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CA 2342974 C 2005/08/16

(11)(21) 2 342 974

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1994/02/24

(41) Mise à la disp. pub./Open to Public Insp.: 1994/09/15

(45) Date de délivrance/Issue Date: 2005/08/16

(62) Demande originale/Original Application: 2 157 288

(30) Priorités/Priorities: 1993/03/01 (025,046) US;
1993/12/15 (168,817) US

(51) Cl.Int.⁷/Int.Cl.⁷ A61K 31/454, A61K 31/5377,
A61K 31/4035, A61K 31/4015, A61K 31/198

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(54) Titre : METHODES ET COMPOSITIONS POUR L'INHIBITION DE L'ANGIOGENESE

(54) Title: METHODS AND COMPOSITIONS FOR INHIBITION OF ANGIOGENESIS

(57) Abrégé/Abstract:

The present invention comprises a group of compounds that effectively inhibit angiogenesis. More specifically, thalidomide and various related compounds such as thalidomide precursors, analogs, metabolites and hydrolysis products have been shown to inhibit angiogenesis. Importantly, these compounds can be administered orally.

METHODS AND COMPOSITIONS FOR INHIBITION OF ANGIOGENESIS**ABSTRACT OF THE DISCLOSURE**

The present invention comprises a group of compounds that effectively inhibit angiogenesis. More specifically, thalidomide and various related compounds such as thalidomide precursors, analogs, metabolites and hydrolysis products have been shown to inhibit angiogenesis. Importantly, these compounds can be administered orally.

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METHODS AND COMPOSITIONS FOR INHIBITION OF ANGIOGENESIS

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This application is a divisional application
of Canadian Patent File No. 2,157,288 filed February
24, 1994.

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Technical Field

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The present invention relates to methods and compositions for preventing unwanted angiogenesis in a human or animal. More particularly, the present invention relates to a method for preventing unwanted angiogenesis, particularly in angiogenesis dependent or associated diseases, by administration of compounds such as thalidomide and related compounds.

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Background of the Invention

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As used herein, the term "angiogenesis" means the generation of new blood vessels into a tissue or organ. Under normal physiological conditions, humans or animals only undergo angiogenesis in very specific restricted situations. For example, angiogenesis is normally observed in wound healing, fetal and embryonal development and formation of the corpus luteum, endometrium and placenta. The control of angiogenesis is a highly regulated system of angiogenic stimulators and inhibitors. The control of angiogenesis has been found to be altered in

- 2 -

certain disease states and, in many cases, the pathological damage associated with the disease is related to the uncontrolled angiogenesis.

Both controlled and uncontrolled angiogenesis are thought to proceed in a similar manner. Endothelial cells and pericytes, surrounded by a basement membrane, form capillary blood vessels. Angiogenesis begins with the erosion of the basement membrane by enzymes released by endothelial cells and leukocytes. The endothelial cells, which line the lumen of blood vessels, then protrude through the basement membrane. Angiogenic stimulants induce the endothelial cells to migrate through the eroded basement membrane. The migrating cells form a "sprout" off the parent blood vessel, where the endothelial cells undergo mitosis and proliferate. The endothelial sprouts merge with each other to form capillary loops, creating the new blood vessel. In the disease state, prevention of angiogenesis could avert the damage caused by the invasion of the new microvascular system.

Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, tumor metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The diverse pathological states created due to unregulated angiogenesis have been grouped together as angiogenic dependent or angiogenic associated diseases. Therapies directed at control of the angiogenic processes could lead to the abrogation or mitigation of these diseases.

One example of a disease mediated by angiogenesis is ocular neovascular disease. This disease is characterized by invasion of new blood vessels into the structures of the eye such as the retina or cornea. It is the most common cause of blindness and is involved in approximately twenty eye diseases. In age-related macular degeneration, the associated visual problems are caused by an ingrowth of chorioidal capillaries through defects in Bruch's membrane with proliferation of fibrovascular tissue beneath the retinal pigment epithelium. Angiogenic damage is

- 3 -

also associated with diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrothalic fibroplasia. Other diseases associated with corneal neovascularization include, but are not limited to, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, 5 atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phlyctenulosis, syphilis, *Mycobacteria* infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex* infections, *Herpes 10 zoster* infections, protozoan infections, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, and corneal graft rejection.

15 Diseases associated with retinal/choroidal neovascularization include, but are not limited to, diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic 20 uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales disease, Bechets disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Bests disease, myopia, optic pits, Stargarts disease, pars planitis, chronic retinal detachment, 25 hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications. Other diseases include, but are not limited to, diseases associated with rubeosis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative 30 vitreoretinopathy.

35 Another disease in which angiogenesis is believed to be involved is rheumatoid arthritis. The blood vessels in the synovial lining of the joints undergo angiogenesis. In addition to forming new vascular networks, the endothelial cells release factors and reactive oxygen species that lead to pannus growth

- 4 -

and cartilage destruction. The factors involved in angiogenesis may actively contribute to, and help maintain, the chronically inflamed state of rheumatoid arthritis.

5 Factors associated with angiogenesis may also have a role in osteoarthritis. The activation of the chondrocytes by angiogenic-related factors contributes to the destruction of the joint. At a later stage, the angiogenic factors would promote new bone formation. Therapeutic intervention that prevents the bone destruction could halt the progress of the disease and provide 10 relief for persons suffering with arthritis.

15 Chronic inflammation may also involve pathological angiogenesis. Such disease states as ulcerative colitis and Crohn's disease show histological changes with the ingrowth of new blood vessels into the inflamed tissues. Bartonellosis, a bacterial infection found in South America, can result in a chronic stage that is characterized by proliferation of vascular endothelial cells. Another pathological role associated with angiogenesis is found in atherosclerosis. The plaques formed within the lumen of blood vessels have been shown to have angiogenic stimulatory activity.

20 One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the tumors are benign and regress without intervention. In more severe cases, the tumors progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate. 25 Therapy-resistant hemangiomas exist that cannot be treated with therapeutics currently in use.

30 Angiogenesis is also responsible for damage found in hereditary diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, tumors of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) 35 or gastrointestinal bleeding and sometimes with pulmonary or hepatic arteriovenous fistula.

- 5 -

Angiogenesis is prominent in solid tumor formation and metastasis. Angiogenic factors have been found associated with several solid tumors such as rhabdomyosarcomas, retinoblastoma, Ewing sarcoma, neuroblastoma, and osteosarcoma. A tumor cannot expand without a blood supply to provide nutrients and remove cellular wastes. Tumors in which angiogenesis is important include solid tumors, and benign tumors such as acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas. Prevention of angiogenesis could halt the growth of these tumors and the resultant damage to the animal due to the presence of the tumor.

It should be noted that angiogenesis has been associated with blood-born tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors.

20 Angiogenesis is important in two stages of tumor
metastasis. The first stage where angiogenesis stimulation is
important is in the vascularization of the tumor which allows
tumor cells to enter the blood stream and to circulate throughout
the body. After the tumor cells have left the primary site, and
25 have settled into the secondary, metastasis site, angiogenesis must
occur before the new tumor can grow and expand. Therefore,
prevention of angiogenesis could lead to the prevention of
metastasis of tumors and possibly contain the neoplastic growth at
the primary site.

30 Knowledge of the role of angiogenesis in the
maintenance and metastasis of tumors has led to a prognostic
indicator for breast cancer. The amount of neovascularization
found in the primary tumor was determined by counting the
microvessel density in the area of the most intense
35 neovascularization in invasive breast carcinoma. A high level of

- 6 -

microvessel density was found to correlate with tumor recurrence. Control of angiogenesis by therapeutic means could possibly lead to cessation of the recurrence of the tumors.

Angiogenesis is also involved in normal physiological processes such as reproduction and wound healing. Angiogenesis is an important step in ovulation and also in implantation of the blastula after fertilization. Prevention of angiogenesis could be used to induce amenorrhea, to block ovulation or to prevent implantation by the blastula.

In wound healing, excessive repair or fibroplasia can be a detrimental side effect of surgical procedures and may be caused or exacerbated by angiogenesis. Adhesions are a frequent complication of surgery and lead to problems such as small bowel obstruction.

Several kinds of compounds have been used to prevent angiogenesis. Taylor et al. have used protamine to inhibit angiogenesis, see Taylor et al., *Nature* 297:307 (1982). The toxicity of protamine limits its practical use as a therapeutic. Folkman et al. have disclosed the use of heparin and steroids to control angiogenesis. See Folkman et al., *Science* 221:719 (1983) and U.S. Patent Nos. 5,001,116 and 4,994,443. Steroids, such as tetrahydrocortisol, which lack gluco and mineral corticoid activity, have been found to be angiogenic inhibitors.

Other factors found endogenously in animals, such as a 4 kDa glycoprotein from bovine vitreous humor and a cartilage derived factor, have been used to inhibit angiogenesis. Cellular factors such as interferon inhibit angiogenesis. For example, interferon α or human interferon β has been shown to inhibit tumor-induced angiogenesis in mouse dermis stimulated by human neoplastic cells. Interferon β is also a potent inhibitor of angiogenesis induced by allogeneic spleen cells. See Sidky et al., *Cancer Research* 47:5155-5161 (1987). Human recombinant α interferon (alpha/A) was reported to be successfully used in the treatment of pulmonary hemangiomatosis, an angiogenesis-

- 7 -

induced disease. See White et al., *New England J. Med.* 320:1197-1200 (1989).

5 Other agents which have been used to inhibit angiogenesis include ascorbic acid ethers and related compounds. See Japanese Kokai Tokkyo Koho No. 58-131978. Sulfated polysaccharide DS 4152 also shows angiogenic inhibition. See Japanese Kokai Tokkyo Koho No. 63-119500. A fungal product, fumagillin, is a potent angiostatic agent *in vitro*. The compound is toxic *in vivo*, but a synthetic derivative, AGM 12470, has been used *in vivo* to treat collagen II arthritis. Fumagillin and O-10 substituted fumagillin derivatives are disclosed in EPO Publication Nos. 0325199A2 and 0357061A1.

15 PCT Application No. WO 92/14455 to Kaplan et al. is directed to a method for controlling abnormal concentration of TNF- α by administering thalidomide or thalidomide derivatives to a patient with toxic concentrations of TNF- α .

20 The above compounds are either topical or injectable therapeutics. Therefore, there are drawbacks to their use as a general angiogenic inhibitor and lack adequate potency. For example, in prevention of excessive wound healing, surgery on internal body organs involves incisions in various structures contained within the body cavities. These wounds are not accessible to local applications of angiogenic inhibitors. Local delivery systems also involve frequent dressings which are impracticable for internal wounds, and increase the risk of 25 infection or damage to delicate granulation tissue for surface wounds.

30 Thus, a method and composition are needed that are capable of inhibiting angiogenesis and which are easily administered. A simple and efficacious method of treatment would be through the oral route. If an angiogenic inhibitor could be given by an oral route, the many kinds of diseases discussed above, and other angiogenic dependent pathologies, could be treated easily. The optimal dosage could be distributed in a form 35 that the patient could self-administer.

Summary of the Invention

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In accordance with the present invention, compositions and methods are provided that are effective in inhibiting unwanted angiogenesis. These compositions are easily administered by different routes including oral and can be given in dosages that are safe and provide angiogenic inhibition at internal sites. The present invention provides a method of treating mammalian diseases mediated by undesired and uncontrolled angiogenesis by administering a composition comprising an anti-angiogenic compound in a dosage sufficient to inhibit angiogenesis.

10

The present invention also includes angiogenic inhibiting compounds that contain an epoxide group. These angiogenic inhibiting compounds can be administered to a human or animal alone or with epoxide hydrolase inhibiting compounds.

15

The present invention is especially useful for treating certain ocular neovascular diseases such as macular degeneration. The compounds which are contemplated as part of the present invention preferably can be given orally to the patient and thereby halt the progression of the disease. Other disease that can be treated using the present invention are diabetic retinopathy, neovascular glaucoma and retrolental fibroplasia.

20

Accordingly, the present invention seeks to provide a compound and method to inhibit unwanted angiogenesis in a human or animal.

25

Further, the present invention seeks to provide a composition of inhibiting angiogenesis by oral administration of the composition.

- 9 -

Still further, the present invention seeks to provide a treatment for diseases mediated by angiogenesis.

Further still, the present invention seeks to provide a treatment for macular degeneration.

5 Yet further, the present invention seeks to provide a treatment for all forms of proliferative vitreoretinopathy including those forms not associated with diabetes.

Moreover, the present invention seeks to provide a treatment for solid tumors.

10 Still further, the present invention seeks to provide a method and composition for the treatment of blood-born tumors such as leukemia.

Further still, the present invention seeks to provide a method and composition for the treatment of hemangioma.

15 Another aspect of the present invention seeks to provide a method and composition for the treatment of retroorbital fibroplasia.

Yet another aspect of the present invention seeks to provide a method and composition for the treatment of psoriasis.

20 Moreover, the present invention seeks to provide a method and composition for the treatment of Kaposi's sarcoma.

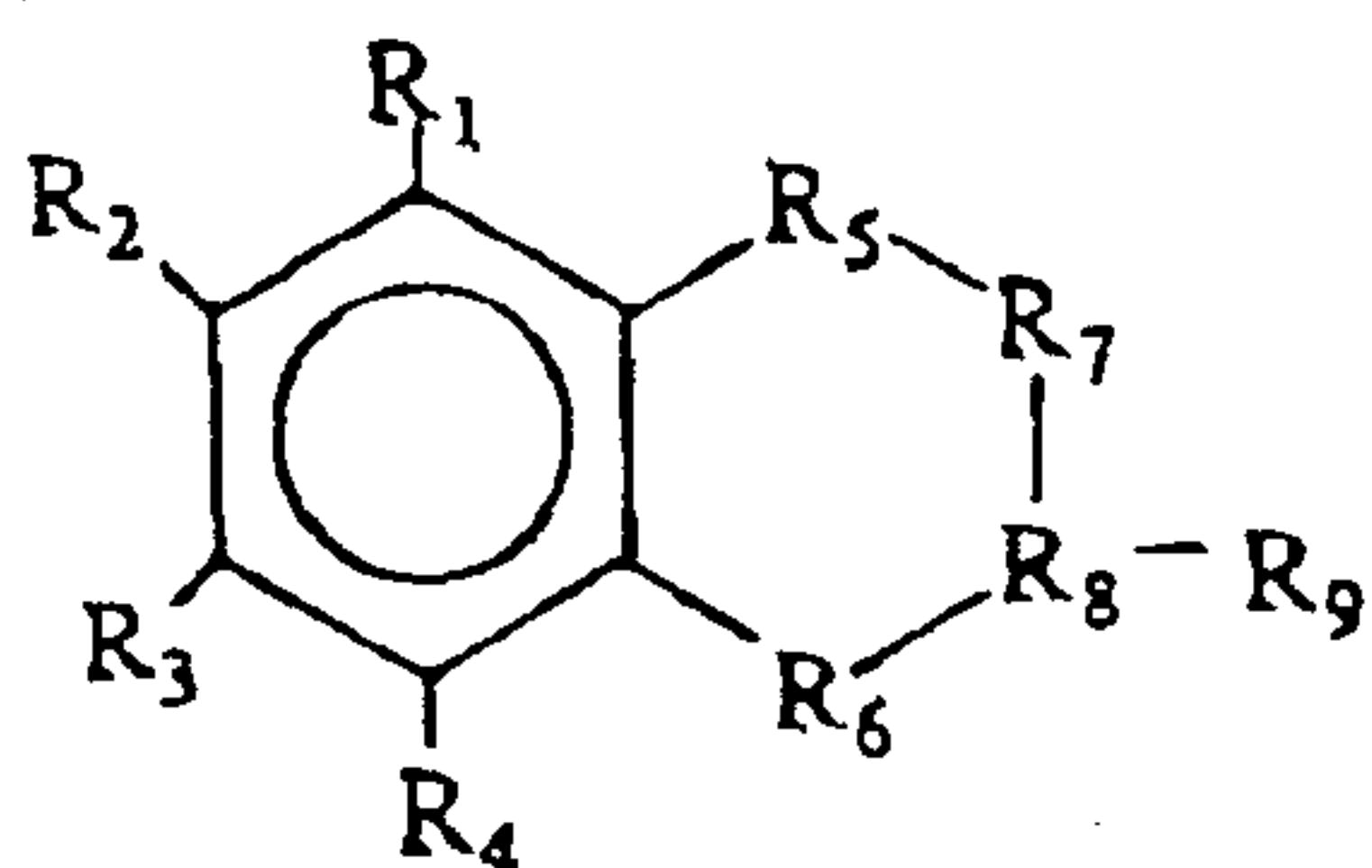
Yet further, the present invention seeks to provide a method and composition for the treatment of Crohn's diseases.

Still further, the present invention seeks to provide a method and composition for the treatment of diabetic retinopathy.

25 The invention in a broad aspect comprehends the use of a composition administered for treating undesired angiogenesis in a human or animal. The composition comprises an effective amount of an angiogenesis-inhibiting compound selected from the group consisting of the following compounds:

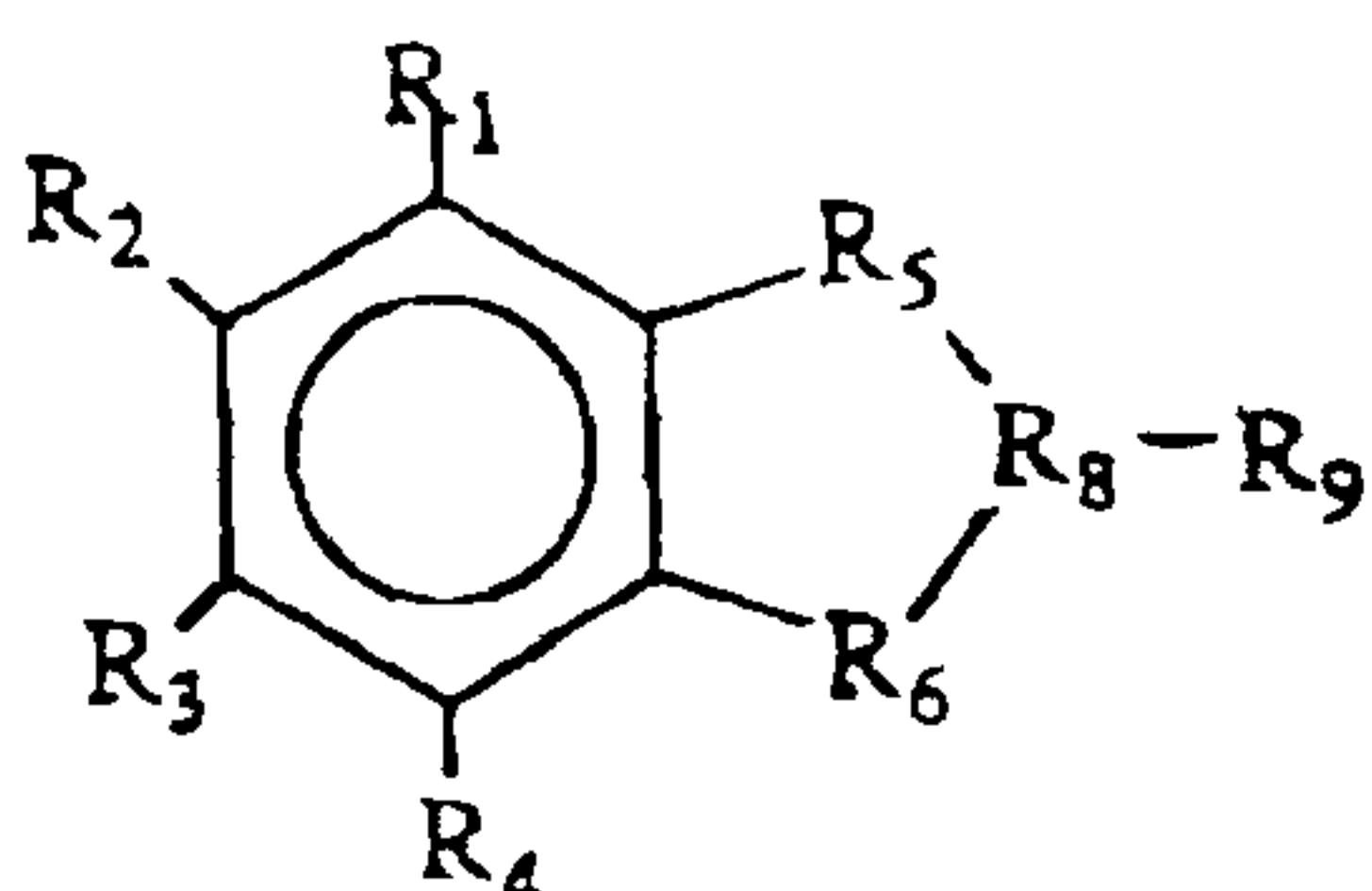
- 9a -

A)



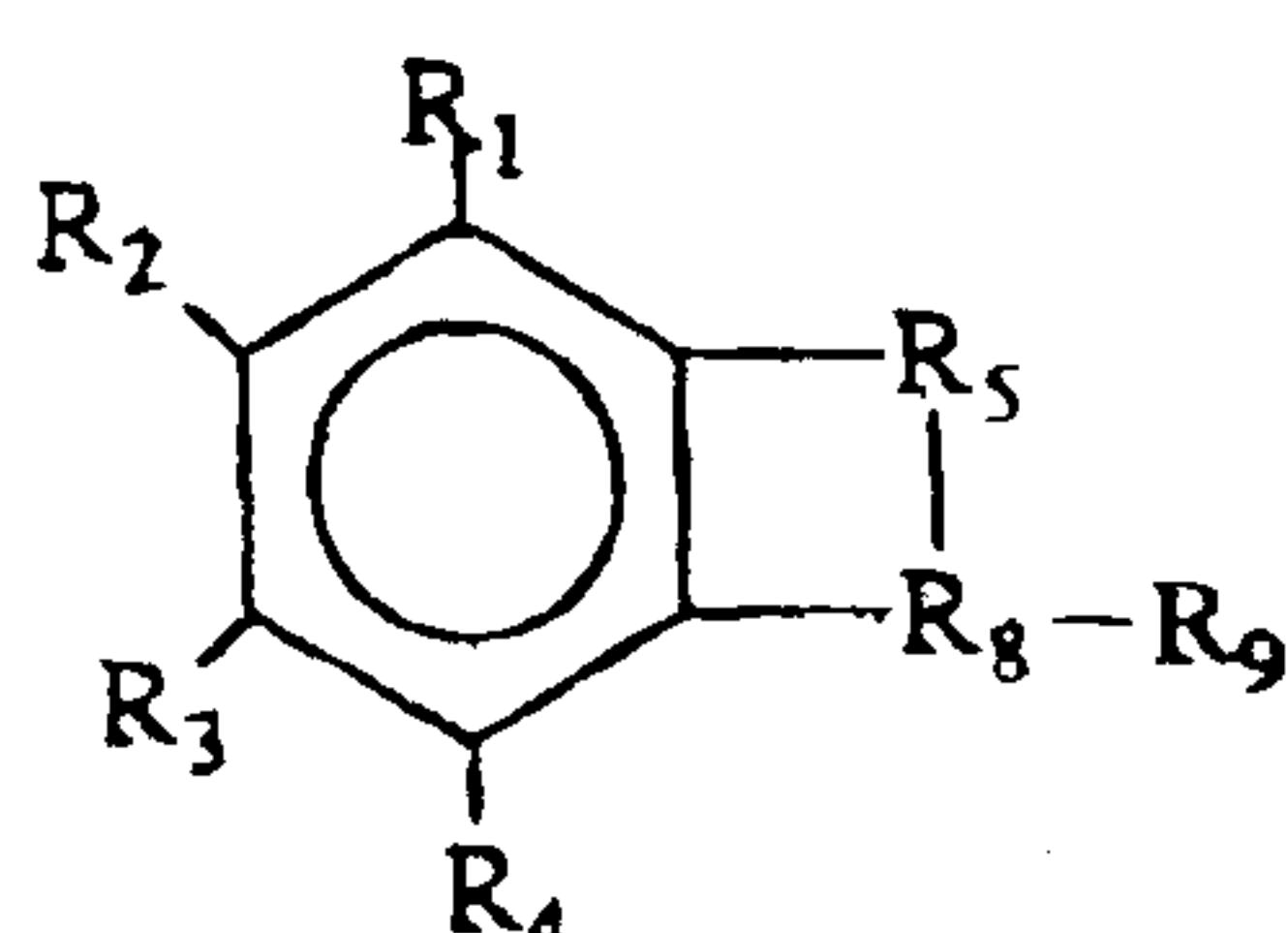
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B)



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C)

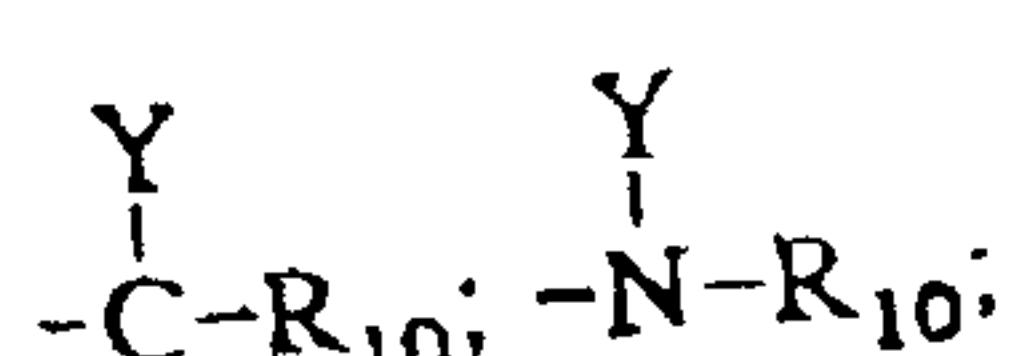


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wherein R_1 , R_2 , R_3 , and R_4 can be selected from: -H; -OH; =O, straight chained and branched alkanes, alkenes, alkynes; cyclic alkanes, alkenes and alkynes; combinations of cyclic and acyclic alkanes, alkenes and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or either moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; $-XO_n$ or $-O-XO_n$ (where $X = N$ and $n = 2$; $X = S$ and $n = 2$ or 3 ; or $X = P$ and $n = 1-3$); and halogens; R_5 , R_6 , R_7 , and R_8 are each independently selected from:

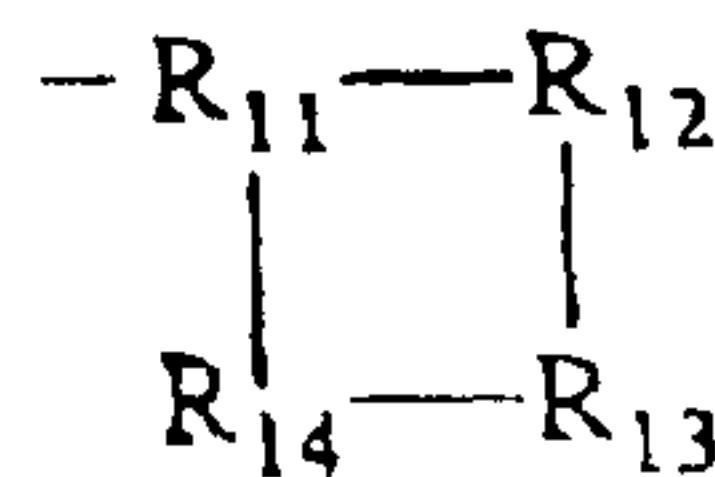


- 9b -

or -O- where Y is optional and is the same as defined above for R₁; and R₁₀ is the same as defined above for R₁, or (where Y is absent) R₁₀ is =O; and R₉ is a moiety having formula D), E), F), G) or H):

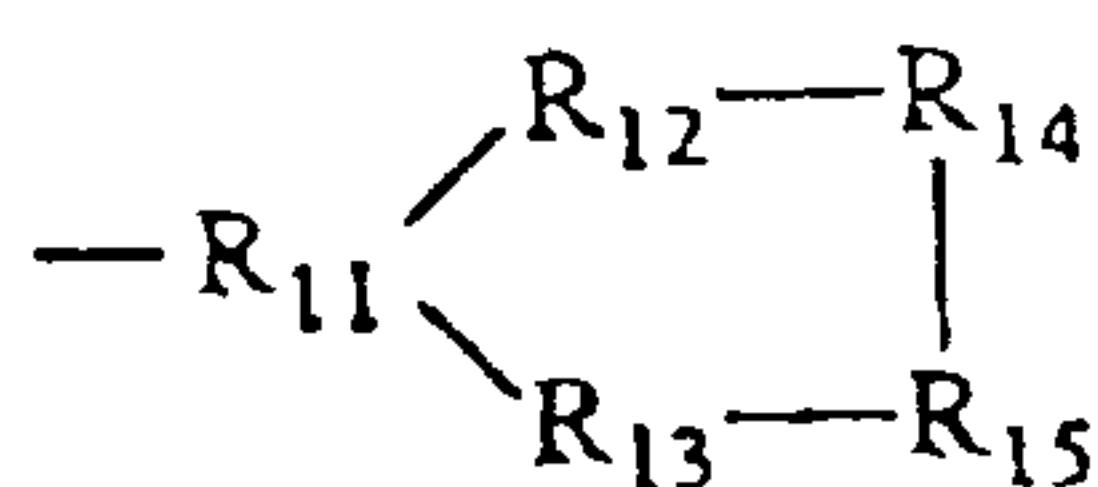
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D)



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E)

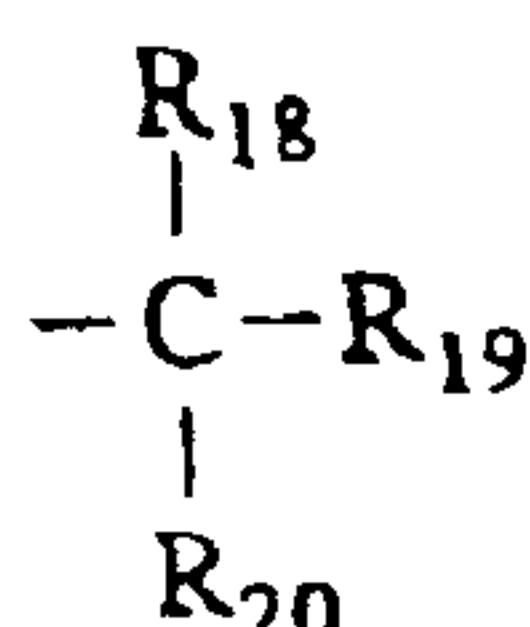


15

where each of R₁₁ - R₁₇ is (independently) the same as defined above for R₅;

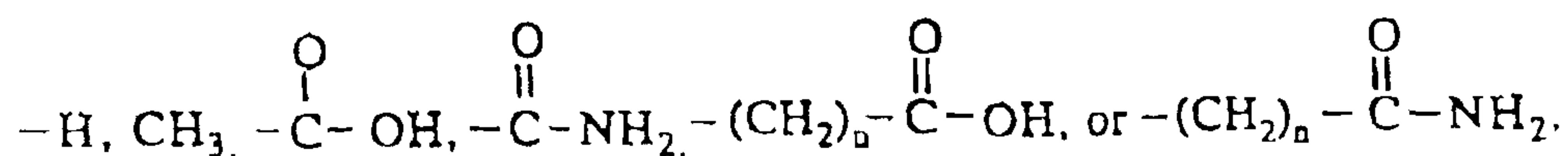
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H)



where R₁₈, R₁₉ and R₂₀ are, independently selected from

25



and n=1 to 4;

provided the compound is not thalidomide.

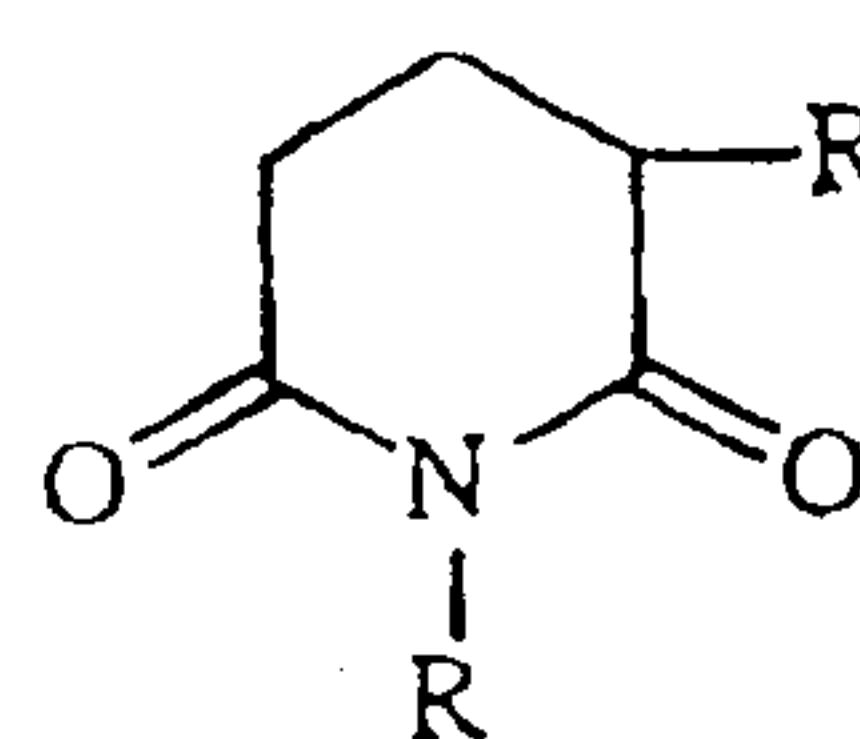
- 9c -

5

The invention in another aspect comprehends the use of a composition administered for treating undesired angiogenesis in a human or animal. The composition comprises an effective amount of an angiogenesis-inhibiting compound selected from the group consisting of the following compounds:

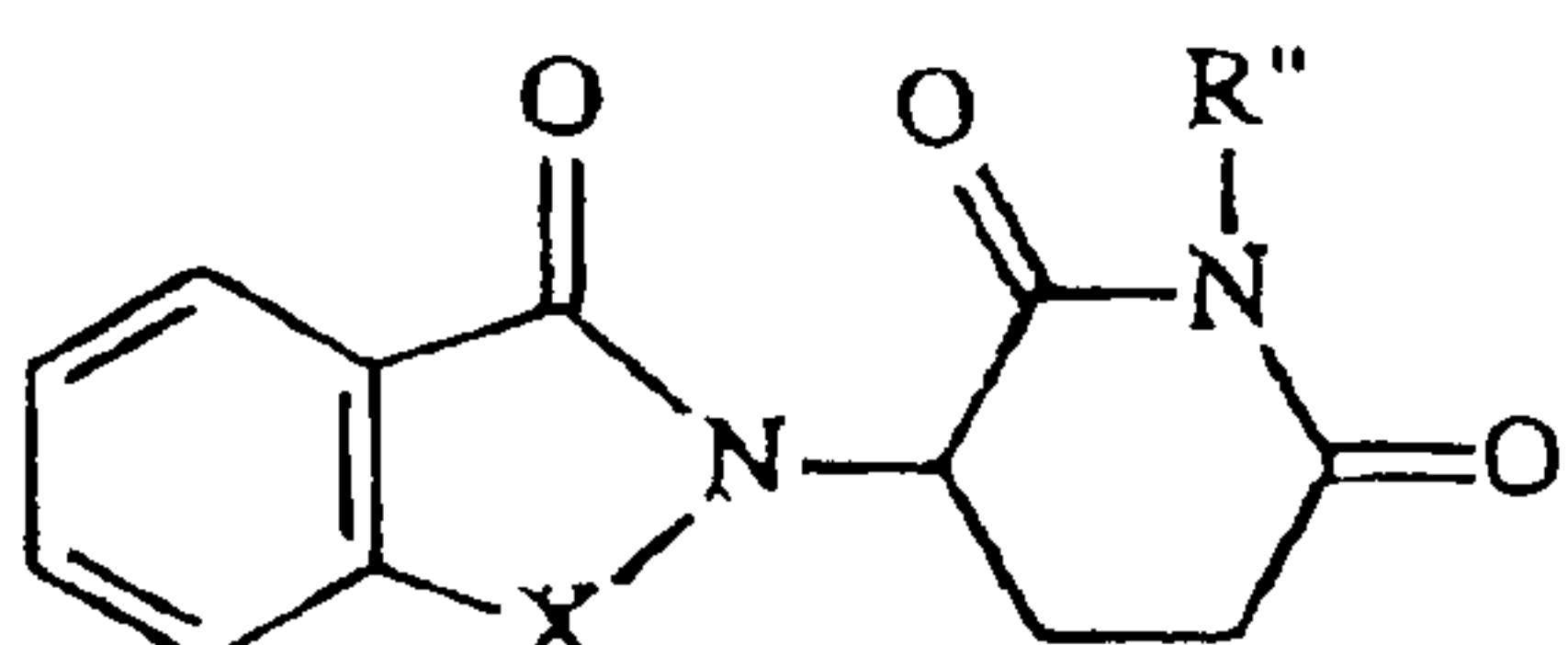
10

(I)



and

(II)



wherein

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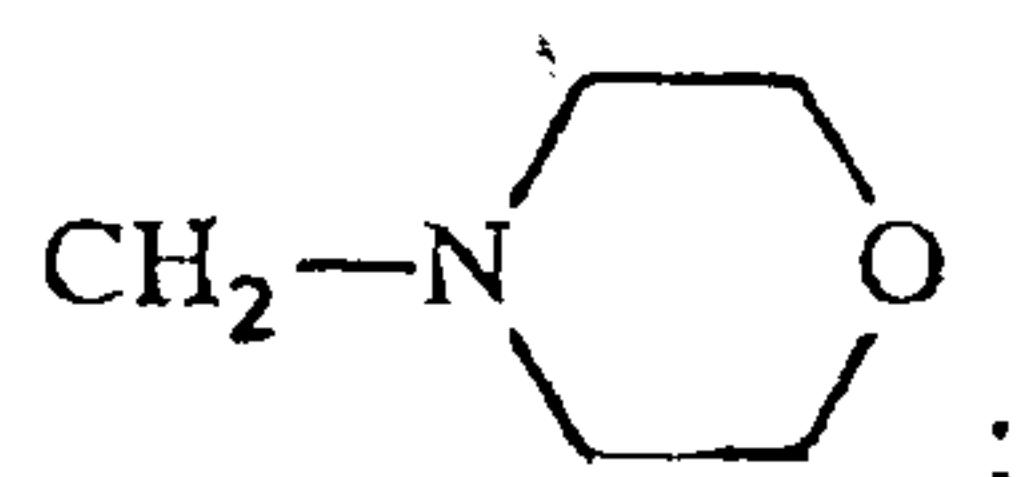
R is selected from the group consisting of H, (C₁-C₆)alkyl, phenyl, and benzyl;

R' is selected from the group consisting of phthalimido and succinimido;

X is CH₂ or C=O; and

20

R'' is H, -CH₂CH₃, -C₆H₅, -CH₂C₆H₅, -CH₂CH=CH₂, or



25

and

(III) hydrolysis products of (II) wherein R'' is H and the piperidino ring or both the piperidino and the imido ring are hydrolyzed provided the compound is not thalidomide.

Further, the invention provides for the use of a composition administered for treating undesired angiogenesis in a human or animal. The composition comprises an effective amount of

- 9d -

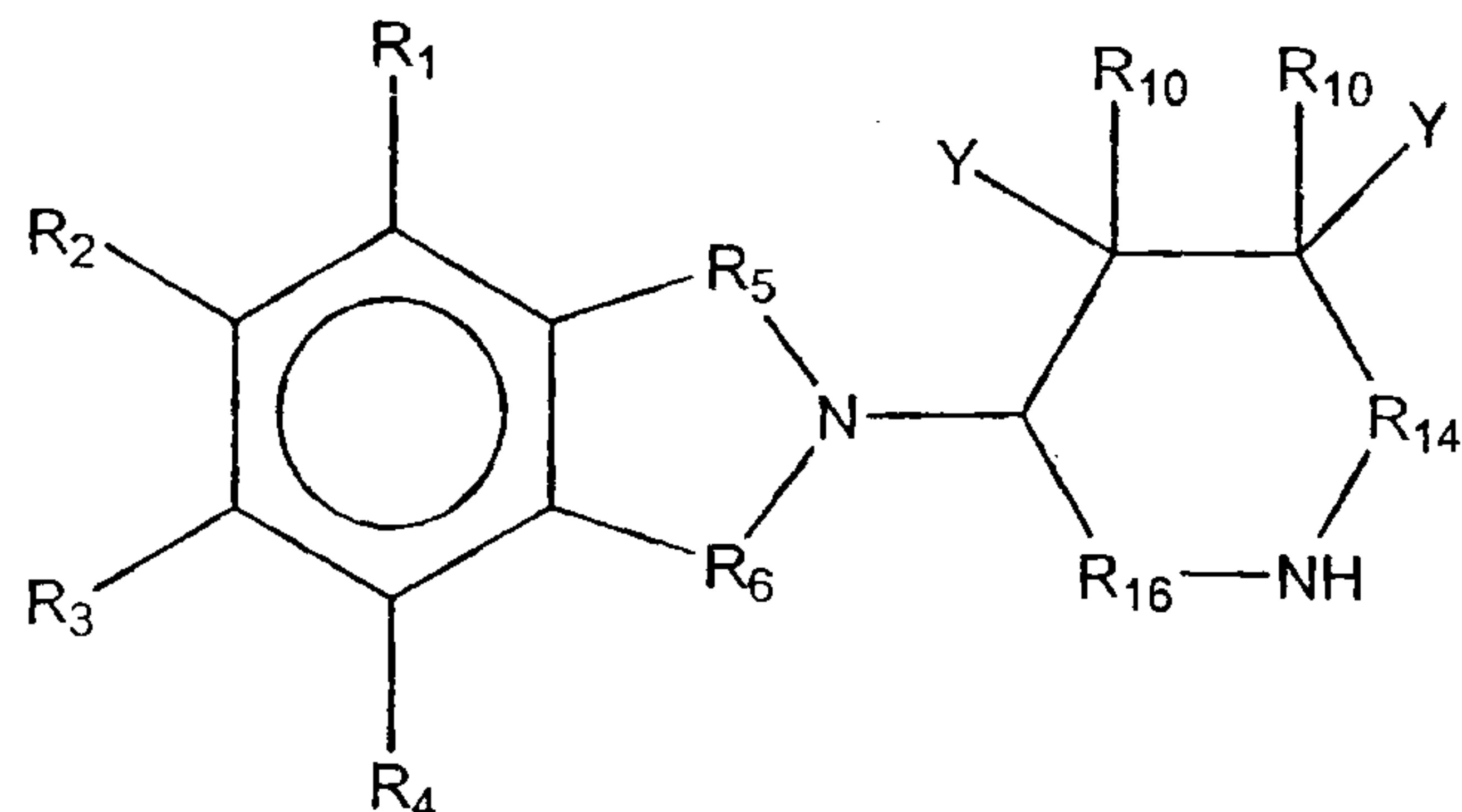
5

an angiogenesis-inhibiting compound selected from the group consisting of α -thalidomide, EM-12, EM-138, phthaloyl glutamic anhydride and phthaloyl glutamic acid and metabolites of thalidomide, EM-12, EM-138, phthaloyl glutamic anhydride and phthaloyl glutamic acid, or mixtures thereof.

Moreover, the invention provides for the use of an angiogenesis inhibiting amount of a compound in administratable form for treating blood-born tumors in a human. The compound comprises the formula:

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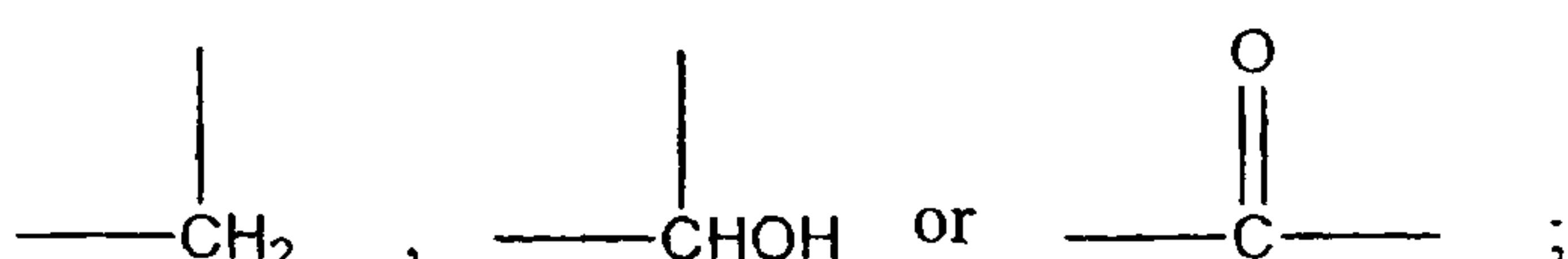
wherein:

20

R₁, R₂, R₃ and R₄ are each independently -H; -OH; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkene; cyclic alkyne; alcohol, aldehyde, ketone, ester or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -NO₂; -SO₂; -SO₃; -PO₃; -O-PO₃ or halogen;

R₅ and R₆ are each independently,

25



Y is optional and each occurrence of Y is -H; -OH; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkene; cyclic alkyne;

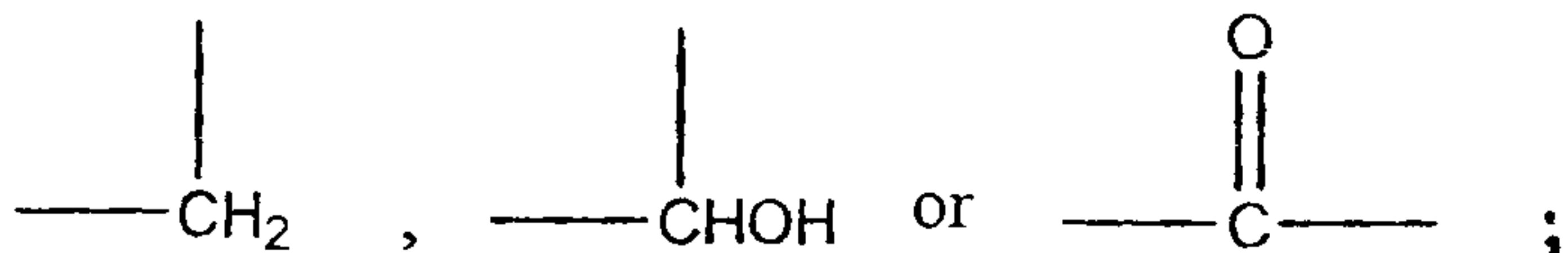
- 9e -

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alcohol, aldehyde, ketone, ester or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -NO₂; -SO₂; -SO₃; -PO₃; -O-PO₃ or halogen; each occurrence of R₁₀ is -H; -OH; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkenecyclic alkyne; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino -NO₂; -SO₂; -SO₃; -PO₃; -O-PO₃; halogen, or when Y is absent R₁₀ is =O; and R₁₄ and R₁₆ are each independently



provided the compound is not thalidomide.

These and other aspects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and the appended claims.

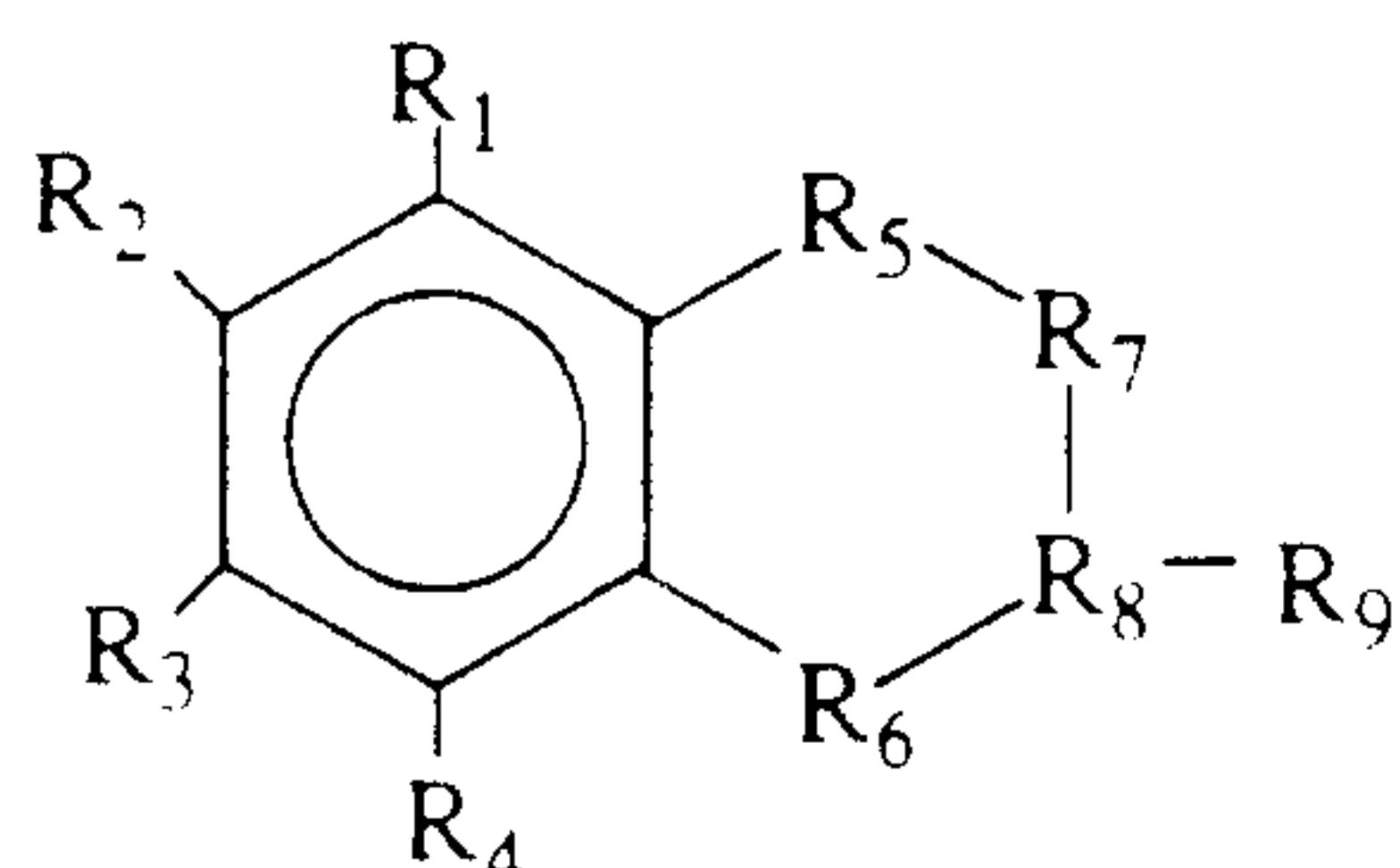
- 10 -

Brief Description of the Figures

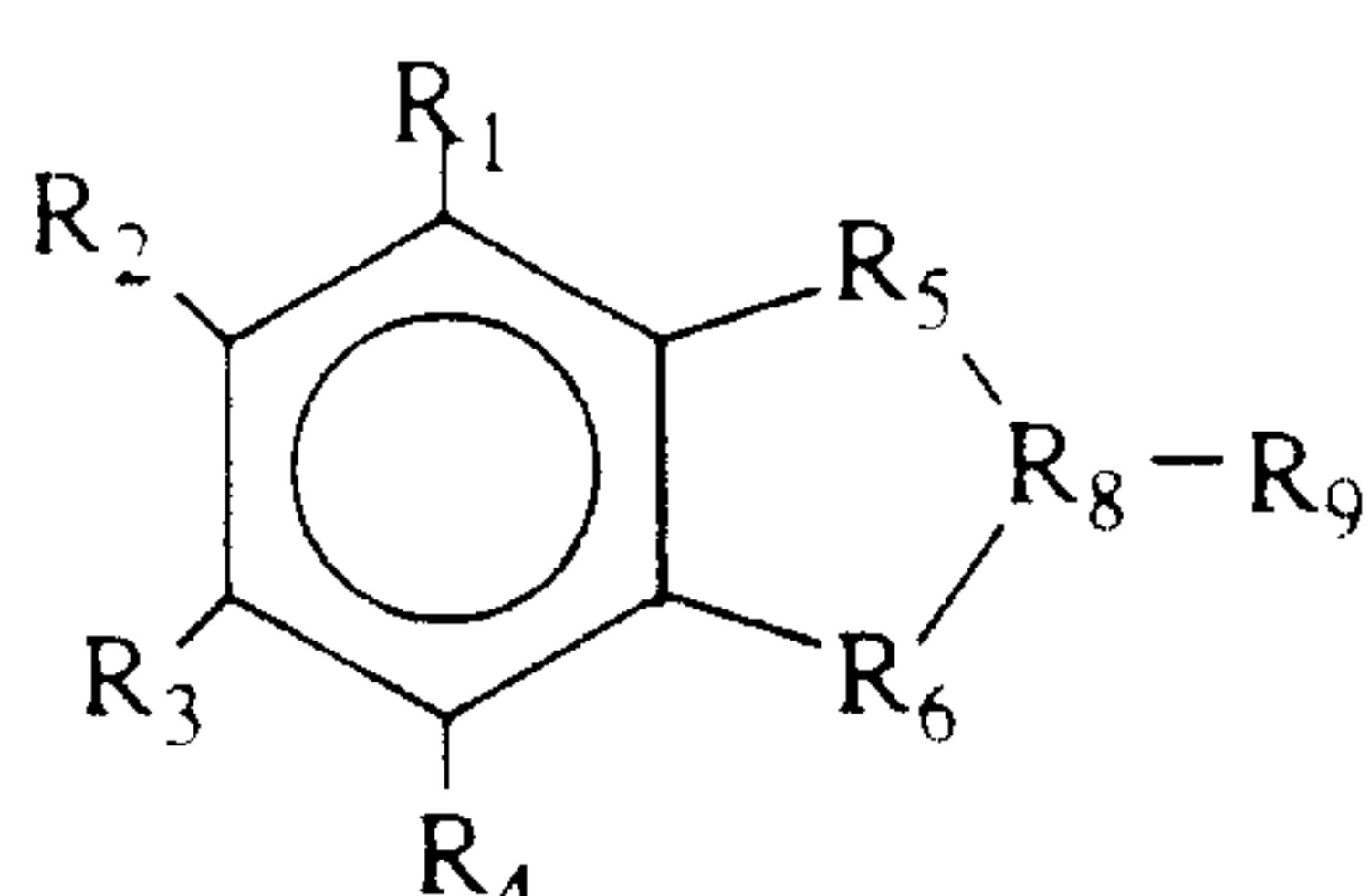
Figures 1 through 3 are a listing of representative compounds in the genus represented by the following general formulas:

5

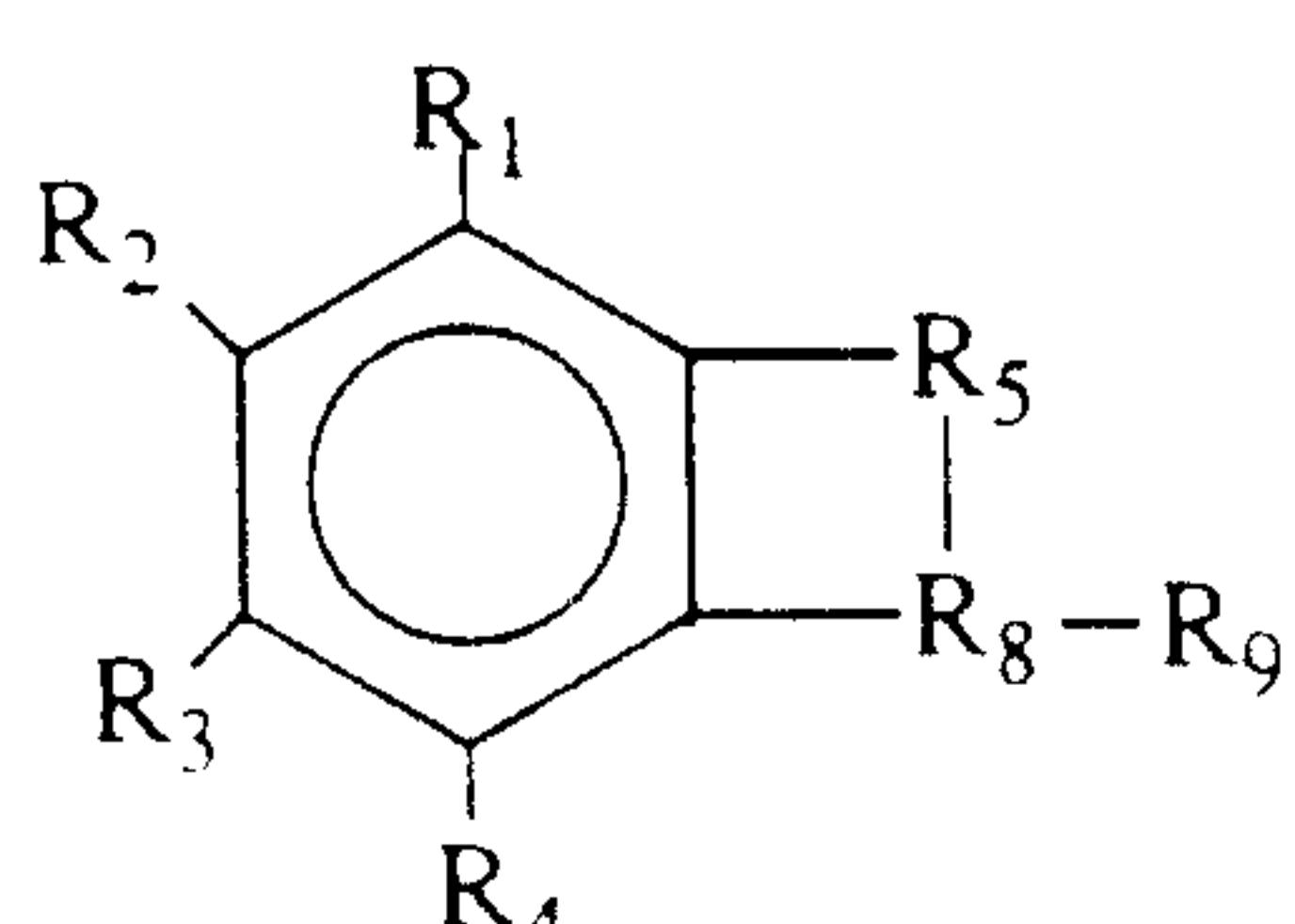
A)



B)

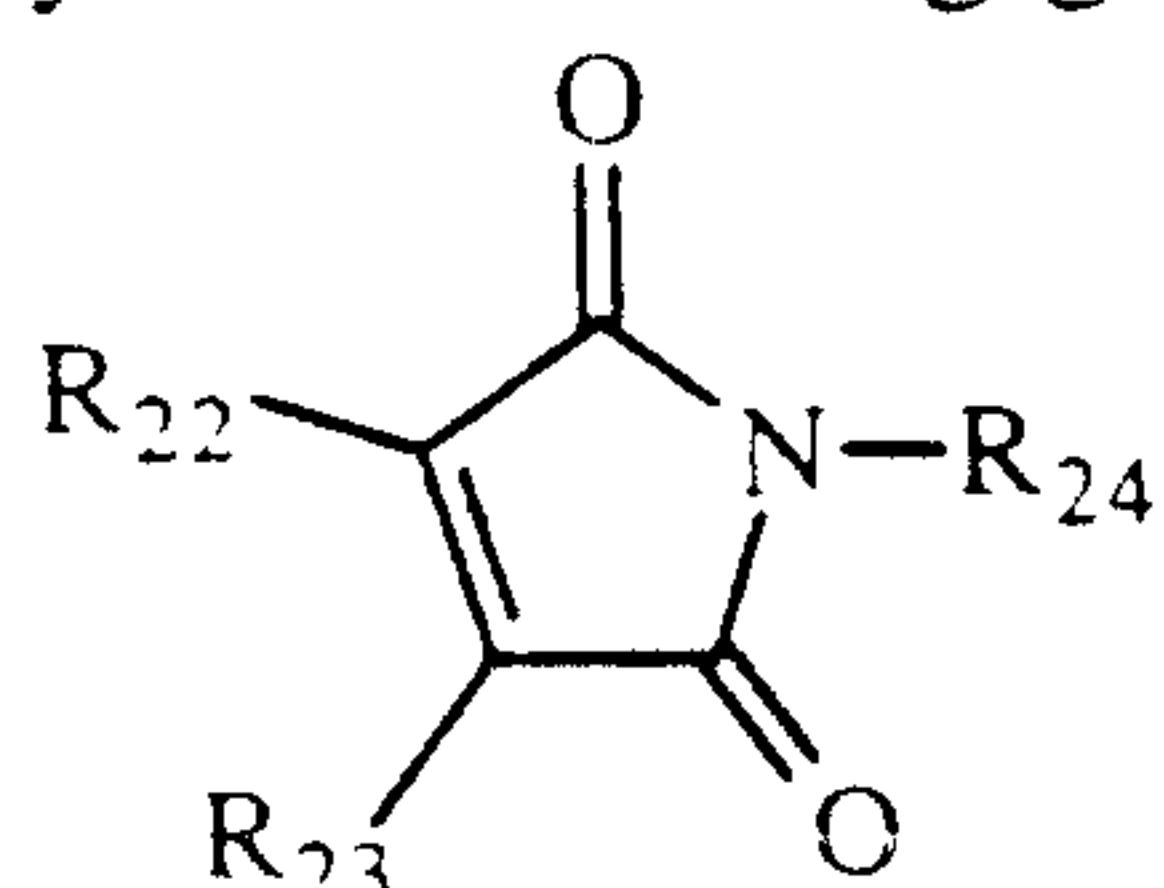


C)



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Figure 4 is a listing of representative compounds in the genus represented by the following general formula:



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Figure 5 is a listing of representative compounds in the genus represented by the following general formula:

- 11 -

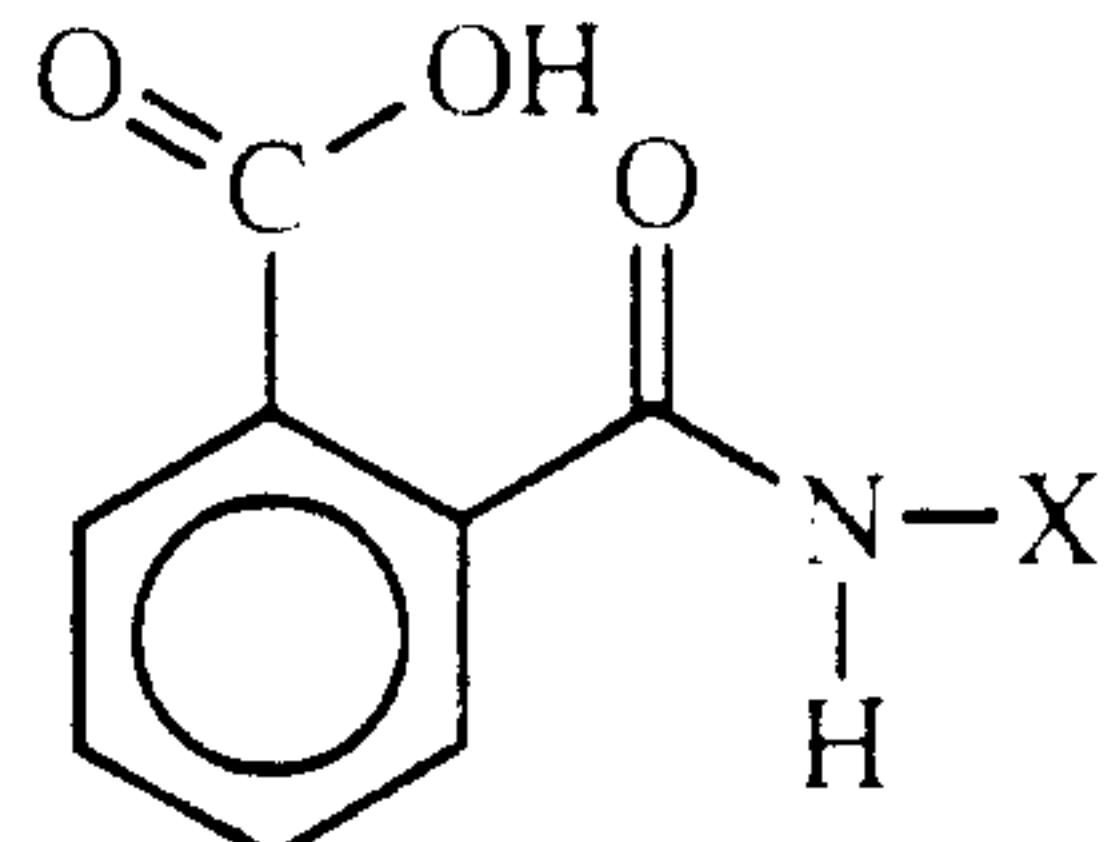


Figure 6 shows the effect of thalidomide and EM12 on angiogenesis in a rabbit cornea model of angiogenesis.

