Title: PHARMACEUTICALLY ACTIVE BENZOXAZOLE, BENZTHIAZOLE AND BENZIMIDAZOLE ACID DERIVATIVES

Abstract: Compounds of formula (I): wherein R¹, R² and R³ are independently, hydrogen, halogen, CF₃, OR, NR'R₃, NR'COR, NR'SO₂R, or C₆H₅ alkyl optionally substituted by hydroxy, C₆H₅ alkoxy or NR'R₃; R⁴ is NR'CONR'R₃, NR'COR, NR'SO₂R, or W-CON'R'R₃, where W is a bond, C₆H₅ alkenylene or C₆H₅ alkylene; and R₂ is Formula (A) methods for their synthesis, pharmaceutical compositions comprising them and their use in medicine, in particular for the treatment of cancer.
PHARMACEUTICALLY ACTIVE BENZOXAZOLE, BENZTHIAZOLE AND
BENZIMIDAZOLE ACID DERIVATIVES

The present invention relates to novel compounds useful as inhibitors of heparanase, methods for
their synthesis, pharmaceutical compositions comprising the novel compounds and their use in medicine,
in particular for the treatment of cancer.

The extracellular matrix (ECM) is not only the structural surround for cells in a multicellular
organism but also acts as a key modulator and mediator of their physiology, differentiation, organisation
and repair. Receptor ligands are stored, concentrated, processed and presented to the cell surface by
components of the ECM, which include free and protein-bound heparan sulfate proteoglycans, free and
protein-bound chondroitins, collagens, and a variety of cell-adhesive integrins, such as, fibronectin. As
such, the ECM is in a constant flux of degradation and synthesis by neighbouring cells.

The ECM is also the principal barrier to tumour growth and metastasis. For a tumour cell to
penetrate this barrier it must sufficiently degrade the ECM components so that there is ample space to
traverse. The ECM must also be degraded in order to provide avenues for new blood vessel formation
(angiogenesis) which are needed to supply the increased nutrient requirements of rapidly growing
tumours.

A broad spectrum of degradative enzymes are secreted by tumor cells to break down the ECM’s
complex composition. However, recent studies have demonstrated that inhibiting even just one ECM
degrading enzyme appears to provide significant benefit in treating cancer. For example, inhibitors of
certain proteases that degrade ECM protein component have been studied in preclinical and clinical trials
as anticancer agents.

Carbohydrates represent a large fraction of the total mass of all ECM. Therefore, tumour cells
secrete large quantities of carbohydrate degrading enzymes as they penetrate the ECM. In fact, there is
good correlation between raised levels of carbohydrate processing enzymes, such as heparanases,
secreted by tumour cells and their metastatic potential (e.g. Vlodavsky et al., (1994) Invasion Metastasis,
14:290-302; (1999) Nature Medicine, 5:793-802). Heparanases, are enzymes that can degrade heparan
sulfate as well as heparin and heparan sulfate proteoglycans.

The carbohydrate fragments generated by glycosidase action also promote the cancer phenotype
since many are growth-stimulatory. For example, heparanase activity can release heparan sulfate
fragments, which can increase the potency of a variety of growth factors, and can also elicit cell growth
stimulation once bound by an appropriate cell surface receptor (e.g. Folkman and Shing (1992) Adv.

Inhibitors of ECM carbohydrate degradation are potent anticancer agents. For example, sulfated
oligosaccharide heparanase inhibitors block tumour metastasis in some animal models (Vlodavsky et al.,
heparanase activity results in the release of growth factors that can stimulate angiogenesis and promote

Heparanase activity correlates with the ability of activated cells of the immune system to leave
the circulation and elicit both inflammatory and autoimmune responses. Interaction of platelets,
granulocytes, T and B lymphocytes, macrophage and mast cells with the subendothelial ECM is
associated with degradation of heparan sulfate by heparanase activity (Vlodavsky et al., (1992) Invasion
Metastasis, 12, 112-127). Heparanase inhibitors may be able to prevent or inhibit the progression of
autoimmune and inflammatory diseases.

Heparinomimetic compounds are currently being developed as anticoagulant and
antiproliferative agents for the control of thrombotic and proliferative disorders (Demir et al., Clin. Appl.
Thromb. Hemost., 2001 Apr; 7(2): 131-40). Thus, a secondary function of heparanase inhibitors may
have a role in cardiovascular diseases including blood-clotting conditions, for example thromboembolic disease, arterial thrombosis and restenosis.

WO01/35967 discloses the use of heparanase inhibitors for the treatment or prevention of congestive heart failure e.g. primary cardiomyopathy. Associated conditions treated or prevented with the inhibitor are especially peripheral oedemas, pulmonary and hepatic congestion, dyspnoea, hydrothorax and ascites. Renal problems, e.g. nocturia can also be treated.

WO02/060374 discloses benzimidazole, benzoxazole and benzothiazole derivatives as heparanase inhibitors.

The present invention provides a novel class of compounds, which can be used as inhibitors of heparanase. These compounds provide the opportunity for establishing new treatments for cancer, angiogenesis, inflammatory and autoimmune conditions and cardiovascular diseases.

The invention provides a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:

![Chemical Structure](image)

wherein

R\(^1\), R\(^2\) and R\(^3\) are independently, hydrogen, halogen, CF\(_3\), OR\(^6\), NR\(^8\)R\(^8\), NR\(^8\)COR\(^8\), NR\(^8\)SO\(_2\)R\(^8\) or C\(_{1-6}\) alkyl optionally substituted by hydroxy, C\(_{1-6}\) alkoxy or NR\(^8\)R\(^8\);  
R\(^4\) is NR\(^8\)CONR\(^8\)R\(^8\), NR\(^8\)COR\(^9\), NR\(^8\)SO\(_2\)R\(^8\), or W-CNR\(^8\)R\(^9\), where W is a bond, C\(_{1-6}\) alkyne, C\(_{2-6}\) alkenylene or C\(_{2-6}\) alkylnylene;  
R\(^5\) is

![Chemical Structure](image)

wherein one of X and Y is CO\(_2\)H or tetrazole, or C\(_{1-6}\) alkyl or C\(_{2-6}\) alkenyl wherein one of the -CH\(_2\)- groups may be replaced with O and wherein the alkyl or alkenyl is substituted with one or more CO\(_2\)H or tetrazole groups, and the other is hydrogen; and Z is NR\(^8\), O or S;  
R\(^6\) is hydrogen or C\(_{1-6}\) alkyl, C\(_{3-6}\) alkenyl or C\(_{3-6}\) alkylnyl any of which is optionally substituted by hydroxy, C\(_{1-6}\) alkoxy or NR\(^8\)R\(^8\);  
R\(^7\) is hydrogen or C\(_{1-6}\) alkyl or C\(_{3-6}\) alkenyl either of which is optionally substituted by C\(_{1-6}\) alkoxy or a 5- or 6-membered heterocyclic ring containing up to three heteroatoms selected from NR\(^8\), S and O;  
R\(^8\) is hydrogen or C\(_{1-6}\) alkyl;  
or the groups R\(^7\) and R\(^8\) may together with the nitrogen to which they are attached form a 5- or 6-membered ring which optionally contains up to two further heteroatoms selected from NR\(^8\), S and O;  
R\(^9\) is a group -W-Ar, wherein W is a bond, C\(_{1-6}\) alkyne, C\(_{2-6}\) alkenylene or C\(_{2-6}\) alkylnylene and Ar is a 5- to 10-membered carbocyclic group or heterocyclic group which contains up to three heteroatoms selected from O, NR\(^{11}\) and S; the Ar group being optionally substituted by one or more substituents selected from C\(_{1-4}\) alkyl, C\(_{2-6}\) alkenyl, C\(_{3-6}\) alkylnyl, halogen, OR\(^6\), CN, CF\(_3\), OCF\(_3\), NR\(^8\)R\(^8\), SO\(_2\)R\(^{10}\), COR\(^{10}\), R\(^{10}\), methylenedioxy, an oxo group and a 5- to 6-membered heteroaryl group which contains up to two heteroatoms selected from S, O and NR\(^8\) and which is optionally substituted by one or more substituents selected from halogen, C\(_{1-6}\) alkyl and OR\(^6\);  
R\(^{10}\) is C\(_{1-6}\) alkyl, C\(_{2-6}\) alkenyl, C\(_{3-6}\) alkylnyl or phenyl optionally substituted by one or more substituents selected from halogen, C\(_{1-6}\) alkyl, C\(_{3-6}\) alkenyl, C\(_{3-6}\) alkylnyl, CF\(_3\), OCF\(_3\), OR\(^6\), CN, and methylenedioxy; and
R\textsuperscript{11} is hydrogen or C\textsubscript{1-6} alkyl optionally substituted by phenyl, wherein the phenyl is optionally substituted by one or more substituents selected from halogen, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{3-6} alkynyl, CF\textsubscript{3}, OCF\textsubscript{3}, OR\textsuperscript{6}, CN, and methylenedioxy.

Preferably, R\textsuperscript{1}, R\textsuperscript{2} and R\textsuperscript{3} are independently, hydrogen, halogen, OR\textsuperscript{6}, NR\textsuperscript{2}R\textsuperscript{8} or C\textsubscript{1-6} alkyl optionally substituted by hydroxy or C\textsubscript{1-6} alkoxy. More preferably R\textsuperscript{1}, R\textsuperscript{2} and R\textsuperscript{3} are independently hydrogen, halogen, OR\textsuperscript{6} or C\textsubscript{1-6} alkyl. Yet more preferably R\textsuperscript{1}, R\textsuperscript{2} or R\textsuperscript{3} are independently hydrogen, halogen or CH\textsubscript{3}. Still more preferably, R\textsuperscript{1} and R\textsuperscript{2} are independently hydrogen or halogen and R\textsuperscript{3} is preferably hydrogen or OR\textsuperscript{6}, especially hydrogen.

R\textsuperscript{4} is preferably NR\textsuperscript{3}CONR\textsuperscript{3}R\textsuperscript{5}, NR\textsuperscript{8}COR\textsuperscript{9} or W-CONR\textsuperscript{3}R\textsuperscript{5}, where W is a bond, C\textsubscript{1-6} alkyne or C\textsubscript{2-6} alkenylene. More preferably, R\textsuperscript{4} is NR\textsuperscript{8}COR\textsuperscript{9} or W-CONR\textsuperscript{3}R\textsuperscript{5}, where W is a bond, C\textsubscript{1-6} alkyne or C\textsubscript{2-6} alkenylene. When R\textsuperscript{4} is W-CONR\textsuperscript{3}R\textsuperscript{5} and W is C\textsubscript{2-6} alkenylene it is preferably C\textsubscript{2} alkenylene and the double bond is preferably in the trans configuration.

Preferably Z is O.

Preferably one of X and Y is C\textsubscript{1-6} alkyl substituted with CO\textsubscript{2}H, e.g. -CH\textsubscript{2}CO\textsubscript{2}H, and the other is hydrogen.

Preferably, Y is hydrogen.

Preferably, R\textsuperscript{5} is hydrogen or C\textsubscript{1-6} alkyl, C\textsubscript{3-6} alkenyl or C\textsubscript{3-6} alkynyl any of which is optionally substituted by hydroxy or C\textsubscript{1-6} alkoxy.

Preferably, R\textsuperscript{6} is hydrogen.

Preferably, R\textsuperscript{7} is a group -W-Ar, wherein W is a bond, C\textsubscript{1-6} alkyne or C\textsubscript{2-6} alkenylene and Ar is a 5- to 10-membered carbocyclic group or heterocyclic group which contains up to three heteroatoms selected from O, NR\textsuperscript{11} and S; wherein if Ar is a 5- to 10-membered carbocyclic group e.g. phenyl, it is optionally substituted by one or more substituents selected from C\textsubscript{1-6} alkyl, C\textsubscript{3-6} alkenyl, C\textsubscript{3-6} alkynyl, halogen, OR\textsuperscript{6}, CN, CF\textsubscript{3}, OCF\textsubscript{3} and methylenedioxy; and if Ar is a 5- to 10-membered heterocyclic group, it is optionally substituted by one or more substituents selected from halogen, OR\textsuperscript{6}, R\textsuperscript{10}, SO\textsubscript{2}R\textsuperscript{10}, an o xo group and a 5- to 6-membered heteroaryl group which contains up to two heteroatoms selected from S and NR\textsuperscript{8}, and which is optionally substituted by one or more substituents selected from halogen, C\textsubscript{1-6} alkyl and OR\textsuperscript{6}.

Preferably R\textsuperscript{10} is phenyl optionally substituted by one or more substituents selected from halogen, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{3-6} alkynyl, CF\textsubscript{3}, OCF\textsubscript{3}, OR\textsuperscript{6}, CN, and methylenedioxy.

Preferably R\textsuperscript{11} is hydrogen or CH\textsubscript{3} optionally substituted by phenyl, wherein the phenyl is optionally substituted by one or more substituents selected from halogen, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{3-6} alkynyl, CF\textsubscript{3}, OCF\textsubscript{3}, OR\textsuperscript{6}, CN, and methylenedioxy.

The configuration of the R\textsuperscript{1} to R\textsuperscript{5} groups is preferably:

When W is part of the group W-CONR\textsuperscript{3}R\textsuperscript{5}, it is preferably C\textsubscript{1-6} alkyne or C\textsubscript{2-6} alkenylene, and more preferably C\textsubscript{2-6} alkenylene.

When W is part of the group -W-Ar, preferably it is a bond or C\textsubscript{2-6} alkenylene and more preferably it is a bond.
In the group NR\(^7\)R\(^8\), when the R\(^7\) and R\(^8\) substituents, together with the nitrogen to which they are attached form a 5- or 6-membered ring, the ring may be, for example, morpholine, piperazine or N-methyl piperazine.

The term "alkyl" and "alkylene" as used herein whether on its own or as part of a larger group e.g. "alkoxy" includes both straight and branched chain radicals. The term alkyl also includes those radicals wherein one or more hydrogen atoms are replaced by fluorine. The terms "alkenyl", "alkenylene", "alkynyl" and "alkynylene" should be interpreted accordingly.

The term "carbocyclic group" as used herein includes, unless otherwise defined, non-aromatic and aromatic, single and fused rings, which rings may be unsaturated or saturated and unsubstituted or substituted. Each carbocyclic ring suitably has from 5 to 10, preferably 5, 6, 9 or 10 ring atoms. Examples of carbocyclic groups, including aromatic ring systems, are as follows: phenyl, naphthyl, indanyl and cycloalkyl, e.g. cyclohexyl. A preferred carbocyclic group is phenyl.

The term "heterocyclic group" as used herein includes, unless otherwise defined, non-aromatic and aromatic, single and fused, rings containing one or more, e.g. up to three, heteroatoms in each ring, each of which is selected from O, S and N, which rings may be unsaturated or saturated and unsubstituted or substituted. Each heterocyclic ring suitably has from 5 to 10, preferably 5, 6, 9 or 10 ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Examples of heterocyclic groups, including heteroaromatic ring systems, are as follows: pyrroldidone, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, pyrrole, quinoline, isoquinolone, pyridine, pyrazine, pyrimidine, oxazole, oxadiazole, imidazole, thiazole, thiophene, tetrazole, indole, furan, thiadiazole, triazole, imidazole, benzoxazole, benzopyran, benzo furan, benzothiophene, benzothiazole, benzoazoxine and benzamidazole. "Heteroaryl" is to be interpreted accordingly.

Specific compounds of the invention that may be mentioned include those provided in the examples. A preferred list of specific compounds of the invention include those compounds provided in Examples 24, 25, 26, 27, 28, 29, 34, 38, 50, 53, 54, 55, 56, 57, 66, 78, 82, 85, 95, 97, and 109. More highly preferred compounds of the invention include those provided in Examples 24, 25, 34, 38, 55 and 78.

A specific group of compounds of the invention that may be mentioned include those wherein R\(^1\), R\(^2\) and R\(^3\) are independently, hydrogen, halogen, CF\(_3\), OR\(^6\), NR\(^7\)R\(^8\), NR\(^8\)COR\(^9\), NR\(^8\)SO\(_2\)R\(^9\) or C\(_{1-6}\) alkyl optionally substituted by hydroxy or C\(_{1-6}\) alkoxy;

R\(^4\) is NR\(^8\)CONR\(^2\)R\(^5\), NR\(^8\)COR\(^9\), NR\(^8\)SO\(_2\)R\(^9\) or CONR\(^2\)R\(^5\);

R\(^5\) is X

Y

Z

wherein one of X and Y is CO\(_2\)H or tetrazole, or C\(_{1-6}\) alkyl or C\(_{3-6}\) alkenyl wherein one of the -CH\(_2\)- groups may be replaced with O and wherein the alkyl or alkenyl is substituted with one or more CO\(_2\)H or tetrazole groups, and the other is hydrogen; and Z is NR\(^8\), O or S;

R\(^6\) is hydrogen or C\(_{1-6}\) alkyl, C\(_{3-6}\) alkenyl or C\(_{3-6}\) alkynyl any of which is optionally substituted by hydroxy, C\(_{1-6}\) alkoxy or NR\(^7\)R\(^8\);

R\(^7\) is hydrogen or C\(_{1-6}\) alkyl or C\(_{3-6}\) alkenyl either of which is optionally substituted by C\(_{1-6}\) alkoxy or a 5- or 6-membered heterocyclic ring containing up to three heteroatoms selected from NR\(^8\), S and O;

R\(^8\) is hydrogen or C\(_{1-6}\) alkyl;

or the groups R\(^7\) and R\(^8\) may together with the nitrogen to which they are attached form a 5- or 6-membered ring which optionally contains up to two further heteroatoms selected from NR\(^8\), S and O;
R^2 is a group -W-Ar, wherein W is a bond, C_{1-6} alkylene or C_{2-5} alkenylene and Ar is phenyl or a 5- to 10-membered heteroaryl group which contains up to three heteroatoms selected from O, N and S; the Ar group being optionally substituted by one or more substituents selected from, halogen, OR^6, CN, CF_3, OCF_3, NR^8, SO_2R^{10}, COR^{10}, R^{10}, methylenedioxy and a 5- to 6-membered heteroaryl group which contains up to two heteroatoms selected from S, O and N, and which is optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl and OR^6; and

R^{10} is C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-4} alkylnyl or phenyl optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkylnyl, CF_3, OCF_3, OR^6, CN, and methylenedioxy.

The compounds of the invention preferably have a molecular weight of less than 800, more preferably less than 600.

Suitable pharmaceutically acceptable salts of the compounds include those derived from inorganic and organic bases. Examples of suitable inorganic bases include the hydroxides, carbonates, and bicarbonates of ammonia, lithium, sodium, calcium, potassium, aluminium, iron, magnesium, zinc and the like. Salts can also be formed with suitable organic bases. Such organic bases are well known in the art and may include amino acids such as arginine and lysine, mono-, di-, or trihydroxalkylamines such as mono-, di-, and triethanolamine, choline, mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and trimethylamine, guanidine; N-methylglucosamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; tris(hydroxymethyl)aminomethane; meglumine; and the like.

Salts may be prepared in a conventional manner using methods well known in the art, for example by treatment of a solution of the compound of formula (I) with a solution of the base, for example, potassium or sodium hydroxide, or potassium or sodium hydrogen carbonate.

The invention also includes prodrugs of the aforementioned compounds. A prodrug is an inactive or protected derivative of an active ingredient or a drug, which is converted to the active ingredient or drug in the body. Examples of prodrugs include pharmaceutically acceptable esters, including C_{1-6} alkyl esters and pharmaceutically acceptable amides, including secondary C_{1-3} alkylamides.

As described herein, for all aspects of the invention, reference to compounds of formula (I) encompasses the pharmaceutically acceptable salts and prodrugs, e.g. esters, thereof.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. Where a compound contains an alkene moiety, the alkene can be presented as a cis or trans isomer or a mixture thereof. When an isomeric form of a compound of the invention is provided substantially free of other isomers, it will preferably contain less than 5% w/w, more preferably less than 2% w/w and especially less than 1% w/w of the other isomers.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing
the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably at least 10% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

The invention also provides processes for preparing a compound of formula (I) from a compound formula (II):

```
R¹
```

```
R²
```

```
R³
```

```
R⁴
```

(II)

wherein \( R^X \) is NO₂, NHR\(^8\), CO₂H or NCO, and \( R^1, R^2, R^3, R^5 \) and \( R^8 \) are as defined for formula (I), by the processes described below.

When \( R^X \) is CO₂H, the group can be protected e.g. as either (i) CO₂CH₂Ph or (ii) CO₂Bu. The CO₂H group may be liberated by reaction with (i) hydrogen and palladium on carbon or (ii) an organic acid, e.g. TFA.

For the following processes a CO₂H substituent on X or Y is suitably protected as an alkyl ester.

A compound of formula (II) where \( R^X \) is NH₂ may be prepared from a corresponding compound of formula (II) where \( R^X \) is NO₂ by methods well known to those skilled in the art, for example hydrogenation with palladium on charcoal catalyst or treatment with Zn and acetic acid. A compound of formula (II) wherein \( R^X \) is NH₂ may be converted to another compound of formula (II) where \( R^X \) is NCO by reaction with, for example, triphosgene. A compound of formula (II) wherein \( R^X \) is NH₂ may be converted to another compound of formula (II) wherein \( R^X \) is NHR\(^8\) and \( R^8 \) is C\(_{1-6}\) alkyl, by an alkylolation or reductive amination reaction using methods well known to those skilled in the art.

Thus the invention provides a process for preparing a compound of formula (I) wherein \( R^4 \) is NR\(^8\)COR\(^9\), comprising treating a compound of formula (II) where \( R^X \) is NHR\(^8\) and \( R^8 \) is as defined for formula (I), with a compound of formula (III):

```
O
```

```
R^9
```

```
OH
```

(III)

wherein \( R^9 \) is as defined for formula (I), in an amide bond formation reaction e.g. by

(i) activation of the carboxylic acid, for example via active ester formation and reaction using, for example DCC/HOBt, TBTU/HOAt or EDC/HOBt in a suitable solvent, e.g. THF, DCM or DMF; or

(ii) conversion to an acid chloride using, for example oxalyl chloride in THF/DMF followed by stirring of the acid chloride in a suitable solvent and base, for example pyridine or a solid supported morpholine.

Compounds of formula (III) may be available through the usual commercial sources and may also be prepared by methods well known to those skilled in the art.

The invention also provides a process for preparing a compound of formula (I) wherein \( R^4 \) is NR\(^8\)CONR\(^9\)\(^R^9\), comprising treating a compound of formula (II) where \( R^X \) is NHR\(^8\) and \( R^8 \) is as defined for formula (I), with a compound of formula (IV):

```
R^8-N====O
```

(IV)

wherein \( R^9 \) is as defined for formula (I), e.g. by stirring at room temperature or with heating in a suitable solvent, for example, THF or DMF.
Alternatively, a compound of formula (II) wherein $R^X$ is NCO is treated with a compound of formula (V):

$$R^8R^9NH$$

(V)

wherein $R^8$ and $R^9$ is as defined for formula (I), e.g. by stirring at room temperature or heating in a suitable solvent, for example THF or DMF.

In a further alternative, a compound of formula (I) wherein $R^4$ is NR$^6$CONR$^2$R$^9$ and $R^8$ and $R^9$ are as defined for formula (I), may be prepared by treating a compound of formula (II) where $R^X$ is NHR$^8$ and $R^9$ is as defined for formula (I), with a chloroformate derivative of formula CICO$_2$R where R is an electron withdrawing group, e.g. p-nitro-phenyl, followed by in situ treatment with a compound of formula (V).

