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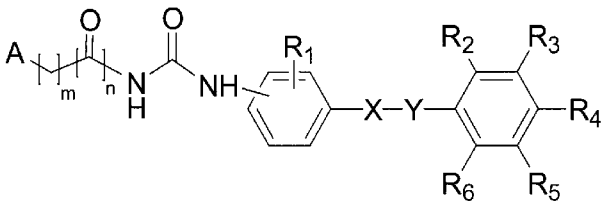
(54) Title: ALKYLUREA DERIVATIVES ACTIVE AGAINST CANCER CELLS



(I)

(57) Abstract: Compounds of formula (I) : wherein A, m, n, R1, X, Y, R2, R3, R4, R5 and R6, as defined herein are provided as useful for the treatment of cancer or for the manufacture of anti-cancer agents.

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Alkylurea derivatives active against cancer cells

Cross-reference to related applications

[0001] This application claims priority from US provisional patent application 61/477,316 filed on April 20, 2011, the content of which is incorporated by reference in its entirety.

Field of the invention

[0002] The present invention relates to substituted alkylurea derivatives and analogs thereof. Particularly, the invention relates to processes for the preparation of these compounds. More particularly, these compounds are useful as anti-cancer agents. Still, the invention relates to the use of these compounds for the manufacture of anti-cancer agents and method of treating cancer with these compounds.

Background of the invention

[0003] Cancer is a disease that seriously jeopardizes the health of human beings. Around the globe, about 6 millions people die of cancer every year, with another 10 millions seriously affected by the disease. According to the estimate of the World Health Organization, in the 21st century, cancer will become the "number one killer" of mankind.

[0004] In the past several decades, many ways of treating cancer became available, mainly including surgery, radiotherapy, chemotherapy, hormonotherapy, gene therapy, and immunotherapy, among which surgery, radiotherapy and chemotherapy have become the major means. Chemotherapy refers to treating cancer with chemical medication. It is the most rapidly expanding field in the diagnosis and treatment of cancer. A great number of new medicines aiming at different targets are ready for clinical application, and developments in research in mechanism of drug action and pharmacokinetics have made the clinical administration routes and means more fitting for killing tumor cells while protecting the normal tissues.

[0005] At present, pharmaceuticals for chemotherapy mainly include: compounds that affects the biosynthesis of nucleic acid (e.g., 5-fluorouracil, amethopterin, cytarabine, hydroxyurea); compounds that directly destroys DNA and prevents its reproduction, e.g. alkylating agents; antineoplastic antibiotics (e.g., cisplatin and

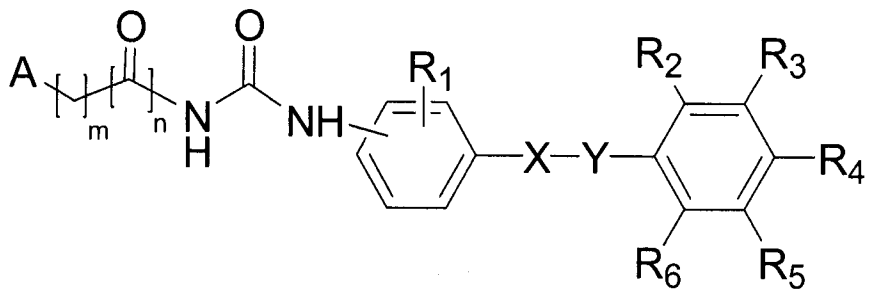
carboplatin); compounds that interferes with the transcription and prevents the synthesis of RNA (e.g., actinomycin D, adriamycin) and other transcription restraining antibiotics; compounds that affects the synthesis of protein (e.g., catharanthines, podophyllotoxins, asparaginase) hormones (e.g., adrenal cortical hormone, estrogen, androgen, tamoxifen, aminoglutethimide). The existing chemotherapies and radiotherapies that are commonly used in treating cancer may cause serious toxic and other side effects that are adverse to the human body.

[0006] *N*-Phenyl-*N'*-(2-chloroethyl)ureas are potent antiproliferative agents acting on a large panel of tumor cell lines and on animal models of cancers. They are mainly known as monoalkylating agents covalently binding to different proteins such as β-tubulin, thioredoxin-1, prohibitin-1 and the mitochondrial voltage-dependent anion channel leading to arrest of the cell cycle progression either in G_2/M or G_0/G_1 phase. Using matrix-assisted laser desorption ionization and electrospray mass spectrometry *N*-phenyl-*N'*-(2-chloroethyl)ureas exhibiting antimicrotubule activity were shown to bind covalently to microtubules through a unique mechanism of nucleophilic addition involving the esterification of the glutamic acid residue at position 198 of β-tubulin (Gluβ198). Of interest, Gluβ198 is located in a small pocket adjacent to the colchicine-binding site and is involved in microtubule stability and dynamics, and a mechanism of resistance to taxotere. A second subclass of CEU derivatives that doesn't interact with tubulin was found to bind to the aspartic acid residue in position 40 of prohibitin isoform 1 through a similar nucleophilic addition.

[0007] Alkylurea derivatives have been developed as a genuine new class of antitumor agents that are active *in vitro* against tumor cells and that are likely to transpose this *in vitro* activity against cancer cells into *in vivo* activity in cancer patients requiring chemotherapy.

Summary of the invention

[0008] In a first aspect of the present invention, there is provided a compound of formula (I):



(I)

wherein:

A is H or halo; m is 1, 2, 3 or 4; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, ω- and ω-1 C_{1-4} alkanol, ω- C_{1-4} alkyl carboxylate and corresponding C_{1-3} esters, -COOR7 wherein R7 is as defined above, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

or X is –CH=CH- and Y is C=O;

or X is C=O, -S- or -C=CH_2-; and Y is absent;

or one of X or Y is N and the other is C and are so linked as to form an imidazole ring;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, C_{1-6} 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters,-COOR7 wherein R7 is selected from: H or C_{1-3} alkyl, NO_2, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, phenoxy, C_{0-6} alkyl-CN, C_{1-6}, 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters, -COOR7, wherein R7 is selected from: H or C_{1-3} alkyl; NO_2, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9), wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; or

R3 and R4; or R4 and R5 are linked to each other and form a 4, 5 or 6 – membered saturated or partially unsaturated ring optionally containing one or two N, O or S atoms thus forming a heterocycle, said ring or heterocycle optionally substituted with C_{1-6} alkyl, OH, halogen, amines, C_{1-4} alkyl-substituted amine, C_{1-4} alkoxy;

or an amino acid derivative, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

[0009] In a second aspect of the present invention, there is provided a compound of formula (I), wherein:

A is H or halo; m is 1, 2, 3; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, ω- and ω-1 C_{1-4} alkanol, ω- C_{1-4} alkyl carboxylate and corresponding C_{1-3} esters, $-COOR_7$ wherein R_7 is as defined above, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

or X is –CH=CH- and Y is C=O;

or X is C=O, -S- or $-C=CH_2-$; and Y is absent;

or one of X or Y is N and the other is C and are so linked as to form an imidazole ring;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, C_{1-6} 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters,-COOR7 wherein R7 is selected from: H or C_{1-3} alkyl, NO_2, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, phenoxy, C_{0-6} alkyl-CN, C_{1-6}, 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters, -COOR7, wherein R7 is selected from: H or C_{1-3} alkyl;

NO_2, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9), wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; and

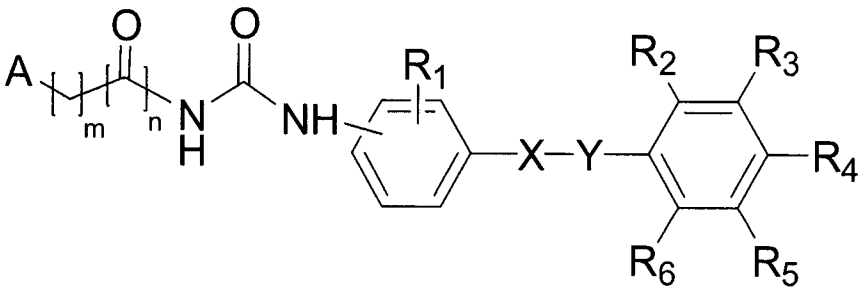
R3 and R4; or R4 and R5 are linked to each other and form a 4, 5 or 6 –membered saturated or partially unsaturated ring optionally containing one or two N, O or S atoms thus forming a heterocycle, said ring or heterocycle optionally substituted with C_{1-6} alkyl, OH, halogen, amines, C_{1-4} alkyl-substituted amine, C_{1-4} alkoxy;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

[0010] In connection with particular aspects of the invention, the compound of any appropriate formula I, and definitions herein are particularly defined (unless otherwise defined) wherein the urea group: A-$[CH_2]_m$-$[CO]_n$-NH-C(O)-NH- is bound to the adjacent phenyl ring (ring A) through positions 3, 4 or 5, more particularly through positions 3 or 4, most particularly through position 4 (para).

[0011] In a third aspect of the present invention, there is provided a compound of formula (I):



(I) wherein:

A is H or halo; m is 1, 2 or 3; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, ω- and ω-1 C_{1-4} alkanol, ω- C_{1-4} alkyl carboxylate and corresponding C_{1-3} esters, -$COOR_7$ wherein R_7 is as defined above, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

or X is –CH=CH- and Y is C=O;

or X is C=O, -S- or -C=CH_2-; and Y is absent;

or one of X or Y is N and the other is C and are so linked as to form an imidazole ring;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, C_{1-6} 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters,-COOR7 wherein R7 is selected from: H or C_{1-3} alkyl, NO_2, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

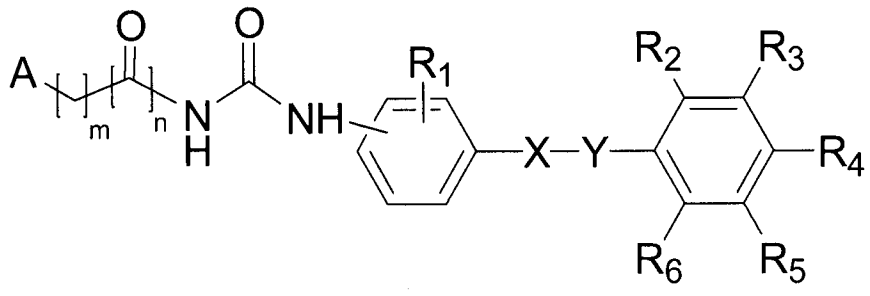
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, phenoxy, C_{0-6} alkyl-CN, C_{1-6}, 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters, -COOR7, wherein R7 is selected from: H or C_{1-3} alkyl; NO_2, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9), wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; and

R3 and R4; or R4 and R5 are linked to each other and form a 4, 5 or 6 –membered saturated or partially unsaturated ring optionally containing one or two N, O or S atoms thus forming a heterocycle, said ring or heterocycle optionally substituted with C_{1-6} alkyl, OH, halogen, amines, C_{1-4} alkyl-substituted amine, C_{1-4} alkoxy;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is CH=CH_2 and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

[0012] In a further aspect of the present invention, there is provided a compound of formula (I):



(I),

A is H, Cl, Br, F or I; m is 1, 2 or 3; n is 0 or 1;
R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4}alkenyl, C_{1-4} alkoxy, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from H, Me and Et;
X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;
or X is –CH=CH- and Y is C=O;
or X is C=O, -S- or C=CH_2; and Y is absent;
R2 and R6 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; and
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9), wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;
or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;
with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is CH=CH_2 and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

[0013] A further aspect of the present invention is directed to a physiological composition comprising at least one compound of Formula I, or a salt thereof, and one or more physiologically-acceptable excipients.

[0014] A further aspect of the present invention is directed to a pharmaceutical composition comprising an effective amount of at least one compound of Formula I, or a salt thereof, and one or more pharmaceutically-acceptable excipients.

[0015] A further aspect of the invention is directed to a method for hindering or blocking cell cycle progression by contacting one or more cells with one or more compound of Formula I.

[0016] A further aspect of the present invention is directed to a method of killing a tumor growth or invasion with one or more compounds of Formula I.

[0017] A further aspect of the present invention is directed to a method of treating a condition that results from abnormal cell growth, cellular differentiation, tumor growth or invasion with one or more compounds of Formula I.

[0018] A further aspect of the invention is directed to a method of treating cancer in a subject suffering therefrom comprising administering a therapeutically effective amount of a compound of Formula I.

[0019] A further aspect of the invention is directed to a use of one or more compound of Formula I for hindering or blocking cell cycle progression of a cell.

[0020] A further aspect of the present invention is directed to a use of one or more compounds of Formula I for killing a tumor growth or cellular invasion in a subject.

[0021] A further aspect of the invention is directed to the use of one or more compounds of formula I for the treatment of cancer in a subject.

[0022] A further aspect of the invention is directed to the use of one or more compounds of formula I for the manufacture of medicament for the treatment of cancer in a subject.

[0023] A further aspect of the present invention is directed to a method of synthesizing compounds of Formula I by following one or more synthetic schemes as defined below.

[0024] The compounds of Formula I may also be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds.

[0025] When any variable occurs more than one time in any constituent of Formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0026] The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result, for example, from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes.

Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabeled compound of the invention, administering it parenterally in a detectable dose to a subject such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

[0027] The invention disclosed herein is also meant to encompass pro-drugs that, when administered *in vivo,* provide the compounds of formula (I) as metabolic products. Such products may result, for example, from the addition of sulfonate, phosphate, boronic acid or amino acid derivatives. Accordingly, the invention includes compounds of formula (I) wherein appropriate R2, R3, R4, R5 or R6 is derivatized with a sulfonate, phosphate, a boronic acid or an amino acid, or a salt thereof.

[0028] Some of the compounds disclosed herein may contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

Detailed description of the invention

Abbreviations

[0029] The abbreviation "EU" as appearing herein means ethylurea(s).

[0030] The abbreviation "CEU" as appearing herein means chloroethylurea(s)

[0031] The abbreviation "CPU" as appearing herein means chloropropylurea(s)

[0032] The abbreviation "SO" as appearing herein means sulfonate(s).

[0033] The abbreviation "SA" as appearing herein means sulfonamide(s).

Definitions

[0034] The term "C_{1-n}alkyl" such as "C_{1-8}alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals, and unless otherwise specified up to n carbons, such as for example C_{1-8} alkyl: methyl, ethyl, propyl (including isopropyl), butyl (including s-butyl, t-butyl and isobutyl), pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, and 2,2,4-trimethylpentyl).

[0035] The term "C_{2-6}alkenyl" is used herein to mean a straight or branched chain radical of 2-6 carbon atoms, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

[0036] The term "alkoxy" or "alkyloxy" refers to any of the above alkyl groups linked to an oxygen atom. Typical examples are methoxy, ethoxy, isopropyloxy, sec-butyloxy, and t-butyloxy.

[0037] The term C_{1-6} 2-ketyl, is used herein to refer to any alkyl having a ketone group (=O).

[0038] The term "hydroxyalkyl" or "alkanol" as employed herein interchangeably refers to any of the above alkyl groups wherein one or more hydrogens thereof are substituted by one or more hydroxyl moieties. The terms ω and ω-1 used herein refer to the position of the hydrolxyl group i.e. ultimate (at the end) and penultimate of the alkyl chain respectively.

[0039] The term "carboxyalkyl" or "alkyl carboxylate" as employed herein interchangeably refers to any of the above alkyl groups wherein one or more hydrogens thereof are substituted by one or more carboxylic acid moieties. The term ω used herein refers to the position of the carboxylate group i.e. ultimate (at the end of the alkyl chain).

[0040] The phrase "saturated or partially unsaturated ring" as employed herein, by itself or as part of another group, refers to a saturated or partially unsaturated ring system having 5 to 10 ring atoms selected from carbon atoms and optionally having 1 or 2 oxygen, nitrogen, or sulfur heteroatoms. Typical saturated examples include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, tetrahydrofuranyl, tetrahydropyranyl,

piperidyl, piperazinyl, quinuclidinyl, morpholinyl, and dioxacyclohexyl. Typical partially unsaturated examples include pyrrolinyl, imidazolinyl, pyrazolinyl, dihydropyridinyl, tetrahydropyridinyl, and dihydropyranyl. Either of these systems can be optionally fused to a benzene ring.

[0041] The term "halogen" or "halo" as employed herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine.

[0042] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0043] The term "chiral center" refers to a carbon atom to which four different groups are attached.

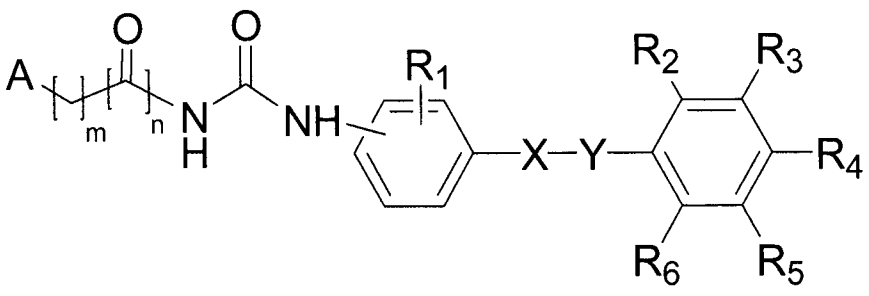
[0044] The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

[0045] The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

[0046] The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule. The term "enantiomeric excess" refers to a mixture wherein one enantiomer is present in a greater concentration than its mirror image molecule.

Detailed description of particular embodiments

[0047] Particularly, the invention provides a compound of formula (I):



(I)

ring A ring B

wherein:

A is H or chloro; m is 1, 2 or 3; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4}alkenyl, or C_{1-4} alkoxy;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH; or X is $CH=CH_2$ and Y is absent;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen,

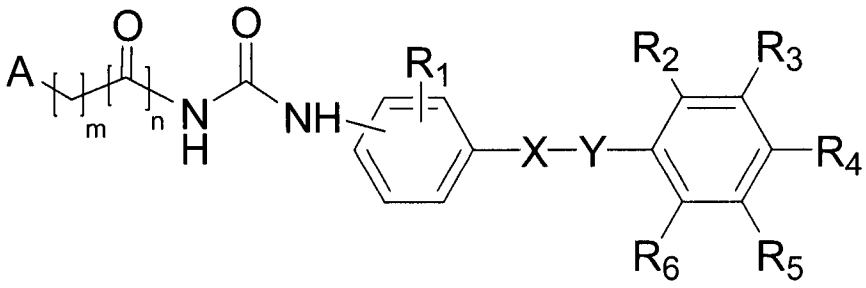
C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-3} alkenyl and C_{1-3} alkoxy; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H, Me, Et, and Pr;

or an amino acid derivative, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H and X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

[0048] Particularly, the invention provides a compound of formula (I)



(I)

ring A ring B

the urea group: A-$[CH_2]_m$-$[CO]_n$-NH-C(O)-NH- is bound to the adjacent phenyl ring A through position 3 or 4;

A is H or chloro; n is 0 or 1: m is 1, 2 or 3;

R1 is H;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

R2 and R6 is each independently selected from the group consisting of: H, halogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkoxy; and
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, $-N(C_{1-4}\text{ alkyl})_2$ and $-NH_2$;
or an amino acid derivative, or a pharmaceutically acceptable salt thereof.

[0049] More particularly, the invention provides a compound of formula (I) wherein the urea group: $A-[CH_2]_m-[CO]_n-NH-C(O)-NH-$ is bound to the adjacent phenyl ring A through position 3 or 4;
A is H or chloro; n is 0 or 1; m is 1, 2 or 3;
R1 is H;
X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;
R2 and R6 is each independently selected from the group consisting of: H, halogen, C_{1-3} alkyl, and C_{1-3} alkoxy;
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(Me)_2$ and $-NH_2$;
or an amino acid derivative, or a pharmaceutically acceptable salt thereof.

[0050] Most particularly, the invention provides a compound of formula (I) wherein: the urea group: $A-[CH_2]_m-[CO]_n-NH-C(O)-NH-$ is bound to the adjacent phenyl ring A through position 3 or 4;
A is H or chloro; n is 0 or 1; m is 1 or 2;
R1 is H;
X is SO_2 and Y is O or NH;
R2 and R6 is each independently selected from the group consisting of: H, halogen, and C_{1-3} alkyl; and
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, and C_{1-6} alkyl;
or an amino acid derivative, or a pharmaceutically acceptable salt thereof.

[0051] Particularly, the invention provides a compound of formula (I), wherein:
A is H or chloro; m is 1 or 2; n is 0 or 1;
R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4}alkenyl, or C_{1-4} alkoxy;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH; or X is $CH=CH_2$ and Y is absent;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen,

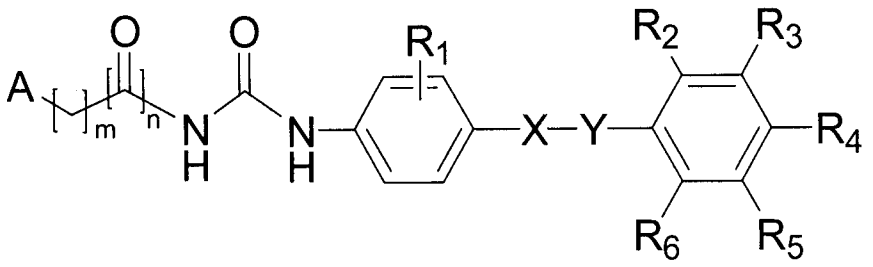
C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-3} alkenyl and C_{1-3} alkoxy; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H, Me, Et, and Pr;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H and X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

[0052] Particularly, the invention provides a compound of formula (Ia), wherein:



(Ia)

A is H or chloro; m is 1 or 2; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4}alkenyl, or C_{1-4} alkoxy;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH; or X is $CH=CH_2$ and Y is absent;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen,

C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-3} alkenyl and C_{1-3} alkoxy; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, and -N-

(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H, Me, Et, and Pr;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H and X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

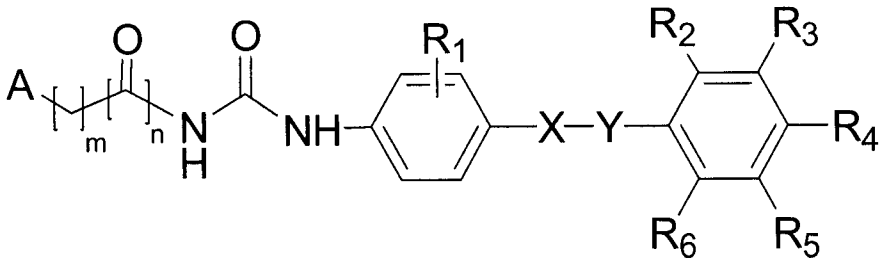
[0053] In connection with particular aspects of the invention, the compound of any appropriate formula (I) or (Ia), and definitions herein are particularly defined wherein R1 is selected from the group consisting of: H and Me.

[0054] In connection with particular aspects of the invention, the compounds of any appropriate formula (I) or (Ia), and definitions herein are particularly defined wherein X is SO_2 and Y is O or NH; or X is O and Y is SO_2.

[0055] In connection with particular aspects of the invention, the compound of any appropriate formula (I) or (Ia), and definitions herein are defined wherein each of R2 and R6 are independently selected from the group consisting of: H, Me, Et, Pr, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, F, Cl, I, and OMe.

[0056] In connection with particular aspects of the invention, the compound of any appropriate formula (I) or (Ia), and definitions herein are particularly defined wherein each of R3, R4 and R5 are independently selected from the group consisting of: H, Me, Et, Pr, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, CH-CN, F, Cl, I, Br, OMe, OEt, OPr, Obutyl, Opentyl, Ohexyl, Ophenyl, $OCH(F)_2$, NH_2, NO_2, $N(Me)_2$,

[0057] Particularly, the invention provides a compound of formula (Ia)



(Ia) wherein:

A is H or chloro; n is 0 when m is 2; n is 1 when m is 1 or 2;

R1 is H or Me;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

R2 and R6 is each independently selected from the group consisting of: H, halogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkoxy; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen,

C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, and $-NH_2$;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof.

[0058] The physiologically/pharmaceutically-acceptable salts of the compounds of Formula (I) or (Ia) (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate.

[0059] Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides like benzyl and phenethyl bromides and others. Preferred acids for forming acid addition salts include HCl, acetic acid, trifluoroacetic acid and fumaric acid.

[0060] In accordance with a particular aspect of the invention, the compounds of formula (I) or (Ia) are selected from: a sulfonate, a phosphate, or a boronic acid derivative thereof.

[0061] A further aspect of the present invention is directed to a composition comprising at least one compound of Formula (I) or (Ia), or a salt thereof, and one or more physiologically-acceptable excipients.

[0062] A further aspect of the present invention is directed to a pharmaceutical composition comprising an effective amount of at least one compound of Formula (I) or (Ia), or a salt thereof, and one or more pharmaceutically-acceptable excipients.

[0063] A further aspect of the invention is directed to a method for hindering or blocking cell cycle progression by contacting one or more cells with one or more compound of Formula (I) or (Ia).

[0064] A further aspect of the present invention is directed to a method of killing a tumor growth or invasion with one or more compounds of Formula (I) or (Ia).

[0065] A further aspect of the present invention is directed to a method of treating a condition that results from abnormal cell growth, cellular differentiation, tumor growth or invasion with one or more compounds of Formula (I) or (Ia).

[0066] A further aspect of the invention is directed to a method of treating cancer in a subject suffering therefrom comprising administering a therapeutically effective amount of a compound of Formula (I) or (Ia).

[0067] A further aspect of the invention is directed to a use of one or more compound of Formula (I) or (Ia) for hindering or blocking cell cycle progression of a cell.

[0068] A further aspect of the present invention is directed to a use of one or more compounds of Formula (I) or (Ia) for killing a tumor growth or cellular invasion in a subject.

[0069] A further aspect of the invention is directed to the use of one or more compounds of formula (I) or (Ia) for the treatment of cancer in a subject.

[0070] A further aspect of the invention is directed to the use of one or more compounds of formula (I) or (Ia) for the manufacture of medicament for the treatment of cancer in a subject.

[0071] In accordance with a particular aspect of the present invention, the subject is a human.

[0072] A further aspect of the present invention is directed to a method of synthesizing compounds of Formula (I) or (Ia) by following one or more synthetic schemes as defined below.

[0073] The compounds of Formula (I) or (Ia) may also be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds.

[0074] When any variable occurs more than one time in any constituent of Formula (I) or (Ia), its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0075] The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result, for example, from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabeled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

[0076] Some of the compounds disclosed herein may contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof.

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

Compositions and Methods of Use

[0077] Compositions of the present invention include pharmaceutical compositions comprising a compound of Formula (I) or (Ia), wherein A, m, n, R1, X, Y, R2, R3, R4, R5 and R6 are defined herein, and one or more pharmaceutically acceptable excipients. Particular compositions of the present invention are pharmaceutical compositions comprising a compound selected from a preferred group of compounds of Formula (I) or (Ia) as defined above, and one or more pharmaceutically acceptable excipients.

