



(86) Date de dépôt PCT/PCT Filing Date: 1998/10/05

(87) Date publication PCT/PCT Publication Date: 1999/04/22

(45) Date de délivrance/Issue Date: 2008/12/02

(85) Entrée phase nationale/National Entry: 2000/04/05

(86) N° demande PCT/PCT Application No.: IB 1998/001540

(87) N° publication PCT/PCT Publication No.: 1999/019300

(30) Priorité/Priority: 1997/10/10 (US60/061,727)

(51) Cl.Int./Int.Cl. *C07D 213/71* (2006.01),
A61K 31/18 (2006.01), *A61K 31/195* (2006.01),
A61K 31/4164 (2006.01), *A61K 31/425* (2006.01),
A61K 31/443 (2006.01), *A61K 31/4439* (2006.01),
A61K 31/444 (2006.01), *A61K 31/4965* (2006.01),
A61K 31/497 (2006.01), *A61K 31/505* (2006.01),
A61K 31/506 (2006.01), ...

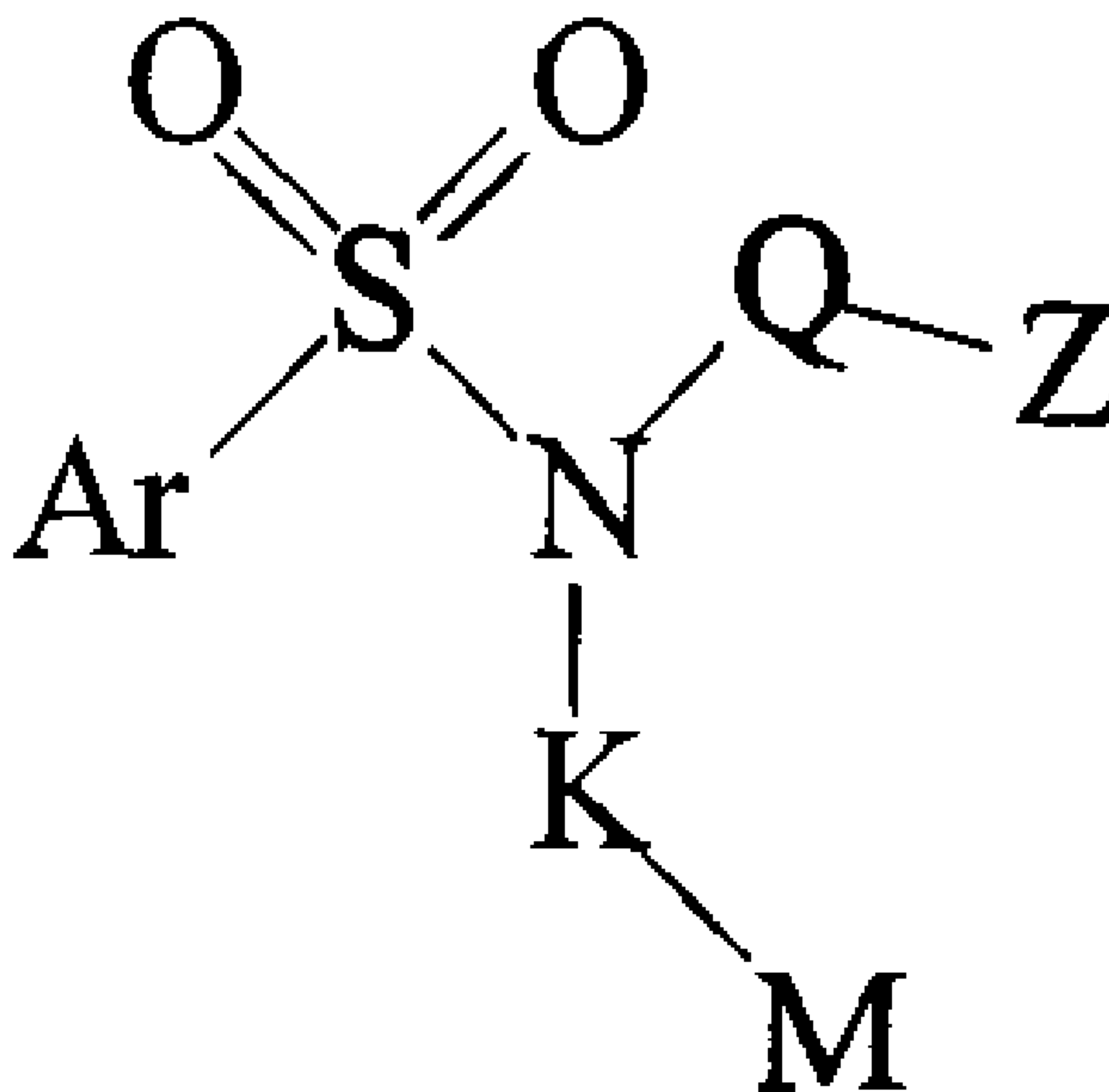
(72) Inventeurs/Inventors:
CAMERON, KIMBERLY O'KEEFE, US;
LEFKER, BRUCE ALLEN, US;
ROSATI, ROBERT LOUIS, US

(73) Propriétaire/Owner:
PFIZER INC., US

(74) Agent: SMART & BIGGAR

(54) Titre : AGONISTES DE LA PROSTAGLANDINE ET LEUR UTILISATION POUR LE TRAITEMENT DES
PROBLEMES OSSEUX

(54) Title: PROSTAGLANDIN AGONISTS AND THEIR USE TO TREAT BONE DISORDERS



(57) **Abrégé/Abstract:**

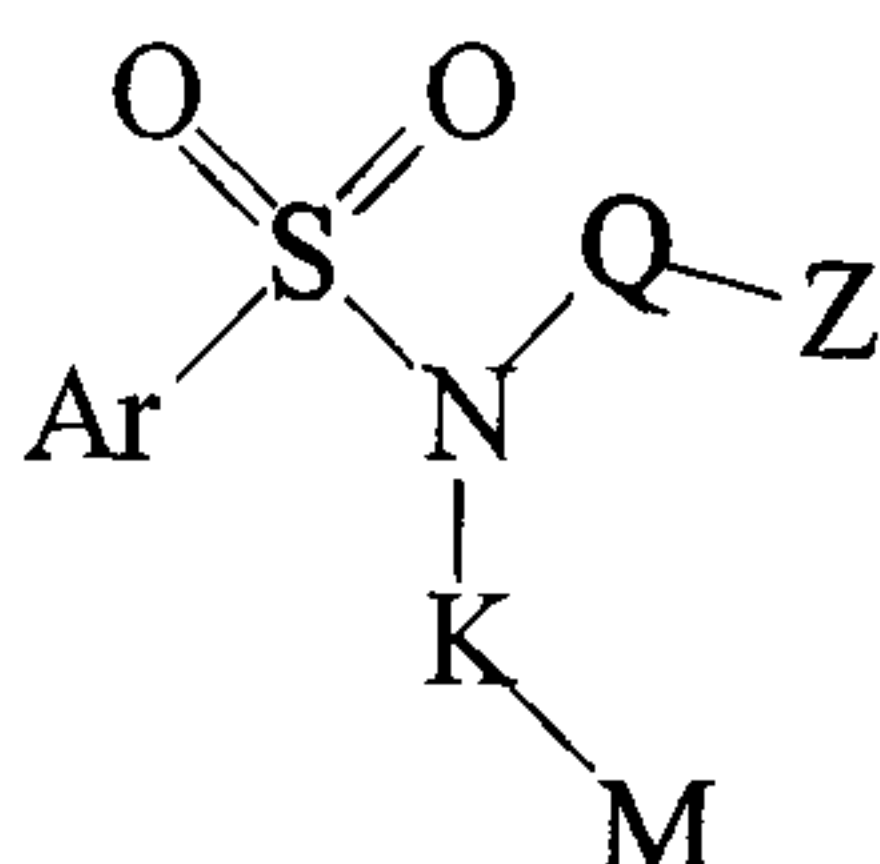
This invention relates to compounds of the Formula: (see above formula) or a pharmaceutically acceptable salt thereof, wherein Ar is an optionally substituted, partially saturated or fully unsaturated monocyclic or partially saturated, fully saturated or fully unsaturated bicyclic or tricyclic ring optionally having 1 or more heteroatoms or an optionally substituted heterocyclic ring; K is a bond or an optionally substituted and optionally mono unsaturated alkylene, thioalkylene, alkylenethioalkylene, alkyleneoxyalkylene or oxyalkylene; M is Ar₃ or Ar₃-Ar₃ which may be interrupted by another group, and wherein Ar₃ is an optionally substituted, partially saturated, fully saturated or fully unsaturated monocyclic, bicyclic or tricyclic ring optionally having 1 or more heteroatoms; and Q is an alkylene spacer that may include an optionally substituted aromatic ring optionally having 1 or 2 heteroatoms and/or another heteroatom containing moiety, such as O, S, SO, SO₂, aminosulfonyl-, sulfonylamino, etc; and Z is -COOH or alkoxycarbonyl; methods of using such compounds, pharmaceutical compositions containing such compounds and kits containing such compounds. The compounds are useful as prostaglandin agonists and are useful for the treatment of bone disorders including osteoporosis.

(51) Cl.Int./Int.Cl. (suite/continued) *A61P 13/12* (2006.01), *A61P 19/00* (2006.01), *A61P 19/08* (2006.01), *A61P 19/10* (2006.01), *A61P 27/06* (2006.01), *C07C 311/00* (2006.01), *C07D 213/38* (2006.01), *C07D 213/70* (2006.01), *C07D 233/06* (2006.01), *C07D 233/84* (2006.01), *C07D 239/24* (2006.01), *C07D 239/26* (2006.01), *C07D 241/12* (2006.01), *C07D 277/20* (2006.01), *C07D 401/12* (2006.01), *C07D 405/12* (2006.01), *C07D 417/12* (2006.01), *C07D 417/14* (2006.01)

72222-402

ABSTRACT

This invention relates to compounds of the
Formula:



5 or a pharmaceutically acceptable salt thereof, wherein Ar is an optionally substituted, partially saturated or fully unsaturated monocyclic or partially saturated, fully saturated or fully unsaturated bicyclic or tricyclic ring optionally having 1 or more heteroatoms or an optionally substituted heterocyclic ring; K is a bond or an optionally substituted and optionally mono unsaturated alkylene, thioalkylene, alkylene-thioalkylene, alkyleneoxyalkylene or
10 oxyalkylene; M is Ar³ or Ar³-Ar³ which may be interrupted by another group, and wherein Ar³ is an optionally substituted, partially saturated, fully saturated or fully unsaturated monocyclic, bicyclic or tricyclic ring optionally having 1 or more heteroatoms; and Q is an alkylene spacer that may
15 include an optionally substituted aromatic ring optionally having 1 or 2 heteroatoms and/or another heteroatom containing moiety, such as O, S, SO, SO₂, aminosulfonyl-, sulfonylamino, etc; and Z is -COOH or alkoxycarbonyl; methods of using such compounds, pharmaceutical compositions
20 containing such compounds and kits containing such compounds. The compounds are useful as prostaglandin agonists and are useful for the treatment of bone disorders including osteoporosis.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

-1-

PROSTAGLANDIN AGONISTS AND THEIR USE TO TREAT BONE DISORDERS
BACKGROUND OF INVENTION

This invention relates to prostaglandin agonists, pharmaceutical compositions containing such agonists and the use of such agonists to prevent
5 bone loss or restore or augment bone mass and to enhance bone healing including the treatment of conditions which present with low bone mass and/or bone defects in vertebrates, and particularly mammals, including humans.

Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility
10 and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated.

15 The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study has estimated that there will be 4.5 million hip fractures worldwide in 2050.

20 Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

There are currently two main types of pharmaceutical therapy for the
25 treatment of osteoporosis. The first is the use of anti-resorptive compounds to reduce the resorption of bone tissue.

Estrogen is an example of an anti-resorptive agent. It is known that estrogen reduces fractures. In addition, Black, et al. in EP 0605193A1 report that estrogen, particularly when taken orally, lowers plasma levels of LDL and raises
30 those of the beneficial high density lipoproteins (HDL's). However, estrogen failed to restore bone back to young adult levels in the established osteoporotic skeleton. Furthermore, long-term estrogen therapy, has been implicated in a variety of disorders, including an increase in the risk of uterine cancer, endometrial cancer

and possibly breast cancer, causing many women to avoid this treatment. The significant undesirable effects associated with estrogen therapy support the need to develop alternative therapies for osteoporosis that have the desirable effect on serum LDL but do not cause undesirable effects.

5 A second type of pharmaceutical therapy for the treatment of osteoporosis is the use of anabolic agents to promote bone formation and increase bone mass. This class of agents is expected to restore bone to the established osteoporotic skeleton.

 U.S. pat. no. 4,112,236 discloses certain interphenylene 8-aza-9-dioxothia-
10 11,12-secoprostaglandins for the treatment of patients with renal impairment.

 Certain prostaglandin agonists are disclosed in GB 1478281, GB1479156 and U.S. pat. nos. 4,175,203, 4,055,596, 4,175,203, 3,987,091 and 3,991,106 as being useful as, for example, renal vasodilators.

 U.S. pat. no. 4,033,996 discloses certain 8-aza-9-oxo(and dioxo)-thia-
15 11,12-secoprostaglandins which are useful as renal vasodilators, for the prevention of thrombus formation, to induce growth hormone release, and as regulators of the immune response.

 French patent no. 897,566 discloses certain amino acid derivatives for the treatment of neurological, mental or cardiovascular disease.

20 J. Org. Chem. 26; 1961; 1437 discloses N-acetyl-N-benzyl-p-aminophenylmercaptoacetic acid.

 U.S. pat. no. 4,761,430 discloses certain arylbenzenesulfonamide compounds as lipid-lowering agents.

 U.S. pat. no. 4,443,477 discloses certain sulphonamidophenylcarboxylic
25 acids as lipid lowering agents.

 U.S. pat. no. 3,528,961 discloses certain ϵ -caprolactam derivatives as dyes.

 U.S. pat. no. 3,780,095 discloses certain acylated anilinocarboxylic acids as cholagogues.

30 U.S. pat. no. 4,243,678 discloses certain acylhydrocarbylaminoalkanoic acids as having utility in the treatment of gastric ulcers, as sebaceous gland excretion inhibitors and for combatting skin inflammation.

U.S. pat. no. 4,386,031 discloses certain N-benzoyl- ω -anilinoalkanecarboxylic acids as antiallergic agents, thrombotic aggregation inhibitors, antiinflammatory agents and lipid-lowering agents.

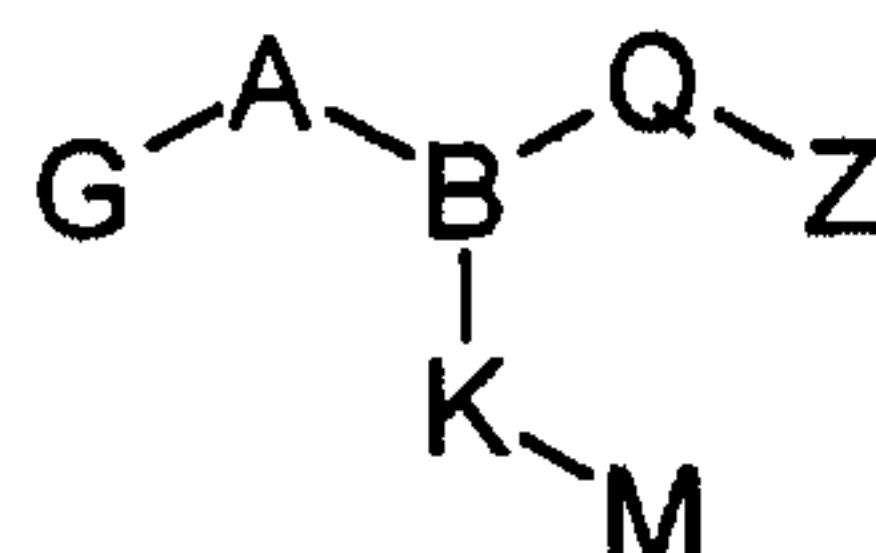
In addition to osteoporosis, approximately, 20-25 million women and an
5 increasing number of men have detectable vertebral fractures as a consequence of reduced bone mass, with an additional 250,000 hip fractures reported yearly in America alone. The latter case is associated with a 12% mortality rate within the first two years and with a 30% rate of patients requiring nursing home care after the fracture. While this is already significant, the economic and medical
10 consequences of convalescence due to slow or imperfect healing of these bone fractures is expected to increase, due to the aging of the general population.

Estrogens have been shown (Bolander et al., 38th Annual Meeting Orthopedic Research Society, 1992) to improve the quality of the healing of appendicular fractures. Therefore, estrogen replacement therapy might appear to
15 be a method for the treatment of fracture repair. However, patient compliance with estrogen therapy is relatively poor due to its side effects, including the resumption of menses, mastodynia, an increased risk of uterine cancer, an increased perceived risk of breast cancer, and the concomitant use of progestins. In addition, men are likely to object to the use of estrogen treatment. The need exists for a
20 therapy which would be beneficial to patients who have suffered debilitating bone fractures and which would increase patient compliance.

Although there are a variety of osteoporosis therapies, there is a continuing need and a continuing search in this field of art for alternative osteoporosis therapies. In addition, there is a need for bone fracture healing therapies. Also,
25 there is a need for therapy which can promote bone re-growth into skeletal areas where defects exist such as defects caused or produced by, for example, tumors in bone. Further, there is a need for therapy which can promote bone re-growth into skeletal areas where bone grafts are indicated.

SUMMARY OF THE INVENTION

This invention is directed to compounds having the Formula I



5

Formula I

prodrugs thereof, and the pharmaceutically acceptable salts of said compounds and prodrugs, wherein

A is SO₂ or CO;

10 G is Ar, Ar¹-V-Ar², Ar-(C₁-C₆)alkylene, Ar-CONH-(C₁-C₆)alkylene, R¹R²-amino, oxy(C₁-C₆)alkylene, amino substituted with Ar, or amino substituted with Ar(C₁-C₄)alkylene and R¹¹, wherein R¹¹ is H or (C₁-C₈)alkyl, R¹ and R² may be taken separately and are independently selected from H and (C₁-C₈)alkyl, or R¹ and R² are taken together with the nitrogen atom of the amino group to form a five- or six-membered azacycloalkyl, said azacycloalkyl optionally containing an oxygen
15 atom and optionally mono-, di- or tri-substituted independently with up to two oxo, hydroxy, (C₁-C₄)alkyl, fluoro or chloro;

B is N or CH;

Q is

20 -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or (C₁-C₄)alkyl,

-(C₄-C₈)alkylene-, said alkylene optionally substituted with up to four substituents independently selected from fluoro or (C₁-C₄)alkyl,

25 -X-(C₁-C₅)alkylene-, said alkylene optionally substituted with up to four substituents independently selected from fluoro or (C₁-C₄)alkyl,

-(C₁-C₅)alkylene-X-, said alkylene optionally substituted with up to four substituents independently selected from fluoro or (C₁-C₄)alkyl,

30 -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or (C₁-C₄)alkyl,

-(C₂-C₄)alkylene-W-X-(C₀-C₃)alkylene-, said alkylenes each optionally substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl,

5 -(C₀-C₄)alkylene-X-W-(C₁-C₃)alkylene-, said alkylenes each optionally substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl,

-(C₂-C₅)alkylene-W-X-W-(C₁-C₃)alkylene-, wherein the two occurrences of W are independent of each other, said alkylenes each optionally substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl,

10 -(C₁-C₄)alkylene-ethenylene-(C₁-C₄)alkylene-, said alkylenes and said ethenylene each optionally substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl,

-(C₁-C₄)alkylene-ethenylene-(C₀-C₂)alkylene-X-(C₀-C₅)alkylene-, said alkylenes and said ethenylene each optionally substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl,

15 -(C₁-C₄)alkylene-ethenylene-(C₀-C₂)alkylene-X-W-(C₁-C₃)alkylene-, said alkylenes and said ethenylene optionally each substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl,

20 -(C₁-C₄)alkylene-ethynylene-(C₁-C₄)alkylene-, said alkylenes and said ethynylene each optionally substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl, or

-(C₁-C₄)alkylene-ethynylene-X-(C₀-C₃)alkylene-, said alkylenes and said ethynylene each optionally substituted with up to four substituents each independently selected from fluoro or (C₁-C₄)alkyl;

25 Z is carboxyl, (C₁-C₆)alkoxycarbonyl, tetrazolyl, 1,2,4-oxadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, (C₁-C₄)alkylsulfonylcarbamoyl or phenylsulfonylcarbamoyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, said (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

M is -Ar³, -Ar⁴-V¹-Ar⁵, -Ar⁴-S-Ar⁵, -Ar⁴-SO-Ar⁵, -Ar⁴-SO₂-Ar⁵ or -Ar⁴-O-Ar⁵;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen;

Ar¹ and Ar² are each independently a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

said Ar, Ar¹ and Ar² moieties are optionally substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to three substituents per moiety independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-

C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-
 5 C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

Ar³, Ar⁴ and Ar⁵ are each independently a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic
 10 ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally
 15 having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

said Ar³, Ar⁴ and Ar⁵ moieties are optionally substituted on carbon or
 20 nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to three substituents per moiety independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-
 25 C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-
 30 C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein said W alkyl groups are optionally substituted on carbon with one to three fluorines;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; said ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R¹, R², R³, R⁴, R⁵, R¹¹, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

V and V¹ are each independently a bond, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio, (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;

with the provisos that:

a. when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl then said (C₅-C₈)cycloalkyl substituents are not substituted at the one position with hydroxy; and

b. when K is a bond; G is phenyl, phenylmethyl, substituted phenyl or substituted phenylmethyl; Q is (C₃-C₈)alkylene; and M is Ar³ or Ar⁴-Ar⁵, then A is sulfonyl.

A preferred group of compounds, designated the A Group, comprises those compounds having the Formula I as shown above, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein B is N; Z is carboxyl, (C₁-C₆)alkoxycarbonyl or tetrazolyl; Ar is phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2H-imidazolyl, 2-imidazolyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 2H-pyranyl, 4H-pyranyl, pyridyl,

piperidiny, 1,4-dioxany, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl,
 1,3,5-triazinyl, 1,2,4-triazinyl, azepinyl, oxepinyl, thiepinyl, cyclopentenyl,
 cyclohexenyl, benzo(b)thienyl, benzoxazolyl, benzimidazolyl, benzthiazolyl,
 quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyl, tetralinyl,
 5 decaliny, 2H-1-benzopyranyl and 1,4-benzodioxan; Ar¹, Ar², Ar³, Ar⁴ and Ar⁵ are
 each independently cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, furyl,
 thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl,
 pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl, 2-
 pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2H-imidazolyl, 2-imidazoliny,

10 imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,
 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 2H-pyranyl, 4H-
 pyranyl, pyridyl, piperidiny, 1,4-dioxany, morpholinyl, 1,4-dithianyl,
 thiomorpholinylpiperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, azepinyl, oxepinyl,
 thiepinyl, 1,2,4-diazepinyl, cyclopentenyl, cyclohexenyl, cycloheptenyl,

15 cyclooctenyl, cyclooctadienyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, 1H-
 isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl,
 isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl,
 benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl,
 quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-

20 naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decaliny, 2H-1-
 benzopyranyl, 1,4-benzodioxan, pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl,
 pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-
 benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-
 benzoxazinyl; and X is tetrahydrofuranyl, phenyl, thiazolyl, thienyl, pyridyl,

25 pyrrazolyl, furanyl or pyrimidyl, wherein X is optionally mono-, di- or tri-substituted
 independently with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy,
 trifluoromethyl or methyl; and wherein each of said Ar, Ar¹ and Ar² groups are
 optionally substituted on carbon or nitrogen with up to three substituents
 independently selected from R³, R⁴ and R⁵; each of said Ar, Ar¹ and Ar² groups are

30 optionally substituted independently on carbon or sulfur with one or two oxo
 groups; each of said Ar³, Ar⁴ and Ar⁵ groups are optionally substituted on carbon
 or nitrogen independently with up to three R³¹, R⁴¹ and R⁵¹ groups and each of

said Ar³, Ar⁴ and Ar⁵ groups are optionally substituted independently on carbon or sulfur with one or two oxo groups.

A group of compounds within the A Group, designated the B Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein A is CO; G is oxy(C₁-C₆)alkylene; Q is

5 -(C₂-C₆)alkylene-O-(C₁-C₃)alkylene-,
 -(C₄-C₈)alkylene-, said -(C₄-C₈)alkylene- optionally substituted with up to
 four substituents independently selected from fluoro or (C₁-C₄)alkyl,
 10 -X-(C₂-C₅)alkylene-,
 -(C₁-C₅)alkylene-X-,
 -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-,
 -(C₂-C₄)alkylene-O-X-(C₀-C₃)alkylene-, or
 -(C₀-C₄)alkylene-X-O-(C₁-C₃)alkylene-; and X is phenyl, thienyl, furanyl or
 15 thiazolyl, wherein X is optionally mono-, di- or tri-substituted with chloro, fluoro,
 methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

Another group of compounds which is preferred within the A Group, designated the C Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein

20 A is CO; G is Ar; Q is

 -(C₂-C₆)alkylene-O-(C₁-C₃)alkylene-,
 -(C₄-C₈)alkylene-, said -(C₄-C₈)alkylene- optionally substituted with up to
 four substituents independently selected from fluoro or (C₁-C₄)alkyl,
 -X-(C₂-C₅)alkylene-,
 25 -(C₁-C₅)alkylene-X-,
 -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-,
 -(C₂-C₄)alkylene-O-X-(C₀-C₃)alkylene-, or
 -(C₀-C₄)alkylene-X-O-(C₁-C₃)alkylene-; and X is phenyl, thienyl, furanyl or
 thiazolyl, wherein X is optionally mono-, di- or tri-substituted with chloro, fluoro,
 30 methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

Another group of compounds which is preferred within the A Group, designated the D Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein

A is CO; G is R¹R²-amino or amino substituted with Ar, or amino substituted with Ar(C₁-C₄)alkylene and R¹¹, wherein R¹¹ is H; Q is

-(C₂-C₆)alkylene-O-(C₁-C₃)alkylene-,

-(C₄-C₈)alkylene-, said -(C₄-C₈)alkylene- optionally substituted with up to

5 four substituents independently selected from fluoro or (C₁-C₄)alkyl,

-X-(C₂-C₅)alkylene-,

-(C₁-C₅)alkylene-X-,

-(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-,

-(C₂-C₄)alkylene-O-X-(C₀-C₃)alkylene-, or

10 -(C₀-C₄)alkylene-X-O-(C₁-C₃)alkylene-; and X is phenyl, thienyl, furanyl or

thiazolyl, wherein X is optionally mono-, di- or tri-substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl; and

wherein R¹ and R² may be taken separately and are independently

selected from H and (C₁-C₈)alkyl, or R¹ and R² are taken together to form a five- or

15 six-membered azacycloalkyl, said azacycloalkyl optionally containing an oxygen atom.

Another group of compounds which is preferred within the G Group, designated the E Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein

20 A is SO₂; G is R¹R²-amino, or amino substituted with Ar and R¹¹; Q is

-(C₂-C₆)alkylene-O-(C₁-C₃)alkylene-,

-(C₄-C₈)alkylene-, said -(C₄-C₈)alkylene- optionally substituted with up to

four substituents independently selected from fluoro or (C₁-C₄)alkyl,

-X-(C₂-C₅)alkylene-,

25 -(C₁-C₅)alkylene-X-,

-(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-,

-(C₂-C₄)alkylene-O-X-(C₀-C₃)alkylene-, or

-(C₀-C₄)alkylene-X-O-(C₁-C₃)alkylene-; and X is phenyl, thienyl, furanyl or

thiazolyl, wherein X is optionally mono-, di- or tri-substituted with chloro, fluoro,

30 methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl; and

wherein R¹ and R² may be taken separately and are independently

selected from H and (C₁-C₈)alkyl, or R¹ and R² are taken together to form a five- or

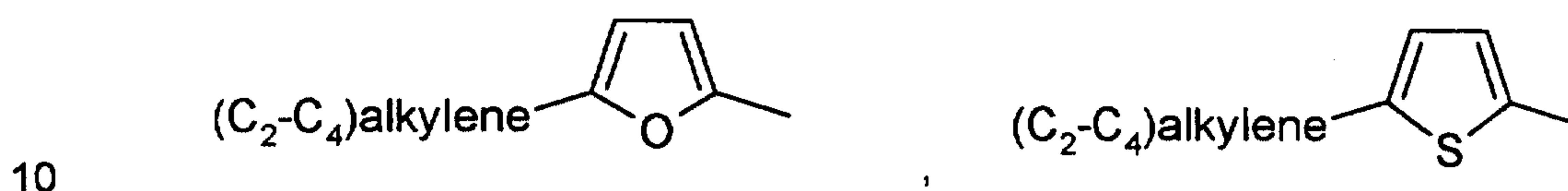
six-membered azacycloalkyl, said azacycloalkyl optionally containing an oxygen atom.

Another group of compounds which is preferred within the A Group, designated the F Group, comprises those compounds, prodrugs thereof and
5 pharmaceutically acceptable salts of said compounds and said prodrugs, wherein A is SO₂; G is Ar, Ar(C₁-C₂)alkylene or Ar¹-V-Ar²; Q is

-(C₂-C₆)alkylene-O-(C₁-C₃)alkylene-,
-(C₄-C₈)alkylene-, said -(C₄-C₈)alkylene- optionally substituted with up to
four substituents independently selected from fluoro or (C₁-C₄)alkyl,
10 -X-(C₂-C₅)alkylene-,
-(C₁-C₅)alkylene-X-,
-(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-,
-(C₂-C₄)alkylene-O-X-(C₀-C₃)alkylene-, or
-(C₀-C₄)alkylene-X-O-(C₁-C₃)alkylene-; and X is phenyl, pyrimidyl, pyridyl,
15 thienyl, tetrahydrofuranyl, furanyl or thiazolyl, wherein X is optionally mono-, di- or tri-substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

A particularly preferred group of compounds within the F Group, designated the FA Group, comprises those compounds, prodrugs thereof and
20 pharmaceutically acceptable salts of said compounds and said prodrugs, wherein G is Ar or Ar-(C₁-C₂)-alkylene; Ar is phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl or 1,3,4-thiadiazolyl wherein each of said Ar groups is optionally substituted on carbon or nitrogen with R¹, R² or R³; Ar⁴ is
25 cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolidinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, thiomorpholinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, azepinyl, oxepinyl or thiepinyl wherein each of said Ar⁴ groups is optionally mono- di- or tri-
30 substituted on carbon or nitrogen with R³¹, R⁴¹ or R⁵¹; Ar⁵ is cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolidinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, 1,4-

dioxanyl, thiomorpholinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, azepinyl, oxepinyl or thiepinyl wherein each of said Ar⁵ groups is optionally mono-di- or tri-substituted on carbon or nitrogen with R³¹, R⁴¹ or R⁵¹; Q is -(C₅-C₇)-alkylene-, -(C₁-C₂)-alkylene-X-(C₁-C₂)-alkylene-, -(C₁-C₂)-X-O-(C₁-C₂)-alkylene-, -
 5 (C₂-C₄)-alkylene-thienyl-, -(C₂-C₄)-alkylene-furanyl- or -(C₂-C₄)-alkylene-thiazolyl-; X is phenyl, pyridyl, pyrimidyl or thienyl; and said X groups are optionally mono-, di- or tri- substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl; said -(C₂-C₄)-alkylene-furanyl- and -(C₂-C₄)-alkylene-thienyl- having a 2,5- substitution pattern, e.g.,



A preferred group of compounds within the FA Group, designated the FB Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein K is methylene, M is Ar⁴-Ar⁵, Ar⁴-O-Ar⁵ or Ar⁴-S-Ar⁵ and Ar is phenyl, pyridyl, pyrazolyl, imidazolyl,
 15 pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted on carbon or nitrogen with R³, R⁴ or R⁵.

A preferred group of compounds within the FB Group, designated the FC Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein M is Ar⁴-Ar⁵; Ar is
 20 phenyl, pyridyl or imidazolyl; Ar⁴ is phenyl, furanyl or pyridyl; and Ar⁵ is cyclopentyl, cyclohexyl, cycloheptyl, phenyl, pyridyl, imidazolyl, pyrimidyl, thienyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl or thiazolyl, wherein Ar, Ar⁴ and Ar⁵ are optionally mono-, di- or tri-substituted on carbon or nitrogen independently with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy.

25 An especially preferred group of compounds within the FC Group, designated the FD Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is -(C₅-C₇)-alkylene-.

30 Another especially preferred group of compounds within the FC Group, designated the FE Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein

Q is $\text{CH}_2\text{-X-CH}_2\text{-}$ and X is metaphenylene optionally mono- or di- substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

A preferred group of compounds within the FE Group are those
 5 compounds, and pharmaceutically acceptable salts and prodrugs thereof, selected from (3-(((pyridine-3-sulfonyl)-(4-pyrimidin-5-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid; (3-(((5-phenyl-furan-2-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid; (3-(((pyridine-3-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid; (3-(((pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-
 10 methyl)-phenyl)-acetic acid; and (3-(((4-pyrazin-2-yl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid.

An especially preferred compound within the FE Group is the compound wherein Ar is pyrid-3-yl; Z is carboxy; M is $\text{Ar}^4\text{-Ar}^5$ wherein Ar^4 is a furanyl ring and Ar^5 is phenyl wherein said phenyl moiety is substituted at the 5-position of said
 15 furanyl ring; and Q is $\text{-CH}_2\text{-X-CH}_2\text{-}$ wherein X is metaphenylene.

Another especially preferred compound within the FE Group is the compound wherein Ar is pyrid-3-yl; Z is carboxy; M is $\text{Ar}^4\text{-Ar}^5$ wherein Ar^4 is phenyl and Ar^5 is pyrimid-2-yl and said pyrimid-2-yl moiety is substituted at the 4-position of said phenyl ring; and Q is $\text{-CH}_2\text{-X-CH}_2\text{-}$ wherein X is metaphenylene.

20 Yet another especially preferred compound within the FE Group is the compound wherein Ar is pyrid-3-yl; Z is carboxy; M is $\text{Ar}^4\text{-Ar}^5$ wherein Ar^4 is phenyl and Ar^5 is thiazol-2-yl and said thiazol-2-yl moiety is substituted at the 4-position of said phenyl ring; and Q is $\text{-CH}_2\text{-X-CH}_2\text{-}$ wherein X is metaphenylene.

Yet another especially preferred compound within the FE Group is the
 25 compound wherein Ar is pyrid-3-yl; Z is carboxy; M is $\text{Ar}^4\text{-Ar}^5$ wherein Ar^4 is phenyl and Ar^5 is pyrimid-5-yl and said pyrimid-5-yl moiety is substituted at the 4-position of said phenyl ring; and Q is $\text{-CH}_2\text{-X-CH}_2\text{-}$ wherein X is metaphenylene.

Yet another especially preferred compound within the FE Group is the
 30 compound wherein Ar is pyrid-3-yl; Z is carboxy; M is $\text{Ar}^4\text{-Ar}^5$ wherein Ar^4 is phenyl and Ar^5 is pyrazin-2-yl and said pyrazin-2-yl is substituted at the 4-position of said phenyl ring; and Q is $\text{-CH}_2\text{-X-CH}_2\text{-}$ wherein X is metaphenylene.

A preferred group of compounds within the FC Group, designated the G Group, comprises those compounds, prodrugs thereof and pharmaceutically

acceptable salts of said compounds and said prodrugs, wherein Q is $-(C_2-C_4)$ -alkylene-thienyl-, $-(C_2-C_4)$ -alkylene-furanyl- or $-(C_2-C_4)$ -alkylene-thiazolyl-.

An especially preferred compound within the G Group is 5-(3-((pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-propyl)-thiophene-2-carboxylic acid.

5 An especially preferred compound within the G Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is n-propylenyl; X is thienyl; Z is carboxy; Ar is 3-pyridyl; Ar⁴ is phenyl; and Ar⁵ is 2-thiazolyl; said 2-thiazolyl being substituted at the 4-position of said phenyl.

10 Another especially preferred group of compounds within the FC Group, designated the H Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-CH_2-X-O-CH_2-$; Ar⁴ is phenyl or pyridyl; said phenyl and pyridyl are optionally substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy,
15 trifluoromethyl and methyl; and X is metaphenylene.

A preferred group of compounds within the H Group are (3-(((4-cyclohexyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid; (3-(((pyridine-3-sulfonyl)-(4-pyridin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid; (3-(((pyridine-3-sulfonyl)-(4-pyridin-3-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid; (3-
20 (((pyridine-3-sulfonyl)-(4-pyridin-4-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid; and (3-(((pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid.

An especially preferred compound within the H Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and
25 said prodrugs, wherein Ar is pyrid-3-yl; Z is carboxy; Ar⁴ is phenyl; Ar⁵ is cyclohexyl; and said cyclohexyl moiety is substituted at the 4-position of said phenyl ring.

Another especially preferred compound within the H Group is the compound wherein Ar is pyrid-3-yl; Z is carboxy; Ar⁴ is phenyl; Ar⁵ is thiazol-2-yl; and said thiazol-2-yl moiety is substituted at the 4-position of said phenyl ring.
30

Yet another especially preferred compound within the H Group is the compound wherein Ar is pyrid-3-yl; Z is carboxy; Ar⁴ is phenyl; Ar⁵ is 2-pyridyl; and said 2-pyridyl moiety is substituted at the 4-position of said phenyl ring.

Yet another especially preferred compound within the H Group is the compound wherein Ar is pyrid-3-yl; Z is carboxy; Ar⁴ is phenyl; Ar⁵ is 3-pyridyl; and said 3-pyridyl moiety is substituted at the 4-position of said phenyl ring.

Yet another especially preferred compound within the H Group is the
 5 compound wherein Ar is pyrid-3-yl; Z is carboxy; Ar⁴ is phenyl; Ar⁵ is 4-pyridyl; and said 4-pyridyl moiety is substituted at the 4-position of said phenyl ring.

A preferred group of compounds within the FA Group, designated the I Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein K is methylene,
 10 G is Ar; Ar is phenyl, pyridazinyl, pyrazolyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, Ar is optionally mono-, di- or tri-substituted with R³, R⁴ or R⁵, and M is Ar³, wherein said Ar³ is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinoliny, isoquinoliny, naphthyl, tetralinyl, 2H-1-
 15 benzopyranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R³¹, chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy.

An especially preferred group of compounds within the I Group are (3-(((2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-
 20 phenyl)-acetic acid; and (3-((benzofuran-2-ylmethyl-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid.

An especially preferred compound within the I Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compound and prodrugs, wherein Ar is pyrid-3-yl; Z is carboxy; M is 6-(1,4-benzodioxan); and Q
 25 is -CH₂-X-CH₂- wherein X is metaphenylene.

Another especially preferred compound within the I Group is the compound wherein Ar is pyrid-3-yl; Z is carboxy; M is 2-benzofuryl; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

Another especially preferred group of compounds within the I Group,
 30 designated the J Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar is phenyl, pyridyl or imidazolyl, said phenyl, pyridyl and imidazolyl optionally substituted independently with chloro, fluoro, methyl, methoxy, difluoromethoxy,

trifluoromethyl or trifluoromethoxy; Ar^3 is phenyl substituted with R^{31} , wherein R^{31} is (C_1-C_7) alkyl, mono-N- or di-N, N- (C_1-C_4) alkylamine, or (C_1-C_5) alkoxy, said (C_1-C_7) alkyl or (C_1-C_5) alkoxy optionally mono-, di- or tri-substituted independently with hydroxy or fluoro; and Ar^3 is further optionally mono- or di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

A preferred group of compounds within the J Group, designated the K Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-(C_5-C_7)$ alkylene-.

Another preferred group of compounds within the J Group, designated the L Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-CH_2-X-CH_2-$ and X is phenyl optionally mono-, di- or tri- substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

An especially preferred group of compounds within the L Group are (3-(((4-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid; (3-(((benzenesulfonyl-(4-butyl-benzyl)-amino)-methyl)-phenyl)-acetic acid; (3-(((4-butyl-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino)-methyl)-phenyl)-acetic acid; and (3-(((4-dimethylamino-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid.

An especially preferred compound within the L Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar is pyrid-3-yl; Z is carboxy; M is phenyl substituted at the 4-position with n-butyl; and Q is $-CH_2-X-CH_2-$ wherein X is metaphenylene.

Another especially preferred compound within the L Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar is phenyl; Z is carboxy; M is phenyl substituted at the 4-position with n-butyl; and Q is $-CH_2-X-CH_2-$ wherein X is metaphenylene.

Yet another especially preferred compound within the L Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar is 4-(1-methyl-imidazolyl); Z is carboxy;

M is phenyl substituted at the 4-position with n-butyl; and Q is $-\text{CH}_2\text{-X-CH}_2\text{-}$ wherein X is metaphenylene.

Yet another especially preferred compound within the L Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar is pyrid-3-yl; Z is carboxy; M is phenyl substituted at the 4-position with dimethylamino; and Q is $-\text{CH}_2\text{-X-CH}_2\text{-}$ wherein X is metaphenylene.

Another preferred group of compounds within the J Group comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-(\text{C}_2\text{-C}_4)\text{alkylene-thienyl}$, $-(\text{C}_2\text{-C}_4)\text{alkylene-furanyl}$ or $-(\text{C}_2\text{-C}_4)\text{alkylene-thiazolyl}$.

A preferred group of compounds within the J Group, designated the M Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-(\text{C}_1\text{-C}_2)\text{-X-O-}(\text{C}_1\text{-C}_2)\text{alkylene-}$ and X is metaphenylene, said X being optionally mono-, di- or tri-substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

An especially preferred group of compounds within the M Group are (3-(((4-dimethylamino-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid and (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid.

An especially preferred compound within the M Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar is pyrid-3-yl; Z is carboxy; M is phenyl substituted at the 4-position with dimethylamino; and Q is $-\text{CH}_2\text{-X-O-CH}_2\text{-}$ wherein X is metaphenylene.

Another especially preferred compound within the M Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar is pyrid-3-yl; Z is carboxy; M is phenyl substituted at the 4-position with *tert*-butyl; and Q is $-\text{CH}_2\text{-X-O-CH}_2\text{-}$ wherein X is metaphenylene.

Another preferred group of compounds within the FA Group, designated the N Group, comprises those compounds, prodrugs thereof and pharmaceutically

acceptable salts of said compounds and said prodrugs, wherein G is Ar; K is (C₂-C₄) alkylene or n-propenylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted with R³, R⁴ or R⁵; and M is Ar³, optionally mono-, di- or tri-

5 substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy and trifluoromethyl.

An especially preferred compound within the N Group is *trans*-(3-(((3-(3,5-dichloro-phenyl)-allyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid.

An especially preferred compound within the N Group is the compound,

10 prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein K is *trans*-n-propenylene, said M group being attached to the 1-position of the n-propenylene and said N atom being attached to the 3-position of the n-propenylene; Ar is pyrid-3-yl; M is phenyl 3,5-disubstituted with chloro; Z is carboxy; and Q is CH₂-X-CH₂- wherein X is metaphenylene.

15 A preferred group of compounds within the N Group, designated the O Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar³ is phenyl optionally substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

20 A preferred group of compounds within the O Group, designated the P Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is -(C₅-C₇)alkylene-.

25 Another group of compounds within the O Group, designated the Q Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is -CH₂-X-CH₂- and X is metaphenylene.

30 Yet another group of compounds within the O Group, designated the R Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is -(C₂-C₄)alkylene-X- and X is furanyl, thienyl or thiazolyl.

Yet another preferred group of compounds within the O Group, designated the S Group, comprises those compounds, prodrugs thereof and pharmaceutically

acceptable salts of said compounds and said prodrugs, wherein Q is $-(C_1-C_2)-X-O-$ (C_1-C_2) alkylene- and X is metaphenylene.

Another preferred group of compounds within the FA Group, designated the T Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein G is Ar; K is thioethylene or oxyethylene, Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally substituted with up to three R^3 , R^4 or R^5 ; and M is Ar^3 , optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

A preferred group of compounds within the T Group, designated the U Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Ar^3 is phenyl.

A preferred group of compounds within the U Group, designated the V Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-(C_5-C_7)$ alkylene-.

Another preferred group of compounds within the U Group, designated the W Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-CH_2-X-CH_2-$ and X is metaphenylene.

Another preferred group of compounds within the U Group, designated the X Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-(C_2-C_4)$ alkylene-X- and X is furanyl, thienyl or thiazolyl.

Another preferred group of compounds within the U Group, designated the Y Group, comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein Q is $-(C_1-C_2)-X-O-$ (C_1-C_2) alkylene- and X is metaphenylene.

An especially preferred compound within the Y Group is (3-(((2-(3,5-dichloro-phenoxy)-ethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid.

An especially preferred compound within the Y Group is the compound, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein K is ethylenyloxy; said M group being attached to the

72222-402

-21-

oxygen atom of the ethylenyloxy group and said N atom being attached to the 2-position of the ethylenyloxy group; Ar is pyrid-3-yl; M is phenyl 3,5-disubstituted with chloro; Z is carboxy and Q is $-\text{CH}_2\text{-X-O-CH}_2\text{-}$ wherein X is a second phenyl ring and said CH_2 and OCH_2 substituents are situated in a meta substitution pattern on said second phenyl ring.

Another preferred group of compounds, designated the Z Group, comprises those compounds of Formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein B is CH.

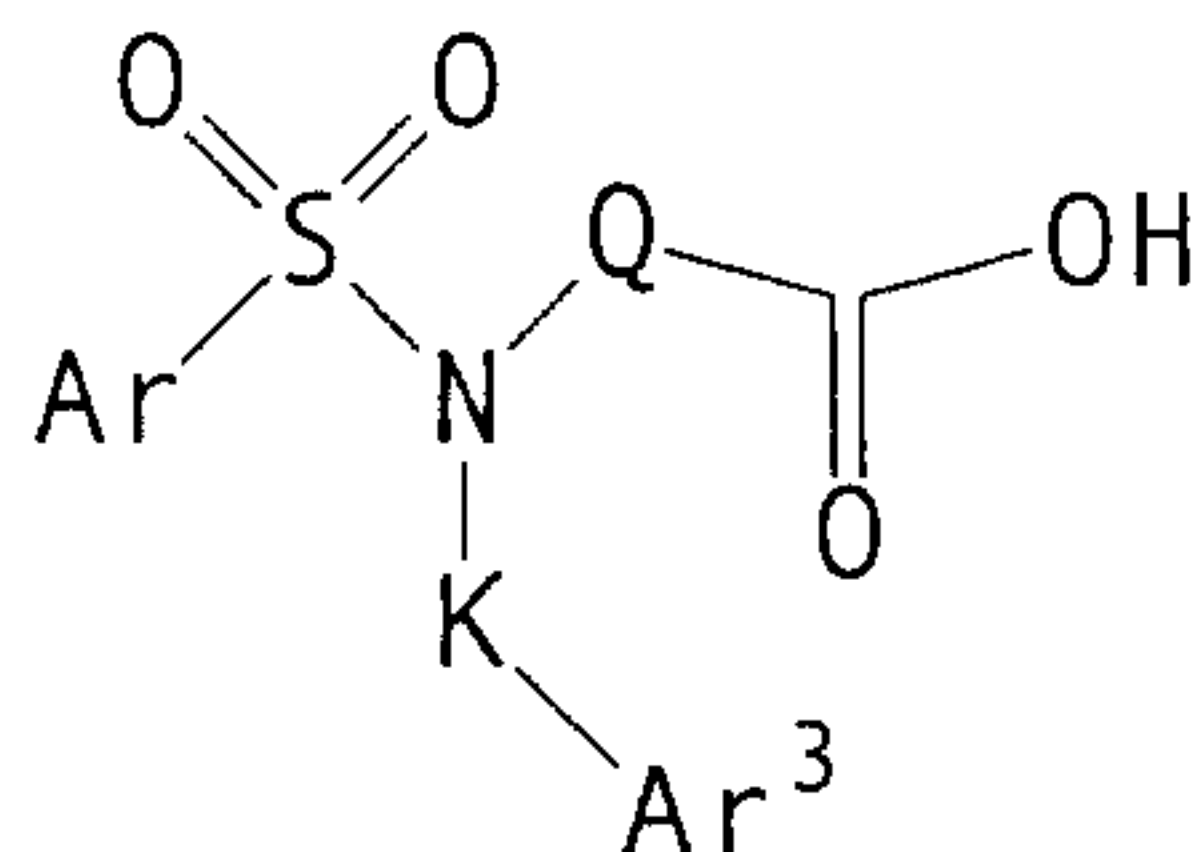
A preferred group of compounds within the Z Group comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein A is CO; G is Ar, K is methylenyl, propylenyl, propenylenyl or oxyethylenyl; M is Ar^3 or $\text{Ar}^4\text{-Ar}^5$; Ar^3 is phenyl or pyridyl; Ar^4 is phenyl, thienyl, pyridyl or furanyl; Ar^5 is $(\text{C}_5\text{-C}_7)$ cycloalkyl, phenyl, pyridyl, imidazolyl, pyrimidyl, thienyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl or thiazolyl; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar, Ar^3 , Ar^4 and Ar^5 are optionally substituted independently with up to three chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

Another especially preferred group of compounds within the Z Group comprises those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein A is CO; G is Ar, K is methylenyl, propylenyl, propenylenyl or oxyethylenyl; M is Ar^3 or $\text{Ar}^4\text{-Ar}^5$; Ar^3 is phenyl or pyridyl; Ar^4 is phenyl, thienyl, pyridyl or furanyl; Ar^5 is $(\text{C}_5\text{-C}_7)$ cycloalkyl, phenyl, pyridyl, imidazolyl, pyrimidyl, thienyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl or thiazolyl; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar, Ar^3 , Ar^4 and Ar^5 are optionally substituted independently with up to three chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

72222-402

-21a-

Another especially preferred group of compounds is a compound of the Formula:



5

wherein:

Q is $-(\text{C}_0\text{-C}_4)\text{alkylene-X-W-(C}_1\text{-C}_3)\text{alkylene-}$, the alkylenes each optionally substituted with up to four substituents each independently selected from fluoro and
 10 $(\text{C}_1\text{-C}_4)\text{alkyl}$,

K is a bond, $(\text{C}_1\text{-C}_9)\text{alkylene}$, thio $(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkylenethio}(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkyleneoxy}(\text{C}_1\text{-C}_4)\text{alkylene}$ or oxy $(\text{C}_1\text{-C}_4)\text{alkylene}$, the $(\text{C}_1\text{-C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when
 15 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four
 20 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected
 25 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from
 30 nitrogen, sulfur and oxygen, the partially or fully

72222-402

-21b-

saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two

5 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

10 selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,

15 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,

20 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

25 Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully

30 saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

72222-402

-21c-

independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully

5 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic,

10 or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl,

15 (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl,

20 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio,

25 (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N- (C_1-C_4) alkyleneaminosulfonyl-, sulfonylamino, N- (C_1-C_4) alkylenesulfonylamino, carboxamido,

30 N- (C_1-C_4) alkylenecarboxamido, carboxamidooxy, N- (C_1-C_4) alkylenecarboxamidooxy, carbamoyl, -mono-N- (C_1-C_4) alkylenecarbamoyl, carbamoyloxy, or -mono-N- (C_1-C_4) alkylenecarbamoyloxy, wherein the W alkyl

72222-402

-21d-

groups are optionally substituted on carbon with one to three fluorines;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

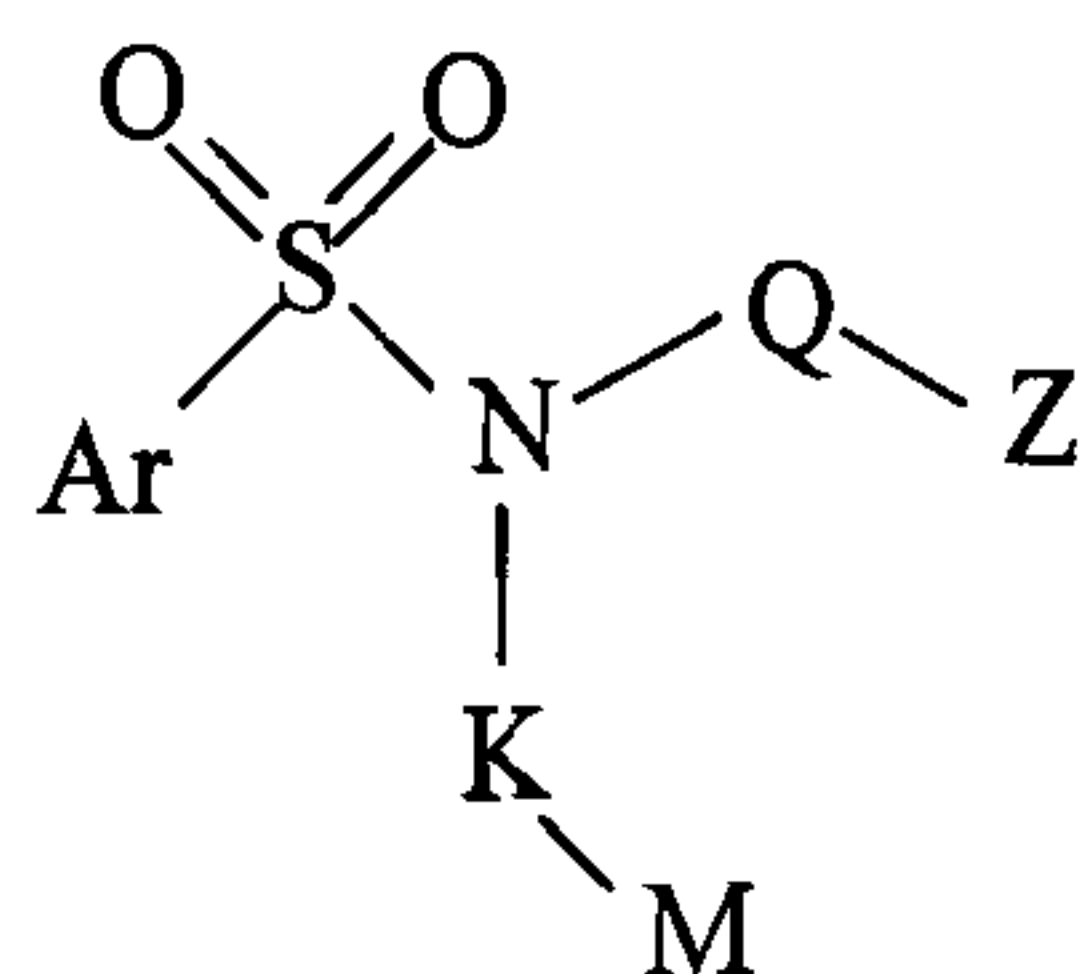
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

with the proviso that when K is (C₂-C₄)alkylene and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl then Ar³ is not substituted at the one position with hydroxy;

or a pharmaceutically acceptable salt thereof.

Another especially preferred group of compounds is a compound having the Formula:

20



Q is -(C₀-C₄)alkylene-X-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents each independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

72222-402

-21e-

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
5 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

M is Ar³;

Ar is a partially saturated or fully unsaturated
10 five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently,
15 optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally
20 having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully
25 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar
30 is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl,

72222-402

-21f-

(C₂-C₇) alkenyl, (C₂-C₇) alkynyl, (C₃-C₇) cycloalkyl,
 (C₃-C₇) cycloalkyl (C₁-C₄) alkyl,
 (C₃-C₇) cycloalkyl (C₁-C₄) alkanoyl, formyl, (C₁-C₈) alkanoyl,
 (C₁-C₆) alkanoyl (C₁-C₆) alkyl, (C₁-C₄) alkanoylamino,
 5 (C₁-C₄) alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄) alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄) alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄) alkylamino, carbamoyl, mono-N- or
 10 di-N,N-(C₁-C₄) alkylcarbamoyl, cyano, thiol, (C₁-C₆) alkylthio,
 (C₁-C₆) alkylsulfinyl, (C₁-C₄) alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄) alkylaminosulfinyl;

Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 15 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 20 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 25 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 30 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,

72222-402

-21g-

halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy (C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl (C₁-C₄)alkyl,

5 (C₃-C₇)cycloalkyl (C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl (C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,

10 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

15 W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-

20 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

X is a five or six membered aromatic ring

25 optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

30 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are

72222-402

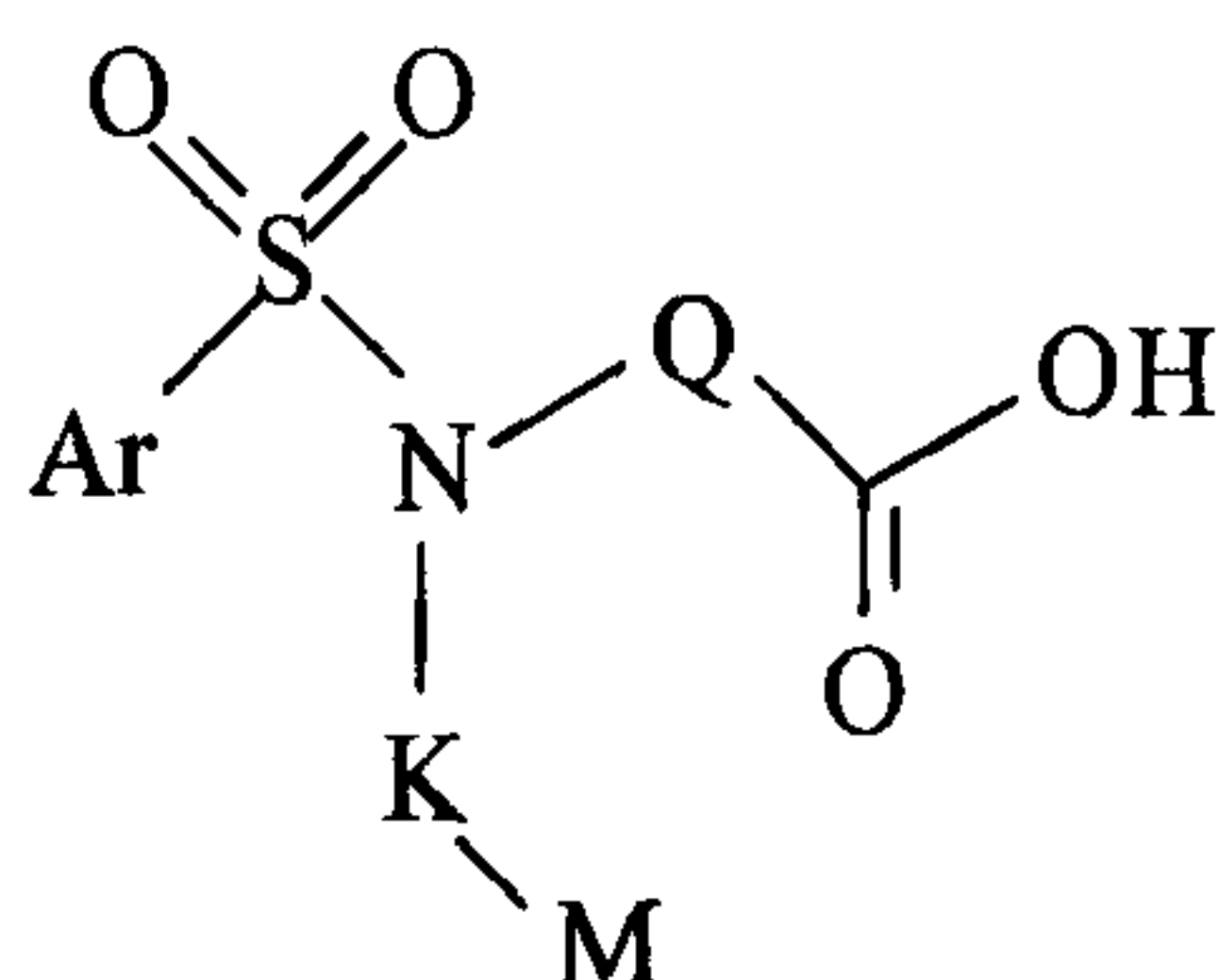
-21h-

optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl
5 or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is
10 a compound having the Formula:



15 Q is -(C₀-C₄)alkylene-X-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents each independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
20 (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or
25 methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and

72222-402

-21i-

nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

5 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

10 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two

15 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

20 selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl,

25 (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino,

30 sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

72222-402

-21j-

M is $-\text{Ar}^3-\text{V}^1-\text{Ar}^3$, $-\text{Ar}^3-\text{S}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}_2-\text{Ar}^3$ or $-\text{Ar}^3-\text{O}-\text{Ar}^3$;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or

72222-402

-21k-

di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

5 W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 10 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 optionally substituted on carbon with one to three
 fluorines;

 X is a five or six membered aromatic ring
 15 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 optionally mono-, di- or tri-substituted independently with
 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy,
 difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

20 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 independently with halo or hydroxy; and

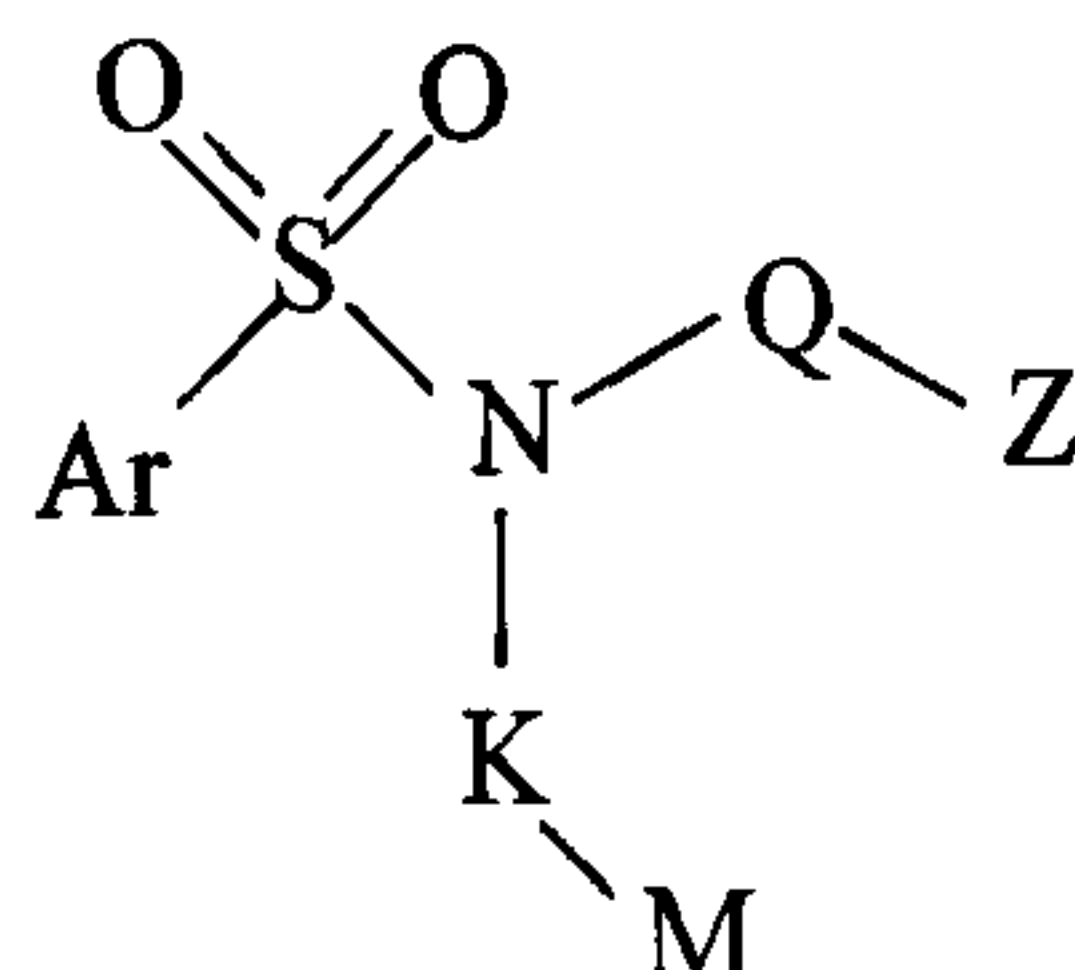
 V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 25 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

72222-402

-211-

Another especially preferred group of compounds is a compound having the Formula:



5

Q is $-(\text{C}_0\text{-C}_4)\text{alkylene-X-W-(C}_1\text{-C}_3)\text{alkylene-}$, the alkylens each optionally substituted with up to four substituents each independently selected from fluoro and
 10 $(\text{C}_1\text{-C}_4)\text{alkyl}$,

Z is $(\text{C}_1\text{-C}_6)\text{alkoxycarbonyl}$;

K is a bond, $(\text{C}_1\text{-C}_9)\text{alkylene}$, thio $(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkylenethio}(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkyleneoxy}(\text{C}_1\text{-C}_4)\text{alkylene}$ or oxy $(\text{C}_1\text{-C}_4)\text{alkylene}$, the
 15 $(\text{C}_1\text{-C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated
 20 five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently,
 25 optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally

72222-402

-21m-

having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is $-Ar^3-V^1-Ar^3$, $-Ar^3-S-Ar^3$, $-Ar^3-SO-Ar^3$, $-Ar^3-SO_2-Ar^3$ or $-Ar^3-O-Ar^3$;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully

72222-402

-21n-

saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

10 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to

15 three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,

20 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

25 tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or

30 di-N,N- (C_1-C_4) alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N- (C_1-C_4) alkyleneaminosulfonyl-, sulfonylamino, N- (C_1-C_4) alkylenesulfonylamino, carboxamido,

72222-402

-210-

N- (C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N- (C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 5 optionally substituted on carbon with one to three
 fluorines;

X is a five or six membered aromatic ring
 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 10 optionally mono-, di- or tri-substituted independently with
 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy,
 difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

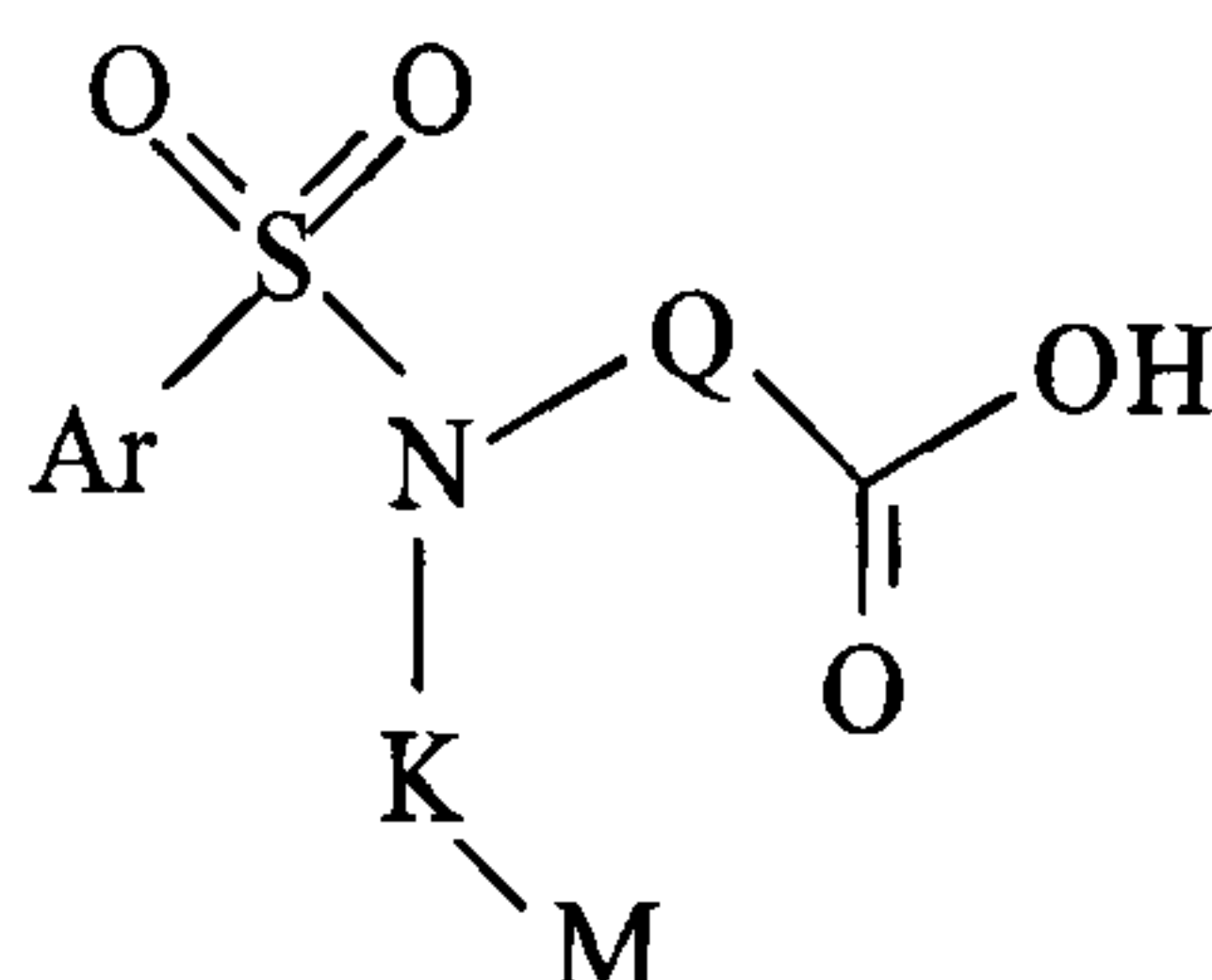
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 15 optionally mono-, di- or tri-substituted on carbon
 independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 20 hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

Another especially preferred group of compounds is
 a compound having the Formula:

25



72222-402

-21p-

Q is $-(C_0-C_4)\text{alkylene-X-W-}(C_1-C_3)\text{alkylene-}$, the alkylenes each optionally substituted with up to four substituents each independently selected from fluoro and $(C_1-C_4)\text{alkyl}$,

5 K is a bond, $(C_1-C_9)\text{alkylene}$, thio $(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or oxy $(C_1-C_4)\text{alkylene}$, the $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-
10 substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and
15 nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a
20 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully
25 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and
30 nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

72222-402

-21q-

selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,
 5 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 10 tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or
 15 di-N,N-(C_1-C_4)alkylaminosulfinyl;

M is Ar^3-Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from
 20 oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and
 25 oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully
 30 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if

72222-402

-21r-

Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

72222-402

-21s-

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

- 5 or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is $-(C_0-C_4)\text{alkylene-X-W-}(C_1-C_3)\text{alkylene-}$, the alkylenes each optionally substituted with up to four
 15 substituents each independently selected from fluoro and $(C_1-C_4)\text{alkyl}$,

Z is $(C_1-C_6)\text{alkoxycarbonyl}$;

K is a bond, $(C_1-C_9)\text{alkylene}$, $\text{thio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$,
 20 $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or $\text{oxy}(C_1-C_4)\text{alkylene}$, the $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

25 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused

72222-402

-21t-

independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a

5 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully

10 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and

15 nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are

20 independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

25 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or

30 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

72222-402

-21u-

M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

72222-402

-21v-

di-N,N- (C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N- (C₁-C₄)alkylaminosulfinyl;

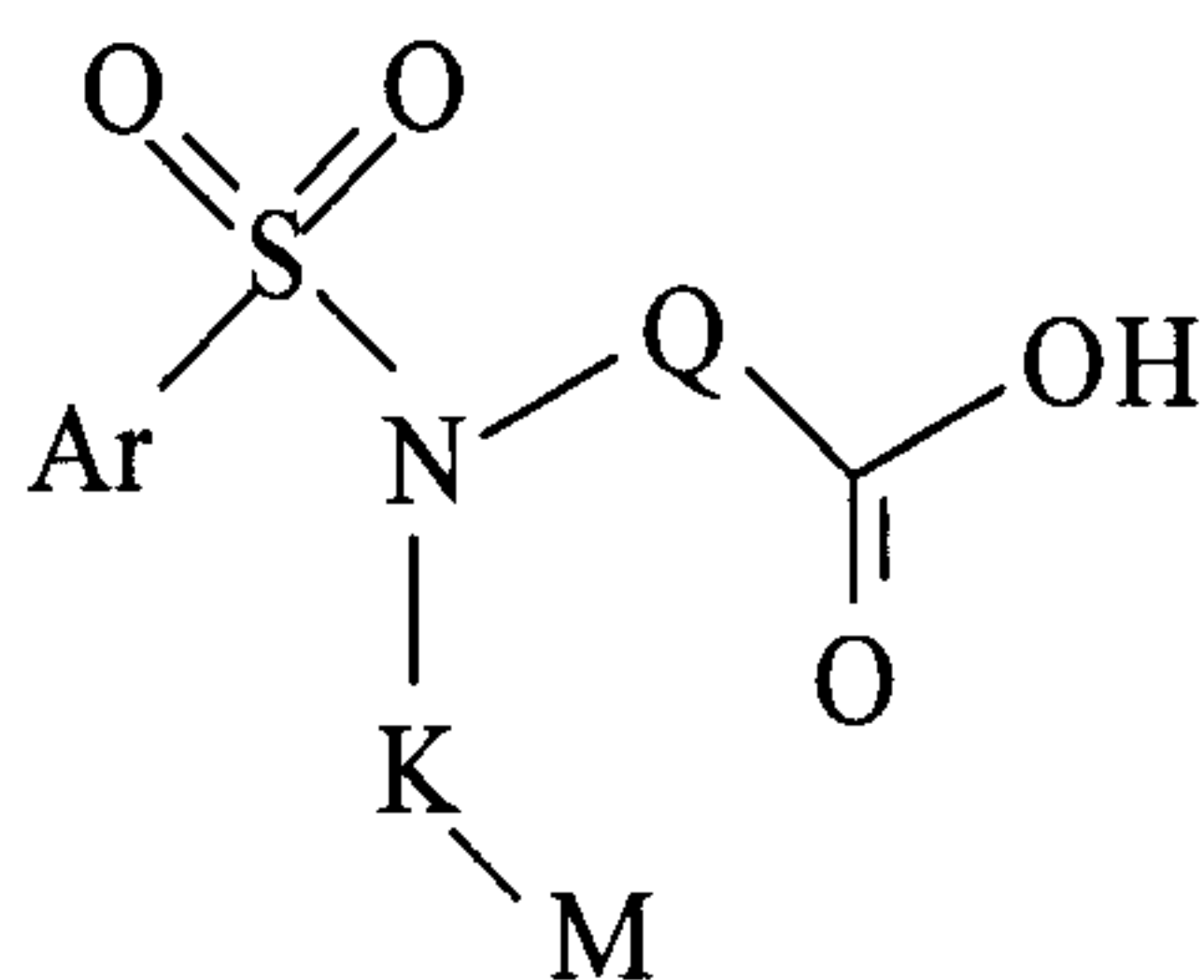
W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-,
 5 -mono-N- (C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N- (C₁-C₄)alkylenesulfonylamino, carboxamido, N- (C₁-C₄)alkylenecarboxamido, carboxamidooxy, N- (C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N- (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 10 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected
 15 independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 20 alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

25 Another especially preferred group of compounds is a compound having the Formula:



72222-402

-21w-

Q is $-(C_4-C_8)$ alkylene-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C_1-C_4) alkyl,

K is a bond, (C_1-C_9) alkylene, thio (C_1-C_4) alkylene,
5 (C_1-C_4) alkylenethio (C_1-C_4) alkylene,
 (C_1-C_4) alkyleneoxy (C_1-C_4) alkylene or oxy (C_1-C_4) alkylene, the
 (C_1-C_9) alkylene optionally mono-unsaturated and wherein, when
K is not a bond, K is optionally mono-, di- or tri-
substituted independently with chloro, fluoro, hydroxy or
10 methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused
15 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a
tricyclic ring consisting of three fused independently
20 partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully
saturated ring, bicyclic ring or tricyclic ring optionally
25 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or
30 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are

72222-402

-21x-

independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,

5 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,

10 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

15 M is Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting

20 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

25 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

30 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,

72222-402

-21y-

or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

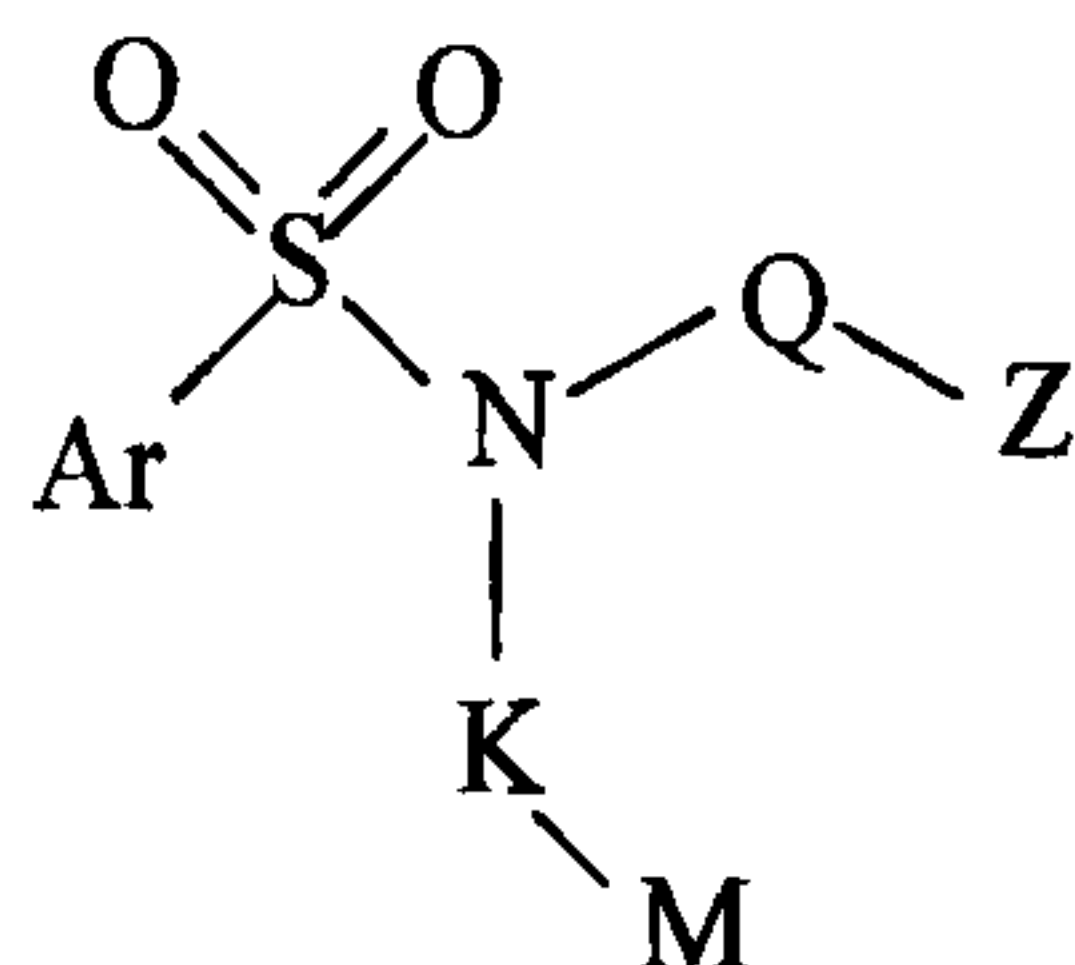
provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:

72222-402

-21z-



5 Q is $-(\text{C}_4\text{-C}_8)\text{alkylene-}$, the alkylene optionally substituted with up to four substituents independently selected from fluoro and $(\text{C}_1\text{-C}_4)\text{alkyl}$,

 Z is $(\text{C}_1\text{-C}_6)\text{alkoxycarbonyl}$;

 K is a bond, $(\text{C}_1\text{-C}_9)\text{alkylene}$, thio $(\text{C}_1\text{-C}_4)\text{alkylene}$,
 10 $(\text{C}_1\text{-C}_4)\text{alkylenethio}(\text{C}_1\text{-C}_4)\text{alkylene}$,
 $(\text{C}_1\text{-C}_4)\text{alkyleneoxy}(\text{C}_1\text{-C}_4)\text{alkylene}$ or oxy $(\text{C}_1\text{-C}_4)\text{alkylene}$, the
 $(\text{C}_1\text{-C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when
 K is not a bond, K is optionally mono-, di- or tri-
 substituted independently with chloro, fluoro, hydroxy or
 15 methyl;

 Ar is a partially saturated or fully unsaturated
 five to eight membered ring optionally having one to four
 heteroatoms selected independently from oxygen, sulfur and
 nitrogen, or a bicyclic ring consisting of two fused
 20 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, taken independently,
 optionally having one to four heteroatoms selected
 independently from nitrogen, sulfur and oxygen, or a
 tricyclic ring consisting of three fused independently
 25 partially saturated, fully saturated or fully unsaturated
 five or six membered rings, taken independently, optionally
 having one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, the partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 30 having one or two oxo groups substituted on carbon or one or

72222-402

-21aa-

two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully

72222-402

-21bb-

unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

5 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to

10 three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, $(\text{C}_1\text{-C}_7)$ alkoxy, $(\text{C}_1\text{-C}_4)$ alkoxy $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl, $(\text{C}_1\text{-C}_7)$ alkyl, $(\text{C}_2\text{-C}_7)$ alkenyl, $(\text{C}_2\text{-C}_7)$ alkynyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl,