Compounds of formula (I) wherein $R^4$ is NR$^6$SO$_2$R$^9$ and $R^8$ and $R^9$ are as defined for formula (I), may be prepared from a compound of formula (II), wherein $R^X$ is NHR$^8$ and $R^9$ is as defined for formula (I), by reaction with the appropriate sulfonyl chloride, R$^2$SO$_2$Cl where $R^9$ is as defined for formula (I).

Compounds of formula (IV) and (V) may be available through the usual commercial sources. They and their derivatives thereof may also be prepared by methods well known to those skilled in the art.

The invention also provides a process for preparing a compound of formula (I) wherein $R^4$ is W-CONR$^2$R$^9$, where W is a bond, comprising treating a compound of formula (II) wherein $R^X$ is CO$_2$H, with a compound of formula (V) in an amide bond formation reaction as described above.

The compounds of formula (II) wherein $R^X$ is NO$_2$, $R^1$, $R^2$, $R^3$ and $R^4$ are as defined for formula (I) and Z is O or S; may be prepared by treatment of a compound of formula (VIa):

$$\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
\text{NO}_2
\end{array}$$

(VIa)

wherein $R^1$, $R^2$ and $R^3$ are as defined for formula (I) and $R^4$ is CO$_2$H or CHO; with a compound of formula (VII):

$$\begin{array}{c}
X \\
\text{NH}_2 \\
Y \\
\text{ZH}
\end{array}$$

(VII)

wherein X and Y are as defined for formula (I) and Z is O or S; by e.g. either:

(i) heating in a condensation/cyclisation reaction using, for example, polyphosphoric acid; or

(ii) firstly coupling a compound of formula (VIa) to a compound of formula (VII) via either an ester/thioester or amide formation reaction using methods well known to those of skill in the art, followed by direct heating or heating with an acidic media with a suitable solvent to effect cyclisation, for example p-toluenesulfonic acid in toluene. Alternatively, this may be achieved via oxidative cyclisation of a Schiff base, derived from the condensation of the 2-aminophenol or 2-aminothiophenol and aldehydes, using various oxidants such as PhI(OAc)$_2$, Pb(OAc)$_4$ or DDQ.

Compounds of formula (II) wherein $R^X$ is CO$_2$CH$_2$Ph or CO$_2$Bu and Z is O or S, may be prepared by reaction of compounds of formula (VIb):
wherein $R^C$ is CH$_3$Ph or 'Bu and $R^A$ is as defined for formula (VIa), with a compound of formula (VII), by a process analogous to the one described above.

Compounds of formulae (VIa), (VIb) and (VII) may be available through the usual commercial sources. They and derivatives thereof may also be prepared by methods well known to those skilled in the art.

The compounds of formula (II) wherein $R^X$ is NO$_2$ and $Z$ is NR$_8$ may be prepared by treatment of a compound of formula (VIa) with a compound of formula (VIII):

wherein X, Y and $R^8$ are as defined for formula (I), in e.g. the following reactions:

(i) if $R^A$ in compound (VIa) is CO$_2$H, heating in a condensation/cyclisation reaction, using for example polyphosphoric acid; or

(ii) if $R^A$ in compound (VIa) is CHO, heating in acetonitrile followed by oxidation, using for example, O$_2$/FeCl$_3$ (cat.) in acetonitrile.

Likewise, compounds of formula (II) wherein $R^X$ is CO$_2$CH$_3$Ph or CO$_2$'Bu and $Z$ is NHR$_8$, may be prepared by treatment of a compound of formula (VIb) with a compound of formula (VIII) in a process analogous to the one described above.

Compounds of formula (VIII) may be prepared by reduction of compounds of formula (IX):

wherein X, Y and $R^8$ are as defined for formula (I), by methods well known to those skilled in the art, for example, hydrogenation with palladium on a charcoal catalyst or treatment with Zn and acetic acid.

Compounds of formula (IX) may be prepared by nitration of compounds of formula (X):

wherein X, Y and $R^8$ are as defined for formula (I), by methods well known to those skilled in the art, for example fuming nitric acid and sulfuric acid or fuming nitric acid and tin (IV) chloride.

Compounds of formula (X) may be available through the usual commercial sources. They and derivatives thereof may also be prepared by methods well known to those skilled in the art.

Compounds of formula (II) where $R^X$ is NO$_2$ and $R^3$ is halogen at a position ortho or para to the $R^X$ group may be converted to corresponding compounds of formula (II) where $R^3$ is OR$_6$ or NR$_7$R$_8$, by reaction with an alcohol or amine via a nucleophilic aromatic substitution.
Compounds of formula (II) where \( R^4 \) is \( NR^8\text{COR}^9 \) or \( NR^8\text{SO}_2\text{R}^9 \) may be prepared from compounds of formula (II) where \( R^x \) is \( NHR^8 \), where \( R^3 \) is as defined for formula (I), by reaction with the appropriate carboxylic acid/chloride or sulfonyl chloride, \( R^x\text{CO}_2\text{H}/(R^x\text{CO}_2\text{Cl}) \) or \( R^x\text{SO}_2\text{Cl} \) where \( R^9 \) is as defined for formula (I).

A compound of formula (II) wherein one of \( X \) and \( Y \) is substituted with a tetrazole group may be made by the conversion of a corresponding compound wherein one of \( X \) and \( Y \) is substituted with \( \text{CN} \) by reaction with, for example, sodium azide and ammonium chloride in a suitable solvent, e.g. DMF.

Compounds of formula (I) wherein \( R^4 \) is \( W\text{-CONR}^8\text{R}^9 \) and \( W \) is \( \text{C}_{1-6} \) alkylene, \( \text{C}_{2-6} \) alkenylene or \( \text{C}_{2-6} \) alkynylene, may be prepared from compounds of formula (XI) or formula (XII):

\[
\text{(XI)} \quad \text{(XII)}
\]

wherein \( R^1, R^2, R^3 \) and \( R^4 \) are as defined for formula (I), \( \cdots \) represents an optional double bond and \( n \) is 0, 1, 2, 3 or 4, by treating a compound of formula (XI) or formula (XII) with an amine of formula \( HNR^8\text{R}^9 \) wherein \( R^4 \) and \( R^9 \) are as defined for formula (I), in an amide bond forming reaction e.g. by:

(i) activation of the carboxylic acid, for example active ester formation and reaction using, for example \( \text{DCC/ClOBt, TBTr/HOAt or EDC/HOBt} \) in a suitable solvent, e.g. THF, DCM or DMF; or

(ii) conversion to an acid chloride using, for example oxalyl chloride in THF/DMF followed by stirring of the acid chloride in a suitable solvent and base, for example pyridine or a solid supported morpholine.

Compounds of formula (XI) and formula (XII) can be prepared from the corresponding esters of formula (XIII) and formula (XIV), respectively:

\[
\text{(XIII)} \quad \text{(XIV)}
\]

wherein e.g. \( R \) is an aliphatic group, e.g. methyl, ethyl or tert-butyl; a benzyl group or an aromatic group, e.g. phenyl, and \( n \) is as defined for formulae (XI) and (XII), by treatment in a base or acid hydrolysis reaction. In the case when \( R \) is benzyl this ester may also be cleaved to the corresponding carboxylic acid by hydrogenolysis using e.g. hydrogen in the presence of a catalyst, e.g. palladium on carbon.

Compounds of formula (XIIIa) can be prepared from compounds of formula (XIIIb):

\[
\text{(XIIIa)} \quad \text{(XIIIb)}
\]

wherein \( R \) and \( n \) are as defined for formulae (XIII) and (XIV), by hydrogenation in the presence of a catalyst e.g. palladium on carbon or platinum in a suitable solvent such as an alcohol e.g. ethanol.

Compounds of formula (XIIIb) and (XIV) can be prepared from compounds of formula (XV):
wherein Hal is Cl, Br or I, by treatment with a compound of formula (XVI) or formula (XVII):

\[
\begin{align*}
\text{(XVI)} & \quad \underset{(\text{CH}_3)n\text{CO}_2\text{R}}{\text{---}}
\end{align*}
\]

\[
\begin{align*}
\text{(XVII)} & \quad \underset{(\text{CH}_3)n\text{CO}_2\text{R}}{\text{---}}
\end{align*}
\]

wherein R and n are as defined for formulae (XIII) and (XIV), in the presence of palladium (II) acetate catalyst with triethylamine and a phospine ligand, e.g. tri-o-tolyphosphine, in a suitable solvent, e.g. DMF preferably with heating to e.g. 100°C.

Compounds of formula (XV) wherein Z is O or S; can be prepared by reacting a compound of formula (XVIII):

\[
\begin{align*}
\text{(XVIII)} & \quad \underset{\text{Hal}}{\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{Hal}
\end{array}}
\end{align*}
\]

wherein \(\text{R}^4\) is \(\text{CO}_2\text{H}\) or \(\text{CHO}\), with a compound of formula (VII):

\[
\begin{align*}
\text{(VII)} & \quad \begin{array}{c}
\text{NH}_2 \\
\text{Y} \\
\text{Z} \\
\text{H}
\end{array}
\end{align*}
\]

wherein X and Y are as defined for formula (I) and Z is O or S; by e.g. either:
(i) heating in a condensation/cyclisation reaction using for example polyphosphoric acid; or
(ii) firstly coupling a compound of formula (VIIa) to a compound of formula (VII) via either an ester/thioester or amide formation reaction using methods well known to those of skill in the art followed by direct heating or heating with an acidic media with a suitable solvent to effect cyclisation, for example p-toluenesulfonic acid in toluene. Alternatively, this may be achieved via oxidative cyclisation of a Schiff base, derived from the condensation of the 2-aminophenol or 2-aminothiophenol and aldehydes, using various oxidants such as \(\text{Ph}(\text{OAc})_2\), \(\text{Pb}(\text{OAc})_4\) or DDQ.

Compounds of formula (XV) wherein Z is \(\text{NR}^5\), may be prepared by treatment of a compound of formula (XVIII) with a compound of formula (VIII):

\[
\begin{align*}
\text{(VIII)} & \quad \begin{array}{c}
\text{NH}_2 \\
\text{Y} \\
\text{NHR}^8
\end{array}
\end{align*}
\]

wherein X, Y and \(\text{R}^8\) are as defined for formula (I), in e.g. the following reactions:
(i) if \(\text{R}^4\) in compound (XVIII) is \(\text{CO}_2\text{H}\), heating in a condensation/cyclisation reaction, using for example polyphosphoric acid; or
(ii) if \(\text{R}^4\) in compound (XVIII) is \(\text{CHO}\), heating in acetonitrile followed by oxidation, using for example, \(\text{O}_2/\text{FeCl}_3\) (cat.) in acetonitrile.

Compounds of formula (XVIII) may be commercially available or readily prepared by methods well known to those skilled in the art.
During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2 nd edition, 1991).

Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable salts and prodrugs thereof.

Any novel intermediate compounds as described herein also fall within the scope of the present invention. In particular the invention provides a compound of formula (II):

\[
\begin{align*}
\text{(II)} \\
R^1 & \equiv \quad R^2 \\
R^3 & \quad R^4 \\
R^5 & \quad R^6
\end{align*}
\]

wherein \(R^x\) is NO₂, NHR³, CO₂H or NCO, and \(R^1, R^2, R^3, R^5\) and \(R^8\) are as defined for formula (I).

The invention also provides the novel intermediate compounds of formulae (XI), (XII), (XIII), (XIV) and (XV). In particular the invention provides a compound of formula (XI) or formula (XII):

\[
\begin{align*}
\text{(XI)} & \quad \text{wherein } R^1, R^2, R^3 \text{ and } R^4 \text{ are as defined for formula (I), } n \text{ represents an optional double bond and } n \text{ is 0, 1, 2, 3 or 4, or an ester thereof.} \\
\text{(XII)} & \quad \text{Preferred intermediate compounds of the invention include the intermediate compounds defined in the Examples.}
\end{align*}
\]

The invention also provides a compound of formula (I) when prepared by any of the above mentioned methods.

The pharmaceutically effective compounds of formula (I) and pharmaceutically acceptable salts and prodrugs thereof, may be administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") with standard pharmaceutical carriers or excipients according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, together with one or more pharmaceutically acceptable carriers or excipients.
The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318, (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, impregnated dressings, sprays, aerosols or oils and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

For applications to the eye or other external tissues, for example the mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.
It should be understood that in addition to the ingredients particularly mentioned above, the formulations may also include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The pharmaceutical formulations according to the invention are preferably adapted for oral administration.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the active ingredient and a sterile vehicle, water being preferred. The active ingredient, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the active ingredient can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the active ingredient is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The active ingredient can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, e.g. from 10-60% by weight, of the active ingredient, depending on the method of administration.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per dose. Such a unit may contain for example 100mg/kg to 1mg/kg depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.
It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e. the number of doses of the compound of formula (I) given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The compounds of the present invention are useful in that they are capable of inhibiting heparanase. Thus, the compounds can be used in the treatment of cancer.

The compounds of the present invention can also be used in combination with one or more additional treatments or therapeutic compounds for cancer. Examples of such treatments include, surgery and radiation therapy. Examples of therapeutic compounds include but are not limited to cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil, paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, tamoxifen, toremifene, megestrol acetate, anastrozole, goserelin, anti-HER2 monoclonal antibody, capecitabine and raloxifene hydrochloride.

The compounds of the present invention can also be used in the treatment of angiogenesis and angiogenesis dependent diseases which include angiogenesis associated with the growth of solid tumours and retinopathy.

The compounds of the present invention can also be used in combination with one or more additional treatments or therapeutic compounds for angiogenesis. Examples of such other therapeutic compounds include but are not limited to recombinant platelet-derived growth factor-BB (Regranex™).

The compounds of the present invention can also be used in the treatment of inflammatory conditions including but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing.

The compounds of the present invention can also be used in the treatment of autoimmune diseases such as but not limited to multiple sclerosis.

The compounds of the present invention can also be used in the treatment of cardiovascular diseases such as but not limited to blood clotting conditions, for example thromboembolic disease, arterial thrombosis and restenosis.

By the term "treating" is meant either prophylactic or therapeutic therapy.

The term cancer or "carcinoma" is a malignant new growth that arises from epithelium, found in skin or, more commonly, the lining of body organs. Carcinomas tend to infiltrate into adjacent tissues and spread (metastasise) to distant organs, for example to bone, liver, lung or the brain. Herein, cancer includes both metastatic tumour cells and tissue and examples include, but not limited to, melanoma, mesothelioma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma, mastocytoma and the following tissue carcinomas: colorectal, colon, prostate, lung, breast, pancreatic, intestinal, renal, gastric, bladder, ovarian, uterine, cervical, hepatic and stomach.

In additional aspects, therefore, the present invention provides:
(i) the use of a compound of formula (I) as an inhibitor of the enzyme heparanase.
(ii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of cancer.
(iii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of angiogenesis and angiogenesis dependent diseases which include angiogenesis associated with the growth of solid tumours and retinopathy.
(iv) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of inflammatory conditions such as but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing.

(v) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of autoimmune diseases such as but not limited to multiple sclerosis.

(vi) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of cardiovascular diseases such as but not limited to blood clotting conditions, for example thromboembolic disease, arterial thrombosis and restenosis.

(vii) a method for the treatment of cancer which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(viii) a method for the treatment of angiogenesis and angiogenesis dependent diseases, which include angiogenesis associated with the growth of solid tumours and retinopathy, which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(ix) a method for the treatment of inflammatory diseases, such as but not limited to rheumatoid arthritis, inflammatory bowel disease, and wound healing which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(x) a method for the treatment of autoimmune diseases, such as but not limited to multiple sclerosis, which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(xi) a method for the treatment of cardiovascular diseases, such as but not limited to blood clotting conditions, for example thromboembolic disease, arterial thrombosis and restenosis which comprises the step of administering to a patient an effective amount of a compound of formula (I).

The invention also provides the use of a compound of formula (I) in the treatment of any of the above mentioned conditions.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention will now be described by reference to the following examples, which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Examples

Example 1: 2-[3-[(4-Bromobenzoyl)amino]phenyl]-5-benzoazoleacetic acid

a) 3-Nitro-4-hydroxyphenylacetic acid methyl ester

\[
\text{MeO}_2\text{C} \quad \begin{array}{c}
\text{NO}_2 \\
\text{OH}
\end{array}
\]

A solution of 4-hydroxy-3-nitropherylacetic acid (5.03g, 25.5mmol) in methanolic hydrochloric acid (60ml) was heated to reflux overnight. The reaction was cooled to room temperature and then concentrated. The residue was diluted with ethyl acetate (150ml) and washed with saturated aqueous sodium hydrogencarbonate solution (200ml). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (2×75ml). The organic fractions were combined and washed with saturated sodium chloride solution (100ml), dried (Na$_2$SO$_4$) and concentrated to give the subtitle compound 5.23g (97%). $^1$H NMR (DMSO) $\delta$ 3.62 (3H, s), 3.70 (2H, s), 7.09 (1H, d), 7.45 (1H, dd), 7.82 (1H, d), 10.86 (1H, bs).

b) 3-Amino-4-hydroxyphenylacetic acid methyl ester
To a stirred solution of 3-nitro-4-hydroxyphenylacetic acid methyl ester (5.23g, 24.8mmol) in a 1:1 mixture of ethyl acetate/ethanol (150ml) under argon was added 10% palladium on activated carbon (300mg). The reaction vessel was purged with hydrogen and stirred for 3 days. The mixture was filtered through celite and washed with 1:1 ethyl acetate/ethanol (150ml). The solvent was removed under reduced pressure to give the subtitle compound, 4.47g (99%). $^1$H NMR (DMSO) δ 3.38 (2H, s), 3.57 (3H, s), 4.48 (1H, bs), 6.26 (1H, dd), 6.48 (1H, d), 6.55 (1H, d), 8.87 (1H, bs).

c) 3-[(3-Nitro)benzoylamino]-4-hydroxyphenylacetic acid methyl ester

To a stirred suspension of 3-amino-4-hydroxyphenylacetic acid methyl ester (4.46g, 24.6mmol) in dichloromethane (150ml) under argon was added triethylamine (6.92ml, 49.2mmol) followed by a solution of 3-nitrobenzoyl chloride (4.57g, 24.6mmol) in dichloromethane (50ml). After stirring overnight the solution was diluted with water (200ml) and the organic layer separated. The aqueous layer was further extracted with dichloromethane (2x50ml) and the organic fractions were combined, washed with saturated aqueous sodium hydrogencarbonate solution (100ml), 2M hydrochloric acid solution (100ml), saturated sodium chloride solution (100ml), dried (Na$_2$SO$_4$) and concentrated to give the subtitle compound, 5.55g (68%). $^1$H NMR (DMSO) δ 3.59 (2H, s), 3.61 (3H, s), 6.85 (1H, d), 6.98 (1H, dd), 7.49 (1H, s), 7.83 (1H, t), 8.38-8.45 (2H, m), 8.78 (1H, s), 9.63 (1H, s), 9.95 (1H, s).

d) 2-[(3-Nitro)phenyl]-5-benzoxazoleacetic acid methyl ester

To a stirred suspension of 3-[(3-nitro)benzoylamino]-4-hydroxyphenylacetic acid methyl ester (5.55g, 16.8mmol) in toluene (160ml) was added p-toluenesulfonic acid monohydrate (6.71g, 35.26mmol). A Dean Stark trap was fitted and the reaction was refluxed overnight. The reaction was cooled to room temperature and the volume of solvent was reduced to 100ml. The mixture was diluted with ethyl acetate (200ml) and washed with saturated aqueous sodium hydrogencarbonate solution (200ml). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (2x100ml). The organic fractions were combined and washed with water (200ml), saturated sodium chloride solution (200ml), dried (Na$_2$SO$_4$) and concentrated to give the subtitle compound, 2.54g (48%). $^1$H NMR (DMSO) δ 3.64 (3H, s), 3.87 (2H, s), 7.40 (1H, dd), 7.77-7.81 (2H, m), 7.92 (1H, t), 8.46 (1H, m), 8.60 (1H, d), 8.86 (1H, t).

e) 2-[(3-Amino)phenyl]-5-benzoxazoleacetic acid methyl ester

To a stirred solution of 2-[(3-nitro)phenyl]-5-benzoxazoleacetic acid methyl ester (2.53g, 8.10mmol) in 1,4-dioxane (100ml) under argon was added 10% palladium on activated carbon (300mg). The reaction vessel was purged with hydrogen and stirred overnight. The mixture was filtered through celite and washed with ethyl acetate (100ml). The solvent was removed under reduced pressure to give the subtitle
compound, 2.13g (93%). \( ^1H \) NMR (DMSO) \( \delta \) 3.63 (3H, s), 3.83 (2H, s), 5.50 (2H, bs), 6.79 (1H, m), 7.22 (1H, t), 7.28-7.34 (2H, m), 7.43 (1H, t), 7.67-7.71 (2H, m).

f) 2-[3-[(4-Bromobenzoyl)amino]phenyl]-5-benzoxazoleacetic acid

![Chemical Structure]

To a solution of 2-[(3-amino)phenyl]-5-benzoxazoleacetic acid methyl ester (0.1g, 0.35mmol) in tetrahydrofuran (3ml) was added morpholine (polymer-bound 1% cross-linked w/dvb, Aldrich Chemical Company, UK, 2.5-4.0 mmol N/g loading, 200mg) followed by a solution of 4-bromobenzoyl chloride (0.12g, 0.53mmol) in tetrahydrofuran (2ml) and the mixture was shaken overnight. Tris-(2-aminoethyl)-amine polystyrene resin (200-200 mesh, Novabiochem, UK, 3.4mmol/g substitution, 200mg) was added and the mixture was shaken for 6 h. The resin was removed by filtration and the filtrate concentrated. The residue was dissolved in THF (2.5ml), a solution of LiOH (30mg, 1.1mmol) in water (0.5ml) was added and the reaction was stirred vigorously overnight. The resulting suspension was acidified with 2M hydrochloric acid, diluted with water (5ml) and the precipitate collected by filtration to give the title compound, 50mg (49%). \( ^1H \) NMR (DMSO) \( \delta \) 3.73 (2H, s), 7.34 (1H, d), 7.60 (1H, t), 7.71-7.79 (4H, m), 7.93-8.04 (4H, m), 8.75 (1H, s), 10.58 (1H, s), 12.35 (1H, bs). MS (APCI-) \( m/z \) 448.6, 451.0.

**Examples 2-20**

The following compounds were prepared according to the method of Example 1f) using the corresponding acid chloride.