[0078] The pharmaceutical compositions of the invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, particularly humans, although the invention is not intended to be so limited.

[0079] The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by subcutaneous, intravenous, intramuscular, intraperitoneal, buccal, or ocular routes, rectally, parenterally, intrasystemically, intravaginally, topically (as by powders, ointments, drops or transdermal patch), or as an oral or nasal spray. Alternatively, or concurrently, administration can be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[0080] In addition to the pharmacologically active compounds, the new pharmaceutical preparations can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

[0081] The pharmaceutical preparations of the present invention are manufactured in a manner that is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0082] Suitable excipients are, in particular, fillers such as saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as, starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as, the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as, sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as, magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which can contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as, acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0083] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and,

optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as, fatty oils or liquid paraffin. In addition, stabilizers may be added.

[0084] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, alkaline solutions and cyclodextrin inclusion complexes. Especially preferred alkaline salts are ammonium salts prepared, for example, with Tris, choline hydroxide, Bis-Tris propane, N-methylglucamine, or arginine. One or more modified or unmodified cyclodextrins can be employed to stabilize and increase the water solubility of compounds of the present invention. Useful cyclodextrins for this purpose are disclosed in U.S. Pat. Nos. 4,727,064, 4,764,604, and 5,024,998.

[0085] In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

[0086] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0087] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

[0088] Topical administration includes administration to the skin or mucosa, including surfaces of the lung and eye. Compositions for topical administration, including those for inhalation, may be prepared as a dry powder which may be pressurized or non-pressurized. In nonpressurized powder compositions, the active ingredients in finely divided form may be used in admixture with a larger-sized pharmaceutically acceptable inert carrier comprising particles having a size, for example, of up to 100 micrometers in diameter. Suitable inert carriers include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0089] Alternatively, the composition may be pressurized and contain a compressed gas, such as nitrogen or a liquefied gas propellant. The liquefied propellant medium and indeed the total composition are preferably such that the active ingredients do not dissolve therein to any substantial extent. The pressurized composition may also contain a surface-active agent. The surface-active agent may be a liquid or solid non-ionic surface-active agent or may be a solid anionic surface-active agent. It is preferred to use the solid anionic surface-active agent in the form of a sodium salt.

[0090] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the drugs.

[0091] The compositions of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art (see, for example, Prescott, Ed., Meth. Cell Biol. 14:33 (1976)).

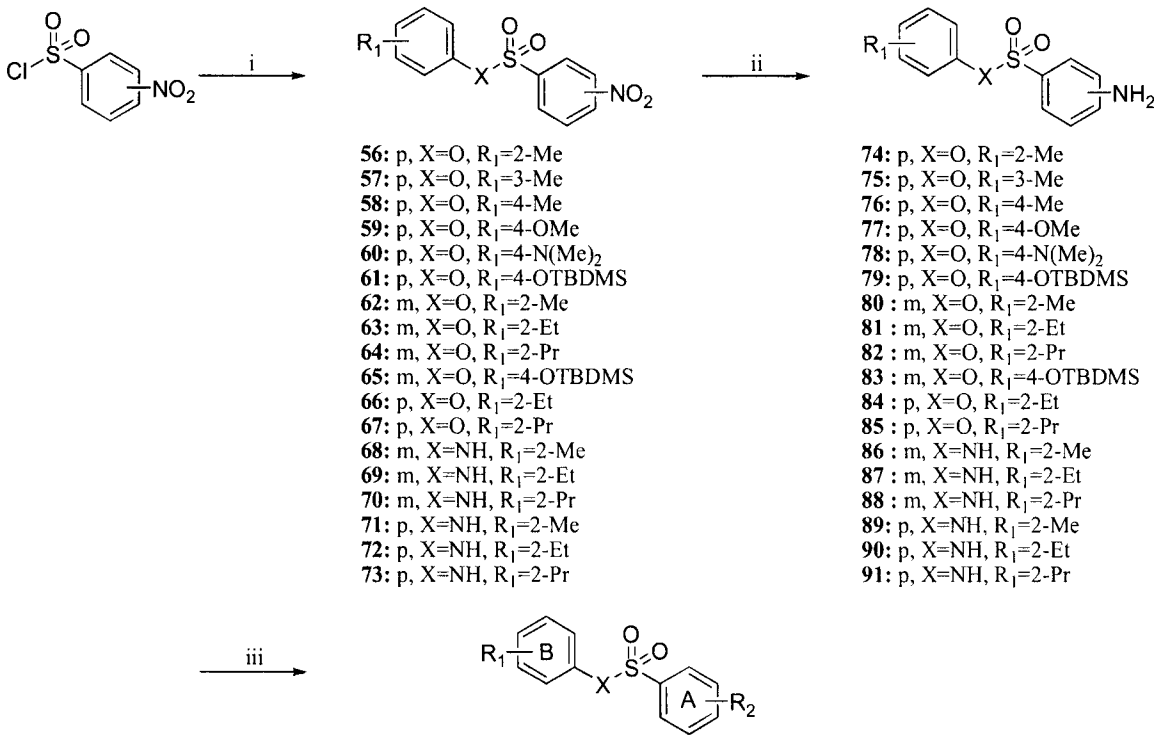
[0092] Compounds of the present invention are useful for treating, inhibiting or preventing abnormal cell growth, cellular differentiation, tumor growth and invasion.

[0093] The compounds of the present invention may be administered in an effective amount within the dosage range of about 0.05 mg/kg to about 200 mg/kg, preferably from about 0.1 mg/kg to about 100 mg/kg body weight. The compounds are preferably administered in compositions in which the compound is present in a concentration of about 1 mg/mL to about 250 mg/mL (e.g., in a solution), or in an amount of about 1 mg to about 200 mg, preferably about 5 mg to about 100 mg (e.g., in one unit of a solid dosage form such as a tablet or capsule). When the composition is in the form of a tablet, the compound of the present invention may comprise about 1 to about 50% (wt/wt), preferably about 5 to about 25% (wt/wt) of the tablet. Compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

[0094] The compounds and compositions according to the invention may also be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing an/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Preparation of compounds of Formula (I)

Scheme 1



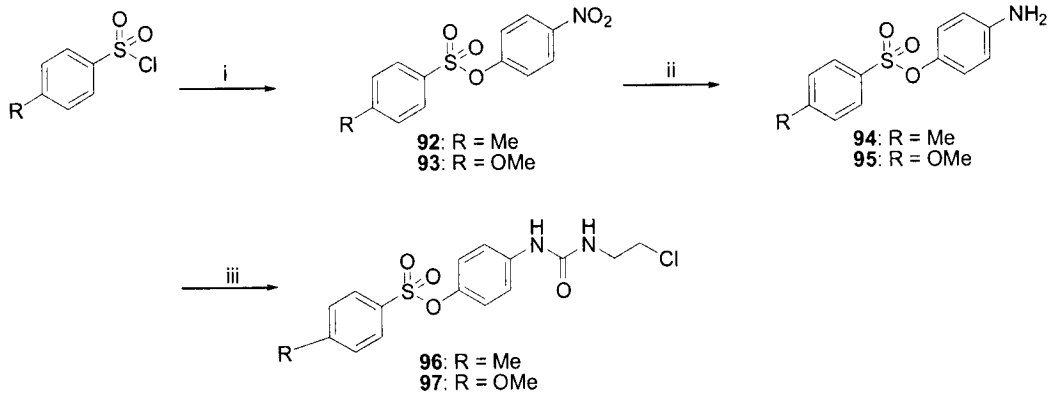
56: p, X=O, R_1=2-Me
57: p, X=O, R_1=3-Me
58: p, X=O, R_1=4-Me
59: p, X=O, R_1=4-OMe
60: p, X=O, R_1=4-N(Me)$_2$
61: p, X=O, R_1=4-OTBDMS
62: m, X=O, R_1=2-Me
63: m, X=O, R_1=2-Et
64: m, X=O, R_1=2-Pr
65: m, X=O, R_1=4-OTBDMS
66: p, X=O, R_1=2-Et
67: p, X=O, R_1=2-Pr
68: m, X=NH, R_1=2-Me
69: m, X=NH, R_1=2-Et
70: m, X=NH, R_1=2-Pr
71: p, X=NH, R_1=2-Me
72: p, X=NH, R_1=2-Et
73: p, X=NH, R_1=2-Pr

74: p, X=O, R_1=2-Me
75: p, X=O, R_1=3-Me
76: p, X=O, R_1=4-Me
77: p, X=O, R_1=4-OMe
78: p, X=O, R_1=4-N(Me)$_2$
79: p, X=O, R_1=4-OTBDMS
80 : m, X=O, R_1=2-Me
81 : m, X=O, R_1=2-Et
82 : m, X=O, R_1=2-Pr
83 : m, X=O, R_1=4-OTBDMS
84 : p, X=O, R_1=2-Et
85 : p, X=O, R_1=2-Pr
86 : m, X=NH, R_1=2-Me
87 : m, X=NH, R_1=2-Et
88 : m, X=NH, R_1=2-Pr
89: p, X=NH, R_1=2-Me
90: p, X=NH, R_1=2-Et
91: p, X=NH, R_1=2-Pr

4: R_2=p-CEU, X=O, R_1=2-Me
5: R_2=p-CEU, X=O, R_1=3-Me
6: R_2=p-CEU, X=O, R_1=4-Me
7: R_2=p-CEU, X=O, R_1=4-OMe
8: R_2=p-CEU, X=O, R_1=4-N(Me)$_2$
9: R_2=p-CEU, X=O, R_1=4-OTBDMS
10: R_2=p-CEU, X=O, R_1=4-OH
11: R_2=m-CEU, X=O, R_1=2-Me
12: R_2=m-CEU, X=O, R_1=2-Et
13: R_2=m-CEU, X=O, R_1=2-Pr
14: R_2=m-CEU, X=O, R_1=4-OTBDMS
15: R_2=m-CEU, X=O, R_1=4-OH
16: R_2=p-CEU, X=O, R_1=2-Et
17: R_2=p-CEU, X=O, R_1=2-Pr
18: R_2=m-CEU, X=NH, R_1=2-Me
19: R_2=m-CEU, X=NH, R_1=2-Et
20: R_2=m-CEU, X=NH, R_1=2-Pr
21: R_2=p-CEU, X=NH, R_1=2-Me
22: R_2=p-CEU, X=NH, R_1=2-Et
23: R_2=p-CEU, X=NH, R_1=2-Pr
24: R_2=m-CPU, X=O, R_1=2-Me
25: R_2=m-CPU, X=O, R_1=2-Et
26: R_2=m-CPU, X=O, R_1=2-Pr
27: R_2=m-CPU, X=O, R_1=4-OTBDMS
28: R_2=m-CPU, X=O, R_1=4-OH
29: R_2=p-CPU, X=O, R_1=2-Me
30: R_2=p-CPU, X=O, R_1=2-Et
31: R_2=p-CPU, X=O, R_1=2-Pr
32: R_2=p-CPU, X=O, R_1=4-OTBDMS
33: R_2=p-CPU, X=O, R_1=4-OH
34: R_2=m-CPU, X=NH, R_1=2-Me
35: R_2=m-CPU, X=NH, R_1=2-Et
36: R_2=m-CPU, X=NH, R_1=2-Pr
37: R_2=p-CPU, X=NH, R_1=2-Me
38: R_2=p-CPU, X=NH, R_1=2-Et
39: R_2=p-CPU, X=NH, R_1=2-Pr
40: R_2=m-EU, X=O, R_1=2-Me
41: R_2=m-EU, X=O, R_1=2-Et
42: R_2=m-EU, X=O, R_1=2-Pr
43: R_2=m-EU, X=O, R_1=4-OTBDMS
44: R_2=m-EU, X=O, R_1=4-OH
45: R_2=p-EU, X=O, R_1=2-Me
46: R_2=p-EU, X=O, R_1=2-Et
47: R_2=p-EU, X=O, R_1=2-Pr
48: R_2=p-EU, X=O, R_1=4-OTBDMS
49: R_2=p-EU, X=O, R_1=4-OH
50: R_2=m-EU, X=NH, R_1=2-Me
51: R_2=m-EU, X=NH, R_1=2-Et
52: R_2=m-EU, X=NH, R_1=2-Pr
53: R_2=p-EU, X=NH, R_1=2-Me
54: R_2=p-EU, X=NH, R_1=2-Et
55: R_2=p-EU, X=NH, R_1=2-Pr

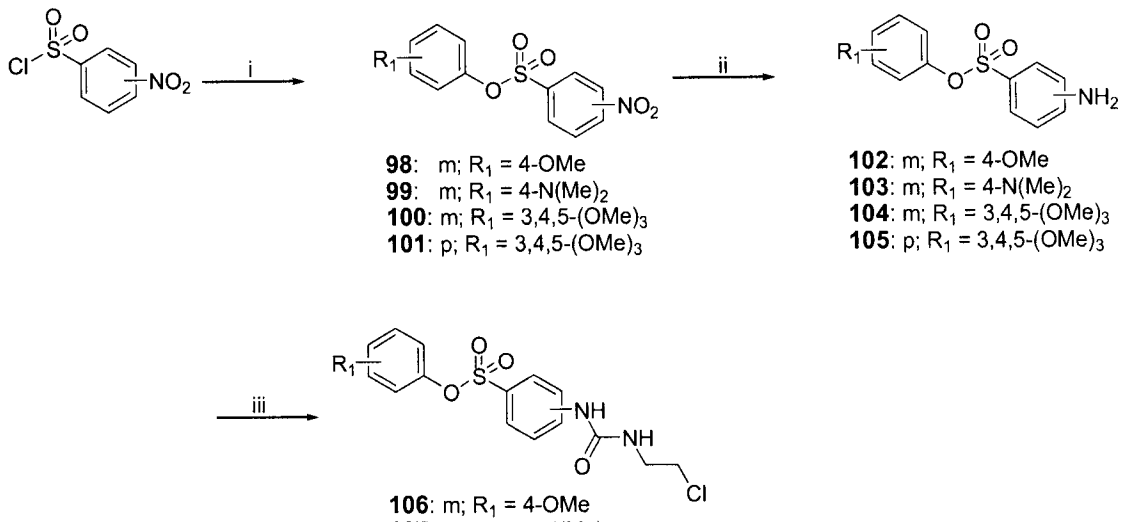
[a]Reagents: (i) relevant phenol, TEA/DCM or relevant aniline, DMAP/CH_3CN; (ii) $SnCl_2.2H_2O$/EtOH or Fe, HCl/EtOH; (iii) relevant isocyanate and appropriate condition method; (iv) TBAF 1M/THF.

Scheme 2



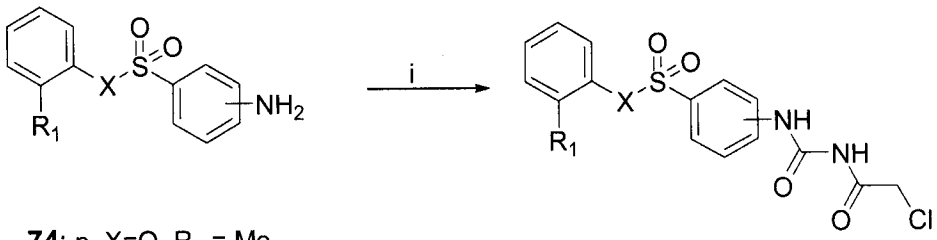
Reagents: (i) relevant phenol, TEA/DCM; (ii) $Na_2S_2O_4$/MeOH and H_2O, $SnCl_2{\cdot}2H_2O$/EtOH or Fe, HCl/EtOH; (iii) relevant isocyanate and appropriate condition method.

Scheme 3



Reagents: (i) relevant phenol, TEA/DCM; (ii) $Na_2S_2O_4$/MeOH and H_2O, $SnCl_2{\cdot}2H_2O$/EtOH or Fe, HCl/EtOH; (iii) relevant isocyanate and appropriate condition method.

Scheme 4



74: p, X=O, R_1 = Me
80: m, X=O, R_1 = Me
81: m, X=O, R_1 = Et
82: m, X=O, R_1 = Pr
84: p, X=O, R_1 = Et
85: p, X=O, R_1 = Pr
88: m, X=NH, R_1 = Pr
89: p, X=NH, R_1 = Me
90: p, X=NH, R_1 = Et
91: p, X=NH, R_1 = Pr

110: p, X=O, R_1 = Me
111: m, X=O, R_1 = Me
112: m, X=O, R_1 = Et
113: m, X=O, R_1 = Pr
114: p, X=O, R_1 = Et
115: p, X=O, R_1 = Pr
116: m, X=NH, R_1 = Pr
117: p, X=NH, R_1 = Me
118: p, X=NH, R_1 = Et
119: p, X=NH, R_1 = Pr

Reagents: relevant isocyanate and appropriate condition method.

Chemistry.

[0095] Scheme 1 depicts the synthetic pathways used for the preparation of substituted alkylurea-SO and alkylurea-SA derivatives. These compounds were prepared by nucleophilic addition of the appropriate phenols or anilines to nitrobenzene-1-sulfonyl chloride. Nitrophenyl sulfonates **56-67** and nitrophenyl sulfonamides **68-73** were reduced into the corresponding anilines **74-91** using iron powder in presence of hydrochloric acid or stannous chloride dihydrate for the compound **59**. Alkylurea-SO and alkylurea-SA derivatives substituted either by a CEU (**4-23**), a CPU (**24-39**) or a EU (**40-55**) moiety were prepared by nucleophilic addition of 2-chloroethylisocyanate, 3-chloropropylisocyanate or ethylisocyanate, respectively on the corresponding anilines. The different nucleophilicity of aniline and electrophilicity of isocyanate used as starting material lead us to use different bases (DMAP and pyridine), solvents (THF, acetonitrile and methylene chloride) and reaction conditions (no heating, heating, microwaves heating) to optimize the yield of the reactions. Removal of the *tert*-butyldimethylsilyl (TBDMS) protecting group on compounds **9**, **14**, **27**, **32**, **43** and **48** into their corresponding phenols was performed in presence of tetra-*n*-butylammonium fluoride (TBAF).

General Procedure for the Synthesis of compounds 4 to 55, 108-119.

[0096] Method A. The appropriate isocyanate (1.2 mmol) was added dropwise to the appropriate aniline (1.0 mmol) in dry methylene chloride or dry tetrahydrofuran (10 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 7 days. The solvent was evaporated under reduced pressure and the compound was purified by flash chromatography.

[0097] Method B. 2-Chloroethylisocyanate (1.2 mmol) and 4-dimethylaminopyridine were added dropwise to a solution of the appropriate aniline (1.0 mmol) in dry tetrahydrofuran (10 mL) under argon atmosphere. The reaction mixture was heated to reflux and stirred for 7 days. Afterward cooling to room temperature, the solvent was evaporated under reduced pressure and the crude compound was purified by flash chromatography.

[0098] Method C. The appropriate isocyanate (2.0 mmol) was added dropwise to appropriate aniline (1.0 mmol) in dry acetonitrile or dry tetrahydrofuran (10 mL). The reaction was performed either in absence or in presence of pyridine (1 mmol). The reaction mixture was stirred from 60 °C to 130 °C under microwave heating (100 W) for 15 at 50 minutes. The solvent was evaporated and the residue dissolved in ethyl acetate. The solution was washed with hydrochloric acid (1N) and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness.

[0099] Method D. The appropriate isocyanate (1.2 mmol) was added dropwise to appropriate aniline, (1.0 mmol) in dry acetonitrile (10 mL) under argon atmosphere. Pyridine (1.0 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 7 days. The solvent was evaporated under reduced pressure and the compound was purified by flash chromatography.

[00100] Method E. Appropriate compound 9, 14, 27, 32, 43 or 48 (0.1 mmol) was dissolved in dry tetrahydrofuran (5 mL). Tetrabutylammonium fluoride (1M) in dry THF was added dropwise. The mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue dissolved with ethyl acetate (40 mL). The solution was washed with 40 mL hydrochloric acid (1N), brine, dried over sodium sulfate, filtered and evaporated to dryness. The crude product was purified by flash chromatography.

General Procedure for the Synthesis of compounds 56-73, 92, 93, 98-101.

[00101] **Method F.** Relevant sulfonyl chloride compounds (7.5 mmol) was dissolved in dry methylene chloride (20 ml) under dry argon atmosphere. Subsequently, selected phenol or aniline (7.5 mmol) and trietylamine were added dropwise to the solution. The reaction mixture was stirred 24 h at room temperature. The solvent was evaporated and the residue dissolved in ethyl acetate. The solution was washed with hydrochloric acid (1N), sodium hydroxide (1N), brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness.

[00102] **Method G.** Relevant 3-nitrobenzene-1-sulfonyl chloride or 4-nitrobenzene-1-sulfonyl chloride (8 mmol) was dissolved in dry acetonitrile (10 ml) under argon atmosphere. Relevant aniline (8 mmol) and 4-dimethylaminopyridine were successively added dropwise and the mixture was stirred for 48 h at room temperature. The solvent was evaporated and the residue dissolved in ethyl acetate. The solution was washed with hydrochloric acid (1N), brine, dried over sodium sulfate, filtered, and evaporated to dryness.

General Procedure for the Synthesis of compounds 74-91, 94, 95, 102-105.

[00103] **Method H.** The appropriate nitro compound (2.0 mmol) was dissolved in a mixture of ethanol and water (40 ml, 10:1). Powdered iron (8.0 mmol) and five drops of hydrochloric acid (12M) were added. The mixture was refluxed overnight. After cooling at room temperature, the solvent was evaporated. Hydrochloric acid (1N) (100 ml) was added and the mixture was extracted with ethyl acetate (100 ml). The organic solutions were pooled, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure.

[00104] **Method I.** To a solution of the appropriate nitro compound (2.0 mmol) in ethanol (40 mL) was added stannous chloride dihydrate (12.0 mmol) and the mixture was refluxed for 6 h. After cooling at room temperature, the solvent was evaporated, the residue was then taken up in 300 mL of sodium hydroxide (1N) and extracted with ether (200 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure.

Examples

Chemical Procedure.

[00105] **General**. Proton NMR spectra were recorded on a Bruker AM-300 spectrometer (Bruker, Germany). Chemical shifts (δ) are reported in parts per million. Reactions using microwave heating were performed on an Initiator system (Biotage, Charlottesville, VA, USA). IR spectra were recorded on a Magna FT-IR spectrometer (Nicolet instrument corporation, Madison, WI, USA). Uncorrected melting points were determined on an electrothermal melting point apparatus. HPLC analyses of compounds 4-8 and 10 were performed on an Acquity UPLC Sample with binary solvent manager equipped with a Quattro Premier™ XE tandem quadrupole mass spectrometer (Waters, Milford, MA, USA). A Waters BECH C18 reversed-phase column (1.7 µm, 2.1 x 50 mm, 50 °C) was eluted within 7 min with a methanol/water linear gradient containing 0.1% TFA at 0.6 mL/min. HPLC analyses of other final compounds were performed on a Prominence LCMS-2020 with binary solvent equiped with UV/VIS photodiode array (Shimadzu, Columbia, Maryland, USA). An Alltech Alltima C18 reversed-phase column (5 µm, 250 mm x 4.6 mm) with an Alltech Alltima C18 pre-column (5 µm, 7.5 x 4.6 mm) was eluted in 30 min with a methanol/water linear gradient at 1.00 mL/min. The purity of final compounds was greater than 95%. All reactions were performed under a dried argon atmosphere. All chemicals were supplied by Aldrich Chemicals (Milwaukee, WI, USA) or VWR International (Mont-Royal, Qc, Canada) and used as received unless specified otherwise. Liquid flash chromatography was performed on silica gel F60, 60A, 40-63 µm supplied by Silicycle (Québec, Qc, Canada) using a FPX flash purification system (Biotage, Charlottesville, VA, USA), and using solvent mixtures expressed as volume/volume ratios. Solvents and reagents were used without purification unless specified otherwise. The progress of all reactions was monitored using TLC on precoated silica gel plates 60 F254 (VWR international, Mont-Royal, Qc, Canada). The chromatograms were viewed under UV light at 254 and/or 265 nm.

Example 1

Synthesis of compounds according to schemes 1, 2, 3 or 4

[00106] **2-Tolyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (4).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 57%; Yellow solid; mp: 101°C; IR δ: 3369 (NH), 1592 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8 .18 (s, 1H, NH), 7.69-7.67 (m, 2H, Ar), 7.53-7.51 (m, 2H, Ar), 7.12-7.04 (m, 3H, Ar), 6.98-6.95 (m, 1H, Ar), 6.12 (t, 1H, J = 4.8 Hz, NH), 3.58 (brs, 4H, 2xCH_2), 2.05 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.1, 148.1, 145.3, 131.8, 131.5, 129.8, 127.9, 127.3, 127.1, 122.2, 118.1, 44.2, 41.9, 16.3; MS (ESI+) *m/z* found 368.9; $C_{16}H_{18}ClN_2O_4S$ (M^+ + H) requires 369.1.

[00107] **3-Tolyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (5).** Method C in dry THF under microwave at 100 °C for 15 min without washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 29%; Orange oil; IR δ: 3348 (NH), 1594 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05 (s, 1H, NH), 7.67-7.64 (m, 2H, Ar), 7.54-7.51 (m, 2H, Ar), 7.13-7.00 (m, 2H, Ar), 6.84 (s, 1H, Ar), 6.70-6.67 (m, 1H, Ar), 6.06 (t, 1H, J = 5.4 Hz, NH), 3.62-3.56 (m, 4H, 2xCH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.0, 149.4, 145.2, 140.2, 129.9, 129.3, 128.1, 127.3, 122.9, 119.0, 117.9, 44.3, 41.9, 21.2; MS (ESI+) *m/z* found 368.9; $C_{16}H_{18}ClN_2O_4S$ (M^+ + H) requires 369.1.

[00108] **4-Tolyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (6). Method A** in dry DCM. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (80:20) to hexanes/ethyl acetate (60:40)). Yield: 33%; Colorless oil; IR δ: 3369 (NH), 1539 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.17 (s, 1H, NH), 7.66-763 (m, 2H, Ar), 7.53-7.50 (m, 2H, Ar), 7.02 (d, 2H, J = 8.4 Hz, Ar), 6.81 (d, 2H, J = 8.4 Hz, Ar), 6.13 (brs, 1H, NH), 3.58 (brs, 4H, 2xCH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.2, 147.2, 145.2, 137.3, 130.3, 129.9, 127.1, 122.0, 118.0, 44.2, 41.9, 20.9; MS (ESI+) *m/z* found 368.9; $C_{16}H_{18}ClN_2O_4S$ (M^+ + H) requires 369.1.