15 $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkanoyl, formyl, $(\text{C}_1\text{-C}_8)$ alkanoyl, $(\text{C}_1\text{-C}_6)$ alkanoyl $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkanoylamino, $(\text{C}_1\text{-C}_4)$ alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

20 tri-N,N,N'- $(\text{C}_1\text{-C}_4)$ alkyl substituted aminocarbonylamino, sulfonamido, $(\text{C}_1\text{-C}_4)$ alkylsulfonamido, amino, mono-N- or di-N,N- $(\text{C}_1\text{-C}_4)$ alkylamino, carbamoyl, mono-N- or di-N,N- $(\text{C}_1\text{-C}_4)$ alkylcarbamoyl, cyano, thiol, $(\text{C}_1\text{-C}_6)$ alkylthio, $(\text{C}_1\text{-C}_6)$ alkylsulfinyl, $(\text{C}_1\text{-C}_4)$ alkylsulfonyl or mono-N- or

25 di-N,N- $(\text{C}_1\text{-C}_4)$ alkylaminosulfinyl;

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

30 provided that when K is $(\text{C}_2\text{-C}_4)$ alkylene and M is Ar^3 and Ar^3 is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar^3 is not substituted at the one position with hydroxy;

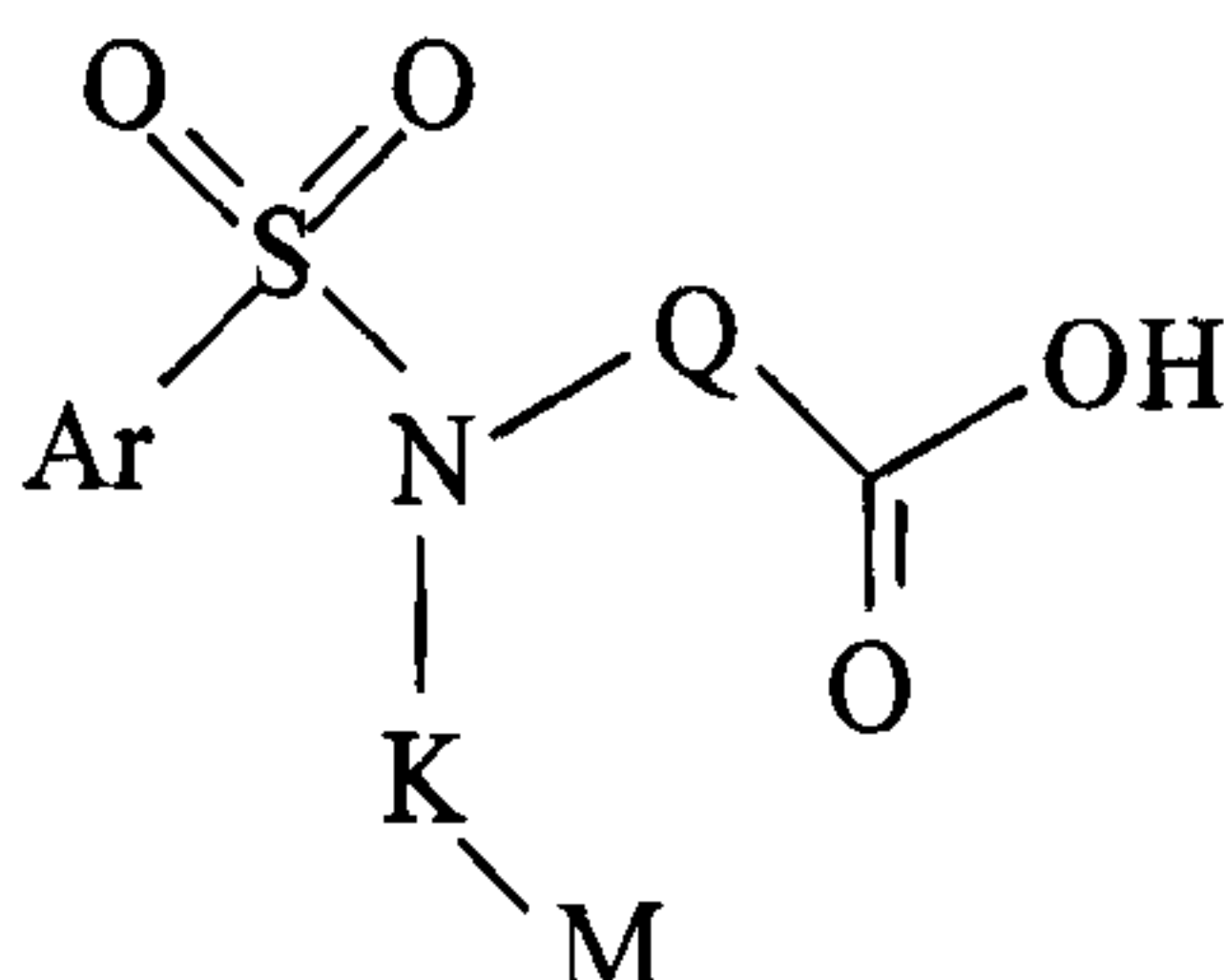
72222-402

-21cc-

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:

5



Q is $-(\text{C}_4-\text{C}_8)\text{alkylene}-$, the alkylene optionally substituted with up to four substituents independently selected from fluoro and $(\text{C}_1-\text{C}_4)\text{alkyl}$,

K is a bond, $(\text{C}_1-\text{C}_9)\text{alkylene}$, thio $(\text{C}_1-\text{C}_4)\text{alkylene}$, $(\text{C}_1-\text{C}_4)\text{alkylenethio}(\text{C}_1-\text{C}_4)\text{alkylene}$, $(\text{C}_1-\text{C}_4)\text{alkyleneoxy}(\text{C}_1-\text{C}_4)\text{alkylene}$ or oxy $(\text{C}_1-\text{C}_4)\text{alkylene}$, the $(\text{C}_1-\text{C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally

72222-402

-21dd-

having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is $-\text{Ar}^3-\text{V}^1-\text{Ar}^3$, $-\text{Ar}^3-\text{S}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}_2-\text{Ar}^3$ or $-\text{Ar}^3-\text{O}-\text{Ar}^3$;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully

72222-402

-21ee-

saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

10 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to

15 three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

20 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

25 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or

30 di-N,N-(C₁-C₄)alkylaminosulfinyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are

72222-402

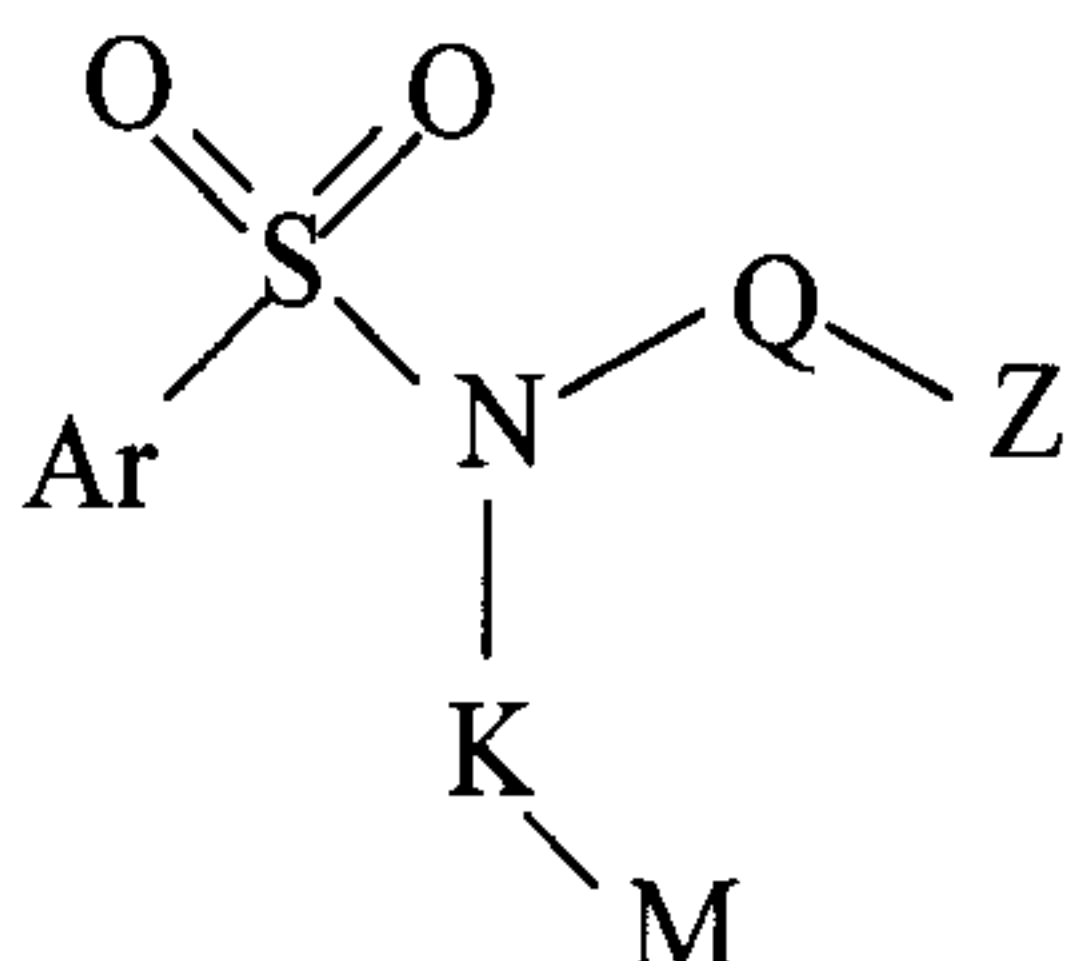
-21ff-

optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

V^1 is thio(C_1-C_4)alkylene, (C_1-C_4)alkylenethio, (C_1-C_4)alkyleneoxy, oxy(C_1-C_4)alkylene or (C_1-C_3)alkylene
 5 optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is
 10 a compound having the Formula:



15 Q is -(C_4-C_8)alkylene-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C_1-C_4)alkyl,

Z is (C_1-C_6)alkoxycarbonyl;

K is a bond, (C_1-C_9)alkylene, thio(C_1-C_4)alkylene,
 20 (C_1-C_4)alkylenethio(C_1-C_4)alkylene,
 (C_1-C_4)alkyleneoxy(C_1-C_4)alkylene or oxy(C_1-C_4)alkylene, the
 (C_1-C_9)alkylene optionally mono-unsaturated and wherein, when
 K is not a bond, K is optionally mono-, di- or tri-
 substituted independently with chloro, fluoro, hydroxy or
 25 methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four

72222-402

-21gg-

heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio,

72222-402

-21hh-

(C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³ or -Ar³-O-Ar³;

5 Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully
 10 saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully
 15 unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
 20 two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and
 25 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 30 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

72222-402

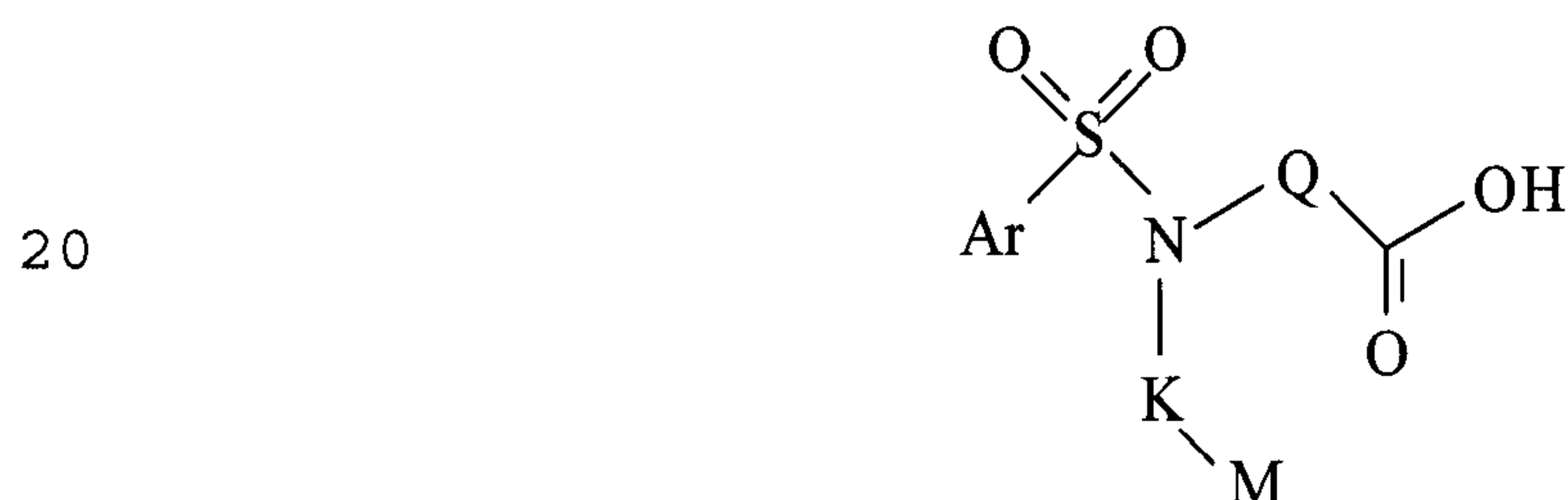
-21ii-

tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 5 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 10 independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 hydroxy or fluoro;
 15 or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

Another especially preferred group of compounds is
 a compound having the Formula:



Q is -(C₄-C₈)alkylene-, the alkylene optionally
 substituted with up to four substituents independently
 selected from fluoro and (C₁-C₄)alkyl,

25 K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
 (C₁-C₄)alkylenethio(C₁-C₄)alkylene,
 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the
 (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
 K is not a bond, K is optionally mono-, di- or tri-

72222-402

-21jj-

substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

72222-402

-21kk-

tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 5 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 10 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 15 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 20 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 25 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 30 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

72222-402

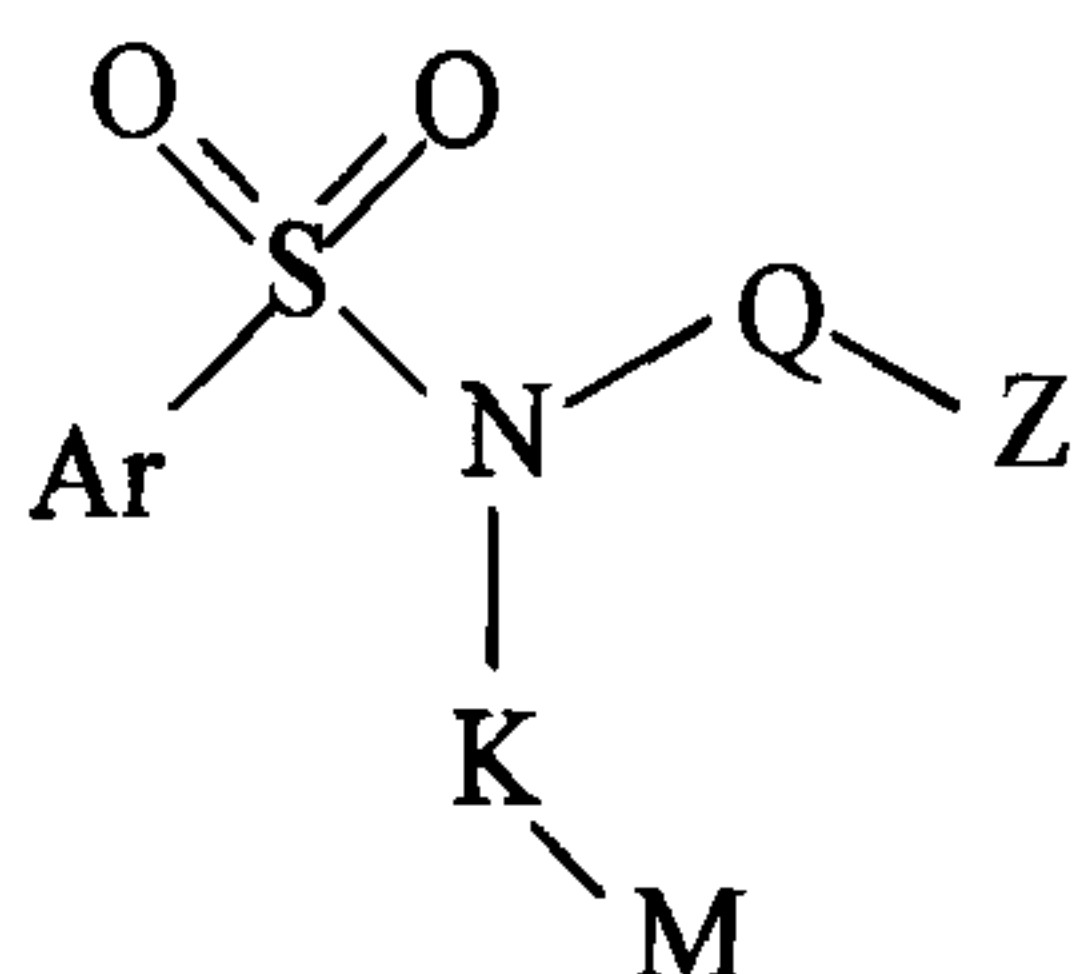
-2111-

(C₁-C₆)alkanoyl (C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is -(C₄-C₈)alkylene-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the

72222-402

-21mm-

(C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

5 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully
 10 unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated
 15 five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
 20 two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both
 25 rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl,
 30 (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

72222-402

-21nn-

(C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 5 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

10 Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully
 15 saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully
 20 unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
 25 two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and
 30 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

72222-402

-2100-

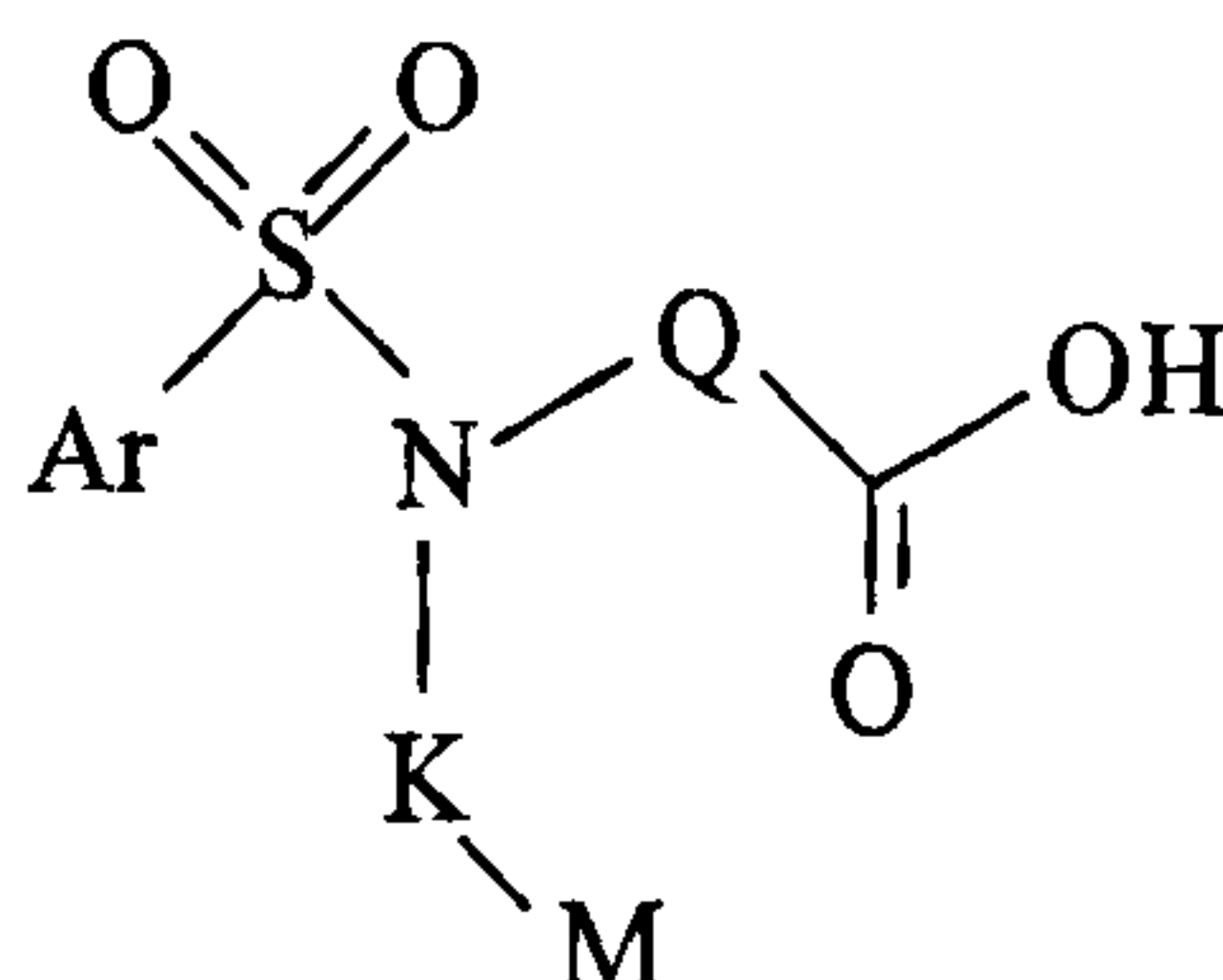
(C₃-C₇) cycloalkyl (C₁-C₄) alkyl,
 (C₃-C₇) cycloalkyl (C₁-C₄) alkanoyl, formyl, (C₁-C₈) alkanoyl,
 (C₁-C₆) alkanoyl (C₁-C₆) alkyl, (C₁-C₄) alkanoylamino,
 (C₁-C₄) alkoxycarbonylamino, hydroxysulfonyl,
 5 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄) alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄) alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄) alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄) alkylcarbamoyl, cyano, thiol, (C₁-C₆) alkylthio,
 10 (C₁-C₆) alkylsulfinyl, (C₁-C₄) alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄) alkylaminosulfinyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 15 independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

Another especially preferred group of compounds is
 a compound having the Formula:

20



Q is -(C₂-C₆) alkylene-W-(C₁-C₃) alkylene-, the
 alkylenes each optionally substituted with up to four
 25 substituents independently selected from fluoro and (C₁-
 C₄) alkyl,

K is a bond, (C₁-C₉) alkylene, thio(C₁-C₄) alkylene,
 (C₁-C₄) alkylenethio(C₁-C₄) alkylene,

72222-402

-21pp-

(C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

72222-402

-21qq-

(C₁-C₆)alkanoyl (C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

10 M is Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,

72222-402

-21rr-

(C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 5 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 10 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 15 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 20 optionally substituted on carbon with one to three
 fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 25 independently with halo or hydroxy; and

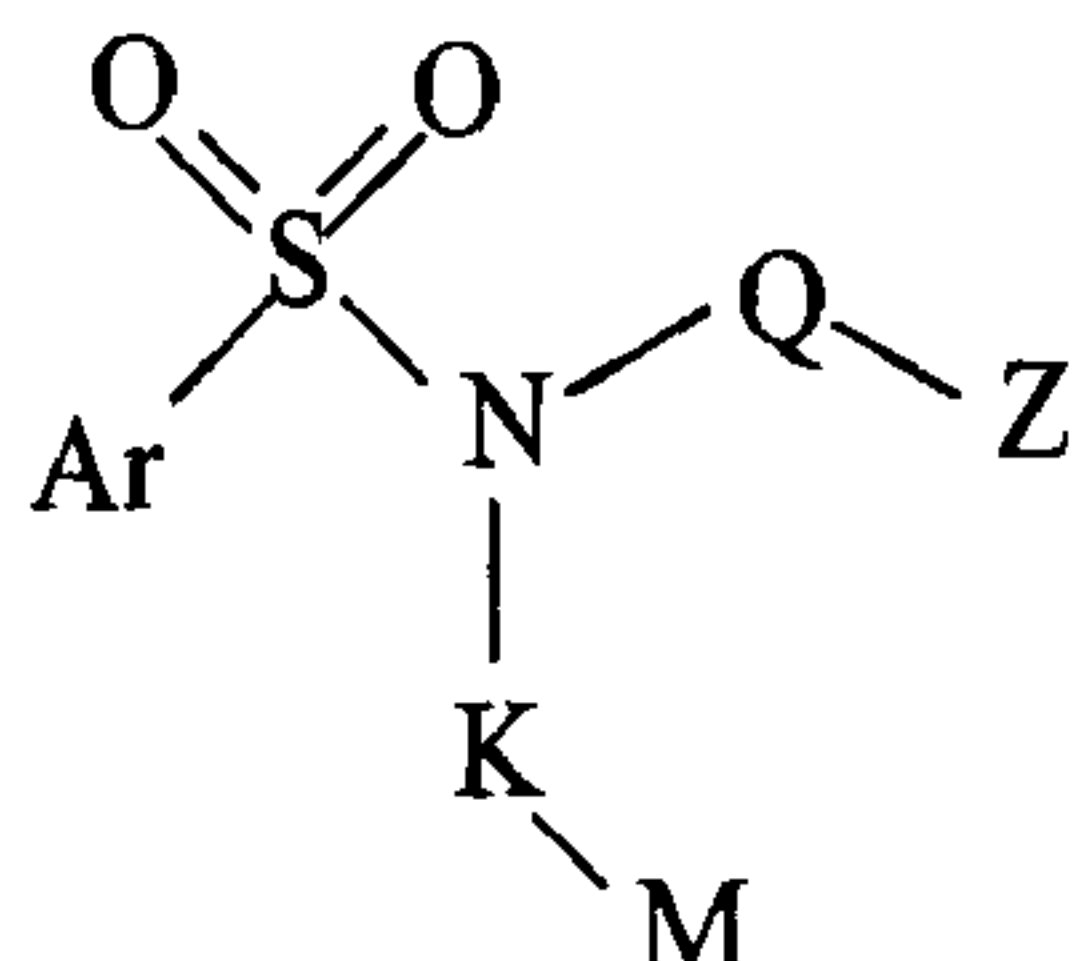
provided that when K is (C₂-C₄)alkylene and M is
 Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl
 or cyclooct-1-yl, then Ar³ is not substituted at the one
 position with hydroxy;

30 or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

72222-402

-21ss-

Another especially preferred group of compounds is a compound having the Formula:



5

Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

10

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

15

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally

20

25

72222-402

-21tt-

having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings,

72222-402

-21uu-

taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 5 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 10 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 15 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 20 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 25 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

30 W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,

72222-402

-21vv-

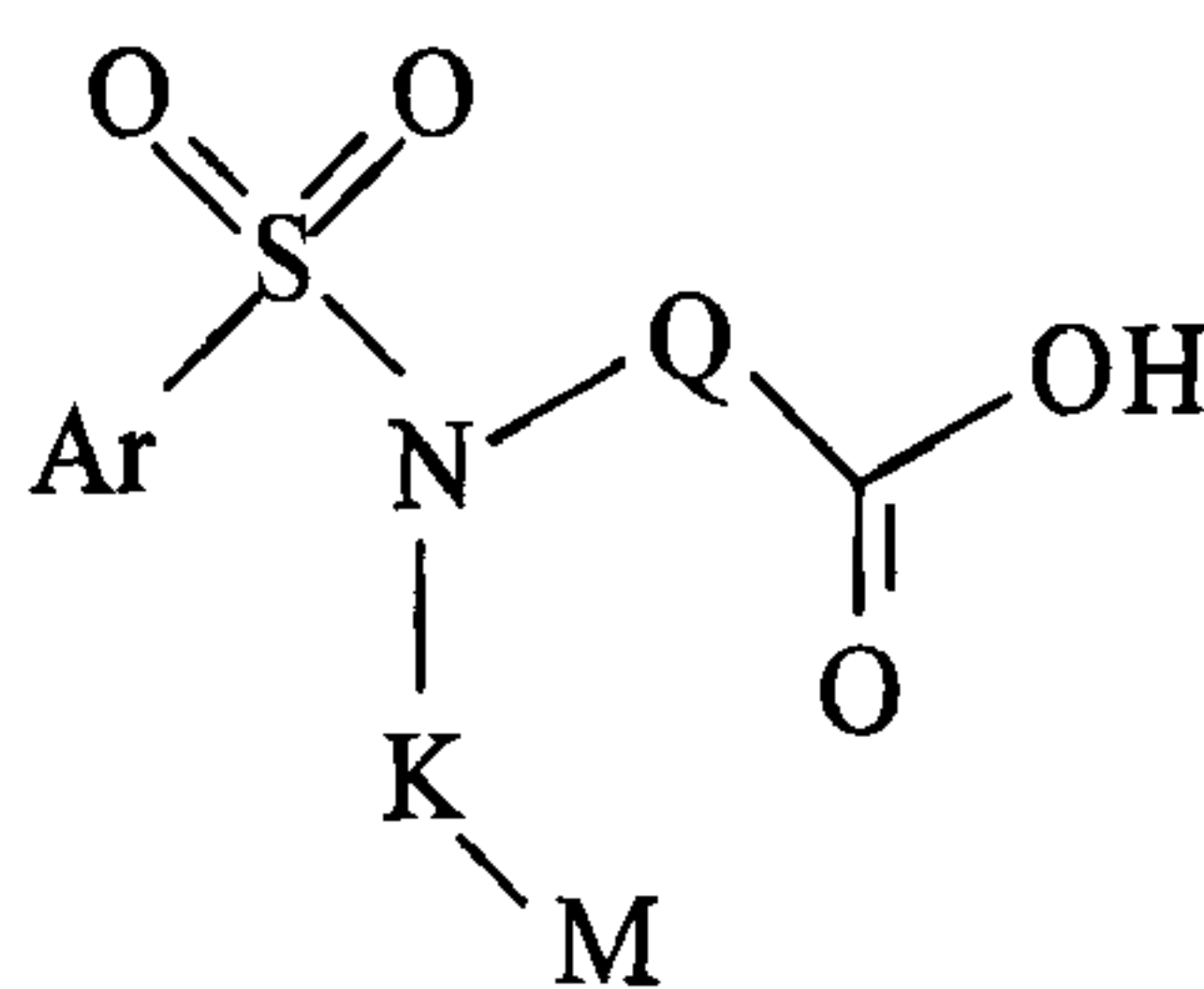
N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



20

Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

25

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the

72222-402

-21ww-

(C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

5 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully
 10 unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated
 15 five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
 20 two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both
 25 rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 30 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

72222-402

-21xx-

(C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 5 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³
 10 or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 15 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused
 20 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally
 25 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to
 30 three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,

72222-402

-21yy-

(C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 5 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 10 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 15 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 20 optionally substituted on carbon with one to three
 fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 25 independently with halo or hydroxy; and

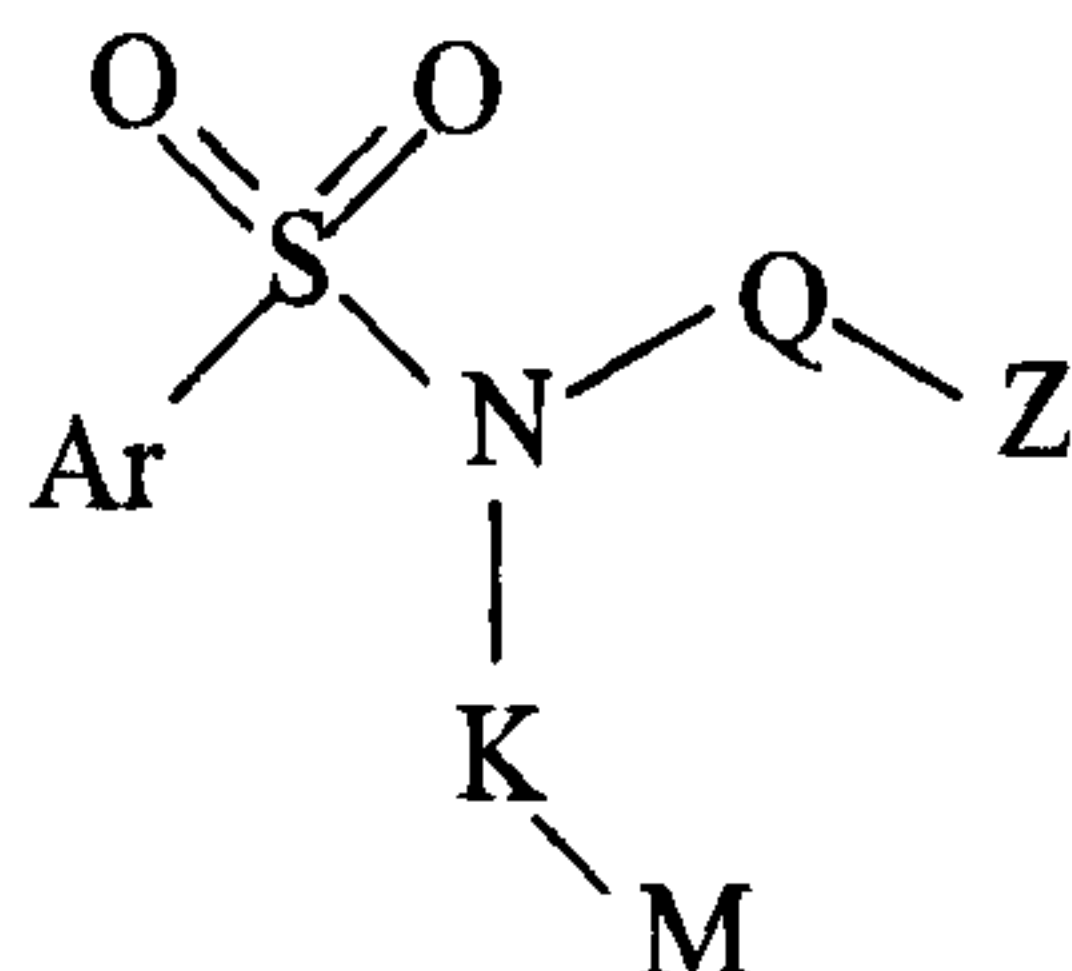
V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 hydroxy or fluoro;

30 or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

72222-402

-21zz-

Another especially preferred group of compounds is a compound having the Formula:



5

Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

10

Z is (C₁-C₆)alkoxycarbonyl;

15

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

20

25

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally

72222-402

-21aaa-

having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is $-\text{Ar}^3-\text{V}^1-\text{Ar}^3$, $-\text{Ar}^3-\text{S}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}_2-\text{Ar}^3$ or $-\text{Ar}^3-\text{O}-\text{Ar}^3$;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully

72222-402

-21bbb-

saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

10 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to

15 three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

20 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

25 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or

30 di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido,

72222-402

-21ccc-

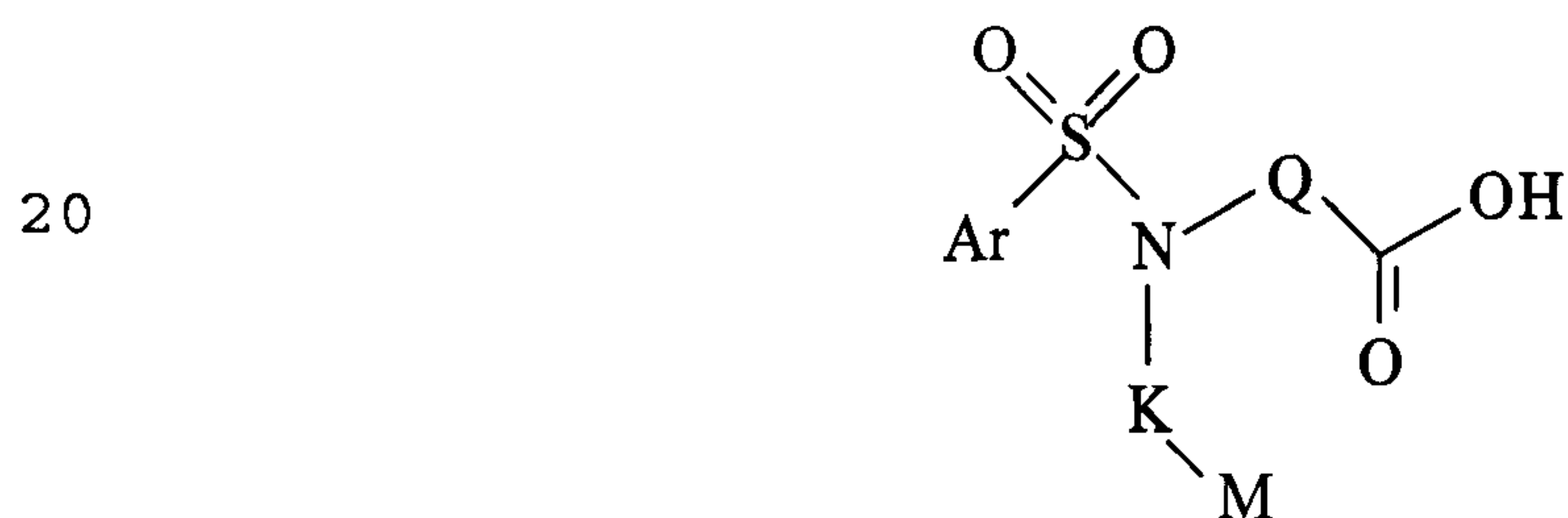
N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 5 optionally substituted on carbon with one to three
 fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 10 independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 hydroxy or fluoro;

15 or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

Another especially preferred group of compounds is
 a compound having the Formula:



Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the
 alkylenes each optionally substituted with up to four
 25 substituents independently selected from fluoro and
 (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
 (C₁-C₄)alkylenethio(C₁-C₄)alkylene,

72222-402

-21ddd-

(C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

72222-402

-21eee-

(C₁-C₆)alkanoyl (C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, 5 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

10 M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting 15 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused 20 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally 25 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to 30 three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,

72222-402

-21fff-

(C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl (C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl (C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl (C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 5 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 10 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 15 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 20 optionally substituted on carbon with one to three
 fluorines; and

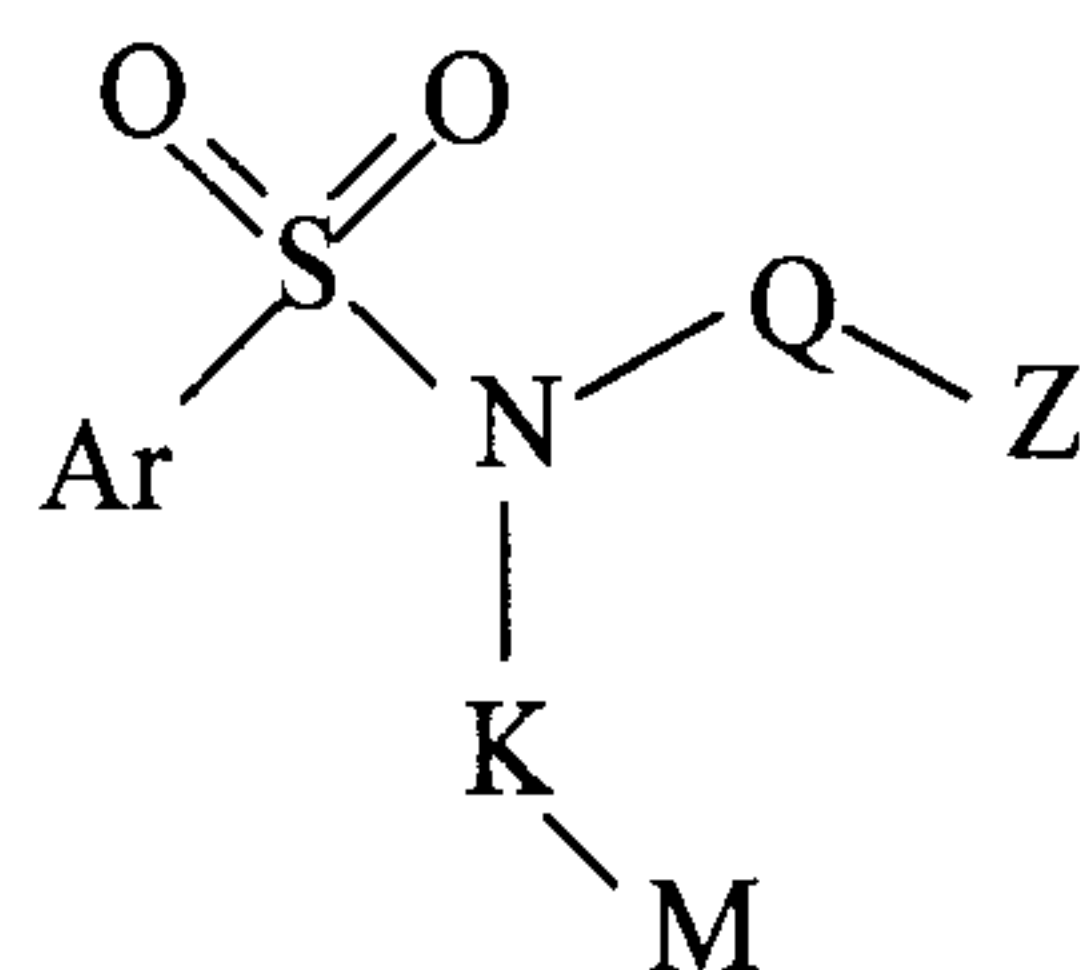
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 25 independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

Another especially preferred group of compounds is
 a compound having the Formula:

72222-402

-21ggg-



5 Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the
alkylenes each optionally substituted with up to four
substituents independently selected from fluoro and (C₁-
C₄)alkyl,

 Z is (C₁-C₆)alkoxycarbonyl;

10 K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
(C₁-C₄)alkylenethio(C₁-C₄)alkylene,
(C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the
(C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
K is not a bond, K is optionally mono-, di- or tri-
15 substituted independently with chloro, fluoro, hydroxy or
methyl;

 Ar is a partially saturated or fully unsaturated
five to eight membered ring optionally having one to four
heteroatoms selected independently from oxygen, sulfur and
20 nitrogen, or a bicyclic ring consisting of two fused
independently partially saturated, fully saturated or fully
unsaturated five or six membered rings, taken independently,
optionally having one to four heteroatoms selected
independently from nitrogen, sulfur and oxygen, or a
25 tricyclic ring consisting of three fused independently
partially saturated, fully saturated or fully unsaturated
five or six membered rings, taken independently, optionally
having one to four heteroatoms selected independently from
nitrogen, sulfur and oxygen, the partially or fully
30 saturated ring, bicyclic ring or tricyclic ring optionally

72222-402

-21hhh-

having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are

independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is Ar^3-Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

72222-402

-21iii-

independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully

5 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic,

10 or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl,

15 (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl,

20 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio,

25 (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-, -mono-N- (C_1-C_4) alkyleneaminosulfonyl-, sulfonylamino, N- (C_1-C_4) alkylenesulfonylamino, carboxamido,

30 N- (C_1-C_4) alkylenecarboxamido, carboxamidooxy, N- (C_1-C_4) alkylenecarboxamidooxy, carbamoyl, -mono-N- (C_1-C_4) alkylenecarbamoyl, carbamoyloxy, or -mono-N- (C_1-C_4) alkylenecarbamoyloxy, wherein the W alkyl groups are

72222-402

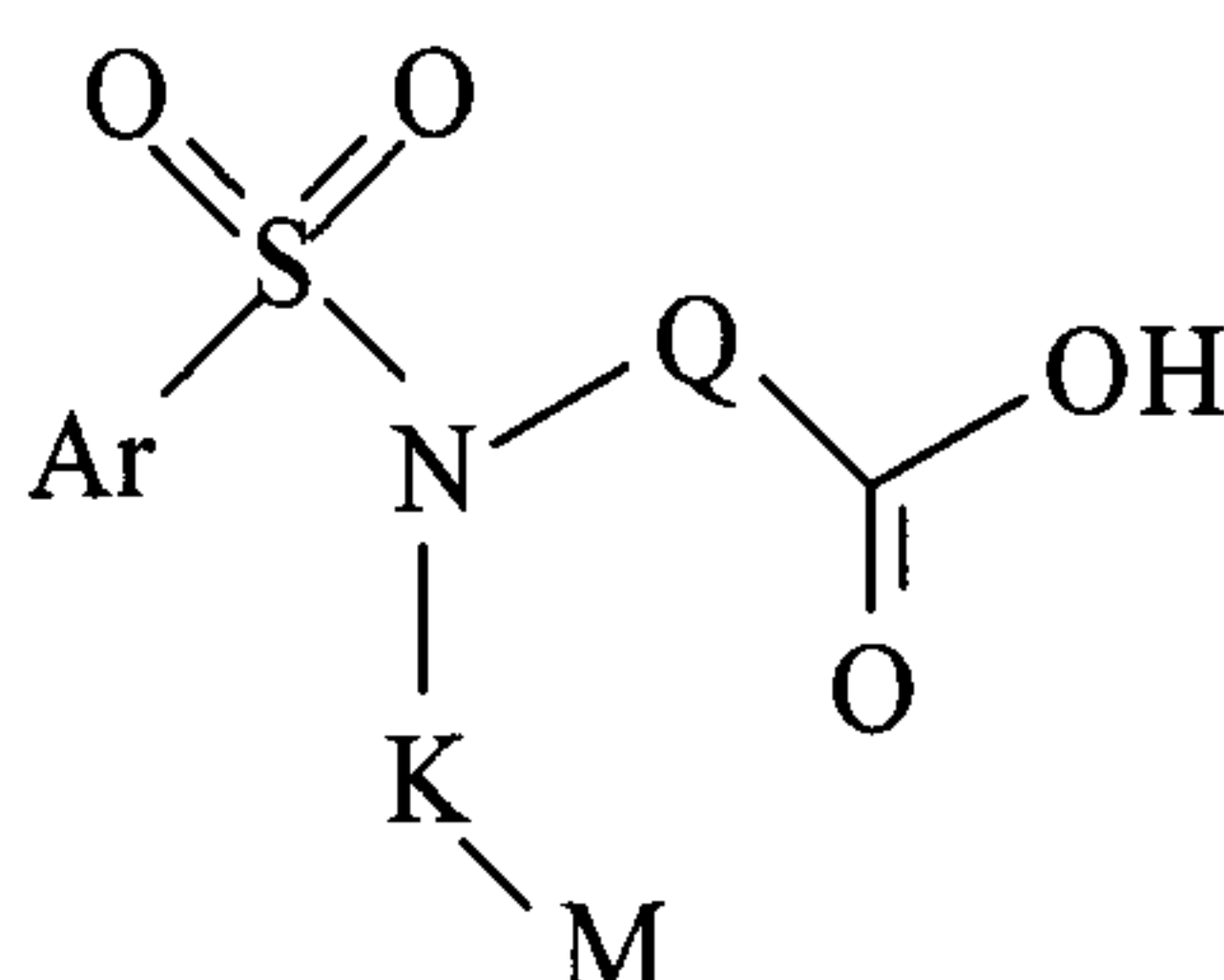
-21jjj-

optionally substituted on carbon with one to three fluorines; and

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are
 5 optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is
 10 a compound having the Formula:



15 Q is $-(C_1-C_3)\text{alkylene-X-}(C_1-C_3)\text{alkylene-}$, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and $(C_1-C_4)\text{alkyl}$,

K is a bond, $(C_1-C_9)\text{alkylene}$, thio $(C_1-C_4)\text{alkylene}$,
 20 $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or oxy $(C_1-C_4)\text{alkylene}$, the $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or
 25 methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and

72222-402

-21kkk-

nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

5 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

10 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two

15 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

20 selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl,

25 (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino,

30 sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

72222-402

-21111-

M is Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

72222-402

-21mmm-

di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring

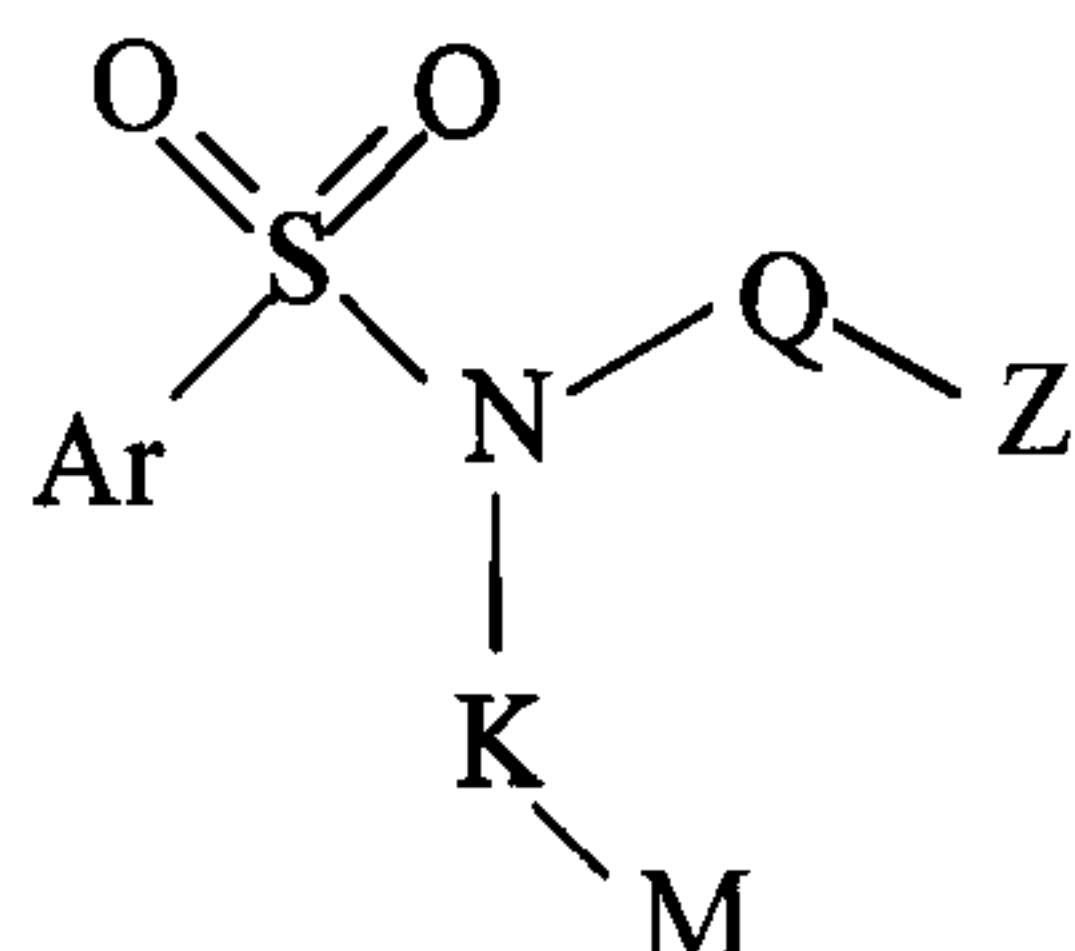
5 optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

10 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is
15 Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

20 Another especially preferred group of compounds is a compound having the Formula:



25

Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four

72222-402

-21nnn-

substituents independently selected from fluoro and
(C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
5 (C₁-C₄)alkylenethio(C₁-C₄)alkylene,
(C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the
(C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
K is not a bond, K is optionally mono-, di- or tri-
substituted independently with chloro, fluoro, hydroxy or
10 methyl;

Ar is a partially saturated or fully unsaturated
five to eight membered ring optionally having one to four
heteroatoms selected independently from oxygen, sulfur and
nitrogen, or a bicyclic ring consisting of two fused
15 independently partially saturated, fully saturated or fully
unsaturated five or six membered rings, taken independently,
optionally having one to four heteroatoms selected
independently from nitrogen, sulfur and oxygen, or a
tricyclic ring consisting of three fused independently
20 partially saturated, fully saturated or fully unsaturated
five or six membered rings, taken independently, optionally
having one to four heteroatoms selected independently from
nitrogen, sulfur and oxygen, the partially or fully
saturated ring, bicyclic ring or tricyclic ring optionally
25 having one or two oxo groups substituted on carbon or one or
two oxo groups substituted on sulfur; or Ar is a fully
saturated five to seven membered ring having one or two
heteroatoms selected independently from oxygen, sulfur and
nitrogen; wherein Ar is optionally substituted on carbon or
30 nitrogen, on one ring if Ar is monocyclic, on one or both
rings if Ar is bicyclic, or on one, two or three rings if Ar
is tricyclic, with up to three substituents independently

72222-402

-21000-

selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,
 5 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 10 tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or
 15 di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from
 20 oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and
 25 oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully
 30 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if

72222-402

-21ppp-

Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

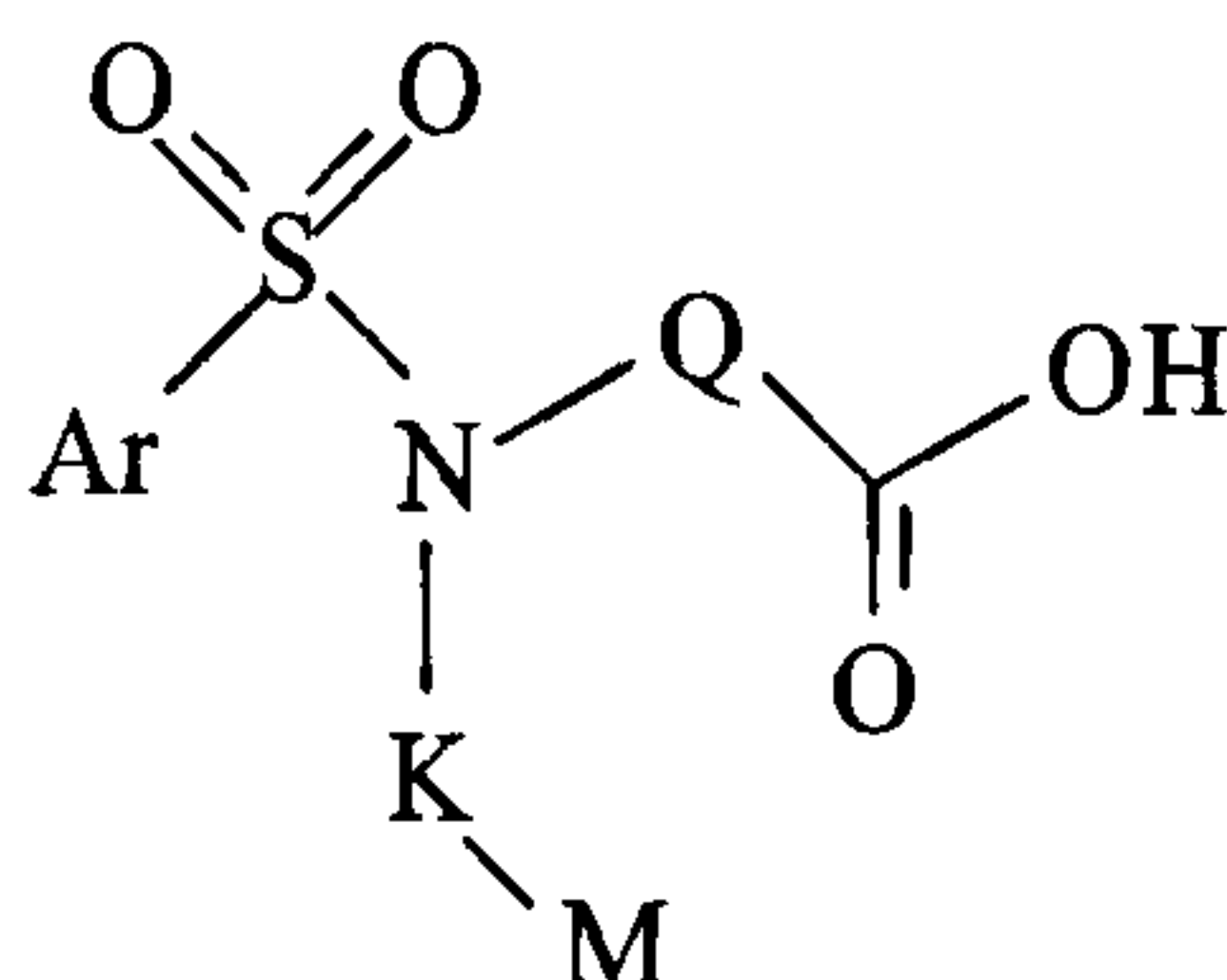
72222-402

-21qqq-

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:

5



Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the
 10 alkylenes each optionally substituted with up to four
 substituents independently selected from fluoro and
 (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
 (C₁-C₄)alkylenethio(C₁-C₄)alkylene,
 15 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the
 (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
 K is not a bond, K is optionally mono-, di- or tri-
 substituted independently with chloro, fluoro, hydroxy or
 methyl;

20 Ar is a partially saturated or fully unsaturated
 five to eight membered ring optionally having one to four
 heteroatoms selected independently from oxygen, sulfur and
 nitrogen, or a bicyclic ring consisting of two fused
 independently partially saturated, fully saturated or fully
 25 unsaturated five or six membered rings, taken independently,
 optionally having one to four heteroatoms selected
 independently from nitrogen, sulfur and oxygen, or a
 tricyclic ring consisting of three fused independently
 partially saturated, fully saturated or fully unsaturated

72222-402

-21rrr-

five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

5 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or

10 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino,

15 (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or

20 di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is $-Ar^3-V^1-Ar^3$, $-Ar^3-S-Ar^3$, $-Ar^3-SO-Ar^3$, $-Ar^3-SO_2-Ar^3$ or $-Ar^3-O-Ar^3$;

30 Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting

72222-402

-21sss-

of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected

72222-402

-21ttt-

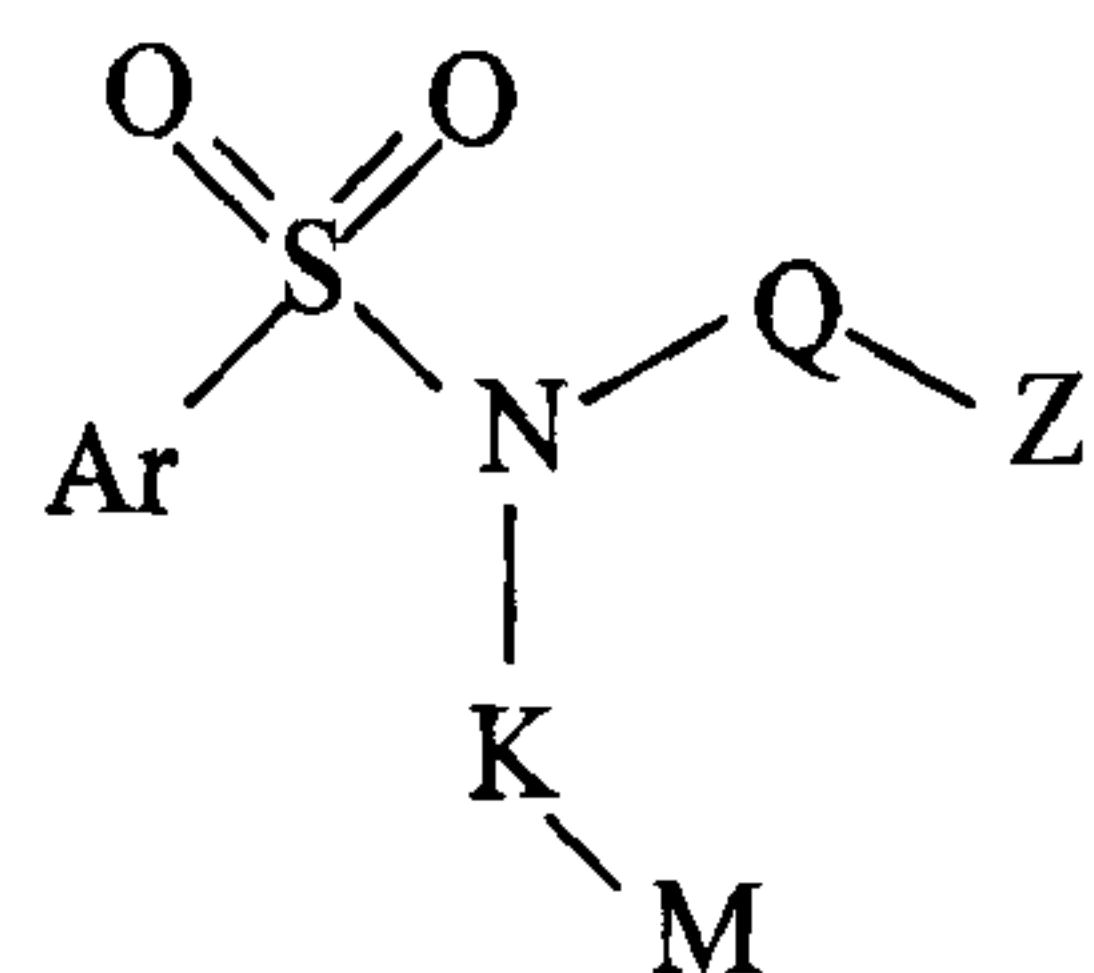
independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

5 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

 V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
10 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

15 Another especially preferred group of compounds is a compound having the Formula:



20

 Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

25 Z is (C₁-C₆)alkoxycarbonyl;

 K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene,

72222-402

-21uuu-

(C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

72222-402

-21vvv-

(C₁-C₆)alkanoyl (C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, 5 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

10 M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³ or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from 15 oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and 20 oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully 25 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, 30 or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,

72222-402

-21www-

(C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 5 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 10 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring
 15 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 optionally mono-, di- or tri-substituted independently with
 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy,
 difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

20 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 independently with halo or hydroxy; and

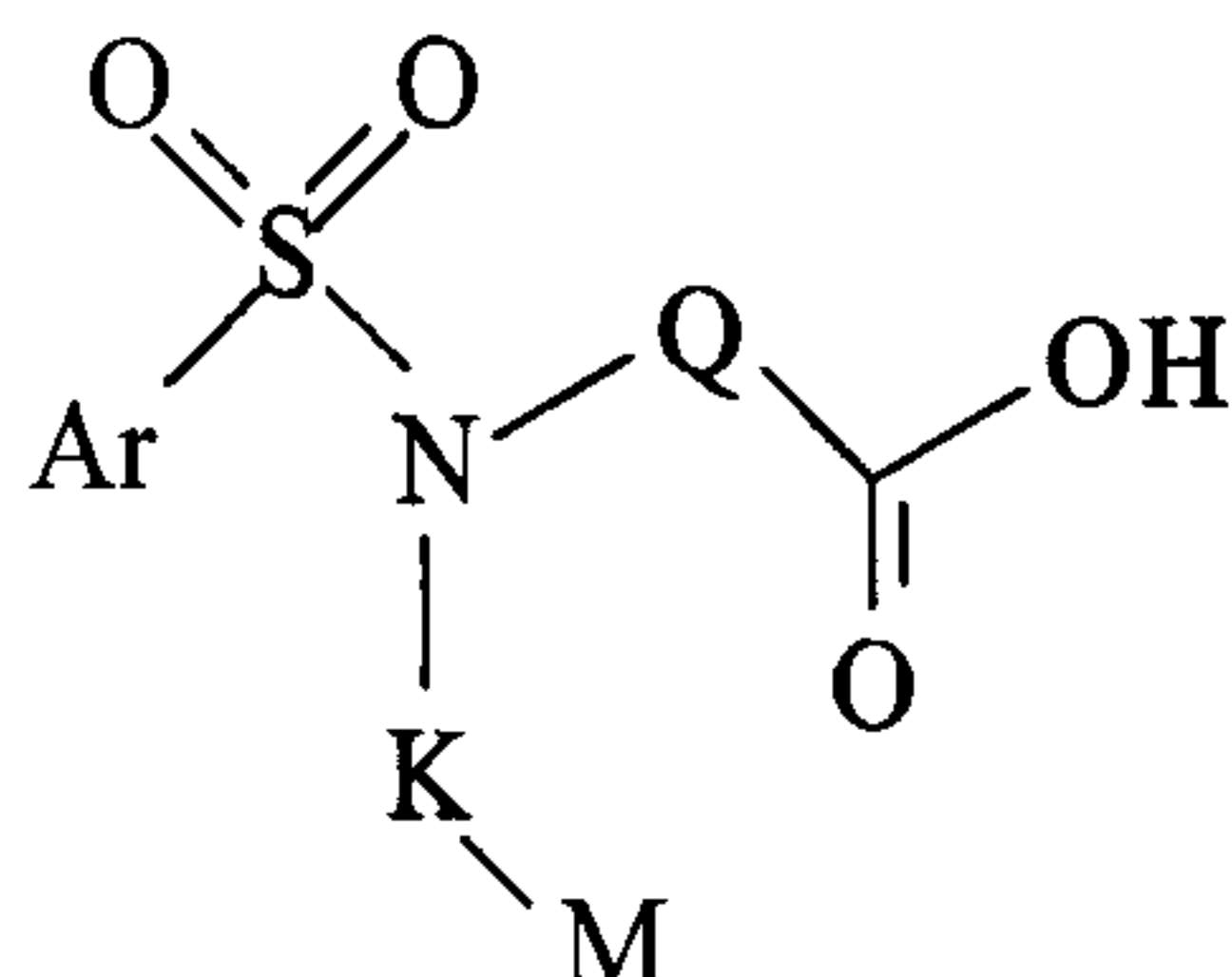
V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 25 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

72222-402

-21xxx-

Another especially preferred group of compounds is a compound having the Formula:



5

Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

10

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

15

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully

20

25

30

72222-402

-21yyy-

saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two

5 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

10 selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl,

15 (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino,

20 sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

25 M is Ar^3-Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting

30 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and

72222-402

-21zzz-

oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from

5 nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if

10 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,

15 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

20 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

25 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected

30 independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

72222-402

-21aaaa-

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

5 or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is $-(C_1-C_3)\text{alkylene-X-(C}_1\text{-C}_3\text{)alkylene-}$, the alkylenes each optionally substituted with up to four
 15 substituents independently selected from fluoro and $(C_1-C_4)\text{alkyl}$,

Z is $(C_1-C_6)\text{alkoxycarbonyl}$;

K is a bond, $(C_1-C_9)\text{alkylene}$, $\text{thio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$,
 20 $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or $\text{oxy}(C_1-C_4)\text{alkylene}$, the $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

25 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused

72222-402

-21bbbb-

independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a

5 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully

10 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and

15 nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are

20 independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

25 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or

30 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

72222-402

-21cccc-

M is $\text{Ar}^3\text{-Ar}^3$;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, $(\text{C}_1\text{-C}_7)$ alkoxy, $(\text{C}_1\text{-C}_4)$ alkoxy $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl, $(\text{C}_1\text{-C}_7)$ alkyl, $(\text{C}_2\text{-C}_7)$ alkenyl, $(\text{C}_2\text{-C}_7)$ alkynyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkanoyl, formyl, $(\text{C}_1\text{-C}_8)$ alkanoyl, $(\text{C}_1\text{-C}_6)$ alkanoyl $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkanoylamino, $(\text{C}_1\text{-C}_4)$ alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- $(\text{C}_1\text{-C}_4)$ alkyl substituted aminocarbonylamino, sulfonamido, $(\text{C}_1\text{-C}_4)$ alkylsulfonamido, amino, mono-N- or di-N,N- $(\text{C}_1\text{-C}_4)$ alkylamino, carbamoyl, mono-N- or

72222-402

-21ddddd-

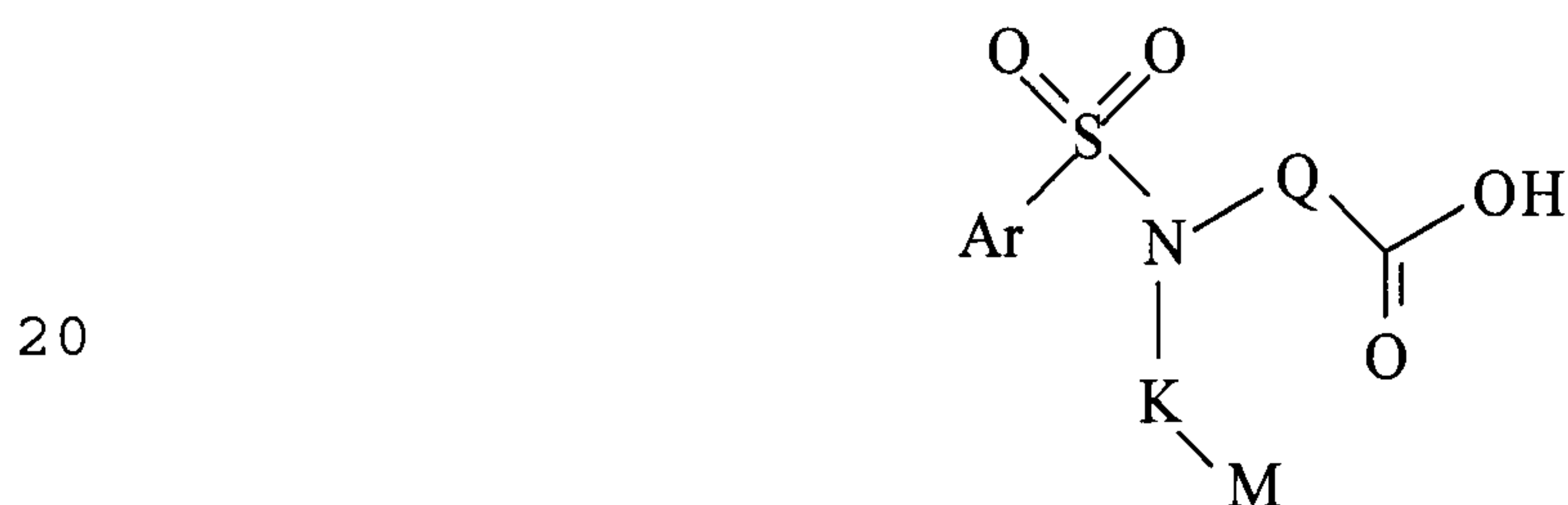
di-N,N- (C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N- (C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when

72222-402

-21eeee-

K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl,

72222-402

-21ffff-

aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 5 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³;

Ar³ is a partially saturated, fully saturated or
 10 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 15 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 20 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 25 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 30 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,

72222-402

-21gggg-

(C₃-C₇) cycloalkyl (C₁-C₄) alkanoyl, formyl, (C₁-C₈) alkanoyl,
 (C₁-C₆) alkanoyl (C₁-C₆) alkyl, (C₁-C₄) alkanoylamino,
 (C₁-C₄) alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 5 tri-N,N,N'-(C₁-C₄) alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄) alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄) alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄) alkylcarbamoyl, cyano, thiol, (C₁-C₆) alkylthio,
 (C₁-C₆) alkylsulfinyl, (C₁-C₄) alkylsulfonyl or mono-N- or
 10 di-N,N-(C₁-C₄) alkylaminosulfinyl;

X is a five or six membered aromatic ring
 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 optionally mono-, di- or tri-substituted independently with
 15 halo, (C₁-C₃) alkyl, trifluoromethyl, trifluoromethoxy,
 difluoromethoxy, hydroxyl, (C₁-C₄) alkoxy, or carbamoyl;

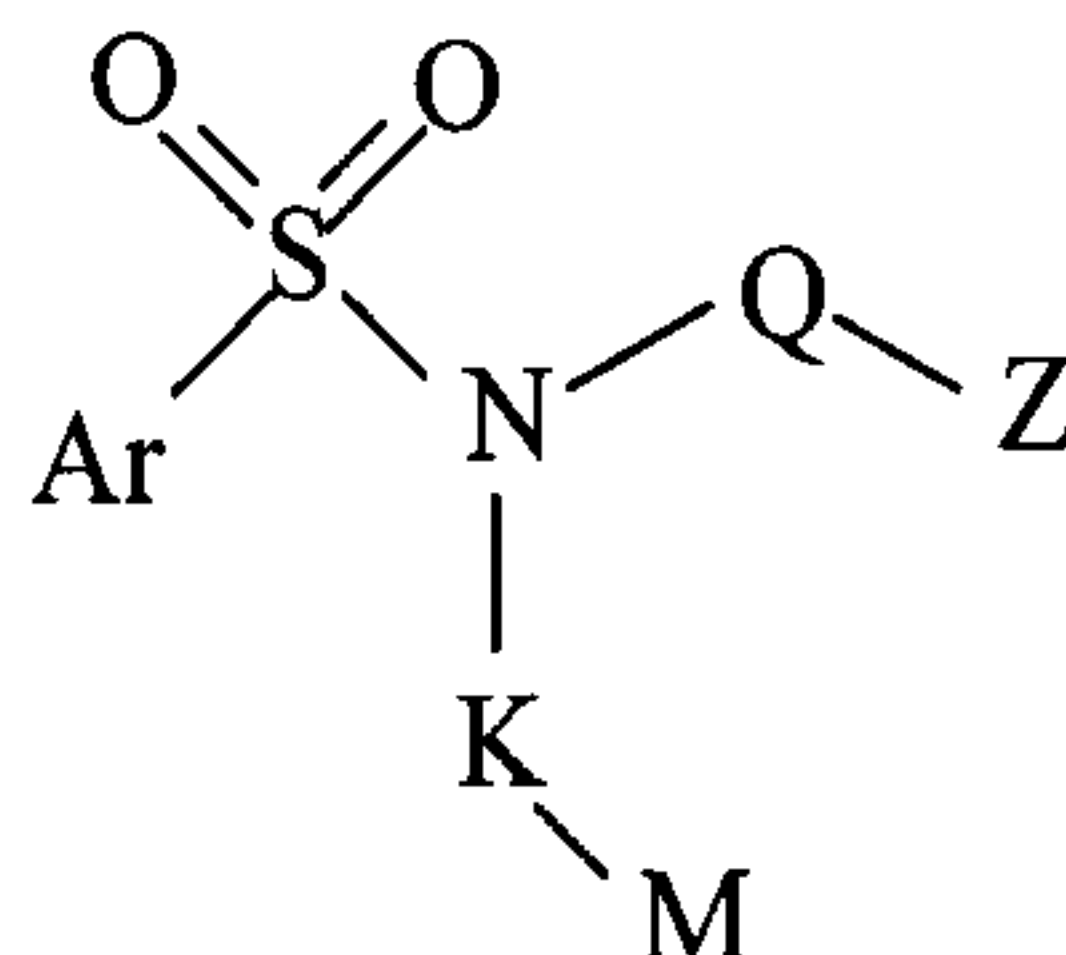
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 20 independently with halo or hydroxy; and

provided that when K is (C₂-C₄) alkylene and M is
 Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl
 or cyclooct-1-yl, then Ar³ is not substituted at the one
 position with hydroxy;
 25 or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

Another especially preferred group of compounds is
 a compound having the Formula:

72222-402

-21hhhh-



5 Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

 Z is (C₁-C₆)alkoxycarbonyl;

 K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
 10 (C₁-C₄)alkylenethio(C₁-C₄)alkylene,
 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

15 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six
 20 membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently,
 25 optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven
 30 membered ring having one or two heteroatoms selected independently

72222-402

-21iiii-

from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents

5 independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl,

10 formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or

15 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar^3 ;

20 Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully

25 saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully

30 unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

72222-402

-21jjjj-

having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

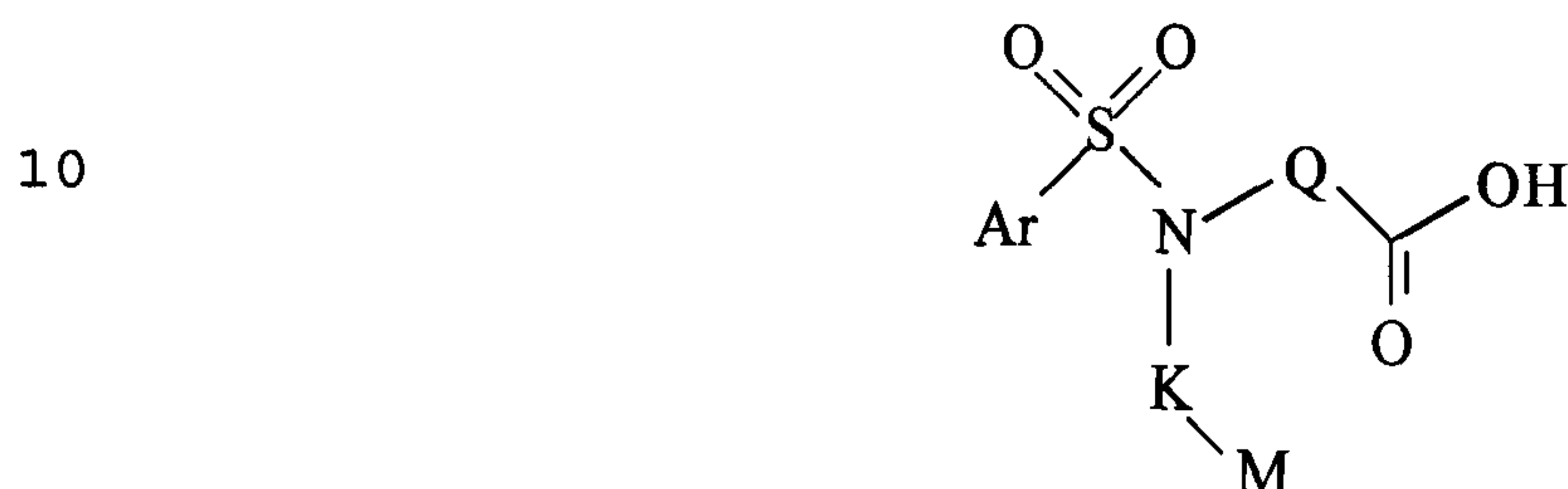
72222-402

-21kkkk-

provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

5 or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently
15 selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
20 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four
25 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

72222-402

-211111-

independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally
 5 having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully
 10 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar
 15 is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,
 20 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 25 tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or
 30 di-N,N-(C_1-C_4)alkylaminosulfinyl;

M is $-\text{Ar}^3-\text{V}^1-\text{Ar}^3$, $-\text{Ar}^3-\text{S}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}_2-\text{Ar}^3$
 or $-\text{Ar}^3-\text{O}-\text{Ar}^3$;

72222-402

-21mmmm-

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,

72222-402

-21nnnn-

(C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

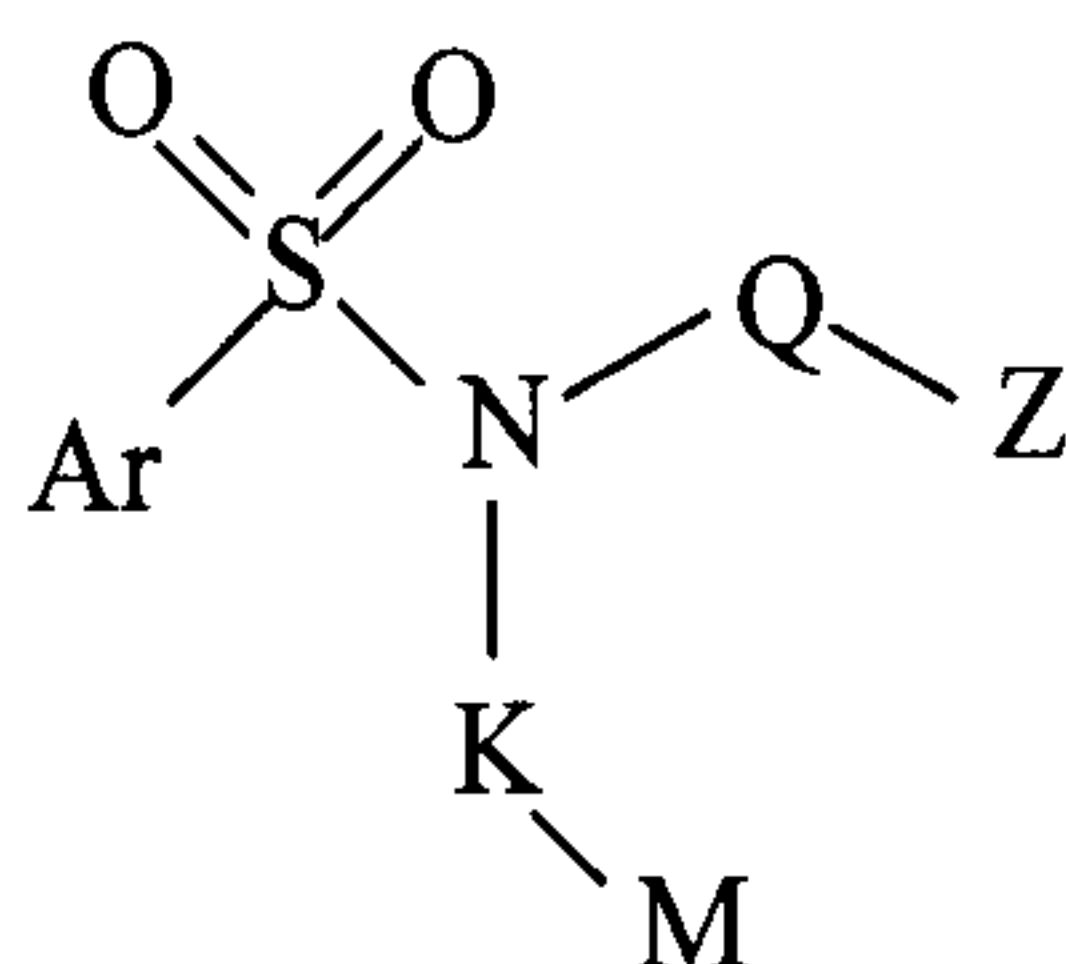
X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio, (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

72222-402

-210000-

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the
5 (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated
10 five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently,
15 optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally
20 having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully
25 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar
30 is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl,

72222-402

-21pppp-

(C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 5 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 10 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³
 or -Ar³-O-Ar³;

15 Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 20 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 25 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 30 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to

72222-402

-21qqqq-

three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C_1-C_3) alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C_1-C_4) alkoxy, or carbamoyl;

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

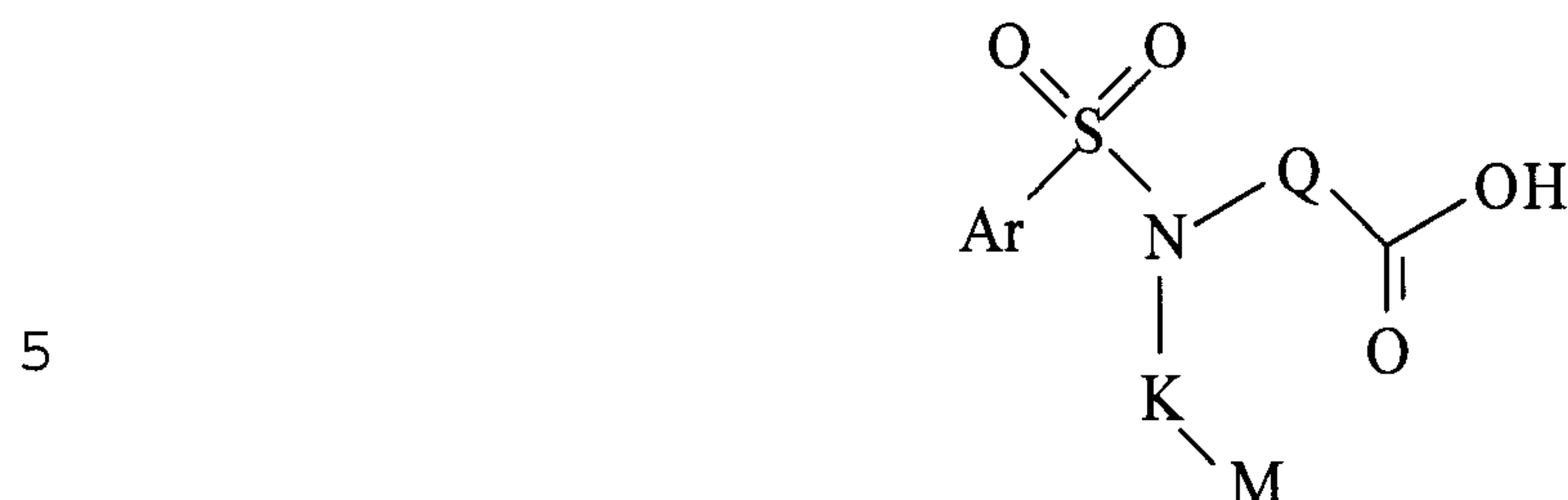
V^1 is thio (C_1-C_4) alkylene, (C_1-C_4) alkylenethio, (C_1-C_4) alkyleneoxy, oxy (C_1-C_4) alkylene or (C_1-C_3) alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

72222-402

-21rrrr-

Another especially preferred group of compounds is a compound having the Formula:



Q is $-(\text{C}_1\text{-C}_5)\text{alkylene-X-}$, the alkylene optionally substituted with up to four substituents independently selected from fluoro and $(\text{C}_1\text{-C}_4)\text{alkyl}$,

10 K is a bond, $(\text{C}_1\text{-C}_9)\text{alkylene}$, $\text{thio}(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkylenethio}(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkyleneoxy}(\text{C}_1\text{-C}_4)\text{alkylene}$ or $\text{oxy}(\text{C}_1\text{-C}_4)\text{alkylene}$, the $(\text{C}_1\text{-C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-
 15 substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and
 20 nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a
 25 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully
 30 saturated ring, bicyclic ring or tricyclic ring optionally

72222-402

-21ssss-

having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are

independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

72222-402

-21tttt-

independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully

5 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,

10 or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,

15 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,

20 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,

25 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring

30 optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

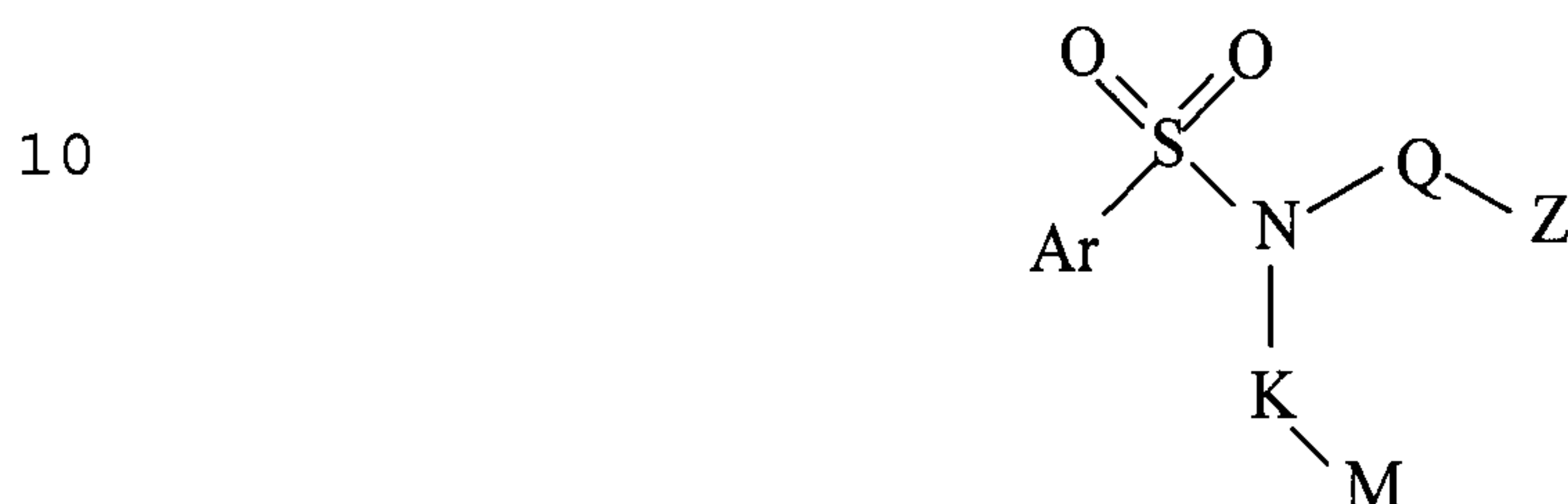
72222-402

-21uuuu-

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

5 or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is $-(C_1-C_5)\text{alkylene-X-}$, the alkylene optionally substituted with up to four substituents independently
15 selected from fluoro and $(C_1-C_4)\text{alkyl}$,

Z is $(C_1-C_6)\text{alkoxycarbonyl}$;

K is a bond, $(C_1-C_9)\text{alkylene}$, $\text{thio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or $\text{oxy}(C_1-C_4)\text{alkylene}$, the
20 $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated
25 five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully

72222-402

-21vvvv-

unsaturated five or six membered rings, taken independently,
 optionally having one to four heteroatoms selected
 independently from nitrogen, sulfur and oxygen, or a
 tricyclic ring consisting of three fused independently
 5 partially saturated, fully saturated or fully unsaturated
 five or six membered rings, taken independently, optionally
 having one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, the partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 10 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; or Ar is a fully
 saturated five to seven membered ring having one or two
 heteroatoms selected independently from oxygen, sulfur and
 nitrogen; wherein Ar is optionally substituted on carbon or
 15 nitrogen, on one ring if Ar is monocyclic, on one or both
 rings if Ar is bicyclic, or on one, two or three rings if Ar
 is tricyclic, with up to three substituents independently
 selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are
 independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy,
 20 (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl,
 (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 25 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 30 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

72222-402

-21www-

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,

72222-402

-21xxxx-

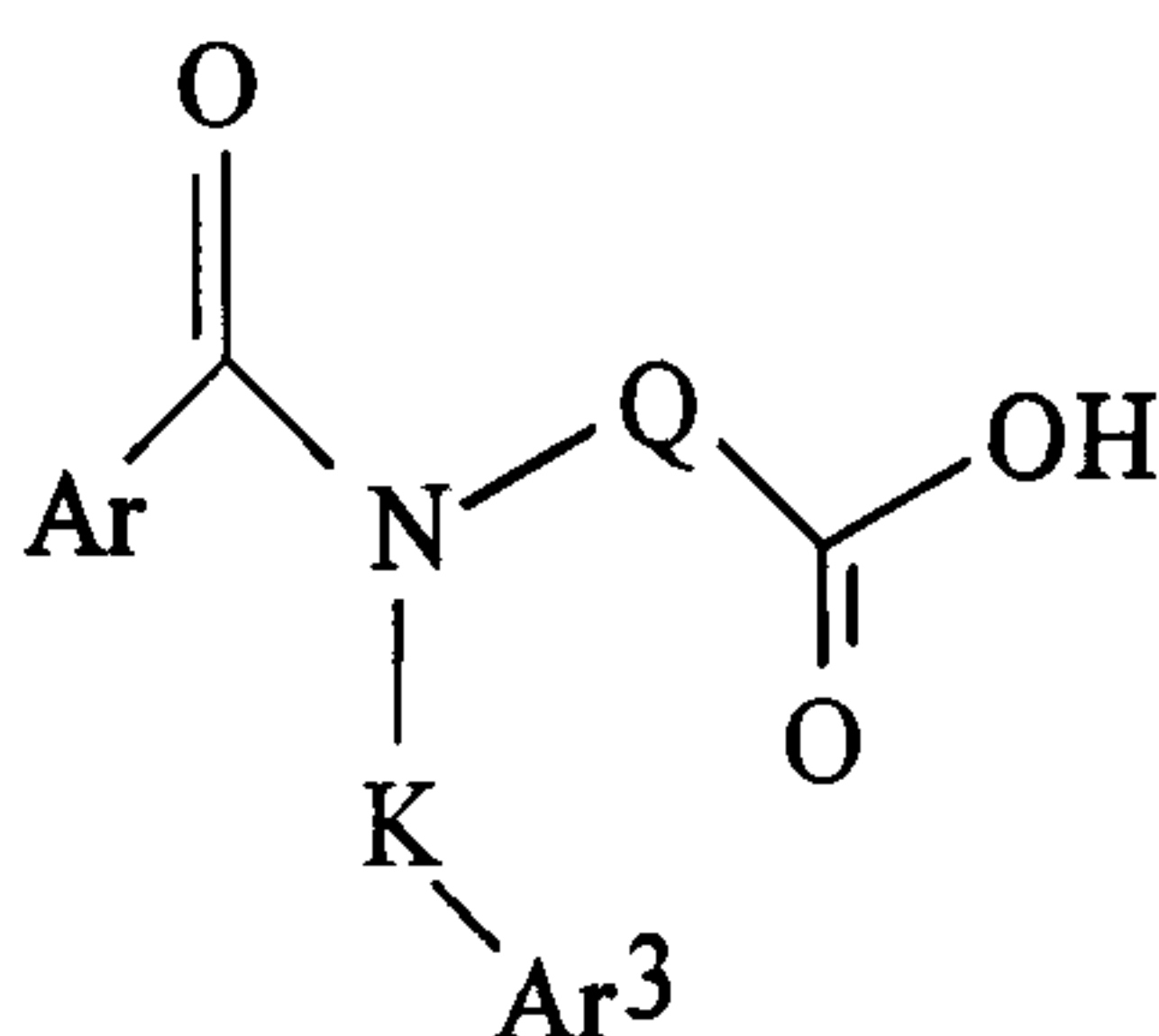
(C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N- (C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

Another especially preferred group of compounds is a compound having the Formula:



Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-

72222-402

-21yyyy-

substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four
 5 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected
 10 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from
 15 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two
 20 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently
 25 selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 30 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

72222-402

-21zzzz-

tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 5 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 10 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 15 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 20 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 25 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 30 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

72222-402

-21aaaaa-

(C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 5 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring
 10 optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

15 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and Ar³ is
 20 cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

25 This invention is also directed to methods for treating vertebrates, e.g., a mammal, having a condition which presents with low bone mass comprising administering to said vertebrate, e.g., a mammal, having a condition which presents with low bone mass a therapeutically effective
 30 amount of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said

compound or said prodrug. Preferably post-menopausal women and men over the age of 60 are treated. Also included are individuals regardless of age who have significantly reduced bone mass, i.e., greater than or equal to 1.5 standard deviations below young normal levels.