5 Figure 7 shows the effect of thalidomide on the area of corneal vascularization in a rabbit cornea model of angiogenesis.

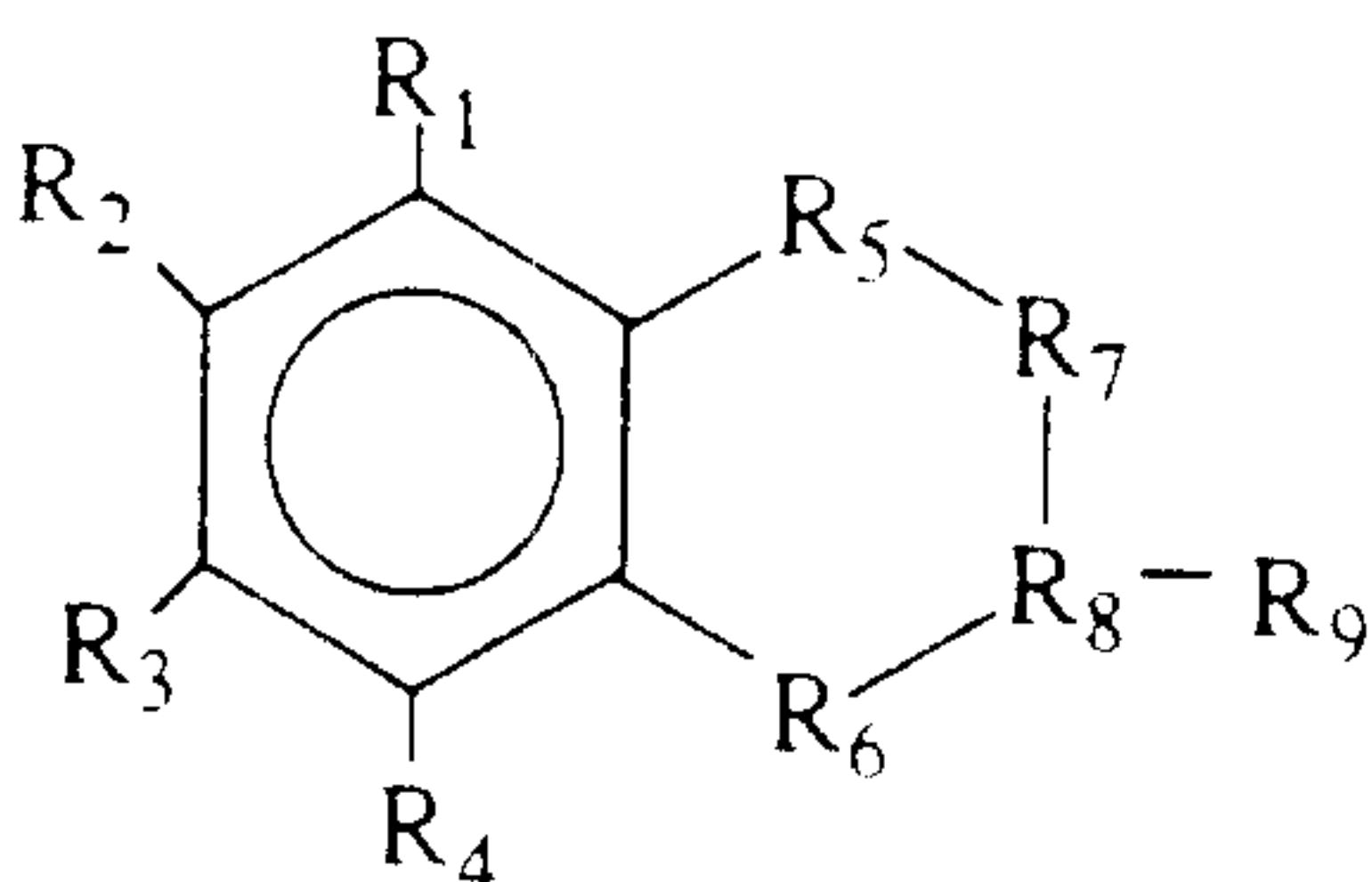
Detailed Description

10 The present invention includes compositions and methods for the treatment of diseases that are mediated by angiogenesis. One embodiment of the present invention is the use of thalidomide or the metabolites of thalidomide as disclosed herein to inhibit unwanted angiogenesis. The present invention also includes compounds which cause dysmelia in the developing 15 fetus and have anti-angiogenic activity. The present invention comprises a method of treating undesired angiogenesis in a human or animal comprising the steps of administering to the human or animal with the undesired angiogenesis a composition comprising 20 an effective amount of a teratogenic compound that is anti-angiogenic.

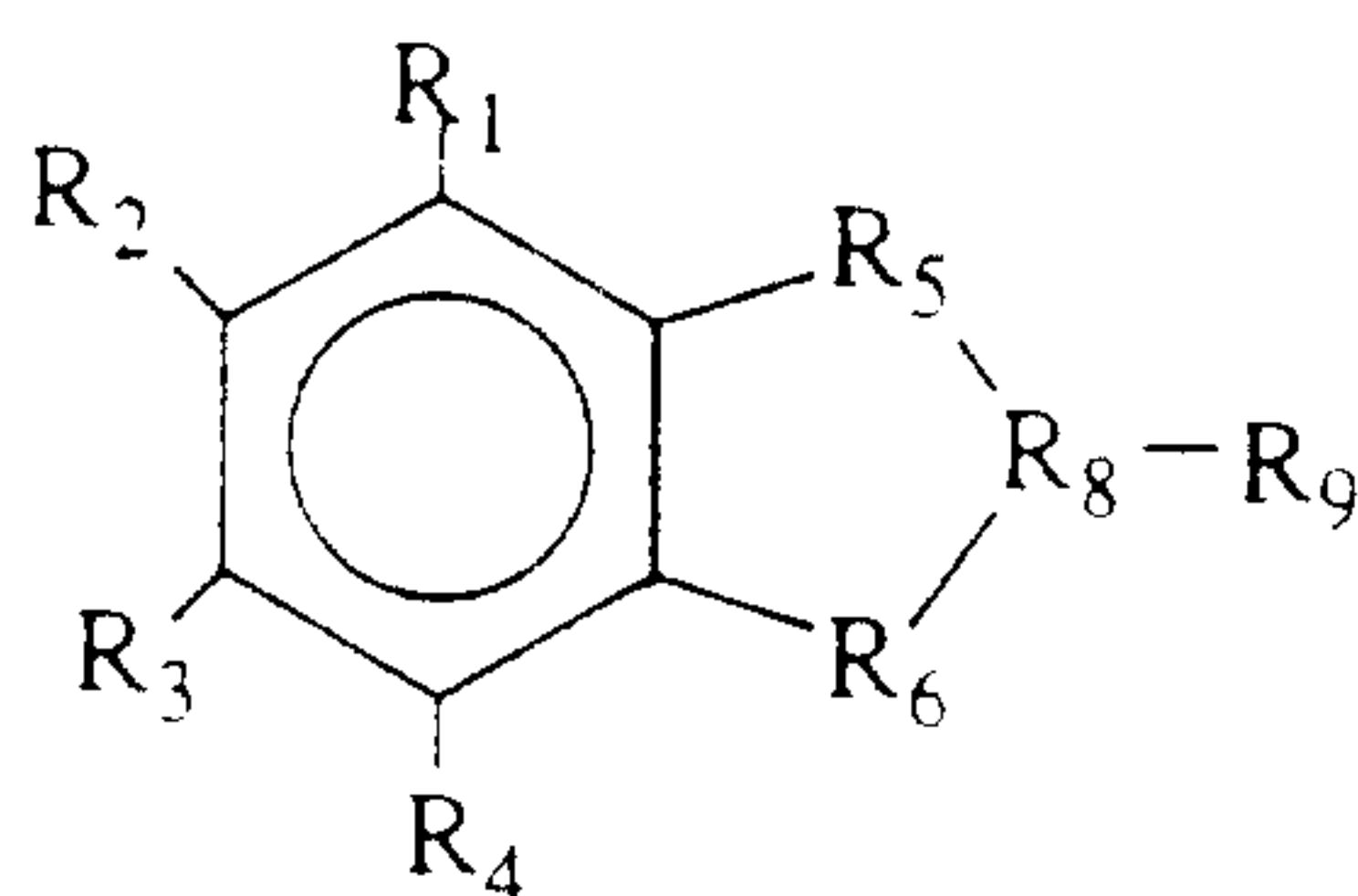
25 Compounds that can be used in accordance with the present invention include compounds included in the following general formulae. Examples of compounds that have anti-angiogenic properties having one of the following three formulae (A), (B), or (C):

- 12 -

A)

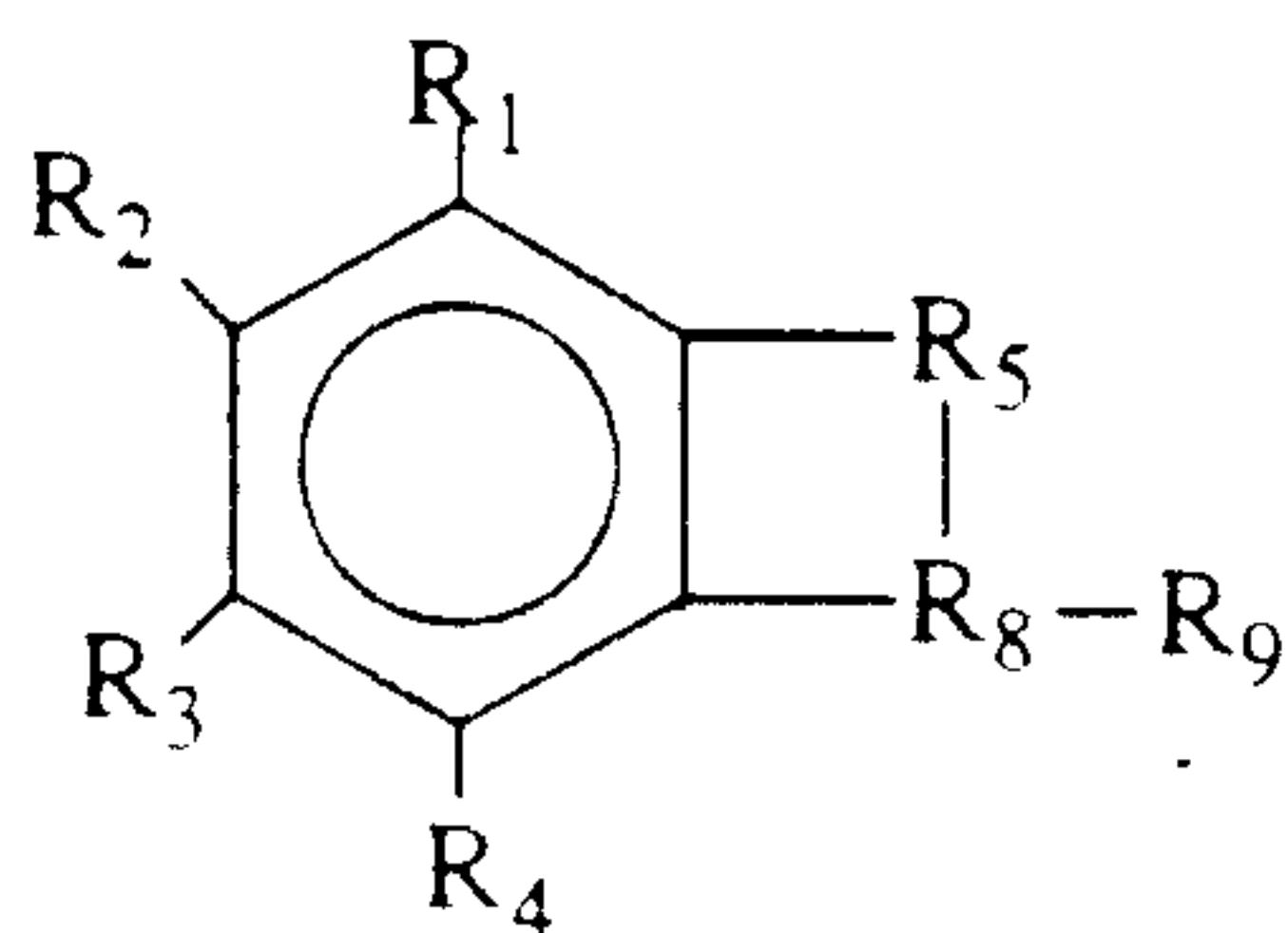


B)



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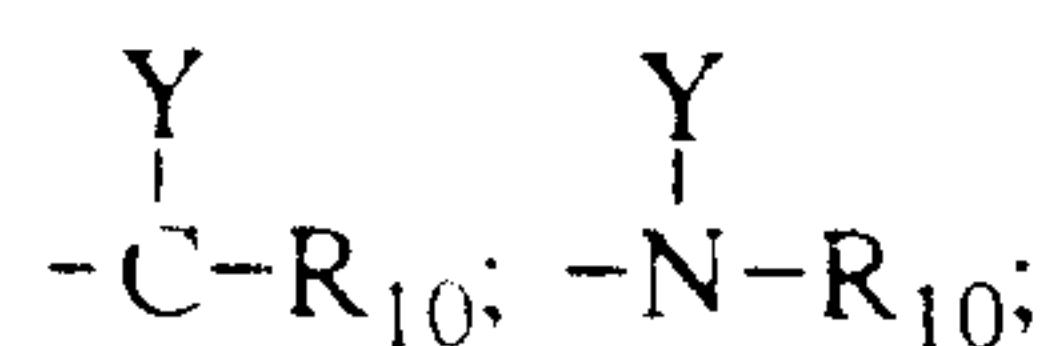
C)



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15

In the above formulae A), B), and C), R₁, R₂, R₃ and R₄ can be selected from: -H; -OH; =O, straight chained and branched alkanes, alkenes, alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -XO_n or -O-XO_n, [where X=N and n=2; X=S and n=2 or 3; or X=P and n=1-3]; and halogens; R₅, R₆, R₇, and R₈ are each independently selected from:

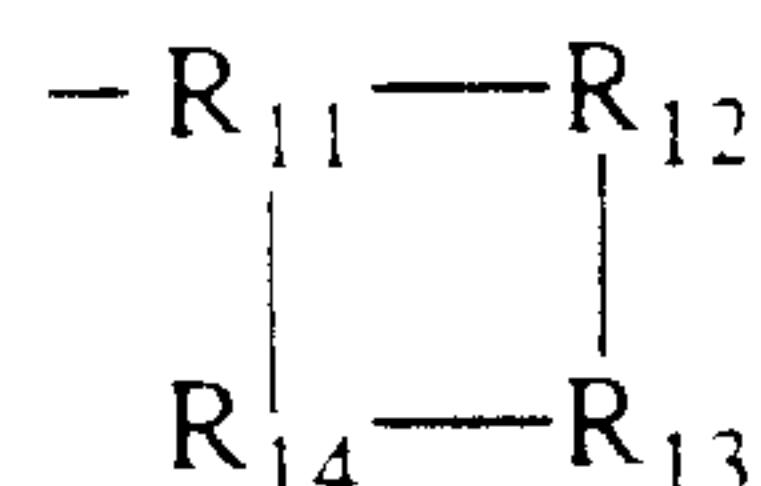


or -O- where Y is optional and is the same as defined above for R₁; and R₁₀ is the same as defined above for R₁, or (where Y is

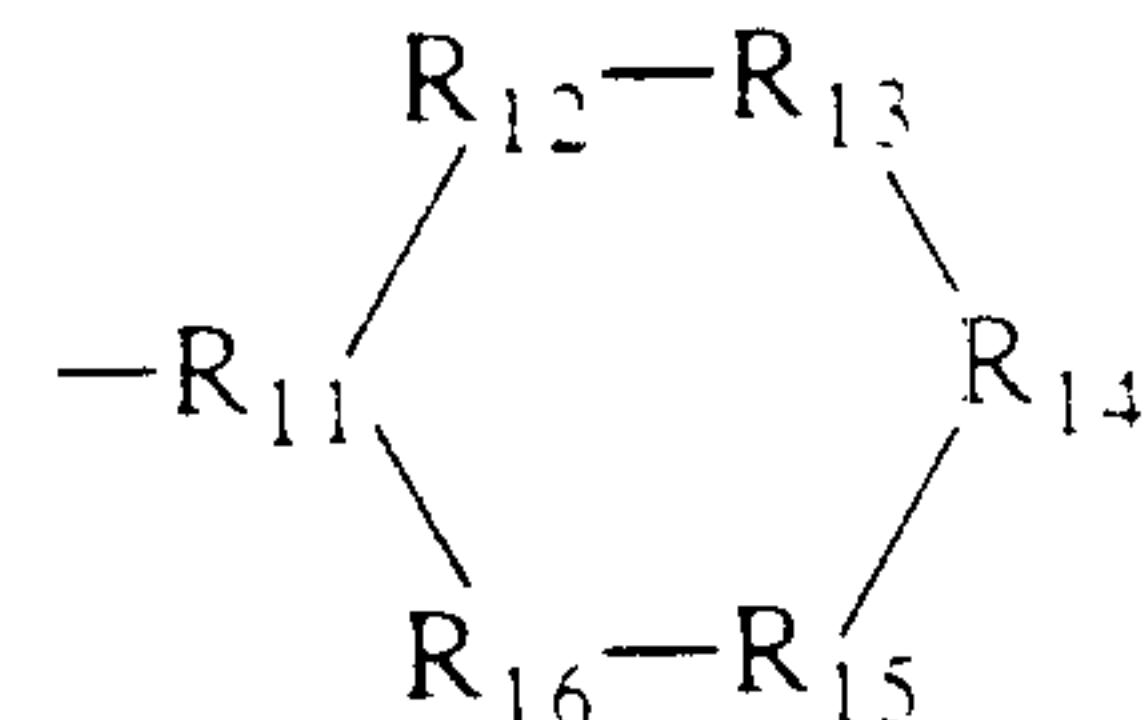
- 13 -

absent) R₁₀ is =O; and R₉ is a moiety having formula D), E), F), G) or H):

D)

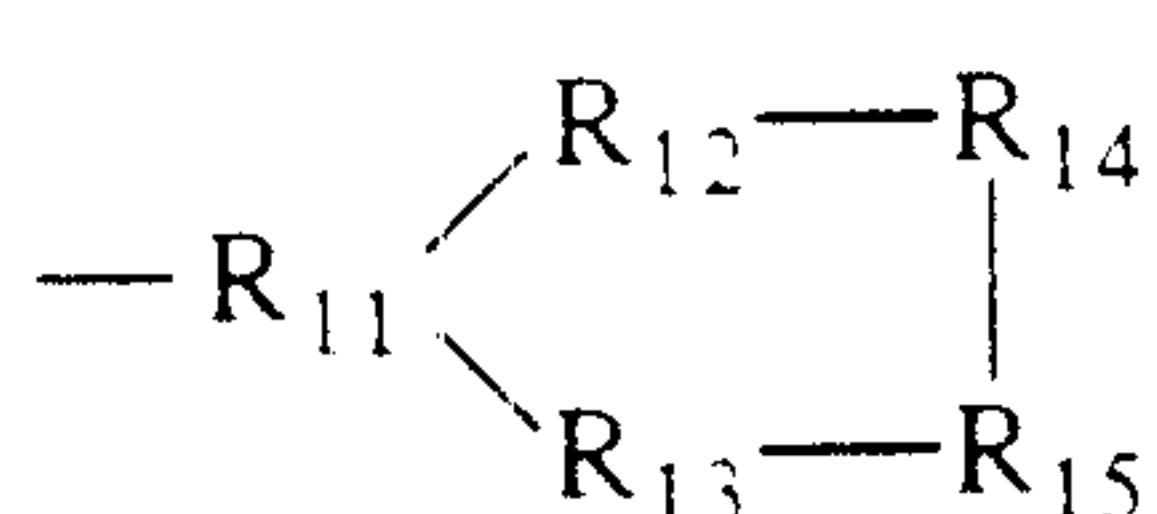


F)

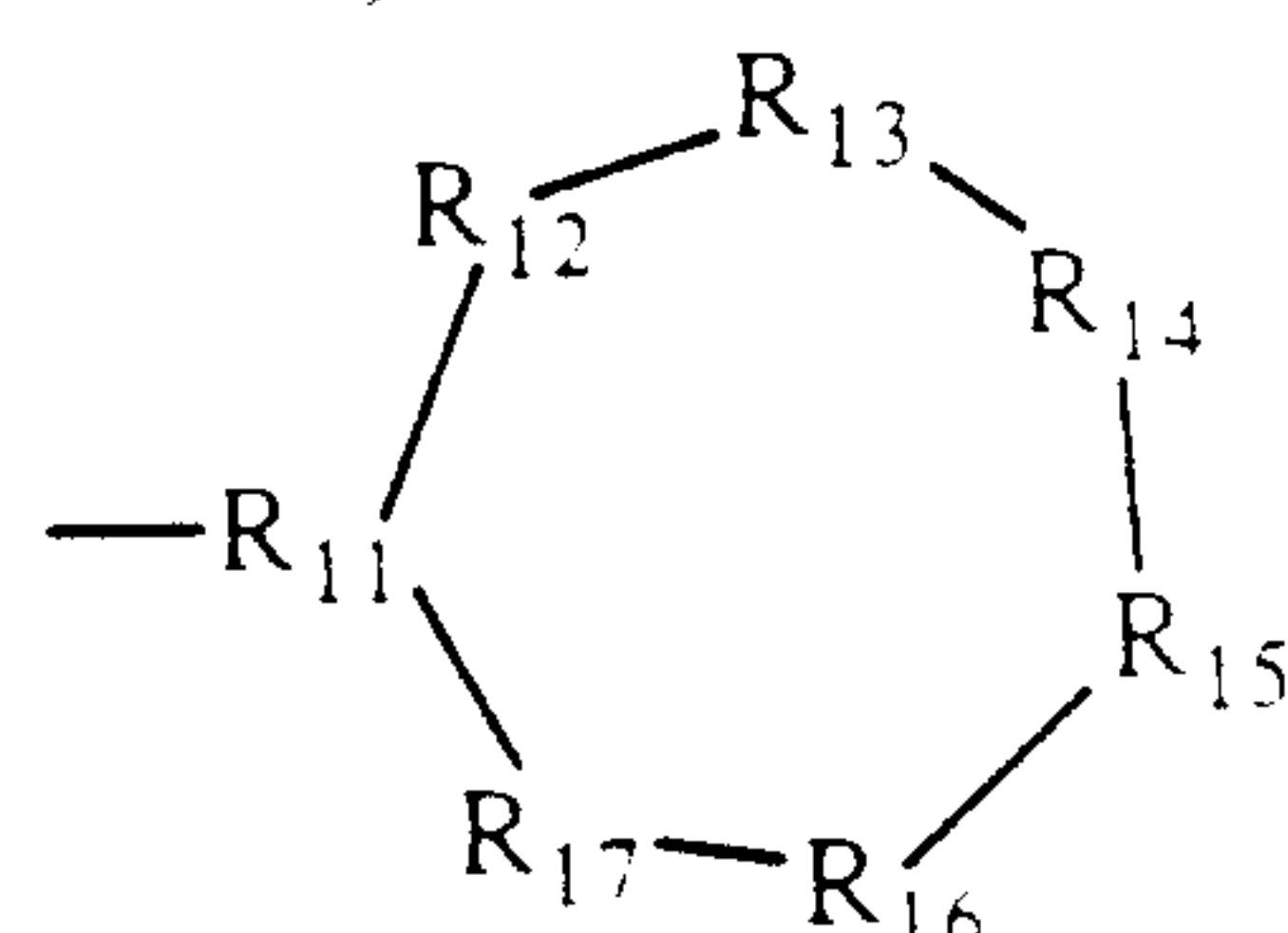


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E)



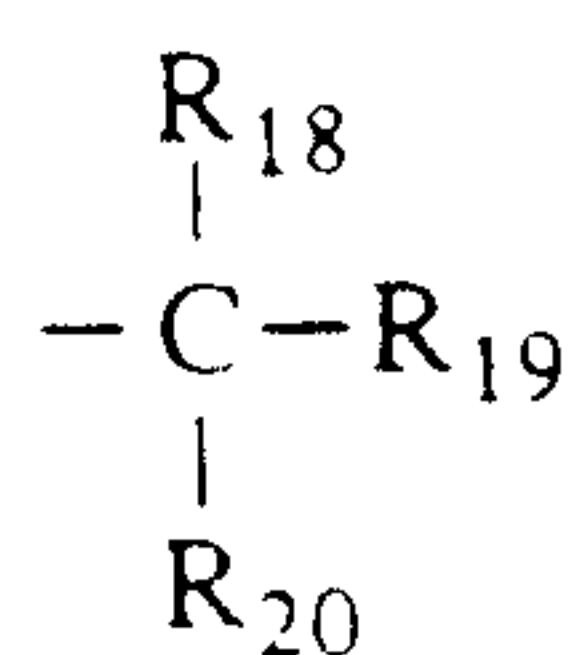
G)



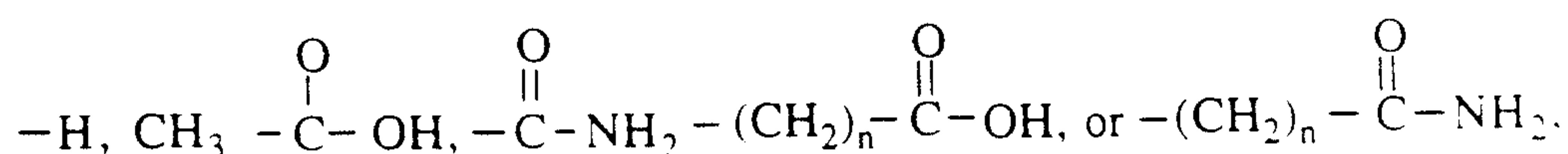
where each of R₁₁ - R₁₇ is (independently) the same as defined above for R₅;

10

H)



where R₁₈, R₁₉ and R₂₀ are, independently selected from



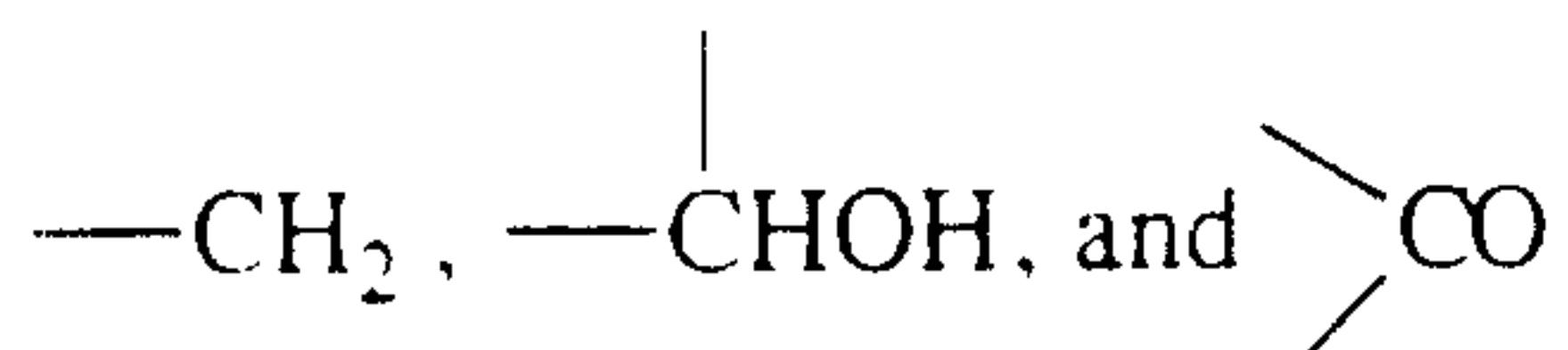
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and n=1 to 4.

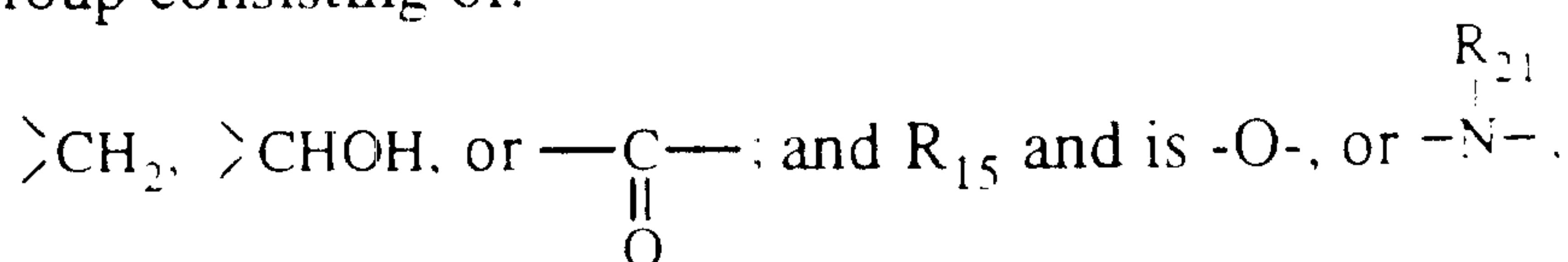
Accordingly, another aspect of the present invention features inhibiting angiogenesis in a mammal by administering a therapeutic composition comprising one of the above-described compounds in a dosage sufficient to inhibit angiogenesis

- 14 -

In preferred embodiments, the compound has formula B), where R₅ and R₆ are selected from the group consisting of:

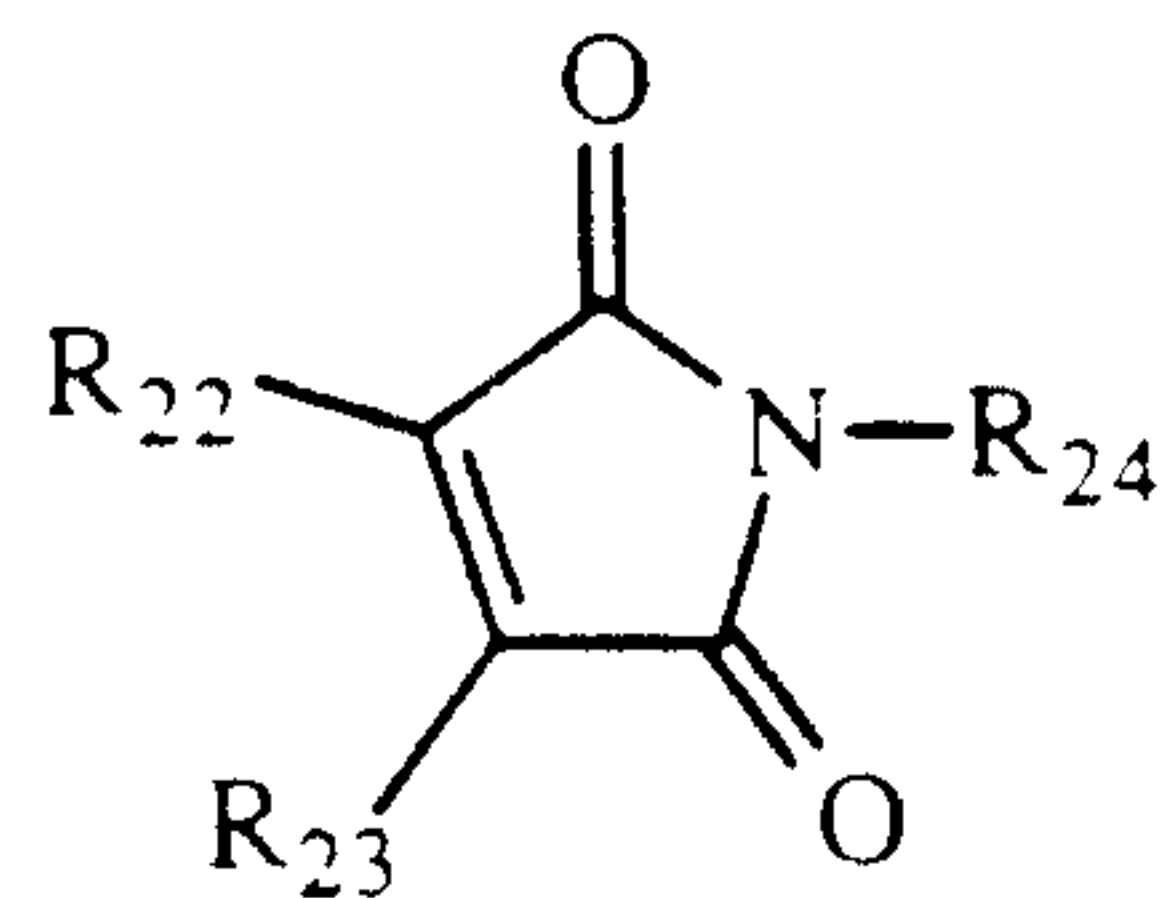


5 and R₉ has formula F) or H); and R₁₄ and R₁₆ are selected from the group consisting of:



10 where R₂₁ is -H, -CH₃, or -OH. Specific preferred compounds according to this aspect of the present invention include thalidomide, its precursors, metabolites and analogs. Particular analogs include EM-12, N-phthaloyl-DL-glutamic acid (PGA) or N-phthaloyl-DL-glutamine anhydride. Examples of compounds that are members of this genus are listed in Figures 1 through 3. It is to be understood that the compounds included as part of the 15 present invention are not to be limited to those compounds shown in Figures 1 through 3 and include all other compounds that are members of the genus described by the general formulas herein.

Compounds of the following formula that have anti-angiogenic properties:

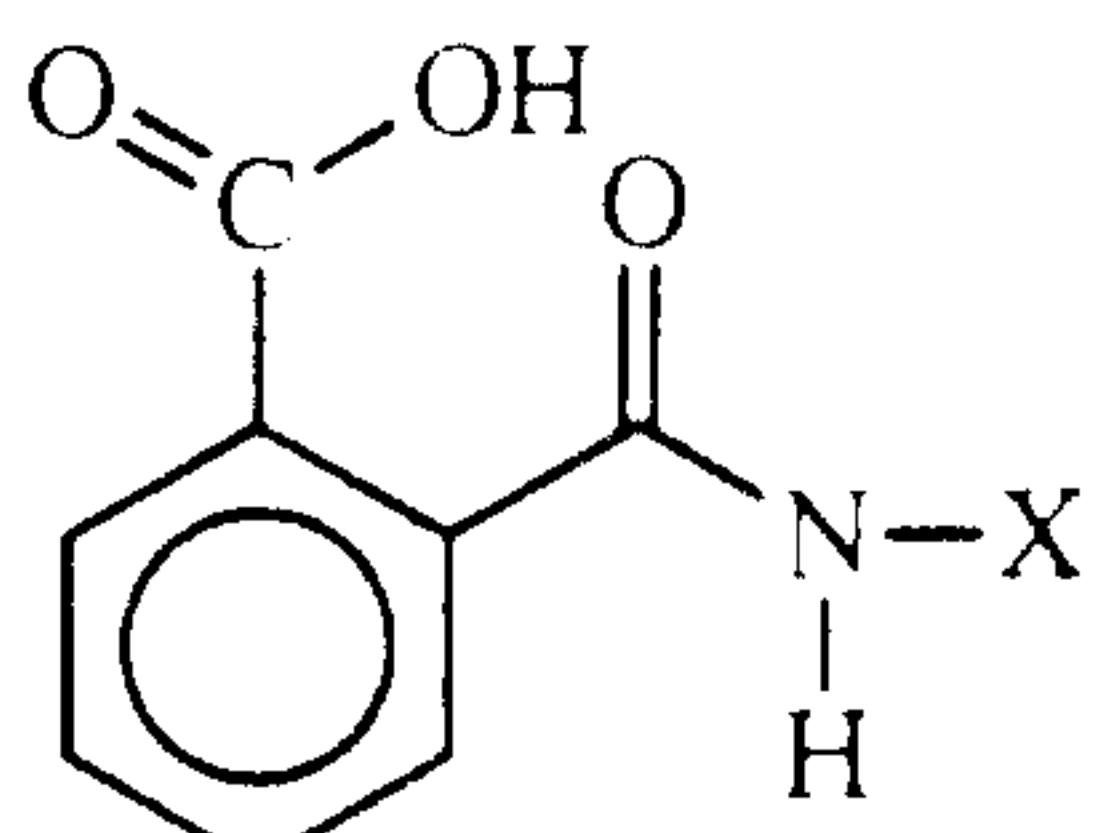


20 where R₂₂ and R₂₃ are (independently), -H, -F, -Cl, -Br, -I, -CH₃, or -CH₂-CH₃; and R₂₄ is -H, -CH₃, or -CH₂-CH₃.

25 The present invention also features inhibiting angiogenesis in a mammal by administering a compound according to the above formulae in a dosage sufficient to inhibit angiogenesis. Examples of specific compounds that are members of this genus are listed in Figure 4.

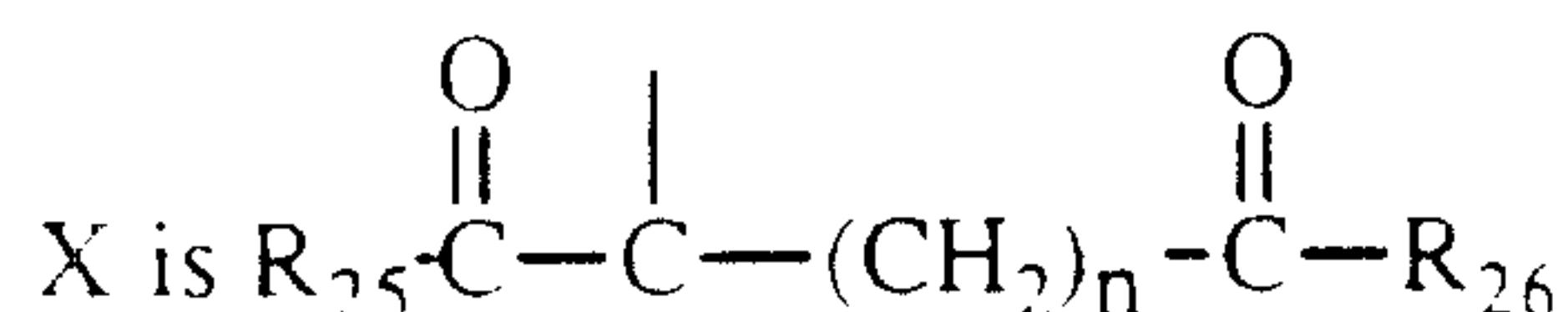
- 15 -

Angiogenesis inhibition hydrolysis products of thalidomide having the following general formula can be used in practicing the present invention:



5

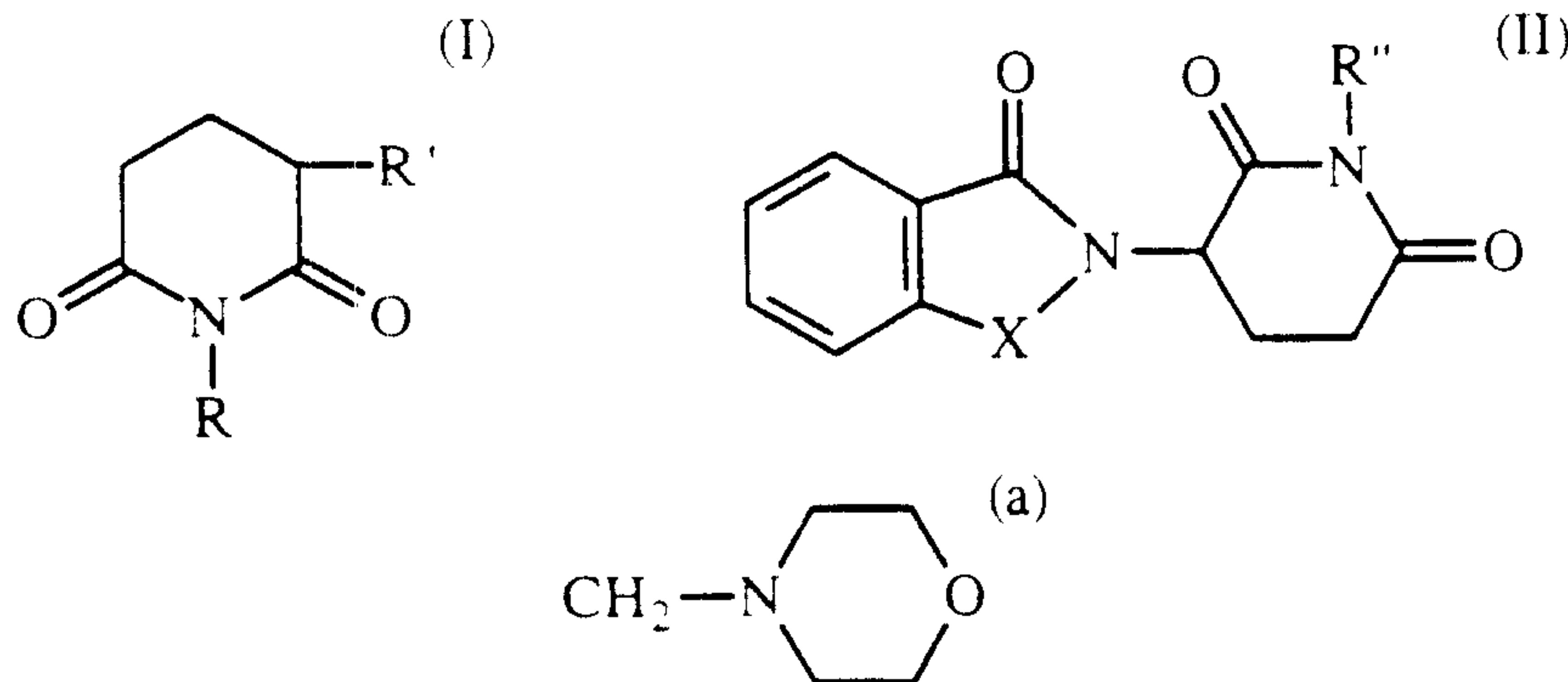
where X is R₆ as defined above, or



10 and R₂₅ and R₂₆ are, independently, -OH, -H, or NH₂, and n=1 through 4. Examples of such compounds are shown in Figure 5.

Angiogenesis inhibition compounds having the following general formula can be used in practicing the present invention:

15



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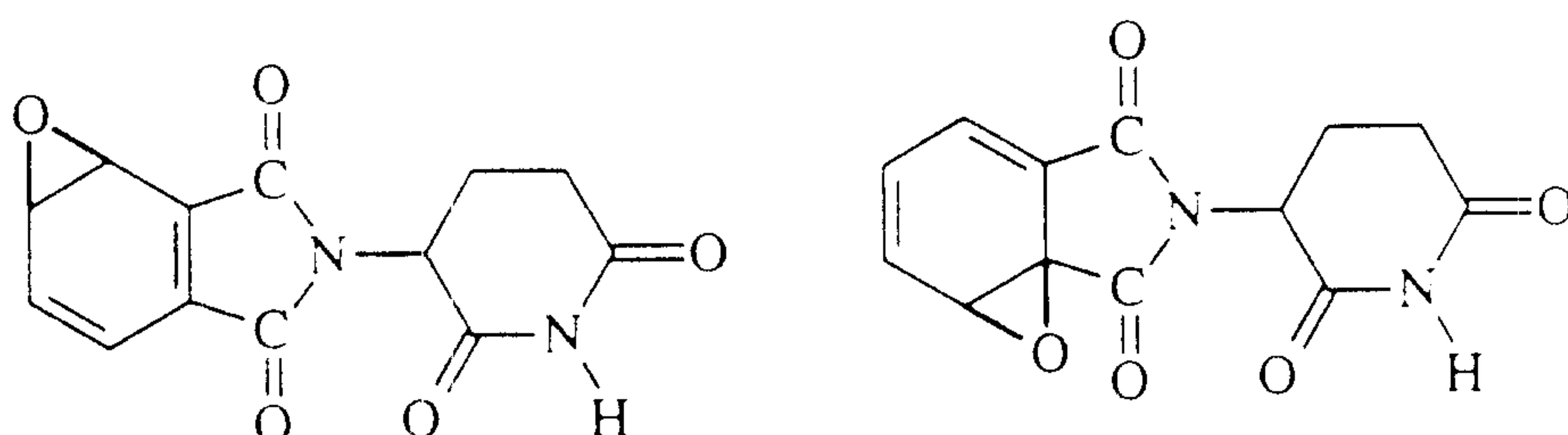
25

wherein compounds of structure (I), wherein R is selected from the group consisting of hydrogen, alkyl radicals of 1 to 6 carbon atoms, the phenyl radical, and the benzyl radical; and wherein R' is selected from the group consisting of the phthalimido radical and the succinimido radical and of structure (II), wherein X is CH₂ or C=O; R'' is H, -CH₂CH₃, -C₆H₅, -CH₂C₆H₅, -CH₂CH=CH₂, or (a) and hydrolysis products of the compounds wherein R'' is H and the piperidino ring or both the piperidino and the imido ring are hydrolyzed.

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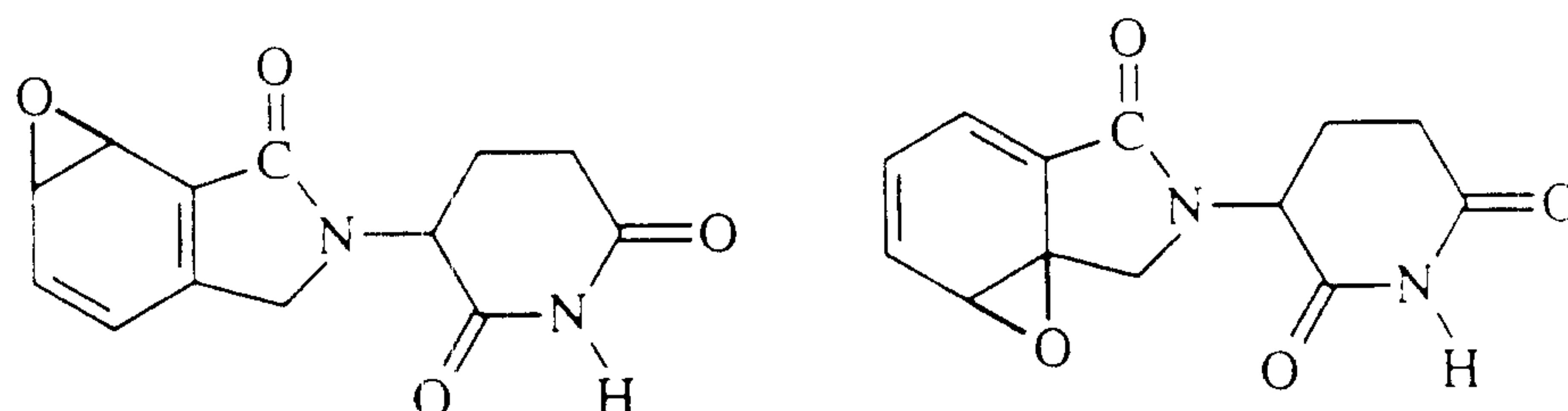
Another set of compounds that are considered part of the present invention are the epoxides of thalidomide, EM-12 and EM-138. Representative epoxide compounds are shown as follows:

5



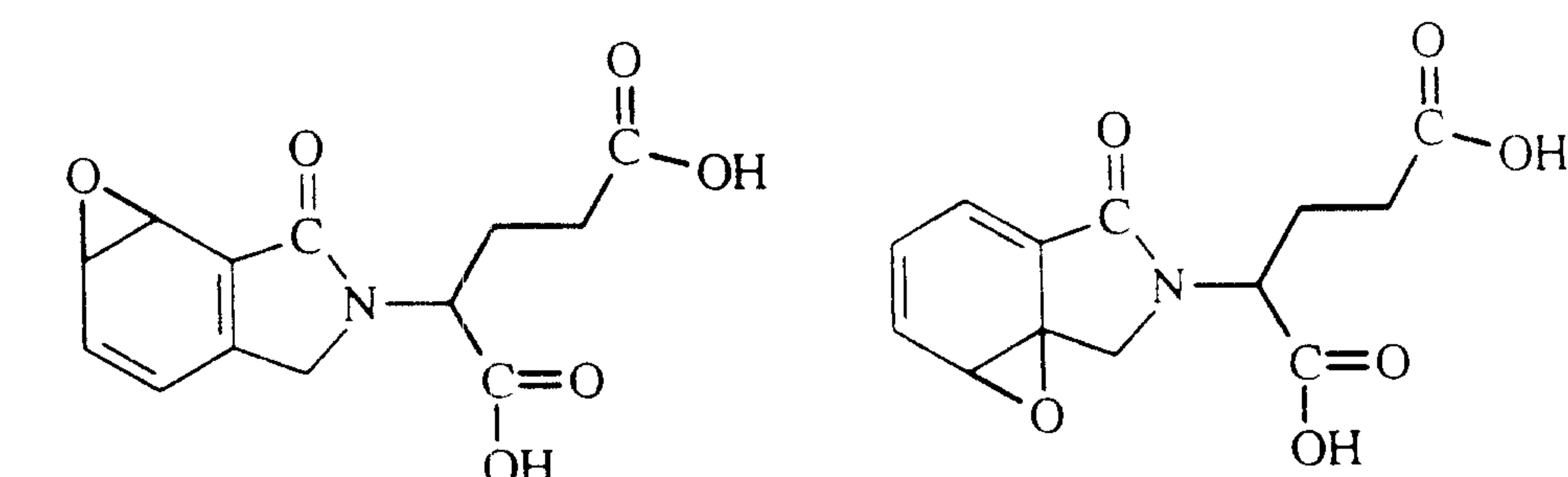
Epoxides of thalidomide

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Epoxides of EM 12

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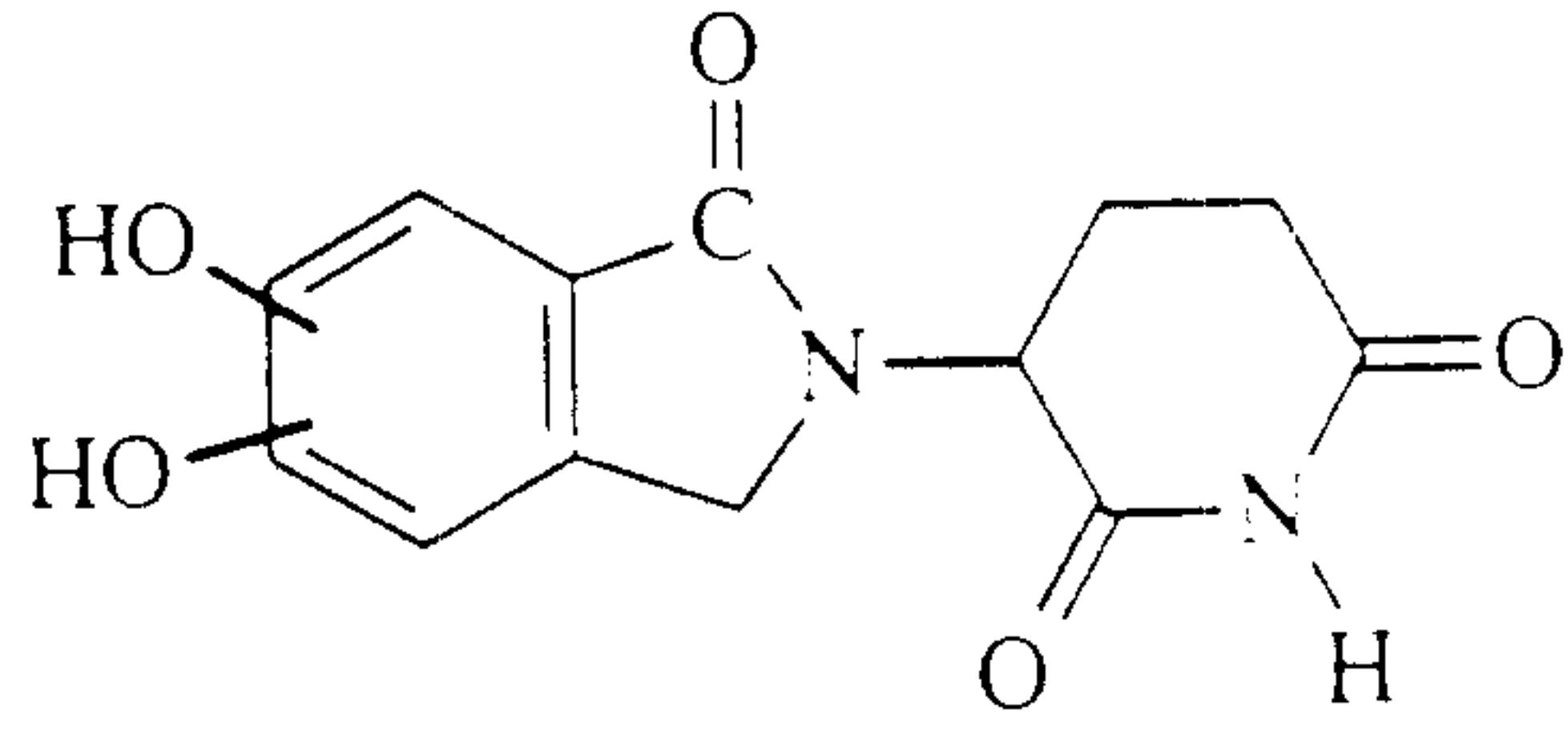
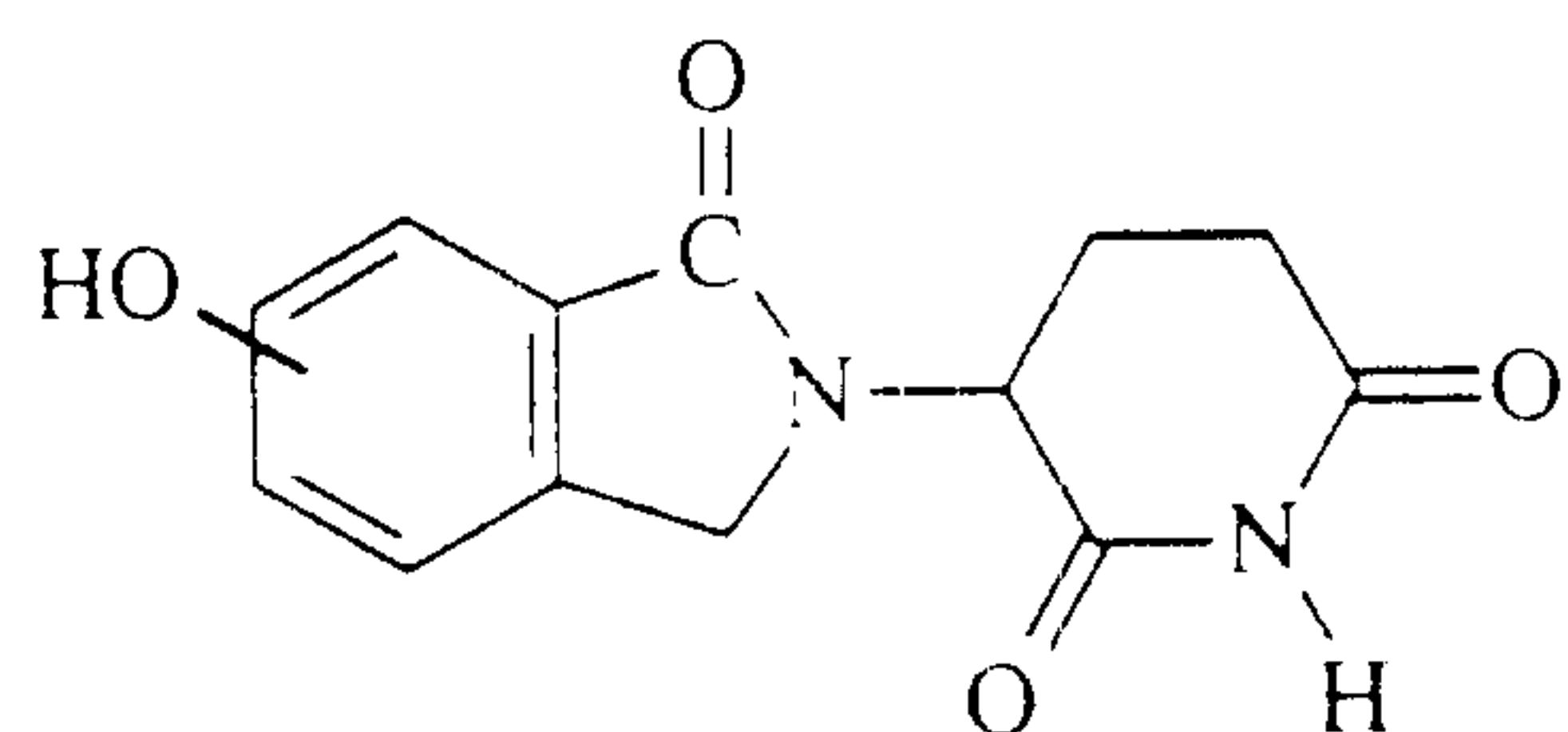
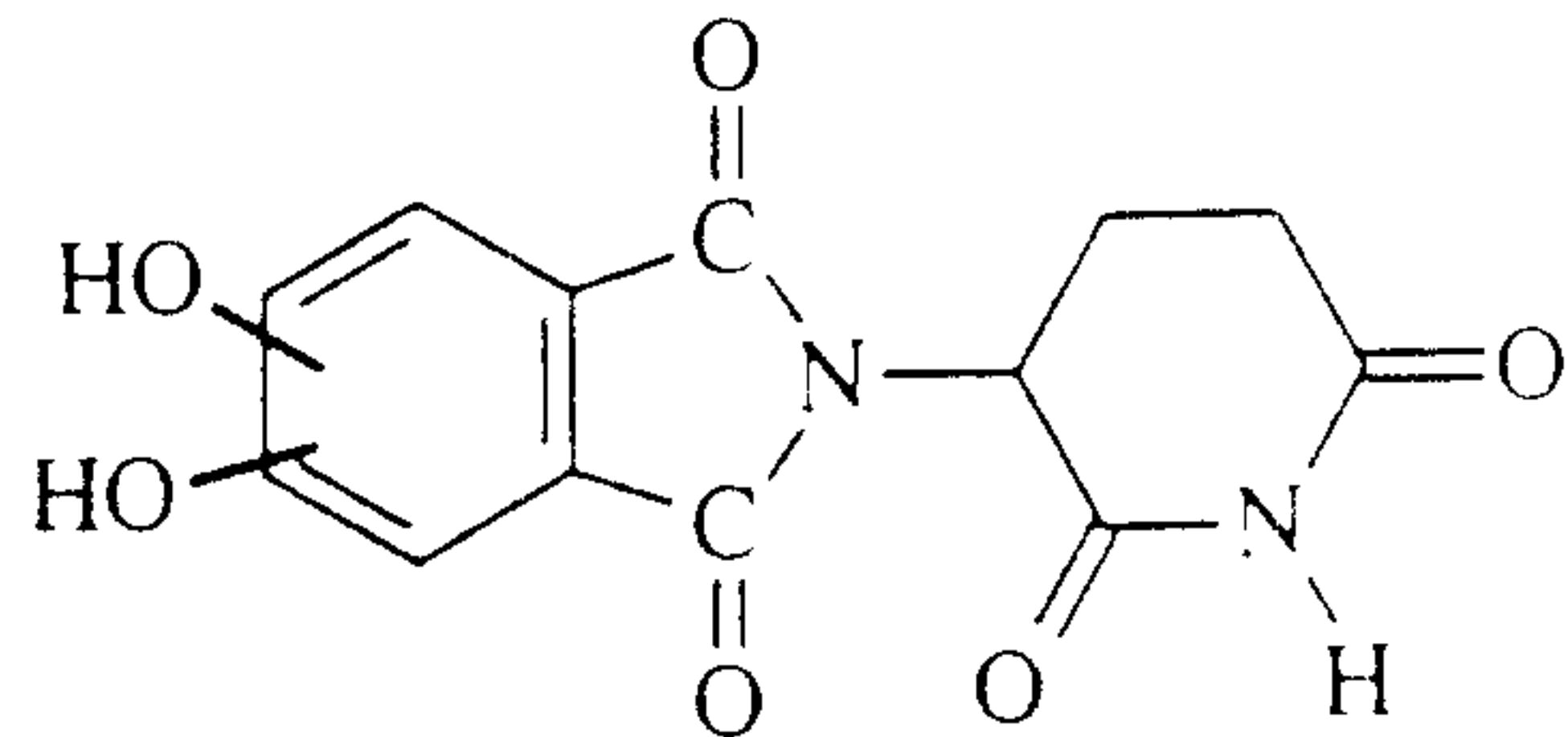
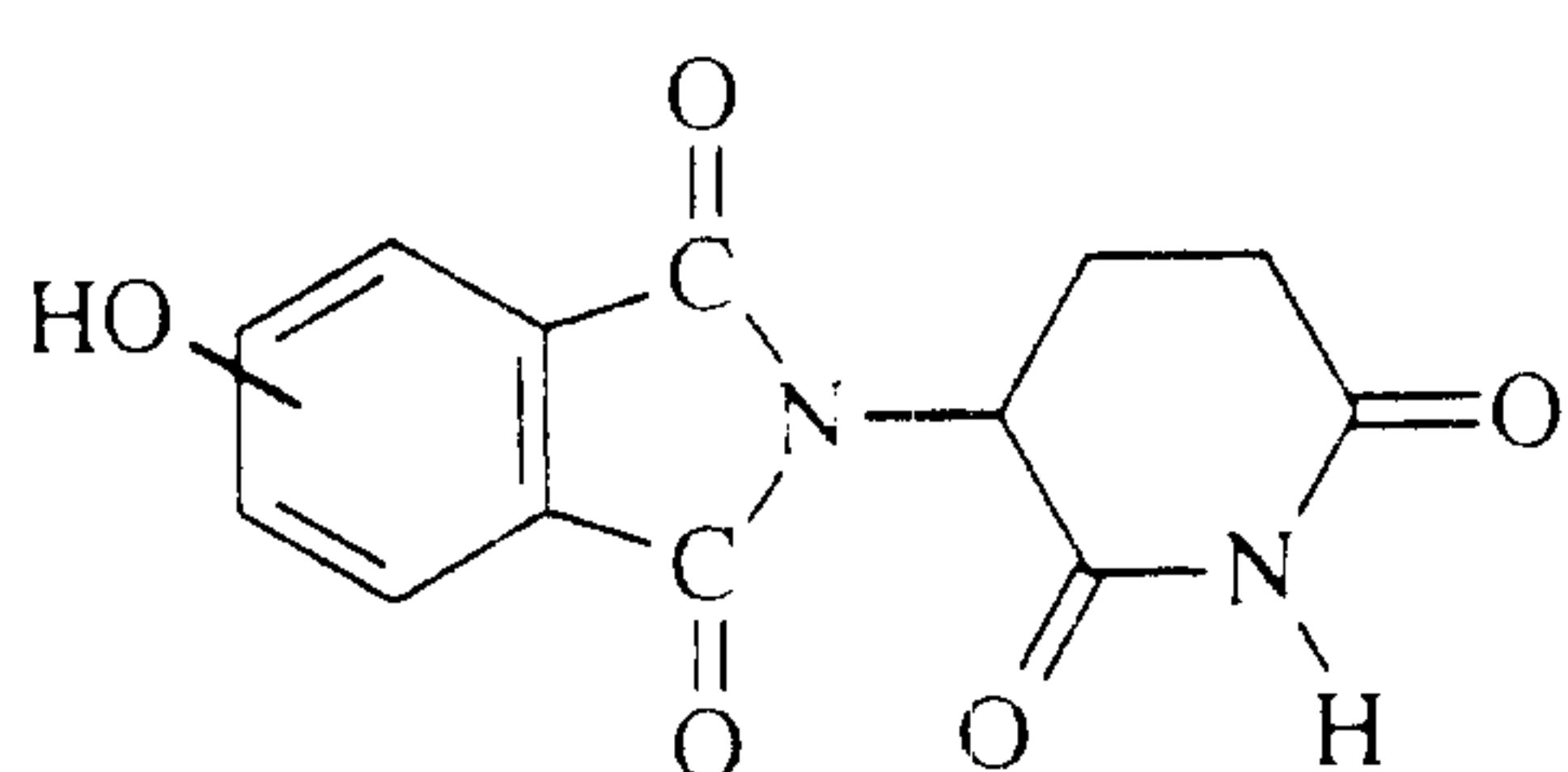
Epoxides of EM 138

