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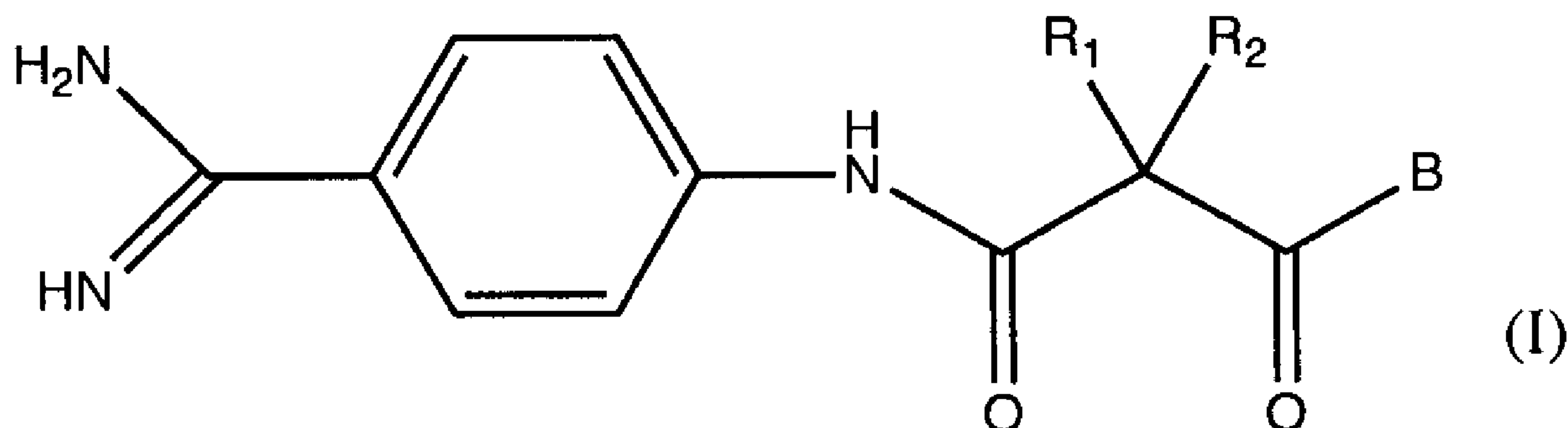
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(54) Titre : DERIVES D'ESTERS DE MALONAMIDE ET D'ESTERS MALONAMIQUES A ACTIVITE
ANTITHROMBOTIQUE

(54) Title: MALONAMIDE AND MALONAMIC ESTER DERIVATIVES WITH ANTITHROMBOTIC ACTIVITY



(57) **Abrégé/Abstract:**

The present invention relates to compounds of formula (I), in which R1, R2 and B have the meanings indicated in the claims. The compounds of formula (I) are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of thromboembolic diseases and restenoses. They are reversible inhibitors of the blood clotting enzyme factor VIIa and can in general be applied in conditions in which an undesired activity of factor VIIa is present or for the cure or prevention of which an inhibition of factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of formula (I), their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

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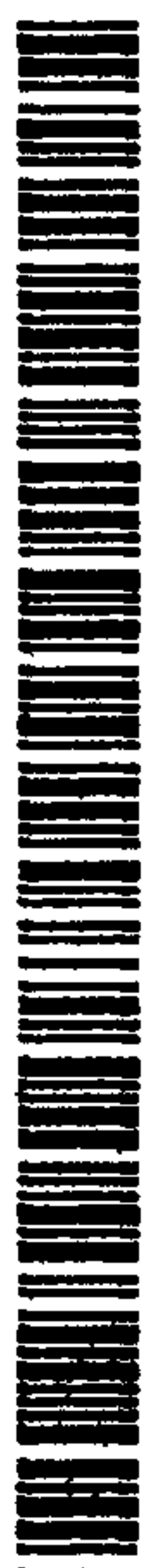
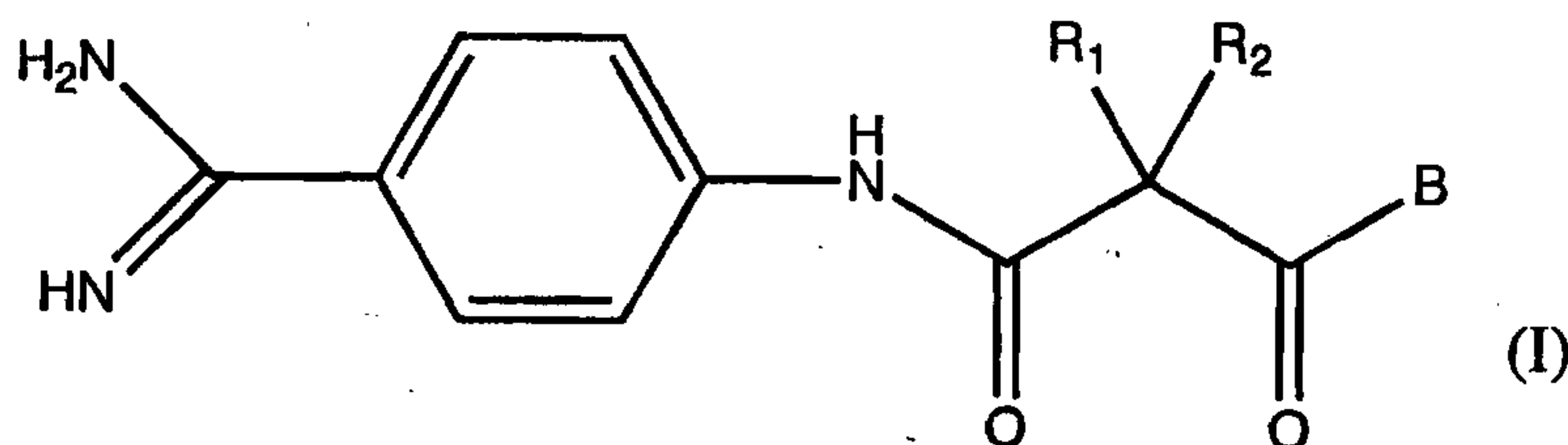
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(54) Title: MALONAMIDE AND MALONAMIC ESTER DERIVATIVES WITH ANTITHROMBOTIC ACTIVITY

(57) Abstract: The present invention relates to compounds of formula (I), in which R₁, R₂ and B have the meanings indicated in the claims. The compounds of formula (I) are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of thromboembolic diseases and restenoses. They are reversible inhibitors of the blood clotting enzyme factor VIIa and can in general be applied in conditions in which an undesired activity of factor VIIa is present or for the cure or prevention of which an inhibition of factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of formula (I), their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.



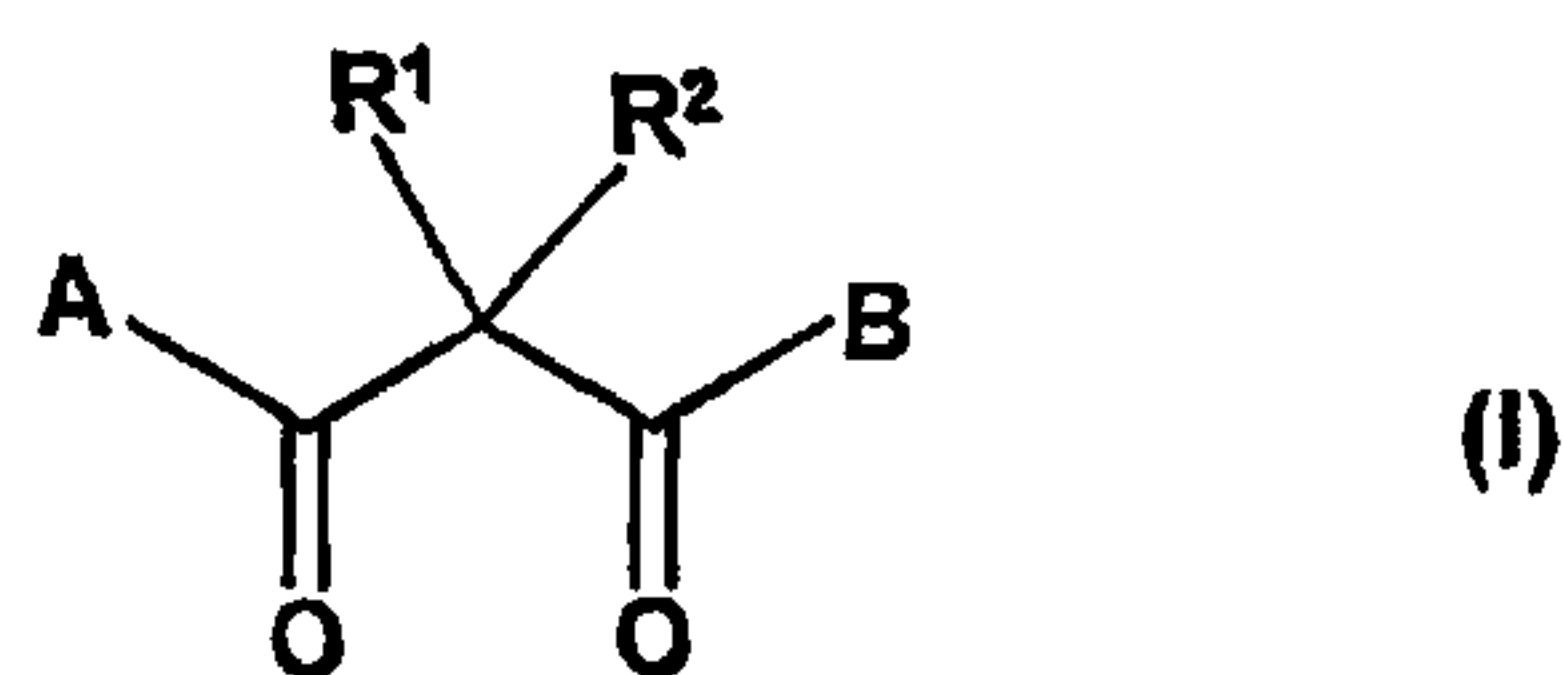
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Description:

Malonamide and malonamic ester derivatives with antithrombotic activity

5

The present invention relates to compounds of the formula I,



in which R¹, R², A and B have the meanings indicated below.

The compounds of the formula I are valuable pharmacologically active compounds.

- 10 They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of thromboembolic diseases and restenoses. They are inhibitors of the blood clotting enzymes, especially factor VIIa and can in general be applied in conditions in which an undesired activity of factor VIIa is present or for the cure or prevention of which an inhibition of factor VIIa is intended. The invention furthermore relates to
- 15 processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

- 20 Normal haemostasis is the result of a complex balance between the processes of clot initiation, formation and clot dissolution. The complex interactions between blood cells, specific plasma proteins and the vascular surface, maintain the fluidity of blood unless injury and blood loss occurs.

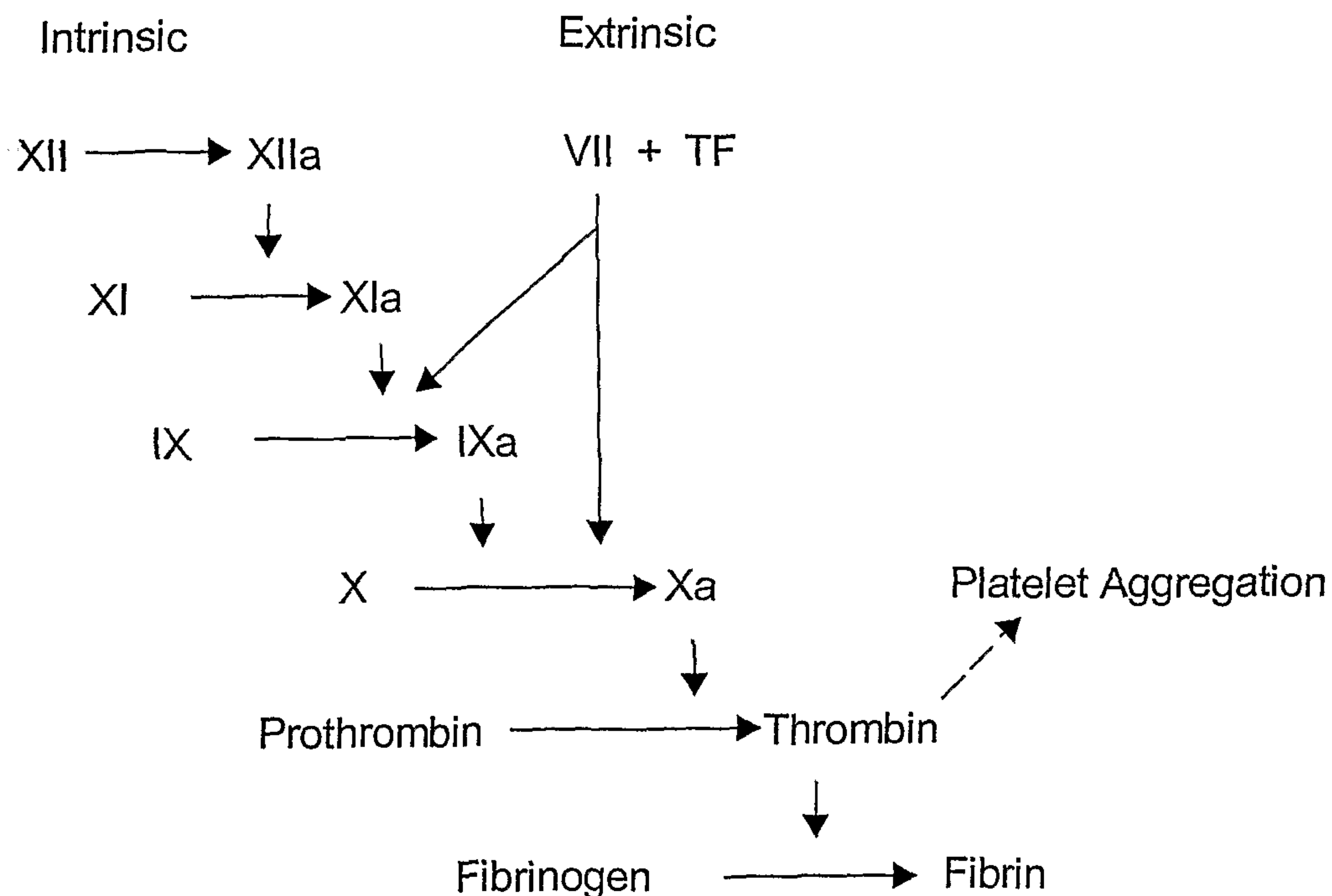
- 25 Many significant disease states are related to abnormal haemostasis. For example, local thrombus formation due to rupture of atherosclerotic plaque is a major cause of acute myocardial infarction and unstable angina. Treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous angioplasty may be accompanied by acute thrombolytic reclosure of the affected vessel.

- 30 There continues to be a need for safe and effective therapeutic anticoagulants to limit or prevent thrombus formation.

The ability to form blood clots is vital to survival. The formation of a blood clot or a thrombus is normally the result of tissue injury which initiates the coagulation cascade and has the effect of slowing or preventing blood flow in wound healing. Other factors which are not directly related to tissue injury like atherosclerosis and inflammation may also initiate the coagulation cascade. In general, a relationship exists between inflammation and the coagulation cascade. Inflammation mediators regulate the coagulation cascade and coagulation components influence the production and activity of inflammation mediators. However, in certain disease states the formation of blood clots within the circulatory system reaches an undesired extent and is itself the source of morbidity potentially leading to pathological consequences. It is nevertheless not desirable in such disease states to completely inhibit the blood clotting system because life threatening hemorrhage would ensue. In the treatment of such states a well-balanced intervention into the blood clotting system is required.

Blood coagulation is a complex process involving a progressively amplified series of enzyme activation reactions in which plasma zymogens are sequentially activated by limited proteolysis. Mechanistically the blood coagulation cascade has been divided into intrinsic and extrinsic pathways, which converge at the activation of factor X; subsequent generation of thrombin proceeds through a single common pathway (see Scheme 1). Present evidence suggests that the intrinsic pathway plays an important role in the maintenance and growth of fibrin formation, while the extrinsic pathway is critical in the initiation phase of blood coagulation (H. Cole, Aust. J. Med. Sci. 16 (1995) 87; G. J. Broze, Blood Coagulation and Fibrinolysis 6, Suppl. 1 (1995) S7). It is generally accepted that blood coagulation is physically initiated upon formation of a factor VIIa/tissue factor(TF) complex. Once formed, this complex rapidly initiates coagulation by activating factors IX and X. The newly generated activated factor X, i. e. factor Xa, then forms a one-to-one complex with factor Va and phospholipids to form a prothrombinase complex, which is responsible for converting soluble fibrinogen to insoluble fibrin via the activation of thrombin from its precursor prothrombin. As time progresses, the activity of the factor VIIa/tissue factor complex (extrinsic pathway) is suppressed by a Kunitz-type protease inhibitor protein, TFPI, which, when complexed to factor Xa, can directly inhibit the proteolytic activity of factor VIIa/tissue factor. In order to maintain the coagulation process in the presence of an inhibited extrinsic system,

additional factor Xa is produced via the thrombin-mediated activity of the intrinsic pathway. Thus, thrombin plays a dual autocatalytic role, mediating its own production and the conversion of fibrinogen to fibrin.



5 Scheme 1: Blood coagulation cascade

The autocatalytic nature of thrombin generation is an important safeguard against uncontrolled bleeding and it ensures that, once a given threshold level of prothrombinase is present, blood coagulation will proceed to completion. Thus, it is most
 10 desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade like factor VIIa activity.

In many clinical applications there is a great need for the prevention of intravascular blood clots or for some anticoagulant treatment. For example, nearly 50 % of patients
 15 who have undergone a total hip replacement develop deep vein thrombosis (DVT). The currently available drugs like heparin and derivatives thereof are not satisfactory in many specific clinical applications. The currently approved therapies include fixed dose low molecular weight heparin (LMWH) and variable dose heparin. Even with these drug regimes 10 % to 20 % of patients develop DVT, and 5 % to 10 % develop bleeding
 20 complications.

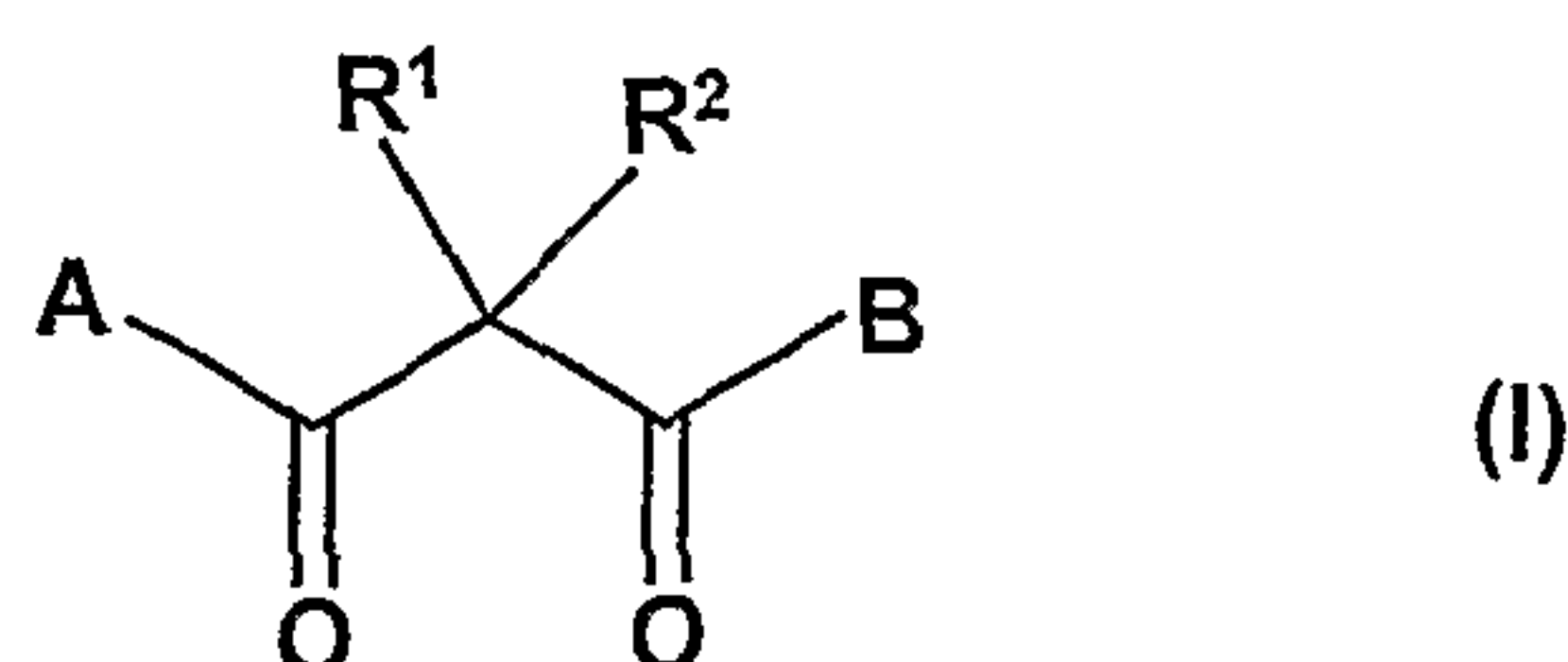
Another clinical situation for which better anticoagulants are needed concerns subjects undergoing transluminal coronary angioplasty and subjects at risk for myocardial infarction or suffering from crescendo angina. The present, conventionally accepted therapy which consists of administering heparin and aspirin, is associated with a 6 % to 8 % abrupt vessel closure rate within 24 hours of the procedure. The rate of bleeding complications requiring transfusion therapy due to the use of heparin also is approximately 7 %. Moreover, even though delayed closures are significant, administration of heparin after termination of the procedures is of little value and can be detrimental.

The widely used blood-clotting inhibitors like heparin and related sulfated polysaccharides like LMWH and heparin sulfate exert their anti-clotting effects by promoting the binding of a natural regulator of the clotting process, anti-thrombin III, to thrombin and to factor Xa. The inhibitory activity of heparin primarily is directed toward thrombin which is inactivated approximately 100 times faster than factor Xa. Hirudin and hirulog are two additional thrombin-specific anticoagulants presently in clinical trials. However, these anticoagulants which inhibit thrombin also are associated with bleeding complications. Preclinical studies in baboons and dogs have shown that targeting enzymes involved at earlier stages of the coagulation cascade, such as factor Xa or factor VIIa, prevents clot formation without producing the bleeding side effects observed with direct thrombin inhibitors (L. A. Harker et al., Thromb. Hemostas. 74 (1995) 464).

Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800 and WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty (L. A. Harker et al., Haemostasis 26 (1996) S1:76) . Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition (L. A. Harker et al., Thromb. Hemostas. 74 (1995) 464).

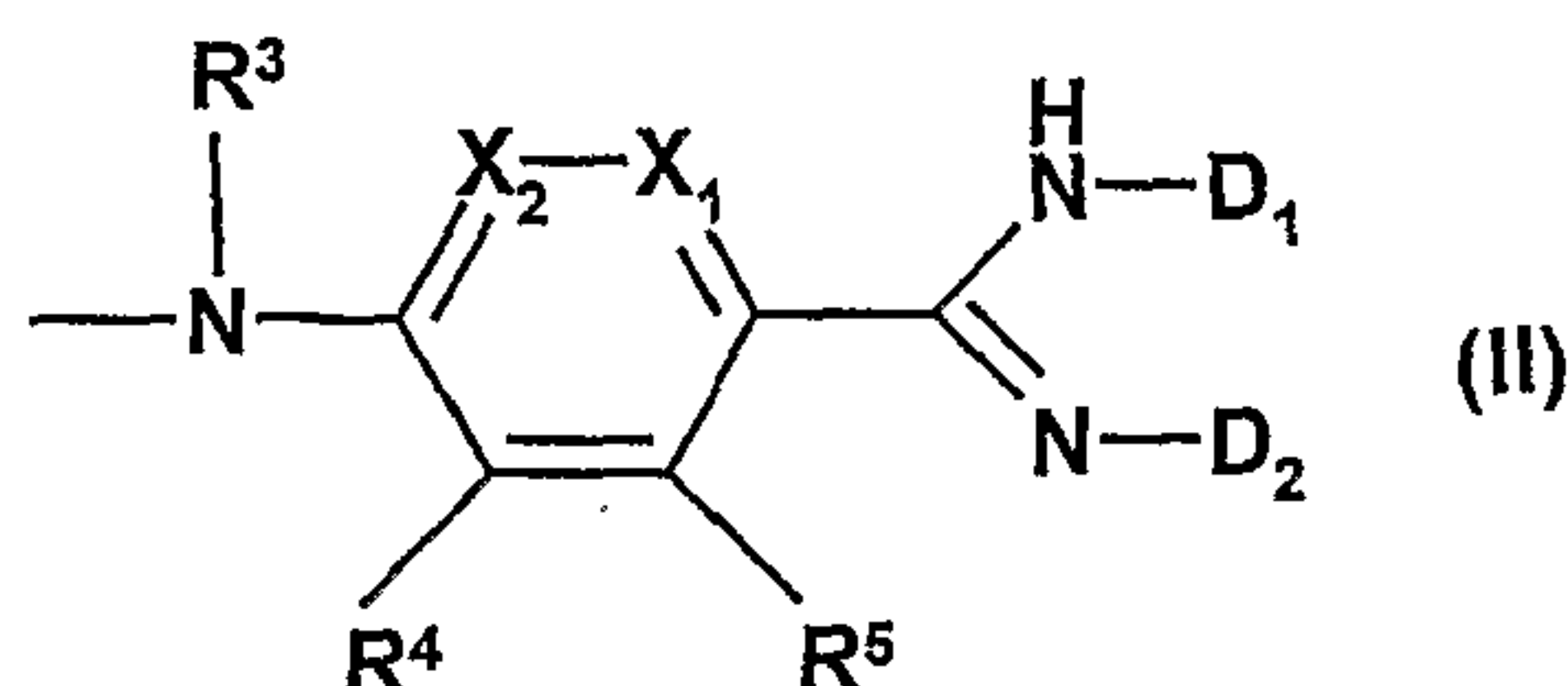
A specific inhibitor of factor VIIa which has a favorable property profile would have substantial practical value in the practice of medicine. In particular, a factor VIIa inhibitor would be effective under circumstances where the present drugs of choice, like heparin and related sulfated polysaccharides, are ineffective or only marginally effective. Certain inhibitors of factor VIIa have already been described. EP-A-987274, for example, discloses compounds containing a tripeptide unit which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is a need for further low molecular weight factor VIIa-specific blood clotting inhibitors that are effective and do not cause unwanted side effects. The present invention satisfies this need by providing novel factor VIIa activity malonicacid derivatives of the formula I.

Thus, a subject of the present invention are compounds of the formula I,



wherein

A is a residue of the formula II



wherein R^3 is hydrogen atom, -OH or $-(C_1-C_6)$ -alkyl,

wherein R^4 and R^5 independently from one another are

1. hydrogen atom,
2. $-(C_1-C_6)$ -alkyl,
3. -OH,
4. $-O-(C_1-C_6)$ -alkyl,
5. halogen,
6. $-NH_2$ or
7. $-NO_2$,

where X_1 and X_2 independently from one another are selected from the group consisting of a carbon atom substituted by R^4 , wherein R^4 is as defined above, and a nitrogen atom,

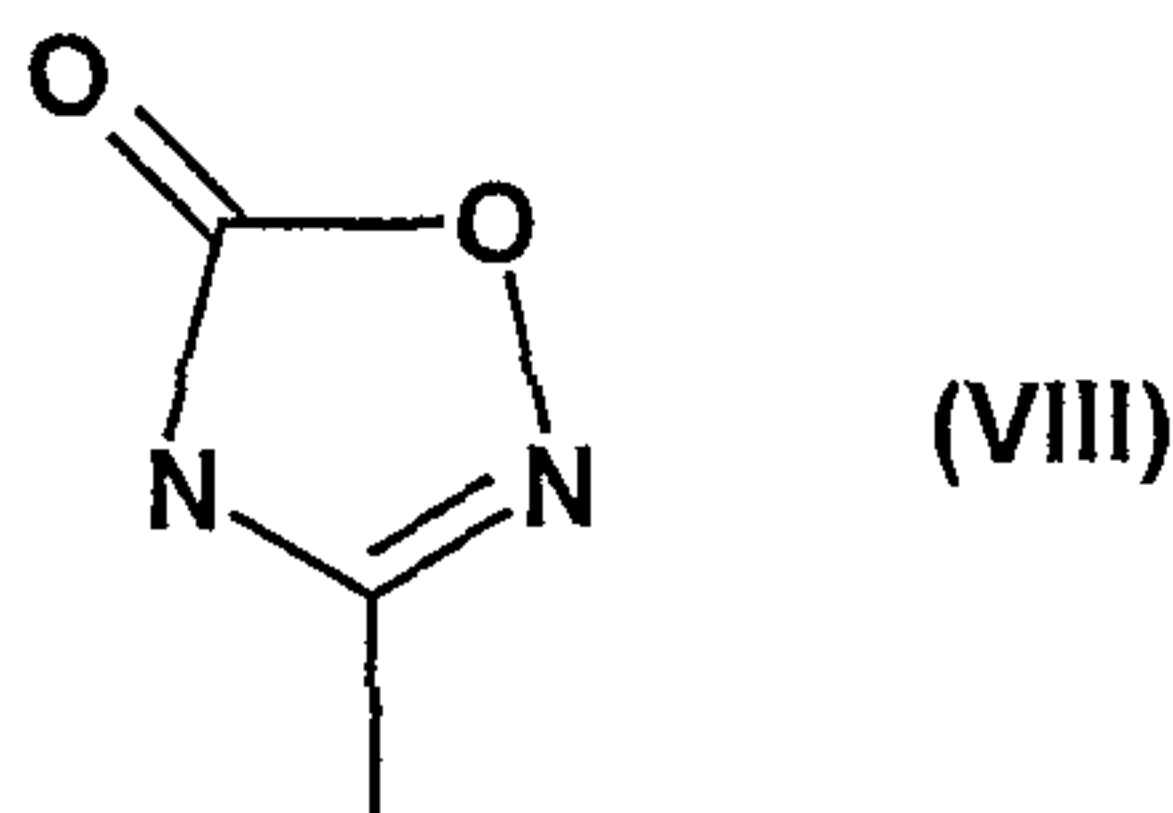
wherein D1 and D2 independently from one another are

1. hydrogen atom,
2. -C(O)-(C₁-C₆)-alkyl,
3. -C(O)-aryl,
4. -C(O)-(C₁-C₆)-alkyl-aryl,
5. -C(O)-O-(C₁-C₆)-alkyl,
6. C(O)-O-(C₁-C₆)-alkyl-aryl or
7. C(O)-O-(C₁-C₆)-aryl, or

D1 is hydrogen atom, when D2 is

1. -OH,
2. -O-C(O)-(C₁-C₆)-alkyl,
3. -O-C(O)-aryl or
4. -O-C(O)-(C₁-C₆)-alkyl-aryl, or

D1 and D2 together with the nitrogen atom to which they are attached form a cycle of the formula VIII



- R¹ is
1. hydrogen atom,
 2. -(C₁-C₆)-alkyl,
 3. -OH,
 4. -O-(C₁-C₆)-alkyl or
 5. -N-(R⁶)₂, wherein R⁶ is independently of one another hydrogen atom, -C(O)-aryl, -C(O)-(C₁-C₆)-alkyl-aryl, -C(O)-(C₁-C₆)-alkyl, -(C₁-C₆)-alkyl, -C(O)-N(H)-aryl, -C(O)-N(H)-(C₁-C₆)-alkyl-aryl, -(C₁-C₆)-N(H)-alkyl, -C(O)-O-aryl, -C(O)-O-(C₁-C₆)-alkyl-aryl, -C(O)-O-(C₁-C₆)-alkyl-, S(O₂)-aryl, -S(O₂)-(C₁-C₆)-alkyl

R² is

1. aryl, wherein aryl is unsubstituted or mono- to tri-substituted independently of one another by

- 1.1. -CF₃,
- 1.2. halogen,
- 1.3. -OH,
- 1.4. -CN,

- 5
- 1.5. sulfo,
 1.6. -NO₂,
 1.7. -NH₂,
 1.8. -O-(C₁-C₆)-alkyl,
 1.9. substituted amino,
 1.10. -COOH,
 1.11. -(C₁-C₆)-alkyl,
 1.12. carbamyl,
 1.13. carbonyl,
 10 1.14. alkoxycarbonyl,
 1.15. methylenedioxy,
 1.16. aryloxy, wherein aryloxy is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.15,
 1.17. -O-(C₁-C₆)-alkyl-aryl, wherein aryl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.15,
 15 1.18. Het-group, wherein Het-group is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.15, or
 20 1.19. -(C₀-C₄)-alkyl-aryl, wherein aryl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.15,
 2. hydrogen atom,
 3. Het-group, wherein the Het-group is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,
 25 4. -(CH₂)_m-Y_n-(CH₂)_o-aryl,
 wherein m, n and o are independently of one another the integer zero, 1 or 2, provided that at least one of m, n and o is not zero, aryl is unsubstituted or mono- to tri-substituted independently as defined under 1.1 to 1.19,
 30 Y is -O-, -S- or -N(R⁶), wherein R⁶ is hydrogen atom or -(C₁-C₆)-alkyl, provided n is the integer 1, or Y is -N(R⁶)-N(R⁶)-, wherein R⁶ is independently of one another hydrogen atom or -(C₁-C₆)-alkyl, or -N=N-, provided n is the integer 2, or
 35

5. $-(CH_2)_m-Y_n-(CH_2)_o$ -Het-group,

wherein m, n and o are independently of one another the integer zero, 1 or 2, provided that at least one of m, n and o is not zero, Het-group is unsubstituted or mono- to tri-substituted independently as defined under 1.1 to 1.19, and Y is as defined above, or

R^1 and R^2 together with the carbon atom to which they are bonded form

1. a (C_3-C_7) -cycloalkyl, wherein cycloalkyl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,

2. a (C_3-C_7) -cycloalkyl, wherein cycloalkyl is unsubstituted or mono- to disubstituted independently of one another and fused to an aryl- or Het-group-ring, which itself is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19, or

3. a Het-group, wherein the Het-group is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,

4. a keto-group, which may partially or even totally exist in a hydrated state, provided that, when R^1 is as defined above under 3, 4 or 5 then R^2 is not directly bond to formula I via a oxygen-, sulfur- or nitrogen-atom,

B is 1. $-N(R^7)-(CH-(R^8))_p$ -aryl,

wherein aryl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,

p is the zero, integer 1 or 2,

R^7 is 1.1 hydrogen atom,

1.2 $-(C_1-C_6)$ -alkyl,

1.3 -OH or

1.4 $-N-(R^6)_2$, wherein R^6 is independently of one another hydrogen atom or $-(C_1-C_6)$ -alkyl,

R^8 is 1.1 hydrogen atom,

1.2 $-(C_1-C_6)$ -alkyl,

1.3 $-(C_2-C_6)$ -alkenyl,

1.4 $-(C_2-C_6)$ -alkinyl,

1.5 $-(C_0-C_3)$ -alkyl- (C_3-C_7) -cycloalkyl,

1.6 -CN

1.7 aryl, aryl is unsubstituted or mono- or di-substituted as defined under 1.1 to 1.19,

1.8 a Het-group, wherein the Het-group is unsubstituted or mono- or di- substituted as defined under 1.1 to 1.19

1.9 $-(CH-(R^8))_p-$ forms a $-(C_3-C_7)$ -cycloalkyl residue or

1.10 $-(C_0-C_4)$ -alkyl $-O-(C_1-C_6)$ -alkyl,

- 5 2. $-O-(CH-(R^8))_p$ -aryl,
wherein aryl, R^8 and p are as defined above,
3. $-N(R^7)-(CH-(R^8))_p$ -Het-group, wherein the Het-group is unsubstituted or mono- or di-substituted as defined under 1.1 to 1.19 and R^7 , R^8 and p are as defined above,
- 10 4. $-N(R^9)-N(R^9)-(CH-(R^8))_q$ -aryl,
wherein aryl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,
q ist the integer zero, 1 or 2, R^9 and R^9 are independently of one another hydrogen, (C_1-C_6) -alkyl or $-(C_1-C_3)$ -alkyl-aryl and R^8 is as defined above,
- 15 5. $-O-N(R^9)-(CH-(R^8))_q$ -aryl,
wherein aryl is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,
q ist the integer zero, 1 or 2, and R^8 and R^9 are as defined above,
- 20 6. $-N(R^9)-N(R^9)-(CH-(R^8))_q$ -Het-group,
wherein Het-group is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,
q ist the integer zero, 1 or 2, and R^8 , R^9 and R^9 are as defined above,
- 25 7. $-O-N(R^9)-(CH-(R^8))_q$ -Het-group,
wherein Het-group is unsubstituted or mono- to tri-substituted independently of one another as defined under 1.1 to 1.19,
q ist the integer zero, 1 or 2, and R^8 and R^9 are as defined above;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically tolerable salts.

30 Preferred are compounds of formula (I), wherein

A is a residue of the formula II, wherein

R^3 is hydrogen atom,

wherein R^4 and R^5 independently from one another are hydrogen atom or halogen,

wherein X_1 and X_2 independently from one another are carbon or nitrogen atom

R^1 is hydrogen atom or $-(C_1-C_2)$ -alkyl,

R^2 is hydrogen atom, phenyl or $-(C_1-C_2)$ -alkyl-phenyl,

5 B is 1. $-N(R^7)-(CH-(R^8))_p$ -aryl,

wherein aryl is indanyl, phenyl, tetralinyl, naphthalinyl, which are unsubstituted or mono- to di-substituted independently of one another by

1.1 Br, Cl or F,

1.2 $-CF_3$,

10 1.3 $-NO_2$,

1.4 methylenedioxy,

1.5 $-OH$

1.6 phenyl,

1.7 phenoxy,

15 1.8 benzyloxy,

1.9 $O-(C_1-C_6)$ -alkyl-phenyl, wherein phenyl is unsubstituted or or mono- to tri-substituted independently of one another by

1.9.1 Br, Cl or F,

1.9.2 $-(C_1-C_4)$ -alkyl or

20 1.9.3 $-NO_2$,

1.10 $-C(O)-O-(C_1-C_4)$ -alkyl,

1.11 $-O-(C_1-C_4)$ -alkyl,

1.12 $-SO_2-(C_1-C_4)$ -alkyl,

1.13 $-COOH$,

25 1.14 $-(C_1-C_3)$ -alkyl or

1.15 methoxyl,

p is the integer zero, 1 or 2,

R^7 is hydrogen atom,

R^8 is 1.1 hydrogen atom,

30 1.2 $-(C_1-C_2)$ -alkyl,

1.3 $-CN$,

1.4 phenyl, wherein phenyl is unsubstituted or mono- or di-substituted by methoxy or halogen,

1.5 $-(C_0-C_2)$ -alkyl- $O-(C_1-C_4)$ -alkyl,

35 1.6 $-(CH-(R^8))$ - forms a $-(C_4-C_6)$ -cycloalkyl residue,

- 1.7 cyclopropylmethyl, or
 1.8 ethinyl,
2. -O-(CH-(R⁸))_p-phenyl,
 wherein phenyl, R⁸ and p are as defined above,
- 5 3. -N(R⁹)-N(R⁹)-(CH-(R⁸))_q-Het-group, wherein the Het-group is quinoxaline, imidazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, thiazolyl, indazolyl, benzothiazolyl, indolyl, indolinyl, or pyridinyl, wherein R⁹ and R⁹ are independently of one another hydrogen or
 10 -(C₁-C₂)-alkyl, R⁸ and q are as defined above under 1. for aryl, Het-group is unsubstituted or mono- to di-substituted independently of one another as defined above under 1. for aryl, or
4. -N(R⁷)-(CH-(R⁸))_p-Het-group, wherein the Het-group is imidazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, thiazolyl, benzothiazolyl, indolyl, indazolyl, indolinyl, or pyridinyl, wherein Het-group is unsubstituted or
 15 mono-substituted by Br, Cl, F, -CF₃, -NO₂, phenyl, phenoxy, methyl, benzyloxy or methoxy, and R⁷, R⁸ and p are as defined above under 1. for aryl.