5 Yet another aspect of this invention is directed to methods for treating osteoporosis, bone fractures, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from
10 osteoporosis, bone fracture, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth an osteoporosis, bone fracture, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating
15 osteoporosis in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from osteoporosis an osteoporosis treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating
20 osteotomy in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g. a mammal having undergone an osteotomy a bone restoration treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein a bone restoration treating amount is an amount of said Formula I compound,
25 prodrug thereof or pharmaceutically acceptable salt of said compound or said prodrug sufficient to restore bone in areas containing bone defects due to said osteotomy. In one aspect the Formula I compound, prodrug thereof or pharmaceutically acceptable salt thereof is applied locally to a site of osteotomy.

Yet another aspect of this invention is directed to methods for treating
30 alveolar or mandibular bone loss in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from an alveolar bone or mandibular loss, an alveolar or mandibular bone

loss treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating bone loss associated with periodontitis in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., mammal suffering from bone loss associated with periodontitis, a bone loss associated with periodontitis treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating childhood idiopathic bone loss in a child comprising administering to a child suffering from childhood idiopathic bone loss a childhood idiopathic bone loss treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating "secondary osteoporosis," which includes glucocorticoid-induced osteoporosis, hyperthyroidism-induced osteoporosis, immobilization-induced osteoporosis, heparin-induced osteoporosis or immunosuppressive-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), by administering to said vertebrate, e.g., a mammal suffering from "secondary osteoporosis," a "secondary osteoporosis" treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating glucocorticoid-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from glucocorticoid-induced osteoporosis, a glucocorticoid-induced osteoporosis treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating hyperthyroidism-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from hyperthyroidism-induced osteoporosis a hyperthyroidism-induced osteoporosis treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating immobilization-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from immobilization-induced osteoporosis, an immobilization-induced
5 osteoporosis treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating heparin-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from
10 heparin-induced osteoporosis, a heparin-induced osteoporosis treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for treating immunosuppressive-induced osteoporosis in a vertebrate, e.g., a mammal
15 (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from immunosuppressive-induced osteoporosis, an immunosuppressive-induced osteoporosis treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

20 Yet another aspect of this invention is directed to methods for treating a bone fracture in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from a bone fracture, a bone fracture treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug. In
25 one aspect of this invention for treating a bone fracture the Formula I compound, prodrug thereof or pharmaceutically acceptable salt of said compound or said prodrug is applied locally to the site of bone fracture. In another aspect of this invention the Formula I compound, prodrug thereof or pharmaceutically acceptable salt of said compound or said prodrug is administered systemically.

30 Yet another aspect of this invention is directed to methods for enhancing bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal which has undergone

facial reconstruction, maxillary reconstruction or mandibular reconstruction, a bone enhancing amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug. In one aspect of this method a Formula I compound, prodrug thereof or pharmaceutically acceptable salt of said compound or said prodrug is applied locally to the site of bone reconstruction.

Yet another aspect of this invention is directed to methods for treating prosthetic ingrowth in a vertebrate, such as promoting bone ingrowth into a bone prosthesis in, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from prosthetic ingrowth, a prosthetic ingrowth treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for inducing vertebral synostosis in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal undergoing surgery for vertebral synostosis, a therapeutically effective amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for enhancing long bone extension in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal suffering from an insufficiently sized long bone, a long bone enhancing amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Yet another aspect of this invention is directed to methods for strengthening a bone graft in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a mammal in receipt of a bone graft, a bone graft strengthening amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug. Additionally, a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug can be used as an alternative to bone graft surgery. In one aspect of this method a Formula I compound, prodrug thereof or pharmaceutically acceptable salt of said compound

or said prodrug is applied locally to the site of the bone graft. In another aspect of this method a Formula I compound, prodrug thereof or pharmaceutically acceptable salt of said compound or said prodrug is applied directly to the bone by injection or direct application to the bone surface.

5 A preferred dosage is about 0.001 to 100 mg/kg/day of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug. An especially preferred dosage is about 0.01 to 10 mg/kg/day of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

10 This invention is also directed to pharmaceutical compositions which comprise a therapeutically effective amount of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

 This invention is also directed to pharmaceutical compositions for the
15 augmentation of bone mass which comprise a bone mass augmenting amount of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

 This invention is also directed to pharmaceutical compositions for the
20 treatment of a condition which presents with low bone mass in a vertebrate, e.g., a mammal (including a human being), which comprise a low bone mass condition treating amount of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

25 This invention is also directed to pharmaceutical compositions for the local or systemic treatment of osteoporosis, bone fractures, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth in a vertebrate, e.g., a mammal (including a human being), which comprises a therapeutically effective amount of a compound of Formula I, a prodrug thereof or a pharmaceutically
30 acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

 This invention is also directed to pharmaceutical compositions for the treatment of "secondary osteoporosis", which includes glucocorticoid-induced

osteoporosis, hyperthyroidism-induced osteoporosis, immobilization-induced osteoporosis, heparin-induced osteoporosis or immunosuppressive-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), which compositions comprise a "secondary osteoporosis" treating amount of a compound
5 of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of osteoporosis in a vertebrate, e.g., a mammal (including a human being), which comprise an osteoporosis treating amount of a compound of the
10 Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for enhancing bone fracture healing in a vertebrate, e.g., a mammal (including a human being), which comprise a bone fracture treating amount of a compound of
15 the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of osteotomy in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g. a mammal having undergone an
20 osteotomy a bone restoration treating amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein a bone restoration treating amount is an amount of said Formula I compound, prodrug thereof or pharmaceutically acceptable salt of said compound or said prodrug sufficient to restore bone in areas containing bone defects due to
25 said osteotomy. In one aspect the Formula I compound, prodrug thereof or pharmaceutically acceptable salt thereof is applied locally to an osteotomy site.

This invention is also directed to pharmaceutical compositions for facilitating bone healing after an osteotomy in a vertebrate, e.g., a mammal (including a human being), comprising administering to said vertebrate, e.g., a
30 mammal having undergone an osteotomy a bone healing amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug. In one aspect the Formula I compound, prodrug

thereof or pharmaceutically acceptable salt thereof is applied locally to an osteotomy site.

This invention is also directed to pharmaceutical compositions for the treatment of alveolar or mandibular bone loss in a vertebrate, e.g., a mammal
5 (including a human being), which comprise an alveolar or mandibular bone loss treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the
10 treatment of childhood idiopathic bone loss in a child which comprise a childhood idiopathic bone loss treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the
15 augmentation of bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction in a vertebrate, e.g., a mammal (including a human being), which comprise a bone healing amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

20 This invention is also directed to pharmaceutical compositions for the treatment of bone loss associated with periodontitis in a vertebrate, e.g., a mammal (including a human being), which comprise a bone loss associated with periodontitis treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a
25 pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of prosthetic ingrowth in a vertebrate, e.g., a mammal (including a human being), which comprise a prosthetic ingrowth treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable
30 salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for inducing vertebral synostosis or spinal fusion in a vertebrate, e.g., a mammal (including a

human being), which comprise a therapeutically effective amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for enhancing bone union in a long bone extension procedure in a vertebrate, e.g., a mammal (including a human being), which comprise a bone mass augmentation treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of glucocorticoid-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), which comprise a glucocorticoid-induced osteoporosis treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hyperthyroidism-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), which comprise a hyperthyroidism-induced osteoporosis treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of immobilization-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being), which comprise an immobilization-induced osteoporosis treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of heparin-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being) which comprise a heparin-induced osteoporosis treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of immunosuppressive-induced osteoporosis in a vertebrate, e.g., a mammal (including a human being) which comprise an immunosuppressive-induced osteoporosis treating amount of a compound of the Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

Yet another aspect of this invention is directed to combinations of the Formula I compounds, prodrugs thereof or pharmaceutically acceptable salts of said compounds or said prodrugs and other compounds as described below.

Yet another aspect of this invention is directed to pharmaceutical compositions comprising a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug and for the use of such compositions for the treatment or prevention of conditions which present with low bone mass, including osteoporosis in a vertebrates, e.g., mammals (e.g., humans, particularly women) or the use of such compositions for other bone mass augmenting uses.

The combinations of this invention comprise a therapeutically effective amount of a first compound, said first compound being a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug; and a therapeutically effective amount of a second compound, said second compound being an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug such as an estrogen agonist/antagonist or a bisphosphonate.

Another aspect of this invention is directed to methods for treating vertebrates, e.g., mammals which present with low bone mass comprising administering to said vertebrate, e.g., a mammal having a condition which presents with low bone mass

a. an amount of a first compound, said first compound being a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug; and

b. an amount of a second compound, said second compound being an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of

said agent or said prodrug such as an estrogen agonist/antagonist or a bisphosphonate.

Such compositions and methods may also be used for other bone mass augmenting uses.

5 A preferred aspect of this method is wherein the condition which presents with low bone mass is osteoporosis.

Another preferred aspect of this method is wherein the first compound and the second compound are administered substantially simultaneously.

Another preferred aspect of this method is wherein the first compound is
10 administered for a period from about one week to about five years.

An especially preferred aspect of this method is wherein the first compound is administered for a period of from about one week to about three years.

Optionally the administration of the first compound is followed by administration of the second compound wherein the second compound is an
15 estrogen agonist/antagonist for a period of from about three months to about three years without the administration of the first compound during the second period of from about three months to about three years.

Alternatively, the administration of the first compound is followed by administration of the second compound wherein the second compound is an
20 estrogen agonist/antagonist for a period greater than about three years without the administration of the first compound during the greater than about three year period.

Another aspect of this invention is a kit comprising:

a. an amount of a Formula I compound, a prodrug thereof or a
25 pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug such as an estrogen agonist/antagonist or a bisphosphonate and a pharmaceutically
30 acceptable carrier or diluent in a second unit dosage form; and

c. container means for containing said first and second dosage forms.

Yet another aspect of this invention is directed to pharmaceutical compositions comprising a compound of Formula I, a prodrug thereof or a

pharmaceutically acceptable salt of said compound or said prodrug and another bone anabolic agent (although the other bone anabolic agent may be a different Formula I compound), a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug and for the use of such compositions for the treatment
5 of conditions which present with low bone mass, including osteoporosis in a vertebrates, e.g., mammals (e.g., humans, particularly women), or the use of such compositions for other bone mass augmenting uses. Such compositions comprise a therapeutically effective amount of a first compound, said first compound being a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of
10 said compound or said prodrug; and a therapeutically effective amount of a second compound, said second compound being another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug.

Another aspect of this invention is directed to methods for treating
15 vertebrates, e.g., mammals which present with low bone mass comprising administering to said vertebrate, e.g., a mammal having a condition which presents with low bone mass

a. an amount of a first compound, said first compound being a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt or prodrug
20 thereof; and

b. an amount of a second compound, said second compound being another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug.

Such compositions and methods may also be used for other bone mass
25 augmenting uses.

A preferred aspect of this method is wherein the condition which presents with low bone mass is osteoporosis.

Another preferred aspect of this method is wherein the first compound and the second compound are administered substantially simultaneously.

30 Another aspect of this invention is a kit comprising:

a. an amount of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. an amount of a second compound, said second compound being another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of said agent or said prodrug in a second unit dosage form; and

c. container means for containing said first and second dosage forms.

5 Where used in any of the above methods, kits and compositions, certain bone anabolic agents, estrogen agonists/antagonists and bisphosphonates are preferred or especially preferred.

Preferred bone anabolic agents include IGF-1, prostaglandins, prostaglandin agonists/antagonists, sodium fluoride, parathyroid hormone (PTH),
10 active fragments of parathyroid hormone, parathyroid hormone related peptides and active fragments and analogues of parathyroid hormone related peptides, growth hormones or growth hormone secretagogues and the pharmaceutically acceptable salts thereof.

Preferred estrogen agonists/antagonists include droloxifene, raloxifene,
15 tamoxifen; 4-hydroxy-tamoxifen; toremifene; centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid;
20 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;
cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-
25 naphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

30 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; and

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline and the pharmaceutically acceptable salts thereof.

Especially preferred estrogen agonists/antagonists include droloxifene;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid;

5 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

10 (-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

15 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

20 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; and the pharmaceutically acceptable salts thereof.

Preferred bisphosphonates include, tiludronic acid, alendronic acid, zoledronic acid, ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid and their pharmaceutically acceptable salts.

25 Any of the above-described kits may further comprise a written matter describing instructions for the use thereof.

It will be recognized that prodrugs and pharmaceutically acceptable salts may be formed from the compounds used as the second compounds in the combinations of this invention. All of such prodrugs and pharmaceutically acceptable salts so formed are within the scope of this invention. Particularly
30 preferred salt forms include droloxifene citrate, raloxifene hydrochloride, tamoxifen citrate and toremifene citrate.

The phrase "condition(s) which presents with low bone mass" refers to a condition where the level of bone mass is below the age specific normal as defined in standards by the World Health Organization "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis (1994). Report of a World Health Organization Study Group. World Health Organization

Technical Series 843". Included in "condition(s) which presents with low bone mass" are primary and secondary osteoporosis. Secondary osteoporosis includes glucocorticoid-induced osteoporosis, hyperthyroidism-induced osteoporosis, immobilization-induced osteoporosis, heparin-induced osteoporosis and
5 immunosuppressive-induced osteoporosis. Also included is periodontal disease, alveolar bone loss, post-osteotomy and childhood idiopathic bone loss. The phrase "condition(s) which presents with low bone mass" also includes long term complications of osteoporosis such as curvature of the spine, loss of height and prosthetic surgery.

10 The phrase "condition(s) which presents with low bone mass" also refers to a vertebrate, e.g., a mammal known to have a significantly higher than average chance of developing such diseases as are described above including osteoporosis (e.g., post-menopausal women, men over the age of 60).

Other bone mass augmenting or enhancing uses include bone restoration,
15 increasing the bone fracture healing rate, replacing bone graft surgery entirely, enhancing the rate of successful bone grafts, bone healing following facial reconstruction or maxillary reconstruction or mandibular reconstruction, prosthetic ingrowth, vertebral synostosis or long bone extension.

The compounds and compositions of this invention may also be used in
20 conjunction with orthopedic devices such as spinal fusion cages, spinal fusion hardware, internal and external bone fixation devices, screws and pins.

Those skilled in the art will recognize that the term bone mass actually refers to bone mass per unit area which is sometimes (although not strictly correctly) referred to as bone mineral density.

25 The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic), palliative and curative treatment.

By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the Formulation, and not deleterious to the recipient thereof.

30 The expression "prodrug" refers to compounds that are drug precursors which, following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form). Exemplary prodrugs

upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the Formula I compounds include but are not limited to substituents wherein the Z moiety is independently carboxyl and the free hydrogen is replaced by (C₁-C₄)alkyl, (C₂-C₇)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having
 5 from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as b-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.

15 Exemplary five to six membered aromatic rings optionally having one or two heteroatoms selected independently from oxygen, nitrogen and sulfur (i.e., X rings) are phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridiazinyl, pyrimidinyl and pyrazinyl.

Exemplary partially saturated, fully saturated or fully unsaturated five to
 20 eight membered rings optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen (i.e., Ar, Ar¹ and Ar²) are cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and phenyl. Further exemplary five membered rings are furyl, thienyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl,
 25 2-imidazolyl, imidazolidinyl, pyrazolyl, 2-pyrazolyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathiolyl.

30 Further exemplary six membered rings are 2H-pyranyl, 4H-pyranyl, pyridyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-

triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl.

5 Further exemplary seven membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

Further exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings consisting of two fused independently partially
 10 saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen are indolizinyl, indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl,
 15 indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, 1,4-benzodioxan, pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-
 20 2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

Exemplary tricyclic rings consisting of three fused independently partially saturated, fully saturated or fully unsaturated five and/or six membered rings, taken independently, optionally having one to four heteroatoms selected
 25 independently from nitrogen, sulfur and oxygen are indacenyl, biphenylenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl, anthracenyl, naphthothienyl, thianthrenyl, xanthenyl, phenoxathiinyl, carbazolyl, carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl and phenoxazinyl. It will be understood that the fully saturated and all partially
 30 unsaturated forms of these rings are within the scope of this invention. Further, it will be understood that nitrogen may be substituted as the heteroatom at any position, including a bridgehead position, in the heterocyclic rings. Further still, it

will be understood that sulfur and oxygen may be substituted as the heteroatom at any non-bridgehead position within the heterocyclic rings.

By alkylene is meant saturated hydrocarbon (straight chain or branched) wherein a hydrogen atom is removed from each of the terminal carbons.

- 5 Exemplary of such groups (assuming the designated length encompasses the particular example) are methylene, ethylene, propylene, butylene, pentylene, hexylene and heptylene.

- By alkenylene is meant a hydrocarbon containing monounsaturations in the form of one double bond wherein said hydrocarbon is straight chain or branched and wherein a hydrogen atom is removed from each of the terminal carbons. Exemplary of such groups (assuming the designated length encompasses the particular example) are ethenylene (or vinylene), propenylene, butenylene, pentenylene, hexenylene and heptenylene.
- 10

- By alkynylene is meant a hydrocarbon containing di-unsaturations in the form of one triple bond wherein said hydrocarbon is straight chain or branched and wherein a hydrogen atom is removed from each of the terminal carbons. Exemplary of such groups (assuming the designated length encompasses the particular example) are ethynylene, propynylene, butynylene, pentynylene, hexynylene and heptynylene.
- 15

- 20 By halo is meant chloro, bromo, iodo, or fluoro.

- By alkyl is meant straight chain saturated hydrocarbon or branched saturated hydrocarbon. Exemplary of such alkyl groups (assuming the designated length encompasses the particular example) are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, neopentyl, tertiary pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl, isohexyl, heptyl and octyl.
- 25

- By alkoxy is meant straight chain saturated alkyl or branched saturated alkyl bonded through an oxy. Exemplary of such alkoxy groups (assuming the designated length encompasses the particular example) are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, neopentoxy, tertiary pentoxy, hexoxy, isohexoxy, heptoxy and octoxy .
- 30

As used herein, the term mono-N- or di-N,N-(C₁-C_x)alkyl... refers to the (C₁-C_x)alkyl moiety taken independently when it is di-N,N-(C₁-C_x)alkyl...(x refers to

integers and is taken independently when two (C₁-C_x)alkyl groups are present, e.g., methylethylamino is within the scope of di-N,N-(C₁-C_x)alkyl).

Unless otherwise stated the "M" moieties defined above are optionally substituted (e.g., the mere listing of a substituent such as R¹ in a subgenus or
5 dependent claim does not mean that M is always substituted with the R¹ moiety unless it is stated that the M moiety is substituted with R¹). However, in the compounds of Formula I, when K is a bond and M is phenyl, said phenyl group is substituted with one to three substituents. Additionally, in the compounds of Formula I, when Ar or Ar¹ is a fully saturated five to eight membered ring, said ring
10 is unsubstituted.

It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate, through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen
15 atom. For example, the term "pyridyl" means 2-, 3-, or 4-pyridyl, the term "thienyl" means 2-, or 3-thienyl, and so forth.

The expression "pharmaceutically acceptable salt" refers to nontoxic anionic salts containing anions such as (but not limited to) chloride, bromide, iodide, sulfate, bisulfate, phosphate, acetate, maleate, fumarate, oxalate, lactate,
20 tartrate, citrate, gluconate, methanesulfonate and 4-toluene-sulfonate. The expression also refers to nontoxic cationic salts such as (but not limited to) sodium, potassium, calcium, magnesium, ammonium or protonated benzathine (N,N'-dibenzylethylenediamine), choline, ethanolamine, diethanolamine, ethylenediamine, meglamine (N-methyl-glucamine), benethamine (N-
25 benzylphenethylamine), piperazine or tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol).

As used herein, the expressions "reaction inert solvent" and "inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the
30 desired product.

The chemist of ordinary skill will recognize that certain compounds of this invention will contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers such as

72222-402

-40-

enantiomers and diastereomers; and configurational isomers such as cis and trans olefins and cis and trans substitution patterns on saturated alicyclic rings. All such isomers and mixtures thereof are included in this invention.

Hydrates and solvates of the compounds of this invention are also
5 included.

DTT means dithiothreitol. DMSO means dimethyl sulfoxide. EDTA means ethylenediamine tetraacetic acid.

The methods and compounds of this invention result in bone formation resulting in decreased fracture rates. This invention makes a significant
10 contribution to the art by providing compounds and methods that increase bone formation resulting in prevention, retardation, and/or regression of osteoporosis and related bone disorders.

Other features and advantages will be apparent from the specification and claims which describe the invention.

15 This invention is also directed to methods for treating glaucoma in a mammal suffering from glaucoma comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

This invention is also directed to methods for treating ocular hypertension
20 in a mammal suffering from ocular hypertension comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

This invention is also directed to a commercial package comprising a pharmaceutical composition of the invention and a written matter describing
25 instructions for the use thereof.

This invention is also directed to a use of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, for treating a vertebrate having a condition which presents with low bone mass; augmenting and maintaining bone mass in a vertebrate; treating a mammal
30 which presents with kidney degeneration; treating glaucoma in a mammal suffering from glaucoma; or treating ocular hypertension in a mammal.

72222-402

-40a-

This invention is also directed to a use of a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, in the manufacture of a medicament for treating a vertebrate having a condition which presents
5 with low bone mass; augmenting and maintaining bone mass in a vertebrate; treating a mammal which presents with kidney degeneration; treating glaucoma in a mammal suffering from glaucoma; or treating ocular hypertension in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

In general the compounds of this invention can be made by processes which include processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of this invention are provided as further features of the invention and are illustrated by the following reaction schemes. Other processes are described in the experimental section.

Some substituents (e.g., carboxyl) may best be prepared through conversion of another functional group (e.g., carboxyl substituents may be prepared through conversion of, e.g., hydroxyl or carboxaldehyde) at a point later in the synthetic sequence.

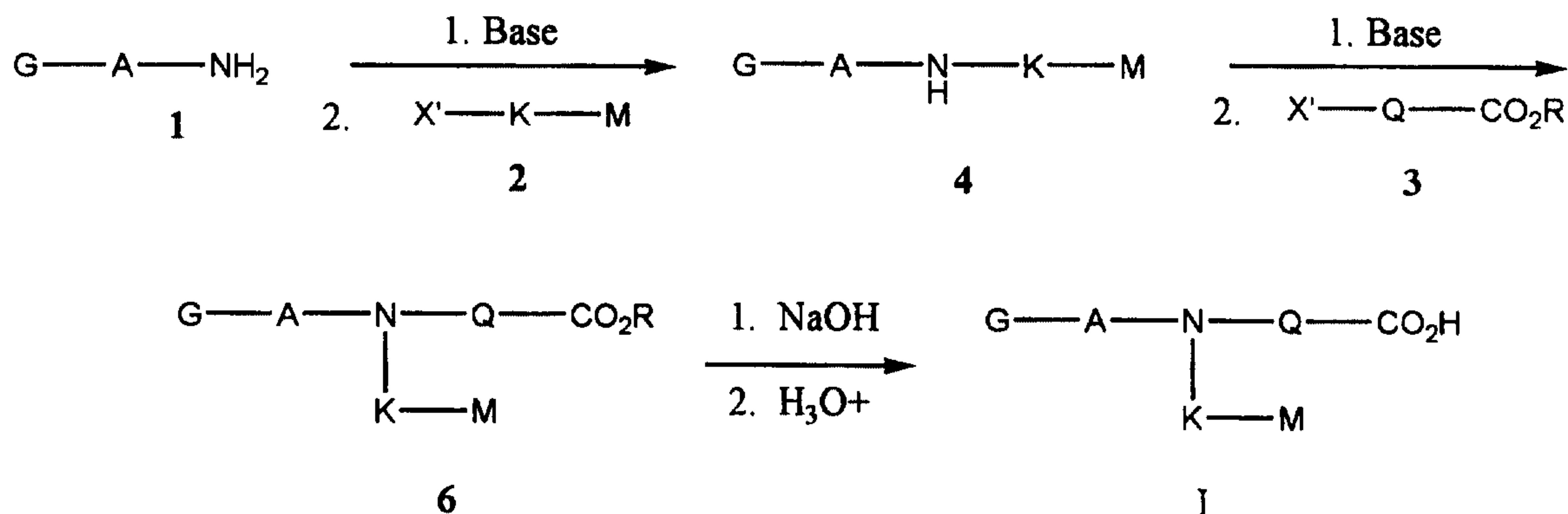
Compounds of Formula I wherein B is nitrogen may be prepared using methods described in SCHEMES 1-5. These methods include (a) sequential alkylation of a sulfonamide or amide with two appropriate alkylating agents, generally alkyl halides or alkyl sulfonates; (b) alkylation of a sulfonamide or amide with an alkyl halide or alkyl sulfonate; or (c) reductive amination of an aldehyde followed by reaction with an acylating agent such as an acyl chloride, a chloroformate, an isocyanate or a chlorocarbonyl amide; or a sulfonylating agent such as a sulfonyl chloride. When performing sequential alkylation, one of the alkylating agents will contain a Q-Z portion, where the Z portion is suitably protected if necessary, and the other alkylating agent will contain a K-M portion, where any functional groups requiring protection are suitably protected. The order of the alkylation, i.e., whether the alkylating agent containing the Q-Z portion is added first or second, will depend upon the reactivity of the electrophilic side chain. When performing a reductive amination, the Q-Z portion may be attached to either the amine reagent or the aldehyde reagent depending upon the ease of preparation of the reagent and the reactivity of the reagents in the reductive amination reaction. The reductive amination is followed by acylation or sulfonylation with an appropriate acylating agent or sulfonyl chloride and, if desired the product is hydrolysed. The starting materials, including amines, aldehydes and alkylating agents, are prepared using methods well known to those skilled in the art. Certain preferred methods for their preparation are described herein.

For example, compounds of Formula I wherein B is N are prepared of the methods set forth in SCHEMES 1 and 2 below. In general, the sequences involve sequential alkylation of an appropriate sulfonamide of Formula 1 or amide of Formula 1 with two appropriate alkyl halides or alkyl sulfonates. SCHEMES 1 and 2 differ only in the order of addition of the two alkylating agents. The alkylation order is typically chosen depending on the reactivity of the electrophilic side-chain. It is generally preferable to react the less reactive electrophilic side chain first. This reduces the amount of dialkylation which occurs in that first alkylation step, thereby resulting in a greater yield of monoalkylated material to be carried on to the next alkylation. In SCHEMES 1 and 2, one of the alkylating agents contains a carboxylic acid or a carboxylic acid isostere, suitably protected with an appropriate protecting group, if necessary. Further, in SCHEMES 1 and 2, the carboxylic acid precursor of Formula 3 is a carboxylic acid ester where R is a suitable carboxylic acid protecting group. Generally, the protecting group is either a straight chain lower alkyl, preferably methyl or ethyl, or a *tert*-butyl or phenyl group. Other acid isosteres can be employed by appropriately modifying SCHEMES 1 and 2 of methods well known to those skilled in the art (e.g., see SCHEME 6 which sets forth the preparation of a tetrazole). Typical alkylating agents are primary, secondary, benzylic or allylic halides and sulfonates and are preferably alkyl bromides or alkyl iodides.

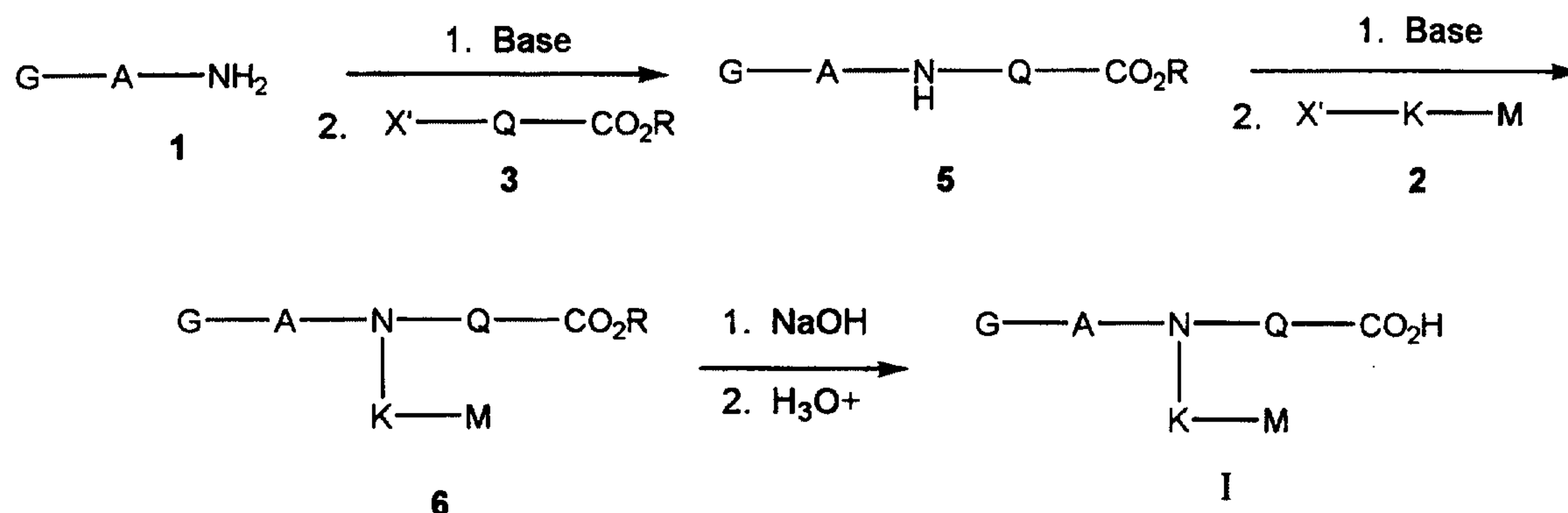
The Formula 1 sulfonamide or amide is converted to its anion with a strong base such as sodium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, potassium *tert*-butoxide, etc. in an aprotic solvent such as dimethylformamide, tetrahydrofuran or N,N-dimethylformamide/benzene at a temperature of about -78°C to about 100°C. The resulting anion is alkylated with an appropriate alkyl halide of Formula 2 or 3 or an appropriate alkyl sulfonate of Formula 2 or 3, wherein X' is the halide or sulfonate portion of the alkylating agent, at a temperature of about 0°C to about 100°C to yield the corresponding mono-alkylated compound of Formula 4 or 5. In some cases, varying amounts of a side-product resulting from dialkylation of the amide or sulfonamide are obtained and can be removed using chromatographic techniques, preferably by flash chromatography (W.C. Still, M. Kahn, A. Mitra, J. Org. Chem. 43, 2923, 1978). After the first alkylation is complete, the compound

- of Formula 4 or 5 is converted to an anion using a suitable base such as sodium hydride, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, potassium bis(trimethylsilyl)amide, potassium tert-butoxide, or potassium carbonate in an aprotic solvent such as N,N-dimethylformamide, tetrahydrofuran,
- 5 N,N- dimethylformamide/benzene, or acetone at a temperature of about -78°C to about 100°C. Alkylation of the anion with an appropriate second alkyl halide of Formula 3 or 2 or alkyl sulfonate of Formula 3 or 2 provides the corresponding dialkylated compound of Formula 6. When R is methyl or ethyl, the ester of Formula 6 is hydrolyzed to the corresponding carboxylic acid of Formula I with a
- 10 dilute aqueous basic solution. This hydrolysis is preferably carried out using sodium or potassium hydroxide in aqueous methanol or ethanol, lithium hydroxide in aqueous alcoholic solvent or aqueous tetrahydrofuran at a temperature of about 0°C to about 80°C. Alternatively, the hydrolysis may be carried out by using methods well known to those skilled in the art, for example, methods described in
- 15 "Protecting Groups in Organic Synthesis," Second Edition, T.W. Greene and P.G.M. Wuts, John Wiley and Sons, Inc., 1991.

SCHEME 1



SCHEME 2



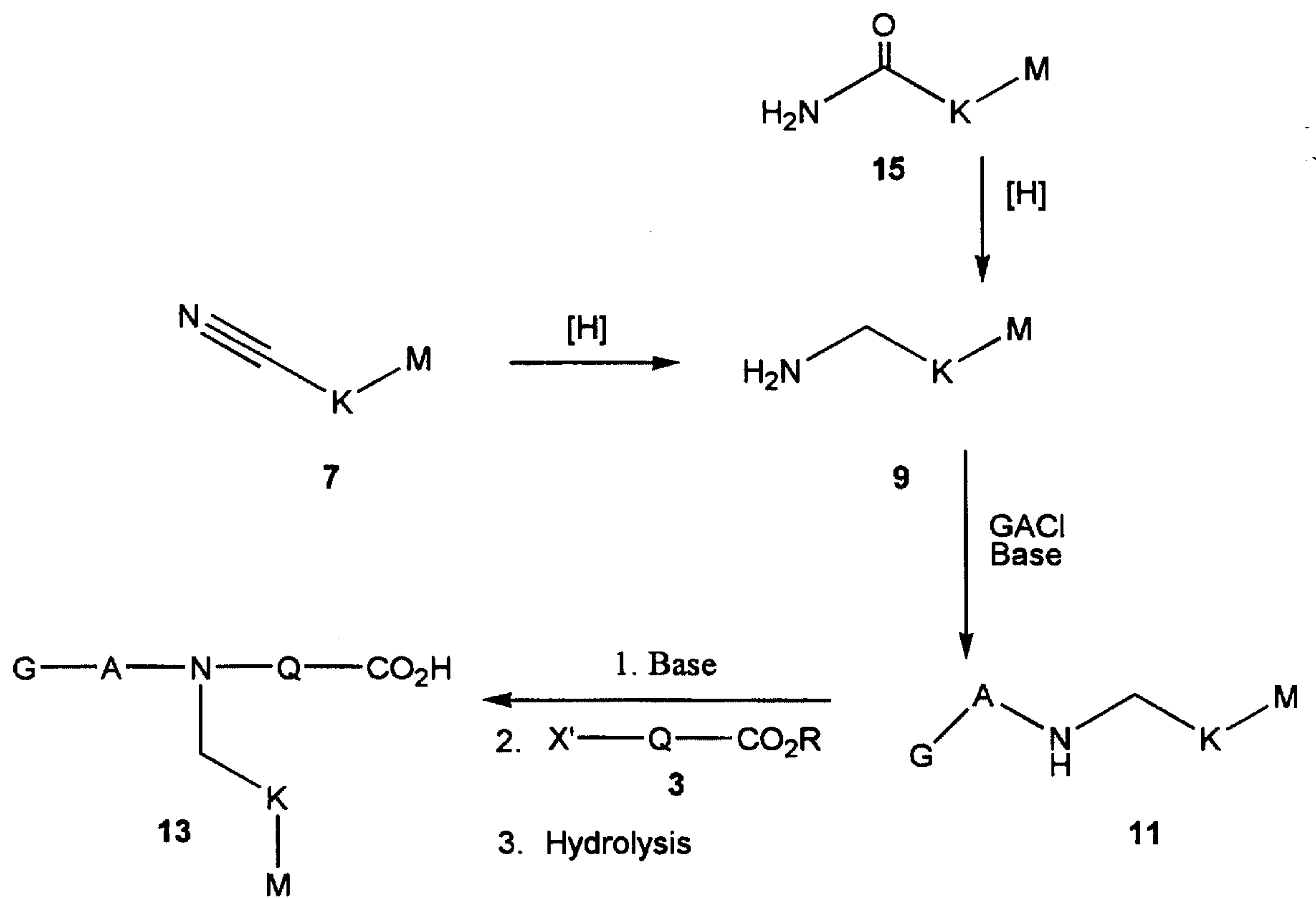
Compounds of Formula I wherein B is N are also prepared from amines as set forth in SCHEMES 3-4. Generally, the appropriate amine starting materials of Formulas 9 and 10 are commercially obtained or can be prepared using methods well known to those skilled in the art (see "The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives," Ed. S. Patai, J. Wiley, New York, 1982). For example, the amine starting materials are prepared from the corresponding nitriles of Formulas 7 or 8. Said nitriles are available from commercial sources or can be prepared using methods well known to those skilled in the art (see Rappaport, "The Chemistry of the Cyano Group," Interscience, New York, 1970 or Patai and Rappaport, "The Chemistry of Functional Groups," pt. 2, Wiley, New York, 1983). The nitrile of Formula 7 or 8 is reduced with a reducing agent such as borane-tetrahydrofuran complex, borane-methyl sulfide complex or lithium aluminum hydride in an aprotic solvent such as tetrahydrofuran or diethyl ether at a temperature of about -78°C to about 60°C. Alternatively, the nitrile is hydrogenated under a hydrogen atmosphere typically at 0 to 50 psi in the presence of Raney nickel or a platinum or palladium catalyst in a protic solvent such as methanol or ethanol at a temperature of about 0°C to about 50°C. It may be desired to add an equivalent of an acid, such as hydrogen chloride, to accomplish the reduction. The amine of Formula 9 or 10 thus obtained is converted to the sulfonamide of Formula 11 or 12 by sulfonylation with a sulfonyl chloride or said amine is converted to an amide of Formula 11 or 12 by acylation with an appropriate acyl chloride. Both the sulfonylation reactions and the

acylation reactions are generally carried out in the presence of a weak base such as triethylamine, pyridine, or 4-methylmorpholine in an aprotic solvent such as methylene chloride or diethyl ether at a temperature of about -20°C to about 50°C. Alternatively, coupling of amines of Formulas 9 or 10 with carboxylic acids are
5 conveniently carried out in an inert solvent such as dichloromethane or N,N-dimethylformamide by a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole hydrate (HOBT) to generate compounds of Formulas 11 or 12. Where the amine is present as the hydrochloride or other
10 salt, it is preferable to add one equivalent of a suitable base such as triethylamine to the reaction mixture. Alternatively, the coupling can be effected with a coupling reagent such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) in an inert solvent such as methanol. Such coupling reactions are generally conducted at temperatures of about -30°C to about 80°C,
15 preferably 0°C to about 25°C. For a discussion of other conditions used for coupling peptides see Houben-Weyl, Vol. XV, part II, E. Wunsch, Ed., George Thieme Verlag, 1974, Stuttgart. Alkylation and if desired, deprotection, of the Formula 11 or 12 compound as described in SCHEMES 1 and 2 affords the corresponding acid Formula 13 and 14 compound. The compounds of Formulas
20 11 and 12 are alkylated in a manner analogous to the alkylation of the compounds of Formulas 1, 4 and 5 of SCHEMES 1 and 2 hereinabove. The alkylated products are deprotected, if necessary, to afford the compounds of Formulas 13 and 14.

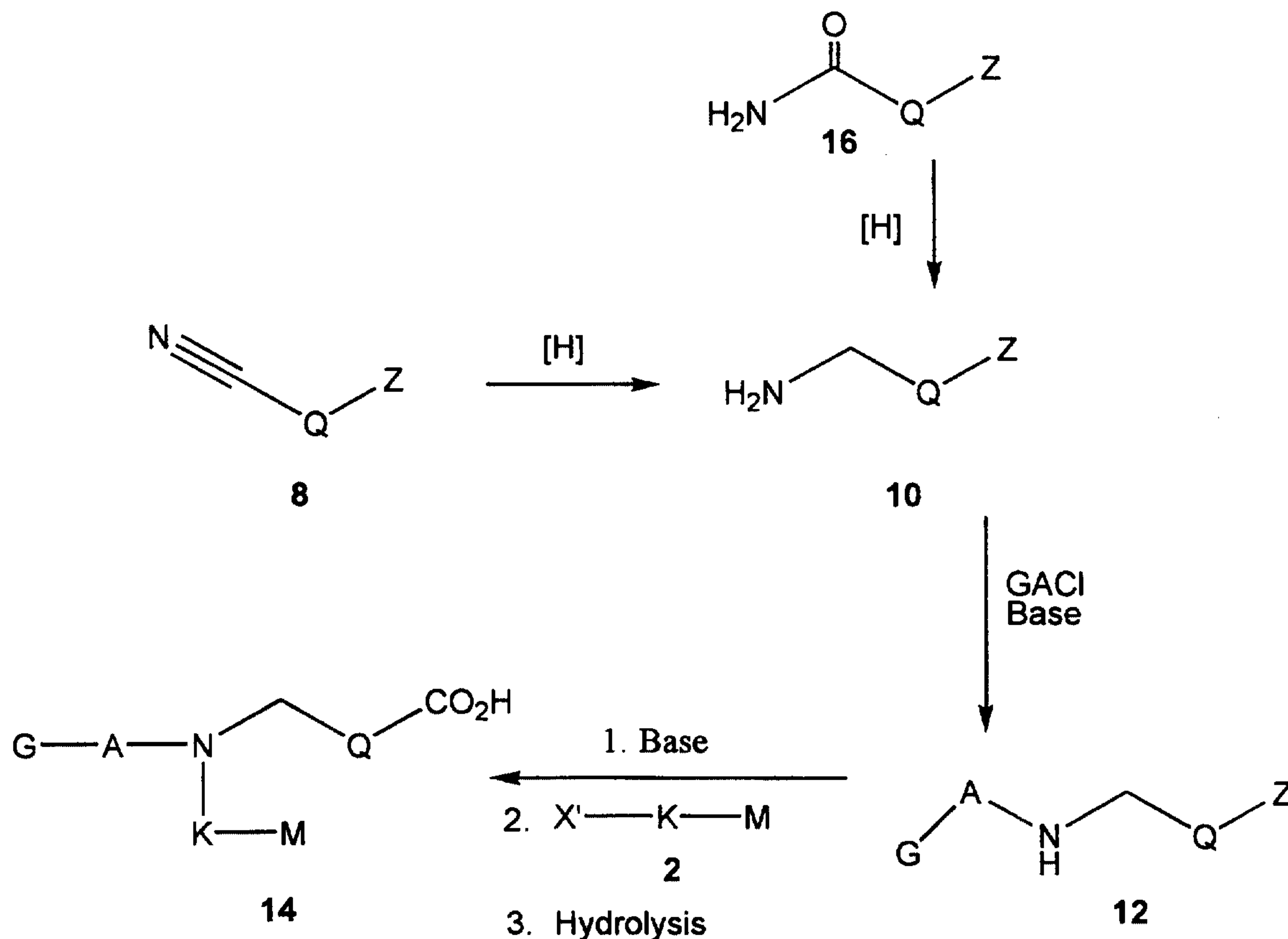
The amines of Formulas 9 and 10 are also prepared via reduction of an
25 appropriate amide of Formulas 15 and 16. This reduction is achieved using reagents such as a borane-tetrahydrofuran complex, a borane-methyl sulfide complex, or diisobutylaluminum hydride in an aprotic solvent such as tetrahydrofuran or diethyl ether at a temperature of about -78°C to about 60°C.

The amines of Formulas 9 and 10 are also obtained from the
30 corresponding nitro precursors by reduction of the nitro group using reducing reagents such as zinc/HCl, hydrogenation in the presence of Raney nickel, palladium, or platinum catalysts, and other reagents as described by P.N. Rylander in "Hydrogenation Methods," Academic Press, New York, 1985.

SCHEME 3



SCHEME 4



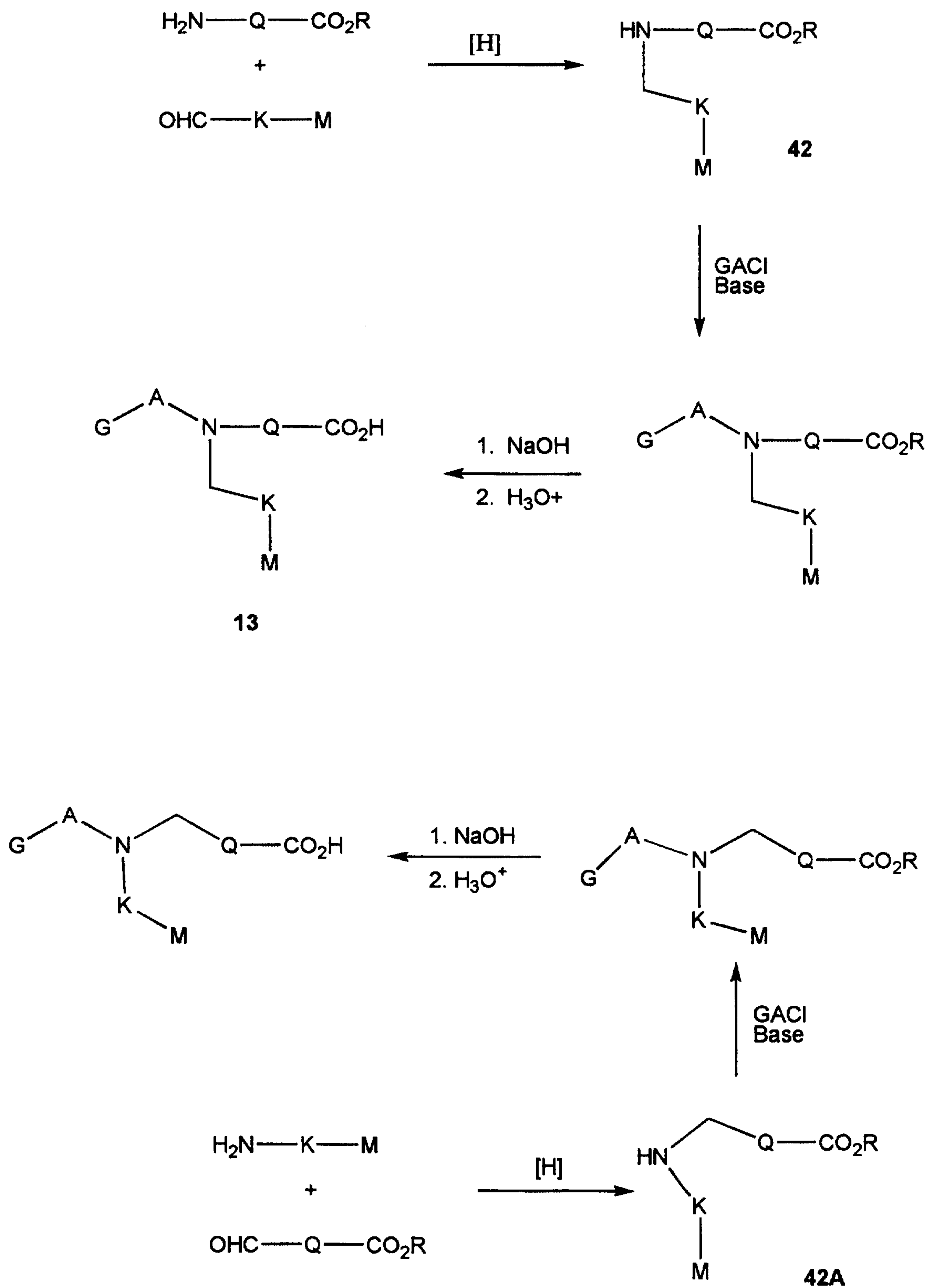
Amines and alkylating agents useful for the above syntheses are described
 5 and prepared as set forth in the section entitled PREPARATIONS below.

Alternatively, the compounds of Formula I wherein B is N are prepared by
 reductive amination of an aldehyde containing the appropriate suitably protected
 acidic functionality with an amine. This sequence is set forth in SCHEME 5.
 Alternatively, the amine may contain the appropriate suitably protected acidic
 10 functionality.

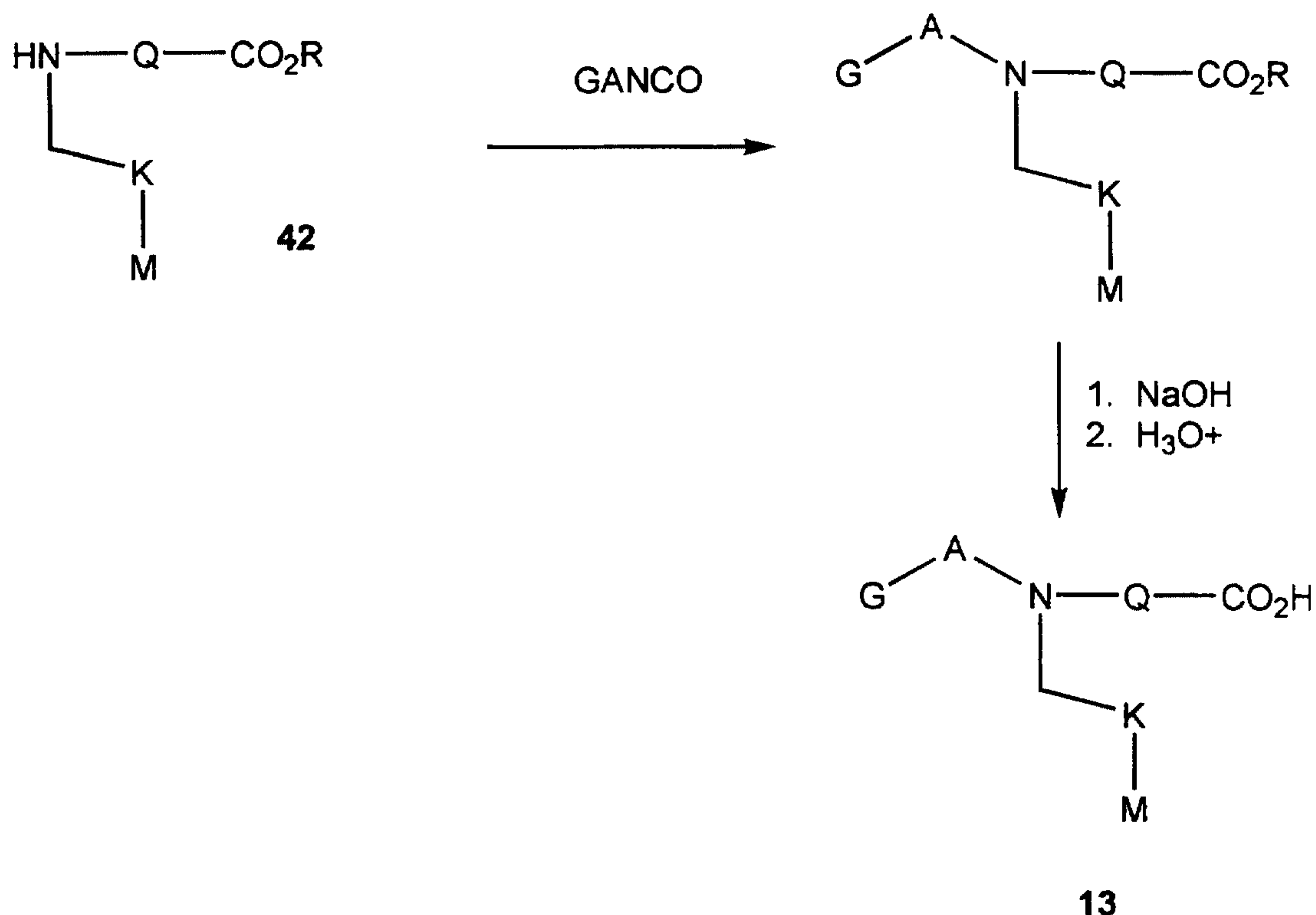
The reductive amination is typically carried out at a pH of between 6 and 8,
 using a reducing agent such as sodium cyanoborohydride or sodium
 triacetoxyborohydride. The reaction is normally performed in a protic solvent such
 as methanol or ethanol at temperatures of about -78°C to about 40°C. (e.g., see
 15 A. Abdel-Magid, C. Maryanoff, K. Carson, Tetrahedron Lett. 39, 31, 5595-5598,
 1990.) The reductive amination reaction may also be carried out using titanium
 isopropoxide and sodium cyanoborohydride (R.J. Mattson et al, J. Org. Chem.

1990, 55, 2552-4) or by preformation of the imine under dehydrating conditions followed by reduction. The resulting amine of Formulas 42 and 42A, is transformed to the desired amide or sulfonamide by coupling with an acid chloride, sulfonyl chloride, or carboxylic acid as set forth in SCHEMES 3 and 4. If desired, the amine
5 intermediate of Formulas 42 or 42A may be converted to a urethane by treatment with a chloroformate or to a tetrasubstituted urea by treatment with a chlorocarbonyl amide. These reactions are performed in the presence of a weak base such as triethylamine, pyridine, or 4-methylmorpholine in an aprotic solvent such as methylene chloride or diethyl ether at a temperature of about -20°C to
10 about 50°C. Conversion of the amine of Formulas 42 or 42A to a trisubstituted urea is accomplished by treatment with an isocyanate in an aprotic solvent such as methylene chloride or diethyl ether at temperatures ranging between -20°C and 50°C (for example, see SCHEME 5A). In cases where the amine is present as the hydrochloride salt, it is preferable to add an equivalent of a suitable base such as
15 triethylamine to the reaction. If desired, hydrolysis of the resulting sulfonamide or amide provides the corresponding acid.

SCHEME 5



SCHEME 5A



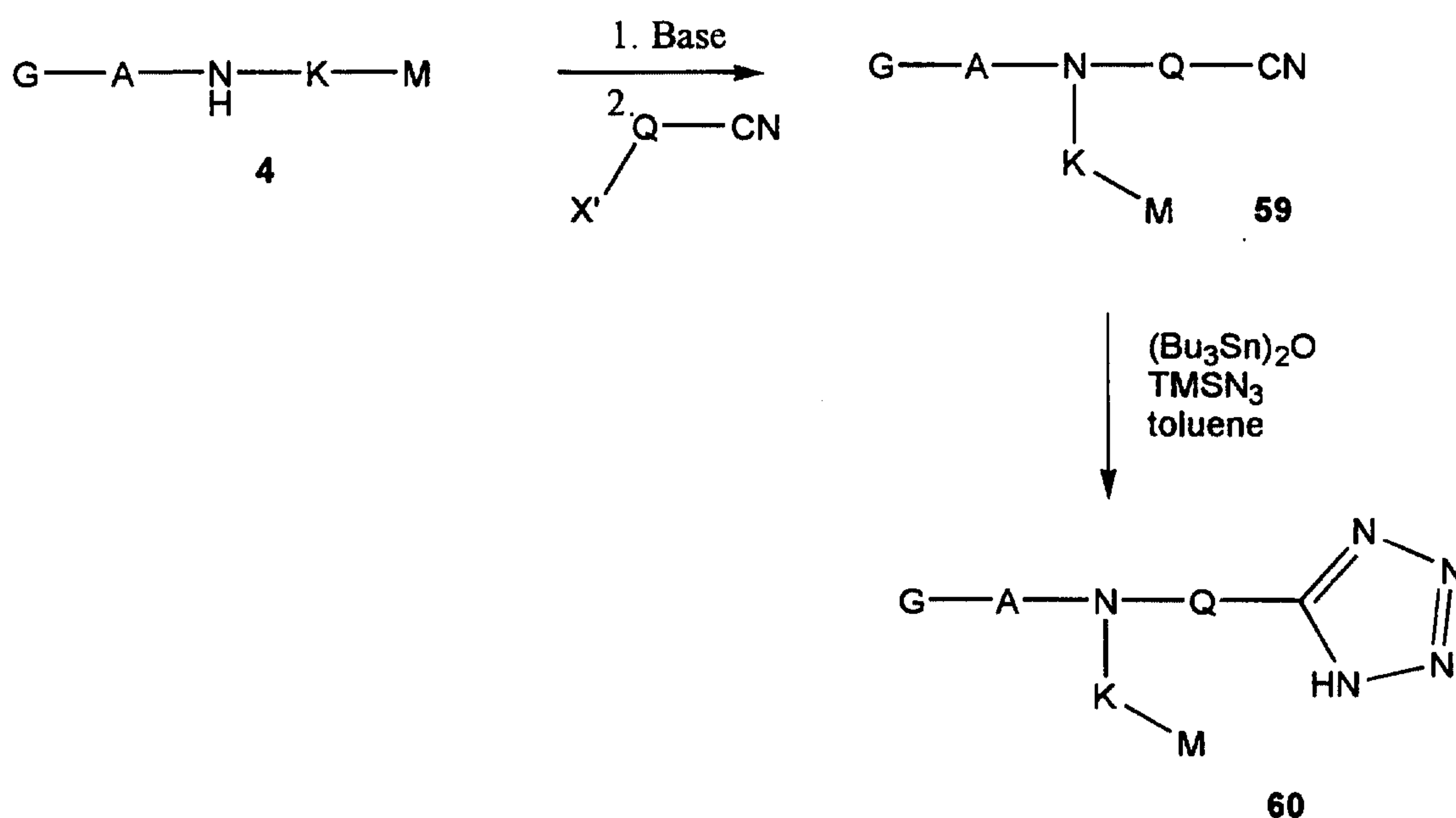
Aldehydes useful in the above SCHEME 5 are described and prepared as set forth in the section entitled PREPARATIONS below.

- 5 Compounds of Formula I where B is N and Z is tetrazolyl are prepared as set forth in SCHEME 6. A sulfonamide or amide of Formula 4 is alkylated with the appropriate alkyl halide or sulfonate (wherein X' is halide or sulfonate), preferably a primary, secondary, benzylic, or allylic alkyl bromide, iodide, or sulfonate, which contains a nitrile to provide a nitrile of Formula 59. This alkylation is achieved by
- 10 treatment of the sulfonamide or amide of Formula 59 with a base such as sodium hydride, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, potassium tert-butoxide, or potassium carbonate in an aprotic solvent such as dimethylformamide, dimethylformamide/benzene, or acetone followed by reaction of the resulting anion with a suitable alkylating agent. Alkylation occurs at a
- 15 temperature of about -78°C to about 100°C. A preferred method for converting the resulting nitrile of Formula 59 to the tetrazole of Formula 60 is treatment of the alkylated nitrile with dibutyltin oxide and trimethylsilylazide, in refluxing toluene

(S.J. Wittenberger and B.G. Donner, J. Org. Chem. 1993, 58, 4139-4141, 1993).
For a review of alternative preparations of tetrazoles see R.N. Butler, Tetrazoles,
In Comprehensive Heterocyclic Chemistry; Potts, K.T. Ed.; Pergamon Press:
Oxford, 1984, Vol. 5, pp 791-838.

5

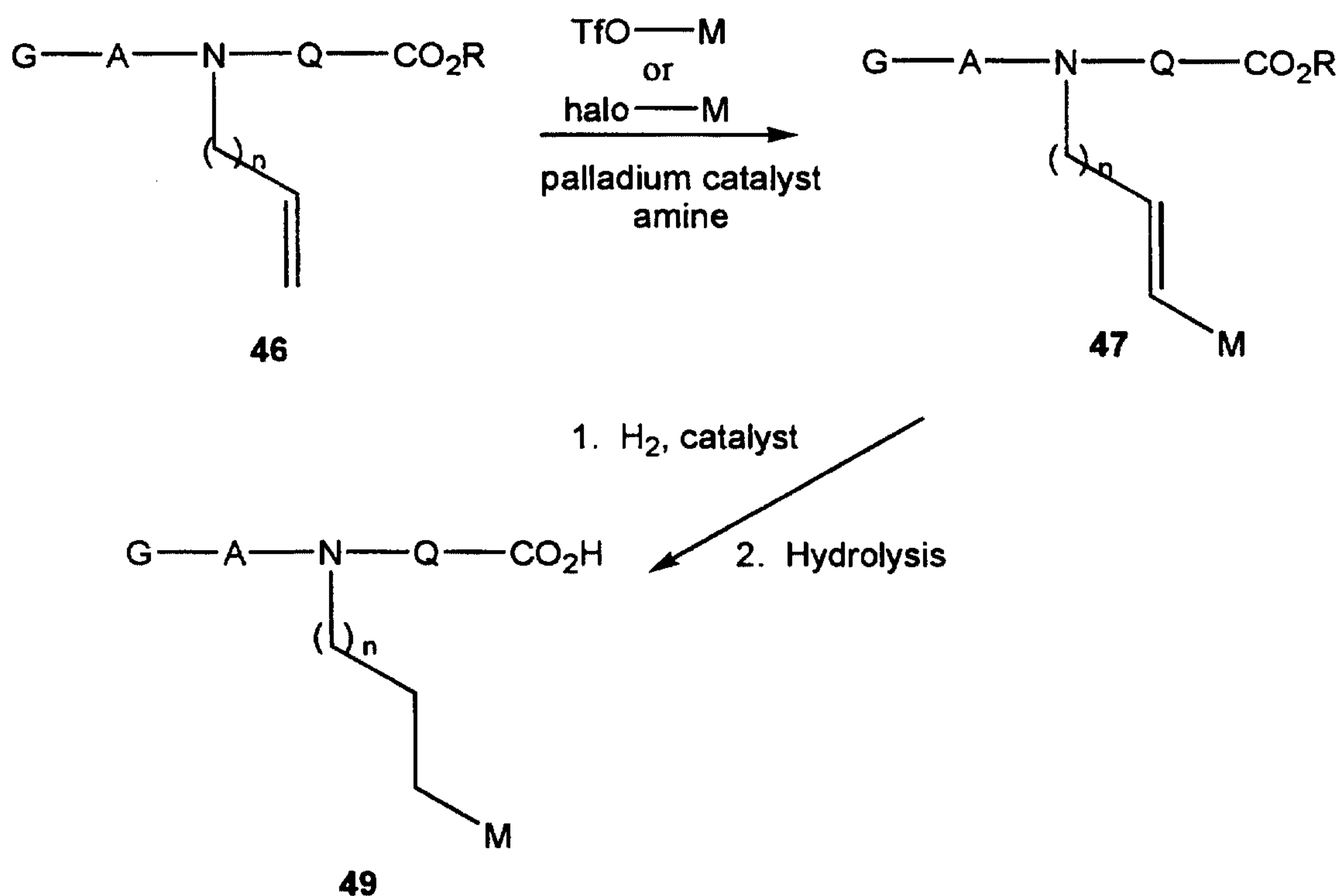
SCHEME 6



Alternatively, certain compounds of Formula I wherein B is N are prepared
as set forth in SCHEME 7. Thus, esters of Formula 46 are prepared using the
procedures described above in SCHEMES 1 and 2. Subsequent Heck coupling of
this intermediate to an arylhalide (preferably an aryl bromide or aryl iodide), an aryl
triflate, or a ring system which contains a vinyl bromide, iodide, or triflate is
accomplished with a palladium catalyst, such as palladium acetate or
tetrakis(triphenylphosphine)palladium(0) in the presence of a trialkylamine, such as
triethylamine. In some cases, an additive such as a triarylphosphine or
triarylsarsene may be added to the reaction. The reaction is typically performed in
an aprotic solvent such as dimethylformamide or acetonitrile at a temperature of
about 0°C to about 150°C (see R.F. Heck in Comp. Org. Syn., Vol. 4, Ch. 4.3, p.
833 or Daves and Hallberg, Chem. Rev. 1989, 89, 1433). If desired, the compound

of Formula 47 can be hydrolyzed to the corresponding acid. Alternatively, the compound of Formula 47 can be hydrogenated and, if desired, further hydrolyzed to the corresponding acid of Formula 49. Hydrogenation is preferably achieved under a hydrogen atmosphere typically at 0 to 50 psi in the presence of a palladium or platinum catalyst in an alcoholic solvent such as ethanol or methanol at a temperature of about 0°C to about 50°C. In cases where M represents a partially saturated ring system, hydrogenation will generate a fully saturated ring system.

SCHEME 7



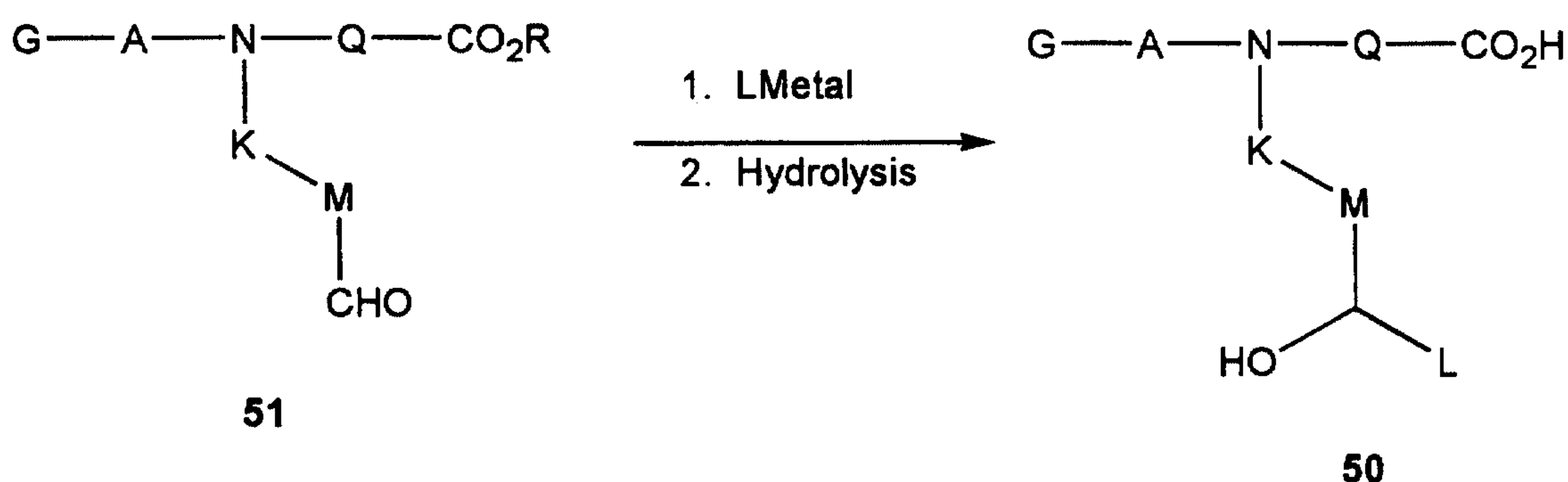
10

Alternatively, certain compounds of Formula I wherein B is N are prepared as described in SCHEME 8. Compounds of Formula 51 are prepared as described in SCHEMES 1 and 2 by alkylation of compounds of Formula 5 with an electrophile of Formula 2 which contains the appropriate functionality on the M ring. At least one of the substituents on the M ring must be suitable for subsequent conversion to an aldehyde. For example, electrophiles of Formula 2

15

containing a protected alcohol on the M ring may be alkylated and then deprotected and oxidized to the aldehyde, using reagents well known to those skilled in the art, to generate compounds of Formula 51. An alternative method is to alkylate with an electrophile of Formula 2 where M contains a vinyl group. After
 5 alkylation, oxidative cleavage of the double bond provides the desired aldehyde of Formula 51. The oxidative cleavage is accomplished by transforming the double bond to the 1,2-diol with catalytic osmium tetroxide and N-methylmorpholine followed by oxidative cleavage to the aldehyde using sodium periodate. Alternatively, oxidative cleavage via ozonolysis followed by reduction using
 10 reagents such as methyl sulfide, triphenylphosphine, zinc/acetic acid, or thiourea, generates the desired aldehyde of Formula 51. Addition of LMetal where LMetal is any organometallic reagent such as an organolithium or a Grignard reagent in an aprotic solvent such as diethyl ether or tetrahydrofuran at a temperature of about -78°C to about 80°C, followed by hydrolysis of the ester as described above,
 15 provides the desired compound of Formula 50.