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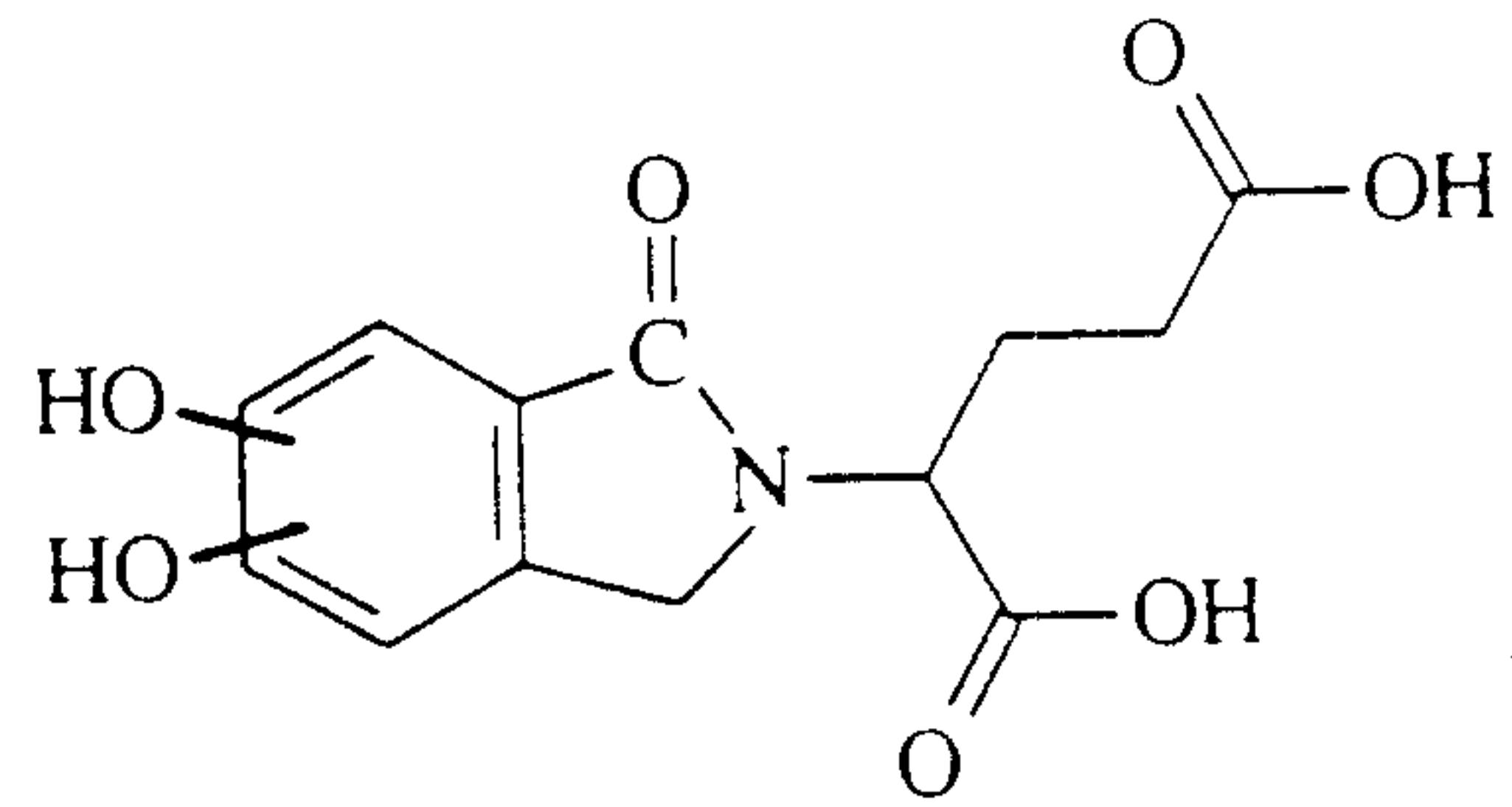
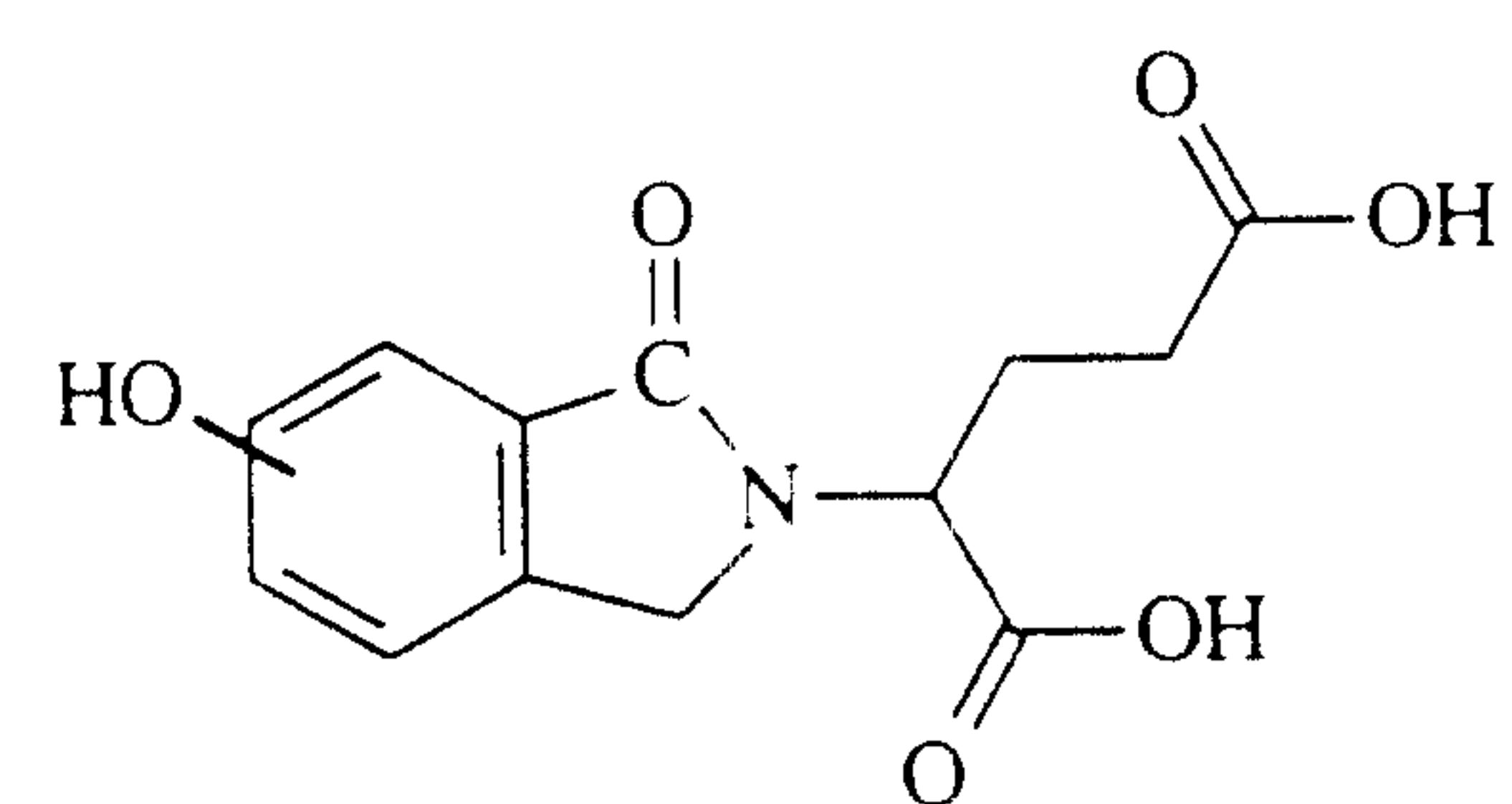
It should be understood that the epoxide can be attached at the 6,1 site on the benzene ring, the 1,2 site, the 2,3 site 3,4 or the 4,5 site. All of these compounds are contemplated as part of the present invention.

The epoxides of the thalidomide, EM-12, and EM 138 can be hydrolyzed to the following compounds:

- 17 -



5



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It is to be understood that the hydroxyl group can be on carbons 1, 2, 3, 4, 5 and 6 of the benzene ring. Also contemplated as part of the present invention are dihydroxyl compounds wherein the two hydroxyl groups are located bis to each other on carbons 1, 2, 3, 5 and 6 of the above compounds. The epoxides, the hydrolysis products of the epoxides, and the hydrolysis products of the thalidomide are all contemplated to be part of the present invention.

15

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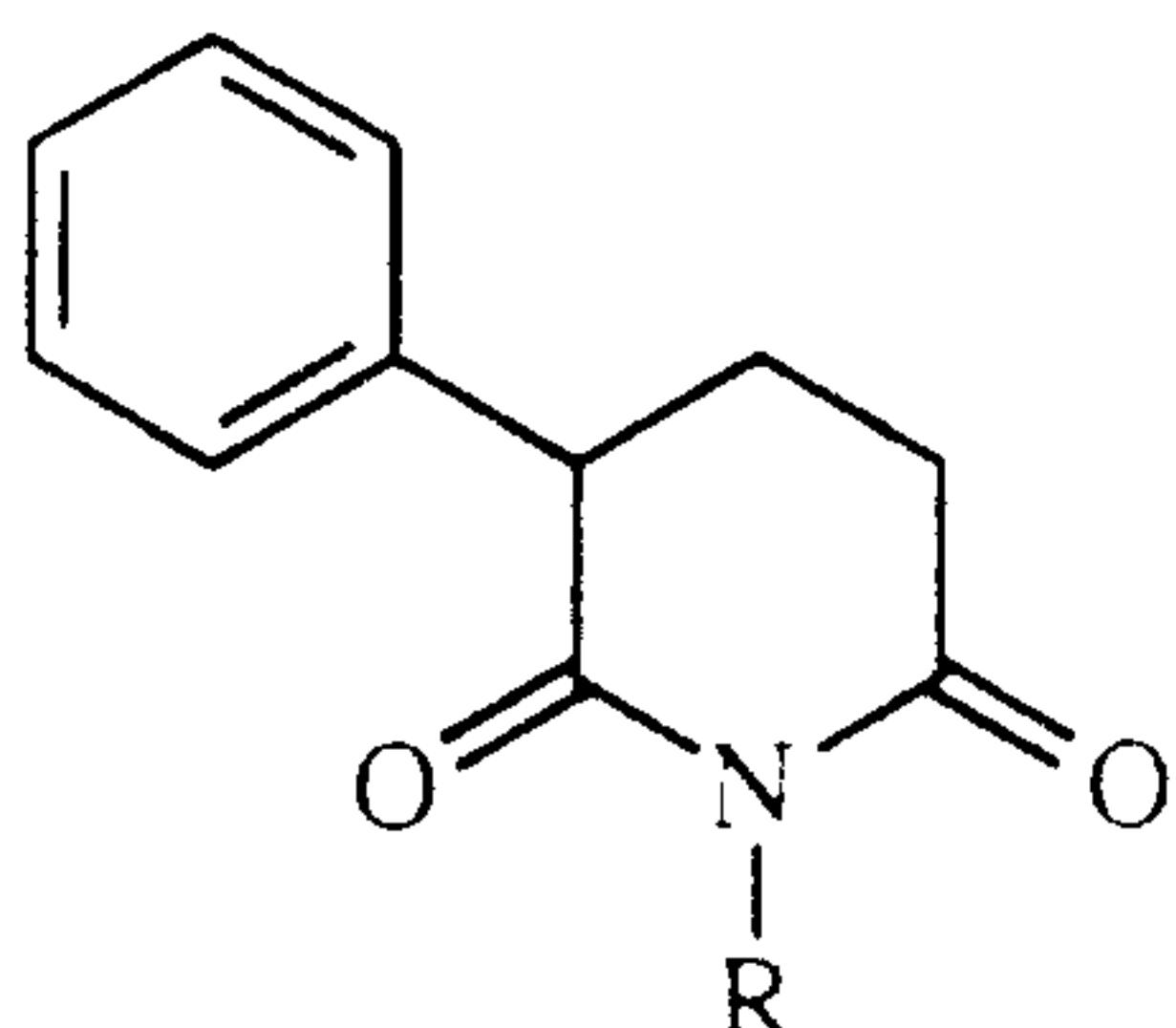
It is known that epoxides are hydrolyzed by a group of enzymes known as epoxide hydrolases. There is a class of compounds which are epoxide hydrolase inhibitors. Examples of these compounds are valpromide (2-propylpentanamide) and valproic acid (2-propylpentanoic acid). Because epoxides are

important angiogenesis inhibitors, it is contemplated as part of the present invention, compositions comprising any of the angiogenesis inhibitors compounds recited herein in combination with epoxide hydrolase inhibitors. The epoxide hydrolase inhibitors can be administered to a human or animal together or sequentially. The epoxide group appears to be an important substituent common to several angiogenesis inhibitors. The use of epoxide hydrolase inhibitors to potentiate the activity of any angiogenesis inhibitor containing an epoxide is contemplated as part of the present invention. For example, the epoxide hydrolase inhibitors can be administered with the following epoxide-containing anti-angiogenesis compounds: AGM 1470, Eponimycin, microbial metabolites of *Scleocobasidium arenarium* designated f/2015, fr/111142 and fr/18487. See Oikawa, *Biochem Biophys. Res. Comm.*, Vol. 81:1070 (1971) and Otsuka, *J. Microbial. Biotech.*, Vol 1:163 (1991).

It is contemplated as an embodiment of the present invention the use of the epoxide containing angiogenesis inhibitors with or without epoxide hydrolase inhibitors as a treatment for diseases mediated by elevated or toxic levels of TNF- α . TNF- α has been recognized as manifesting a dose dependent toxicity. If present at low levels for a long period of time, TNF- α can result in cachexia. Cachexia is a general weight loss and wasting occurring in the course of some chronic diseases such as cancer, opportunistic infections of AIDS, inflammatory diseases, parasitic diseases, tuberculosis, and high dose IL-2 therapy. The epoxide containing angiogenesis inhibitors, with or without epoxide hydrolase inhibitors, are also effective in treating diseases such as septic shock, leprosy and graft vs. host disease.

Other embodiments are within the present invention. For example, other dysmelia-causing compounds can be used according to the present invention, e.g. 4-methylphthalic acid, pyridoxine, vasopressin, acetazolamide, or a compound having the following formula (where R= H, -OH, or -CH₃):

- 19 -



Other compounds which are teratogens, such as valproic acid (2-propylpentanoic acid), the retinoids, such as cis-retinoic acid, and rifampin may also be used in accordance with the invention.

5 In summary, the preferred compounds are thalidomide, as well as analogs, hydrolysis products, metabolites and precursors of thalidomide that are teratogenic, and, more specifically, that cause dysmelia. However, it is to be understood that it is not necessary for a compound to have both teratogenic activity and angiogenesis inhibiting activity to be considered part of the present invention. Dysmelia-causing compounds can be identified by the general procedures of Helm, *Arzneimittelforschung*, 31(i/6):941-949 (1981), in which rabbit pups are examined after exposure to the compound in utero. The 10 compounds can generally be purchased, e.g., from Andrus Pharmaceuticals, Beltsville, MD, or synthesized according to known procedures. It is to be understood that the compounds of the present invention can exist as enantiomers and that the 15 racemic mixture of enantiomers or the isolated enantiomers are all considered as within the scope of the present invention.

20 Many of the compounds that are contemplated as part of the present invention can be enriched in optically active enantiomers of the compounds specified above. Specifically, Blaschke has reported that the S enantiomers may be disproportionately responsible for the dysmelia-producing effect of these compounds. See, generally Blaschke, *Arzneimittelforschung* 29:1640-1642 (1979). The above 25 described articles generally describe procedures to obtain optically active preparations of the compounds of interest. See, e.g. Shealy et al., *Chem. Indus.* 1030 (1965); and Casini et al., 30

- 20 -

Farmaco Ed. Sci. 19:563 (1964).

The compounds described above can be provided as pharmaceutically acceptable formulations using formulation methods known to those of ordinary skill in the art. These formulations can be administered by standard routes. In general, the combinations may be administered by the topical, transdermal, oral, rectal or parenteral (e.g., intravenous, subcutaneous or intramuscular) route. In addition, the combinations may be incorporated into biodegradable polymers allowing for sustained release of the compound, the polymers being implanted in the vicinity of where drug delivery is desired, for example, at the site of a tumor. The biodegradable polymers and their use are described, for example, in detail in Brem et al., *J. Neurosurg.* 74:441-446 (1991).

The dosage of the compound will depend on the condition being treated, the particular compound, and other clinical factors such as weight and condition of the human or animal and the route of administration of the compound. It is to be understood that the present invention has application for both human and veterinary use. For oral administration to humans, a dosage of between approximately 0.1 to 300 mg/kg/day, preferably between approximately 0.5 and 50 mg/kg/day, and most preferably between approximately 1 to 10 mg/kg/day, is generally sufficient.

The formulations include those suitable for oral, rectal, ophthalmic, (including intravitreal or intracameral) nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal, and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into associate the active ingredient with liquid

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carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as 5 capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, etc.

10 A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, 15 preservative, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally coated or scored and may be formulated so as to provide a slow or controlled release of the active 20 ingredient therein.

Formulations suitable for topical administration in the mouth include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising 25 the ingredient to be administered in a suitable liquid carrier.

Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered in a pharmaceutical acceptable carrier. A preferred topical delivery system is a 30 transdermal patch containing the ingredient to be administered.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

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5 Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of 20 to 500 microns which is administered in the manner in which snuff is administered, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations, wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

10 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

15 Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The 20 formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) conditions requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection 25 solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

30 Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the administered ingredient.

It should be understood that in addition to the ingredients, particularly mentioned above, the formulations of the present invention may include other agents conventional in the art having regard to the type of formulation in question, for

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example, those suitable for oral administration may include flavoring agents.

Diseases associated with corneal neovascularization that can be treated according to the present invention include but are not limited to, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrobulbar fibroplasia, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phlyctenulosis, syphilis, *Mycobacteria* infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex* infections, *Herpes zoster* infections, protozoan infections, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis, systemic lupus, polyarteritis, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, and corneal graft rejection.

Diseases associated with retinal/choroidal neovascularization that can be treated according to the present invention include, but are not limited to, diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosus, retinopathy of prematurity, Eales disease, Bechets disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Bests disease, myopia, optic pits, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications. Other diseases include, but are not limited to, diseases associated with rubeosis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, whether or not associated with diabetes.

- 24 -

Another disease which can be treated according to the present invention is rheumatoid arthritis. It is believed that the blood vessels in the synovial lining of the joints undergo angiogenesis. In addition to forming new vascular networks, the endothelial cells release factors and reactive oxygen species that lead to pannus growth and cartilage destruction. The factors involved in angiogenesis may actively contribute to, and help maintain, the chronically inflamed state of rheumatoid arthritis.

Another disease that can be treated according to the present invention are hemangiomas, Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, solid or blood borne tumors and acquired immune deficiency syndrome.

This invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims.

Example I

The chick embryo chorioallantoic membrane assay described by Crum et al., *Science* 230:1375 et seq. (1985), is used to identify compounds that do not require further metabolic conversion. See also, U.S. Patent 5,001,116, hereby incorporated by reference, which describes the CAM assay at col. 7 of the patent. Briefly, fertilized chick embryos are removed from their shell on day 3 or 4, and a methylcellulose disc containing the compound is implanted on the chorioallantoic membrane. The embryos are examined 48 hours later and, if a clear avascular zone appears around the methylcellulose disc, the diameter of that zone is measured.

- 25 -

Example II

Rabbit cornea angiogenesis assay

Pellets for implantation into rabbit corneas were made by mixing 110 μ l of saline containing 12 μ g of recombinant bFGF (Takeda Pharmaceuticals-Japan) with 40 mg of sucralfate (Bukh Meditec-Denmark); this suspension was added to 80 μ l of 12% hydron (Interferon Sciences) in ethanol. 10 μ l aliquots of this mixture was then pipetted onto teflon pegs and allowed to dry producing approximately 17 pellets. A pellet was implanted into corneal micropockets of each eye of an anesthetized female New Zealand white rabbit, 2mm from the limbus followed by topical application of erythromycin ointment onto the surface of the cornea. The animals were fed daily from 2 days post-implantation by gastric lavage with either drug suspended in 0.5% carboxymethyl cellulose or 0.5% carboxymethyl cellulose alone. Thalidomide was purchased from Andrulus Pharmaceutical (Maryland) and the EM-12 and Supidimide were kindly provided by Grunenthal GMBH (Germany). The animals were examined with a slit lamp every other day in a masked manner by the same corneal specialist. The area of corneal neovascularization was determined by measuring with a reticule the vessel length (L) from the limbus and the number of clock hours (C) of limbus involved. A formula was used to determine the area of a circular band segment: $C/12 * 3.1416 [r^2 - (r-L)^2]$ where r=6 mm the measured radius of the rabbit cornea. Various mathematical models were utilized to determine the amount of vascularized cornea and this formula was found to provide the most accurate approximation of the area of the band of neovascularization that grows towards the pellet.

It is important to note that the rabbit cornea assay is preferable because it will generally recognize compounds that are inactive *per se* but are metabolized to yield active compounds. Thalidomide related compounds, as shown below in Example III, are known to be teratogens and are candidates for use in the present invention.

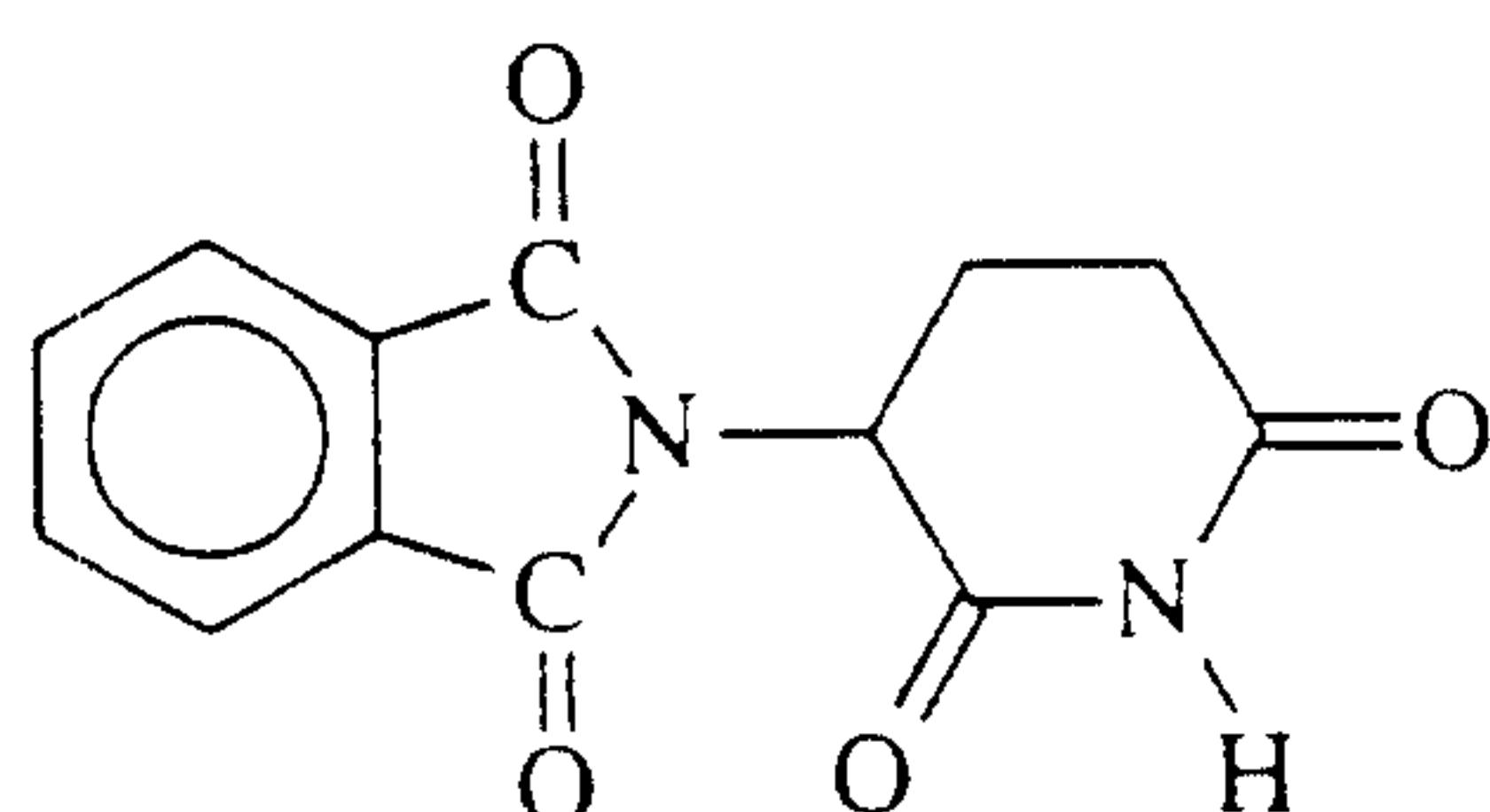
- 26 -

Example III

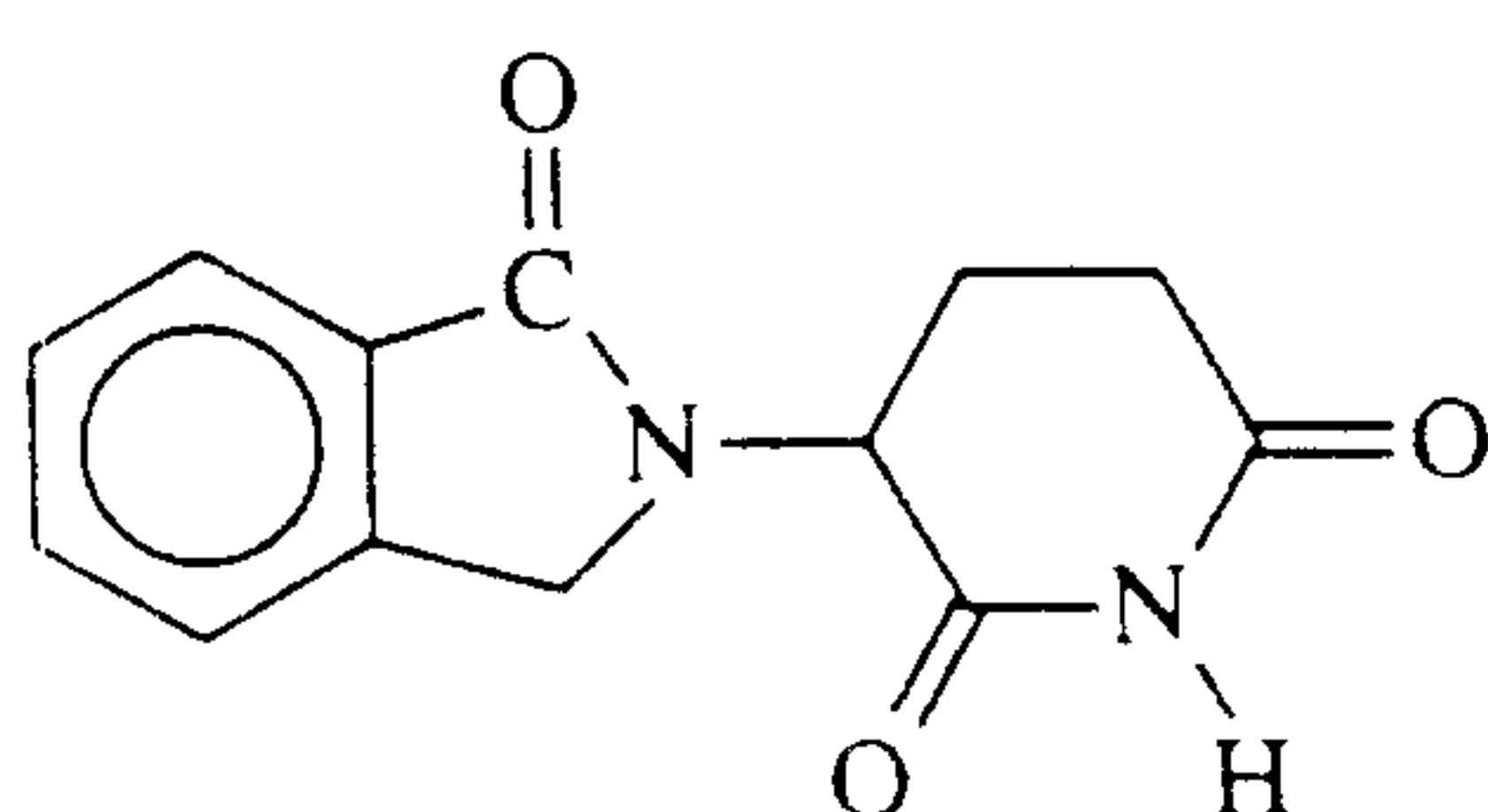
Inhibition of bFGF induced corneal neovascularization by thalidomide and related analog expressed as percent of median control on day 8

5 Pellets containing bFGF and sucralfate were implanted into micropockets of both corneas of rabbits according to Example II. Vessel ingrowth into clear cornea from the limbus was first noted on day 2 and treatments (200 mg/kg orally) were begun on this day. The area of corneal neovascularization was measured from day 4 through day 12. Day 8 measurements were 10 used for comparison between groups. No regression of vessels and near maximal neovascularization was seen at this time point. Statistical analysis was performed with ANOVA with ranked data 15 to account for interexperimental variation and to guard against a non-normal distribution of data (i.e. outliers) by utilizing a nonparametric method.

The compounds tested were as follows:

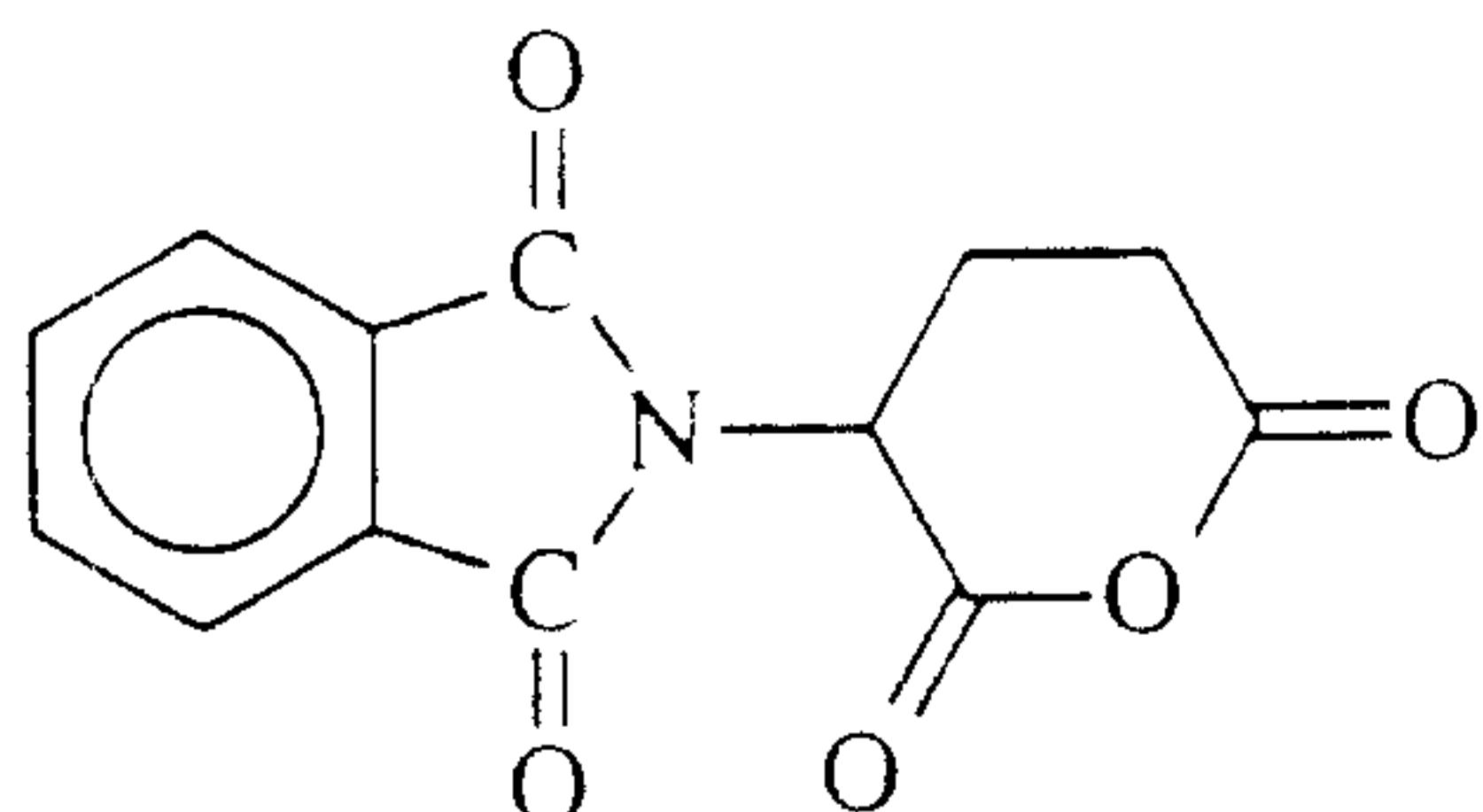


20 thalidomide

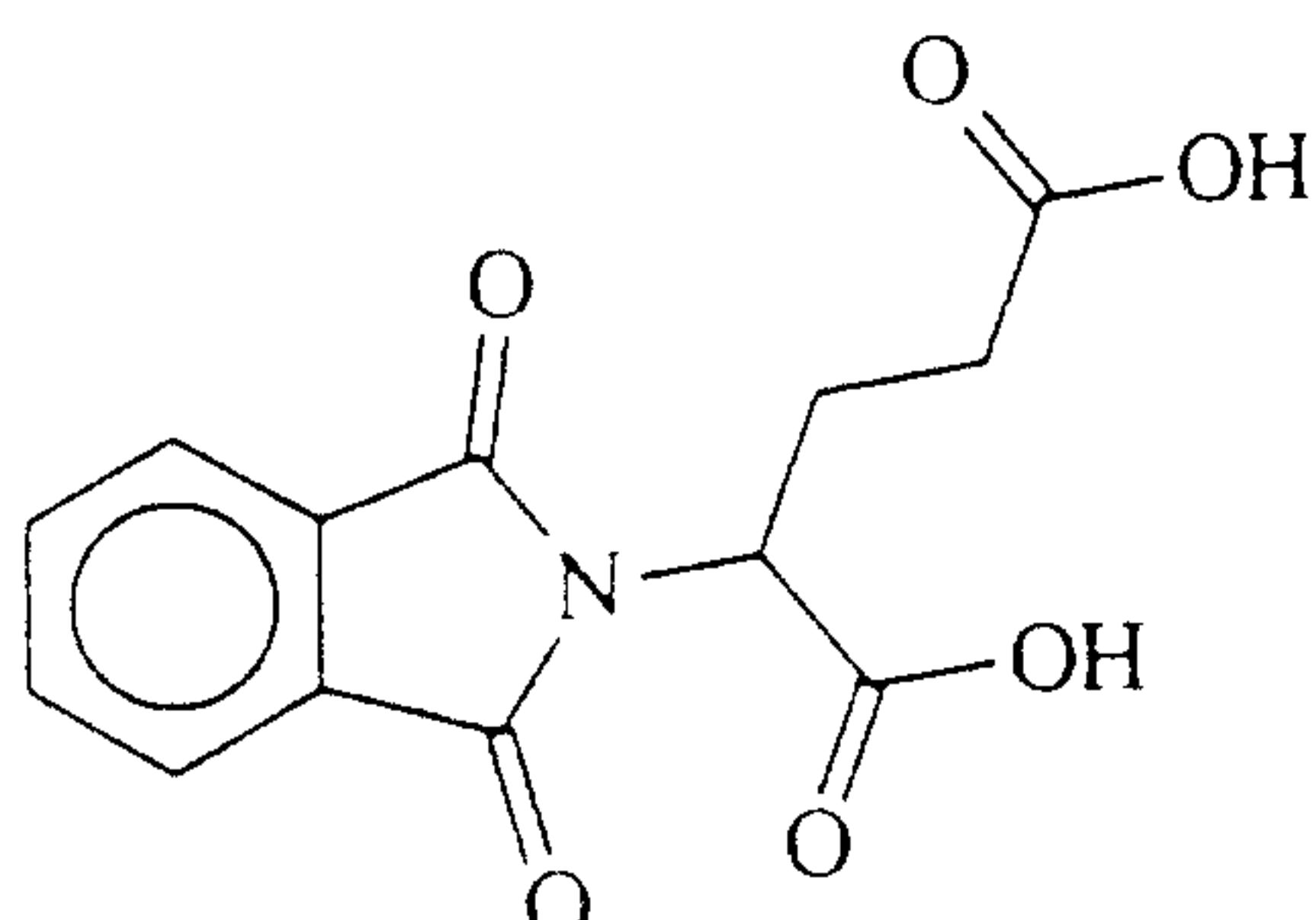


EM-12

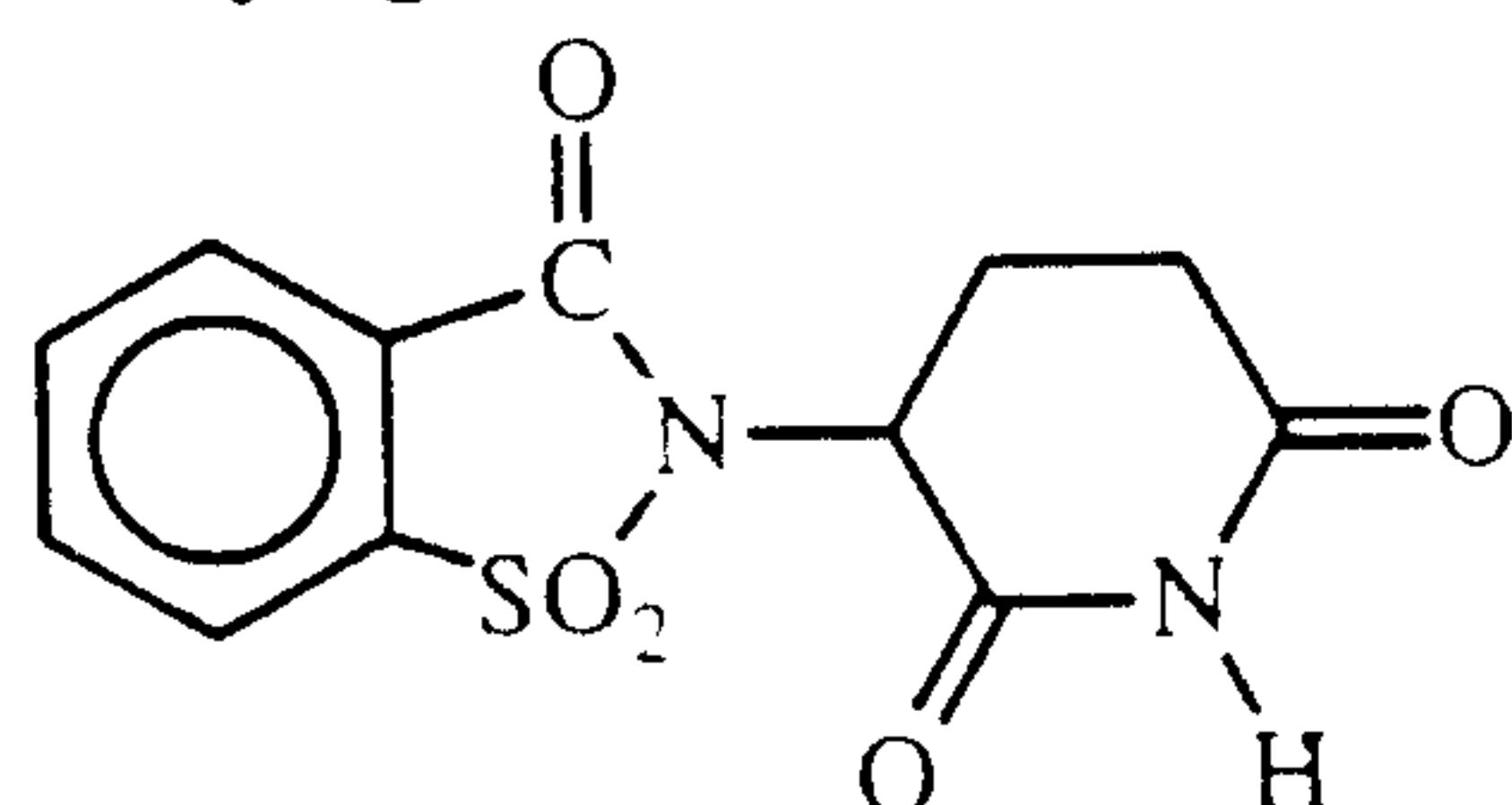
- 27 -



phthaloyl glutamic anhydride (PGA)



5 phthaloyl glutamic acid (PG Acid)



supidimide.

Treatment with a dose of (200 mg/kg) of thalidomide resulted in an inhibition of the area of vascularized cornea that ranged from 30-51% in three experiments with a median inhibition of 36% (Figure 6) (n=30 eyes, p=0.0001. 2 way ANOVA with ranked data). The inhibition of angiogenesis by thalidomide was seen after only two doses (Figure 7). The rabbits did not demonstrate obvious sedation and there were no signs of toxicity or weight loss. The teratogenic analog EM-12, which shares the other properties of thalidomide was also inhibitory, with a median inhibition of 42% (n=10 eyes, p=0.002. 1-way ANOVA with ranked data). Supidimide, a nonteratogenic analog of thalidomide that retains the sedative properties of thalidomide, exhibited no activity (area 107% of control, n=10 eyes, not statistically different from control). Other analogs, PGA and PG acid displayed weaker inhibitory effects than thalidomide (data

- 28 -

not shown). The density of vessel ingrowth in thalidomide-treated animals was also markedly reduced.

Example IV

5 *EM-12 in rabbit cornea assay*

EM-12 was tested in the rabbit cornea assay described in Example II at 100 mg/kg/day and showed 21% inhibition, and at 200mg/kg/day the assay showed 43% inhibition.

10

Example V

Phthaloyl glutamic acid in CAM

Phthaloyl glutamic acid was tested in the above described CAM assay and exhibit an avascular zone with a mild scar.

15

Example VI

Phthaloyl glutamic acid in rabbit cornea assay

Phthaloyl glutamic acid described above at 200 mg/kg and exhibited 29% inhibition of angiogenesis.

20

Example VII

Phthaloyl glutamic anhydride in CAM assay

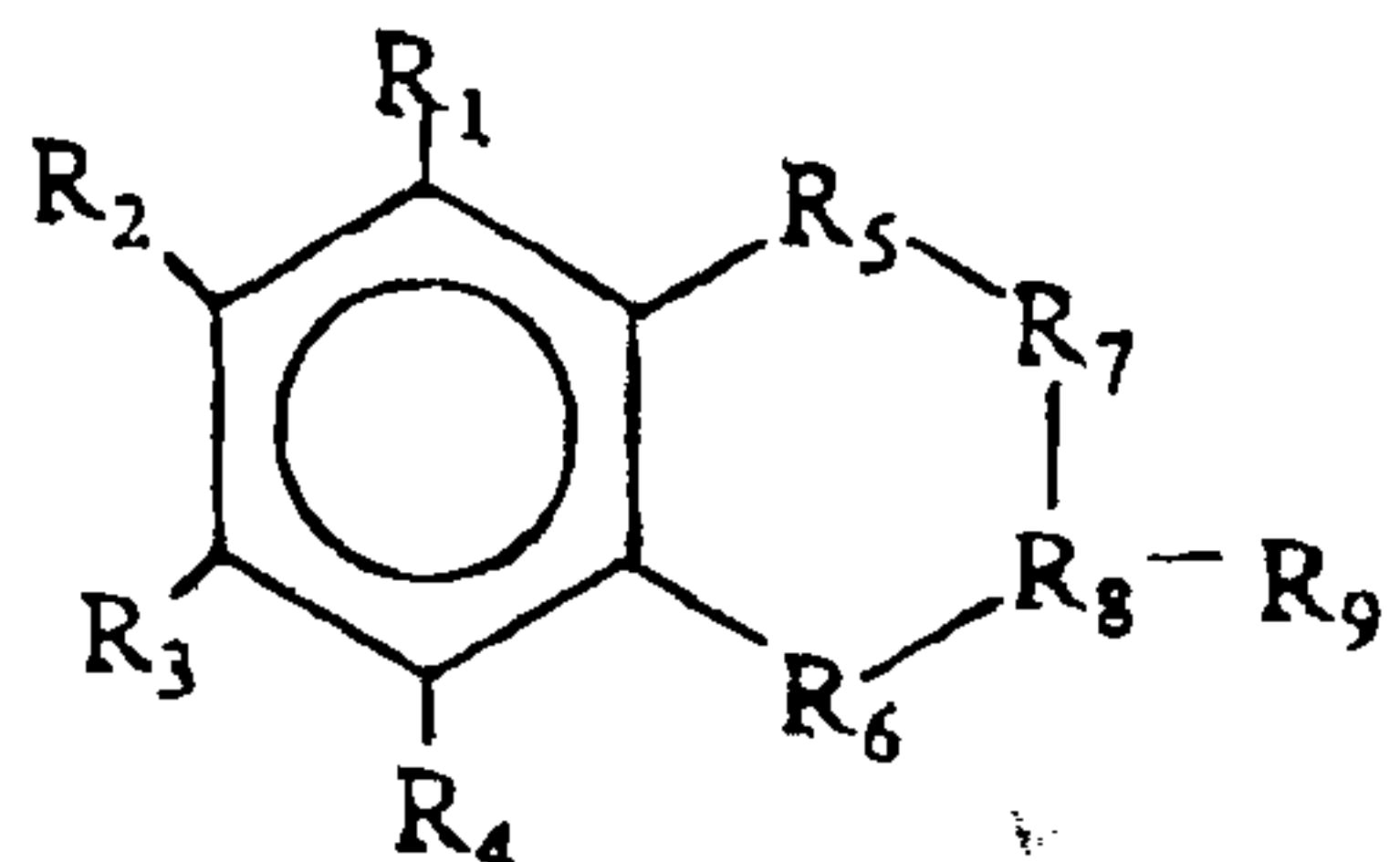
Phthaloyl glutamic anhydride was test in the CAM assay described above and exhibited an avascular zone.

25 It should be understood, of course, that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the invention as set forth in the appended claims.