As used herein, the term alkyl is to be understood in the broadest sense to mean
 20 hydrocarbon residues which can be linear, i. e. straight-chain, or branched and which can be acyclic or cyclic groups or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not
 25 located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another group, for example in an alkoxy group (alkyl-O-), an alkoxycarbonyl group or an arylalkyl group. Examples of alkyl groups containing 1, 2, 3, 4, 5 or 6 carbon atoms are methyl, ethyl, propyl, butyl, pentyl or hexyl, the n-isomers of all these groups, isopropyl, isobutyl,
 30 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tert-butyl or tert-pentyl.

Unsaturated alkyl groups are, for example, alkenyl groups such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-

hexenyl or 1,3-pentadienyl, or alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butylnyl. Alkyl groups can also be unsaturated when they are substituted.

Examples of cyclic alkyl groups are cycloalkyl groups containing 3, 4, 5, 6 or 7 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which can also be substituted and/or unsaturated. Unsaturated cyclic alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom. The term alkyl as used herein also comprises cycloalkyl-substituted alkyl groups like cyclopropylmethyl-, cyclobutylmethyl-, cyclopentylmethyl-, 1-cyclopropylethyl-, 1-cyclobutylethyl-, 1-cyclopentylethyl-, 2-cyclopropylethyl-, 2-cyclobutylethyl-, 2-cyclopentylethyl-, 3-cyclopropylpropyl-, 3-cyclobutylpropyl-, etc. in which groups the cycloalkyl subgroup as well as acyclic subgroup can be unsaturated and/or substituted.

Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like (C₁-C₆)-alkyl is to be understood as comprising, among others, saturated acyclic (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, cycloalkyl-alkyl groups like (C₃-C₇)-cycloalkyl-(C₁-C₃)-alkyl- wherein the total number of carbon atoms can range from 4 to 7, and unsaturated (C₂-C₆)-alkyl like (C₂-C₆)-alkenyl or (C₂-C₆)-alkynyl. Similarly, a group like (C₁-C₄)-alkyl is to be understood as comprising, among others, saturated acyclic (C₁-C₄)-alkyl, (C₃-C₄)-cycloalkyl, cyclopropyl-methyl-, and unsaturated (C₂-C₄)-alkyl like (C₂-C₄)-alkenyl or (C₂-C₄)-alkynyl.

The term aryl refers to a monocyclic or polycyclic hydrocarbon residue in which at least one carbocyclic ring is present that has a conjugated pi electron system. In a (C₆-C₁₄)-aryl group from 6 to 14 ring carbon atoms are present. Examples of (C₆-C₁₄)-aryl groups are phenyl, naphthyl, indanyl, tetralinyl, biphenyl, fluorenyl or anthracenyl. Examples of (C₆-C₁₀)-aryl groups are phenyl or naphthyl. Unless stated otherwise, and irrespective of any specific substituents bonded to aryl groups which are indicated in the definition of the compounds of the formula I, aryl groups, for example phenyl, naphthyl or fluorenyl, can in general be unsubstituted or substituted by one or more, for example one, two or three, identical or different substituents. Aryl groups can be bonded via any desired position, and in substituted aryl groups the substituents can be located in any desired position.

In monosubstituted phenyl groups the substituent can be located in the 2-position, the 3-position or the 4-position, with the 3-position and the 4-position being preferred. If a phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In phenyl groups carrying three substituents the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position, or 3,4,5-position. Naphthyl groups can be 1-naphthyl and 2-naphthyl. In substituted naphthyl groups the substituents can be located in any positions, for example in monosubstituted 1-naphthyl groups in the 2-, 3-, 4-, 5-, 6-, 7-, or 8-position and in monosubstituted 2-naphthyl groups in the 1-, 3-, 4-, 5-, 6-, 7-, or 8-position. Biphenyl groups can be biphenyl-2-yl, biphenyl-3-yl or biphenyl-4-yl. Fluorenyl groups can be bonded via the 1-, 2-, 3-, 4- or 9-position. In monosubstituted fluorenyl groups bonded via the 9-position the substituent is preferably present in the 1-, 2-, 3- or 4-position.

The above statements relating to aryl groups correspondingly apply to divalent groups derived from aryl groups, i. e. to arylene groups like phenylene which can be unsubstituted or substituted 1,2-phenylene, 1,3-phenylene or 1,4-phenylene, or naphthylene which can be unsubstituted or substituted 1,2-naphthalenediyl, 1,3-naphthalenediyl, 1,4-naphthalenediyl, 1,5-naphthalenediyl, 1,6-naphthalenediyl, 1,7-naphthalenediyl, 1,8-naphthalenediyl, 2,3-naphthalenediyl, 2,6-naphthalenediyl or 2,7-naphthalenediyl. The above statements also correspondingly apply to the aryl subgroup in arylalkyl- groups. Examples of arylalkyl- groups which can also be unsubstituted or substituted in the aryl subgroup as well as in the alkyl subgroup, are benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1-methyl-3-phenyl-propyl, 1-naphthylmethyl, 2-naphthylmethyl, 1-(1-naphthyl)ethyl, 1-(2-naphthyl)ethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, or 9-fluorenylmethyl. All the above explanations also corresponding apply to aromatic rings which may be condensed (or fused) to a ring formed by the groups R^1 and R^2 and the carbon atom to which these groups are attached.

The "Het group" comprises groups containing 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms in the parent monocyclic or bicyclic heterocyclic ring system. In monocyclic Het groups the heterocyclic ring preferably is a 3-membered, 4-membered, 5-membered, 6-membered or 7-membered ring, particularly preferably a 5-membered or 6-membered ring. In

bicyclic Het groups preferably two fused rings are present one of which is a 5-membered ring or 6-membered heterocyclic ring and the other of which is a 5-membered or 6-membered heterocyclic or carbocyclic ring, i. e. a bicyclic ring Het preferably contains 8, 9 or 10 ring atoms, particularly preferably 9 or 10 ring atoms.

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Het comprises saturated heterocyclic ring systems which do not contain any double bonds within the rings, as well as unsaturated heterocyclic ring systems including mono-unsaturated and poly-unsaturated heterocyclic ring systems which contain one or more, for example one, two, three, four or five, double bonds within the rings provided that the resulting system is stable. Unsaturated rings may be partially unsaturated or non-aromatic, or they may be aromatic, i. e. double bonds within the rings in the Het group may be arranged in such a manner that a conjugated pi electron system results. Aromatic rings in a Het group may be 5-membered or 6-membered rings, i. e. aromatic groups in a Het group contain 5 to 10 ring atoms. Aromatic rings in a Het group thus comprise 5-membered and 6-membered monocyclic heterocycles and bicyclic heterocycles composed of two 5-membered rings, one 5-membered ring and one 6-membered ring, or two 6-membered rings. In bicyclic aromatic groups in a Het group one or both rings may contain heteroatoms. Aromatic Het groups may also be referred to by the customary term heteroaryl for which all the definitions and explanations above and below relating to Het correspondingly apply. These explanations relating to the saturation/unsaturation in heterocyclic ring systems representing the Het group correspondingly apply to any other heterocyclic ring system that can be present in a compound of the formula I, for example to a ring formed by R¹ and R² together with the carbon atom to which these groups are bonded, and the ring systems that may be condensed to this ring.

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In a Het group and any other heterocyclic group preferably 1 or 2 identical or different ring heteroatoms selected from nitrogen, oxygen and sulfur atoms are present. In general, the ring heteroatoms can be present in any desired combination and in any desired positions with respect to each other provided that the resulting heterocyclic system is known in the art and is stable and suitable as a subgroup in a drug substance. Examples of parent structures of heterocycles from which the Het group any other heterocyclic groups can be derived are aziridine, oxirane, azetidine, pyrrole, furan, thiophene, dioxole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyran, thiopyran, pyridazine,

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pyrimidine, pyrazine, 1,4-dioxine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, indole, isoindole, benzofuran, benzothiophene, 1,3-benzodioxole, benzo[1,4]dioxine, 4H-benzo[1,4]oxazine, indazole, benzimidazole, benzoxazole, benzothiazole, quinoline, isoquinoline, chromane, isochromane, cinnoline, quinazoline, quinoxaline, phthalazine, pyridoimidazoles, pyridopyridines, pyridopyrimidines, etc. as well as ring systems which result from the listed heterocycles by fusion (or condensation) of a carbocyclic ring, for example benzo-fused, cyclopenta-fused, cyclohexa-fused or cyclohepta-fused derivatives of these heterocycles.

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The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the Het groups and other heterocyclic groups could only be derived from the respective unsaturated ring system.

The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, for example a Het group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially

hydrogenated analogues of the before-listed heterocycles from which a Het group and any other heterocyclic group may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (= morpholine), 2,3-dihydrobenzo[1,4]dioxine, 3,4-dihydro-2H-benzo[1,4]oxazine, perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc.

The Het group and other any other heterocyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom, if applicable. Thus, for example, a pyrrolyl group can be pyrrol-1-yl, pyrrol-2-yl or pyrrol-3-yl, a pyrrolidinyl group can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl group can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl group can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be furan-2-yl or fur-3-yl, thienyl can be thiophen-2-yl or

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thiophen-3-yl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= pyrimidin-6-yl) or pyrimidin-5-yl, piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Indolyl can be indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl or indol-7-yl. Similarly benzimidazolyl, benzoxazolyl and benzothiazol groups can be bonded via the 2-position and via any of the positions 4, 5, 6, and 7. Quinolinyl can be quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-5-yl, quinolin-7-yl or quinolin-8-yl, isoquinolinyl can be isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl or isoquinolin-8-yl. In addition to being bonded via any of the positions indicated for quinolinyl and isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl and 1,2,3,4-tetrahydroisoquinolinyl can also be bonded via the nitrogen atoms in 1-position and 2-position, respectively.

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The term "substituted amino" refers to $N(R^{10})_x$ where R^{10} is an alkyl or aryl, and x is 1 or 2. The term "sulfo" refers to $S(O)_yR^{11}$ where R^{11} is an alkyl, aryl, amino, or substituted amino and y is zero, one or two. The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine. The term "-(C₀-C₄)-alkyl-aryl" is understood as meaning an aryl, which substituted by no -CH₂- residue in the case of C₀-alkyl, -CH₂- residue in the case of C₁-alkyl, -CH₂-CH₂- residue in the case of C₂-alkyl, -CH₂-CH₂-CH₂- residue in the case of C₃-alkyl, -CH₂-CH₂-CH₂-CH₂- residue in the case of C₄-alkyl.

20

Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

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Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution,
5 for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

10 Physiologically tolerable salts of the compounds of formula I are nontoxic salts that are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxy group COOH, are for example alkali metal salts or alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with
15 physiologically tolerable quaternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)-amine. Basic groups contained in the compounds of the formula I, for example amino groups or amidino groups, form acid
20 addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. The present invention also includes acid
25 addition salts of compounds of the formula I which contain, for example, two basic groups, with one or two acid equivalents.

Salts of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an
30 inorganic or organic acid or base in a solvent or diluent, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiological tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as
intermediates for carrying out further chemical modifications of the compounds of the
35 formula I or as starting materials for the preparation of physiologically tolerable salts.

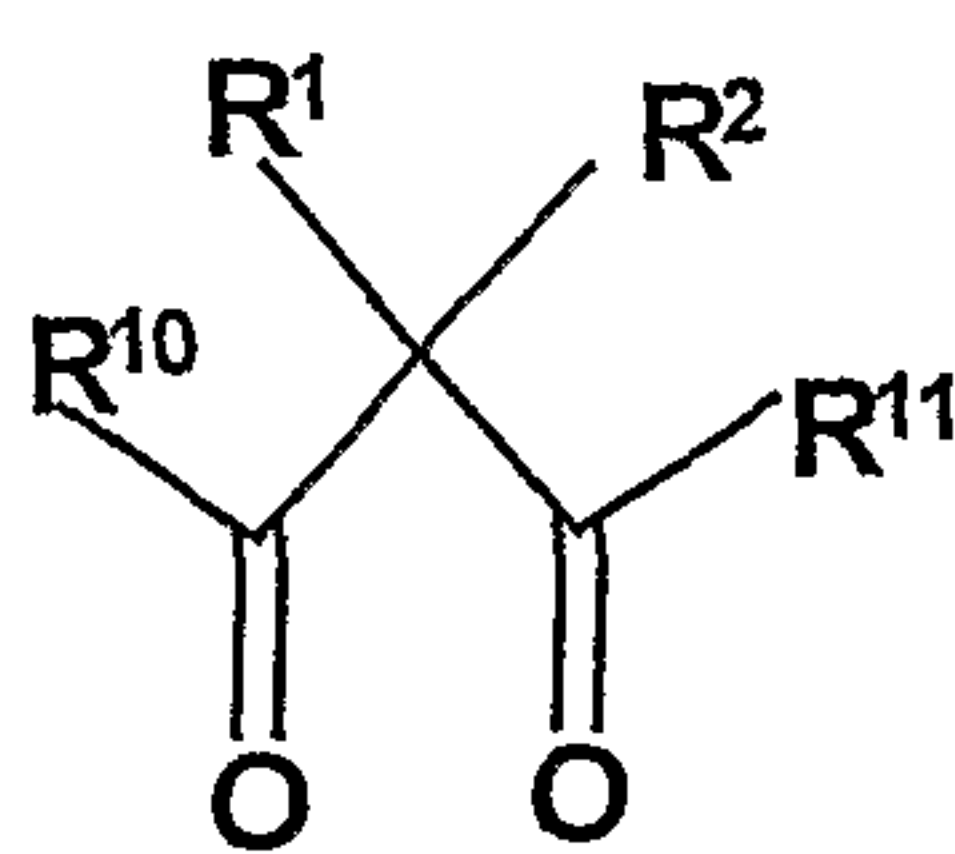
The anions of the mentioned acids that may be present in acid addition salts of the compounds of the formula I, are also examples of anions that may be present in the compounds of the formula I if they contain one or more positively charged groups like trialkylammonio- substituents, i. e. groups of the formula $(\text{alkyl})_3\text{N}^+$ bonded via the positively charged nitrogen atom, representing R^{10} , or quaternized ring nitrogen atoms in heterocyclic groups. In general a compound of the formula I contains one or more physiologically tolerable anions or anion equivalents as counterions, if it contains one or more permanently positively charged groups like trialkylammonio. Compounds of the formula I which simultaneously contain a basic group or a positively charged group and an acidic group, for example an amidino group and a carboxy group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols. The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives including esters and amides of acid groups, as well as active metabolites of the compounds of the formula I.

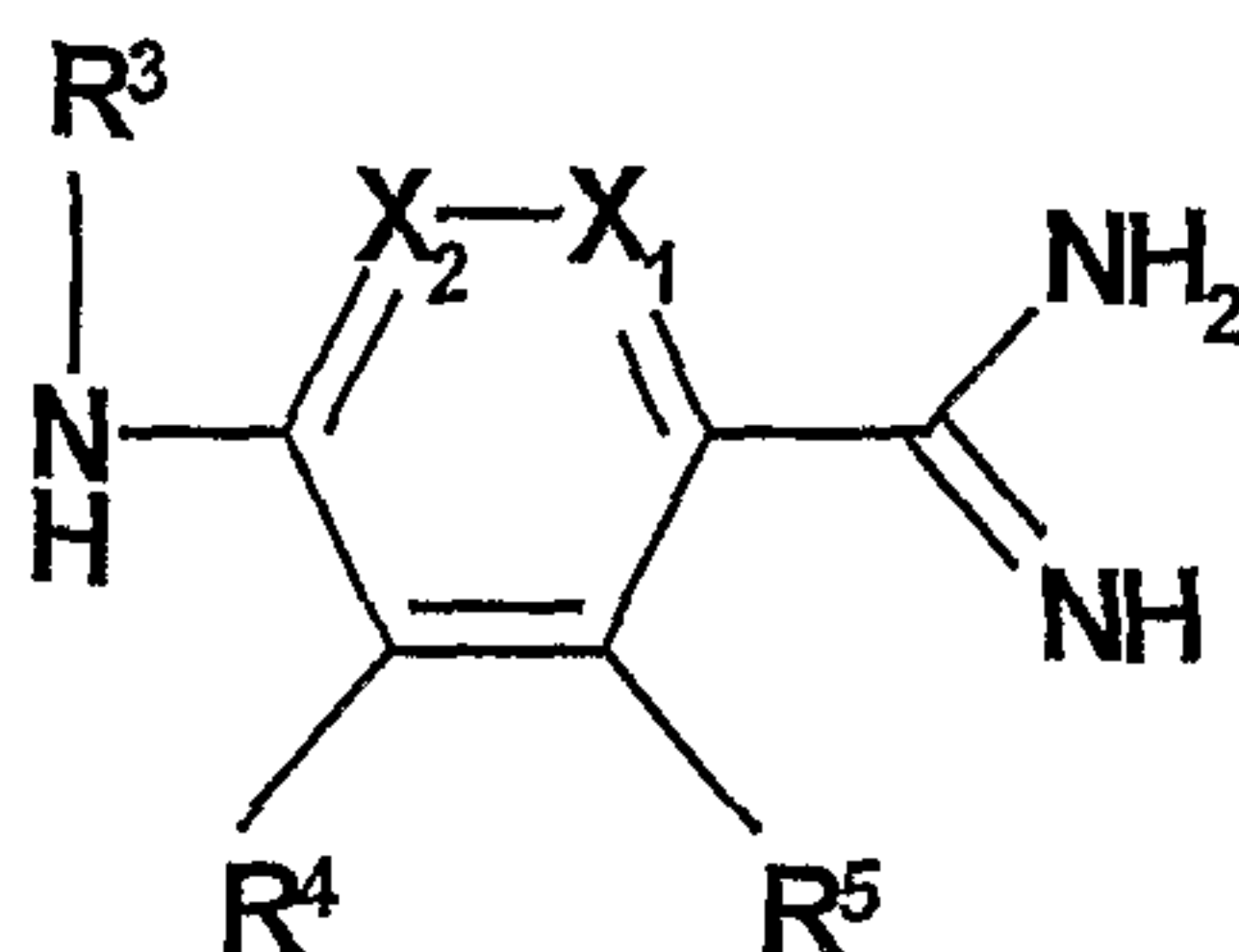
The present invention also relates to processes of preparation by which the compounds of the formula I are obtainable. The compounds of the formula I can generally be prepared by linkage of two or more fragments (or building blocks) which can be derived retrosynthetically from the formula I. In the preparation of the compounds of the formula I it can generally be advantageous or necessary in the course of the synthesis to introduce functional groups which could lead to undesired reactions or side reactions in a synthesis step in the form of precursors which are later converted into the desired functional groups. As examples of precursor groups cyano groups may be mentioned which may later be converted into amidino groups, or nitro groups which may be converted into amino groups. Protecting groups (or blocking groups) that may be present on functional groups include allyl, tert-butyl, benzyl, allyloxycarbonyl (Alloc), tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Z) and 9-fluorenylmethoxycarbonyl (Fmoc) as protecting groups for hydroxy, carboxylic acid, amino and amidino groups.

In particular, in the preparation of the compounds of the formula I building blocks can be connected by performing one or more condensation reactions and/or addition reactions

such as amide couplings, i. e. by forming an amide bond between a carboxylic acid group of one building block and an amino group of another building block. For example, compounds of the formula I can be prepared by linking the building blocks of the formulae III, IV, and V



(III)



(IV)

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wherein R^{10} and R^{11} are independently from each other a -OH group, an acid chloride, an ester like a (C₁-C₄)-alkyl ester or an activated ester, or a mixed anhydride, or any other activated species resulting from the reaction of the carboxylic acid with coupling reagents, and R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , X_1 , X_2 , B, p and aryl are as defined for formula I, by means of forming in a manner known per se an amide bond between the carboxylic acid derivative depicted in formula III and the NHR^3 group depicted in formula IV and an amide bond or ester bond between the carboxylic acid derivative depicted in formula III and the -OH- or -NH-group depicted in formula V.

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The starting compounds of the formulae III, IV and V, and other compounds which are employed in the synthesis of the compounds of formula I for introducing certain structural units, are commercially available or can be readily prepared from commercially available compounds or by analogously procedures described below or in the literature which is readily available to those skilled in the art.

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For the preparation of the compounds of formula I first the compounds of the formulae III and IV may be linked and the resulting intermediate product then be condensed with a compound of the formula V to give a compound of the formula I. Just so, first the compounds of the formulae III and V may be condensed and the resulting intermediate product then be linked to a compound of the formula IV to give a compound of the formula I. After any such reaction step in the course of such syntheses protecting and deprotecting steps and conversions of precursor groups into the desired final groups may be carried out and further modifications may be made.

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Various general methods for the formation of an amide bond that can be employed in the synthesis of the compounds of formula I are just so well known to those skilled in the art, for example from peptide chemistry. An amide coupling step can favorably be carried out by employing a free carboxylic acid, i. e. a compound of the formula III, activating that carboxylic acid group, preferably in situ, by means of a customary coupling reagent such as a carbodiimide like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC), or an N,N'-carbonyldiazole like N,N'-carbonyldi-imidazole, or a uronium salt like O-((cyano(ethoxycarbonyl)methylene)amino)-1,1,3,3-tetramethyluronium tetrafluoroborate (TOTU) or O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or a chloroformic acid ester like ethyl chloroformate or isobutyl chloroformate, or tosyl chloride, or propylphosphonic acid anhydride, or others, and then reacting the activated carboxylic acid derivative with an amino compound of the formula IV. An amide bond can also be formed by reacting an amino compound with a carboxylic acid halide, in particular a carboxylic acid chloride, which can be prepared in a separate step or in situ from a carboxylic acid and, for example, thionyl chloride, or an carboxylic acid ester or thioester, for example a methyl ester, ethyl ester, phenyl ester, nitrophenyl ester, pentafluorophenyl ester, methylthio ester, phenylthio ester or pyridin-2-ylthio ester, i. e. with a compound of the formula III.

The activation reactions and coupling reactions are usually performed in the presence of an inert solvent (or diluent), for example in the presence of an aprotic solvent like dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (DCM), dimethylsulfoxide (DMSO), hexamethyl phosphoric triamide (HMPT), 1,2-dimethoxyethane (DME), dioxane, or others, or in a mixture of such solvents. Depending on the specific process, the reaction temperature may be varied over a wide range and be, for example, from about -20°C to the boiling temperature of the solvent or diluent. Also depending on the specific process, it may be necessary or advantageous to add in a suitable amount one or more auxiliary agents, for example a base like a tertiary amine, such as triethylamine or diisopropylethylamine, or an alkali metal alcoholate, such as sodium methoxide or potassium tert-butoxide, for adjusting the pH or neutralizing an acid that is formed or for liberating the free base of an amino compound that is employed in the form of an acid addition salt, or an N-hydroxyazole like 1-hydroxybenzotriazole, or a catalyst like 4-dimethylaminopyridine. Details on methods for the preparation of activated carboxylic acid derivatives and the formation of amide bonds and ester bonds as well as source literature are given in various standard references

like, for example, J. March, Advanced Organic Chemistry, 4th ed., John Wiley & Sons, 1992; or Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag.

- 5 Protective groups that may still be present in the products obtained in the coupling reaction are then removed by standard procedures. For example, tert-butyl protecting groups, in particular a tert-butoxycarbonyl group which is a protected form of an amidino group, can be deprotected, i. e. converted into the amidino group, by treatment with trifluoroacetic acid. As already explained, after the coupling reaction also functional
- 10 groups can be generated from suitable precursor groups. In addition, a conversion into a physiologically tolerable salt or a prodrug of a compound of the formula I can then be carried out by known processes.

- In general, a reaction mixture containing a final compound of the formula I or an
- 15 intermediate is worked up and, if desired, the product is then purified by customary processes known to those skilled in the art. For example, a synthesized compound can be purified using well known methods such as crystallization, chromatography or reverse phase-high performance liquid chromatography (RP-HPLC) or other methods of separation based, for example, on the size, charge or hydrophobicity of the compound.
- 20 Similarly, well known methods such as amino acid sequence analysis, NMR, IR and mass spectrometry (MS) can be used for characterizing a compound of the invention.

- The compounds of the formula I, which on account of its chemical structure occurs in enantiomeric forms, can be resolved into the pure enantiomers by salt formation with
- 25 enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups.

- 30 The compounds of the formula I can be isolated either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts. The preparation of physiologically tolerable salts of compounds of the formula I capable of salt formation, including their stereoisomeric forms, is carried out in a manner known per se. With basic reagents such as hydroxides, carbonates, hydrogencarbonates,
- 35 alkoxides and also ammonia or organic bases, for example trimethyl- or triethylamine,

ethanolamine or triethanolamine or alternatively basic amino acids, for example lysine, ornithine or arginine, the carboxylic acids form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts. If the compounds of the formula I contain basic groups, stable acid addition salts can also be prepared using strong acids. For this, both
5 inorganic and organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, benzenesulfonic, p-toluenesulfonic, 4-bromobenzenesulfonic, cyclohexylamidodisulfonic, trifluoromethylsulfonic, acetic, oxalic, tartaric, succinic or trifluoroacetic acid are suitable.

- 10 The compounds of the formula I can especially prepared by starting from malonic acid diesters, compounds of the formula III, wherein R^{10} and R^{11} are identical or different, preferably methyl, ethyl, benzyl, t.butyl. The selective cleavage of one ester group can be accomplished by applying the appropriate method, as described e. g. in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd ed., Wiley, New
15 York, 1999. The protective groups e.g. methyl, ethyl or benzyl can be cleaved by e. g. 1 eq. of KOH in Ethanol and subsequent acidification and extraction. As an alternative, suitable protected derivatives or precursors of the amidines of residue A can be used, e. g. the cyanides, hydroxyamidines or other.

- 20 The compounds of the formula I can also prepared by starting from malonic acids, compounds of the formula III, wherein R^{10} and R^{11} are both hydrogen atoms. The free malonic diacids can be transformed to a salt, e. g. the DIPEA- or triethylamine salt by using one equivalent of an appropriate base, and then transformed to a mono acid chloride with e. g. thionyl chloride or other related reagents. This acid chloride will then
25 be reacted with an amine (B), or the, e. g., amidino aniline (A) or the respective derivative or precursor, e. g. , cyanide. The second component to complete the synthesis, can then be introduced, followed, if necessary, by transformation of the amidine and/or one or more deprotection steps. Alternatively, it is as well possible, to use standard coupling procedures for the synthesis of the mono-amide from the diacid,
30 but separation from remaining diacid and symmetrical diamide is then often necessary.

- The compounds of the formula I can also prepared by starting from phenyl acetic acids or related substituted acetic acids or their esters. When R^1 is hydrogen atom and R^2 is e. g. aryl, especially phenyl, it is possible to apply the well-known carboxylation reaction for
35 the synthesis of malonic acid derivatives, resulting in malonic acid diesters (depending

on the starting compounds used: mixed or non-mixed) or mono esters. As a starting material, e. g. a (substituted) phenyl acetic acid ester (methyl, ethyl, tbutyl preferred) has first to be deprotonated by using BuLi, phenolate, LDA, NaNH₂, NaH or related strong bases followed by CO₂ or CO₂-equivalents like diethylcarbonate or chloroformates.

- 5 Therefore, it is possible to synthesize mono-esters if CO₂ is used in this reaction circumventing single ester cleavage or mixed diesters if e. g. diethylcarbonate is used together with a different ester group of the e. g. phenyl acetate.

Next steps will be accomplished as described above resulting in the diamides as being subject of the invention.

- 10 B: Malonic acid ester amides (this comprises all compounds containing an amidino bearing group A connected to the parents malonate via the amide bond and an ester moiety $-C(=O)-O-$ as part of B in the general formula I; malonamic esters)

1. Starting from malonic acid diesters or the thus resulting mono esters:

- 15 For the introduction of the desired residue as part of B it is possible

(a) to esterify an appropriate monoester of the starting malonate and then, after selective cleavage of the protective second ester to couple the amidine or amidine equivalent/ precursor as described above.

- 20 (b) Alternatively, it is as well possible, first to couple the amine of the finally amidino containing residue resulting in the malonamic ester, than to cleave the protective ester group and esterify with the desired alcohol, followed by deprotection steps, if necessary.

2. Starting from malonic acids:

- 25 By using the above mentioned method, it is as well possible, to esterify the acid chloride with an alcohol of component B (which is present in the final product), followed by introduction of the amidine containing group or amidine precursor A.

- 30 3. Starting from phenyl acetic acids or related substituted acetic acids or their esters

The carboxylation reaction can be performed in the same manner as described above, preferably using benzyl- or tbutyl-esters of the starting side chain containing acid. If a second ester-group was introduced in the carboxylation reaction, first selective cleavage of one ester should be accomplished, then esterification with the desired alcohol as part
35 of B, present in the final product. After second selective cleavage of the remaining ester

protective group coupling with the amidine- or amidine precursor containing residue has to be done, eventually followed by deprotection step(s).

Alternatively, the order of introduction of both residues can be changed, as described above for the diamide synthesis. Another possibility is the introduction of the finally present ester group as part of B in general formula I into e. g. phenyl acetic acid or the related starting acid, followed then by the carboxylation reaction and the coupling of the amidine or amidine precursor, if necessary, after cleavage of the protective second ester and followed by deprotection/transformation of the amidine precursor.

Amidine and amidine precursors

At least two different principle ways for the introduction of the amidine containing moiety A in general formula I are possible:

1. Separate building block synthesis or using commercially available compounds, yet containing the amidine and using this building block in the coupling reaction. Optionally, the amidine can be protected using standard procedures for protective group introduction.
2. Amidine precursors are usually the corresponding nitriles. So from synthetic reasons it might sometimes be advisable to do the transformation to the amidine in any later stage of the synthesis or, often most convenient, even on the last stage, therefore eventually circumventing problems during synthesis.

Several methods for the transformation of the cyanide to the amidine are known; which method will be used depends on the specific chemistry of the transformation and the potential interactions with functionalities and other problems with the target molecule. Particularly useful in the present case is the pinner reaction or the nucleophilic addition of hydroxylamine to the nitrile, followed by hydrogenation or the hydroxyamidine. If the latter method is used, it is as well possible, to use the intermediate hydroxyamidine in e. g. coupling reactions, doing the hydrogenation on a latter stage or the last stage of the synthesis.

Amidines and hydroxyamidines might as well be used in a protected state.

Amidines and hydroxyamidines can be modified by special residues which will function as prodrugs or as protective groups during synthesis and being prodrugs, too.

Known groups of that kind are especially derivatives of carboxylic acids and carbamic acids like phenoxycarbonyl, benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, benzoyl, acetyl etc.

- 5 Chirality of starting materials: Amines or alcohols to be coupled to the malonate, containing asymmetric centers, can be used in chiral or racemic or any other stereoisomeric form including all kinds of mixtures.

- 10 The invention also relates to pharmaceuticals which comprise an efficacious amount of at least one compound of the formula I and/or of a physiologically tolerable salt of the compounds of the formula I and/or an optionally stereoisomeric form of the compounds of the formula I, together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

- 15 The compounds of the present invention inhibit the activity of the blood coagulation enzyme factor VIIa either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor VIIa into the prothrombinase complex.

- 20 Because of their factor VIIa inhibitory activity the compounds of the formula I are useful pharmacologically active compounds which are suitable, for example, for influencing blood coagulation (or blood clotting) and fibrinolysis and for the treatment, including therapy and prophylaxis, of diseases such as, for example, cardiovascular disorders, thromboembolic diseases or restenoses. The compounds of the formula I and their
25 physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations which permit enteral or parenteral administration and which contain, as active constituent, an effective amount of at least
30 one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs and a pharmaceutically acceptable carrier.

- The present invention therefore also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or
35 medicaments), to the use of the compounds of the formula I and/or their physiologically

tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor VIIa or for influencing blood coagulation or fibrinolysis or for the treatment, including therapy and prophylaxis, of the diseases mentioned above or below, for example for the production of pharmaceuticals for the treatment of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor VIIa or for influencing blood coagulation or fibrinolysis or for the treatment of the diseases mentioned above or below, for example for use in the treatment, including therapy and prophylaxis, of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxes. The present invention furthermore relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs and a pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances (or vehicles) and/or additives (or excipients).

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carrier substances and/or additives being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. Carrier substances for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carrier substances for the production of solutions, for

example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carrier substances for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 to about 90 % by weight of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 to about 1000 mg, preferably from about 1 to about 500 mg.

In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain one or more additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

As inhibitors of factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the therapy and prophylaxis of conditions in which the activity of factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor VIIa or decreasing its activity, or for the prevention, alleviation or cure of which an inhibition of factor VIIa or a decrease in

its activity is desired by the physician. As inhibition of factor VIIa influences blood coagulation and fibrinolysis the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

Conditions in which a compound of the formula I and/or a physiologically tolerable salt thereof and/or a prodrug thereof can be favorably used include, for example, cardiovascular disorders, thromboembolic diseases or complications associated, for example, with infection or surgery. The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment, including therapy and prophylaxis, of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis which can occur following surgery. In view of their pharmacological activity the compounds of the invention can replace other anticoagulant agents such as heparin. The use of a compound of the invention can result, for example, in a cost saving as compared to other anticoagulants.

When using the compounds of the formula I the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from about 0.01 to about 100 mg/kg.

preferably from about 0.1 to about 50 mg/kg, in particular from about 0.1 to about 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it
5 may be necessary to deviate upwards or downwards from the daily dose indicated.

A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation of the blood
10 sample. Further, a compound of the formula I and its salts can be used for diagnostic purposes, for example in in vitro diagnoses, and as an auxiliary or tool in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor VIIa or to isolate factor VIIa in a substantially purified form. A compound of the invention can be labeled with, for example, a radioisotope, and
15 the labeled compound bound to factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used advantageously as a probe to detect the location or amount of factor VIIa activity in vivo, in vitro or ex vivo.

20 Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

25 It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not limit the present invention.

Examples

30

Abbreviations

Boc	tert. butyl oxycarbonyl
DIPEA	Diisopropyl-ethylamine
35 DMF	N,N-Dimethylformamide

DMSO	Dimethylsulfoxide
NEM	N-Ethylmorpholine
NEt ₃	triethylamine
rt	room temperature
5 THF	Tetrahydrofuran
TOTU	O-(Cyano(ethoxycarbonyl)methyleneamino)-1,1,3,3-tetramethyluronium tetrafluoroborate
Z	benzyl oxycarbonyl

- 10 When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tert-butyl group or when a compound was purified by chromatography using an eluent which contained such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was
- 15 obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt.

20 Example 1: N-(4-CARBAMIMIDOYL-PHENYL)-2-PHENYL-MALONAMIC ACID BENZYL ESTER

- 10 g (37 mmol) phenyl malonic acid monobenzyl ester and 7,7 g (37 mmol) 4-amidino aniline hydrochloride were dissolved in 60 ml DMF and cooled to 0°C. 12,2 g (37 mmol) TOTU and 19 ml (111 mmol) DIPEA were added and the mixture stirred at rt overnight.
- 25 The solvent was removed, the residue taken up in ethyl acetate and extracted with 10 % sodium carbonat solution and brine. After drying over sodium sulfate the solution was evaporated to dryness and digenerated with diethyl ether twice. The remaining solid product was sufficient pure. Yield: 9,7 g ESI-MS (M+H): 388,10

30 Example 2: N-(4-CARBAMIMIDOYL-PHENYL)-2-PHENYL-MALONAMIC ACID sodium salt

8,26 g (19,5 mmol) of the benzyl ester from example 1 werde dissolved in 100 ml THF and stirred overnight with 20 ml 2 M aqueous NaOH. The solvent was removed after

filtration, water was added and the solution extracted with diethyl ether. The aqueous phase was freeze dried and sufficient pure for further derivatization.