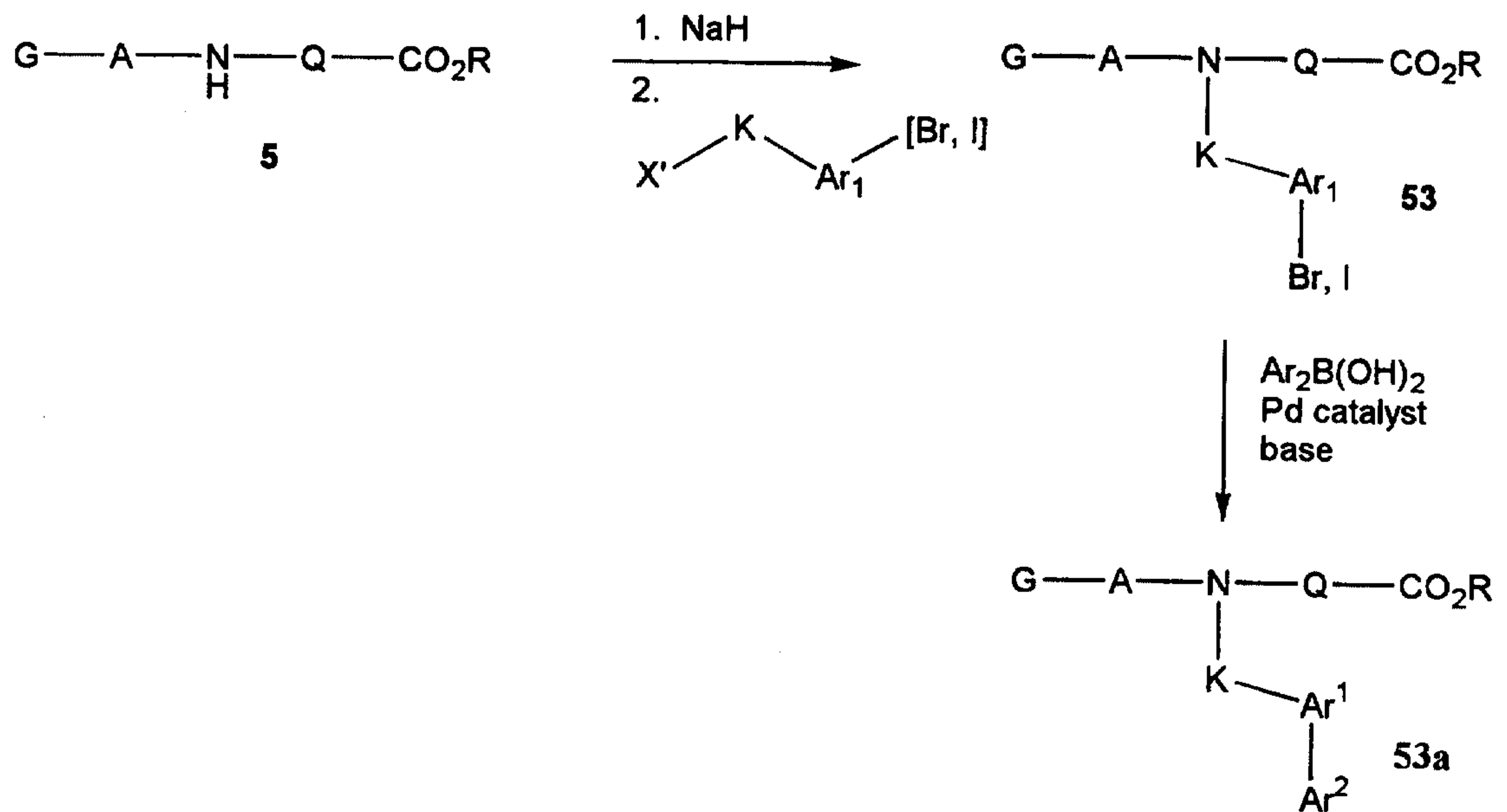
SCHEME 8



20 Alternatively, certain compounds of Formula I wherein B is N are prepared as described in SCHEME 9. The appropriate sulfonamide or amide of Formula 5 is alkylated using the conditions described in SCHEMES 1 and 2. The alkylating agent is an electrophile which contains an aromatic bromide or iodide or a ring system which contains a vinyl bromide or iodide (Ar^1) to provide compounds of
 25 Formula 53. Suzuki-type coupling of the compound of Formula 53 thus obtained

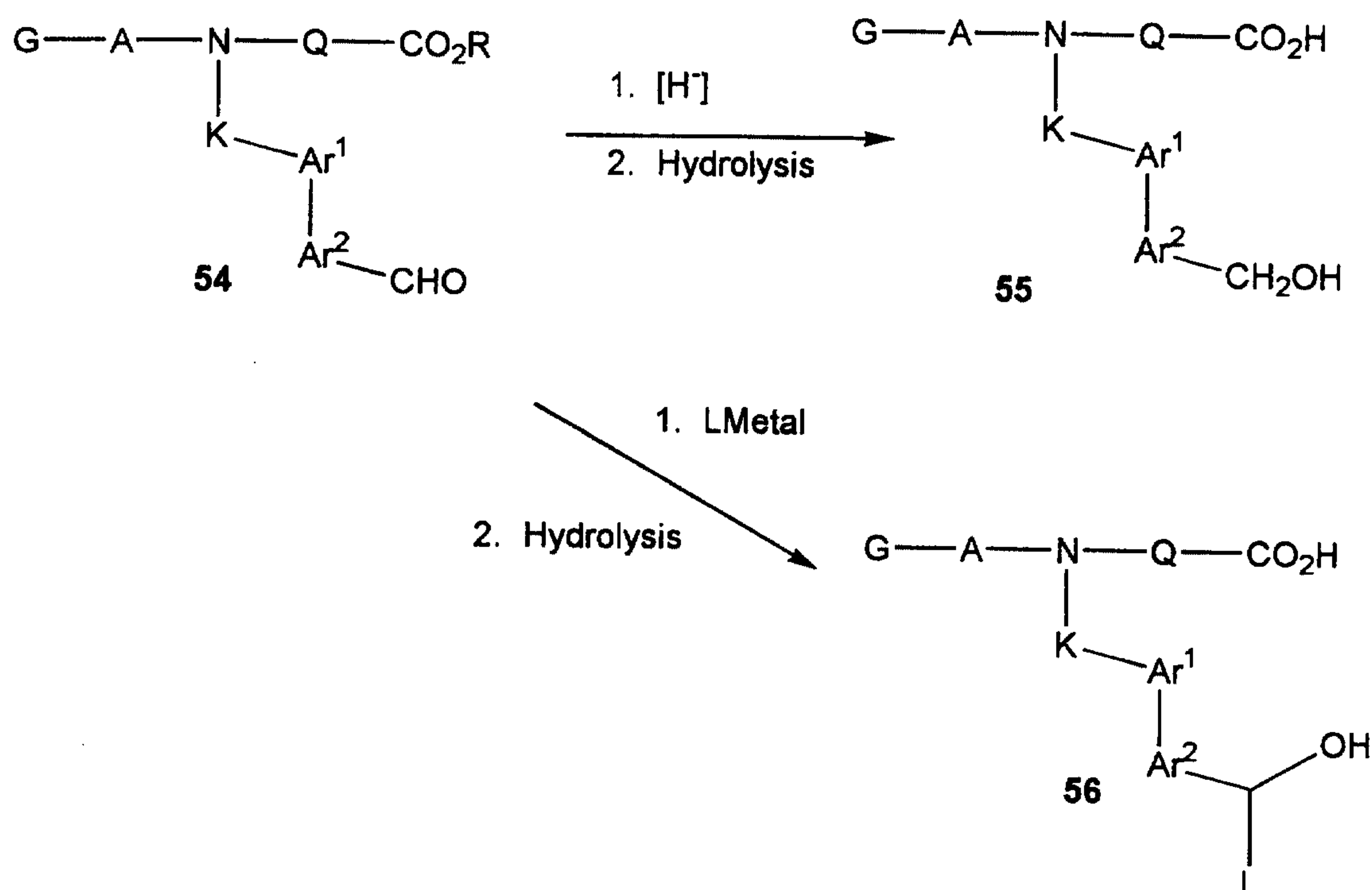
with an aryl boronic acid (Ar^2) provides Formula 53a compounds. For a review of the Suzuki reaction see A.R. Martin and Y. Yang in *Acta Chem. Scand.* 1993, 47, 221. The coupling reaction is achieved using about two equivalents of a base, such as sodium carbonate, potassium carbonate, sodium hydroxide, thallium hydroxide or potassium phosphate, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), palladium acetate, palladium chloride, tris(dibenzylideneacetone)dipalladium(0) or [1,4-bis(diphenylphosphine)butane]palladium(0). The reaction may be run in an aqueous alcoholic solvent such as methanol or ethanol; or in other aqueous solvents such as aqueous tetrahydrofuran, aqueous acetone, aqueous glycol dimethyl ether, or aqueous benzene at temperatures ranging from about 0°C to about 120°C. When Ar^1 is a partially saturated ring, reduction of the ring to provide a saturated ring system may, if desired, be performed at this point. This transformation is achieved by hydrogenating the partially saturated ring in the presence of a catalyst such as palladium or platinum in an alcoholic solvent (ethanol or methanol) and/or ethyl acetate. Ester hydrolysis of compounds of Formulas 53 or 53a, if desired, provides the corresponding acid. The resulting acids may contain functional groups on either of the ring systems (Ar^1 or Ar^2) which can be modified using methods well known to those skilled in the art. Examples of such modifications are shown in SCHEME 10.

SCHEME 9



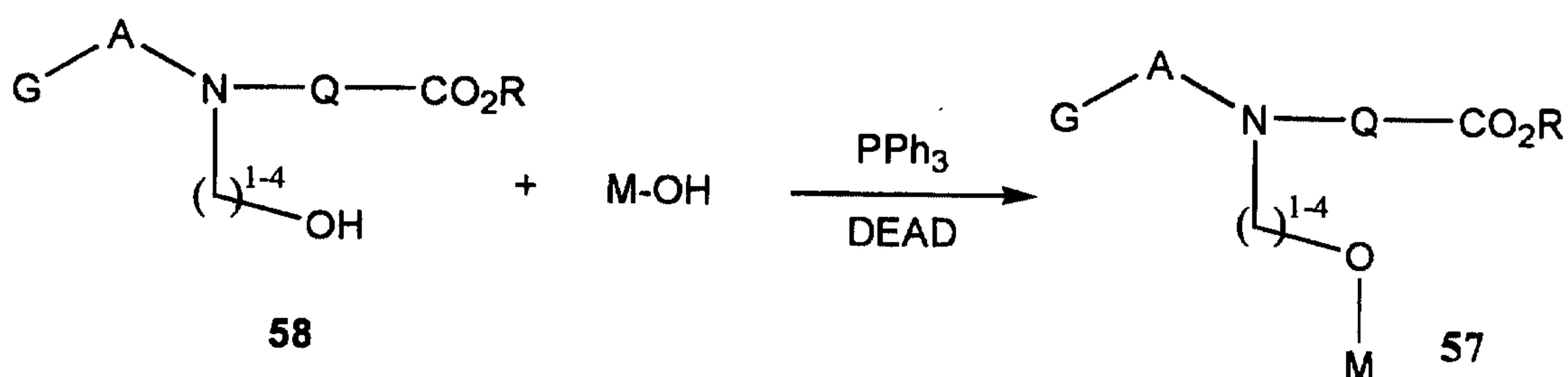
Compounds of Formula 54 which contain an aldehyde functional group are prepared using methods described in SCHEMES 8 and 9. Of SCHEME 10, treatment of a compound of Formula 54 with an appropriate organometallic reagent (LMetal), such as an organolithium or Grignard reagent, in an aprotic solvent such as diethyl ether or tetrahydrofuran at a temperature of about -78°C to about 80°C , followed by hydrolysis of the ester, provides compounds of Formula 56. Alternatively, reduction of the aldehyde followed by hydrolysis provides Formula 55 compounds.

SCHEME 10



Alternatively, certain compounds of Formula I wherein B is N are prepared as described in SCHEME 11. The starting alcohols of Formula 58 are prepared of methods well known to persons skilled in the art, for example, by using methods described in SCHEMES 1 and 2. It will be recognized by a person of ordinary skill in the art that protecting groups may be required in the synthesis of certain of these alcohols. Intermediate 58 is coupled with a variety of aryl alcohols (M is as defined above) using Mitsunobu coupling conditions (for a review see O. Mitsunobu, *Synthesis*, 1, 1981). Typically the coupling is achieved by addition of a coupling agent such as triphenylphosphine and diethyl azodicarboxylate or diisopropyl azodicarboxylate in an inert solvent such as methylene chloride or tetrahydrofuran at a temperature of about 0°C to about 80°C. If desired, subsequent hydrolysis yields the corresponding acid.

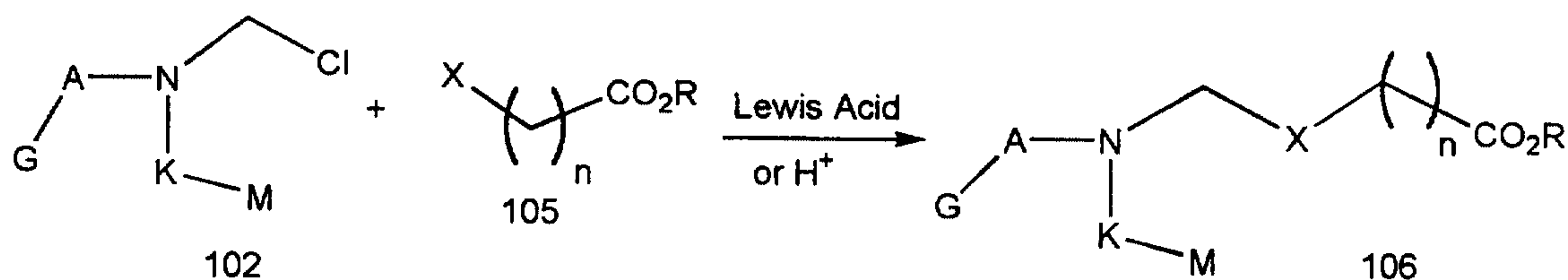
SCHEME 11



Alternatively, certain compounds of Formula I wherein B is N are prepared as described in SCHEME 12. A compound of Formula 102 is added to a compound of Formula 105 (wherein X is as defined above for the compound of Formula I) in the presence of a Lewis acid such as titanium tetrachloride or a mineral acid such as hydrochloric acid. If desired the ester of Formula 106 can be converted to the corresponding acid by hydrolysis or deprotection.

10

SCHEME 12



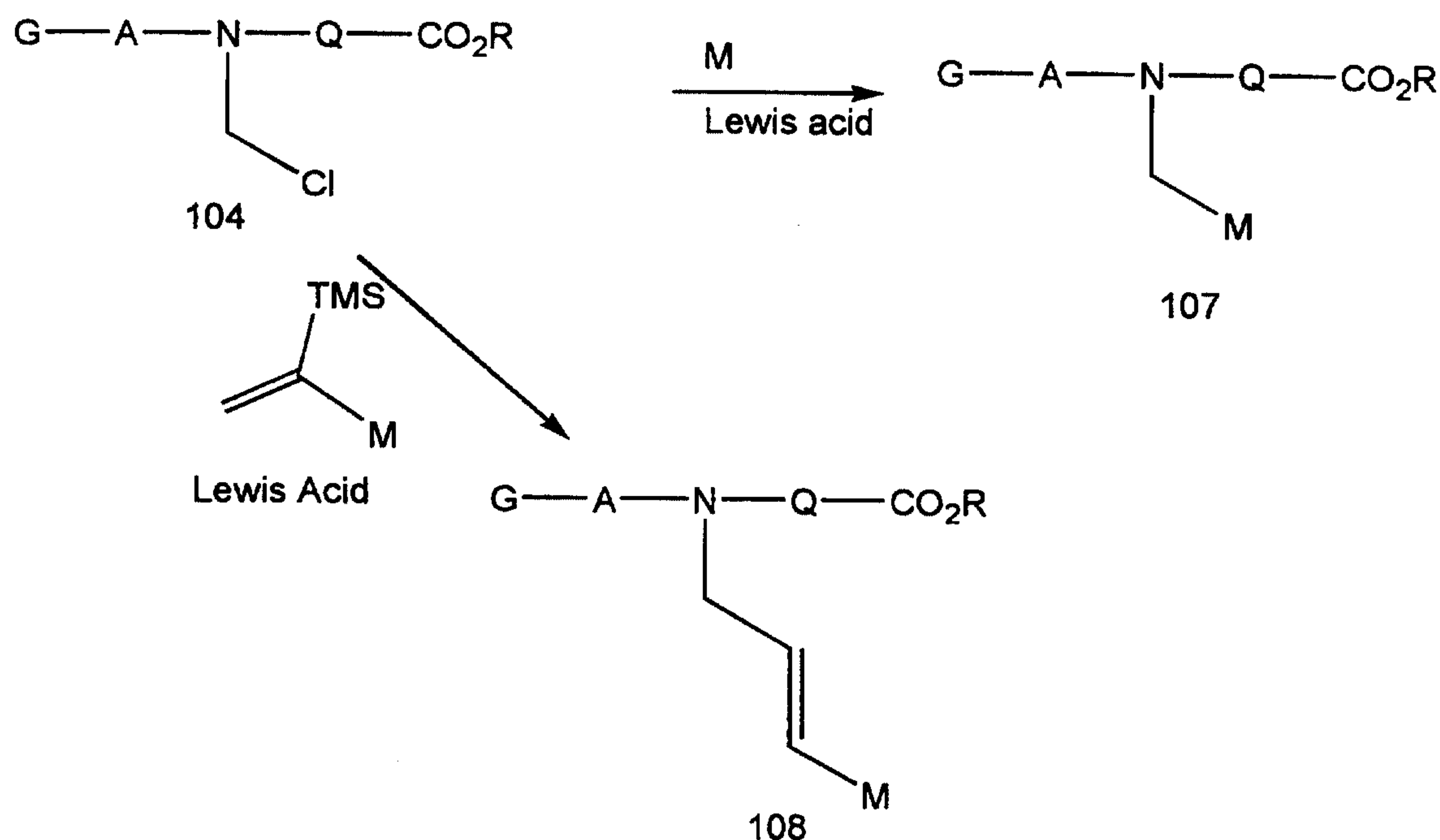
Alternatively, certain compounds of Formula I wherein B is N are prepared as described in SCHEME 13. Chloromethyl compounds of Formula 104 are treated with the appropriate substituted aromatic ring system, M, such as 4-ethoxybenzene or thiophene in the presence of a Lewis acid such as titanium tetrachloride or a mineral acid such as hydrochloric acid in an aprotic solvent such as chloroform at a temperature of about 0°C to about 80°C to yield compounds of Formula 107 which may subsequently be hydrolyzed or deprotected as described above to yield the corresponding carboxylic acids. Alternatively, chloromethyl compounds of Formula 104 can be treated with a Lewis acid such as titanium tetrachloride and an appropriately substituted vinyl silane in an aprotic solvent such as methylene chloride at a temperature of about -50°C to about 50°C to give

20

compounds of Formula 108. If desired, the compounds of Formula 108 may subsequently be hydrolyzed or deprotected as described above to yield the corresponding acid. If desired, reduction of the double bond can be accomplished using conditions described in SCHEME 7.

5

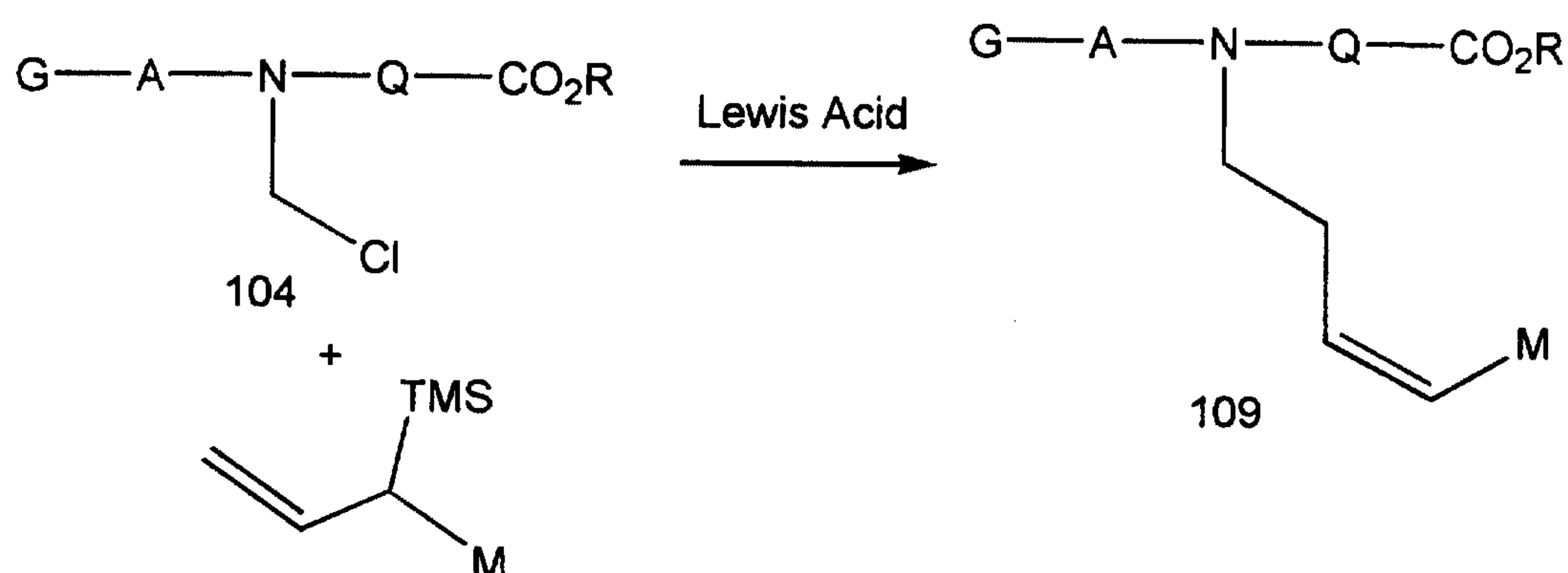
SCHEME 13



Alternatively, certain compounds of Formula I wherein B is N are prepared as described in SCHEME 14. Chloromethyl compounds of Formula 104 are treated with a Lewis acid such as titanium tetrachloride and an appropriately substituted allyl silane in an aprotic solvent such as chloroform at a temperature of about 0°C to about 80°C to give compounds of Formula 109 which may subsequently be hydrolyzed or deprotected as described above to afford the corresponding carboxylic acids.

15

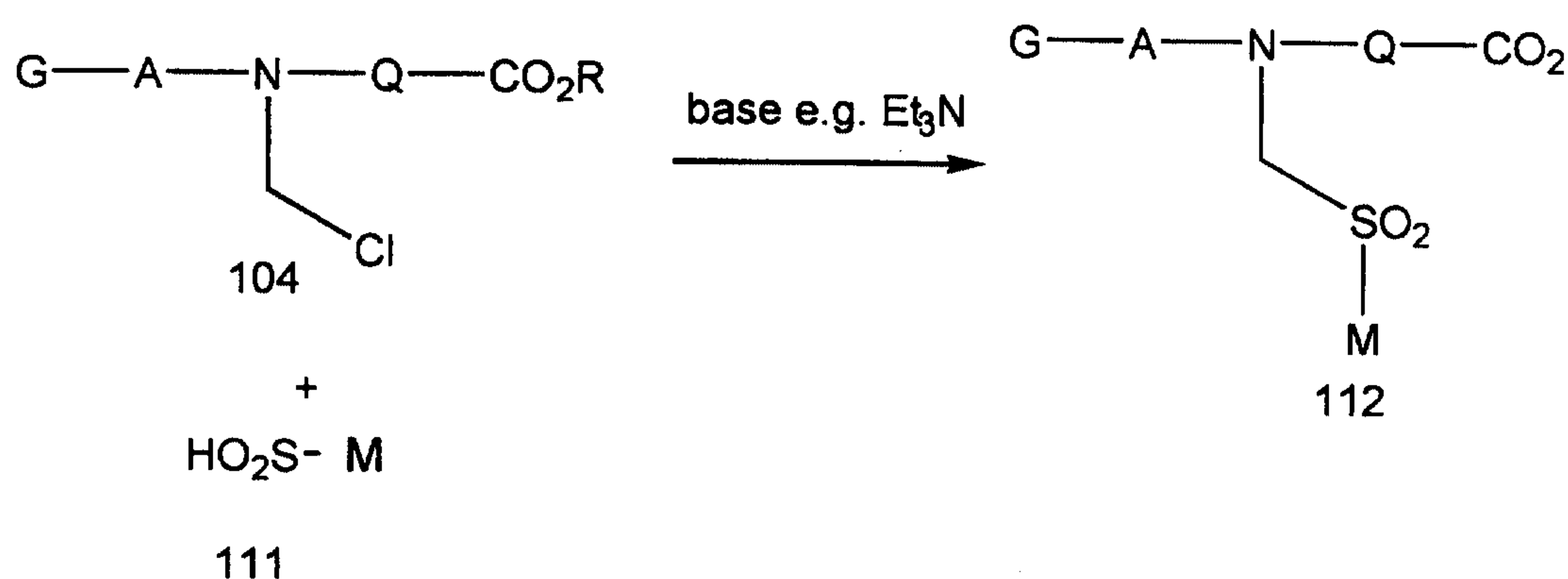
SCHEME 14



Alternatively, certain compounds of Formula I wherein B is N are prepared as described in SCHEME 15. Chloromethyl compounds of Formula 104 are treated with a sulfinic acid of Formula 111 in the presence of a base such as triethylamine in an aprotic solvent such as chloroform at a temperature of about -30°C to about 50°C to give compounds of Formula 112 which may subsequently be hydrolyzed or deprotected as described above to yield the corresponding acid.

10

SCHEME 15

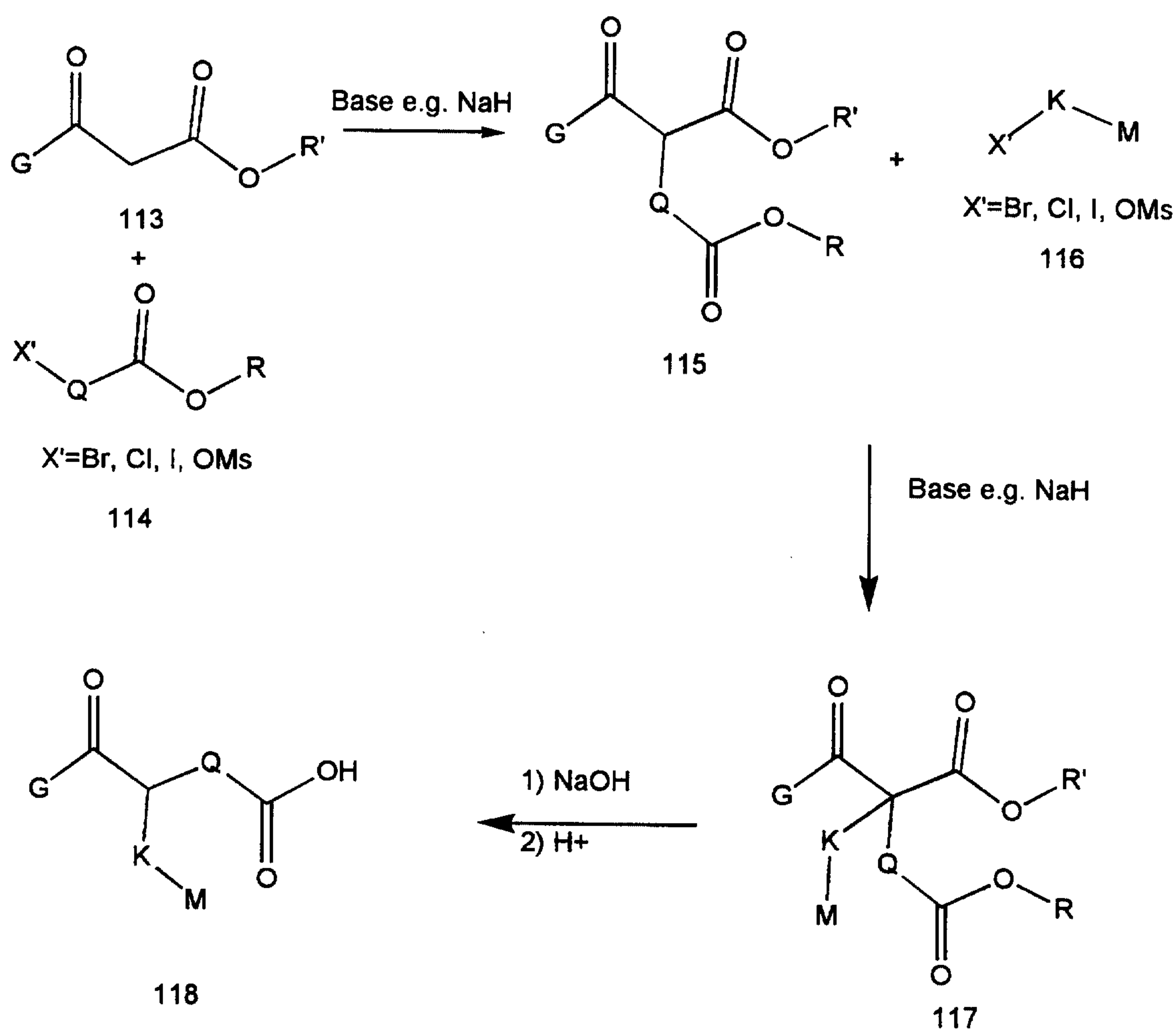


Formula I compounds wherein B is C(H) and Q, G, M and K are as described above in the Summary of the Invention can be prepared of SCHEME 16. Formula 113 beta-ketoesters are alkylated sequentially with Formula 114 compounds to form Formula 115 compounds followed by alkylation with Formula 116 compounds to give Formula 117 compounds (J. Med. Chem. 26, 1993, p335-

15

- 41). Alkylations can be carried out in a suitable solvent such as DMF, THF, ether, or benzene using an appropriate base such as sodium hydride, LDA, or potassium carbonate at a temperature of about -78°C to about 80°C. The resulting Formula 117 disubstituted keto esters are hydrolyzed and decarboxylated to give the corresponding Formula 118 compound by using an aqueous base such as sodium hydroxide to hydrolyze the ester, followed by an acidic quench such as with aqueous hydrochloric acid to effect decarboxylation.

SCHEME 16



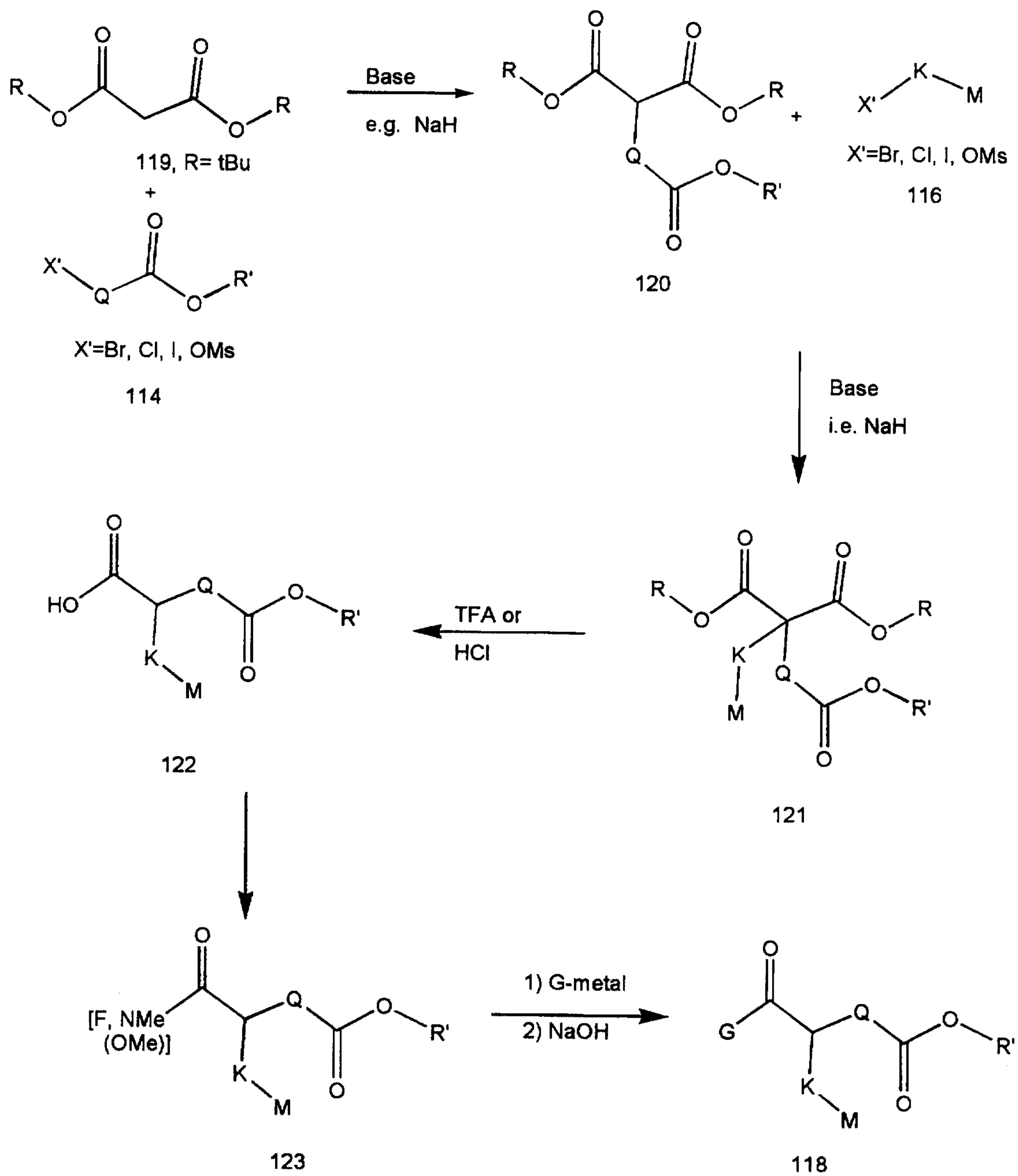
10

Alternatively, Formula I compounds wherein B is C(H) and G, Q, M and K are as described above in the Summary of the Invention may be prepared of SCHEME 17. Sequential alkylation of a malonate derivative of Formula 119

provides the Formula 121 dialkylated compound. Deprotection of the ester group by treatment with a strong acid such as TFA or HCl in ethanol at a temperature of about -20°C to about 50°C leads to the Formula 122 decarboxylated product. Conversion of the acid to an acid chloride using thionyl chloride or oxalyl chloride in an aprotic solvent at a temperature of about -78°C to about 50°C or to a Weinreb amide using methoxymethyl amine in the presence of a suitable coupling agent such as DCC or DEC in an aprotic solvent at a temperature of about -30°C to about 50°C provides Formula 123 compounds. Formula 123 compounds are suitable substrates for addition of various organometallic species, e.g., Grignard reagents and organo-cadmium reagents which, after hydrolysis of the terminal ester, provide the keto-acid compounds of Formula 118.

Alternatively, Formula 118 compounds can be prepared using methods described previously in Schemes 7-11 where one or both of the side chains are further functionalized after attachment to the alkanoyl fragment.

SCHEME 17



PREPARATIONS

Amines, Amides and Sulfonamides

Certain amides or sulfonamides described by Formulas 21, 22, and 23

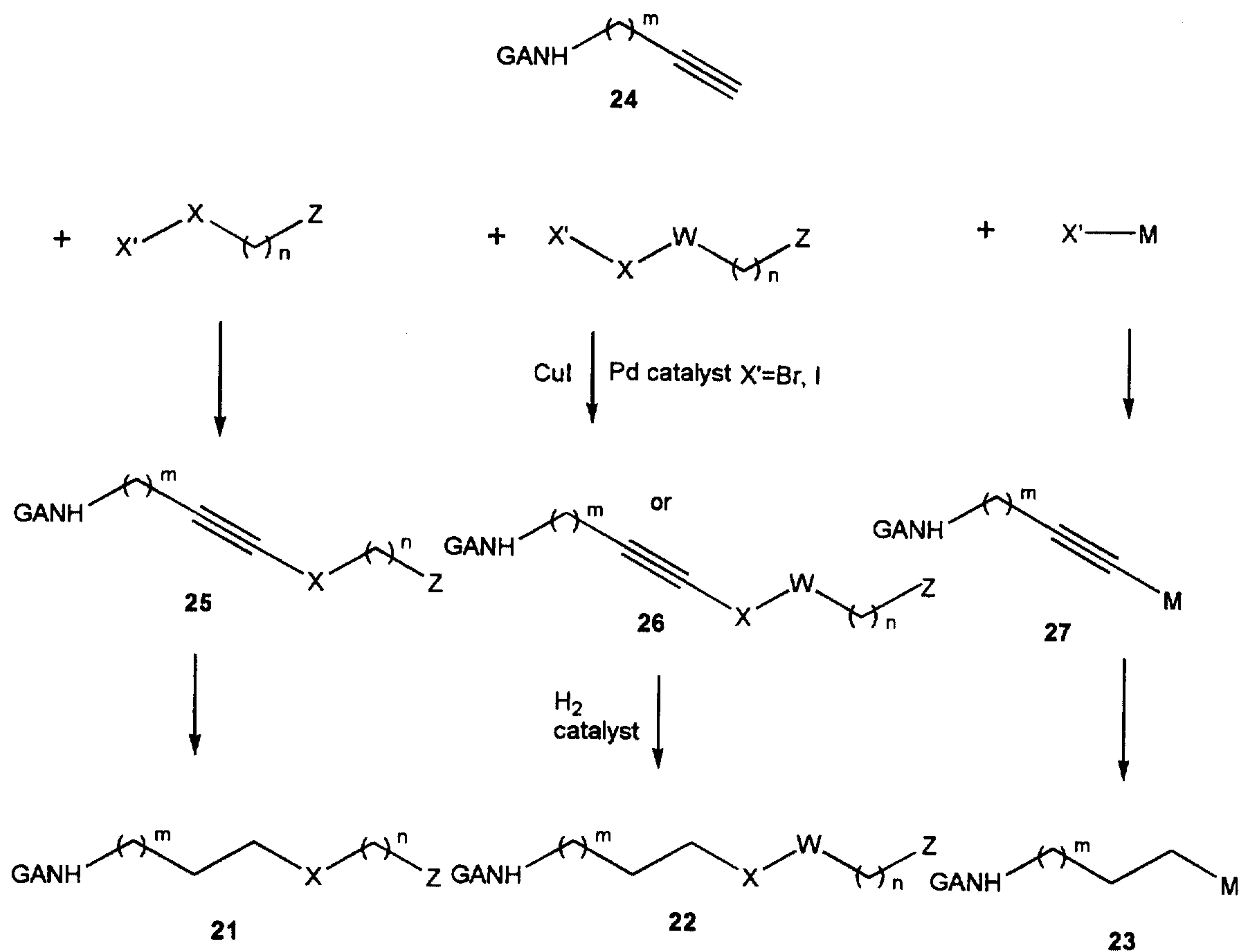
5 wherein W and Z are as described above in the Summary of the Invention and X and M are aromatic or saturated ring systems are prepared as set forth in SCHEME 18. Alkynyl amides or sulfonamides of Formulas 25, 26 and 27 are prepared by coupling an alkynyl sulfonamide or alkynyl amide of Formula 24 to an aromatic or vinyl halide, preferably an aromatic or vinyl bromide or iodide wherein

10 W and Z are as defined above and where X and M represent an aromatic ring or a partially saturated ring system. The coupling is typically accomplished in the presence of copper iodide, a palladium catalyst, such as palladium chloride, bis(triphenylphosphine)palladium dichloride, or tetrakis(triphenylphosphine)palladium(0), and an amine such as triethylamine,

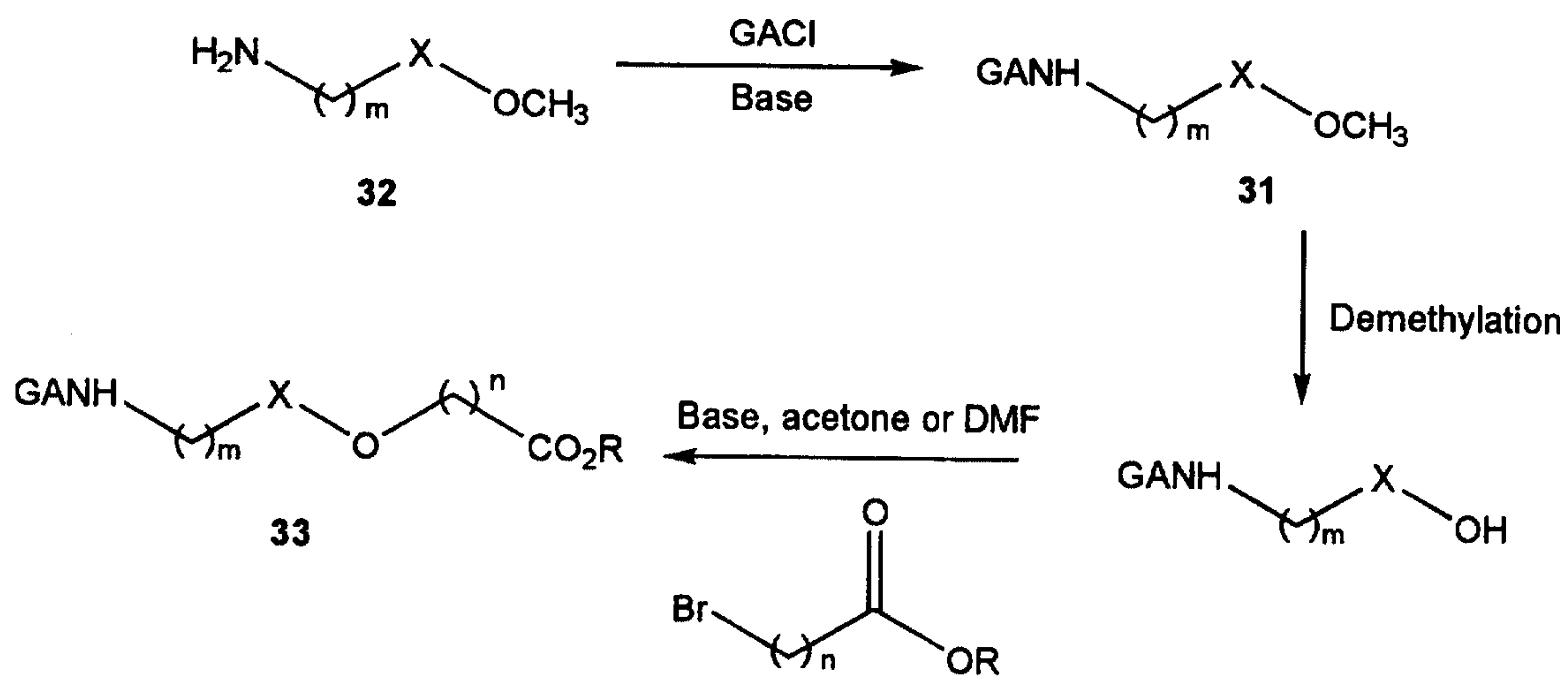
15 diisopropylamine, or butylamine in an aprotic solvent such as acetonitrile at a temperature of about 0°C to about 100°C. The alkynes of Formulas 25, 26 and 27 are converted to the corresponding alkanes of Formulas 21, 22 or 23 via hydrogenation in the presence of a palladium or platinum catalyst in a solvent such as methanol, ethanol, and/or ethyl acetate at a temperature of about 0°C to about

20 50°C. In the case where M represents a partially saturated ring system, hydrogenation will convert M to a fully saturated ring system. Alternatively, the alkynes are converted to cis-alkenes using the Lindlar catalyst (Pd-CaCO₃-PbO) or other suitable catalyst. Alkylation and deprotection as described in SCHEMES 1 and 2 affords the corresponding compounds of Formula I.

SCHEME 18



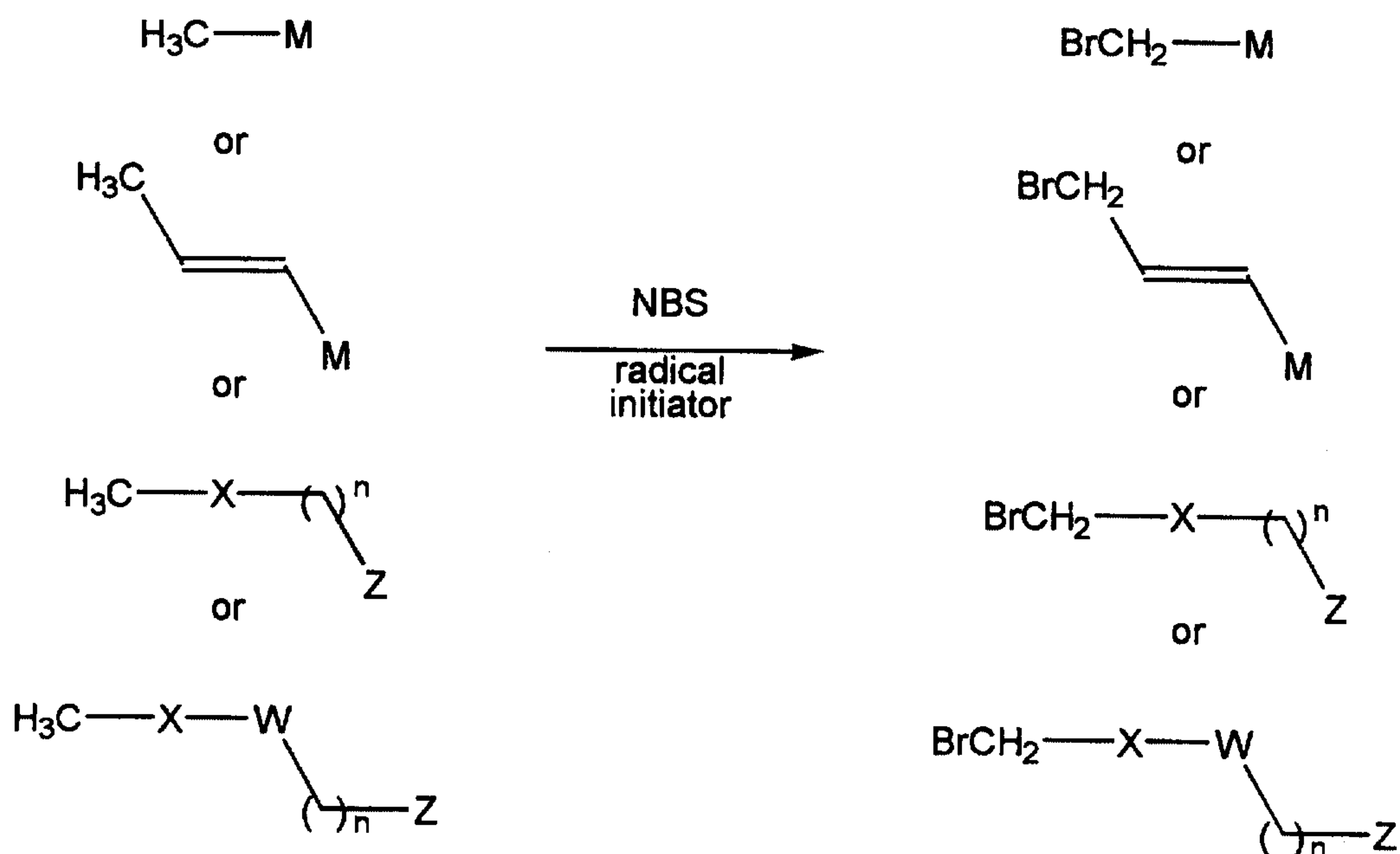
SCHEME 19



Compounds of Formula 33 are prepared from a suitable amine of Formula 32 (e.g., methoxyarylalkylamine). Amines of Formula 32 are commercially available or are prepared by methods well known to those skilled in the art (for example, see SCHEME 4). Amines of Formula 32 are converted to sulfonamides or amides of Formula 31 using methods, for example, described in SCHEME 3 and 4. The resulting aromatic methyl ether of Formula 31 is deprotected with reagents such as boron tribromide, pyridinium hydrochloride, hydrogen bromide/acetic acid, or other reagents as described in Protecting Groups in Organic Synthesis, Second Edition, T.W. Greene and P.G.M. Wuts, John Wiley and Sons, Inc., 1991. Alkylation with a bromoalkylester using a mild base such as potassium carbonate in an aprotic solvent such as dimethylformamide or acetone at a temperature of about 0°C to about 100°C generates an amide or sulfonamide of Formula 33.

15

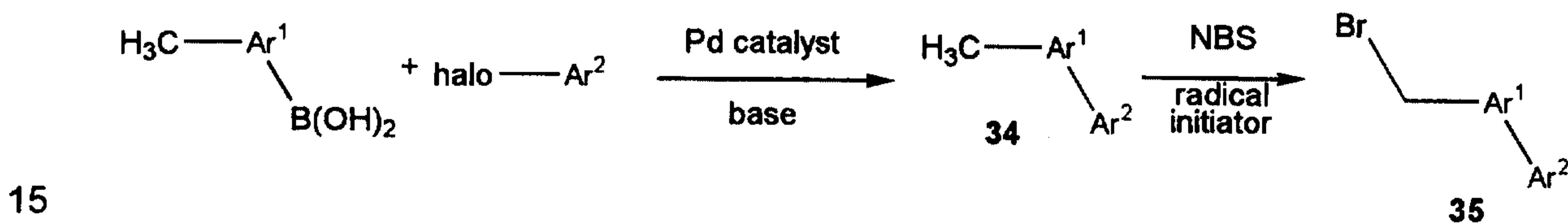
SCHEME 20



ALKYLATING AGENTS

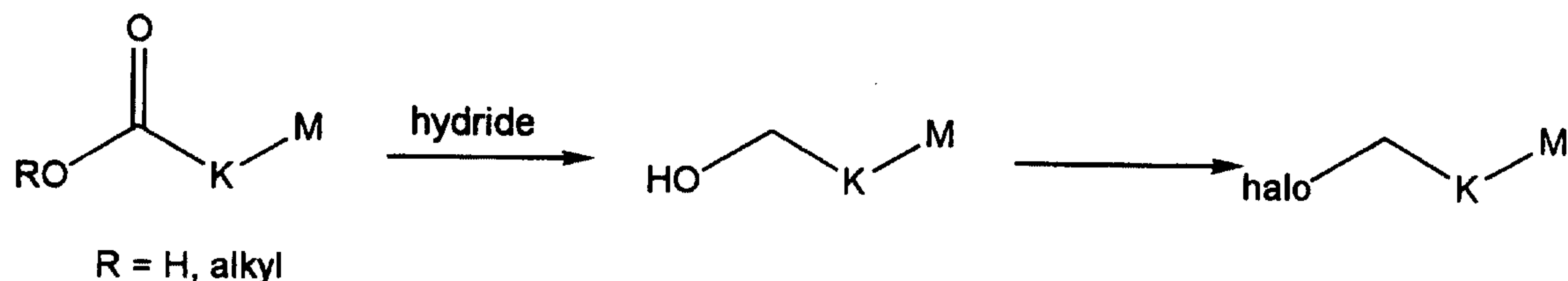
Numerous methods exist for the synthesis of the desired alkylating agents used in the above procedures and are known to those skilled in the art (see "The Chemistry of the Carbon-Halogen Bond," Ed. S. Patai, J. Wiley, New York, 1973 and "The Chemistry of Halides, Pseudo-Halides, and Azides," Eds. S. Patai and Z. Rappaport, J. Wiley, New York, 1983). Some examples are shown in SCHEMES 20-24. As shown in SCHEME 20, tolyl or allylic substrates can be converted via halogenation to benzylic or allylic bromides wherein M, X, W and Z are as described above in the Summary of the Invention. This reaction is typically performed with N-bromosuccinimide (NBS) in the presence of a radical initiator such as 2,2'-azobisisobutyronitrile (AIBN) or a peroxide, preferably benzoyl peroxide. Alternatively, the reaction can be initiated with light. The reaction is performed in an inert solvent such as carbon tetrachloride or chloroform at a temperature of about 50°C to about 100°C.

SCHEME 21



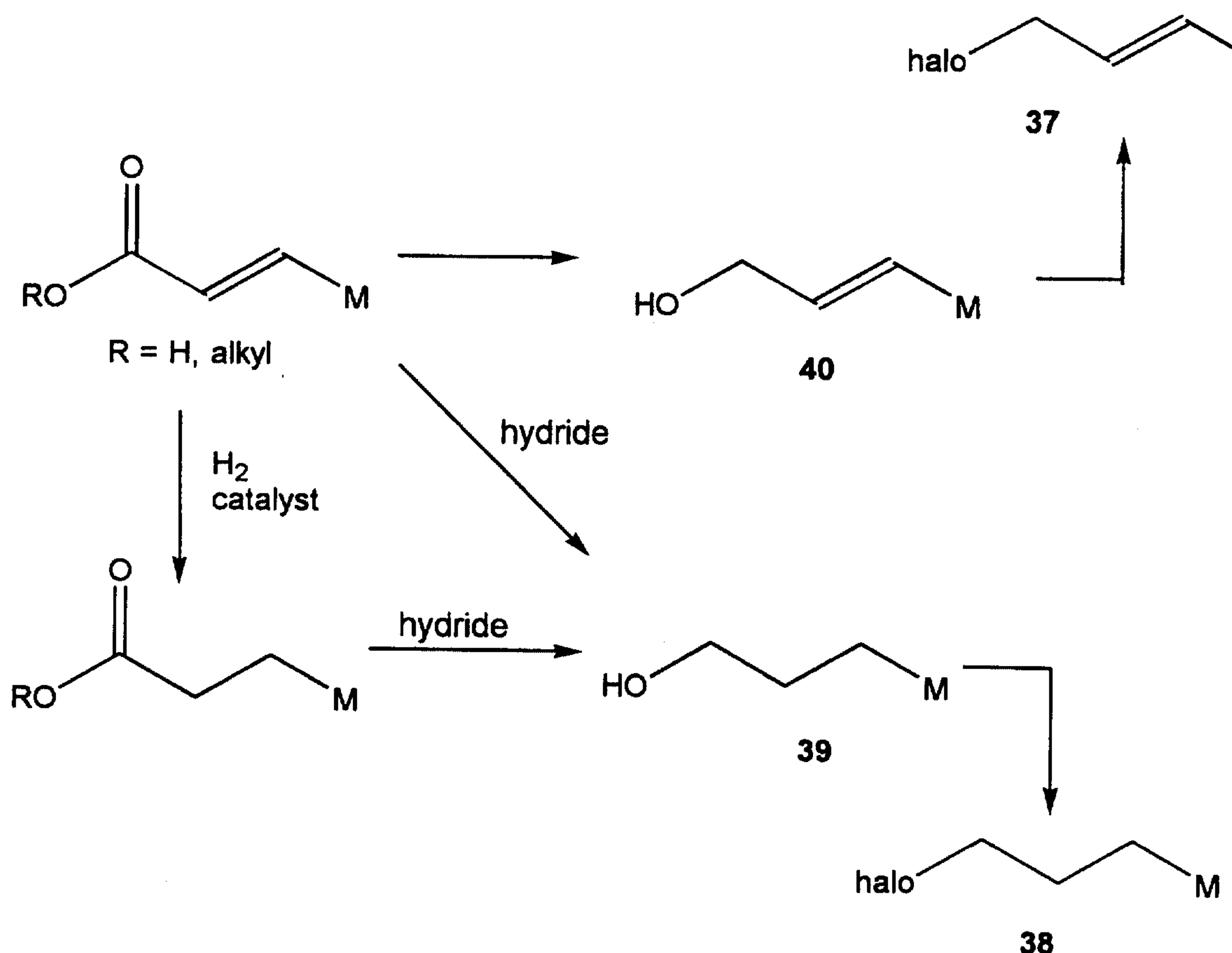
SCHEME 21 sets forth the synthesis of alkylating agents useful for preparing compounds of Formula I where M represents a biaryl or aryl cyclic group. Suzuki-type coupling of an aryl iodide or bromide or a ring system containing a vinyl bromide or iodide (Ar^2) with a methylaryl boronic acid (Ar^1) using the conditions described in SCHEME 9 provides compounds of Formula 34. Where a vinyl bromide or iodide is used, compounds of Formula 34 can be reduced to generate a fully saturated ring. The reduction is accomplished by hydrogenation in the presence of palladium or platinum catalysts typically in protic solvents such as methanol or ethanol; or in tetrahydrofuran or ethyl acetate. Halogenation of the methyl group using reagents and conditions as described in SCHEME 20 provides alkylating agents of Formula 35.

SCHEME 22



Another common method for accessing alkyl halides is by halogenation of an alcohol or an alcohol derivative. Alcohols are obtained from commercial sources or can be prepared using methods well known to those skilled in the art. For example, SCHEME 22 sets forth the reduction of a carboxylic acid or ester to the corresponding alcohol using reagents such as, but not limited to, sodium borohydride, lithium aluminum hydride, borane-tetrahydrofuran complex, borane-methyl sulfide complex, etc. The corresponding alkyl chlorides are typically prepared from the alcohols with reagents such as hydrogen chloride, thionyl chloride, phosphorous pentachloride, phosphorous oxychloride, or triphenylphosphine/carbon tetrachloride. For the preparation of alkyl bromides, the alcohol is commonly treated with reagents such as hydrogen bromide, phosphorous tribromide, triphenylphosphine/bromine, or carbonyldiimidazole/allyl bromide (Kamijo, T., Harada, H., Iizuka, K. Chem. Pharm. Bull. 1983, 38, 4189). To access alkyl iodides, an appropriate alcohol is typically reacted with reagents such as triphenylphosphine/iodine/imidazole or hydrogen iodide. Alternatively, alkyl chlorides can be converted to the more reactive alkyl bromides or alkyl iodides by reaction with an inorganic salt such as sodium bromide, lithium bromide, sodium iodide, or potassium iodide in solvents such as acetone or methyl ethyl ketone. Alkyl sulfonates can also be used as electrophiles or can be converted to alkyl halides. Alkyl sulfonates are prepared from the corresponding alcohol using a mild base such as triethylamine or pyridine and a sulfonyl chloride in an inert solvent such as methylene chloride or diethyl ether. If desired, conversion to the halide is accomplished by treating the alkyl sulfonate with an inorganic halide (sodium iodide, sodium bromide, potassium iodide, potassium bromide, lithium chloride, lithium bromide, etc) or a tetrabutylammonium halide.

SCHEME 23



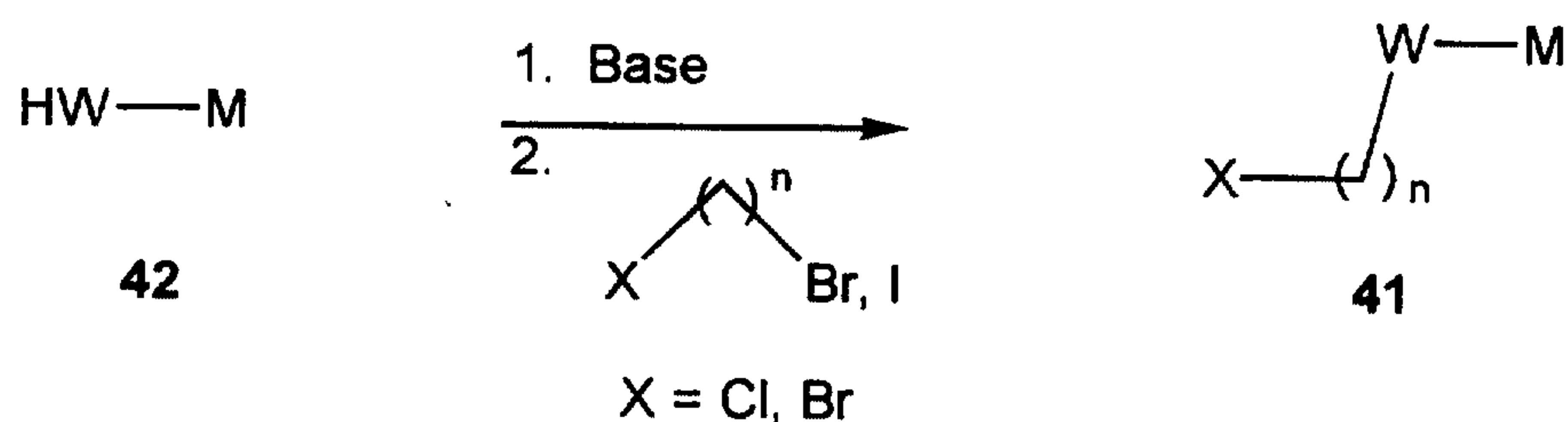
Cinnamic acids or esters are commonly available from commercial sources and can be converted to alkylating agents of Formulas 37 or 38 as follows (see

5 SCHEME 23). The cinnamic acid or ester derivatives are reduced by hydrogenation in the presence of palladium or platinum catalysts typically in protic solvents (e.g., methanol or ethanol), tetrahydrofuran, or ethyl acetate. Reduction and conversion to the alkyl halide or sulfonate as described in SCHEME 22 provides the compounds of Formula 38. Where appropriate, the cinnamic acids or

10 esters are converted directly to the alcohols of Formula 39 by treating those cinnamic acids or esters with reagents such as lithium aluminum hydride in an inert solvent such as tetrahydrofuran and diethyl ether. Alternatively, the cinnamic acid or ester can be reduced to an allylic alcohol of Formula 40 using reagents such as lithium aluminum hydride/aluminum chloride, diisobutylaluminum hydride or lithium

borohydride. Conversion to the allylic halide or sulfonate as described in SCHEME 22 provides the compounds of Formula 37.

SCHEME 24



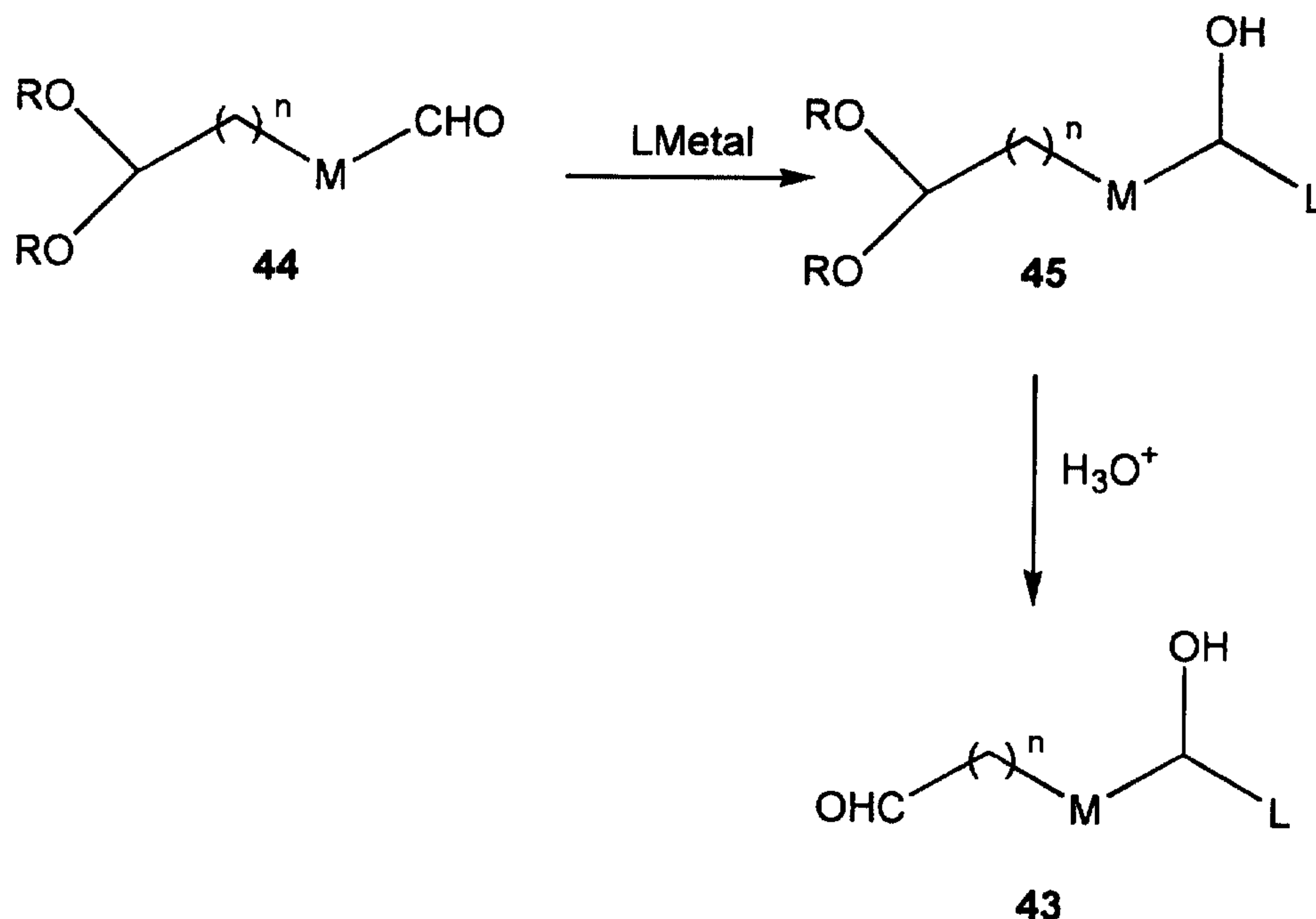
5

The preparation of alkylating agents of Formula 41 wherein W and M are as described above in the Summary of the Invention is set forth in SCHEME 24. Compounds of Formula 42 can be alkylated with a variety of bases. The choice of

10 base is dependent on the nature of W and M. Some preferred bases include, but are not limited to, sodium hydroxide, sodium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide and potassium tert-butoxide. Treatment of the resulting anion with one of a variety of

15 dialkylhalides generates the desired alkylating agents of Formula 41. For the preparation of compounds where W is an oxygen and M is an aromatic ring, it is preferred to form the alkoxide anion with sodium hydroxide followed by addition of a dihaloalkane, e.g. dibromoalkane. The reaction is normally performed in water at about 75°C to about 125°C.

SCHEME 25



Aldehydes useful for the method described in SCHEME 5 are available from commercial sources or can be prepared from available intermediates using methods well known to those skilled in the art (for a general reference see "The Chemistry of the Carbonyl Group," Ed. S. Patai, Interscience, New York (1966-70)). SCHEME 25 demonstrates an exemplary method used to prepare Formula 43 hydroxy aldehydes where M in SCHEME 5 contains a hydroxy substituted alkyl group. Treatment of a dialdehyde, where one of the aldehydes is protected as an acetal of Formula 44 wherein the OR groups are conventional substituents used in an acetal protecting group, with an organometallic reagent (LMetal), preferably an organolithium or Grignard reagent, in an inert solvent such as tetrahydrofuran or diethyl ether, provides compounds of Formula 45. Subsequent acetal hydrolysis under mildly acidic conditions, e.g., dilute hydrogen chloride, Amberlyst-15® resin, silica gel, or other reagents as described in "Protecting Groups in Organic Synthesis," Second Edition, T.W. Greene and P.G.M. Wuts, John Wiley and Sons, Inc., 1991 provides the desired hydroxy aldehydes of Formula 43.

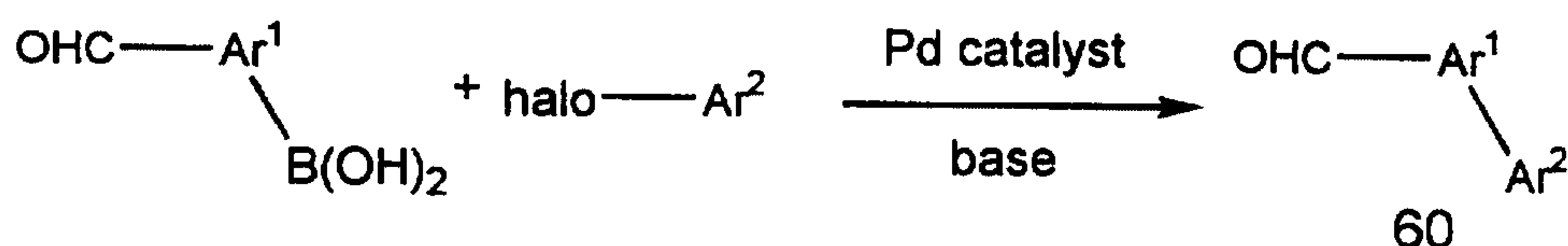
Aldehydes useful for the method described in SCHEME 5 may be prepared using the methods described in SCHEMES 26-28. For example, as shown in SCHEME 26, an aryl boronic acid which contains an aldehyde can be coupled to an aryl bromide, aryl iodide, or a ring system which contains a vinyl bromide or

iodide using the Suzuki protocol described for SCHEME 9 to provide aldehydes of Formula 60.

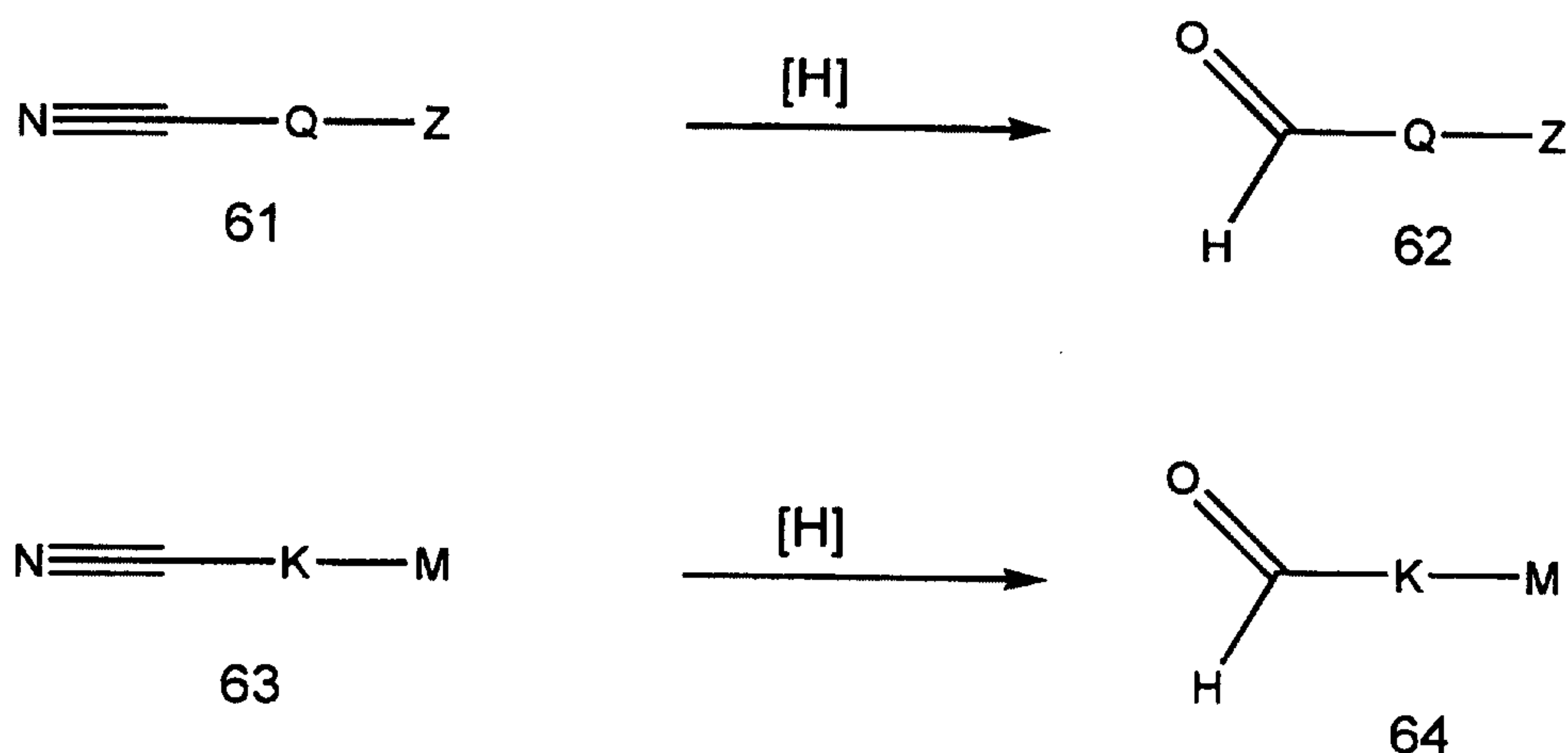
SCHEME 27 describes the preparation of aldehydes of Formula 62 which contain a suitably protected acid moiety and can be used for the preparation of compounds of Formula 42A described in SCHEME 5. Selective reduction of nitriles (see SCHEMES 3-4 for preparations) of Formula 61 provides aldehydes of Formula 62. A preferred method for this reduction involves heating the nitrile with aluminum-nickel (Raney) alloy in the presence of an acid such as formic acid. Aldehydes of Formula 64 useful for the preparation of compounds of Formula 42 (SCHEME 5) may be prepared from starting nitriles of Formula 63 by treatment with a variety of reducing agents such as diisobutylaluminum hydride, tin (II) chloride/hydrogen chloride, or lithium triethoxyalanate.

A method for the preparation of proprionaldehydes of Formula 65 is described in SCHEME 28 and follows the procedures described by Kang (J. Org. Chem. 1996, 61, 2604) and by Jeffery (J. Chem. Soc. Chem. Commun. 1984, 19, 1287). An aryl iodide or bromide is coupled to allyl alcohol in the presence of a suitable palladium catalyst, preferably palladium acetate. The reaction is performed in a suitable polar, aprotic solvent, preferably dimethylformamide, with addition of a base, such as sodium bicarbonate, and an ammonium salt, such as tetrabutylammonium chloride and provides proprionaldehydes of Formula 65.

SCHEME 26

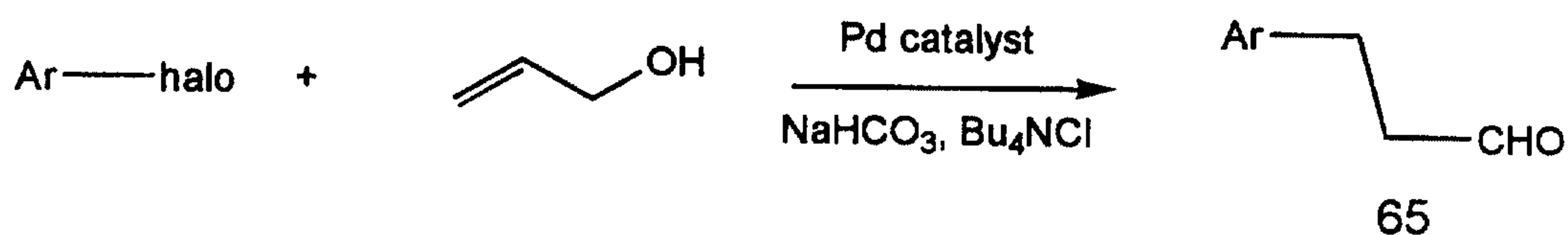


SCHEME 27



5

SCHEME 28



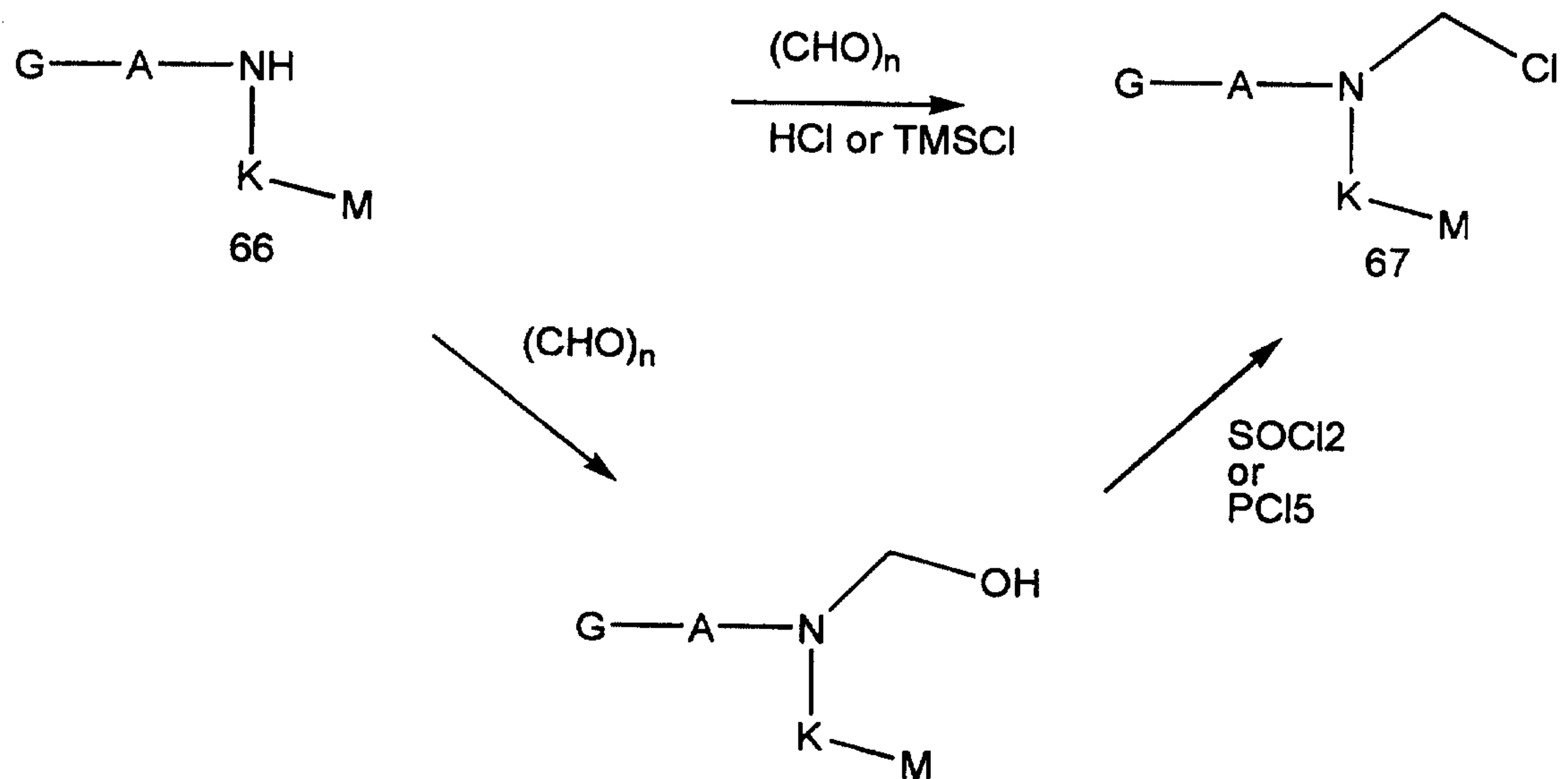
10

CHLOROMETHYL INTERMEDIATES

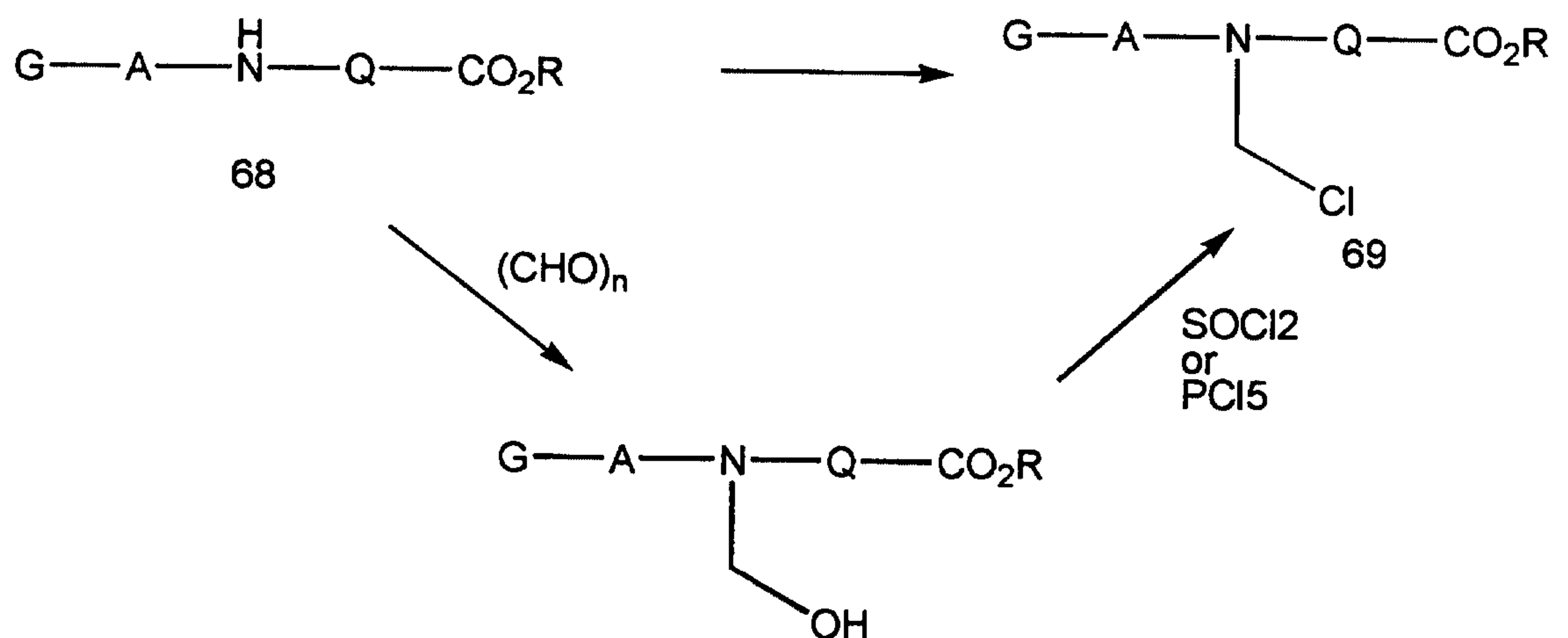
Intermediate chloromethyl compounds can be prepared as described in SCHEMES 29 and 30. In general, the appropriate Formula 66 or 68 sulfonamide or carboxamide is treated with a formaldehyde equivalent such as paraformaldehyde in an inert organic solvent such as methylene chloride or chloroform with a suitable catalyst such as HCl, zinc chloride or trimethylsilyl chloride at temperatures ranging from about 0°C to about 60°C to give the Formula 67 and 69 chloromethyl derivatives, respectively.