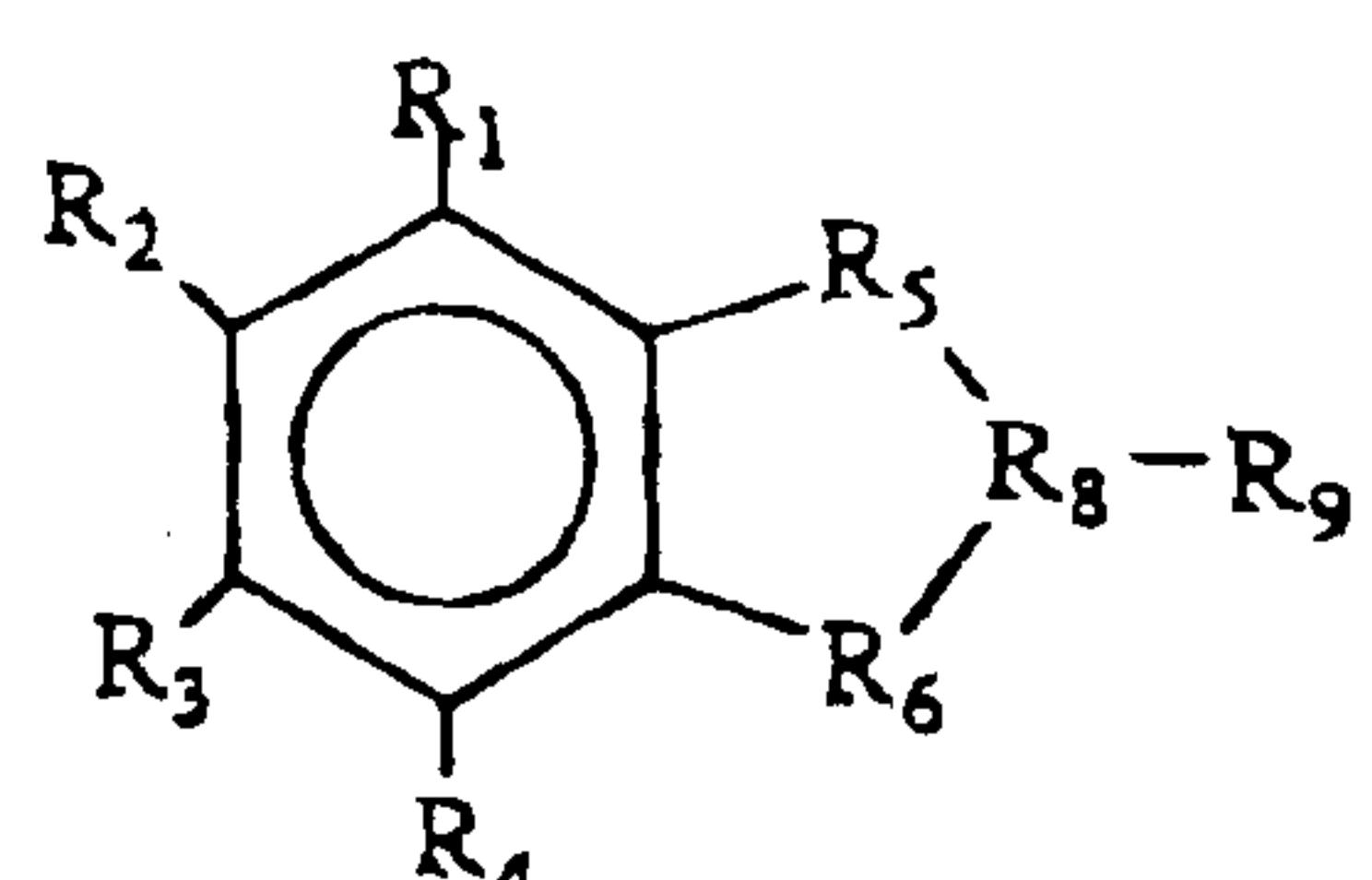
WHAT IS CLAIMED IS:

1. The use of a composition administered for treating undesired angiogenesis in a human or animal wherein the composition comprises an effective amount of an angiogenesis-inhibiting compound selected from the group consisting of the following compounds:

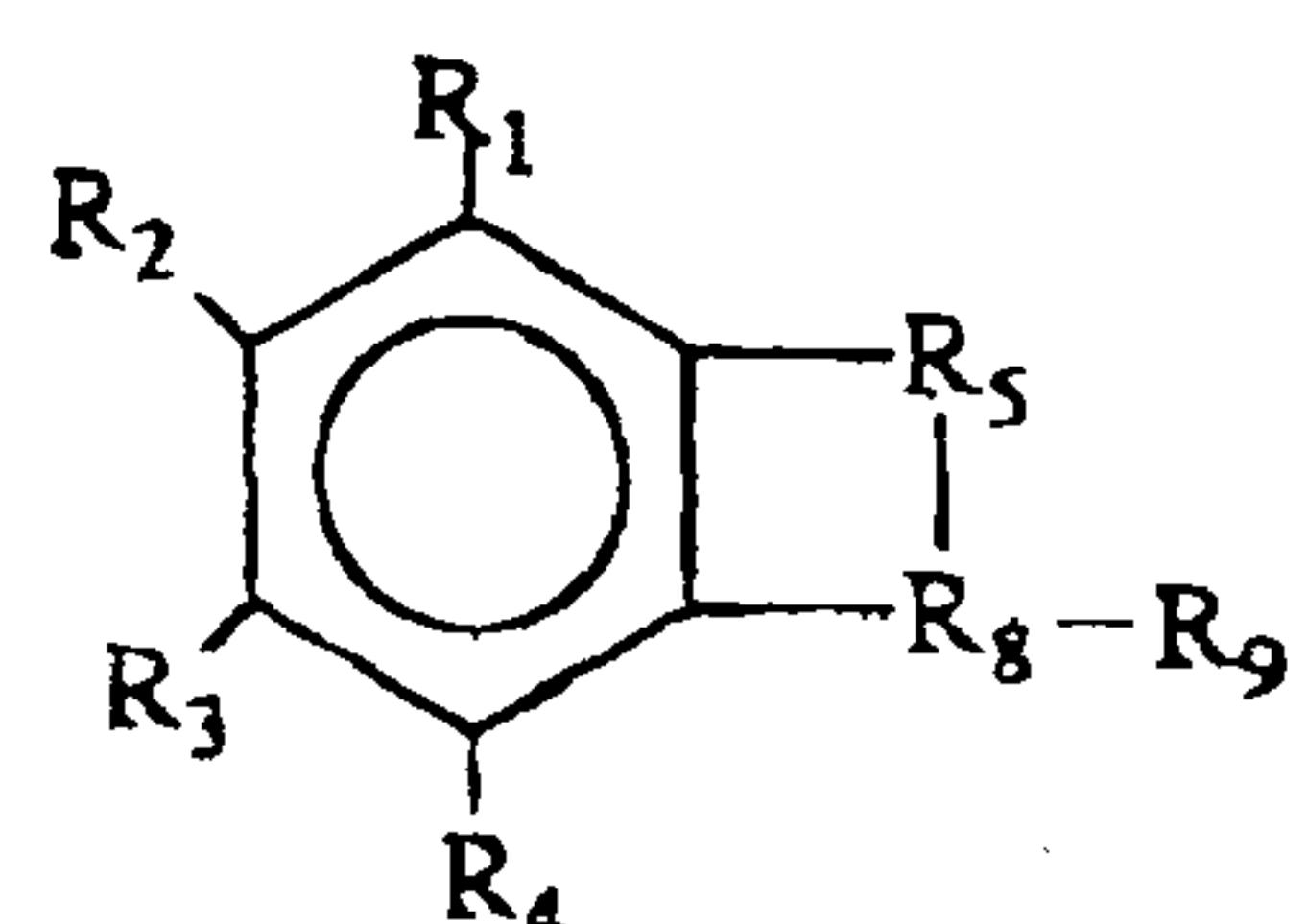
A)



B)

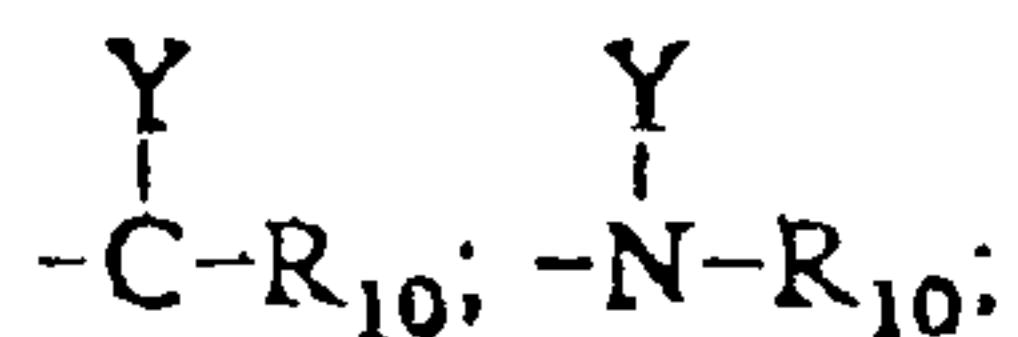


C)



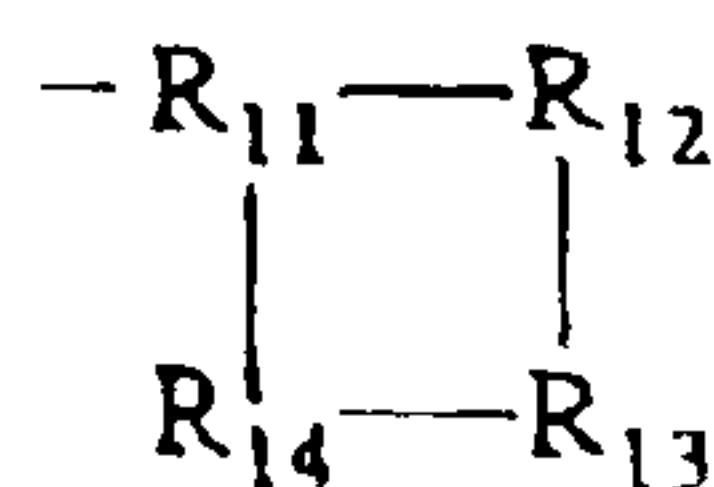
wherein R₁, R₂, R₃, and R₄ can be selected from: -H; -OH; =O, straight chained and branched alkanes, alkenes, alkynes; cyclic alkanes, alkenes and alkynes; combinations of cyclic and acyclic alkanes, alkenes and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -XO_n or -O-XO_n, (where X=N and n=2; X=S and n=2 or 3; or

$X=P$ and $n=1-3$); and halogens; R_5 , R_6 , R_7 , and R_8 are each independently selected from:

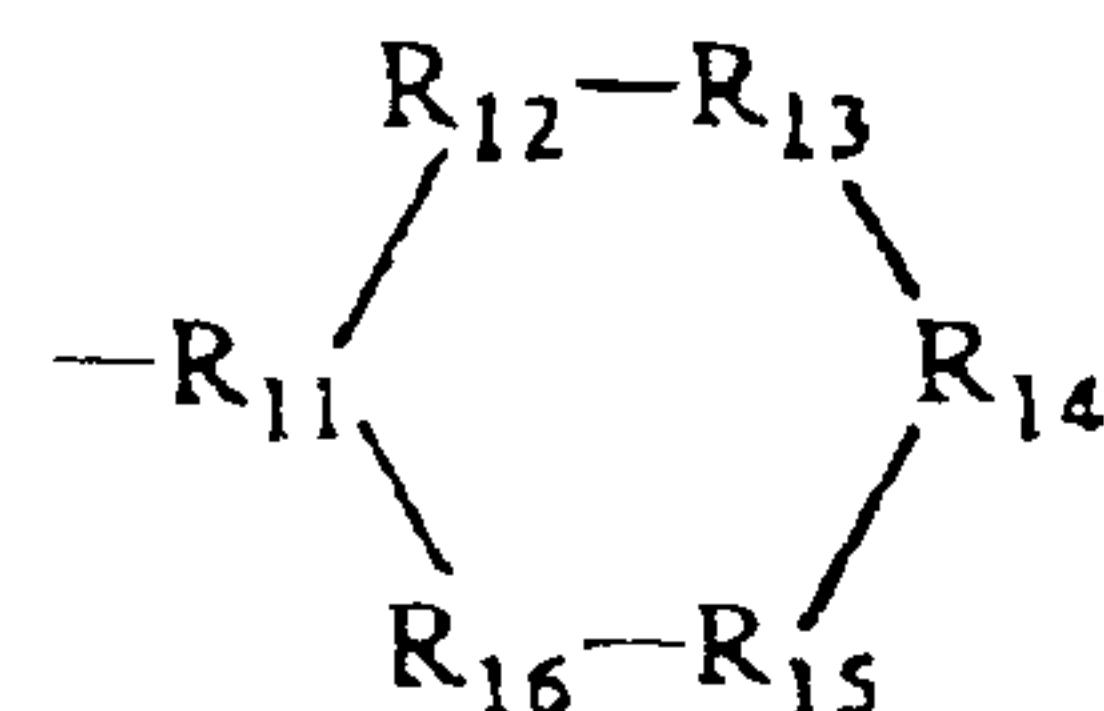


or $-O-$ where Y is optional and is the same as defined above for R_1 ; and R_{10} is the same as defined above for R_1 , or (where Y is absent) R_{10} is $=O$; and R_9 is a moiety having formula D), E), F), G) or H):

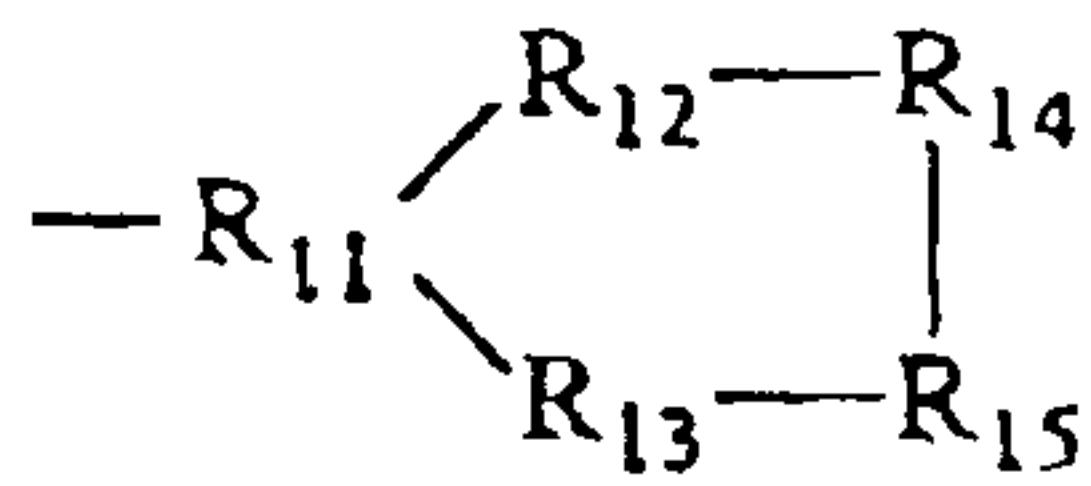
D)



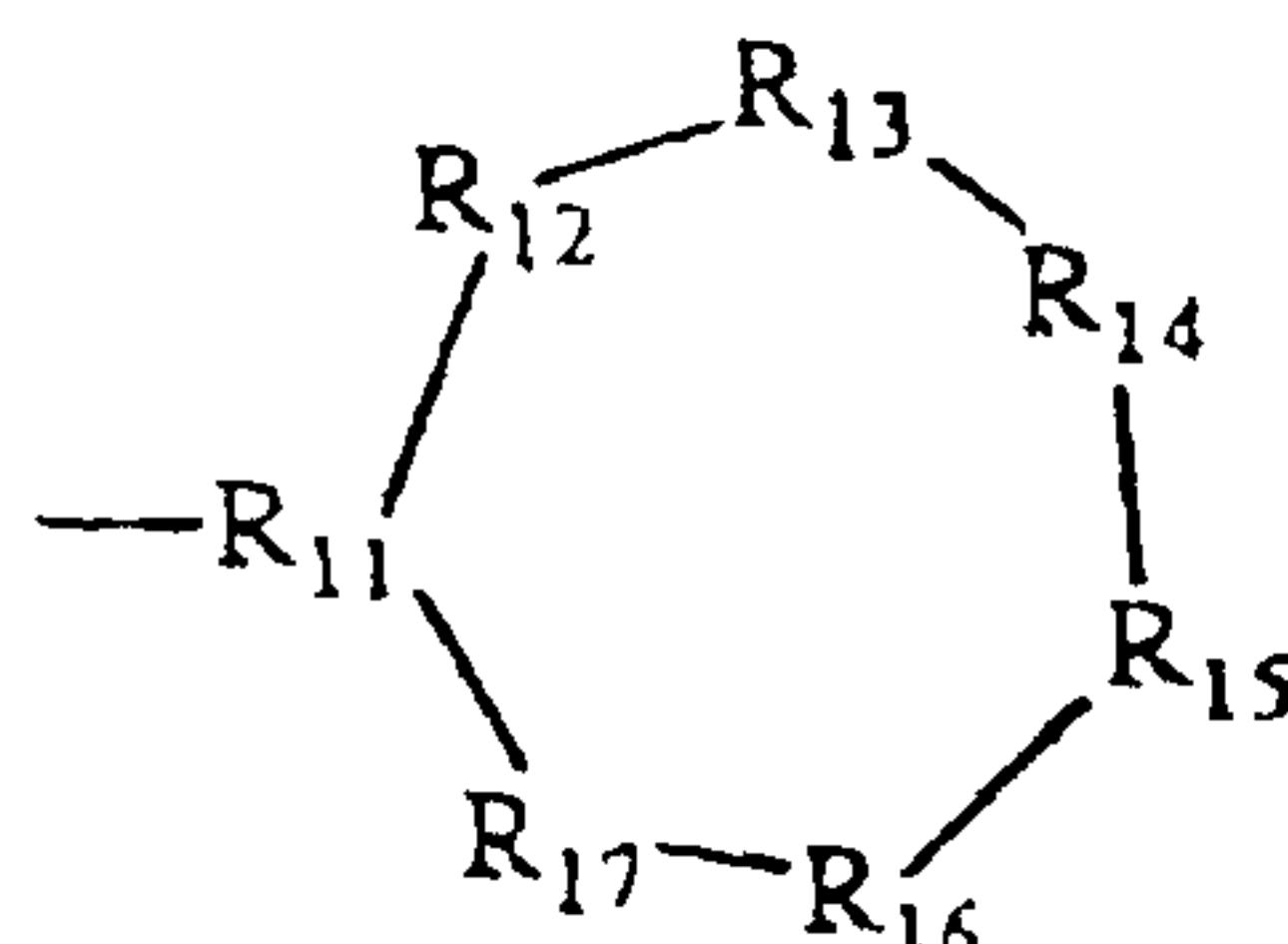
F)



E)

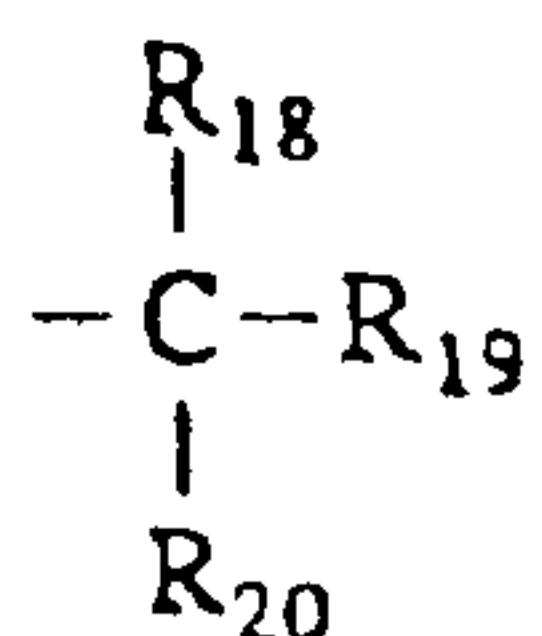


G)

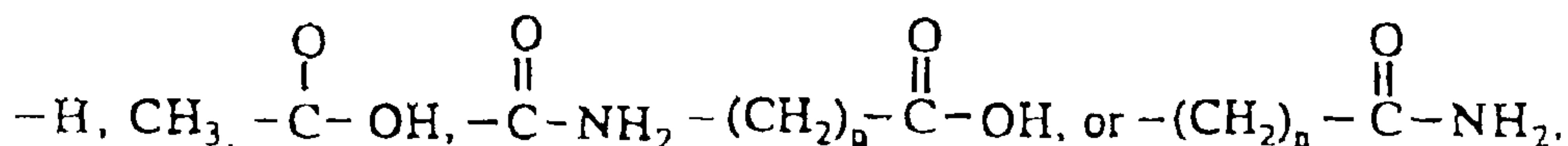


where each of R_{11} - R_{17} is (independently) the same as defined above for R_5 :

H)



where R_{18} , R_{19} and R_{20} are, independently selected from

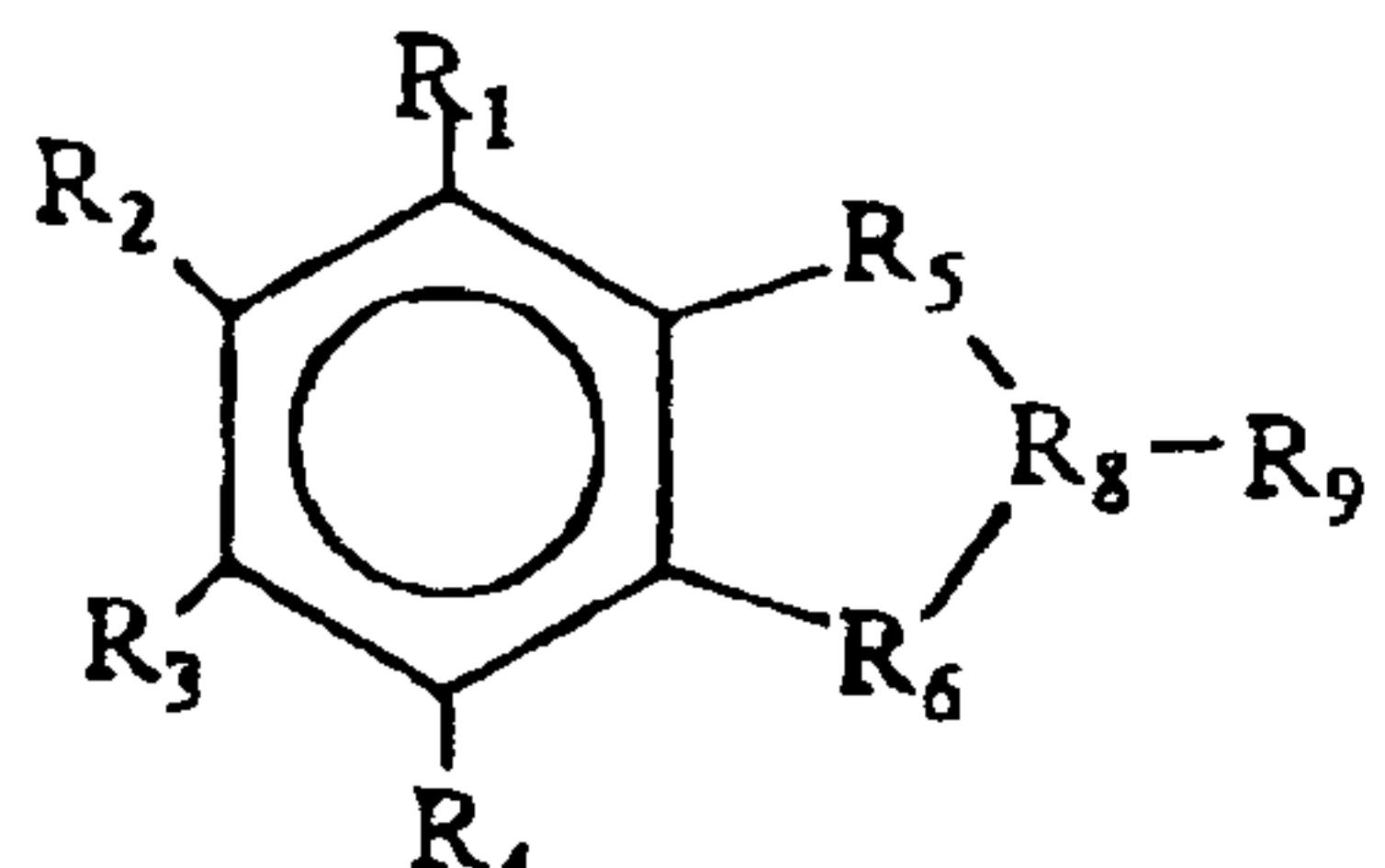


and $n=1$ to 4;

provided the compound is not thalidomide.

- 31 -

2. The use according to claim 1, wherein the compound has the following formula:



and R₅ and R₆ are selected from the group consisting of

—CH₂, —CHOH and —CO

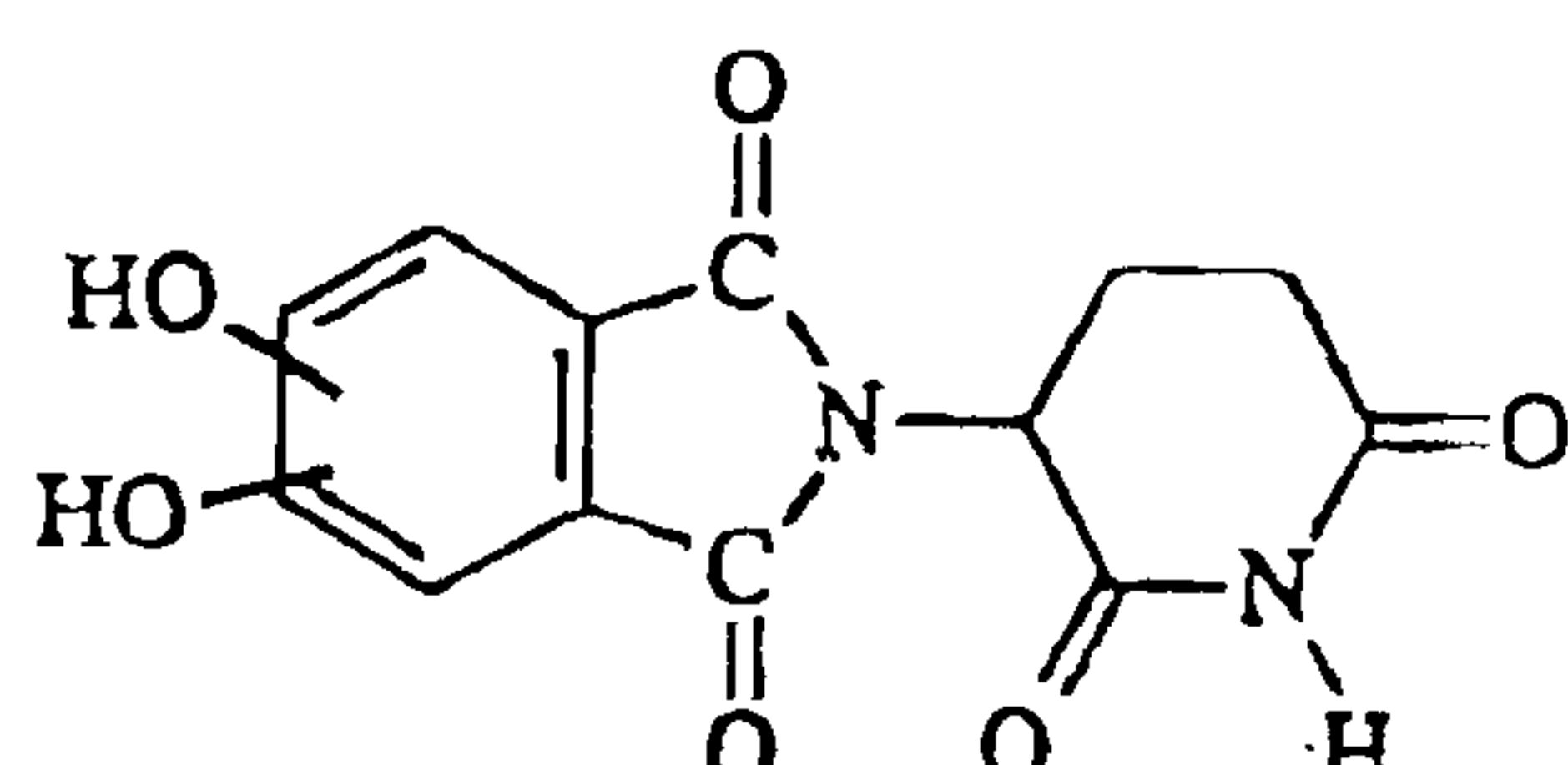
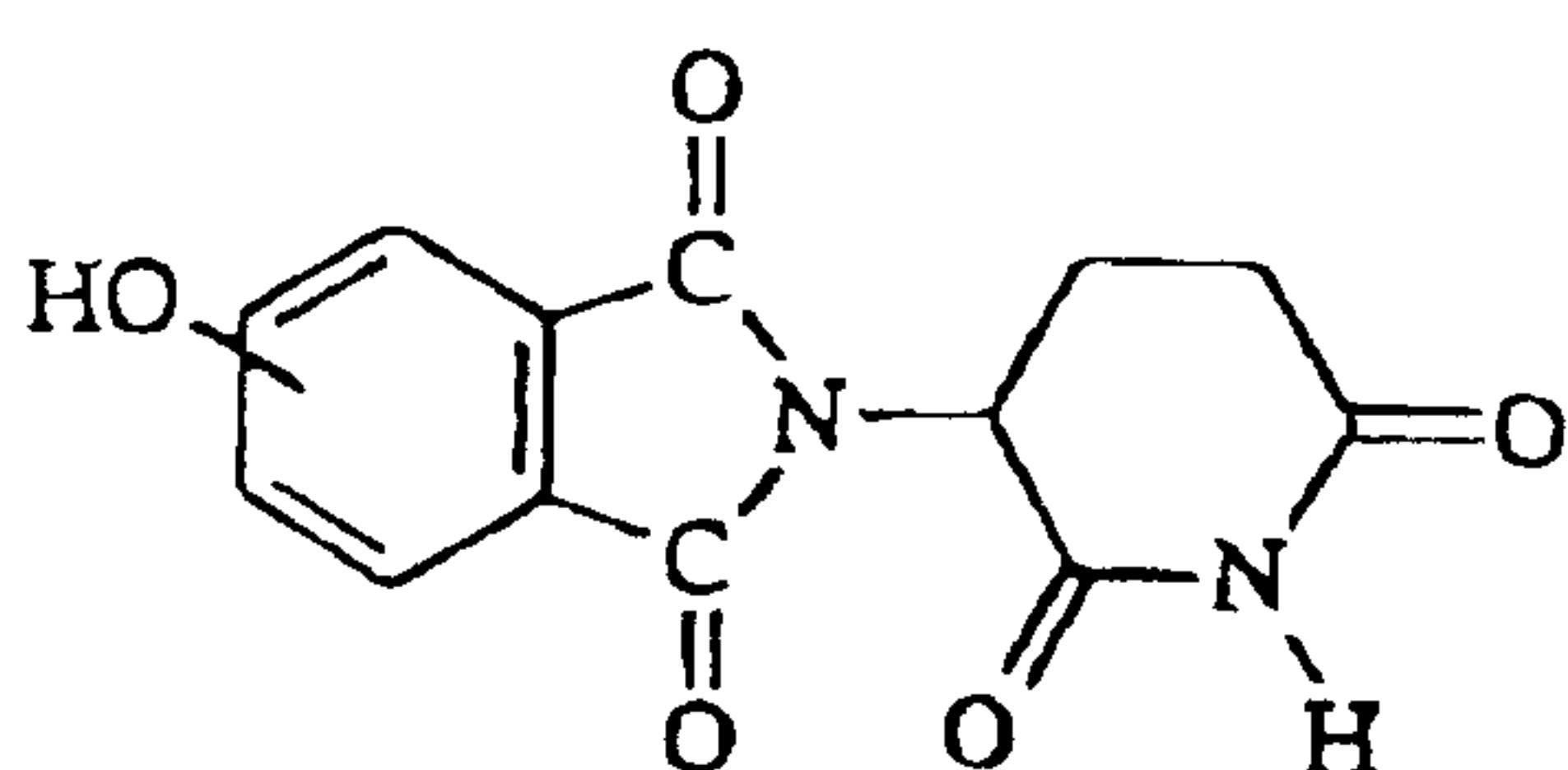
and in which R₉ has formula F) or H) and R₁₄ and R₁₆ are selected from the group consisting of,

—CH₂, —CHOH, or —C₂₁—; and R₁₅ and is —O—, or —N—, $\begin{array}{c} \text{R}_{21} \\ | \\ \text{C} \\ \parallel \\ \text{O} \end{array}$

where R₂₁ is —H, —CH₃, or —OH.

3. The use according to claim 1, wherein the compound is a thalidomide metabolite or hydrolysis product.

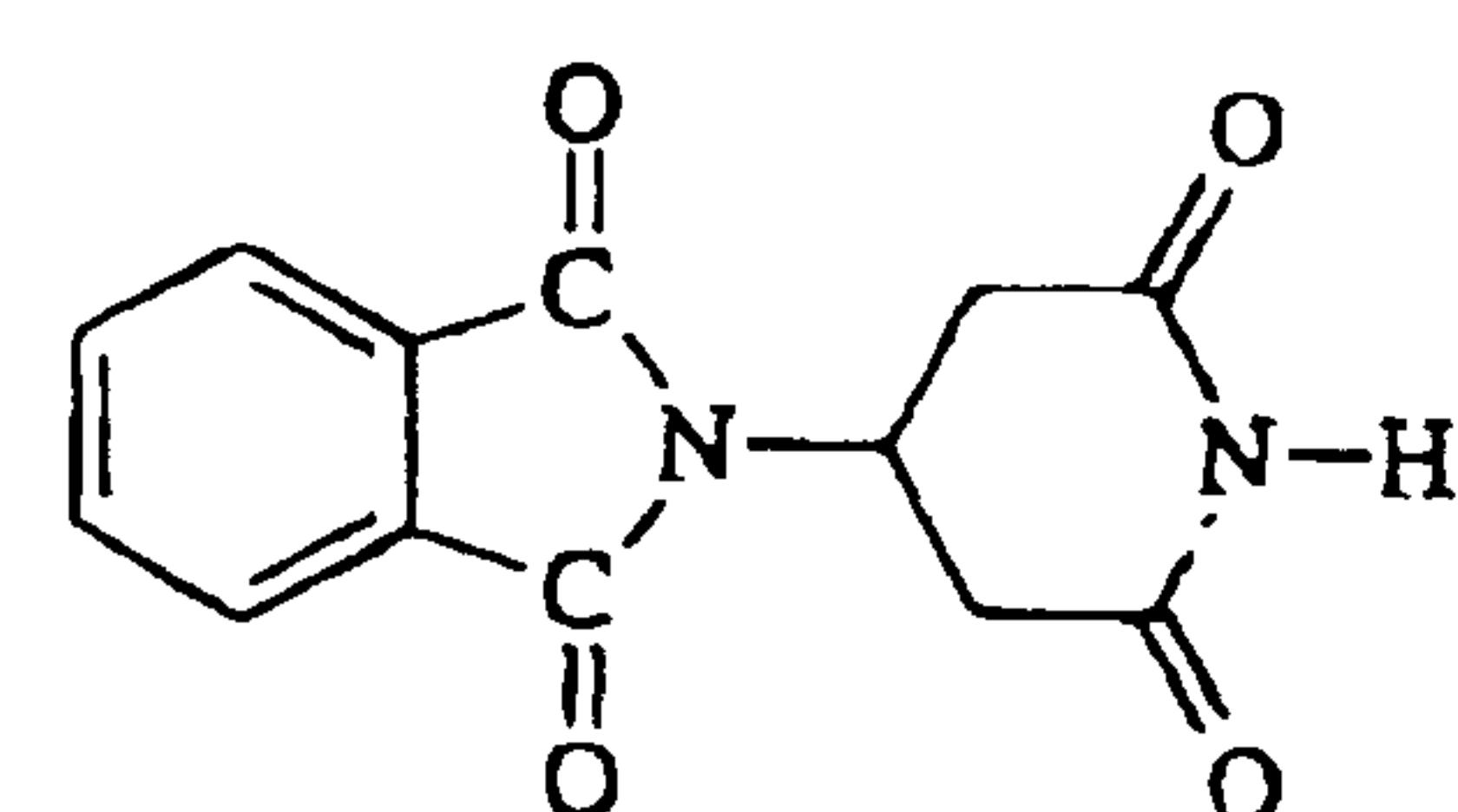
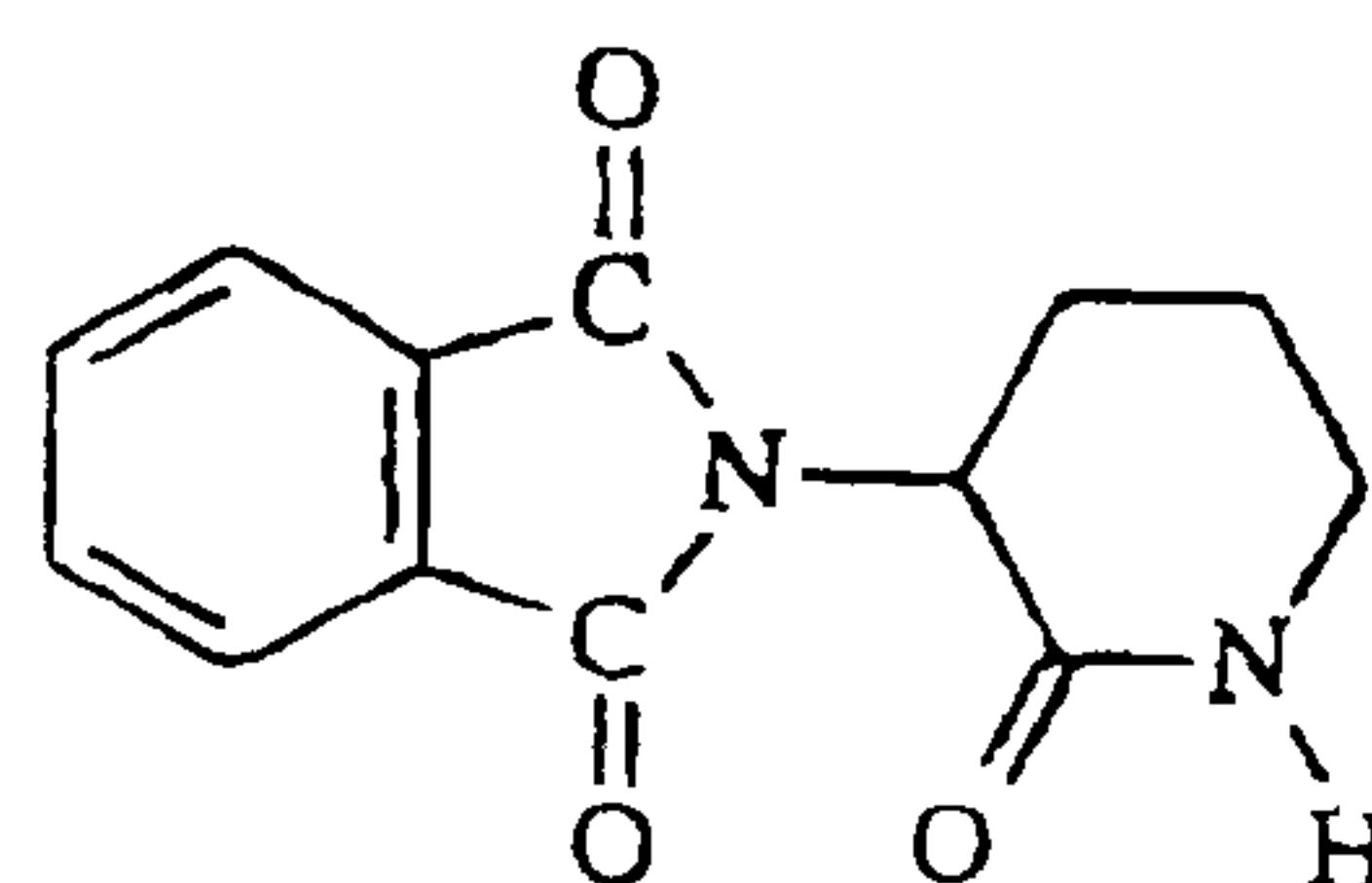
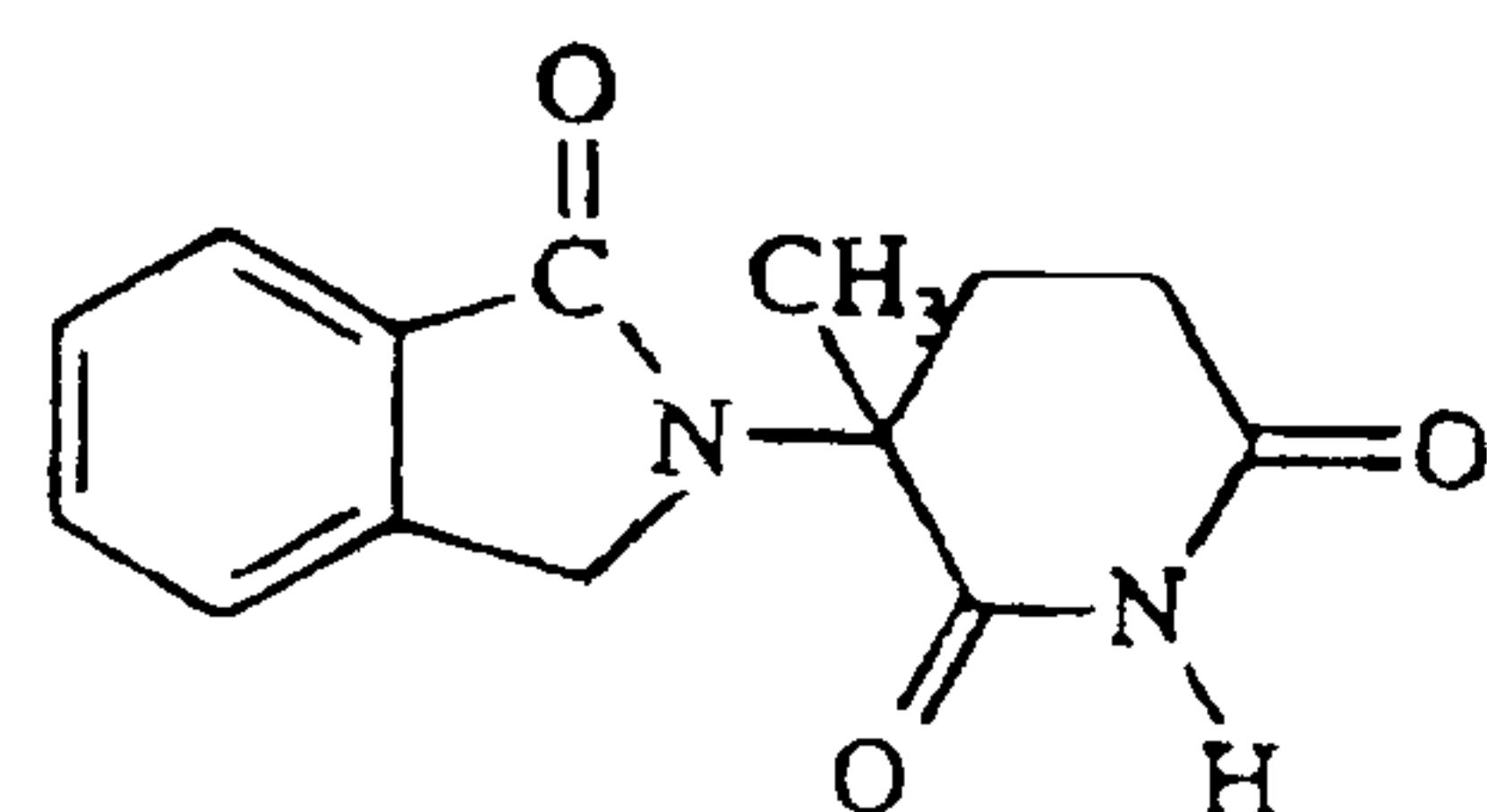
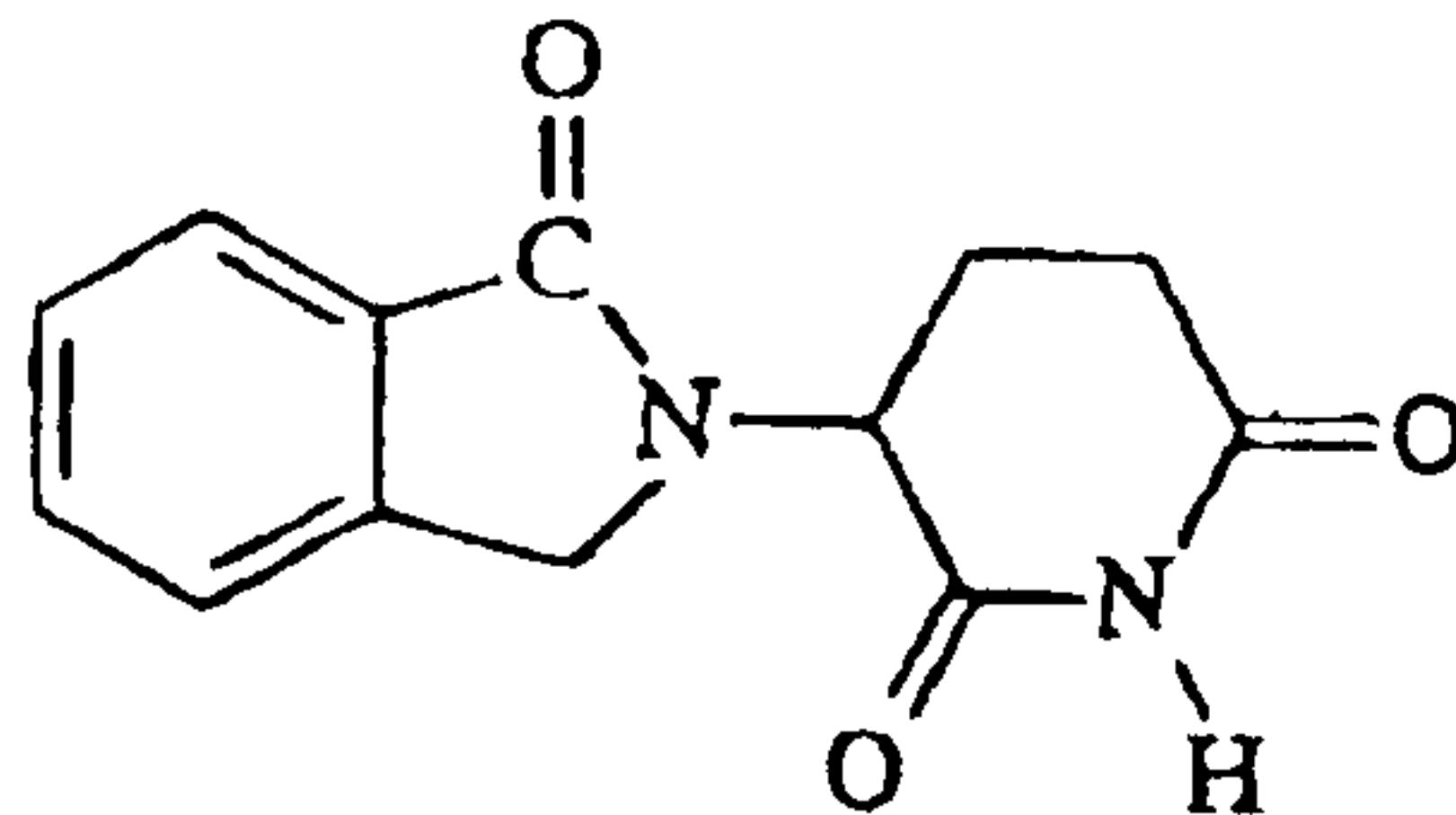
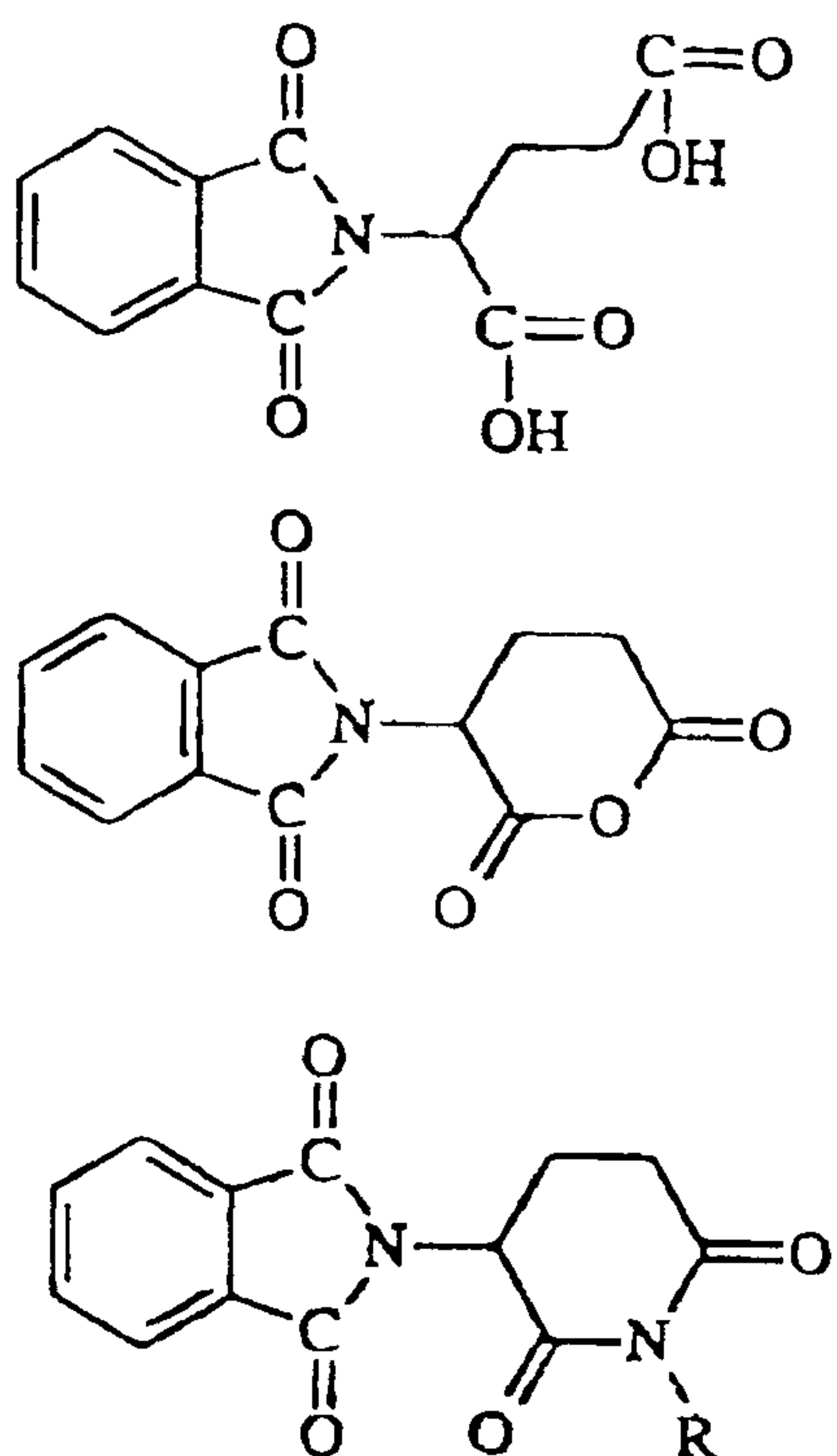
4. The use according to claim 1, wherein the compound is selected from the group consisting of the following compounds:



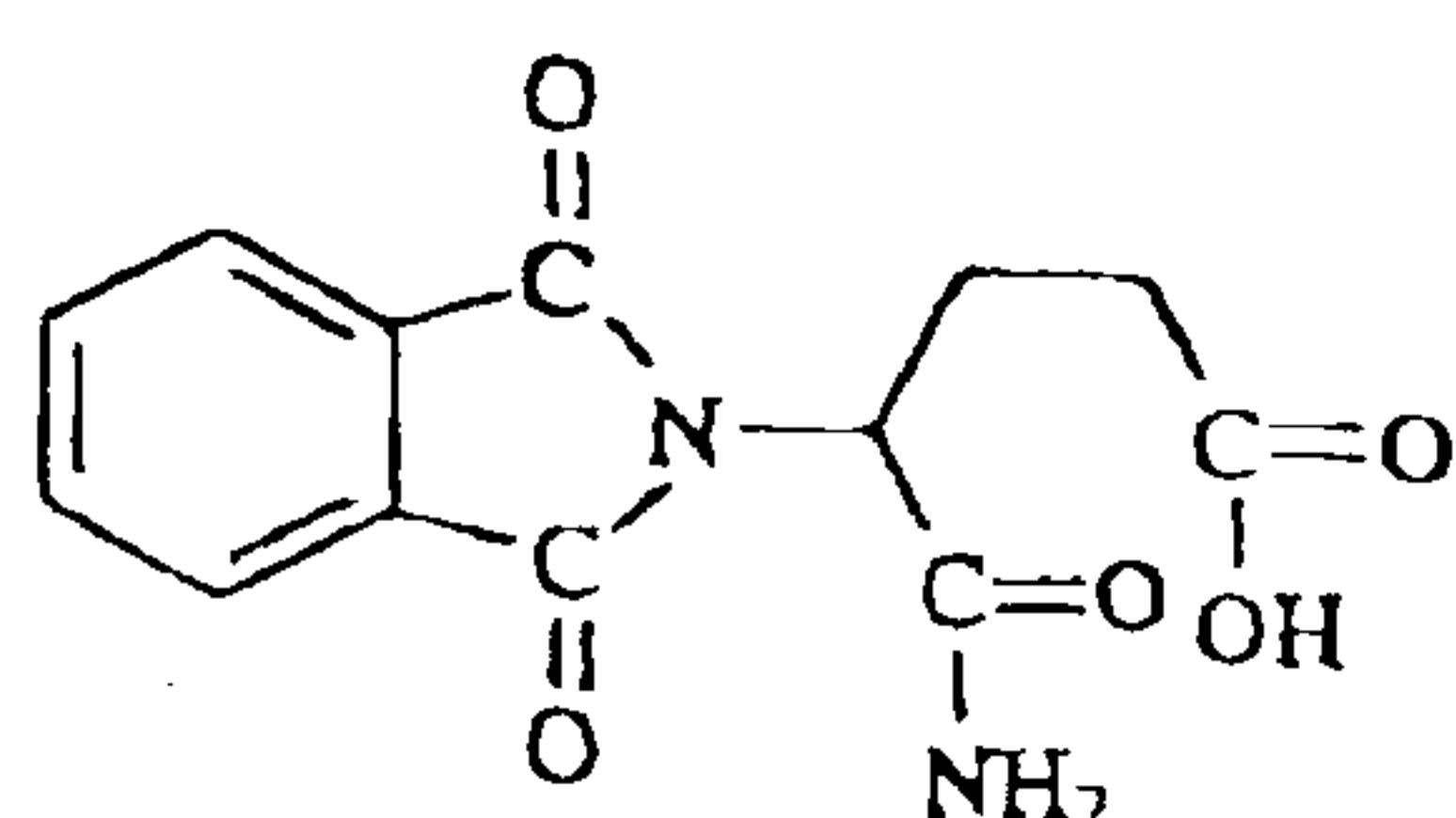
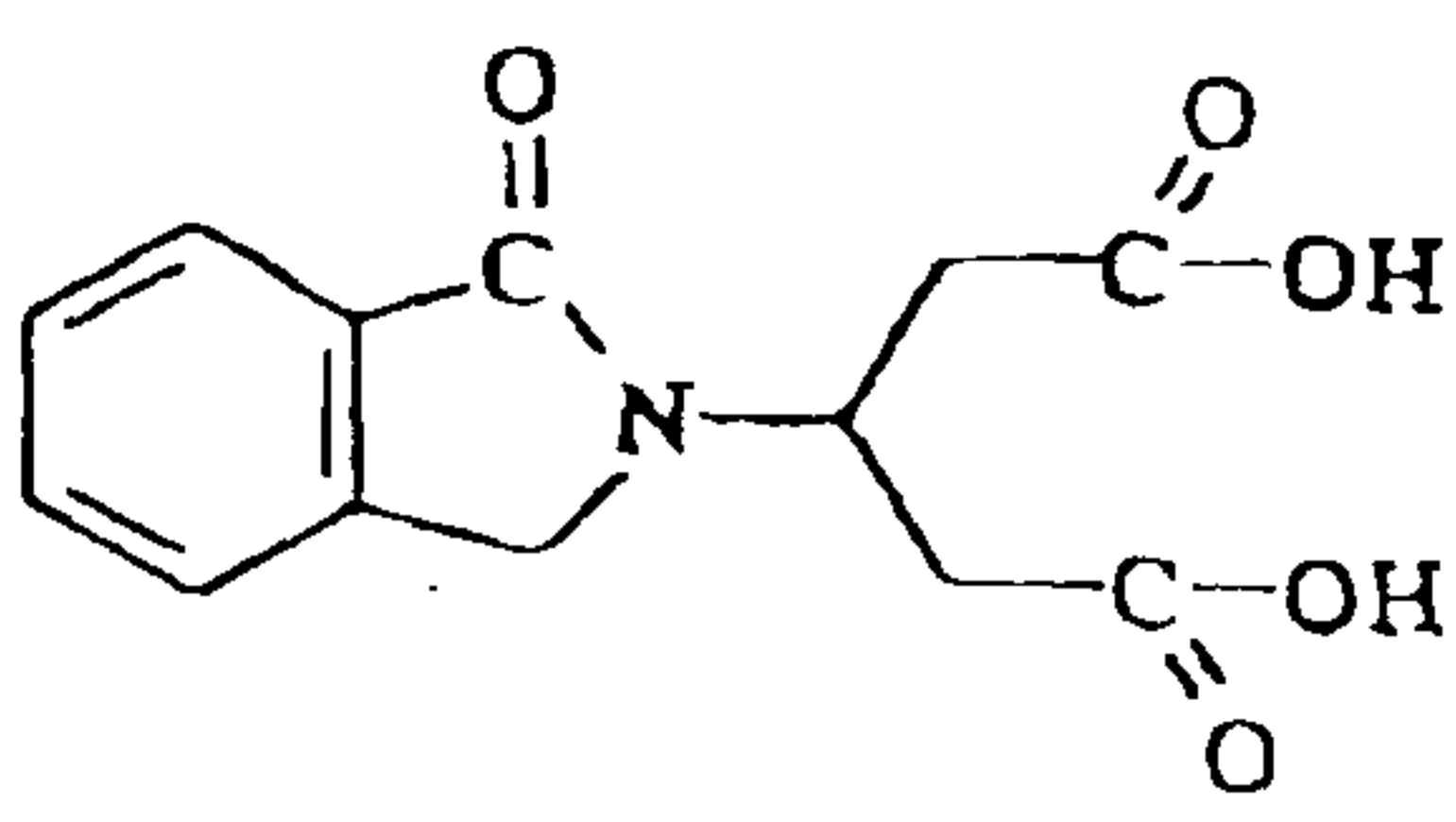
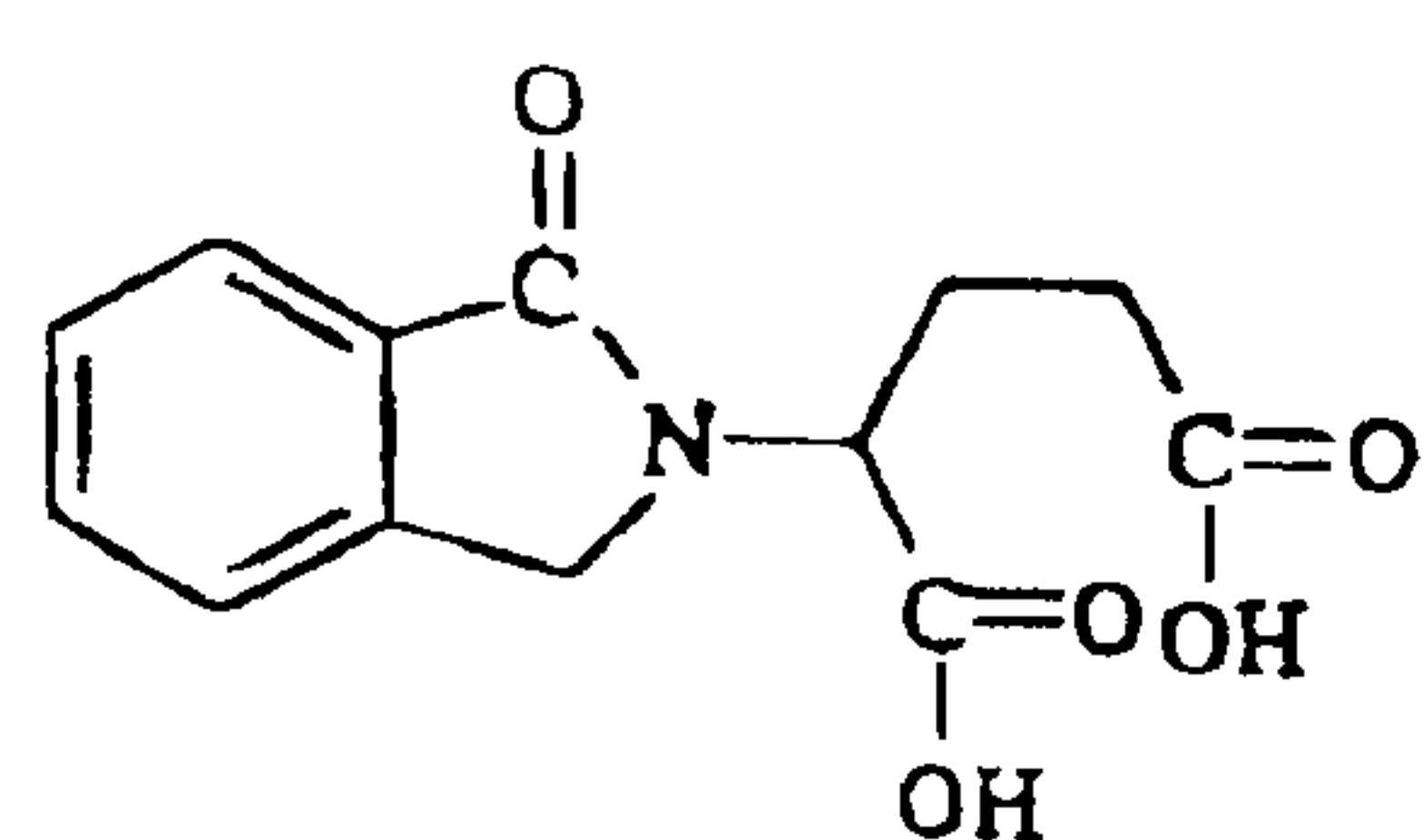
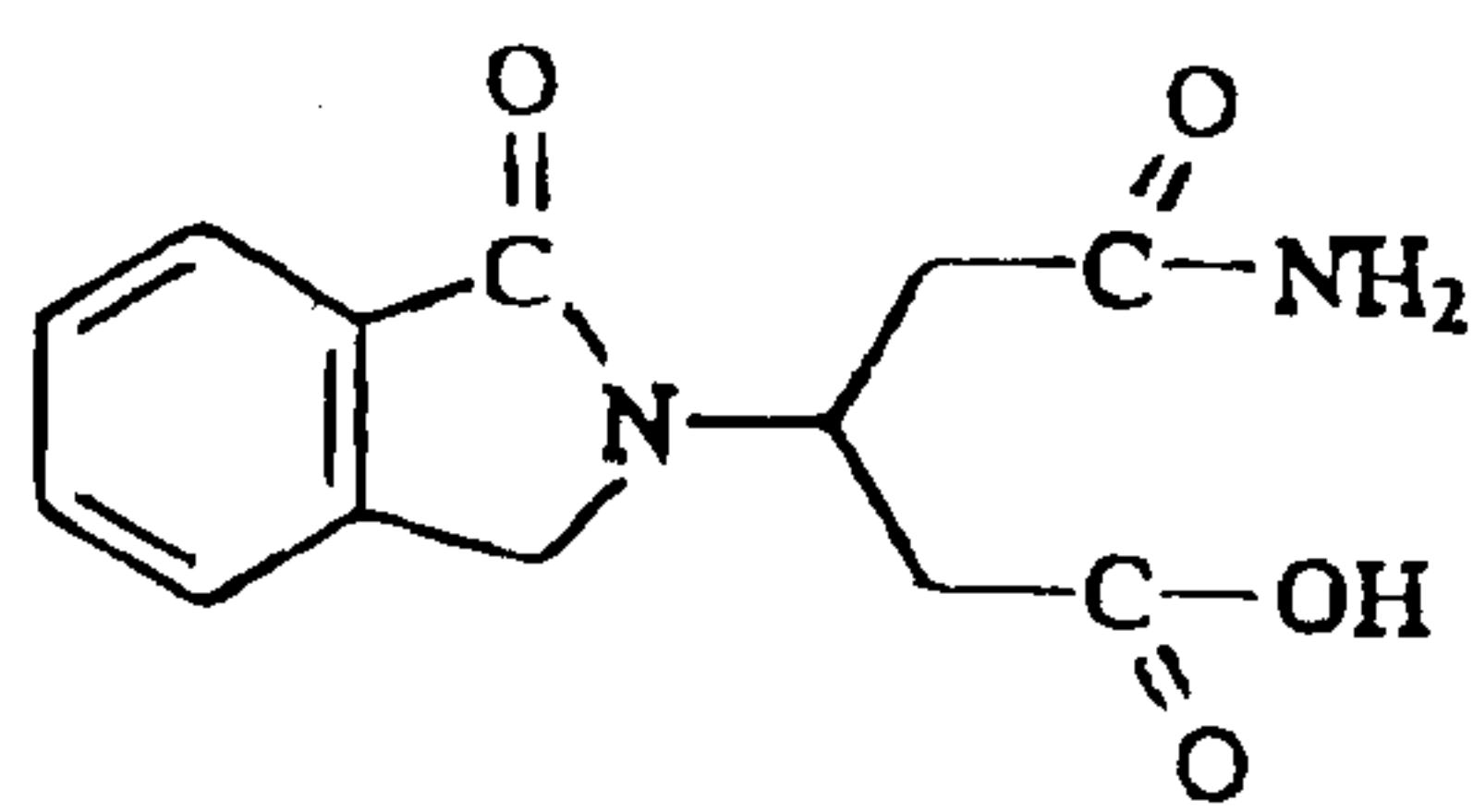
5. The use according to claim 1, wherein the compound is selected from the group consisting of N-phthaloyl-DL-glutamic acid (PGA) and N-phthaloyl-DL-glutamine anhydride.