<table>
<thead>
<tr>
<th>Example</th>
<th>R</th>
<th>( ^1H ) NMR (DMSO) ( \delta )</th>
<th>MS (APCI-) ( m/z )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2#</td>
<td>![Chemical Structure]</td>
<td>3.74 (2H, s), 7.29-7.36 (2H, m), 7.55 (1H, dt), 7.63 (1H, t), 7.74 (2H, m), 7.95 (2H, m), 8.07 (1H, d), 8.59 (1H, s), 8.74 (1H, s), 10.86 (1H, s), 12.47 (1H, bs)</td>
<td>445.0</td>
</tr>
<tr>
<td>3#</td>
<td>![Chemical Structure]</td>
<td>3.74 (2H, s), 7.35 (1H, dd), 7.52-7.83 (8H, m), 8.03 (2H, m), 8.74 (1H, s), 11.12 (1H, s), 12.42 (1H, bs)</td>
<td>471.9</td>
</tr>
<tr>
<td>4#</td>
<td>![Chemical Structure]</td>
<td>2.65 (3H, s), 3.74 (2H, s), 7.23 (1H; dd), 7.34 (1H, dd), 7.60 (1H, t), 7.71-7.84 (4H, m), 7.90-7.97 (2H, m), 8.68 (1H, s), 10.51 (1H, s), 12.43 (1H, bs)</td>
<td>474.0</td>
</tr>
<tr>
<td>5#</td>
<td>![Chemical Structure]</td>
<td>2.40 (3H, s), 3.75 (2H, s), 7.33-7.40 (3H, m), 7.63 (1H, t), 7.72-7.77 (2H, m), 7.97 (1H, d), 8.09 (2H, d), 8.17 (1H, d), 8.50 (1H, s), 8.83 (1H, s), 10.55 (1H, s), 12.45</td>
<td>468.1</td>
</tr>
<tr>
<td>Example</td>
<td>R</td>
<td>$^1$H NMR (DMSO) $\delta$</td>
<td>MS (APCI-) m/z</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
<td>----------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>3.74 (2H, s), 7.34 (1H, dd), 7.58-7.76 (5H, m), 7.94 (1H, d), 8.02-8.07 (3H, m), 8.76 (1H, s), 10.61 (1H, s), 12.46 (1H, bs)</td>
<td>404.9</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2.41 (3H, s), 3.73 (2H, s), 7.33 (1H, dd), 7.58 (1H, t), 7.70-7.78 (4H, m), 7.85 (1H, d), 7.93-8.00 (3H, m), 8.61 (1H, s), 8.78 (1H, s), 10.62 (1H, s), 12.41 (1H, bs)</td>
<td>566.3</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>3.71 (2H, s), 3.72 (2H, s), 7.32 (1H, dd), 7.40 (4H, s), 7.54 (1H, t), 7.68-7.78 (3H, m), 7.87 (1H, d), 8.59 (1H, s), 10.52 (1H, s)</td>
<td>418.7</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>2.38 (3H, s), 2.69 (3H, s), 3.74 (2H, s), 7.33-7.37 (3H, m), 7.61 (1H, t), 7.74 (2H, m), 7.92 (4H, m), 8.69 (1H, s), 10.53 (1H, s), 12.47 (1H, bs)</td>
<td>482.1</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>3.74 (2H, s), 7.34 (1H, dd), 7.62 (1H, t), 7.74 (2H, m), 7.96 (3H, d), 8.04 (1H, d), 8.22 (2H, d), 8.77 (1H, s), 10.77 (1H, s)</td>
<td>439.0</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>2.62 (3H, s), 3.74 (2H, s), 7.35 (1H, dd), 7.50 (1H, m), 7.59-7.66 (3H, m), 7.71-7.77 (2H, m), 7.97 (1H, d), 8.07 (1H, d), 8.16 (2H, d), 8.84 (1H, s), 10.69 (1H, s), 12.45 (1H, bs)</td>
<td>452.0</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>3.73 (2H, s), 7.34 (1H, dd), 7.63 (1H, t), 7.71-7.78 (3H, m), 7.86-7.99 (4H, m), 8.73 (1H, s), 10.94 (1H, s)</td>
<td>457.0</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>2.71 (3H, s), 3.74 (2H, s), 7.34 (1H, dd), 7.55-7.64 (2H, m), 7.71-7.77 (2H, m), 7.92-8.04 (3H, m), 8.19 (1H, d), 8.68-8.72 (2H, m), 10.59 (1H, s), 12.40 (1H, bs)</td>
<td>469.0</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>3.74 (2H, s), 7.34 (1H, dd), 7.51-7.64 (2H, m), 7.71-7.76 (2H, m), 7.84 (1H, dd), 7.95 (1H, d), 8.00-8.05 (2H, m), 8.22 (1H, s), 8.75 (1H, s), 10.63 (1H, s)</td>
<td>450.8</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>3.69 (1H, t), 3.74 (2H, s), 4.99 (2H, d), 6.94 (1H, d), 7.23 (1H, d), 7.34 (1H, dd), 7.49 (1H, dd), 7.59 (1H, t), 7.66-7.80 (4H, m), 7.86-7.92 (2H, m), 8.71 (1H, s), 10.53 (1H, s), 12.45 (1H, bs)</td>
<td>484.9</td>
</tr>
<tr>
<td>Example</td>
<td>R</td>
<td>$^1$H NMR (DMSO) $\delta$</td>
<td>MS (APCI-) $m/z$</td>
</tr>
<tr>
<td>---------</td>
<td>---</td>
<td>--------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>16</td>
<td><img src="image1" alt="Structure" /></td>
<td>3.74 (2H, s), 7.34 (1H, dd), 7.55-7.68 (5H, m), 7.71-7.76 (3H, m), 7.82-7.85 (2H, m), 7.91 (1H, d), 8.09 (1H, d), 8.69 (1H, s), 10.34 (1H, s), 12.42 (1H, bs)</td>
<td>464.0</td>
</tr>
<tr>
<td>17</td>
<td><img src="image2" alt="Structure" /></td>
<td>3.66 (1H, t), 3.74 (2H, s), 4.97 (2H, d), 6.88 (1H, d), 7.09 (1H, t), 7.20 (1H, d), 7.34 (1H, dd), 7.43 (1H, dt), 7.56-7.66 (2H, m), 7.71-7.76 (2H, m), 8.6-7.91 (3H, m), 8.71 (1H, s), 10.53 (1H, s), 12.43 (1H, bs)</td>
<td>451.0</td>
</tr>
<tr>
<td>18</td>
<td><img src="image3" alt="Structure" /></td>
<td>3.74 (2H, s), 7.35 (1H, dd), 7.57-7.66 (4H, m), 7.72-7.77 (2H, m), 7.97 (1H, d), 8.16-8.22 (3H, m), 8.55 (1H, s), 8.84 (1H, s), 10.58 (1H, s), 12.42 (1H, bs)</td>
<td>454.0</td>
</tr>
<tr>
<td>19</td>
<td><img src="image4" alt="Structure" /></td>
<td>3.73 (2H, s), 4.00 (2H, s), 7.32 (1H, dd), 7.43 (1H, dd), 7.56 (1H, t), 7.68-7.79 (4H, m), 7.89 (1H, d), 8.01-8.06 (2H, m), 8.61 (1H, s), 10.60 (1H, s), 12.41 (1H, bs)</td>
<td>475.1</td>
</tr>
<tr>
<td>20</td>
<td><img src="image5" alt="Structure" /></td>
<td>3.78 (2H, s), 4.49 (1H, s), 7.38 (1H, dd), 7.65 (1H, t), 7.71 (2H, d), 7.75 (1H, s), 7.78 (1H, d), 7.98 (1H, d), 8.07 (3H, d), 8.81 (1H, s), 10.66 (1H, s)</td>
<td>395.1</td>
</tr>
</tbody>
</table>

*Carboxylic acids were converted to their corresponding acid chlorides before use.

Example 21: 2-[[3-[(4-Bromobenzoyl)amino]-4-methoxy]phenyl]-5-benzoxazoleacetic acid

### a) 2-[[3-Nitro-4-methoxy]phenyl]-5-benzoxazoleacetic acid methyl ester

![Structure](image6)

Prepared by the method of Example 1c) and 1d), from 3-nitro-4-methoxybenzoyl chloride (215mg, 1mmol) and 3-amino-4-hydroxyphenylacetic acid (167mg, 1.0mmol) the subtitle compound was obtained, 154mg (45%). MS (APCI-) $m/z$: 342.3.

### b) 2-[[3-Amino-4-methoxy]phenyl]-5-benzoxazoleacetic acid methyl ester

![Structure](image7)

Prepared by the method of Example 1e) from 2-[[3-nitro-4-methoxy]phenyl]-5-benzoxazoleacetic acid methyl ester (154mg, 0.45mmol) the subtitle compound was obtained, 125mg (89%). MS (APCI+) $m/z$: 313.3.

### c) 2-[[3-[(4-Bromobenzoyl)amino]-4-methoxy]phenyl]-5-benzoxazoleacetic acid methyl ester
4-Bromobenzoyl chloride (49mg, 0.23mmol) was added to a solution of 2-[(3-amino-4-methoxy)phenyl]-5-benzoxazoleacetic acid methyl ester (47mg, 0.15mmol) in THF (5ml) containing morpholine (polymer-bound 1% cross-linked w/dvb, Aldrich Chemical Company, UK, 2.5-4.0 mmol N/g loading, 200mg). After shaking overnight, Tris-(2-aminoethyl)-amine polystyrene resin (200-200 mesh, Novabiochem, UK, 3.4mmol/g substitution, 200mg) was added and the mixture was shaken for 6 h. The resin was removed by filtration and the filtrate was concentrated to give the subtitle compound, 64mg (87%). MS (APCI-m/z): 494.9.

d) 2-[[3-[(4-Bromobenzoyl)amino]-4-methoxy]phenyl]-5-benzoxazoleacetic acid

A solution of lithium hydroxide (16mg, 0.65mmol) in water (1ml) was added to a solution of 2-[[3-[(4-bromobenzoyl)amino]-4-methoxy]phenyl]-5-benzoxazoleacetic acid methyl ester (64mg, 0.13mmol) in THF (3ml). After stirring overnight the reaction was acidified with 2M HCl, the precipitate was filtered and dried under vacuum to give the title compound, 54mg (86%). $^1$H NMR (DMSO) $\delta$ 3.72 (2H, s), 3.96 (3H, s), 7.29 (1H, dd), 7.34 (1H, d), 7.66 (1H, s), 7.70 (1H, d), 7.77 (2H, d), 7.85 (1H, d), 7.94 (2H, d), 8.05 (1H, d). MS (APCI-m/z): 478.8, 480.9.

a) 3-Hydroxy-4-[[3-nitrobenzoyl]amino]benzoic acid methyl ester

To a stirred solution of methyl 4-amino-3-hydroxybenzoate (4.09g, 24.5mmol) in ethyl acetate (50ml) was added triethylamine (6.88ml, 49.0mmol) followed by a solution of 3-nitrobenzoyl chloride (5.0g, 26.9mmol) in ethyl acetate (30ml). After stirring overnight the reaction was filtered and the solid triturated with 2M hydrochloric acid, filtered, washed with water and dried under vacuum to give the subtitle compound, 4.9g (64%). $^1$H NMR (DMSO) $\delta$ 3.84 (3H, s), 7.49 (1H, dd), 7.54 (1H, d), 7.84 (1H, t), 7.93 (1H, d), 8.38-8.46 (2H, m), 8.76 (1H, s), 10.01 (1H, bs), 10.36 (1H, bs).

b) 2-(3-Nitrophenyl)benzoxazolyl-5-carboxylic acid methyl ester
3-Hydroxy-4-(3-nitrobenzoylamino)benzoic acid methyl ester (7.39g) was heated to 230°C overnight. The resulting solid was suspended in dichloromethane and sonicated. The mixture was filtered and the filtrate concentrated. The residue was purified by flash column chromatography (using dichloromethane as eluent) to give the subtitle compound, 1.65g (24%). ¹H NMR (DMSO) δ 3.91 (3H, s), 7.91-7.98 (2H, m), 8.05 (1H, dd), 8.36 (1H, s), 8.50 (1H, m), 8.62 (1H, d), 8.86 (1H, t).

c) 2-(3-Aminophenyl)-benzoxazolyl-5-carboxylic acid methyl ester

Prepared by the method of Example 1e) from 2-(3-nitrophenyl)benzoxazolyl-5-carboxylic acid methyl ester (1.50g) the subtitle compound was obtained, 1.36g (100%). ¹H NMR (DMSO) δ 3.90 (3H, s), 5.53 (2H, bs), 6.83 (1H, m), 7.26 (1H, t), 7.38 (1H, m), 7.47 (1H, t), 7.88 (1H, d), 8.02 (1H, dd), 8.28 (1H, d).

d) 2-[3-[(4-Bromophenyl)amino]carbonylamino]phenyl]benzoxazolyl-5-carboxylic acid methyl ester

4-Bromophenylisocyanate (73mg, 0.37mmol) was added to a solution of 2-(3-aminophenyl)-benzoxazolyl-5-carboxylic acid methyl ester (50mg, 0.19mmol) in THF and the reaction heated to 40°C overnight. The reaction was concentrated to give the subtitle compound, 87mg (96%). MS (APCI-) m/z: 464.0, 465.9.

e) 2-[3-[(4-Bromophenyl)amino]carbonylamino]phenyl]benzoxazolyl-5-carboxylic acid

Lithium hydroxide (22mg, 0.93mmol) in water (1ml) was added to a solution of 2-[3-[(4-bromophenyl)amino]carbonylamino]phenyl]benzoxazolyl-5-carboxylic acid methyl ester (87mg, 0.18mmol) in THF. After stirring at room temperature overnight the reaction was acidified with 2M HCl and the precipitate filtered and dried under vacuum to give the title compound, 31mg (41%). ¹H NMR (DMSO) δ 7.48 (4H, s), 7.52-7.62 (2H, m), 7.85-7.91 (2H, m), 8.04 (1H, dd), 8.30 (1H, s), 8.55 (1H, s), 8.94 (1H, bs), 9.11 (1H, bs), 13.16 (1H, bs). MS (APCI-) m/z: 449.6, 451.8.

Example 23: 2-[3-(4-Bromobenzoylamino)phenyl]-5-α-methyl-benzoxazoloeacetic acid
a) 2-[(3-Nitrophenyl)-5-α-methyl-benzoxazolylacetic acid methyl ester

To a solution of tetrabutylammonium hydrogen sulfate (0.65g, 1.91mmol) and sodium hydroxide (0.15g, 3.82mmol) in water (10ml) was added a solution of [2-(3-nitrophenyl)benzoxazolyl-5-yl]acetic acid methyl ester (0.30g, 0.95mmol) in dichloromethane (10ml) followed by iodomethane (0.48ml, 7.63mmol). The reaction was stirred vigorously for 3 days. The dichloromethane layer was separated and the solvent was removed under reduced pressure. The residue was triturated with diethyl ether (70ml) filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (using petrol/ethylacetate 5:2 as eluent) to give the subtitle compound, 17mg (16%). 1H NMR (DMSO) δ 1.48 (3H, d), 3.60 (3H, s), 4.02 (1H, q), 7.42 (1H, dd), 7.78-7.83 (2H, m), 7.93 (1H, t), 8.48 (1H, m), 8.61 (1H, d), 8.86 (1H, m).
b) 2-[(3-Amino)phenyl]-5-α-methyl-benzoxazolylacetic acid methyl ester

Prepared by the method of Example 1e) from 2-[(3-nitrophenyl)-5-α-methyl-benzoxazolylacetic acid methyl ester (62mg, 2.0mmol) the subtitle compound was obtained 57mg (100%). 1H NMR (DMSO) δ 1.46 (3H, d), 3.59 (3H, s), 3.97 (1H, q), 5.50 (2H, bs), 6.79 (1H, m), 7.22 (1H, t), 7.32 (2H, m), 7.42 (1H, m), 7.67-7.72 (2H, m).
c) 2-[3-(4-Bromobenzoylamino)phenyl]-5-α-methyl-benzoxazolylacetic acid

Prepared by the method of Example 1f) from 2-[(3-amino)phenyl]-5-α-methyl-benzoxazolylacetic acid methyl ester (57mg, 0.19mmol) and 4-bromobenzoyl chloride (63mg, 0.29mmol) the title compound was obtained, 53mg (75%). 1H NMR (DMSO) δ 1.44 (3H, d), 3.86 (1H, q), 7.38 (1H, dd), 7.61 (1H, t), 7.72-7.80 (4H, m), 7.93-8.04 (4H, m), 8.75 (1H, s), 10.61 (1H, s), 12.42 (1H, bs). MS (APCI)-m/z: 463.0, 464.8.

Example 24: 2-[2-Chloro-4-[(4-bromo)phenylacryloylamino]phenyl]-5-benzoxazolylacetic acid
a) 3-[(2-Chloro-4-nitro)benzoyl]amino]-4-hydroxy-phenylacetic acid methyl ester

To a stirred solution of methyl 3-amino-4-hydroxyphenylacetate (0.5g, 2.76mmol) in tetrahydrofuran (10ml) under argon was added a solution of 2-chloro-4-nitrobenzoyl chloride (0.61g, 2.76mmol) in
tetrahydrofuran (10ml). After stirring overnight the solvent was removed under reduced pressure and the product was used directly in the next step.

b) 2-[(2-Chloro-4-nitrophenyl)-5-benzoazoleacetic acid methyl ester

\[
\text{MeO}_2\text{C} \quad \text{Cl} \quad \text{N} \quad \text{O} \quad \text{NO}_2
\]

To a stirred suspension of Example 24a) (1g, 2.76mmol) in toluene (25ml) was added para-toluensulfonic acid monohydrate (1.1g, 5.80mmol). A Dean Stark trap was fitted and the reaction was refluxed at 160°C for 2 h and then allowed to cool to room temperature. The mixture was partitioned with ethyl acetate (100ml) and saturated aqueous sodium hydrogencarbonate solution (100ml). The organic layer was removed and the aqueous layer was further extracted with ethyl acetate (100ml). The organic fractions were combined and washed with water (100ml), saturated sodium chloride solution (50ml), dried (Na$_2$SO$_4$) and concentrated to give the subtitle compound (0.71g, 75%). $^1$H NMR (DMSO) $\delta$ 3.64 (3H, s), 3.88 (2H, s), 7.45 (1H, dd), 7.83 (2H, m), 8.38 (1H, dd), 8.46 (1H, d), 8.52 (1H, d).

c) 2-[(2-Chloro-4-amino)phenyl]-5-benzoazoleacetic acid methyl ester

\[
\text{MeO}_2\text{C} \quad \text{Cl} \quad \text{N} \quad \text{O} \quad \text{NH}_2
\]

To a suspension of Example 24b) (0.71g, 2.06mmol) in a 1:1 mixture of acetic acid / ethanol (60ml) was added zinc dust (1.35g, 20.6mmol). After 3.5 h the zinc salts were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was diluted with dichloromethane (100ml) and neutralised with saturated aqueous sodium hydrogencarbonate solution (3 x 50ml), washed with saturated sodium chloride solution, dried (Na$_2$SO$_4$) and concentrated to give a brown foam (0.56g, 87%). $^1$H NMR (DMSO) $\delta$ 3.63 (3H, s), 3.81 (2H, s), 6.20 (2H, bs), 6.66 (1H, dd), 6.77 (1H, d), 7.26 (1H, dd), 7.64 (2H, m), 7.86 (1H, d).

d) 2-[2-Chloro-4-[3-(4-bromophenyl)acryloylamino]phenyl]-5-benzoazoleacetic acid methyl ester

\[
\text{MeO}_2\text{C} \quad \text{Cl} \quad \text{N} \quad \text{O} \quad \text{NH} \quad \text{H} \quad \text{Br}
\]

To a solution of Example 24c) (0.36g, 1.12mmol) in pyridine (5ml) was added a suspension of 4-bromocinnamoyl chloride in pyridine (5ml). After stirring overnight the pyridine was removed under reduced pressure and the residue was partitioned between ethylacetate (100ml) and 2M HCl (50ml). The organic layer was removed and the aqueous layer was further extracted with ethylacetate (2 x 50ml). The combined organic fractions were washed with saturated sodium chloride solution (50ml), saturated aqueous sodium hydrogencarbonate solution (2 x 50ml), saturated sodium chloride solution (50ml), dried (Na$_2$SO$_4$) and concentrated to yield a brown solid. The crude compound was triturated with ethylacetate / petrol to yield a yellow powder (0.17g, 29%). $^1$H NMR (DMSO) $\delta$ 3.64 (3H, s), 3.85 (2H, s), 6.86 (1H, d), 7.36 (1H, dd), 7.60-7.68 (5H, m), 7.73-7.80 (3H, m), 8.16-8.18 (2H, m), 10.75 (1H, bs). MS (APCI negative) 522.8, 525.3.

e) 2-[2-Chloro-4-[3-(4-bromophenyl)acryloylamino]phenyl]-5-benzoazoleacetic acid

\[
\text{HO}_2\text{C} \quad \text{Cl} \quad \text{N} \quad \text{O} \quad \text{NH} \quad \text{H} \quad \text{Br}
\]
A solution of lithium hydroxide (0.023g, 0.95mmol) in water (0.5ml) was added to a solution of Example 24d) (0.1g, 0.19mmol) in tetrahydrofuran (2.5ml) and the reaction was stirred vigorously overnight. The resulting suspension was acidified with 2M hydrochloric acid and the precipitate was collected by filtration to yield the title compound as a yellow powder (0.064g, 66%). 1H NMR (DMSO) δ 3.74 (2H, s), 6.85 (1H, d), 7.35 (1H, dd), 7.60-7.79 (8H, m), 8.18 (2H, m), 10.73 (1H, s), 12.37 (1H, bs). MS (APCI positive) 511.0, 513.1.

Example 25: trans 2-[4-(3-(4-Bromophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 4-Hydroxy-3-(3-fluoro-4-nitrobenzoylamo)phenylacetic acid methyl ester
Prepared by the method of Example 1c), from 4-hydroxy-3-aminophenylacetic acid methyl ester (14.6g, 80.8mmol) and 3-fluoro-4-nitrobenzoyl chloride (16.5g, 80.8mmol) the subtitle compound was obtained (28.2g, 100%). The crude product was used directly in the next reaction without purification.

b) 2-(3-Fluoro-4-nitrophenyl)benzoxazol-5-ylacetic acid methyl ester
Prepared by the method of Example 1d), from 4-hydroxy-3-(3-fluoro-4-nitrobenzoylamino)phenylacetic acid methyl ester (28.2g, 80.8mmol) the subtitle compound was obtained (20.4g, 76%). 1H NMR (DMSO) δ 8.38 (t, 1H), 8.27 (dd, 1H), 8.21 (d, 1H), 7.80 (m, 2H), 7.43 (dd, 1H), 3.87 (s, 2H), 3.63 (s, 3H).

c) 2-(3-Fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester
Prepared by the method of Example 1e), from 2-(3-fluoro-4-nitrophenyl)benzoxazole-5-yl]acetic acid methyl ester (20.4g, 61.8mmol) the subtitle compound was obtained (14.4g, 77%). 1H NMR (DMSO) δ 7.22 (m, 2H), 7.61 (m, 2H), 7.23 (dd, 1H), 6.90 (t, 1H), 6.05 (m, 1H), 3.80 (s, 2H), 3.62 (s, 3H).

d) trans 3-(4-Bromophenyl)-2-propenoic acid chloride
Oxalyl chloride (109µl, 1.25mmol) was added dropwise to a solution of trans 3-(4-bromophenyl)-2-propenoic acid (57mg, 0.25mmol) in THF containing DMF (1 drop). After 30 min the reaction was concentrated to give the subtitle compound (61mg, 100%). The crude product was used directly in the next reaction without purification.

e) trans 2-[4-(3-(4-Bromophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(4-bromophenyl)-2-propenoic acid chloride (61mg, 0.25mmol) the title compound was obtained (35mg, 42%). 1H NMR (DMSO) δ 12.36 (s, 1H), 10.30 (s, 1H), 8.53 (m, 1H), 8.03 (m, 2H), 7.72-7.58 (m, 7H), 7.33 (dd, 1H), 7.20 (dd, 1H), 3.73 (s, 2H). MS: 497m/z (M+H)+.

Example 26: trans 2-[4-(3-(3-Bromophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(3-Bromophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(4-bromophenyl)-2-propenoic acid (113mg, 0.50mmol) the subtitle compound was obtained (123mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-(3-(3-Bromophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid
Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (100mg, 0.33mmol) and trans 3-(3-bromophenyl)-2-propenoic acid chloride (123mg, 0.50mmol) the title compound was obtained (89mg, 55%). H NMR (DMSO) δ 12.39 (s, 1H), 10.25 (s, 1H), 8.54 (m, 1H), 8.04 (m, 2H), 7.88 (s, 1H), 7.71 (d, 1H), 7.66 (m, 4H), 7.44 (t, 1H), 7.34 (dd, 1H), 7.24 (dd, 1H), 3.74 (s, 2H). MS: 497m/z (M+H)^+. 