15

SCHEME 29



SCHEME 30

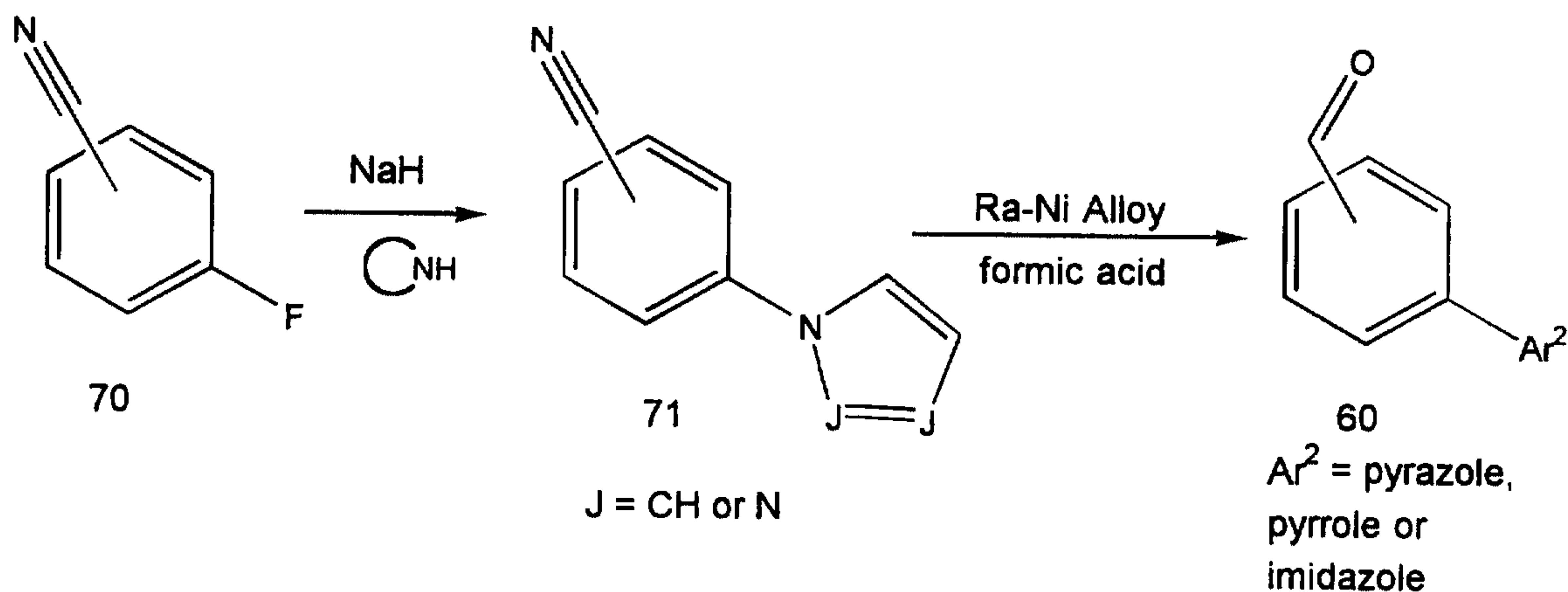


5

SCHEME 31 sets forth the synthesis of biaryl aldehydes of Formula 60. Fluorobenzonitriles of Formula 70 are heated with a nucleophilic group such as a pyrrazole or imidazole in a suitable solvent, preferably DMF to effect displacement of the fluoro group yielding intermediates of Formula 71. The desired biaryl aldehydes of Formula 60 are obtained by reduction of the nitrile via hydrogenation

10

with Raney alloy in formic acid, or by reduction with a hydride source such as diisobutylaluminum hydride.



5

It will be recognized that the compounds of Formula I of this invention can exist in radiolabelled form, i.e., said compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number ordinarily found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine and chlorine include ³H, ¹⁴C, ³²P, ³⁵S, ¹⁸F and ³⁶Cl, respectively. Compounds of Formula I of this invention which contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, radioisotopes are particularly preferred for their ease of preparation and detectability. Radiolabelled compounds of Formula I of this invention can generally be prepared of methods well known to those skilled in the art. Conveniently, such radiolabelled compounds can be prepared by carrying out the procedures disclosed in the above Schemes and/or in the Examples and Preparations below by substituting a readily available radiolabelled reagent for a non-radiolabelled reagent.

20

Those skilled in the art will recognize that anti-resorptive agents (for example progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen, estrogen/progestin combinations, Premarin®, estrone, estriol or 17α- or 17β-ethynyl estradiol) may be used in conjunction with the compounds of this invention.

25

Exemplary progestins are available from commercial sources and include: algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate,

72222-402

-75-

chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynestone, ethynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogestosterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestone, and tigestol.

10 Preferred progestins are medroxyprogesterone, norethindrone and norethynodrel.

Exemplary bone resorption inhibiting polyphosphonates include polyphosphonates of the type disclosed in U.S. Patent 3,683,080. Preferred polyphosphonates are geminal diphosphonates (also referred to as bis-phosphonates). Tiludronate disodium is an especially preferred polyphosphonate. Ibandronic acid is an especially preferred polyphosphonate. Alendronate is an especially preferred polyphosphonate. Zoledronic acid is an especially preferred polyphosphonate. Other preferred polyphosphonates are 6-amino-1-hydroxy-hexylidene-bisphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt. Hydrolyzable esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1,1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1,1-diphosphonic acid, ethane-2-amino-1,1-diphosphonic acid, propane-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-N,N-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-3,3-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid, N,N-dimethylamino methane diphosphonic acid, N(2-hydroxyethyl) amino methane diphosphonic acid, butane-4-amino-1-hydroxy-1,1-diphosphonic acid, pentane-5-amino-1-hydroxy-1,1-diphosphonic acid, hexane-6-

amino-1-hydroxy-1,1-diphosphonic acid and pharmaceutically acceptable esters and salts thereof.

In particular, the compounds of this invention may be combined with a mammalian estrogen agonist/antagonist. Any estrogen agonist/antagonist may be used as the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit bone turnover and/or prevent bone loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art of standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods, and Eriksen E.F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S.J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H.W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described and referenced below.

A preferred estrogen agonist/antagonist is droloxifene: (phenol, 3-(1-(4-(2-(dimethylamino)ethoxy)phenyl)-2-phenyl-1-butenyl)-, (E)-) and related compounds which are disclosed in U.S. patent 5,047,431.

Another preferred estrogen agonist/antagonist is 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid, which is disclosed in Willson et al., Endocrinology, 1997, 138, 3901-3911.

Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine, 2-(-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)) and related compounds which are disclosed in U.S. patent 4,536,516.

Another related compound is 4-hydroxy tamoxifen which is disclosed in U.S. patent 4,623,660.

72222-402

-77-

A preferred estrogen agonist/antagonist is raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)ethoxy)phenyl)-hydrochloride) which is disclosed in U.S. patent 4,418,068.

5 Another preferred estrogen agonist/antagonist is toremifene: (ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. patent 4,996,225.

10 Another preferred estrogen agonist/antagonist is centchroman: 1-(2-((4-(methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-pyrrolidine, which is disclosed in U.S. patent 3,822,287. Also preferred is levormeloxifene.

15 Another preferred estrogen agonist/antagonist is idoxifene: (E)-1-(2-(4-(1-(4-iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrrolidinone, which is disclosed in U.S. patent 4,839,155.

20 Another preferred estrogen agonist/antagonist is 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]- benzo[b]thiophen-6-ol which is disclosed in U.S. Patent No. 5,488,058.

Another preferred estrogen agonist/antagonist is 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol which is disclosed in U.S. patent 5,484,795.

25 Another preferred estrogen agonist/antagonist is (4-(2-(2-azabicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT publication no. WO 95/10513 assigned to Pfizer Inc.

30 Other preferred estrogen agonist/antagonists include compounds as described in commonly assigned U.S. patent 5,552,412. Especially preferred compounds described therein are:

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

72222-402

-78-

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

5 *cis*-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

10 *cis*-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; and

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

Other estrogen agonist/antagonists are described in U.S. patent 4,133,814. U.S. patent 4,133,814 discloses derivatives of 2-phenyl-3-aryl-benzothiophene and
15 2-phenyl-3-arylbenzothiophene-1-oxide.

Those skilled in the art will recognize that other bone anabolic agents, also referred to as bone mass augmenting agents, may be used in conjunction with the compounds of this invention. A bone mass augmenting agent is a compound that
20 augments bone mass to a level which is above the bone fracture threshold as detailed in the World Health Organization Study World Health Organization, "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis (1994). Report of a WHO Study Group. World Health Organization Technical Series 843."

25 Any prostaglandin, or prostaglandin agonist/antagonist may be used as the second compound in certain aspects of this invention. This includes utilizing two different compounds of Formula I of this invention. Those skilled in the art will recognize that IGF-1, sodium fluoride, parathyroid hormone (PTH), active fragments of parathyroid hormone, growth hormone or growth hormone
30 secretagogues may also be used. The following paragraphs describe exemplary second compounds of this invention in greater detail.

Any prostaglandin may be used as the second compound in certain aspects of this invention. The term prostaglandin refers to compounds which are

analogues of the natural prostaglandins PGD₁, PGD₂, PGE₂, PGE₁ and PGF₂ which are useful in the treatment of osteoporosis. These compounds bind to the prostaglandin receptors. Such binding is readily determined by those skilled in the art of standard assays (e.g., An S. et al., Cloning and Expression of the EP₂ Subtype of Human Receptors for Prostaglandin E₂, Biochemical and Biophysical Research Communications, 1993, 197(1):263-270).

Prostaglandins are alicyclic compounds related to the basic compound prostanoic acid. The carbon atoms of the basic prostaglandin are numbered sequentially from the carboxylic carbon atom through the cyclopentyl ring to the terminal carbon atom on the adjacent side chain. Normally the adjacent side chains are in the trans orientation. The presence of an oxo group at C-9 of the cyclopentyl moiety is indicative of a prostaglandin within the E class while PGE₂ contains a trans unsaturated double bond at the C₁₃-C₁₄ and a cis double bond at the C₅-C₆ position.

A variety of prostaglandins are described and referenced below. However, other prostaglandins will be known to those skilled in the art. Exemplary prostaglandins are disclosed in U.S. patents 4,171,331 and 3,927,197.

Norrdin et al., The Role of Prostaglandins in Bone In Vivo, Prostaglandins Leukotriene Essential Fatty Acids 41, 139-150, 1990 is a review of bone anabolic prostaglandins.

Any prostaglandin agonist/antagonist may be used as the second compound in certain aspects of this invention. The term prostaglandin agonist/antagonist refers to compounds which bind to prostaglandin receptors (e.g., An S. et al., Cloning and Expression of the EP₂ Subtype of Human Receptors for Prostaglandin E₂, Biochemical and Biophysical Research Communications, 1993, 197(1):263-270) and mimic the action of prostaglandin *in vivo* (e.g., stimulate bone formation and increase bone mass). Such actions are readily determined by those skilled in the art of standard assays. Eriksen E.F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S.J. et al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, *Inv. Radiol.*, 1996, 31(1):50-62; Wahner H.W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin

72222-402

-80-

Dunitz Ltd., London 1994, pages 1-296. A variety of these compounds are described and referenced below. However, other prostaglandin agonists/antagonists will be known to those skilled in the art. Exemplary prostaglandin agonists/antagonists are disclosed as follows.

- 5 Commonly assigned U.S. patent 3,932,389 discloses 2-descarboxy-2-(tetrazol-5-yl)-11-desoxy-15-substituted-omega-pentanorprostaglandins useful for bone formation activity.

 Commonly assigned U.S. patent 4,018,892 discloses 16-aryl-13,14-dihydro-PGE₂ p-biphenyl esters useful for bone formation activity.

- 10 Commonly assigned U.S. patent 4,219,483 discloses 2,3,6-substituted-4-pyrones useful for bone formation activity.

 Commonly assigned U.S. patent 4,132,847 discloses 2,3,6-substituted-4-pyrones useful for bone formation activity.

- U.S. patent 4,000,309 discloses 16-aryl-13,14-dihydro-PGE₂ p-biphenyl esters
15 useful for bone formation activity.

 U.S. patent 3,982,016 discloses 16-aryl-13,14-dihydro-PGE₂ p-biphenyl esters useful for bone formation activity.

 U.S. patent 4,621,100 discloses substituted cyclopentanes useful for bone formation activity.

- 20 U.S. patent 5,216,183 discloses cyclopentanones useful for bone formation activity.

- Sodium fluoride may be used as the second compound in certain aspects of this invention. The term sodium fluoride refers to sodium fluoride in all its forms (e.g., slow release sodium fluoride, sustained release sodium fluoride). Sustained
25 release sodium fluoride is disclosed in U.S. patent 4,904,478.

 The activity of sodium fluoride is readily determined by those skilled in the art of biological protocols (e.g., see Eriksen E.F.

et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S.J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H.W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296).

Bone morphogenetic protein may be used as the second compound of this invention (e.g., see Ono, et al., Promotion of the Osteogenetic Activity of Recombinant Human Bone Morphogenetic Protein by Prostaglandin E1, Bone, 1996, 19(6), 581-588).

Any parathyroid hormone (PTH) may be used as the second compound in certain aspects of this invention. The term parathyroid hormone refers to parathyroid hormone, fragments or metabolites thereof and structural analogs thereof which can stimulate bone formation and increase bone mass. Also included are parathyroid hormone related peptides and active fragments and analogs of parathyroid related peptides (see PCT publication no. WO 94/01460). Such bone anabolic functional activity is readily determined by those skilled in the art of standard assays (e.g., see Eriksen E.F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S.J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H.W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described and referenced below. However, other parathyroid hormones will be known to those skilled in the art. Exemplary parathyroid hormones are disclosed in the following references.

"Human Parathyroid Peptide Treatment of Vertebral Osteoporosis", Osteoporosis Int., 3, (Supp 1):199-203.

"PTH 1-34 Treatment of Osteoporosis with Added Hormone Replacement Therapy: Biochemical, Kinetic and Histological Responses" Osteoporosis Int. 1:162-170.

Any growth hormone or growth hormone secretagogue may be used as the second compound in certain aspects of this invention. The term growth hormone secretagogue refers to a compound which stimulates the release of growth hormone or mimics the action of growth hormone (e.g., increases bone formation

leading to increased bone mass). Such actions are readily determined by those skilled in the art of standard assays well known to those of skill in the art. A variety of these compounds are disclosed in the following published PCT patent applications: WO 95/14666; WO 95/13069; WO 94/19367; WO 94/13696; and
5 WO 95/34311. However, other growth hormones or growth hormone secretagogues will be known to those skilled in the art.

In particular a preferred growth hormone secretagogue is N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:MK-677.

10 Other preferred growth hormone secretagogues include

2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide or its L-tartaric acid salt;

2-amino-N-(1-(R)-benzyloxymethyl-2-(3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl)isobutyramide;

2-amino-N-(2-(3a-(R)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)benzyloxymethyl-2-oxo-ethyl)isobutyramide; and

2-amino-N-(1-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide.

Some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in Formula I precursors). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily
25 determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

30 The starting materials and reagents for the above described compounds are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, many of the compounds used herein are related to, or are derived from, compounds found in

nature, in which there is a large scientific interest and commercial need, and accordingly many such compounds are commercially available or are reported in the literature or are easily prepared from other commonly available substances by methods which are reported in the literature. Such compounds include, for
5 example, prostaglandins.

It will be recognized by persons of ordinary skill in the art that some of the compounds of this invention have at least one asymmetric carbon atom and therefore are enantiomers or diastereomers. Diastomeric mixtures can be separated into their individual diastereomers on the basis of their physicochemical
10 differences by methods known *per se* as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing, including both chemical hydrolysis methods and
15 microbial lipase hydrolysis methods, e.g., enzyme catalyzed hydrolysis) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomers, enantiomers and mixtures thereof are considered as part of this invention. Also, some of the compounds of this invention are atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

20 Many of the compounds of this invention, including the compounds of Formula I, the anti-resorptive agents, bone anabolic agents, prostaglandin agonists/antagonists, parathyroid hormones, growth hormones and growth hormone secretagogues, are acidic and they form a salt with a pharmaceutically acceptable cation. Some of the compounds of this invention, including the
25 compounds of Formula I, the anti-resorptive agents, bone anabolic agents, prostaglandin agonists/antagonists, parathyroid hormones, growth hormones and growth hormone secretagogues, are basic and they form a salt with a pharmaceutically acceptable anion. All such salts are within the scope of this invention and they can be prepared by conventional methods. For example, they
30 can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by

precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

In addition, when the compounds of this invention, including the compounds of Formula I, the anti-resorptive agents, bone anabolic agents, 5 prostaglandin agonists/antagonists, parathyroid hormones, growth hormones and growth hormone secretagogues, form hydrates or solvates they are also within the scope of the invention.

In addition, all prodrugs of the compounds of this invention, including the compounds of Formula I, the anti-resorptive agents, bone anabolic agents, 10 prostaglandin agonists/antagonists, parathyroid hormones, growth hormones and growth hormone secretagogues, are within the scope of this invention.

The compounds of this invention, prodrugs thereof and pharmaceutically acceptable salts of said compounds and prodrugs are all adapted to therapeutic use as agents that stimulate bone formation and increase bone mass in a 15 vertebrates, e.g., mammals, and particularly humans. Since bone formation is closely related to the development of osteoporosis and bone related disorders, these compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, by virtue of their action on bone, prevent, arrest and/or regress osteoporosis.

20 The utility of the compounds of the present invention as medical agents in the treatment of conditions which present with low bone mass (e.g., osteoporosis) in a vertebrates, e.g., mammals (e.g. humans, particularly the female) is demonstrated by the activity of the compounds of this invention in conventional assays, including an *in vivo* assay, a receptor binding assay, a cyclic AMP assay 25 and a fracture healing assay (all of which are described below). The *in vivo* assay (with appropriate modifications within the skill in the art) may be used to determine the activity of other anabolic agents as well as the prostaglandin agonists of this invention. The estrogen agonist/antagonist protocol may be used to determine the activity of estrogen agonists/antagonists in particular and also other anti-resorptive 30 agents (with appropriate modifications within the skill in the art). The combination and sequential treatment protocol described below is useful for demonstrating the utility of the combinations of the anabolic agents (e.g., the compounds of this invention) and anti-resorptive agents (e.g., estrogen agonists/antagonists)

described herein. Such assays also provide a means whereby the activities of the compounds of this invention (or the other anabolic agents and anti-resorptive agents described herein) can be compared to each other and with the activities of other known compounds. The results of these comparisons are useful for
5 determining dosage levels in a vertebrates, e.g., mammals, including humans, for the treatment of such diseases.

Anabolic Agent In Vivo Assay

The activity of anabolic bone agents in stimulating bone formation and increasing bone mass can be tested in intact male or female rats, sex hormone
10 deficient male (orchidectomy) or female (ovariectomy) rats.

Male or female rats at different ages (such as 3 months of age) can be used in the study. The rats are either intact or castrated (ovariectomized or orchidectomized), and subcutaneously injected or gavaged with prostaglandin agonists at different doses (such as 1, 3, or 10 mg/kg/day) for 30 days. In the
15 castrated rats, treatment is started at the next day after surgery (for the purpose of preventing bone loss) or at the time bone loss has already occurred (for the purpose of restoring bone mass). During the study, all rats are allowed free access to water and a pelleted commercial diet (Teklad Rodent Diet #8064, Harlan Teklad, Madison, WI) containing 1.46% calcium, 0.99% phosphorus and 4.96 IU/g
20 of Vitamin D₃. All rats are given subcutaneous injections of 10 mg/kg calcein on days 12 and 2 before sacrifice. The rats are sacrificed. The following endpoints are determined:

Femoral Bone Mineral Measurements:

The right femur from each rat is removed at autopsy and scanned using
25 dual energy X-ray absorptiometry (DXA, QDR 1000/W, Hologic Inc., Waltham, MA) equipped with "Regional High Resolution Scan" software (Hologic Inc., Waltham, MA). The scan field size is 5.08 x 1.902 cm, resolution is 0.0254 x 0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and bone area, bone mineral content (BMC), and bone mineral density (BMD) of whole
30 femora (WF), distal femoral metaphyses (DFM), femoral shaft (FS), and proximal femora (PF) are determined.

Tibial Bone Histomorphometric Analyses:

The right tibia is removed at autopsy, dissected free of muscle, and cut into three parts. The proximal tibia and the tibial shaft are fixed in 70% ethanol, dehydrated in graded concentrations of ethanol, defatted in acetone, then embedded in methyl methacrylate (Eastman Organic Chemicals, Rochester, NY).

5 Frontal sections of proximal tibial metaphyses at 4 and 10 μm thickness are cut using a Reichert-Jung Polycut S microtome. The 4 μm sections are stained with modified Masson's Trichrome stain while the 10 μm sections remained unstained. One 4 μm and one 10 μm sections from each rat are used for cancellous bone histomorphometry.

10 Cross sections of tibial shaft at 10 μm thickness are cut using a Reichert-Jung Polycut S microtome. These sections are used for cortical bone histomorphometric analysis.

Cancellous bone histomorphometry: A Bioquant OS/2 histomorphometry system (R&M Biometrics, Inc., Nashville, TN) is used for the static and dynamic
15 histomorphometric measurements of the secondary spongiosa of the proximal tibial metaphyses between 1.2 and 3.6 mm distal to the growth plate-epiphyseal junction. The first 1.2 mm of the tibial metaphyseal region needs to be omitted in order to restrict measurements to the secondary spongiosa. The 4 μm sections are used to determine indices related to bone volume, bone structure, and bone
20 resorption, while the 10 μm sections are used to determine indices related to bone formation and bone turnover.

I) Measurements and calculations related to trabecular bone volume and structure: (1) Total metaphyseal area (TV, mm^2): metaphyseal area between 1.2 and 3.6 mm distal to the growth plate-epiphyseal junction. (2) Trabecular bone
25 area (BV, mm^2): total area of trabeculae within TV. (3) Trabecular bone perimeter (BS, mm): the length of total perimeter of trabeculae. (4) Trabecular bone volume (BV/TV, %): $\text{BV} / \text{TV} \times 100$. (5) Trabecular bone number (TBN, $\#/\text{mm}$): $1.199 / 2 \times \text{BS} / \text{TV}$. (6) Trabecular bone thickness (TBT, μm): $(2000 / 1.199) \times (\text{BV} / \text{BS})$. (7) Trabecular bone separation (TBS, μm): $(2000 \times 1.199) \times (\text{TV} - \text{BV})$.

30 II) Measurements and calculations related to bone resorption: (1) Osteoclast number (OCN, $\#$): total number of osteoclast within total metaphyseal area. (2) Osteoclast perimeter (OCP, mm): length of trabecular perimeter covered

by osteoclast. (3) Osteoclast number/mm (OCN/mm, #/mm): OCN / BS . (4) Percent osteoclast perimeter (%OCP, %): $OCP / BS \times 100$.

III) Measurements and calculations related to bone formation and turnover:

- (1) Single-calcein labeled perimeter (SLS, mm): total length of trabecular perimeter labeled with one calcein label. (2) Double-calcein labeled perimeter (DLS, mm): total length of trabecular perimeter labeled with two calcein labels. (3) Inter-labeled width (ILW, μm): average distance between two calcein labels. (4) Percent mineralizing perimeter (PMS, %): $(SLS/2 + DLS) / BS \times 100$. (5) Mineral apposition rate (MAR, $\mu m/day$): $ILW / \text{label interval}$. (6) Bone formation rate/surface ref. (BFR/BS, $\mu m^2/d/\mu m$): $(SLS/2 + DLS) \times MAR / BS$. (7) Bone turnover rate (BTR, %/y): $(SLS/2 + DLS) \times MAR / BV \times 100$.

Cortical bone histomorphometry: A Bioquant OS/2 histomorphometry system (R&M Biometrics, Inc., Nashville, TN) is used for the static and dynamic histomorphometric measurements of tibial shaft cortical bone. Total tissue area, marrow cavity area, periosteal perimeter, endocortical perimeter, single labeled perimeter, double labeled perimeter, and interlabeled width on both periosteal and endocortical surface are measured, and cortical bone area (total tissue area - marrow cavity area), percent cortical bone area (cortical area / total tissue area $\times 100$), percent marrow area (marrow cavity area / total tissue area $\times 100$), periosteal and endocortical percent labeled perimeter [(single labeled perimeter/2+double labeled perimeter) / total perimeter $\times 100$], mineral apposition rate (interlabeled width/intervals), and bone formation rate [mineral apposition rate $\times$ [(single labeled perimeter/2+double labeled perimeter) / total perimeter] are calculated.

Statistics

Statistics can be calculated using StatView 4.0 packages (Abacus Concepts, Inc., Berkeley, CA). The analysis of variance (ANOVA) test followed by Fisher's PLSD (Stat View, Abacus Concepts Inc., 1918 Bonita Ave, Berkeley, CA 94704-1014) are used to compare the differences between groups.

Determination of cAMP Elevation in 293-S Cell Lines Stably Overexpressing

Recombinant Human EP₂ and EP₄ Receptors.

cDNAs representing the complete open reading frames of the human EP₂ and EP₄ receptors are generated by reverse transcriptase polymerase chain reaction using oligonucleotide primers based on published sequences (1, 2) and

RNA from primary human kidney cells (EP₂) or primary human lung cells (EP₄) as templates. cDNAs are cloned into the multiple cloning site of pcDNA3 (Invitrogen Corporation, 3985B Sorrento Valley Blvd., San Diego, CA 92121) and used to transfect 293-S human embryonic kidney cells via calcium phosphate co-precipitation. G418-resistant colonies are expanded and tested for specific [³H]PGE₂ binding. Transfectants demonstrating high levels of specific [³H]PGE₂ binding are further characterized by Scatchard analysis to determine B_{max} and K_ds for PGE₂. The lines selected for compound screening have approximately 338,400 receptors per cell and a K_d = 12 nM for PGE₂ (EP₂), and approximately 256,400 receptors per cell and a K_d = 2.9 nM for PGE₂ (EP₄). Constitutive expression of both receptors in parental 293-S cells is negligible. Cells are maintained in RPMI supplemented with fetal bovine serum (10% final) and G418 (700 ug/ml final).

cAMP responses in the 293-S/EP₂ and 293-S/EP₄ lines are determined by detaching cells from culture flasks in 1 ml of Ca⁺⁺ and Mg⁺⁺ deficient PBS via vigorous pounding, adding serum-free RPMI to a final concentration of 1 X 10⁶ cells/ml, and adding 3-isobutyl-1-methylxanthine (IBMX) to a final concentration of 1 mM. One milliliter of cell suspension is immediately aliquoted into individual 2 ml screwcap microcentrifuge and incubated for 10 minutes, uncovered, at 37 °C, 5% CO₂, 95% relative humidity. The compound to be tested is then added to cells at 1:100 dilutions such that final DMSO or ethanol concentrations is 1%. Immediately after adding compound, the tubes are covered, mixed by inverting two times, and incubated at 37 °C for 12 minutes. Samples are then lysed by incubation at 100 °C for 10 minutes and immediately cooled on ice for 5 minutes. Cellular debris is pelleted by centrifugation at 1000 X g for 5 minutes, and cleared lysates are transferred to fresh tubes. cAMP concentrations are determined using a commercially available cAMP radioimmunoassay kit RIA (NEK-033, DuPont/NEN Research Products, 549 Albany St., Boston, MA 02118) after diluting cleared lysates 1:10 in cAMP RIA assay buffer (included in kit). Typically, one treats cells with 6-8 concentrations of the compound to be tested in 1 log increments. EC₅₀ calculations are performed on a calculator using linear regression analysis on the linear portion of the dose response curves.

References

1. Regan, J.W. Bailey, T.J. Pepperl, D.J. Pierce, K.L. Bogardus, A.M. Donello, J.E. Fairbairn, C.E. Kedzie, K.M. Woodward, D.F. and Gil, D.W. 1994 Cloning of a Novel Human Prostaglandin Receptor with Characteristics of the Pharmacologically Defined EP₂ Subtype. Mol. Pharmacology 46:213-220.
- 5 2. Bastien, L., Sawyer, N., Grygorczyk, R., Metters, K., and Adam, M. 1994 Cloning, Functional Expression, and Characterization of the Human Prostaglandin E₂ Receptor EP₂ Subtype. J. Biol. Chem. Vol 269, 16:11873-11877.

Assay for Binding to Prostaglandin E₂ Receptors

Membrane Preparation: All operations are performed at 4 °C. Transfected
10 cells expressing prostaglandin E₂ type 1 receptors (EP₁), type 2 (EP₂), type 3 (EP₃) or type 4 (EP₄) receptors are harvested and suspended to 2 million cells per ml in Buffer A [50 mM Tris-HCl (pH 7.4) , 10 mM MgCl₂, 1 mM EDTA, 1 mM Pefabloc peptide, (Boehringer Mannheim Corp., Indianapolis, IN), 10 uM Phosphoramidon peptide, (Sigma, St. Louis, MO), 1 uM pepstatin A peptide, (Sigma, St. Louis, MO),
15 10 uM elastatinal peptide, (Sigma, St. Louis, MO), 100 uM antipain peptide, (Sigma, St. Louis, MO)]. The cells are lysed by sonification with a Branson Sonifier (Model #250, Branson Ultrasonics Corporation, Danbury, CT) in 2 fifteen second bursts. Unlysed cells and debris are removed by centrifugation at 100 x g for 10 min. Membranes are then harvested by centrifugation at 45,000 x g for 30
20 minutes. Pelleted membranes are resuspended to 3-10 mg protein per ml, protein concentration being determined of the method of Bradford [Bradford, M., Anal. Biochem., 72, 248 (1976)]. Resuspended membranes are then stored frozen at -80 °C until use.

Binding Assay: Frozen membranes prepared as above are thawed and
25 diluted to 1 mg protein per ml in Buffer A above. One volume of membrane preparation is combined with 0.05 volume test compound or buffer and one volume of 3 nM ³H-prostaglandin E₂ (#TRK 431, Amersham, Arlington Heights, IL) in Buffer A. The mixture (205 µL total volume) is incubated for 1 hour at 25°C. The membranes are then recovered by filtration through type GF/C glass fiber filters (#1205-401, Wallac, Gaithersburg, MD) using a Tomtec harvester (Model Mach
30 II/96, Tomtec, Orange, CT). The membranes with bound ³H-prostaglandin E₂ are trapped by the filter, while the buffer and unbound ³H-prostaglandin E₂ pass through the filter into waste. Each sample is then washed 3 times with 3 ml of [50

mM Tris-HCl (pH 7.4), 10 mM MgCl₂, 1 mM EDTA]. The filters are then dried by heating in a microwave oven. To determine the amount of ³H-prostaglandin bound to the membranes, the dried filters are placed into plastic bags with scintillation fluid and counted in a LKB 1205 Betaplate reader (Wallac, Gaithersburg, MD).

- 5 IC₅₀s are determined from the concentration of test compound required to displace 50% of the specifically bound ³H-prostaglandin E₂.

The full length EP₁ receptor is made as disclosed in Funk et al., Journal of Biological Chemistry, 1993, 268, 26767-26772. The full length EP₂ receptor is made as disclosed in Regan et al., Molecular Pharmacology, 1994, 46, 213-220.

- 10 The full length EP₃ receptor is made as disclosed in Regan et al., British Journal of Pharmacology, 1994, 112, 377-385. The full length EP₄ receptor is made as disclosed in Bastien, Journal of Biological Chemistry, 1994, 269, 11873-11877. These full length receptors are used to prepare 293S cells expressing the EP₁, EP₂, EP₃ and EP₄ receptors.

- 15 293S cells expressing either the human EP₁, EP₂, EP₃ or EP₄ prostaglandin E₂ receptors are generated according to methods known to those skilled in the art. Typically, PCR (polymerase chain reaction) primers corresponding to the 5' and 3' ends of the published full length receptor are made according to the well known methods disclosed above and are used in an RT-PCR reaction using the total RNA
20 from human kidney (for EP₁), human lung (for EP₂), human lung (for EP₃) or human lymphocytes (for EP₄) as a source. PCR products are cloned by the TA overhang method into pCR2.1 (Invitrogen, Carlsbad, CA) and identity of the cloned receptor is confirmed by DNA sequencing.

- 25 293S cells (Mayo, Dept. of Biochemistry, Northwestern Univ.) are transfected with the cloned receptor in pcDNA3 by electroporation. Stable cell lines expressing the receptor are established following selection of transfected cells with G418.

- 30 Clonal cell lines expressing the maximal number of receptors are chosen following a whole cell ³H-PGE₂ binding assay using unlabeled PGE₂ as a competitor.

FRACTURE HEALING ASSAYS

ASSAY FOR EFFECTS ON FRACTURE HEALING AFTER SYSTEMIC ADMINISTRATION

Fracture Technique: Sprage-Dawley rats at 3 months of age are
5 anesthetized with Ketamine. A 1 cm incision is made on the anteromedial aspect
of the proximal part of the right tibia or femur. The following describes the tibial
surgical technique. The incision is carried through to the bone, and a 1 mm hole is
drilled 4 mm proximal to the distal aspect of the tibial tuberosity 2 mm medial to the
anterior ridge. Intramedullary nailing is performed with a 0.8 mm stainless steel
10 tube (maximum load 36.3 N, maximum stiffness 61.8 N/mm, tested under the
same conditions as the bones). No reaming of the medullary canal is performed. A
standardized closed fracture is produced 2 mm above the tibiofibular junction by
three-point bending using specially designed adjustable forceps with blunt jaws.
To minimize soft tissue damage, care is taken not to displace the fracture. The
15 skin is closed with monofilament nylon sutures. The operation is performed under
sterile conditions. Radiographs of all fractures are taken immediately after nailing,
and rats with fractures outside the specified diaphyseal area or with displaced
nails are excluded. The remaining animals are divided randomly into the following
groups with 10 - 12 animals per each subgroup per time point for testing the
20 fracture healing. The first group receives daily gavage of vehicle (water : 100%
Ethnanol = 95 : 5) at 1 ml/rat, while the others receive daily gavage from 0.01 to
100 mg/kg/day of the compound to be tested (1 ml/rat) for 10, 20, 40 and 80 days.

At 10, 20, 40 and 80 days, 10 - 12 rats from each group are anesthetized
with Ketamine and sacrificed by exsanguination. Both tibiofibular bones are
25 removed by dissection and all soft tissue is stripped. Bones from 5 - 6 rats for each
group are stored in 70% ethanol for histological analysis, and bones from another
5 - 6 rats for each group are stored in a buffered Ringer's solution (+4°C, pH 7.4)
for radiographs and biomechanical testing which is performed.

Histological Analysis: The methods for histologic analysis of fractured bone
30 have been previously published by Mosekilde and Bak (The Effects of Growth
Hormone on Fracture Healing in Rats: A Histological Description. Bone, 14:19-27,
1993). Briefly, the fracture site is sawed 8 mm to each side of the fracture line,
embedded undecalcified in methymethacrylate, and cut frontals sections on a

Reichert-Jung Polycut microtome in 8 μ m thick. Masson-Trichrome stained mid-frontal sections (including both tibia and fibula) are used for visualization of the cellular and tissue response to fracture healing with and without treatment. Sirius red stained sections are used to demonstrate the characteristics of the callus structure and to differentiate between woven bone and lamellar bone at the fracture site. The following measurements are performed: (1) fracture gap - measured as the shortest distance between the cortical bone ends in the fracture, (2) callus length and callus diameter, (3) total bone volume area of callus, (4) bony tissue per tissue area inside the callus area, (5) fibrous tissue in the callus, and (6) cartilage area in the callus.

Biomechanical Analysis: The methods for biomechanical analysis have been previously published by Bak and Andreassen (The Effects of Aging on Fracture Healing in Rats. Calcif Tissue Int 45:292-297, 1989). Briefly, radiographs of all fractures are taken prior to the biomechanical test. The mechanical properties of the healing fractures are analyzed by a destructive three- or four-point bending procedure. Maximum load, stiffness, energy at maximum load, deflection at maximum load, and maximum stress are determined.

ASSAY FOR EFFECTS ON FRACTURE HEALING AFTER LOCAL ADMINISTRATION

Fracture Technique: Female or male beagle dogs at approximately 2 years of age are used under anesthesia in the study. Transverse radial fractures are produced by slow continuous loading in three-point bending as described by Lenehan et al. (Lenehan, T. M.; Balligand, M.; Nunamaker, D.M.; Wood, F.E.: Effects of EHDP on Fracture Healing in Dogs. J Orthop Res 3:499-507; 1985). The wire is pulled through the fracture site to ensure complete anatomical disruption of the bone. Thereafter, local delivery of prostaglandin agonists to the fracture site is achieved by slow release of compound delivered by slow release pellets or by administration of the compounds in a suitable Formulation such as a paste gel solution or suspension for 10, 15, or 20 weeks.

Histological Analysis: The methods for histologic analysis of fractured bone have been previously published by Peter et al. (Peter, C.P.; Cook, W.O.; Nunamaker, D.M.; Provost, M. T.; Seedor, J.G.; Rodan, G.A. Effects of alendronate on fracture healing and bone remodeling in dogs. J. Orthop. Res.

14:74-70, 1996) and Mosekilde and Bak (The Effects of Growth Hormone on Fracture Healing in Rats: A Histological Description. Bone, 14:19-27, 1993). Briefly, after sacrifice, the fracture side is sawed 3 cm to each side of the fracture line, embedded undecalcified in methymethacrylate, and cut on a Reichert-Jung Polycut microtome in 8 µm thick of frontal sections. Masson-Trichrome stained mid-frontal sections (including both tibia and fibula) are used for visualization of the cellular and tissue response to fracture healing with and without treatment. Sirius red stained sections are used to demonstrate the characteristics of the callus structure and to differentiate between woven bone and lamellar bone at the fracture site. The following measurements are performed: (1) fracture gap - measured as the shortest distance between the cortical bone ends in the fracture, (2) callus length and callus diameter, (3) total bone volume area of callus, (4) bony tissue per tissue area inside the callus area, (5) fibrous tissue in the callus, (6) cartilage area in the callus.

Biomechanical Analysis: The methods for biomechanical analysis have been previously published by Bak and Andreassen (The Effects of Aging on Fracture Healing in Rats. Calcif Tissue Int 45:292-297, 1989) and Peter et al. (Peter, C.P.; Cook, W.O.; Nunamaker, D.M.; Provost, M. T.; Seedor, J.G.; Rodan, G.A. Effects of Alendronate On Fracture Healing And Bone Remodeling In Dogs. J. Orthop. Res. 14:74-70, 1996). Briefly, radiographs of all fractures are taken prior to the biomechanical test. The mechanical properties of the healing fractures are analyzed by a destructive three- or four-point bending procedures. Maximum load, stiffness, energy at maximum load, deflection at maximum load, and maximum stress are determined.

ESTROGEN AGONIST/ANTAGONIST PROTOCOL

Estrogen agonist/antagonists are a class of compounds which inhibit bone turnover and prevent estrogen-deficiency induced bone loss. The ovariectomized rat bone loss model has been widely used as a model of postmenopausal bone loss. Using this model, one can test the efficacy of the estrogen agonist/antagonist compounds in preventing bone loss and inhibiting bone resorption.

Sprague-Dawley female rats (Charles River, Wilmington, MA) at different ages (such as 5 months of age) are used in these studies. The rats are singly housed in 20 cm X 32 cm X 20 cm cages during the experimental period. All rats

are allowed free access to water and a pelleted commercial diet (Agway ProLab 3000, Agway County Food, Inc., Syracuse, NY) containing 0.97% calcium, 0.85% phosphorus, and 1.05 IU/g of Vitamin D₃

5 A group of rats (8 to 10) are sham-operated and treated p.o. with vehicle (10% ethanol and 90% saline, 1 ml/day), while the remaining rats are bilaterally ovariectomized (OVX) and treated with either vehicle (p.o.), 17 β -estradiol (Sigma, E-8876, E₂, 30 μ g/kg, daily subcutaneous injection), or estrogen agonist/antagonists (such as droloxifene at 5, 10, or 20 mg/kg, daily p.o.) for a certain period (such as 4 weeks). All rats are given subcutaneous injections of 10
10 mg/kg calcein (fluorochrome bone marker) 12 and 2 days before being sacrificed in order to examine the dynamic changes in bone tissue. After 4 weeks of treatment, the rats are sacrificed and autopsied. The following endpoints are determined:

Body Weight Gain: Body weight at autopsy minus body weight at surgery.

15 Uterine Weight and Histology: The uterus is removed from each rat during autopsy, and weighed immediately. Thereafter, the uterus is processed for histologic measurements such as uterine cross-sectional tissue area, stromal thickness, and luminal epithelial thickness.

Total Serum Cholesterol: Blood is obtained by cardiac puncture and
20 allowed to clot at 4°C, and then centrifuged at 2,000 g for 10 min. Serum samples are analyzed for total serum cholesterol using a high performance cholesterol calorimetric assay (Boehringer Mannheim Biochemicals, Indianapolis, IN).

Femoral Bone Mineral Measurements: The right femur from each rat is removed at autopsy and scanned using dual energy X-ray absorptiometry (DEXA, QDR 1000/W, Hologic Inc., Waltham, MA) equipped with "Regional High
25 Resolution Scan" software (Hologic Inc., Waltham, MA). The scan field size is 5.08 x 1.902 cm, resolution is 0.0254 x 0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and bone area, bone mineral content (BMC), and bone mineral density (BMD) of whole femora (WF), distal femoral metaphyses (DFM), femoral shaft (FS), and proximal femora (PF) are determined.
30

Proximal Tibial Metaphyseal Cancellous Bone Histomorphometric Analyses: The right tibia is removed at autopsy, dissected free of muscle, and cut into three parts. The proximal tibia is fixed in 70% ethanol, dehydrated in graded

concentrations of ethanol, defatted in acetone, then embedded in methyl methacrylate (Eastman Organic Chemicals, Rochester, NY). Frontal sections of proximal tibial metaphyses at 4 and 10 μm thickness are cut using a Reichert-Jung Polycut S microtome. One 4 μm and one 10 μm sections from each rat are used
 5 for cancellous bone histomorphometry. The 4 μm sections are stained with modified Masson's Trichrome stain while the 10 μm sections remained unstained.

A Bioquant OS/2 histomorphometry system (R&M Biometrics, Inc., Nashville, TN) is used for the static and dynamic histomorphometric measurements of the secondary spongiosa of the proximal tibial metaphyses
 10 between 1.2 and 3.6 mm distal to the growth plate-epiphyseal junction. The first 1.2 mm of the tibial metaphyseal region is omitted in order to restrict measurements to the secondary spongiosa. The 4 μm sections are used to determine indices related to bone volume, bone structure, and bone resorption, while the 10 μm sections are used to determine indices related to bone formation
 15 and bone turnover.

I. Measurements and calculations related to trabecular bone volume and structure:

1. Total metaphyseal area (TV, mm^2): metaphyseal area between 1.2 and 3.6 mm distal to the growth plate-epiphyseal junction.
2. Trabecular bone area (BV, mm^2): total area of trabeculae within TV.
- 20 3. Trabecular bone perimeter (BS, mm): the length of total perimeter of trabeculae.
4. Trabecular bone volume (BV/TV, %): $\text{BV} / \text{TV} \times 100$.
5. Trabecular bone number (TBN, $\#/\text{mm}$): $1.199 / 2 \times \text{BS} / \text{TV}$.
6. Trabecular bone thickness (TBT, μm): $(2000 / 1.199) \times (\text{BV} / \text{BS})$.
- 25 7. Trabecular bone separation (TBS, μm): $(2000 \times 1.199) \times (\text{TV} - \text{BV})$.

II. Measurements and calculations related to bone resorption:

1. Osteoclast number (OCN, $\#$): total number of osteoclast within total metaphyseal area.
2. Osteoclast perimeter (OCP, mm): length of trabecular perimeter covered
 30 by osteoclast.
3. Osteoclast number/mm (OCN/mm, $\#/\text{mm}$): OCN / BS .
4. Percent osteoclast perimeter (%OCP, %): $\text{OCP} / \text{BS} \times 100$.

III. Measurements and calculations related to bone formation and turnover:

1. Single-calcein labeled perimeter (SLS, mm): total length of trabecular perimeter labeled with one calcein label.
2. Double-calcein labeled perimeter (DLS, mm): total length of trabecular perimeter labeled with two calcein labels.
3. Inter-labeled width (ILW, μm): average distance between two calcein labels.
4. Percent mineralizing perimeter (PMS, %): $(\text{SLS}/2 + \text{DLS}) / \text{BS} \times 100$.
5. Mineral apposition rate (MAR, $\mu\text{m}/\text{day}$): $\text{ILW} / \text{label interval}$.
6. Bone formation rate/surface ref. (BFR/BS, $\mu\text{m}^2/\text{d}/\mu\text{m}$): $(\text{SLS}/2 + \text{DLS}) \times \text{MAR} / \text{BS}$.
7. Bone turnover rate (BTR, %/y): $(\text{SLS}/2 + \text{DLS}) \times \text{MAR} / \text{BV} \times 100$.

Statistics

Statistics are calculated using StatView 4.0 packages (Abacus Concepts, Inc., Berkeley, CA). The analysis of variance (ANOVA) test followed by Fisher's PLSD (Stat View, Abacus Concepts Inc. 1918 Bonita Ave, Berkeley, CA 94704-1014) is used to compare the differences between groups.

COMBINATION AND SEQUENTIAL TREATMENT PROTOCOL

The following protocols can of course be varied by those skilled in the art. For example, intact male or female rats, sex hormone deficient male (orchidectomy) or female (ovariectomy) rats may be used. In addition, male or female rats at different ages (such as 12 months of age) can be used in the studies. The rats can be either intact or castrated (ovariectomized or orchidectomized), and administered to with anabolic agents such as the compounds of this invention at different doses (such as 1, 3 or 6 mg/kg/day) for a certain period (such as two weeks to two months), and followed by administration of an anti-resorptive agent such as droloxifene at different doses (such as 1, 5, 10 mg/kg/day) for a certain period (such as two weeks to two months), or a combination treatment with both anabolic agent and anti-resorptive agent at different doses for a certain period (such as two weeks to two months). In the castrated rats, treatment can be started on the next day after surgery (for the purpose of preventing bone loss) or at the time bone loss has already occurred (for the purpose of restoring bone mass).

The rats are sacrificed under ketamine anesthesia. The following endpoints are determined:

Femoral bone mineral measurements are performed as described above in the estrogen agonist/antagonist protocol.

- 5 Lumbar Vertebral Bone Mineral Measurements: Dual energy X-ray absorptiometry (QDR 1000/W, Hologic, Inc., Waltham, MA) equipped with a "Regional High Resolution Scan" software (Hologic, Inc., Waltham, MA) is used to determine the bone area, bone mineral content (BMC), and bone mineral density (BMD) of whole lumbar spine and each of the six lumbar vertebrae (LV1 - 6) in the
10 anesthetized rats. The rats are anesthetized by injection (i.p.) of 1 ml/kg of a mixture of ketamine/rompun (ratio of 4 to 3), and then placed on a rat platform. The scan field sized is 6 x 1.9 cm, resolution is 0.0254 x 0.0127 cm, and scan speed is 7.25 mm/sec. The whole lumbar spine scan image is obtained and analyzed. Bone area (BA), and bone mineral content (BMC) is determined, and
15 bone mineral density is calculated (BMC divided by BA) for the whole lumbar spine and each of the six lumbar vertebrae (LV1 - 6).

Proximal tibial metaphyseal cancellous bone histomorphometric analyses are performed as described above for in the estrogen agonist/antagonist protocol.

- 20 Measurements and calculations related to trabecular bone volume and structure are performed as described above in the estrogen agonist/antagonist protocol. Further, measurements and calculations related to bone resorption are also performed as described above in the estrogen agonist/antagonist protocol. Still further, measurements and calculations related to bone formation and turnover are performed as described above in the estrogen agonist/antagonist
25 protocol. Further still, the data obtained is analyzed using the statistical manipulations described above in the estrogen agonist/antagonist protocol.

Kidney Regeneration Assay

- The role of an prostaglandin agonist in kidney regeneration is investigated by the ability of Prostaglandin E₂ (PGE₂) or a prostaglandin agonist to induce the
30 expression of Bone Morphogenetic Protein 7 (BMP-7) in wild type 293S cells and in 293S cells transfected with EP₂.

Methods: 293S and EP2 293S cells are grown in Dulbecco's Modified Eagle medium (DMEM, Gibco, BRL; Gaithersburg, MD). One day prior to

treatment with PGE₂ or an prostaglandin agonist, cells are plated at a density of 1.5 x10⁶ cells /10 cm dish. Generally about 16 to 24 hours later the cell monolayer is washed once with OptiMEM (Gibco, BRL; Gaithersburg, MD) followed by the addition of 10 ml OptiMEM/dish in the presence and absense of vehicle (DMSO),

5 PGE₂ (10⁻⁶M) or a prostaglandin agonist (10⁻⁶M). Cells are harvested and RNA is extracted at 8, 16 and 24 hours. Northern blot analysis of total RNA (20 mg/lane) is carried out by probing the blots with ³²P-labeled BMP-7 probe. The blots are normalized for RNA loading by hybridization with ³²P-labeled 18s ribosomal RNA probe. PGE₂ and prostaglandin agonists induce the expression of BMP-7 in the

10 EP₂ 293S cells in a time dependent manner. Such induction of expression is generally not observed in the parental cell line. Given the known role of BMP-7 in kidney regeneration and the ability of an prostaglandin agonist to induce BMP-7 expression in 293S kidney cells in a time and receptor specific manner indicates a role for prostaglandin agonist in kidney regeneration.

15 Administration of the compounds of this invention can be via any method which delivers a compound of this invention systemically and/or locally (e.g., at the site of the bone fracture, osteotomy, or orthopedic surgery). These methods include oral routes, parenteral, intraduodenal routes, etc. Generally, the compounds of this invention are administered orally, but parenteral administration

20 (e.g., intravenous, intramuscular, transdermal, subcutaneous, rectal or intramedullary) may be utilized, for example, where oral administration is inappropriate for the target or where the patient is unable to ingest the drug.

The compounds are used for the treatment and promotion of healing of bone fractures and osteotomies by the local application (e.g., to the sites of bone

25 fractures of osteotomies) of the compounds of this invention or compositions thereof. The compounds of this invention are applied to the sites of bone fractures or osteotomies, for example, either by injection of the compound in a suitable solvent (e.g., an oily solvent such as arachis oil) to the cartilage growth plate or, in cases of open surgery, by local application thereto of such compounds in a

30 suitable carrier or diluent such as bone-wax, demineralized bone powder, polymeric bone cements, bone sealants, etc. Alternatively, local application can be achieved by applying a solution or dispersion of the compound in a suitable carrier or diluent onto the surface of, or incorporating it into solid or semi-solid implants

conventionally used in orthopedic surgery, such as dacron-mesh, gel-foam and kiel bone, or prostheses.

The compounds of this invention may also be applied locally to the site of the fracture or osteotomy in a suitable carrier or diluent in combination with one or
5 more of the anabolic agents or bone anti-resorptive agents described above.

Such combinations within the scope of this invention can be co-administered simultaneously or sequentially in any order, or a single pharmaceutical composition comprising a Formula I compound, a prodrug thereof or a pharmaceutical salt of said compound or said prodrug as described above
10 and a second compound as described above in a pharmaceutically acceptable carrier or diluent can be administered.

For example, a bone anabolic agent can be used in this invention alone or in combination with an anti-resorptive agent for three months to three years, followed by an anti-resorptive agent alone for three months to three years, with
15 optional repeat of the full treatment cycle. Alternatively, for example, the bone anabolic agent can be used alone or in combination with an anti-resorptive agent for three months to three years, followed by an anti-resorptive agent alone for the remainder of the patient's life. For example, in one preferred mode of administration, a Formula I compound, or a prodrug thereof or a pharmaceutically
20 acceptable salt of said compound or said prodrug as described above may be administered once daily and a second compound as described above (e.g., estrogen agonist/antagonist) may be administered daily in single or multiple doses. Alternatively, for example, in another preferred mode of administration the two compounds may be administered sequentially wherein the Formula I compound,
25 prodrug thereof or pharmaceutically acceptable salt of said compound or said prodrug as described above may be administered once daily for a period of time sufficient to augment bone mass to a level which is above the bone fracture threshold (World Health Organization Study "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis (1994). Report of a
30 World Health Organization Study Group. World Health Organization Technical Series 843") followed by administration of a second compound, as described above (e.g., estrogen agonist/antagonist), daily in single or multiple doses. It is

preferred that the first compound as described above is administered once daily in a rapid delivery form such as oral delivery.

In any event, the amount and timing of compounds administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgment of the prescribing physician. Thus, because of patient to patient variability, the dosages given below are a guideline and the physician may titrate doses of the drug to achieve the treatment (e.g., bone mass augmentation) that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of factors such as bone mass starting level, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

In general an amount of a compound of this invention is used that is sufficient to augment bone mass to a level which is above the bone fracture threshold (as detailed in the World Health Organization Study previously cited herein).

In general an effective dosage for the anabolic agents used in this invention described above is in the range of 0.001 to 100 mg/kg/day, preferably 0.01 to 50 mg/kg/day.

The following paragraphs provide preferred dosage ranges for various anti-resorptive agents.

The amount of the anti-resorptive agent to be used is determined by its activity as a bone loss inhibiting agent. This activity is determined by means of the pharmacokinetics of an individual compound and its minimal versus maximal effective dose in inhibition of bone loss using a protocol such as described above (e.g., Estrogen Agonist/Antagonist Protocol).

In general, an effective dosage for an anti-resorptive agent is about 0.001 mg/kg/day to about 20 mg/kg/day.

In general, an effective dosage for progestins is about 0.1 to 10 mg per day; the preferred dose is about 0.25 to 5 mg per day.

In general, an effective dosage for polyphosphonates is determined by its potency as a bone resorption inhibiting agent of standard assays.

Ranges for the daily administration of some polyphosphonates are about 0.001 mg/kg/day to about 20 mg/kg/day.

In general an effective dosage for the treatment of this invention, for example the bone resorption treatment of this invention, for the estrogen
5 agonists/antagonists of this invention is in the range of 0.01 to 200 mg/kg/day, preferably 0.5 to 100 mg/kg/day.

In particular, an effective dosage for droloxifene is in the range of 0.1 to 40 mg/kg/day, preferably 0.1 to 5 mg/kg/day.

In particular, an effective dosage for raloxifene is in the range of 0.1 to 100
10 mg/kg/day, preferably 0.1 to 10 mg/kg/day.

In particular, an effective dosage for tamoxifen is in the range of 0.1 to 100 mg/kg/day, preferably 0.1 to 5 mg/kg/day.

In particular, an effective dosage for 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]- benzo[b]thiophen-6-ol is 0.001 to 1 mg/kg/day.

15 In particular, an effective dosage for
cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

20 *cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

25 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline

30 is in the range of 0.0001 to 100 mg/kg/day, preferably 0.001 to 10 mg/kg/day.

In particular, an effective dosage for 4-hydroxy tamoxifen is in the range of 0.0001 to 100 mg/kg/day, preferably 0.001 to 10 mg/kg/day.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle or diluent. Thus, the compounds of this invention can be administered individually or together in any
5 conventional oral, parenteral, rectal or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch
10 and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules;
15 preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water,
20 ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with
25 sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g., topical) administration, dilute sterile,
30 aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this

disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

5 Pharmaceutical compositions of the invention may contain 0.1%-95% of the compound(s) of this invention, preferably 1%-70%. In any event, the composition or Formulation to be administered will contain a quantity of a compound(s) of this invention in an amount effective to treat the disease/condition of the subject being treated, e.g., a bone disorder.

10 Since the present invention has an aspect that relates to the augmentation and maintenance of bone mass by treatment with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of Formula I a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug
15 and a second compound as described above. The kit comprises container means for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the
20 separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

25 An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or
30 capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic

foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

- 5 It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the dosage form so specified should be ingested. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday,
- 10 Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. Also, a daily dose of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug can consist of
- 15 several tablets or capsules and vice versa. The memory aid should reflect this.

 In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a

20 mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

- 25 The compounds of this invention either alone or in combination with each other or other compounds generally will be administered in a convenient Formulation. The following Formulation examples only are illustrative and are not intended to limit the scope of the present invention.

 In the Formulations which follow, "active ingredient" means a compound or

30 compounds of this invention.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.25-100
Starch, NF	0-650
Starch flowable powder	0-50
Silicone fluid 350 centistokes	0-15

- 5 A tablet Formulation is prepared using the ingredients below:

Formulation 2: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Cellulose, microcrystalline	200-650
Silicon dioxide, fumed	10-650
Stearate acid	5-15

The components are blended and compressed to form tablets.

- 10 Alternatively, tablets each containing 0.25-100 mg of active ingredients are made up as follows:

Formulation 3: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredients, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° - 60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.25-100 mg of active ingredient per 5 ml dose are made as follows:

Formulation 4: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.25-100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified Water to	5 mL

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

5 The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant, cooled to 30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Suppositories are prepared as follows:

Formulation 6: Suppositories

10

Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

15 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

An intravenous Formulation is prepared as follows:

Formulation 7: Intravenous Solution

Ingredient	Quantity
Active ingredient	20 mg
Isotonic saline	1,000 mL

20 The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

The active ingredient above may also be a combination of agents.

The abbreviations "Me", "Et", "iPr", "Tf", "Bu", "Ph", "EDC" and "Ac", where used herein, define the terms "methyl", "ethyl", isopropyl, "triflyl", "butyl", "phenyl", "1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride" and "acetyl",
5 respectively.

GENERAL EXPERIMENTAL PROCEDURES

Unless otherwise specified, all reactions were performed under an inert atmosphere such as nitrogen (N₂).

NMR spectra were recorded on a Varian XL-300 (Varian Co., Palo Alto, California), a Bruker AM-300 spectrometer (Bruker Co., Billerica, Massachusetts) or a Varian Unity 400 at about 23°C at 300 or 400 MHz for proton and 75.4 MHz for carbon nuclei. Chemical shifts are expressed in parts per million downfield from trimethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; bs=broad singlet. Resonances designated as
10 exchangeable did not appear in a separate NMR experiment where the sample was shaken with several drops of D₂O in the same solvent. Atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a Fisons Platform II Spectrometer. Chemical ionization mass spectra were obtained on a Hewlett-Packard 5989 instrument (Hewlett-Packard Co., Palo Alto, California) (ammonia
15 ionization, PBMS). Where the intensity of chlorine or bromine-containing ions are described the expected intensity ratio was observed (approximately 3:1 for ³⁵Cl/³⁷Cl-containing ions) and 1:1 for ⁷⁹Br/⁸¹Br-containing ions) and the intensity of only the lower mass ion is given.

Column chromatography was performed with either Baker Silica Gel (40 μm) (J.T. Baker, Phillipsburg, N.J.) or Silica Gel 60 (EM Sciences, Gibbstown, N.J.) in glass columns under low nitrogen pressure. Radial Chromatography was performed using a Chromatotron® (model 7924T, Harrison Research). Medium pressure chromatography was performed on a Flash 40 Biotage System (Biotage Inc, Dyax Corp., Charlottesville, Virginia). Unless otherwise specified, reagents
20 were used as obtained from commercial sources. Dimethylformamide, 2-propanol, acetonitrile, methanol, tetrahydrofuran, and dichloromethane, when used as reaction solvents, were the anhydrous grade supplied by Aldrich Chemical Company (Milwaukee, Wisconsin). The terms "concentrated" and "coevaporated"

refer to removal of solvent at water aspirator pressure on a rotary evaporator with a bath temperature of less than 45°C. Reactions conducted at "0-20°C" or "0-25°C" were conducted with initial cooling of the vessel in an insulated ice bath which was allowed to warm to room temperature over several hours. The

5 abbreviation "min" and "h" stand for "minutes" and "hours" respectively.

Example 17-((4-Butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-heptanoic acidStep A: Reductive Amination

7-(4-Butyl-benzylamino)-heptanoic acid methyl ester. A solution of 7-amino-
5 heptanoic acid methyl ester hydrochloride, prepared of Preparation 1, (1.12 g, 5.9
mmol), 4-butyl-benzaldehyde (0.915 g, 5.65 mmol) and triethylamine (0.83 mL,
5.98 mmol) in 20 mL MeOH was stirred at room temperature for 3 hours. After
cooling to 0°C, NaBH₄ (0.342 g, 9.04 mmol) was added and the reaction was
stirred for 15 minutes at room temperature. The mixture was quenched with 1:1
10 NaHCO₃:H₂O and the MeOH was removed *in vacuo*. The resulting residue was
diluted with CH₂Cl₂ and the organic solution was washed with water and brine,
dried over MgSO₄, filtered and concentrated *in vacuo* to afford the title compound
of Step A (1.4 g). ¹H NMR (400 MHz, CDCl₃) δ 7.08-7.38 (m, 4H), 3.62 (s, 2H),
3.29 (s, 3H), 2.52-2.66 (m, 4H), 2.25 (t, 2H), 1.53-1.63 (m, 6H), 1.25-1.40 (m, 6H),
15 0.85 (t, 3H); MS 306 (M+1).

Step B: Amide formation

7-((4-Butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-heptanoic acid methyl ester. A
solution of 7-(4-butyl-benzylamino)-heptanoic acid methyl ester prepared of
Example 1, Step A (0.10 g, 0.33 mmol), N,N-diisopropylethylamine (0.85 g 0.66
20 mmol) and pyridine-3-sulfonyl chloride hydrochloride, prepared of Preparation 2,
(0.070 g, 0.33 mmol) in 3 mL CH₂Cl₂ was stirred at room temperature overnight.
The mixture was diluted with CH₂Cl₂ and the organic solution was washed with
water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The
product was purified by flash chromatography on silica gel (10% EtOAc/hexanes
25 to 30% EtOAc/hexanes) to afford the title compound of Step B. ¹H NMR (400
MHz, CDCl₃) δ 9.01 (s, 1H), 8.75 (d, 1H), 8.04 (d, 1H), 7.41 (dd, 1H), 7.23 (m,
4H), 4.30 (s, 2H), 3.62 (s, 3H), 3.08 (t, 2H), 2.55 (t, 2H), 2.19 (t, 2H), 1.10-1.58 (m,
12H), 0.87 (t, 3H); MS 447 (M+1).

Step C: Ester Hydrolysis

30 7-((4-Butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-heptanoic acid. A solution of 7-((4-
butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-heptanoic acid methyl ester prepared of
Example 1, Step B (0.040 g, 0.158 mmol), in 2 mL MeOH and 0.5 mL 2N NaOH
was stirred at room temperature overnight. The mixture was quenched with 2N

HCl and was diluted with CH₂Cl₂. The organic layer was washed with 1N HCl and water, dried over MgSO₄, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (2% MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂) to afford the title compound (42 mg). ¹H NMR (400 MHz, CDCl₃) δ 9.09 (s, 1H), 8.77 (d, 1H), 8.08 (d, 1H), 7.48 (dd, 1H), 7.09 (m, 4H), 4.32 (s, 2H), 3.12 (s, 2H), 2.55 (t, 2H), 2.25 (t, 2H), 1.12-1.58 (m, 12H), 0.88 (t, 3H); MS 431 (M-1).

Examples 1a-1an

Examples 1a-1an were prepared from the appropriate starting materials in a manner analogous to the method of Example 1, with variations in reaction time, temperature, and reagents as noted.

Example 1a

7-(Benzenesulfonyl-(4-butyl-benzyl)-amino)-heptanoic acid

¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, 2H), 7.51-7.59 (m, 3H), 7.11 (m, 4H), 4.28 (s, 2H), 3.07 (t, 2H), 2.57 (t, 2H), 2.24 (t, 2H), 1.51-1.59 (m, 2H), 1.44-1.49 (m, 2H), 1.27-1.35 (m, 4H), 1.08-1.15 (m, 4H), 0.91 (t, 3H); MS 430 (M-1).

Example 1b

(3-(((1-Methyl-1H-indol-3-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, (CDCl₃) δ 8.93 (s, 1H), 8.66 (s, 1H), 7.96 (d, 1H), 7.39 (d, 1H), 7.01-7.37 (m, 9H), 6.77 (s, 1H), 4.56 (s, 2H), 4.41 (s, 2H), 3.66 (s, 3H), 3.52 (s, 2H); MS 448 (M-1).

Example 1c

(3-(((5-Phenyl-furan-2-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, (CDCl₃) δ 8.02 (d, 1H), 7.22-7.34 (m, 12H), 6.42 (d, 1H), 6.17 (d, 1H), 4.45 (s, 2H), 4.40 (s, 2H), 3.60 (s, 2H); MS 461 (M-1).

Example 1d

(3-(((5-Benzyl-pyridin-2-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-
acetic acid

- 5 Step A: Reaction time of 3.5 h at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 8.97 (s, 1H), 8.71 (d, 1H), 8.15 (s, 1H), 7.98 (d, 1H), 7.44 (d, 1H), 7.04-7.34 (m, 10H), 4.54 (s, 2H), 4.43 (s, 2H), 3.87 (s, 2H), 3.50 (s, 2H); MS 486 (M-1).

Example 1e

3-(((4-Phenethylsulfanyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-
acetic acid

10

Step A: Reaction time of 4 h at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 1H), 7.50 (bs, 1H), 6.90-7.38 (m, 15H), 4.31 (s, 4H), 3.49 (s, 2H), 3.11 (t, 2H), 2.87 (t, 2H); MS 531 (M-1).

Example 1f

- 15 (3-(((3-Hydroxy-4-propoxy-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-
acetic acid

Step A: Reaction time of 3.5 h at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 8.95 (s, 1H), 8.72 (s, 1H), 7.98 (d, 1H), 7.37 (m, 1H), 7.13-7.23 (m, 2H), 6.94-7.00 (m, 2H), 6.55-6.68 (m, 3H), 4.55 (s, 2H), 4.31 (s, 2H), 3.95 (t, 2H), 3.52 (s, 2H),
20 1.78 (m, 2H), 0.99 (t, 3H).

Example 1g

(3-(((4-Pentyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

- Step A: Reaction time of 3.5 h at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.74 (s, 1H), 8.00 (d, 1H), 7.39 (m, 1H), 7.14-7.26 (m, 2H), 6.95-7.05
25 (m, 6H), 4.35 (s, 4H), 3.54 (s, 2H), 2.54 (t, 2H), 1.56 (m, 2H), 1.29 (m, 4H), 0.88 (t, 3H); MS 465 (M-1).

Example 1h

(3-(((4-Methylsulfamoyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic
acid

- 30 Step A: Reaction time of 3.5 h at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 9.06 (s, 1H), 8.85 (s, 1H), 8.16 (d, 1H), 7.53-7.64 (m, 3H), 6.91-7.26 (m, 6H), 4.39 (s, 2H), 4.35 (s, 2H), 3.50 (s, 2H), 2.63 (s, 3H); MS 488 (M-1).

Example 1i

(3-(((4-Isopropoxy-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

Step A: Reaction time of 3.5 h at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 8.97 (s, 1H), 8.74 (s, 1H), 8.03 (m, 1H), 7.42 (m, 1H), 6.94-7.25 (m, 6H), 6.72 (m, 2H), 4.48 (m, 1H), 4.32 (m, 4H), 3.52 (s, 2H), 1.29 (t, 6H); MS 453 (M-1).

Example 1j

(3-(((4-Chloro-thiophen-2-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

Step A: Reaction time of 3.5 h at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 9.01 (s, 1H), 8.79 (s, 1H), 8.07 (d, 1H), 7.45 (m, 1H), 7.20-7.29 (m, 2H), 7.12 (d, 1H), 7.10 (s, 1H), 7.07 (s, 1H), 4.46 (s, 2H), 4.42 (s, 2H), 3.60 (s, 2H); MS 435 (M-1).

Example 1k

(3-(((4-Butyl-benzyl)-(4-nitro-benzenesulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 8.23 (m, 2H), 7.85 (m, 2H), 7.15-7.25 (m, 2H), 6.95-7.02 (m, 6H), 4.32 (m, 4H), 3.53 (s, 2H), 2.52 (m, 2H), 1.51 (m, 2H), 1.30 (m, 2H), 0.89 (t, 3H); MS 495 (M-1).

Example 1l

(3-(((4-Butyl-benzyl)-(4-cyano-benzenesulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, 1H), 7.67-7.84 (m, 3H), 6.89-7.24 (m, 8H), 4.46 (s, 1H), 4.38 (s, 1H), 4.32 (m, 2H), 3.54 (s, 1H), 3.38 (s, 1H), 2.55 (m, 2H), 1.58 (m, 2H), 1.33 (m, 2H), 1.29 (s, 1H), 0.89 (t, 3H); MS 475 (M-1).

Example 1m

(3-(((4-Butyl-benzyl)-(3-fluoro-benzenesulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 7.58 (m, 1H), 7.45 (m, 1H), 6.92-7.24 (m, 10H), 4.29 (m, 4H), 3.52 (d, 2H), 2.52 (d, 2H), 1.52 (m, 2H), 1.29 (m, 2H), 0.90 (m, 3H); MS 468 (M-1).

Example 1n(3-(((4-Butyl-benzyl)-(5-pyridin-2-yl-thiophene-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

- 5 Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 7.81 (m, 2H), 7.17-7.27 (m, 6H), 6.94-7.16 (m, 6H), 4.29 (d, 4H), 3.55 (s, 2H), 2.54 (m, 2H), 1.54 (m, 2H), 1.31 (m, 2H), 0.91 (t, 3H); MS 533 (M-1).

Example 1o(3-(((4-Butyl-benzyl)-(toluene-4-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

- 10 Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, 2H), 7.24-7.29 (m, 2H), 7.11-7.19 (m, 2H), 6.87-7.01 (m, 2H), 4.26(d, 4H), 3.52 (s, 2H), 2.55 (m, 2H), 2.43 (s, 3H), 1.54 (m, 2H), 1.32 (m, 2H), 0.91 (t, 3H); MS 464 (M-1).

Example 1p

- 15 (3-(((2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.76 (s, 1H), 8.02 (d, 1H), 7.40 (m, 1H), 7.14-7.26 (m, 2H), 7.02 (d, 1H), 6.96 (s, 1H), 6.72 (d, 1H), 6.59 (m, 2H), 4.35 (s, 2H), 4.25 (s, 2H), 4.20 (s, 4H), 3.55 (s, 2H); MS 453 (M-1).

20

Example 1q(3-((Benzofuran-2-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 9.05 (s, 1H), 8.66 (s, 1H), 8.04 (d, 1H), 7.11-7.42 (m, 9H), 6.44 (s, 1H), 4.45 (s, 1H), 4.39 (s, 1H), 3.59 (s, 1H); MS 435 (M-1).

Example 1r

- 25 (3-(((4-Butyl-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 7.58 (s, 1H), 7.28 (s, 1H), 6.99-7.26 (m, 8H), 4.33 (d, 4H), 3.65 (s, 3H), 3.52 (s, 2H), 2.54 (t, 2H), 1.54 (m, 2H), 1.32 (m, 2H), 0.91 (t, 3H); MS 454 (M-1).

Example 1s

(3-(((4-Imidazol-1-yl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

- 5 ^1H NMR (400 MHz, CD_3OD) δ 9.45 (m, 1H), 9.44 (s, 1H), 9.03 (m, 1H), 8.91 (d, 1H), 8.19 (t, 1H), 8.04 (m, 1H), 7.77 (s, 1H), 7.61 (d, 2H), 7.53 (d, 2H), 7.11 (m, 4H), 4.70 (s, 2H), 4.51 (s, 2H), 3.33 (s, 2H); MS 461 (M-1).

Example 1t

(3-(((Pyridine-3-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid

- 10 ^1H NMR (400 MHz, CDCl_3) δ 9.10 (s, 1H), 8.80 (m, 3H), 8.14 (d, 1H), 8.02 (d, 2H), 7.47 (m, 1H), 7.06-7.25 (m, 6H), 6.83 (s, 1H), 4.40 (s, 2H), 4.33 (s, 2H), 3.41 (s, 2H); MS 473 (M-1).

Example 1u

- 15 (3-(((Pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid
 ^1H NMR (400 MHz, CDCl_3) δ 9.11 (s, 1H), 8.85 (s, 1H), 8.15 (d, 1H), 7.87 (s, 2H), 7.63 (d, 2H), 7.51 (m, 1H), 7.37 (s, 1H), 7.07-7.27 (m, 6H), 6.83 (s, 1H), 4.37 (s, 2H), 4.33 (s, 2H), 3.41 (s, 2H).

Example 1v

- 20 (3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid

- Step B: N,N-diisopropylethylamine was replaced by triethylamine. ^1H NMR (400 MHz, CDCl_3) δ 7.85 (s, 1H), 7.59 (m, 2H), 7.47 (s, 1H), 7.34 (s, 1H), 7.07-7.25 (m, 6H), 6.88 (s, 1H), 4.46 (s, 2H), 4.38 (s, 2H), 3.77 (s, 3H), 3.40 (s, 2H); MS 483 (M-1).
- 25 1).

Example 1w

(3-(((4-Dimethylamino-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

- Step A: Reaction time of 4 h at room temperature. Step B: N,N-diisopropylethylamine was replaced by triethylamine. ^1H NMR (400 MHz, CD_3OD) δ 8.09 (d, 1H), 7.09-7.16 (m, 2H), 6.93-6.99 (m, 7H), 6.65 (d, 2H), 5.36 (s, 2H), 4.32 (s, 2H), 4.27 (s, 2H), 2.89 (s, 6H); MS 438 (M-1).
- 30

Example 1x(3-(((4-Cyclohexyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid

Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400
5 MHz, CDCl₃) δ 8.95 (s, 1H), 8.73 (d, 1H), 8.00 (d, 1H), 7.39 (m, 1H), 7.17 (t, 1H),
7.13 (d, 2H), 7.08 (d, 2H), 6.81 (d, 1H), 6.73 (d, 1H), 6.61 (s, 1H), 4.54 (s, 2H),
4.34 (s, 4H), 2.43 (m, 1H), 1.81 (d, 4H), 1.37 (t, 4H), 1.23 (m, 1H); MS 495 (M+1),
493 (M-1).

Example 1y

10 (3-(((2-(3,5-Dichloro-phenoxy)-ethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-
phenoxy)-acetic acid

Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400
MHz, CDCl₃) δ 9.07 (s, 1H), 8.78 (d, 1H), 8.12 (d, 1H), 7.47 (m, 1H), 7.25 (m, 1H),
6.82-6.91 (m, 4H), 6.53 (s, 2H), 4.61 (s, 2H), 4.47 (s, 2H), 3.91 (t, 2H), 3.54 (t, 2H);
15 MS 511 (M+1), 509 (M-1).

Example 1z

(3-(((4-Dimethylamino-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-
acetic acid

Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400
20 MHz, CDCl₃) δ 8.91 (s, 1H), 8.79 (m, 1H), 8.04 (d, 1H), 7.43 (m, 1H), 7.16 (t, 1H),
6.94 (d, 2H), 6.81 (d, 2H), 6.64 (d, 2H), 6.49 (s, 1H), 4.51 (s, 2H), 4.28 (s, 4H),
2.91 (s, 6H); MS 456 (M+1), 454 (M-1).

Example 1aa

(3-(((4-tert-Butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid

25 Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400
MHz, CDCl₃) δ 8.95 (s, 1H), 8.74 (s, 1H), 7.99 (d, 1H), 7.39 (m, 1H), 7.25 (m, 2H),
7.15 (t, 1H), 7.04 (d, 2H), 6.81 (d, 1H), 6.72 (d, 1H), 6.62 (s, 1H), 4.55 (s, 2H), 4.35
(s, 4H), 1.27 (s, 9H); MS 469 (M+1), 467 (M-1).

Example 1ab

(3-(((3-(3-Chloro-phenyl)-propyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid

- 5 Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.77 (d, 1H), 8.07 (d, 1H), 7.48 (m, 1H), 7.21 (m, 2H), 6.91 (s, 1H), 6.86 (m, 3H), 6.78 (s, 1H), 4.61 (s, 2H), 4.31 (s, 2H), 3.15 (t, 2H), 2.43 (t, 2H), 1.68 (m, 2H); MS 475 (M+1), 473 (M-1).

Example 1ac

- 10 (3-(((4-tert-Butyl-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid

Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (s, 1H), 7.08-7.31 (m, 6H), 6.70-6.78 (m, 3H), 4.54 (s, 2H), 4.35 (s, 4H), 3.68 (s, 3H), 1.27 (s, 9H); MS 469.9 (M-1).

15

Example 1ad

(3-(((4-Cyclohexyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

- Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (bs, 1H), 8.75 (bs, 1H), 7.98 (d, 1H), 7.39 (bs, 1H), 6.97-7.25 (m, 8H), 4.36 (d, 4H), 3.54 (s, 2H), 2.44 (s, 1H), 1.72-1.82 (m, 4H), 1.24-1.36 (m, 5H); MS 476.9 (M-1).
- 20

Example 1ae

(3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-phenoxy-benzyl)-amino)-methyl)-phenyl)-acetic acid

- Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (s, 1H), 7.06-7.37 (m, 10H), 6.94 (d, 2H), 6.83 (d, 2H), 4.38 (s, 4H), 3.71 (s, 3H), 1.72-1.82 (m, 4H), 3.56 (s, 2H); MS 490 (M-1).
- 25

Example 1af(3-(((4-Phenoxy-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 9.00 (bs, 1H), 8.76 (bs, 1H), 8.04 (d, 1H), 7.41 (t, 1H), 7.35 (m, 1H), 6.86-7.32 (m, 10H), 6.84 (d, 2H), 4.37 (d, 4H), 3.54 (s, 2H); MS 487 (M-1).

Example 1ag(3-(((4-(2-Oxo-pyrrolidin-1-yl)-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 9.06 (bs, 1H), 8.80 (bs, 1H), 8.14 (m, 1H), 7.47 (m, 1H), 6.96-7.26 (m, 7H), 4.28 (m, 4H), 3.78 (m, 2H), 3.35 (m, 2H), 2.59 (m, 2H), 2.11 (m, 2H); MS 478 (M-1).

Example 1ah(3-((Benzo[1,3]dioxol-5-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.76 (s, 1H), 8.04 (d, 1H), 7.41 (m, 1H), 7.14-7.20 (m, 2H), 7.00 (d, 1H), 6.94 (s, 1H), 6.64 (t, 2H), 6.55 (d, 1H), 4.34 (s, 2H), 4.26 (s, 2H), 3.54 (s, 2H); MS 439 (M-1).

Example 1ai(3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-pyrimidin-5-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid

Step B: N,N-diisopropylethylamine was replaced by triethylamine. ¹H NMR (400 MHz, CDCl₃) δ 9.18 (s, 1H), 8.91 (s, 2H), 7.05-7.54 (m, 11H), 4.49 (s, 2H), 4.40 (s, 2H), 3.75 (s, 3H), 3.55 (s, 2H); MS 476 (M-1).

Example 1aj(3-(((Pyridine-3-sulfonyl)-(4-pyrimidin-5-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CD₃OD) δ 9.17 (s, 1H), 9.01 (s, 1H), 8.77 (s, 1H), 7.57 (m, 4H), 7.45 (d, 2H), 7.05-7.16 (m, 5H), 4.48 (s, 2H), 4.43 (s, 2H), 3.45 (s, 2H).

Example 1ak

(3-(((4-Pyrazin-2-yl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

- 5 ¹H NMR (400 MHz, DMSO-d₆) δ 9.18 (s, 1H), 9.02 (s, 1H), 8.83 (d, 1H), 8.68 (s, 1H), 8.57 (s, 1H), 8.25 (d, 1H), 7.96 (d, 2H), 7.60 (m, 1H), 7.26 (d, 2H), 7.15 (m, 2H), 7.05 (m, 2H), 4.42 (s, 2H), 4.41 (s, 2H).

Example 1al

(3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid

- 10 ¹H NMR (400 MHz, CDCl₃) δ 8.78 (d, 2H), 7.94 (d, 2H), 7.54 (s, 1H), 7.44 (s, 1H), 7.22-7.03 (m, 6H), 6.87 (s, 1H), 4.45 (s, 2H), 4.39 (s, 2H), 3.73 (s, 3H), 3.38 (s, 2H); MS 476 (M-1).

Example 1am

- 15 (3-(((4-Butyl-benzyl)-phenylmethanesulfonyl-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 7.31-6.96 (m, 13H), 4.13 (s, 2H), 4.05 (s, 2H), 4.03 (s, 2H), 3.62 (s, 2H), 2.60 (t, 2H), 1.58 (m, 2H), 1.33 (m, 2H), 0.91 (t, 3H); MS 464 (M-1).

20

Example 1an

5-(3-((Pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-propyl)-thiophene-2-carboxylic acid

- Step A: Triethylamine was replaced with N,N-diisopropylethylamine. ¹H NMR (400 MHz, CDCl₃) δ 9.18 (d, 1H), 8.82 (d, 1H), 8.05 (d, 1H), 7.73-7.20 (m, 8H), 6.60 (d, 25 1H), 4.35 (s, 2H), 3.22 (t, 2H), 2.70 (t, 2H), 1.85-1.70 (m, 2H).

Example 2

(3-(((2-(3-Chloro-phenoxy)-ethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

Step A: Alkylation

- 30 (3-(((2-(3-Chloro-phenoxy)-ethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid methyl ester. To a solution of sodium hydride (60% in mineral oil, 0.016 g, 0.3996 mmol) in 2 mL DMF was added (3-((pyridine-3-sulfonylamino)-methyl)-phenyl)-acetic acid methyl ester (from Preparation 14, 0.096 g, 0.333 mmol) at 0°C

and the reaction was stirred at room temperature for 30 minutes. After cooling to 0°C, 1-(2-bromo-ethoxy)-3-chloro-benzene (from Preparation 29, 0.094 g, 0.399 mmol) was added and the reaction was stirred at room temperature overnight. The DMF was removed *in vacuo*. The residue was diluted with EtOAc and the organic solution was washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (0.5% MeOH/CH₂Cl₂ to 2% MeOH/CH₂Cl₂) to afford the title compound of Step A (0.025 g). MS 475 (M+1).

Step B: Ester Hydrolysis

(3-(((2-(3-Chloro-phenoxy)-ethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid. A solution of the compound of Example 2, Step A (0.025 g, 0.053 mmol), in 2 mL MeOH and 0.5 mL 2N NaOH was stirred at room temperature overnight. The mixture was quenched with 2N HCl and was diluted with CH₂Cl₂. The organic layer was washed with 1N HCl and water, dried over MgSO₄, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (2% MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂) to afford the title compound (20 mg). ¹H NMR (400 MHz, CDCl₃) δ 9.05 (s, 1H), 8.77 (d, 1H), 8.11 (d, 1H), 7.43 (m, 1H), 7.08-7.27 (m, 5H), 6.89 (d, 1H), 6.62 (s, 1H), 6.55 (d, 1H), 4.51 (s, 2H), 3.95 (t, 2H), 3.59 (s, 4H); MS 495 (M-2).