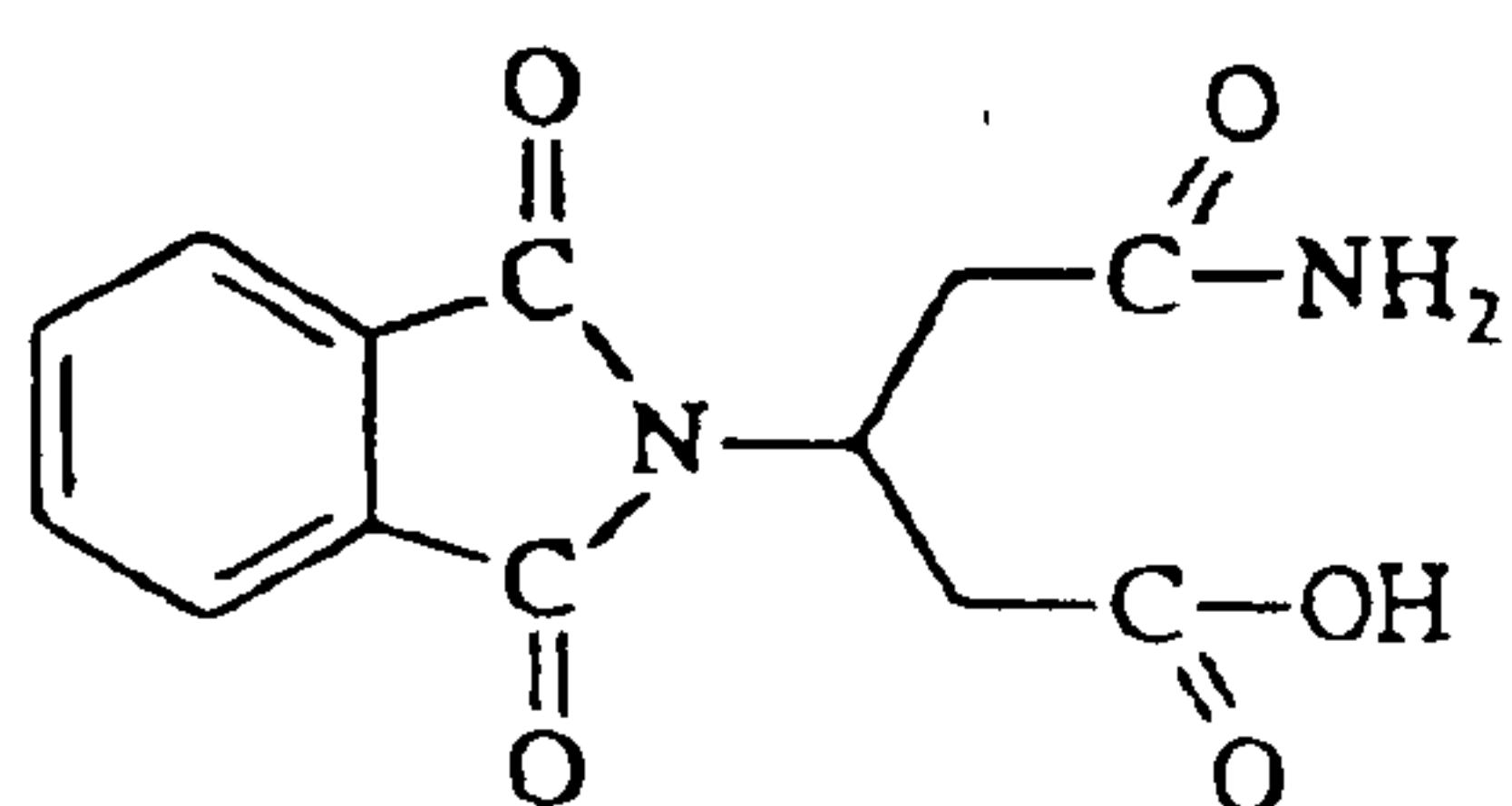
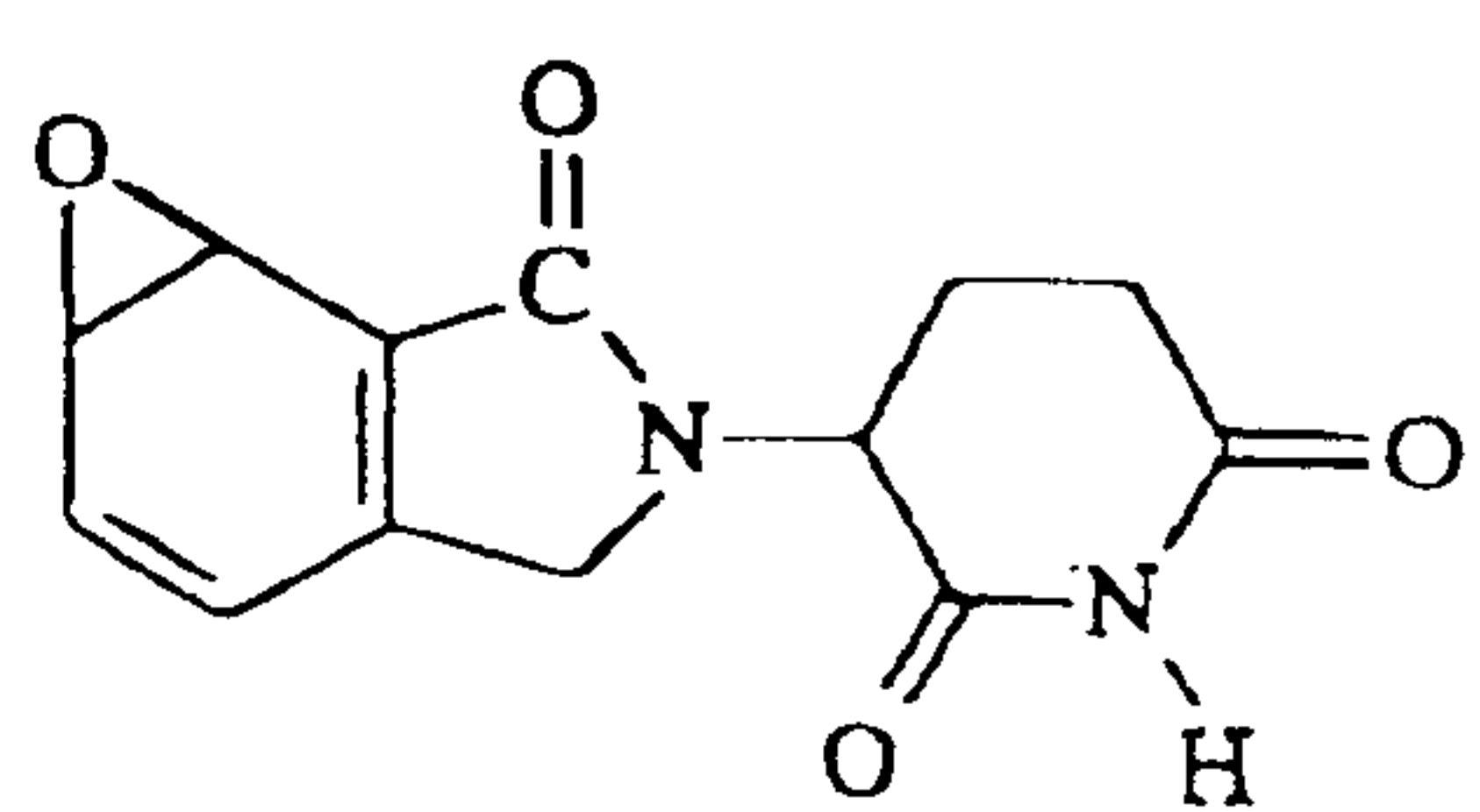
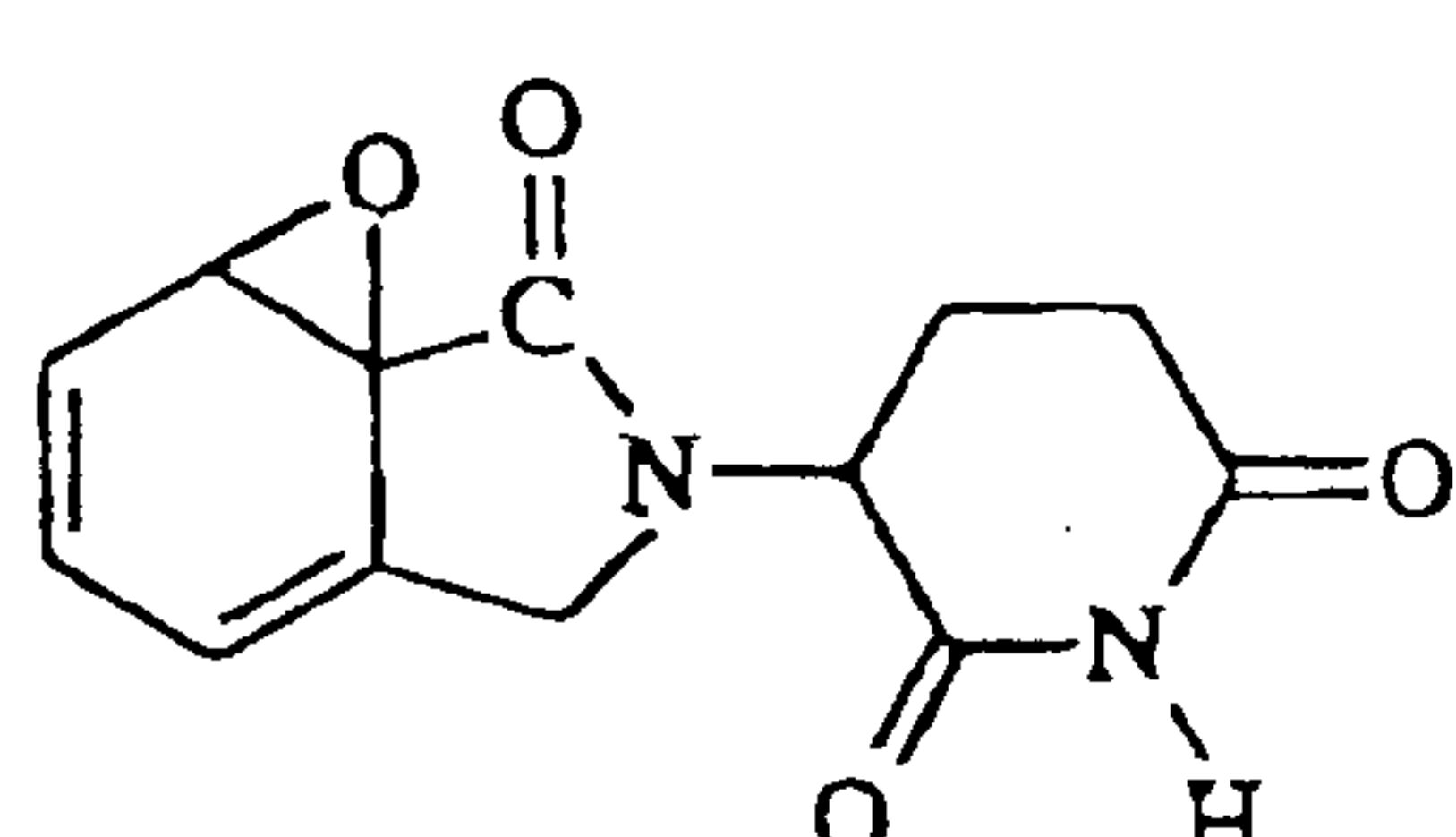
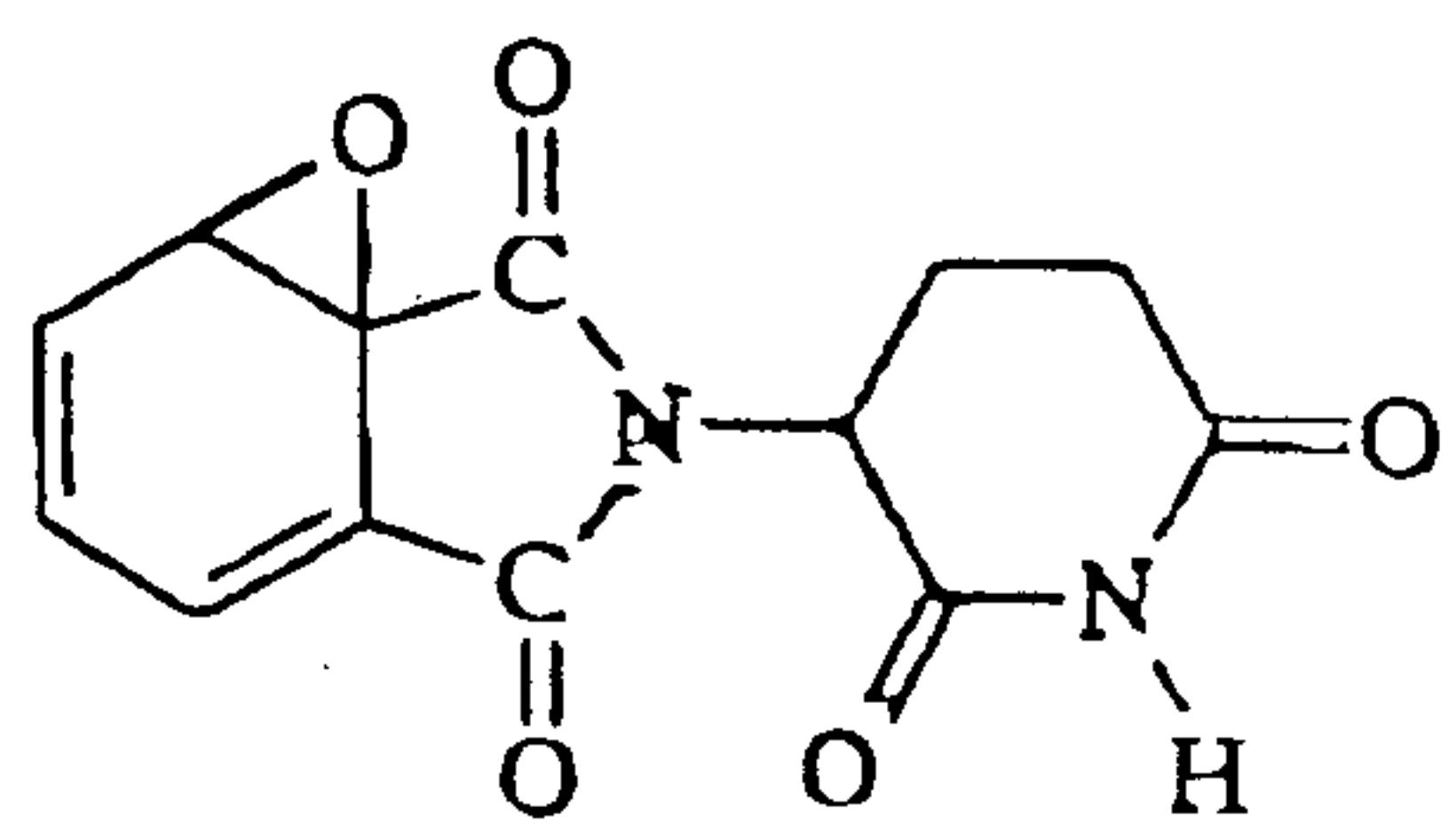
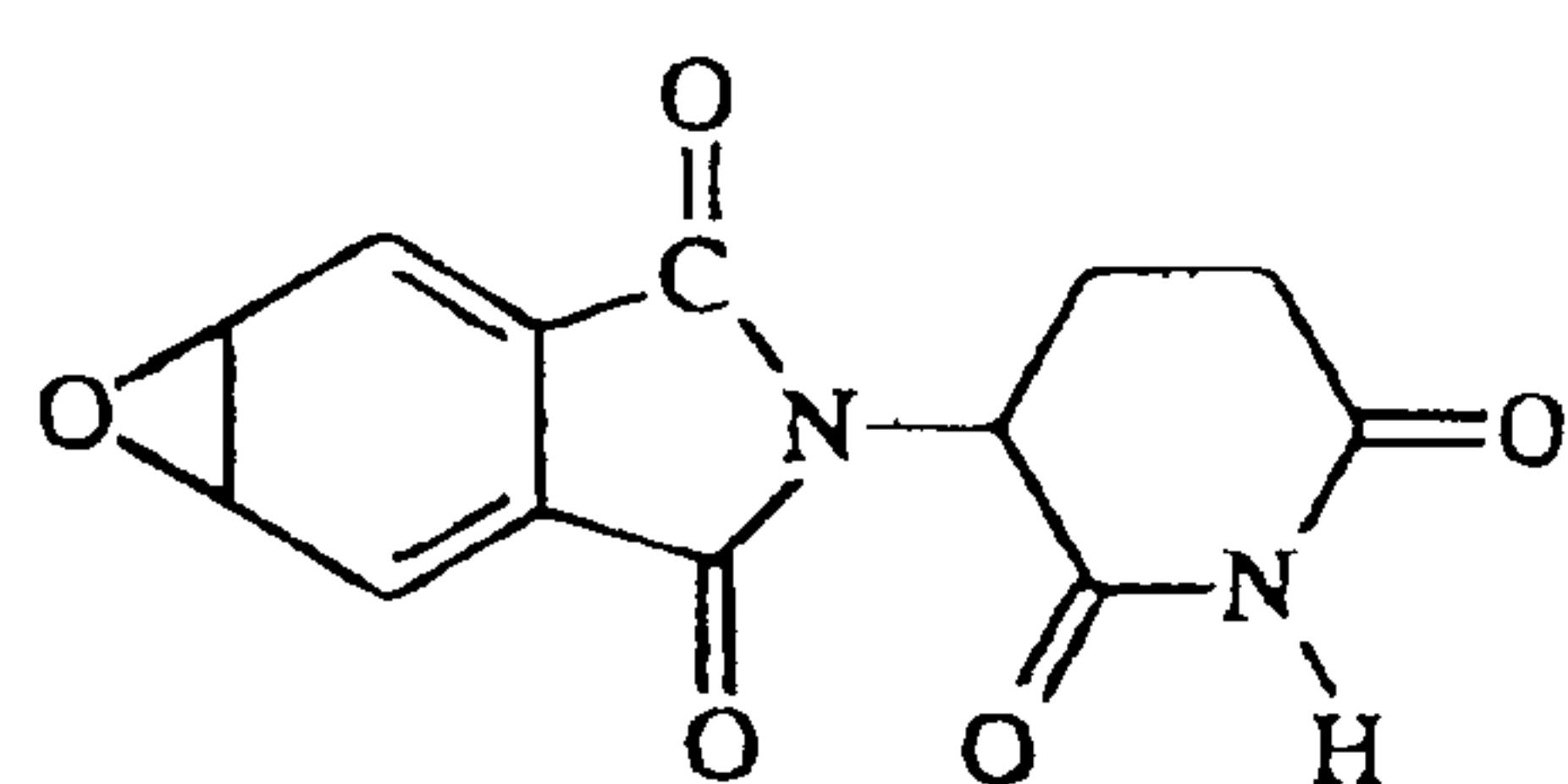
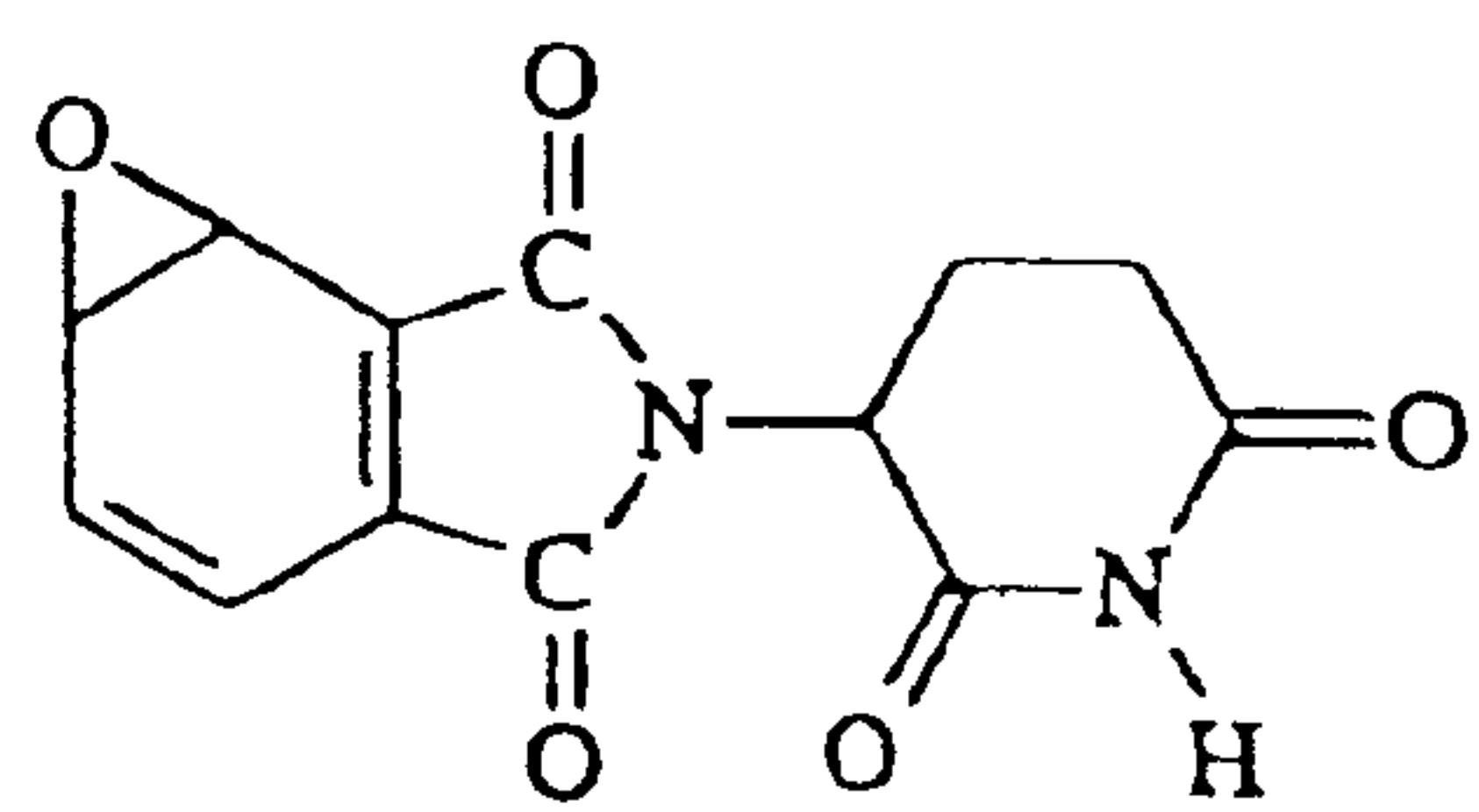
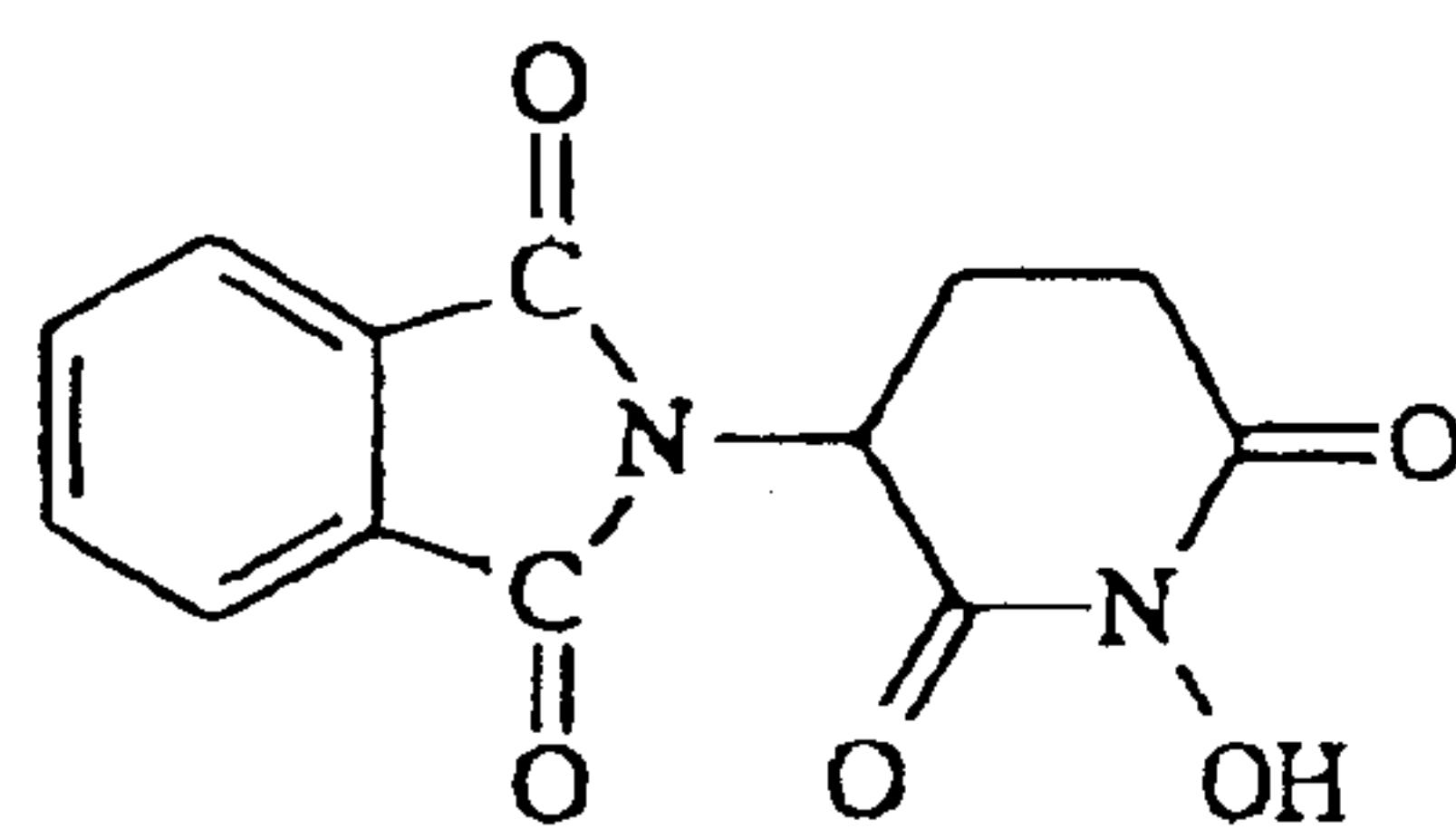
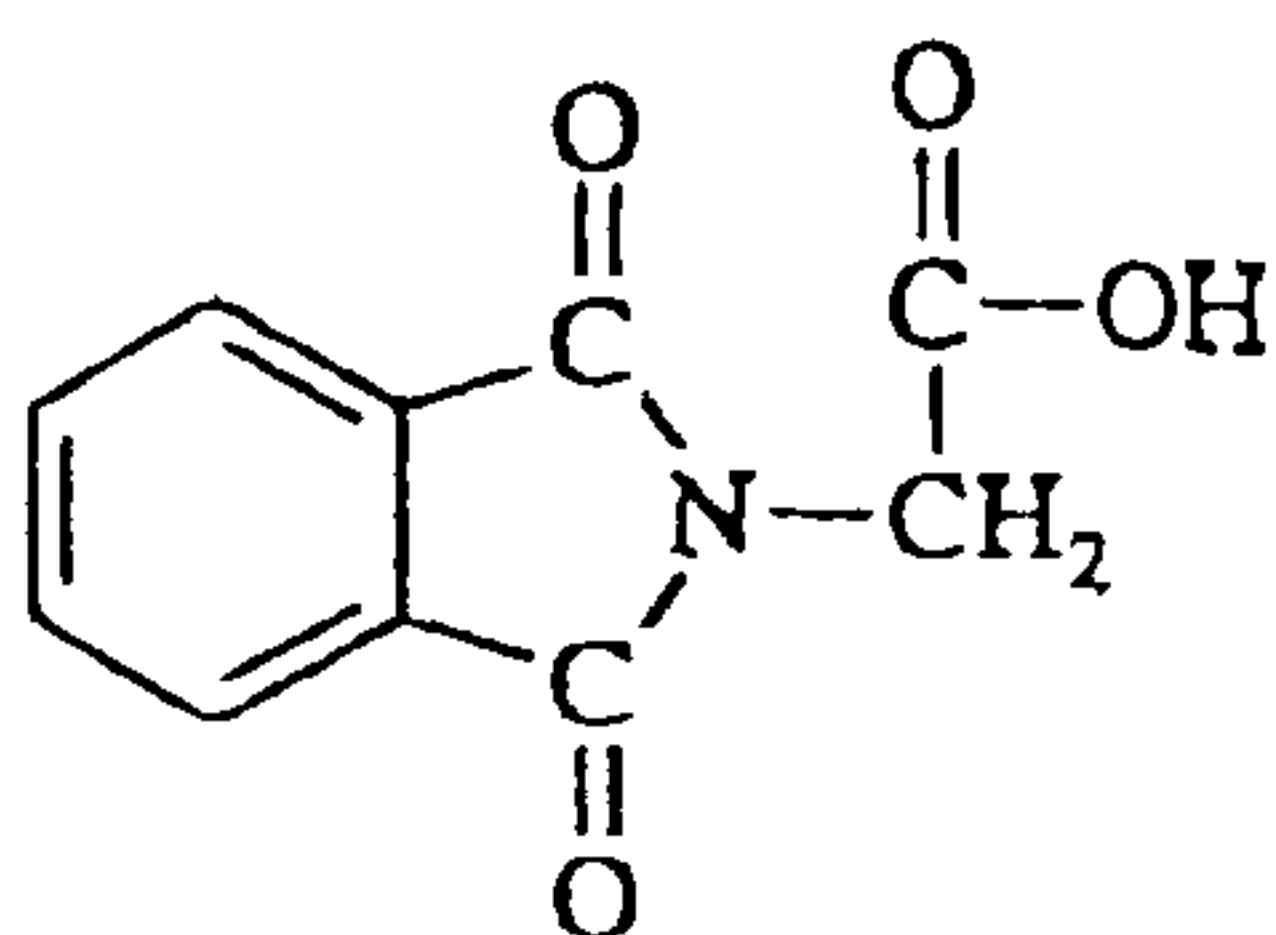
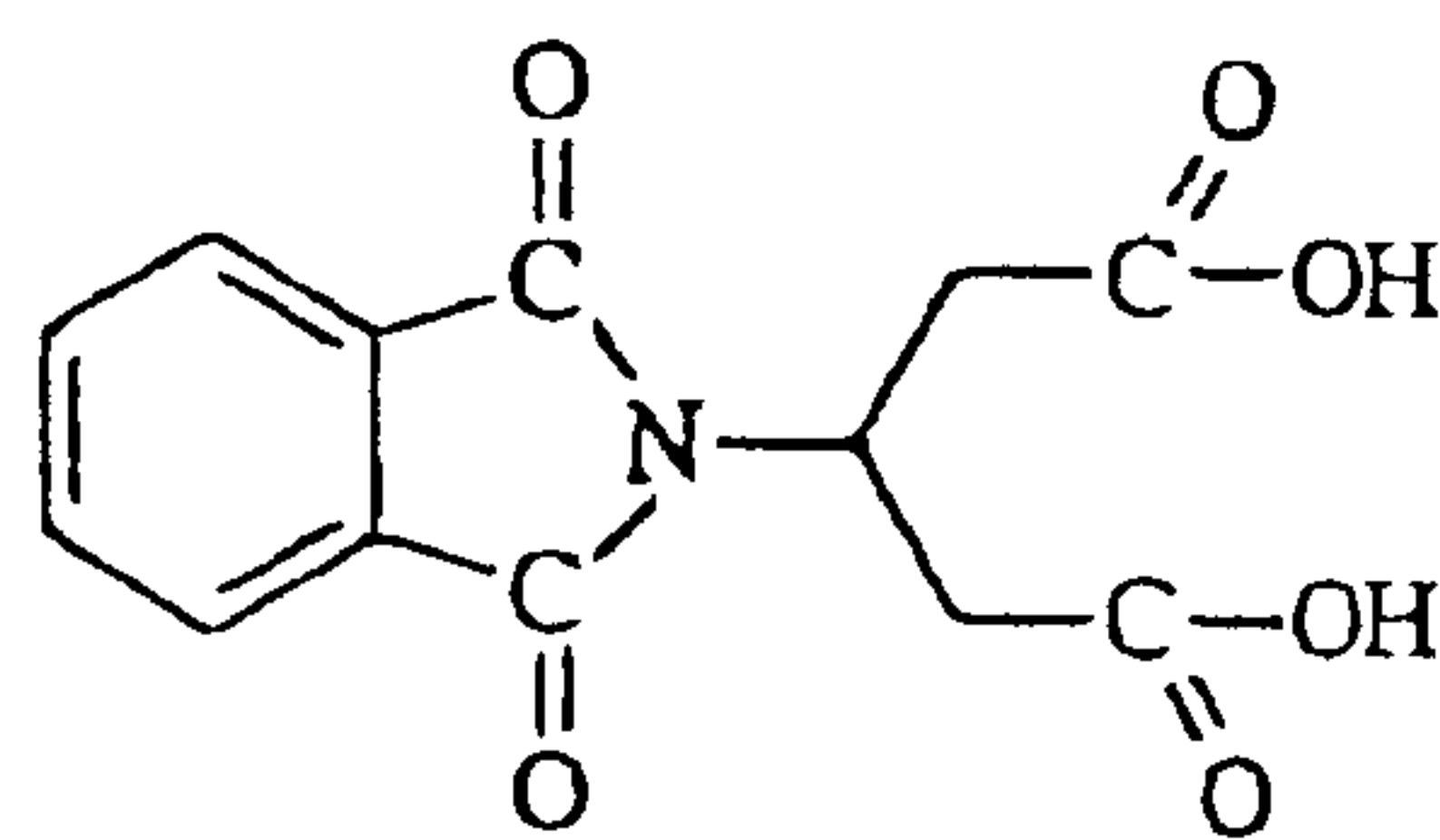
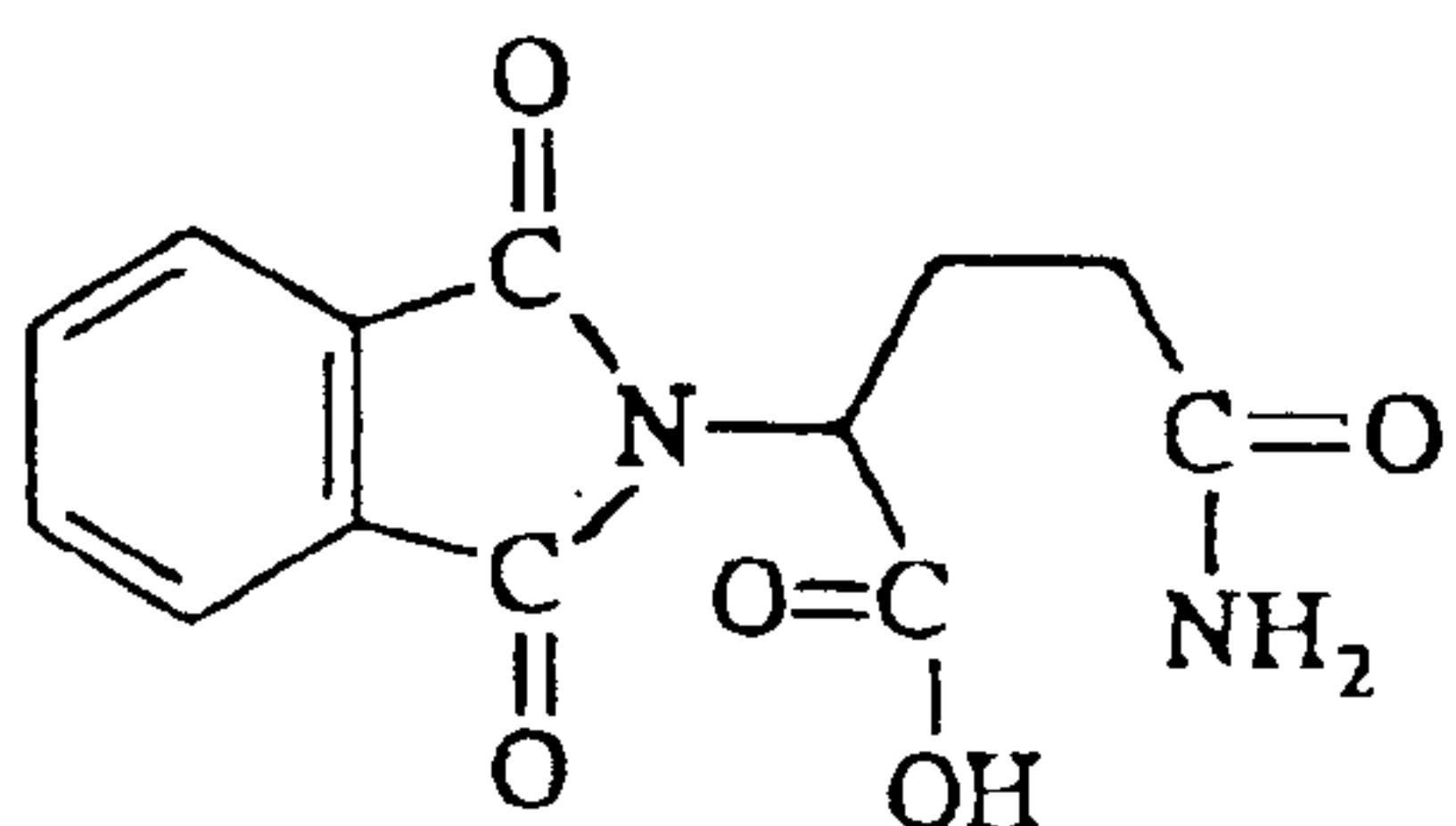
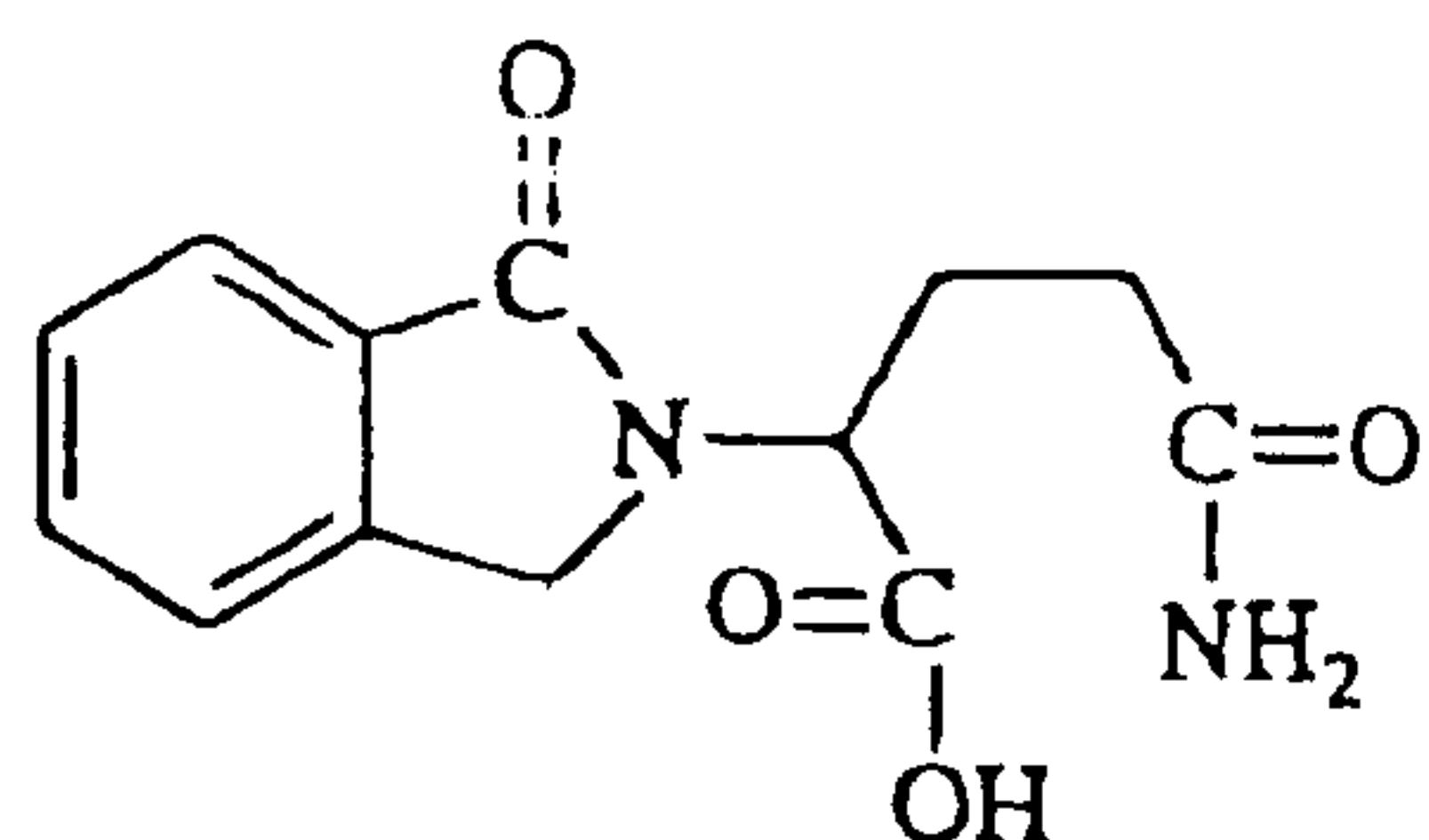
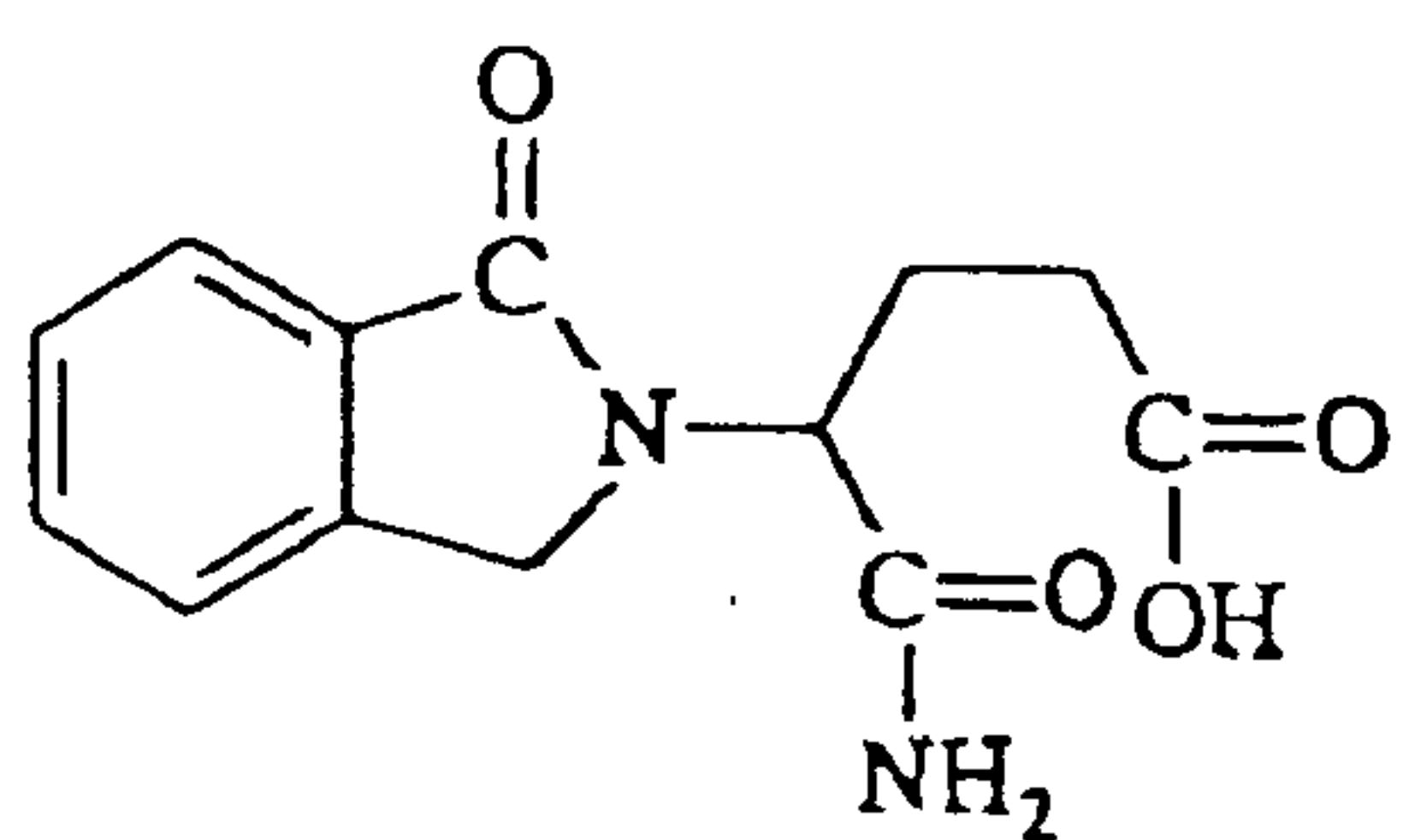
6. The use according to claim 1, wherein the compound is EM-12.

