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(54) Title: HYDROCARBYLSULFONYL-SUBSTITUTED PYRIDINES AND THEIR USE IN THE TREATMENT OF CANCER



(I)

(57) Abstract: There is provided compounds of formula I (I) or pharmaceutically-acceptable salts thereof, wherein L, R¹, R², R³ and X have meanings provided in the description, which compounds are useful in the treatment of cancers.

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HYDROCARBYLSULFONYL-SUBSTITUTED PYRIDINES AND THEIR USE IN THE TREATMENT OF CANCER

Field of the Invention

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The present invention relates to novel compounds and compositions, and their use in the treatment of cancer. In particular, the invention relates to novel compounds, compositions and methods for the treatment of cancers through specific and potent inhibition of thioredoxin reductase with minimal inhibition of glutathione reductase.

10

Background of the Invention

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The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

20

Although the increased understanding of the role of oncogenes, and the development of new anticancer treatments and diagnosis, have improved the life expectancy of cancer patients, there is still a high medical need to find more effective and less toxic treatments for cancers, such as breast cancer, head and neck cancer, melanoma, glioblastoma, leukaemia, and colon and lung cancer.

25

It is well known that excessive production of reactive oxygen species is a common feature of cancer cells due to their distorted metabolism and exaggerated replicative drive. Cancer cells are able to survive their unnaturally high production of reactive oxygen species through concomitant upregulation of robust antioxidant defence mechanisms.

30

Radiotherapy and chemotherapy protocols compete against antioxidant defence mechanisms, further increasing reactive oxygen species levels beyond adapted thresholds through targeting of multiple cellular compartments and targets. Thus, sensitization of cancer cells to their endogenous reactive oxygen species production can additionally induce cancer cell death. In contrast, normal cells have reserved capacity to combat oxidative stress. With this in mind, it has been suggested that if reactive oxygen species levels could be further increased, or the cellular defences against reactive oxygen species could be deliberately impaired, these systems may serve to allow for a possible therapeutic mechanism of action for anticancer therapy (Luo, J., Solimini, N.L. & Elledge, S.J., *Cell*,

35

136, 823 (2009); Trachootham, D., Alexandre, J. & Huang, P., *Nat Rev Drug Discov*, **8**, 579 (2009)).

Increased tolerance to oxidative stress of cancer cells can occur through activation of the two major antioxidant systems in human and other mammals: the glutathione and thioredoxin systems. Concomitant inhibition of the glutathione and thioredoxin systems therefore has been proposed as a mechanism for anticancer activity (Harris, I.S., *et al.*, *Cancer Cell* **27**, 211 (2015); Mandal, P.K., *et al.*, *Cancer Res*, **70**, 9505-9514 (2010); Fath, M.A., Ahmad, I.M., Smith, C.J., Spence, J. & Spitz, D.R., *Clin Cancer Res.*, **17**, 6206 (2011)).

Cytosolic thioredoxin reductase is a key enzyme for the whole cytosolic thioredoxin system, which in turn is responsible for a cascade of signalling events and antioxidant activities (Arnér, E. S. J., *Biochim Biophys Acta*, **1790**, 495-526 (2009)). A high expression level of cytosolic thioredoxin reductase in various cancers correlates to a more severe cancer phenotype, chemotherapeutic drug resistance, and poor prognosis.

However, as normal, non-cancerous cells require either the glutathione or the thioredoxin systems for survival (Arnér, E.S. & Holmgren, A., *Eur J Biochem*, **267**, 6102 (2000); Lillig, C.H., Berndt, C. & Holmgren, A., *Biochim Biophys Acta*, **1780**, 1304 (2008); Prigge, J.R., *et al.*, *Free Radic Biol Med*, **52**, 803 (2012)), it is difficult to therapeutically target both of these antioxidant systems without triggering major unwanted toxicities.

It has been suggested that several chemotherapeutic protocols for anticancer treatment involve inhibition of cytosolic thioredoxin reductase together with other components of the cell (Becker, K. *et al.* *Eur. J. Biochem.*, **267**, 6118 (2000)). For example, motexafin gadolinium, marketed as a radiosensitizing drug and thioredoxin reductase inhibitor, is also a potent ribonucleotide reductase inhibitor (Hashemy, S. I., Ungerstedt, J. S., Zahedi Avval, F. & Holmgren, A., *J Biol Chem*, **281**, 10691 (2006)). Auranofin, a potent thioredoxin reductase inhibitor, concomitantly localizes to and damages the mitochondria (Cox, A.G., Brown, K.K., Arnér, E.S. & Hampton, M.B., *Biochem Pharmacol*, **76**, 1097-1109 (2008); Krishnamurthy, D., *et al.*, *J Med Chem*, **51**, 4790 (2008); Rigobello, M.P., Folda, A., Baldoin, M.C., Scutari, G. & Bindoli, A., *Free Radic Res*, **39**, 687 (2005)).

The structure and function of thioredoxin reductase, biological effects associated with its inhibition, such as in its potential as a mechanism for cancer treatment, and compounds

previously disclosed as potential inhibitors are reviewed in Zhang, B. *et al.*, *Expert Opinion on Therapeutic Patents* (2016).

5 The present innovation relates to the development and usage of novel compounds specifically and potently targeting cytosolic thioredoxin reductase, without targeting the closely related flavoprotein glutathione reductase that supports the function of the glutathione system, as a means of obtaining a new efficient anticancer treatment that at the same time presents limited toxic side effects.