Examples 2a-2c

Examples 2a-2c were prepared from the appropriate starting materials in a manner analogous to the method of Example 2.

Example 2a

Trans-(3-(((3-(3,5-Dichloro-phenyl)-allyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 9.08 (bs, 1H), 8.81 (bs, 1H), 8.11 (d, 1H), 7.48 (bs, 1H), 7.12-7.28 (m, 4H), 6.98 (s, 2H), 6.19 (d, 1H), 5.86 (m, 1H), 4.38 (s, 2H), 3.93 (d, 2H), 3.58 (s, 2H).

Example 2b

(3-(((2-(3,5-Dichloro-phenoxy)-ethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 8.96 (bs, 1H), 8.70 (bs, 1H), 8.04 (d, 1H), 7.41 (m, 1H), 7.24-7.09 (m, 4H), 6.86 (s, 1H), 6.47 (s, 2H), 4.44 (s, 2H), 3.86 (m, 2H), 3.49 (s, 2H), 3.31 (m, 2H).

Example 2c

5 (3-(((4-(1-Hydroxy-hexyl)-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 8.91 (bs, 1H), 8.72 (bs, 1H), 8.03 (d, 1H), 7.40 (bs, 1H), 7.16-6.99 (m, 7H), 6.81 (s, 1H), 4.57 (t, 1H), 4.29 (s, 4H), 3.43 (m, 2H), 1.70 (m, 1H), 1.61 (m, 1H), 1.32-1.16 (m, 8H), 0.82 (t, 3H).

10

Example 3

5-(3-((2-Benzylsulfanyl-ethyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

Step A: Reductive Amination

15 5-(3-(2-Benzylsulfanyl-ethylamino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester. Step A was performed in a manner analogous to the method of Step A of Example 1.

Step B: Amide Formation

20 5-(3-((2-Benzylsulfanyl-ethyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester. Step B was performed in a manner analogous to the method of Step B of Example 1, except triethylamine was used in place of N,N-diisopropylethylamine.

Step C: Ester Hydrolysis

25 5-(3-((2-Benzylsulfanyl-ethyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid•TFA. A solution of 5-(3-((2-benzylsulfanyl-ethyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester prepared of Example 3, Step B (0.038 g) in 1 mL CH₂Cl₂ was cooled to 0°C and 1 mL TFA was added. The mixture was warmed to room temperature and was stirred for 1 h. The CH₂Cl₂ and TFA were removed by evaporation, azeotroping with added CH₂Cl₂ to yield the title compound (46.3 mg). MS 475 (M-1).

30 Examples 3a-3i were prepared from the appropriate starting materials in a manner analogous to the method of Example 3 with variations thereto noted.

Example 3a

5-(3-((2-(3-Chloro-phenylsulfanyl)-ethyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 5 ^1H NMR (400 MHz, CD_3OD) δ 8.93 (s, 1H), 8.78 (d, 1H), 8.21 (d, 1H), 7.64 (m, 1H), 7.57 (s, 1H), 7.35 (s, 1H), 7.19-7.28 (m, 3H), 6.87 (s, 1H), 3.16-3.35 (m, 6H), 2.87 (t, 2H), 1.89 (t, 2H); MS 497,499 (M^+).

Example 3b

(3-(((Pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•2TFA

- 10 ^1H NMR (400 MHz, CDCl_3) δ 9.40 (bs, 1H), 8.98 (s, 1H), 8.84 (s, 1H), 8.28 (m, 1H), 8.10 (s, 1H), 7.78 (m, 2H), 7.68 (m, 1H), 7.51 (s, 1H), 7.24 (m, 3H), 7.12 (t, 1H), 6.77 (m, 1H), 6.48 (s, 1H), 4.53 (s, 2H), 4.45 (s, 2H), 4.34 (s, 2H); MS 494 ($\text{M}-1$).

Example 3c

- 15 (3-(((Pyridine-3-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•2HCl

The TFA salt was converted to the HCl salt by stirring in 2 equivalents 1N HCl followed by removal of water and drying *in vacuo*. ^1H NMR (400 MHz, CD_3OD) δ 9.00 (d, 2H), 8.78 (d, 1H), 8.25 (d, 2H), 8.08 (t, 1H), 7.60 (t, 1H), 7.42 (m, 3H),
20 7.11 (m, 1H), 6.81 (d, 1H), 6.72 (m, 3H), 4.65 (s, 2H), 4.60 (s, 2H), 4.49 (s, 2H).

Example 3d

(3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•2TFA

- ^1H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.85 (d, 1H), 7.76 (d, 2H), 7.70 (s, 1H),
25 7.60 (d, 1H), 7.26 (d, 2H), 7.09 (t, 1H), 6.75 (d, 2H), 6.68 (s, 1H), 4.51 (s, 2H), 4.41 (s, 2H), 4.35 (s, 2H), 3.76 (s, 3H); MS 498 (M^+).

Example 3e

(3-(((Pyridine-3-sulfonyl)-(4-pyridin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid •HCl

- 30 No triethylamine was used in Step A. The TFA salt was converted to the HCl salt by stirring in 2 equivalents 1N HCl followed by removal of water and drying *in vacuo*. MS 490 ($\text{M}+1$), 488 ($\text{M}-1$).

Example 3f

(3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-pyridin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•HCl

5 No triethylamine was used in Step A. The TFA salt was converted to the HCl salt by stirring in 2 equivalents 1N HCl followed by removal of water and drying *in vacuo*. MS 493 (M+1), 491 (M-1).

Example 3g

(3-(((Pyridine-3-sulfonyl)-(4-pyridin-3-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•HCl

10 No triethylamine was used in Step A. The TFA salt was converted to the HCl salt by stirring in 2 equivalents 1N HCl followed by removal of water and drying *in vacuo*. MS 490 (M+1), 488 (M-1).

Example 3h

(3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-pyridin-3-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•HCl

15 No triethylamine was used in Step A. The TFA salt was converted to the HCl salt by stirring in 2 equivalents 1N HCl followed by removal of water and drying *in vacuo*. MS 493 (M+1), 491 (M-1).

Example 3i

(3-(((Pyridine-3-sulfonyl)-(4-pyridin-4-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid •HCl

20 No triethylamine was used in Step A. The TFA salt was converted to the HCl salt by stirring in 2 equivalents 1N HCl followed by removal of water and drying *in vacuo*. MS 490 (M+1), 488 (M-1).

Example 4

5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

Step A: Sulfonamide formation

30 5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid methyl ester. A solution of 5-(3-(3-(3-chloro-phenyl)-propylamino)-propyl)-thiophene-2-carboxylic acid methyl ester (from Preparation 8, 0.0855 g, 0.243 mmol), triethylamine (0.0541 g 0.534 mmol), and pyridine-3-sulfonyl chloride hydrochloride (from Preparation 2, 0.0572 g, 0.267 mmol) in 10 mL CH₂Cl₂

combined at 0°C was stirred at room temperature overnight. The organic solution was washed with water, saturated NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated *in vacuo* to afford the title compound of Step A as an oil. MS 494 (M+1).

5

Step B: Ester Hydrolysis

5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid. A solution of 5-(3-((3-(3-chloro-phenyl)-propyl)-(pyridine-3-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid methyl ester prepared of Example 4, Step B (0.119 g, 0.241 mmol), in 5 mL EtOH and 0.72 mL 1N NaOH was stirred at room temperature overnight. The reaction mixture was adjusted to pH 6.2 and the layers were separated. The organic solution was washed with water, dried over MgSO₄, filtered and concentrated *in vacuo* to afford the title compound (16 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 1H, J=8), 7.70 (d, 1H, J=4), 7.30-7.60 (m, 6H), 6.75 (d, 1H, J=4), 3.20 (m, 4H), 2.95 (t, 2H, J=7), 2.60 (t, 2H, J=7), 1.70-2.00 (m, 4H); MS 478 (M+1), 476 (M-1).

15

Examples 4a-4h

Examples 4a-4h were prepared from the appropriate starting in a manner analogous to the method of Example 4.

Example 4a

5-(3-((3-(3-Chloro-phenyl)-propyl)-(4-methoxy-benzenesulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

20

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, J=7), 7.00-7.40 (m, 8H), 6.80 (d, 1H, J=4), 3.89 (s, 3H), 3.10 (m, 4H), 2.95 (t, 2H, J=7), 2.50 (t, 2H, J=7), 1.70-2.00 (m, 2H); MS 508 (M+1), 506 (M-1).

25

Example 4b

5-(3-((Benzo[1,2,5]thiadiazole-4-sulfonyl)-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.00-7.70 (m, 8H), 6.70 (d, 1H, J=4), 3.05 (m, 4H), 2.90 (t, 2H, J=7), 2.54 (t, 2H, J=7), 1.72-1.92 (m, 2H); MS 536 (M+), 535 (M-1).

Example 4c5-(3-(Benzenesulfonyl-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 5 ^1H NMR (400 MHz, CDCl_3) δ 6.70-7.92 (m, 11H), 3.26 (m, 4H), 3.05 (m, 4H), 2.73 (m, 2H), 2.50 (m, 2H), 1.70 (m, 2H); MS 578(M+1), 576 (M-1).

Example 4d5-(3-((3-(3-Chloro-phenyl)-propyl)-phenylmethanesulfonyl-amino)-propyl)-thiophene-2-carboxylic acid

- 10 ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, 1H, J=4), 7.00-7.40 (m, 9H), 6.85 (d, 1H, J=4), 3.00 (m, 4H), 2.60 (m, 2H), 2.40 (m, 2H), 1.60-1.80 (m, 2H); MS 490 (M-1).

Example 4e5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridine-3-sulfonyl)-amino)-propyl)-furan-2-carboxylic acid

- 15 ^1H NMR (400 MHz, CDCl_3) δ 9.00 (m, 1H), 8.70 (m, 1H), 8.00 (d, 1H, J=6), 7.50 (m, 1H), 6.80-7.04 (m, 6H), 3.20 (m, 4H), 2.78 (m, 2H), 2.50 (m, 2H), 1.62-2.00 (m, 4H); MS 463 (M+1), 461 (M-1).

Example 4f5-(3-((3-(3-Chloro-phenyl)-propyl)-(naphthalene-2-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 20 ^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, 1H, J=2), 7.00-8.00 (m, 11H), 6.80 (d, 1H, J=4), 3.20 (m, 4H), 2.82 (t, 2H, J=7), 2.60 (t, 2H, J=7), 1.80-2.00 (m, 2H); MS 528.9 (M+1).

Example 4g5-(3-((3-(3-Chloro-phenyl)-propyl)-(naphthalene-1-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 25 ^1H NMR (400 MHz, CDCl_3) δ 8.60 (d, 1H, J=5), 6.95-8.22 (m, 11H), 6.70 (d, 1H, J=4), 3.20 (m, 4H), 2.40 (t, 2H, J=7), 1.72-1.95 (m, 4H); MS 528.9 (M+1).

Example 4h5-(3-((2-Acetylamino-4-methyl-thiazole-5-sulfonyl)-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid

30

¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, 1H, J=4), 7.00-7.30 (m, 4H), 3.60 (d, 1H, J=3.8), 2.80 (t, 2H, J=7.0), 2.60 (t, 2H, J=6.8), 2.40 (s, 3H), 2.30 (s, 3H), 1.70-2.00 (m, 4H); MS 556 (M+1), 554 (M-1).

Example 5

5 5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridine-3-carbonyl)-amino)-propyl)-thiophene-2-carboxylic acid

Step A: Amide formation

5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridine-3-carbonyl)-amino)-propyl)-thiophene-2-carboxylic acid methyl ester. A solution of 5-(3-(3-(3-chloro-phenyl)-propylamino)-propyl)-thiophene-2-carboxylic acid methyl ester (from Preparation 8, 0.075 g, 0.213 mmol), DCC (0.0483 g 0.234 mmol) and nicotinic acid (0.0289 g, 0.234 mmol) in 10 mL CH₂Cl₂ was stirred at room temperature overnight. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in 15 mL EtOAc and the insolubles were removed via filtration. The organic solution was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the title compound of Step A as an oil (113 mg). MS 457 (M+).

Step B: Ester Hydrolysis

Step B was performed in a manner analogous to the method of Step B of Example 4. ¹H NMR (400 MHz, CDCl₃) δ 8.60 (d, 1H, J=8), 6.80-7.70 (m, 8H), 6.60 (d, 1H, J=4), 3.25 (m, 4H), 2.80 (m, 2H), 2.45 (m, 2H), 1.60-2.05 (m, 4H); MS 443 (M+1), 441 (M-1).

Examples 5a-5b

Examples 5a-5b were prepared from the appropriate starting in a manner analogous to the method of Example 5.

Example 5a

5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridin-2-yl-acetyl)-amino)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 8.60 (m, 1H), 7.00-7.80 (m, 8H), 6.60 (m, 1H), 4.00 (s, 2H), 3.32 (m, 4H), 2.72 (m, 2H), 2.50 (m, 2H), 1.70-2.00 (m, 4H); MS 457 (M+1), 455 (M-1).

Example 5b5-(3-((3-(3-Chloro-phenyl)-propyl)-(pyridin-3-yl-acetyl)-amino)-propyl)-thiophene-2-carboxylic acid

5 ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.80 (m, 2H), 7.00-7.50 (m, 7H), 6.70 (d, 1H, J=4), 3.60 (s, 2H), 3.10-3.40 (m, 4H), 2.80 (m, 2H), 2.60 (m, 2H), 1.70-2.00 (m, 4H); MS 457 (M+1), 455 (M-1).

Example 65-(3-((2-Chloro-benzenesulfonyl)-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid

10

Step A: Amide formation

5-(3-((2-Chloro-benzenesulfonyl)-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester. A stock solution of 5-(3-(3-(3-chloro-phenyl)-propylamino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester (from Preparation 9, 0.10 g, 0.254 mmol) in 10 mL CH₂Cl₂ was prepared and 1 mL of the solution (0.010 g, 0.0254 mmol) was added to a 1 dram vial. To this was added triethylamine (0.78 mL, 0.056 mmol) and 2-chloro-benzenesulfonyl chloride (0.0059 g, 0.028 mmol). The reaction was stirred overnight at room temperature and was diluted with 2 mL CH₂Cl₂. The organic solution was washed with 3 mL of 15 5.5% aqueous HCl solution (2X) and 3 mL saturated bicarbonate solution (2X). The organic layer was dried with MgSO₄ and was concentrated to yield the title compound of Step A (10 mg). 20

Step B: Ester Hydrolysis

5-(3-((2-Chloro-benzenesulfonyl)-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid. A solution of 5-(3-((2-chloro-benzenesulfonyl)-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester prepared of Example 6, Step A (0.010 g, 0.010 mmol) in 4N HCl in 1,4 dioxane (3 mL) and the reaction was stirred overnight at room temperature. HCl (g) was bubbled in until reaction was determined to be complete by thin layer 25 chromatography. The reaction mixture was concentrated *in vacuo*. The resulting organic residue was azeotroped with CCl₄ to produce a powder (5 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 1H, J=4), 7.00-7.72 (m, 8H), 6.75 (d, 1H, J=4), 3.20- 30

3.40 (m, 4H), 2.81 (m, 2H), 2.52 (m, 2H), 1.90 (m, 2H), 1.80 (m, 2H), 1.20 (m, 2H); MS 509.9 (M-1).

Examples 6a-6j

Examples 6a-6j were prepared from the appropriate starting material in a manner
5 analogous to the method of Example 6.

Example 6a

5-(3-((3-(3-Chloro-phenyl)-propyl)-(2,5-dimethyl-benzenesulfonyl)-amino)-propyl)-
thiophene-2 carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, J=7), 7.00-7.40 (m, 7H), 6.80 (d, 1H,
10 J=4), 3.32 (m, 4H), 2.50 (s, 3H), 2.36 (s, 3H), 1.84 (m, 2H), 1.75 (m, 2H), 1.22 (m,
2H); MS 506.1 (M+1), 504.1 (M-1).

Example 6b

5-(3-((3-(3-Chloro-phenyl)-propyl)-(2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

15 ¹H NMR (400 MHz, CDCl₃) δ 6.80-7.92 (m, 9H), 3.20 (m, 4H), 2.80 (m, 2H), 1.75-
2.00 (m, 4H), 1.20 (m, 2H); MS 594.0 (M-1+Cl).

Example 6c

5-(3-((4-(2-Carboxy-benzoylamino)-butane-1-sulfonyl)-(3-(3-chloro-phenyl)-propyl)-
amino)-propyl)-thiophene-2-carboxylic acid

20 ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, J=6), 7.62 (d, 1H, J=4), 7.55 (d, 1H,
J=8), 7.45-7.20 (m, 6H), 6.80-6.90 (m, 10H), 3.22 (m, 4H), 2.70 (m, 2H), 2.60 (m,
2H), 1.80-2.00 (m, 4H), 1.22 (m, 2H); MS 620.1 (M-1).

Example 6d

5-(3-((3-(3-Chloro-phenyl)-propyl)-(4-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-
25 benzenesulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.60-7.92 (m, 4H), 6.80 (m, 7H), 3.22 (m, 4H), 2.80
(m, 2H), 2.60 (m, 2H), 1.82 (m, 2H), 1.22 (m, 2H); MS 587.1 (M-1).

Example 6e

5-(3-((3-(3-Chloro-phenyl)-propyl)-(2-methoxycarbonyl-benzenesulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 5 ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, 1H, $J=4$), 7.00-7.70 (m, 8H), 6.85 (d, 1H, $J=4$), 3.90 (s, 3H), 3.31 (m, 4H), 2.70 (m, 2H), 2.50 (m, 2H), 1.82-2.00 (m, 4H), 1.20 (m, 2H); MS 534.1 (M-1).

Example 6f

5-(3-((4-Bromo-benzenesulfonyl)-(3-(3-chloro-phenyl)-propyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 10 ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, 1H, $J=4$), 7.00-7.70 (m, 8H), 6.80 (d, 1H, $J=4$), 3.10 (m, 4H), 2.86 (m, 2H), 2.55 (m, 2H), 1.90 (m, 2H), 1.80 (m, 2H); MS 557.9 (M+1), 555.9 (M-1).

Example 6g

- 15 5-(3-((3-(3-Chloro-phenyl)-propyl)-(4-(1,1-dimethyl-propyl)-benzenesulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

^1H NMR (400 MHz, CDCl_3) δ 7.95 (d, 1H, $J=4$), 7.00-7.80 (m, 8H), 6.80 (d, 1H, $J=4$), 3.20 (m, 4H), 2.80 (m, 2H), 2.50 (m, 2H), 1.30 (s, 3H), 1.70-1.90 (m, 4H), 1.55 (m, 2H), 0.60 (t, 3H, $J=7$); MS 548 (M+1).

20

Example 6h

5-(3-((3-(3-Chloro-phenyl)-propyl)-(3,5-dimethyl-isoxazole-4-sulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 25 ^1H NMR (400 MHz, CDCl_3) δ 6.95-7.40 (m, 4H), 6.80 (d, 1H, $J=8$), 6.75 (d, 1H, $J=8$), 2.91 (m, 2H), 2.60 (s, 3H), 2.40 (m, 2H), 2.20 (s, 3H), 1.72-1.92 (m, 4H), 1.20 (m, 2H); MS 495 (M-1).

Example 6i

5-(3-((3-(3-Chloro-phenyl)-propyl)-(2,5-dimethoxy-benzenesulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 30 ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, 1H, $J=4$), 7.00-7.50 (m, 7H), 6.80 (d, 1H, $J=4$), 4.00 (s, 3H), 3.80 (s, 3H), 3.25 (m, 4H), 2.85 (m, 2H), 2.52 (m, 2H), 1.70-2.00 (m, 2H); MS 538.1 (M+1), 536.1 (M-1).

Example 6j

5-(3-((3-(3-Chloro-phenyl)-propyl)-(2-fluoro-benzenesulfonyl)-amino)-propyl)-thiophene-2-carboxylic acid

- 5 ¹H NMR (400 MHz, CDCl₃) δ 7.00-8.00 (m, 9H), 6.80 (d, 1H, J=7.2), 3.30 (m, 4H), 2.85 (m, 2H), 2.55 (m, 2H), 1.70-2.00 (m, 4H), 1.20 (m, 2H); MS 494.1 (M-1).

Example 7

5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-ethyl-ureido)-propyl)-thiophene-2-carboxylic acid

10

Step A: Isocyanate addition

- 5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-ethyl-ureido)-propyl)-thiophene-2-carboxylic acid tert-butyl ester. A stock solution of 5-(3-(3-(3-chloro-phenyl)-propylamino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester (from Preparation 9, 0.10 g, 0.254 mmol) in 10 mL CH₂Cl₂ was prepared and 1 mL (0.010 g, 0.0254 mmol) was added to a 1 dram vial. Triethylamine (0.7 mL, 0.051 mmol) and ethyl isocyanate (0.004 g, 0.051 mmol) were added and the mixture was stirred overnight at room temperature. The solution was diluted with 2 mL CH₂Cl₂. The organic solution was washed with 3 mL of 5.5% aqueous HCl solution (2X) followed by 3 mL saturated bicarbonate solution (2X). The organic layer was dried with MgSO₄ and was concentrated to yield the title compound of Step A (10 mg).

15

20

Step B: Ester Hydrolysis

- Step B was performed in a manner analogous to the method of Step B of Example 6. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, J=4), 7.00-7.40 (m, 4H), 6.80 (d, 1H, J=4), 3.20 (m, 6H), 2.80 (m, 2H), 2.60 (m, 2H), 1.80-2.00 (m, 4H), 1.05 (t, 3H, J=7); MS 409.1 (M+1), 407.1 (M-1).

25

Examples 7a-7j

Examples 7a-7j were prepared from the appropriate starting materials in a manner analogous to the method of Example 7.

Example 7a5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-isopropyl-ureido)-propyl)-thiophene-2-carboxylic acid

5 ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, 1H, $J=4$), 7.00-7.40 (m, 4H), 6.80 (d, 1H, $J=4$), 3.20 (m, 4H), 2.85 (m, 2H), 2.60 (m, 2H), 1.75-2.00 (m, 4H), 1.05 (d, 6H, $J=7$); MS 423.1 (M+1), 421.1 (M-1).

Example 7b5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-phenyl-ureido)-propyl)-thiophene-2-carboxylic acid

10 ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, 1H, $J=7$), 7.00-7.50 (m, 9H), 6.80 (d, 1H, $J=4$), 3.20 (m, 4H), 2.90 (m, 2H), 2.60 (m, 2H), 1.80-2.00 (m, 4H); MS 457.1 (M+1), 455.2 (M-1).

Example 7c5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-(3,4-dichloro-phenyl)-ureido)-propyl)-thiophene-2-carboxylic acid

15 ^1H NMR (400 MHz, CDCl_3) δ 6.80-7.60 (m, 9H), 3.20 (m, 4H), 2.90 (m, 2H), 2.60 (m, 2H), 1.86-2.00 (m, 4H); MS 527.0 (M+1), 525.0 (M-1).

Example 7d5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-propyl-ureido)-propyl)-thiophene-2-carboxylic acid

20 ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, 1H, $J=4$), 7.00-7.30 (m, 4H), 6.80 (d, 1H, $J=4$), 3.20-3.30 (m, 5H), 2.95 (t, 2H, $J=7$), 2.60 (t, 2H, $J=7$), 1.70-2.00 (m, 4H), 0.95 (t, 3H, $J=7$); MS 423 (M+1), 421 (M-1).

Example 7e5-(3-(3-(4-Chloro-phenyl)-1-(3-(3-chloro-phenyl)-propyl)-ureido)-propyl)-thiophene-2-carboxylic acid

25 ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, 1H, $J=4$), 7.00-7.30 (m, 8H), 6.80 (d, 1H, $J=4$), 3.22 (m, 4H), 2.90 (m, 2H), 2.65 (m, 2H), 1.69-2.02 (m, 4H); MS 491 (M+1), 489 (M-1).

Example 7f

5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-(2,3-dichloro-phenyl)-ureido)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.70 (bs, 1H), 7.00-7.30 (m, 7H), 6.80 (bs, 1H), 3.20 (m, 4H), 2.80 (m, 2H), 2.60 (m, 2H), 1.75-2.00 (m, 4H); MS 527 (M+1), 525.1 (M-1).

Example 7g

5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-(3,5-dichloro-phenyl)-ureido)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, J=4), 7.00-7.30 (m, 7H), 6.80 (d, 1H, J=4), 3.20 (m, 4H), 2.80 (m, 2H), 2.60 (m, 2H), 1.70-2.00 (m, 4H); MS 527.1 (M+1), 525.1 (M-1).

Example 7h

5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-(2,6-difluoro-phenyl)-ureido)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, J=4), 7.00-7.30 (m, 7H), 6.80 (d, 1H, J=4), 3.20 (m, 4H), 2.86 (m, 2H), 2.65 (m, 2H), 1.73-1.95 (m, 4H); MS 493.1 (M+1), 491.1 (M-1).

Example 7i

5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-(4-fluoro-phenyl)-ureido)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.70 (bs, 1H), 7.00-7.60 (m, 8H), 6.80 (bs, 1H), 3.30 (m, 4H), 2.90 (m, 2H), 2.60 (m, 2H), 1.80-2.00 (m, 4H); MS 475.1 (M+1), 473.1 (M-1).

Example 7j

5-(3-(3-Butyl-1-(3-(3-chloro-phenyl)-propyl)-ureido)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.70 (bs, 1H), 7.00-7.20 (m, 4H), 6.80 (bs, 1H), 3.20 (m, 6H), 2.90 (m, 2H), 2.60 (m, 2H), 1.70-2.00 (m, 4H), 0.95 (t, 3H, J=6.8); MS 437.2 (M+1), 435.2 (M-1).

Example 85-(3-((3-(3-Chloro-phenyl)-propyl)-(pyrrolidine-1-carbonyl)-amino)-propyl)-thiophene-2-carboxylic acidStep A: Amide formation

5 5-(3-(1-(3-(3-Chloro-phenyl)-propyl)-3-ethyl-ureido)-propyl)-thiophene-2-carboxylic acid tert-butyl ester. A stock solution of 5-(3-(3-(3-chloro-phenyl)-propylamino)-propyl)-thiophene-2-carboxylic acid tert-butyl ester (from Preparation 9, 0.10 g, 0.254 mmol) in 10 mL CH₂Cl₂ was prepared and 1 mL (0.010 g, 0.0254 mmol) was added to a 1 dram vial. Triethylamine (0.7 mL, 0.051 mmol) and ethyl isocyanate
10 (0.004 g, 0.051 mmol) were added and the reaction was stirred overnight at room temperature. The reaction was diluted with 2 mL CH₂Cl₂ and the organic solution was washed with 3 mL of 5.5% aqueous HCl solution (2X) followed by 3 mL saturated bicarbonate solution (2X). The organic layer was dried with MgSO₄ and concentrated to yield the title compound of Step A (10 mg).

15

Step B: Ester Hydrolysis

Step B was performed in a manner analogous to the method of Step B of Example 6. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, 1H, J=4), 7.00-7.40 (m, 4H), 6.80 (d, 1H, J=4), 3.20 (m, 8H), 2.80 (m, 2H), 2.60 (m, 2H), 1.70-2.00 (m, 8H), 1.20 (m, 4H); MS 435.1 (M+1), 433.2 (M-1).

20

Examples 8a-8c

Examples 8a-8c were prepared from the appropriate starting material in a manner analogous to the method of Example 8.

Example 8a5-(3-((3-(3-Chloro-phenyl)-propyl)-(morpholine-4-carbonyl)-amino)-propyl)-thiophene-2-carboxylic acid

25

¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, 1H, J=4), 7.00-7.40 (m, 4H), 6.80 (d, 1H, J=4), 3.60 (m, 4H), 3.00-3.20 (m, 8H), 2.80 (m, 2H), 2.60 (m, 2H), 1.70-2.00 (m, 4H); MS 451.1 (M+1), 449.2 (M-1).

Example 8b5-(3-((3-(3-Chloro-phenyl)-propyl)-isopropoxycarbonyl-amino)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 6.70 (d, 1H, J=4), 7.00-7.30 (m, 4H), 6.80 (d, 1H, J=4), 3.20 (m, 4H), 2.80 (t, 2H, J=6.7), 2.60 (t, 2H, J=6.7), 1.80-2.00 (m, 4H), 1.01 (d, 6H); MS 424 (M+1), 422 (M-1).

Example 8c5-(3-((3-(3-Chloro-phenyl)-propyl)-propoxycarbonyl-amino)-propyl)-thiophene-2-carboxylic acid

¹H NMR (400 MHz, CDCl₃) δ 7.70 (bs, 1H), 7.00-7.30 (m, 4H), 6.80 (bs, 1H), 4.00 (t, 2H, J=6.8), 3.30 (m, 4H), 2.80 (m, 2H), 2.60 (m, 2H), 1.40-2.00 (m, 6H), 0.90 (t, 3H, J=7); MS 424 (M+1), 422.2 (M-1).

Example 9(3-(((4-Butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

15

Step A: Reductive Amination

(3-((4-Butyl-benzylamino)-methyl)-phenyl)-acetic acid methyl ester. A solution of 4-butyl-benzylamine (from Preparation 15, 0.918 g, 6 mmol) in MeOH was added to 4N HCl in dioxane (0.75 mL, 3 mmol) followed by addition of (3-formyl-phenyl)-acetic acid methyl ester (from Preparation 13, 0.534 g, 3.0 mmol). NaCNBH₃ (0.194 mL, 3 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was diluted with EtOAc and 2N NaOH was added. The organic solution was dried over MgSO₄, filtered, and concentrated *in vacuo*. The product was purified via flash chromatography (50% hexanes, 50% EtOAc, 0.1% Et₃N) to afford the title compound of Step A. ¹H NMR (400 MHz, CDCl₃) δ 7.08-7.38 (m, 8H), 3.75 (s, 2H), 3.73 (s, 2H), 3.70 (s, 3H), 3.62 (s, 2H), 2.61 (t, 2H), 1.58 (m, 2H), 1.37 (m, 2H), 0.92 (t, 3H); MS 326 (M+1).

25

Step B: Amide Formation

(3-(((4-Butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid methyl ester. Step B was performed in a manner analogous to the method of Step

30

B of Example 1 to provide the title compound.

Step C: Ester Hydrolysis

(3-(((4-Butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid. Step C was performed in a manner analogous to the method of Step C of Example 1 to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.99 (bs, 1H), 8.74 (bs, 1H), 7.99 (d, 1H), 7.36 (bs, 1H), 7.20-7.25 (m, 2H), 6.95-7.19 (m, 6H), 4.33 (s, 4H), 3.3.54 (s, 2H), 2.54 (m, 2H), 1.54 (m, 2H), 1.32 (m, 2H), 0.91 (t, 3H).

Examples 9a-9d

Examples 9a-9d were prepared from the appropriate starting materials in a manner analogous to the method of Example 9.

10

Example 9a(3-((Benzenesulfonyl-(4-butyl-benzyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, 2H), 7.46-7.58 (m, 3H), 7.24 (s, 1H), 7.14 (m, 2H), 6.86-6.98 (m, 5H), 4.29 (d, 4H), 3.51 (s, 2H), 2.52 (t, 2H), 1.53 (m, 2H), 1.30 (m, 2H), 0.90 (t, 2H); MS 450 (M-1).

15

Example 9b(3-(((4-Butyl-benzyl)-(thiophene-2-sulfonyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 7.53 (m, 2H), 7.16 (m, 2H), 6.89-7.14 (m, 7H), 4.27 (d, 4H), 3.52 (s, 2H), 2.49 (t, 2H), 1.51 (m, 2H), 1.29 (m, 2H), 0.88 (t, 2H); MS 456 (M-1).

20

Example 9c(3-(((4-Acetylamino-benzenesulfonyl)-(4-butyl-benzyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 7.69 (m, 2H), 7.49 (d, 2H), 7.06-7.23 (m, 6H), 6.91 (d, 1H), 6.68 (s, 1H), 4.30 (d, 4H), 3.44 (s, 2H), 2.54 (t, 2H), 2.17 (s, 3H), 1.54 (m, 2H), 1.29 (m, 2H), 0.89 (t, 2H); MS 507(M-1).

25

Example 9d(3-(((Benzo[1,2,5]oxadiazole-4-sulfonyl)-(4-butyl-benzyl)-amino)-methyl)-phenyl)-acetic acid

¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, 1H), 7.88 (d, 2H), 7.36 (t, 1H), 7.07 (s, 2H), 6.90-6.96 (m, 6H), 5.3 (d, 4H), 3.46 (s, 2H), 2.46 (t, 2H), 1.47 (m, 2H), 1.26 (m, 2H), 0.88 (t, 2H); MS 4.92 (M-1).

30

Example 10

(3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•HCl

Step A: Reductive Amination

- 5 (3-((4-Pyrimidin-2-yl-benzylamino)-methyl)-phenoxy)-acetic acid t-butyl ester. Step A was performed in a manner analogous to the method of Step A of Example 1.

Step B: Amide Formation

- (3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid tert-butyl ester. Step B was performed in a manner
10 analogous to the method of Step B of Example 1 using triethylamine in place of N,N-diisopropylethylamine as base.

Step C: Ester Hydrolysis

- (3-(((1-Methyl-1H-imidazole-4-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid•HCl. A solution of (3-(((1-methyl-1H-imidazole-4-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid tert-butyl ester
15 prepared of Example 10, Step B (0.094 g, 0.17 mmol) in 1N HCl in diethyl ether was stirred for 20 minutes as a precipitate formed. To the mixture was added 1 mL water and 1 mL dioxane and the reaction was stirred for 3 hours. The solvent was removed *in vacuo*, azeotroping with ethanol to yield the title compound as a
20 solid (54 mg). ¹H NMR (400 MHz, CD₃OD) δ 9.09 (m, 2H), 8.95 (bs, 1H), 8.24 (d, 2H), 8.04 (s, 1H), 7.71 (s, 1H), 7.44 (d, 2H), 7.13 (m, 1H), 6.82 (d, 1H), 6.76 (d, 1H), 6.69 (s, 1H), 4.61 (s, 2H), 4.54 (s, 2H), 4.46 (s, 2H), 3.92 (s, 3H); MS 494 (M+1).

Examples 11a-11z, 12a-12z

- 25 Examples 11a-11z, 12a-12z were prepared from the appropriate starting materials in a manner analogous to the method of Example 1, with variations in reaction time, temperature, and reagents as noted.

Example 11a

- 3-(3-[[Benzenesulfonyl-(4-pyrazin-2-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid
30

Step A: Reductive Amination

- 3-{3-[(4-Pyrazin-2-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester.
The title compound of Step A was prepared from 3-(3-aminomethyl-phenyl)-

propionic acid methyl ester hydrochloride salt, of Preparation 44, and 4-pyrazin-2-yl-benzaldehyde, of Preparation 27, using the method described in Example 1, Step A except the imine was formed in MeOH at reflux over 2 h. ¹H NMR (400 MHz, CDCl₃) δ 9.01 (s, 1H), 8.62 (dd, 1H), 8.49 (d, 1H), 7.98 (d, 2H), 7.66 (m, 1H), 7.54-7.43 (m, 3H), 7.24 (m, 1H), 7.09 (m, 1H), 3.88 (s, 2H), 3.80 (s, 2H), 3.66 (s, 3H), 2.94 (t, 2H), 2.63 (t, 2H); MS 362 (M+1).

Step B: Amide Formation

3-(3-[[Benzenesulfonyl-(4-pyrazin-2-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid methyl ester. The title compound of Step B was prepared from 3-{3-[(4-pyrazin-2-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester, of Step A, and benzenesulfonyl chloride following the method described in Example 1, Step B using triethylamine in place of N,N-diisopropylethylamine. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.60 (m, 1H), 8.50 (d, 1H), 7.87 (m, 4H), 7.63 (m, 1H), 7.56 (m, 2H), 7.17 (d, 2H), 7.12 (m, 1H), 7.02 (d, 1H), 6.87 (d, 1H), 6.78 (s, 1H), 4.37 (s, 2H), 4.32 (s, 2H), 3.64 (s, 3H), 2.78 (t, 2H), 2.47 (t, 2H); MS 502 (M+1).

Step C: Ester Hydrolysis

3-(3-[[Benzenesulfonyl-(4-pyrazin-2-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid. The title compound was prepared following the method described in Example 1, Step C from 3-(3-[[benzenesulfonyl-(4-pyrazin-2-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid methyl ester of Step B. MS 486 (M-1).

Example 11b

3-(3-[[Benzenesulfonyl-(4-pyridin-3-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid

Step A: Reductive Amination

3-{3-[(4-Pyridin-3-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester. The title compound of Step A was prepared from 3-(3-aminomethyl-phenyl)-propionic acid methyl ester hydrochloride salt, of Preparation 44, and 4-pyridin-3-yl-benzaldehyde, of Preparation 23, using the method described in Example 1, Step A. ¹H NMR (400 MHz, CDCl₃) δ 8.81 (d, 1H), 8.55 (dd, 1H), 7.84 (m, 1H), 7.53 (d, 2H), 7.44 (d, 2H), 7.33 (m, 1H), 7.26-7.18 (m, 3H), 7.07 (d, 1H), 3.84 (s, 2H), 3.79 (s, 2H), 3.64 (s, 3H), 2.92 (t, 2H), 2.61 (t, 2H); MS 361 (M+1).

Step B: Amide Formation

3-(3-[[Benzenesulfonyl-(4-pyridin-3-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid methyl ester. The title compound of Step B was prepared from 3-{3-[(4-pyridin-3-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester, of Step A, and benzenesulfonyl chloride following the method described in Example 1, Step B using triethylamine in place of N,N-diisopropylethylamine. ¹H NMR (400 MHz, CDCl₃) δ 8.79 (s, 1H), 8.58 (d, 1H), 7.87 (m, 3H), 7.61 (m, 1H), 7.54 (m, 2H), 7.40 (m, 3H), 7.18 (m, 3H), 7.03 (d, 1H), 6.88 (d, 1H), 6.79 (s, 1H), 4.36 (s, 2H), 4.33 (s, 2H), 3.65 (s, 3H), 2.79 (t, 2H), 2.48 (t, 2H); MS 501 (M+1).

Step C: Ester Hydrolysis

3-(3-[[Benzenesulfonyl-(4-pyridin-3-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid. The title compound was prepared following the method described in Example 1, Step C from 3-(3-[[benzenesulfonyl-(4-pyridin-3-yl-benzyl)-amino]-methyl]-phenyl)-propionic acid methyl ester of Step B. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.63 (d, 1H), 8.46 (d, 1H), 7.90 (m, 3H), 7.63 (m, 3H), 7.40 (d, 2H), 7.22 (m, 2H), 6.91 (m, 3H), 6.75 (d, 1H), 4.36 (s, 2H), 4.27 (s, 2H), 2.81 (t, 2H), 2.56 (t, 2H); MS 485 (M-1).

Example 11c

20 7-[(Pyridine-2-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-heptanoic acid

Step A: Reductive Amination

7-(4-Thiazol-2-yl-benzylamino)-heptanoic acid methyl ester. The title compound was prepared following the procedure described in Step A of Example 1 from 7-amino-heptanoic acid methyl ester hydrochloride, of Preparation 1, and 4-thiazol-2-yl-benzaldehyde, of Preparation 25. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, 2H), 7.84 (d, 1H), 7.38 (d, 2H), 7.30 (d, 1H), 3.82 (s, 2H), 3.65 (s, 3H), 2.62 (t, 2H), 2.29 (t, 2H), 1.61 (m, 2H), 1.51 (m, 2H), 1.33 (m, 4H); MS 333 (M+1).

Step B: Sulfonamide Formation

30 7-[(Pyridine-2-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-heptanoic acid methyl ester. The title compound of Step B was prepared following the procedure described in Step B of Example 1 from 7-(4-thiazol-2-yl-benzylamino)-heptanoic acid methyl ester, of Step A and pyridine-2-sulfonyl chloride hydrochloride, of Preparation 47. ¹H NMR (400 MHz, CDCl₃) δ 9.06 (d, 1H), 8.81 (m, 1H), 8.10 (m, 1H), 7.91 (d, 2H),

7.86 (m, 1H), 7.46 (m, 1H), 7.34 (m, 3H), 4.39 (s, 2H), 3.62 (s, 3H), 3.15 (t, 2H), 2.21 (t, 2H), 1.48 (m, 2H), 1.37 (m, 2H), 1.15 (m, 4H); MS 474 (M+1).

Step C: Ester Hydrolysis

5 7-[(Pyridine-2-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-heptanoic acid: The title compound was prepared following the procedure described in Step C of Example 1 from 7-[(pyridine-2-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-heptanoic acid methyl ester, of Step B. ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H), 8.81 (m, 1H), 8.11 (m, 1H), 7.87 (m, 3H), 7.48 (m, 1H), 7.37 (m, 3H), 4.37 (s, 2H), 3.14 (t, 2H), 2.23 (t, 2H), 1.51 (m, 2H), 1.48 (m, 2H), 1.13 (m, 4H).

10

Example 11d

(3-[(4-Butyl-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-methyl)-phenyl)-acetic acid

Step A: Amide Formation

15 (3-[(4-Butyl-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-methyl)-phenyl)-acetic acid methyl ester. The title compound of Step B was prepared following the procedure described in Step B of Example 1 from {3-[(4-butyl-benzylamino)-methyl]-phenyl}-acetic acid methyl ester, prepared in Step A of Example 9, and 1-methyl-1H-imidazole-4-sulfonyl chloride. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (s, 1H), 7.34 (s, 1H), 7.18-7.02 (m, 8H), 4.38 (s, 4H), 3.71 (s, 3H), 3.68 (s, 3H), 3.52 (s, 20 2H), 2.55 (t, 2H), 1.55 (m, 2H), 1.32 (m, 2H), 0.91 (t, 3H); MS 470 (M+1).

Step B: Ester Hydrolysis

25 (3-[(4-Butyl-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-methyl)-phenyl)-acetic acid. The title compound was prepared following the procedure described in Step C of Example 1 from (3-[(4-butyl-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-methyl)-phenyl)-acetic acid methyl ester of Step A. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (s, 1H), 7.28 (s, 1H), 7.15-6.99 (m, 8H), 4.36 (s, 2H), 4.33 (s, 2H), 3.65 (s, 3H), 3.52 (s, 2H), 2.54 (t, 2H), 1.54 (m, 2H), 1.32 (m, 2H), 0.91 (t, 3H); MS 454 (M-1).

Example 11e3-(3-[(1-Methyl-1H-imidazole-4-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-methyl)-phenyl)-propionic acid

5

Step A: Reductive Amination3-{3-[(4-Thiazol-2-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester.

The title compound of Step A was prepared from 3-(3-aminomethyl-phenyl)-propionic acid methyl ester hydrochloride salt, of Preparation 44, and 4-thiazol-2-yl-benzaldehyde, of Preparation 25, using the method described in Example 1, Step A, except the imine was formed in MeOH at reflux over 2 h. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, 2H), 7.85 (d, 1H), 7.43 (d, 2H), 7.31 (d, 1H), 7.28-7.09 (m, 4H), 3.84 (s, 2H), 3.79 (s, 2H), 3.66 (s, 3H), 2.94 (t, 2H), 2.63 (t, 2H); MS 367 (M+1).

10

Step B: Amide Formation

15

3-(3-[(1-Methyl-1H-imidazole-4-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-methyl)-phenyl)-propionic acid methyl ester. The title compound of Step B was prepared from 3-{3-[(4-thiazol-2-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester, of Step A, and 1-methyl-1H-imidazole-4-sulfonyl chloride following the method described in Example 1, Step B. MS 511 (M+1).

20

Step C: Ester Hydrolysis

3-(3-[(1-Methyl-1H-imidazole-4-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-methyl)-phenyl)-propionic acid. The title compound was prepared following the method described in Example 1, Step C from 3-(3-[(1-methyl-1H-imidazole-4-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-methyl)-phenyl)-propionic acid methyl ester of Step B. ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, 2H), 7.69 (d, 2H), 7.59 (s, 1H), 7.46 (s, 1H), 7.36 (m, 1H), 7.19 (d, 2H), 7.15-6.99 (m, 3H), 6.88 (s, 1H), 4.46 (s, 2H), 4.37 (s, 2H), 3.76 (s, 3H), 2.80 (t, 2H), 2.50 (t, 2H); MS 495 (M-1).

25

Example 11f7-[(4-Pyrazol-1-yl-benzyl)-(pyridine-2-sulfonyl)-amino]-heptanoic acid

30

Step A: Reductive Amination

7-(4-Pyrazol-1-yl-benzylamino)-heptanoic acid methyl ester. The title compound of Step A was prepared from 7-amino-heptanoic acid methyl ester hydrochloride, of Preparation 1, and 4-pyrazol-1-yl-benzaldehyde, of Preparation 42, using the

method described in Example 1, Step A. ¹H NMR (400 MHz, CDCl₃) δ 7.90 (m, 1H), 7.70 (d, 1H), 7.63 (d, 2H), 7.39 (d, 2H), 6.45 (m, 1H), 3.80 (s, 2H), 3.65 (s, 3H), 2.61 (t, 2H), 2.29 (t, 2H), 1.63-1.32 (m, 4H), 1.25 (m, 4H); MS 316 (M+1).

Step B: Amide Formation

5 7-[(4-Pyrazol-1-yl-benzyl)-(pyridine-2-sulfonyl)-amino]-heptanoic acid methyl ester.

The title compound of Step B was prepared from 7-(4-pyrazol-1-yl-benzylamino)-heptanoic acid methyl ester, of Step A, and pyridine-2-sulfonyl chloride hydrochloride, of Preparation 47, following the method described in Example 1, Step B using triethylamine in place of N,N-diisopropylethylamine. ¹H NMR (400
10 MHz, CDCl₃) δ 9.06 (m, 1H), 8.80 (dd, 1H), 8.10 (m, 1H), 7.92 (d, 1H), 7.71 (d, 1H), 7.65 (d, 2H), 7.48 (m, 1H), 7.36 (d, 2H), 6.46 (d, 1H), 4.38 (s, 2H), 3.62 (s, 3H), 3.14 (t, 2H), 2.21 (t, 2H), 1.48 (m, 2H), 1.36 (m, 2H), 1.25 (m, 4H); MS 457 (M+1).

Step C: Ester Hydrolysis

15 7-[(4-Pyrazol-1-yl-benzyl)-(pyridine-2-sulfonyl)-amino]-heptanoic acid. The title compound was prepared following the method described in Example 1, Step C, from 7-[(4-pyrazol-1-yl-benzyl)-(pyridine-2-sulfonyl)-amino]-heptanoic acid methyl ester of Step B. ¹H NMR (400 MHz, CDCl₃) δ 9.07 (d, 1H), 8.82 (dd, 1H), 8.12 (m, 1H), 7.88 (d, 1H), 7.74 (d, 1H), 7.62 (d, 2H), 7.48 (m, 1H), 7.41 (d, 2H), 6.48 (m,
20 1H), 4.35 (s, 2H), 3.13 (t, 2H), 2.22 (t, 2H), 1.47 (m, 2H), 1.32 (m, 2H), 1.17 (m, 4H); MS 441 (M-1).

Example 11g

7-[(4-Pyrazol-1-yl-benzyl)-(pyridine-3-sulfonyl)-amino]-heptanoic acid

Step A: Amide Formation

25 7-[(4-Pyrazol-1-yl-benzyl)-(pyridine-3-sulfonyl)-amino]-heptanoic acid methyl ester.

The title compound of Step A was prepared from 7-(4-pyrazol-1-yl-benzylamino)-heptanoic acid methyl ester, of Example 11f, Step A, and pyridine-3-sulfonyl chloride hydrochloride, of Preparation 2, following the method described in Example 1, Step B using triethylamine in place of N,N-diisopropylethylamine. ¹H
30 NMR (400 MHz, CDCl₃) δ 8.70 (m, 1H), 7.99-7.87 (m, 3H), 7.71 (d, 1H), 7.63 (d, 2H), 7.46 (m, 1H), 7.42 (d, 2H), 6.46 (dd, 1H), 4.56 (s, 2H), 3.62 (s, 3H), 3.25 (t, 2H), 2.20 (t, 2H), 1.46 (m, 2H), 1.34 (m, 2H), 1.25 (m, 4H); MS 457 (M+1).

Step B: Ester Hydrolysis

7-[(4-Pyrazol-1-yl-benzyl)-(pyridine-3-sulfonyl)-amino]-heptanoic acid. The title compound was prepared following the method described in Example 1, Step C, from 7-[(4-pyrazol-1-yl-benzyl)-(pyridine-3-sulfonyl)-amino]-heptanoic acid methyl ester of Step B. ¹H NMR (400 MHz, CDCl₃) δ 8.71 (m, 1H), 7.99 (d, 1H), 7.90 (m, 2H), 7.74 (d, 1H), 7.60 (d, 2H), 7.48 (m, 3H), 6.47 (m, 1H), 4.56 (s, 2H), 3.24 (t, 2H), 2.20 (t, 2H), 1.46 (m, 2H), 1.29 (m, 2H), 1.12 (m, 2H), 1.05 (m, 2H); MS 441 (M-1).

Example 11h

3-(3-{[Benzenesulfonyl-(4-pyrazol-1-yl-benzyl)-amino]-methyl}-phenyl)-propionic acid

Step A: Reductive Amination

3-{3-[(4-Pyrazol-1-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester.

The title compound of Step A was prepared from 3-(3-aminomethyl-phenyl)-propionic acid methyl ester hydrochloride salt, of Preparation 44, and 4-pyrazol-1-yl-benzaldehyde, of Preparation 42, using the method described in Example 1, Step A except the imine was formed in MeOH at reflux over 2 h. ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 1H), 7.44 (d, 2H), 7.32 (d, 2H), 7.24 (m, 2H), 7.17 (m, 3H), 7.07 (d, 1H), 3.82 (s, 2H), 3.77 (s, 2H), 3.64 (s, 3H), 2.92 (t, 2H), 2.61 (t, 2H); MS 350 (M+1).

Step B: Amide Formation

3-(3-{[Benzenesulfonyl-(4-pyrazol-1-yl-benzyl)-amino]-methyl}-phenyl)-propionic acid methyl ester. The title compound of Step B was prepared from 3-{3-[(4-

pyrazol-1-yl-benzylamino)-methyl]-phenyl}-propionic acid methyl ester of Step A and benzenesulfonyl chloride following the method described in Example 1, Step B using triethylamine in place of N,N-diisopropylethylamine. ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, 2H), 7.84 (s, 1H), 7.64-7.53 (m, 3H), 7.20 (m, 5H), 7.11 (m, 1H), 7.02 (d, 1H), 6.84 (d, 1H), 6.78 (d, 1H), 4.33 (s, 2H), 4.31 (s, 2H), 3.65 (s, 3H), 2.78 (t, 2H), 2.47 (t, 2H); MS 490 (M+1).

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

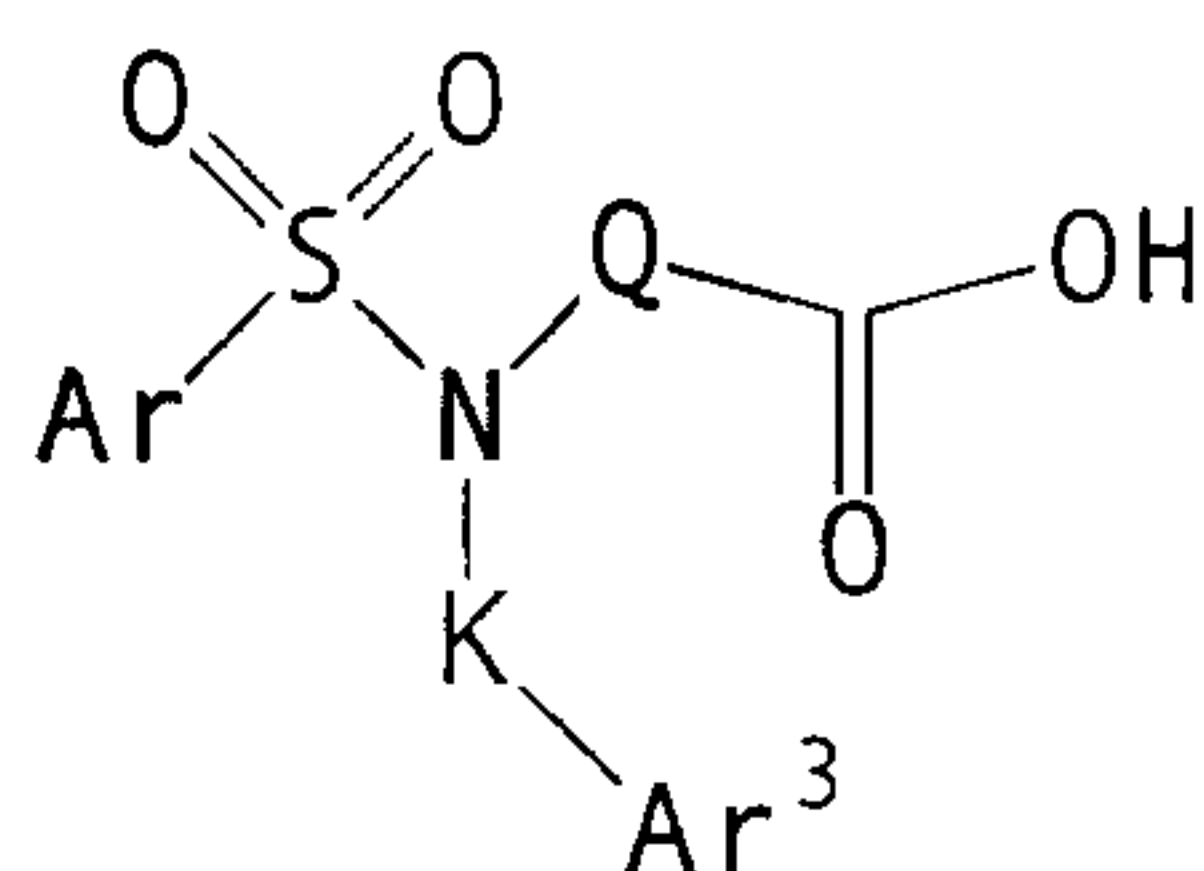
NOTE: For additional volumes please contact the Canadian Patent Office.

72222-402

-225-

CLAIMS:

1. A compound of the Formula:



wherein:

Q is $-(C_0-C_4)$ alkylene-X-W- (C_1-C_3) alkylene-, the alkylenes each optionally substituted with up to four substituents each independently selected from fluoro and (C_1-C_4) alkyl,

K is a bond, (C_1-C_9) alkylene, thio (C_1-C_4) alkylene, (C_1-C_4) alkylenethio (C_1-C_4) alkylene, (C_1-C_4) alkyleneoxy (C_1-C_4) alkylene or oxy (C_1-C_4) alkylene, the (C_1-C_9) alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

72222-402

-226-

nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully

5 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar

10 is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,

15 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

20 tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or

25 di-N,N- (C_1-C_4) alkylaminosulfinyl;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting

30 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and

72222-402

-227-

oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from

5 nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if

10 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,

15 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

20 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

25 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,

30 N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or

72222-402

-228-

-mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

X is a five or six membered aromatic ring
 5 optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

10 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

with the proviso that when K is (C₂-C₄)alkylene and
 15 Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl then Ar³ is not substituted at the one position with hydroxy;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1, wherein Ar is
 20 phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrimidinyl, pyrazinyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2H-imidazolyl, 2-imidazolinyl,
 25 imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 2H-pyranyl, 4H-pyranyl, pyridyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl,
 30 thiomorpholinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, azepinyl, oxepinyl, thiepinyl,

72222-402

-229-

cyclopentenyl, cyclohexenyl, benzo(b)thienyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl or 1,4-benzodioxan,
 5 and wherein Ar is optionally substituted on carbon or nitrogen independently with up to three substituents independently selected from R³, R⁴ and R⁵ and Ar is optionally substituted independently on carbon or sulfur with one or two oxo groups.

10 3. The compound or salt of claim 1 or 2, wherein, Ar³ is cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl,
 15 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2H-imidazolyl, 2-imidazolyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 2H-pyranyl, 4H-pyranyl,
 20 pyridyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinylpiperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, azepinyl, oxepinyl, thiepinyl, 1,2,4-diazepinyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclooctadienyl, indolizinyl,
 25 indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl,
 30 quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, 1,3-benzodioxolyl,

72222-402

-230-

2,3-dihydrobenzofuranyl, 1,4-benzodioxan,
pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl,
pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl,
2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl,
5 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl or
4H-1,4-benzoxazinyl, and wherein Ar³ is optionally
substituted on carbon or nitrogen independently with up to
three R³¹, R⁴¹ and R⁵¹ groups and Ar³ is optionally substituted
independently on carbon or sulfur with one or two oxo
10 groups.

4. The compound or salt of any one of claims 1 to 3,
wherein X is tetrahydrofuranyl, phenyl, thiazolyl, thienyl,
pyridyl, pyrazolyl, furanyl or pyrimidyl, wherein X is
optionally mono-, di- or tri-substituted with chloro,
15 fluoro, methoxy, difluoromethoxy, trifluoromethoxy,
trifluoromethyl or methyl.

5. The compound or salt of any one of claims 1 to 4,
wherein Ar is phenyl, pyridazinyl, pyrazolyl, pyrazinyl,
pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, and Ar
20 is optionally mono-, di- or tri-substituted with R³, R⁴ or
R⁵.

6. The compound or salt of any one of claims 1 to 5,
wherein Ar is phenyl, pyridyl or imidazolyl, the phenyl,
pyridyl and imidazolyl optionally substituted independently
25 with chloro, fluoro, methyl, methoxy, difluoromethoxy,
trifluoromethyl or trifluoromethoxy.

7. The compound or salt of any one of claims 1 to 6,
wherein Ar is phenyl, pyridyl or imidazolyl, and is
optionally mono-, di- or tri-substituted on carbon or
30 nitrogen independently with chloro, fluoro, methyl, methoxy,
difluoromethoxy, trifluoromethyl or trifluoromethoxy.

72222-402

-231-

8. The compound or salt of any one of claims 1 to 7, wherein Ar is pyrid-3-yl.

9. The compound or salt of any one of claims 1 to 7, wherein Ar is phenyl.

5 10. The compound or salt of any one of claims 1 to 7, wherein Ar is 4-(1-methyl-imidazolyl).

11. The compound or salt of any one of claims 1 to 7, wherein Ar is 4-chloro-phenyl.

12. The compound or salt of any one of claims 1 to 7,
10 wherein Ar is 2-thiazolyl.

13. The compound or salt of any one of claims 1 to 12, wherein Ar³ is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl,
15 isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R³¹, chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy.

14. The compound or salt of any one of claims 1 to 13,
20 wherein Ar³ is phenyl substituted with R³¹, wherein R³¹ is (C₁-C₇)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylamine, or (C₁-C₅)alkoxy, the (C₁-C₇)alkyl or (C₁-C₅)alkoxy optionally mono-, di- or tri-substituted with independently hydroxy or fluoro; and Ar³ is further optionally mono- or di-substituted
25 with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

15. The compound or salt of any one of claims 1 to 14, wherein Ar³ is phenyl substituted at the 4-position with n-butyl.

72222-402

-232-

16. The compound or salt of any one of claims 1 to 14, wherein Ar³ is phenyl substituted at the 4-position with dimethylamino.

17. The compound or salt of any one of claims 1 to 14,
5 wherein Ar³ is phenyl substituted at the 4-position with *tert*-butyl.

18. The compound or salt of any one of claims 1 to 14, wherein Ar³ is phenyl optionally substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy
10 or trifluoromethyl.

19. The compound or salt of any one of claims 1 to 14, wherein Ar³ is phenyl 3,5-disubstituted with chloro.

20. The compound or salt of any one of claims 1 to 14, wherein Ar³ is phenyl.

15 21. The compound or salt of any one of claims 1 to 13, wherein Ar³ is pyridyl.

22. The compound or salt of any one of claims 1 to 13, wherein Ar³ is 6-(1,4-benzodioxan).

23. The compound or salt of any one of claims 1 to 13,
20 wherein Ar³ is 2-benzofuryl.

24. The compound or salt of any one of claims 1 to 23, wherein W is oxy.

25. The compound or salt of any one of claims 1 to 24, wherein Q is -CH₂-X-O-CH₂-.

25 26. The compound or salt of any one of claims 1 to 25, wherein X is phenyl, pyridyl, pyrimidyl, thienyl, furanyl or thiazolyl, wherein X is optionally mono-, di- or tri-

72222-402

-233-

substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

27. The compound or salt of any one of claims 1 to 26, wherein X is phenyl optionally mono-, di- or tri-substituted
5 with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

28. The compound or salt of any one of claims 1 to 27, wherein X is metaphenylene optionally mono-, di- or tri-substituted with chloro, fluoro, methoxy, difluoromethoxy,
10 trifluoromethoxy, trifluoromethyl or methyl.

29. The compound or salt of any one of claims 1 to 28, wherein X is metaphenylene.

30. The compound or salt of any one of claims 1 to 26, wherein X is furanyl, thienyl or thiazolyl.

15 31. The compound or salt of any one of claims 1 to 30, wherein K is (C₂-C₄)alkylene or n-propenylene.

32. The compound or salt of any one of claims 1 to 31, wherein K is *trans*-n-propenylene.

33. The compound or salt of any one of claims 1 to 30,
20 wherein K is methylenyl, propylenyl, propenylenyl or oxyethylenyl.

34. The compound or salt of any one of claims 1 to 30, wherein K is ethylenyloxy, the Ar³ group being attached to the oxygen atom of the ethylenyloxy group and the N atom
25 being attached to the 2-position of the ethylenyloxy group.

35. The compound or salt of any one of claims 1 to 30, wherein K is thioethylene or oxyethylene, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

72222-402

-234-

36. The compound or salt of any one of claims 1 to 30, wherein K is methylene.

37. The compound (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid, or a
5 pharmaceutically acceptable salt thereof.

38. The compound (3-(((4-dimethylamino-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid.

39. The compound (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid.

10 40. The compound (3-(((2-(3,5-dichloro-phenoxy)-ethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid.

41. The compound (3-{[(4-chloro-benzenesulfonyl)-(4-thiazol-2-yl-benzyl)-amino]-methyl}-phenoxy)-acetic acid.

15 42. The compound (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid sodium salt.

43. A pharmaceutical composition for treating a vertebrate having a condition which presents with low bone mass, which comprises (a) a therapeutically effective amount
20 of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42, and (b) a pharmaceutically acceptable carrier or diluent.

44. The pharmaceutical composition of claim 43,
25 wherein the condition is osteoporosis, osteotomy, childhood idiopathic bone loss or bone loss associated with periodontitis.

45. The pharmaceutical composition of claim 44, wherein osteoporosis is in a human.

72222+402 '

-235-

46. The pharmaceutical composition of claim 45, wherein the osteoporosis is glucocorticoid-induced osteoporosis, hyperthyroidism-induced osteoporosis, immobilization-induced osteoporosis, heparin-induced
5 osteoporosis or immunosuppressive-induced osteoporosis.

47. A pharmaceutical composition for augmenting and maintaining bone mass in a vertebrate, which comprises (a) a therapeutically effective amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt
10 thereof or the compound of claim 42, and (b) a pharmaceutically acceptable carrier or diluent.

48. The pharmaceutical composition of claim 47, for bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction, for inducing
15 vertebral synostosis, for enhancing long bone extension, for enhancing the healing rate of a bone graft or for enhancing prosthetic ingrowth.

49. The pharmaceutical composition of claim 47, for treating a bone fracture in a human.

20 50. A pharmaceutical composition which comprises (a) the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42, and (b) a pharmaceutically acceptable carrier or diluent.

25 51. The pharmaceutical composition of claim 50, for the treatment of osteoporosis.

52. The pharmaceutical composition of claim 50, for the augmentation of bone mass.

53. The pharmaceutical composition of claim 50, for
30 the treatment of a bone fracture.

72222-402

-236-

54. The pharmaceutical composition of claim 50, for the treatment of a condition which presents with low bone mass in a human.

55. A pharmaceutical composition comprising:

5 (a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42;

(b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the
10 agent or the prodrug; and

(c) a pharmaceutical carrier or diluent.

56. The pharmaceutical composition of claim 55, wherein the anti-resorptive agent is droloxifene; raloxifene; tamoxifen; 4-hydroxy-tamoxifen; toremifene;
15 centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalene-2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone;
20 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid;

2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;
25

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

72222-402

-237-

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

5 1-(4'-pyrrolidonoethoxyphenyl)-2-(4''-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; or

10 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

57. The pharmaceutical composition of claim 55, wherein the anti-resorptive agent is tiludronic acid, alendronic acid, zoledronic acid, ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

58. A pharmaceutical composition for treating a vertebrate having a condition which presents with low bone mass, which comprises:

(a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42; and

25 (b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

59. The pharmaceutical composition of claim 58, wherein the anti-resorptive agent is droloxifene;

72222-402

-238-

raloxifene; tamoxifen; 4-hydroxy-tamoxifen; toremifene;
centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-
phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-
naphthalene-2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-
ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-
benzo[b]thiophen-3-yl)-methanone;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic
acid;

2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-
ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-
ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-
phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-
phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-
6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-
(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-
ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-
1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or a
pharmaceutically acceptable salt of the agent or the
prodrug.

60. A pharmaceutical composition of claim 58, wherein
the anti-resorptive agent is tiludronic acid, alendronic

72222-402

-239-

acid, zoledronic acid, ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

5 61. A kit comprising:

(a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof and the compound of claim 42 in a first unit dosage form;

10 (b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and

(c) container means for containing the first and second dosage forms.

15 62. The kit of claim 61, wherein the anti-resorptive agent is droloxifene; raloxifene; tamoxifen; 4-hydroxy-tamoxifen; toremifene; centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalene-2-ol; (4-(2-(2-aza-

20 bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid;

25 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

72222-402

-240-

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis--1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

5 1-(4'-pyrrolidonoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; or

10 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

63. The kit of claim 61, wherein the anti-resorptive agent is tiludronic acid, alendronic acid, zoledronic acid, 15 ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

64. The kit of any one of claims 61 to 63 further 20 comprising a written matter describing instructions for the use of components (a) and (b) for treating a vertebrate having a condition which presents with low bone mass or for augmenting and maintaining bone mass in a vertebrate.

65. A pharmaceutical composition comprising:

25 (a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42;

72222-402

-241-

(b) an amount of another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug; and

(c) a pharmaceutical carrier or diluent.

5 66. The pharmaceutical composition of claim 65, wherein the bone anabolic agent in component (b) is IGF-1, bone morphogenetic protein, prostaglandin, a prostaglandin agonist/antagonist, sodium fluoride, parathyroid hormone (PTH), an active fragment or fragments of parathyroid
10 hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

67. A pharmaceutical composition for treating a mammal which presents with low bone mass, which composition
15 comprises:

(a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42; and

(b) an amount of another bone anabolic agent, a
20 prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

68. The pharmaceutical composition of claim 67, wherein the bone anabolic agent in component b is IGF-1, a bone morphogenetic protein, a prostaglandin, a prostaglandin
25 agonist/antagonist, sodium fluoride, parathyroid hormone (PTH), an active fragment or fragments of parathyroid hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

72222-402

-242-

69. A pharmaceutical composition for treating a mammal which presents with kidney degeneration, which comprises:

(a) a kidney regenerating effective amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42, and

(b) a pharmaceutically acceptable carrier or diluent.

70. A kit comprising:

(a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42 in a first unit dosage form;

(b) an amount of another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug in a second unit dosage form; and

(c) container means for containing the first and second dosage forms.

71. The kit of claim 70, wherein the bone anabolic agent in component (b) is IGF-1, bone morphogenetic protein, a prostaglandin, a prostaglandin agonist/antagonist, sodium fluoride, parathyroid hormone (PTH), an active fragment or fragments of parathyroid hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

72. The kit of claim 70 or 71 further comprising a written matter describing instructions for the use of components (a) and (b) for treating a mammal which presents with low bone mass or for augmenting and maintaining bone mass in a vertebrate.

72222-402

-243-

73. A pharmaceutical composition for augmenting and maintaining bone mass in a vertebrate, which comprises:

(a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof
5 or the compound of claim 42; and

(b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

74. The pharmaceutical composition of claim 73,
10 wherein the anti-resorptive agent is droloxifene;
raloxifene; tamoxifen; 4-hydroxy-tamoxifen; toremifene;
centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-
phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-
naphthalene-2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-
15 ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-
benzo[b]thiophen-3-yl)-methanone;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic
acid;

2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-
20 ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-
ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-
phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

25 *cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-
phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-
6-hydroxy-1,2,3,4-tetrahydronaphthalene;

72222-402

-244-

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; or

5 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

75. The pharmaceutical composition of claim 73,
10 wherein the anti-resorptive agent is, tiludronic acid, alendronic acid, zoledronic acid, ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

15 76. A pharmaceutical composition for augmenting and maintaining bone mass in a vertebrate, which comprises:

(a) an amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42; and

20 (b) an amount of another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

77. A pharmaceutical composition of claim 76, wherein the bone anabolic agent in component b is IGF-1, bone
25 morphogenetic protein, a prostaglandin, a prostaglandin agonist/antagonist, sodium fluoride, parathyroid hormone (PTH), an active fragment or fragments of parathyroid hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a pharmaceutically acceptable salt of
30 the agent or the prodrug.

72222-402

-245-

78. A pharmaceutical composition for treating glaucoma in a mammal suffering from glaucoma, which comprises:

(a) a therapeutically effective amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42, and

(b) a pharmaceutically acceptable carrier or diluent.

79. A pharmaceutical composition for treating ocular hypertension in a mammal suffering from ocular hypertension, which comprises:

(a) a therapeutically effective amount of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42, and

(b) a pharmaceutically acceptable carrier or diluent.

80. A commercial package comprising the pharmaceutical composition of any one of claims 43 to 49, 51 to 54, 58 to 60, 67 to 69 and 73 to 79 and a written matter describing instructions for the use thereof.

81. Use of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42 for treating a vertebrate having a condition which presents with low bone mass; augmenting and maintaining bone mass in a vertebrate; treating a mammal which presents with kidney degeneration; treating glaucoma in a mammal suffering from glaucoma; or treating ocular hypertension in a mammal.

82. Use of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the

72222-402

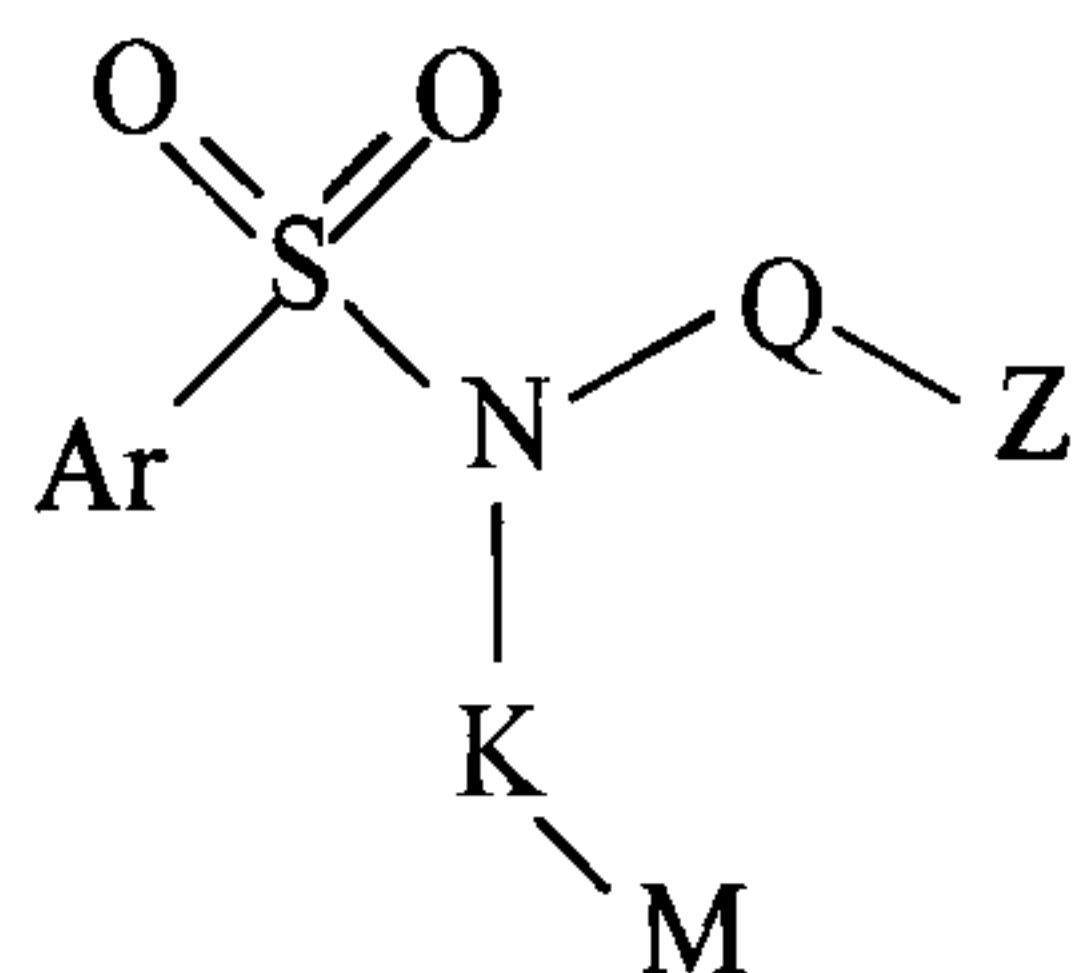
-246-

compound of claim 42 in the manufacture of a medicament for
treating a vertebrate having a condition which presents with
low bone mass; augmenting and maintaining bone mass in a
vertebrate; treating a mammal which presents with kidney
5 degeneration; treating glaucoma in a mammal suffering from
glaucoma; or treating ocular hypertension in a mammal.

72222-402

-247-

83. A compound having the Formula:



5

Q is $-(\text{C}_0\text{-C}_4)\text{alkylene-X-W-(C}_1\text{-C}_3)\text{alkylene-}$, the alkynes each optionally substituted with up to four substituents each independently selected from fluoro and $(\text{C}_1\text{-C}_4)\text{alkyl}$,

10 Z is $(\text{C}_1\text{-C}_6)\text{alkoxycarbonyl}$;

K is a bond, $(\text{C}_1\text{-C}_9)\text{alkylene}$, thio $(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkylenethio}(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkyleneoxy}(\text{C}_1\text{-C}_4)\text{alkylene}$ or oxy $(\text{C}_1\text{-C}_4)\text{alkylene}$, the $(\text{C}_1\text{-C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when
 15 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

M is Ar^3 ;

Ar is a partially saturated or fully unsaturated
 20 five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently,
 25 optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally

72222-402

-248-

having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four

72222-402

-249-

heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having

5 one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is

10 optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,

15 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

20 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or

25 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-,

30 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-

72222-402

-250-

(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

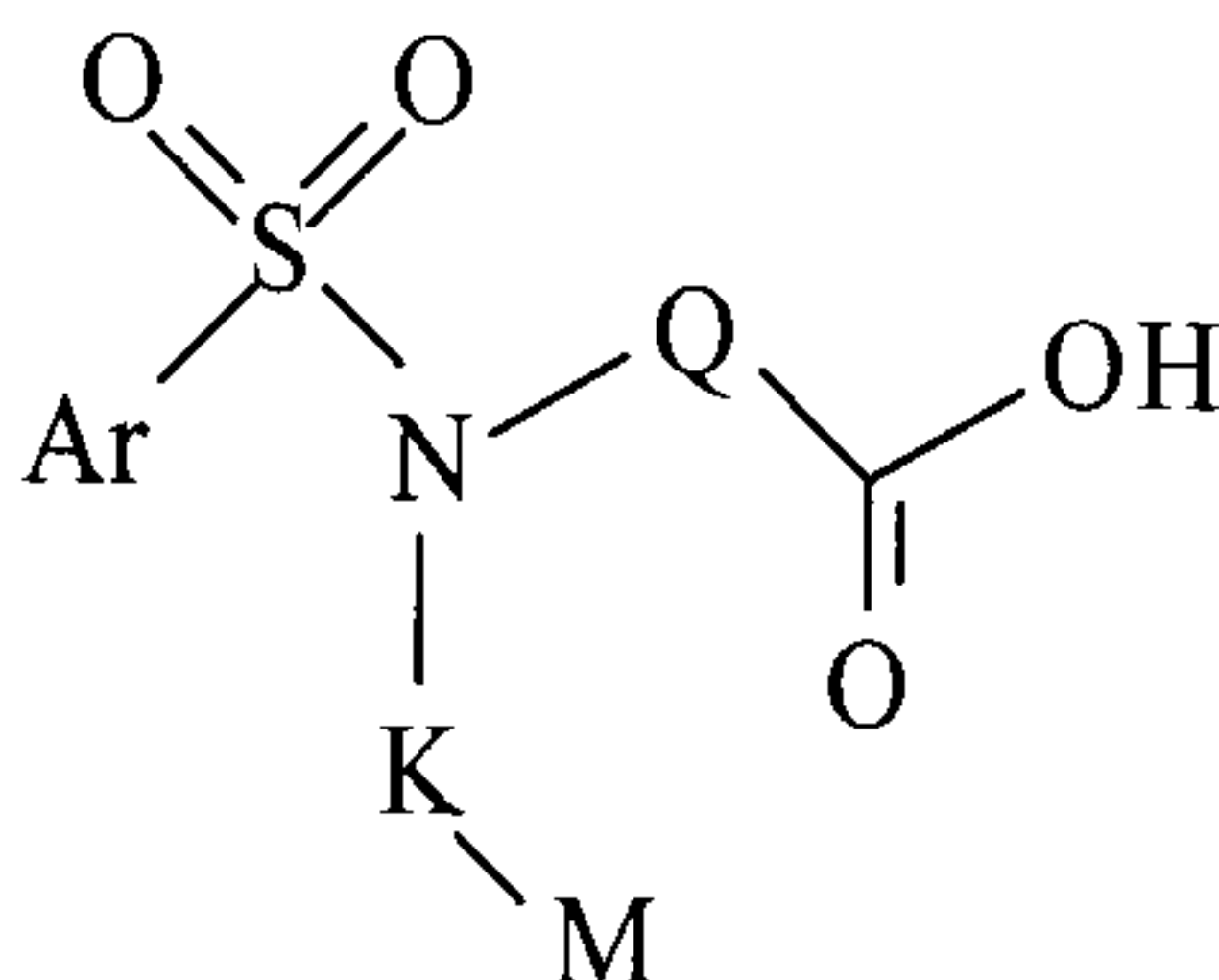
5 X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy,
10 difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

15 provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of
20 the compound or prodrug.

84. A compound having the Formula:



25

Q is -(C₀-C₄)alkylene-X-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four

72222-402

-251-

substituents each independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene,

5 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

10 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully
15 unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated
20 five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
25 two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both
30 rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy,

72222-402

-252-

(C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl,
 (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 5 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 10 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³
 15 or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 20 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 25 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 30 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,

72222-402

-253-

or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

72222-402

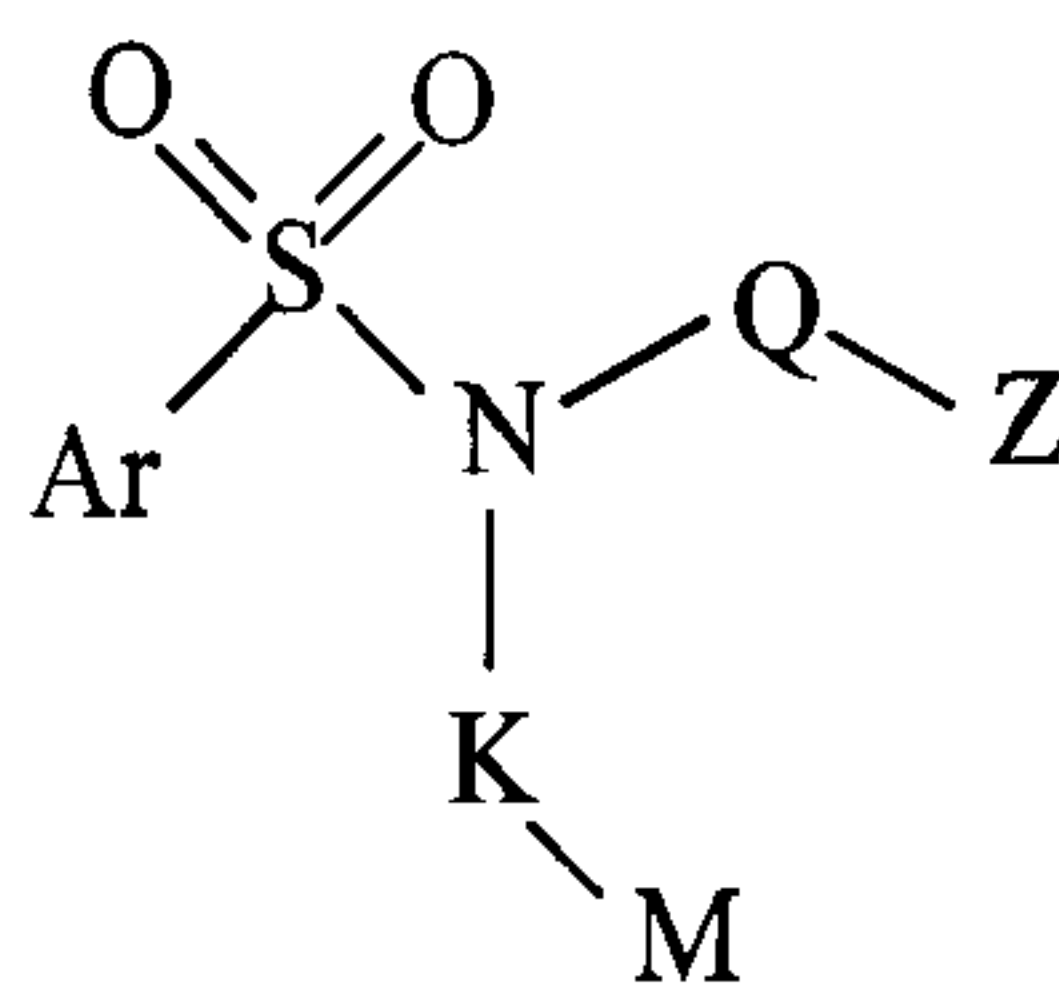
-254-

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

5 V^1 is thio(C_1 - C_4)alkylene, (C_1 - C_4)alkylenethio, (C_1 - C_4)alkyleneoxy, oxy(C_1 - C_4)alkylene or (C_1 - C_3)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of
10 the compound or prodrug.