Example 27: 2-[4-(6-Chloro-4H-1-benzopyran-3-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 6-Chloro-4H-1-benzopyran-3-carboxylic acid chloride
Prepared by the method of Example 25d), from 6-chloro-4H-1-benzopyran-3-carboxylic acid (57mg, 0.25mmol) the subtitle compound was obtained (61mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(6-Chloro-4H-1-benzopyran-3-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 6-chloro-4H-1-benzopyran-3-carboxylic acid chloride (61mg, 0.25mmol) the title compound was obtained (42mg, 53%). H NMR (DMSO) δ 12.38 (s, 1H), 10.22 (s, 1H), 8.04 (m, 2H), 7.94 (t, 1H), 7.71 (m, 2H), 7.52 (s, 1H), 7.41 (d, 1H), 7.34 (d, 1H), 7.30 (dd, 1H), 6.92 (d, 1H), 5.03 (s, 2H), 3.74 (s, 2H). MS: 477m/z (M-H)^-.

Example 28: trans 2-[4-(3-(3-Cyanophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(3-Cyanophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(3-cyanophenyl)-2-propenoic acid (43mg, 0.25mmol) the subtitle compound was obtained (46mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-(3-(3-Cyanophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3-cyanophenyl)-2-propenoic acid chloride (46mg, 0.25mmol) the title compound was obtained (35mg, 48%). H NMR (DMSO) δ 12.40 (s, 1H), 10.30 (s, 1H), 8.52 (t, 1H), 8.04 (m, 4H), 7.89 (d, 1H), 7.70 (m, 4H), 7.34 (dd, 1H), 7.30 (d, 1H), 3.74 (s, 2H). MS: 440m/z (M-H)^-.

Example 29: trans 2-[4-(3-(4-Cyanophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid
a) *trans* 3-(4-Cyanophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d, from *trans* 3-(4-cyanophenyl)-2-propenoic acid (43mg, 0.25mmol) the subtitle compound was obtained (46mg, 100%). The crude product was used directly in the next reaction without purification.

b) *trans* 2-[4-[3-(4-Cyanophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

![Chemical Structure](image)

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and *trans* 3-(4-cyanophenyl)-2-propenoic acid chloride (46mg, 0.25mmol) the title compound was obtained (29mg, 39%). $^1$H NMR (DMSO) $\delta$ 12.43 (s, 1H), 10.36 (s, 1H), 8.52 (t, 1H), 8.04 (m, 2H), 7.93 (d, 2H), 7.83 (d, 2H), 7.71 (m, 3H), 7.33 (m, 2H), 3.74 (s, 2H). MS: 440m/z (M-H$^-$).

Example 30: 2-[4-(Benzo[b]thiophene-2-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) Benzo[b]thiophene-2-carboxylic acid chloride
Prepared by the method of Example 25d, from benzo[b]thiophene-2-carboxylic acid (49mg, 0.25mmol) the subtitle compound was obtained (53mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(Benzo[b]thiophene-2-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

![Chemical Structure](image)

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and benzo[b]thiophene-2-carboxylic acid chloride (53mg, 0.25mmol) the title compound was obtained (24mg, 32%). $^1$H NMR (DMSO) $\delta$ 12.39 (s, 1H), 10.68 (s, 1H), 8.43 (s, 1H), 8.08 (d, 2H), 8.03 (m, 3H), 7.73 (d, 1H), 7.71 (s, 1H), 7.51 (m, 2H), 7.34 (dd, 1H), 3.74 (s, 2H). MS: 445m/z (M-H$^-$).

Example 31: 2-[4-[2-(4-Chlorophenyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 2-(4-Chlorophenyl)-4-thiazolecarboxylic acid chloride
Prepared by the method of Example 25d, from 2-(4-chlorophenyl)-4-thiazolecarboxylic acid (60mg, 0.25mmol) the subtitle compound was obtained (65mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-[2-(4-Chlorophenyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid

![Chemical Structure](image)

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 2-(4-chlorophenyl)-4-thiazolecarboxylic acid chloride (65mg,
Example 32: trans 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(2,4-Dichlorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d, from trans 3-(2,4-dichlorophenyl)-2-propenoic acid (54 mg, 0.25 mmol) the subtitle compound was obtained (58 mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50 mg, 0.17 mmol) and trans 3-(2,4-dichlorophenyl)-2-propenoic acid chloride (58 mg, 0.25 mmol) the subtitle compound was obtained (25 mg, 31%). 1H NMR (DMSO) δ 10.39 (s, 1H), 8.52 (t, 1H), 8.04 (m, 2H), 7.86 (d, 1H), 7.74 (m, 4H), 7.59 (dd, 1H), 7.35 (dd, 1H), 7.26 (d, 1H), 3.74 (s, 2H). MS: 485 m/z (M+H)+.

Example 33: trans 2-[4-[3-(3-Cyano-4-methoxyphenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(3-Cyano-4-methoxyphenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d, from trans 3-(3-cyano-4-methoxyphenyl)-2-propenoic acid (100 mg, 0.52 mmol) the subtitle compound was obtained (115 mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-[3-(3-Cyano-4-methoxyphenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (142 mg, 0.47 mmol) and trans 3-(3-cyano-4-methoxyphenyl)-2-propenoic acid chloride (115 mg, 0.52 mmol) the title compound was obtained (37 mg, 17%). 1H NMR (DMSO) δ 12.45 (s, 1H), 10.22 (s, 1H), 8.53 (t, 1H), 8.00 (m, 4H), 7.69 (m, 2H), 7.61 (d, 1H), 7.36 (d, 1H), 7.32 (dd, 1H), 7.13 (d, 1H), 3.97 (s, 3H), 3.74 (s, 2H). MS: 472 m/z (M+H)+.

Example 34: 2-[4-(6-Chloro-2H-1-benzopyran-3-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 6-Chloro-2H-1-benzopyran-3-carboxylic acid chloride
Prepared by the method of Example 25d, from 6-chloro-2H-1-benzopyran-3-carboxylic acid (53 mg, 0.25 mmol) the subtitle compound was obtained (57 mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(6-Chloro-2H-1-benzopyran-3-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid
Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 6-chloro-2H-1-benzopyran-3-carboxylic acid chloride (57mg, 0.25mmol) the title compound was obtained (13mg, 16%). $^1$H NMR (DMSO) δ 12.38 (s, 1H), 10.22 (s, 1H), 8.04 (m, 2H), 7.95 (t, 1H), 7.72 (m, 2H), 7.52 (s, 1H), 7.34 (m, 3H), 6.93 (d, 1H), 5.04 (s, 2H), 3.74 (s, 2H). MS: 479 m/z (M+H)$^+$.  

**Example 35:**  2-[4-(5-Chloro-1H-indole-2-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid  

a)  5-Chloro-1H-indole-2-carboxylic acid chloride  
Prepared by the method of Example 25d), from 5-chloro-1H-indole-2-carboxylic acid (49mg, 0.25mmol) the subtitle compound was obtained (52mg, 100%). The crude product was used directly in the next reaction without purification.

b)  2-[4-(5-Chloro-1H-indole-2-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid  

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 5-chloro-1H-indole-2-carboxylic acid chloride (52mg, 0.25mmol) the title compound was obtained (26mg, 34%). $^1$H NMR (DMSO) δ 12.38 (s, 1H), 12.06 (s, 1H), 10.43 (s, 1H), 8.06 (m, 3H), 7.76 (m, 3H), 7.49 (m, 2H), 7.34 (dd, 1H), 7.26 (dd, 1H), 3.75 (s, 2H). MS: 462 m/z (M+H)$^+$.  

**Example 36:**  2-[4-[2-(4-Methylphenyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid  

a)  2-(4-Methylphenyl)-4-thiazolecarboxylic acid chloride  
Prepared by the method of Example 25d), from 2-(4-methylphenyl)-4-thiazolecarboxylic acid (55mg, 0.25mmol) the subtitle compound was obtained (59mg, 100%). The crude product was used directly in the next reaction without purification.

b)  2-[4-[2-(4-Methylphenyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid  

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 2-(4-methylphenyl)-4-thiazolecarboxylic acid chloride (59mg, 0.25mmol) the title compound was obtained (6mg, 7%). $^1$H NMR (DMSO) δ 12.47 (s, 1H), 10.29 (s, 1H), 8.56 (s, 1H), 8.31 (t, 1H), 8.13 (s, 1H), 8.10 (d, 1H), 8.01 (d, 2H), 7.74 (d, 1H), 7.73 (s, 1H), 7.40 (d, 2H), 7.36 (d, 1H), 3.74 (s, 2H), 2.42 (s, 3H). MS: 488 m/z (M+H)$^+$.  

**Example 37:**  2-[4-[2-(2-Thienyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid
a) **2-(2-Thienyl)-4-thiazolecarboxylic acid chloride**

Prepared by the method of Example 25d), from 2-(2-thienyl)-4-thiazolecarboxylic acid (53mg, 0.25mmol) the subtitle compound was obtained (56mg, 100%). The crude product was used directly in the next reaction without purification.

b) **2-[4-[2-(2-Thienyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid**

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 2-(2-thienyl)-4-thiazolecarboxylic acid chloride (56mg, 0.25mmol) the title compound was obtained (9mg, 11%).\(^1\)H NMR (DMSO) \(\delta\) 12.40 (s, 1H), 10.02 (s, 1H), 8.53 (s, 1H), 8.34 (t, 1H), 8.08 (m, 2H), 7.84 (m, 2H), 7.73 (d, 1H), 7.71 (s, 1H), 7.34 (dd, 1H), 7.24 (t, 1H), 3.74 (s, 2H). MS: 480m/z (M+H)^+.

Example 38: **2-[4-[3-(4-Chlorophenyl)-5-isoxazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid**

a) **3-(4-Chlorophenyl)-5-isoxazolecarboxylic acid chloride**

Prepared by the method of Example 25d), from 3-(4-chlorophenyl)-5-isoxazolecarboxylic acid (100mg, 0.447mmol) the subtitle compound was obtained (107mg, 100%). The crude product was used directly in the next reaction without purification.

b) **2-[4-[3-(4-Chlorophenyl)-5-isoxazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid**

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (121.9mg, 0.406mmol) and 3-(4-chlorophenyl)-5-isoxazolecarboxylic acid chloride (107mg, 0.447mmol) the title compound was obtained (45mg, 59%).\(^1\)H NMR (DMSO) \(\delta\) 12.39 (s, 1H), 10.99 (s, 1H), 8.11-7.94 (m, 6H), 7.73 (m, 2H), 7.64 (d, 2H), 7.35 (d, 1H), 3.75 (s, 2H). MS: 491m/z (M+H)^+.

Example 39: **2-[4-(5-Bromo-1H-indole-2-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid**

a) **5-Bromo-1H-indole-2-carboxylic acid chloride**

Prepared by the method of Example 25d), from 5-bromo-1H-indole-2-carboxylic acid (60mg, 0.25mmol) the subtitle compound was obtained (64mg, 100%). The crude product was used directly in the next reaction without purification.

b) **2-[4-(5-Bromo-1H-indole-2-carbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid**

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 5-bromo-1H-indole-2-carboxylic acid chloride (64mg, 0.25mmol)
the title compound was obtained (23mg, 27%). $^1$H NMR (DMSO) δ 12.07 (s, 1H), 10.44 (s, 1H), 8.07 (m, 3H), 7.94 (s, 1H), 7.72 (m, 2H), 7.45 (m, 2H), 7.36 (m, 2H), 3.74 (s, 2H). MS: 508m/z (M+H)$^+$. 

Example 40: 2-[4-[2-(2,4-Difluorophenyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 2-(2,4-Difluorophenyl)-4-thiazolecarboxylic acid chloride

Prepared by the method of Example 25d), from 2-(2,4-difluorophenyl)-4-thiazolecarboxylic acid (60mg, 0.25mmol) the subtitle compound was obtained (65mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-[2-(2,4-Difluorophenyl)-4-thiazolecarbonylamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 2-(2,4-difluorophenyl)-4-thiazolecarboxylic acid chloride (65mg, 0.25mmol) the title compound was obtained (22mg, 30%). $^1$H NMR (DMSO) δ 12.44 (s, 1H), 10.30 (s, 1H), 8.69 (s, 1H), 8.52 (m, 1H), 8.24 (t, 1H), 8.08 (m, 2H), 7.71 (m, 2H), 7.59 (m, 1H), 7.41 (m, 1H), 7.34 (dd, 1H), 3.74 (s, 2H). MS: 510m/z (M+H)$^+$. 

Example 41: 2-[4-(2-Phenyl-4-thiazolecarbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 2-Phenyl-4-thiazolecarboxylic acid chloride

Prepared by the method of Example 25d), from 2-phenyl-4-thiazolecarboxylic acid (51mg, 0.25mmol) the subtitle compound was obtained (54mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(2-Phenyl-4-thiazolecarbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 2-phenyl-4-thiazolecarboxylic acid chloride (54mg, 0.25mmol) the title compound was obtained (66mg, 84%). $^1$H NMR (DMSO) δ 12.47 (s, 1H), 10.23 (s, 1H), 8.61 (s, 1H), 8.30 (t, 1H), 8.10 (m, 4H), 7.73 (d, 1H), 7.71 (s, 1H), 7.58 (m, 3H), 7.35 (d, 1H), 3.74 (s, 2H). MS: 474m/z (M+H)$^+$. 

Example 42: 2-[4-(5-Chloro-benzo[b]thiophene-3-acetamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 5-Chloro-benzo[b]thiophene-3-acetic acid chloride

Prepared by the method of Example 25d), from 5-chloro-benzo[b]thiophene-3-acetic acid (57mg, 0.25mmol) the subtitle compound was obtained (61mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(5-Chloro-benzo[b]thiophene-3-acetamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid
Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 5-chloro-benzo[b]thiophene-3-acetic acid chloride (61mg, 0.25mmol) the title compound was obtained (52mg, 63%). \(^1\)H NMR (DMSO) \(\delta\) 12.38 (s, 1H), 10.40 (s, 1H), 8.29 (t, 1H), 8.02 (m, 4H), 7.72 (m, 3H), 7.42 (dd, 1H), 7.33 (dd, 1H), 4.11 (s, 2H), 3.73 (s, 2H). MS: 495m/z (M+H)⁺.

Example 43: 2-[4-[3-(2,4-Difluorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(2,4-Difluorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(2,4-difluorophenyl)-2-propenoic acid (46mg, 0.25mmol) the subtitle compound was obtained (49mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-[3-(2,4-Difluorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(2,4-difluorophenyl)-2-propenoic acid chloride (49mg, 0.25mmol) the title compound was obtained (27mg, 36%). \(^1\)H NMR (DMSO) \(\delta\) 12.44 (s, 1H), 10.38 (s, 1H), 8.51 (t, 1H), 8.03 (m, 2H), 7.70 (m, 4H), 7.42 (m, 1H), 7.32 (d, 1H), 7.23 (m, 2H), 3.74 (s, 2H). MS: 453m/z (M+H)⁺.

Example 44: trans 2-[4-[3-[5-Chloro-2-(2-propynyloxy)phenyl]-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-[5-Chloro-2-(2-propynyloxy)phenyl]-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-[5-chloro-2-(2-propynyloxy)phenyl]-2-propenoic acid (59mg, 0.25mmol) the subtitle compound was obtained (63mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-[3-[5-Chloro-2-(2-propynyloxy)phenyl]-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-[5-chloro-2-(2-propynyloxy)phenyl]-2-propanoic acid chloride (59mg, 0.25mmol) the title compound was obtained (51mg, 60%). \(^1\)H NMR (DMSO) \(\delta\) 12.39 (s, 1H), 10.23 (s, 1H), 8.54 (t, 1H), 8.03 (m, 2H), 7.81 (d, 1H), 7.72 (d, 1H), 7.67 (dd, 2H), 7.49 (dd, 1H), 7.33 (dd, 1H), 7.24 (m, 2H), 4.98 (d, 2H), 3.74 (s, 2H), 3.67 (t, 1H). MS: 505m/z (M+H)⁺.
Example 45: trans 2-[4-[3-[4-(3-Fluoropropoxy)phenyl]-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylactic acid

a) trans 3-[4-(3-Fluoropropoxy)phenyl]-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-[4-(3-fluoropropoxy)phenyl]-2-propenoic acid (56mg, 0.25mmol) the subtitle compound was obtained (59mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-[3-[4-(3-Fluoropropoxy)phenyl]-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylactic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester (50mg, 0.17mmol) and trans 3-[4-(3-fluoropropoxy)phenyl]-2-propenoic acid chloride (59mg, 0.25mmol) the title compound was obtained (14mg, 17%). \(^1\)H NMR (DMSO) \(\delta\) 12.38 (s, 1H), 10.16 (s, 1H), 8.53 (t, 1H), 8.01 (m, 2H), 7.72 (m, 2H), 7.60 (m, 3H), 7.33 (dd, 1H), 7.05 (m, 3H), 4.70 (t, 1H), 4.55 (t, 1H), 4.14 (t, 2H), 3.74 (s, 2H), 2.17 (t, 1H), 2.09 (t, 1H). MS: 493 m/z (M+H)^+.

Example 46: 2-[4-(3-(2-Chlorophenyl)-5-isoxazolcarbonylamino)-3-fluorophenyl]benzoxazol-5-ylactic acid

a) 3-(2-Chlorophenyl)-5-isoxazolcarboxylic acid chloride
Prepared by the method of Example 25d), from 3-(2-chlorophenyl)-5-isoxazolcarboxylic acid (56mg, 0.25mmol) the subtitle compound was obtained (59mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-[3-(2-Chlorophenyl)-5-isoxazolcarbonylamino]-3-fluorophenyl]benzoxazol-5-ylactic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester (50mg, 0.17mmol) and 3-(2-chlorophenyl)-5-isoxazolcarboxylic acid chloride (59mg, 0.25mmol) the title compound was obtained (51mg, 62%). \(^1\)H NMR (DMSO) \(\delta\) 12.42 (s, 1H), 11.05 (s, 1H), 8.10 (m, 2H), 7.96 (t, 1H), 7.76 (m, 5H), 7.63 (m, 1H), 7.57 (dd, 1H), 7.36 (dd, 1H), 3.75 (s, 2H). MS: 492 m/z (M+H)^+.

Example 47: trans 2-[4-(3-(2-Chloro-4-fluorophenyl)-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylactic acid

a) trans 3-(2-Chloro-4-fluorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(2-chloro-4-fluorophenyl)-2-propenoic acid (50mg, 0.25mmol) the subtitle compound was obtained (54mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-[3-(2-Chloro-4-fluorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylactic acid
Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(2-chloro-4-fluorophenyl)-2-propenoic acid chloride (54mg, 0.25mmol) the title compound was obtained (20mg, 25%). ¹H NMR (DMSO) δ 12.35 (s, 1H), 10.36 (s, 1H), 8.52 (t, 1H), 8.03 (m, 2H), 7.84 (m, 2H), 7.70 (m, 2H), 7.59 (dd, 1H), 7.38 (m, 1H), 7.33 (dd, 1H), 7.20 (d, 1H), 3.73 (s, 2H). MS: 469m/z (M+H)⁺.

Example 48: 2-[4-(1,2-Dihydro-2-oxo-1-benzyl-3-pyridinecarboxamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid
a) 1,2-Dihydro-2-oxo-1-benzyl-3-pyridinecarboxylic acid chloride
Prepared by the method of Example 25d), from 1,2-dihydro-2-oxo-1-benzyl-3-pyridinecarboxylic acid (57mg, 0.25mmol) the subtitle compound was obtained (61mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(1,2-Dihydro-2-oxo-1-benzyl-3-pyridinecarboxamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 1,2-dihydro-2-oxo-1-benzyl-3-pyridinecarboxylic acid chloride (61mg, 0.25mmol) the title compound was obtained (7mg, 8%). ¹H NMR (DMSO) δ 12.68 (d, 1H), 12.40 (s, 1H), 8.73 (t, 1H), 8.53 (dd, 1H), 8.33 (dd, 1H), 8.04 (m, 2H), 7.69 (m, 2H), 7.34 (m, 6H), 6.70 (t, 1H), 5.34 (s, 2H), 3.73 (s, 2H). MS: 498m/z (M+H)⁺.

Example 49: 2-[4-(1,2-Dihydro-2-oxo-1-[4-(trifluoromethyl)benzyl]-3-pyridinecarboxamino]-3-fluorophenyl]benzoxazol-5-ylacetic acid
a) 1,2-Dihydro-2-oxo-1-[4-(trifluoromethyl)benzyl]-3-pyridinecarboxylic acid chloride
Prepared by the method of Example 25d), from 1,2-dihydro-2-oxo-1-(4-(trifluoromethyl)benzyl)-3-pyridinecarboxylic acid (75mg, 0.25mmol) the subtitle compound was obtained (79mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(1,2-Dihydro-2-oxo-1-(4-(trifluoromethyl)benzyl)-3-pyridinecarboxamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 1,2-dihydro-2-oxo-1-(4-(trifluoromethyl)benzyl)-3-pyridinecarboxylic acid chloride (75mg, 0.25mmol) the title compound was obtained (70mg, 74%). ¹H NMR (DMSO) δ 12.60 (d, 1H), 12.40 (s, 1H), 8.72 (t, 1H), 8.54 (dd, 1H), 8.37 (dd, 1H), 8.02 (m, 2H), 7.74-7.66 (m, 4H), 7.54 (d, 2H), 7.30 (dd, 1H), 6.73 (t, 1H), 5.42 (s, 2H), 3.72 (s, 2H). MS: 566m/z (M+H)⁺.

Example 50: 2-[4-(2-Fluoro-3-phenyl-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid
a) 2-Fluoro-3-phenyl-2-propenoic acid chloride
Prepared by the method of Example 25d), from 2-fluoro-3-phenyl-2-propenoid acid (42mg, 0.25mmol) the subtitle compound was obtained (46mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(2-Fluoro-3-phenyl-2-propenamido)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 2-fluoro-3-phenyl-2-propenoic acid chloride (46mg, 0.25mmol) the title compound was obtained (14mg, 19%). $^1$H NMR (DMSO) $\delta$ 12.39 (s, 1H), 10.44 (s, 1H), 8.07 (m, 2H), 7.91 (t, 1H), 7.73 (m, 4H), 7.48 (m, 3H), 7.35 (dd, 1H), 7.10 (d, 1H), 3.74 (s, 2H). MS: 435m/z (M+H)$^+$.  

Example 51: 2-[4-(1,2-Dihydro-2-oxo-1-(3-(trifluoromethyl)benzyl)-3-pyridinecarbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 1,2-Dihydro-2-oxo-1-(3-(trifluoromethyl)benzyl)-3-pyridinecarboxylic acid chloride
Prepared by the method of Example 25d), from 1,2-dihydro-2-oxo-1-(3-(trifluoromethyl)benzyl)-3-pyridinecarboxylic acid (75mg, 0.25mmol) the subtitle compound was obtained (79mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(1,2-Dihydro-2-oxo-1-(3-(trifluoromethyl)benzyl)-3-pyridinecarbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 1,2-dihydro-2-oxo-1-(3-(trifluoromethyl)benzyl)-3-pyridinecarboxylic acid chloride (79mg, 0.25mmol) the title compound was obtained (20mg, 21%). $^1$H NMR (DMSO) $\delta$ 12.63 (d, 1H), 12.41 (s, 1H), 8.73 (t, 1H), 8.54 (dd, 1H), 8.41 (dd, 1H), 8.04 (m, 2H), 7.81 (s, 1H), 7.67 (m, 5H), 7.32 (dd, 1H), 6.74 (t, 1H), 5.43 (s, 2H), 3.73 (s, 2H). MS: 566m/z (M+H)$^+$.  