10 In particular, the inventors have unexpectedly found that novel, pyridinyl sulfone compounds may achieve highly selective inhibition of cytosolic thioredoxin reductase by acting as strongly-binding (and, in some cases, effectively irreversible) inhibitors of the enzyme without causing significant inhibition of glutathione reductase.

15 Specifically, by potently inhibiting thioredoxin reductase selectively over glutathione reductase, the novel pyridinyl sulfones have the potential to be effective against cancer forms having dysfunctional redox status, with minimal general toxic effects to normal cells. Such inhibitors may also be a suitable adjuvant therapy to be used in conjunction with radiotherapies or other chemotherapeutic approaches. Based on these surprising results,
20 the present invention aims to provide new treatments for cancers.

Certain alkylsulfonyl-nitropyridines have been synthesized or alleged commercially available but with no use ascribed to them, as described in: Talik, Z., *et al.*, *Prace Naukowe Akademii Ekonomicznej imienia Oskara Langego we Wroclawiu* **255**, 137 (1984); Talik, T.;
25 Talik, Z., *Pol. J. Chem.*, **52**, 163 (1978) and Moshchitskii, S. D., *et al.*, *Khim. Get. Soedin.*, 802 (1975).

International patent application WO 03/093250 claims e.g. 6-methoxy-2-(methylsulfonyl)-3-nitropyridine as an intermediate for the synthesis of compounds used for CNS related
30 disorders.

European patent application EP 220857 claims e.g. 6-(isobutylsulfonyl)-5-nitropyridin-2-yl methanesulfonate and its use as an insecticide, acaricide and nematocide.

35 Jamoulle, J.C., *et al.*, *Ann. Pharm. Fr.* **41**, 61 (1983) describes certain alkylsulfonyl-nitropyridines as parasitocidals.

Certain alkylsulfonyl-nitropyridines are mentioned in Jamouille, J.C.; Lapiere, C.L., J. Pharm. Belg. **30**, 114 (1975).

5 US patent application 4456469 and European patent application EP 35893 describe certain alkylsulfonyl-nitropyridines as herbicides.

International patent application WO 2015/081813 and Chinese patent applications CN 105503827, CN 105085483, CN 104987324 and CN 10467221 describe compounds useful in the treatment of cancer where certain nitropyridines substituted with an
10 alkylsulfonyl group have been used as synthetic intermediates.

International patent application WO 97/08147 and German patent application DE 19531348 describe certain alkylsulfonylnitropyridines as fungicides for agricultural use.

15 International patent application WO 99/36391 describes two benzenesulfonamides as therapeutic agents. Neither contains a pyridine ring having a nitro substituent.

International patent application WO 2007/124546 describes 3-cyano-4,6-diarylsubstituted pyridines useful for the treatment of viral infections. However, none of the exemplified
20 compounds contain a nitro substituted pyridine linked *via* a sulfonyl moiety to an optionally substituted alkyl group.

International patent application WO 95/29897 describes certain (H⁺/K⁺)ATPase inhibitors and their use in treating viral infections. However, none of the exemplified compounds
25 contain a nitro substituted pyridine linked *via* a sulfonyl moiety to an optionally substituted alkyl group.

International patent application WO 98/54139 describes a process for the preparation of pyridines linked to, for example, a propyl group *via* a sulfonyl group. However, none of the
30 exemplified compounds contain a nitro substituted pyridine linked *via* a sulfonyl moiety to an optionally substituted alkyl group.

International patent applications WO 99/010320 and WO 99/017777 describe certain compounds and their use in treating conditions such as cancer. However, none of the
35 exemplified compounds contain a nitro substituted pyridine linked *via* a sulfonyl moiety to an optionally substituted alkyl group.

International patent application WO 01/064642 describes certain compounds and their use in treating coagulation disorders. However, none of the exemplified compounds contain a nitro substituted pyridine linked *via* a sulfonyl moiety to an optionally substituted alkyl group.

5

Chinese patent application CN 102206172 describes certain antiviral compounds. However, none of the exemplified compounds contain a nitro substituted pyridine linked *via* a sulfonyl moiety to an optionally substituted alkyl group.

10 International patent application WO 2007/076875 describes compounds acting on the serotonin transporter. However, none of the exemplified compounds contain a nitro substituted pyridine linked *via* a sulfonyl moiety to an optionally substituted alkyl group.

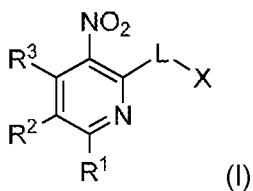
Detailed Description of the Invention

15

It has now been found that certain nitro substituted pyridines linked *via* a sulfonyl moiety to an optionally substituted alkyl, alkenyl or alkynyl group have surprising properties which render such compounds useful in the treatment of cancers.