85. A compound having the Formula:



15

Q is $-(C_0$ - C_4)alkylene- X - W -(C_1 - C_3)alkylene-, the alkylenes each optionally substituted with up to four substituents each independently selected from fluoro and (C_1 - C_4)alkyl,

20 Z is (C_1 - C_6)alkoxycarbonyl;

K is a bond, (C_1 - C_9)alkylene, thio(C_1 - C_4)alkylene, (C_1 - C_4)alkylenethio(C_1 - C_4)alkylene, (C_1 - C_4)alkyleneoxy(C_1 - C_4)alkylene or oxy(C_1 - C_4)alkylene, the (C_1 - C_9)alkylene optionally mono-unsaturated and wherein, when
25 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

72222-402

-255-

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently

10 partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

15 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or

20 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or

30

72222-402

-256-

di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³
 5 or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 10 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused
 15 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally
 20 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to
 25 three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 30 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,

72222-402

-257-

aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 5 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 10 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 15 optionally substituted on carbon with one to three
 fluorines;

X is a five or six membered aromatic ring
 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 20 optionally mono-, di- or tri-substituted independently with
 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy,
 difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 25 optionally mono-, di- or tri-substituted on carbon
 independently with halo or hydroxy; and

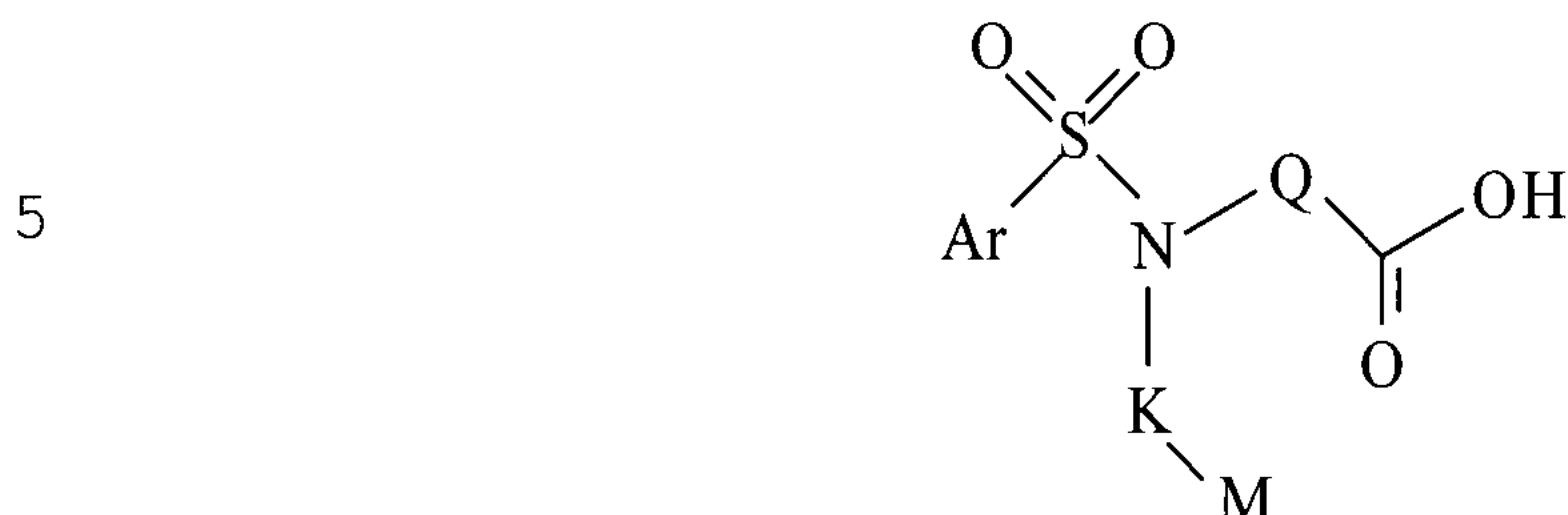
V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 30 hydroxy or fluoro;

72222-402

-258-

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

86. A compound having the Formula:



Q is $-(\text{C}_0\text{-C}_4)\text{alkylene-X-W-(C}_1\text{-C}_3)\text{alkylene-}$, the alkylenes each optionally substituted with up to four
 10 substituents each independently selected from fluoro and $(\text{C}_1\text{-C}_4)\text{alkyl}$,

K is a bond, $(\text{C}_1\text{-C}_9)\text{alkylene}$, thio $(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkylenethio(C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkyleneoxy(C}_1\text{-C}_4)\text{alkylene}$ or oxy $(\text{C}_1\text{-C}_4)\text{alkylene}$, the
 15 $(\text{C}_1\text{-C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated
 20 five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently,
 25 optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally

72222-402

-259-

having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings,

72222-402

-260-

taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 5 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 10 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 15 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 20 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 25 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

30 W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,

72222-402

-261-

N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three
 5 fluorines;

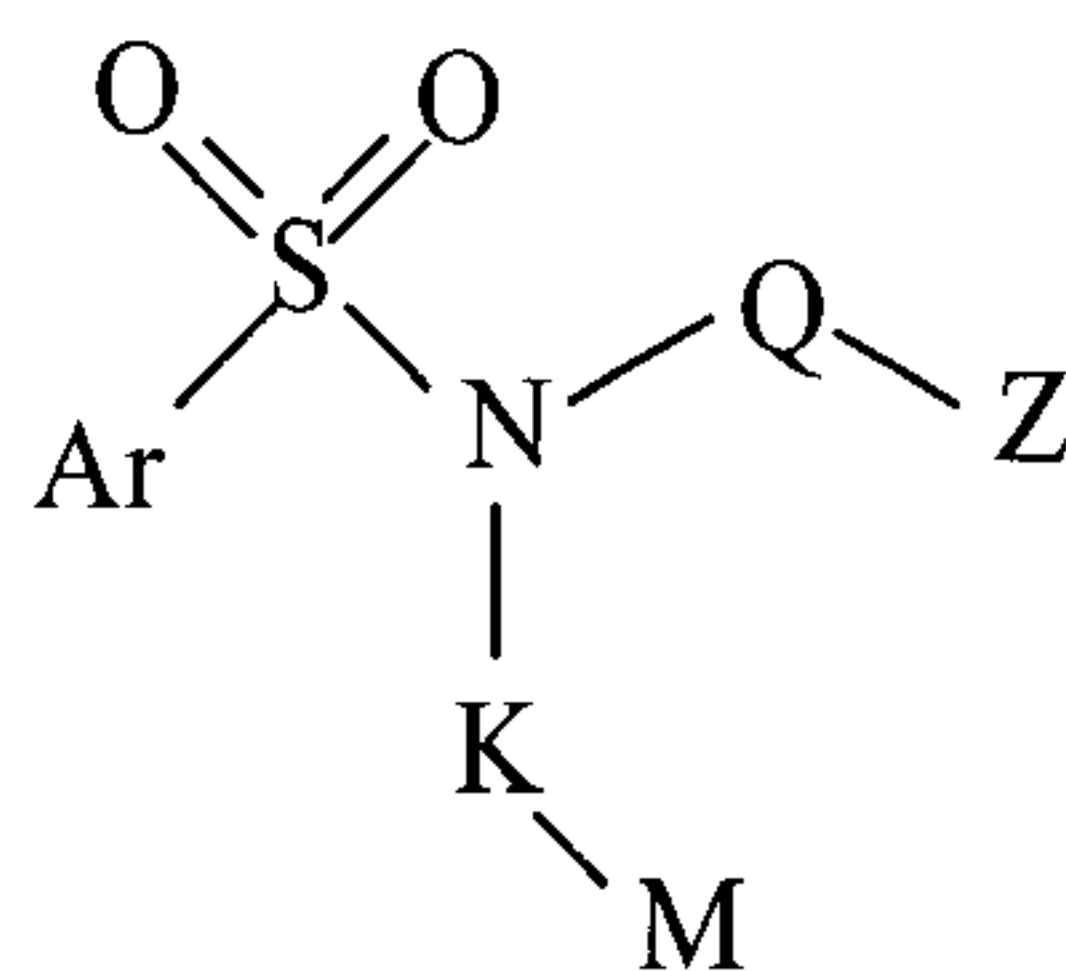
X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with
 10 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon
 15 independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

87. A compound having the Formula:

20



Q is -(C₀-C₄)alkylene-X-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four
 25 substituents each independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

72222-402

-262-

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when

5 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four

10 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

15 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

20 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two

25 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

30 selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

72222-402

-263-

(C₃-C₇) cycloalkyl (C₁-C₄) alkyl,
 (C₃-C₇) cycloalkyl (C₁-C₄) alkanoyl, formyl, (C₁-C₈) alkanoyl,
 (C₁-C₆) alkanoyl (C₁-C₆) alkyl, (C₁-C₄) alkanoylamino,
 (C₁-C₄) alkoxycarbonylamino, hydroxysulfonyl,
 5 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄) alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄) alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄) alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄) alkylcarbamoyl, cyano, thiol, (C₁-C₆) alkylthio,
 10 (C₁-C₆) alkylsulfinyl, (C₁-C₄) alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄) alkylaminosulfinyl;

M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 15 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 20 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 25 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 30 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,

72222-402

-264-

halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 5 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 10 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

15 W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-,
 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
 N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
 N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
 20 (C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
 (C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
 optionally substituted on carbon with one to three
 fluorines;

X is a five or six membered aromatic ring
 25 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 optionally mono-, di- or tri-substituted independently with
 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy,
 difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

30 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are

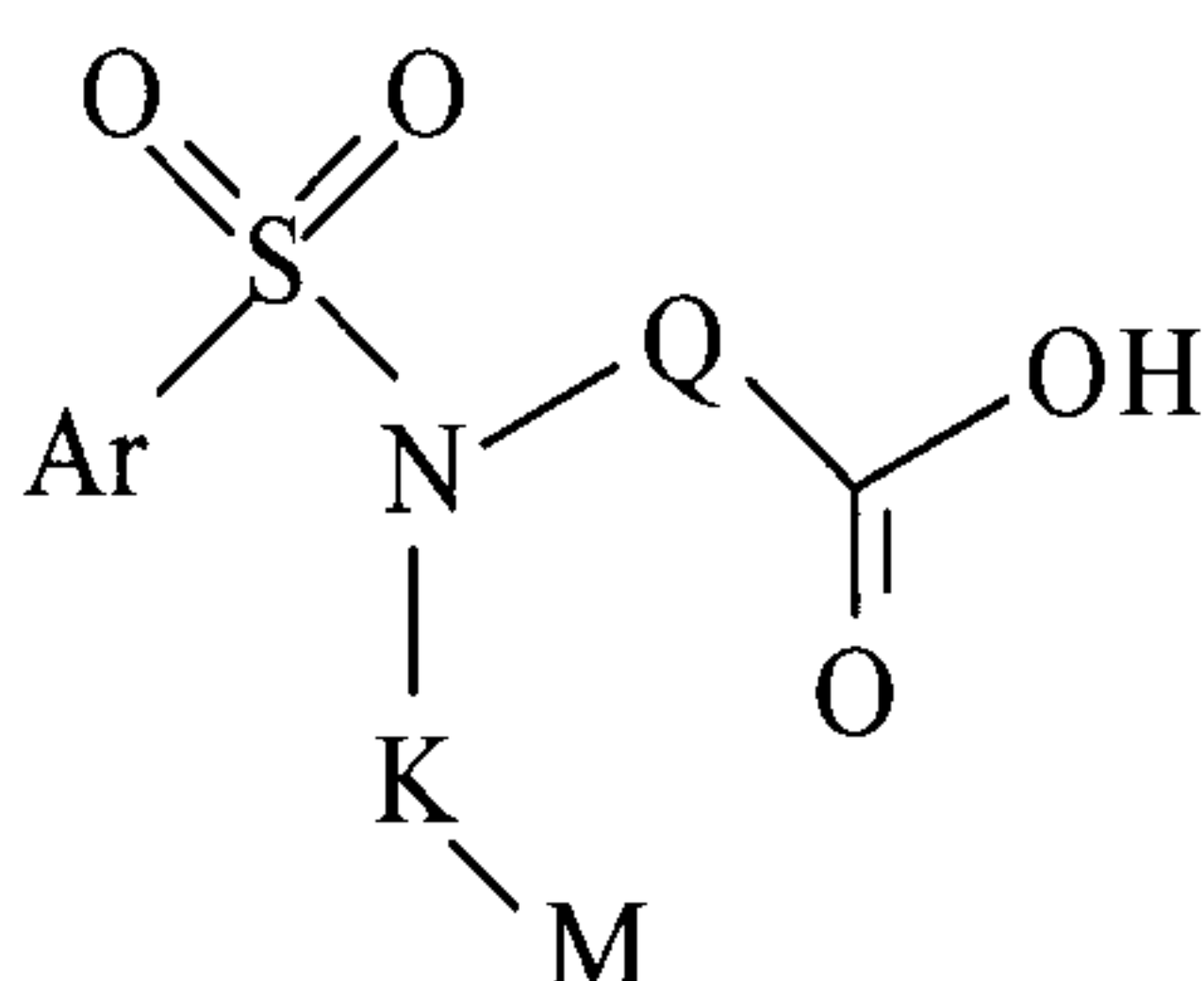
72222-402

-265-

optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

5 88. A compound having the Formula:



10 Q is $-(\text{C}_4-\text{C}_8)\text{alkylene}-$, the alkylene optionally substituted with up to four substituents independently selected from fluoro and $(\text{C}_1-\text{C}_4)\text{alkyl}$,

K is a bond, $(\text{C}_1-\text{C}_9)\text{alkylene}$, thio $(\text{C}_1-\text{C}_4)\text{alkylene}$, $(\text{C}_1-\text{C}_4)\text{alkylenethio}(\text{C}_1-\text{C}_4)\text{alkylene}$,
 15 $(\text{C}_1-\text{C}_4)\text{alkyleneoxy}(\text{C}_1-\text{C}_4)\text{alkylene}$ or oxy $(\text{C}_1-\text{C}_4)\text{alkylene}$, the $(\text{C}_1-\text{C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

20 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully
 25 unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated

72222-402

-266-

five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully

72222-402

-267-

saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

10 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to

15 three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

20 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

25 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or

30 di-N,N-(C₁-C₄)alkylaminosulfinyl;

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are

72222-402

-268-

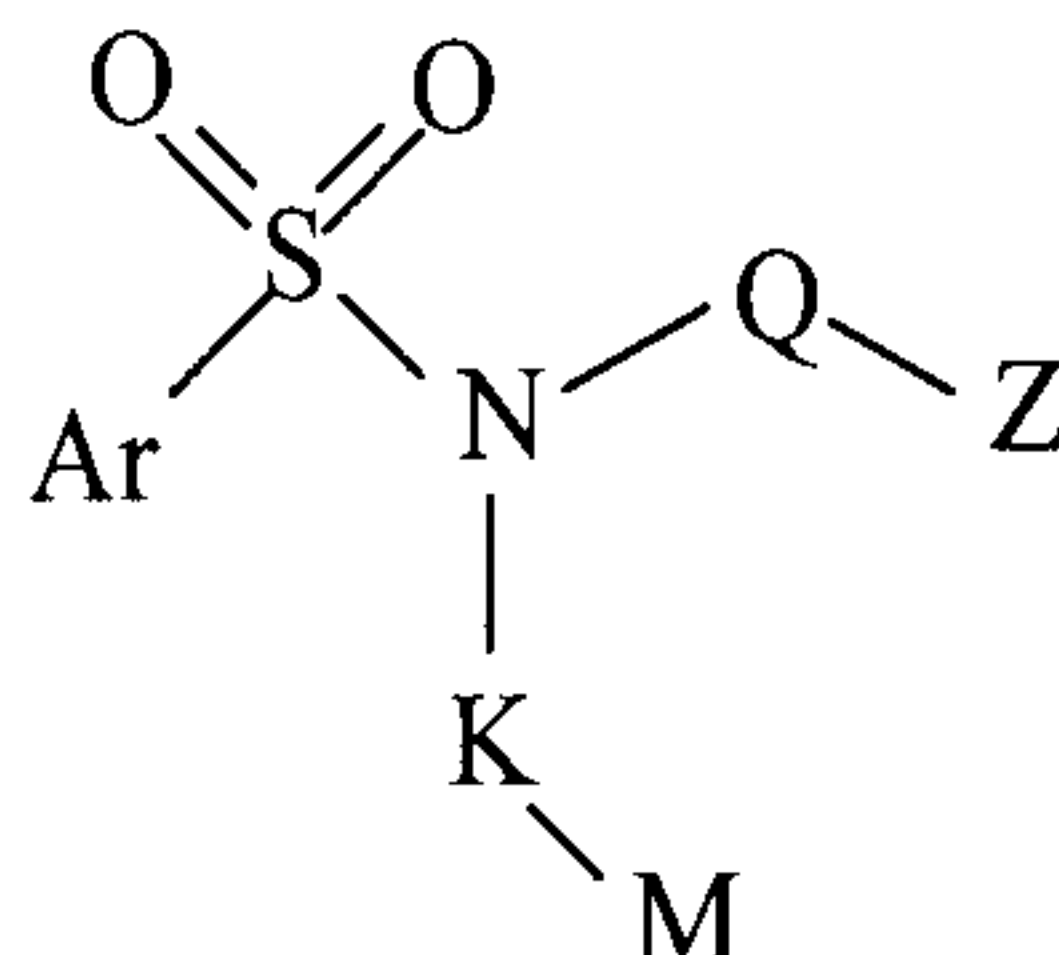
optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl
5 or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

89. A compound having the Formula:

10



Q is -(C₄-C₈)alkylene-, the alkylene optionally
15 substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene,
20 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

25 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and

72222-402

-269-

nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

5 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

10 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two

15 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

20 selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl,

25 (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino,

30 sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N-(C_1-C_4)alkylaminosulfinyl;

72222-402

-270-

M is Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

72222-402

-271-

di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

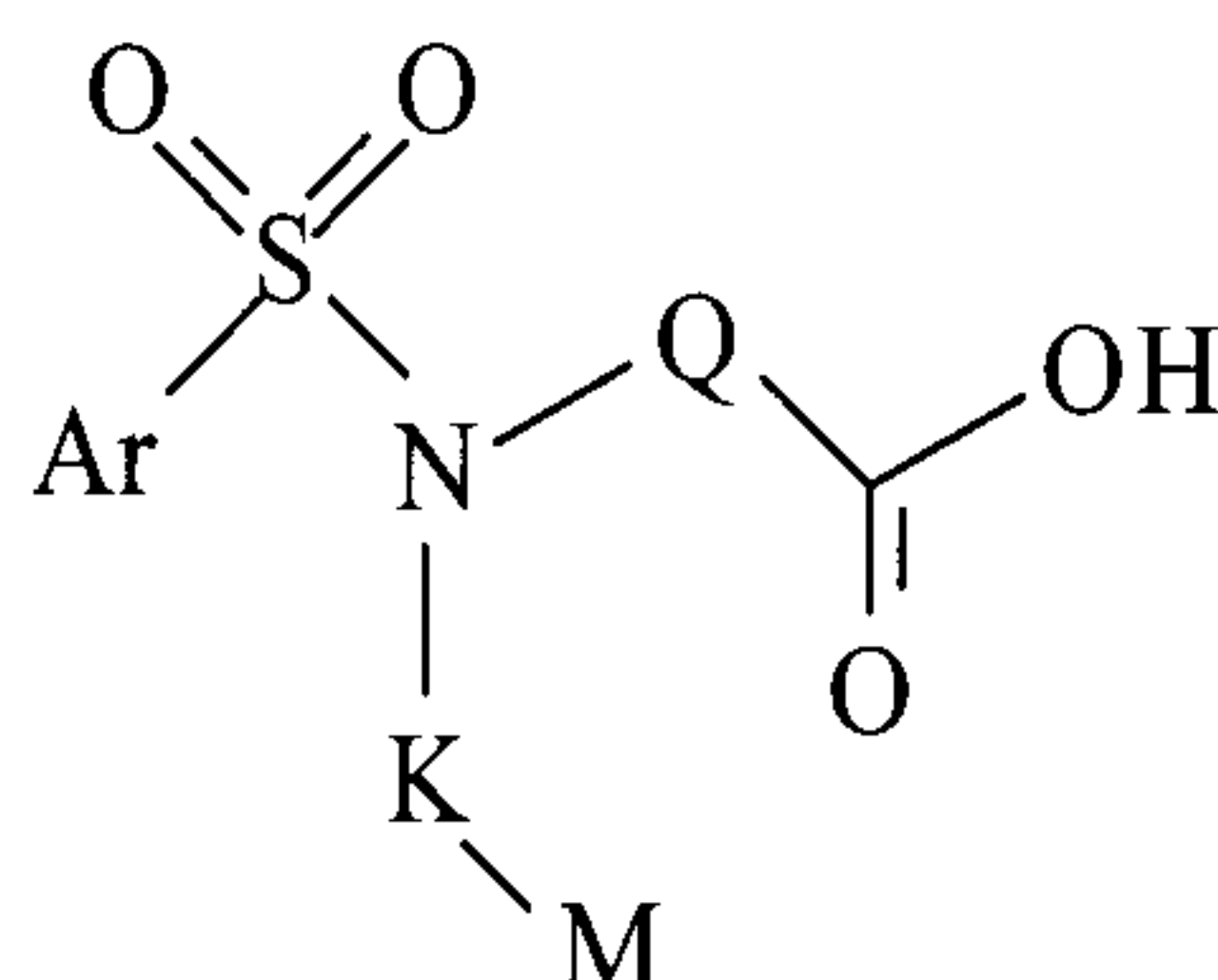
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

90. A compound having the Formula:

15



Q is -(C₄-C₈)alkylene-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

72222-402

-272-

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a

10 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

15 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully

20 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or

25 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are

independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

72222-402

-273-

di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³
 5 or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 10 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 15 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 20 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 25 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 30 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,

72222-402

-274-

aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 5 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 10 optionally mono-, di- or tri-substituted on carbon
 independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
 (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 optionally mono- or di-substituted independently with
 15 hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

91. A compound having the Formula:



Q is -(C₄-C₈)alkylene-, the alkylene optionally
 substituted with up to four substituents independently
 25 selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

72222-402

-275-

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when

5 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four

10 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

15 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

20 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two

25 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

30 selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

72222-402

-276-

(C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 5 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 10 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³
 or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or
 15 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 20 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 25 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 30 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and

72222-402

-277-

R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

5 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

10 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or

15 di-N,N-(C₁-C₄)alkylaminosulfinyl;

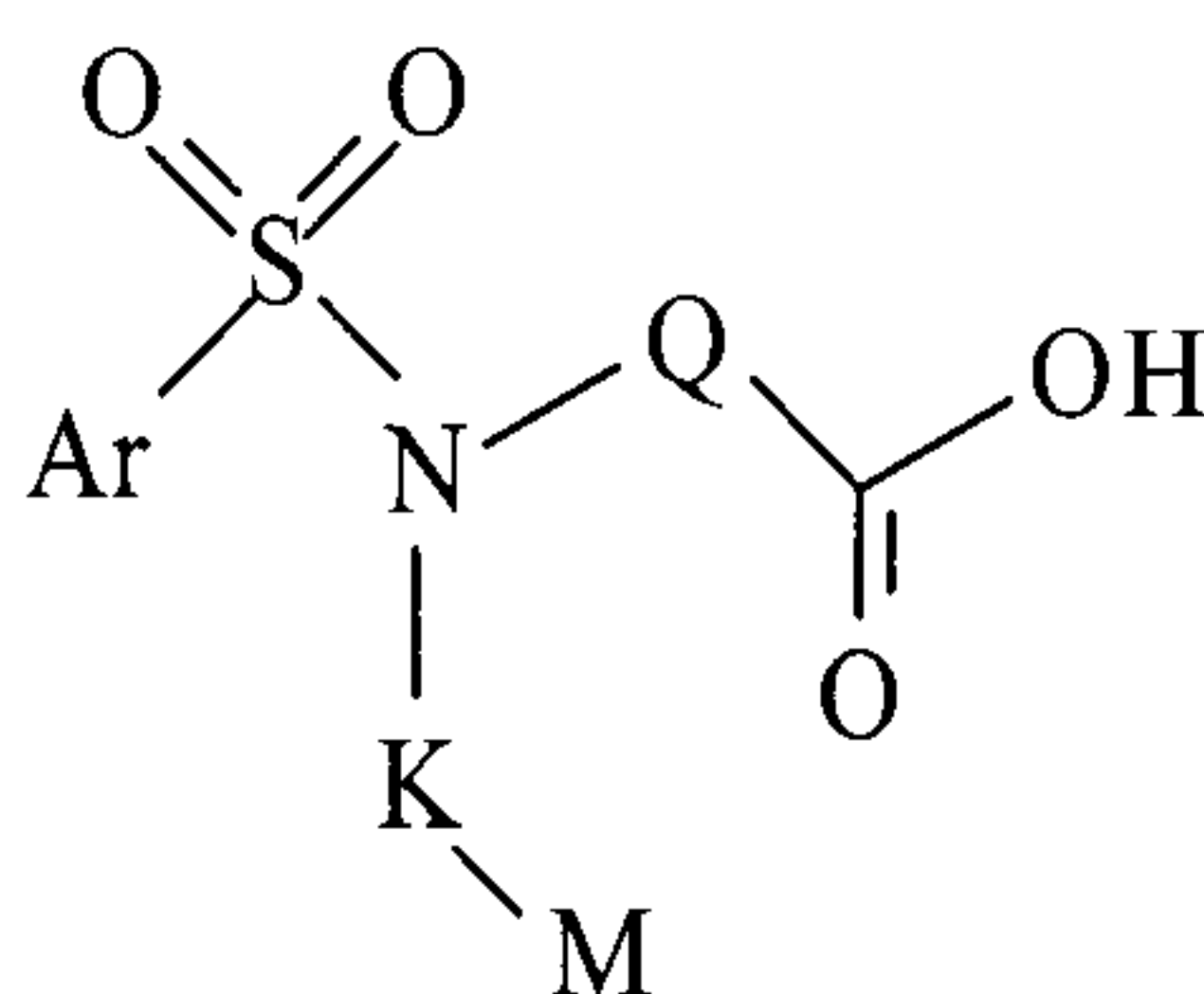
R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

20 V^1 is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio, (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of

25 the compound or prodrug.

92. A compound having the Formula:



72222-402

-278-

Q is $-(C_4-C_8)$ alkylene-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C_1-C_4) alkyl,

K is a bond, (C_1-C_9) alkylene, thio (C_1-C_4) alkylene,
5 (C_1-C_4) alkylenethio (C_1-C_4) alkylene,
 (C_1-C_4) alkyleneoxy (C_1-C_4) alkylene or oxy (C_1-C_4) alkylene, the
 (C_1-C_9) alkylene optionally mono-unsaturated and wherein, when
K is not a bond, K is optionally mono-, di- or tri-
substituted independently with chloro, fluoro, hydroxy or
10 methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused
15 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently
20 partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally
25 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or
30 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are

72222-402

-279-

independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,

5 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,

10 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

15 M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting

20 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

25 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

30 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,

72222-402

-280-

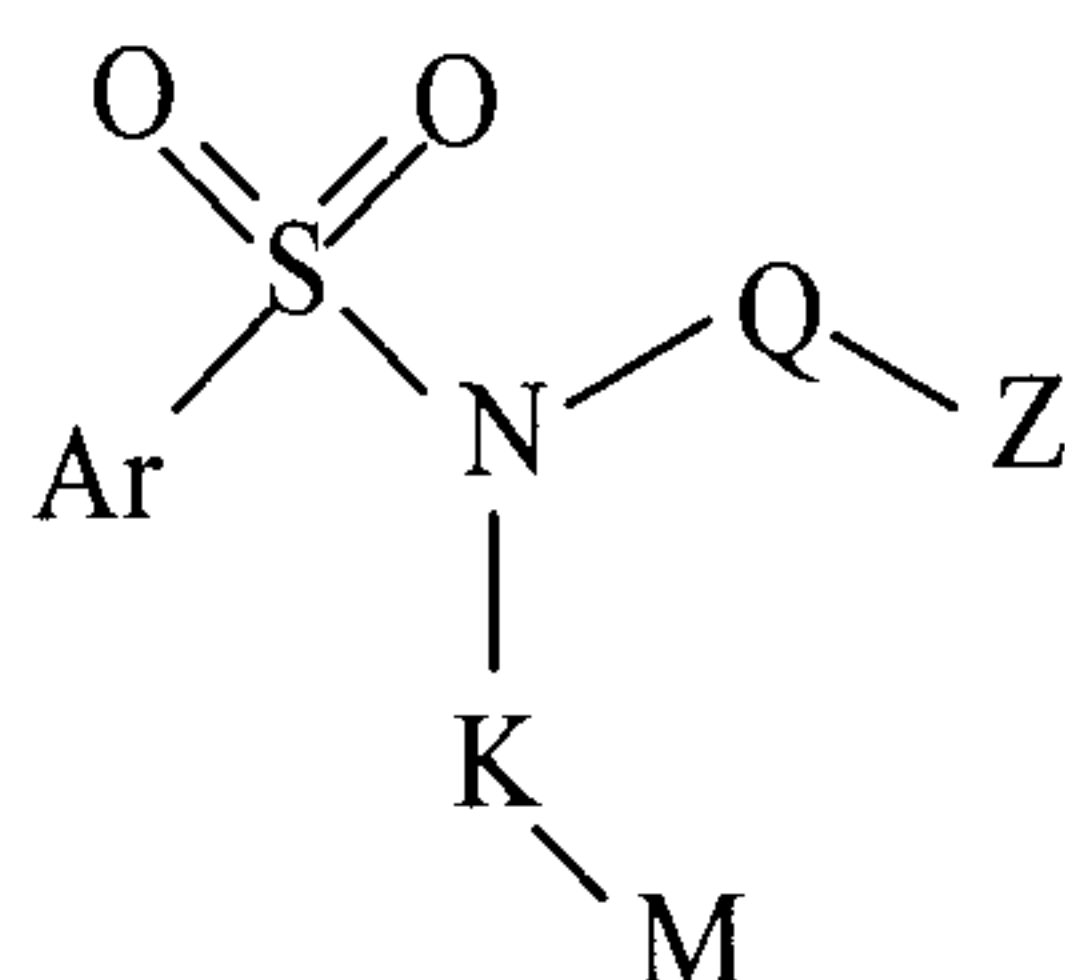
or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, $(\text{C}_1\text{-C}_7)$ alkoxy, $(\text{C}_1\text{-C}_4)$ alkoxy $(\text{C}_1\text{-C}_4)$ alkyl,
 5 $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl, $(\text{C}_1\text{-C}_7)$ alkyl, $(\text{C}_2\text{-C}_7)$ alkenyl, $(\text{C}_2\text{-C}_7)$ alkynyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkanoyl, formyl, $(\text{C}_1\text{-C}_8)$ alkanoyl, $(\text{C}_1\text{-C}_6)$ alkanoyl $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkanoylamino,
 10 $(\text{C}_1\text{-C}_4)$ alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-($\text{C}_1\text{-C}_4$)alkyl substituted aminocarbonylamino, sulfonamido, $(\text{C}_1\text{-C}_4)$ alkylsulfonamido, amino, mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylamino, carbamoyl, mono-N- or
 15 di-N,N-($\text{C}_1\text{-C}_4$)alkylcarbamoyl, cyano, thiol, $(\text{C}_1\text{-C}_6)$ alkylthio, $(\text{C}_1\text{-C}_6)$ alkylsulfinyl, $(\text{C}_1\text{-C}_4)$ alkylsulfonyl or mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylaminosulfinyl; and

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are
 20 optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

93. A compound having the Formula:

25



72222-402

-281-

Q is $-(C_4-C_8)$ alkylene-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C_1-C_4) alkyl,

Z is (C_1-C_6) alkoxycarbonyl;

5 K is a bond, (C_1-C_9) alkylene, thio (C_1-C_4) alkylene, (C_1-C_4) alkylenethio (C_1-C_4) alkylene, (C_1-C_4) alkyleneoxy (C_1-C_4) alkylene or oxy (C_1-C_4) alkylene, the (C_1-C_9) alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-
10 substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and
15 nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a
20 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully
25 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and
30 nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar

72222-402

-282-

is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N-(C_1-C_4)alkylaminosulfinyl;

M is Ar^3-Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is

72222-402

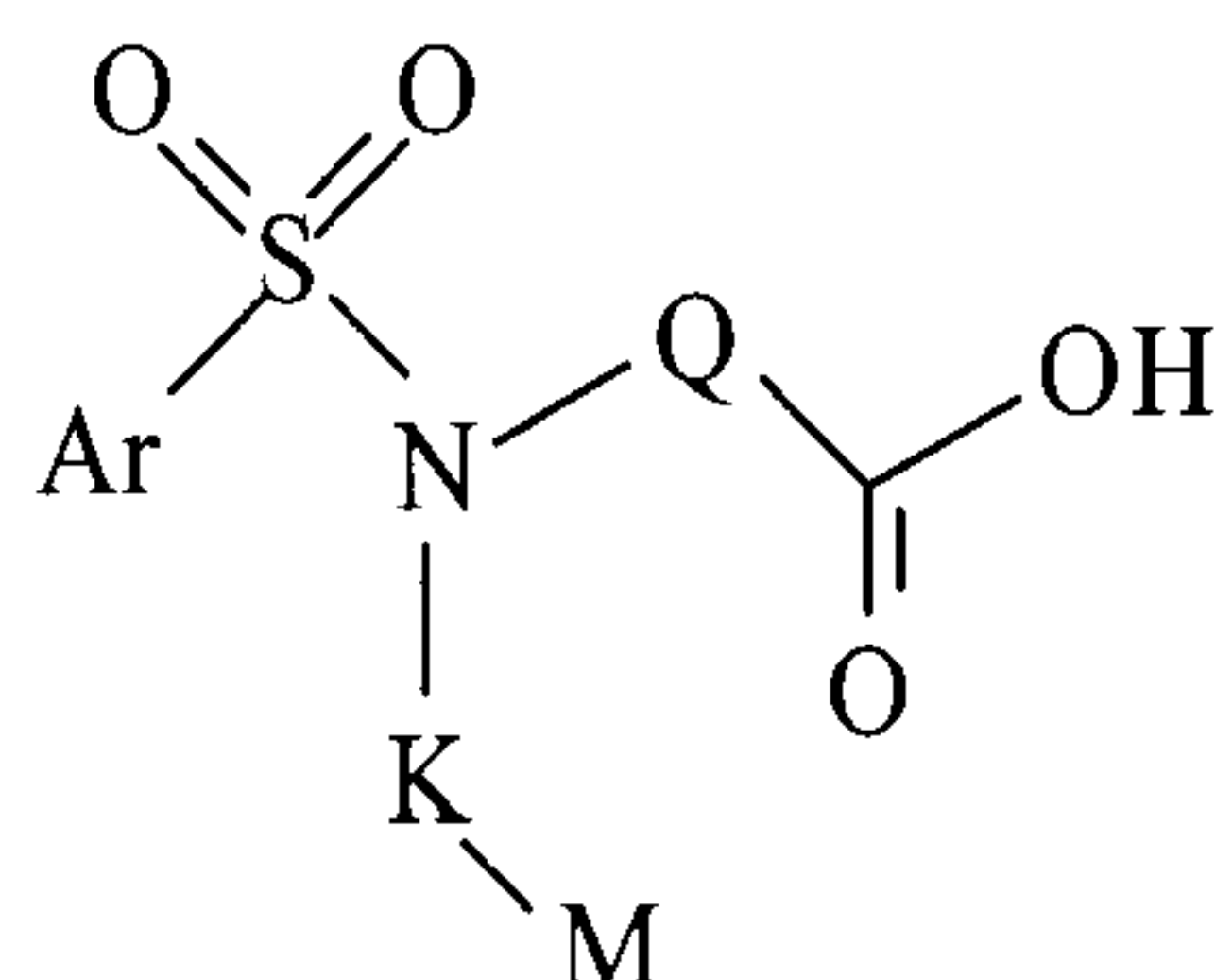
-283-

optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, $(\text{C}_1\text{-C}_7)$ alkoxy, $(\text{C}_1\text{-C}_4)$ alkoxy $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl, $(\text{C}_1\text{-C}_7)$ alkyl, $(\text{C}_2\text{-C}_7)$ alkenyl, $(\text{C}_2\text{-C}_7)$ alkynyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkanoyl, formyl, $(\text{C}_1\text{-C}_8)$ alkanoyl, $(\text{C}_1\text{-C}_6)$ alkanoyl $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkanoylamino, $(\text{C}_1\text{-C}_4)$ alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-($\text{C}_1\text{-C}_4$)alkyl substituted aminocarbonylamino, sulfonamido, $(\text{C}_1\text{-C}_4)$ alkylsulfonamido, amino, mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylamino, carbamoyl, mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylcarbamoyl, cyano, thiol, $(\text{C}_1\text{-C}_6)$ alkylthio, $(\text{C}_1\text{-C}_6)$ alkylsulfinyl, $(\text{C}_1\text{-C}_4)$ alkylsulfonyl or mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylaminosulfinyl; and

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

94. A compound having the Formula:



72222-402

-284-

Q is $-(C_2-C_6)\text{alkylene}-W-(C_1-C_3)\text{alkylene}-$, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and $(C_1-C_4)\text{alkyl}$,

5 K is a bond, $(C_1-C_9)\text{alkylene}$, thio $(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or oxy $(C_1-C_4)\text{alkylene}$, the $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-
10 substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and
15 nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a
20 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully
25 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and
30 nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently

72222-402

-285-

selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,
 5 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 10 tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or
 15 di-N,N-(C_1-C_4)alkylaminosulfinyl;

M is Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from
 20 oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and
 25 oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully
 30 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if

72222-402

-286-

Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

72222-402

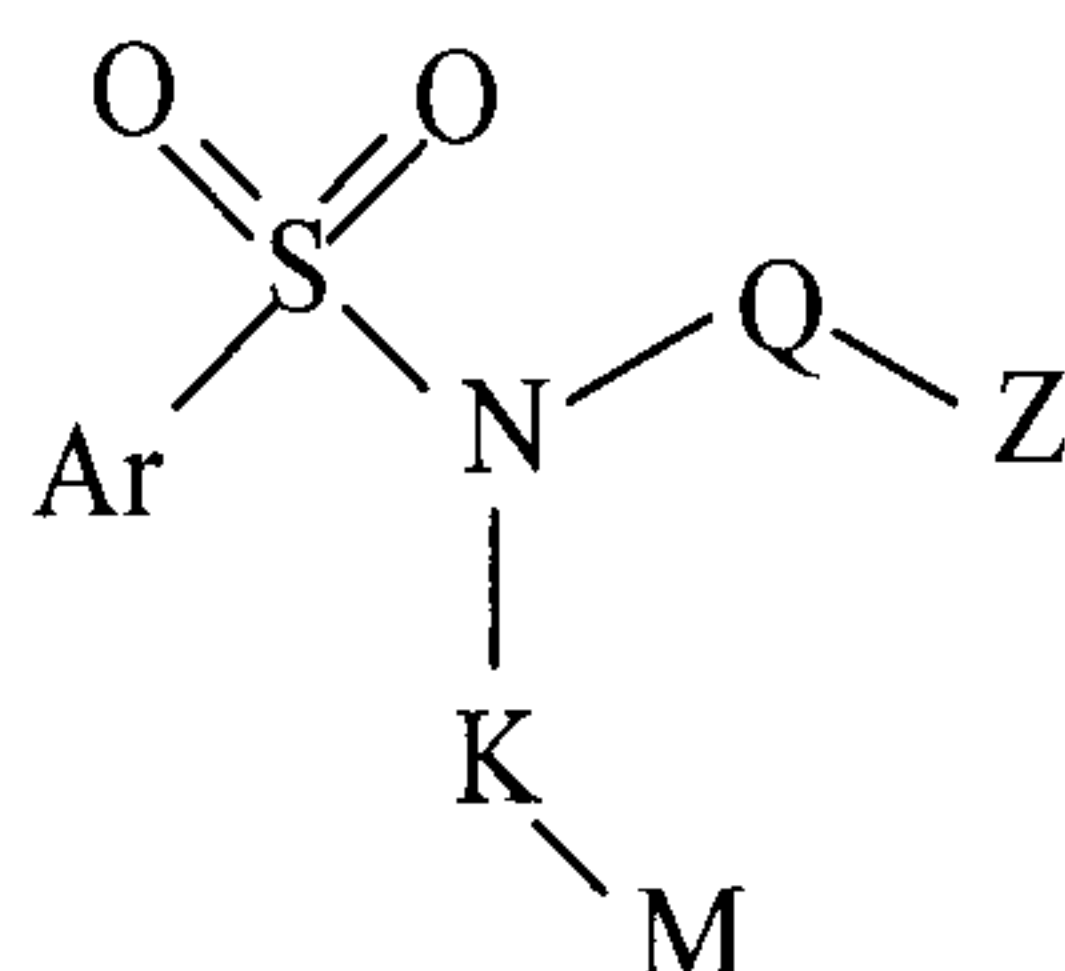
-287-

provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

5 or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

95. A compound having the Formula:

10



15

Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

20

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

25

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully

72222-402

-288-

unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently

5 partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

10 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or

15 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy,

20 (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

25 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

30 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³;

72222-402

-289-

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,

72222-402

-290-

(C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

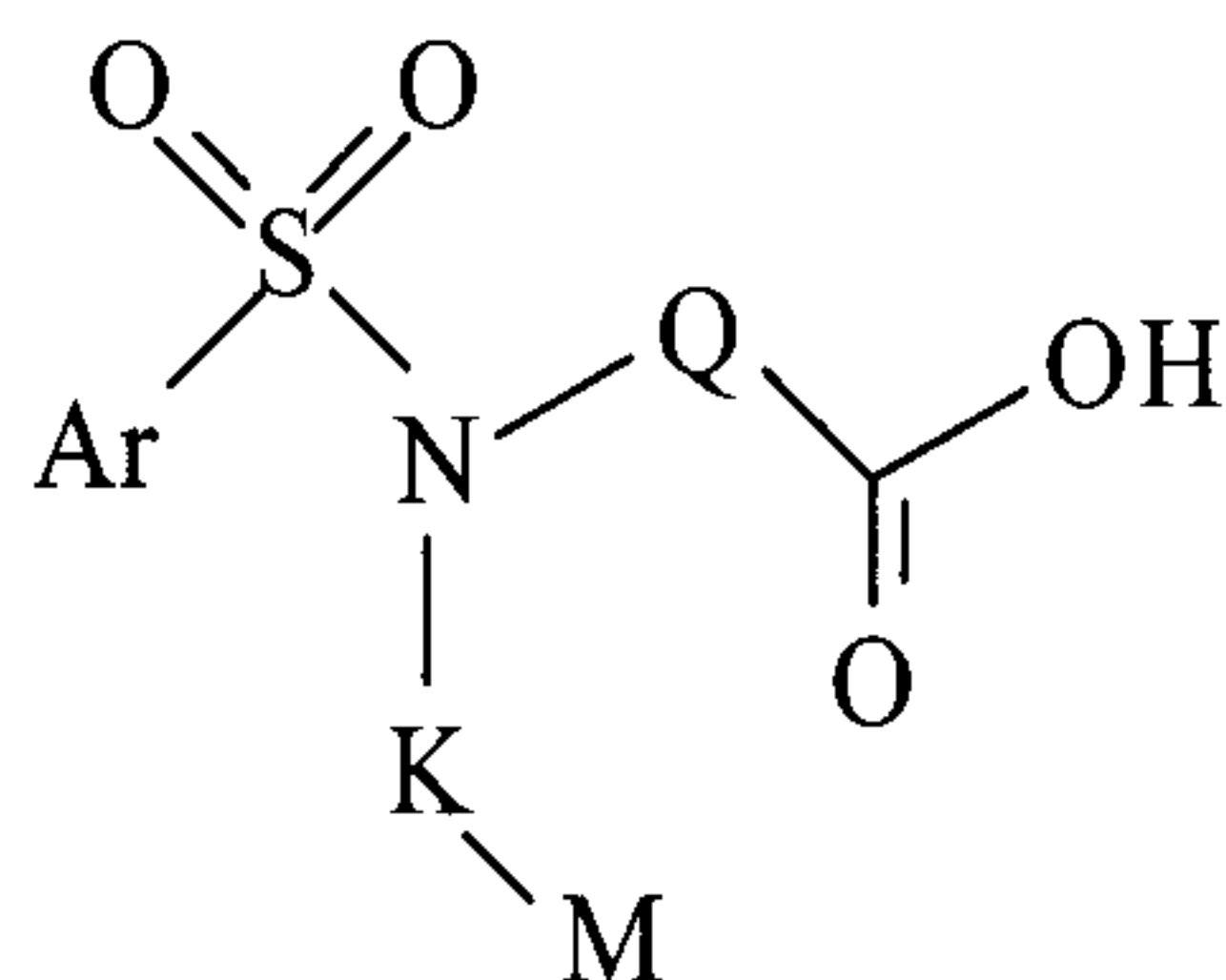
W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-,
-mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
5 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
10 optionally substituted on carbon with one to three
fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
alkyl, alkylene, alkenylene or alkynylene moiety, are
optionally mono-, di- or tri-substituted on carbon
15 independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is
Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl
or cyclooct-1-yl, then Ar³ is not substituted at the one
position with hydroxy;

20 or a prodrug thereof, or a pharmaceutically acceptable salt of
the compound or prodrug.

96. A compound having the Formula:



25

Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the
alkylenes each optionally substituted with up to four

72222-402

-291-

substituents independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene,

5 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

10 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully
15 unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated
20 five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
25 two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both
30 rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy,

72222-402

-292-

(C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, 5 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or 10 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³ 15 or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting 20 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused 25 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally 30 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,

72222-402

-293-

or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio, (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene

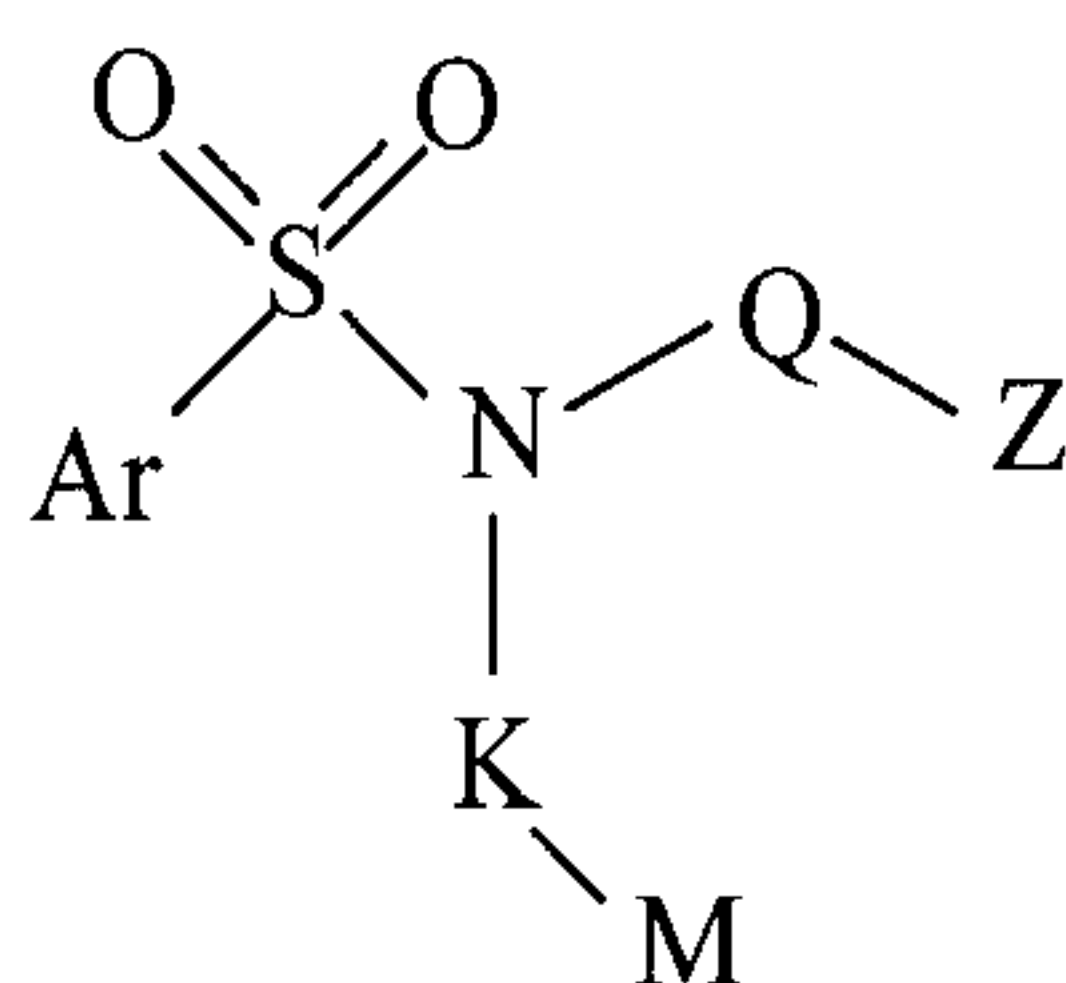
72222-402

-294-

optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

5 97. A compound having the Formula:



10 Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

15 K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-
 20 substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and
 25 nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

72222-402

-295-

independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally
 5 having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully
 10 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar
 15 is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,
 20 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 25 tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or
 30 di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is $-\text{Ar}^3-\text{V}^1-\text{Ar}^3$, $-\text{Ar}^3-\text{S}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}-\text{Ar}^3$, $-\text{Ar}^3-\text{SO}_2-\text{Ar}^3$ or $-\text{Ar}^3-\text{O}-\text{Ar}^3$;

72222-402

-296-

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,

72222-402

-297-

(C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

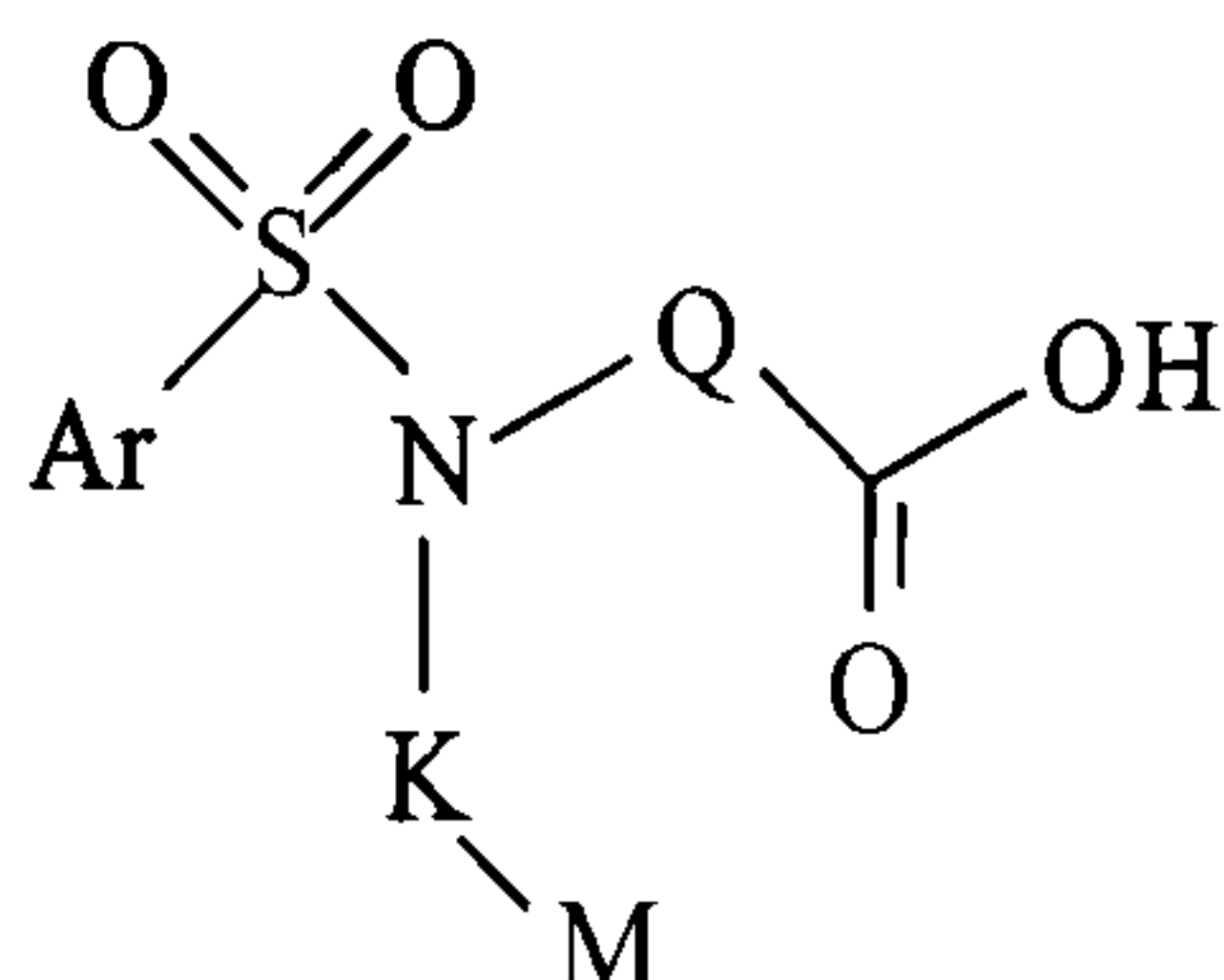
W is oxy, thio, sulfino, sulfonyl, aminosulfonyl-,
-mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino,
5 N-(C₁-C₄)alkylenesulfonylamino, carboxamido,
N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy,
N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-
(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-
(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are
10 optionally substituted on carbon with one to three
fluorines;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
alkyl, alkylene, alkenylene or alkynylene moiety, are
optionally mono-, di- or tri-substituted on carbon
15 independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio,
(C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
optionally mono- or di-substituted independently with
hydroxy or fluoro;

20 or a prodrug thereof, or a pharmaceutically acceptable salt of
the compound or prodrug.

98. A compound having the Formula:



25

Q is -(C₂-C₆)alkylene-W-(C₁-C₃)alkylene-, the
alkylenes each optionally substituted with up to four

72222-402

-298-

substituents independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene,

5 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

10 Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully
15 unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated
20 five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
25 two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both
30 rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy,

72222-402

-299-

(C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, 5 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or 10 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

15 Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully 20 saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully 25 unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or 30 two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to

72222-402

-300-

three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines; and

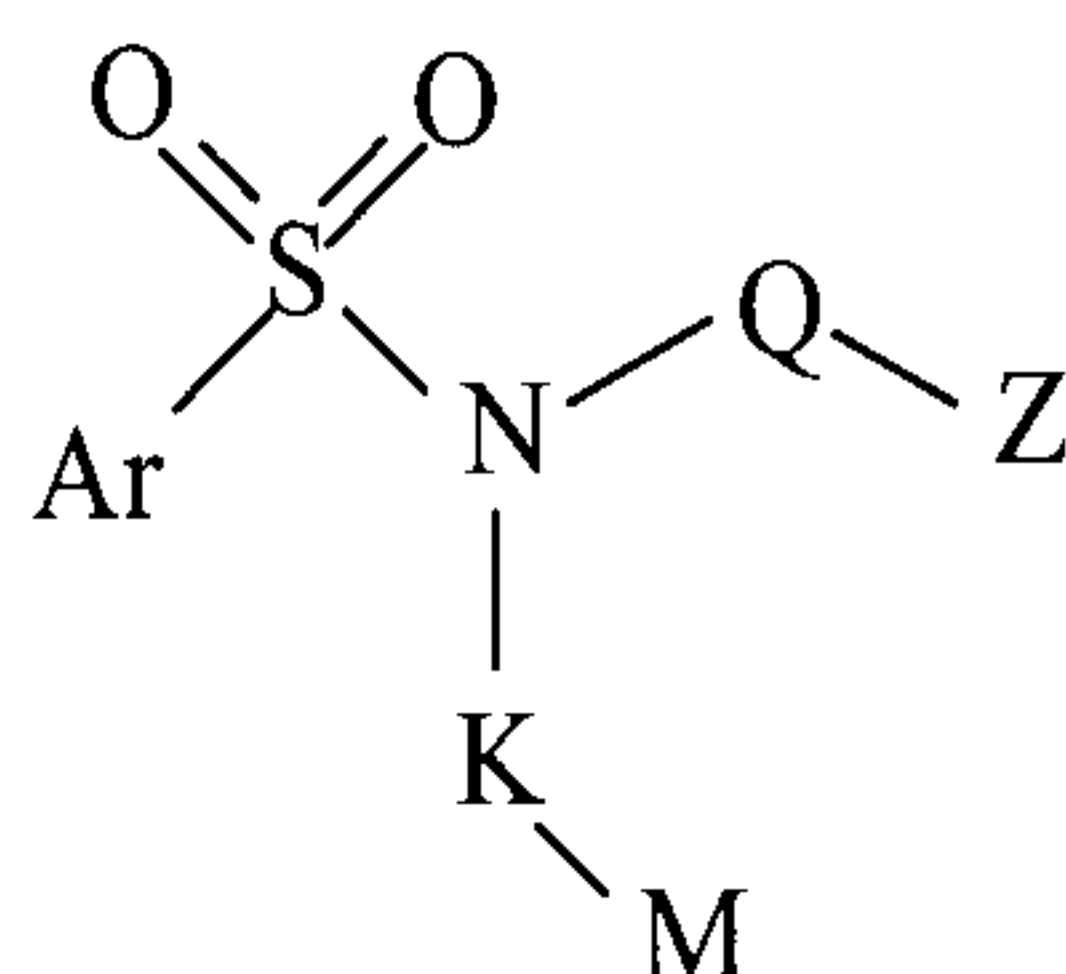
R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

72222-402

-301-

99. A compound having the Formula:



5

Q is $-(\text{C}_2-\text{C}_6)\text{alkylene}-\text{W}-(\text{C}_1-\text{C}_3)\text{alkylene}-$, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and $(\text{C}_1-\text{C}_4)\text{alkyl}$,

10 Z is $(\text{C}_1-\text{C}_6)\text{alkoxycarbonyl}$;

K is a bond, $(\text{C}_1-\text{C}_9)\text{alkylene}$, thio $(\text{C}_1-\text{C}_4)\text{alkylene}$, $(\text{C}_1-\text{C}_4)\text{alkylenethio}(\text{C}_1-\text{C}_4)\text{alkylene}$, $(\text{C}_1-\text{C}_4)\text{alkyleneoxy}(\text{C}_1-\text{C}_4)\text{alkylene}$ or oxy $(\text{C}_1-\text{C}_4)\text{alkylene}$, the $(\text{C}_1-\text{C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when
 15 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four
 20 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected
 25 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

72222-402

-302-

nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully

5 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar

10 is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,

15 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

20 tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or

25 di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is Ar^3-Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from

30 oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four

72222-402

-303-

heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having

5 one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is

10 optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,

15 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

20 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or

25 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

W is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-,

30 -mono-N-(C₁-C₄)alkyleneaminosulfonyl-, sulfonylamino, N-(C₁-C₄)alkylenesulfonylamino, carboxamido, N-(C₁-C₄)alkylenecarboxamido, carboxamidooxy, N-(C₁-C₄)alkylenecarboxamidooxy, carbamoyl, -mono-N-

72222-402

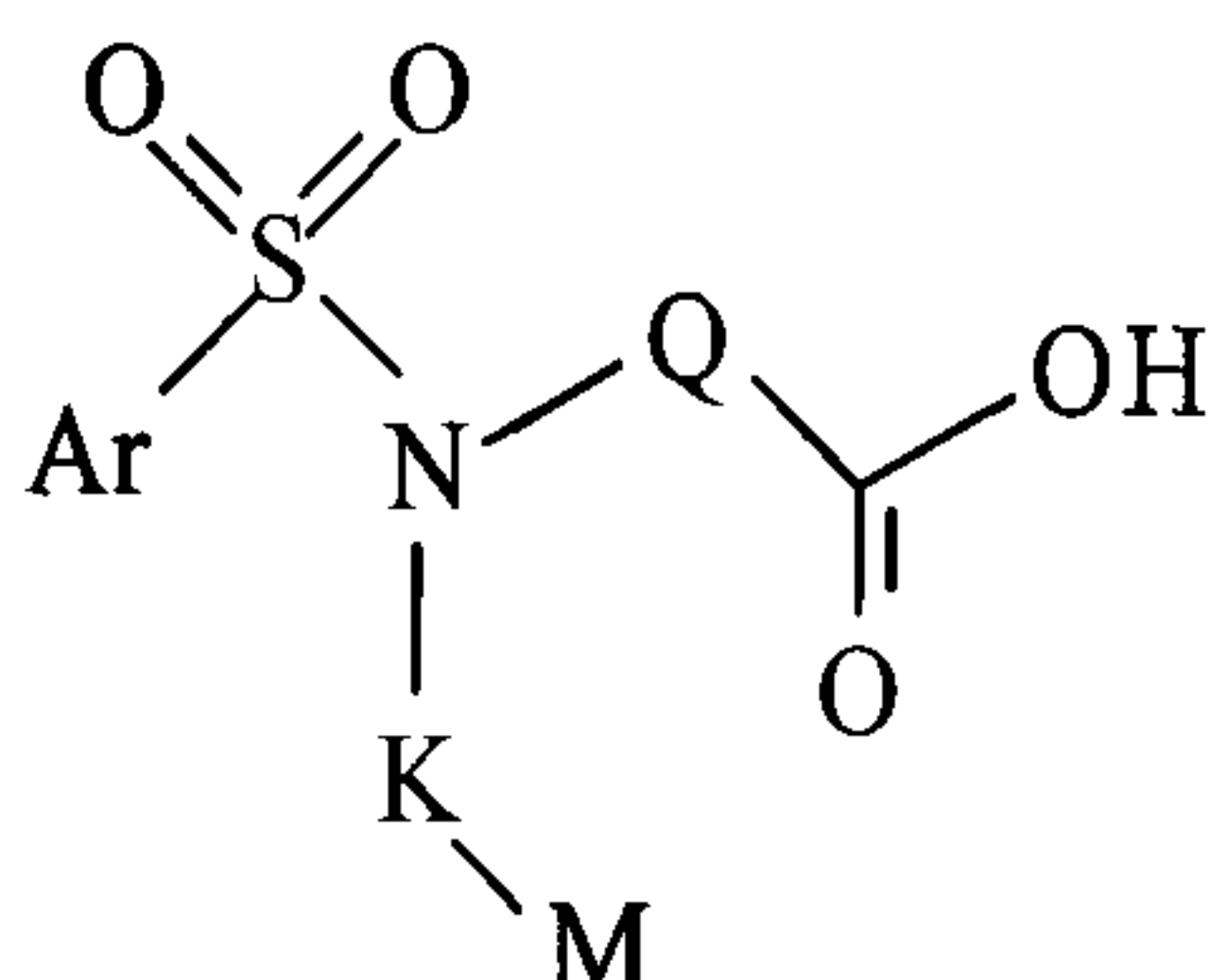
-304-

(C₁-C₄)alkylenecarbamoyl, carbamoyloxy, or -mono-N-(C₁-C₄)alkylenecarbamoyloxy, wherein the W alkyl groups are optionally substituted on carbon with one to three fluorines; and

5 R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of
10 the compound or prodrug.

100. A compound having the Formula:



15

Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

20 K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-
25 substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four

72222-402

-305-

heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R³, R⁴ and R⁵ wherein R³, R⁴ and R⁵ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,

72222-402

-306-

(C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³;

Ar³ is a partially saturated, fully saturated or
 5 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 10 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 15 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 20 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 25 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 30 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,
 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl,
 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,

72222-402

-307-

sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 5 di-N,N-(C₁-C₄)alkylaminosulfinyl;

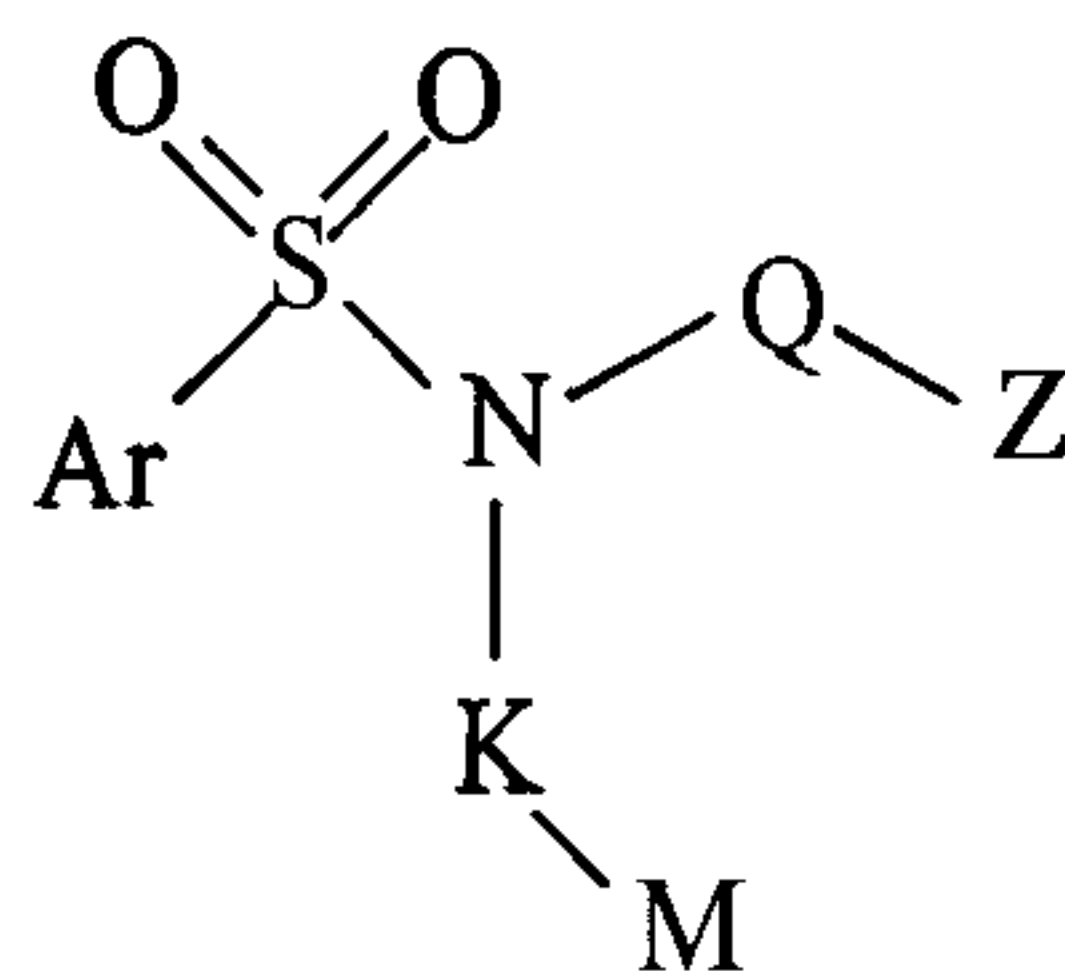
X is a five or six membered aromatic ring
 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 optionally mono-, di- or tri-substituted independently with
 10 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy,
 difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 15 independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and M is
 Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl
 or cyclooct-1-yl, then Ar³ is not substituted at the one
 position with hydroxy;

20 or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

101. A compound having the Formula:



25

Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the
 alkylenes each optionally substituted with up to four

72222-402

-308-

substituents independently selected from fluoro and
(C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
5 (C₁-C₄)alkylenethio(C₁-C₄)alkylene,
(C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the
(C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
K is not a bond, K is optionally mono-, di- or tri-
substituted independently with chloro, fluoro, hydroxy or
10 methyl;

Ar is a partially saturated or fully unsaturated
five to eight membered ring optionally having one to four
heteroatoms selected independently from oxygen, sulfur and
nitrogen, or a bicyclic ring consisting of two fused
15 independently partially saturated, fully saturated or fully
unsaturated five or six membered rings, taken independently,
optionally having one to four heteroatoms selected
independently from nitrogen, sulfur and oxygen, or a
tricyclic ring consisting of three fused independently
20 partially saturated, fully saturated or fully unsaturated
five or six membered rings, taken independently, optionally
having one to four heteroatoms selected independently from
nitrogen, sulfur and oxygen, the partially or fully
saturated ring, bicyclic ring or tricyclic ring optionally
25 having one or two oxo groups substituted on carbon or one or
two oxo groups substituted on sulfur; or Ar is a fully
saturated five to seven membered ring having one or two
heteroatoms selected independently from oxygen, sulfur and
nitrogen; wherein Ar is optionally substituted on carbon or
30 nitrogen, on one ring if Ar is monocyclic, on one or both
rings if Ar is bicyclic, or on one, two or three rings if Ar
is tricyclic, with up to three substituents independently

72222-402

-309-

selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,
 5 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 10 tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or
 15 di-N,N-(C_1-C_4)alkylaminosulfinyl;

M is Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from
 20 oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and
 25 oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully
 30 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if

72222-402

-310-

Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

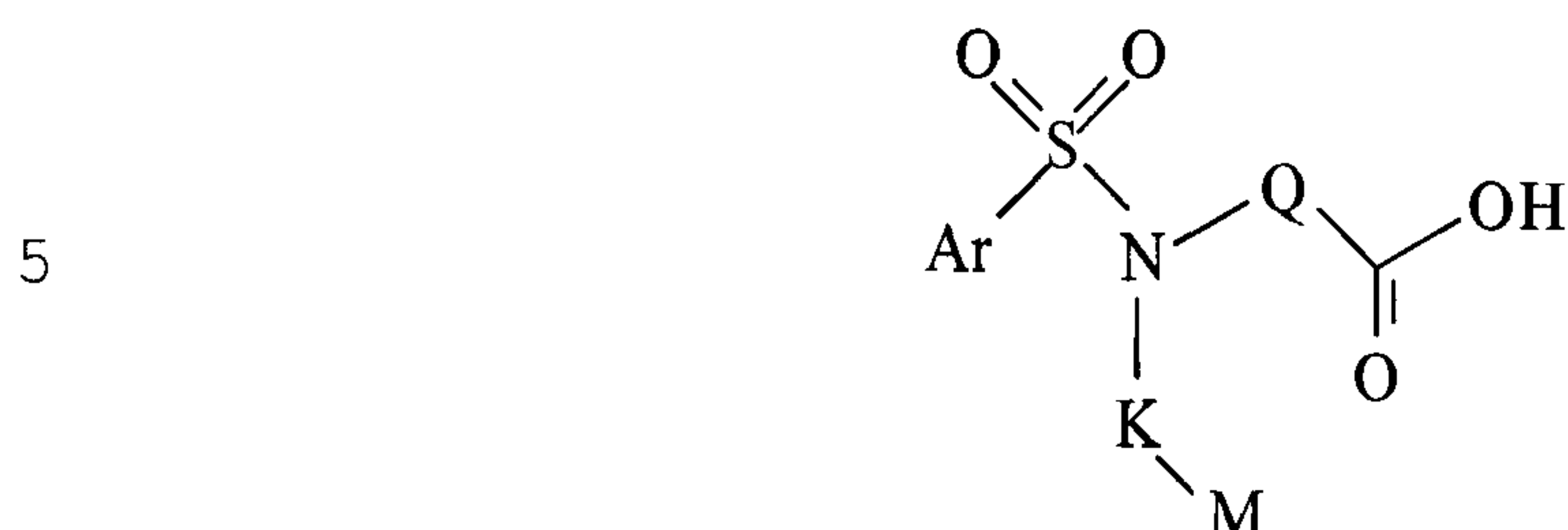
provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

72222-402

-311-

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

102. A compound having the Formula:



Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally

72222-402

-312-

having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N-(C_1-C_4)alkylaminosulfinyl;

M is $-Ar^3-V^1-Ar^3$, $-Ar^3-S-Ar^3$, $-Ar^3-SO-Ar^3$, $-Ar^3-SO_2-Ar^3$ or $-Ar^3-O-Ar^3$;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully

72222-402

-313-

saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

10 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to

15 three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

20 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

25 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or

30 di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring

72222-402

-314-

optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

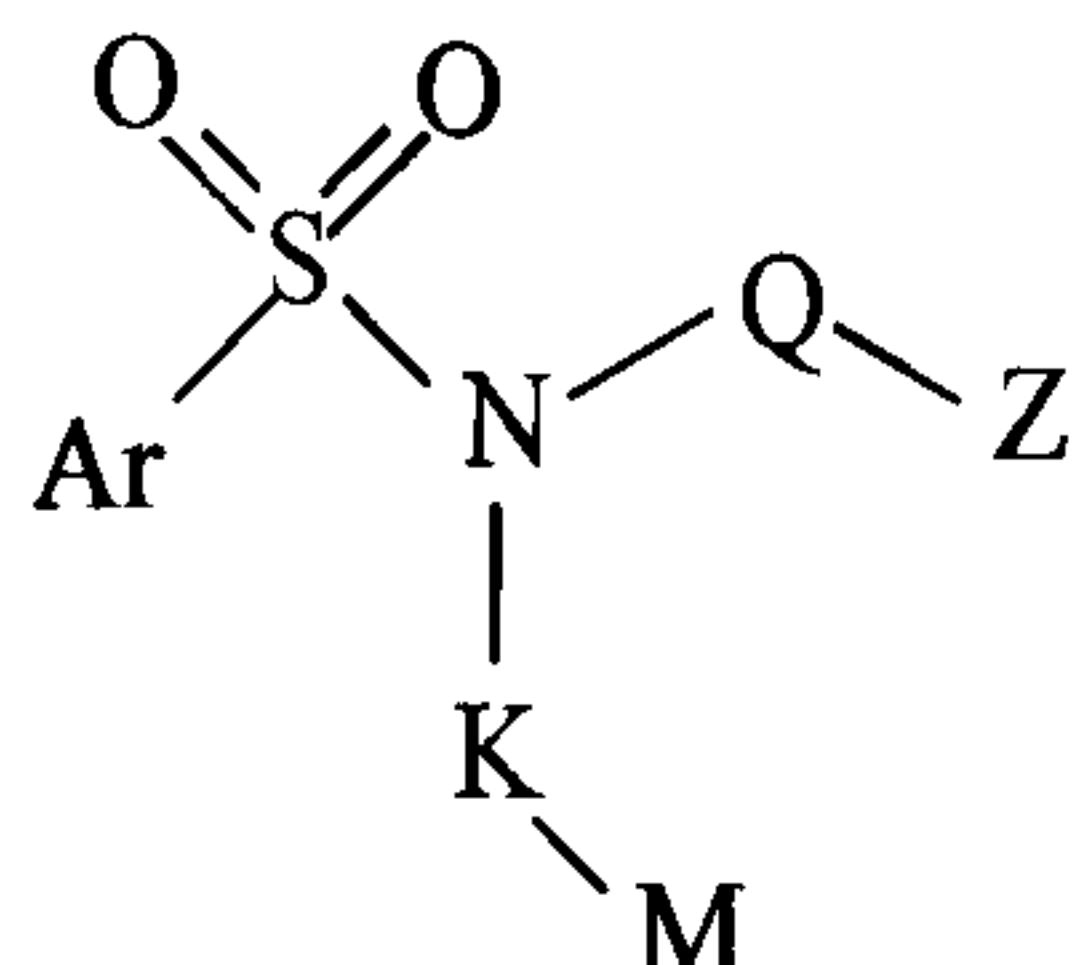
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 5 alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio, (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene
 10 optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

103. A compound having the Formula:

15



Q is -(C₁-C₃)alkylene-X-(C₁-C₃)alkylene-, the
 20 alkylenes each optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
 25 (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when

72222-402

-315-

K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated
 5 five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently,
 10 optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally
 15 having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully
 20 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar
 25 is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,
 30 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl,

72222-402

-316-

aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 5 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³ or -Ar³-O-Ar³;

10 Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully
 15 saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully
 20 unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or
 25 two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and
 30 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,

72222-402

-317-

(C₃-C₇) cycloalkyl (C₁-C₄) alkyl,
 (C₃-C₇) cycloalkyl (C₁-C₄) alkanoyl, formyl, (C₁-C₈) alkanoyl,
 (C₁-C₆) alkanoyl (C₁-C₆) alkyl, (C₁-C₄) alkanoylamino,
 (C₁-C₄) alkoxycarbonylamino, hydroxysulfonyl,
 5 aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 tri-N,N,N'-(C₁-C₄) alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄) alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄) alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄) alkylcarbamoyl, cyano, thiol, (C₁-C₆) alkylthio,
 10 (C₁-C₆) alkylsulfinyl, (C₁-C₄) alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄) alkylaminosulfinyl;

X is a five or six membered aromatic ring
 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 15 optionally mono-, di- or tri-substituted independently with
 halo, (C₁-C₃) alkyl, trifluoromethyl, trifluoromethoxy,
 difluoromethoxy, hydroxyl, (C₁-C₄) alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 20 optionally mono-, di- or tri-substituted on carbon
 independently with halo or hydroxy; and

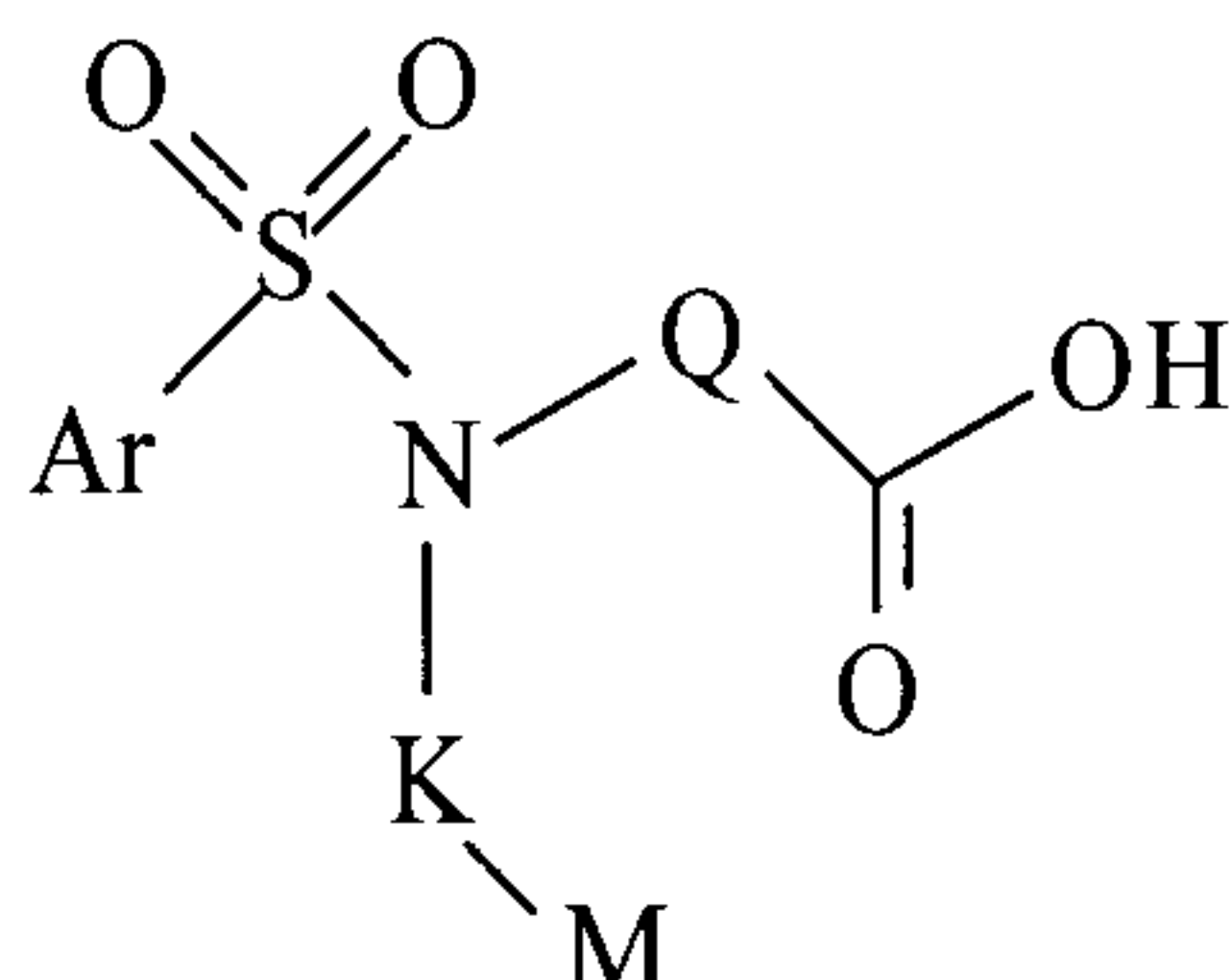
V¹ is thio(C₁-C₄) alkylene, (C₁-C₄) alkylenethio,
 (C₁-C₄) alkyleneoxy, oxy(C₁-C₄) alkylene or (C₁-C₃) alkylene
 optionally mono- or di-substituted independently with
 25 hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

