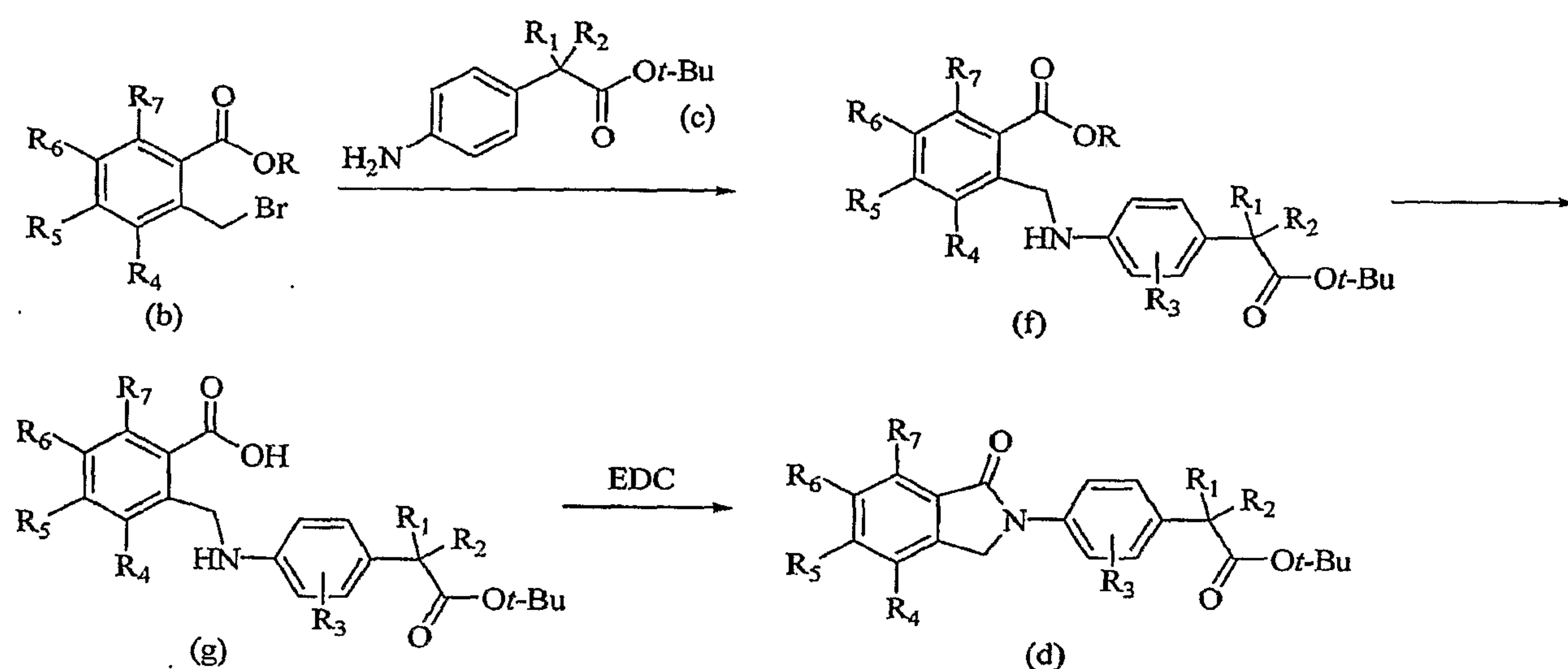
Flow Diagram 1



[0040] In some cases the reaction of Formula (b) compounds with Formula (c) compounds results in the production of uncyclized intermediates, as illustrated in Flow Diagram 2 where the uncyclized intermediate is indicated by Formula (f). Hydrolysis of the

lower esters of Formula (f) compounds results in Formula (g) acids, which can be treated with a coupling reagent (e.g., EDC) to provide compounds of Formula (d). The compound of Formula (d) can then be hydrolyzed to provide a compound of Formula (e) as illustrated in Flow Diagram 1.

Flow Diagram 2



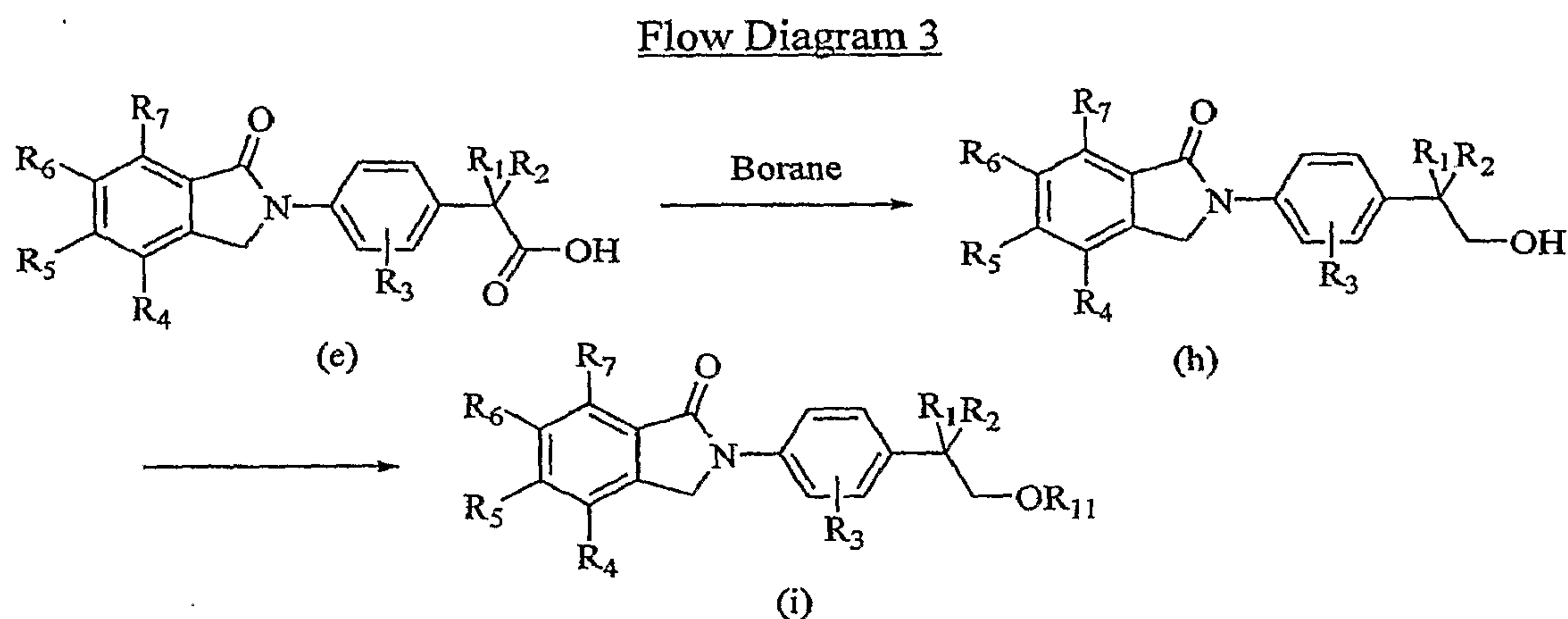
[0041] When Formula (d) compounds are prepared according to Flow Diagram 1 or 2 with a halogen (e.g., bromide) at R_3 , R_4 , R_5 , R_6 or R_7 (e.g., by utilizing a compound of Formula (a) containing a halogen at the desired position as a starting material), the Formula (d) compounds can be further derivatized by conventional procedures. For example, aryl, heteroaryl, alkyl, and amine derivatives can be prepared utilizing cross-coupling reactions such the Suzuki, Stille and Buchwald among others.

[0042] When Formula (d) compounds are prepared according to Flow Diagram 1 or 2 with a nitro group at R_3 , R_4 , R_5 , R_6 or R_7 (e.g., by utilizing a compound of Formula (a) containing a nitro group at the desired position as a starting material), the Formula (d) compounds can be reduced to provide an amine, which can be further derivatized using conventional techniques to provide secondary amines, tertiary amines, amides and sulfonamides.

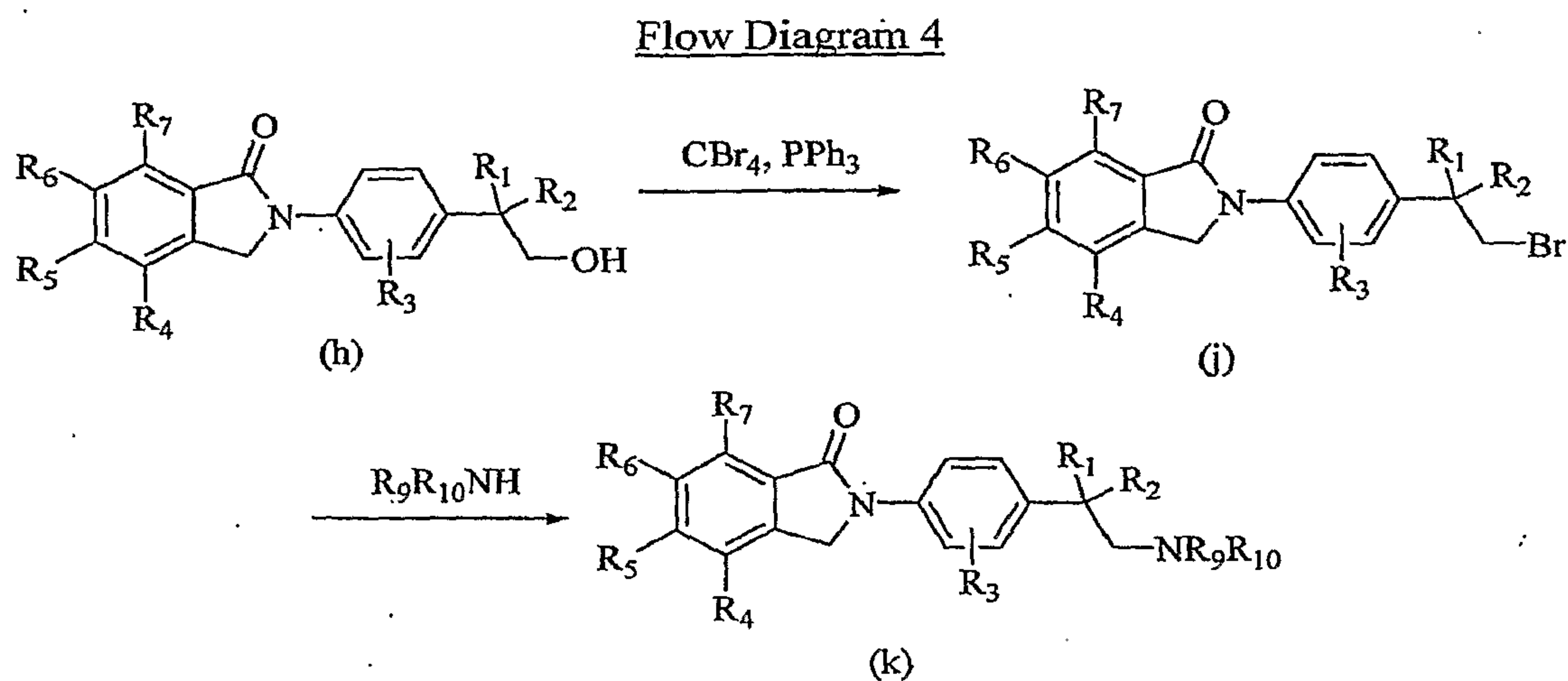
[0043] When Formula (d) compounds are prepared according to Flow Diagram 1 or 2 with a phenol group at R_3 , R_4 , R_5 , R_6 or R_7 (e.g., by utilizing a compound of Formula (a) containing a phenol group at the desired position as a starting material), the Formula (d) compound can be further derivatized by conventional procedures to provide ethers and esters.

[0044] The acid group of Formula (e) compounds prepared according to Flow Diagram 1 or 2 can be derivatized by conventional procedures to provide functional acid derivatives such as esters, amides, and nitriles, or converted to acid isosteres such as acyl sulfonamides, hydroxamic acids, etc.

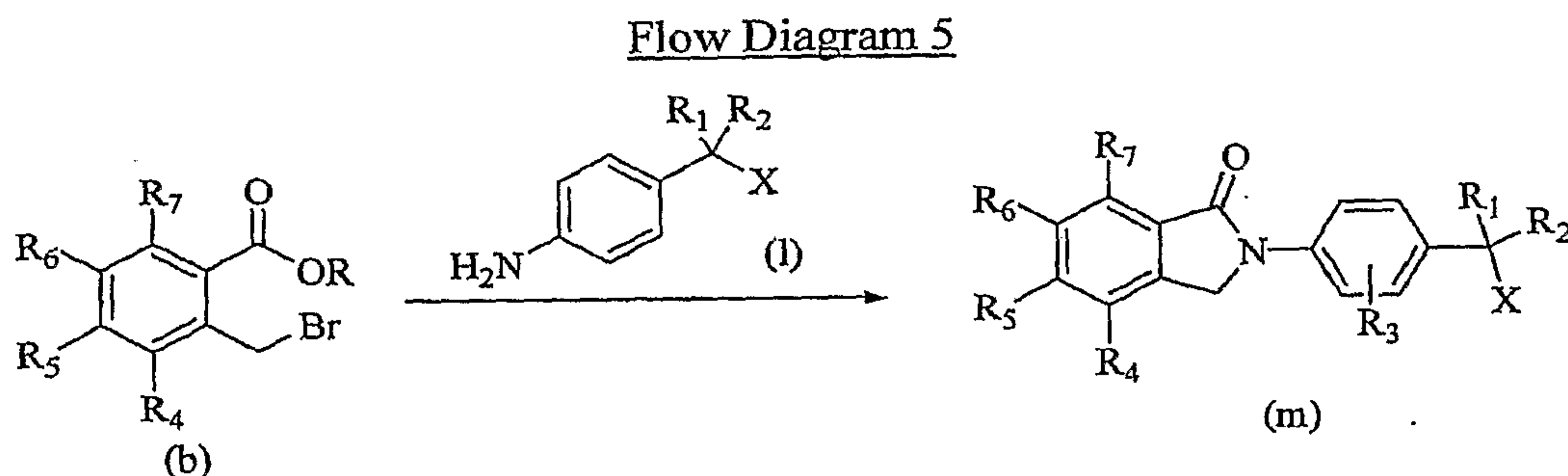
[0045] As illustrated in Flow Diagram 3, Formula (e) acids can be reduced with a reducing reagent (e.g., borane) to provide compounds of Formula (h). Formula (h) compounds can be derivatized by conventional procedures to afford ethers of Formula (i).



[0046] As illustrated in Flow Diagram 4, Formula (h) compounds can be converted to Formula (j) compounds using a reagent such as triphenylphosphine/carbontetrabromide. Formula (j) compounds can then be reacted with a variety of amines to provide a compound of Formula (k).



[0047] Alternatively, as shown in Flow Diagram 5, some various acid modified analogs can be prepared by cyclization of compounds of Formula (l) with Formula (b) compounds to afford compounds of Formula (m).



[0048] The invention, thus, provides a method of preparing a compound of Formula I or II comprising one or more of the steps set forth above (e.g., Flow Diagrams 1-5) as well as compounds of any of Formulas (a) - (m), which are useful, for example, as intermediates in the preparation of a compound of Formula I or II.

[0049] Any one or more of the compounds of the invention described herein can be formed as a composition, such as a pharmaceutical composition, comprising a compound of the invention and a carrier, especially a pharmaceutically acceptable carrier. The pharmaceutical composition can comprise more than one compound of the invention. Alternatively, or in addition, the pharmaceutical composition can comprise one or more compounds of the invention in combination with other pharmaceutically active agents or drugs. Examples of such other pharmaceutically active agents or drugs that may be suitable for use in combination with one or more compound of the invention include drugs that enhance translational read-through (e.g., WO 2004/009558, gentamycin or other aminoglycoside antibiotics), drugs that inhibit one or more histone deacetylase enzymes (e.g., valproate, phenylbutyrate, or hydroxyurea), or drugs that increase SMN expression via other mechanisms. The compounds of the invention also can be administered or formulated in combination with anticancer agents or other antibiotics. Suitable anticancer agents include, without limitation, alkylating agents; nitrogen mustards; folate antagonists; purine antagonists; pyrimidine antagonists; spindle poisons; topoisomerase inhibitors; apoptosis inducing agents; angiogenesis inhibitors; podophyllotoxins; nitrosoureas; cisplatin; carboplatin; interferon; asparaginase; tamoxifen; leuprolide; flutamide; megestrol; mitomycin; bleomycin; doxorubicin; irinotecan; and taxol. Other antibiotics include macrolides (e.g.,

tobramycin), cephalosporins (e.g., cephalexin, cephadrine, cefuroxime, cefprozil, cefaclor, cefixime, or cefadroxil), clarithromycin, erythromycin, penicillins (e.g., penicillin V), and quinolones (e. g., ofloxacin, ciprofloxacin, or norfloxacin).

[0050] The composition further comprises a carrier. The carrier can be any suitable carrier. Preferably, the carrier is a pharmaceutically acceptable carrier. With respect to pharmaceutical compositions, the carrier can be any of those conventionally used and is limited only by physio-chemical considerations, such as solubility and lack of reactivity with the active compound(s), and by the route of administration. It will be appreciated by one of skill in the art that, in addition to the following described pharmaceutical composition, the compounds and inhibitors of the present inventive methods can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes.

[0051] The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, and diluents, are well-known to those skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active agent(s) and one which has no detrimental side effects or toxicity under the conditions of use.

[0052] The choice of carrier will be determined in part by the particular compound of the invention and other active agents or drugs used, as well as by the particular method used to administer the compound and/or inhibitor. Accordingly, there are a variety of suitable formulations of the pharmaceutical composition of the present inventive methods. The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration are exemplary and are in no way limiting. One skilled in the art will appreciate that these routes of administering the compound of the invention are known, and, although more than one route can be used to administer a particular compound, a particular route can provide a more immediate and more effective response than another route.

[0053] Injectable formulations are among those formulations that are preferred in accordance with the present invention. The requirements for effective pharmaceutical carriers for injectable compositions are well-known to those of ordinary skill in the art (See, e.g., *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986)).

[0054] Topical formulations are well-known to those of skill in the art. Such formulations are particularly suitable in the context of the present invention for application to the skin.

[0055] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the inhibitor dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

[0056] The compounds of the invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. Such spray formulations also may be used to spray mucosa.

[0057] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compounds of the

invention can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, dimethylsulfoxide, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0058] Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[0059] Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-b-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[0060] The parenteral formulations will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5% to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried

(lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0061] Additionally, the compounds of the invention, or compositions comprising such compounds, can be made into suppositories by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

[0062] One of ordinary skill in the art will readily appreciate that the compounds of the invention described herein can be modified in any number of ways to increase the therapeutic efficacy of the compound. For instance, the compound or inhibitor could be conjugated either directly or indirectly through a linker to a targeting moiety. The practice of conjugating compounds or inhibitors to targeting moieties is known in the art. The term "targeting moiety" as used herein, refers to any molecule or agent that specifically recognizes and binds to a cell-surface receptor, such that the targeting moiety directs the delivery of the compound or inhibitor to a population of cells on which surface the receptor is expressed. Targeting moieties include, but are not limited to, antibodies, or fragments thereof, peptides, hormones, growth factors, cytokines, and any other naturally- or non-naturally-existing ligands, which bind to cell surface receptors. The term "linker" as used herein, refers to any agent or molecule that bridges the compound or inhibitor to the targeting moiety. One of ordinary skill in the art recognizes that sites on the compounds or inhibitors, which are not necessary for the function of the compound or inhibitor, are ideal sites for attaching a linker and/or a targeting moiety, provided that the linker and/or targeting moiety, once attached to the compound or inhibitor, do(es) not interfere with the function of the compound or inhibitor.

[0063] Alternatively, the compounds of the invention described herein can be modified into a depot form, such that the manner in which the compound of the invention is released into the body to which it is administered is controlled with respect to time and location within the body (see, e.g., U.S. Patent No. 4,450,150). Depot forms of compounds or inhibitors can be, for example, an implantable composition comprising the compound or inhibitor and a porous material, such as a polymer, wherein the compound or inhibitor is encapsulated by or

diffused throughout the porous material. The depot is then implanted into the desired location within the body and the compound or inhibitor is released from the implant at a predetermined rate by diffusing through the porous material.

[0064] In some contexts, the compounds of the invention can be advantageously administered via an implanted pump that allows intrathecal delivery. Such a delivery method is especially useful for delivery of drugs to the CNS when the drugs administered do not otherwise sufficiently penetrate the blood-brain barrier.

[0065] The compounds of the invention described herein can be administered to a cell in vitro. As used herein, the term "in vitro" means that the cell is not in a living organism. The compounds of the invention also can be administered to a cell in vivo. As used herein, the term "in vivo" means that the cell is a part of a living organism or is the living organism. Furthermore, the compounds of the invention can be administered to a host in vivo or ex vivo. The term "ex vivo" as used herein refers to the administration of a compound to a cell or a population of cells in vitro, followed by administration of the cell or population of cells to a host.

[0066] Furthermore, the compounds of the invention or composition comprising one or more of the compounds can be administered alone, or in conjunction with of an agent that enhances the efficacy of the compounds of the invention. Such agents can include, for instance, any of the other active agents described herein with respect to the pharmaceutical composition, which agents can be administered in a composition separate from the composition comprising the compounds of the invention.

[0067] The amount or dose of the compounds of the invention should be sufficient to effect a therapeutic or prophylactic response in the host over a reasonable time frame. The appropriate dose will depend upon the nature and severity of the disease or affliction to be treated or prevented, as well as by other factors. For instance, the dose also will be determined by the existence, nature and extent of any adverse side effects that might accompany the administration of a particular compound or inhibitor. Ultimately, the attending physician will decide the dosage of the compound or inhibitor of the present invention with which to treat each individual patient, taking into consideration a variety of factors, such as age, body weight, general health, diet, sex, inhibitor to be administered, route of administration, and the severity of the condition being treated. Typically doses might be, for example, 0.1 mg to 1 g daily, such as 5 mg to 500 mg daily.

[0068] The compounds of the invention can be administered to a cell, preferably to a cell of a host. Hosts include, for example, bacteria, yeast, fungi, plants, and mammals. Preferably, the host is a mammal. For purposes of the present invention, mammals include, but are not limited to, the order Rodentia, such as mice, and the order Logomorpha, such as rabbits. It is preferred that the mammals are from the order Carnivora, including Felines (cats) and Canines (dogs). It is more preferred that the mammals are from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). It is most preferred that the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). An especially preferred mammal is the human. Furthermore, the host can be the unborn offspring of any of the forgoing hosts, especially mammals or humans, in which case any screening of the host or cells of the host, or administration of compounds to the host or cells of the host, can be performed in utero.

[0069] The compounds can be used for any purpose including, without limitation, the treatment, prevention, or diagnosis of a disease or condition, the screening of compounds that can be used to treat, prevent, or diagnose a disease or condition, or the research of the underlying mechanisms or causes of a disease or condition, which research can be used, for example, in the development of methods to treat, prevent, or diagnose the disease or condition. Without wishing to be bound by any particular theory, it is believed that the compounds of the invention are particularly useful with respect to diseases and conditions involving the under-expression of survival motor neuron protein (SMN), diseases and conditions that can be ameliorated by modulation of translational stop codons (e.g., UAA, UAG, UGA; both normal, naturally occurring and mutation introduced stop codons), and diseases and conditions associated with elevated glutamate levels in the central nervous system (CNS) and/or that could be ameliorated by increases in EAAT2 expression.

[0070] Preferred compounds of the invention can be used to increase SMN expression in a cell that comprises an SMN2 gene, particularly a cell that does not comprise an SMN1 gene, or that comprises a defective or deleted SMN1 gene. Thus, one aspect of the invention provides a method of increasing SMN expression in a cell comprising administering a compound of the invention to a cell comprising a nucleic acid that encodes SMN2, desirably a cell that comprises a defective or deleted SMN1 gene, whereby SMN expression is increased.

[0071] SMN1 and SMN2 refer to two different genes that each encode SMN protein, but that differ by a single base pair. The base pair change in SMN2 results in decreased expression of SMN due to an alternative splicing mechanism that results in an unstable protein that is missing exon 7. As a result, SMN2 transcripts typically are not properly expressed, and SMN protein is produced primarily by SMN1. Most patients that exhibit under-expression of SMN have a defective or mutant SMN1 gene, but an intact SMN2 gene. Without wishing to be bound by any particular theory, it is believed that the compounds of the invention increase the expression of SMN2 via a post-transcriptional mechanism, possibly by increasing translation or otherwise suppressing the effects of translational stop codons introduced by improper splicing of the SMN2 transcript.

[0072] The increase in expression of SMN after administration of a compound of the invention can be any increase as compared to the expression level of SMN in the cell in the absence of the compound of the invention. Typically, the cell will have a defective or mutant SMN1 protein and/or reduced levels of SMN protein expression in the absence of a compound of the invention. Methods for detecting and measuring increased SMN expression, particularly through expression of SMN2, are known in the art and described herein.

[0073] The cell to which the compound of the invention is administered preferably is in a host. Suitable hosts are as previously described herein. The host is desirably a mammal, especially a human. The method of this aspect of the invention is most suitable for use in conjunction with a host that is afflicted with a disease or at risk for developing a disease, such as a disease associated with the under-expression of SMN. Such diseases include, for example, spinal muscular atrophy (SMA). Preferably, one or more symptoms of the disease are prevented, reduced, or eliminated subsequent to administration of the compound of the invention, thereby effectively treating or preventing the disease to at least some degree. Accordingly, the method of the invention can be used to treat or prevent such a disease.

[0074] In a related aspect, the invention provides a method of increasing in a cell the expression of a nucleic acid that encodes a translational stop codon. The stop codon can be a normally occurring stop codon, or a stop codon introduced by mutation or frameshift, particularly a nonsense stop codon. The method comprises administering a compound of the invention to a cell comprising a nucleic acid that encodes a translational stop codon, whereby expression of the nucleic acid is increased. Without wishing to be bound by any particular theory, it is believed that the compounds of the invention permit translational (ribosomal)

read-through of stop codons, especially those introduced by mutation or frameshift. According to a preferred aspect of the invention, the stop codon is one that is introduced by a mutation of frameshift, and the compound of the invention permits translational read-through of the stop codon, preferably without interfering with the effect of normal stop codons (e.g., stop codons not introduced by mutation or frameshift, which do not interfere with the production of a full-length protein). The compounds, thus, increase expression of the protein products of such nucleic acids. Compounds of the invention may also modulate gene expression through effects on naturally occurring stop codons.

[0075] As used herein, the term “translational stop codon introduced by mutation or frameshift” means any stop codon that results in the premature or otherwise unusual termination of translation and consequential production of a truncated gene product or protein. Translational stop codons introduced by mutation or frameshift include, for example, those that result in a gene product that has reduced stability or reduced activity (or no activity) as compared to the normal, full-length protein product, or results in the reduction or complete absence of a protein product. Translational stop codons introduced by mutation or frameshift also include, for example, those that result in a mRNA that is a target of non-sense-mediated RNA decay. The translational stop codon can be present in the DNA or RNA of any type of cell, and can arise through any type of mutagenesis or frameshift event. For example, the nucleic acid that encodes the translational stop codon can be, without limitation, a defective SMN1 gene or a defective or normal SMN2 gene, or any transcript thereof. In particular, the alternative splicing event that occurs during SMN2 expression, which results in the deletion of SMN exon 7, also creates a nonsense stop codon. The nucleic acid comprising the stop codon can be endogenous to the cell, or a nucleic acid introduced into the cell, for example, by a virus. Without wishing to be bound by any particular theory, it is believed that the compounds of the invention can increase expression of SMN by suppressing the effects of the nonsense stop codons, possibly by allowing translational read-through of the stop codon or by suppressing nonsense-mediated mRNA decay.

[0076] An appropriate screening assay can be employed to determine whether a cell or host comprises a nucleic acid that encodes a translational stop codon introduced by mutation or frameshift. For instance, the DNA or RNA of a cell (e.g., a cell of a host or an organism that is pathogenic to the host) can be sequenced or subject to Southern Blot, polymerase chain reaction (PCR), use of the Short Tandem Repeat (STR), or polymorphic length restriction fragments (RFLP) analysis to determine if a nonsense mutation is present. Alternatively, it

can be determined if a cell (e.g., a cell of a host) expresses altered levels of a protein encoded by the nucleic acid using western blot or other immunoassays. Other methods of determining whether a nucleic acid that encodes a premature translational stop codon are available.

[0077] The cell to which the compound of the invention is administered preferably is in a host. Suitable hosts are as previously described herein. The host is desirably a mammal, especially a human.

[0078] The method of this aspect of the invention is most suitable for use in conjunction with a host that is afflicted with a disease, or at risk for developing a disease, associated with a translational stop codon introduced by mutation or frameshift. The types of diseases associated with translational stop codons introduced by mutation or frameshift, the symptoms of which can be ameliorated by the suppression of premature translation termination and/or nonsense-mediated mRNA decay, include, but are not limited to, genetic diseases, autoimmune diseases, blood diseases, collagen diseases, diabetes, neurodegenerative diseases, proliferative diseases, cardiovascular diseases, pulmonary diseases, inflammatory diseases, central nervous system diseases, infectious diseases (bacterial and viral), cancers (including tumors and other cancers), especially cancers associated with p53 mutations.

[0079] Specific examples of genetic diseases include, without limitation, SMA, amyloidosis, hemophilia, Alzheimer's disease, Tay Sachs disease, Niemann Pick disease, atherosclerosis, gigantism, dwarfism, hypothyroidism, hyperthyroidism, aging, obesity, Parkinson's disease, Huntington's disease, cystic fibrosis, muscular dystrophy, heart disease, kidney stones, ataxia-telangiectasia, familial hypercholesterolemia, retinitis pigmentosa, Duchenne muscular dystrophy, and Marfan syndrome.

[0080] Specific examples of inflammatory and autoimmune diseases include, without limitation, arthritis, rheumatoid arthritis, osteoarthritis, and graft versus host disease. Specific examples of blood diseases include, without limitation, hemophilia, Von Willebrand disease, ataxia-telangiectasia, thalassemia (e.g., β -thalassemia), and kidney stones.

[0081] Specific examples of blood diseases include, without limitation, hemophilia, Von Willebrand disease, ataxia-telangiectasia, thalassemia (e.g., β -thalassemia), and kidney stones.

[0082] Specific examples of collagen diseases include, without limitation, osteogenesis imperfecta and cirrhosis.

[0083] Specific examples of central nervous system diseases include, without limitation, multiple sclerosis, muscular dystrophy, Duchenne muscular dystrophy, Alzheimer's disease,

Huntington's Disease, Tay Sachs disease, late infantile neuronal ceroidlipofuscinosis (LINCL), Leber's hereditary optic neuropathy, and Parkinson's disease.

[0084] Specific examples of infectious diseases include, without limitation, HIV/AIDS, viral hepatitis, HPV infection, and *Pseudomonas aeruginosa* infection.

[0085] Specific examples of cancers include cancer of the head and neck, eye, skin, mouth, throat, esophagus, chest, bone, lung, colon, sigmoid, rectum, stomach, prostate, breast, ovaries, kidney, liver, pancreas, brain, intestine, heart or adrenals. More particularly, cancers include solid tumor, sarcoma, carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovium, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, Kaposi's sarcoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, a blood-born tumor, acute lymphoblastic leukemia, acute lymphoblastic B-cell leukemia, acute lymphoblastic T-cell leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute monoblastic leukemia, acute erythroleukemic leukemia, acute megakaryoblastic leukemia, acute myelomonocytic leukemia, acute nonlymphocytic leukemia, acute undifferentiated leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, or multiple myeloma. See, e.g., Harrison's Principles of Internal Medicine, Eugene Braunwald et al., eds., pp.491-762 (15th ed. 2001).

[0086] Diseases, such as cancers, associated with p53 mutations that result in a translational stop codon include, but are not limited to, the diseases and mutations described in Masuda et al., *Tokai J Exp Clin Med.* 25 (2): 69-77 (2000); Oh et al., *Mol Cells* 10 (3): 275-80 (2000); Li et al., *Lab Invest.* 80 (4): 493-9 (2000); Yang et al., *Zhonghua Zhong Liu Za Zhi* 21 (2):114-8 (1999); Finkelstein et al., *Mol Diagn.* 3(1): 37-41 (1998); Kajiyama et al., *Dis Esophagus.* 11 (4): 279-83 (1998); Kawamura et al., *Leuk Res.* 23 (2): 115-26 (1999);

Radig et al., *Hum Pathol.* 29 (11): 1310-6 (1998); Schuyer et al., *Int J Cancer* 76 (3): 299-303 (1998); Wang-Gohrke et al., *Oncol Rep.* 5(1): 65-8 (1998); Fulop et al., *J Reprod Med.* 43 (2): 119-27 (1998); Ninomiya et al., *J Dermatol Sci.* 14 (3):173-8 (1997); Hsieh et al., *Cancer Lett.* 100 (1- 2): 107-13 (1996); Rall et al., *Pancreas.* 12(1): 10-7 (1996); Fukutomi et al., *NipponRinsho* 53 (11): 2764-8 (1995); Frebourg et al., *Am J Hum Genet.* 56 (3): 608-15 (1995); Dove et al., *Cancer Surv.* 25: 335-55 (1995); Adamson et al., *Br J Haematol.* 89(1): 61-6 (1995); Grayson et al., *Am J Pediatr Hematol Oncol.* 16 (4): 341-7 (1994); Lepelley et al., *Leukemia* 8 (8): 1342-9 (1994); McIntyre et al., *J Clin Oncol.* 12 (5): 925-30 (1994); Horio et al., *Oncogene.* 9 (4): 1231-5 (1994); Nakamura et al., *Jpn J Cancer Res.* 83 (12): 1293-8 (1992); Davidoff et al., *Oncogene.* 7(1): 127-33 (1992); and Ishioka et al., *Biochem Biophys Res Commun.* 177 (3): 901-6 (1991).

[0087] Preferably, one or more symptoms of the disease are prevented, reduced, or eliminated subsequent to administration of the compound of the invention, thereby effectively treating or preventing the disease to at least some degree. Accordingly, the method of the invention can be used to treat or prevent such a disease.

[0088] In yet another related aspect, the invention provides a method of increasing the expression of excitatory amino acid transporter (EAAT2) in a cell comprising administering a compound of the invention to a cell comprising a nucleic acid that encodes EAAT2, whereby expression of EAAT2 is increased. Certain diseases (e.g., Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and epilepsy) and other conditions, such as stroke or other trauma to the CNS, are associated with elevated glutamate levels in the CNS that can be toxic, leading to brain damage or even death. Cellular uptake of glutamate via the EAAT2 transporter is responsible, at least in part, for maintaining appropriately low glutamate levels in the CNS. Without wishing to be bound by any particular theory, it is believed that the compounds of the invention can activate or enhance EAAT2 expression, thereby advantageously lowering glutamate levels in the CNS. Methods of detecting and measuring increased EAAT2 expression are known in the art and described, for instance, in Rothstein et al., *Nature*, 43(3), 73-7 (2005).

[0089] The cell to which the compound of the invention is administered preferably is in a host. Suitable hosts are as previously described herein. The host is desirably a mammal, especially a human. The method of this aspect of the invention is most suitable for use in conjunction with a host that is afflicted with a disease or condition, or at risk for developing a disease or condition, associated with decreased expression of EAAT2 or elevated glutamate

levels in the CNS. Such diseases and conditions include, for example, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), epilepsy, stroke, and other forms of CNS trauma. Preferably, one or more symptoms of the disease or condition are prevented, reduced, or eliminated subsequent to administration of the compound of the invention, thereby effectively treating or preventing the disease or condition to at least some degree. Accordingly, the method of the invention can be used to treat or prevent such a disease or condition.

[0090] In addition to the foregoing characteristics, preferred compounds of the invention are able to penetrate the blood-brain barrier so as to accumulate in therapeutically effective amounts, and do not have significant cyclooxygenase (Cox) inhibitory activity (e.g., has less than toxic levels of Cox inhibitory activity).

27

Table 1

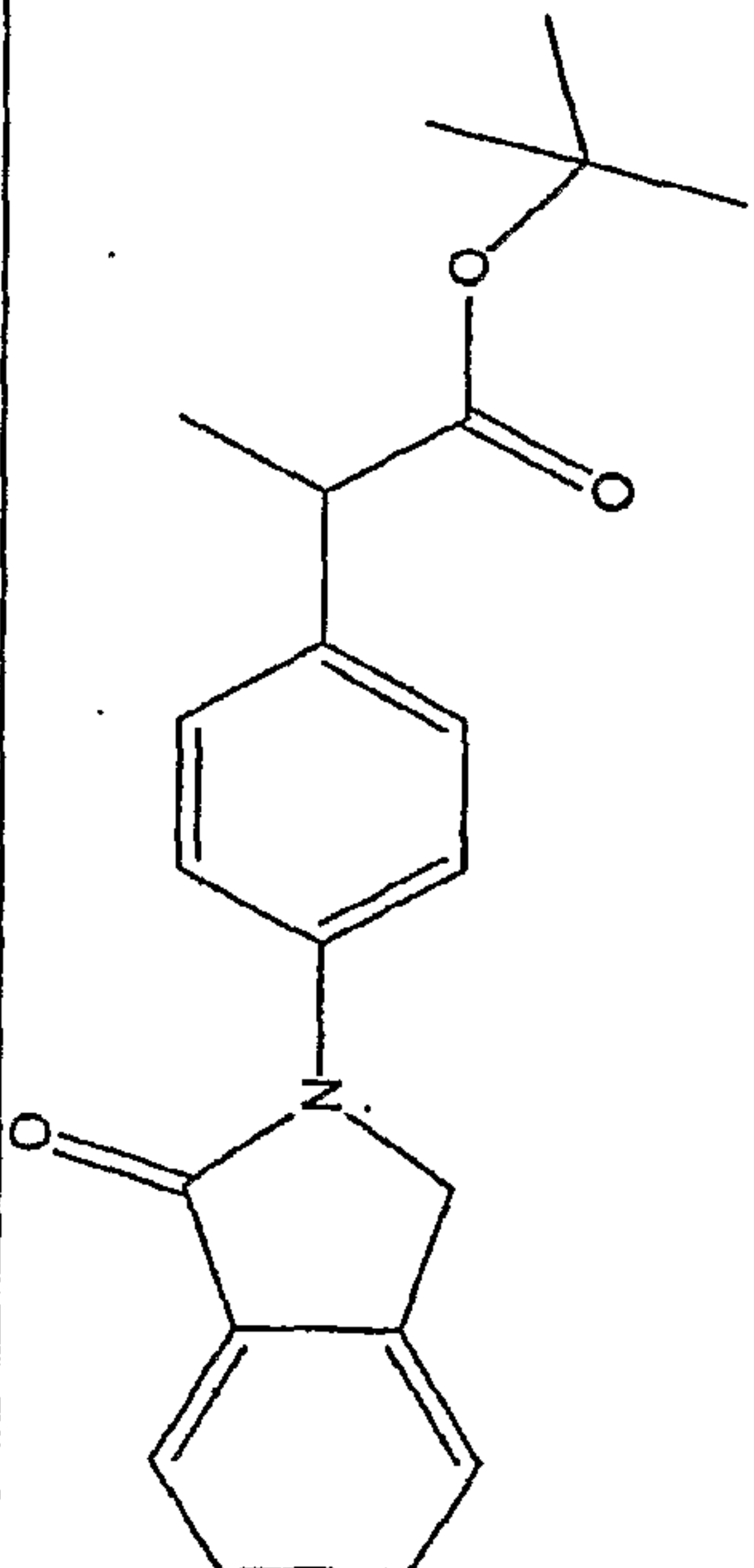
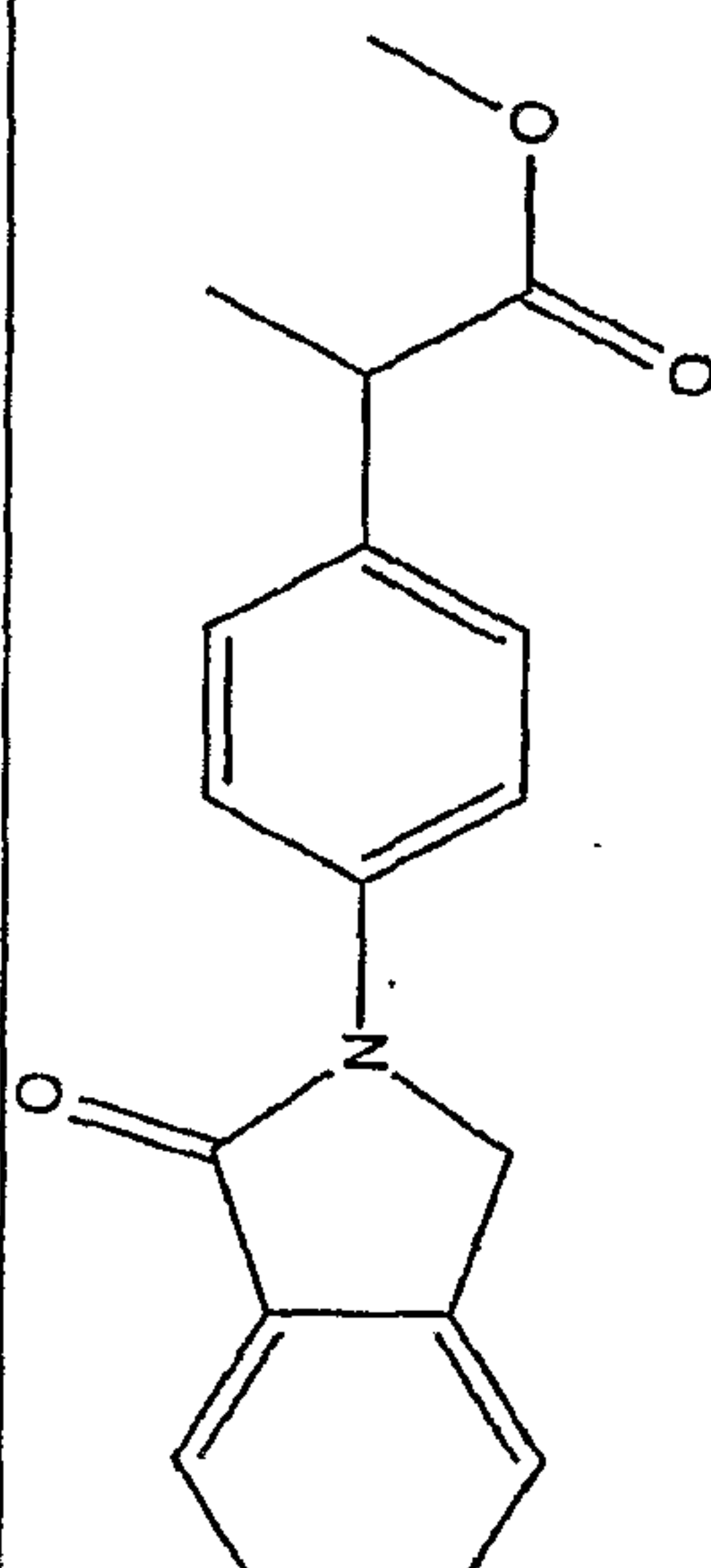
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			Avg EC50 (μ M)	Avg MaxFold Increase
1		ALB- 111730	1.66	1.267
2		ALB- 111731	0.174	1.431

Table 1

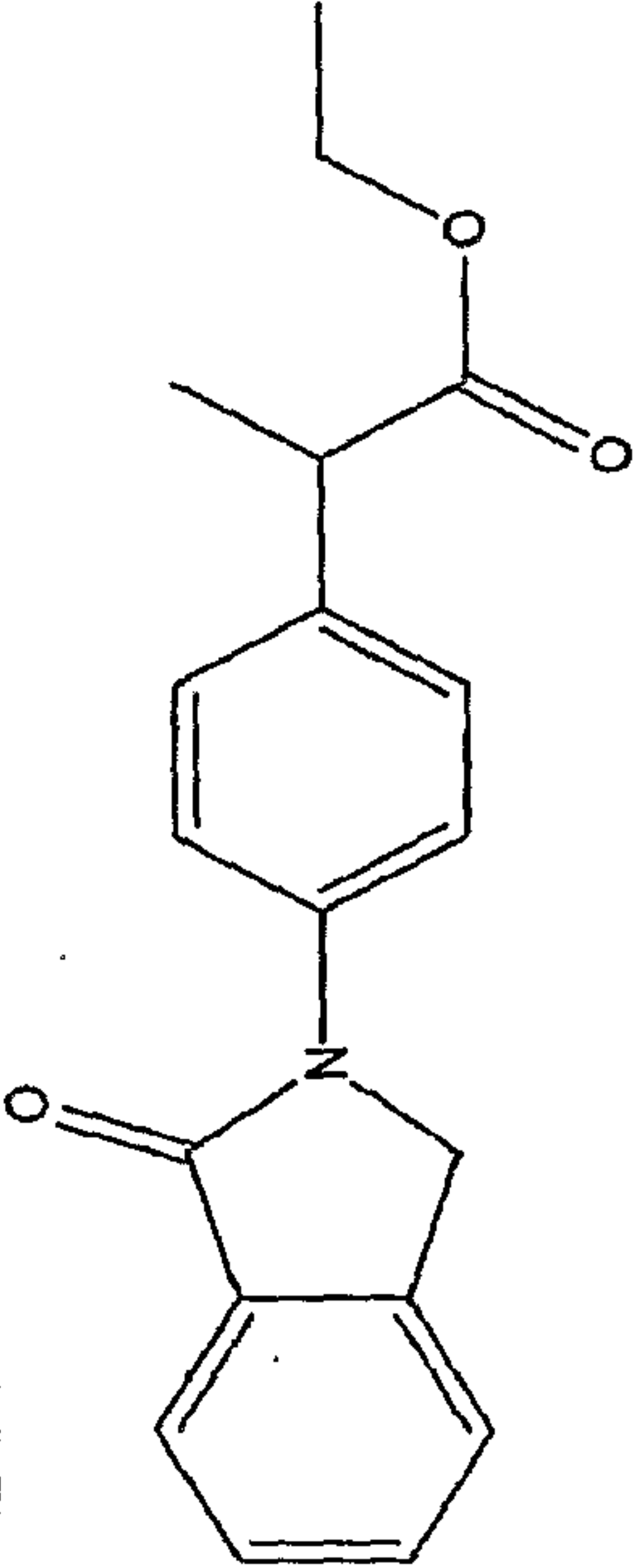
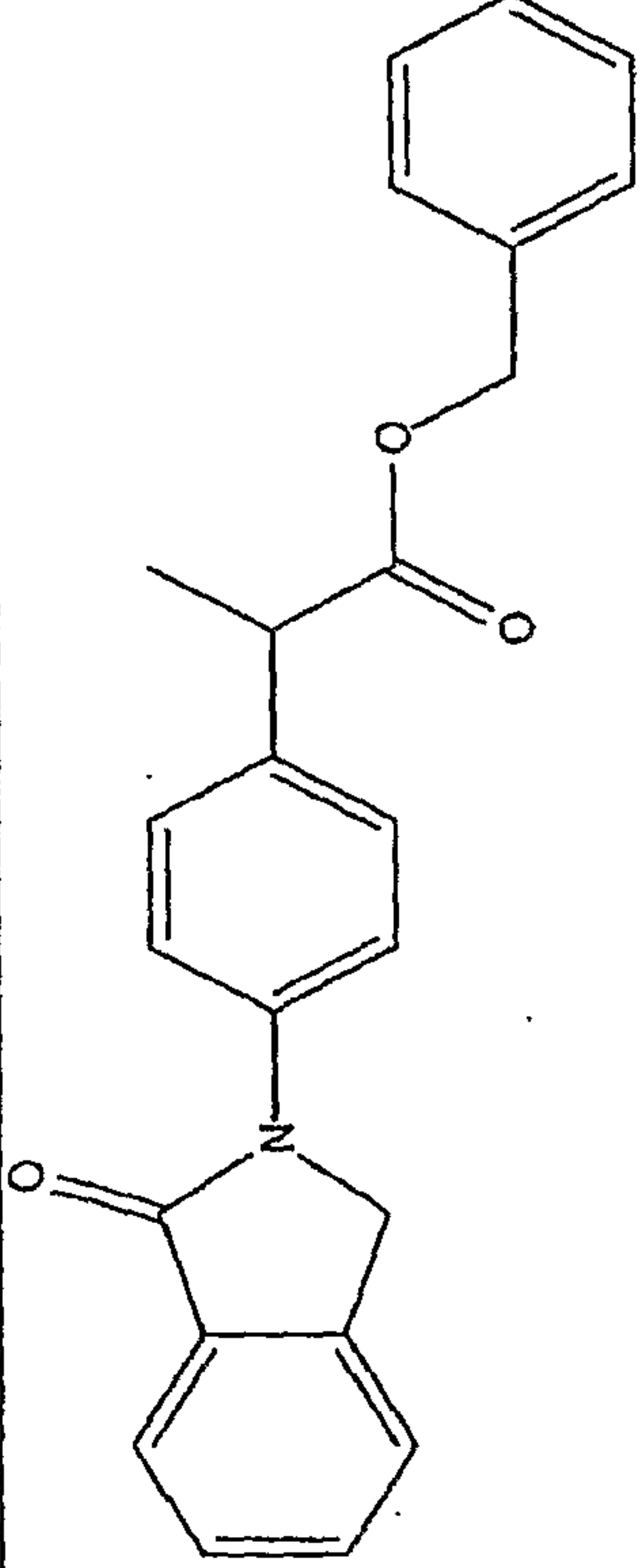
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3		ALB- 111732	0.325	1.414
4		ALB- 111733	0.528	1.56

Table 1

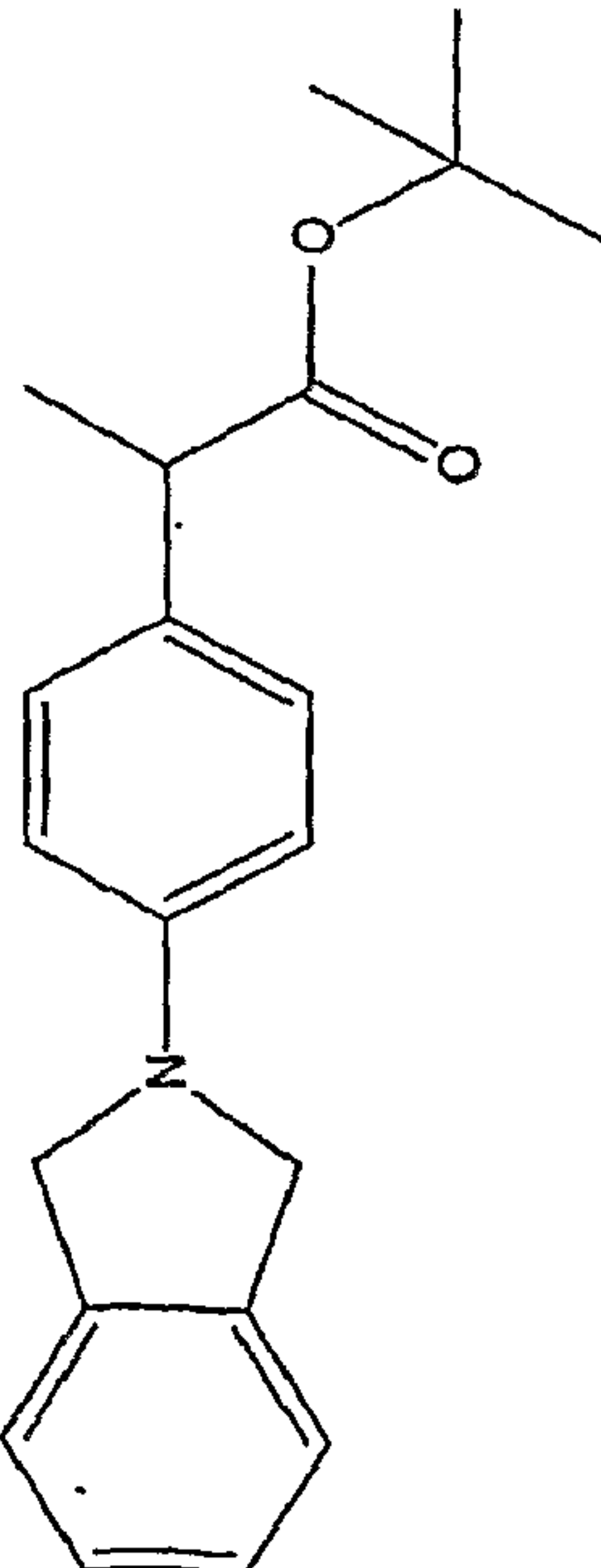
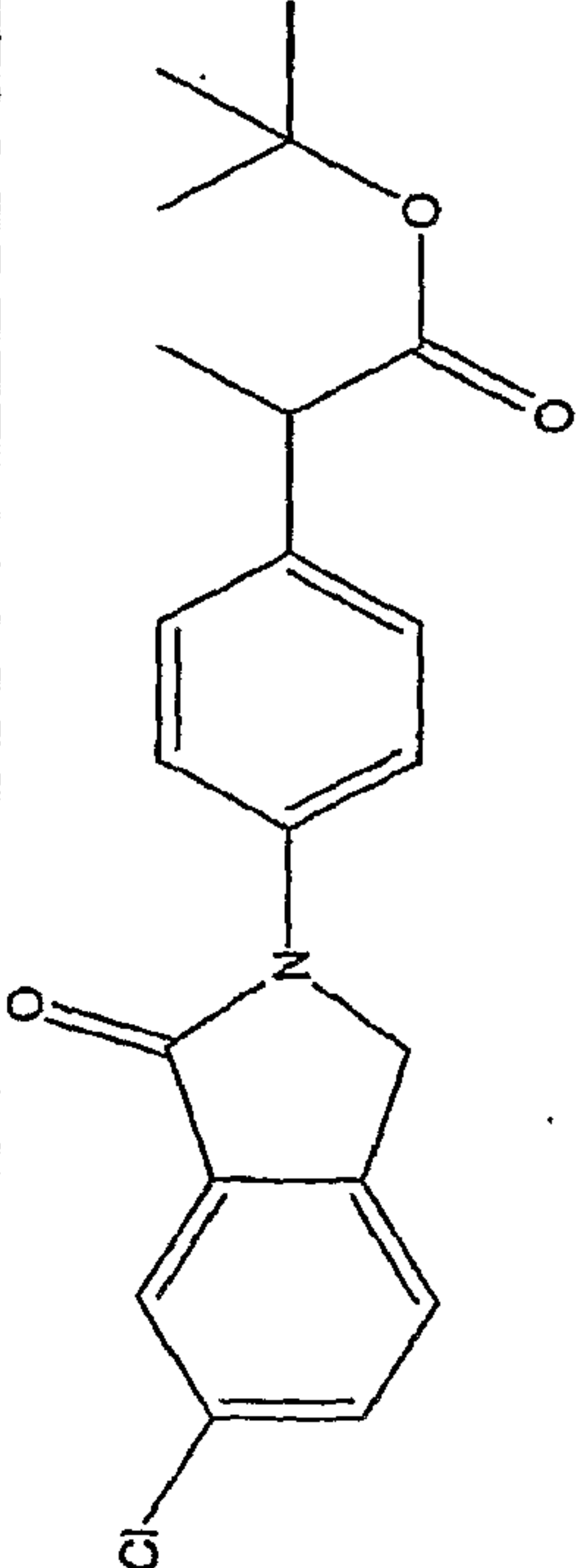
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5		ALB- 111738	2.295	1.172
6		ALB- 111740	2.023	1.487

Table 1

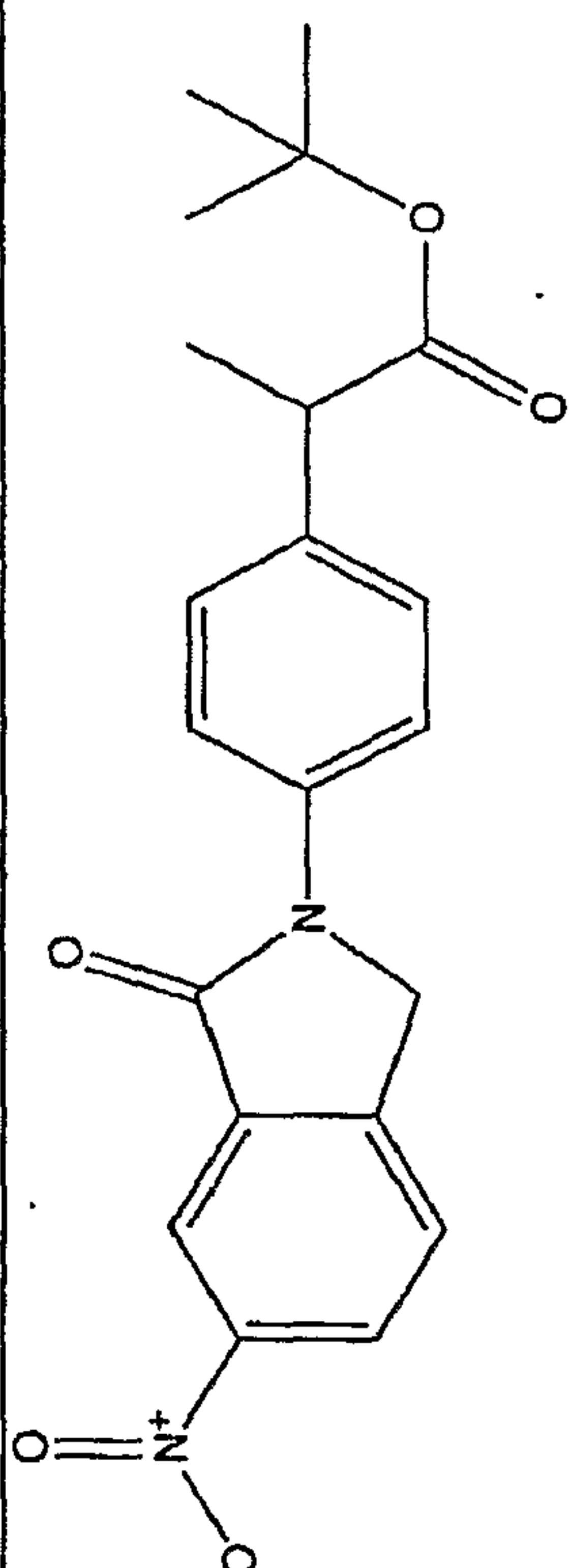
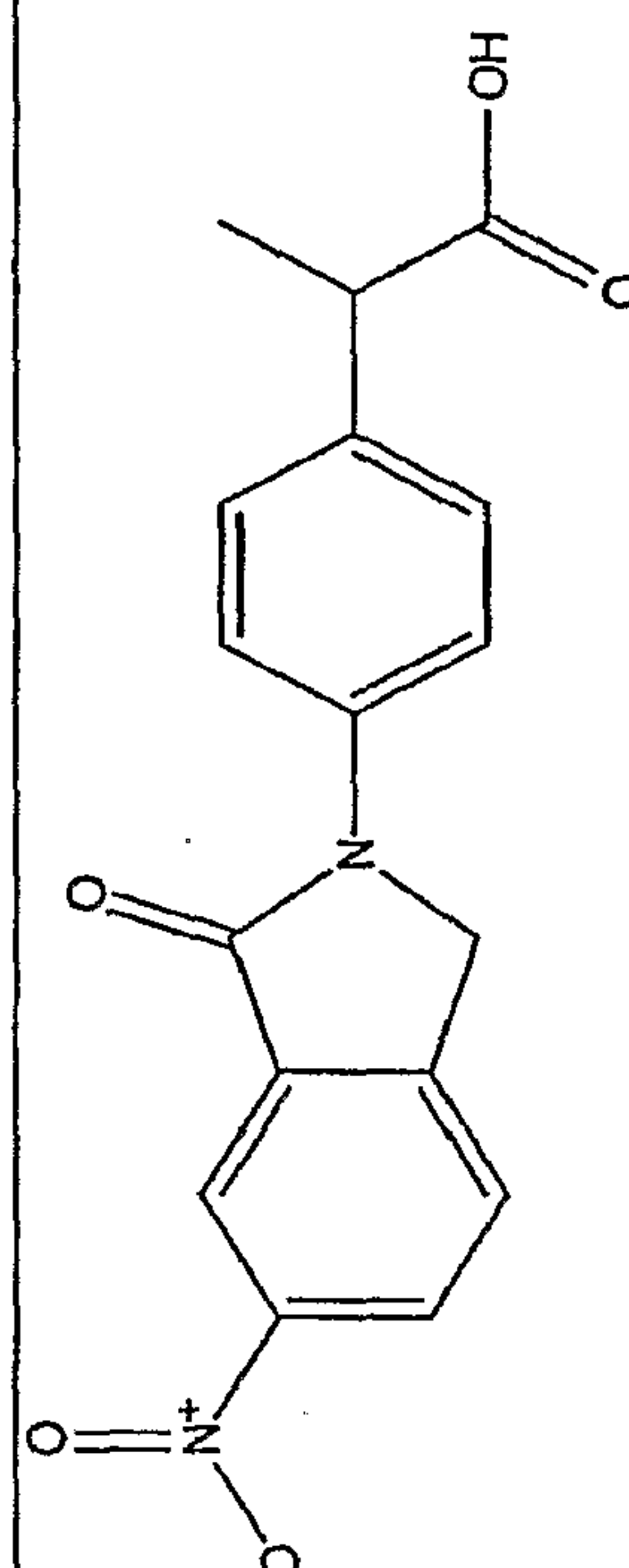
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			Avg EC50 (uM)	Avg MaxFold Increase
7		ALB- 111741	0.875	1.116
8		ALB- 111742	17.865	1.329

Table I

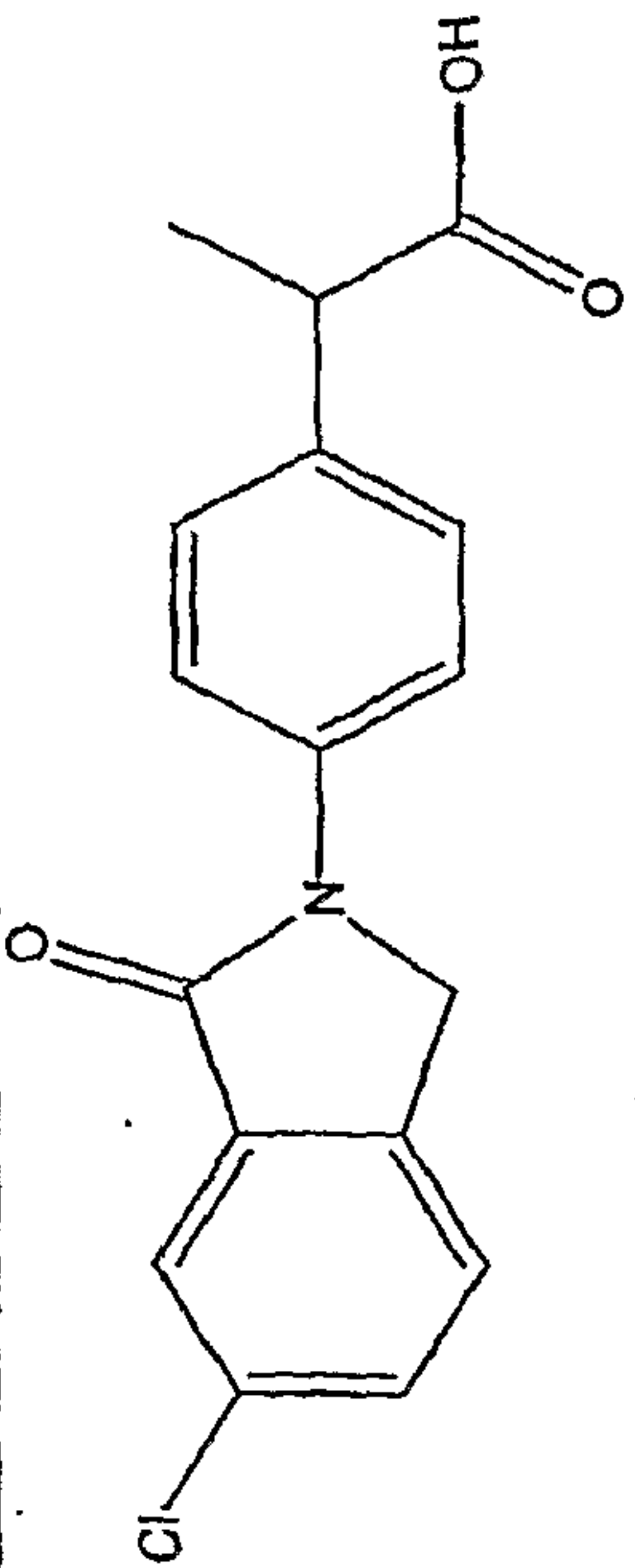
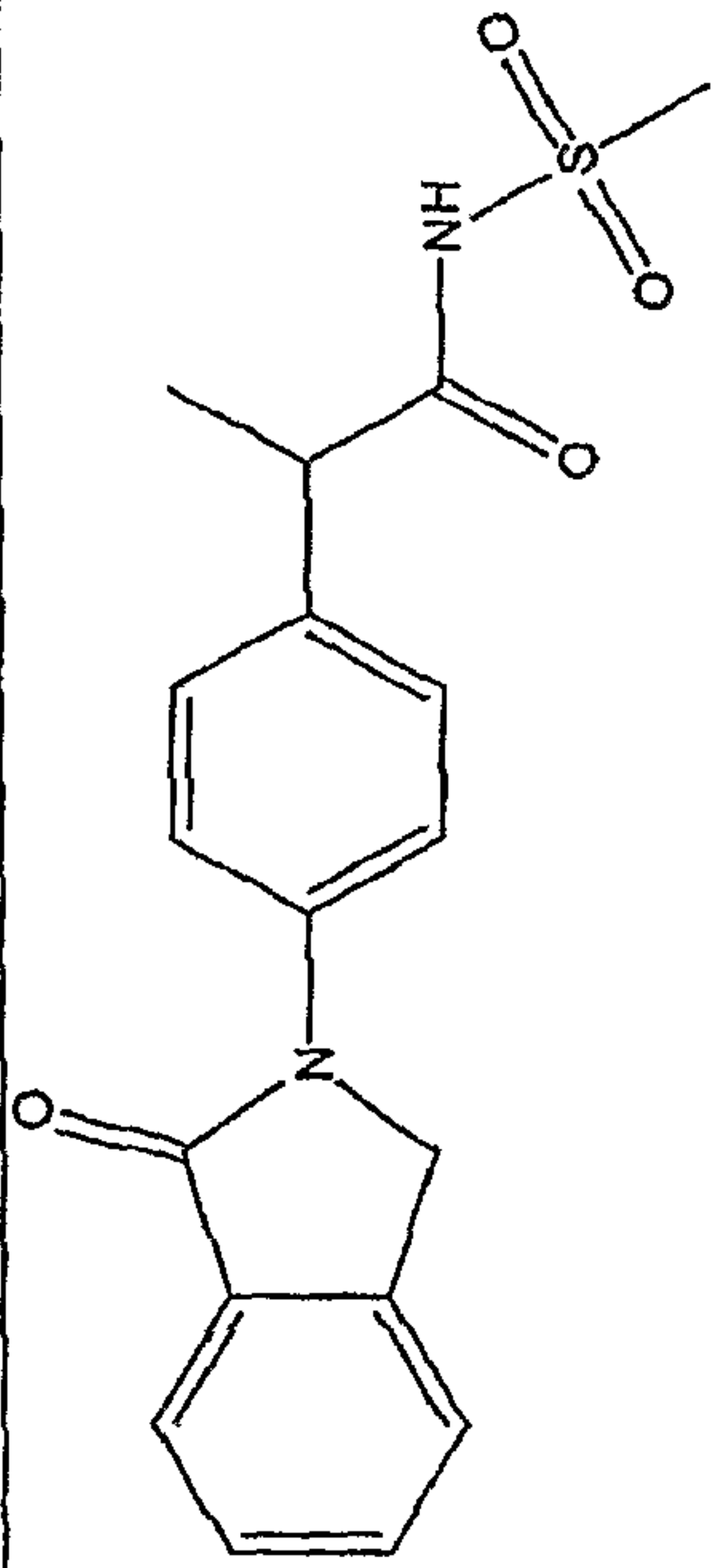
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9		ALB- 111743	0.267	1.67
10		ALB- 111744		1.135

Table 1

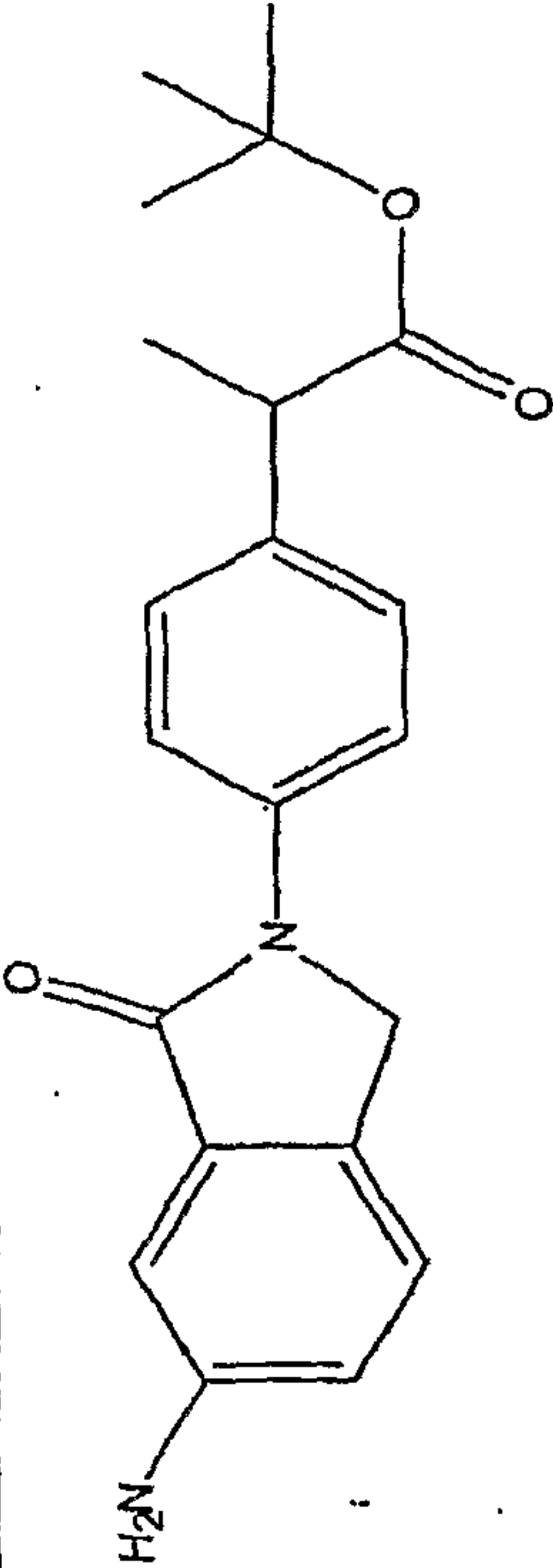
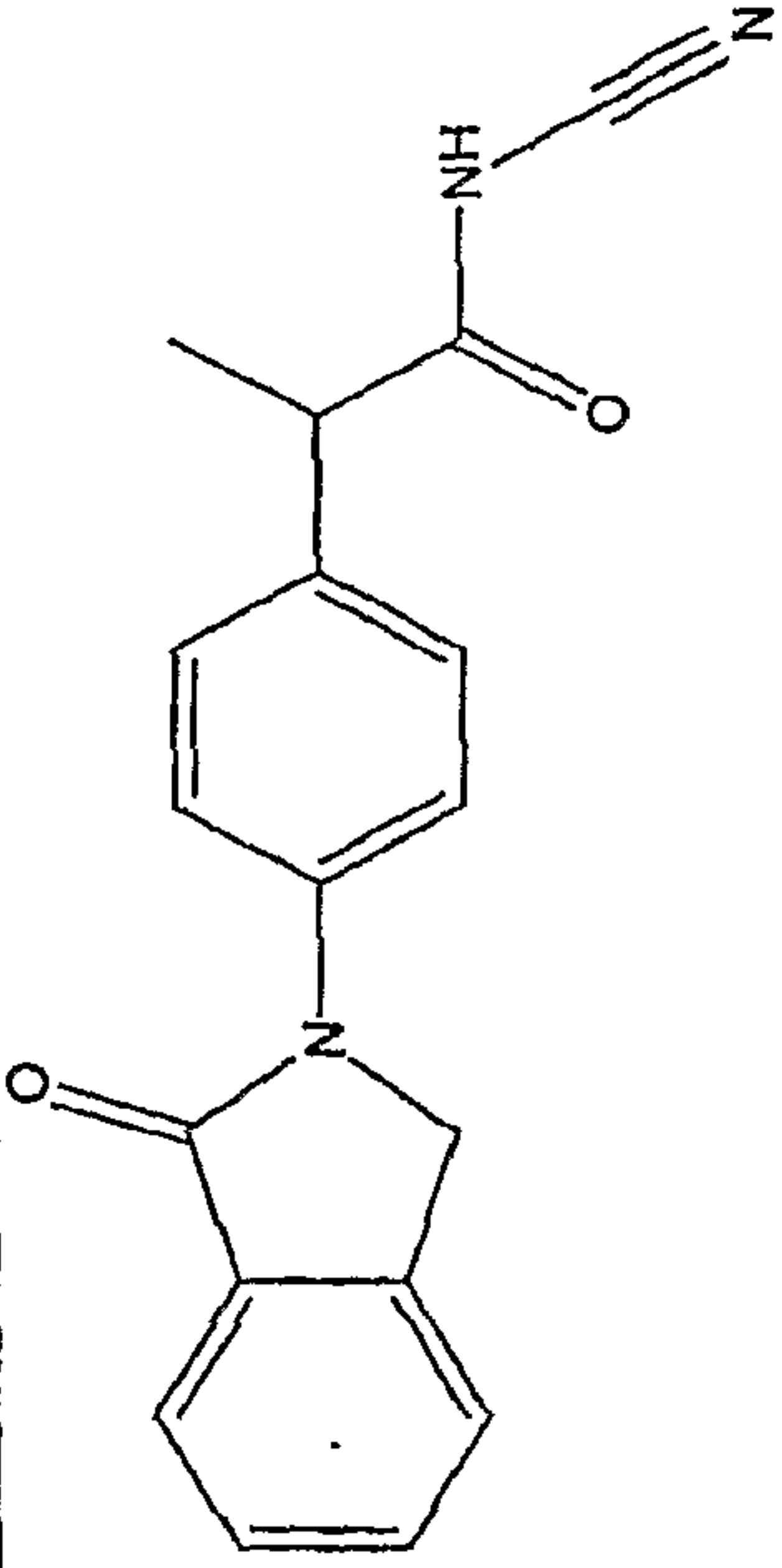
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11		ALB- 111745	2.124	1.168
12		ALB- 111746		1.112

Table 1

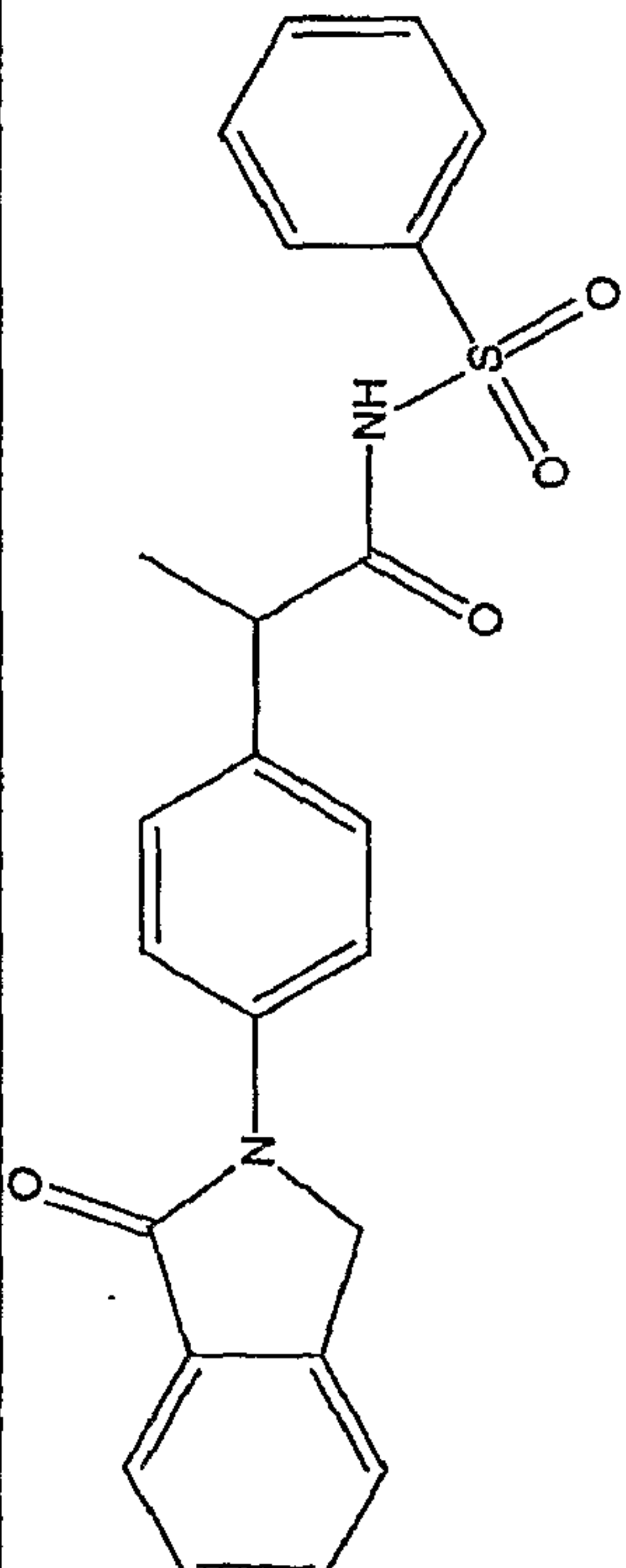
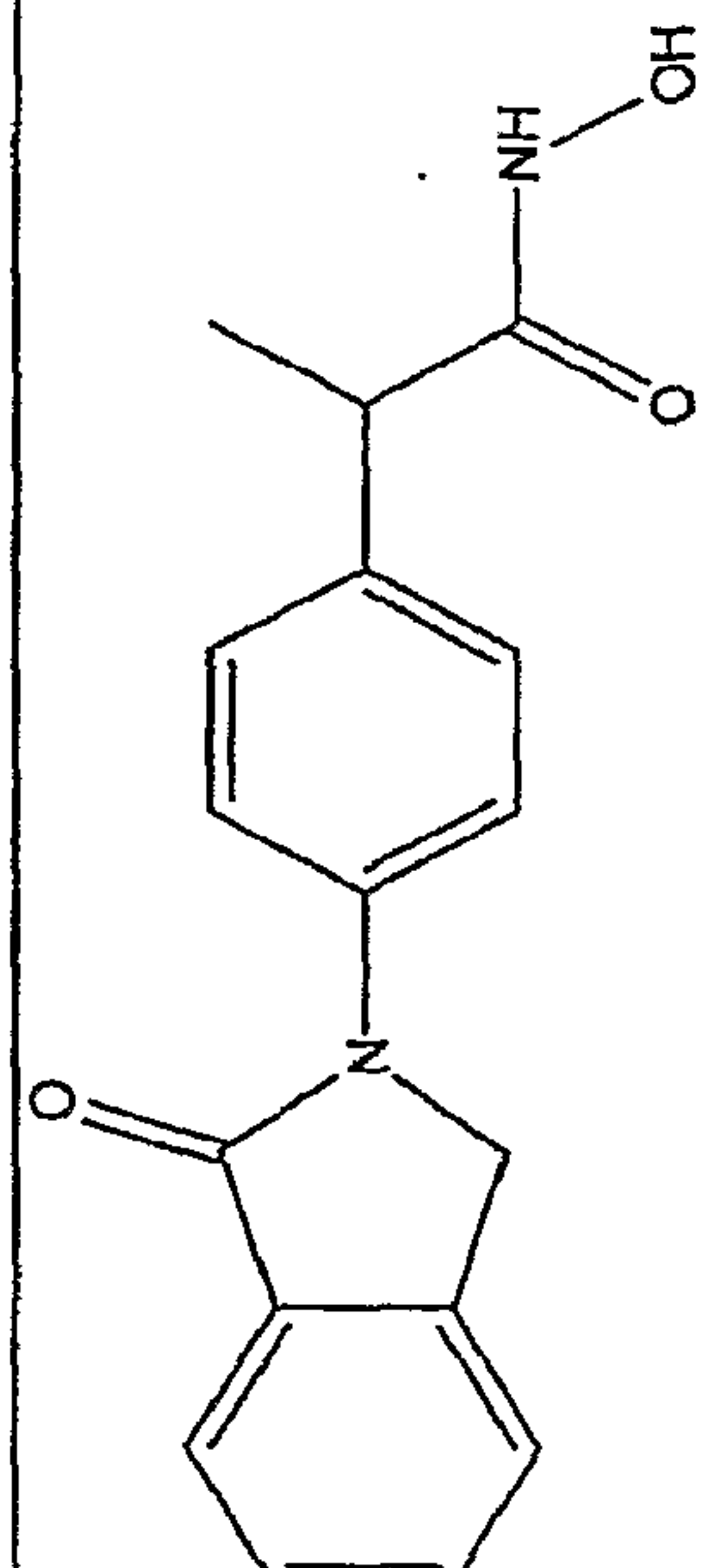
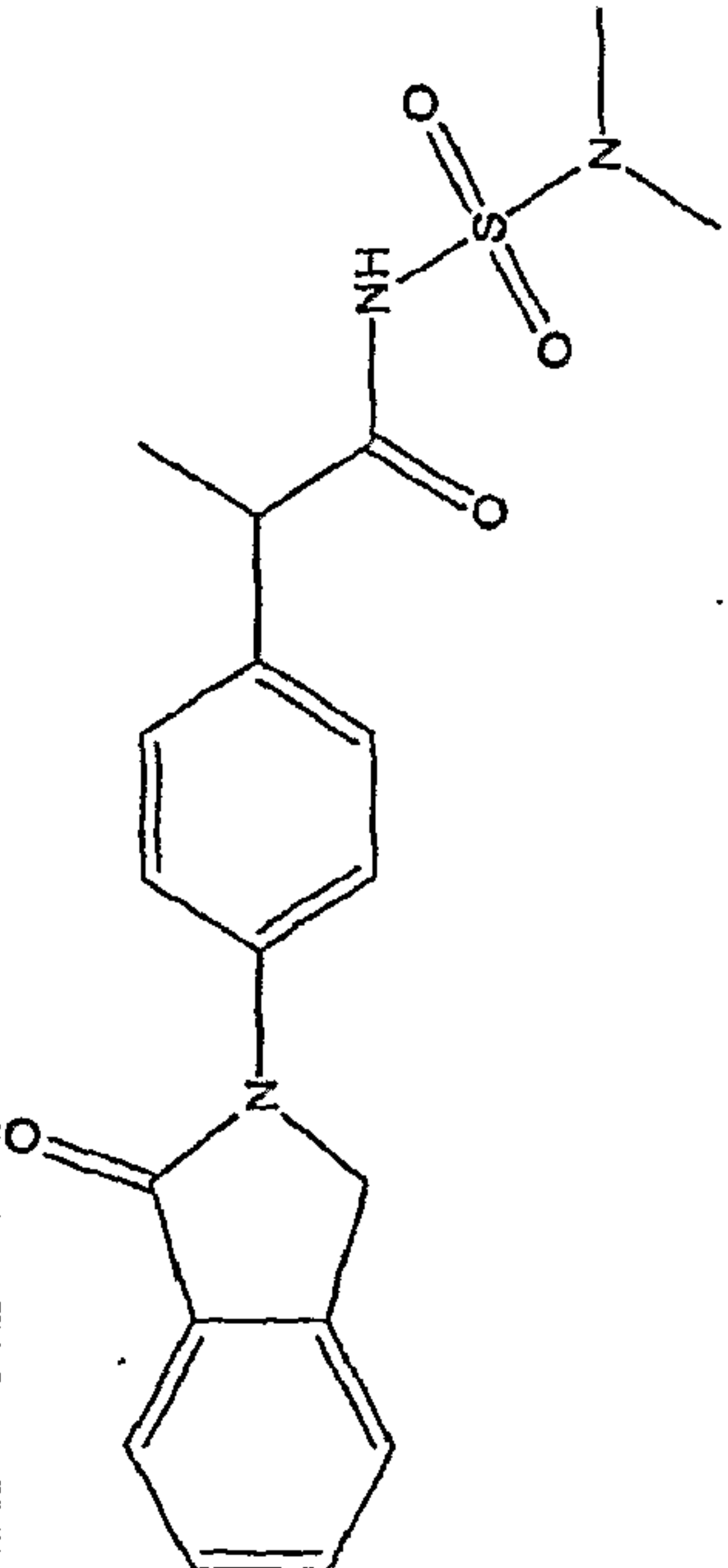
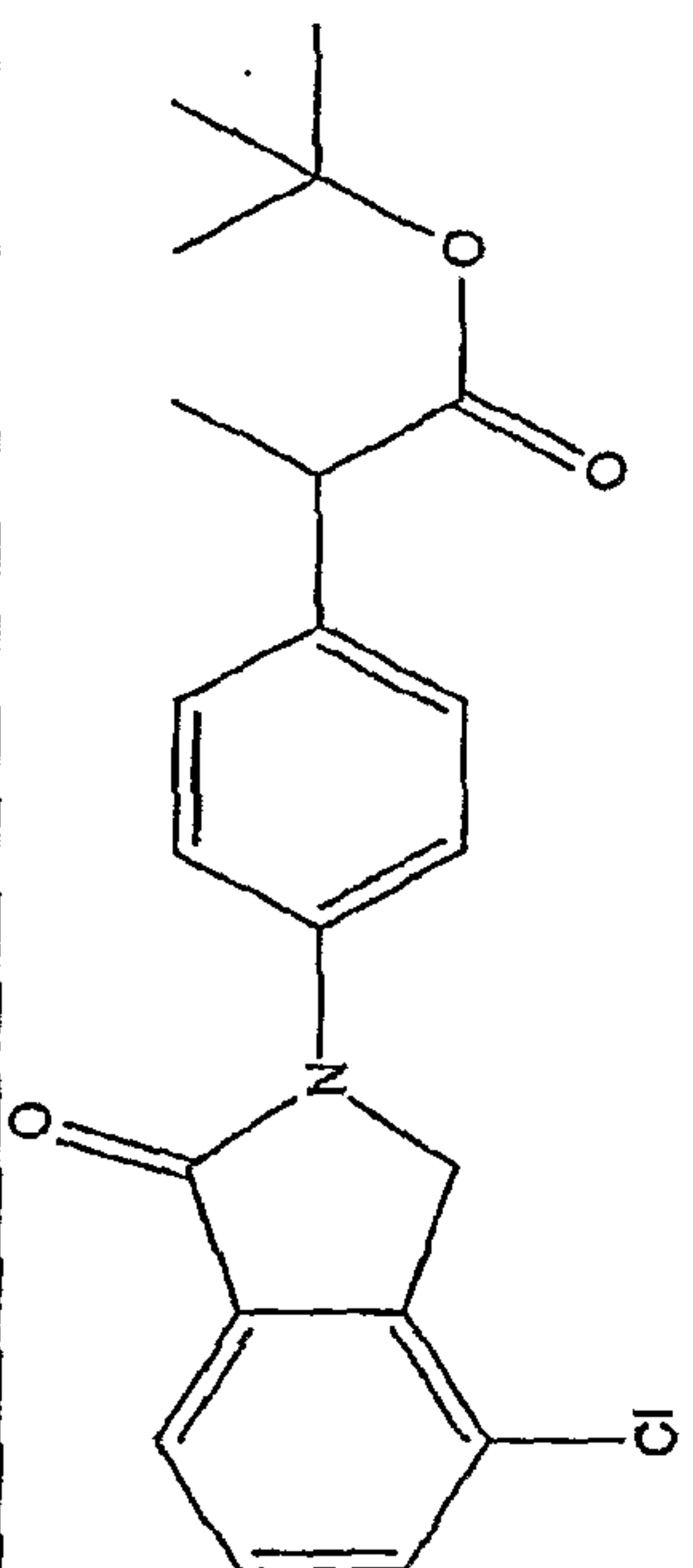
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13		ALB- 111747		1.042
14		ALB- 111748	2.266	1.377

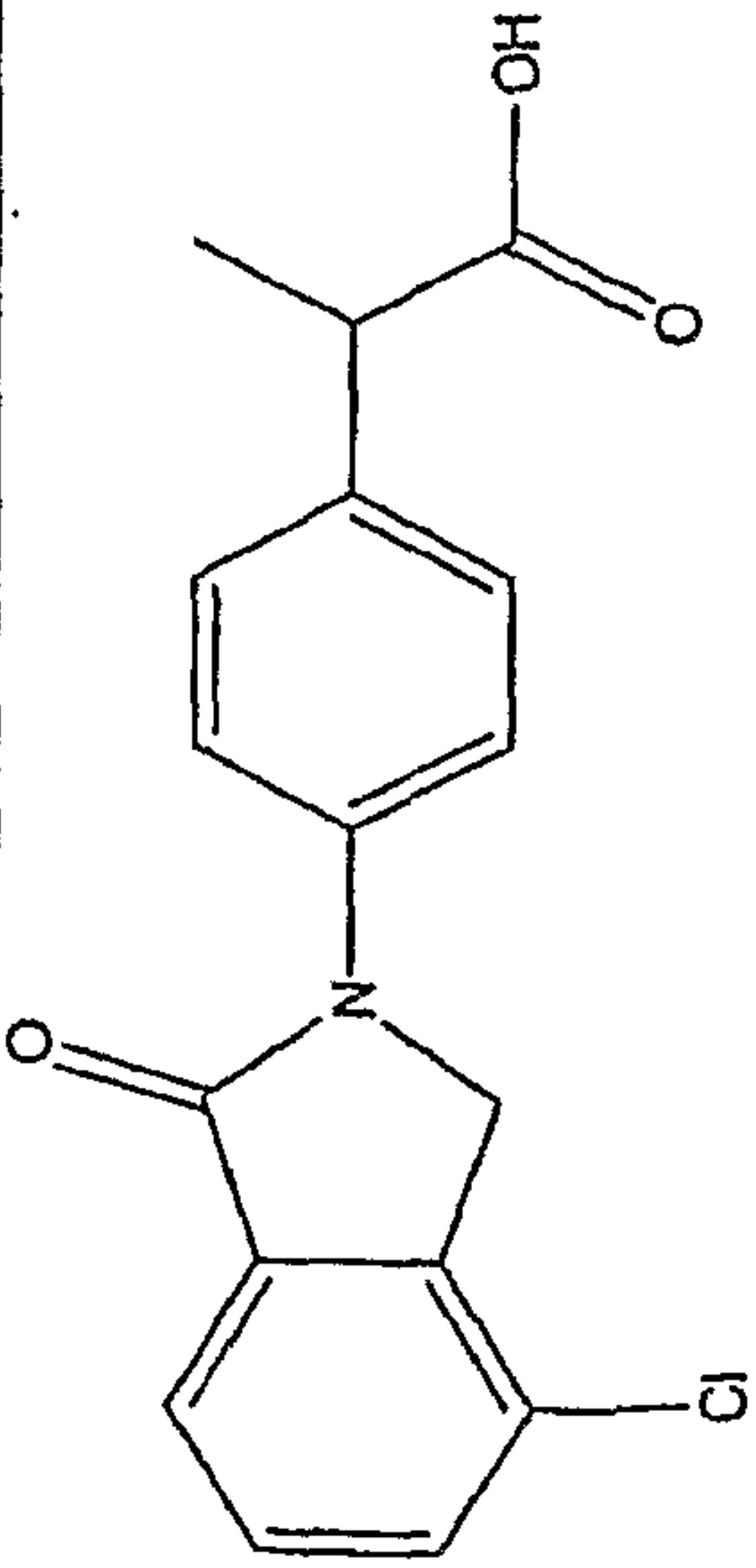
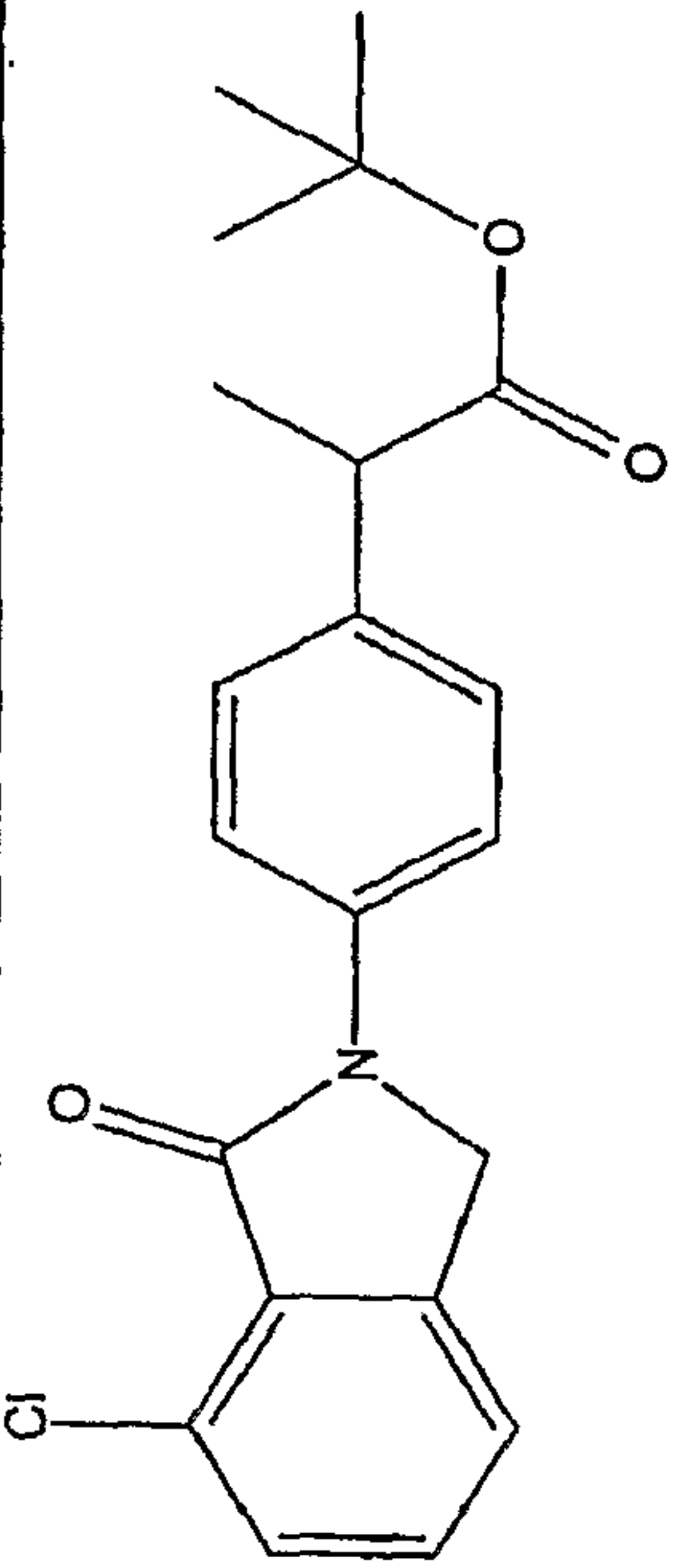
Table 1

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			Avg EC50 (μ M)	Avg MaxFold Increase
15		ALB- 111749	13.971	1.163
16		ALB- 111760		1.067

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μM)	Avg MaxFold Increase
17	 <chem>CC(C)(OC(=O)c1ccc(cc1)N2C(=O)c3cc(Cl)ccc3c2)c4ccccc4</chem>	ALB-111761	5.559	1.194
18	 <chem>CC(C(O)Cc1ccc(cc1)N2C(=O)c3cc(Cl)ccc3c2)C4=CC=CC=C4</chem>	ALB-111762	0.358	1.38

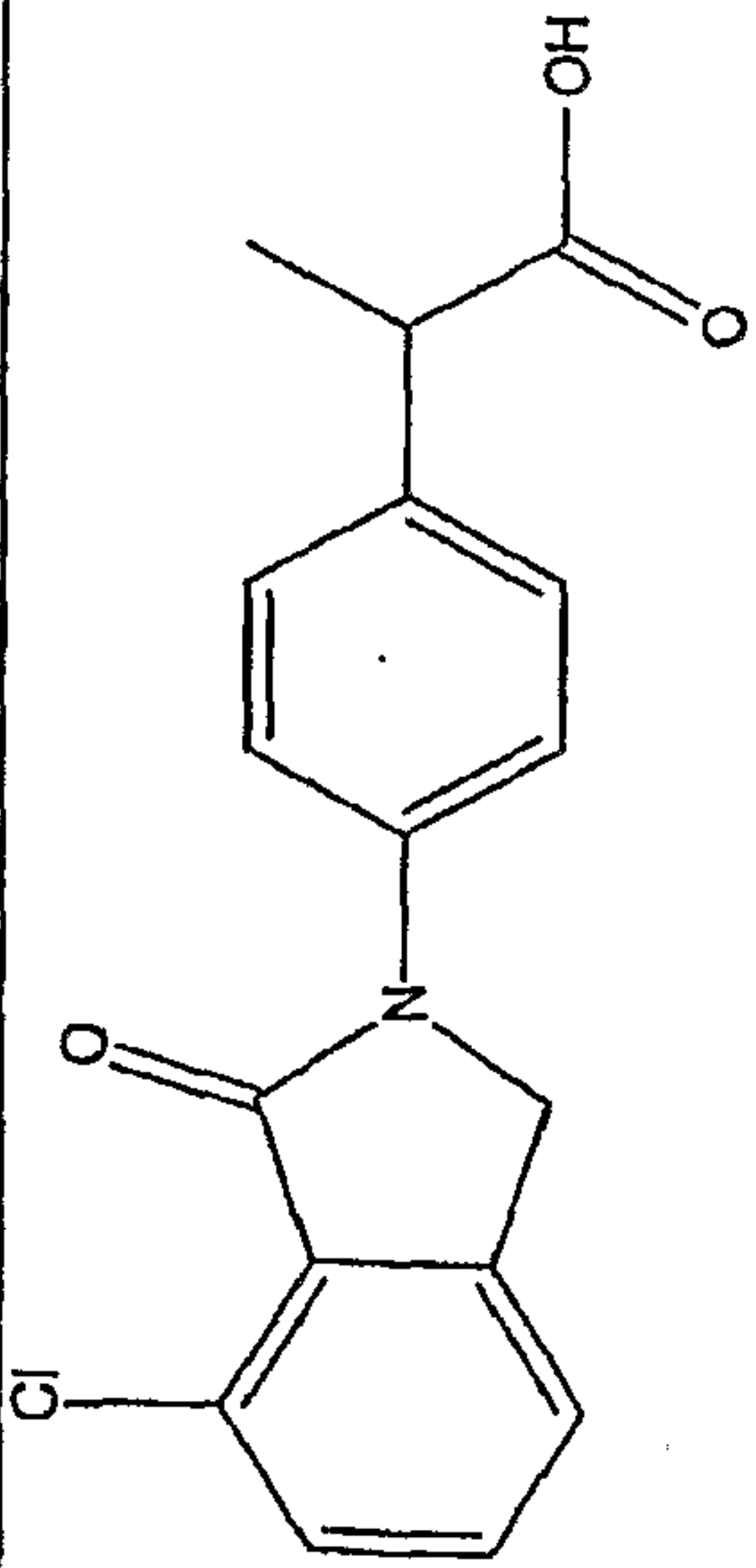
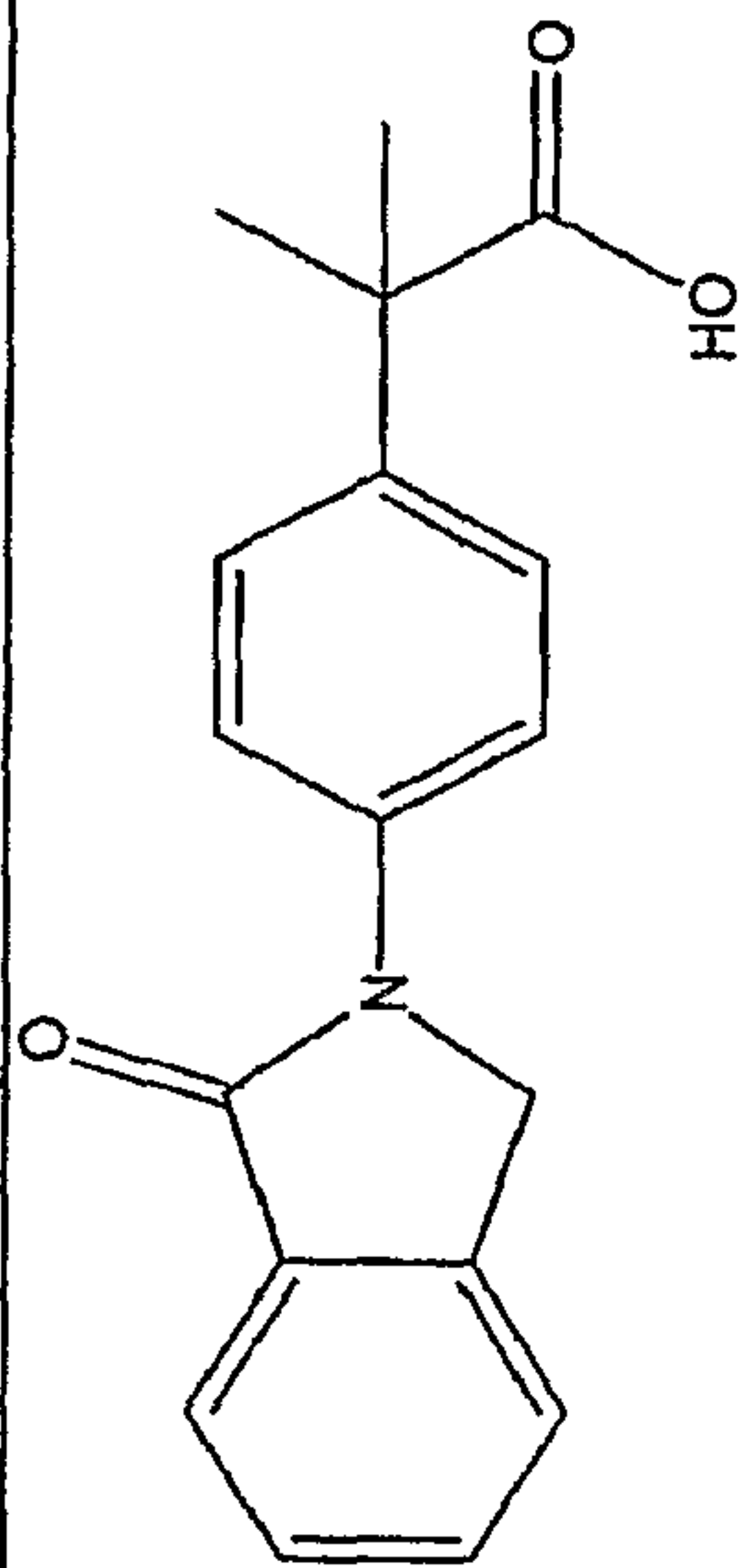
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
19		ALB- 111763	13.868	1.169
20		ALB- 111783	1.562	1.129

37

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
21		ALB- 111784	1.129	1.408
22		ALB- 111796	3.516	1.221

39

Table 1

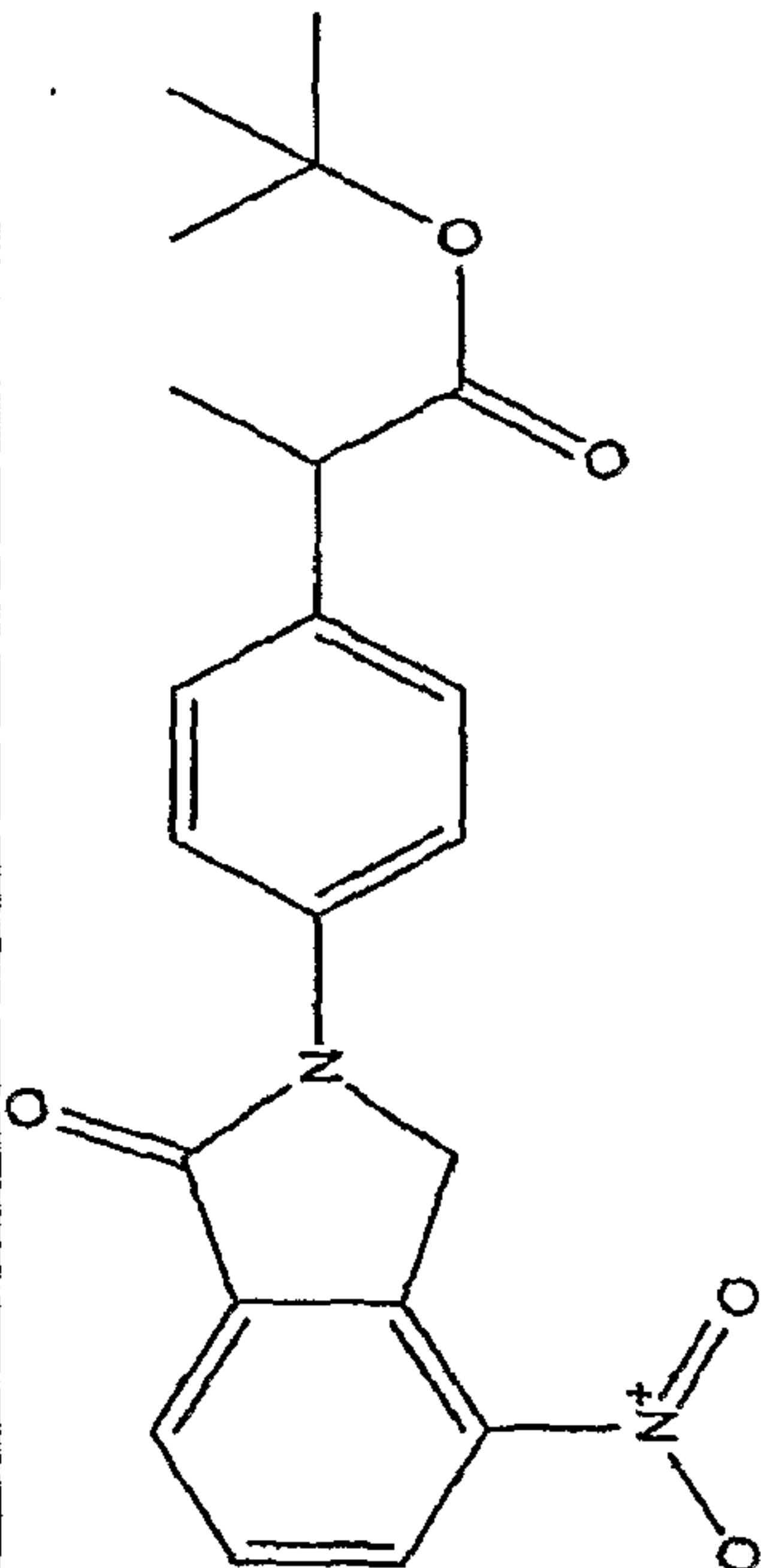
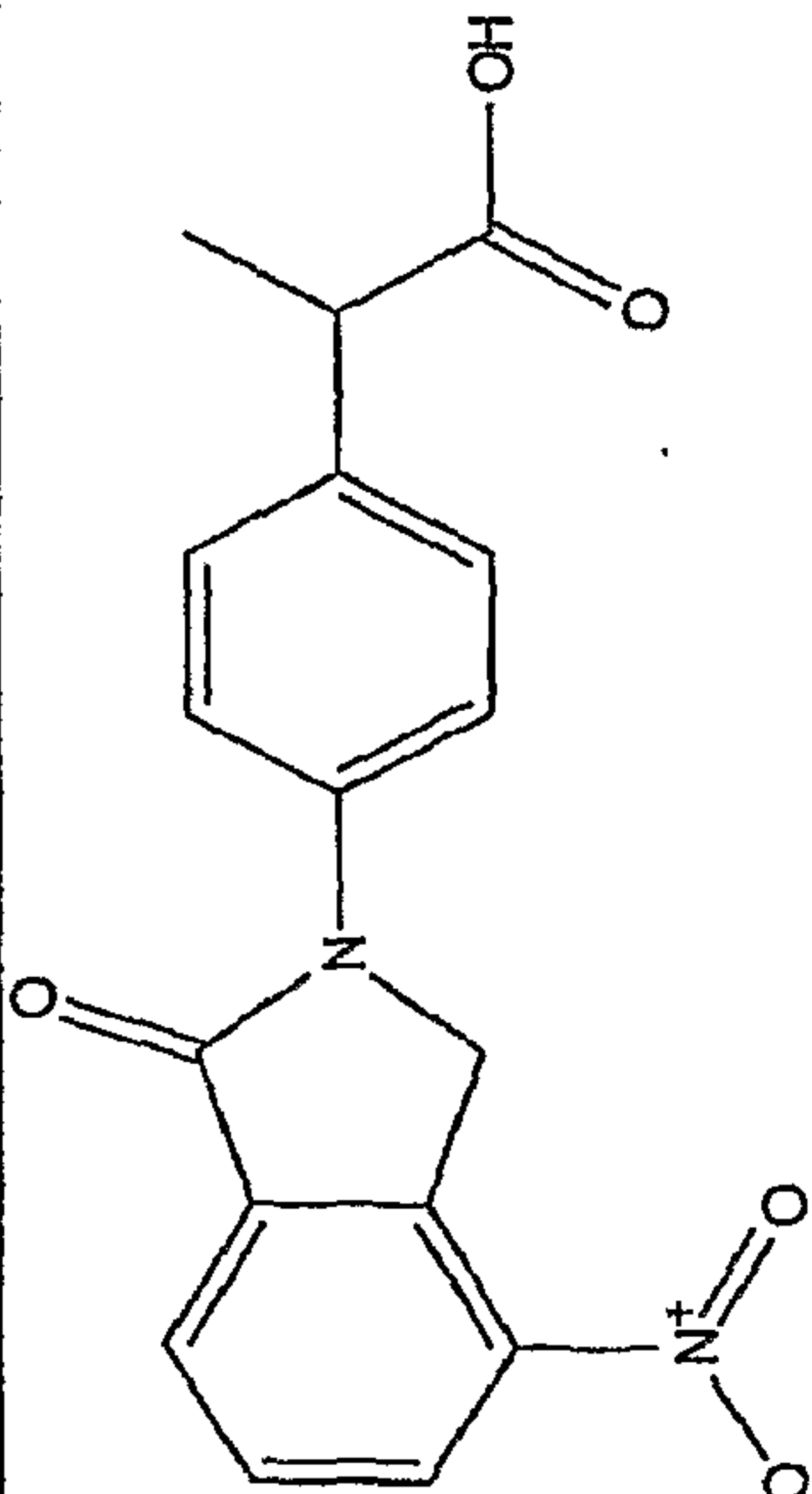
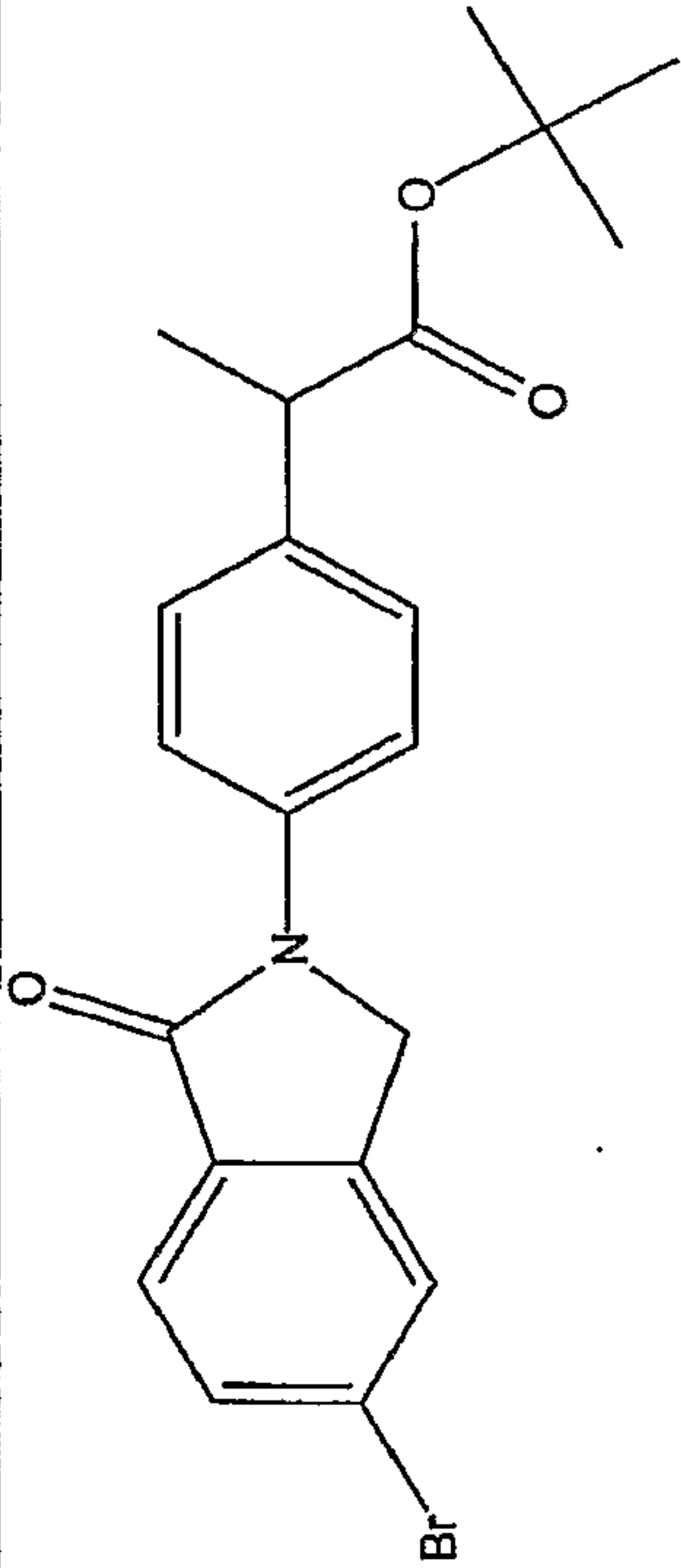
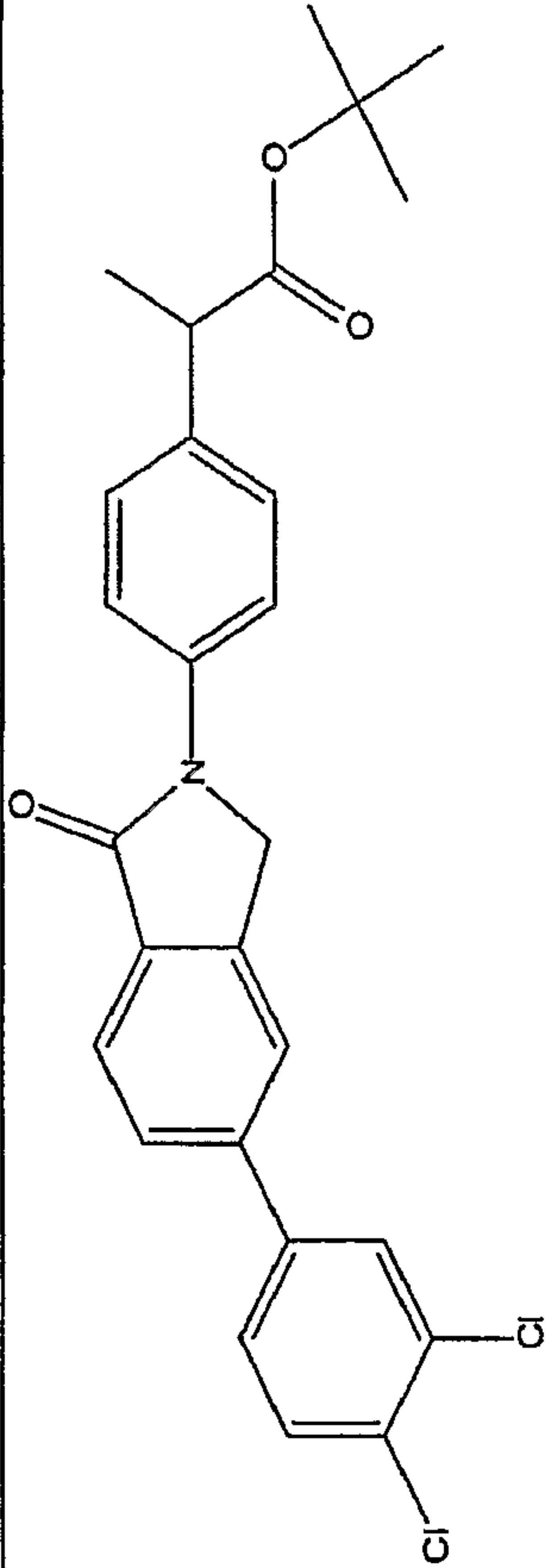
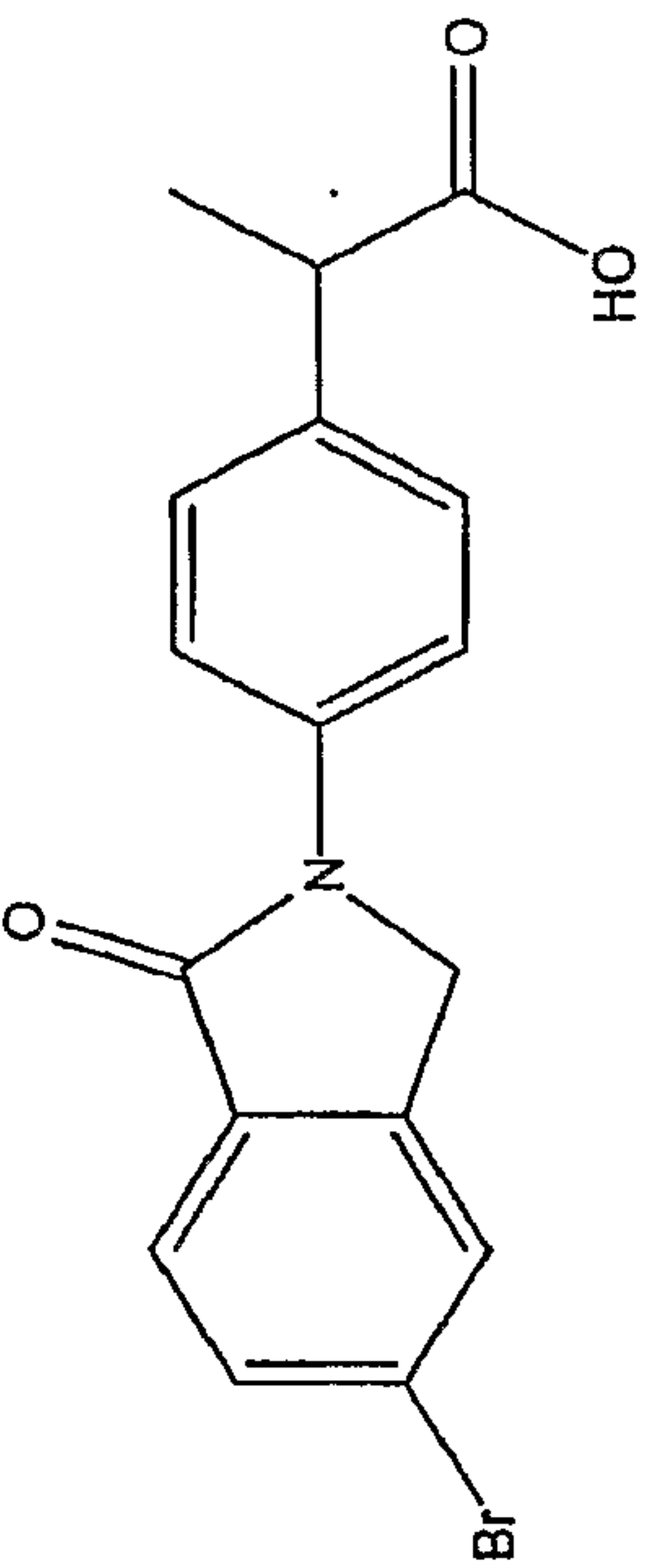
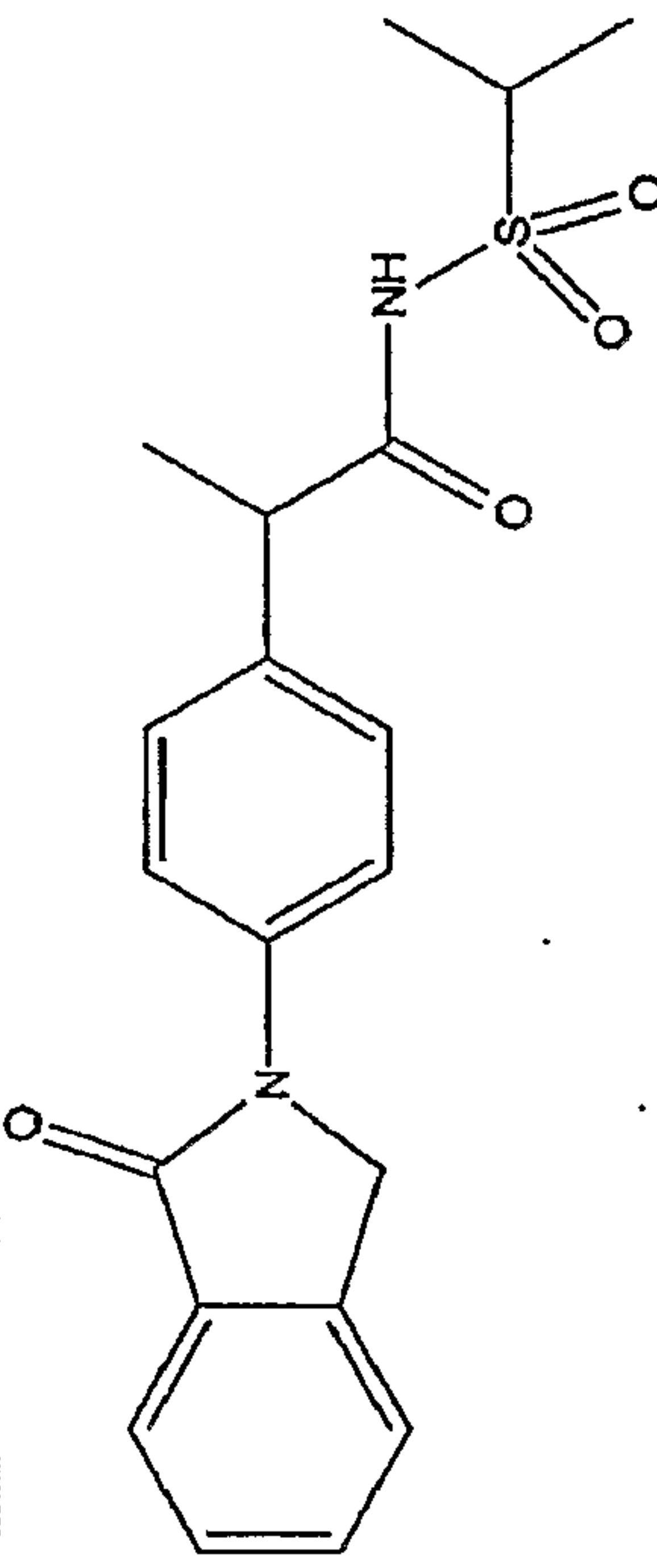
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25		ALB- 111843	2.002	1.202
26		ALB- 111844		1.158

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
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27		ALB- 111853	21.38	1.102
28		ALB- 111854		1.036

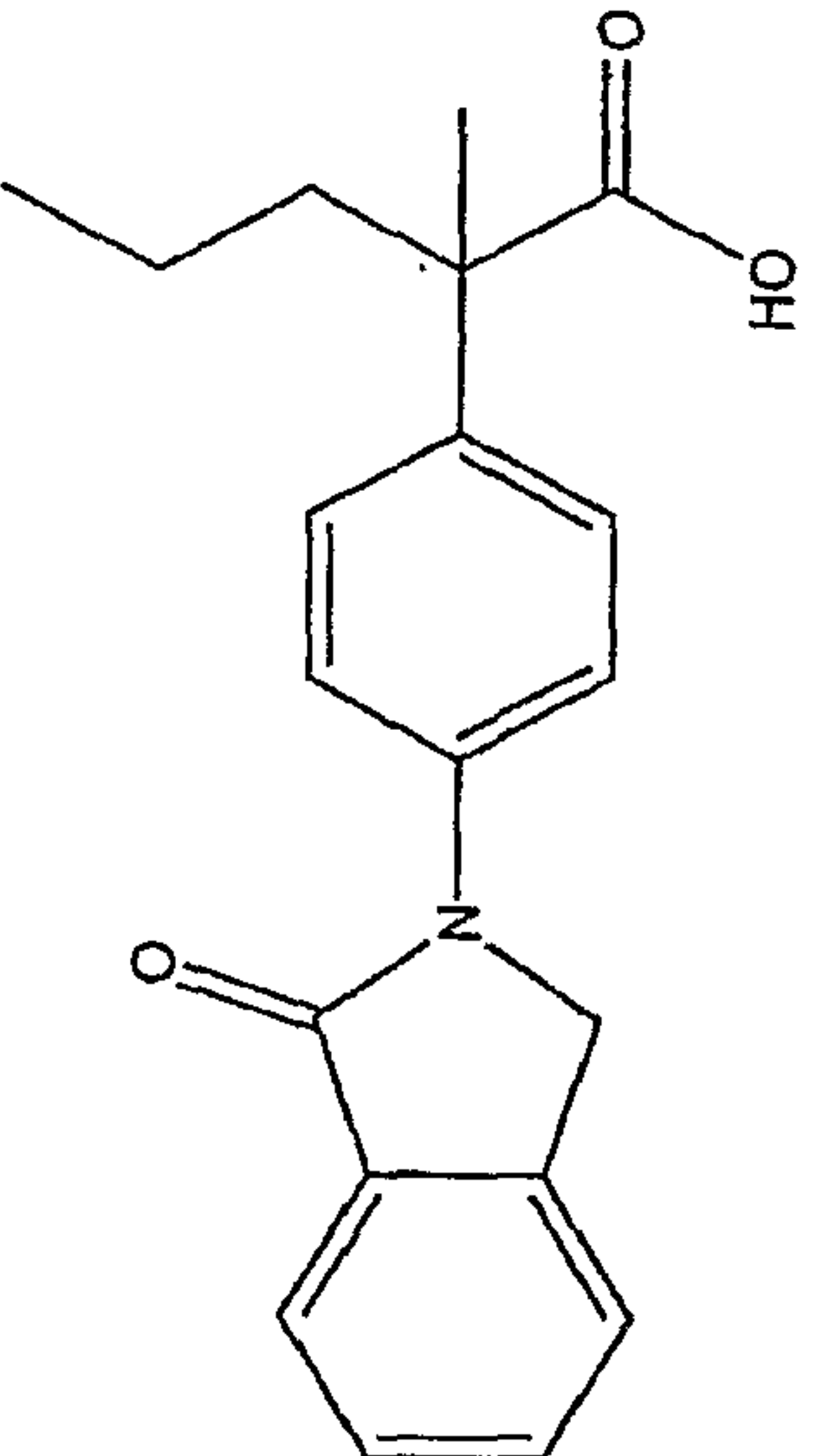
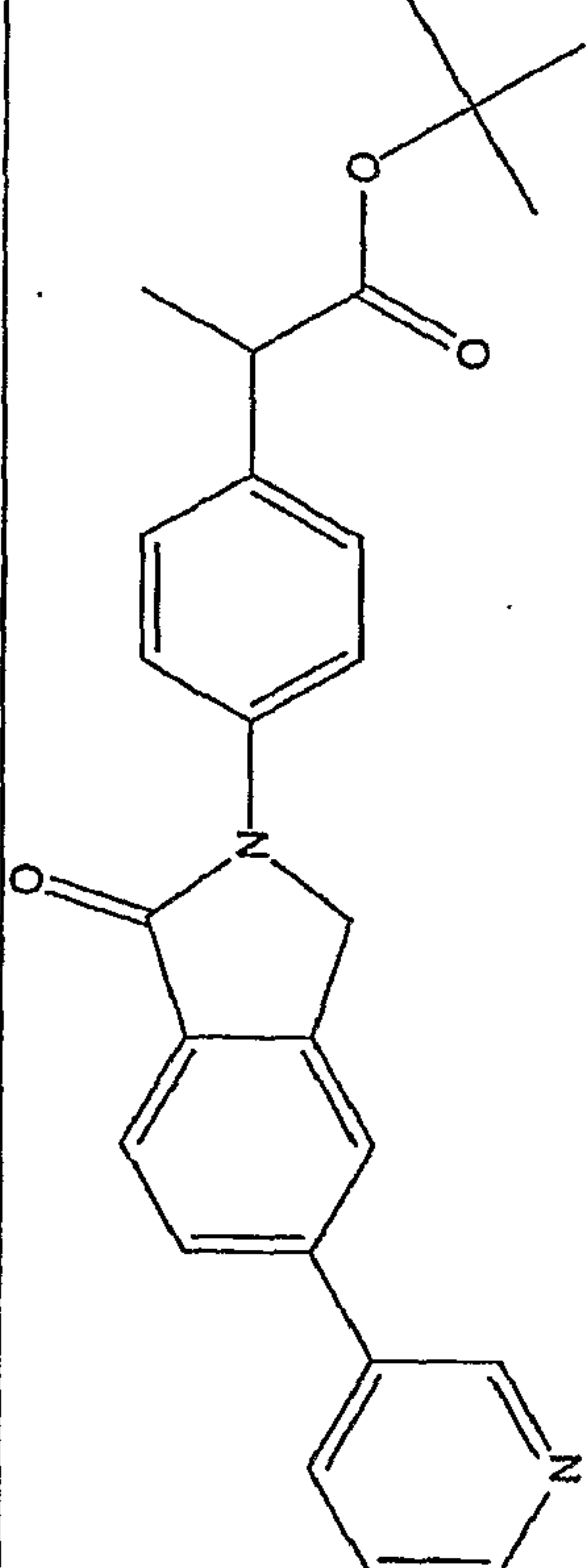
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
29		ALB- 111855	0.553	1.355
30		ALB- 111856	0.568	1.142

42

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
31		ALB- 111857		1.07
32		ALB- 111884		1.032

43

Table 1

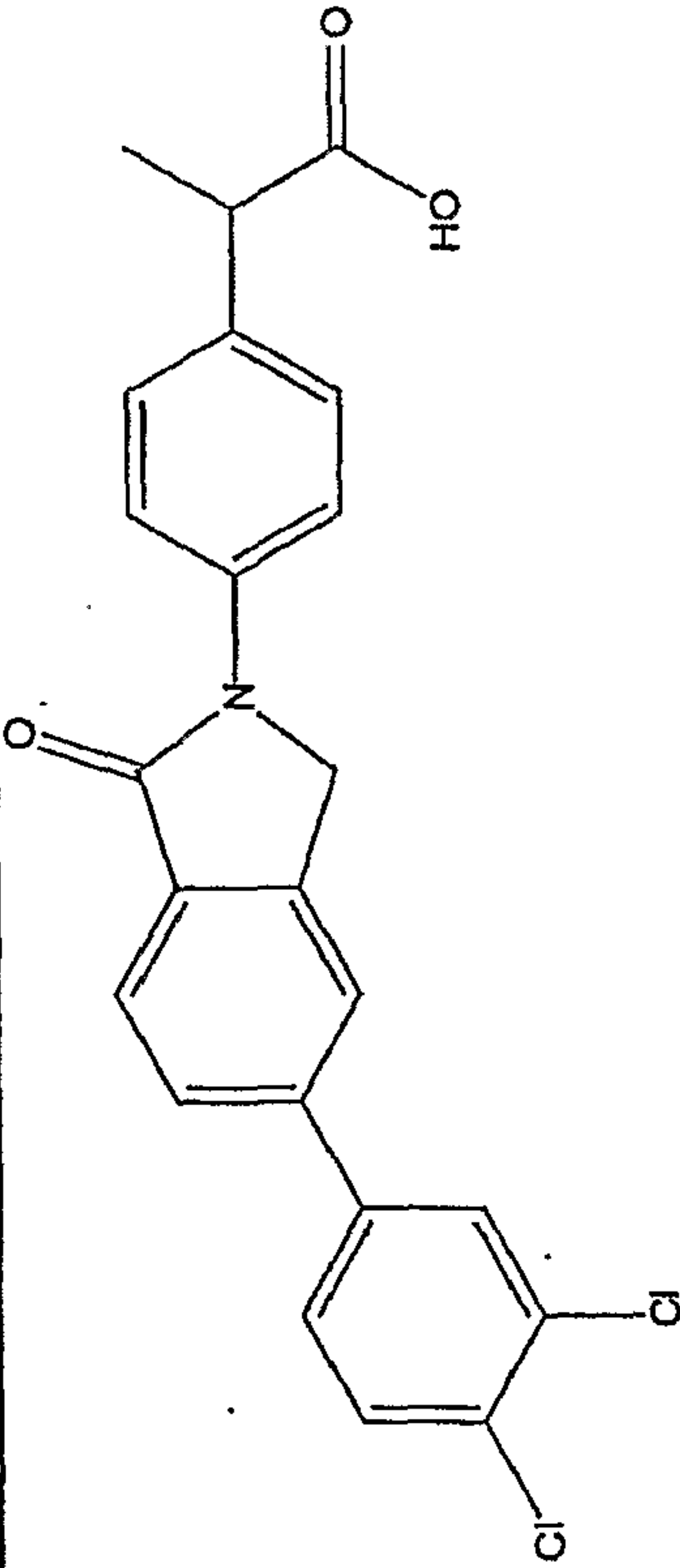
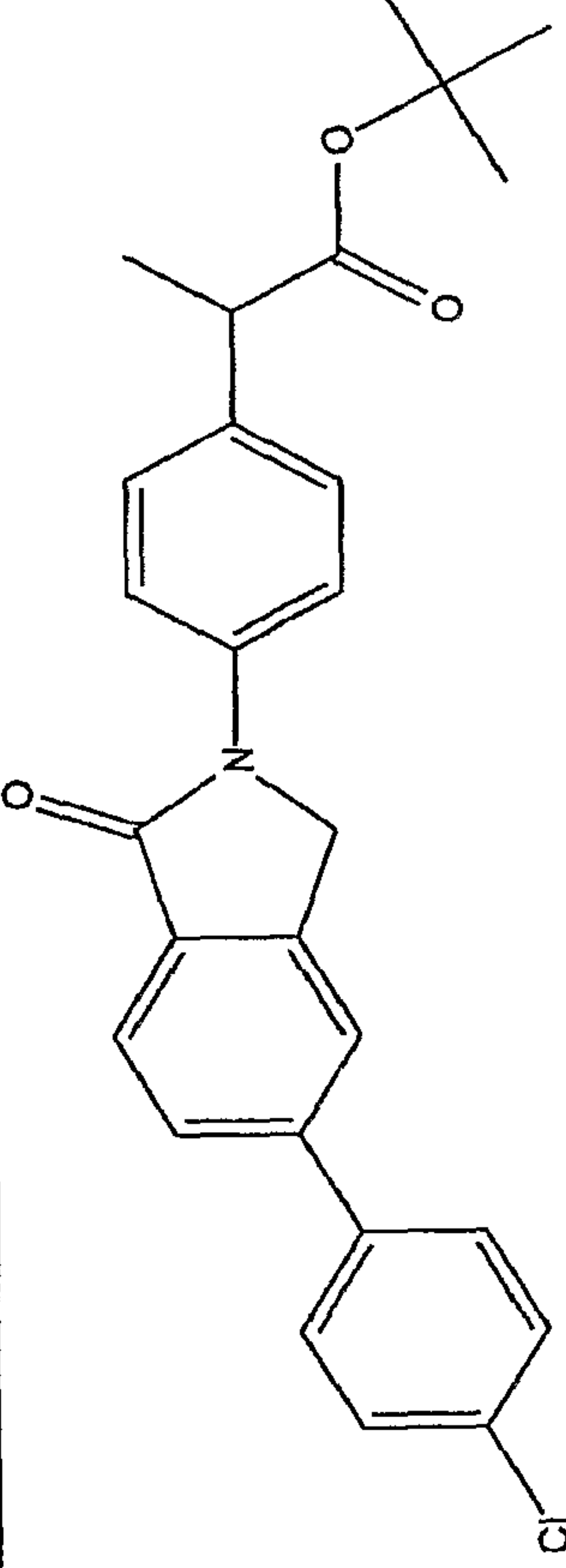
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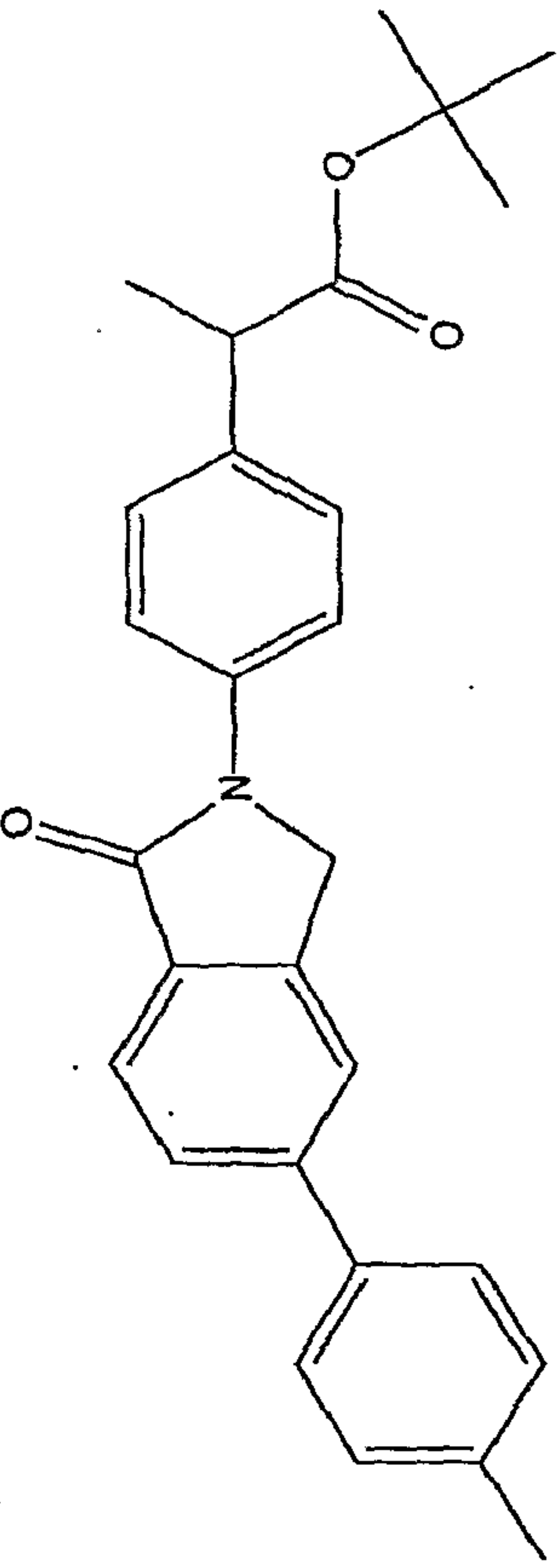
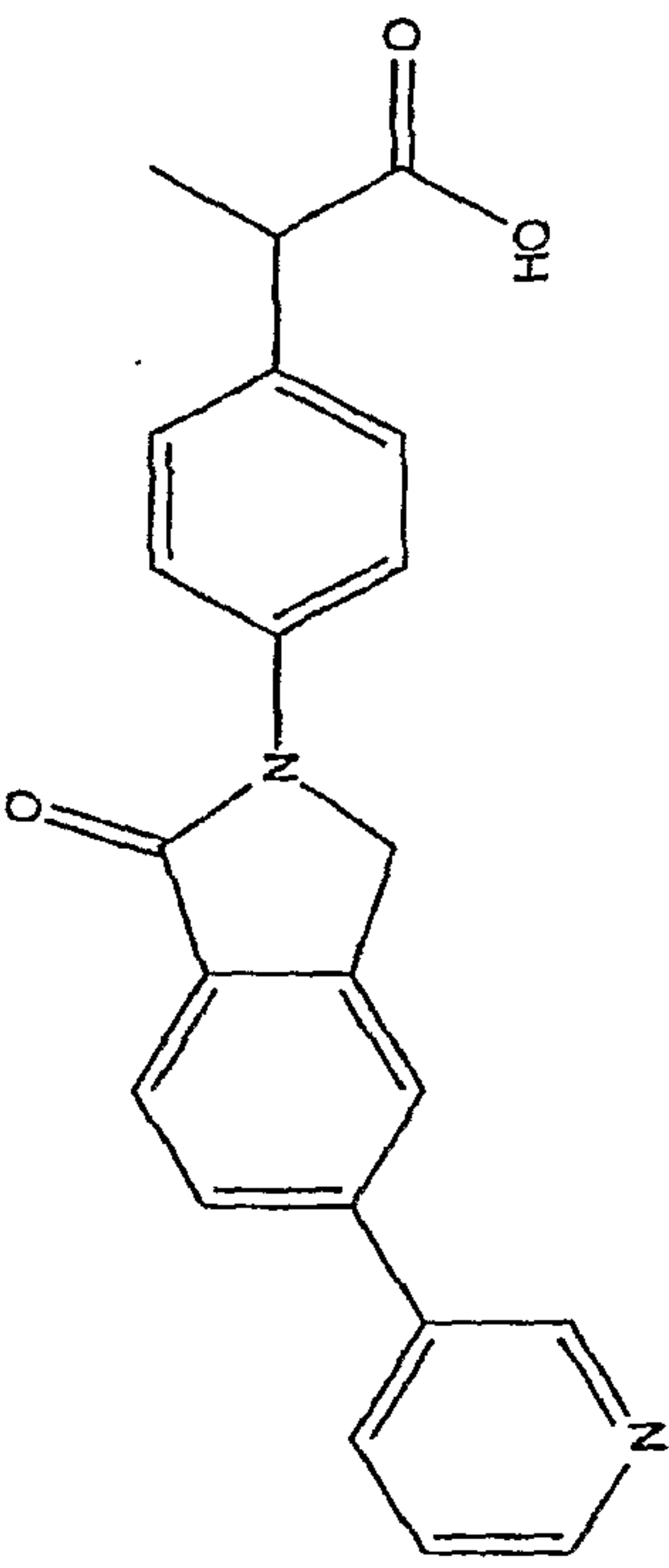
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Table 1

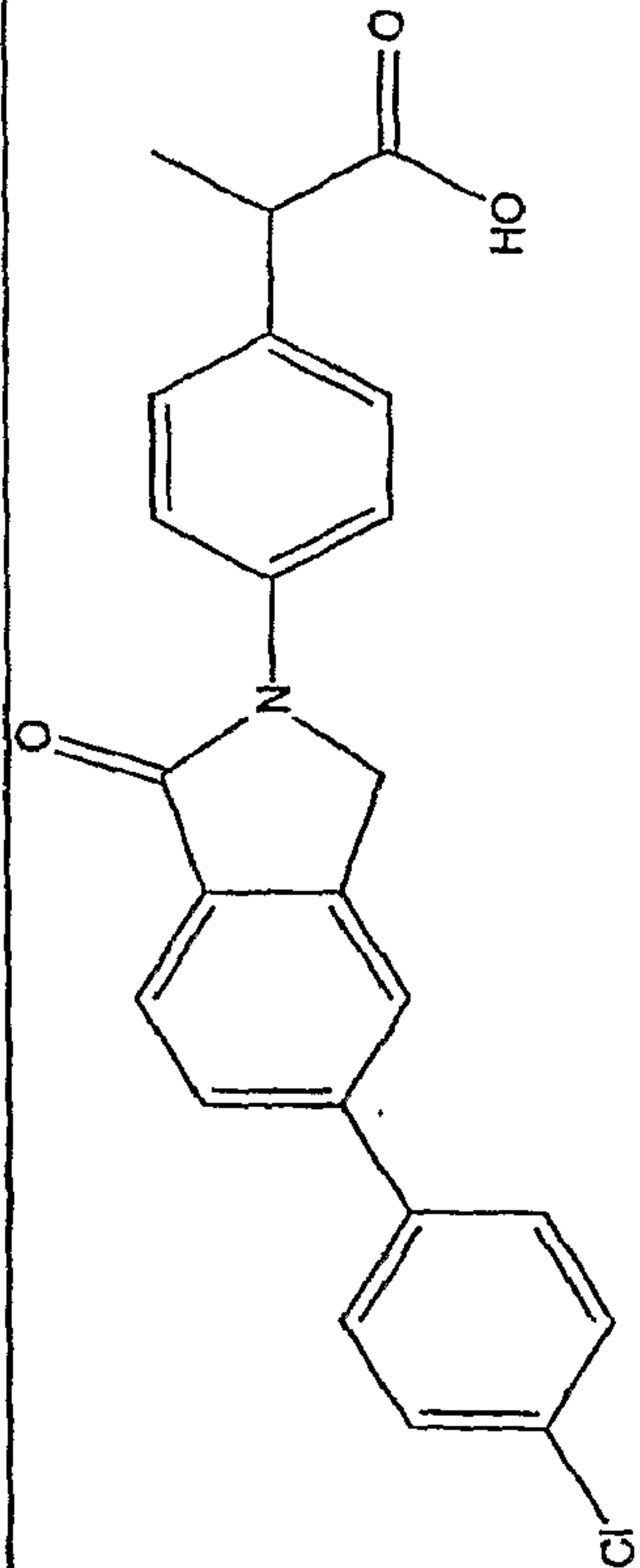
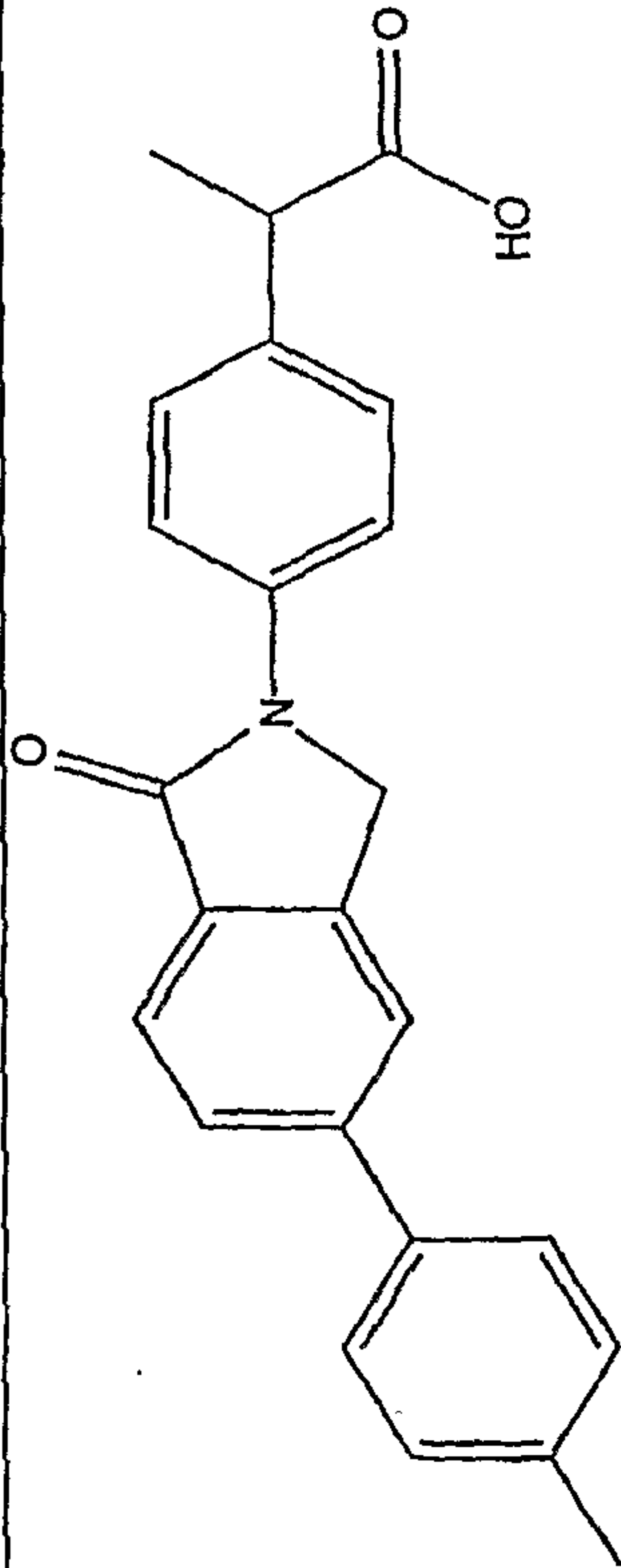
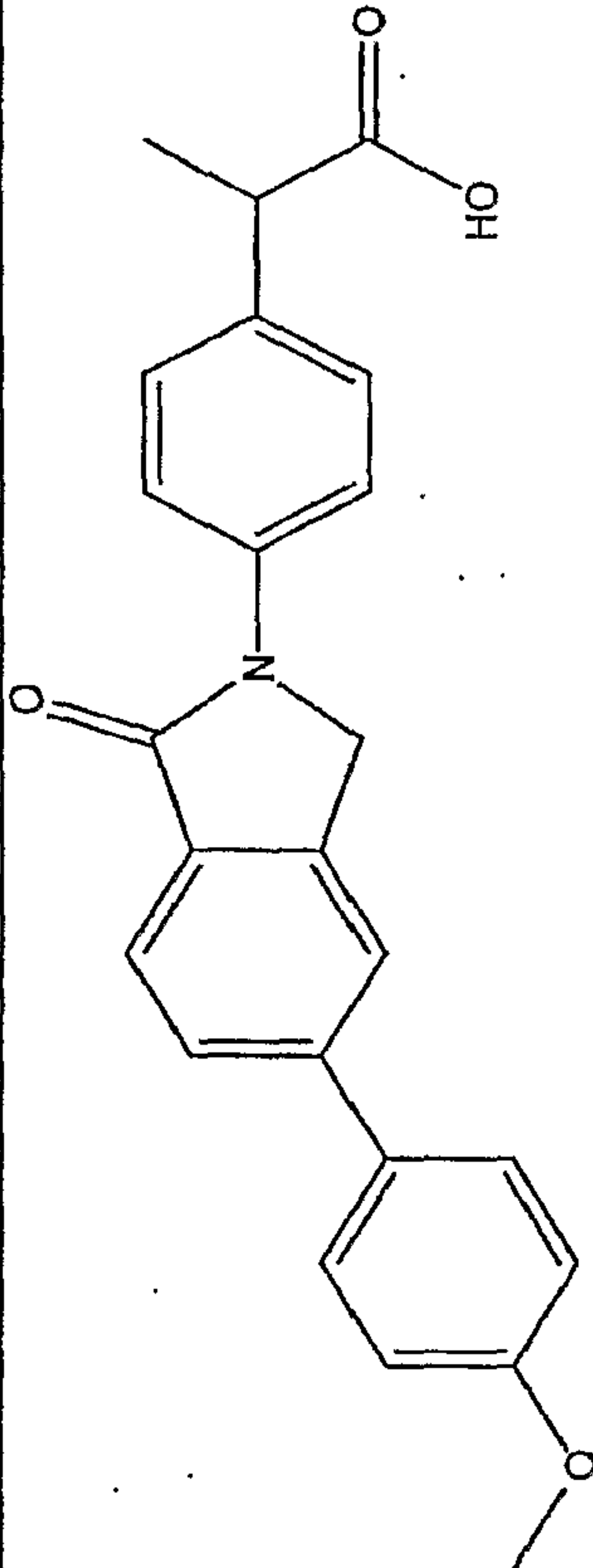
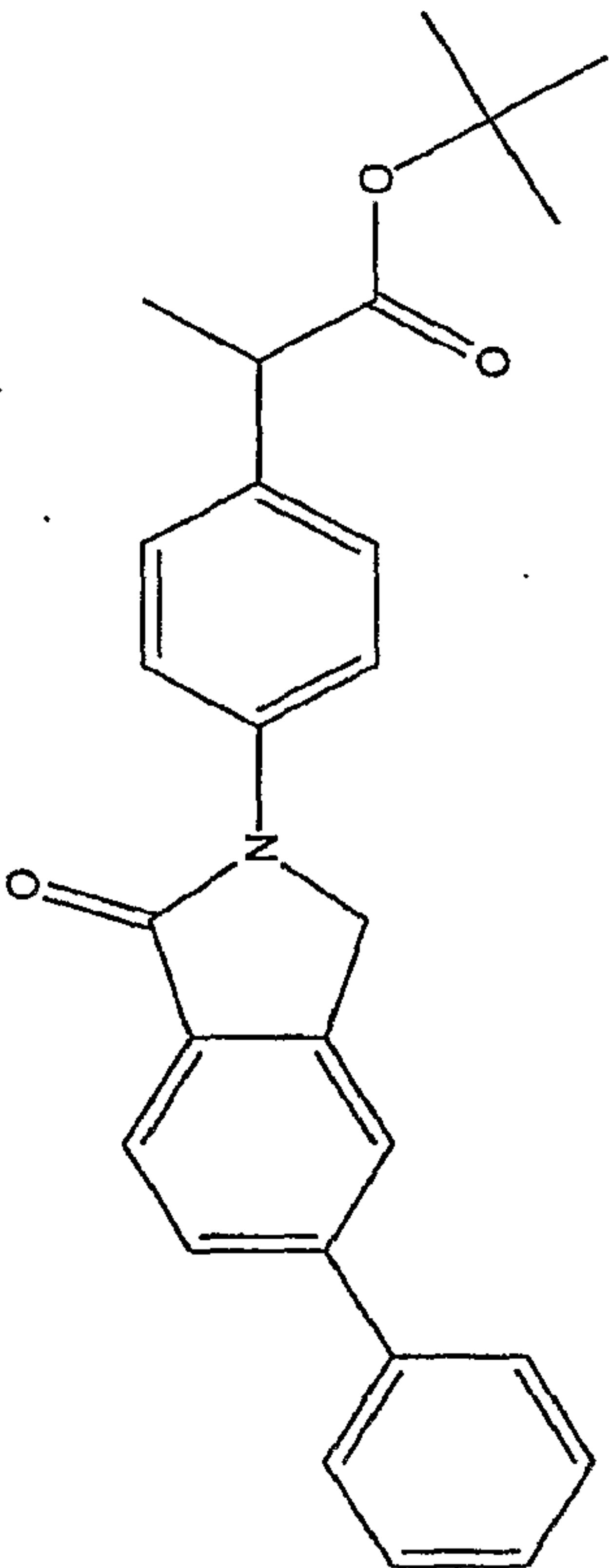
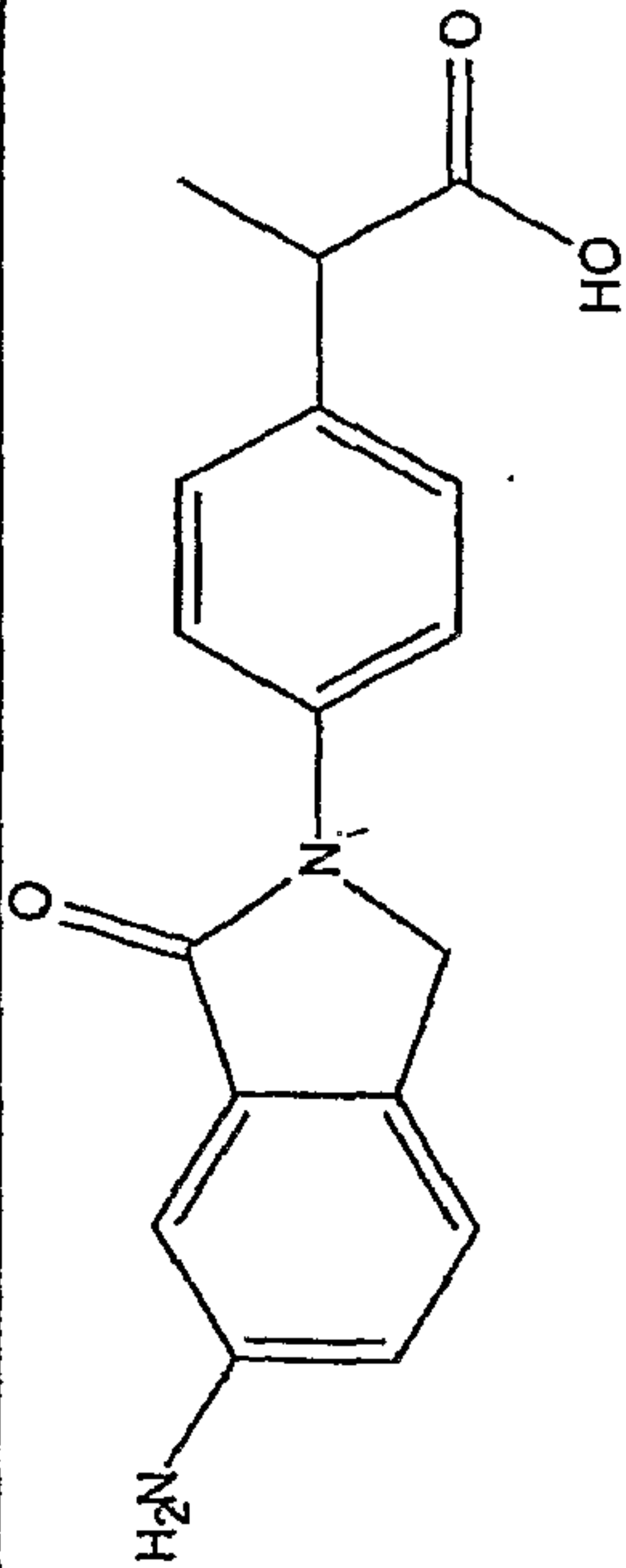
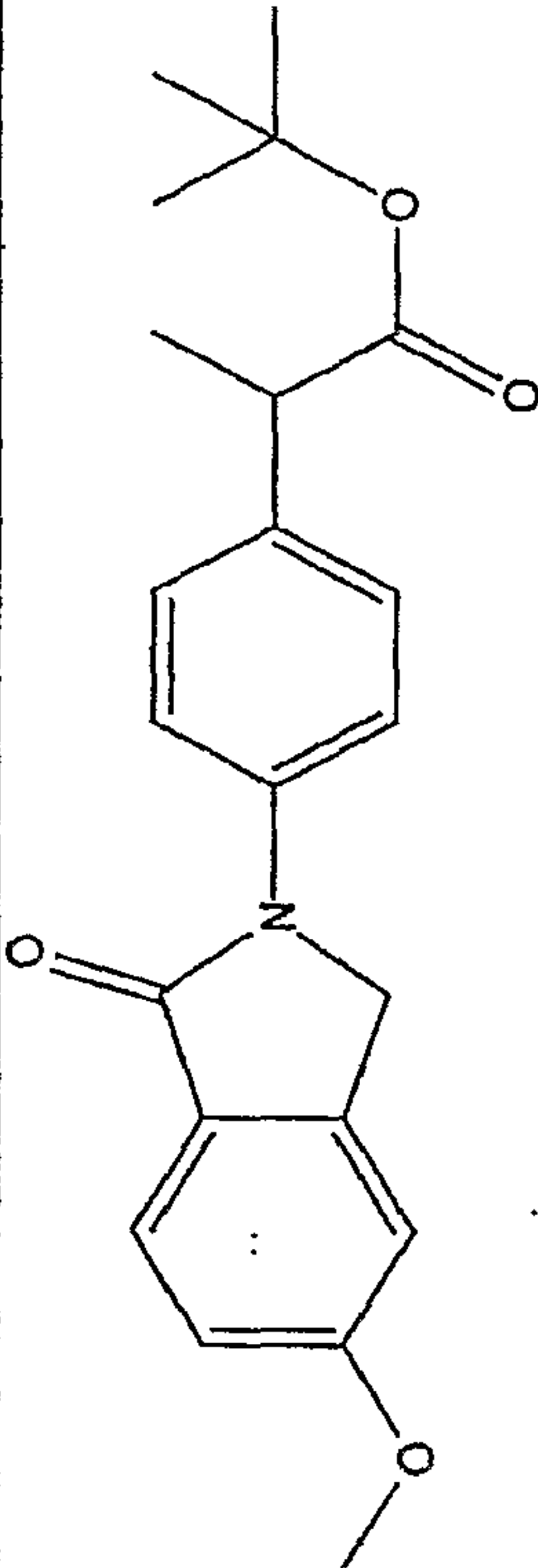
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
37		ALB- 111890	7.74	1.161
38		ALB- 111891	8.88	1.314

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
39		ALB- 111892	4.307	1.459
40		ALB- 111888		1.105

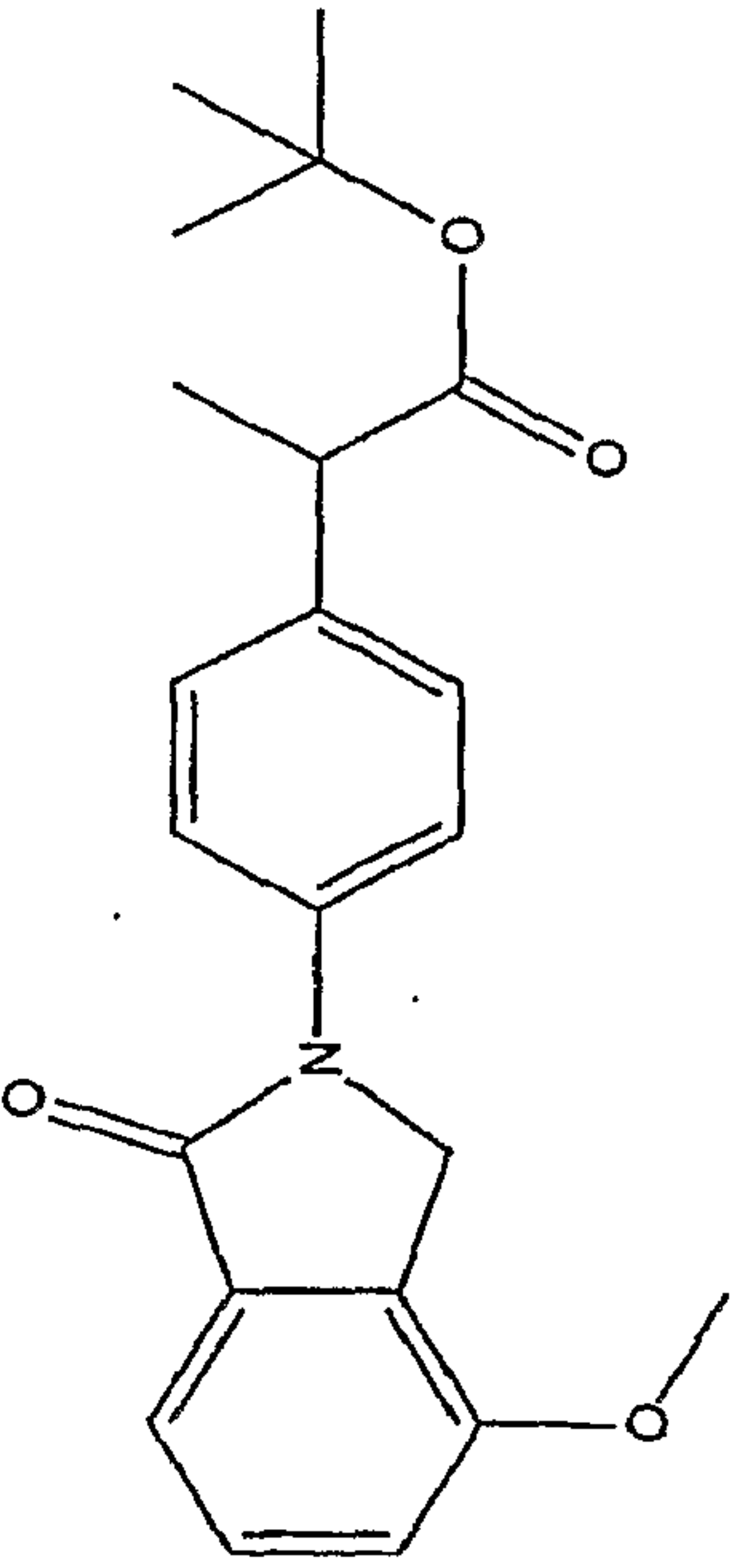
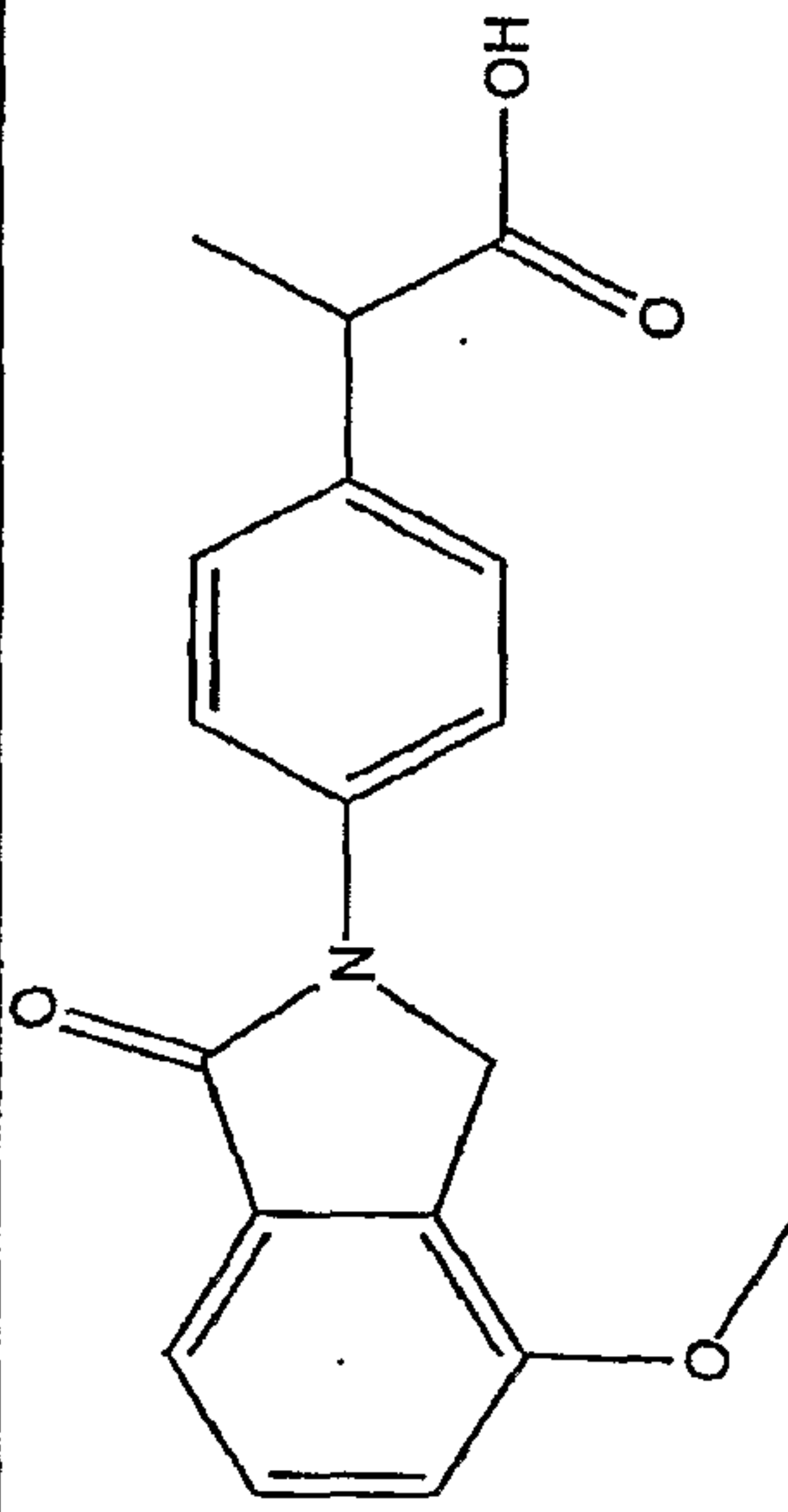
47

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
41		ALB- 111883a	1.257	1.173
42		ALB- 111893		1.091

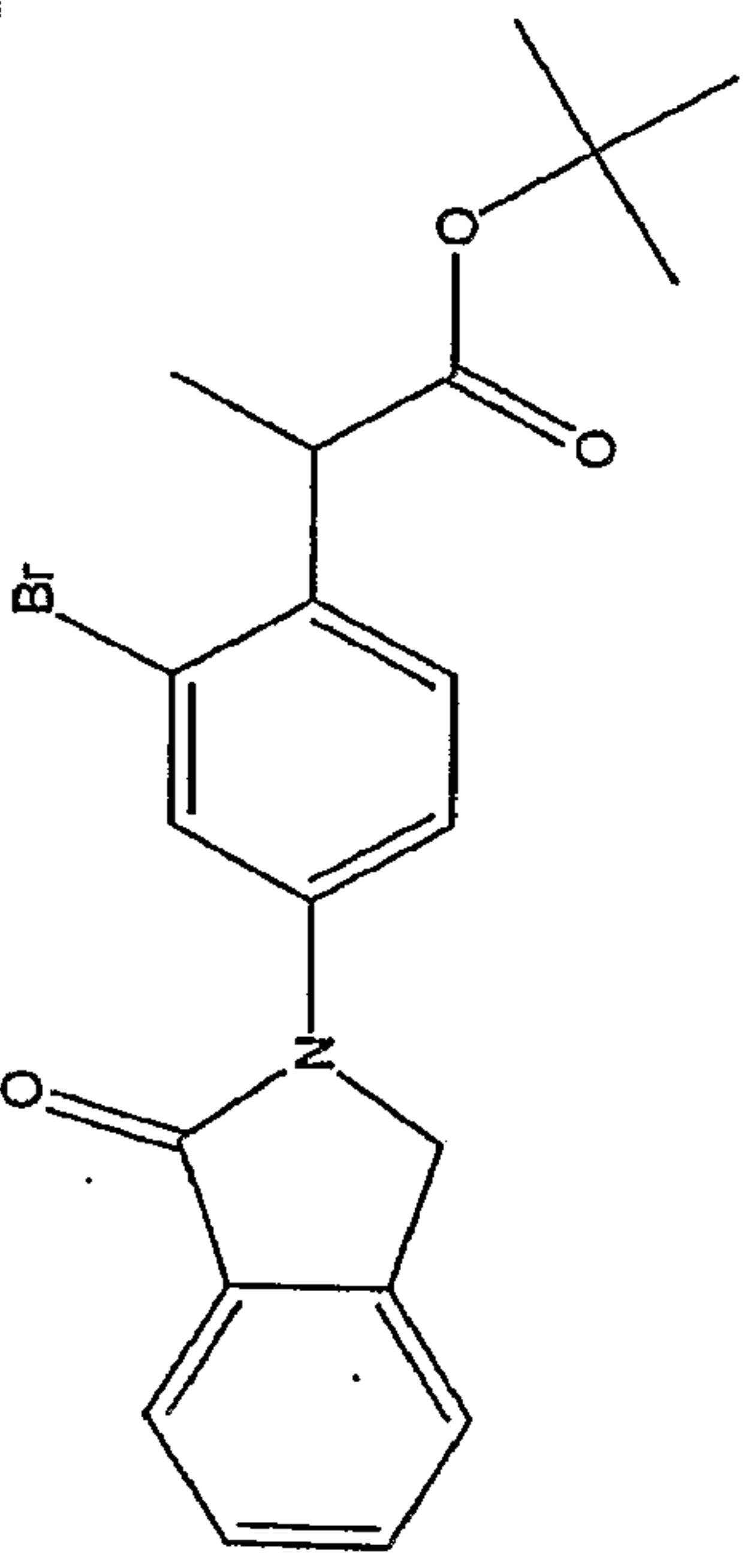
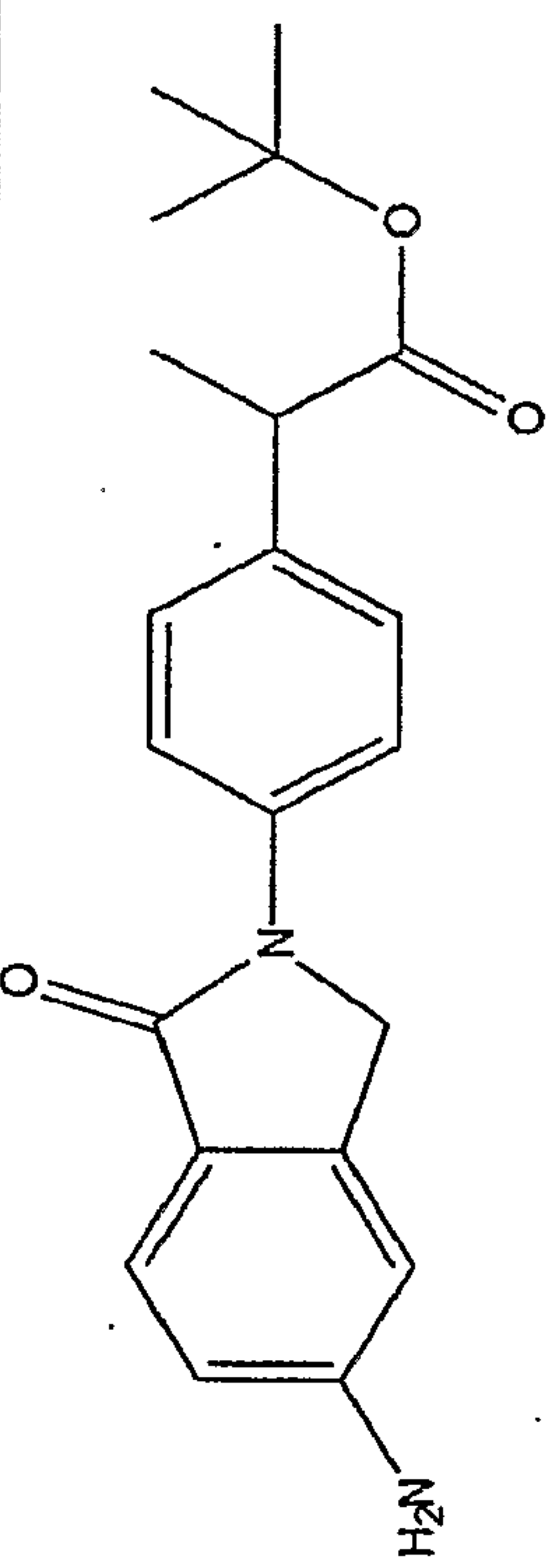
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
43		ALB- 111894	3.163	1.289
44		ALB- 111895		1.152

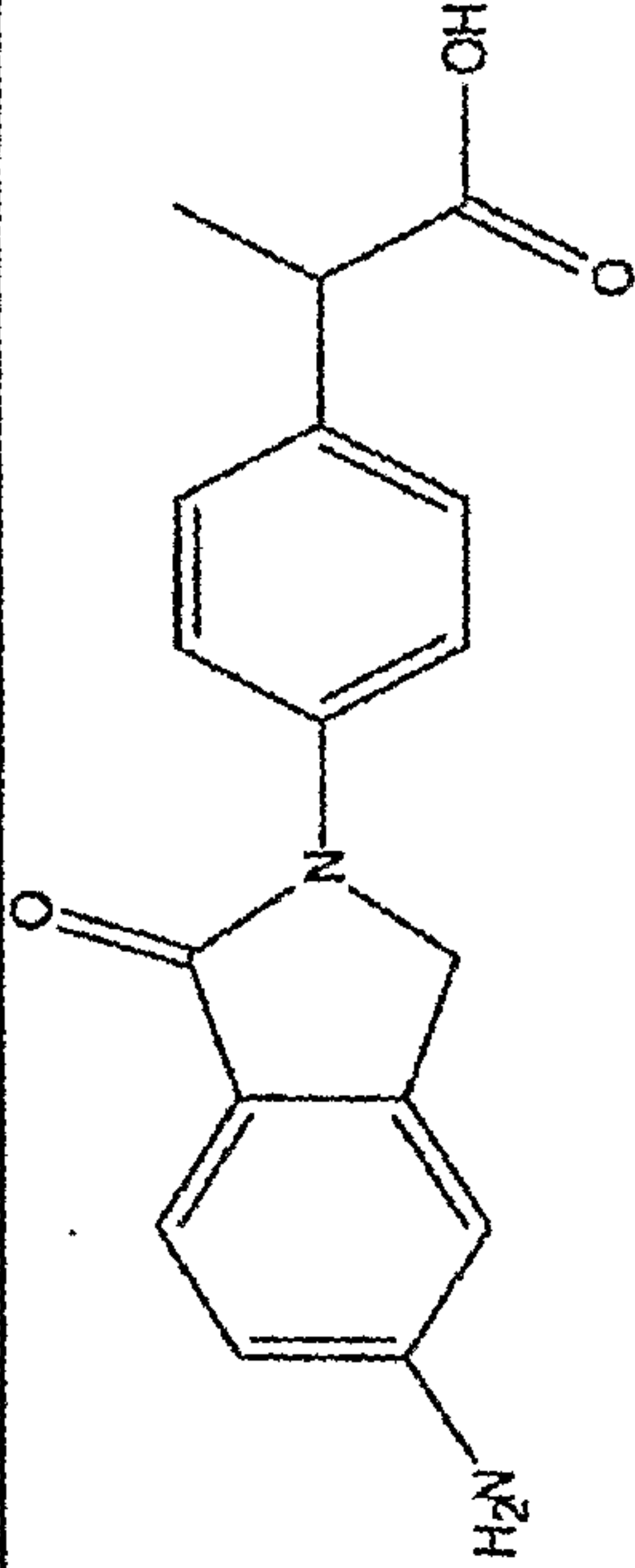
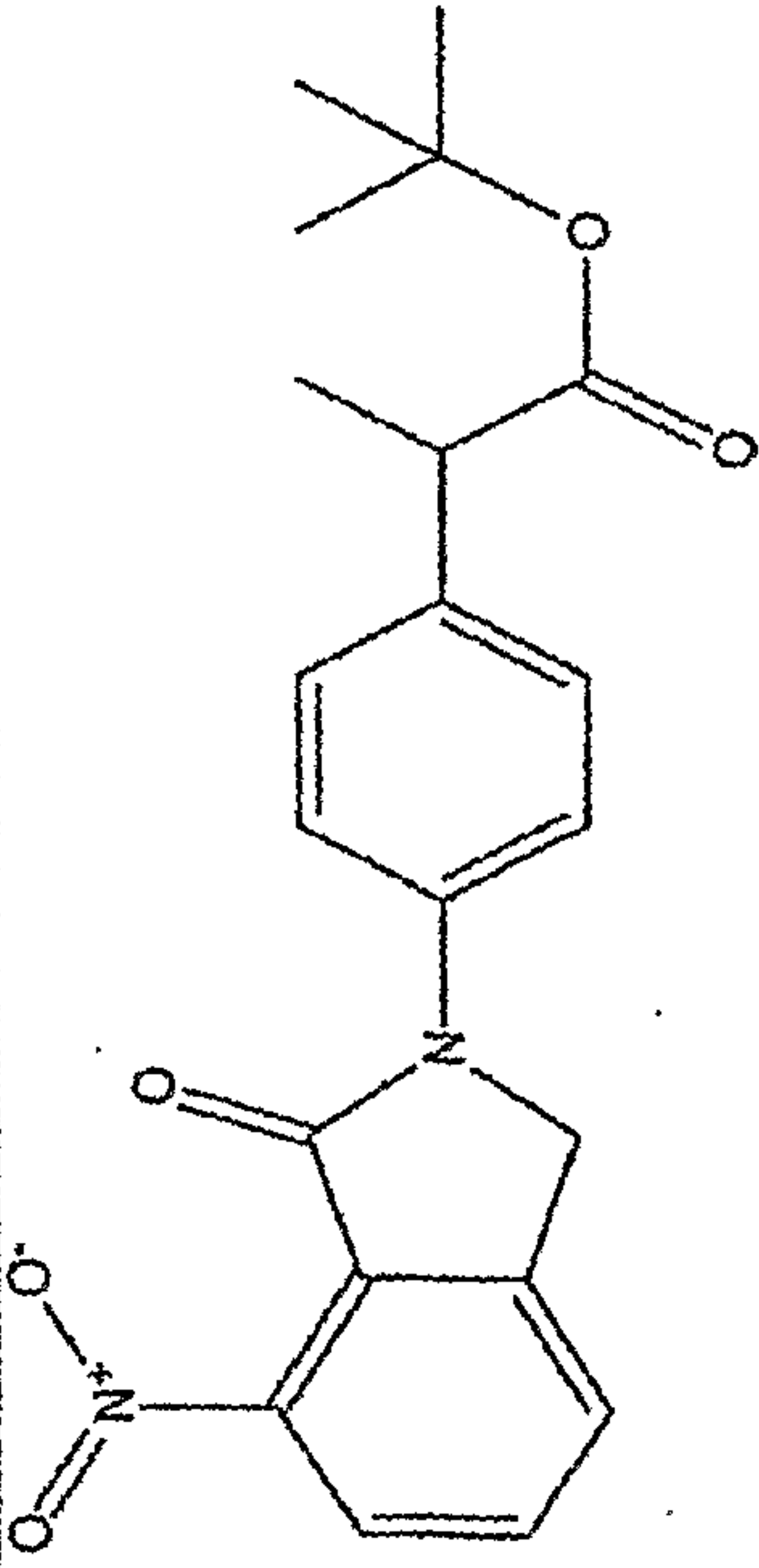
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
45		ALB- 111882	2.831	1.235
46		ALB- 111949	5.221	1.286