[00109] **4-Methoxyphenyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (7).** Method A in THF. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (80:20)). Yield: 46%; colorless oil; IR δ: 1500 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.92 (s, 1H, NH), 7.64-7.62 (m, 2H, Ar), 7.50-7.48 (m, 2H, Ar), 6.86-6.83 (m, 2H, Ar), 6.75-6.72 (m, 2H, Ar), 5.97 (t, 1H, J = 5.2 Hz, NH), 3.72 (s, 3H, CH_3), 3.62-3.57 (m, 4H, 2xCH_2); ^{13}C NMR ($CDCl_3$): δ 158.4, 154.9, 145.1, 142.8, 130.0,

127.1, 123.3, 118.0, 114.6, 55.6, 44.3, 42.0; MS (ESI+) *m/z* found 385.0; $C_{16}H_{18}ClN_2O_5S$ (M^+ + H) requires 385.1.

[00110] **4-(Dimethylamino)phenyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (8).** Method C in dry THF under microwave at 60 °C for 15 min without washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (95:5)). Yield: 22%; White sticky solid; IR δ: 3355 (NH), 1569 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.95 (s, 1H, NH), 7.65-7.63 (m, 2H, Ar), 7.51-7.49 (m, 2H, Ar), 6.78-6.76 (m, 2H, Ar), 6.50-6.48 (m, 2H, Ar), 5.98 (t, 1H, J = 5.3 Hz, NH), 3.63-3.57 (m, 4H, 2xCH_2), 2.87 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 154.9, 149.4, 145.1, 139.9, 129.9, 127.4, 122.8, 117.9, 112.5, 44.3, 41.9, 40.5; MS (ESI+) *m/z* found 397.9; $C_{17}H_{21}ClN_3O_4S$ (M^+ + H) requires 398.1.

[00111] **4-(*tert*-Butyldimethylsilyloxy)phenyl 4-[3-(2-chloroethyl)ureido] benzenesulfonate (9).** Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (80:20)). Yield: 99%; Yellow oil; IR δ: 3321 (NH), 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96 (s, 1H, NH), 7.65-7.51 (m, 4H, Ar), 6.82-6.68 (m, 4H, Ar), 5.97 (brs, 1H, NH), 3.61 (brs, 4H, 2xCH_2), 0.94 (s, 9H, 3xCH_3), 0.15 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 154.8, 154.7, 145.2, 143.3, 130.0, 127.1, 123.3, 120.8, 118.0, 44.3, 42.0, 25.6, 18.2, -4.5.

[00112] **4-Hydroxyphenyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (10).** Method E. The crude product was purified by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol (90:10)). Yield: 80%; White solid; mp: 247 °C; IR δ: 3625-3050 (OH), 1686 (C=O), 1334 (OH) cm^{-1}; ^1H NMR (acetone-d_6): δ 8.60 (s, 1H, NH), 7.89-7.86 (m, 2H, Ar), 7.73-7.70 (m, 2H, Ar), 6.85-6.82 (m, 2H, Ar), 6.78-6.75 (m, 2H, Ar), 6.37 (brs, 1H, NH), 4.04 (t, 2H, J = 7.9 Hz, CH_2), 3.65-3.60 (m, 2H, CH_2), 3.31 (brs, 1H, OH); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 158.5, 156.1, 145.6, 141.6, 129.2, 126.3, 122.9, 116.1, 115.7, 44.4, 36.6; MS (ESI-) *m/z* found 369.0; $C_{15}H_{14}ClN_2O_5S$ (M^- - H) requires 369.0.

[00113] **2-Tolyl 3-[3-(2-chloroethyl)ureido]benzenesulfonate (11).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 57%; Sticky solid; IR δ: 3330 (NH), 1658 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.26 (s, 1H, NH), 7.97 (s, 1H, Ar), 7.68-7.65 (m, 1H, Ar), 7.83-7.30 (m, 2H, Ar), 7.14-7.02 (m, 3H, Ar), 6.93-6.90 (m, 1H, Ar), 6.18 (brs, 1H, NH), 3.57 (s, 4H, 2xCH_2), 2.07 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.7, 148.2, 140.4, 136.3, 131.7, 131.5, 129.9, 127.2, 127.0, 124.6, 122.1, 122.0, 118.0, 44.2, 41.9, 16.3; MS (APSI+) *m/z* found 369.1; $C_{16}H_{18}ClN_2O_4S$ (M^+ + H) requires 369.1.

[00114] **2-Ethylphenyl 3-[3-(2-chloroethyl)ureido]benzenesulfonate (12).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 53%; Colorless oil; IR δ: 3343 (NH), 1658 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.17 (s, 1H, NH), 7.95 (s, 1H, Ar), 7.70-7.68 (m, 1H, Ar), 7.41-7.34 (m, 2H, Ar), 7.19-7.03 (m, 3H, Ar), 6.92-6.90 (m, 1H, Ar), 6.08 (brs, 1H, NH), 3.56 (s, 4H, 2xCH_2), 2.50 (q, 2H, J = 7.5 Hz, CH_2), 1.07 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.8, 147.7, 140.4, 137.2, 136.4, 130.0, 127.4, 127.0, 124.6, 121.9, 121.9, 118.0, 102.7, 44.1, 41.9, 22.8, 14.1; MS (APSI+) *m/z* found 383.1; $C_{17}H_{20}ClN_2O_4S$ (M^+ + H) requires 383.1.

[00115] **2-Propylphenyl 3-[3-(2-chloroethyl)ureido]benzenesulfonate (13).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 12%; Yellow oil; IR δ: 3300 (NH), 1657 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.42 (s, 1H, NH), 8.08 (s, 1H, Ar) 7.57-7.55 (m, 1H, Ar), 7.38-7.32 (m, 2H, Ar), 7.14-7.05 (m, 3H, Ar), 6.93-6.91 (m, 1H, Ar), 6.29 (brs, 1H, NH), 3.55 (s, 4H, 2xCH_2), 2.45-2.41 (m, 2H, CH_2), 1.49-1.45 (m, 2H, CH_2), 0.84-0.80 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.9, 147.9, 140.4, 136.5, 135.8, 130.7, 129.9, 127.2, 127.0, 124.6, 121.9, 118.0, 102.7, 44.1, 41.9, 31.8, 23.0, 13.9; MS (APSI+) *m/z* found 397.1; $C_{18}H_{22}ClN_2O_4S$ (M^+ + H) requires 397.1.

[00116] **4-(*tert*-Butyldimethylsilyloxy)phenyl 3-[3-(2-chloroethyl)ureido] benzenesulfonate (14).** Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 85%; White sticky solid; IR δ: 3004 (NH), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.16 (s, 1H, NH), 7.90 (s, 1H, Ar), 7.75-7.72 (m, 1H, Ar), 7.33-7.24 (m, 2H, Ar), 6.82-6.79 (m, 2H, Ar), 6.69-6.66 (m, 2H, Ar), 6.09 (brs, 1H, NH), 3.61 (s, 4H, 2xCH_2), 0.93 (s, 9H, 3xCH_3), 0.14 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 155.3, 154.7, 143.3, 140.4, 135.3, 129.8, 124.6, 123.2, 122.3, 120.8, 118.0, 44.3, 42.0, 25.6, 18.2, -4.5.

[00117] **4-Hydroxyphenyl 3-[3-(2-chloroethyl)ureido]benzenesulfonate (15).** Method E. The crude product was purified by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol (90:10)). Yield: 78%; White solid; mp: 156 °C; IR δ: 3500-3100 (OH), 1688 (C=O), 1330 (OH) cm^{-1}; ^1H NMR (acetone-d_6): δ 8.60 (s, 1H, NH), 8.29 (s, 1H, Ar), 7.93-7.90 (m, 1H, Ar), 7.57-7.52 (m, 1H, Ar), 7.40-7.37 (m, 1H, Ar), 6.90-6.86 (m, 2H, Ar), 6.80-6.76 (m, 2H, Ar), 6.27 (brs, 1H, NH), 4.00 (t, 2H, J = 7.9 Hz, CH_2), 3.63-3.58 (m, 2H, CH_2), 2.87 (brs, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 158.9, 155.6, 155.6, 142.4, 141.0, 135.7, 129.4, 123.2, 123.1, 121.9, 115.9, 44.8, 37.0; MS (APSI+) *m/z* found 371.1; $C_{15}H_{16}ClN_2O_5S$ (M^+ + H) requires 371.0.

[00118] **2-Ethylphenyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (16).** Method C in dry MeCN under microwave at 130°C for 40 min with washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (75:25) to hexanes/ethyl acetate (50:50)). Yield: 8%; White solid; mp: 127-128 °C; IR δ: 3338 (NH), 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.44 (s, 1H, NH), 7.86-7.83 (m, 2H, Ar), 7.73-7.70 (m, 2H, Ar), 7.27-6.97 (m, 4H, Ar), 4.03-3.95 (m, 4H, 2xCH_2), 2.53-2.45 (m, 2H, CH_2), 1.12-1.07 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 154.5, 147.8, 143.9, 137.2, 130.5, 129.9, 129.6, 127.2, 126.9, 122.0, 117.7, 43.6, 41.9, 22.8, 14.1; MS (APSI+) *m/z* found 383.1; $C_{17}H_{20}ClN_2O_4S$ (M^+ + H) requires 383.1.

[00119] **2-Propylphenyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (17).** Method C in dry MeCN under microwave at 130 °C for 50 min with washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (75:25) to hexanes/ethyl acetate (50:50)). Yield: 75%; Yellow solid; mp: 95 °C; IR δ: 3326 (NH), 1669 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.76-7.73 (m, 2H, Ar), 7.54-7.52 (m, 2H, Ar), 7.32 (brs, 1H, NH), 7.29-6.99 (m, 4H, Ar), 5.58 (brs, 1H, NH), 3.65-3.64 (m, 4H, 2xCH_2), 2.43 (t, 2H, J = 7.7 Hz, CH_2), 1.57-1.51 (m, 2H, CH_2), 0.86 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 154.3, 148.0, 144.7, 135.8, 130.7, 129.8, 128.7, 127.1, 127.0, 122.0, 118.1, 44.4, 42.0, 31.9, 23.0, 13.9; MS (APSI+) *m/z* found 397.1; $C_{18}H_{22}ClN_2O_4S$ (M^+ + H) requires 397.1.

[00120] **3-[3-(2-Chloroethyl)ureido]-*N*-2-tolylbenzenesulfonamide (18).** Method B. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)) and was crystallized with methylene chloride and filtered. Yield: 45%; White solid; mp: 164-165 °C; IR δ: 3267 (NH), 1642 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.58 (s, 1H, NH), 9.06 (s, 1H, NH), 7.94 (s, 1H, Ar), 7.62-7.01 (m, 7H, Ar), 6.51 (brs, 1H, NH), 3.71-3.68 (m, 2H, CH_2), 3.48-3.45 (m, 2H, CH_2), 2.05 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.8, 141.3, 141.0, 134.9, 134.3, 130.7, 129.5, 126.5, 126.4, 126.3, 121.3, 119.2, 115.4, 44.3, 41.3, 17.7; MS (APSI-) *m/z* found 366.0; $C_{16}H_{17}ClN_3O_3S$ (M^- - H) requires 366.1.

[00121] **3-[3-(2-Chloroethyl)ureido]-*N*-(2-ethylphenyl)benzenesulfonamide (19).** Method B. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)) and was crystallized with methylene chloride and filtered. Yield: 35%; White solid; mp: 170-171 °C; IR δ: 3274 (NH), 1643 (C=O); ^1H NMR (DMSO-d_6): δ 9.58 (s, 1H, NH), 9.06 (s, 1H, NH), 7.95 (s, 1H, Ar), 7.63-6.91 (m, 7H, Ar), 6.50 (brs, 1H, NH), 3.72-3.68 (m, 2H, CH_2), 3.47-3.45 (m, 2H, CH_2), 2.58-2.54 (m, 2H, CH_2), 1.01 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.9, 141.3, 141.0, 140.5, 134.2,

129.5, 129.0, 126.8, 126.6, 126.2, 121.2, 119.2, 115.4, 44.3, 41.3, 23.2, 14.4; MS (APCI-) *m/z* found 379.9; $C_{17}H_{19}ClN_3O_3S$ (M^- - H) requires 380.1.

[00122] **3-[3-(2-Chloroethyl)ureido]-*N*-(2-propylphenyl)benzenesulfonamide (20).** Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (80:20)). Yield: 12%; Yellow solid; mp: 207 °C; IR δ: 3318 (NH), 1633 (C=O) cm^{-1}; ^1H NMR (acetone-d_6): δ 8.55 (s, 1H, NH), 8.01-7.98 (m, 1H, Ar), 7.81 (s, 1H, Ar), 7.52-6.92 (m, 6H, Ar), 6.41 (brs, 1H, NH), 3.74-3.70 (m, 2H, CH_2), 3.61-3.57 (m, 2H, CH_2), 2.48-2.42 (m, 2H, CH_2), 1.63-1.53 (m, 2H, CH_2), 0.87 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR (acetone-d_6): δ 160.1, 150.4, 146.4, 144.8, 138.3, 137.0, 135.5, 134.7, 134.6, 131.4, 129.0, 126.9, 123.1, 49.1, 46.9, 37.9, 27.9, 19.0; MS (APSI-) *m/z* found 393.9; $C_{18}H_{21}ClN_3O_3S$ (M^- - H) requires 394.1.

[00123] **4-[3-(2-Chloroethyl)ureido]-*N*-2-tolylbenzenesulfonamide (21).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)) and was recrystallized with methanol and filtered. Yield: 40%; Yellowish solid; mp: 134-135 °C; IR δ: 3074 (NH), 1683 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 8.97 (s, 2H, 2xNH), 7.79-7.64 (m, 4H, Ar), 7.38-7.26 (m, 4H, Ar), 6.31 (brs, 1H, NH), 3.87-3.75 (m, 4H, 2xCH_2), 2.24 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.7, 144.3, 135.1, 134.1, 132.7, 130.7, 127.9, 126.4, 126.3, 117.0, 44.3, 41.3, 17.7; MS (APSI+) *m/z* found 368.1; $C_{16}H_{19}ClN_3O_3S$ (M^+ + H) requires 368.1.

[00124] **4-[3-(2-Chloroethyl)ureido]-*N*-(2-ethylphenyl)benzenesulfonamide (22).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)) and was recrystallized with methanol and filtered. Yield: 10%; White solid; mp: 214-215 °C; IR δ: 3100 (NH), 1682 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 7.53-7.40 (m, 4H, Ar), 7.13-7.01 (m, 4H, Ar), 3.60-3.49 (m, 4H, 2xCH_2), 2.38 (q, 2H, J = 7.6 Hz, CH_2), 0.99 (t, 3H, J = 7.6, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.7, 144.2, 140.3, 134.4, 132.3, 128.9, 128.0, 126.6, 126.5, 126.1, 117.0, 44.3, 41.2, 23.1, 14.4; MS (APSI+) *m/z* found 382.1; $C_{17}H_{21}ClN_3O_3S$ (M^+ + H) requires 382.1.

[00125] **4-[3-(2-Chloroethyl)ureido]-*N*-(2-propylphenyl)benzenesulfonamide (23).** Method B. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)) and was crystallized with methylene chloride and filtered. Yield: 21%; White solid; mp: 178-180 °C; IR δ: 3376 (NH), 1684 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.36 (s, 1H, NH), 9.15 (s, 1H, NH), 7.64-7.57 (m, 4H, Ar), 7.21-6.91 (m, 4H, Ar), 6.62 (brs, 1H, NH), 3.73-3.69 (m, 2H, CH_2), 3.48-3.46 (m, 2H, CH_2), 2.55-2.47 (m, 2H, CH_2), 1.44-1.39 (m, 2H, CH_2), 0.85 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (DMSO-

d_6): δ 154.7, 144.2, 138.8, 134.6, 132.4, 129.6, 128.0, 126.4, 126.4, 126.1, 117.0, 44.3, 41.3, 32.3, 22.9, 14.0; MS (APSI-) *m/z* found 393.9; $C_{18}H_{21}ClN_3O_3S$ (M^- - H) requires 394.1.

[00126] **2-Tolyl 3-[3-(3-chloropropyl)ureido]benzenesulfonate (24).** Method C in dry MeCN under microwave at 130 °C for 45 min with washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 45%; White solid; mp: 129 °C; IR δ: 3327 (NH), 1626 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.05 (s, 1H, NH), 8.19 (s, 1H, Ar), 7.70-6.67 (m, 1H, Ar), 7.54-7.52 (m, 1H, Ar), 7.37-7.21 (m, 4H, Ar), 6.99-6.97 (m, 1H, Ar), 6.45 (brs, 1H, NH), 3.69-3.67 (m, 2H, CH_2), 3.25-3.23 (m, 2H, CH_2), 2.06 (s, 3H, CH_3), 1.93-1.91 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6): δ 160.2, 153.0, 147.0, 140.8, 137.0, 136.2, 135.3, 132.5, 128.5, 127.1, 125.3, 121.3, 48.3, 41.9, 37.8, 21.0; MS (APSI+) *m/z* found 383.1; $C_{17}H_{20}ClN_2O_4S$ (M^+ + H) requires 383.1.

[00127] **2-Ethylphenyl 3-[3-(3-chloropropyl)ureido]benzenesulfonate (25).** Method C in dry MeCN under microwave at 130 °C for 45 min with washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (75:25) to hexanes/ethyl acetate (25:75)). Yield: 36%; Yellowish oil; mp: 102 °C; IR δ: 3326 (NH), 1633 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.04 (s, 1H, NH), 8.21 (s, 1H, Ar), 7.69-7.67 (m, 1H, Ar), 7.56-7.51 (m, 1H, Ar), 7.40-7.23 (m, 4H, Ar), 6.99-6.67 (m, 1H, Ar), 6.45 (t, 1H, J = 5.6 Hz, NH), 3.71-3.67 (m, 2H, CH_2), 3.27-3.20 (m, 2H, CH_2), 2.52-2.45 (m, 2H, CH_2), 1.94-1.89 (m, 2H, CH_2), 1.06 (t, 3H, J = 7.6 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 160.2, 152.5, 147.0, 141.8, 140.8, 135.3, 132.7, 132.5, 128.5, 126.9, 125.2, 121.2, 48.2, 1.9, 37.8, 27.4, 19.3; MS (APSI+) *m/z* found 397.1; $C_{18}H_{22}ClN_2O_4S$ (M^+ + H) requires 397.1.

[00128] **2-Propylphenyl 3-[3-(3-chloropropyl)ureido]benzenesulfonate (26).** Method C in dry MeCN under microwave at 130 °C for 45 min with washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, chloroform to chloroform/ethyl acetate (80:20)). Yield: 55%; White solid; mp: 100 °C; IR δ: 1634 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.29 (s, 1H, NH), 8.02 (s, 1H, Ar), 7.64-7.61 (m, 1H, Ar), 7.41-7.31 (m, 2H, Ar), 7.18-7.03 (m, 3H, Ar), 6.93-6.91 (m, 1H, Ar), 6.00 (brs, 1H, NH), 3.54 (t, 2H, J = 6.2 Hz, CH_2), 3.40-3.36 (m, 2H, CH_2), 2.44 (t, 2H, J = 7.7 Hz, CH_2), 1.97-1.89 (m, 2H, CH_2), 1.55-1.42 (m, 2H, CH_2), 0.86-0.81 (t, 3H, J = 7.3, CH_3); ^{13}C NMR ($CDCl_3$): δ 156.1, 148.0, 140.6, 136.5, 135.8, 130.7, 129.9, 127.2, 127.0, 124.5, 121.9, 121.8, 117.9, 42.4, 37.5, 32.5, 31.8, 23.0, 13.9; MS (APSI+) *m/z* found 411.2; $C_{19}H_{24}ClN_2O_4S$ (M^+ + H) requires 411.1.

[00129] **4-(*tert*-Butyldimethylsilyloxy)phenyl 3-[3-(3-chloropropyl)ureido] benzenesulfonate (27).** Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (95:5)). Yield: 83%;

Yellowish oil; IR δ: 1662 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.24 (s, 1H, NH), 8.06 (s, 1H, Ar), 7.57-7.55 (m, 1H, Ar), 7.28-7.21 (m, 2H, Ar), 6.81-6.78 (m, 2H, Ar), 6.69-6.67 (m, 2H, Ar), 6.05 (brs, 1H, NH), 3.59-3.55 (m, 2H, CH_2), 3.44-3.40 (m, 2H, CH_2), 1.98-1.95 (m, 2H, CH_2), 0.93 (s, 9H, 3xCH_3), 0.14 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 156.1, 154.6, 143.3, 140.6, 135.4, 129.6, 124.6, 123.2, 122.2, 120.8, 118.0, 42.4, 37.5, 32.6, 25.6, 18.1, -4.5.

[00130] 4-Hydroxyphenyl 3-[3-(3-chloropropyl)ureido]benzenesulfonate (28). Method E. The crude product was purified by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol (90:10)). Yield: 60%; Yellowish oil; IR δ: 3450-3050 (OH), 1666 (C=O), 1364 (OH) cm^{-1}; ^1H NMR (acetone-d_6): δ 8.12-8.11 (m, 1H, Ar), 7.78-7.63 (m, 1H, Ar), 7.44-7.28 (m, 2H, Ar), 6.84-6.68 (m, 4H, Ar), 3.67-3.62 (m, 2H, CH_2), 3.38-3.34 (m, 2H, CH_2), 2.02-1.94 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6): δ 157.0, 155.8, 143.1, 142.5, 136.6, 130.3, 124.0, 124.0, 121.7, 117.9, 116.6, 43.3, 37.8, 33.7; MS (APSI+) *m/z* found 385.1; $C_{16}H_{18}ClN_2O_5S$ (M^+ + H) requires 385.1.

[00131] 2-Tolyl 4-[3-(3-chloropropyl)ureido]benzenesulfonate (29). Method C in dry MeCN under microwave at 130 °C for 45 min with washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 41%; Sticky solid; IR δ: 3395 (NH), 1675 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90 (s, 1H, NH), 7.70-6.67 (m, 2H, Ar), 7.53-7.50 (m, 2H, Ar), 7.14-6.96 (m, 4H, Ar), 3.58-3.54 (m, 2H, CH_2), 3.42-3.38 (m, 2H, CH_2), 2.06 (s, 3H, CH_3), 2.00-1.92 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 155.2, 148.1, 145.3, 131.8, 131.5, 129.8, 127.8, 127.3, 127.1, 122.2, 118.0, 42.3, 37.5, 32.3, 16.3; MS (APSI+) *m/z* found 383.1; $C_{17}H_{20}ClN_2O_4S$ (M^+ + H) requires 383.1.

[00132] 2-Ethylphenyl 4-[3-(3-chloropropyl)ureido]benzenesulfonate (30). Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (75:25) to hexanes/ethyl acetate (25:75)). Yield: 85%; Yellowish sticky solid; IR δ: 3363 (NH), 1664 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.07 (s, 1H, NH), 7.71-7.68 (m, 2H, Ar), 7.54-7.51 (m, 2H, Ar), 7.19-7.07 (m, 3H, Ar), 6.98-6.96 (m, 1H, Ar), 5.88 (brs, 1H, NH), 3.56-3.52 (m, 2H, CH_2), 3.41-3.36 (m, 2H, CH_2), 2.48 (q, 2H, J = 7.6 Hz, CH_2), 1.96-1.92 (m, 2H, CH_2), 1.08 (t, 3H, J = 7.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.4, 147.7, 145.4, 137.2, 130.0, 129.7, 127.8, 127.4, 127.0, 121.9, 118.0, 42.3, 37.5, 32.4, 22.8, 14.1; MS (APSI+) *m/z* found 397.1; $C_{18}H_{22}ClN_2O_4S$ (M^+ + H) requires 397.1.

[00133] 2-Propylphenyl 4-[3-(3-chloropropyl)ureido]benzenesulfonate (31). Method C in dry MeCN under microwave at 130 °C for 45 min with washing with HCl (1N). The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (75:25) to hexanes/ethyl acetate (25:75)). Yield: 27%; Yellow oil; IR δ: 3352 (NH), 1672

(C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.72-7.50 (m, 4H, Ar), 7.16-6.96 (m, 4H, Ar), 3.58-3.54 (m, 2H, CH_2), 3.41-3.37 (m, 2H, CH_2), 2.43-3.39 (m, 2H, CH_2), 1.99-1.94 (m, 2H, CH_2), 1.55-1.45 (m, 2H, CH_2), 0.86-0.81 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.1, 147.9, 145.1, 135.7, 130.8, 129.7, 128.1, 127.2, 127.0, 121.9, 118.1, 42.3, 37.6, 32.3, 31.8, 23.0, 13.9; MS (APSI+) *m/z* found 411.2; $C_{19}H_{24}ClN_2O_4S$ (M^+ + H) requires 411.1.

[00134] 4-(*tert*-Butyldimethylsilyloxy)phenyl 4-[3-(3-chloropropyl)ureido] benzenesulfonate (32). Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)). Yield: 60%; Yellowish oil; IR δ: 3303 (NH), 1672 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.89 (s, 1H, NH), 7.65-7.62 (m, 2H, Ar), 7.52-7.50 (m, 2H, Ar), 6.82-6.79 (m, 2H, Ar), 6.72-6.68 (m, 2H, Ar), 5.78 (brs, 1H, NH), 3.58-3.55 (m, 2H, CH_2), 3.41-3.37 (m, 2H, CH_2), 1.98-1.94 (m, 2H, CH_2), 0.95-0.91 (s, 9H, 3xCH_3), 0.15 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 155.2, 154.7, 145.4, 143.3, 130.0, 126.9, 123.3, 120.8, 117.9, 42.3, 37.5, 32.4, 25.6, 18.1, -4.5.

[00135] 4-Hydroxyphenyl 4-[3-(3-chloropropyl)ureido]benzenesulfonate (33). Method E. The crude product was purified by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol (90:10)). Yield: 63%; Yellowish oil; IR δ: 3620-3375 (OH), 1678 (C=O), 1359 (OH); ^1H NMR (DMSO-d_6): δ 9.67 (s, 1H, OH), 9.17 (s, 1H, NH), 7.64 (s, 4H, Ar), 6.80-6.68 (m, 4H, Ar), 6.54 (t, 1H, J = 5.6, NH), 3.72-3.67 (m, 2H, CH_2), 3.28-3.22 (m, 2H, CH_2), 1.97-1.88 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6): δ 156.2, 154.7, 146.3, 141.4, 129.7, 125.1, 123.1, 117.1, 115.9, 43.0, 36.7, 32.5; MS (APSI+) *m/z* found 385.1; $C_{16}H_{18}ClN_2O_5S$ (M^+ + H) requires 385.1.

[00136] 3-[3-(3-Chloropropyl)ureido]-*N*-2-tolylbenzenesulfonamide (34). Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (70:30)) and recrystallized with methanol and filtered. Yield: 40%; Yellowish solid; mp: 150 °C; IR δ: 3353 (NH), 1648 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.55 (s, 1H, NH), 8.85 (s, 1H, NH), 7.91 (s, 1H, Ar), 7.58-7.56 (m, 1H, Ar), 7.40-7.35 (m, 1H, Ar), 7.16-7.08 (m, 4H, Ar), 6.70-6.67 (m, 1H, Ar), 6.33 (t, 1H, J = 5.5 Hz, NH), 3.70-3.66 (m, 2H, CH_2), 3.25-3.19 (m, 2H, CH_2), 2.03 (s, 3H, CH_3), 1.95-1.88 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6): δ 155.0, 141.2, 134.9, 134.2, 130.7, 129.4, 126.4, 126.3, 121.2, 118.9, 115.3, 113.1, 43.1, 36.6, 32.6, 17.7; MS (APSI+) *m/z* found 382.1; $C_{17}H_{21}ClN_3O_3S$ (M^+ + H) requires 382.1.