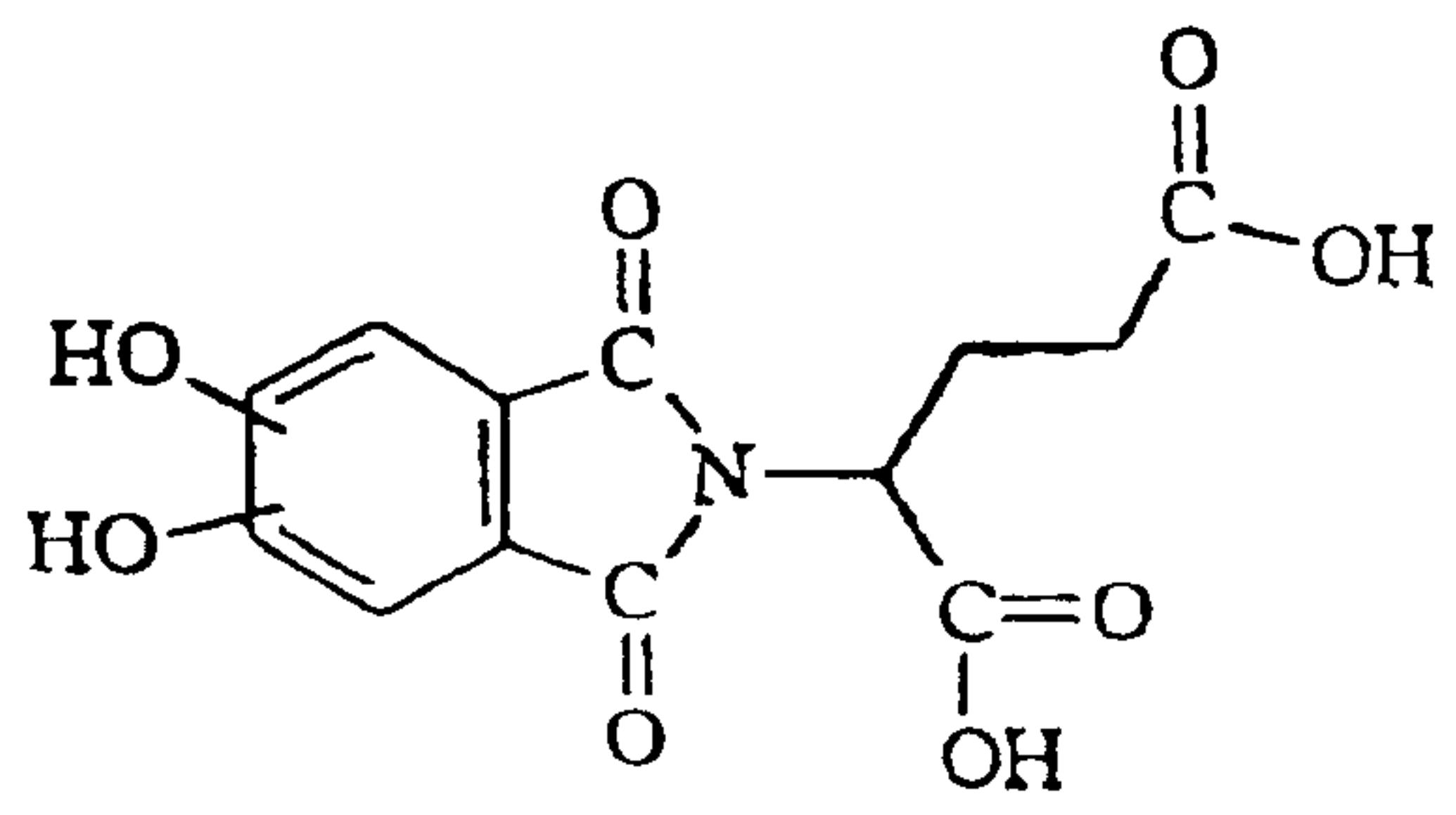
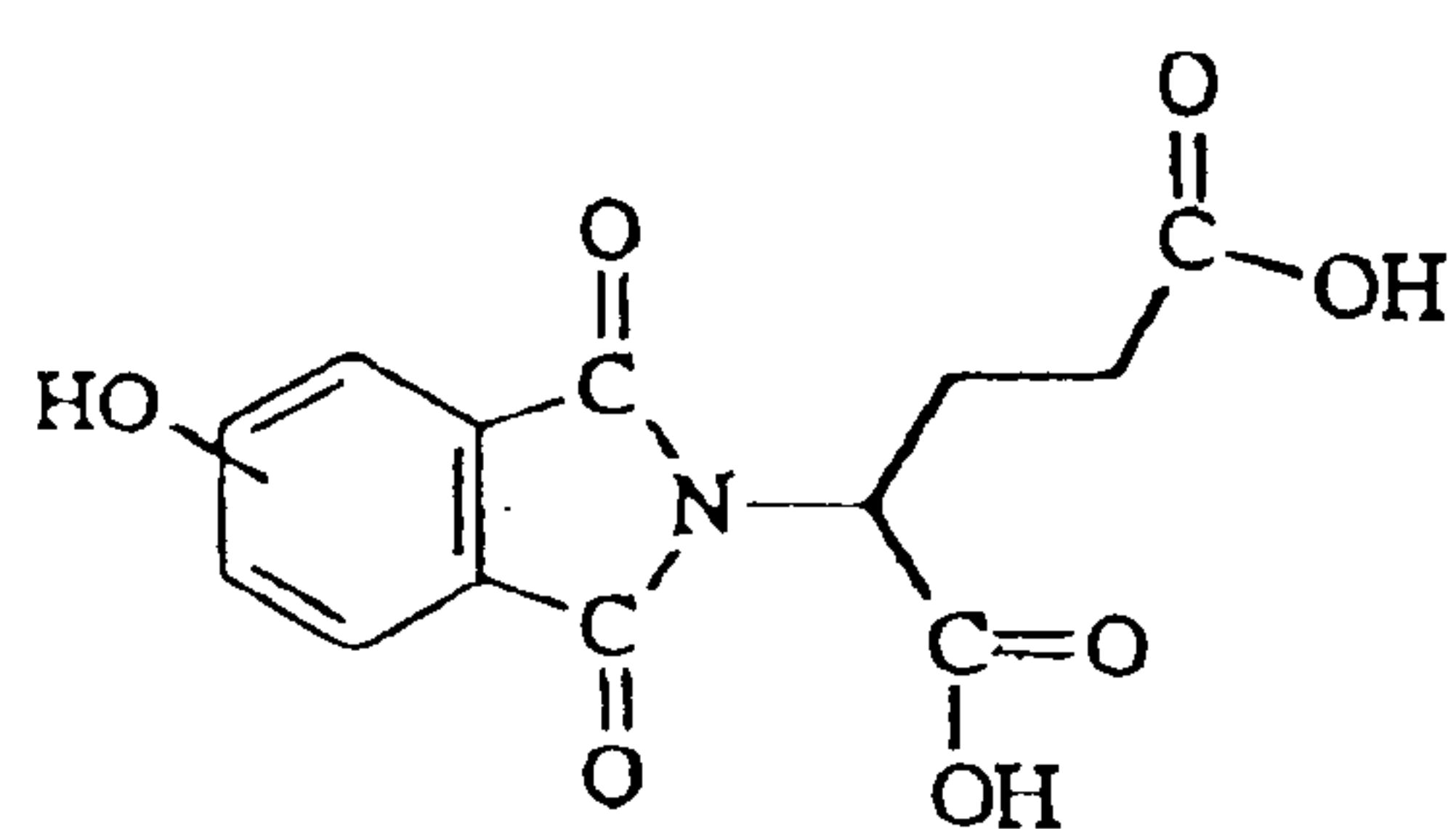
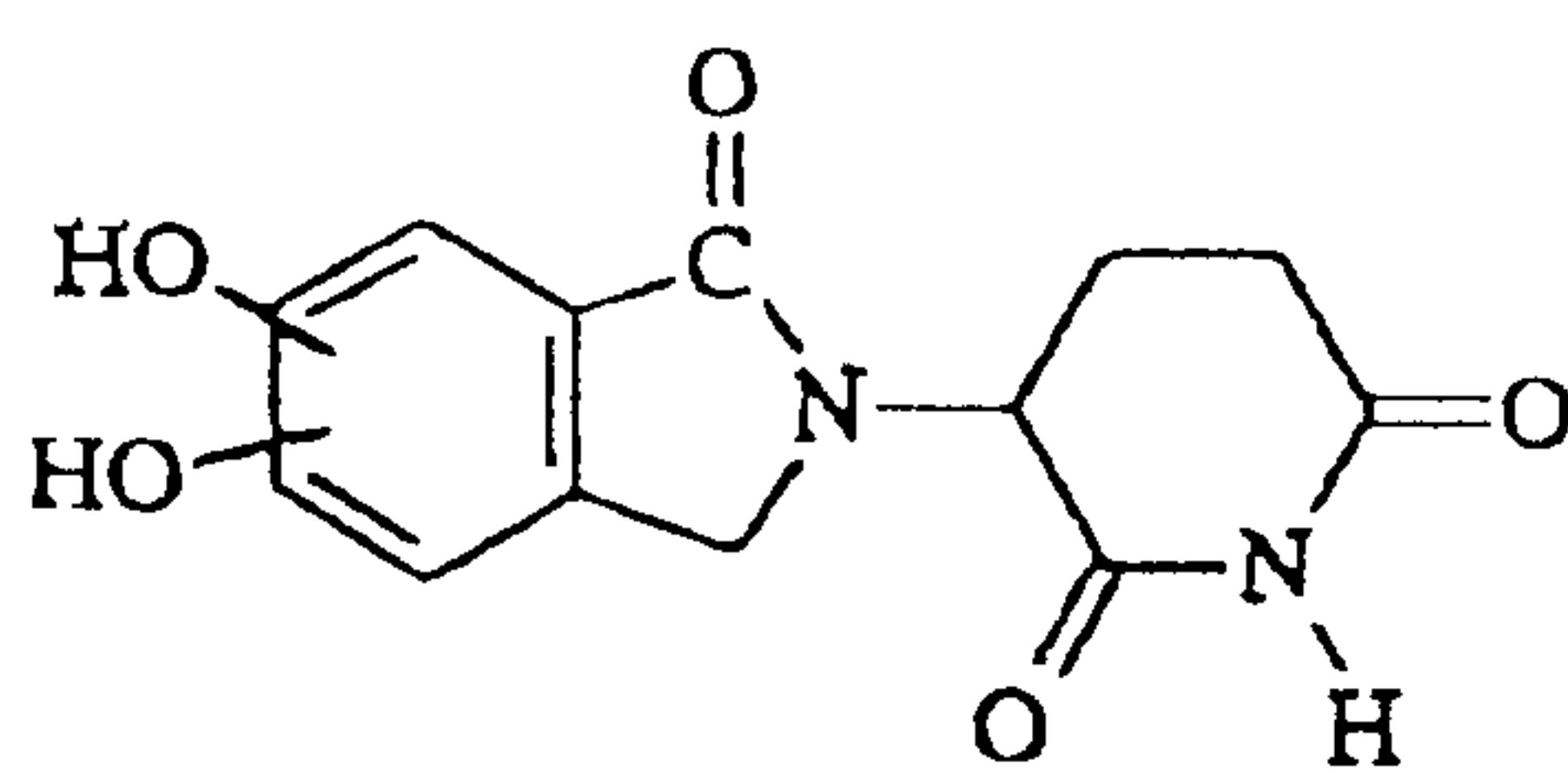
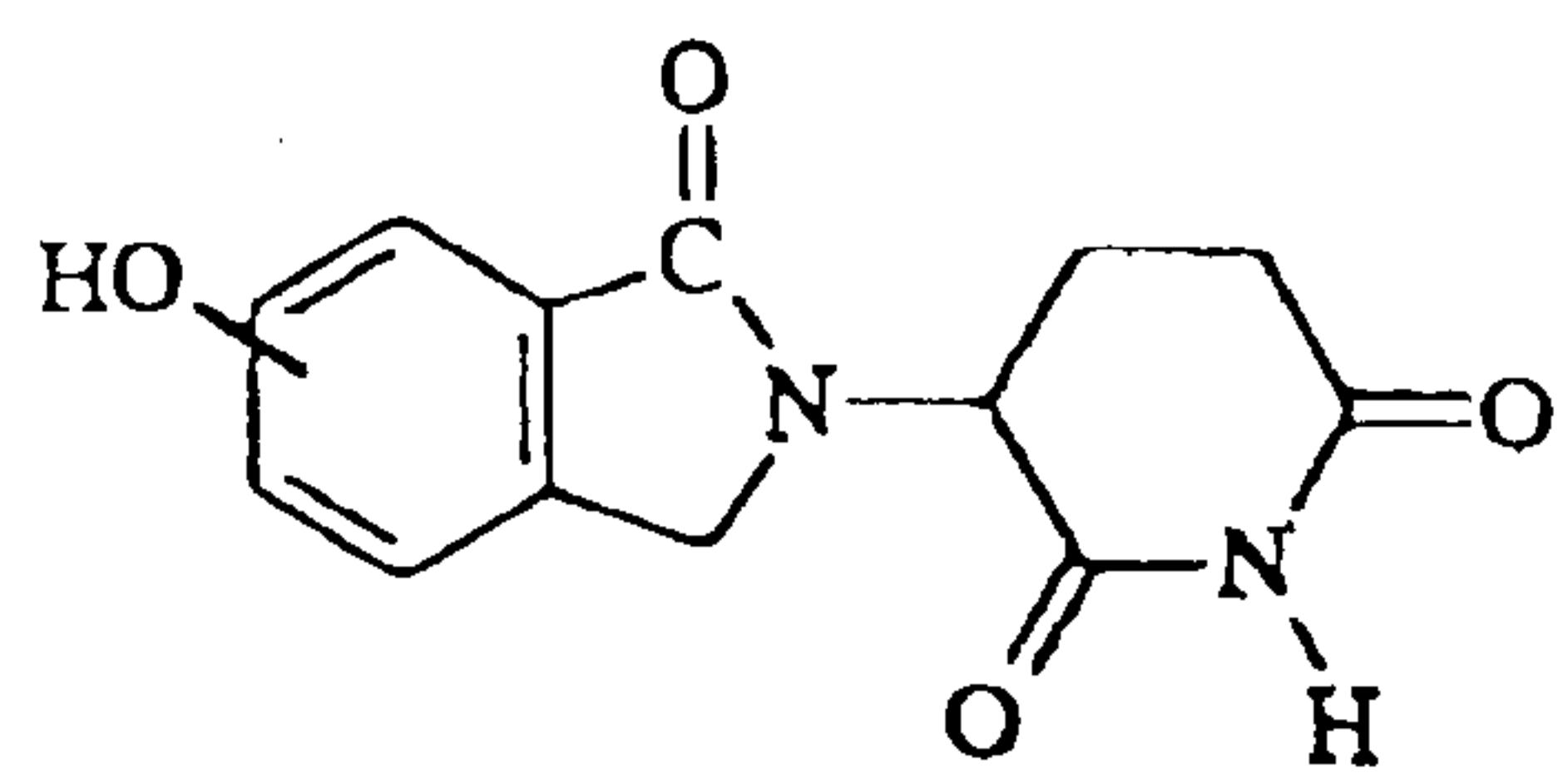
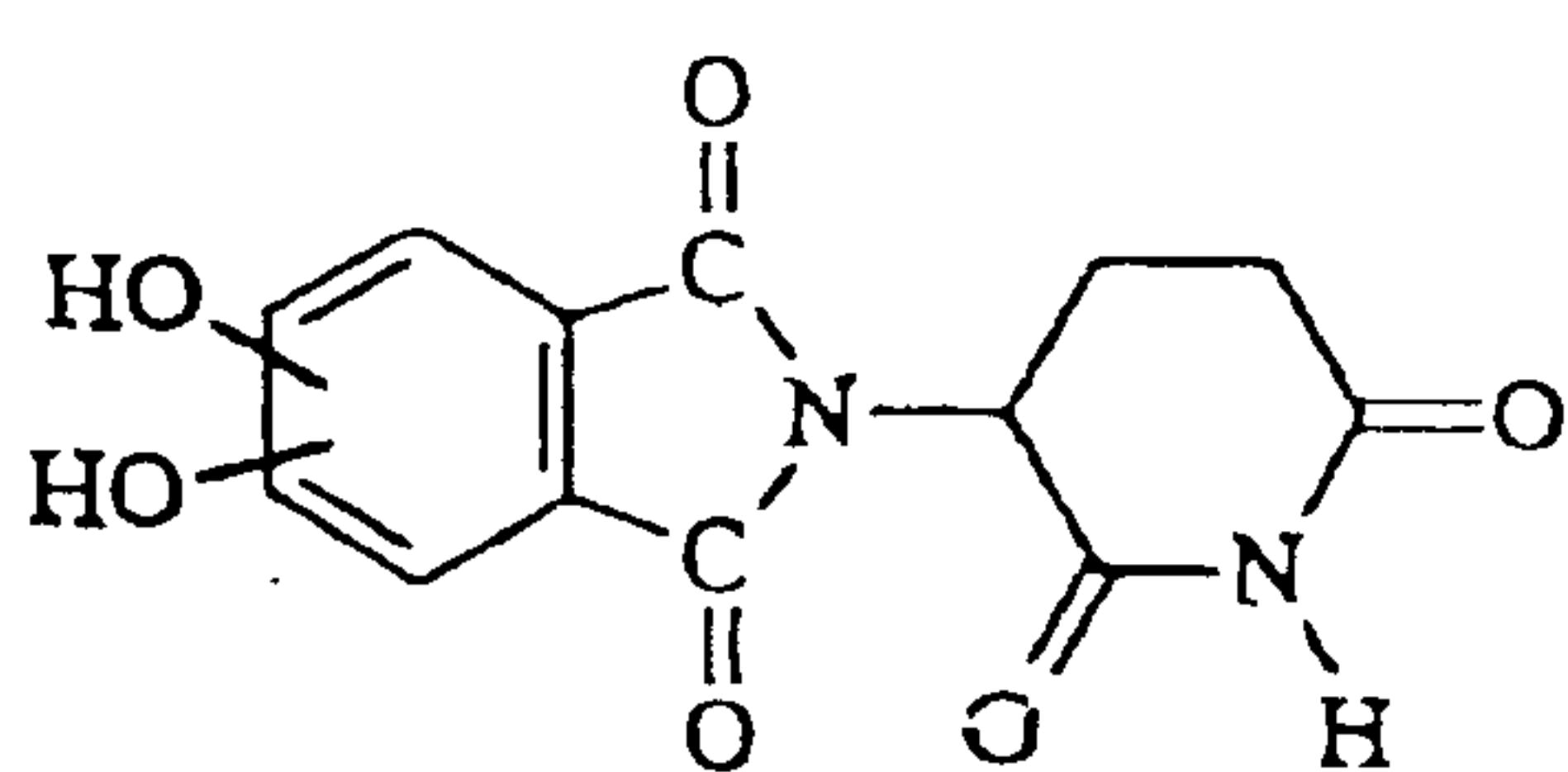
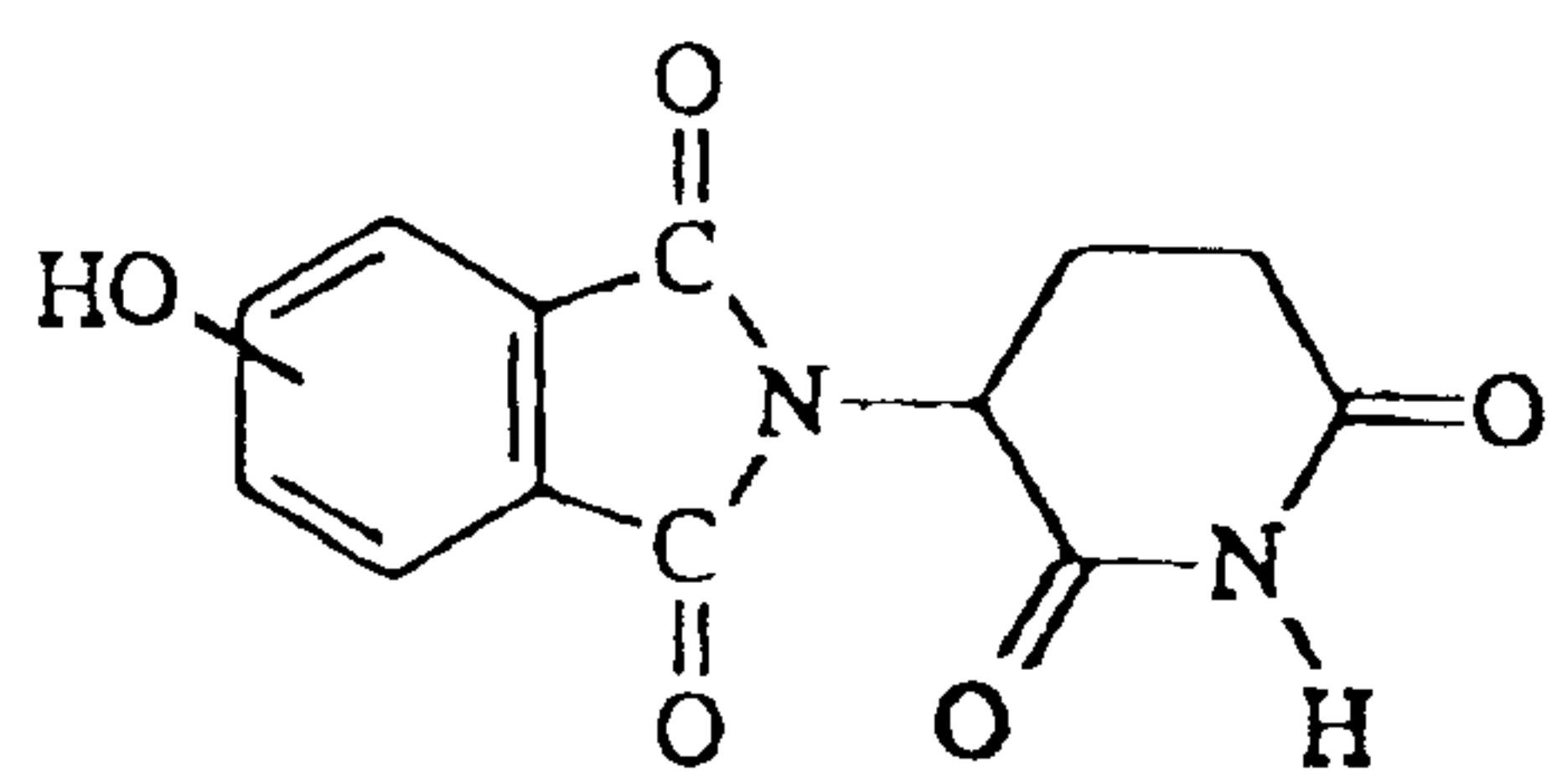
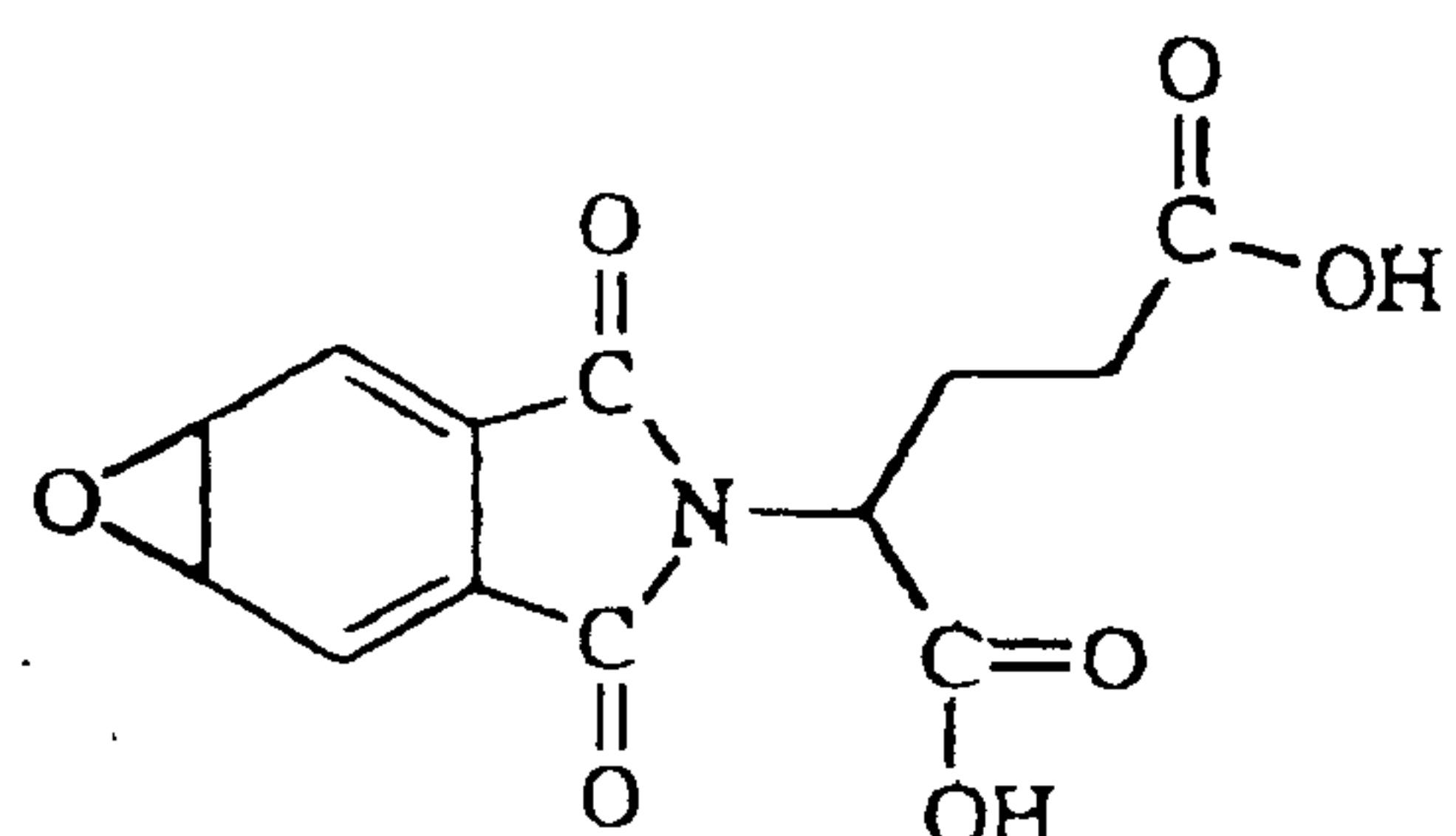
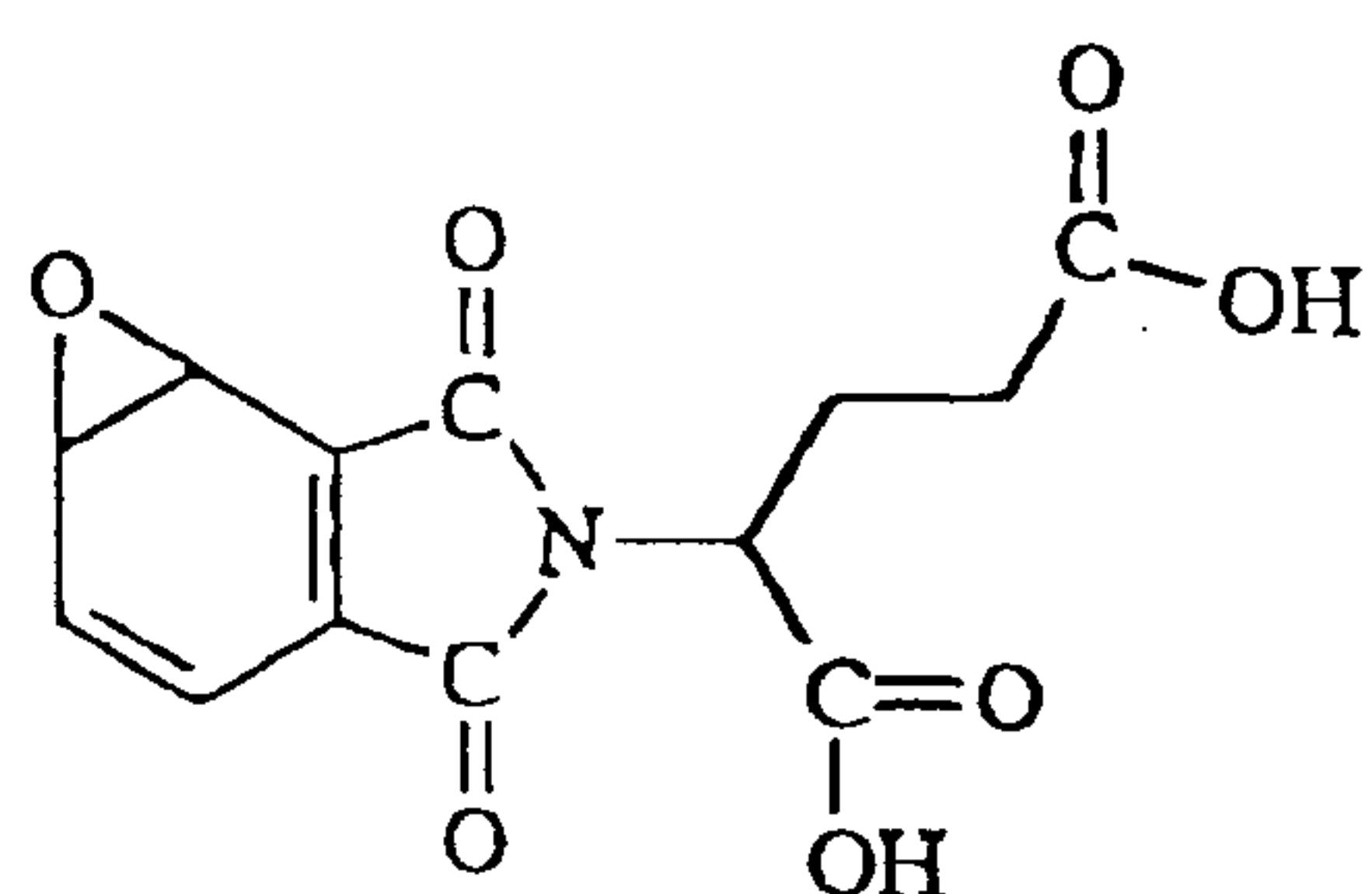
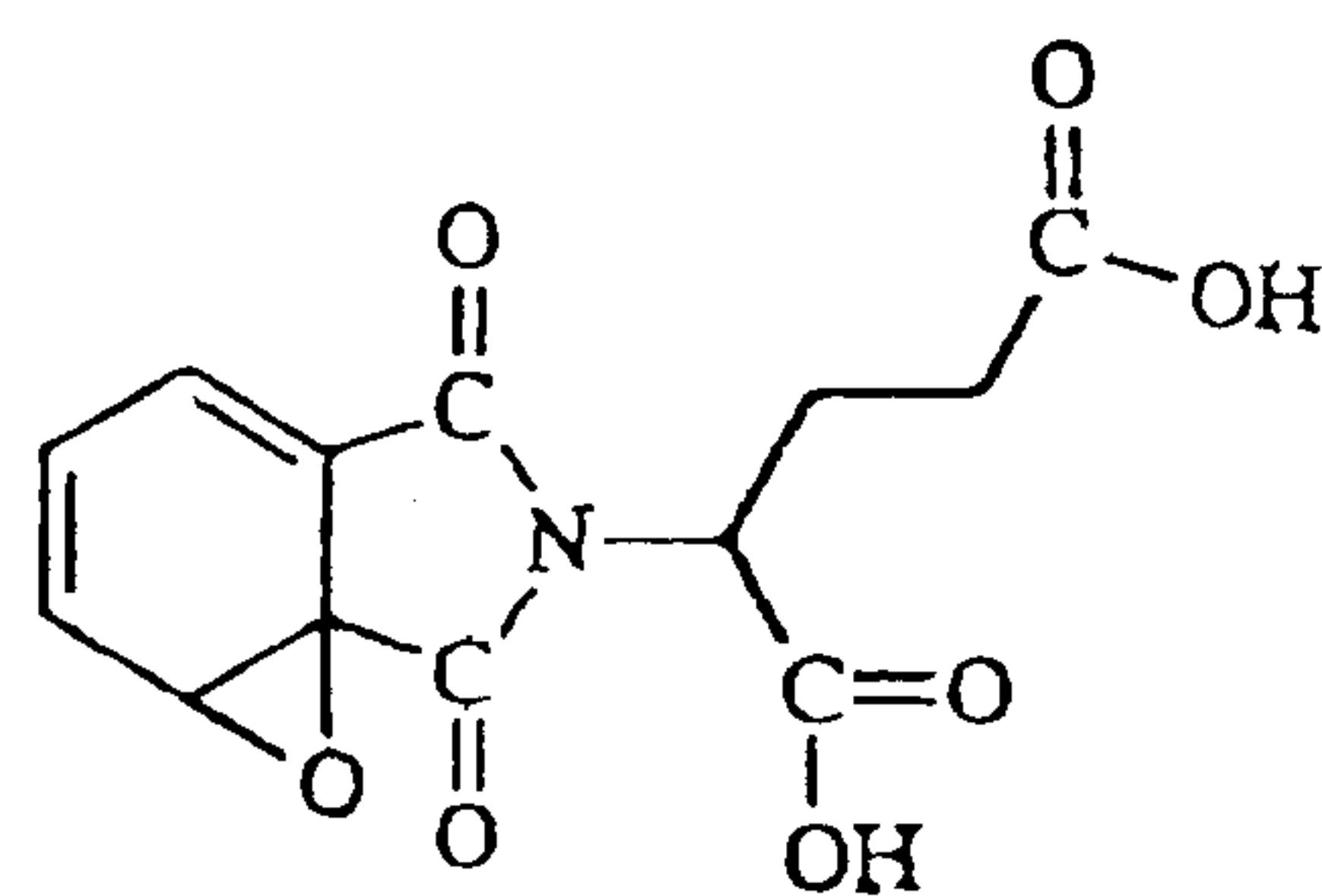
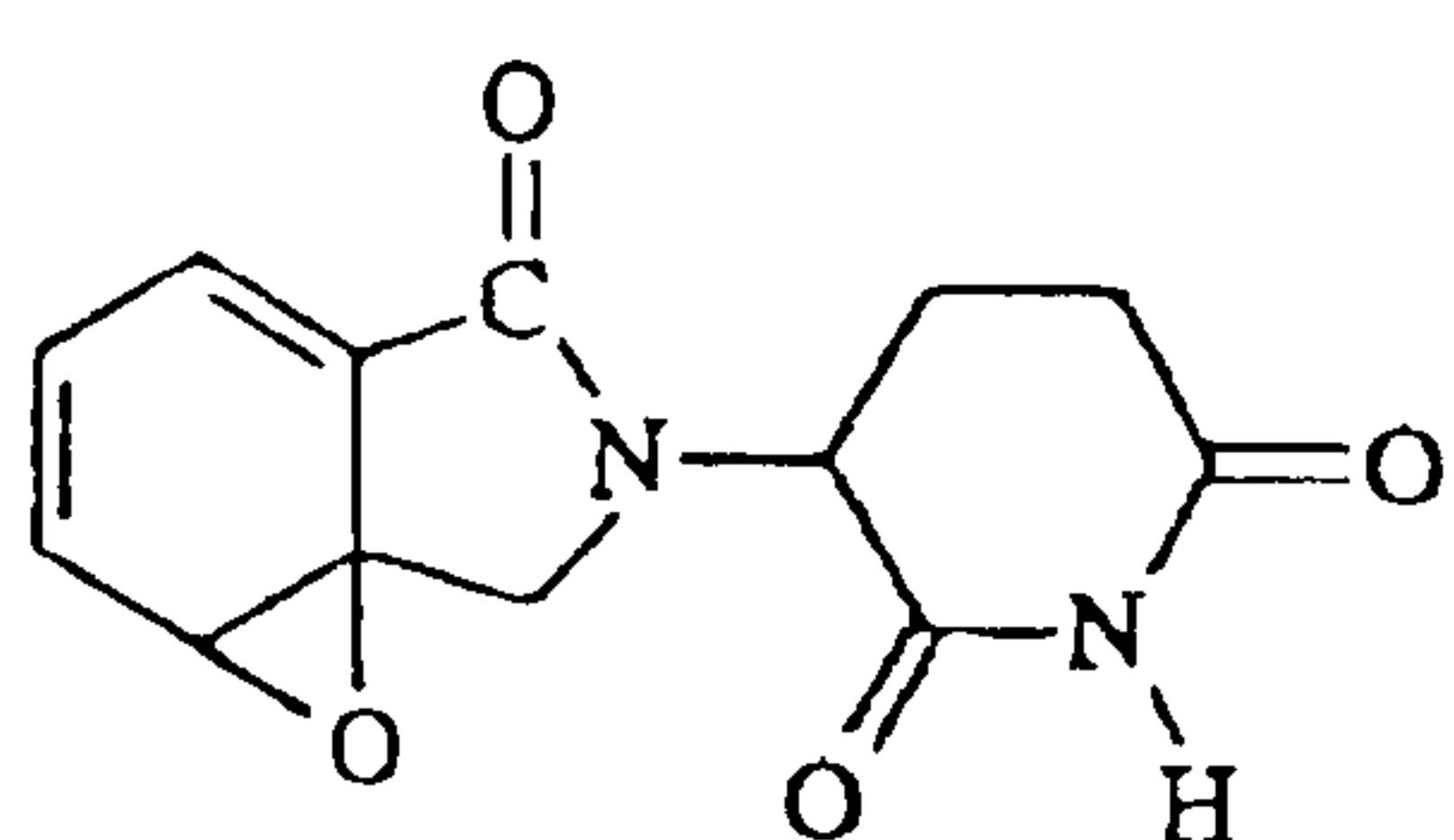
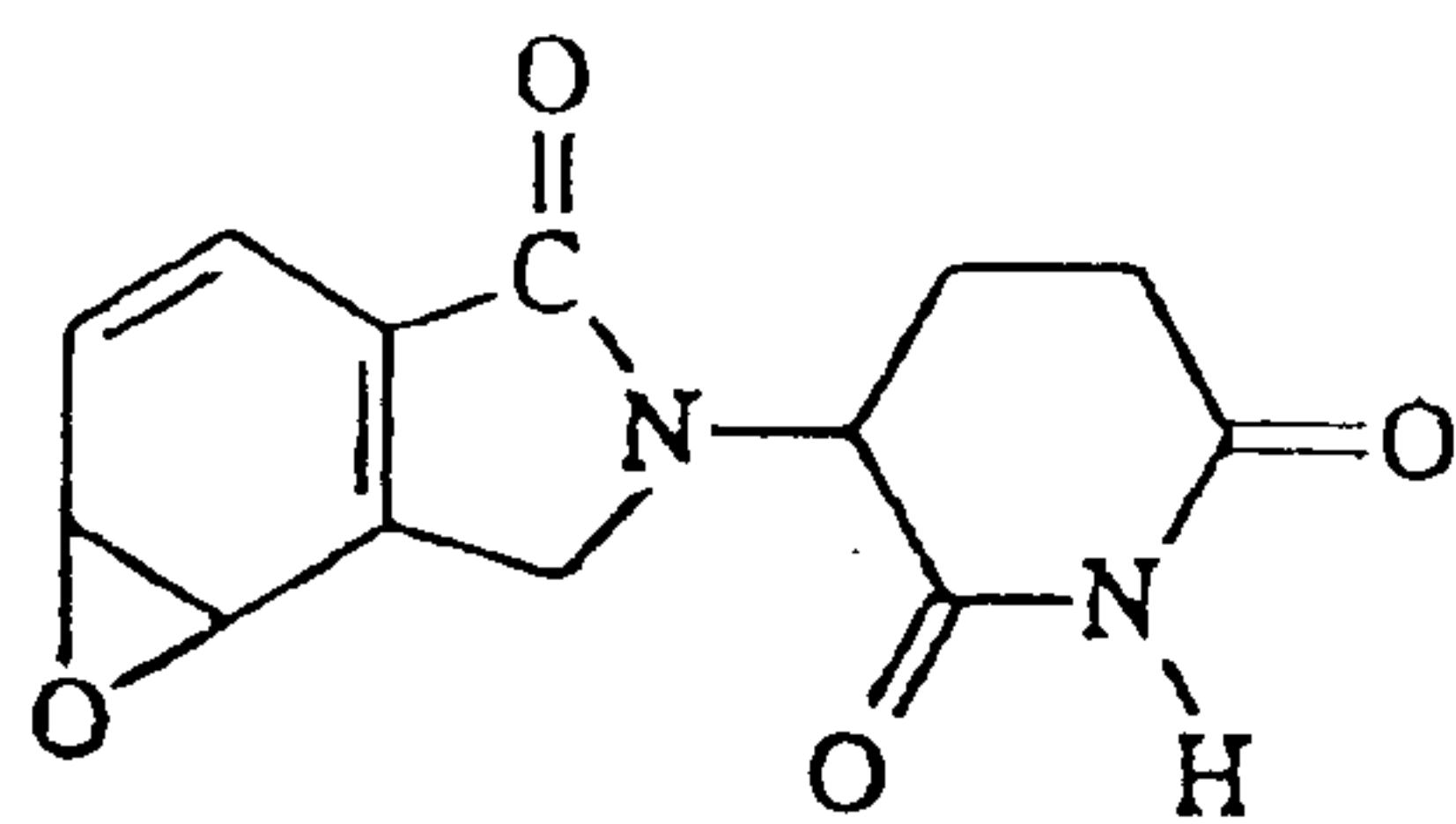
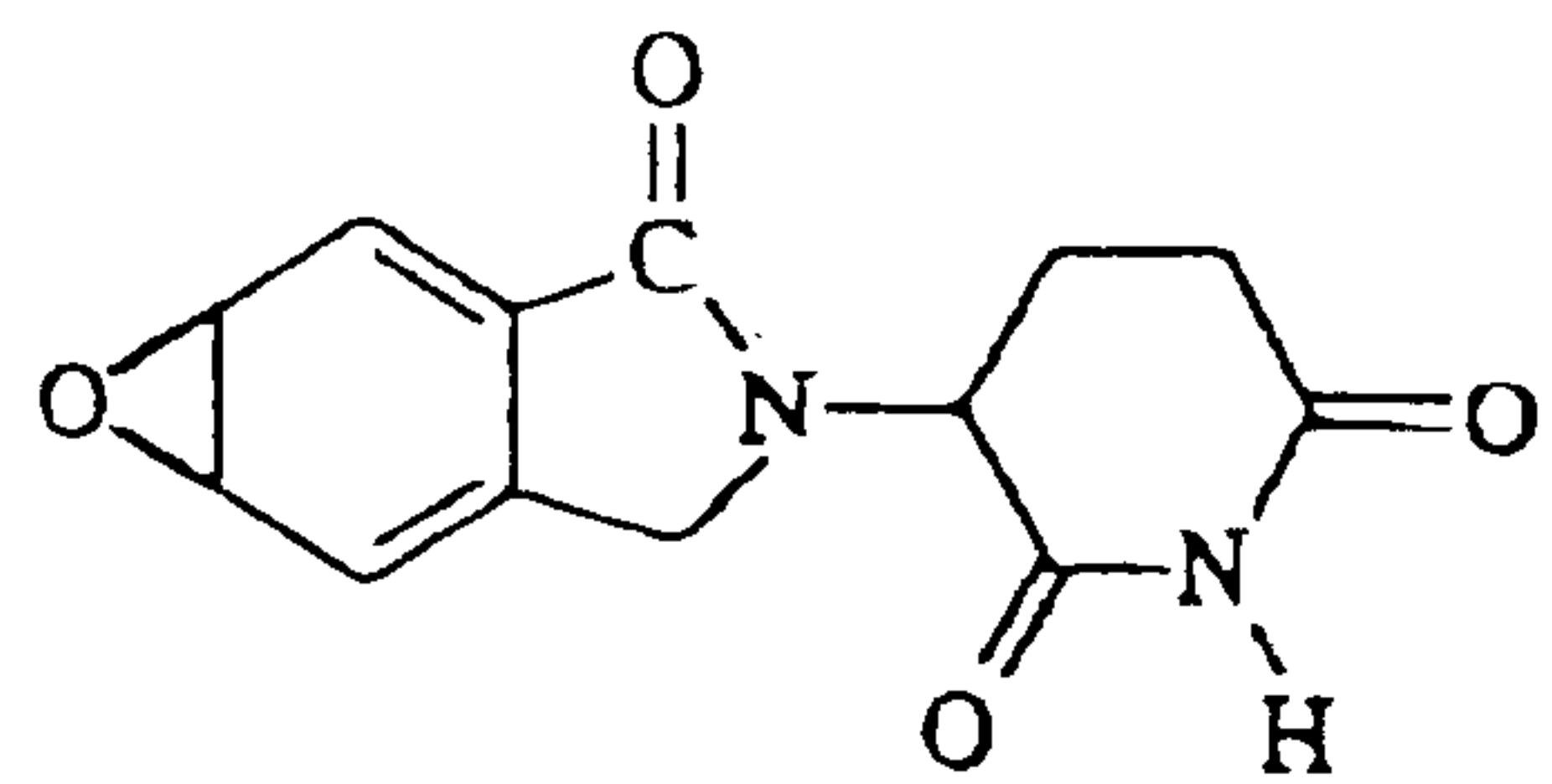
7. The use according to claim 1, wherein the compound is selected from the group of compounds shown below:

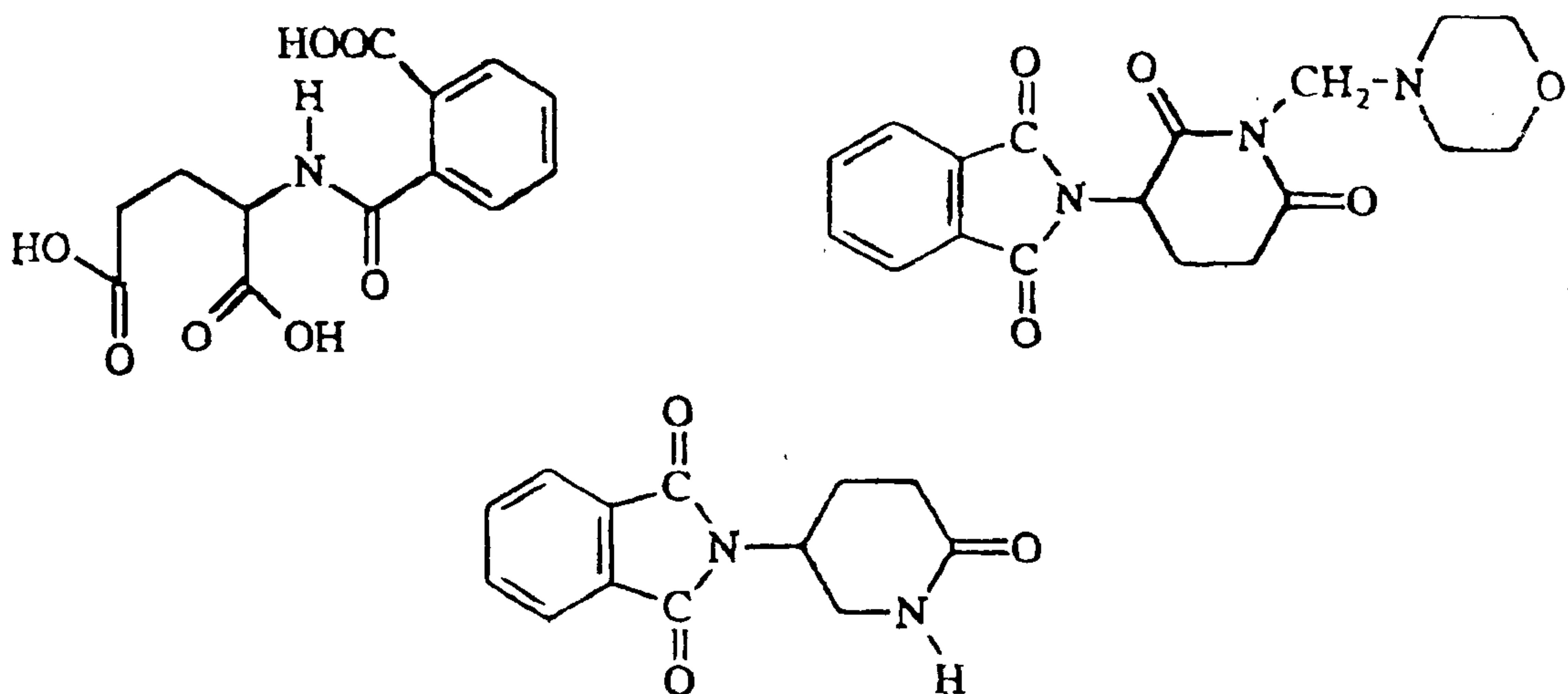


Where R = -H, -OH, or -CH₃



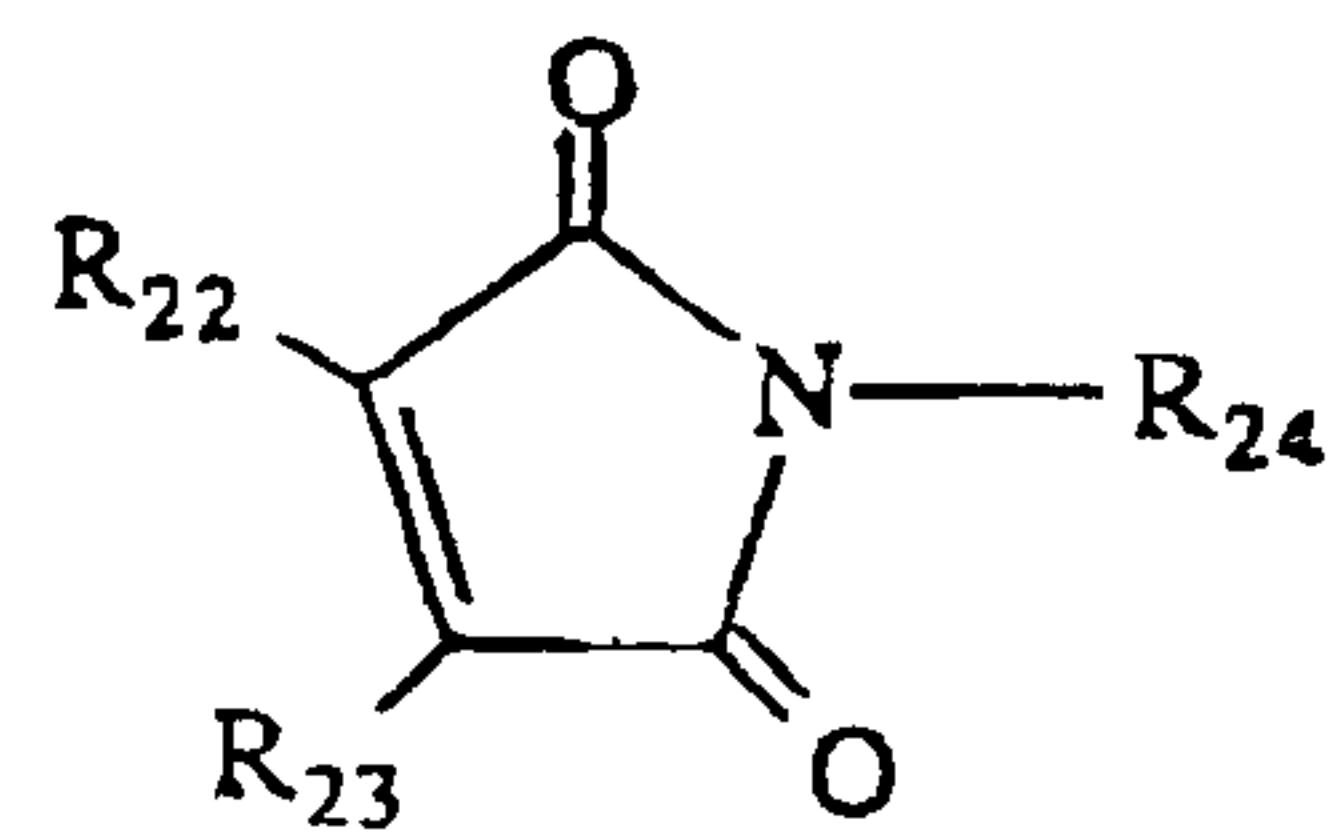






8. The use according to claim 1, wherein the composition further comprises an epoxide hydrolase inhibitor.

9. The use of a composition administered for treating undesired angiogenesis in a human or animal wherein a composition comprises an effective amount of an angiogenesis-inhibiting compound selected from the group consisting of the following compounds:

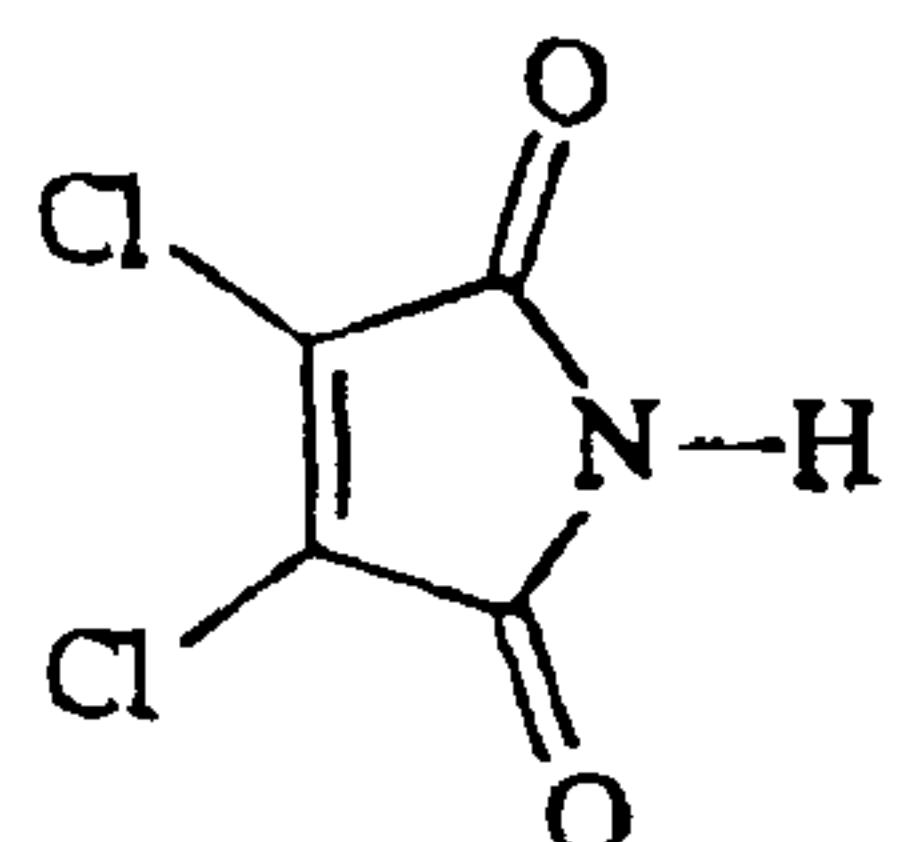
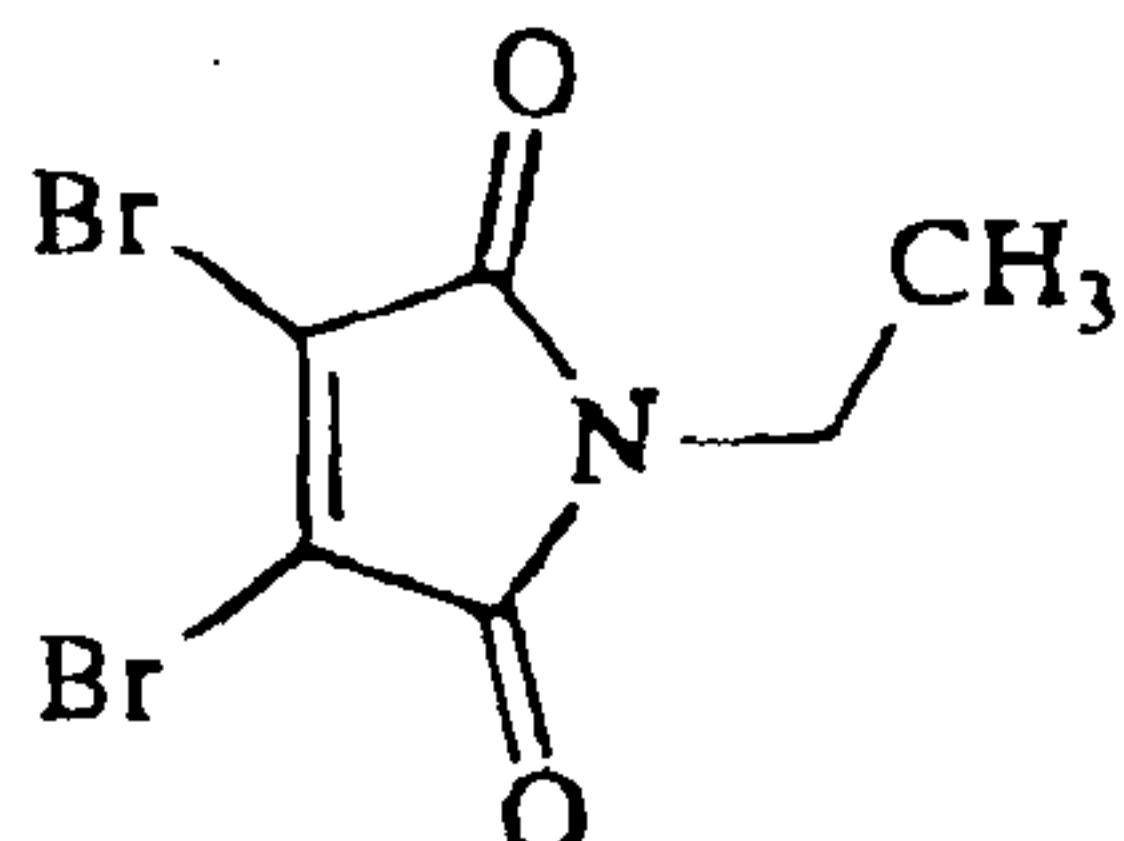
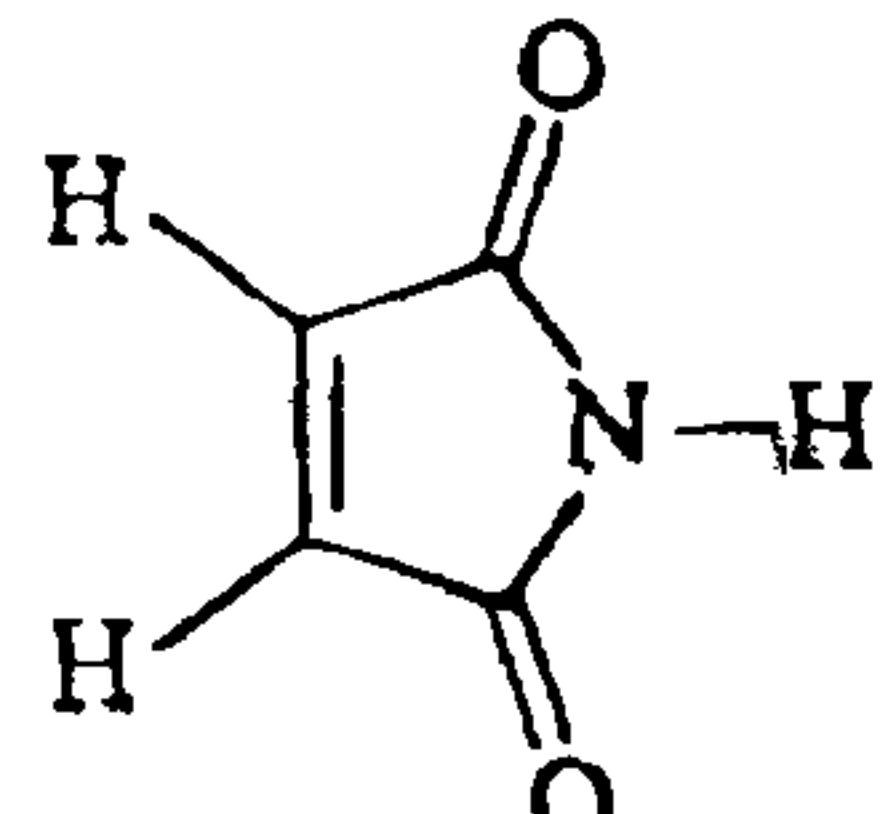
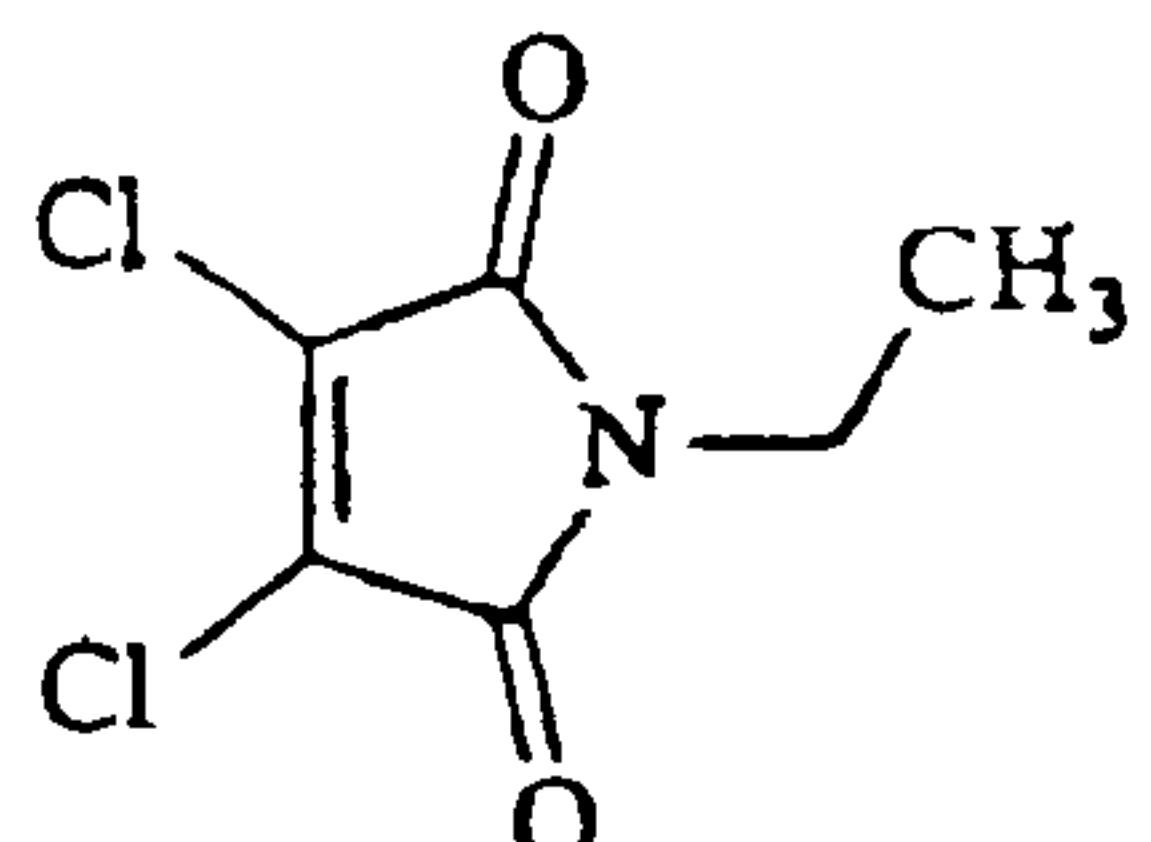
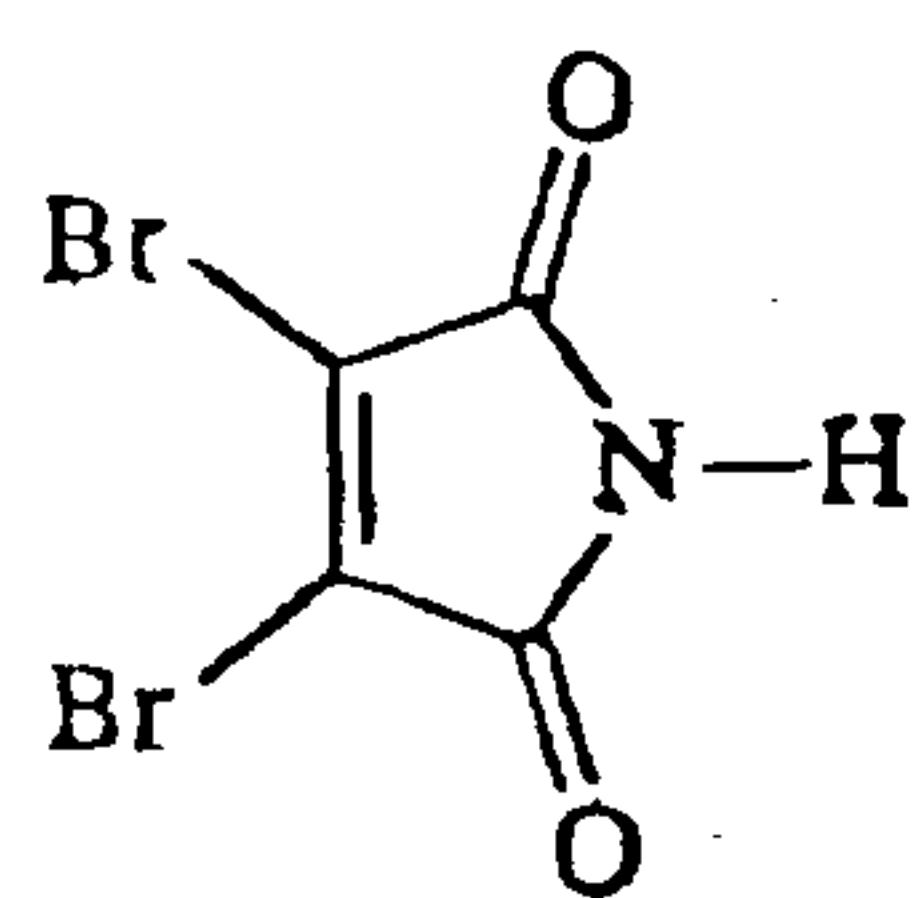
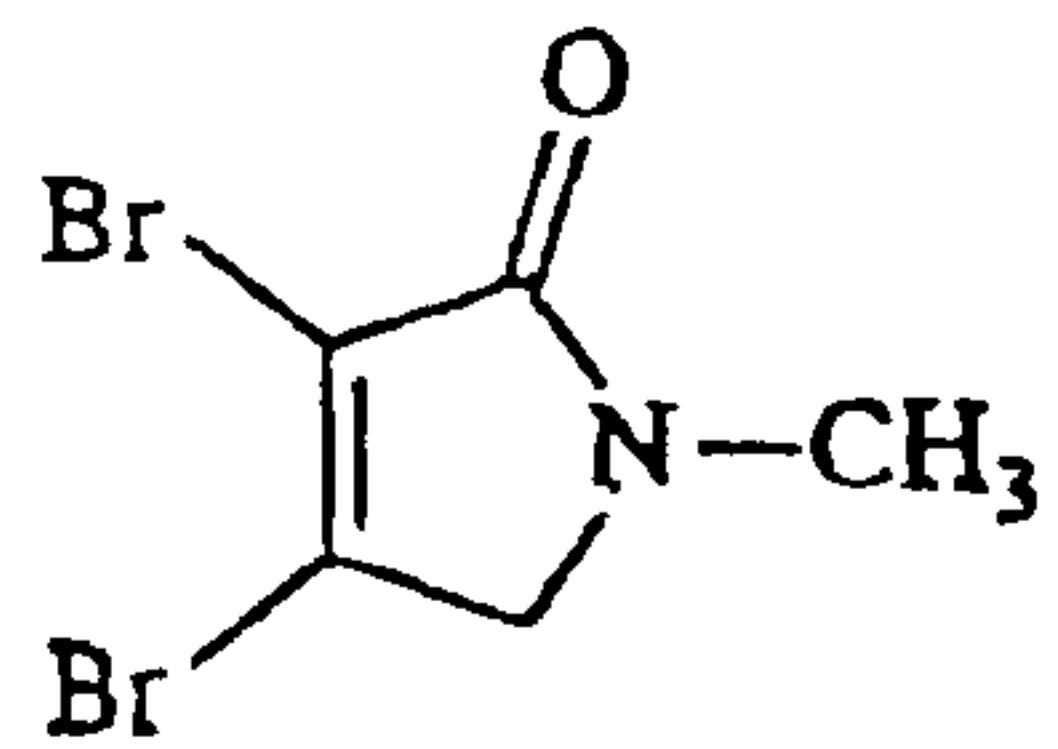
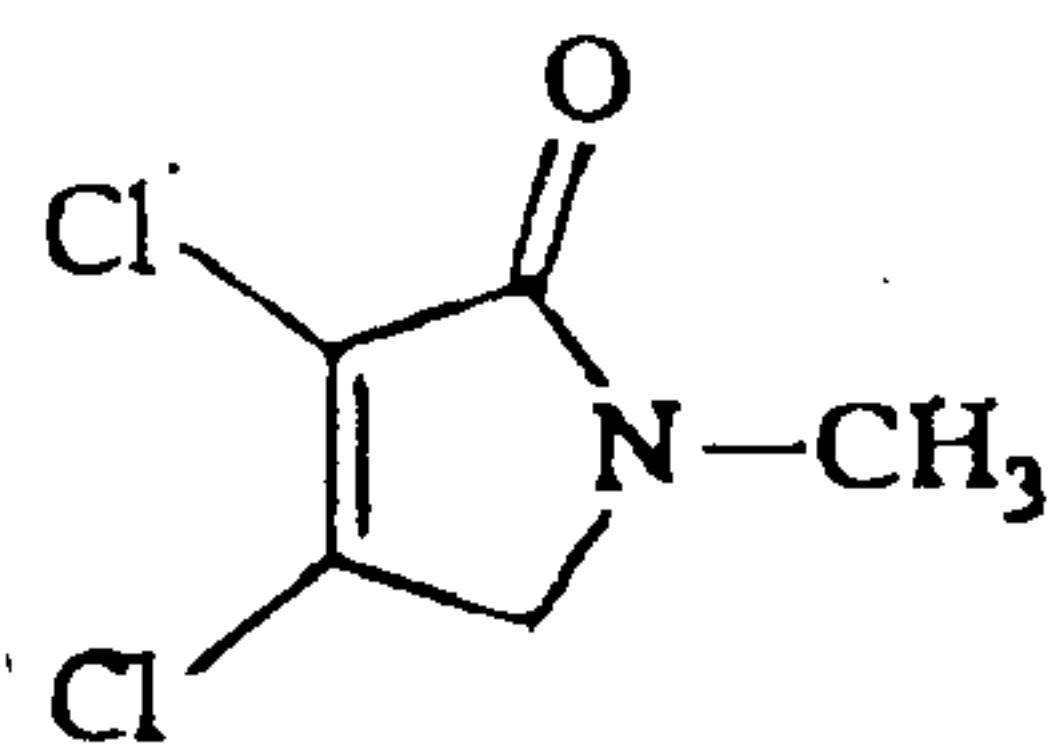


where R_{21} and R_{23} are (independently), -H, -F, -Cl, -Br, -I, -CH₃, or -CH₂-CH₃ and R_{24} is -H, -OH, -CH₃, or -CH₂-CH₃.

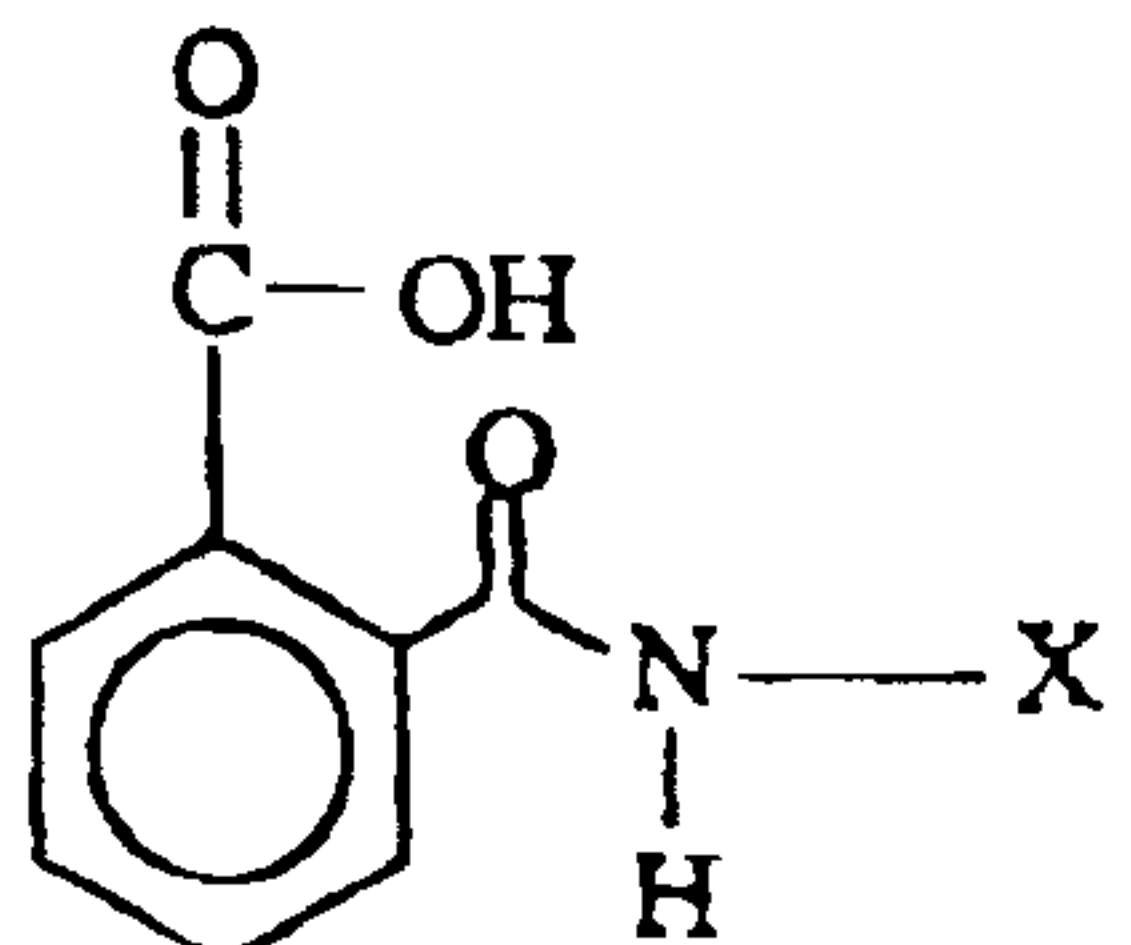
10. The use according to claim 9, wherein the composition further comprises an epoxide hydrolase inhibitor.