Yield: 2,6 g ESI-MS (M+H): 298,10

5 Example 3: N-(4-CARBAMIMIDOYL-PHENYL)-N'-[1-(4-NITRO-PHENYL)-ETHYL]-2-PHENYL-MALONAMIDE, FORMIATE

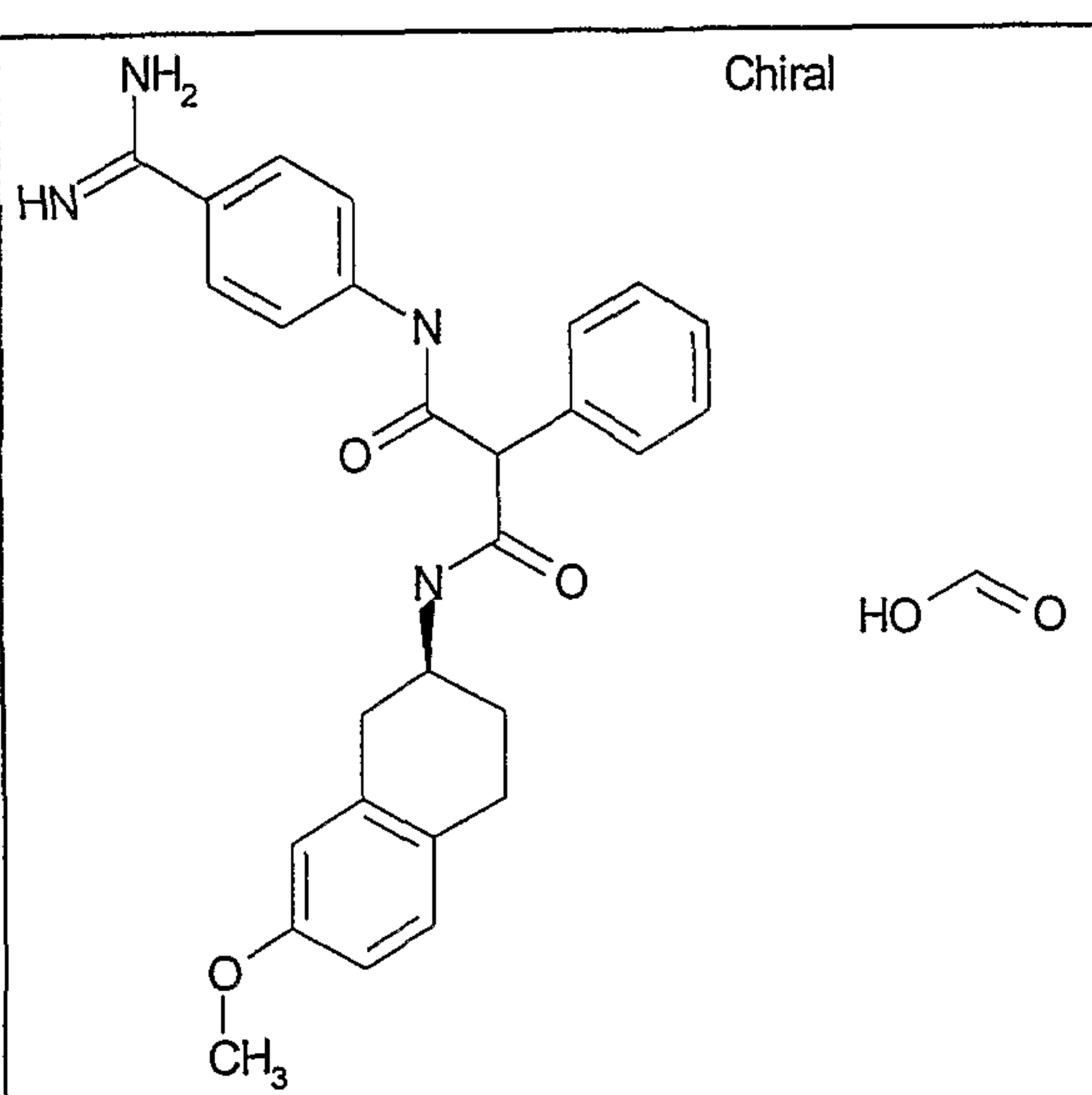
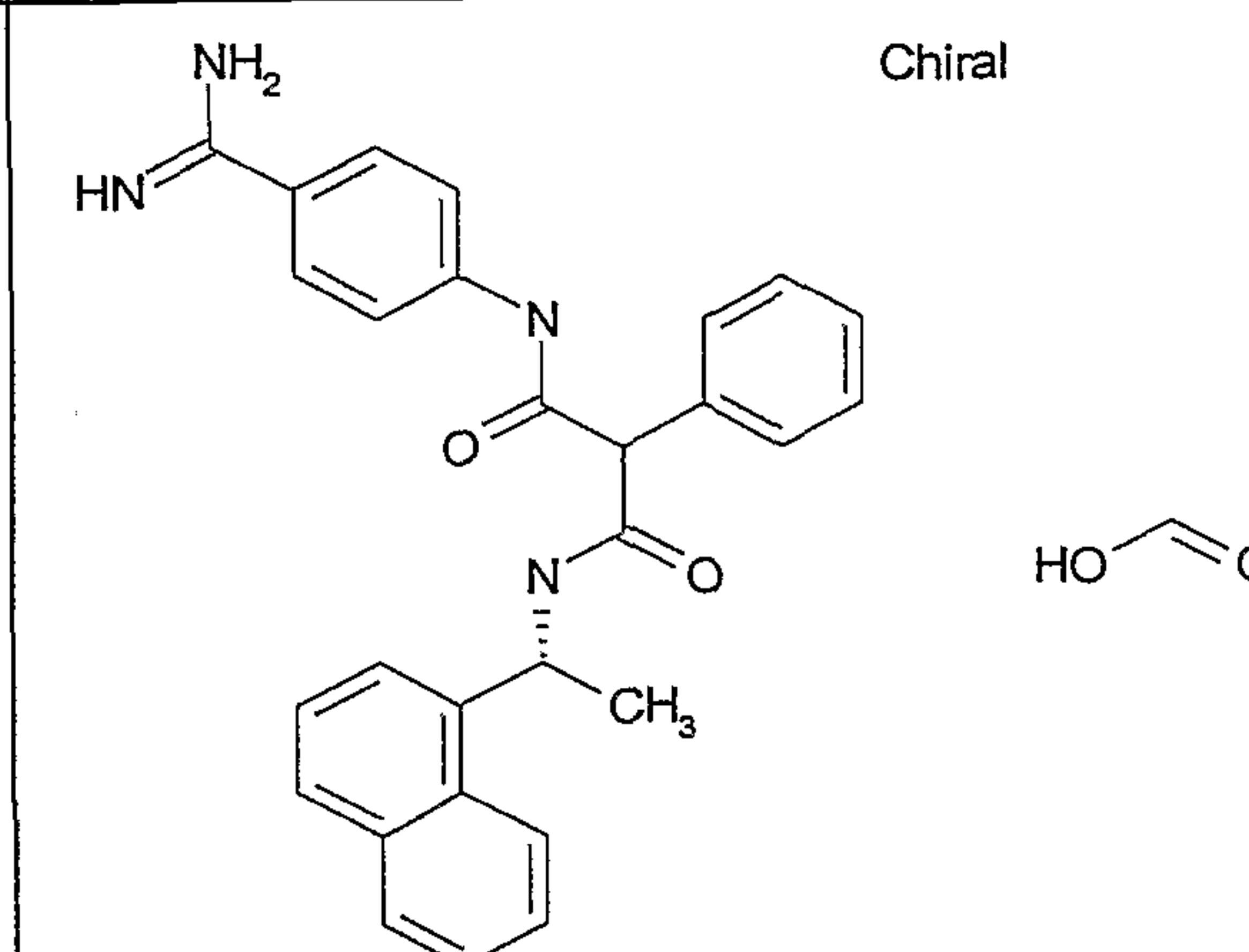
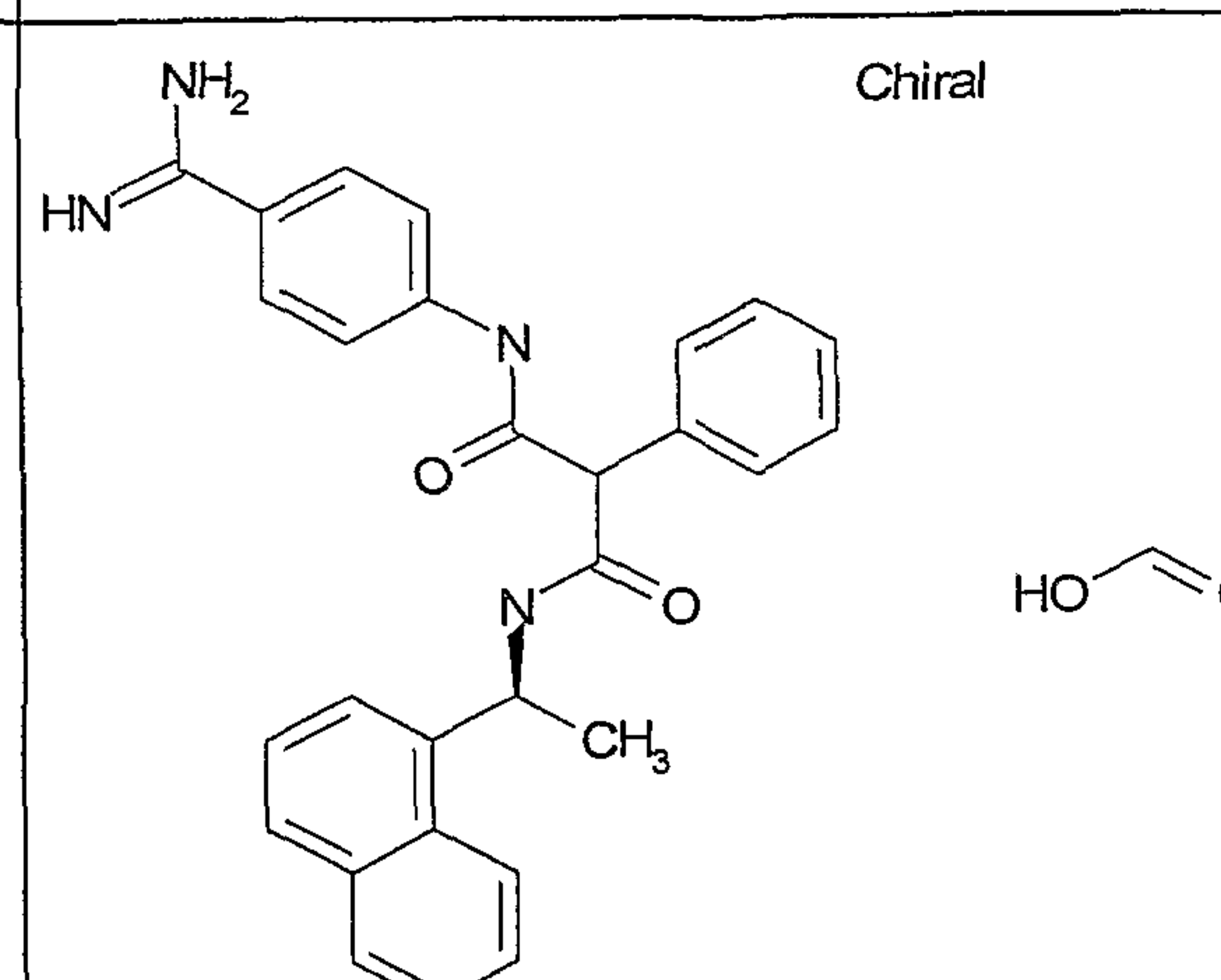
75 mg (0,235 mmol) of the sodium salt from example 2 were dissolved in 2,5 ml DMF. 85 mg (0,265 mmol) TOTU in 2,5 ml DMF were added and stirred for 30 min at rt. Then
10 34 µl (0,265 mmol) NEM and 53,7 mg (0,265 mmol) of (S)-1-(4-nitrophenyl)-ethylamine in 0,5 ml of DMF was added and the mixture stirred at rt overnight. After filtration the filtrate was evaporated to dryness and purified by prep. RP-HPLC.

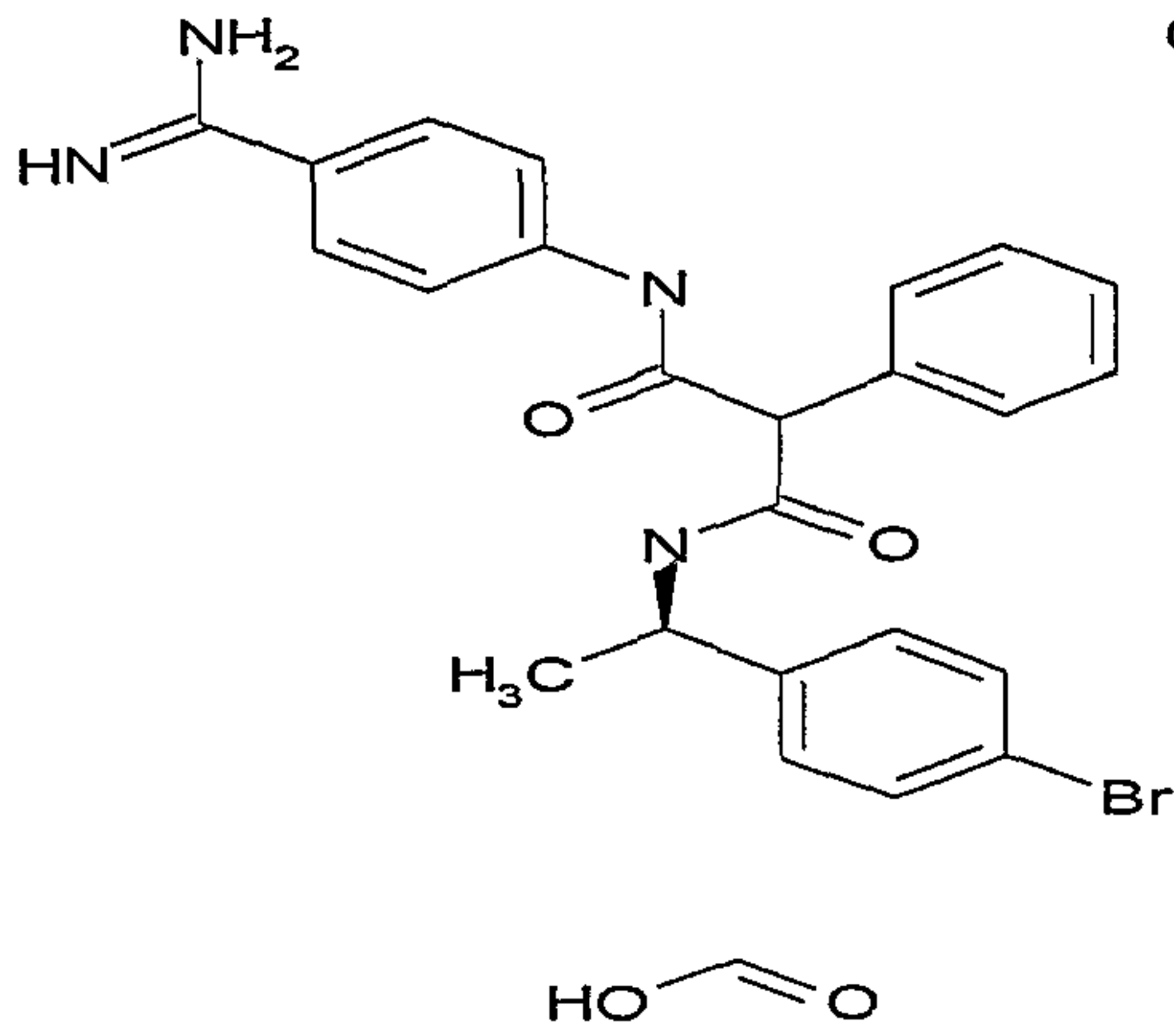
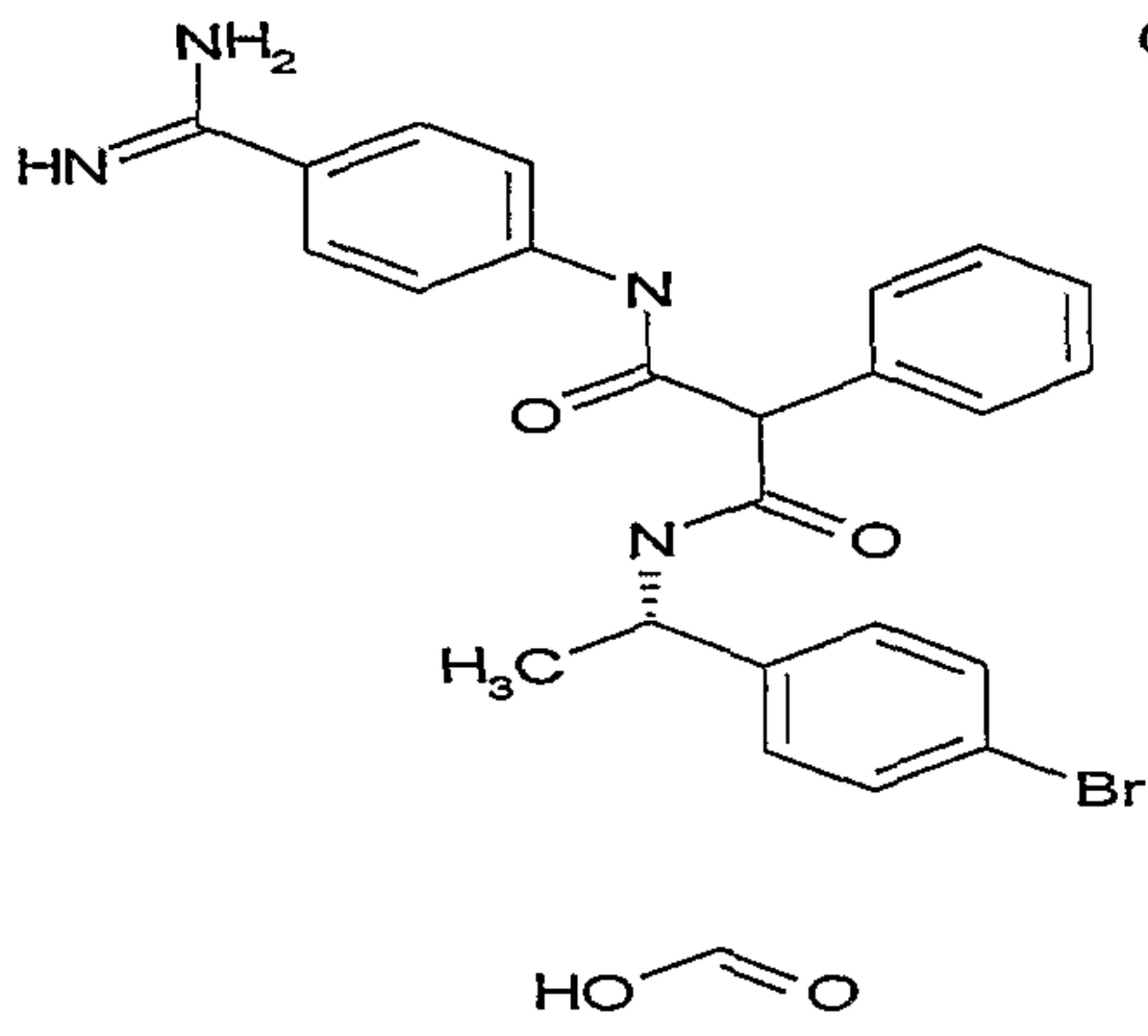
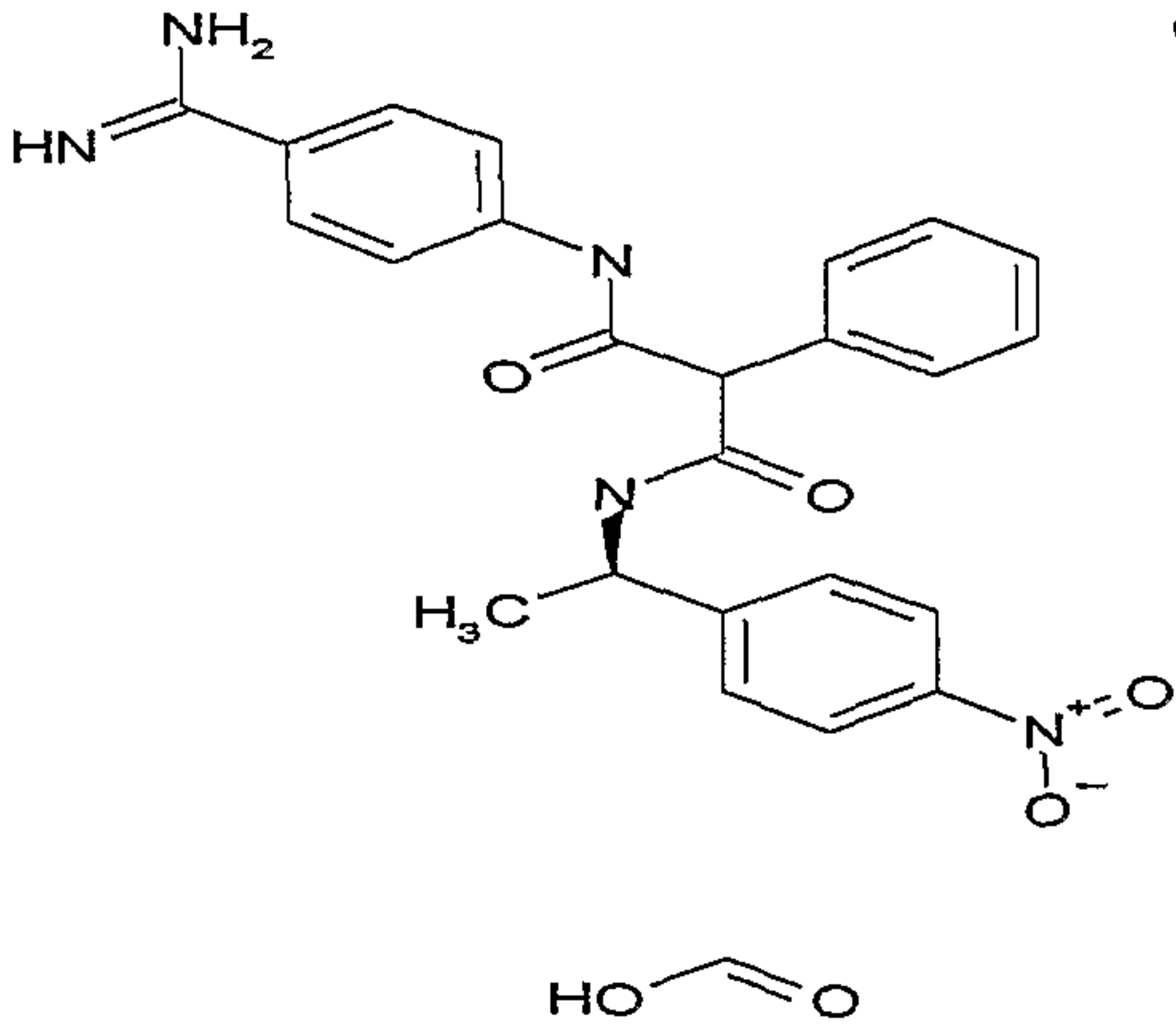
Yield: 12 mg ESI-MS(M+H): 446,17.

15 Analogously to the above examples the following example compounds were prepared. The examples in Table 1 show the structures of the prepared compounds.

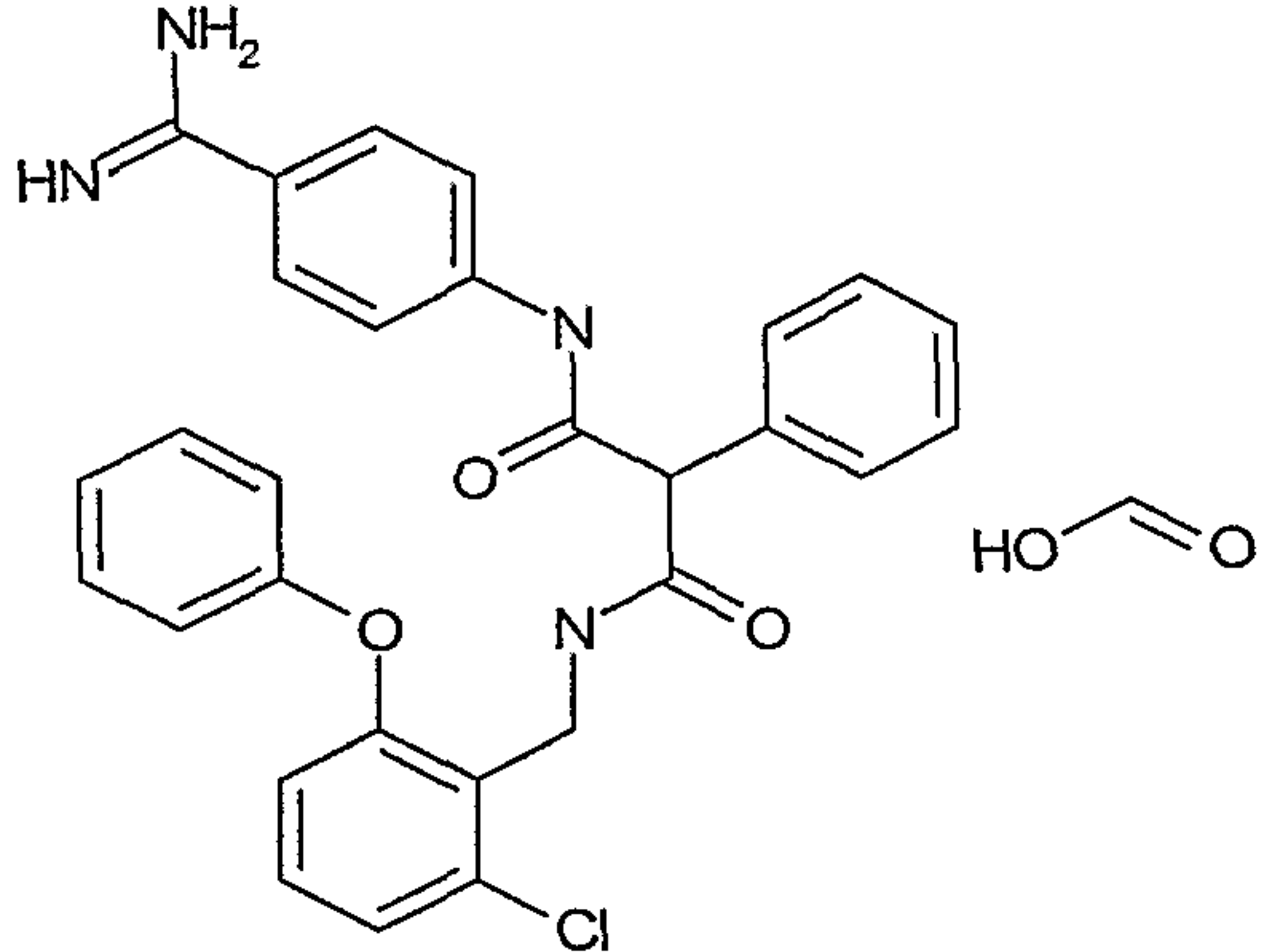
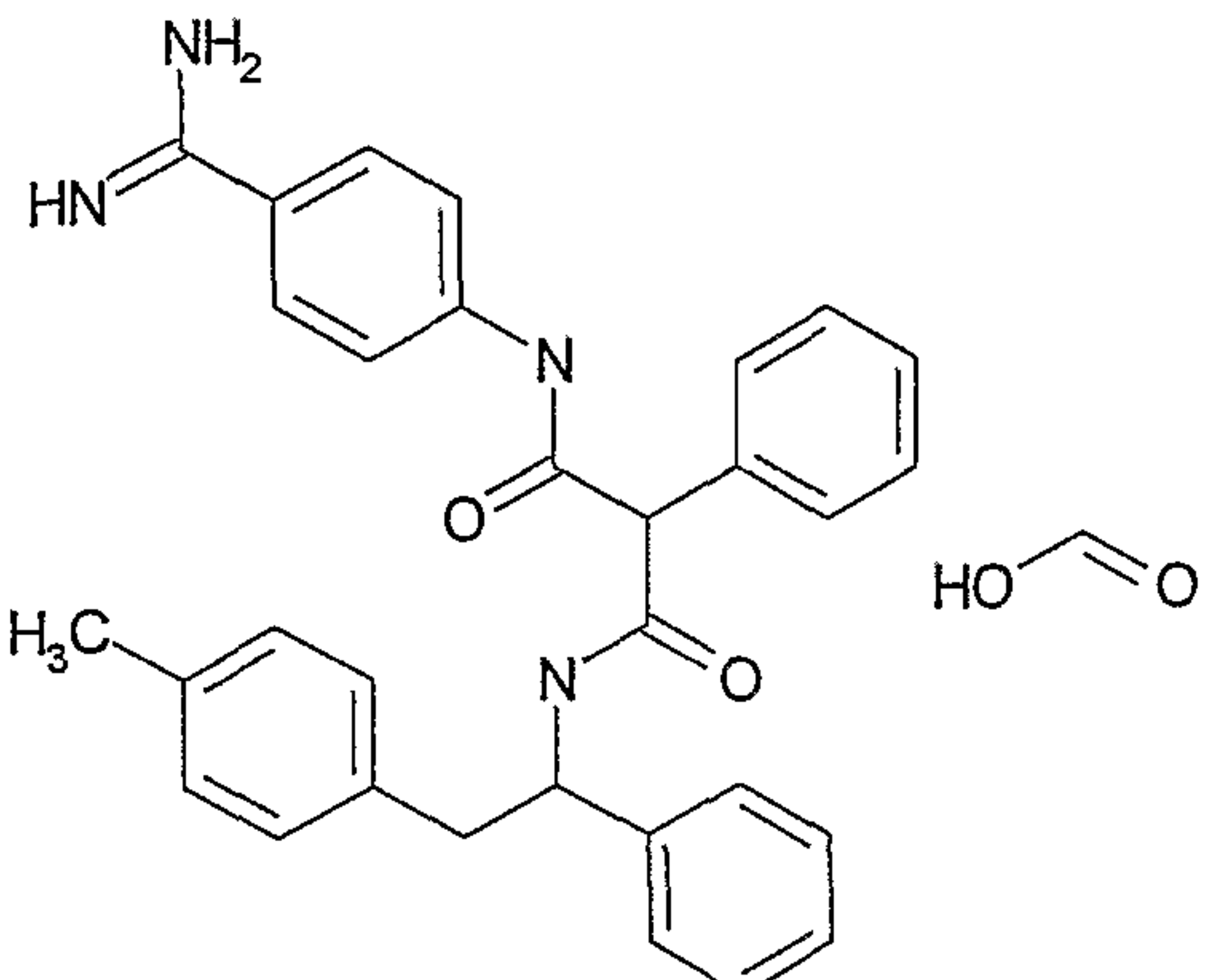
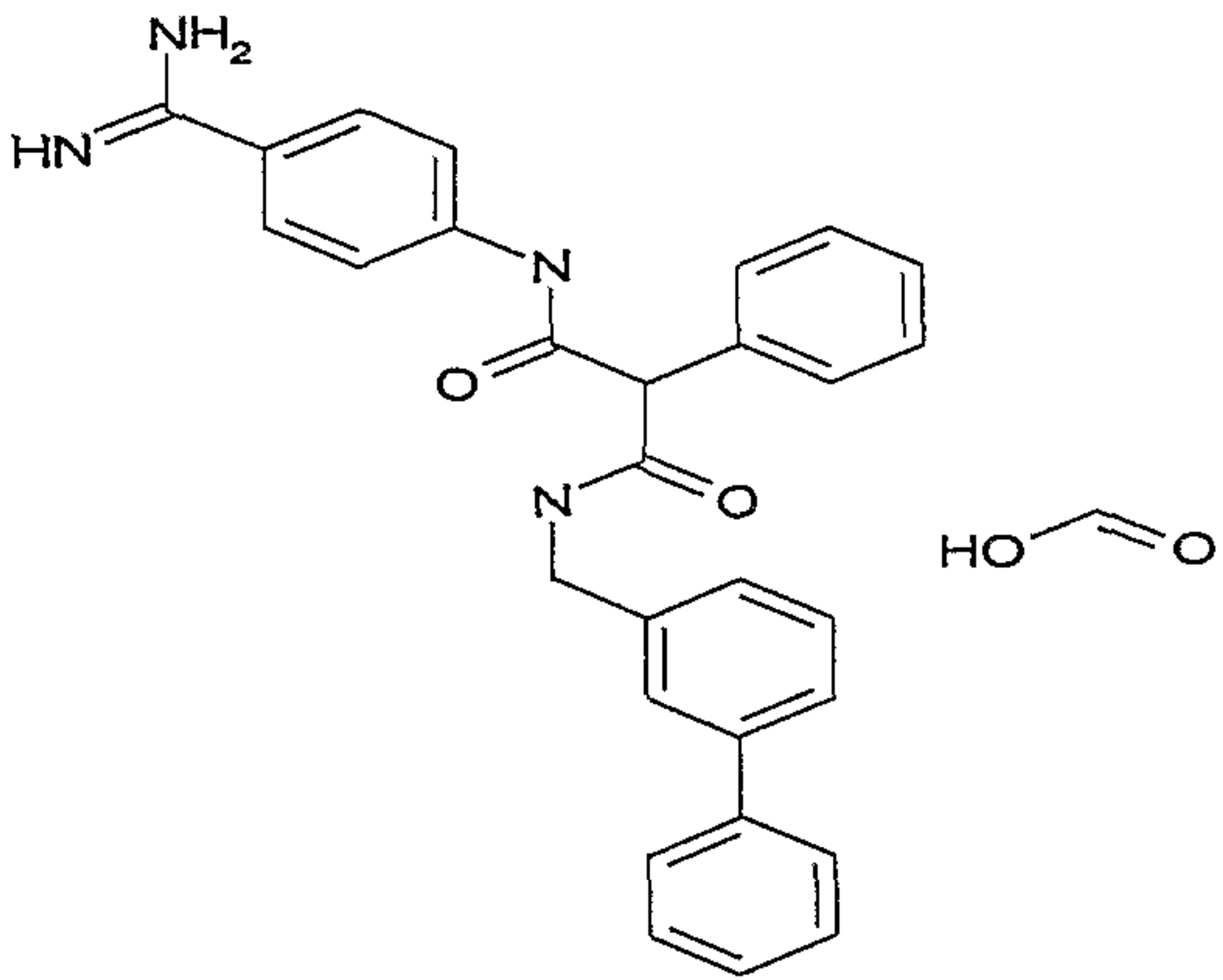
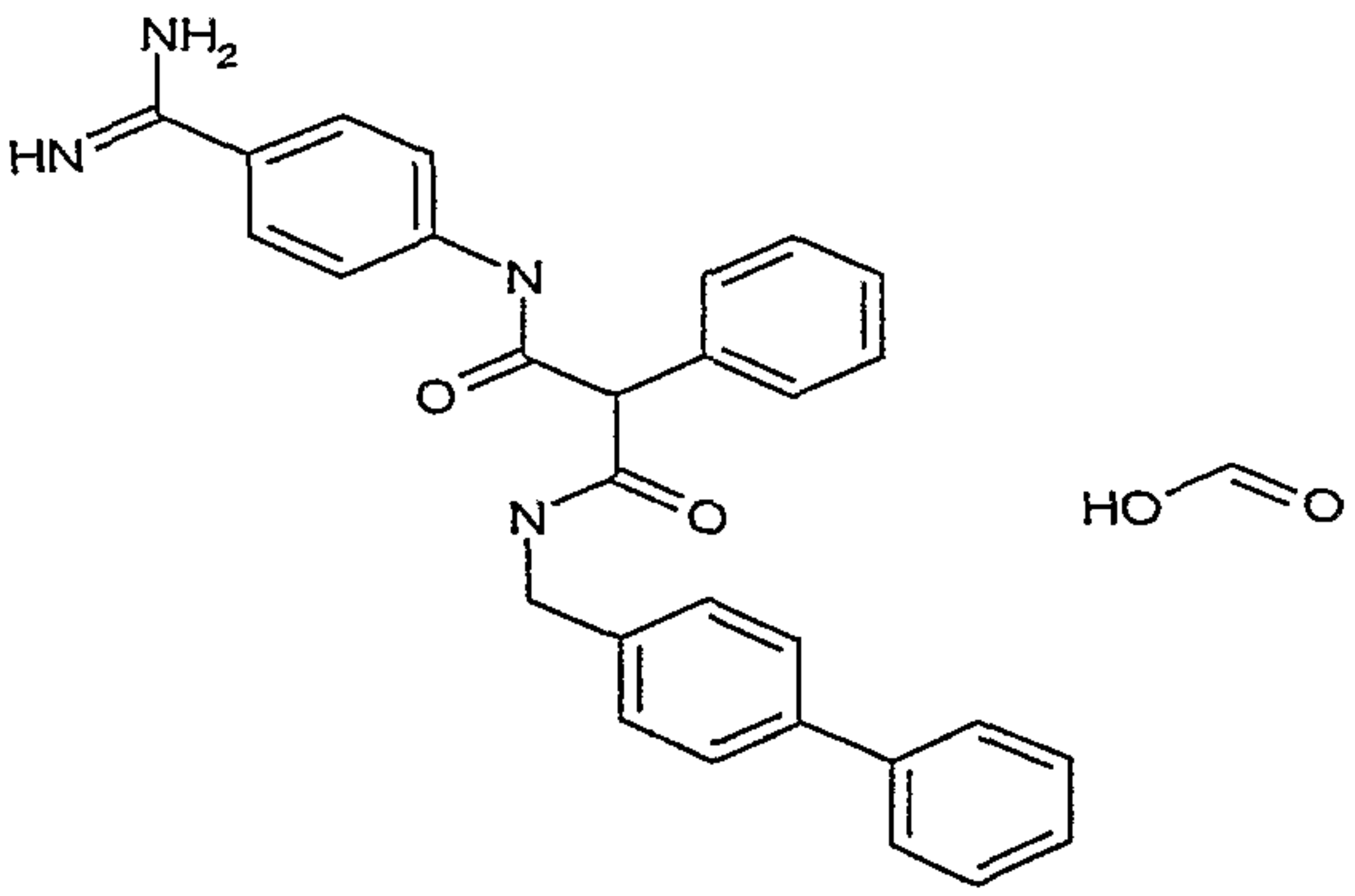
Table 1:

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
4		$C_{25}H_{24}N_4O_2 \cdot C H_2 O_2$	458,5154	412,19
5		$C_{25}H_{25}ClN_4O_2 \cdot C H_2 O_2$	494,9763	448,17
6		$C_{24}H_{21}N_5O_2 \cdot C H_2 O_2$	457,4877	411,17
7		$C_{29}H_{25}ClN_4O_2 \cdot C H_2 O_2$	543,0203	496,17

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
8	Chiral  HO-COOH	$C_{27}H_{28}N_4O_3$ $C H_2 O_2$	502,568	456,22
9	Chiral  HO-COOH	$C_{28}H_{26}N_4O_2$ $C H_2 O_2$	496,5642	450,21
10	Chiral  HO-COOH	$C_{28}H_{26}N_4O_2$ $C H_2 O_2$	496,5642	450,21