20 Compounds of the invention

In a first aspect of the invention, there is provided a compound of formula I



25

or a pharmaceutically acceptable salt thereof, wherein:

L represents $-S(O)_n-$;

30 n represents 2 or 1;

X represents C_{1-12} alkyl, C_{2-12} alkenyl or C_{2-12} alkynyl each optionally substituted by one or more groups independently selected from Y;

R¹ represents halo, -N(R^{j1})R^{k1}, -OR^{l1} or -SR^{m1};

R² and R³ each independently represent H, halo, R^{a1}, -CN, -A^{a1}-C(Q^{a1})R^{b1}, -A^{b1}-C(Q^{b1})N(R^{c1})R^{d1}, -A^{c1}-C(Q^{c1})OR^{e1}, -A^{d1}-S(O)_pR^{f1},
 5 -A^{e1}-S(O)_pN(R^{g1})R^{h1}, -A^{f1}-S(O)_pORⁱ¹, -N₃, -N(R^{j1})R^{k1}, -N(H)CN, -NO₂, -ONO₂, -OR^{l1} or -SR^{m1};

each A^{a1} to A^{f1} independently represents a single bond, -N(R^{p1})- or -O-;

10 each Q^{a1} to Q^{c1} independently represents =O, =S, =NRⁿ¹ or =N(OR^{o1});

each R^{a1} and R^{f1} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl each optionally substituted by one or more groups independently selected from G^{1a}, heterocyclyl optionally substituted by one or more groups independently selected from G^{1b}, aryl
 15 optionally substituted by one or more groups independently selected from G^{1c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{1d};

each R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{g1}, R^{h1}, Rⁱ¹, R^{j1}, R^{k1}, R^{l1}, R^{m1}, Rⁿ¹, R^{o1} and R^{p1} independently represents H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl each optionally substituted by one or
 20 more groups independently selected from G^{1a}, heterocyclyl optionally substituted by one or more groups independently selected from G^{1b}, aryl optionally substituted by one or more groups independently selected from G^{1c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{1d};

25 any of R^{c1} and R^{d1}, R^{g1} and R^{h1} and/or R^{j1} and R^{k1} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^{1b}, C₁₋₃ alkyl, C₂₋₃ alkenyl or C₂₋₃ alkynyl each optionally substituted by one or more G^{1a}, and =O;

30 each G^{1a} and G^{1b} independently represents halo, -CN, -N(R^{a2})R^{b2}, -OR^{c2}, -SR^{d2} or =O;

each R^{a2}, R^{b2}, R^{c2} and R^{d2} independently represents H, or C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl each optionally substituted by one or more fluoro; or

35 R^{a2} and R^{b2} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom

and which ring optionally is substituted by one or more groups independently selected from fluoro and C₁₋₃ alkyl, C₂₋₃ alkenyl or C₂₋₃ alkynyl each optionally substituted by one or more fluoro;

5 each Y independently represents halo, R^{a3}, -CN, -A^{a2}-C(Q^{a2})R^{b3}, -A^{b2}-C(Q^{b2})N(R^{c3})R^{d3}, -A^{c2}-C(Q^{c2})OR^{e3}, -A^{d2}-S(O)_qR^{f3}, -A^{e2}-S(O)_qN(R^{g3})R^{h3}, -A^{f2}-S(O)_qORⁱ³, -N₃, -N(R^{j3})R^{k3}, -N(H)CN, -NO₂, -ONO₂, -OR^{l3}, -SR^{m3} or =O;

each Q^{a2} to Q^{c2} independently represents =O, =S, =NRⁿ³ or =N(OR^{o3});

10

each A^{a2} to A^{f2} independently represents a single bond, -N(R^{p3})- or -O-;

each R^{a3} independently represents heterocyclyl optionally substituted by one or more groups independently selected from G^{2b}, aryl optionally substituted by one or more groups
15 independently selected from G^{2c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{2d};

each R^{f3} independently represents C₁₋₆ alkyl optionally substituted by one or more groups independently selected from G^{2a}, heterocyclyl optionally substituted by one or more groups
20 independently selected from G^{2b}, aryl optionally substituted by one or more groups independently selected from G^{2c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{2d};

each R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{g3}, R^{h3}, Rⁱ³, R^{j3}, R^{k3}, R^{l3}, R^{m3}, Rⁿ³, R^{o3} and R^{p3} independently
25 represents H, C₁₋₆ alkyl optionally substituted by one or more groups independently selected from G^{2a}, heterocyclyl optionally substituted by one or more groups independently selected from G^{2b}, aryl optionally substituted by one or more groups independently selected from G^{2c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{2d}; or

30

any two R^{c3} and R^{d3}, R^{g3} and R^{h3} and/or R^{j3} and R^{k3} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from heterocyclyl optionally substituted by one or
35 more groups independently selected from G^{2b}, aryl optionally substituted by one or more groups independently selected from G^{2c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{2d}, and =O;

each G^{2a} independently represents halo, $-CN$, $-N(R^{i4})R^{k4}$, $-OR^{l4}$, $-SR^{m4}$ or $=O$;

each G^{2b} independently represents halo, R^{a4} , $-CN$, $-N(R^{i4})R^{k4}$, $-OR^{l4}$, $-SR^{m4}$ or $=O$;

5

each G^{2c} and G^{2d} independently represents halo, R^{a4} , $-CN$, $-A^{a3}-C(Q^{a4})R^{b4}$, $-A^{b3}-C(Q^{b3})N(R^{c4})R^{d4}$, $-A^{c3}-C(Q^{c3})OR^{e4}$, $-A^{d3}-S(O)_qR^{f4}$, $-A^{e3}-S(O)_qN(R^{g4})R^{h4}$, $-A^{f3}-S(O)_qOR^{i4}$, $-N_3$, $-N(R^{i4})R^{k4}$, $-N(H)CN$, $-NO_2$, $-ONO_2$, $-OR^{l4}$ or $-SR^{m4}$;

10 each Q^{a3} to Q^{c3} independently represents $=O$, $=S$, $=NR^{n4}$ or $=N(OR^{o4})$;

each A^{a3} to A^{f3} independently represents a single bond, $-N(R^{p4})-$ or $-O-$;