11. The use according to claim 9, wherein the compound is selected from the group

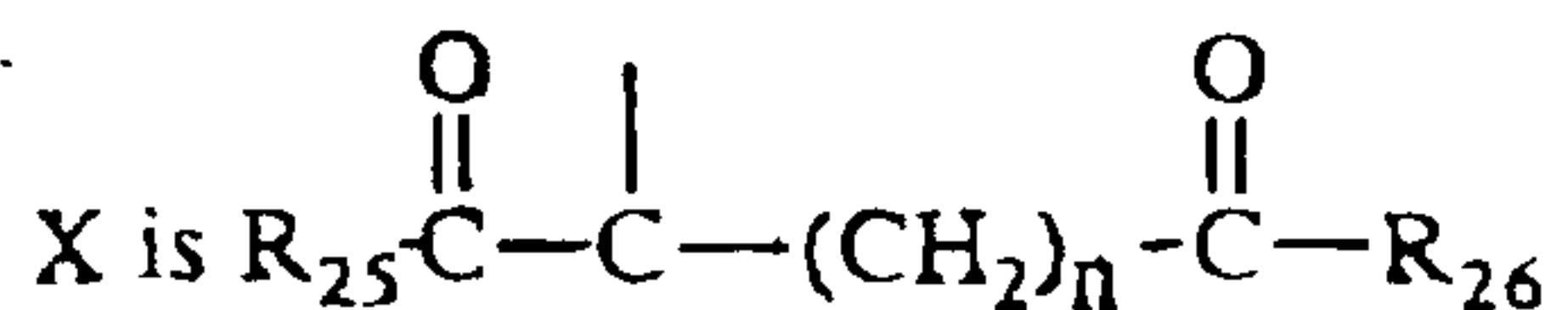
of compounds shown below:



12. The use of a compound administered for treating undesired angiogenesis in a human or animal wherein the compound is selected from the group consisting of the following compounds:

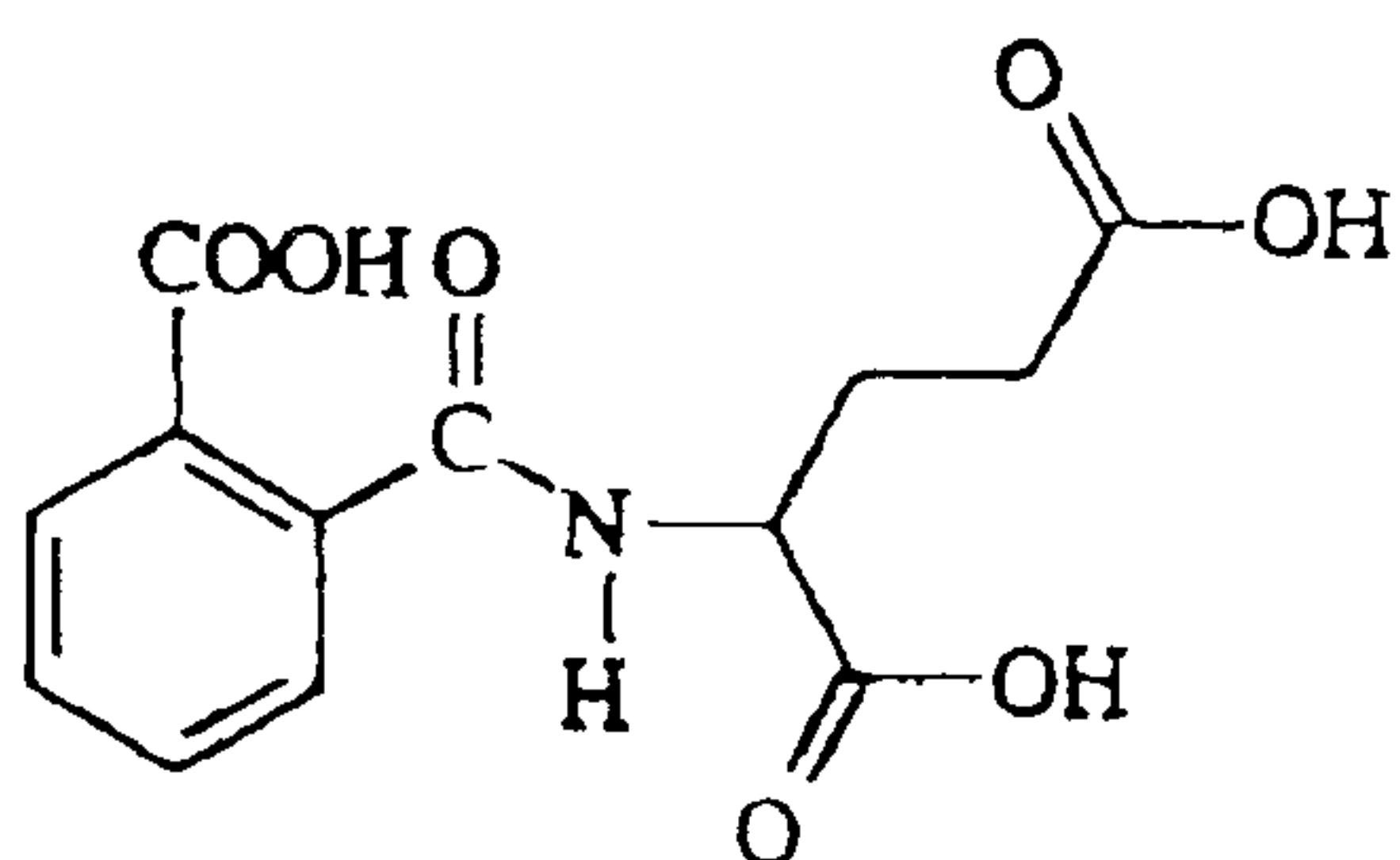
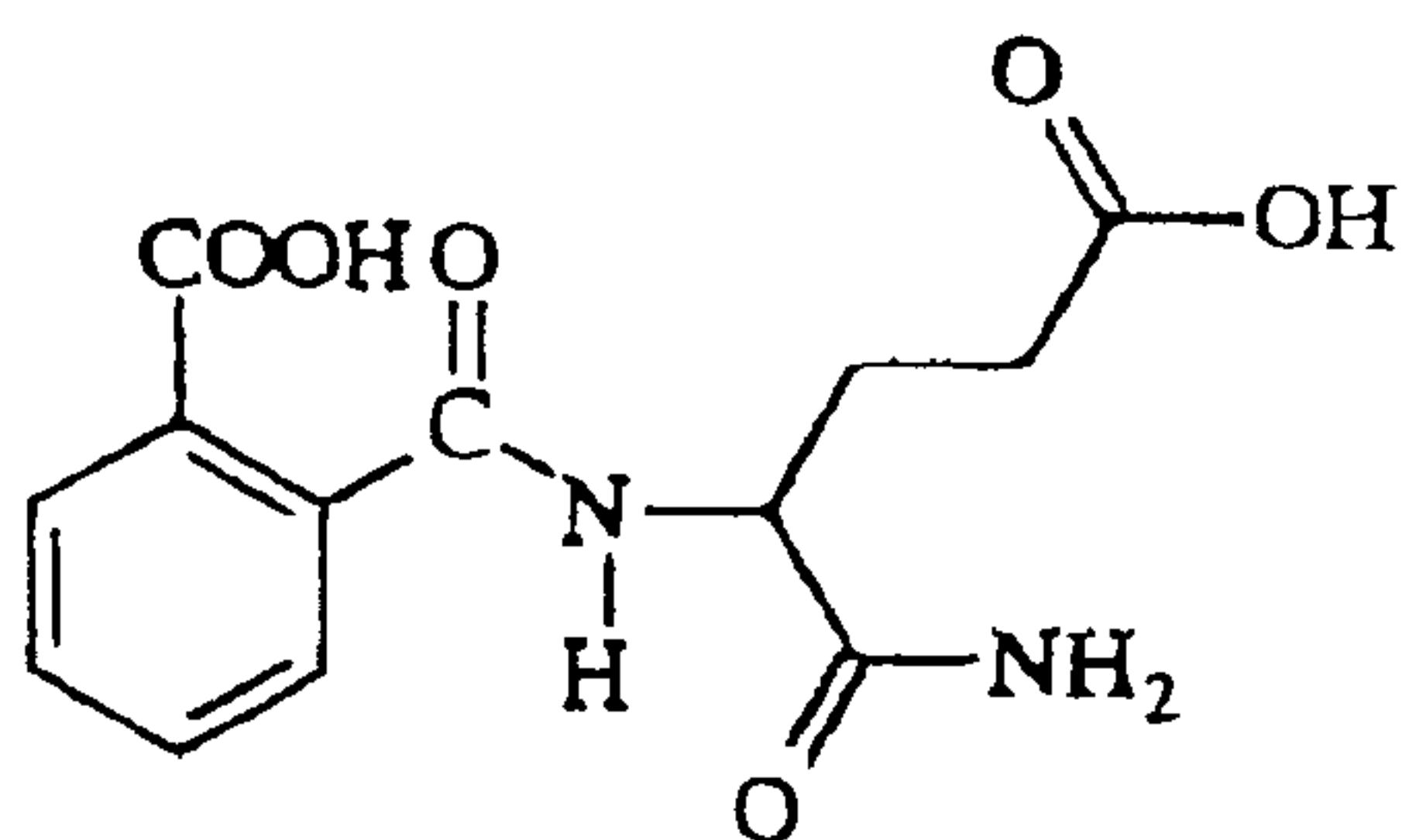
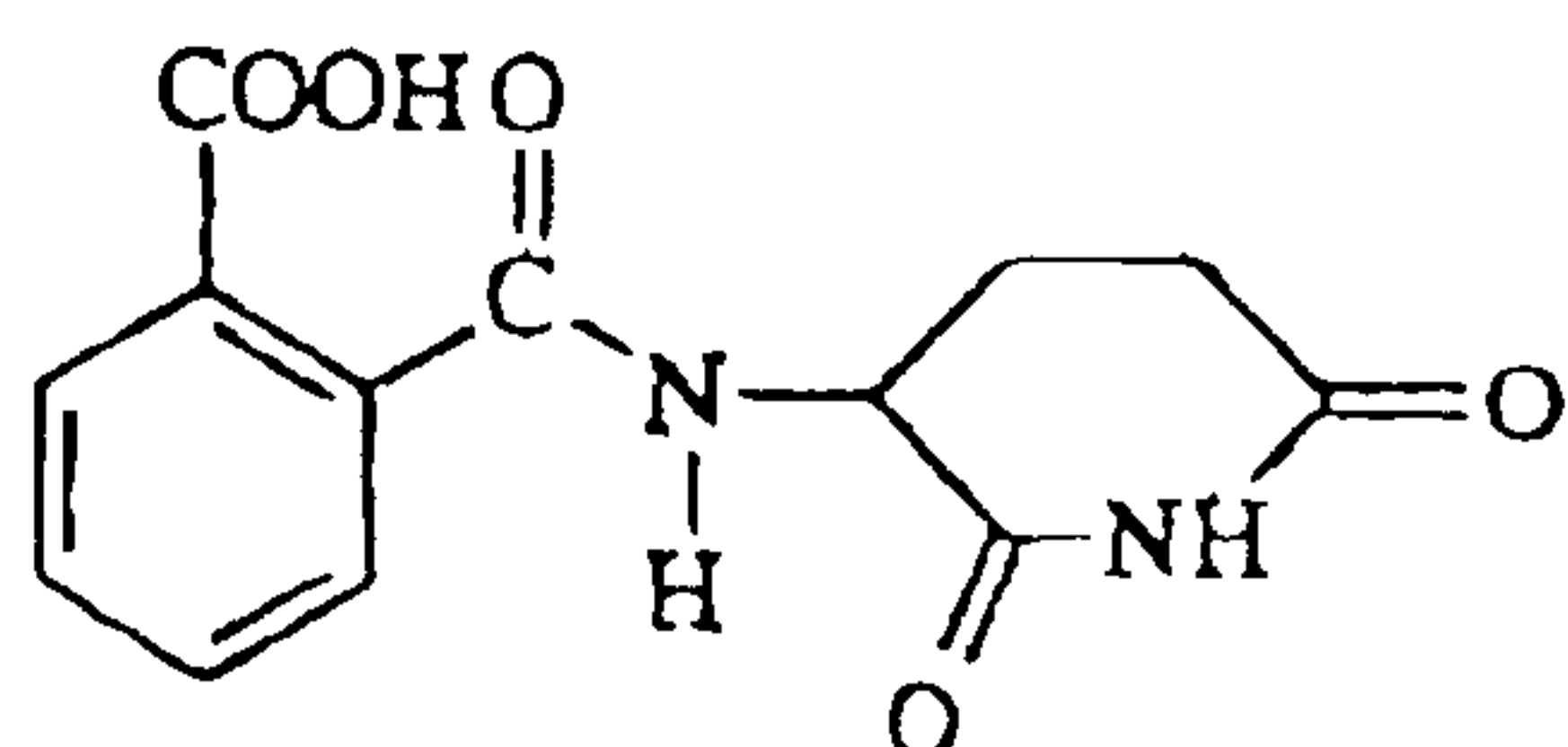
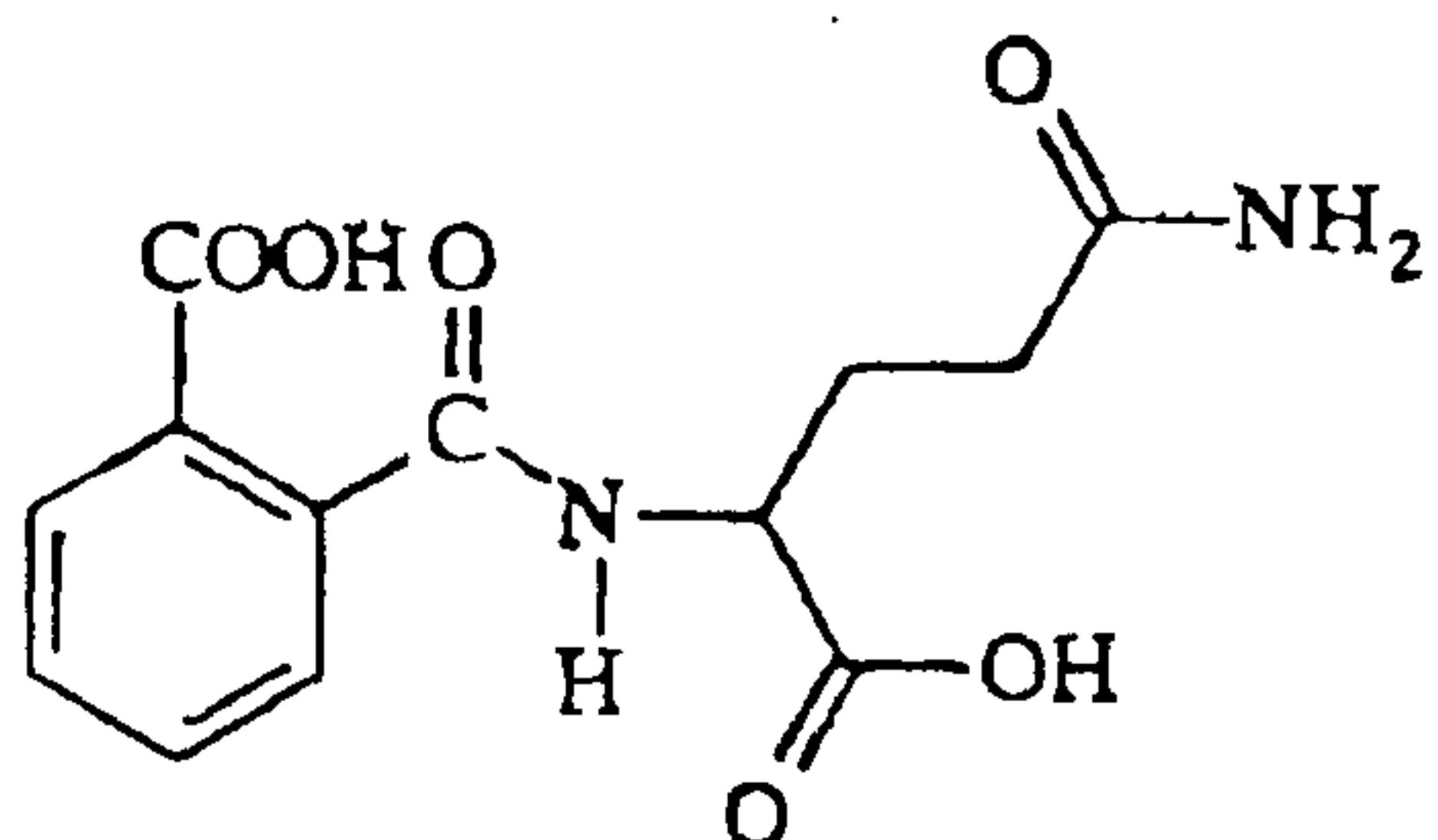


where X is R_6 as defined above, or X is



and R₂₅ and R₂₆ are, independently, -OH, -H, or -NH₂.

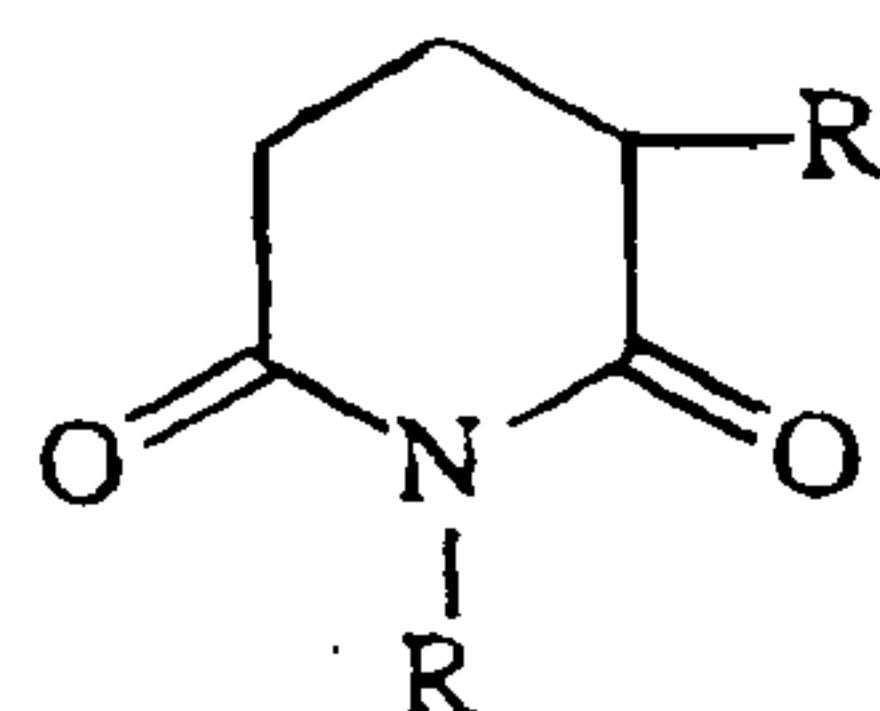
13. The use according to claim 12, wherein the compound is selected from the group consisting of the compounds shown below:



14. The use according to claim 12, wherein the composition further comprises an epoxide hydrolase inhibitor.

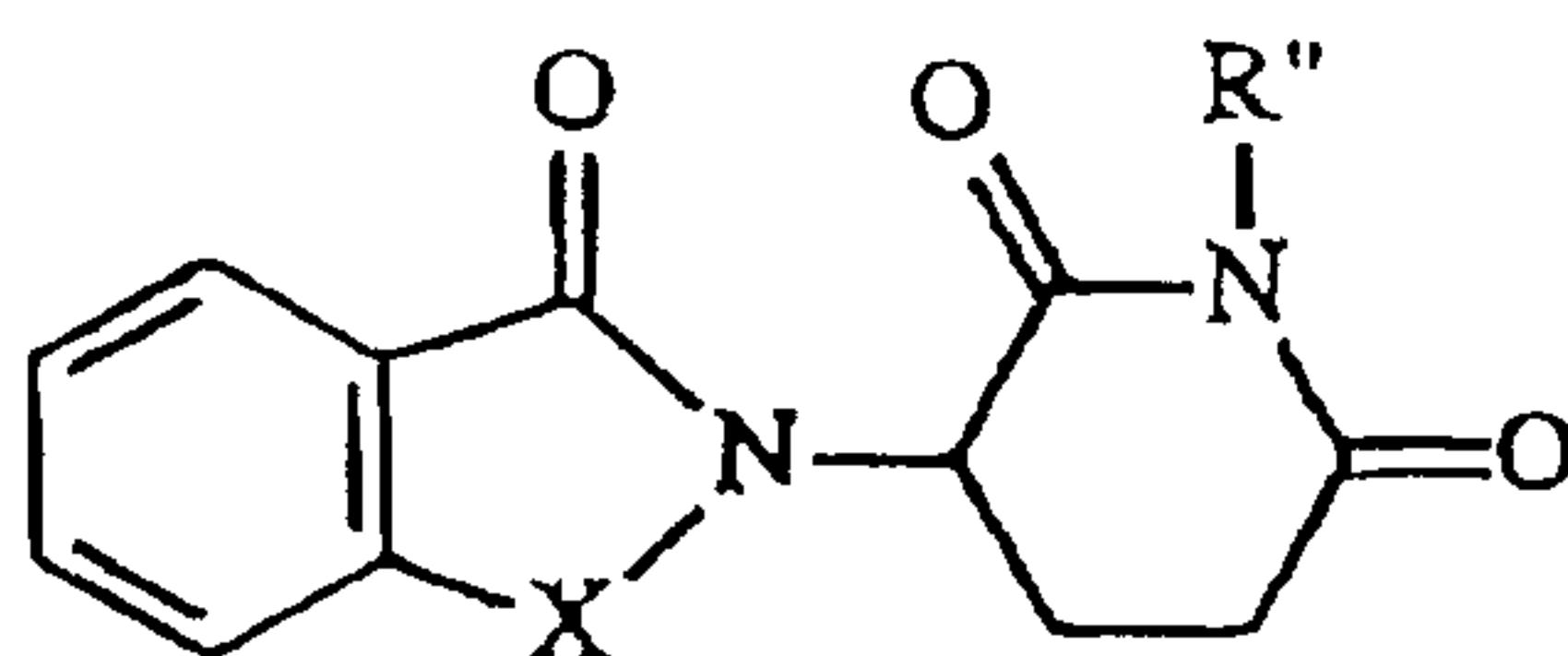
15. The use of a composition administered for treating undesired angiogenesis in a human or animal wherein the composition comprises an effective amount of an angiogenesis-inhibiting compound selected from the group consisting of the following compounds:

(I)



and

(II)



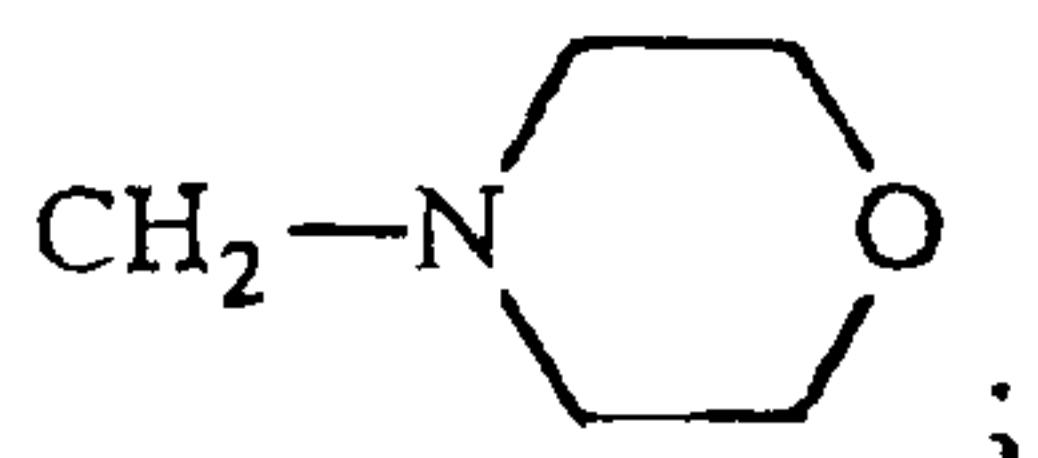
wherein

R is selected from the group consisting of H, (C₁-C₆)alkyl, phenyl, and benzyl;

R' is selected from the group consisting of phthalimido and succinimido;

X is CH₂ or C=O; and

R'' is H, -CH₂CH₃, -C₆H₅, -CH₂C₆H₅, -CH₂CH=CH₂, or



and

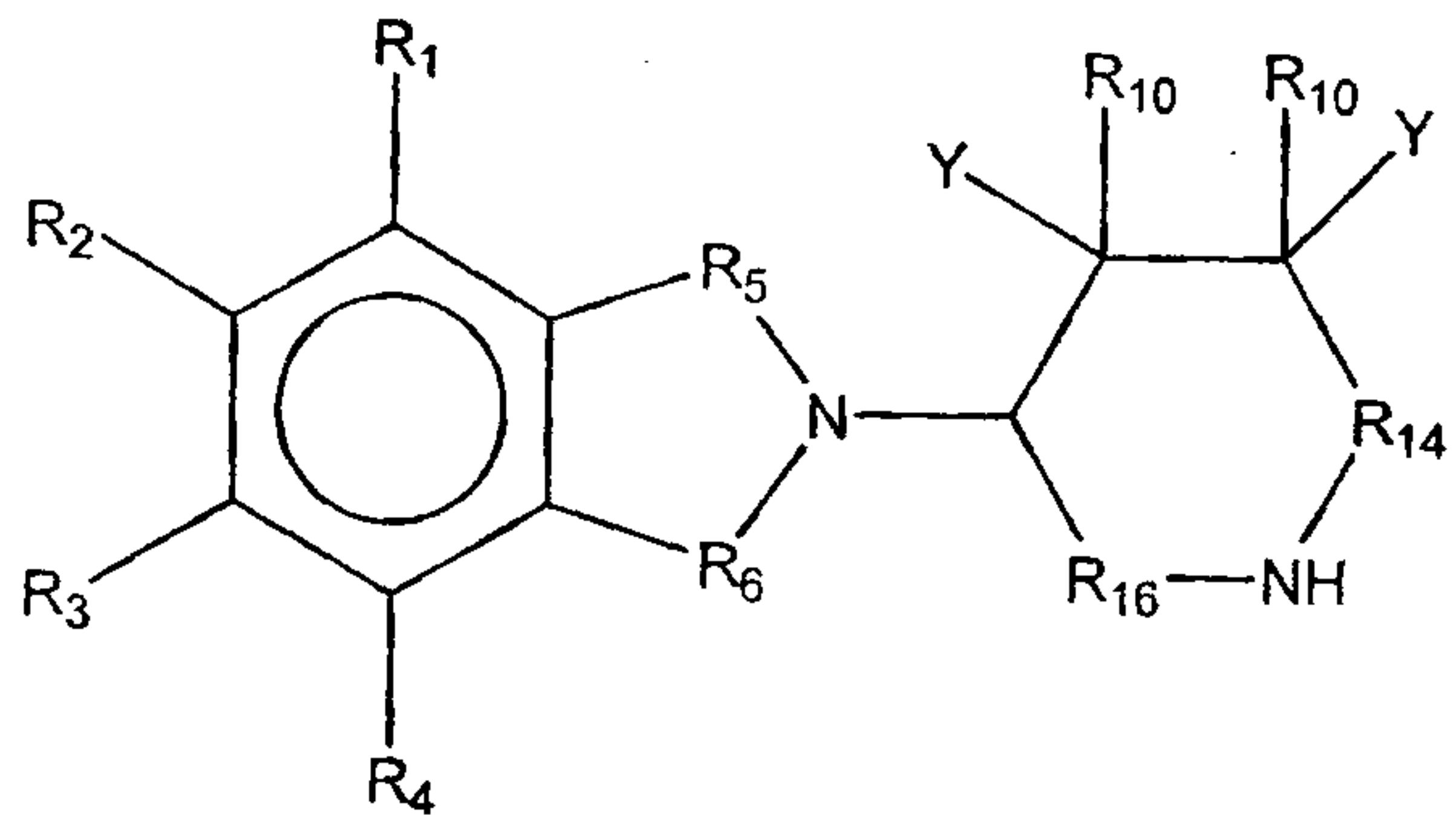
(III) hydrolysis products of (II) wherein R'' is H and the piperidino ring or both the piperidino and the imido ring are hydrolyzed;

provided the compound is not thalidomide.

16. The use of a composition administered for treating undesired angiogenesis in a human or animal wherein the composition comprises an effective amount of an angiogenesis-inhibiting compound selected from the group consisting of α -thalidomide, EM-12, EM-138, phthaloyl glutamic anhydride and phthaloyl glutamic acid and metabolites of thalidomide, EM-12, EM-138, phthaloyl glutamic anhydride and phthaloyl glutamic acid, or mixtures thereof.

17. The use according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16, wherein the undesired angiogenesis occurs in a disease selected from the group consisting of diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogren's syndrome, acne rosacea, phlyctenulosis, syphilis, *Micobacteria* infections other than leprosy, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex* infections, *Herpes zoster* infections, protozoan infections, Kaposi's sarcoma, Mooren's ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis, systemic lupus erythematosis, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, radial keratotomy, macular degeneration, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales' disease, Behcet's disease, infections causing retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, post-laser complications, rubeosis, abnormal proliferation of fibrovascular or fibrous tissue, proliferative vitreoretinopathy, Bartonellosis, hemangiomas, Osler-Weber-Rendu disease, solid tumors, blood-borne tumors, acquired immune deficiency syndrome, ocular neovascular disease, age-related macular degeneration, osteoarthritis, diseases caused by chronic inflammation, Crohn's disease, ulcerative colitis, tumors of rhabdomyosarcoma, tumors of retinblastoma, tumors of Ewing's sarcoma, tumors of neuroblastoma, tumors of osteosarcoma, leukemia, psoriasis, atherosclerosis, acoustic neuroma, neurofibroma, trachoma, pyogenic granulomas and pemphigoid.

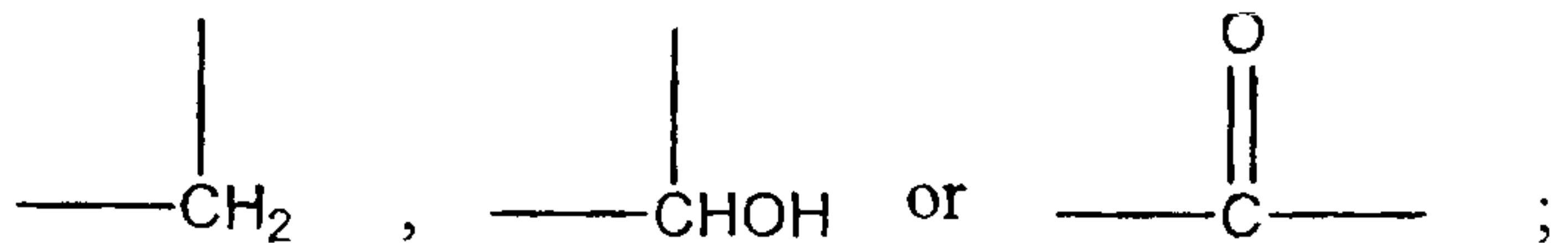
18. The use of an angiogenesis inhibiting amount of a compound in administratable form for treating solid tumors in a human comprising administering to a human in need wherein the compound comprises the formula:



wherein:

R₁, R₂, R₃ and R₄ are each independently -H; -OH; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkene; cyclic alkyne; alcohol, aldehyde, ketone, ester or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -NO₂; -SO₂; -SO₃; -PO₃; -O-PO₃ or halogen;

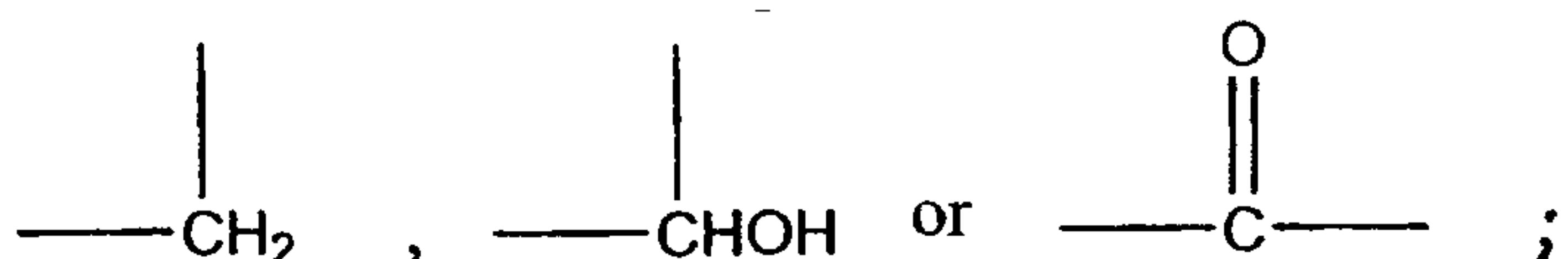
R₅ and R₆ are each independently,



Y is optional and each occurrence of Y is -H; -OH; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkene; cyclic alkyne; alcohol, aldehyde, ketone, ester or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -NO₂; -SO₂; -SO₃; -PO₃; -O-PO₃ or halogen;

each occurrence of R₁₀ is -H; -OH; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkenecyclic alkyne; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic,

cyclic, or combination acyclic/cyclic moieties; aza; amino $-\text{NO}_2$; $-\text{SO}_2$; $-\text{SO}_3$; $-\text{PO}_3$; $-\text{O-PO}_3$; halogen, or when Y is absent R_{10} is $=\text{O}$; and R_{14} and R_{16} are each independently

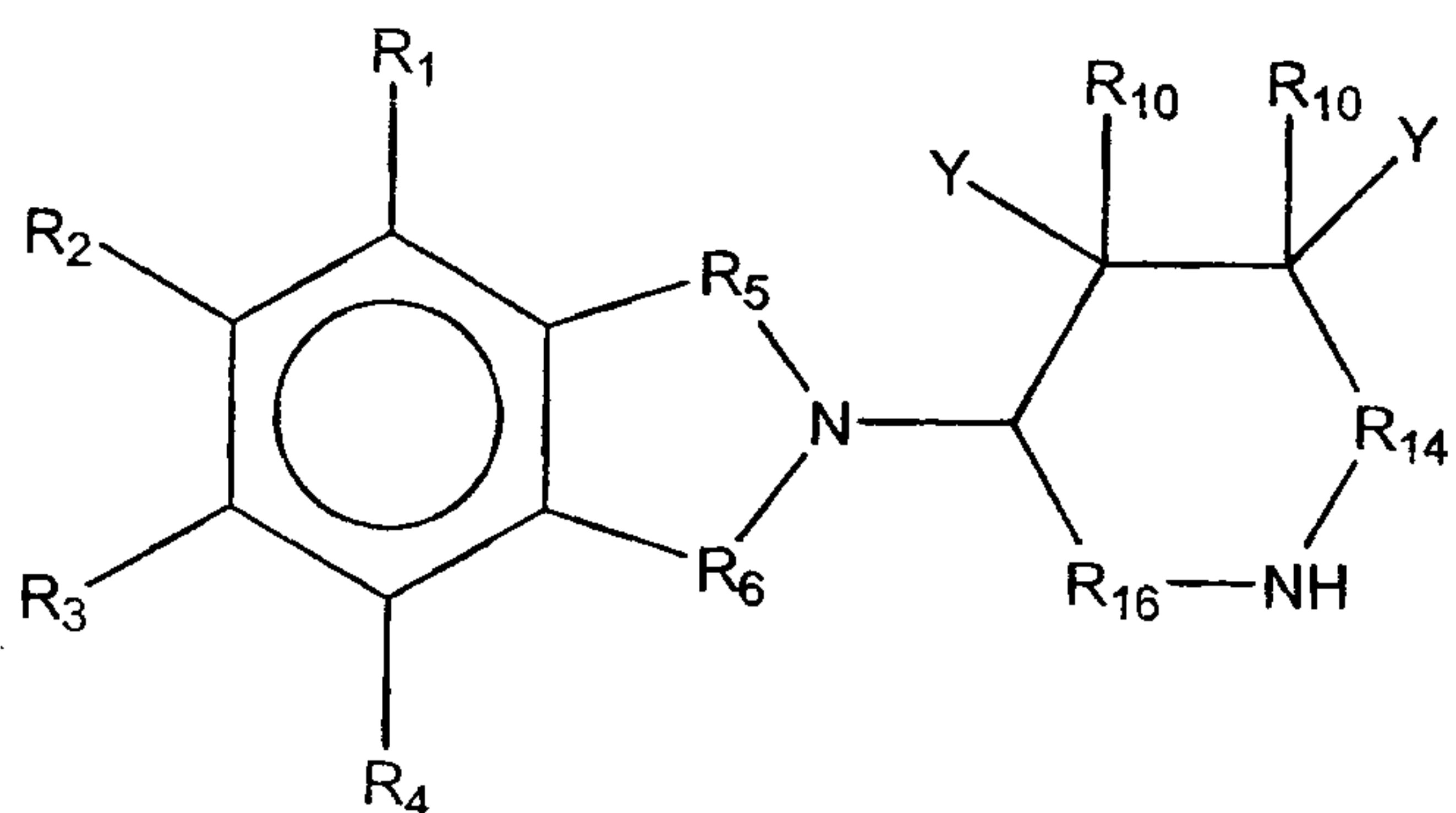


provided the compound is not thalidomide.

19. The use according to claim 18 wherein the solid tumour is of the group consisting of breast carcinoma, rhabdomyosarcoma, retinoblastoma, Ewing sarcoma, neuroblastoma, osteosarcoma, acoustic neuroma, neurofibroma, trachoma and pyogenic granuloma.

20. The use according to claim 19 wherein the solid tumour is breast carcinoma.

21. The use of an angiogenesis inhibiting amount of a compound in administratable form for treating blood-born tumors in a human wherein the compound comprises the formula:

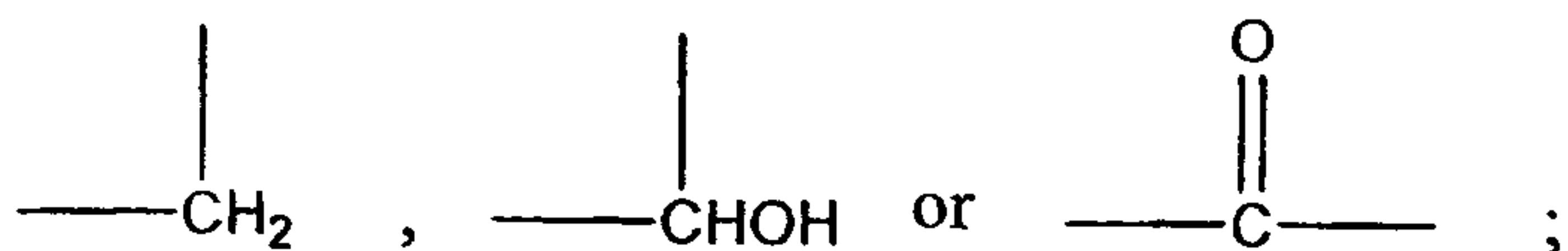


wherein:

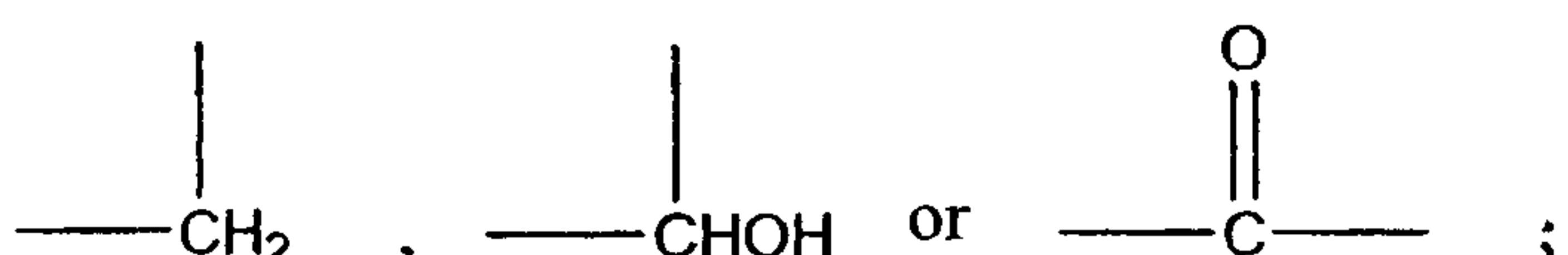
R_1 , R_2 , R_3 and R_4 are each independently $-\text{H}$; $-\text{OH}$; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkene; cyclic alkyne; alcohol, aldehyde, ketone, ester or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; $-\text{NO}_2$; $-\text{SO}_2$; $-\text{SO}_3$; $-\text{PO}_3$; $-\text{O-PO}_3$ or halogen;

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R_5 and R_6 are each independently,



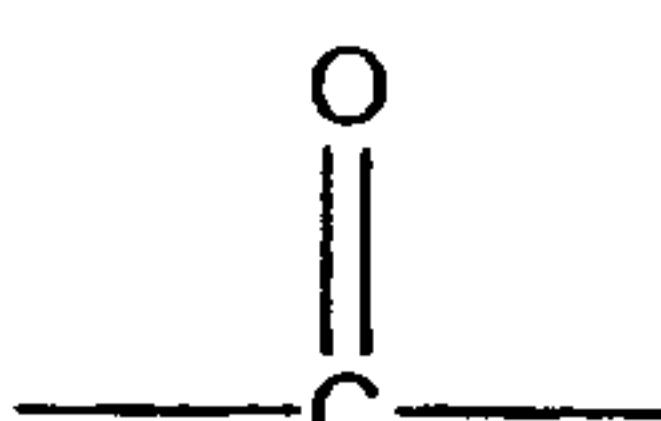
Y is optional and each occurrence of Y is $-H$; $-OH$; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkene; cyclic alkyne; alcohol, aldehyde, ketone, ester or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; $-NO_2$; $-SO_2$; $-SO_3$; $-PO_3$; $-O-PO_3$ or halogen; each occurrence of R_{10} is $-H$; $-OH$; straight chained or branched alkane; straight chained or branched alkene; straight chained or branched alkyne; cyclic alkane; cyclic alkenecyclic alkyne; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino $-NO_2$; $-SO_2$; $-SO_3$; $-PO_3$; $-O-PO_3$; halogen, or when Y is absent R_{10} is $=O$; and R_{14} and R_{16} are each independently



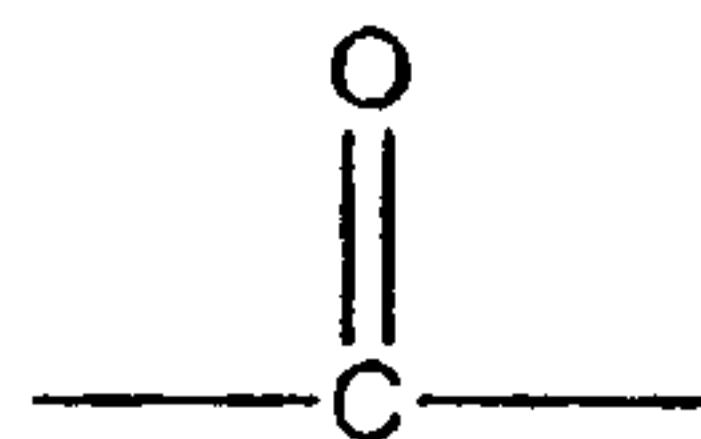
provided the compound is not thalidomide.

22. The use according to claim 21 wherein the blood-born tumour is leukemia.

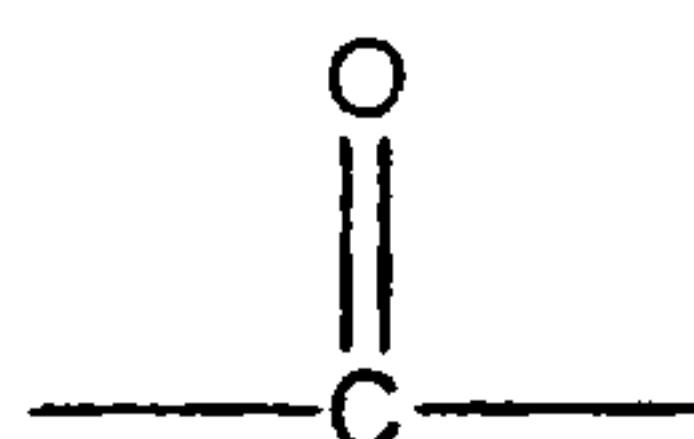
23. The use according to claim 18 or 21, wherein R_{14} and R_{16} are both



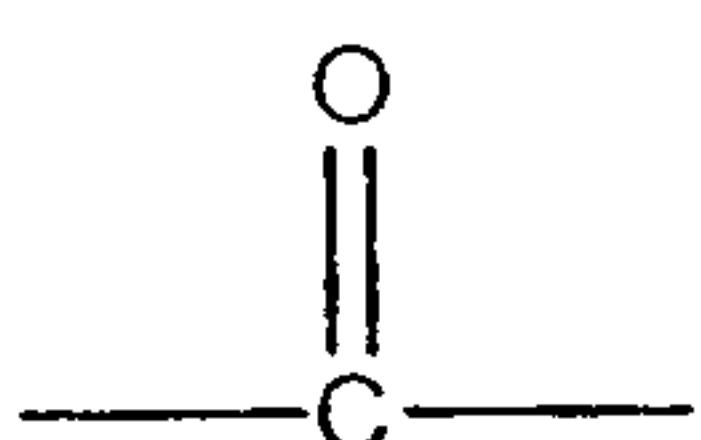
24. The use according to claim 18 or 21, wherein R_5 is



25. The use according to claim 18 or 21, wherein R₆ is



26. The use according to claim 18 or 21, wherein R₅ and R₆ are both



27. The use according to claim 26 wherein R₁, R₂, R₃ or R₄ is -OH.

28. The use according to claim 18 or 21, wherein the amount administrable form is such as to provide between approximately 0.1 and approximately 300 mg/kg/day.

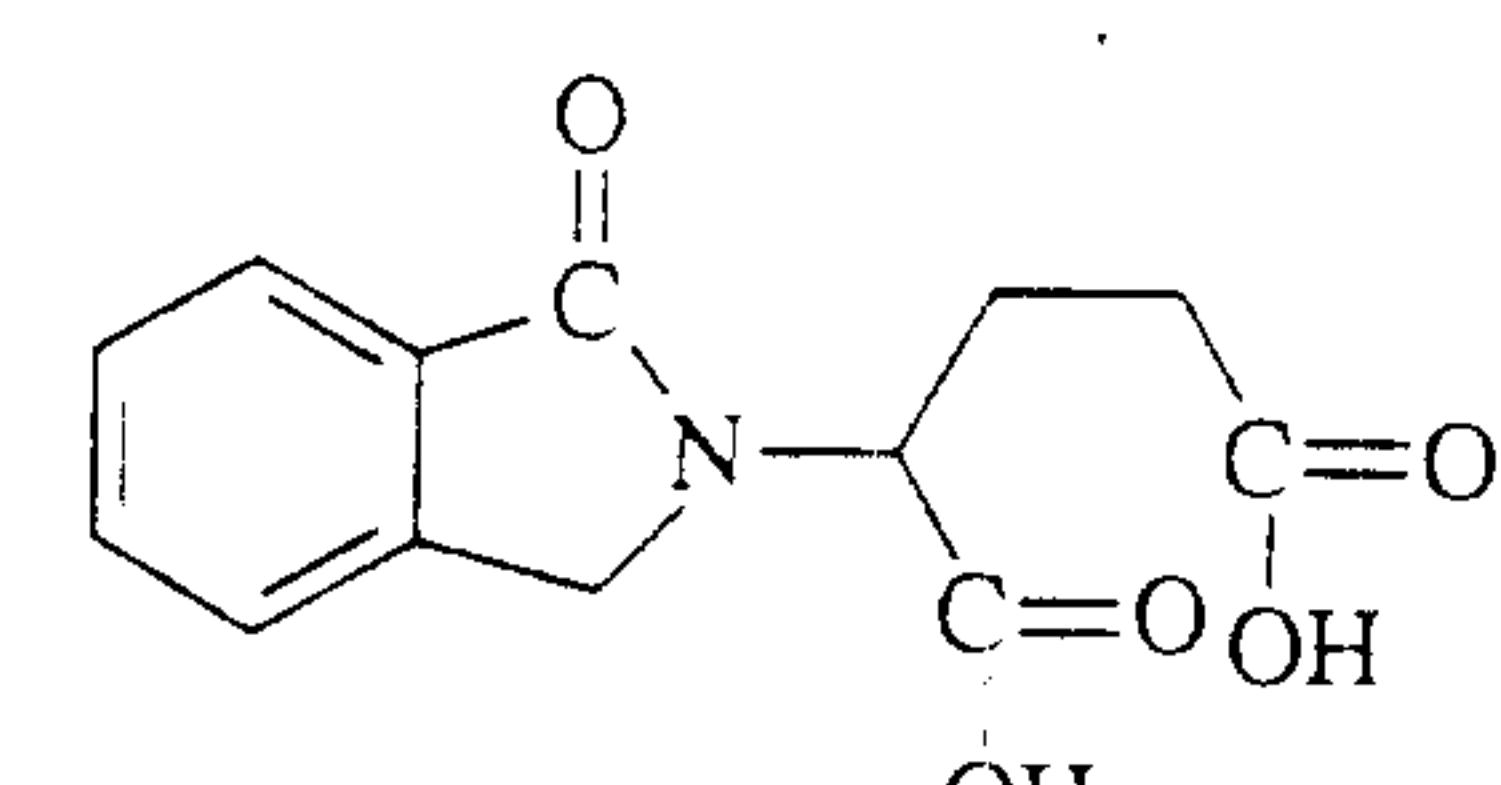
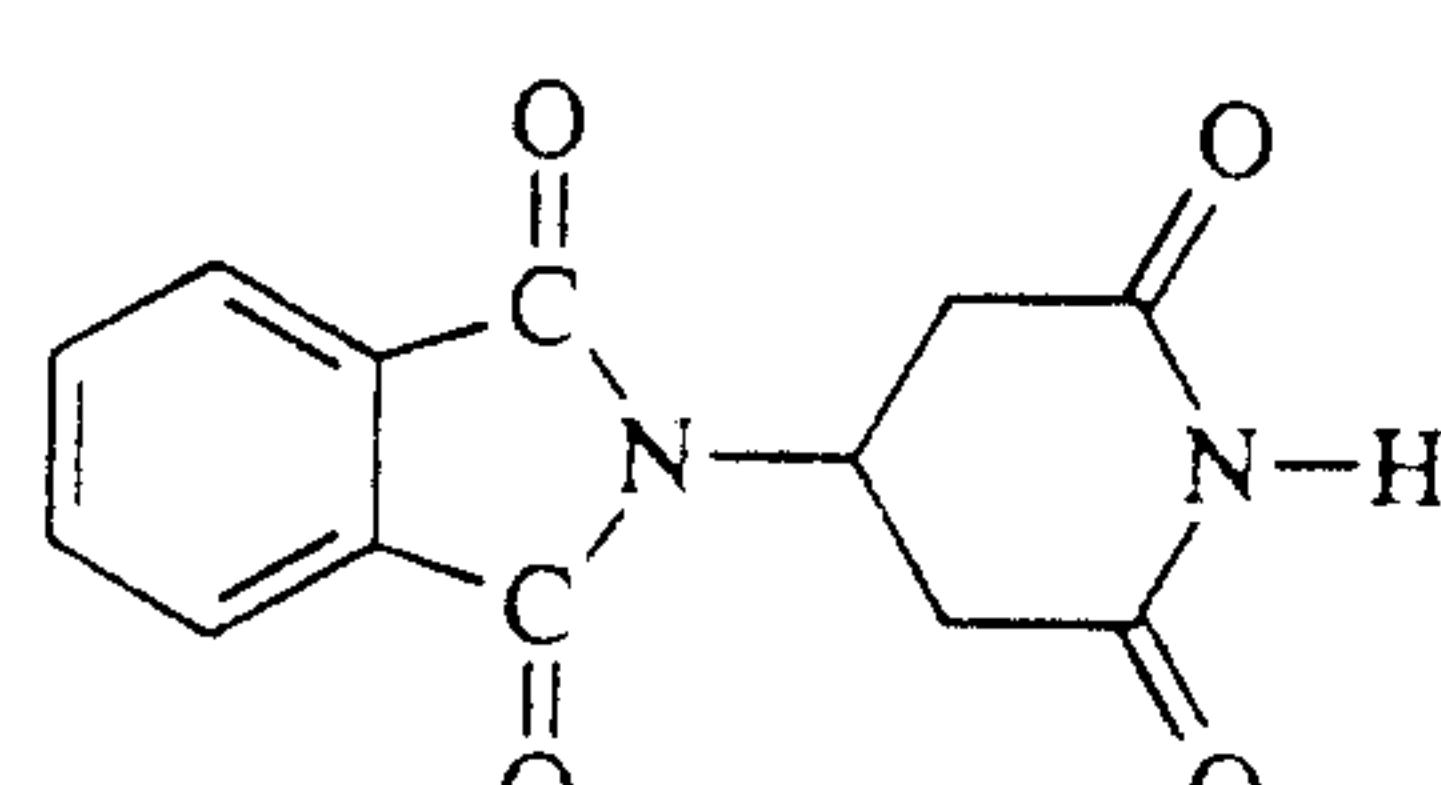
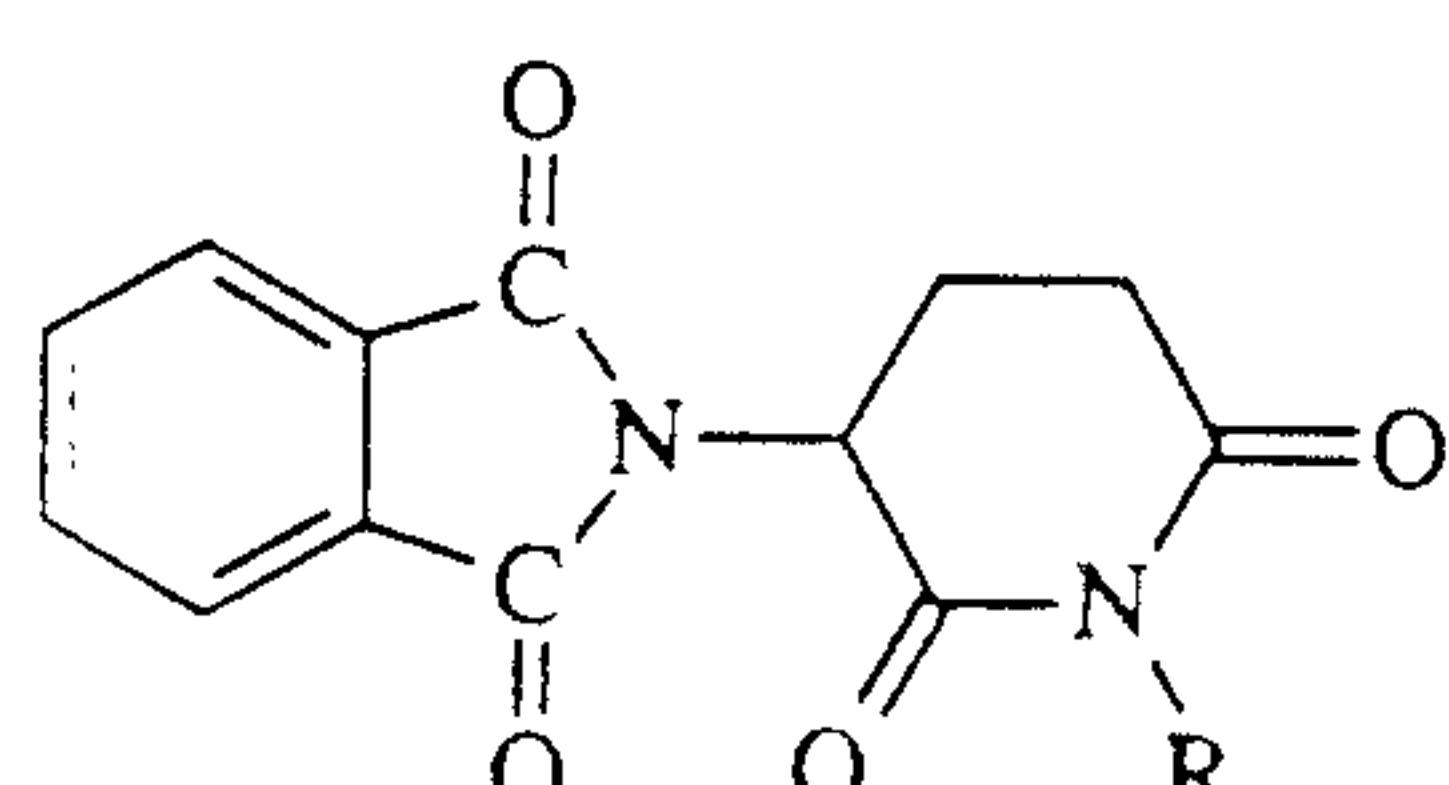
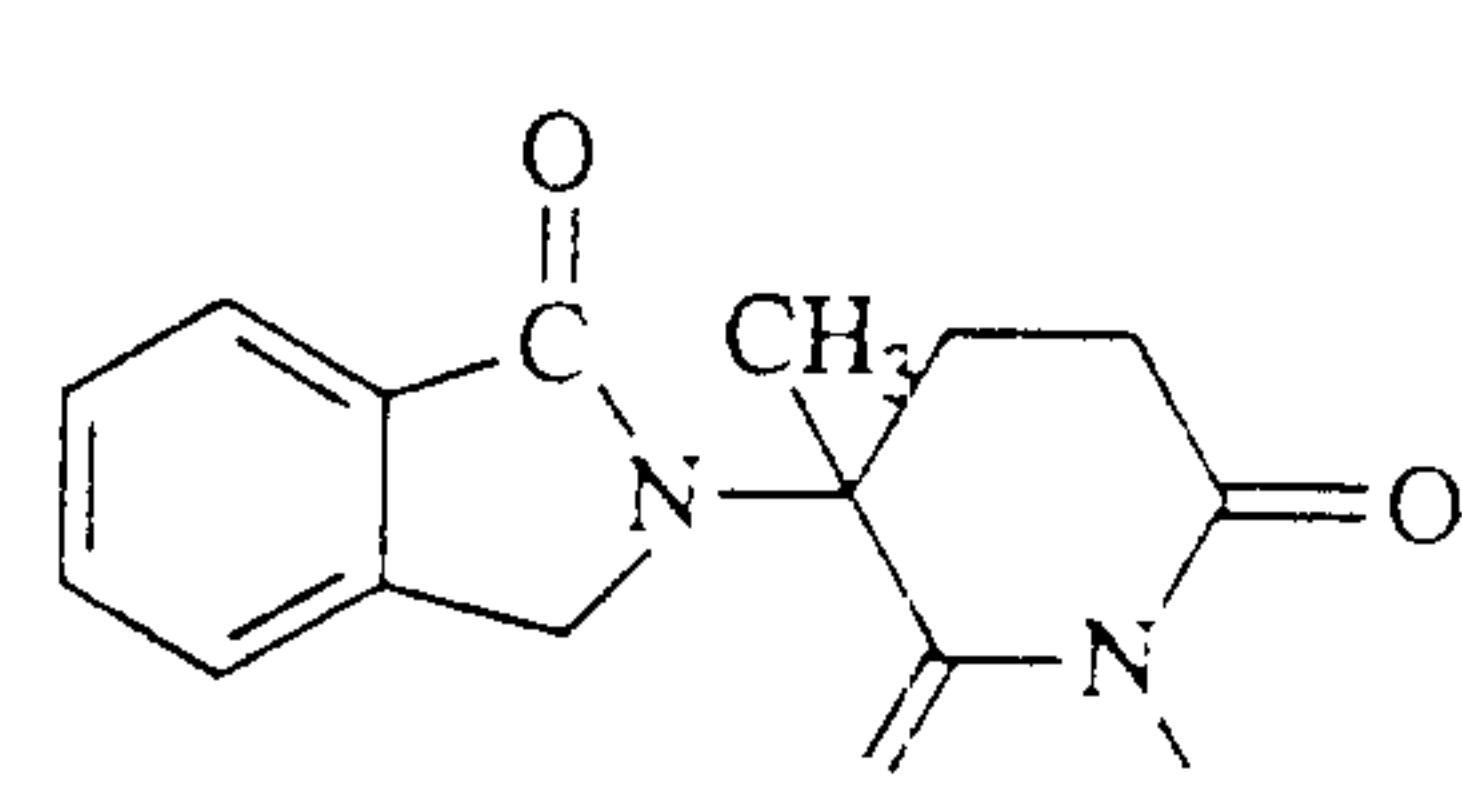
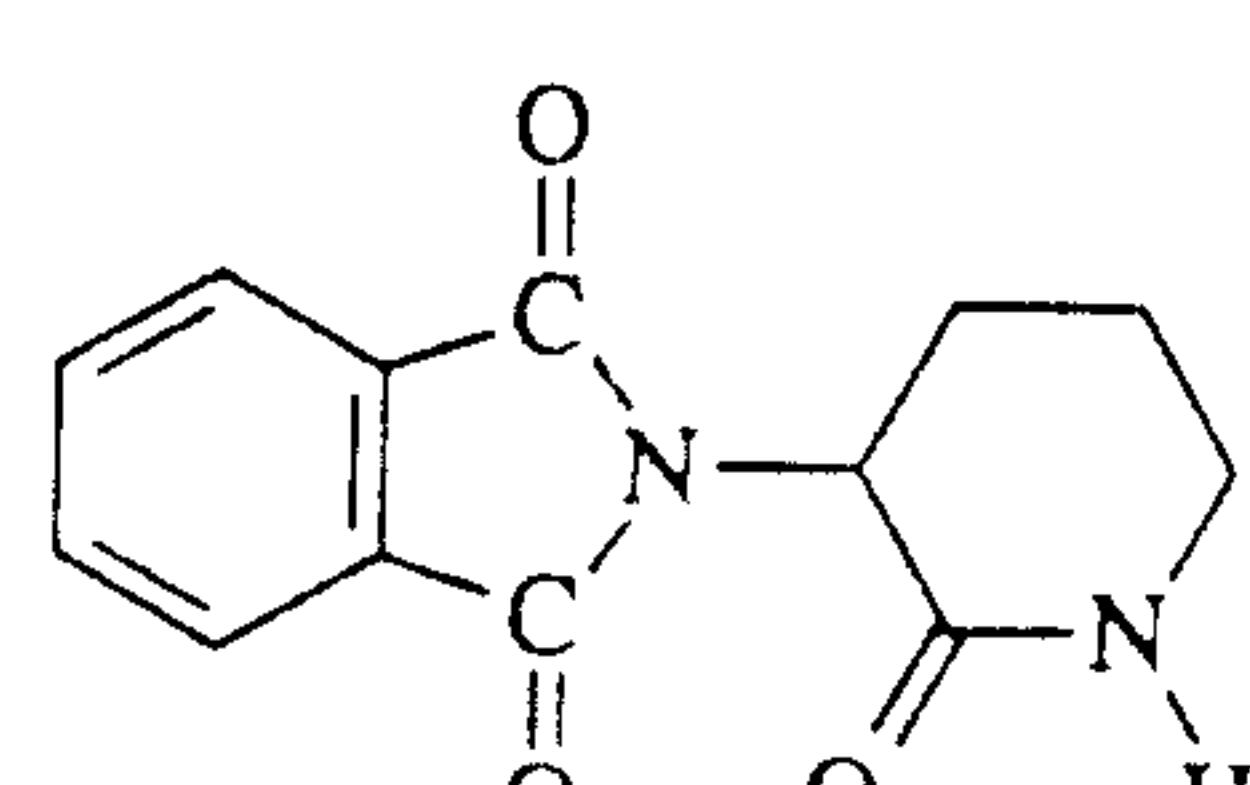
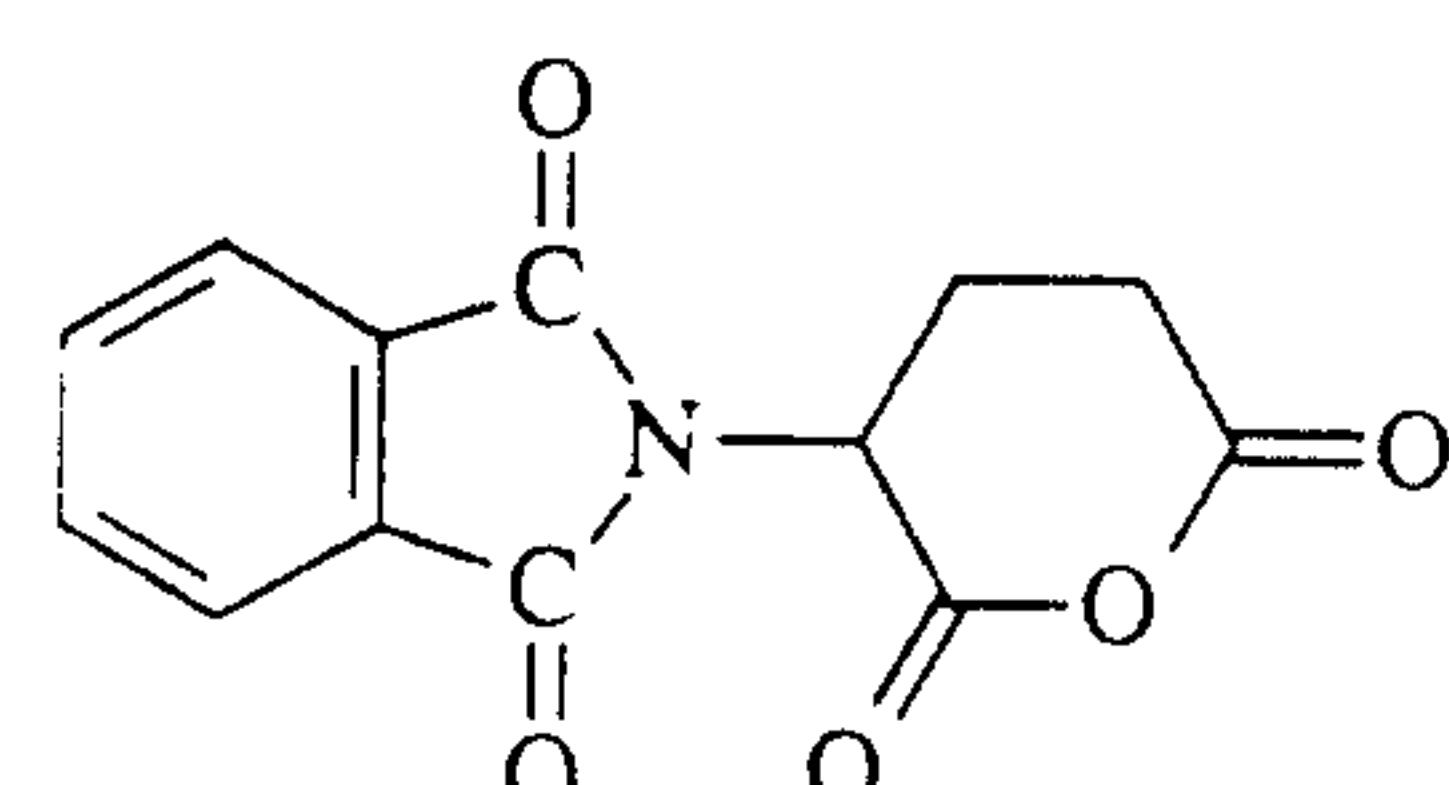
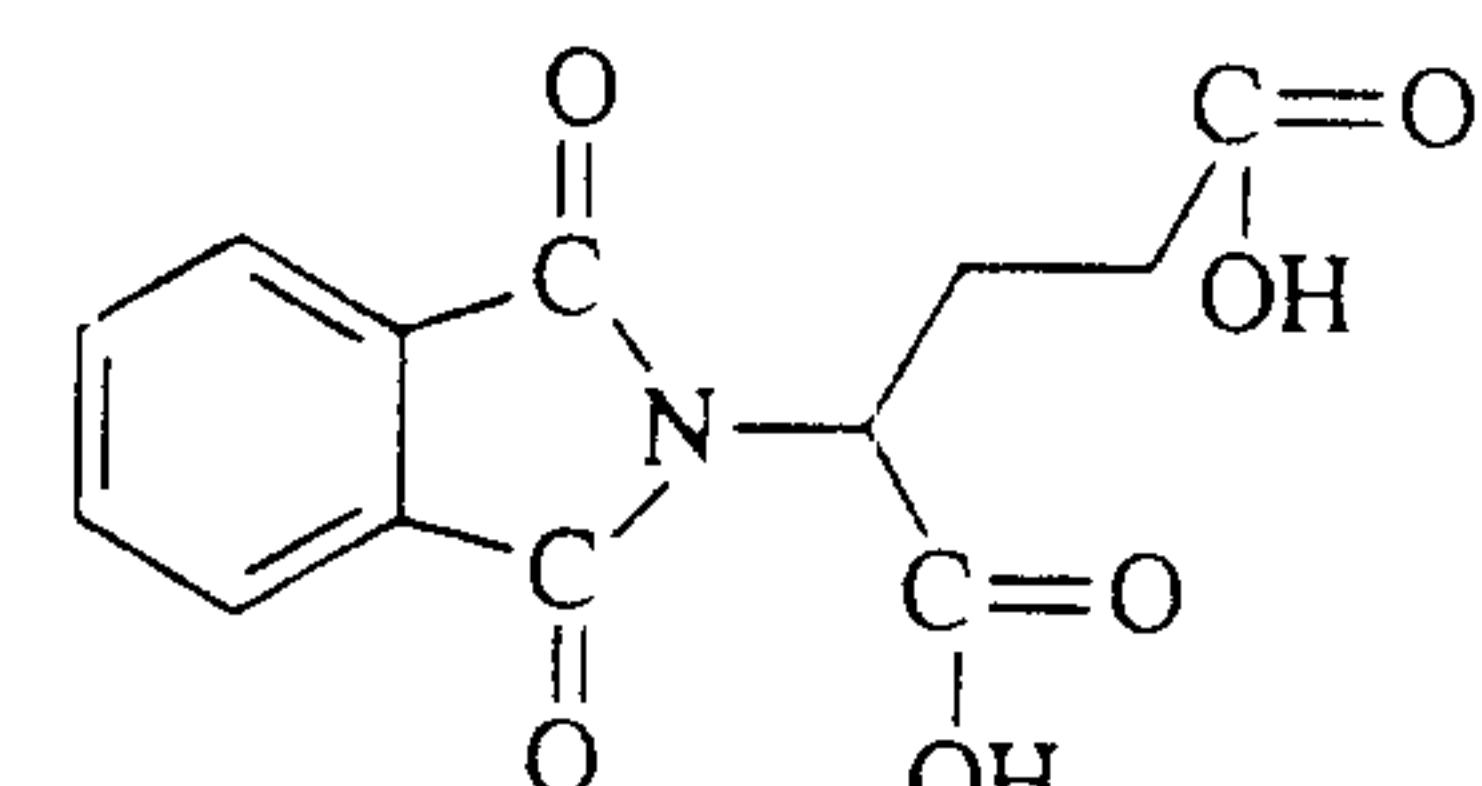
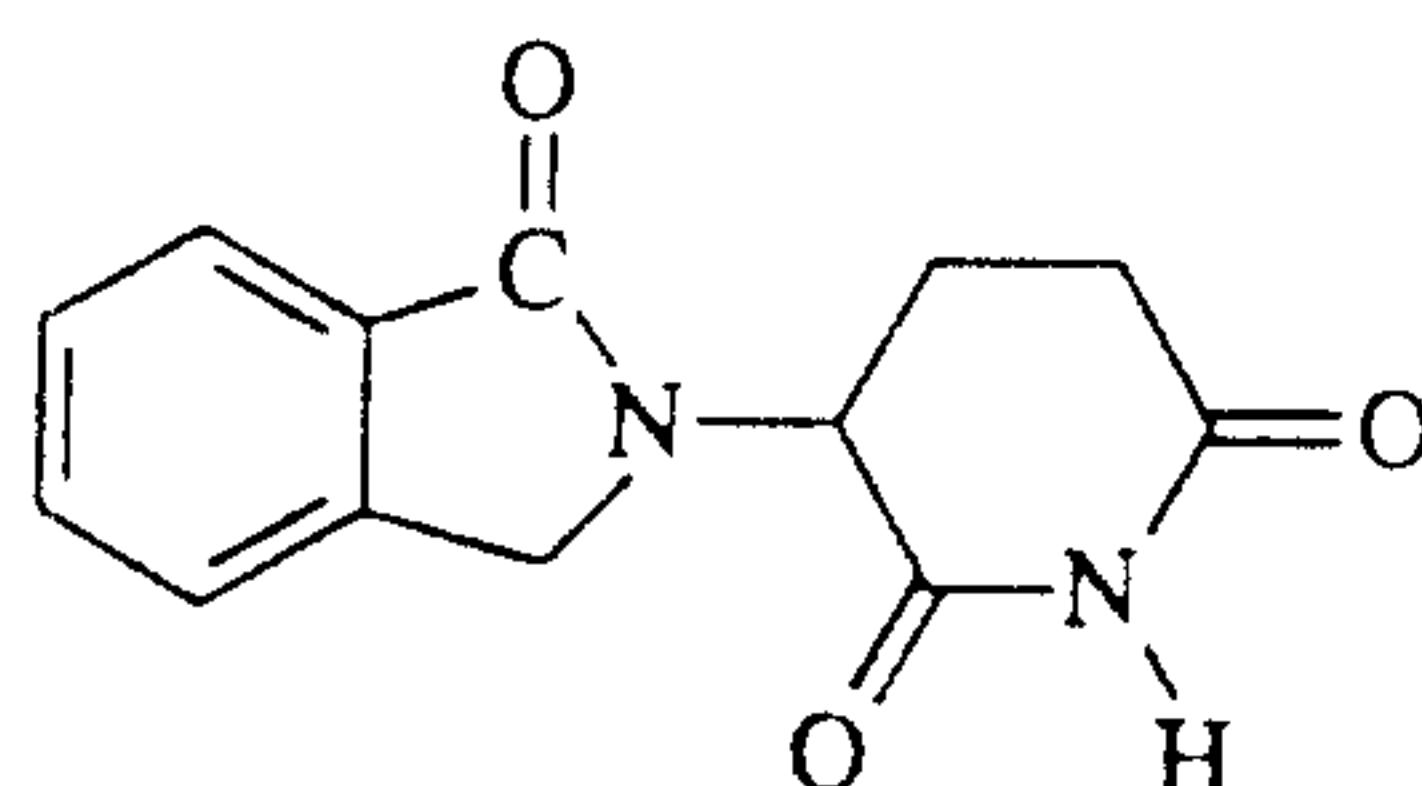
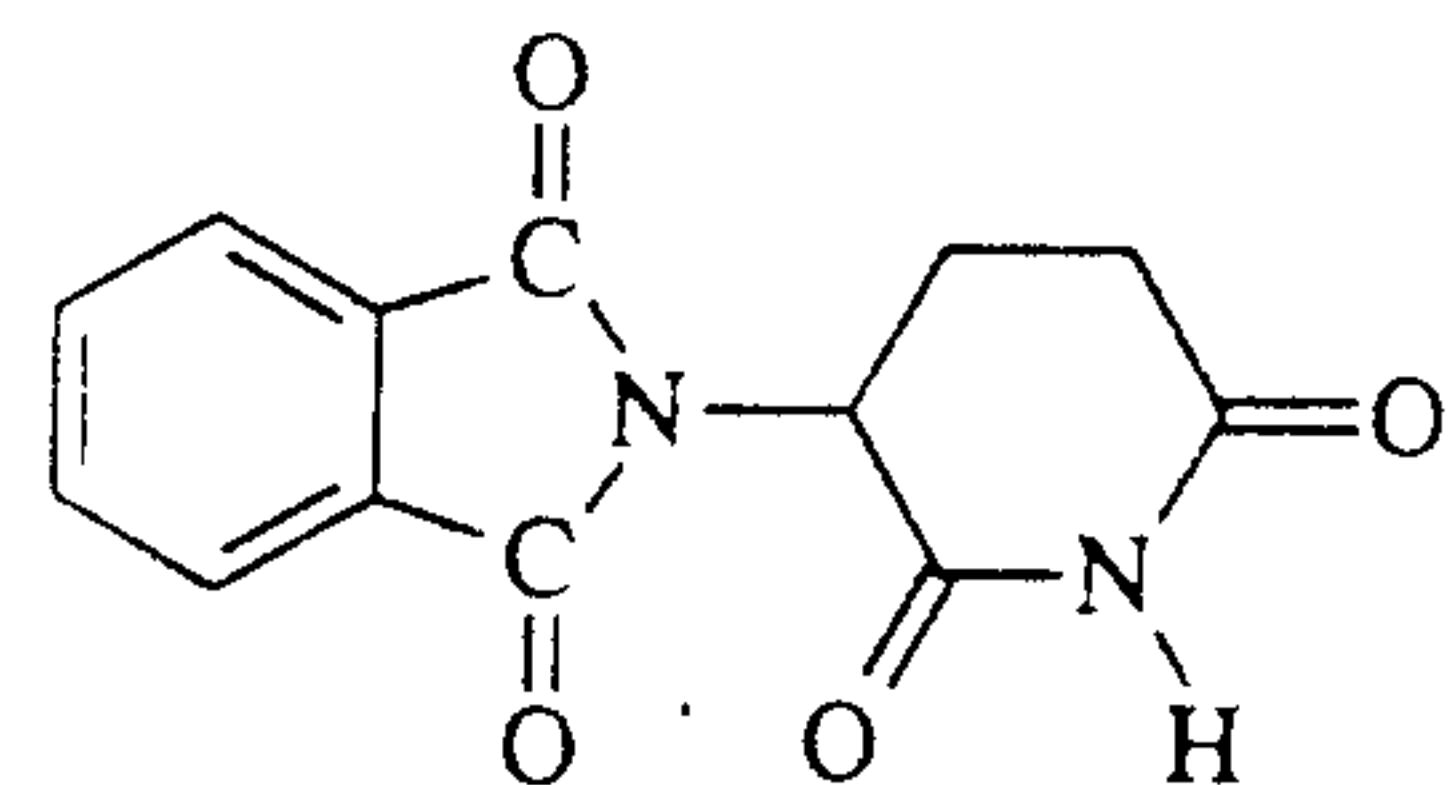
29. The use according to claim 28 wherein the amount administrable form is such as to provide between approximately 0.5 and approximately 50 mg/kg/day.