Example 52: 2-[4-(1,2-Dihydro-2-oxo-1-(3-chlorobenzyl)-3-pyridinecarbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) 1,2-Dihydro-2-oxo-1-(3-chlorobenzyl)-3-pyridinecarboxylic acid chloride
Prepared by the method of Example 25d), from 1,2-dihydro-2-oxo-1-(3-chlorobenzyl)-3-pyridinecarboxylic acid (66mg, 0.25mmol) the subtitle compound was obtained (70mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-(1,2-Dihydro-2-oxo-1-(3-chlorobenzyl)-3-pyridinecarbonylamino)-3-fluorophenyl]benzoxazol-5-ylacetic acid
Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and 1,2-dihydro-2-oxo-1-(3-chlorobenzyl)-3-pyridinecarboxylic acid chloride (70mg, 0.25mmol) the title compound was obtained (70mg, 79%). $^1$H NMR (DMSO) $\delta$ 12.63 (d, 1H), 12.43 (s, 1H), 8.73 (t, 1H), 8.52 (dd, 1H), 8.36 (dd, 1H), 8.03 (m, 2H), 7.69 (m, 2H), 7.40 (m, 5H), 6.72 (t, 1H), 5.33 (s, 2H), 3.73 (s, 2H). MS: 532m/z (M+H)$^+$. 

Example 53: trans 2-[4-[3-(3-Trifluoromethyl-4-fluorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(3-Trifluoromethyl-4-fluorophenyl)-2-propenoic acid methyl ester
3-Trifluoromethyl-4-fluorobenzaldehyde (250mg, 1.30mmol) and methyl(triphenylphosphineanylidene)acetate (520mg, 1.56mmol) in dichloromethane (5ml) were stirred at room temperature for 5 min. The solvent was removed under reduced pressure and the residue was purified using column chromatography the subtitle compound was obtained (267mg, 83%).

b) trans 3-(3-Trifluoromethyl-4-fluorophenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(3-trifluoromethyl-4-fluorophenyl)-2-propenoic acid methyl ester (267mg, 1.08mmol) the subtitle compound was obtained (170mg, 67%). $^1$H NMR (CDCl$_3$) $\delta$ 7.78 (m, 2H), 7.27 (d, 1H), 6.46 (d, 1H).

c) trans 3-(3-Trifluoromethyl-4-fluorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(3-trifluoromethyl-4-fluorophenyl)-2-propenoic acid (59mg, 0.25mmol) the subtitle compound was obtained (63mg, 100%). The crude product was used directly in the next reaction without purification.

d) trans 2-[4-[3-(3-Trifluoromethyl-4-fluorophenyl)-2-propenamido]-3-fluorophenyl]-benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3-trifluoromethyl-4-fluorophenyl)-2-propenoic acid chloride (63mg, 0.25mmol) the title compound was obtained (19mg, 23%). $^1$H NMR (DMSO) $\delta$ 12.39 (s, 1H), 10.28 (s, 1H), 8.54 (m, 1H), 8.05 (m, 4H), 7.75 (d, 1H), 7.70 (m, 2H), 7.64 (dd, 1H), 7.34 (dd, 1H), 7.25 (d, 1H), 3.74 (s, 2H). MS: 503m/z (M+H)$^+$. 

Example 54: trans 2-[4-[3-(3-Trifluoromethyl-5-fluorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-yl] acetic acid

a) 3-(3-Trifluoromethyl-5-fluorophenyl)-2-propanoic acid methyl ester
Prepared by the method of Example 53a), from 3-trifluoromethyl-5-fluorobenzaldehyde (250mg, 1.30mmol) the subtitle compound was obtained (310mg, 96%).

b) trans 3-(3-Trifluoromethyl-5-fluorophenyl)-2-propanoic acid
Prepared by the method of Example 25d), from trans 3-(3-trifluoromethyl-5-fluorophenyl)-2-propanoic acid methyl ester (310mg, 1.25mmol) the subtitle compound was obtained (240mg, 82%). $^1$H NMR (DMSO) $\delta$ 7.98 (m, 2H), 7.67 (m, 2H), 6.79 (d, 1H).

c) trans 3-(3-Trifluoromethyl-5-fluorophenyl)-2-propanoic acid chloride
Prepared by the method of Example 21d), from trans 3-(3-trifluoromethyl-5-fluorophenyl)-2-propanoic acid (59mg, 0.25mmol) the subtitle compound was obtained (63mg, 100%). The crude product was used directly in the next reaction without purification.
d) \textit{trans} 2-[4-[3-(Trifluoromethyl)-5-fluorophenyl]-2-propenamido]-3-fluorophenyl]-benzoxazol-5-yl] acetic acid

\[
\text{HO}_2\text{C} - \begin{array}{c}
\text{N} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{H} \\
\text{O} \\
\text{F}
\end{array} - \text{N} - \text{C} - \text{F} - \text{C} - \text{F} - \text{H} - \text{O} - \text{C} - \text{H} - \text{F} - \text{F} - \text{H}
\]

Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and \textit{trans} 3-(3-trifluoromethyl)-5-fluorophenyl]-2-propenoic acid chloride (63mg, 0.25mmol) the title compound was obtained (12mg, 14%). $^1$H NMR (DMSO) $\delta$ 12.41 (s, 1H), 10.33 (s, 1H), 8.53 (t, 1H), 8.04 (m, 2H), 7.90 (s, 1H), 7.84 (d, 1H), 7.74 (d, 2H), 7.70 (d, 2H), 7.35 (m, 2H), 3.73 (s, 2H). MS: 503m/z (M+H)$^+$. 

Example 55: \textit{trans} 2-[4-[3-(2-Fluoro-4-trifluoromethylphenyl)-2-propenamido]-3-fluorophenyl]-benzoxazol-5-ylacetic acid

a) \textit{trans} 3-(2-Fluoro-4-trifluoromethylphenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a, from 2-fluoro-4-trifluoromethylbenzaldehyde (250mg, 1.30mmol) the subtitle compound was obtained (250mg, 77%).

b) \textit{trans} 3-(2-Fluoro-4-trifluoromethylphenyl)-2-propenoic acid
Prepared by the method of Example 21d, from trans-3-(2-fluoro-4-trifluoromethylphenyl)-2-propenoic acid methyl ester (250mg, 1.01mmol) the subtitle compound was obtained (173mg, 73%). $^1$H NMR (DMSO) $\delta$ 8.09 (t, 1H), 7.78 (d, 1H), 7.68-7.62 (m, 2H), 6.74 (d, 1H).

c) \textit{trans} 3-(2-Fluoro-4-trifluoromethylphenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d, from trans 3-(2-fluoro-4-trifluoromethylphenyl)-2-propenoic acid (59mg, 0.25mmol) the subtitle compound was obtained (63mg, 100%). The crude product was used directly in the next reaction without purification.

d) \textit{trans} 2-[4-[3-(2-Fluoro-4-trifluoromethylphenyl)-2-propenamido]-3-fluorophenyl]-benzoxazol-5-ylacetic acid

\[
\text{HO}_2\text{C} - \begin{array}{c}
\text{N} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{H} \\
\text{O} \\
\text{F}
\end{array} - \text{N} - \text{C} - \text{F} - \text{C} - \text{F} - \text{H} - \text{O} - \text{C} - \text{H} - \text{F} - \text{F} - \text{H}
\]

Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and \textit{trans} 3-(2-fluoro-4-trifluoromethylphenyl)-2-propenoic acid chloride (63mg, 0.25mmol) the subtitle compound was obtained (16mg, 19%). $^1$H NMR (DMSO) $\delta$ 12.37 (s, 1H), 10.49 (s, 1H), 8.52 (m, 1H), 8.04 (m, 2H), 7.96 (t, 1H), 7.82 (s, 1H), 7.72 (m, 4H), 7.40 (dd, 1H), 7.33 (dd, 1H), 3.74 (s, 2H). MS: 503m/z (M+H)$^+$. 

Example 56: \textit{trans} 2-[4-[3-(3,4-Dichlorophenyl)-2-propenamido]-3-fluorophenyl]-benzoxazol-5-ylacetic acid

a) \textit{trans} 3-(3,4-Dichlorophenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a, from 3,4-dichlorobenzaldehyde (250mg, 1.43mmol) the subtitle compound was obtained (260mg, 79%).

b) \textit{trans} 3-(3,4-Dichlorophenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(3,4-dichlorophenyl)-2-propenoic acid methyl ester (260mg, 1.13mmol) the subtitle compound was obtained (210mg, 86%). $^1$H NMR (DMSO) δ 8.03 (s, 1H), 7.73-7.65 (m, 2H), 7.56 (d, 1H), 6.66 (d, 1H).

c) trans 3-(3,4-Dichlorophenyl)-2-propenoic acid chloride

Prepared by the method of Example 25d), from trans 3-(3,4-dichlorophenyl)-2-propenoic acid (56mg, 0.25mmol) the subtitle compound was obtained (59mg, 100%). The crude product was used directly in the next reaction without purification.

d) trans 2-[4-[3-(3,4-Dichlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl]benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3,4-dichlorophenyl)-2-propenoic acid chloride (59mg, 0.25mmol) the title compound was obtained (5mg, 7%). $^1$H NMR (DMSO) δ 12.35 (s, 1H), 10.27 (s, 1H), 8.54 (m, 1H), 8.04 (m, 2H), 7.94 (m, 1H), 7.73 (t, 2H), 7.67 (m, 3H), 7.33 (dd, 1H), 7.26 (dd, 1H), 3.73 (s, 2H). MS: 483m/z (M-H)$^+$. 

Example 57: trans 2-[4-[3-(3-Chloro-4-fluorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(3-Chloro-4-fluorophenyl)-2-propenoic acid methyl ester

Prepared by the method of Example 53a), from 3-chloro-4-fluorobenzaldehyde (250mg, 1.58mmol) the subtitle compound was obtained (277mg, 82%).

b) trans 3-(3-Chloro-4-fluorophenyl)-2-propenoic acid

Prepared by the method of Example 21d), from trans 3-(3-chloro-4-fluorophenyl)-2-propenoic acid methyl ester (277mg, 1.29mmol) the subtitle compound was obtained (122mg, 47%). $^1$H NMR (DMSO) δ 8.01 (dd, 1H), 7.74 (m, 1H), 7.55 (d, 1H), 7.46 (t, 1H), 6.59 (d, 1H).

c) trans 3-(3-Chloro-4-fluorophenyl)-2-propenoic acid chloride

Prepared by the method of Example 25d), from trans 3-(3-chloro-4-fluorophenyl)-2-propenoic acid (50mg, 0.25mmol) the subtitle compound was obtained (55mg, 100%). The crude product was used directly in the next reaction without purification.

d) 2-[4-[3-(3-Chloro-4-fluorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid methyl ester

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl]benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3-chloro-4-fluorophenyl)-2-propenoic acid chloride (55mg, 0.25mmol) the title compound was obtained (9mg, 12%). $^1$H NMR (DMSO) δ 12.38 (s, 1H), 10.24 (s, 1H), 8.52 (t, 1H), 8.04 (m, 2H), 7.90 (dd, 1H), 7.71 (m, 3H), 7.63 (d, 1H), 7.53 (t, 1H), 7.33 (dd, 1H), 7.17 (d, 1H), 3.73 (s, 2H). MS: 469m/z (M+H)$^+$. 

Example 58: trans 2-[4-[3-(2-Fluoro-3-chlorophenyl)-2-propenamido]-3-fluorophenyl] benzoxazol-5-ylacetic acid

a) trans 3-(2-Fluoro-3-chlorophenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a), from 2-fluoro-3-chlorobenzaldehyde (250mg, 1.58mmol) the subtitle compound was obtained (312mg, 92%).

b) trans 3-(2-Fluoro-3-chlorophenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(2-fluoro-3-chlorophenyl)-2-propenoic acid methyl ester (312mg, 1.45mmol) the subtitle compound was obtained (245mg, 84%). $^1$H NMR (DMSO) δ 7.83 (t, 1H), 7.67-7.60 (m, 2H), 7.28 (t, 1H), 6.65 (d, 1H).

c) trans 3-(2-Fluoro-3-chlorophenyl)-2-propenoic chloride
Prepared by the method of Example 25d), from trans 3-(2-fluoro-3-chlorophenyl)-2-propenoic acid (50mg, 0.25mmol) the subtitle compound was obtained (55mg, 100%). The crude product was used directly in the next reaction without purification.

d) 2-[4-[3-(2-Fluoro-3-chlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(2-fluoro-3-chlorophenyl)-2-propenoic chloride (55mg, 0.25mmol) the title compound was obtained (13mg, 17%). $^1$H NMR (DMSO) δ 12.39 (s, 1H), 10.43 (s, 1H), 8.50 (m, 1H), 8.30 (m, 2H), 7.69 (m, 5H), 7.31 (m, 3H), 3.73 (s, 2H). MS: 469m/z (M+H)*.

Example 59: trans 2-[4-[3-(3-Trifluoromethyl-4-chlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(3-Trifluoromethyl-4-chlorophenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a), from 3-trifluoromethyl-4-chlorobenzaldehyde (250mg, 1.21mmol) the subtitle compound was obtained (270mg, 85%).

b) trans 3-(3-Trifluoromethyl-4-chlorophenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(3-trifluoromethyl-4-chlorophenyl)-2-propenoic acid methyl ester (270mg, 1.02mmol) the subtitle compound was obtained (215mg, 84%). $^1$H NMR (DMSO) δ 8.17 (s, 1H), 8.04 (dd, 1H), 7.76 (d, 1H), 7.67 (d, 1H), 6.73 (d, 1H).

c) trans 3-(3-Trifluoromethyl-4-chlorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(3-trifluoromethyl-4-chlorophenyl)-2-propenoic acid (62mg, 0.25mmol) the subtitle compound was obtained (67mg, 100%). The crude product was used directly in the next reaction without purification.

d) trans 2-[4-[3-(3-Trifluoromethyl-4-chlorophenyl)-2-propenamido]-3-fluorophenyl] benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3-trifluoromethyl-4-chlorophenyl)-2-propenoic acid chloride (67mg, 0.25mmol) the title compound was obtained (9mg, 10%). $^1$H NMR (DMSO) δ 10.31 (s, 1H), 8.55 (t, 1H), 8.12 (d, 2H), 8.02 (d, 1H), 7.97 (d, 1H), 7.84 (d, 1H), 7.76 (d, 1H), 7.70 (m, 2H), 7.35 (s, 1H), 7.31 (d, 1H), 3.74 (s, 2H). MS: 519m/z (M+H)*.
Example 60:  trans 2-[4-[3-(3,5-Dibromophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a)  trans 3-(3,5-Dibromophenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a, from 3,5-dibromobenzaldehyde (250mg, 0.95mmol) the subtitle compound was obtained (130mg, 43%).

b)  trans 3-(3,5-Dibromophenyl)-2-propenoic acid
Prepared by the method of Example 21d, from trans 3-(3,5-dibromophenyl)-2-propenoic acid methyl ester (130mg, 0.41mmol) the subtitle compound was obtained (70mg, 56%). ¹H NMR (DMSO) δ 7.98 (s, 2H), 7.86 (s, 1H), 7.52 (d, 1H), 6.70 (d, 1H).

c)  trans 3-(3,5-Dibromophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d, from trans 3-(3,5-dibromophenyl)-2-propenoic acid (76mg, 0.25mmol) the subtitle compound was obtained (81mg, 100%). The crude product was used directly in the next reaction without purification.

d)  trans 2-[4-[3-(3,5-Dibromophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3,5-dibromophenyl)-2-propenoic acid chloride (81mg, 0.25mmol) the title compound was obtained (7mg, 7%). ¹H NMR (DMSO) δ 10.33 (s, 1H), 8.65 (dd, 1H), 8.14 (m, 2H), 8.01 (s, 3H), 7.82 (m, 2H), 7.71 (d, 1H), 7.44 (m, 2H), 3.74 (s, 2H). MS: 575m/z (M+H)⁺.

Example 61:  trans 2-[4-[3-(3,5-Dichlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a)  trans 3-(3,5-Dichlorophenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a, from 3,5-dichlorobenzaldehyde (250mg, 1.42mmol) the subtitle compound was obtained (240mg, 73%).

b)  trans 3-(3,5-Dichlorophenyl)-2-propenoic acid
Prepared by the method of Example 21d, from trans 3-(3,5-dichlorophenyl)-2-propenoic acid methyl ester (240mg, 1.04mmol) the subtitle compound was obtained (205mg, 91%). ¹H NMR (DMSO) δ 7.83 (s, 2H), 7.65 (s, 1H), 7.55 (d, 1H), 6.72 (d, 1H).

c)  trans 3-(3,5-Dichlorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d, from trans 3-(3,5-dichlorophenyl)-2-propenoic acid (54mg, 0.25mmol) the subtitle compound was obtained (59mg, 100%). The crude product was used directly in the next reaction without purification.

d)  trans 2-[4-[3-(3,5-Dichlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f, from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3,5-dichlorophenyl)-2-propenoic acid chloride (59mg,
0.25 mmol the title compound was obtained (23 mg, 28%). $^1$H NMR (DMSO) δ 12.39 (s, 1H), 10.27 (s, 1H), 8.53 (t, 1H), 8.04 (m, 2H), 7.71 (m, 5H), 7.62 (d, 1H), 7.32 (m, 2H), 3.74 (s, 2H). MS: 485 m/z (M+H)$^+$.

Example 62: trans 2-[4-[3-(2,4-Difluoro-5-chlorophenyl)-2-propenamido]-3-fluorophenyl] benzoxazol-5-ylacetic acid

a) trans 3-(2,4-Difluoro-5-chlorophenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a), from 2,4-difluoro-5-chlorobenzaldehyde (250 mg, 1.42 mmol) the subtitle compound was obtained (300 mg, 91%).

b) trans 3-(2,4-Difluoro-5-chlorophenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(2,4-difluoro-5-chlorophenyl)-2-propenoic acid methyl ester (300 mg, 1.29 mmol) the subtitle compound was obtained (270 mg, 96%). $^1$H NMR (DMSO) δ 7.73 (m, 1H), 7.50 (d, 1H), 7.30 (m, 1H), 6.60 (d, 1H).

c) trans 3-(2,4-Difluoro-5-chlorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(2,4-difluoro-5-chlorophenyl)-2-propenoic acid (54 mg, 0.25 mmol) the subtitle compound was obtained (59 mg, 100%). The crude product was used directly in the next reaction without purification.

d) trans 2-[4-[3-(2,4-Difluoro-5-chlorophenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50 mg, 0.17 mmol) and trans 3-(2,4-difluoro-5-chlorophenyl)-2-propenoic acid chloride (59 mg, 0.25 mmol) the title compound was obtained (12 mg, 15%). $^1$H NMR (DMSO) δ 12.39 (s, 1H), 10.57 (s, 1H), 8.52 (dt, 1H), 8.04 (m, 2H), 7.72 (m, 3H), 7.62 (d, 1H), 7.45 (dd, 1H), 7.33 (m, 2H), 3.74 (s, 2H). MS: 487 m/z (M+H)$^+$.

Example 63: trans 2-[4-[3-(3-Fluoro-4-methoxyphenyl)-2-propenamido]-3-fluorophenyl] benzoxazol-5-ylacetic acid

a) trans 3-(3-Fluoro-4-methoxyphenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a), from 3-fluoro-4-methoxybenzaldehyde (250 mg, 1.62 mmol) the subtitle compound was obtained (320 mg, 94%).

b) trans 3-(3-Fluoro-4-methoxyphenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(3-fluoro-4-methoxyphenyl)-2-propenoic acid methyl ester (320 mg, 1.52 mmol) the subtitle compound was obtained (270 mg, 91%).

c) trans 3-(3-Fluoro-4-methoxyphenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(3-fluoro-4-methoxyphenyl)-2-propenoic acid (50 mg, 0.25 mmol) the subtitle compound was obtained (54 mg, 100%). The crude product was used directly in the next reaction without purification.

d) trans 2-[4-[3-(3-Fluoro-4-methoxyphenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

...
Prepared by the method of Example 1a), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3-fluoro-4-methoxyphenyl)-2-propenoic acid chloride (54mg, 0.25mmol) the title compound was obtained (7mg, 9%). 1H NMR (DMSO) δ 10.18 (s, 1H), 8.52 (t, 1H), 8.03 (m, 2H), 7.72 (d, 1H), 7.69 (s, 1H), 7.59 (d, 1H), 7.49 (m, 2H), 7.32 (d, 1H), 7.27 (t, 1H), 7.06 (d, 1H), 3.90 (s, 3H), 3.73 (s, 2H). MS: 465m/z (M+H)+.

Example 64: trans 2-[4-[3-(2-Fluoro-3-trifluoromethylphenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(2-Fluoro-3-trifluoromethylphenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a), from 2-fluoro-3-trifluoromethylbenzaldehyde (250mg, 1.30mmol) the subtitle compound was obtained (278mg, 86%).

b) trans 3-(2-Fluoro-3-trifluoromethylphenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(2-fluoro-3-trifluoromethylphenyl)-2-propenoic acid methyl ester (278mg, 1.12mmol) the subtitle compound was obtained (195mg, 74%). 1H NMR (CDCl3) δ 7.91 (d, 1H), 7.77 (t, 1H), 7.66 (t, 1H), 7.30 (t, 1H), 6.60 (d, 1H).

c) trans 3-(2-Fluoro-3-trifluoromethylphenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(2-fluoro-3-trifluoromethylphenyl)-2-propenoic acid (59mg, 0.25mmol) the subtitle compound was obtained (63mg, 100%). The crude product was used directly in the next reaction without purification.

d) trans 2-[4-[3-(2-Fluoro-3-trifluoromethylphenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(2-fluoro-3-trifluoromethylphenyl)-2-propenoic acid chloride (63mg, 0.25mmol) the title compound was obtained (21mg, 25%). 1H NMR (DMSO) δ 10.49 (s, 1H), 8.51 (t, 1H), 8.03 (m, 3H), 7.85 (t, 1H), 7.73 (d, 1H), 7.70 (s, 2H), 7.53 (t, 1H), 7.40 (d, 1H), 7.32 (dd, 1H), 3.72 (s, 2H). MS: 503m/z (M+H)+.

Example 65: trans 2-[4-[3-(2-Trifluoromethylphenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid

a) trans 3-(2-Trifluoromethylphenyl)-2-propenoic acid methyl ester
Prepared by the method of Example 53a), from 2-trifluoromethylbenzaldehyde (250mg, 1.44mmol) the subtitle compound was obtained (260mg, 78%).

b) trans 3-(2-Trifluoromethylphenyl)-2-propenoic acid
Prepared by the method of Example 21d), from trans 3-(2-trifluoromethylphenyl)-2-propenoic acid methyl ester (260mg, 1.13mmol) the subtitle compound was obtained (205mg, 83%). 1H NMR (CDCl3) δ 8.04 (d, 1H), 7.85-7.99 (m, 2H), 7.73 (t, 1H), 7.62 (t, 1H), 6.63 (d, 1H).

c) trans 3-(2-Trifluoromethylphenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from -3-(2-trifluoromethylphenyl)-2-propenoic acid (54mg, 0.25mmol) the subtitle compound was obtained (59mg, 100%). The crude product was used directly in the next reaction without purification.

d) trans 2-[4-[3-(2-Trifluoromethylphenyl)-2-propenamido]-3-fluorophenyl]benzoxazol-5-ylacetic acid
Prepared by the method of Example 1f), from 2-(3-fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(2-trifluoromethylphenyl)-2-propenoic acid chloride (59mg, 0.25mmol) the title compound was obtained (5mg, 6%). $^1$H NMR (DMSO) δ 10.45 (s, 1H), 8.53 (t, 1H), 8.04 (m, 2H), 7.81 (m, 7H), 7.35 (dd, 1H), 7.28 (d, 1H), 3.74 (s, 2H). MS: 485 m/z (M+H)$^+$. 