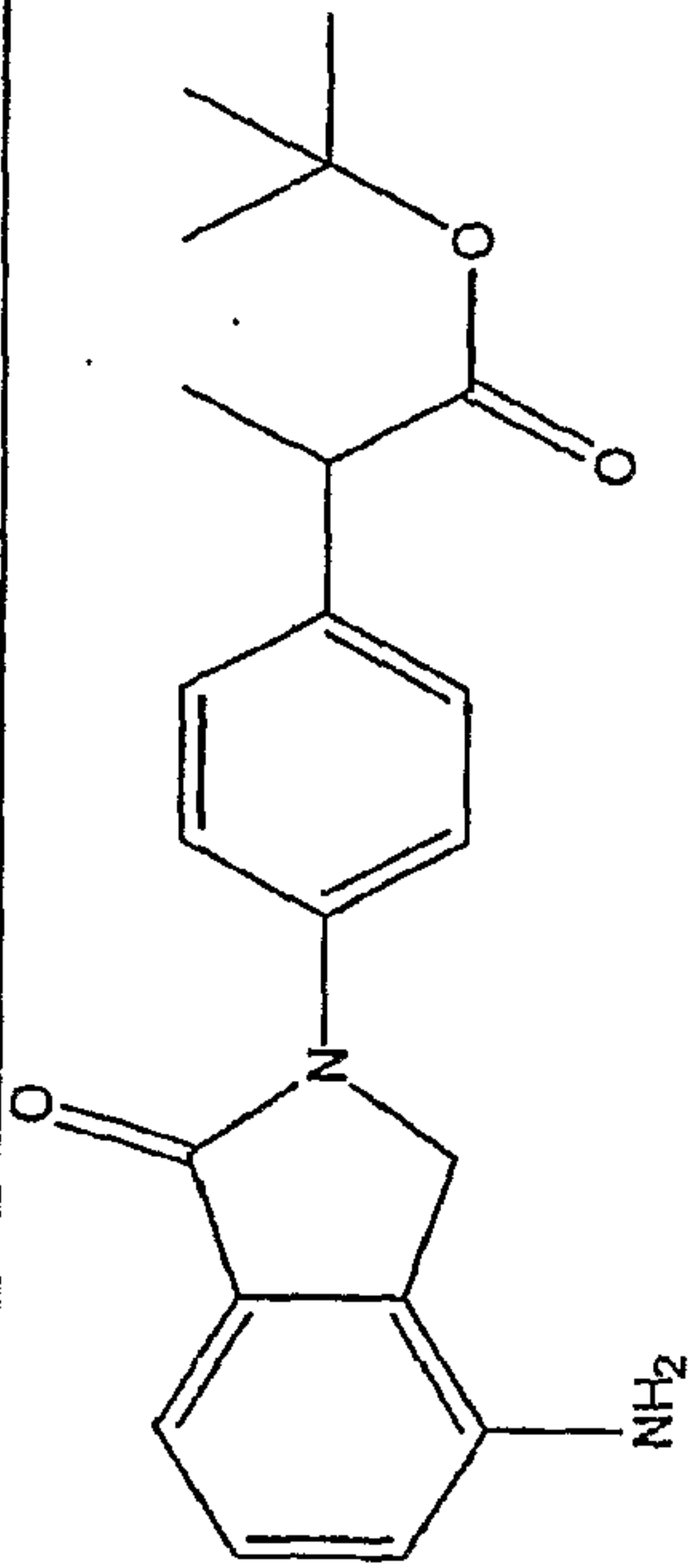
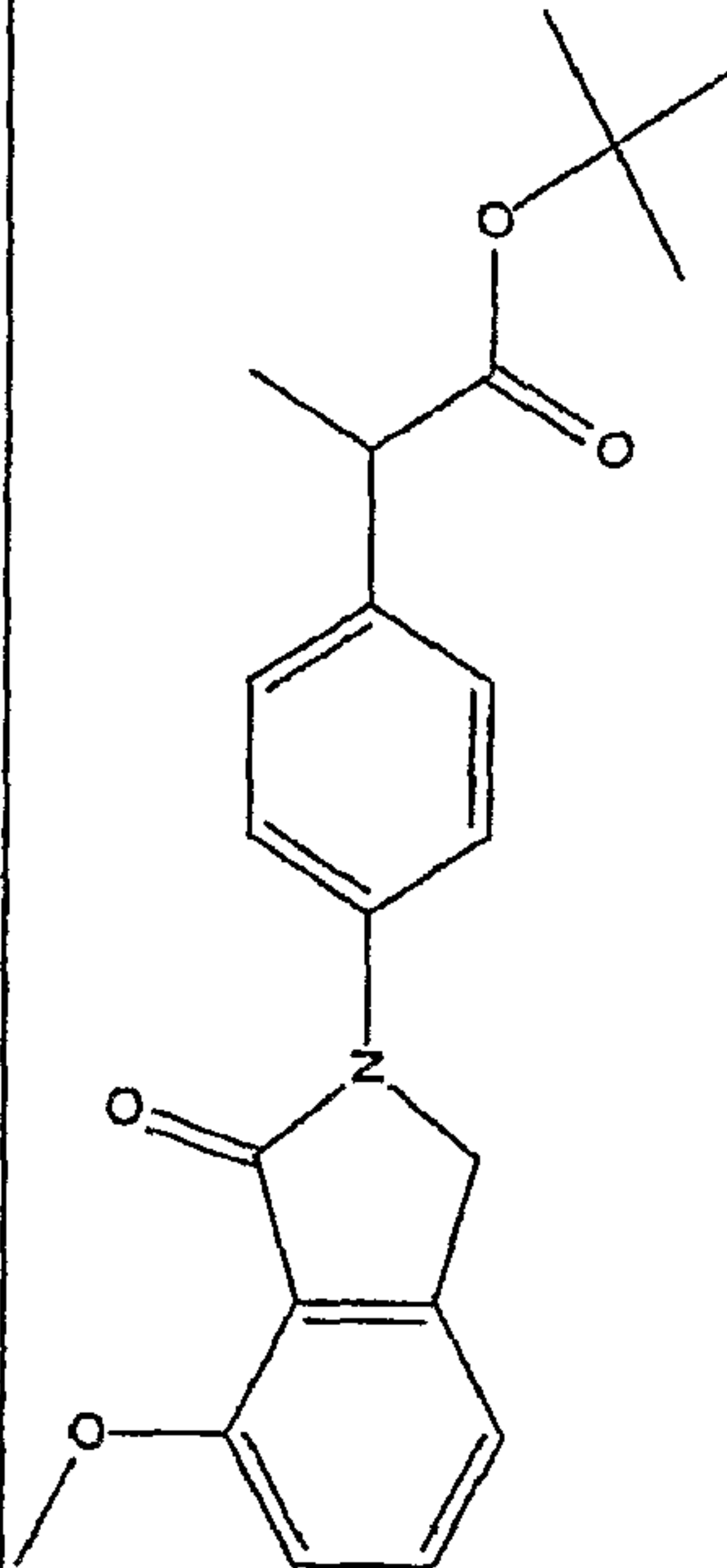
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
47		ALB- 111950a		1.072
48		ALB- 111951		1.199

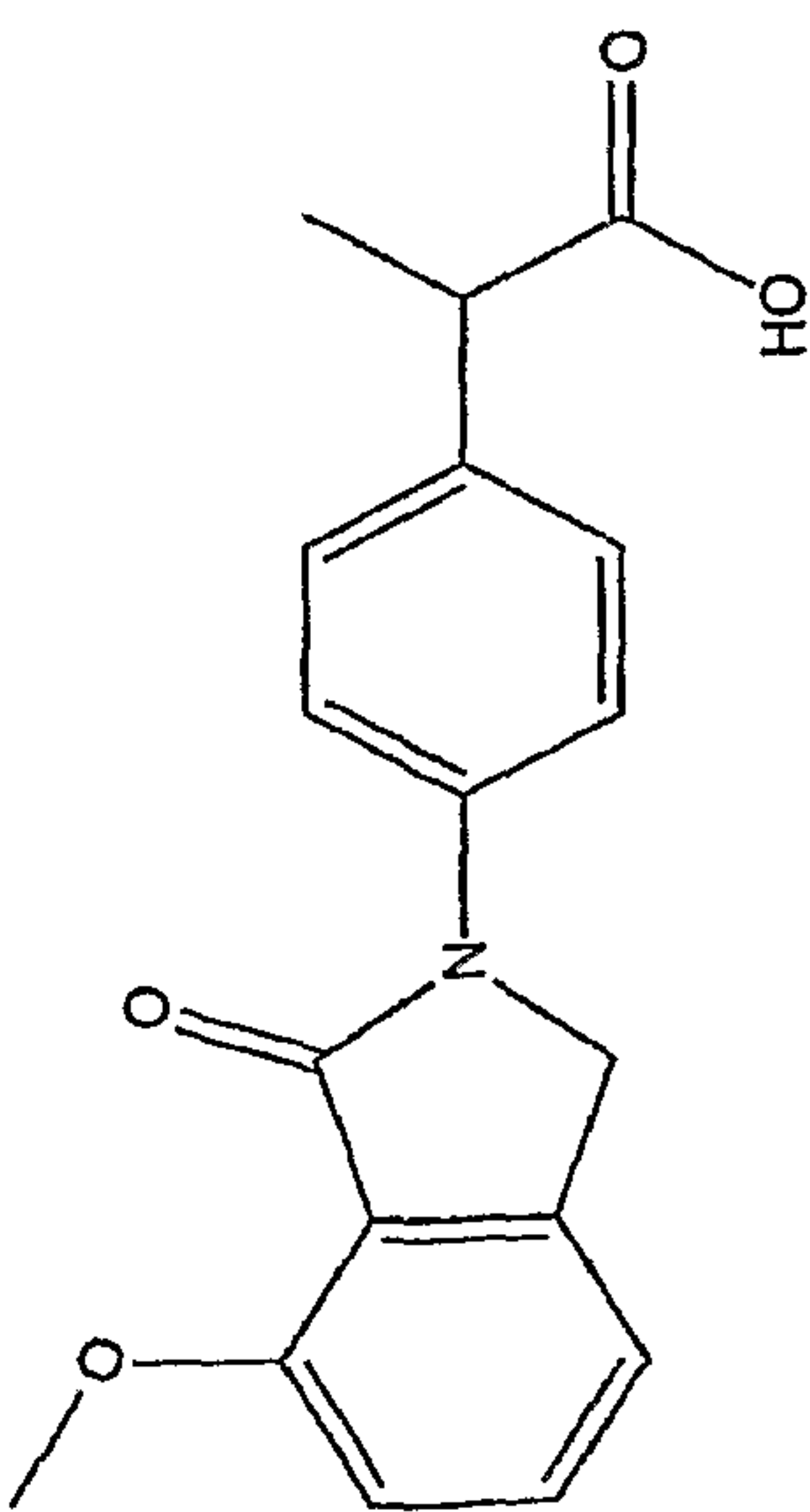
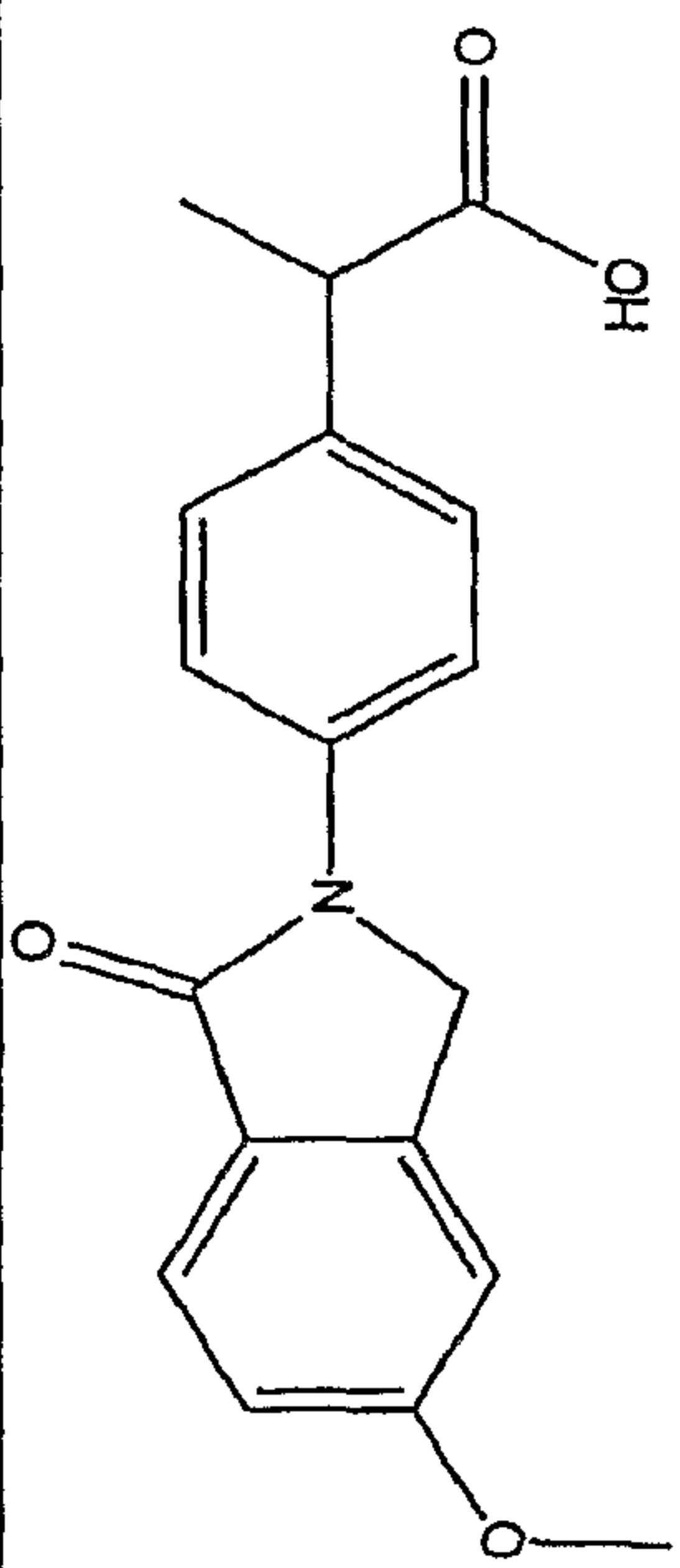
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
49		ALB- 111952		1.039
50		ALB- 111955	0.396	1.076

52

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
51		ALB- 111957		1.233
52		ALB- 111959	0.451	1.264

53

Table 1

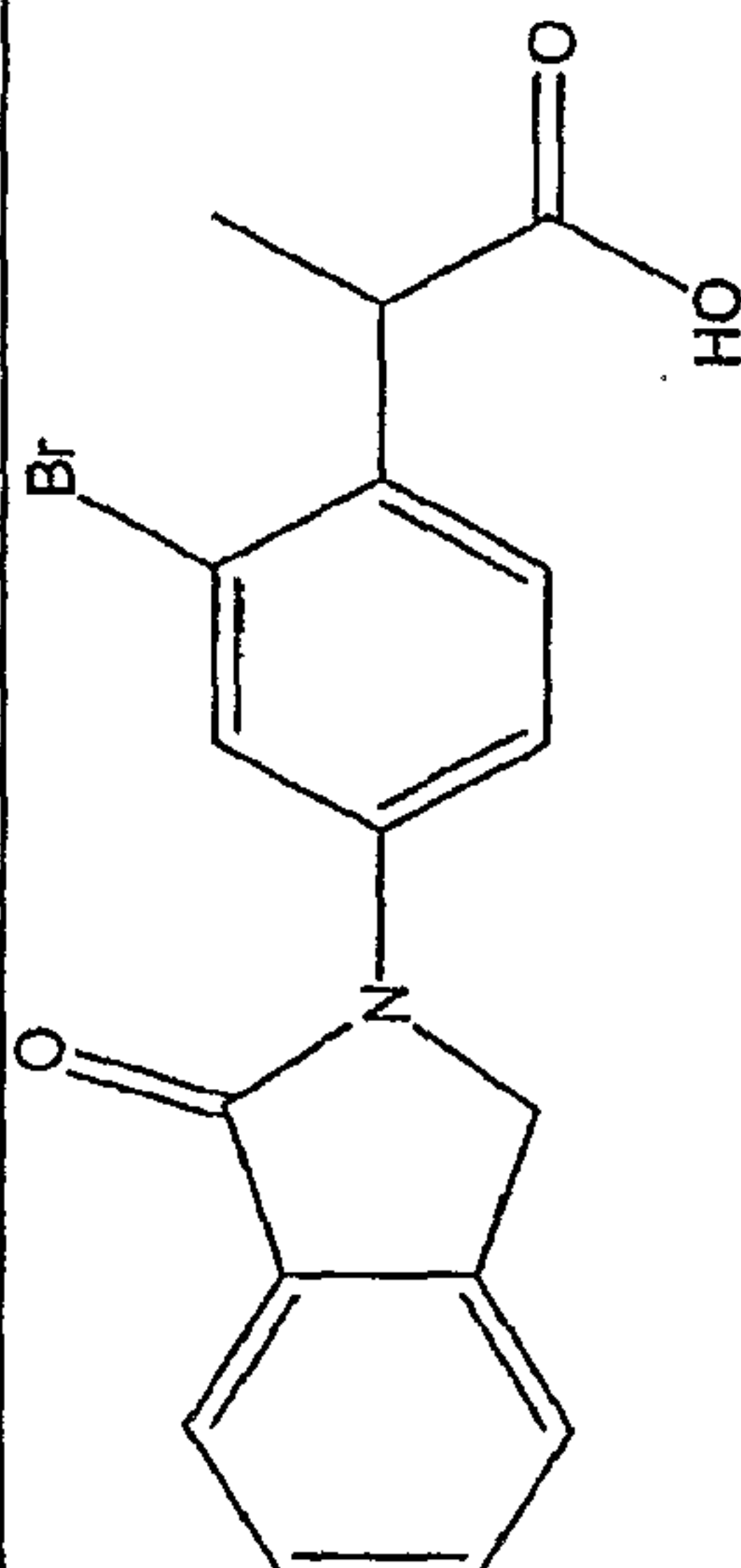
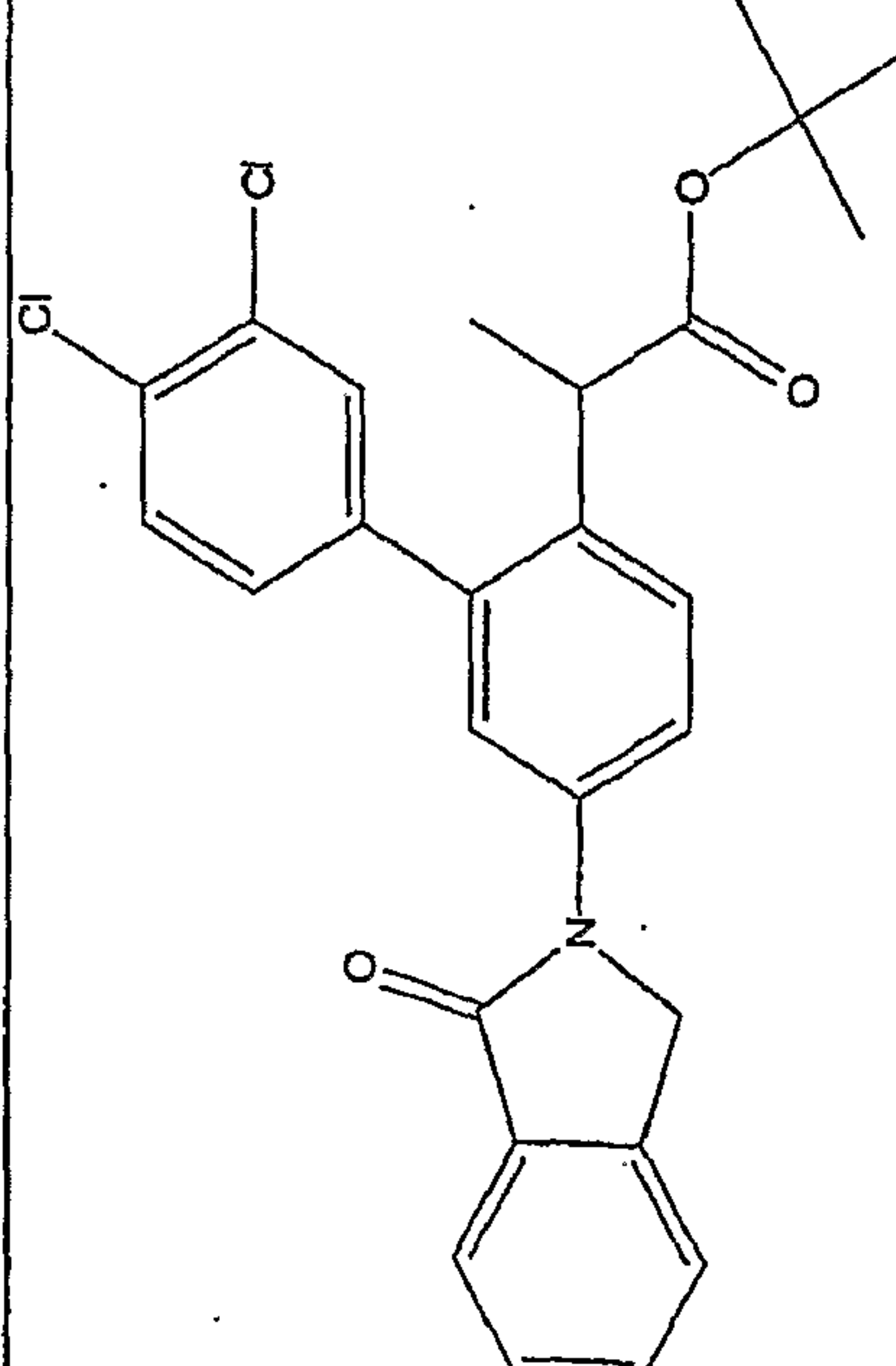
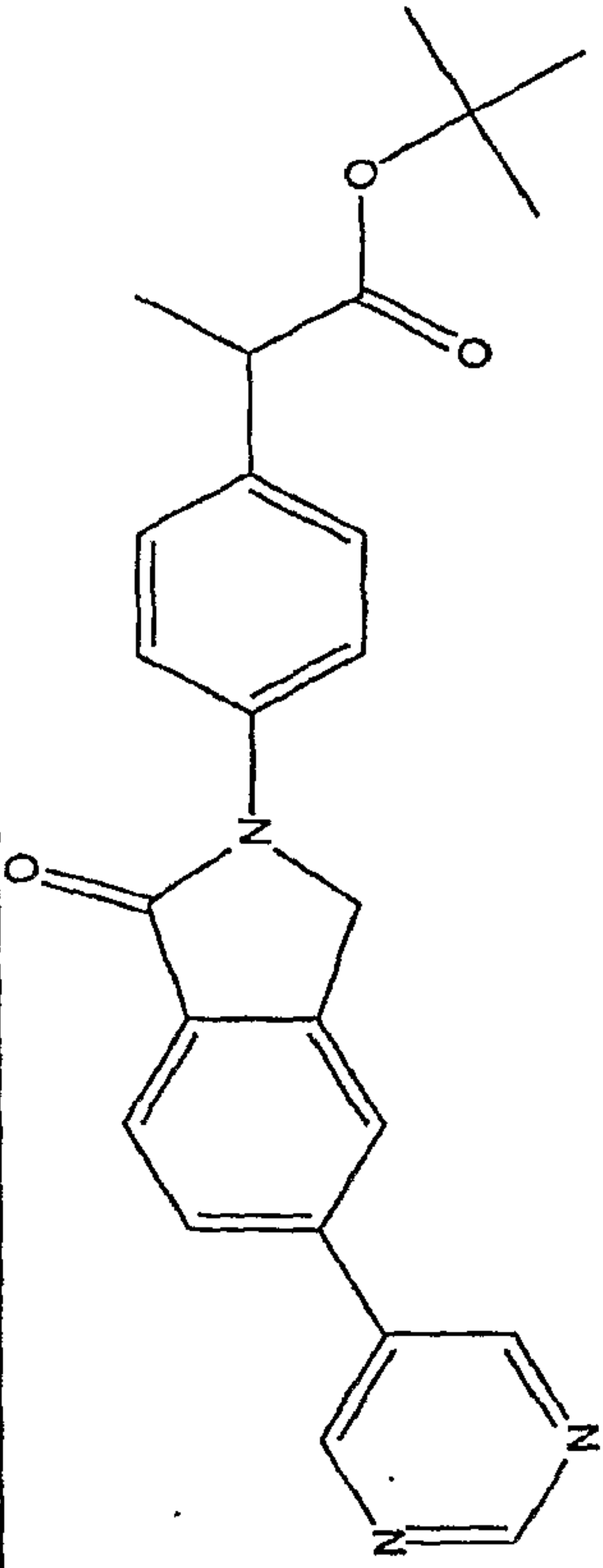
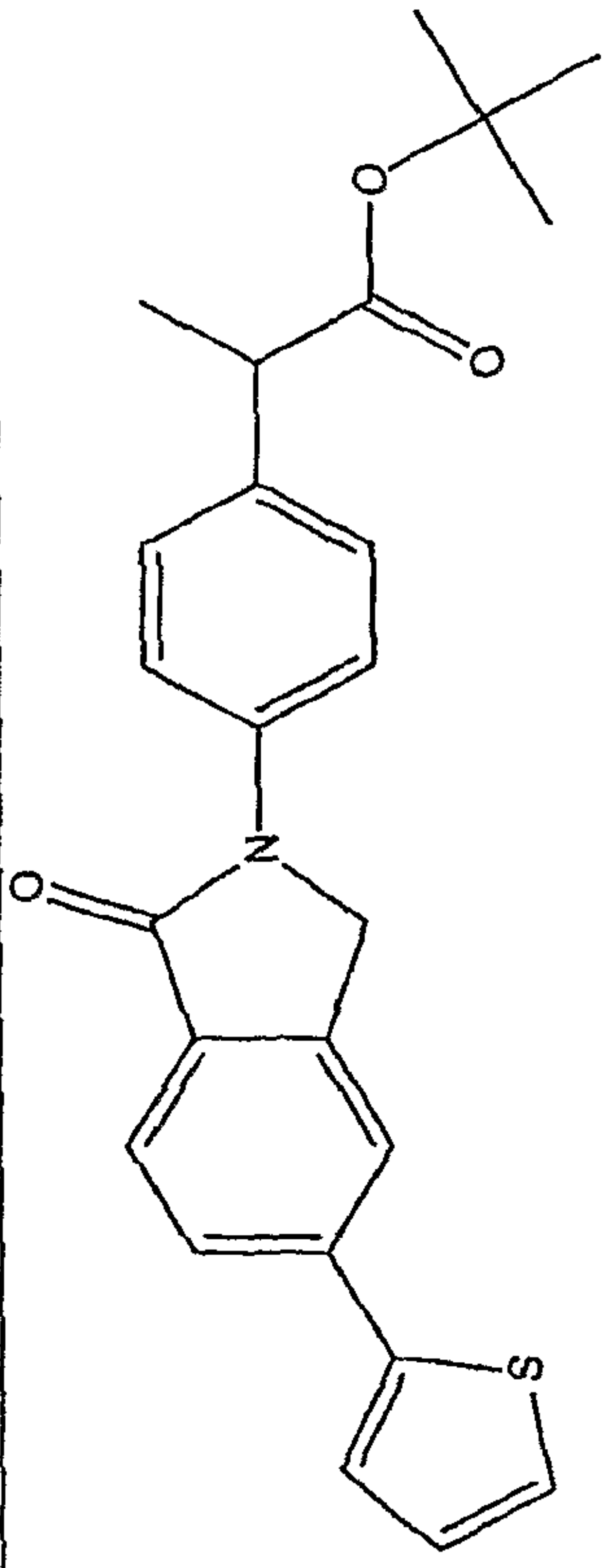
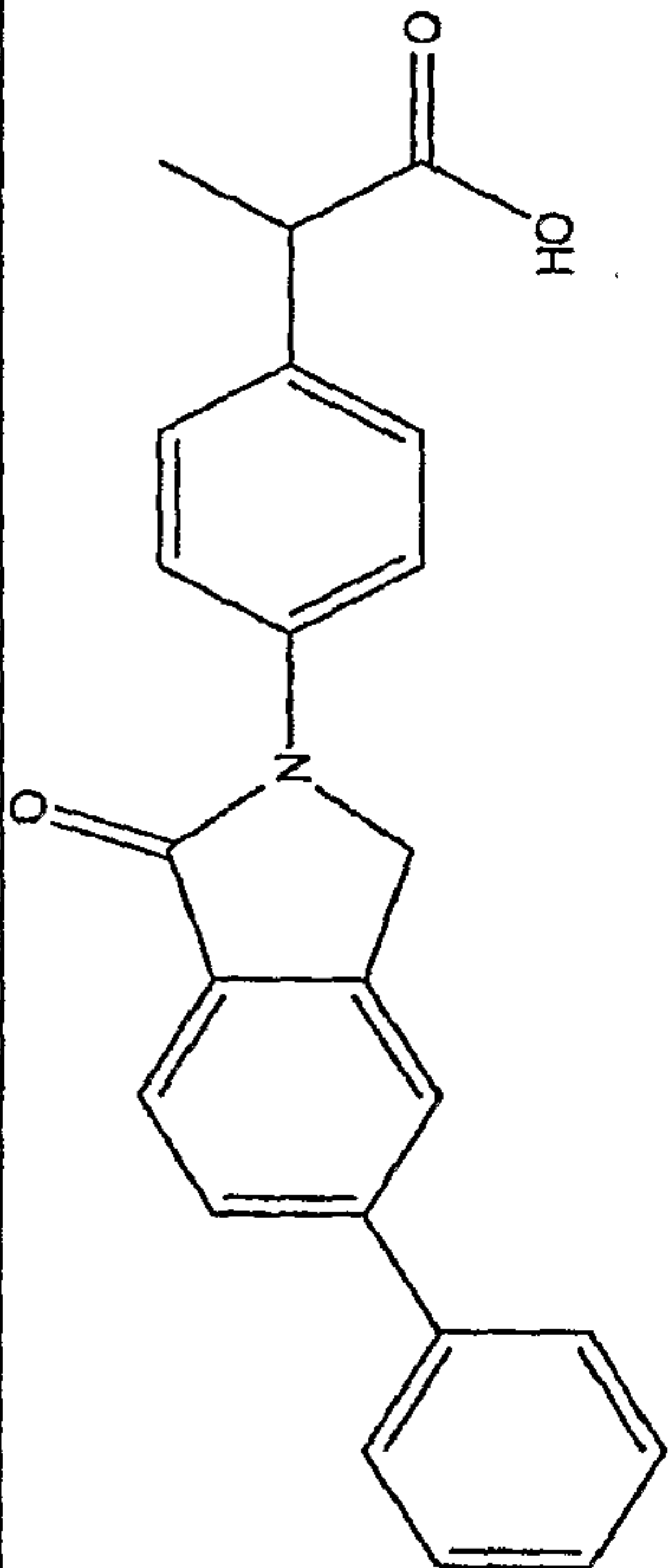
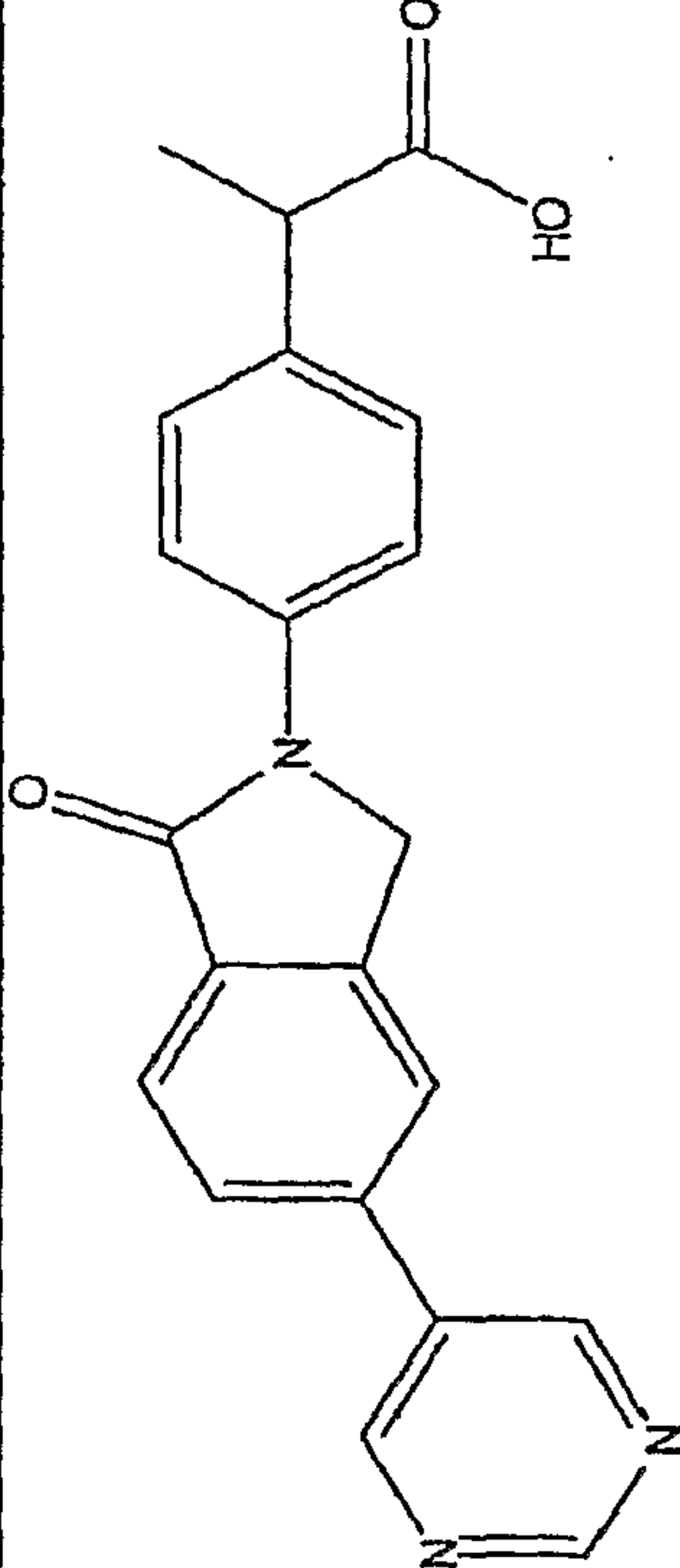
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			Avg EC50 (μ M)	Avg MaxFold Increase
53		ALB- 111962		1.084
54		ALB- 111963		1.025

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
55		ALB- 111991		1.087
56		ALB- 111992		1.012

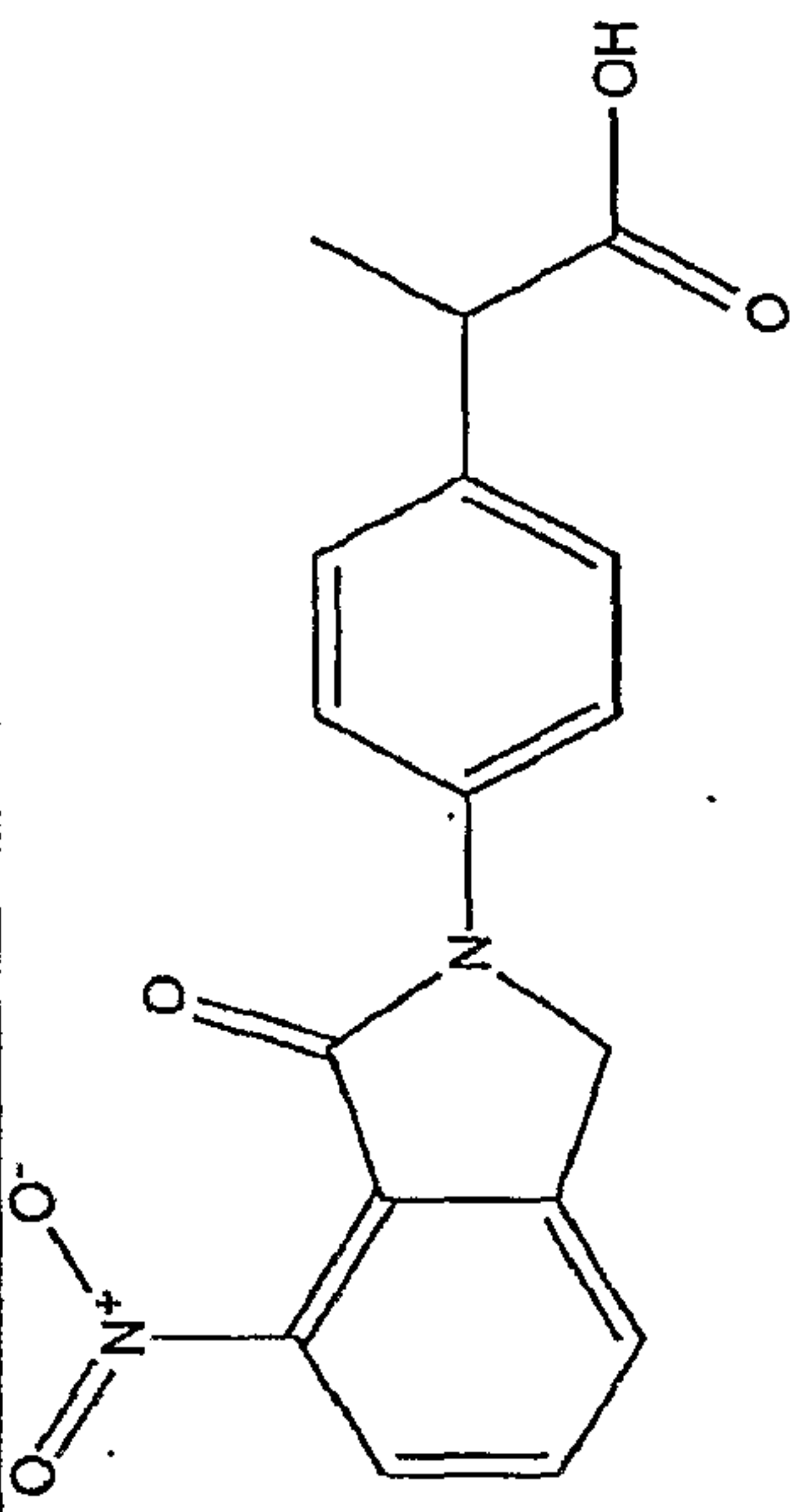
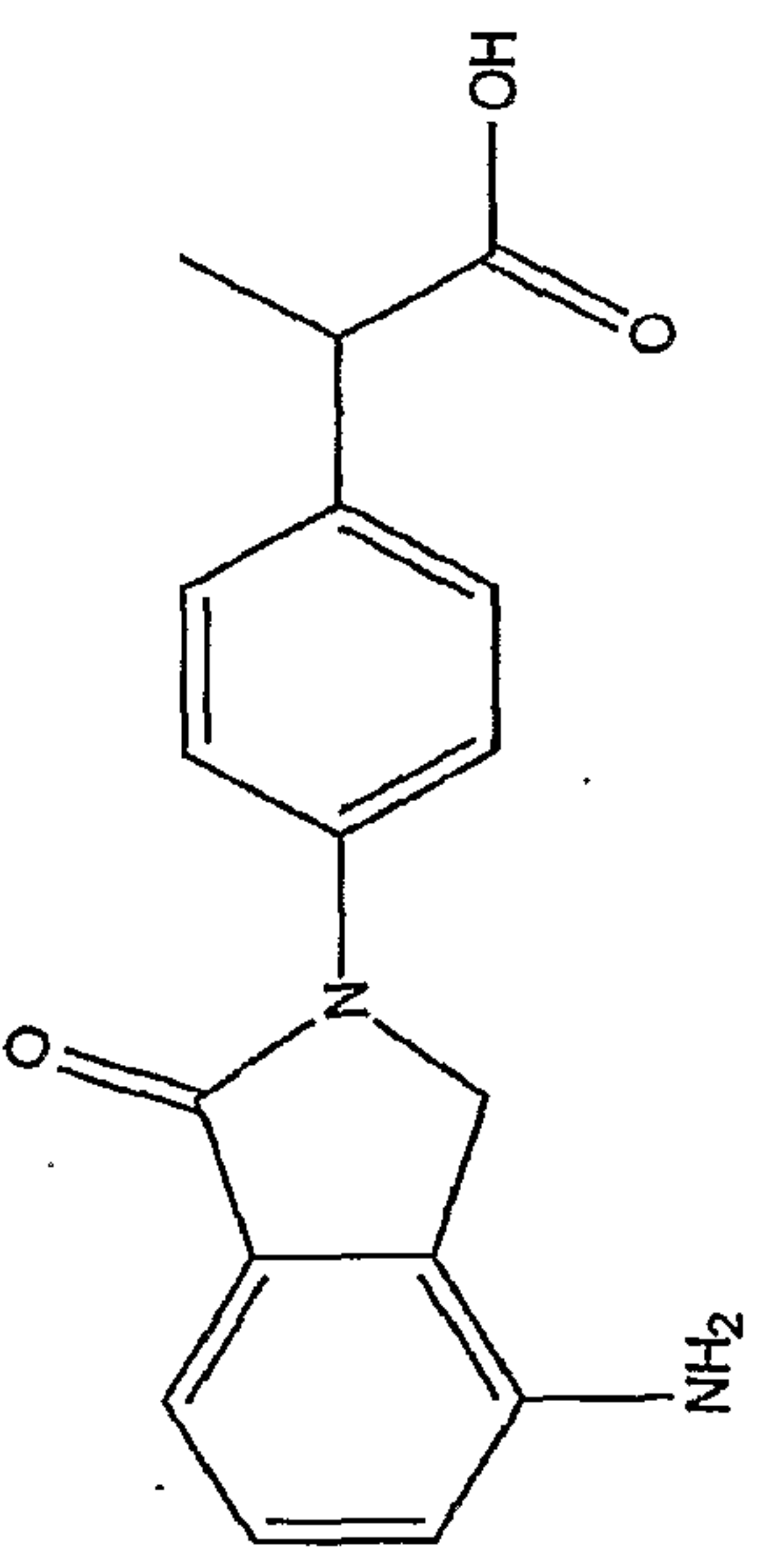
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
57		ALB- 111993	2.948	1.544
58		ALB- 111994	4.178	1.383

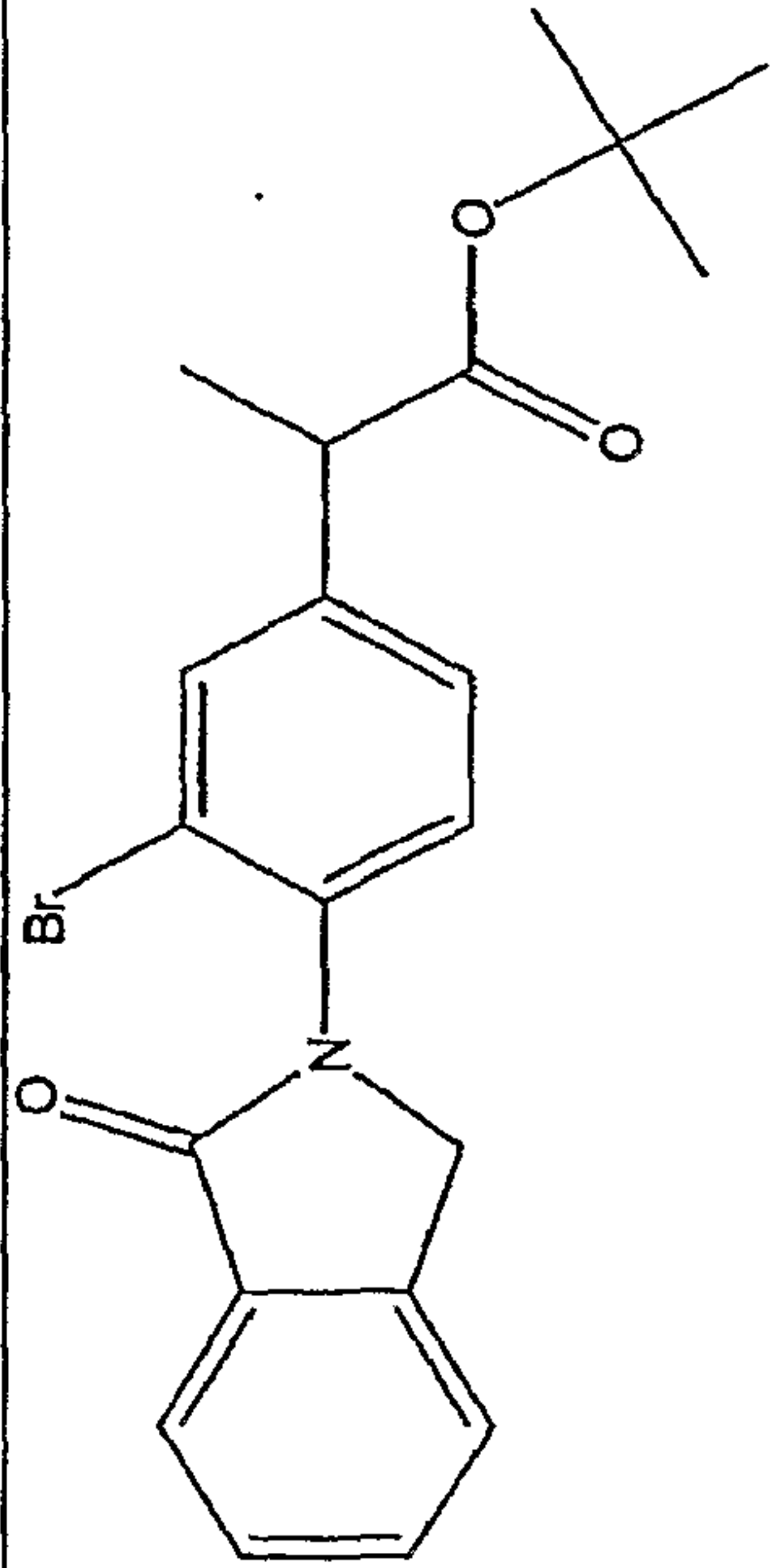
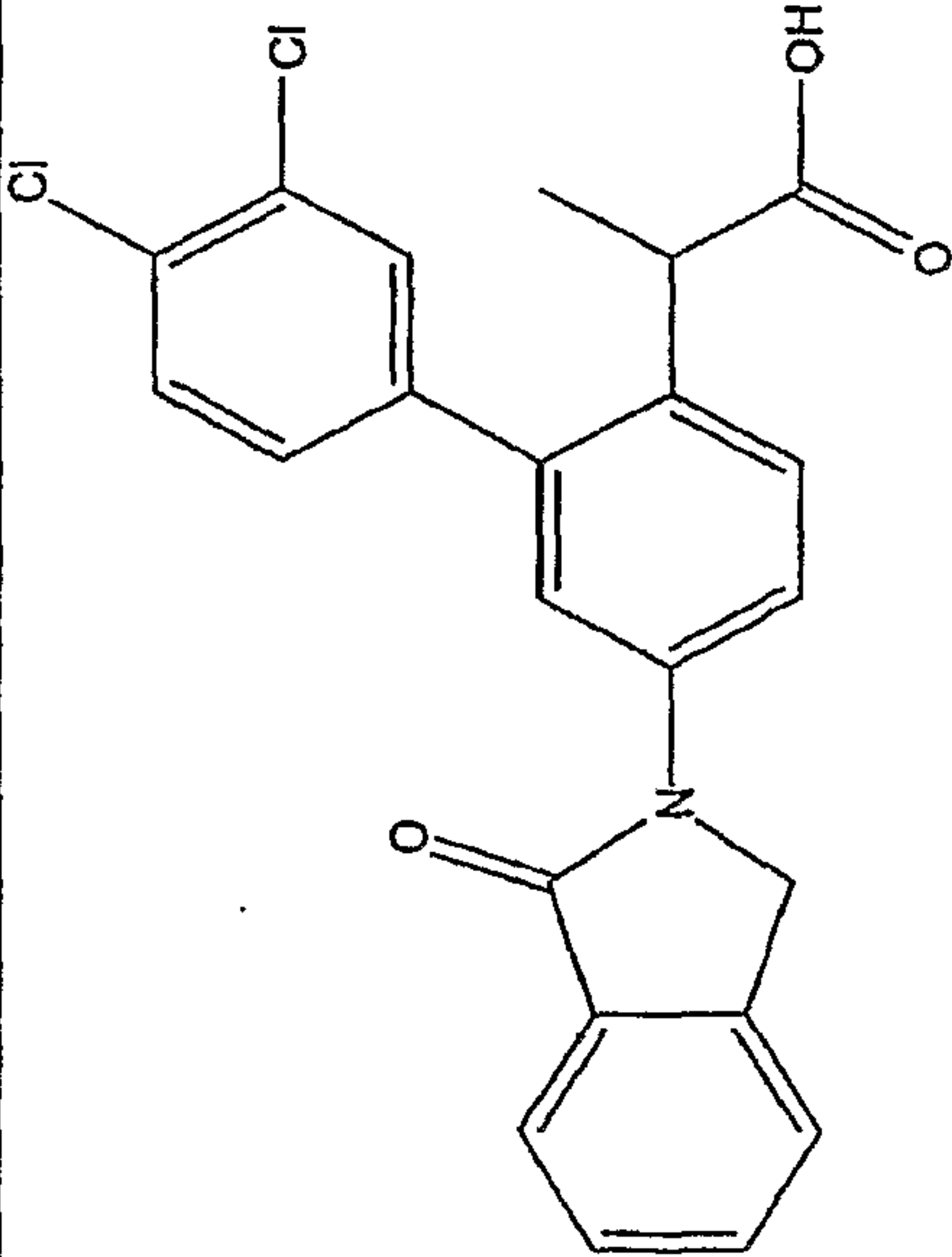
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
59		ALB- 111995	11.978	1.245
60		ALB- 111996a		1.107

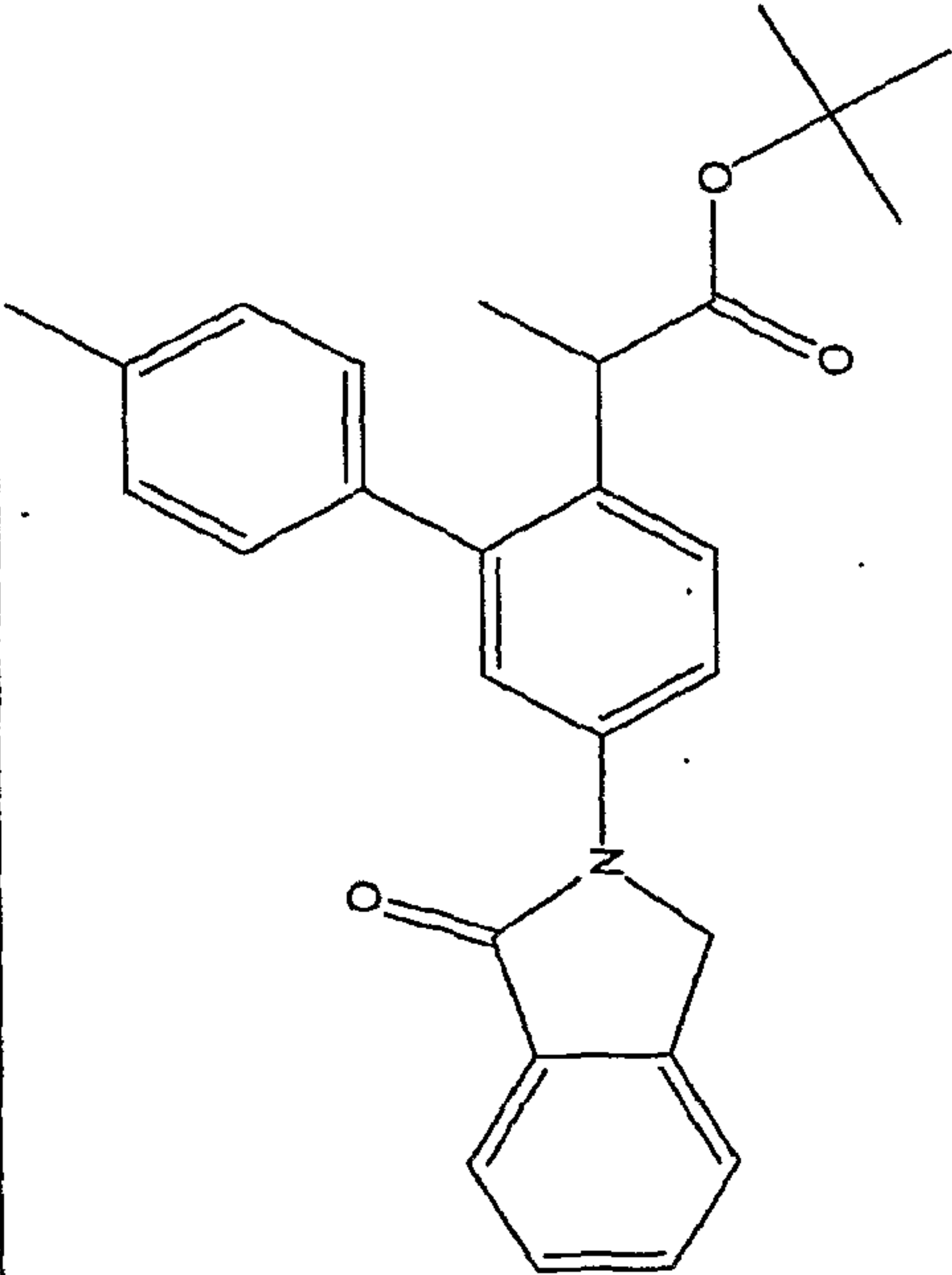
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
61		ALB- 111998		1.044
62		ALB- 111999		1.047

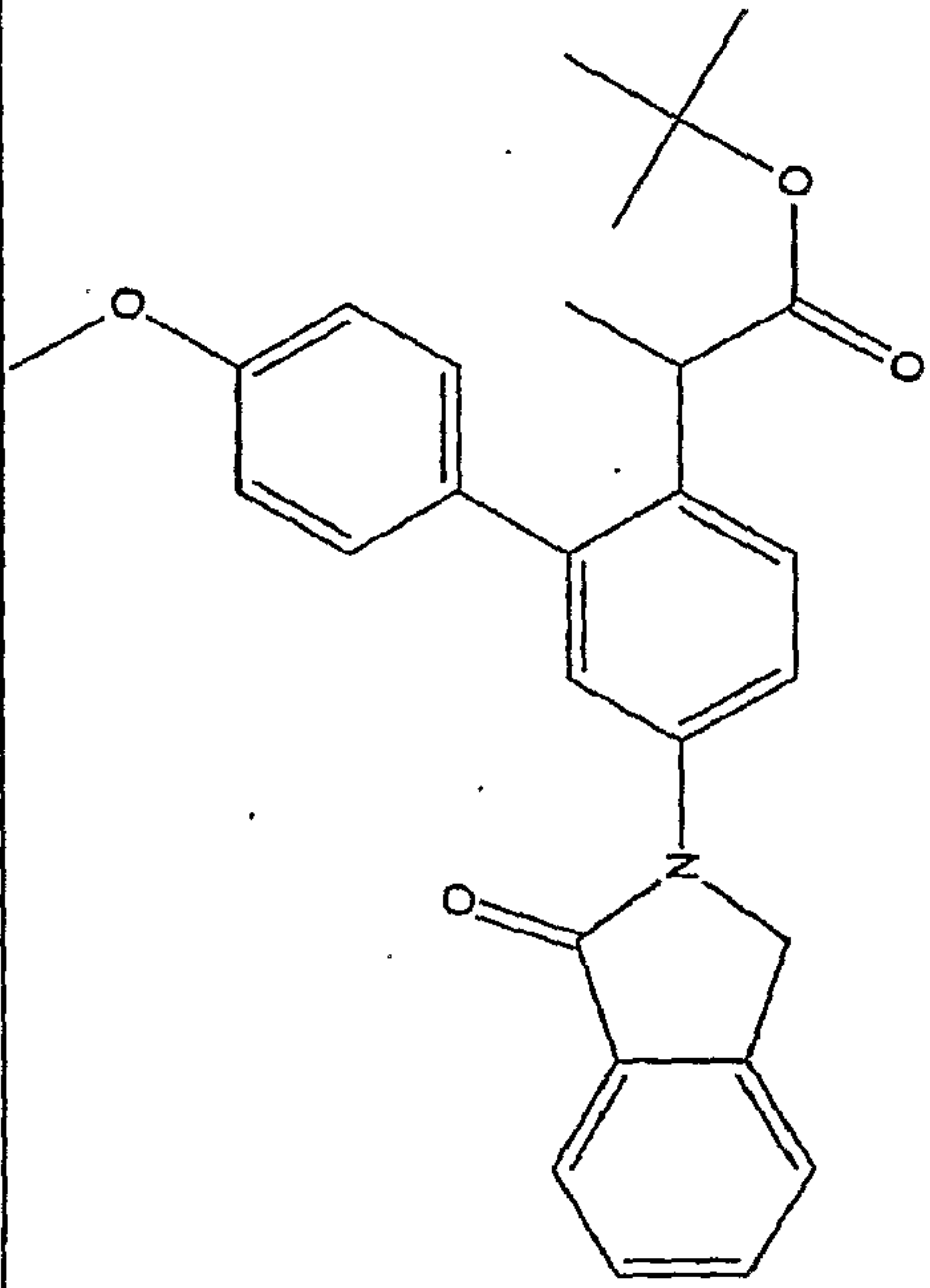
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
63		ALB- 112000		1.058

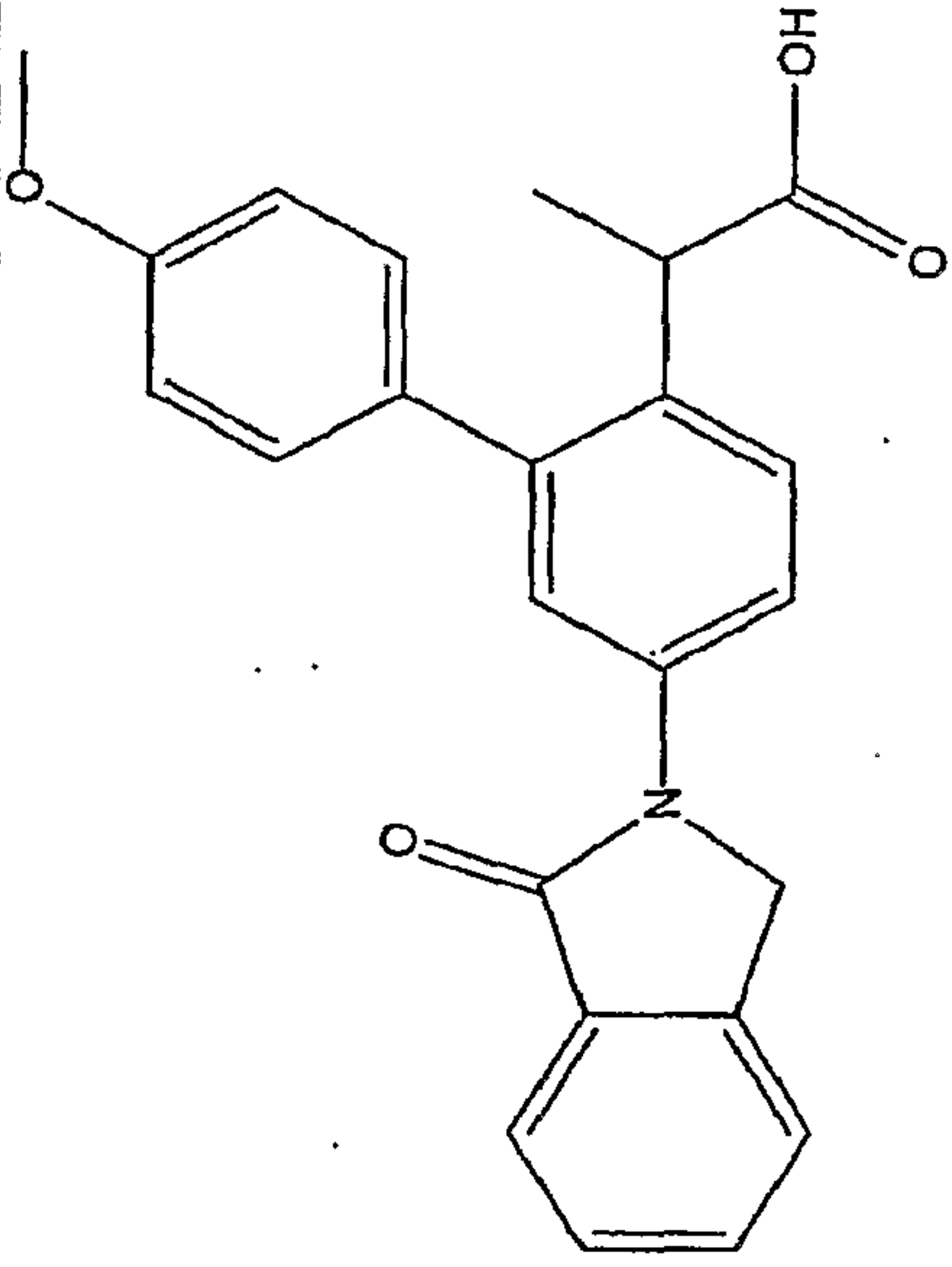
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
64		ALB- 112001		1.021

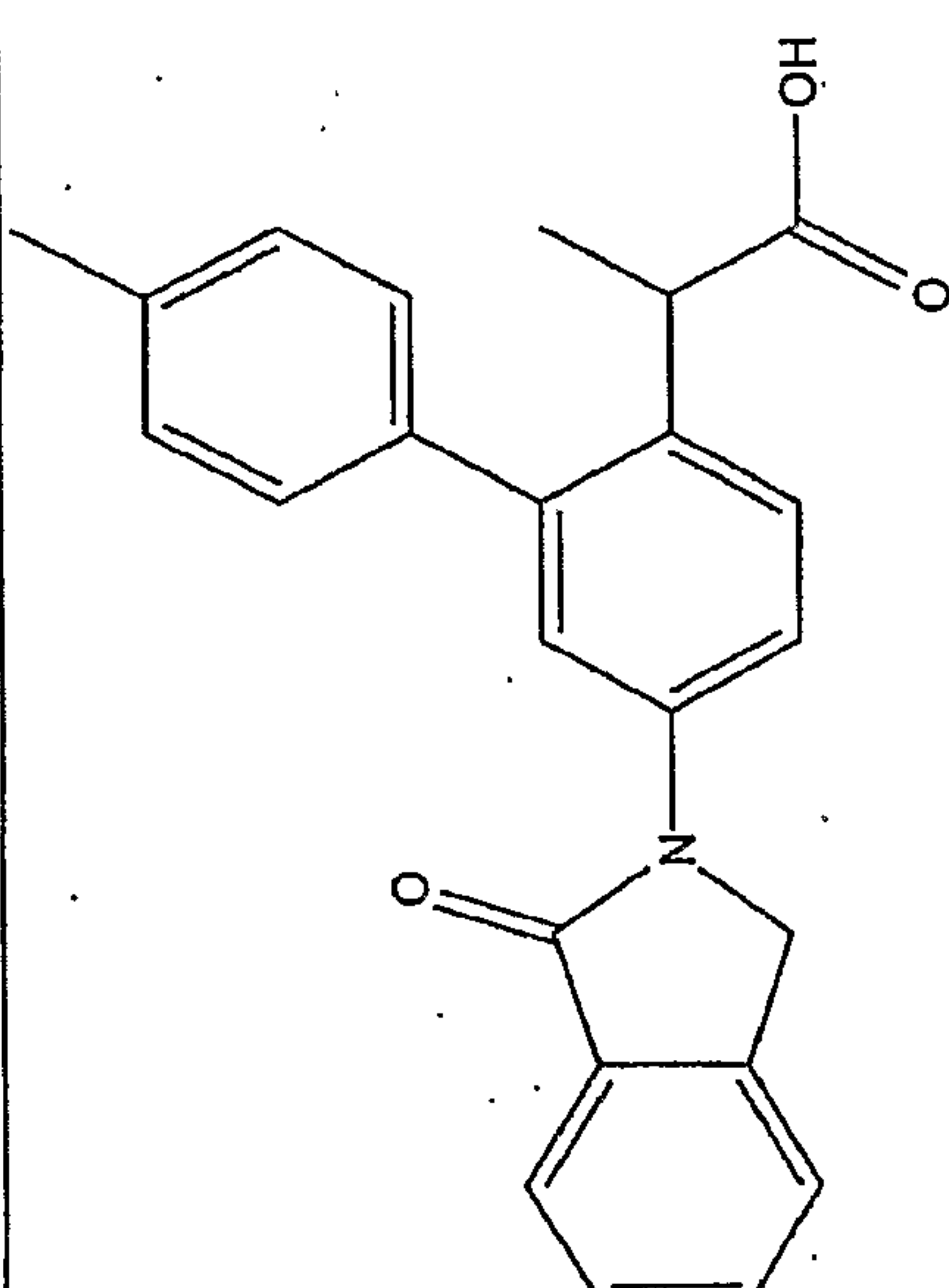
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
65		ALB- 112002		1.078

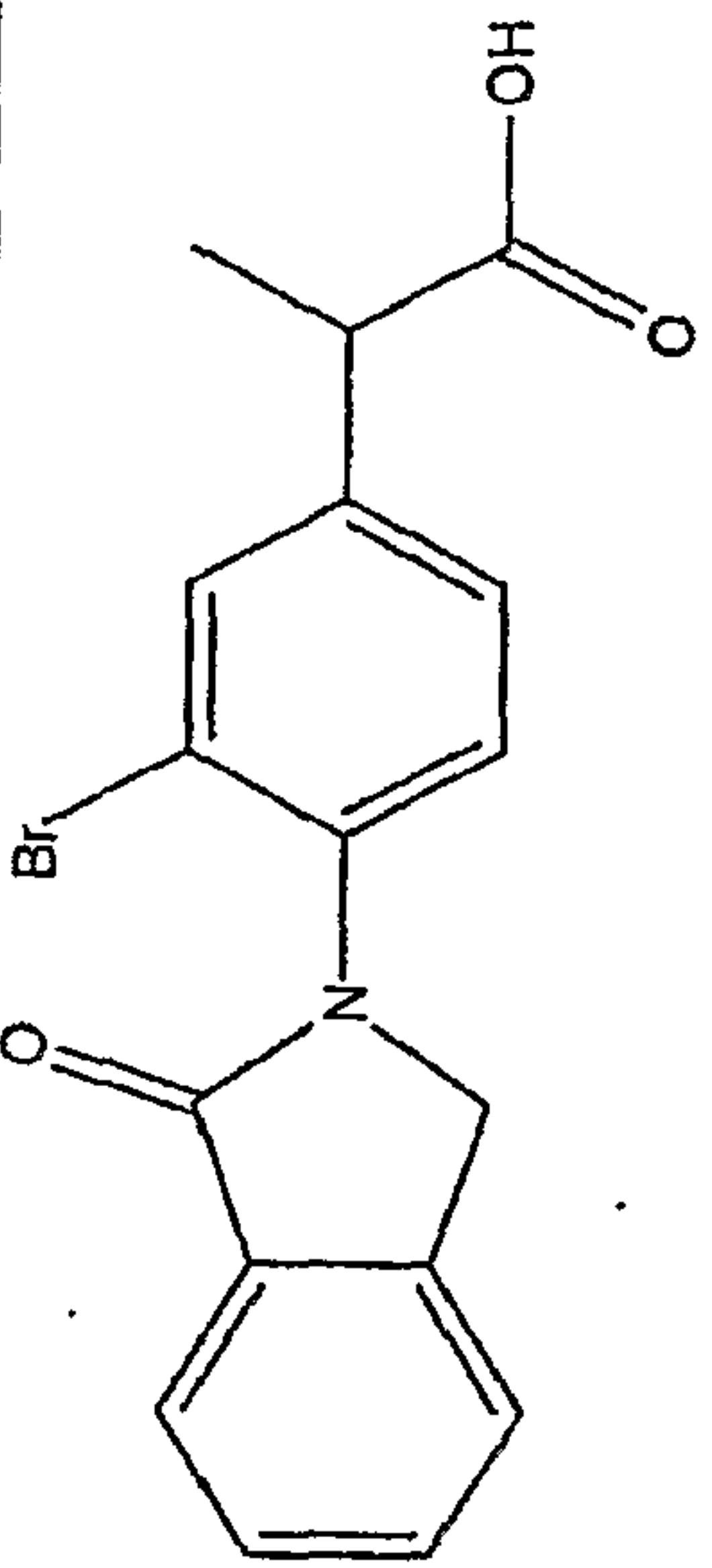
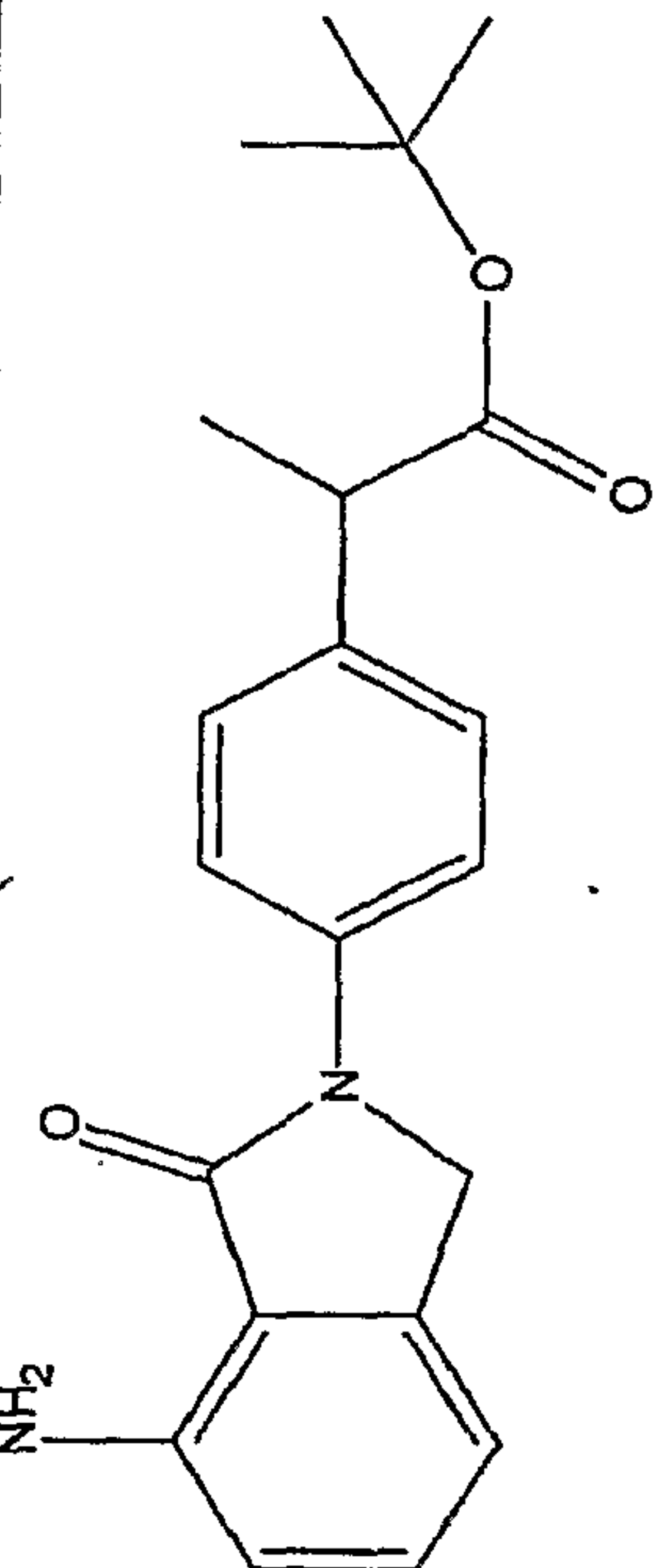
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
66		ALB- 112003	2.056	1.089

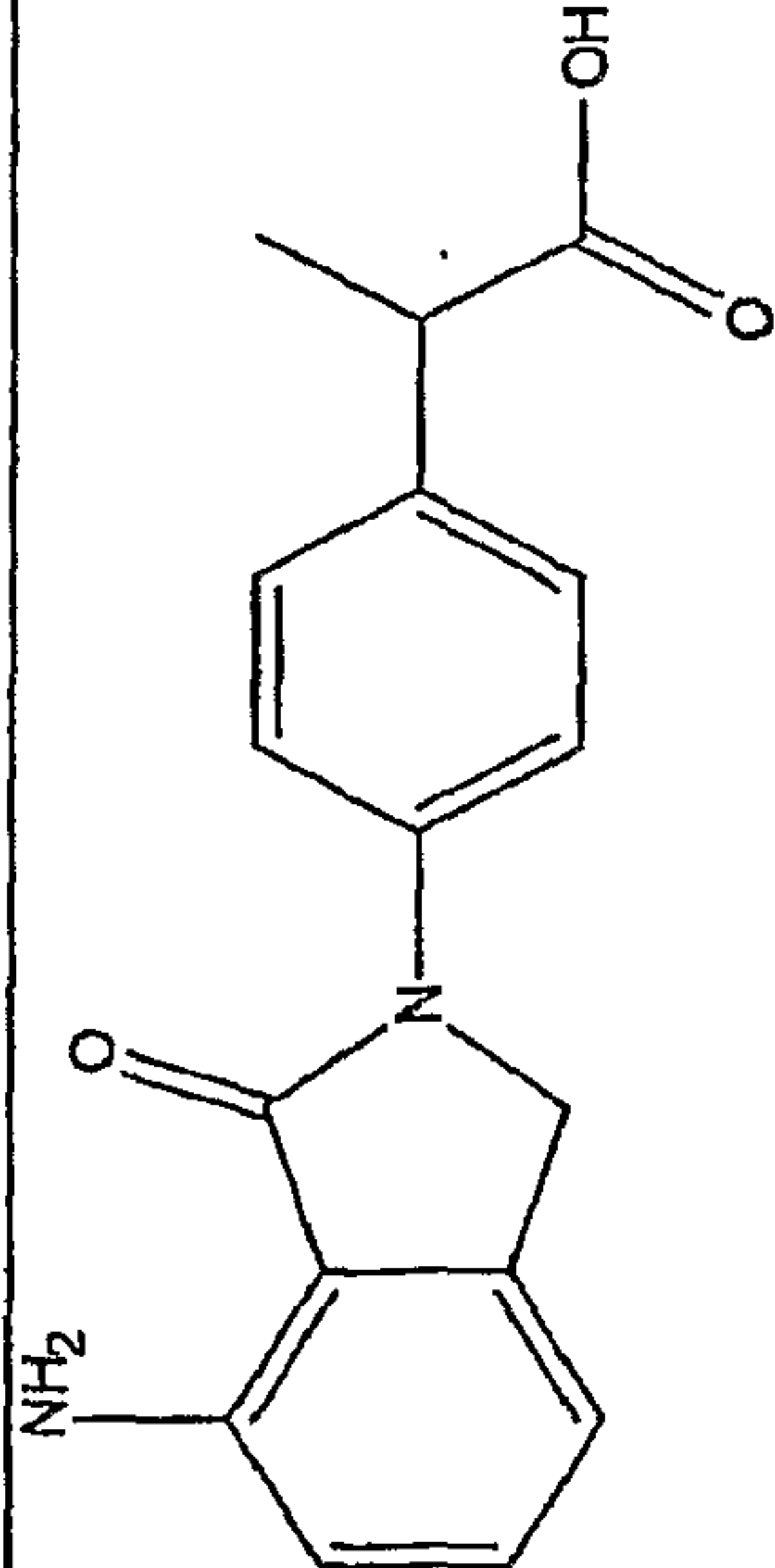
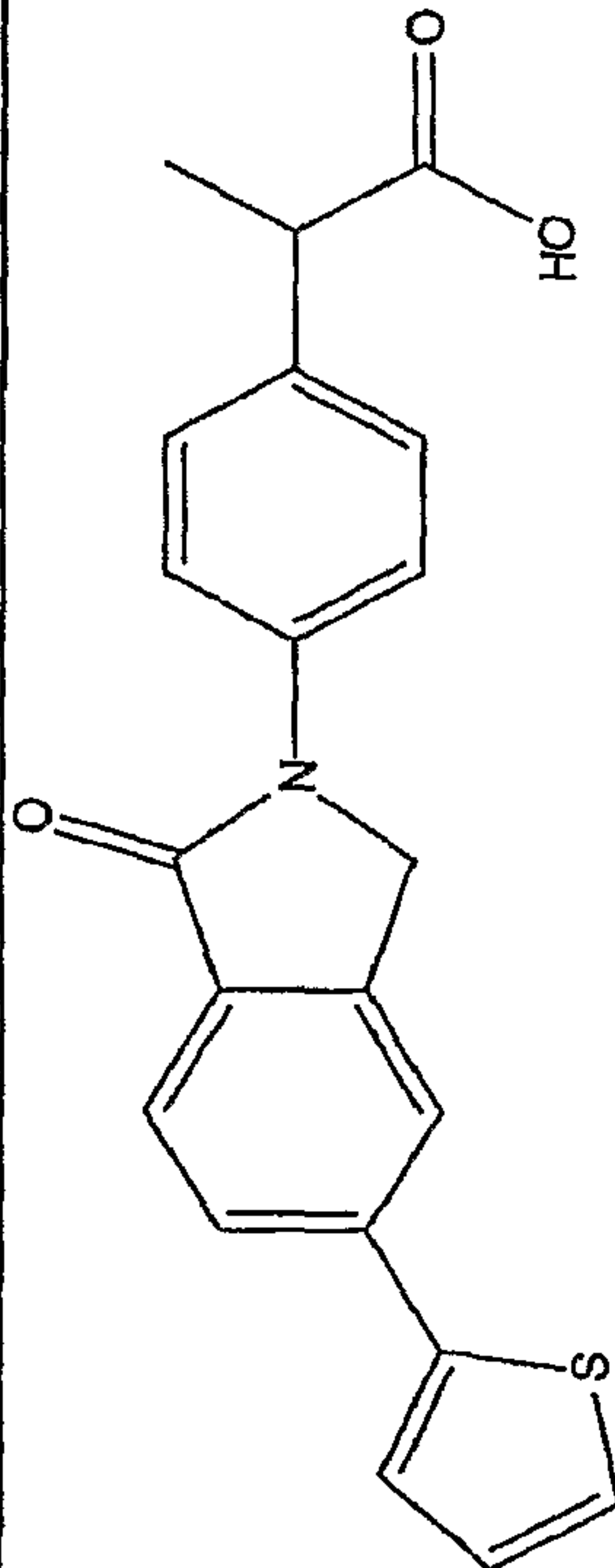
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
67				
		ALB- 112004	1.253	1.085
68				
		ALB- 112061	3.736	1.274

63

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
69		ALB- 112062a	0.329	1.414
70		ALB- 112063	0.909	1.202

64

Table 1

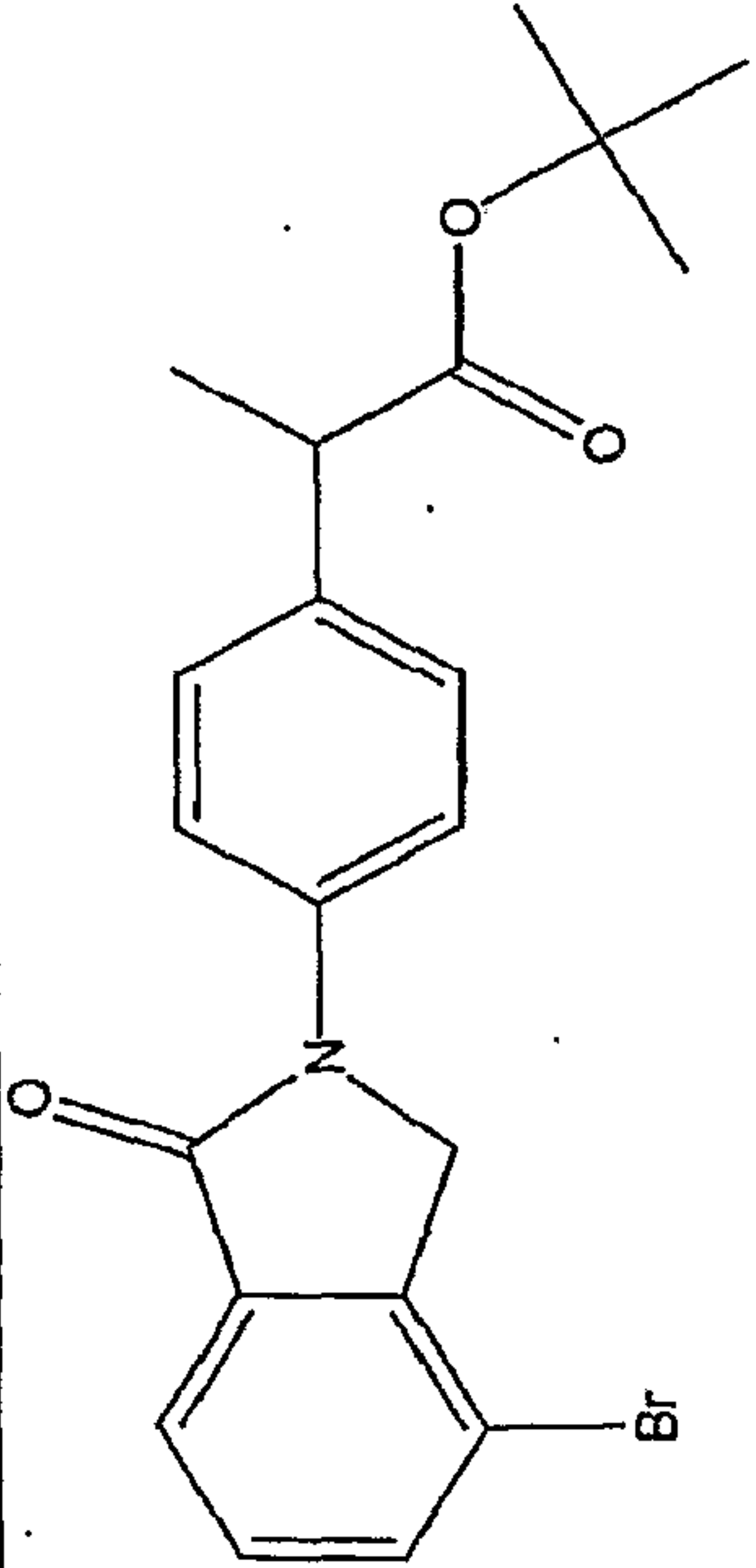
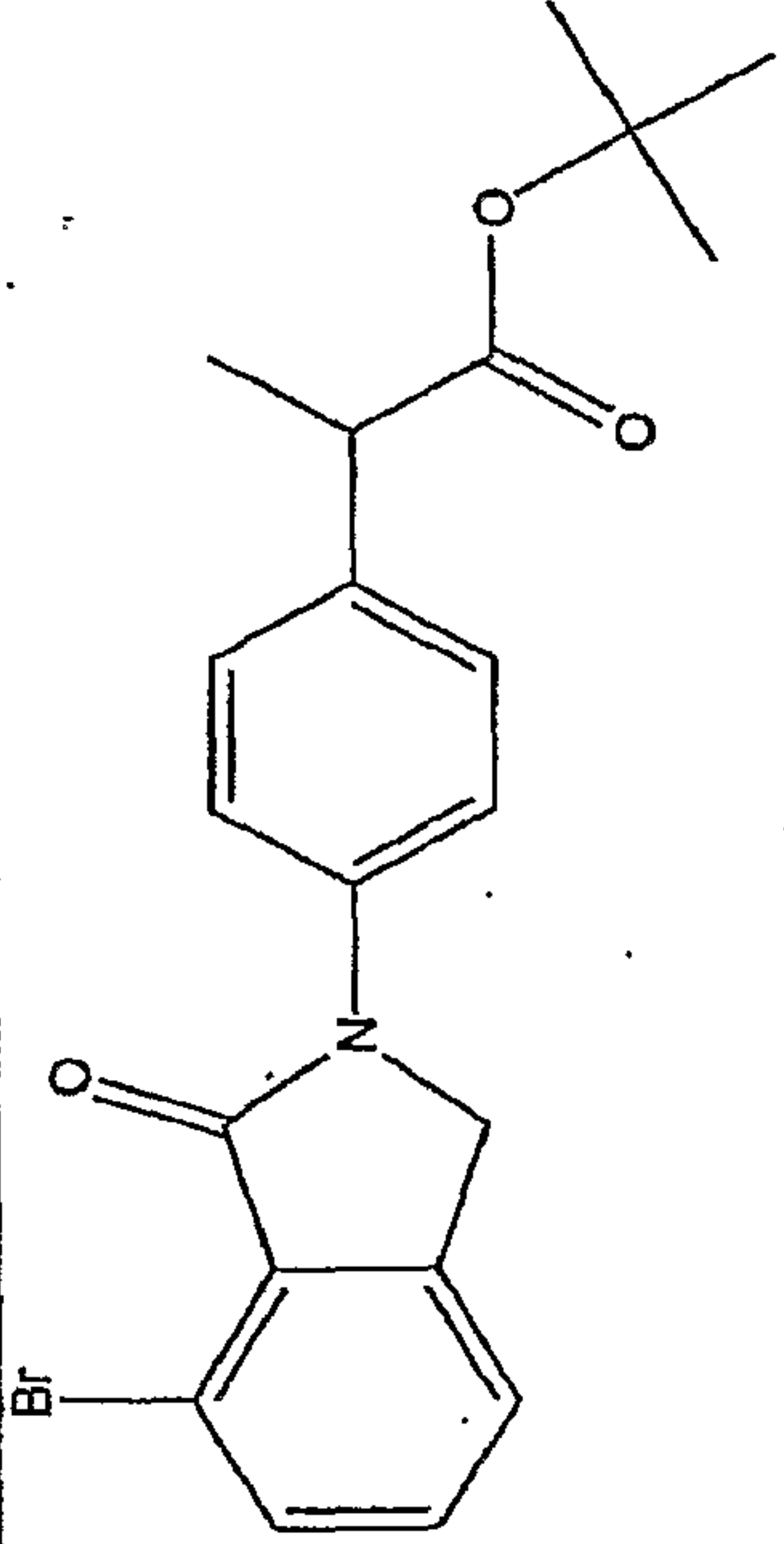
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
71		ALB- 112064		1.044
72		ALB- 112065	1.34	1.22

Table 1

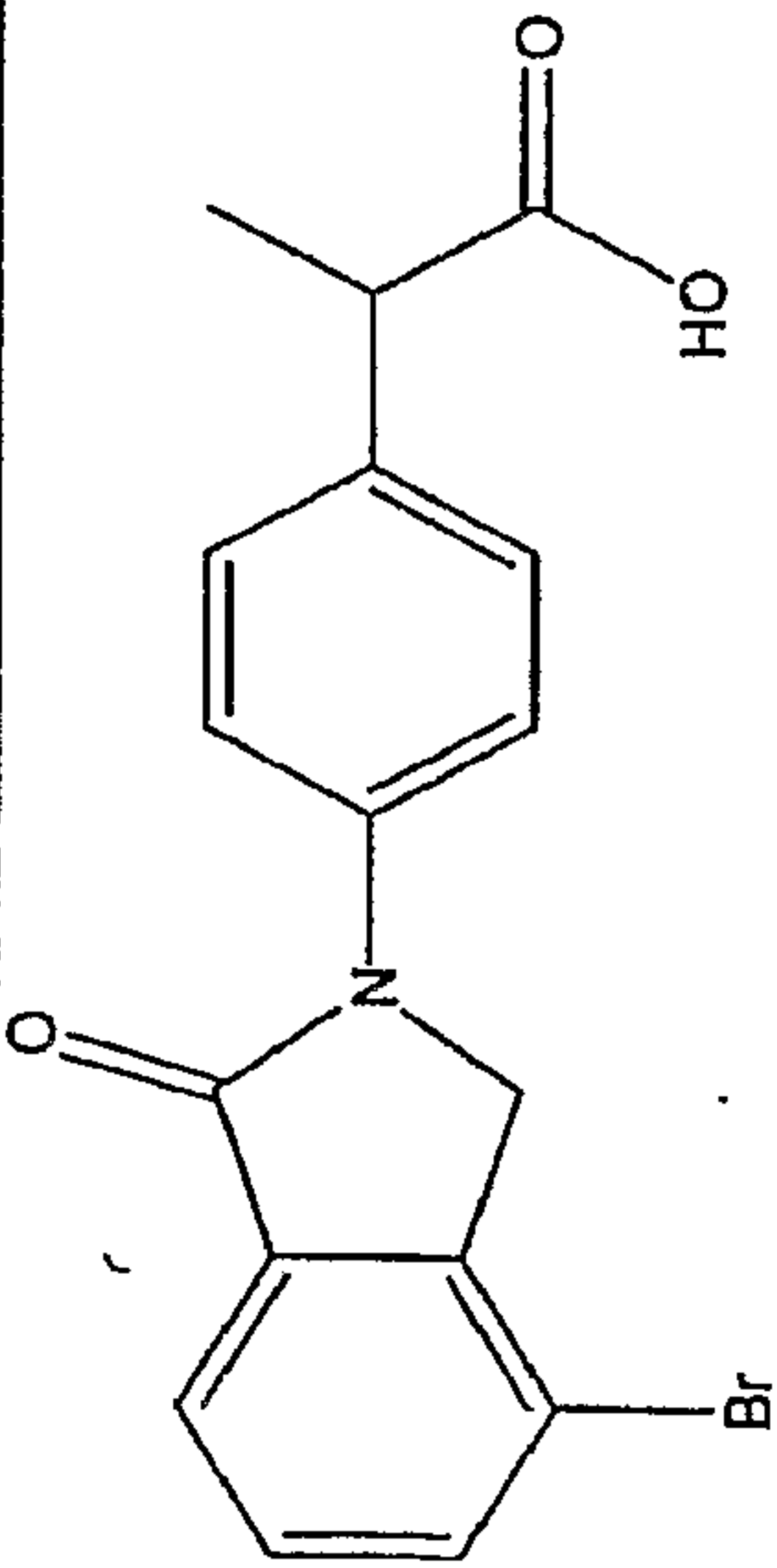
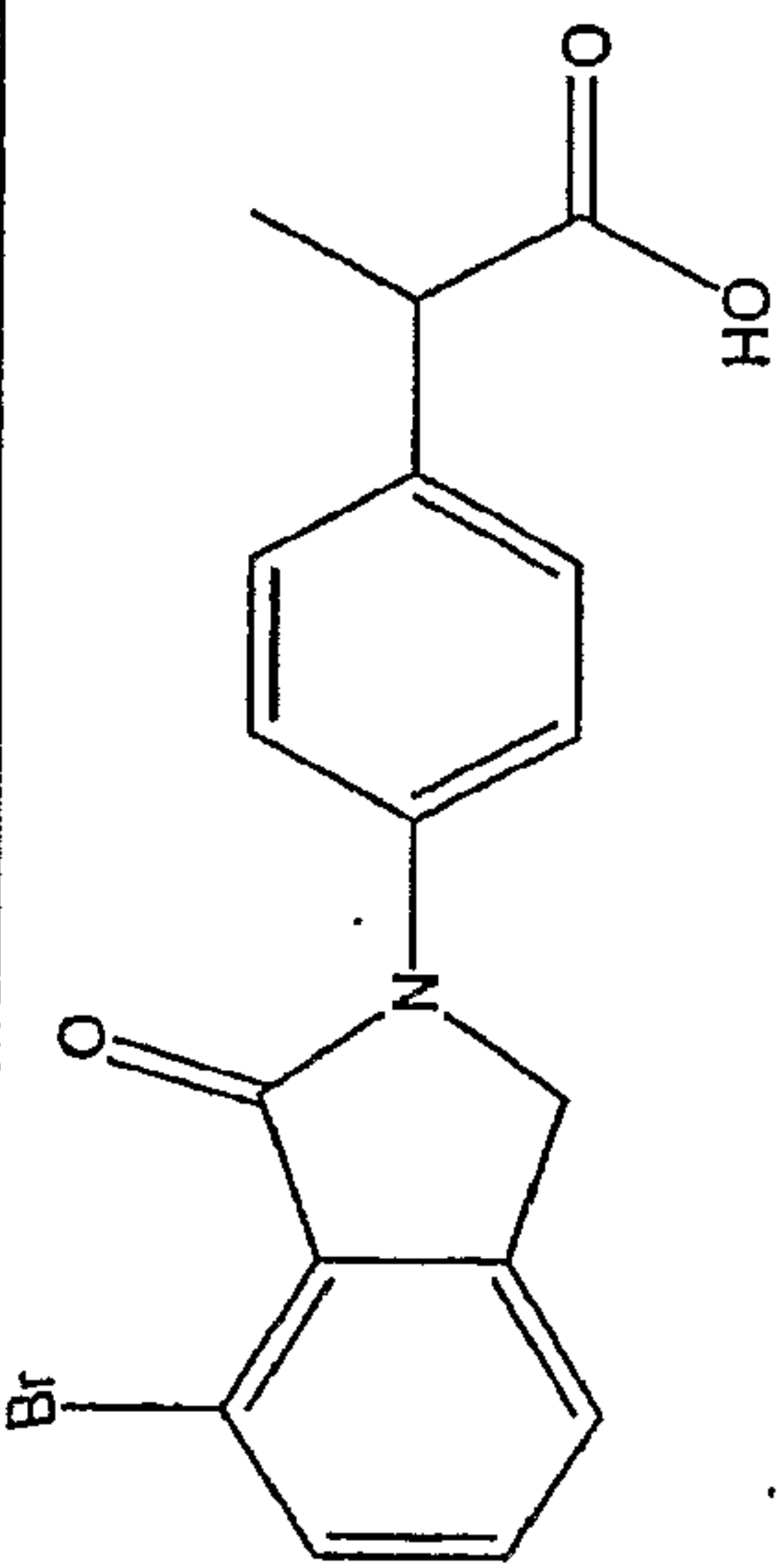
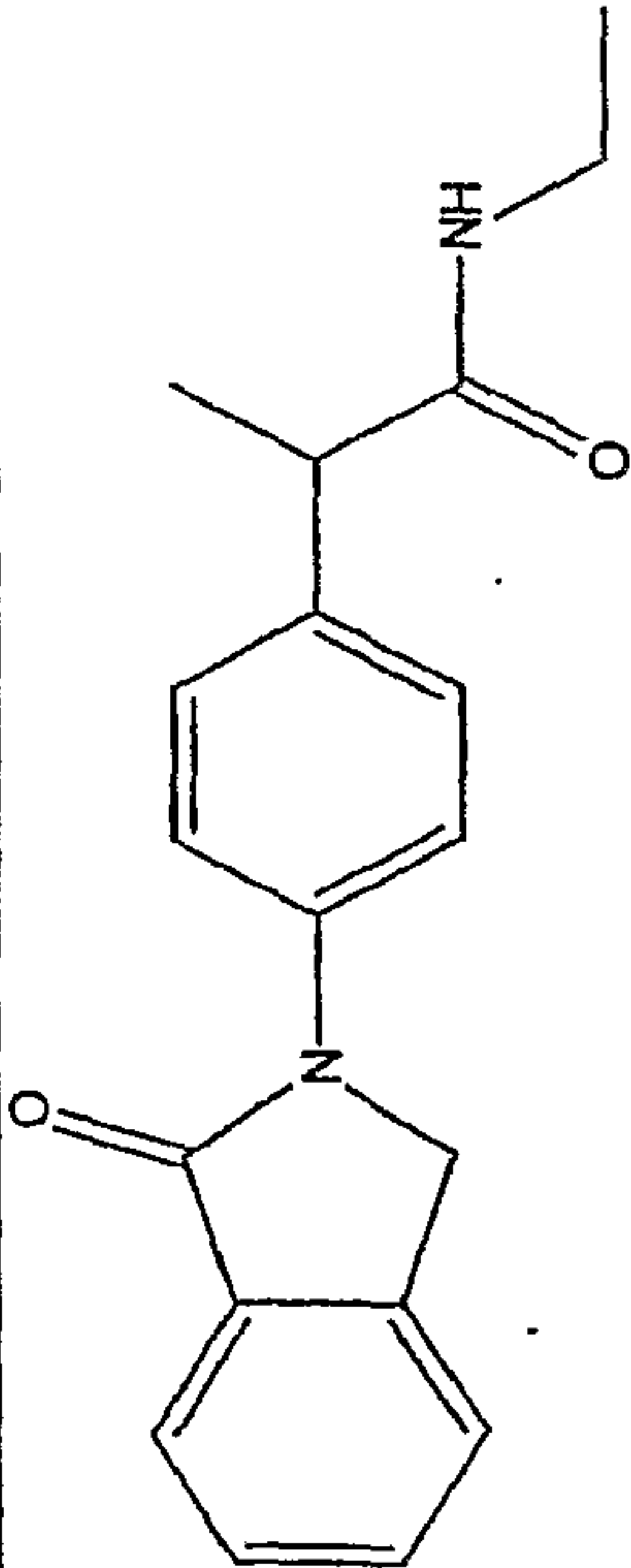
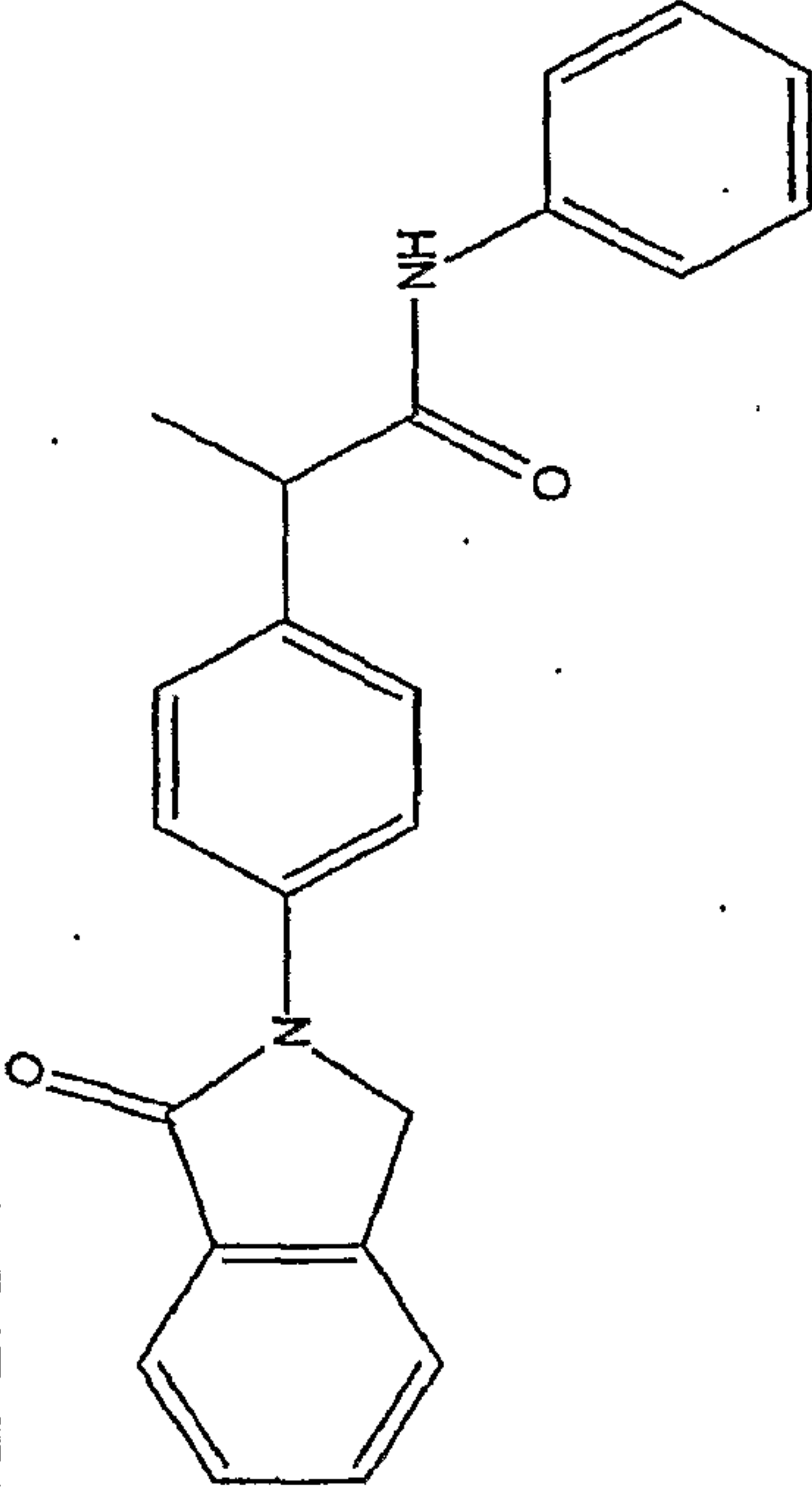
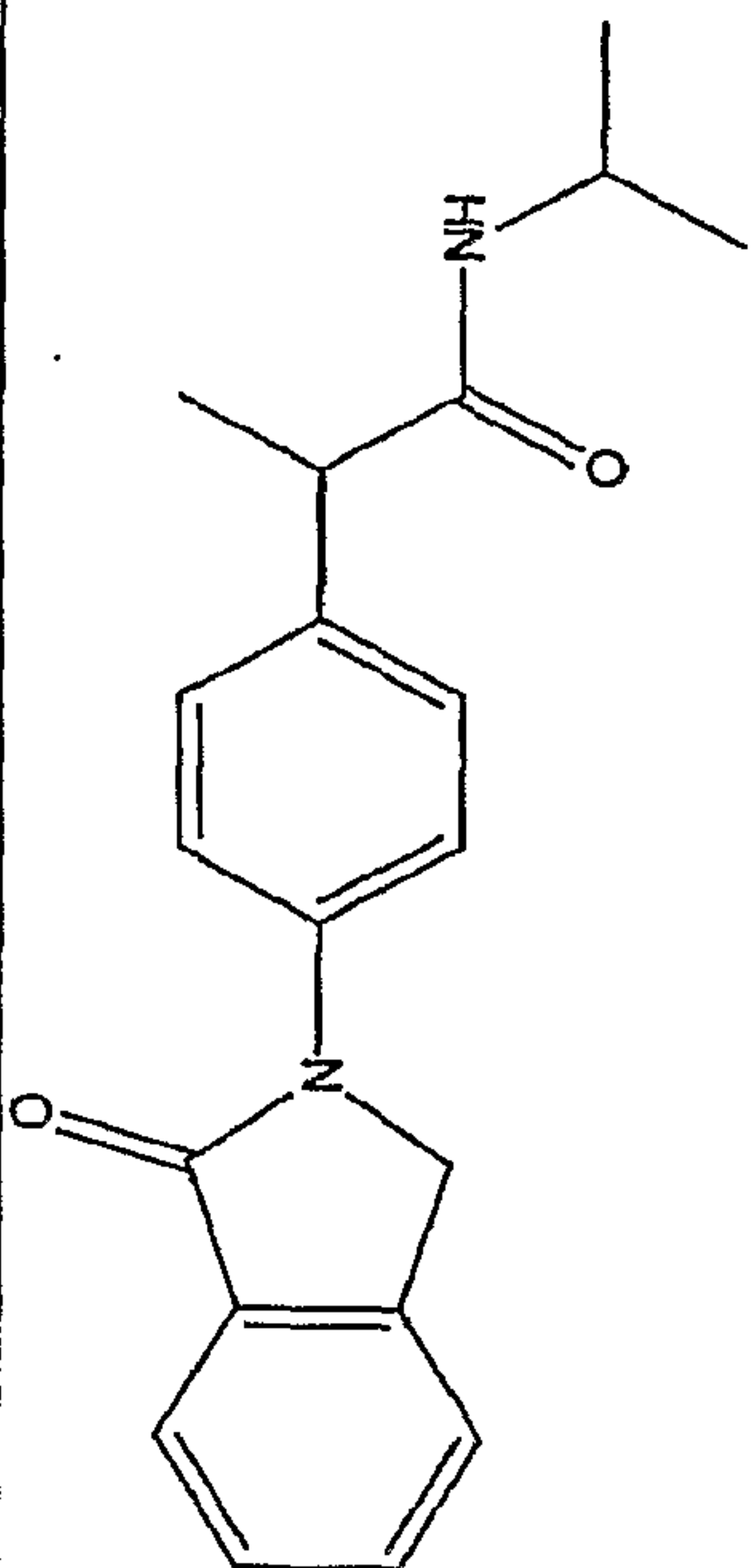
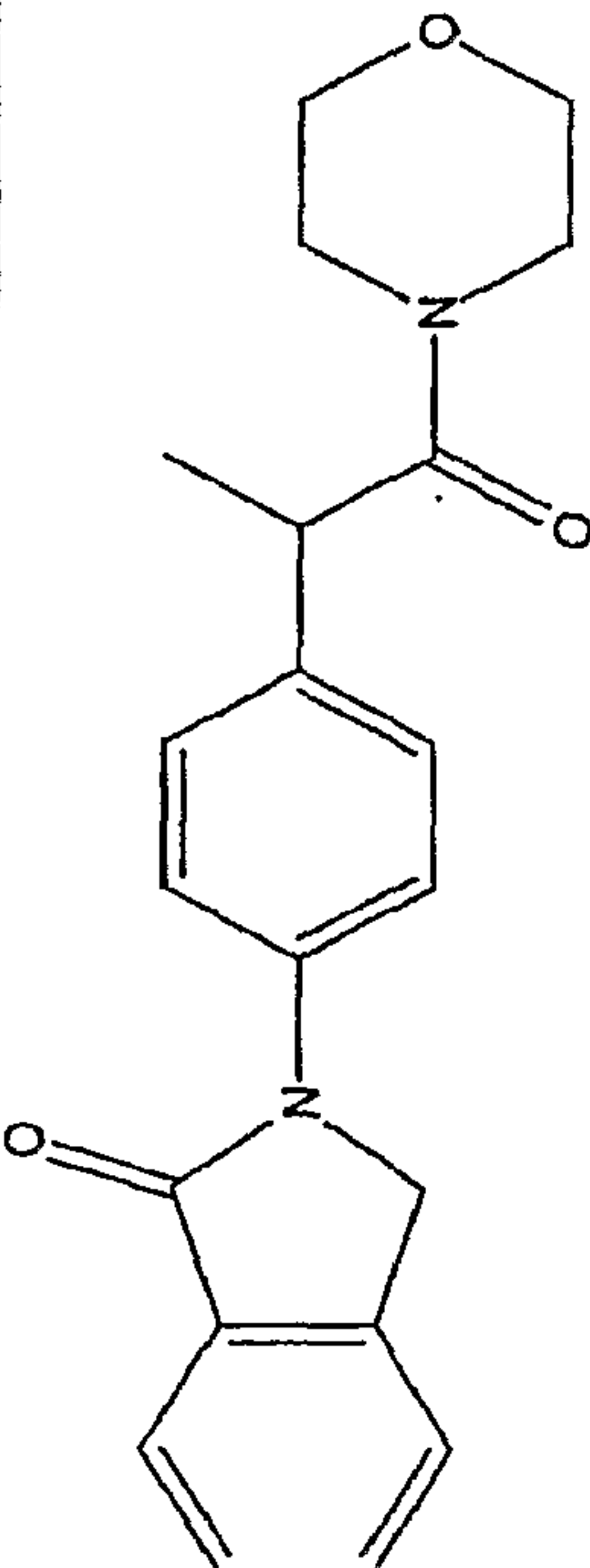
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
73		ALB- 112066	21.777	1.122
74		ALB- 112067	9.713	1.36

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
75		ALB- 112073		1.179
76		ALB- 112075	0.578	1.25

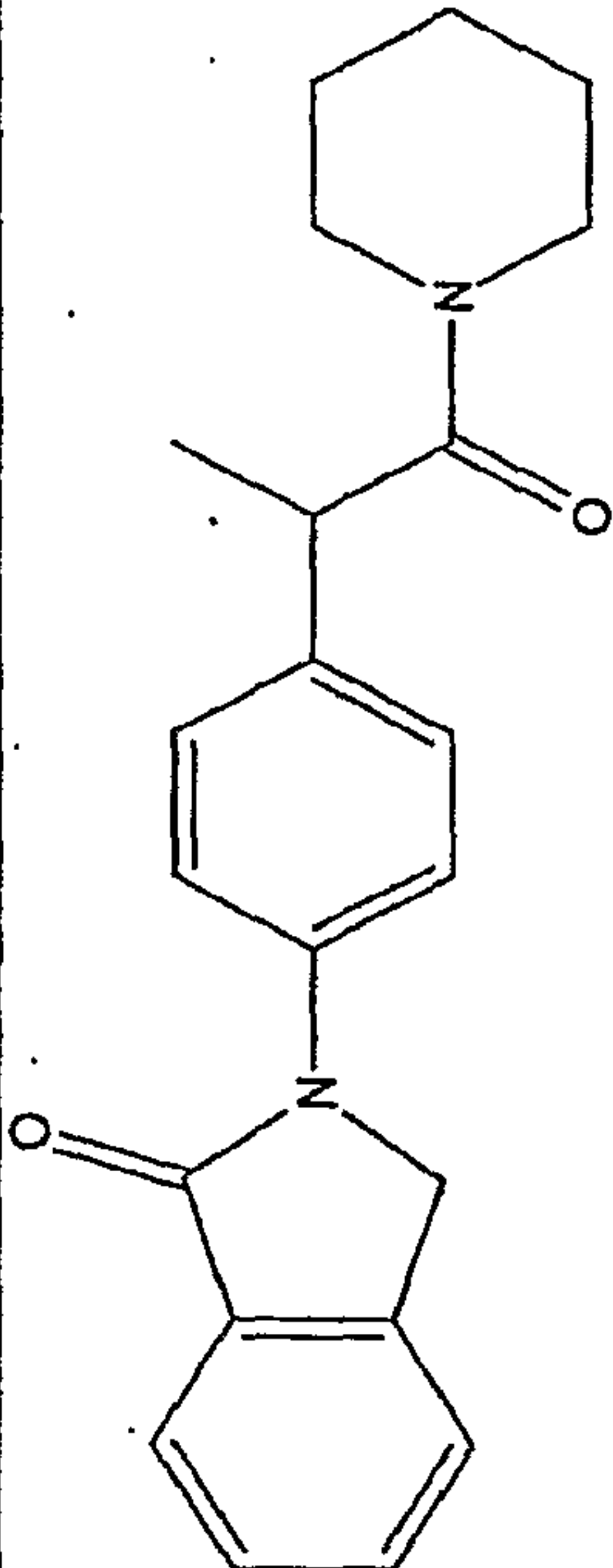
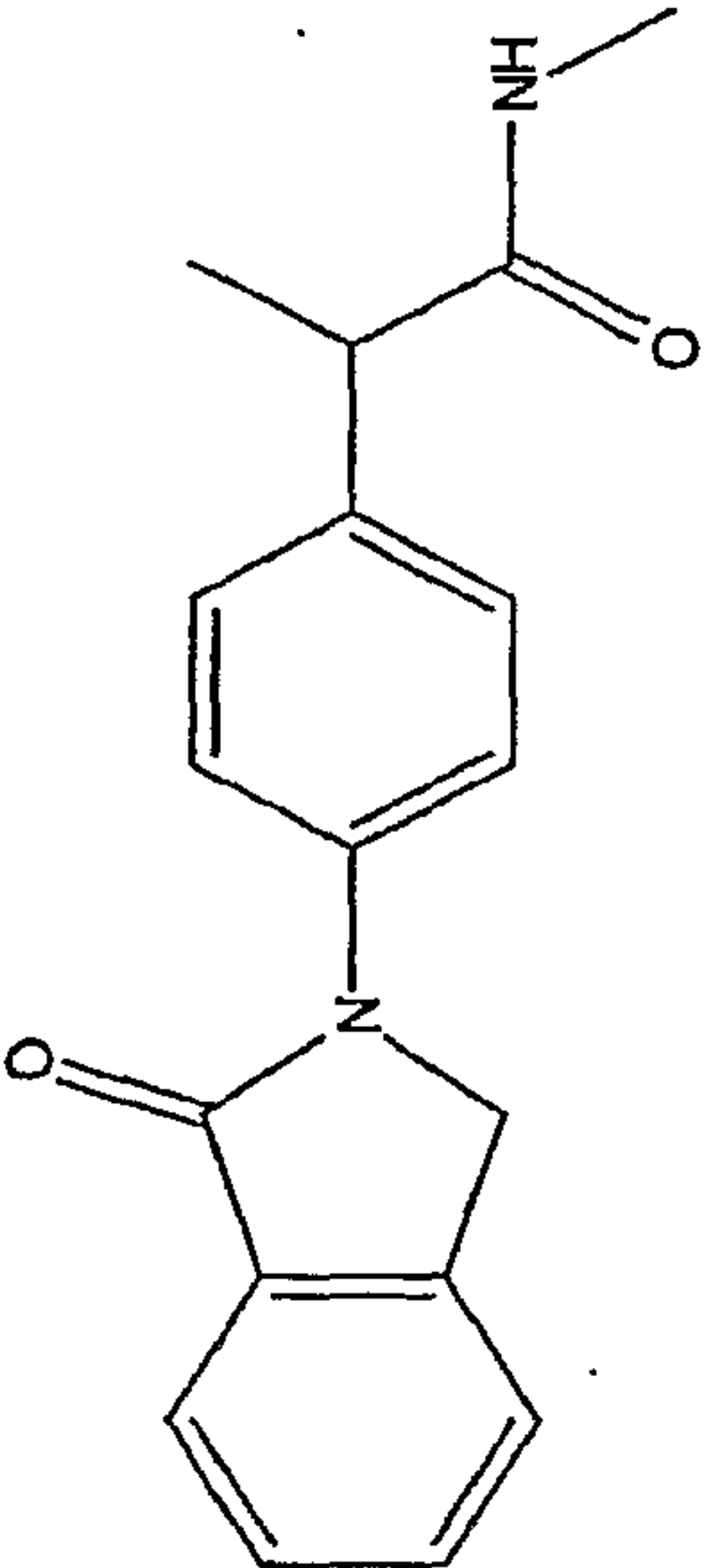
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
77		ALB- 112076	1.372	1.125
78		ALB- 112077		1.094

68

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
79		ALB- 112078		1.153
80		ALB- 112079		1.139

69

Table 1

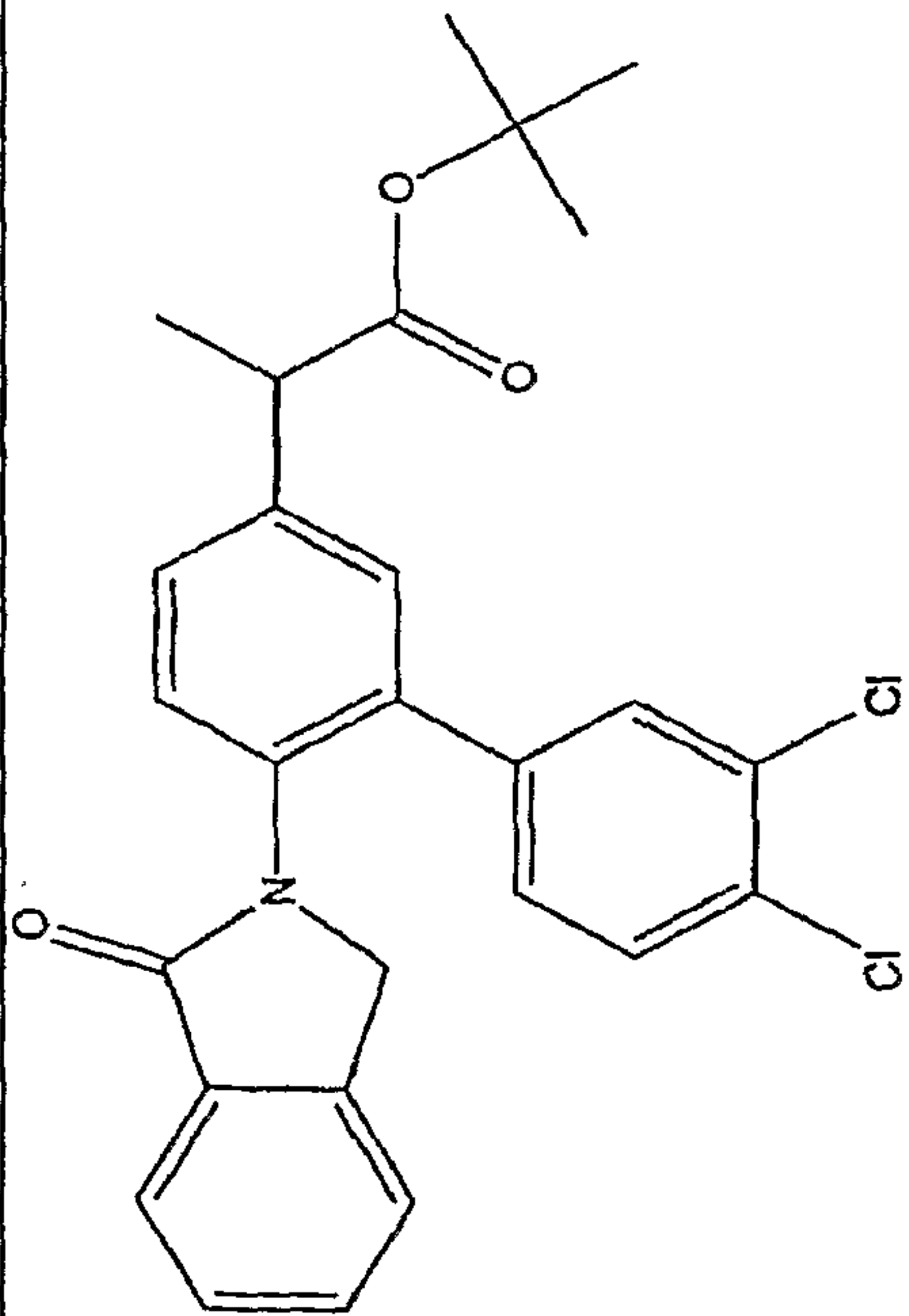
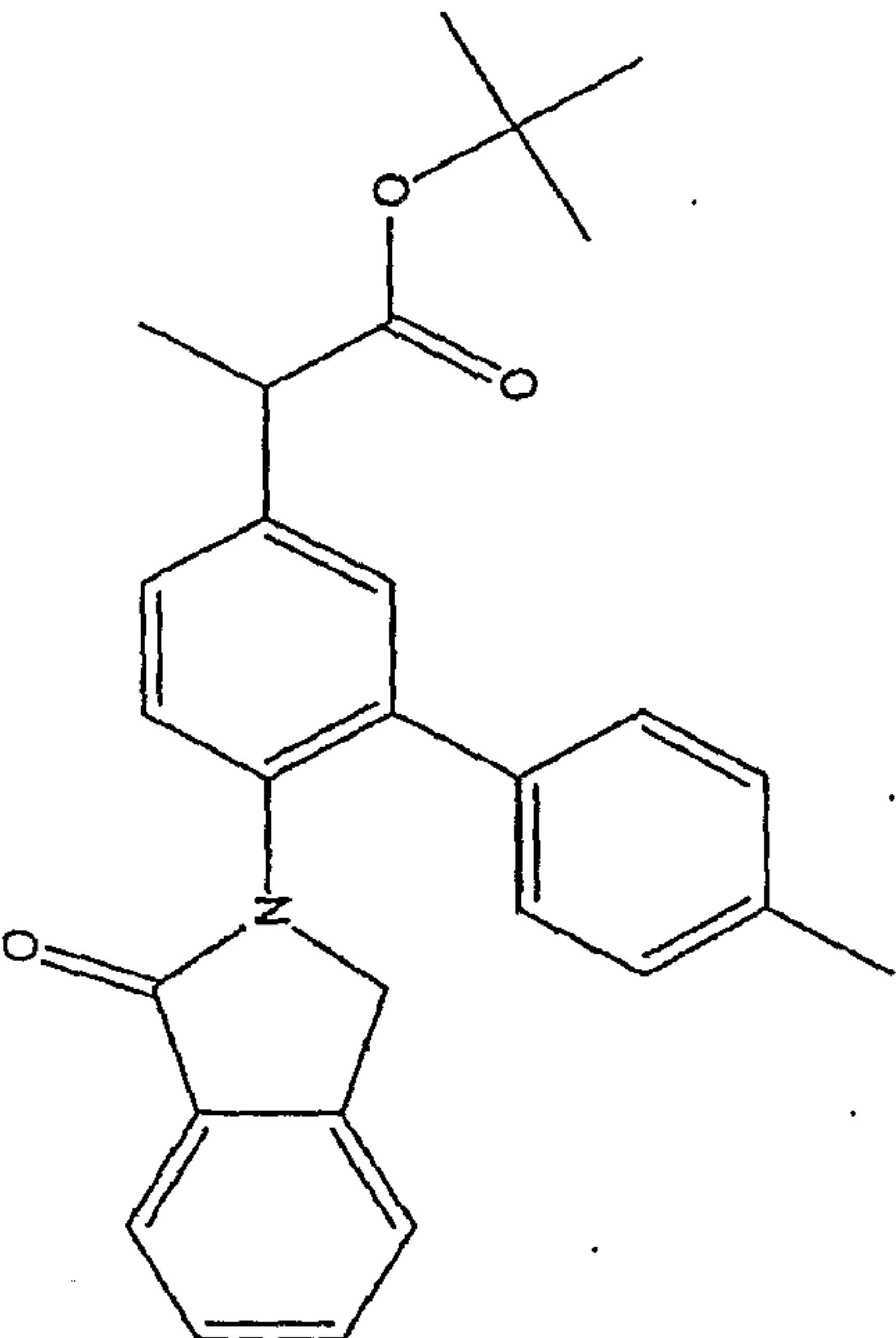
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
81		ALB- 112080		1.033

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
82		ALB- 112081		1.026

71

Table 1

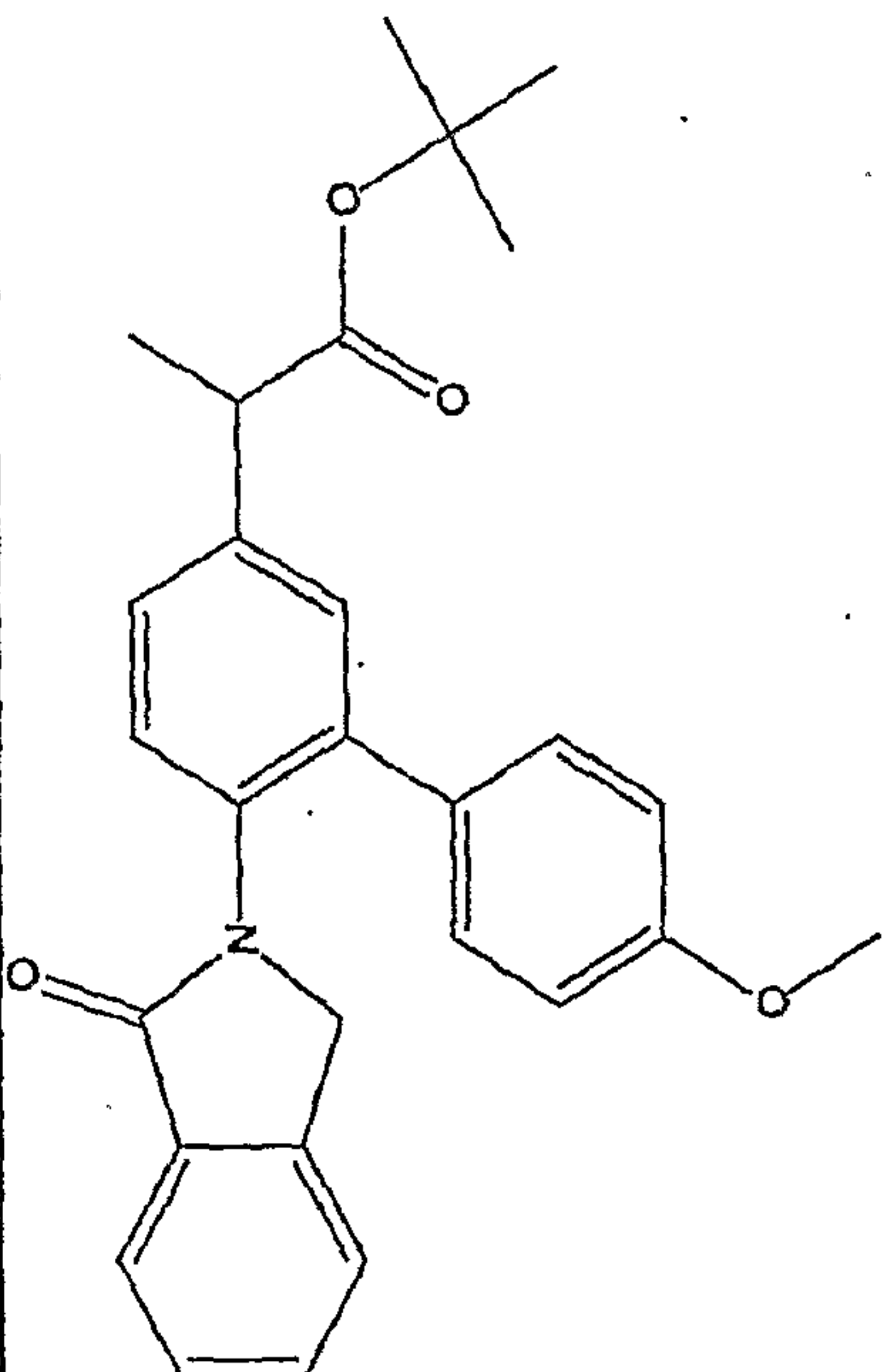
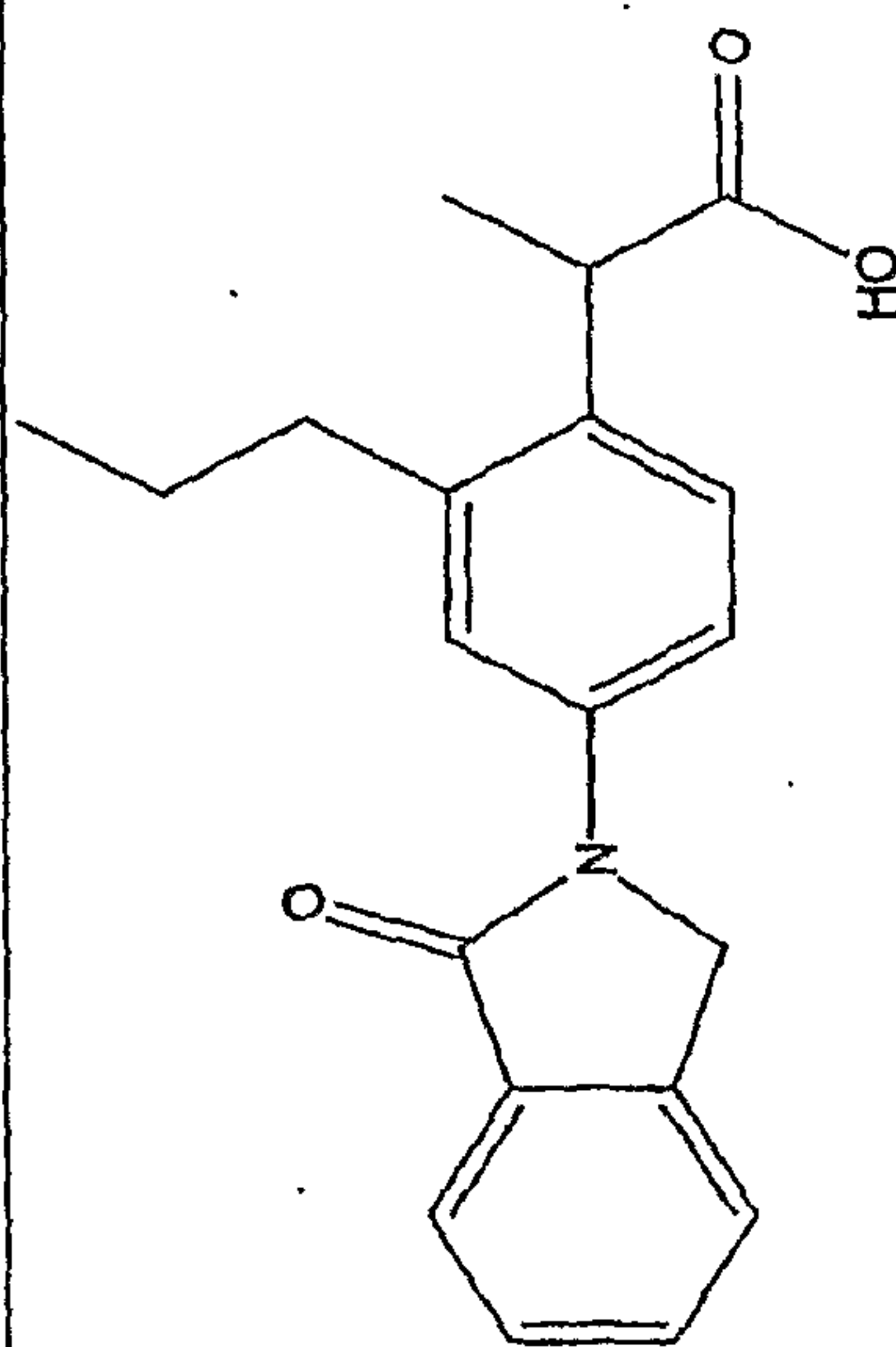
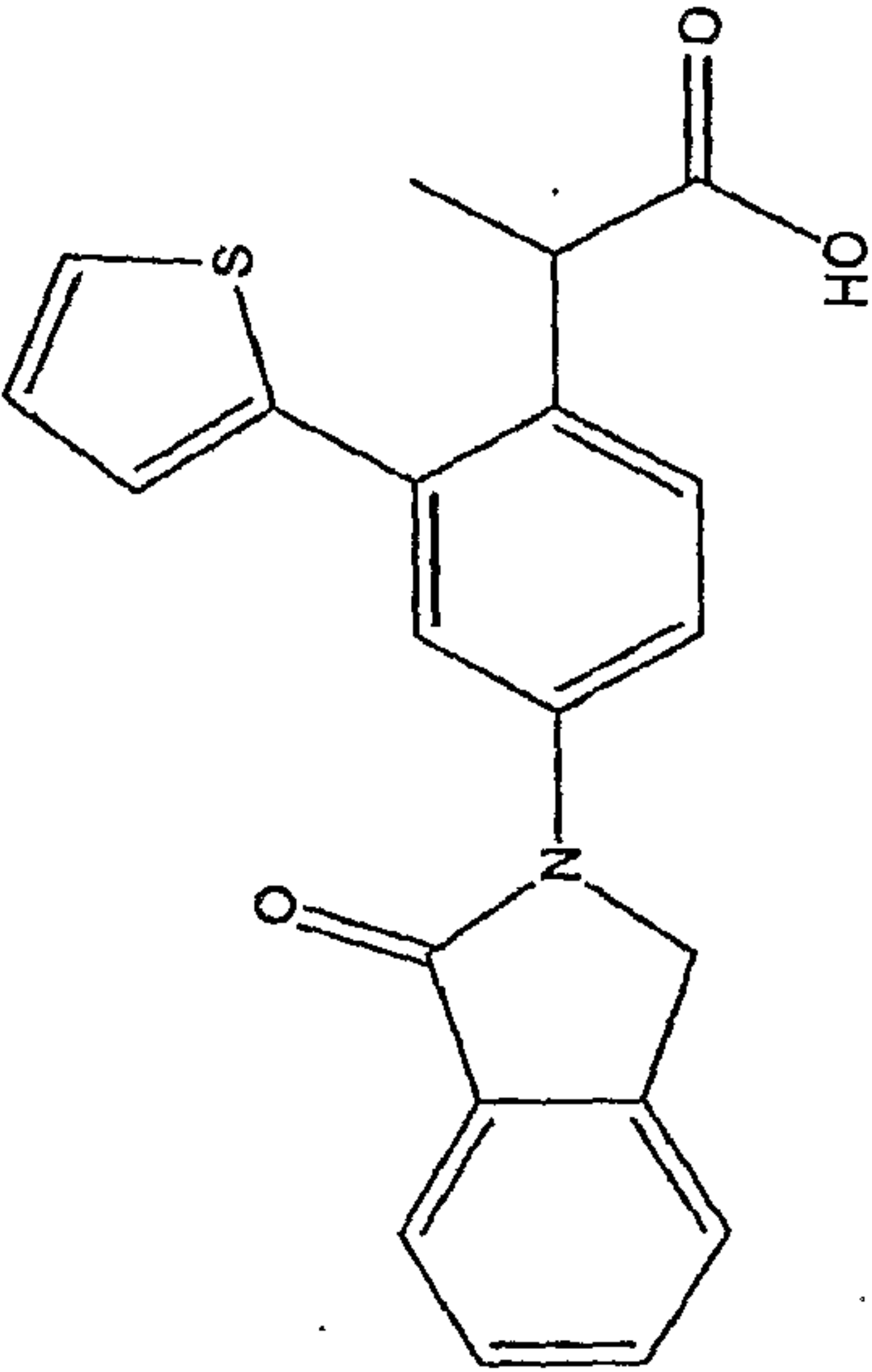
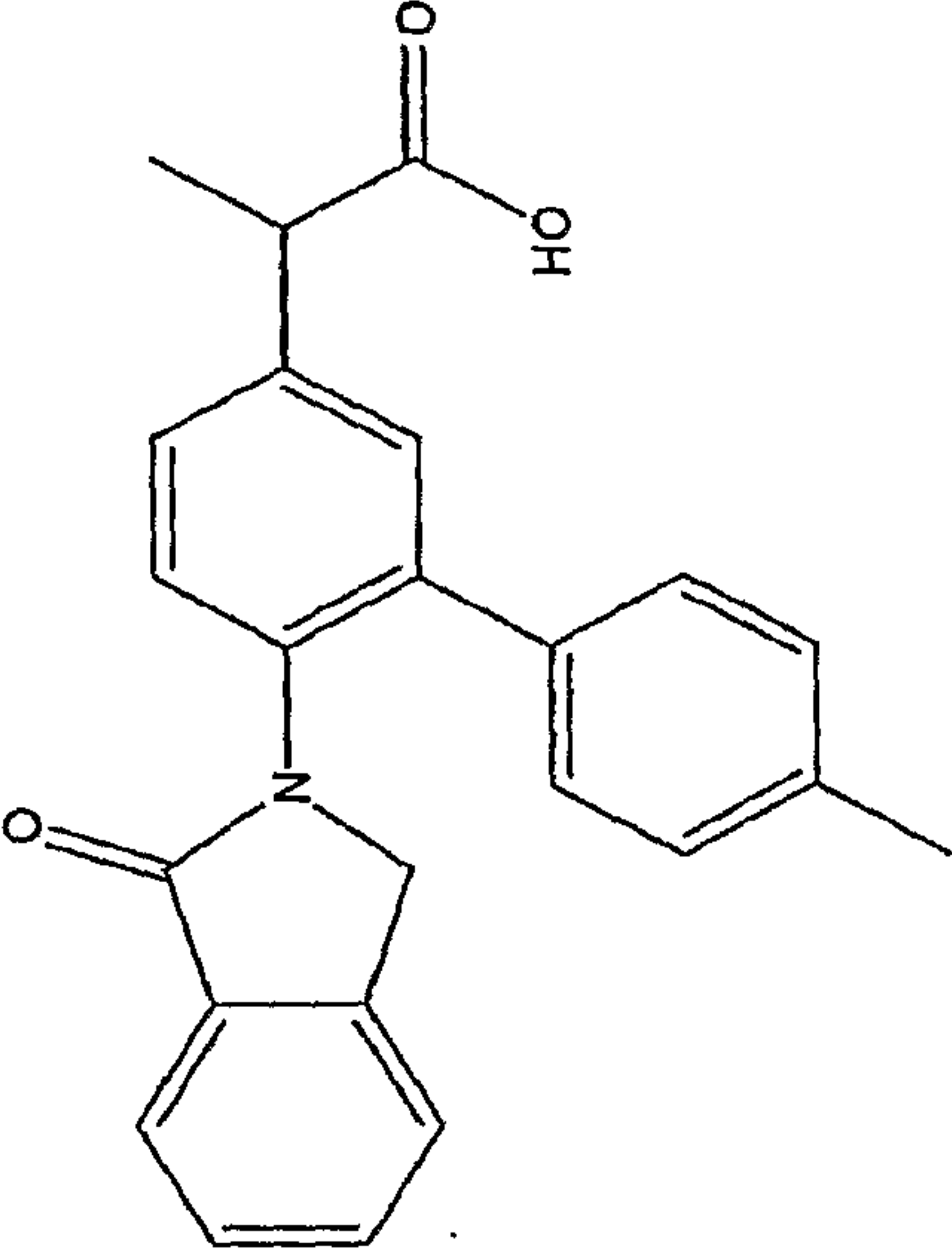
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			Avg EC50 (μ M)	Avg MaxFold Increase
83		ALB- 112082		1.123
84		ALB- 112083		1.095

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
85		ALB- 112084		1.114
86		ALB- 112085		1.083

73

Table 1

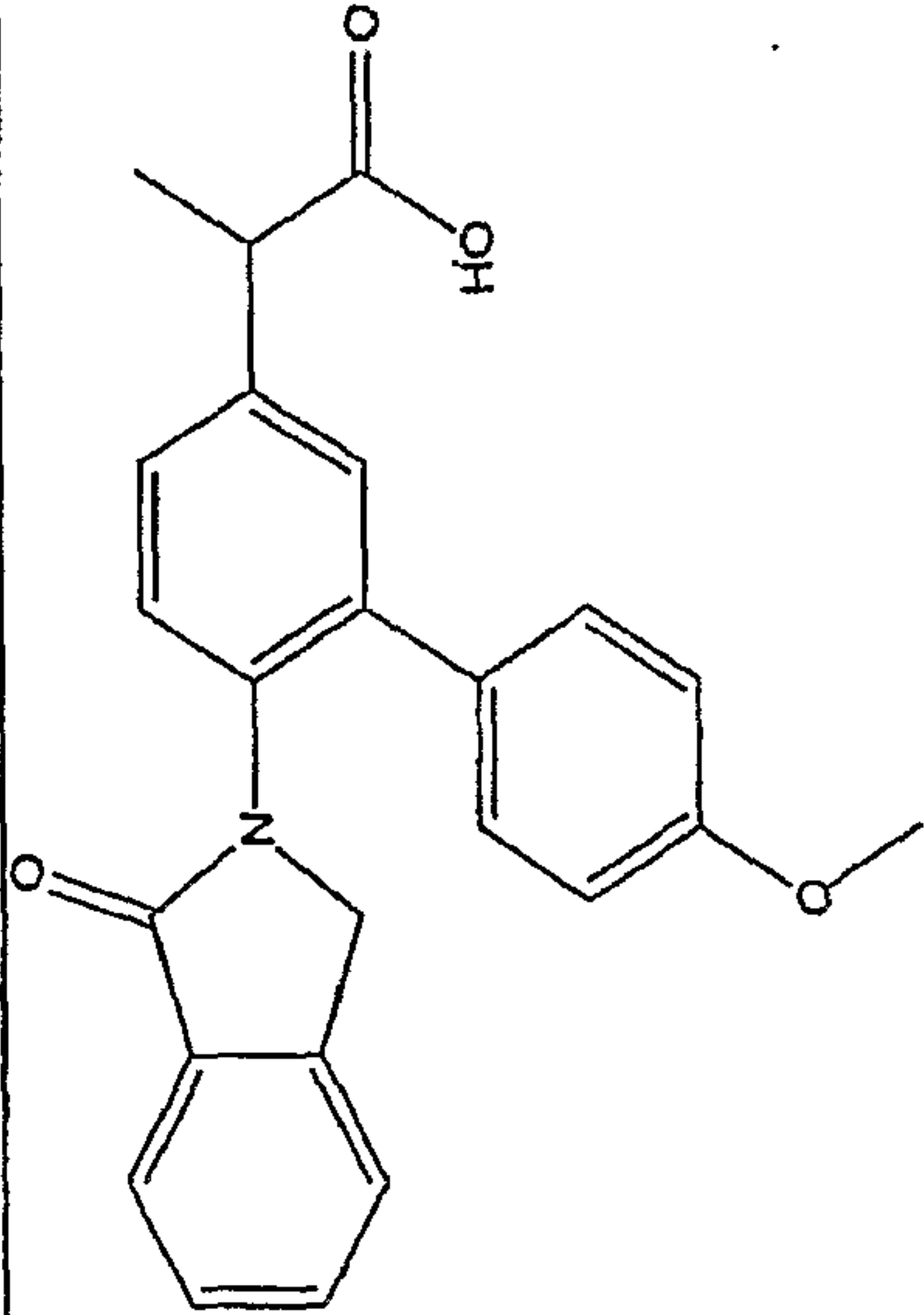
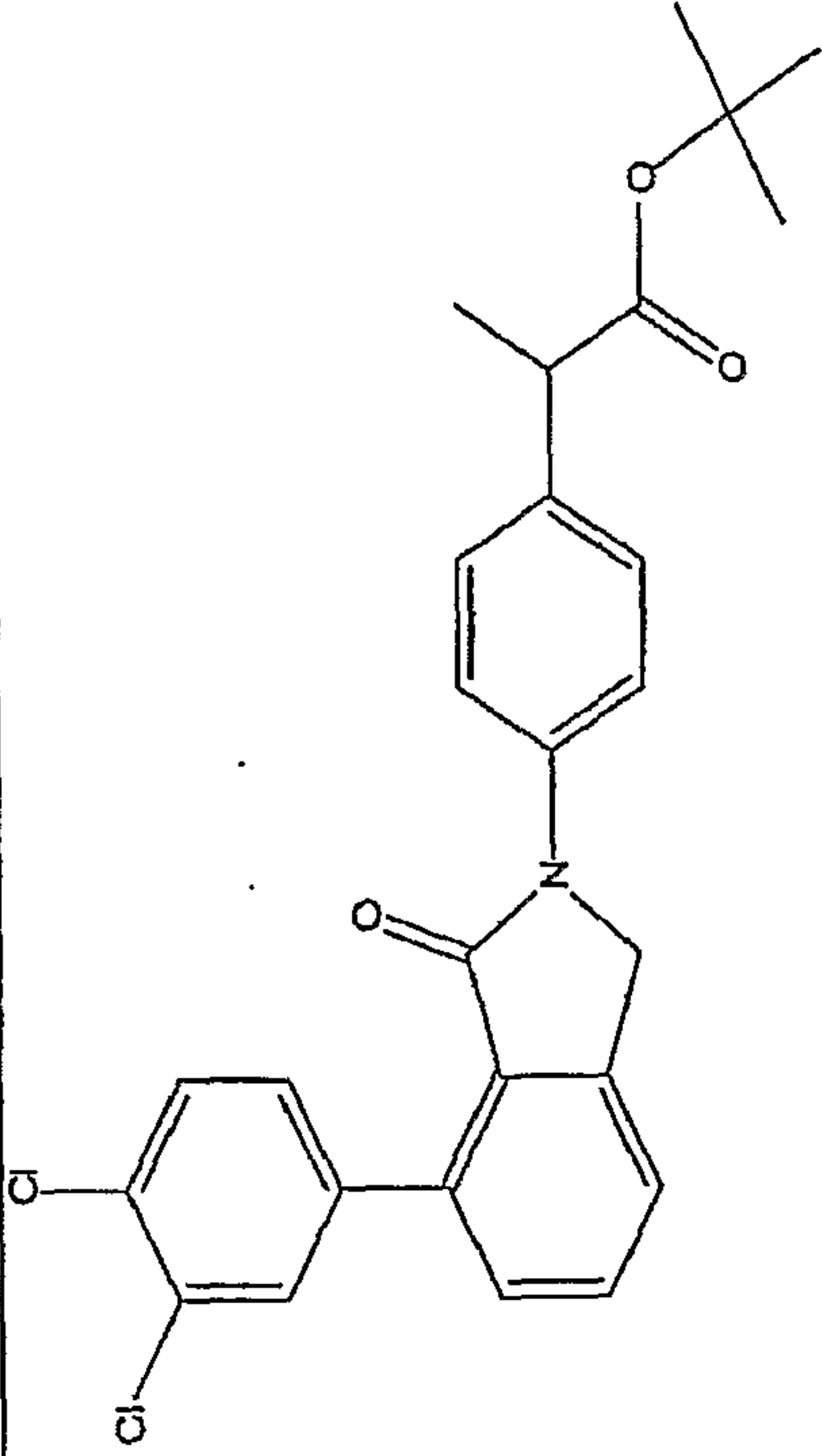
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
87		ALB- 112086		1.081
88		ALB- 112149		1.064

Table 1

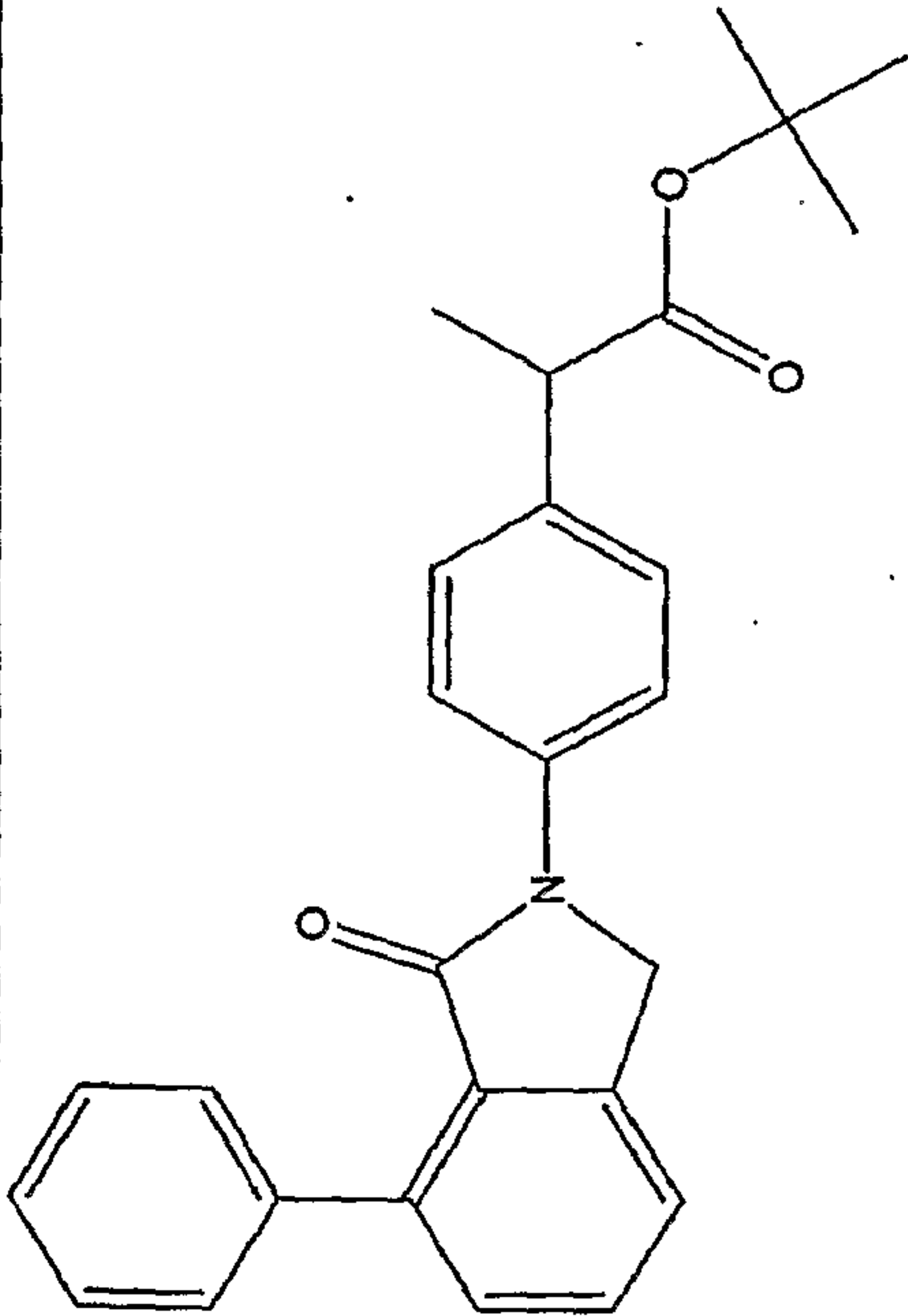
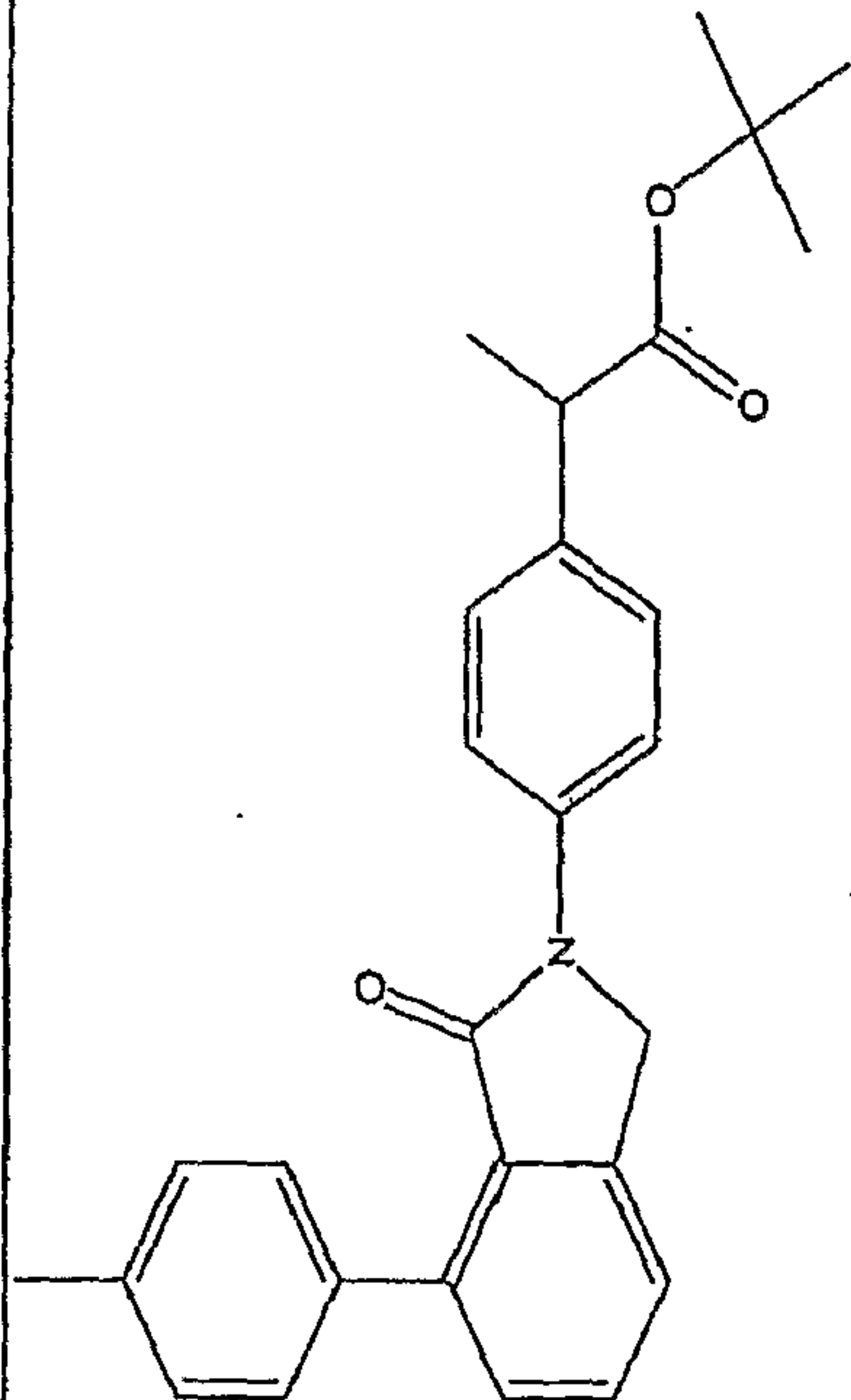
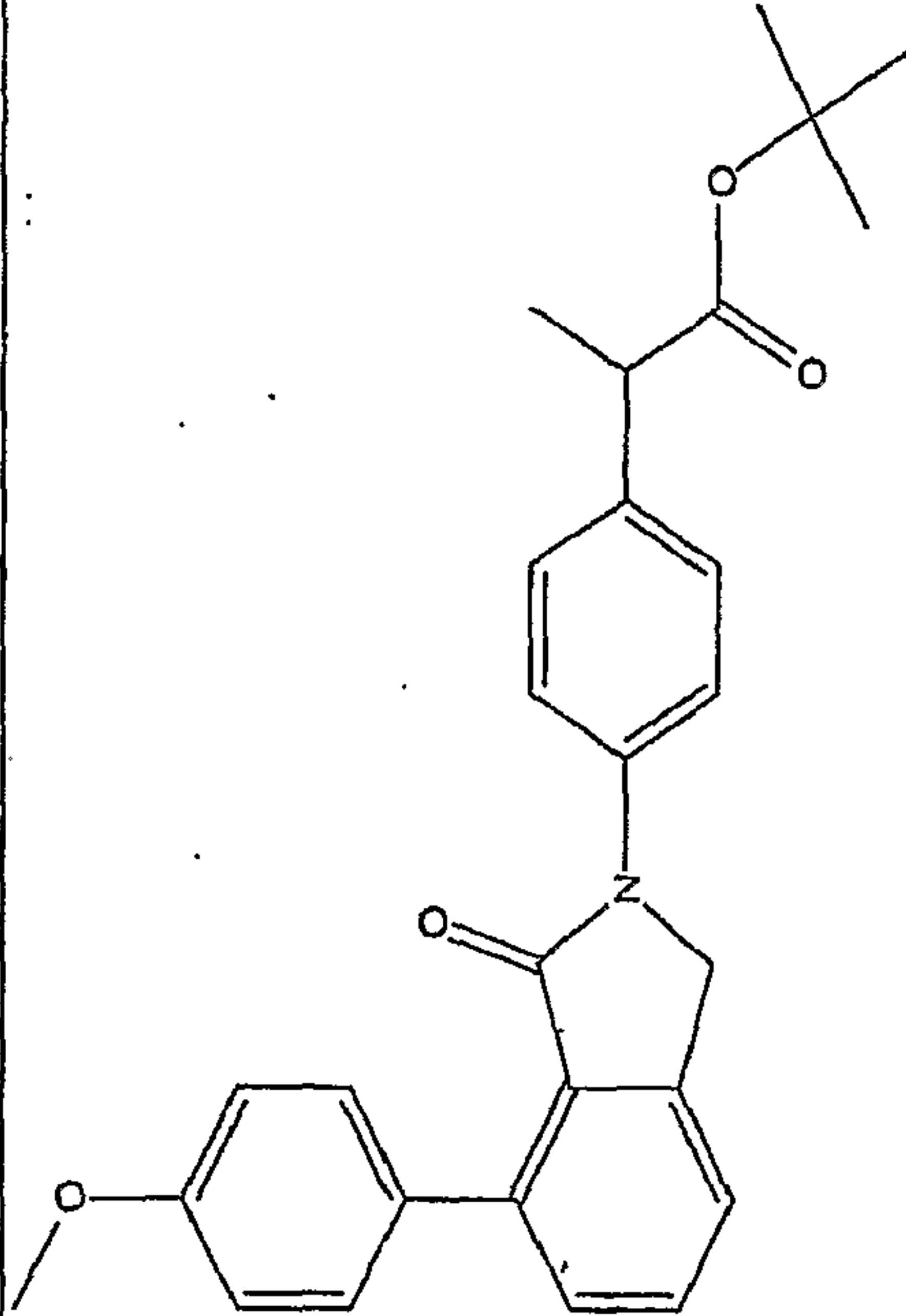
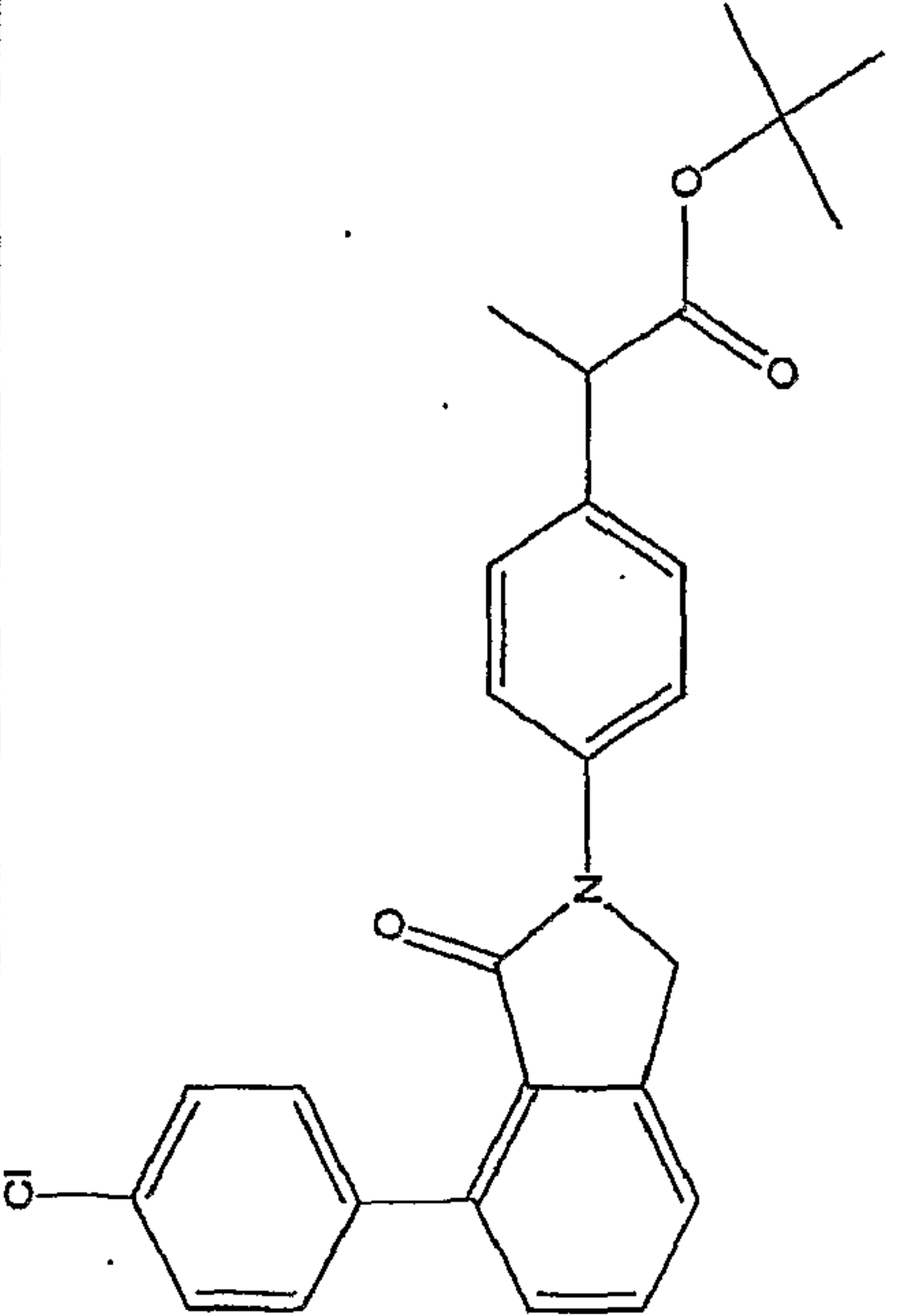
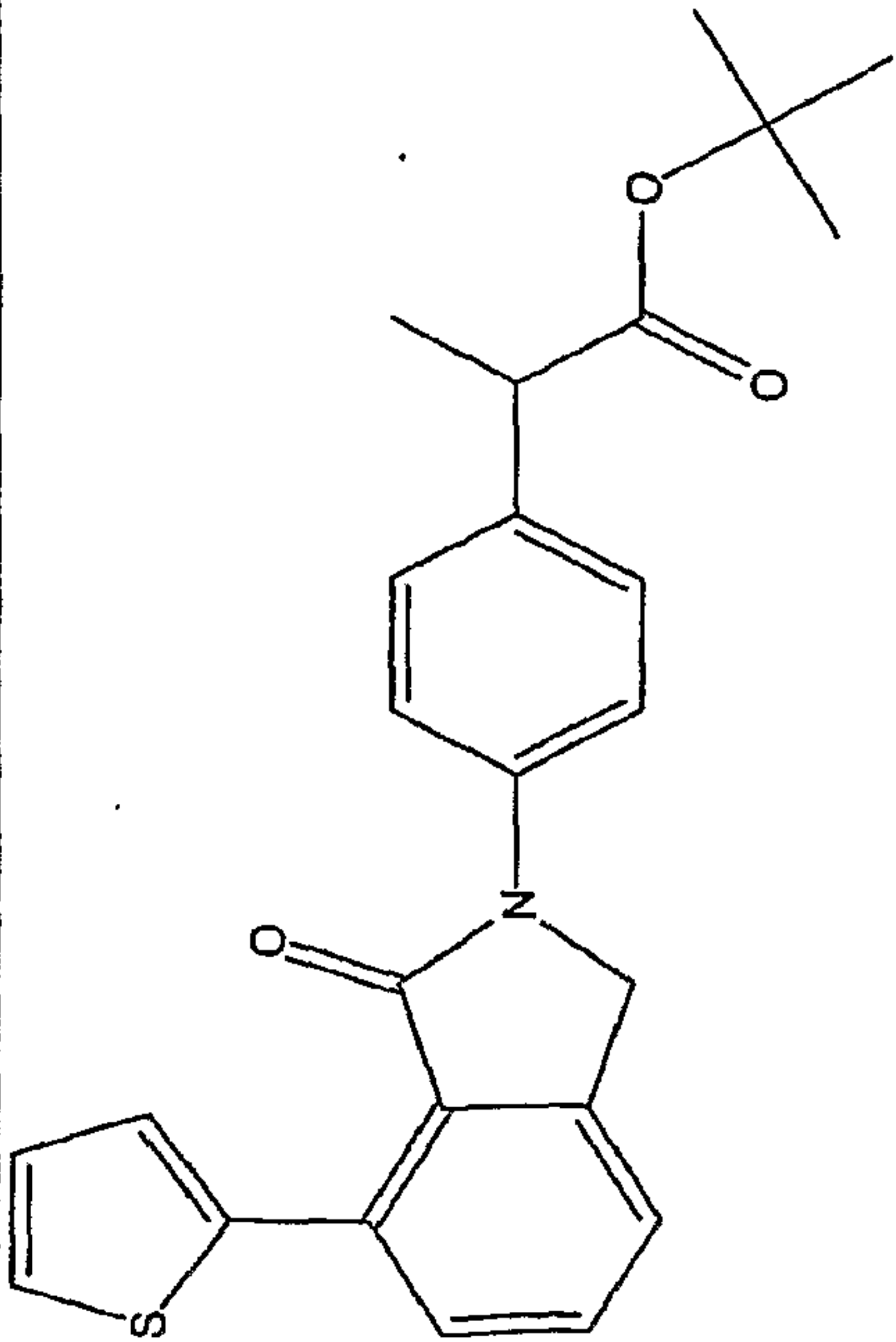
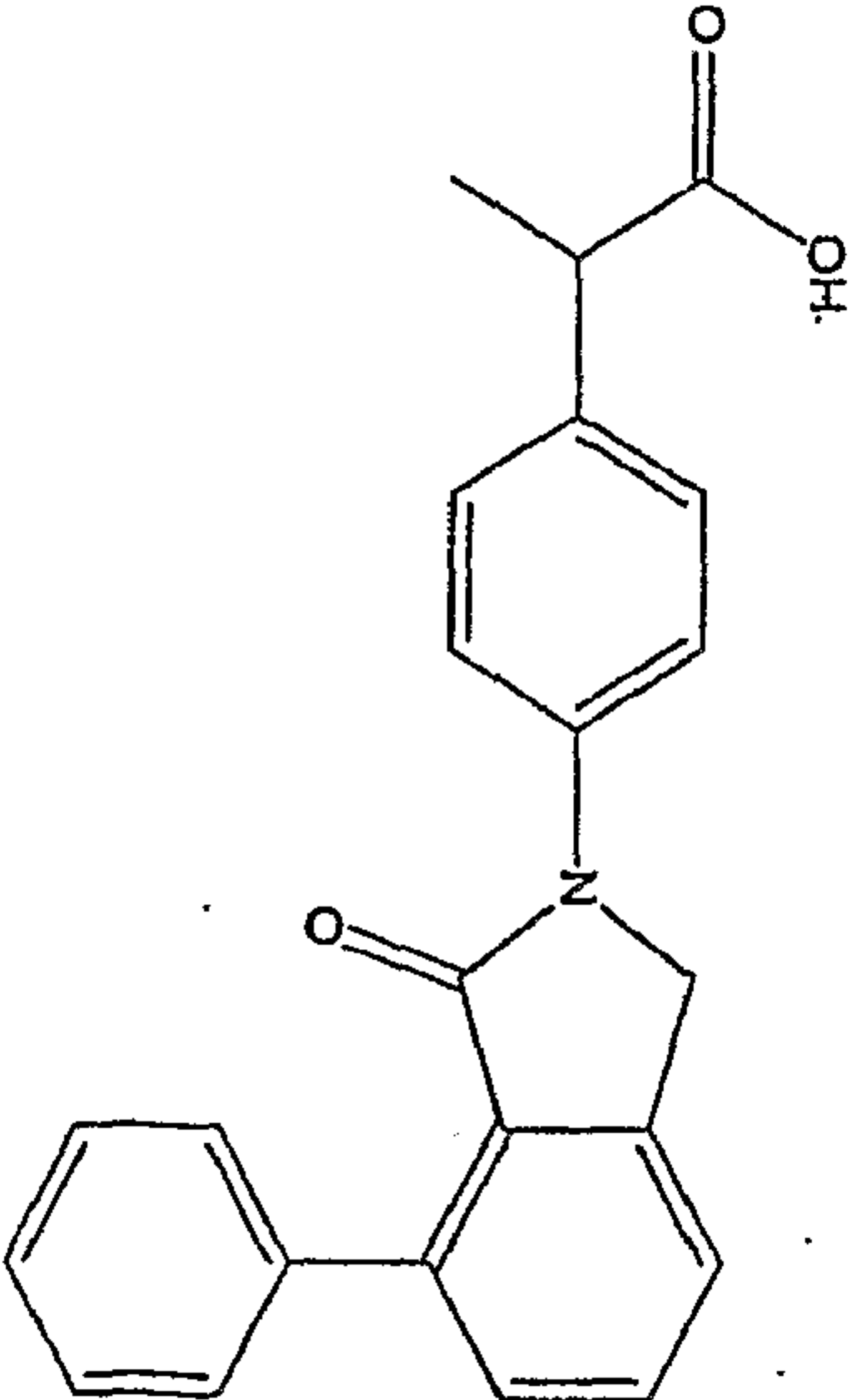
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			Avg EC50 (μ M)	Avg MaxFold Increase
89		ALB- 112150		1.096
90		ALB- 112151		1.114

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
91		ALB- 112152		1.036
92		ALB- 112153		1.022

76

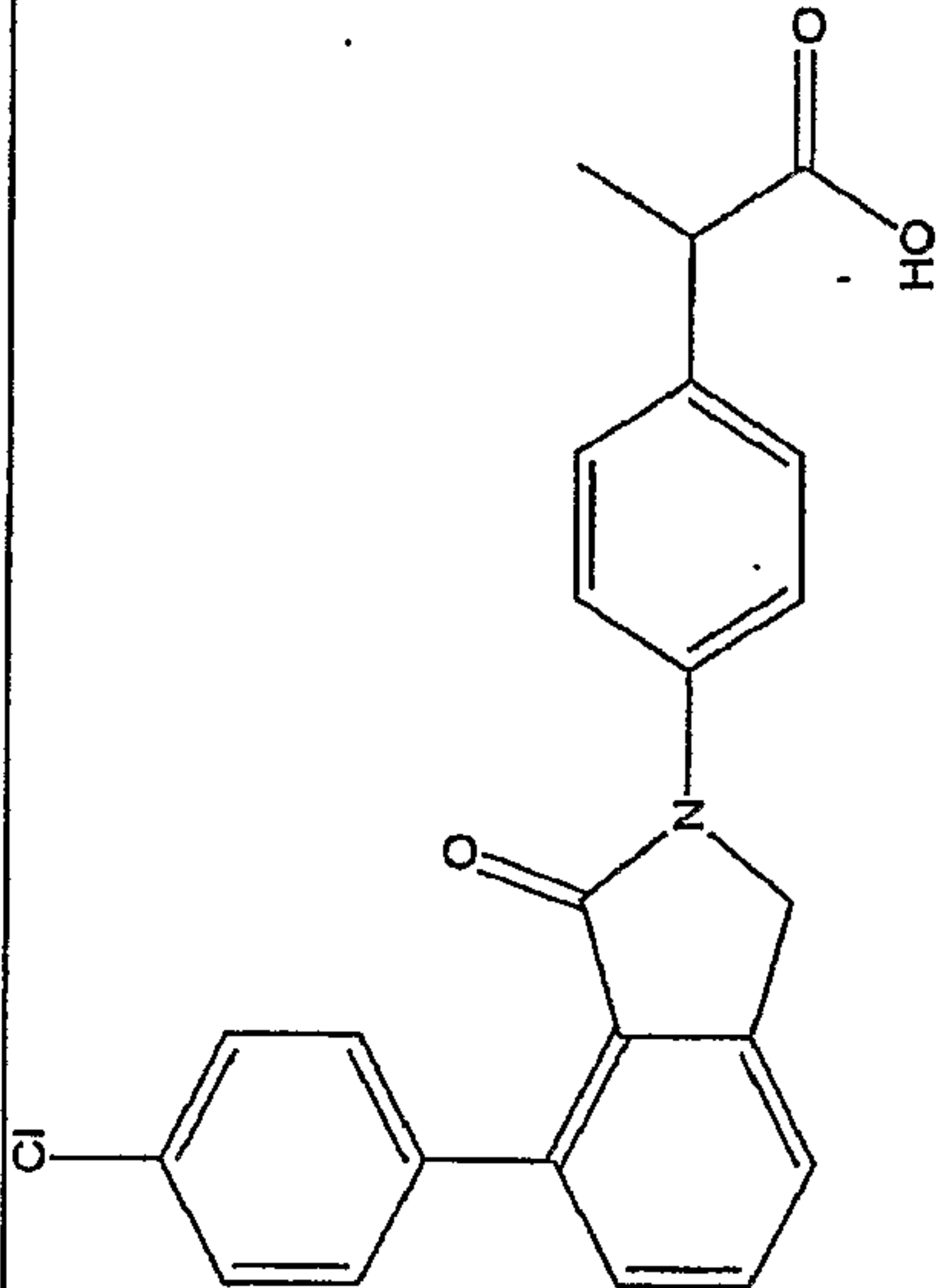
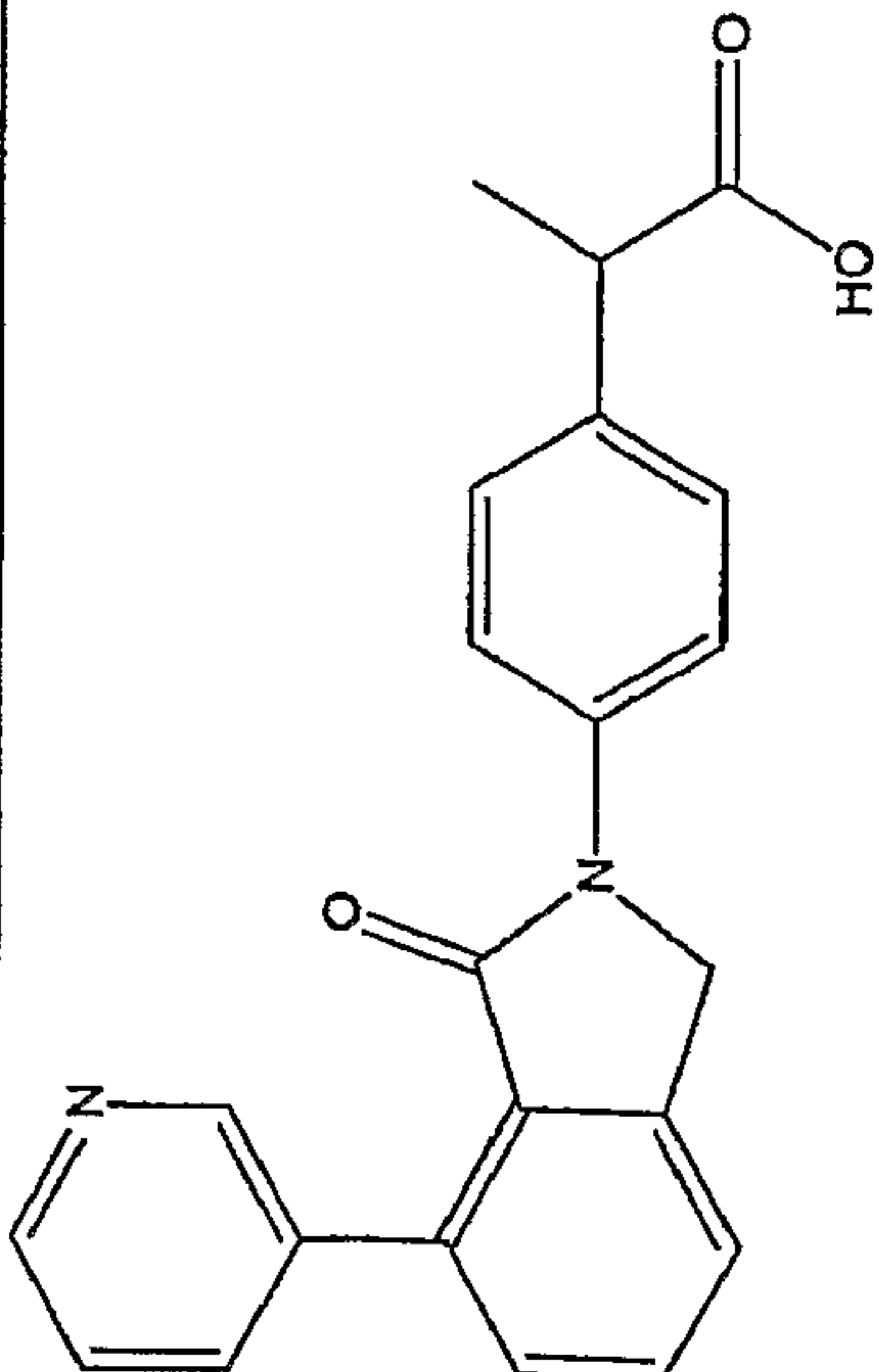
Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
93		ALB- 112154	26.348	1.112
94		ALB- 112155	26.348	1.185

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μM)	Avg MaxFold Increase
95	 <chem>Cc1ccc(cc1C2=CC=C3C(=O)N(C4=CC=C(C=C4)C(=O)O)CC3=C2)c5ccccc5</chem>	ALB-112174		1.183
96	 <chem>COc1ccc(cc1C2=CC=C3C(=O)N(C4=CC=C(C=C4)C(=O)O)CC3=C2)c5ccccc5</chem>	ALB-112156		1.27

78

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
97		ALB- 112175	16.926	1.366
98		ALB- 112157	20.512	1.196

79

Table 1

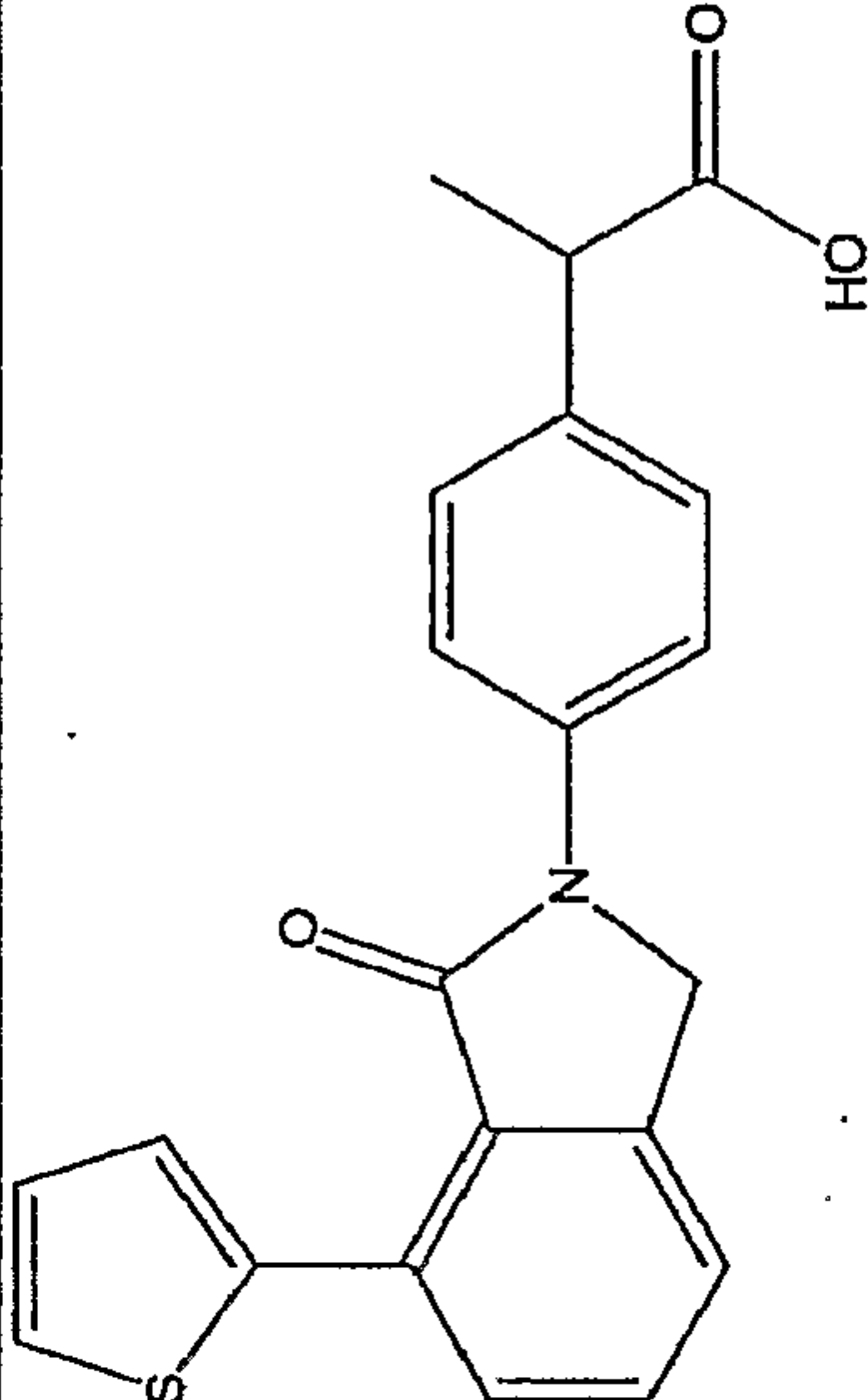
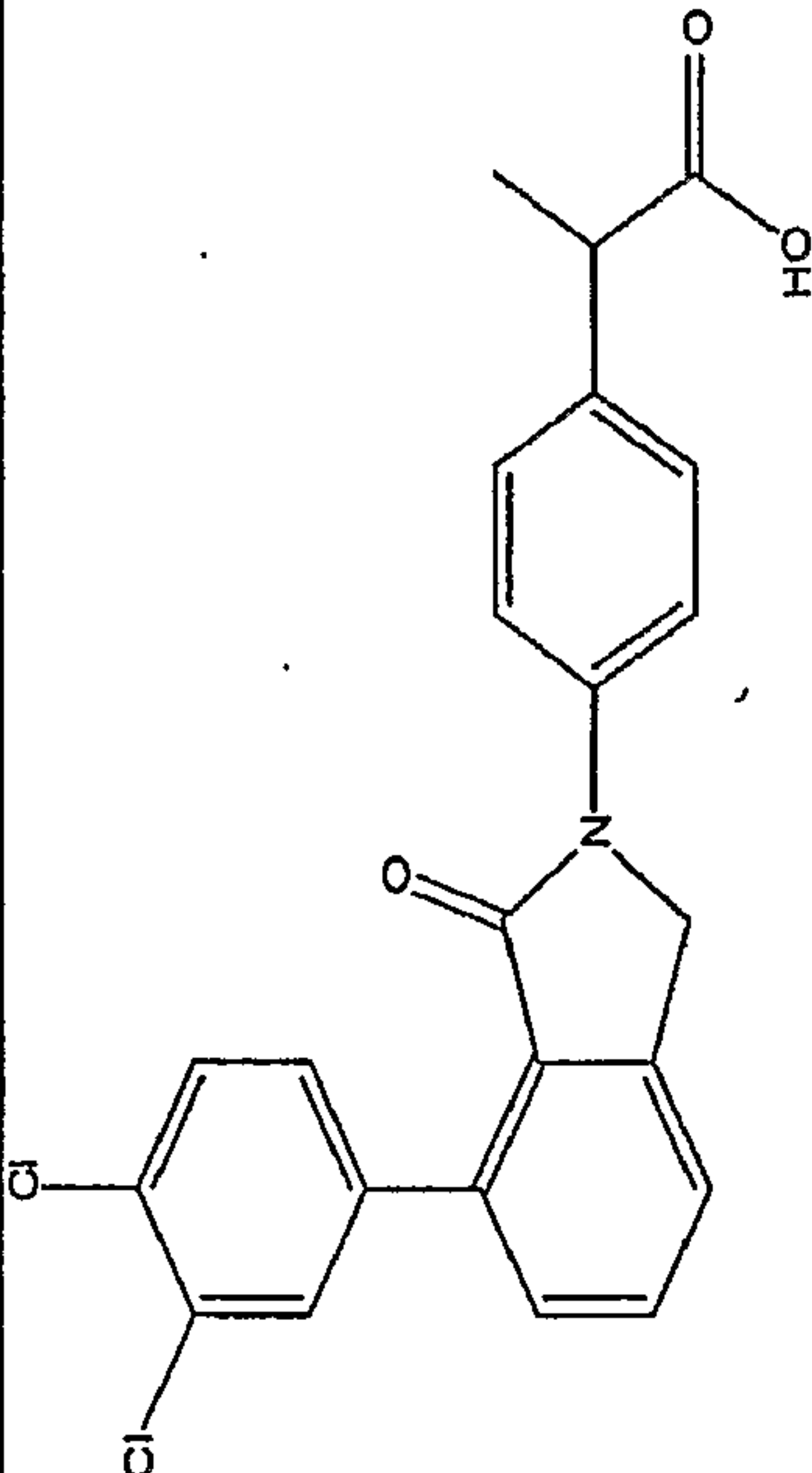
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
99		ALB- 112158	11.429	1.239
100		ALB- 112159		1.477

Table 1

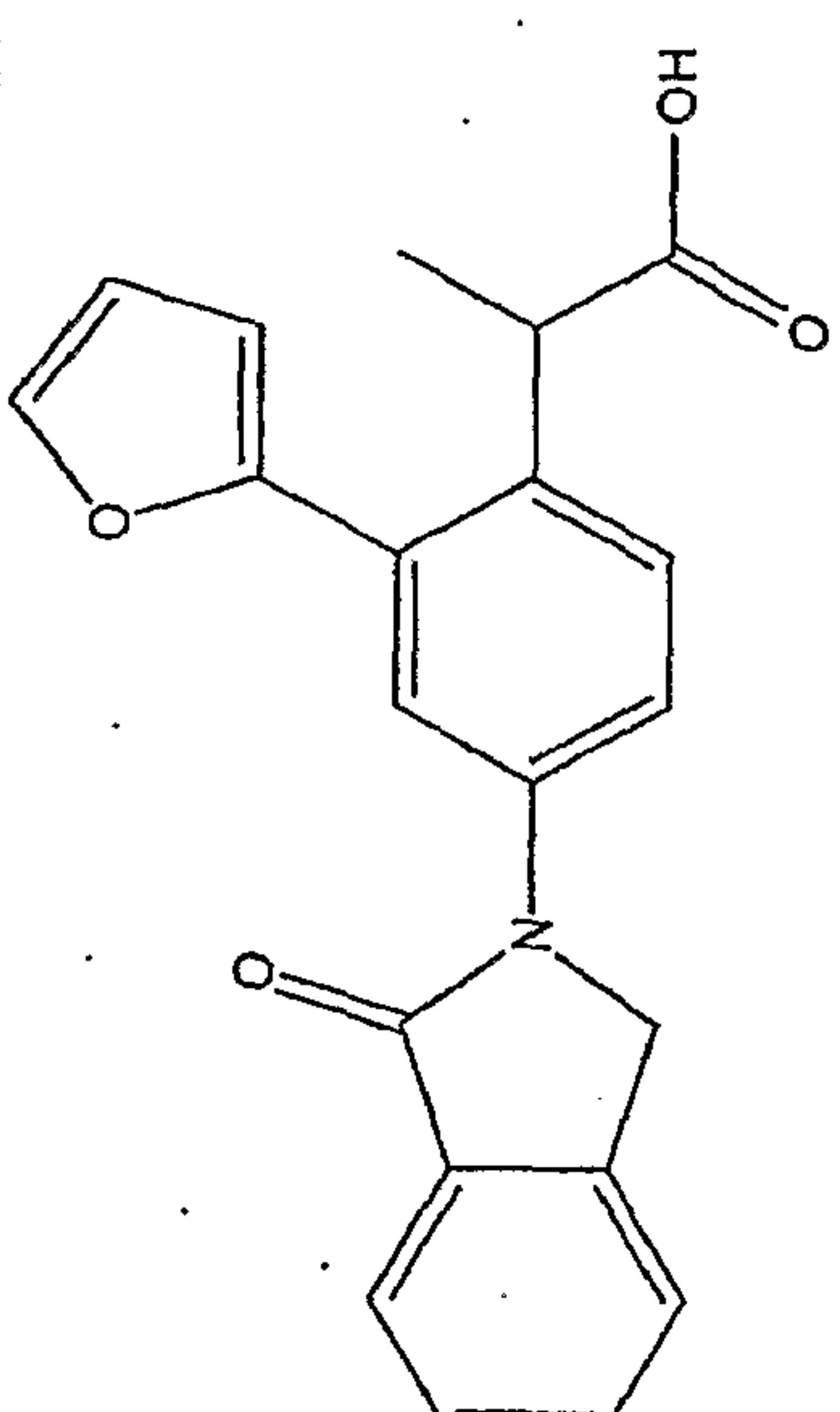
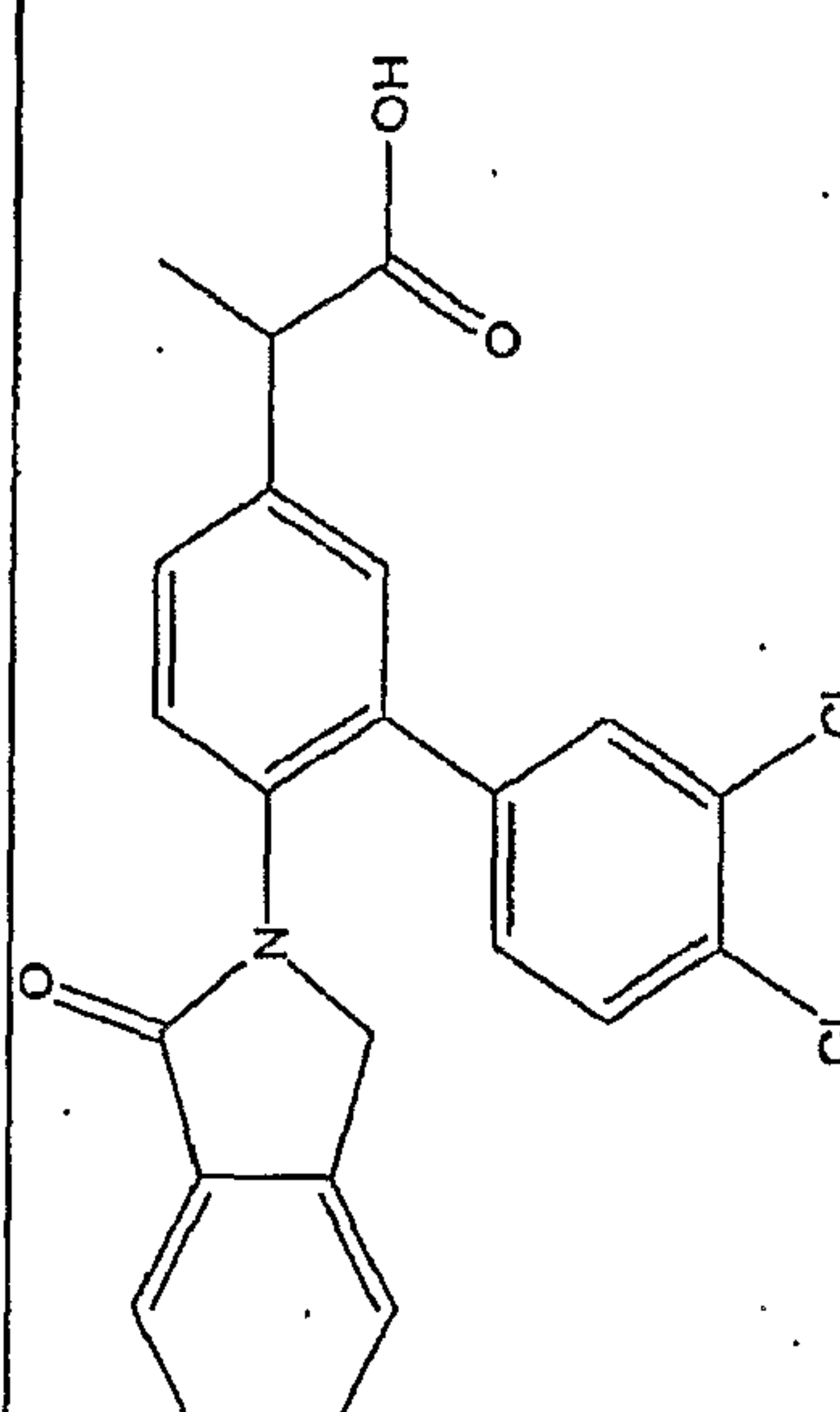
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			Avg EC50 (μ M)	Avg MaxFold Increase
101		ALB- 112160		1.024
102		ALB- 112161		1.096