15 each R^{a4} and R^{f4} independently represents C_{1-6} alkyl optionally substituted by one or more groups independently selected from G^{3a} , heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} , aryl optionally substituted by one or more groups independently selected from G^{3c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{3d} ;

20 each R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{i4} , R^{j4} , R^{k4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} and R^{p4} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^{3a} or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} , aryl optionally substituted by one or more groups independently selected from G^{3c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{3d} ; or

25 any of R^{c4} and R^{d4} , R^{g4} and R^{h4} and/or R^{i4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected G^{3b} ;

30

each G^{3a} and G^{3b} independently represents halo, R^{a5} , $-CN$, $-N(R^{b5})R^{c5}$, $-OR^{d5}$, $-SR^{e5}$ or $=O$;

35 each R^{a5} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^4 ;

each R^{b5} , R^{c5} , R^{d5} and R^{e5} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^4 ;
or

5 each R^{b5} and R^{c5} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^4 ;

10 each G^4 independently represents halo, R^{a6} , -CN, -N(R^{b6}) R^{c6} , -OR^{d6} or =O;

each R^{a6} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more fluoro;

15 each R^{b6} , R^{c6} and R^{d6} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more fluoro; and

each p and q independently represents 1 or 2,

20 which compounds may be referred to herein as compounds of the invention,

but with the provisos that the compound of formula I does not represent:

(A)

- 25 2-((1-chloropropan-2-yl)sulfonyl)-6-methoxy-3-nitropyridine,
2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethane-1-sulfonamide,
2-((2-chloroethyl)sulfonyl)-6-methoxy-3-nitropyridine,
2-((4-chlorobutan-2-yl)sulfonyl)-6-methoxy-3-nitropyridine,
2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethane-1-sulfonyl chloride,
30 2-((3-chloro-2-methylpropyl)sulfonyl)-6-methoxy-3-nitropyridine,
2-((3-chloropropyl)sulfonyl)-6-methoxy-3-nitropyridine,
6-methoxy-3-nitro-2-(vinylsulfonyl)pyridine,
6-methoxy-2-(methylsulfonyl)-3-nitropyridine,
6-(2,6-dichloro-4-(trifluoromethyl)phenoxy)-2-(methylsulfonyl)-3-nitropyridine,
35 6-(2,6-dichloro-4-(trifluoromethoxy)phenoxy)-2-(methylsulfonyl)-3-nitropyridine, or
6-(2,6-dichloro-4-(trifluoromethyl)phenoxy)-2-(ethylsulfonyl)-3-nitropyridine;

or

(B)

2-(butylsulfinyl)-3-nitro-pyridine;

5

or

(C)

3-[(3-nitro-2-pyridinyl)sulfinyl]-2-propenoic acid methyl ester,

10 3-[(3-nitro-2-pyridinyl)sulfinyl]-2-propenoic acid ethyl ester,

6-[(2-methylpropyl)sulfinyl]-5-nitro-2-methanesulfonate-2-pyridinol,

3-chloro-2-[(6-chloro-3-nitro-2-pyridinyl)sulfinyl]-benzoic acid ethyl ester,

3-nitro-2-[(4-piperidinylmethyl)sulfinyl]-pyridine,

3-nitro-2-[(3-pyrrolidinylmethyl)sulfinyl]-pyridine,

15 3-nitro-2-[(3-piperidinylmethyl)sulfinyl]-pyridine,

3-nitro-2-[(2-pyrrolidinylmethyl)sulfinyl]-pyridine,

3-nitro-2-[(2-piperidinylmethyl)sulfinyl]-pyridine,

4-[[[(3-nitro-2-pyridinyl)sulfinyl]methyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester,

3-[[[(3-nitro-2-pyridinyl)sulfinyl]methyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester,

20 3-[[[(3-nitro-2-pyridinyl)sulfinyl]methyl]-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester,

2-[[[(3-nitro-2-pyridinyl)sulfinyl]methyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester,

2-[[[(3-nitro-2-pyridinyl)sulfinyl]methyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester,

6-[2,6-dichloro-4-(trifluoromethoxy)phenoxy]-2-(methylsulfinyl)-3-nitro-pyridine, or

25 6-[2,6-dichloro-4-(trifluoromethyl)phenoxy]-2-(ethylsulfinyl)-3-nitro-pyridine.

For the avoidance of doubt, compounds of formula I and pharmaceutically acceptable salts thereof, not including the provisos, may be referred to herein as compounds of the invention. Similarly, references to compounds of the first aspect of the invention will refer to compounds of formula I as defined in the first aspect of the invention, including the provisos, and pharmaceutically acceptable salts thereof. As such, compounds of the first aspect of the invention represent a particular embodiment of compounds of the invention.

30

The skilled person will understand that references herein to compounds of the invention will include references to all embodiments and particular forms thereof.

35

Unless indicated otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

- 5 Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques
10 (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

- Particular acid addition salts that may be mentioned include carboxylate salts (e.g.
15 formate, acetate, trifluoroacetate, propionate, isobutyrate, heptanoate, decanoate, caprate, caprylate, stearate, acrylate, caproate, propiolate, ascorbate, citrate, glucuronate, glutamate, glycolate, α -hydroxybutyrate, lactate, tartrate, phenylacetate, mandelate, phenylpropionate, phenylbutyrate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, dinitrobenzoate, *o*-acetoxybenzoate, salicylate,
20 nicotinate, isonicotinate, cinnamate, oxalate, malonate, succinate, suberate, sebacate, fumarate, malate, maleate, hydroxymaleate, hippurate, phthalate or terephthalate salts), halide salts (e.g. chloride, bromide or iodide salts), sulfonate salts (e.g. benzenesulfonate, methyl-, bromo- or chloro-benzenesulfonate, xylenesulfonate, methanesulfonate, ethanesulfonate, propanesulfonate, hydroxyethanesulfonate, 1- or 2- naphthalene-
25 sulfonate or 1,5-naphthalenedisulfonate salts) or sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate or nitrate salts, and the like.