Example 66: trans 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-3-methylphenyl]benzoxazol-5-ylacetic acid

a) 4-Hydroxy-3-(3-methyl-4-nitrobenzoylamino)phenylacetic acid methyl ester

Prepared by the method of Example 1c), from 4-hydroxy-3-aminophenylacetic acid methyl ester (1.5g, 8.30mmol) and 3-methyl-4-nitrobenzoyl chloride (1.65g, 8.30mmol) the subtitle compound was obtained (1.4g, 50%). The product was used directly in the next reaction without purification.

b) 2-(3-Methyl-4-nitrophenyl)benzoxazol-5-ylacetic acid methyl ester

Prepared by the method of Example 1d), from 4-hydroxy-3-(3-methyl-4-nitrobenzoylamino)phenylacetic acid methyl ester (1.4g, 4.07mmol) the subtitle compound was obtained (490mg, 37%). $^1$H NMR (DMSO) δ 8.31 (s, 1H), 8.20 (m, 2H), 7.78 (m, 2H), 7.40 (dd, 1H), 3.86 (s, 2H), 3.64 (s, 3H), 2.64 (s, 3H).

c) 2-(3-Methyl-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester

Prepared by the method of Example 1e), from 2-(3-methyl-4-nitrophenyl)benzoxazole-5-ylacetic acid methyl ester (800mg, 2.45mmol) the subtitle compound was obtained (800mg, 100%). $^1$H NMR (DMSO) δ 7.74 (m, 2H), 7.57 (m, 2H), 7.19 (dd, 1H), 6.72 (d, 1H), 5.76 (s, 2H), 3.79 (s, 2H), 3.62 (s, 3H), 2.14 (s, 3H).

d) trans 3-(2,4-Dichlorophenyl)-2-propenoic acid chloride

Prepared by the method of Example 25d), from trans 3-(2,4-dichlorophenyl)-2-propenoic acid (50mg, 0.24mmol) the subtitle compound was obtained (52mg, 100%). The crude product was used directly in the next reaction without purification.

e) trans 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-3-methylphenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 1f), from 2-(3-methyl-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(2,4-dichlorophenyl)-2-propenoic acid chloride (52mg, 0.24mmol) the title compound was obtained (25mg, 31%). $^1$H NMR (DMSO) δ 9.72 (s, 1H), 8.07 (m, 3H), 7.85 (d, 1H), 7.79 (dd, 2H), 7.70 (d, 1H), 7.67 (s, 1H), 7.58 (dd, 1H), 7.30 (dd, 1H), 7.19 (dd, 1H), 3.73 (s, 2H), 2.41 (s, 3H). MS: 482.1 m/z (M+H)$^+$. 

Example 67: trans 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-2-chlorophenyl]benzoxazol-5-ylacetic acid

a) 4-Hydroxy-3-(2-chloro-4-nitrobenzoylamino)phenylacetic acid methyl ester

Prepared by the method of Example 1c), from (4-hydroxy-3-aminophenyl)acetic acid methyl ester (5.0g, 27.60mmol) and 2-chloro-4-nitrobenzoyl chloride (6.07g, 27.60mmol) the subtitle compound was obtained (10.07g, 100%). The crude product was used directly in the next reaction without purification.
b) 2-(2-Chloro-4-nitrophenyl)benzoxazol-5-ylactic acid methyl ester
Prepared by the method of Example 1d), from 4-hydroxy-3-(2-chloro-4-nitrobenzoylamino)phenylacetic acid methyl ester (10.07g, 27.60mmol) the subtitle compound was obtained (6.92g, 72%). \(^1\)H NMR (DMSO) \(\delta\) 8.52 (d, 1H), 8.45 (d, 1H), 8.37 (dd, 1H), 7.82 (m, 2H), 7.44 (dd, 1H), 3.88 (s, 2H), 3.63 (s, 3H).

c) 2-(2-Chloro-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester
Prepared by the method of Example 1e), from 2-(2-chloro-4-nitrophenyl)benzoxazole-5-ylactic acid methyl ester (6.92g, 19.96mmol) the subtitle compound was obtained (1.77g, 28%). \(^1\)H NMR (DMSO) \(\delta\) 7.86 (d, 1H), 7.64 (m, 2H), 7.52 (dd, 1H), 6.77 (d, 1H), 6.66 (dd, 1H), 6.20 (s, 2H), 3.82 (s, 2H), 3.63 (s, 3H).

d) \(\text{trans} 3-(2,4-Dichlorophenyl)-2-propenoic acid chloride\)
Prepared by the method of Example 25d), from \(\text{trans} 3-(2,4-dichlorophenyl)-2\)-propenoic acid (50mg, 0.24mmol) the subtitle compound was obtained (52mg, 100%). The crude product was used directly in the next reaction without purification.

e) \(\text{trans} 2-[4-\text{[3-(2,4-Dichlorophenyl)-2-propanamido]-2-chlorophenyl]benzoxazol-5-ylactic acid}\)

Prepared by the method of Example 1f), from 2-(2-chloro-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester (50mg, 0.16mmol) and \(\text{trans} 3-(2,4-dichlorophenyl)-2\)-propenoic acid chloride (52mg, 0.24mmol) the title compound was obtained (14mg, 17%). \(^1\)H NMR (DMSO) \(\delta\) 12.40 (s, 1H), 10.86 (s, 1H), 8.18 (d, 1H), 8.17 (s, 1H), 7.87 (d, 1H), 7.80 (d, 1H), 7.76 (m, 4H), 7.56 (dd, 1H), 7.36 (dd, 1H), 6.90 (d, 1H), 3.74 (s, 2H). MS: 501.1m/z (M-H)^-.

Example 68: \(\text{trans} 2-[4-\text{[3-(3-Bromophenyl)-2-propanamido]-2-chlorophenyl]benzoxazol-5-ylactic acid}\)

a) \(\text{trans} 3-(3-Bromophenyl)-2-propenoic acid chloride\)
Prepared by the method of Example 25d), from \(\text{trans} 3-(3\)-bromophenyl)-2-propenoic acid (50mg, 0.24mmol) the subtitle compound was obtained (54mg, 100%). The crude product was used directly in the next reaction without purification.

b) \(\text{trans} 2-[4-\text{[3-(3-Bromophenyl)-2-propanamido]-2-chlorophenyl]benzoxazol-5-ylactic acid}\)

Prepared by the method of Example 1f), from 2-(2-chloro-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester (50mg, 0.16mmol) and \(\text{trans} 3-(3\)-bromophenyl)-2-propenoic acid chloride (54mg, 0.24mmol) the title compound was obtained (44mg, 54%). \(^1\)H NMR (DMSO) \(\delta\) 10.82 (s, 1H), 8.22 (t, 1H), 7.98 (dd, 1H), 7.89 (s, 1H), 7.65 (m, 6H), 7.44 (t, 1H), 7.34 (dd, 1H), 6.88 (d, 1H), 3.72 (s, 2H). MS: 496.2m/z (M+H)^+.

Example 69: \(\text{trans} 2-[4-\text{[3,(3,4-Methylenedioxyphenyl)-2-propanamido]-phenyl]benzoxazol-5-ylactic acid}\)

a) 4-Hydroxy-3-(4-nitrobenzoylamino)phenylacetic acid methyl ester
Prepared by the method of Example 1c), from (4-hydroxy-3-aminophenyl)acetic acid methyl ester (1.0g, 5.52mmol) and 4-nitrobenzoyl chloride (1.02g, 5.52mmol) the subtitle compound was obtained (1.75g, 83%). The crude product was used directly in the next reaction without purification.

b) 2-(4-Nitrophenyl)benzoxazol-5-y lacetic acid methyl ester
Prepared by the method of Example 1d), from 4-hydroxy-3-(4-nitrobenzoylamino)phenylacetic acid methyl ester (1.75g, 5.30mmol) the subtitle compound was obtained (1.20g, 80%). ¹H NMR (DMSO) δ 8.44 (s, 3H), 7.80 (m, 2H), 7.41 (dd, 1H), 3.87 (s, 2H), 3.64 (s, 3H).

c) 2-(4-Aminophenyl)benzoxazol-5-y lacetic acid methyl ester
Prepared by the method of Example 1e), from 2-(4-nitrophenyl)benzoxazole-5-y lacetic acid methyl ester (1.20g, 3.85mmol) the subtitle compound was obtained (0.65g, 50%). ¹H NMR (DMSO) δ 7.85 (m, 2H), 7.58 (m, 2H), 7.19 (dd, 1H), 6.69 (d, 2H), 5.98 (s, 2H), 3.79 (s, 2H), 3.62 (s, 3H).

d) trans 3-(3,4-Methylenedioxyphenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(3,4-methylenedioxyphenyl)-2-propenoic acid (51mg, 0.27mmol) the subtitle compound was obtained (36mg, 100%). The crude product was used directly in the next reaction without purification.

e) trans 2-[4-3-(3,4-Methylenedioxyphenyl)-2-propenamido]phenyl]benzoxazol-5-y lacetic acid

Prepared by the method of Example 1f), from 2-(4-aminophenyl)benzoxazol-5-y lacetic acid methyl ester (50mg, 0.177mmol) and trans 3-(3,4-methylenedioxyphenyl)-2-propenoic acid chloride (55mg, 0.266mmol) the title compound was obtained (15mg, 19%). ¹H NMR (DMSO) δ 10.58 (s, 1H), 8.17 (d, 2H), 7.94 (d, 2H), 7.70 (d, 1H), 7.66 (s, 1H), 7.56 (d, 1H), 7.30 (dd, 1H), 7.19 (m, 2H), 6.99 (d, 1H), 6.75 (d, 1H), 6.10 (s, 2H), 3.73 (s, 2H). MS: 443.3m/z (M+H)⁺.

Example 70: trans 2-[4-3-(4-Bromophenyl)-2-propenamido]phenyl]benzoxazol-5-y lacetic acid
a) trans 3-(4-Bromophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(4-bromophenyl)-2-propenoic acid (50mg, 0.266mmol) the subtitle compound was obtained (55mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-3-(4-Bromophenyl)-2-propenamido]phenyl]benzoxazol-5-y lacetic acid

Prepared by the method of Example 1f), from 2-(4-aminophenyl)benzoxazol-5-y lacetic acid methyl ester (50mg, 0.18mmol) and trans 3-(4-bromophenyl)-2-propenoic acid chloride (55mg, 0.27mmol) the title compound was obtained (25mg, 30%). ¹H NMR (DMSO) δ 10.61 (s, 1H), 8.19 (d, 2H), 7.94 (d, 2H), 7.68 (m, 7H), 7.32 (dd, 1H), 6.90 (d, 1H), 3.73 (s, 2H). MS: 478.0m/z (M+H)⁺.

Example 71: trans 2-[4-3-(3-Bromophenyl)-2-propenamido]phenyl]benzoxazol-5-y lacetic acid
a) trans 3-(3-Bromophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(3-bromophenyl)-2-propenoic acid (50mg, 0.26mmol) the subtitle compound was obtained (55mg, 100%). The crude product was used directly in the next reaction without purification.

b) 2-[4-3-(3-Bromophenyl)-2-propenamido]phenyl]benzoxazol-5-y lacetic acid
 Prepared by the method of Example 1f, from 2-(4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3-bromophenyl)-2-propenoic acid chloride (55mg, 0.26mmol) the title compound was obtained (20mg, 23%). $^1$H NMR (DMSO) δ 10.69 (s, 1H), 8.19 (d, 2H), 7.95 (d, 2H), 7.87 (s, 1H), 7.65 (m, 5H), 7.43 (t, 1H), 7.30 (d, 1H), 6.95 (d, 1H), 3.73 (s, 2H). MS: 478.0m/z (M+H)$^+$.  

**Example 72: trans 2-[4-[3-(3,5-Difluorophenyl)-2-propenamido]phenyl]benzoxazol-5-ylacetic acid**

**a) trans 3-(3,5-Difluorophenyl)-2-propenoic acid chloride**

Prepared by the method of Example 25d, from trans 3-(3,5-difluorophenyl)-2-propenoic acid (50mg, 0.26mmol) the subtitle compound was obtained (54mg, 100%). The crude product was used directly in the next reaction without purification.

**b) trans 2-[4-[3-(3,5-Difluorophenyl)-2-propenamido]phenyl]benzoxazol-5-ylacetic acid**

Prepared by the method of Example 1f, from 2-(4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.17mmol) and trans 3-(3,5-difluorophenyl)-2-propenoic acid chloride (54mg, 0.27mmol) the title compound was obtained (20mg, 26%). $^1$H NMR (DMSO) δ 10.65 (s, 1H), 8.19 (d, 2H), 7.95 (d, 2H), 7.70 (d, 1H), 7.63 (d, 2H), 7.42 (m, 2H), 7.31 (m, 2H), 6.93 (d, 1H), 3.73 (s, 2H). MS: 435.1m/z (M+H)$^+$.  

**Example 73: 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-2-fluorophenyl]benzoxazol-5-ylacetic acid**

**a) 4-Hydroxy-3-(2-fluoro-4-nitrobenzoylamino)phenylacetic acid methyl ester**

Prepared by the method of Example 1c, from (4-hydroxy-3-aminophenyl)acetic acid methyl ester (1.0g, 5.52mmol) and 2-fluoro-4-nitrobenzoyl chloride (1.12g, 5.52mmol) the subtitle compound was obtained (2.0g, 100%). The crude product was used directly in the next reaction without purification.

**b) 2-(2-Fluoro-4-nitrophenyl)benzoxazol-5-ylacetic acid methyl ester**

Prepared by the method of Example 1d, from 4-hydroxy-3-(2-fluoro-4-nitrobenzoylamino)phenylacetic acid methyl ester (2.0g, 5.75mmol) the subtitle compound was obtained (600mg, 33%). $^1$H NMR (DMSO) δ 7.86 (m, 2H), 7.58 (m, 2H), 6.70 (m, 2H).

**c) 2-(2-Fluoro-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester**

Prepared by the method of Example 1e, from 2-(2-fluoro-4-nitrophenyl)benzoxazole-5-ylacetic acid methyl ester (600mg, mmol) the subtitle compound was obtained (400mg, 73%). $^1$H NMR (DMSO) δ 7.84 (t, 1H), 7.61 (m, 2H), 7.22 (d, 1H), 6.53 (dd, 1H), 6.45 (dd, 1H).

**d) trans 3-(2,4-Dichlorophenyl)-2-propenoic acid chloride**

Prepared by the method of Example 25d, from trans 3-(2,4-dichlorophenyl)-2-propenoic acid (52mg, 0.24mmol) the subtitle compound was obtained (56mg, 100%). The crude product was used directly in the next reaction without purification.

**e) trans 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-2-fluorophenyl]benzoxazol-5-ylacetic acid**
Prepared by the method of Example 1f), from 2-(2-fluoro-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester (50mg, 0.17mmol) and trans 3-(2,4-dichlorophenyl)-2-propenoic acid chloride (56mg, 0.24mmol) the title compound was obtained (5mg, 6%). $^1$H NMR (DMSO) δ 10.94 (s, 1H), 8.22 (t, 1H), 7.99 (dd, 1H), 7.82 (m, 5H), 7.59 (m, 2H), 7.32 (dd, 1H), 6.92 (d, 1H), 3.74 (s, 2H). MS: 485.1m/z (M+H)$^+$.  

Example 74: trans 2-[4-[3-(Bromophenyl)-2-propenamido]-2-fluorophenyl]benzoxazol-5-ylactic acid  

a) trans 3-(3-Bromophenyl)-2-propenoic acid chloride  
Prepared by the method of Example 25d), from trans 3-(3-bromophenyl)-2-propenoic acid (54mg, 0.24mmol) the subtitle compound was obtained (59mg, 100%). The crude product was used directly in the next reaction without purification.

b) trans 2-[4-[3-(3-Bromophenyl)-2-propenamido]-2-fluorophenyl]benzoxazol-5-ylactic acid  

Prepared by the method of Example 1f), from trans 2-(2-fluoro-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester (50mg, 0.17mmol) and trans 3-(3-bromophenyl)-2-propenoic acid chloride (59mg, 0.24mmol) the title compound was obtained (5mg, 6%). $^1$H NMR (DMSO) δ 10.82 (s, 1H), 8.22 (t, 1H), 7.98 (dd, 1H), 7.89 (s, 1H), 7.69 (m, 6H), 7.44 (t, 1H), 7.33 (dd, 1H), 6.90 (d, 1H), 3.74 (s, 2H). MS: 496.0m/z (M+H)$^+$.  

Example 75: trans 2-[4-[3-(2,4-Dichlorophenyl)-2-propenamido]-2-methoxyphenyl]benzoxazol-5-ylactic acid  

a) 4-Hydroxy-3-(2-methoxy-4-nitrobenzoylamino)phenylacetic acid methyl ester  
Prepared by the method of Example 1c), from 4-hydroxy-3-aminophenylacetic acid methyl ester (1.0g, 5.52mmol) and 2-methoxy-4-nitrobenzoyl chloride (1.12g, 5.52mmol) the subtitle compound was obtained (1.99g, 100%). The crude product was used directly in the next reaction without purification.

b) 2-(2-Methoxy-4-nitrophenyl)benzoxazol-5-ylactic acid methyl ester  
Prepared by the method of Example 1d), from [4-hydroxy-3-(2-methoxy-4-nitrobenzoylamino)phenyl]acetic acid methyl ester (1.99g, 5.52mmol) the subtitle compound was obtained (0.68g, 36%). $^1$H NMR (DMSO) δ 8.31 (d, 1H), 7.99 (m, 2H), 7.77 (m, 2H), 7.38 (dd, 1H), 4.08 (s, 3H), 3.86 (s, 2H), 3.63 (s, 3H).

c) 2-(2-Methoxy-4-aminophenyl)benzoxazol-5-ylactic acid methyl ester  
Prepared by the method of Example 1e), from 2-(2-methoxy-4-nitrophenyl)benzoxazol-5-ylactic acid methyl ester (0.68g, 1.99mmol) the subtitle compound was obtained (0.27g, 44%). $^1$H NMR (DMSO) δ 7.75 (d, 1H), 7.56 (m, 2H), 7.16 (dd, 1H), 6.33 (d, 1H), 6.28 (dd, 1H), 5.98 (d, 1H), 3.82 (s, 3H), 3.78 (s, 2H), 3.62 (s, 3H).

d) trans 3-(2,4-Dichlorophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from \textit{trans} 3-(2,4-dichlorophenyl)-2-propenoic acid (271mg, 1.25mmol) the subtitle compound was obtained (293g, 100%). The crude product was used directly in the next reaction without purification.

\textit{e) trans} 2-\{4-[3-(2,4-Dichlorophenyl)-2-propenamido]-2-methoxyphenyl\}benzoxazol-5-ylacetic acid

\[
\text{HO}_2\text{C-} \begin{array}{c}
\text{N} \\
\text{Cl} \\
\text{Cl}
\end{array} \text{H} \begin{array}{c}
\text{H} \\
\text{H} \\
\text{Cl}
\end{array} \text{Cl}
\]

Prepared by the method of Example 1f), from 2-(methoxy-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.16mmol) and \textit{trans} 3-(2,4-dichlorophenyl)-2-propenoic chloride (56mg, 0.24mmol) the title compound was obtained (32mg, 40%). \textit{1}H NMR (DMSO) \(\delta\) 10.75 (s, 1H), 8.05 (d, 1H), 7.82 (m, 4H), 7.67 (m, 2H), 7.57 (dd, 1H), 7.42 (dd, 1H), 7.28 (dd, 1H), 6.94 (d, 1H), 3.94 (s, 3H), 3.73 (s, 2H). MS: 497.0m/z (M+H)^+.

\textbf{Example 76:} \textit{trans} 2-\{4-[3-(2-Fluoro-4-bromophenyl)-2-propenamido]-2-methoxyphenyl\}benzoxazol-5-ylacetic acid

\textit{a) trans} 3-(2-Fluoro-4-bromophenyl)-2-propenoic acid chloride

Prepared by the method of Example 25d), from \textit{trans} 3-(2-fluoro-4-bromophenyl)-2-propenoic acid (306mg, 1.25mmol) the subtitle compound was obtained (331mg, 100%). The crude product was used directly in the next reaction without purification.

\textit{b) trans} 2-\{4-[3-(2-Fluoro-4-bromophenyl)-2-propenamido]-2-methoxyphenyl\}benzoxazol-5-ylacetic acid

\[
\text{HO}_2\text{C-} \begin{array}{c}
\text{N} \\
\text{Br}
\end{array} \text{F} \begin{array}{c}
\text{H} \\
\text{O}
\end{array} \text{O}
\]

Prepared by the method of Example 1f), from 2-(methoxy-4-aminophenyl)benzoxazol-5-ylacetic acid methyl ester (50mg, 0.16mmol) and \textit{trans} 3-(2-fluoro-4-bromophenyl)-2-propenoic acid chloride (64mg, 0.24mmol) the title compound was obtained (25mg, 30%). \textit{1}H NMR (DMSO) \(\delta\) 10.72 (s, 1H), 8.03 (d, 1H), 7.72 (m, 6H), 7.54 (dd, 1H), 7.44 (dd, 1H), 7.27 (dd, 1H), 7.01 (d, 1H), 3.94 (s, 3H), 3.72 (s, 2H). MS: 527.0m/z (M+H)^+.

\textbf{Example 77:} \textit{trans} 2-\{4-[3-(4-Bromophenyl)-2-propenamido]-2-chlorophenyl\}benzoxazol-6-ylacetic acid

\textit{a) 3-Hydroxyphenylacetic acid methyl ester}

Prepared by the method of Example 1a), from 3-hydroxyphenylacetic acid (2.0g, 13.15mmol) the subtitle compound was obtained (2.15g, 98%).