Table I

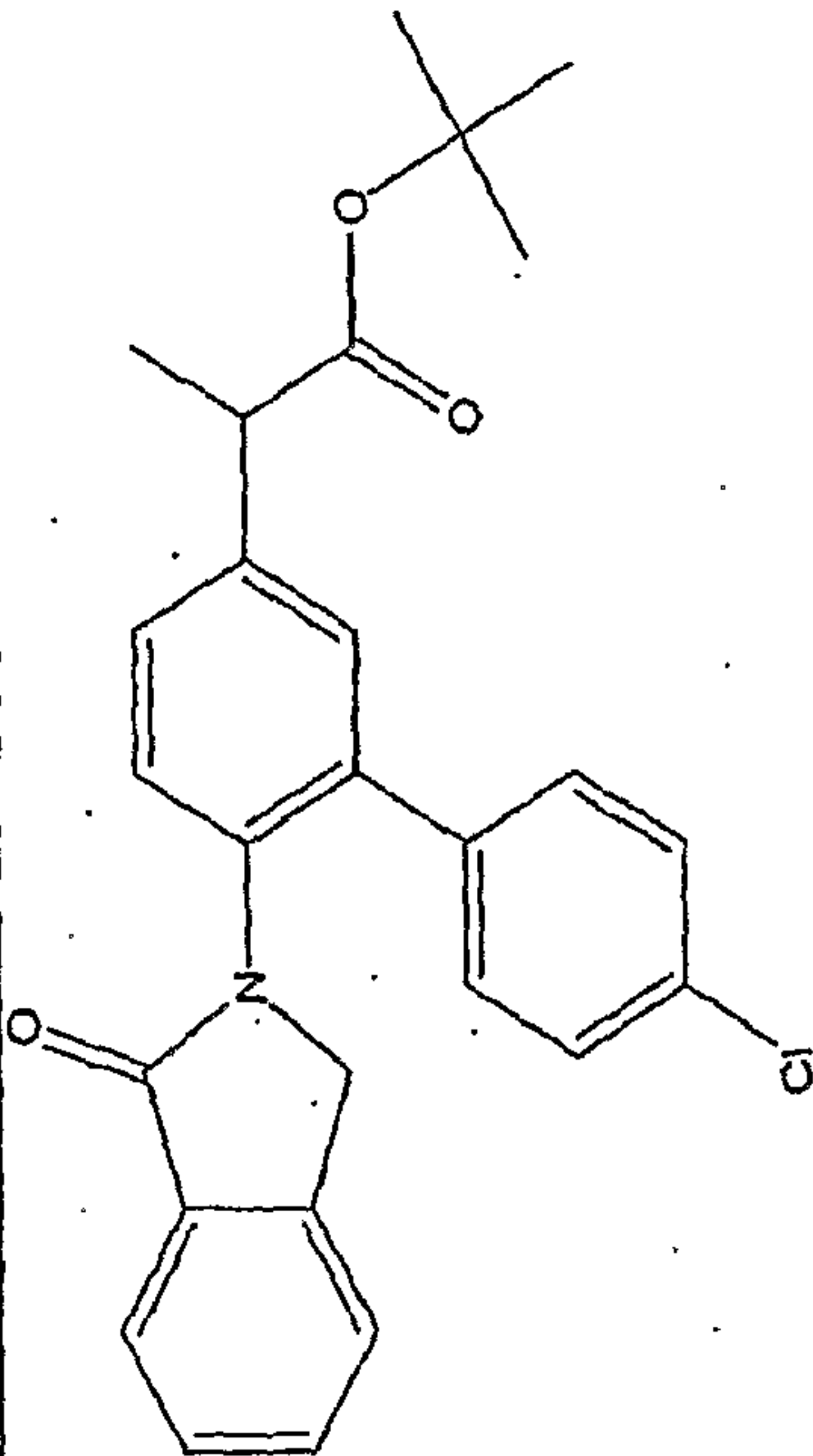
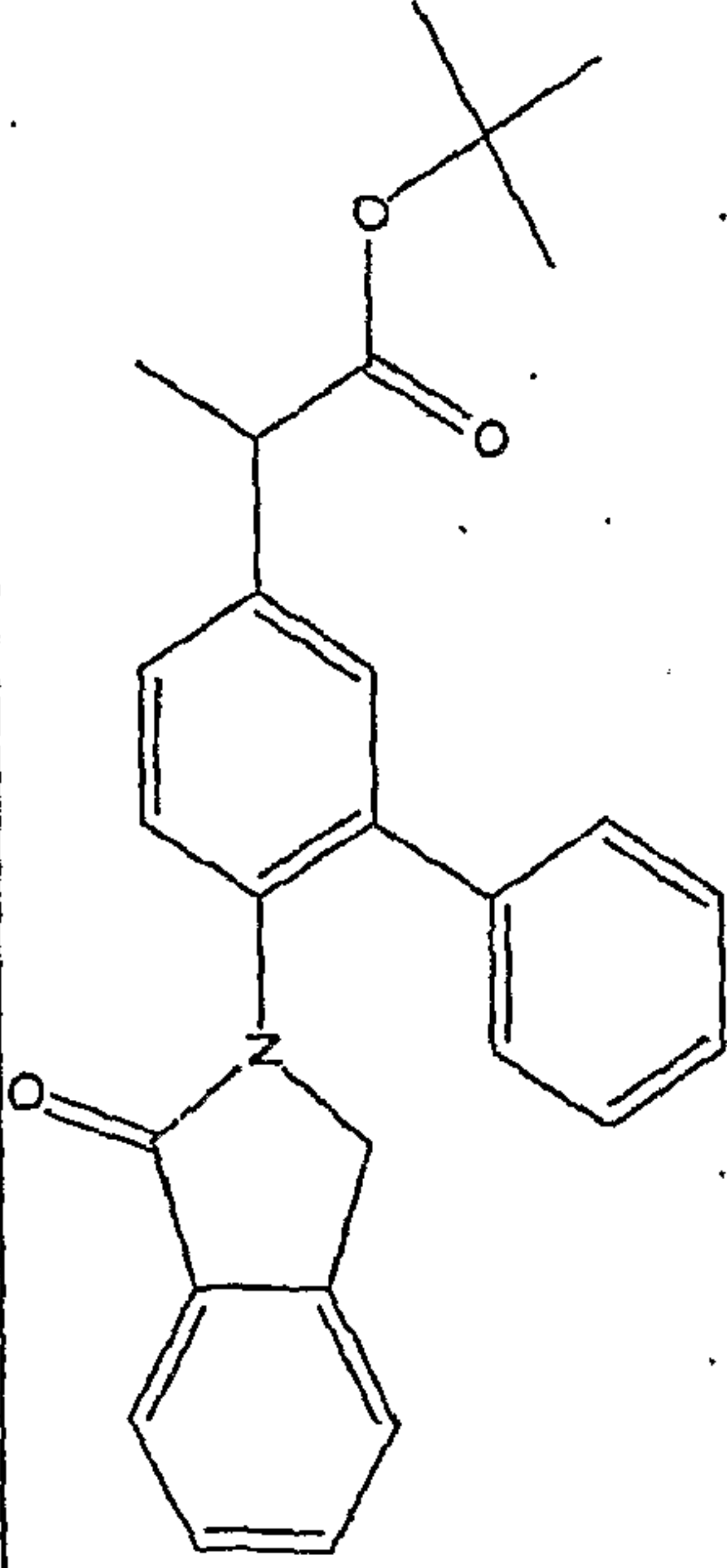
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
103		ALB- 112162		1.032
104		ALB- 112163		1.029

Table 1

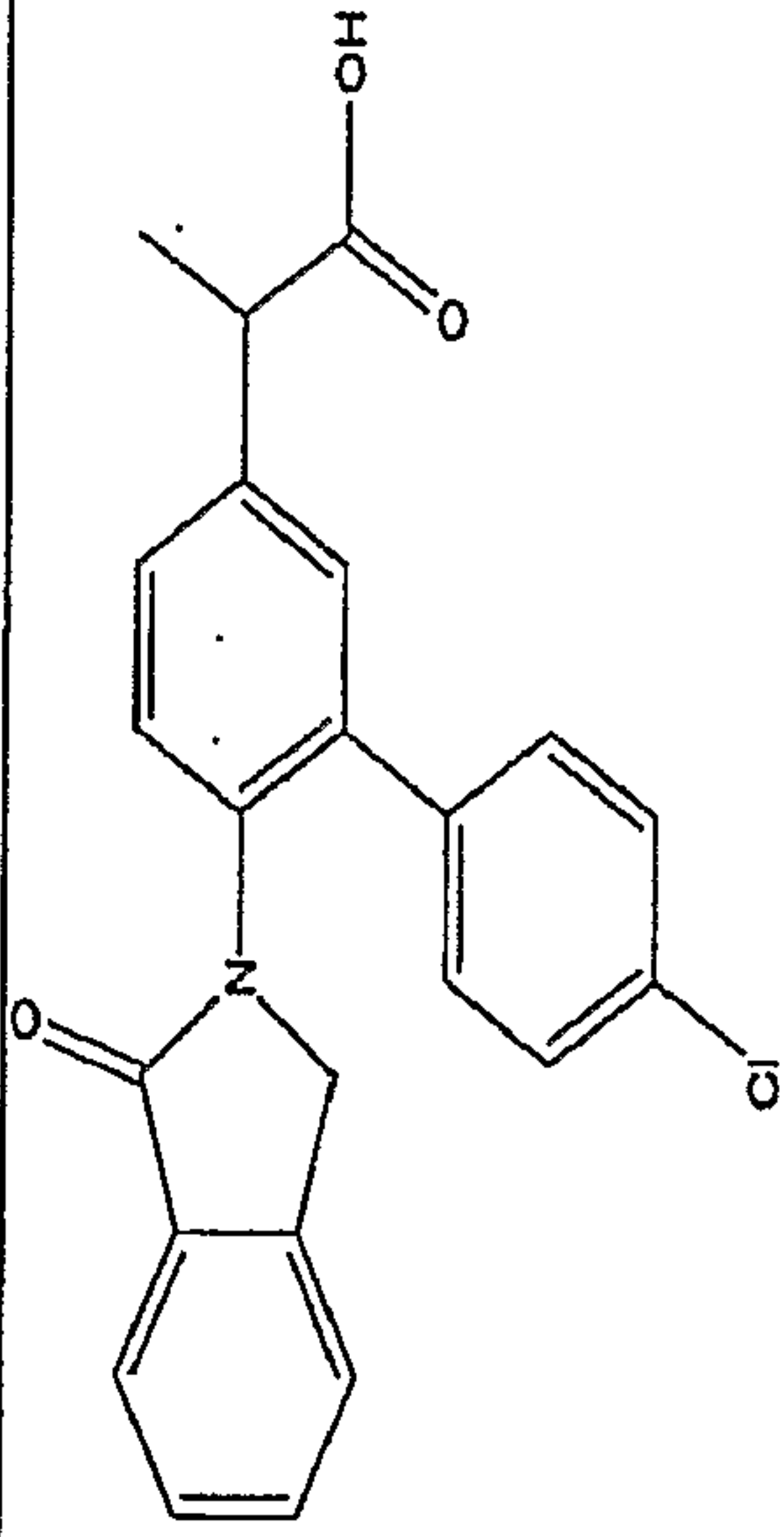
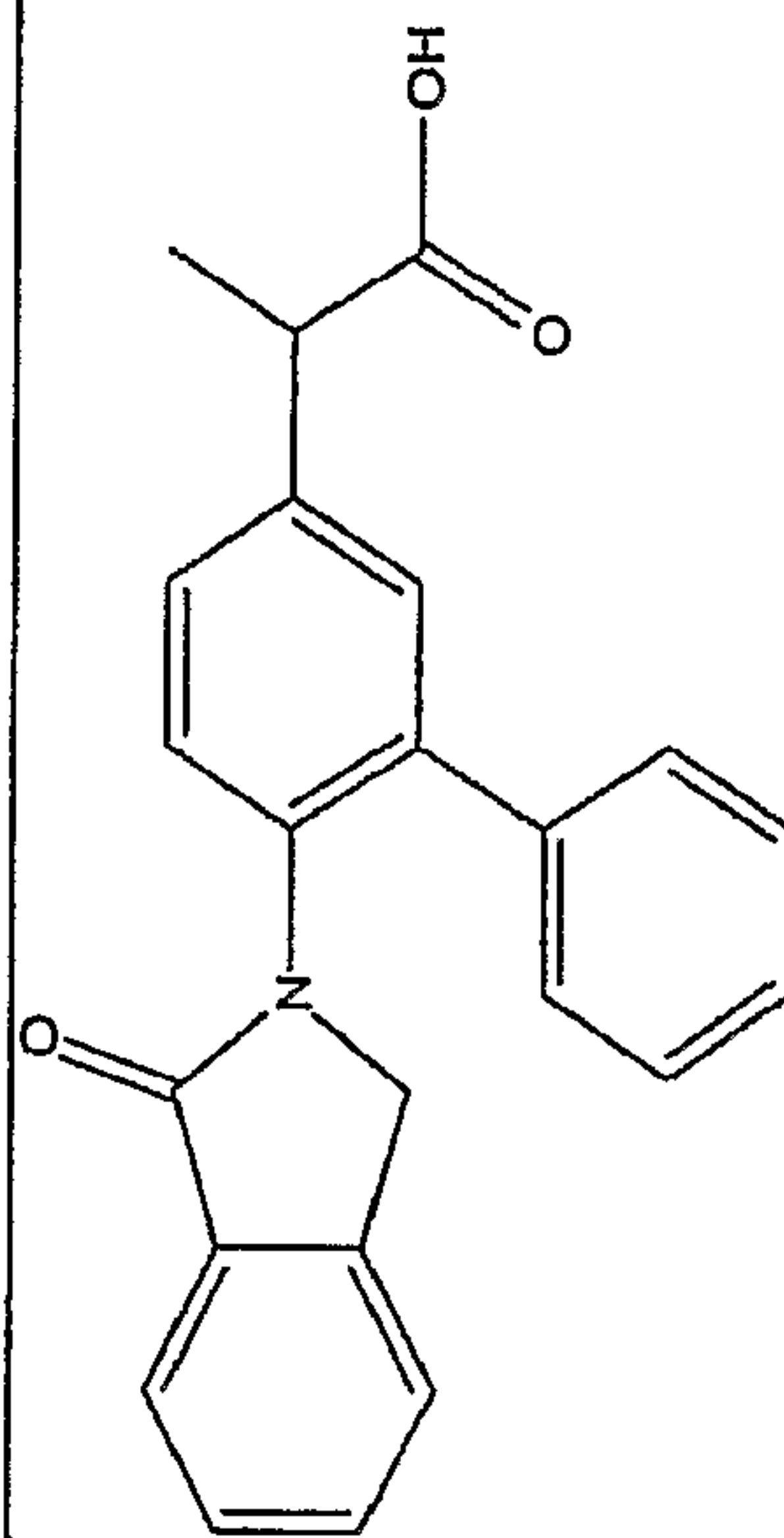
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
105		ALB- 112164		1.052
106		ALB- 112165		1.146

Table 1

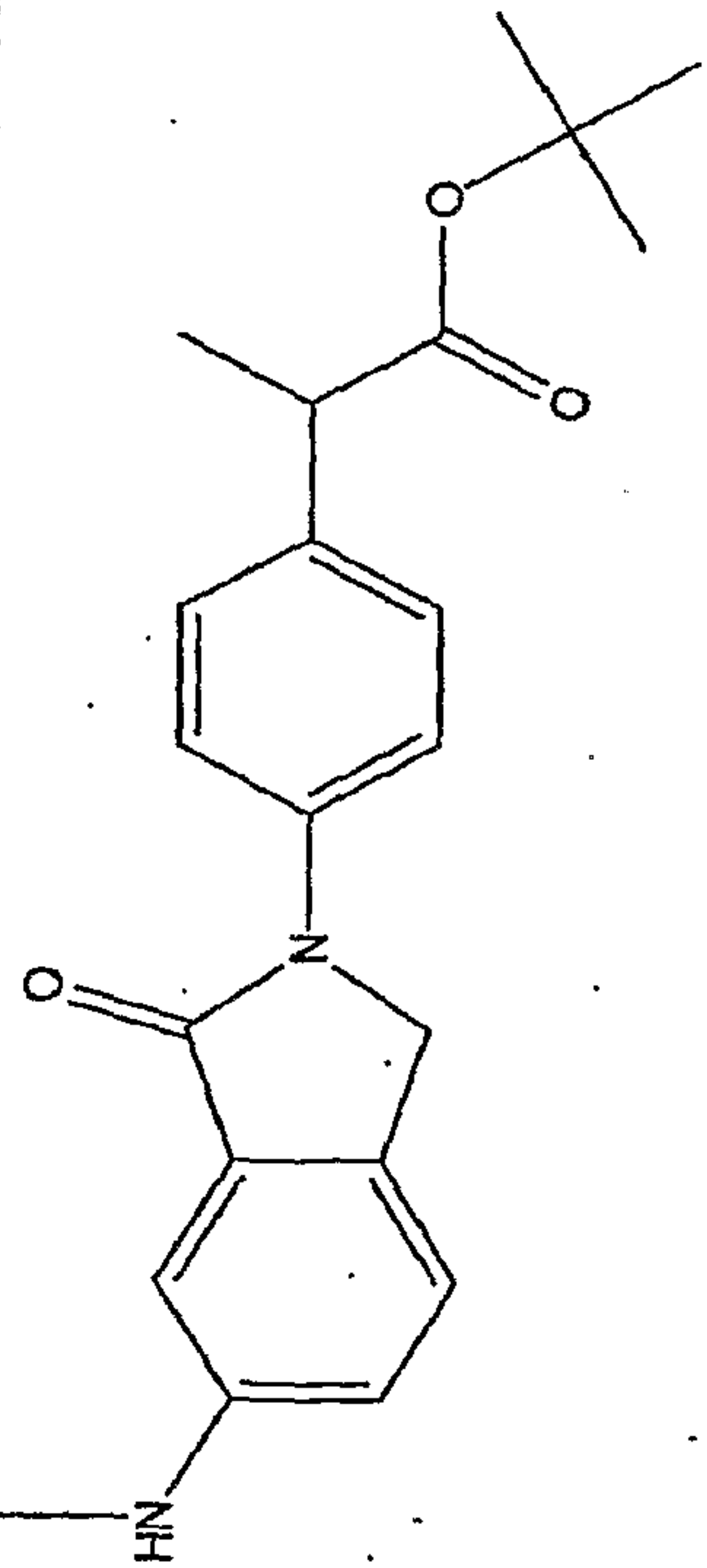
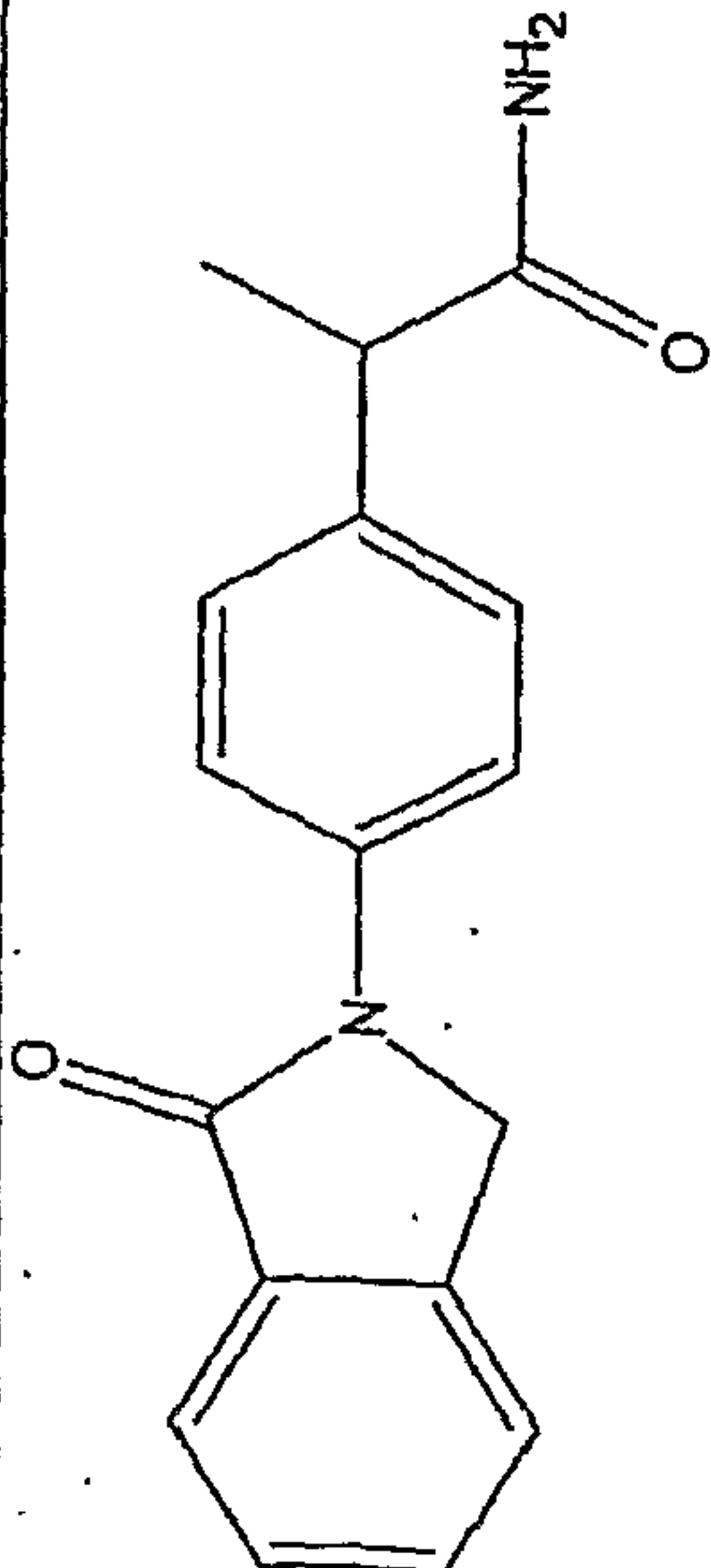
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
107		ALB- 112170	1.038	1.275
108		ALB- 112171	6.716	1.34

Table 1

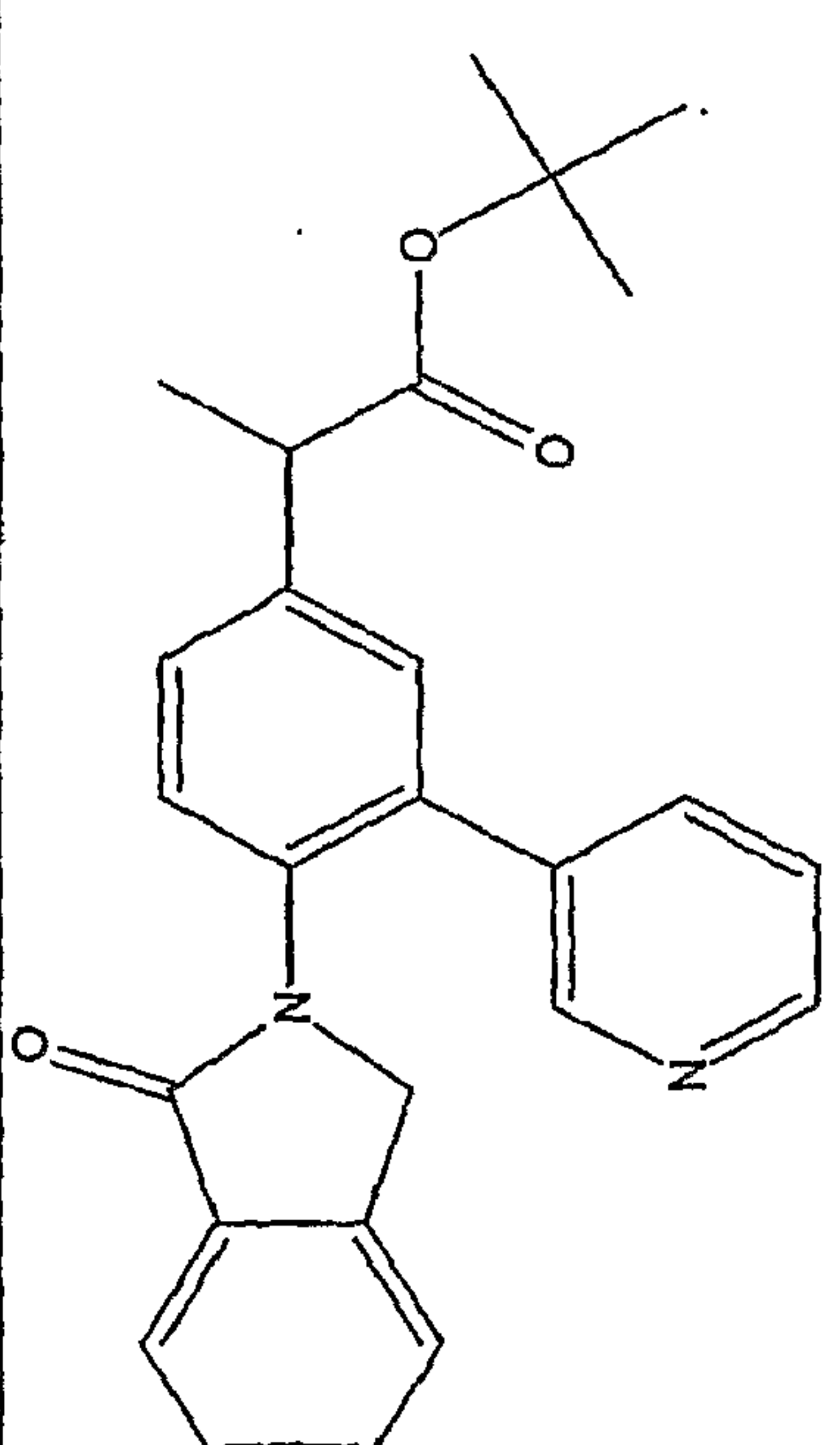
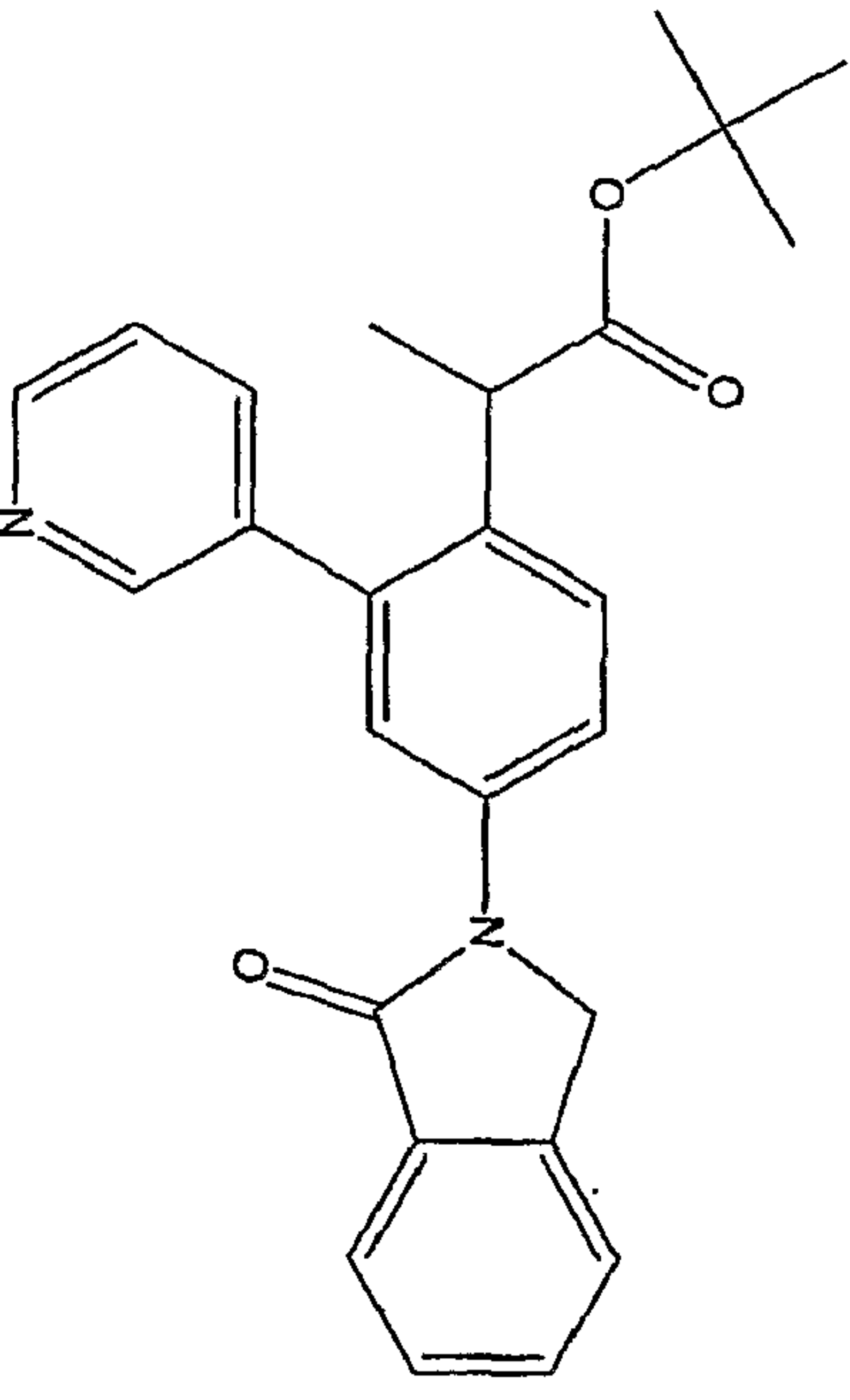
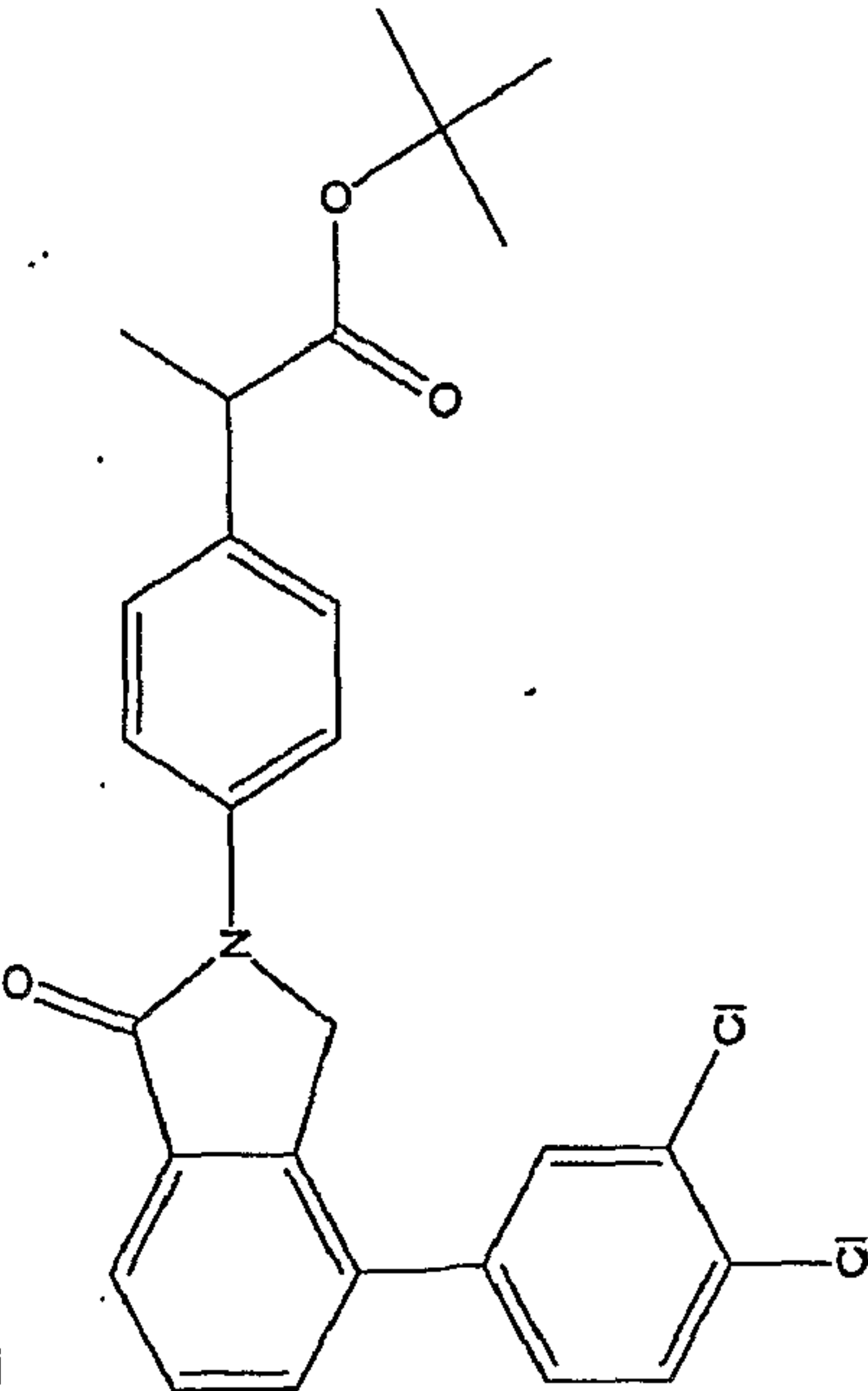
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
109		ALB- 112172		1.041

Table I

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
110		ALB- 112173		1.004

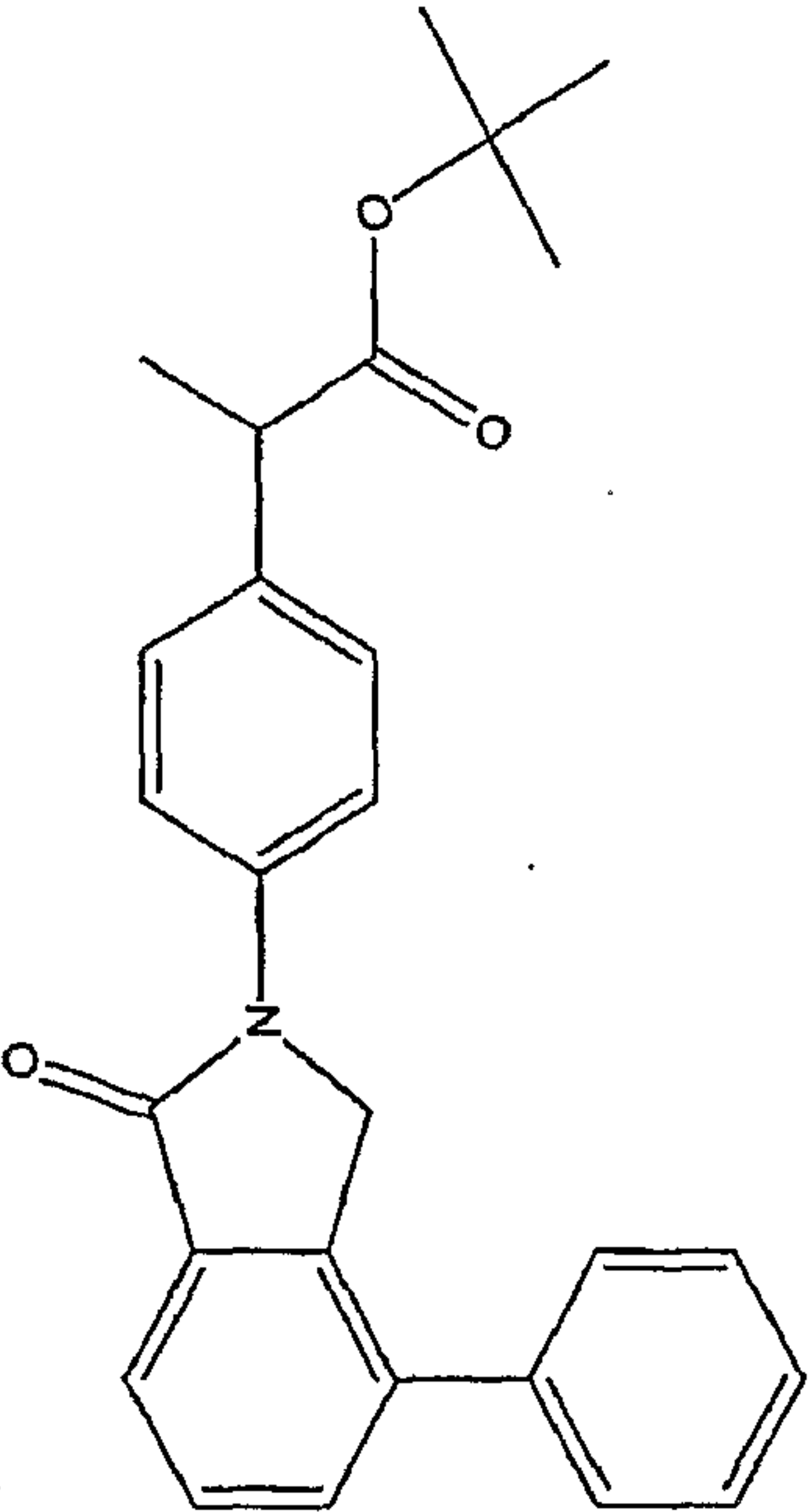
86

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
111		ALB- 112186		1.079

87

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
112		ALB- 112187		1.075

88

Table 1

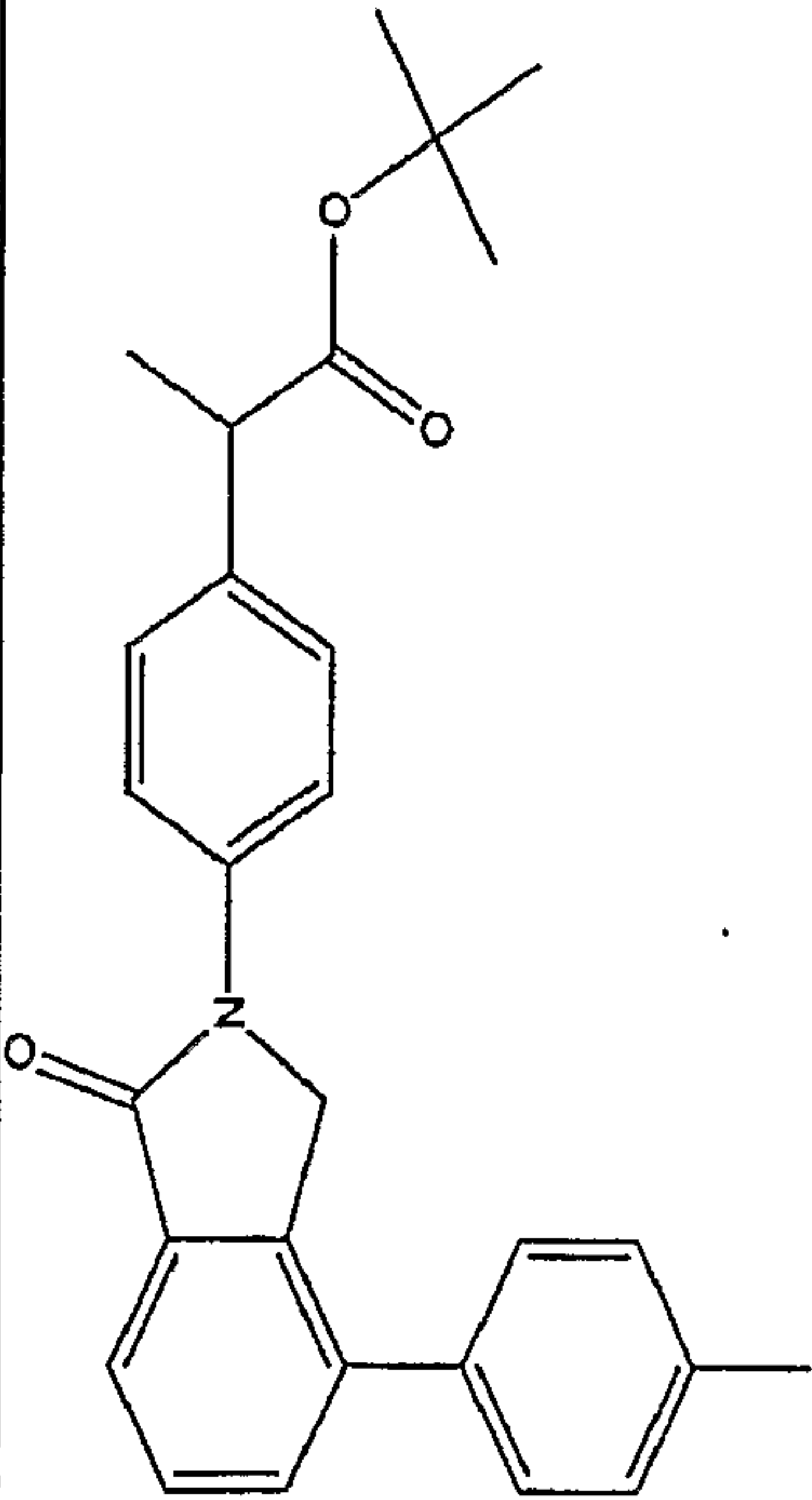
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
113		ALB- 112188		1.082

Table 1

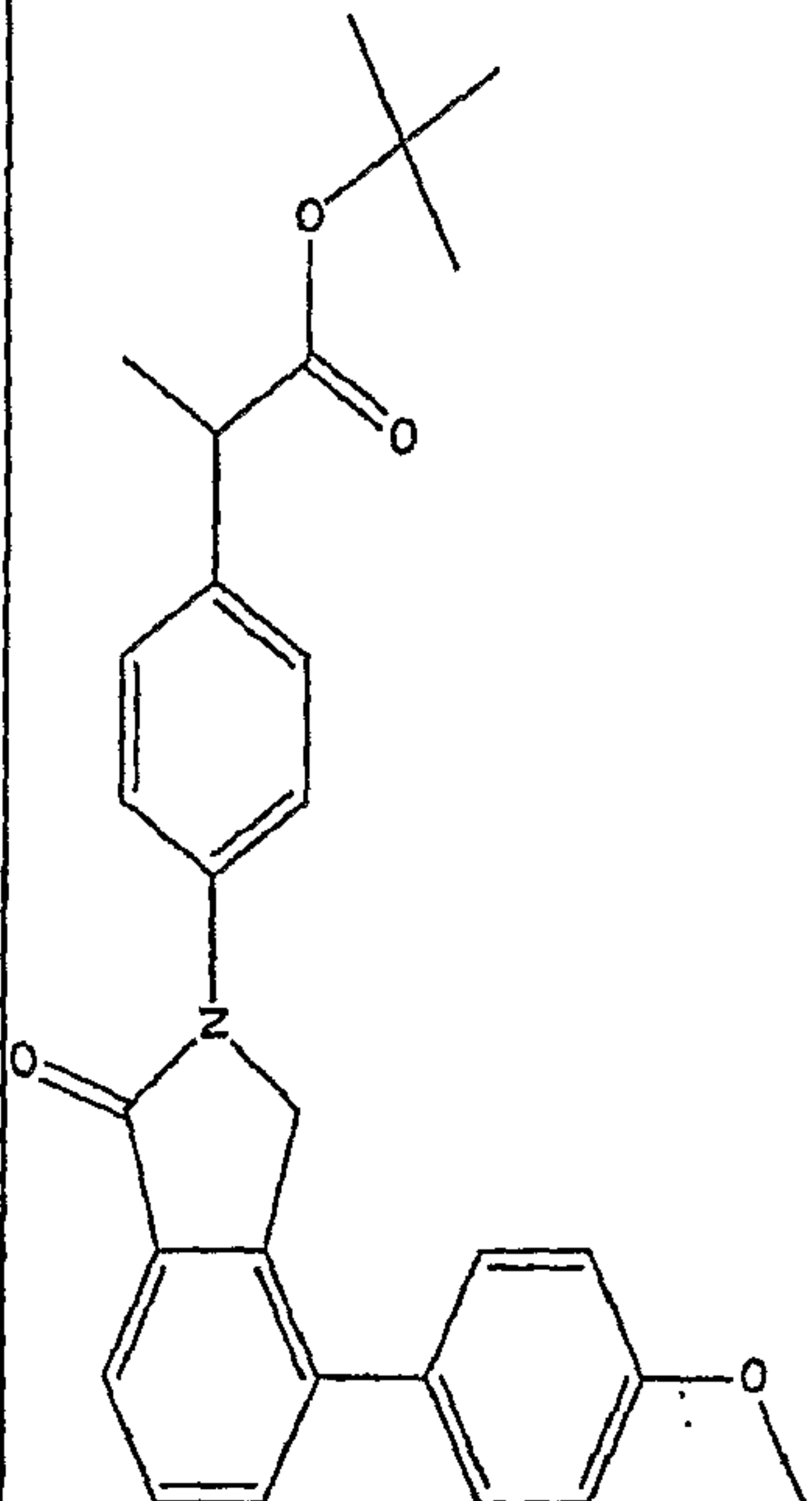
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
114		ALB- 112189		1.066

Table 1

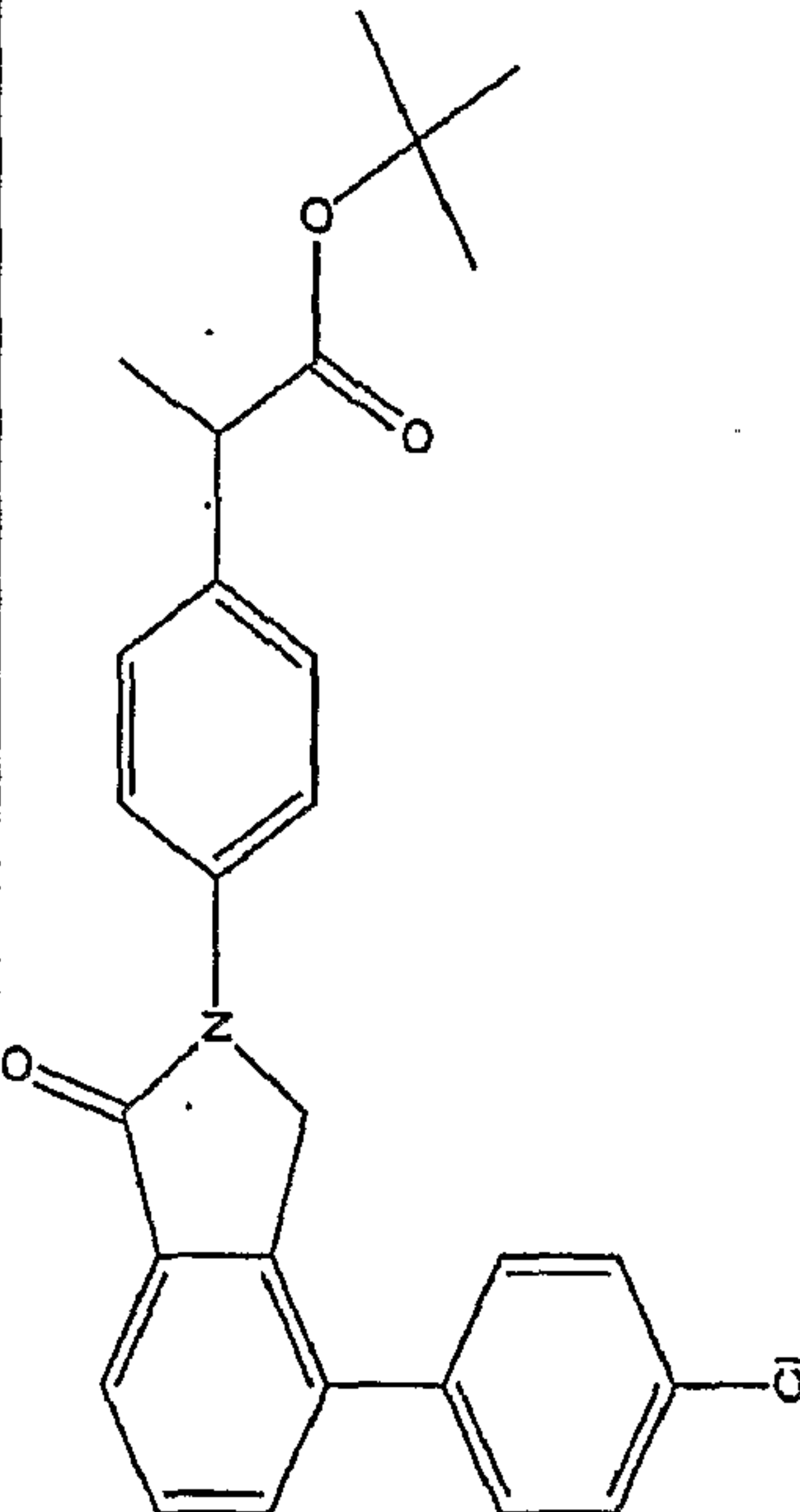
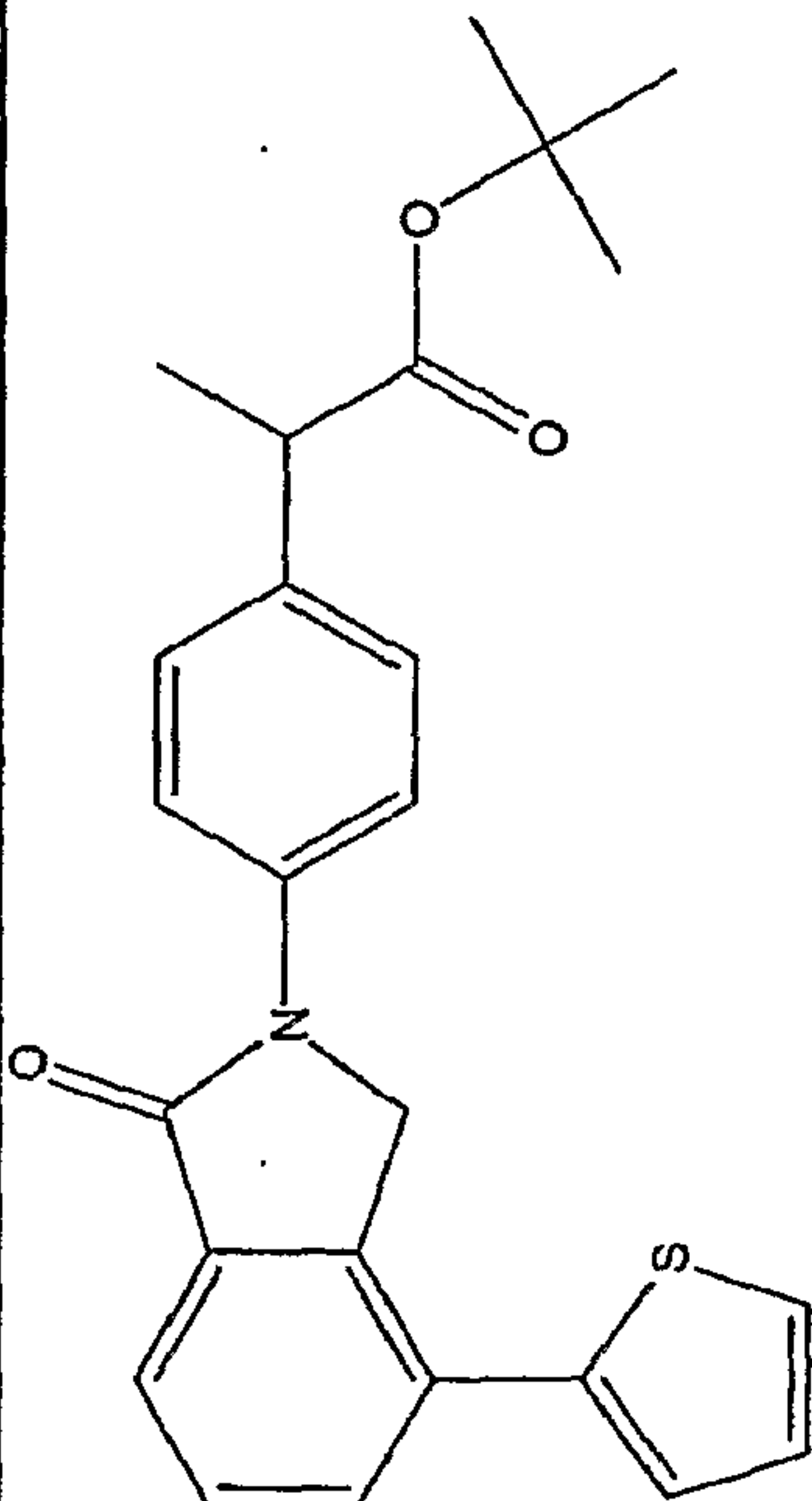
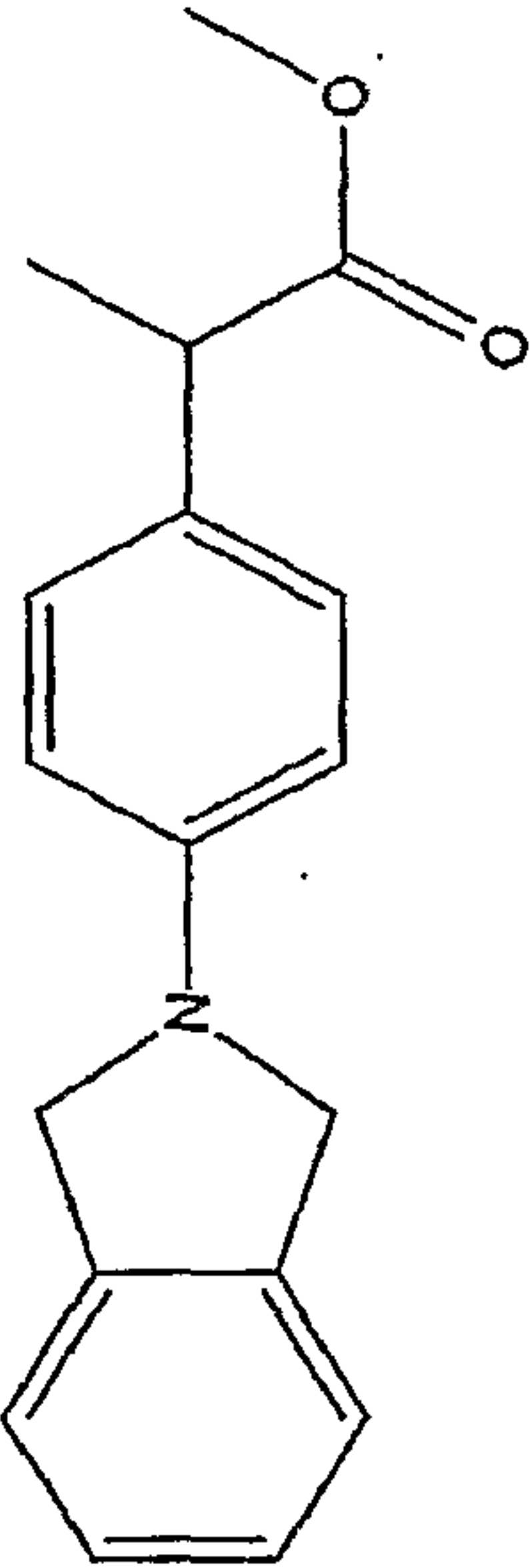
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
115		ALB- 112190		1.099
116		ALB- 112191		1.124

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
117		ALB- 112192	5.721	1.412

92

Table 1

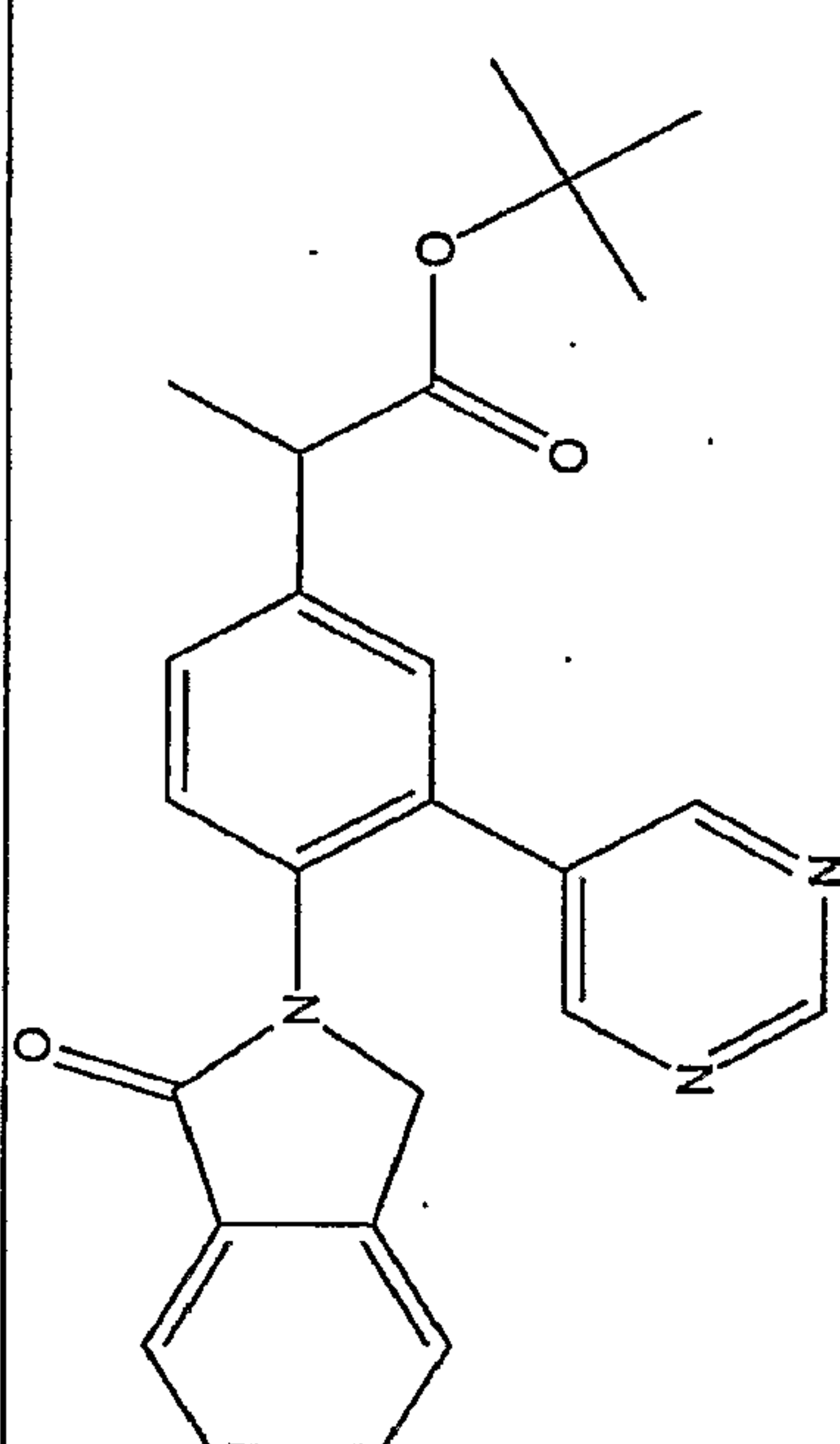
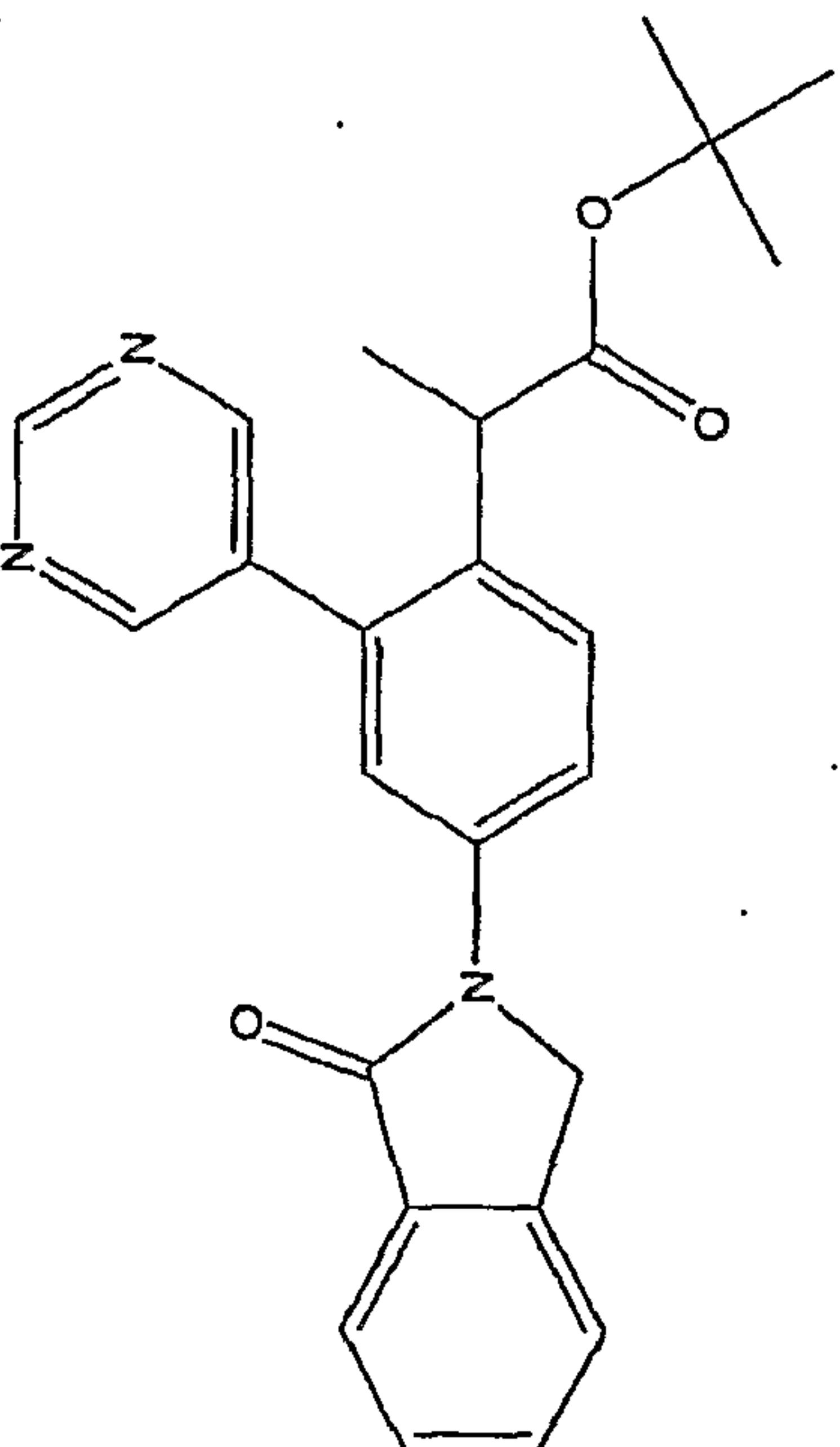
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
118	 <chem>CC(C)C(=O)OC(C)(C)C1=CC=C(C=C1C2=CC=CC=C2N3C(=O)C4=CC=CC=C4N3C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=N7)C8=CC=CC=N8</chem>	ALB- 112194		1.098

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
119		ALB- 112195		1.061

94

Table 1

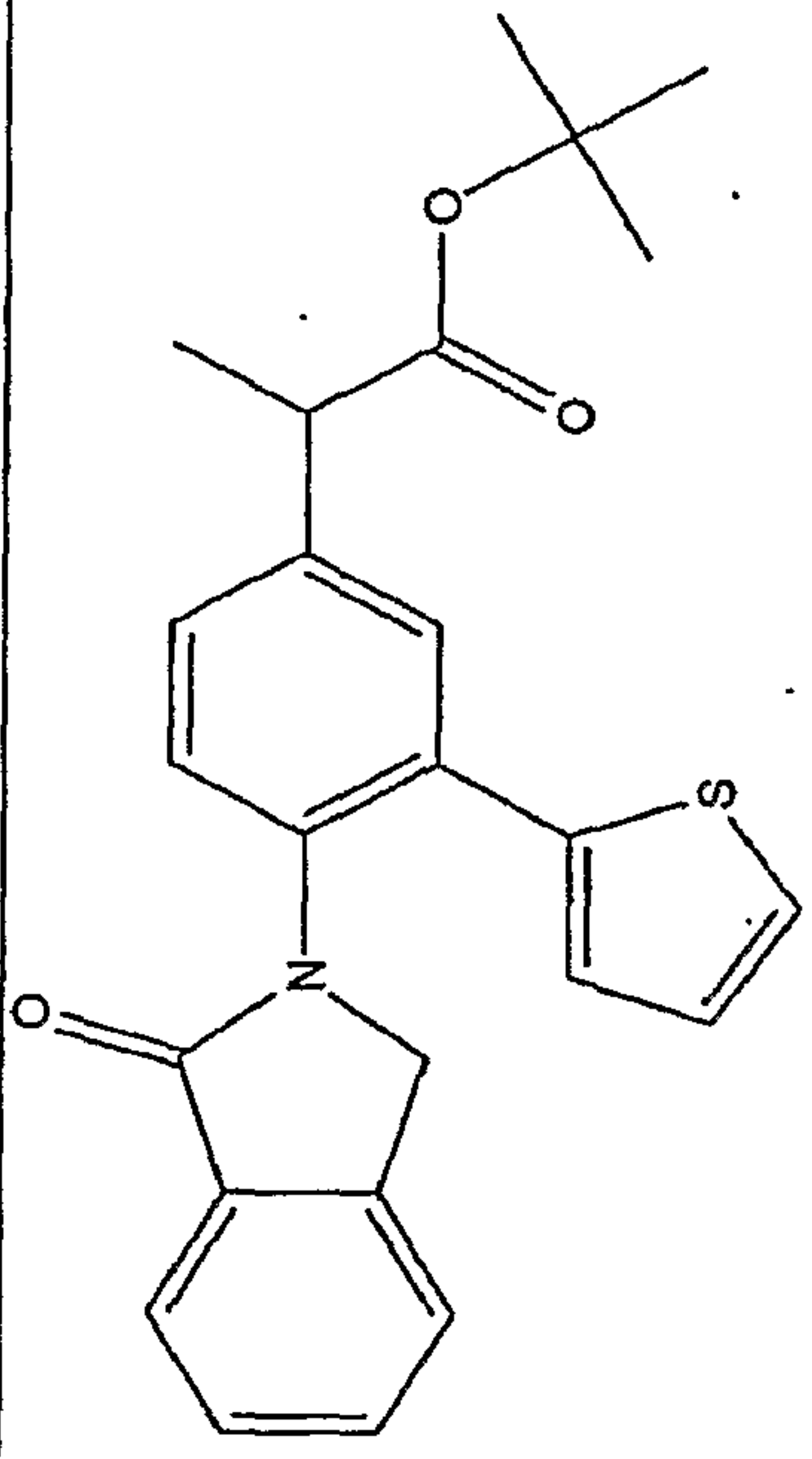
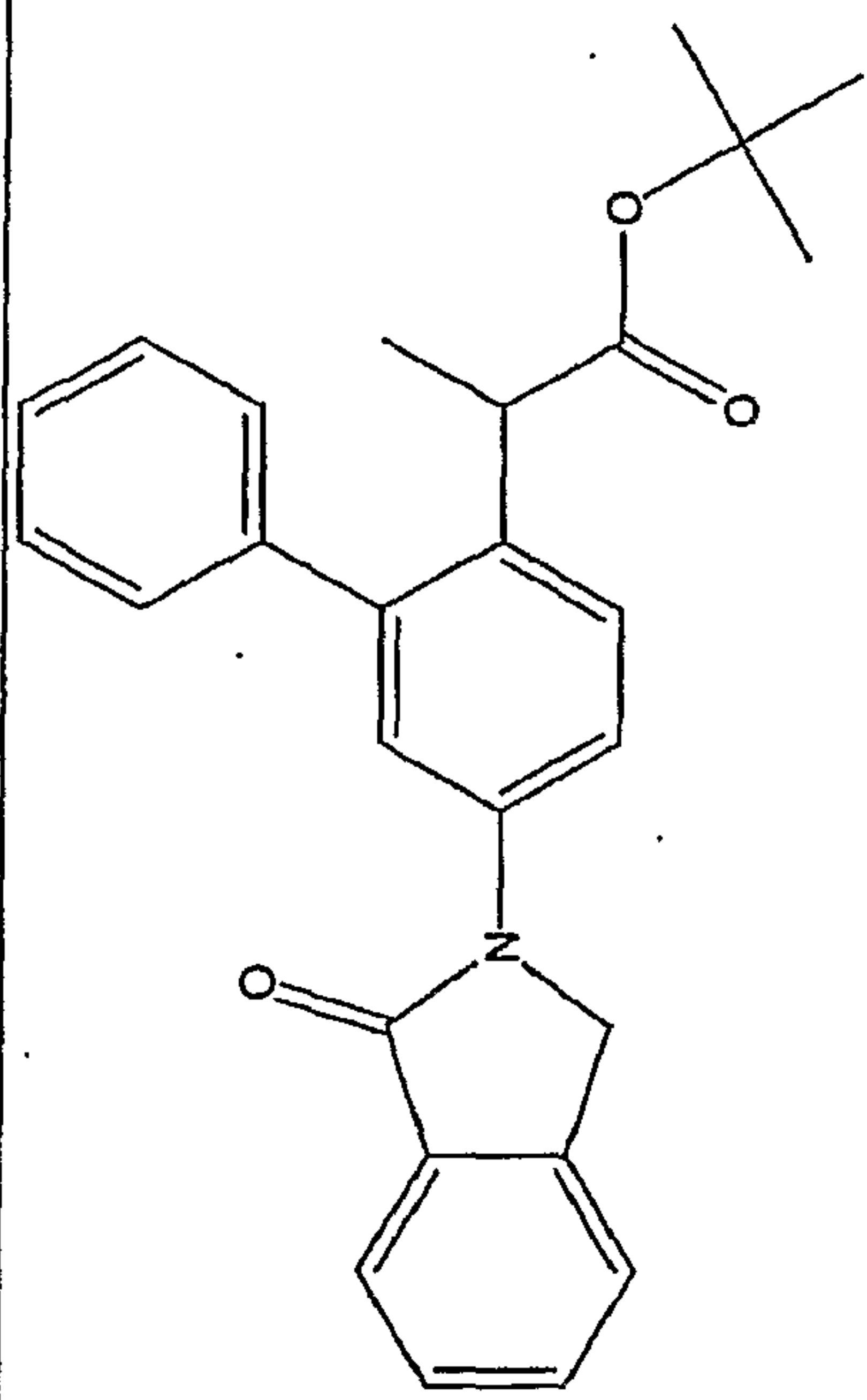
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
120		ALB- 112196		1.095
121		ALB- 112197		1.069

Table 1

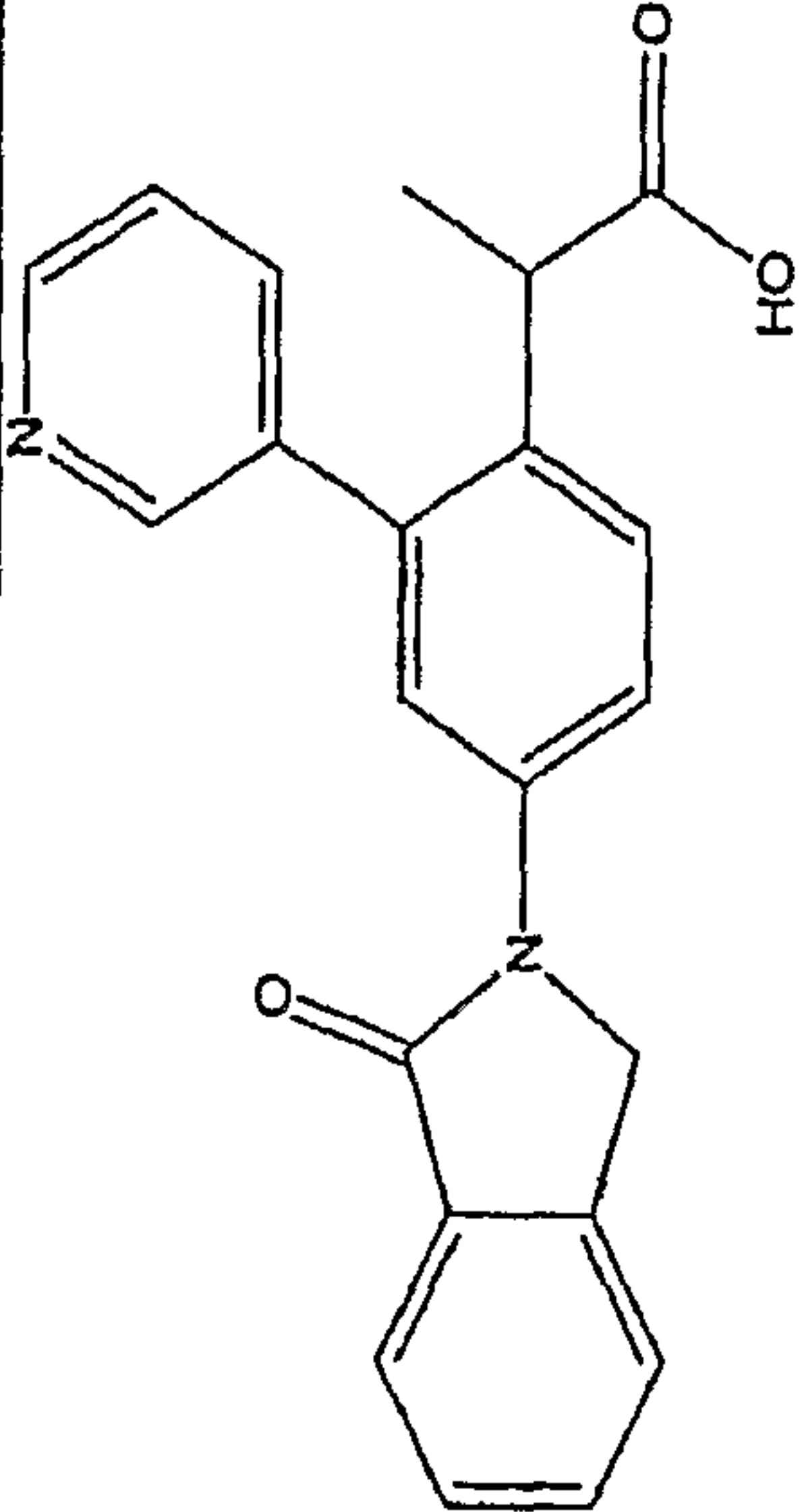
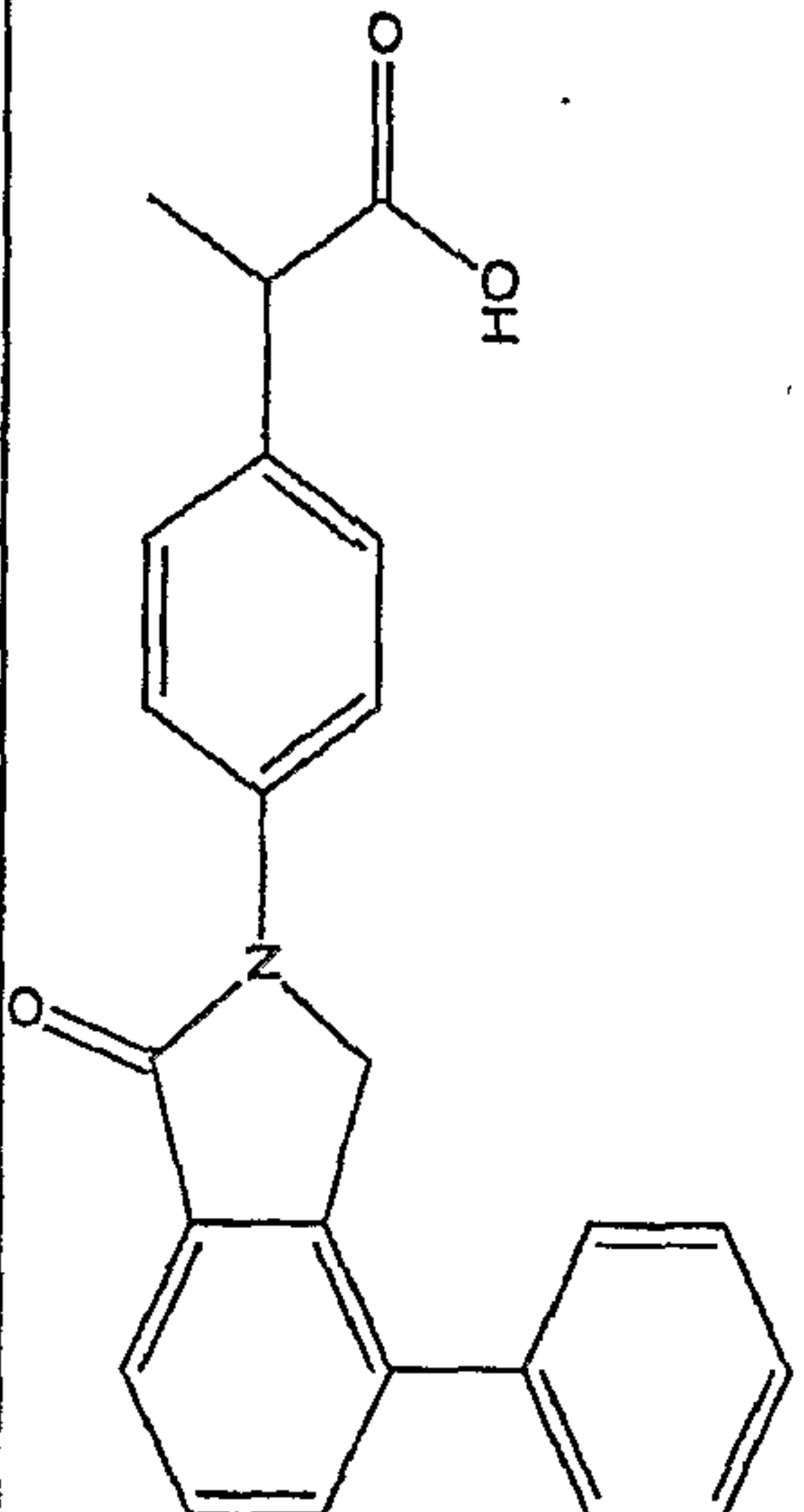
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
123		ALB- 112199		1.083
124		ALB- 112220		1.223

Table 1

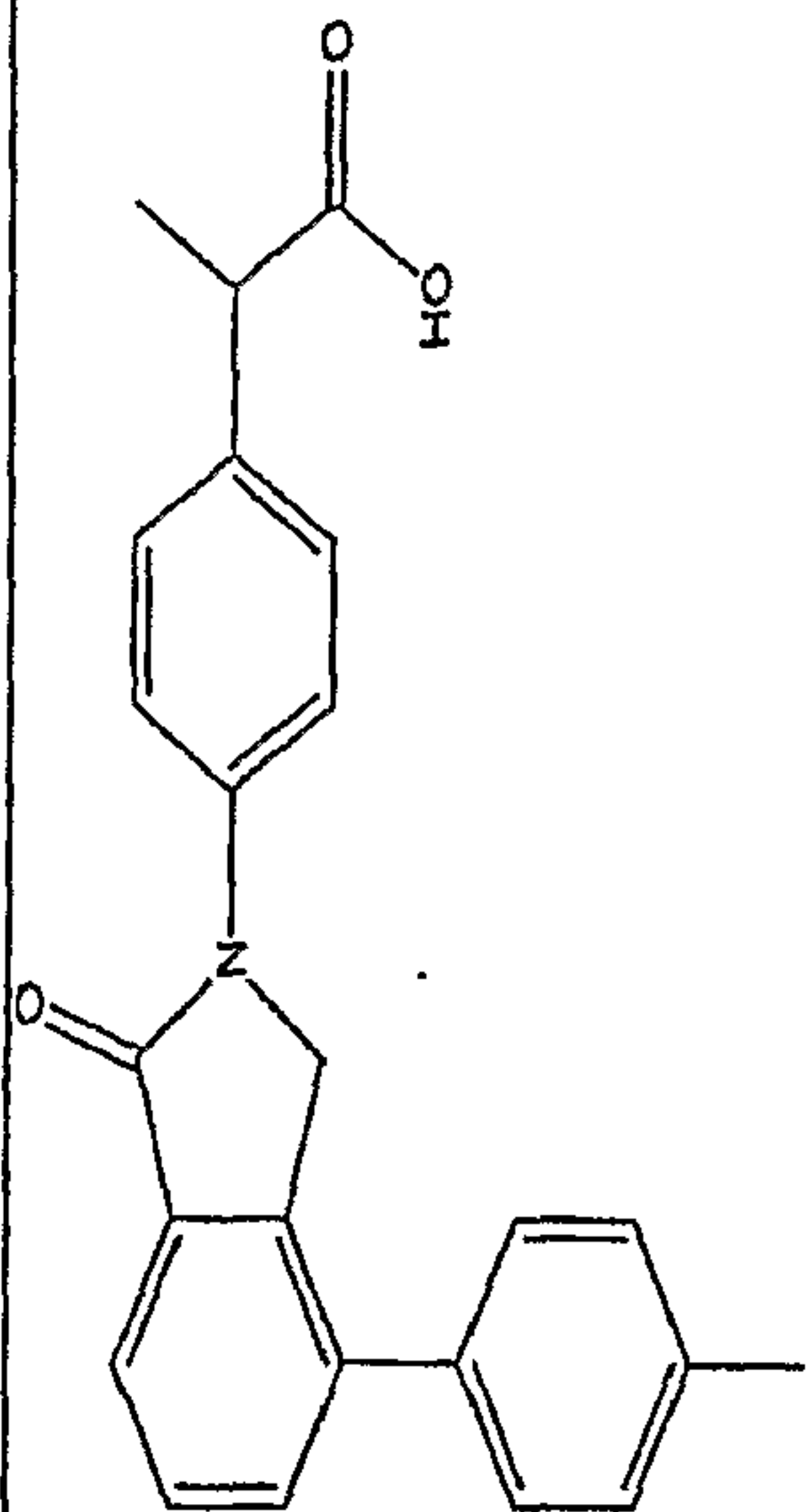
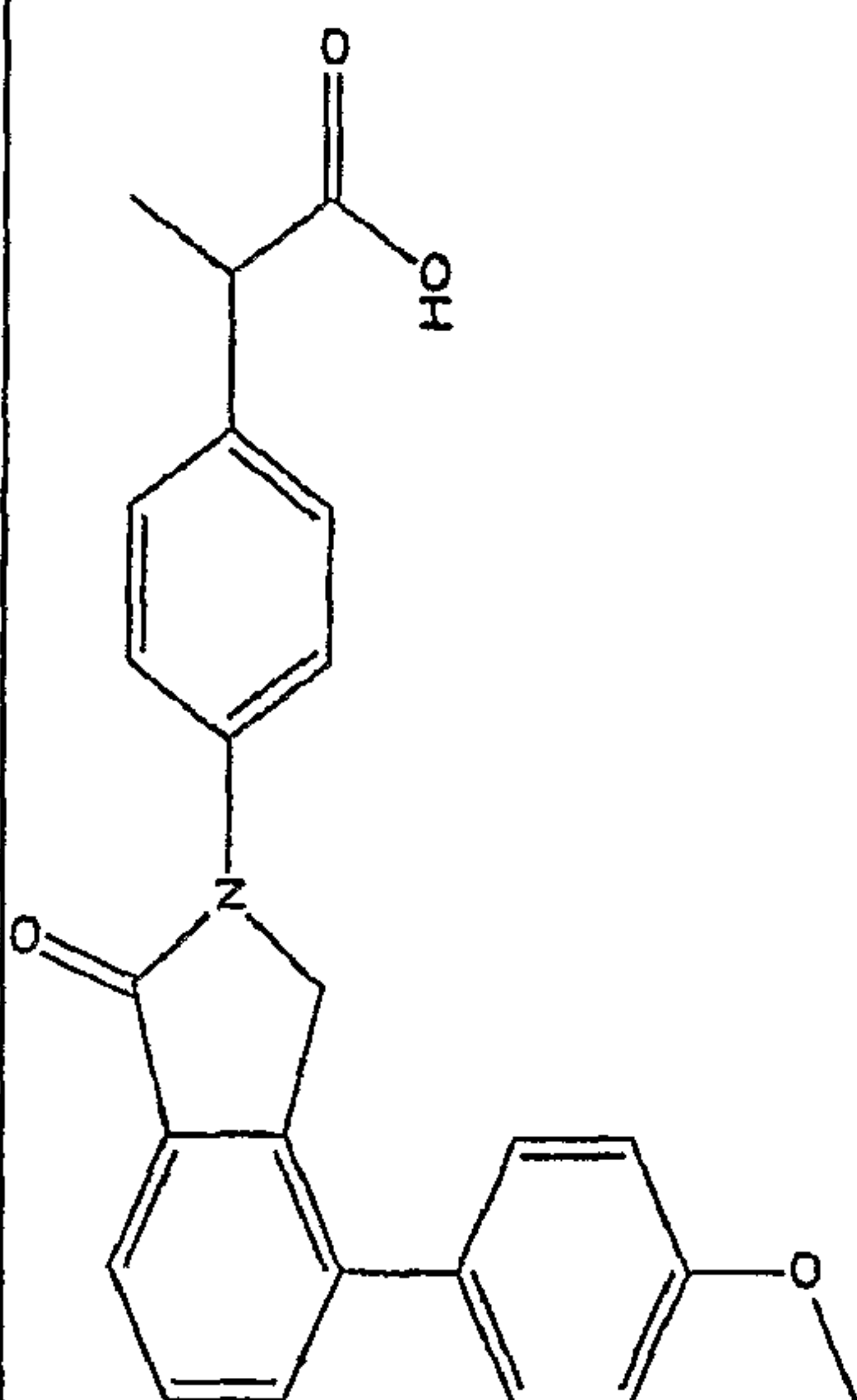
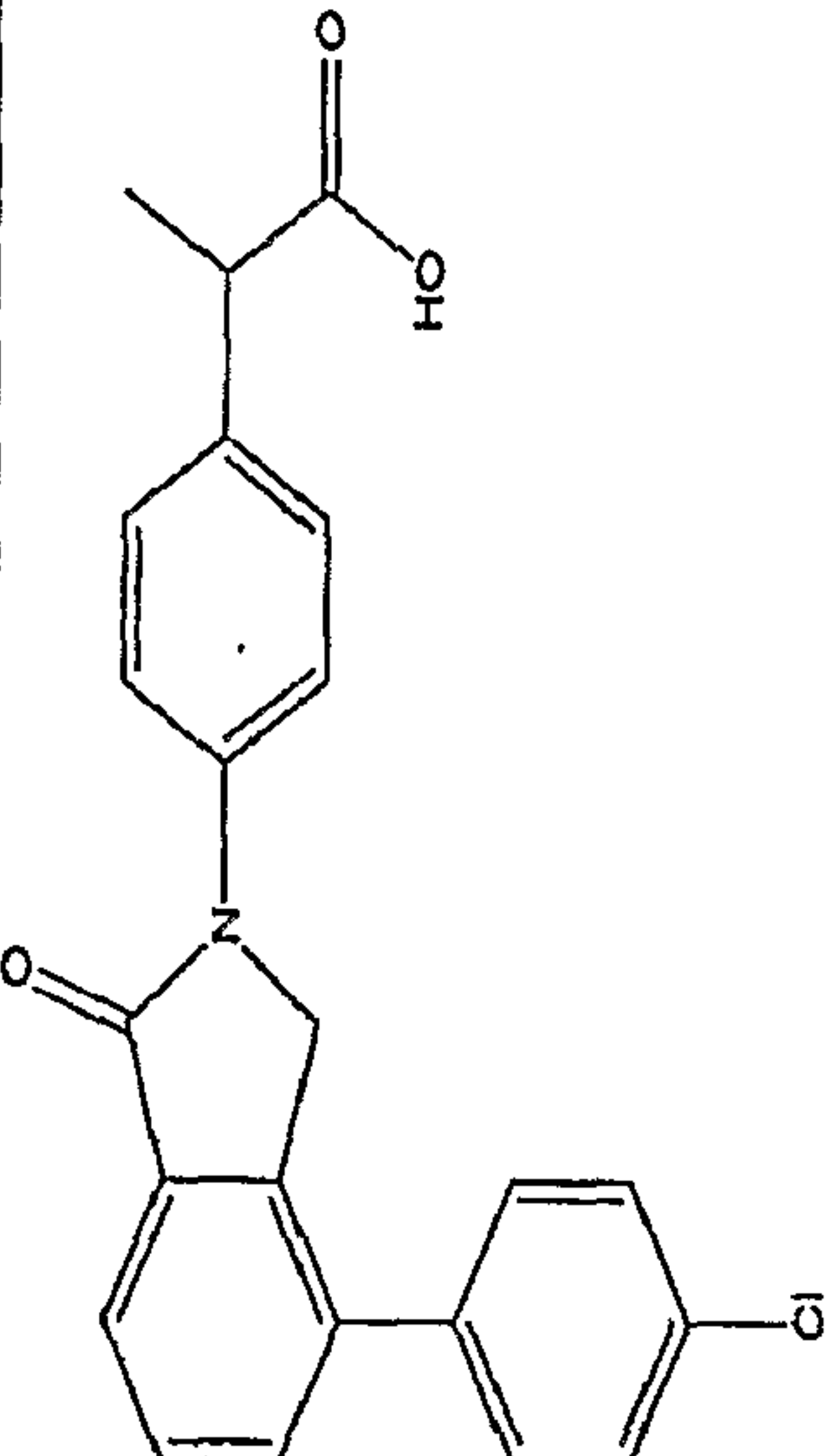
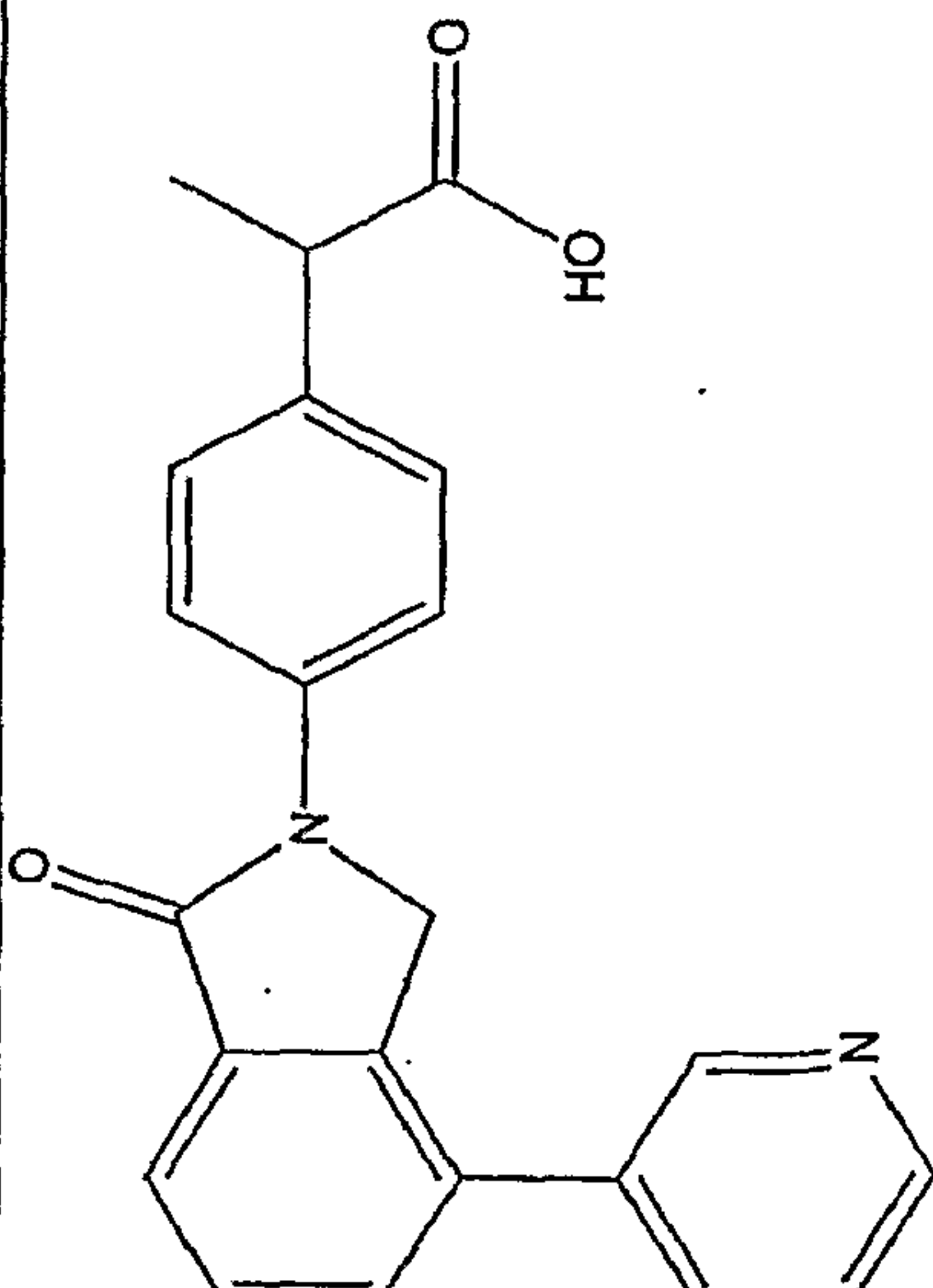
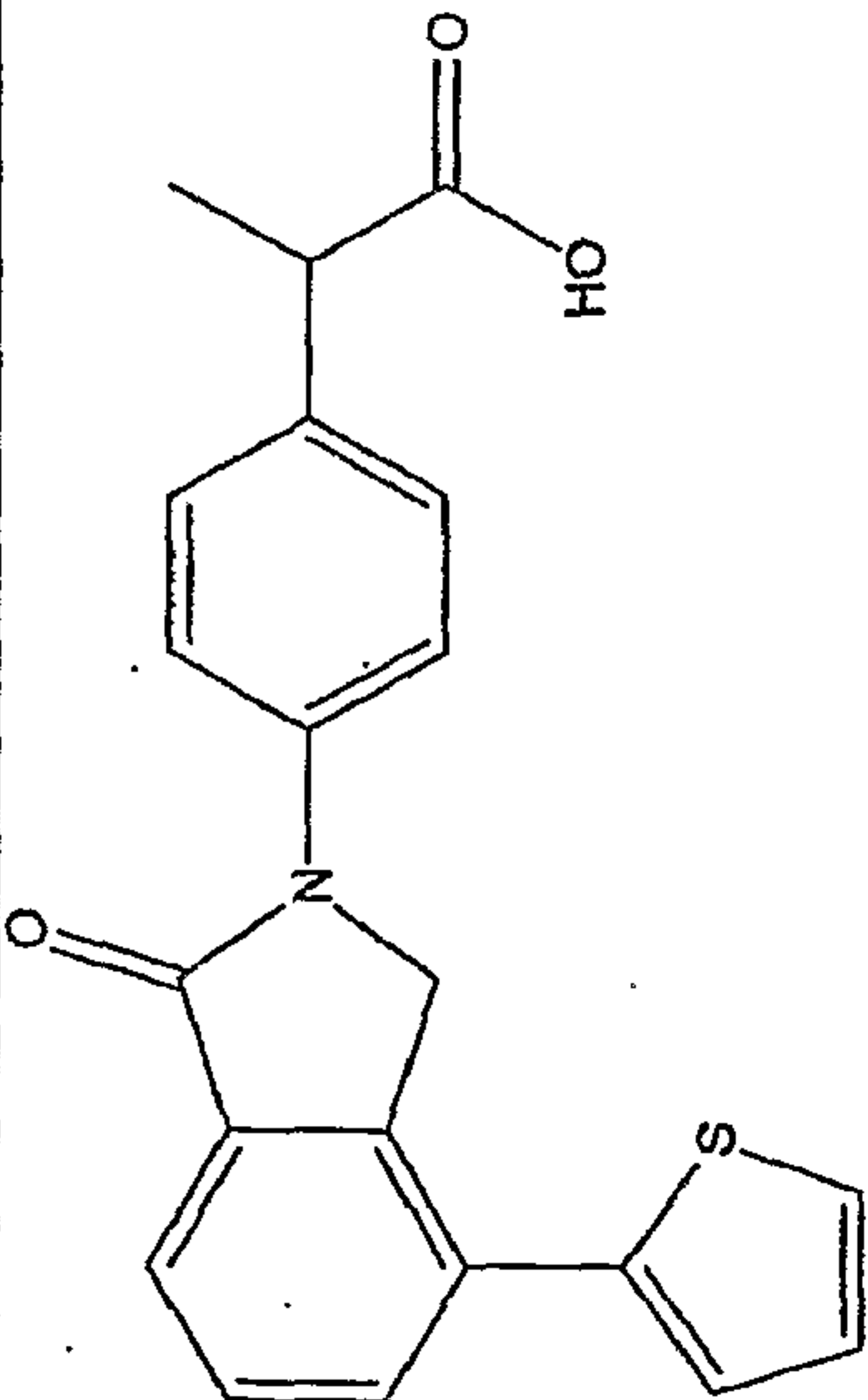
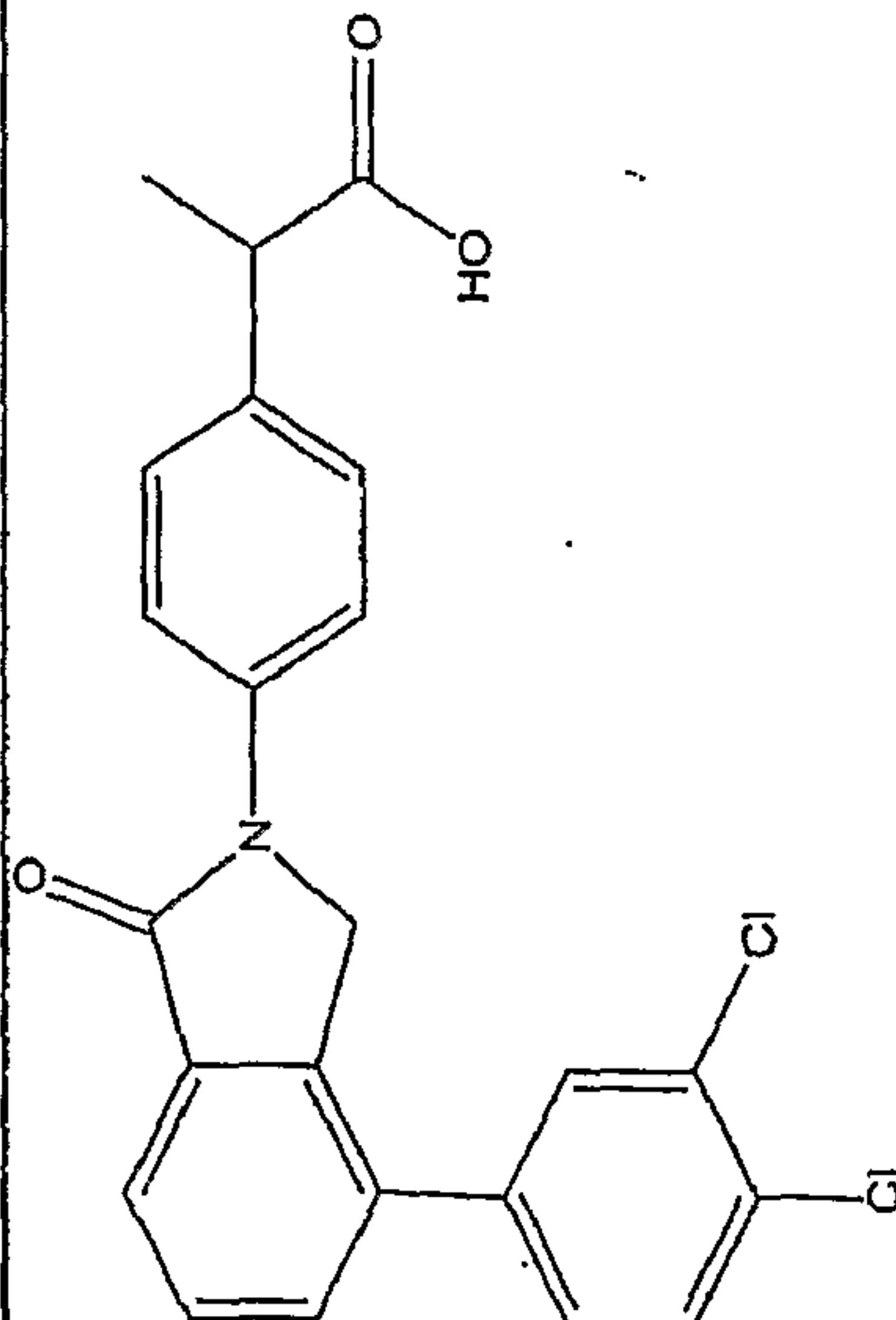
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
125		ALB- 112221		1.326
126		ALB- 112222		1.415

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
127		ALB- 112223	10.965	1.306
128		ALB- 112224		1.301

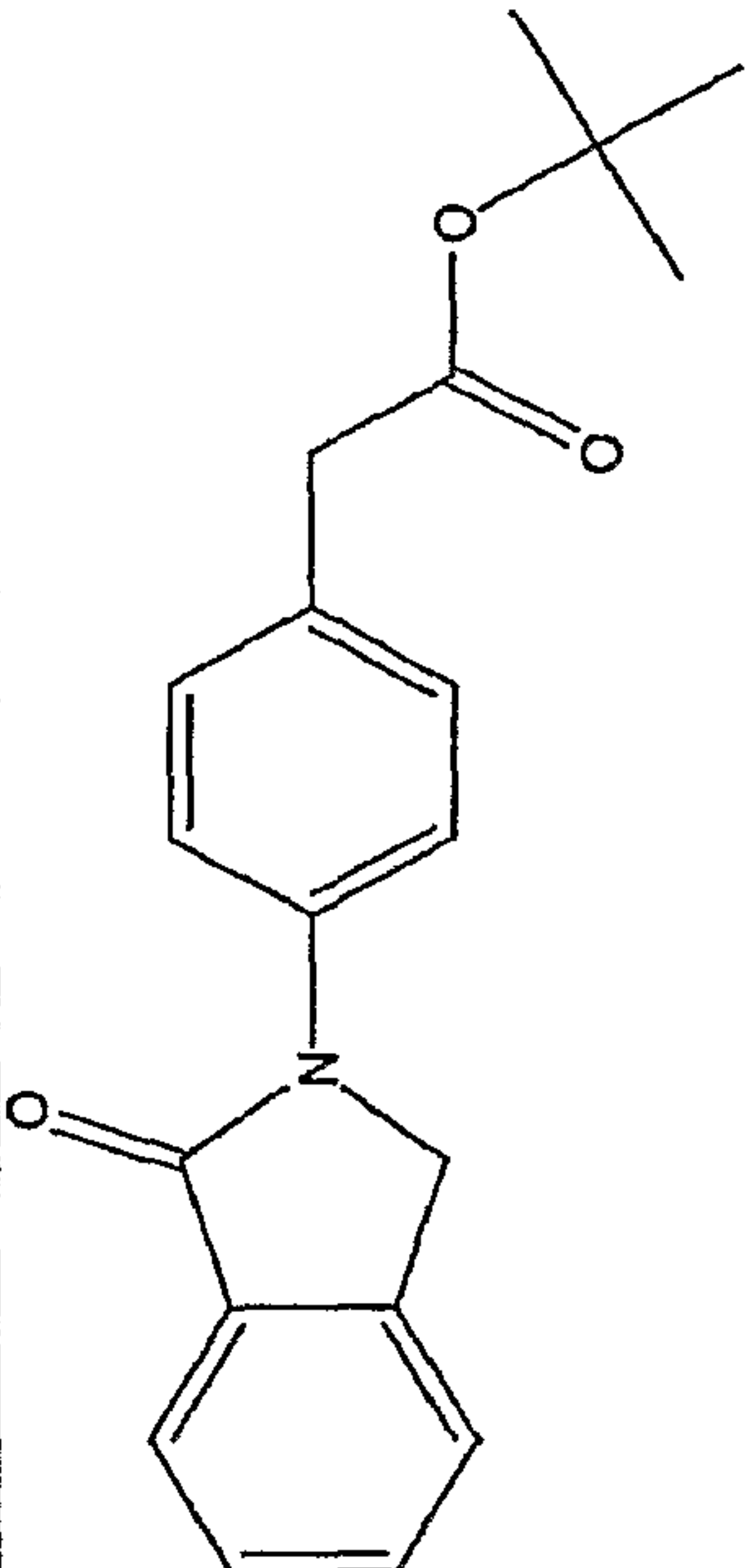
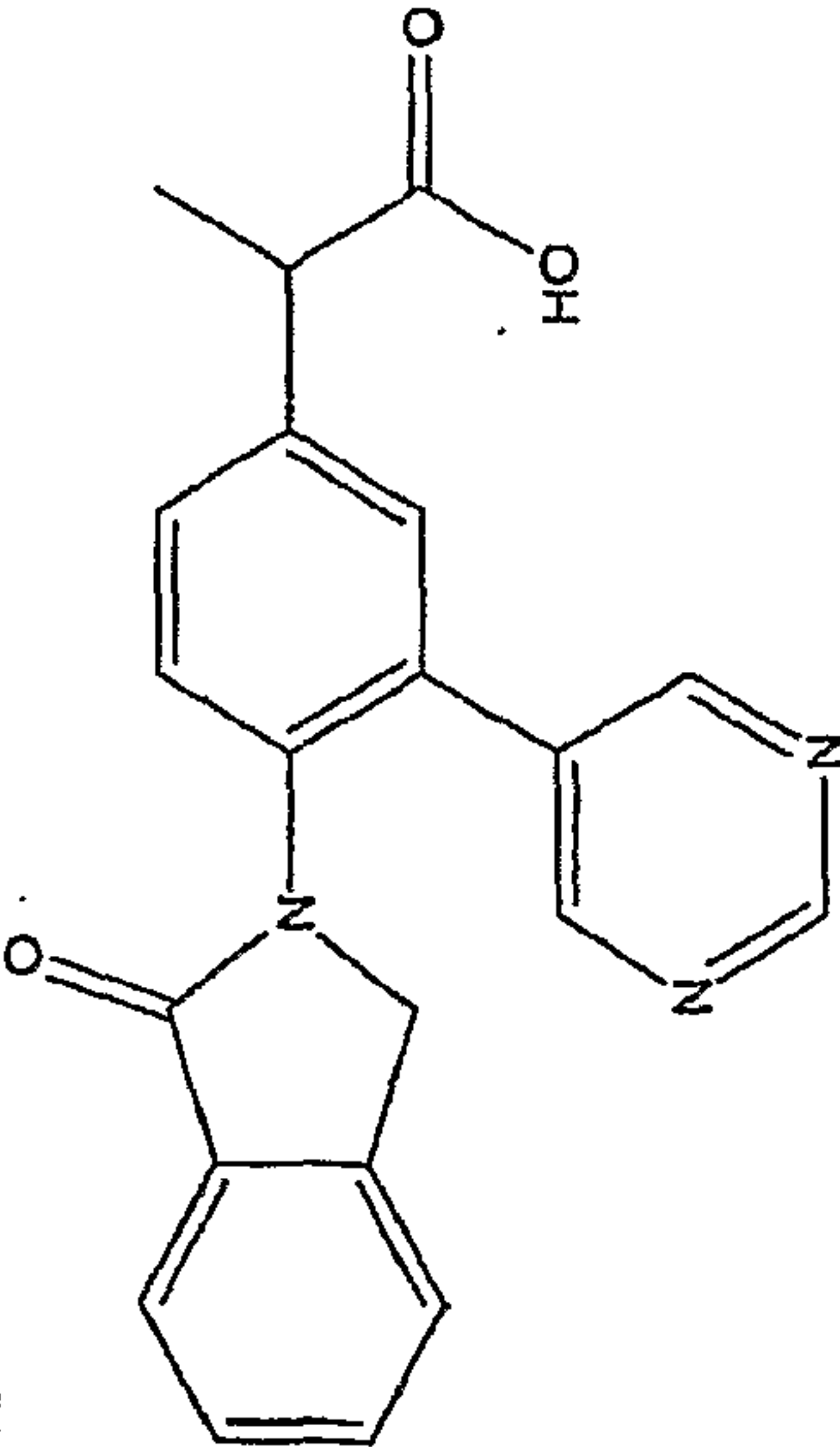
99

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
129		ALB- 112225		1.068
130		ALB- 112226	26.242	1.443

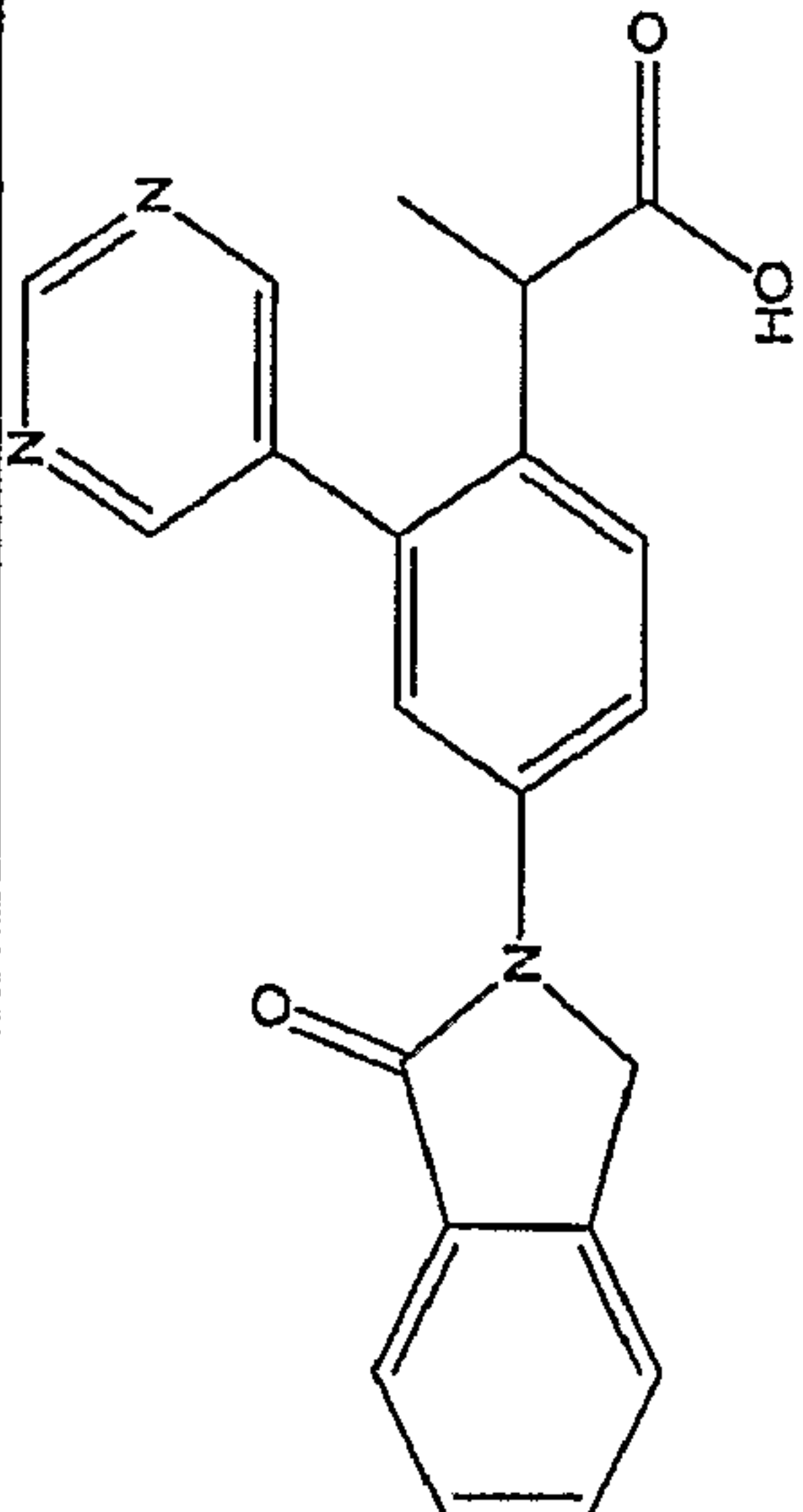
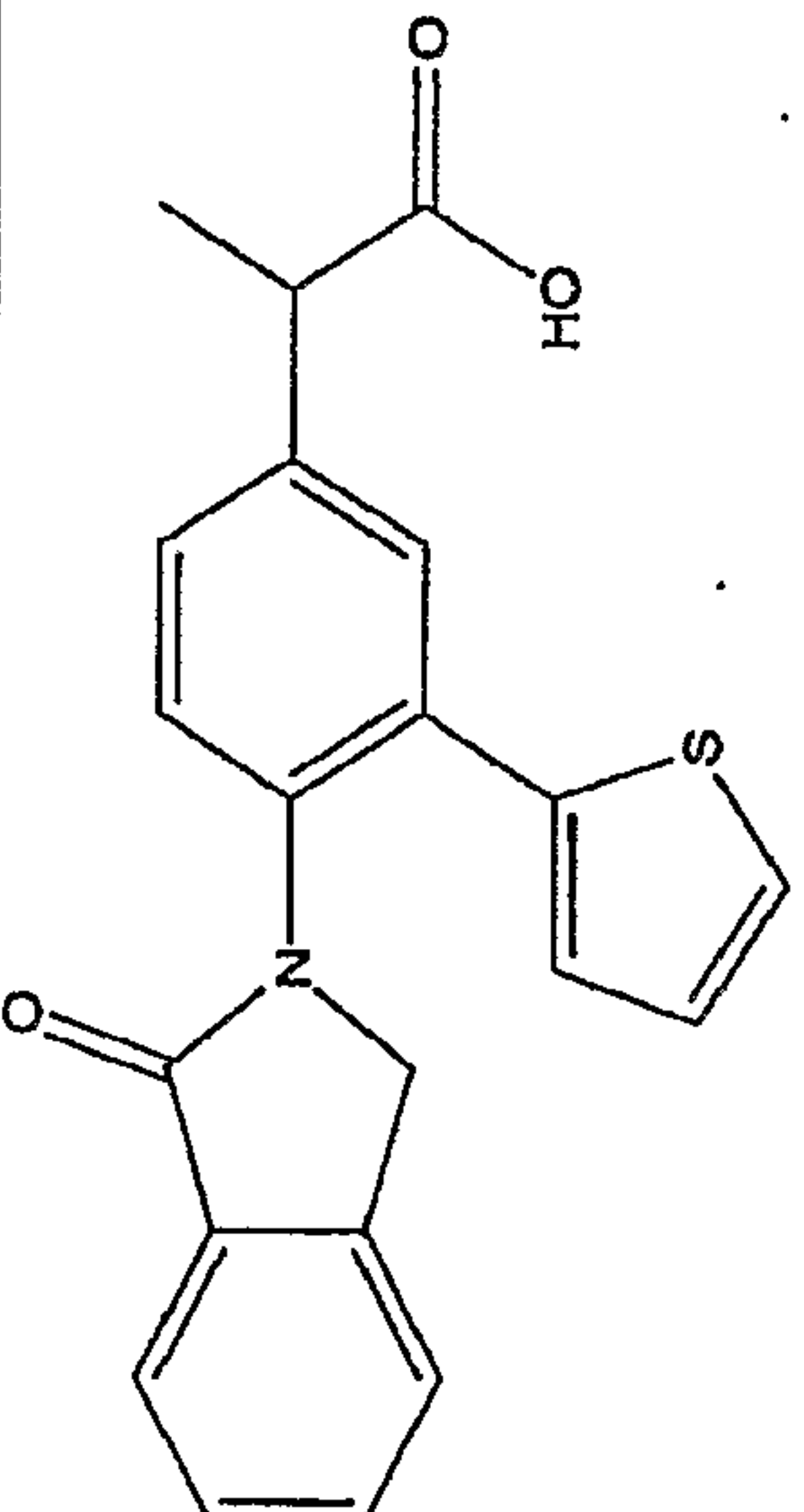
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
131		ALB- 112230		1.099
132		ALB- 112231		1.085

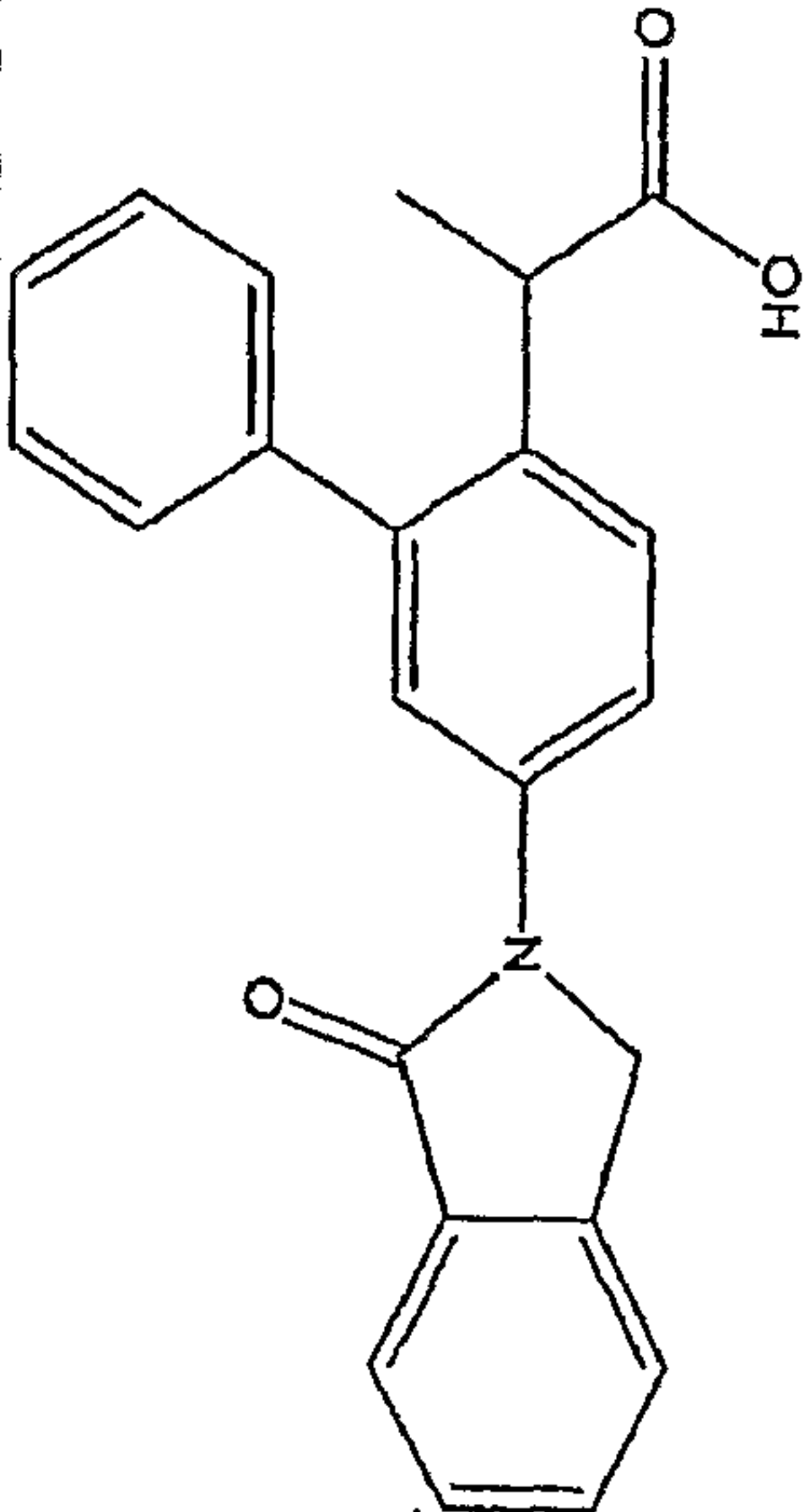
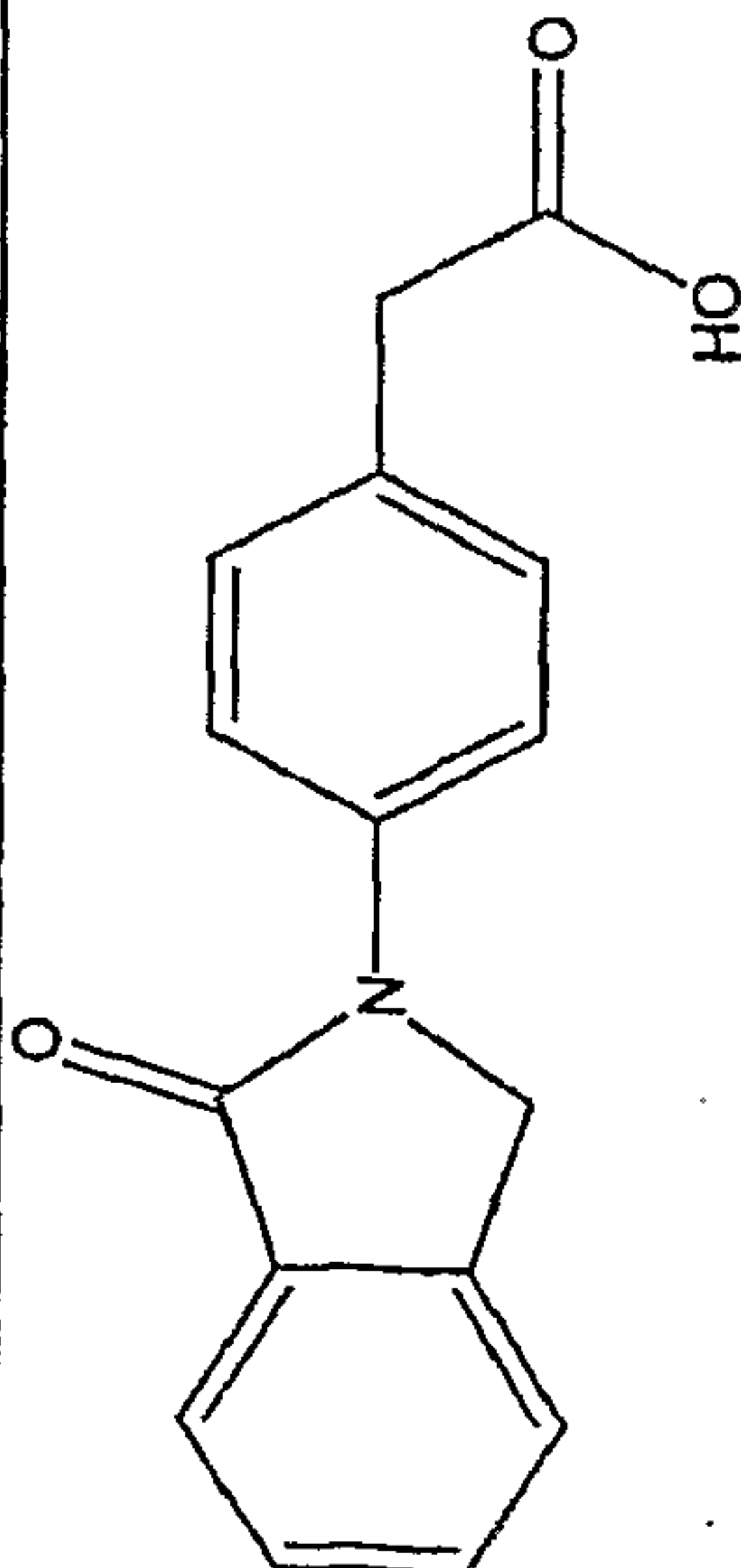
101

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
133		ALB- 112232		1.048
134		ALB- 112233		1.027

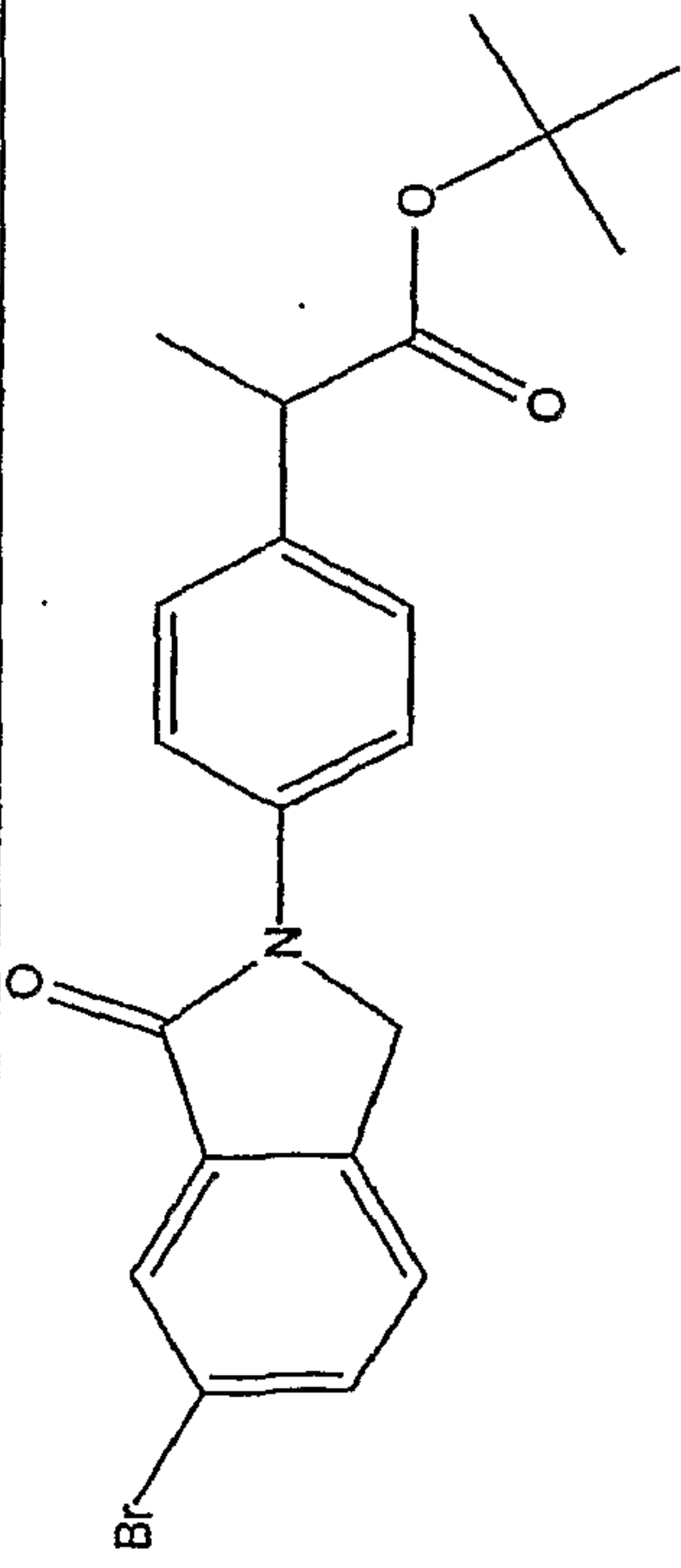
102

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay. (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
135				
		ALB- 112234	25.351	1.262
136				
		ALB- 112235		0.941

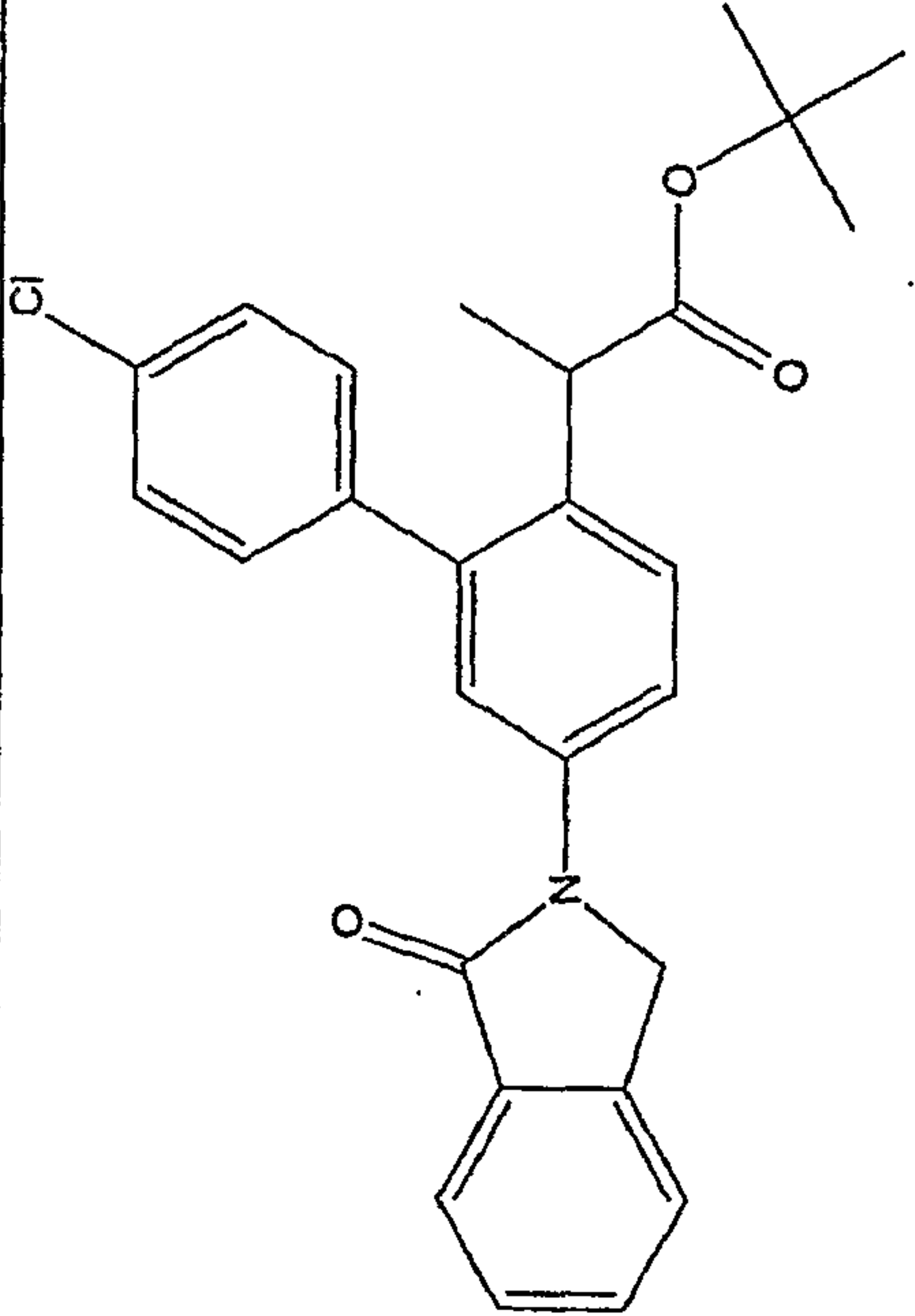
103

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
137		ALB- 112327	4.208	1.465

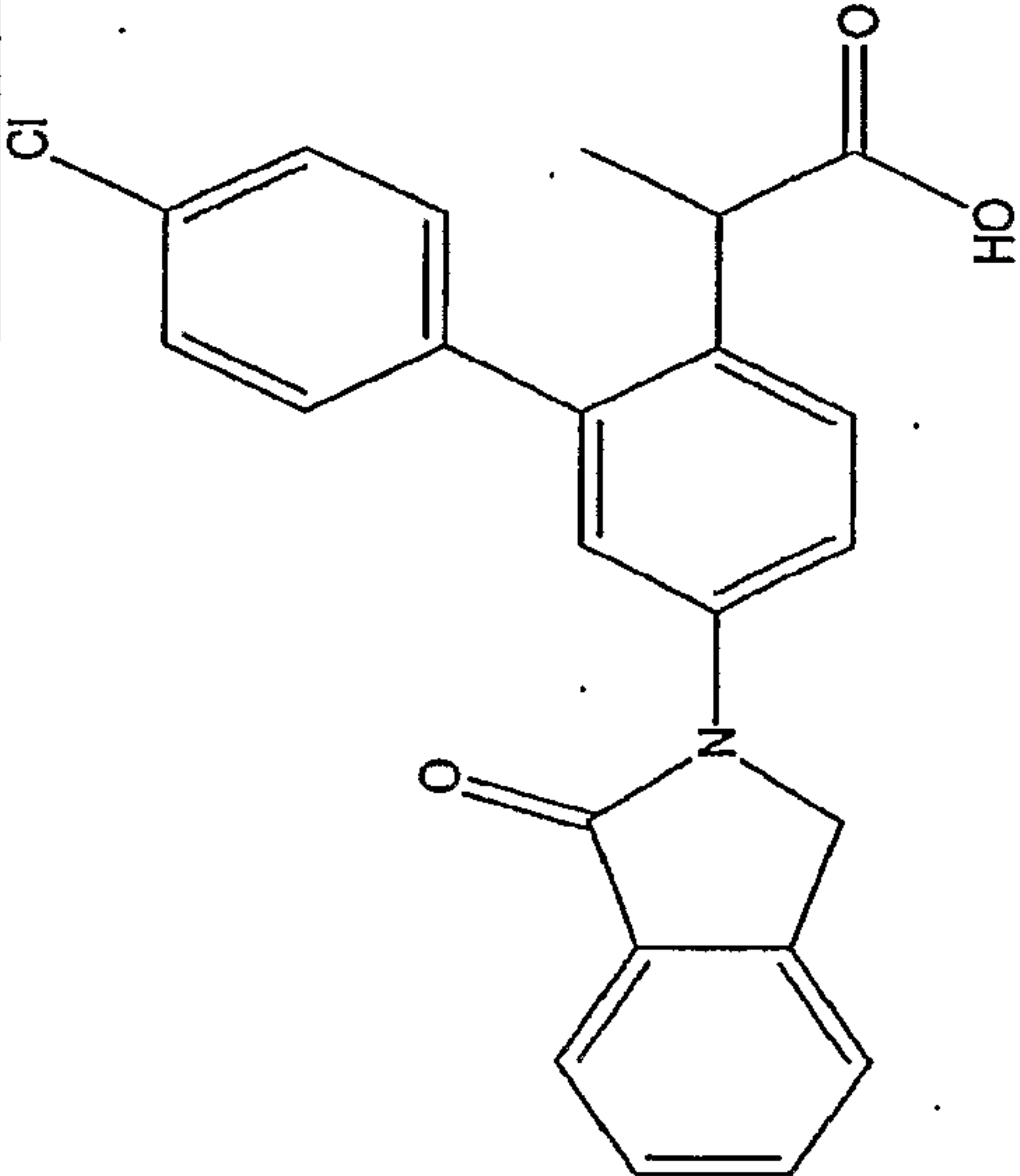
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
138	 <chem>CC(=O)OC(C)C1=CC=C(C=C1C2=CC=C(C=C2)N3C(=O)C4=CC=CC=C4C3=O)C5=CC=C(C=C5)Cl</chem>	ALB- 112328		1.043

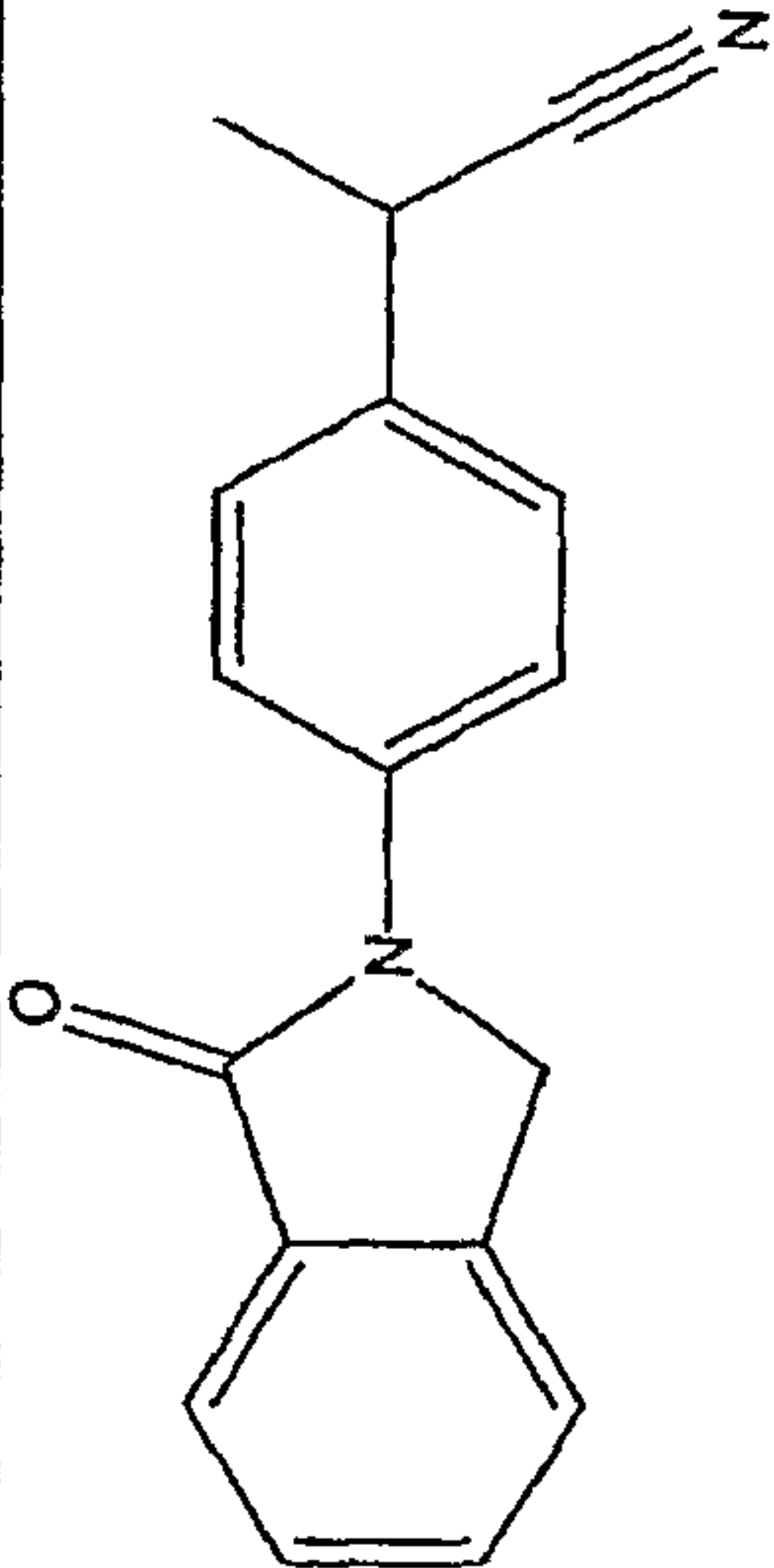
105

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
139		ALB- 112329		1.091

106

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
140		ALB- 112330	0.259	1.462

107

Table 1

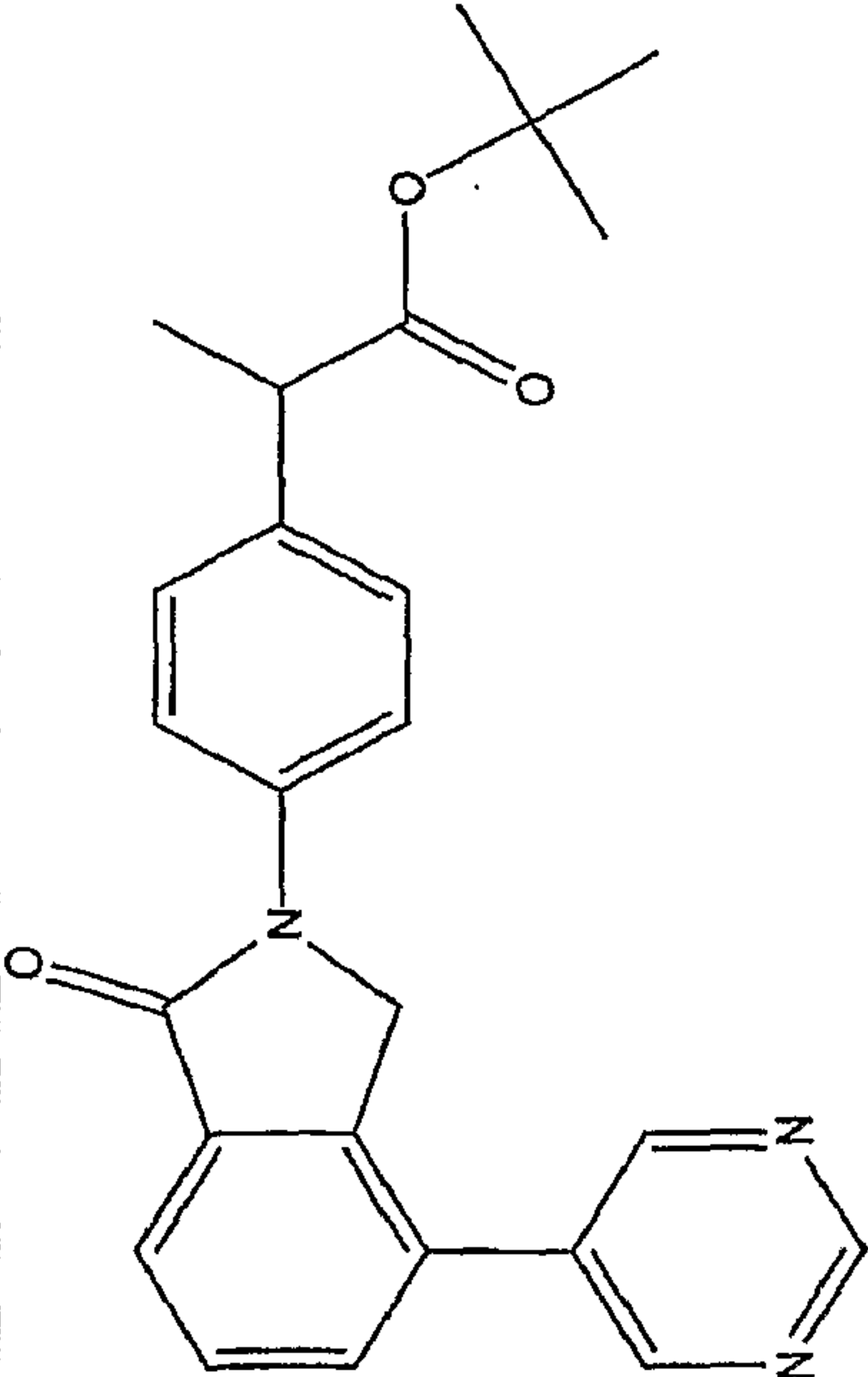
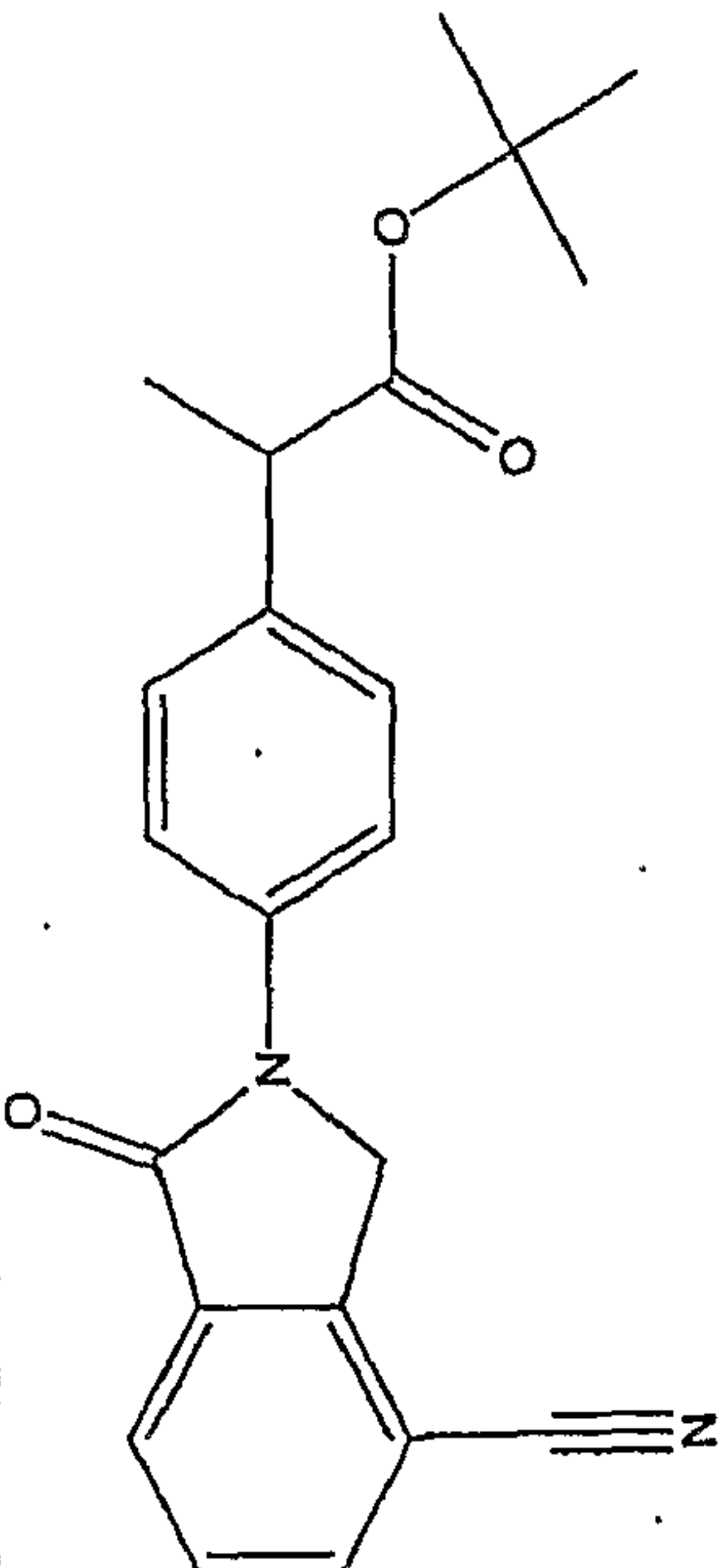
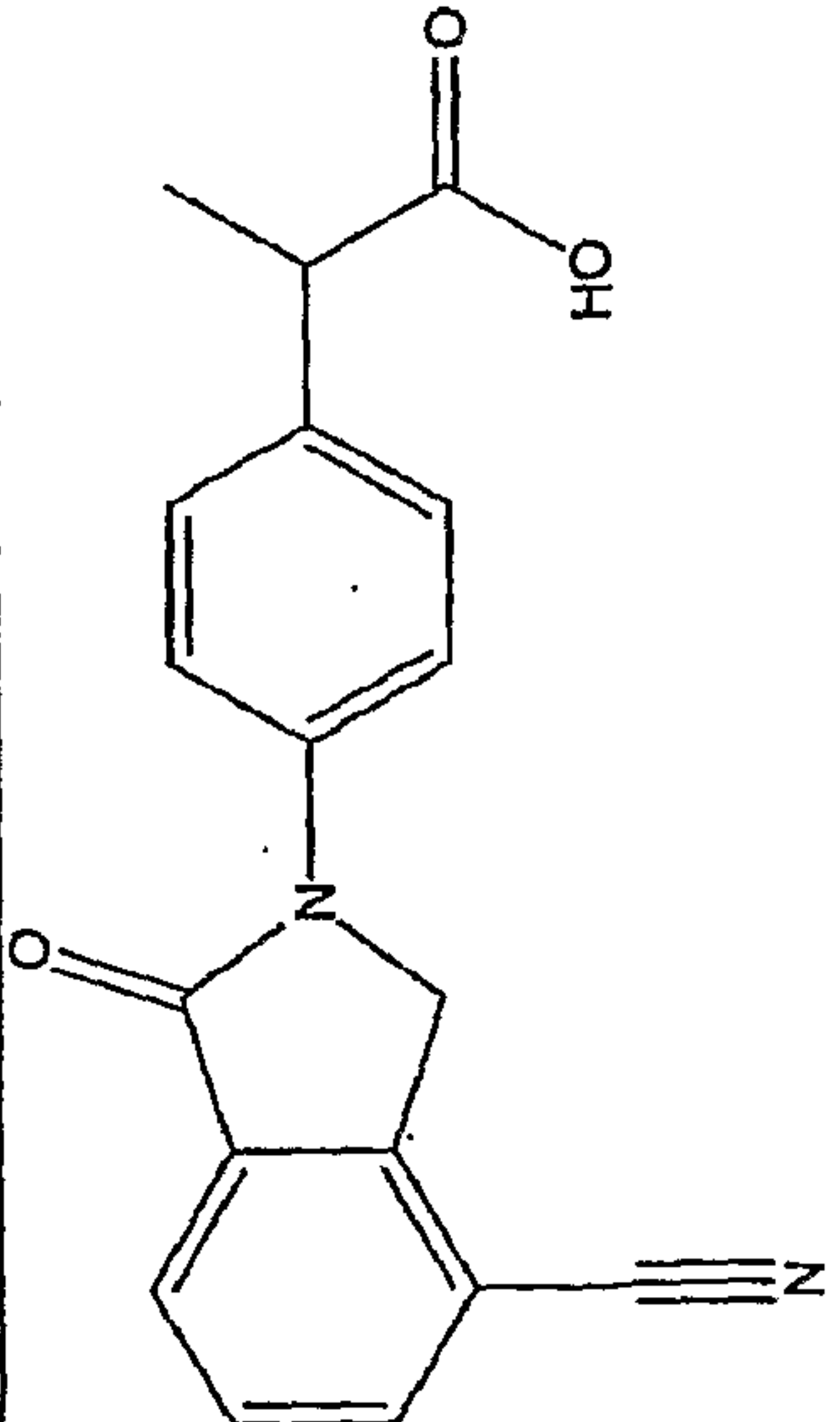
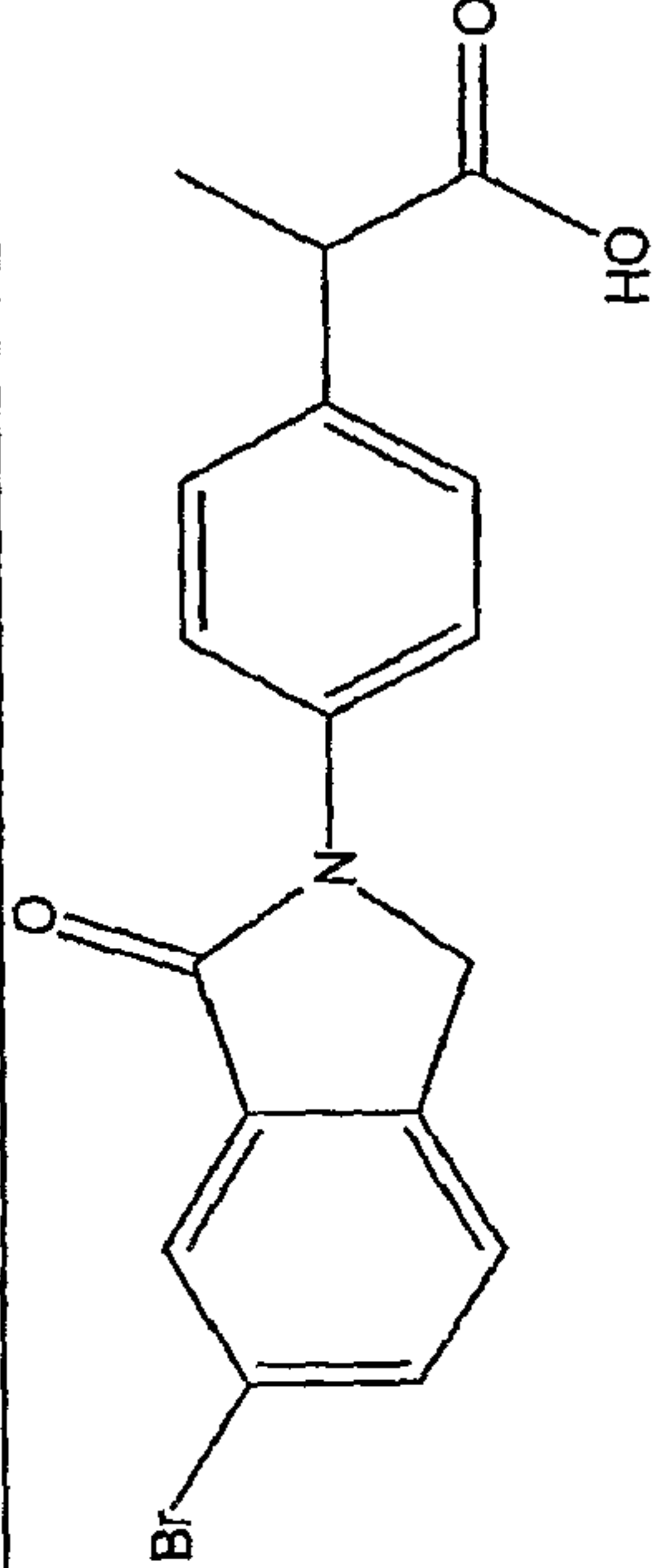
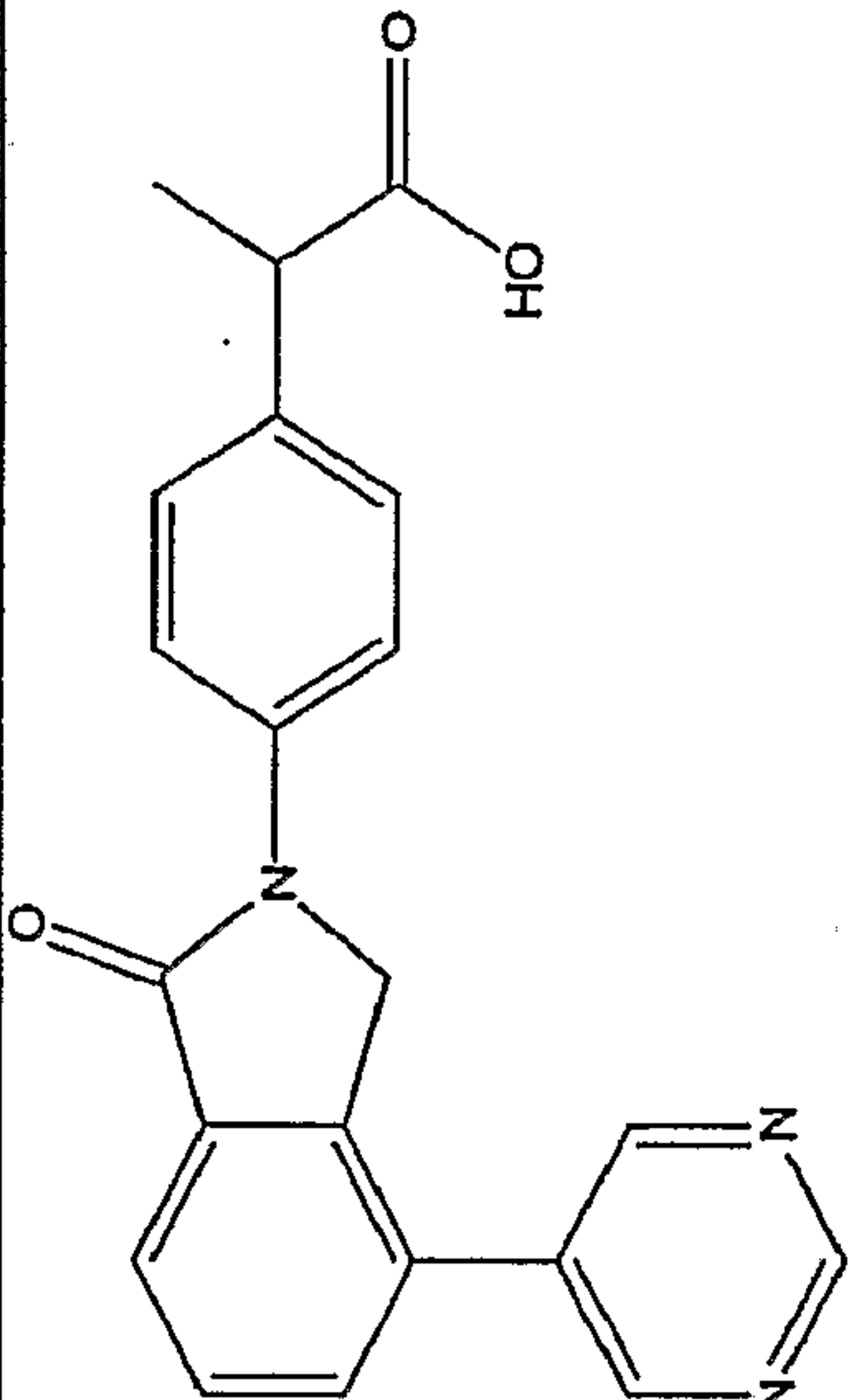
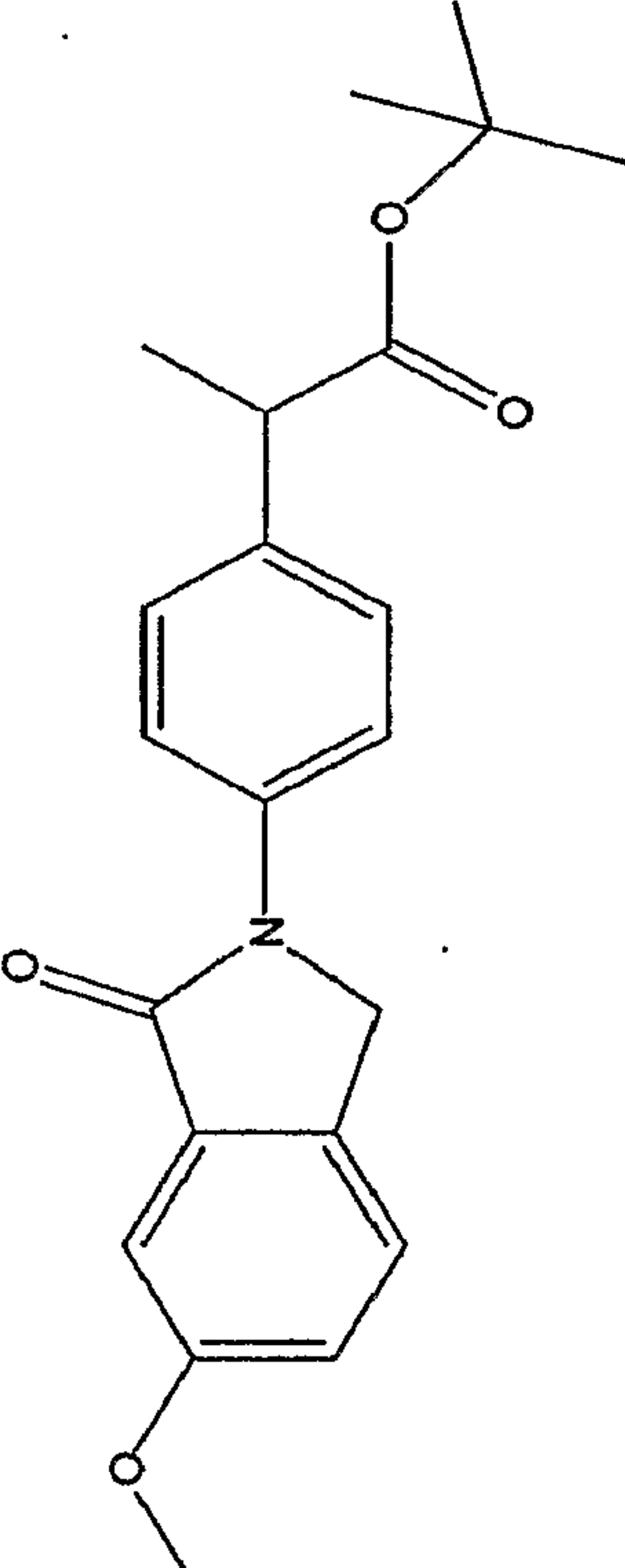
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
141		ALB- 112349		1.064
142		ALB- 112350		1.182

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
143		ALB- 112351		1.205
144		ALB- 112352	0.13	1.718

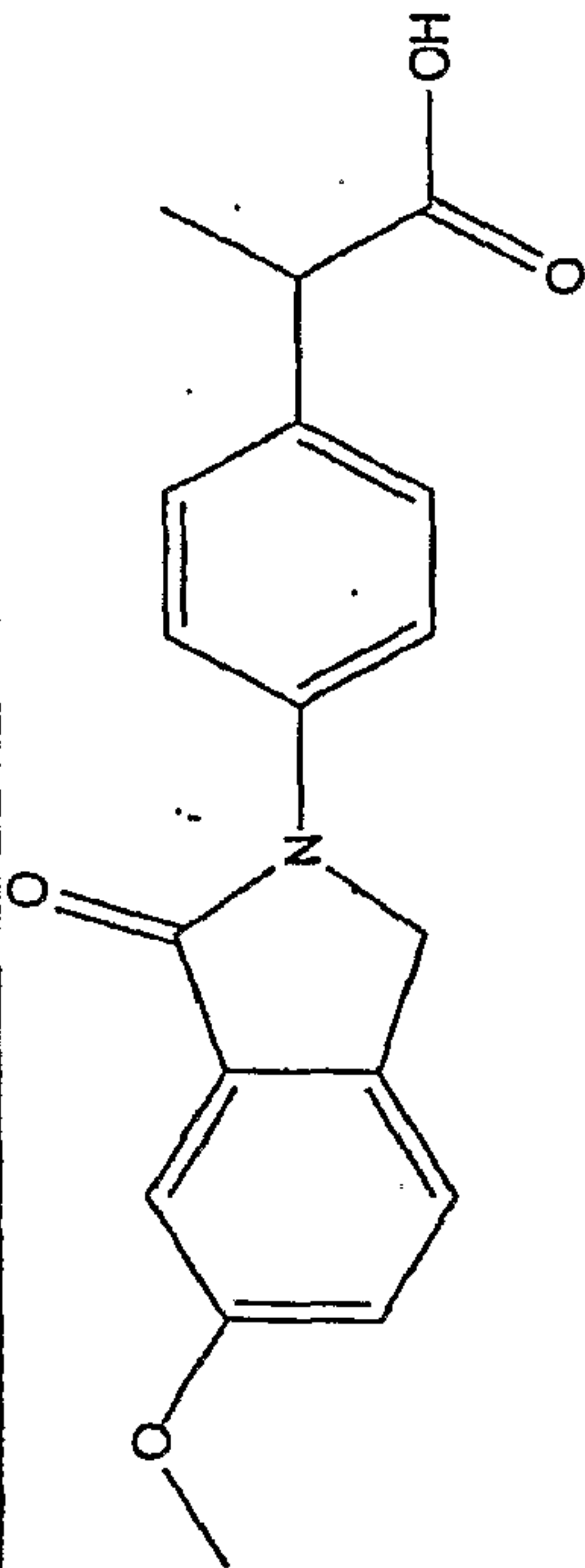
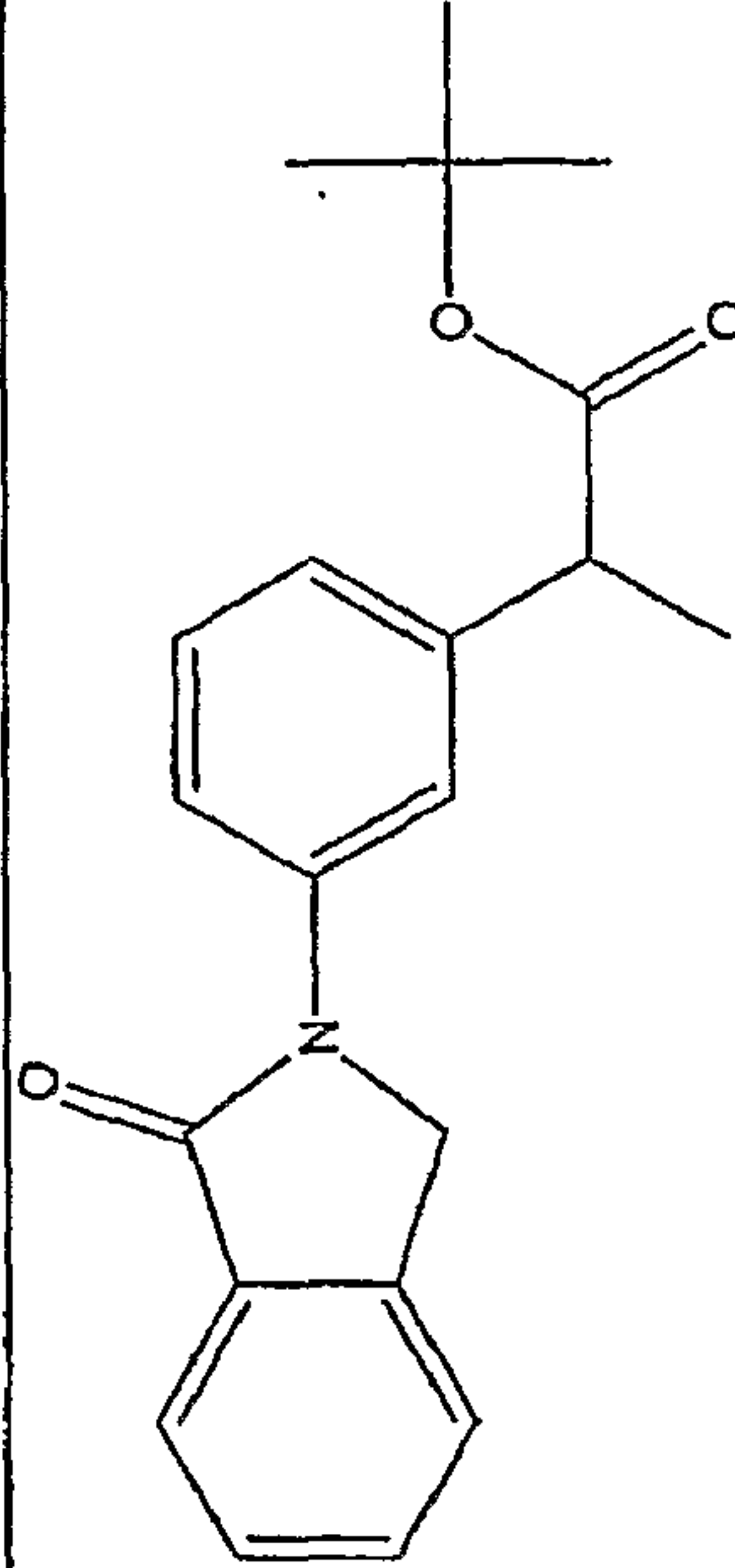
109

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
145		ALB- 112353	15.977	1.529
146		ALB- 112354	0.801	1.464

110

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
147		ALB- 112355	0.083	1.848
148		ALB- 112361		1.095

111

Table 1

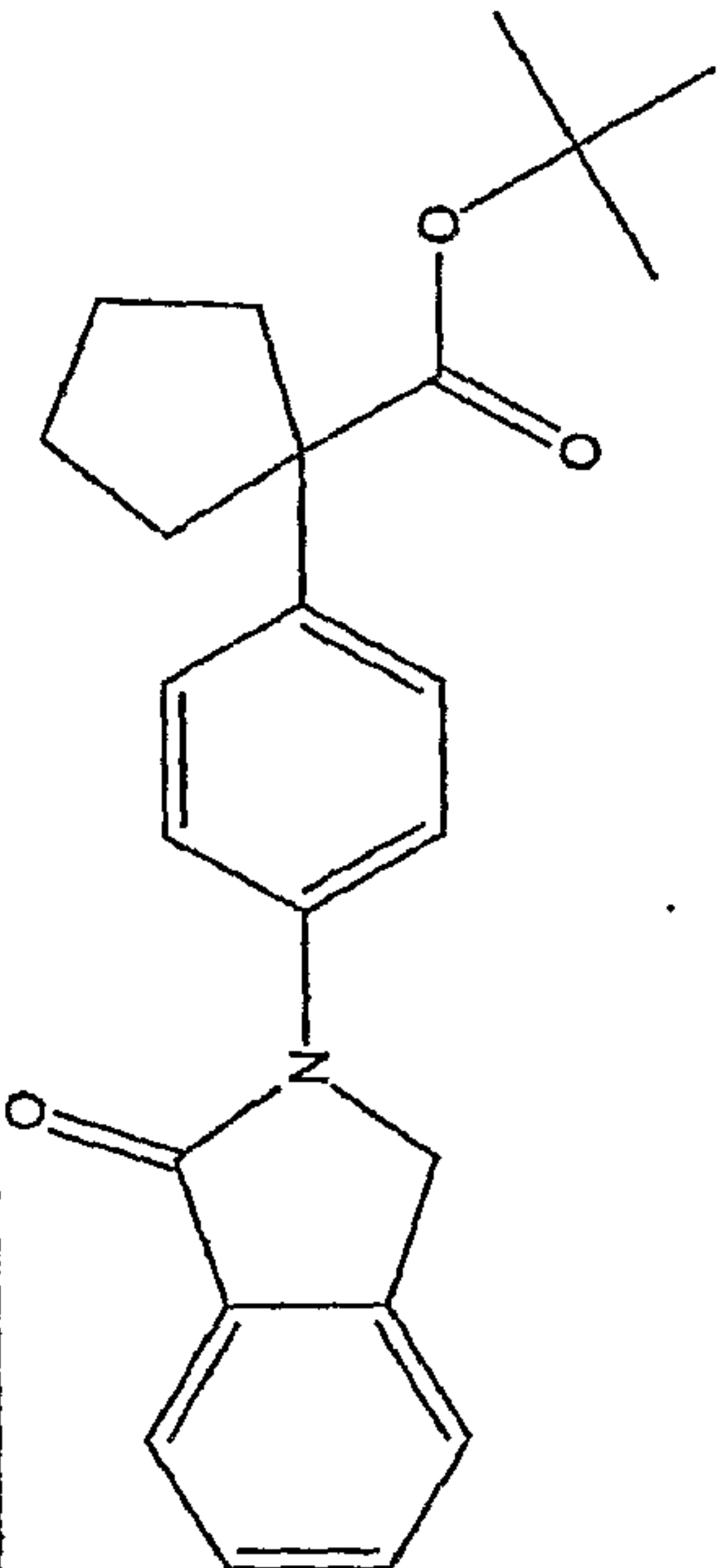
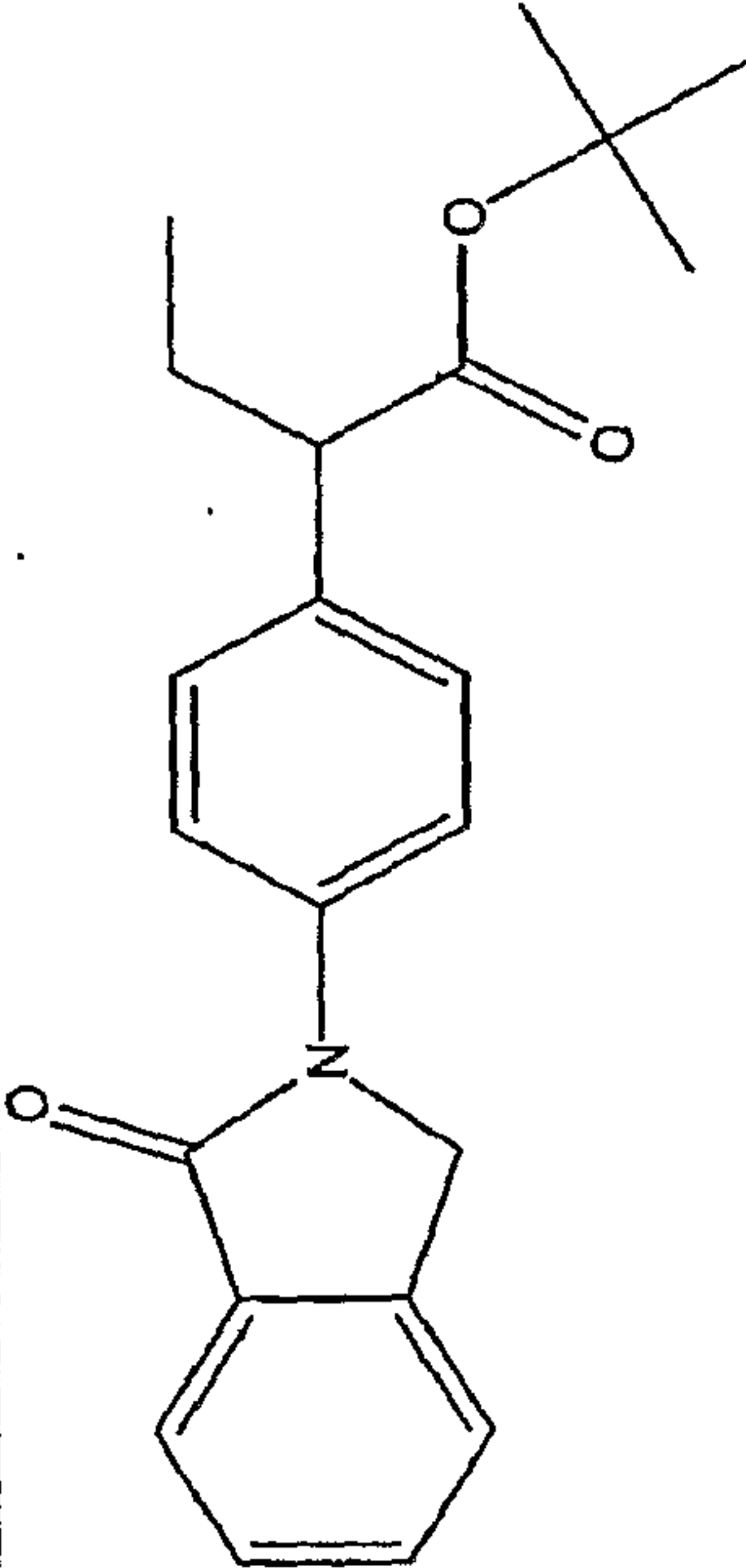
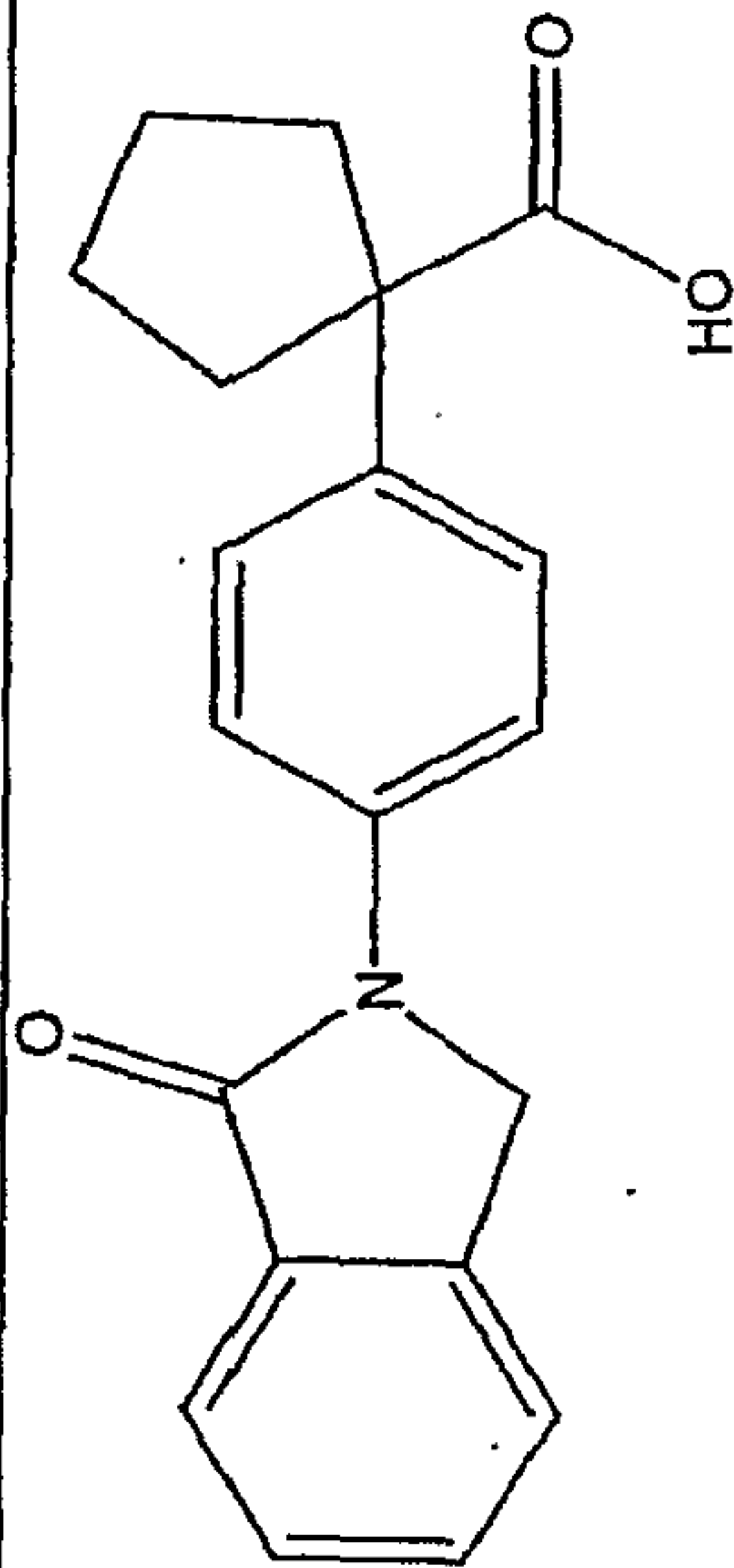
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
149		ALB- 112362		1.053
150		ALB- 112364	3.258	1.214

Table 1

CC(C)(C)OC(=O)C1CC1C2=CC=CC=C2C3=C(C4=CC=CC=C4C5=C(C(=O)O)C=C5)N3

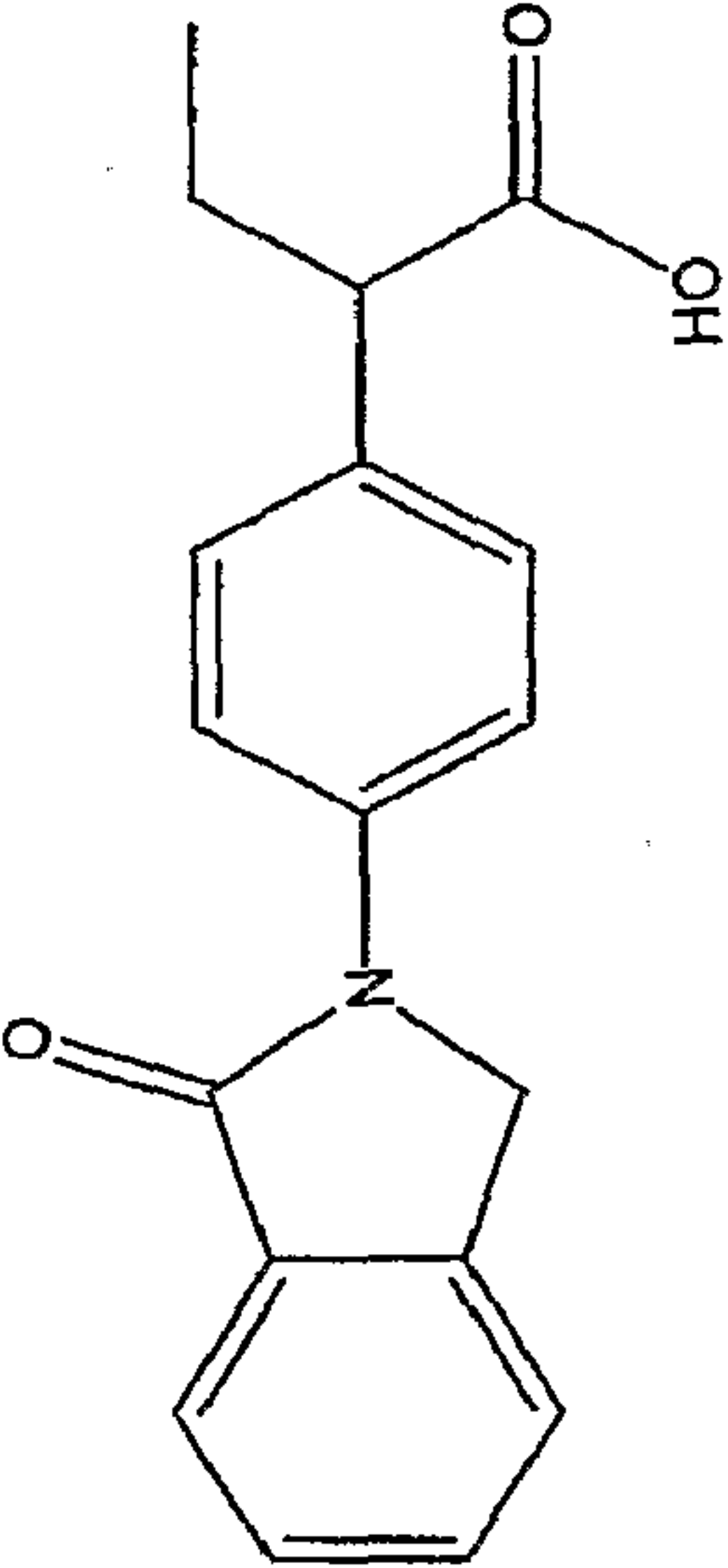
113

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
152		ALB- 112431		1.208

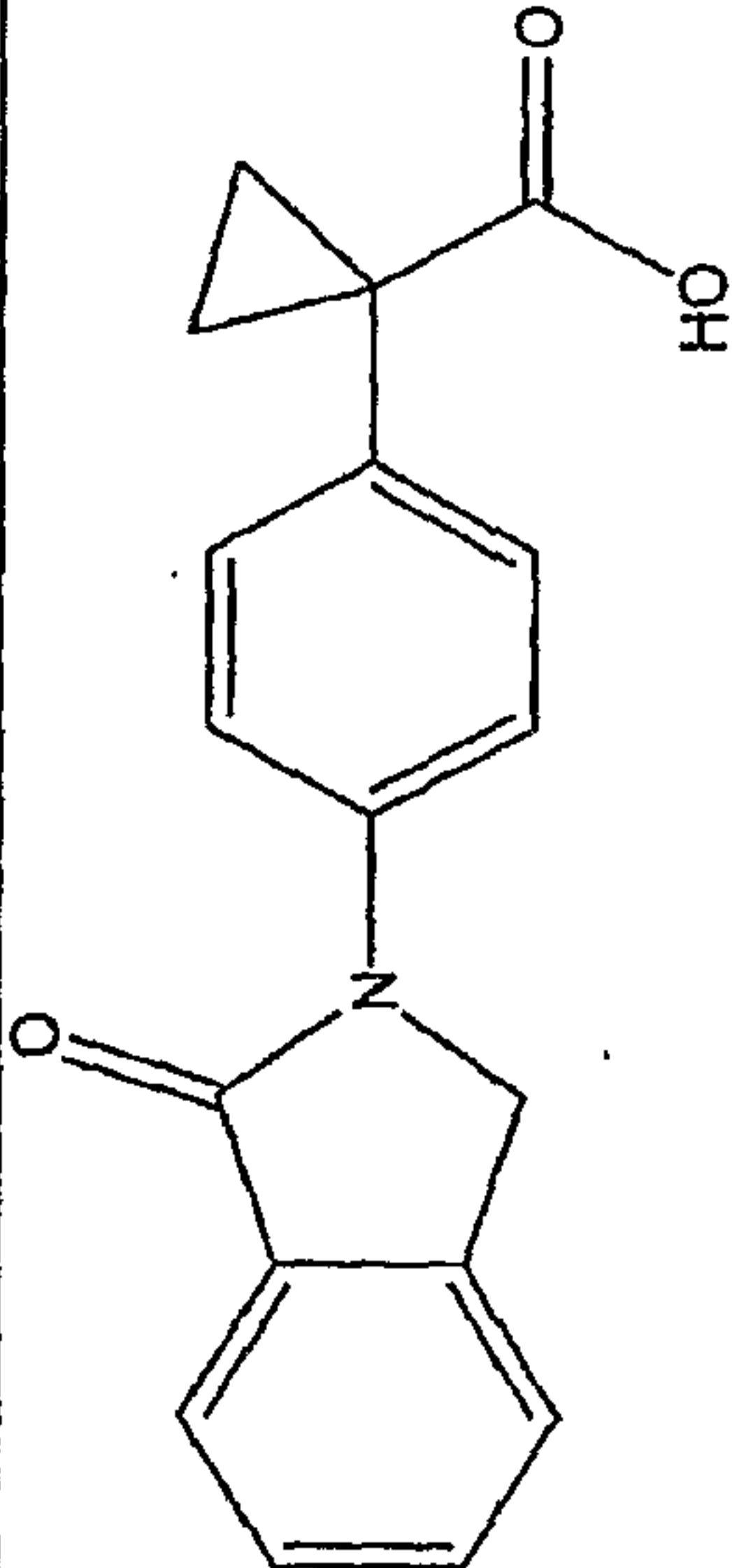
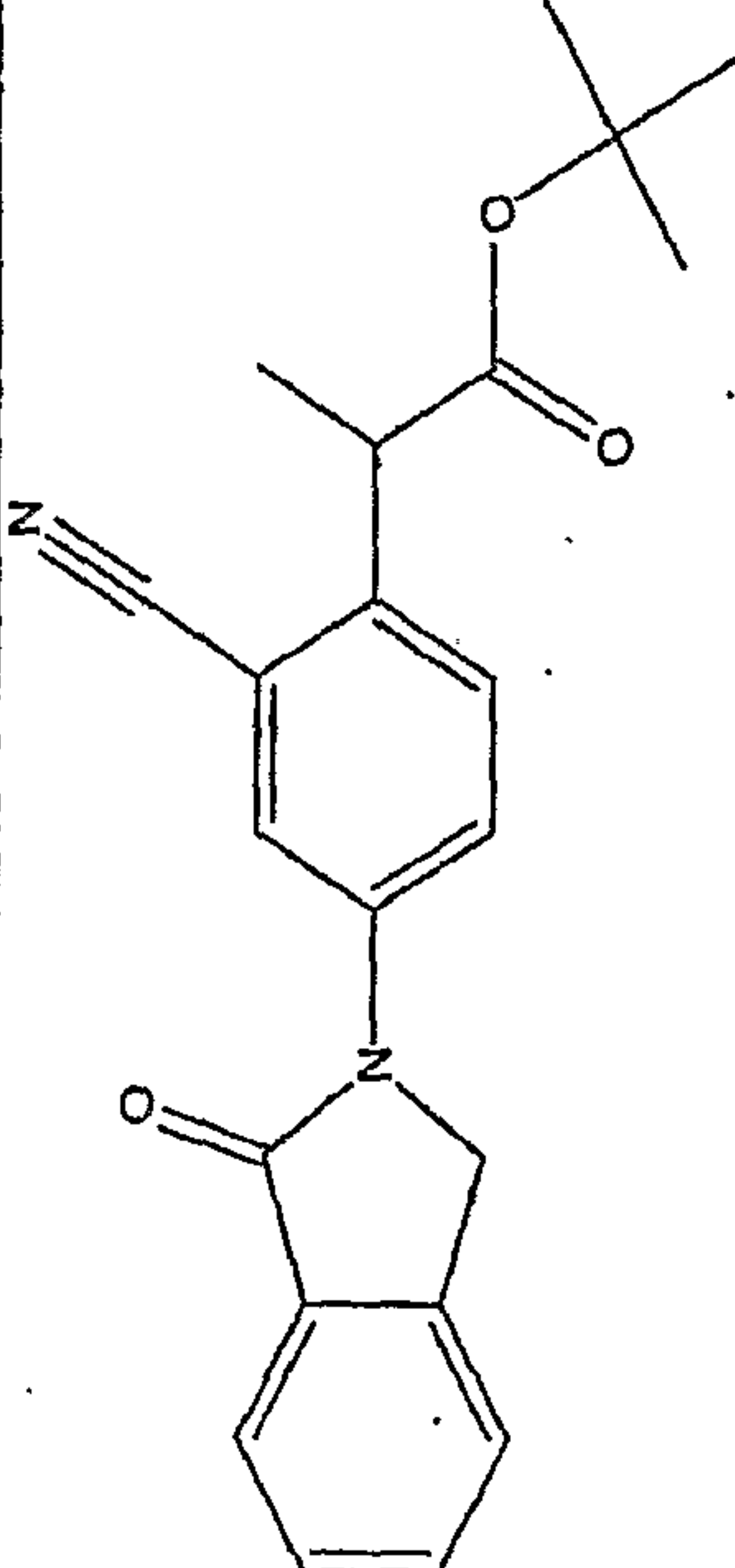
114