- Particular base addition salts that may be mentioned include salts formed with alkali metals
30 (such as Na and K salts), alkaline earth metals (such as Mg and Ca salts), organic bases (such as ethanolamine, diethanolamine, triethanolamine, tromethamine and lysine) and inorganic bases (such as ammonia and aluminium hydroxide). More particularly, base addition salts that may be mentioned include Mg, Ca and, most particularly, K and Na salts.

35

For the avoidance of doubt, compounds of the invention may exist as solids, and thus the scope of the invention includes all amorphous, crystalline and part crystalline forms

thereof, and may also exist as oils. Where compounds of the invention exist in crystalline and part crystalline forms, such forms may include solvates, which are included in the scope of the invention. Compounds of the invention may also exist in solution.

- 5 Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

- Compounds of the invention may also exhibit tautomerism. All tautomeric forms and
10 mixtures thereof are included within the scope of the invention.

- Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation.
- 15 The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material
20 with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution); for example, with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures
25 thereof are included within the scope of the invention.

As used herein, references to halo and/or halogen will independently refer to fluoro, chloro, bromo and iodo (for example, fluoro and chloro).

- 30 Unless otherwise specified, C_{1-z} alkyl groups (where z is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-z} cycloalkyl group). When there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic (so forming a C_{3-z} partial cycloalkyl
35 group). Part cyclic alkyl groups that may be mentioned include cyclopropylmethyl and cyclohexylethyl. When there is a sufficient number of carbon atoms, such groups may also be multicyclic (e.g. bicyclic or tricyclic) or spirocyclic.

Unless otherwise specified, C_{2-z} alkenyl groups (where z is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{4-z} cycloalkenyl group). When there is a sufficient number (i.e. a minimum of five) of carbon atoms, such groups may also be part cyclic. Part cyclic alkenyl groups that may be mentioned include cyclopentenylmethyl and cyclohexenylmethyl. When there is a sufficient number of carbon atoms, such groups may also be multicyclic (e.g. bicyclic or tricyclic) or spirocyclic.

Unless otherwise specified, C_{2-z} alkynyl groups (where z is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, be branched-chain.

For the avoidance of doubt, the skilled person will understand that the term alkyl will refer to saturated hydrocarbon moieties, whereas the term alkenyl will refer to unsaturated hydrocarbon moieties containing at least one carbon-carbon double bond and the term alkynyl will refer to unsaturated hydrocarbon moieties containing at least one carbon-carbon triple bond, which alkyl, alkenyl and alkynyl groups may be referred to collectively as hydrocarbonyl groups. Further, such unsaturated hydrocarbon moieties will be referred to by reference to the highest degree of unsaturation comprised therein (e.g. a hydrocarbon moiety comprising at least one carbon-carbon double bond and at least one carbon-carbon triple bond will be referred to as alkynyl, although such moieties may also be referred to using terms such as "alkenyl alkynyl" and the like).

As used herein, the term heterocyclyl may refer to non-aromatic monocyclic and bicyclic heterocyclyl groups (which groups may further be bridged) in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten and, most preferably, between three and eight, e.g. a 5- or 6-membered heterocyclyl group). Further, such heterocyclyl groups may be saturated, forming a heterocycloalkyl, or unsaturated containing one or more carbon-carbon or, where possible, carbon-heteroatom or heteroatom-heteroatom double and/or triple bonds, forming for example a C_{2-z} (e.g. C_{4-z}) heterocycloalkenyl (where z is the upper limit of the range) or a C_{7-z} heterocycloalkynyl group. C_{2-z} heterocyclyl groups that may be mentioned include 7-azabicyclo-[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octanyl, aziridinyl, azetidiny, 2,3-dihydroisothiazolyl, dihydropyranyl, dihydropyridinyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl

(including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazoliny, isothiazolidinyl, morpholinyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, 5 pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuryl, tetrahydropyridinyl (such as 1,2,3,4-tetrahydropyridinyl and 1,2,3,6-tetrahydropyridinyl), thietanyl, thiiranyl, thiolanyl, tetrahydrothiopyranyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocyclyl groups may, where appropriate, be located on any atom in the ring system including a 10 heteroatom. Further, in the case where the substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocyclyl group, forming a so-called "spiro"-compound. The point of attachment of heterocyclyl groups may be *via* any atom in the ring system including (where appropriate) a further heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present 15 as part of the ring system. Heterocyclyl groups may also be in the *N*- or *S*- oxidised form.

At each occurrence when mentioned herein, particular heterocyclyl groups that may be mentioned include 3- to 8-membered heterocyclyl groups (e.g. a 4- to 6-membered heterocyclyl group).

20

As may be used herein, the term aryl includes references to C₆₋₁₄ (e.g. C₆₋₁₀) aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C₆₋₁₀ aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (e.g. phenyl, naphthyl and the like, such 25 as phenyl). For the avoidance of doubt, the point of attachment of substituents on aryl groups may be *via* any carbon atom of the ring system.