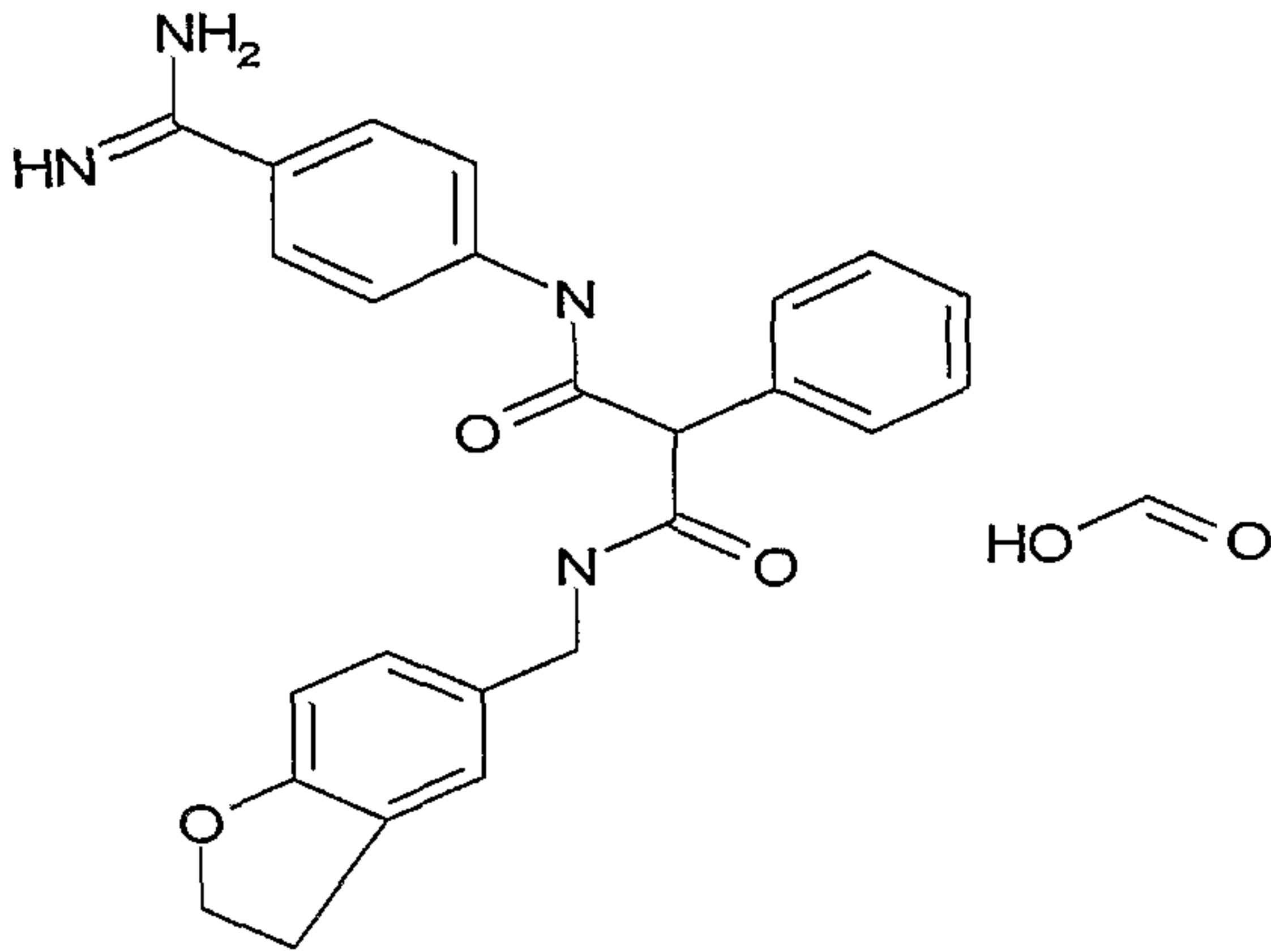
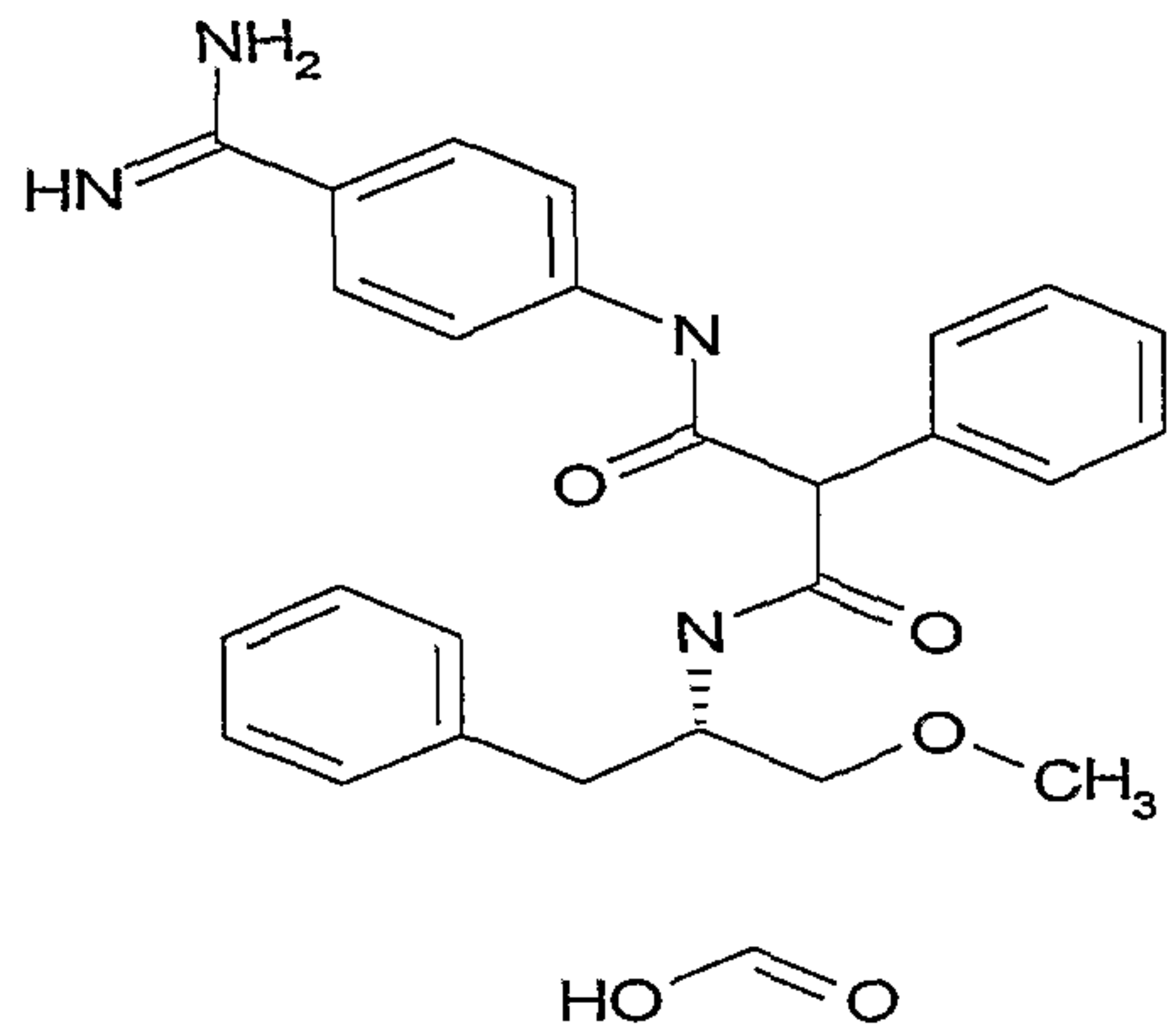
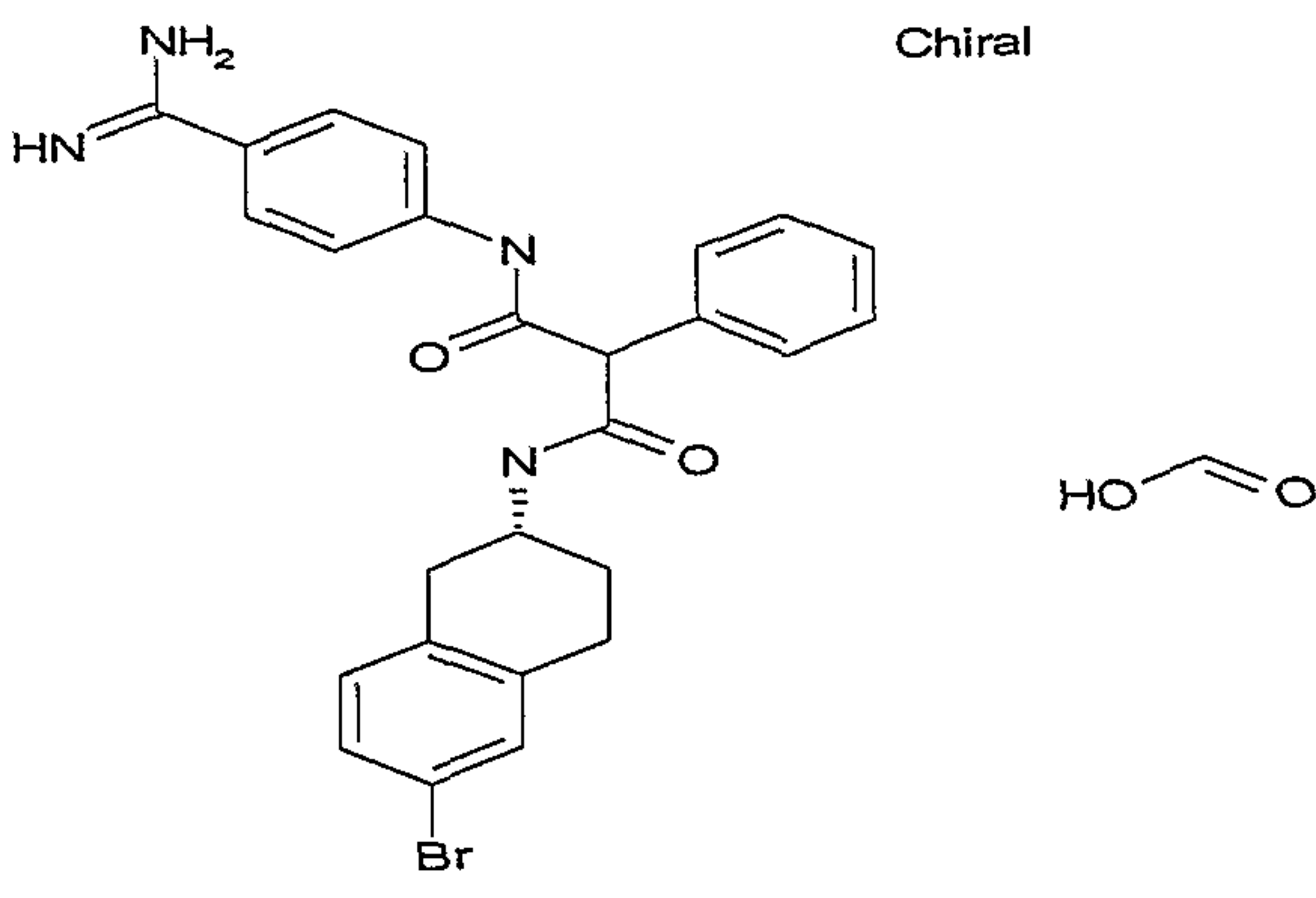
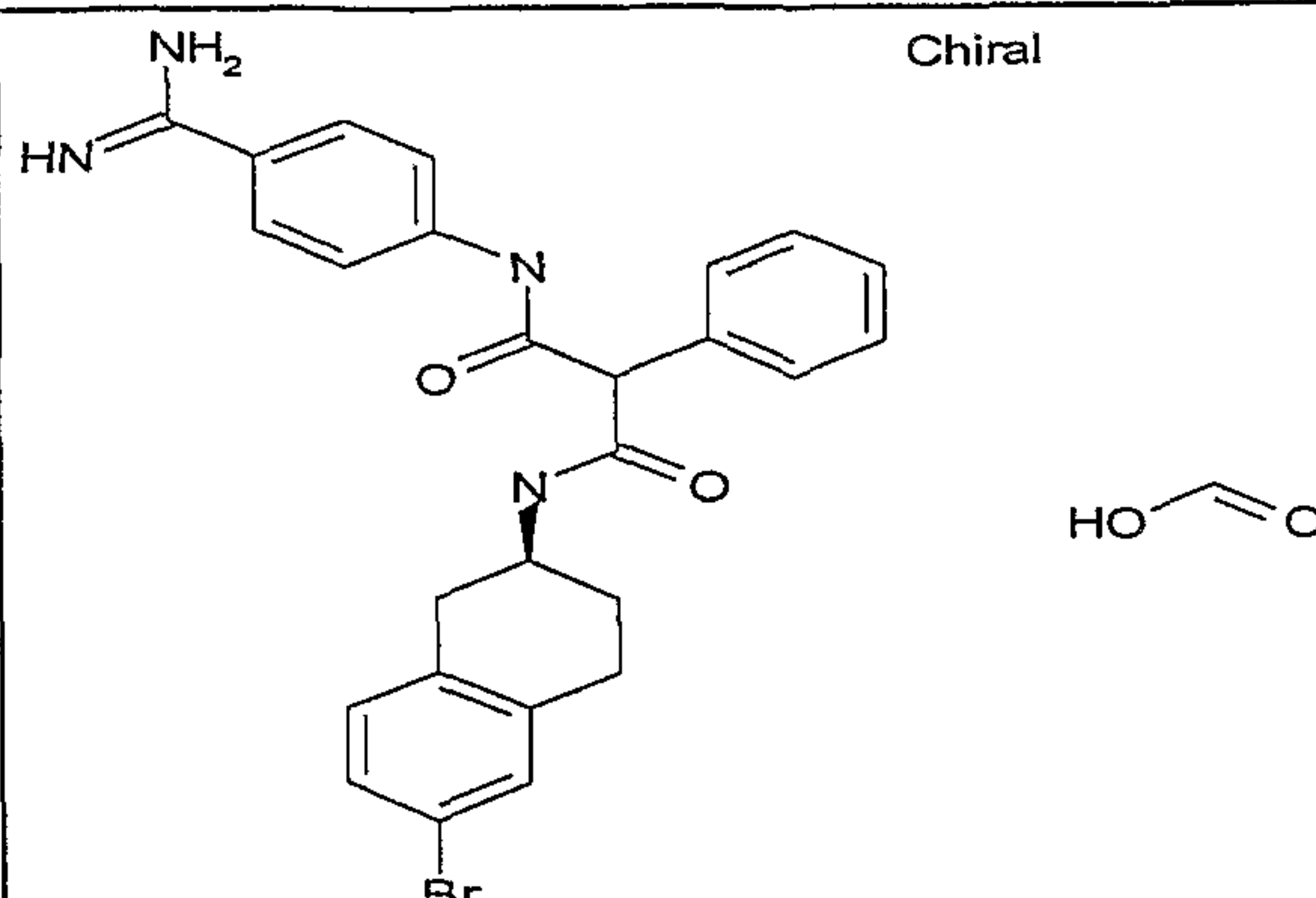
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
11	Chiral  HO-CH₂-OH	$C_{24}H_{23}BrN_4O_2 \cdot C H_2 O_2$	525,4005	478,1
12	Chiral  HO-CH₂-OH	$C_{24}H_{23}BrN_4O_2 \cdot C H_2 O_2$	525,4005	478,1
13	Chiral  HO-CH₂-OH	$C_{24} H_{23} N_5 O_4 \cdot C H_2 O_2$	491,5015	445,17

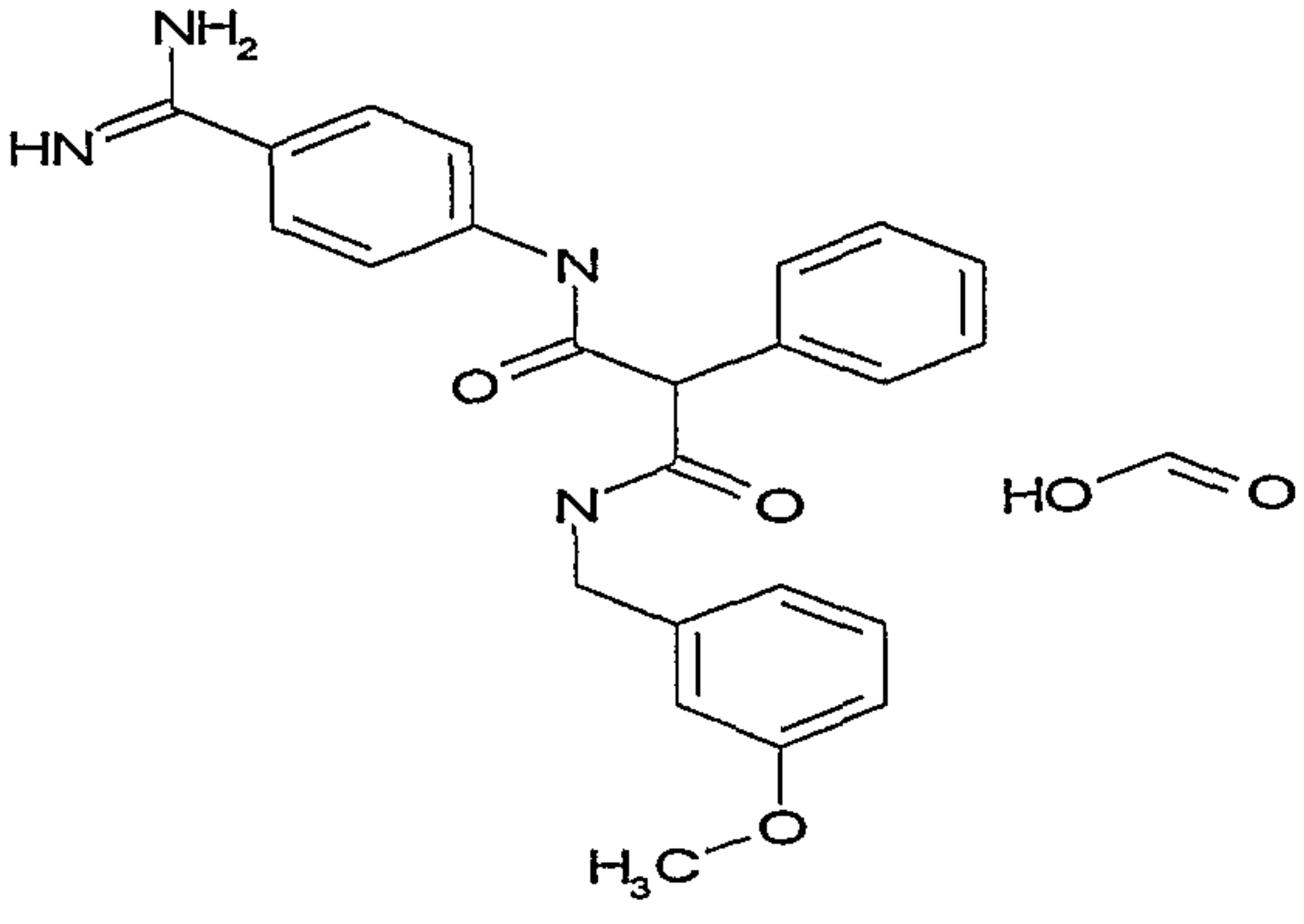
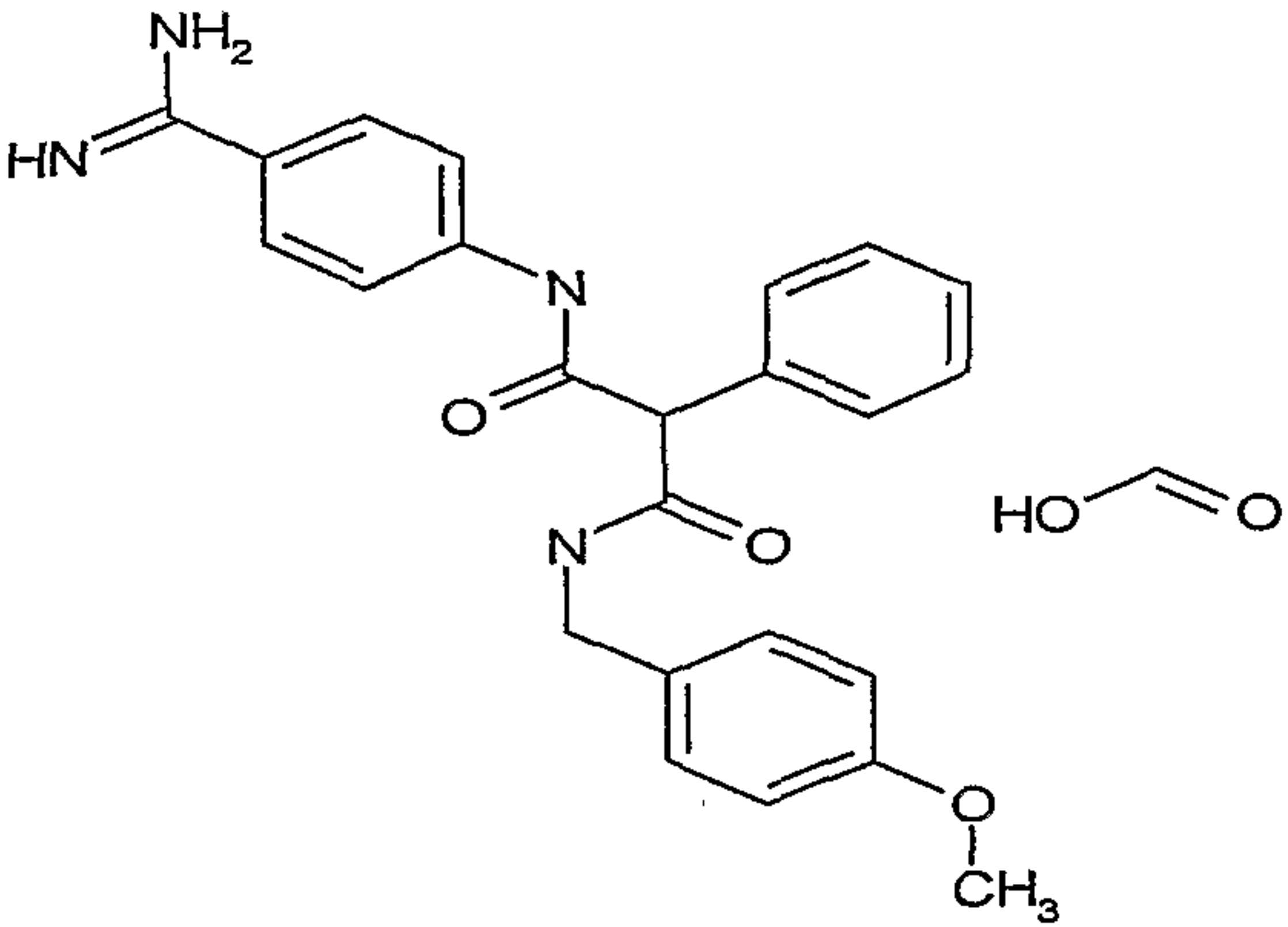
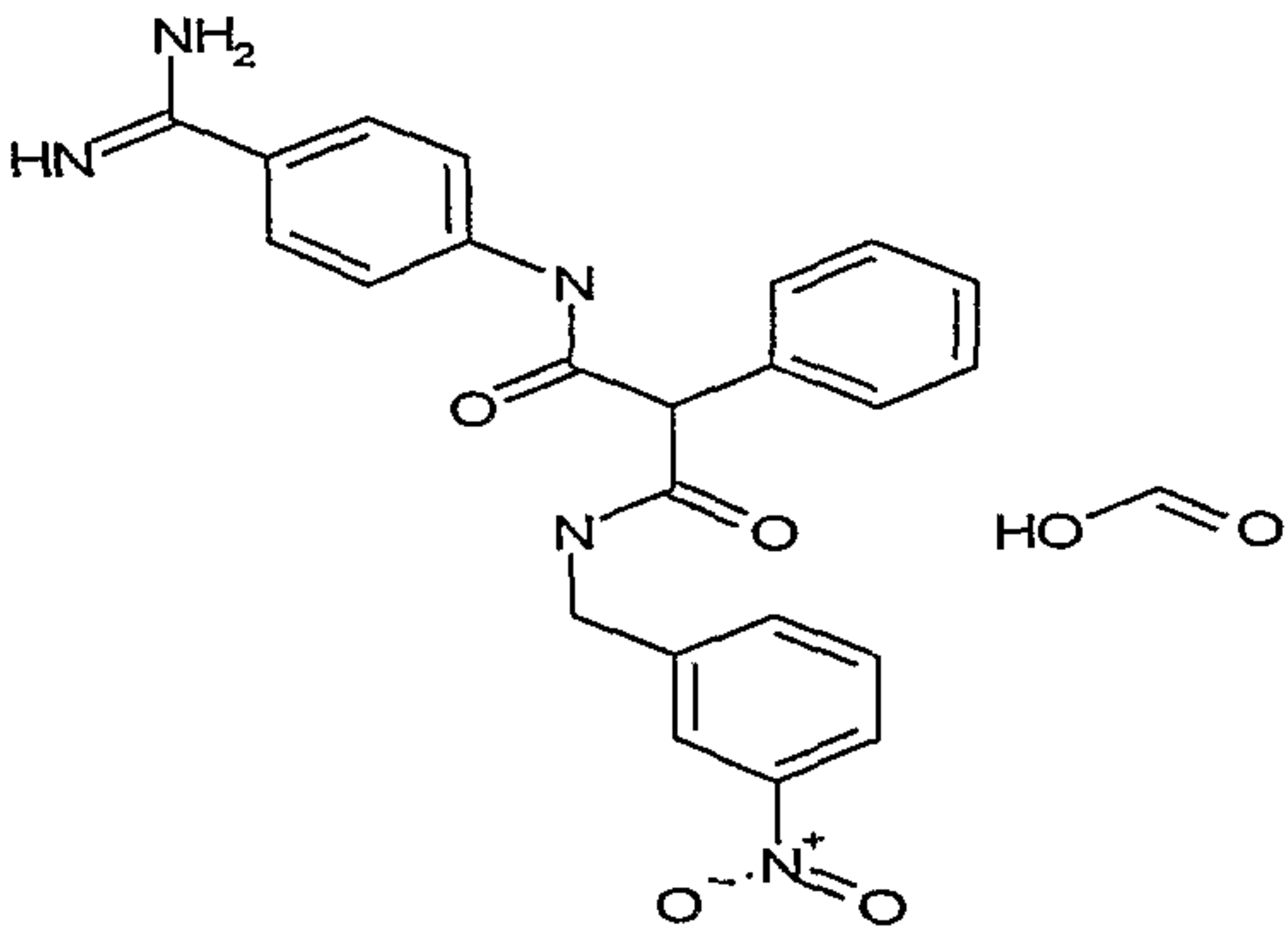
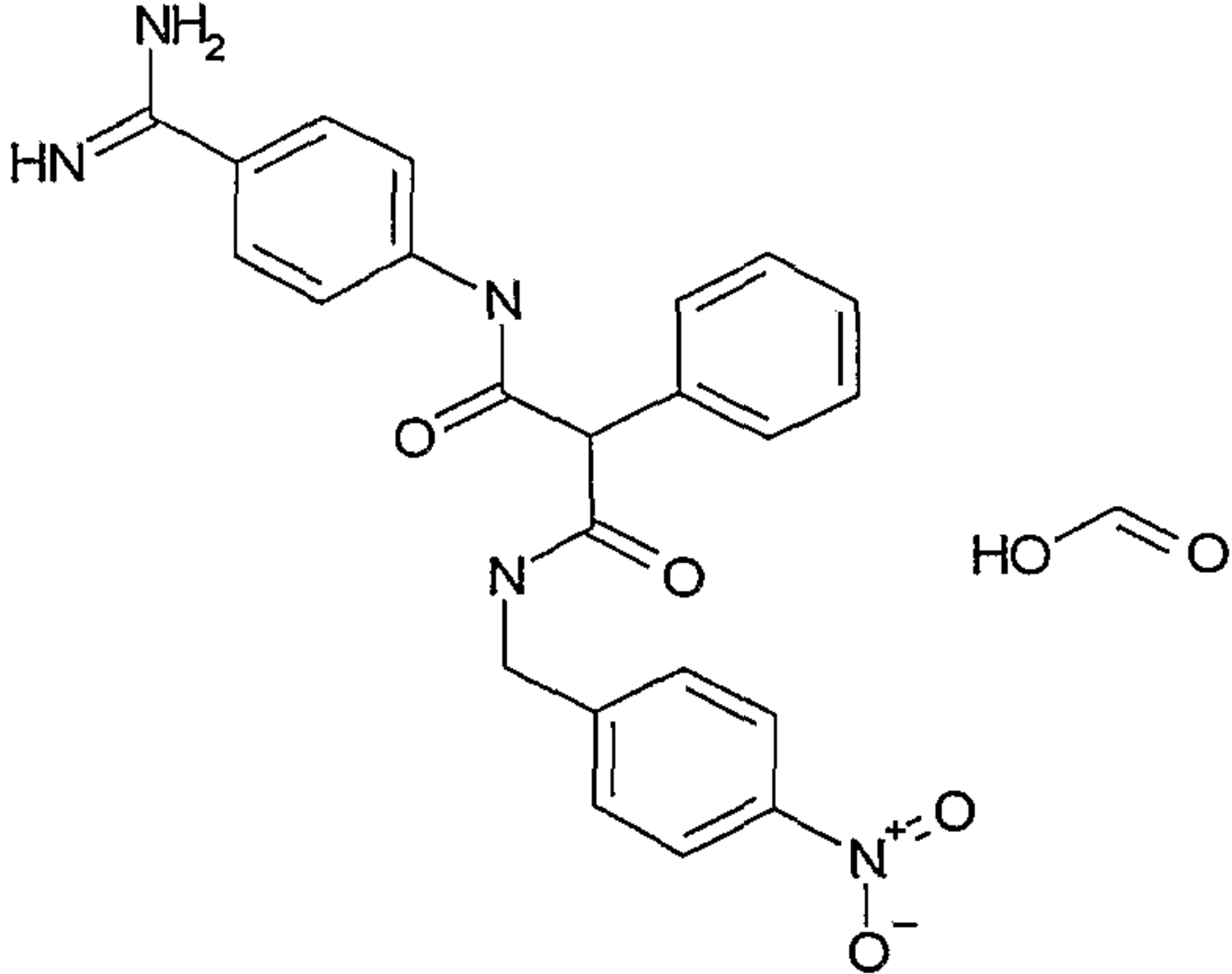
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
14	Chiral HO-COOH	$C_{28}H_{26}N_4O_2$ $C_2H_2O_2$	496,5642	450,21
15	HO-COOH	$C_{28}H_{25}N_5O_2$ $C_2H_2O_2$	509,5633	463,2
16	HO-COOH	$C_{25}H_{26}N_4O_4$ $C_2H_2O_2$	492,5292	446,2

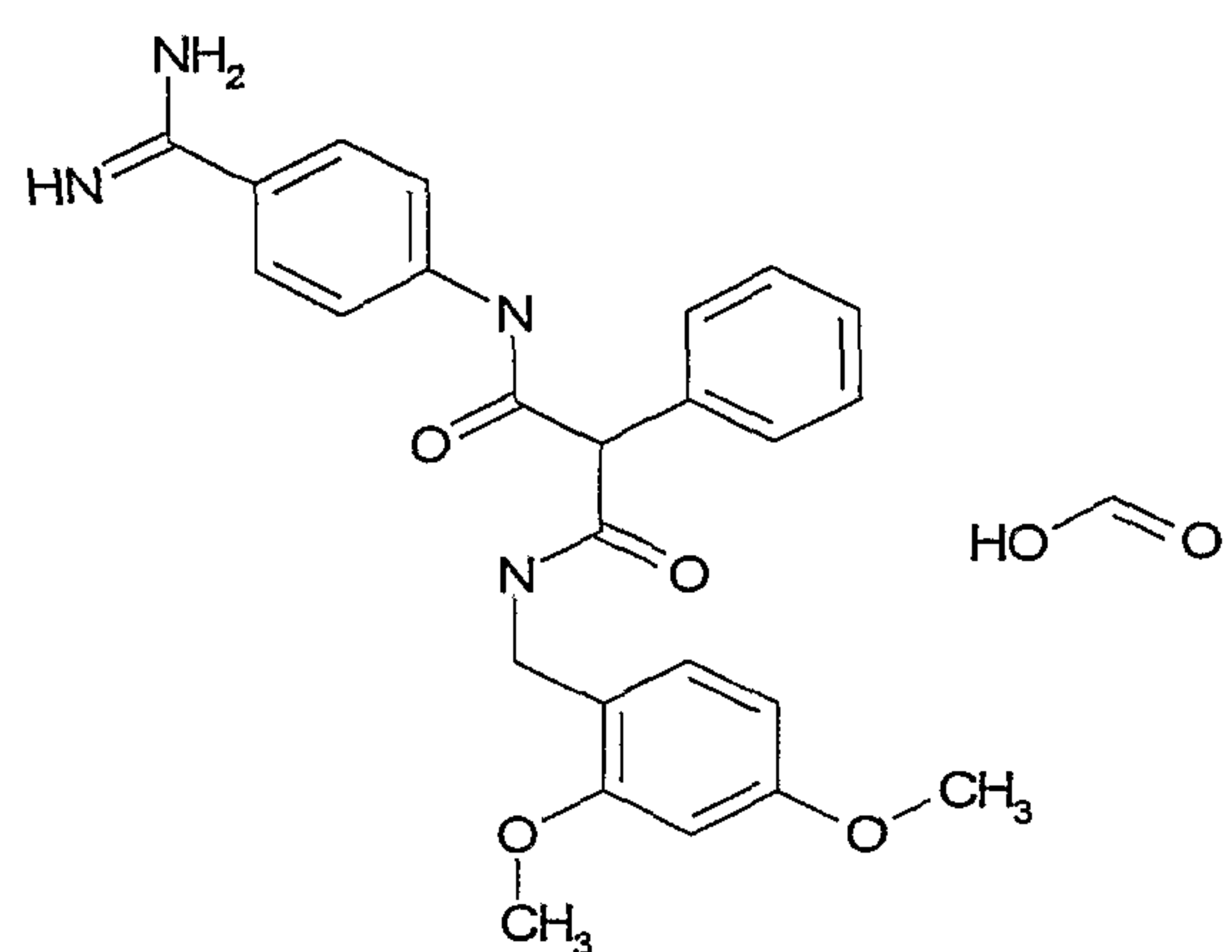
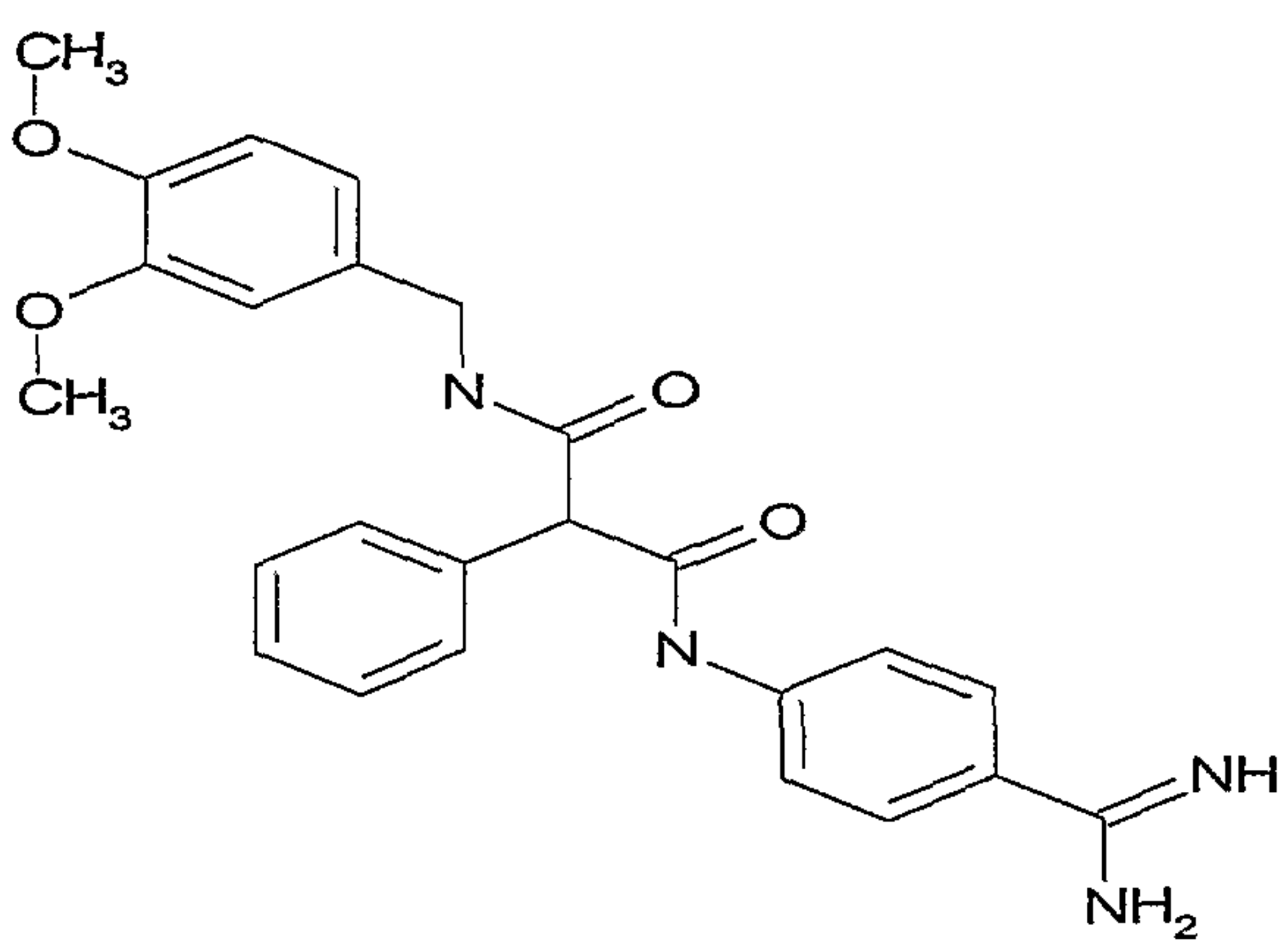
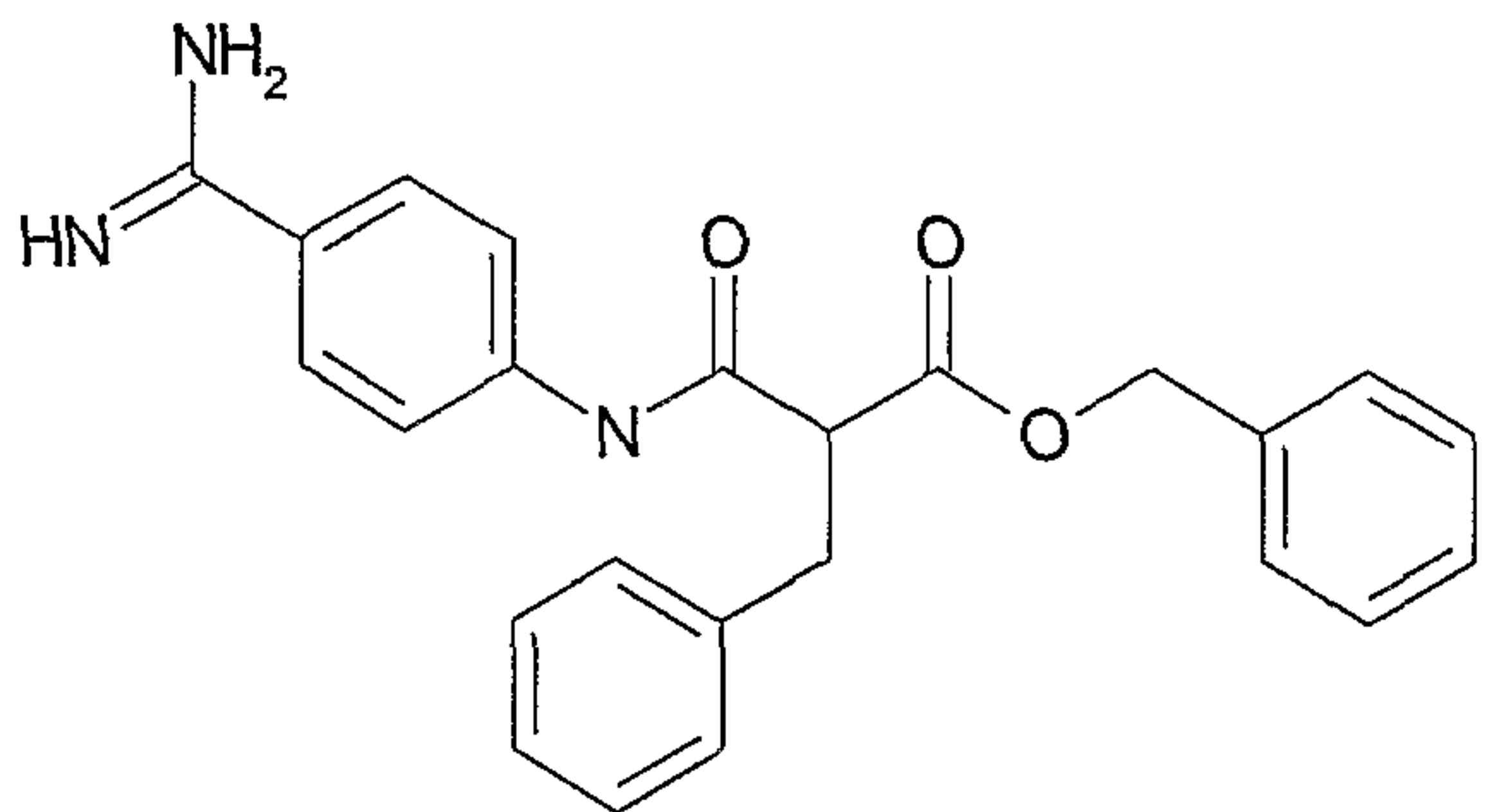
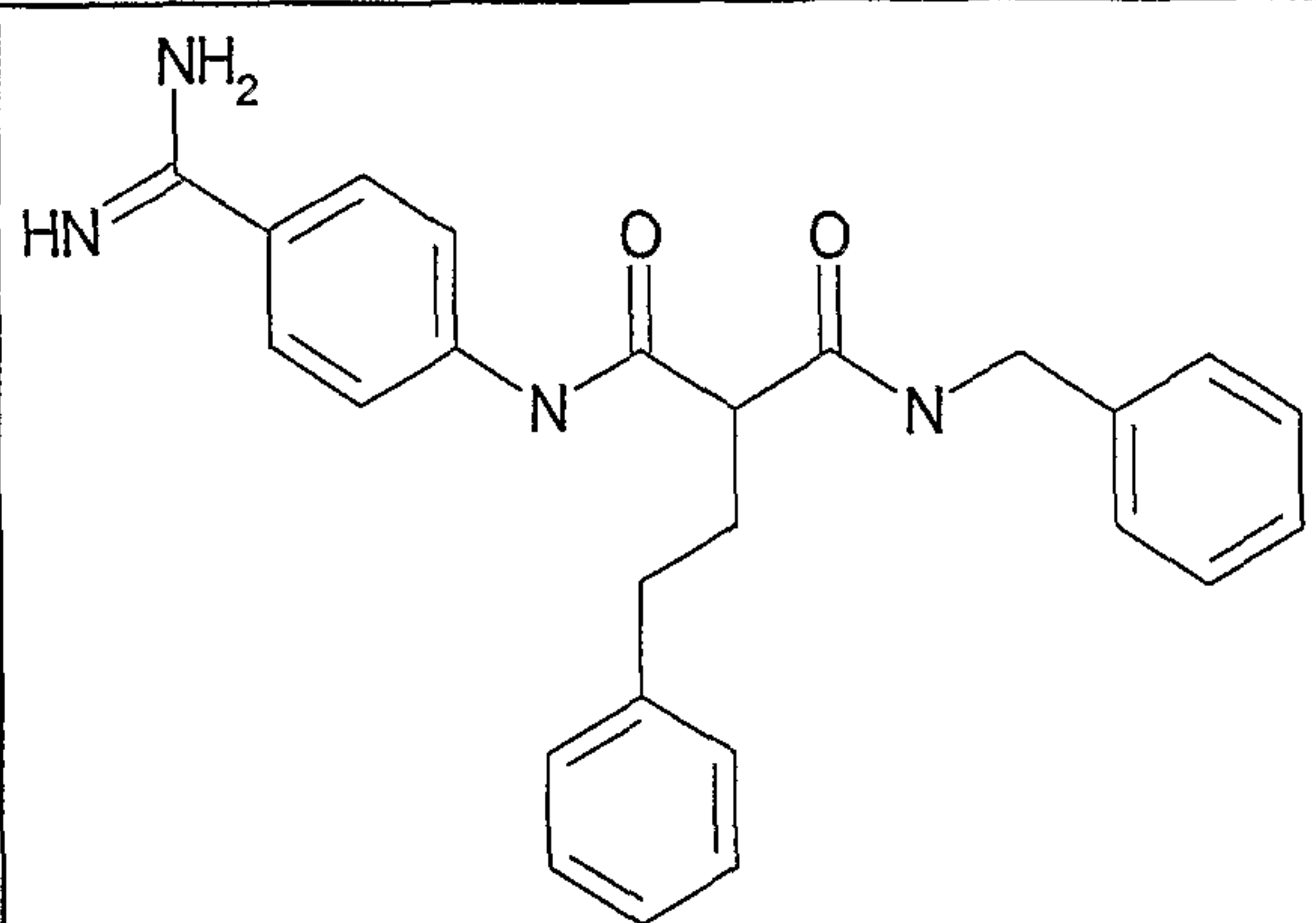
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
17		$C_{29}H_{25}ClN_4O_3 \cdot C H_2 O_2$	559,0193	512,16
18		$C_{31} H_{30} N_4 O_2 \cdot C H_2 O_2$	536,6288	490,24
19		$C_{29} H_{26} N_4 O_2 \cdot C H_2 O_2$	508,5752	462,21
20		$C_{29} H_{26} N_4 O_2 \cdot C H_2 O_2$	508,5752	462,21