72222-402

-318-

104. A compound having the Formula:



5

Q is $-(\text{C}_1\text{-C}_3)\text{alkylene-X-(C}_1\text{-C}_3)\text{alkylene-}$, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and $(\text{C}_1\text{-C}_4)\text{alkyl}$,

10 K is a bond, $(\text{C}_1\text{-C}_9)\text{alkylene}$, thio $(\text{C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkylenethio(C}_1\text{-C}_4)\text{alkylene}$, $(\text{C}_1\text{-C}_4)\text{alkyleneoxy(C}_1\text{-C}_4)\text{alkylene}$ or oxy $(\text{C}_1\text{-C}_4)\text{alkylene}$, the $(\text{C}_1\text{-C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-
 15 substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and
 20 nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a
 25 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully
 30 saturated ring, bicyclic ring or tricyclic ring optionally

72222-402

-319-

having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

72222-402

-320-

independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

72222-402

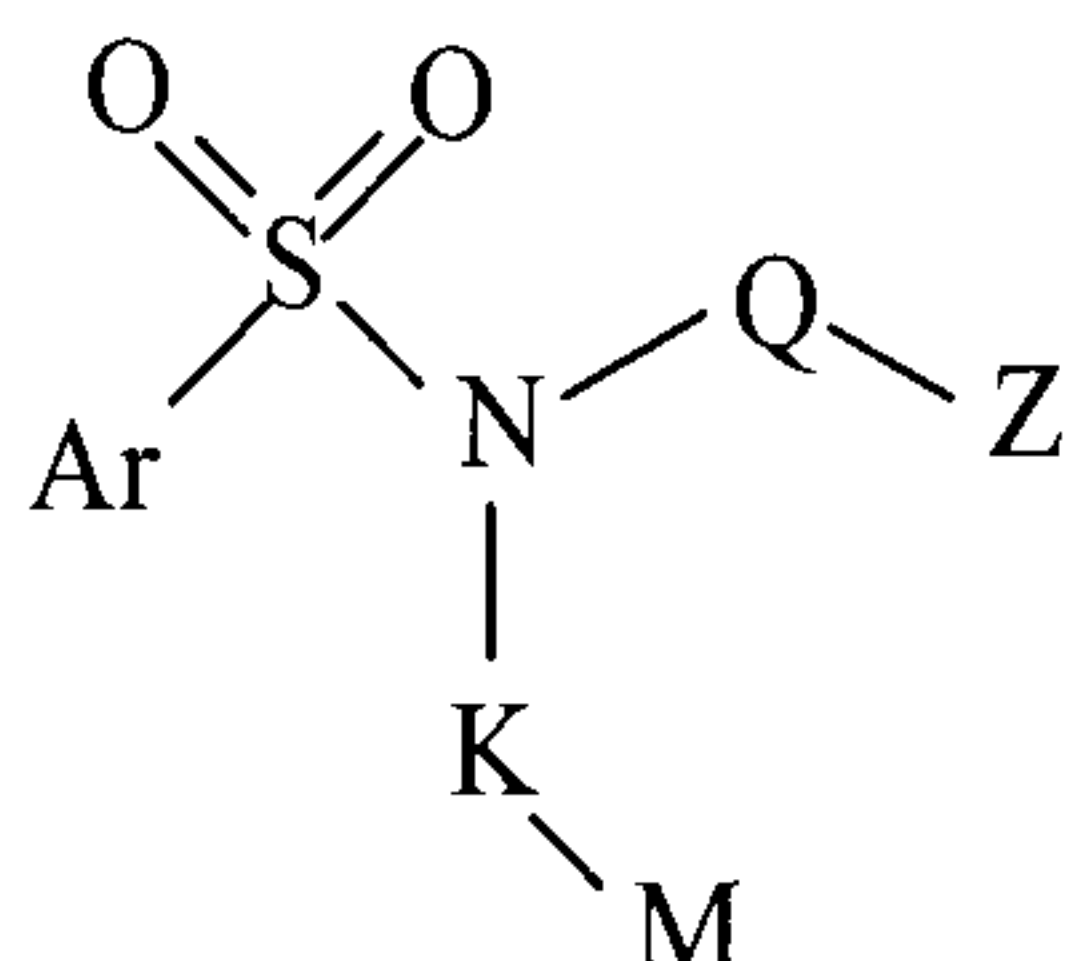
-321-

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

5 or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

105. A compound having the Formula:

10



15

Q is $-(C_1-C_3)\text{alkylene-X-(C}_1\text{-C}_3\text{)alkylene-}$, the alkylenes each optionally substituted with up to four substituents independently selected from fluoro and $(C_1-C_4)\text{alkyl}$,

Z is $(C_1-C_6)\text{alkoxycarbonyl}$;

20

K is a bond, $(C_1-C_9)\text{alkylene}$, thio $(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$, $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or oxy $(C_1-C_4)\text{alkylene}$, the $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

25

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully

72222-402

-322-

unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently

5 partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

10 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or

15 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy,

20 (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

25 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

30 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

72222-402

-323-

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,

72222-402

-324-

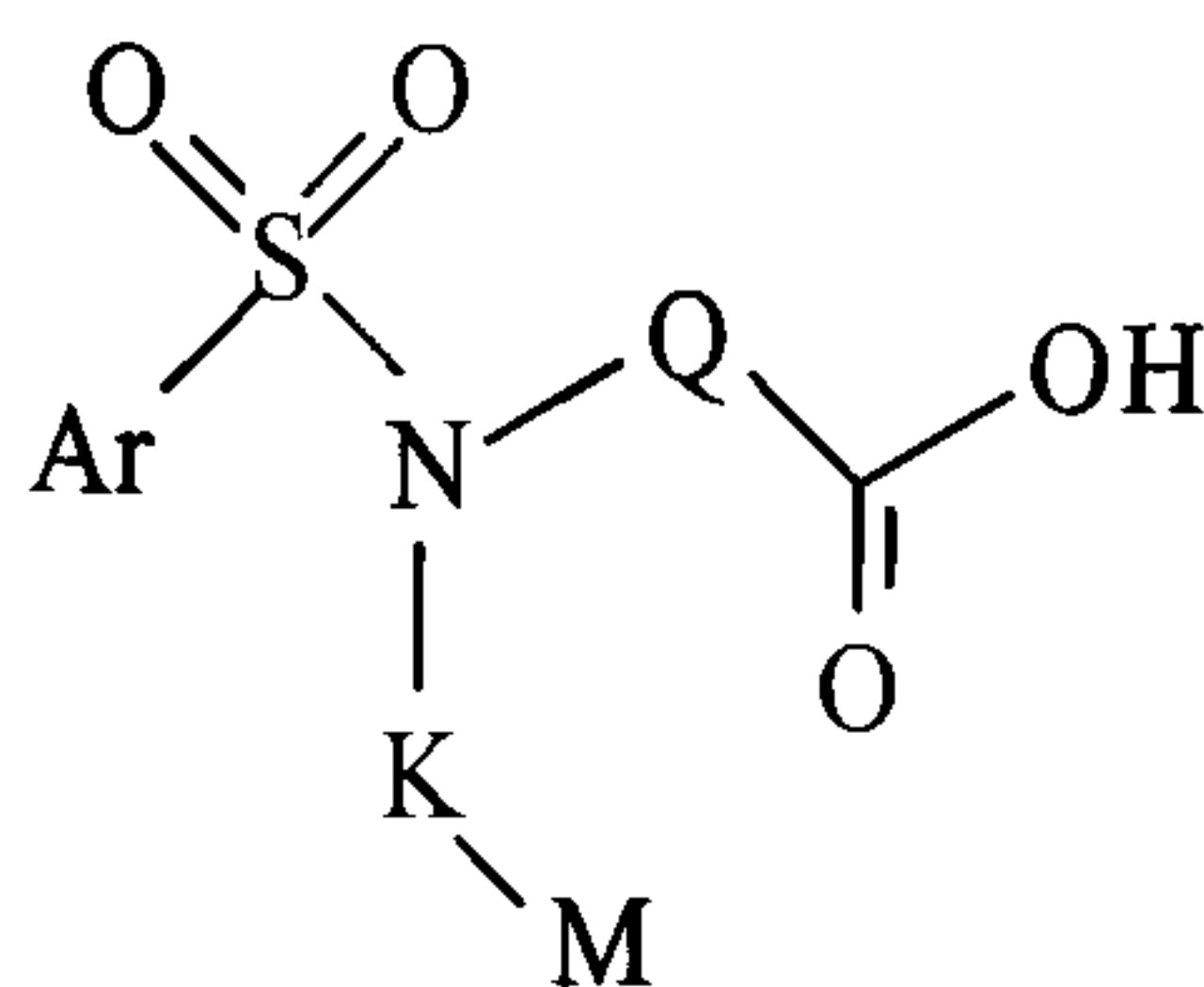
(C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

106. A compound having the Formula:



Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-

72222-402

-325-

substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four
 5 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected
 10 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from
 15 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two
 20 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently
 25 selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl,
 30 (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

72222-402

-326-

tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 5 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³;

Ar³ is a partially saturated, fully saturated or
 fully unsaturated five to eight membered ring optionally
 10 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 taken independently, optionally having one to four
 15 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 one to four heteroatoms selected independently from
 20 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 optionally substituted on carbon or nitrogen, on one ring if
 25 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 30 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,

72222-402

-327-

(C₁-C₆)alkanoyl (C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, 5 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

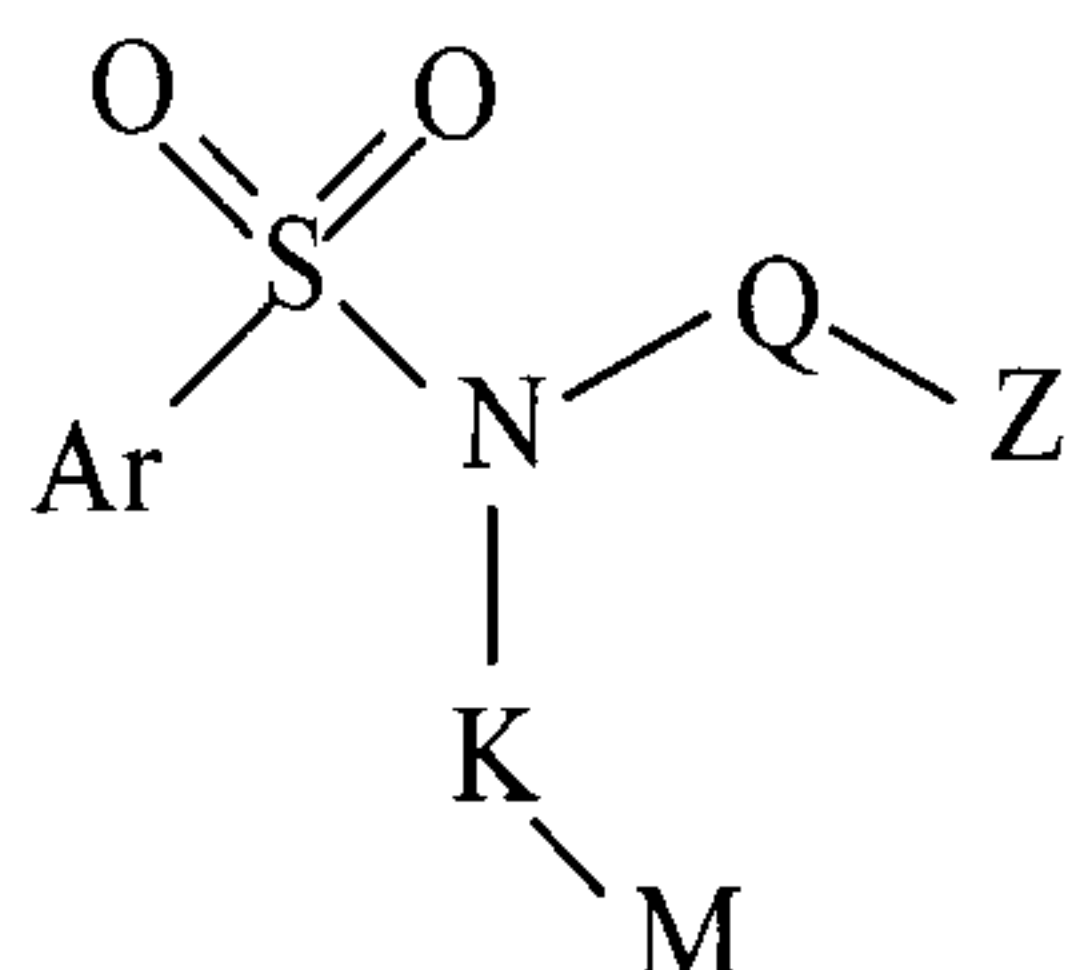
10 X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, 15 difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

20 provided that when K is (C₂-C₄)alkylene and M is Ar³ and Ar³ is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar³ is not substituted at the one position with hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of 25 the compound or prodrug.

107. A compound having the Formula:



72222-402

-328-

Q is $-(C_1-C_5)$ alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C_1-C_4) alkyl,

Z is (C_1-C_6) alkoxycarbonyl;

5 K is a bond, (C_1-C_9) alkylene, thio (C_1-C_4) alkylene, (C_1-C_4) alkylenethio (C_1-C_4) alkylene, (C_1-C_4) alkyleneoxy (C_1-C_4) alkylene or oxy (C_1-C_4) alkylene, the (C_1-C_9) alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-substituted
10 independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially
15 saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully
20 unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups
25 substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two
30 or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are

72222-402

-329-

independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,

5 (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,

10 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

15 M is Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting

20 of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused

25 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

30 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,

72222-402

-330-

or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, $(\text{C}_1\text{-C}_7)$ alkoxy, $(\text{C}_1\text{-C}_4)$ alkoxy $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl, $(\text{C}_1\text{-C}_7)$ alkyl, $(\text{C}_2\text{-C}_7)$ alkenyl, $(\text{C}_2\text{-C}_7)$ alkynyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkanoyl, formyl, $(\text{C}_1\text{-C}_8)$ alkanoyl, $(\text{C}_1\text{-C}_6)$ alkanoyl $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkanoylamino, $(\text{C}_1\text{-C}_4)$ alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-($\text{C}_1\text{-C}_4$)alkyl substituted aminocarbonylamino, sulfonamido, $(\text{C}_1\text{-C}_4)$ alkylsulfonamido, amino, mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylamino, carbamoyl, mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylcarbamoyl, cyano, thiol, $(\text{C}_1\text{-C}_6)$ alkylthio, $(\text{C}_1\text{-C}_6)$ alkylsulfinyl, $(\text{C}_1\text{-C}_4)$ alkylsulfonyl or mono-N- or di-N,N-($\text{C}_1\text{-C}_4$)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with halo, $(\text{C}_1\text{-C}_3)$ alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, $(\text{C}_1\text{-C}_4)$ alkoxy, or carbamoyl;

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

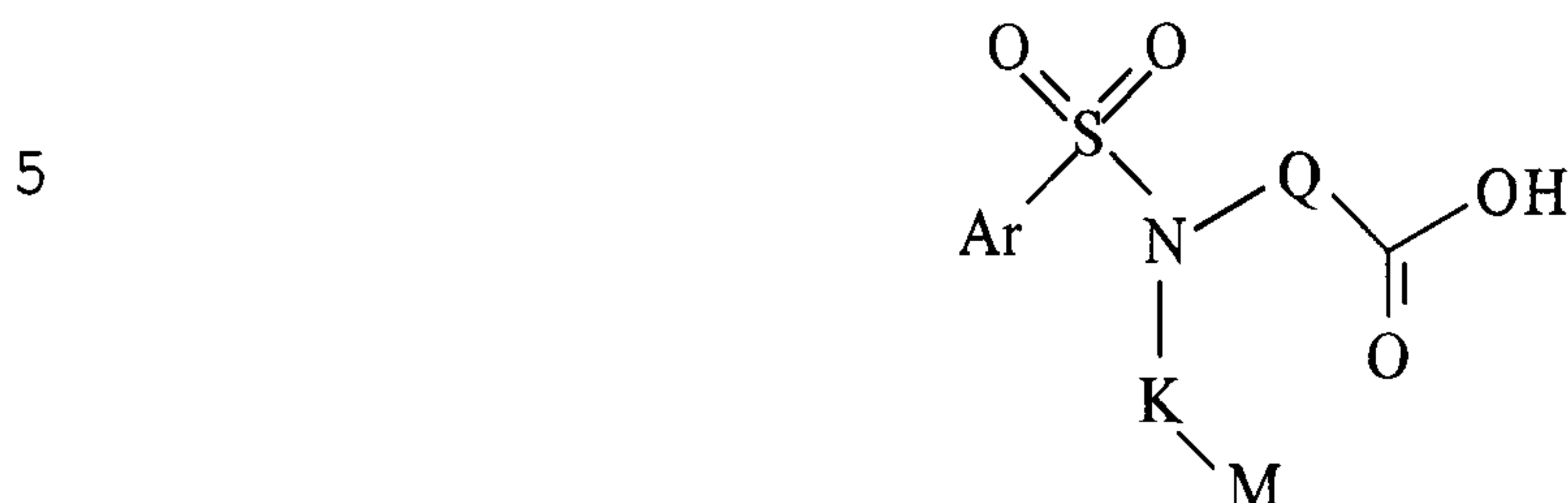
provided that when K is $(\text{C}_2\text{-C}_4)$ alkylene and M is Ar^3 and Ar^3 is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl, then Ar^3 is not substituted at the one position with hydroxy;

72222-402

-331-

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

108. A compound having the Formula:



Q is $-(\text{C}_1-\text{C}_5)\text{alkylene-X-}$, the alkylene optionally substituted with up to four substituents independently selected from fluoro and $(\text{C}_1-\text{C}_4)\text{alkyl}$,

10

K is a bond, $(\text{C}_1-\text{C}_9)\text{alkylene}$, thio $(\text{C}_1-\text{C}_4)\text{alkylene}$, $(\text{C}_1-\text{C}_4)\text{alkylenethio}(\text{C}_1-\text{C}_4)\text{alkylene}$, $(\text{C}_1-\text{C}_4)\text{alkyleneoxy}(\text{C}_1-\text{C}_4)\text{alkylene}$ or oxy $(\text{C}_1-\text{C}_4)\text{alkylene}$, the $(\text{C}_1-\text{C}_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when

15 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four

20 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected

25 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

72222-402

-332-

nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully

5 saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar

10 is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl,

15 (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

20 tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or

25 di-N,N- (C_1-C_4) alkylaminosulfinyl;

M is $-Ar^3-V^1-Ar^3$, $-Ar^3-S-Ar^3$, $-Ar^3-SO-Ar^3$, $-Ar^3-SO_2-Ar^3$ or $-Ar^3-O-Ar^3$;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally

30 having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings,

72222-402

-333-

taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

30 X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with

72222-402

-334-

halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

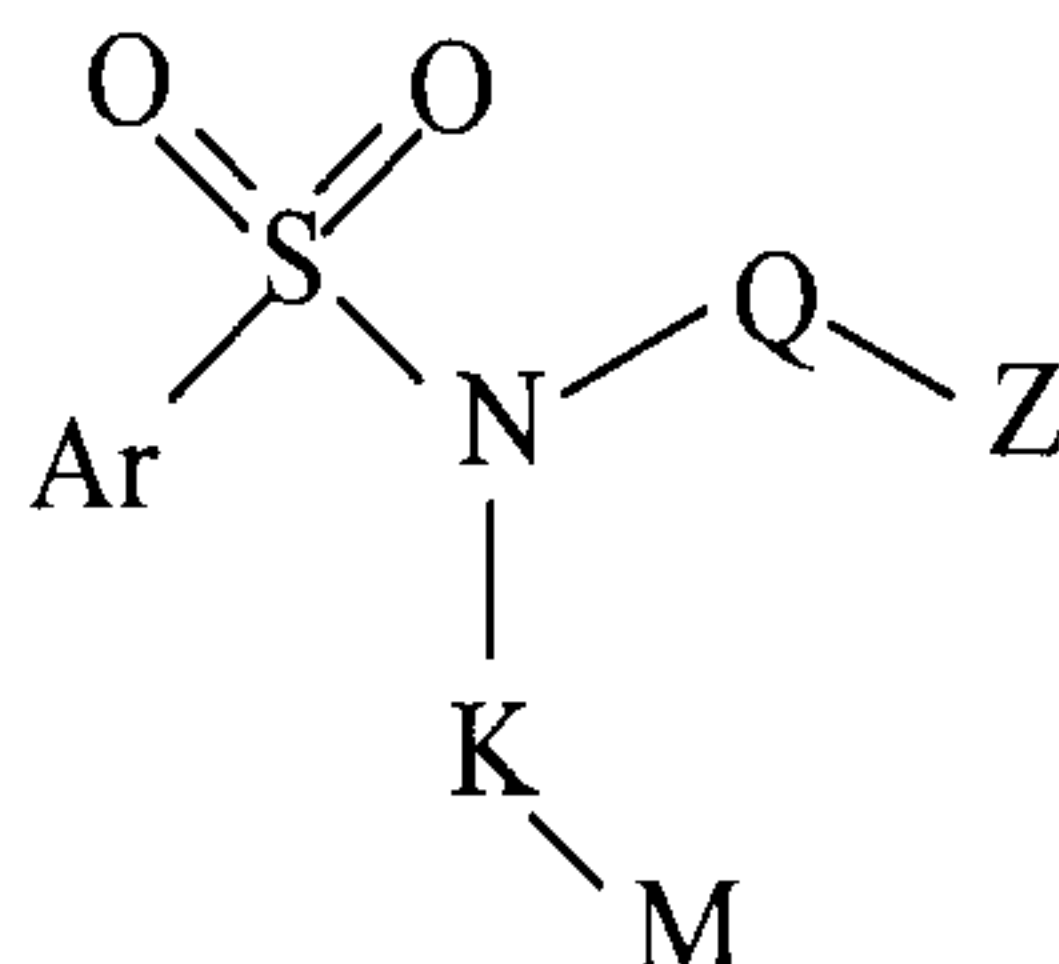
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio, (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

109. A compound having the Formula:

15



Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when K is not a bond, K is optionally mono-, di- or tri-

72222-402

-335-

substituted independently with chloro, fluoro, hydroxy or methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four
 5 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected
 10 independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from
 15 nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two
 20 heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently
 25 selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl,
 30 (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

72222-402

-336-

tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,
 sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 5 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is -Ar³-V¹-Ar³, -Ar³-S-Ar³, -Ar³-SO-Ar³, -Ar³-SO₂-Ar³
 or -Ar³-O-Ar³;

Ar³ is a partially saturated, fully saturated or
 10 fully unsaturated five to eight membered ring optionally
 having one to four heteroatoms selected independently from
 oxygen, sulfur and nitrogen, or a bicyclic ring consisting
 of two fused independently partially saturated, fully
 saturated or fully unsaturated five or six membered rings,
 15 taken independently, optionally having one to four
 heteroatoms selected independently from nitrogen, sulfur and
 oxygen, or a tricyclic ring consisting of three fused
 independently partially saturated, fully saturated or fully
 unsaturated five or six membered rings, optionally having
 20 one to four heteroatoms selected independently from
 nitrogen, sulfur and oxygen, said partially or fully
 saturated ring, bicyclic ring or tricyclic ring optionally
 having one or two oxo groups substituted on carbon or one or
 two oxo groups substituted on sulfur; wherein Ar³ is
 25 optionally substituted on carbon or nitrogen, on one ring if
 Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic,
 or on one, two or three rings if Ar³ is tricyclic, with up to
 three substituents independently selected from R³¹, R⁴¹ and
 R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 30 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl,
 (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl,
 (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl,
 (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,

72222-402

-337-

(C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or
 5 tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 10 di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with
 15 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

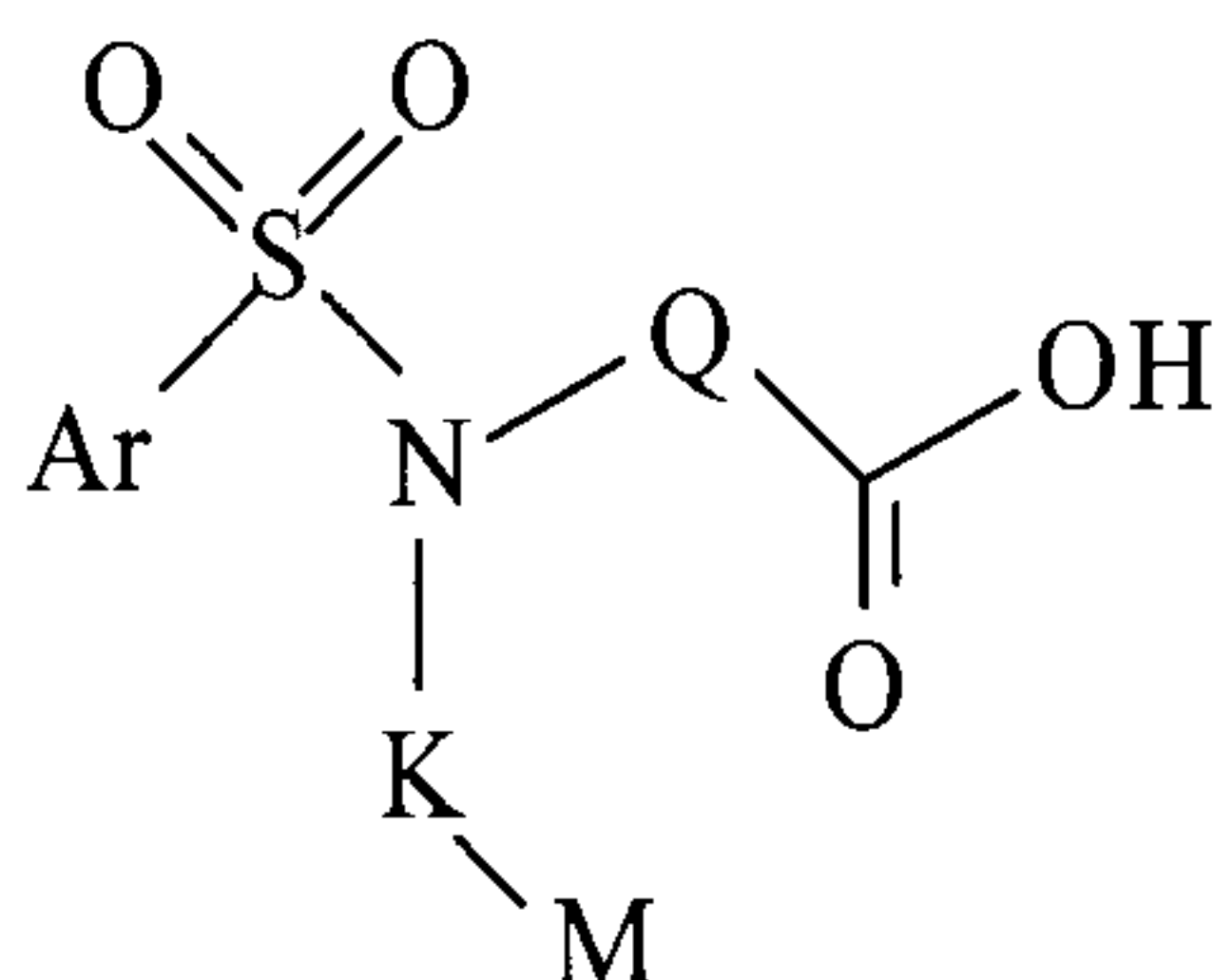
R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon
 20 independently with halo or hydroxy; and

V¹ is thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio, (C₁-C₄)alkyleneoxy, oxy(C₁-C₄)alkylene or (C₁-C₃)alkylene optionally mono- or di-substituted independently with hydroxy or fluoro;
 25 or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

72222-402

-338-

110. A compound having the Formula:



5

Q is $-(C_1-C_5)\text{alkylene-X-}$, the alkylene optionally substituted with up to four substituents independently selected from fluoro and $(C_1-C_4)\text{alkyl}$,

K is a bond, $(C_1-C_9)\text{alkylene}$, thio $(C_1-C_4)\text{alkylene}$,
 10 $(C_1-C_4)\text{alkylenethio}(C_1-C_4)\text{alkylene}$,
 $(C_1-C_4)\text{alkyleneoxy}(C_1-C_4)\text{alkylene}$ or oxy $(C_1-C_4)\text{alkylene}$, the
 $(C_1-C_9)\text{alkylene}$ optionally mono-unsaturated and wherein, when
 K is not a bond, K is optionally mono-, di- or tri-
 substituted independently with chloro, fluoro, hydroxy or
 15 methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused
 20 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently
 25 partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally
 30 having one or two oxo groups substituted on carbon or one or

72222-402

-339-

two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

M is Ar³-Ar³;

Ar³ is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully

72222-402

-340-

unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally

5 having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to

10 three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, $(\text{C}_1\text{-C}_7)$ alkoxy, $(\text{C}_1\text{-C}_4)$ alkoxy $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl, $(\text{C}_1\text{-C}_7)$ alkyl, $(\text{C}_2\text{-C}_7)$ alkenyl, $(\text{C}_2\text{-C}_7)$ alkynyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl,

15 $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl $(\text{C}_1\text{-C}_4)$ alkanoyl, formyl, $(\text{C}_1\text{-C}_8)$ alkanoyl, $(\text{C}_1\text{-C}_6)$ alkanoyl $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkanoylamino, $(\text{C}_1\text{-C}_4)$ alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or

20 tri-N,N,N'- $(\text{C}_1\text{-C}_4)$ alkyl substituted aminocarbonylamino, sulfonamido, $(\text{C}_1\text{-C}_4)$ alkylsulfonamido, amino, mono-N- or di-N,N- $(\text{C}_1\text{-C}_4)$ alkylamino, carbamoyl, mono-N- or di-N,N- $(\text{C}_1\text{-C}_4)$ alkylcarbamoyl, cyano, thiol, $(\text{C}_1\text{-C}_6)$ alkylthio, $(\text{C}_1\text{-C}_6)$ alkylsulfinyl, $(\text{C}_1\text{-C}_4)$ alkylsulfonyl or mono-N- or

25 di-N,N- $(\text{C}_1\text{-C}_4)$ alkylaminosulfinyl;

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with

30 halo, $(\text{C}_1\text{-C}_3)$ alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, $(\text{C}_1\text{-C}_4)$ alkoxy, or carbamoyl; and

R^3 , R^4 , R^5 , R^{31} , R^{41} and R^{51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are

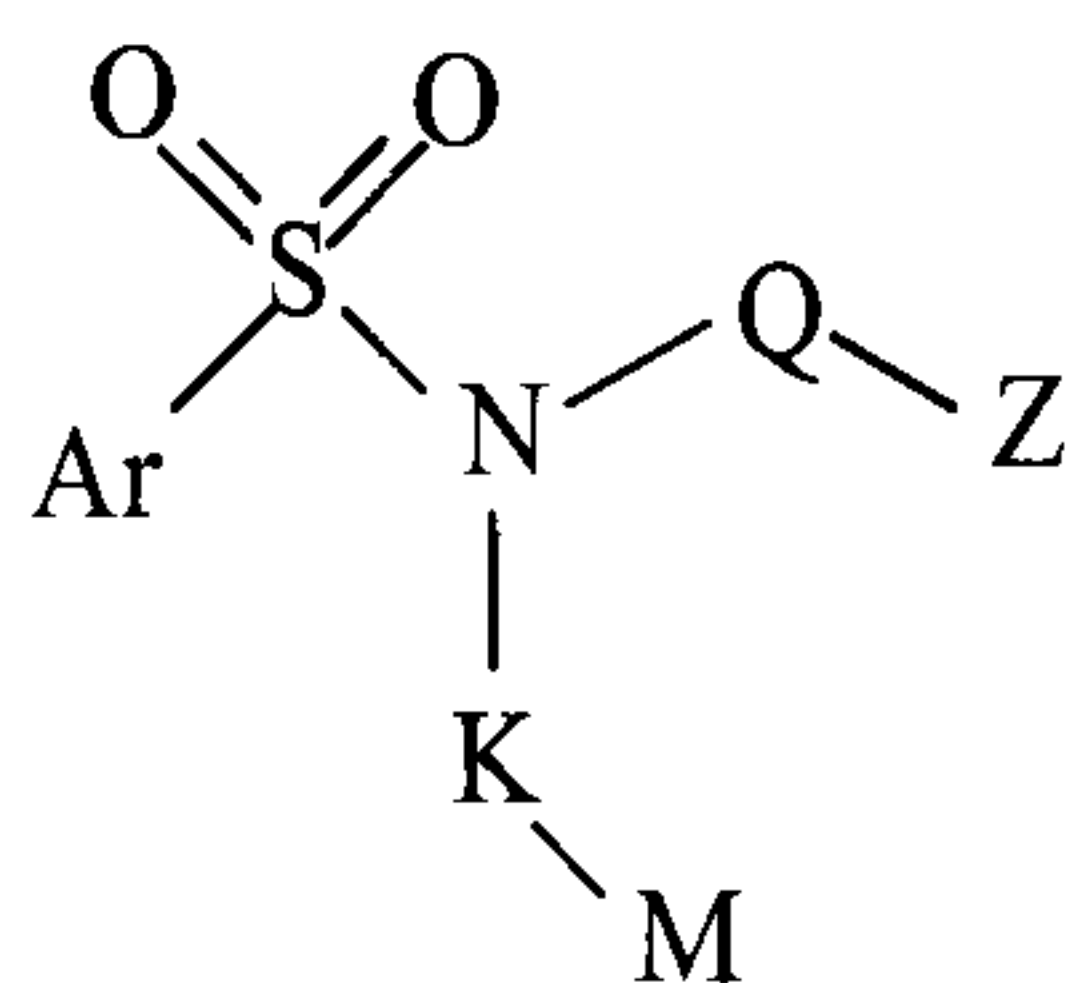
72222-402

-341-

optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

5 111. A compound having the Formula:



10 Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently selected from fluoro and (C₁-C₄)alkyl,

Z is (C₁-C₆)alkoxycarbonyl;

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene,
 15 (C₁-C₄)alkylenethio(C₁-C₄)alkylene,
 (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the
 (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
 K is not a bond, K is optionally mono-, di- or tri-
 substituted independently with chloro, fluoro, hydroxy or
 20 methyl;

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused
 25 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a

72222-402

-342-

tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino, (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C_1-C_4)alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N-(C_1-C_4)alkylamino, carbamoyl, mono-N- or di-N,N-(C_1-C_4)alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N-(C_1-C_4)alkylaminosulfinyl;

30 M is Ar^3-Ar^3 ;

Ar^3 is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from

72222-402

-343-

oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four

5 heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having one to four heteroatoms selected independently from

10 nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar^3 is optionally substituted on carbon or nitrogen, on one ring if

15 Ar^3 is monocyclic, on one or both rings if Ar^3 is bicyclic, or on one, two or three rings if Ar^3 is tricyclic, with up to three substituents independently selected from R^{31} , R^{41} and R^{51} wherein R^{31} , R^{41} and R^{51} are independently hydroxy, nitro, halo, carboxy, (C_1-C_7) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl,

20 (C_1-C_4) alkoxycarbonyl, (C_1-C_7) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl (C_1-C_4) alkanoyl, formyl, (C_1-C_8) alkanoyl, (C_1-C_6) alkanoyl (C_1-C_6) alkyl, (C_1-C_4) alkanoylamino,

25 (C_1-C_4) alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'- (C_1-C_4) alkyl substituted aminocarbonylamino, sulfonamido, (C_1-C_4) alkylsulfonamido, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, carbamoyl, mono-N- or

30 di-N,N- (C_1-C_4) alkylcarbamoyl, cyano, thiol, (C_1-C_6) alkylthio, (C_1-C_6) alkylsulfinyl, (C_1-C_4) alkylsulfonyl or mono-N- or di-N,N- (C_1-C_4) alkylaminosulfinyl;

72222-402

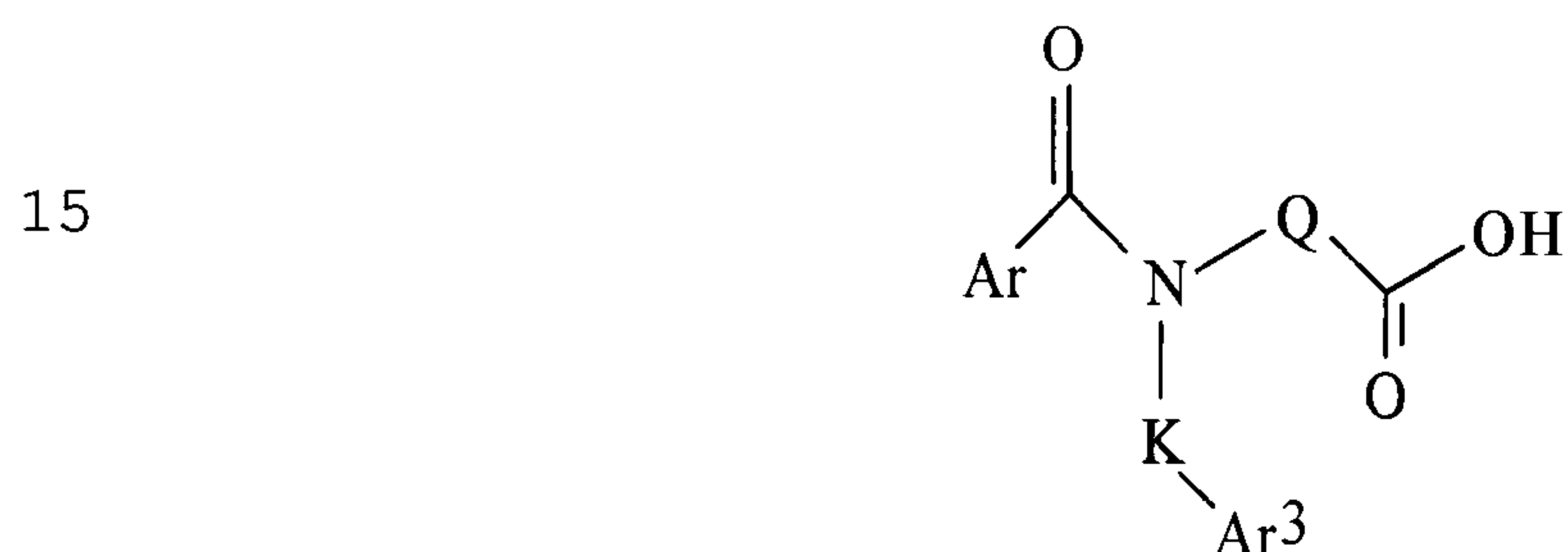
-344-

X is a five or six membered aromatic ring optionally having one or two heteroatoms selected independently from oxygen, nitrogen, and sulfur; the ring optionally mono-, di- or tri-substituted independently with
 5 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl; and

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon
 10 independently with halo or hydroxy;

or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug.

112. A compound having the Formula:



Q is -(C₁-C₅)alkylene-X-, the alkylene optionally substituted with up to four substituents independently
 20 selected from fluoro and (C₁-C₄)alkyl,

K is a bond, (C₁-C₉)alkylene, thio(C₁-C₄)alkylene, (C₁-C₄)alkylenethio(C₁-C₄)alkylene, (C₁-C₄)alkyleneoxy(C₁-C₄)alkylene or oxy(C₁-C₄)alkylene, the (C₁-C₉)alkylene optionally mono-unsaturated and wherein, when
 25 K is not a bond, K is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl;

72222-402

-345-

Ar is a partially saturated or fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused

5 independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a

10 tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, the partially or fully

15 saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; or Ar is a fully saturated five to seven membered ring having one or two heteroatoms selected independently from oxygen, sulfur and nitrogen; wherein Ar is optionally substituted on carbon or

20 nitrogen, on one ring if Ar is monocyclic, on one or both rings if Ar is bicyclic, or on one, two or three rings if Ar is tricyclic, with up to three substituents independently selected from R^3 , R^4 and R^5 wherein R^3 , R^4 and R^5 are independently hydroxy, nitro, halo, carboxy, (C₁-C₇)alkoxy,

25 (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl,

(C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl, (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino,

30 (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or

72222-402

-346-

di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfinyl;

Ar³ is a partially saturated, fully saturated or
 5 fully unsaturated five to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings,
 10 taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five or six membered rings, optionally having
 15 one to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur; wherein Ar³ is
 20 optionally substituted on carbon or nitrogen, on one ring if Ar³ is monocyclic, on one or both rings if Ar³ is bicyclic, or on one, two or three rings if Ar³ is tricyclic, with up to three substituents independently selected from R³¹, R⁴¹ and R⁵¹ wherein R³¹, R⁴¹ and R⁵¹ are independently hydroxy, nitro,
 25 halo, carboxy, (C₁-C₇)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₇)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkanoyl, formyl, (C₁-C₈)alkanoyl,
 30 (C₁-C₆)alkanoyl(C₁-C₆)alkyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C₁-C₄)alkyl substituted aminocarbonylamino,

72222-402

-347-

sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or
 di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or
 di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₆)alkylthio,
 (C₁-C₆)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or
 5 di-N,N-(C₁-C₄)alkylaminosulfinyl;

X is a five or six membered aromatic ring
 optionally having one or two heteroatoms selected
 independently from oxygen, nitrogen, and sulfur; the ring
 optionally mono-, di- or tri-substituted independently with
 10 halo, (C₁-C₃)alkyl, trifluoromethyl, trifluoromethoxy,
 difluoromethoxy, hydroxyl, (C₁-C₄)alkoxy, or carbamoyl;

R³, R⁴, R⁵, R³¹, R⁴¹ and R⁵¹, when containing an
 alkyl, alkylene, alkenylene or alkynylene moiety, are
 optionally mono-, di- or tri-substituted on carbon
 15 independently with halo or hydroxy; and

provided that when K is (C₂-C₄)alkylene and Ar³ is
 cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or
 cyclooct-1-yl, then Ar³ is not substituted at the one
 position with hydroxy;

20 or a prodrug thereof, or a pharmaceutically acceptable salt of
 the compound or prodrug.

113. The compound of any one of claims 83 to 112, a
 prodrug thereof or a pharmaceutically acceptable salt of the
 compound or the prodrug, wherein Ar is phenyl, furyl,
 25 thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl,
 pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl,
 pyrimidinyl, pyrazinyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl,
 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl,
 2H-imidazolyl, 2-imidazolyl, imidazolidinyl,
 30 2-pyrazolinyl, pyrazolidinyl, 1,2,3-oxadiazolyl,
 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,

72222-402

-348-

1,2,3-triazolyl, 1,2,4-triazolyl, 2H-pyranyl, 4H-pyranyl, pyridyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, azepinyl, oxepinyl, 5 thiopinyl, cyclopentenyl, cyclohexenyl, benzo(b)thienyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl or 1,4-benzodioxan; and wherein each Ar is optionally 10 substituted on carbon or nitrogen independently with up to three substituents independently selected from R³, R⁴ and R⁵, on carbon or sulfur with one or two oxo groups, on carbon or nitrogen independently with up to three R³¹, R⁴¹ and R⁵¹ groups and on carbon or sulfur with one or two oxo groups.

15 114. The compound of any one of claims 83 to 112, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar³ is cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 20 isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2H-imidazolyl, 2-imidazolyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 25 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 2H-pyranyl, 4H-pyranyl, pyridyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinylpiperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, azepinyl, oxepinyl, thiopinyl, 30 1,2,4-diazepinyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclooctadienyl, indolizinyll, indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl,

72222-402

-349-

isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl,
 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl,
 benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyll,
 quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl,
 5 quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl,
 indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl,
 2H-1-benzopyranyl, 1,4-benzodioxan, pyrido(3,4-b)-pyridinyl,
 pyrido(3,2-b)-pyridinyl, pyrido(4,3-b)-pyridinyl,
 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl,
 10 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl,
 2H-1,2-benzoxazinyl or 4H-1,4-benzoxazinyl.

115. The compound of any one of claims 83 to 87 and 100
 to 112, a prodrug thereof or a pharmaceutically acceptable
 salt of the compound or of the prodrug, wherein X is
 15 tetrahydrofuranyl, phenyl, thiazolyl, thienyl, pyridyl,
 pyrrazolyl, furanyl or pyrimidyl, wherein X is optionally
 mono-, di- or tri-substituted independently with chloro,
 fluoro, methoxy, difluoromethoxy, trifluoromethoxy,
 trifluoromethyl or methyl.

20 116. The compound of any one of claims 83 to 87 and 94
 to 99, a prodrug thereof or a pharmaceutically acceptable
 salt of the compound or of the prodrug, wherein W is O.

117. The compound of any one of claims 83 to 87 and 100
 to 112, a prodrug thereof or a pharmaceutically acceptable
 25 salt of the compound or of the prodrug, wherein X is phenyl,
 thienyl, furanyl or thiazolyl, wherein X is optionally
 mono-, di- or tri-substituted with chloro, fluoro, methoxy,
 difluoromethoxy, trifluoromethoxy, trifluoromethyl or
 methyl.

30 118. The compound of any one of claims 83 to 112, a
 prodrug thereof or a pharmaceutically acceptable salt of the
 compound or the prodrug, wherein Ar is phenyl, furyl,

72222-402

-350-

thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl or 1,3,4-thiadiazolyl wherein each of the Ar groups is
5 optionally substituted on carbon or nitrogen with R³.

119. The compound of any one of claims 83 to 112, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar³ is cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, furyl, thienyl,
10 pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolidinyl, 1,4-dioxanyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, thiomorpholinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, azepinyl,
15 oxepinyl or thiepinyl wherein each of the Ar³ groups is optionally mono- di- or tri-substituted on carbon or nitrogen with R³¹, R⁴¹ or R⁵¹.

120. The compound of any one of claims 83 to 87 and 100 to 112, a prodrug thereof or a pharmaceutically acceptable
20 salt of the compound or of the prodrug, wherein X is phenyl, pyridyl, pyrimidyl or thienyl; and the X groups are optionally mono-, di- or tri- substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

25 121. The compound of any one of claims 83 to 112, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein K is methylene.

122. The compound of any one of claims 83 to 112, a prodrug thereof or a pharmaceutically acceptable salt of the
30 compound or the prodrug, wherein Ar is phenyl, pyridyl, pyrazolyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, and

72222-402

-351-

wherein Ar is optionally mono-, di- or tri-substituted on carbon or nitrogen with R³, R⁴ or R⁵.

123. The compound of any one of claims 83 to 112, a prodrug thereof or a pharmaceutically acceptable salt of the
5 compound or the prodrug, wherein Ar is phenyl, pyridyl or imidazolyl, and Ar³ is phenyl, furanyl, pyridyl, cyclopentyl, cyclohexyl, cycloheptyl, imidazolyl, pyrimidyl, thienyl, pyridazinyl, pyrazinyl, pyrazolyl or thiazolyl, and wherein Ar and Ar³ are optionally mono-, di- or tri-substituted on
10 carbon or nitrogen independently with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy.

124. The compound of any one of claims 88 to 93, a prodrug thereof or a pharmaceutically acceptable salt of the
15 compound or the prodrug, wherein Q is -(C₅-C₇)alkylene-.

125. The compound of any one of claims 100 to 105, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is CH₂-X-CH₂- and X is metaphenylene optionally mono- or di- substituted with
20 chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

126. The compound (3-(((pyridine-3-sulfonyl)-(4-pyrimidin-5-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

25 127. The compound (3-(((5-phenyl-furan-2-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

128. The compound (3-(((pyridine-3-sulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino)-methyl)-phenyl)-acetic
30 acid, or a pharmaceutically acceptable salt thereof.

72222-402

-352-

129. The compound (3-(((pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

130. The compound (3-(((4-pyrazin-2-yl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or
5 a pharmaceutically acceptable salt thereof.

131. The compound, prodrug or salt of claim 104, wherein Ar is pyrid-3-yl; M is Ar³-Ar³ wherein one Ar³ is a furanyl ring and one Ar³ is a phenyl wherein the phenyl
10 moiety is substituted at the 5-position of the furanyl ring; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

132. The compound, prodrug or salt of claim 104, wherein Ar is pyrid-3-yl; M is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is pyrimid-2-yl and the pyrimid-2-yl
15 moiety is substituted at the 4-position of the phenyl ring; and Q is -CH₂-X-CH₂-wherein X is metaphenylene.

133. The compound, prodrug or salt of claim 104, wherein Ar is pyrid-3-yl; M is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is thiazol-2-yl and the thiazol-2-yl
20 moiety is substituted at the 4-position of the phenyl ring; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

134. The compound, prodrug or salt of claim 104, wherein Ar is pyrid-3-yl; M is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is pyrimid-5-yl and the pyrimid-5-yl
25 moiety is substituted at the 4-position of the phenyl ring; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

135. The compound, prodrug or salt of claim 104, wherein Ar is pyrid-3-yl; M is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is pyrazin-2-yl and the pyrazin-2-yl is

72222-402

-353-

substituted at the 4-position of the phenyl ring; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

136. The compound 5-(3-((pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-propyl)-thiophene-2-carboxylic acid, or a pharmaceutically acceptable salt thereof.

137. The compound of any one of claims 83 to 87, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -CH₂-X-O-CH₂-; Ar³ is phenyl or pyridyl; the phenyl and pyridyl are optionally substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl and methyl; and X is metaphenylene.

138. The compound (3-(((4-cyclohexyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof.

139. The compound (3-(((pyridine-3-sulfonyl)-(4-pyridin-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof.

140. The compound (3-(((pyridine-3-sulfonyl)-(4-pyridin-3-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof.

141. The compound (3-(((pyridine-3-sulfonyl)-(4-pyridin-4-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof.

142. The compound (3-(((pyridine-3-sulfonyl)-(4-thiazol-2-yl-benzyl)-amino)-methyl)-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof.

143. The compound, prodrug or salt of claim 86, wherein Q is -CH₂-X-O-CH₂-; X is metaphenylene; Ar is pyrid-3-yl; M

72222-402

-354-

is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is cyclohexyl; and the cyclohexyl moiety is substituted at the 4-position of the phenyl ring.

144. The compound, prodrug or salt of claim 86, wherein
5 Q is -CH₂-X-O-CH₂-; X is metaphenylene; Ar is pyrid-3-yl; M is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is thiazol-2-yl; and the thiazol-2-yl moiety is substituted at the 4-position of the phenyl ring.

145. The compound, prodrug or salt of claim 86, wherein
10 Q is -CH₂-X-O-CH₂-; X is metaphenylene; Ar is pyrid-3-yl; M is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is 2-pyridyl; and the 2-pyridyl moiety is substituted at the 4-position of the phenyl ring.

146. The compound, prodrug or salt of claim 86, wherein
15 Q is -CH₂-X-O-CH₂-; X is metaphenylene; Ar is pyrid-3-yl; M is Ar³-Ar³ and one Ar³ is phenyl and one Ar³ is 3-pyridyl; and the 3-pyridyl moiety is substituted at the 4-position of the phenyl ring.

147. The compound, prodrug or salt of claim 86, wherein
20 Q is -CH₂-X-O-CH₂-; X is metaphenylene; Ar is pyrid-3-yl; M is Ar³-Ar³ and one Ar³ is phenyl and one Ar³ is 4-pyridyl; and the 4-pyridyl moiety is substituted at the 4-position of the phenyl ring.

148. The compound of claim 83, 88, 89, 94, 95, 100,
25 101, 106 or 107, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein K is methylene; Ar is phenyl, pyridazinyl, pyrazolyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, Ar is optionally mono-, di- or tri-substituted with R³, R⁴ or R⁵;
30 and M is Ar³, wherein Ar³ is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl,

72222-402

-355-

benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R^{31} , chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy.

149. The compound (3-(((2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

150. The compound (3-((benzofuran-2-ylmethyl-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

151. The compound, prodrug or salt of claim 100, wherein Ar is pyrid-3-yl; M is 6-(1,4-benzodioxan); and Q is $-CH_2-X-CH_2-$ wherein X is metaphenylene.

152. The compound, prodrug or salt of claim 100, wherein Ar is pyrid-3-yl; M is 2-benzofuryl; and Q is $-CH_2-X-CH_2-$ wherein X is metaphenylene.

153. The compound of claim 148, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar is phenyl, pyridyl or imidazolyl, the phenyl, pyridyl and imidazolyl optionally substituted independently with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; Ar^3 is phenyl substituted with R^{31} , wherein R^{31} is (C_1-C_7) alkyl, mono-N- or di-N, N- (C_1-C_4) alkylamine, or (C_1-C_5) alkoxy, the (C_1-C_7) alkyl or (C_1-C_5) alkoxy optionally mono-, di- or tri-substituted with independently hydroxy or fluoro; and Ar^3 is further optionally mono- or di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

72222-402

-356-

154. The compound of claim 88 or 89, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is $-(C_5-C_7)\text{alkylene-}$; K is methylene; Ar is phenyl, pyridazinyl, pyrazolyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, Ar is optionally mono-, di- or tri-substituted with R^3 , R^4 or R^5 ; and M is Ar^3 , wherein Ar^3 is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R^{31} , chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy.
155. The compound of claim 100 or 101, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is $-CH_2-X-CH_2-$; X is phenyl optionally mono-, di- or tri- substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl; K is methylene; Ar is phenyl, pyridazinyl, pyrazolyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, Ar is optionally mono-, di- or tri-substituted with R^3 , R^4 or R^5 ; and M is Ar^3 , wherein Ar^3 is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R^{31} , chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy.
156. The compound (3-(((4-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

72222-402

-357-

157. The compound (3-((benzenesulfonyl-(4-butyl-benzyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

158. The compound (3-(((4-butyl-benzyl)-(1-methyl-1H-
5 imidazole-4-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

159. The compound (3-(((4-dimethylamino-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

10 160. The compound, prodrug or salt of claim 100, wherein Ar is pyrid-3-yl; M is phenyl substituted at the 4-position with n-butyl; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

161. The compound, prodrug or salt of claim 100, wherein
15 Ar is phenyl; M is phenyl substituted at the 4-position with n-butyl; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

162. The compound, prodrug or salt of claim 100, wherein Ar is 4-(1-methyl-imidazolyl); M is phenyl substituted at the 4-position with n-butyl; and Q is -CH₂-X-CH₂- wherein X is
20 metaphenylene.

163. The compound, prodrug or salt of claim 100, wherein Ar is pyrid-3-yl; M is phenyl substituted at the 4-position with dimethylamino; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

25 164. The compound of any one of claims 106 to 111, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -(C₂-C₄)-alkylene-thienyl-, -(C₂-C₄)-alkylene-furanyl- or -(C₂-C₄)-alkylene-thiazolyl-.

72222-402

-358-

165. The compound, prodrug or salt of claim 110, wherein Q is n-propylenylthienyl; Ar is 3-pyridyl; M is Ar³-Ar³ wherein one Ar³ is phenyl and one Ar³ is 2-thiazolyl; the 2-thiazolyl being substituted at the 4-position of the
5 phenyl.

166. The compound, prodrug or salt of claim 164, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar is phenyl, pyridyl or imidazolyl, the phenyl, pyridyl and imidazolyl optionally
10 substituted independently with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; Ar³ is phenyl substituted with R³¹, wherein R³¹ is (C₁-C₇)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylamine, or (C₁-C₅)alkoxy, the (C₁-C₇)alkyl or (C₁-C₅)alkoxy optionally
15 mono-, di- or tri-substituted with independently hydroxy or fluoro; and Ar³ is further optionally mono- or di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

167. The compound of any one of claims 83 to 87, a
20 prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -(C₁-C₂)-X-O-(C₁-C₂)alkylene-.

168. The compound, salt or prodrug of claim 167, wherein X is metaphenylene, the X being optionally mono-,
25 di- or tri-substituted with chloro, fluoro, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl or methyl.

169. The compound, salt or prodrug of claim 168, wherein Ar is phenyl, pyridyl or imidazolyl, the phenyl,
30 pyridyl and imidazolyl optionally substituted independently with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; Ar³ is phenyl

72222-402

-359-

substituted with R^{31} , wherein R^{31} is (C_1-C_7) alkyl, mono-N- or di-N, N- (C_1-C_4) alkylamine, or (C_1-C_5) alkoxy, the (C_1-C_7) alkyl or (C_1-C_5) alkoxy optionally mono-, di- or tri-substituted with independently hydroxy or fluoro; and Ar^3 is further
5 optionally mono- or di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

170. The compound (3-(((4-dimethylamino-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid,
10 or a pharmaceutically acceptable salt thereof.

171. The compound (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof.

172. The compound, prodrug or salt of claim 83, wherein
15 Ar is pyrid-3-yl; M is phenyl substituted at the 4-position with dimethylamino; and Q is $-CH_2-X-O-CH_2-$ wherein X is metaphenylene.

173. The compound, prodrug or salt of claim 83, wherein
Ar is pyrid-3-yl; M is phenyl substituted at the 4-position
20 with *tert*-butyl; and Q is $-CH_2-X-O-CH_2-$ wherein X is metaphenylene.

174. The compound of claim 83, 88, 89, 94, 95, 100, 101, 106 or 107, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein K is
25 (C_2-C_4) alkylene or n-propenylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted with R^3 , R^4 or R^5 ; and M is Ar^3 , optionally mono-, di- or tri-substituted with chloro, fluoro, methyl,
30 methoxy, difluoromethoxy, trifluoromethoxy and trifluoromethyl.

72222-402

-360-

175. The compound *trans*-(3-(((3-(3,5-dichloro-phenyl)-allyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenyl)-acetic acid, or a pharmaceutically acceptable salt thereof.

176. The compound, prodrug or salt of claim 100,
5 wherein K is *trans*-n-propenylene, the M group being attached to the 1-position of the n-propenylene and the N atom being attached to the 3-position of the n-propenylene; Ar is pyrid-3-yl; M is phenyl 3,5-disubstituted with chloro; and Q is -CH₂-X-CH₂- wherein X is metaphenylene.

10 177. The compound of claim 174, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar³ is phenyl optionally substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

15 178. The compound of claim 88 or 89, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -(C₅-C₇)alkylene-; K is (C₂-C₄)alkylene or n-propenylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or
20 thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted with R³, R⁴ or R⁵; and M is Ar³, and wherein Ar³ is phenyl optionally substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

25 179. The compound, prodrug or salt of claim 100 or 101, wherein Q is -CH₂-X-CH₂- and X is metaphenylene; K is (C₂-C₄)alkylene or n-propenylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or
30 tri-substituted with R³, R⁴ or R⁵; and M is Ar³, and wherein Ar³ is phenyl optionally substituted with chloro, fluoro,

72222-402

-361-

methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

180. The compound of claim 106 or 107, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is $-(C_2-C_4)\text{alkylene-X-}$ and X is furanyl, thienyl or thiazolyl; K is $(C_2-C_4)\text{alkylene}$ or n-propenylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted with R^3 , R^4 or R^5 ; and M is Ar^3 , and wherein Ar^3 is phenyl optionally substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

181. The compound of claim 83, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is $-(C_1-C_2)\text{-X-O-}(C_1-C_2)\text{alkylene-}$ and X is metaphenylene; K is $(C_2-C_4)\text{alkylene}$ or n-propenylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted with R^3 , R^4 or R^5 ; and M is Ar^3 , and wherein Ar^3 is phenyl optionally substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

182. The compound of claim 83, 88, 89, 94, 95, 100, 101, 106 or 107, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein K is thioethylene or oxyethylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally substituted with up to three R^3 , R^4 or R^5 ; and M is Ar^3 , optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

72222-402

-362-

183. The compound of claim 182, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar³ is phenyl.

184. The compound of claim 88 or 89, a prodrug thereof
5 or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -(C₅-C₇)alkylene-; K is thioethylene or oxyethylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally substituted with up to
10 three R³, R⁴ or R⁵; and M is Ar³, optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl, and wherein Ar³ is phenyl.

185. The compound of claim 100 or 101, a prodrug
15 thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -CH₂-X-CH₂- and X is metaphenylene; K is thioethylene or oxyethylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is
20 optionally substituted with up to three R³, R⁴ or R⁵; and M is Ar³, optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl, and wherein Ar³ is phenyl.

186. The compound of claim 106 or 107, a prodrug
25 thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -(C₂-C₄)alkylene-X- and X is furanyl, thienyl or thiazolyl; K is thioethylene or oxyethylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or
30 thiazolyl, wherein Ar is optionally substituted with up to three R³, R⁴ or R⁵; and M is Ar³, optionally mono-, di- or tri-substituted with chloro, fluoro, methyl,

72222-402

-363-

difluoromethoxy, trifluoromethoxy or trifluoromethyl, and wherein Ar³ is phenyl.

187. The compound of claim 83, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -(C₁-C₂)-X-O-(C₁-C₂)alkylene- and X is metaphenylene; K is thioethylene or oxyethylene; Ar is phenyl, pyrazolyl, pyridazinyl, pyrazinyl, pyridyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally substituted with up to three R³, R⁴ or R⁵; and M is Ar³, optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl, and wherein Ar³ is phenyl.

188. The compound of any one of claims 100 to 105, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is (C₁-C₂)alkylene-X-(C₁-C₂)alkylene.

189. The compound of claim 100 or 101, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein K is methylene; Q is -CH₂-X-CH₂-CH₂- or -CH₂-X-CH₂-CH(CH₃)-; X is metaphenylene being optionally mono- or di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; M is Ar³; Ar³ is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R³¹, chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; R³¹ is (C₁-C₇)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylamine, or (C₁-C₅)alkoxy, the (C₁-C₇)alkyl or

72222-402

-364-

(C₁-C₅)alkoxy optionally mono-, di- or tri-substituted with independently hydroxy or fluoro; and Ar is phenyl, pyridyl, pyrazolyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted on
5 carbon with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy, or mono- or di-substituted on nitrogen with methyl or trifluoromethoxy.

190. The compound of claim 104 or 105, a prodrug
10 thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein K is methylene; Q is -CH₂-X-CH₂-CH₂- or -CH₂-X-CH₂-CH(CH₃)-; X is metaphenylene being optionally mono- or di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or
15 trifluoromethoxy; M is Ar³-Ar³ wherein one Ar³ is phenyl, thienyl, furanyl or pyridyl, optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy, and one Ar³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
20 cycloheptyl, phenyl, pyridyl, imidazolyl, pyrimidyl, thienyl, pyridazinyl, pyrazinyl, pyrazolyl or thiazolyl, optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl; and Ar is phenyl, pyridyl, pyrazolyl,
25 imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted on carbon with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy, or mono- or di-substituted on nitrogen with methyl or trifluoromethoxy.

30 191. The compound of claim 83, or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or of the prodrug, wherein K is methylene; Q is -CH₂-X-O-CH₂- or -CH₂-X-O-CH(CH₃)-; X is metaphenylene optionally mono- or

72222-402

-365-

di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; M is Ar³; Ar³ is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R³¹, chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; R³¹ is (C₁-C₇)alkyl, mono-N- or di-N, N-(C₁-C₄)alkylamine, or (C₁-C₅)alkoxy, the (C₁-C₇)alkyl or (C₁-C₅)alkoxy optionally mono-, di- or tri-substituted with independently hydroxy or fluoro; and Ar is phenyl, pyridyl, pyrazolyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted on carbon with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy, or mono- or di-substituted on nitrogen with methyl or trifluoromethoxy.

192. The compound of claim 86 or 87, or a prodrug thereof, or a pharmaceutically acceptable salt of the compound or of the prodrug, wherein K is methylene; Q is -CH₂-X-O-CH₂- or -CH₂-X-O-CH(CH₃)-; X is metaphenylene optionally mono- or di-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; M is Ar³-Ar³ wherein one Ar³ is phenyl, thienyl, furanyl or pyridyl, optionally mono-, di- or tri-substituted with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy, and one Ar³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, pyridyl, imidazolyl, pyrimidyl, thienyl, pyridazinyl, pyrazinyl, pyrazolyl or thiazolyl, optionally mono-, di- or tri-substituted with chloro,

72222-402

-366-

fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl; and Ar is phenyl, pyridyl, pyrazolyl, imidazolyl, pyrimidyl, thienyl or thiazolyl, wherein Ar is optionally mono-, di- or tri-substituted on carbon with

5 chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy, or mono- or di-substituted on nitrogen with methyl or trifluoromethoxy.

193. The compound of claim 100 or 101, a prodrug thereof or a pharmaceutically acceptable salt of the

10 compound or the prodrug, wherein Q is $-\text{CH}_2\text{-X-CH}_2\text{-CH}_2\text{-}$; Ar is phenyl, 3-fluoro-phenyl, 3-chloro-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 2-thiazolyl, 2-thienyl, 2-(5-chloro-thienyl), 2-pyridyl, 3-pyridyl or 4-(1-methyl-imidazolyl); M is Ar^3 ; Ar^3 is cyclopentyl, cyclohexyl, phenyl, thienyl,

15 pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl or 1,4-benzodioxan and is optionally mono-, di- or

20 tri-substituted with R^{31} , chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; R^{31} is $(\text{C}_1\text{-C}_7)$ alkyl or $(\text{C}_1\text{-C}_5)$ alkoxy, the $(\text{C}_1\text{-C}_7)$ alkyl or $(\text{C}_1\text{-C}_5)$ alkoxy optionally mono-, di- or tri-substituted with independently hydroxy or fluoro; and X is metaphenylene.

25 194. The compound of claim 83, a prodrug thereof or a pharmaceutically acceptable salt of the compound or of the prodrug, wherein Q is $-\text{CH}_2\text{-X-O-CH}_2\text{-}$; Ar is phenyl, 3-fluoro-phenyl, 3-chloro-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 2-thiazolyl, 2-thienyl, 2-(5-chloro-thienyl), 2-pyridyl,

30 3-pyridyl or 4-(1-methyl-imidazolyl); M is Ar^3 ; Ar^3 is cyclopentyl, cyclohexyl, phenyl, thienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuryl, benzo(b)thienyl, benzoxazolyl, benzthiazolyl, quinolinyl,

72222-402

-367-

isoquinolinyl, naphthyl, tetralinyl, 2H-1-benzopyranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl or 1,4-benzodioxan and is optionally mono-, di- or tri-substituted with R^{31} , chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethyl or trifluoromethoxy; R^{31} is (C₁-C₇)alkyl or (C₁-C₅)alkoxy, the (C₁-C₇)alkyl or (C₁-C₅)alkoxy optionally mono-, di- or tri-substituted with independently hydroxy or fluoro; and X is metaphenylene.

195. The compound of claim 86 or 87, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is -CH₂-X-O-CH₂- or -CH₂-X-O-CH(CH₃)-; Ar is phenyl, 3-fluoro-phenyl, 3-chloro-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 2-thiazolyl, 2-thienyl, 2-(5-chloro-thienyl), 2-pyridyl, 3-pyridyl or 4-(1-methyl-imidazolyl); M is Ar³-Ar³, wherein both Ar³ are independently optionally mono- or di-substituted with chloro or fluoro; and X is metaphenylene.

196. The compound of claim 86, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar is 4-chlorophenyl; Q is CH₂-X-O-CH₂; X is metaphenylene; M is Ar³-Ar³, wherein one Ar³ is paraphenylene; and one Ar³ is 2-thiazolyl.

197. The compound of claim 104 or 105, a prodrug thereof or a pharmaceutically acceptable salt of the compound or of the prodrug, wherein Q is -CH₂-X-CH₂-CH₂- or -CH₂-X-CH₂-CH(CH₃)-; Ar is phenyl, 3-fluoro-phenyl, 3-chloro-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 2-thiazolyl, 2-thienyl, 2-(5-chloro-thienyl), 2-pyridyl, 3-pyridyl or 4-(1-methyl-imidazolyl); M is Ar³-Ar³, wherein both Ar³ are independently optionally mono- or di-substituted with chloro or fluoro; and X is metaphenylene.

72222-402

-368-

198. The compound of claim 104, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Q is CH₂-X-CH₂CH₂; X is metaphenylene; Ar is phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 2-thiazolyl, 2-thienyl, 2-(5-chloro-thienyl), 2-pyridyl or 3-pyridyl; M is Ar³-Ar³, wherein a first Ar³ is phenyl substituted at the para position with a second Ar³, the first Ar³ additionally being optionally substituted with chloro or fluoro; and the second Ar³ is cyclopentyl, cyclohexyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-imidazolyl, 2-pyrimidyl, 5-pyrimidyl, 2-thienyl, 6-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 2-thiazolyl or 5-pyridazinyl optionally mono- or di-substituted on carbon with chloro, fluoro, methyl, methoxy, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

199. The compound 3-(3-{[(pyridine-3-sulfonyl)-(4-pyridin-3-yl-benzyl)-amino]-methyl}-phenyl)-propionic acid, or a pharmaceutically acceptable salt thereof.

200. The compound 3-(3-{[(4-chloro-benzenesulfonyl)-(4-pyrazin-2-yl-benzyl)-amino]-methyl}-phenyl)-propionic acid, or a pharmaceutically acceptable salt thereof.

201. The compound 3-(3-{[(4-pyrazin-2-yl-benzyl)-(thiazole-2-sulfonyl)-amino]-methyl}-phenyl)-propionic acid, or a pharmaceutically acceptable salt thereof.

202. The compound 3-(3-{[(4-chloro-benzenesulfonyl)-(4-pyrimidin-2-yl-benzyl)-amino]-methyl}-phenyl)-propionic acid, or a pharmaceutically acceptable salt thereof.

203. The compound of claim 198, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar is 3-pyridyl; the first Ar³ is paraphenylene; and the second Ar³ is 3-pyridyl.

72222-402

-369-

204. The compound of claim 198, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar is 4-chloro-phenyl; the first Ar³ is paraphenylene; and the second Ar³ is 2-pyrazinyl.

5 205. The compound of claim 198, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar is 4-chloro-phenyl; the first Ar³ is paraphenylene; and the second Ar³ is 2-pyrimidinyl.

10 206. The compound of claim 198, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein Ar is 2-thiazolyl; the first Ar³ is paraphenylene; and the second Ar³ is 2-pyrazinyl.

15 207. The compound of claim 112, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug, wherein K is methylenyl, propylenyl, propenylenyl or oxyethylenyl; Ar³ is phenyl or pyridyl; and wherein Ar and Ar³ are optionally substituted independently with up to three chloro, fluoro, methyl, difluoromethoxy, trifluoromethoxy or trifluoromethyl.

20 208. A pharmaceutical composition for treating a vertebrate having a condition which presents with low bone mass, which comprises (a) a therapeutically effective amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the
25 compound or the prodrug, and (b) a pharmaceutically acceptable carrier or diluent.

209. The pharmaceutical composition of claim 208, wherein the condition is osteoporosis, osteotomy, childhood idiopathic bone loss or bone loss associated with
30 periodontitis.

72222-402

-370-

210. The pharmaceutical composition of claim 209, wherein osteoporosis is in a human.

211. The pharmaceutical composition of claim 210, wherein the osteoporosis is glucocorticoid-induced
5 osteoporosis, hyperthyroidism-induced osteoporosis, immobilization-induced osteoporosis, heparin-induced osteoporosis or immunosuppressive-induced osteoporosis.

212. A pharmaceutical composition for augmenting and maintaining bone mass in a vertebrate, which comprises (a) a
10 therapeutically effective amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug and (b) a pharmaceutically acceptable carrier or diluent.

213. The pharmaceutical composition of claim 212, for
15 bone healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction, for inducing vertebral synostosis, for enhancing long bone extension, for enhancing the healing rate of a bone graft or for enhancing prosthetic ingrowth.

20 214. The pharmaceutical composition of claim 212, for treating a bone fracture in a human.

215. A pharmaceutical composition which comprises (a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of
25 the compound or the prodrug and (b) a pharmaceutically acceptable carrier or diluent.

216. The pharmaceutical composition of claim 215, for the treatment of osteoporosis.

217. The pharmaceutical composition of claim 215, for
30 the augmentation of bone mass.

72222-402

-371-

218. The pharmaceutical composition of claim 215, for the treatment of a bone fracture.

219. The pharmaceutical composition of claim 215, for the treatment of a condition which presents with low bone
5 mass in a human.

220. A pharmaceutical composition comprising:

(a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug;

10 (b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug; and

(c) a pharmaceutical carrier or diluent.

221. The pharmaceutical composition of claim 220,
15 wherein the anti-resorptive agent is droloxifene; raloxifene; tamoxifen; 4-hydroxy-tamoxifen; toremifene; centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalene-2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-
20 (6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid;

2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

25 *cis*-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

72222-402

-372-

(-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

5 cis-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

10 cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; or

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

15 222. A pharmaceutical composition of claim 220, wherein the anti-resorptive agent is tiludronic acid, alendronic acid, zoledronic acid, ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a prodrug thereof or a pharmaceutically acceptable salt of the
20 agent or the prodrug.

223. The pharmaceutical composition for treating a vertebrate having a condition which presents with low bone mass, which comprises:

(a) an amount of a compound of any one of
25 claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug; and

(b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

72222-402

-373-

224. The pharmaceutical composition of claim 223,
 wherein the anti-resorptive agent is droloxifene;
 raloxifene; tamoxifen; 4-hydroxy-tamoxifen; toremifene;
 centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-
 5 phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalene-
 2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-
 (6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-
 methanone;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic
 10 acid;

2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-
 ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-
 ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

15 (-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-
 phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-
 phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-
 20 6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-
 fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-
 ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; or

25 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-
 hydroxy-1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or
 a pharmaceutically acceptable salt of the agent or the
 prodrug.

72222-402

-374-

225. A pharmaceutical composition of claim 223, wherein the anti-resorptive agent is tiludronic acid, alendronic acid, zoledronic acid, ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a
5 prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

226. A kit comprising:

(a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically
10 acceptable salt of the compound or the salt in a first unit dosage form;

(b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug and a pharmaceutically acceptable
15 carrier or diluent in a second unit dosage form; and

(c) container means for containing the first and second dosage forms.

227. A kit of claim 226, wherein the anti-resorptive agent is droloxifene; raloxifene; tamoxifen; 4-hydroxy-
20 tamoxifen; toremifene; centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalene-2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone;

25 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid;

2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

72222-402

-375-

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

5 *cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis--1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

10 1-(4'-pyrrolidonoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; or

15 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

228. A kit of claim 226, wherein the anti-resorptive agent is tiludronic acid, alendronic acid, zoledronic acid, ibandronic acid, risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

229. A pharmaceutical composition comprising:

25 (a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug;

72222-402

-376-

(b) an amount of another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug; and

(c) a pharmaceutical carrier or diluent.

5 230. The pharmaceutical composition of claim 229, wherein the bone anabolic agent in component (b) is IGF-1, bone morphogenetic protein, prostaglandin, a prostaglandin agonist/antagonist, sodium fluoride, parathyroid hormone (PTH), an active fragment or fragments of parathyroid
10 hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

231. A pharmaceutical composition for treating a mammal which presents with low bone mass, which composition
15 comprises:

(a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug; and

(b) an amount of another bone anabolic agent, a
20 prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

232. The pharmaceutical composition of claim 231, wherein the bone anabolic agent in component (b) is IGF-1, a bone morphogenetic protein, a prostaglandin, a prostaglandin
25 agonist/antagonist, sodium fluoride, parathyroid hormone (PTH), an active fragment or fragments of parathyroid hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

72222-402

-377-

233. A pharmaceutical composition for treating a mammal which presents with kidney degeneration, which comprises:

(a) a kidney regenerating effective amount of a compound of any one of claims 83 to 207, a prodrug thereof
5 or a pharmaceutically acceptable salt of the compound or the said prodrug, and

(b) a pharmaceutically acceptable carrier or diluent.

234. A kit comprising:

10 (a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug in a first unit dosage form;

(b) an amount of another bone anabolic agent, a
15 prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug in a second unit dosage form; and

(c) container means for containing the first and second dosage forms.

235. A kit of claim 234, wherein the bone anabolic
20 agent in component (b) is IGF-1, bone morphogenetic protein, a prostaglandin, a prostaglandin agonist/antagonist, sodium fluoride, parathyroid hormone (PTH), an active fragment or fragments of parathyroid hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a
25 pharmaceutically acceptable salt of the agent or the prodrug.

236. A pharmaceutical composition for augmenting and maintaining bone mass in a vertebrate, which comprises:

72222-402

-378-

(a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug; and

(b) an amount of an anti-resorptive agent, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

237. The pharmaceutical composition of claim 236, wherein the anti-resorptive agent is droloxifene; raloxifene; tamoxifen; 4-hydroxy-tamoxifen; toremifene; centchroman; levormeloxifene; idoxifene; 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalene-2-ol; (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone;

3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid;

2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol;

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

72222-402

-379-

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; or

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, a prodrug thereof or a
5 pharmaceutically acceptable salt of the agent or the prodrug.

238. The pharmaceutical composition of claim 236, wherein the anti-resorptive agent is, tiludronic acid, alendronic acid, zoledronic acid, ibandronic acid,
10 risedronic acid, etidronic acid, clodronic acid, and pamidronic acid, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

239. A pharmaceutical composition for augmenting and maintaining bone mass in a vertebrate, which comprises:

15 (a) an amount of a compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug; and

(b) an amount of another bone anabolic agent, a prodrug thereof or a pharmaceutically acceptable salt of the
20 agent or the prodrug.

240. A pharmaceutical composition of claim 239, wherein the bone anabolic agent in component (b) is IGF-1, bone morphogenetic protein, a prostaglandin, a prostaglandin agonist/antagonist, sodium fluoride, parathyroid hormone
25 (PTH), an active fragment or fragments of parathyroid hormone, a growth hormone or a growth hormone secretagogue, a prodrug thereof or a pharmaceutically acceptable salt of the agent or the prodrug.

72222-402

-380-

241. A pharmaceutical composition for treating glaucoma in a mammal suffering from glaucoma, which comprises:

(a) a therapeutically effective amount of a compound of any one of claims 83 to 207, a prodrug thereof
5 or a pharmaceutically acceptable salt of the compound or the prodrug, and

(b) a pharmaceutically acceptable carrier or diluent.

242. A pharmaceutical composition for treating ocular
10 hypertension in a mammal suffering from ocular hypertension, which comprises:

(a) a therapeutically effective amount of a compound of any one of claims 83 to 207, a prodrug thereof
or a pharmaceutically acceptable salt of the compound or the
15 prodrug, and

(b) a pharmaceutically acceptable carrier or diluent.

243. The kit of claim 226, 227 or 228, further comprising instructions for the use of components (a) and
20 (b) for treating a vertebrate having a condition which presents with low bone mass or for augmenting and maintaining bone mass in a vertebrate.

244. The kit of claim 234 or 235, further comprising instructions for the use of components (a) and (b) for
25 treating a mammal which presents with low bone mass or for augmenting and maintaining bone mass in a vertebrate.

245. A commercial package comprising the pharmaceutical composition of any one of claims 208 to 214, 216 to 219, 223

72222+402 `

-381-

to 225, 231 to 233 and 236 to 242, and instructions for the use thereof.

246. Use of the compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of
5 the compound or prodrug in the manufacture of a medicament for treating a vertebrate having a condition which presents with low bone mass; augmenting and maintaining bone mass in a vertebrate; treating a mammal which presents with kidney degeneration; treating glaucoma in a mammal suffering from
10 glaucoma; or treating ocular hypertension in a mammal.

247. Use of the compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug for treating a vertebrate having a condition which presents with low bone mass; augmenting and
15 maintaining bone mass in a vertebrate; treating a mammal which presents with kidney degeneration; treating glaucoma in a mammal suffering from glaucoma; or treating ocular hypertension in a mammal.

248. Use of the compound of any one of claims 1 to 41 or
20 a pharmaceutically acceptable salt thereof or the compound of claim 42 for treating a bone fracture in a human.

249. Use of the compound of any one of claims 1 to 41 or a pharmaceutically acceptable salt thereof or the compound of claim 42 in the manufacture of a medicament for treating a
25 bone fracture in a human.

250. Use of the compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug in the manufacture of a medicament for treating a bone fracture in a human.

72222-402

-382-

251. Use of the compound of any one of claims 83 to 207, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug for treating a bone fracture in a human.

5 252. The compound (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof for use in the treatment of a bone fracture in a human.

10 253. The compound (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid for use in the treatment of a bone fracture in a human.

254. The compound (3-(((4-tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid sodium salt for use in the treatment of a bone fracture in a human.

SMART & BIGGAR

OTTAWA, CANADA

PATENT AGENTS