[00137] 3-[3-(3-Chloropropyl)ureido]-*N*-(2-ethylphenyl)benzenesulfonamide (35). Method D. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (40:60) to hexanes/ethyl acetate (10:90)) and recrystallized with methanol and filtered. Yield: 14%; Yellowish solid; mp: 125 °C; IR δ: 3316 (NH), 1641 (C=O) cm^{-1}; ^1H NMR

(DMSO-d_6): δ 9.05 (s, 1H, NH), 7.97 (s, 1H, Ar), 7.77-7.75 (m, 1H, Ar), 7.53-7.43 (m, 2H, Ar), 7.27-7.22 (m, 3H, Ar), 6.97-6.95 (m, 1H, Ar), 6.42 (t, 1H, J = 5.5, NH), 3.69 (t, 2H, J = 6.4 Hz, CH_2), 3.25-3.21 (m, 2H, CH_2), 2.26 (q, 2H, J = 7.3 Hz, CH_2), 1.96-1.87 (m, 2H, CH_2), 0.98 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR (acetone-d_6/$CDCl_3$): δ 156.2, 147.4, 141.9, 140.0, 132.1, 131.1, 130.1, 129.9, 126.9, 124.9, 122.5, 118.8, 117.4, 43.2, 37.8, 33.7, 24.2, 14.3; MS (APSI-) *m/z* found 393.9; $C_{18}H_{21}ClN_3O_3S$ (M^- - H) requires 394.1.

[00138] **3-[3-(3-Chloropropyl)ureido]-*N*-(2-propylphenyl)benzenesulfonamide (36).** Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (80:20)) and recrystallized with methanol and filtered. Yield: 6%; Yellowish solid; mp: 112 °C; IR δ: 3319 (NH), 1642 (C=O); ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H, NH), 8.85 (s, 1H, NH), 7.93 (s, 1H, Ar), 7.58-756 (m, 1H, Ar), 7.41-7.36 (m, 1H, Ar), 7.20-7.05 (m, 4H, Ar), 6.93-6.91 (m, 1H, Ar), 6.33 (brs, 1H, NH), 3.70-3.66 (m, 2H, CH_2), 3.25-3.19 (m, 2H, CH_2), 2.48-2.43 (m, 2H, CH_2), 1.94-1.86 (m, 2H, CH_2), 1.41-1.28 (m, 2H, CH_2), 0.81 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 155.0, 141.2, 139.0, 138.8, 134.4, 129.6, 129.4, 126.6, 126.5, 126.2, 121.1, 119.0, 115.3, 43.1, 36.7, 32.6, 32.3, 22.9, 14.0; MS (ESI-) *m/z* found 408.1; $C_{19}H_{23}ClN_3O_3S$ (M^- - H) requires 408.1.

[00139] **4-[3-(3-Chloropropyl)ureido]-*N*-2-tolylbenzenesulfonamide (37**). Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (80:20)) and was recrystallized with methanol and filtered. Yield: 20%; White solid; mp: 204-205 °C; IR δ: 3079 (NH), 1678 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.35 (s, 1H, NH), 8.95 (s, 1H, NH), 7.56-7.49 (m, 4H, Ar), 7.13-7.00 (m, 4H, Ar), 6.45 (brs, 1H, NH), 3.70-3.66 (m, 2H, CH_2), 3.27-3.21 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 1.93-1.89 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6): δ 154.8, 144.5, 135.1, 134.0, 132.1, 130.7, 127.9, 126.4, 126.3, 126.2, 116.9, 43.0, 36.6, 32.5, 17.7; MS (ESI-) *m/z* found 380.1; $C_{17}H_{19}ClN_3O_3S$ (M^- - H) requires 380.1.

[00140] **4-[3-(3-Chloropropyl)ureido]-*N*-(2-ethylphenyl)benzenesulfonamide (38).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (90:10)) and was recrystallized with methanol and filtered. Yield: 13%; White solid; mp: 192 °C; IR δ: 3076 (NH), 1679 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$/ DMSO-d_6): δ 7.54-7.41 (m, 4H, Ar), 7.18-7.03 (m, 4H, Ar), 3.58 (t, 2H, J = 6.3 Hz, CH_2), 3.36-3.31 (m, 2H, CH_2), 2.38 (q, 2H, J = 7.5 Hz, CH_2), 1.99-1.91 (m, 2H, CH_2), 1.01 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 155.5, 145.6, 140.4, 135.5, 133.3, 129.7, 129.0, 127.2, 126.9, 126.8, 117.8, 43.2, 37.8, 33.7, 24.1, 14.7; MS (ESI-) *m/z* found 394.1; $C_{18}H_{21}ClN_3O_3S$ (M^- - H) requires 394.1.

[00141] **4-[3-(3-Chloropropyl)ureido]-*N*-(2-propylphenyl)benzenesulfonamide (39).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (95:15)) and was recrystallized with methanol and filtered. Yield: 11%; White solid; mp: 219-220 °C; IR δ: 3277 (NH), 1657 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.11 (s, 1H, NH), 7.80-7.60 (m, 4H, Ar), 7.44-7.08 (m, 4H, Ar), 6.54-6.48 (m, 2H, 2xNH), 3.51-3.47 (m, 2H, CH_2), 3.26-3.22 (m, 2H, CH_2), 1.95-1.90 (m, 2H, CH_2), 1.78-1.73 (m, 2H, CH_2), 1.61-1.59 (m, 2H, CH_2), 0.91 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.8, 152.7, 145.4, 142.9, 134.1, 130.9, 130.5, 129.9, 129.6, 127.1, 116.6, 43.0, 37.8, 36.7, 32.6, 22.5, 14.1; MS (APSI-) *m/z* found 408.0; $C_{19}H_{23}ClN_3O_3S$ (M^- - H) requires 408.1.

[00142] **2-Tolyl 3-(3-ethylureido)benzenesulfonate (40).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride/ethyl acetate (92:8) to methylene chloride/ethyl acetate (88:12)). Yield: 80%; Yellowish sticky solid; IR δ: 3317 (NH), 1655 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.27 (s, 1H, NH), 8.00 (s, 1H, Ar), 7.63-7.61 (m, 1H, Ar), 7.35-7.27 (m, 2H, Ar), 7.09-7.03 (m, 3H, Ar), 6.93-6.90 (m, 1H, Ar), 5.89 (brs, 1H, NH), 3.26-3.19 (m, 2H, CH_2), 2.07 (s, 3H, CH_3), 1.07 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 156.1, 148.2, 140.8, 136.4, 131.7, 131.5, 129.8, 127.2, 127.0, 124.4, 122.1, 121.6, 117.9, 35.0, 16.3, 15.1; MS (APSI+) *m/z* found 335.1; $C_{16}H_{19}N_2O_4S$ (M^+ + H) requires 335.1.

[00143] **2-Ethylphenyl 3-(3-ethylureido)benzenesulfonate (41).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride/ethyl acetate (92:8) to methylene chloride/ethyl acetate (88:12)). Yield: 78%; White solid; mp: 76-78 °C; IR δ: 3297 (NH), 1655 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.27 (s, 1H, NH), 7.99 (s, 1H, Ar), 7.66-7.63 (m, 1H, Ar), 7.39-7.32 (m, 2H, Ar), 7.17-7.01 (m, 3H, Ar), 6.94-9.91 (m, 1H, Ar), 5.88 (brs, 1H, NH), 3.25-3.19 (m, 2H, CH_2), 2.51 (q, 2H, J = 7.5, CH_2), 1.14-1.04 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 156.0, 147.8, 140.8, 137.2, 136.5, 129.9, 129.8, 127.3, 126.9, 124.3, 121.9, 121.5, 117.9, 35.0, 22.8, 15.1, 14.0; MS (APSI+) *m/z* found 349.1; $C_{17}H_{21}N_2O_4S$ (M^+ + H) requires 349.1.

[00144] **2-Propylphenyl 3-(3-ethylureido)benzenesulfonate (42).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride/ethyl acetate (92:8) to methylene chloride/ethyl acetate (88:12)). Yield: 99%; Sticky solid; IR δ: 3343 (NH), 1655 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.28 (s, 1H, NH), 8.03 (s, 1H, Ar), 7.62-7.60 (m, 1H, Ar), 7.41-7.29 (m, 2H, Ar), 7.16-7.02 (m, 3H, Ar), 6.95-6.92 (m, 1H, Ar), 5.90 (brs, 1H, NH), 3.25-3.18 (m, 2H, CH_2), 2.44 (t, 2H, J = 7.7 Hz, CH_2), 1.52-1.44 (m, 2H, CH_2), 1.06 (t, 3H, J = 7.1 Hz, CH_3), 0.82 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ

156.1, 148.0, 140.8, 136.6, 135.8, 130.7, 129.8, 127.1, 127.0, 124.4, 121.9, 121.5, 117.9, 35.0, 31.8, 23.0, 15.1, 13.8; MS (APSI+) *m/z* found 363.1; $C_{18}H_{23}N_2O_4S$ (M^+ + H) requires 363.1.

[00145] **4-(*tert*-Butyldimethylsilyloxy)phenyl 3-(3-ethylureido)benzenesulfonate (43).** Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (75:25)). Yield: 48%; Yellowish oil; IR δ: 3370 (NH), 1659 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.98 (s, 1H, NH), 7.83 (s, 1H, Ar), 7.79-7.76 (m, 1H, Ar), 7.30-7.26 (m, 2H, Ar), 6.82-6.79 (m, 2H, Ar), 6.68-6.65 (m, 2H, Ar), 5.60 (brs, 1H, NH), 3.29-3.22 (m, 2H, CH_2), 1.13-1.08 (m, 2H, CH_2), 0.93 (s, 9H, 3xCH_3), 0.13 (s, 6H, 2xCH_3); ^{13}C NMR (DMSO-d_6): δ 155.8, 154.6, 143.4, 140.7, 135.4, 129.7, 124.5, 123.2, 122.0, 120.7, 117.9, 35.1, 25.6, 18.1, 15.2, -4.5.

[00146] **4-Hydroxyphenyl 3-(3-ethylureido)benzenesulfonate (44).** Method E. The crude product was purified by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol (90:10)). Yield: 50%; White sticky solid; IR δ: 1649 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.67 (s, 1H, OH), 8.95 (s, 1H, NH), 8.09 (s, 1H, Ar), 7.66-7.26 (m, 3H, Ar), 6.82-6.68 (m, 4H, Ar), 6.27 (t, 1H, J = 5.1 Hz, NH), 3.14-3.09 (m, 2H, CH_2), 1.06 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 156.3, 154.8, 141.8, 141.3, 134.9, 129.9, 123.0, 123.0, 120.2, 116.2, 116.0, 34.1, 15.3; MS (APSI+) *m/z* found 337.1; $C_{15}H_{17}N_2O_5S$ (M^+ + H) requires 337.1.

[00147] **2-Tolyl 4-(3-ethylureido)benzenesulfonate (45).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate 90:10)). Yield: 70%; White solid; mp: 137-138 °C; IR δ: 3363 (NH), 1663 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.08 (s, 1H, NH), 7.66-7.63 (m, 2H, Ar), 7.55-7.52 (m, 2H, Ar), 7.11-7.06 (m, 3H, Ar), 6.96-6.93 (m, 1H, Ar), 5.69 (brs, 1H, NH), 3.27-3.19 (m, 2H, CH_2), 2.05 (s, 3H, CH_3), 1.09 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.5, 148.2, 145.8, 131.7, 131.5, 129.7, 127.4, 127.2, 126.9, 122.2, 117.8, 34.9, 16.3, 15.2; MS (APSI+) *m/z* found 335.1; $C_{16}H_{19}N_2O_4S$ (M^+ + H) requires 335.1.

[00148] **2-Ethylphenyl 4-(3-ethylureido)benzenesulfonate (46).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (65:35) to hexanes/ethyl acetate (55:45)). Yield: 83%; Orange solid; mp: 123 °C; IR δ: 3389 (NH), 1671 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.19 (s, 1H, NH), 7.72-769 (m, 2H, Ar), 7.56-7.52 (m, 2H, Ar), 7.18-7.07 (m, 3H, Ar), 6.99-6.96 (m, 1H, Ar), 5.81 (brs, 1H, NH), 3.28-3.22 (m, 2H, CH_2), 2.49 (q, 2H, J = 7.5 Hz, CH_2), 1.12-1.05 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 155.5, 147.7, 145.6, 137.2, 130.0, 129.7, 127.4, 126.9, 121.9, 117.9, 102.6, 35.0, 22.8, 15.2, 14.0; MS (APSI+) *m/z* found 349.1; $C_{17}H_{21}N_2O_4S$ (M^+ + H) requires 349.1.

[00149] **2-Propylphenyl 4-(3-ethylureido)benzenesulfonate (47).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (65:35) to hexanes/ethyl acetate (55:45)). Yield: 73%; Yellowish solid; mp: 108 °C; IR δ: 3383 (NH), 1666 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.08 (s, 1H, NH), 7.72-7.69 (m, 2H, Ar), 7.55-7.52 (m, 2H, Ar), 7.16-7.06 (m, 3H, Ar), 6.99-6.97 (m, 1H, Ar), 5.67 (brs, 1H, NH), 3.26-3.22 (m, 2H, CH_2), 2.42 (t, 2H, J = 7.7 Hz, CH_2), 1.55-1.43 (m, 2H, CH_2), 1.10 (t, 3H, J = 7.2 Hz, CH_3), 0.83 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 155.3, 147.9, 145.5, 135.7, 130.7, 129.7, 127.8, 127.2, 127.0, 122.0, 117.8, 35.1, 31.8, 23.0, 15.2, 13.9; MS (APSI+) *m/z* found 363.1; $C_{18}H_{23}N_2O_4S$ (M^+ + H) requires 363.1.

[00150] **4-(*tert*-Butyldimethylsilyloxy)phenyl 4-(3-ethylureido)benzenesulfonate (48).** Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (75:25)). Yield: 53%; Yellowish oil; IR δ: 3357 (NH), 1665 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93 (s, 1H, NH), 7.66-7.60 (m, 2H, Ar), 7.49-7.42 (m, 2H, Ar), 7.86-7.78 (m, 2H, Ar), 6.72-6.66 (m, 2H, Ar), 5.50 (brs, 1H, NH), 3.28-3.20 (m, 2H, CH_2), 1.15-1.05 (m, 3H, CH_3), 0.92 (s, 9H, 3xCH_3), 0.14 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 155.1, 154.6, 145.5, 143.4, 131.0, 129.9, 123.3, 120.7, 117.7, 35.7, 25.6, 18.1, 15.2, -4.5.

[00151] **4-Hydroxyphenyl 4-(3-ethylureido)benzenesulfonate (49).** Method E. The crude product was purified by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol (90:10)). Yield: 66%; White oil; IR δ: 3450-3075 (OH), 1666 (C=O), 1357 (OH) cm^{-1}; ^1H NMR (acetone-d_6): δ 8.48 (s, 1H, NH), 7.73-7.63 (m, 4H, Ar), 6.84-6.75 (m, 4H, Ar), 6.02 (brs, 1H, NH), 3.27-3.21 (m, 2H, CH_2), 1.12 (t, 3H, J = 7.1 Hz, CH_3), 3.08 (brs, 1H, OH); ^{13}C NMR (acetone-d_6): δ 156.9, 155.2, 147.3, 143.2, 130.5, 127.2, 124.1, 117.9, 116.5, 35.2, 15.5; MS (APSI+) *m/z* found 337.1; $C_{15}H_{17}N_2O_5S$ (M^+ + H) requires 337.1.

[00152] **3-(3-Ethylureido)-*N*-2-tolylbenzenesulfonamide (50).** Method D. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (50:50) to ethyl acetate) and was recrystallized with methanol and filtered. Yield: 15%; White solid; mp: 199-200 °C; IR δ: 3333 (NH), 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 9.55 (s, 1H, NH), 8.81 (s, 1H, NH), 7.90 (s, 1H, Ar), 7.59-7.57 (m, 1H, Ar), 7.40-7.35 (m, 1H, Ar), 7.16-7.08 (m, 4H, Ar), 7.00-6.97 (m, 1H, Ar), 6.17 (brs, 1H, NH), 3.16-3.07 (m, 2H, CH_2), 2.03 (s, 3H, CH_3), 1.06 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.9, 141.3, 141.2, 135.0, 134.2, 130.7, 129.4, 126.4, 126.4, 126.3, 121.1, 118.8, 115.2, 34.0, 17.7, 15.4; MS (APSI+) *m/z* found 334.2; $C_{16}H_{20}N_3O_3S$ (M^+ + H) requires 334.1.

[00153] ***N*-(2-Ethylphenyl)-3-(3-ethylureido)benzenesulfonamide (51).** Method A in dry DCM. The crude product was purified by flash chromatography (silica gel,

hexanes/ethyl acetate (40:60) to hexanes/ethyl acetate (80:20)) and was recrystallized with methanol and filtered. Yield: 4%; Yellowish solid; mp: 229-230 °C; IR δ: 3312 (NH), 1643 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.97 (s, 1H, NH), 7.96 (s, 1H, NH), 7.78-7.76 (m, 1H, Ar), 7.53-7.24 (m, 6H, Ar), 6.97-6.95 (m, 1H, Ar), 6.23 (brs, 1H, NH), 3.18-3.11 (m, 2H, CH_2), 2.28-2.24 (m, 2H, CH_2), 1.22-0.95 (m, 6H, 2xCH_3); ^{13}C NMR (DMSO-d_6): δ 154.8, 145.7, 141.6, 139.0, 132.1, 131.6, 130.6, 129.7, 129.2, 126.5, 123.0, 120.2, 116.7, 34.1, 22.8, 15.4, 13.8; MS (APSI-) *m/z* found 346.0; $C_{17}H_{20}N_3O_3S$ (M^- - H) requires 346.1.

[00154] 3-(3-Ethylureido)-*N*-(2-propylphenyl)benzenesulfonamide (52). Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (75:25)) and was recrystallized with methanol and filtered. Yield: 11%; Yellowish solid; mp: 147 °C; IR δ: 3288 (NH), 1649 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.54 (s, 1H, NH), 8.81 (s, 1H, NH), 7.93 (s, 1H, Ar), 7.60-7.57 (m, 1H, Ar), 7.41-6.91 (m, 6H, Ar), 3.17-3.10 (m, 2H, CH_2), 2.47 (m, 2H, J = 7.8 Hz, CH_2), 1.41-1.32 (m, 2H, CH_2), 1.06 (t, 3H, J = 7.1 Hz, CH_3), 0.82 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.8, 141.3, 141.2, 138.8, 134.4, 129.6, 129.3, 126.6, 126.5, 126.1, 121.0, 118.8, 115.3, 34.0, 32.3, 22.9, 15.4, 14.0; MS (APSI+) *m/z* found 362.2; $C_{18}H_{24}N_3O_3S$ (M^+ + H) requires 362.2.

[00155] 4-(3-Ethylureido)-*N*-2-tolylbenzenesulfonamide (53). Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (75:25)) and was recrystallized with methanol and filtered. Yield: 15%; White solid; mp: 246-247 °C; IR δ: 3051 (NH), 1679 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6): 7.46-7.22 (m, 4H, Ar), 7.12-6.91 (m, 4H, Ar), 3.15 (q, 2H, J = 7.2 Hz, CH_2), 1.92 (s, 3H, CH_3), 1.04 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.7, 144.6, 135.1, 134.0, 131.9, 130.7, 127.8, 126.4, 126.3, 126.2, 116.8, 34.0, 17.7, 15.3; MS (APSI-) *m/z* found 331.9; $C_{16}H_{18}N_3O_3S$ (M^- - H) requires 332.1.

[00156] *N*-(2-Ethylphenyl)-4-(3-ethylureido)benzenesulfonamide (54). Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate (75:25)) and was recrystallized with methanol and filtered. Yield: 53%; White solid; mp: 223-224 °C; IR δ: 3107 (NH), 1683 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.35 (s, 1H, NH), 8.91 (s, 1H, NH), 7.55-7.49 (m, 4H, Ar), 7.21-7.05 (m, 4H, Ar), 6.89 (t, 1H, J = 5.4 Hz, NH), 3.17-3.08 (m, 2H, CH_2), 2.55-2.48 (m, 2H, CH_2), 1.22-1.05 (m, 6H, 3xCH_3); ^{13}C NMR (DMSO-d_6): δ 154.5, 144.5, 140.2, 134.4, 131.9, 128.9, 127.9, 126.5, 126.4, 126.1, 116.8, 34.0, 23.1, 15.3, 14.4; MS (APSI+) *m/z* found 346.0; $C_{17}H_{20}N_3O_3S$ (M^+ + H) requires 346.1.

[00157] 4-(3-Ethylureido)-*N*-(2-propylphenyl)benzenesulfonamide (55). Method A in dry DCM. The crude product was purified by flash chromatography (silica gel, methylene

chloride to methylene chloride/ethyl acetate (75:25)) and was recrystallized with methanol and filtered. Yield: 21%; Yellowish solid; mp: 203 °C; IR δ: 3098 (NH), 1678 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 9.02 (s, 1H, NH), 8.77 (s, 1H, NH), 7.51-7.44 (m, 4H, Ar), 7.10-6.88 (m, 4H, Ar), 6.14 (brs, 1H, NH), 3.19-3.11 (m, 2H, CH_2), 2.46 (t, 2H, J = 7.9 Hz, CH_2), 1.45-1.32 (m, 2H, CH_2), 1.08 (t, 3H, J = 7.1 Hz, CH_3), 0.82 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.8, 144.4, 138.5, 134.5, 131.9, 129.3, 127.7, 126.0, 125.9, 125.7, 116.5, 34.0, 33.3, 22.9, 15.2, 13.8; MS (APSI-) *m/z* found 360.0; $C_{18}H_{22}N_3O_3S$ (M^- - H) requires 360.1.

[00158] 2-Tolyl 4-nitrobenzenesulfonate (56). Method F. Yield: 98%; Yellowish solid; mp: 84-85 °C; IR δ: 1533 (NO_2), 1191 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.35 (d, 2H, J = 8.8 Hz, Ar), 8.06 (d, 2H, J = 8.8 Hz, Ar), 7.19-7.10 (m, 3H, Ar), 6.96-6.93 (m, 1H, Ar), 2.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 151.0, 148.0, 141.7, 132.0, 131.4, 129.8, 127.6, 127.3, 124.5, 121.9, 16.3.

[00159] 3-Tolyl 4-nitrobenzenesulfonate (57). Method F. Yield: 97%; Yellowish solid; mp: 94-95 °C; IR δ: 1533 (NO_2), 1351 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.35 (d, 2H, J = 8.8 Hz, Ar), 8.02 (d, 2H, J = 8.8 Hz, Ar), 7.19-7.06 (m, 2H, Ar), 6.86 (s, 1H, Ar), 6.73-6.70 (m, 1H, Ar), 2.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 151.0, 149.2, 141.1, 140.6, 129.9, 129.6, 128.5, 124.3, 122.7, 118.8, 21.2.

[00160] 4-Tolyl 4-nitrobenzenesulfonate (58). Method F. Yield: 96%. White solid; mp: 94-95 °C; IR v: 1520 (NO_2), 1199 (S=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.35 (d, 2H, J = 8.7 Hz, Ar), 8.01 (d, 2H, J = 8.7 Hz, Ar), 7.09 (d, 2H, J = 8.2 Hz, Ar), 6.85 (d, 2H, J = 8.2 Hz, Ar), 2.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 151.0, 147.1, 141.0, 137.8, 130.5, 129.9, 124.3, 121.8, 20.8.

[00161] 4-Methoxyphenyl 4-nitrobenzenesulfonate (59). Method F. Yield: 89%. White solid; mp: 150-151 °C; IR v: 1540 (NO_2), 1378 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.47 (d, 2H, J = 8.7 Hz, Ar), 8.14 (d, 2H, J = 8.7 Hz, Ar), 7.02-6.91 (m, 4H, Ar), 3.74 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 158.3, 151.1, 142.1, 139.6, 130.1, 125.0, 123.2, 115.1, 55.6.

[00162] 4-(Dimethylamino)phenyl 4-nitrobenzenesulfonate (60). Method F. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (90:10) to hexanes/ethyl acetate (70:30)). Yield: 41%; Orange solid; mp: 129-130 °C; IR δ: 1513 (NO_2), 1187 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.47-8.44 (m, 2H, Ar), 8.14-8.11 (m, 2H, Ar), 6.86-6.83 (m, 2H, Ar), 6.64-6.61 (m, 2H, Ar), 2.87 (s, 6H, 2xCH_3); ^{13}C NMR (DMSO-d_6): δ 149.4, 139.0, 130.1, 124.9, 122.4, 112.5, 40.1.

[00163] 4-(*tert*-Butyldimethylsilyloxy)phenyl 4-nitrobenzenesulfonate (61). Method F. Yield: 96%; Yellowish solid; mp: 94-95 °C; IR δ: 1495 (NO_2), 1377 (NO_2) cm^{-1}; ^1H

NMR ($CDCl_3$): δ 8.33 (d, 2H, J = 8.7 Hz, Ar), 7.98 (d, 2H, J = 8.7 Hz, Ar), 6.84-6.70 (m, 4H, Ar), 0.92 (s, 9H, 3xCH_3), 0.15 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 154.9, 151.0, 143.1, 140.9, 130.0, 124.3, 123.1, 121.0, 25.6, 18.1, -4.5.

[00164] **2-Tolyl 3-nitrobenzenesulfonate (62).** Method F. Yield: 91%; White solid; mp: 63-64 °C; IR δ: 1533 (NO_2), 1351 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.70 (s, 1H, Ar), 8.53 (d, 1H, J = 8.0 Hz, Ar), 8.20 (d, 1H, J = 7.7 Hz, Ar), 7.83-7.77 (m, 1H, Ar), 7.21-7.14 (m, 3H, Ar), 6.98 (d, 1H, J = 7.3 Hz, Ar), 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.2, 148.0, 138.1, 133.8, 132.0, 131.3, 130.9, 128.7, 127.7, 127.3, 123.5, 122.0, 16.3.

[00165] **2-Ethylphenyl 3-nitrobenzenesulfonate (63).** Method F. Yield: 78%; Colorless oil; IR δ: 1533 (NO_2), 1381 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.75 (s, 1H, Ar), 8.54 (d, 1H, J = 7.7 Hz, Ar), 8.23 (d, 1H, J = 7.7 Hz, Ar) 8.21-7.80 (m, 1H, Ar), 7.24-7.13 (m, 3H, Ar), 7.02-7.00 (m, 1H, Ar), 2.52 (q, 2H, J = 7.6 Hz, CH_2), 1.13 (t, 3H, J = 7.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.3, 147.5, 138.3, 137.0, 133.7, 130.7,130.2, 128.6, 127.8, 127.2, 123.6, 121.8, 22.8, 14.04.