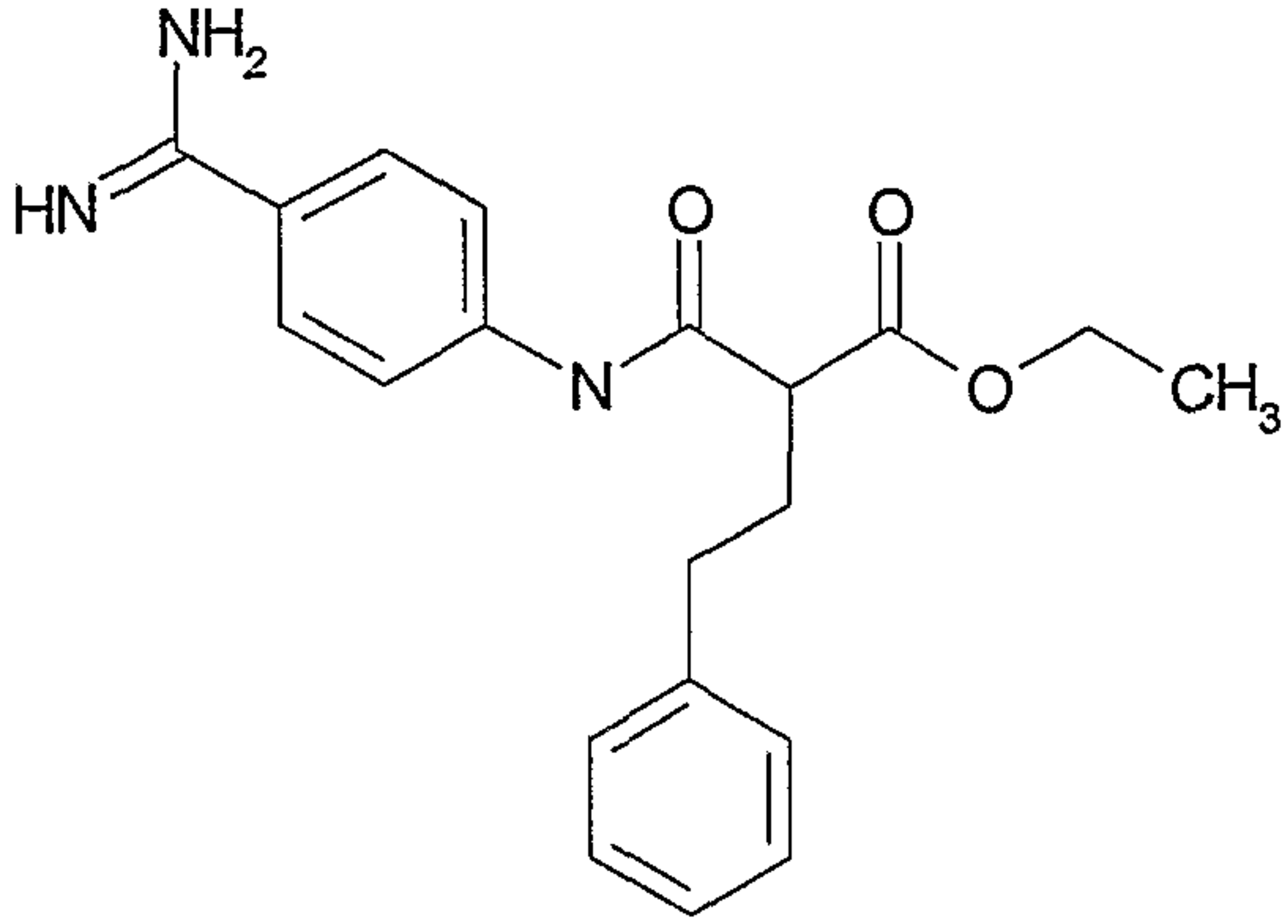
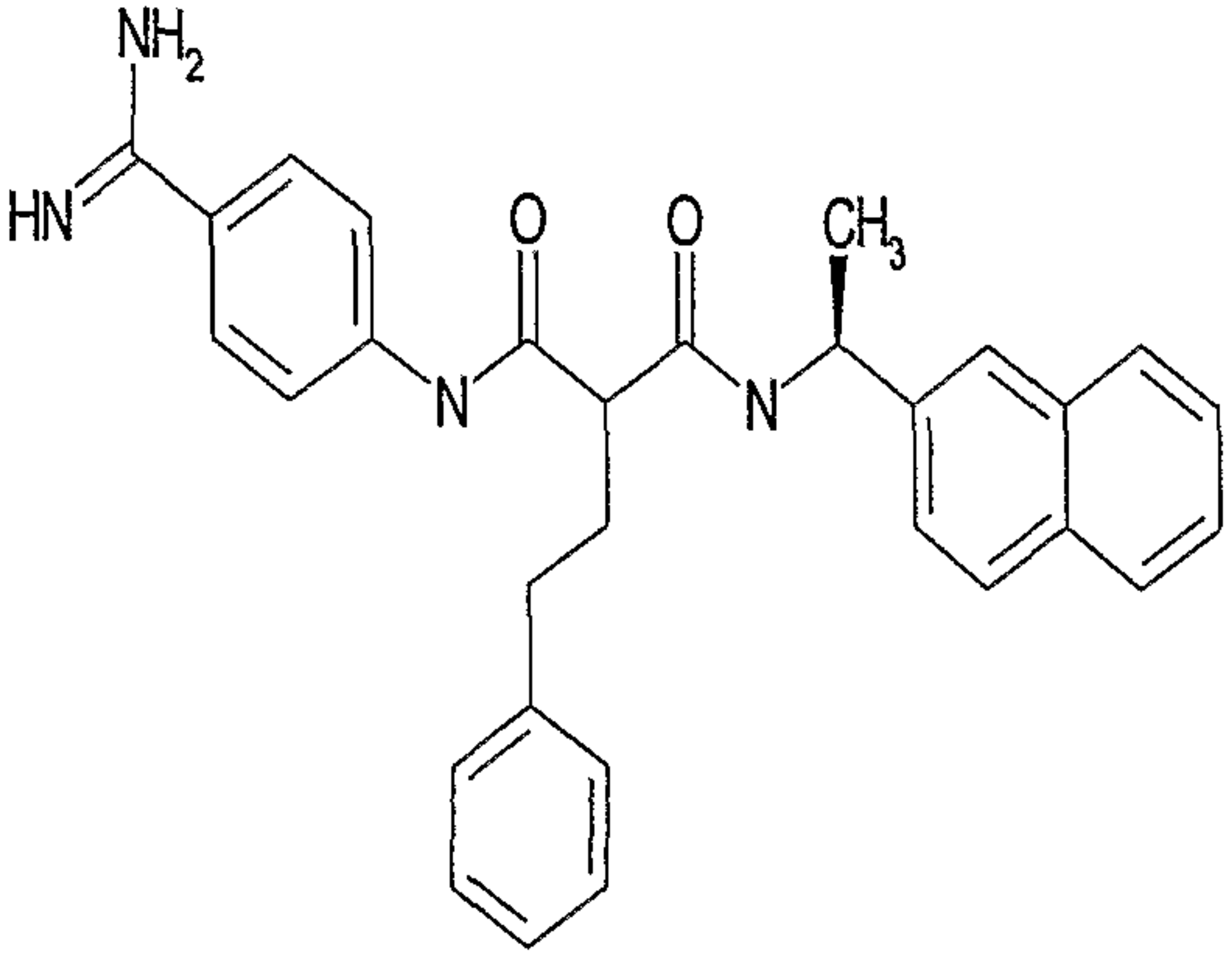
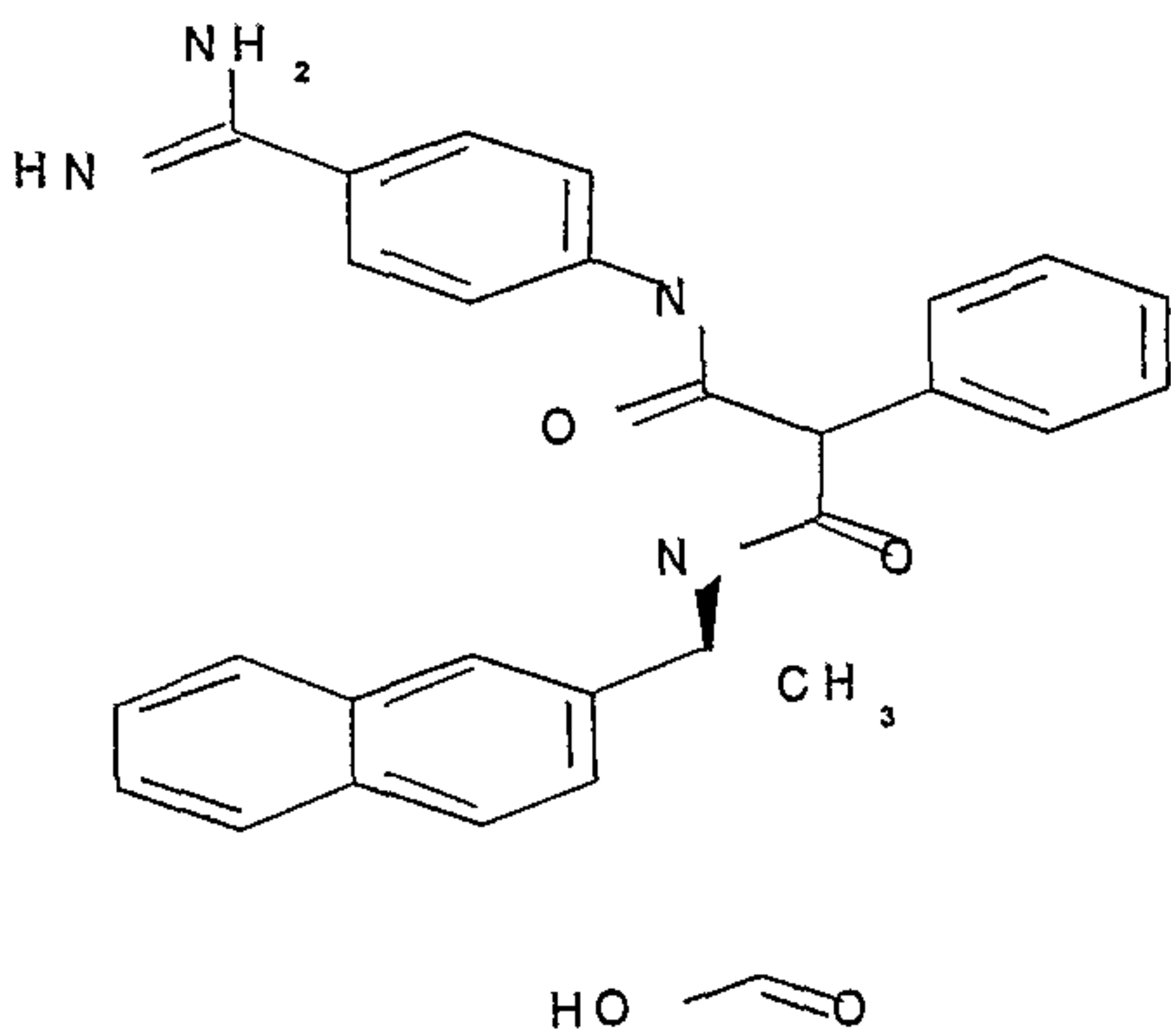
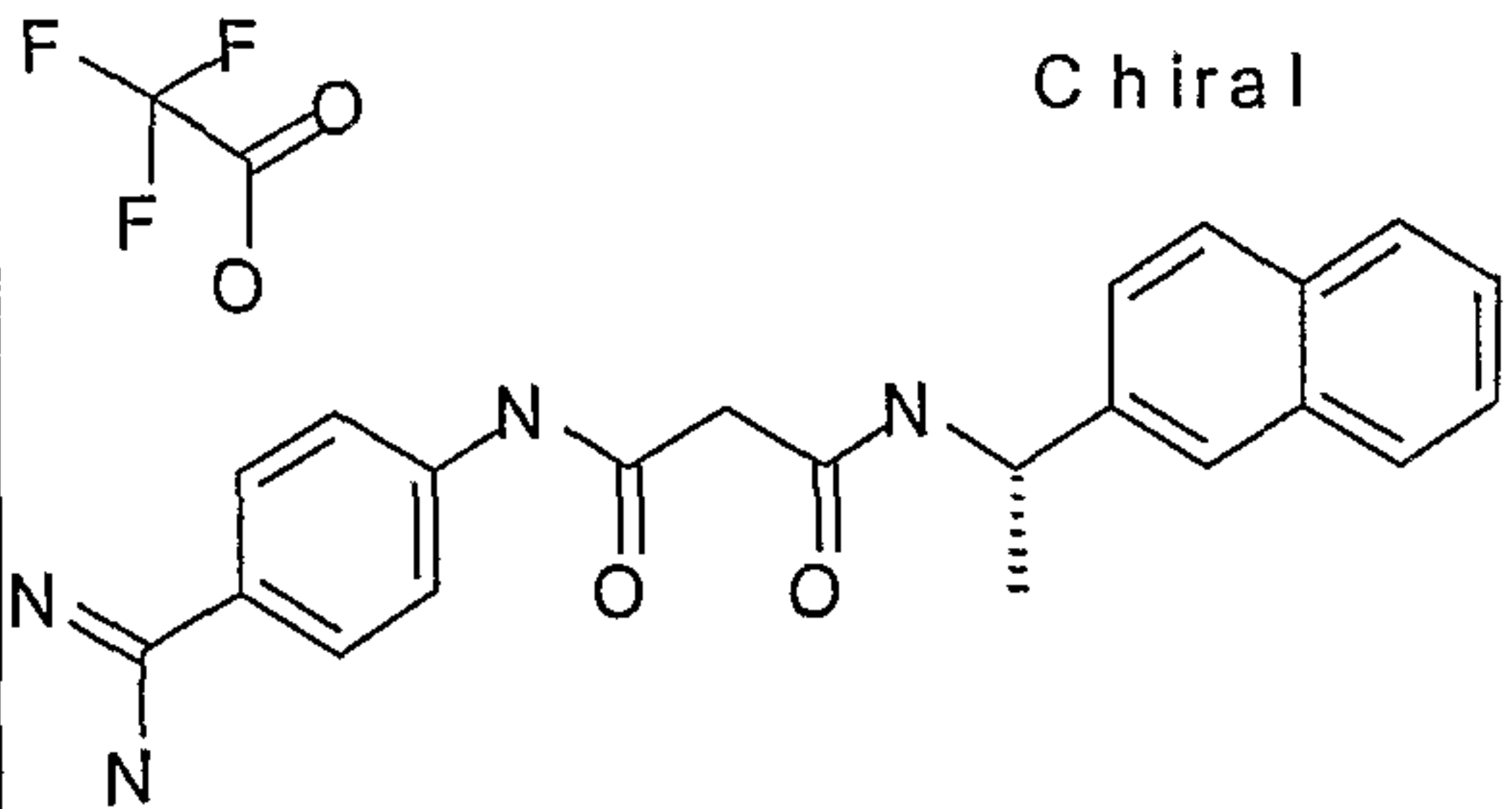
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
21		$C_{29}H_{26}N_4O_2 \cdot CH_2O_2$	508,5752	462,21
22		$C_{31}H_{30}N_4O_4 \cdot CH_2O_2$	568,6268	522,23
23		$C_{24}H_{23}BrN_4O_2 \cdot CH_2O_2$	525,4005	478,1
24	Chiral	$C_{24}H_{23}ClN_4O_2 \cdot CH_2O_2$	480,9495	434,15

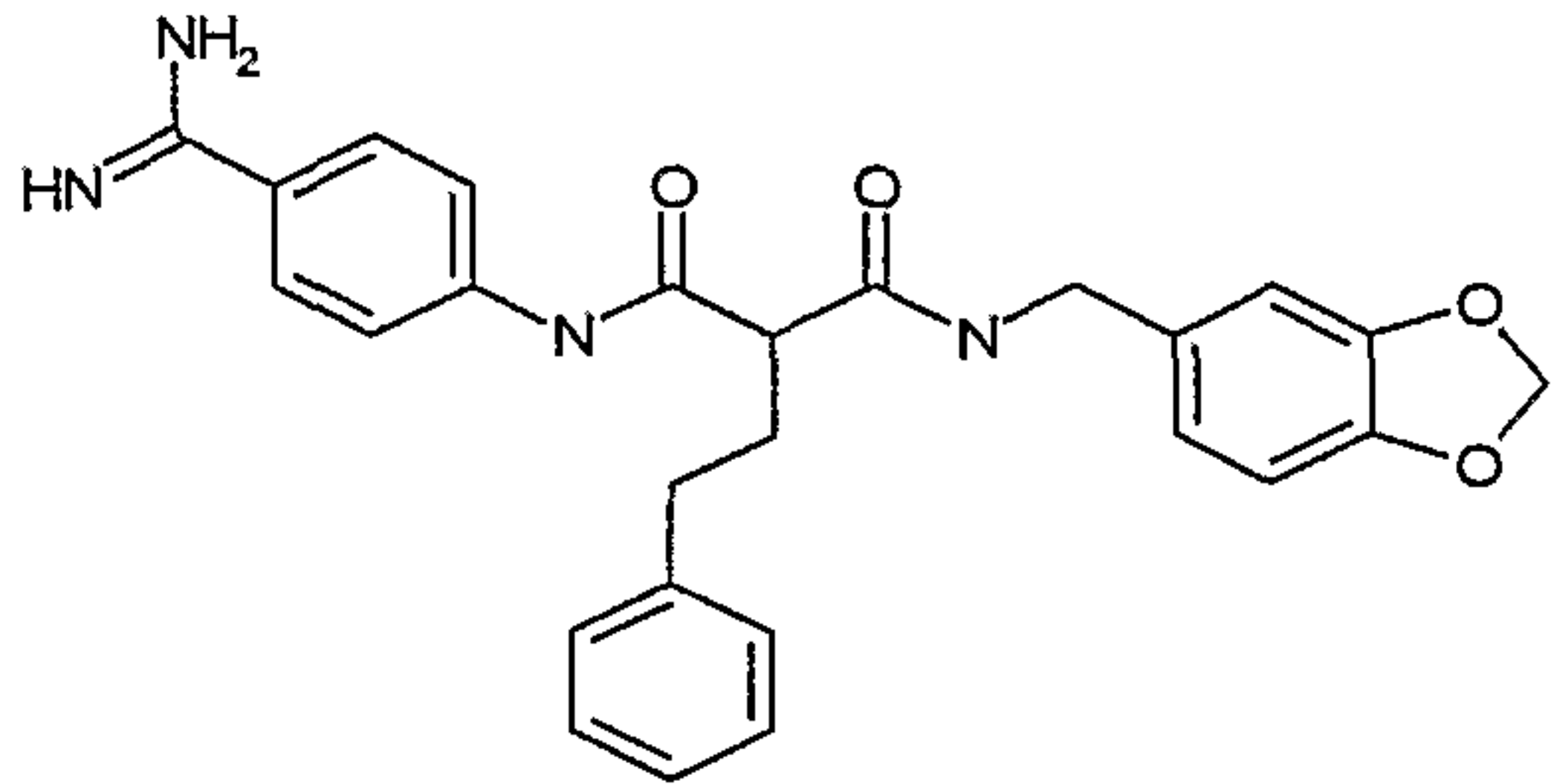
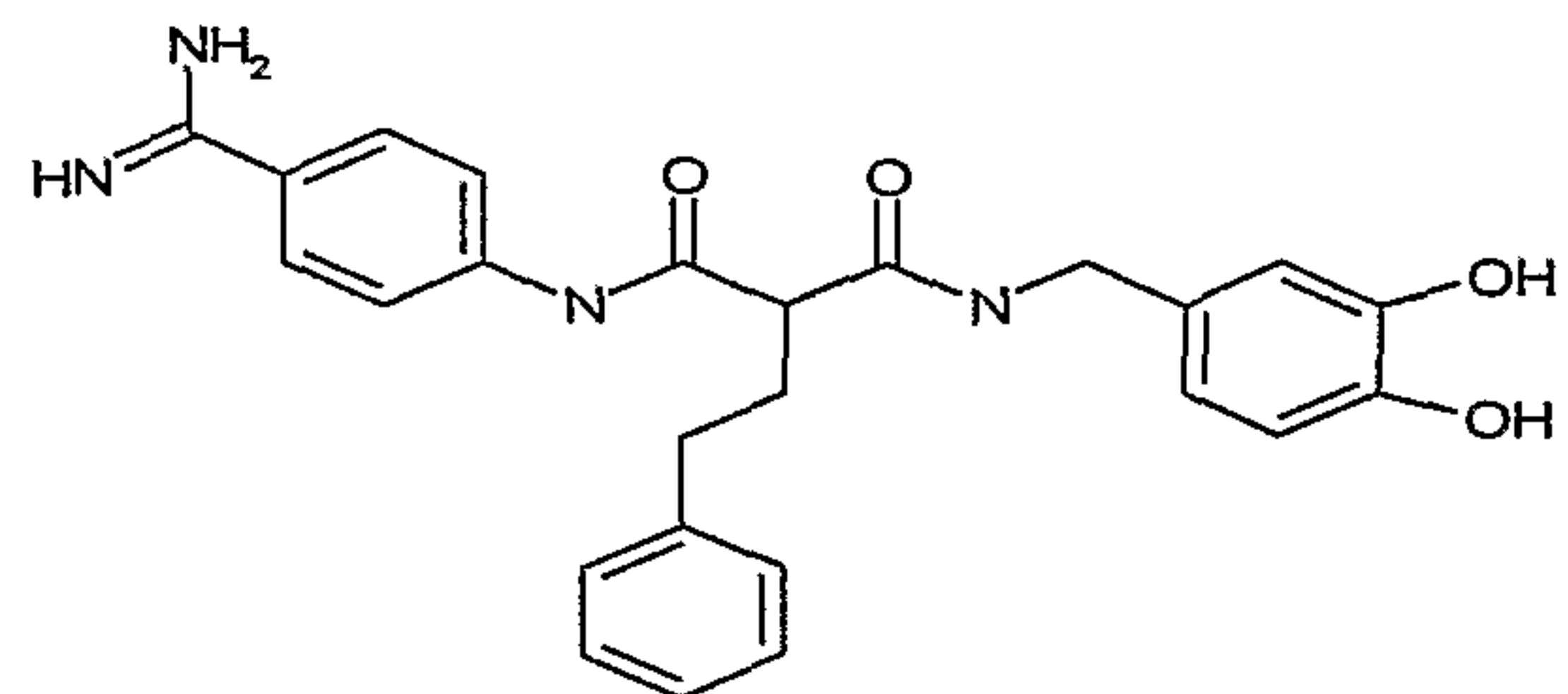
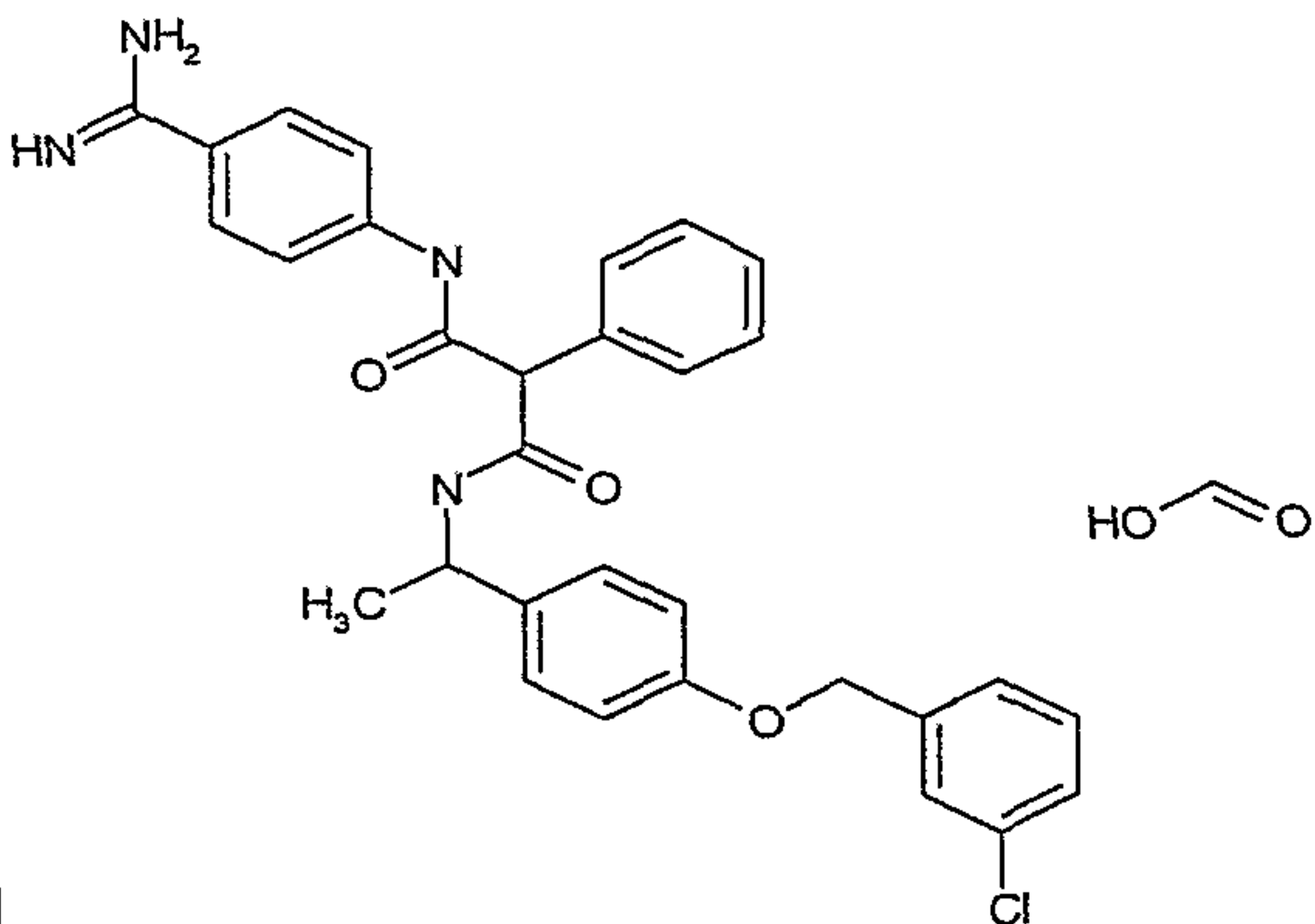
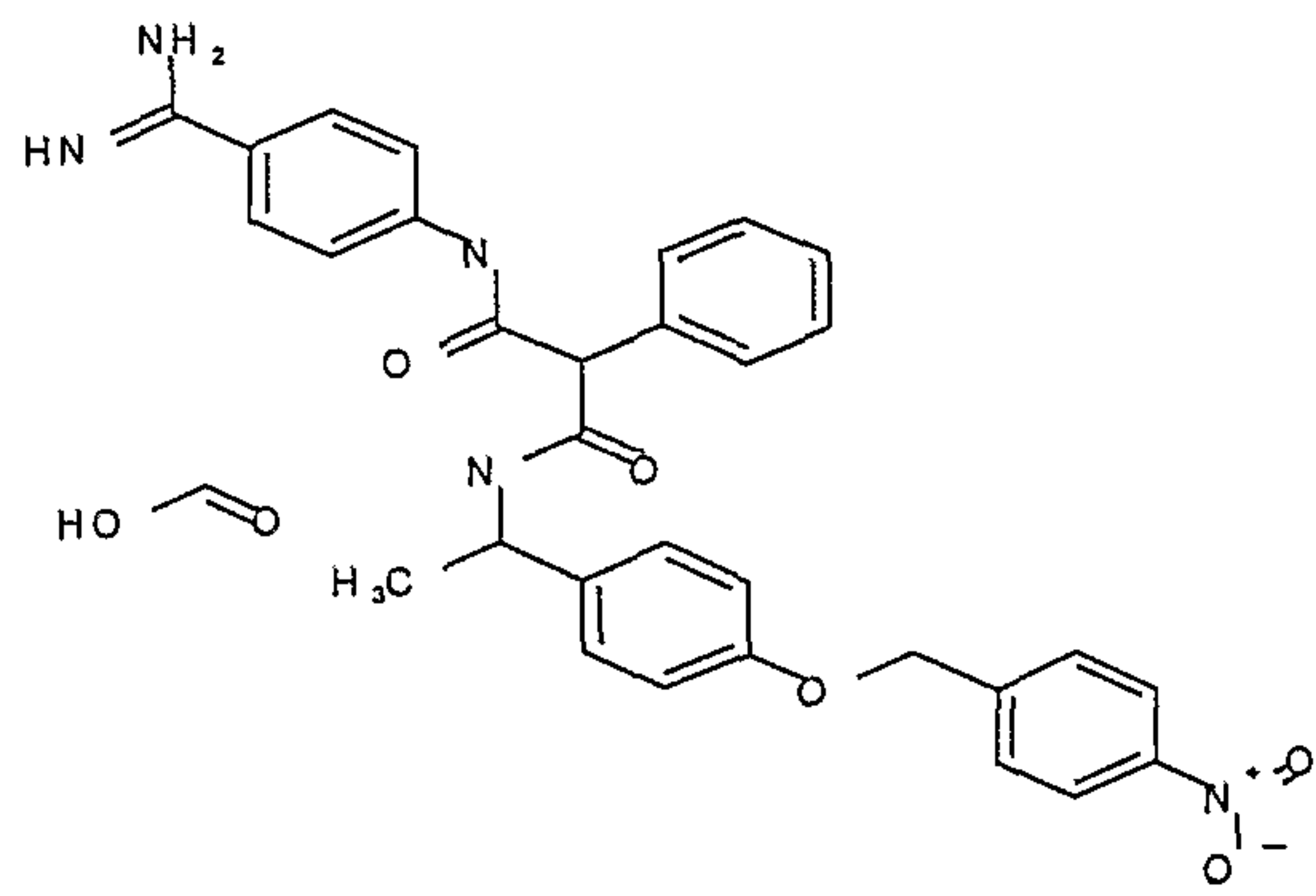
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
25	Chiral HO-C=O	$C_{25}H_{26}N_4O_3 \cdot C H_2 O_2$	476,5302	430,2
26	Chiral HO-C=O	$C_{25}H_{26}N_4O_3 \cdot C H_2 O_2$	476,5302	430,2
27	HO-C=O	$C_{24}H_{20}F_4N_4O_2 \cdot C H_2 O_2$	518,4648	472,15
28	HO-C=O	$C_{25}H_{22}N_6O_2S \cdot C H_2 O_2$	516,5796	470,15