\textit{b) 3-Hydroxy-4-nitrophenylacetic acid methyl ester}

To a solution of 3-hydroxyphenylacetic acid methyl ester (1.85g, 11.13mmol), acetic acid (15ml) and dichloromethane (45ml) was added 70% \textit{aq.} HNO\(_3\) (0.72ml, 11.13mmol) in acetic acid (15ml) dropwise at -30°C. The reaction was allowed to warm to room temperature over 2 h. The reaction mixture was concentrated under reduced pressure and then diluted with EtOAc (100ml). The solution was washed with water (100ml) and \textit{aq.} NaHCO\(_3\) (100ml). The aqueous layer was extracted with EtOAc (2x100ml) and the combined organic layers were washed with water (100ml) and brine, dried and concentrated in
vacuo to give the subtitle compound (0.52g, 22%). $^1$H NMR (DMSO) $\delta$ 10.97 (s, 1H), 7.87 (d, 1H), 7.04 (d, 1H), 6.88 (dd, 1H), 3.76 (s, 2H), 3.62 (s, 3H).

c) 3-Hydroxy-4-aminophenylacetic acid methyl ester
Prepared by the method of Example 1c), from 3-hydroxy-4-nitrophenylacetic acid methyl ester (0.52g, 2.46mmol) the subtitle compound was obtained (0.23g, 51%). $^1$H NMR (DMSO) $\delta$ 8.96 (s, 1H), 6.55 (d, 1H), 6.50 (d, 1H), 6.41 (dd, 1H), 3.57 (s, 3H), 3.39 (s, 2H).

d) 3-Hydroxy-4-(2-chloro-4-nitrobenzoylamino)phenylacetic acid methyl ester
Prepared by the method of Example 1c), from 3-hydroxy-4-aminophenylacetic acid methyl ester (221mg, 1.22mmol) and 2-chloro-4-nitrobenzoyl chloride (268g, 1.22mmol) the subtitle compound was obtained (445g, 100%). The crude product was used directly in the next reaction without purification.

e) 2-(2-Chloro-4-nitrophenyl)benzoxazol-6-yllacetic acid methyl ester
Prepared by the method of Example 1d), from 2,3-hydroxy-4-(2-chloro-4-nitrobenzoylamino)phenylacetic acid methyl ester (379g, 1.10mmol) the subtitle compound was obtained (132mg, 38%). $^1$H NMR (DMSO) $\delta$ 7.85 (d, 1H), 7.64 (d, 2H), 7.26 (dd, 1H), 6.77 (d, 1H), 6.66 (dd, 1H), 6.20 (s, 2H), 3.80 (s, 2H), 3.63 (s, 3H).

f) 2-(2-Chloro-4-aminophenyl)benzoxazol-6-yllacetic acid methyl ester
Prepared by the method of Example 1e), from 2-(2-chloro-4-nitrophenyl)benzoxazole-6-yllacetic acid methyl ester (379g, 1.10mmol) the subtitle compound was obtained (132mg, 38%). $^1$H NMR (DMSO) $\delta$ 7.85 (d, 1H), 7.64 (d, 2H), 7.26 (dd, 1H), 6.77 (d, 1H), 6.66 (dd, 1H), 6.20 (s, 2H), 3.80 (s, 2H), 3.63 (s, 3H).

g) trans 3-(4-Bromophenyl)-2-propenoic acid chloride
Prepared by the method of Example 25d), from trans 3-(4-bromophenyl)-2-propenoic acid (53.8mg, 0.237mmol) the subtitle compound was obtained (58.2mg, 100%). The crude product was used directly in the next reaction without purification.

h) trans 2-[4-[3-(4-Bromophenyl)-2-propenamido]-2-chlorophenyl]benzoxazol-6-yllacetic acid

\[
\text{\begin{align*}
\text{\begin{array}{c}
\text{Cl} \\
\text{C} \\
\text{O} \\
\text{H}
\end{array} \end{align*}}
\]

Prepared by the method of Example 1f), from 2-[4-(3-bromophenyl)-2-propenamido)-2-chlorophenyl]benzoxazol-6-yllacetic acid methyl ester (33mg, 0.06mmol) the title compound was obtained (20g, 62%). $^1$H NMR (DMSO) $\delta$ 12.37 (s, 1H), 10.73 (s, 1H), 8.17 (d, 1H), 8.16 (s, 1H), 7.77 (dd, 1H), 7.67 (m, 7H), 7.34 (dd, 1H), 6.85 (d, 1H), 3.74 (s, 2H). MS: 513.1m/z (M+H)+.

Example 78: trans 2-[4-[3-(4-Bromophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

a) 2-(4-Bromophenyl)benzoxazol-5-yllacetic acid methyl ester
Prepared by the method of Example 1c) and 1d), from 4-hydroxy-3-aminophenylacetic acid (5.0g, 28.0mmol) and 2-fluoro-4-bromobenzoyl chloride (6.15g, 28.0mmol) the subtitle compound was obtained (4.29g, 43%). $^1$H NMR (DMSO) $\delta$ 8.12 (d, 2H), 7.83 (d, 2H), 7.74 (m, 2H), 7.35 (dd, 1H), 3.84 (s, 2H), 3.63 (s, 3H).

b) trans 2-[3-[4-[5-Methoxycarbonylmethyl]benzoxazol-2-yl]phenyl]propenoic acid tert butyl ester
2-(4-Bromophenyl)benzoxazol-5-yllacetic acid methyl ester (4.29g, 12.3mmol), tert butyl acrylate (5.30ml, 37.2mmol), palladium (II) acetate (56mg, 0.25mmol), triethylamine (5.22ml, 37.2mmol), and trio-tolylphosphine (226mg, 0.74mmol) were suspended in DMF (15ml) and heated to 100°C overnight.
The cooled reaction mixture was diluted with water (50ml) and extracted with ethyl acetate (3x50ml). The combined organic fractions were washed with water, dried over sodium sulphate and concentrated. The residue was subjected to flash column chromatography using 20-30%ethyl acetate/petroleum ether as eluent to give the subtitle compound (2.54g, 52%). $^1$H NMR (DMSO) δ 8.20 (d, 2H), 7.93 (d, 2H), 7.74 (m, 2H), 7.63 (d, 1H), 7.35 (dd, 1H), 6.68 (d, 1H), 3.85 (s, 2H), 3.63 (s, 3H), 1.50 (s, 9H).

c) trans 2-[3-[4-[(5-Methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid
Trifluoroacetic acid (25ml) was added to a solution of trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid $^\ast$ butyl ester (2.54g, 6.40mmol) in dichloromethane (25ml) and the reaction stirred at room temperature for 30 min. The reaction was concentrated to give the subtitle compound (2.20g, 99%). $^1$H NMR (DMSO) δ 8.20 (d, 2H), 7.93 (d, 2H), 7.75 (m, 2H), 7.68 (d, 1H), 7.35 (dd, 1H), 6.68 (d, 1H), 3.89 (s, 2H), 3.63 (s, 3H).

d) trans 2-[4-[3-(4-Bromophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Oxalyl chloride (68μl, 75mmol) was added to a solution of trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) in THF (2.5ml) containing 1 drop of DMF. After 30 min the reaction was concentrated and the residue dissolved in THF (2.5ml) and added dropwise to a solution of 4-bromoaniline (52mg, 0.3mmol) and triethylamine (42ml, 0.3mmol) in THF (2.5ml). After stirring overnight a solution of lithium hydroxide (18mg, 0.75mmol) in water (1ml) was added and the reaction stirred overnight. The reaction was acidified with 2M HCl and the precipitate filtered and dried under vacuum to give the title compound (60mg, 84%). $^1$H NMR (DMSO) δ 10.45 (s, 1H), 8.27 (d, 2H), 7.86 (d, 2H), 7.75-7.65 (m, 5H), 7.53 (d, 2H), 7.35 (dd, 1H), 6.97 (d, 1H), 3.74 (s, 2H). MS: 474.9(M-H$^-$).

Example 79: trans 2-[4-[3-(3-Fluoro-4-methoxyphenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 3-fluoro-4-methoxyaniline (31mg, 0.22mmol) the title compound was obtained (52mg, 78%). $^1$H NMR (DMSO) δ 10.35 (s, 1H), 8.26 (d, 2H), 7.85 (d, 2H), 7.75 (m, 4H), 7.67 (d, 1H), 7.35 (dd, 1H), 7.16 (t, 1H), 6.93 (d, 1H), 3.82 (s, 3H), 3.74 (s, 2H). MS: 445.0 (M-H$^-$).

Example 80: trans 2-[4-[3-(3-Bromophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 3-bromoaniline (24μl, 0.22mmol) the title compound was obtained (54mg, 76%). $^1$H NMR (DMSO) δ 10.51 (s, 1H), 8.27 (d, 2H), 8.09 (s, 1H), 7.87 (d, 2H), 7.76-7.59 (m, 4H), 7.37-7.26 (m, 3H), 6.97 (d, 1H), 3.75 (s, 2H). MS: 474.8 (M-H$^-$).
Example 81: trans 2-[4-[3-(Indan-5-ylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 5-aminopyridin (29mg, 0.22mmol) the title compound was obtained (42mg, 64%). $^1$H NMR (DMSO) δ 10.18 (s, 1H), 8.26 (d, 2H), 7.85 (d, 2H), 7.73 (m, 2H), 7.64 (m, 2H), 7.42 (d, 1H), 7.35 (dd, 1H), 7.18 (d, 1H), 6.98 (d, 1H), 3.74 (s, 2H), 2.84 (m, 4H), 2.01 (m, 2H). MS: 437.1 (M-H)^-.

Example 82: trans 2-[4-[3-(2,4-Dichlorophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 2,4-dichloroaniline (35mg, 0.22mmol) the title compound was obtained (48mg, 69%). $^1$H NMR (DMSO) δ 9.83 (s, 1H), 8.27 (d, 2H), 8.02 (m, 1H), 7.88 (d, 2H), 7.71 (m, 3H), 7.46 (dd, 1H), 7.35 (d, 1H), 7.28 (dd, 1H), 6.68 (d, 1H), 3.75 (s, 2H). MS: 464.9 (M-H)^-.

Example 83: trans 2-[4-[3-(2-Fluoro-3-chlorophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 2-fluoro-3-chloroaniline (24μl, 0.22mmol) the title compound was obtained (52mg, 77%). $^1$H NMR (DMSO) δ 10.21 (s, 1H), 8.27 (d, 2H), 8.09 (m, 1H), 7.87 (d, 2H), 7.71 (m, 3H), 7.35 (m, 2H), 7.24 (m, 2H), 3.75 (s, 2H). MS: 448.7 (M-H)^-.

Example 84: trans 2-[4-[3-(4-Bromophenylmethylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 4-bromobenzylamine (40mg, 0.22mmol) the title compound was obtained (46mg, 62%). $^1$H NMR (DMSO) δ 8.77 (t, 1H), 8.23 (d, 2H), 7.81 (d, 2H), 7.72 (m, 2H), 7.55 (m, 3H), 7.34 (d, 1H), 7.27 (d, 2H), 6.83 (d, 1H), 4.39 (d, 2H), 3.74 (s, 2H). MS: 496.2 (M-H)^-.
Example 85: trans 2-[4-[3-(2,5-Difluorophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[[5-methoxycarbonylmethyl]benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 2,5-difluoroaniline (22μl, 0.22mmol) the title compound was obtained (48mg, 74%). 1H NMR (DMSO) δ 10.21 (s, 1H), 8.27 (s, 2H), 8.12 (m, 1H), 7.86 (d, 2H), 7.72 (m, 3H), 7.34 (m, 3H), 7.00 (m, 1H), 3.74 (s, 2H). MS: 432.7 (M-H).

Example 86: trans 2-[4-[3-(3-Chloro-4-fluorophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[5-methoxycarbonylmethyl]benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 3-chloro-4-fluoroaniline (32mg, 0.22mmol) the title compound was obtained (51mg, 75%). 1H NMR (DMSO) δ 10.53 (s, 1H), 8.26 (d, 2H), 8.06 (dd, 1H), 7.87 (d, 2H), 7.71 (m, 3H), 7.57 (m, 1H), 7.39 (m, 2H), 6.92 (d, 1H), 3.74 (s, 2H). MS: 449.2 (M-H).

Example 87: trans 2-[4-[3-(3-Oxazol-5-yl)phenylamino]-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[[5-methoxycarbonylmethyl]benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 5-(3-aminophenyl)oxazole (35mg, 0.22mmol) the title compound was obtained (55mg, 79%). 1H NMR (DMSO) δ 10.57 (s, 1H), 8.53 (s, 1H), 8.33 (d, 2H), 8.20 (s, 1H), 7.92 (d, 2H), 7.76 (m, 3H), 7.52 (m, 2H), 7.40 (dd, 1H), 7.06 (d, 1H), 3.79 (s, 2H). MS: 464.0 (M-H).

Example 88: trans 2-[4-[3-(2-Chloro-5-fluorophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[5-methoxycarbonylmethyl]benzoxazol-2-yl]phenyl]propenoic acid (50mg, 0.15mmol) and 2-fluoro-6-chloroaniline (32mg, 0.22mmol) the title compound was obtained (54mg, 80%). 1H NMR (DMSO) δ 10.23 (s, 1H), 8.32 (m, 1H), 8.26 (d, 2H), 7.86 (d, 2H), 7.72 (m, 3H), 7.40-7.20 (m, 4H), 3.74 (s, 2H). MS: 449.2 (M-H).

Example 89: trans 2-[4-[3-(2,3-Difluorophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid
Prepared by the method of Example 78d) from, trans 2-[3-[(5-methoxy carbonylmethyl)benzoxazol-2-yl][phenyl]]propenoic acid (50mg, 0.15mmol) and 2,3-difluoroaniline (22μl, 0.22mmol) the title compound was obtained (45mg, 69%). 1H NMR (DMSO) δ 10.24 (s, 1H), 8.27 (d, 2H), 7.93 (m, 1H), 7.87 (d, 2H), 7.71 (m, 3H), 7.35 (dd, 1H), 7.22 (m, 3H), 3.74 (s, 2H). MS: 432.9 (M-H)^+.

Example 90: trans 2-[4-[(4-Chlorophenyl)methylamino]-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[(5-methoxycarbonylmethyl)benzoxazol-2-yl][phenyl]]propenoic acid (50mg, 0.15mmol) and 4-chlorobenzylamine (27μl, 0.22mmol) the title compound was obtained (47mg, 70%). 1H NMR (DMSO) δ 8.77 (s, 1H), 8.22 (d, 2H), 7.81 (d, 2H), 7.72 (m, 2H), 7.56 (d, 1H), 7.42-7.32 (m, 5H), 6.83 (d, 1H), 4.41 (d, 2H), 3.74 (s, 2H). MS: 445.3 (M-H)^+.

Example 91: trans 2-[4-[(2,4-Difluorophenylamino)-3-oxo-1-propenyl]phenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[(5-methoxycarbonylmethyl)benzoxazol-2-yl][phenyl]]propenoic acid (50mg, 0.15mmol) and 2,4-difluoroaniline (22μl, 0.22mmol) the title compound was obtained (52mg, 80%). 1H NMR (DMSO) δ 10.05 (s, 1H), 8.27 (d, 2H), 8.08 (m, 1H), 7.85 (d, 2H), 7.70 (m, 3H), 7.36 (m, 2H), 7.15 (m, 2H), 3.74 (s, 2H). MS: 432.6 (M-H)^+.

Example 92: trans 2-[4-[(3-Indan-5-ylamino)-3-oxo-1-propenyl]-2-fluorophenyl]benzoxazol-5-ylacetic acid

a) 2-(2-Fluoro-4-bromophenyl)benzoxazol-5-ylacetic acid methyl ester
Prepared by the method of Example 1c) and 1d), from 3-hydroxy-4-aminophenylacetic acid (4.1g, 22.8mmol) and 2-fluoro-4-bromobenzoyl chloride (5.41g, 22.8mmol) the subtitle compound was obtained (4.63g, 56%). 1H NMR (DMSO) δ 8.15 (t, 1H), 7.89 (dd, 1H), 7.57 (m, 2H), 7.67 (dd, 1H), 7.37 (dd, 1H), 3.86 (s, 2H), 3.63 (s, 3H).

b) trans 2-[3-[(5-Methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]propenoic acid

trans 2-[3-[(5-Methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]propenoic acid 1butyl ester
Prepared by the method of Example 78b), from 2-(2-fluoro-4-bromophenyl)benzoxazol-5-ylacetic acid methyl ester (2.31g, 6.34mmol) and tert butylacrylate (2.80ml, 19.0mmol) the subtitle compound was obtained (2.08g, 80%) 1H NMR (DMSO) δ 8.22 (t, 1H), 7.92 (dd, 1H), 7.77 (m, 3H), 7.62 (d, 1H), 7.38 (d, 1H), 6.76 (d, 1H), 3.86 (s, 2H), 3.63 (s, 3H), 1.50 (s, 9H).

c) trans 2-[3-[(5-Methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]propenoic acid

Prepared by the method of Example 78c), from trans 2-[3-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]propenoic acid 1butyl ester (1.38g, 3.35mmol) the subtitle compound was obtained
(1.18g, 99%). $^1$H NMR (DMSO) $\delta$ 8.23 (t, 1H), 7.91 (d, 1H), 7.77 (m, 3H), 7.66 (d, 1H), 7.38 (d, 1H), 6.76 (d, 1H), 3.86 (s, 2H), 3.63 (s, 3H).

d) $\text{trans} \ 2-[4-\{3-\text{Indan}-5\text{-ylamino}\}-3\text{-oxo-1-propenyl}]\text{-2-fluorophenyl} \text{benzoxazol-5-ylacetic acid}$

Prepared by the method of Example 78d) from $\text{trans} \ 2-[3-\{4-(5\text{-methoxycarbonylmethyl} \text{benzoxazol}-2\text{-yl}]\text{-2-fluorophenyl}\} \text{propenoic acid} (50mg, 0.14mmol) and 5\text{-aminoidan} (28mg, 0.21mmol) the title compound was obtained (56mg, 88%). $^1$H NMR (DMSO) $\delta$ 10.21 (s, 1H), 8.29 (t, 1H), 7.78-7.60 (m, 6H), 7.39 (m, 2H), 7.18 (d, 1H), 6.98 (d, 1H), 3.75 (s, 2H), 2.83 (m, 4H), 2.01 (m, 2H). MS: 455.3 (M-H)$^+$.

**Example 93:** $\text{trans} \ 2-[4-\{2,4\text{-Dichlorophenylamino}\}-3\text{-oxo-1-propenyl}]\text{-2-fluorophenyl} \text{benzoxazol-5-ylacetic acid}$

Prepared by the method of Example 78d) from, $\text{trans} \ 2-[3-\{4-(5\text{-methoxycarbonylmethyl} \text{benzoxazol}-2\text{-yl}]\text{-2-fluorophenyl}\} \text{propenoic acid} (50mg, 0.14mmol) and 2,4-dichloroaniline (34mg, 0.21mmol) the title compound was obtained (58mg, 86%). $^1$H NMR (DMSO) $\delta$ 9.84 (s, 1H), 8.30 (t, 1H), 8.01 (d, 1H), 7.79-7.66 (m, 6H), 7.46 (dd, 1H), 7.38-7.28 (m, 2H), 3.75 (s, 2H). MS: 482.9 (M-H)$^+$.

**Example 94:** $\text{trans} \ 2-[4-\{3-\text{Bromophenylamino}\}-3\text{-oxo-1-propenyl}]\text{-2-fluorophenyl} \text{benzoxazol-5-ylacetic acid}$

Prepared by the method of Example 78d) from, $\text{trans} \ 2-[3-\{4-(5\text{-methoxycarbonylmethyl} \text{benzoxazol}-2\text{-yl}]\text{-2-fluorophenyl}\} \text{propenoic acid} (50mg, 0.14mmol) and 3\text{-bromoaniline} (23$$\mu$mol, 0.21mmol) the title compound was obtained (56mg, 81%). $^1$H NMR (DMSO) $\delta$ 10.52 (s, 1H), 8.29 (t, 1H), 8.08 (s, 1H), 7.79-7.57 (m, 6H), 7.38-7.26 (m, 3H), 6.96 (d, 1H), 3.75 (s, 2H). MS: 495.1 (M-H)$^+$.

**Example 95:** $\text{trans} \ 2-[4-\{3,4\text{-Dichlorophenylamino}\}-3\text{-oxo-1-propenyl}]\text{-2-fluorophenyl} \text{benzoxazol-5-ylacetic acid}$

Prepared by the method of Example 78d) from, $\text{trans} \ 2-[3-\{4-(5\text{-methoxycarbonylmethyl} \text{benzoxazol}-2\text{-yl}]\text{-2-fluorophenyl}\} \text{propenoic acid} (50mg, 0.14mmol) and 3,4-dichloroaniline (34mg, 0.21mmol) the title compound was obtained (56mg, 83%). $^1$H NMR (DMSO) $\delta$ 10.64 (s, 1H), 8.29 (t, 1H), 8.11 (d, 1H), 7.79-7.56 (m, 7H), 7.37 (dd, 1H), 6.94 (d, 1H), 3.75 (s, 2H). MS: 483.2 (M-H)$^+$.

**Example 96:** $\text{trans} \ 2-[4-\{3\text{-Fluoro-3-chlorophenylamino}\}-3\text{-oxo-1-propenyl}]\text{-2-fluorophenyl} \text{benzoxazol-5-ylacetic acid}$
Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 2-fluoro-3-chloroaniline (23µl, 0.21mmol) the title compound was obtained (52mg, 80%). 'H NMR (DMSO) δ 10.24 (s, 1H), 8.30 (t, 1H), 8.07 (m, 1H), 7.78-7.67 (m, 5H), 7.36 (m, 2H), 7.24 (m, 2H), 3.75 (s, 2H). MS: 466.6 (M-H)^-.

Example 97: trans 2-[4-[(4-cyanophenylamino)-3-oxo-1-propenyl]-2-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 4-cyanoaniline (25mg, 0.21mmol) the title compound was obtained (58mg, 94%). 'H NMR (DMSO) δ 10.85 (s, 1H), 8.30 (t, 1H), 7.90 (m, 2H), 7.83-7.69 (m, 7H), 7.37 (d, 1H), 7.03 (d, 1H), 3.75 (s, 2H). MS: 440.0 (M-H)^-.

Example 98: trans 2-[4-[(4-Bromophenylamino)-3-oxo-1-propenyl]-2-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 4-bromoaniline (36mg, 0.21mmol) the title compound was obtained (56mg, 81%). 'H NMR (DMSO) δ 10.46 (s, 1H), 8.29 (t, 1H), 7.77-7.64 (m, 7H), 7.54 (m, 2H), 7.38 (d, 1H), 6.69 (d, 1H), 3.75 (s, 2H). MS: 495.2 (M-H)^-.

Example 99: trans 2-[4-[(3-Fluoro-4-methoxyphenylamino)-3-oxo-1-propenyl]-2-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 3-fluoro-4-methoxyaniline (30mg, 0.21mmol) the title compound was obtained (54mg, 83%). 'H NMR (DMSO) δ 10.39 (s, 1H), 8.29 (t, 1H), 7.78-7.62 (m, 6H), 7.36 (m, 2H), 7.16 (t, 1H), 6.95 (d, 1H), 3.81 (s, 3H), 3.75 (s, 2H). MS: 463.3 (M-H)^-.

Example 100: trans 2-[4-[(2,5-Difluorophenylamino)-3-oxo-1-propenyl]-2-fluorophenyl]benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 2,5-difluoroaniline (21µl, 0.21mmol) the title
compound was obtained (59mg, 93%). $^1$H NMR (DMSO) δ 10.24 (s, 1H), 8.31 (t, 1H), 8.12 (m, 1H), 7.78-7.67 (m, 5H), 7.40-7.28 (m, 3H), 7.01 (m, 1H), 3.75 (s, 2H). MS: 450.9 (M-H)$^+$.  

**Example 101:** trans 2-[4-[3-(3-Chloro-4-fluorophenylamino)-3-oxo-1-propenyl]-2-fluorophenyl] benzoxazol-5-ylacetic acid

![Chemical Structure](image)

Prepared by the method of Example 78d) from, trans 2-[3-[4-[[5-methoxycarbonylmethyl]benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 3-chloro-4-fluoroaniline (31mg, 0.21mmol) the title compound was obtained (58mg, 88%). $^1$H NMR (DMSO) δ 10.56 (s, 1H), 8.29 (t, 1H), 8.06 (dd, 1H), 7.79-7.65 (m, 5H), 7.56 (m, 1H), 7.40 (m, 2H), 6.95 (d, 1H), 3.75 (s, 2H). MS: 467.3 (M-H)$^+$.  

**Example 102:** trans 2-[4-[3-(3-Oxazol-5-yl)phenylamino]-3-oxo-1-propenyl]-2-fluorophenyl] benzoxazol-5-ylacetic acid

![Chemical Structure](image)

Prepared by the method of Example 78d) from, trans 2-[3-[4-[[5-methoxycarbonylmethyl]benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 5-(3-aminophenyl)oxazole (34mg, 0.21mmol) the title compound was obtained (55mg, 81%). $^1$H NMR (DMSO) δ 10.52 (s, 1H), 8.49 (s, 1H), 8.30 (t, 1H), 8.14 (s, 1H), 7.79-7.66 (m, 7H), 7.47 (m, 2H), 7.34 (dd, 1H), 7.02 (d, 1H), 3.76 (s, 2H). MS: 481.7 (M-H)$^+$.  