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
153		ALB- 112433	4.185	1.325

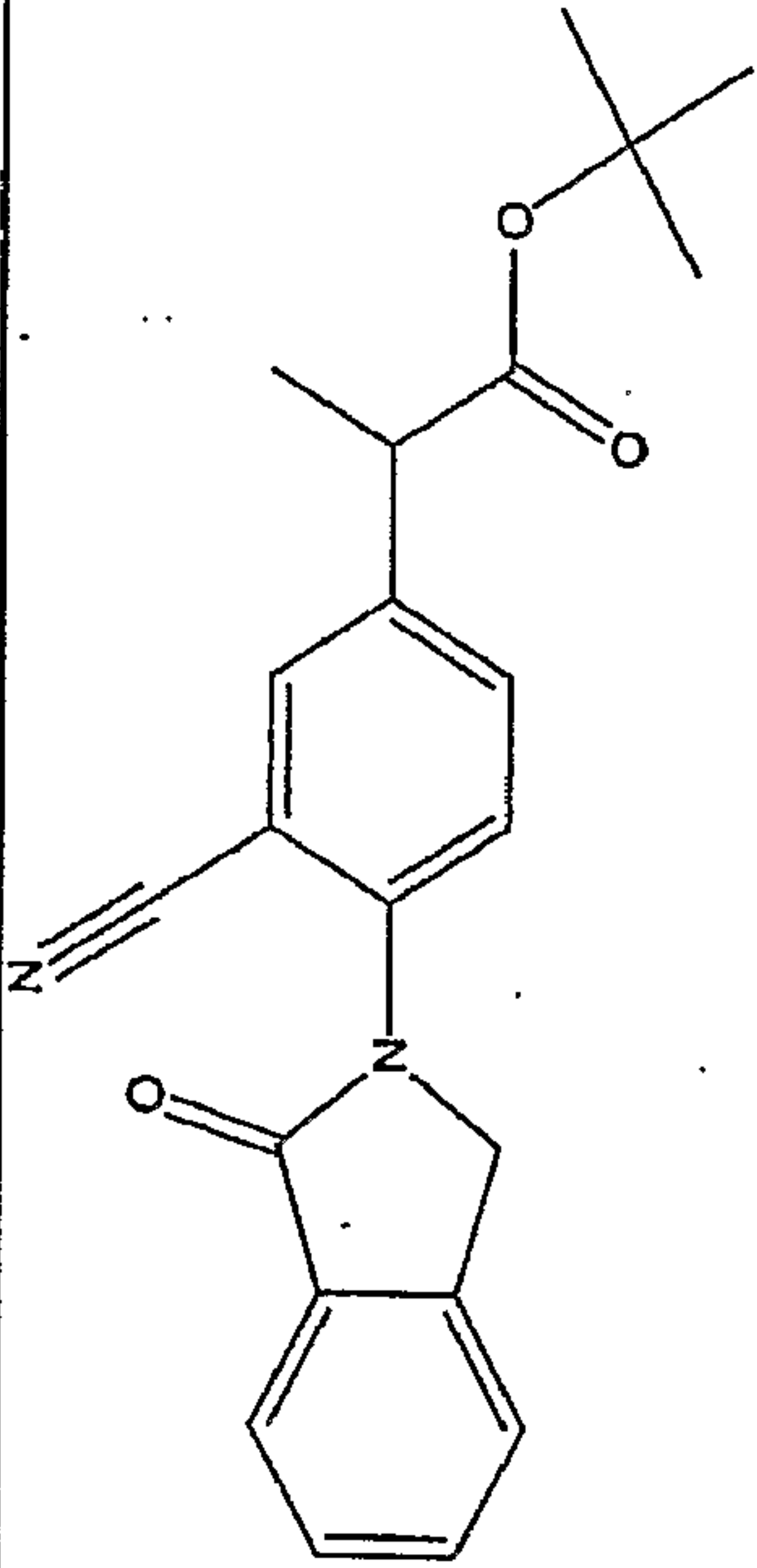
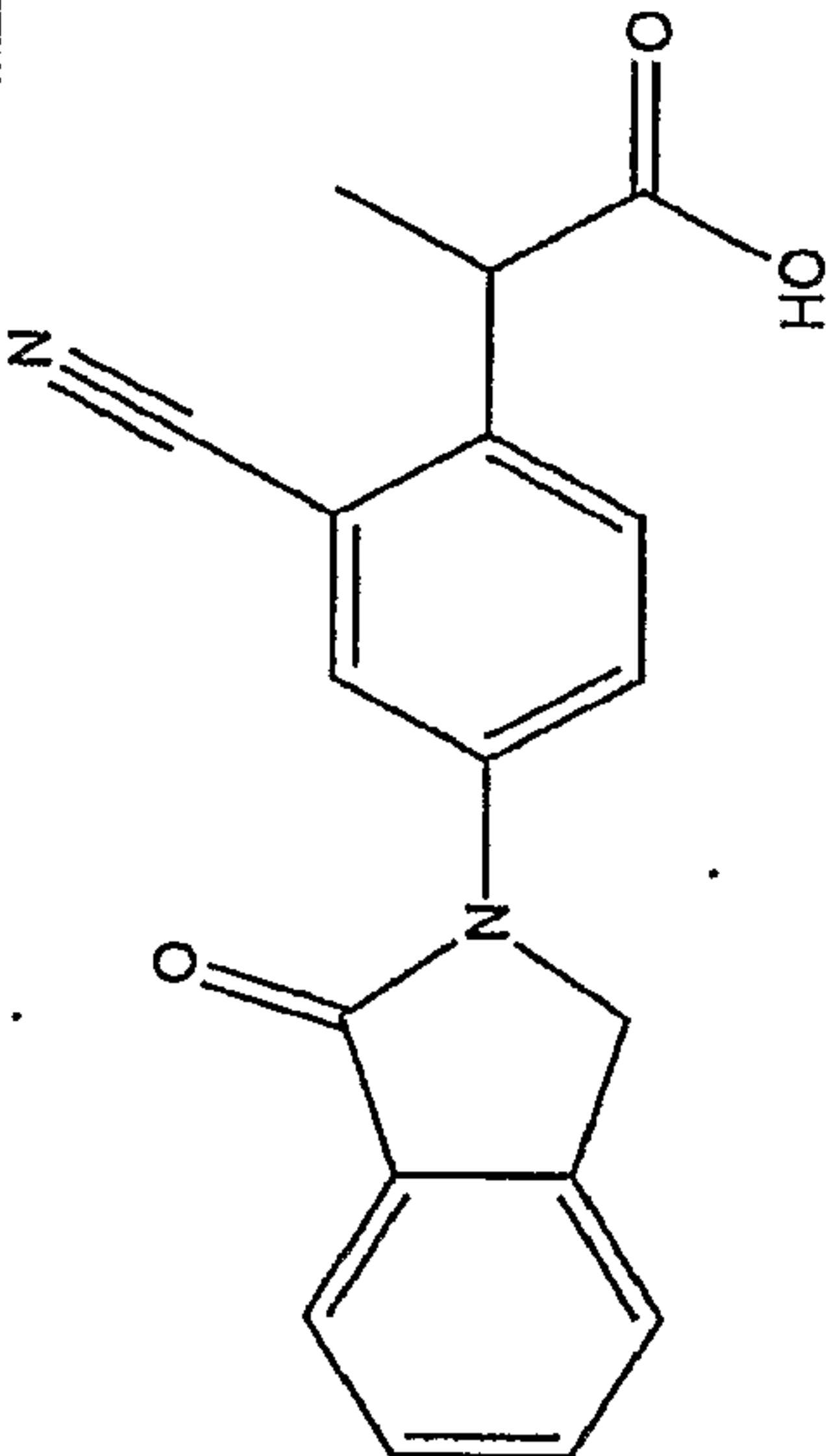
115

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
154		ALB- 112434	5.984	1.28
155		ALB- 112435	5.984	1.2

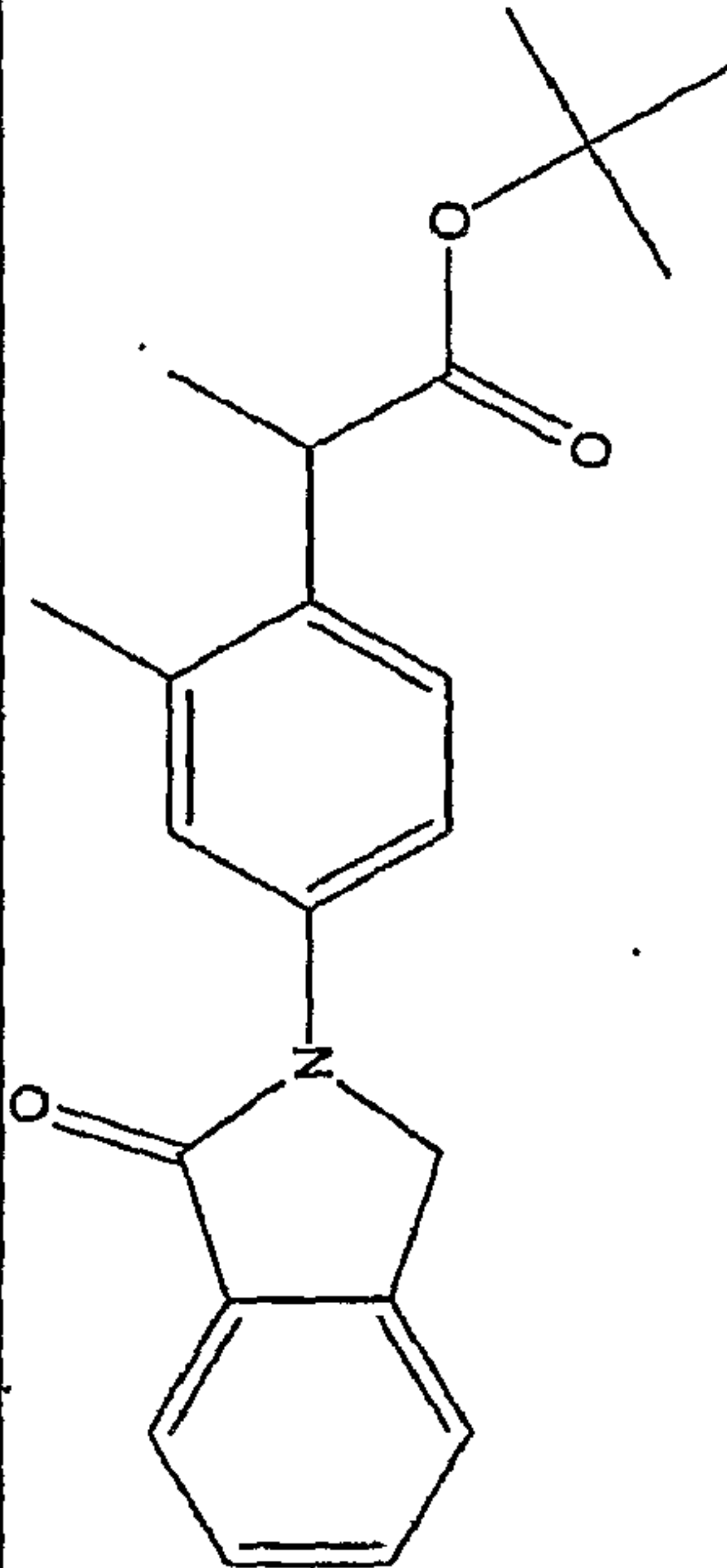
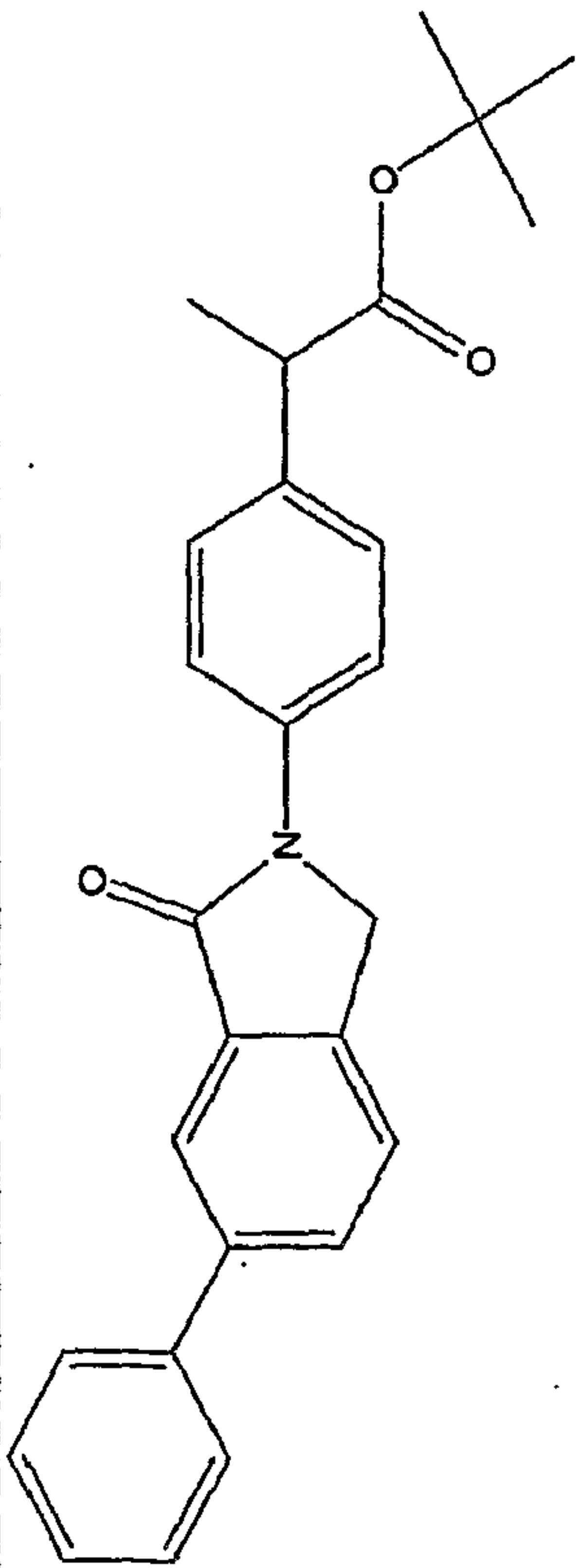
116

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
156		ALB- 112436		1.071
157		ALB- 112437		1.09

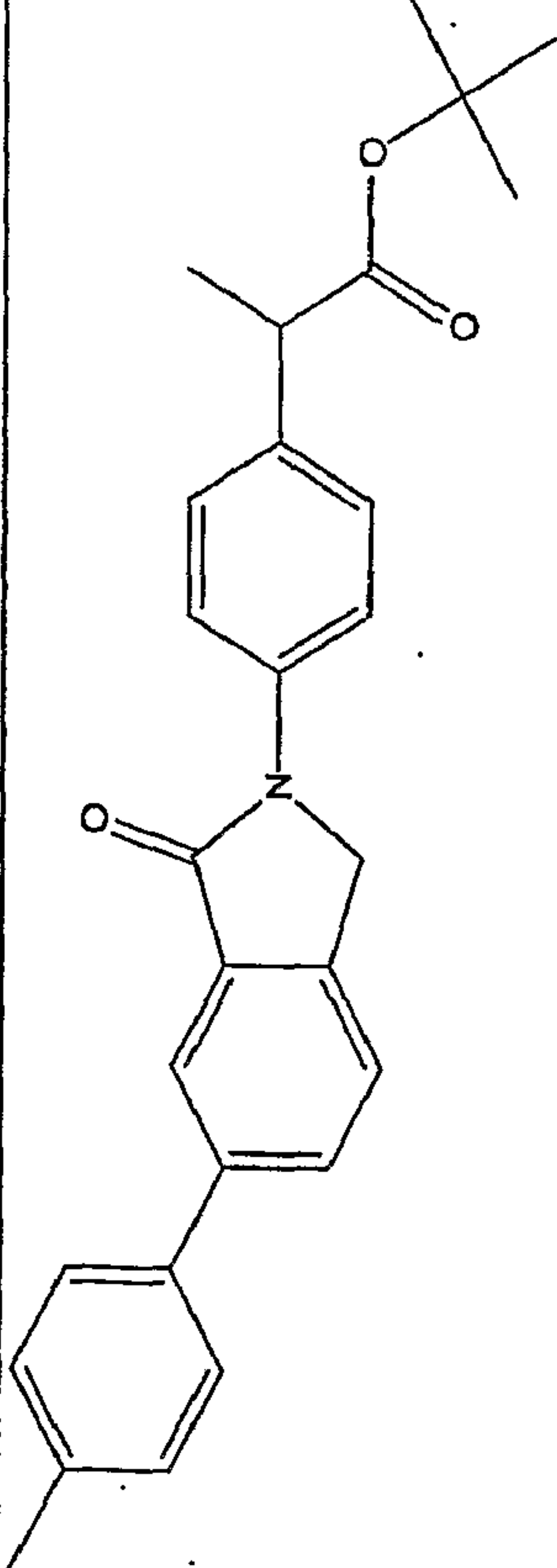
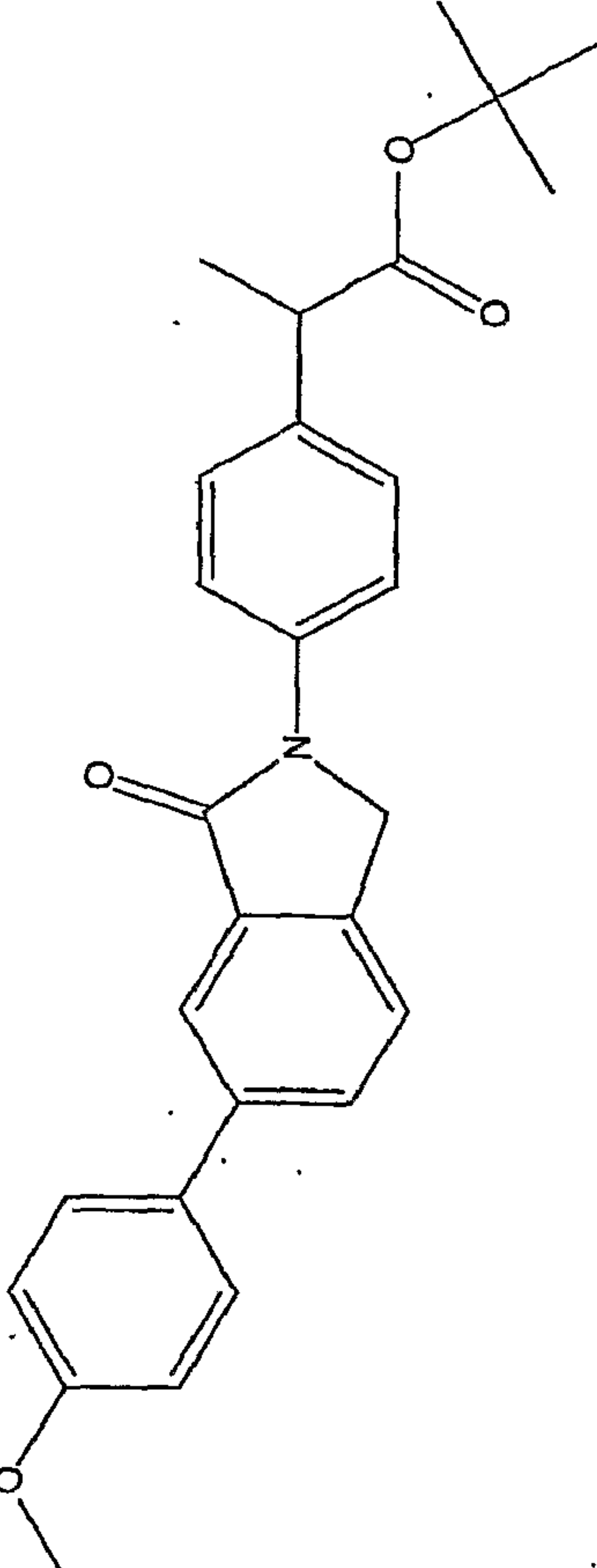
117

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
158		ALB- 112438	2.714	1.421
159		ALB- 112441		1.084

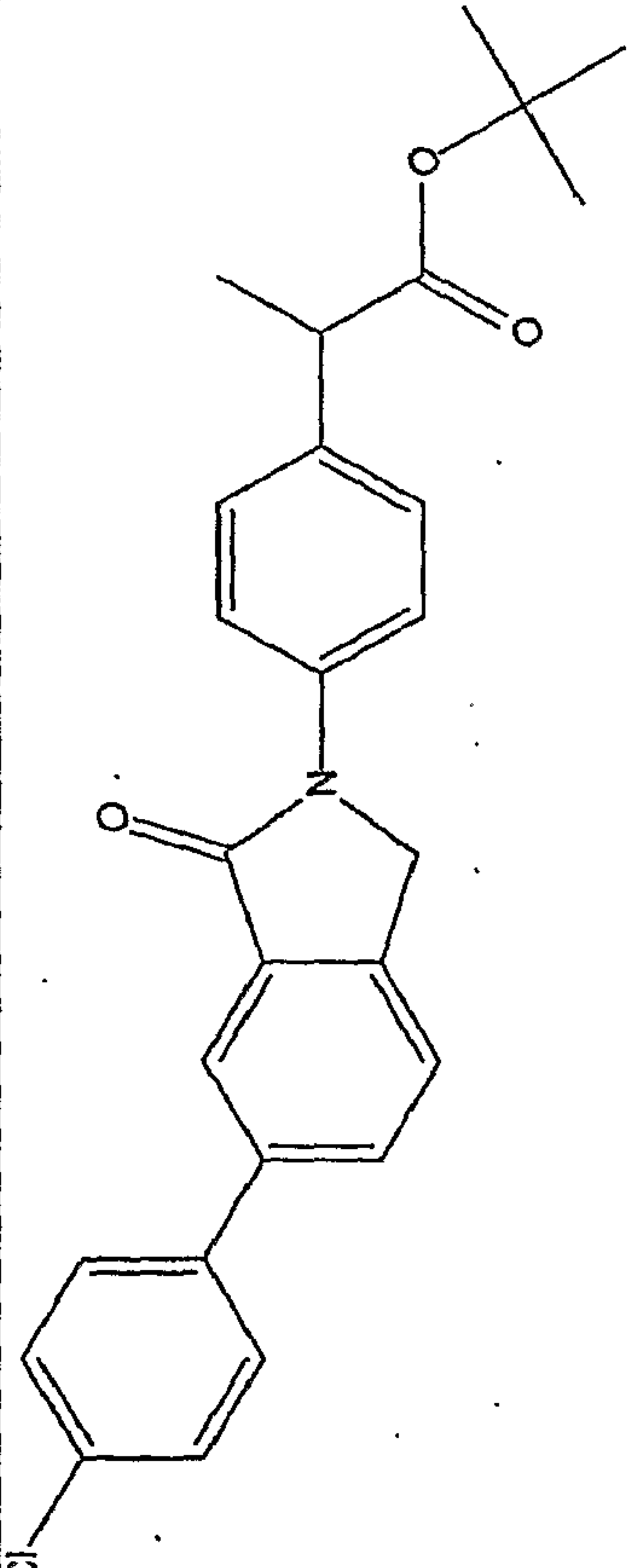
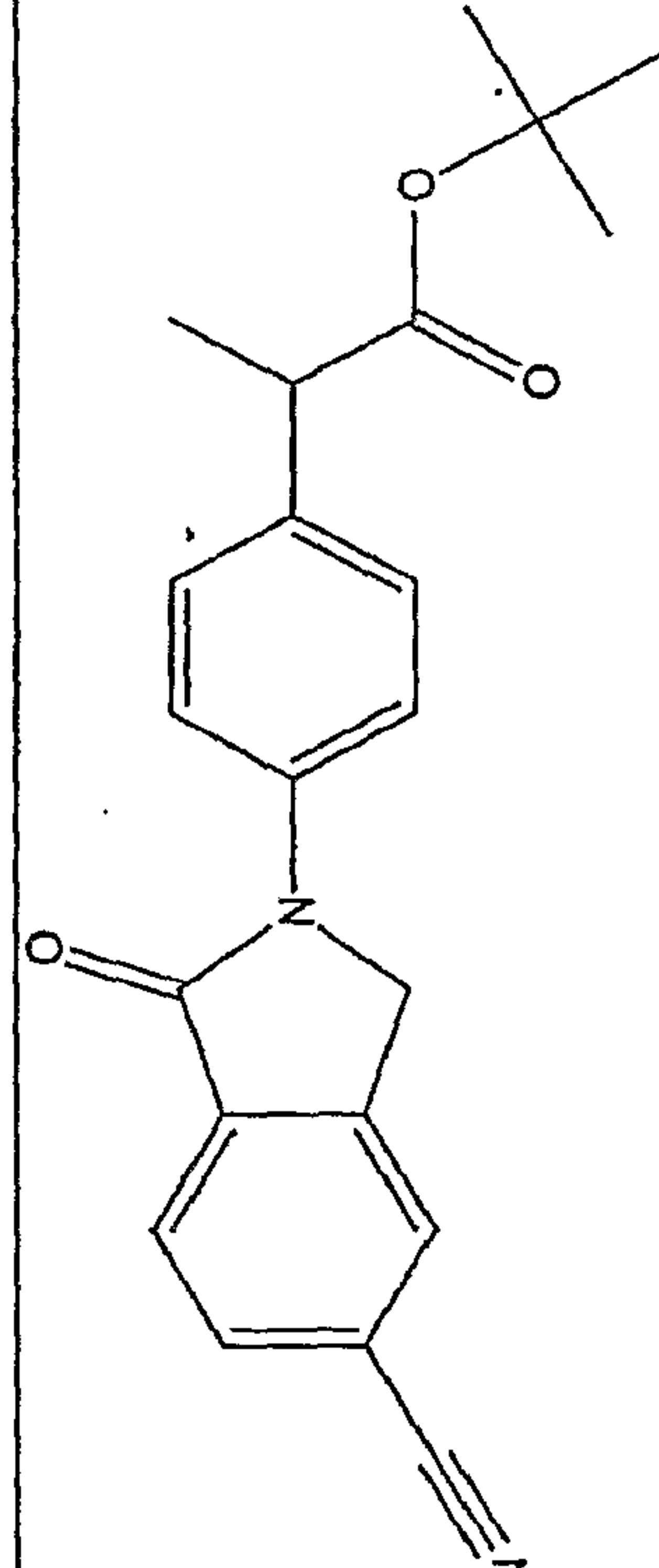
118

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
160		ALB- 112442		1.115
161		ALB- 112450		1.091

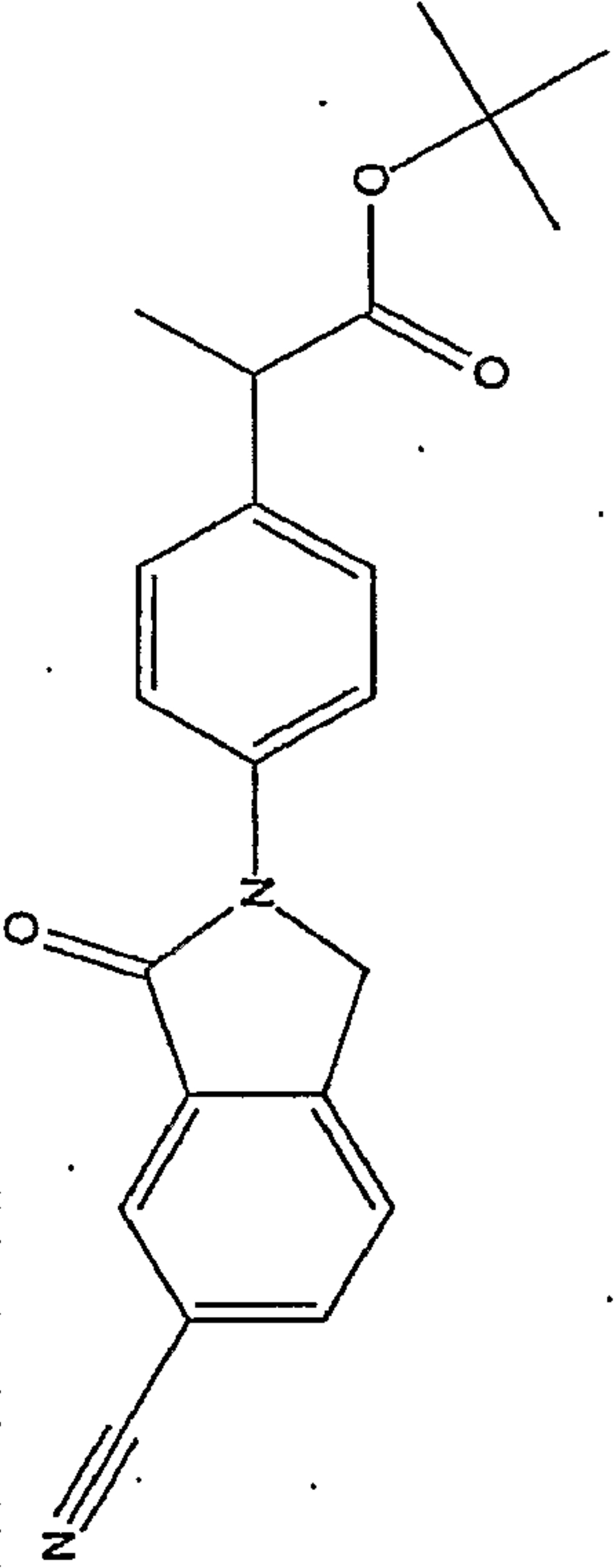
119

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
162		ALB- 112443		1.068
163		ALB- 112444	0.307	1.045

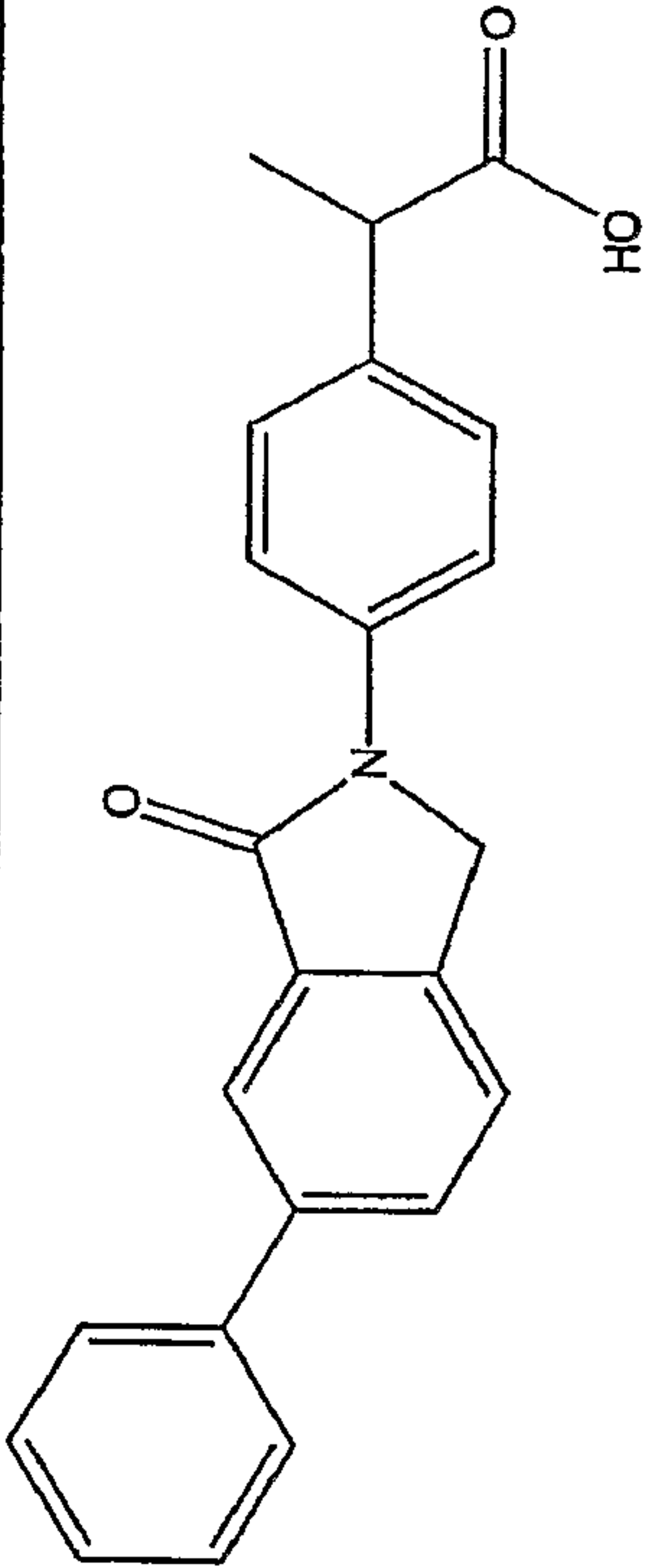
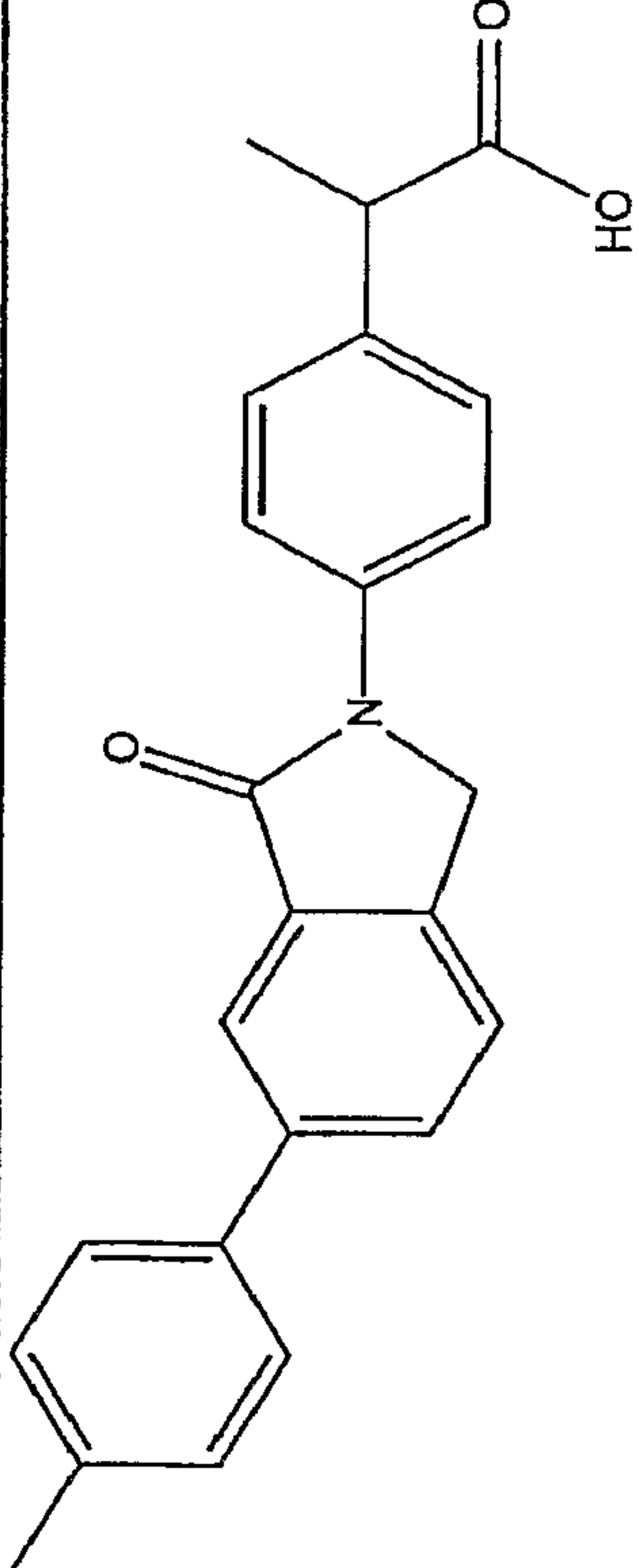
120

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
164		ALB- 112445		1.133

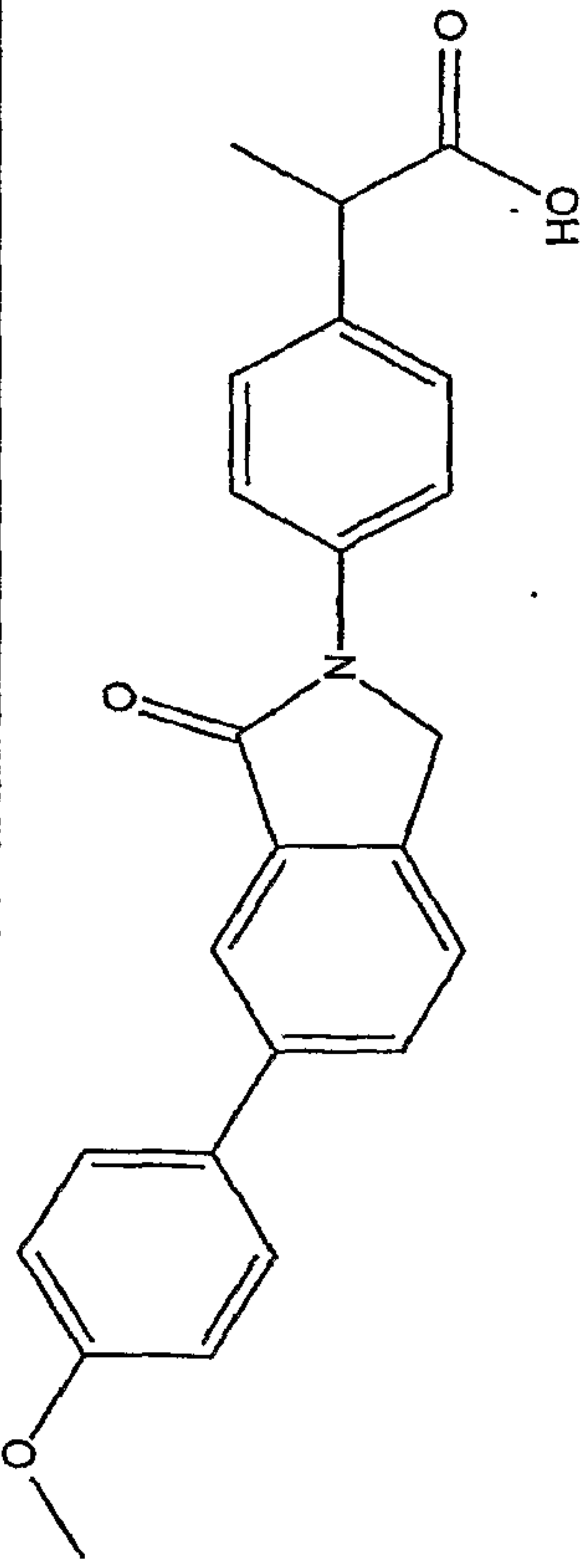
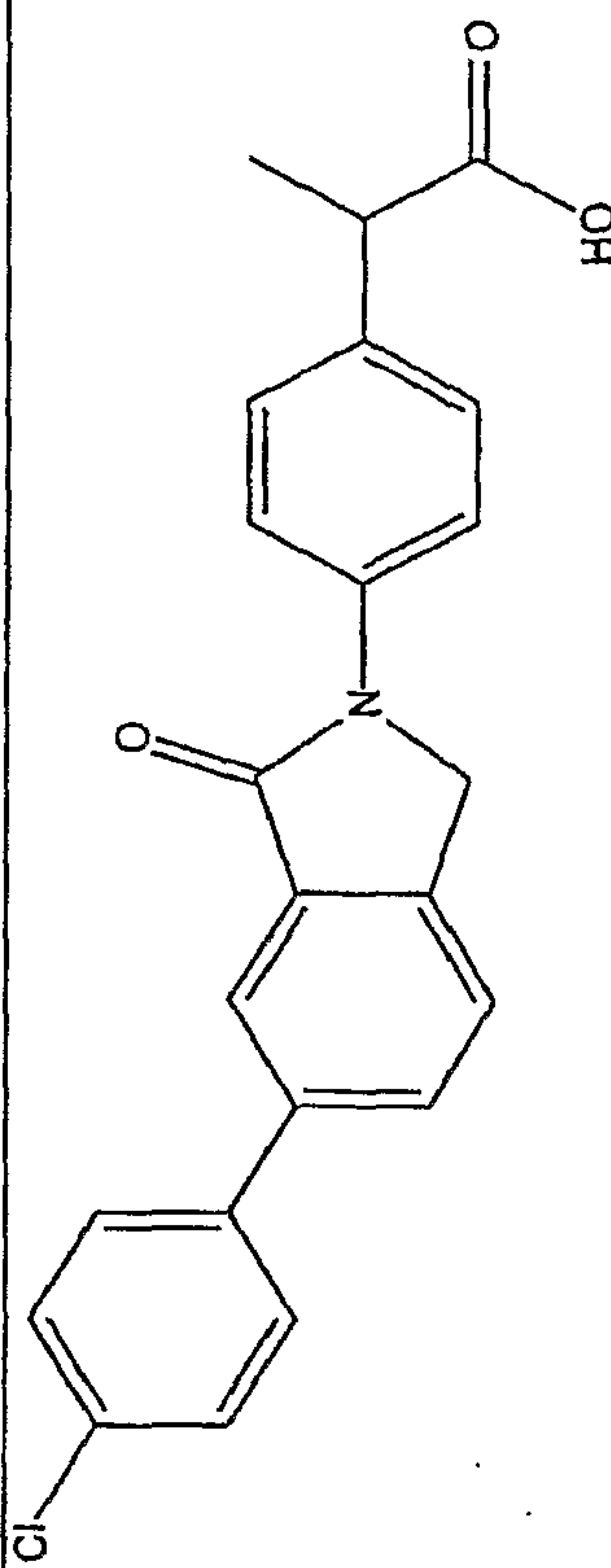
121

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
165				
		ALB- 112446	1.7	1.451
166				
		ALB- 112447	2.018	1.266

122

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
167				
168		ALB- 112448	6.188	1.546
		ALB- 112449		1.157

123

Table 1

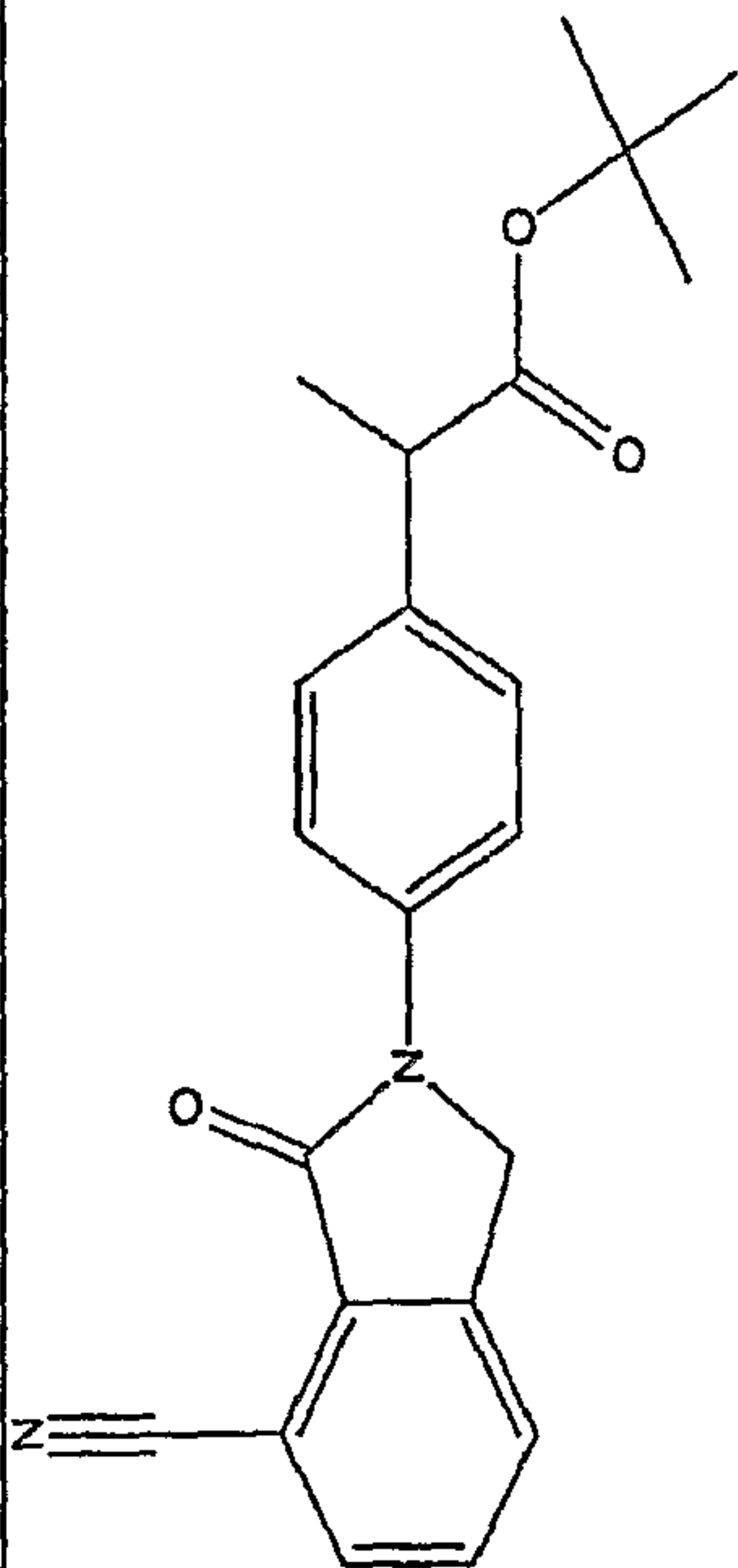
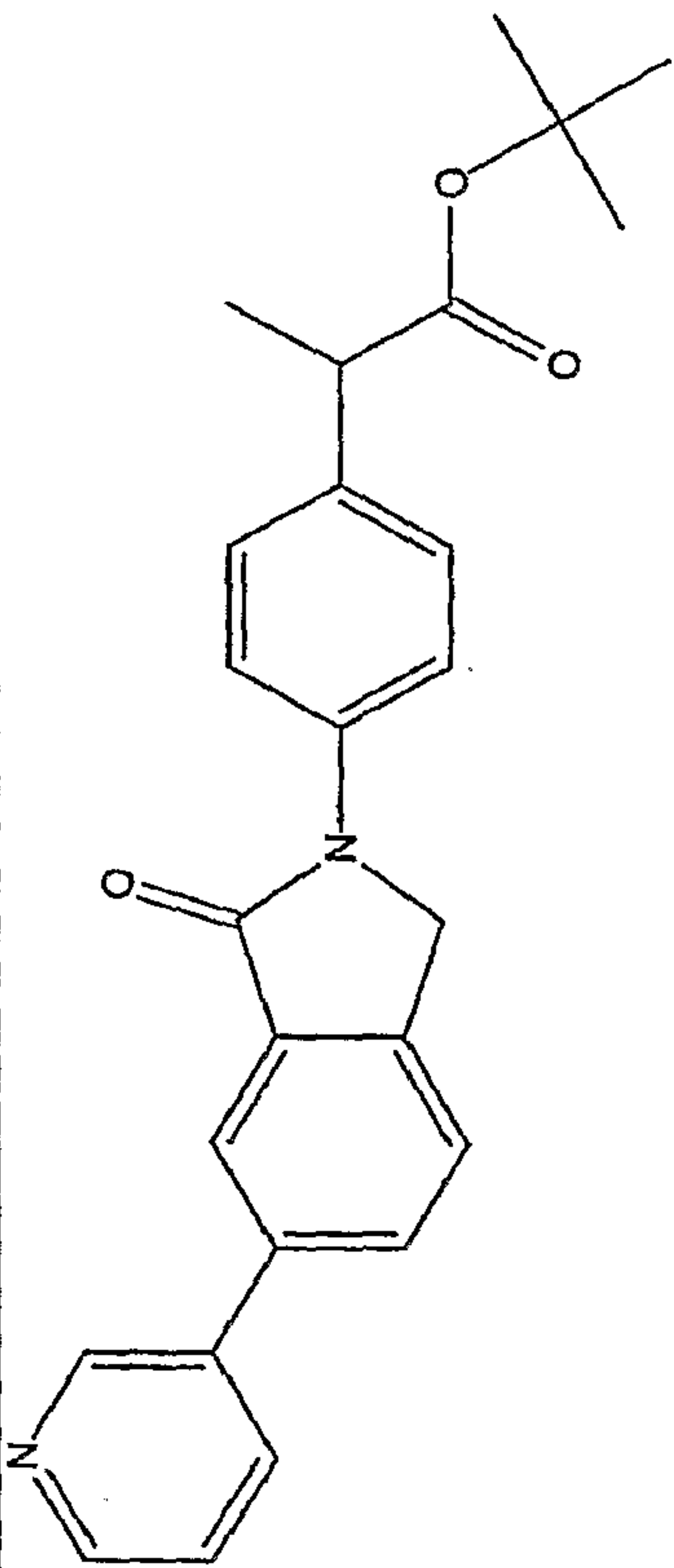
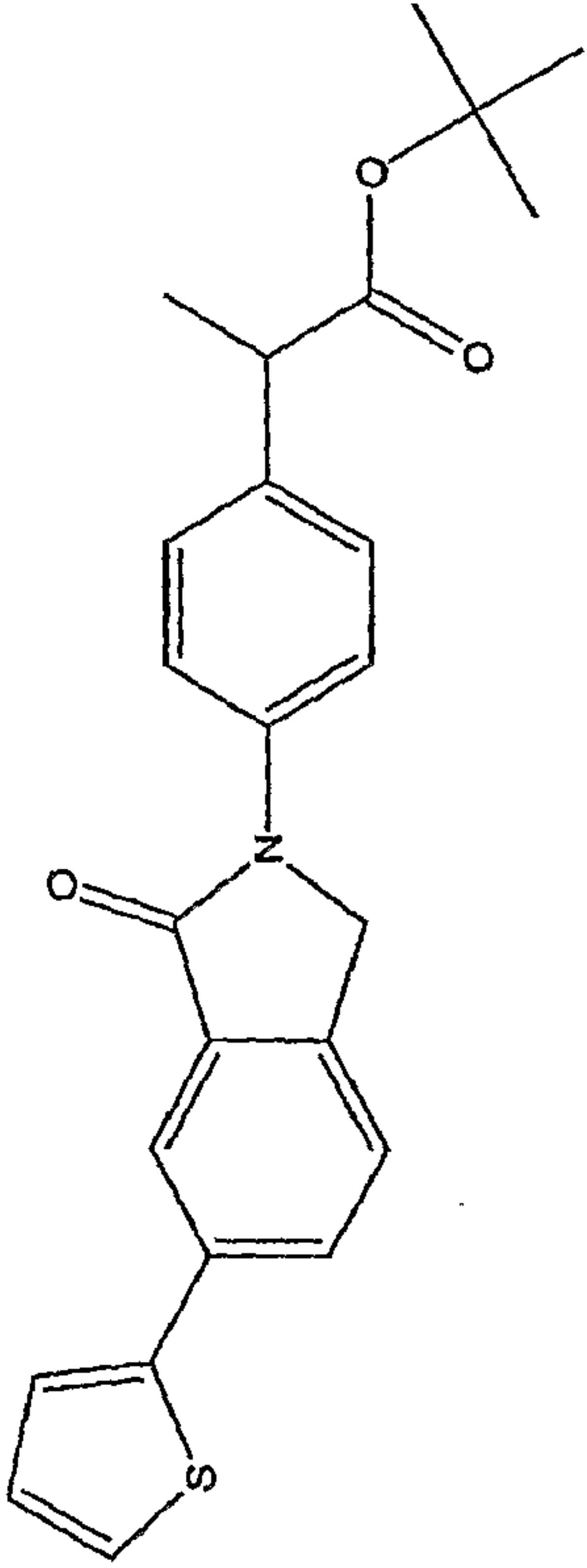
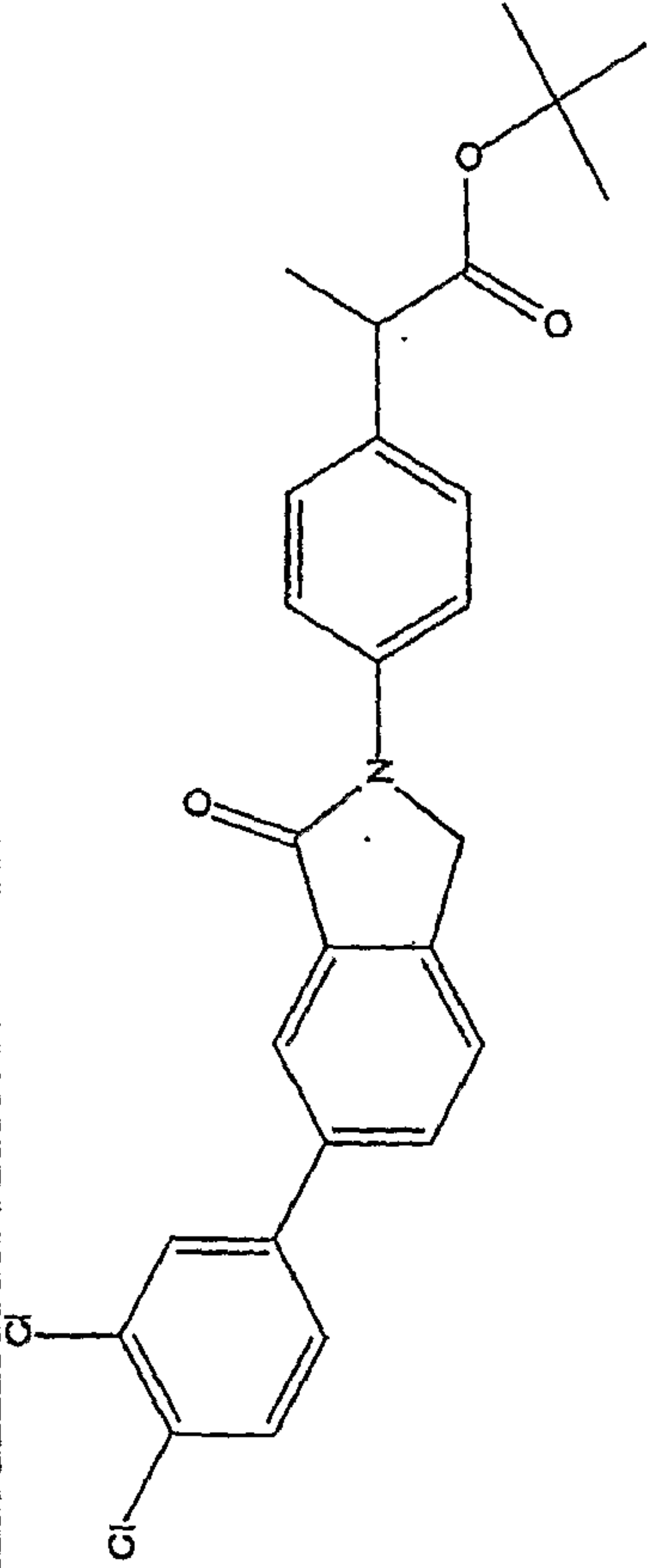
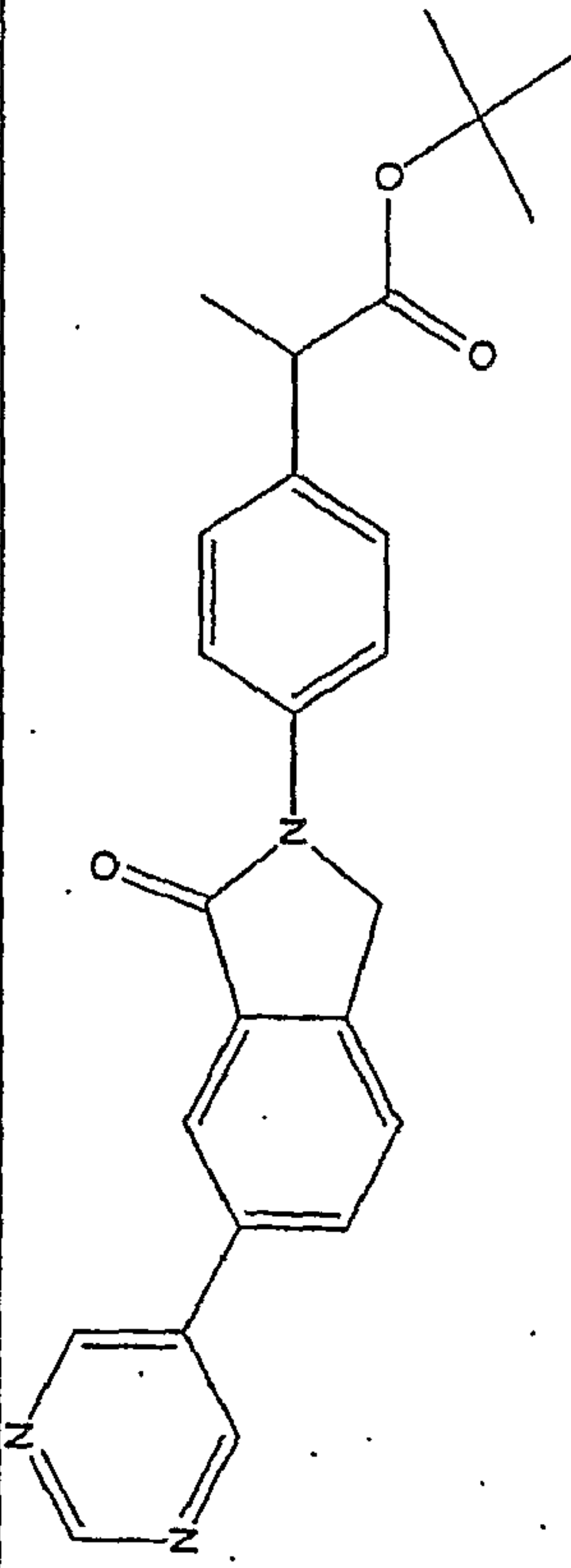
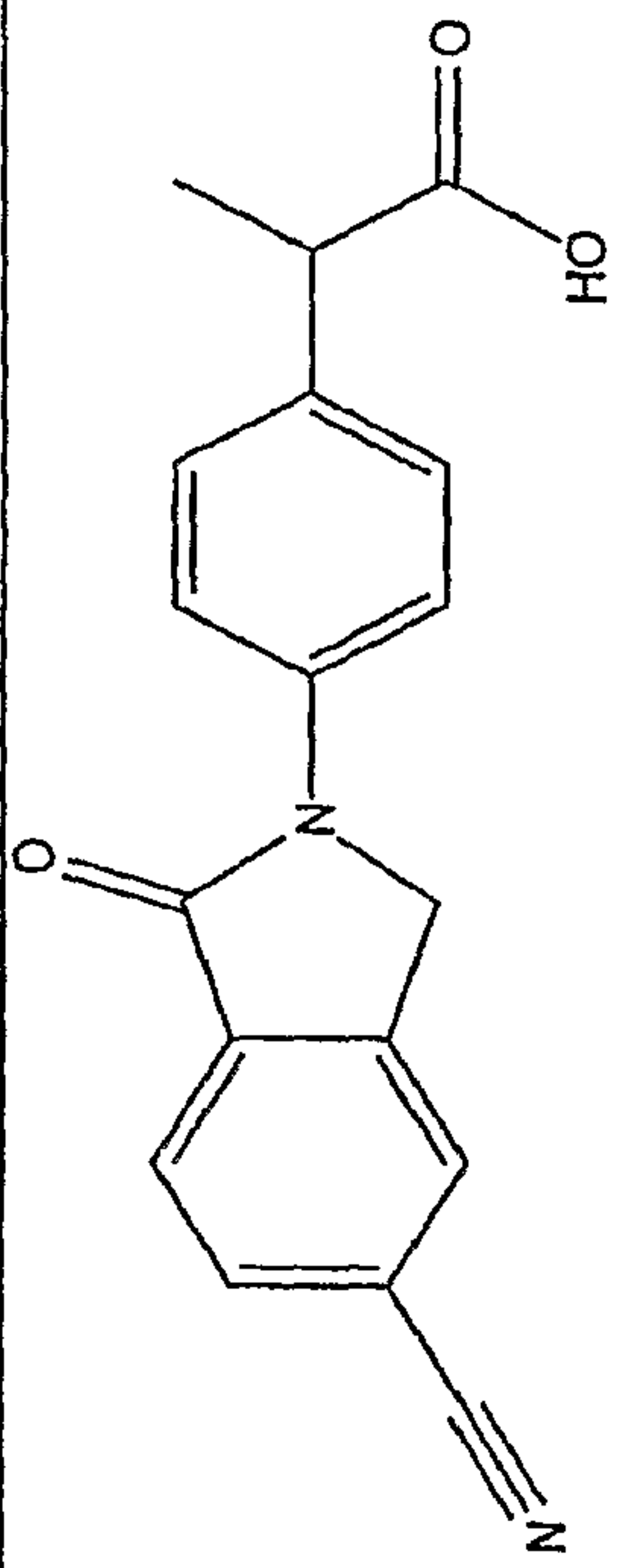
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
169		ALB- 112472	0.002	1.123
170		ALB- 112473	0.002	1.031

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
171		ALB- 112474	0.114	1.176
172		ALB- 112475	0.114	1.047

125

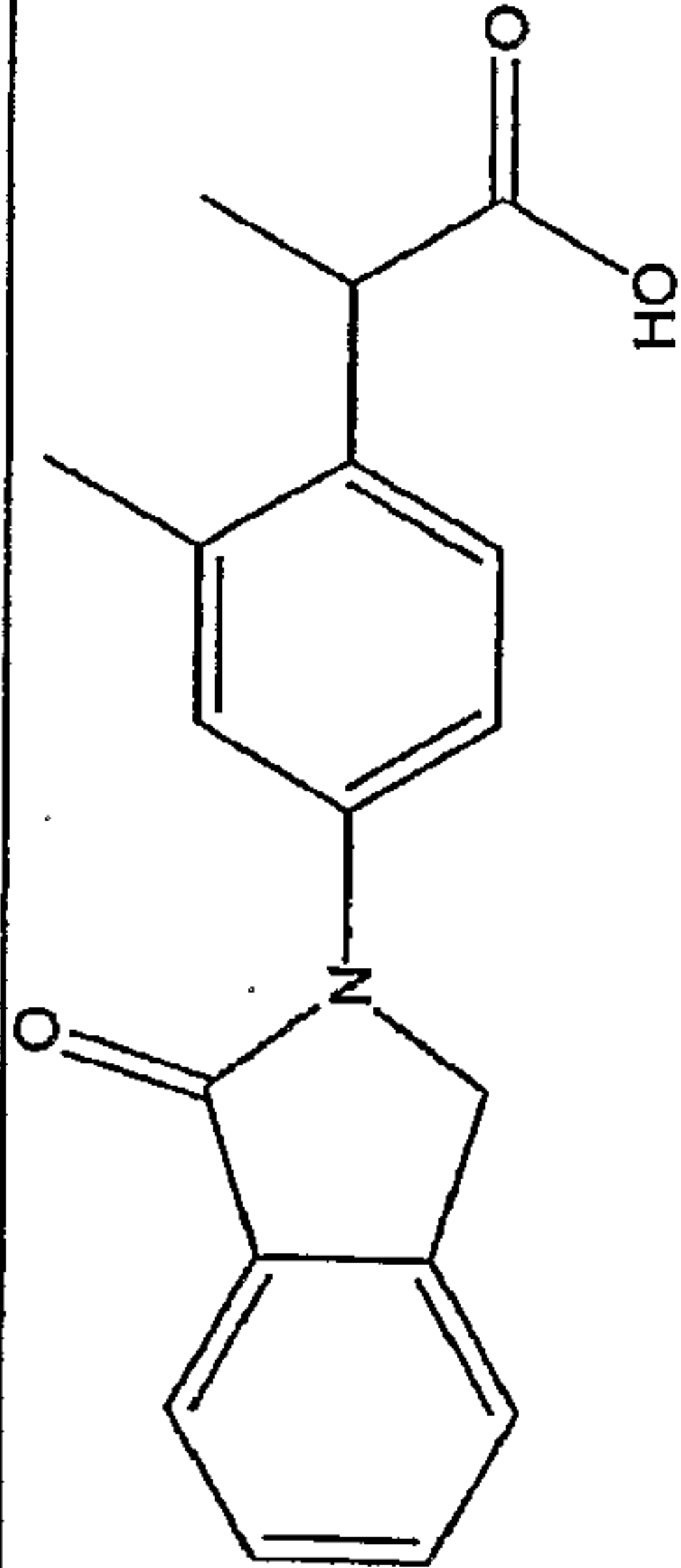
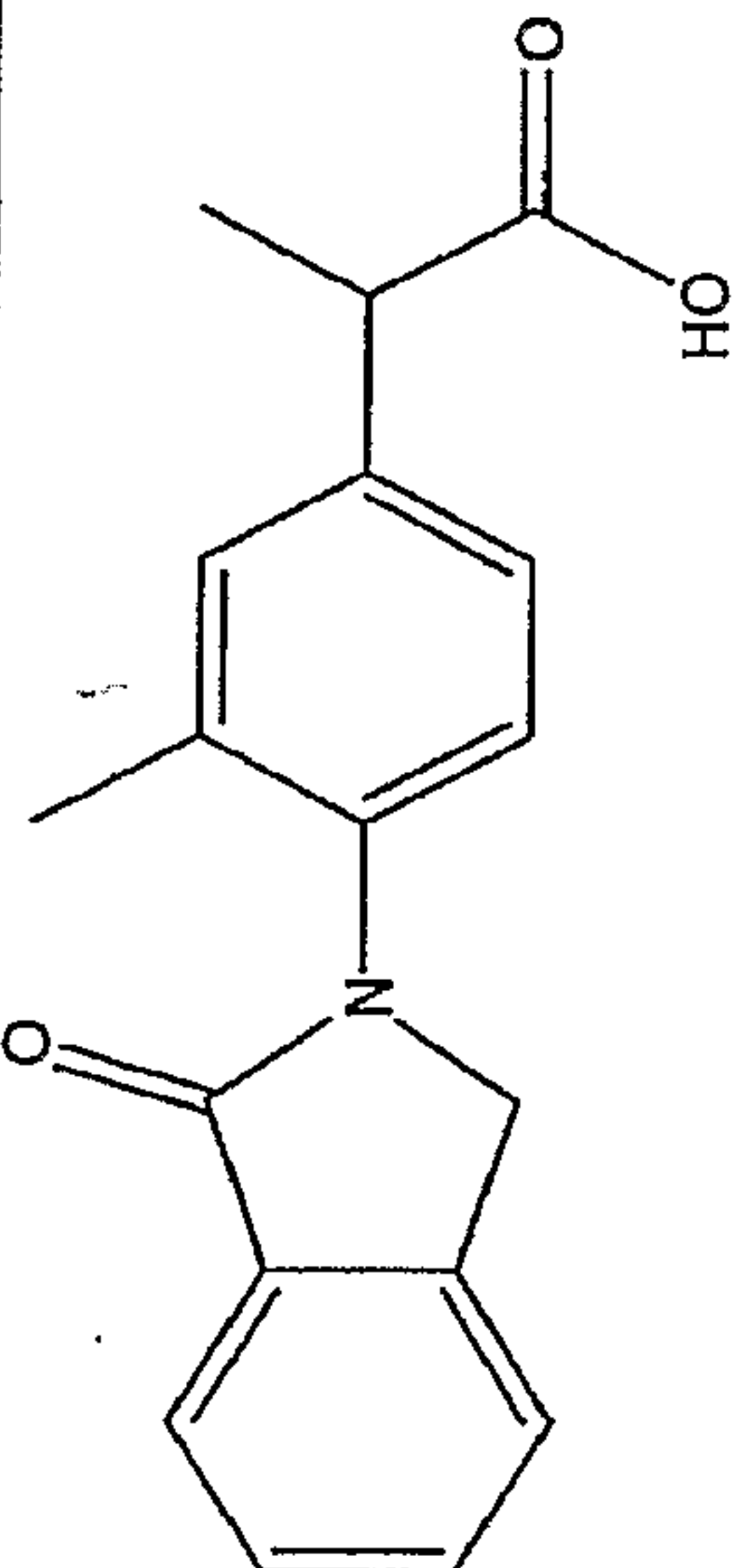
Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
173		ALB- 112476		1.081
174		ALB- 112477	6.982	1.179

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μM)	Avg MaxFold Increase
175	 <chem>N#Cc1ccc2c(c1)c(=O)n(c2)C3=CC=C(C=C3)C(C)C(=O)O</chem>	ALB- 112478	2.04	1.231
176	 <chem>COC(=O)C(C)C1=CC=C(C=C1)N2C(=O)c3ccccc3c2C4=CC=C(C=C4)C5=CC=CC=C5C5=O</chem>	ALB- 112483		1.034

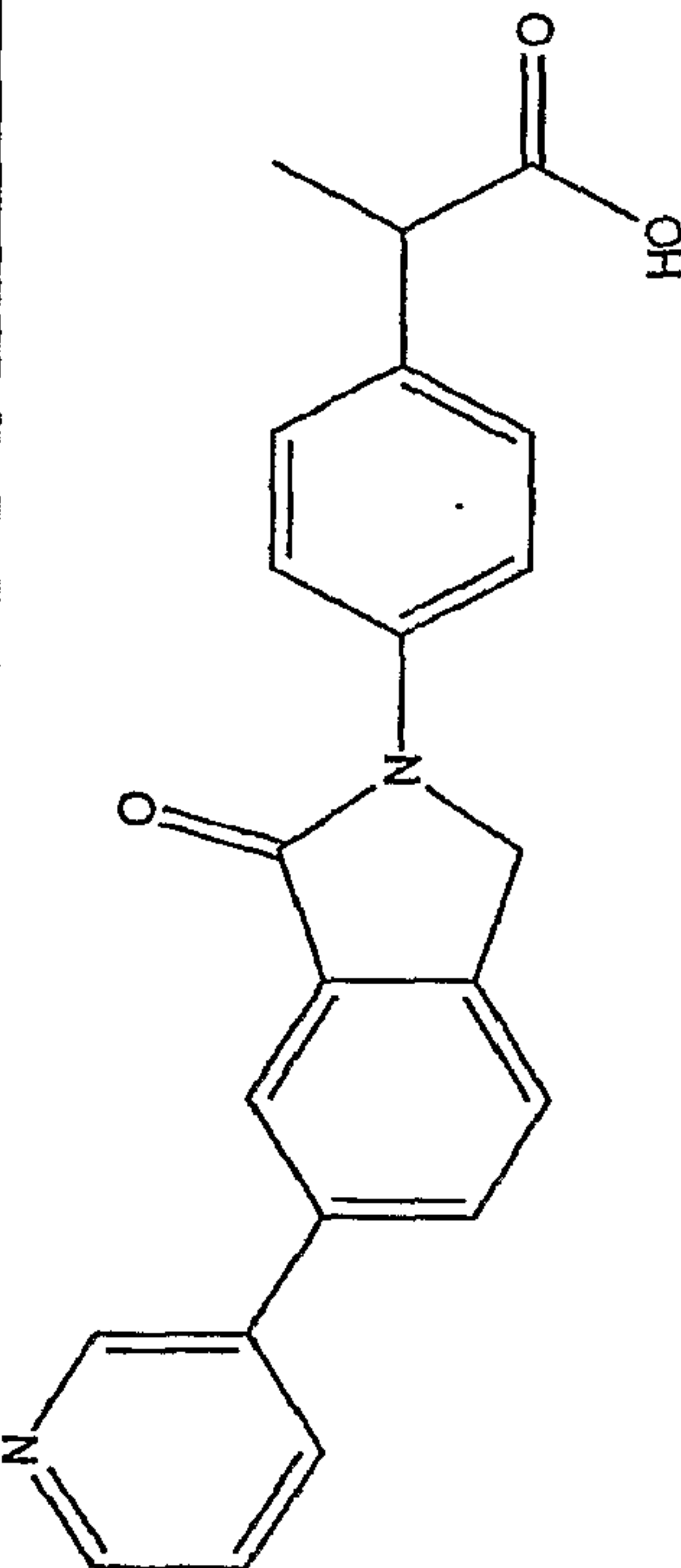
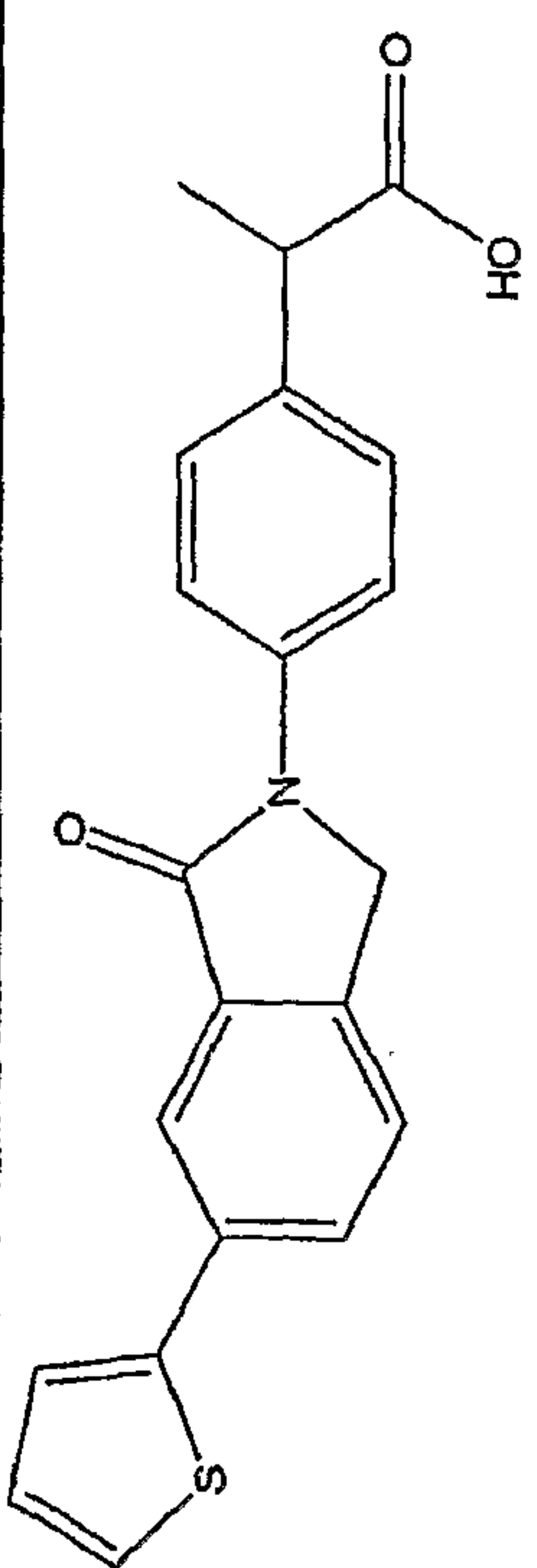
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
177		ALB- 112485		1.304
178		ALB- 112487		1.173

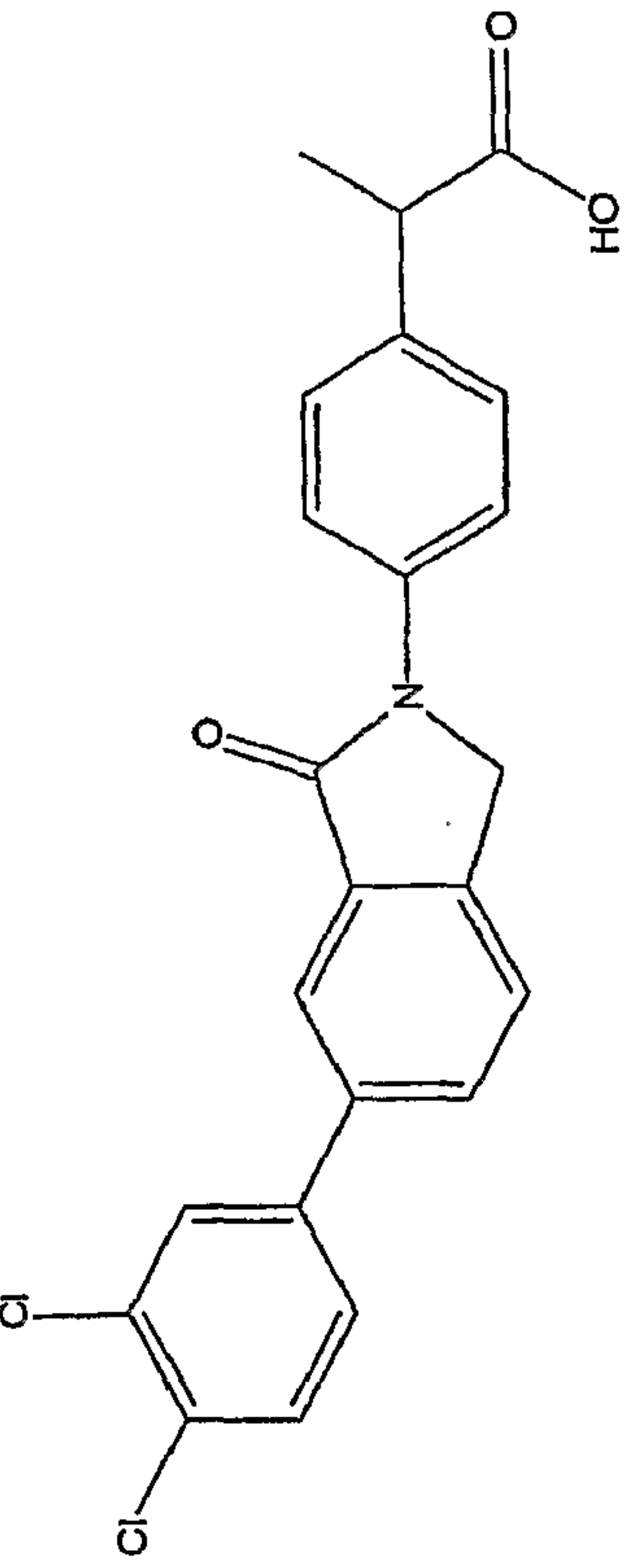
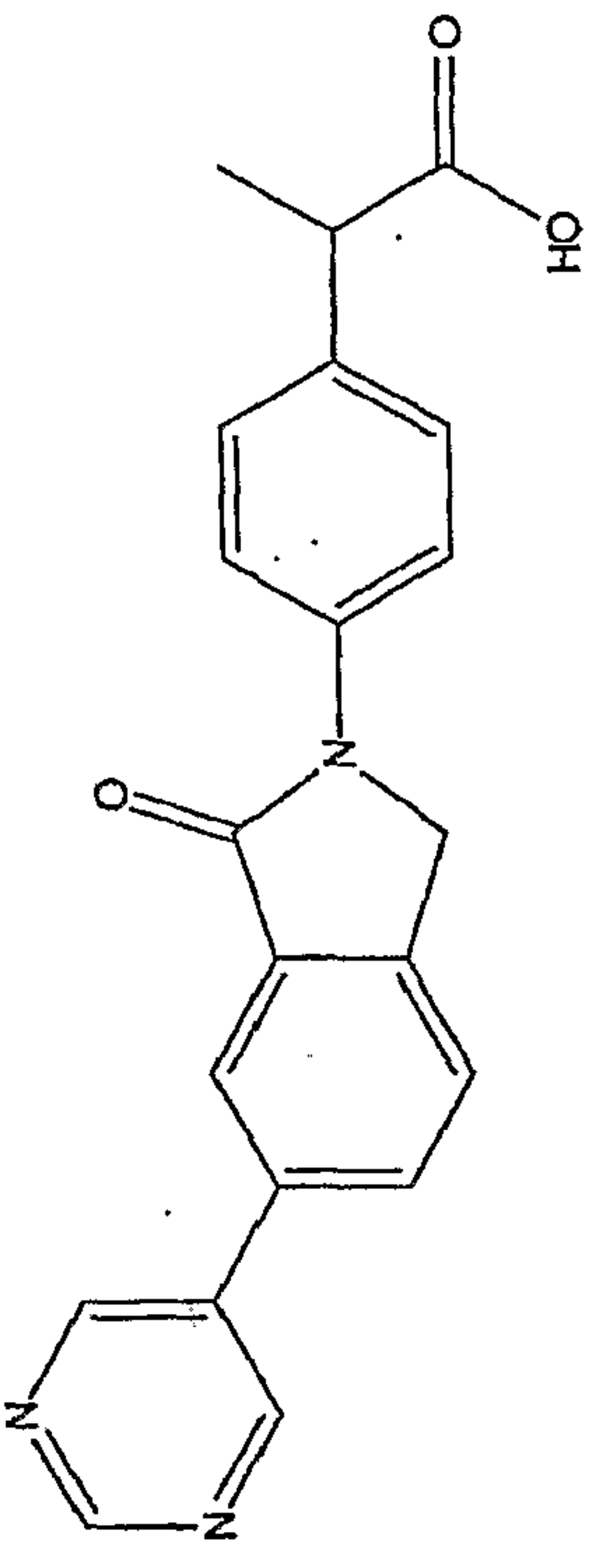
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
179		ALB- 112514		1.252
180		ALB- 112515	0.494	1.623

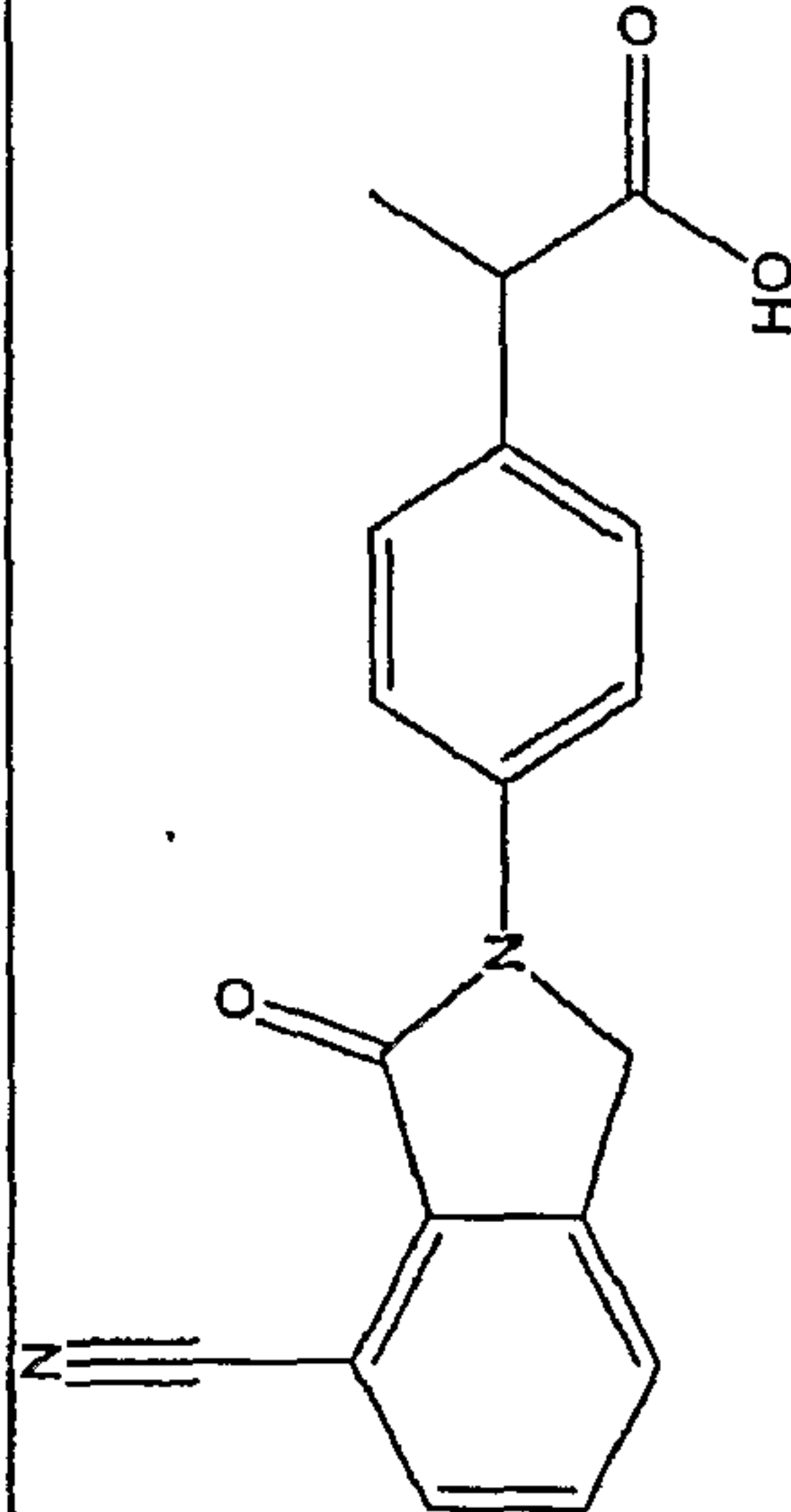
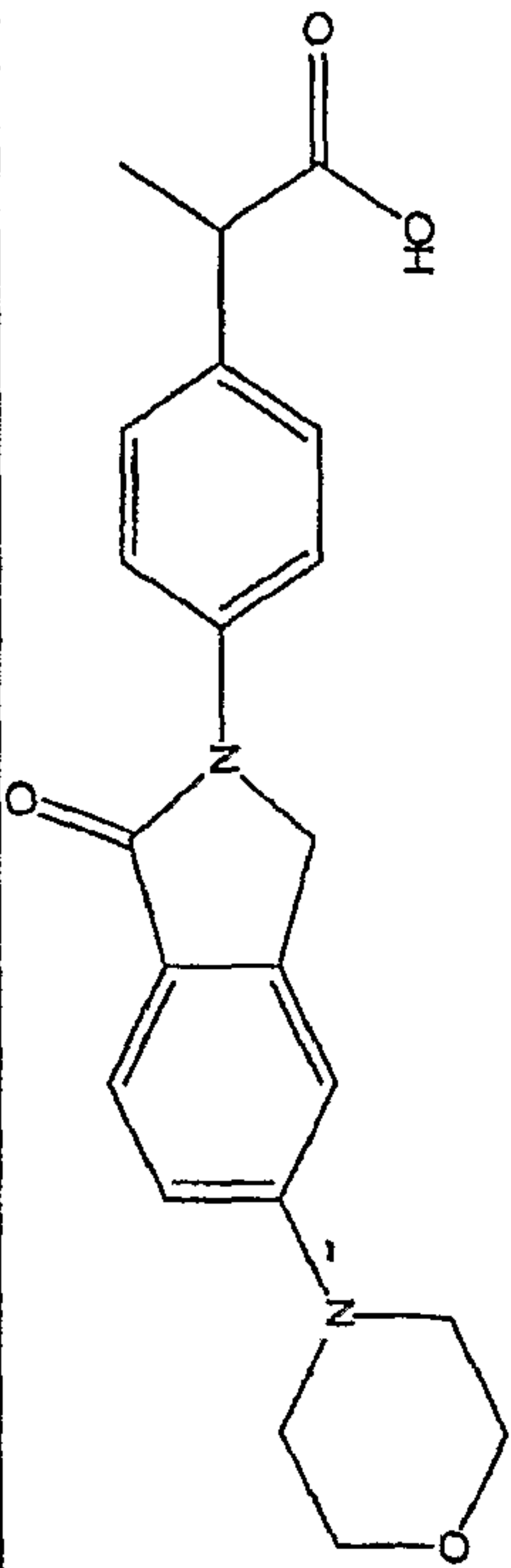
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
181		ALB- 112516		1.199
182		ALB- 112517		1.255

130

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
183		ALB- 112518		1.117
184		ALB- 112554		1.062

131

Table 1

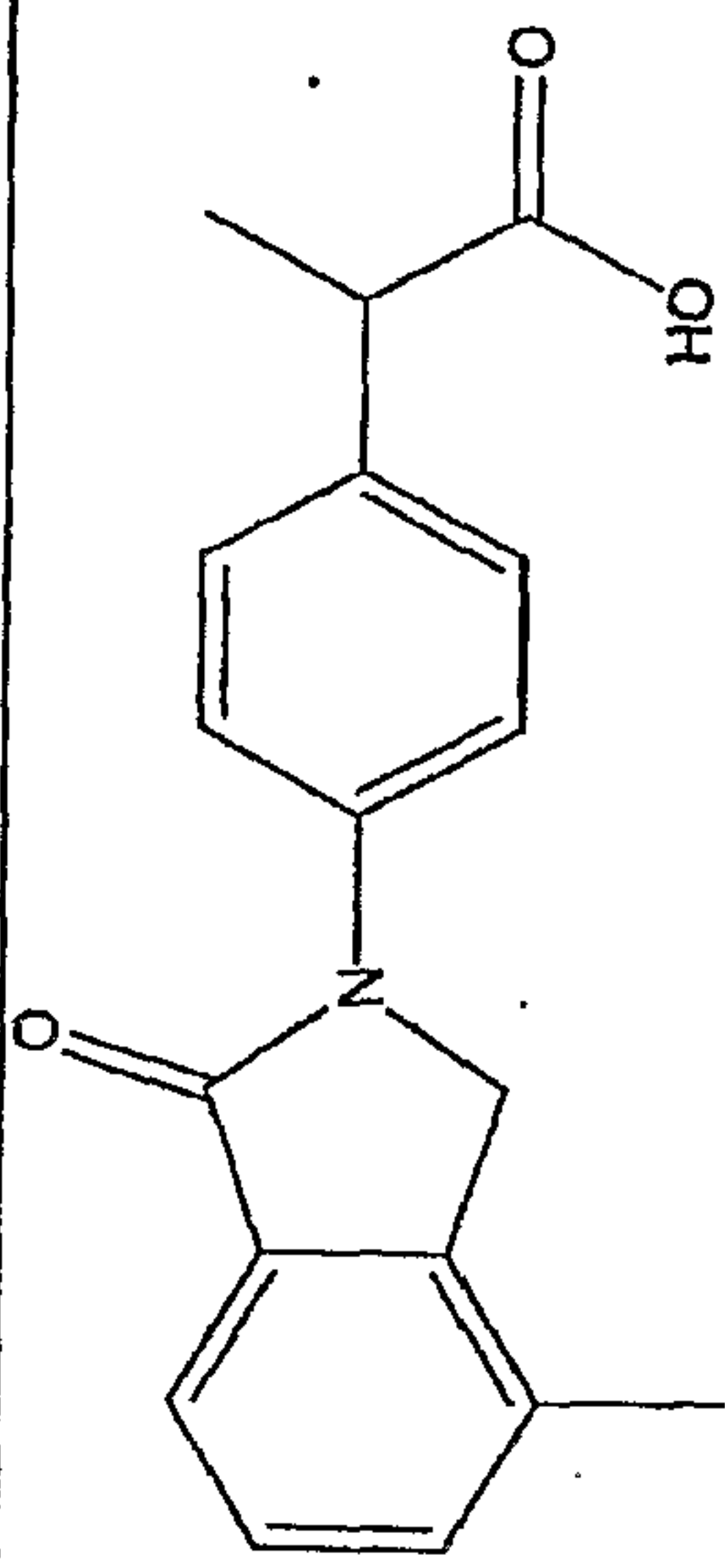
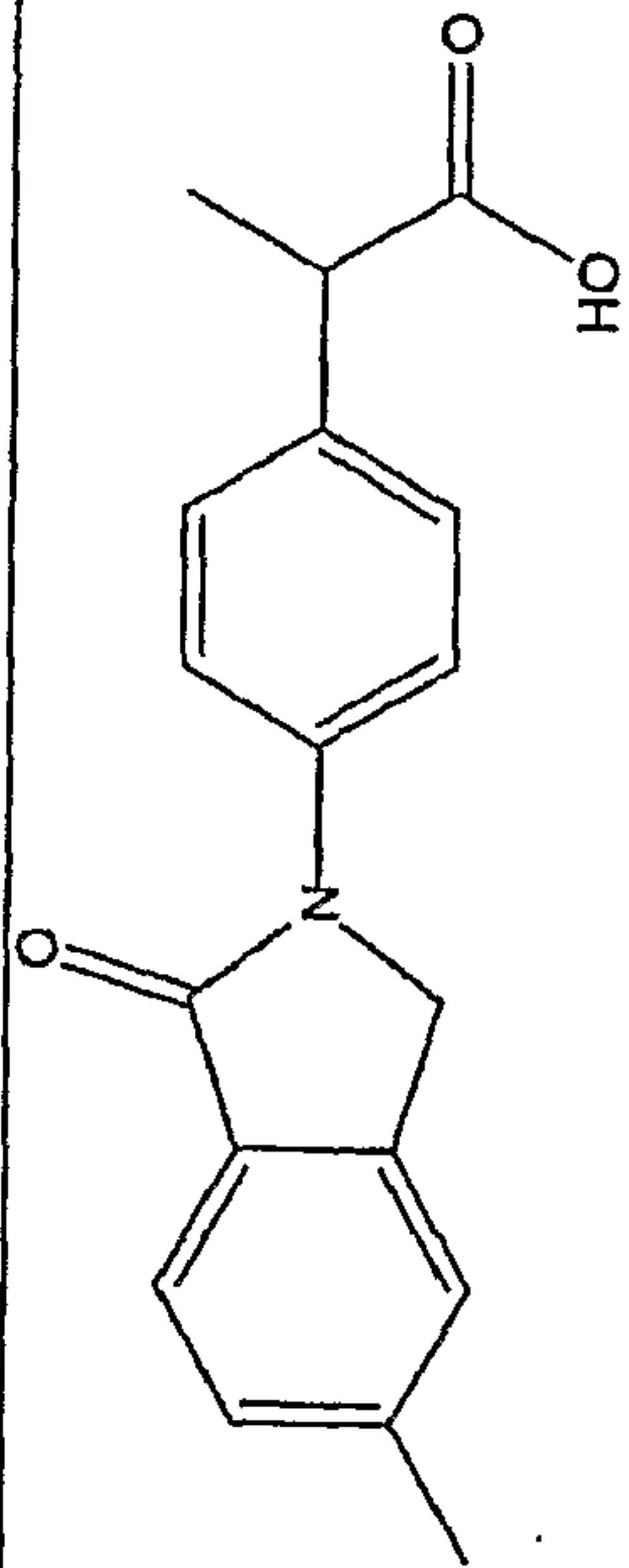
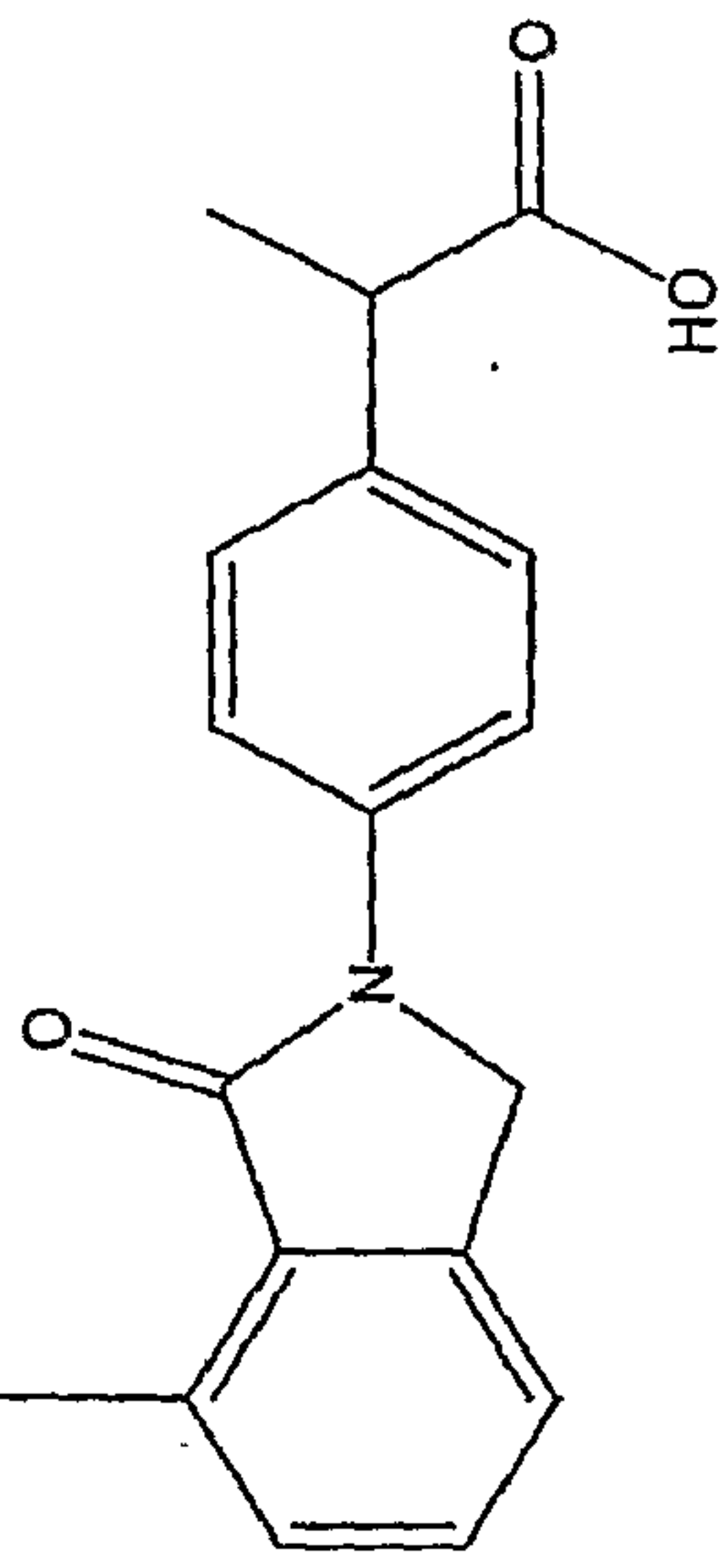
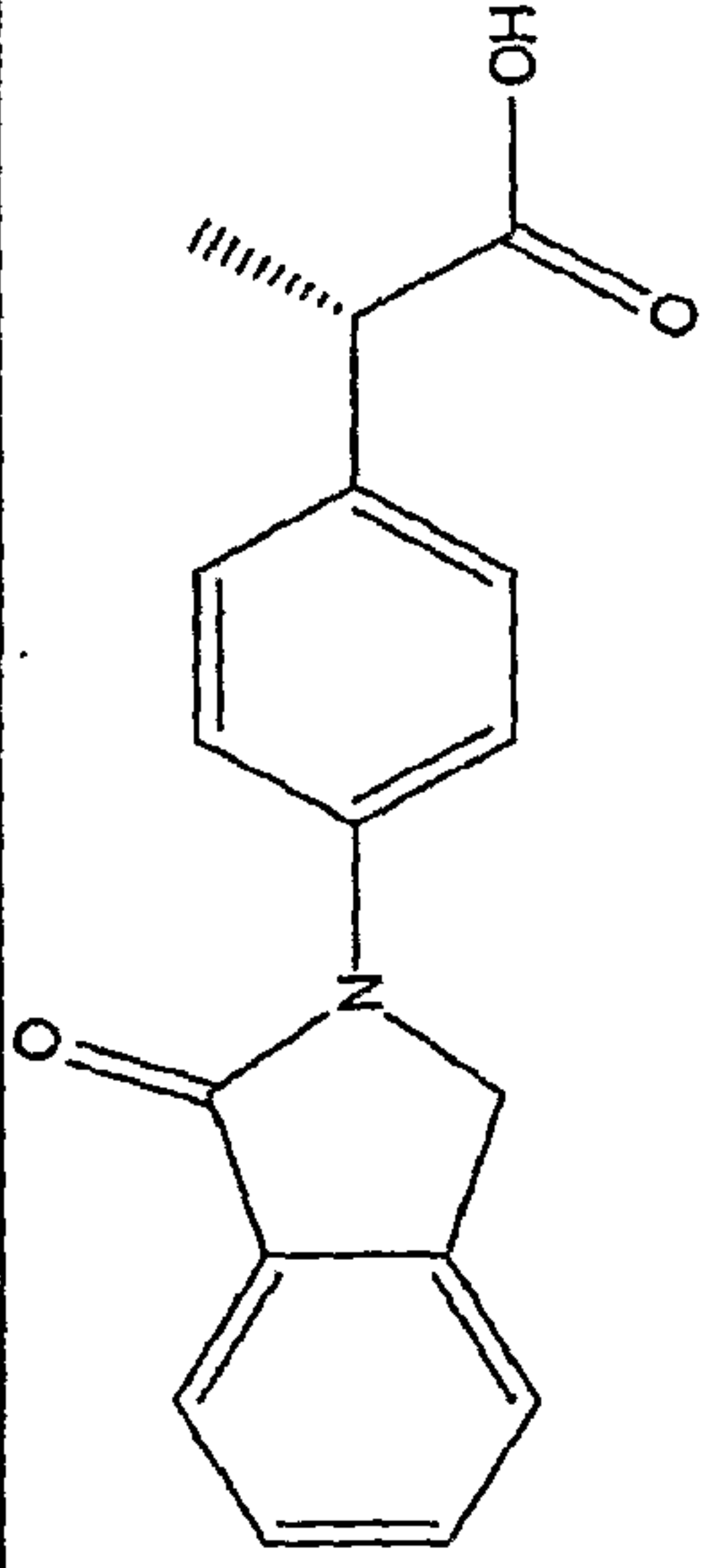
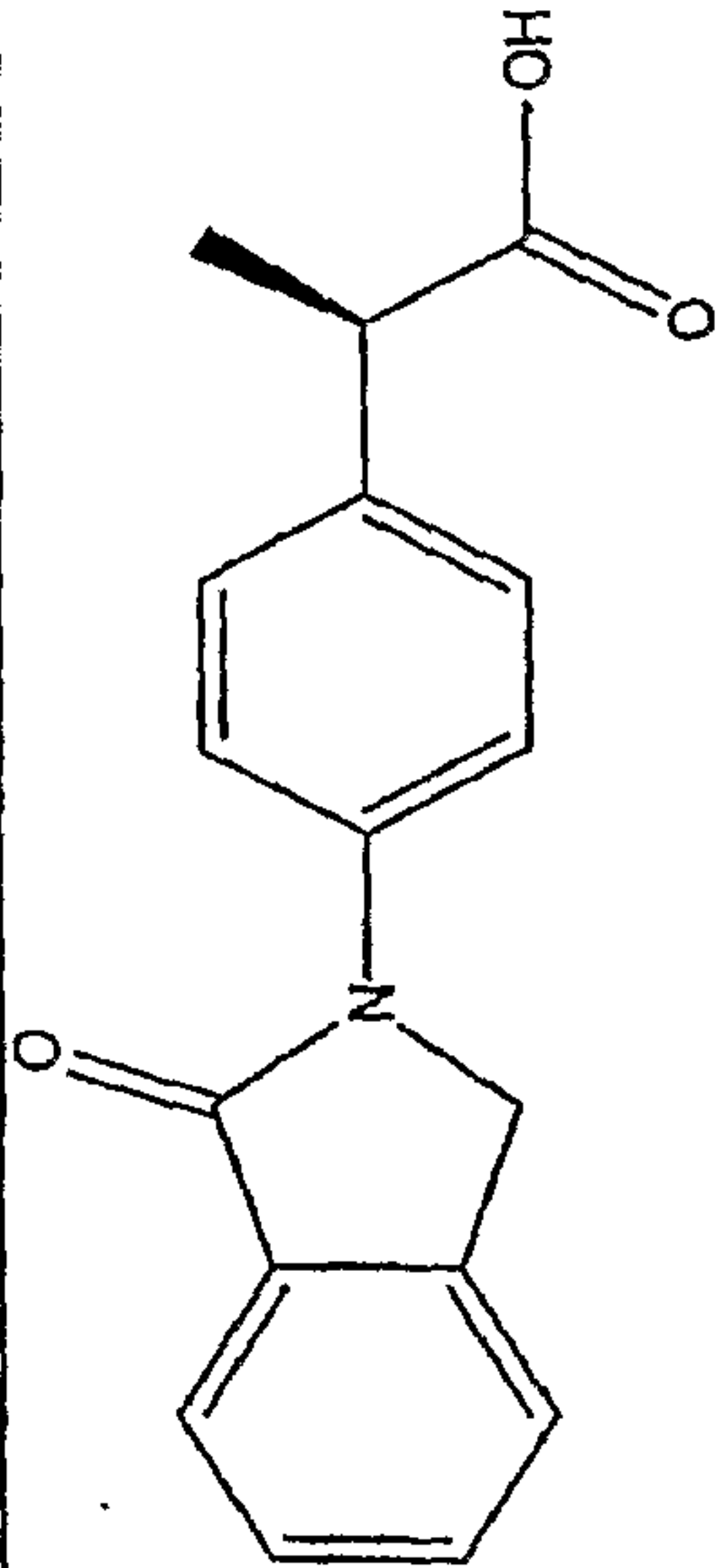
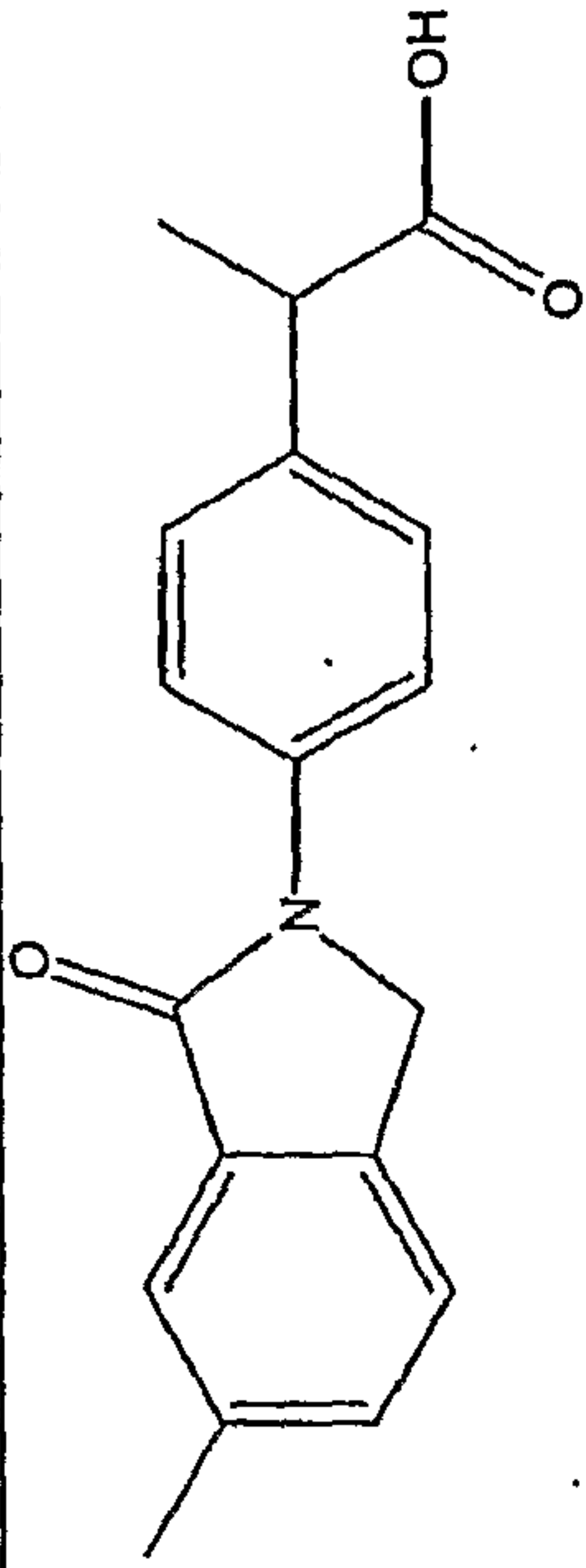
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			Avg EC50 (μ M)	Avg MaxFold Increase
185		ALB- 112555	5.902	1.641
186		ALB- 112556	0.146	1.565

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
187		ALB- 112557	0.288	1.734
188		ALB- 112837	8.538	1.396

- 133

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
189		ALB- 112941	0.28	1.483
190		ALB- 112954	0.33	1.617

134

Table 1

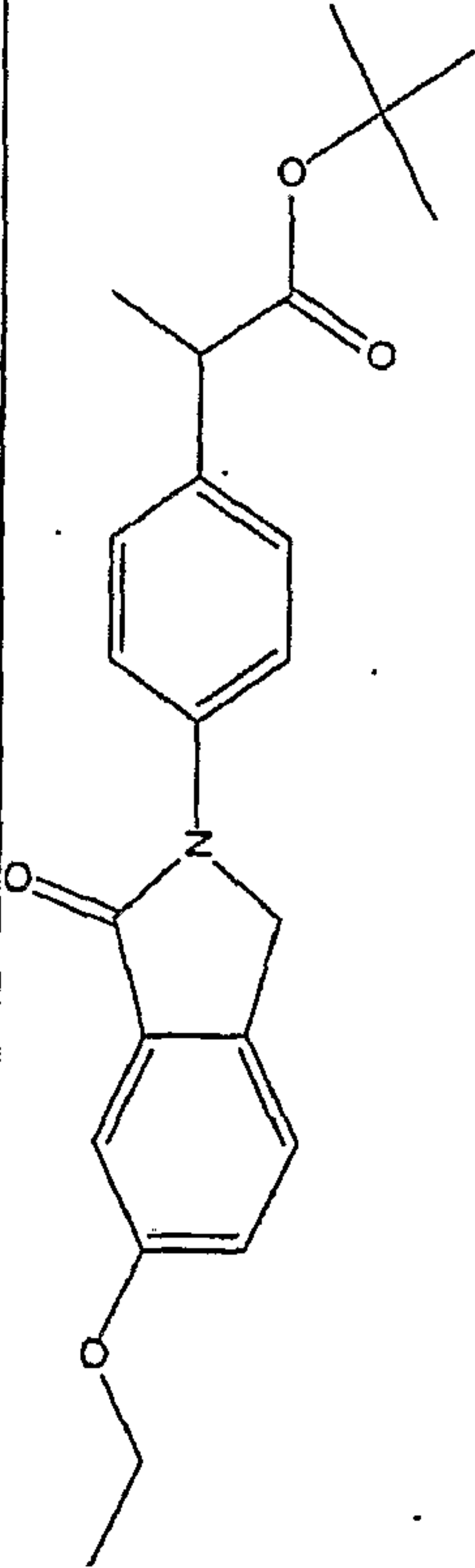
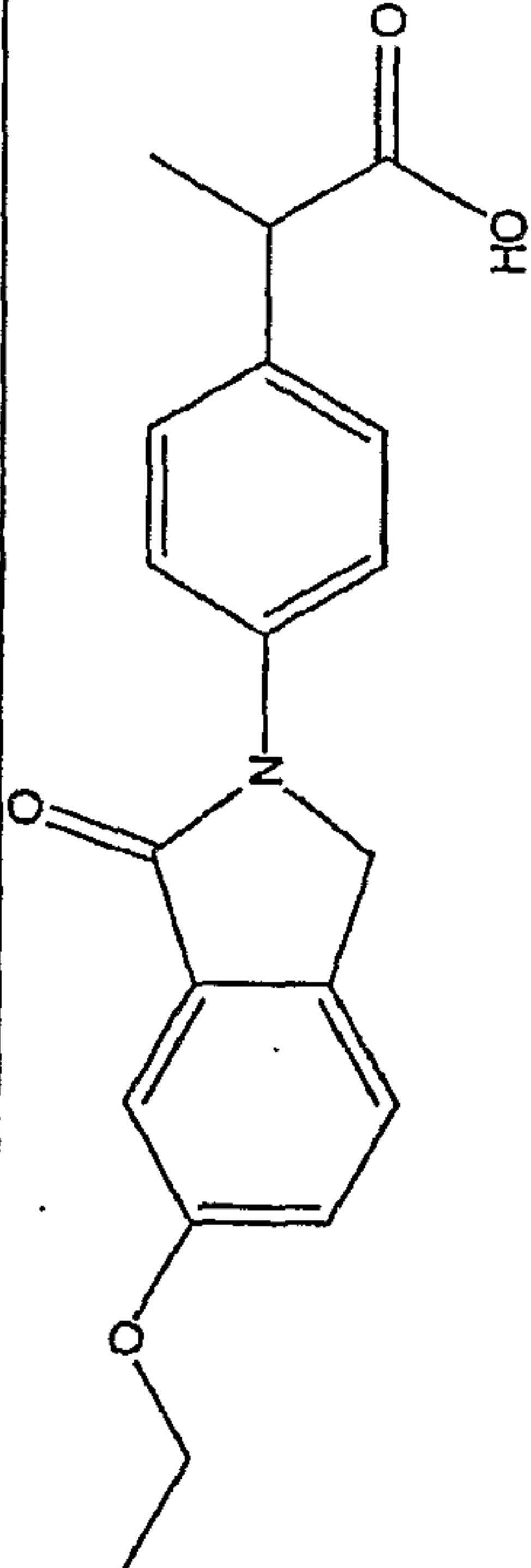
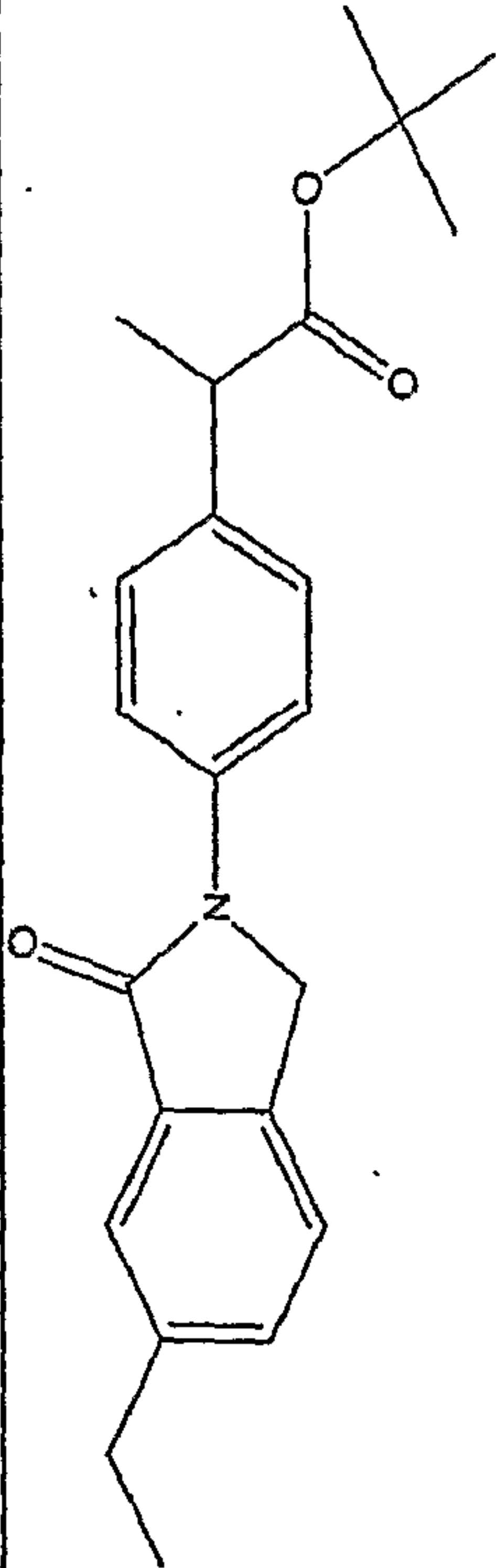
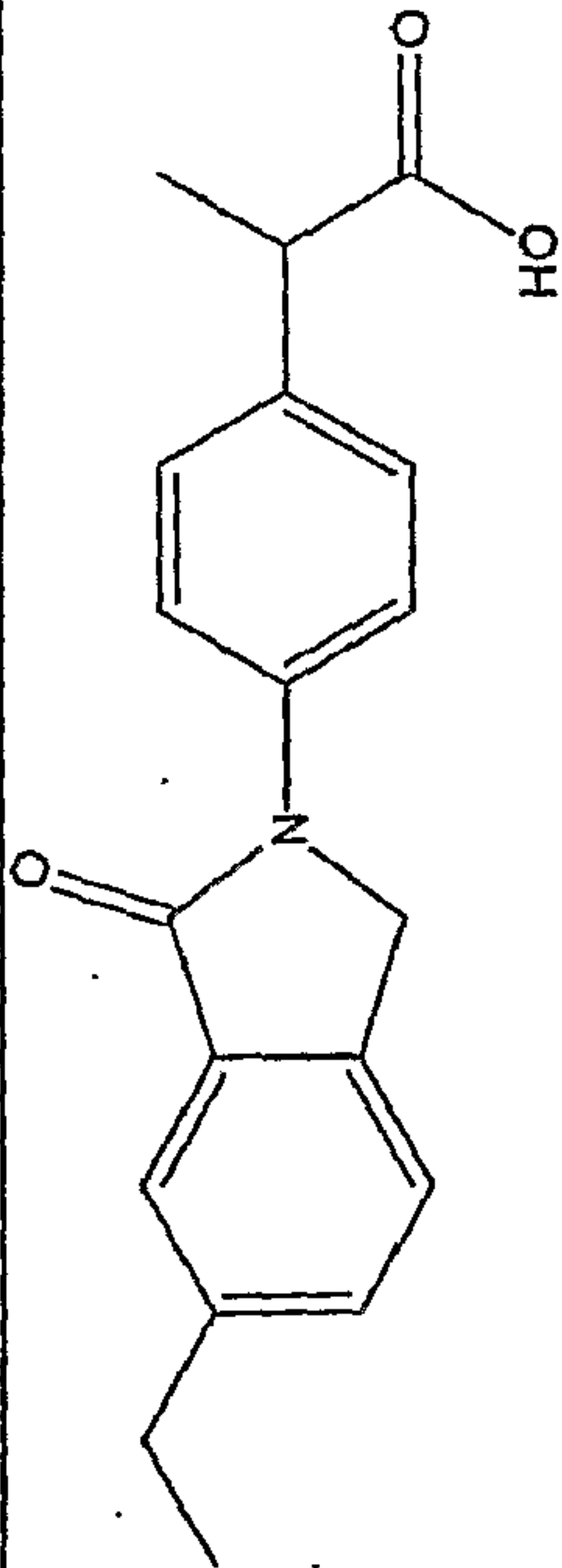
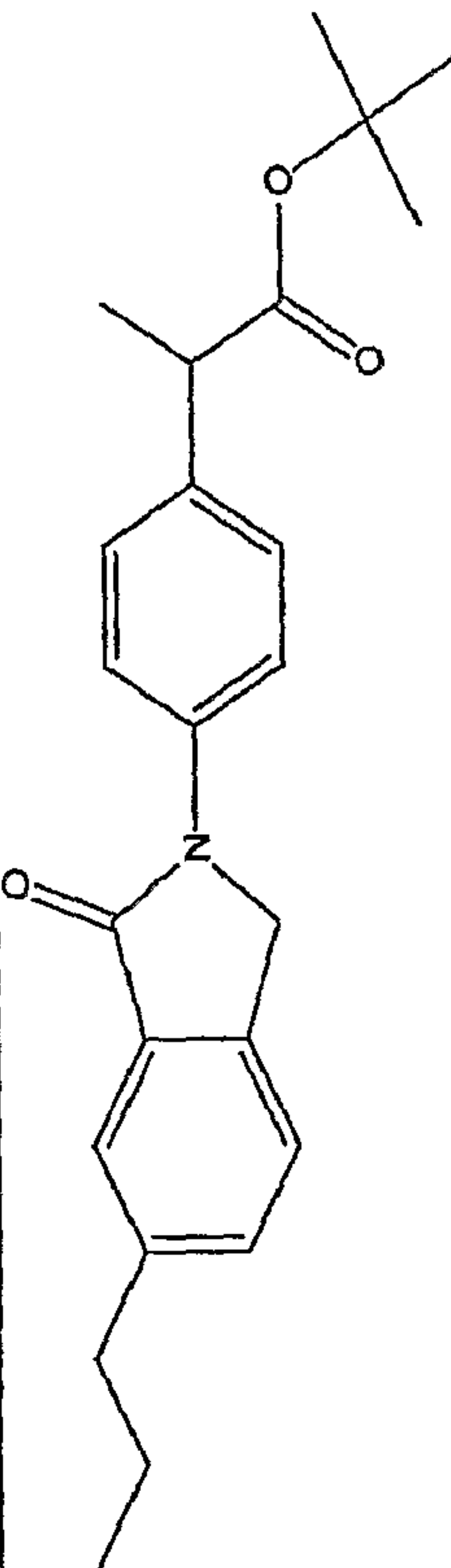
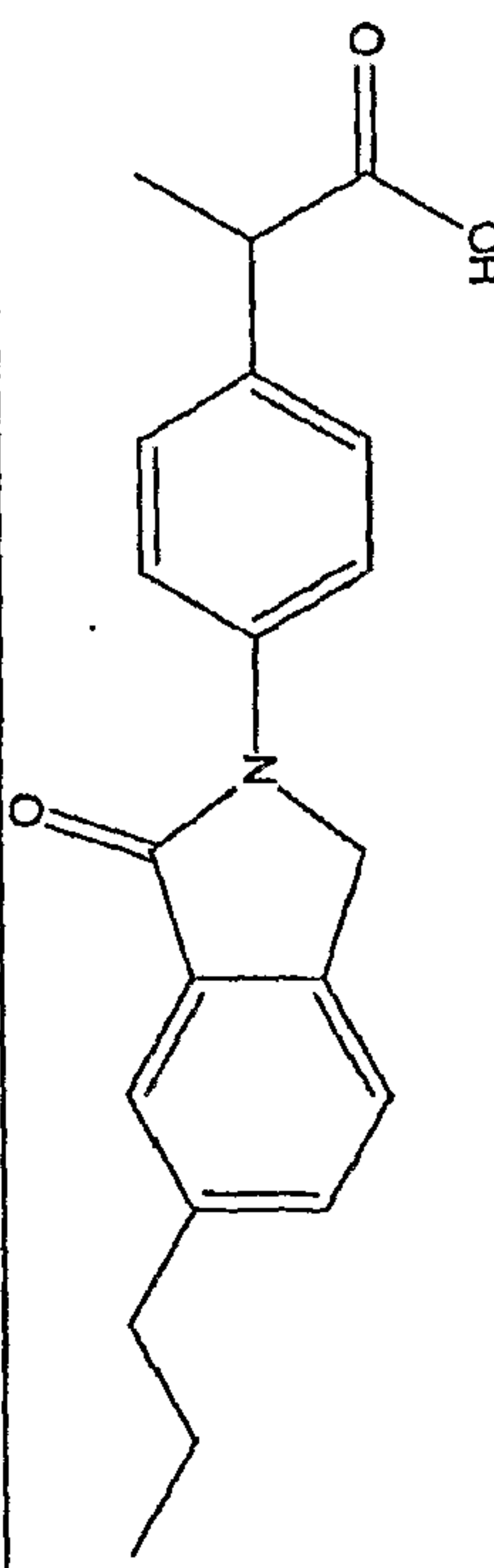
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
191				
		ALB- 113101	0.242	1.377
192				
		ALB- 113102	0.062	1.827

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
193		ALB- 113211	0.786	1.369
194		ALB- 113212	0.103	1.868

136

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
195		ALB- 113213	0.565	1.234
196		ALB- 113310	0.049	2.096

137

Table I

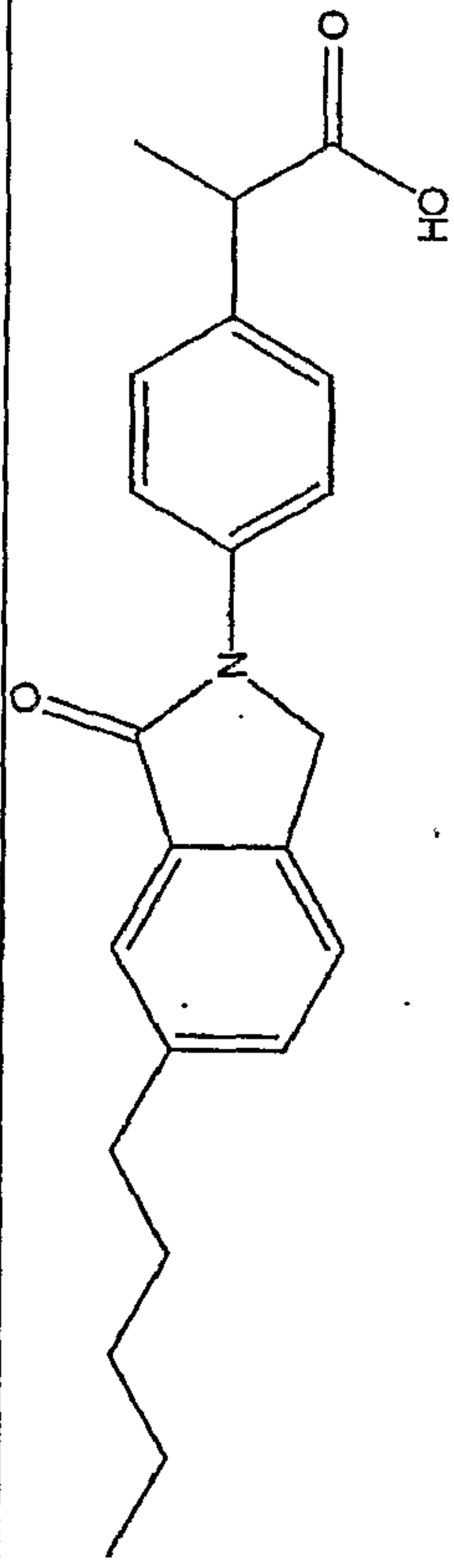
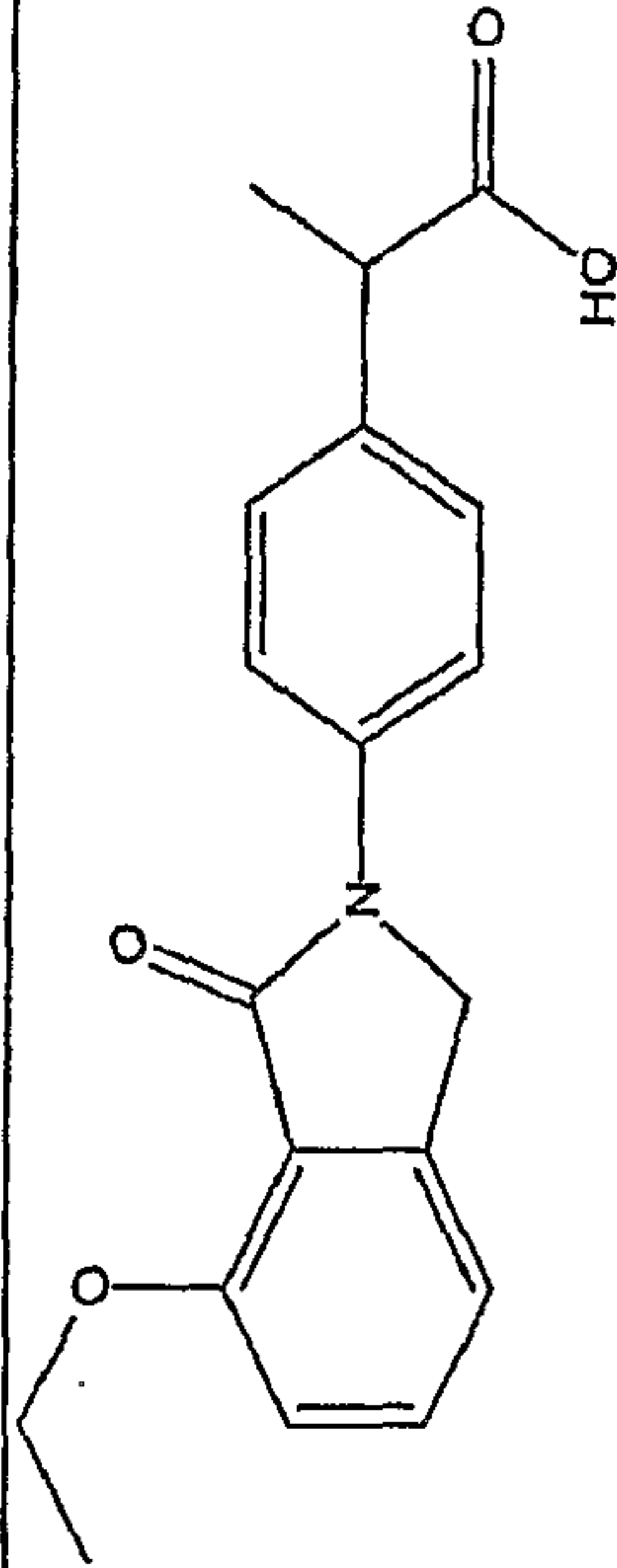
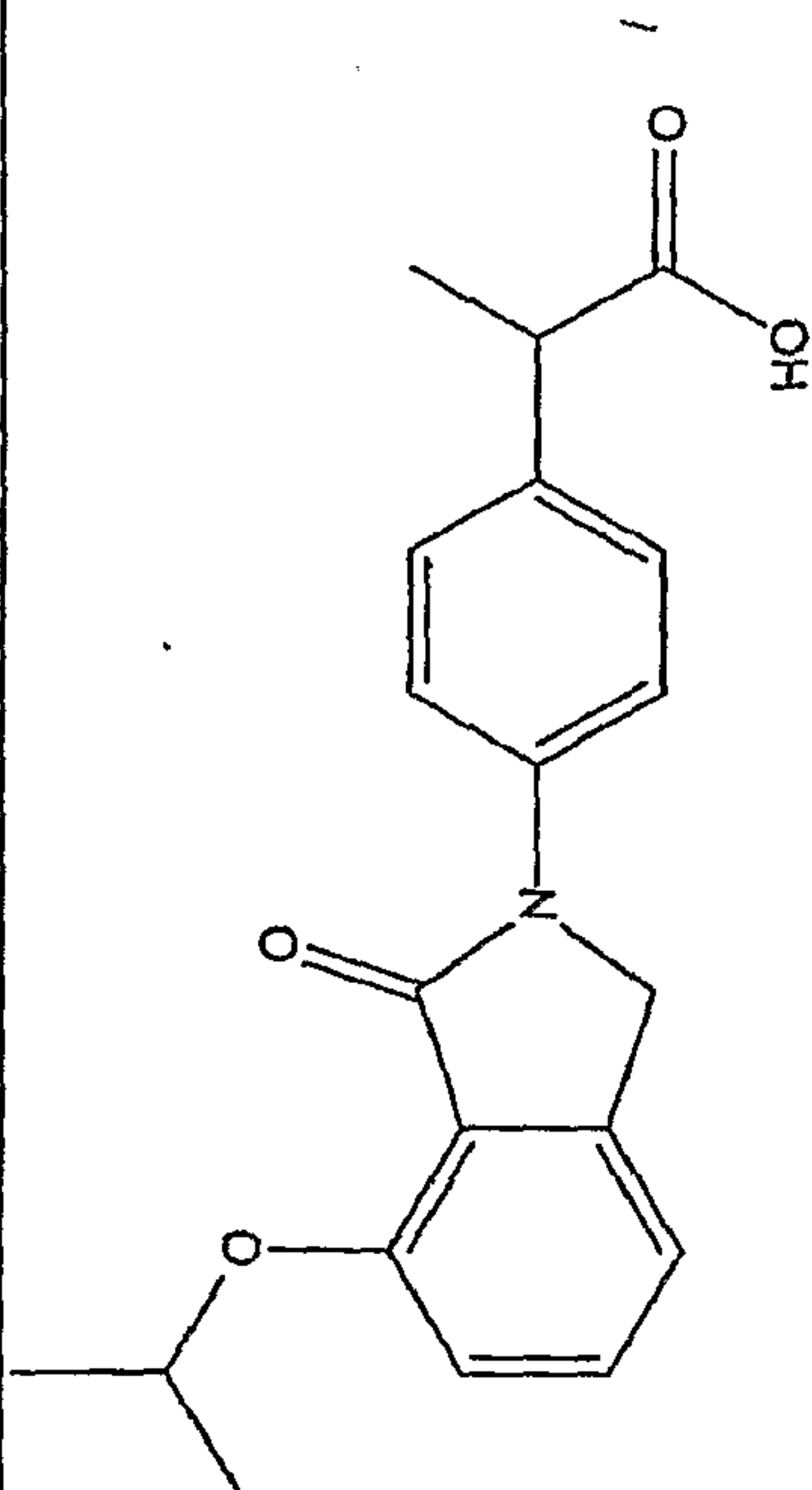
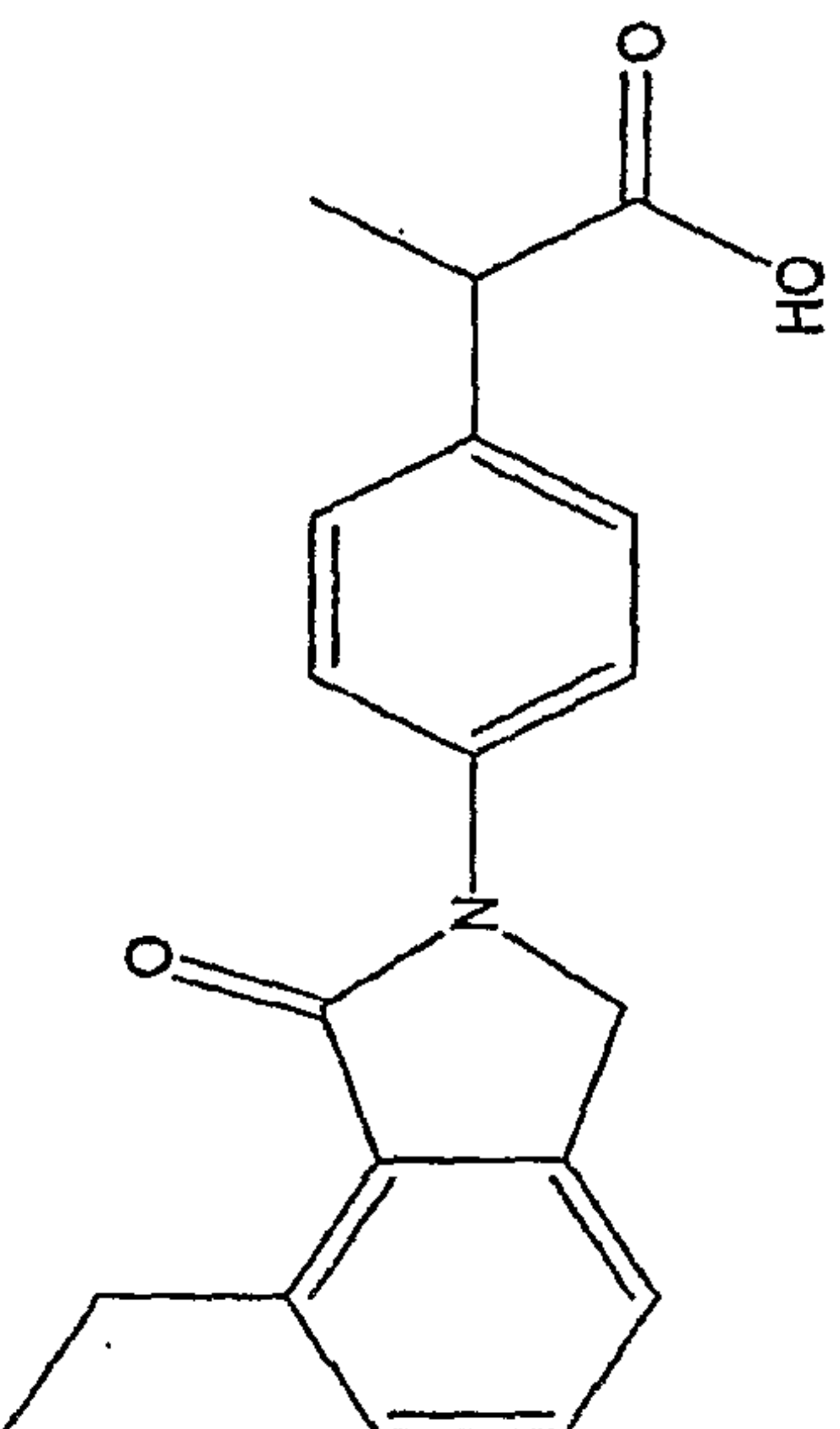
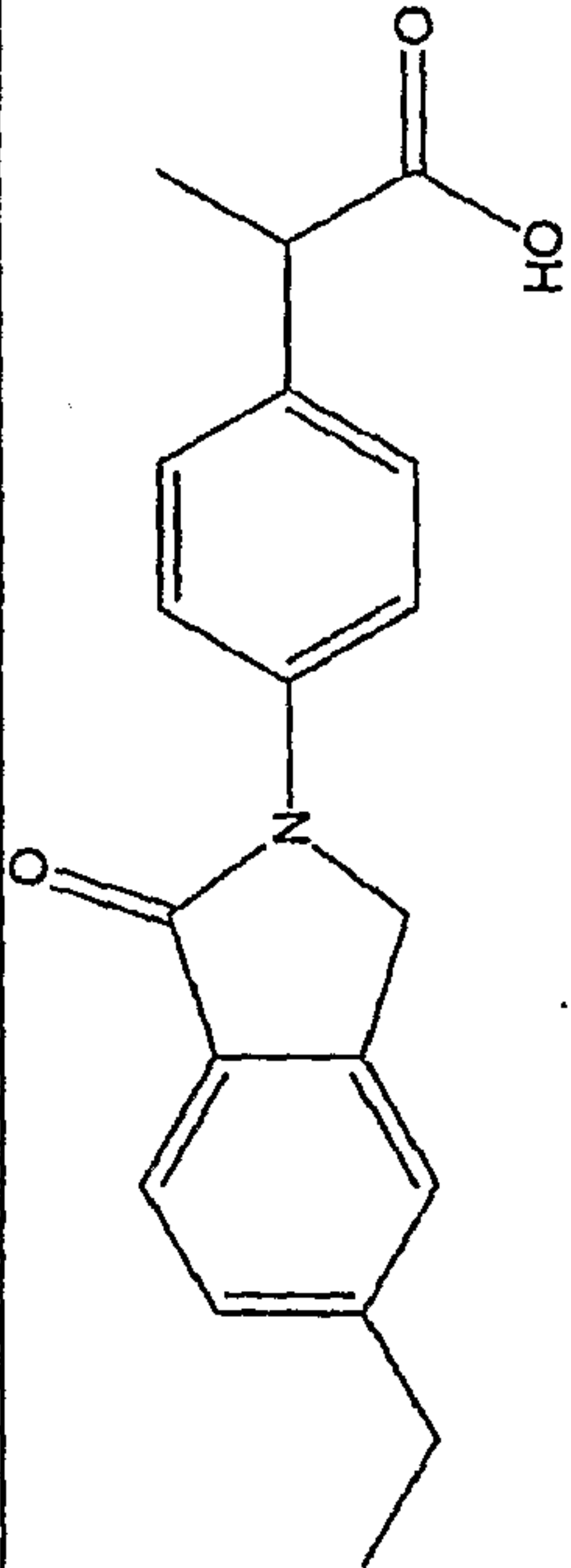
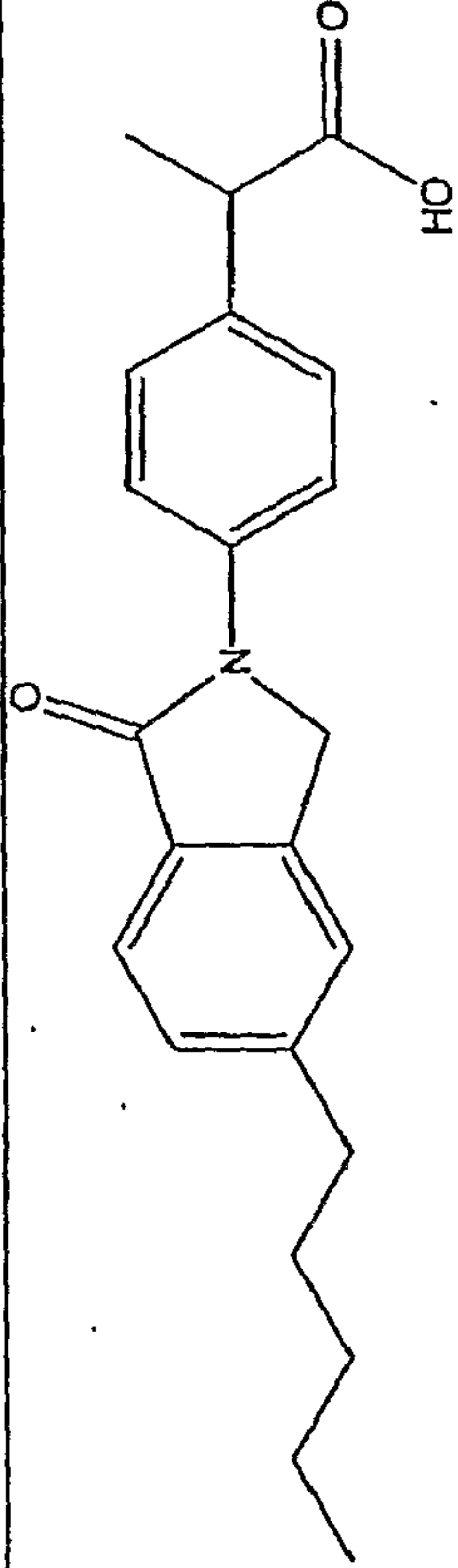
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
197		ALB- 113388	1.115	1.766
198		ALB- 113391	15.251	1.46

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
199		ALB-113392	4.861	1.647
200		ALB-113395	1.845	1.486

139

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
201		ALB- 113490	0.218	1.482
202		ALB- 113491		1.124

140

Table 1

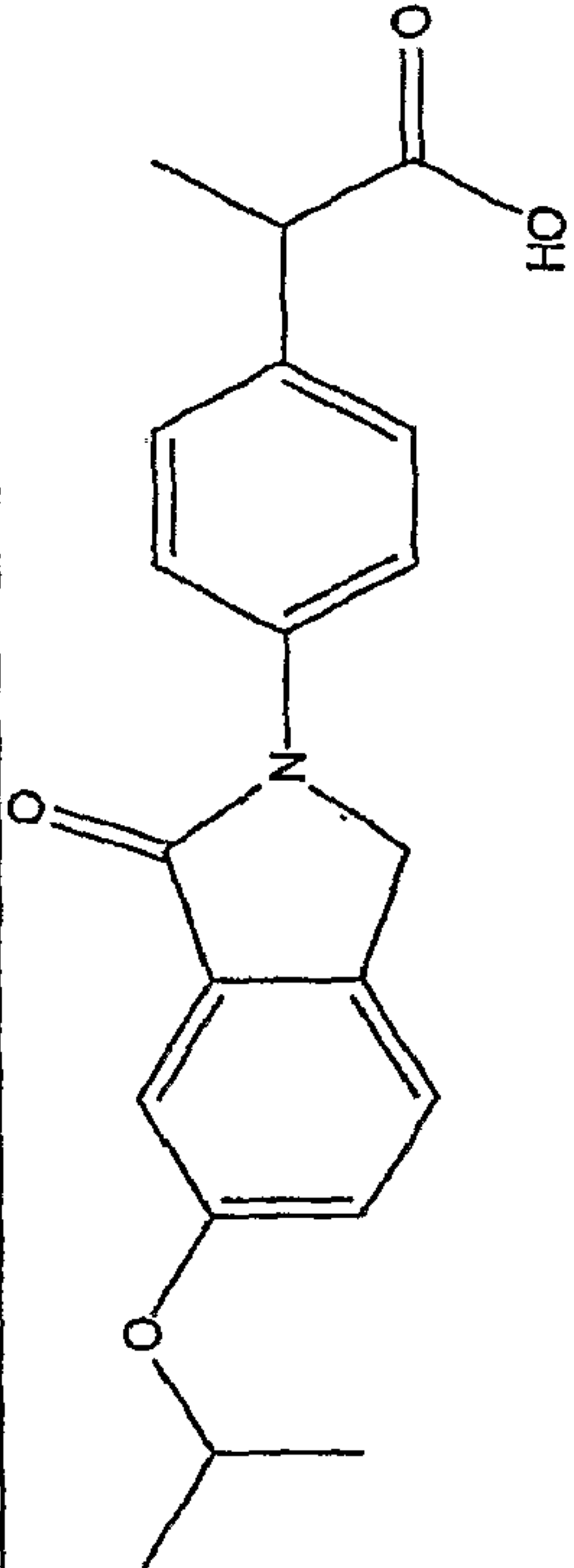
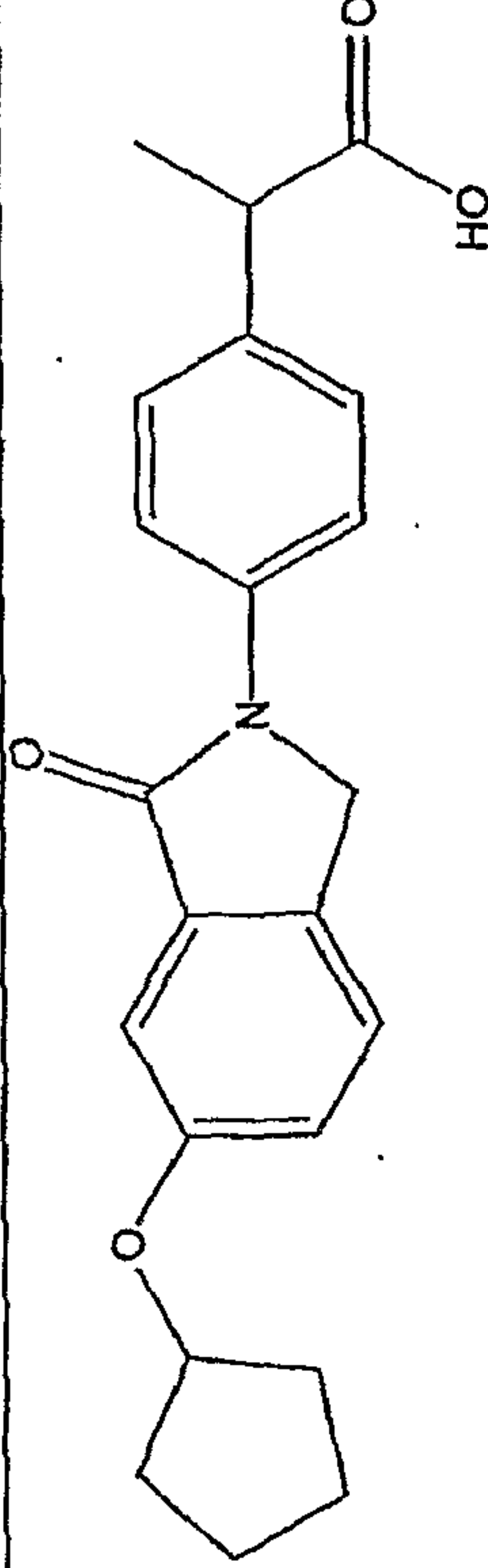
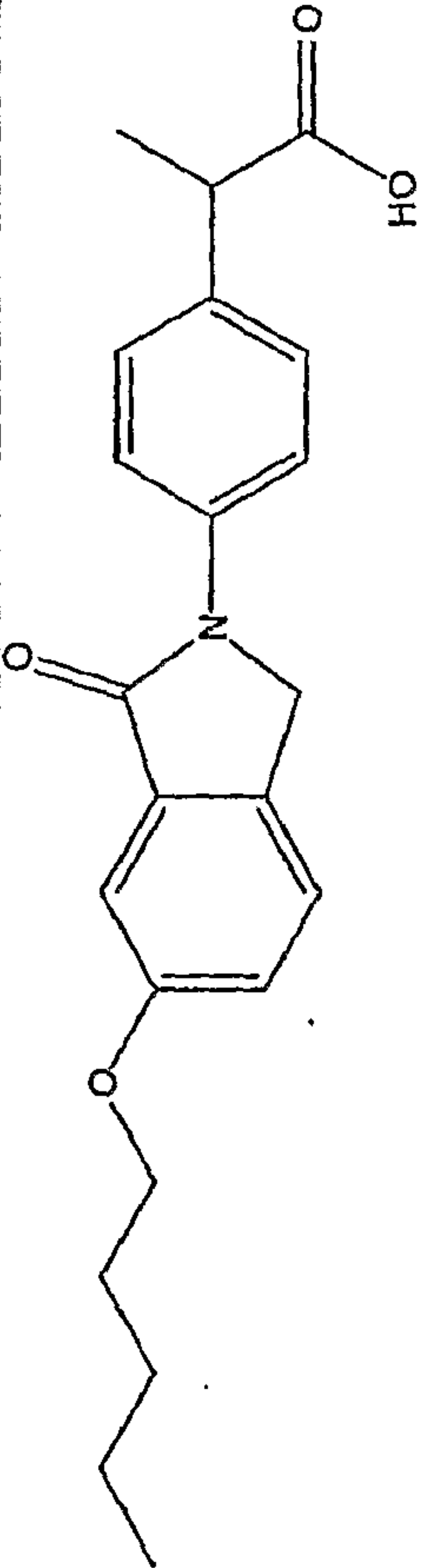
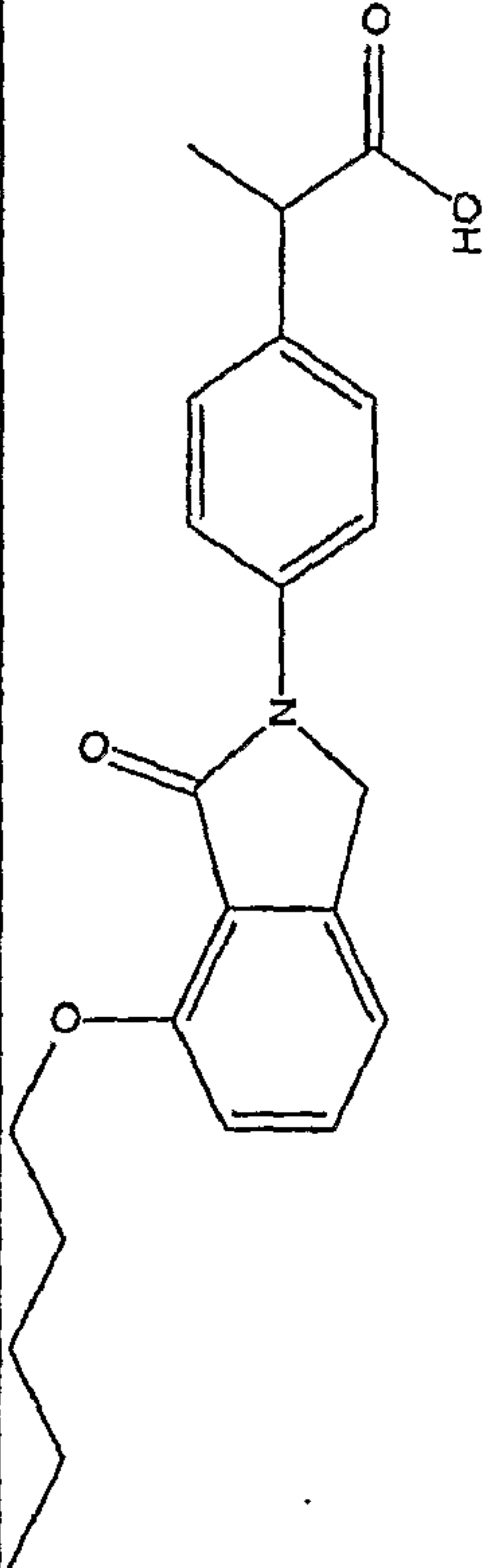
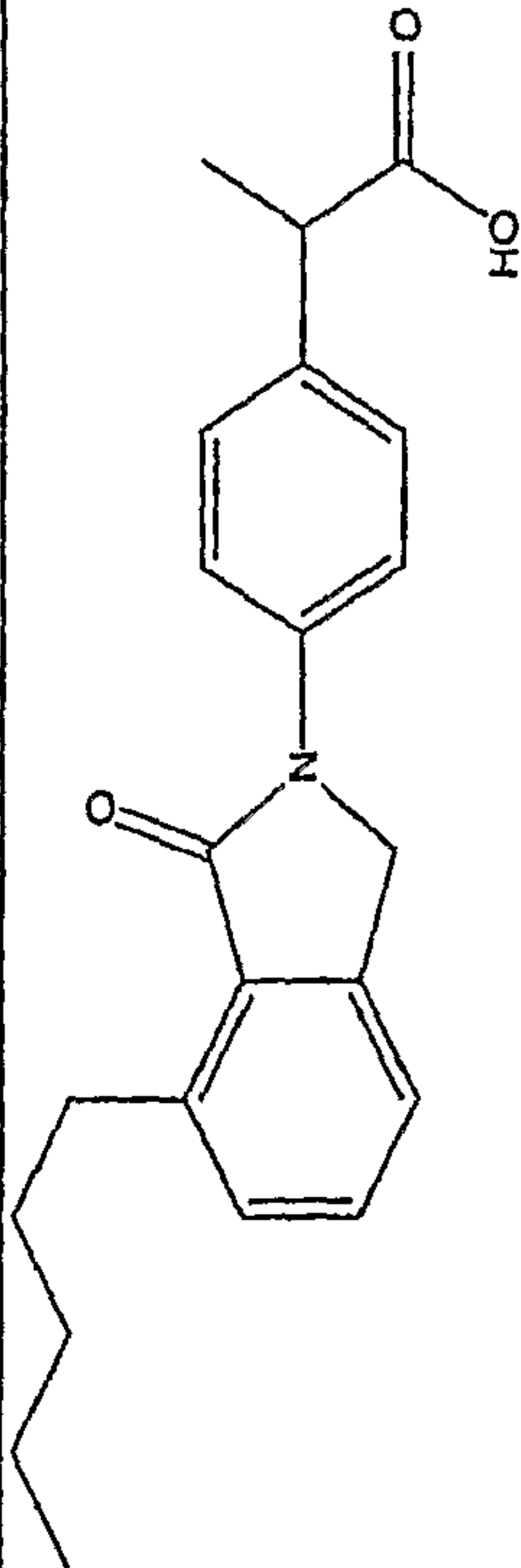
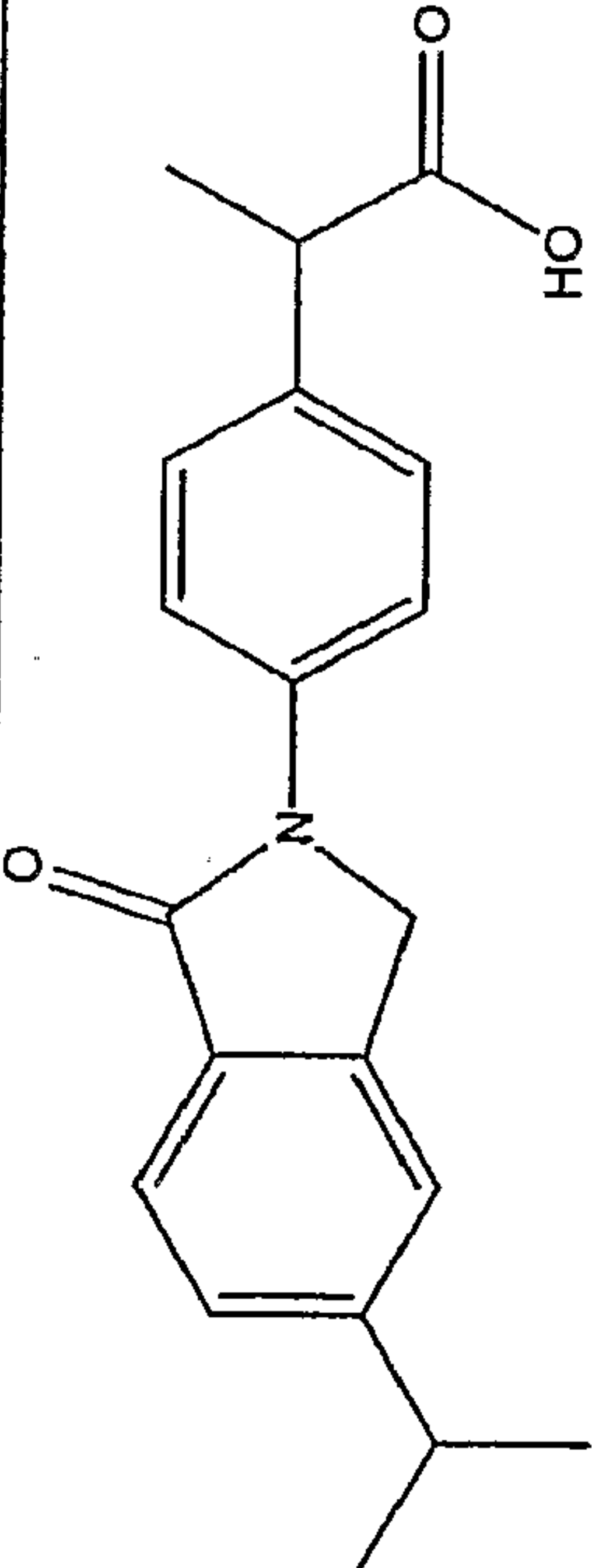
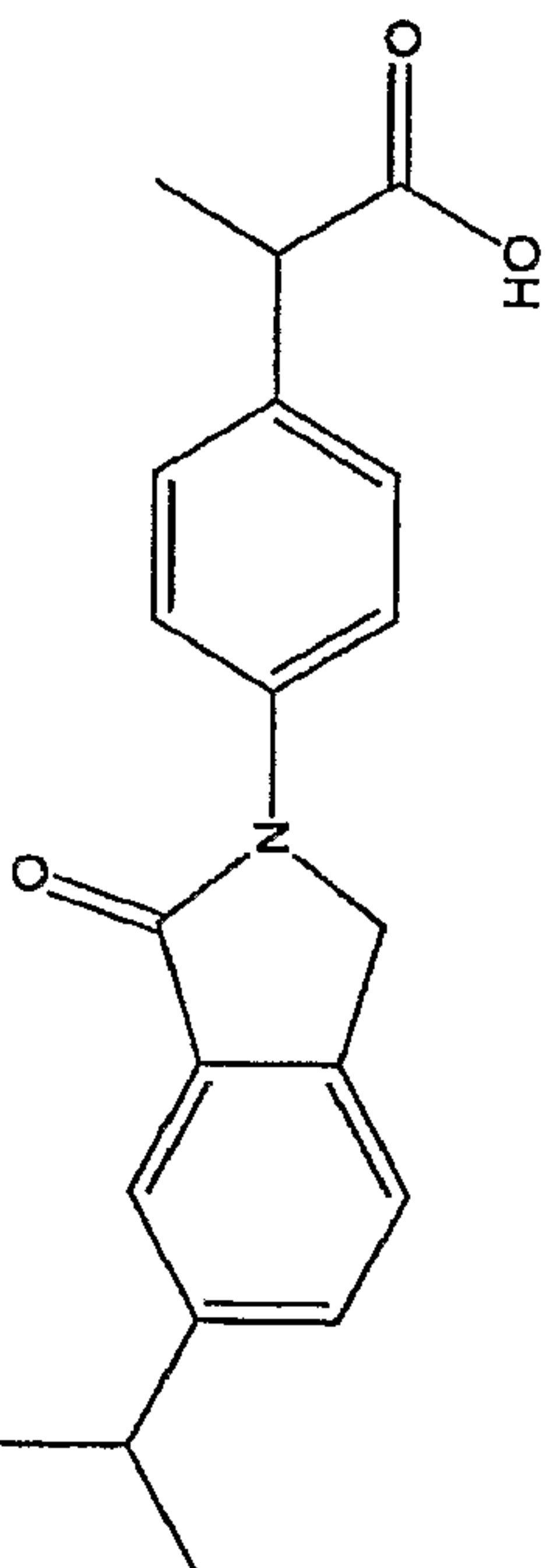
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			Avg EC50 (μ M)	Avg MaxFold Increase
203				
		ALB- 113492	0.024	1.669
204				
		ALB- 113493	0.081	1.885

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
205		ALB- 113494	1.169	1.749
206		ALB- 113495	18.292	1.348
207		ALB- 113497		1.178

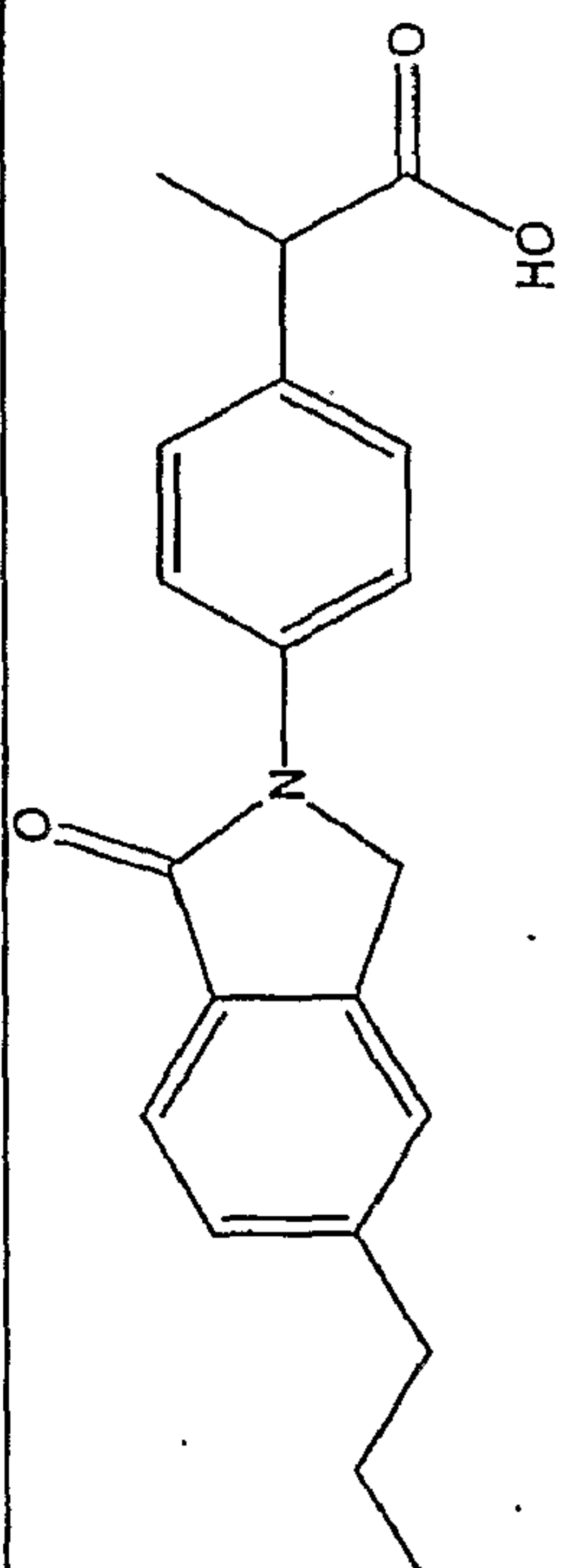
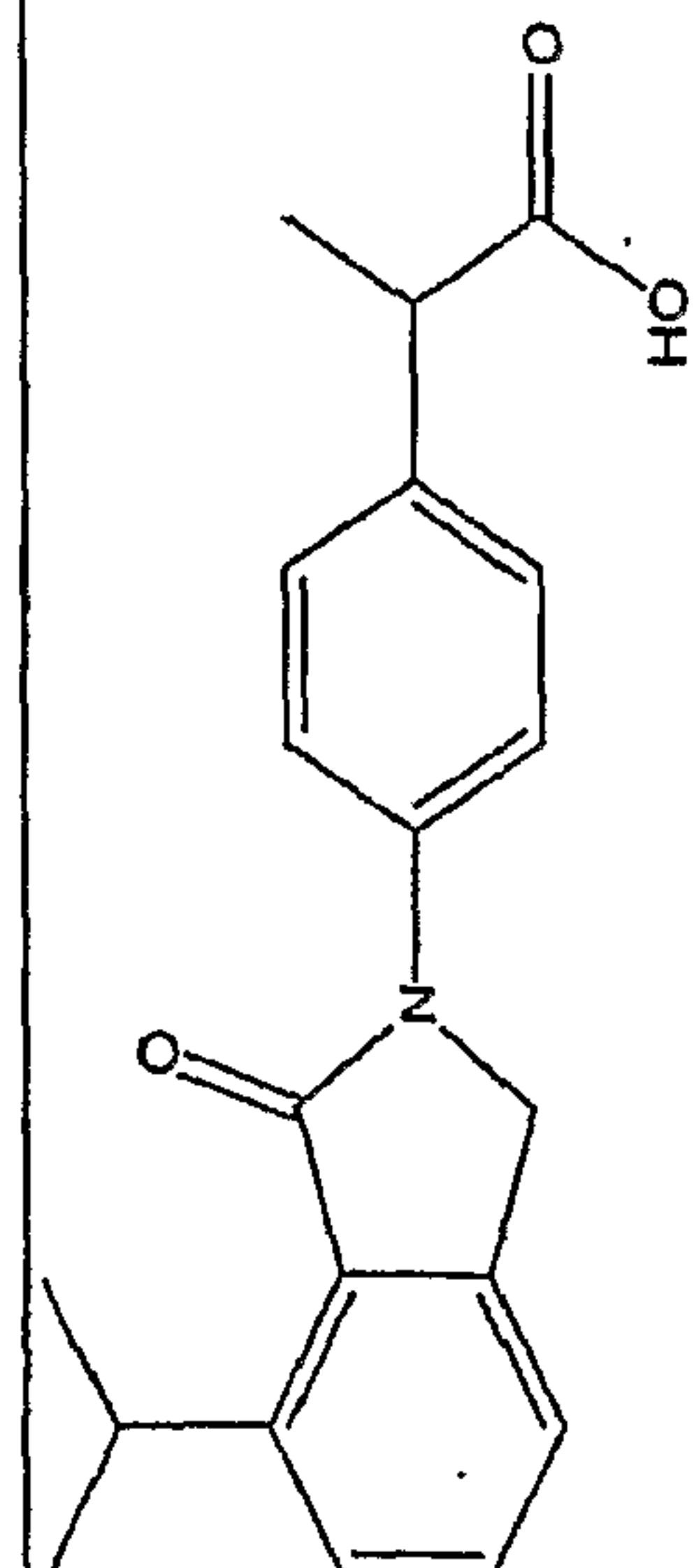
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
208		ALB- 113561		1.205
209		ALB- 113563	0.055	1.796

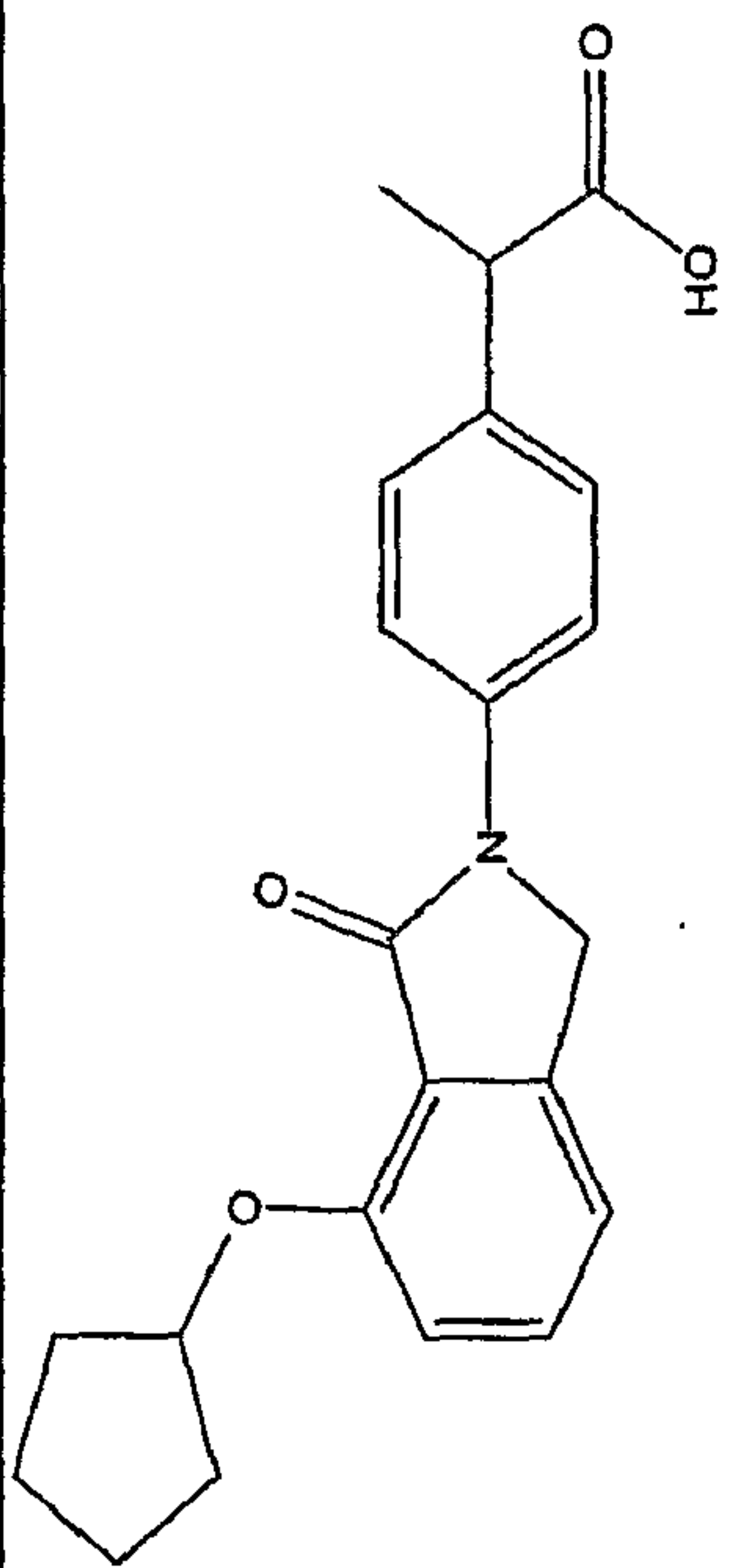
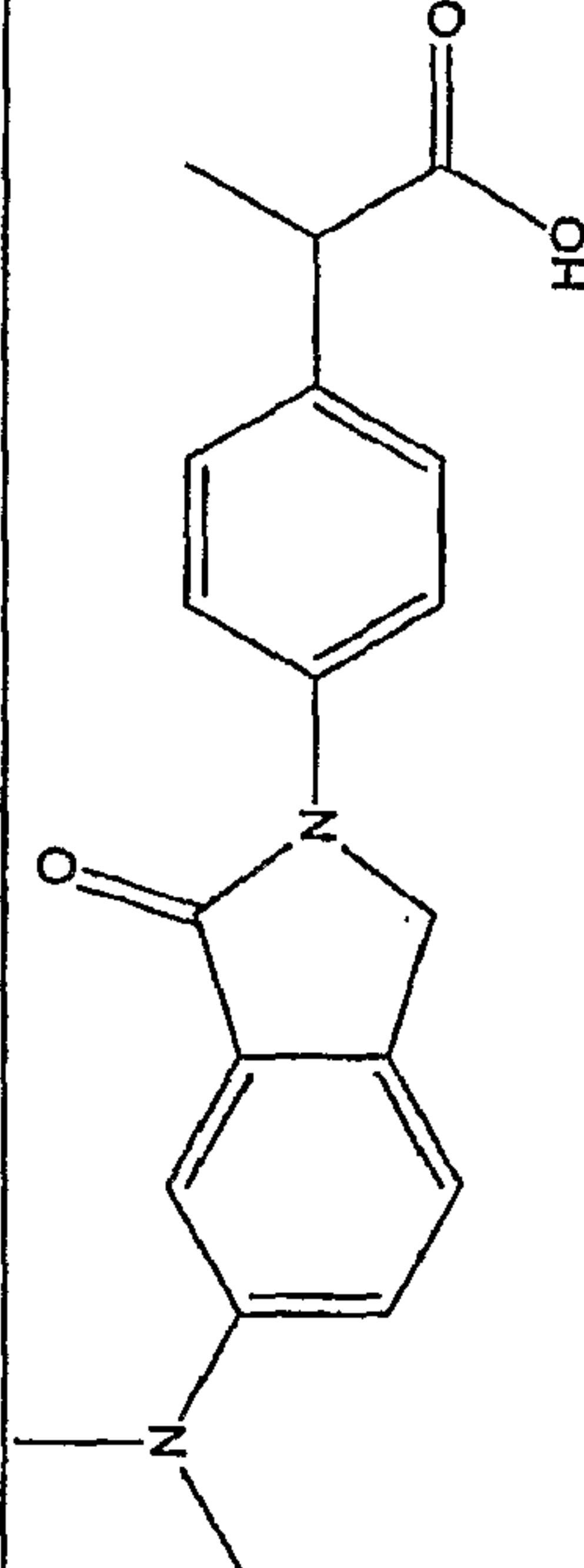
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
210		ALB- 113564		1.055
211		ALB- 113565		1.185

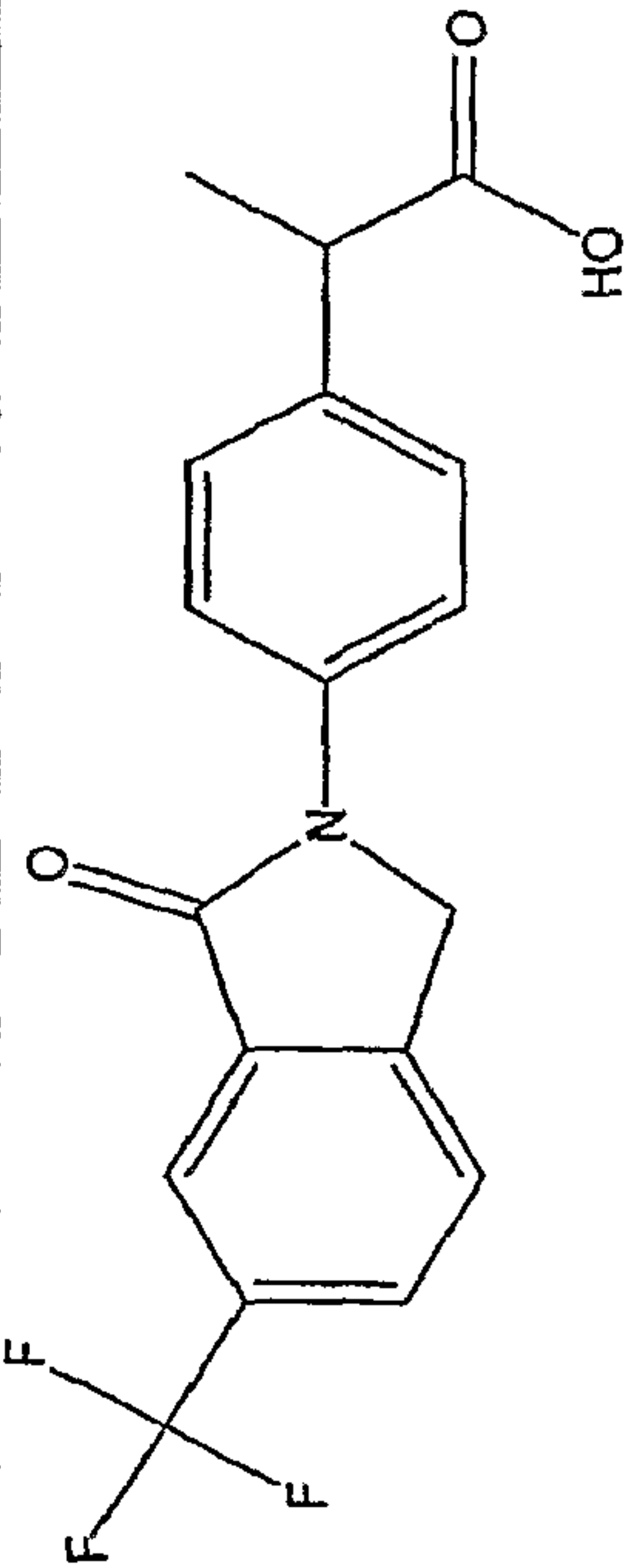
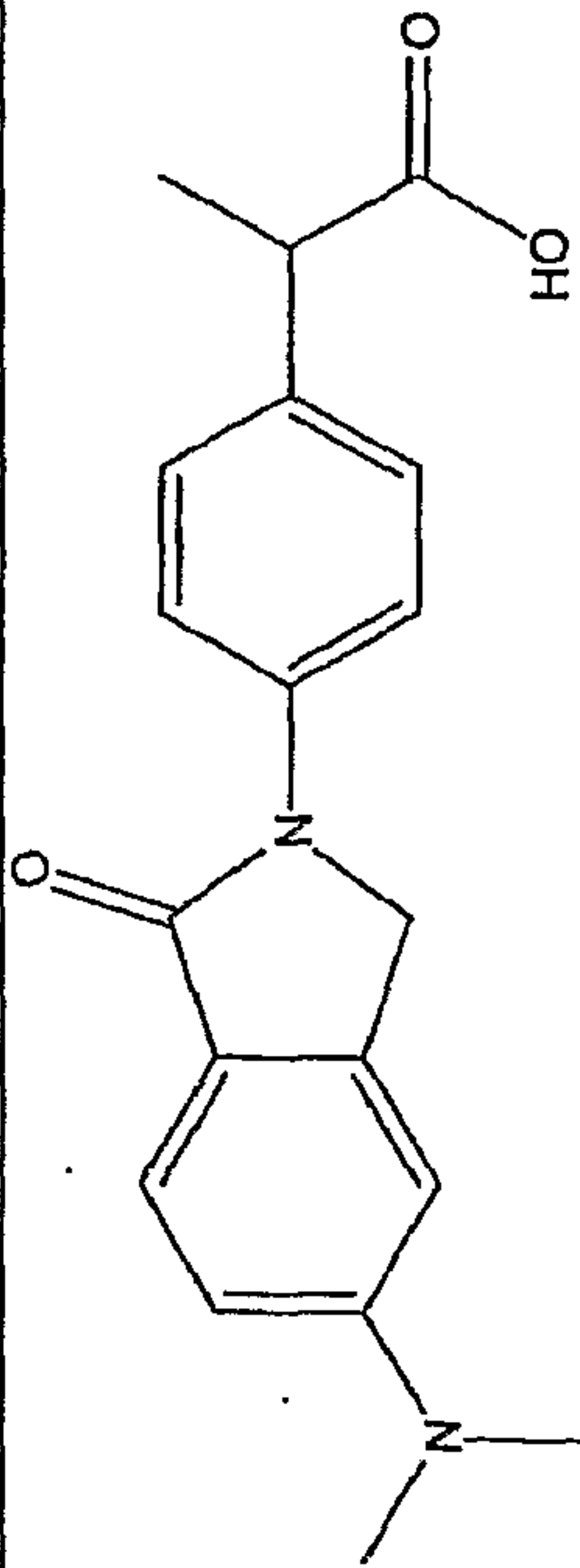
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
212		ALB- 113566	5.154	1.958
213		ALB- 113648	0.028	1.604

145

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
214		ALB- 113652	1.494	1.656
215		ALB- 113646		1.051