As may be used herein, the term heteroaryl (or heteroaromatic) includes references to 5- to 14- (e.g. 5- to 10-) membered heteroaromatic groups containing one or more 30 heteroatoms selected from oxygen, nitrogen and/or sulfur. Such heteroaryl groups may comprise one, two, or three rings, of which at least one is aromatic. Substituents on heteroaryl/heteroaromatic groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl/heteroaromatic groups may be *via* any atom in the ring system including (where appropriate) a heteroatom. 35 Bicyclic heteroaryl/heteroaromatic groups may comprise a benzene ring fused to one or more further aromatic or non-aromatic heterocyclic rings, in which instances, the point of attachment of the polycyclic heteroaryl/heteroaromatic group may be *via* any ring including

the benzene ring or the heteroaryl/heteroaromatic or heterocyclyl ring. Examples of heteroaryl/heteroaromatic groups that may be mentioned include pyridinyl, pyrrolyl, furanyl, thiophenyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, imidazolyl, imidazopyrimidinyl, imidazothiazolyl, thienothiophenyl, pyrimidinyl, furopyridinyl, indolyl, azaindolyl, pyrazinyl, pyrazolopyrimidinyl, indazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzofuranyl, benzothiophenyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl and purinyl. The oxides of heteroaryl/ heteroaromatic groups are also embraced within the scope of the invention (e.g. the *N*-oxide). As stated above, heteroaryl includes polycyclic (e.g. bicyclic) groups in which one ring is aromatic (and the other may or may not be aromatic). Hence, other heteroaryl groups that may be mentioned include e.g. benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, dihydrobenzo[*d*]isothiazole, 3,4-dihydrobenz[1,4]oxazinyl, dihydrobenzothiophenyl, indolinyl, 5*H*,6*H*,7*H*-pyrrolo[1,2-*b*]pyrimidinyl, 1,2,3,4-tetrahydroquinolinyl, thiochromanyl and the like.

15

For the avoidance of doubt, as used herein, references to heteroatoms will take their normal meaning as understood by one skilled in the art. Particular heteroatoms that may be mentioned include phosphorus, selenium, tellurium, silicon, boron, oxygen, nitrogen and sulfur (e.g. oxygen, nitrogen and sulfur).

20

For the avoidance of doubt, references to polycyclic (e.g. bicyclic) groups (e.g. when employed in the context of heterocyclyl groups) will refer to ring systems wherein more than two scissions would be required to convert such rings into a straight chain, with the minimum number of such scissions corresponding to the number of rings defined (e.g. the term bicyclic may indicate that a minimum of two scissions would be required to convert the rings into a straight chain). For the avoidance of doubt, the term bicyclic (e.g. when employed in the context of heterocyclyl groups) may refer to groups in which the second ring of a two-ring system is formed between two adjacent atoms of the first ring, and may also refer to groups in which two non-adjacent atoms are linked by either an alkylene or heteroalkylene chain (as appropriate), which later groups may be referred to as bridged.

For the avoidance of doubt, when an aryl or an heteroaryl group is substituted with a group *via* a double bond, such as =O, it is understood that the aryl or heteroaryl group is partly aromatic, i.e. the aryl or heteroaryl group consists of at least two rings where at least one ring is not aromatic.

35

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature).

5 All isotopes of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention. Hence, the compounds of the invention also include deuterated compounds, i.e. in which one or more hydrogen atoms are replaced by the hydrogen isotope deuterium.

10 For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in the situation in which two or more Y groups are present, those Y groups may be the same or different. Similarly, where two or more Y groups are present and each represent R^{a3} , the R^{a3} groups in
15 question may be the same or different. Likewise, when more than one R^{a1} is present and each independently represents C_{1-6} alkyl substituted by one or more G^{1a} group, the identities of each G^{1a} are in no way interdependent.

For the avoidance of doubt, when a term such as " A^{a1} to A^{f1} " is employed herein, this will
20 be understood by the skilled person to mean A^{a1} , A^{b1} , A^{c1} , A^{d1} , A^{e1} and A^{f1} inclusively. Unless otherwise stated, the same reasoning will apply to other such terms used herein.

The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include
25 those that are sufficiently robust to survive isolation, e.g. from a reaction mixture, to a useful degree of purity.

All embodiments of the invention and particular features mentioned herein may be taken in isolation or in combination with any other embodiments and/or particular features
30 mentioned herein (hence describing more particular embodiments and particular features as disclosed herein) without departing from the disclosure of the invention.

Particular compounds of the invention that may be mentioned include those in which n represents 2.

35

Further compounds of the invention that may be mentioned include those in which n represents 1.

Particular compounds of the invention that may be mentioned include those in which X represents C₁₋₈ alkyl, C₂₋₈ alkenyl or C₂₋₈ alkynyl (e.g. C₂₋₈ alkyl).

- 5 More particularly, compounds of the invention that may be mentioned include those in which:

when X represents C₁ alkyl (such as in embodiments where X represents C₁₋₈ alkyl), X is substituted with at least one (e.g. one) Y group; and/or (e.g. and)

10

when X represents other than C₁ alkyl (e.g. where X represents C₂₋₈ alkyl, such as in embodiments where X represents C₁₋₈ alkyl), X is optionally substituted with at least one (e.g. one) Y group (e.g. X is unsubstituted).

- 15 Thus, in particular embodiments of compounds of the invention, X does not represent unsubstituted C₁ alkyl (although, for the avoidance of doubt, such a feature of any embodiments described herein is not herein referred to as a "proviso").