[00166] **2-Propylphenyl 3-nitrobenzenesulfonate (64).** Method F. Yield: 80%; Yellowish oil; IR δ: 1533 (NO_2), 1381 (NO_2) cm^{-1};^1H NMR ($CDCl_3$): δ 8.75 (s, 1H, Ar), 8.55 (d, 1H, J = 7.9 Hz, Ar), 8.23 (d, 1H, J = 7.9 Hz, Ar), 7.82-7.77 (m, 1H, Ar), 7.23-7.15 (m, 3H, Ar), 7.05-7.03 (m, 1H, Ar), 2.44 (t, 2H, J = 7.8 Hz, CH_2), 1.58-1.47 (m, 2H, CH_2), 0.87 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.3, 147.7, 138.4, 135.5, 133.7, 130.9, 130.7, 128.6, 127.6, 127.3, 123.6, 121.8, 31.9, 23.0, 13.9.

[00167] **4-(*tert*-Butyldimethylsilyloxy)phenyl 3-nitrobenzenesulfonate (65).** Method F. Yield: 95%; Yellowish oil; IR δ: 1542 (NO_2), 1377 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.65 (s, 1H, Ar), 8.52-8.50 (m, 1H, Ar), 8.14-8.12 (m, 1H, Ar), 7.78-7.73 (m, 1H, Ar), 6.86-6.83 (m, 2H, Ar), 6.75-6.72 (m, 2H, Ar), 0.95 (s, 9H, 3xCH_3), 0.17 (s, 6H, 2xCH_2); ^{13}C NMR ($CDCl_3$): δ 155.0, 148.2, 143.0, 137.4, 133.9, 130.6, 128.6, 123.8, 123.1, 121.0, 25.6, 18.2, -4.5.

[00168] **2-Ethylphenyl 4-nitrobenzenesulfonate (66).** Method F. Yield: 90%; White solid; mp: 82 °C; IR δ: 1530 (NO_2), 1376 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.39 (d, 2H, J = 8.7 Hz, Ar), 8.10 (d, 2H, J = 8.7 Hz, Ar), 7.25-7.12 (m, 3H, Ar), 7.00-6.97 (m, 1H, Ar), 2.50 (q, 2H, J = 7.5 Hz, CH_2), 1.12 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 150.9, 147.6, 141.8, 137.0, 130.2, 129.7, 127.8, 127.2, 124.4, 121.7, 22.9, 14.04.

[00169] **2-Propylphenyl 4-nitrobenzenesulfonate (67).** Method F. Yield: 85%; Yellowish solid; mp: 58 °C; IR δ: 1525 (NO_2), 1375 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.40 (d, 2H, J = 8.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar), 7.23-7.13 (m, 3H, Ar), 7.02-6.99 (m, 1H, Ar), 2.42 (t, 2H, J = 7.7 Hz, CH_2), 1.59-1.46 (m, 2H, CH_2), 0.87 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR

($CDCl_3$): δ 150.9, 147.8, 141.9, 135.6, 131.0, 129.7, 127.6, 127.2, 124.4, 121.8, 31.9, 23.0, 13.9.

[00170] **3-Nitro-*N*-2-tolylbenzenesulfonamide (68).** Method G. Yield: 94%; White solid; mp: 156 °C; IR δ: 1529 (NO_2), 1354 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.03 (s, 1H, NH), 8.51-8.44 (m, 2H, Ar), 8.09-8.06 (m, 1H, Ar), 7.91-7.86 (m, 1H, Ar), 7.20-6.91 (m, 4H, Ar), 2.06 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 147.8, 142.1, 134.7, 134.2, 132.6, 131.4, 131.0, 127.4, 127.0, 126.8, 126.6, 121.4, 17.7.

[00171] ***N*-(2-Ethylphenyl)-3-nitrobenzenesulfonamide (69).** Method F. The crude product was purified by recrystallized with methanol and filtered. Yield: 56%; White solid; mp: 159-160 °C; IR δ: 1532 (NO_2), 1352 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.74 (s, 1H, Ar), 8.59-8.56 (m, 1H, Ar), 8.37-8.34 (m, 1H, Ar), 7.87-7.82 (m, 1H, Ar), 7.53-7.42 (m, 2H, Ar), 7.24-7.18 (m, 1H, Ar), 6.87-6.85 (m, 1H, Ar), 2.28 (q, 2H, J = 7.5 Hz, CH_2), 1.09 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.2, 145.6, 140.9, 134.5, 131.6, 131.5, 131.4, 130.6, 130.1, 128.8, 126.9, 124.3, 23.6, 14.0.

[00172] **3-Nitro-*N*-(2-propylphenyl)benzenesulfonamide (70).** Method G. Yield: 55%; Yellowish solid; mp: 64-65 °C; IR δ: 1529 (NO_2), 1350 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.60-8.55 (m, 1H, Ar), 8.40-8.34 (m, 1H, Ar), 8.05-8.02 (m, 1H, Ar), 7.69-7.63 (m, 1H, Ar), 7.16-7.07 (m, 4H, Ar), 2.34 (t, 2H, J = 7.7 Hz, CH_2), 1.43-1.33 (m, 2H, CH_2), 0.81 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.2, 141.7, 136.4, 134.6, 132.8, 130.4, 130.2, 127.4, 127.2, 127.1, 124.9, 122.5, 32.7, 23.2, 13.8.

[00173] **4-Nitro-*N*-2-tolylbenzenesulfonamide (71).** Method G. Yield: 86%; Orange solid; mp: 158°C; IR δ: 1528 (NO_2), 1343 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$/MeOD): δ 7.93-7.90 (m, 2H, Ar), 7.52-7.49 (m, 2H, Ar), 6.74-6.62 (m, 4H, Ar), 1.65 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 149.7, 146.1, 134.6, 134.1, 131.0, 128.2, 127.0, 126.8, 126.6, 124.6, 17.7.

[00174] ***N*-(2-Ethylphenyl)-4-nitrobenzenesulfonamide (72).** Method G. Yield: 84%; Orange solid; mp: 149°C; IR δ: 1531 (NO_2), 1344 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.19-8.16 (m, 2H, Ar), 7.83-7.77 (m, 2H, Ar), 7.39-6.77 (m, 4H, Ar), 2.34 (q, 2H, J = 7.5 Hz, CH_2), 0.92 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 149.7, 146.2, 140.9, 133.4, 129.2, 128.3, 127.3, 126.9, 126.4, 124.6, 23.22, 14.5.

[00175] **4-Nitro-*N*-(2-propylphenyl)benzenesulfonamide (73).** Method G. Yield: 91%; White solid; mp: 120-121 °C; IR δ: 1530 (NO_2), 1343 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.25-9.22 (m, 2H, Ar), 8.78-8.75 (m, 2H, Ar), 8,26-7.64 (m, 4H, Ar), 3.27 (t, 2H, J = 7.9 Hz, CH_2), 2.21-2.13 (m, 2H, CH_2), 1.61 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 151.0, 146.2, 133.6, 130.2, 129.9, 128.3, 127.2, 126.5, 125.0, 124.6, 32.3, 23.0, 13.9.

[00176] **2-Tolyl 4-aminobenzenesulfonate (74).** Method H. Yield: 88%; Yellowish solid; mp: 66-67 °C; IR δ: 3387 (NH_2), 1592 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55-7.53 (m, 2H, Ar), 7.13-7.10 (m, 3H, Ar), 7.04-7.00 (m, 1H, Ar), 6.62-6.60 (m, 2H, Ar), 4.41 (brs, 2H, NH_2), 2.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 153.1, 148.3, 131.5, 131.4, 130.3, 126.7, 122.3, 121.4, 113.5, 16.4.

[00177] **3-Tolyl 4-aminobenzenesulfonate (75).** Method H. Yield: 92%; White solid; mp: 67-68 °C; IR δ: 3389 (NH_2), 1592 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$/MeOD): δ 7.45-7.42 (m, 2H, Ar), 7.05-7.00 (m, 1H, Ar), 6.94-6.91 (m, 1H, Ar), 6.75 (s, 1H, Ar), 6.66-6.58 (m, 3H, Ar), 4.37 (brs, 2H, NH_2), 2.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$/MeOD): δ 152.2, 149.6, 139.9, 130.5, 129.2, 127.8, 123.0, 121.8, 119.2, 114.1, 21.0.

[00178] **4-Tolyl 4-aminobenzenesulfonate (76).** Method H. Yield: 92%. Orange solid; mp: 130-132 °C; IR v: 3394 (NH_2), 1596 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52 (d, 2H, J = 8.5 Hz, Ar), 7.05 (d, 2H, J = 8.5 Hz, Ar), 6.85 (d, 2H, J = 8.5 Hz, Ar), 6.61 (d, 2H, J = 8.5 Hz, Ar), 4.36 (brs, 2H, NH_2), 2.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 152.1, 147.6, 136.8, 130.7, 130.0, 122.5, 122.2, 113.8, 20.9.

[00179] **4-Methoxyphenyl 4-aminobenzenesulfonate (77).** Method I. Yield: 97%. Orange solid; mp: 161-162 °C; IR v: 1594 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.38 (d, 2H, J = 8.8 Hz, Ar), 6.89 (s, 4H, Ar), 6.62 (d, 2H, J = 8.8 Hz, Ar), 6.37 (brs, 2H, NH_2), 3.72 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 157.7, 154.5, 142.8, 130.4, 123.3, 117.9, 114.6, 112.8, 55.5.

[00180] **4-(Dimethylamino)phenyl 4-aminobenzenesulfonate (78).** Method H. Yield: 98%; White solid; mp: 192-194 °C; IR δ: 1593 (NH_2) cm^{-1}; ^1H NMR (acetone-d_6): δ 7.46-7.43 (m, 2H, Ar), 6.82-6.73 (m, 4H, Ar), 6.63-6.60 (m, 2H, Ar), 5.76 (brs, 2H, NH_2), 2.90 (s, 6H, 2xCH_3); ^{13}C NMR (acetone-d_6): δ 154.8, 150.1, 141.3, 131.3, 123.6, 121.7, 113.8, 113.1, 40.5.

[00181] **4-(*tert*-Butyldimethylsilyloxy)phenyl 4-aminobenzenesulfonate (79).** Method H. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate (90:10) to hexanes/ethyl acetate (70:30)). Yield: 66%; Orange solid; mp: 91-93 °C; IR δ: 1644 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50 (d, 2H, J = 8.7 Hz, Ar), 6.84-6.81 (m, 2H, Ar), 6.71-6.68 (m, 2H, Ar), 6.60 (d, 2H, J = 8.7 Hz, Ar), 4.33 (brs, 2H, NH_2), 0.95 (s, 9H, 3xCH_3), 0.19 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 154.3, 152.0, 143.8, 130.8, 123.5, 122.4, 120.6, 113.7, 25.6, 18.2, -4.5.

[00182] **2-Tolyl 3-aminobenzenesulfonate (80).** Method H. Yield: 56%; Yellow solid; mp: 86 °C; IR δ: 3463 (NH_2), 3364 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27-6.89 (m, 8H, Ar), 4.52 (brs, 2H, NH_2), 2.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.4, 145.9, 137.0, 131.7, 131.6, 130.2, 127.0, 126.9, 122.3, 121.0, 118.8, 114.5, 16.3.

[00183] **2-Ethylphenyl-3-aminobenzenesulfonate (81).** Method H. Yield: 46%; Orange solid; mp: 52 °C; IR δ: 3478 (NH_2), 3385 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.31-6.88 (m, 8H, Ar), 4.73 (brs, 2H, NH_2), 2.53 (q, 2H, J = 7.5 Hz, CH_2), 1.11 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 147.9, 145.2, 137.3, 137.1, 130.2, 129.9, 127.2, 126.9, 122.1, 121.4, 119.2, 114.9, 22.8, 14.0.

[00184] **2-Propylphenyl-3-aminobenzenesulfonate (82).** Method H. Yield: 8.7%; Orange oil; IR δ: 3489 (NH_2), 3397 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26-7.00 (m, 8H, Ar), 4.87 (brs, 2H, NH_2), 2.45 (t, 2H, J = 7.8 Hz, CH_2), 1.56-1.46 (m, 2H, CH_2), 0.87 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.1, 144.8, 137.3, 135.8, 130.6, 130.3, 127.0, 126.9, 122.1, 121.6, 119.5, 115.2, 31.8, 23.0, 13.9.

[00185] **4-(*tert*-Butyldimethylsilyloxy)phenyl-3-aminobenzenesulfonate (83).** Method H. Yield: 73%; Yellow solid; mp: 101 °C; IR δ: 3495 (NH_2), 3391 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.29 (s, 1H, Ar), 7.98-7.96 (m, 1H, Ar), 7.62-7.60 (m, 1H, Ar), 7.54-7.46 (m, 1H, Ar), 6.87-6.80 (m, 2H, Ar), 6.74-6.68 (m, 2H, Ar), 4.42 (brs, 2H, NH_2), 0.95 (s, 9H, 3xCH_3), 0.16 (s, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 154.5, 146.1, 143.6, 136.1, 130.0, 123.3, 120.8, 120.7, 118.9, 114.6, 25.6, 18.2, -4.5.

[00186] **2-Ethylphenyl-4-aminobenzenesulfonate (84).** Method H. Yield: 95%; Orange solid; mp: 71 °C; IR δ: 3467 (NH_2), 3375 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48-7.45 (m, 2H, Ar), 7.30-7.20 (m, 3H, Ar), 7.01-6.98 (m, 1H, Ar), 6.68-6.65 (m, 2H, Ar), 6.41 (brs, 2H, NH_2), 2.46 (q, 2H, J = 7.5 Hz, CH_2), 1.05 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 154.7, 147.6, 136.8, 130.3, 129.8, 127.0, 121.9, 118.7, 112.8, 22.2, 14.1.

[00187] **2-Propylphenyl-4-aminobenzenesulfonate (85).** Method H. Yield: 93%; White solid; mp: 93-94 °C; IR δ: 3473 (NH_2), 3378 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.59 (d, 2H, J = 8.4 Hz, Ar), 7.18-7.03 (m, 4H, Ar), 6.66 (d, 2H, J = 8.4 Hz, Ar), 4.51 (brs, 2H, NH_2), 2.44 (t, 2H, J = 7.8 Hz, CH_2), 1.55-1.48 (m, 2H, CH_2), 0.87 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 151.7, 148.2, 135.9, 130.6, 130.5, 126.8, 123.7, 122.3, 122.3, 114.1, 31.8, 23.0, 14.0.

[00188] **3-Amino-*N*-2-tolylbenzenesulfonamide (86).** Method H. Yield: 41%; Brown solid; mp: 102-103 °C; IR δ: 3404 (NH_2), 3341 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.40 (s, 1H, NH), 7.26-6.76 (m, 8H, Ar), 5.64 (brs, 2H, NH_2), 2.04 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 148.8, 141.3, 135.2, 134.1, 130.6, 129.5, 126.3, 126.2, 126.2, 117.6, 113.7, 111.4, 17.7.

[00189] **3-Amino-*N*-(2-ethylphenyl)benzenesulfonamide (87).** Method H. Yield: 52%; Yellow solid; mp: 145-147 °C; IR δ: 3453 (NH_2), 3371 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 8.06 (s, 1H, NH), 7.40-6.83 (m, 8H, Ar), 5.27 (brs, 2H, NH_2) 2.31 (q, 2H,

J = 7.4 Hz, CH_2), 1.01 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 147.8, 146.0, 139.2, 132.4, 131.5, 130.0, 129.3, 128.7, 125.8, 119.8, 116.0, 113.6, 22.7, 13.7.

[00190] **3-Amino-*N*-(2-propylphenyl)benzenesulfonamide (88).** Method H. Yield: 91%; Yellow solid; mp: 144-145 °C; IR δ: 3400 (NH_2), 3254 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.37 (s, 1H, NH), 7.27-6.72 (m, 8H, Ar), 4.81 (brs, 2H, NH_2), 2.24-2.19 (m, 2H, CH_2), 1.22-1.10 (m, 2H, CH_2), 0.61-0.56 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 147.2, 145.3, 140.0, 132.8, 132.0, 130.3, 129.7, 129.5, 126.1, 120.0, 118.3, 114.4, 32.6, 22.9, 14.4.

[00191] **4-Amino-*N*-2-tolylbenzenesulfonamide (89).** Method H. Yield: 89%; Orange solid; mp: 148-149 °C; IR δ: 3478 (NH_2), 3380 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.04 (s, 1H, NH), 7.28 (d, 2H, J = 8.6 Hz, Ar), 7.13-7.00 (m, 4H, Ar), 6.55 (d, 2H, J = 8.6 Hz, Ar), 5.95 (brs, 2H, NH_2), 2.03 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 152.7, 135.6, 133.7, 130.6, 128.6, 126.2, 126.1, 125.9, 125.6, 112.6, 17.7.

[00192] **4-Amino-*N*-(2-ethylphenyl)benzenesulfonamide (90).** Method H. Yield: 57%; Orange solid; mp: 171 °C; IR δ: 3479 (NH_2), 3380 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.04 (s, 1H, NH), 7.31 (d, 2H, J = 8.5 Hz, Ar), 7.19-6.93 (m, 4H, Ar), 6.57 (d, 2H, J = 8.5 Hz, Ar), 5.95 (brs, 2H, NH_2), 2,54 (q, 2H, J = 7.5 Hz, CH_2), 1.01 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 152.7, 139.9, 134.9, 128.8, 128.7, 126.2, 126.0, 125.7, 112.6, 112.3, 23.1, 14.4.

[00193] **4-Amino-*N*-(2-propylphenyl)benzenesulfonamide (91).** Method H. Yield: 77%; Orange solid; mp: 153-154 °C; IR δ: 3475 (NH_2), 3379 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$/MeOD): δ 7.05-6.66 (m, 8H, Ar), 6.27 (brs, 2H, NH_2), 2.08 (t, 2H, J = 7.8 Hz, CH_2), 1.13-1.03 (m, 2H, CH_2), 0.53 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C NMR (DMSO-d_6): δ 154.2, 152.7, 138.3, 135.1, 130.6, 129.5, 128.6, 126.1, 125.9, 125.7, 112.6, 112.3, 32.3, 22.9, 14.0.

[00194] **4-Nitrophenyl 4-methylbenzenesulfonate (92).** Method F. Yield: 99%. mp: 89-90°C; IR v: 1530 (NO_2), 1377 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.15-8.13 (m, 2H, Ar), 7.69 (d, 2H, J = 8.2 Hz, Ar), 7.32 (d, 2H, J = 8.2 Hz, Ar), 7.17-7.14 (m, 2H, Ar), 2.42 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 153.9, 146.3, 146.2, 131.7, 130.1, 128.4, 125.4, 123.2, 21.7.

[00195] **4-Nitrophenyl 4-methoxybenzenesulfonate (93).** Method F. Yield: 84%. mp: 82-83°C; IR v: 1593 (NO_2), 1347 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.12 (d, 2H, J = 9.1 Hz, Ar), 7.70 (d, 2H, J = 9.0 Hz, Ar), 7.14 (d, 2H, J = 9.1 Hz, Ar), 6.95 (d, 2H, J = 9.0 Hz, Ar), 3.83 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 164.6, 154.0, 146.1, 130.7, 125.7, 125.4, 123.3, 114.7, 55.8.

[00196] **4-Aminophenyl 4-methylbenzenesulfonate (94).** Method I. Yield: 87%. mp: 140-141 °C; IR v: 3369 (NH_2), 1505 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.68 (d, 2H, J = 8.2 Hz,

Ar), 7.29 (d, 2H, J = 8.2 Hz, Ar), 6.75-6.71 (m, 2H, Ar), 6.53-6.50 (m, 2H, Ar), 3.65 (s, 2H, NH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 145.3, 141.7, 129.6, 128.6, 123.2, 115.4, 21.7.

[00197] **4-Aminophenyl 4-methoxybenzenesulfonate (95).** Method I. Yield: 99%. mp: 110-112 °C; IR v: 3360 (NH_2), 1504 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.72-7.68 (m, 2H, Ar), 6.96-6.92 (m, 2H, Ar), 6.72-6.70 (m, 2H, Ar), 6.52-6.49 (m, 2H, Ar), 3.86 (s, 3H, CH_3), 3.62 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ: 164.0, 145.4, 141.7, 130.8, 126.8, 123.3, 115.3, 114.2, 55.7.

[00198] **4-[3-(2-Chloroethyl)ureido]phenyl 4-methylbenzenesulfonate (96).** Method A. The crude product was crystallized with methylene chloride and filtered. Yield: 99%. mp: 149-150 °C; IR v: 3356 (NH), 1645 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.80 (s, 1H, NH), 7.71 (d, 2H, J = 8.2 Hz, Ar), 7.47 (d, 2H, J = 8.2 Hz, Ar), 7.37-7.34 (m, 2H, Ar), 6.88-6.85 (m, 2H, Ar), 6.44 (t, 1H, J = 5.7 Hz, NH), 3.65 (t, 2H, J = 6.0 Hz, CH_2), 3.44-3.38 (m, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 154.9, 145.7, 142.9, 139.4, 131.5, 130.2, 128.3, 122.4, 118.5, 44.3, 41.2, 21.2; MS (ESI) m/z: 369.0 $[M+H]^+$.

[00199] **4-[3-(2-Chloroethyl)ureido]phenyl 4-methoxybenzenesulfonate (97).** Method A. The crude product was filtered off and recrystallized with methylene chloride/hexanes 50:50 and filtered. Yield: 97%. mp: 137-138 °C; IR v: 3323 (NH), 1645 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.80 (brs, 1H, NH), 7.76-7.73 (m, 2H, Ar), 7.36 (d, 2H, J = 8.9 Hz, Ar), 7.17 (d, 2H, J = 8.9 Hz, Ar), 6.87-6.84 (m, 2H, Ar), 6.44 (t, 1H, J = 5.8 Hz, NH), 3.88 (s, 3H, CH_3), 3.65 (t, 2H, J = 5.8 Hz, CH_2), 3.44-3.38 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$ + MeOD) δ: 164.1, 155.8, 144.2, 138.4, 130.7, 126.3, 122.7, 119.3, 114.3, 55.6, 44.4, 41.6; MS (ESI) m/z: 384.9 $[M+H]^+$.

[00200] **4-Methoxyphenyl 3-nitrobenzenesulfonate (98).** Method F. Yield: 98%. mp: 84-85 °C; IR v: 1502 (NO_2), 1379 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.64-8.62 (m, 1H, Ar), 8.47-8.46 (m, 1H, Ar), 8.24-8.22 (m, 1H, Ar), 7.98-7.93 (m, 1H, Ar), 7.02-7.00 (m, 2H, Ar), 6.92-6.89 (m, 2H, Ar), 3.72 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 158.3, 148.1, 142.1, 135.6, 134.2, 131.9, 129.5, 123.3, 123.0, 115.0, 55.5.

[00201] **4-(Dimethylamino)phenyl 3-nitrobenzenesulfonate (99).** Method F. The crude product was purified by flash chromatography (silica gel, hexanes to hexanes/ethyl acetate 85:15). Yield: 34%. mp: 142-143 °C; IR v: 1528 (NO_2), 1371 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.66-8.63 (m, 1H, Ar), 8.47-8.46 (m, 1H, Ar), 8.26-8.24 (m, 1H, Ar), 8.00-7.95 (m, 1H, Ar), 6.89-6.86 (m, 2H, Ar), 6.65-6.62 (m, 2H, Ar), 2.88 (s, 6H, 2x CH_3); ^{13}C NMR (DMSO-d_6) δ: 149.5, 148.1, 139.0, 136.0, 134.2, 131.9, 129.4, 122.9, 122.5, 112.5.

[00202] **3,4,5-Trimethoxyphenyl 3-nitrobenzenesulfonate (100).** Method F. The crude product was recrystallised from cold ether. Yield: 64%. mp: 123-125 °C; IR v: 3094

(OMe), 1606 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.66 (d, 1H, J = 8.0 Hz, Ar), 8.53 (s, 1H, Ar), 8.31 (d, 1H, J = 8.0 Hz, Ar), 8.01-7.96 (m, 1H, Ar), 6.42 (s, 2H, Ar), 3.65 (s, 6H, 2x CH_3), 3.63 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 153.3, 148.2, 144.6, 135.5, 134.4, 131.8, 129.6, 123.2, 100.2, 56.2, 45.5.

[00203] **3,4,5-Trimethoxyphenyl 4-nitrobenzenesulfonate (101).** Method F. The crude product was purified by recrystallisation from cold ether. Yield: 86%. mp: 182-185 °C; IR v: 3105 (OMe), 1606 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.48 (d, 2H, J = 7.0 Hz, Ar), 8.21 (d, 2H, J = 7.0 Hz, Ar), 6.40 (s, 2H, Ar), 3.66 (s, 6H, 2x CH_3), 3.64 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 153.3, 151.1, 144.6, 139.5, 130.3, 125.0, 100.0, 56.2, 45.4.

[00204] **4-Methoxyphenyl 3-aminobenzenesulfonate (102)**. Method I. Yield: 99%. IR v: 1501 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.29-7.23 (m, 1H, Ar), 7.01 (s, 1H, Ar), 6.94-6.87 (m, 6H, Ar), 5.77 (s, 2H, NH_2), 3.73 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 157.9, 149.8, 142.6, 134.9, 130.0, 123.1, 119.3, 114.8, 114.5, 112.0, 55.5.

[00205] **4-(Dimethylamino)phenyl 3-aminobenzenesulfonate (103)**. Method I. Yield: 93%. mp: 84-85 °C; IR v: 3384 (NH_2), 1516 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.24-7.18 (m, 1H, Ar), 7.13-7.09 (m, 2H, Ar), 6.87-6.80 (m, 3H, Ar), 6.54-6.51 (m, 2H, Ar), 4.01 (s, 2H, NH_2), 2.88 (s, 6H, 2x CH_3); ^{13}C NMR ($CDCl_3$) δ: 149.4, 147.5, 140.2, 136.2, 129.9, 122.8, 120.1, 117.8, 113.8, 112.5, 40.6.

[00206] **3,4,5-Trimethoxyphenyl 3-aminobenzenesulfonate (104)**. Method I. The crude product was purified by flash chromatography (silica gel, methylene chloride). Yield: 99%. mp: 121-124 °C; IR v: 3472, 3380 (NH_2), 1608 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.33-7.27 (m, 1H, Ar), 7.06-7.05 (m, 1H, Ar), 6.99-6.91 (m, 2H, Ar), 6.28 (s, 2H, Ar), 5.77 (brs, 2H, NH_2), 3.66 (s, 6H, 2x CH_3), 3.63 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 153.0, 149.8, 145.1, 136.3, 134.9, 130.1, 119.3, 114.6, 112.3, 100.0, 60.1, 56.0.