146

Table 1

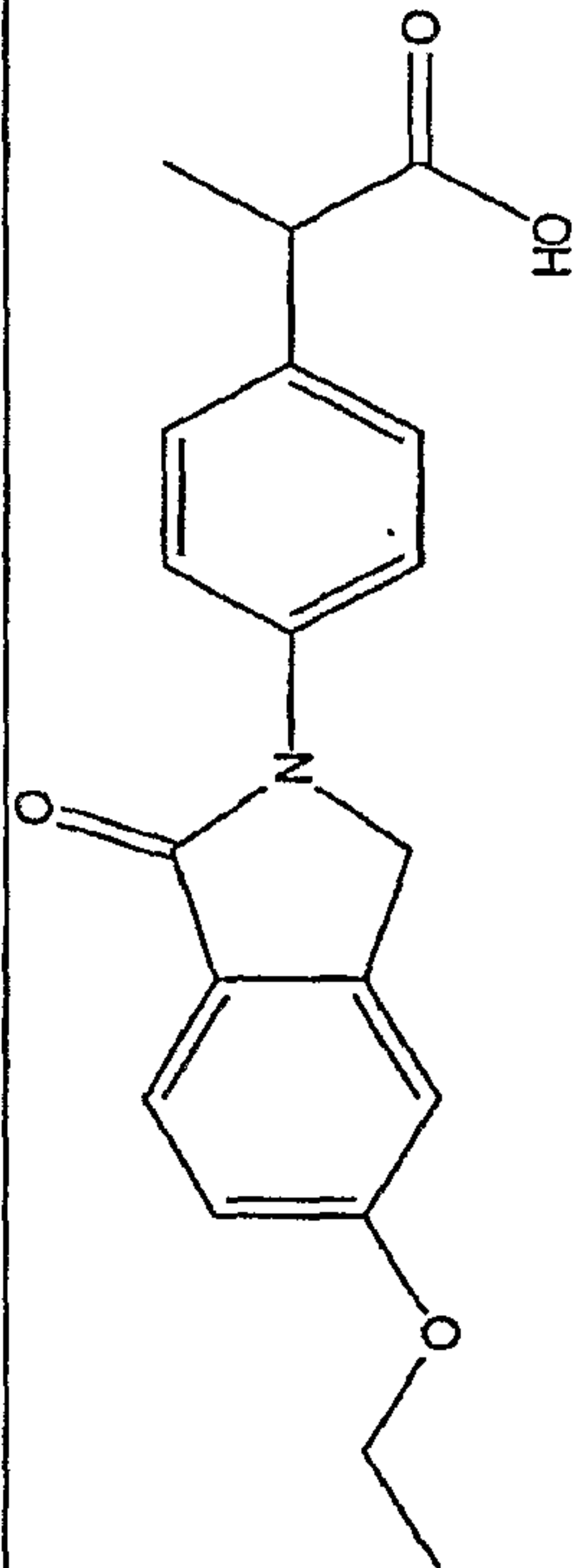
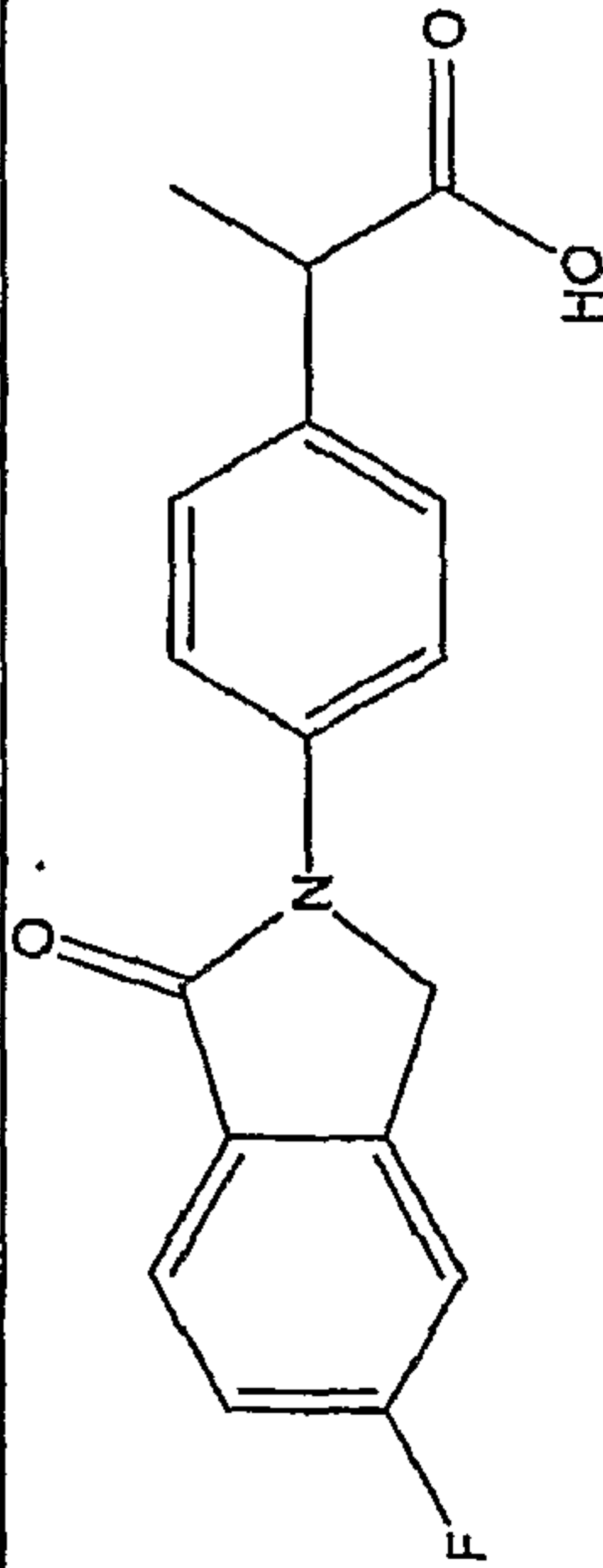
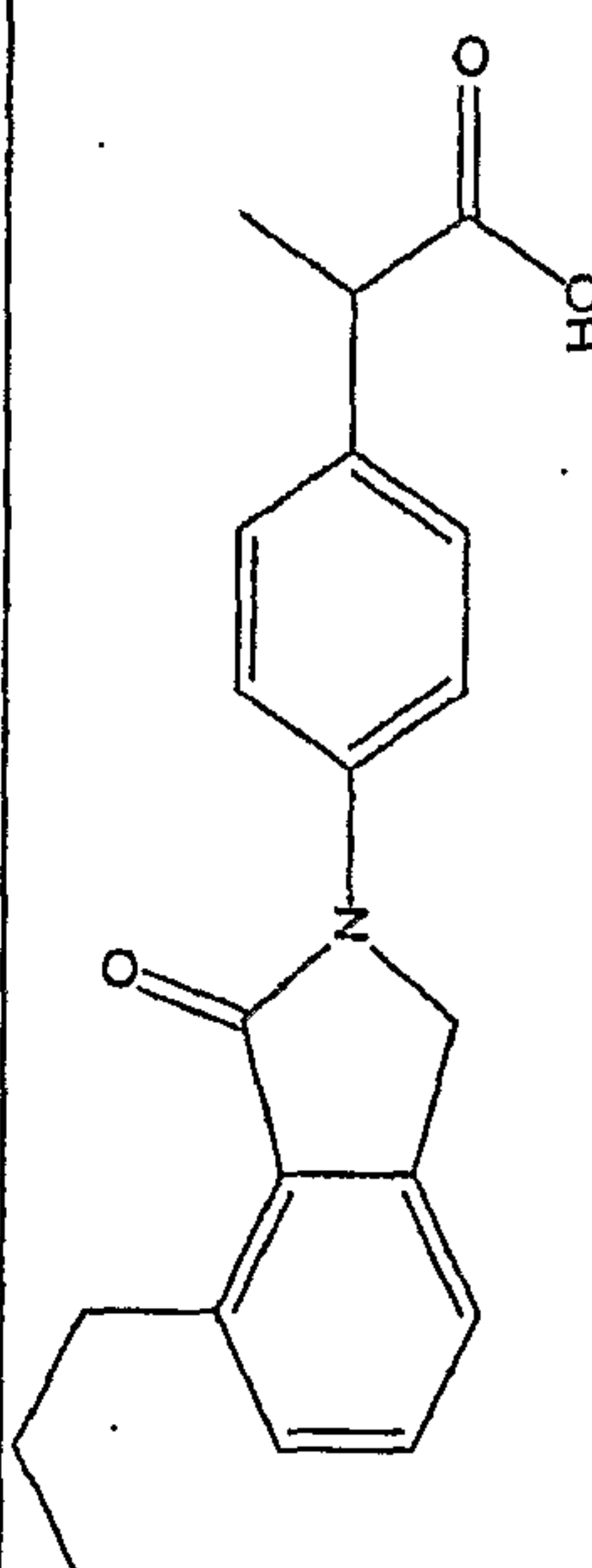
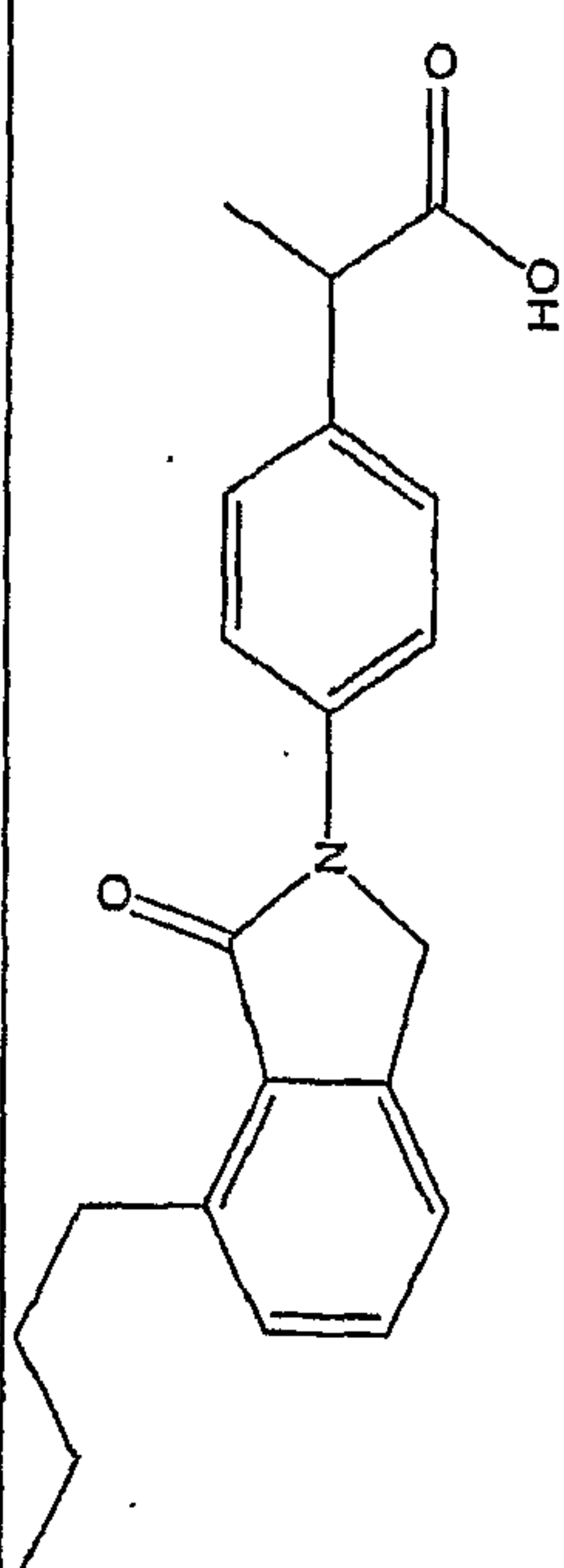
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
216		ALB- 113649		1.132
217		ALB- 113754	0.142	1.701

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
218		ALB- 113756	15.733	1.331
219		ALB- 113757		1.182

148

Table 1

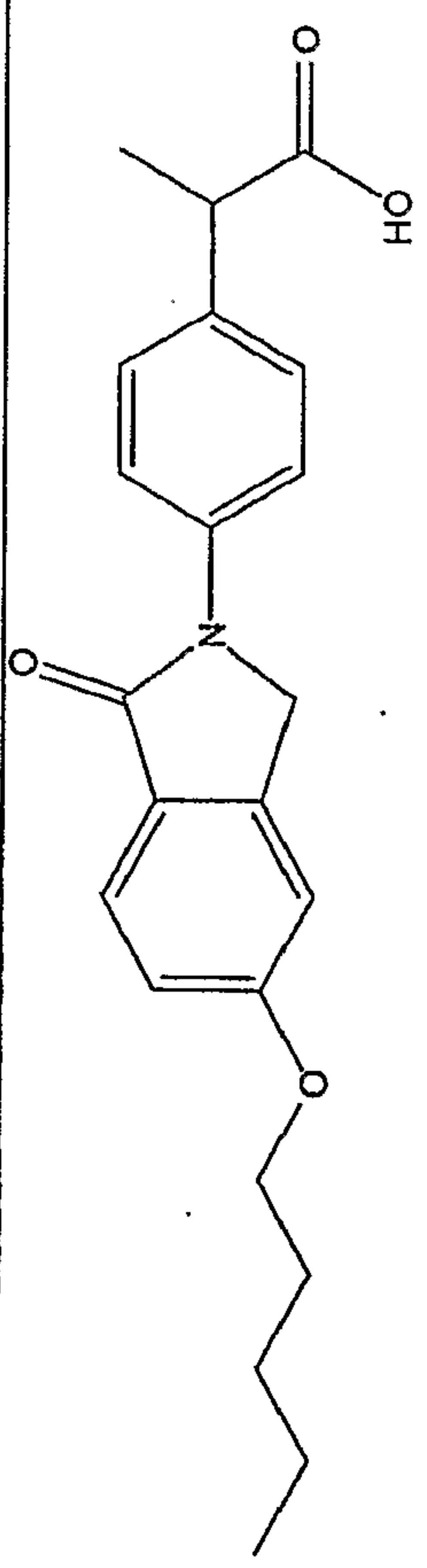
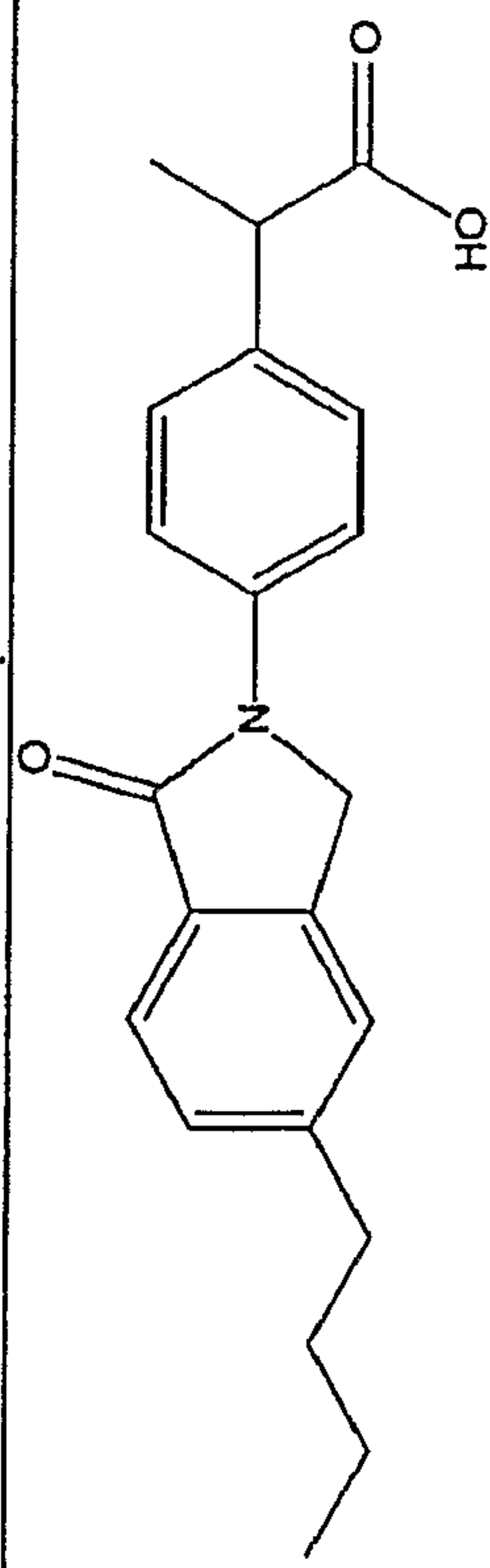
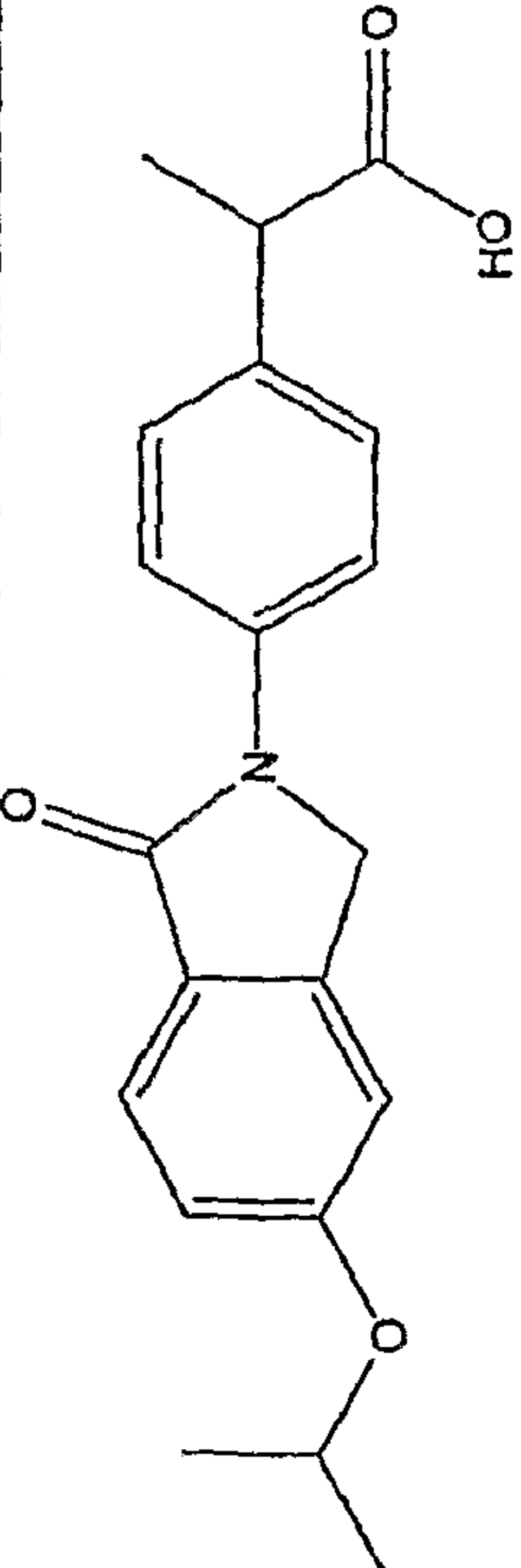
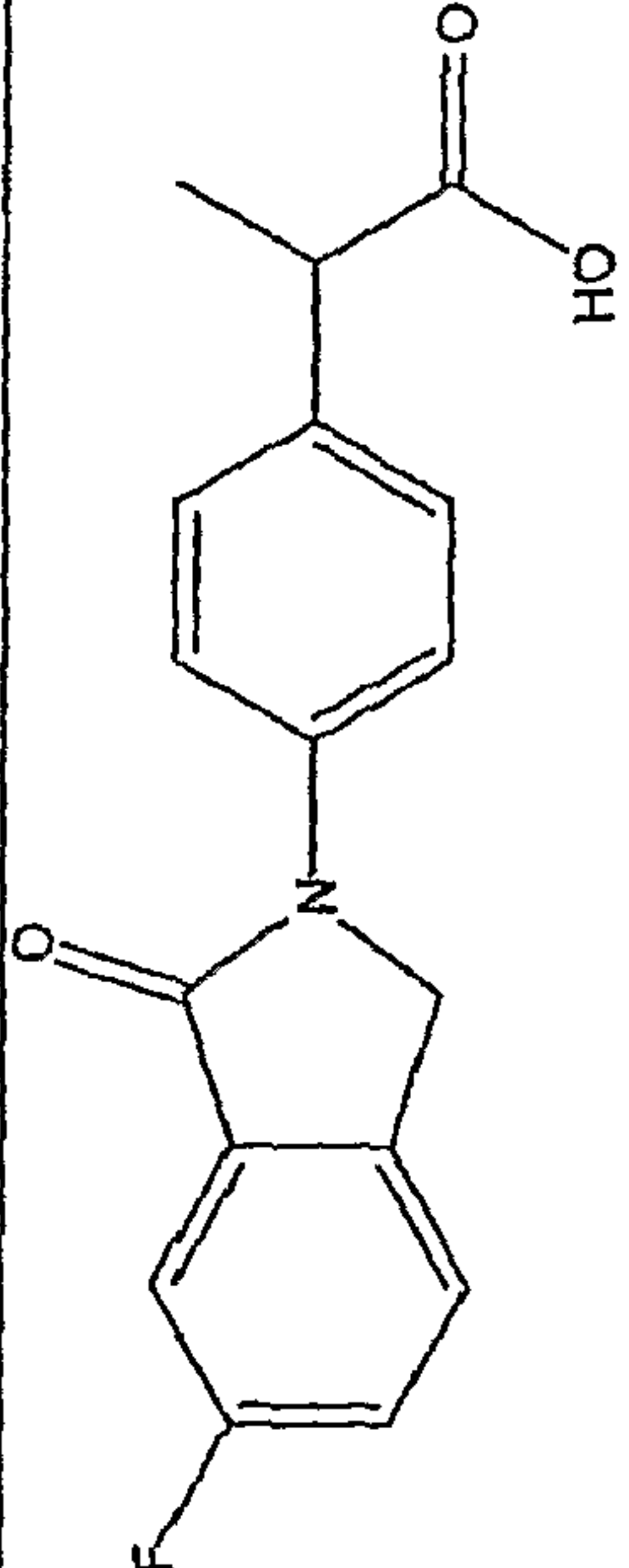
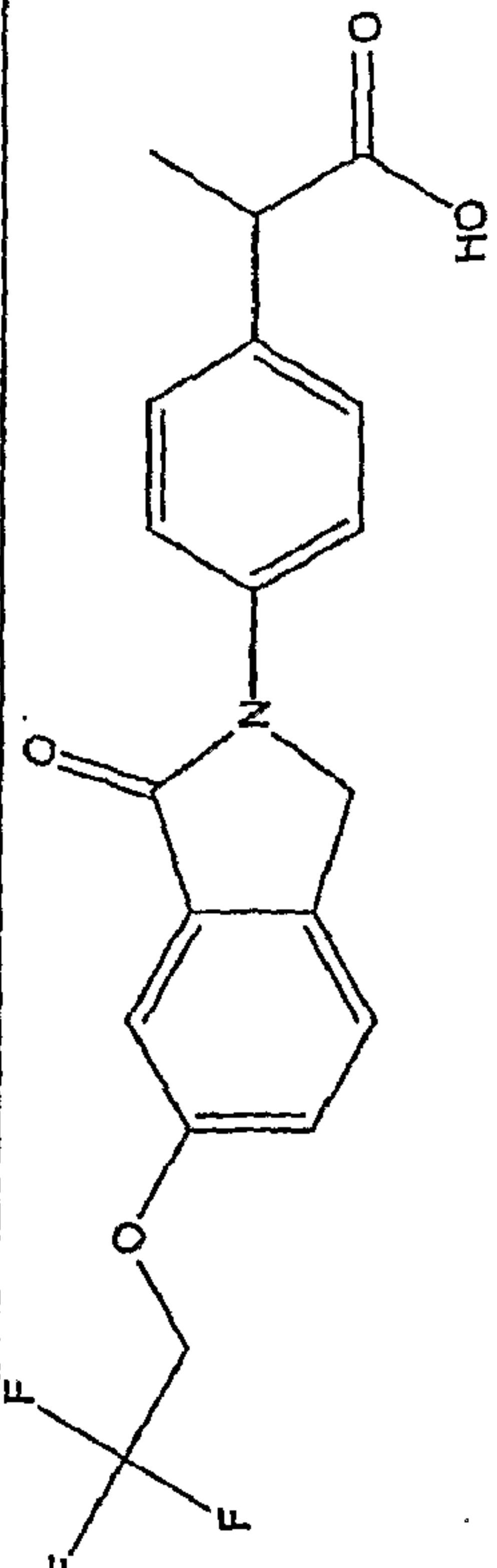
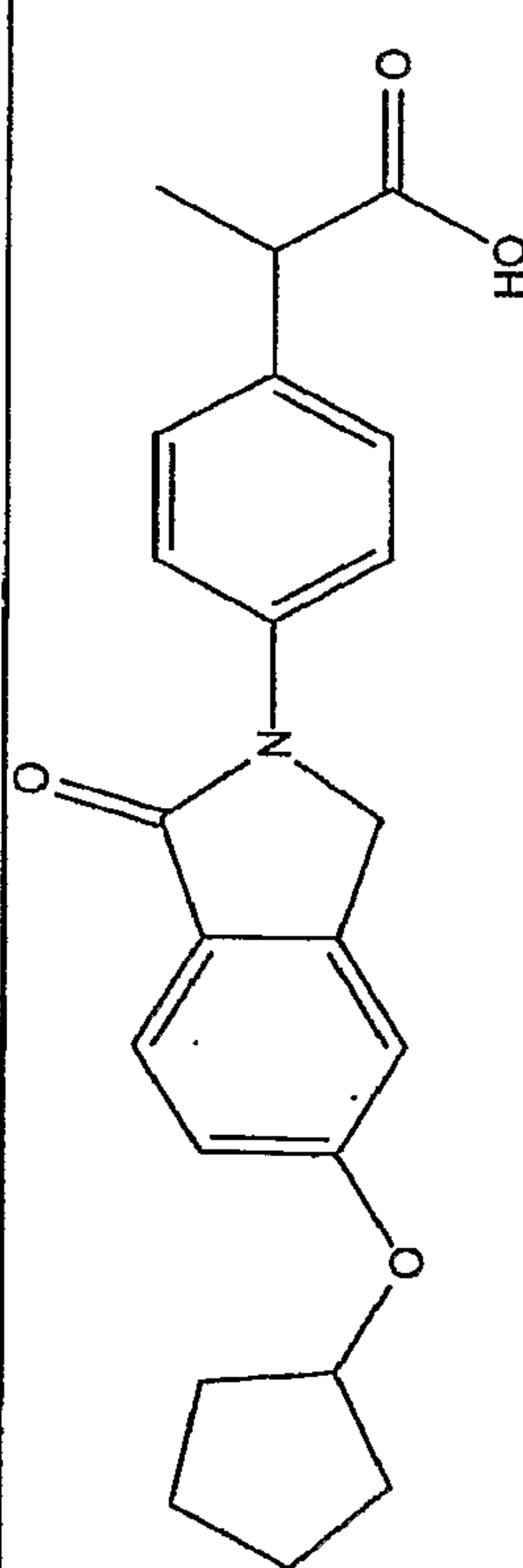
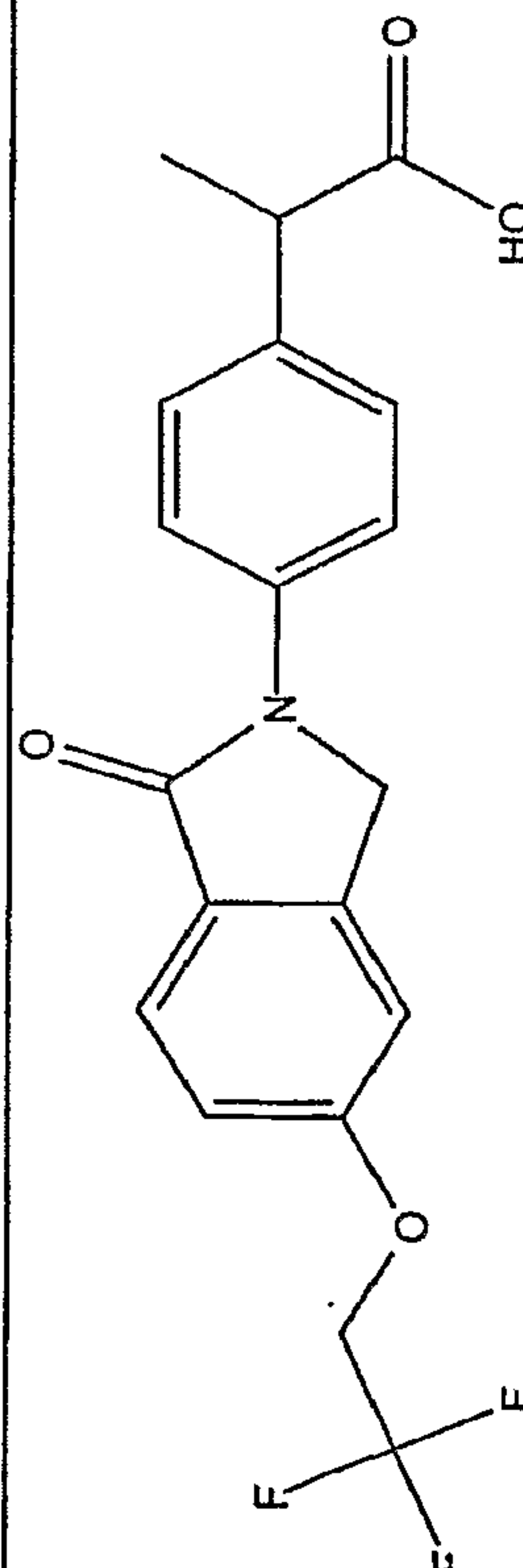
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
220		ALB- 113759	0.51	1.22
221		ALB- 113835		1.149

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
222		ALB- 113834		1.098
223		ALB- 113836	0.544	1.78
224		ALB- 113966	0.663	1.778

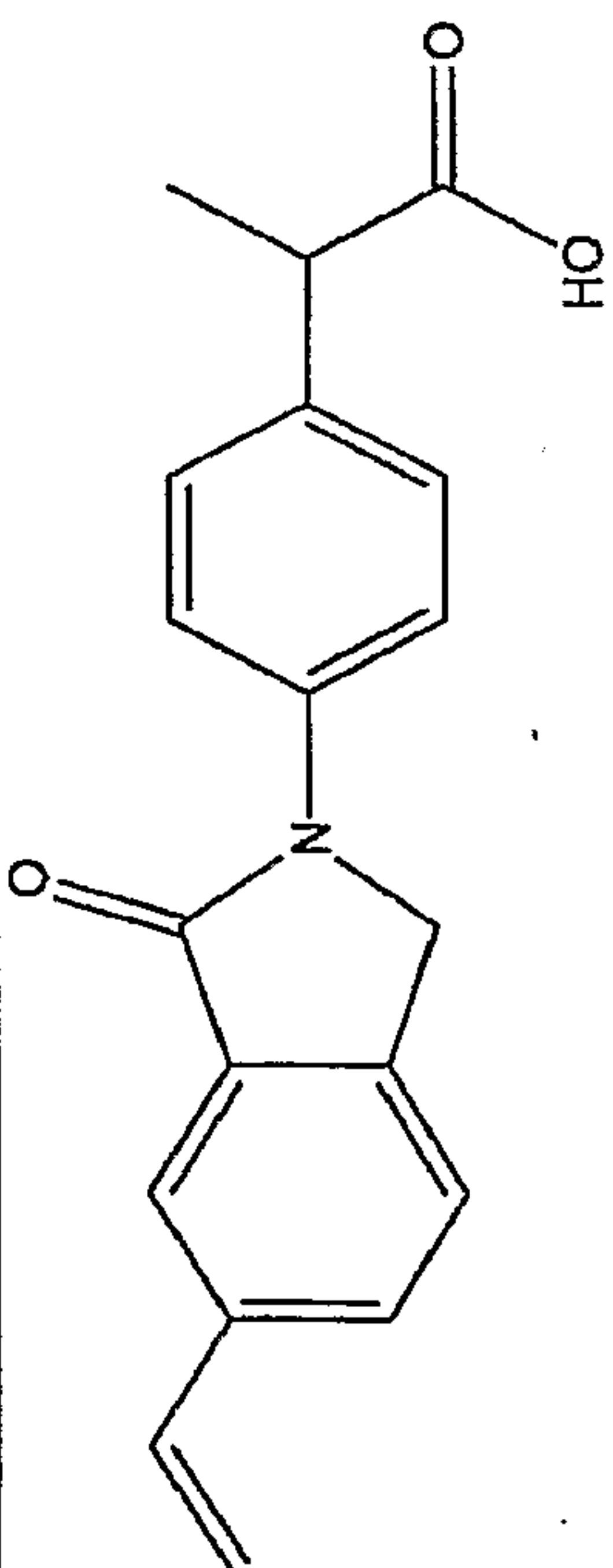
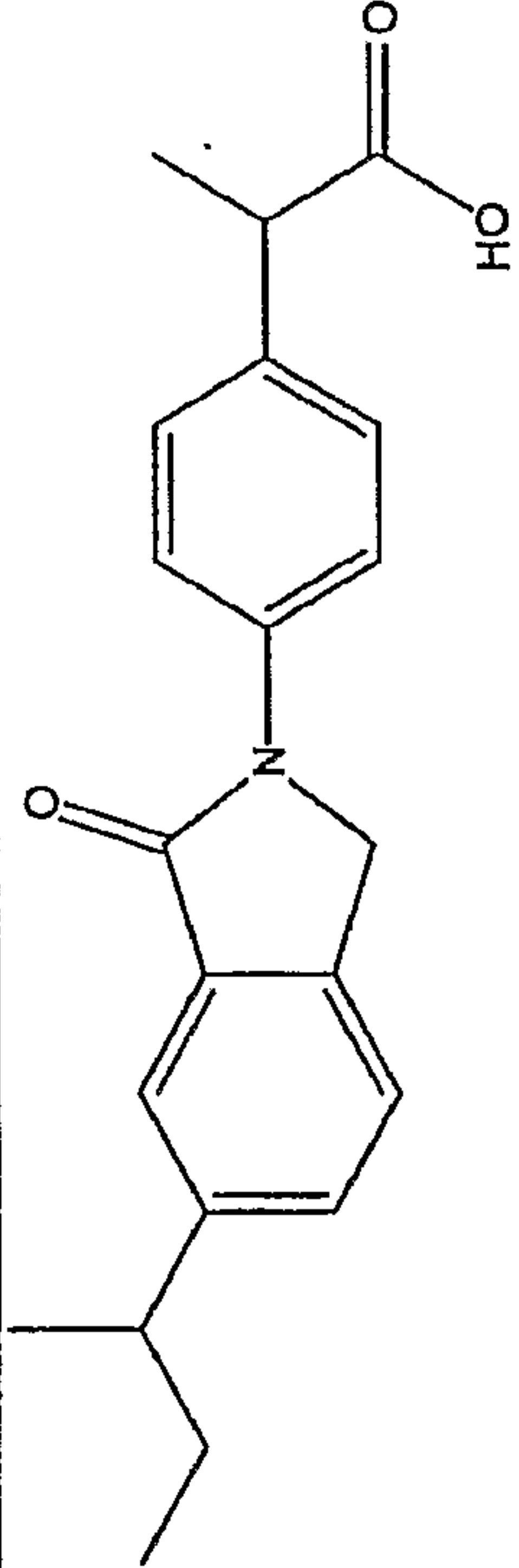
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
225		ALB- 113963		1.141
226		ALB- 113964		1.08

151

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
227		ALB- 113965	0.079	1.828
228		ALB- 114088	0.078	2.191

152

Table 1

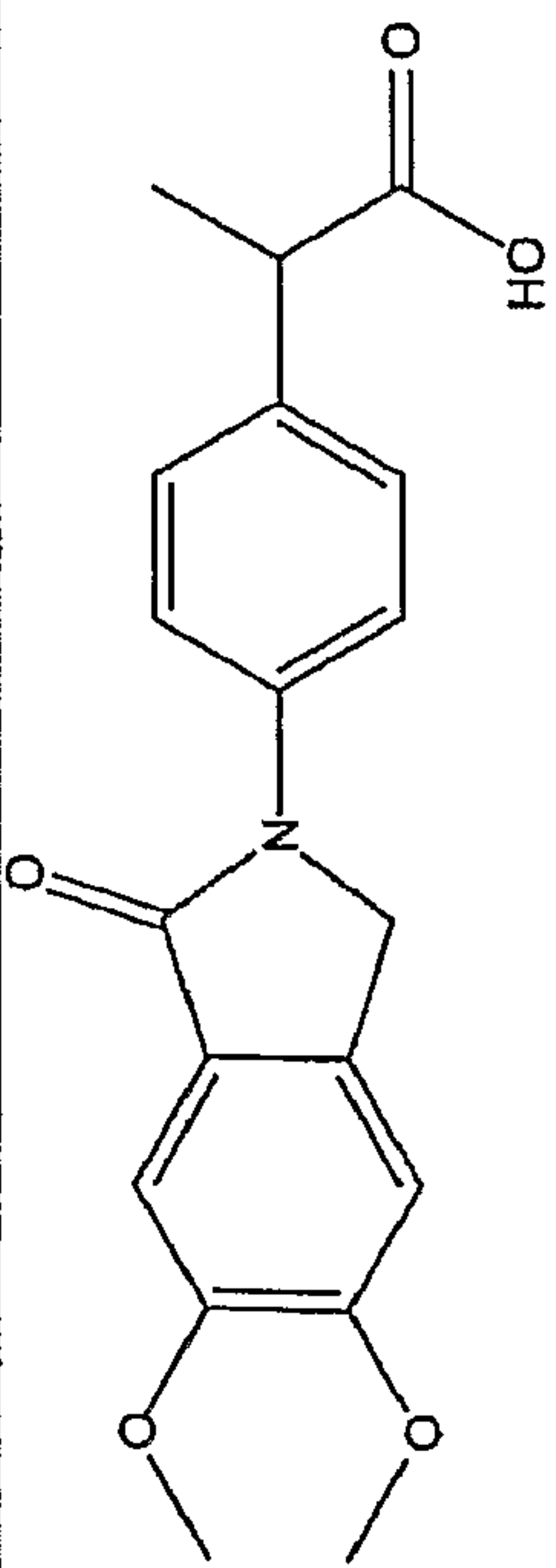
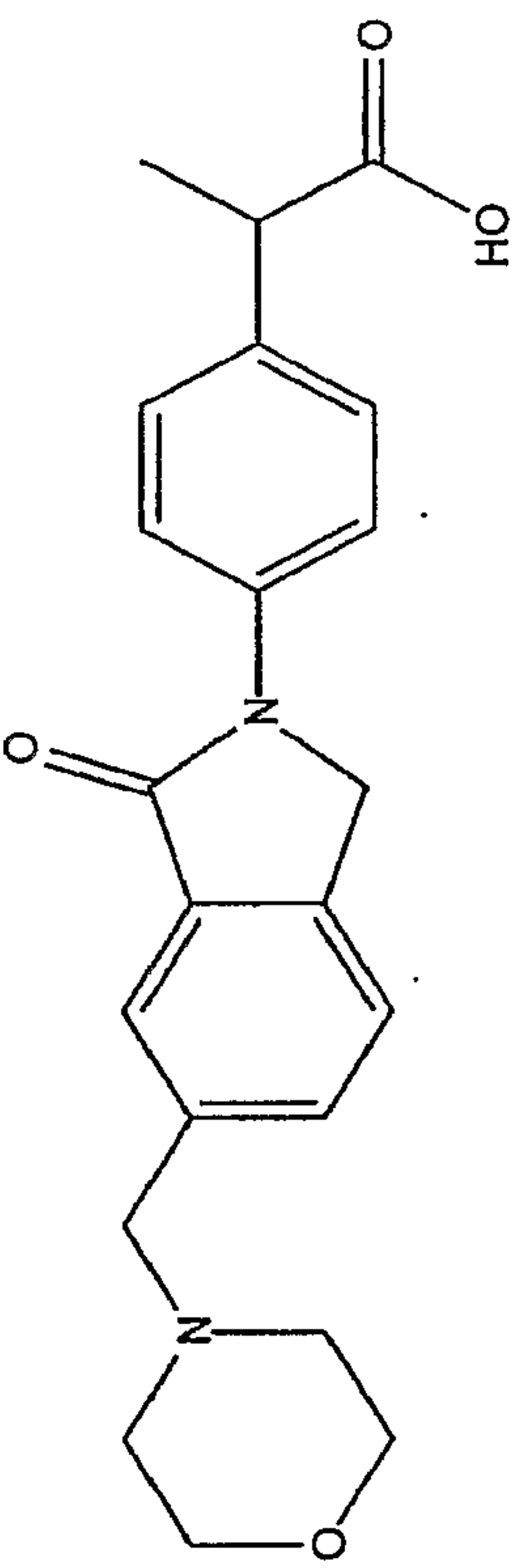
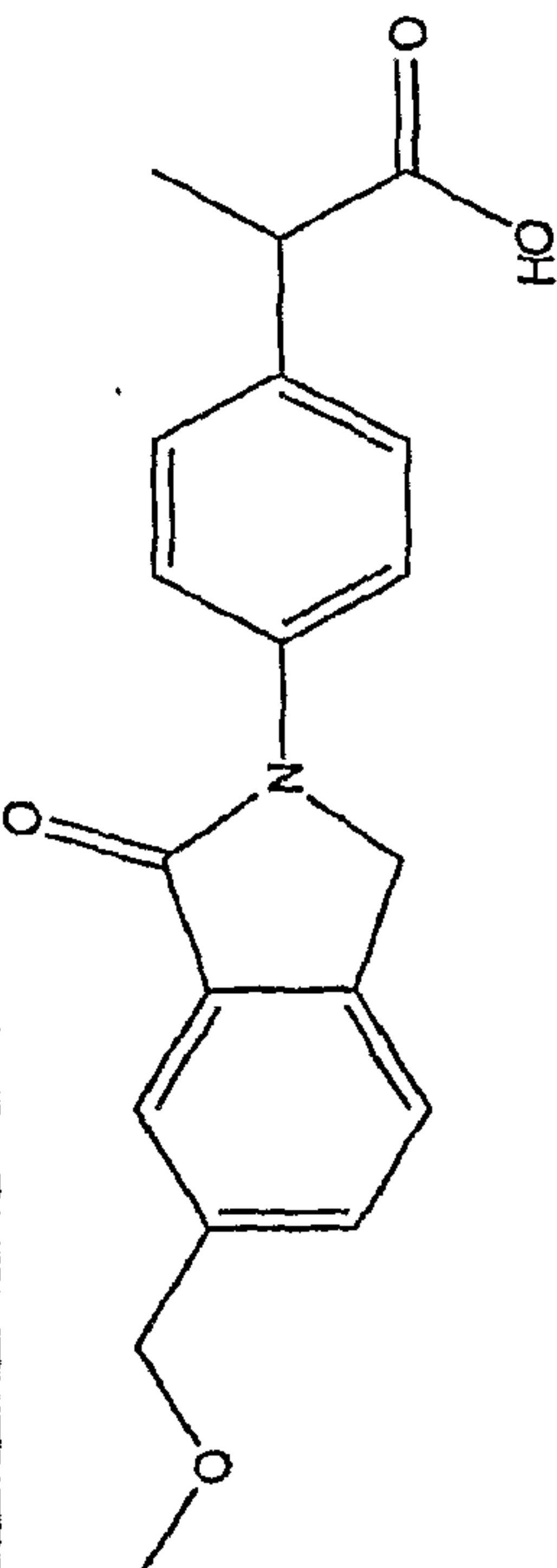
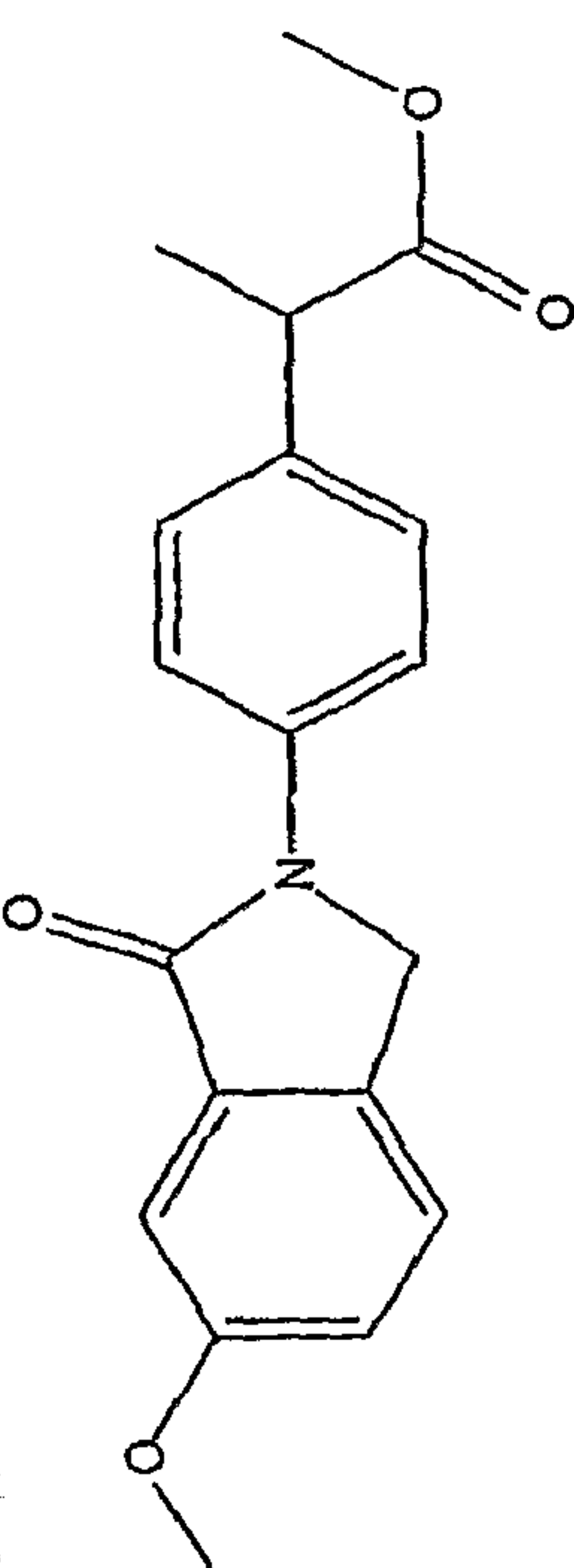
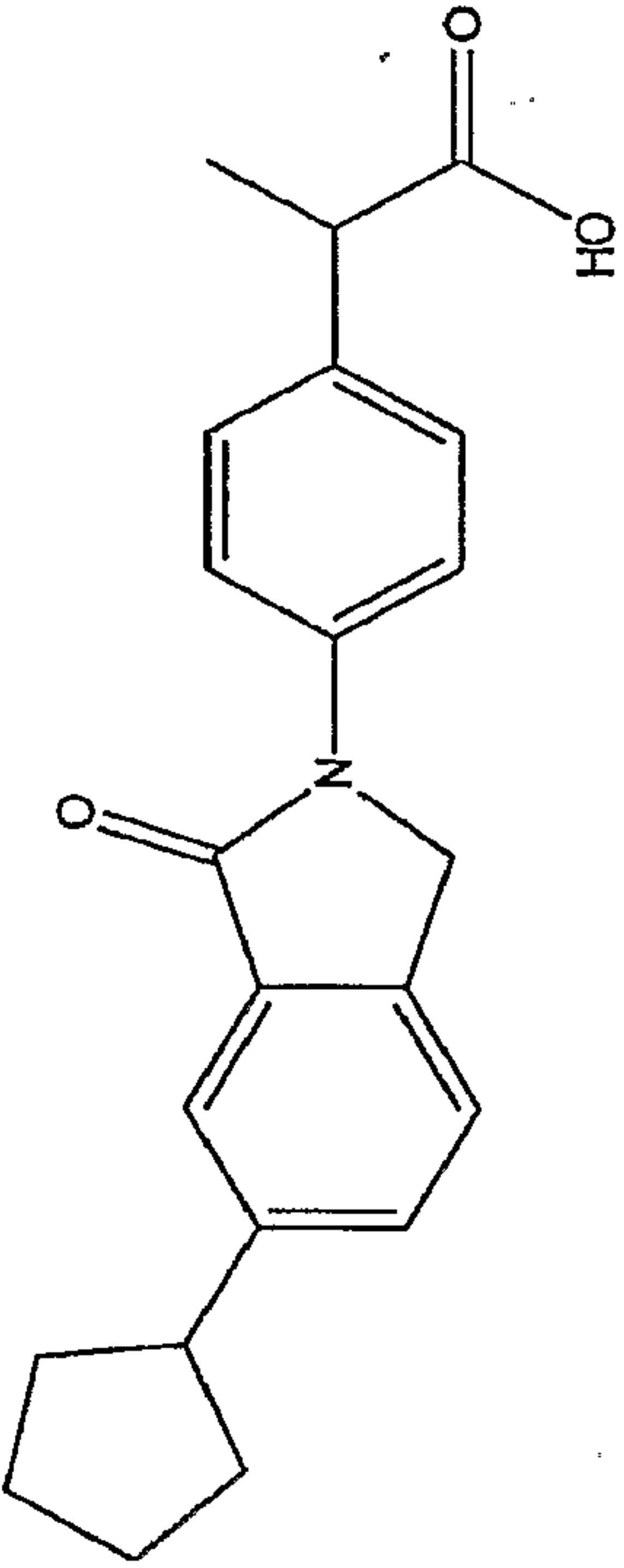
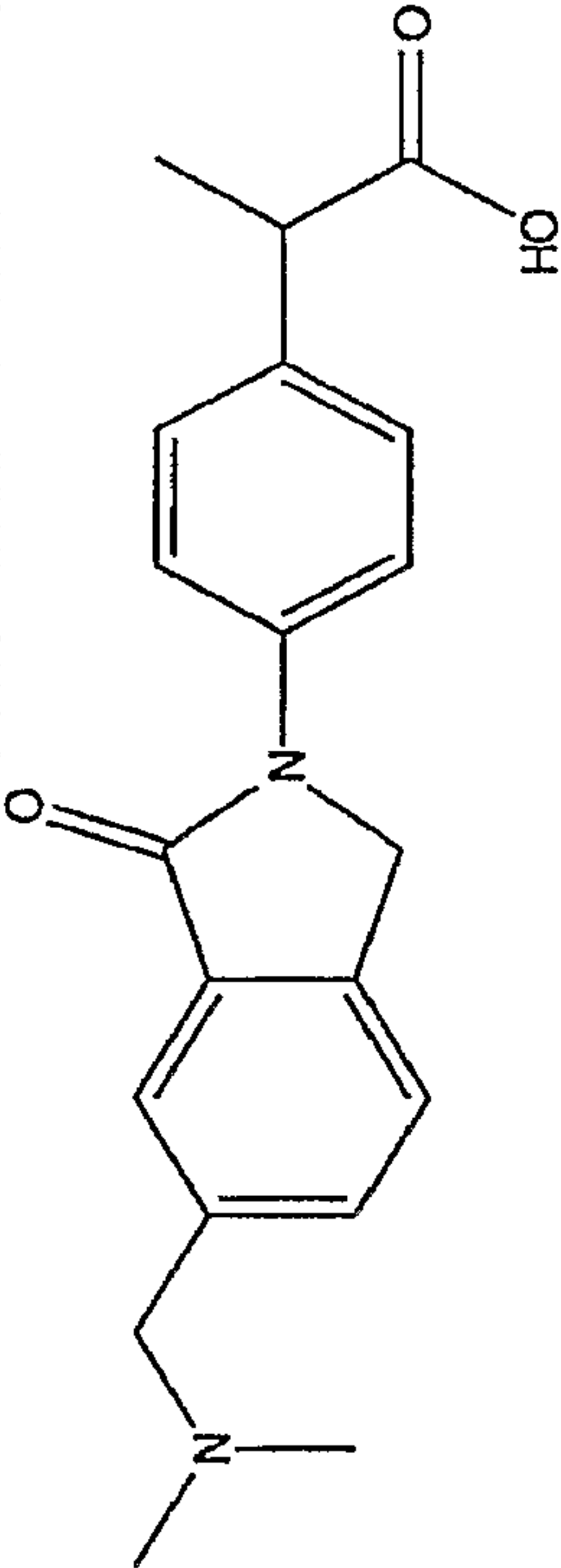
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
229		ALB- 114437	1.905	1.201
230		ALB- 114438	1.905	1.273

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
231		ALB- 114439	0.052	1.511
232		ALB- 114441	0.076	1.673

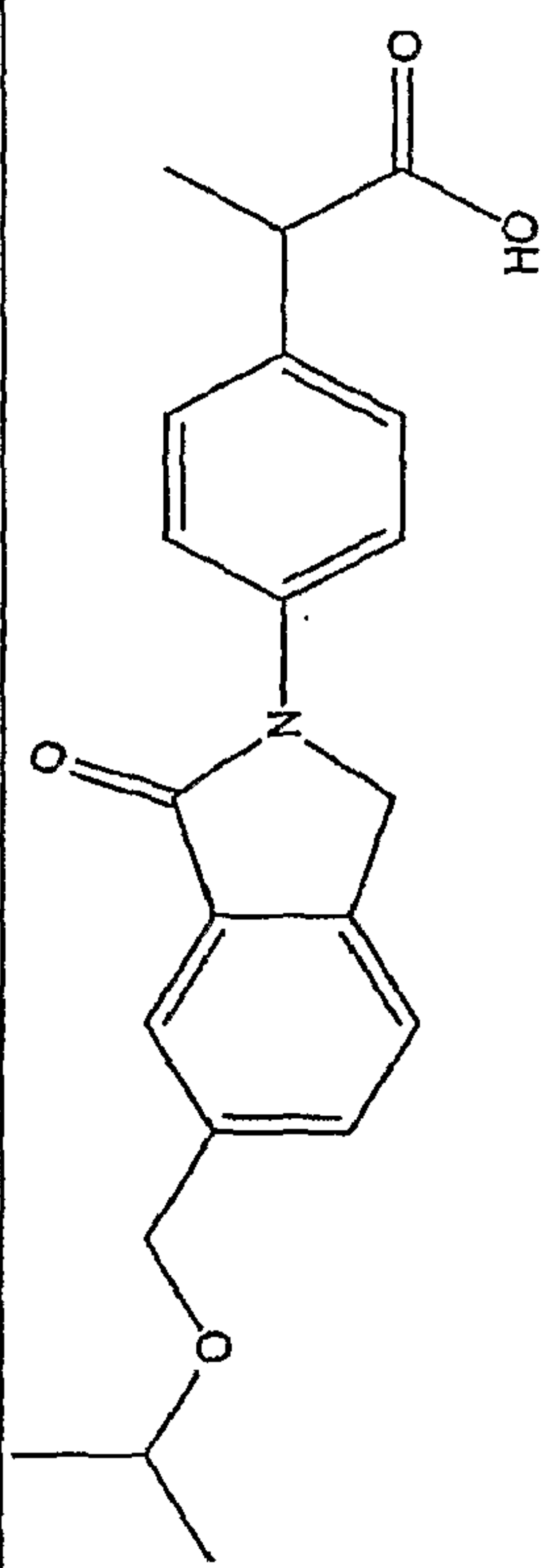
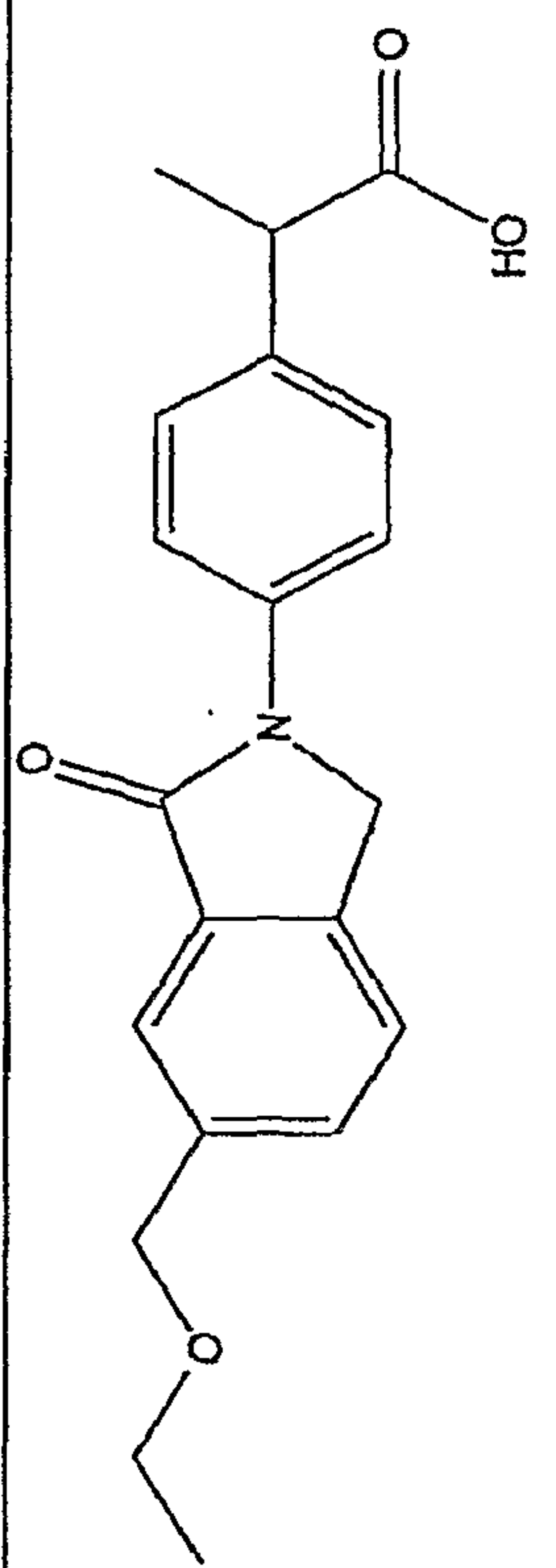
154

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
233		ALB- 114607	0.035	1.509
234		ALB- 114608		1.228

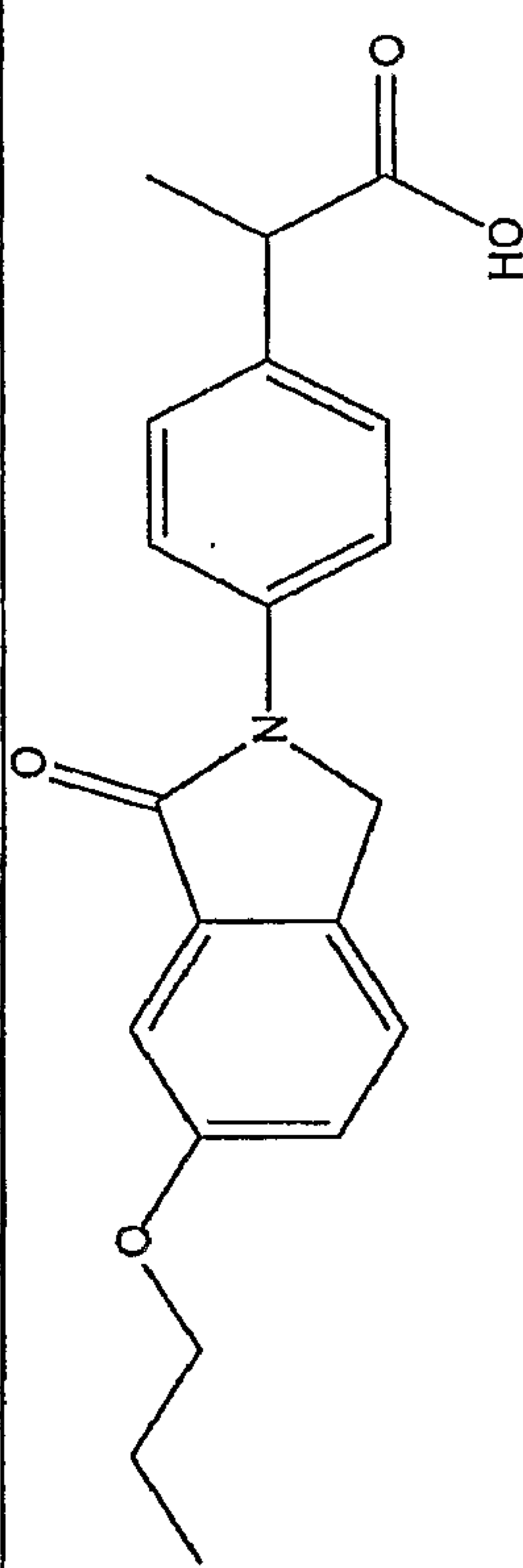
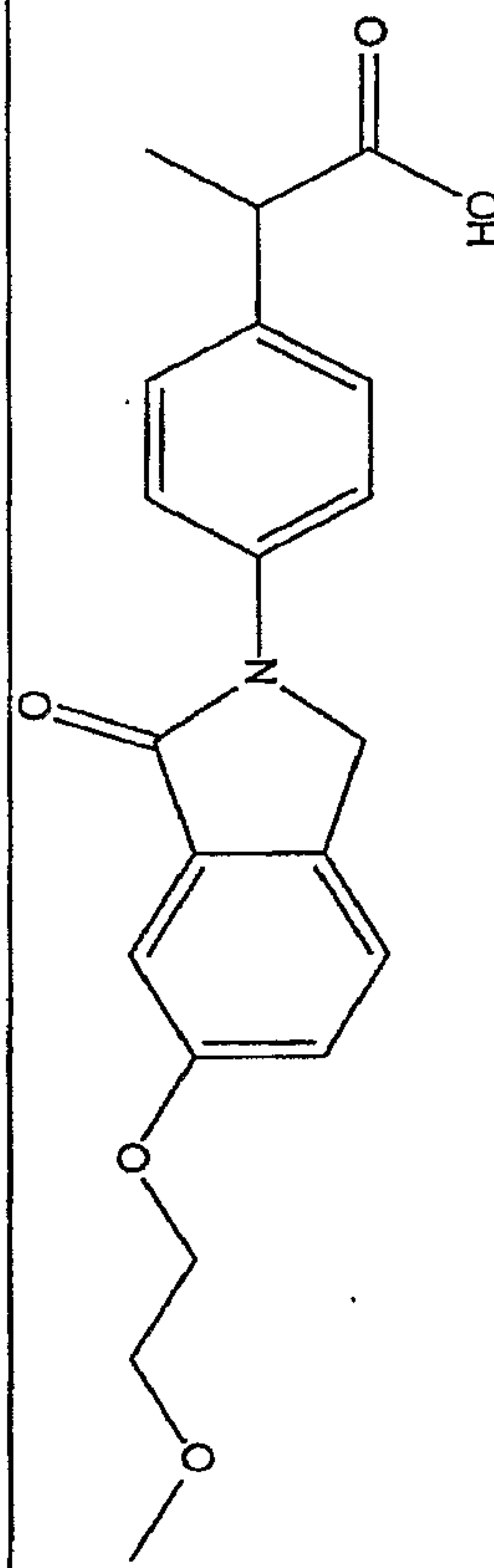
156

Table I

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
237		ALB- 114741	0.067	1.674
238		ALB- 114742	0.042	1.576

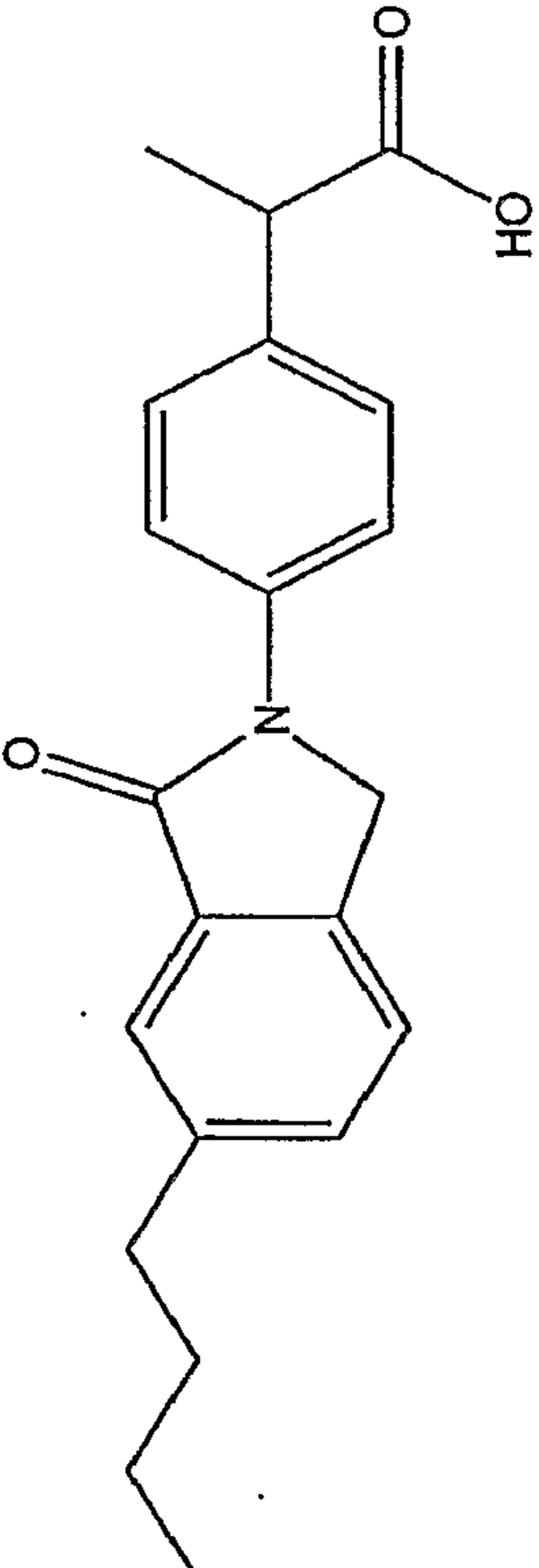
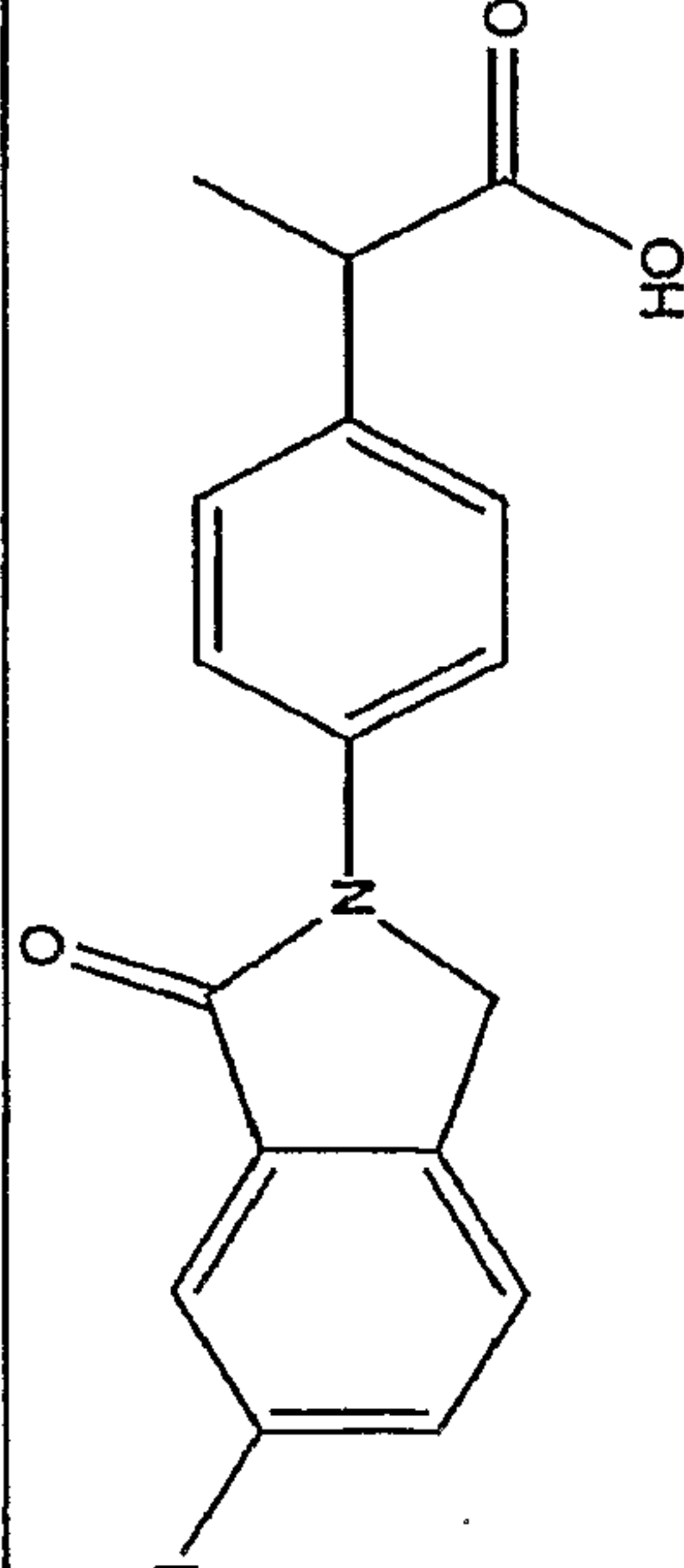
157

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
239				
		ALB- 114934	0.033	1.867
240				
		ALB- 115071	0.824	1.386

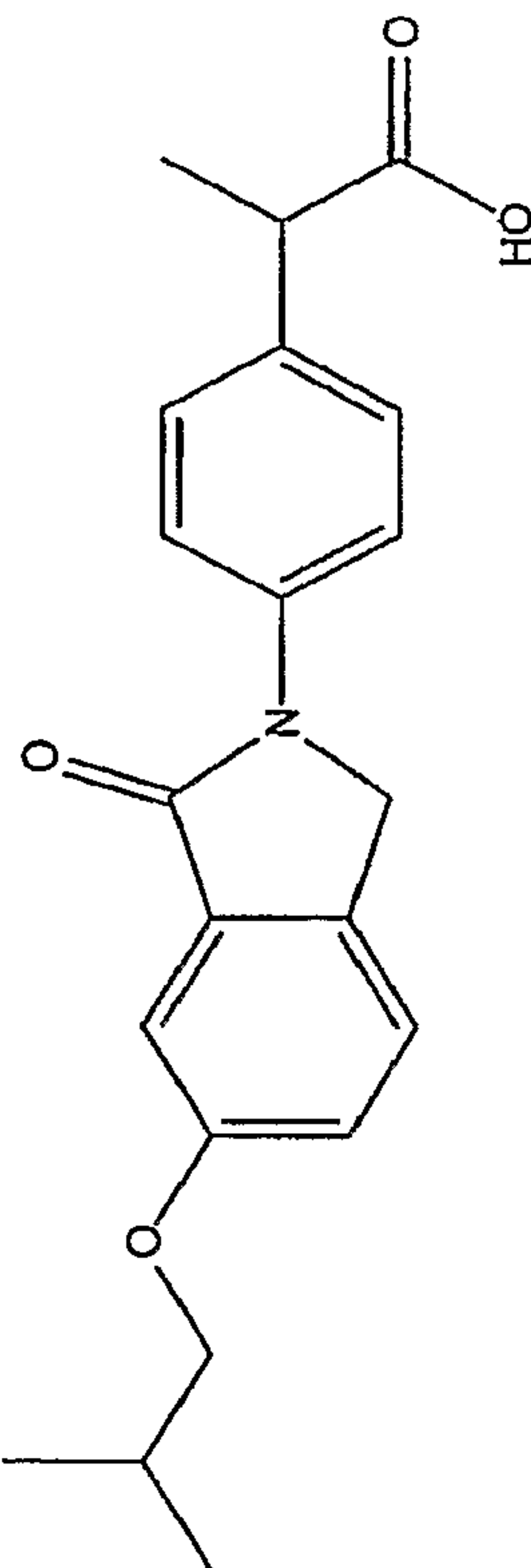
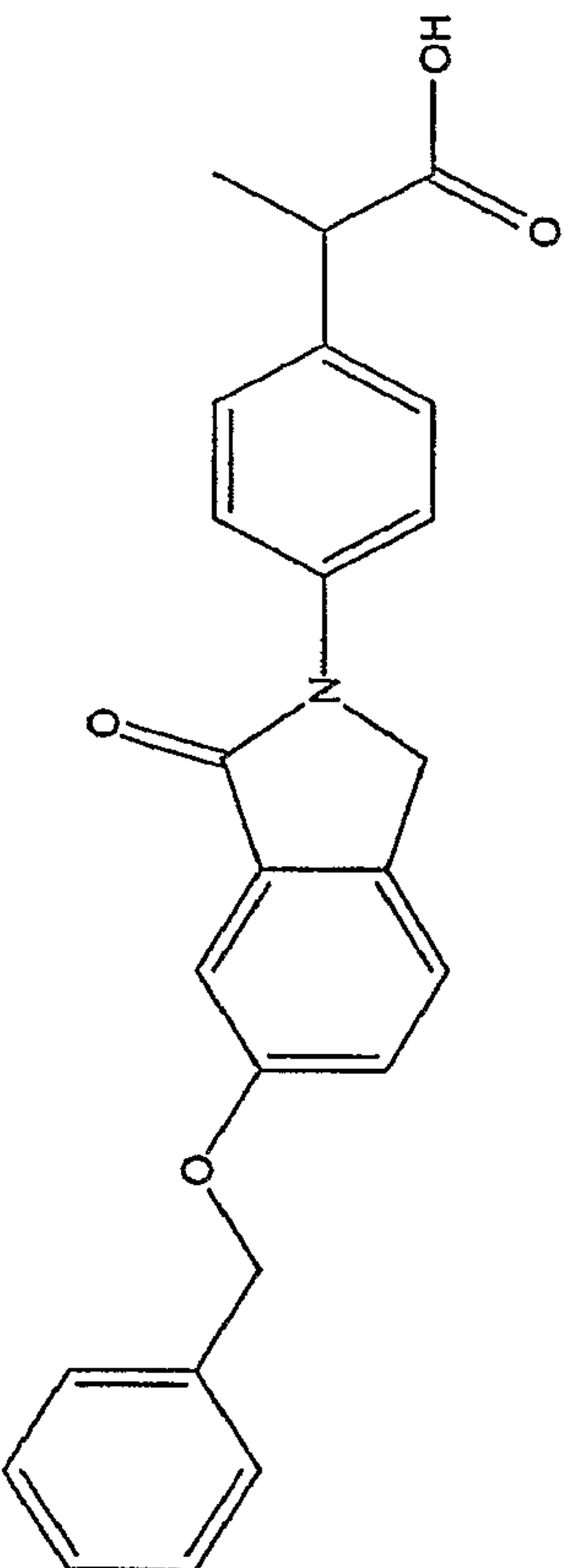
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
241		ALB- 115086	0.061	2.061
242		ALB- 115216	0.075	1.873

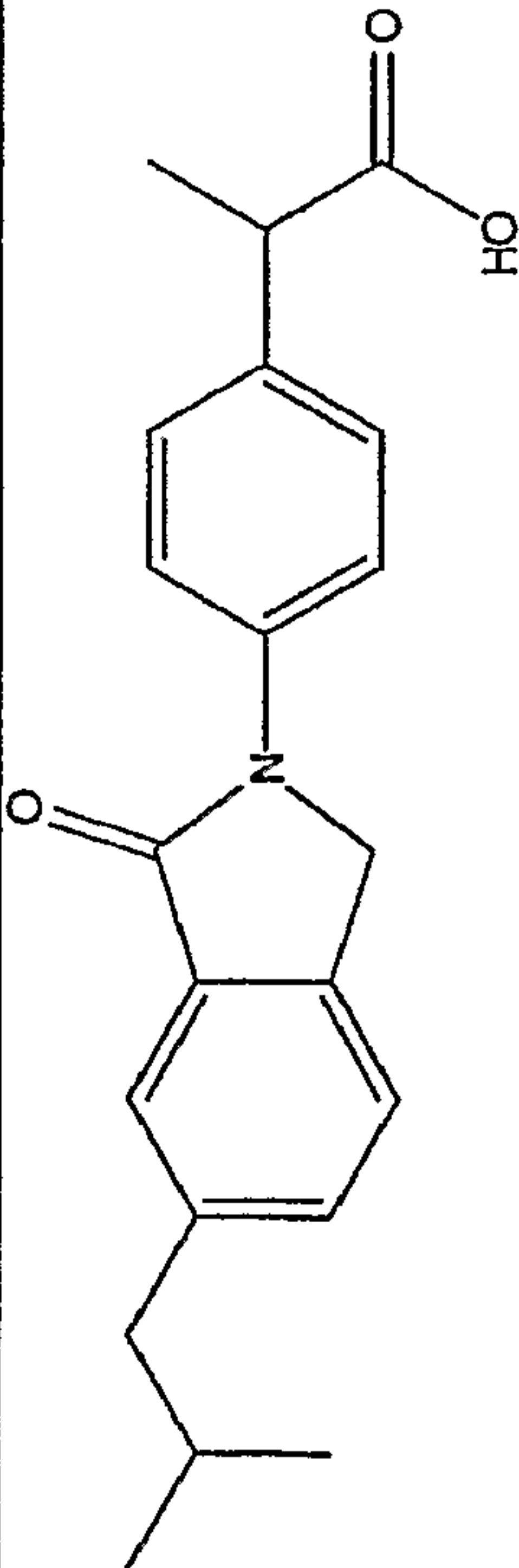
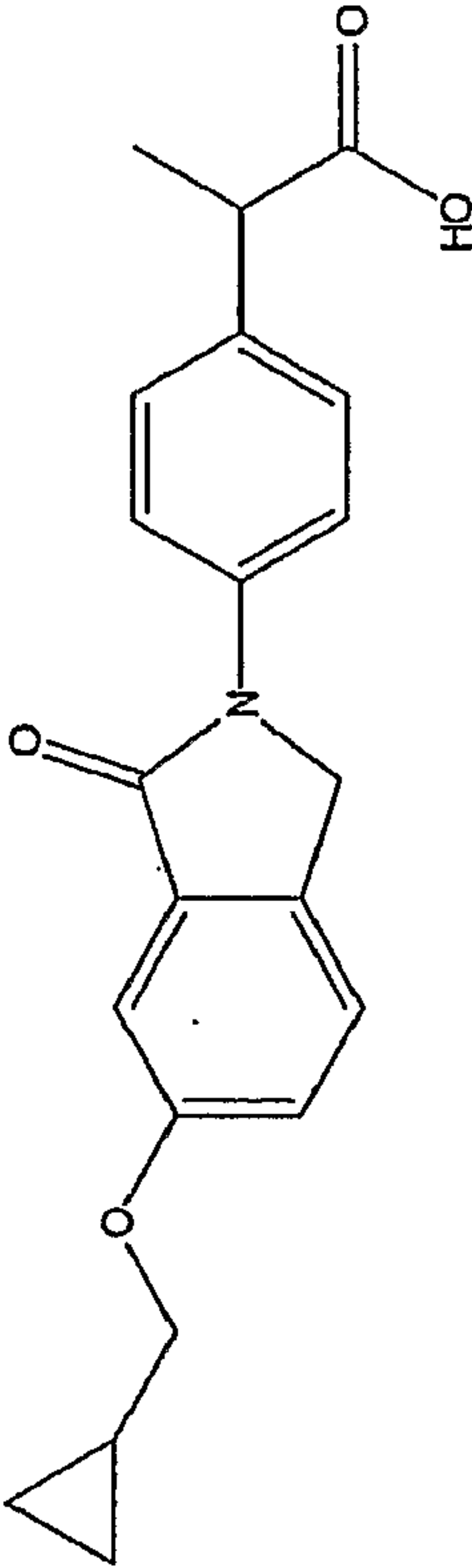
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
243		ALB- 115325	0.074	1.571
244		ALB- 115326		1.241

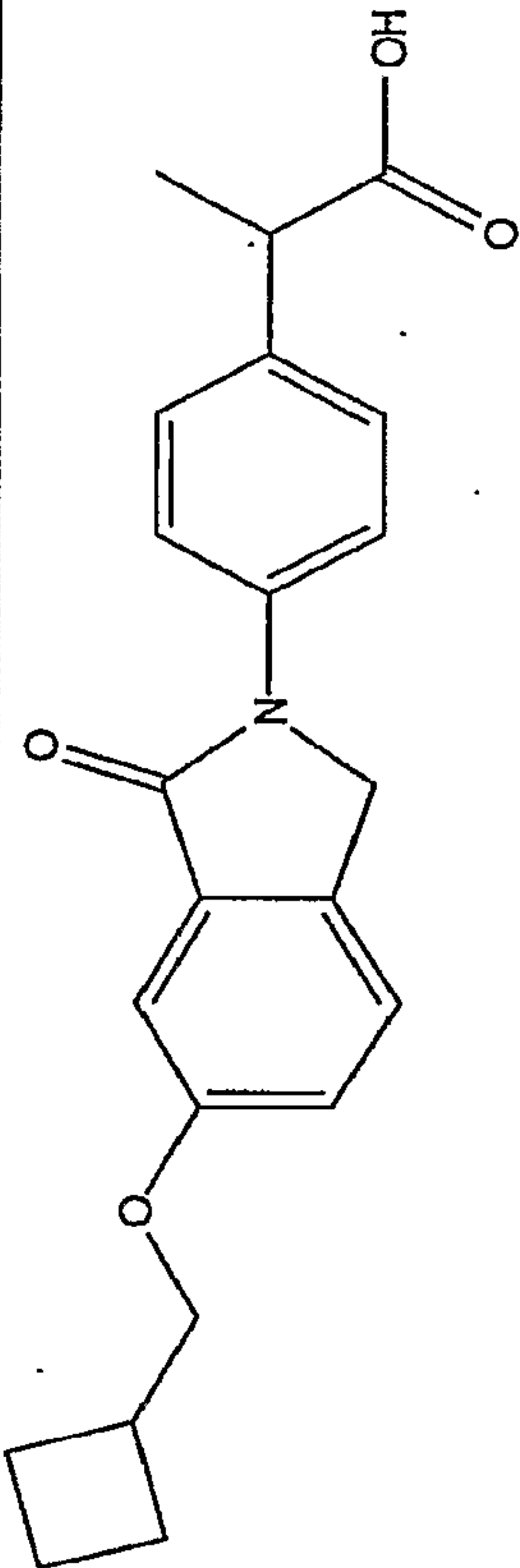
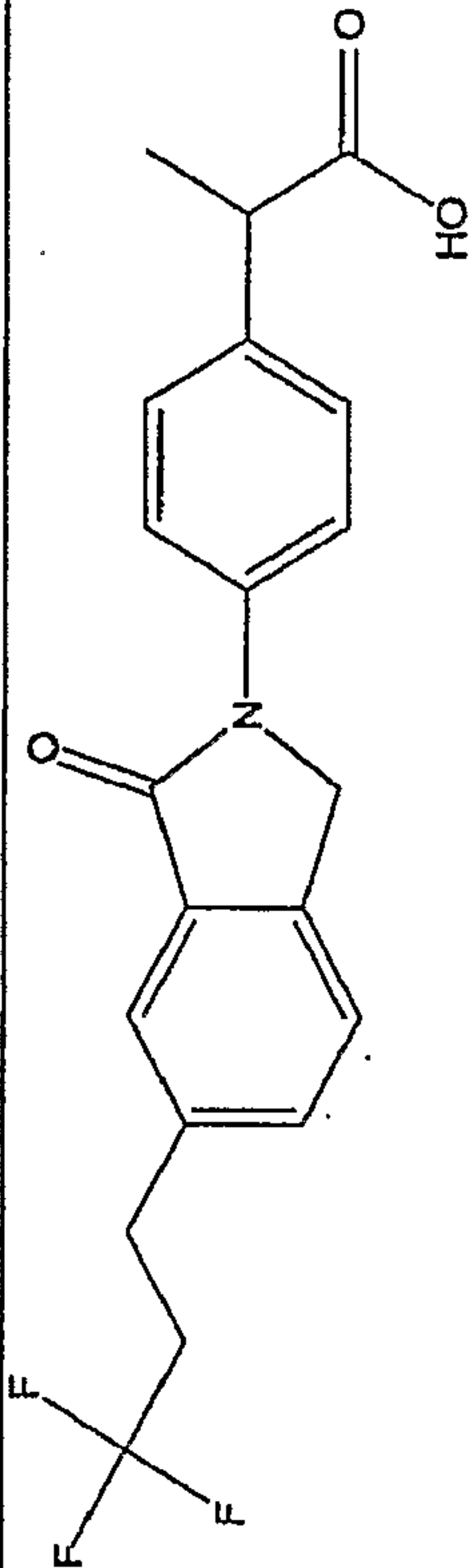
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
245		ALB- 115426	0.013	1.961
246		ALB- 115500	0.115	1.536

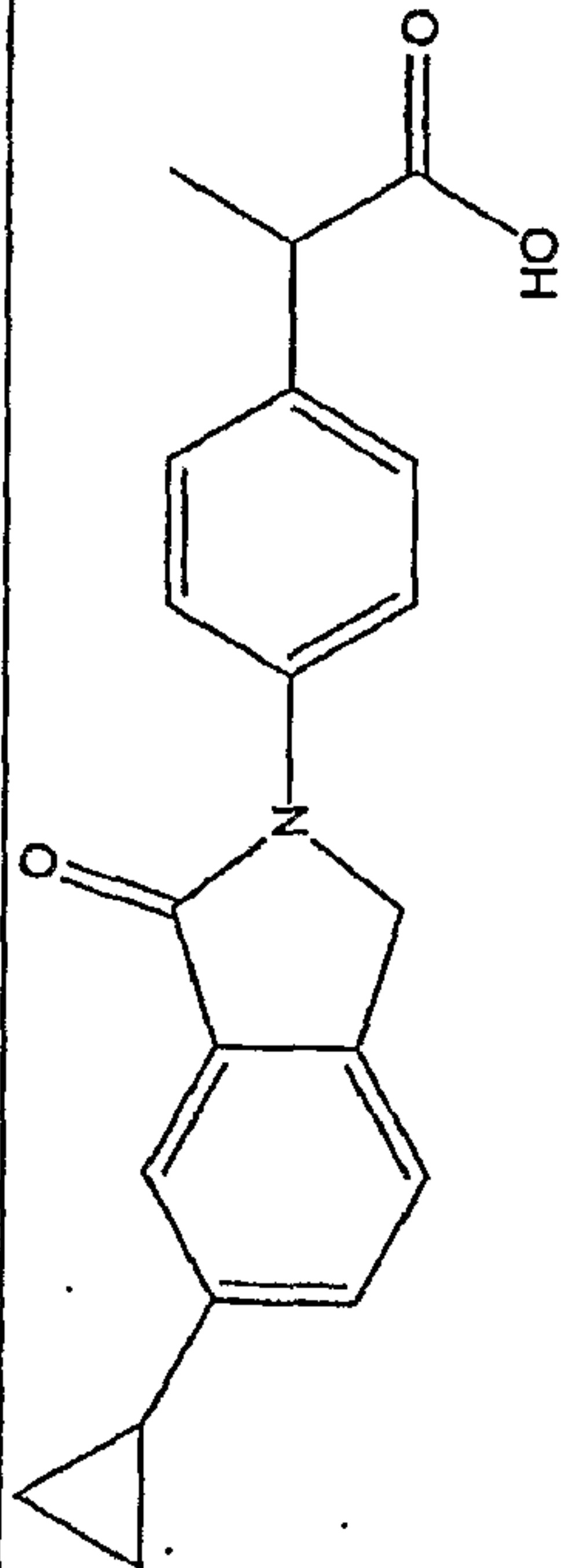
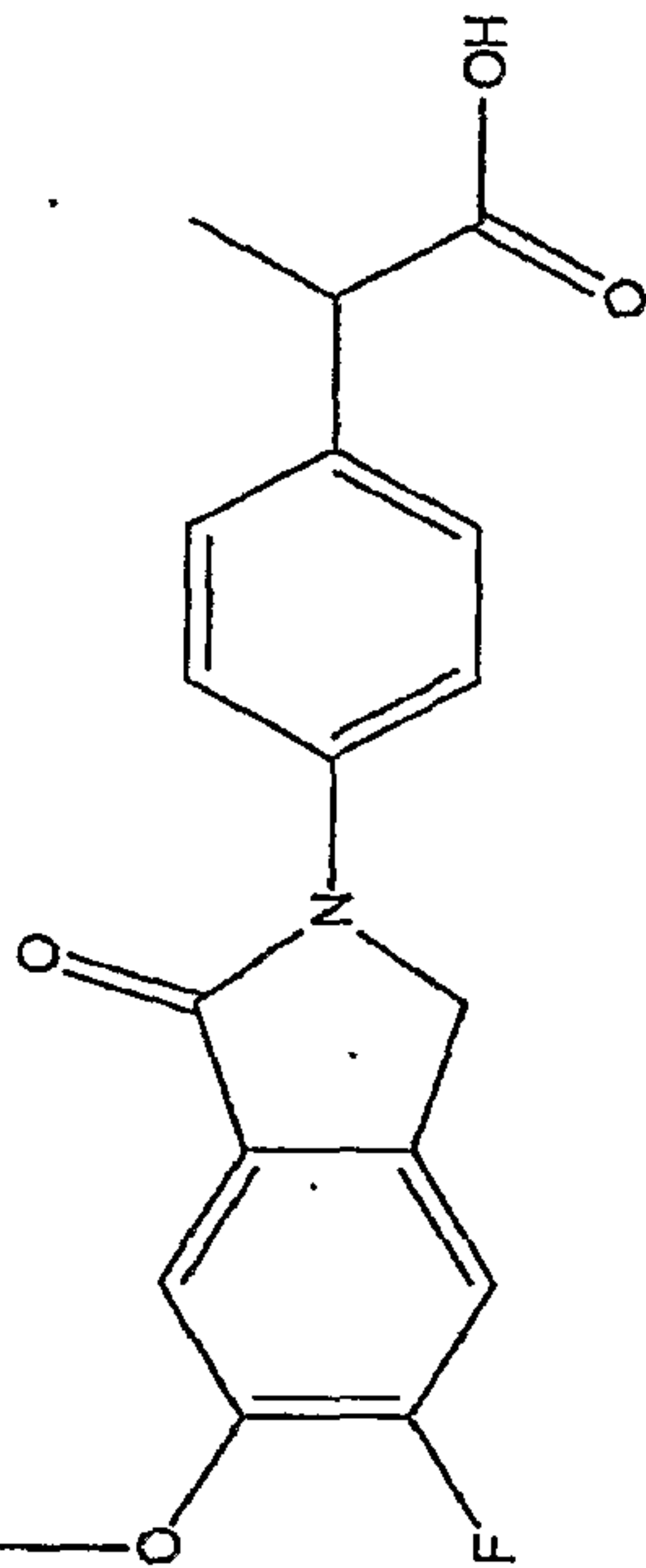
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
247		ALB- 115585	0.083	1.477
248		ALB- 115588	0.356	1.704

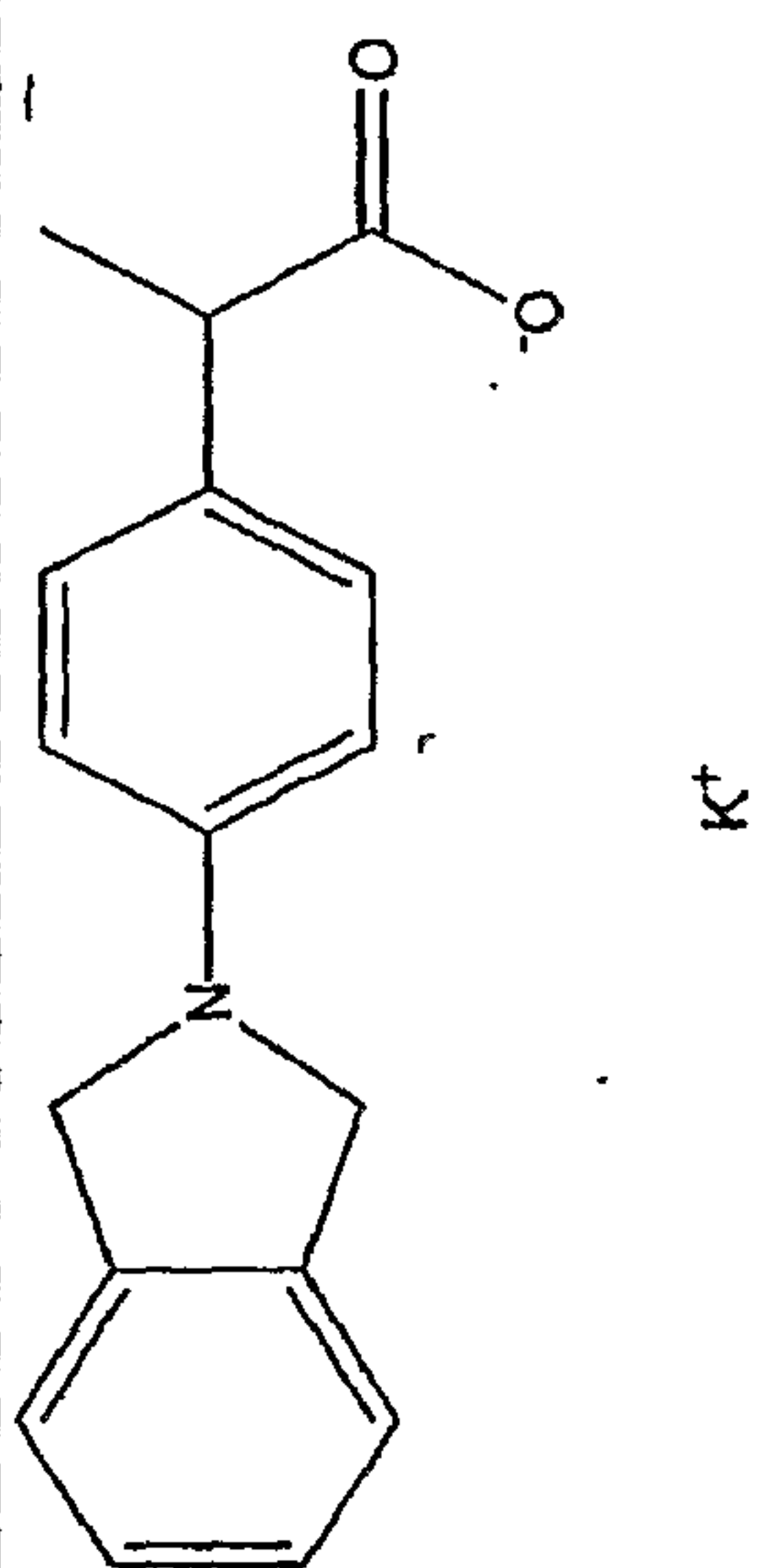
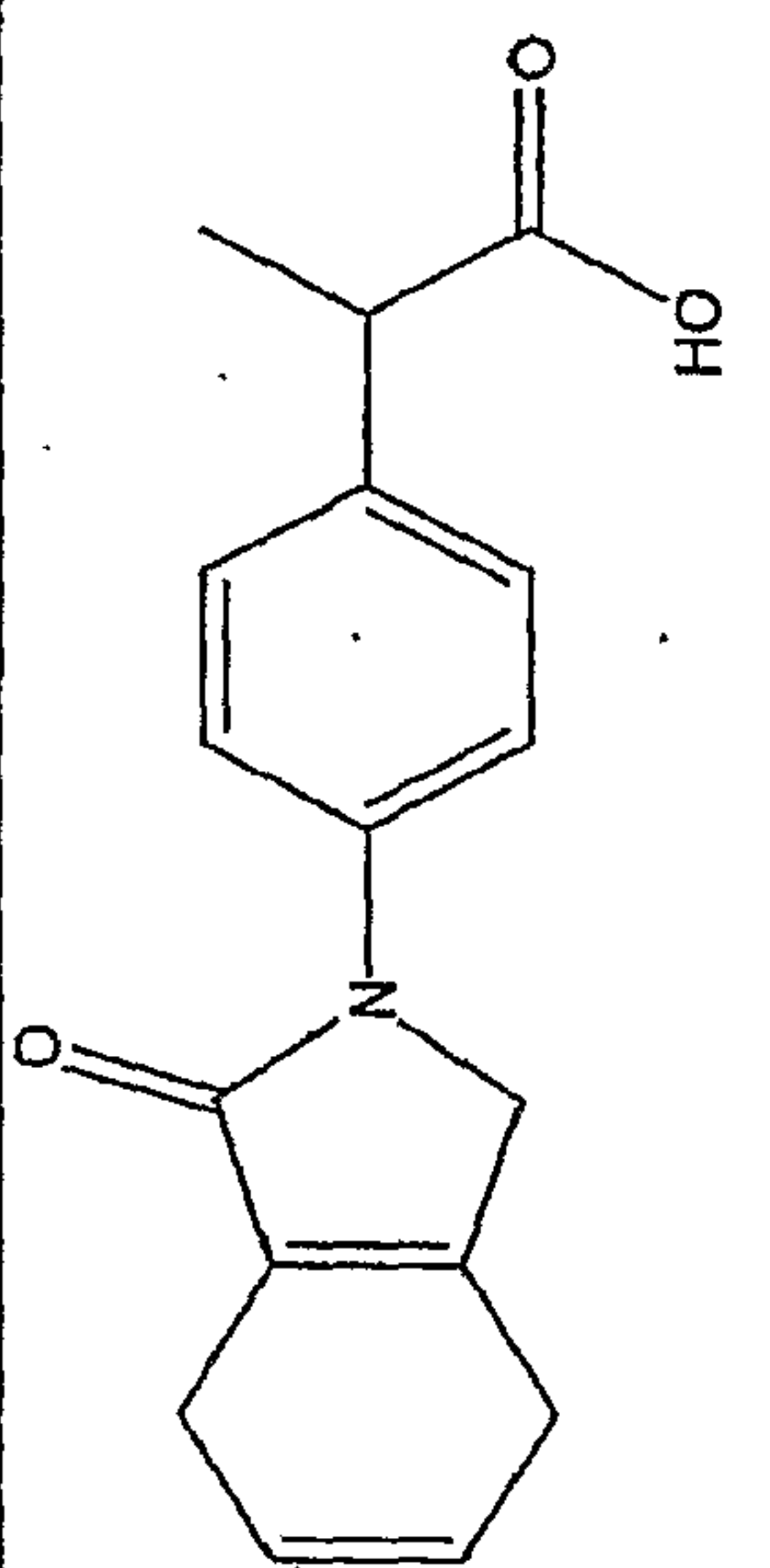
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
249		ALB- 115716	0.029	1.593
250		ALB- 119048	0.255	1.536

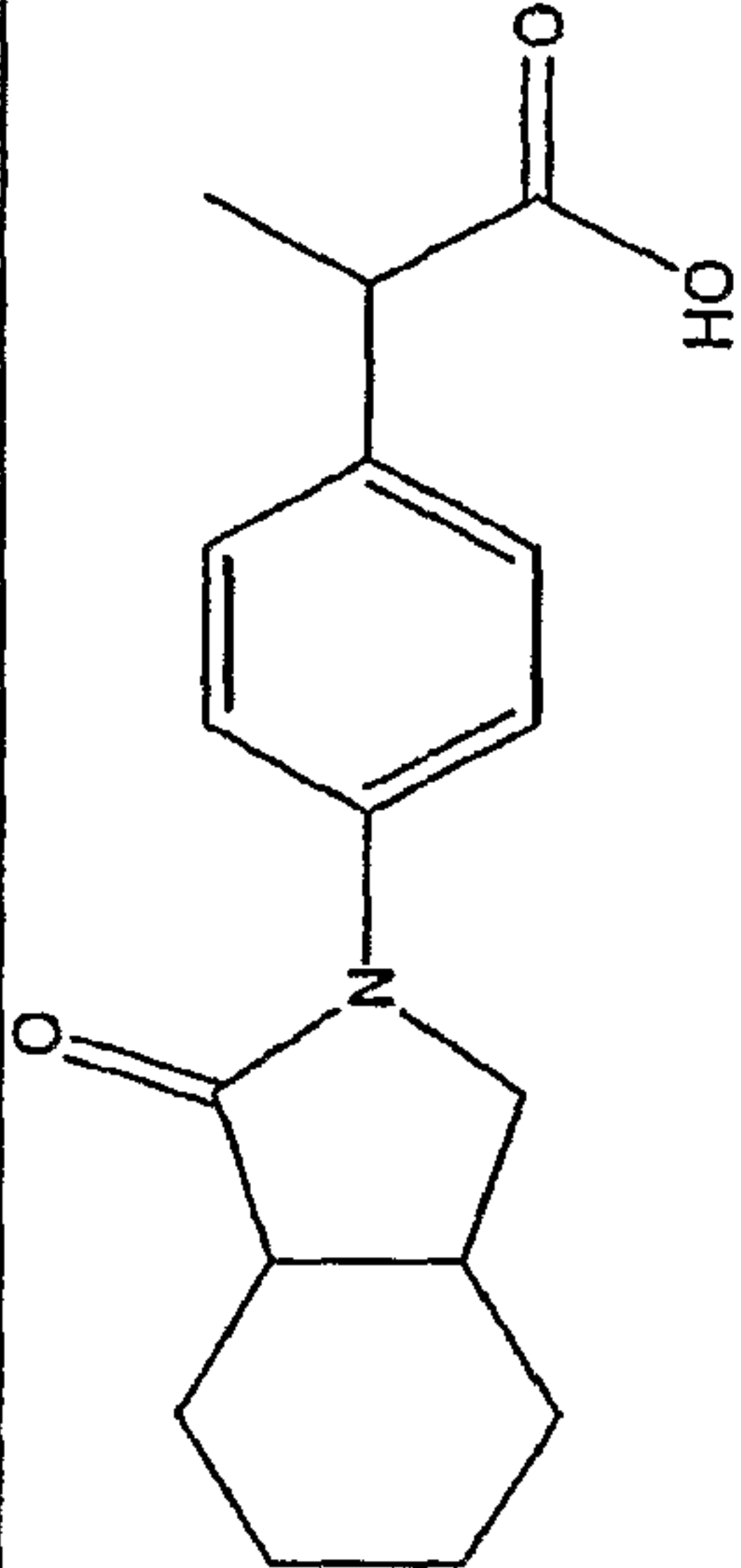
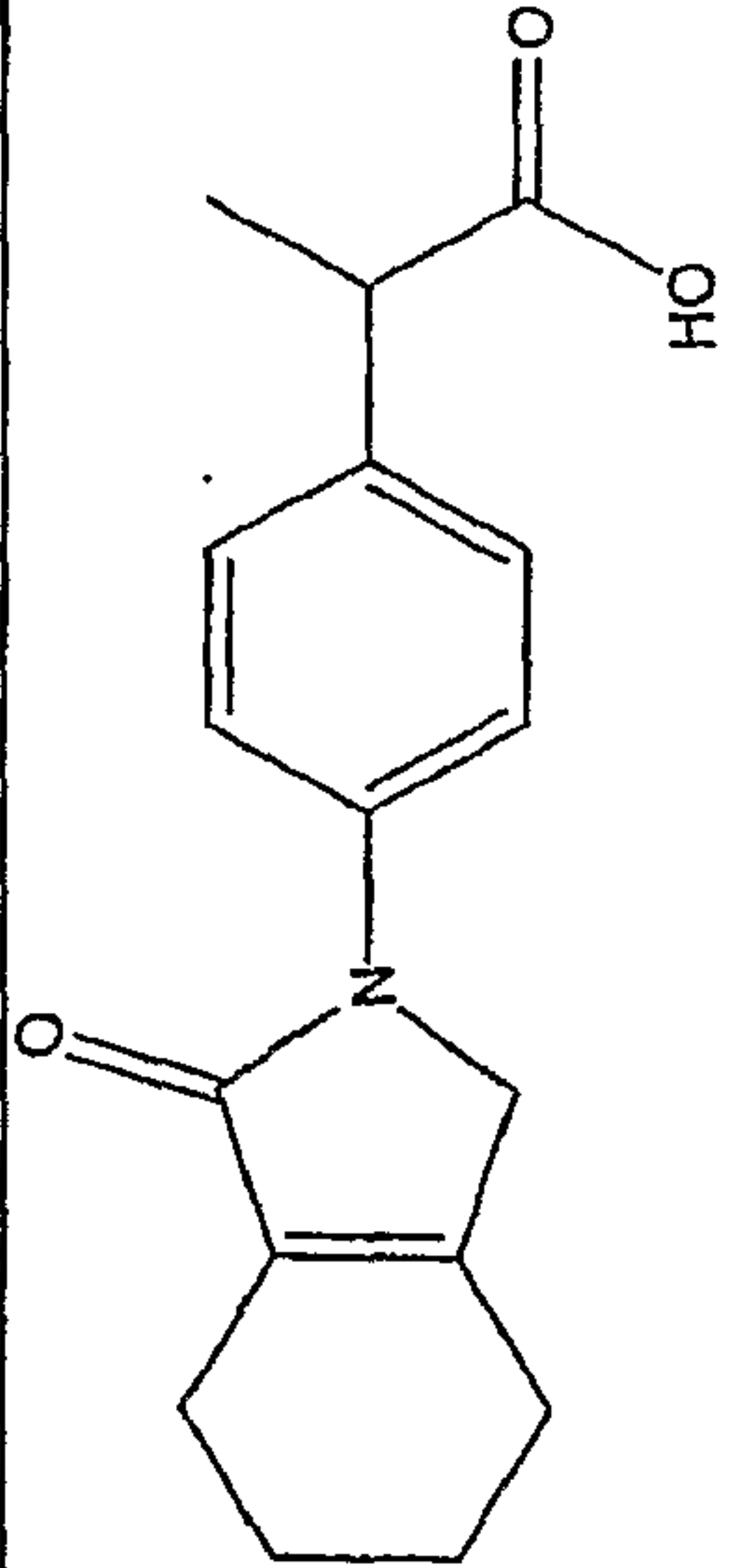
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
251	 <chem>CC(C(=O)[O-])c1ccc(Nc2c3ccccc3ccc2)cc1.[K+]</chem>	ALB- 112227	1.424	1.504
252	 <chem>CC(C(=O)O)c1ccc(Nc2c3ccccc3c(=O)c2)cc1</chem>	ALB- 112896	1.011	1.578

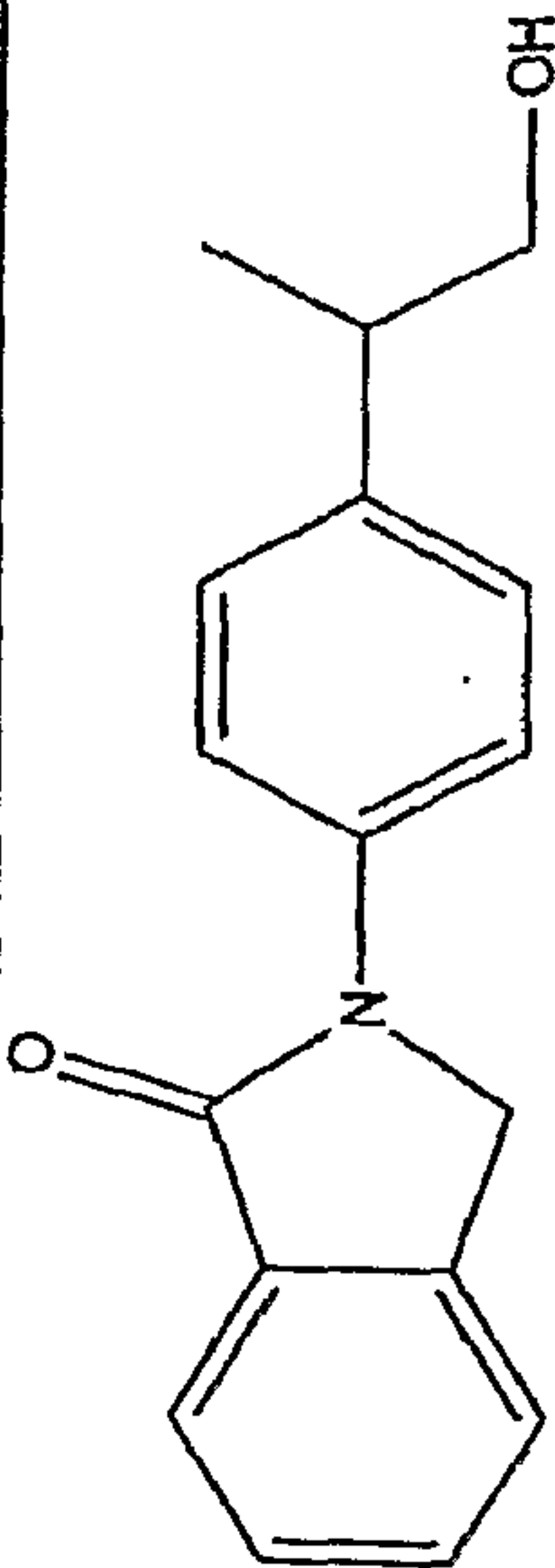
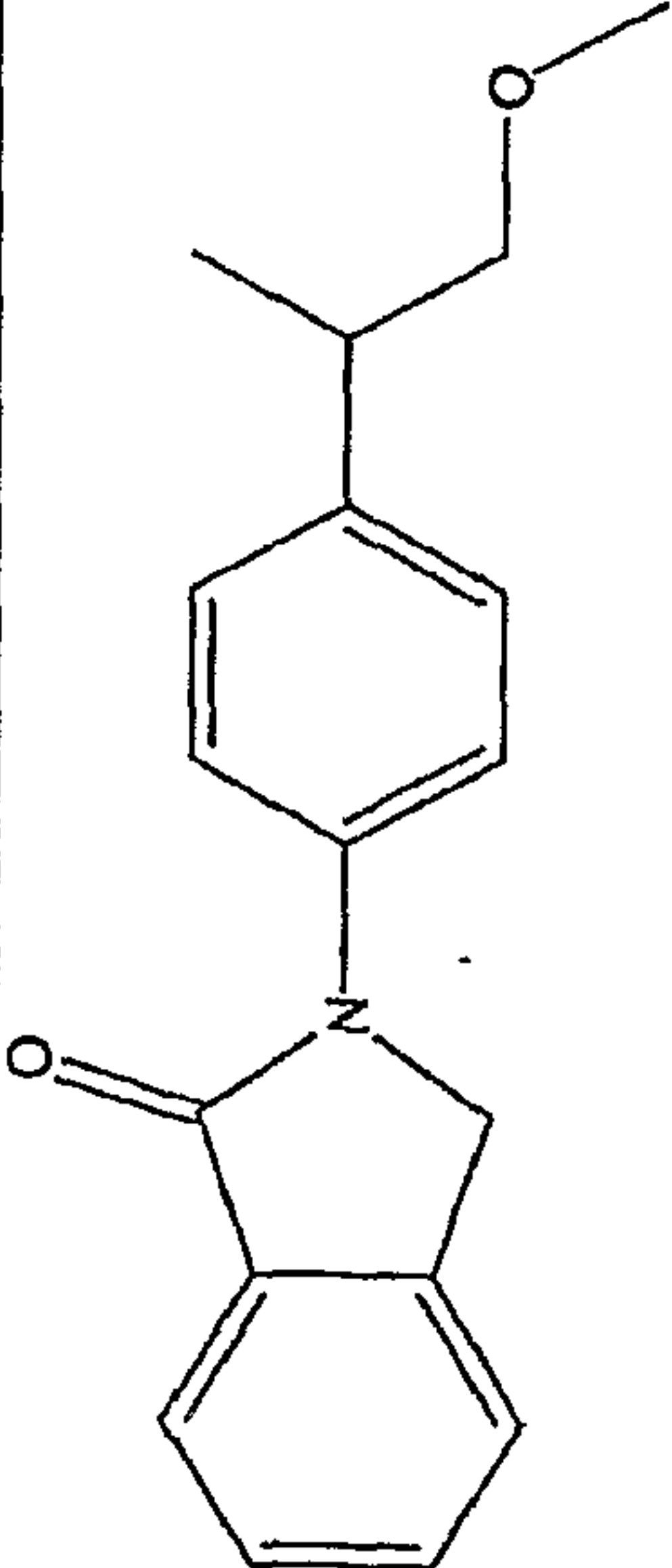
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
253		ALB- 112901	5.815	1.487
254		ALB- 112951	0.279	1.792

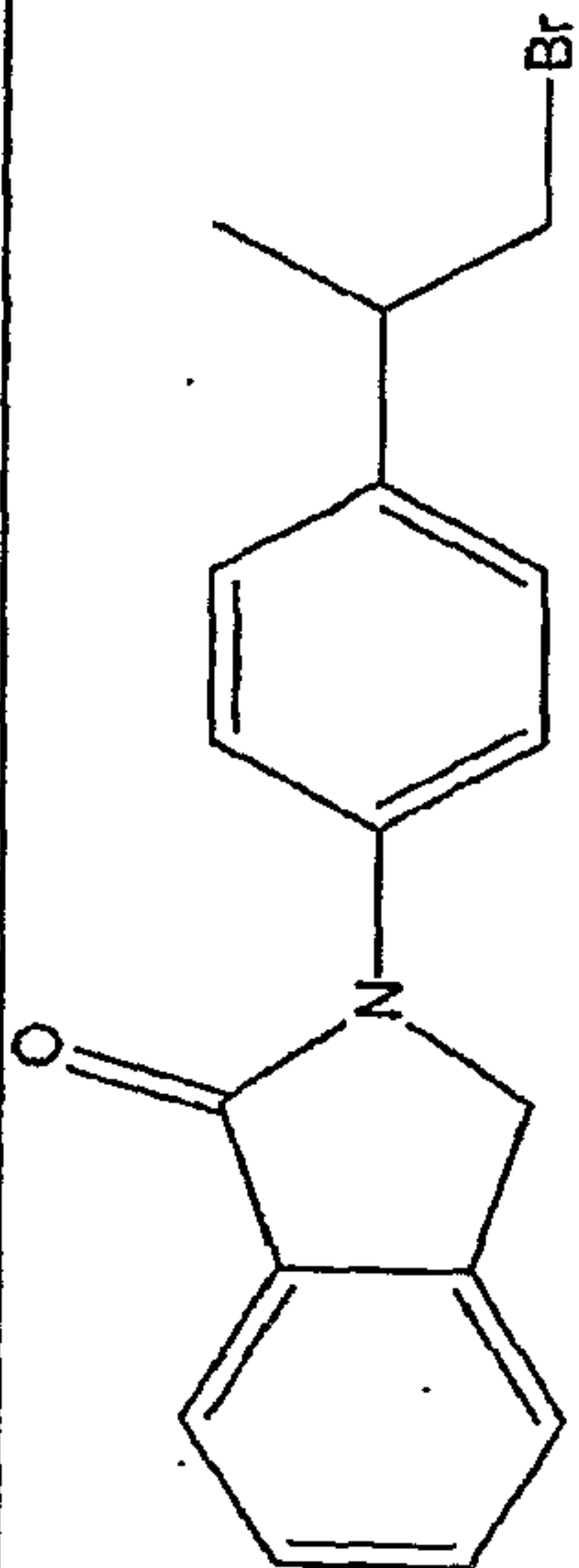
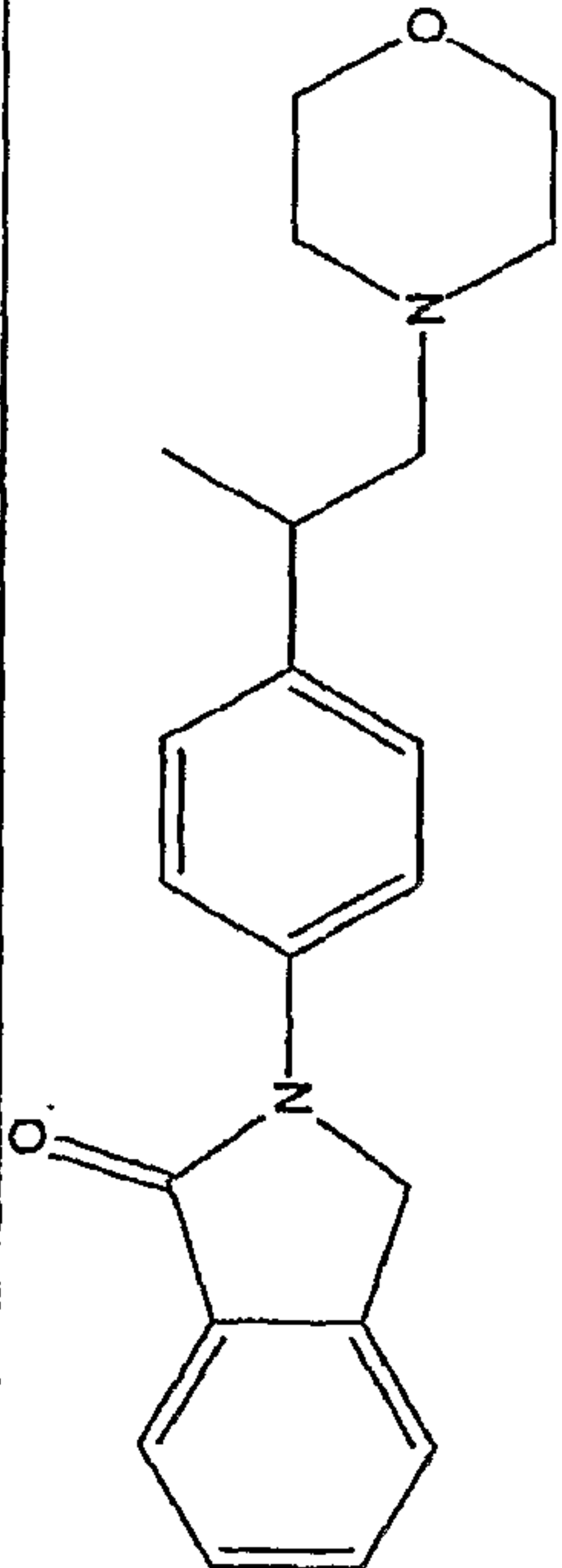
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
255		ALB- 113309	0.144	1.194
256		ALB- 113389	0.179	1.337

166

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
257		ALB- 113651	0.209	1.437
258		ALB- 113758	1.4	1.292

167

Table 1

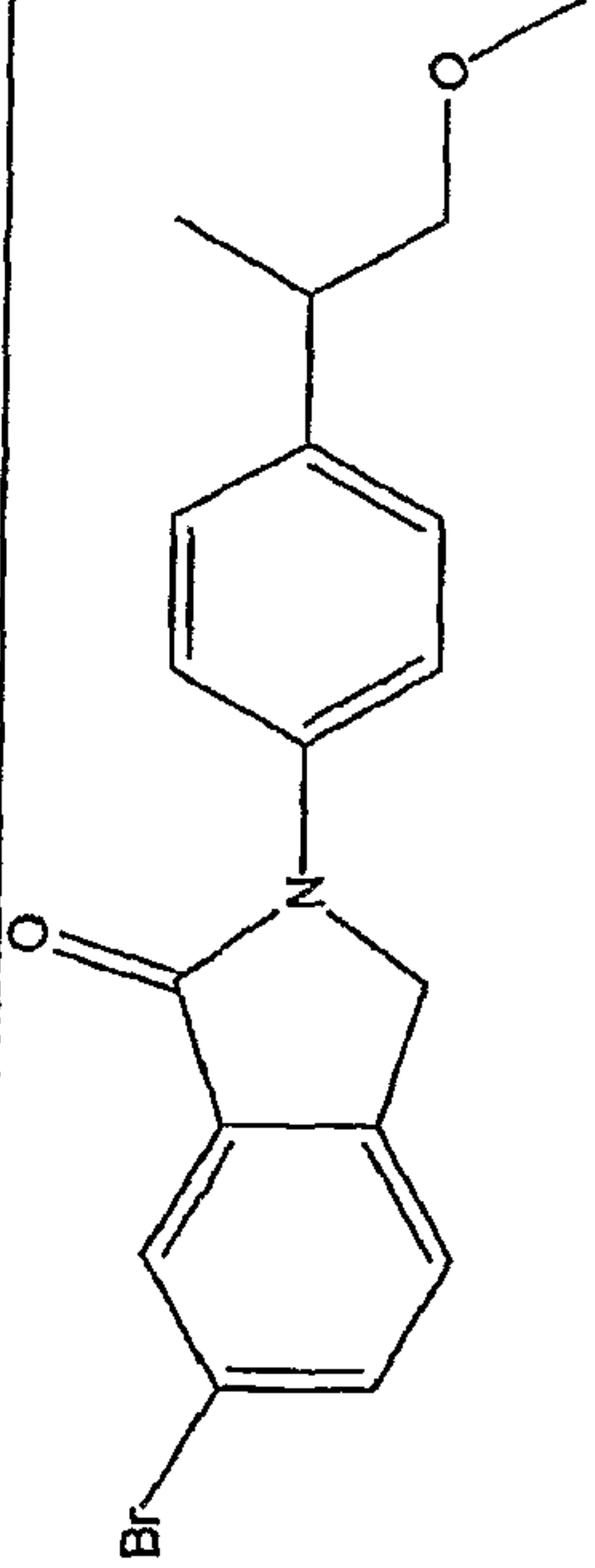
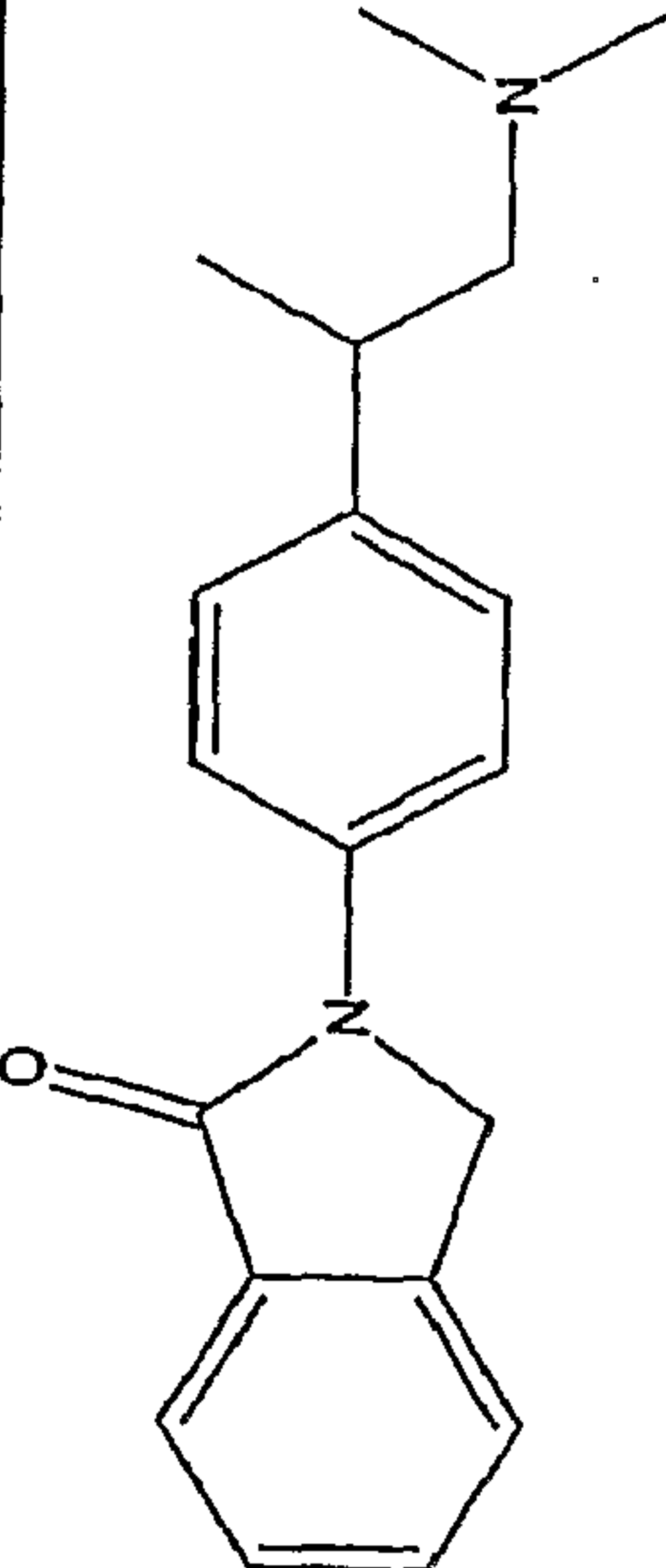
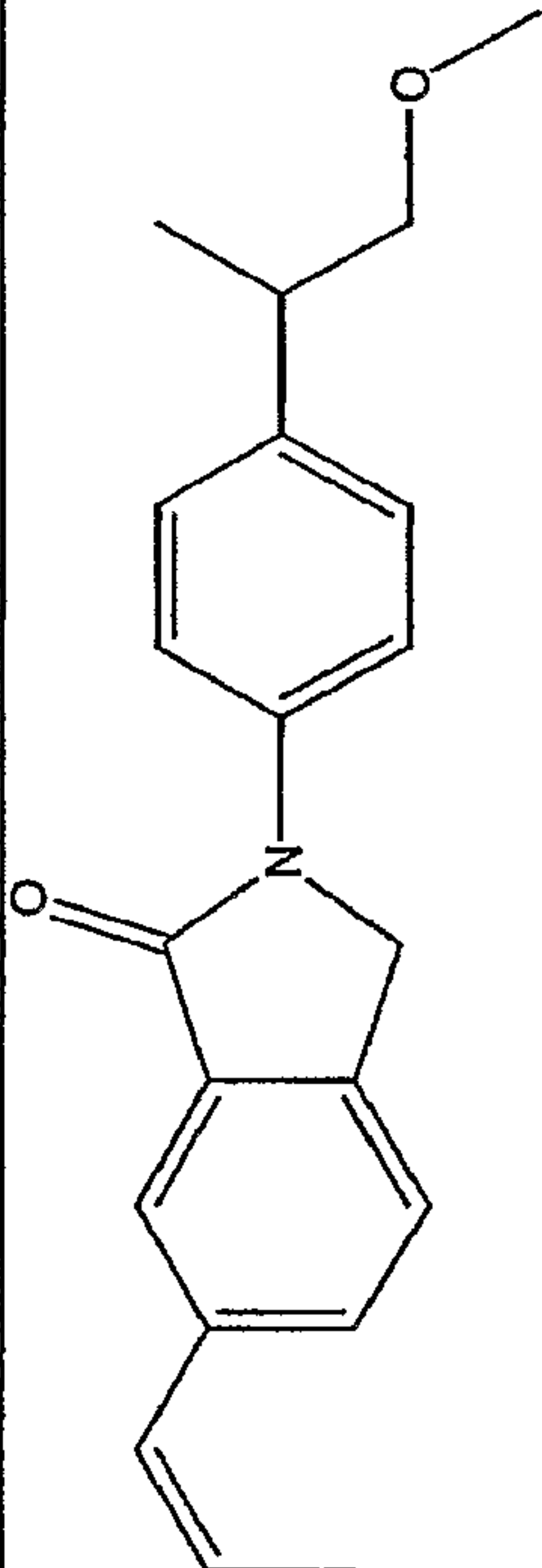
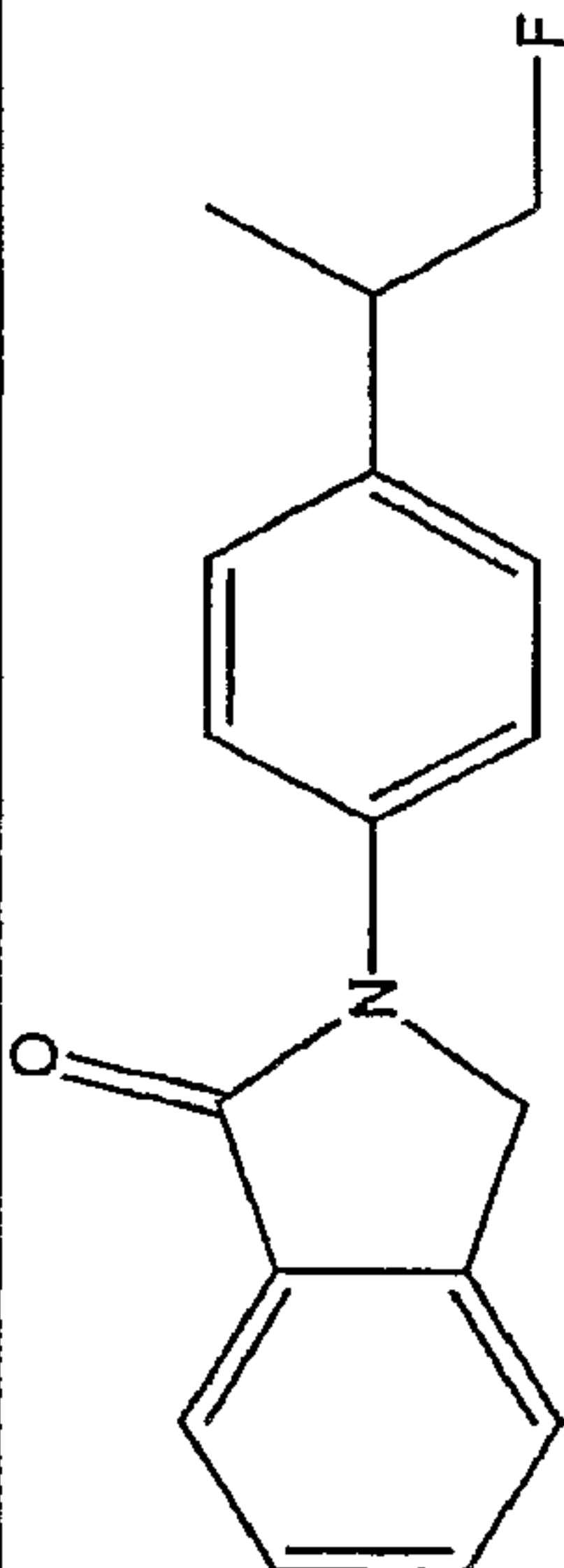
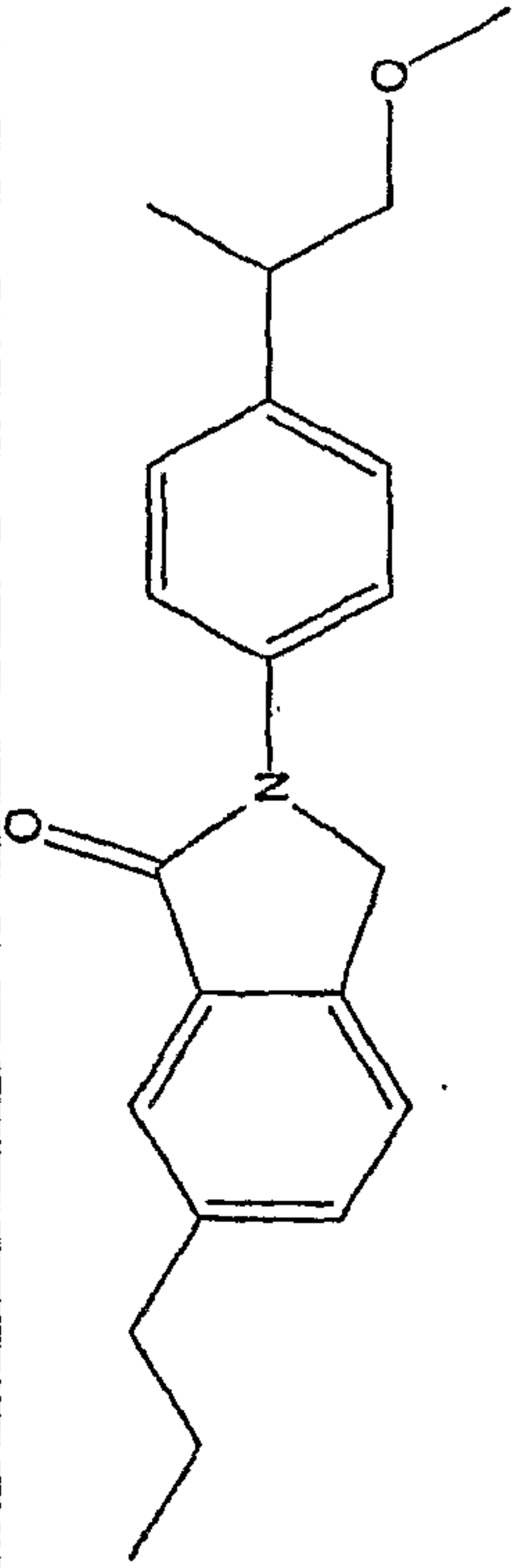
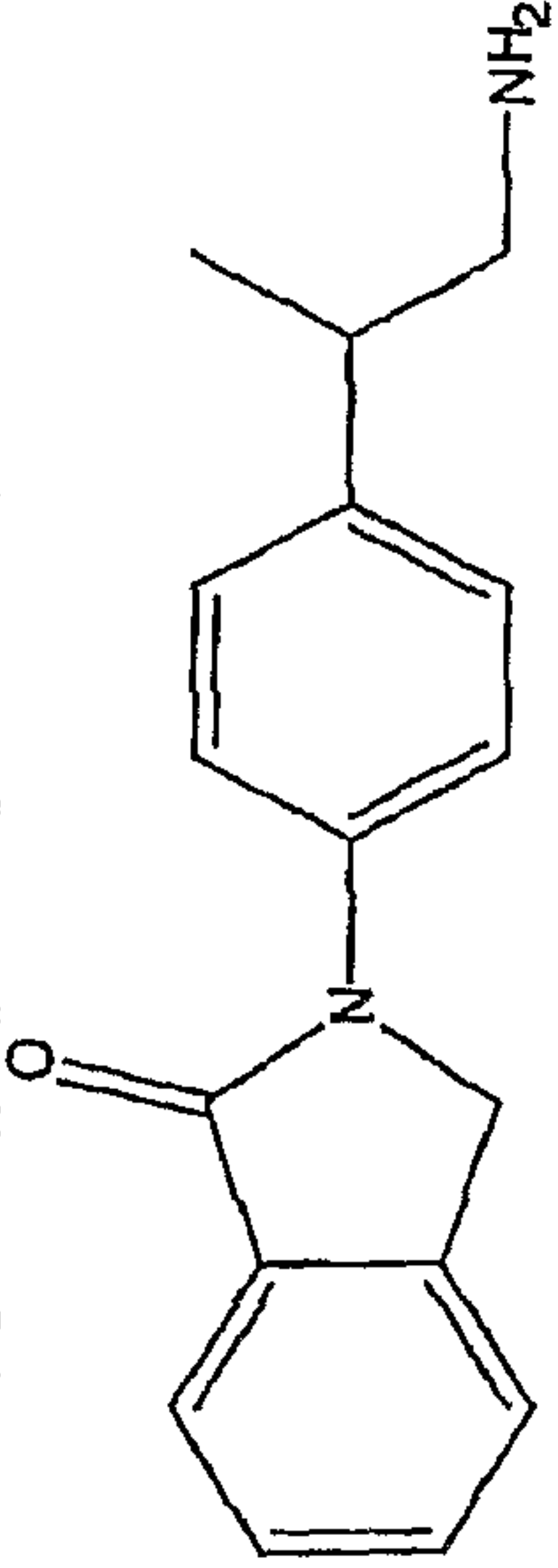
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
259		ALB- 113967	0.159	1.538
260		ALB- 113968	6.026	1.373

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
261		ALB- 114089	0.902	1.548
262		ALB- 114090	0.214	1.465

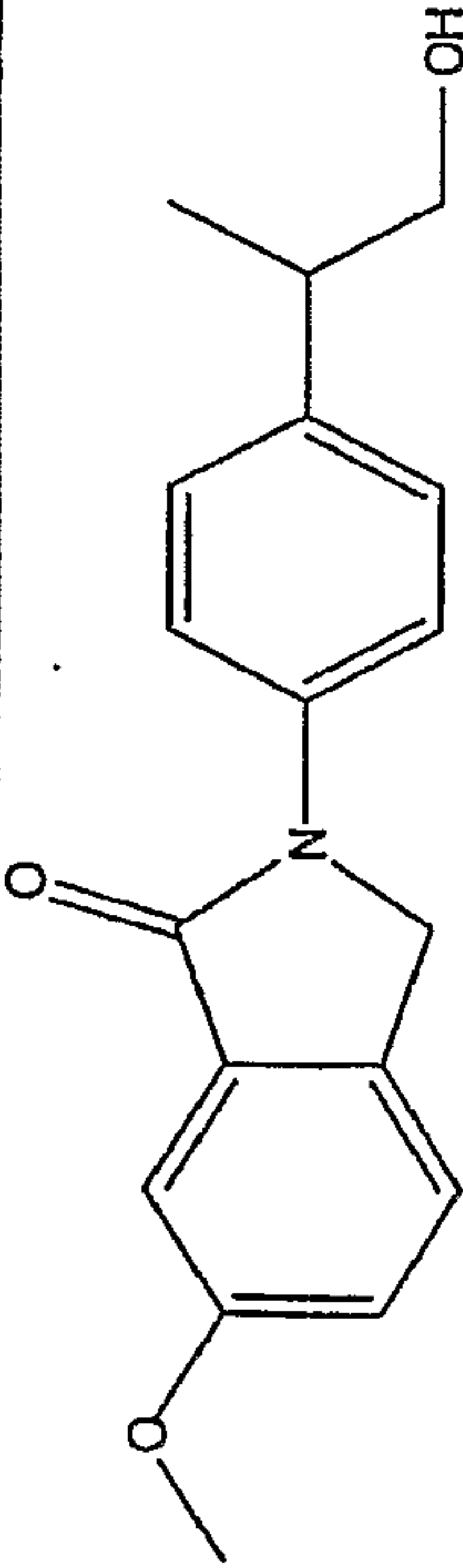
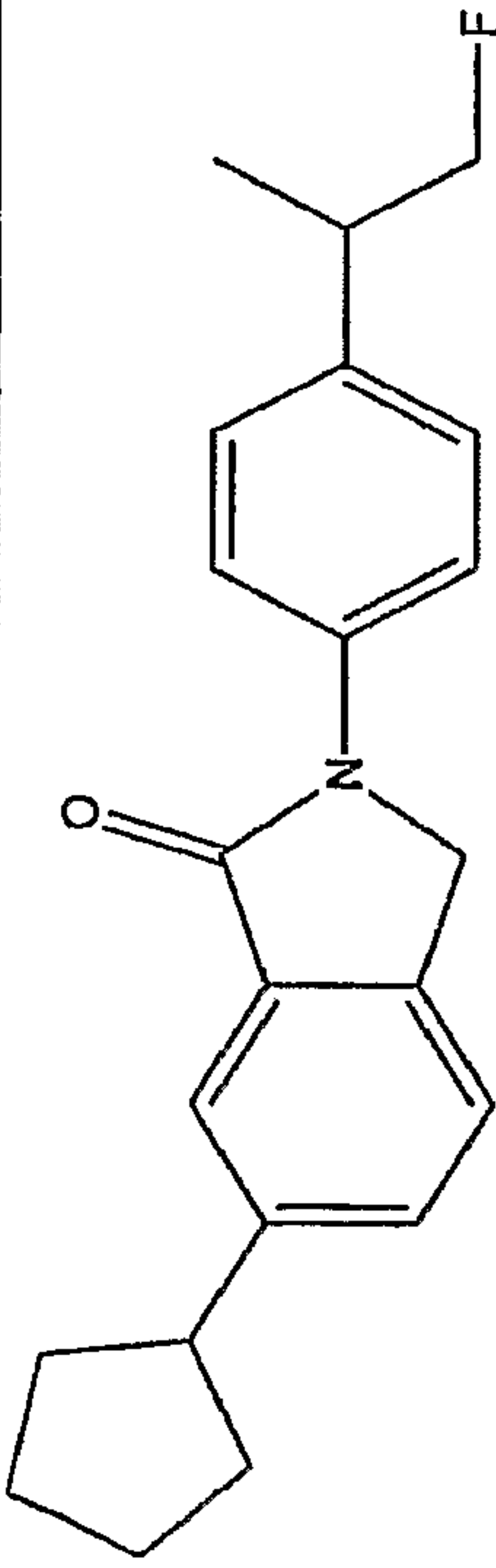
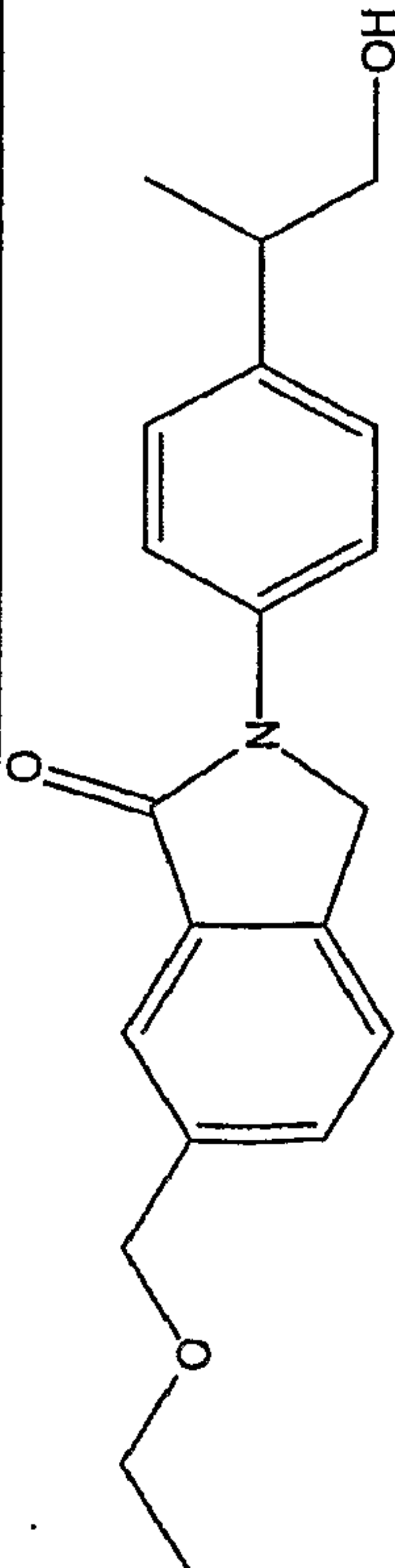
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
263		ALB- 114091	0.699	1.458
264		ALB- 114604	0.303	1.394

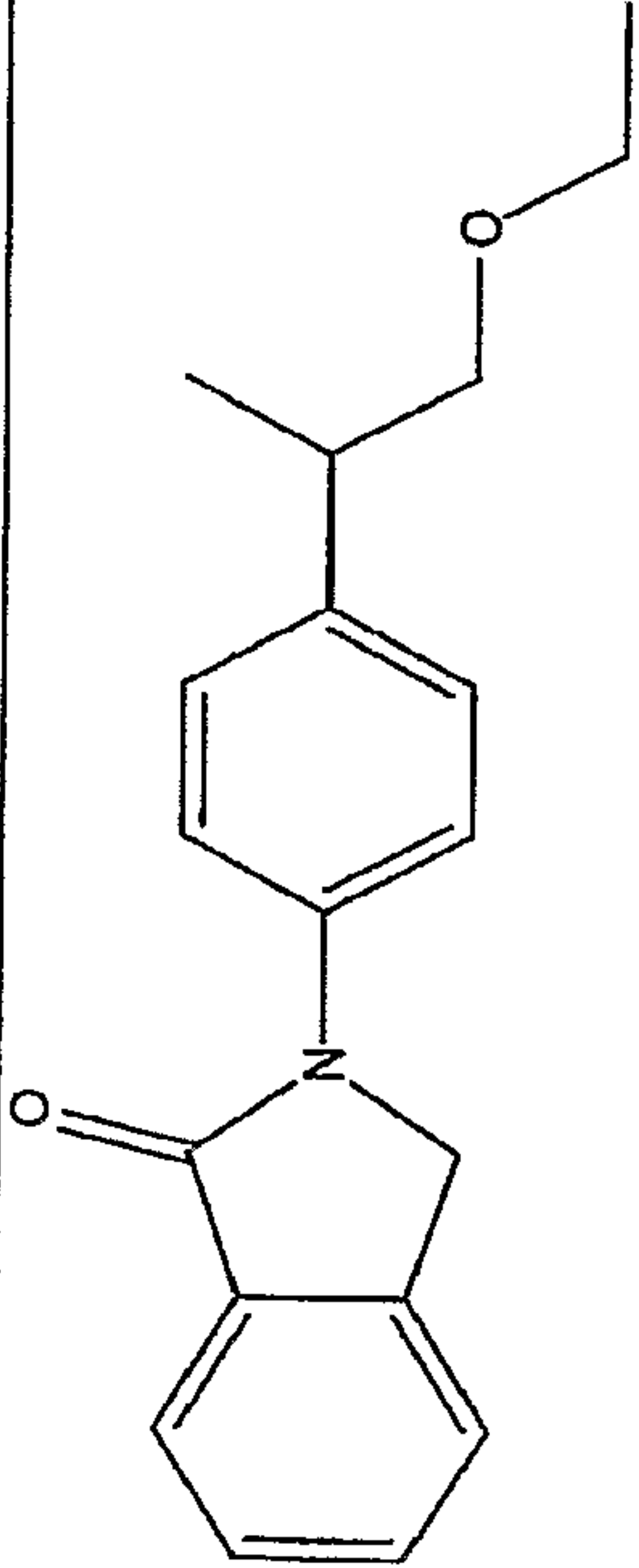
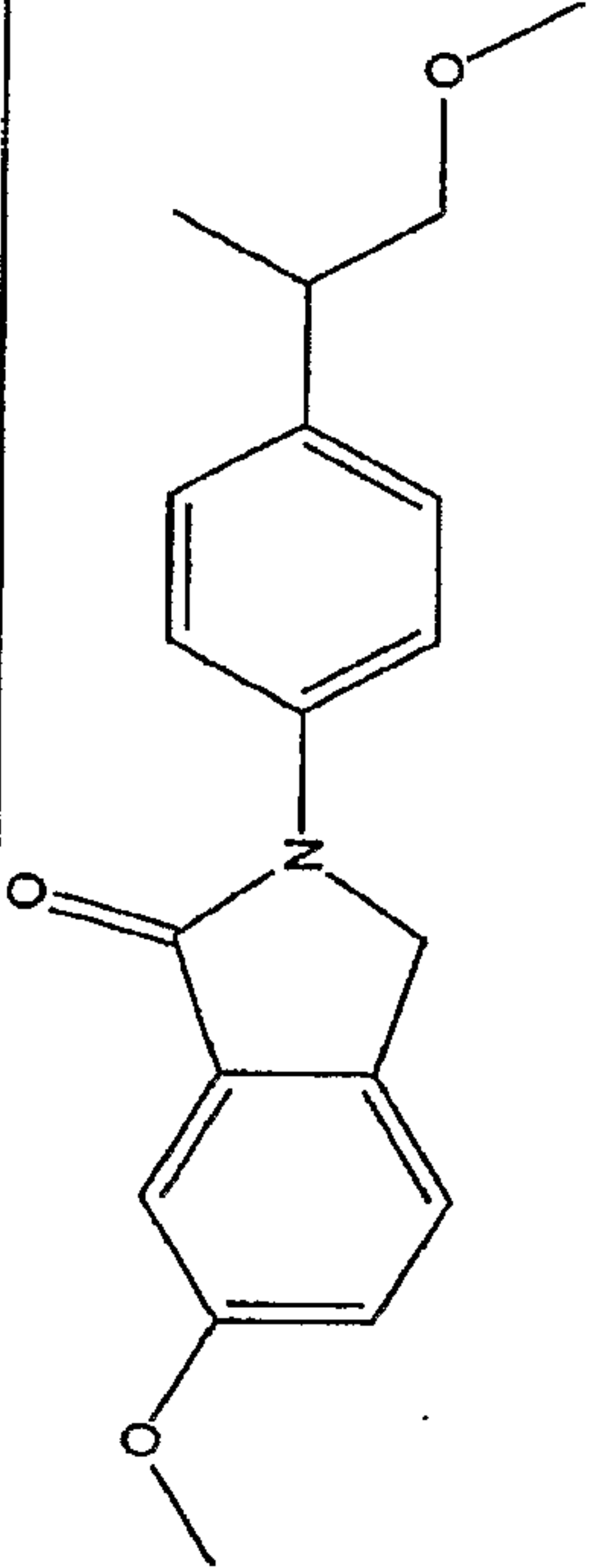
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
265		ALB- 114606	0.181	1.311
266		ALB- 114740	0.822	1.223
267		ALB- 114743	0.448	1.366

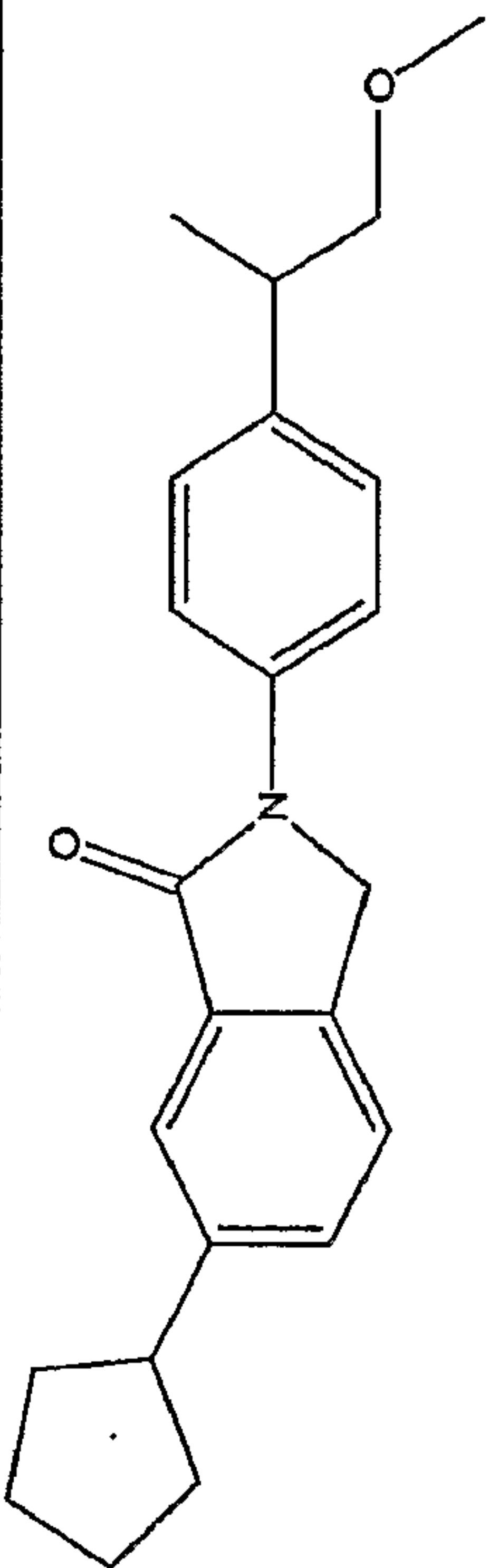
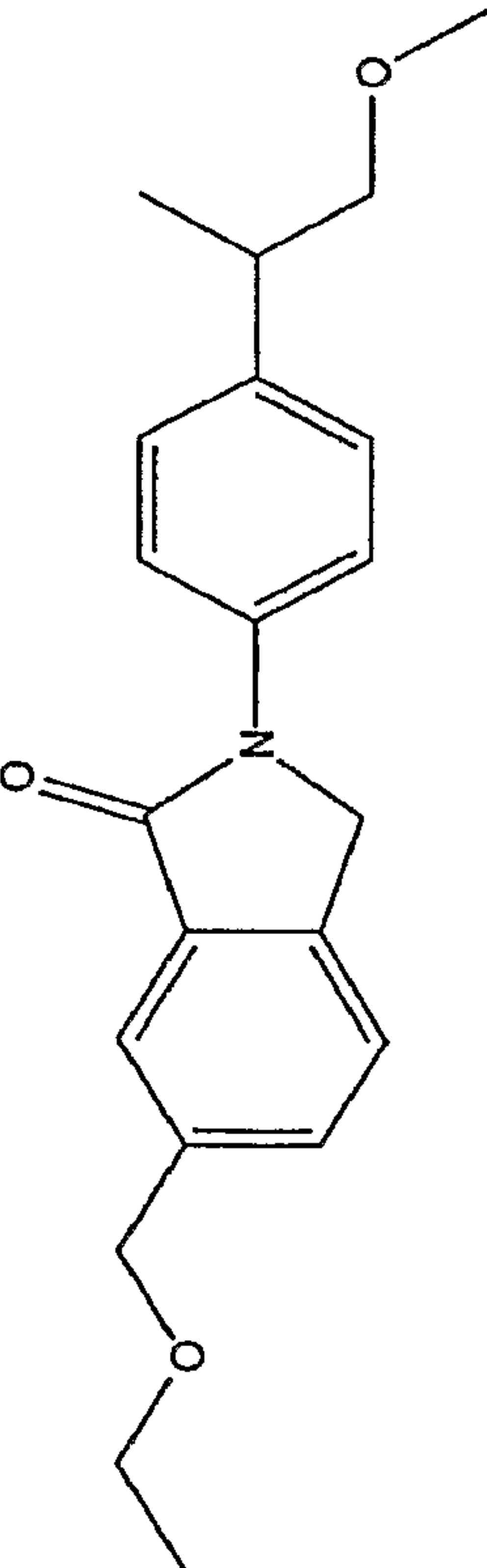
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
268		ALB- 114744		1.179
269		ALB- 114783	0.186	1.372

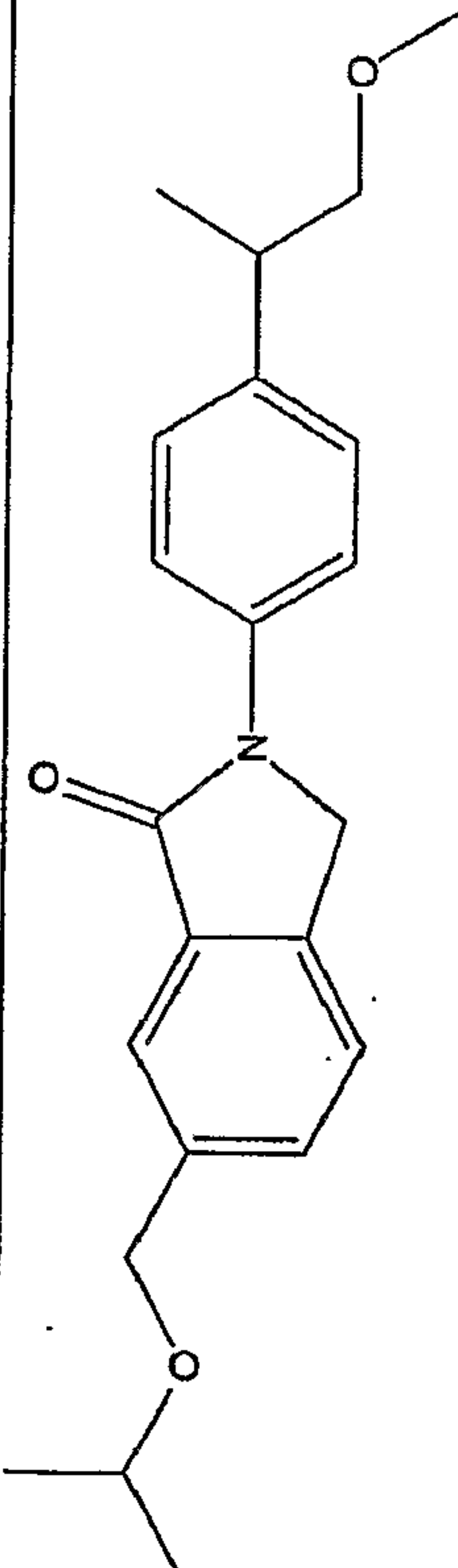
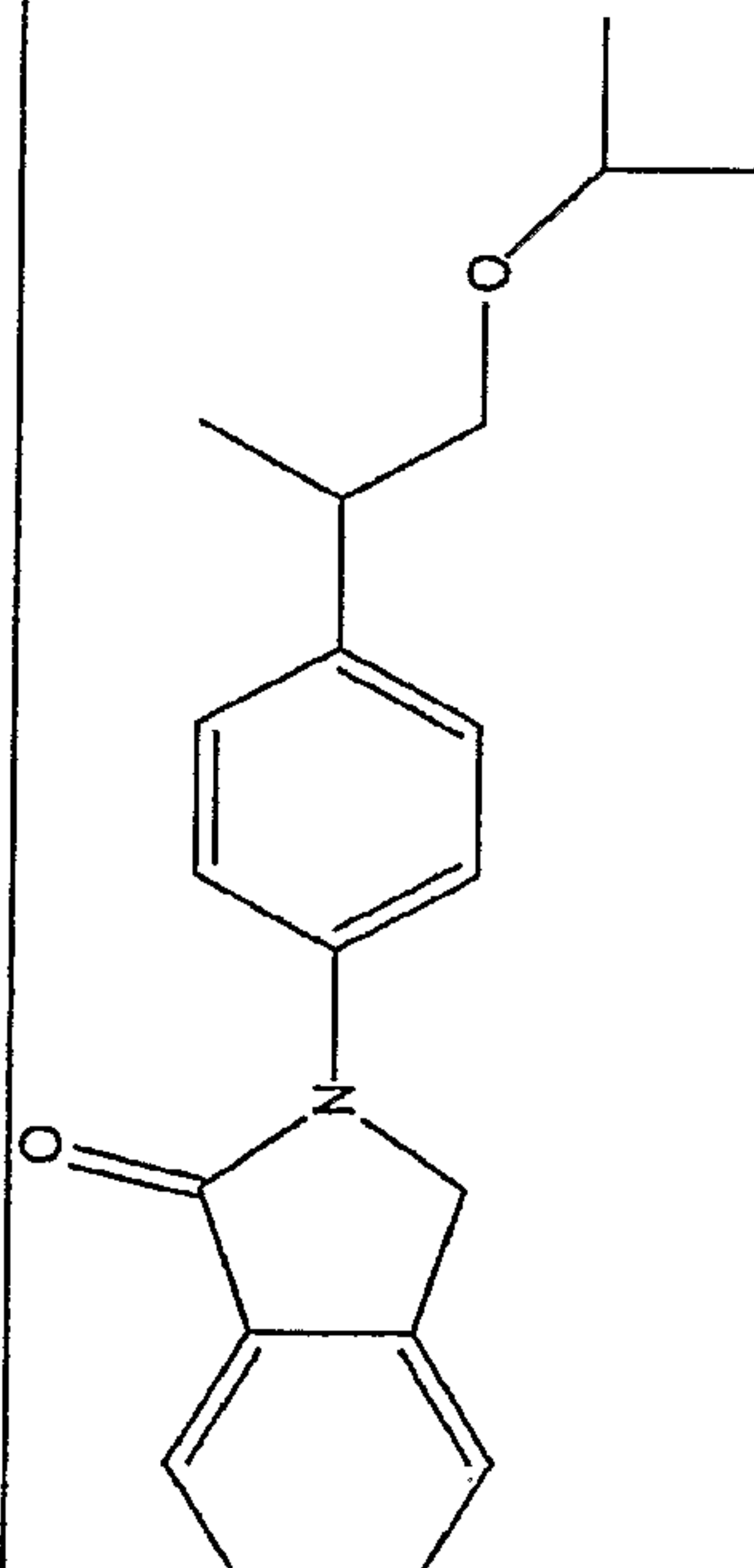
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
270		ALB- 114845		1.151
271		ALB- 114846	0.493	1.296

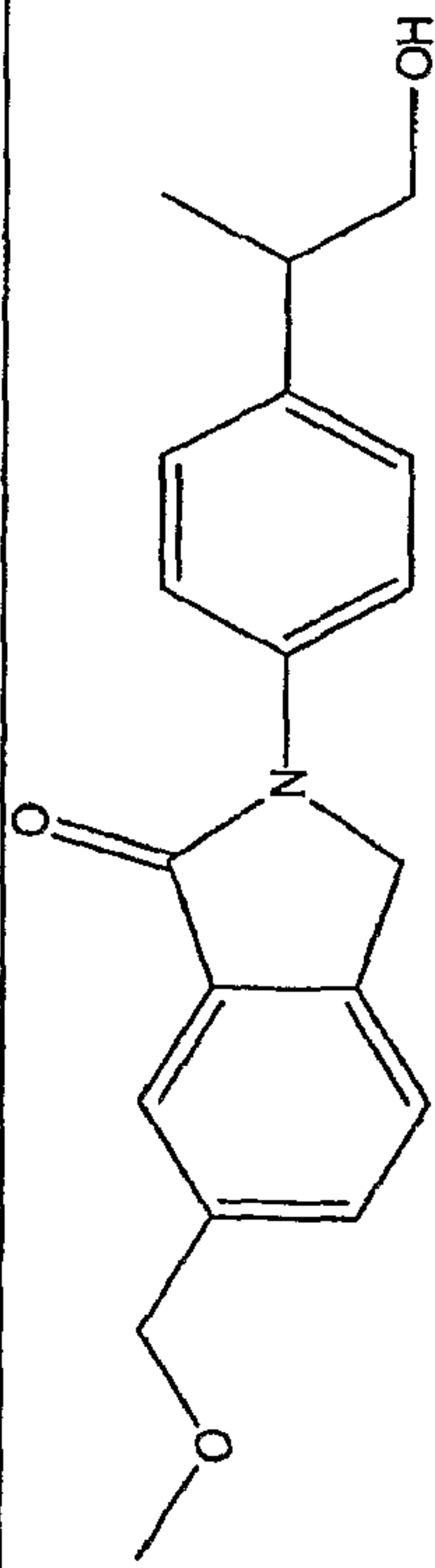
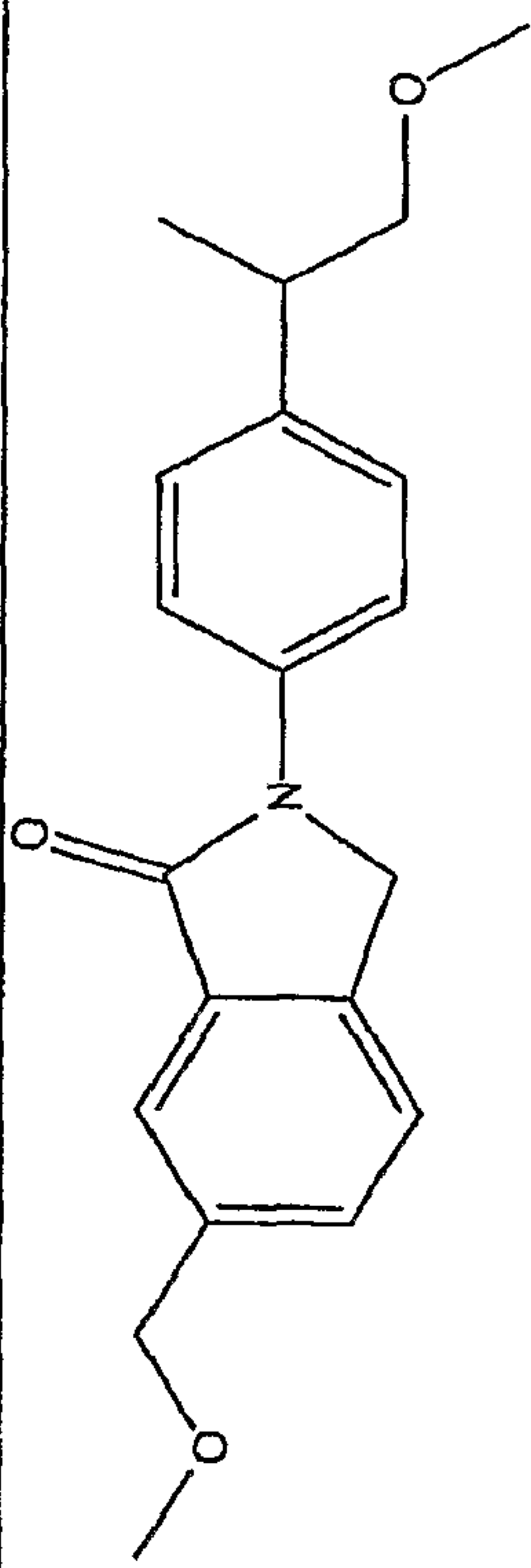
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
272		ALB- 114847	0.977	1.225
273		ALB- 114935	0.977	1.257

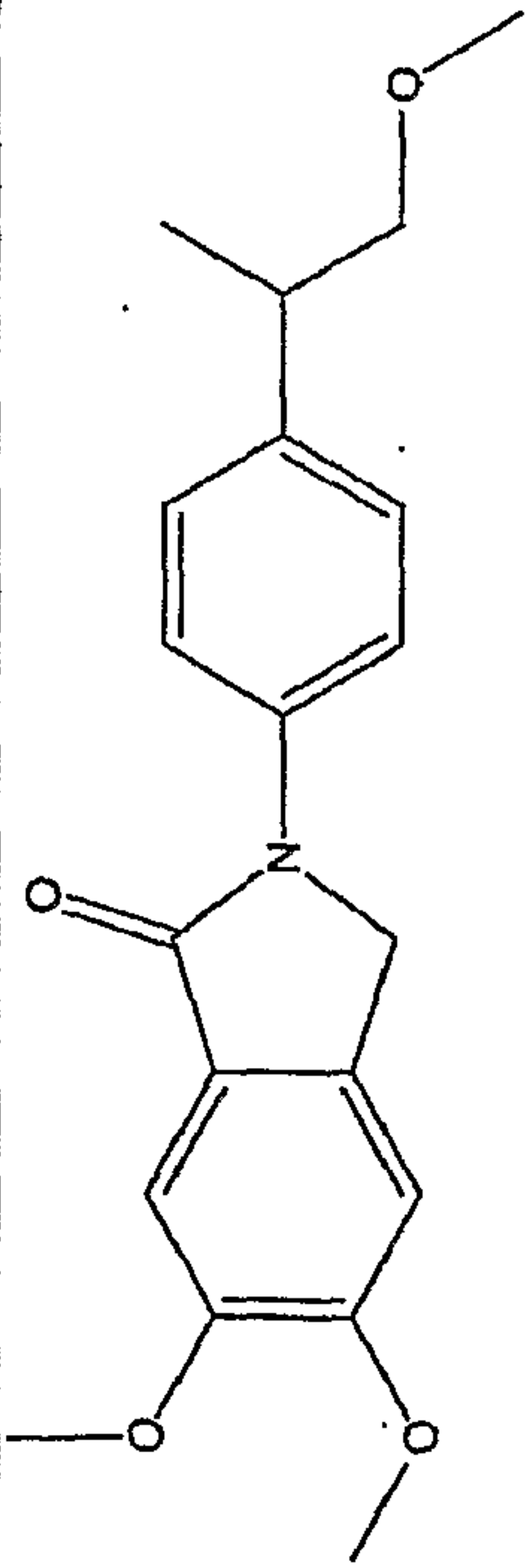
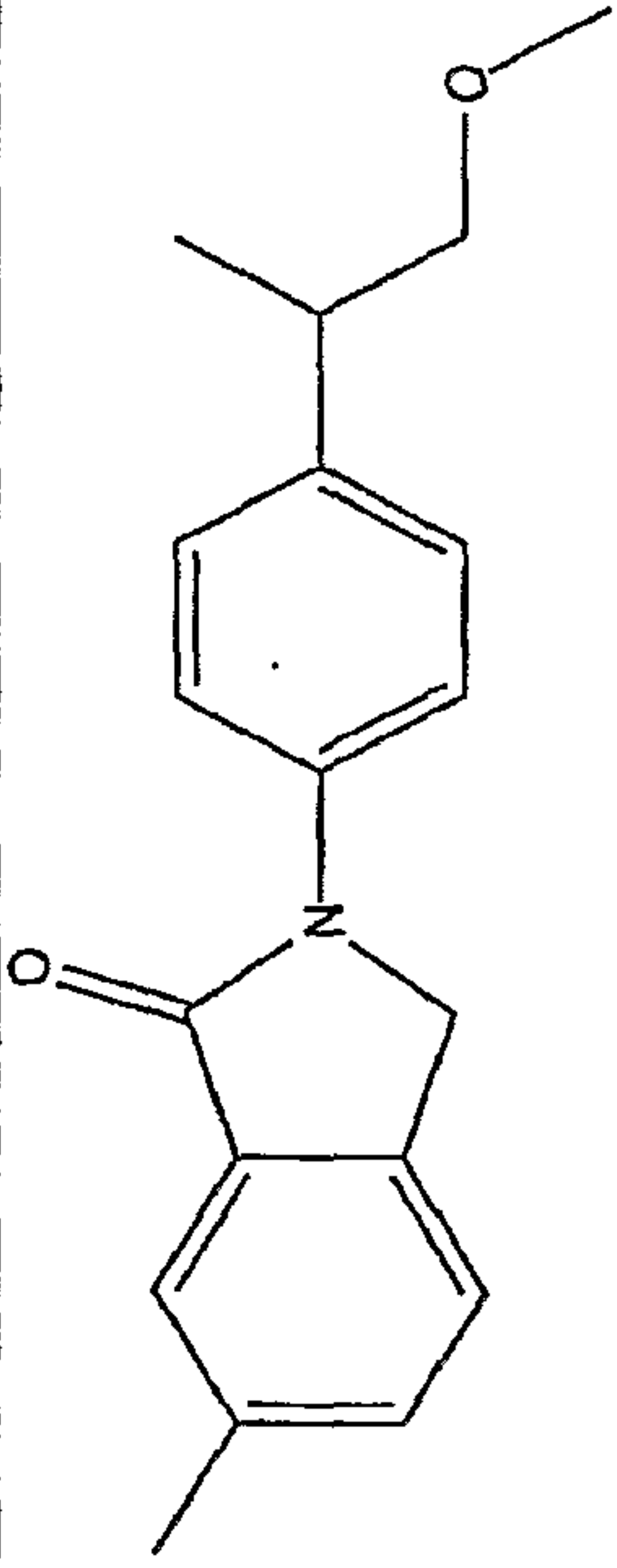
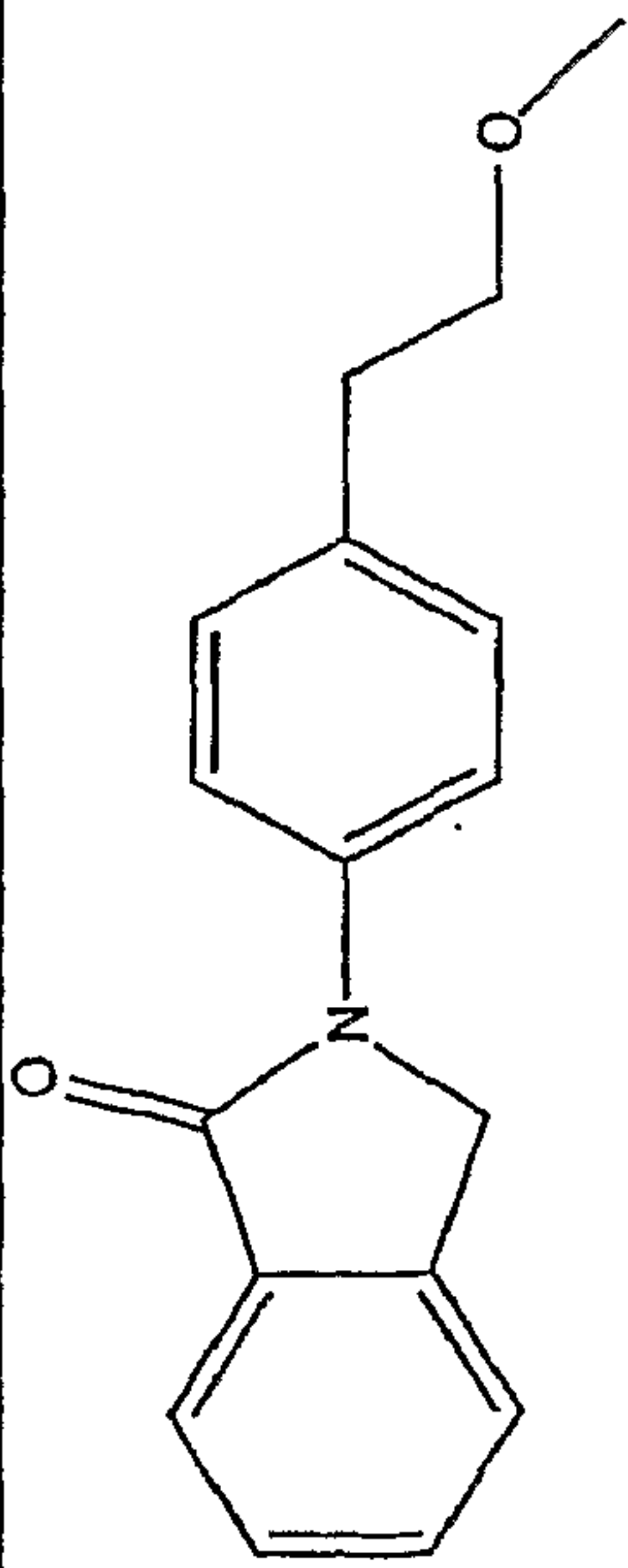
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
274		ALB- 114941	0.299	1.351
275		ALB- 114942	0.217	1.331

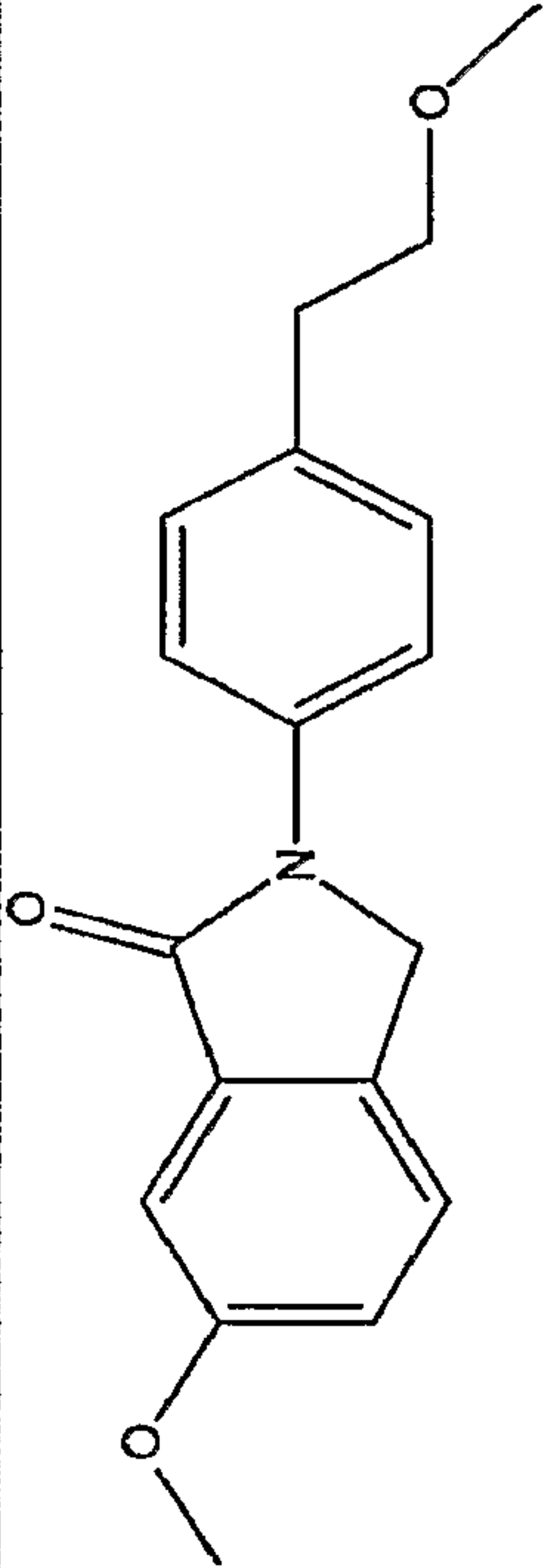
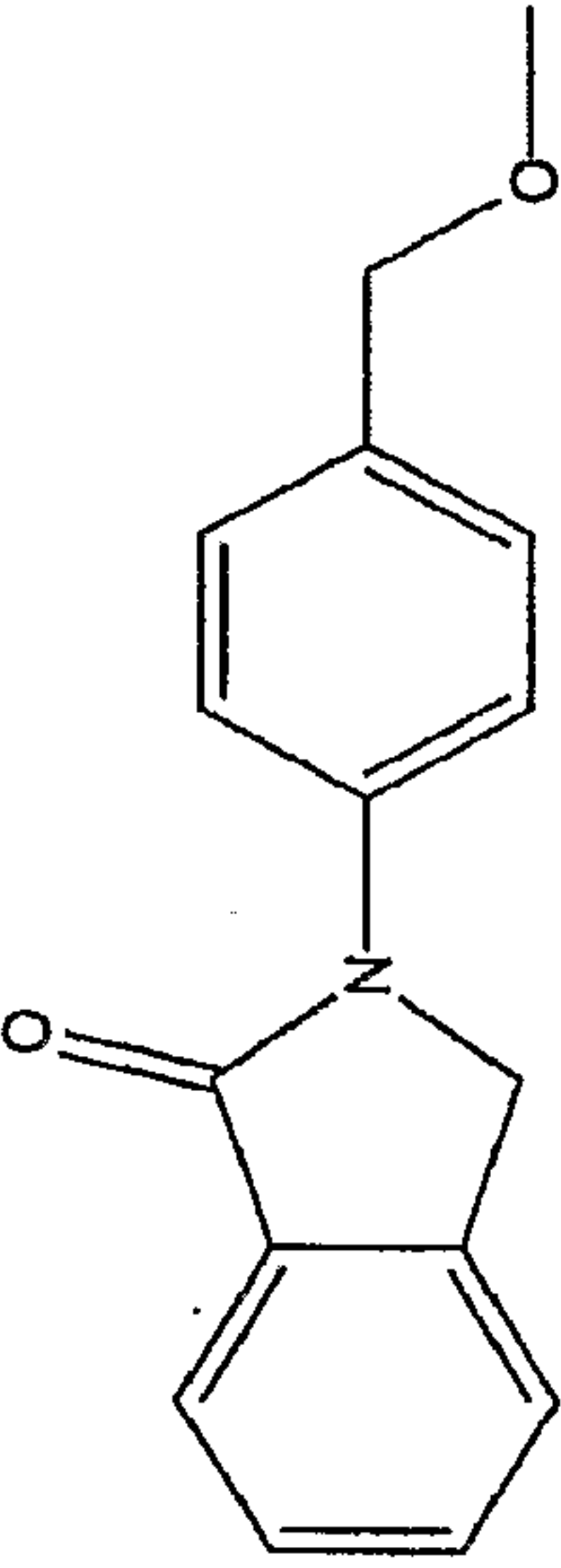
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
276		ALB- 114943	1.315	1.348
277		ALB- 115072	0.032	1.28
278		ALB- 115073		1.191

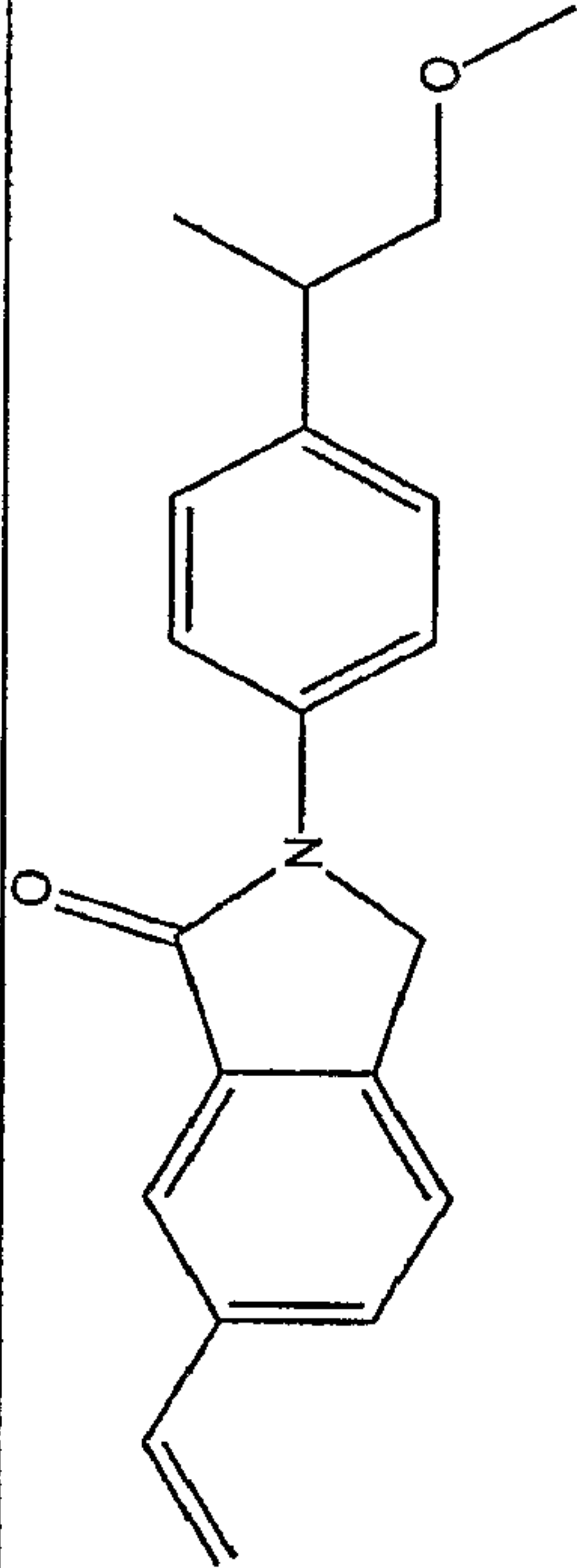
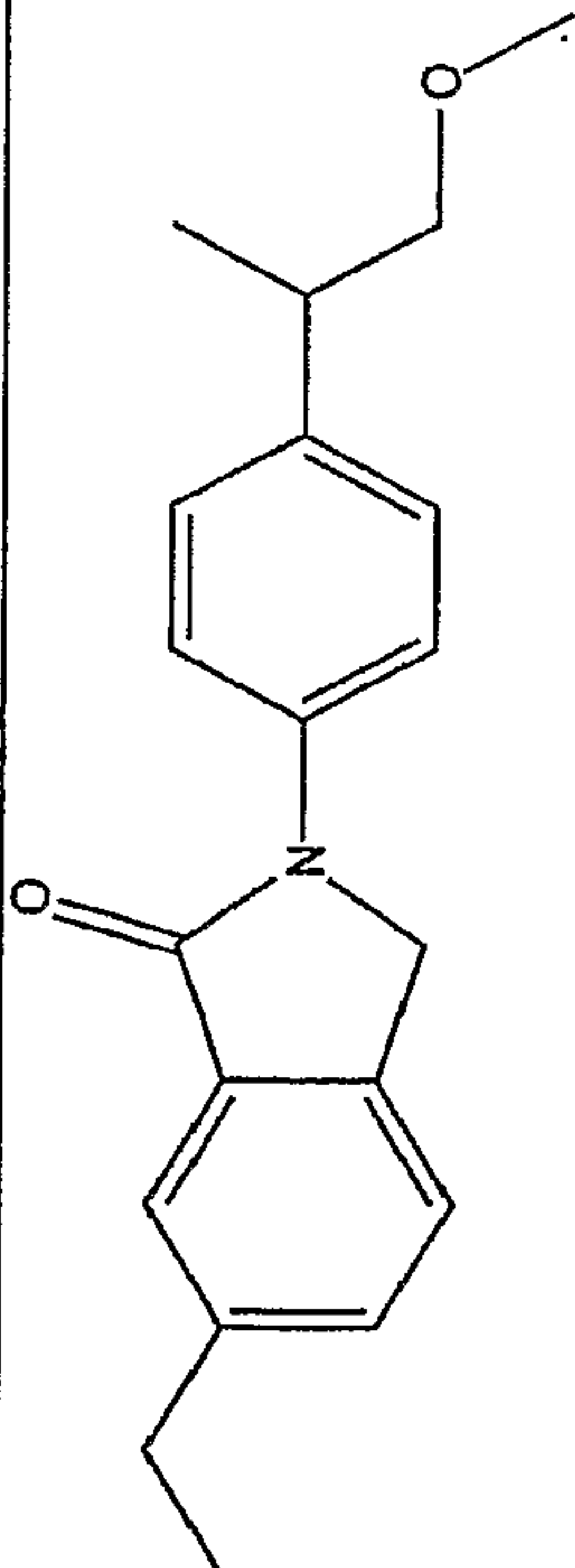
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
279		ALB- 115217		1.259
280		ALB- 115323		1.104