- Further compounds of the invention that may be mentioned include those in which X represents unsubstituted C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl or C₂₋₁₂ alkynyl (e.g. C₂₋₈ alkyl, C₂₋₈ alkenyl or C₂₋₈ alkynyl, such as C₂₋₈ alkyl).

- Yet further compounds of the invention that may be mentioned include those in which X represents unsubstituted C₃₋₈ alkyl, C₃₋₈ alkenyl or C₃₋₈ alkynyl (e.g. C₃₋₈ alkyl, such as cyclic or part cyclic C₃₋₆ alkyl).

- Yet further compounds of the invention that may be mentioned include those in which X represents unsubstituted C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl or C₂₋₁₂ alkynyl (e.g. C₂₋₈ alkyl, C₂₋₈ alkenyl or C₂₋₈ alkynyl, such as C₂₋₈ alkyl).

30

Particular compounds of the invention that may be mentioned include those in which each Y independently represents halo, R^{a3}, -CN, -C(O)N(R^{c3})R^{d3}, -N(R^{p3})C(O)R^{b3} (e.g. -N(H)C(O)R^{b3}), -C(O)OR^{e3}, -N(R^{j3})R^{k3}, -OR^{l3}, -SR^{m3} or =O.

- 35 More particular compounds of the invention that may be mentioned include those in which each Y independently represents halo (e.g. fluoro) or, particularly, R^{a3}, -C(O)N(R^{c3})R^{d3}, -N(H)C(O)R^{b3}, -C(O)OR^{e3}, -N(R^{j3})R^{k3} or -OR^{l3}.

Particular compounds of the invention (i.e. compounds of formula I, including compounds of the first aspect of the invention) that may be mentioned include those in which:

- 5 X represents C₂₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₂₋₆ alkyl, such as C₂₋₃ alkyl) substituted by one or more groups independently selected from Y;

each Y independently represents halo, -CN, -A^{a2}-C(O)R^{b3}, -A^{b2}-C(O)N(R^{c3})R^{d3}, -A^{c2}-C(O)OR^{e3}, -A^{d2}-S(O)_qR^{f3}, -A^{e2}-S(O)_qN(R^{g3})R^{h3}, -N(Rⁱ³)R^{k3}, -OR^{l3}, -SR^{m3} or =O;

10

each Q^{a2} to Q^{c2} independently represents =O, =S, =NRⁿ³ or =N(OR^{o3});

each A^{a2} to A^{e2} independently represents a single bond, -N(R^{p3})- or -O-;

- 15 each R^{f2} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G^{2a}, heterocyclyl optionally substituted by one or more groups independently selected from G^{2b}, aryl optionally substituted by one or more groups independently selected from G^{2c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{2d};

20

each R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{g3}, R^{h3}, R^{j3}, R^{k3}, R^{l3}, R^{m3}, Rⁿ³, R^{o3} and R^{p3} independently represents H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G^{2a}, heterocyclyl optionally substituted by one or more groups independently selected from G^{2b}, aryl optionally substituted by one or more groups independently selected from G^{2c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{2d}, or

25

any two R^{c3} and R^{d3}, R^{g3} and R^{h3} and/or R^{j3} and R^{k3} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from heterocyclyl optionally substituted by one or more groups independently selected from G^{2b}, aryl optionally substituted by one or more groups independently selected from G^{2c}, or heteroaryl optionally substituted by one or more groups independently selected from G^{2d}, and =O;

30

- 35 each G^{2a} independently represents halo, -CN, -N(Rⁱ⁴)R^{k4}, -OR^{l4}, -SR^{m4} or =O;

each G^{2b} independently represents halo, R^{a4}, -CN, -N(Rⁱ⁴)R^{k4}, -OR^{l4}, -SR^{m4} or =O;

each G^{2c} and G^{2d} independently represents halo, R^{a4} , $-CN$, $-A^{a3}-C(Q^{a3})R^{b4}$, $-A^{b3}-C(Q^{b3})N(R^{c4})R^{d4}$, $-A^{c3}-C(Q^{c4})OR^{e4}$, $-A^{d3}-S(O)_qR^{f4}$, $-A^{e3}-S(O)_qN(R^{g4})R^{h4}$, $-A^{f3}-S(O)_qOR^{i4}$, $-N_3$, $-N(R^{j4})R^{k4}$, $-N(H)CN$, $-NO_2$, $-ONO_2$, $-OR^{l4}$ or $-SR^{m4}$;

5

each Q^{a3} to Q^{c3} independently represents $=O$, $=S$, $=NR^{n4}$ or $=N(OR^{o4})$;

each A^{a3} to A^{f3} independently represents a single bond, $-N(R^{p4})-$ or $-O-$;

10 each R^{a3} and R^{f3} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^{3a} , or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} ;

15 each R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{i4} , R^{j4} , R^{k4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} and R^{p4} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^{3a} or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} , or
 20 any of R^{c4} and R^{d4} , R^{g4} and R^{h4} and/or R^{j4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected G^{3b} ;

25

each G^{3a} and G^{3b} independently represents halo, R^{a5} , $-CN$, $-N(R^{b5})R^{c5}$, $-OR^{d5}$, $-SR^{e5}$ or $=O$;

each R^{a5} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^4 ;

each R^{b5} , R^{c5} , R^{d5} and R^{e5} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^4 , or

30 each R^{b5} and R^{c5} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected G^4 ;

35

each G^4 independently represents halo, R^{a6} , $-CN$, $-N(R^{b6})R^{c6}$, $-OR^{d6}$ or $=O$;

each R^{a6} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) optionally substituted by one or more fluoro;

- 5 each R^{b6} , R^{c6} and R^{d6} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro; and/or (e.g. and)

each p and q independently represents 1 or 2.