[00207] **3,4,5-Trimethoxyphenyl 4-aminobenzenesulfonate (105)**. Method I. The crude product was purified by flash chromatography (silica gel, methylene chloride). Yield: 56%. mp: 133-134 °C; IR v: 3458 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.46 (d, 2H, J = 8.7 Hz, Ar), 6.66 (d, 2H, J = 8.7 Hz, Ar), 6.40 (s, 2H, NH_2), 6.25 (s, 2H, Ar), 3.66 (s, 6H, 2x CH_3), 3.63 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 154.8, 152.9, 145.3, 130.7, 117.8, 112.7, 112.6, 100.2, 60.1, 56.0.

[00208] **4-Methoxyphenyl 3-[3-(2-chloroethyl)ureido]benzenesulfonate (106)**. Method A. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate 90:10). Yield: 85%; IR v: 3315 (NH), 1662 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.32 (s, 1H, NH), 8.02 (s, 1H, Ar), 7.56-7.53 (m, 1H, Ar), 7.29-7.27 (m, 2H, Ar), 6.85-6.82 (m, 2H, Ar), 6.71-6.68 (m, 2H, Ar), 6.23 (brs, 1H, NH), 3.68 (s, 3H,

CH_3), 3.58 (s, 4H, 2x CH_2); ^{13}C NMR ($CDCl_3$) δ: 158.3, 155.8, 142.8, 140.4, 135.5, 129.7, 124.6, 123.2, 122.2, 118.1, 114.6, 55.6, 44.1, 41.9; MS (ESI) m/z: 385.0 $[M+H]^+$.

[00209] **4-(Dimethylamino)phenyl 3-[3-(2-chloroethyl)ureido]benzenesulfonate (107)**. Method A. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate 80:20). Yield: 76%; mp: 134-135 °C; IR v: 3300 (NH), 1653 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.59 (s, 1H, NH), 8.19-8.17 (m, 1H, Ar), 7.79-7.76 (m, 1H, Ar), 7.49-7.44 (m, 1H, Ar), 7.36-7.33 (m, 1H, Ar), 6.87-6.82 (m, 2H, Ar), 6.63-6.59 (m, 2H, Ar), 6.32 (t, 1H, J = 5.0 Hz, NH), 3.69 (t, 2H, J = 5.0 Hz, CH_2), 3.59-3.53 (m, 2H, CH_2), 2.89 (s, 6H, 2x CH_3); ^{13}C NMR (acetone-d_6) δ: 155.6, 150.3, 142.3, 140.9, 137.0, 130.3, 123.9, 123.4, 121.9, 118.0, 113.2, 44.6, 42.5, 40.5; MS (ESI) m/z: 398.0 $[M+H]^+$.

[00210] **3,4,5-Trimethoxyphenyl 3-[3-(2-chloroethyl)ureido]benzenesulfonate (108)**. Method A. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate 75:25). Yield: 38%. IR v: 1604 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.54 (brs, 1H, NH), 8.28 (s, 1H, Ar), 7.73 (d, 1H, J = 8.0 Hz, Ar), 7.55-7.50 (m, 1H, Ar), 7.43 (d, 1H, J = 8.0 Hz, Ar), 6.34-6.27 (m, 3H, Ar and NH), 3.77-3.65 (m, 11H, 3x CH_3 and CH_2), 3.59-3.53 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 155.5, 154.4, 146.4, 142.4, 138.0, 136.6, 130.5, 124.1, 122.0, 118.3, 101.0, 60.5, 56.4, 44.2, 42.5; MS (ESI) m/z: 445.0 $[M+H]^+$.

[00211] **3,4,5-Trimethoxyphenyl 4-[3-(2-chloroethyl)ureido]benzenesulfonate (109)**. Method A. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride/ethyl acetate 75:25). Yield: 36%. mp: 153-154 °C; IR v: 3342 (NH), 1604 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.70 (s, 1H, NH), 7.77-7.74 (m, 4H, Ar), 6.35 (t, 1H, J = 5.0 Hz, NH), 6.29 (s, 2H, Ar), 3.73-3.67 (m, 11H, 3x CH_3 and CH_2), 3.60-3.54 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 155.2, 154.4, 147.1, 146.4, 137.9, 130.7, 127.5, 118.1, 101.0, 60.5, 56.4, 44.6, 42.5; MS (ESI) m/z: 445.0 $[M+H]^+$.

[00212] **O-Tolyl 4-(3-(2-chloroacetyl)ureido)benzenesulfonate (110).** Method D. The crude product was purified by flash chromatography (silica gel, hexanes:ethyl acetate (75:25) to hexanes:ethyl acetate (50:50)). Yield: 7 %; IR: 3386 (NH), 1627 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.58 (m, 2H, Ar), 7.11 (m, 3H, Ar), 7.01 (m, 1H, Ar), 6.66 (m, 2H, Ar), 4.24 (s, 2H, CH_2), 2.09 (s, 3H, CH_3).

[00213] **O-Tolyl 3-(3-(2-chloroacetyl)ureido)benzenesulfonate (111)**. Method A. The crude product was recrystallized with methanol and filtred. Yield: 75 %; mp: 151°C; IR: 3250 (NH), 1695 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ11.02 (s, 1H, NH), 10.42 (s, 1H, NH), 8.35 (m, 1H, Ar), 7.86 (m, 1H, Ar), 7.62 (m, 2H, Ar), 7.27 (m, 3H, Ar), 7.01 (m, 1H, Ar), 4.44

(s, 2H, CH_2), 2.08 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ183.11, 168.52, 150.48, 147.76, 138.87, 135.78, 131.83, 130.96, 130.51, 127.43, 125.96, 123.07, 121.88, 118.47, 43.31, 15.85.

[00214] 2-Ethylphenyl 3-(3-(2-chloroacetyl)ureido)benzenesulfonate (112). Method A. The crude product was recrystallized with methanol and filtred. Yield: 86 %; mp: 112°C; IR: 3191 (NH), 1698 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ10.50 (s, 1H, NH), 9.32 (s, 1H, NH), 8.15 (s, 1H, Ar), 7.84-7.81 (m, 1H, Ar), 7.65-7.49 (m, 2H, Ar), 7.26-6.99 (m, 4H, Ar), 4.19 (s, 2H, CH_2), 2.57-2.49 (m, 2H, CH_2), 1.14-1.09 (m, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 168.53, 150.49, 147.29, 138.89, 136.64, 135.86, 130.53, 130.21, 127.38, 125.94, 123.01, 121.70, 118.41, 44.03, 43.31, 22.24, 14.10.

[00215] 2-Propylphenyl 3-(3-(2-chloroacetyl)ureido)benzenesulfonate (113). Method A. The crude product was purified by flash chromatography (silica gel, hexanes:ethyl acetate (80:20) to hexanes:ethyl acetate (70:30)) and was recrystallized with methanol and filtred. Yield: 78 %; mp: 115°C; IR: 3237 (NH), 1698 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ11.26 (s, 1H, NH), 10.43 (s, 1H, NH), 8.37 (s, 1H, Ar), 7.85 (m, 1H, Ar), 7.63 (m, 2H, Ar), 7.29 (m, 3H, Ar), 7.04 (m, 1H, Ar), 4.43 (s, 2H, CH_2), 2.40 (t, 2H, J = 7.7 Hz, CH_2), 1.44 (m, 2H, CH_2), 0.82 (t, 3H, J = 7.3 Hz, CH_3).

[00216] 2-Ethylphenyl 4-(3-(2-chloroacetyl)ureido)benzenesulfonate (114). Method D. The crude product was purified by flash chromatography (silica gel, hexanes:ethyl acetate (70:30) to hexanes:ethyl acetate (65:35)). Yield: 7 %; IR: 3250 (NH), 1711 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ10.62 (s, 1H, NH), 9.33 (s, 1H, NH), 7.83 (m, 2H, Ar), 7.68 (m, 2H, Ar), 7.18 (m, 3H, Ar), 7.00 (m, 1H, Ar), 4.20 (s, 2H, CH_2), 2.47 (m, 2H, CH_2), 1.09 (t, 3H, J = 7.5 Hz, CH_3).

[00217] 2-Propylphenyl 4-(3-(2-chloroacetyl)ureido)benzenesulfonate (115). Method A. The crude product was purified by flash chromatography (silica gel, hexanes:ethyl acetate (70:30) to hexanes:ethyl acetate (65:35)). Yield: 76 %; mp: 135 °C ; IR: 3244 (NH), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ10.62 (s, 1H, NH), 9.30 (s, 1H, NH), 7.84 (m, 2H, Ar), 7.70 (m, 2H, Ar), 7.10 (m, 4H, Ar), 4.21 (s, 2H, CH_2), 2.41 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 0.86 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ168.5, 150.0, 148.0, 142.2, 135.7, 131.4, 130.7, 129.8, 127.1, 127.0, 122.1, 119.9, 42.5, 31.8, 23.0, 13.9.

[00218] 2-Chloro-*N*-(3-(*N*-(2-propylphenyl)sulfamoyl)phenylcarbamoyl) acetamide (116). Method D. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride:ethyl acetate (75:25). Yield: 7 %; mp: 140°C; IR: 3237 (NH), 1696 (C=O) cm^{-1}; ^1H NMR (Acetone-d_6): δ10.53 (s, 1H, NH), 10.04 (s, 1H,

NH), 8.11 (s, 1H, Ar), 7.93-7.92 (m, 1H, Ar), 7.91-7.57 (m, 2H, Ar), 7.44-7.42 (m, 2H, Ar), 7.17-7.15 (m, 1H, Ar), 7.01-6.98 (m, 1H, Ar), 4.48 (s, 2H, CH_2), 2.48-2.44 (m, 2H, CH_2), 1.58-1.55 (m, 2H, CH_2), 0.89-0.84 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ163.8, 145.5, 140.7, 135.6, 133.1, 128.0, 127.4, 126.1, 125.3, 125.2, 121.9, 121.1, 120.6, 115.9, 38.1, 28.2, 18.5, 9.9.

[00219] **2-chloro-*N*-(4-(*N*-o-tolylsulfamoyl)phenylcarbamoyl)acetamide (117).** Method A. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride:ethyl acetate (90:10)) and was recrystallized with methanol and filtred. Yield: 9 %; mp: 189-190°C; IR: 3254 (NH), 1702 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ11.01 (s, 1H, NH), 10.39 (s, 1H, NH), 9.50 (s, 1H, NH), 7.73-7.60 (m, 4H, Ar), 7.15-6.96 (m, 4H, Ar), 4.43 (s, 2H, CH_2), 2.02 (s, 3H, CH_3).

[00220] **2-chloro-*N*-(4-(*N*-(2-ethylphenyl)sulfamoyl)phenylcarbamoyl) acetamide (118).** Method A. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride:ethyl acetate (75:25)) and was recrystallized with methanol and filtred. Yield: 10 %; mp: 173°C; ^1H NMR (DMSO-d_6): δ10.49 (s, 1H, NH), 10.28 (s, 1H, NH), 7.65-7.53 (m, 4H, Ar), 7.17-7.02 (m, 4H, Ar), 6.45 (bs, 1H, NH), 4.16 (s, 2H, CH_2), 2.42-2.35 (m, 2H, CH_2), 1.02-0.97 (m, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ168.6, 155.6, 144.5, 140.3, 134.4, 132.1, 128.9, 127.9, 126.6, 126.5, 126.1, 116.9, 41.5, 23.2, 14.4.

[00221] **2-chloro-*N*-(4-(*N*-(2-propylphenyl)sulfamoyl)phenylcarbamoyl)acetamide (119).** Method A. The crude product was purified by flash chromatography (silica gel, methylene chloride to methylene chloride:ethyl acetate (75:25)) and was recrystallized with methanol and filtred. Yield: 7 %; mp: 158°C; IR: 3274 (NH), 1703 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ10.97 (s, 1H, NH), 10.36 (s, 1H, NH), 9.44 (s, 1H, NH), 7.70-7.59 (m, 4H, Ar), 7.14-6.83 (m, 4H, Ar), 4.39 (s, 2H, CH_2), 2.43-2.40 (m, 2H, CH_2), 1.37-1.29 (m, 2H, CH_2), 0.80-0.76 (m, 3H, CH_3).

Biological Methods.

[00222] **Antiproliferative Activity.** Human colon carcinoma HT-29, human skin melanoma M21, and human breast carcinoma MCF-7 cells were purchased from the American Type Culture Collection (Manassas, VA). The cells were cultured in high glucose DMEM supplemented with 5% (v/v) foetal bovine serum (Hyclone, Logan, UT). The cells were maintained at 37 °C in a water-saturated atmosphere containing 5% CO_2. The growth inhibition potency of all compounds was assessed using the procedure described by the National Cancer Institute for its drugs screening program.[1] Briefly, 96-well microtiter plates were seeded with 100 µL of a

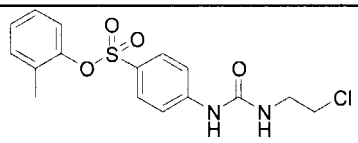
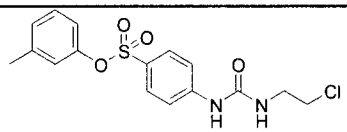
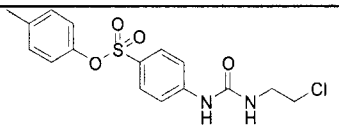
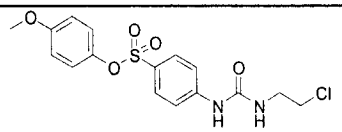
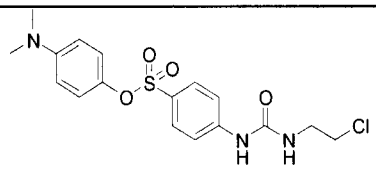
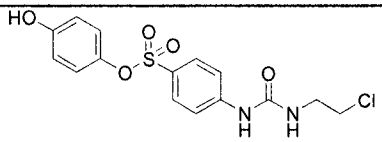
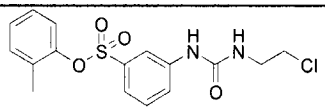
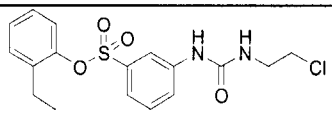
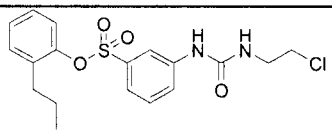
suspension in the culture medium of HT-29 (4 X 10^3), M21 (3.5 X 10^3) or MCF-7 (3 X 10^3) cells per well. Plates were incubated at 37 °C, 5% CO_2 for 24 h. Freshly solubilized drugs in DMSO (40 mM) were diluted in fresh culture medium and aliquots of 100 µL containing a twofold serially diluted concentrations of the drug were added. Final drug concentrations ranged from 200 µM to 780 nM. DMSO was maintained lower than 0.5% to avoid any related toxicity. Plates were incubated for 48 h. Growth was stopped by addition of cold trichloroacetic acid to the wells (10% final concentration), followed by incubation for 1 h at 4 °C. Plates were washed 5-times with water. Seventy-five microliters of a sulforhodamine B solution (0.1% w/v) in 1% acetic acid were added to each well, and the plates were incubated for 15 min at room temperature. After staining, unbound dye was removed by washing 5-times with 1% acetic acid. Bonded dye was solubilized in 20 mM Tris base, and the absorbance was read at optimal wavelength (530-568 nm) using a µQuant Universal Microplate Spectrophotometer (Biotek, Winooski, VT). The results were compared with those of control reference plates fixed on the treatment day and the percentage of cell growth inhibition was calculated for each drug. The experiments were performed at least twice in triplicate. The assays were considered valid when the variability among data for a given set of conditions, within the same experiment, was less than 10% with respect to the mean value.

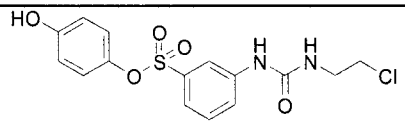
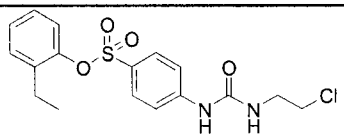
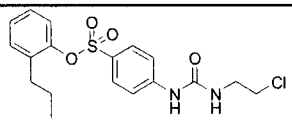
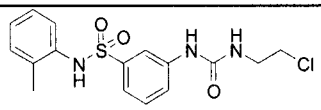
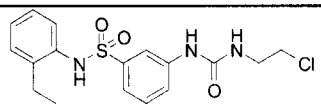
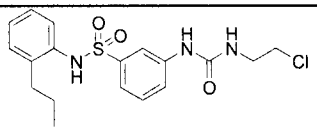
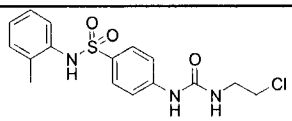
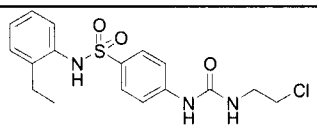
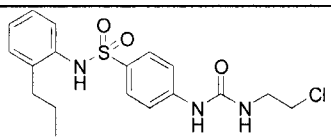
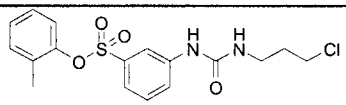
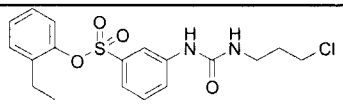
Results

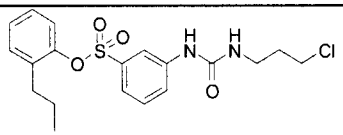
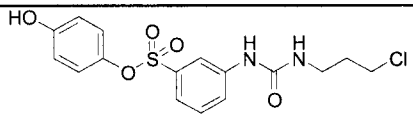
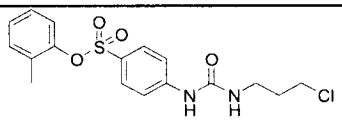
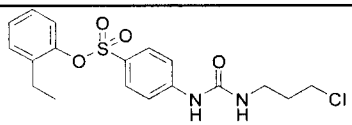
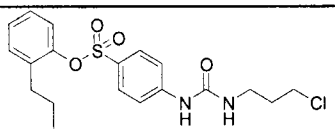
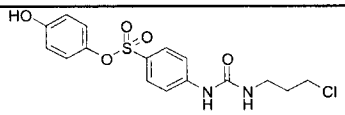
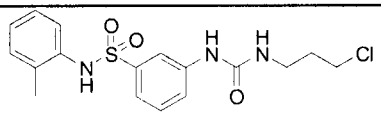
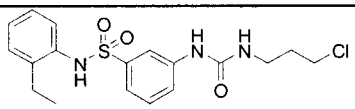
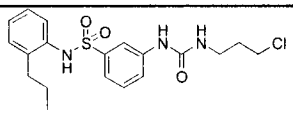
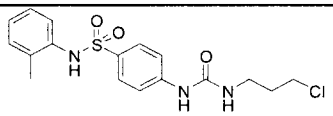
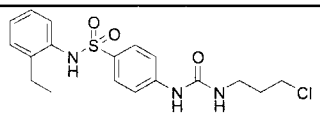
[00223] The antiproliferative activity of alkylurea-SOs and alkylurea-SAs was assessed on three human cancer cell lines, namely HT-29 colon carcinoma, M21 skin melanoma and MCF-7 breast carcinoma. These cell lines were selected as representatives of tumor cells originating from the three germ layers. The antiproliferative activity was evaluated by sulforhodamine B method according to the NCI/NIH Developmental Therapeutics Program.[1] The results are summarized in **Table 1** and are expressed as the concentration of drug inhibiting cell growth by 50% (IC_{50}). The antiproliferative activity of several alkylureas-SOs was better or at least similar to cisplatin (cDDP) that exhibits IC_{50}s of 20, 17, and 9.6 µM on HT-29, M21, and MCF-7 cells, respectively. There are alkylurea-SAs that show antiproliferative activity at similar levels as cDDP.

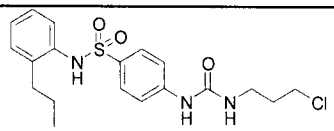
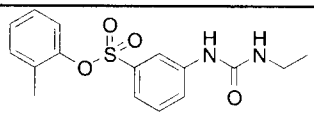
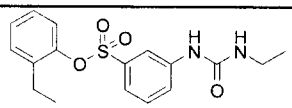
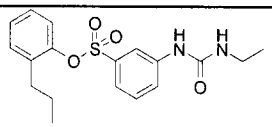
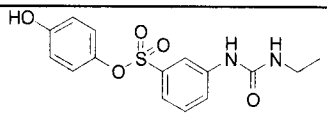
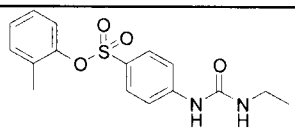
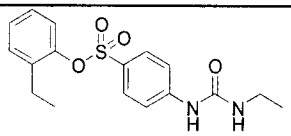
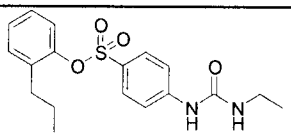
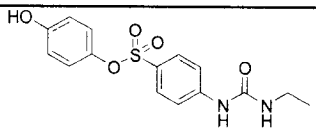
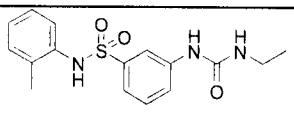
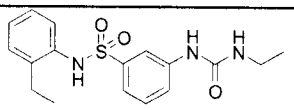
[00224] All compounds presented in **Table 1** were found to be active in at least one of the above-mentioned assay.

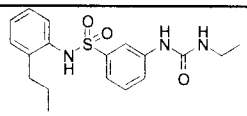
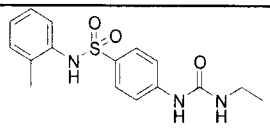
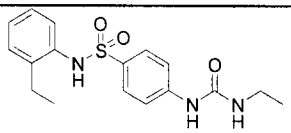
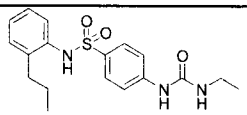
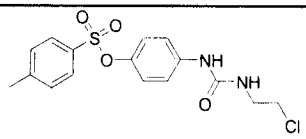
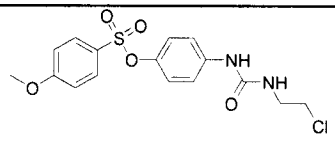
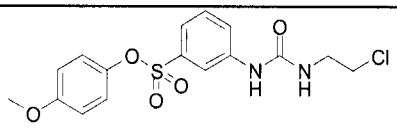
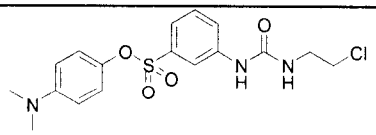
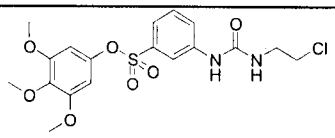
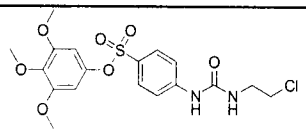
Table 1

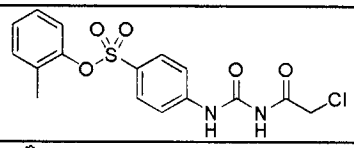
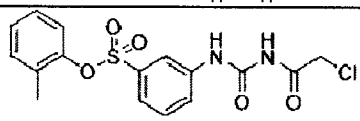
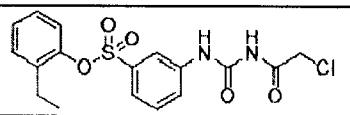
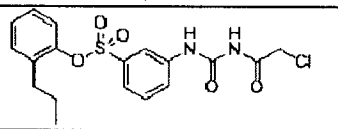
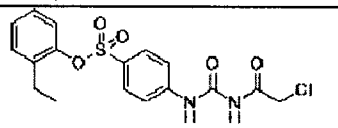
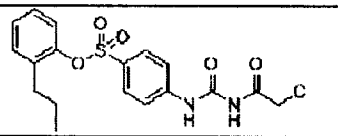
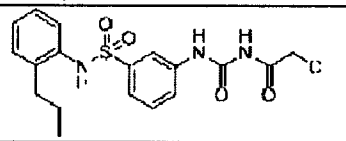
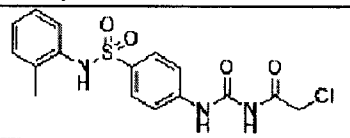
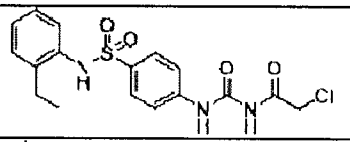
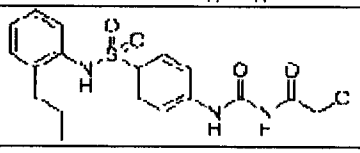
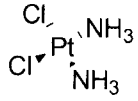
Cpd #	Structure	IC_{50} (μM)		
		HT-29	M21	MCF-7
4		4.7	2.8	4.8
5		11	7.2	17
6		30	21	33
7		18	18	27
8		39	43	58
10		1.5	1.2	1.3
11		33	40	41
12		4.3	4.8	5.3
13		15	17	17

Cpd #	Structure	IC_{50} (μM)		
		HT-29	M21	MCF-7
15		120	73	87
16		17	13	19
17		2.5	2.1	3.6
18		71	91	86
19		48	65	46
20		15	17	16
21		55	63	60
22		40	68	33
23		21	29	29
24		21	29	27
25		23	24	25

Cpd #	Structure	IC_{50} (μM)		
		HT-29	M21	MCF-7
26		14	15	14
28		51	49	51
29		26	25	27
30		15	15	15
31		13	13	15
33		50	47	51
34		42	60	52
35		96	>200	43
36		15	23	18
37		64	>200	> 200
38		> 200	>200	> 200

Cpd #	Structure	IC_{50} (μM)		
		HT-29	M21	MCF-7
39		26	38	35
40		44	51	55
41		33	30	31
42		25	25	24
44		75	42	64
45		12	3.1	4.5
46		12	2.5	3.4
47		2.4	0.8	1.3
49		12	4.3	8.0
50		102	131	108
51		15	>100	48

Cpd #	Structure	IC_{50} (μM)		
		HT-29	M21	MCF-7
52		41	60	40
53		> 200	>200	> 200
54		86	90	91
55		32	41	37
96		29	28	45
97		37	32	48
106		35	34	63
107		17	12	41
108		21	31	26
109		1.8	0.80	5.0

Cpd #	Structure	IC_{50} (μM)		
		HT-29	M21	MCF-7
110		14.3	19.2	18.3
111		8.9	3,3	4,6
112		8.6	3.0	4.4
113		9.9	3.2	4.5
114		9.1	14	8.6
115		13	10	9.4
116		5.8	2.4	2.1
117		6.7	1.8	4.3
118		6.3	4.4	7.0
119		5.2	1.8	3.6
cDDP		20	17	9.6
DMSO		n.e.	n.e.	n.e.