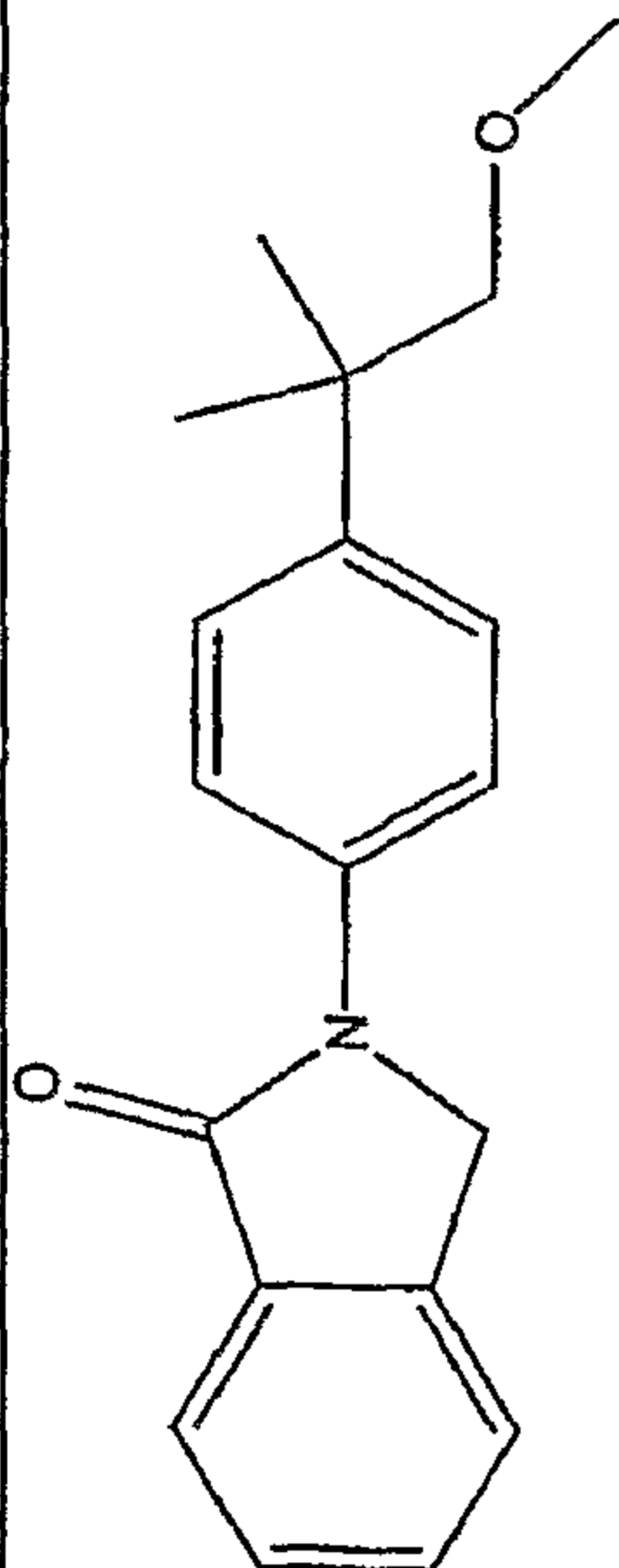
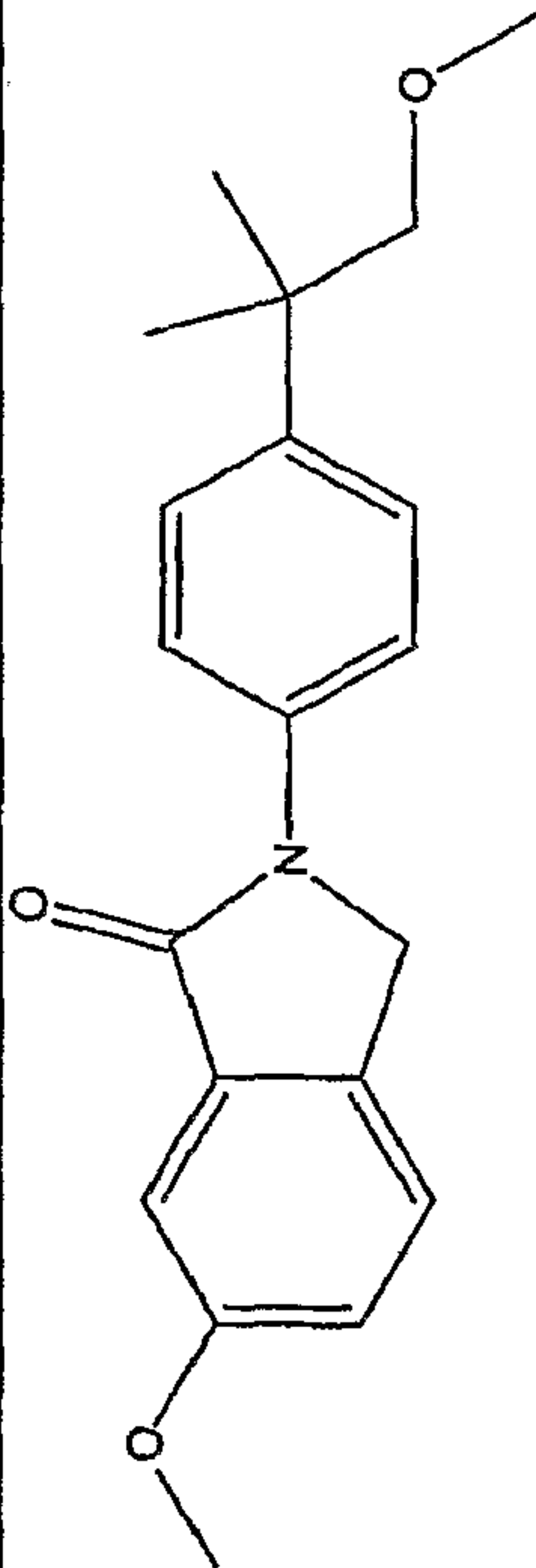
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
281		ALB- 115327	0.076	1.43
282		ALB- 115328	0.298	1.497

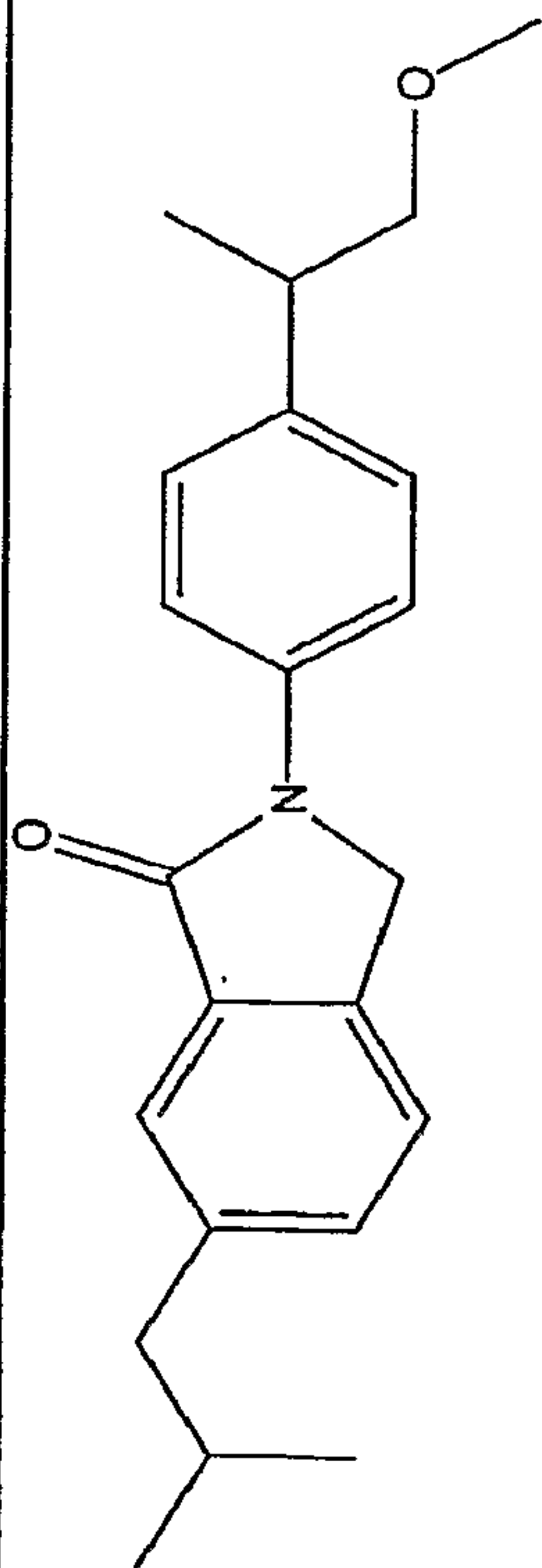
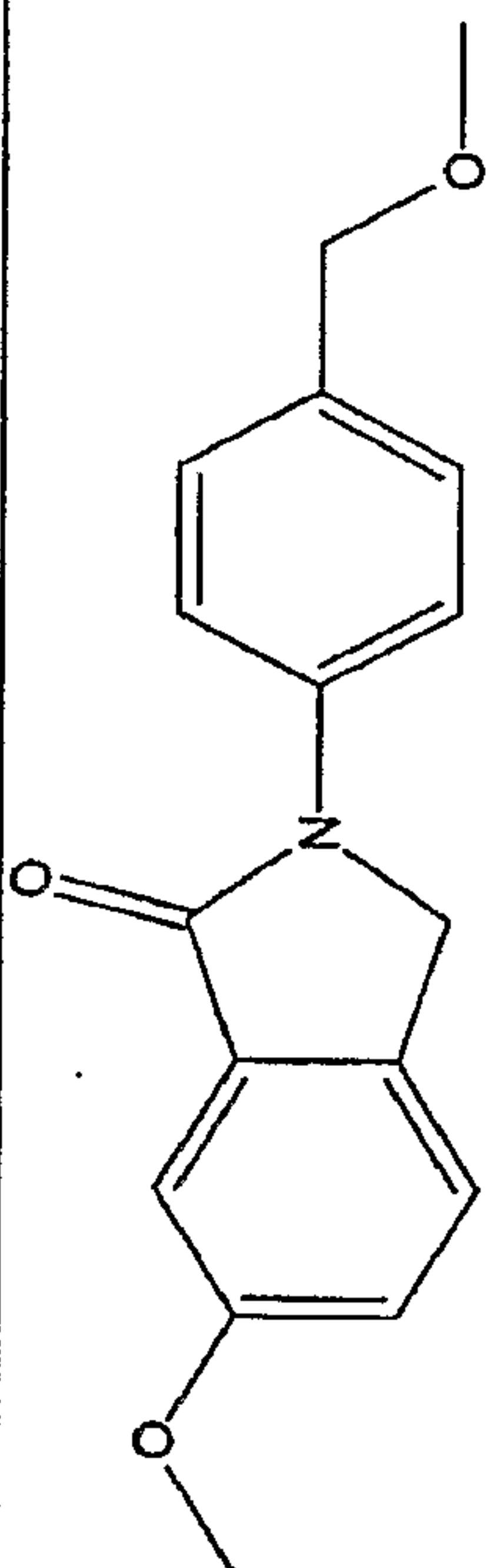
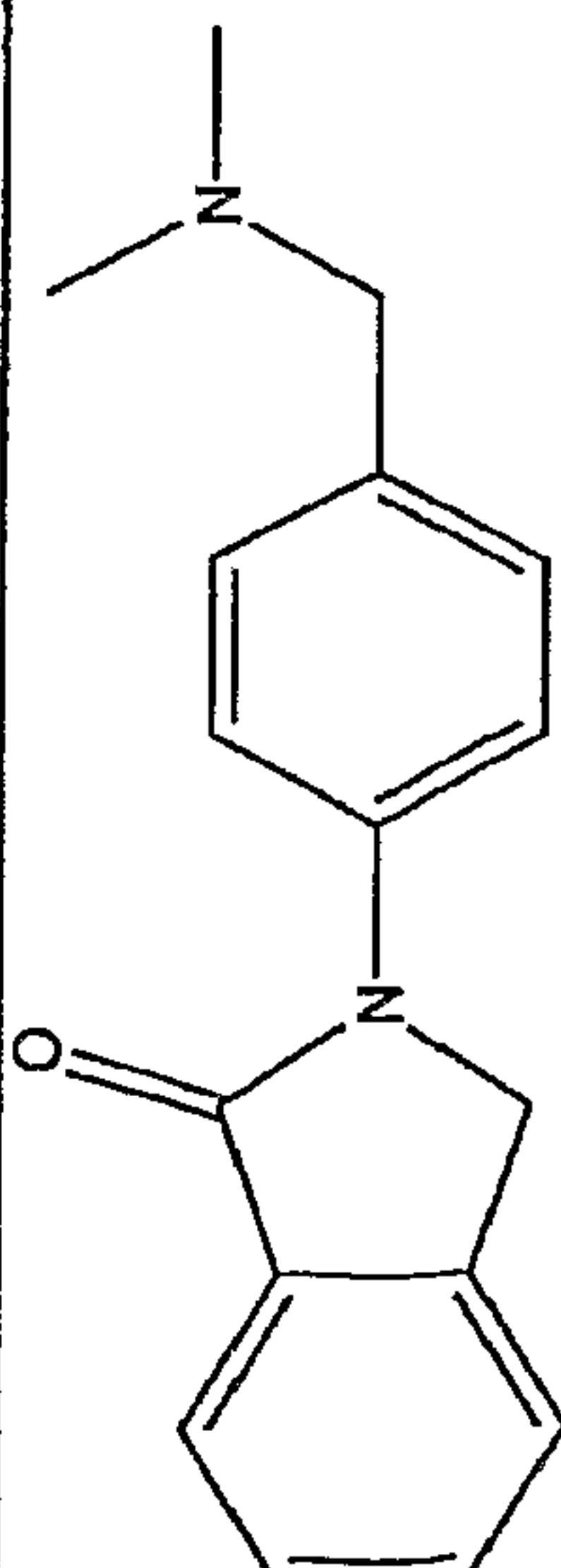
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
283		ALB- 115427		1.311
284		ALB- 115706	0.66	1.259

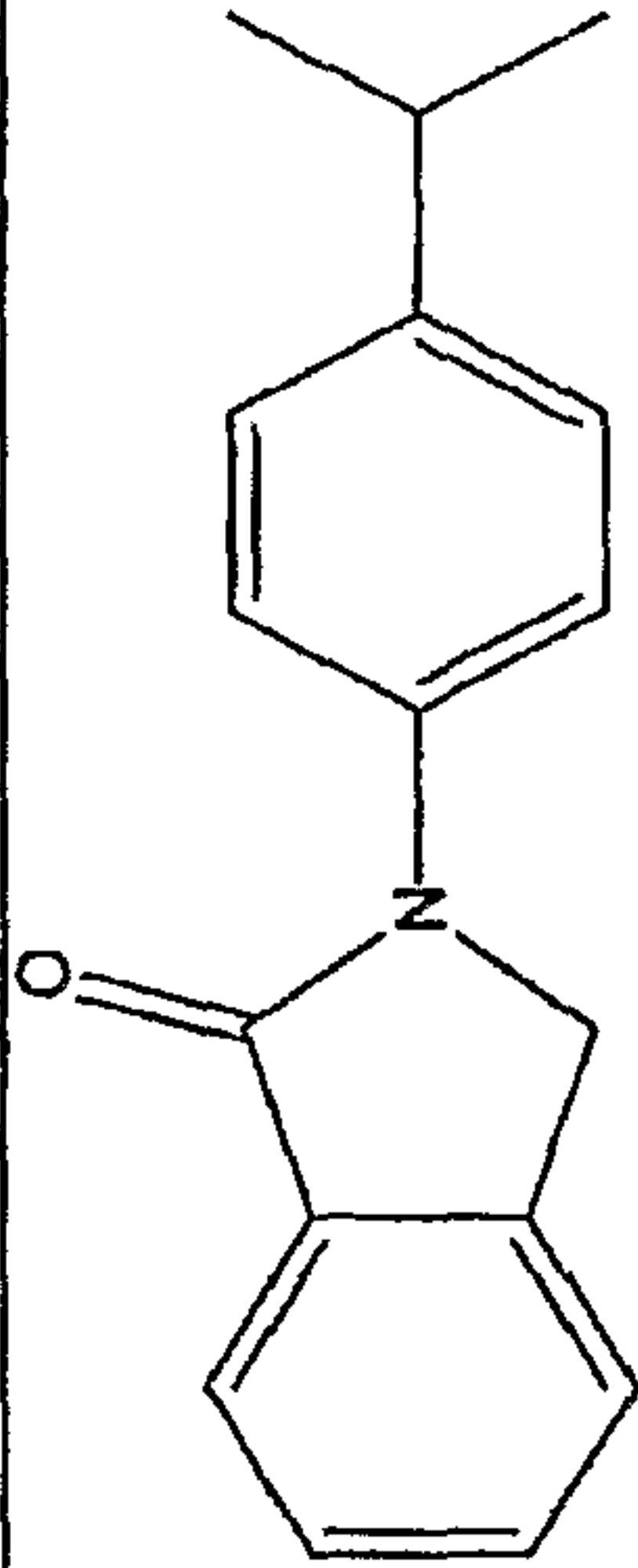
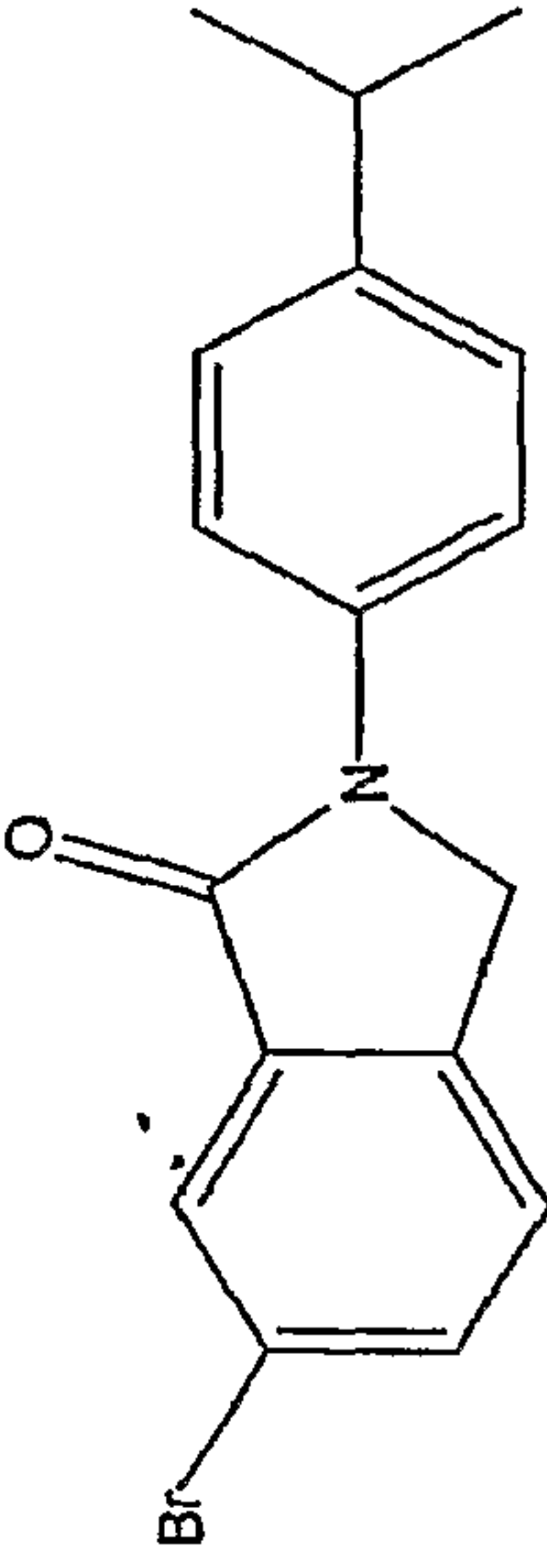
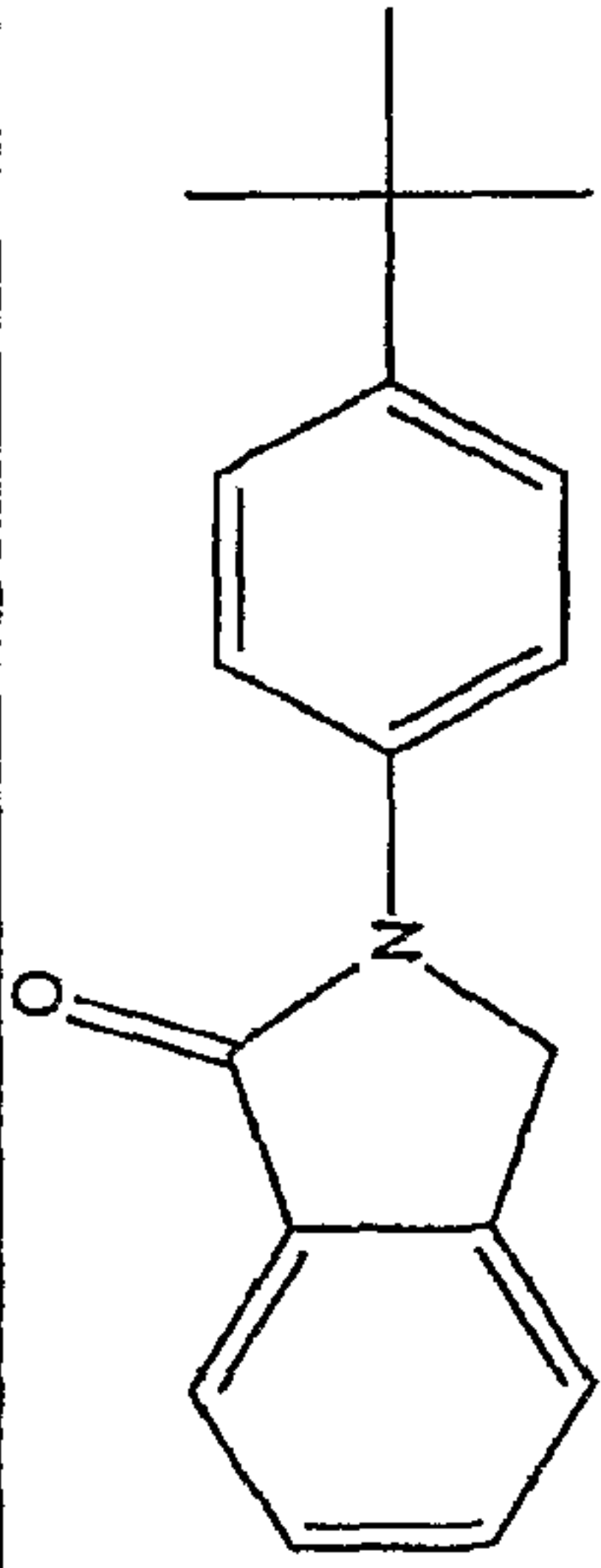
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
285		ALB- 115976	0.179	1.288
286		ALB- 116067		1.238
287		ALB- 116255	0.05	1.095

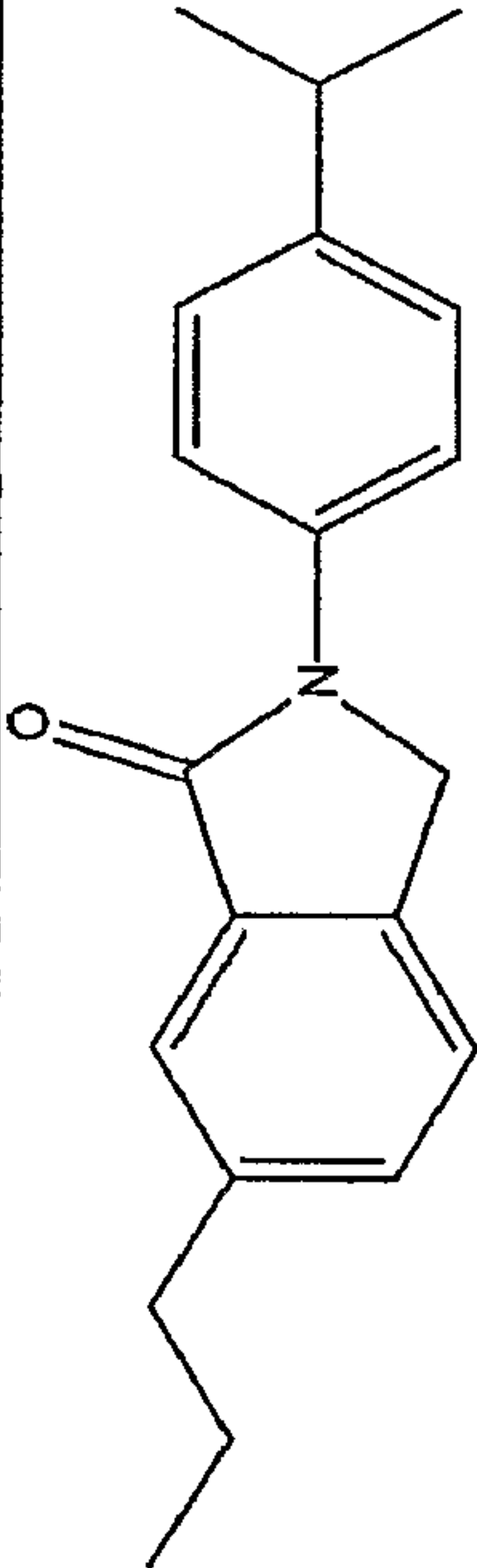
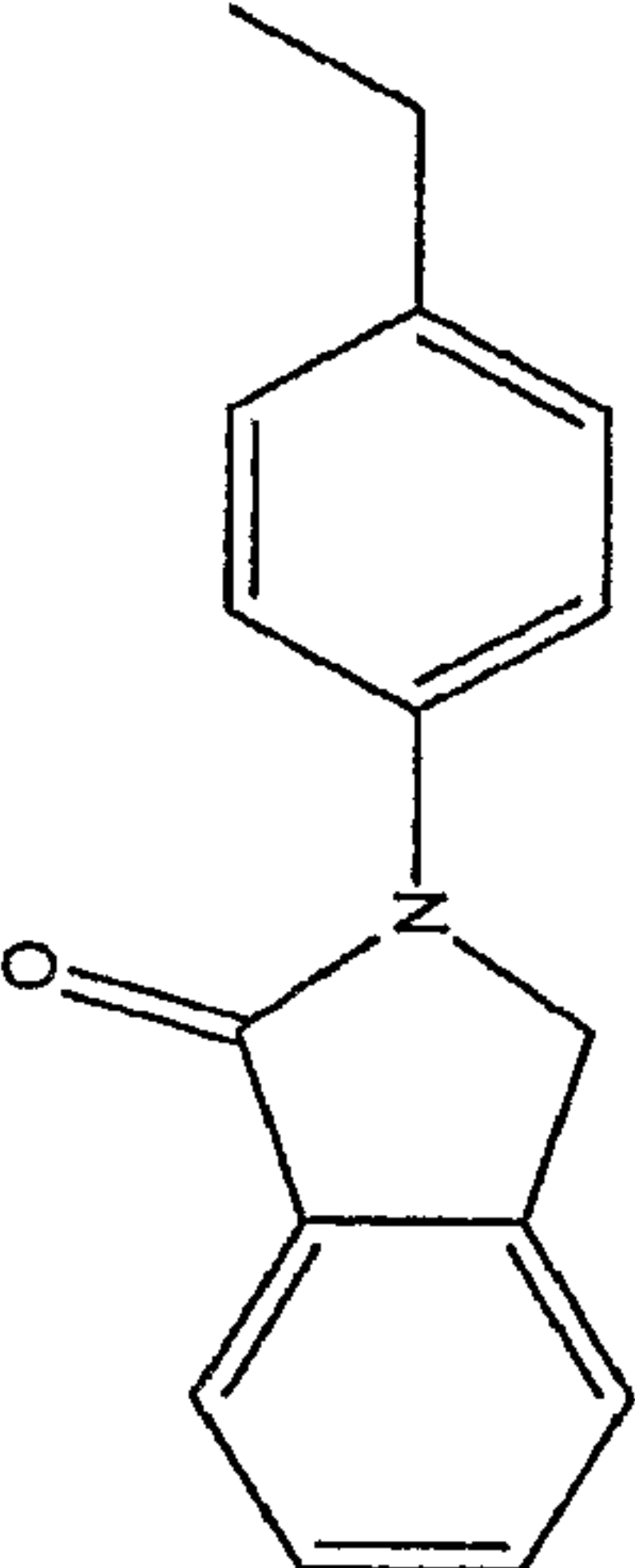
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
288		ALB- 114274	0.052	1.397
289		ALB- 114901	0.193	1.521
290		ALB- 114936	0.131	1.41

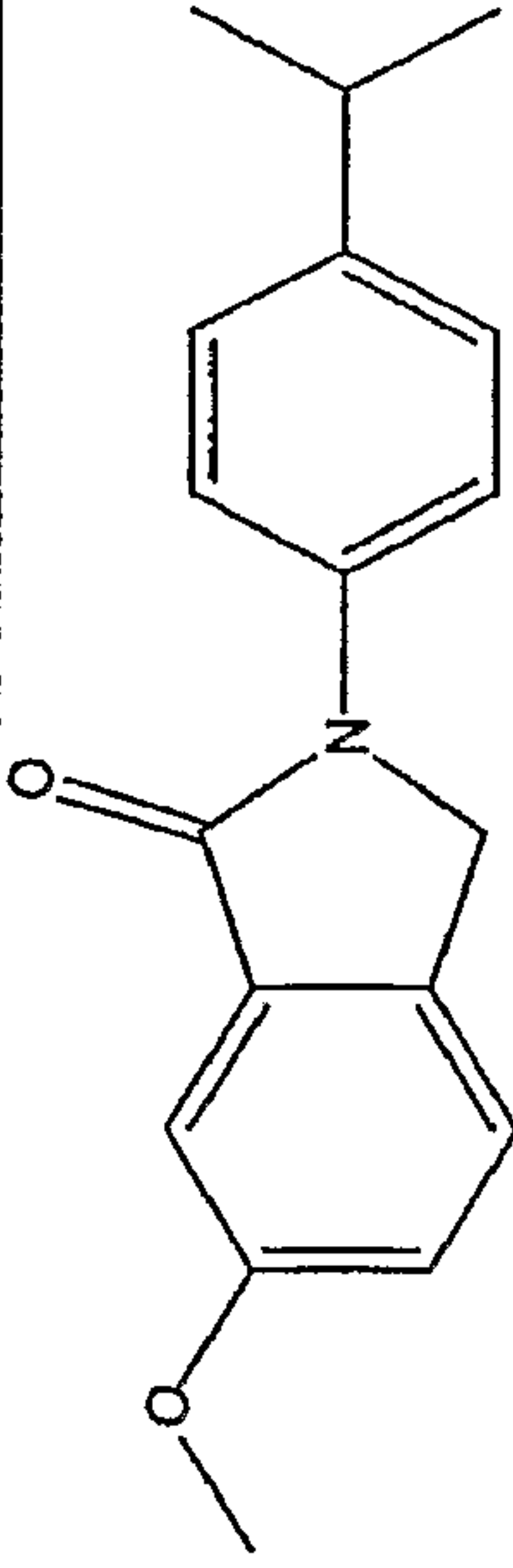
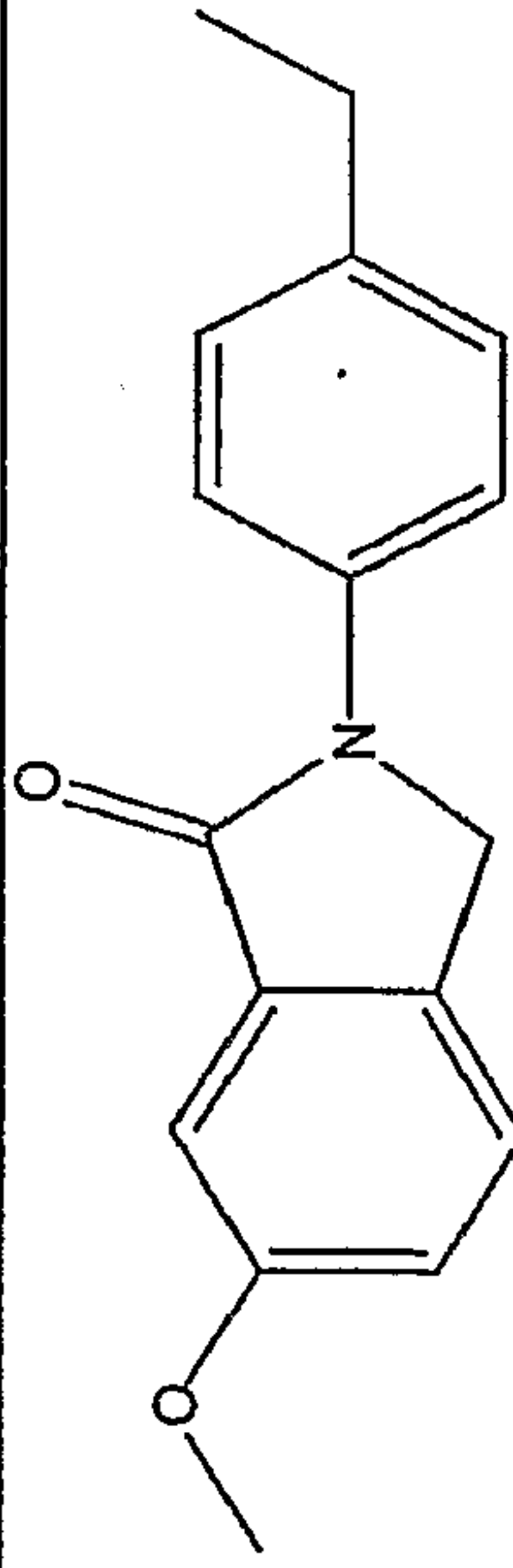
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
291		ALB- 114939	0.298	1.431
292		ALB- 114940	0.097	1.365

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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
293		ALB- 115069	0.081	1.496
294		ALB- 115085	0.058	1.468

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Table 1

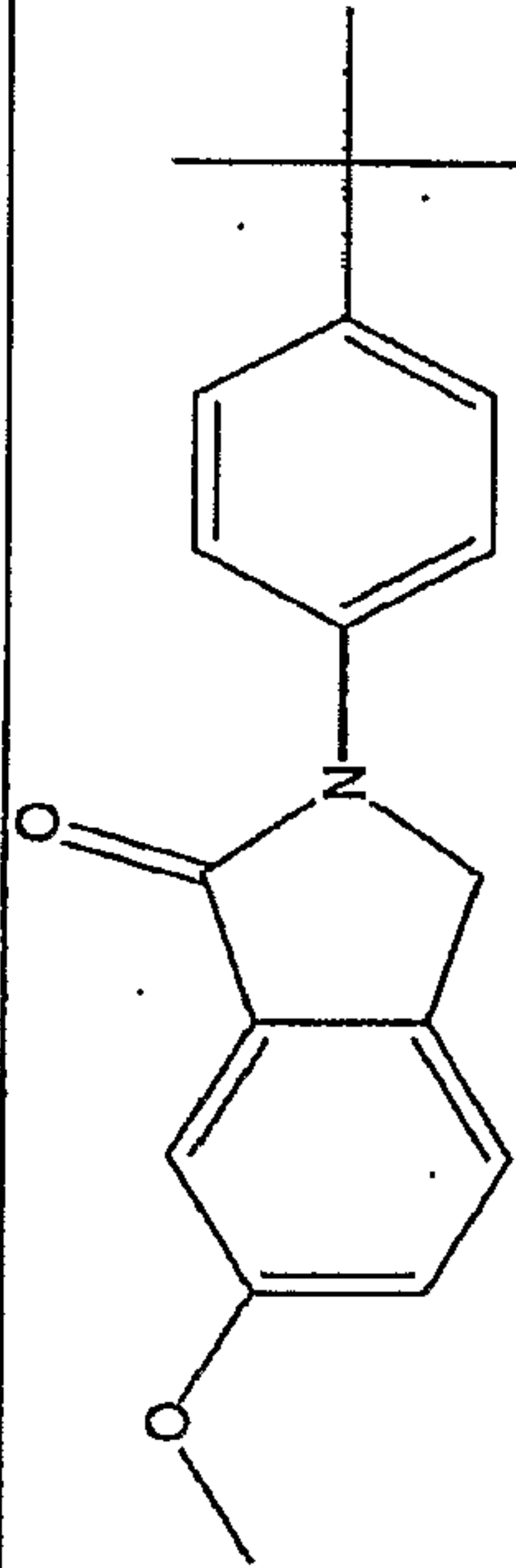
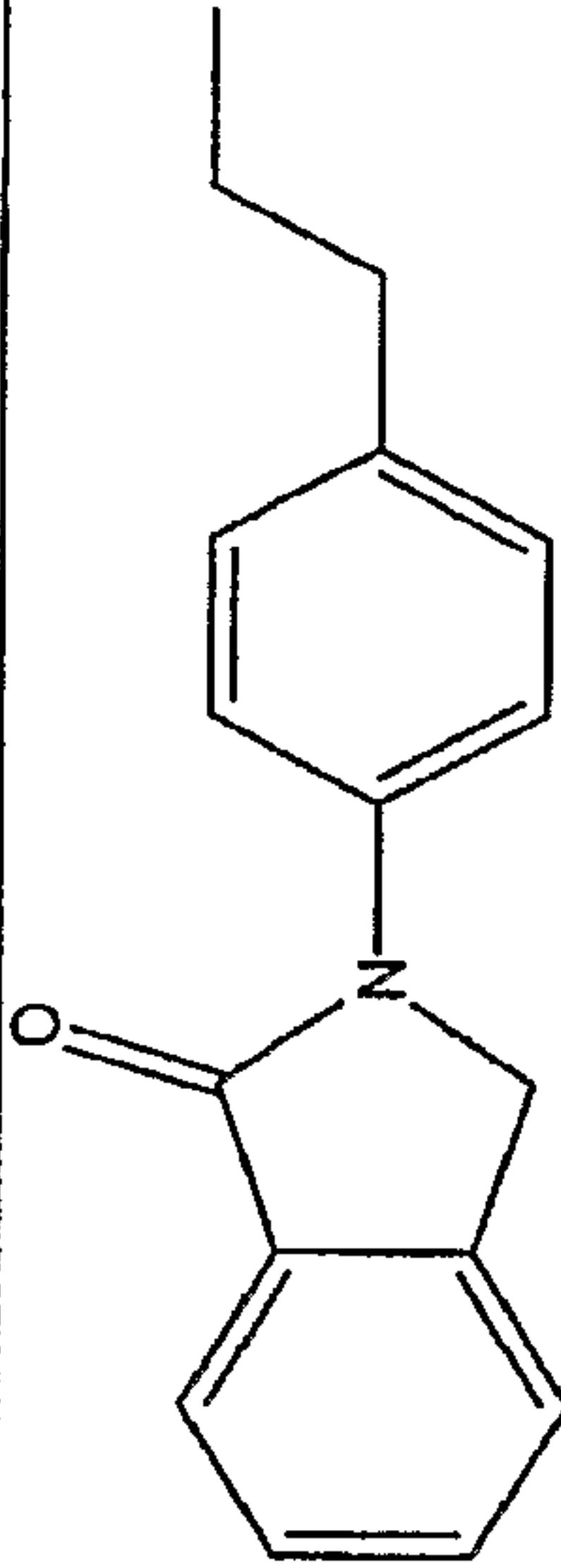
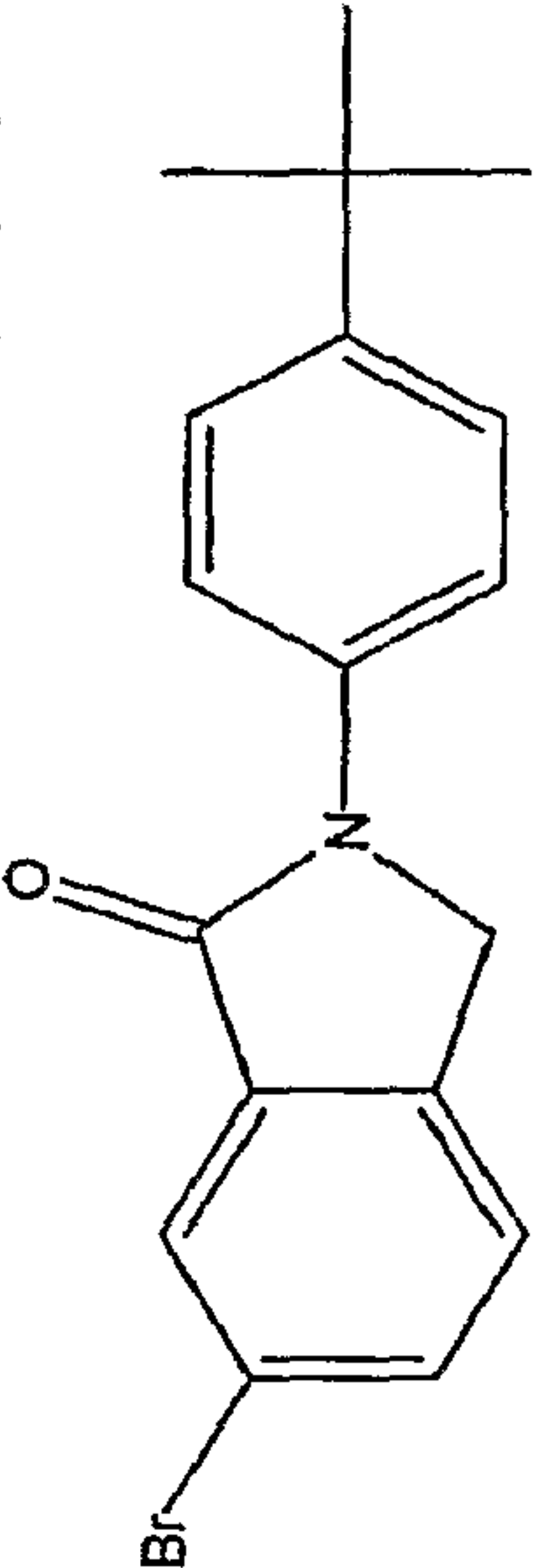
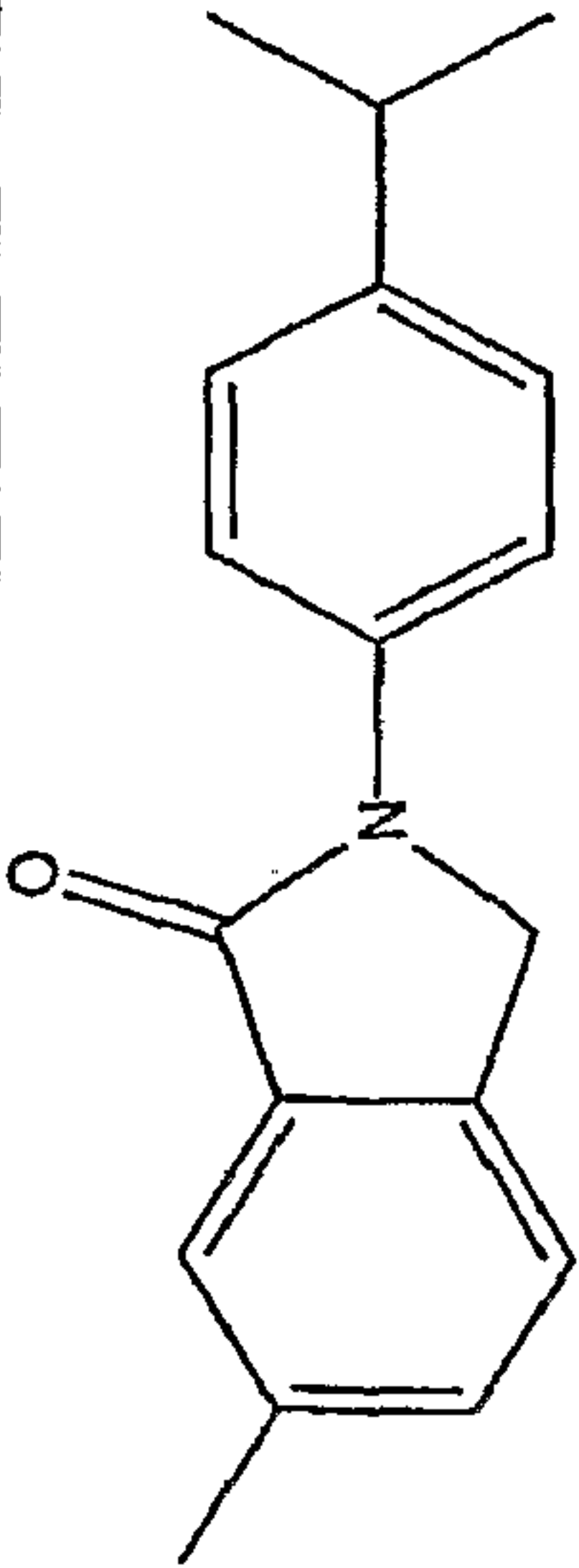
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			Avg EC50 (uM)	Avg MaxFold Increase
295		ALB- 115210	0.324	1.468
296		ALB- 115499	0.083	1.274

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
297		ALB- 115583	0.184	1.368
298		ALB- 115586	0.097	1.325

185

Table 1

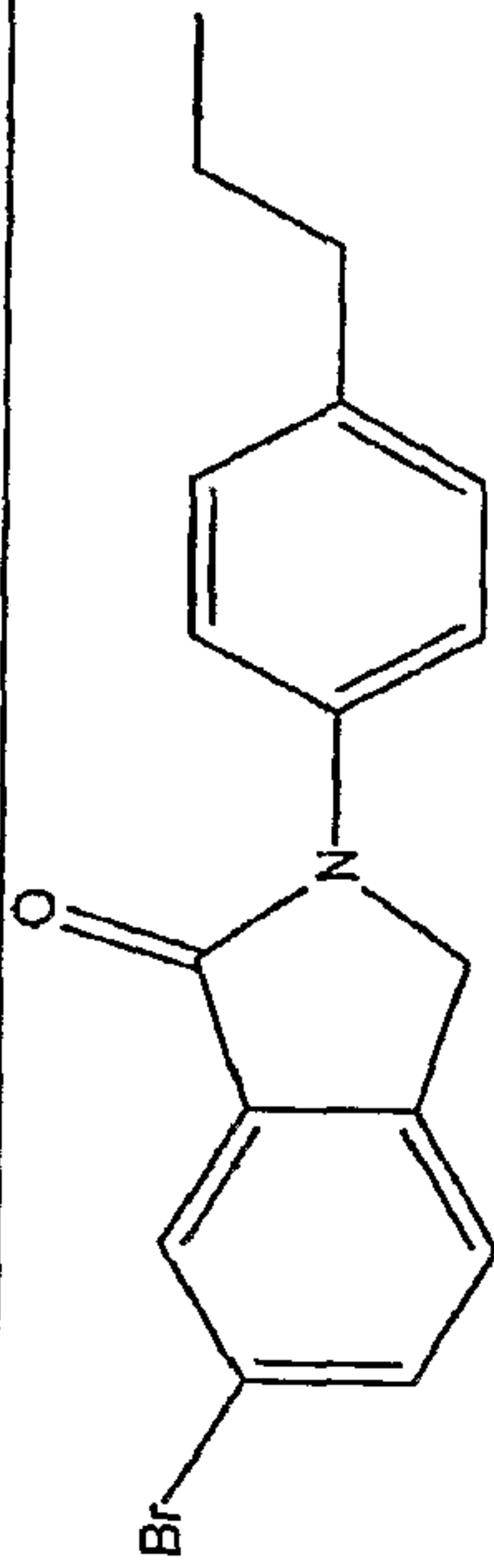
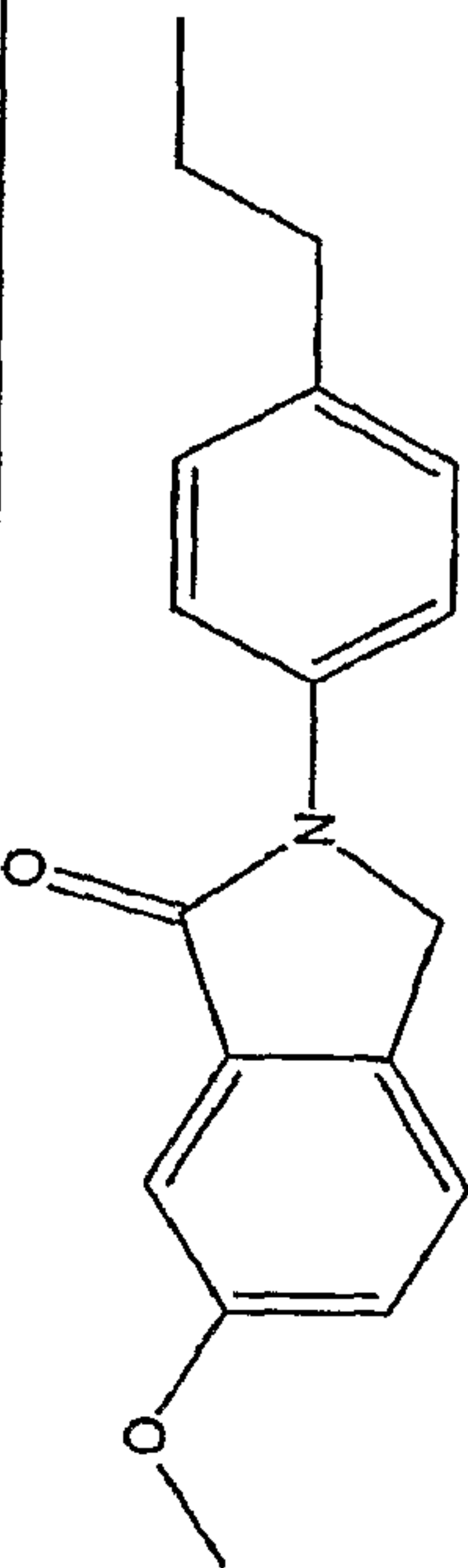
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
299		ALB- 115589	0.143	1.394
300		ALB- 115708		1.103

Table 1

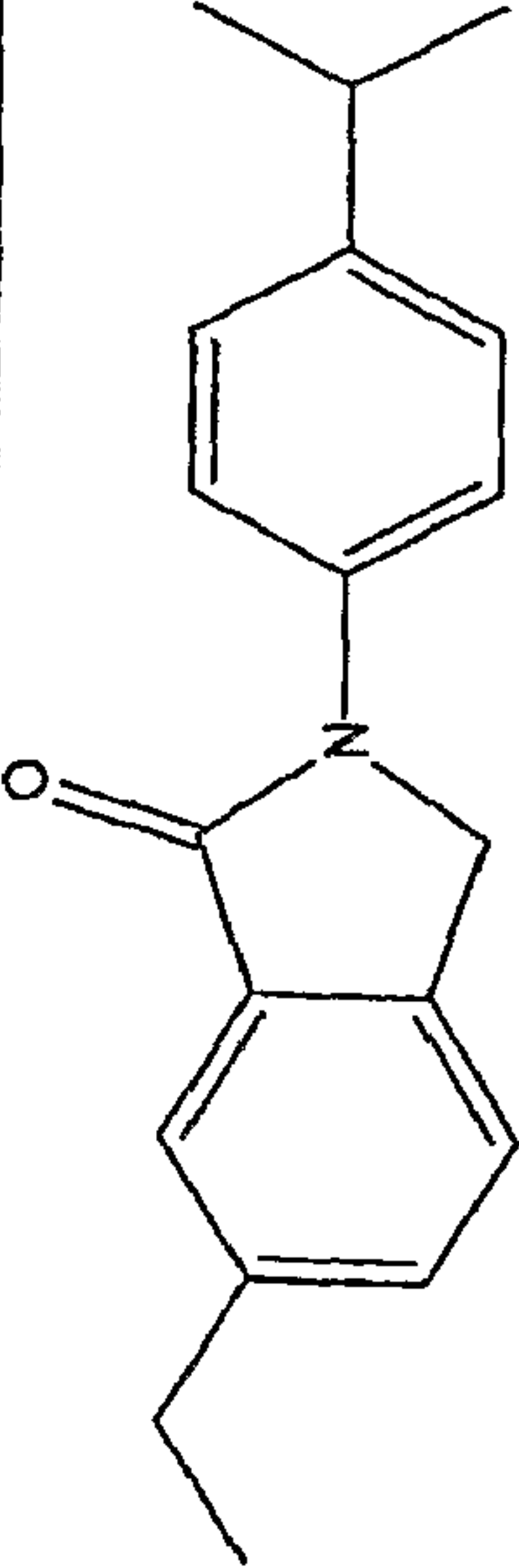
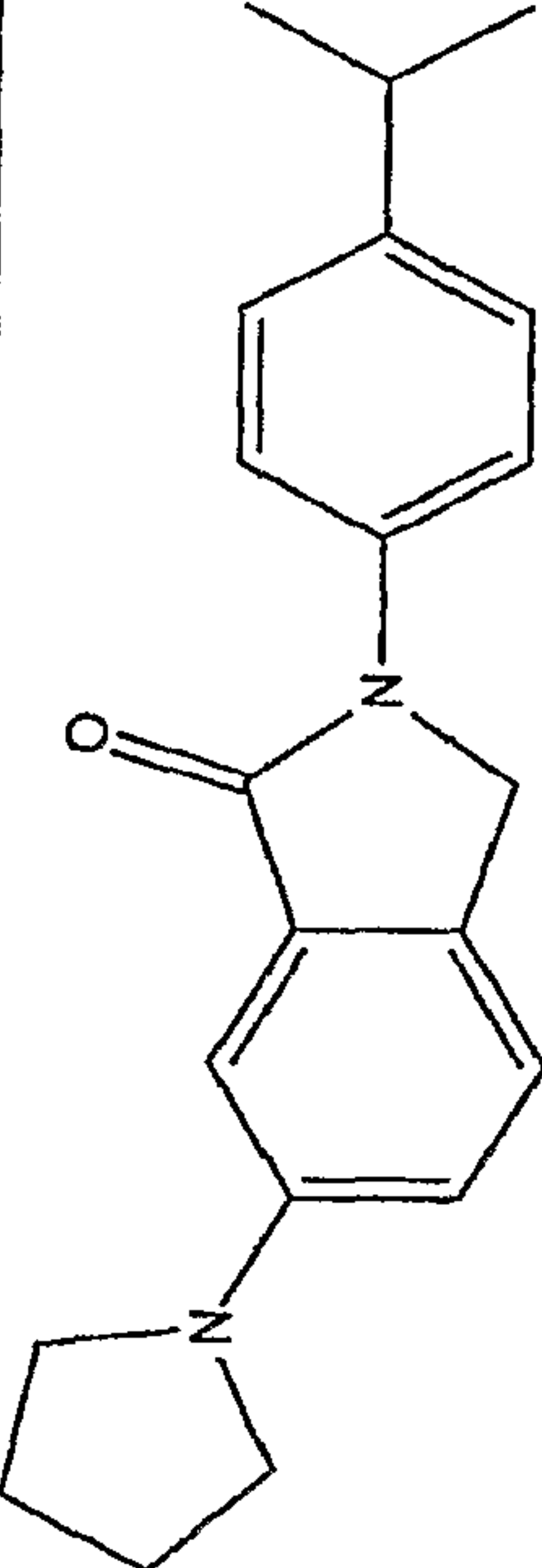
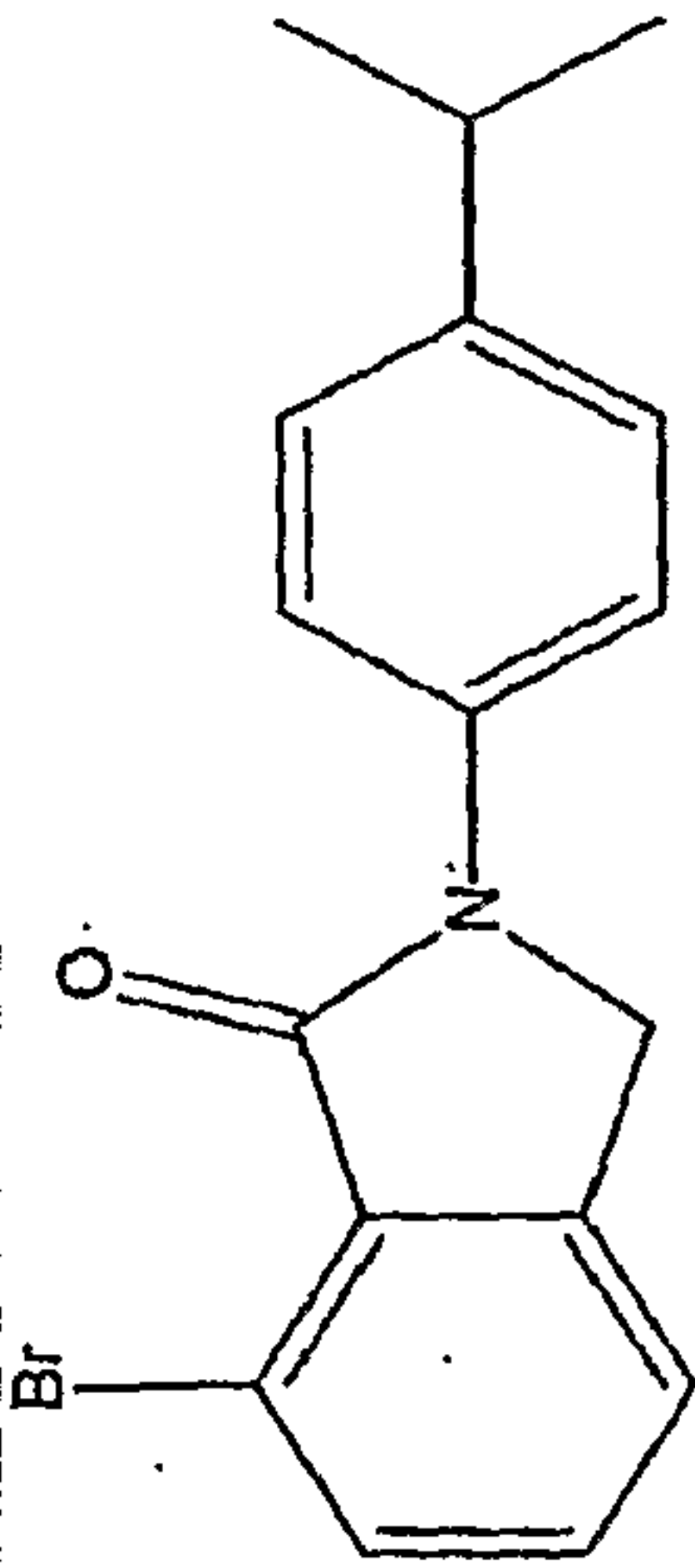
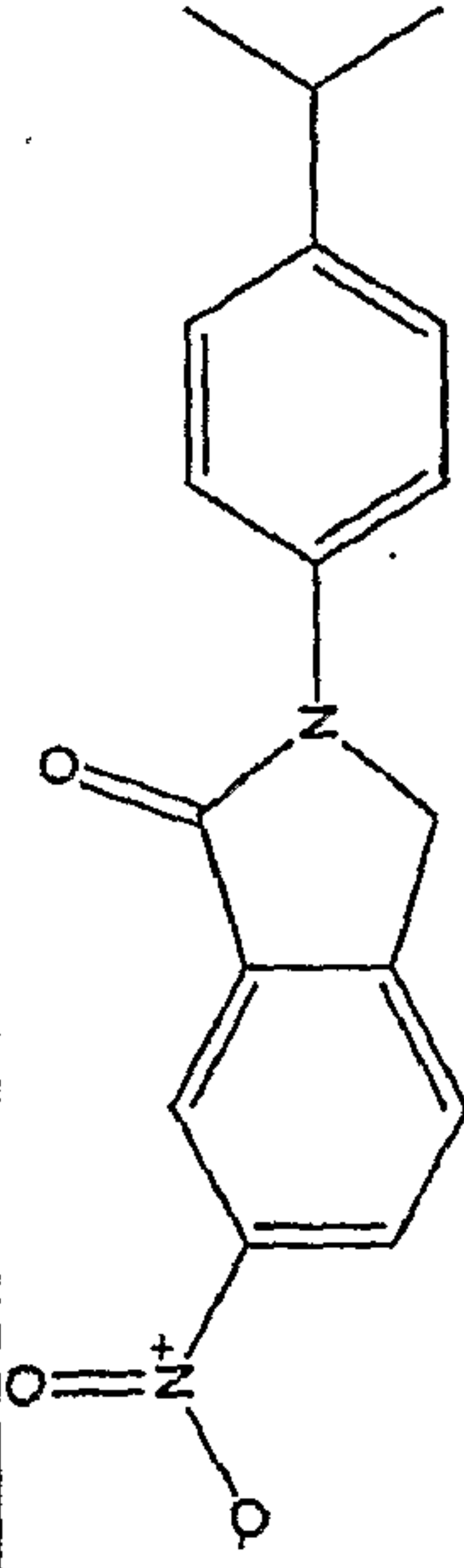
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
301		ALB- 115713	0.061	1.366
302		ALB- 115715		1.058

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
303		ALB- 115801	0.144	1.454
304		ALB- 115804	0.624	1.352

188

Table 1

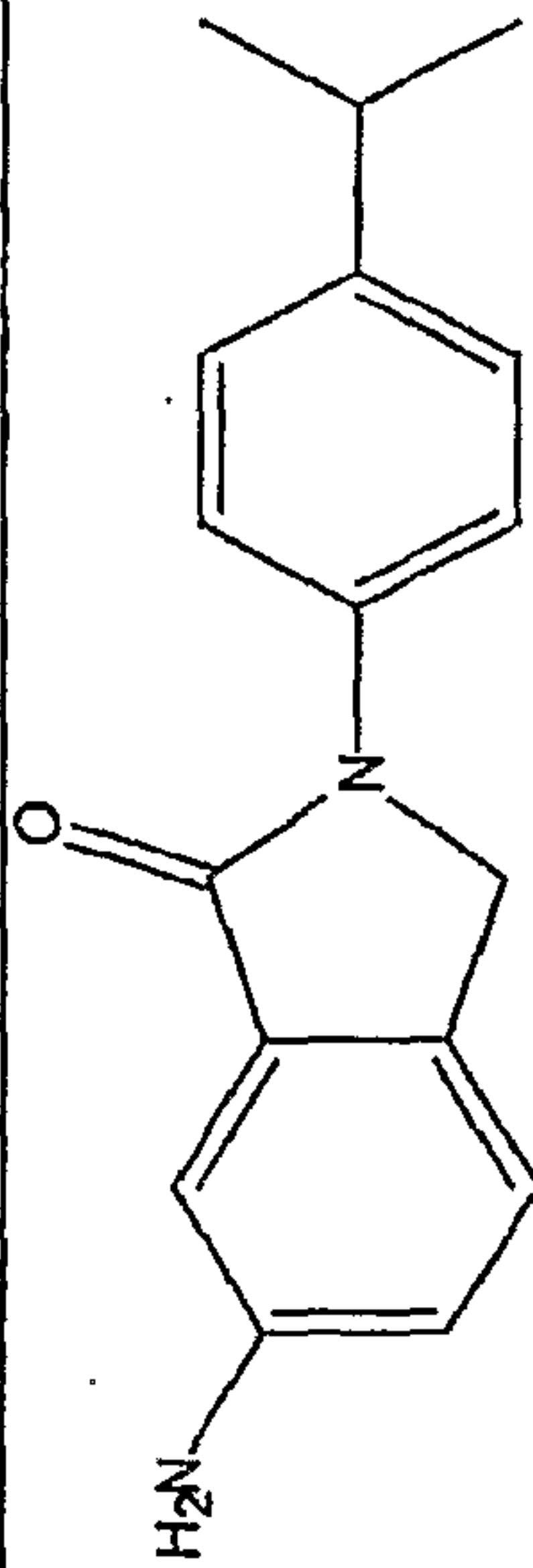
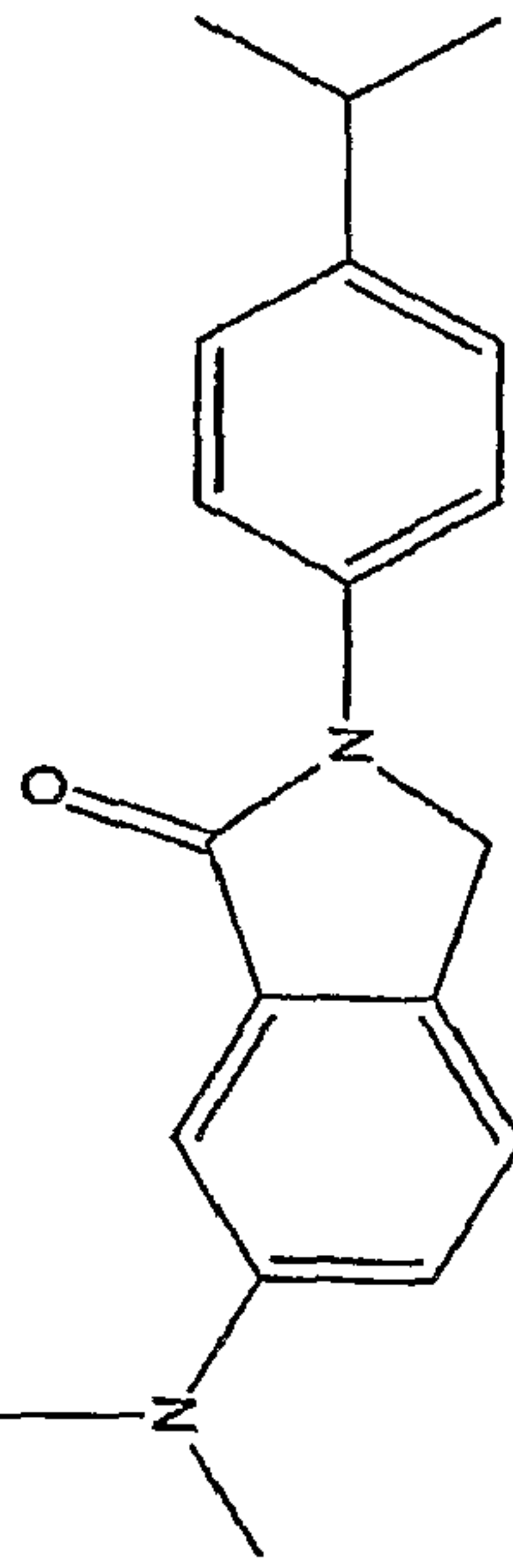
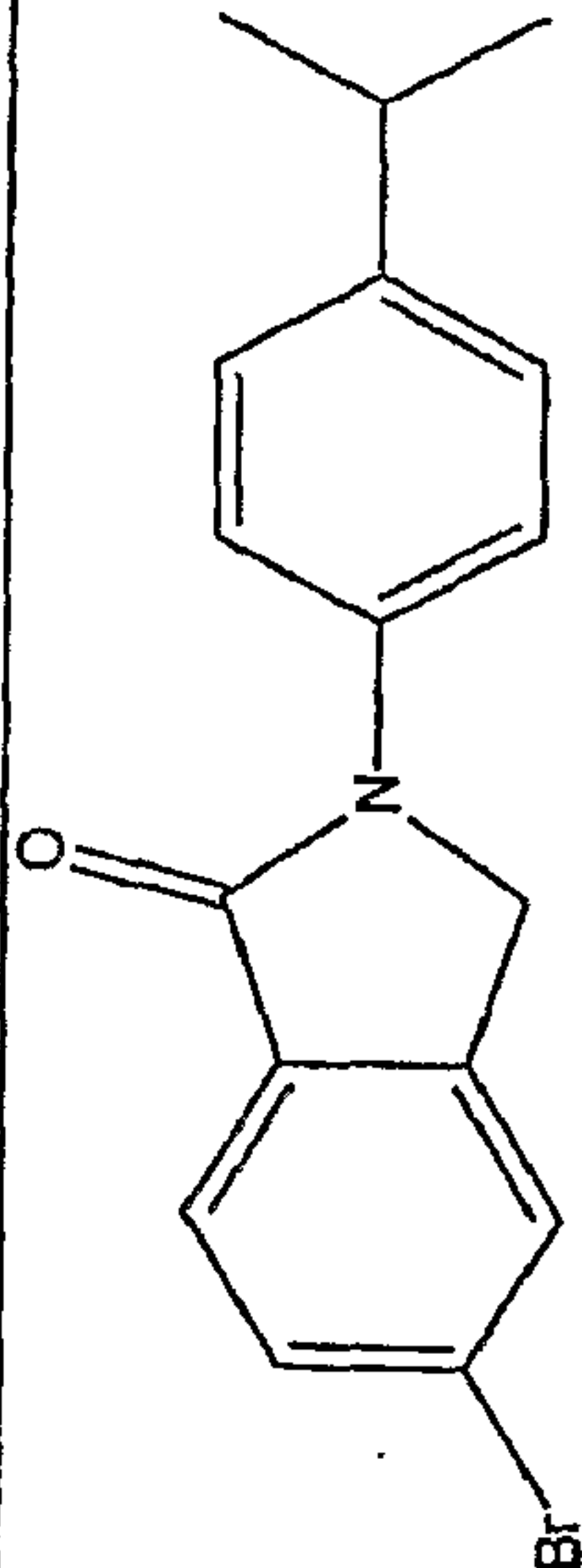
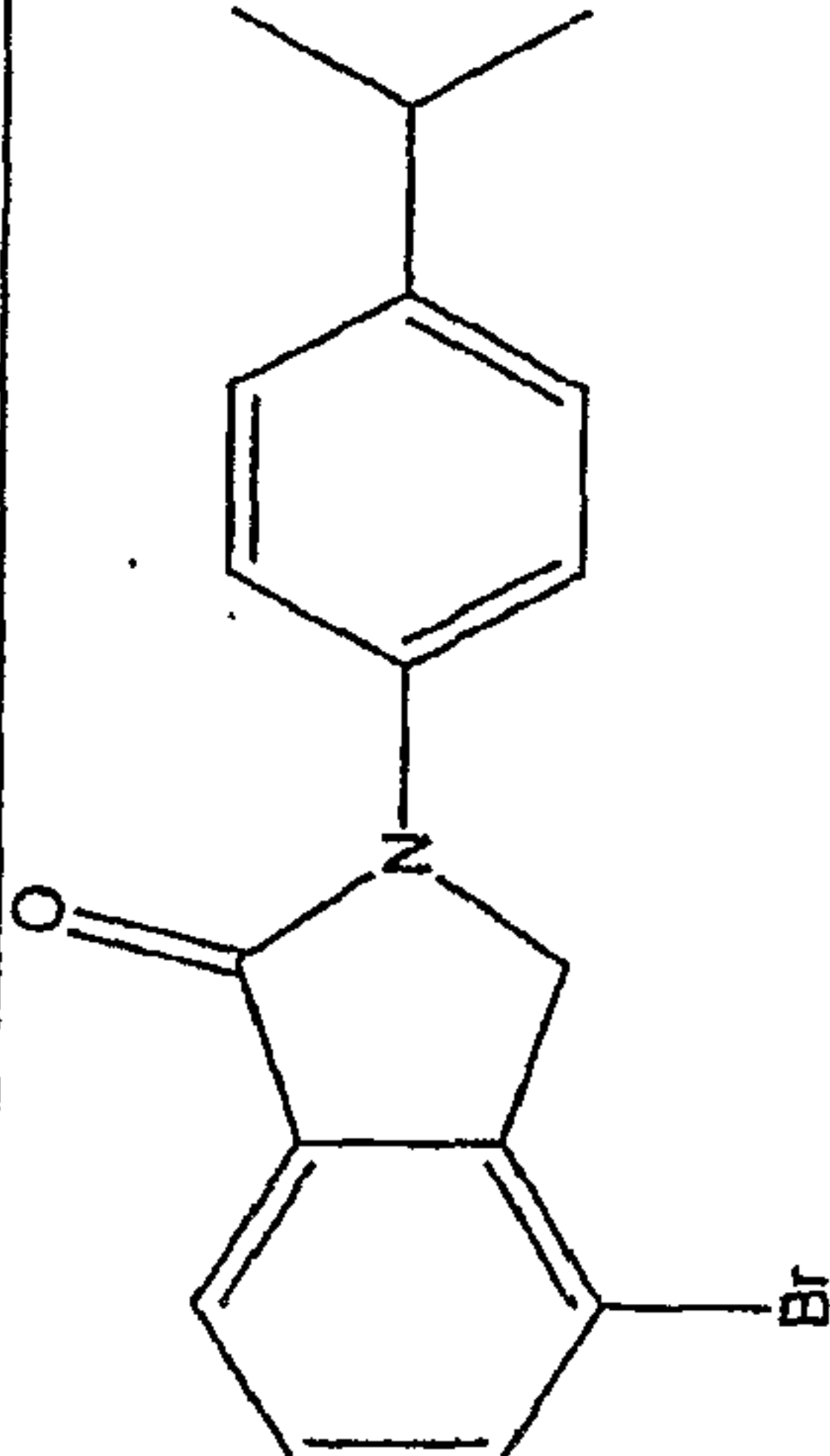
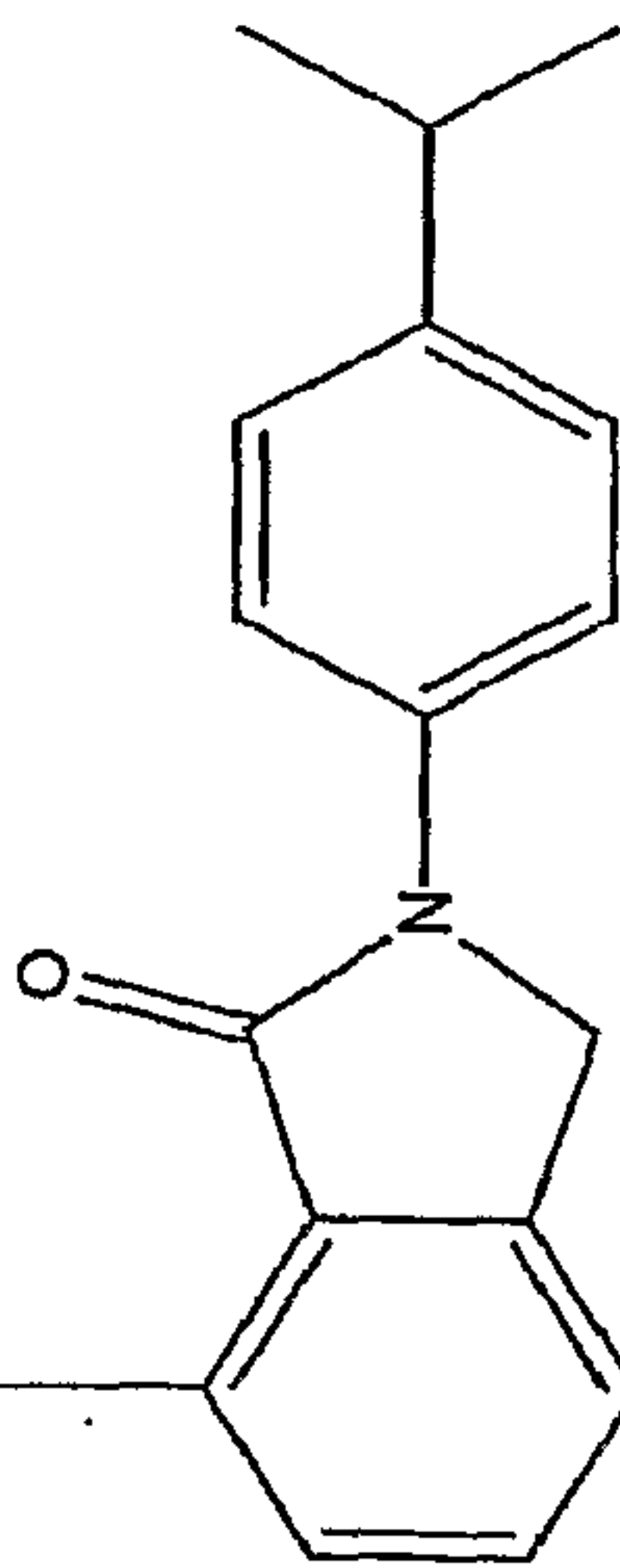
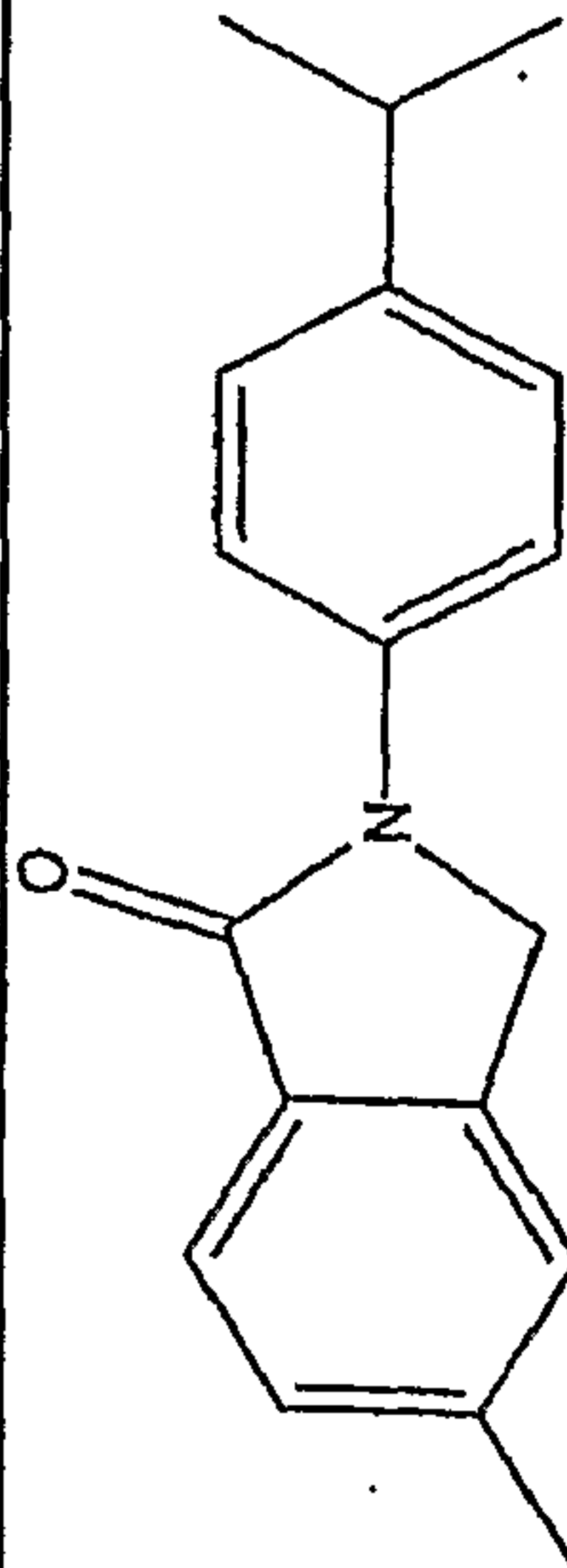
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
305		ALB- 115805	0.099	1.418
306		ALB- 115806	0.041	1.465

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
307		ALB- 115810	0.145	1.44
308		ALB- 115811		1.156

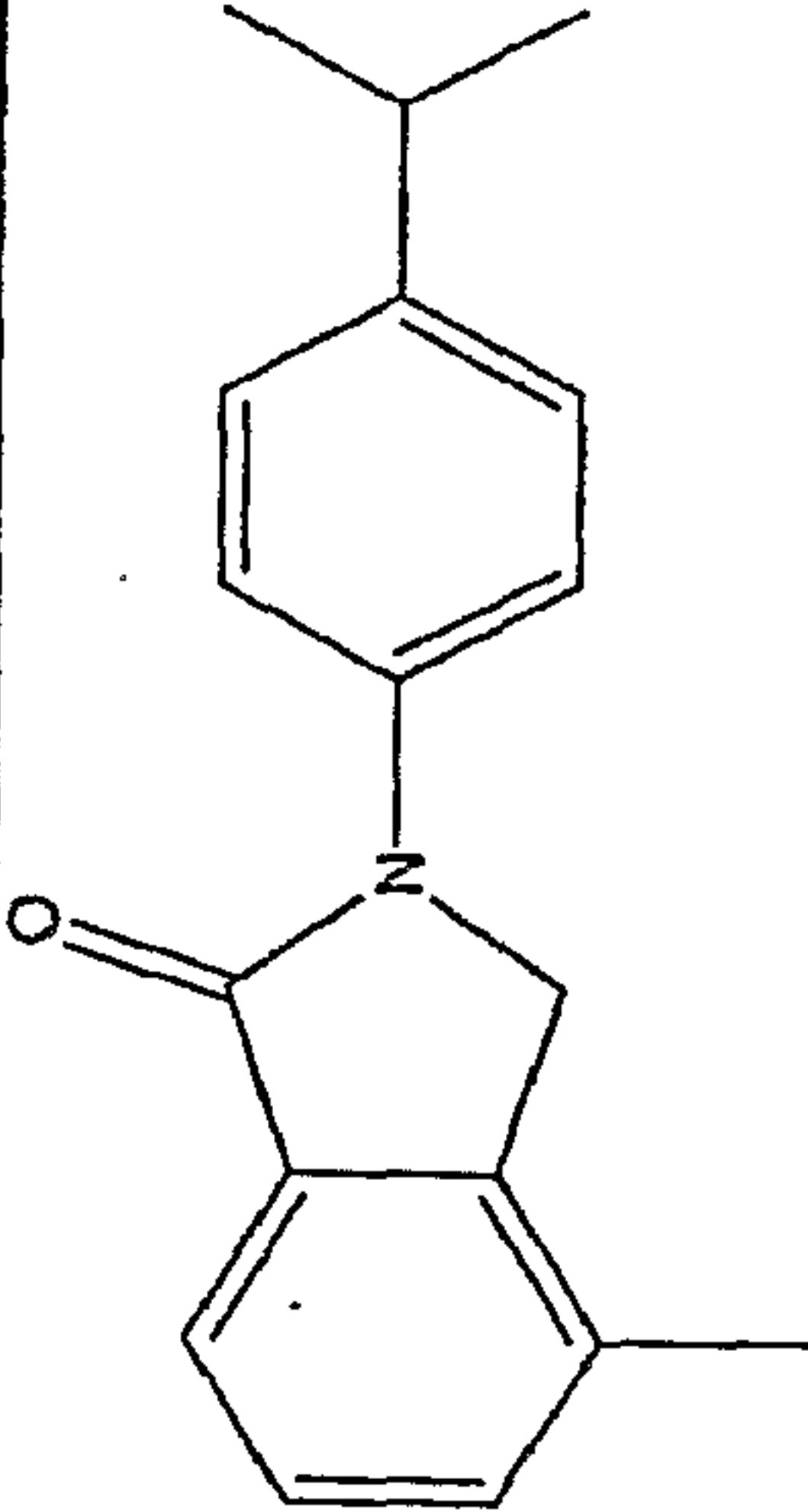
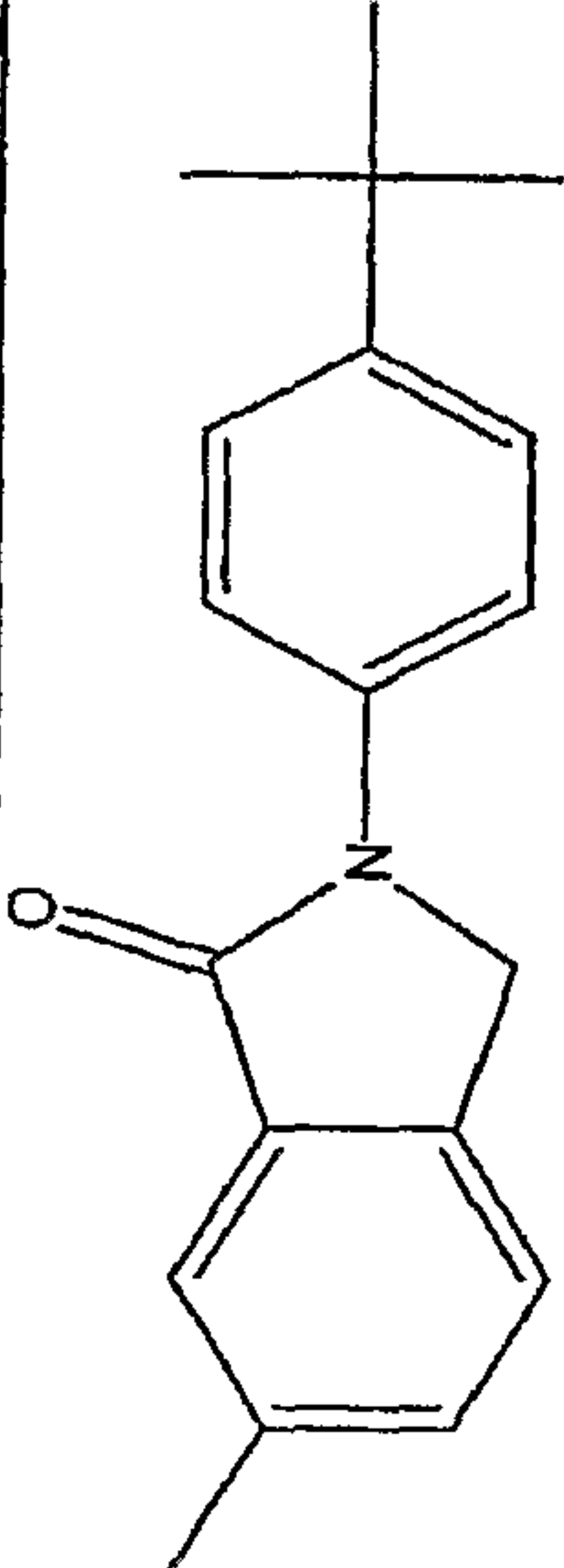
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
309		ALB- 115812	0.163	1.347
310		ALB- 115948	0.03	1.418

191

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
311		ALB- 115947	0.114	1.391
312		ALB- 116068	0.051	1.347

192

Table 1

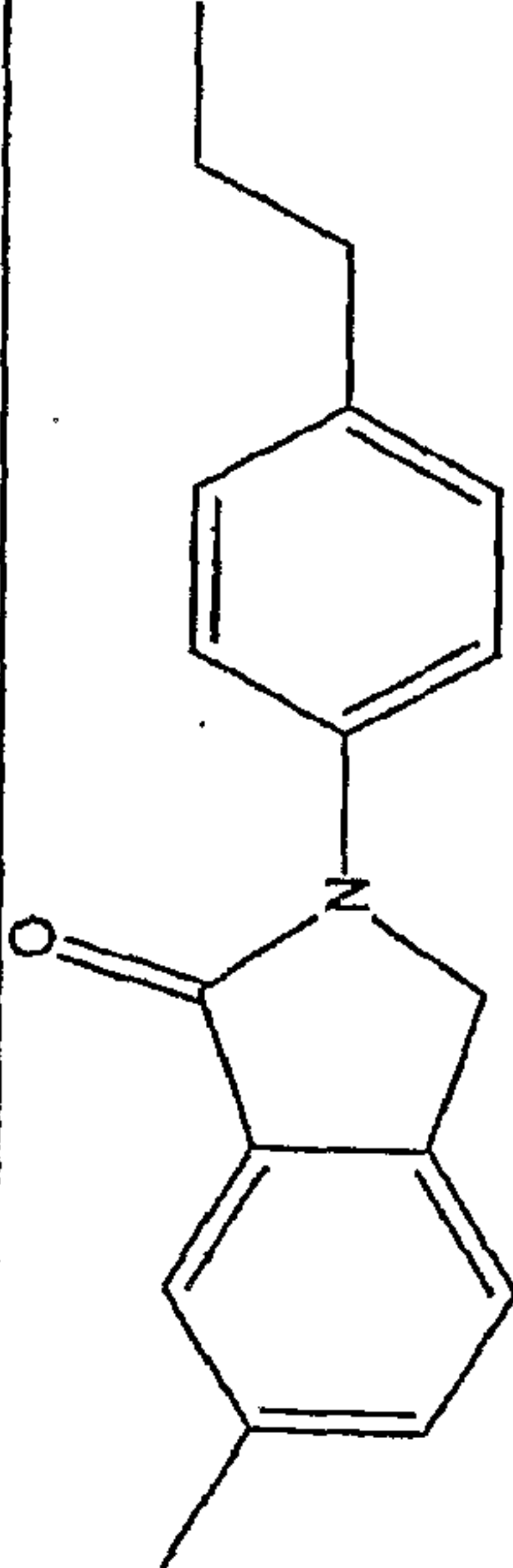
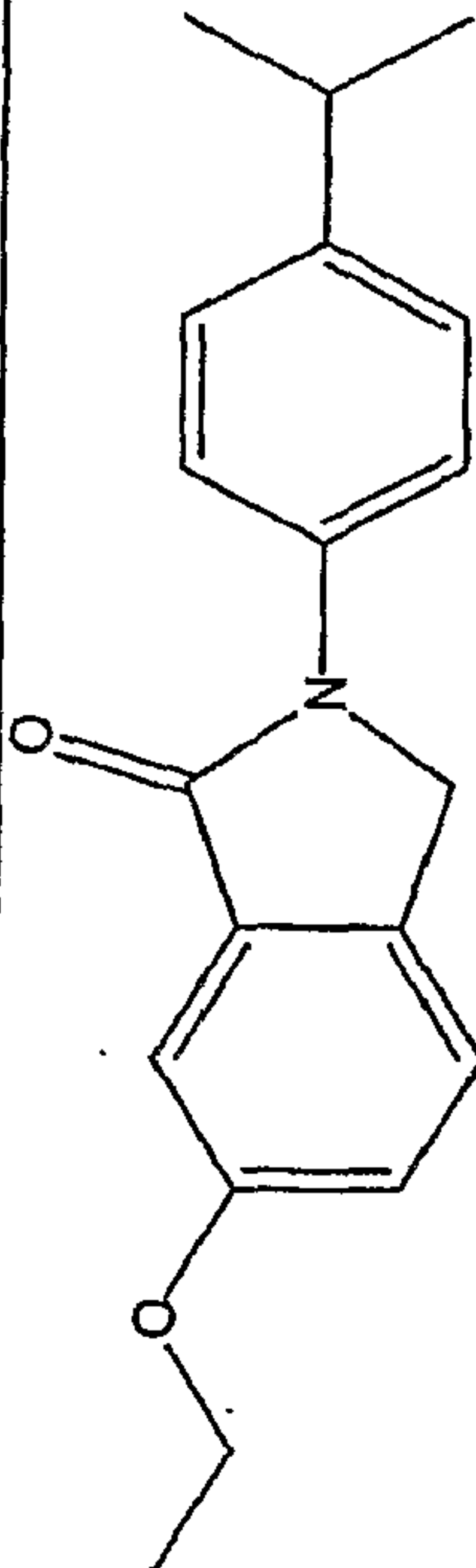
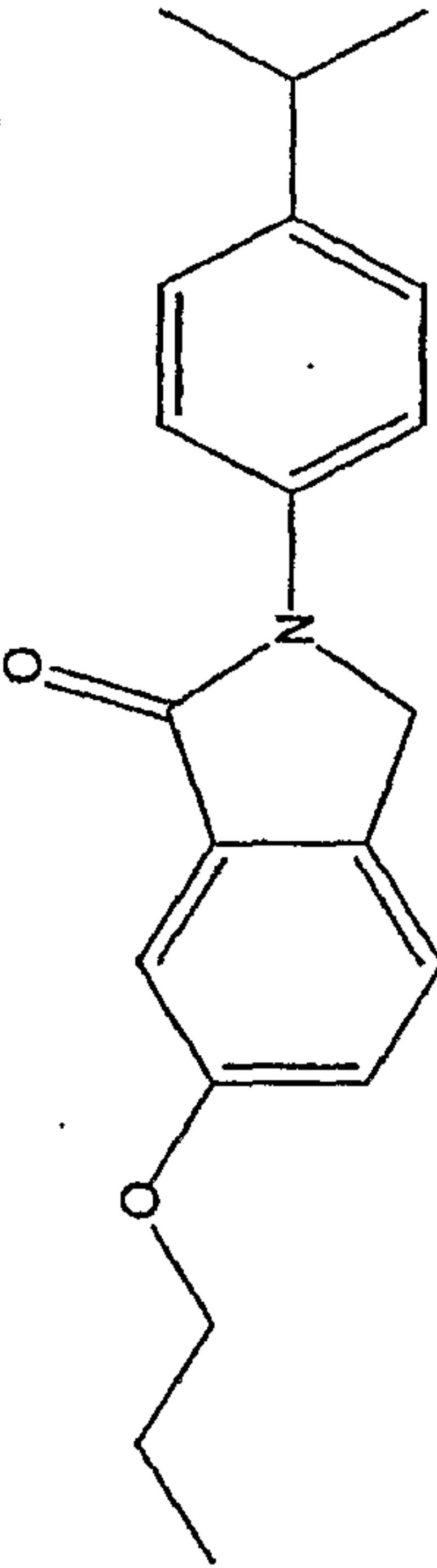
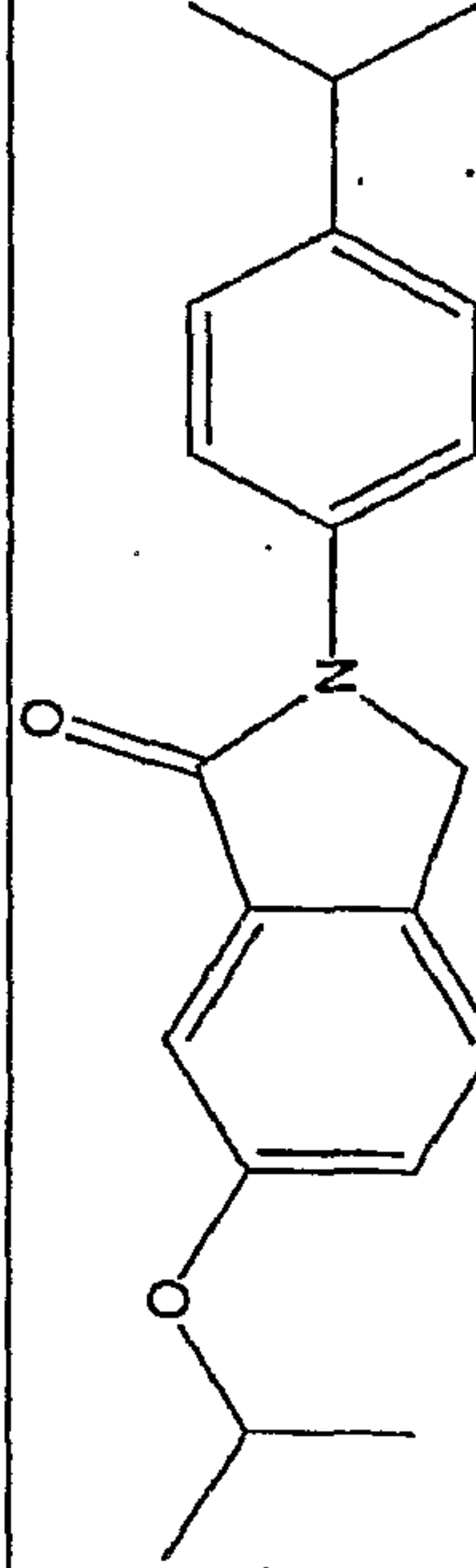
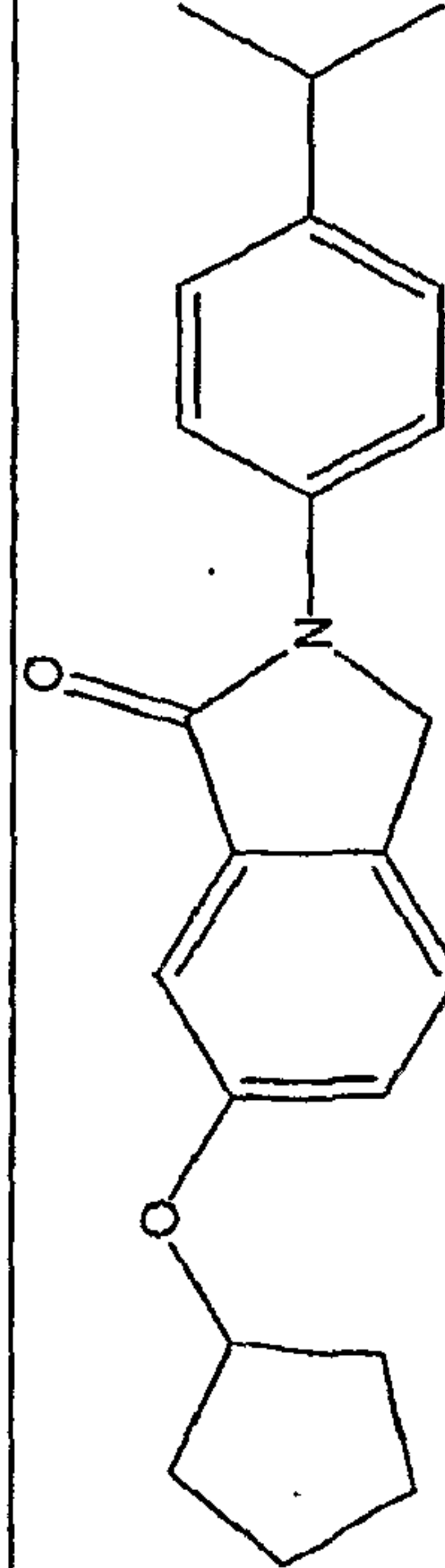
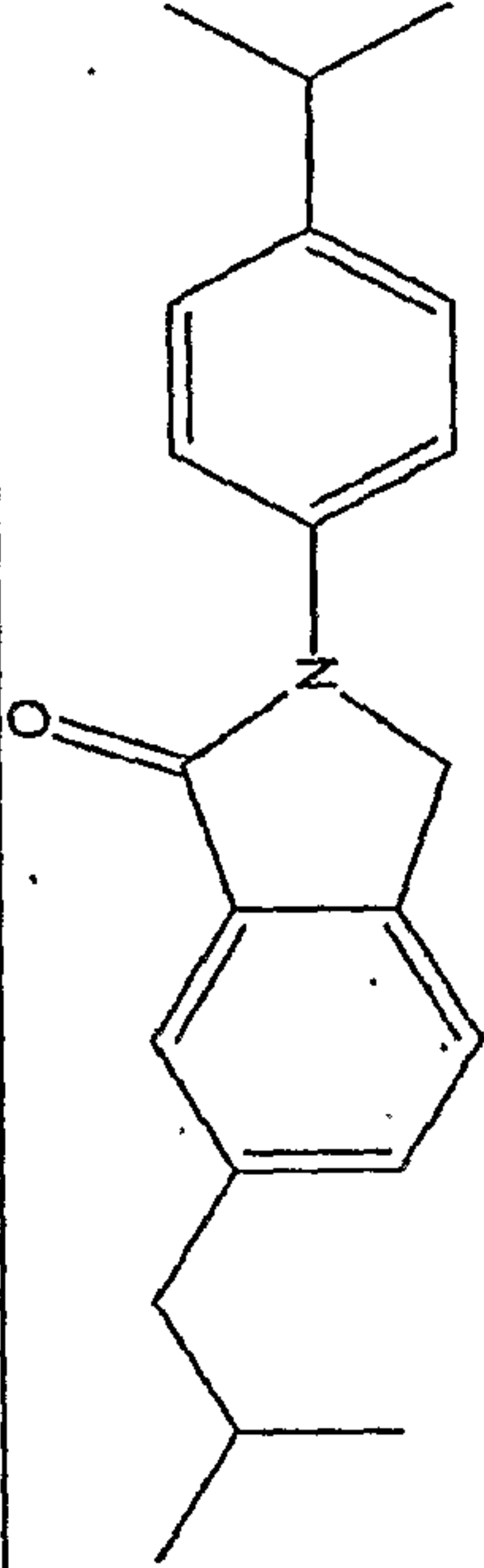
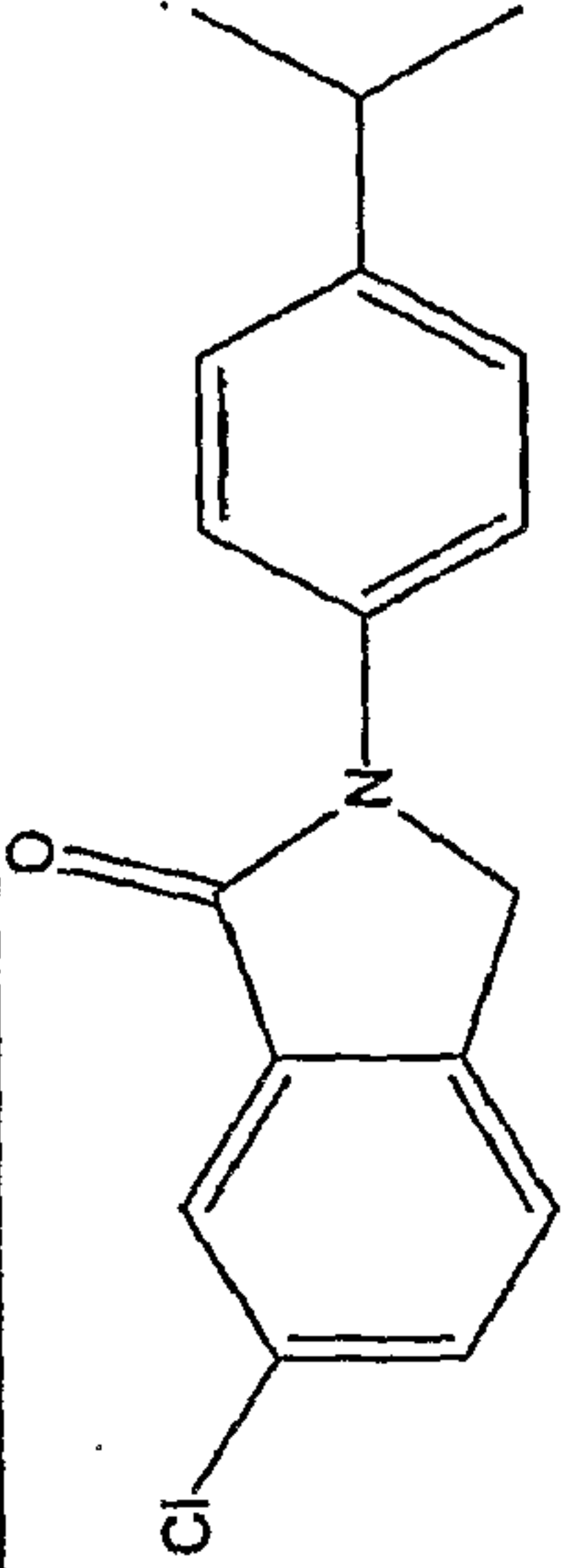
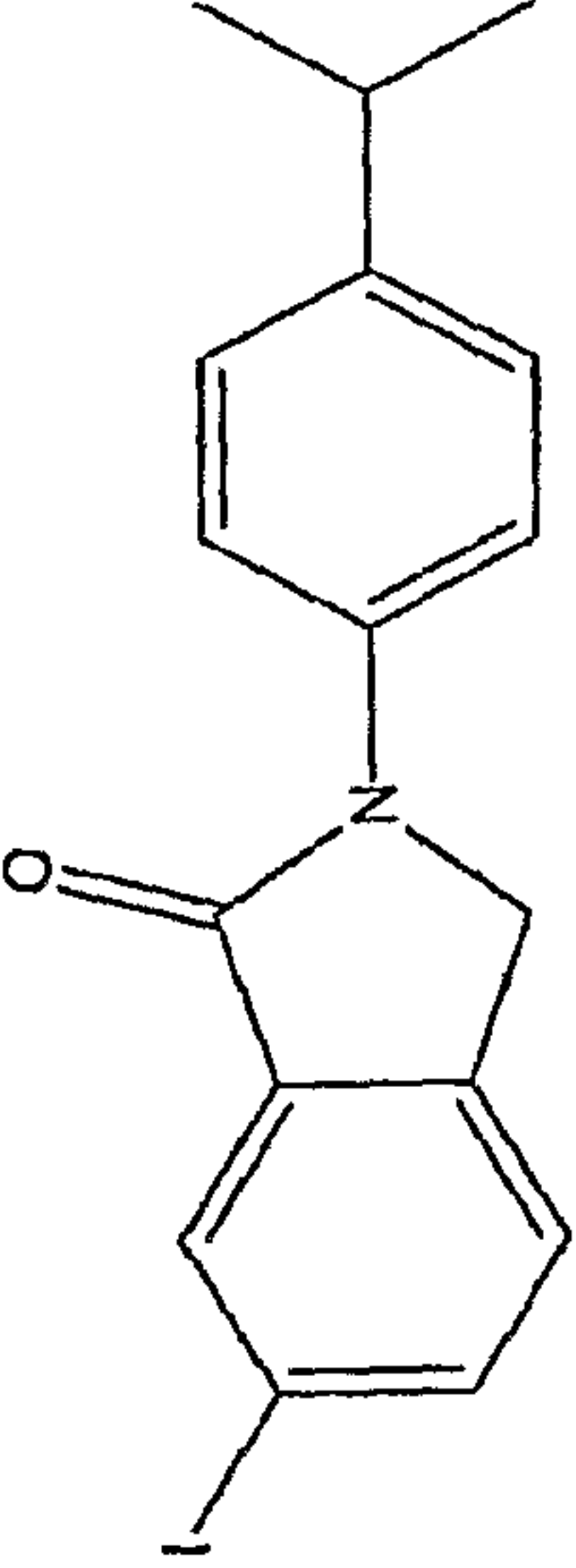
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
313				
		ALB-116071	0.016	1.35
314				
		ALB-116074	0.31	1.506

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
315		ALB- 116075	0.188	1.258
316		ALB- 116076	0.072	1.352
317		ALB- 116077		1.176

194

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
318		ALB- 116245	0.219	1.356
319		ALB- 116246	0.031	1.35
320		ALB- 116247	0.277	1.515

195

Table 1

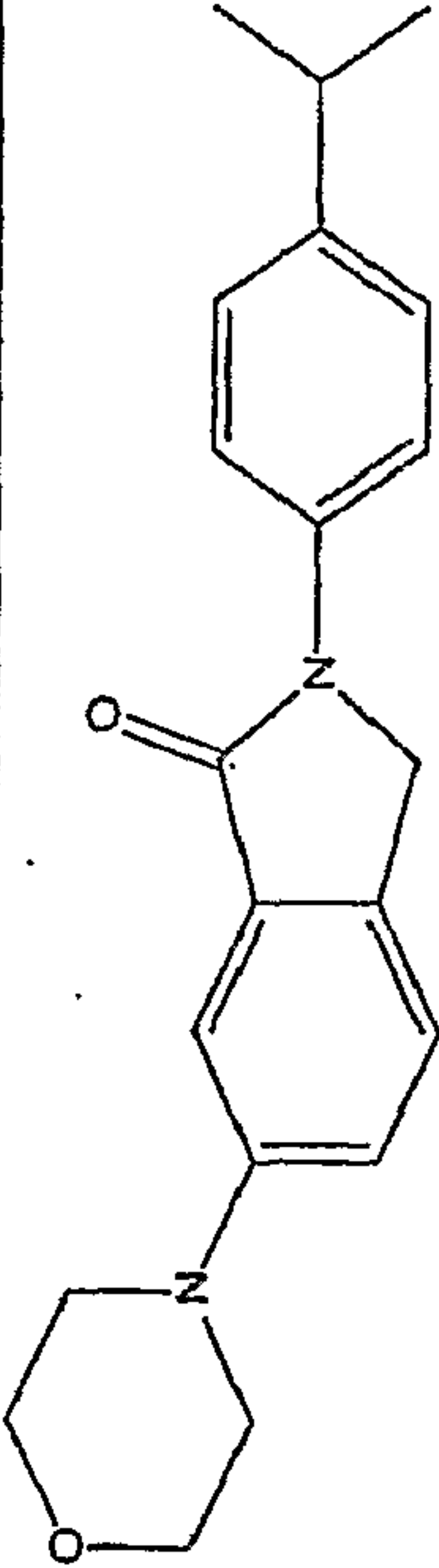
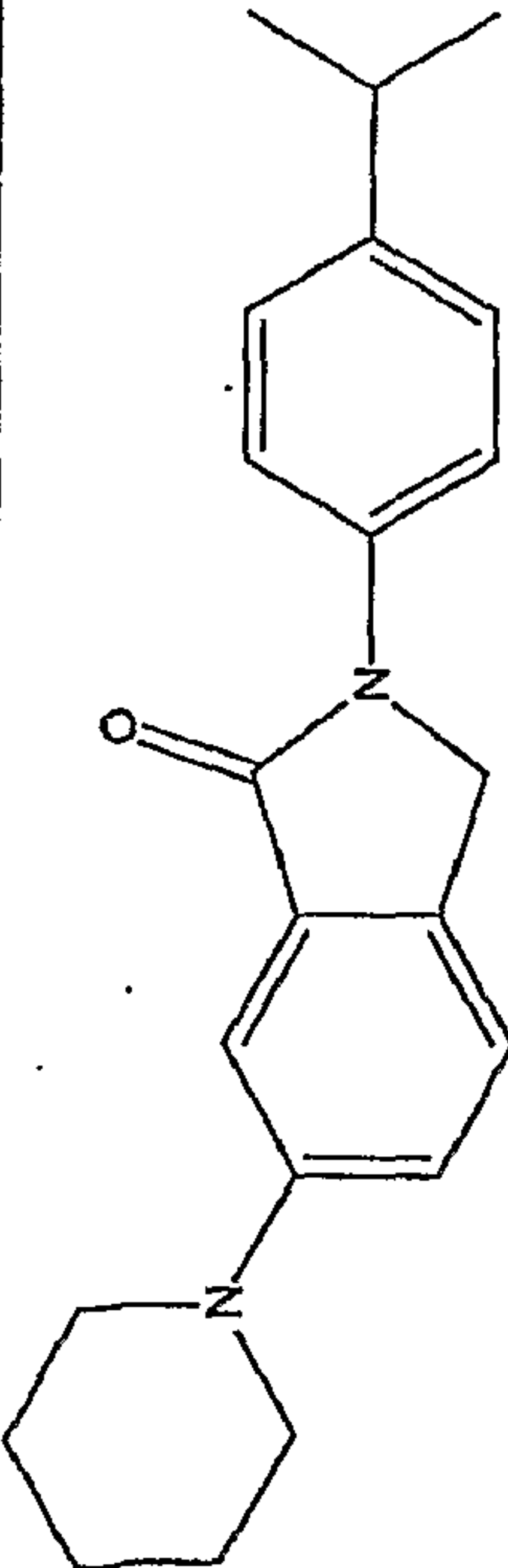
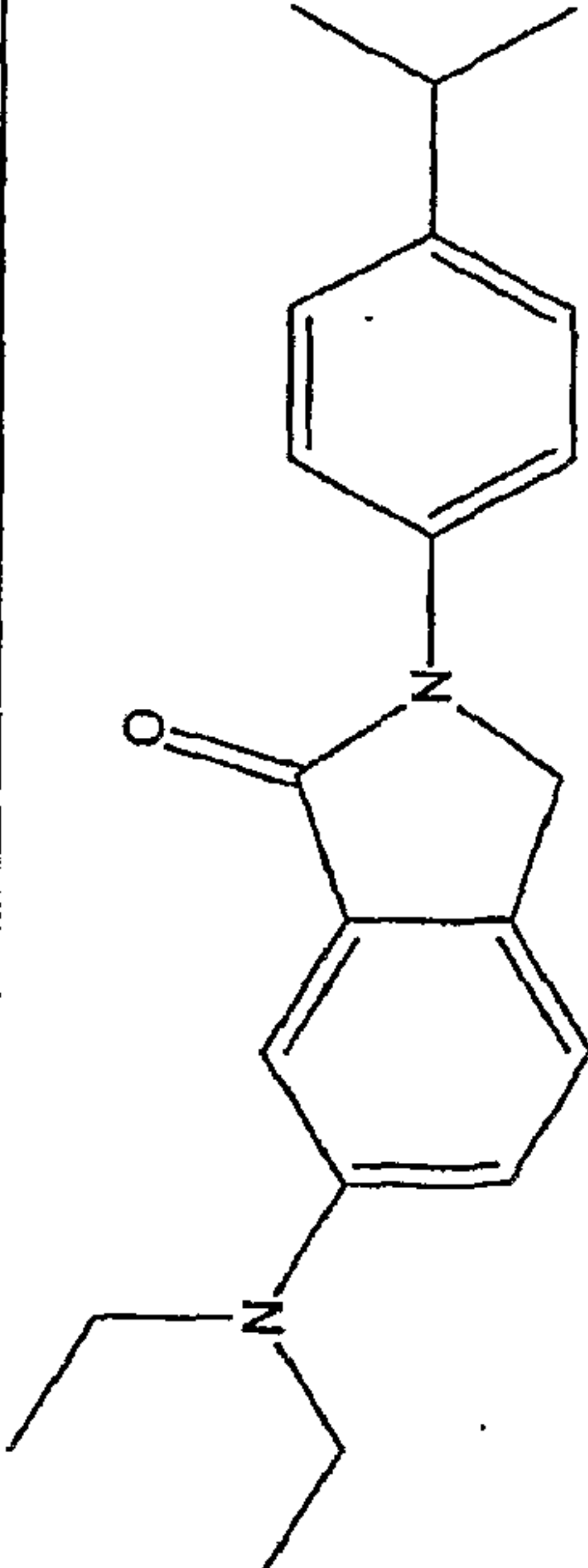
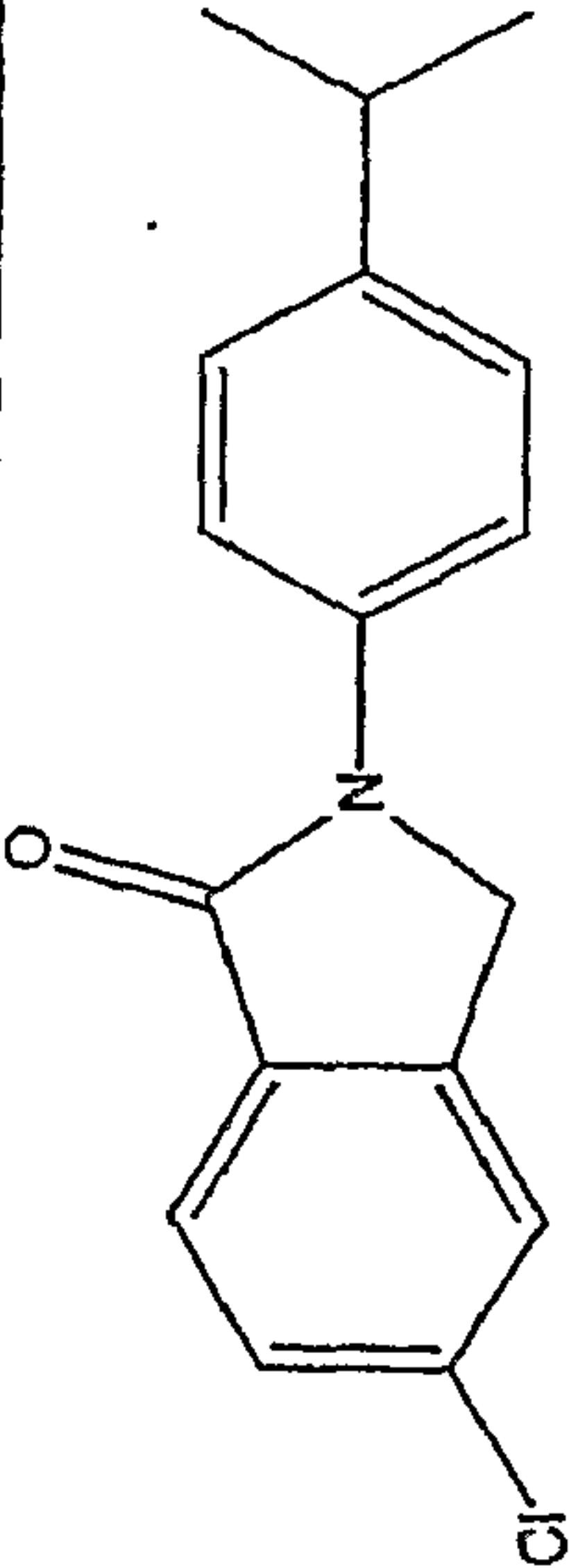
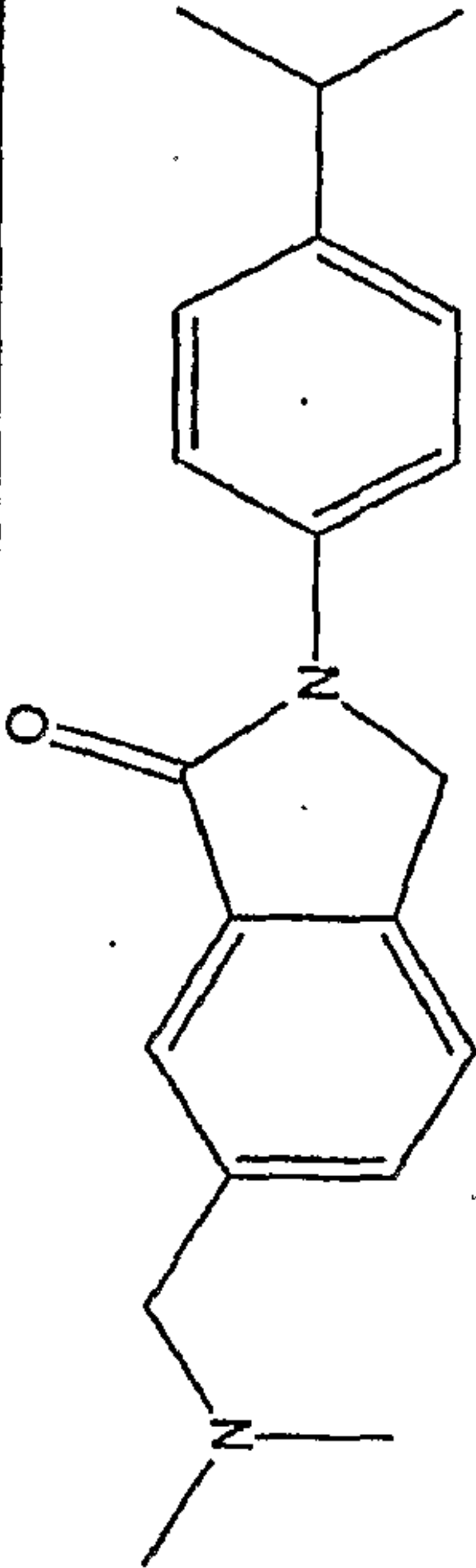
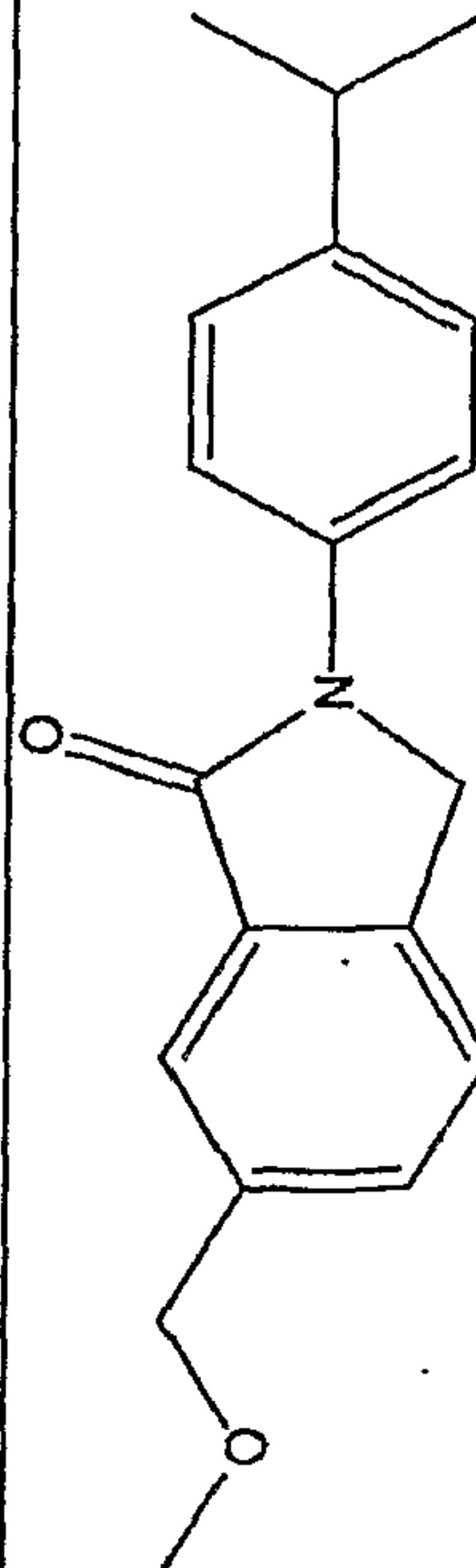
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
321		ALB- 116368		1.081
322		ALB- 116418		1.149
323		ALB- 116639	0.121	1.188

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
324		ALB- 116932	0.081	1.45
325		ALB- 116934		1.053
326		ALB- 116935	0.078	1.521

197

Table 1

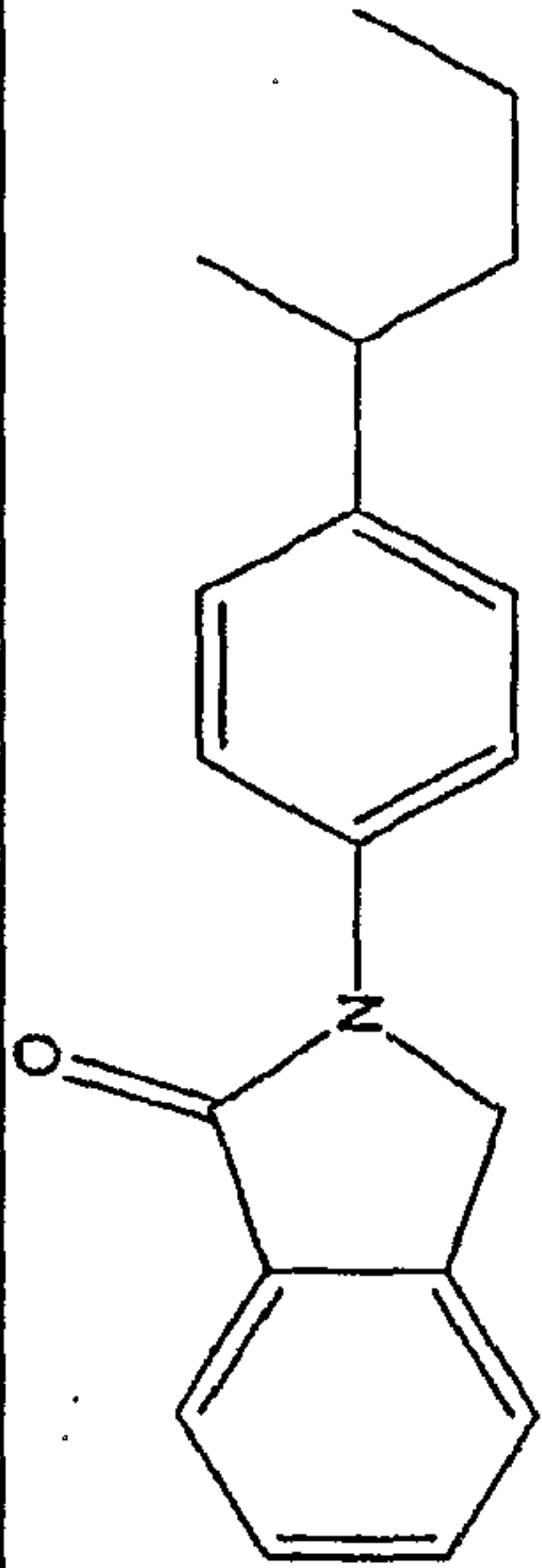
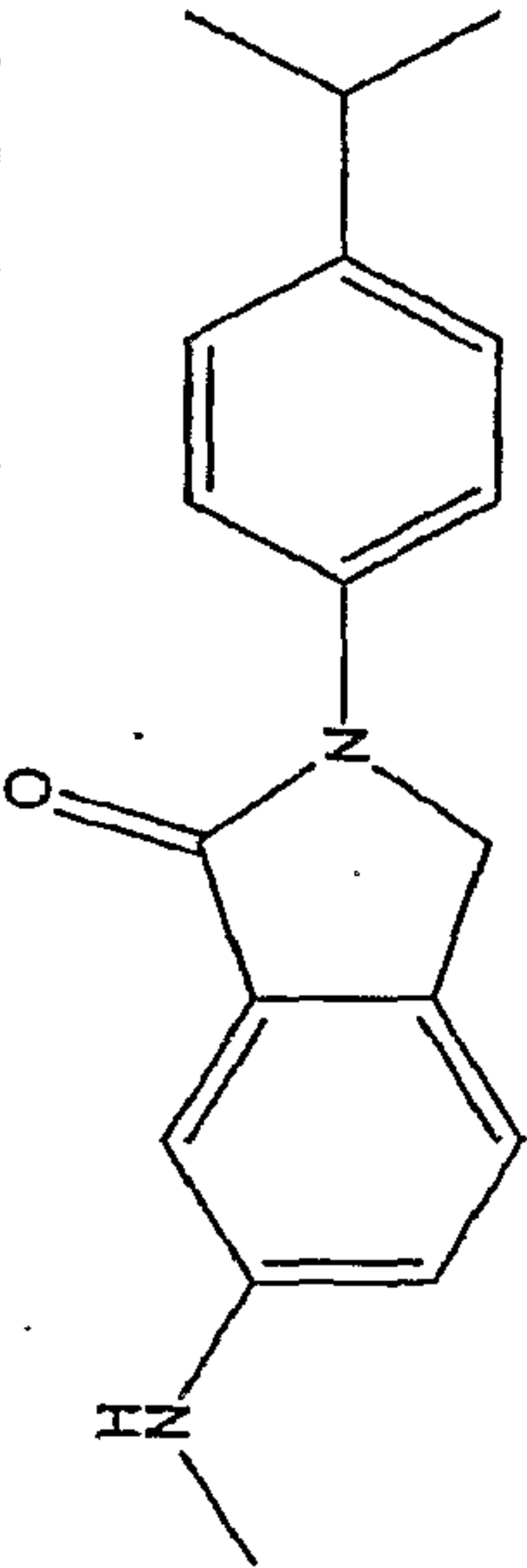
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
327		ALB- 117045	0.07	1.247
328		ALB- 117046	0.09	1.44

Table 1

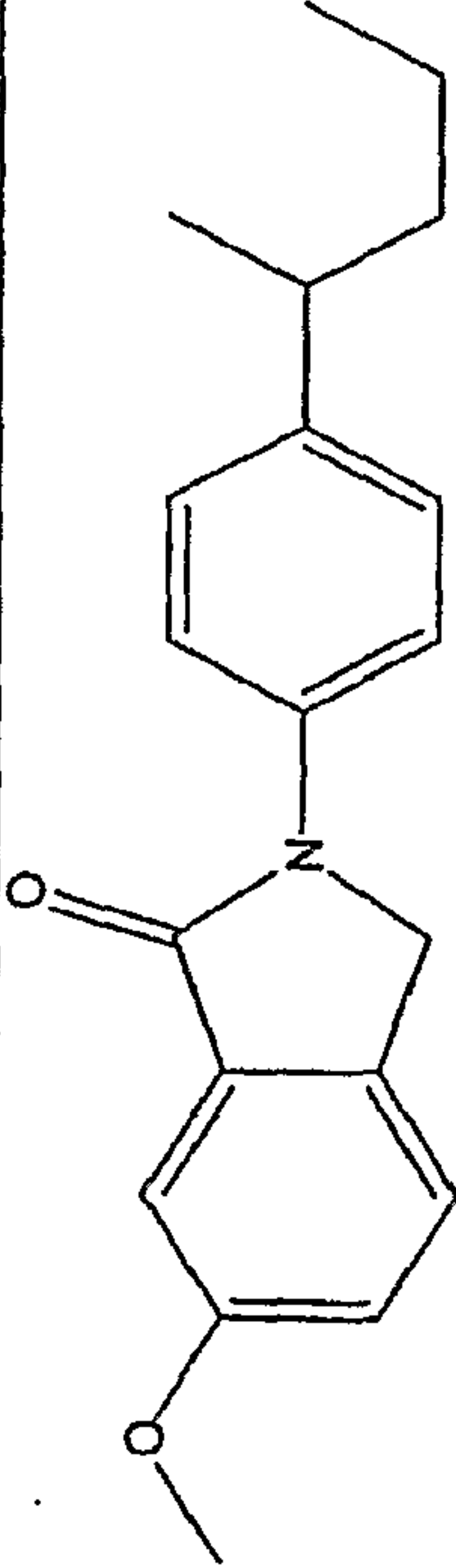
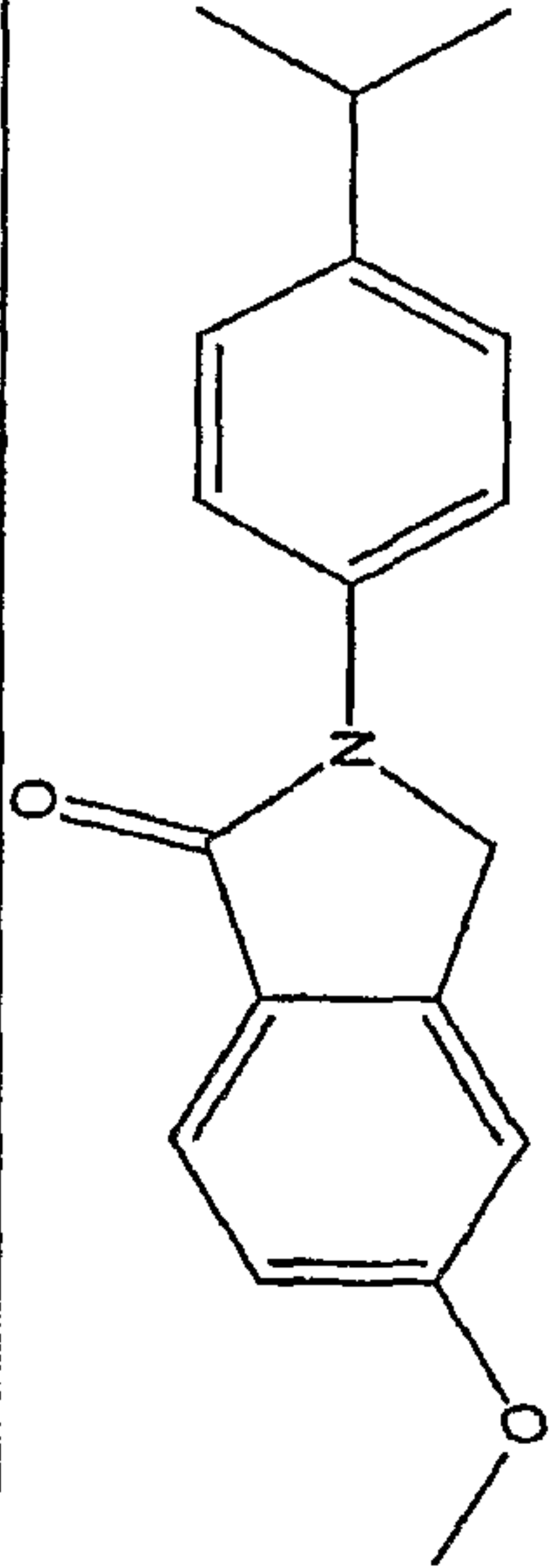
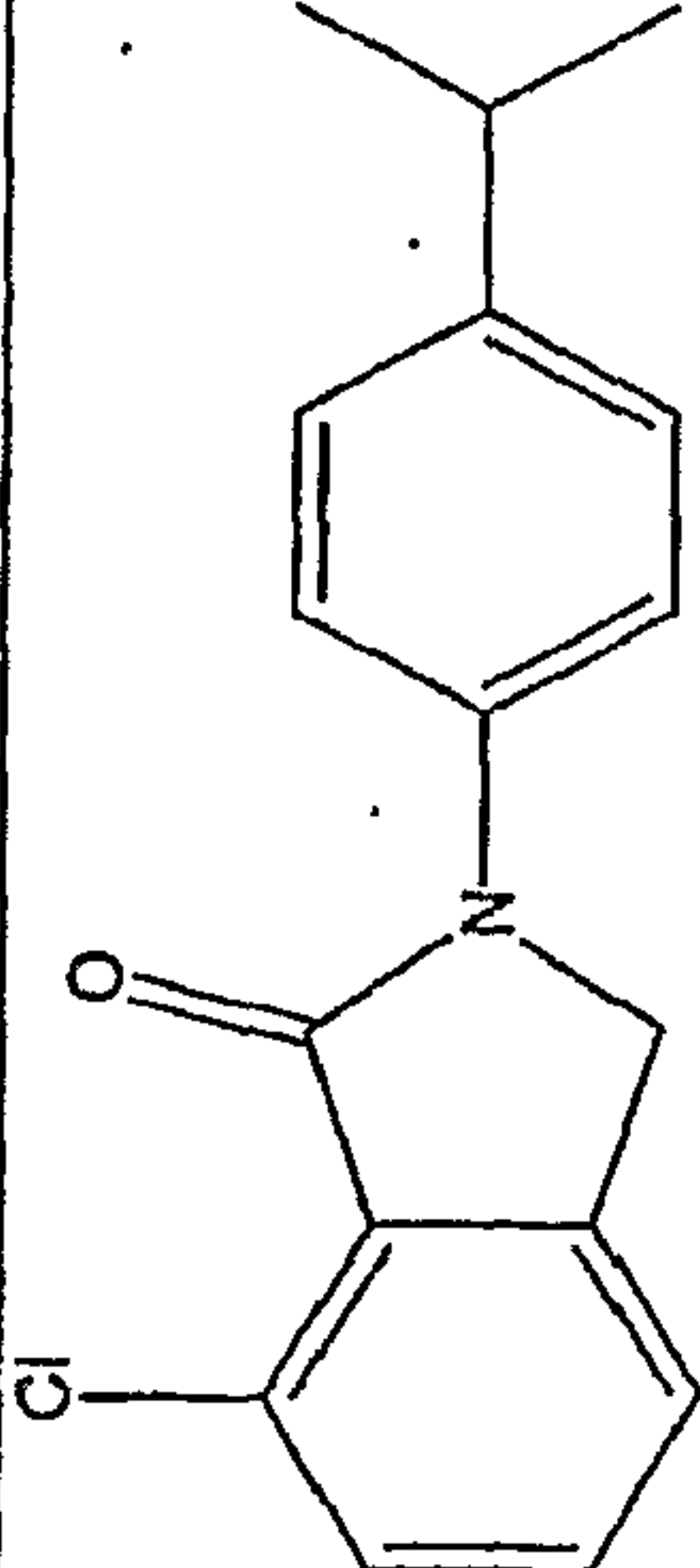
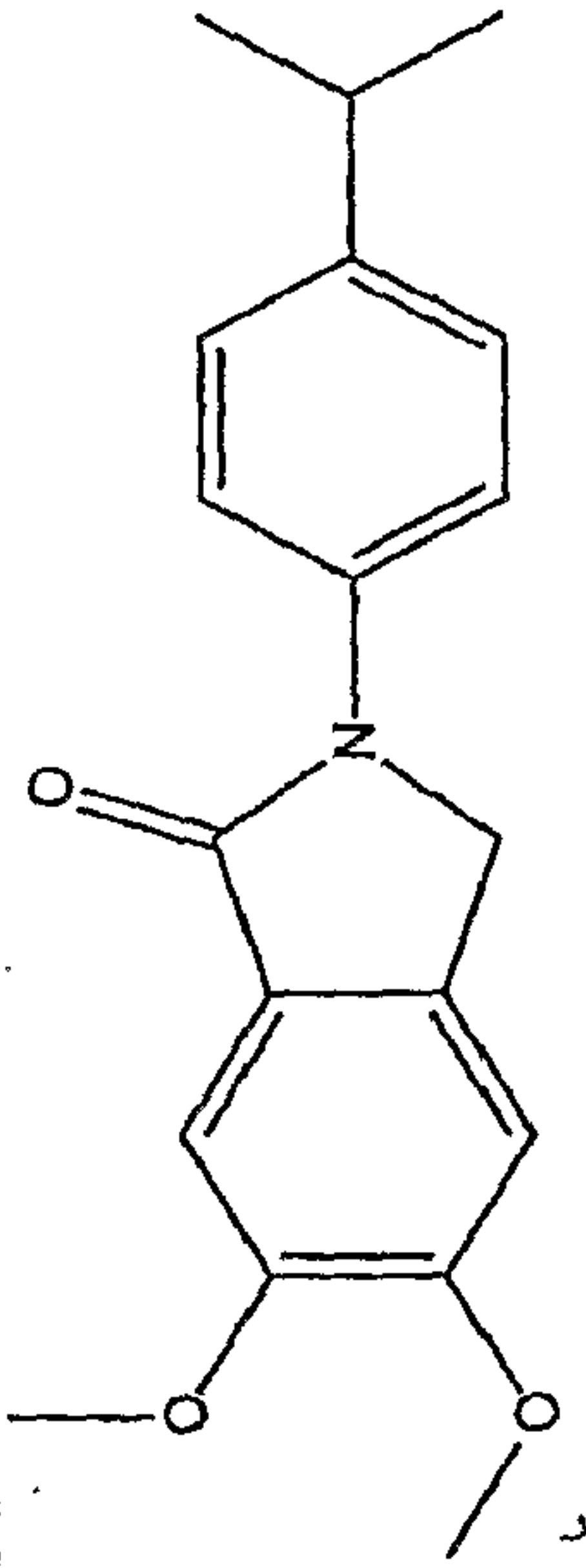
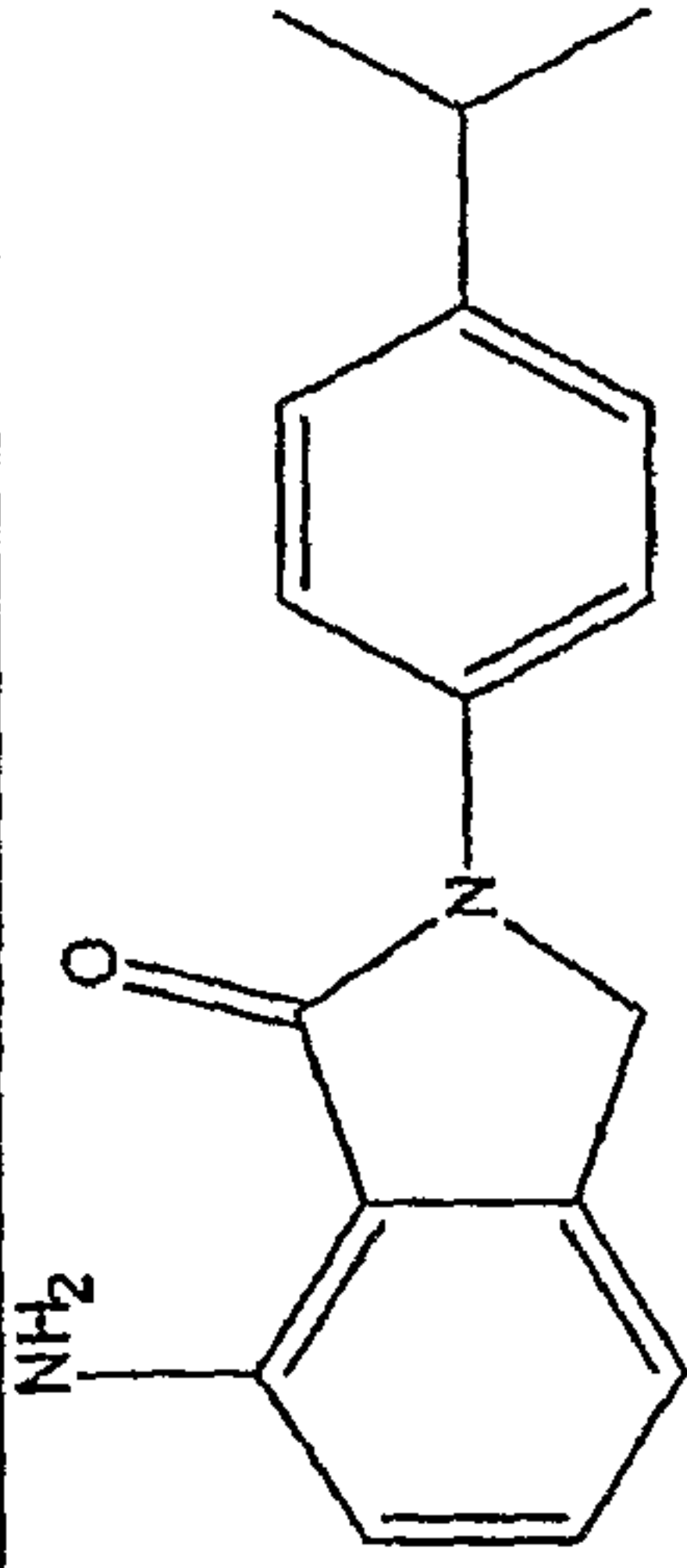
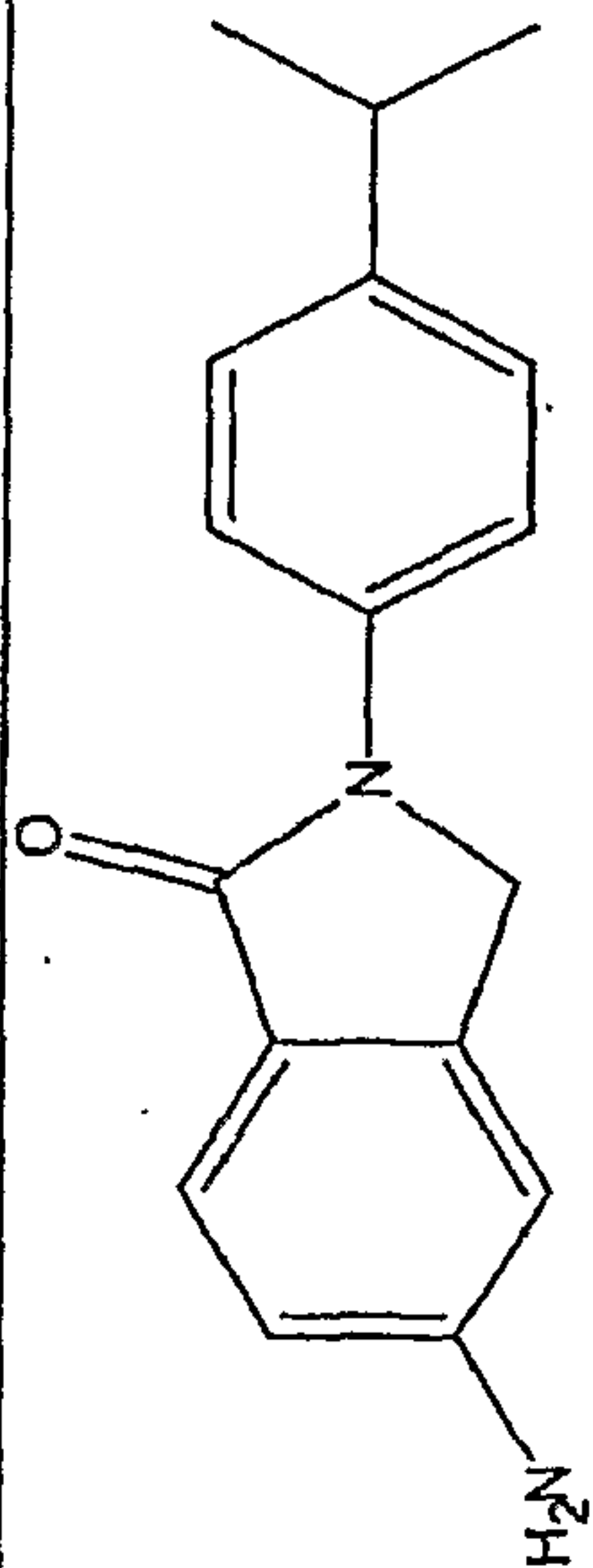
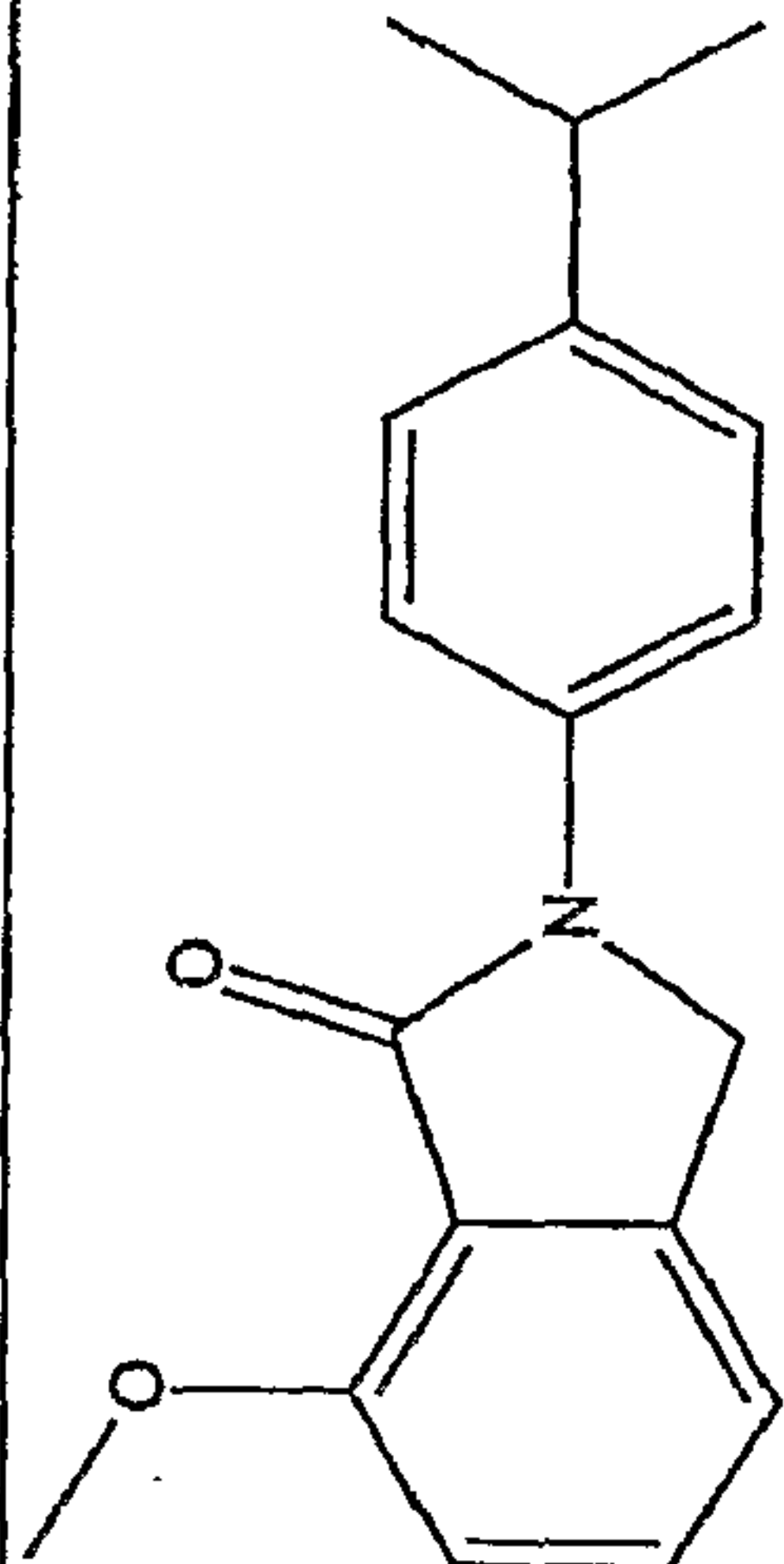
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
329		ALB- 117451	2.906	1.735
330		ALB- 117453	0.18	1.276
331		ALB- 117454	0.47	1.509

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
332		ALB- 117572	0.319	1.472
333		ALB- 117574	0.163	1.727

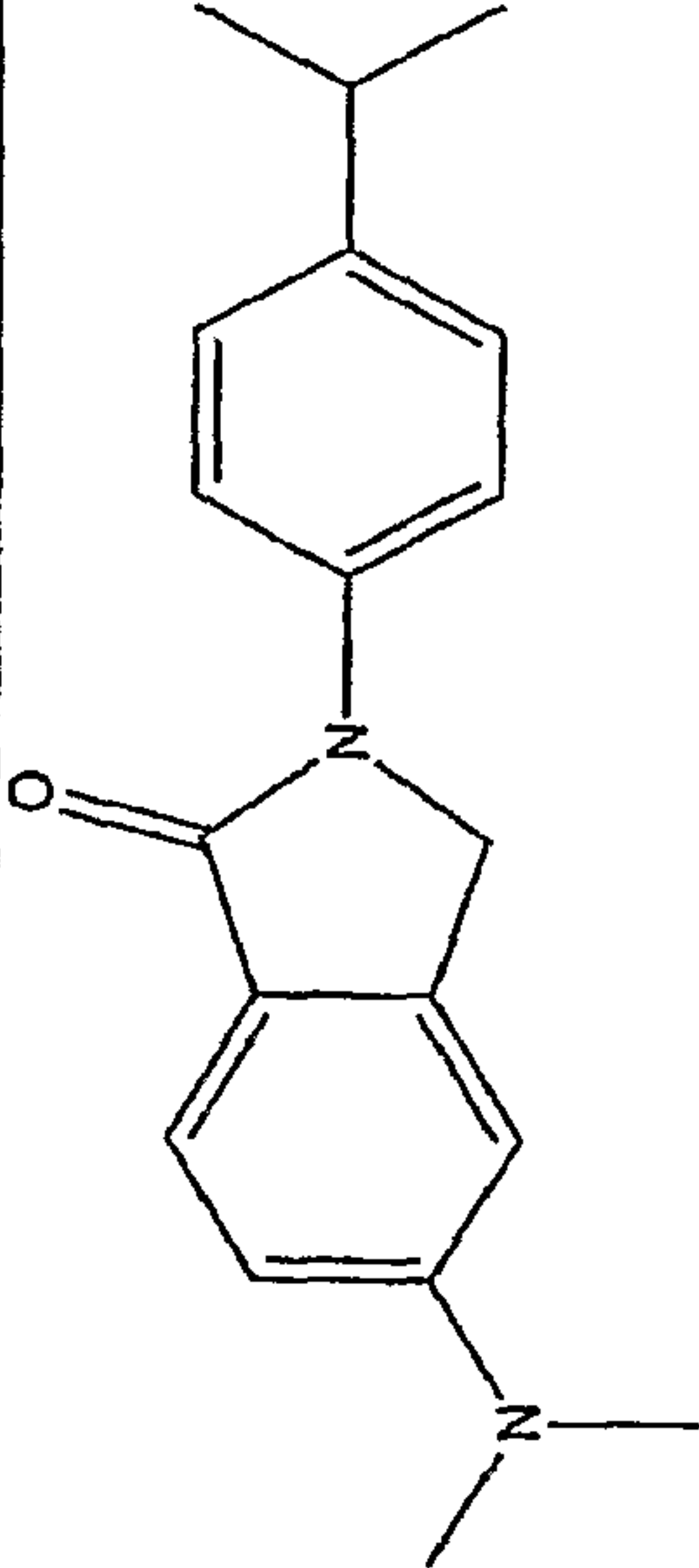
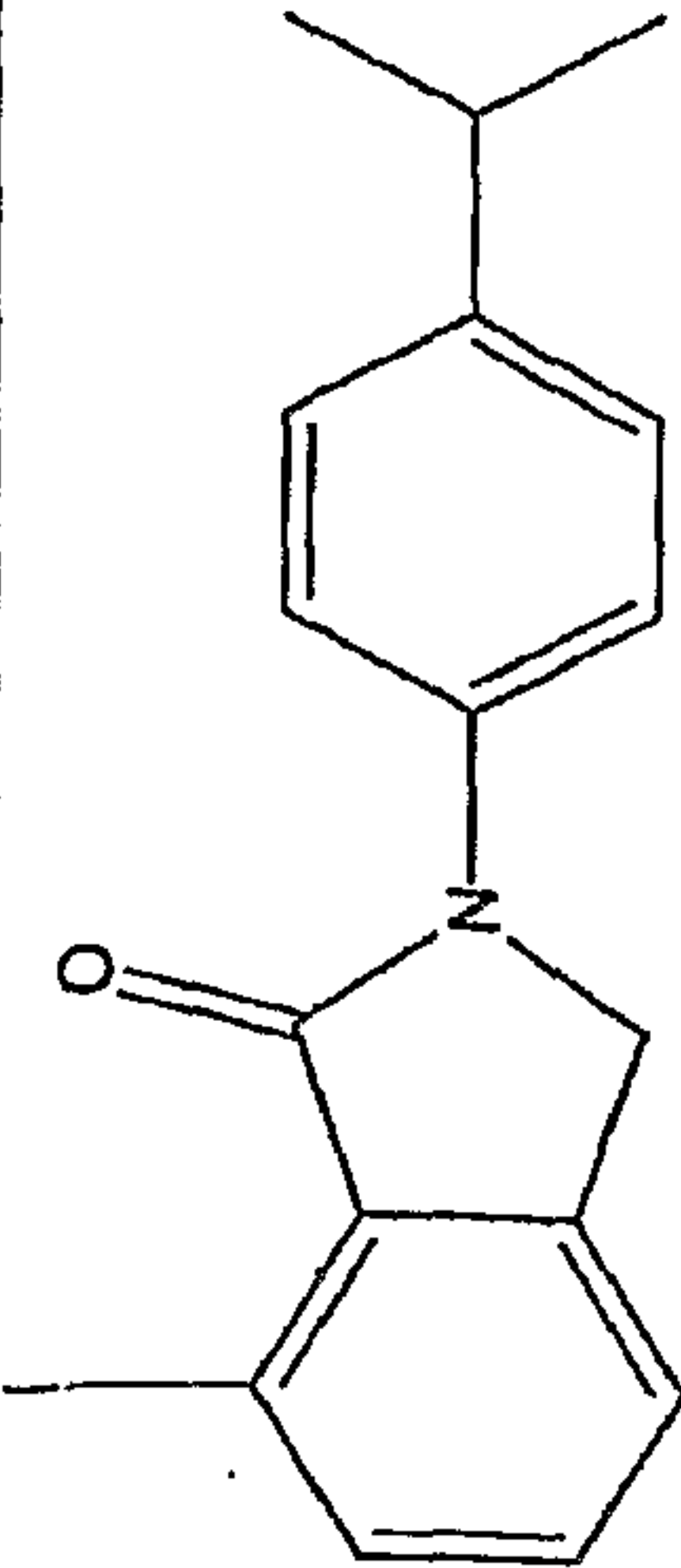
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
334		ALB- 117747	0.034	1.486
335		ALB- 117748	0.166	1.343

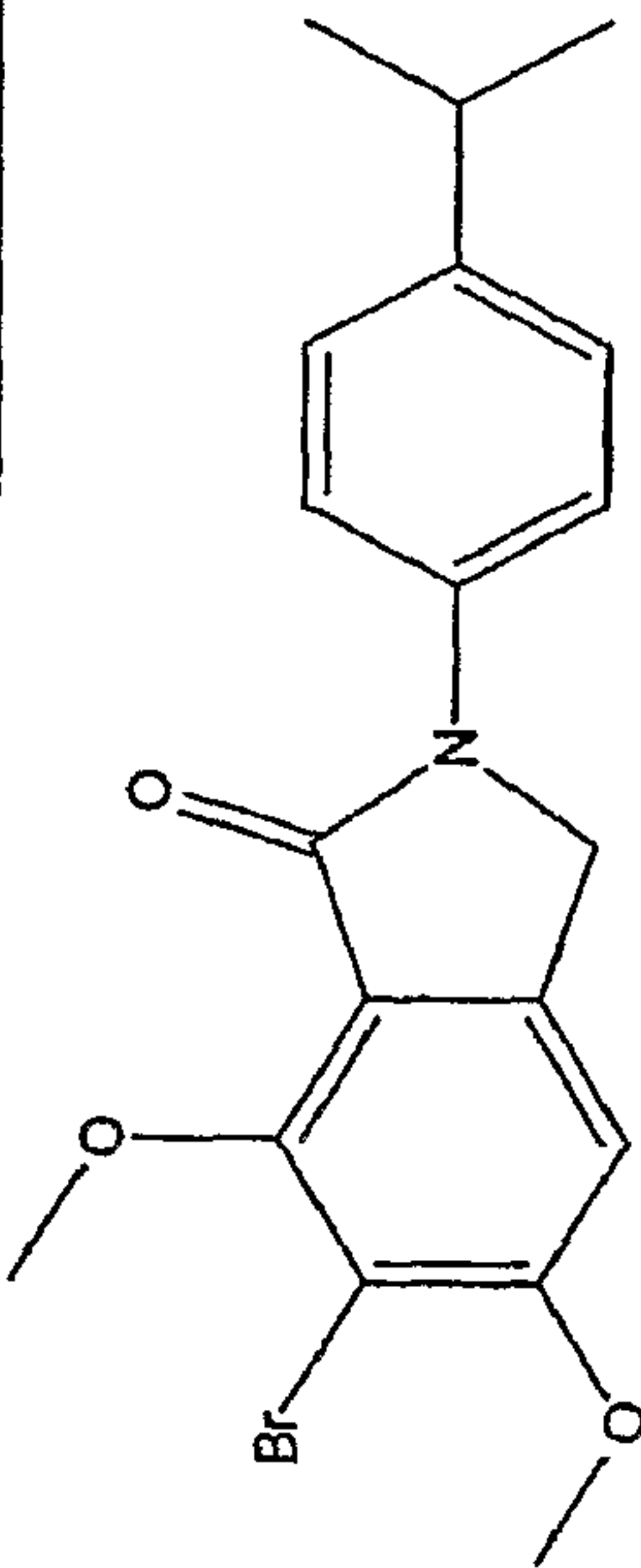
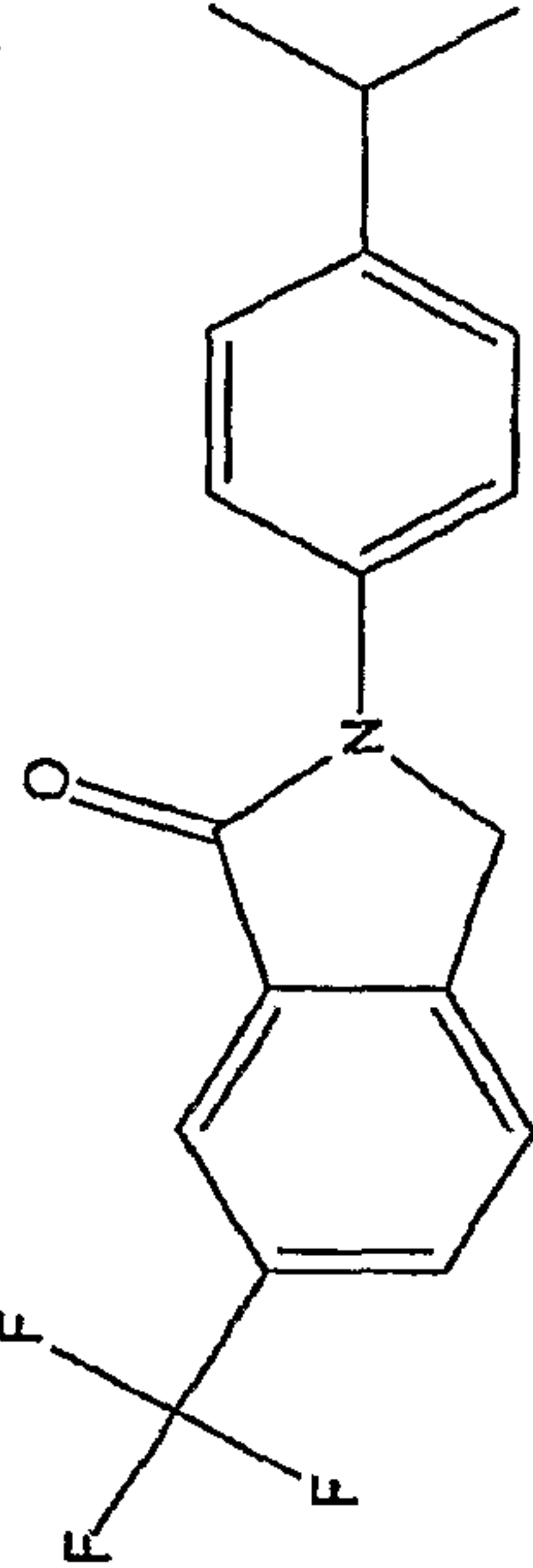
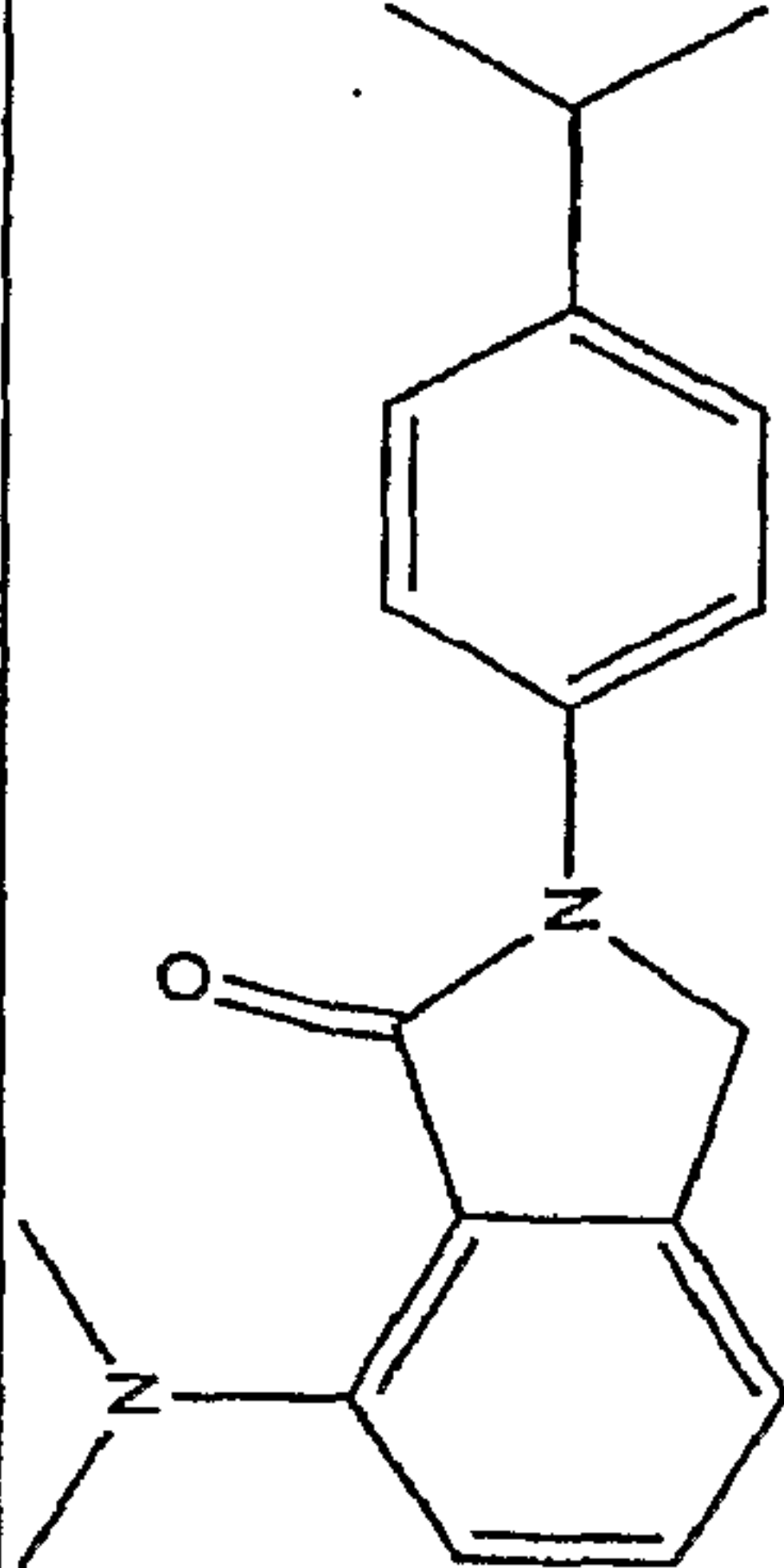
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
336		ALB- 117752	0.042	1.376
337		ALB- 117753	0.183	1.602

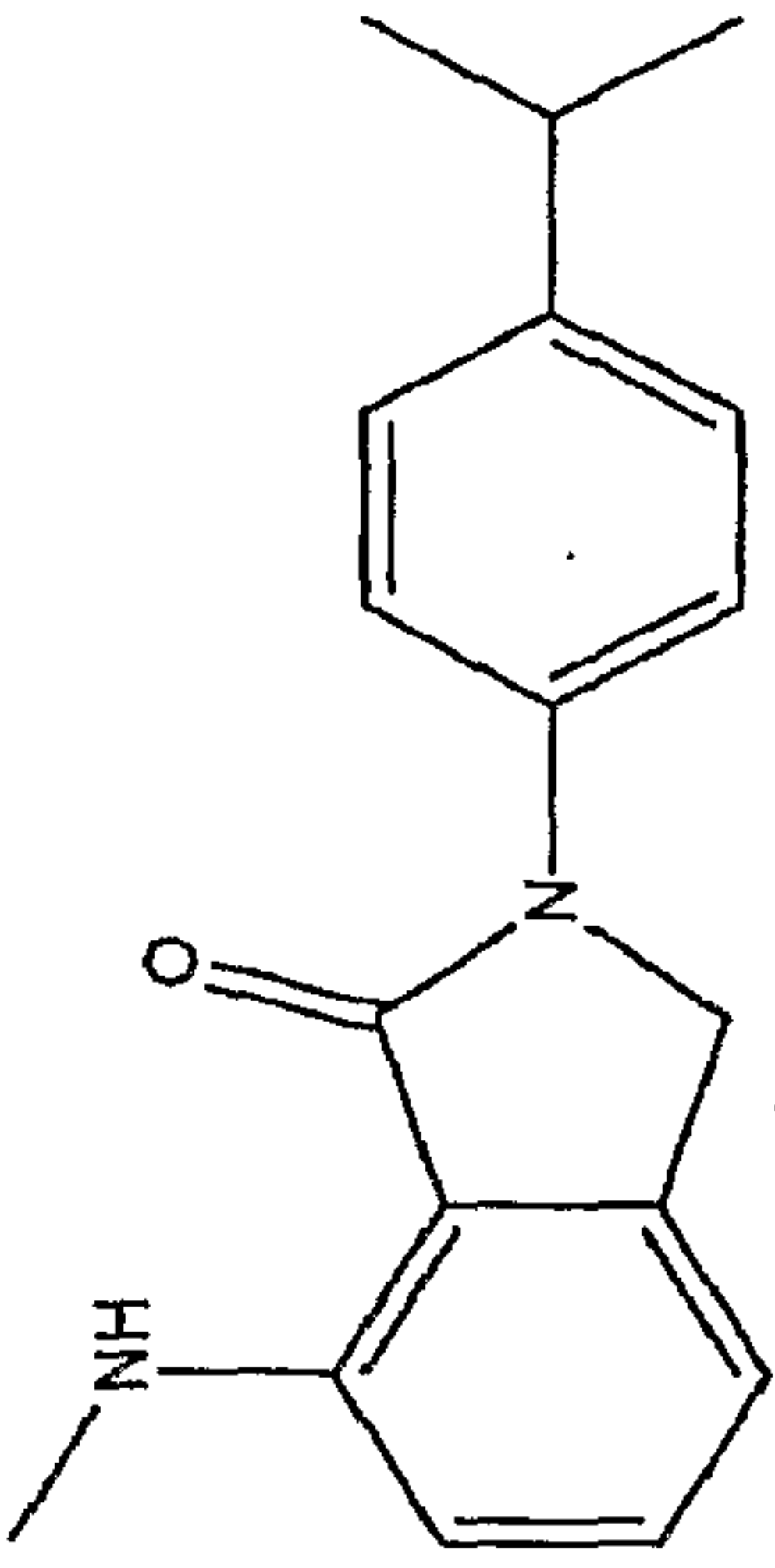
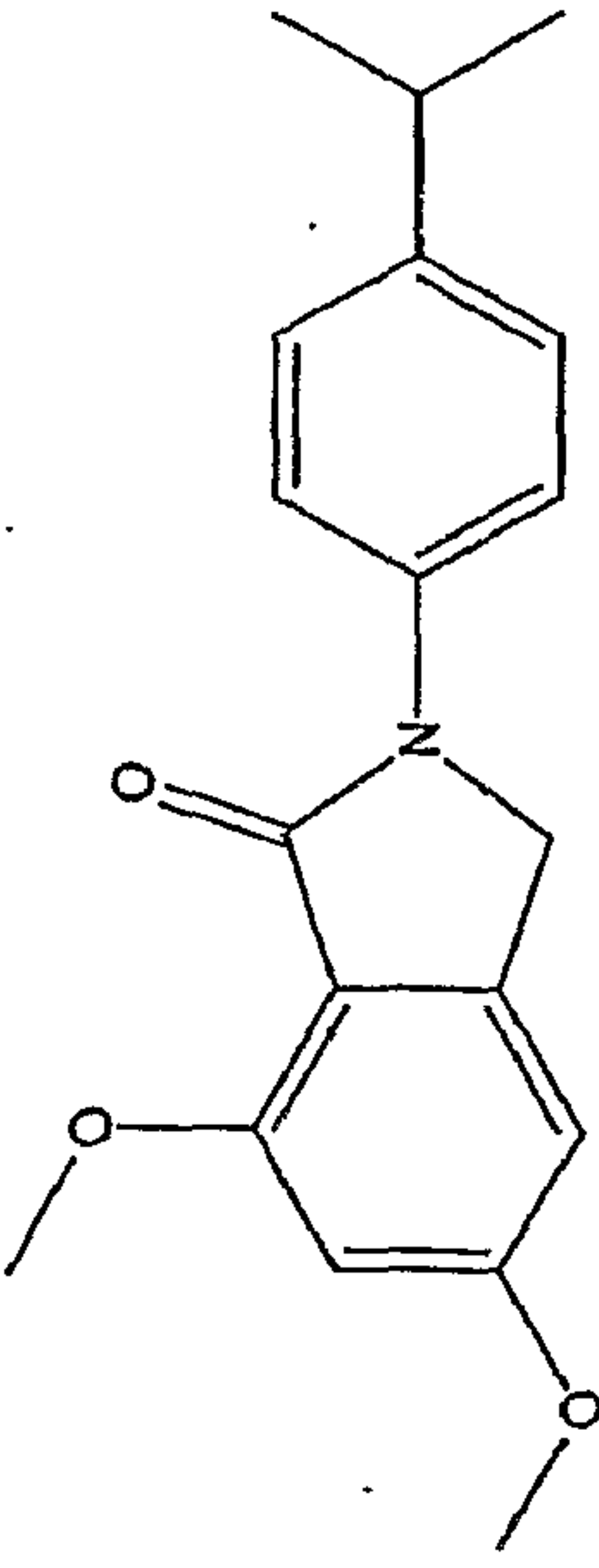
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
338		ALB- 117901		1.067
339		ALB- 117902	1.103	1.573
340		ALB- 117904	4.37	1.46

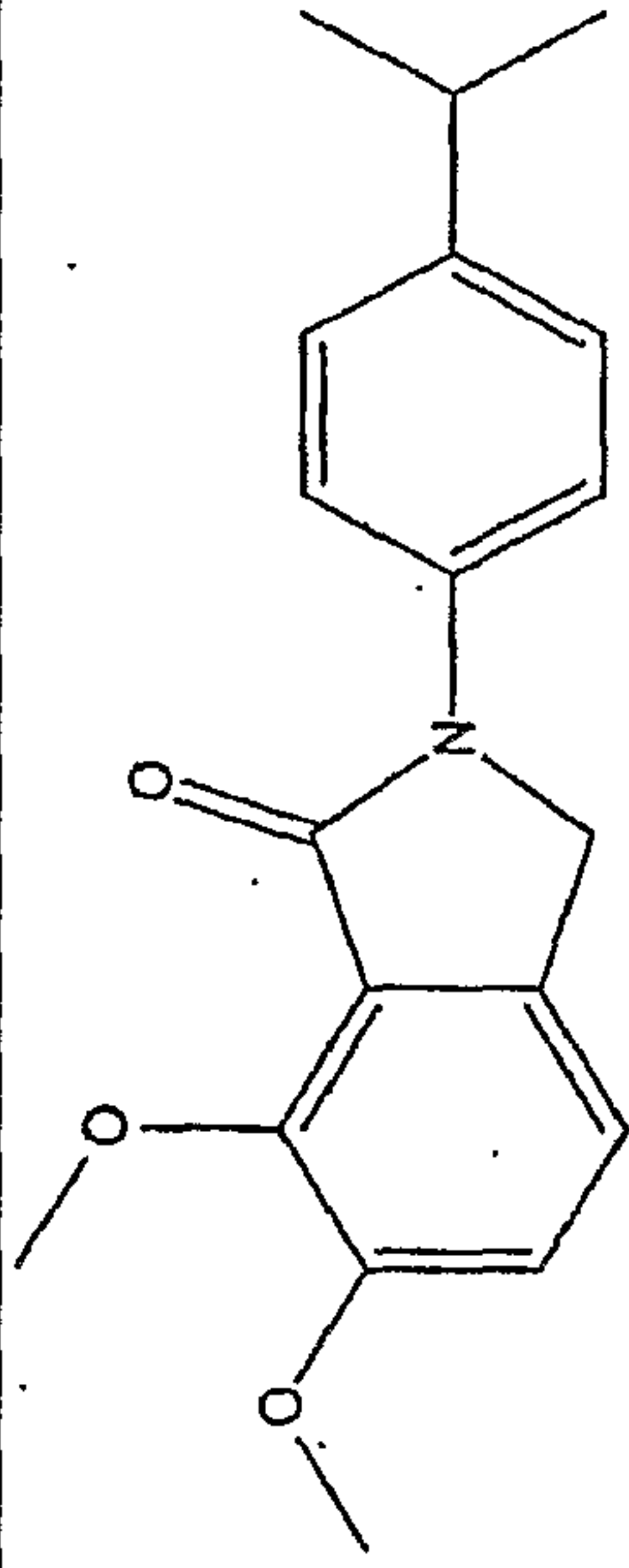
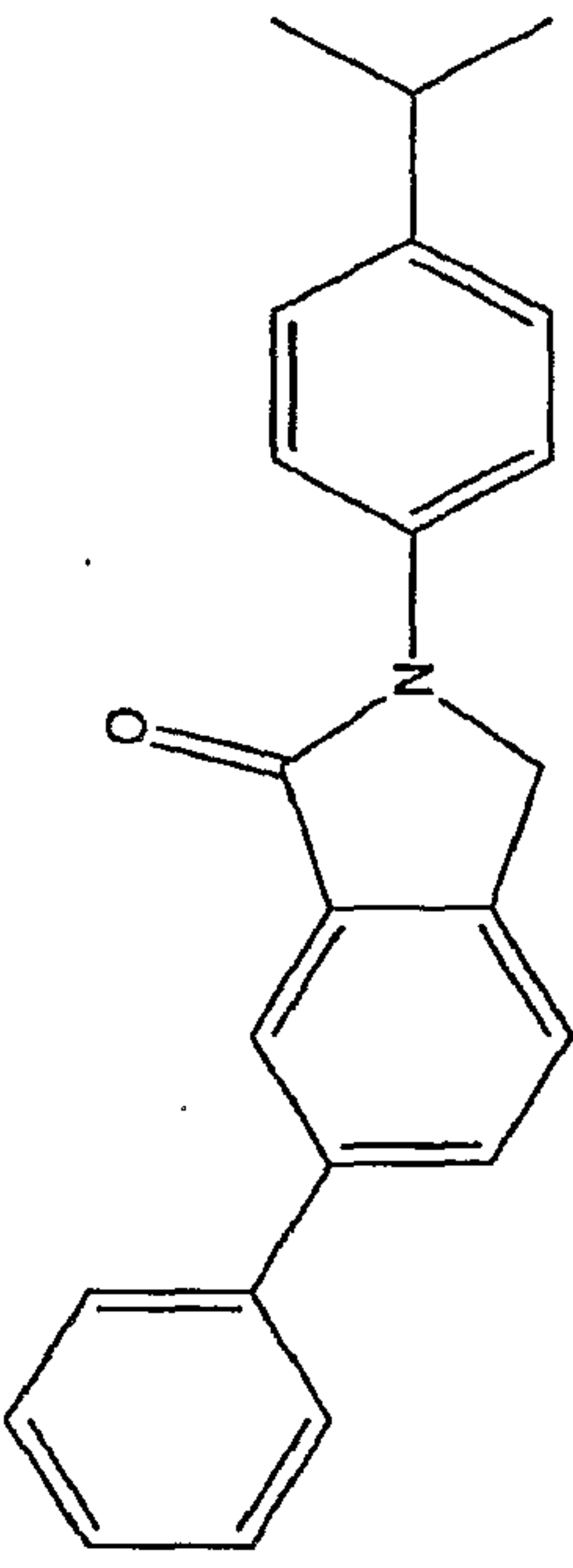
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
341		ALB- 117905	0.414	1.552
342		ALB- 118034	0.447	1.302

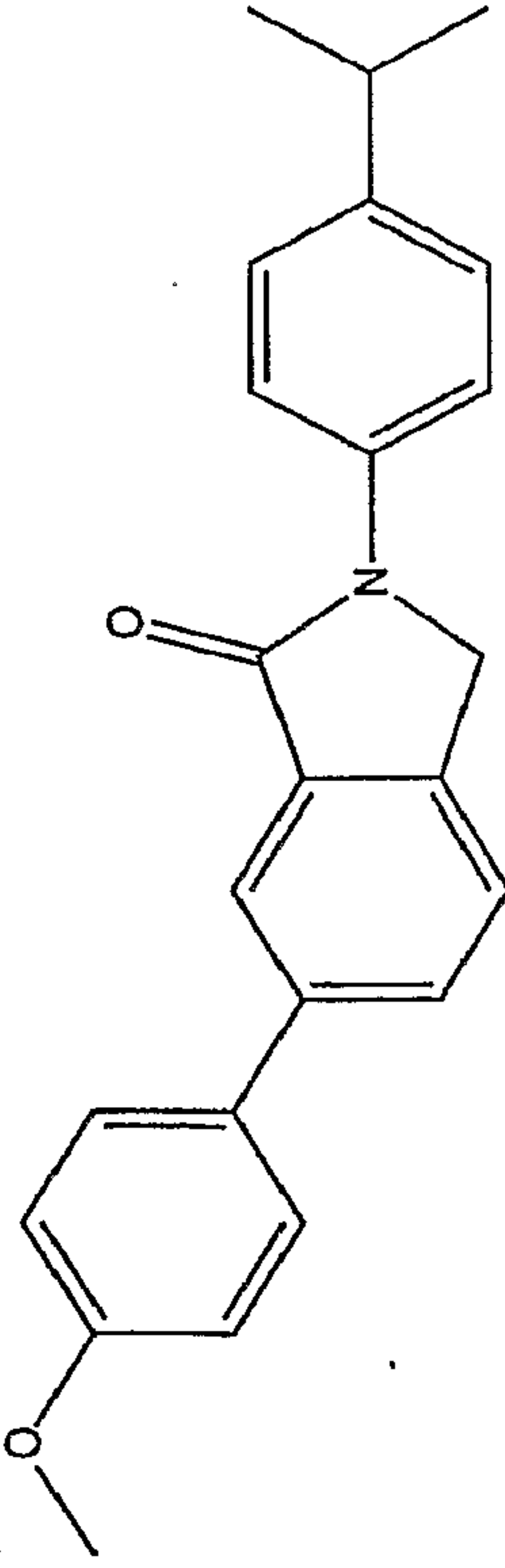
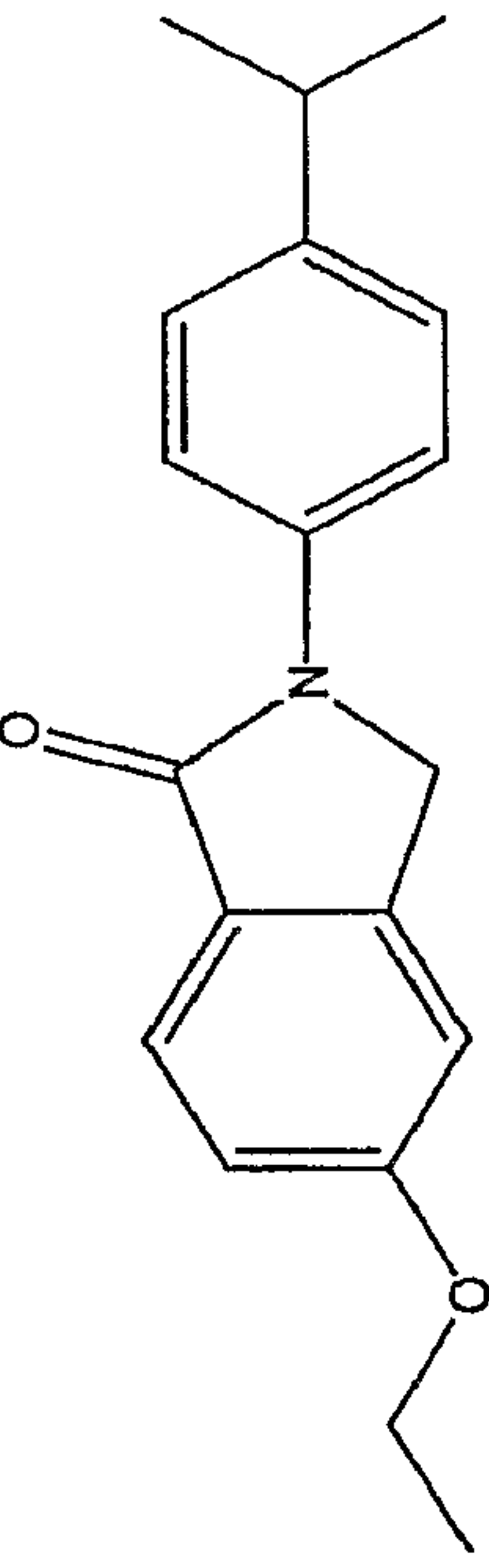
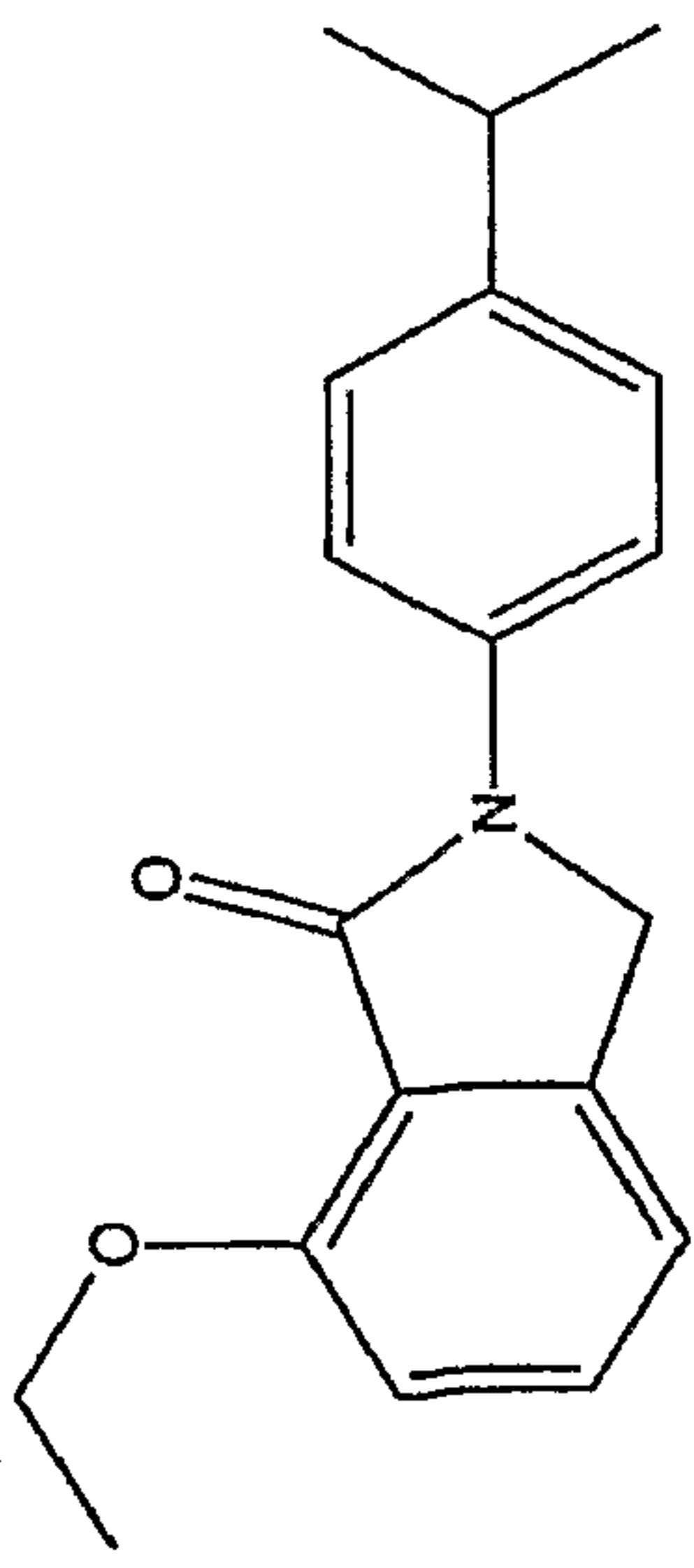
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
343		ALB- 118036	2.668	1.288
344		ALB- 118037	0.937	1.336