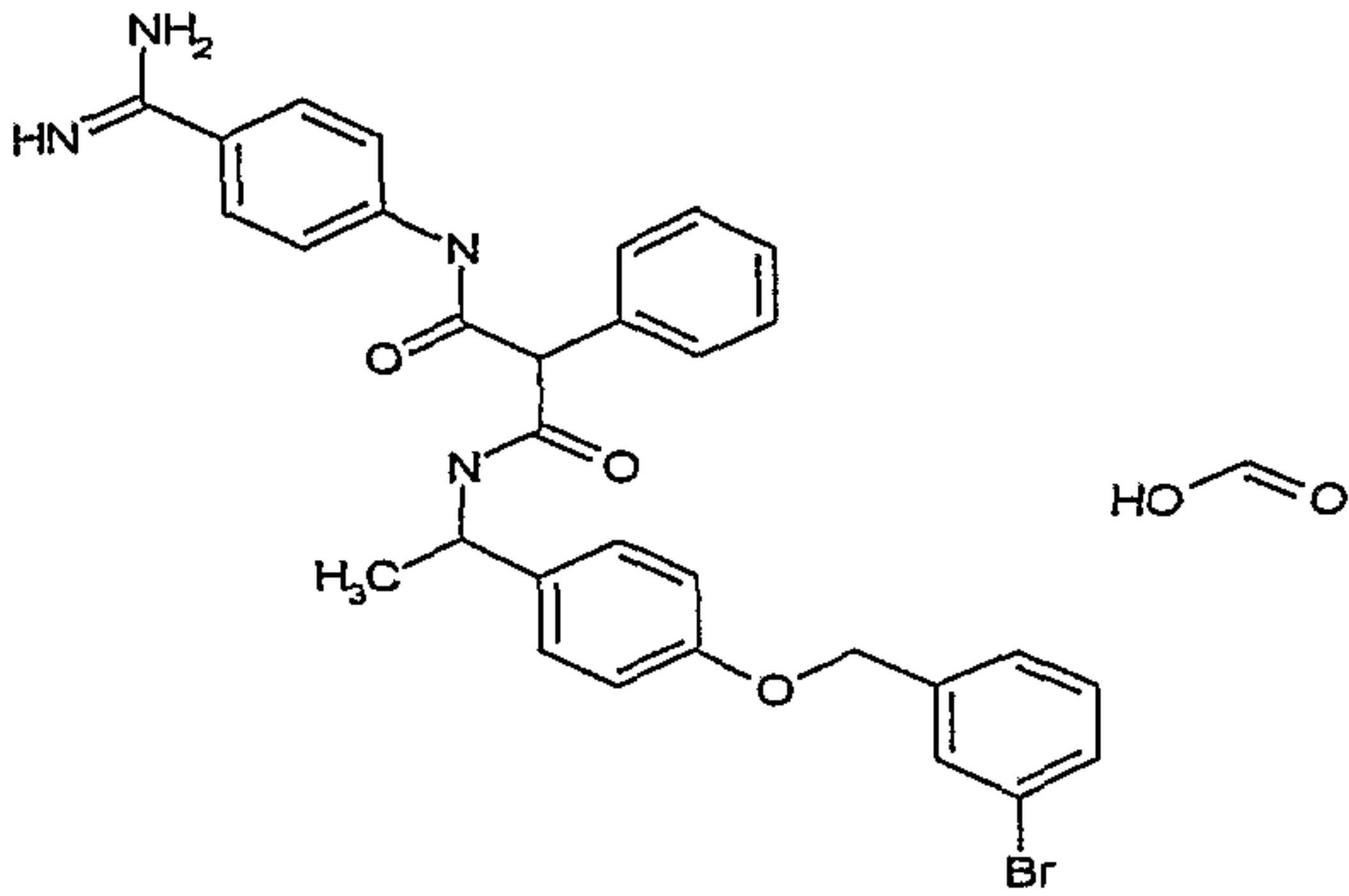
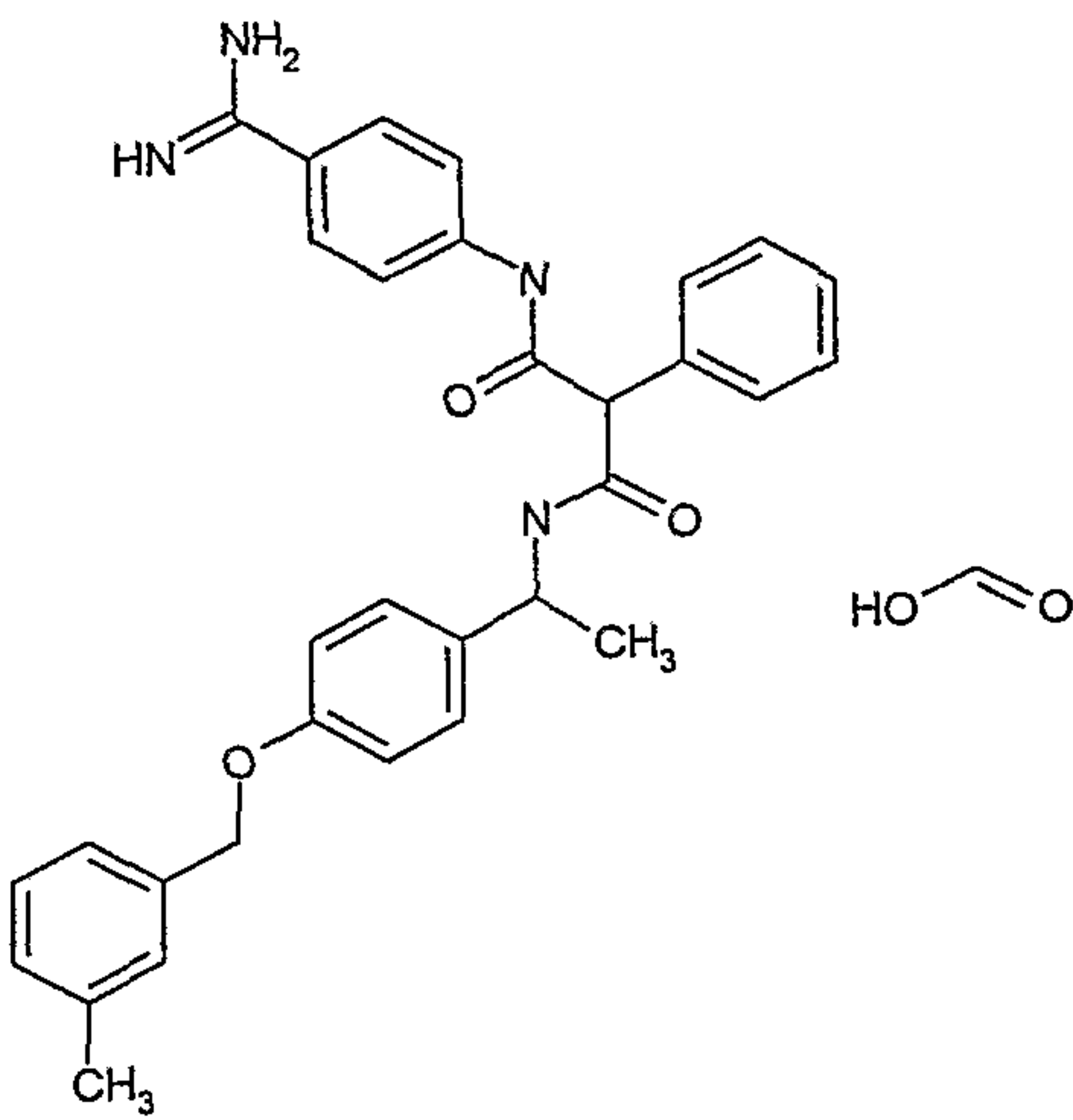
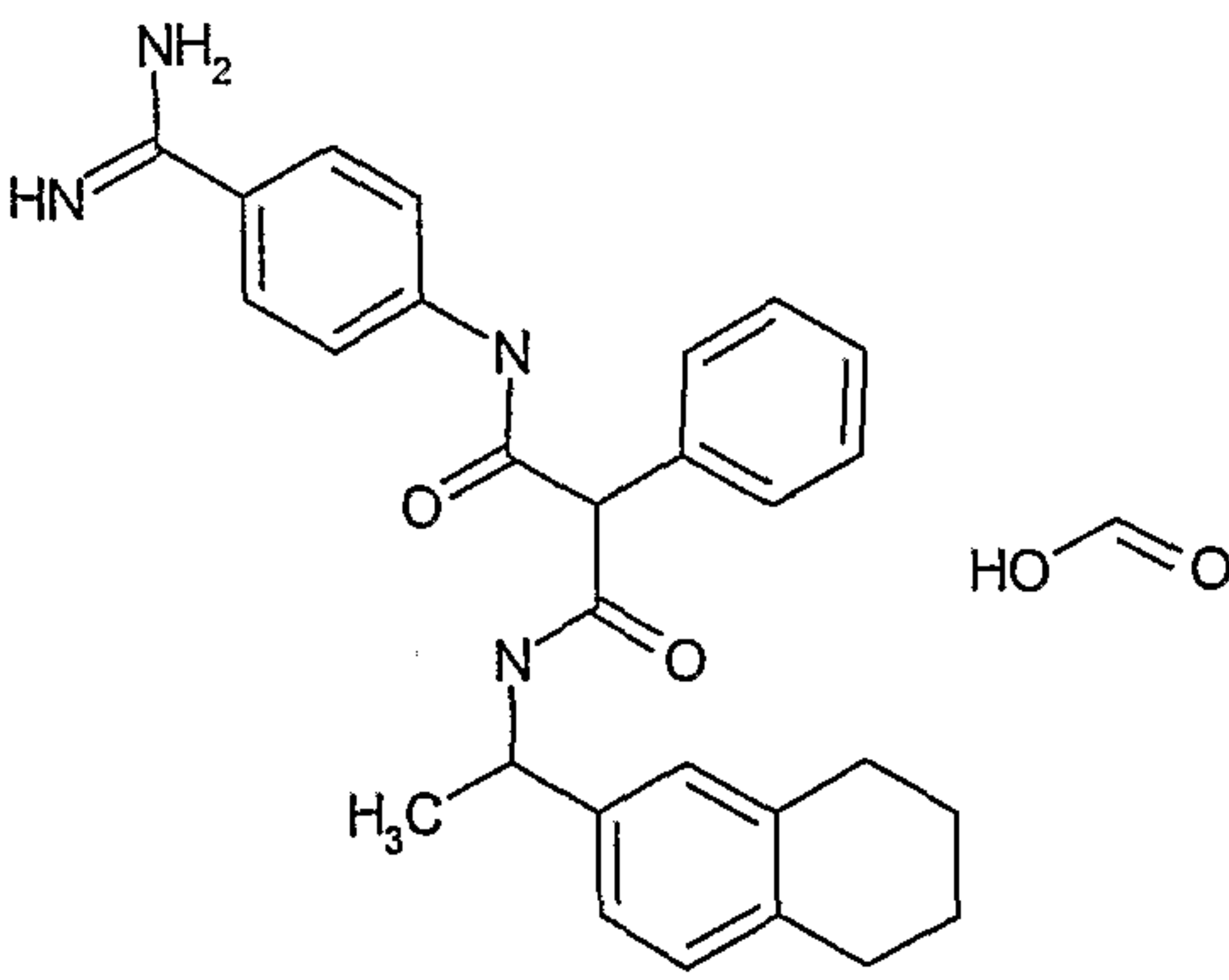
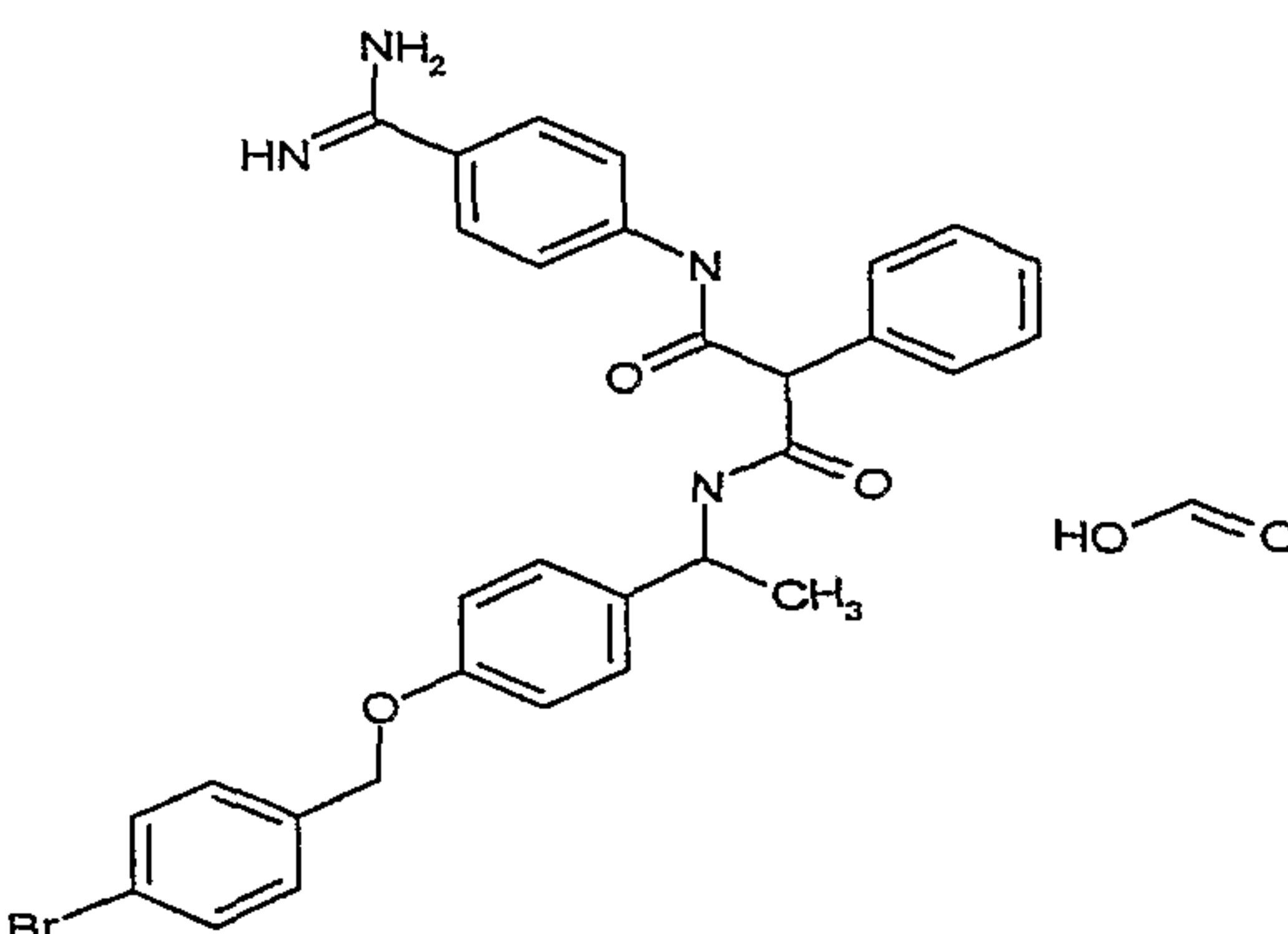
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
29		$C_{25}H_{24}N_4O_3 \cdot C H_2 O_2$	474,5144	428,18
30	Chiral 	$C_{26}H_{28}N_4O_3 \cdot C H_2 O_2$	490,557	444,22
31	Chiral 	$C_{26}H_{25}BrN_4O_2 \cdot C H_2 O_2$	551,4383	504,12
32	Chiral 	$C_{26}H_{25}BrN_4O_2 \cdot C H_2 O_2$	551,4383	504,12

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
33		$C_{24}H_{24}N_4O_3$ $C H_2 O_2$	462,5034	416,18
34		$C_{24}H_{24}N_4O_3$ $C H_2 O_2$	462,5034	416,18
35		$C_{23}H_{21}N_5O_4$ $C H_2 O_2$	477,4747	431,16
36		$C_{23}H_{21}N_5O_4$ $C H_2 O_2$	477,4747	431,16

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
37		$C_{25}H_{26}N_4O_4 \cdot C H_2 O_2$	492,5292	446,2
38		$C_{25}H_{26}N_4O_4$	446,5044	447,15
39		$C_{24}H_{23}N_3O_3$	401,4637	402,1
40		$C_{25}H_{26}N_4O_2$	414,5064	415,2

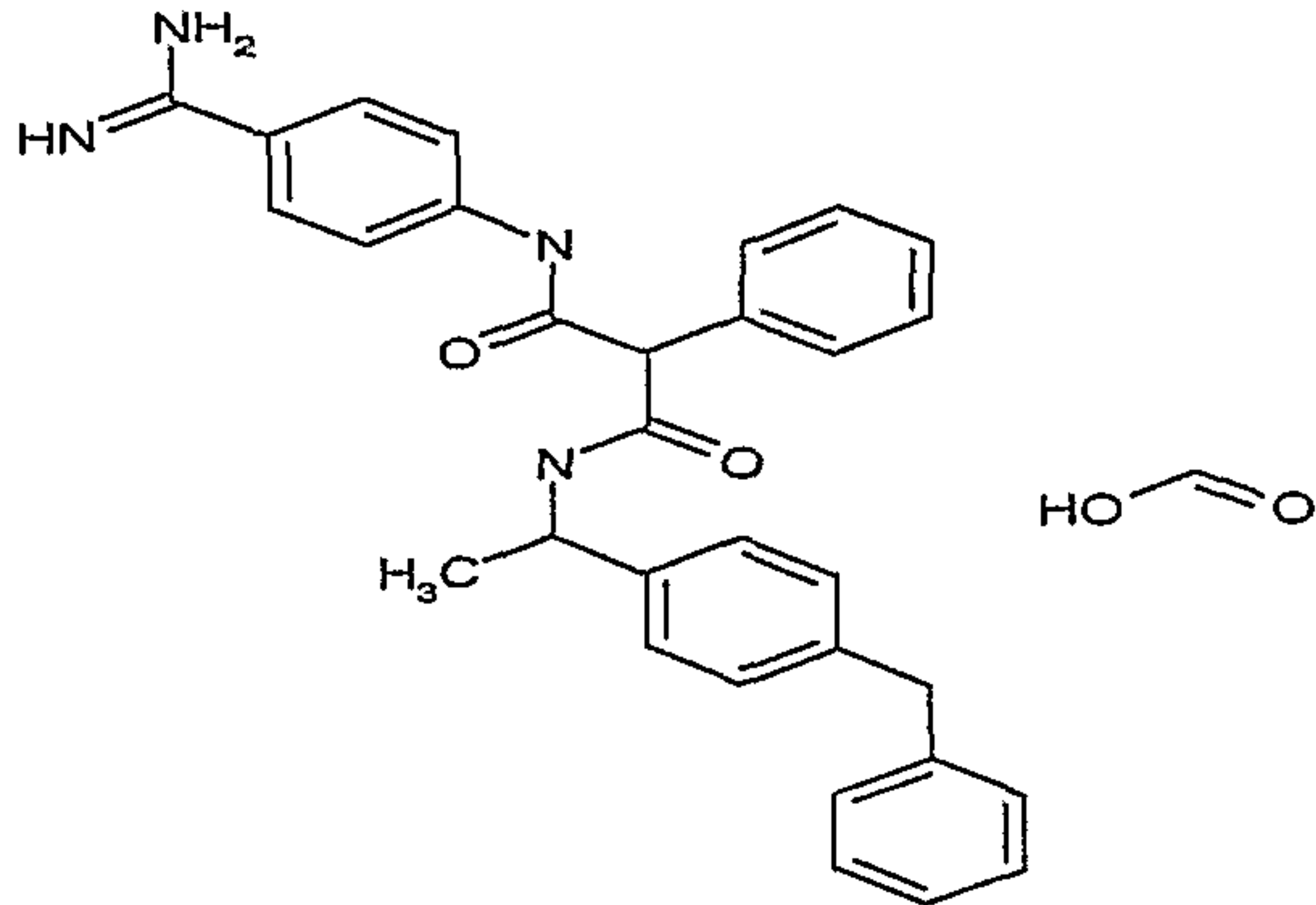
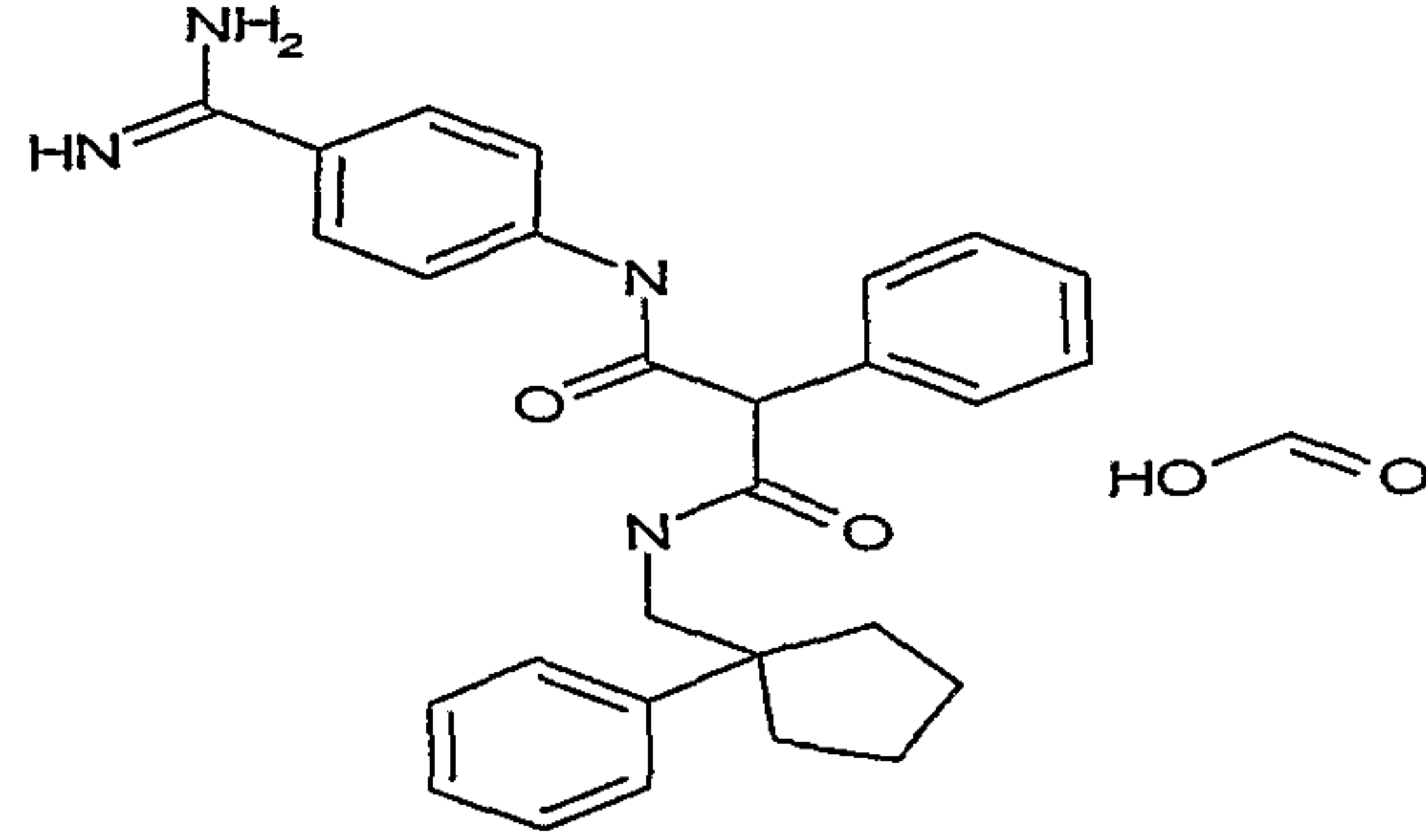
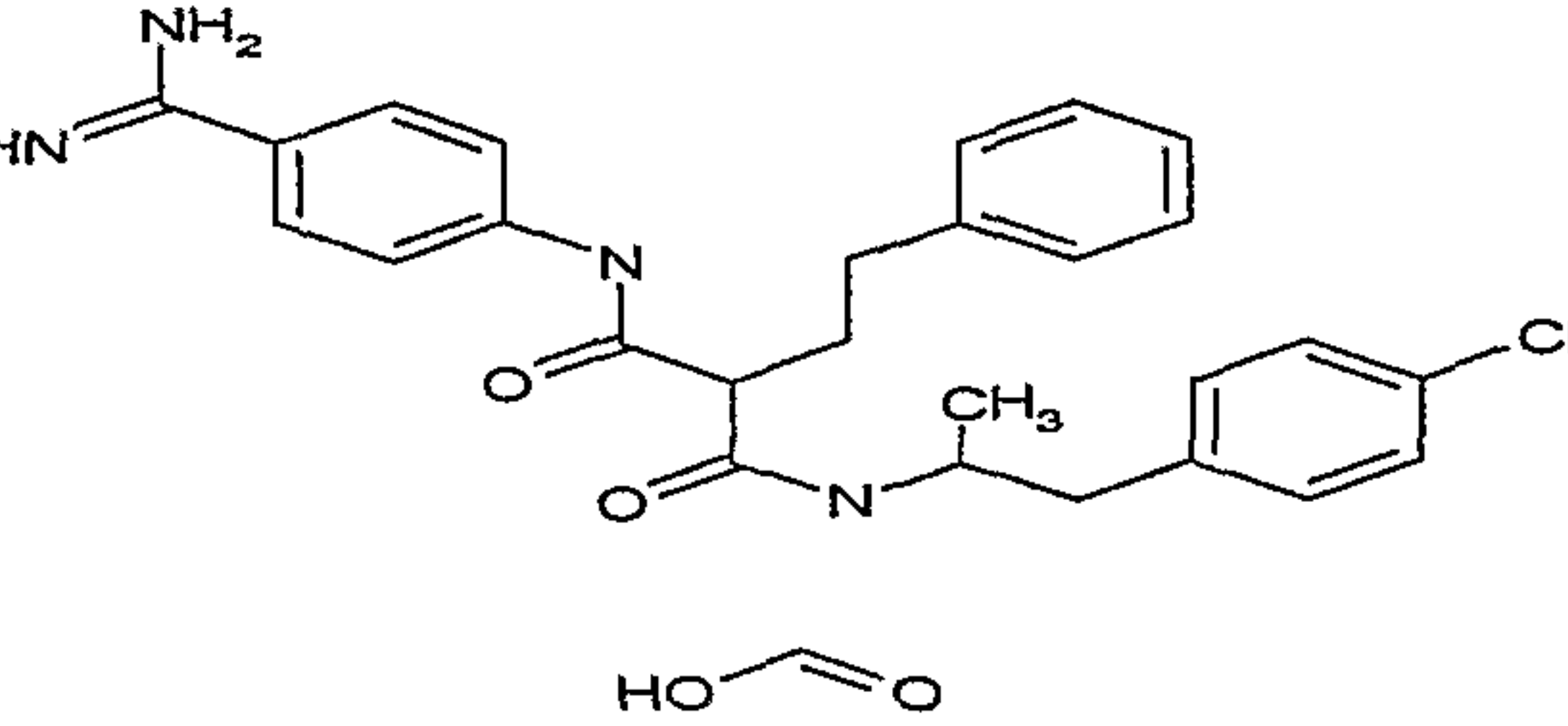
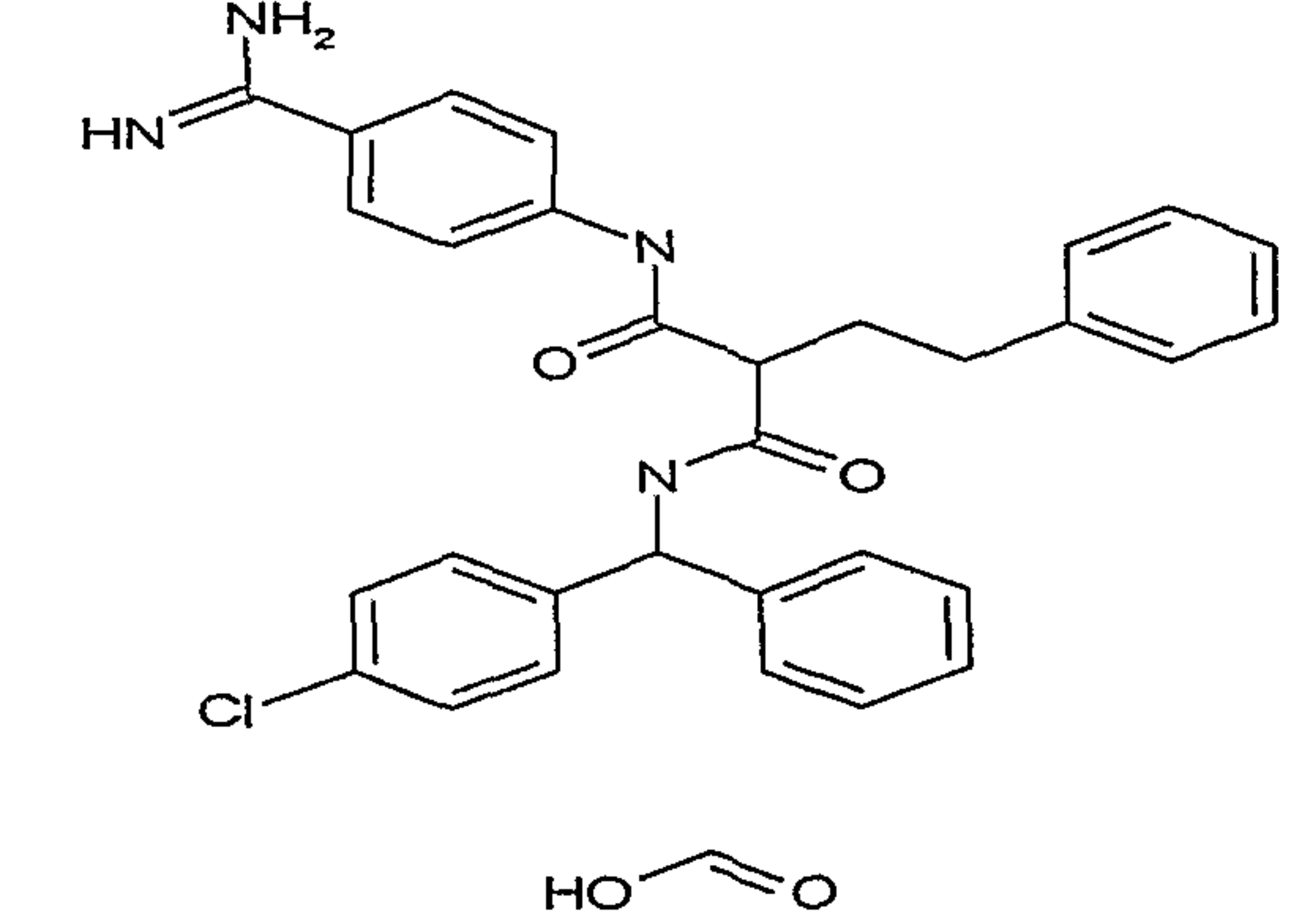
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
41		$C_{20} H_{23} N_3 O_3$	353,4197	354,1
42	Chiral 	$C_{30} H_{30} N_4 O_2$	478,593	478,8
43	Chiral 	$C_{28} H_{26} N_4 O_2 \cdot C H_2 O_2$	496,5642	450,21
44	Chiral 	$C_{22} H_{22} N_4 O_2 \cdot C_2 H F_3 O_2$	488,46	375,20

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
45		C ₁₄ H ₁₉ N ₃ O ₃	458,515	459,1
46		C ₂₅ H ₂₆ N ₄ O ₄	446,504	447,1
47		C ₃₁ H ₂₉ Cl N ₄ O ₃ CH ₂ O ₂	587,073	540,19
48		C ₃₁ H ₂₉ N ₅ O ₅ . CH ₂ O ₂	597,625	551,22

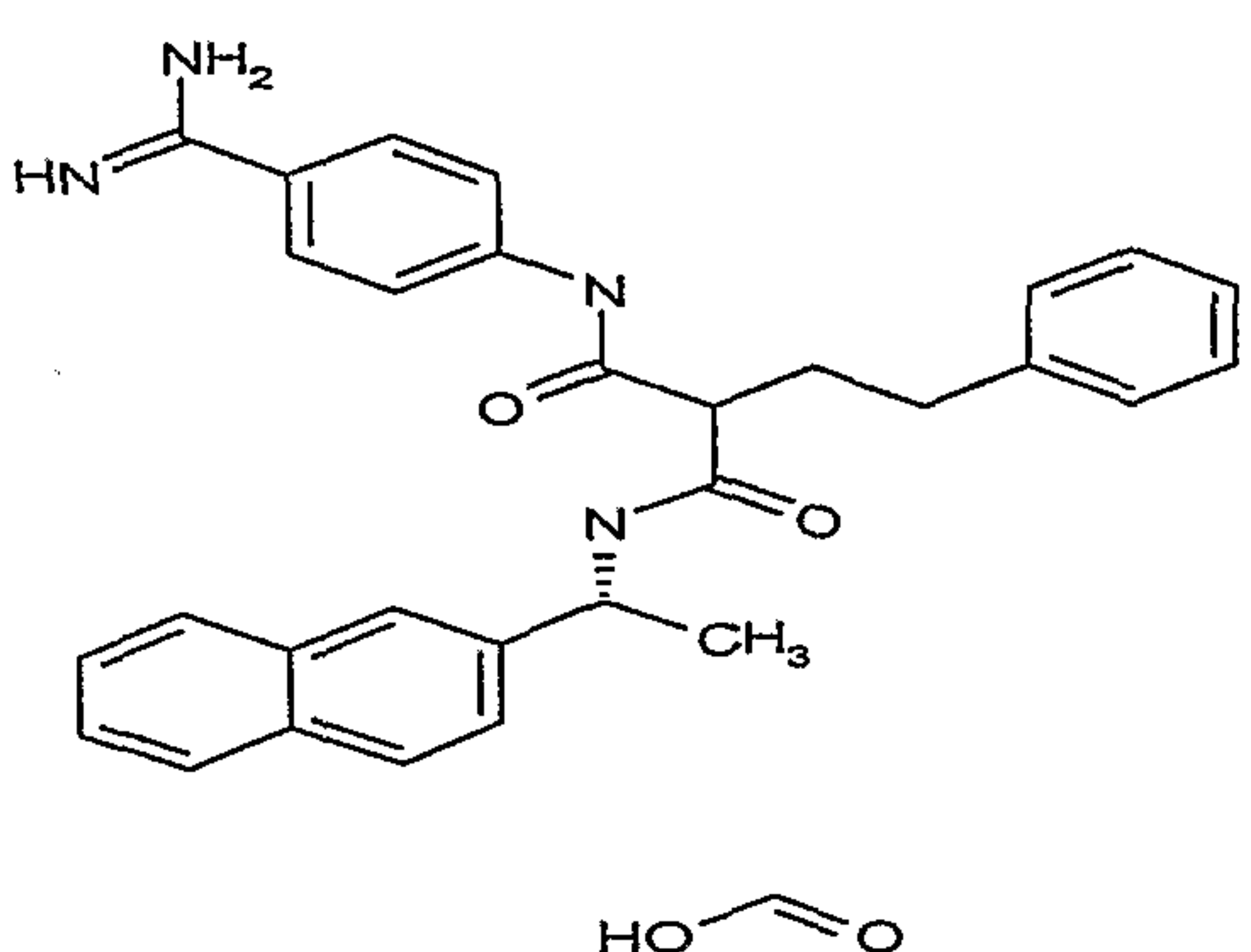
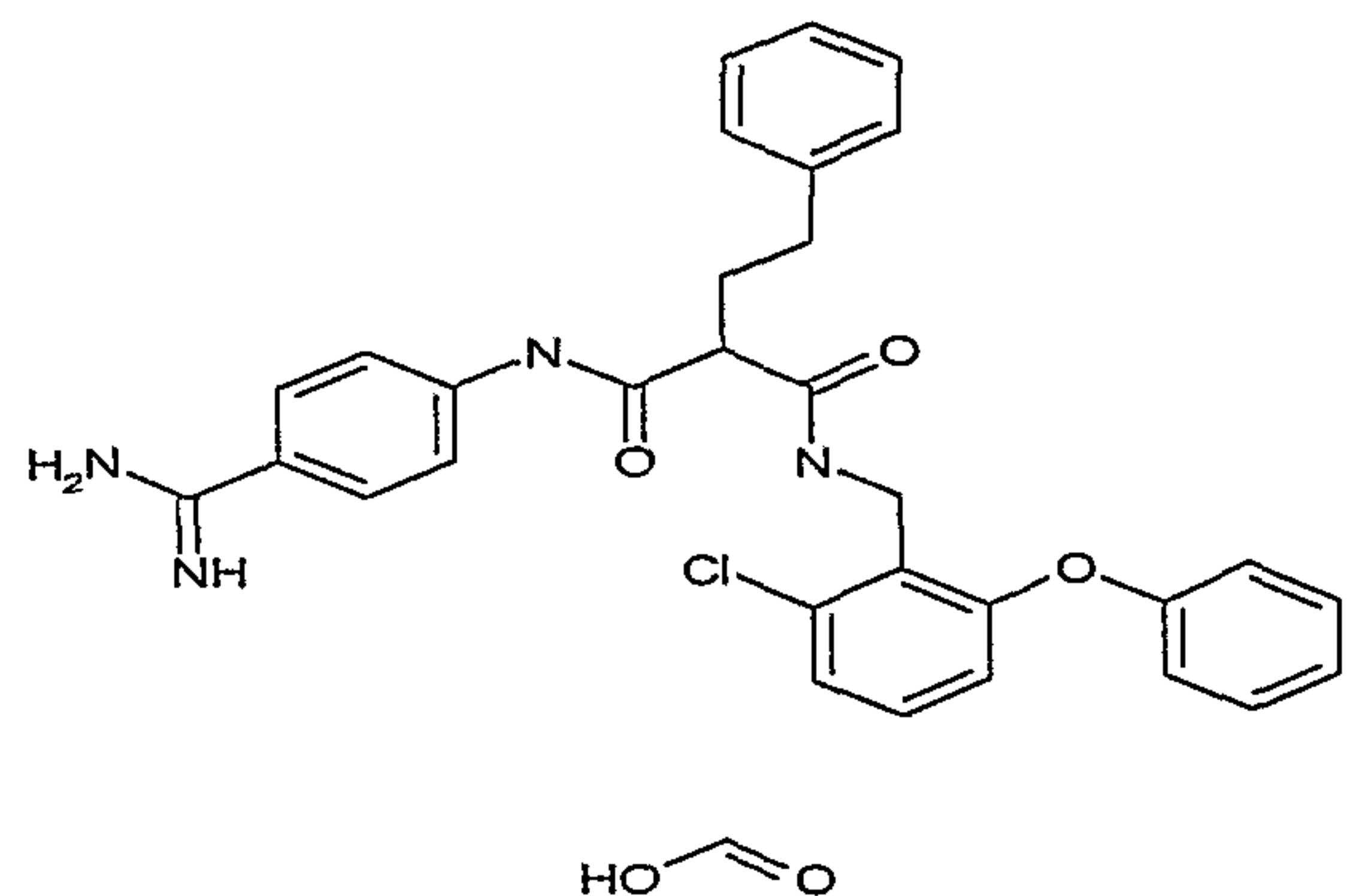
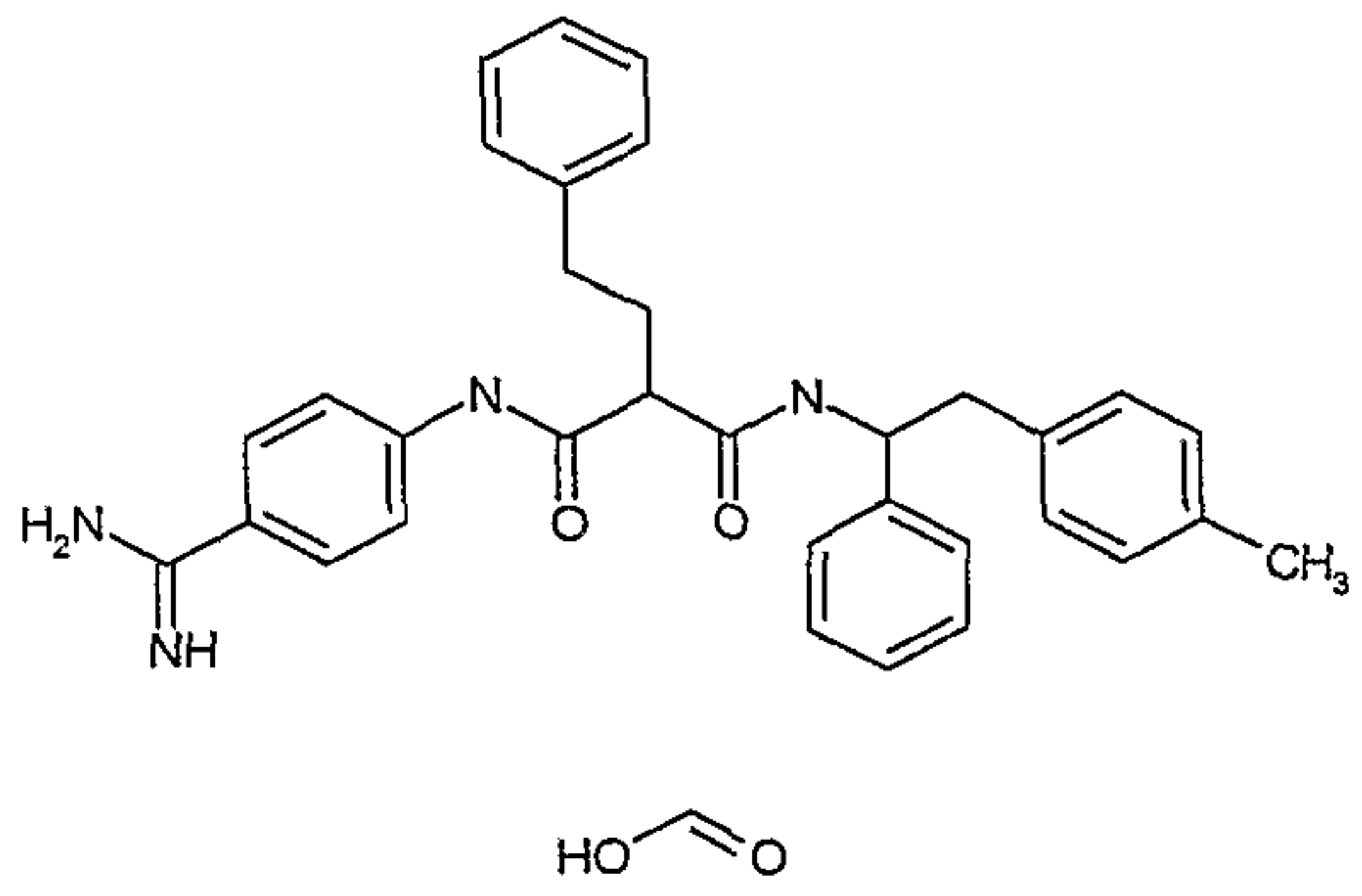
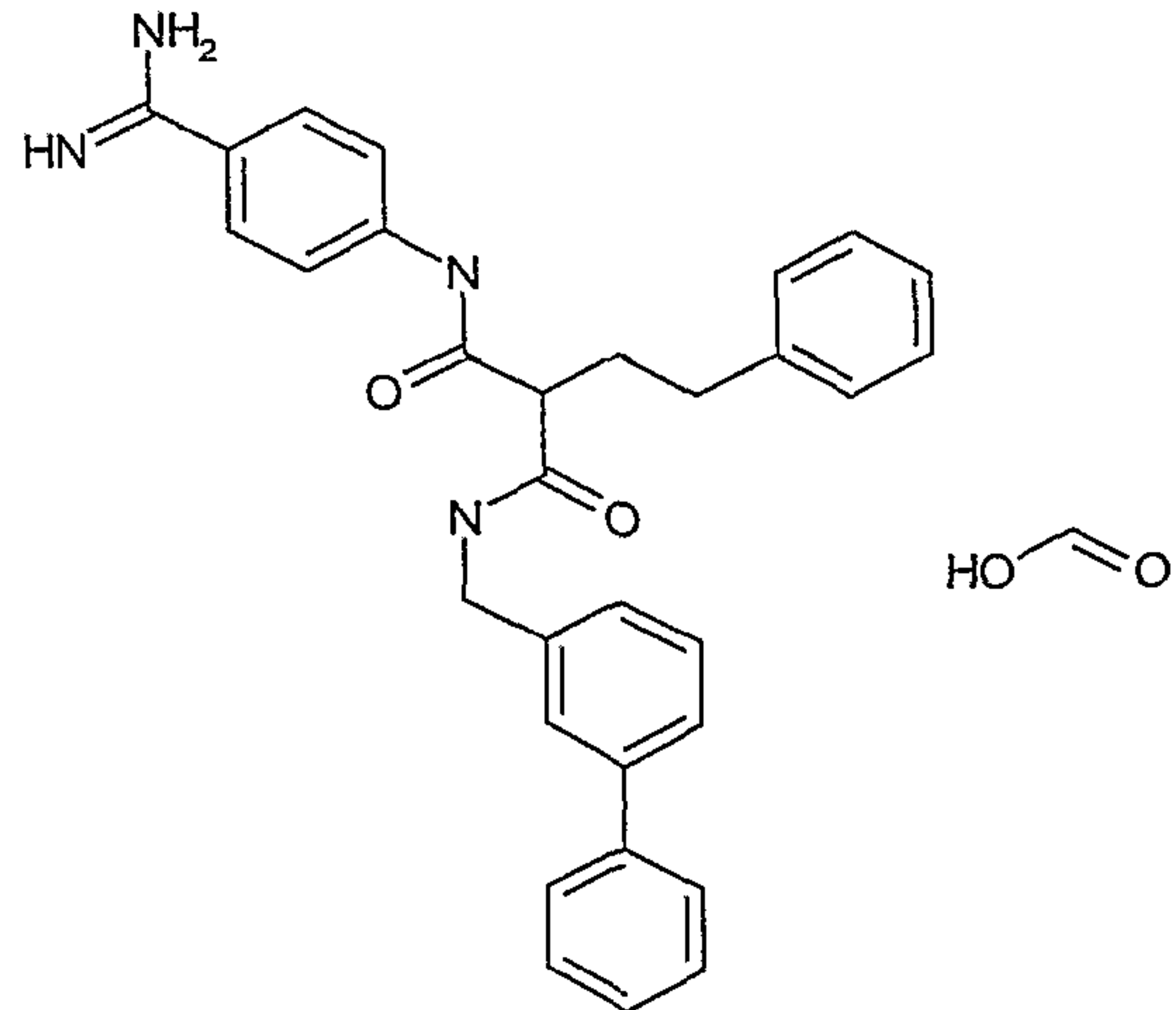
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
49		$C_{31}H_{29}BrN_4O_3 \cdot CH_2O_2$	631,524	584,14
50		$C_{32}H_{32}N_4O_3 \cdot CH_2O_2$	566,655	520,25
51		$C_{28}H_{30}N_4O_2 \cdot CH_2O_2$	500,596	454,24
52		$C_{31}H_{29}BrN_4O_3 \cdot CH_2O_2$	631,524	584,14