Discussion

[00225] As depicted in **Table 1**, replacing the sulfonyl group bridging the phenyl rings A and B by a bioisosteric sulfonamide bridge lowered significantly the antiproliferative activity. Moreover, the structure-activity relationship study shows that the position of the pharmacophoric moiety on the phenyl ring A has an important impact on the antiproliferative activity. The transposition of the pharmacophoric CEU, CPU and EU moieties from position 4 to position 3 on the aromatic ring A decreased significantly the antiproliferative activity.

[00226] Structure-activity relationship study also showed that the nature of the pharmacophoric moiety is important. Derivatives bearing pharmacophoric EU and CEU moities exhibited antiproliferative activities in the same range and were more potent than their counterparts bearing a CPU moiety. Interestingly, certain compounds bearing an EU moiety were potent antiproliferative agents.

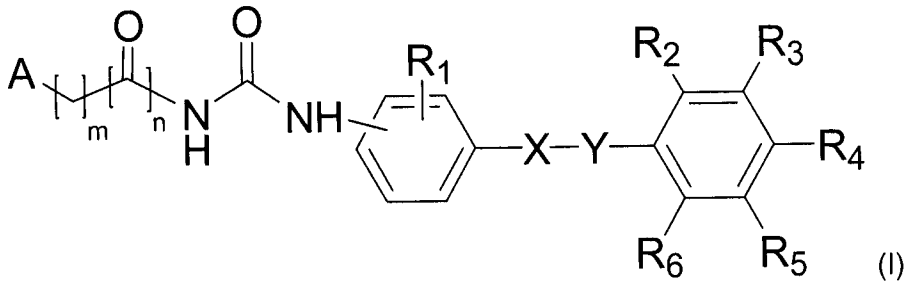
[00227] Another key element of the cytocidal activity of alkylurea-SOs is related to modifications of the alkyl or the hydroxyl substituents on the phenyl ring B. The molecule can be substituted either in position 4 by a hydroxyl or by an alkyl (methyl, ethyl, propyl) group at position 2 without affecting significantly the antiproliferative activity.

Reference

[1] National Cancer Institute (NCI/NIH), Developmental therapeutics program human tumor cell line screen, URL : http://dtpncinihgov/branches/btb/ivclsp.html.

CLAIMS

1. A compound of formula (I):



(I)

ring A ring B

wherein:

A is H or halo; m is 1, 2, 3 or 4; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, ω- and ω-1 C_{1-4} alkanol, ω- C_{1-4} alkyl carboxylate and corresponding C_{1-3} esters, -COOR7 wherein R7 is as defined above, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

or X is –CH=CH- and Y is C=O;

or X is C=O, -S- or -C=CH_2-; and Y is absent;

or one of X or Y is N and the other is C and are so linked as to form an imidazole ring;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, C_{1-6} 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters,-COOR7 wherein R7 is selected from: H or C_{1-3} alkyl, NO_2, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, phenoxy, C_{0-6} alkyl-CN, C_{1-6}, 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-}

$_6$ alkyl carboxylate and corresponding C_{1-3} esters, -COOR7, wherein R7 is selected from: H or C_{1-3} alkyl; NO_2, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9), wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; or

R3 and R4; or R4 and R5 are linked to each other and form a 4, 5 or 6 – membered saturated or partially unsaturated ring optionally containing one or two N, O or S atoms thus forming a heterocycle, said ring or heterocycle optionally substituted with C_{1-6} alkyl, OH, halogen, amines, C_{1-4} alkyl-substituted amine, C_{1-4} alkoxy;

or an amino acid derivative, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

2. The compound of formula (I) as defined in claim 1, wherein:

A is H or halo; m is 1, 2 or 3; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, ω- and ω-1 C_{1-4} alkanol, ω- C_{1-4} alkyl carboxylate and corresponding C_{1-3} esters, -COOR7 wherein R7 is as defined above, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

or X is –CH=CH- and Y is C=O;

or X is C=O, -S- or -C=CH_2-; and Y is absent;

or one of X or Y is N and the other is C and are so linked as to form an imidazole ring;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, C_{1-6} 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters,-COOR7 wherein R7 is selected from: H or C_{1-3} alkyl, NO_2, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, phenoxy, C_{0-6} alkyl-CN, C_{1-6}, 2-ketyl, ω- and ω-1 C_{1-6} alkanol, ω- C_{1-6} alkyl carboxylate and corresponding C_{1-3} esters, -COOR7, wherein R7 is selected from: H or C_{1-3} alkyl; NO_2, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9), wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; or

R3 and R4; or R4 and R5 are linked to each other and form a 4, 5 or 6 – membered saturated or partially unsaturated ring optionally containing one or two N, O or S atoms thus forming a heterocycle, said ring or heterocycle optionally substituted with C_{1-6} alkyl, OH, halogen, amines, C_{1-4} alkyl-substituted amine, C_{1-4} alkoxy;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

3. The compound of formula (I) as defined in claim 2, wherein:

A is H, Cl, Br, F or I; m is 1, 2 or 3; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4}alkenyl, C_{1-4} alkoxy,

-NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from H, Me and Et;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

or X is –CH=CH- and Y is C=O;

or X is C=O, -S- or $C=CH_2$; and Y is absent;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl; and

R3, R4 and R5 is each independently selected from the group consisting of:

H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, -NH-C(O)-C_{1-3} alkyl, and -N-(R8)(R9), wherein R8 and R9 is each independently selected from the group consisting of: H and C_{1-3} alkyl;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

4. The compound of formula (I) as defined in claim 3, wherein:

A is H or chloro; m is 1 or 2; n is 0 or 1;

R1 is H, OH, halogen, unbranched C_{1-6} alkyl, branched C_{1-4} alkyl, C_{1-4}alkenyl, or C_{1-4} alkoxy;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH; or X is $CH=CH_2$ and Y is absent;

R2 and R6 is each independently selected from the group consisting of: H, OH, halogen,

C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-3} alkenyl and C_{1-3} alkoxy; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, O-alkylhalo, and -N-(R8)(R9) wherein R8 and R9 is each independently selected from the group consisting of: H, Me, Et, and Pr;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that, when A is Cl, m is 2, n is 0, the urea is linked to the phenyl through position 3 or 4, R1 is H, X is $CH=CH_2$ and Y is absent, then R4 *is not* OMe and R5 *is not* OH.

5. The compound of formula (I) as defined in claim 1 wherein:

the urea group: A-$[CH_2]_m$-$[CO]_n$-NH-C(O)-NH- is bound to the adjacent phenyl ring A through position 3 or 4;

A is H or chloro; n is 0 or 1: m is 1, 2 or 3;
R1 is H;
X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;
R2 and R6 is each independently selected from the group consisting of: H, halogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkoxy; and
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, -N(C_{1-4} alkyl)$_2$ and -NH_2;
or an amino acid derivative, or a pharmaceutically acceptable salt thereof.

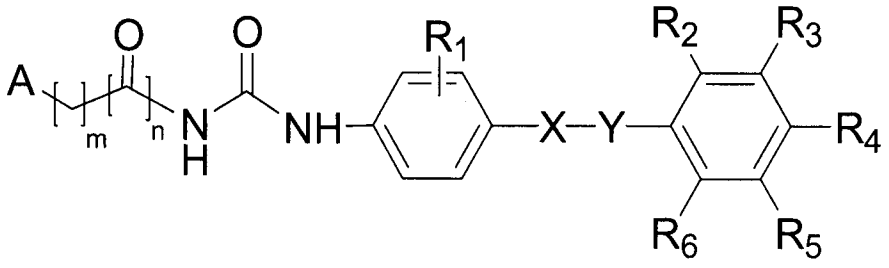
6. The compound of formula (I) as defined in claim 5, wherein:

the urea group: A-[CH_2]$_m$-[CO]$_n$-NH-C(O)-NH- is bound to the adjacent phenyl ring A through position 3 or 4;
A is H or chloro; n is 0 or 1: m is 1, 2 or 3;
R1 is H;
X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;
R2 and R6 is each independently selected from the group consisting of: H, halogen, C_{1-3} alkyl, and C_{1-3} alkoxy;
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, -N(Me)$_2$ and -NH_2;
or an amino acid derivative, or a pharmaceutically acceptable salt thereof.

7. The compound of formula (I) as defined in claim 6, wherein:

the urea group: A-[CH_2]$_m$-[CO]$_n$-NH-C(O)-NH- is bound to the adjacent phenyl ring A through position 3 or 4;
A is H or chloro; n is 0 or 1: m is 1 or 2;
R1 is H;
X is SO_2 and Y is O or NH;
R2 and R6 is each independently selected from the group consisting of: H, halogen, and C_{1-3} alkyl; and
R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, and C_{1-6} alkyl;
or an amino acid derivative, or a pharmaceutically acceptable salt thereof.

8. A compound of formula (Ia)



(Ia)

wherein:

A is H or chloro; n is 0 when m is 2; n is 1 when m is 1 or 2;

R1 is H or Me;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

R2 and R6 is each independently selected from the group consisting of: H, halogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkoxy; and

R3, R4 and R5 is each independently selected from the group consisting of: H, OH, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, and $-NH_2$;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof.

9. The compound of formula (Ia) as defined in claim 8, wherein:

A is chloro; n is 0 when m is 2; or n is 1 when m is 1; R1 is H;

X is O or NH when Y= SO_2; and X= SO_2 when Y is O or NH;

R2 and R6 is each independently selected from the group consisting of: H, Cl, Br, F, I, Me, Et, Pr, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OH, OMe, OEt and OPr;

R3, R4 and R5 is each independently selected from the group consisting of: H, Cl, Br, F, I, Me, Et, Pr, Bu, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OH, OMe, OEt and OPr;

or a sulfonate, a phosphate, a boronic acid or an amino acid derivative thereof, or a pharmaceutically acceptable salt thereof.

10. The compound of formula I as defined in any one of claims 1 to 9, wherein group: A-$[CH_2]_m$-$[CO]_n$-NH-C(O)-NH- is bound to adjacent phenyl ring through position 3, 4 or 5.

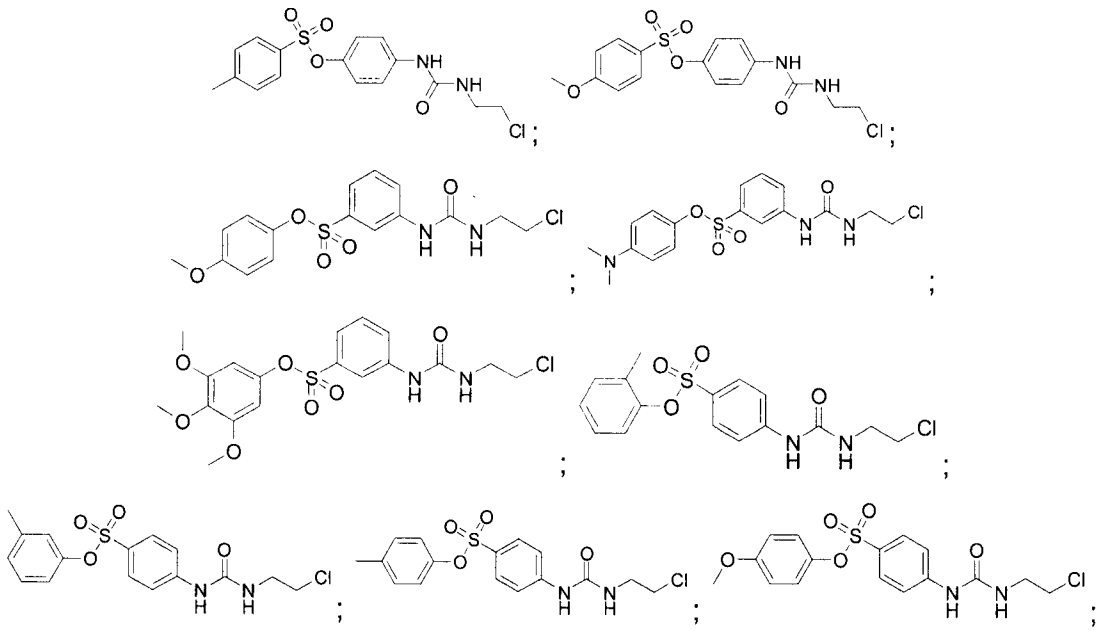
11. The compound of formula I as defined in any one of claims 1 to 9, wherein R1 is selected from the group consisting of: H and Me.

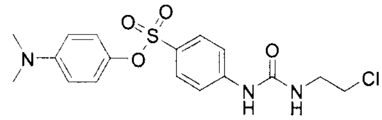
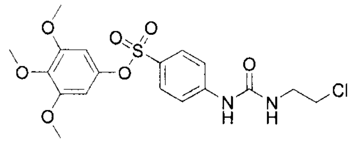
12. The compound of formula I as defined in any one of claims 1 to 9, wherein X is SO_2 and Y is O or NH; or X is O and Y is SO_2.

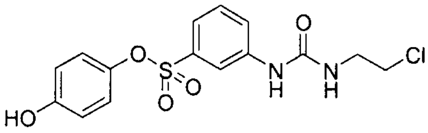
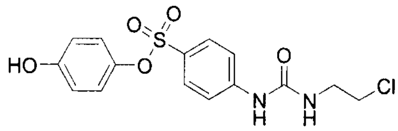
13. The compound of formula I as defined in any one of claims 1 to 12, wherein each of R2 and R6 are independently selected from the group consisting of: H, Me, Et, Pr, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, F, Cl, I, and OMe.

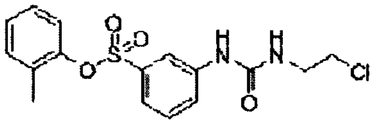
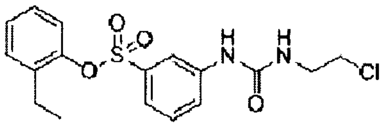
14. The compound of formula I as defined in any one of claims 1 to 13, wherein each of R3, R4 and R5 are independently selected from the group consisting of: H, Me, Et, Pr, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, CH-CN, F, Cl, I, Br, OMe, OEt, OPr, Obutyl, Opentyl, Ohexyl, Ophenyl, $OCH(F)_2$, NH_2, NO_2, $N(Me)_2$.

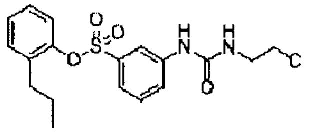
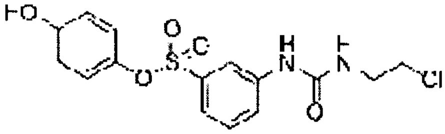
15. The compound of claim 1, selected from the group consisting of:

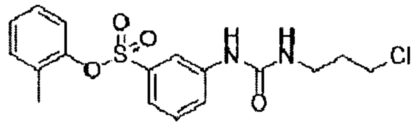
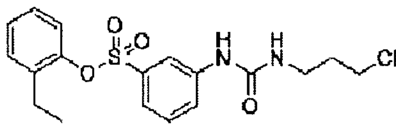


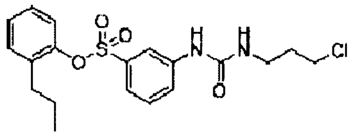
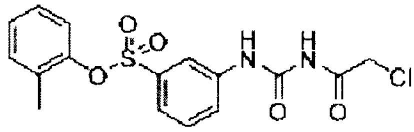
 ;  ;

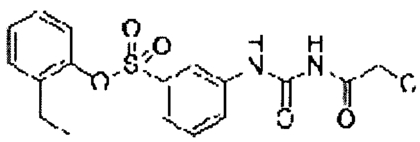
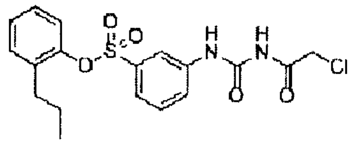
 ;  ;

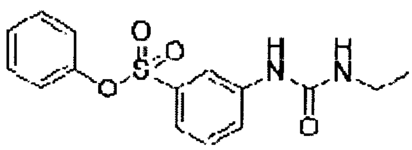
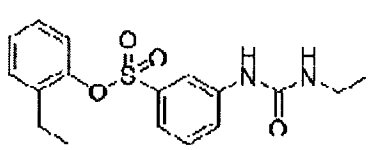
 ;  ;

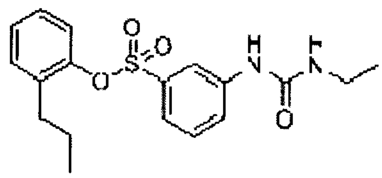
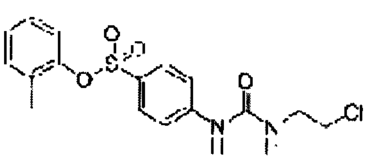
 ;  ;

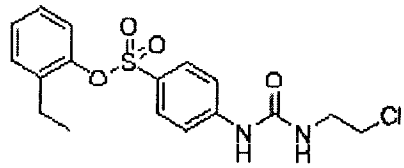
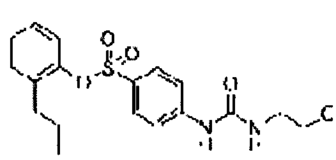
 ;  ;

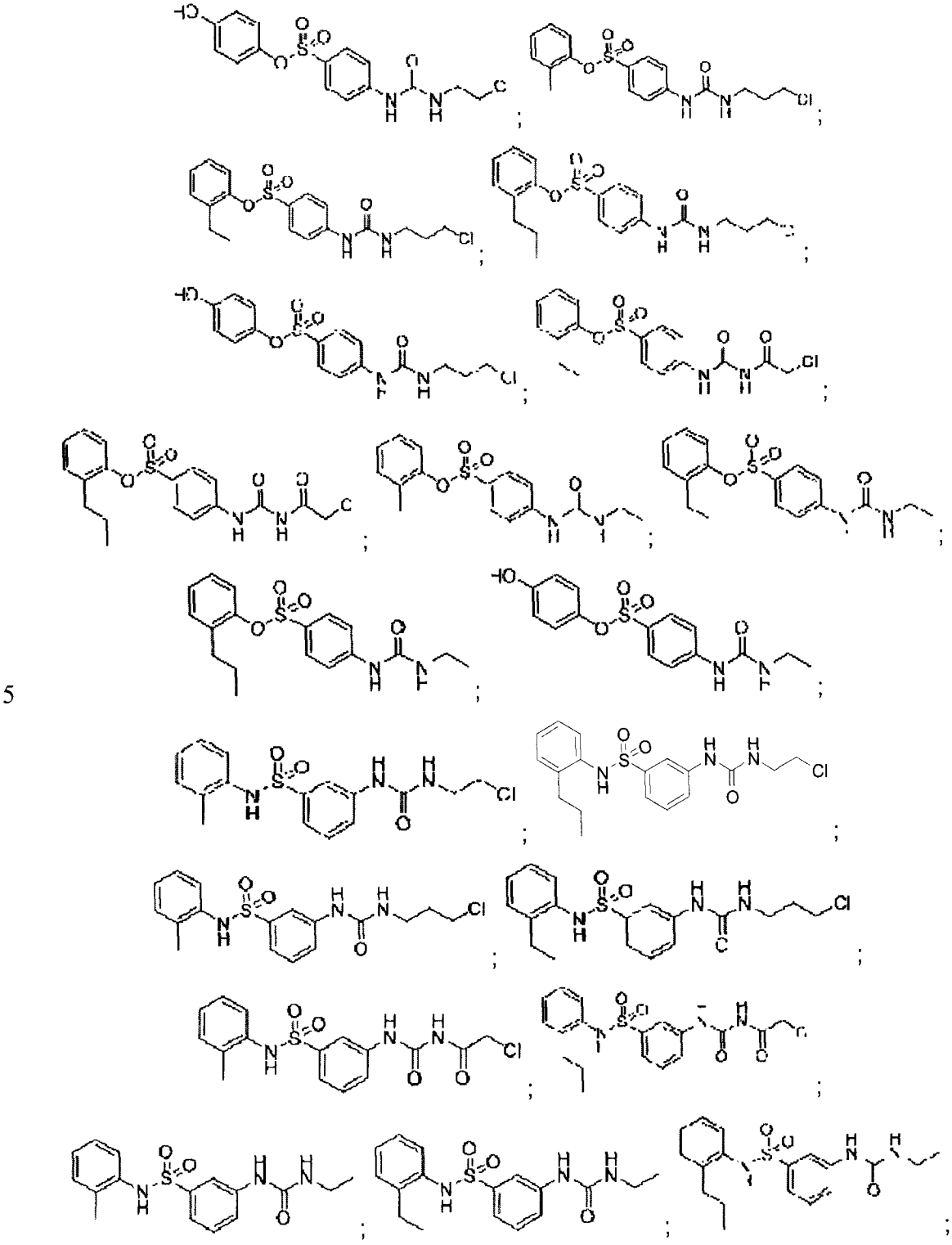
 ;  ;

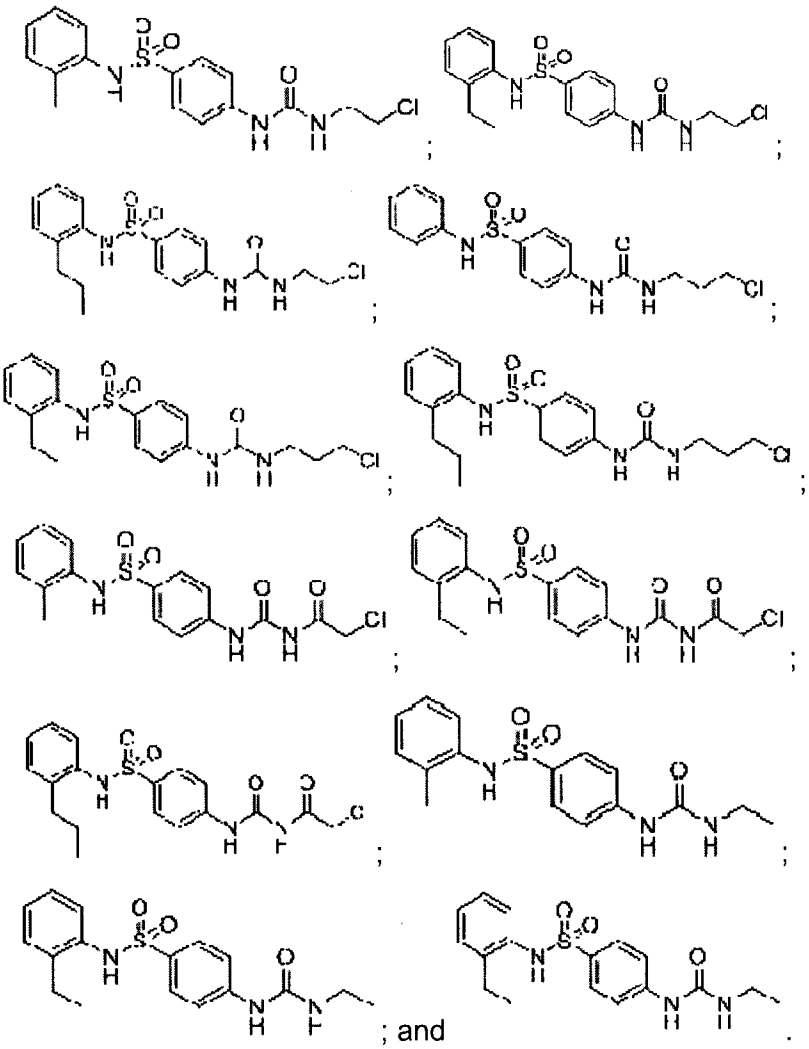
 ;  ;

 ;  ;

 ;  ;

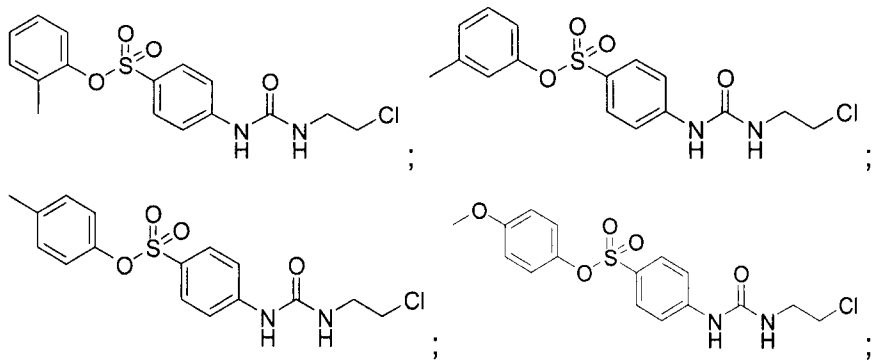
 ;  ;

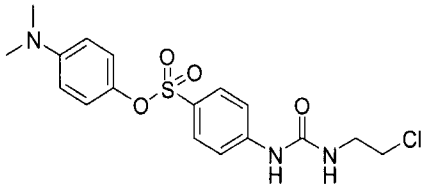




; and .