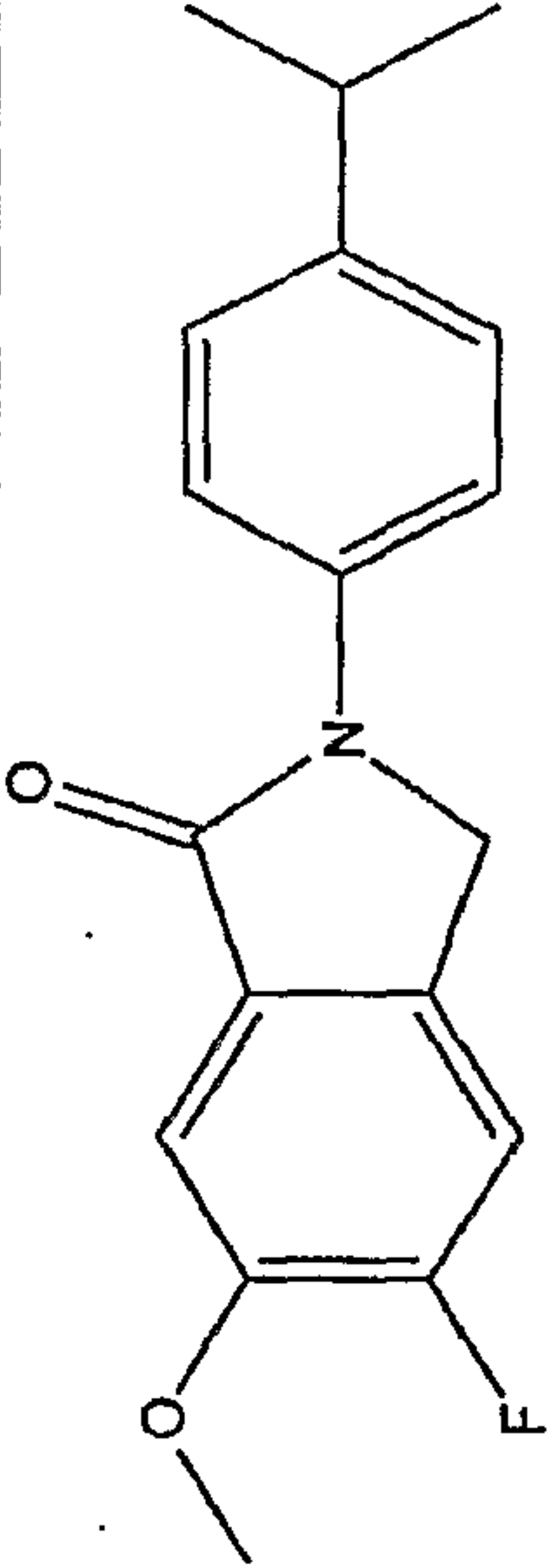
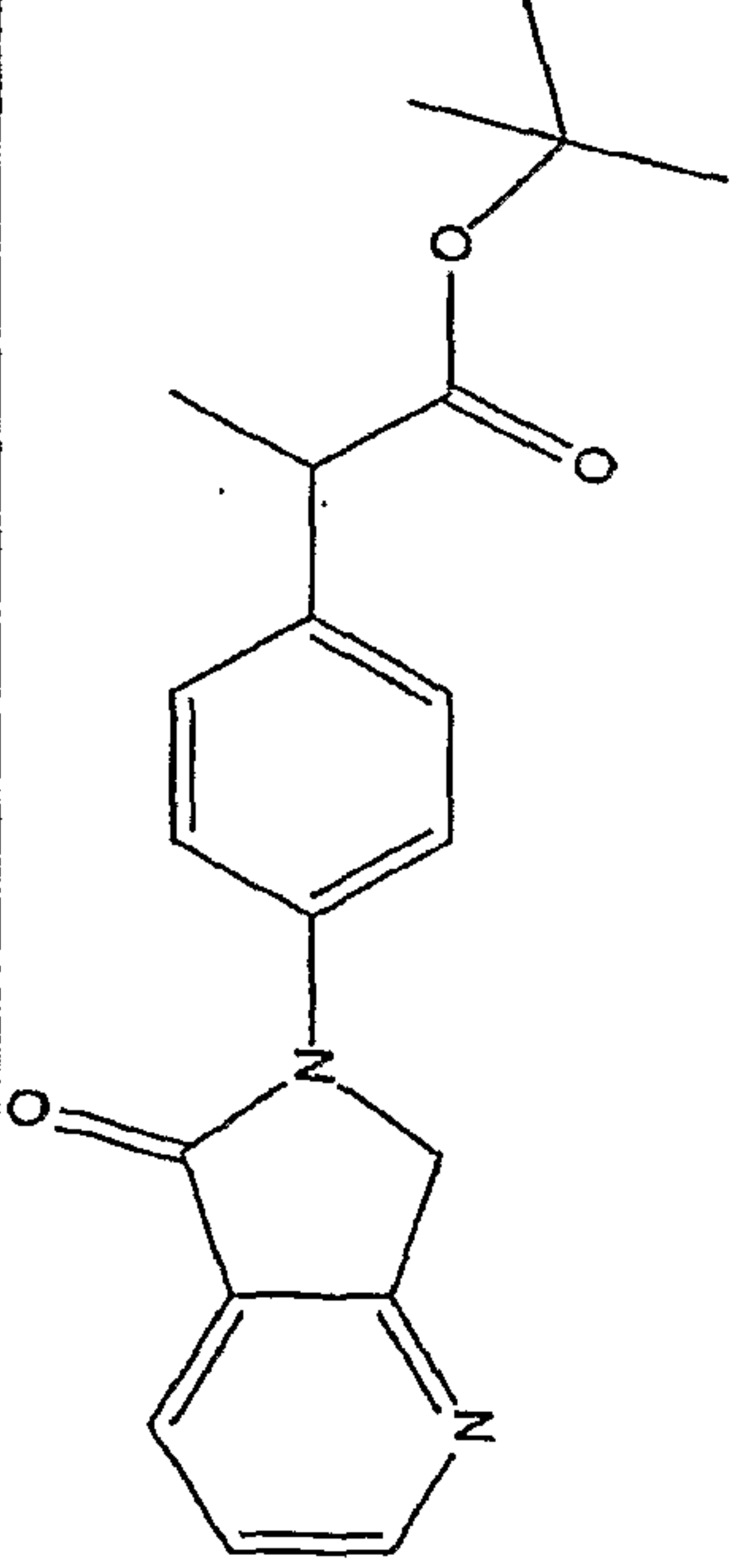
205

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
345		ALB- 118038		1.077
346		ALB- 118276		1.047
347		ALB- 118278	1.376	1.5

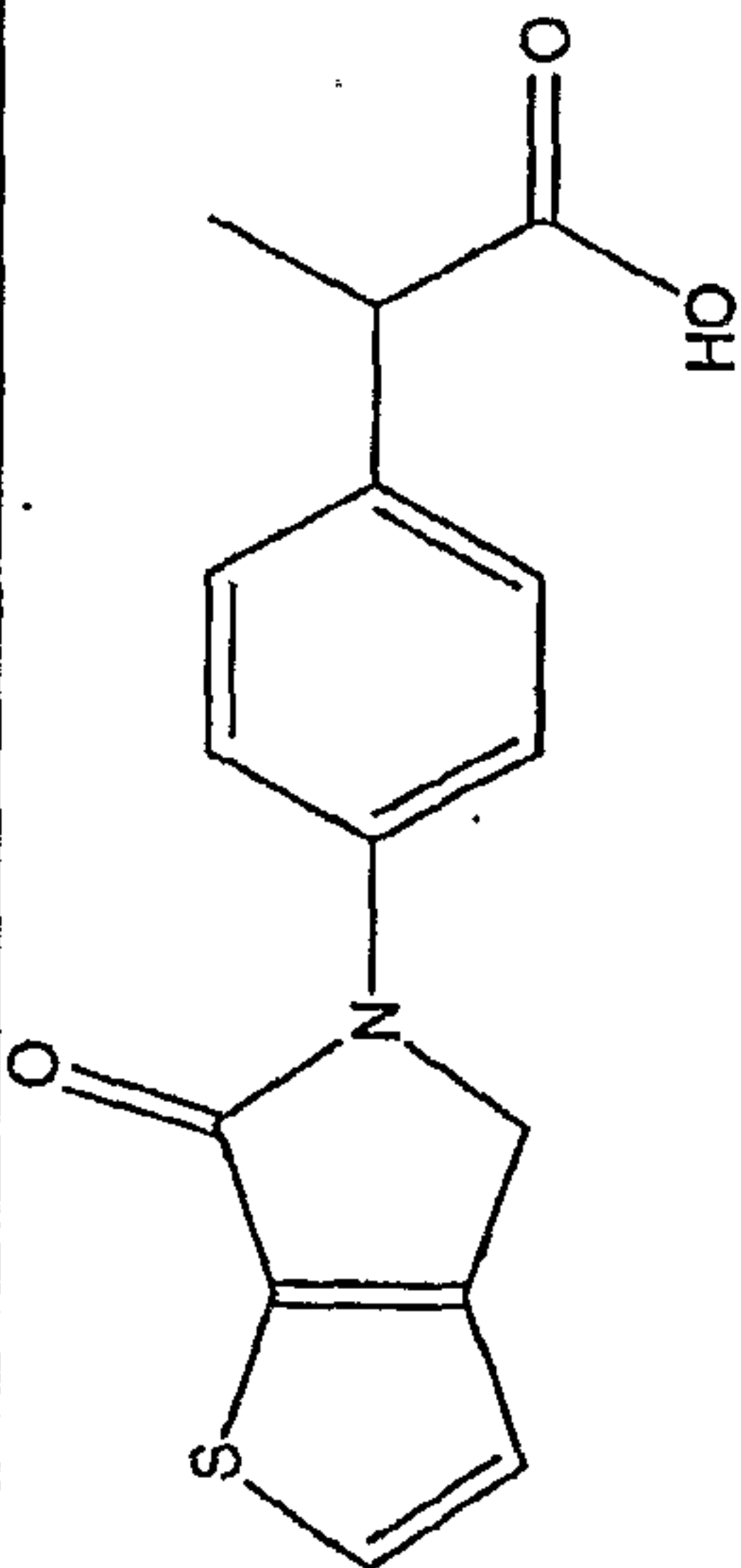
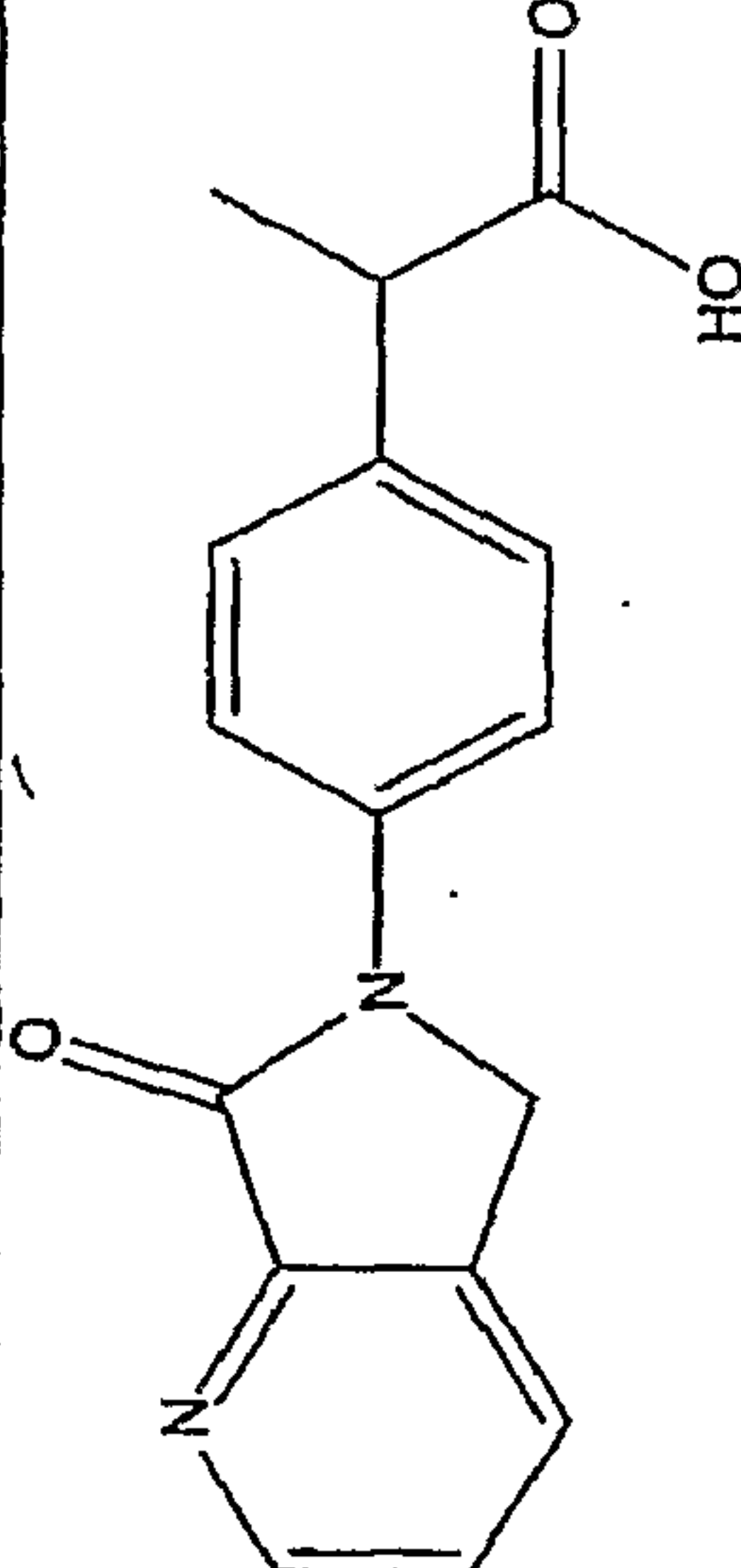
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
348		ALB- 118413	0.119	1.385
349		ALB- 112087		1.052

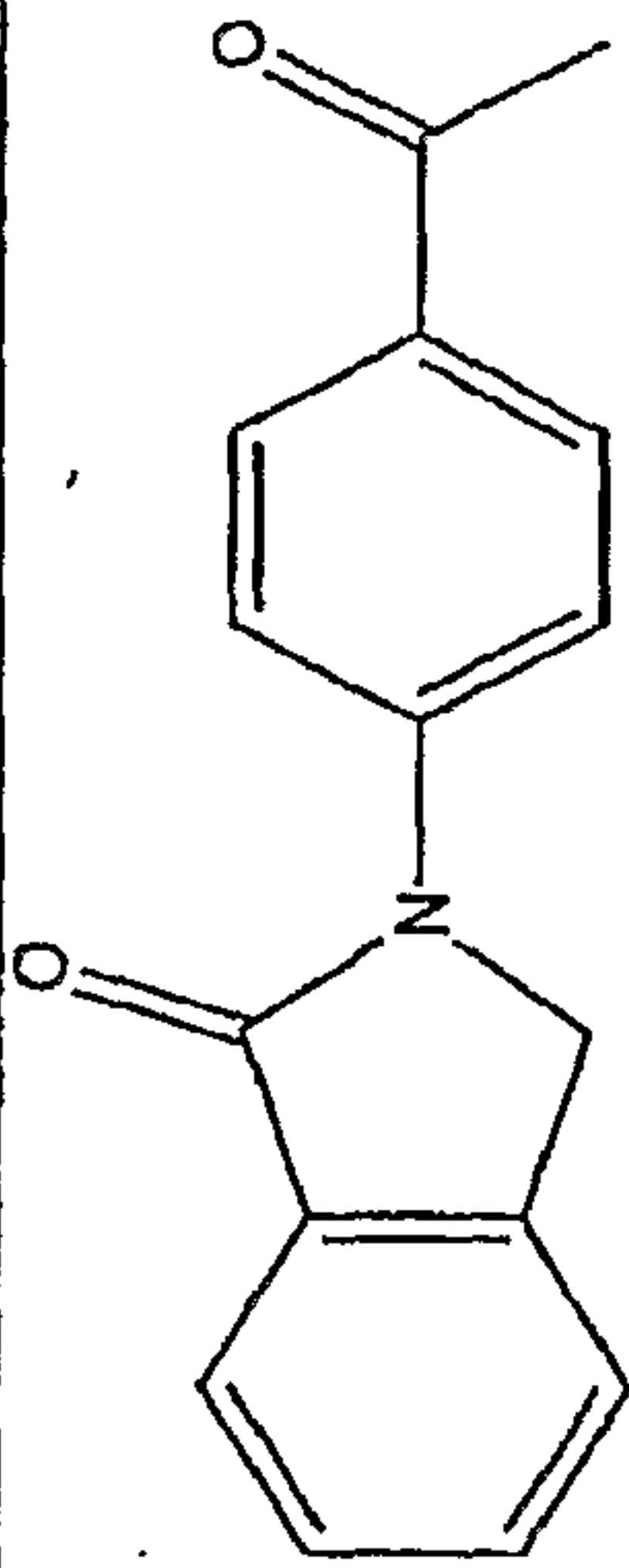
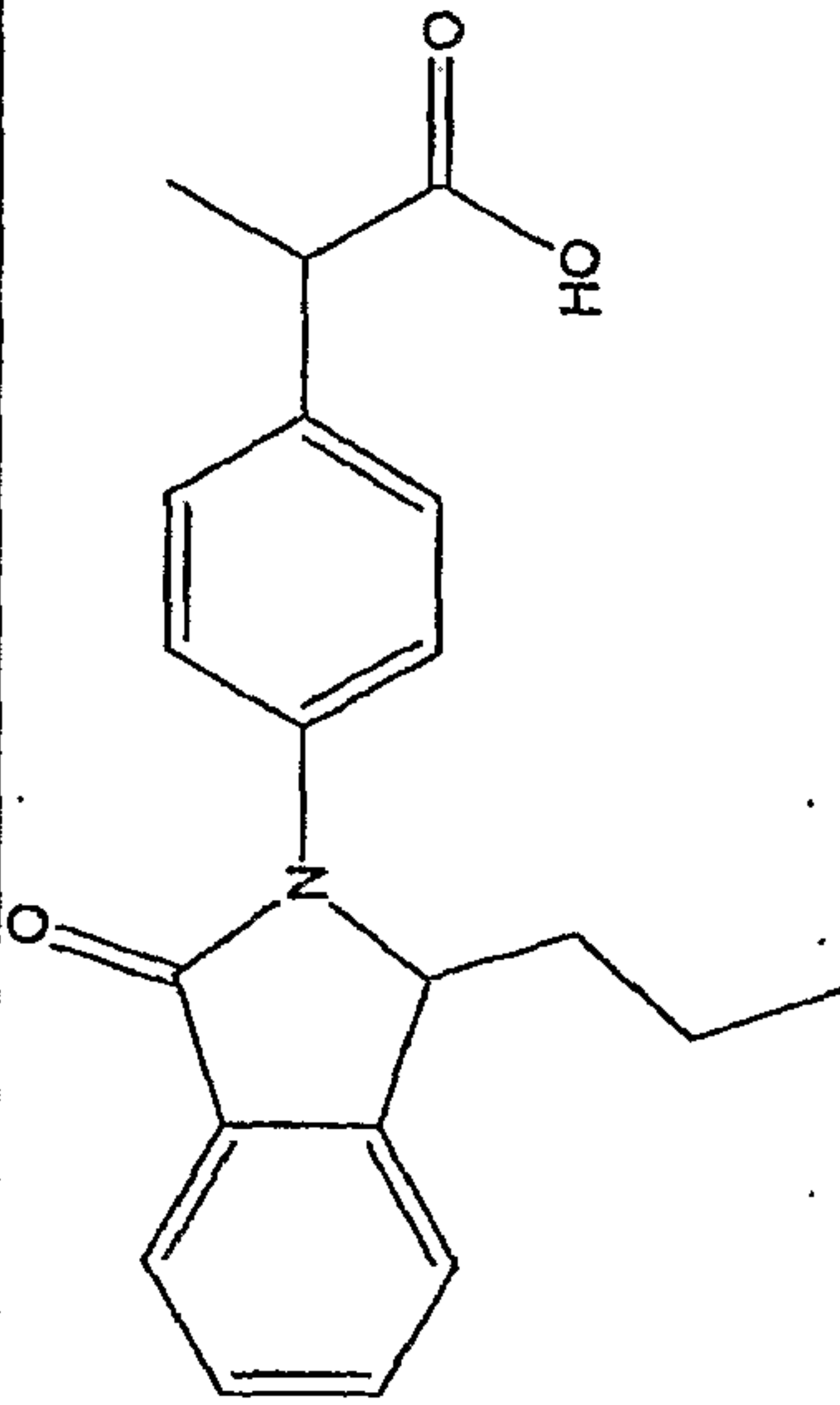
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
350		ALB- 112228	0.669	1.272
351		ALB- 112229a		1.13

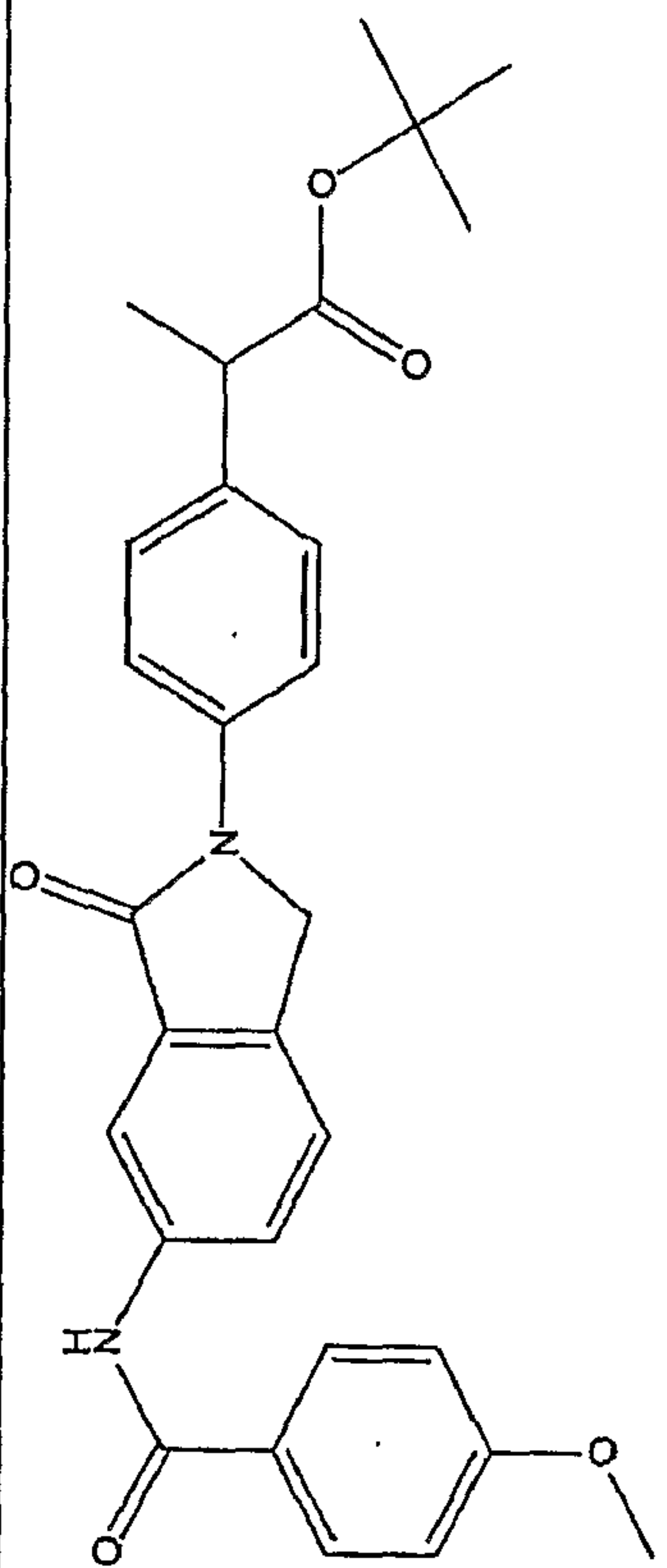
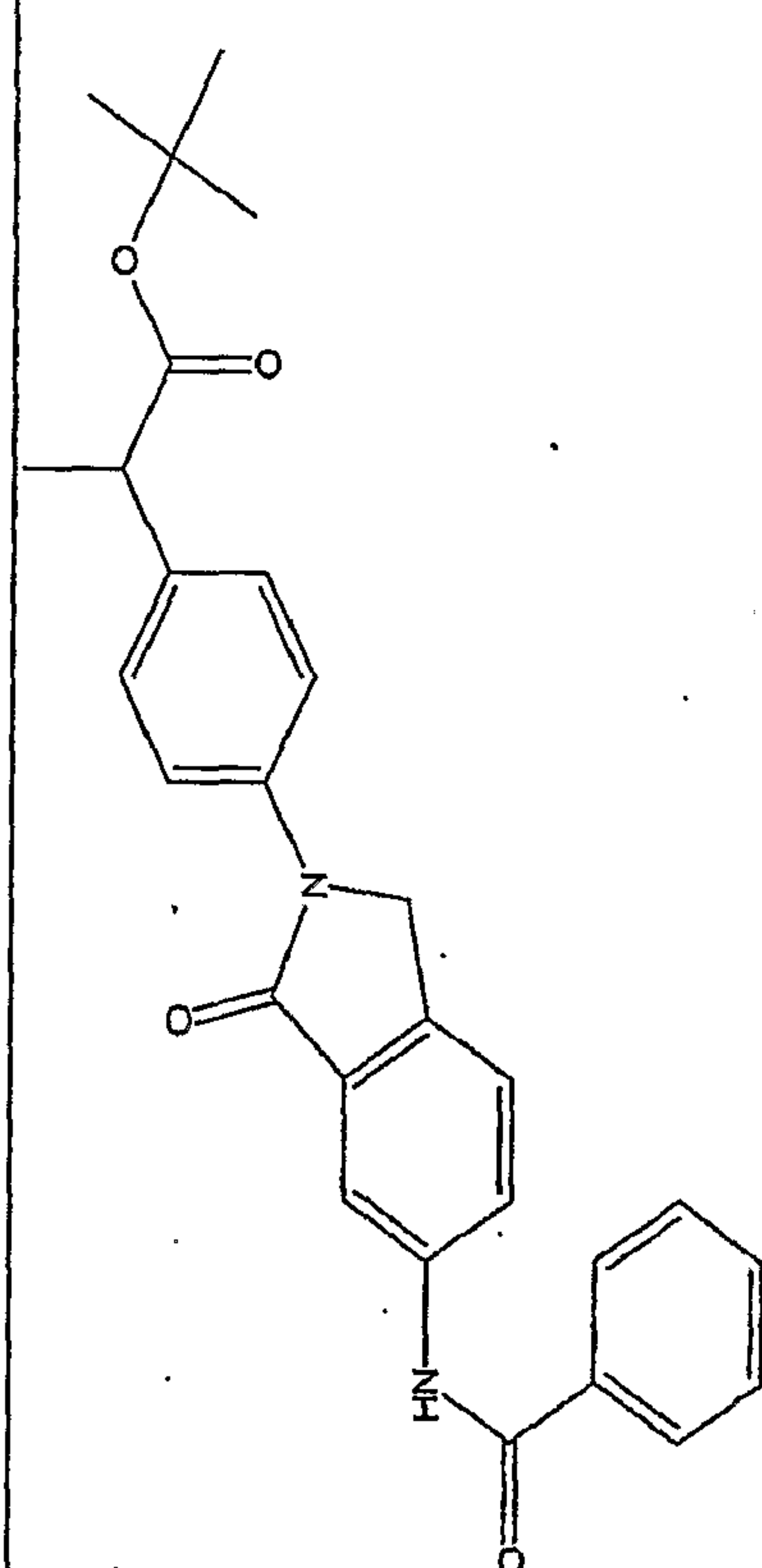
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
352		ALB- 112360	0.424	1.137
353		ALB- 111795	25.81	1.411

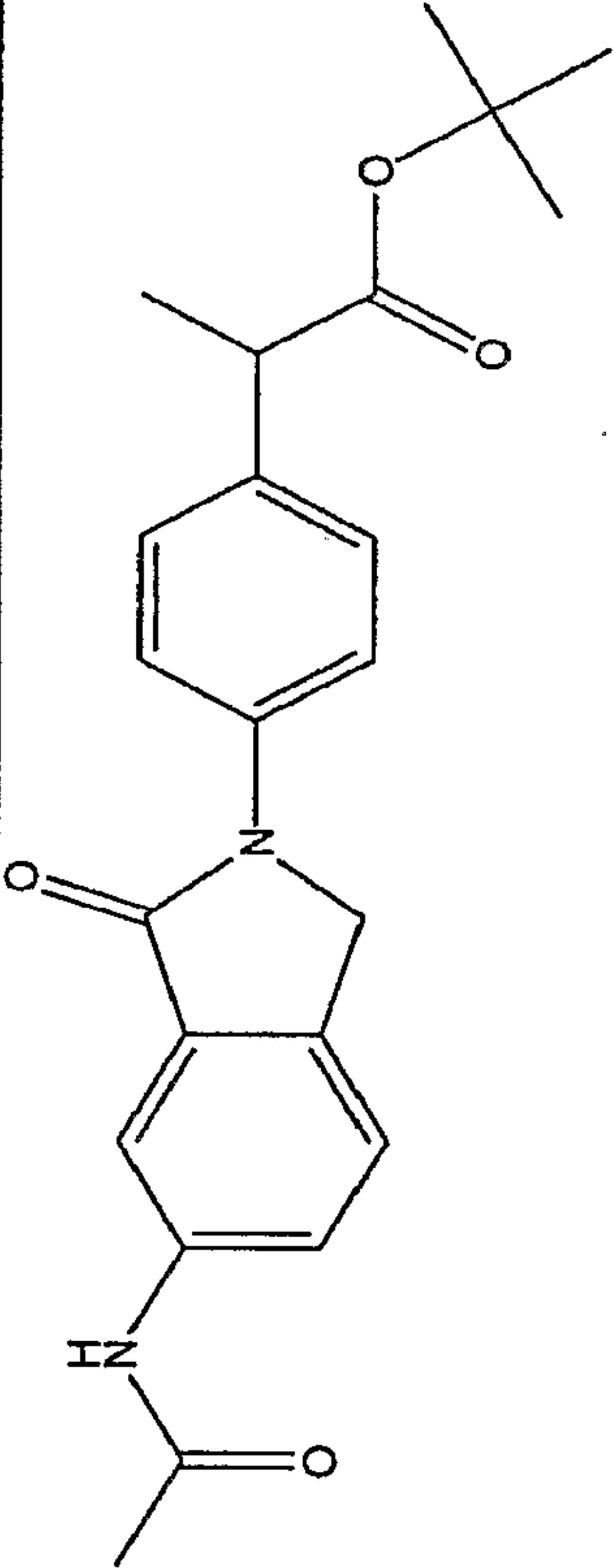
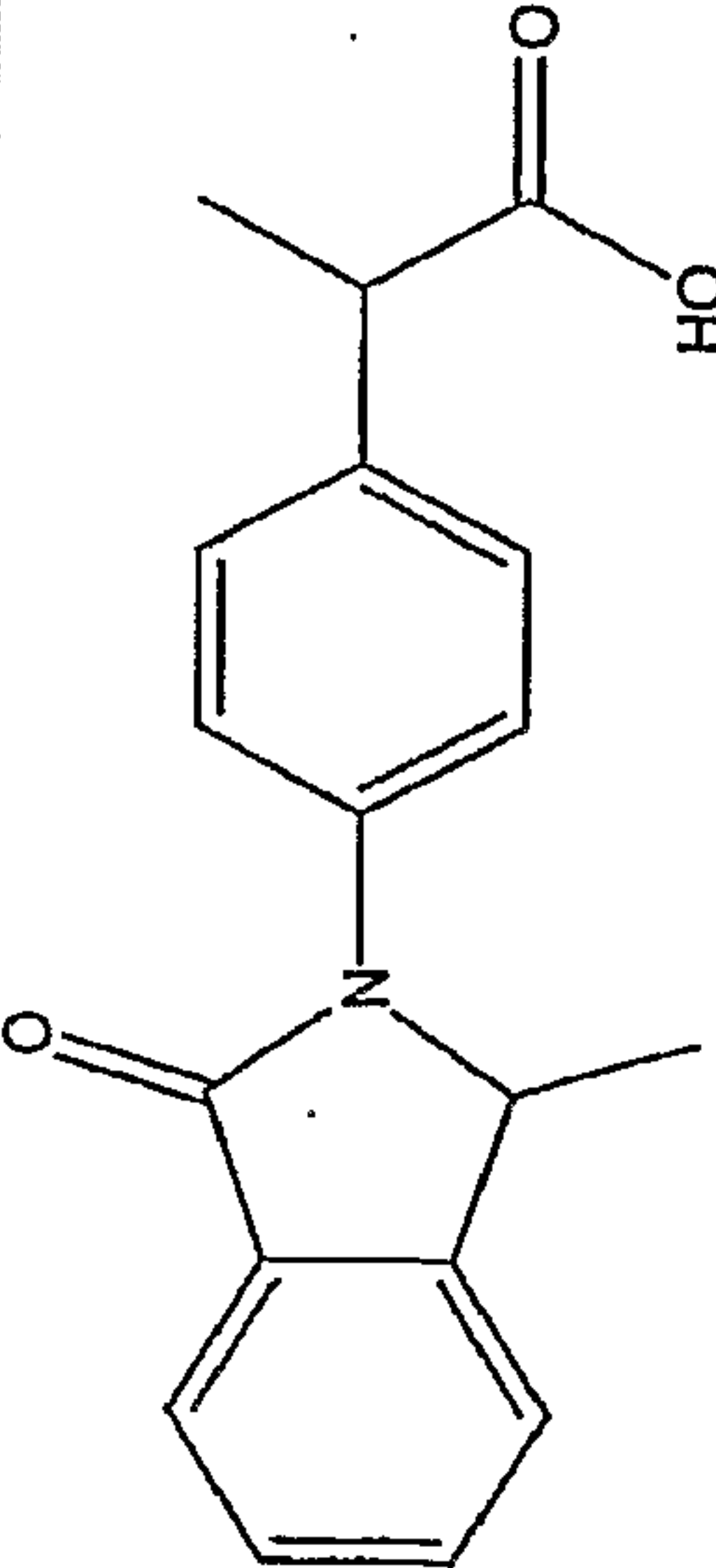
209

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
354		ALB- 111954		1.039
355		ALB- 111958		1.057

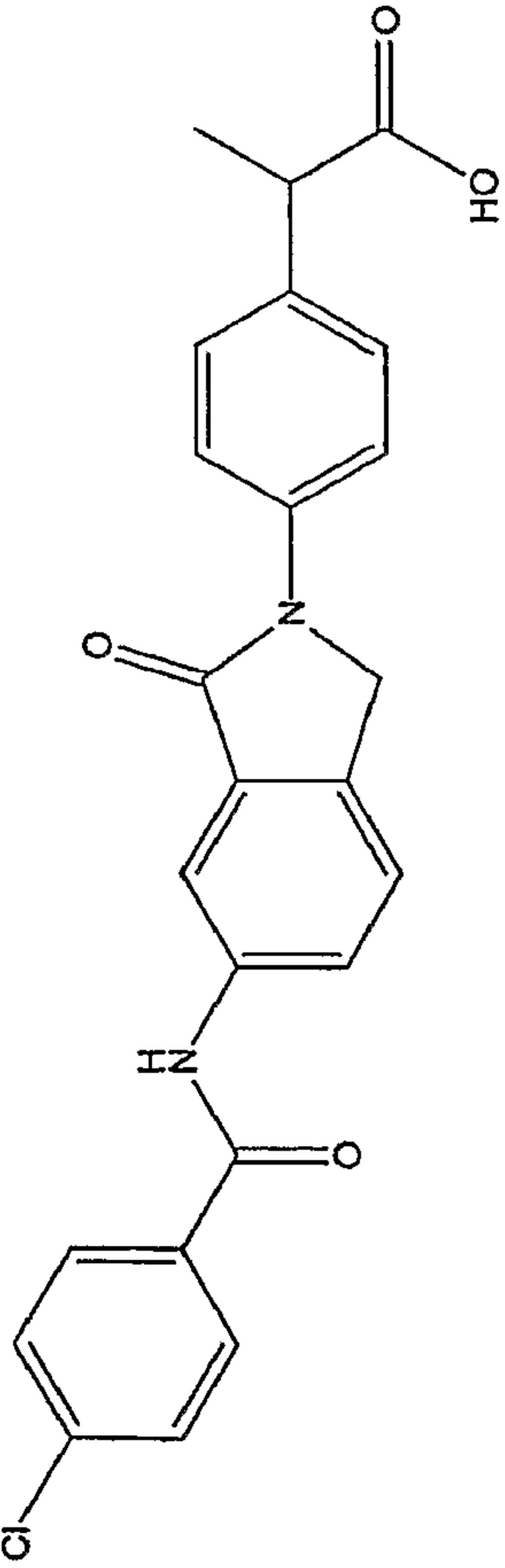
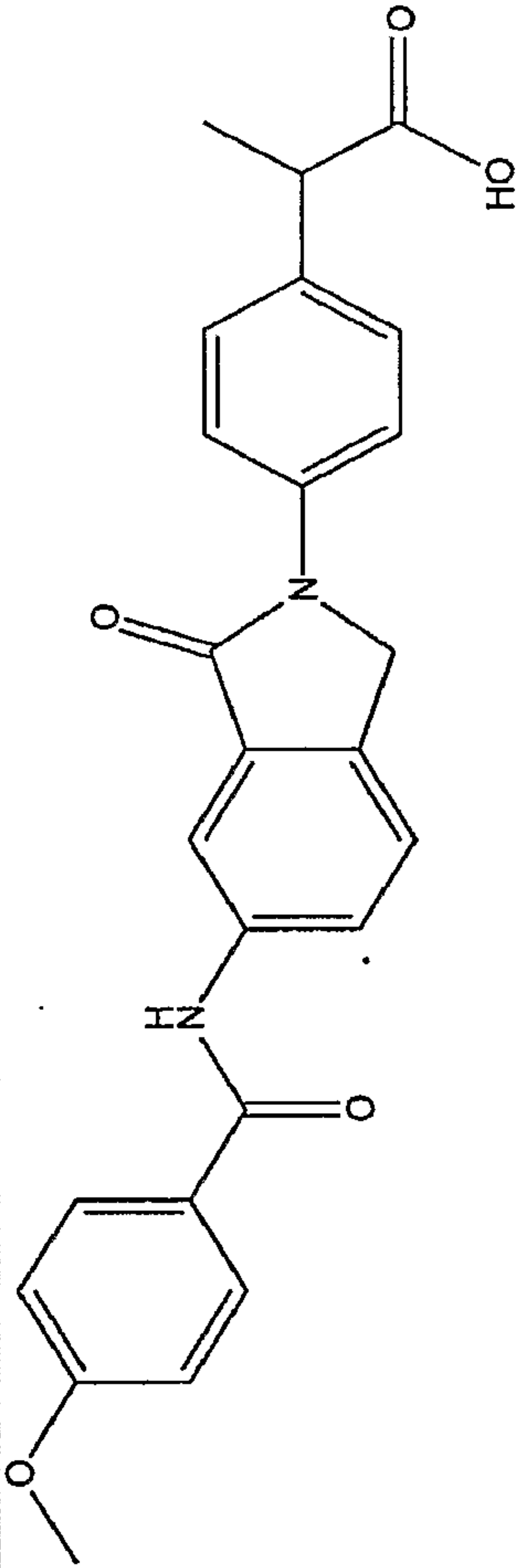
210

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
356		ALB- 111960	6.622	1.237
357		ALB- 111964	1.425	1.627

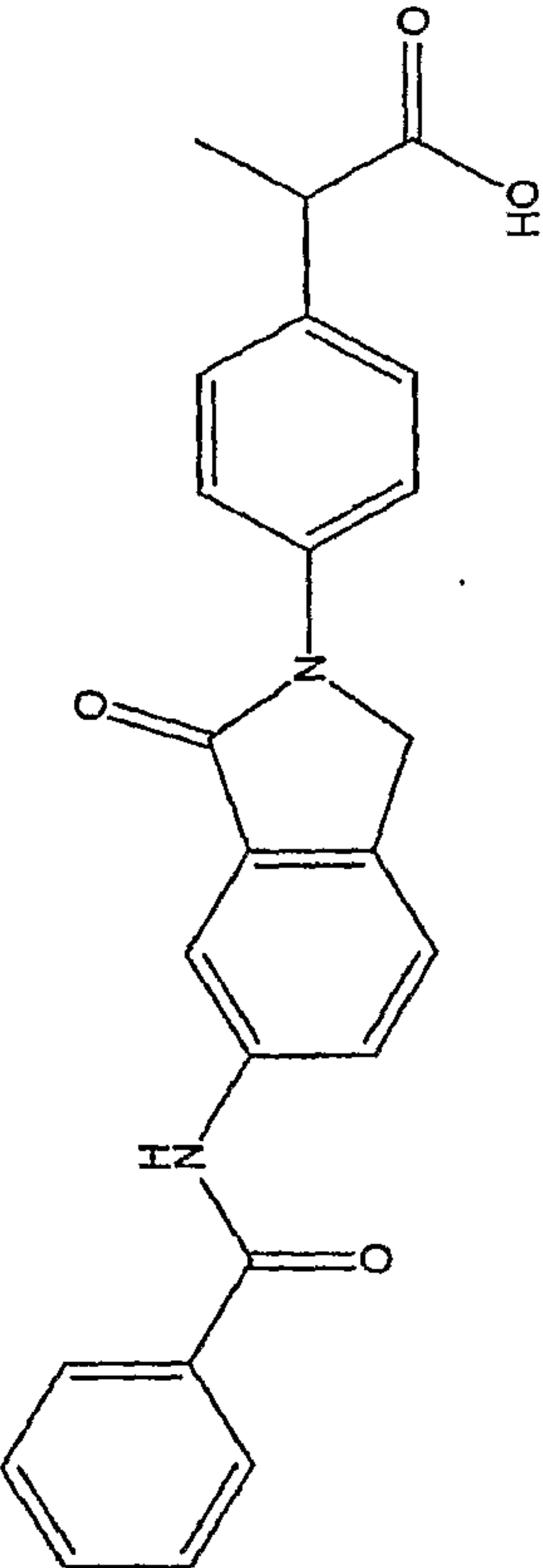
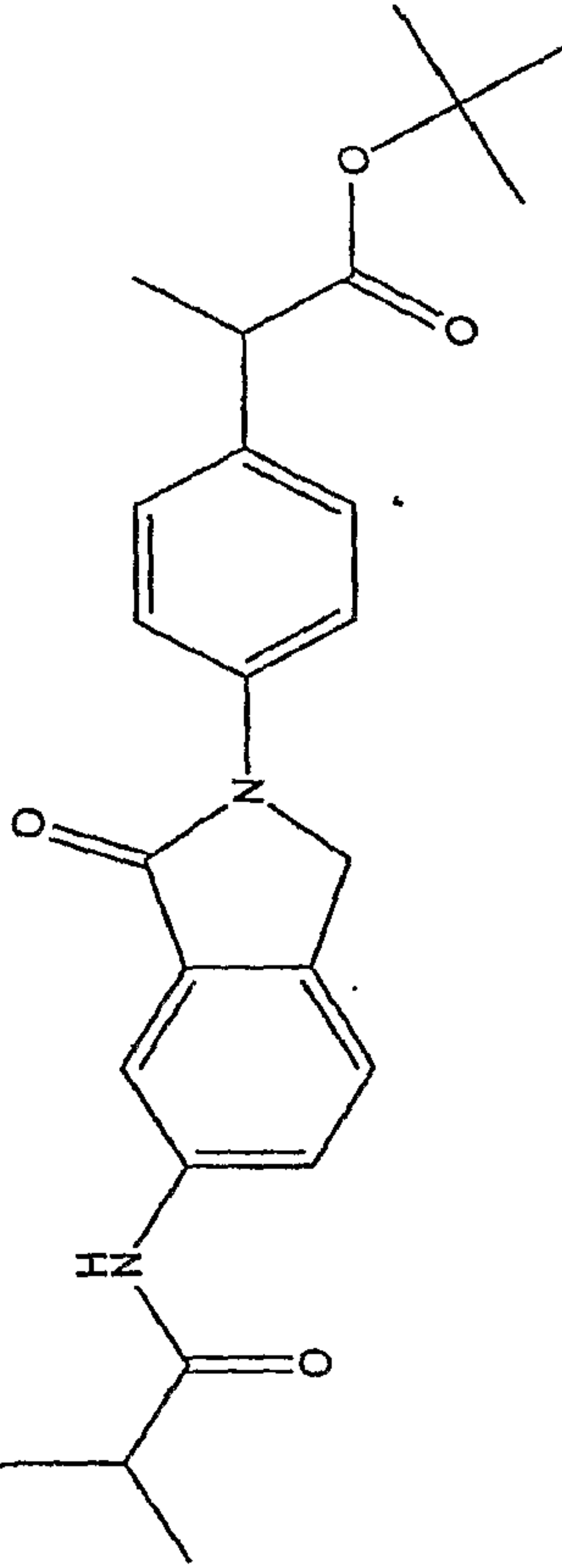
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
358		ALB- 111983	9.465	1.065
359		ALB- 111984	9.465	1.188

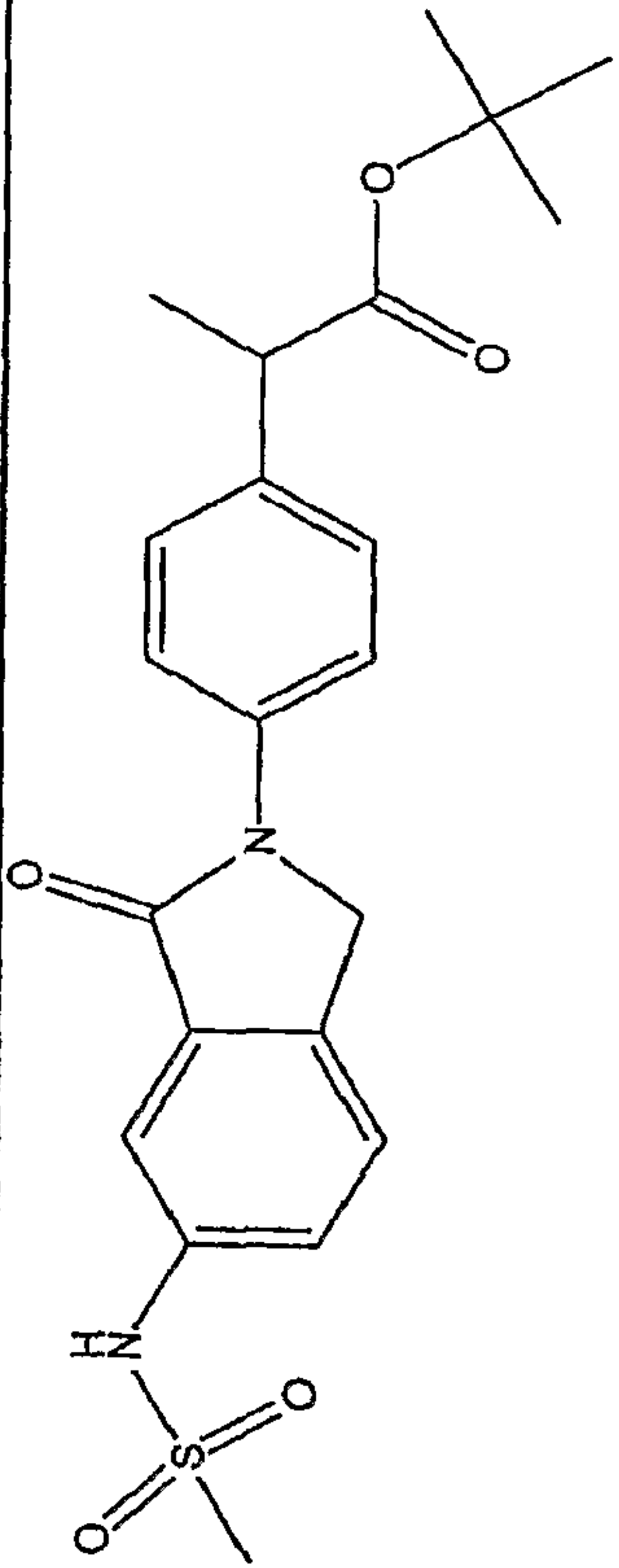
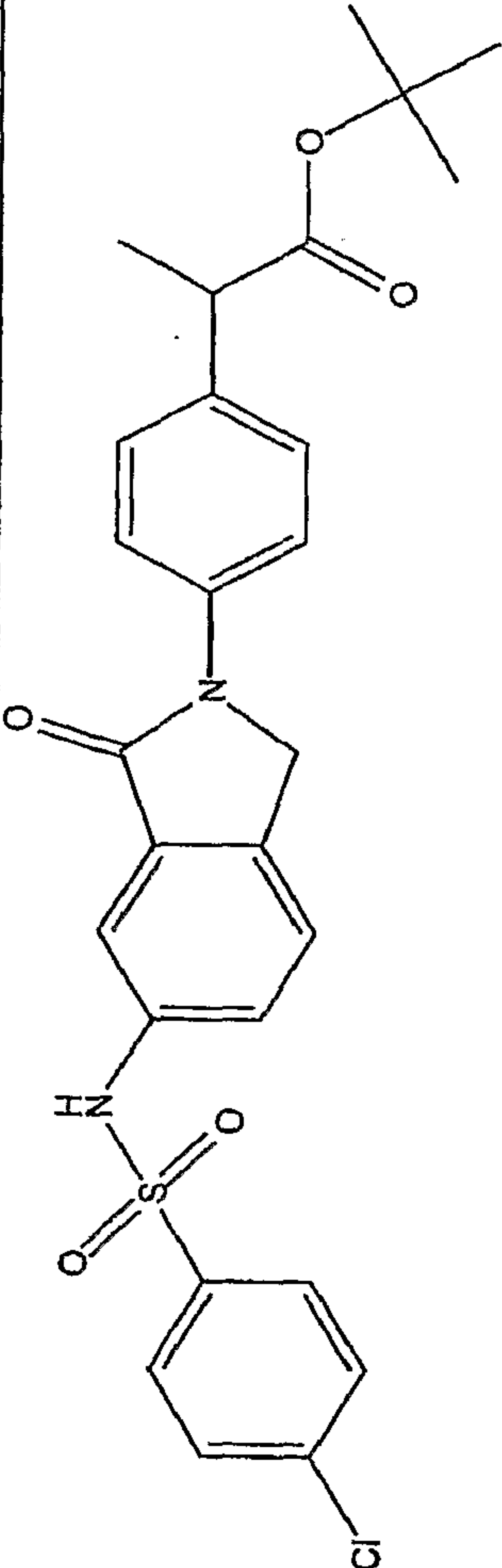
212

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
360		ALB- 111986		1.056
361		ALB- 111989		1.065

213

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
362		ALB- 111997	0.175	1.006
363		ALB- 112070		1.106

214

Table I

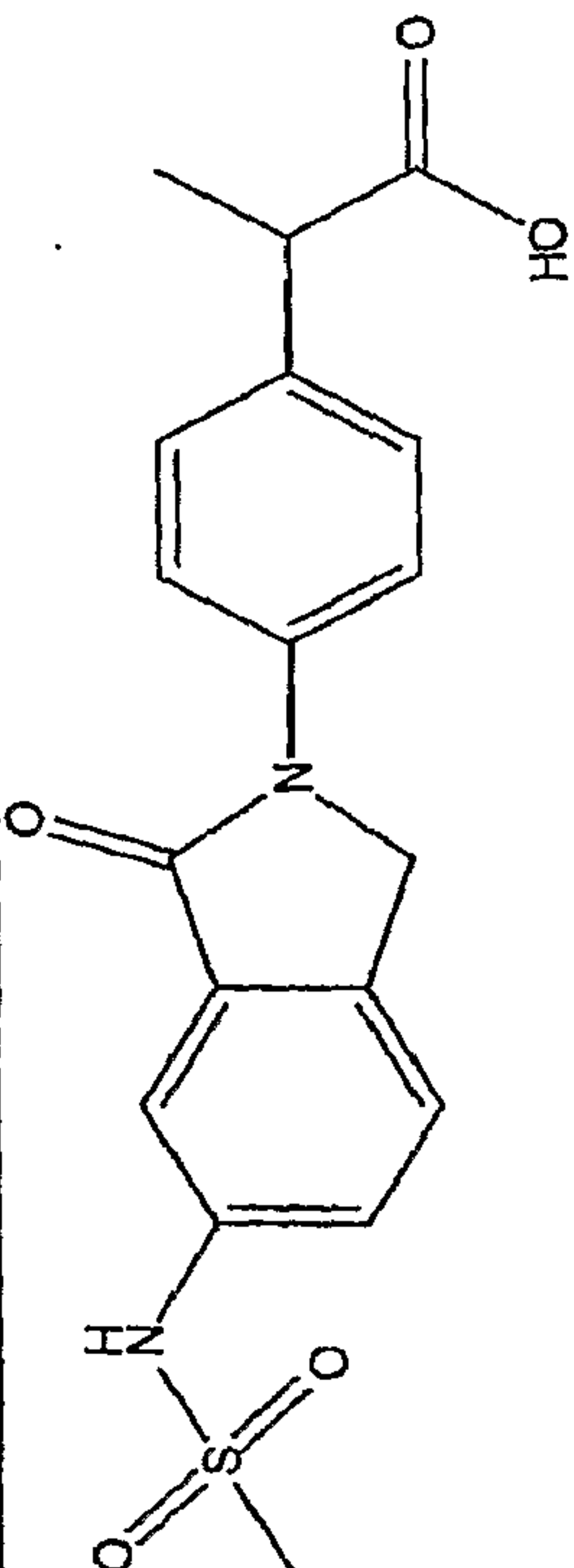
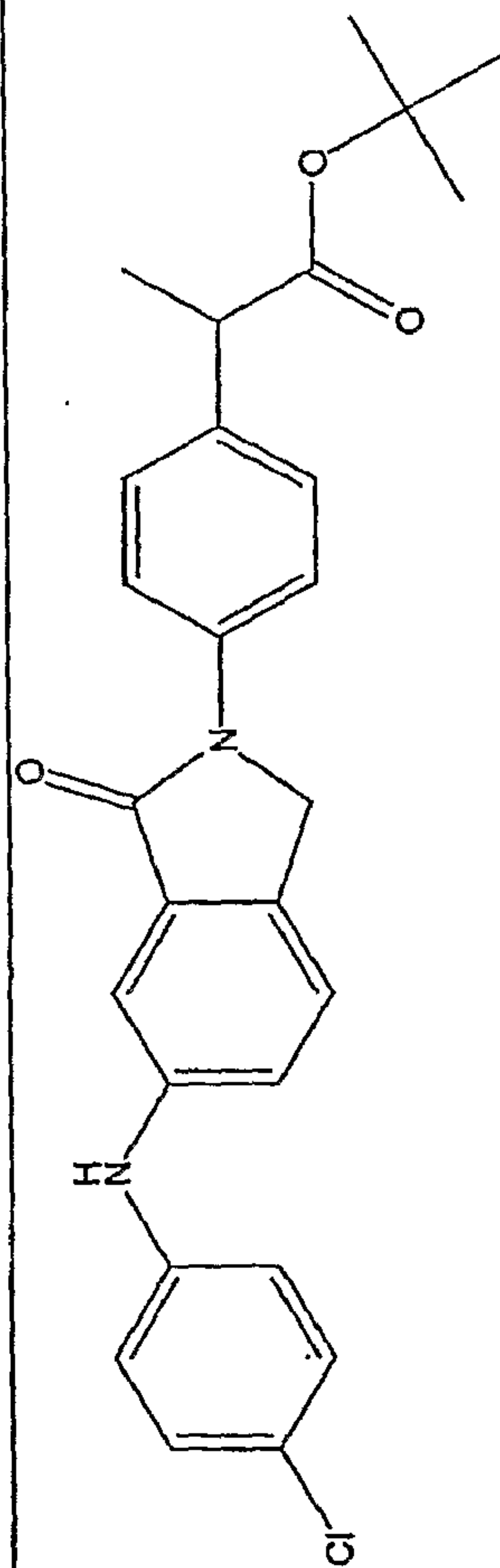
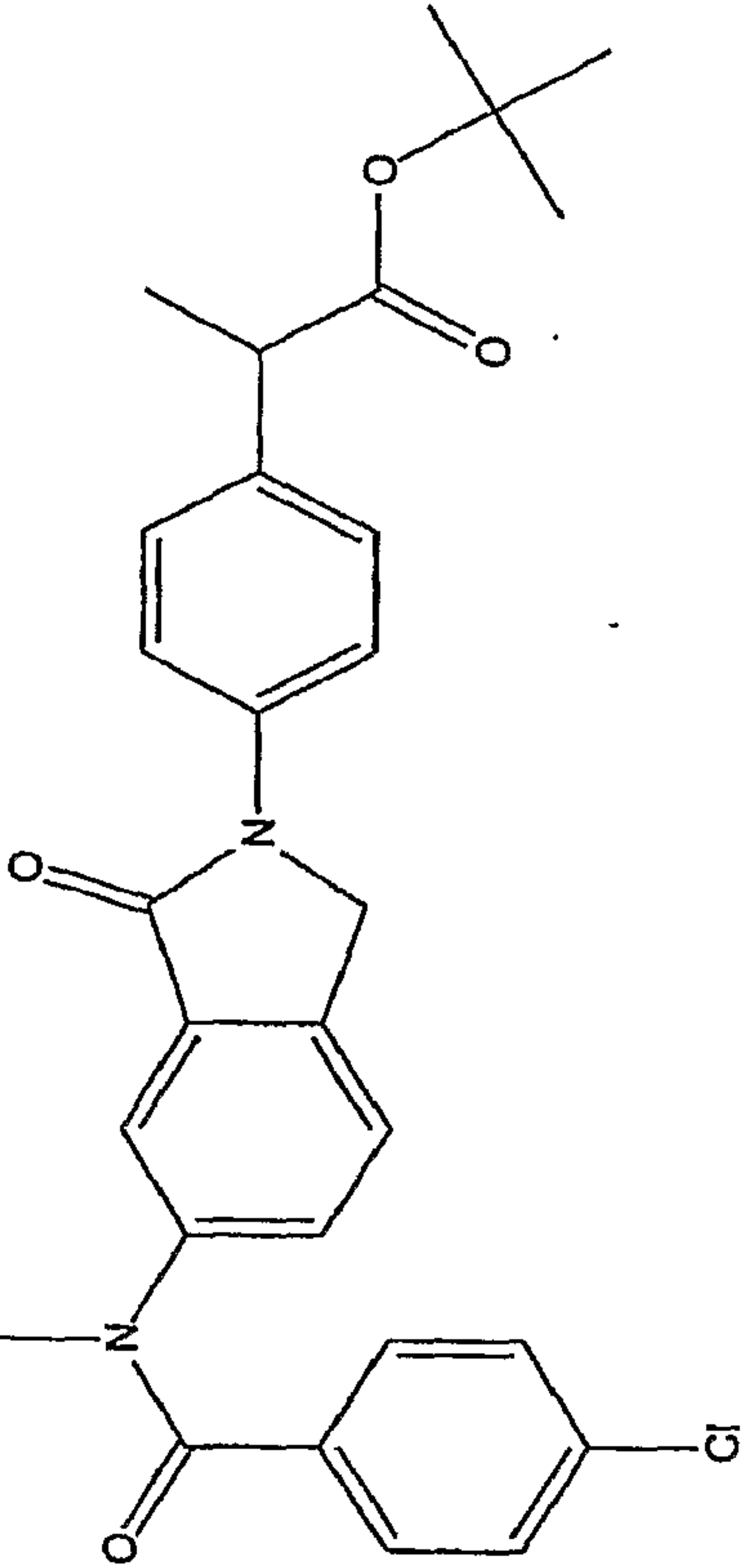
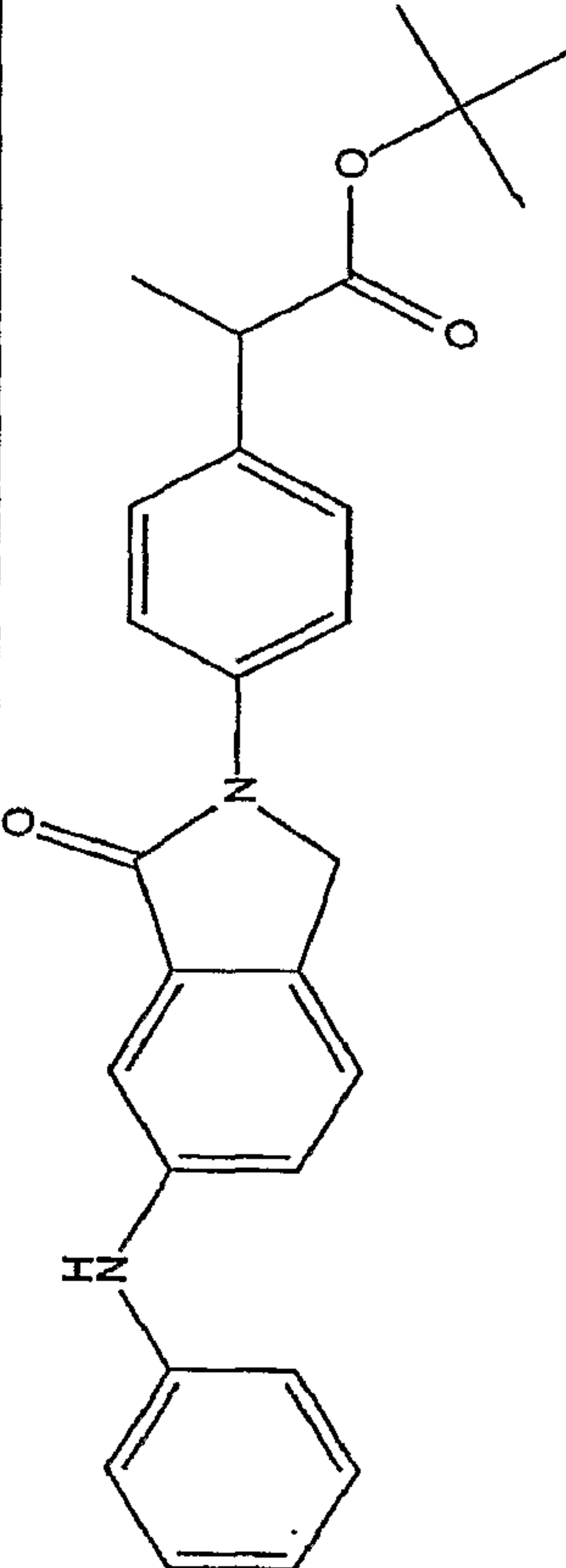
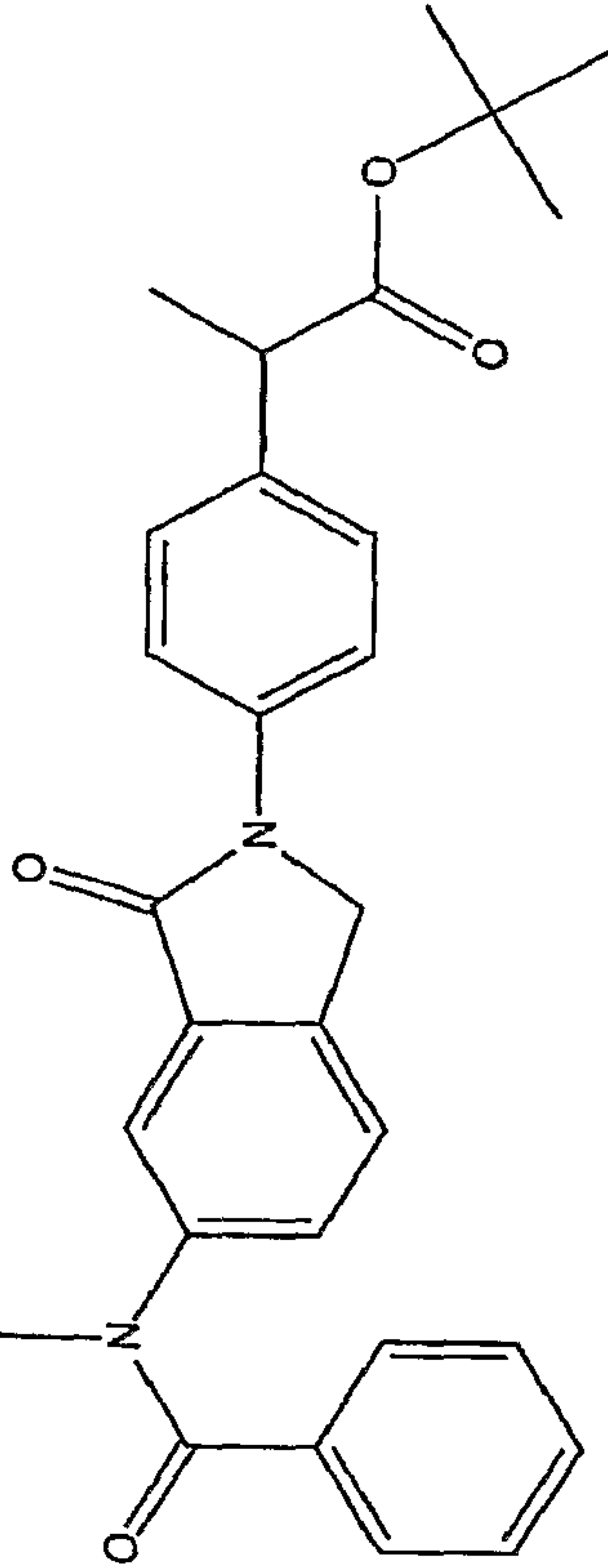
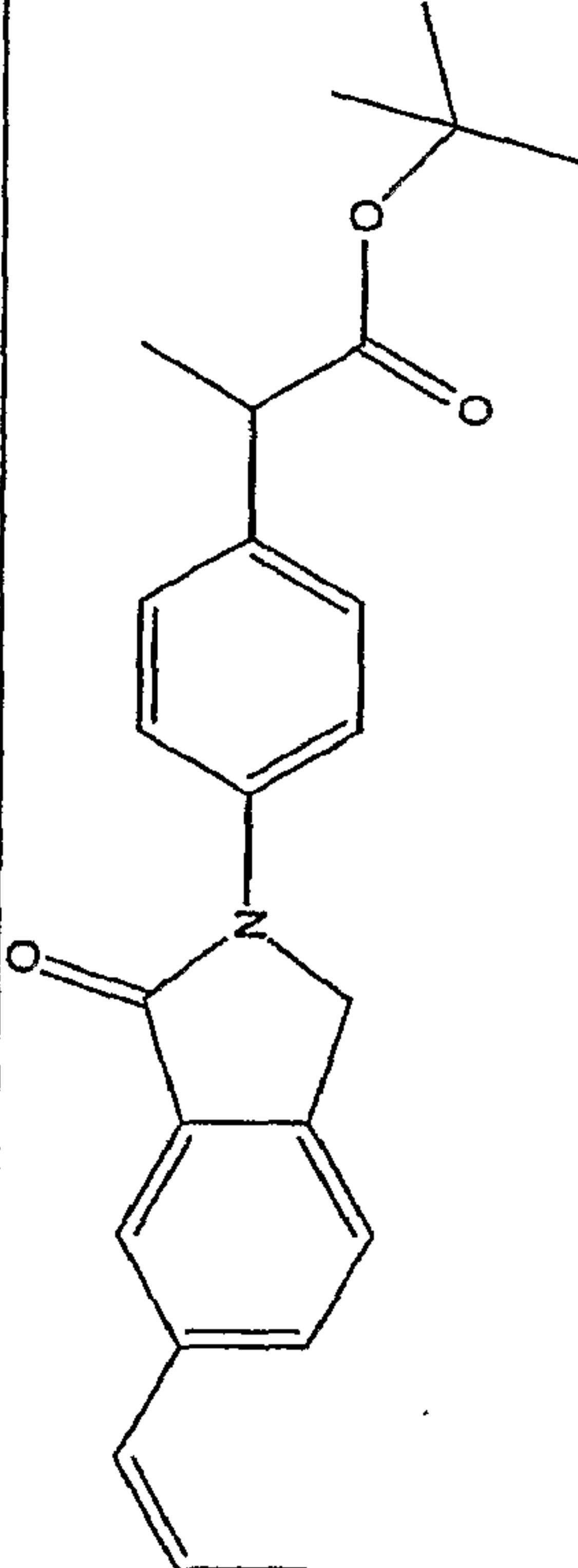
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
364		ALB- 112071		1.068
365		ALB- 112166		1.036

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
366		ALB- 112167		1.012
367		ALB- 112168		1.153

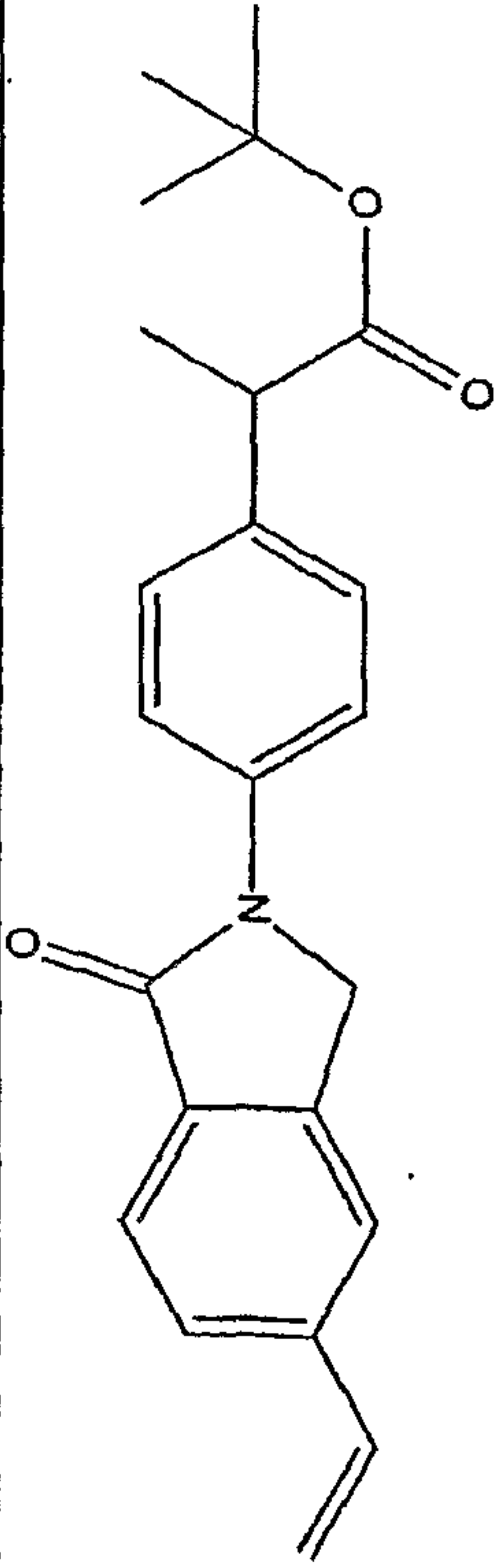
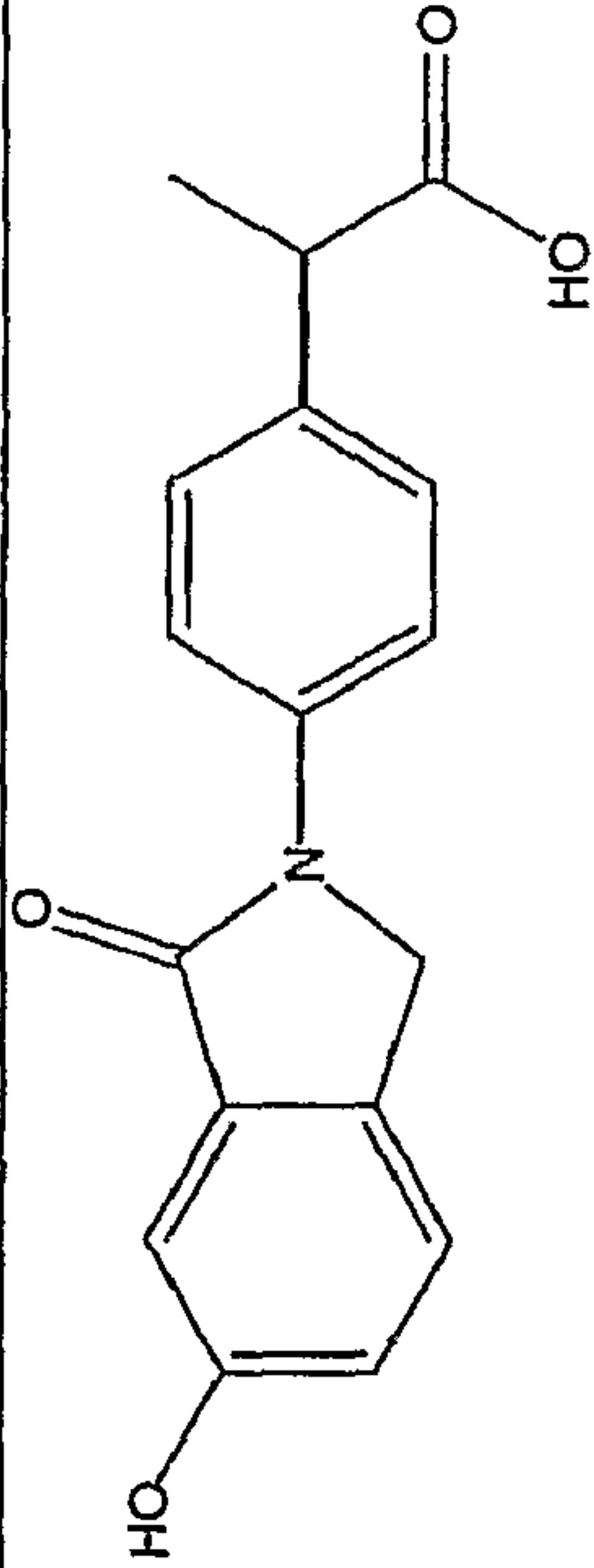
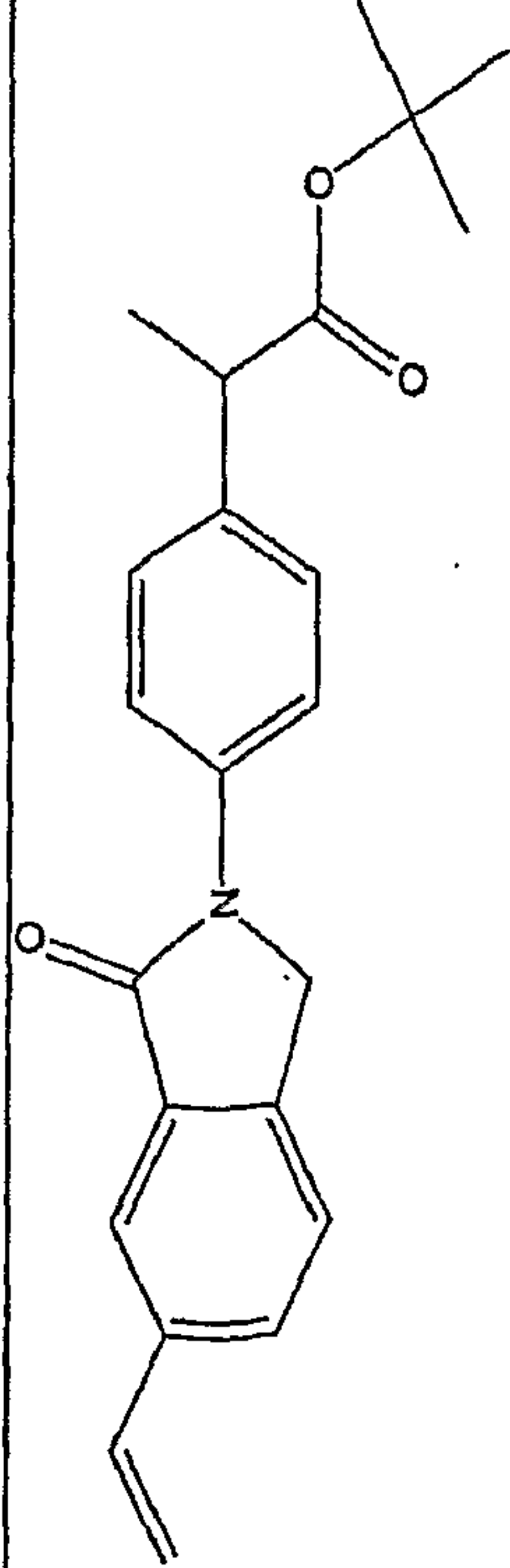
216

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
368		ALB- 112169	3.736	1.068
369		ALB- 113000	3.736	1.309

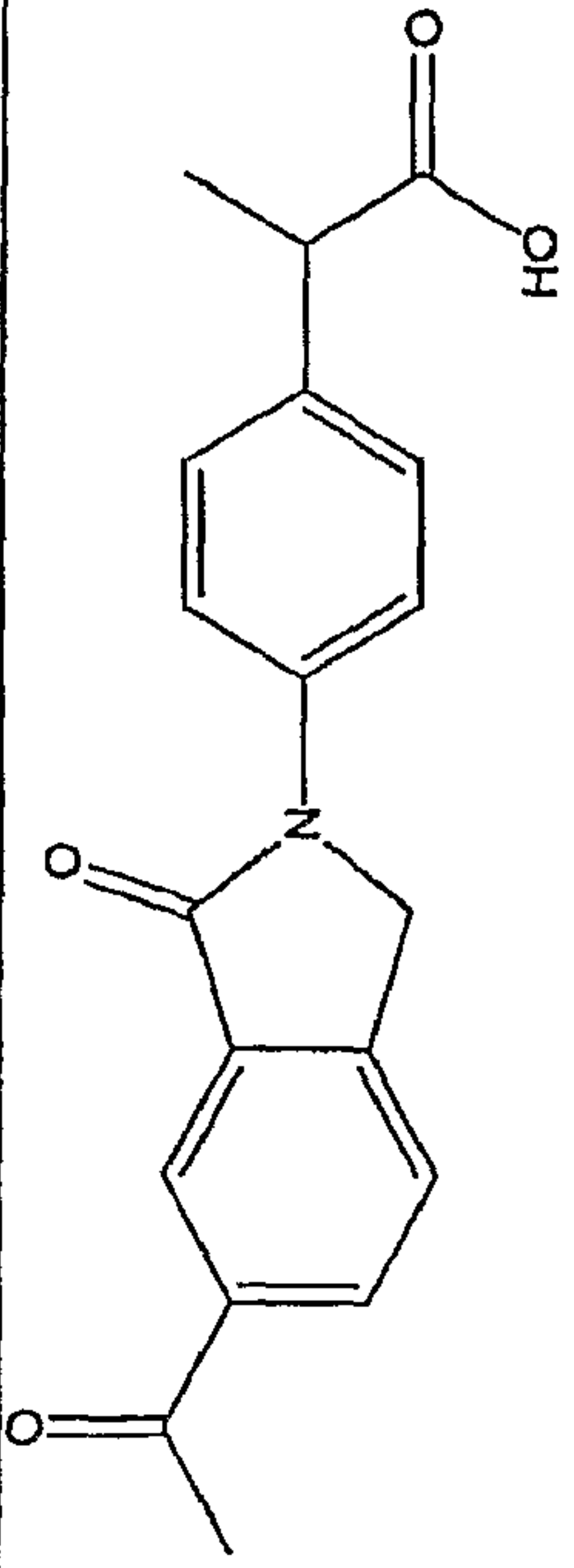
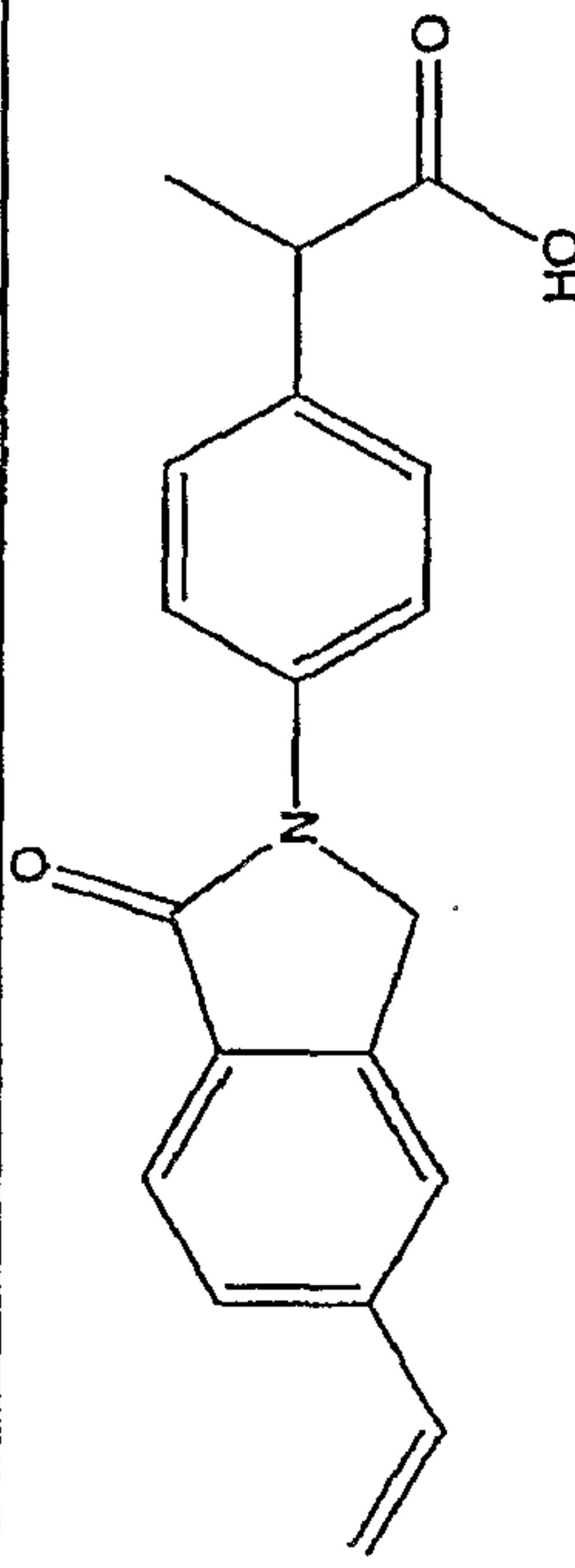
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
370		ALB- 113100	0.101	1.053
371		ALB- 113103		1.041
372		ALB- 113210	2.877	1.151

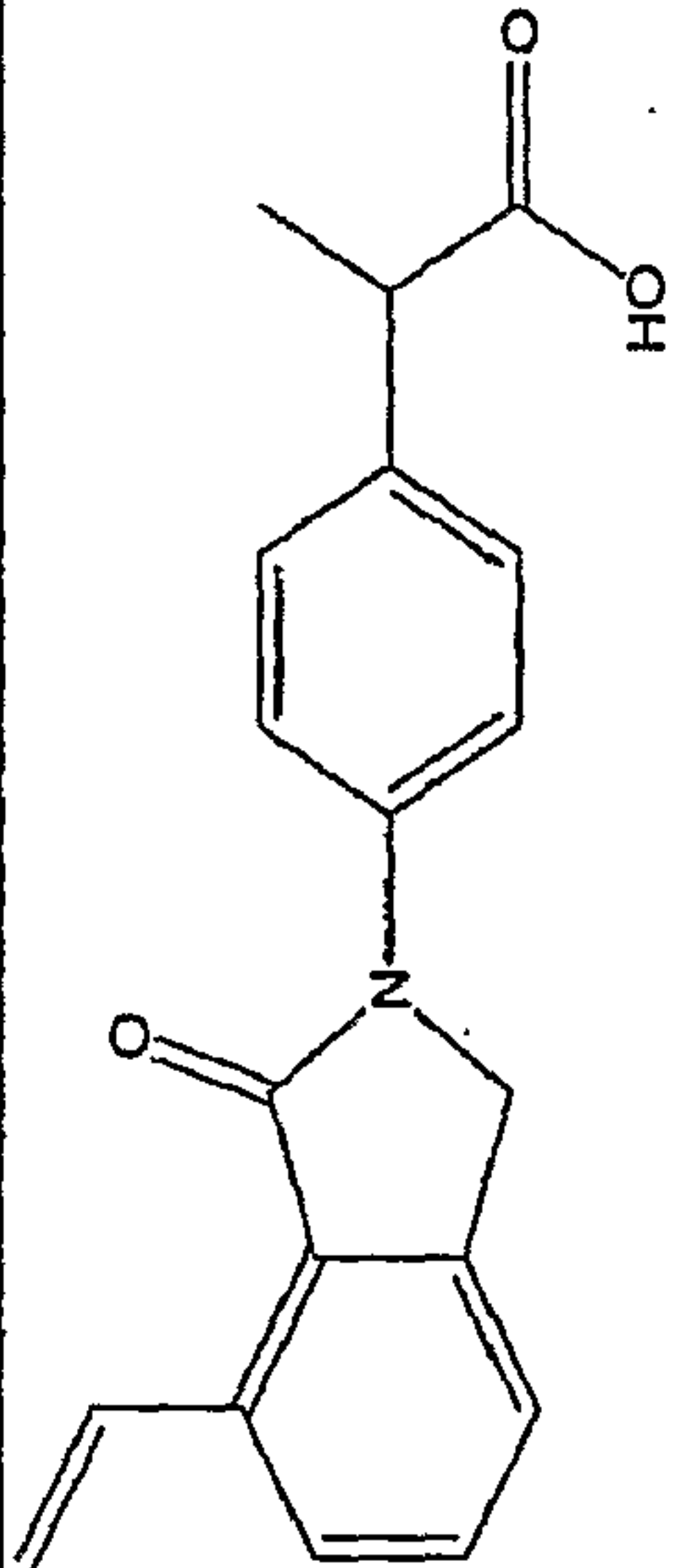
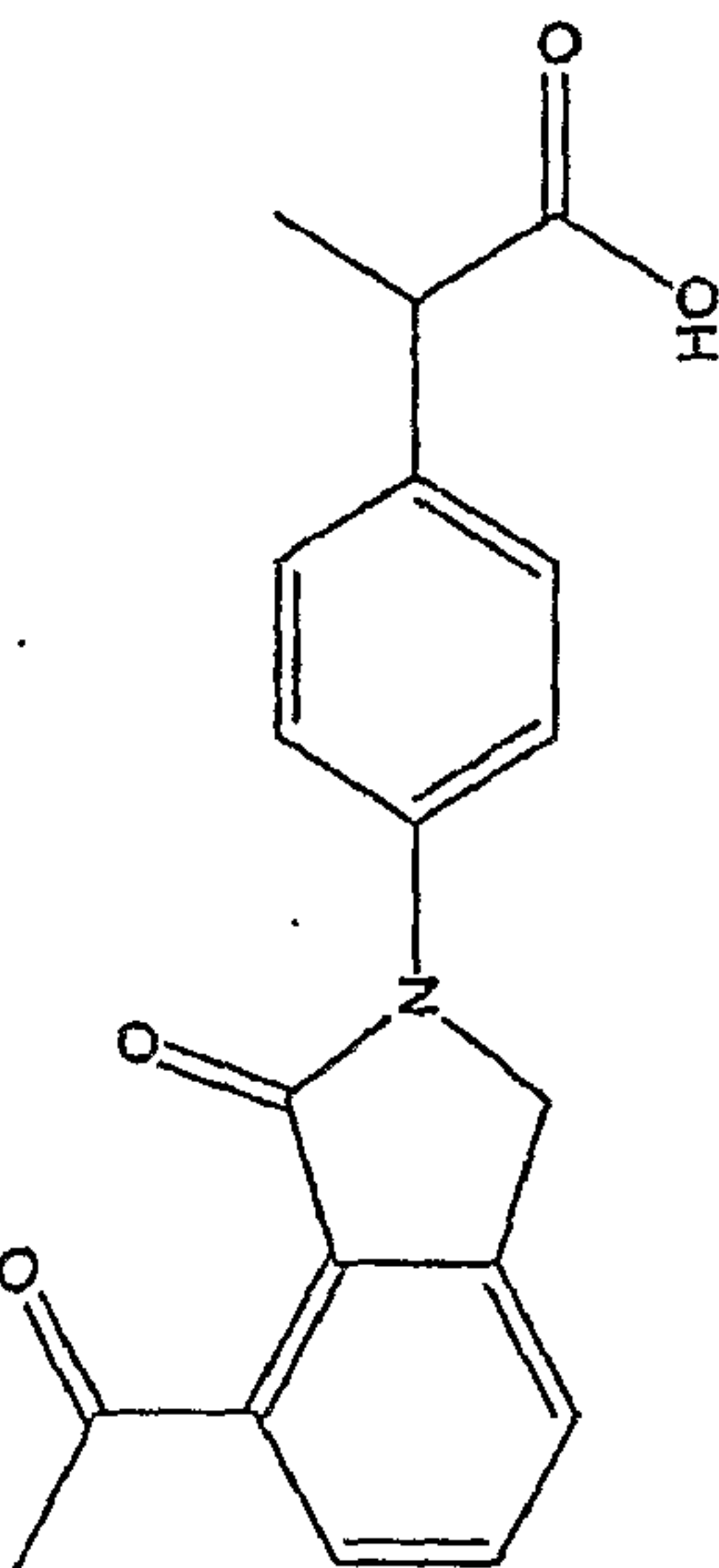
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
373		ALB- 113387	0.05	1.175
374		ALB- 113390	10.413	1.295

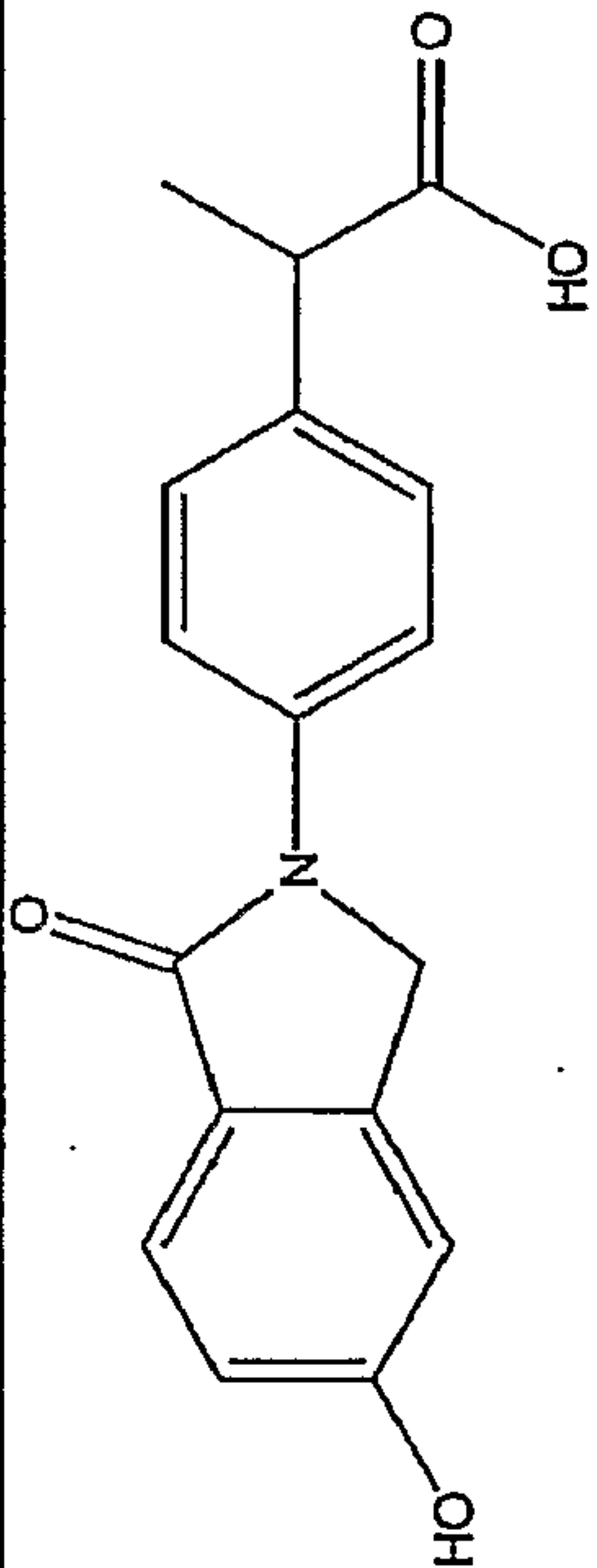
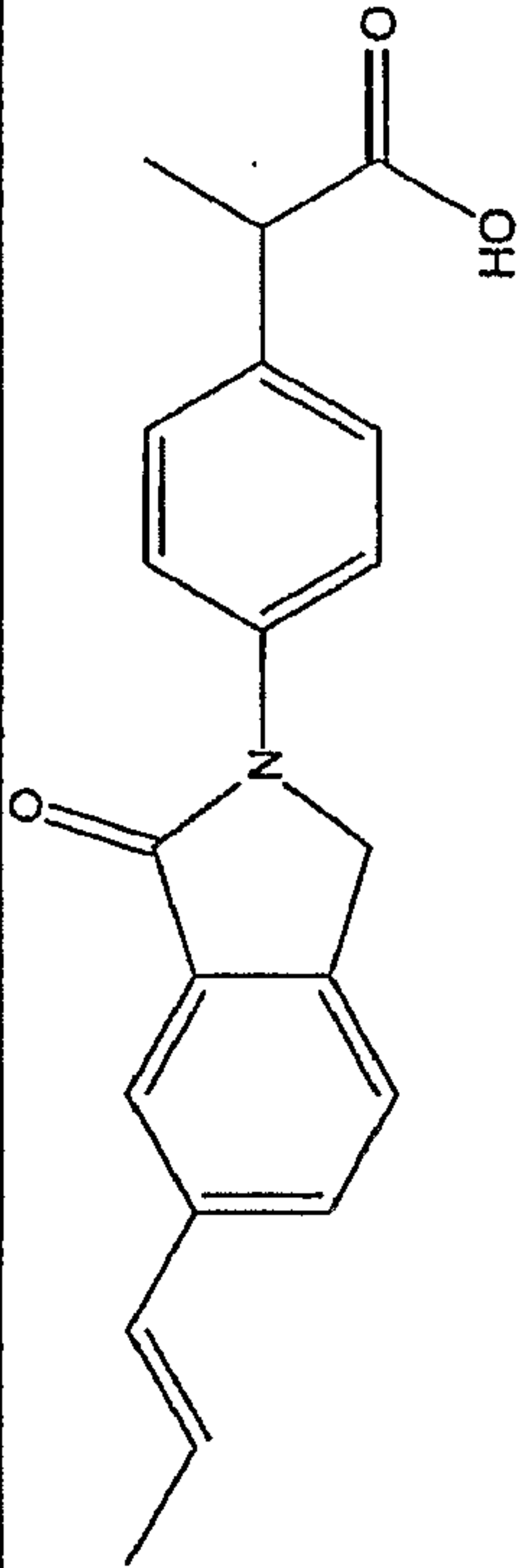
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
375		ALB- 113393	0.209	1.205
376		ALB- 113496		1.183

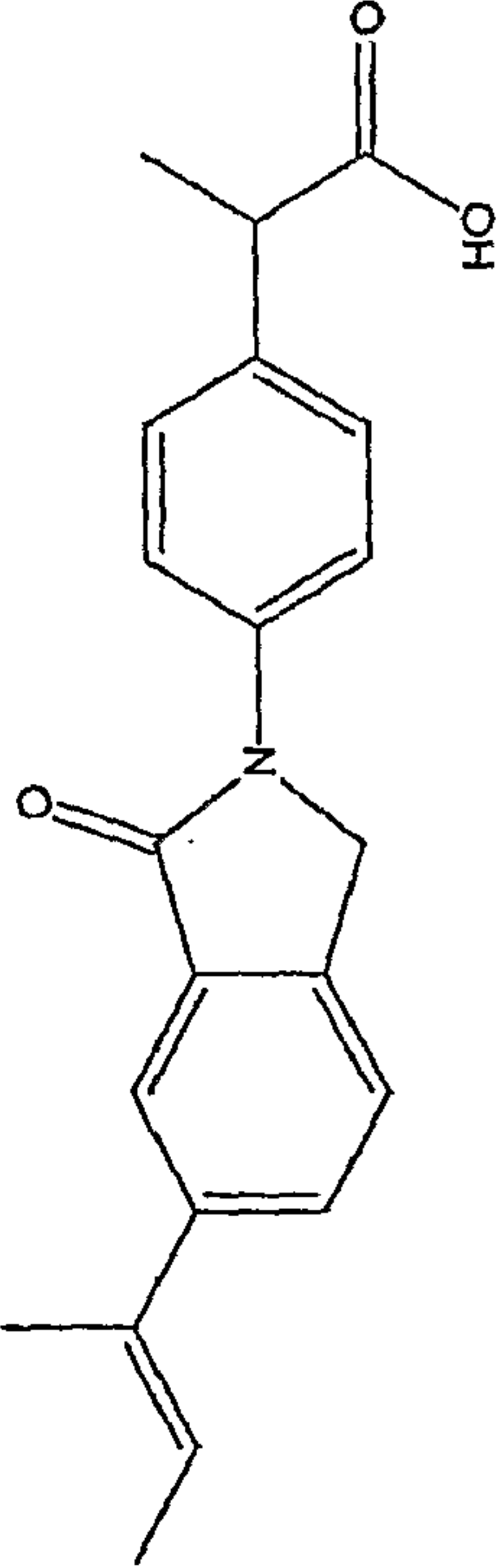
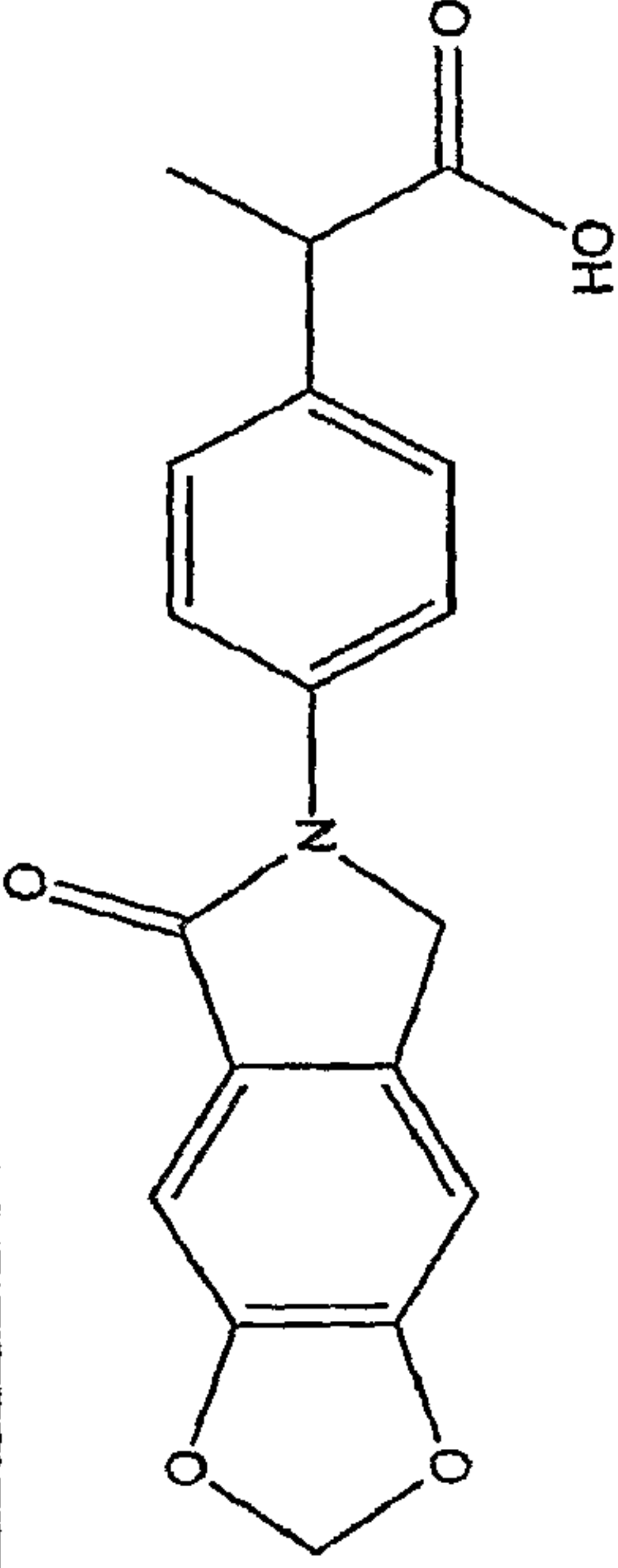
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
377		ALB- 113560		1.052
378		ALB- 114086	0.088	1.985

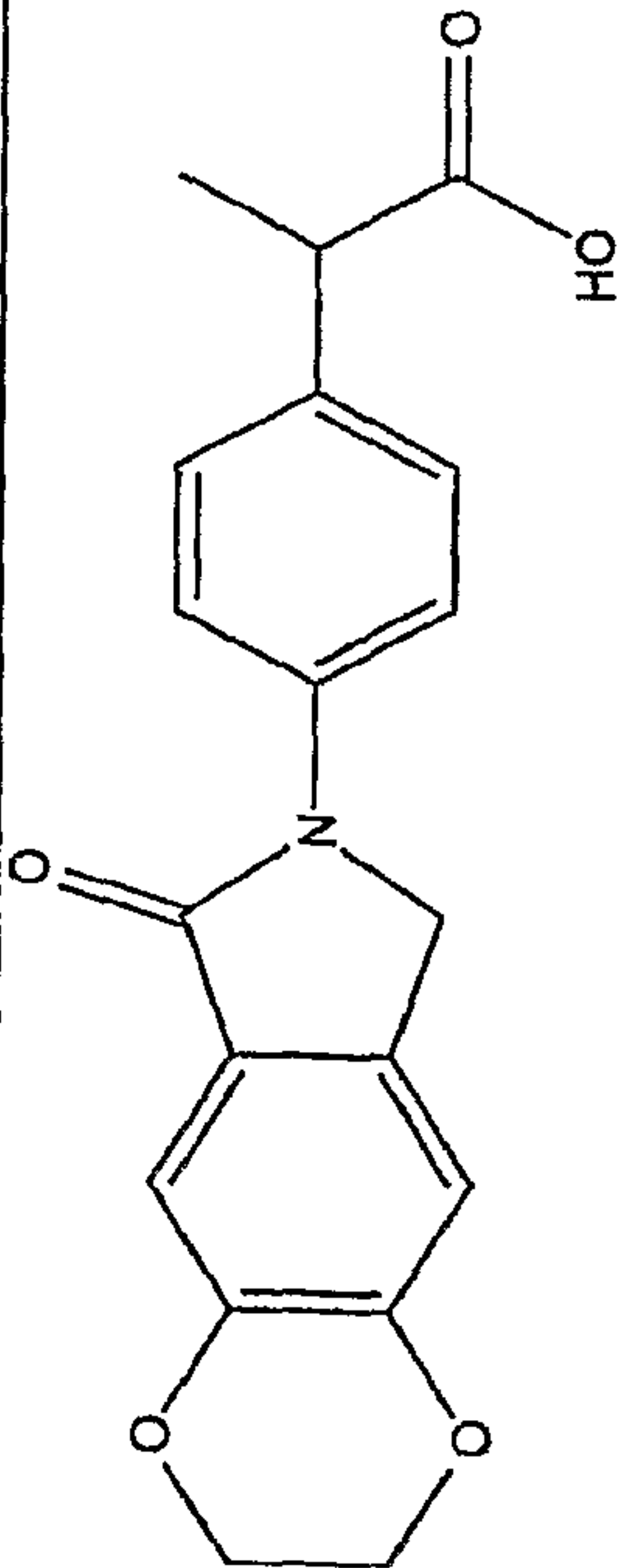
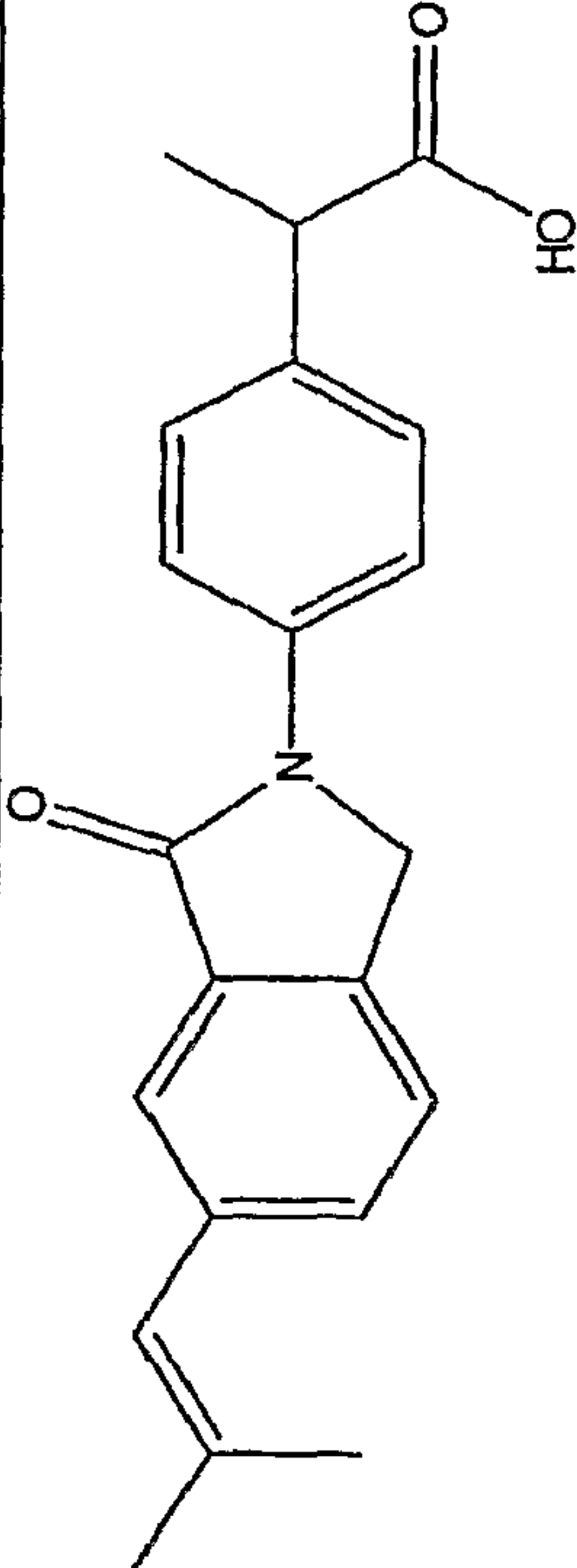
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Table I

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
379		ALB- 114087	0.226	1.878
380		ALB- 114782	0.081	1.653

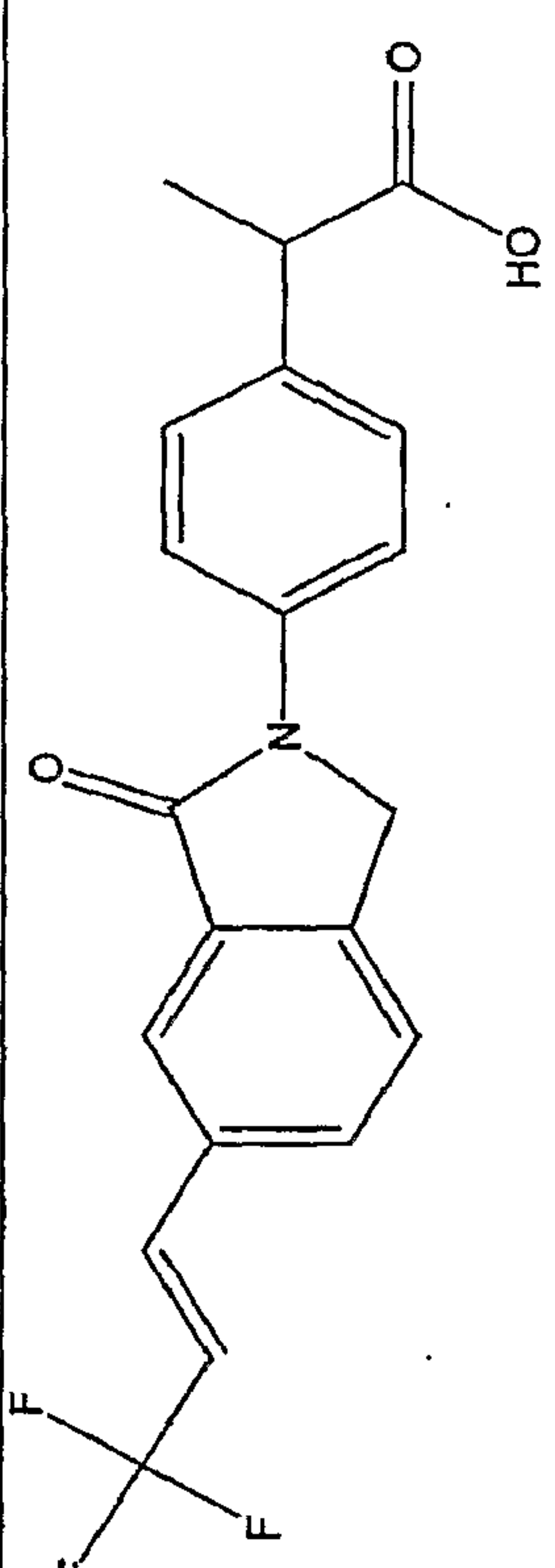
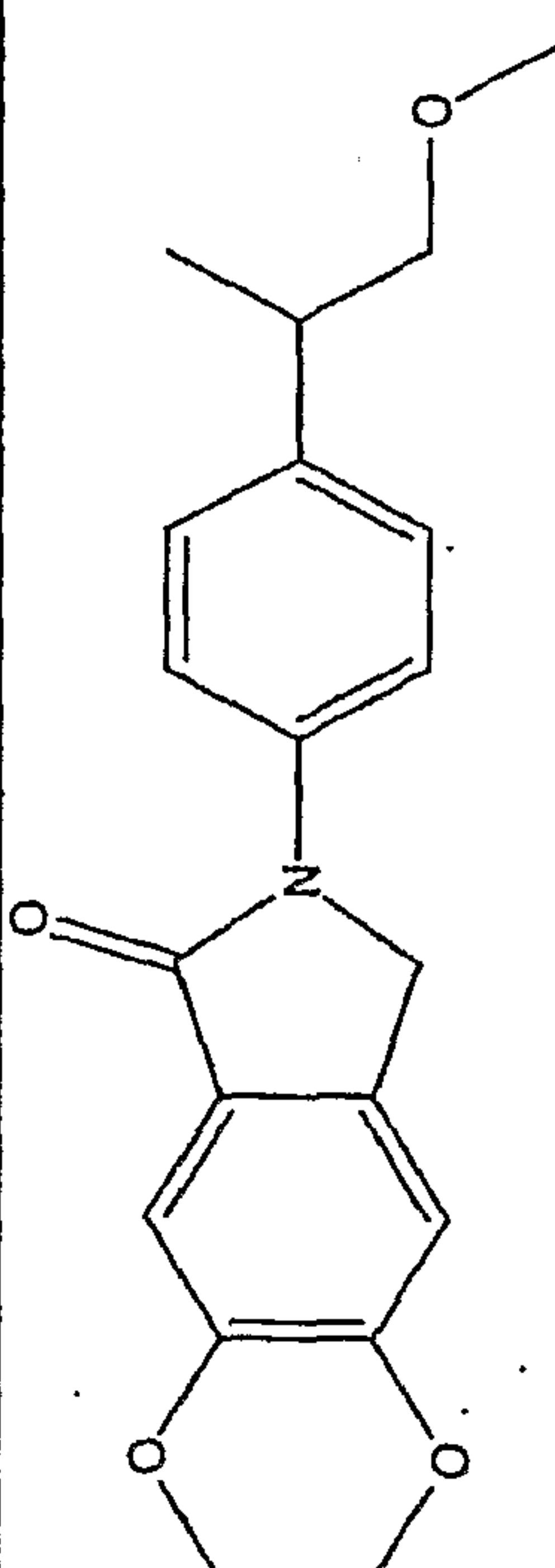
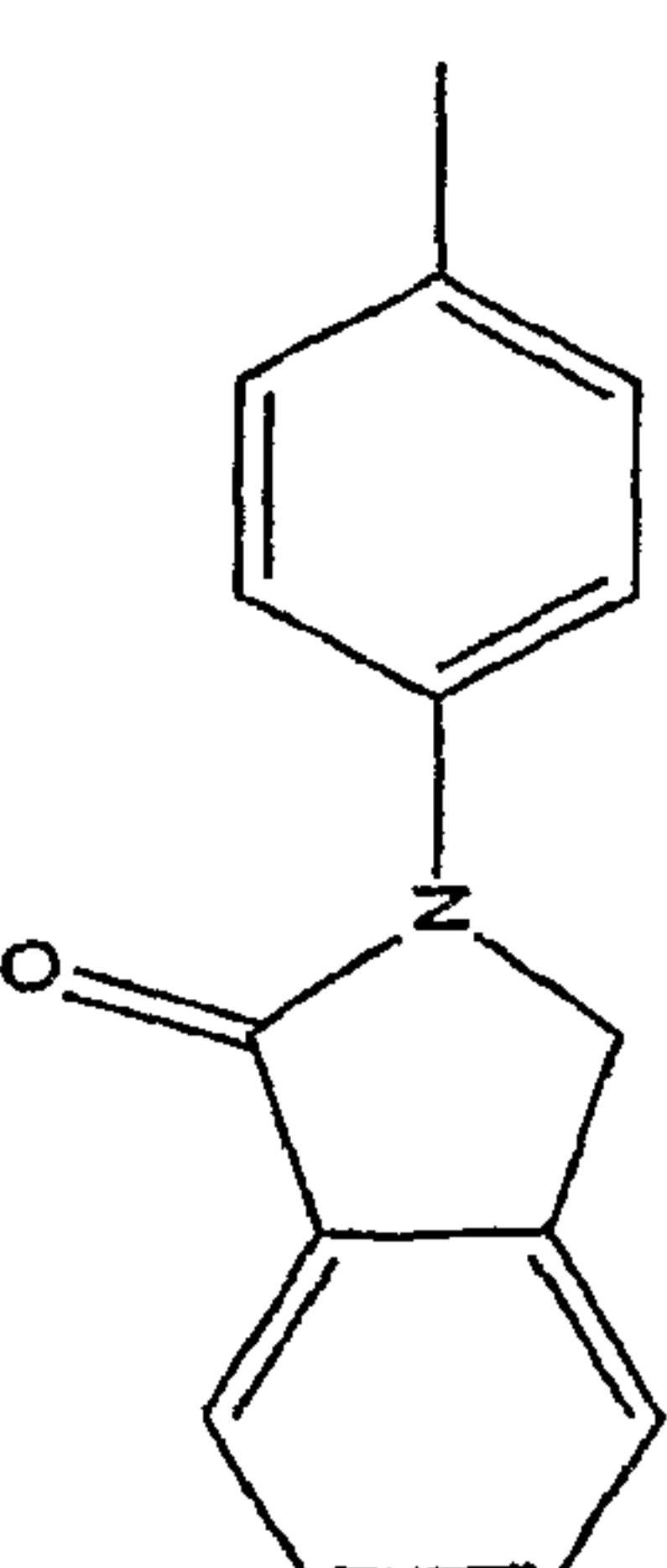
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
381		ALB- 114844	0.008	1.358
382		ALB- 115425	0.018	1.947

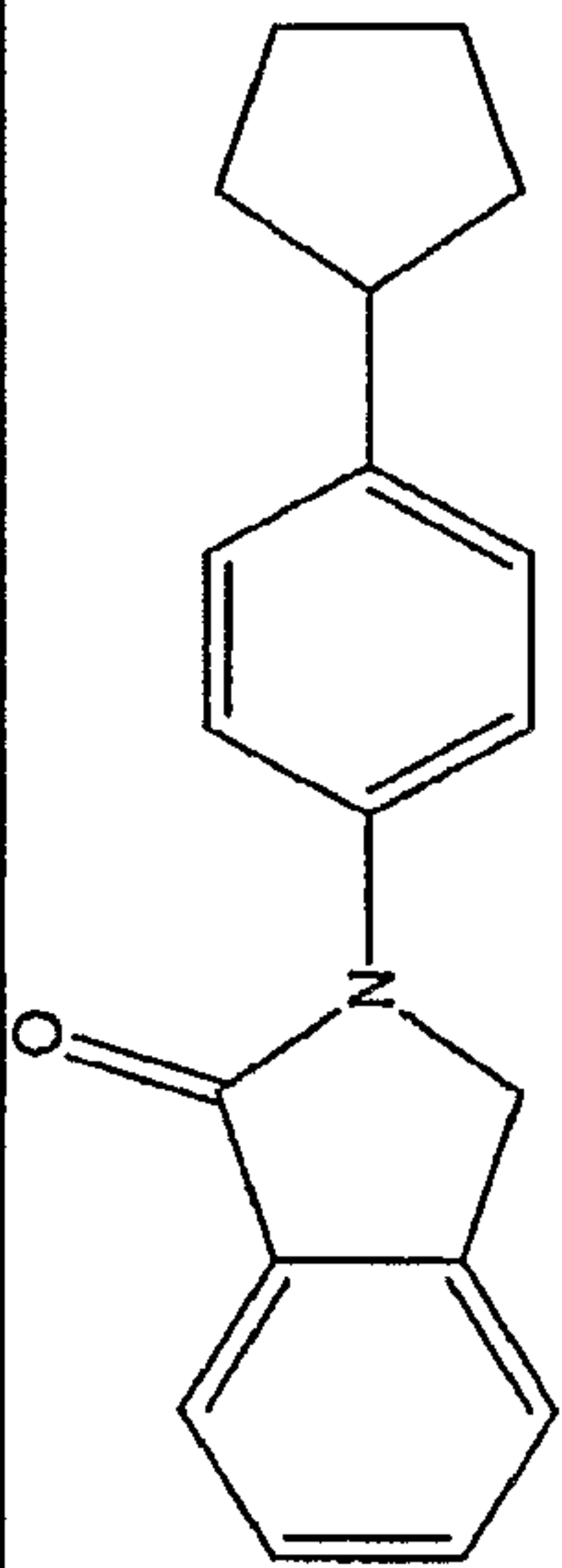
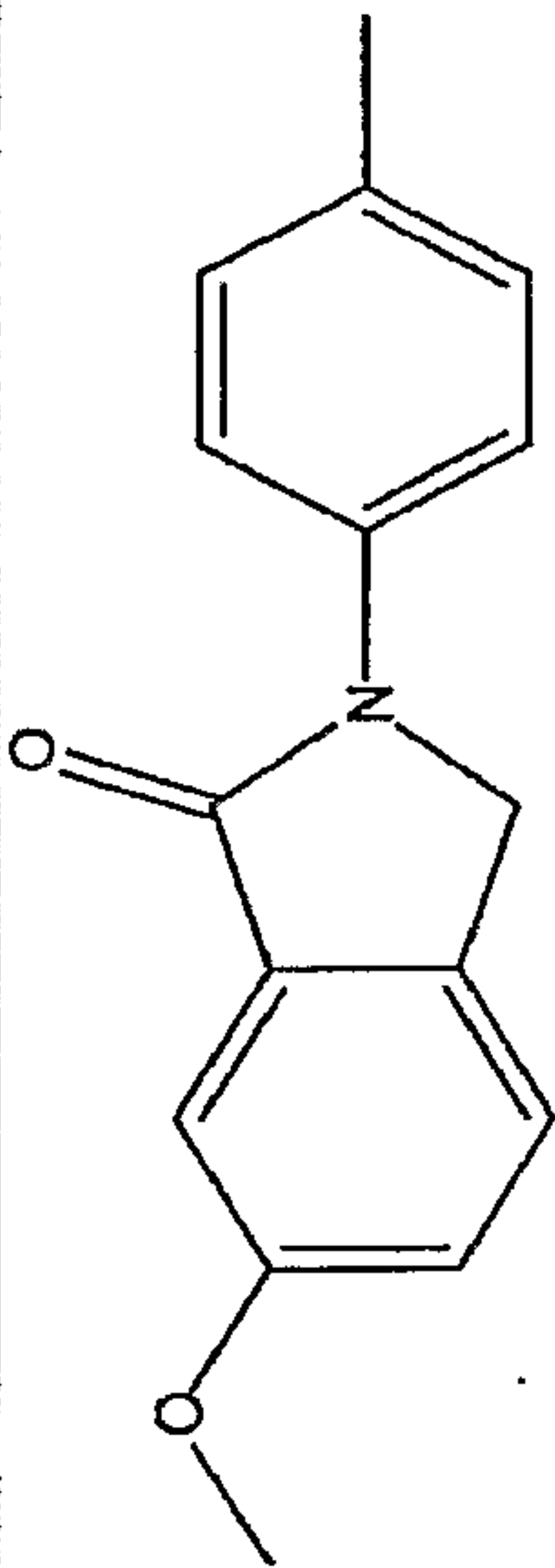
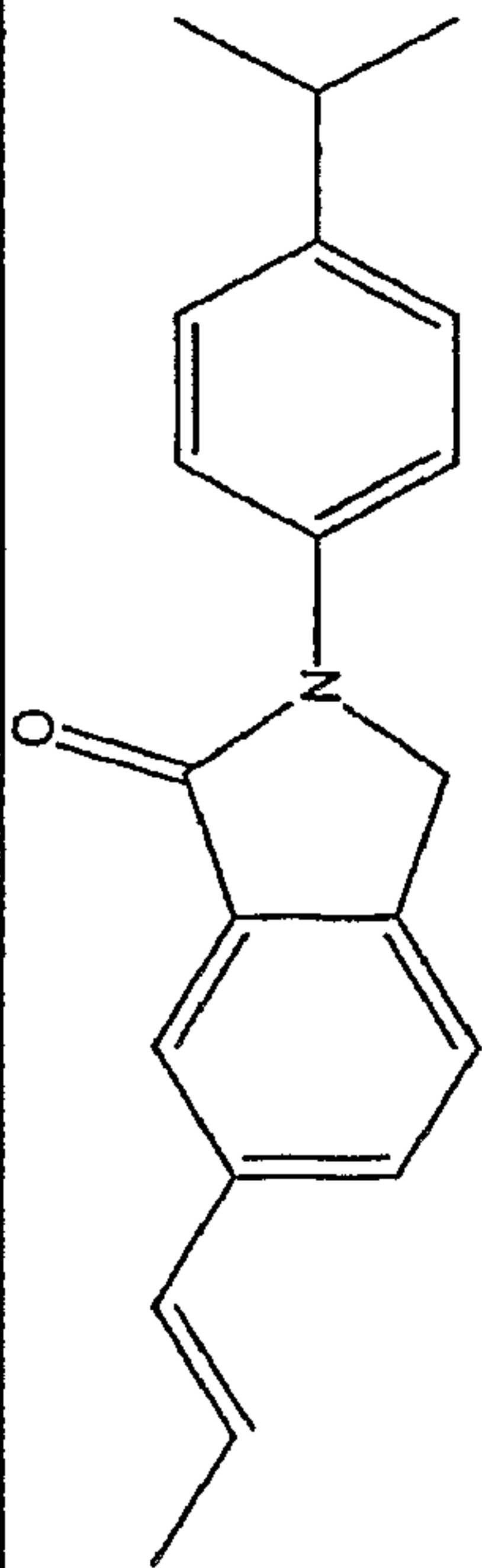
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
383		ALB- 115501	2.32	1.387
384		ALB- 116361	3.561	1.895
385		ALB- 114898	0.302	1.361

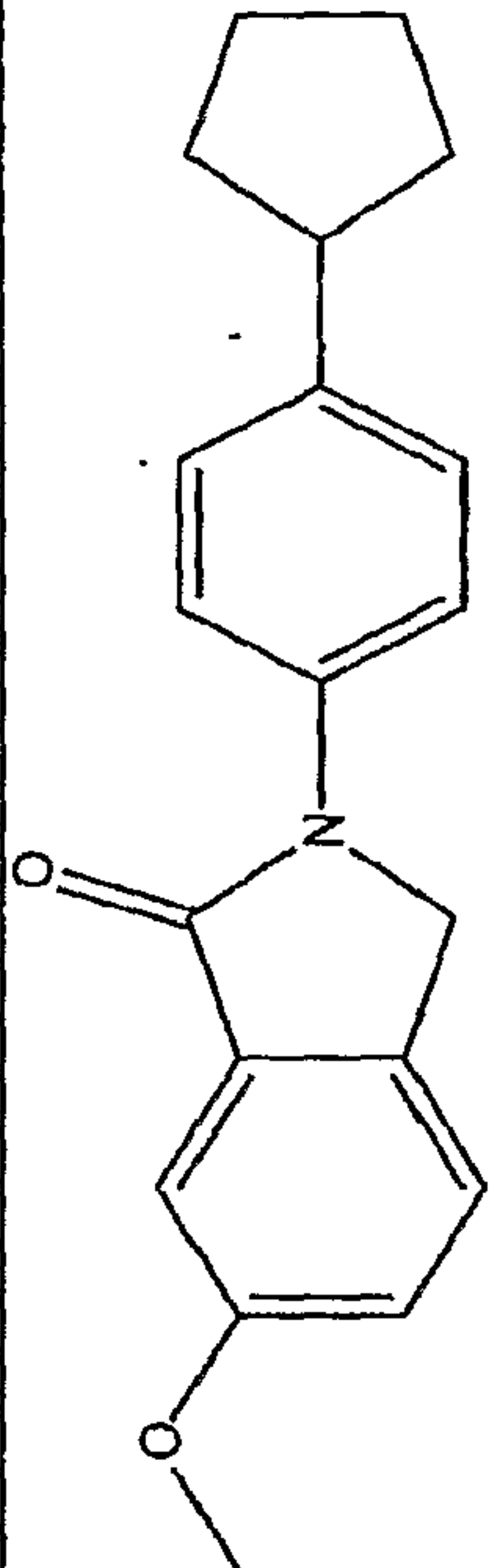
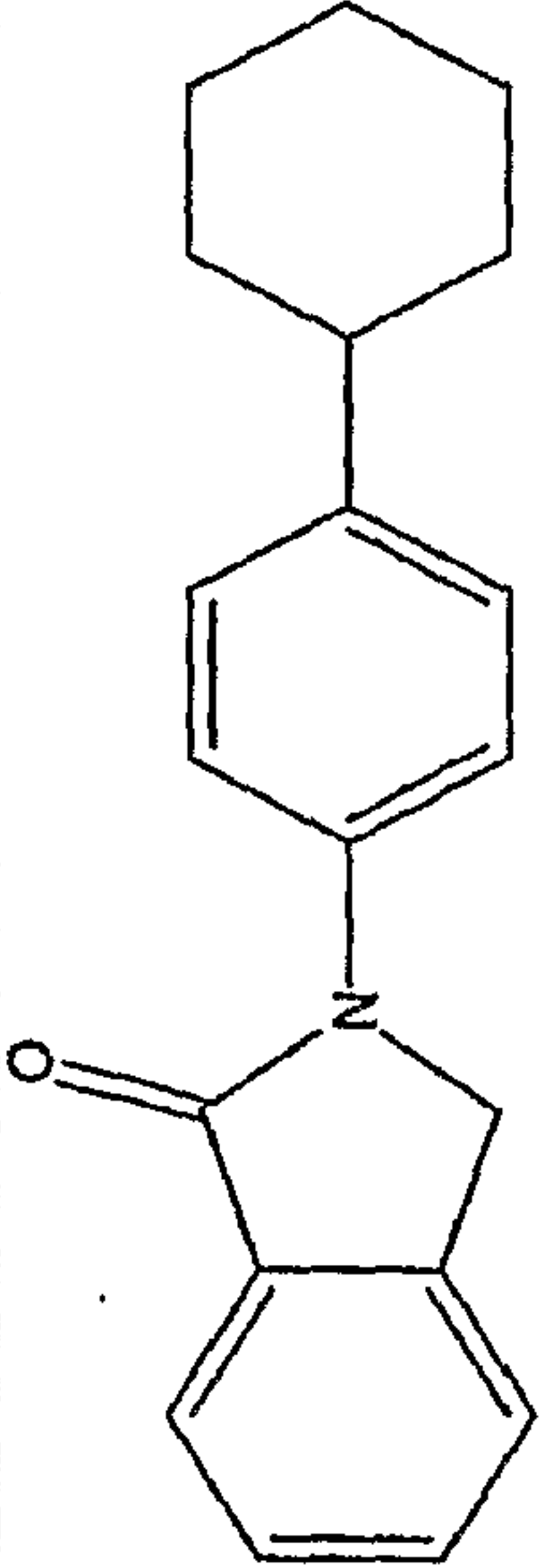
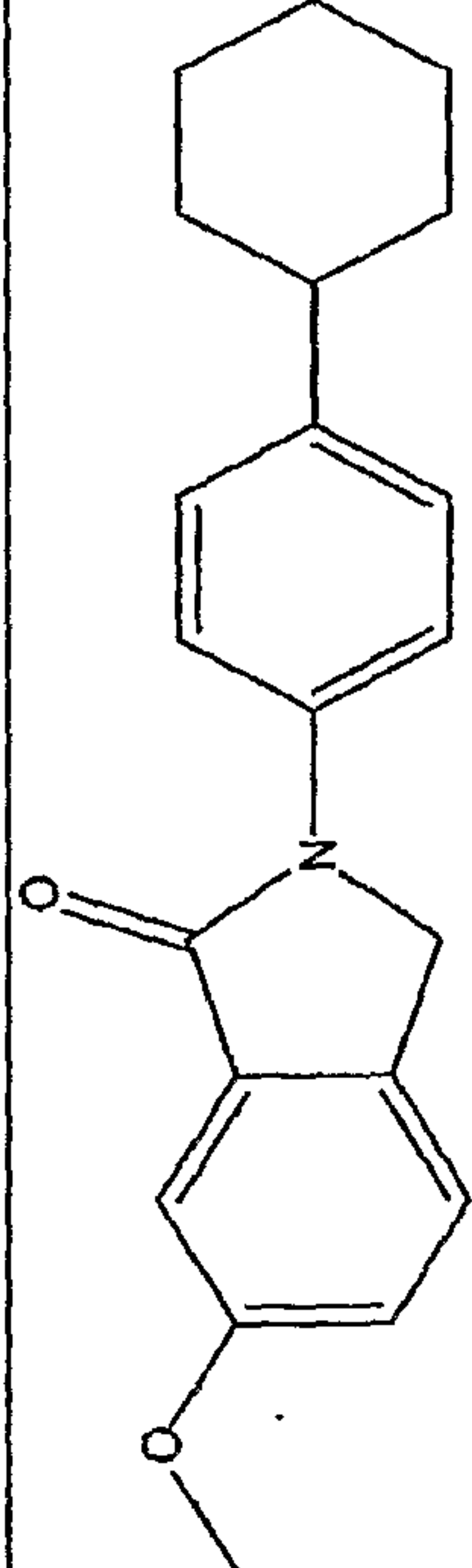
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
386		ALB- 115068	0.053	1.412
387		ALB- 115084	0.06	1.386
388		ALB- 115319		1.24

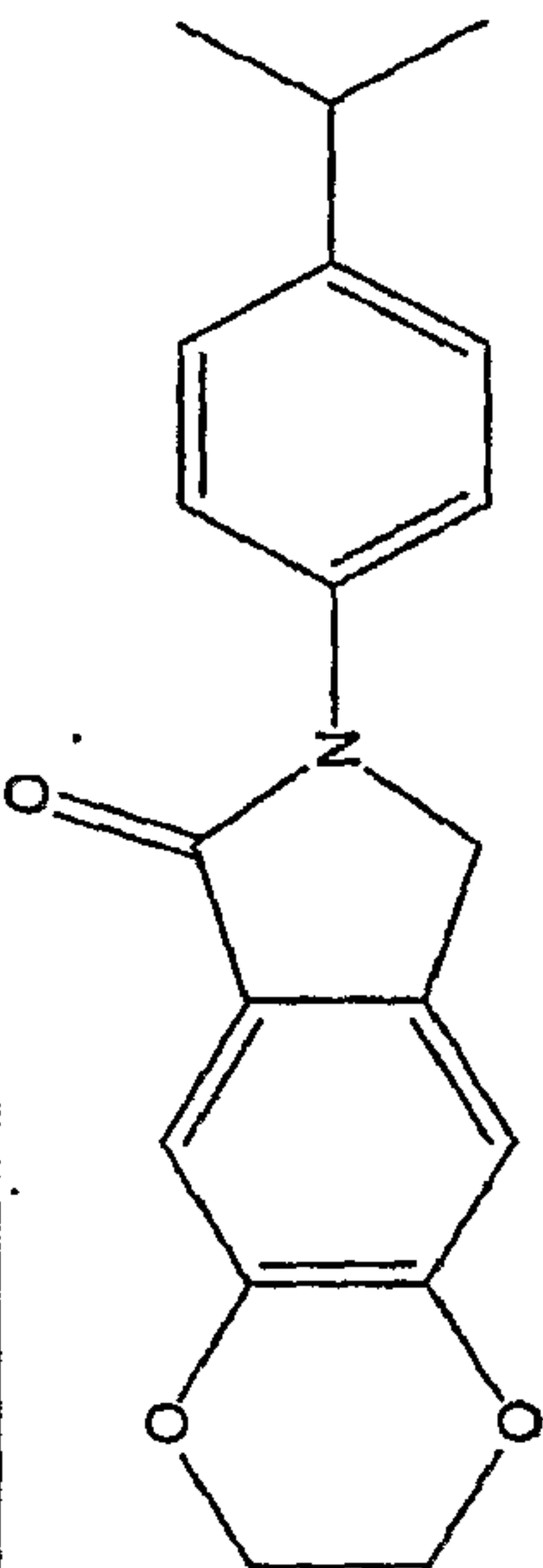
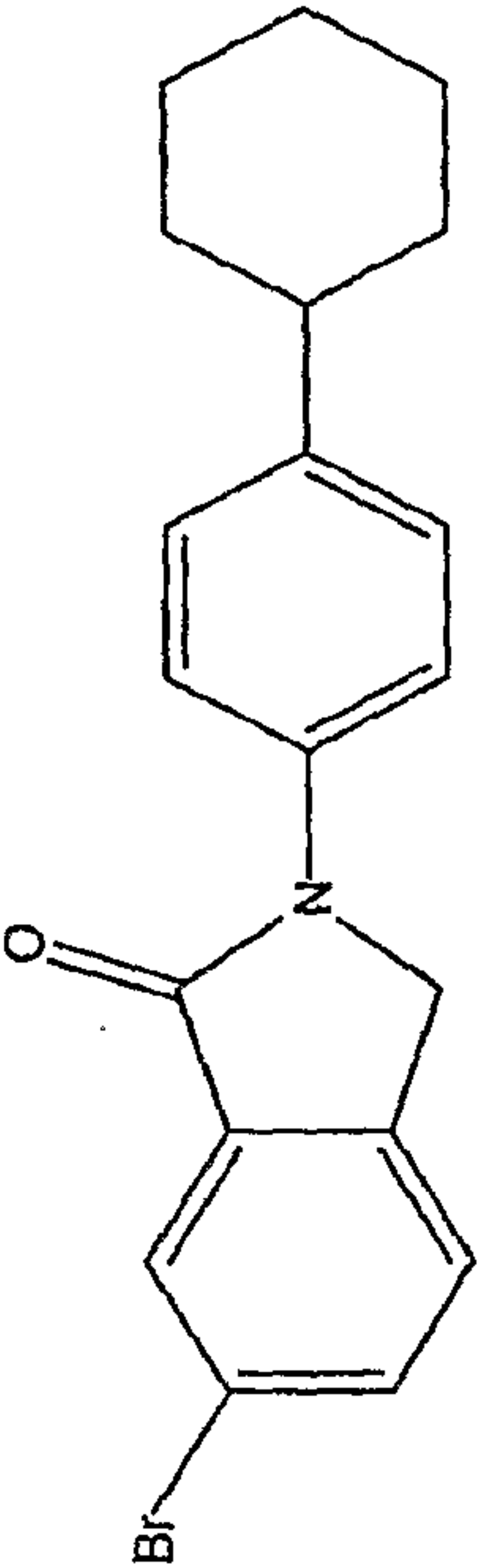
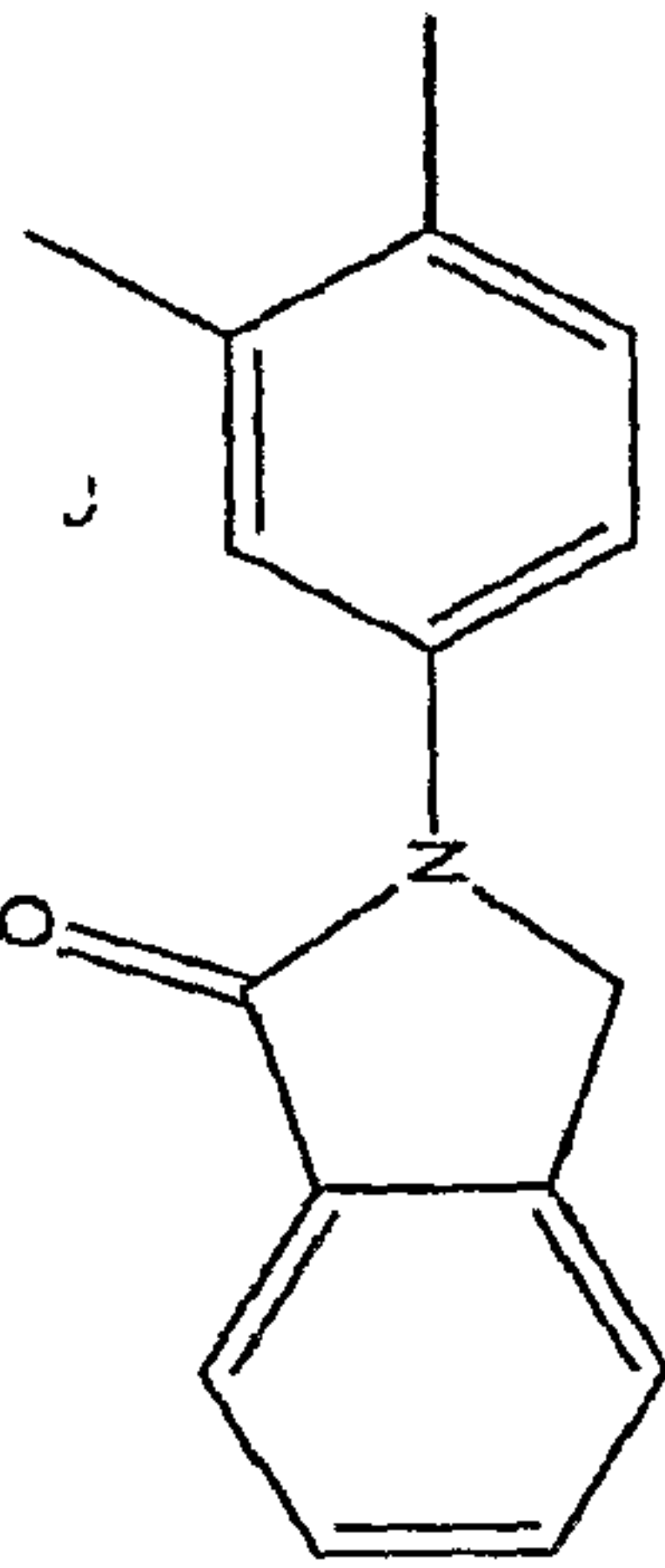
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
389		ALB- 115422	0.399	1.272
390		ALB- 115423	0.029	1.205
391		ALB- 115496	0.556	1.386

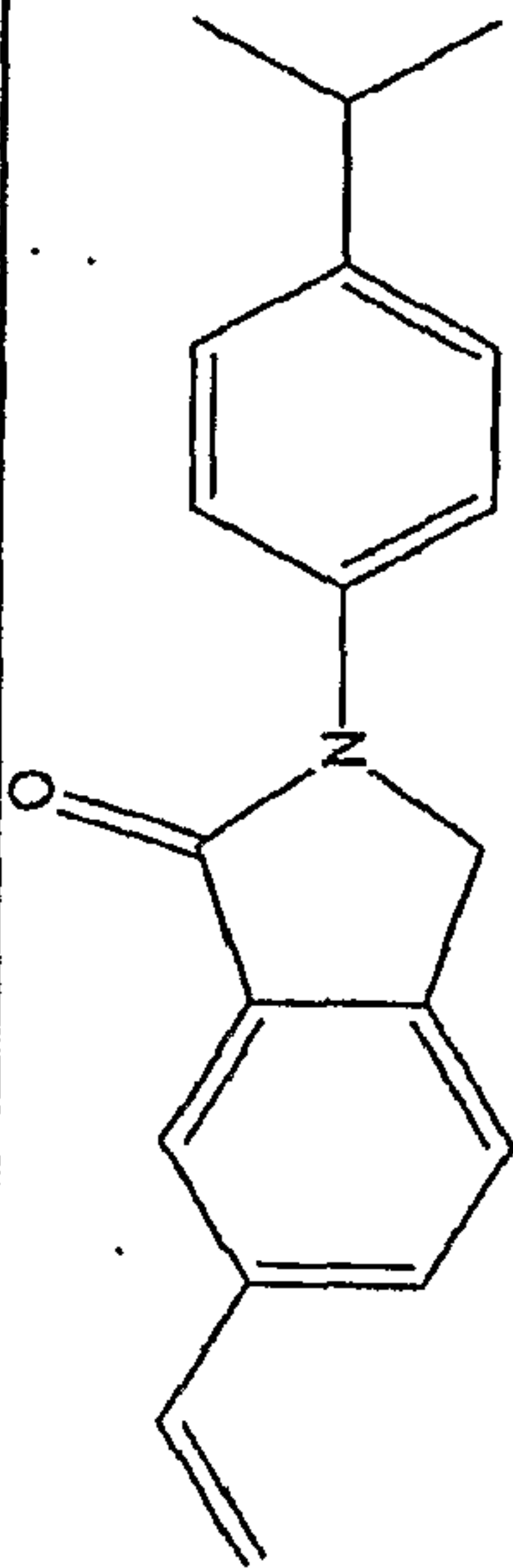
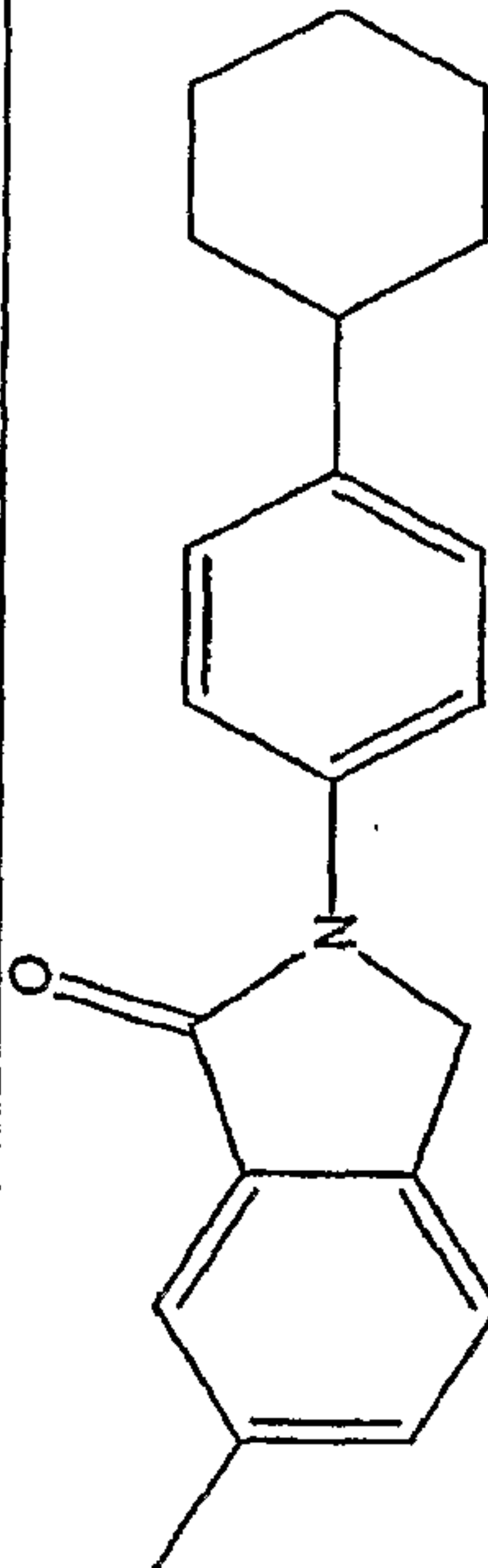
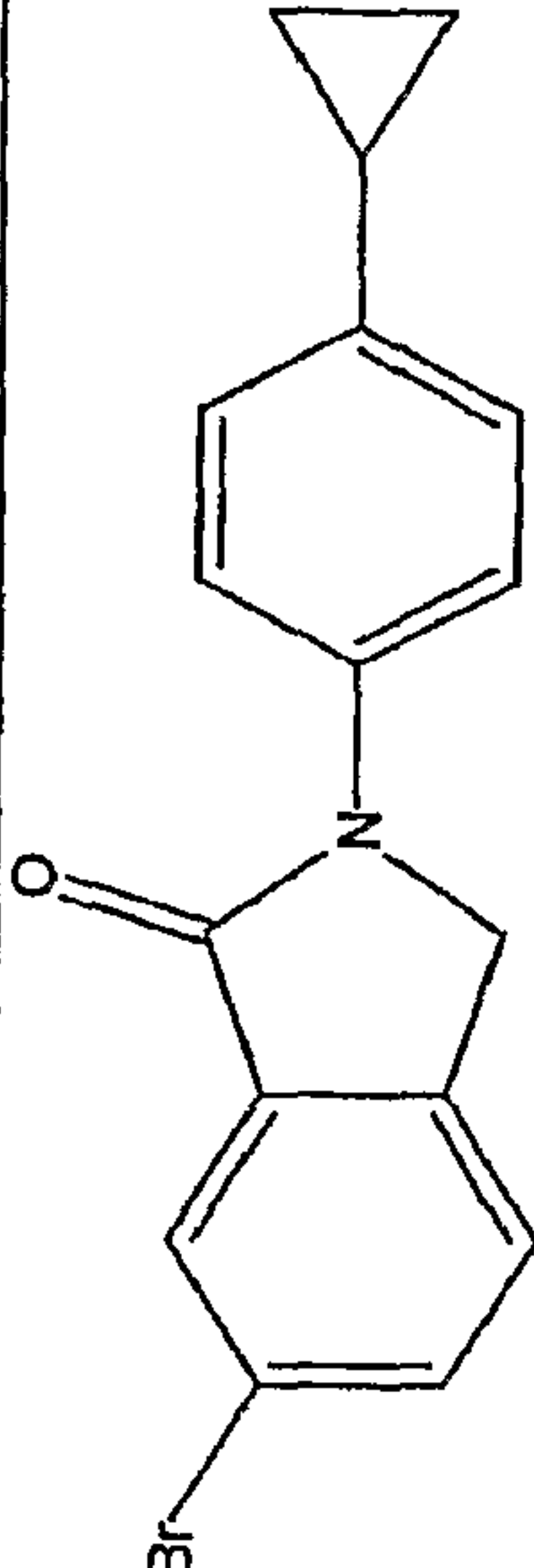
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
392		ALB- 115498	0.203	1.834
393		ALB- 115590		1.11
394		ALB- 115711	0.274	1.327

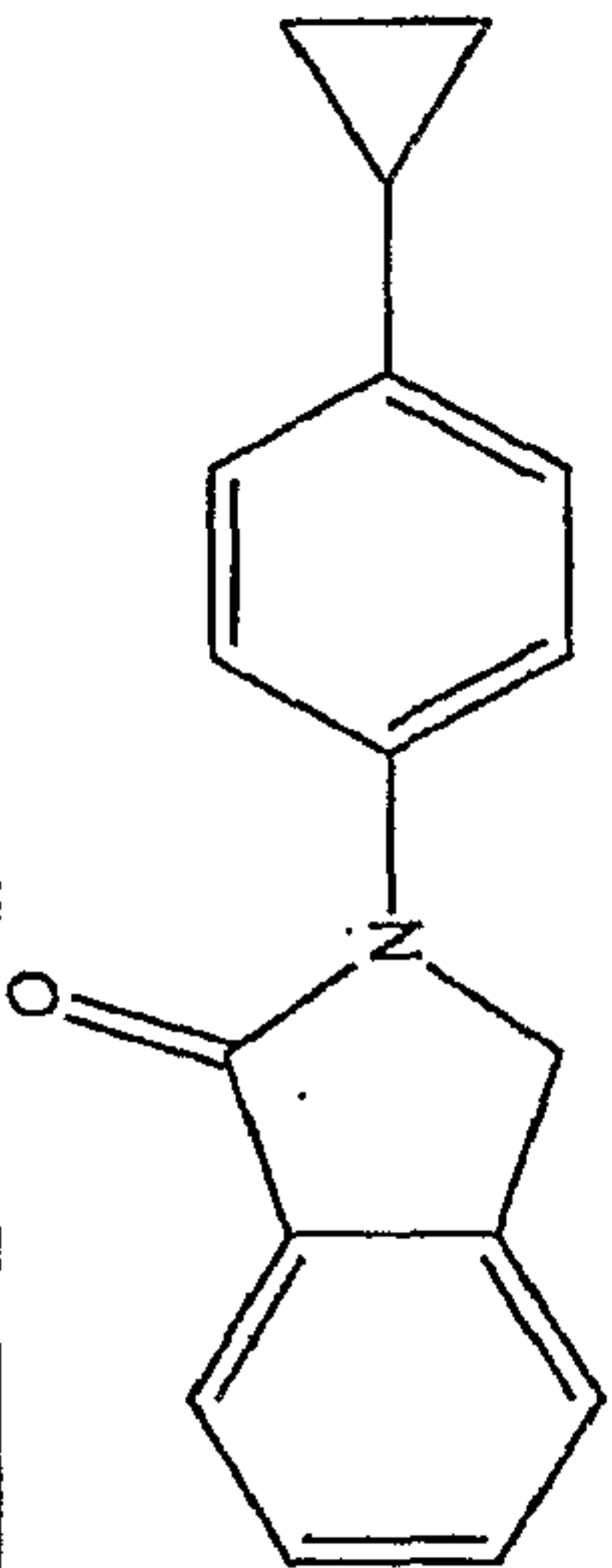
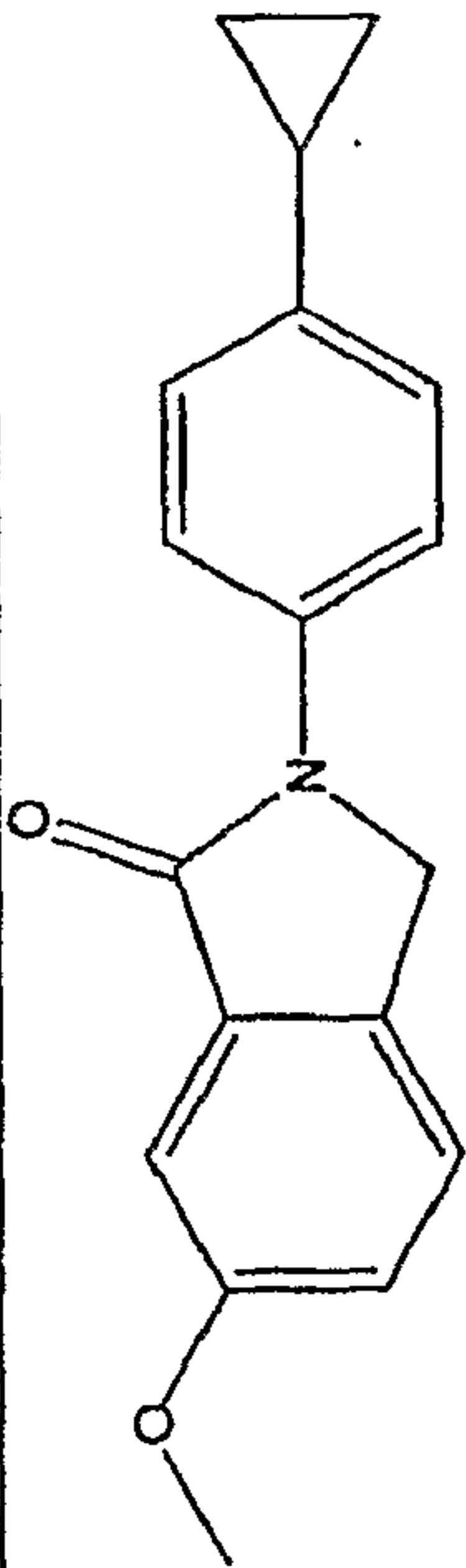
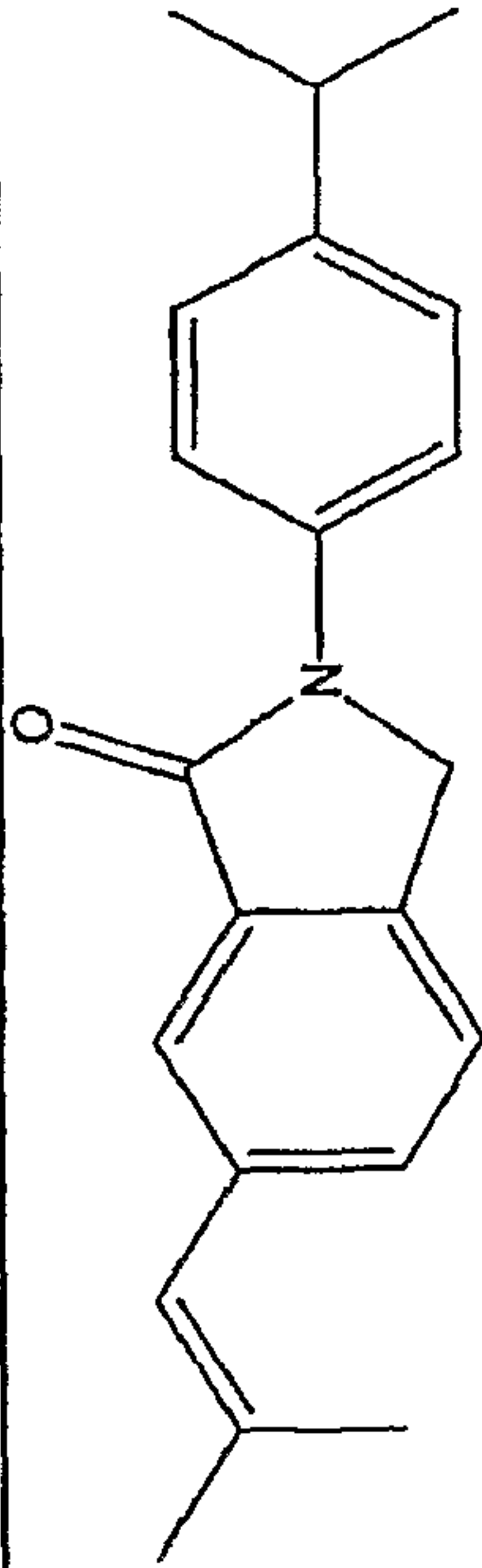
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
395		ALB- 115714	0.053	1.37
396		ALB- 115717		1.063
397		ALB- 115718	0.022	1.322

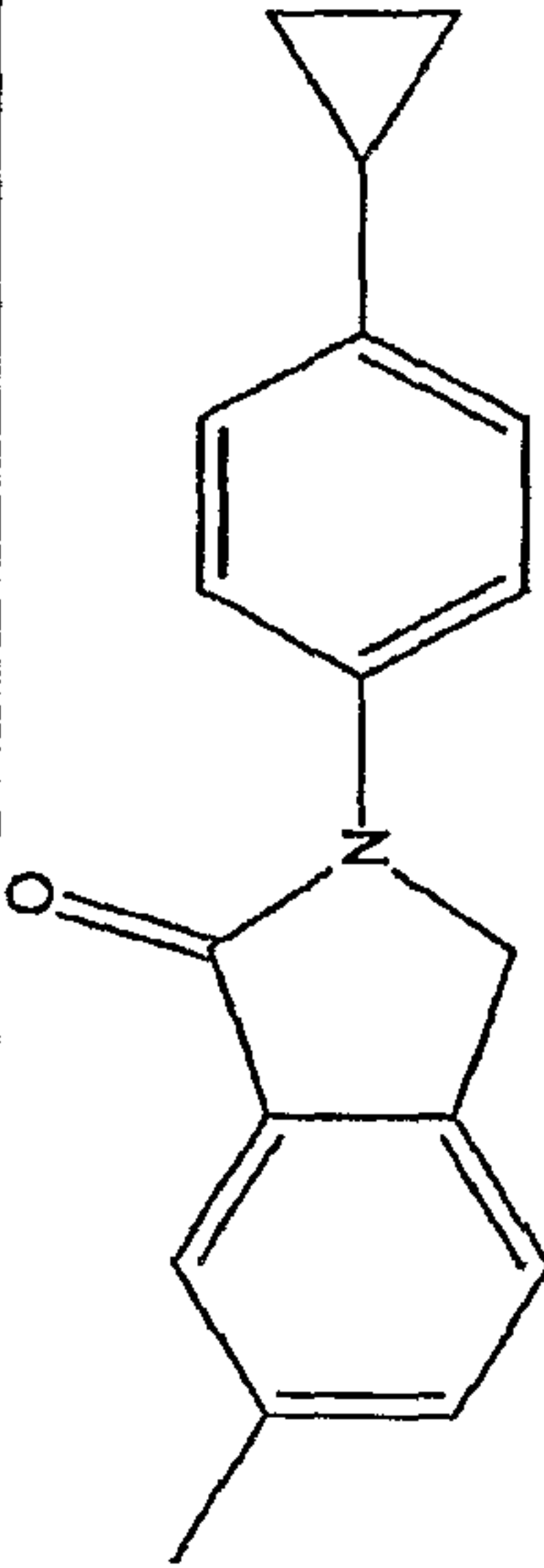
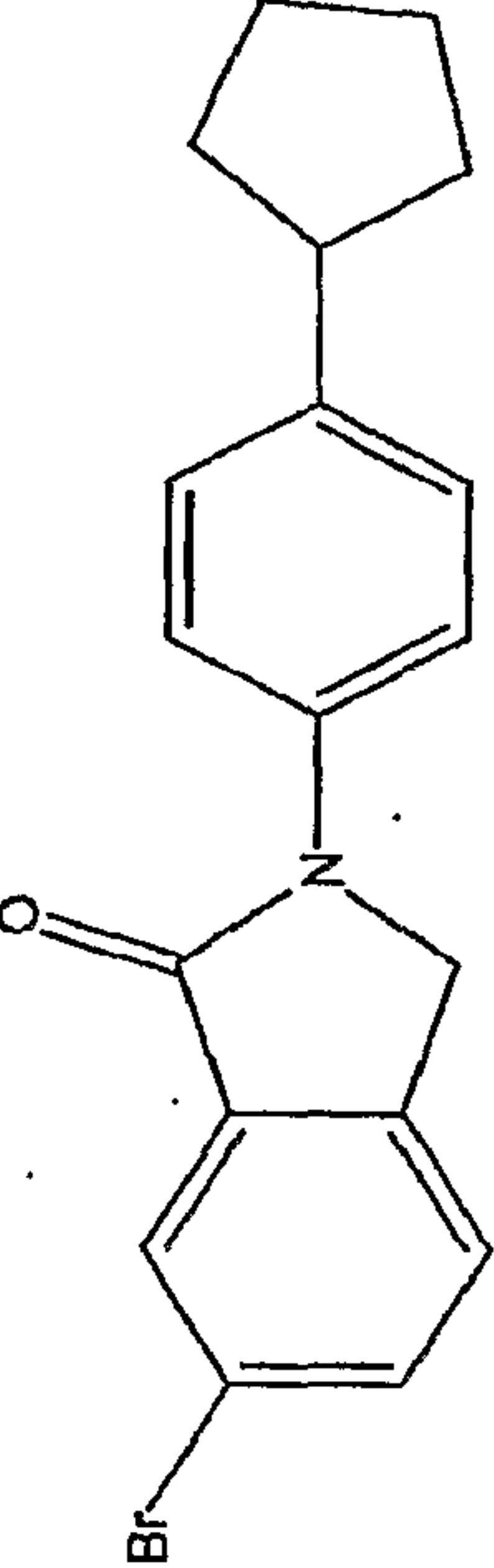
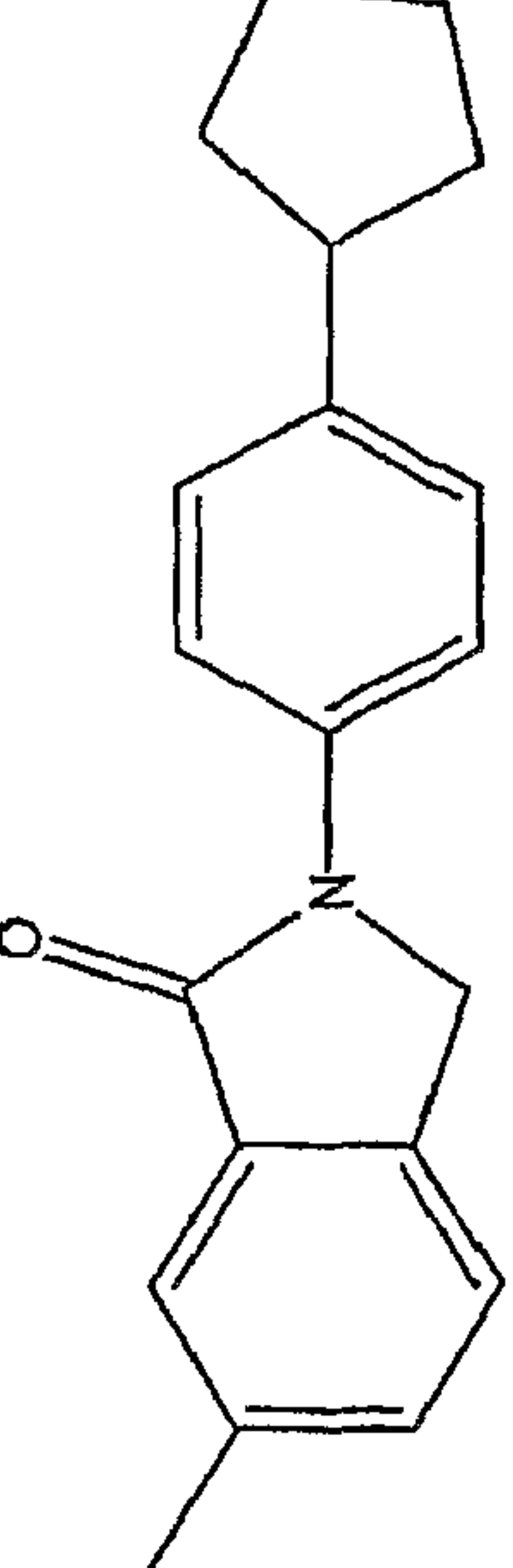
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
398		ALB- 115802	0.061	1.28
399		ALB- 115803	0.015	1.26
400		ALB- 115807	0.155	1.305

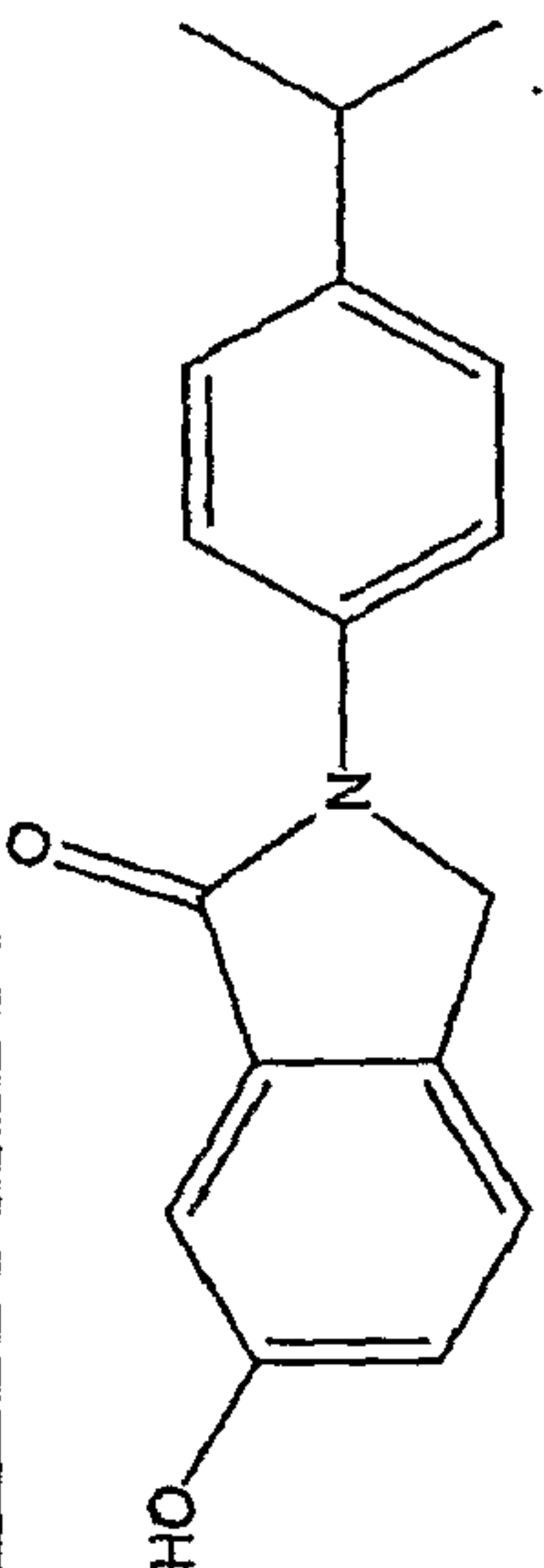
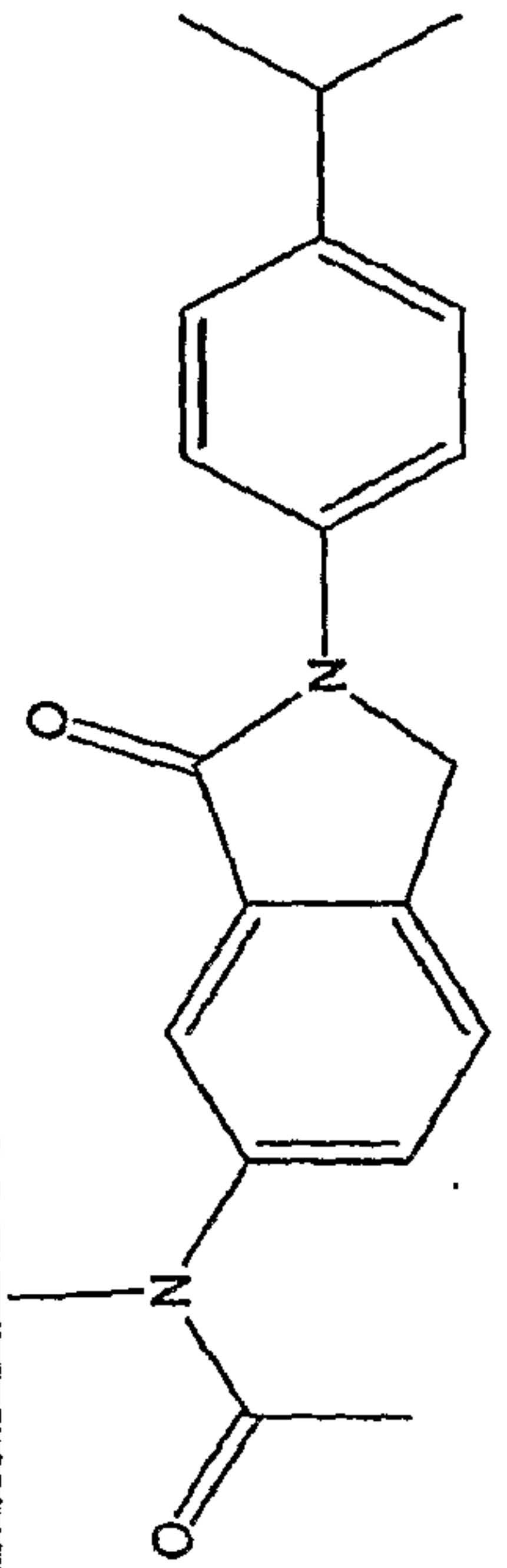
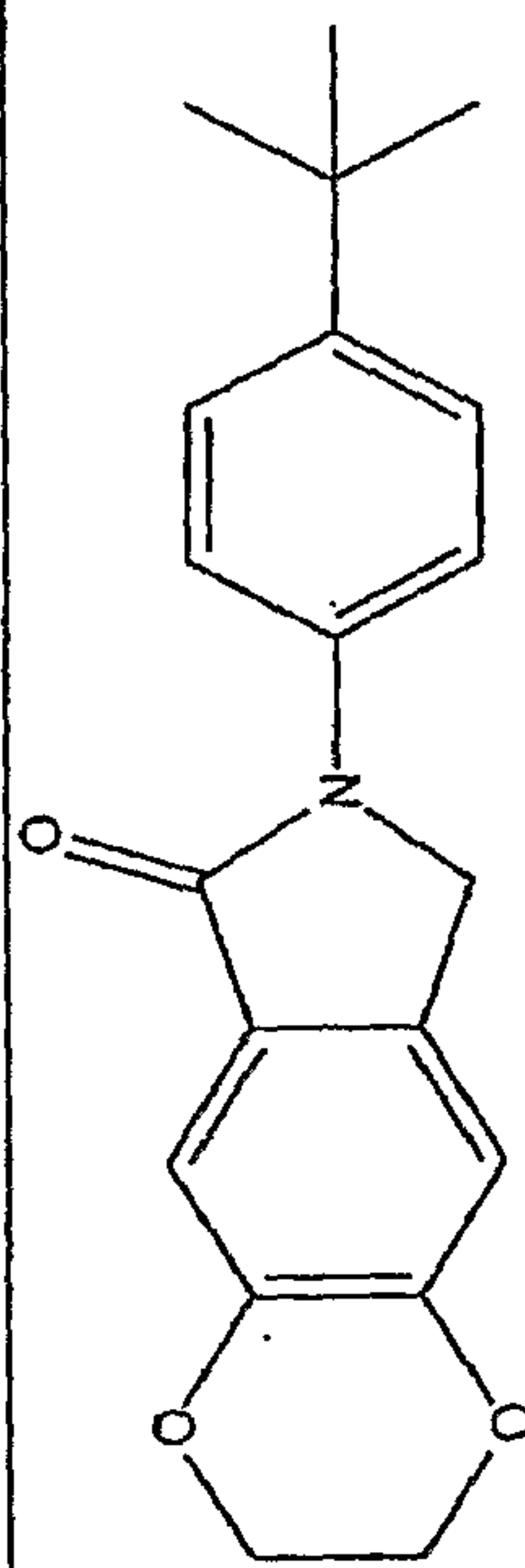
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
401		ALB- 115949	0.006	1.366
402		ALB- 116072	0.068	1.36
403		ALB- 116073		1.076

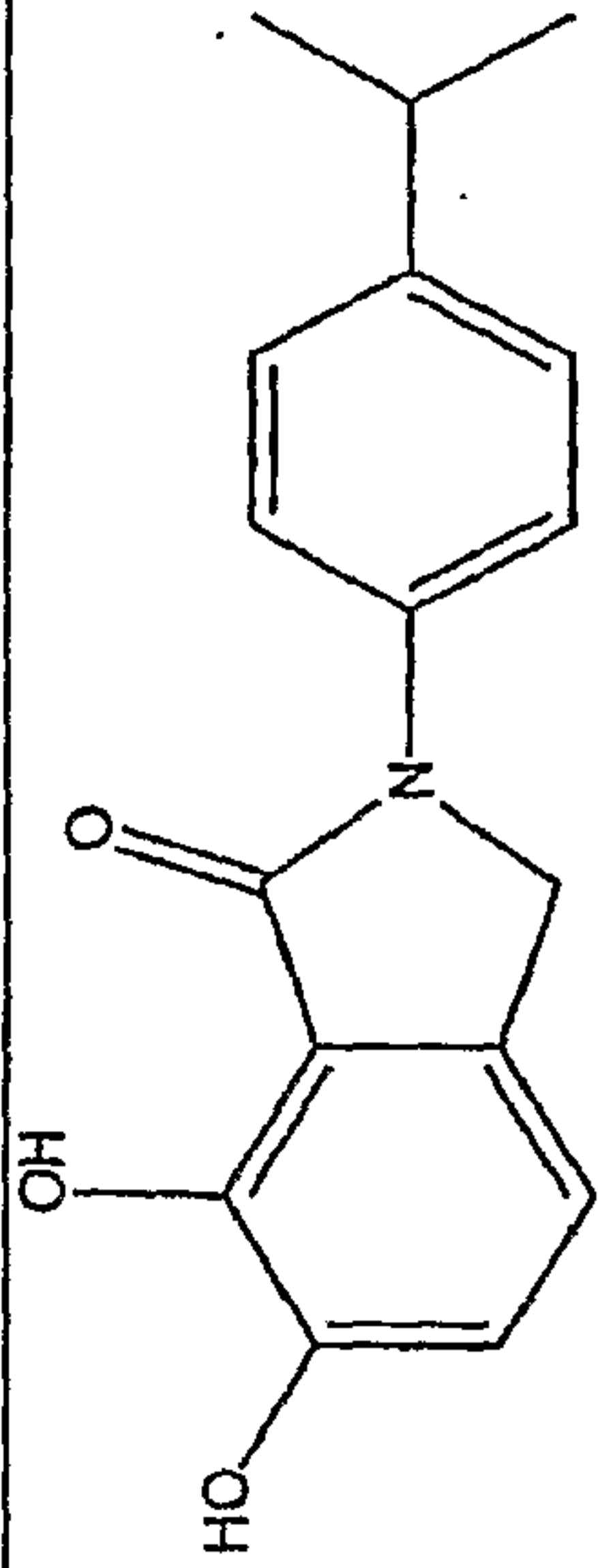
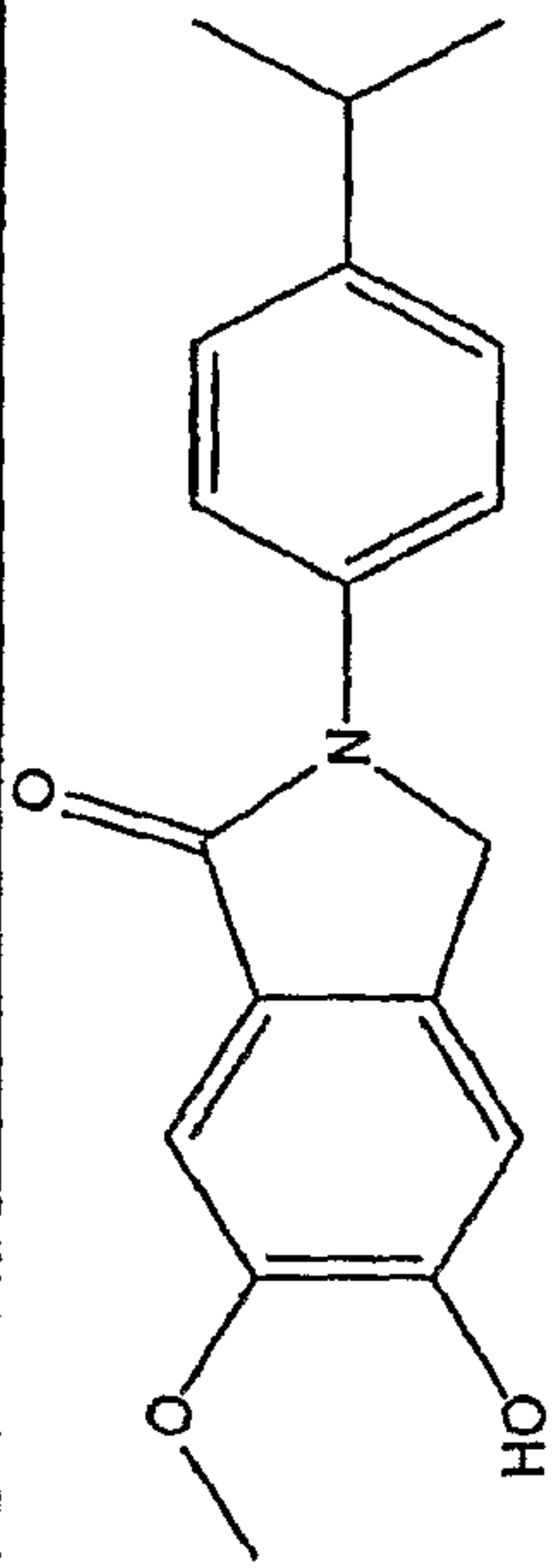
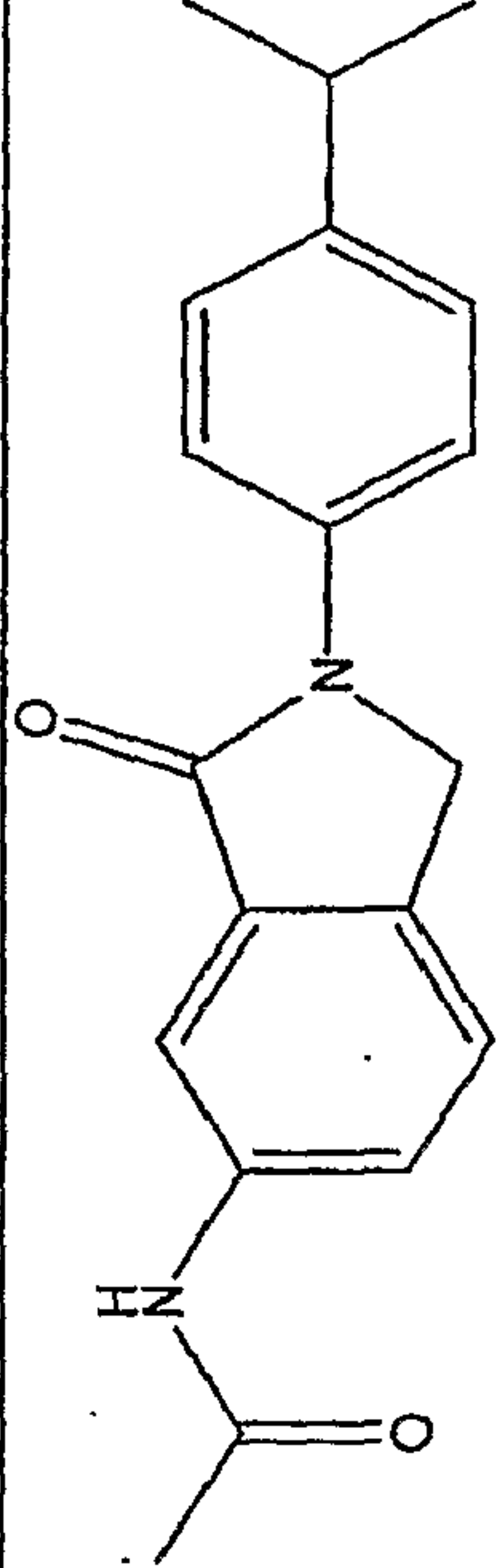
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
404		ALB- 116078	0.267	1.644
405		ALB- 117047	0.269	1.387
406		ALB- 117452	0.289	1.397

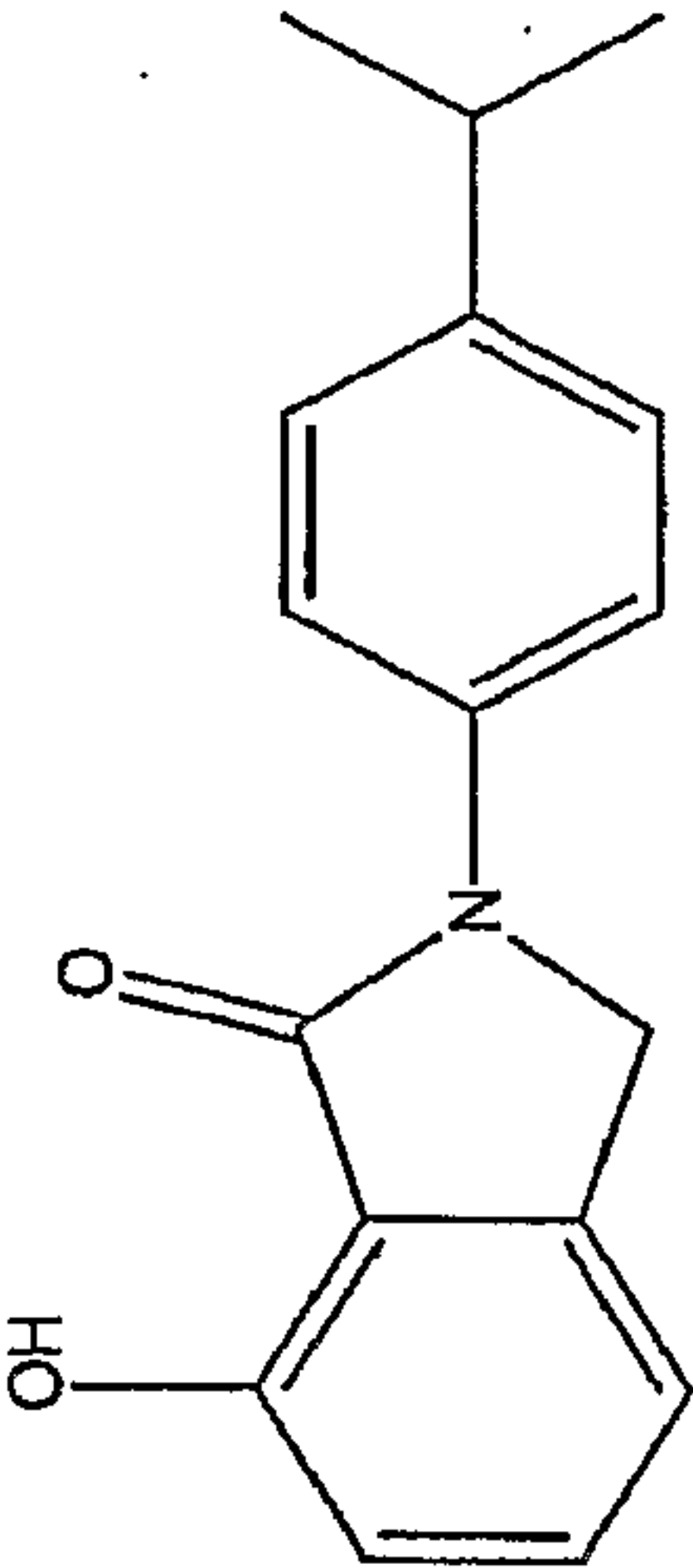
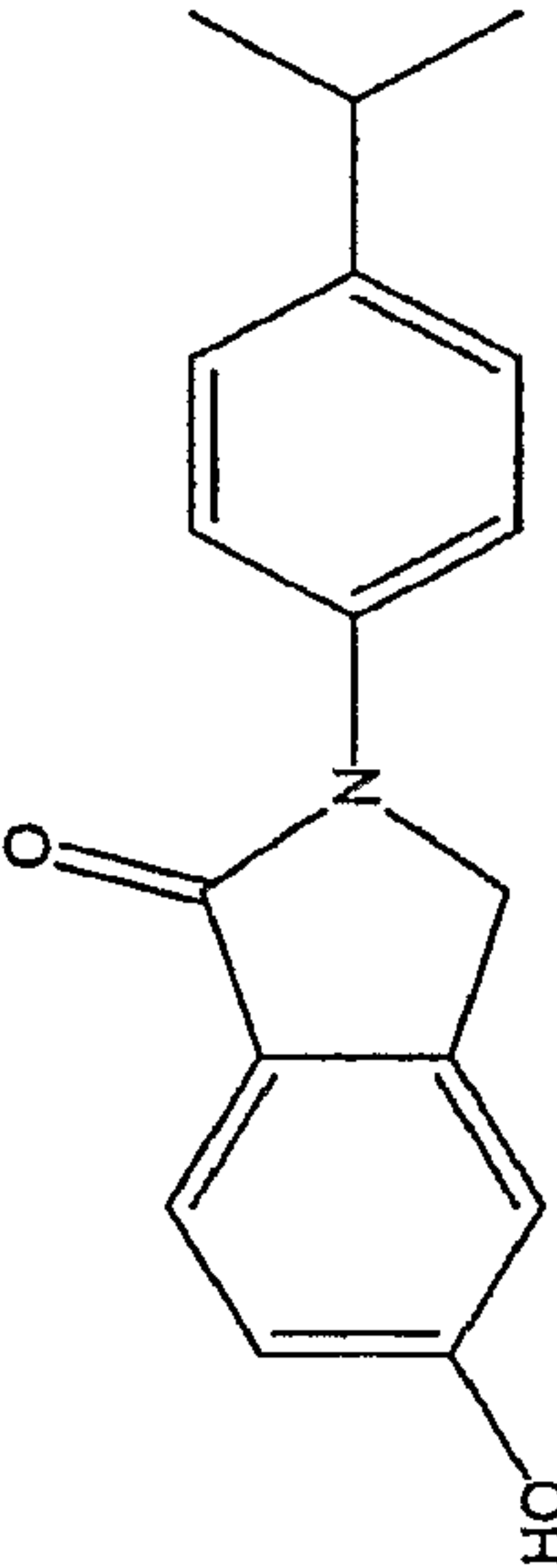
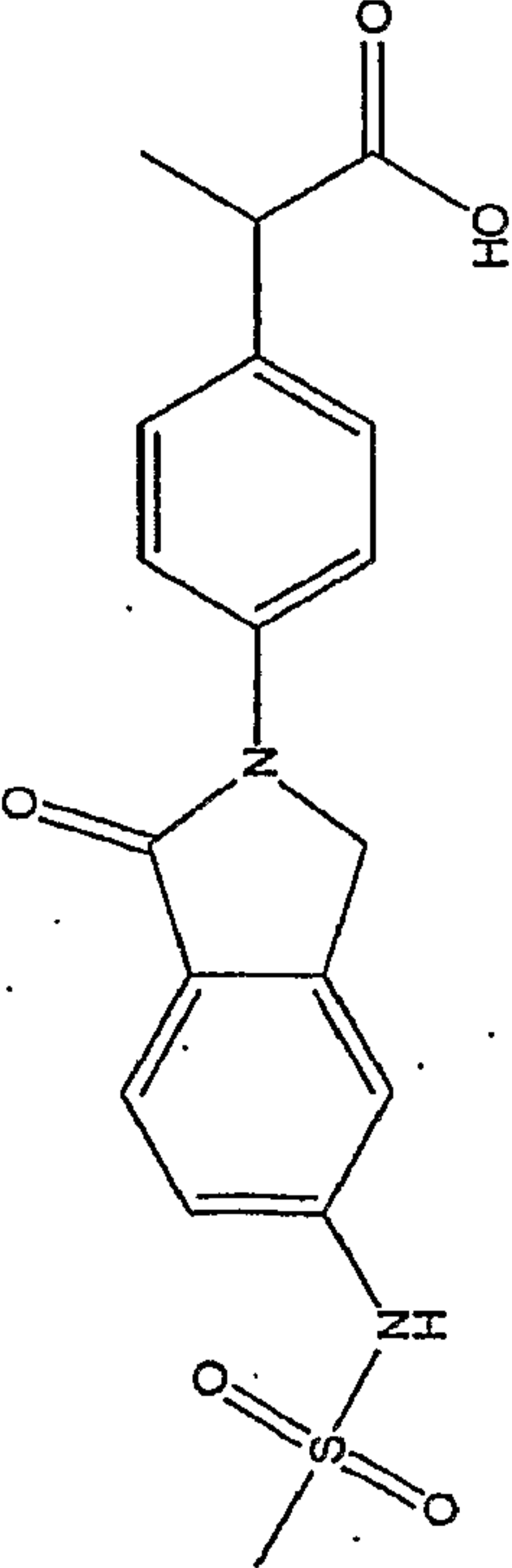
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
407		ALB- 117903		1.069
408		ALB- 118035		1.131
409		ALB- 118157	0.203	1.511