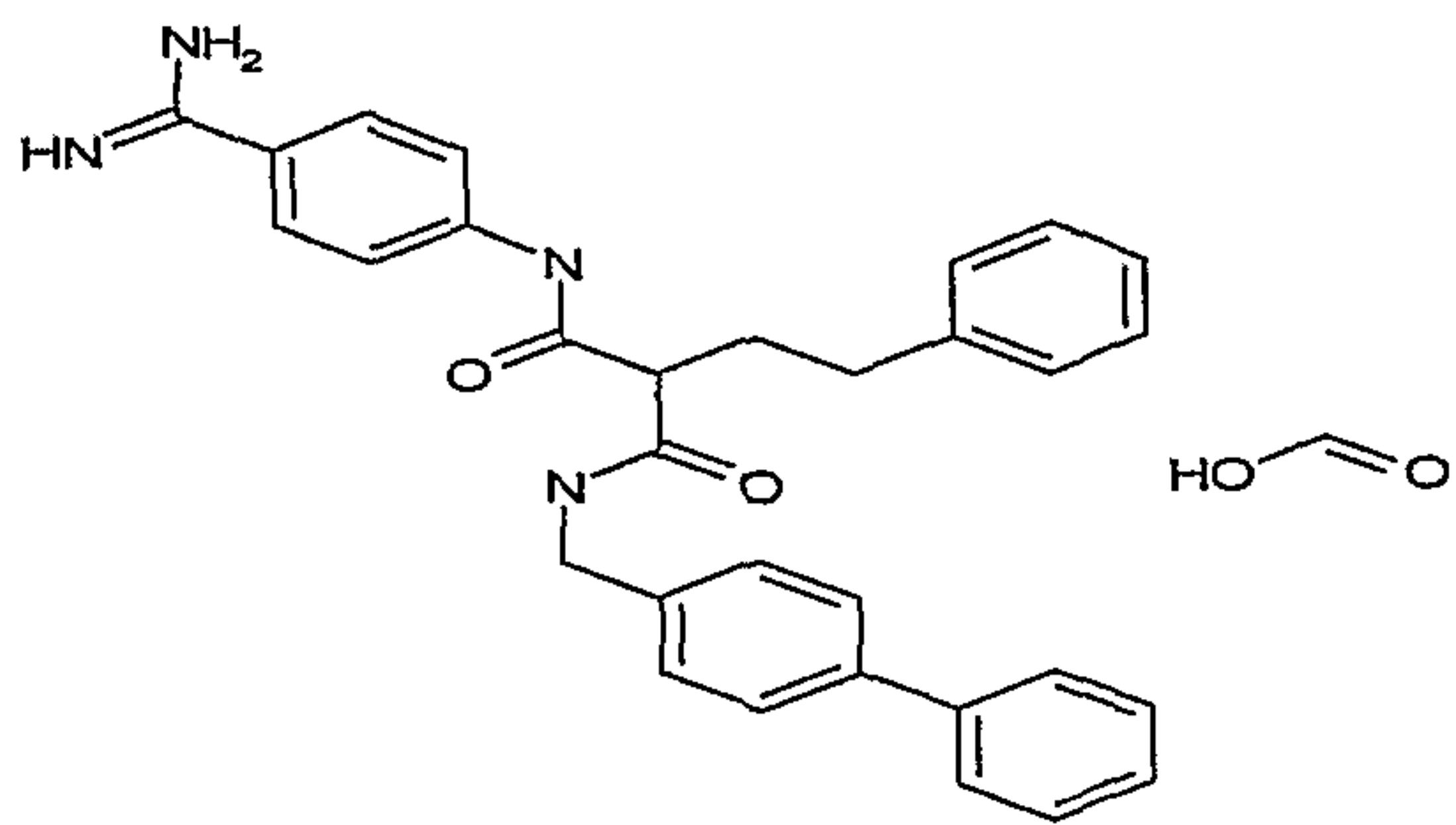
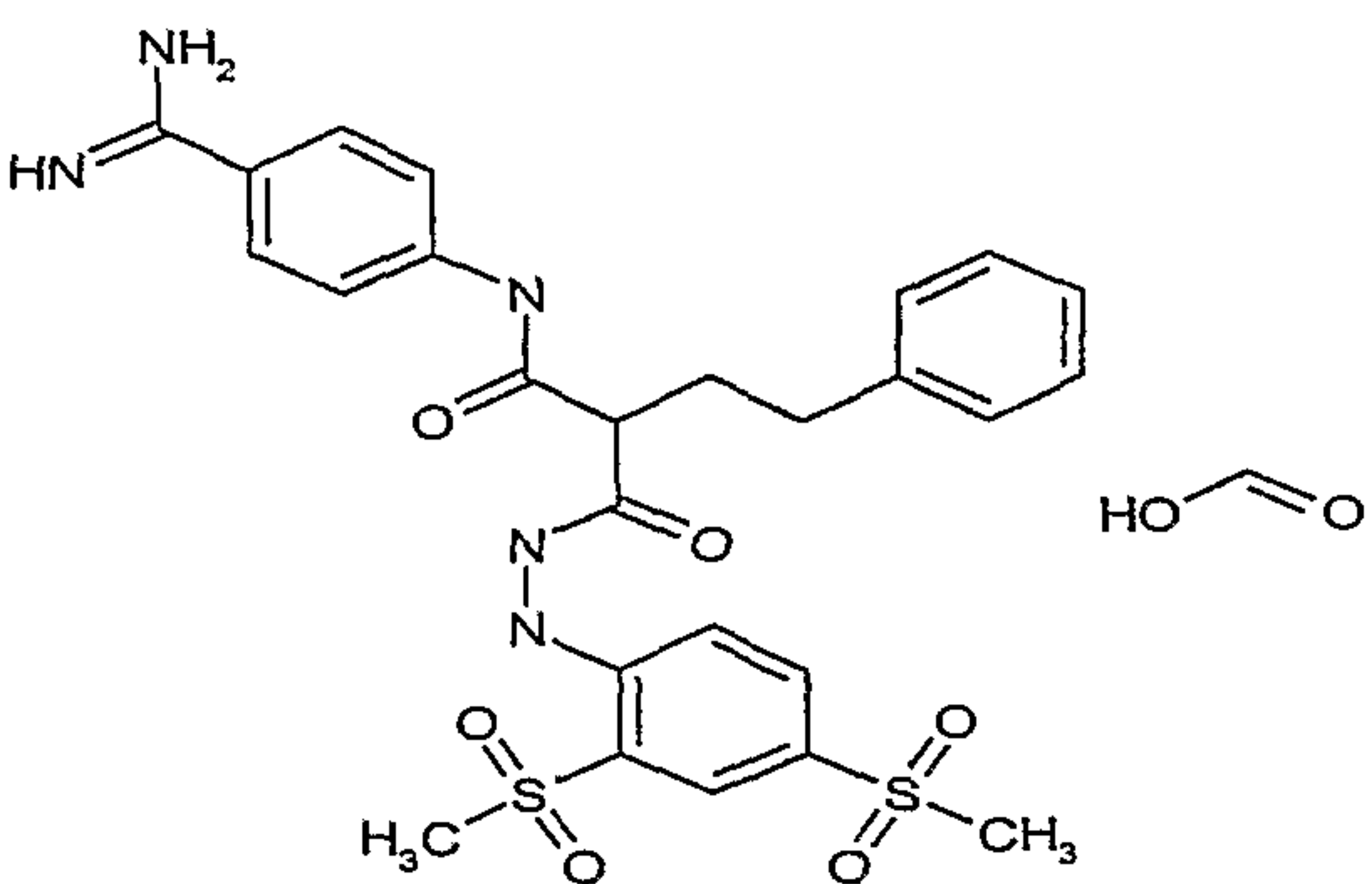
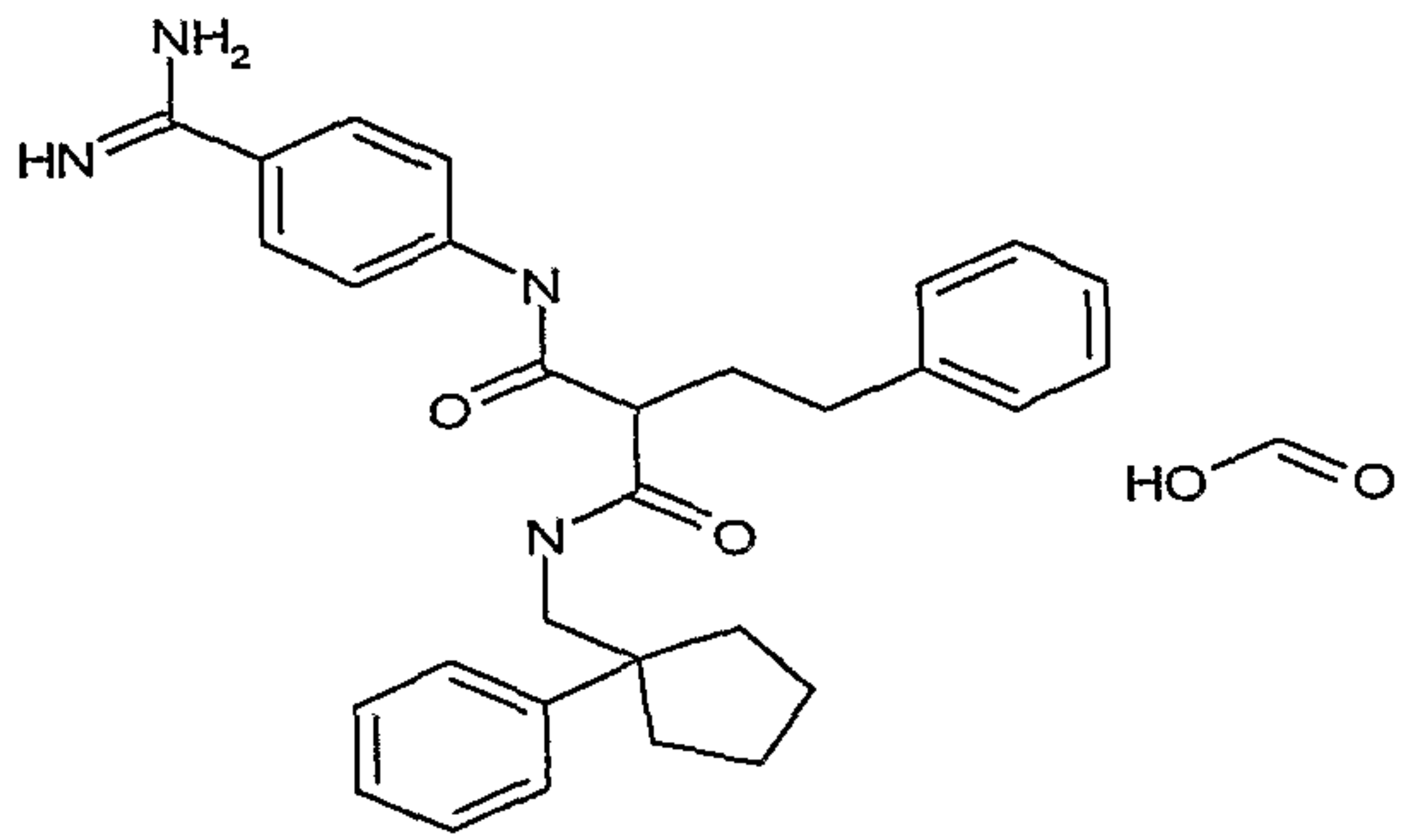
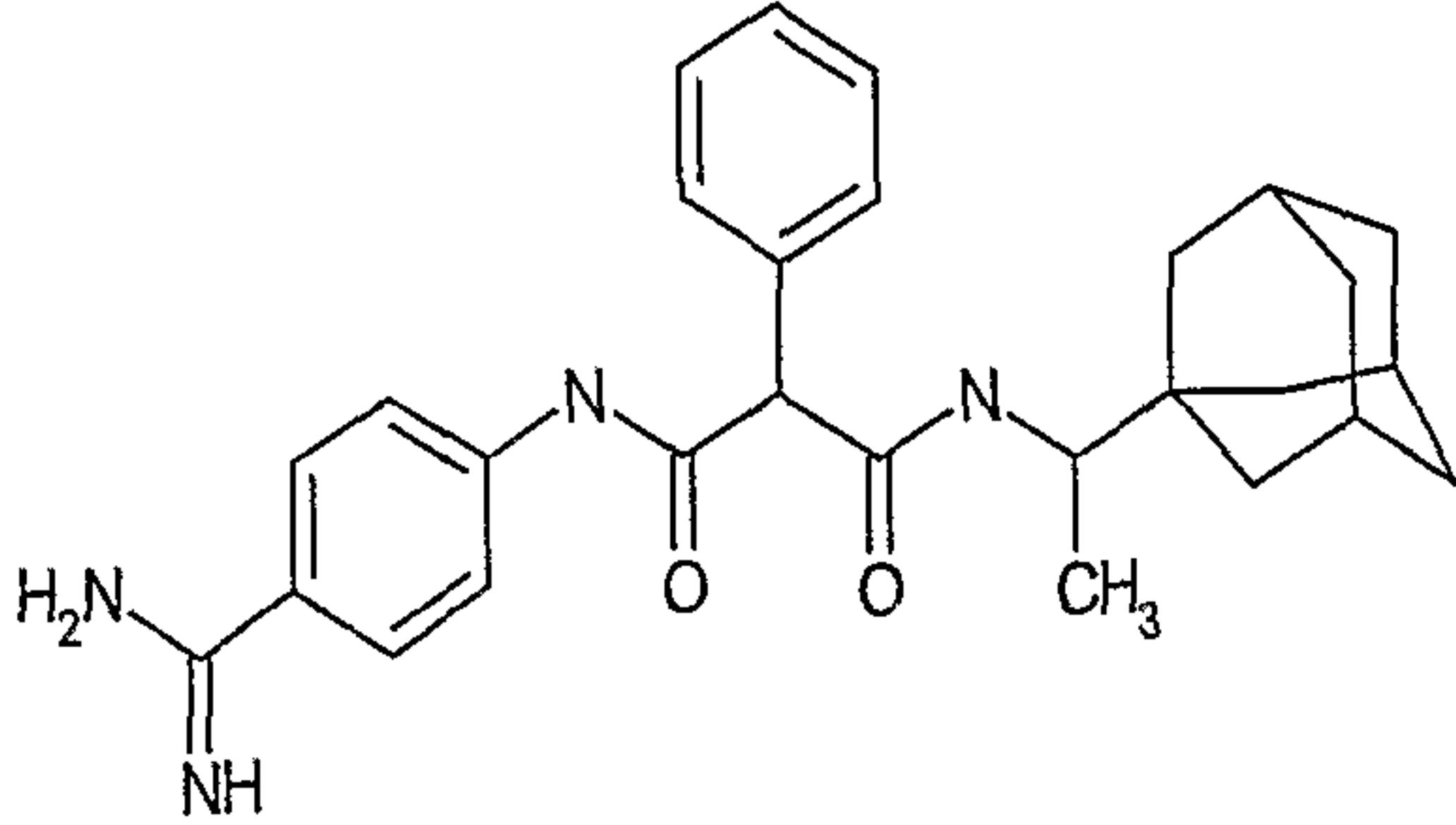
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
53		$C_{26}H_{26}N_4O_4 \cdot CH_2O_2$	504,54	458,20
54		$C_{25}H_{23}F_3N_4O_2 \cdot CH_2O_2$	514,502	514,51
55		$C_{24}H_{22}Cl_2N_4O_2 \cdot CH_2O_2$	515,395	468,11
56		$C_{30}H_{28}N_4O_3 \cdot CH_2O_2$	538,601	492,22
57		$C_{29}H_{32}N_4O_5 \cdot CH_2O_2$	562,62	516,24

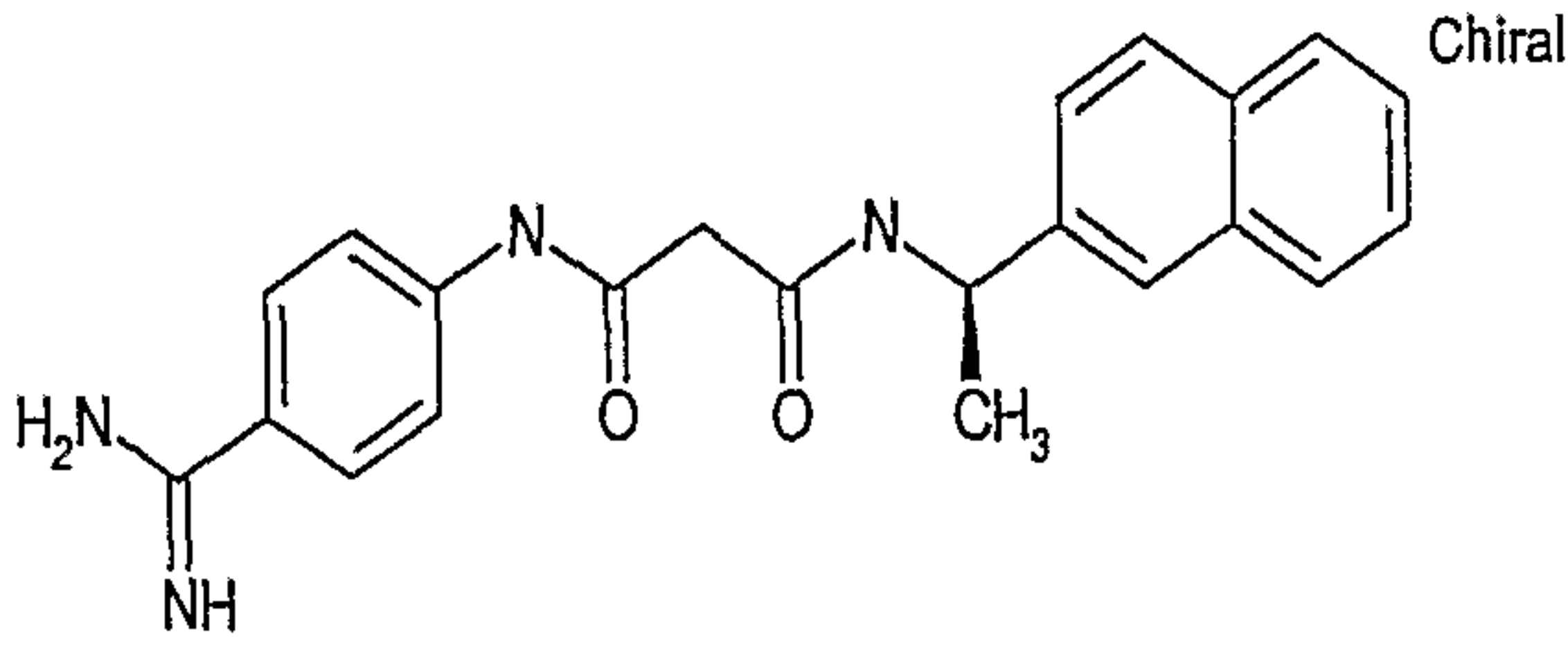
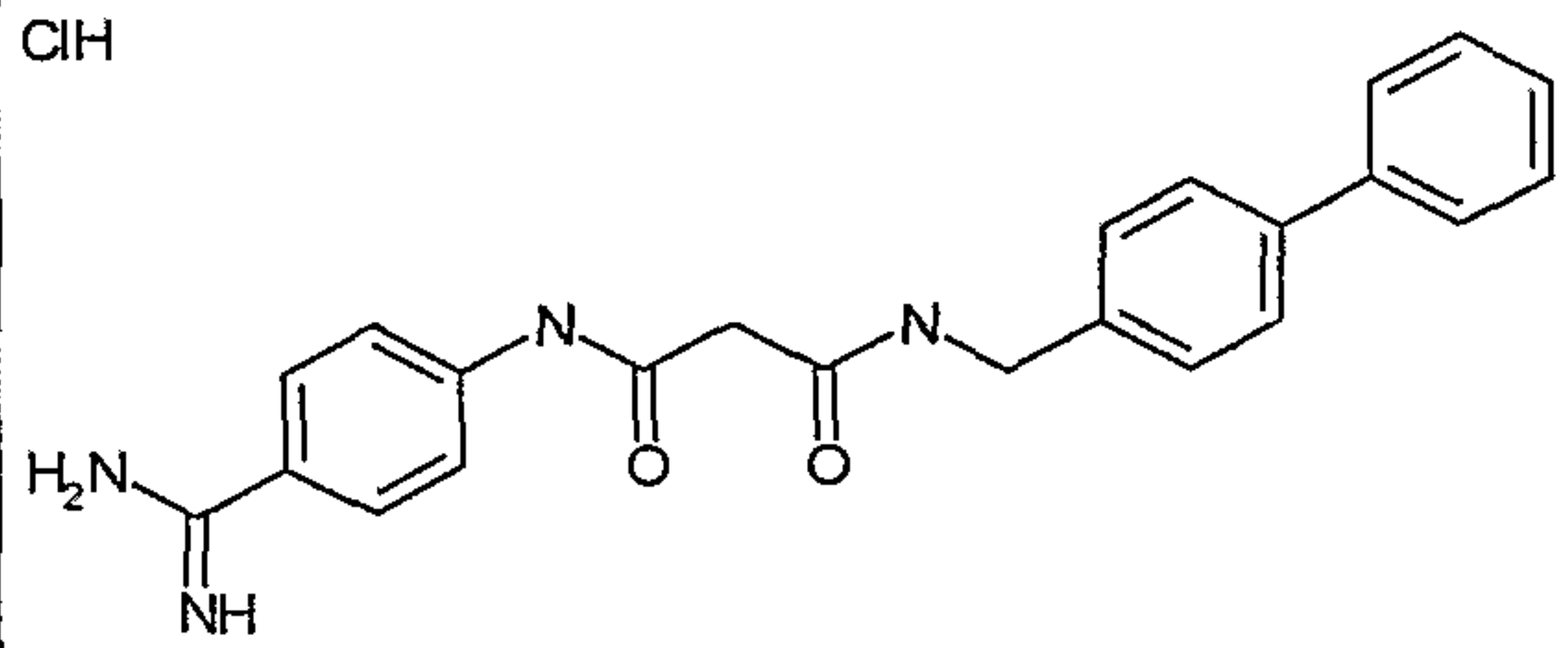
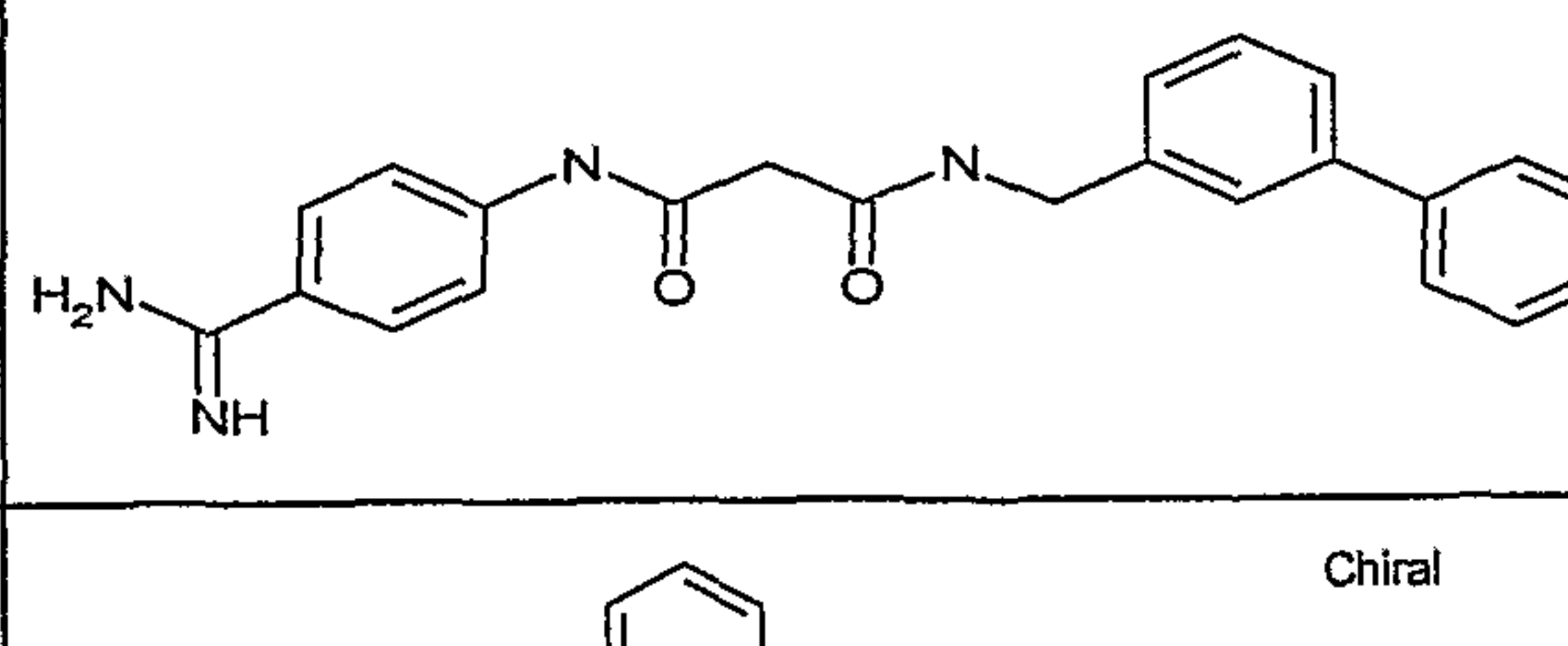
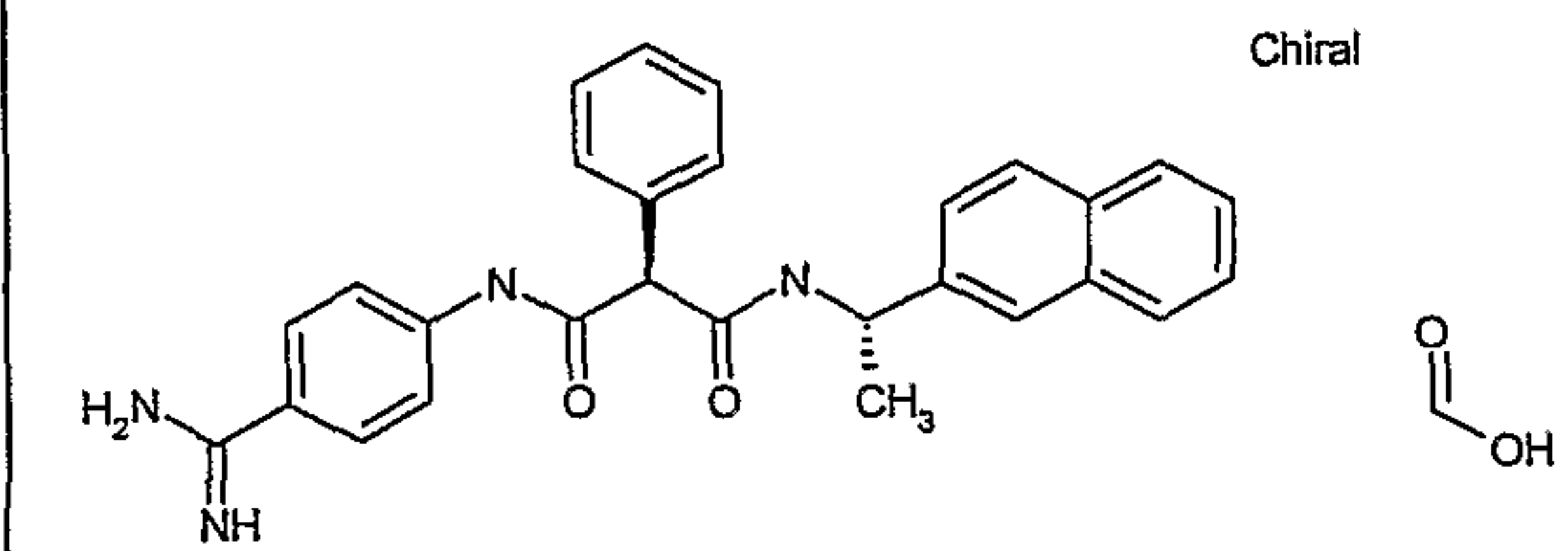
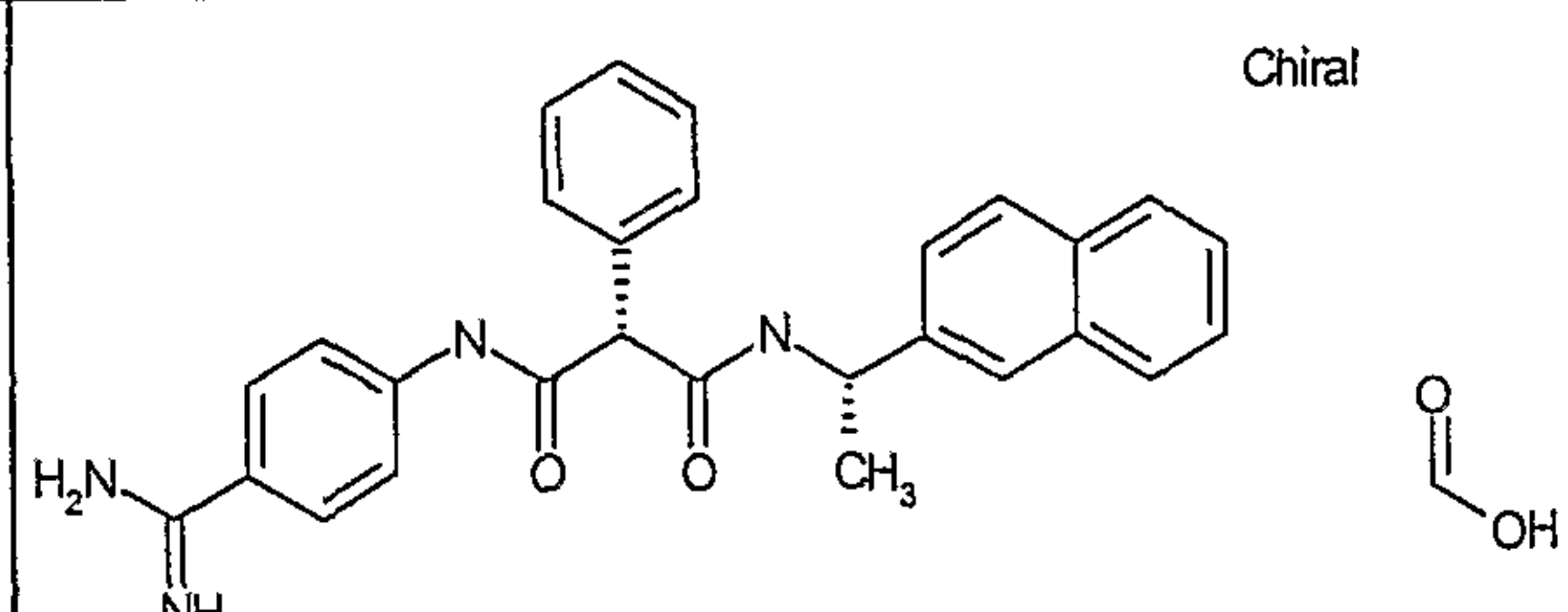
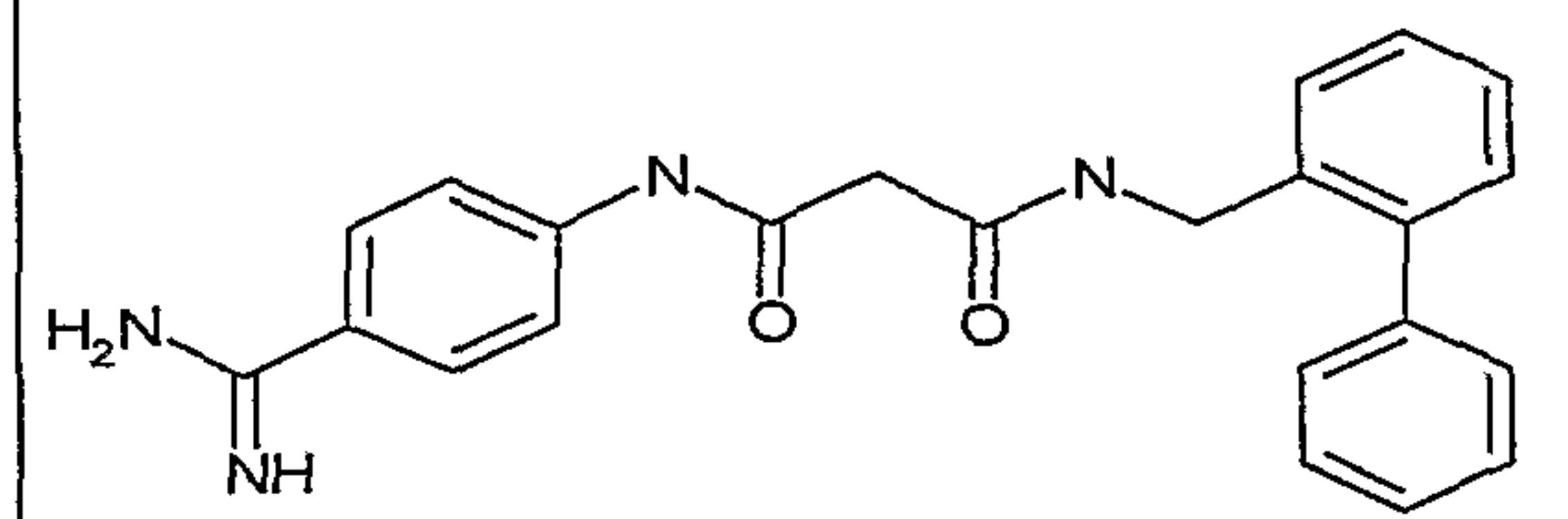
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
58		$C_{26}H_{26}N_4O_5$ $C H_2 O_2$	520,539	474,19
59		$C_{26}H_{26}N_4O_4$ $C H_2 O_2$	504,54	458,2
60		$C_{32}H_{32}N_4O_3$ $C H_2 O_2$	566,655	520,25
61		$C_{25}H_{23}N_7O_2$ $C H_2 O_2$	499,529	453,19