30. The use according to claim 29 wherein the amount administrable form is such as to provide between approximately 1 and approximately 10 mg/kg/day.

31. The use according to claim 18 or 21, wherein the administrable form of the compound includes a pharmaceutical acceptable carrier.

32. The use according to claim 18 or 21, wherein the administrable form of the compound provides oral, parenteral, transdermal or topical usage.

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Where R = -H, -OH, or -CH₃

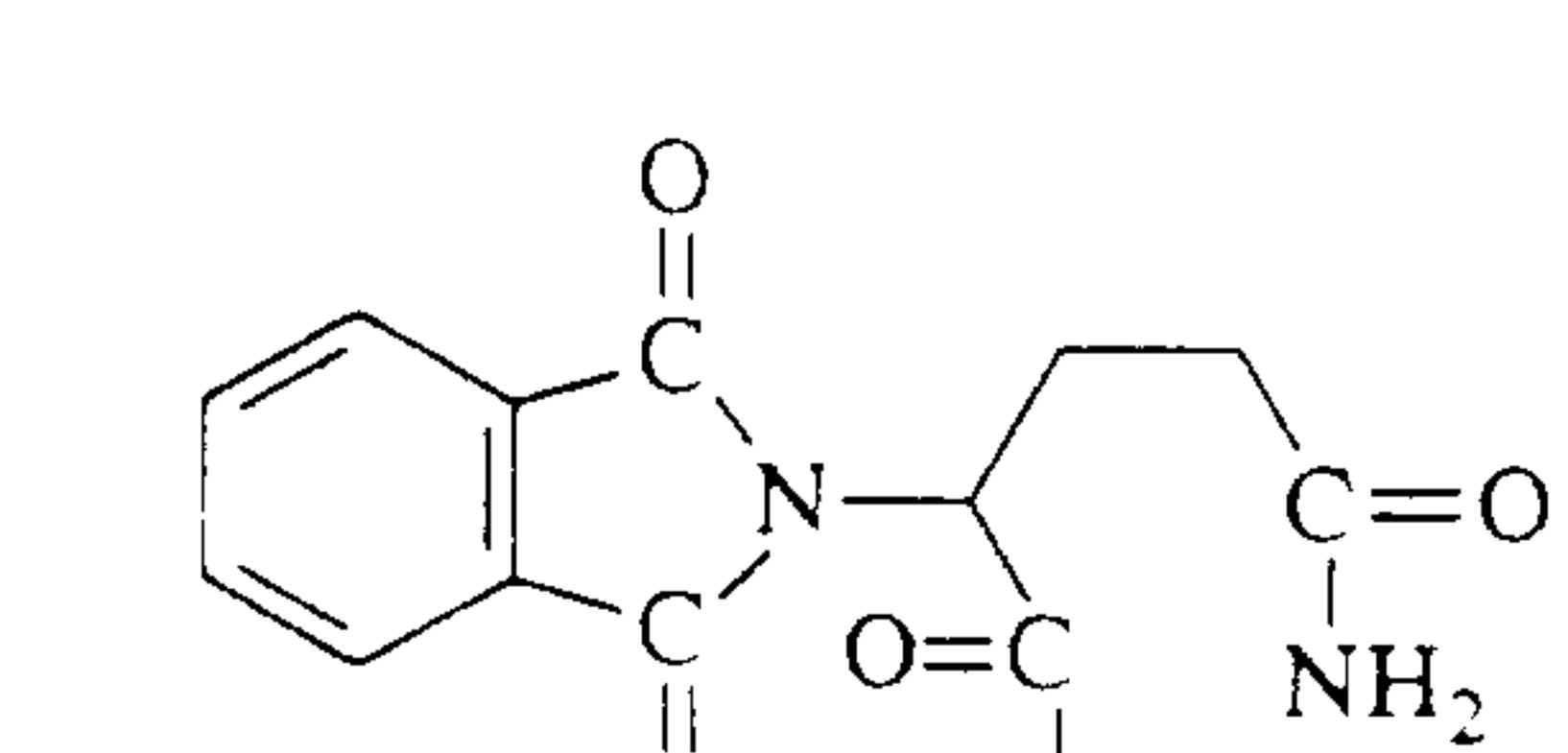
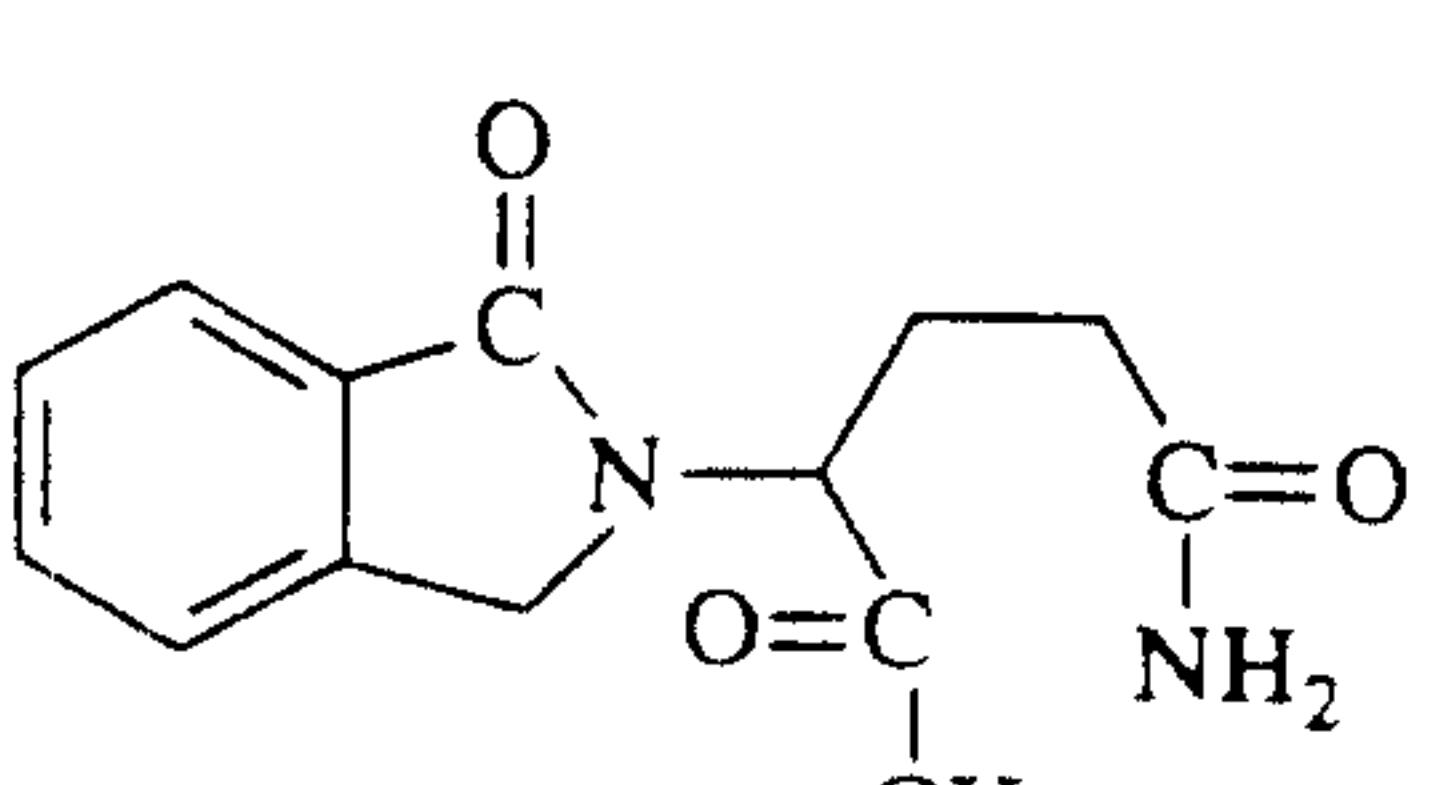
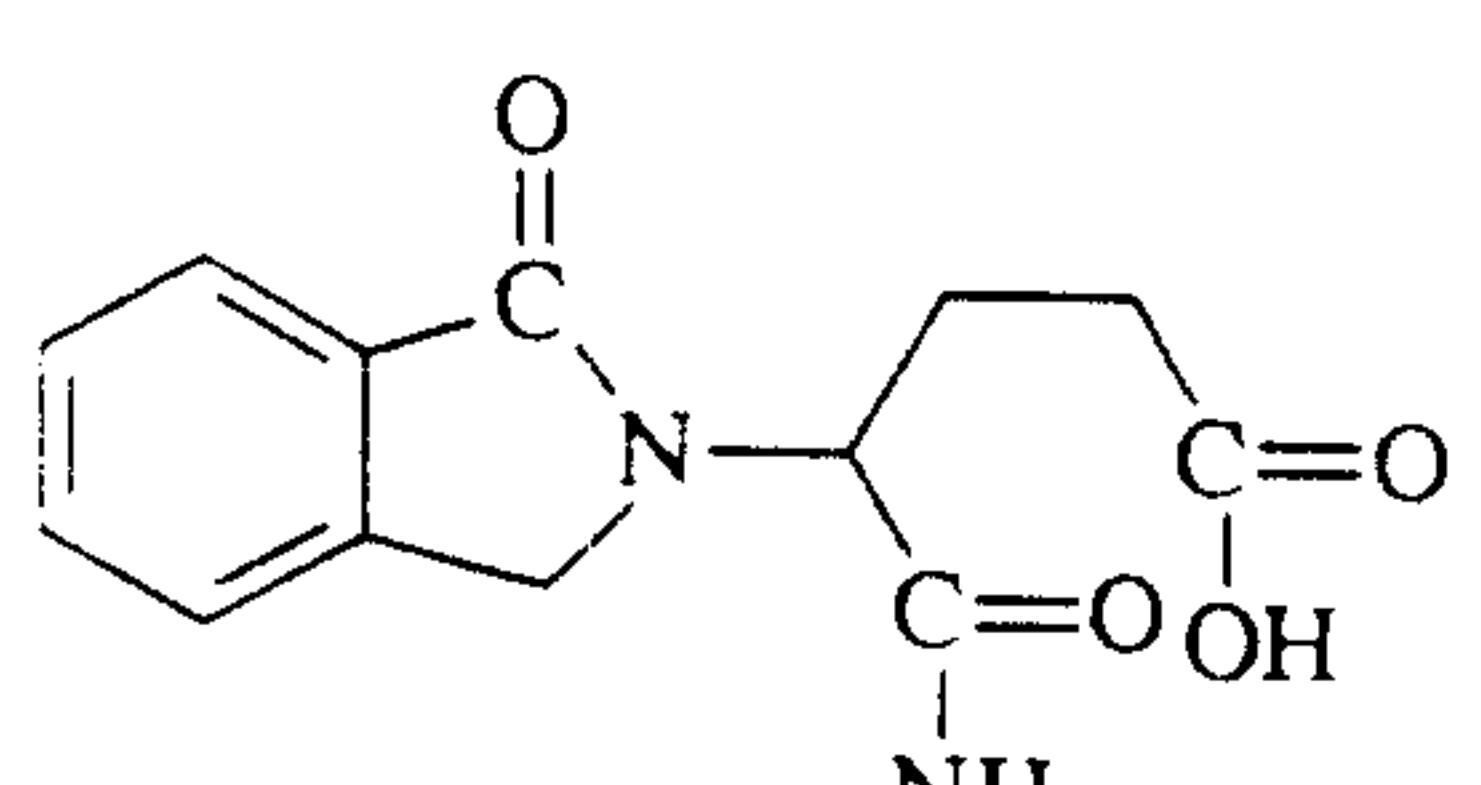
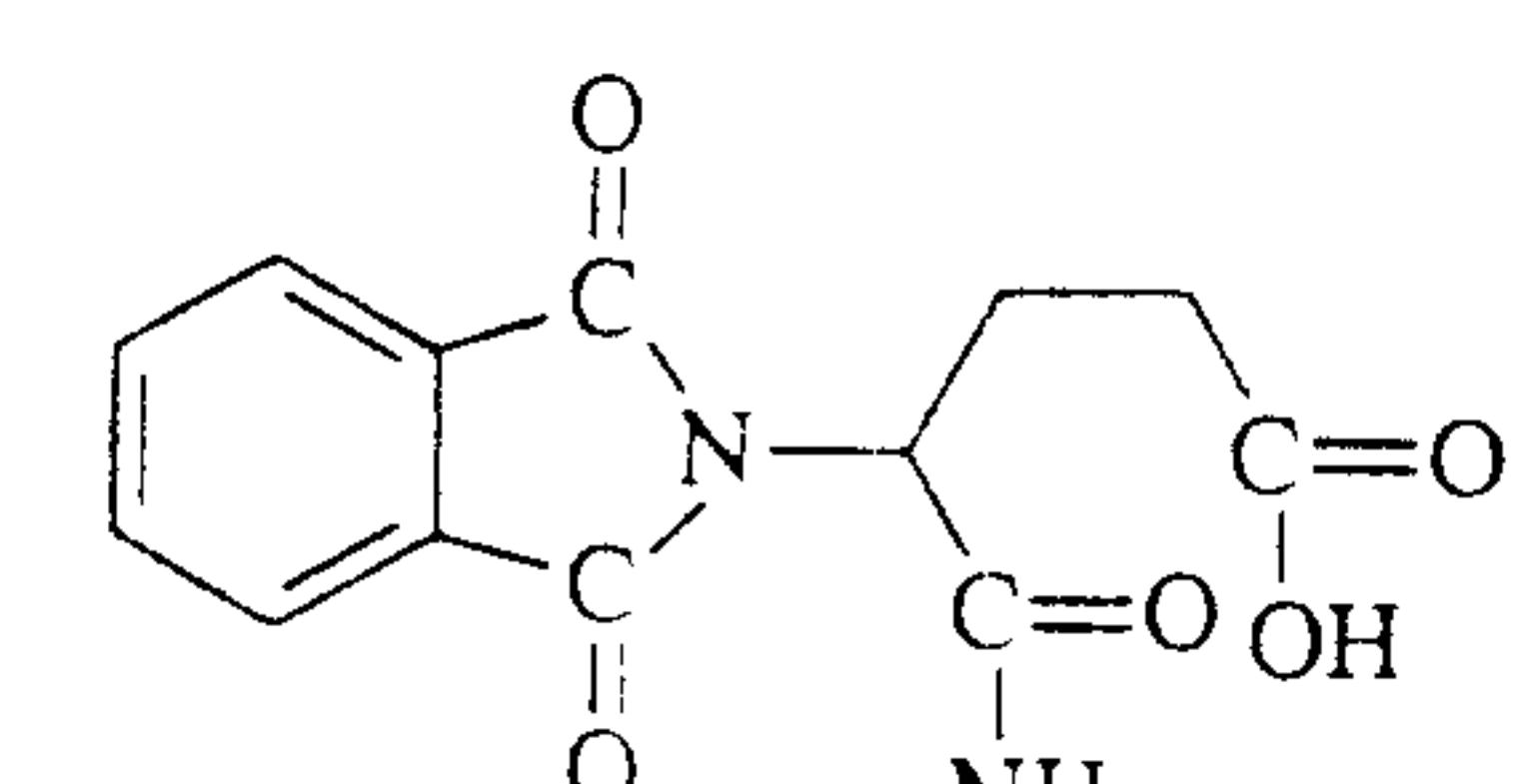
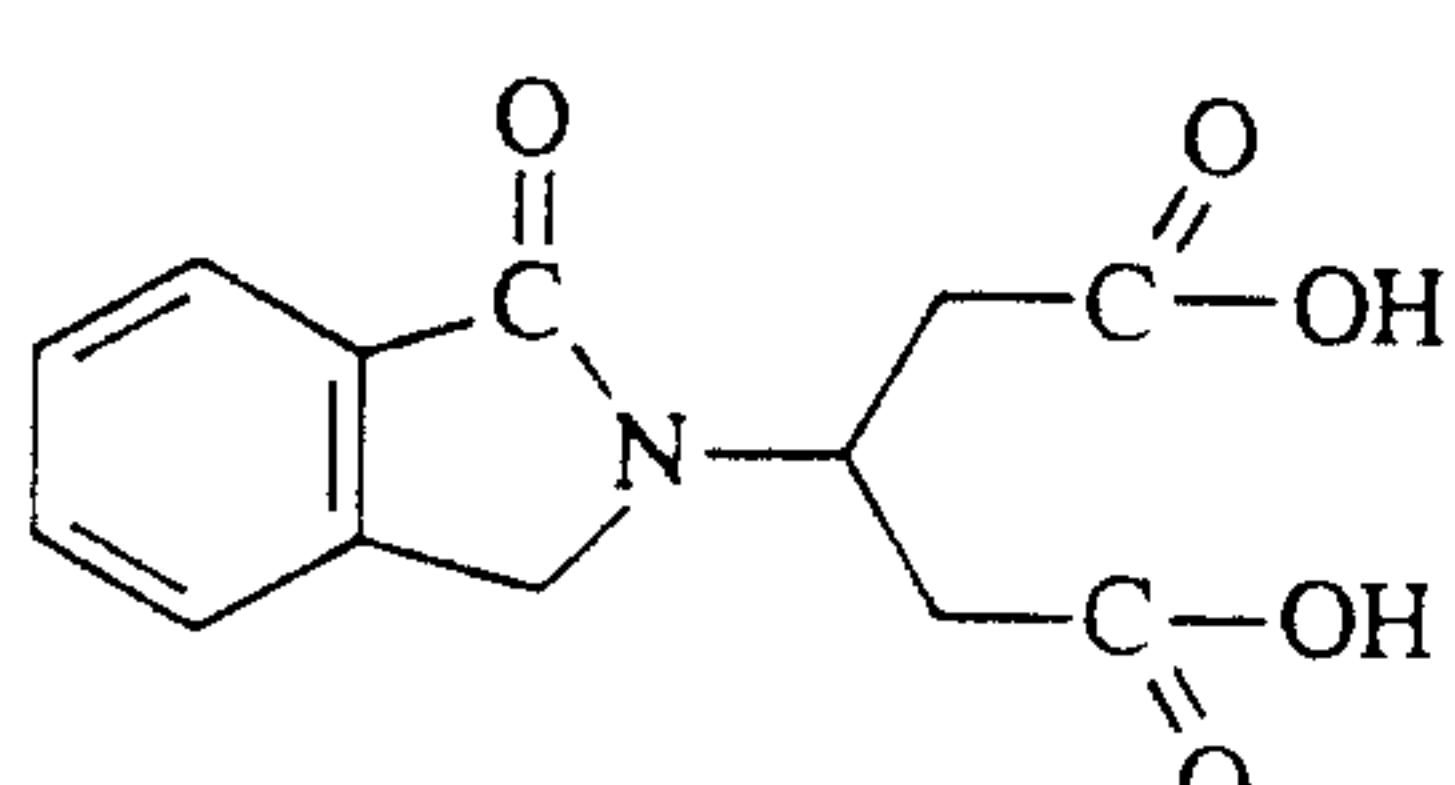
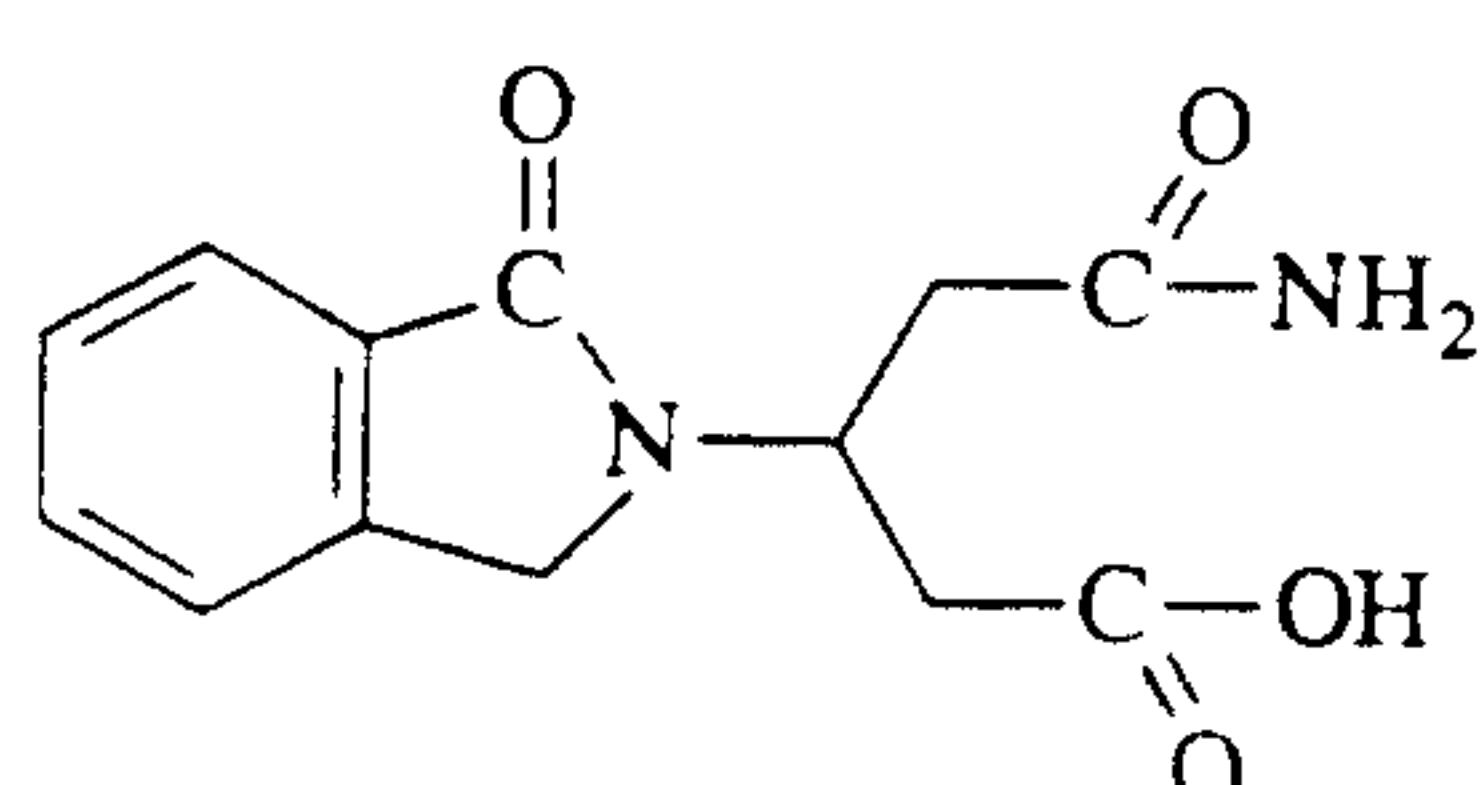


Figure 1

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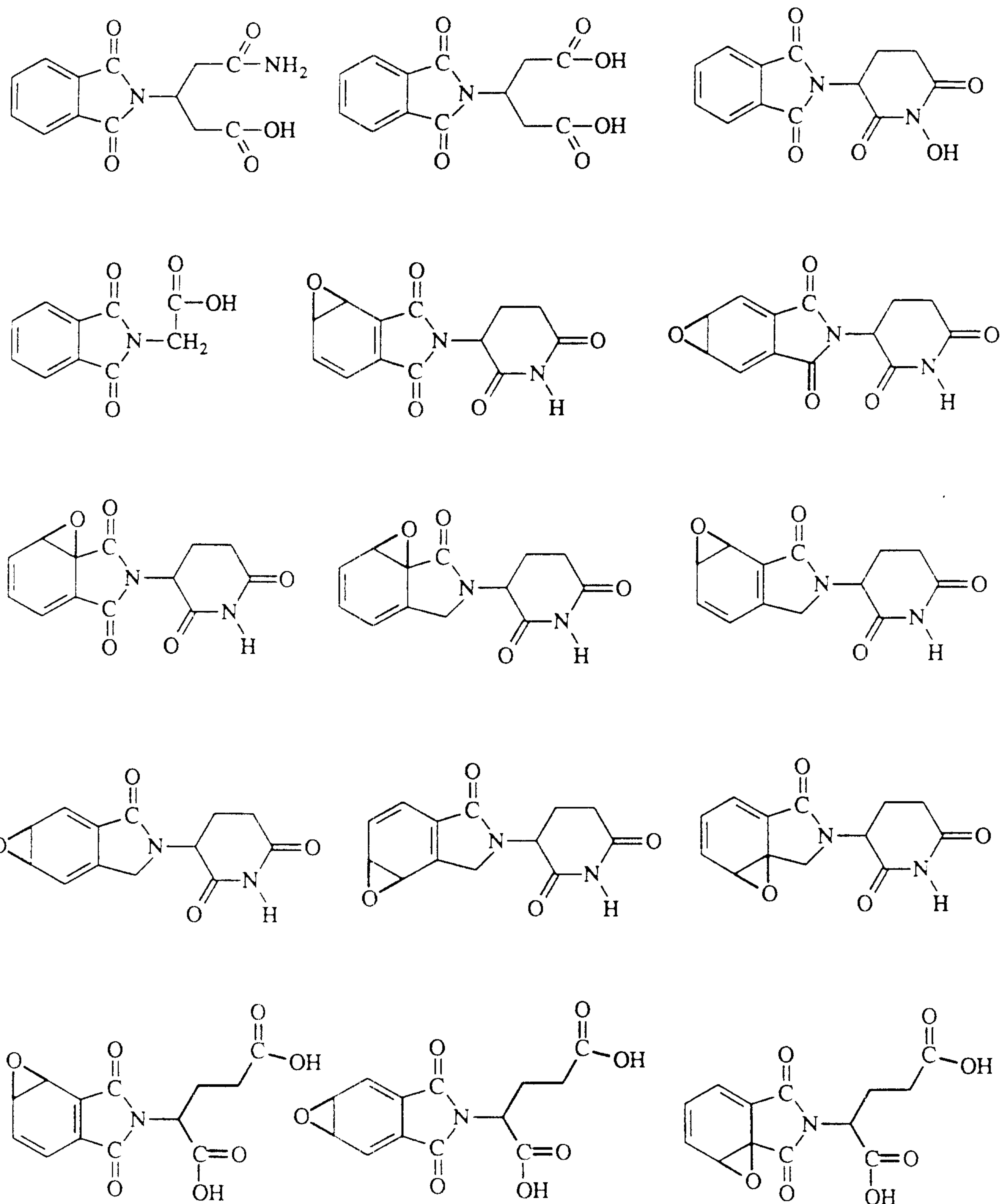


Figure 2

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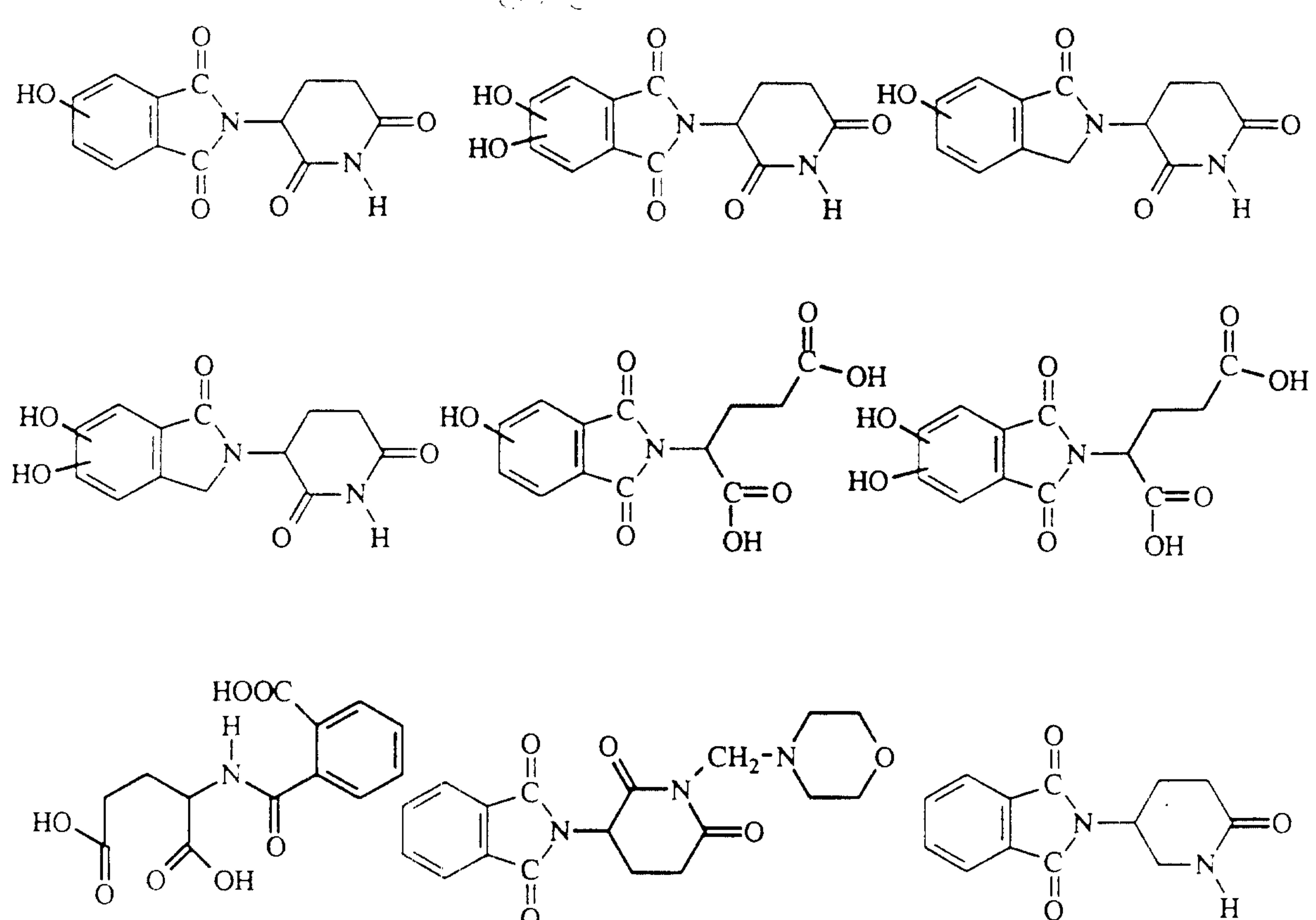


Figure 3

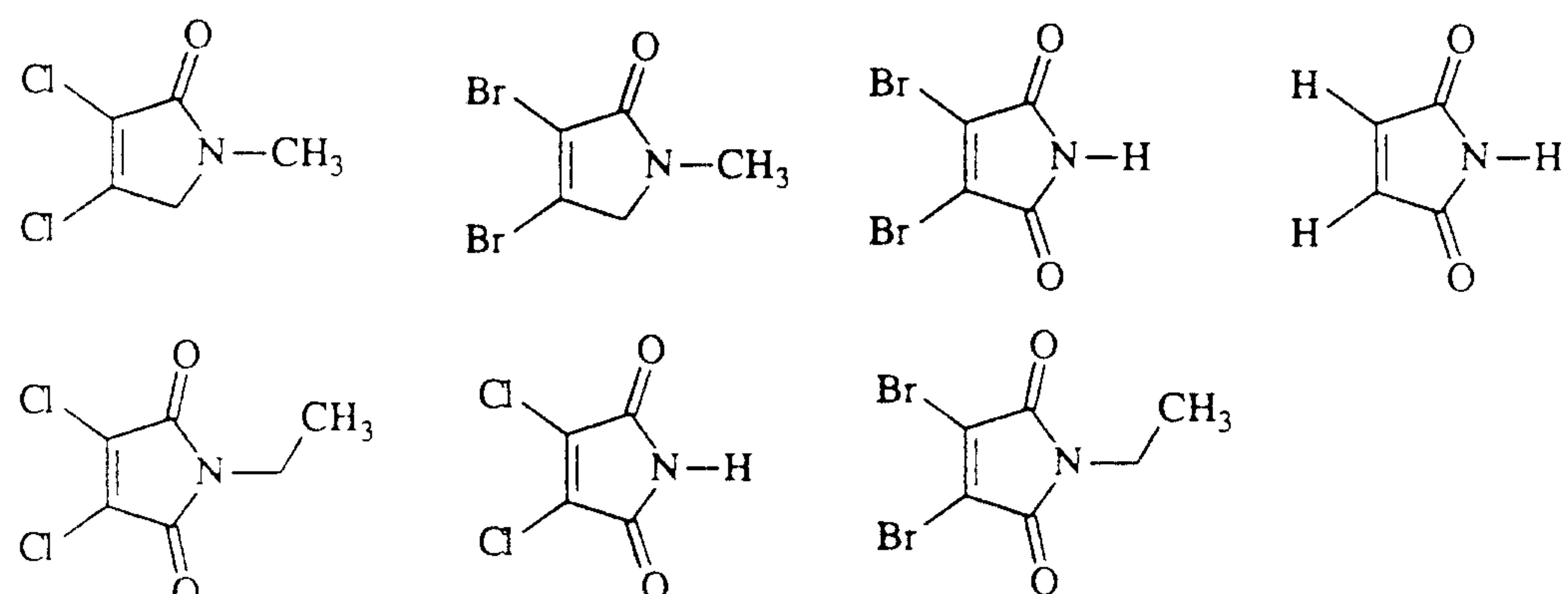


Figure 4

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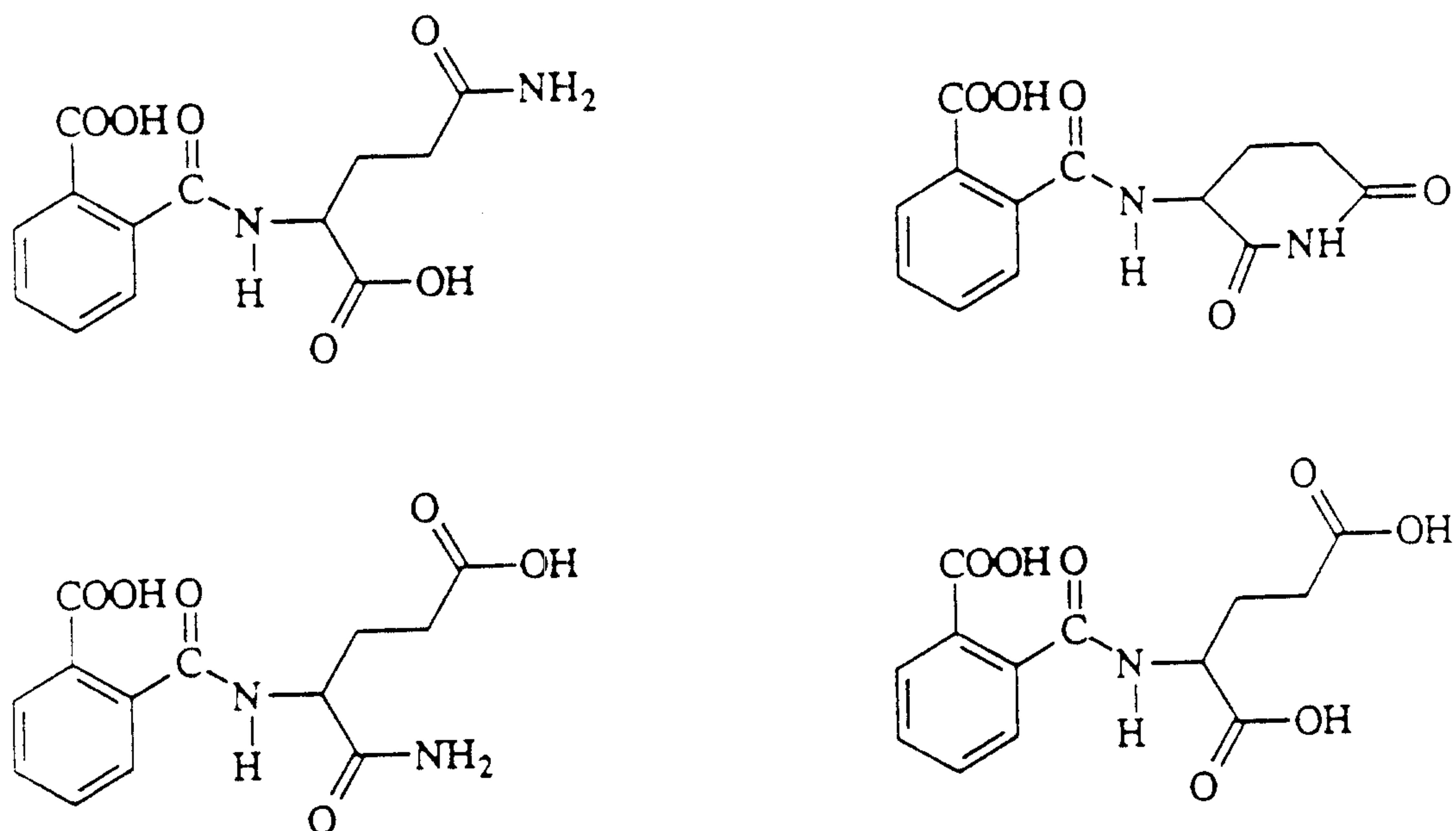


Figure 5

Autograde supplement

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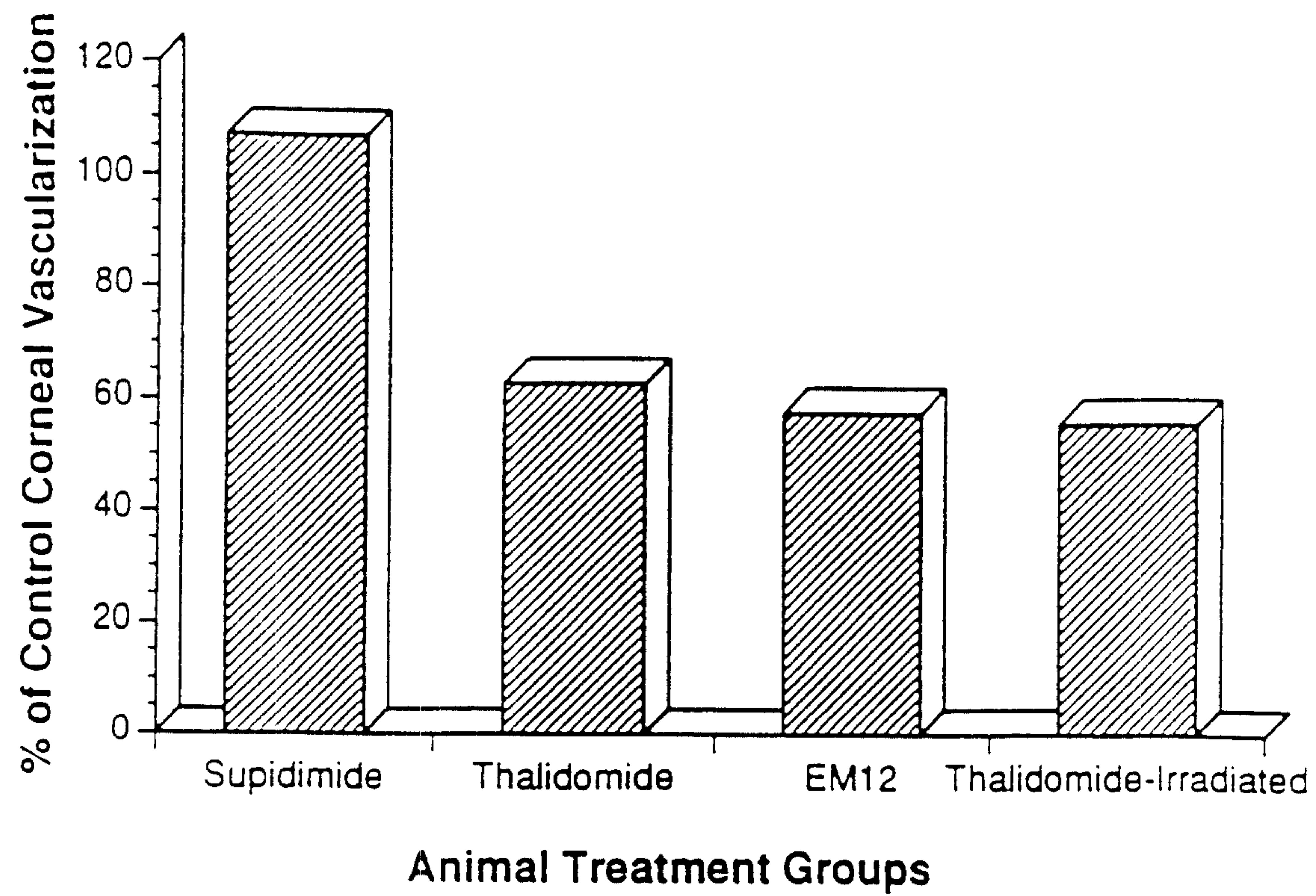
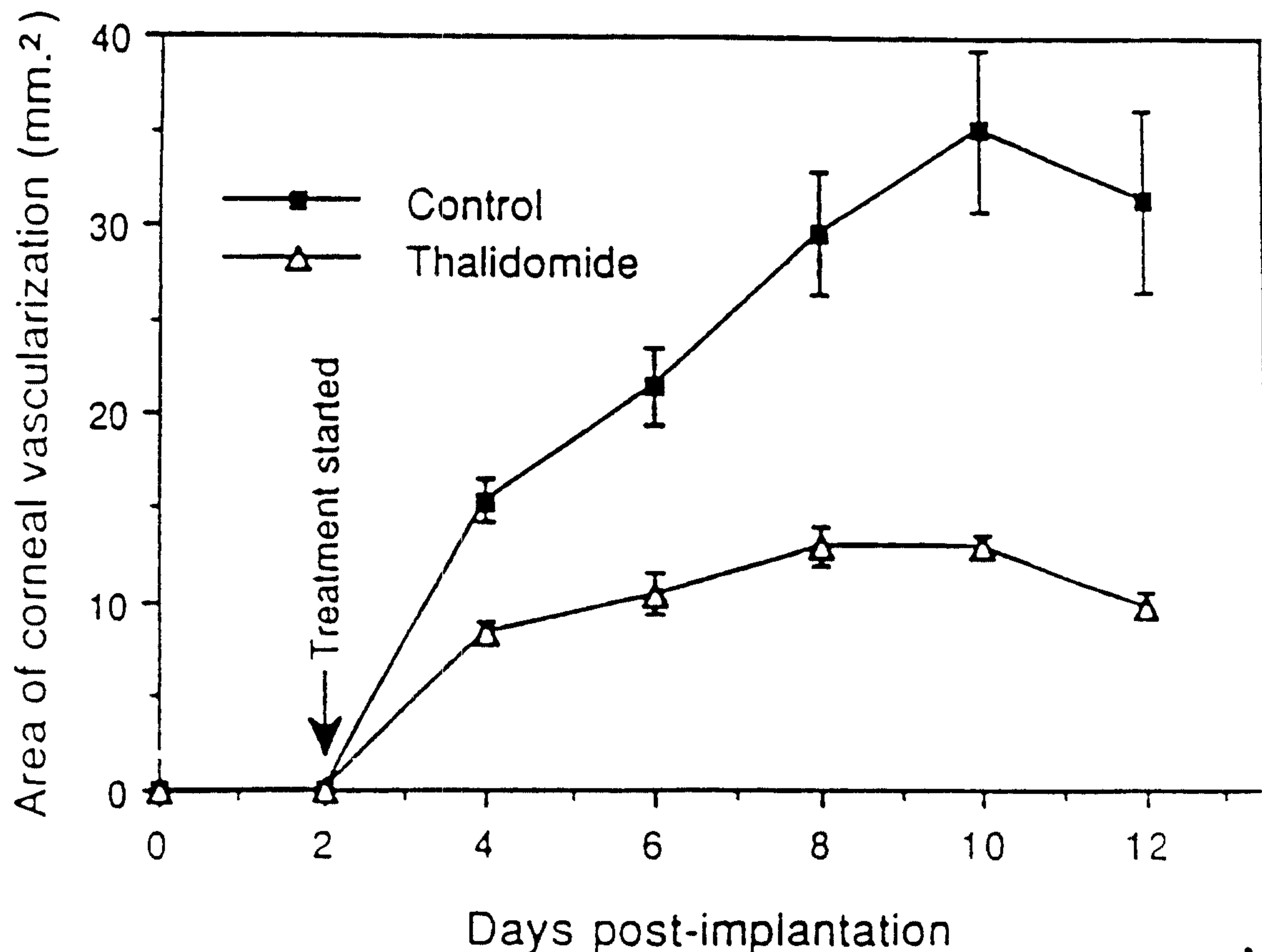


Figure 6

FIGURE 7
SUBSTITUTE SHEET (RULE 26)

Substance disclosed
P. P. M. A. M. S.