**Example 103:** trans 2-[4-[3-(2,4-Difluorophenylamino)-3-oxo-1-propenyl]-2-fluorophenyl] benzoxazol-5-ylacetic acid

![Chemical Structure](image)

Prepared by the method of Example 78d) from, trans 2-[3-[4-[[5-methoxycarbonylmethyl]benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 2,4-difluoroaniline (21μL, 0.21mmol) the title compound was obtained (47mg, 74%). $^1$H NMR (DMSO) δ 10.08 (s, 1H), 8.30 (t, 1H), 8.06 (m, 1H), 7.78-7.65 (m, 5H), 7.38 (m, 2H), 7.19 (d, 1H), 7.12 (m, 1H), 3.75 (s, 2H). MS: 451.0 (M-H)$^+$.  

**Example 104:** trans 2-[4-[3-(2,3-Difluorophenylamino)-3-oxo-1-propenyl]-2-fluorophenyl] benzoxazol-5-ylacetic acid

![Chemical Structure](image)

Prepared by the method of Example 78d) from, trans 2-[3-[4-[[5-methoxycarbonylmethyl]benzoxazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 2,3-difluoroaniline (21μL, 0.21mmol) the title compound was obtained (56mg, 88%). $^1$H NMR (DMSO) δ 10.27 (s, 1H), 8.31 (t, 1H), 7.91 (m, 1H), 7.78-7.67 (m, 5H), 7.37 (dd, 1H), 7.27-7.49 (m, 3H), 3.75 (s, 2H). MS: 451.4 (M-H)$^+$.
Example 105: \( \text{trans} \) 2-[4-[3-(2-Chloro-4-fluorophenylamino)-3-oxo-1-propenyl]-2-fluorophenyl] benzoazol-5-ylactic acid

Prepared by the method of Example 78d) from, \( \text{trans} \) 2-[3-[4-[(5-methoxy carbonylmethyl)benzoazol-2-yl]-2-fluorophenyl]]propenoic acid (50mg, 0.14mmol) and 2-chloro-4-fluoroaniline (25\( \mu \)l, 0.21mmol) the title compound was obtained (60mg, 91%). \(^1\)H NMR (DMSO) \( \delta \) 9.84 (s, 1H), 8.30 (t, 1H), 7.91 (m, 1H), 7.80-7.66 (m, 5H), 7.56 (dd, 1H), 7.37 (dd, 1H), 7.31-7.22 (m, 2H), 3.75 (s, 2H). MS: 467.0 (M-H).

Example 106: \( \text{trans} \) 2-[4-[3-(4-Bromophenylamino)-3-oxo-1-propenyl]-2-chlorophenyl]]benzoazol-5-ylactic acid

a) 2-(2-Chloro-4-bromophenyl)benzoazol-5-ylactic acid methyl ester
Prepared by the method of Example 1c) and 1d), from 3-hydroxy-4-aminophenylacetic acid (1.59g, 8.51mmol) and 2-chloro-4-bromobenzoyl chloride (2.16g, 8.51mmol) the subtitle compound was obtained (710mg, 25%). \(^1\)H NMR (DMSO) \( \delta \) 8.09 (d, 1H), 8.04 (s, 1H), 7.82-7.76 (m, 3H), 7.39 (dd, 1H), 3.86 (s, 2H), 3.63 (s, 3H).

b) \( \text{trans} \) 2-[3-[4-[(5-Methoxy carbonylmethyl)benzoazol-2-yl]-2-chlorophenyl]]propenoic acid 4-butyl ester
Prepared by the method of Example 78b), from 2-(2-chloro-4-bromophenyl)benzoazol-5-ylactic acid methyl ester (1.21g, 3.20mmol) and tert butylacrylate (1.40ml, 9.60mmol) the subtitle compound was obtained (715mg, 52%). \(^1\)H NMR (DMSO) \( \delta \) 8.17 (d, 1H), 8.10 (s, 1H), 7.91 (d, 1H), 7.77 (m, 2H), 7.61 (d, 1H), 7.39 (dd, 1H), 6.78 (d, 1H), 3.87 (s, 2H), 3.63 (s, 3H), 1.50 (s, 9H).

c) \( \text{trans} \) 2-[3-[4-[(5-Methoxy carbonylmethyl)benzoazol-2-yl]-2-chlorophenyl]]propenoic acid 4-butyl ester (715mg, 1.67mmol) the subtitle compound was obtained (641mg, 99%). \(^1\)H NMR (DMSO) \( \delta \) 8.18 (d, 1H), 8.09 (s, 1H), 7.91 (dd, 1H), 7.77 (m, 2H), 7.65 (d, 1H), 7.39 (dd, 1H), 6.78 (d, 1H), 3.87 (s, 2H), 3.63 (s, 3H).

d) \( \text{trans} \) 2-[4-[(3-(4-Bromophenylamino)-3-oxo-1-propenyl)-2-chlorophenyl]benzoazol-5-ylactic acid

Prepared by the method of Example 78d) from, \( \text{trans} \) 2-[3-[4-[(5-methoxy carbonylmethyl)benzoazol-2-yl]-2-chlorophenyl]]propenoic acid (40mg, 0.11mmol) and 4-bromoaniline (18mg, 0.17mmol) the title compound was obtained (43mg, 76%). \(^1\)H NMR (DMSO) \( \delta \) 10.55 (s, 1H), 8.26 (d, 1H), 7.98 (s, 1H), 7.84-7.64 (m, 6H), 7.54 (d, 2H), 7.39 (d, 1H), 7.25 (d, 1H), 3.76 (s, 2H). MS: 511.1 (M-H).

Example 107: \( \text{trans} \) 2-[4-[3-(2-Chloro-4-fluorophenylamino)-3-oxo-1-propenyl]-2-chlorophenyl] benzoazol-5-ylactic acid

Prepared by the method of Example 78d) from, \( \text{trans} \) 2-[3-[4-[(5-methoxy carbonylmethyl)benzoazol-2-yl]-2-chlorophenyl]]propenoic acid (40mg, 0.11mmol) and 2-chloro-4-fluoroaniline (20\( \mu \)l, 0.17mmol) the title compound was obtained (37mg, 69%). \(^1\)H NMR (DMSO) \( \delta \) 10.23 (s, 1H), 8.26 (d, 1H), 8.09 (t, 1H), 56
Example 108: trans 2-[3-(3,4-Dichlorophenylamino)-3-oxo-1-propanyl]-2-chlorophenyl benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-2-chlorophenyl]propenoic acid (40mg, 0.11mmol) and 3,4-dichloroaniline (28mg, 0.17mmol) the title compound was obtained (33mg, 60%). $^1$H NMR (DMSO) δ 10.63 (s, 1H), 8.25 (d, 1H), 8.11 (d, 1H), 7.99 (s, 1H), 7.83 (d, 1H), 7.75 (m, 2H), 7.69 (d, 1H), 7.59 (m, 2H), 7.38 (d, 1H), 6.96 (d, 1H), 3.75 (s, 2H). MS: 500.3 (M-H)^+.

Example 109: trans 2-[3-(4-Bromophenylamino)-3-oxo-1-propanyl]-3-fluorophenyl benzoxazol-5-ylacetic acid

a) 2-(3-Fluoro-4-bromophenyl)benzoxazol-5-ylacetic acid methyl ester
Prepared by the method of Example 1c) and 1d), from 3-hydroxy-4-aminophenylacetic acid (376mg, 0.21mmol) and 3-fluoro-4-bromobenzoyl chloride (541mg, 2.28mmol) the subtitle compound was obtained (630mg, 76%). $^1$H NMR (DMSO) δ 8.08 (d, 1H), 7.97 (m, 2H), 7.75 (m, 2H), 7.38 (d, 1H), 3.85 (s, 2H), 3.64 (s, 3H).

b) trans 2-[3-[4-[(5-Methoxycarbonylmethyl)benzoxazol-2-yl]-3-fluorophenyl]propenoic acid butyl ester
Prepared by the method of Example 78b), from 2-(3-fluoro-4-bromophenyl)benzoxazol-5-ylacetic acid methyl ester (200mg, 0.54mmol) and tert butyl acrylate (120µl, 0.82mmol) the subtitle compound was obtained (158mg, 70%). $^1$H NMR (DMSO) δ 8.13-7.99 (m, 3H), 7.75 (m, 2H), 7.65 (d, 1H), 7.37 (dd, 1H), 6.71 (d, 1H), 3.85 (s, 2H), 3.64 (s, 3H), 1.50 (s, 9H).

c) trans 2-[3-[4-[(5-Methoxycarbonylmethyl)benzoxazol-2-yl]-3-fluorophenyl]propenoic acid butyl ester
Prepared by the method of Example 78c), from trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-3-fluorophenyl]propenoic acid butyl ester (148mg, 0.36mmol) the subtitle compound was obtained (115mg, 99%). $^1$H NMR (DMSO) δ 8.12-8.00 (m, 3H), 7.77-7.67 (m, 3H), 7.37 (d, 1H), 6.73 (d, 1H), 3.85 (s, 2H), 3.63 (s, 3H).

d) trans 2-[3-(4-Bromophenylamino)-3-oxo-1-propanyl]-3-fluorophenyl benzoxazol-5-ylacetic acid

Prepared by the method of Example 78d) from, trans 2-[3-[4-[(5-methoxycarbonylmethyl)benzoxazol-2-yl]-3-fluorophenyl]propenoic acid (50mg, 0.14mmol) and 4-bromoaniline (36mg, 0.21mmol) the title compound was obtained (48mg, 70%). $^1$H NMR (DMSO) δ 10.51 (s, 1H), 8.12-8.01 (m, 2H), 7.94 (t, 1H), 7.76-7.66 (m, 5H), 7.53 (m, 2H), 7.37 (d, 1H), 7.05 (d, 1H), 3.75 (s, 2H). MS: 494.3(M-H)^+.

Biological Data

The biological activity of the compounds of the invention may be tested in the following assay systems:
**Heparanase assay:** The assay is based upon the use of the specific binding of basic fibroblast growth factor (bFGF) to heparan sulfate. Heparan sulphate can be detected via binding of bFGF using a horse radish peroxidase-conjugated bFGF antibody. Following cleavage of high molecular weight heparan sulfate by heparanase, the smaller material generated will no longer adhere to the surface of a 96 well plate and hence heparanase activity can be followed as a reduction in bFGF binding.

Nunc Maxisorp 96-well plates are coated for 16h at RT with 100µl/well 0.04mg/ml heparan sulfate in PBS. The wells are then aspirated and blocked for 1h with 200µl/well 1% BSA-PBS. Following five washes with 0.01% BSA, 0.05% Tween20 PBS (wash buffer), 100µl of recombinant human basic FGF (90ng/ml in 0.1% BSA/PBS) is added per well and the plate is incubated at room temperature for 1h.

After a further five washes with the wash buffer, 10µl of test compound (in 10% DMSO) and 90µl of human heparanase in 100mM sodium acetate, 5mM CaCl₂, pH 5.5 are added to each well and the plate incubated for 2h at 37°C. The wells are washed again with wash buffer and 100µl of bFGF antibody-horse radish peroxidase conjugate added. The plate is incubated at room temperature for 1h and washed again five times with wash buffer. 100µl of TMB peroxidase substrate is added and the colour allowed to develop for 10 min. The reaction is stopped with 50µl 1M H₂SO₄ and the colour read at 450nm on a plate reader.

**Angiogenesis Assay:** A commercial angiogenesis assay for analysing the angiogenic or anti-angiogenic properties of test compounds (AngioKit catalogue no. ZHA-1000, TCS CellWorks Ltd, Buckingham, U.K) was used. In this assay, human endothelial cells were co-cultured with other human cells in a specifically designed medium. The endothelial cells initially form small islands within the culture matrix. They subsequently proliferate and then enter a migratory phase during which they move through the matrix to form threadlike tubule structures. These gradually join up (by 12-14 days) to form networks of anatomising tubules which closely resemble a capillary bed structure. These tubules stain positive for von Willebrand’s Factor, Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1 or CD31) and Intercellular Adhesion Molecule-2 (ICAM-2).

The assay is supplied as growing cultures at the earliest stage of tubule formation in a 24 well plate format. It is designed so that test compounds and conditioned media can be added to the cultures within individual wells. The resulting effect on tubule formation can then be monitored. Positive and negative test agents are provided in the kit, e.g. Vascular Endothelial Growth Factor (VEGF) and sumarin. All reagents were included as part of the kit and the assay was performed according to the protocol supplied by TCS CellWorks Ltd. Briefly, on day 1, fresh growth medium, medium plus control agent or medium plus test compound was added to the cells and the cultures were incubated at 37°C, 5% CO₂. Test compounds were dissolved in DMSO and the final concentration of DMSO in the medium did not exceed 0.1% (v/v). The specified medium was changed at days 4, 7 and 9 and the cells were monitored for growth. On day 11, the cells were washed with Dulbecco’s Phosphate-Buffered Saline (PBS) and fixed using 70% ethanol (-20°C) for 30min at room temperature. After fixing, the cells were washed and treated with blocking buffer, 1% BSA in PBS. The cells were stained for PECAM-1 on the same day, following standard immunohistochemistry procedures well known to those skilled in the art, using mouse anti-human CD31 as the primary antibody and a goat anti-mouse IgG alkaline phosphate conjugate. Tubule formation was quantitatively assessed by measuring PECAM-1 positive staining using the image analysis program “Matrox inspector” to evaluate the percentage tubule staining relative to an untreated control.
The following table gives the heparanase and angiogenesis inhibitory activity of representative compounds of the invention.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition of Heparanase (IC\textsubscript{50} microM)</th>
<th>Angiogenesis (IC\textsubscript{50} microM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>11</td>
<td>3.0</td>
<td>5.0</td>
</tr>
<tr>
<td>24</td>
<td>0.4</td>
<td>7.5</td>
</tr>
<tr>
<td>25</td>
<td>0.45</td>
<td>1.0</td>
</tr>
<tr>
<td>28</td>
<td>0.8</td>
<td>2.0</td>
</tr>
<tr>
<td>29</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>38</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>55</td>
<td>0.8</td>
<td>0.25</td>
</tr>
<tr>
<td>78</td>
<td>0.7</td>
<td>0.25</td>
</tr>
<tr>
<td>95</td>
<td>0.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>
CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:

   ![Chemical Structure](image)

   (I)

   wherein
   
   R¹, R² and R³ are independently, hydrogen, halogen, CF₃, OR⁶, NR⁷R⁸, NR⁸COR¹⁰, NR⁸SO₂R¹⁰ or C₁₋₆ alkyl optionally substituted by hydroxy, C₁₋₆ alkoxy or NR⁷R⁸;
   
   R⁴ is NR⁸CONR⁹R⁸, NR⁸COR⁹, NR⁸SO₂R⁹, or W-CONNR⁸R⁹, where W is a bond, C₁₋₆ alkyne, C₂₋₆ alkenylene or C₂₋₆ alkyneylene;
   
   R⁵ is

   wherein one of X and Y is CO₂H or tetrazole, or C₁₋₆ alkyl or C₂₋₆ alkenyl wherein one of the -CH₂⁻ groups may be replaced with O and wherein the alkyl or alkenyl is substituted with one or more CO₂H or tetrazole groups, and the other is hydrogen; and Z is NR⁷, O or S;
   
   R⁶ is hydrogen or C₁₋₆ alkyl, C₃₋₆ alkenyl or C₃₋₆ alkynyl any of which is optionally substituted by hydroxy, C₁₋₆ alkoxy or NR⁸R⁹;
   
   R⁷ is hydrogen or C₁₋₆ alkyl or C₃₋₆ alkenyl either of which is optionally substituted by C₁₋₆ alkoxy or a 5- or 6-membered heterocyclic ring containing up to three heteroatoms selected from NR⁸, S and O;
   
   R⁸ is hydrogen or C₁₋₆ alkyl;
   
   or the groups R⁷ and R⁸ may together with the nitrogen to which they are attached form a 5- or 6-membered ring which optionally contains up to two further heteroatoms selected from NR⁸, S and O;
   
   R⁹ is a group -W-Ar, wherein W is a bond, C₁₋₆ alkyne, C₂₋₆ alkenylene or C₂₋₆ alkynylene and Ar is a 5- to 10-membered carbocyclic group or heterocyclic group which contains up to three heteroatoms selected from O, NR¹¹ and S; the Ar group being optionally substituted by one or more substituents selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, halogen, OR⁶, CN, CF₃, OCF₃, NR⁷R⁸, SO₂R¹⁰, COR¹⁰, R¹⁰, methylenedioxy, an oxo group and a 5- to 6-membered heteroaryl group which contains up to two heteroatoms selected from S, O and NR⁸ and which is optionally substituted by one or more substituents selected from halogen, C₁₋₆ alkyl and OR⁶;
   
   R¹⁰ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl or phenyl optionally substituted by one or more substituents selected from halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, CF₃, OCF₃, OR⁶, CN, and methylenedioxy; and
   
   R¹¹ is hydrogen or C₁₋₆ alkyl optionally substituted by phenyl, wherein the phenyl is optionally substituted by one or more substituents selected from halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, CF₃, OCF₃, OR⁶, CN, and methylenedioxy.

2. A compound according to claim 1 where R¹, R² and R³ are independently, hydrogen, halogen, OR⁶, NR⁷R⁸ or C₁₋₆ alkyl optionally substituted by hydroxy or C₁₋₆ alkoxy.
3. A compound according to claim 1 or 2 where R⁴ is NR⁸COR⁸, NR⁸CONR⁸R⁹, or W-CONR⁸R⁹, where W is a bond, C₁₋₆ alkyne or C₂₋₄ alkenylene.

4. A compound according to any one of the preceding claims where Z is O.

5. A compound according to any one of the preceding claims where R⁴ is hydrogen or C₁₋₆ alkyl, C₃₋₆ alkenyl or C₃₋₆ alkynyl any of which is optionally substituted by hydroxy or C₁₋₆ alkoxy.

6. A compound according to any one of the preceding claims where R⁹ is a group -W-Ar, wherein W is a bond, C₁₋₆ alkyne or C₂₋₆ alkenylene and Ar is a 5- to 10-membered carbocyclic group or heterocyclic group which contains up to three heteroatoms selected from O, NR¹¹ and S; wherein if Ar is a 5- to 10-membered carbocyclic group it is optionally substituted by one or more substituents selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, halogen, OR⁸, CN, CF₃, OCF₃ and methylenedioxy; and if Ar is a 5- to 10-membered heterocyclic group, it is optionally substituted by one or more substituents selected from halogen, OR⁸, R¹⁰, SO₂R¹⁰, an oxo group and a 5- to 6-membered heteroaryl group which contains up to two heteroatoms selected from S and NR⁸, and which is optionally substituted by one or more substituents selected from halogen, C₁₋₆ alkyl and OR⁸.

7. A compound according to any one of the preceding claims where R¹ and R² are hydrogen or halogen.

8. A compound according to any one of the preceding claims where R³ is hydrogen or OR⁸.

9. A compound according to any one of the preceding claims where the configuration of the R⁴ to R⁹ groups is:

   R¹ R² R³
   R⁴ R⁵ R⁶
   or

   R¹ R² R³
   R⁴ R⁵ R⁶

10. A compound of formula (I) as described in any one of Examples 1 to 109 or a pharmaceutically acceptable salt or prodrug thereof.

11. A compound as defined in any one of claims 1 to 10 for use in medicine.

12. A process for the preparation of a compound as defined in any one of claims 1 to 10 which comprises:
   a) when R⁴ is NR⁸COR⁸, treating a compound of formula (II):

   (II)

   wherein R⁵ is NR⁸, and R¹, R², R³ and R⁸ are as defined for claim 1, with a compound of formula (III):
wherein \( R^9 \) is as defined in claim 1, in an amide bond formation reaction; or

b) when \( R^4 \) is \( NR^5 CONR^5 R^8 \):

(i) treating a compound of formula (II) where \( R^X \) is \( NHR^8 \) and \( R^5 \) is as defined in claim 1, with a compound of formula (IV):

\[
\begin{align*}
R^9 - N & \equiv \equiv O \\
(IV)
\end{align*}
\]

wherein \( R^9 \) is as defined in claim 1; or

(ii) treating a compound of formula (II) wherein \( R^X \) is NCO with a compound of formula (V):

\[
\begin{align*}
R^9 - NH_2 \\
(V)
\end{align*}
\]

wherein \( R^9 \) is as defined in claim 1; or

(iii) treating a compound of formula (II) where \( R^X \) is \( NHR^8 \) and \( R^5 \) is as defined in claim 1, with a chloroformate derivative of formula \( ClCO_2 R \) where \( R \) is an electron withdrawing group, followed by treatment with a compound of formula (V); or

c) when \( R^4 \) is \( NR^5 SO_2 R^8 \) and \( R^5 \) and \( R^8 \) are as defined in claim 1, treating a compound of formula (II), wherein \( R^X \) is \( NHR^8 \) and \( R^5 \) is as defined in claim 1, by reaction with a sulfonyl chloride of formula \( R^5 SO_2 Cl \) wherein \( R^9 \) is as defined in claim 1; or

d) when \( R^4 \) is \( W - CONR^5 R^5 \) and \( W \) is a bond, treating a compound of formula (II) wherein \( R^X \) is \( CO_2 H \), with a compound of formula (V) in an amide bond formation reaction; or

e) when \( R^4 \) is \( W - CONR^5 R^5 \) and \( W \) is \( C_{1-6} \) alkenylene, \( C_{2-6} \) alkenylene or \( C_{2-6} \) alkynylene, treating a compound of formula (XI) or formula (XII):

\[
\begin{align*}
\text{(XI)} \\
\text{(XII)}
\end{align*}
\]

wherein \( R^1, R^2, R^3 \) and \( R^5 \) are as defined for formula (I), \( \equiv \equiv \) represents an optional double bond and \( n \) is 0, 1, 2, 3 or 4, with an amine of formula \( HNR^5 R^9 \), wherein \( R^5 \) and \( R^9 \) are as defined for claim 1, in an amide bond forming reaction.

13. A pharmaceutical formulation comprising a compound as defined in any one of claims 1 to 10 together with a pharmaceutically acceptable carrier or excipient.

14. The use of a compound as defined in any one of claims 1 to 10 in the manufacture of a medicament for the inhibition of heparanase.

15. The use of a compound as defined in any one of claims 1 to 10 in the manufacture of a medicament for the treatment of a subject with cancer.
16. The use of a compound as defined in any one of claims 1 to 10 in the manufacture of a medicament for the treatment of a disease selected from angiogenesis or an angiogenesis dependent disease, an inflammatory disease, an autoimmune disease and a cardiovascular disease.

17. A compound of formula (II):

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{R}^6 \\
\text{R}^8 \\
\end{array}
\]

\[
(\text{II})
\]

wherein \( R^X \) is NO\(_2\), NHR\(^8\), CO\(_2\)H or NCO, and \( R^1, R^2, R^3, R^5 \) and \( R^8 \) are as defined in claim 1.

18. A compound of formula (XI) or formula (XII):

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{R}^6 \\
\end{array} \quad \begin{array}{c}
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{R}^6 \\
\end{array} \quad \text{(CH}_2\text{nCO}_2\text{H)}
\]

\[
(XI) \quad (XII)
\]

wherein \( R^1, R^2, R^3 \) and \( R^5 \) are as defined in claim 1, ---- represents an optional double bond and \( n \) is 0, 1, 2, 3 or 4, or an ester thereof.