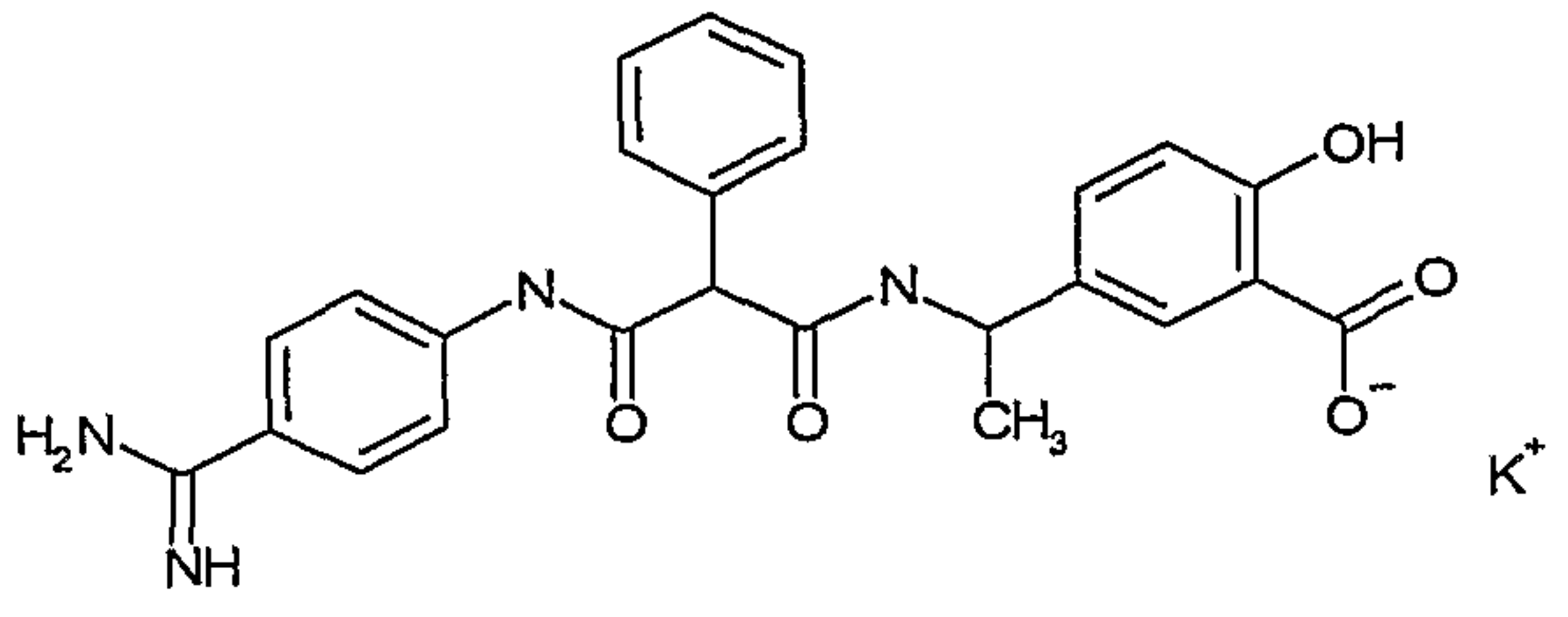
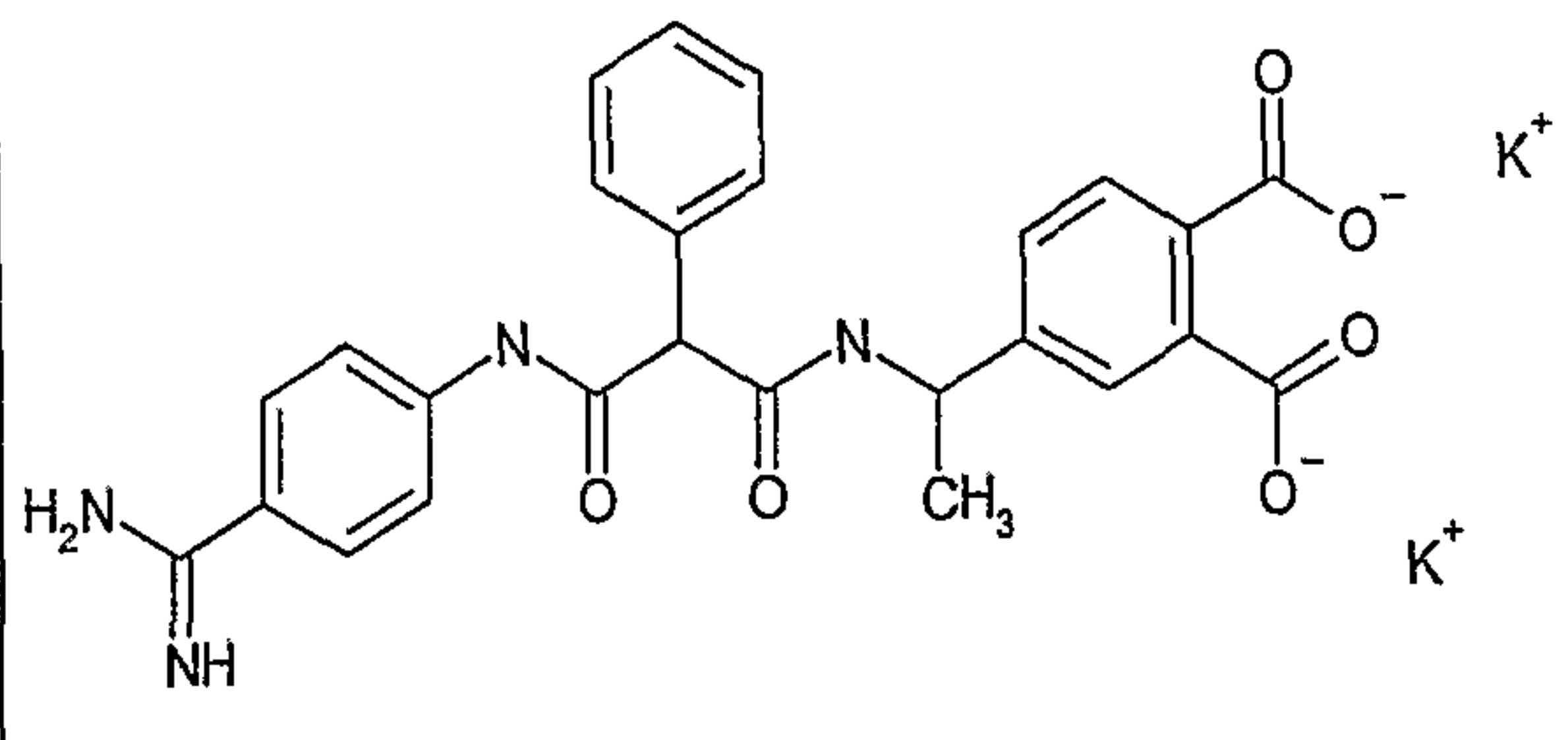
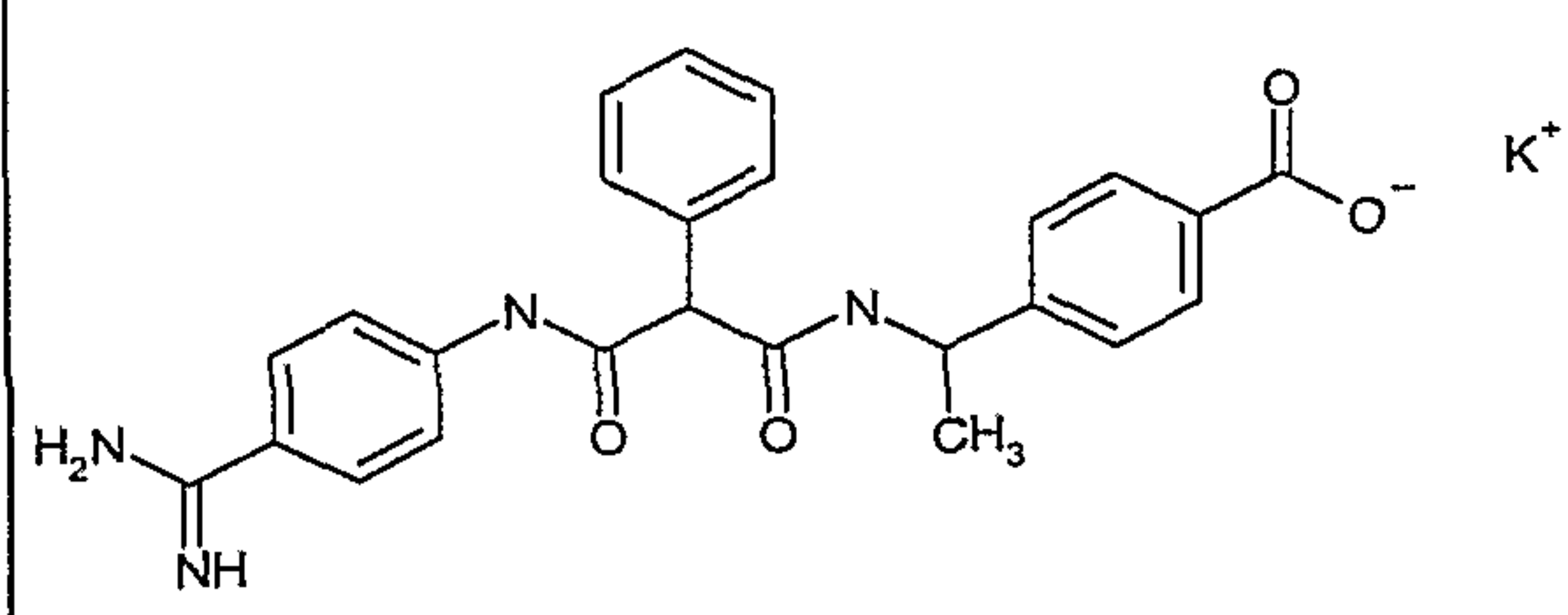
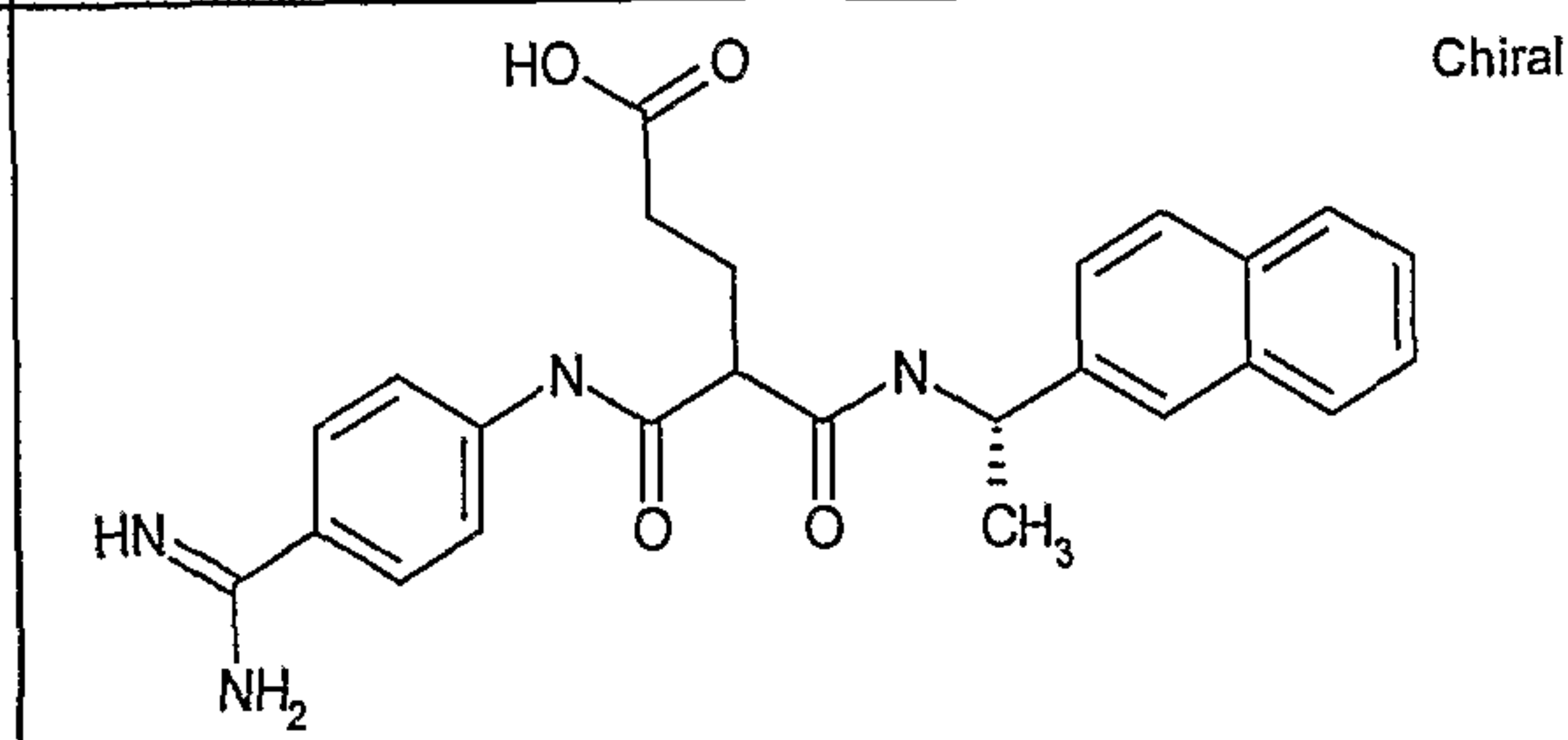
Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
62		$C_{31}H_{30}N_4O_2 \cdot CH_2O_2$	536,629	490,24
63		$C_{28}H_{30}N_4O_2 \cdot CH_2O_2$	500,596	454,24
64		$C_{27}H_{29}ClN_4O_2 \cdot CH_2O_2$	523,03	477,0
65		$C_{31}H_{29}ClN_4O_2 \cdot CH_2O_2$	571,074	525,0

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
66	Chiral HO-COOH	$C_{29}H_{32}N_4O_3 \cdot C H_2 O_2$	530,622	485,0
67	Chiral HO-COOH	$C_{30}H_{30}N_4O_2 \cdot CH_2 O_2$	524,618	479,0
68	Chiral HO-COOH	$C_{26}H_{27}BrN_4O_2 \cdot CH_2 O_2$	553,454	506,9
69	Chiral HO-COOH	$C_{26}H_{27}BrN_4O_2 \cdot CH_2 O_2$	553,454	506,9

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
70	 Chiral HO-C(=O)-	$C_{30}H_{30}N_4O_2 \cdot CH_2O_2$	524,618	479,0
71	 HO-C(=O)-	$C_{31}H_{29}ClN_4O_3 \cdot CH_2O_2$	587,073	541,0
72	 HO-C(=O)-	$C_{33}H_{34}N_4O_2 \cdot CH_2O_2$	564,682	519,1
73	 HO-C(=O)-	$C_{31}H_{30}N_4O_2 \cdot CH_2O_2$	536,629	491,0

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
74		$C_{31}H_{30}N_4O_2 \cdot CH_2O_2$	536,629	491,0
75		$C_{26}H_{29}N_5O_6S_2 \cdot CH_2O_2$	617,701	571,9
76		$C_{30}H_{34}N_4O_2 \cdot CH_2O_2$	528,649	483,1
77		$C_{28}H_{34}N_4O_2$	458,603	459,3

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
78		$C_{22} H_{22} N_4 O_2$	374,442	375,2
79	ClH 	$C_{23} H_{22} N_4 O_2 \cdot Cl H$	422,914	388,4
80	ClH 	$C_{23} H_{22} N_4 O_2 \cdot Cl H$	422,914	388,2
81	Chiral 	$C_{28} H_{26} N_4 O_2 \cdot CH_2 O_2$	496,564	450,2
82	Chiral 	$C_{28} H_{26} N_4 O_2 \cdot CH_2 O_2$	496,564	450,2
83	ClH 	$C_{23} H_{22} N_4 O_2 \cdot Cl H$	422,914	387,2

Example No.	Structure	Empirical formula	molecular weight	ESI-MS (M+ H)
84		$C_{25} H_{23} N_4 O_5 \cdot K$	498,578	461,1
85		$C_{26} H_{22} N_4 O_6 \cdot 2 K$	564,678	489,2
86		$C_{25} H_{23} N_4 O_4 \cdot K$	482,579	454,2
87		$C_{25} H_{26} N_4 O_4$	446,504	447,3

Pharmacological testing

The ability of the compounds of the formula I to inhibit factor VIIa or other enzymes like factor Xa, thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC_{50} value, which is related to the inhibition constant K_i . Purified enzymes are used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis is determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant K_i , the IC_{50} value is corrected for competition with substrate using the formula

$$K_i = IC_{50} / \{1 + (\text{substrate concentration} / K_m)\}$$

wherein K_m is the Michaelis-Menten constant (Chen and Prusoff, *Biochem. Pharmacol.* 22 (1973), 3099-3108; I. H. Segal, *Enzyme Kinetics*, 1975, John Wiley & Sons, New York, 100-125).

5 a) Factor VIIa (FVIIa) Assay

The inhibitory activity (expressed as inhibition constant K_i (FVIIa)) of the compounds of formula I towards factor VIIa/tissue factor activity was determined using a chromogenic assay essentially as described previously (J. A. Ostrem et al., *Biochemistry* 37 (1998) 1053-1059 which is incorporated herein by reference). Kinetic assays were conducted at 25°C in half-area microtiter plates (Costar Corp., Cambridge, Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A typical assay consisted of 25 µl human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40 µl of inhibitor dilutions in 10 % DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM $CaCl_2$, 0.05 % PEG 8000, pH 8.15). Following a 15 minute preincubation period, the assay was initiated by the addition of 35 µl of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500 µM final concentration).

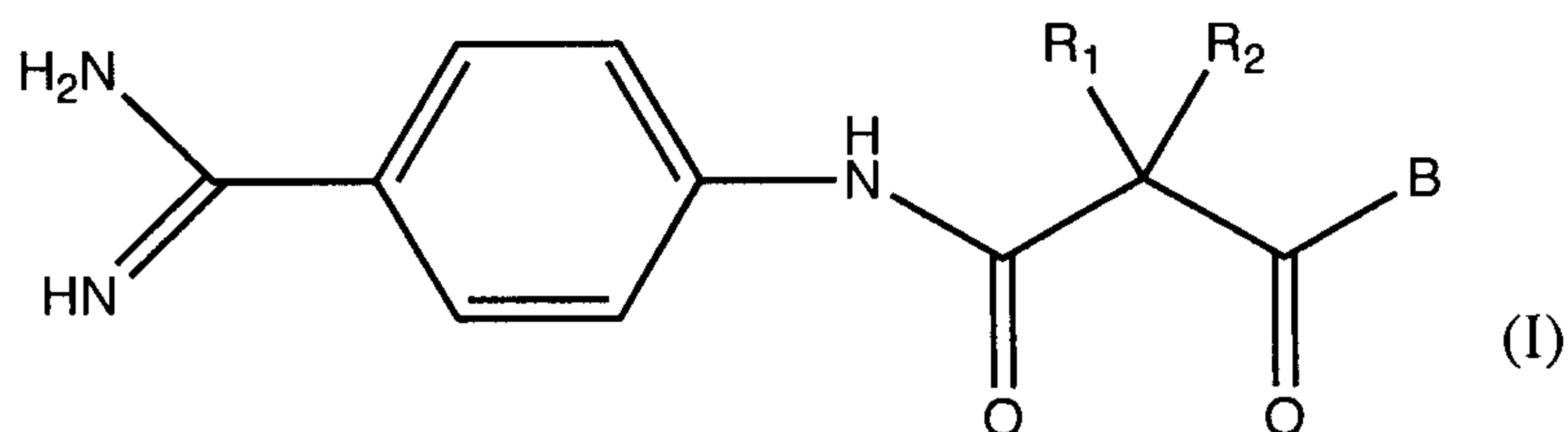
20 The following test results (inhibition constants K_i (FVIIa)) were obtained.

Example Compound	K_i (FVIIa) (µM)	Example Compound	K_i (FVIIa) (µM)
1	14	26	0,381
3	0,198	28	6,02
6	3,825	35	3,005
8	7,116	38	17,35
12	0,301	40	2,81
17	6,615	42	17,061
20	5,134	43	0,124
23	0,157	44	0,376

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A compound of the formula I

5



wherein

R¹ is 1. hydrogen atom,

10

2. -(C₁-C₆)-alkyl,

3. -OH,

4. -O-(C₁-C₆)-alkyl or

5. -N-(R⁶)₂, wherein R⁶ is independently of one another hydrogen atom, -C(O)-aryl, -C(O)-(C₁-C₆)-alkyl-aryl, -C(O)-(C₁-C₆)-alkyl, -C₁-C₆-alkyl, -C(O)-N(H)-aryl, -C(O)-N(H)-(C₁-C₆)-alkyl-aryl, -C₁-C₆-N(H)-alkyl, -C(O)-O-aryl, -C(O)-O-(C₁-C₆)-alkyl-aryl, -C(O)-O-(C₁-C₆)-alkyl, S(O₂)-aryl or -S(O₂)-(C₁-C₆)-alkyl,

15

R² is 1. aryl, wherein aryl is unsubstituted or mono- to tri-substituted independently of one another by

20

1.1. -CF₃,

1.2. halogen,

1.3. -OH,

1.4. -CN,

1.5. S(O)_yR¹² wherein R¹² is alkyl, aryl, amino, or substituted amino, and y is zero, one or two,

25

1.6. -NO₂,

1.7. -NH₂,

1.8. -O-(C₁-C₆)-alkyl,

1.9. substituted amino,

30

1.10. -COOH,

1.11. -(C₁-C₆)-alkyl,

- 1.12. carbamyl,
- 1.13. carbonyl,
- 1.14. alkoxy carbonyl,
- 1.15. methylenedioxy,
- 5 1.16. aryloxy, wherein aryloxy is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.15,
- 10 1.17. -O-(C₁-C₆)-alkyl-aryl, wherein aryl is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.15,
- 1.18 Het-group, wherein Het-group is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.15, or
- 15 1.19. -(C₀-C₄)-alkyl-aryl, wherein aryl is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.15,
2. hydrogen atom,
3. Het-group, wherein the Het-group is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,
- 20 4. -(CH₂)_m-Y_n-(CH₂)_o-aryl,
wherein m, n and o are independently of one another the integer zero, 1 or 2, provided that at least one of m, n and o is not zero, aryl is unsubstituted or mono- to tri-substituted independently with groups as defined under 1.1 to 1.19,
- 25 Y is -O-, -S- or -N(R⁶), wherein R⁶ is hydrogen atom or -(C₁-C₆)-alkyl, provided n is the integer 1, or Y is -N(R⁶)-N(R⁶)-, wherein R⁶ is independently of one another hydrogen atom or -(C₁-C₆)-alkyl, or -N=N-, provided n is the integer 2, or
- 30 5. -(CH₂)_m-Y_n-(CH₂)_o-Het-group,
wherein m, n and o are independently of one another the integer zero, 1 or 2, provided that at least one of m, n and o is not zero, Het-group is unsubstituted or mono- to tri-substituted

independently with groups as defined under 1.1 to 1.19, and Y is as defined above, or

R¹ and R² together with the carbon atom to which they are bonded form

1. a (C₃-C₇)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,
2. a (C₃-C₇)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-to disubstituted independently of one another and fused to an aryl-or Het-group-ring, which itself is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19, or
3. a Het-group, wherein the Het-group is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,
4. a keto-group, which may partially or even totally exist in a hydrated state,

provided that, when R¹ is as defined above under 3, 4 or 5 then R² is not directly bond to formula I via a oxygen-, sufur- or nitrogen-atom,

- B is
1. -N(R⁷)-(CH-(R⁸))_p-aryl,
- wherein aryl in the group -N(R⁷)-(CH-(R⁸))_p-aryl is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,
- p is the integer zero, 1 or 2,
- R⁷ is
- 1.1 hydrogen atom,
 - 1.2 -(C₁-C₆)-alkyl,
 - 1.3 -OH,
 - 1.4 -N-(R⁶)₂, wherein R⁶ is independently of one another hydrogen atom or -(C₁-C₆)-alkyl,
- R⁸ is
- 1.1 hydrogen atom,
 - 1.2 -(C₁-C₆)-alkyl,
 - 1.3 -(C₂-C₆)-alkenyl,
 - 1.4 -(C₂-C₆)-alkynyl,
 - 1.5 -(C₀-C₃)-alkyl-(C₃-C₇)-cycloalkyl,
 - 1.6 -CN,

1.7 aryl, aryl is unsubstituted or mono- or di-substituted with groups as defined under 1.1 to 1.19,

5 1.8 a Het-group, wherein the Het-group is unsubstituted or mono- or di- substituted with groups as defined under 1.1 to 1.19

1.9 $-(CH-(R^8))_p-$ forms a $-(C_3-C_7)$ -cycloalkyl residue or

1.10 $-(C_0-C_4)$ -alkyl $-O-(C_1-C_6)$ -alkyl,

2. $-O-(CH-(R^8))_p$ -aryl,

10 wherein aryl, R^8 and p are as defined above,

3. $-N(R^7)-(CH-(R^8))_p$ -Het-group, wherein the Het-group is unsubstituted or mono- or di-substituted with groups as defined under 1.1 to 1.19 and R^7 , R^8 and p are as defined above,

4. $-N(R^9)-N(R^{9'})-(CH-(R^8))_q$ -aryl,

15 wherein aryl is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,

q is the integer zero, 1 or 2, R^9 and $R^{9'}$ are independently of one another hydrogen, (C_1-C_6) -alkyl or $-(C_1-C_3)$ -alkyl-aryl and R^8 is as defined above,

20

5. $-O-N(R^9)-(CH-(R^8))_q$ -aryl,

wherein aryl is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,

25

q is the integer zero, 1 or 2, and R^8 and R^9 are as defined above,

6. $-N(R^9)-N(R^{9'})-(CH-(R^8))_q$ -Het-group,

wherein Het-group is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,

30

q is the integer zero, 1 or 2, and R^8 , $R^{9'}$ and R^9 are as defined above,

7. $-O-N(R^9)-(CH-(R^8))_q$ -Het-group,

wherein Het-group is unsubstituted or mono- to tri-substituted independently of one another with groups as defined under 1.1 to 1.19,

q is the integer zero, 1 or 2, and R⁸ and R⁹ are as defined above;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically tolerable salts.

2. A compound of the formula I as claimed in claim 1, wherein

R¹ is hydrogen atom or -(C₁-C₂)-alkyl,

R² is hydrogen atom, phenyl or -(C₁-C₂)-alkyl-phenyl,

B is 1. -N(R⁷)-(CH-(R⁸))_p-aryl,

wherein aryl is indanyl, phenyl, tetralinyl, naphthalinyl, which are unsubstituted or mono- to di-substituted independently of one another by

1.1 Br, Cl or F,

1.2 -CF₃,

1.3 -NO₂,

1.4 methylenedioxy,

1.5 -OH,

1.6 phenyl,

1.7 phenoxy,

1.8 benzyloxy,

1.9 O-(C₁-C₆)-alkyl-phenyl, wherein phenyl is unsubstituted or or mono-to tri-substituted independently of one another by

1.9.1 Br, Cl or F,

1.9.2 -(C₁-C₄)-alkyl or

1.9.3 -NO₂,

1.10 -C(O)-O-(C₁-C₄)-alkyl,

1.11 -O-(C₁-C₄)-alkyl,

1.12 -SO₂-(C₁-C₄)-alkyl,

1.13 -COOH,

1.14 -(C₁-C₃)-alkyl or

1.15 methoxyl,

p is the integer zero, 1 or 2,

R⁷ is hydrogen atom,

R⁸ is 1.1 hydrogen atom,

5 1.2 -(C₁-C₂)-alkyl,

1.3 -CN,

1.4 phenyl, wherein phenyl is unsubstituted or mono-
or di-substituted by methoxy or halogen,

1.5 -(C₀-C₂)-alkyl-O-(C₁-C₄)-alkyl,

10 1.6 -(CH-(R⁸))- forms a -(C₄-C₆)-cycloalkyl residue,

1.7 cyclopropylmethyl, or

1.8 ethynyl,

2. -O-(CH-(R⁸))_p-phenyl,

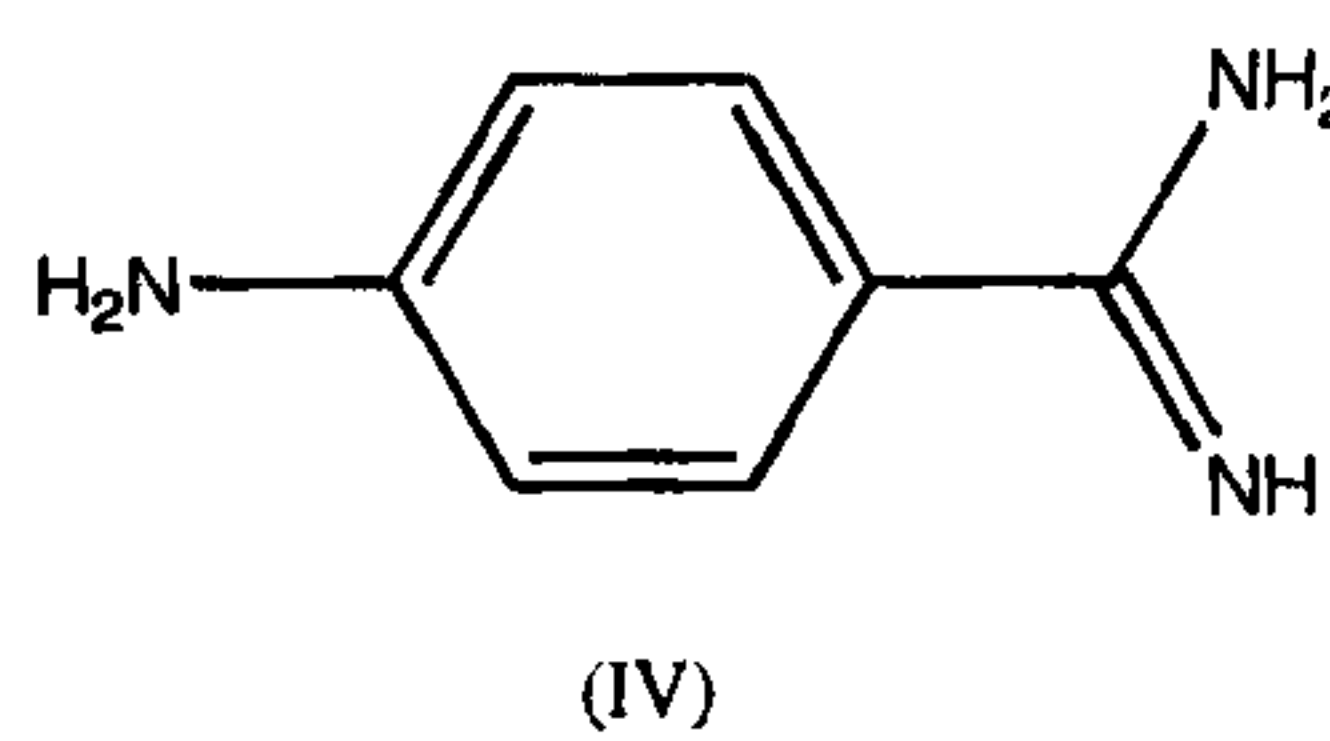
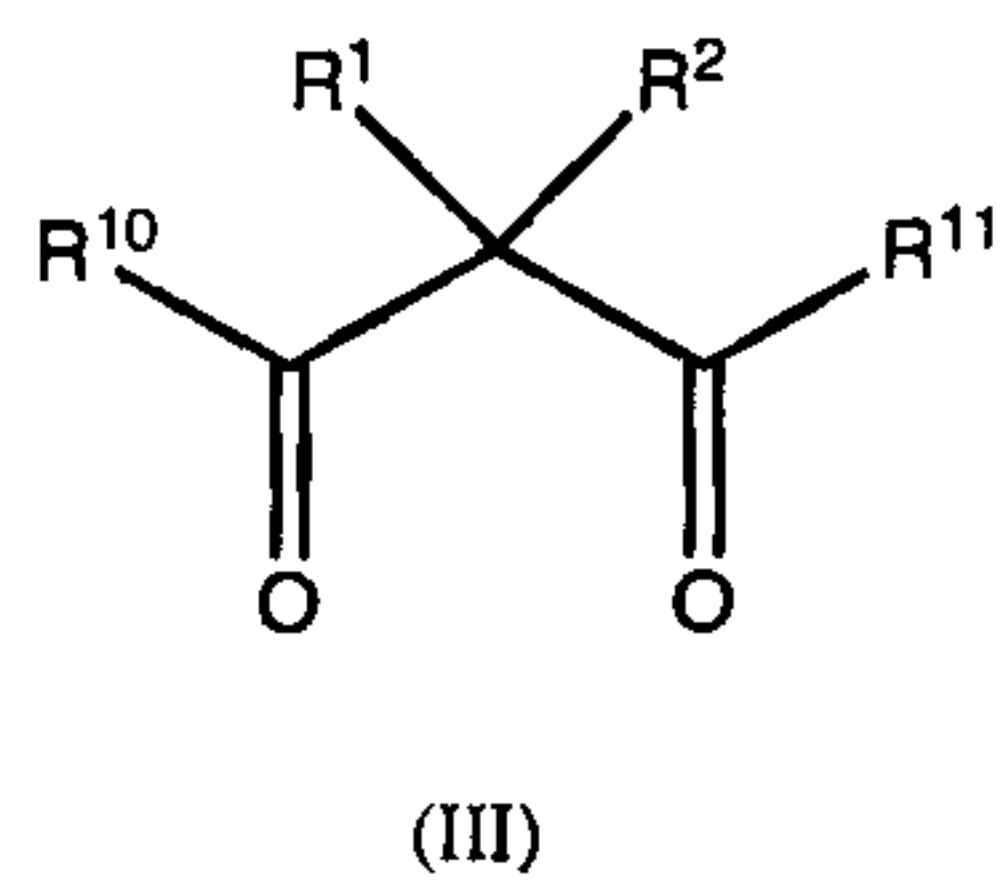
wherein phenyl, R⁸ and p are as defined above,

15 3. -N(R⁹)-N(R^{9'})-(CH-(R⁸))_q-Het-group, wherein the Het-
group is quinoxaline, imidazolyl, benzimidazolyl, oxazolyl,
benzoxazolyl, thiazolyl, indazolyl, benzothiazolyl, indolyl,
indolinyl, or pyridinyl, wherein R⁹ and R^{9'} are
independently of one another hydrogen or -(C₁-C₂)-alkyl,
20 R⁸ and q are as defined above under 1. for aryl, Het-
group is unsubstituted or mono- to di-substituted
independently of one another with groups as defined
above under 1. for aryl, or

25 4. -N(R⁷)-(CH-(R⁸))_p-Het-group, wherein the Het-group is
imidazolyl, benzimidazolyl, oxazolyl, benzoxazolyl,
thiazolyl, benzothiazolyl, indolyl, indazolyl, indolinyl, or
pyridinyl, wherein Het-group is unsubstituted or mono-
substituted by Br, Cl, F, -CF₃, -NO₂, phenyl, phenoxy,
methyl, benzyloxy or methoxy, and R⁷, R⁸ and p are as
30 defined above under 1. for aryl.

3. A process for the preparation of a compound of formula I as claimed in any one of claims 1 or 2, comprising linking the building blocks of the formulae III, IV and V

60



H - B
(V)

wherein R^{10} and R^{11} are independently from each other a -OH group, an acid chloride, a (C₁-C₄)-alkyl ester or an activated ester, or a mixed anhydride, and R^1 , R^2 , R^7 , R^8 , B, p and aryl are as defined in claim 1, by means of forming an amide bond between the carboxylic acid derivative depicted in formula III and the NH₂ group depicted in formula IV and an amide bond or ester bond between the carboxylic acid derivative depicted in formula III and the -OH- or -NH-group depicted in formula V.

4. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in any one of claims 1 to 2 and/or a physiologically tolerable salt thereof and a pharmaceutically acceptable carrier.
5. A compound of the formula I as claimed in any one of claims 1 to 2 and/or a physiologically tolerable salt thereof for use as an inhibitor of factor VIIa.
6. A compound of the formula I as claimed in any one of claims 1 to 2 and/or a physiologically tolerable salt thereof for inhibiting or reducing blood clotting or inflammatory response or for use in the treatment of cardiovascular disorders, thromboembolic diseases or restenoses.