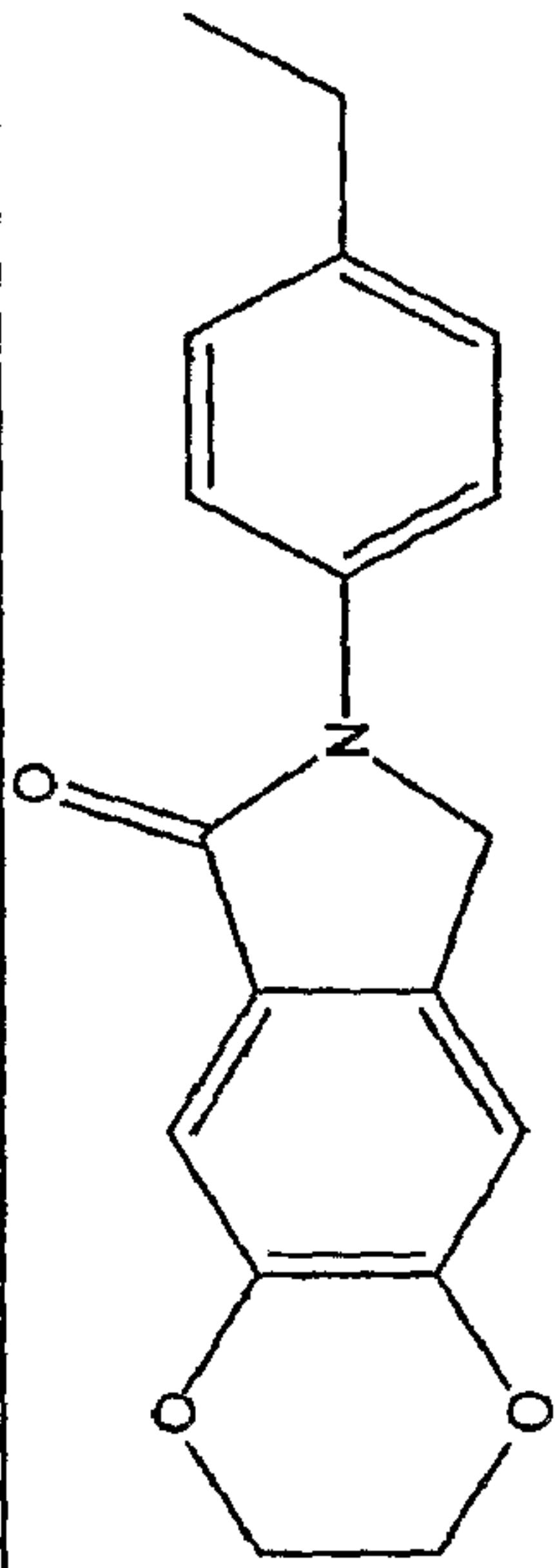
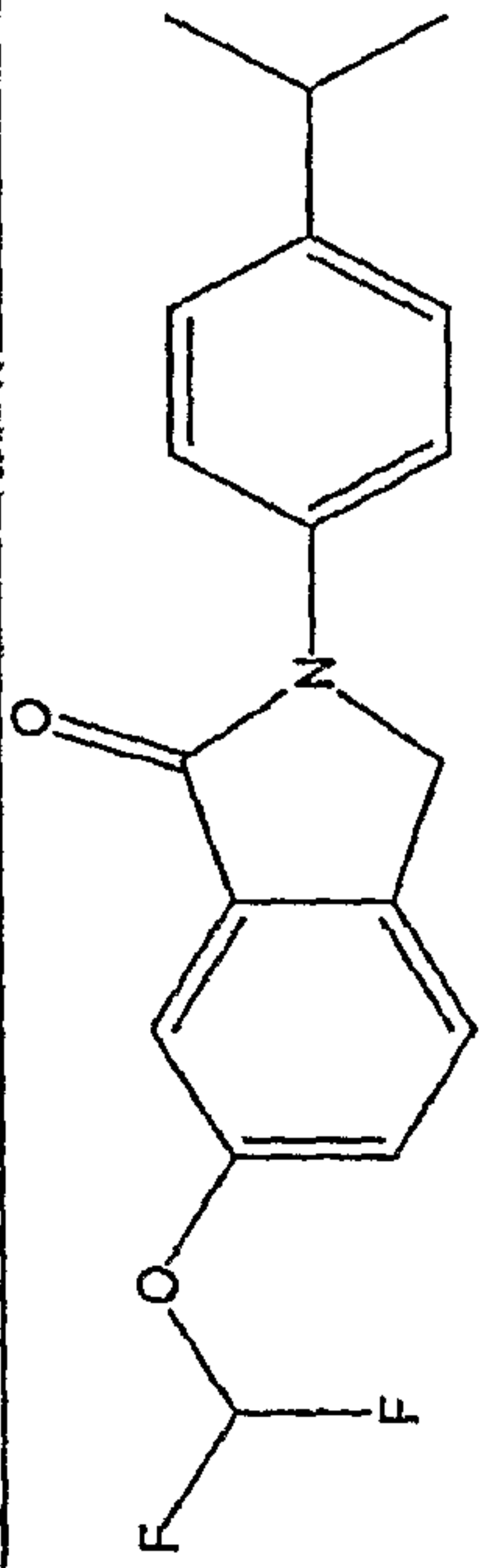
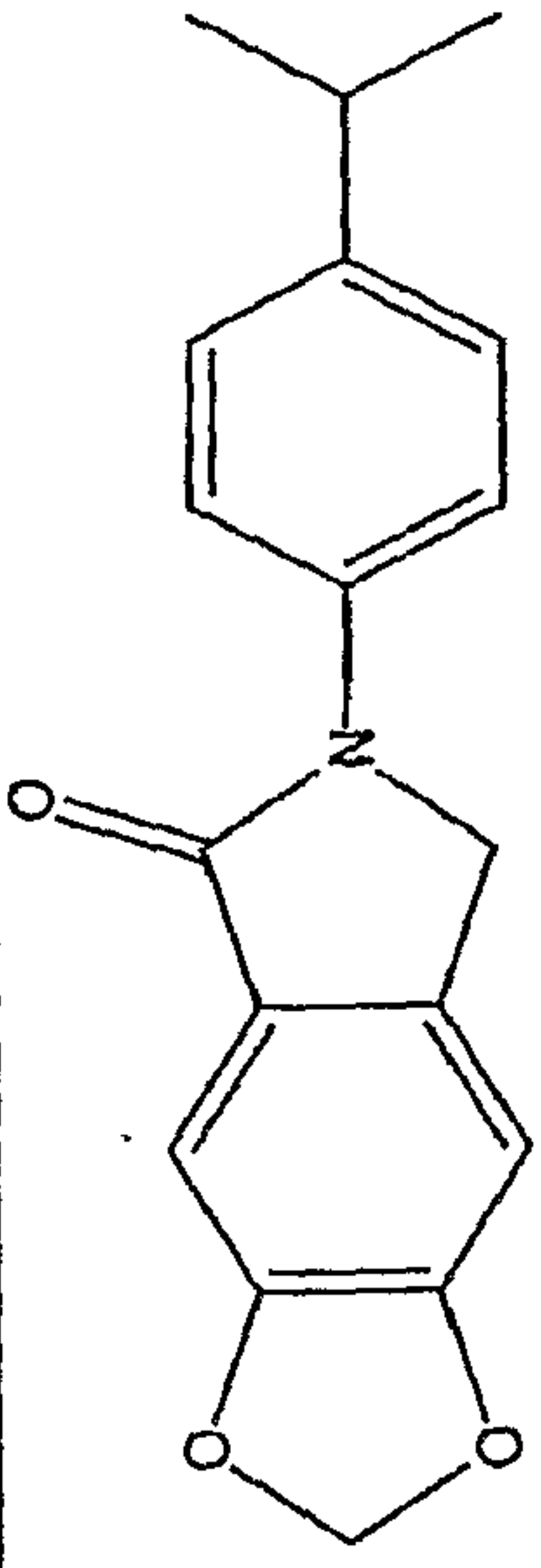
232

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
410		ALB- 118158	0.733	1.544
411		ALB- 118277	0.027	1.153
412		ALB- 113647		1.106

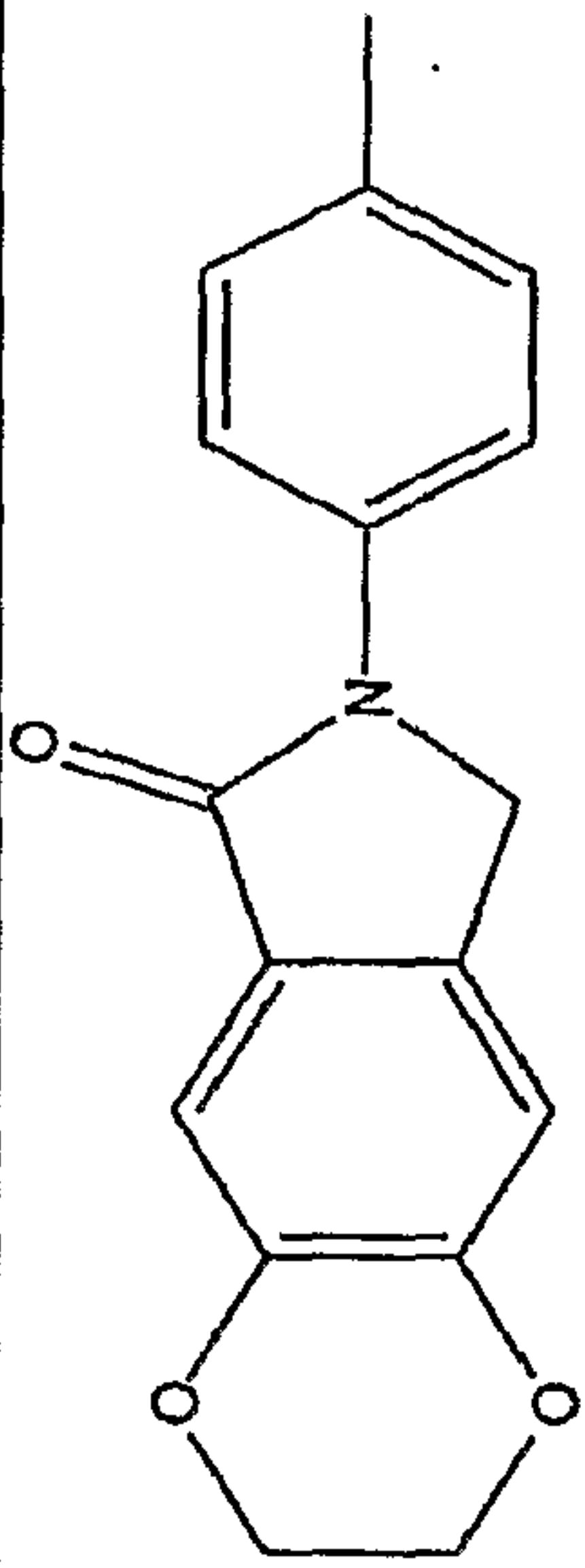
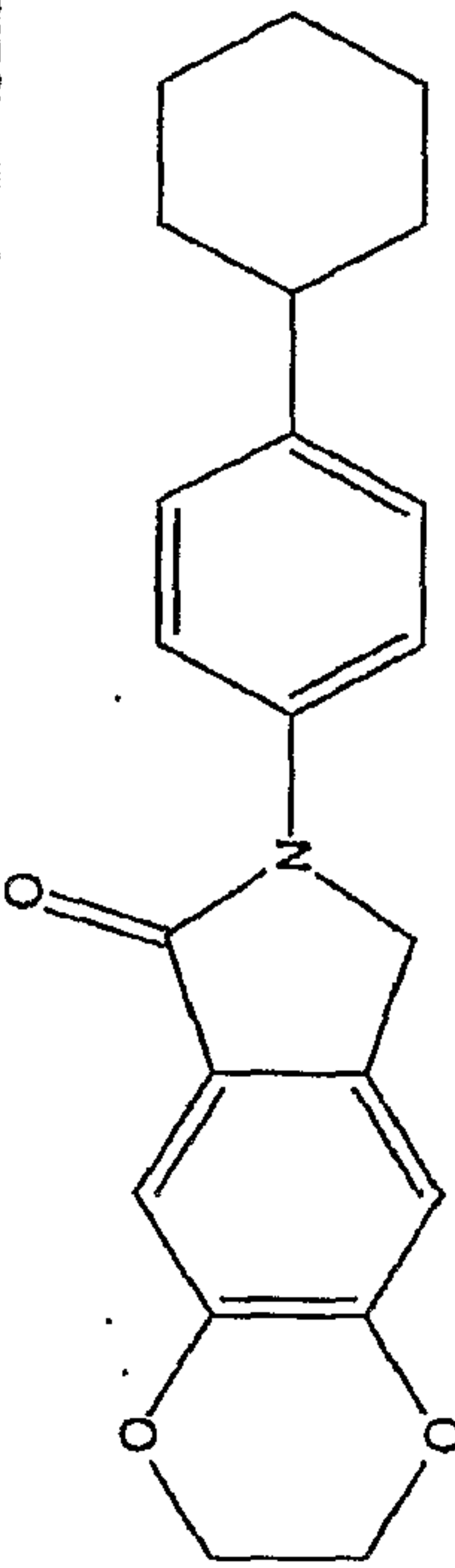
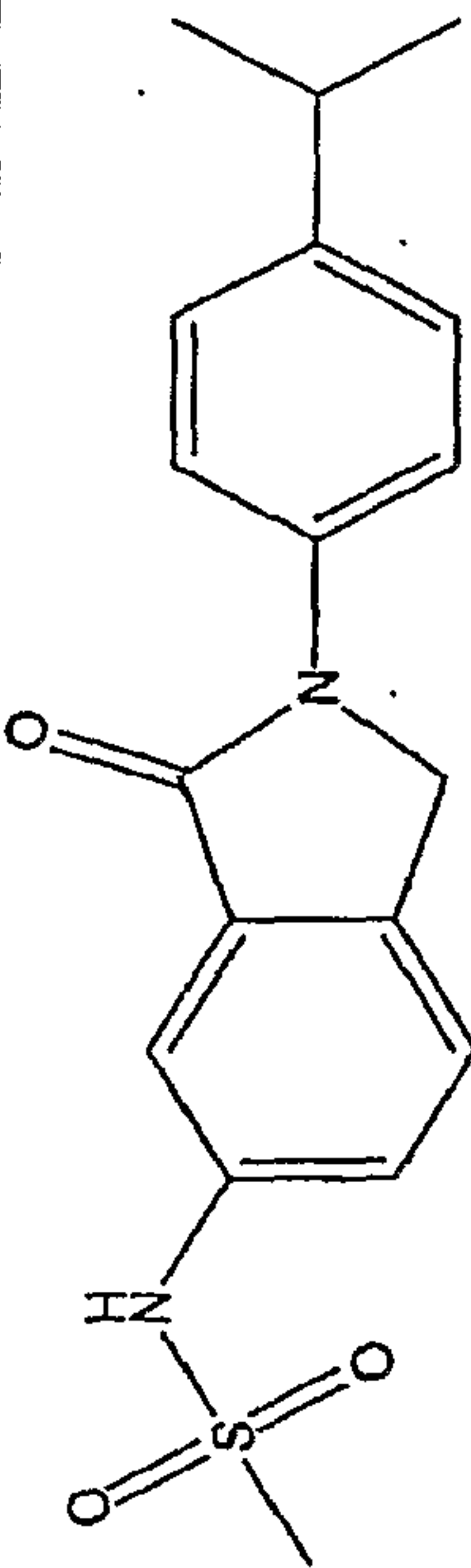
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
413		ALB- 116240	0.033	1.623
414		ALB- 116244	0.599	1.568
415		ALB- 116362	0.123	1.521

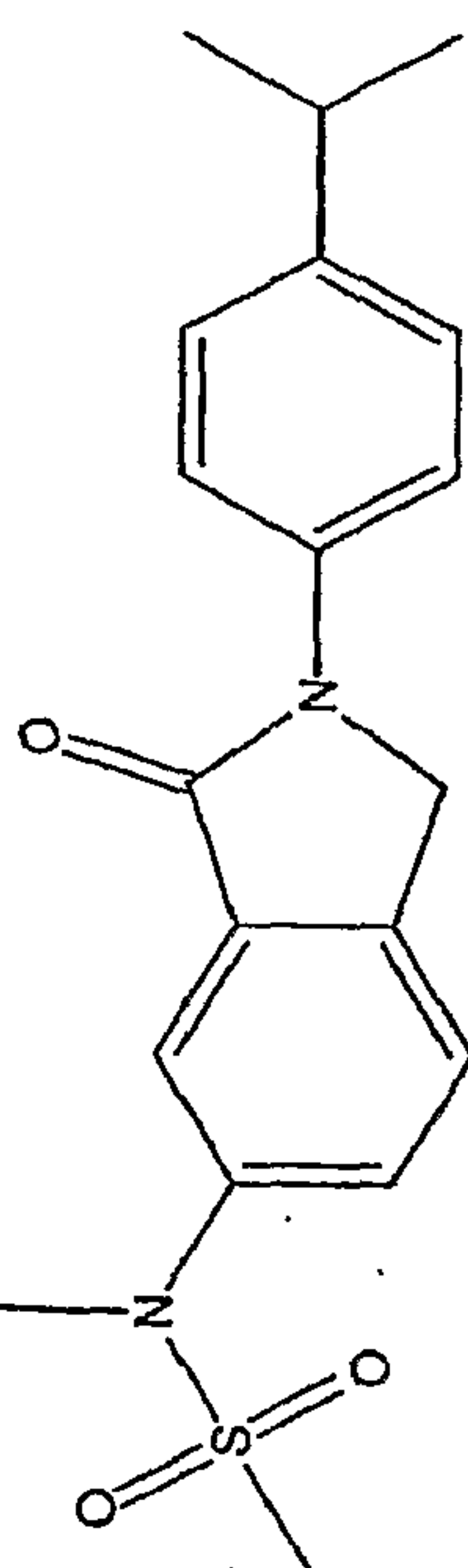
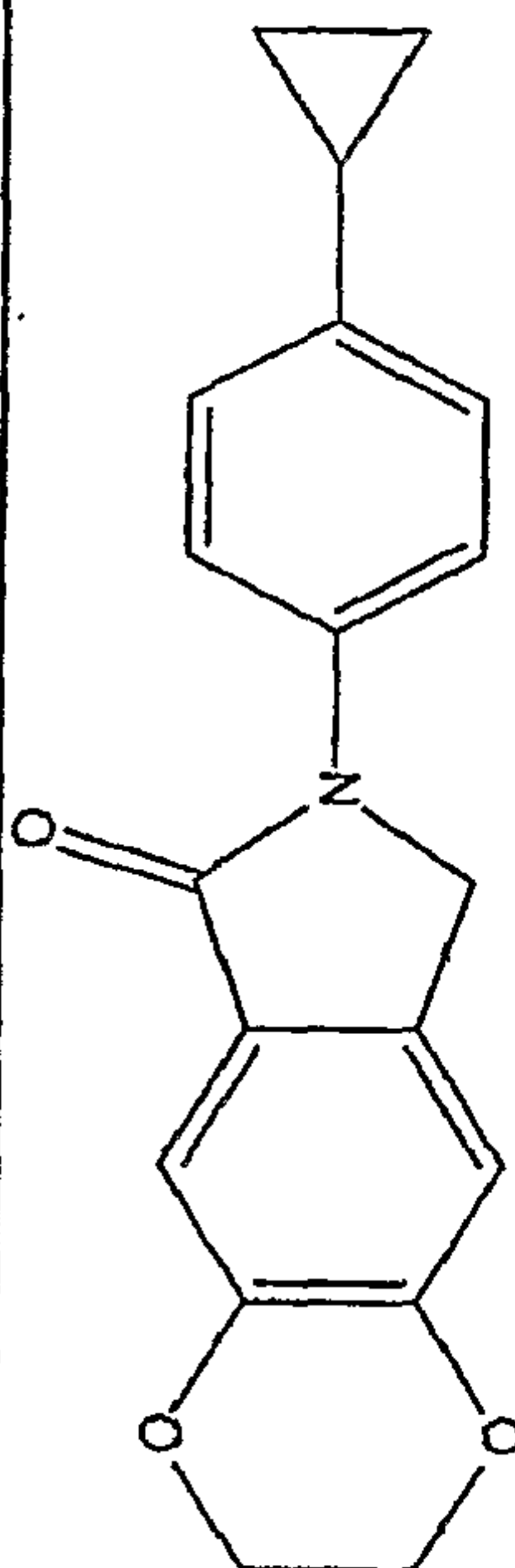
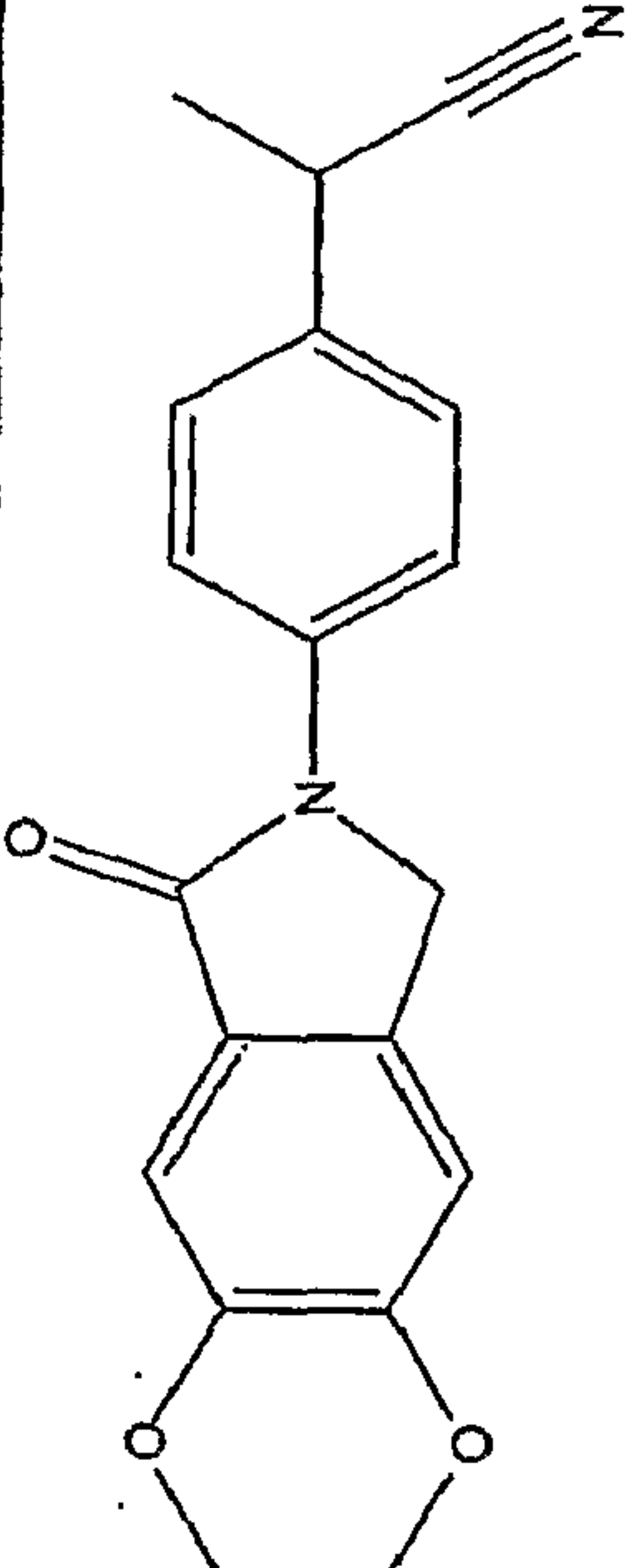
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
416		ALB- 116363	0.024	1.536
417		ALB- 116417		1.112
418		ALB- 116486	0.757	1.492

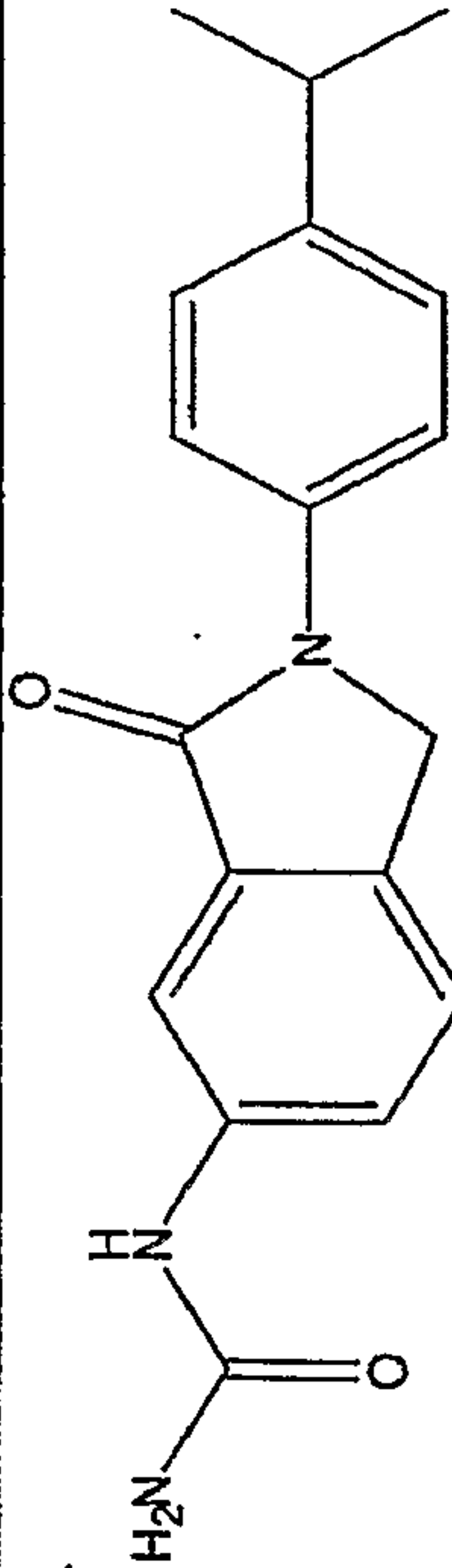
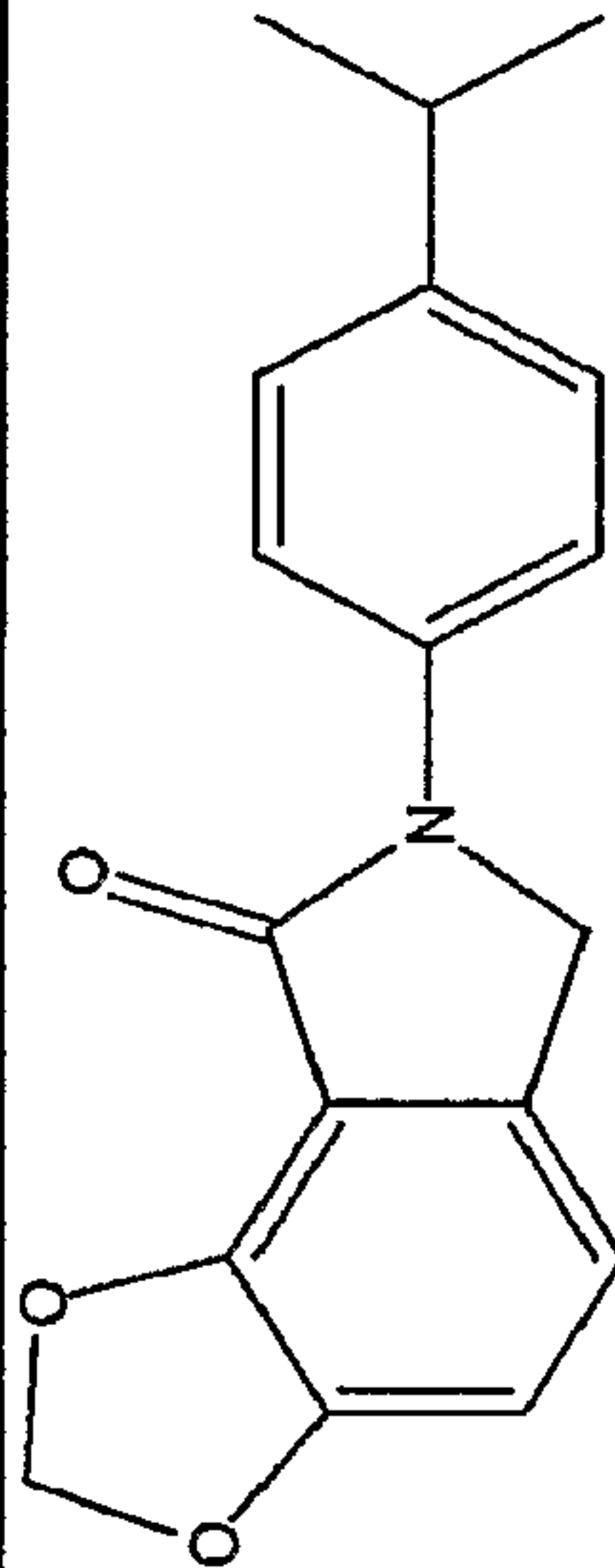
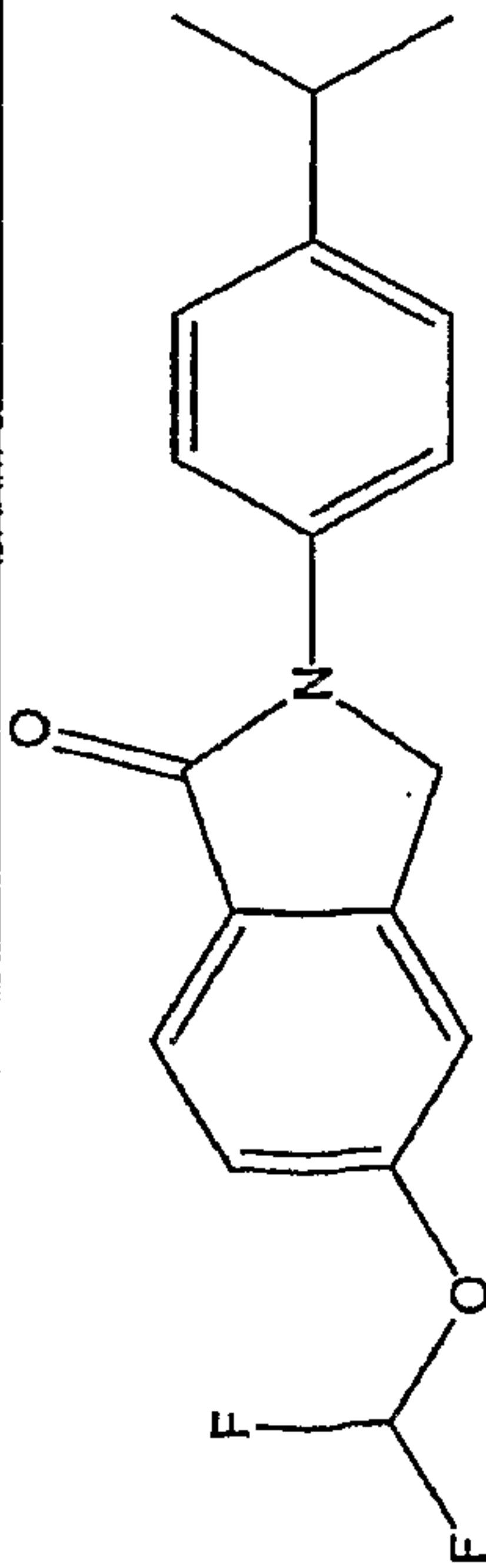
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
419		ALB- 116638	0.166	1.515
420		ALB- 117043	0.068	1.566
421		ALB- 117571	0.401	1.297

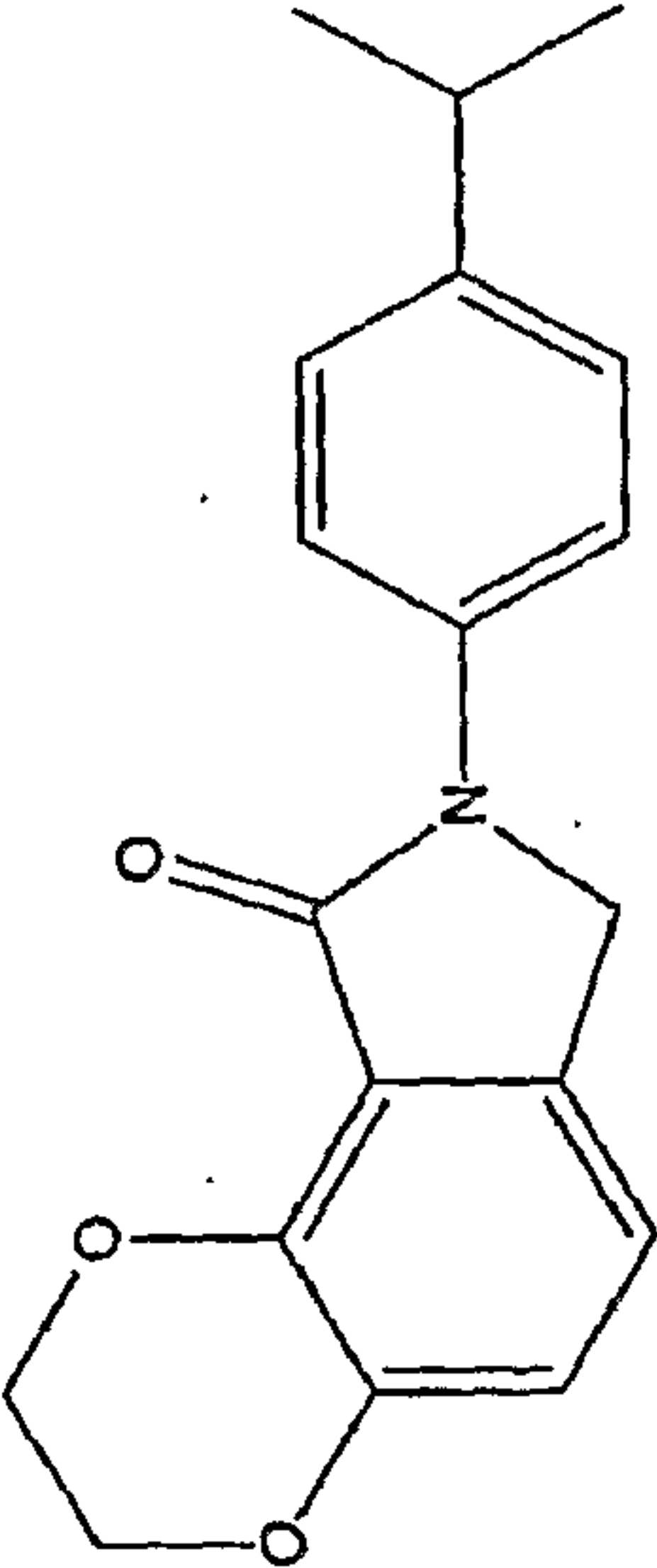
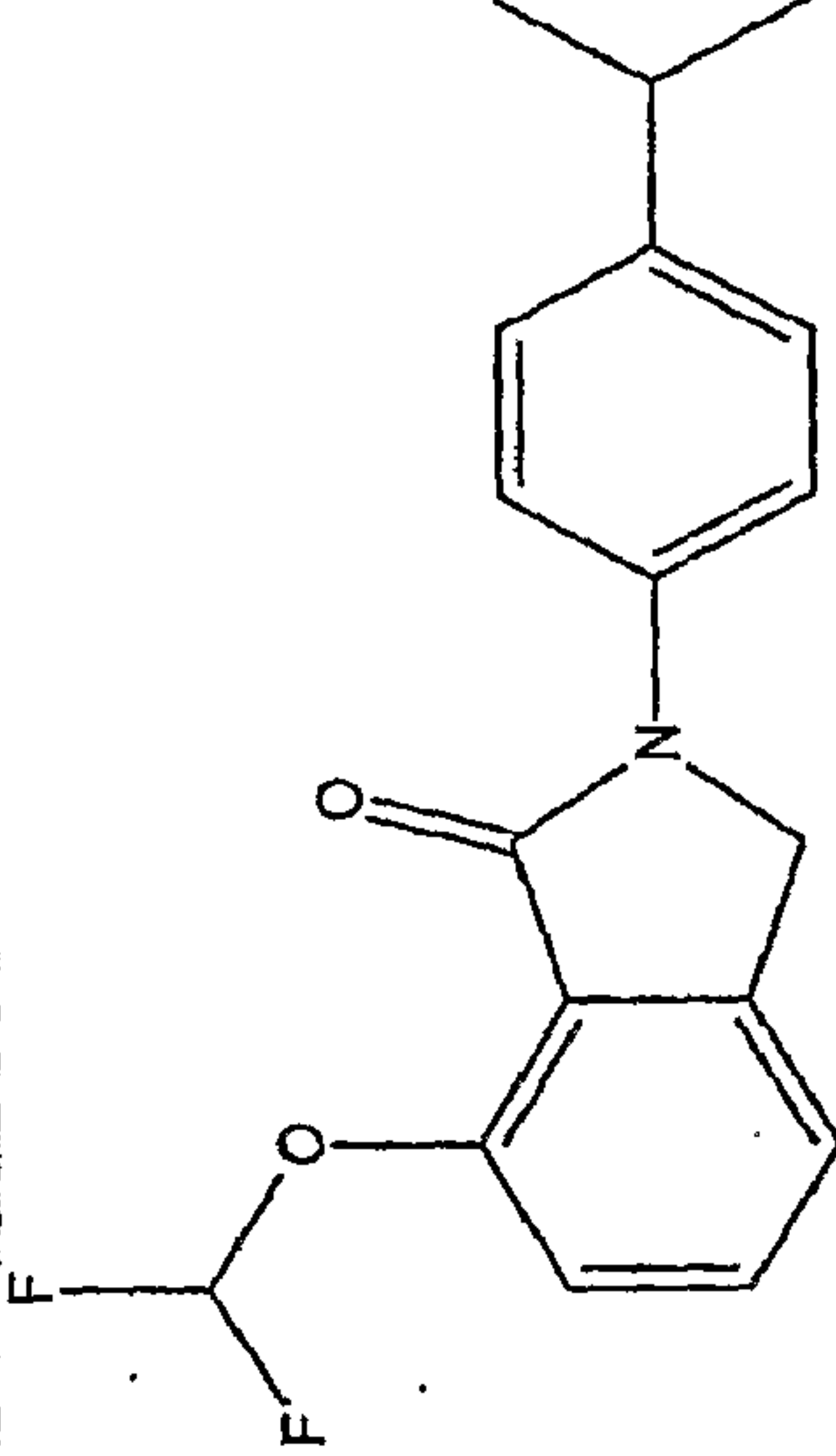
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
422		ALB- 117573	0.345	1.671
423		ALB- 117751	0.027	1.34
424		ALB- 118159	2.086	1.317

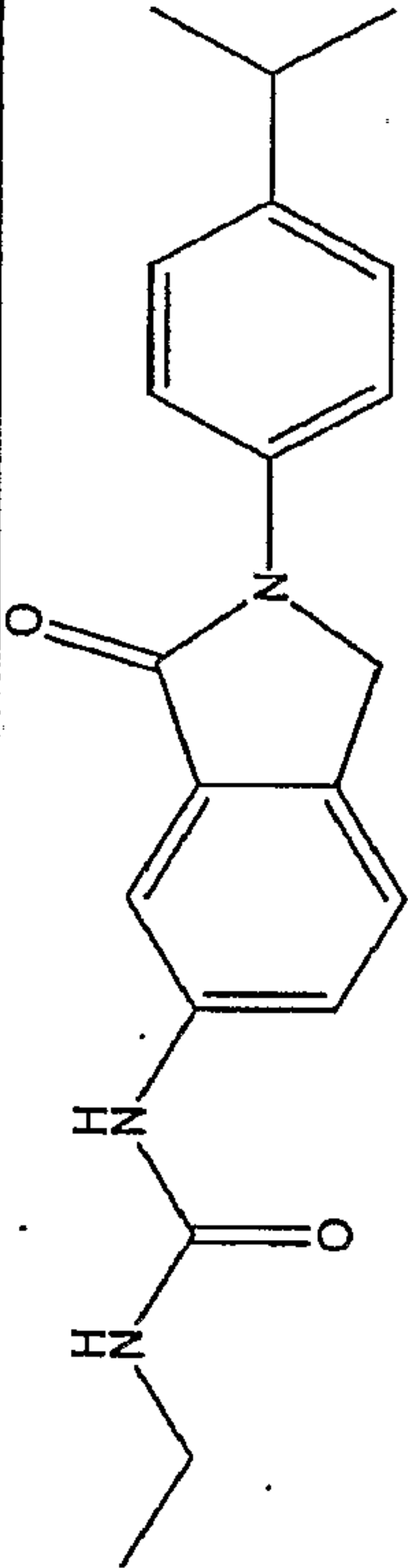
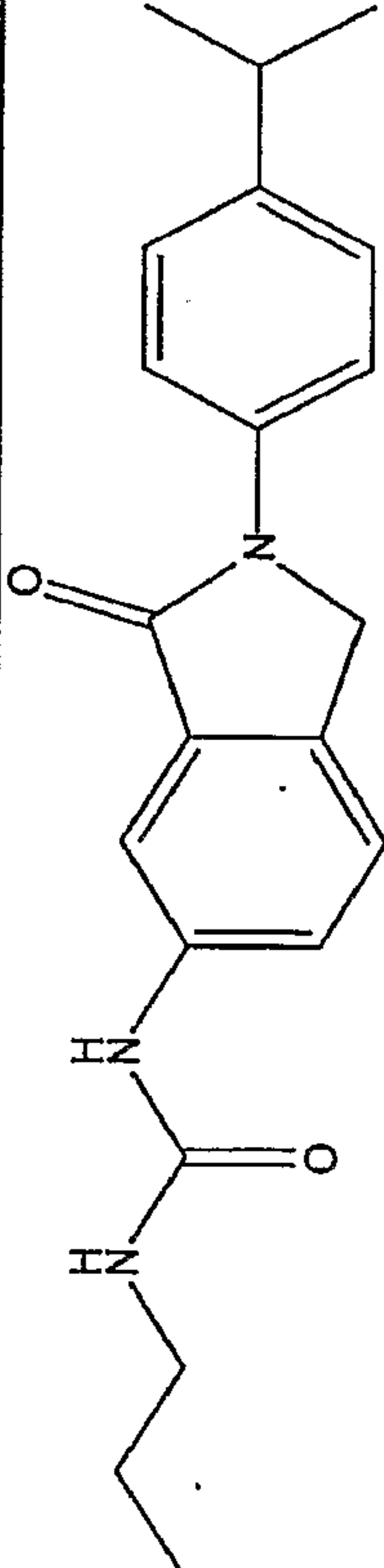
237

Table I

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
425		ALB- 118160	0.046	1.428
426		ALB- 118279	0.22	1.553

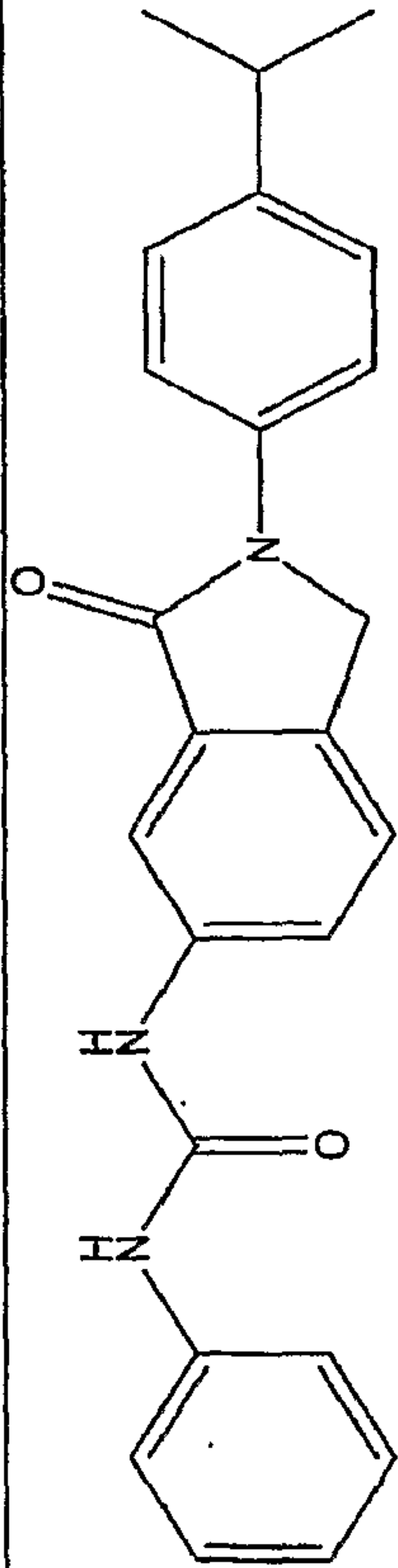
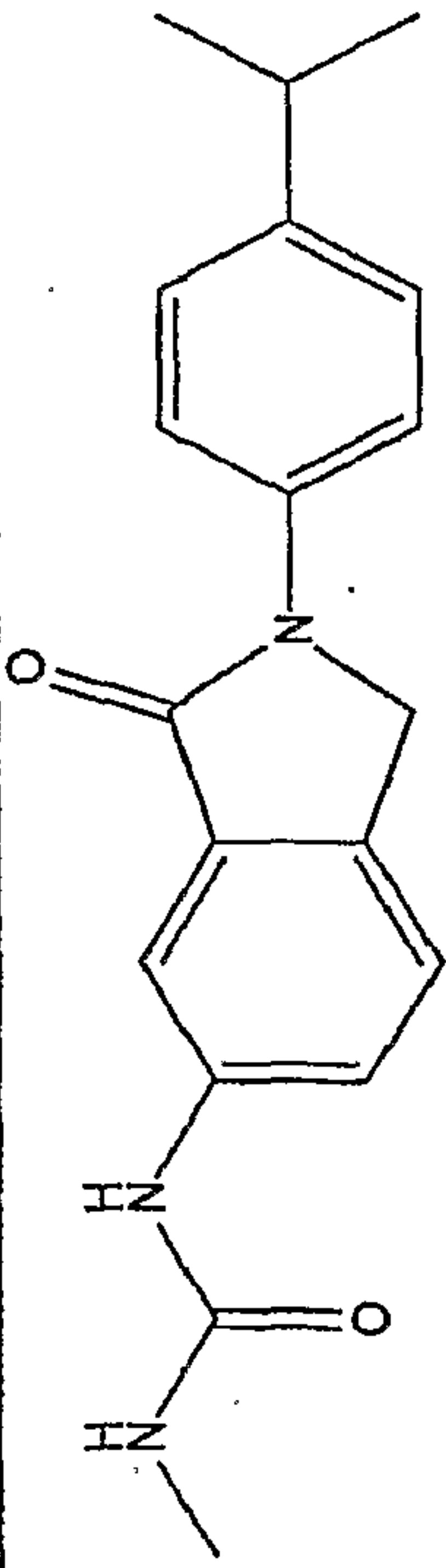
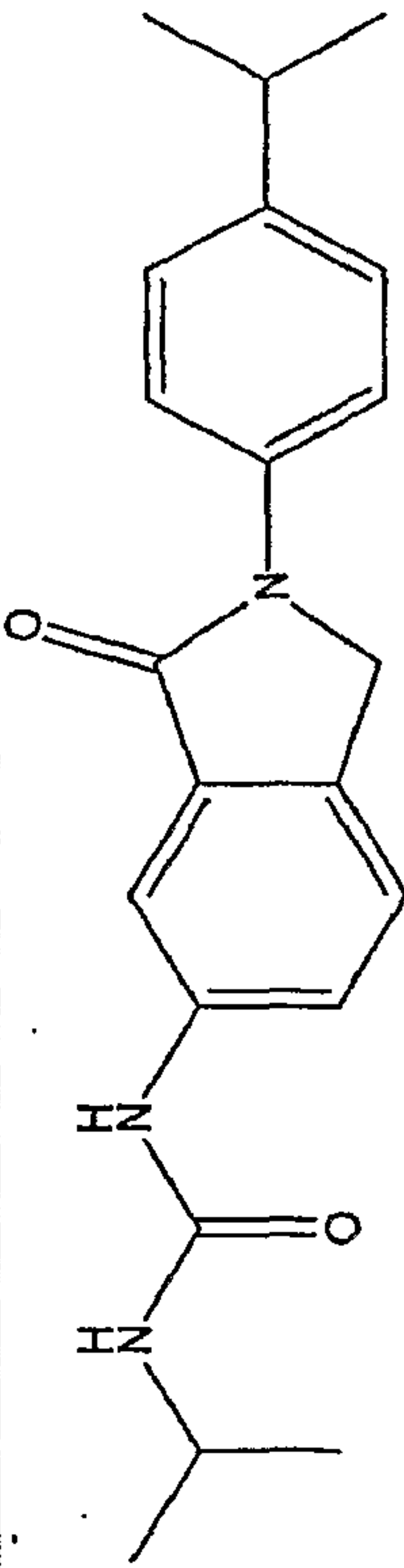
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
427		ALB- 118414	3.526	1.355
428		ALB- 118415	13.188	1.4

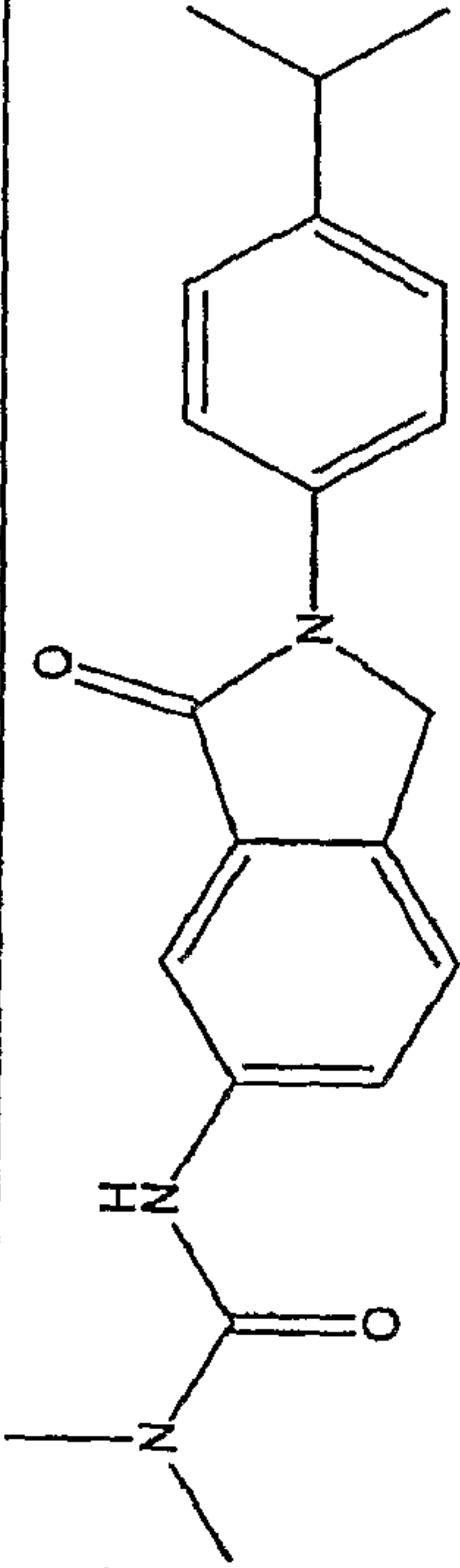
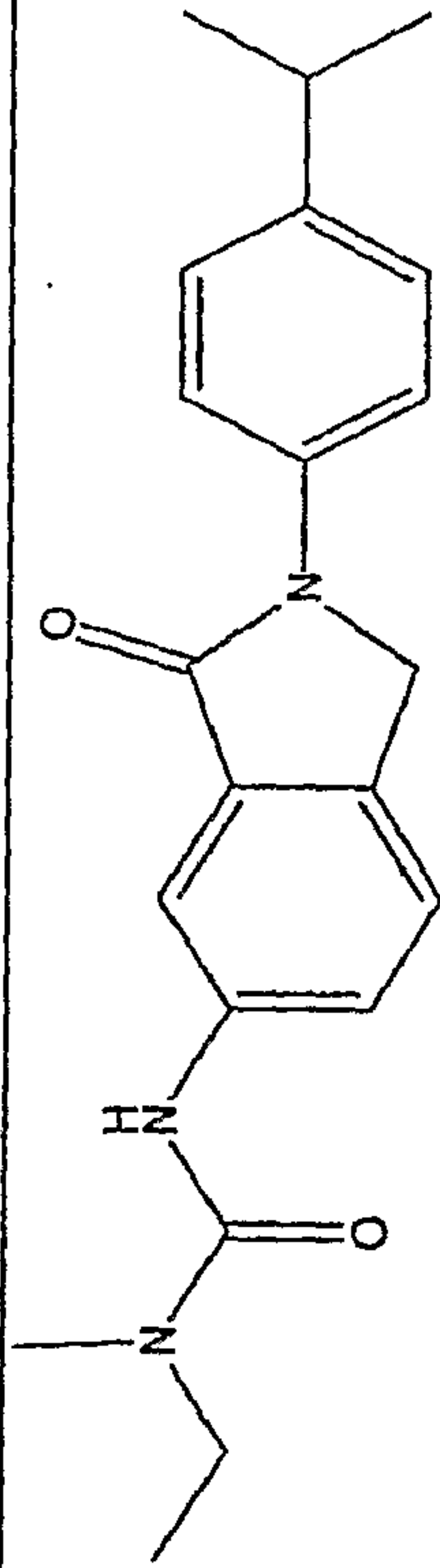
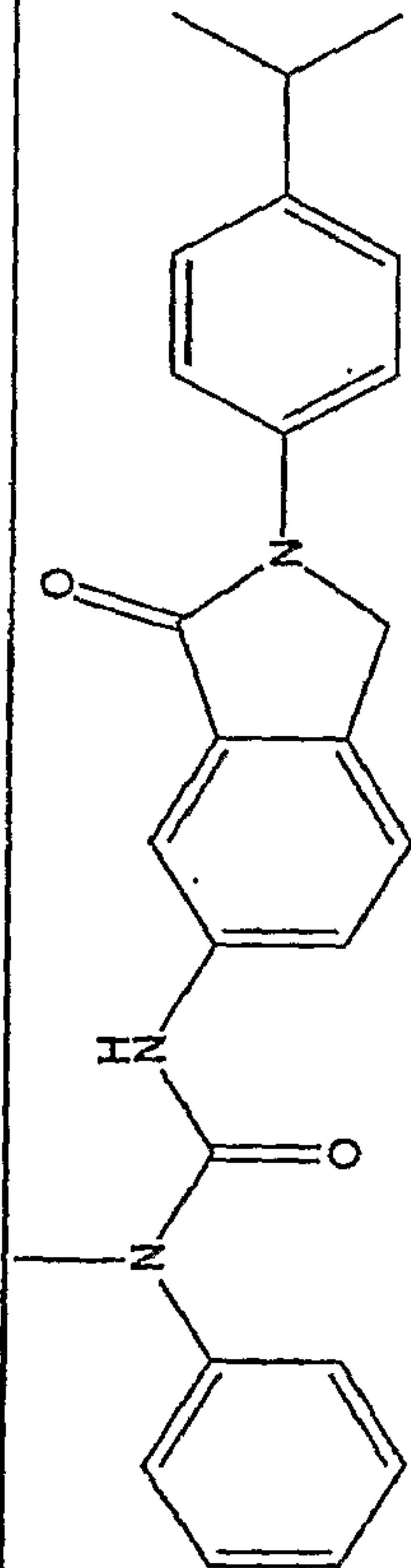
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
429		ALB- 118416		1.17
430		ALB- 118558	0.865	1.584
431		ALB- 118559		1.098

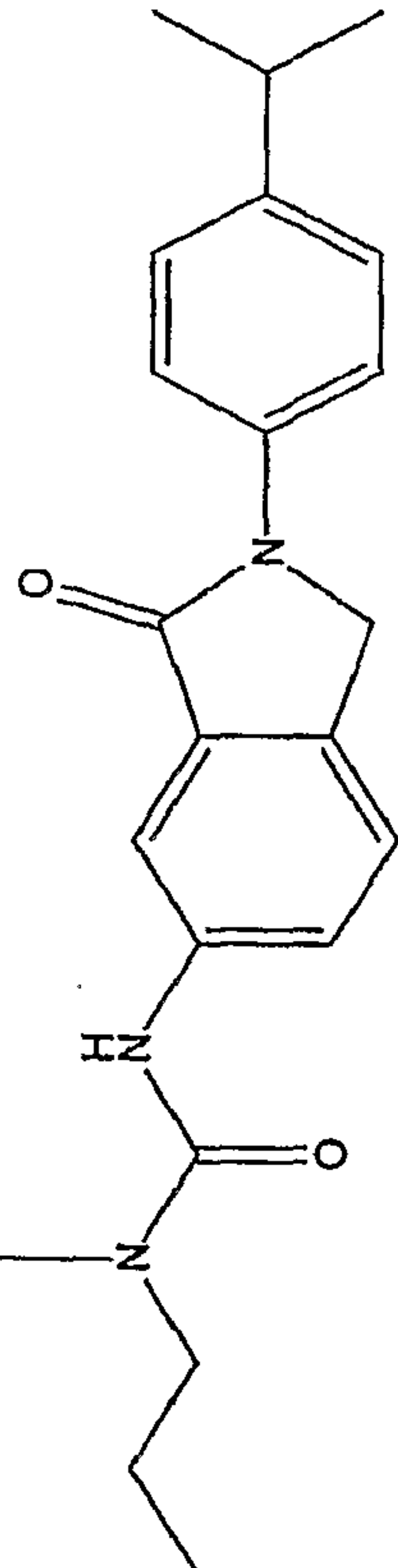
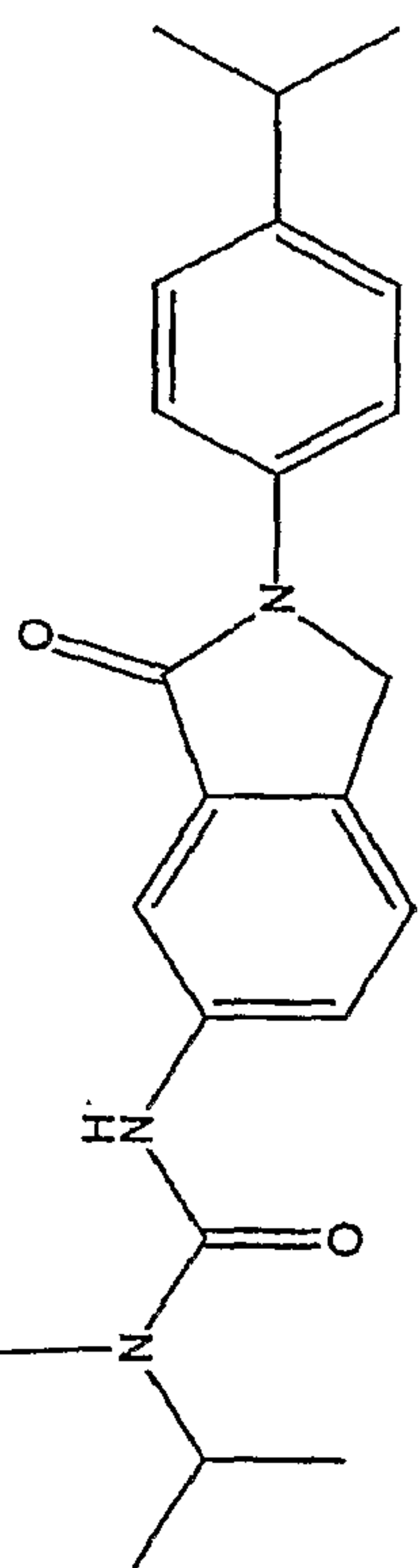
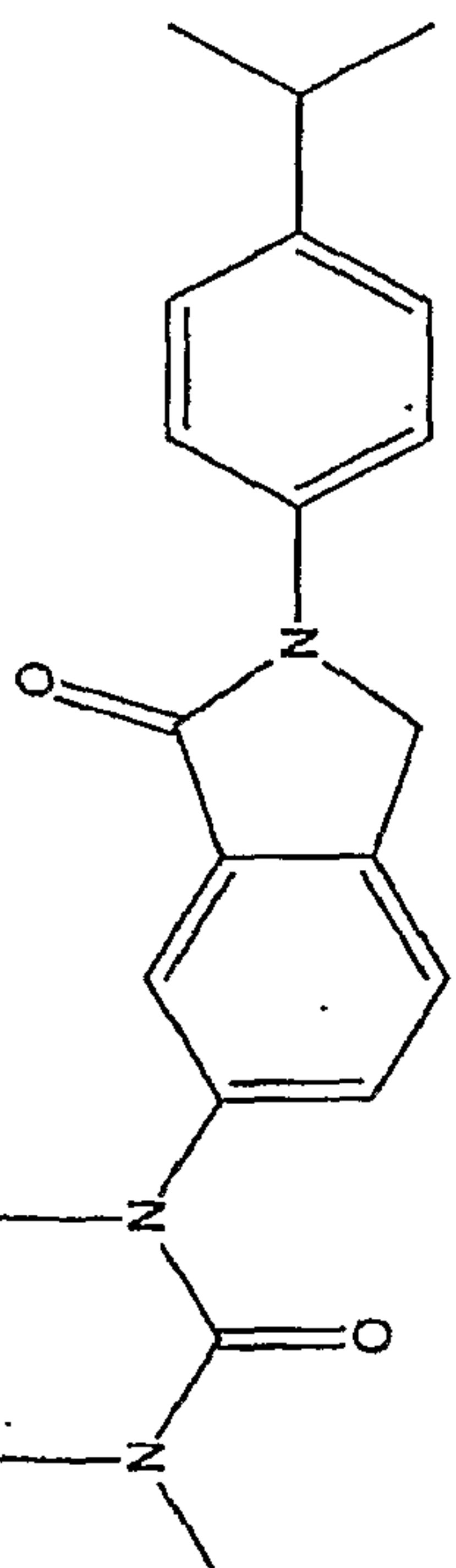
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Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
432		ALB- 118731	0.854	1.197
433		ALB- 118732		1.153
434		ALB- 118733		1.118

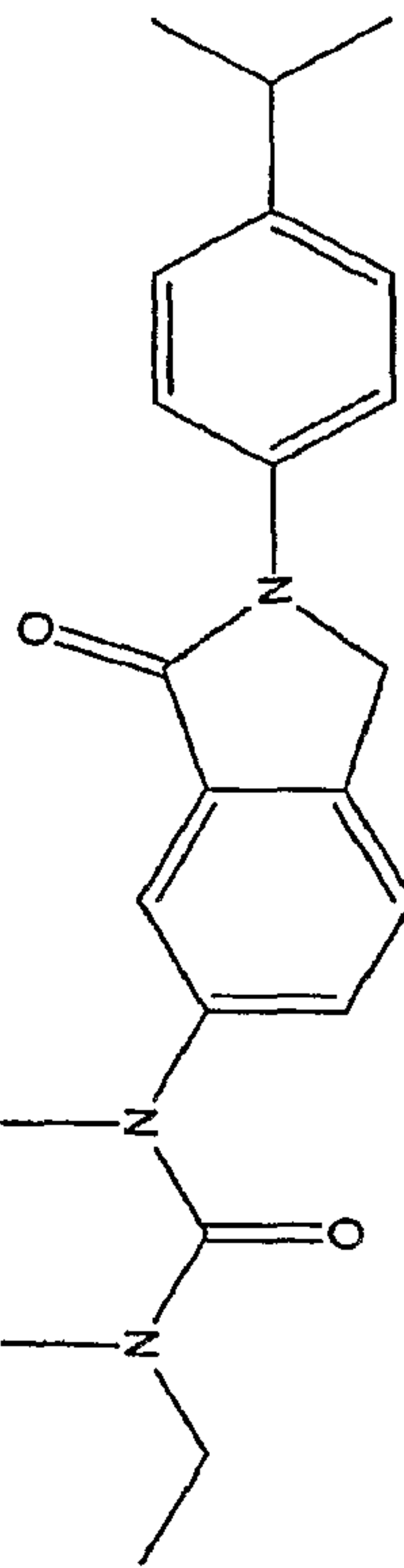
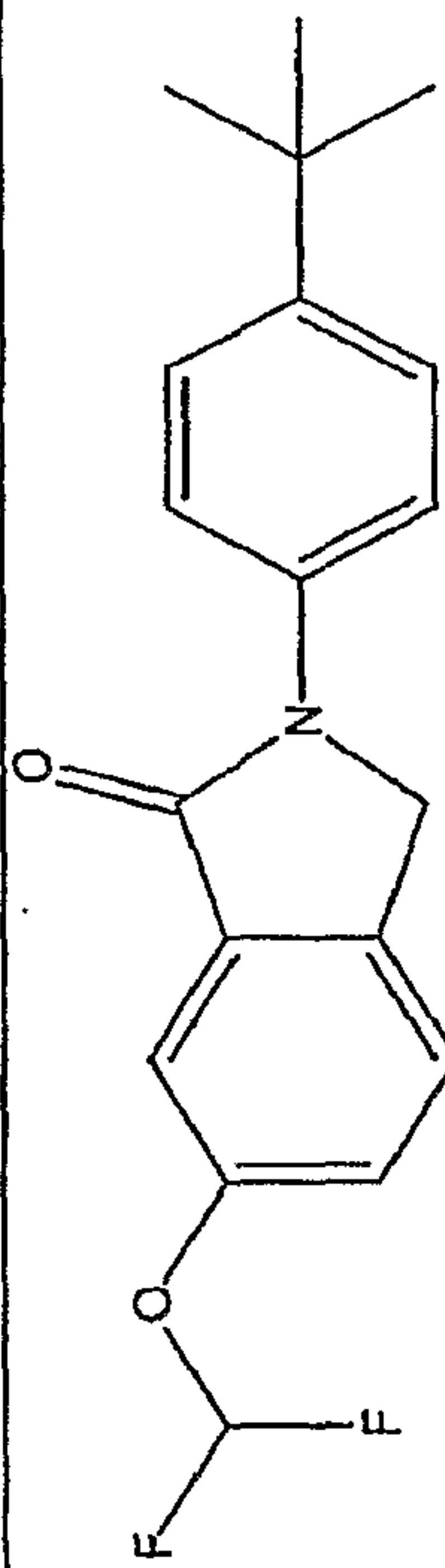
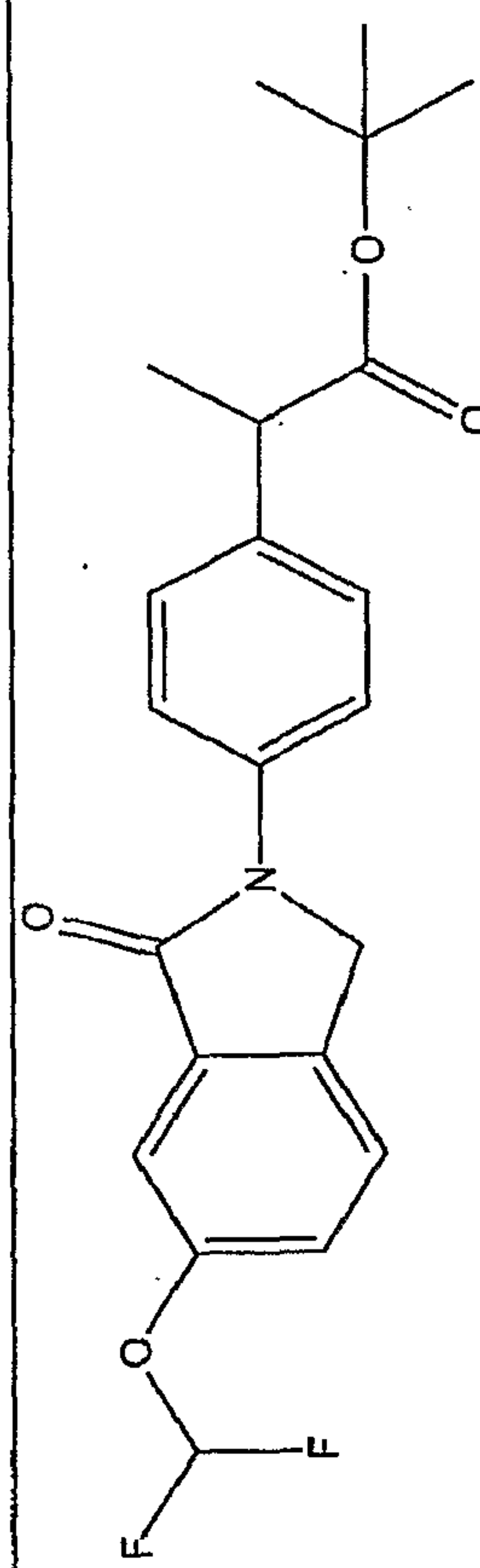
241

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
435		ALB- 118898		1.063
436		ALB- 118899		1.076
437		ALB- 118901	0.493	1.311

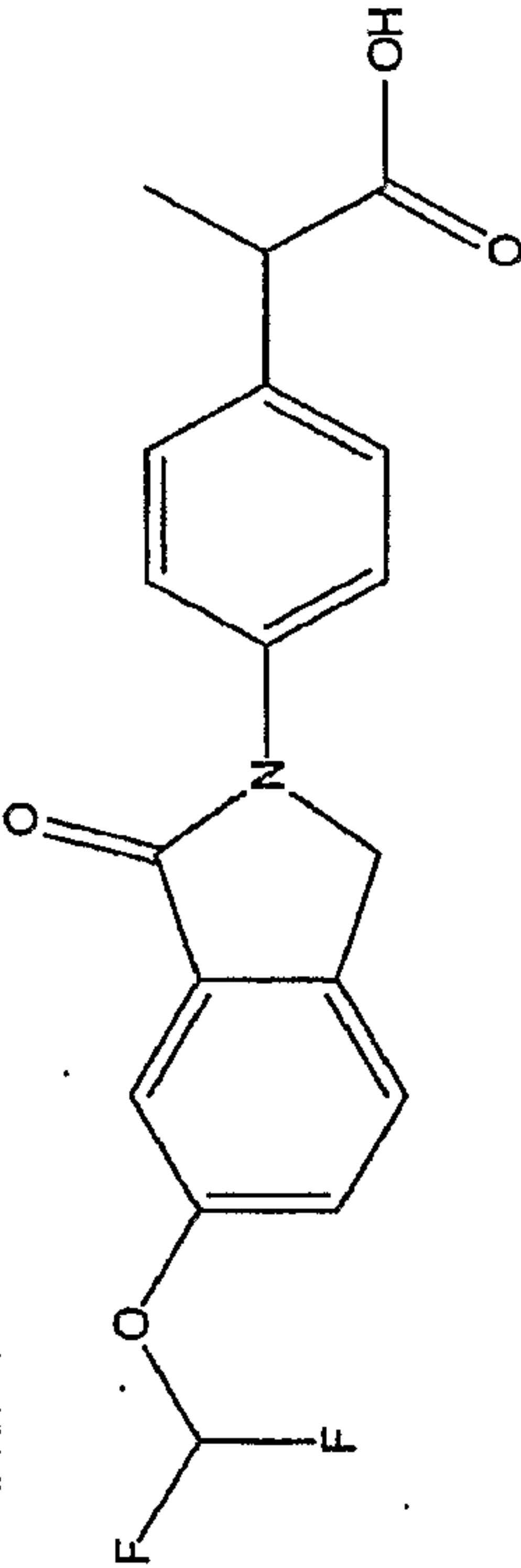
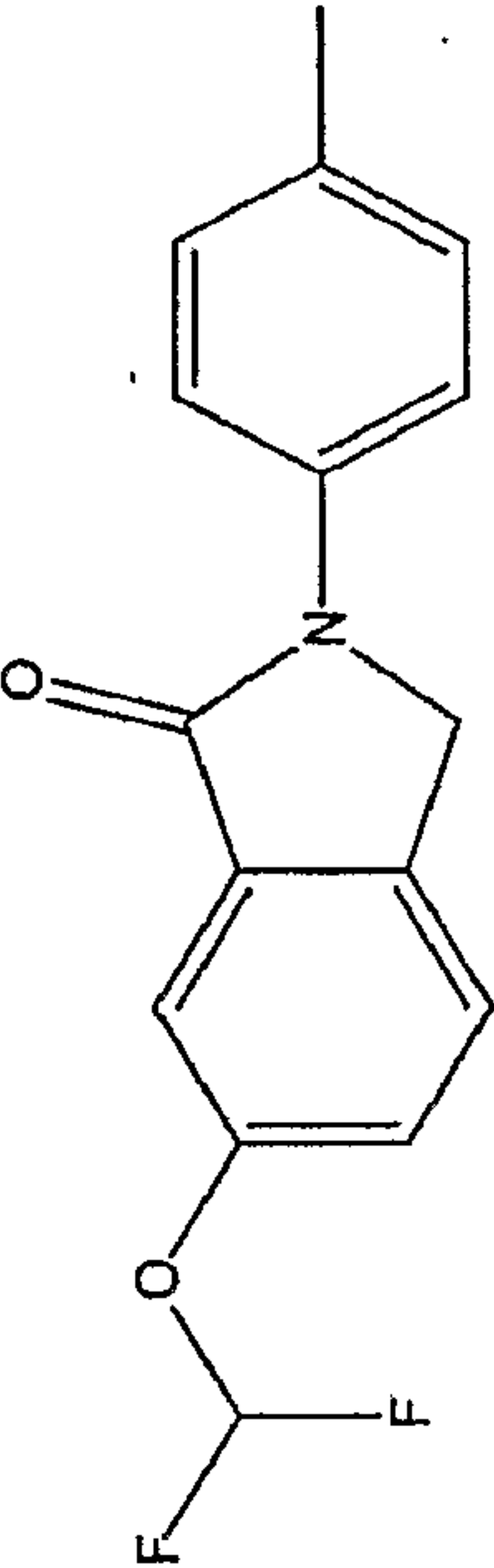
242

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
438		ALB- 119049		1.085
439		ALB- 119043	0.992	1.386
440		ALB- 119336	0.718	1.213

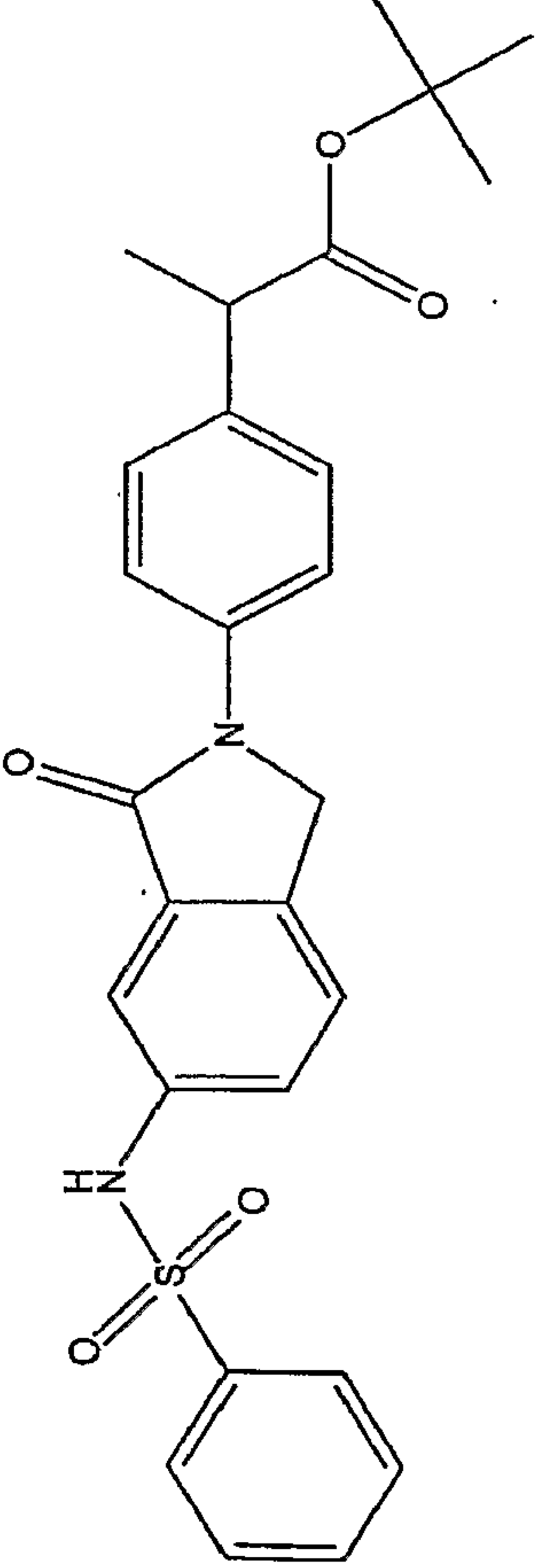
243

Table 1

No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (μ M)	Avg MaxFold Increase
441		ALB- 119335	0.051	1.537
442		ALB- 119515	0.146	1.456

244

Table 1

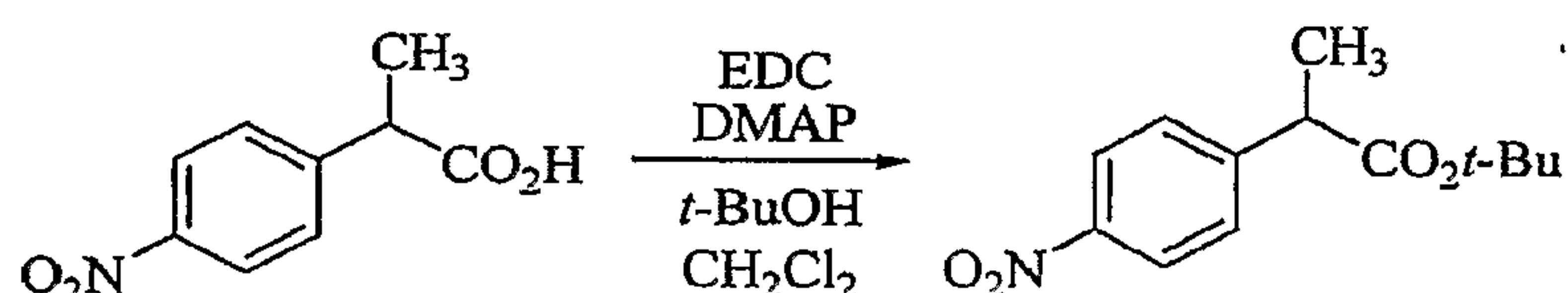
No.	STRUCTURE	Identifier	SMN Splice Reporter Assay (Example 10)	
			Avg EC50 (uM)	Avg MaxFold Increase
443		ALB- 112072		1.073

[0091] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope. Some compounds are referenced in the Examples by identifier codes starting with "ALB." These codes are correlated with the structure of the molecule in Table 1.

EXAMPLE 1

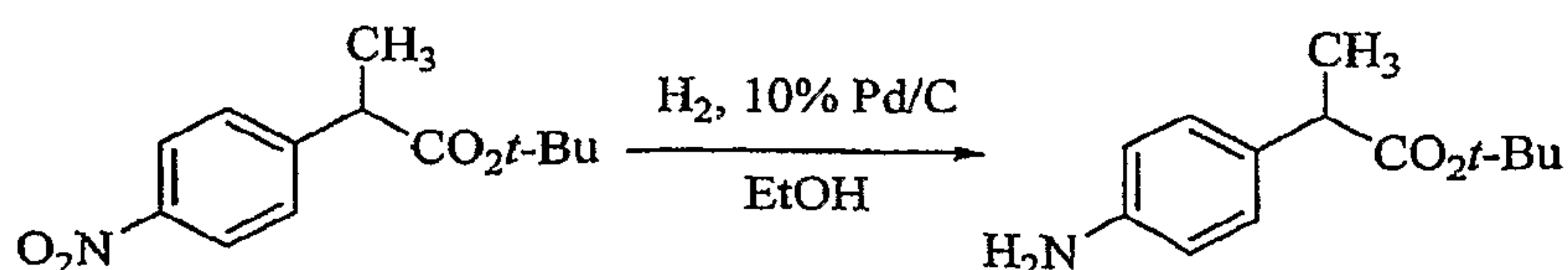
[0092] This example illustrates the preparation of 2-(4-(6-chloro-1-oxoisindolin-2-yl)phenyl) propanoic acid.

[0093] Step A: Synthesis of tert-butyl 2-(4-nitrophenyl)propanoate as an intermediate



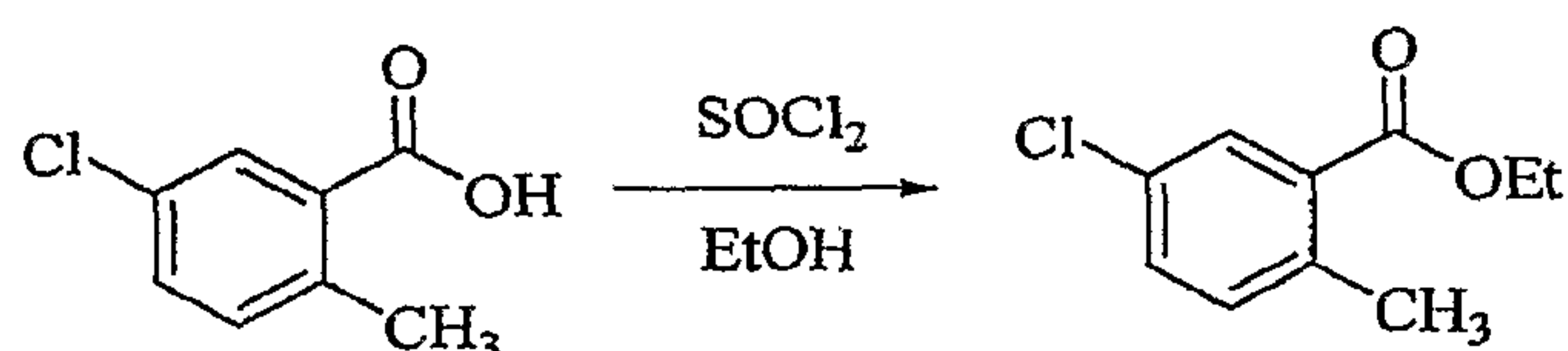
[0094] A mixture of 2-(4-nitrophenyl)propanoic acid (15.0 g, 76.9 mmol), dimethylaminopyridine (4.70 g, 38.4 mmol) and tert-butanol (8.10 mL, 84.6 mmol) in methylene chloride (300 mL) was stirred at 0 °C for 2 h. After this time, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (17.0 g, 84.6 mmol) was added and the reaction stirred for a further 2 h. The ice bath was then removed and the reaction left to stir at room temperature overnight. After this time, the solvents were concentrated under reduced pressure and the solids redissolved in ethyl acetate (200 mL). The organic layer was then washed with saturated sodium bicarbonate (200 mL), 1 M citric acid (200 mL) and brine (200 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 1:20 ethyl acetate/hexanes) afforded tert-butyl 2-(4-nitrophenyl)propanoate (14.4 g, 75%) as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 8.19 (d, *J* = 9.2 Hz, 2H), 7.46 (d, *J* = 9.2 Hz, 2H), 3.73 (q, *J* = 7.1 Hz, 1H), 1.49 (d, *J* = 7.1 Hz, 3H), 1.40 (s, 9H).

[0095] Step B: Synthesis of tert-butyl 2-(4-aminophenyl)propanoate as an intermediate



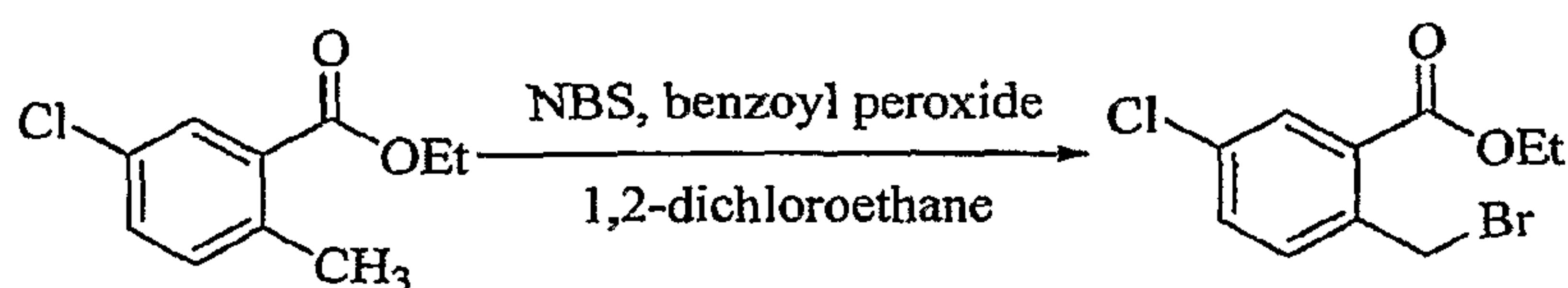
[0096] A mixture of tert-butyl 2-(4-nitrophenyl)propanoate (14.4 g, 57.3 mmol) and 10% palladium on carbon (1.44 g, 10% by weight) in ethanol (150 mL) was shaken under an atmosphere of hydrogen at 40 psi for 2 h. After this time, the reaction was filtered through diatomaceous earth, and concentrated under reduced pressure to afford tert-butyl 2-(4-aminophenyl)propanoate (12.5 g, 99%) as an orange oil: ^1H NMR (300 MHz, CDCl_3) δ 7.07 (d, $J = 9.1$ Hz, 2H), 6.63 (d, $J = 9.1$ Hz, 2H), 3.60 (s, 2H), 3.49 (q, $J = 7.1$ Hz, 1H), 1.40 (d, 3H), 1.38 (s, 9H); ESI MS m/z 222 $[\text{M} + \text{H}]^+$.

[0097] Step C: Synthesis of ethyl 5-chloro-2-methylbenzoate as an intermediate



[0098] A mixture of 5-chloro-2-methylbenzoic acid (3.00 g, 17.5 mmol) in ethanol (30 mL) was cooled to 0°C with an ice bath and thionyl chloride (12.5 mL, 105.5 mmol) was added dropwise, over 30 minutes. After this time, the mixture was warmed to room temperature for 1 h, then transferred to an oil bath, and heated to 70°C overnight. The mixture was then cooled to room temperature and concentrated under reduced pressure. The solids obtained were then redissolved in diethyl ether (50 mL) and washed with 1 N sodium hydroxide (50 mL), brine (50 mL), dried over magnesium sulfate, and concentrated under reduced pressure to afford ethyl 5-chloro-2-methylbenzoate as a clear oil: ^1H NMR (500 MHz, CDCl_3) δ 7.88 (d, $J = 2.5$ Hz, 1H), 7.34 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.17 (d, $J = 8.5$ Hz, 1H), 4.36 (q, $J = 7.5$ Hz, 2H), 2.56 (s, 3H), 1.39 (t, $J = 7.5$ Hz, 3H); ESI MS m/z 199 $[\text{M} + \text{H}]^+$.

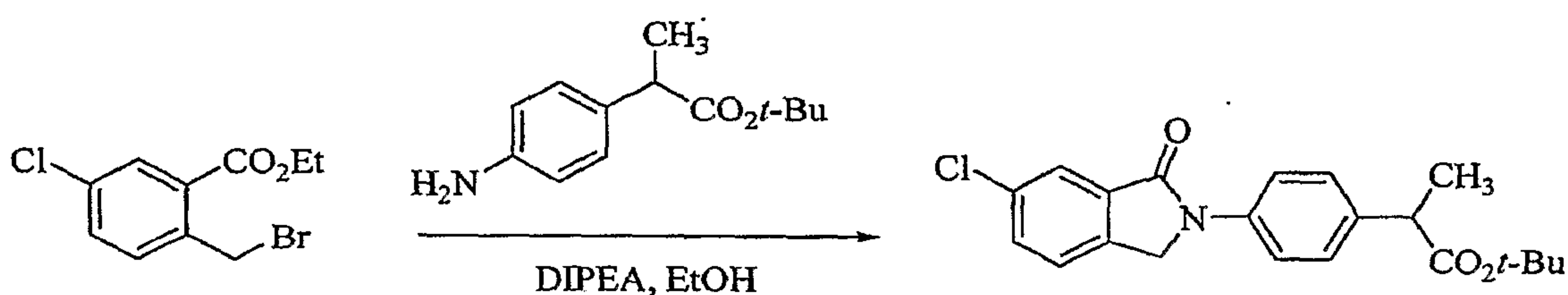
[0099] Step D: Synthesis of ethyl 2-(bromomethyl)-5-chlorobenzoate as an intermediate



[00100] A mixture of ethyl 5-chloro-2-methylbenzoate (3.20 g, 16.1 mmol), N-bromosuccinimide (3.15 g, 17.7 mmol) and benzoyl peroxide (0.39 g, 1.61 mmol) in 1,2-dichloroethane (90 mL) was heated to 75°C in an oil bath for 4 h. After this time, the mixture was cooled to room temperature and the organic layer was washed with water (45

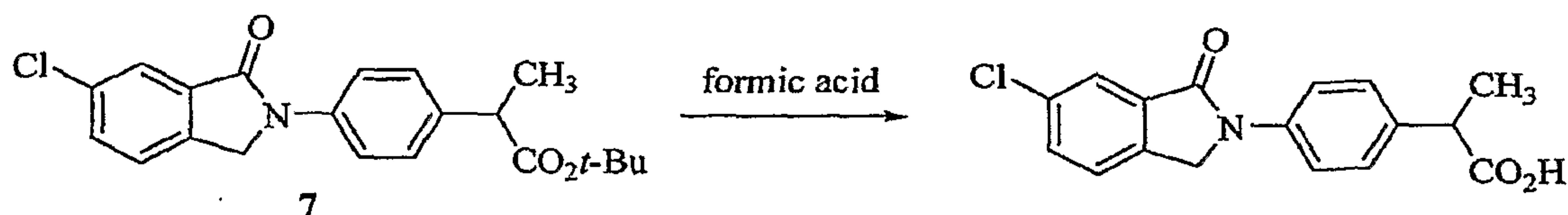
mL) and brine (45 mL). The organic layer was then dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (silica, 1:20 ethyl acetate/hexanes) afforded ethyl 2-(bromomethyl)-5-chlorobenzoate (3.09 g, 68%) as a clear oil: ^1H NMR (500 MHz, CDCl_3) 7.94 (d, $J = 2.5$ Hz, 1H), 7.46 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 4.91 (s, 2H), 4.42 (q, $J = 7.0$ Hz, 2H), 1.43 (t, $J = 7.0$ Hz, 3H); ESI MS m/z 279 $[(M + 2) + H]^+$.

[00101] Step E: Synthesis of tert-butyl 2-(4-(6-chloro-1-oxoisindolin-2-yl)phenyl)propanoate



[00102] A mixture of tert-butyl 2-(4-aminophenyl)propanoate (0.24 g, 1.08 mmol), ethyl 2-(bromomethyl)-5-chlorobenzoate (0.25 g, 0.901 mmol) and N,N -diisopropylethylamine (0.14 g, 1.08 mmol) in ethanol (5 mL) was heated in a sealed tube at 100 °C overnight. After this time, the mixture was cooled with an ice bath and the solids collected by filtration to afford tert-butyl 2-(4-(6-chloro-1-oxoisindolin-2-yl)phenyl)propanoate (0.18 g, 55%) as a white solid: mp 169–171 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, $J = 2.5$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 2H), 7.56 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 8.5$ Hz, 2H), 4.84 (s, 2H), 3.63 (m, 1H), 1.45 (d, $J = 7.5$ Hz, 3H), 1.41 (s, 9H); ESI MS m/z 404 $[M + H + \text{CH}_3\text{OH}]^+$.

[00103] Step F: Synthesis of 2-(4-(6-chloro-1-oxoisindolin-2-yl)phenyl)propanoic acid



[00104] A mixture of tert-butyl 2-(4-(6-chloro-1-oxoisindolin-2-yl)phenyl)propanoate (0.157 g, 0.422 mmol) and formic acid (15.7 mL) was stirred overnight at room temperature. The mixture was then concentrated under reduced pressure, suspended in hexanes (5 mL), sonicated, and the solids collected by filtration to afford 2-(4-(6-chloro-1-oxoisindolin-2-

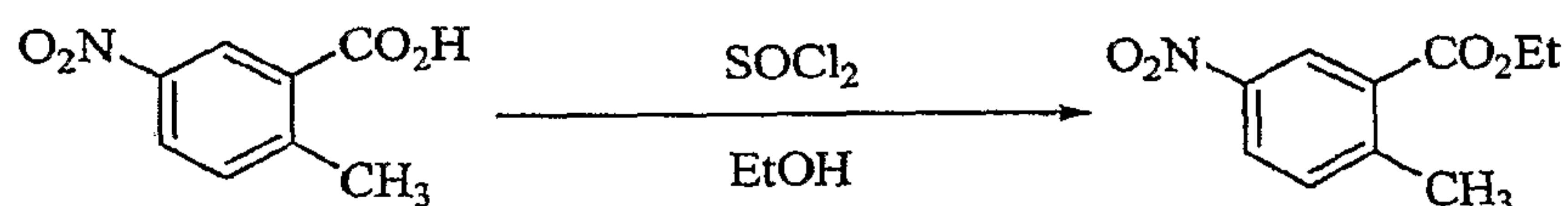
248

yl)phenyl)propanoic acid (0.118 g, 89%) as a white solid: mp 235–248 °C (dec); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.35 (br s, 1H), 7.83 (d, $J = 8.5$ Hz, 2H), 8.44 (s, 1H), 7.78 (m, 2H), 7.51 (m, 2H), 5.02 (s, 2H), 3.69 (q, $J = 7.0$ Hz, 1H), 1.38 (d, $J = 7.0$ Hz, 3H); ESI MS m/z 348 $[\text{M} + \text{H} + \text{CH}_3\text{OH}]^+$.

EXAMPLE 2

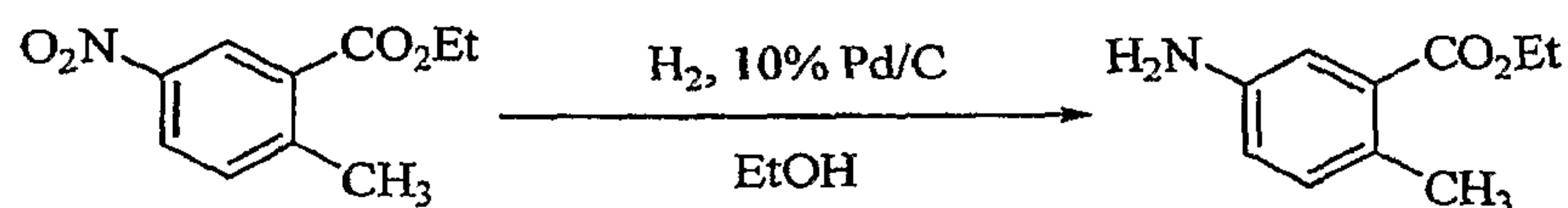
[00105] This example illustrates the preparation of 2-(4-(1-oxo-6-propylisoindolin-2-yl)phenyl)propanoic acid

[00106] Step A: Synthesis of ethyl 2-methyl-5-nitrobenzoate as an intermediate

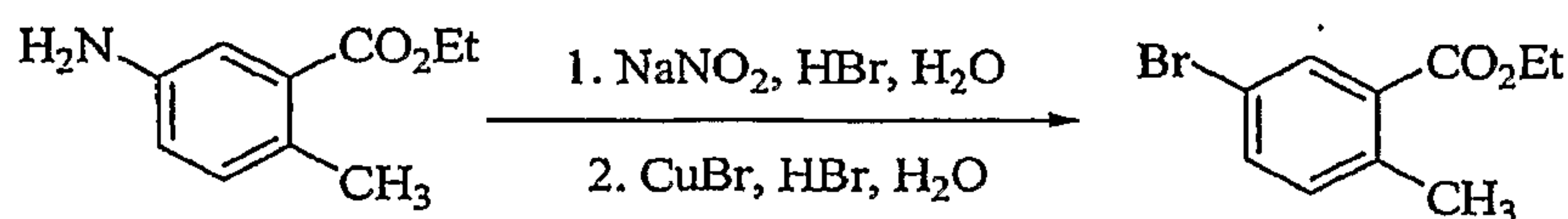


[0100] A mixture of 2-methyl-5-nitrobenzoic acid (10.0 g, 55.2 mmol) in ethanol (200 ml) was cooled to 0 °C with an ice bath and thionyl chloride (16.0 mL, 220 mmol) was added dropwise over 10 min. After this time, the mixture was warmed to room temperature for 1 h, then transferred to an oil bath and heated to reflux overnight. The mixture was then cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (silica, 9:1 hexanes/ethyl acetate) afforded ethyl 2-methyl-5-nitrobenzoate (12.4 g, quant.) as a pale yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 8.76 (d, $J = 2.5$ Hz, 1H), 8.24 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 4.42 (q, $J = 7.2$ Hz, 2H), 2.72 (s, 3H), 1.44 (t, $J = 7.1$ Hz, 3H).

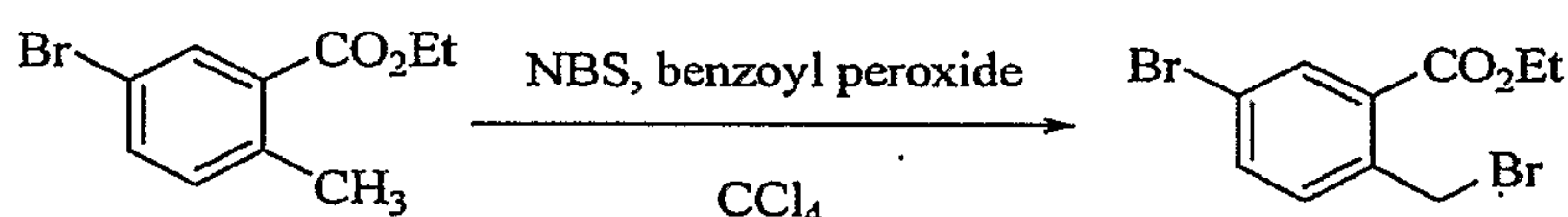
[0101] Step B: Synthesis of ethyl 5-amino-2-methylbenzoate as an intermediate



[0102] A mixture of ethyl 2-methyl-5-nitrobenzoate (11.5 g, 54 mmol) and 10% Pd/C (1.2 g) in ethanol (200 mL) was shaken under an atmosphere of hydrogen at 40 psi for 18 h. After this time, the mixture was filtered through diatomaceous earth and concentrated under reduced pressure to provide ethyl 5-amino-2-methylbenzoate (9.77 g, 98%) as an off-white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.25 (d, $J = 2.6$ Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 1H), 6.74 (d, $J = 8.1$ Hz, 1H), 4.33 (q, $J = 7.2$ Hz, 2H), 2.46 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H).

[0103] Step C: Synthesis of ethyl 5-bromo-2-methylbenzoate as an intermediate

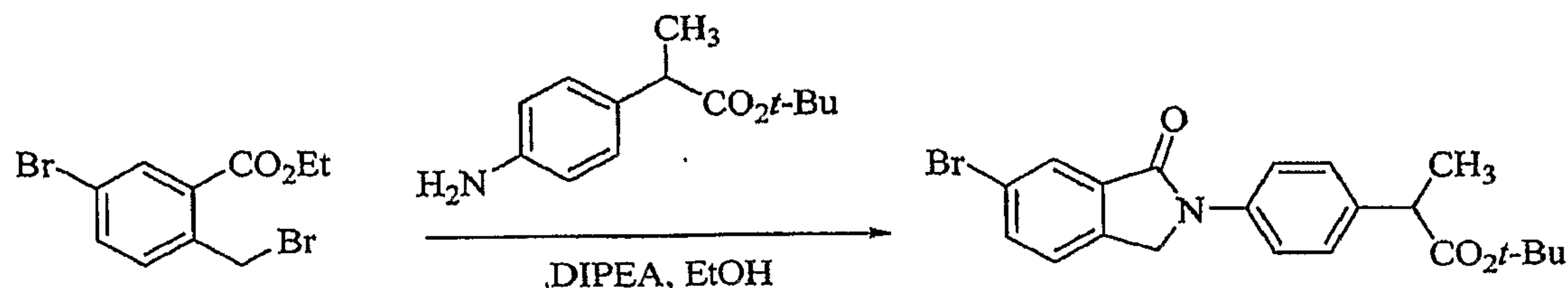
[0104] A mixture of ethyl 5-amino-2-methylbenzoate (1.50 g, 8.3 mmol) in 48% HBr (12 mL) and water (24 mL) was cooled with an ice-bath for 15 min.. Sodium nitrite (0.59 g, 8.6 mmol) was then added dropwise as a solution in water (2 mL), and the resulting mixture stirred for 5 min. After this time, the mixture was added to an ice-cold mixture of copper (I) bromide (1.40 g, 9.90 mmol) in 48% HBr (5 mL) and water (12 mL). The resulting mixture was heated to 70 °C for 1 h. After this time, the reaction mixture was cooled to room temperature and diluted with diethyl ether (150 mL). The organic layer was washed with 1 N hydrochloric acid (50 mL), water (50 mL), and brine (50 mL) then dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, gradient 1-10%, hexanes/ethyl acetate) afforded 1.4 g (69%) of ethyl 5-bromo-2-methylbenzoate as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.12 (dd, *J* = 8.2 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.54 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); ESI MS *m/z* 404 [M + H]⁺.

[0105] Step D: Synthesis of ethyl 5-bromo-2-(bromomethyl)benzoate as an intermediate

[0106] A mixture of ethyl 5-bromo-2-methylbenzoate (7.52 g, 30.9 mmol), *N*-bromosuccinimide (6.05 g, 34.0 mmol) and benzoyl peroxide (0.75 g, 3.10 mmol) in carbon tetrachloride (150 mL) was heated to 70 °C in an oil bath for 18 h. After this time, the mixture was cooled to room temperature and the solids removed by filtration. The filtrate was then concentrated under reduced pressure and purified by flash chromatography (silica, gradient 1-10%, ethyl acetate/hexanes) afforded ethyl 5-bromo-2-(bromomethyl)benzoate (7.57 g, 76%) as a clear oil: ¹H NMR (300 MHz, CDCl₃) 8.09 (d, *J* = 2.2 Hz, 1H), 7.61 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 4.90 (s, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

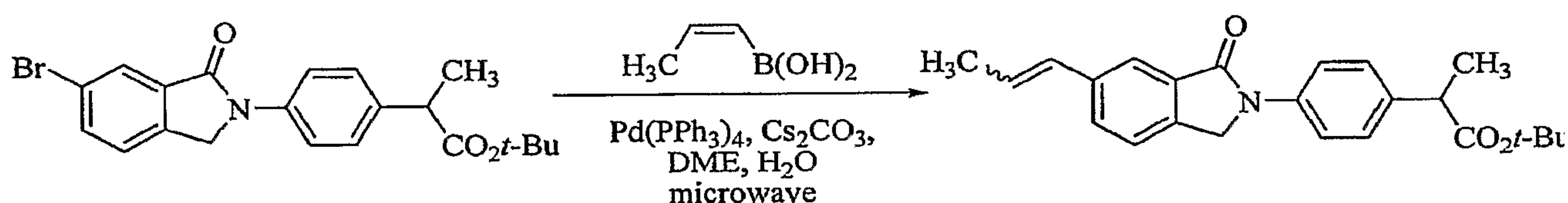
[0107] Step E: Synthesis of tert-butyl 2-(4-(6-bromo-1-oxoisindolin-2-yl)phenyl)propanoate

250



[0108] A mixture of ethyl 5-bromo-2-(bromomethyl)benzoate (4.00 g, 12.4 mmol), tert-butyl 2-(4-aminophenyl)propanoate (3.4 g, 15.4 mmol) and *N,N*-diisopropylethylamine (1.98 g, 15.4 mmol) in ethanol (120 mL) was heated in a sealed tube at 100 °C overnight. After this time, the mixture was cooled with an ice bath and the solids collected by filtration to afford tert-butyl 2-(4-(6-bromo-1-oxoisindolin-2-yl)phenyl)propanoate (2.00 g, 39%) as a white solid: mp 164–165 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.06 (d, *J* = 1.7 Hz, 1H), 7.81–7.77 (m, 2H), 7.71 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.38–7.34 (m, 2H), 4.81 (s, 2H), 3.63 (q, *J* = 7.1 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.41 (s, 9H); ESI MS *m/z* 448 [M + H + CH₃OH]⁺.

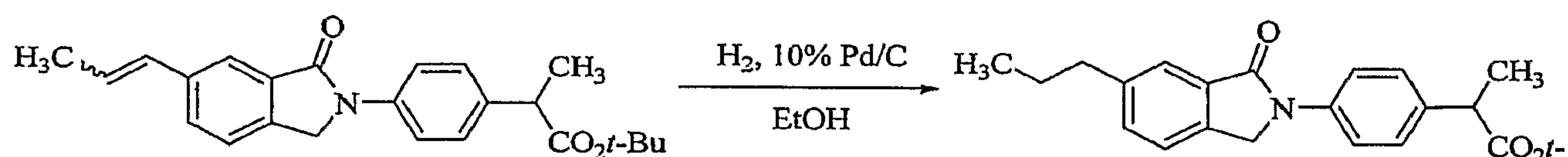
[0109] Step F: Synthesis of tert-butyl 2-(4-(1-oxo-6-(prop-1-enyl)isindolin-2-yl)phenyl)propanoate



[0110] A mixture of tert-butyl 2-(4-(6-bromo-1-oxoisindolin-2-yl)phenyl)propanoate (0.200 g, 0.48 mmol), *cis*-1-propene-1-boronic acid (0.413 g, 4.8 mmol), tetrakis(triphenylphosphine)palladium(0) (0.554 g, 0.48 mmol), and cesium carbonate (0.470 g, 1.44 mmol) in 5:2 DME/water (7 mL) was heated in a microwave reactor for 20 min at 120 °C. The mixture was cooled to room temperature, then diluted with ethyl acetate (8 mL). The reaction mixture was concentrated and purified by flash chromatography (silica, gradient 1–20%, ethyl acetate/hexanes) afforded tert-butyl 2-(4-(1-oxo-6-(prop-1-enyl)isindolin-2-yl)phenyl)propanoate (0.144 g, 77%) as a yellow solid: mp 125–130 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.96–7.80 (m, 2H), 7.75–7.65 (m, 1H), 7.54–7.34 (m, 4H), 6.53–6.33 (m, 1H), 5.93–5.87 (m, 1H), 4.84–4.80 (m, 2H), 3.66–3.60 (m, 1H), 1.94–1.91 (m, 3H), 1.47–1.45 (m,

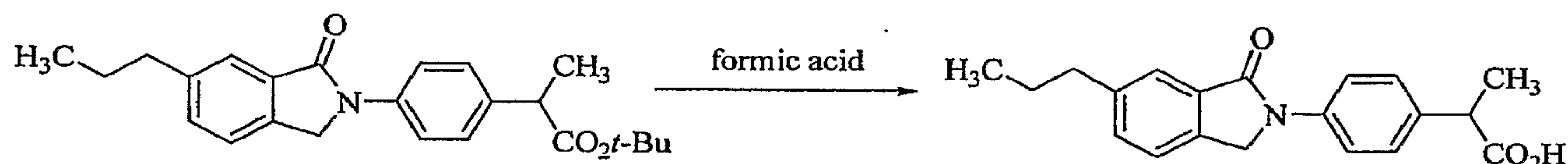
3H), 1.41 (s, 9H) [6:4 mixture of olefin isomers determined by NMR]; ESI MS m/z 378 $[M + H]^+$.

[0111] Step G: Synthesis of tert-butyl 2-(4-(1-oxo-6-propylisoindolin-2-yl)phenyl)propanoate



[0112] A mixture of tert-butyl 2-(4-(1-oxo-6-(prop-1-enyl)isoindolin-2-yl)phenyl)propanoate (0.140 g, 0.37 mmol) and 10% Pd/C (140 mg) in ethanol (5 mL) was shaken under an atmosphere of hydrogen at 35 psi for 2 h. After this time, the mixture was filtered through diatomaceous earth and concentrated under reduced pressure. Purification by flash column chromatography (silica, gradient 1-20%, ethyl acetate/hexanes) provided tert-butyl 2-(4-(1-oxo-6-propylisoindolin-2-yl)phenyl)propanoate (0.099 g, 71%) as a white solid: mp 110–115 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (d, $J = 8.6$ Hz, 2H), 7.74 (s, 1H), 7.41–7.37 (m, 4H), 4.81 (s, 2H), 3.77 (q, $J = 7.1$ Hz, 1H), 2.70 (t, $J = 7.4$ Hz, 2H), 1.73–1.65 (m, 2H), 1.54 (d, $J = 7.2$ Hz, 3H), 0.95 (t, $J = 7.3$ Hz, 3H); ESI MS m/z 380 $[M + H]^+$.

[0113] Step H: Synthesis of 2-(4-(1-oxo-6-propylisoindolin-2-yl)phenyl)propanoic acid

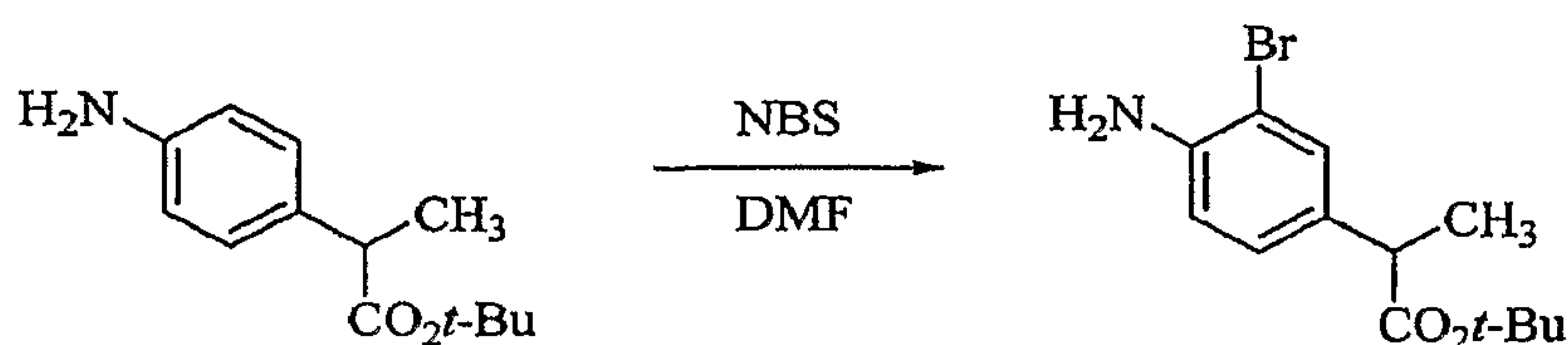


[0114] A mixture of tert-butyl 2-(4-(1-oxo-6-propylisoindolin-2-yl)phenyl)propanoate (0.084 g, 0.22 mmol) and formic acid (15 mL) was stirred overnight at room temperature. The mixture was then concentrated under reduced pressure, suspended in hexanes (5 mL), sonicated, and the solid collected by filtration to afford 2-(4-(1-oxo-6-propylisoindolin-2-yl)phenyl)propanoic acid (0.041 g, 57%) as a white solid: mp 175–177 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (d, $J = 8.6$ Hz, 2H), 7.74 (s, 1H), 7.41–7.37 (m, 4H), 4.81 (s, 2H), 3.77 (q, $J = 7.1$ Hz, 1H), 2.70 (t, $J = 7.4$ Hz, 2H), 1.73–1.65 (m, 2H), 1.54 (d, $J = 7.2$ Hz, 3H), 0.95 (t, $J = 7.3$ Hz, 3H); ESI MS m/z 324 $[M + H]^+$.

EXAMPLE 3

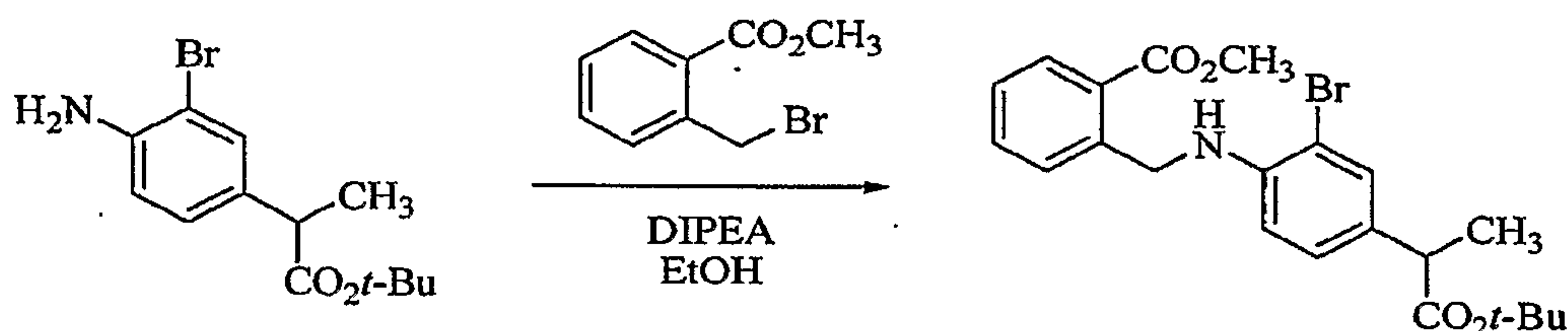
[0115] This example illustrates the preparation of tert-butyl 2-(3-bromo-4-(1-oxoisindolin-2-yl)phenyl)propanoate

[0116] Step A: Synthesis of tert-butyl 2-(4-amino-3-bromophenyl)propanoate as an intermediate



[0117] To a solution of tert-butyl 2-(4-aminophenyl)propanoate (5.00 g, 22.6 mmol) in DMF (15 mL) was added a solution of *N*-bromosuccinimide (4.22 g, 23.7 mmol) in DMF (15 mL) at room temperature which was maintained by water bath. The mixture was stirred overnight, poured into water and extracted with ethyl acetate. The organic layer was separated, washed with water, then brine, dried over sodium sulfate, and filtered. After concentration, the residue was purified by flash chromatography (9:1 hexanes/ethyl acetate) to give tert-butyl 2-(4-amino-3-bromophenyl)propanoate (6.00 g, 85%) as a brown oil: ¹H NMR (500 MHz, CDCl₃) δ 7.34 (d, *J* = 1.6 Hz, 1H), 7.04 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 4.01 (br s, 2H), 3.46 (q, *J* = 7.1 Hz, 1H), 1.39 (m, 12H).

[0118] Step B: Synthesis of methyl 2-((2-bromo-4-(1-tert-butoxy-1-oxopropan-2-yl)phenylamino)methyl)benzoate as an intermediate

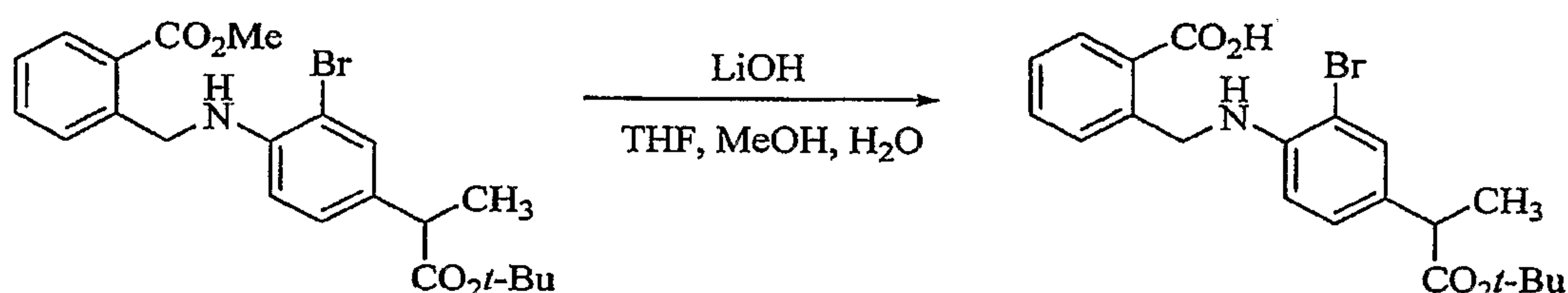


[0119] A mixture of tert-butyl 2-(4-amino-3-bromophenyl)propanoate (6.50 g, 21.7 mmol), methyl 2-(bromomethyl)benzoate (4.97 g, 21.7 mmol), diisopropylethylamine (2.80 g, 21.7 mmol), and ethanol (180 mL) was heated at 120 °C in a sealed vial overnight. After cooling to room temperature, the mixture was concentrated and the residue purified by flash chromatography (92:8 hexanes/ethyl acetate) to afford methyl 2-((2-bromo-4-(1-tert-butoxy-1-oxopropan-2-yl)phenylamino)methyl)benzoate (4.72 g, 48%) as thick oil: ¹H NMR (500

253

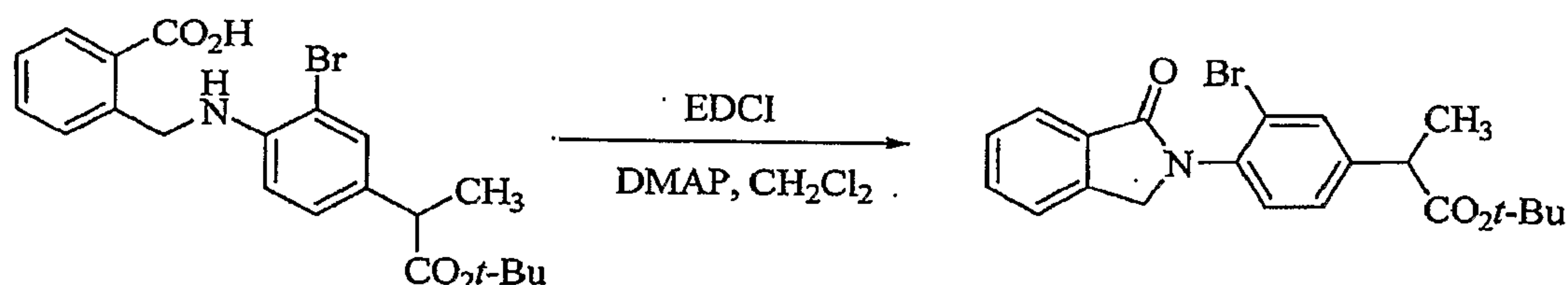
MHz, CDCl₃) δ 7.98 (m, 1H), 7.47 (m, 2H), 7.37–7.31 (m, 2H), 7.01 (dd, J = 8.4, 2.0 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 5.03 (br t, J = 6.1 Hz, 1H), 4.75 (d, J = 6.2 Hz, 2H), 3.92 (s, 3H), 3.43 (q, J = 7.2 Hz, 1H), 1.38 (s, 9H), 1.37 (d, J = 7.2 Hz, 3H); ESI MS m/z 450 [(M + 2) + H]⁺.

[0120] Step C: Synthesis of 2-((2-bromo-4-(1-tert-butoxy-1-oxopropan-2-yl)phenylamino)methyl)benzoic acid as an intermediate



[0121] A mixture of methyl 2-((2-bromo-4-(1-tert-butoxy-1-oxopropan-2-yl)phenylamino)methyl)benzoate (4.57 g, 10.2 mmol), lithium hydroxide (0.733 g, 30.6 mmol), tetrahydrofuran (100 mL), methanol (20 mL), and water (30 mL) was stirred overnight. The mixture was poured into water (200 mL) and the whole was acidified with 2 N HCl. The mixture was then extracted with ethyl acetate (150 mL) and the organic layer was washed with brine (100 mL), dried over sodium sulfate, and filtered. Evaporation of the solvents and drying under reduced pressure gave 2-((2-bromo-4-(1-tert-butoxy-1-oxopropan-2-yl)phenylamino)methyl)benzoic acid (4.40 g, 99%) as a thick oil: ¹H NMR (500 MHz, CDCl₃) δ 8.14 (d, J = 7.6 Hz, 1H), 7.53 (m, 2H), 7.38 (m, 2H), 7.03 (dd, J = 8.4, 2.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 4.80 (s, 2H), 3.44 (q, J = 7.1 Hz, 1H), 1.39 (s, 9H), 1.38 (d, J = 7.2 Hz, 3H).

[0122] Step D: Synthesis of tert-butyl 2-(3-bromo-4-(1-oxoisindolin-2-yl)phenyl)propanoate

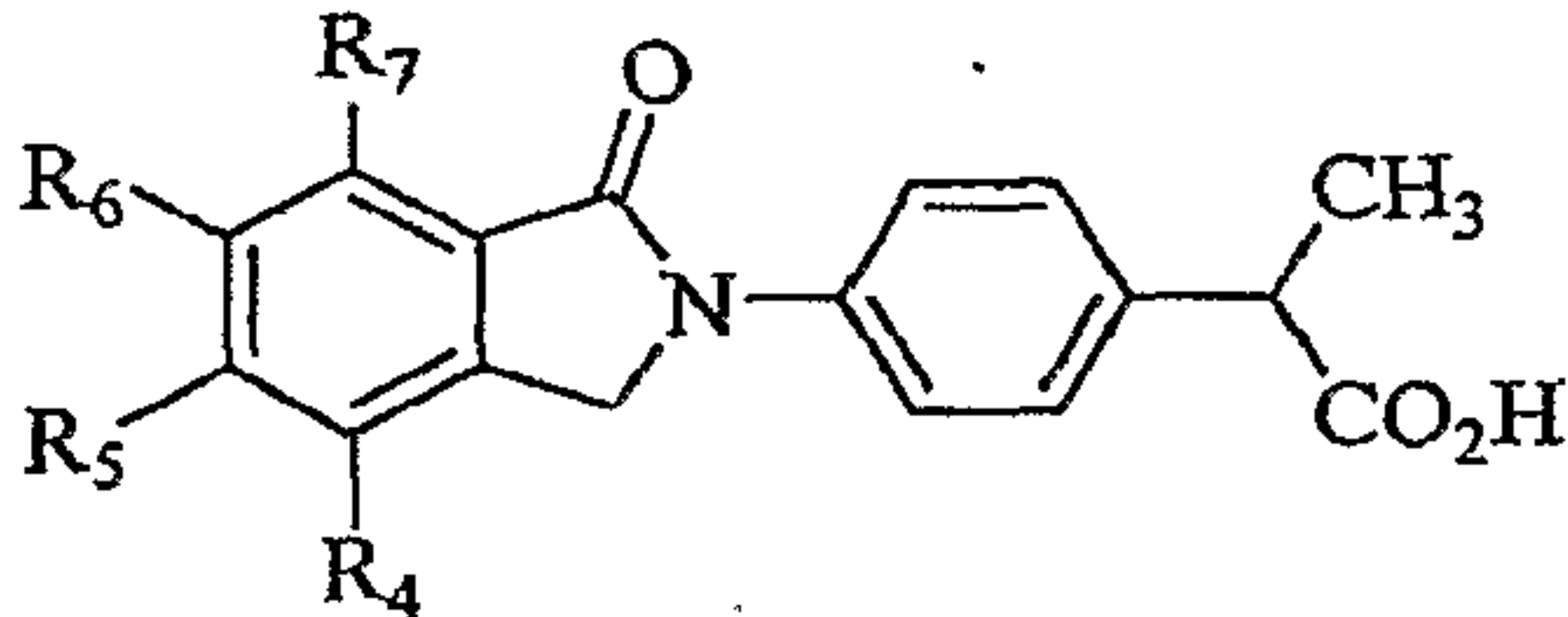


[0123] A mixture of 2-((2-bromo-4-(1-tert-butoxy-1-oxopropan-2-yl)phenylamino)methyl)benzoic acid (4.40 g, 10.1 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.13 g, 11.1 mmol) and 4-dimethylaminopyridine (0.617 g,

5.05 mmol) in methylene chloride (80 mL) was stirred at 0 °C and was allowed to warm to room temperature overnight. The mixture was then concentrated and the residue was purified by flash chromatography (silica, 4:1 hexanes/ethyl acetate) to afford tert-butyl 2-(3-bromo-4-(1-oxoisindolin-2-yl)phenyl)propanoate (3.55 g, 85%) as white foam: ¹H NMR (500 MHz, CDCl₃) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.64–7.50 (m, 4H), 7.35 (d, *J* = 1.0 Hz, 2H), 4.79 (s, 2H), 3.63 (q, *J* = 7.2 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.44 (s, 9H); ESI MS *m/z* 418 [(*M* + 2) + H]⁺.

[0124] Following the procedure of Example 1 (Step F), but substituting the appropriate *t*-butyl ester, the compounds of Table 2 were prepared.

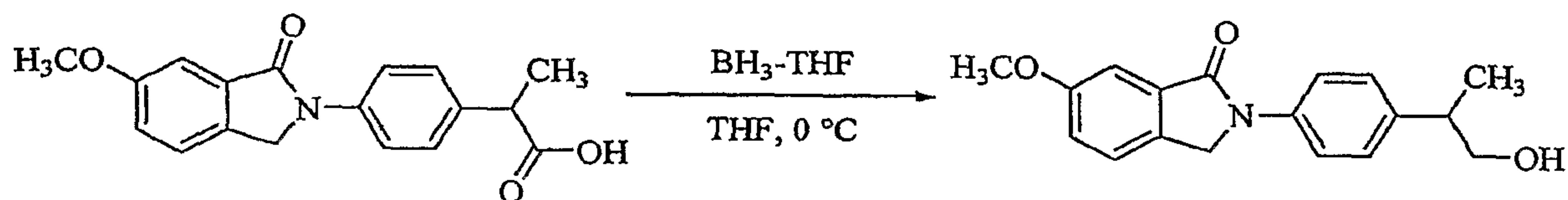
Table 2

					
R ₄	R ₅	R ₆	R ₇	mp °C	<i>m/z</i>
H	H	H	Cl	236-238	316 [M + H] ⁺
H	H	H	OCH ₃	275	310 [M - H] ⁻
H	H	H	NO ₂	234-236	327 [M + H] ⁺
H	H	H	Br	245-249	360 [M + H] ⁺
H	H	H	phenyl	202-207	358 [M + H] ⁺
H	H	H	CH ₃	179-182	296 [M + H] ⁺
H	H	H	O- <i>i</i> -Pr	168-172	340 [M + H] ⁺
H	H	OCH ₃	H	196-198	312 [M + H] ⁺
H	H	phenyl	H	255-263	358 [M + H] ⁺
H	H	CN	H	225-233	307 [M + H] ⁺
H	H	OE _t	H	172-175	326 [M + H] ⁺
H	H	OCHF ₂	H	202-204	380 [M + H + CH ₃ OH] ⁺
H	OCH ₃	OCH ₃	H	227-232	340 [M - H] ⁻
H	F	OCH ₃	H	250-252	330 [M + H] ⁺
H	Cl	H	H	238-242	316 [M + H] ⁺
H	Br	H	H	253-256	360 [M + H] ⁺
H	NH ₂	H	H	237-240	297 [M + H] ⁺
Cl	H	H	H	171-174	316 [M + H] ⁺
OCH ₃	H	H	H	174-178	310 [M - H] ⁻

EXAMPLE 4

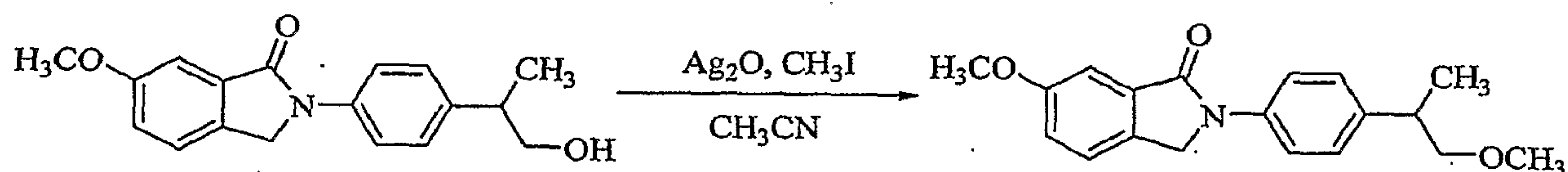
[0125] This example illustrates the preparation of 6-methoxy-2-(4-(1-methoxypropan-2-yl)phenyl)isoindolin-1-one

[0126] Step A: Synthesis of 2-(4-(1-hydroxypropan-2-yl)phenyl)-6-methoxyisoindolin-1-one as an intermediate



[0127] A mixture of 2-(4-(6-methoxy-1-oxoisoindolin-2-yl)phenyl)propanoic acid (0.102 g, 0.33 mmol) and borane-tetrahydrofuran complex (0.83 mL, 1 M in tetrahydrofuran, 0.83 mmol) in tetrahydrofuran (2 mL) at 0 °C was stirred for 3 h. After this time, the reaction mixture was diluted with water (5 mL) and ethyl acetate (5 mL) and the mixture stirred vigorously for 18 h at room temperature. The aqueous layer was separated and extracted with ethyl acetate (25 mL), and the combined organic layers dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford an off-white solid. Purification by flash chromatography (silica, 1:1 ethyl acetate/hexanes) afforded 2-(4-(1-hydroxypropan-2-yl)phenyl)-6-methoxyisoindolin-1-one (0.081 g, 84%) as a white solid: mp 135–138 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (dd, *J* = 8.6, 1.9 Hz, 2H), 7.41–7.39 (m, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.16 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.79 (s, 2H), 3.89 (s, 3H), 3.72 (d, *J* = 6.8 Hz, 2H), 2.98 (q, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H); ESI MS *m/z* 298 [M + H]⁺.

[0128] Step B: Synthesis of 6-methoxy-2-(4-(1-methoxypropan-2-yl)phenyl)isoindolin-1-one



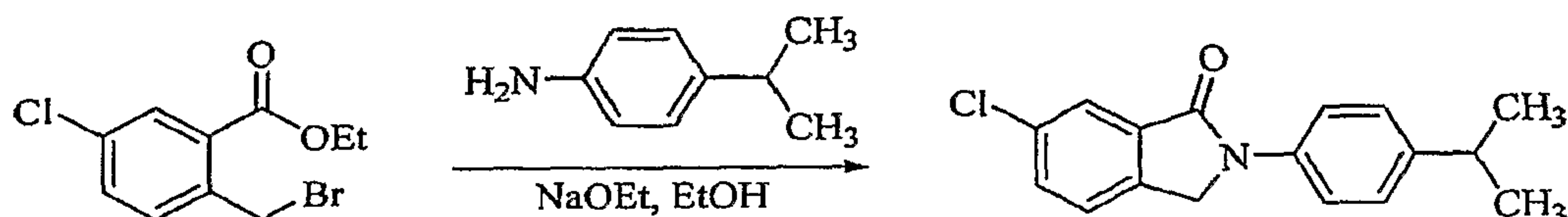
[0129] A mixture of 2-(4-(1-hydroxypropan-2-yl)phenyl)-6-methoxyisoindolin-1-one (0.042 g, 0.14 mmol), silver oxide (0.196 g, 0.42 mmol), iodomethane (0.070 mL) and 4 Å molecular sieves (0.050 g) in acetonitrile (2 mL) was stirred for 96 h at room temperature. After this time, the mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under

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reduced pressure to afford an off-white solid. Purification by flash chromatography (silica, 1:1 ethyl acetate/hexanes) afforded 6-methoxy-2-(4-(1-methoxypropan-2-yl)phenyl)isoindolin-1-one (0.031 g, 72%) as a white solid: mp 116–118 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.78 (dd, $J = 8.7, 2.0$ Hz, 2H), 7.40–7.38 (m, 2H), 7.29 (dd, $J = 8.6, 1.9$ Hz, 2H), 7.15 (dd, $J = 8.3, 2.4$ Hz, 1H), 4.78 (m, 2H), 3.89 (s, 3H), 3.55–3.41 (m, 2H), 3.34 (s, 3H), 3.04 (q, $J = 7.0$ Hz, 1H), 1.29 (d, $J = 7.0$ Hz, 3H); ESI MS m/z 312 $[\text{M} + \text{H}]^+$.

EXAMPLE 5

[0130] This example illustrates the preparation of 6-chloro-2-(4-isopropylphenyl)isoindolin-1-one.

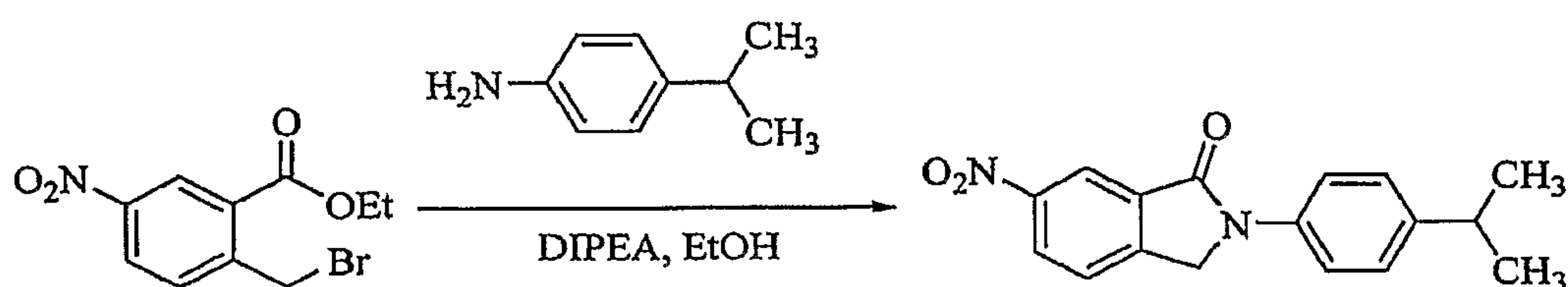


[0131] A mixture of ethyl 2-(bromomethyl)-5-chlorobenzoate (0.553 g, 1.99 mmol), 4-isopropylaniline (0.269 g, 1.99 mmol) and sodium ethoxide (0.406 g, 5.97 mmol) in ethanol (40 mL) was heated at reflux overnight. After this time, the mixture was cooled to room temperature and concentrated under vacuum. The mixture was partitioned between 1 N HCl and ethyl acetate. The organic layer was separated, washed with 1 N HCl, then with 1:1 water/brine solution, dried over sodium sulfate and filtered. Concentration under vacuum and recrystallization from ethyl acetate afforded 6-chloro-2-(4-isopropylphenyl)isoindolin-1-one (0.302 g, 53%) as an off-white solid: m.p. 206–209 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, $J = 1.9$ Hz, 1H), 7.73 (dt, $J = 8.6, 2.7$ Hz, 2H), 7.55 (dd, $J = 8.1, 1.9$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.30 (dt, $J = 8.5, 2.5$ Hz, 2H), 4.83 (s, 2H), 2.96–2.90 (m, 1H), 1.26 (d, 6H); ESI MS m/z 286 $[\text{M} + \text{H}]^+$.

EXAMPLE 6

[0132] This example illustrates the preparation of 2-(4-isopropylphenyl)-6-nitroisoindolin-1-one.

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[0133] A mixture of ethyl 2-(bromomethyl)-5-nitrobenzoate (1.88 g, 6.52 mmol), 4-isopropylaniline (1.11 mL, 7.83 mmol) and *N,N*-diisopropylethylamine (1.36 mL, 7.83 mmol) in ethanol (75 mL) was heated in a sealed tube at 110 °C overnight. After this time, the mixture was cooled to room temperature and the solid collected by filtration to afford 2-(4-isopropylphenyl)-6-nitroisoindolin-1-one (1.45 g, 75%) as a yellow solid: mp 225–227 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.77 (d, *J* = 2.0 Hz, 1H) 8.48 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.76–7.69 (m, 3H), 7.32 (d, *J* = 8.6 Hz, 2H), 2.94 (sept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H); ESI MS *m/z* 297 [M + H]⁺.

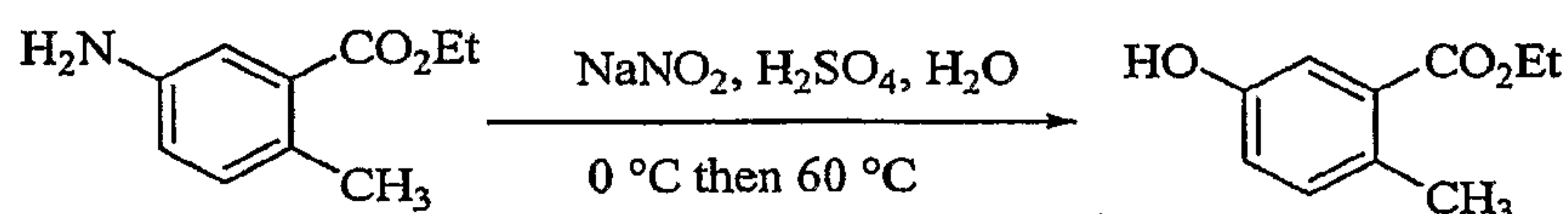
Table 3

R ₄	R ₅	R ₆	R ₇	R ₁	R ₂	X	mp °C	<i>m/z</i>
H	H	H	OCH ₃	CH ₃	H	CH ₃	93-96	282 [M + H] ⁺
H	H	Br	H	CH ₃	H	CH ₃	205-208	331 [M + H] ⁺
H	H	OCH ₃	H	CH ₃	H	CH ₃	152-160	282 [M + H] ⁺
H	H	OCHF ₂	H	CH ₃	H	CH ₃	155-157	318 [M + H] ⁺
H	H	NO ₂	H	CH ₃	H	CH ₃	225-227	297 [M + H] ⁺
H	H	CF ₃	H	CH ₃	H	CH ₃	176-179	320 [M + H] ⁺
H	Cl	H	H	CH ₃	H	CH ₃	197-200	286 [M + H]
H	H	CH ₃	H	CH ₃	CH ₃	CH ₃	175-182	280 [M + H]
H	H	H	H	CH ₃	CH ₃	CH ₃	148-163	266 [M + H]
H	H	OCH ₃	H	CH ₃	CH ₃	CH ₃	146-150	296 [M + H]
H	H	Br	H	CH ₃	CH ₃	CH ₃	225-228	345 [M + H]
H	H	Br	H	H	H	Et	192-196	330 [M + H]
H	H	OCH ₃	H	CH ₃	H	<i>n</i> -Pr	103-106	310 [M + H]
H	H	OCHF ₂	H	CH ₃	CH ₃	CH ₃	171-172	332 [M + H] ⁺

[0134] Following the procedure of Example 6, but substituting the appropriate aniline or benzyl bromide, the compounds of Table 3 were prepared.

EXAMPLE 7

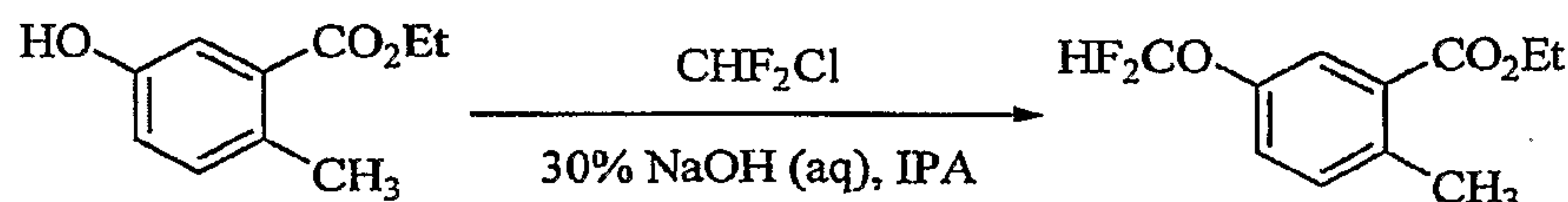
[0135] This example illustrates the preparation of ethyl 5-hydroxy-2-methylbenzoate as an intermediate



[0136] A mixture of ethyl 5-amino-2-methylbenzoate (14.4 g, 80.3 mmol) in aqueous 5% sulfuric acid (300 mL) was cooled with an ice-bath for 15 min.. Sodium nitrite (6.09 g, 88.3 mmol) was then added dropwise as a solution in water (50 mL), and the resulting mixture stirred for at 0 °C for 30 min. After this time, the resulting mixture was heated to 60 °C for 18 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (150 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, gradient 0-40%, hexanes/ethyl acetate) afforded 12.48 g (86%) of ethyl 5-hydroxy-2-methylbenzoate as red-brown solid: ¹H NMR (300 MHz, CDCl₃) δ 7.44 (d, *J* = 2.8 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 8.3, 2.8 Hz, 1H), 5.44 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); ESI MS *m/z* 181 [M + H]⁺.

EXAMPLE 8

[0137] This example illustrates the preparation of ethyl 5-(difluoromethoxy)-2-methylbenzoate as an intermediate



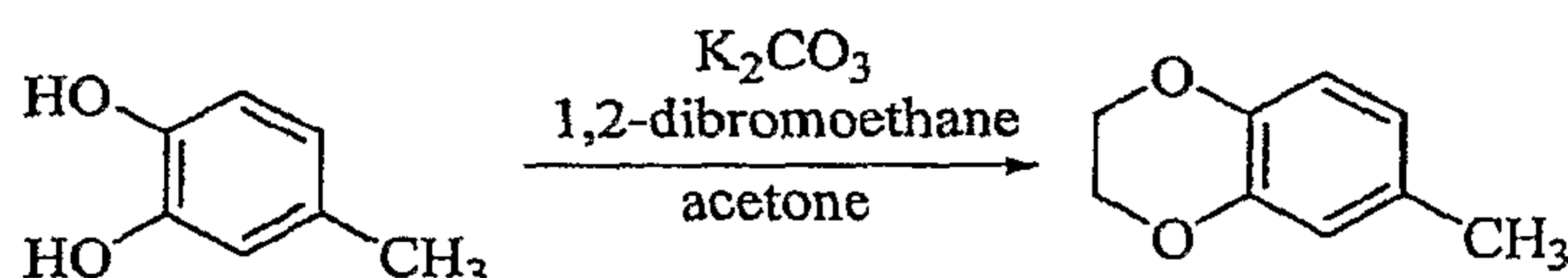
[0138] A mixture of ethyl 5-hydroxy-2-methylbenzoate (3.29 g, 18.2 mmol) in aqueous 30% sodium hydroxide (20 mL) and isopropyl alcohol (20 mL) was charged with 20 psi of chlorodifluoromethane in a high pressure flask, and stirred at room temperature for 10 min. After this time, the resulting mixture was heated at 50 °C for 0.5 h. After this time, the

reaction mixture was cooled to room temperature and diluted with dichloromethane (50 mL) and water (200 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, gradient 0-7%, hexanes/ethyl acetate) afforded 2.50 g (59%) of ethyl 5-(difluoromethoxy)-2-methylbenzoate as colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 7.67 (d, $J = 2.5$ Hz, 1H), 7.26–7.22 (m, 1H), 7.18–7.16 (m, 1H), 6.50 (t, $J = 73.6$ Hz, 1H), 4.37 (q, $J = 7.0$ Hz, 2H), 2.57 (s, 3H), 1.40 (t, $J = 7.0$ Hz, 3H); ESI MS m/z 231 $[\text{M} + \text{H}]^+$.

EXAMPLE 9

[0139] The following example illustrates the preparation of ethyl 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate as an intermediate.

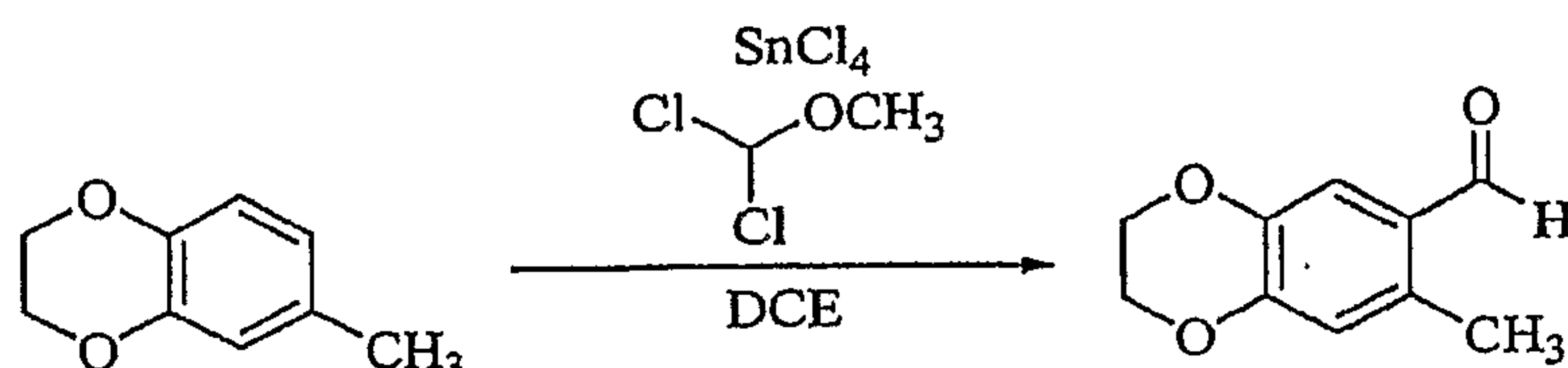
[0140] Step A: Synthesis of 6-methyl-2,3-dihydrobenzo[b][1,4]dioxine



[0141] A mixture of 4-methylbenzene-1,2-diol (10.0 g, 80.5 mmol) and potassium carbonate (111.3 g, 805.0 mmol) in acetone (300 mL) was stirred at room temperature for 1 h. After this time, 1,2-dibromoethane (27.7 mL, 322.0 mmol) was added and the reaction stirred at reflux for 5 d. After this time, the solvents were removed under reduced pressure and the solids redissolved in water (500 mL). The aqueous layer was then extracted three times with ethyl acetate (200 mL). The combined organic extracts were then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 1:20 ethyl acetate/hexanes) afforded 6-methyl-2,3-dihydrobenzo[b][1,4]dioxine (6.4 g, 54%) as a green oil: ^1H NMR (500 MHz, CDCl_3) δ 6.74 (d, $J = 8.5$ Hz, 1H), 6.67 (d, $J = 2.0$ Hz, 1H), 6.63 (dd, $J = 2.0, 8.0$ Hz, 1H), 4.22 (m, 4H), 2.24 (s, 3H).

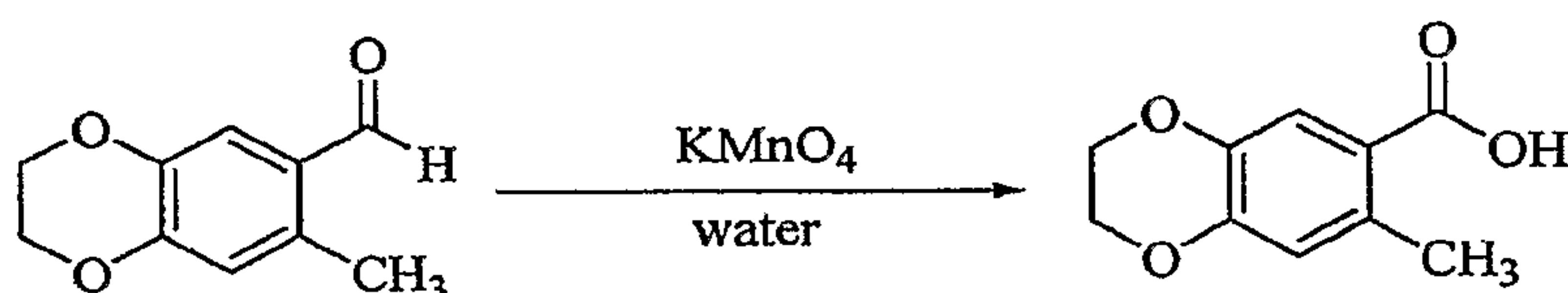
[0142] Step B: Synthesis of 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde

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[0143] A mixture of 6-methyl-2,3-dihydrobenzo[b][1,4]dioxine (6.4 g, 42.8 mmol) and 1,2-dichloroethane (250 mL) was cooled to 0 °C and then stirred for 1 h. After this time, dichloromethyl methyl ether (11.5 mL, 128.5 mmol) was then added and the reaction stirred for 1 h then, tin (IV) chloride (7.52 mL, 64.3 mmol) was added portion wise to the reaction over 3 h, and the reaction then allowed to warm to room temperature overnight. After this time, the reaction was poured into 3 N hydrochloric acid (150 mL) and the organic layer extracted three times with dichloromethane (100 mL). The combined organic extracts were then dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (4.8 g, 79%) as an off-white solid; ¹H NMR (500 MHz, CDCl₃) δ 10.07 (s, 1H), 7.33 (s, 1H), 6.72 (s, 1H), 4.28 (m, 4H), 2.55 (s, 3H).

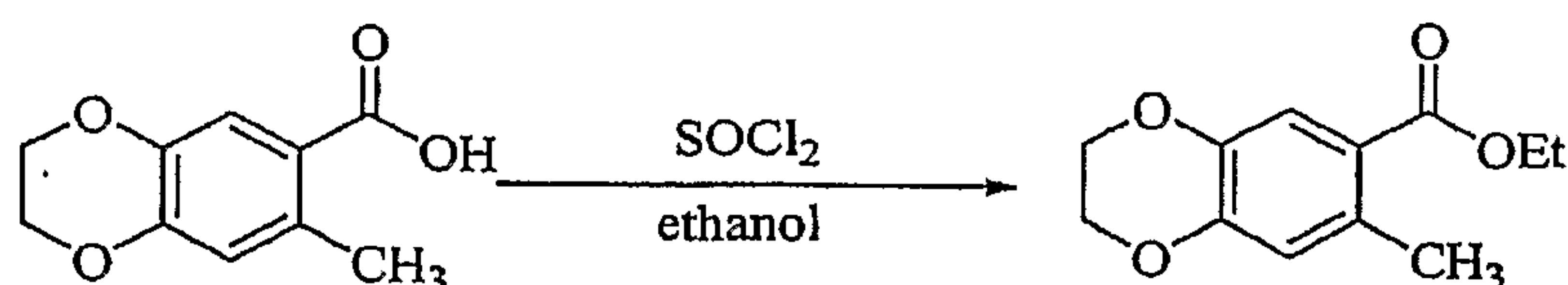
[0144] Step C: Synthesis of 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid



[0145] A mixture of 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (2.0 g, 11.2 mmol) in water (100 mL) was heated to 70 °C and stirred for 1 h. Potassium permanganate (2.3 g, 14.6 mmol) in water (50 mL) was then added portion wise over 4 h. After this time, the mixture was cooled to room temperature and 10% potassium hydroxide (50 mL) was then added. The solids were removed by filtration and washed with water (100 mL) and the basic solution then acidified with 2 N hydrochloric acid. The precipitate that formed was collected by filtration, washed with water, and dried in a vacuum oven overnight to afford 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid (1.7 g, 78%) as a white solid; ¹H NMR (500 MHz, DMSO-d₆) δ 12.49 (s, 1H), 7.33 (s, 1H), 6.76 (s, 1H), 4.25 (m, 4H), 2.40 (s, 3H).

[0146] Step D: Synthesis of ethyl 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate

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[0147] A mixture of 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid (1.72 g, 8.8 mmol) in ethanol (100 mL) was cooled to 0 °C and stirred for 1 h prior to dropwise addition of thionyl chloride (3.9 mL, 53.2 mmol) over 1 h. After this time, the mixture was warmed to room temperature for 1 h, then transferred to an oil bath, and heated to 70 °C overnight. The mixture was then cooled to room temperature and 2 N hydrochloric acid (50 mL) added slowly followed by diethyl ether (50 mL). The aqueous layer was extracted twice with diethyl ether (50 mL), the combined organic layers washed with brine (100 mL), dried over magnesium sulfate, and concentrated under reduced pressure to afford ethyl 7-methyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (1.7 g, 89%) as a white solid: ¹H NMR (500 MHz, CDCl₃) δ 7.51 (s, 1H), 6.70 (s, 1H), 4.30 (q, J = 7.0, 7.5 Hz, 2H), 4.26 (m, 4H), 2.49 (s, 3H), 1.36 (t, J = 7.0, 7.5 Hz, 3H).

EXAMPLE 10

[0148] This example demonstrates the ability of compounds of the invention to increase SMN expression in cervical carcinoma cell lines.

[0149] As previously discussed, SMN1 is the gene deleted in SMA patients; the SMN2 gene remains intact in both SMA and normal patients. Therefore, SMN2 provides a potential means of increasing SMN production in SMA patients and is, thus, a target for developing SMA treatments. SMN2 is identical to SMN1 with the exception of a single base pair change that results in reduced expression of the gene. The reduction is based on the creation of an alternatively spliced RNA that produces an unstable protein carrying a deletion of exon 7. Both full length SMN and exon 7 deleted SMN are produced by the SMN2 gene via alternative RNA splicing, but the major product is the unstable deleted form.

[0150] Cervical carcinoma cell lines were transformed with a SMN2-linked luciferase-reporter gene construct. The reporter is designed to detect shifts in the alternative splicing of SMN2 sequences. In particular, the reporter is constructed as a fusion of the alternatively spliced sequences of the SMN2 gene and the luciferase gene. Luciferase sequences are in the correct translational reading frame only when the SMN2 sequences are spliced according to

the normal SMN1 mechanism (e.g., splicing to include exon 7), which allows for translation of the stable SMN protein. Compounds were tested in the assay by administering the compound to the cell line and detecting an increase in the luciferase activity. The assay is described in greater detail in Zhang et al., *Gene Ther.*, 8, 1532-8 (2001). Compounds were administered as described in Lunn et al., *Chem. & Biol.*, 11, 1489-1493 (2004).

[0151] The compounds tested and the results are reported in Table 1. The results are reported as a fold-increase over a baseline reading of transformed cells without any test compound. The EC50 value also is reported in Table 1 for some compounds.

[0152] Indoprofen increases luciferase activity in this assay. Although this assay is designed to detect correction of the SMN2 splicing defect, it is known that indoprofen does not increase luciferase expression in this assay via effects on splicing. Nonetheless, the effects of indoprofen detected in this assay have been shown to extend to an increase in production of SMN from the endogenous SMN2 gene in SMA patient fibroblasts.

[0153] Many of the tested compounds increased luciferase activity in the assay, indicating that the compounds of the invention can be used to increase expression of SMN from the endogenous SMN2 gene.

EXAMPLE 11

[0154] This example demonstrates the ability of compounds of the invention to increase GEMs in fibroblasts from SMA patients.

[0155] SMN protein can be found in punctate nuclear particles called "gems" (Liu and Dreyfuss, *EMBO J.* 15(14): 3555-3565 (1996)). In fibroblast cells derived from SMA patients, the number of gems corresponds to disease severity as follows: severe type 1 patients have approximately 5 gems per 100 nuclei; mild type 3 patients have 20-50 gems per 100 nuclei; normal individuals have approximately 100-150 gems per 100 nuclei (Coover et al., *Hum Mol Genet* 6(8): 1205-1214 (1997), Young et al., *Exp Cell Res* 265(2): 252-261 (2001)).

[0156] Gems are detectable by immunohistochemistry and gem counts in patient fibroblasts have been used to test the ability of compounds to increase SMN protein levels (Mattis et al., *Hum Genet* 120:589-601 (2006)). Following these methods, fibroblast cells from a type 1 SMA patient (3813 cells, Coriell Cell Repositories) were treated for 48 hours with the compounds indicated in Table 2 (reference number – structure correlation is provided in Table 1). The cells were then fixed and incubated with a monoclonal antibody

against SMN (4B7, Wolstencroft et al., *Hum Mol Genet* 14:1199-1210 (2005)). A FITC-conjugated anti-mouse secondary antibody was used to visualize the labeled gems. The positive control in these experiments was provided by fibroblasts from the same patient treated with 1000 μ M valproic acid. The results are presented in Table 4.

[0157] As the results in Table 4 show, treatment of the cells with each of the compounds increased the number of SMN-containing gems in patient fibroblasts.

Table 4

Compound	Concentration (μ M)	Number of gems per 100 nuclei		
		Treated Cells	Untreated Cells	Positive Control
ALB-112355	0.45	5.3	2	31
ALB-115806	0.4	8	2	31
ALB-113310	3	53.5	4.75	48.5
ALB-115069	1	45.25	4.75	48.5
ALB-115498	1	14.3	2	31
ALB-116244	0.1	44	4.67	38.7

EXAMPLE 12

[0158] The following example demonstrates that compounds of the invention can increase activation of the glutamate transporter promoter.

[0159] The astroglial glutamate transporter, GLT-1/EAAT-2, is responsible for the majority of glutamate transport in the brain and spinal cord. To identify compounds capable of inducing EAAT-2 expression, we used a cell-based reporter assay consisting of COS-7 cells stably transfected with a plasmid containing a 2.7 Kb fragment of the human GLT-1/EAAT-2 promoter driving expression of the luciferase reporter (Rothstein et al., *Nature* 433:73-77 (2005)). The cell isolate used is designated Cos7 pE2P-GL3 (clone 4). Cells were incubated with compound at the indicated concentrations for 48 h prior to measuring luciferase reporter activity using the Bright-Glo Luciferase Assay System (Promega). Luminescence was measured using a Wallac Trilux microplate luminometer. Results from each plate were normalized to the DMSO treated control wells and expressed as fold-induction. EC₅₀ values were calculated using GraphPad Prism software. The results are presented in Table 5.

[0160] The results show that some tested compounds significantly increased glutamate transporter promoter activity.

Table 5

Compound ID	Max Fold-Induction	EC50 (nM)
Positive Control	1.61	nd
ALB-112354	1.93	221.2
ALB-112171	1.9	459.8
ALB-113968	1.78	1266
ALB-116361	1.54	6.79
ALB-116255	1.2	NA
ALB-116486	1.17	NA
ALB-115806	0.87	NA
ALB-115498	0.86	NA

EXAMPLE 13

[0161] This example demonstrates the use of compounds of the invention to promote translational read-through of a stop codon.

[0162] This assay is described in detail in WO 01/44516 A2. This is a cell-based luciferase reporter assay designed to detect translational read-through via insertion of a translational stop codon within the luciferase coding sequence. In the presence of compounds that promote read-through of translational stop codons, active luciferase is produced and detected via chemiluminescence. We have shown that indoprofen analogs are active in two versions of this assay- one containing a UGA stop codon and one containing a UAG stop codon. The data in the table is from the luciferase reporter containing the UAG stop codon. This is the first stop codon downstream of the improper splice junction between exons 6 and 8 in the human SMN2 transcript. The results are reported in Table 6.

Table 6

Compound ID	Conc at Max Fold (uM)	MaxFold Increase
Positive Control	1	4.7
Indoprofen	4	2.3
ALB-117573	100	4.4
ALB-113310	1	3.7
ALB-117572	11	3.6
ALB-113648	1	3.3
ALB-116078	4	3.3
ALB-114441	4	3.2
ALB-117454	4	3.1
ALB-115812	11	3.0
ALB-113652	11	2.9
ALB-115210	4	2.9
ALB-116074	4	2.9
ALB-117046	4	2.9
ALB-115948	1	2.8
ALB-116244	4	2.8
ALB-111743	4	2.7
ALB-112355	1	2.7
ALB-116246	4	2.7
ALB-114274	1	2.6
ALB-114783	11	2.6
ALB-113967	4	2.6
ALB-114901	4	2.6
ALB-114844	0.4	2.4
ALB-116486	100	2.4
ALB-116932	4	2.4
ALB-115084	1	2.3
ALB-115586	4	2.3
ALB-116362	0.7	2.3
ALB-112171	33	2.2
ALB-117452	4	2.2
ALB-117451	11	2.1
ALB-112354	100	2.0
ALB-115806	1	2.0
ALB-117902	4	2.0
ALB-113213	33	1.9
ALB-116935	4	1.9

EXAMPLE 14

[0163] This example demonstrates the plasma and brain pharmacokinetics of compounds of the invention.

[0164] Compounds were formulated in solution using the method of cosolvency as described by Lee et al., *Int. J. Pharmaceutics*, 253: 111–119 (2003). FVB or CD-1 mice, approximately 5 weeks old, were given a single dose of compound at the indicated concentration. Compounds were administered orally, with the exception of ALB-116638 and ALB-117573, which were administered IV. Three to five mice were euthanized at various times between 15 minutes and 24 hours after dosing and brain and plasma were harvested. Tissues were homogenized in acetonitrile and analyzed on an API 4000 LC/MS/MS system coupled with an Agilent 1100 series liquid chromatograph. All pharmacokinetic analyses were conducted using WinNonlin (Version 4.01; Pharsight, Palo Alto, CA) with the exception of brain/plasma ratios, which were calculated using Microsoft Excel 2000. AUC values are the area under the concentration-time curve from time zero to the last measured time point. The half life values are extrapolated from 3–4 time points taken at less than 4 hours after dosing.

Table 7

ALB #	Dose (mg/kg)	Brain AUC (h*ng/g)	Plasma AUC (h*ng/mL)	Brain/Plasma Ratio	Brain T1/2 (hours)	Plasma T1/2 (hours)
112355	5	570.0	21099.0	0.03	2.6	7.6
113967	5	170.5	595.4	0.29	1.1	1.5
115210	5	553.8	10.7	51.7	0.6	9.4
115210	25	5950.9	396.9	15	2.9	1.1
116935	5	338.1	nd	nd	9.4	nd
115498	5	163.8	47.8	3.43	0.5	0.6
116638	5	537.2	nd	nd	7.3	nd
117573	5	64.5	nd	nd	7.4	nd

EXAMPLE 15

[0165] Westerns blots were performed using the methods of Mattis et al., *Hum Genet* 120:589-601 (2006)). SMA type I fibroblasts (3813 cells; Coriell Cell Repositories)

were treated with compounds for 48 hours. Monoclonal anti-SMN antibody 4B7 (Wolstencroft et al., Hum Mol Genet 14:1199-1210 (2005)) was used to identify SMN. Actin was used as an internal normalization standard and detected with an anti-actin polyclonal rabbit antibody (Sigma-Aldrich). Tobramycin was used for the positive control compound treatment. DMSO is the untreated negative control. The results are presented in Table 8. Values are presented as the ratio of the signals obtained for SMN and Actin.

Table 8

Compound	Concentration (uM)	SMN:Actin Ratio
DMSO	n/a	1
Tobramycin	320	1.5
ALB-113310	0.1	4.8
	1	6.2
ALB-115069	0.1	4.3
	1	5.7

[0166] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

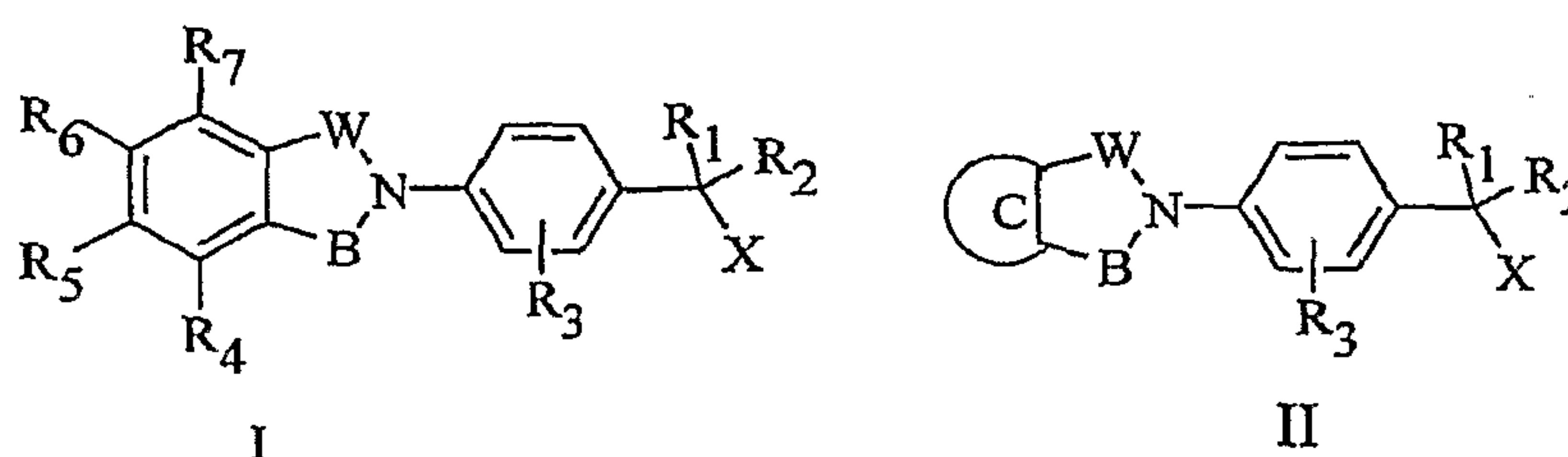
[0167] The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise

claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0168] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIM(S):

1. A compound of Formula I or II:



wherein,

W is selected from the group consisting of C(O), C(S), and CH₂;

B is CH₂ or CH(C_nH_{2n+1}), wherein n is an integer from 1 to 8;

C is selected from the group consisting of a fused thiophene ring, a fused pyridine ring, and a cyclohexane ring, any of which can be saturated or contain one or two non-conjugated double bonds;

R₁ and R₂ are independently selected from the group consisting of H and C₁-C₃ alkyl, or R₁ and R₂ may be taken together with the carbon atom to which they are attached to form a C₃-C₆ cycloalkyl ring or a carbonyl group;

R₃ is selected from the group consisting of H, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, CN, NO₂, heteroaryl, and phenyl optionally substituted with any combination of one to five halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₁-C₄ alkoxy;

R₄, R₅, R₆ and R₇ are independently selected from the group consisting of H, hydroxyl, halogen, CN, NO₂, sulfonamide, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, C₂-C₈ alkenyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkylamino, morpholine, heteroaryl, arylamino, arylalkylamino, phenyl, and C(O)R', NR'(COR''), NR'SO₂R'' and NR'(CONR'''R'''), wherein in R', R'' and R''' are independently H, C₁-C₆ alkyl, phenyl or substituted phenyl, and wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, arylamino, arylalkylamino, and morpholine, and the phenyl is optionally substituted with one or more members selected from the group consisting of halogen, NO₂, CN, C₁-C₄ alkyl, C₁-

C₄ haloalkyl, and C₁-C₄ alkoxy, or R₄ and R₅, R₅ and R₆, or R₆ and R₇ taken together with the carbon atoms to which they are attached form a ring;

X is selected from the group consisting of H;

CN;

C(O)OR₈, wherein R₈ is H or C₁-C₆ alkyl, wherein the C₁-C₈ alkyl optionally is substituted with one or members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, phenyl, and morpholine;

C(O)NR₉R₁₀ or CH₂NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine;

CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl optionally is substituted with one or members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine;

CH₂Z, wherein Z is halogen;

C(O)NHOH;

C(O)NHCN;

C(O)N(R₁)SO₂R₁₃, wherein R₁₃ is C₁-C₄ alkyl, phenyl, or substituted phenyl;

C₁-C₈ alkyl, optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino; and

C₂-C₈ alkenyl optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino;

provided that when the compound is a compound of Formula I, and each of R₄, R₅, R₆ and R₇ are H, then X is not C(O)OH.

2. The compound of claim 1, wherein:

W is selected from the group consisting of C(O), C(S), and CH₂;

B is CH₂;

C is selected from the group consisting of a fused thiophene ring, a fused pyridine ring, and cyclohexane ring, any of which can be saturated or contain one or two non-conjugated double bonds;

R₁ and R₂ are independently selected from the group consisting of H and C₁-C₃ alkyl, or R₁ and R₂ may be taken together with the carbon atom to which they are attached to form a C₃-C₅ cycloalkyl ring or a carbonyl group;

R₃ is selected from the group consisting of H, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, CN, NO₂, heteroaryl, and phenyl optionally substituted with any combination of one to five halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₁-C₄ alkoxy;

R₄, R₅, R₆ and R₇ are independently selected from the group consisting of H, halogen, CN, NO₂, sulfonamide, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, morpholine, heteroaryl, and phenyl, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine, and the phenyl is optionally substituted with one or more members selected from the group consisting of halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxy;

X is selected from the group consisting of X is selected from a group consisting of CN;

C(O)OR₈, wherein R₈ is H or C₁-C₆ alkyl, wherein the C₁-C₈ alkyl optionally is substituted with one or members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, phenyl, and morpholine;

C(O)NR₉R₁₀ or CH₂NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine;

CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl optionally is substituted with one or members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine;

CH₂Z, wherein Z is halogen;

C(O)NHOH;

C(O)NH₂;

C(O)N(R₁)SO₂R₁₃, wherein R₁₃ is C₁-C₄ alkyl, phenyl, or substituted phenyl;

C₁-C₈ alkyl, optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino; and

C₂-C₈ alkenyl optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino;

provided that when the compound is a compound of Formula I, and each of R₄, R₅, R₆ and R₇ are H, then X is not C(O)OH.

3. The compound of claim 1, wherein at least one of R₄, R₅, R₆ and R₇ are independently selected from the group consisting of CN, NO₂, sulfonamide, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkylamino, morpholine, heteroaryl, arylamino, arylalkylamino, and C(O)R', NR'(COR''), NR'SO₂R'' and NR'(CONR''R'''), wherein in R', R'' and R''' are independently H, C₁-C₆ alkyl, phenyl or substituted phenyl, and wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, arylamino, arylalkylamino, and morpholine, and the phenyl is optionally substituted with one or more members selected from the group consisting of halogen, NO₂, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxy, or R₄ and R₅, R₅ and R₆, or R₆ and R₇ taken together with the carbon atoms to which they are attached form a ring.

4. The compound of any of claims 1-3, wherein X is selected from the group consisting of

CN;

C(O)NR₉R₁₀ or CH₂NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine;

CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl optionally is substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine;

CH₂Z, wherein Z is halogen;

C(O)NHOH;

C(O)NHCN;

C(O)N(R₁)SO₂R₁₃, wherein R₁₃ is C₁-C₄ alkyl, phenyl, or substituted phenyl;

C₁-C₈ alkyl, optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino; and

C₂-C₈ alkenyl optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino.

5. The compound of any of claims 1-4, wherein the compound is a compound of Formula I.

6. The compound of any of claims 1-5, wherein W is C(O).

7. The compound of any of claims 1-6, wherein B is CH₂.

8. The compound of any of claims 1-7, wherein R₁ and R₂ are independently selected from the group consisting of H and C₁-C₃ alkyl.

9. The compound of any of claims 1-8, wherein R₁ is H and R₂ is CH₃.

10. The compound of any of claims 1-3 or 5-9, wherein X is selected from the group consisting of

CN;

C(O)OR₈, wherein R₈ is H or C₁-C₆ alkyl;

CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl is optionally substituted one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine;

CH₂NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine; and

CH₂Z, wherein Z is halogen.

11. The compound of claim 10, wherein X is C(O)OH.
12. The compound of any of claims 1-11, wherein R₃, R₄, and R₇ are H.
13. The compound of any of claims 1-12, wherein R₅ and R₆ are independently selected from the group consisting of H, halogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, and morpholine, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine.
14. The compound of any of claims 1-13, wherein R₅ is H.
15. The compound of any of claims 1-14, wherein R₆ is selected from the group consisting of halogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, and morpholine, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine.
16. The compound of claim 15, wherein R₆ is selected from the group consisting of halogen, C₁-C₃ alkyl, C₁-C₆ alkoxy, C₁-C₄ dialkyl amino, and C₁-C₄ haloalkyl.
17. The compound of claim 16, wherein R₆ is selected from the group consisting of chloro, bromo, methyl, ethyl, propyl, *i*-propyl, methoxy, ethoxy, propoxy, *i*-propoxy, cyclohexyloxy, dimethylamino, and CF₃.
18. The compound of any of claims 1-11, wherein R₃, R₄, R₅, and R₆ are H.
19. The compound of any of claims 1-11 and 18, wherein R₇ is selected from the group consisting of halogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl,

amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, and morpholine, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine.

20. The compound of claim 19, wherein R₇ is C₁-C₈ alkyl, amino, or C₁-C₄ alkylamino.

21. The compound of claim 20, wherein R₇ is methyl, ethyl, propyl, or amino.

22. The compound of any of claims 1-11, wherein R₃, R₄, R₆, and R₇ are H.

23. The compound of any of claims 1-11 and 22, wherein R₅ is selected from the group consisting of CN, halogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₄ haloalkyl, amino, C₁-C₄ dialkyl amino, C₁-C₄ alkylamino, C₁-C₆ cycloalkyl amino, and morpholine, wherein the C₁-C₈ alkyl is optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine.

24. The compound of claim 23, wherein R₅ is methyl, ethyl, propyl, or CN.

25. The compound of any of claims 1-11, wherein at least one of R₃, R₄, R₅, R₆, or R₇ is hydroxyl, C₁-C₆ haloalkoxy, C₁-C₈ alkenyl, C(O)R', NR'(COR''), NR'SO₂R'' and NR'(CONR''R'''), wherein in R', R'' and R''' are independently H, C₁-C₆ alkyl, phenyl or substituted phenyl, or C₁-C₈ alkyl substituted with an arylamino or arylalkylamino.

26. The compound of claim 25, wherein at least one of R₃, R₄, R₅, R₆, or R₇ is a C₁-C₆ haloalkoxy.

27. The compound of claim 26, wherein the haloalkoxy is -OCHF₂.

28. The compound of any of claims 1-11, wherein at least one of R₄ and R₅, R₅ and R₆, or R₆ and R₇, taken together with the carbon to which they are attached, form a ring.

29 The compound of claim 28, wherein the ring is a 5 or 6 member heterocyclic ring.

30. The compound of claim 29, wherein the ring is a dioxane or dioxolane ring.

31. The compound of any of claims 1-3, 5-9, and 12-30, wherein X is selected from the group consisting of

CN;

C(O)OR₈, wherein R₈ is C₁-C₆ alkyl, optionally substituted with a phenyl;

C(O)NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine;

CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl optionally is substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine;

CH₂NR₉R₁₀, wherein R₉ and R₁₀ are as defined above,

CH₂Z, wherein Z is halogen;

C(O)NHOH;

C(O)NHCN; and

C(O)N(R₁)SO₂R₁₃, wherein R₁₃ is C₁-C₄ alkyl, phenyl, or substituted phenyl.

32. The compound of claim 31, wherein X is selected from the group consisting of

CN;

C(O)OR₈, wherein R₈ is C₁-C₆ alkyl, optionally substituted with a phenyl;

CH₂OR₁₁, wherein R₁₁ is H, C₁-C₈ alkyl, or C₁-C₆ cycloalkyl, wherein the C₁-C₈ alkyl is optionally substituted one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkyl amino, C₁-C₆ alkylamino, cycloalkylamino, and morpholine;

CH₂NR₉R₁₀, wherein R₉ and R₁₀ are independently selected from the group consisting of H and C₁-C₆ alkyl, or R₉ and R₁₀ together with the nitrogen to which they are attached form a C₅-C₆ cycloalkyl ring or a heteroring such as morpholine; and

CH₂Z, wherein Z is halogen.

33. The compound of claim 32, wherein X is C(O)OR₈, wherein R₈ is C₁-C₆ alkyl, optionally substituted with a phenyl, or X is CH₂Z, wherein Z is halogen.

34. The compound of claim 33, wherein X is C(O)OR₈, and R₈ is methyl, ethyl, propyl, butyl, *t*-butyl, or benzyl.

35. The compound of any of claims 1-3, 5-9, and 12-30, wherein X is selected from the group consisting of

C₁-C₈ alkyl, optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino; and

C₁-C₈ alkenyl, optionally substituted with one or more members selected from the group consisting of C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₆ dialkylamino, and C₁-C₆ alkylamino.

36. The compound of claim 35, wherein X is a C₁-C₆ alkyl.

37. The compound of claim 36, wherein X is methyl.

38. The compound of any of claims 1-3, 5-9, and 12-30, wherein X is H.

39. The compound of any of claims 1, 2, 4-9, and 31-38, wherein R₃, R₄, R₅, R₆, and R₇ are H.

40. A compound of Table 1.

41. A racemic mixture of the enantiomers of the compound of any of claims 1-40.

42. A composition comprising a compound of any of claims 1-40, or the racemic mixture of claim 41, and a carrier.

43. The composition of claim 42, wherein the carrier is a pharmaceutically acceptable carrier.

44. A method of increasing SMN expression in a cell comprising administering a compound of any of claims 1-40 to a cell comprising a nucleic acid encoding SMN2, wherein the cell optionally is in a host, whereby SMN expression is increased.

45. The method of claim 44, wherein the host is a mammal.

46. The method of claim 45, wherein the mammal is a human afflicted with a disease associated with under-expression of SMN.

47. The method of claim 46, wherein the disease is SMA.

48. A method of increasing in a cell the expression of a nucleic acid that encodes a translational stop codon, the method comprising administering a compound of any of claims 1-40 to a cell comprising a nucleic acid that encodes a translational stop codon, wherein the cell optionally is in a host, whereby expression of the nucleic acid is increased.

49. The method of claim 48, wherein the stop codon has been introduced by mutation or frameshift.

50. The method of claim 49, wherein the host is a mammal.

51. The method of claim 50, wherein the mammal is a human afflicted with a disease associated with the translational stop codon introduced by mutation or frameshift.

52. The method of claim 51, wherein the disease is cancer, diabetes, cystic fibrosis, muscular dystrophy.

53. A method of increasing the expression of excitatory amino acid transporter (EAAT2) in a cell comprising administering to a cell comprising a nucleic acid that encodes

EAAT2 a compound of any of claims 1-40, wherein the cell optionally is in a host, whereby the expression of EAAT2 is increased.

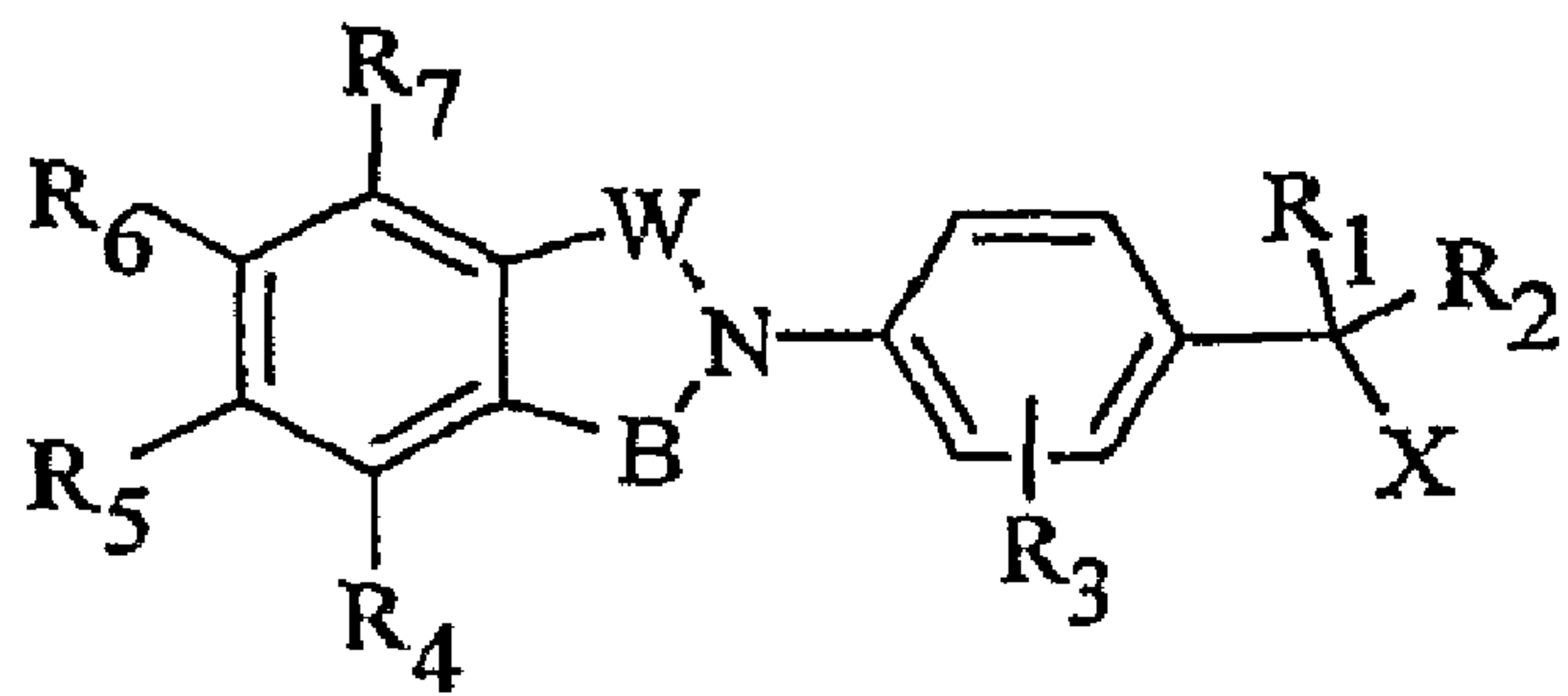
54. The method of claim 53, wherein the host is a mammal.

55. The method of claim 54, wherein the mammal is a human that has an elevated level of glutamate in the central nervous system.

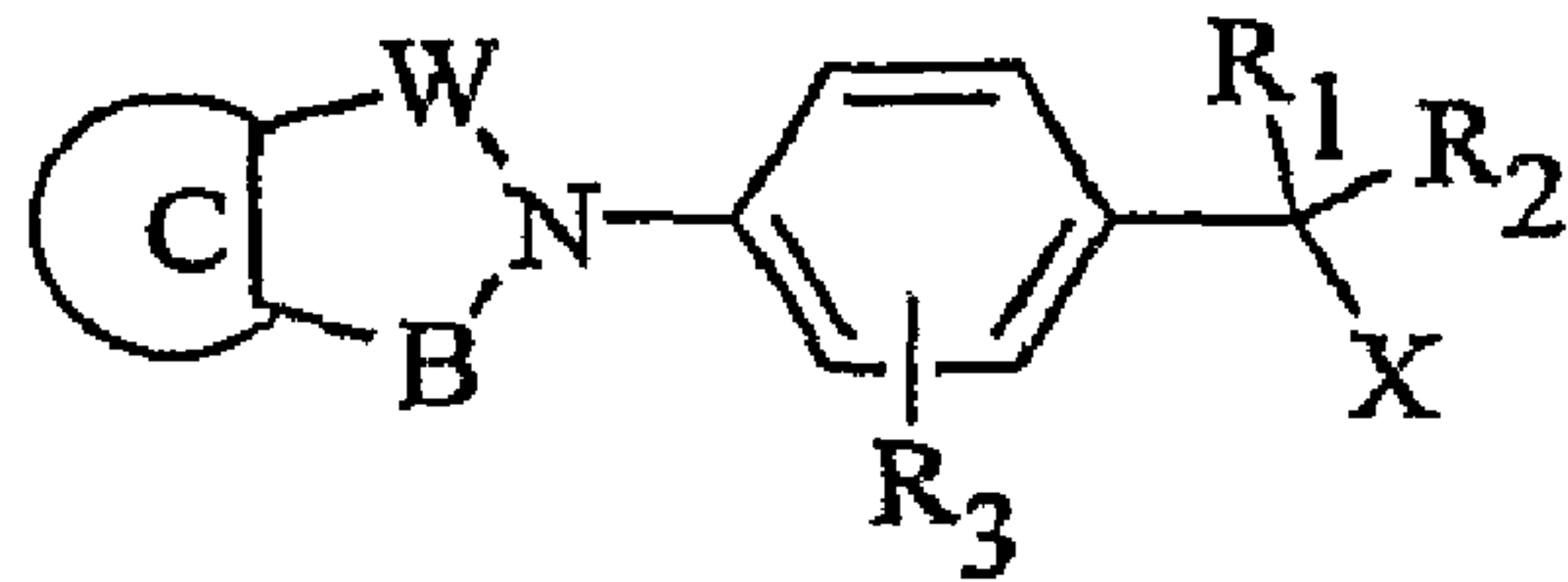
56. The method of claim 54, wherein the mammal is a human that has suffered stroke or trauma to an area of the central nervous system.

57. The method of claim 54, wherein the mammal is a human that is afflicted with a disease, optionally, a neurodegenerative disease.

58. The method of claim 57, wherein the disease is Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's Disease, or epilepsy.



I



II