16. The compound of claim 1, selected from the group consisting of:

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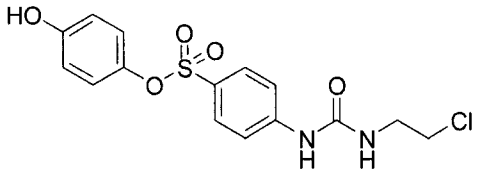
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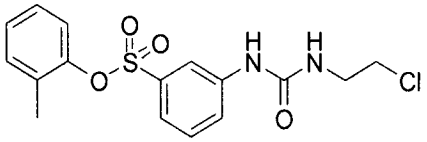
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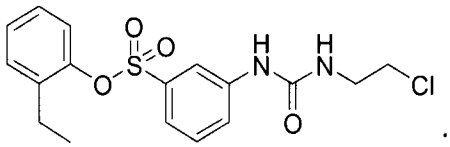
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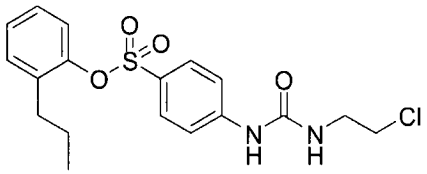
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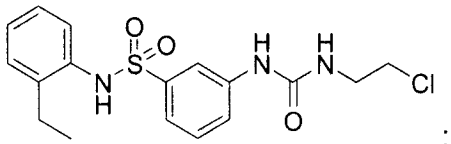
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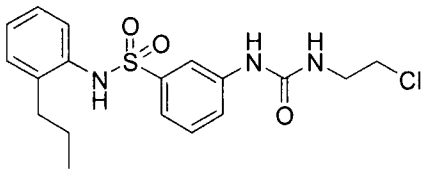
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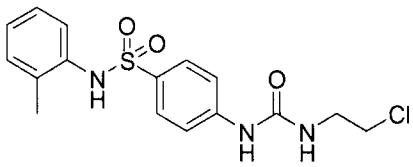
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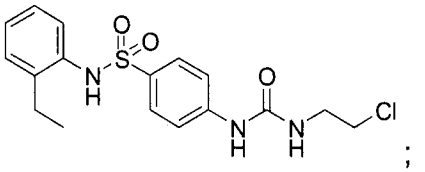
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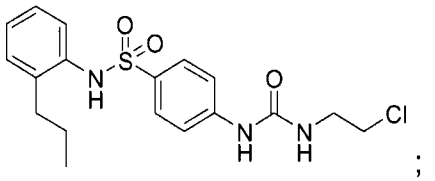
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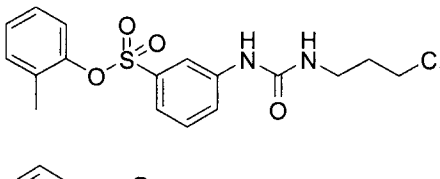
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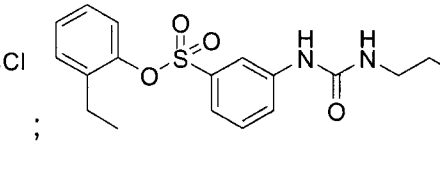
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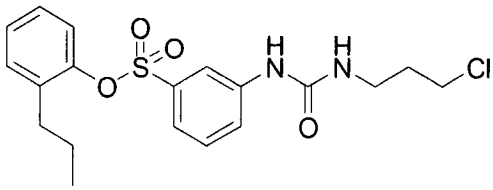
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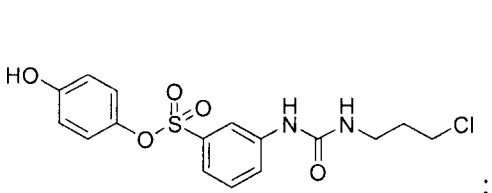
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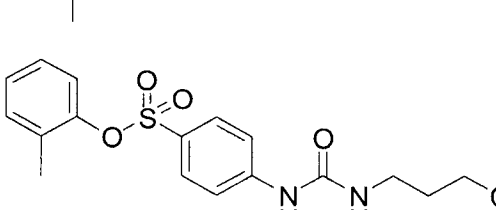
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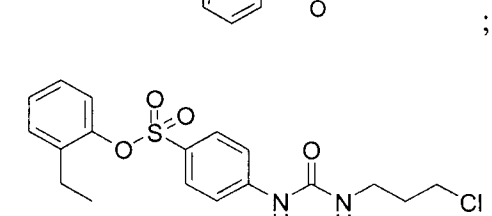
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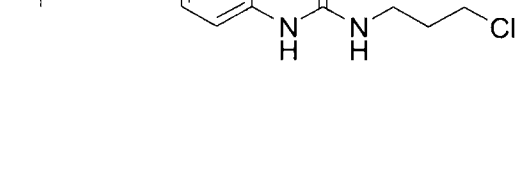
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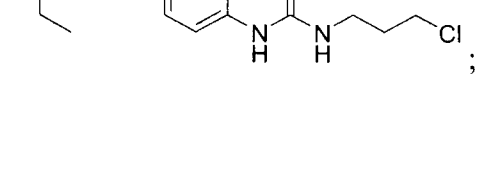
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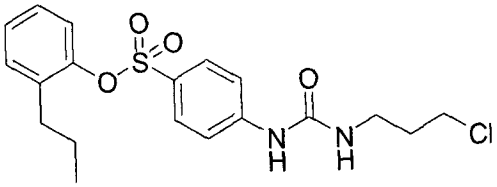
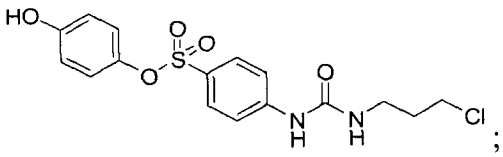
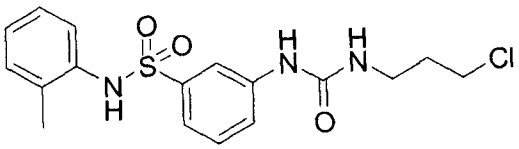
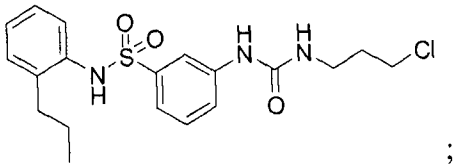
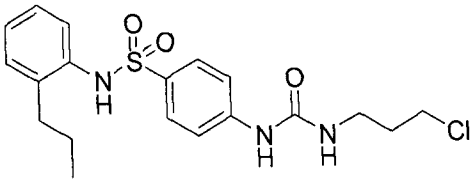
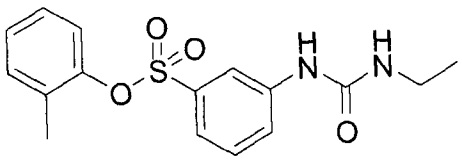
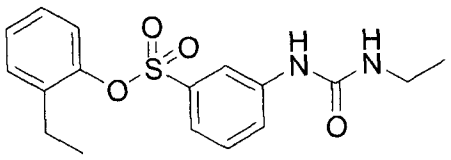
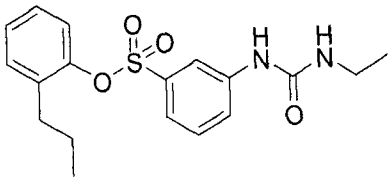
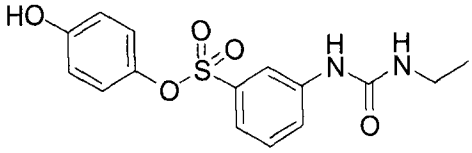
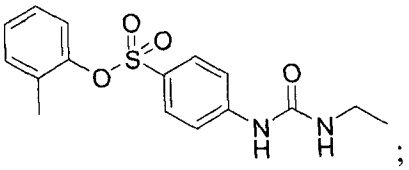
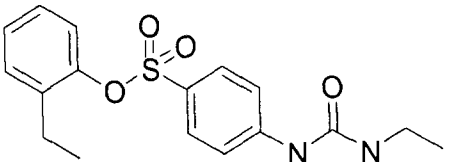
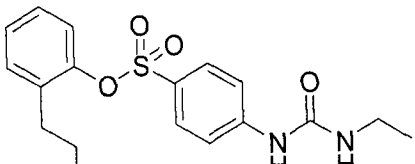
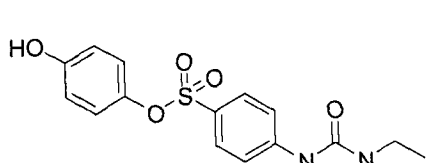
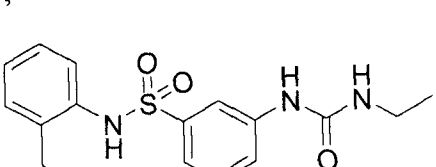
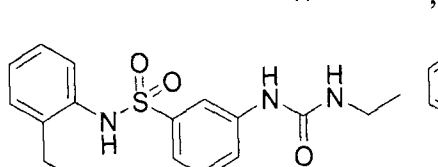
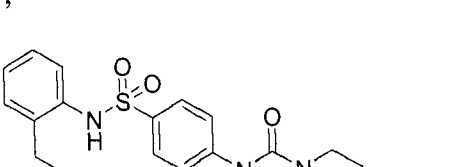
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
 ;
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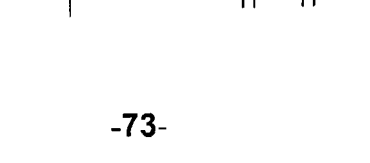
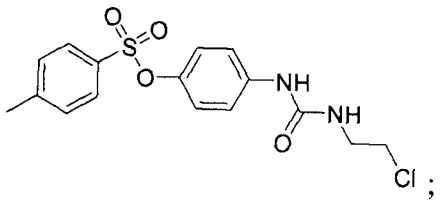
 ;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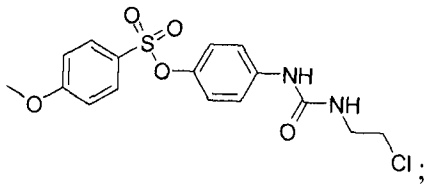
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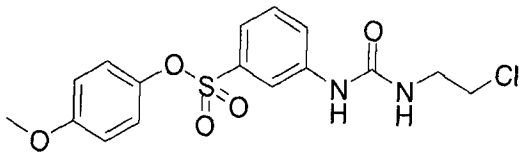
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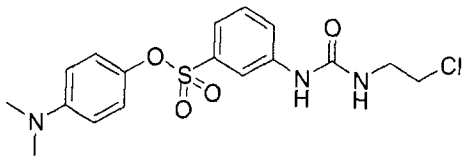
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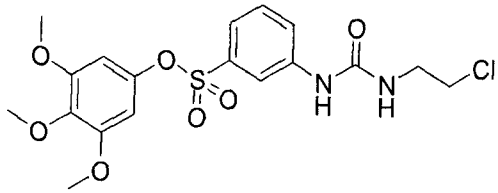
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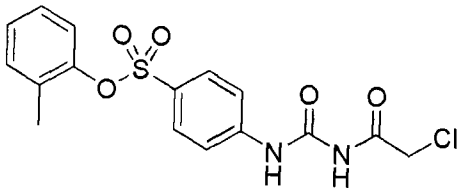
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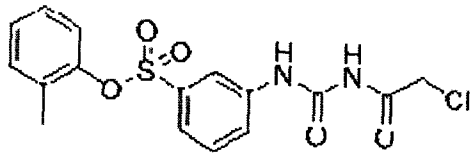
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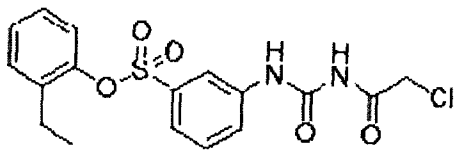
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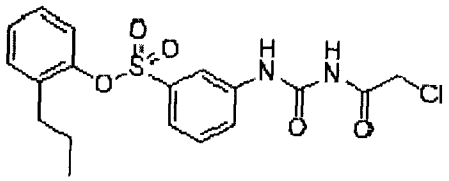
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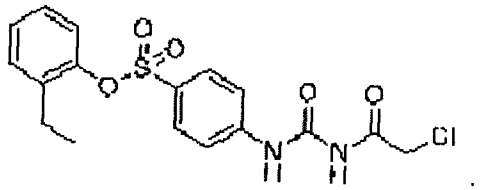
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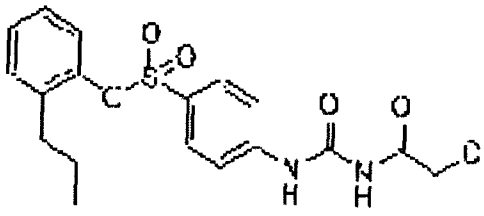
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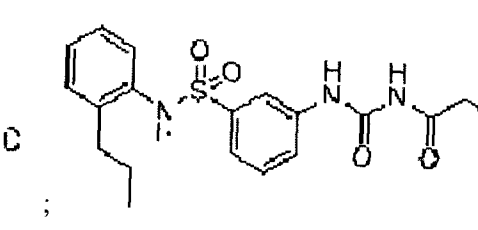
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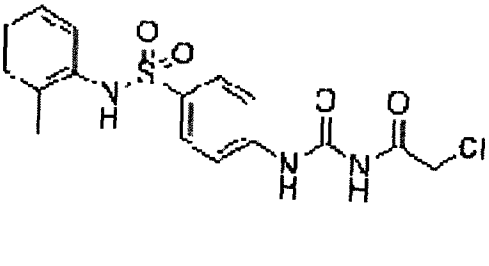
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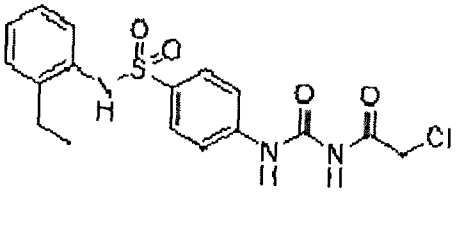
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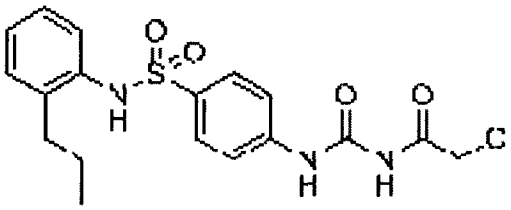
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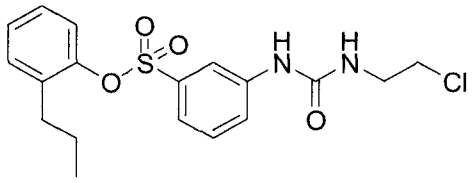
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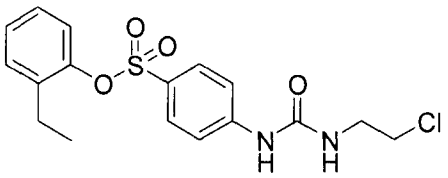
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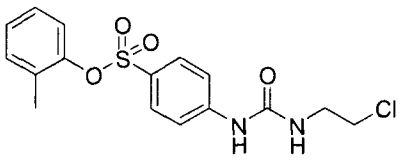
17. The compound of claim 1, selected from the group consisting of: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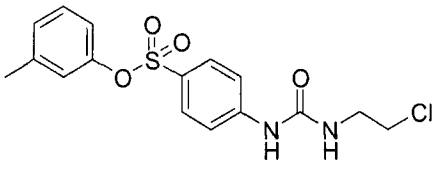
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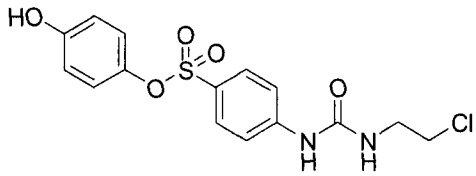
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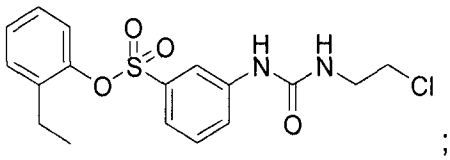
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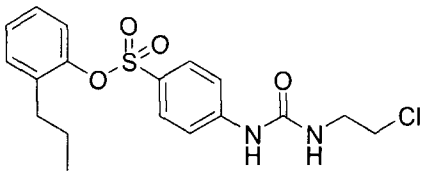
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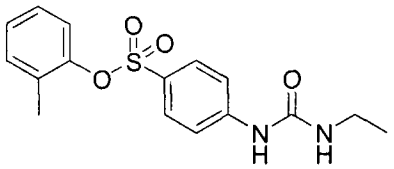
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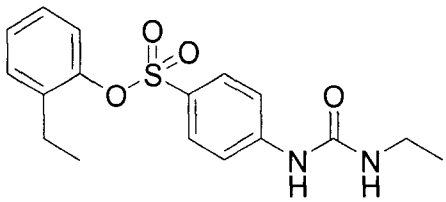
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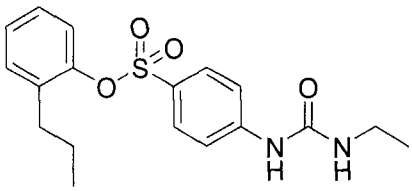
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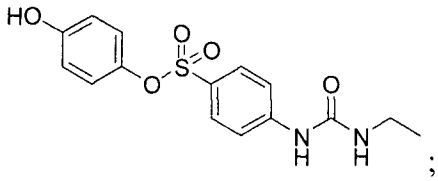
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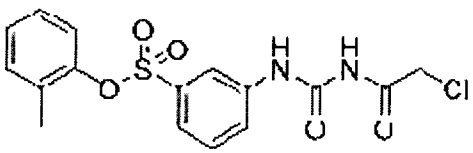
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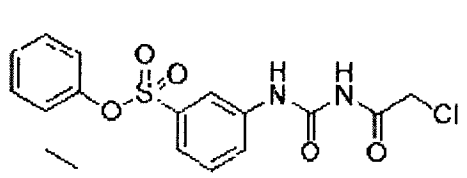
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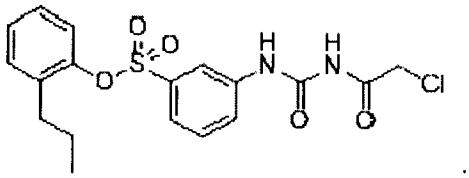
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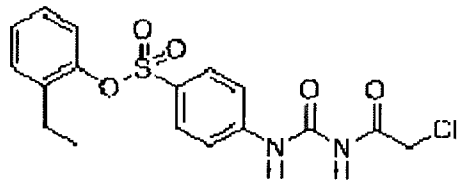
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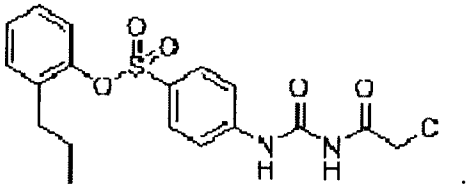
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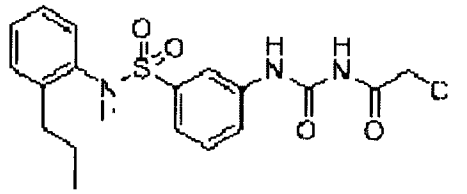
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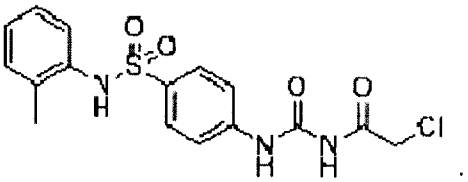
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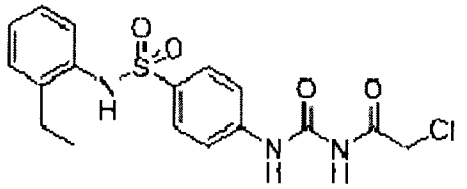
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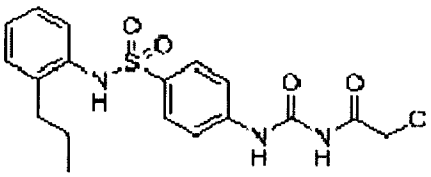
.

18. A physiological composition comprising at least one compound of any one of claims 1 to 17, in admixture with at least one physiologically-acceptable excipient.

19. A pharmaceutical composition comprising at least one compound of any one of claims 1 to 17, in admixture with at least one pharmaceutically-acceptable excipient.

20. A method for hindering or blocking cell cycle progression by contacting one or more cells with one or more compounds of any one of claims 1 to 17, or with a composition of claim 15.

21. A method of treating a condition that results from abnormal cell growth, cellular differentiation, tumor growth or invasion with one or more compounds of any one of claims 1 to 17, or with a composition of claim 18.

22. A method of treating cancer, said method comprising administering a therapeutically effective amount of a compound of any one of claims 1 to 17, or of a composition of claim 18, to a patient suffering from said cancer.

23. Use of one or more compound of any one of claims 1 to 17, or a composition of claim 18, for blocking cell cycle progression.

24. Use of one or more compound of any one of claims 1 to 17, or a composition of claim 18, for the treatment of cancer.

25. A compound as defined in any one of claims 1 to 17, for use in the prevention of cell cycle progression.

26. The composition as defined in claim 18, for use in the prevention of cell cycle progression.

27. A compound as defined in any one of claims 1 to 17, for use in the treatment of cancer.

28. A composition as defined in claim 19, for use in the treatment of cancer.

29. Use of a compound as defined in any one of claims 1 to 17, for the manufacture of a medicament for the treatment of cancer in a subject.

30. The use of claim 29, wherein said subject is a human.

31. The compound according to any one of claims 1, 5, 6, 7, 15-17, wherein said compound is a phosphate, a sulfonate or a boronic acid derivative.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2012/000361

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07C 309/72*** (2006.01) , ***A61K 31/18*** (2006.01) , ***A61K 31/255*** (2006.01) , ***A61P 35/00*** (2006.01) , ***C07C 311/47*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: ***C07C 309/72*** (2006.01), ***A61K 31/18*** (2006.01), ***A61K 31/255*** (2006.01), ***A61P 35/00*** (2006.01), ***C07C 311/47*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN CAPlus (structure search + keywords = alkylurea, anti-cancer, proliferation, neoplastic, alkylating agent), Canadian Patent Database (IPC + keywords)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2011/100840 A1 (Gaudreault et al.) 25 August 2011 (25-08-2011) *Examples 5-6, 30-41 & Claims*	1-17
X	US 3,970,752 (Aichinger et al.) 20 July 1976 (20-07-1976) *columns 7-8*	1-3, 10-11, 13-14
X	US 4,026,697 (Cross) 31 May 1977 (31-05-1977) *Table 1, Compound 4*	1-3, 10-11, 13-14
X	US 4,504,490 (Rösner et al.) 12 March 1985 (12-03-1985) *columns 12-15*	1-3, 10, 12-14
X	US 5,714,127 A (DeWitt et al.) 3 February 1998 (03-02-1998) *Table 5, compounds 1 & 5*	1-3, 10, 13-14
X	EP 0472053 B1 (Yoshino et al.) 17 June 1998 (17-06-1998) *Example 104 & Claim 1*	1-2, 13-14, 18-31

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2012 (05-07-2012)	23 July 2012 (23-07-2012)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Tung Siu (819) 934-6735

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 20-22

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 20-22 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 20-22.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CN 102060780 A (Jiang et al.) 18 May 2011 (18-05-2011) *Examples 7 & 9*	1-2, 11, 13-14
X	JP 57-185219 (Shinichi et al.) 15 November 1982 (15-11-1982) *Table 1, Compound 26*	1-2, 13-14, 18-31
X	*J. Med. Chem.*, **2010**, 53, pp. 7756-7766 (Alexiou et al.) *Scheme 2 & Table 1, Compound 2i*	1-14, 18-19
P, X	*J. Med. Chem.*, **2011**, 54, pp. 4559-4580 (Fortin et al.) 23 May 2011 (23-05-2011) *Scheme 1, Compound 8*	1-17

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2011100840A1	25 August 2011 (25-08-2011)	None	
US3970752A	20 July 1976 (20-07-1976)	AU475802B2	2 September 1976 (02-09-1976)
		AU6681174A	25 September 1975 (25-09-1975)
		BE812549A1	20 September 1974 (20-09-1974)
		BR7402174D0	05 November 1974 (05-11-1974)
		CA1008860A1	19 April 1977 (19-04-1977)
		CH605848A5	13 October 1978 (13-10-1978)
		DE2313721A1	03 October 1974 (03-10-1974)
		FR2230354A1	20 December 1974 (20-12-1974)
		FR2230354B1	10 November 1977 (10-11-1977)
		GB1425789A	18 February 1976 (18-02-1976)
		HU168729B	28 July 1976 (28-07-1976)
		IE39078L	20 September 1974 (20-09-1974)
		IE39078B1	02 August 1978 (02-08-1978)
		IL44433A	31 August 1977 (31-08-1977)
		IL44433D0	31 July 1974 (31-07-1974)
		JP49125382A	30 November 1974 (30-11-1974)
		JP49125511A	02 December 1974 (02-12-1974)
		LU69647A1	17 October 1974 (17-10-1974)
		NL7403613A	24 September 1974 (24-09-1974)
		PL88676B1	30 September 1976 (30-09-1976)
		SU531487A3	05 October 1976 (05-10-1976)
		US3948893A	06 April 1976 (06-04-1976)
		ZA7401772A	29 January 1975 (29-01-1975)
US4026697A	31 May 1977 (31-05-1977)	US3988300A	26 October 1976 (26-10-1976)
US4504490A	12 March 1985 (12-03-1985)	AT28630T	15 August 1987 (15-08-1987)
		AU1867983A	08 March 1984 (08-03-1984)
		CA1214182A1	18 November 1986 (18-11-1986)
		DE3232959A1	08 March 1984 (08-03-1984)
		DE3372756D1	03 September 1987 (03-09-1987)
		DK401683D0	02 September 1983 (02-09-1983)
		DK401683A	05 March 1984 (05-03-1984)
		EP0105196A2	11 April 1984 (11-04-1984)
		EP0105196A3	03 April 1985 (03-04-1985)
		EP0105196B1	29 July 1987 (29-07-1987)
		ES525335D0	01 November 1984 (01-11-1984)
		ES8500898A1	01 February 1985 (01-02-1985)
		ES533932D0	16 March 1985 (16-03-1985)
		ES8503649A1	16 June 1985 (16-06-1985)
		FI833119D0	01 September 1983 (01-09-1983)
		FI833119A	05 March 1984 (05-03-1984)
		GR78941A1	02 October 1984 (02-10-1984)
		HU193531B	28 October 1987 (28-10-1987)
		IL69640D0	30 December 1983 (30-12-1983)
		JP59076050A	28 April 1984 (28-04-1984)
		MA19892A1	01 April 1984 (01-04-1984)
		NO833158A	05 March 1984 (05-03-1984)
		NZ205468A	31 July 1985 (31-07-1985)
		PH19980A	26 August 1986 (26-08-1986)
		PT77285A	01 October 1983 (01-10-1983)
		PT77285B	09 April 1986 (09-04-1986)
		ZA8306515A	25 April 1984 (25-04-1984)

-/-- continued on extra sheet

Continuation of Patent Family Annex:

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US5714127A	03 February 1998 (03-02-1998)	AU5355894A	09 May 1994 (09-05-1994)
		AU8416391A	07 January 1992 (07-01-1992)
		DE69109676D1	14 June 1995 (14-06-1995)
		EP0532706B1	10 May 1995 (10-05-1995)
		EP0663856A1	26 July 1995 (26-07-1995)
		JPH08502482A	19 March 1996 (19-03-1996)
		MX9306219A	29 April 1994 (29-04-1994)
		US5230996A	27 July 1993 (27-07-1993)
		US5278189A	11 January 1994 (11-01-1994)
		US5324483B1	24 September 1996 (24-09-1996)
		US5567391A	22 October 1996 (22-10-1996)
		US5582801A	10 December 1996 (10-12-1996)
		US5593642A	14 January 1997 (14-01-1997)
		US5612002A	18 March 1997 (18-03-1997)
		US5650418A	22 July 1997 (22-07-1997)
		US5702672A	30 December 1997 (30-12-1997)
		US5766556A	16 June 1998 (16-06-1998)
		WO9119488A1	26 December 1991 (26-12-1991)
		WO9408711A1	28 April 1994 (28-04-1994)
EP0472053A2	26 February 1992 (26-02-1992)	AT167473T	15 July 1998 (15-07-1998)
		AU636239B2	22 April 1993 (22-04-1993)
		AU8249391A	27 February 1992 (27-02-1992)
		CA2049496A1	21 February 1992 (21-02-1992)
		CA2049496C	04 February 1997 (04-02-1997)
		CN1059519A	18 March 1992 (18-03-1992)
		CN1036650C	10 December 1997 (10-12-1997)
		CN1136036A	20 November 1996 (20-11-1996)
		DE69129611T2	17 December 1998 (17-12-1998)
		EP0472053B1	17 June 1998 (17-06-1998)
		FI913815A	21 February 1992 (21-02-1992)
		HU912676D0	28 January 1992 (28-01-1992)
		HUT59663A	29 June 1992 (29-06-1992)
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