- 10 More particular compounds of the invention that may be mentioned include those in which: X represents C_{2-8} alkyl (e.g. C_{2-5} alkyl) substituted by one or more groups independently selected from Y;

- each Y independently represents fluoro, $-N(H)-C(O)R^{b3}$, $-C(O)OR^{e3}$, $-N(H)-S(O)_2R^{f3}$,
15 $-S(O)_2R^{f3}$, $-N(H)-S(O)_qN(R^{g3})R^{h3}$, $-N(R^{j3})R^{k3}$ or $-OR^{l3}$;

- each R^{b3} , R^{e3} , R^{f3} , R^{g3} , R^{h3} , R^{e3} , R^{j3} , R^{k3} and R^{l3} independently represents H or C_{1-3} alkyl, or
any two R^{g3} and R^{h3} and/or R^{j3} and R^{k3} are linked together to form, together with the
nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally
20 contains one further nitrogen and which ring optionally is substituted by one or more C_{1-3}
alkyl.

Yet more particular compounds of the invention that may be mentioned include those in which:

25

X represents C_{2-5} alkyl, C_{2-5} alkenyl or C_{2-5} alkynyl (e.g. C_{2-5} alkyl) substituted by one or more groups independently selected from Y;

each Y independently represents fluoro, $-N(R^{j3})R^{k3}$ or $-OR^{l3}$; and/or

30

each R^{j3} , R^{k3} and R^{l3} independently represents H or C_{1-3} alkyl (e.g. $-CH_3$), or
 R^{j3} and R^{k3} are linked together to form, together with the nitrogen atom to which they are
attached, a 3- to 6-membered ring (e.g. a 5- to 6-membered ring), which ring optionally
contains one further nitrogen and which ring optionally is substituted by one or more (e.g.
35 one) C_{1-3} alkyl (e.g. $-CH_3$).

Particular compounds of the invention that may be mentioned include those in which:

X represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl, such as C₁₋₄ alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

5

Y represents R^{a3};

R^{a3} represents heterocyclyl optionally substituted by one or more groups independently selected from G^{2b};

10

each G^{2b} independently represents halo, R^{a4}, -CN, -C(O)R^{b4}, -N(R^{j4})R^{k4}, -OR^{l4}, -SR^{m4} or =O;

each R^{a4} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl)

15

each optionally substituted by one or more groups independently selected from G^{3a}, or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b};

each R^{b4}, R^{j4}, R^{k4}, R^{l4} and R^{m4} independently represents H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) optionally substituted by one or more groups independently selected from G^{3a}, or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b}, or

20

R^{j4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected G^{3b};

25

each G^{3a} and G^{3b} independently represents halo, R^{a5}, -CN, -N(R^{b5})R^{c5}, -OR^{d5}, -SR^{e5} or =O; each R^{a5} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G⁴;

30

each R^{b5}, R^{c5}, R^{d5} and R^{e5} independently represents H, or C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G, or

each R^{b5} and R^{c5} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected G⁴;

35

each G^4 independently represents halo, R^{a6} , $-CN$, $-N(R^{b6})R^{c6}$, $-OR^{d6}$ or $=O$;

each R^{a6} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro;

5

each R^{b6} , R^{c6} and R^{d6} independently represents H or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro; and/or (e.g. and)

each p and q independently represents 1 or 2.

10

More particular compounds of the invention that may be mentioned include those in which:

X represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl, such as C_{1-4} alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

15

Y represents R^{a3} ;

R^{a3} represents heterocyclyl optionally substituted by one or more groups independently selected from G^{2b} ;

20

each G^{2b} independently represents fluoro, R^{a4} , $-C(O)R^{b4}$, $-N(R^{i4})R^{k4}$, $-OR^{l4}$ or $=O$;

each R^{a4} independently represents C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl (e.g. C_{1-4} alkyl) each optionally substituted by one or more groups independently selected from G^{3a} ;

25

each R^{b4} , R^{i4} , R^{k4} and R^{l4} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^{3a} ;

30

each G^{3a} independently represents fluoro, R^{a5} , $-OR^{d5}$ or $=O$;

each R^{a5} independently represents C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl (e.g. C_{1-4} alkyl) optionally substituted by one or more fluoro; and/or (e.g. and)

35

each R^{d5} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro.

Yet more particular compounds of the invention that may be mentioned include those in which:

- 5 X represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₄ alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

Y represents R^{a3};

10

R^{a3} represents heterocyclyl optionally substituted by one or more (e.g. one) G^{2b};

each G^{2b} independently represents R^{a4} or -C(O)R^{b4}; and/or (e.g. and)

- 15 each R^{a4} and R^{b4} independently represents C₁₋₄ alkyl (e.g. -CH₃).

Even more particular compounds of the invention that may be mentioned include those in which:

- 20 X represents C₁₋₂ alkyl optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

Y represents R^{a3}; and/or (e.g. and)

- 25 R^{a3} represents piperidiny (e.g. 1-piperidiny), such as unsubstituted piperidiny.

Particular compounds of the invention that may be mentioned include those in which:

- 30 X represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₄ alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

Y represents R^{a3};

- 35 R^{a3} represents aryl optionally substituted by one or more groups independently selected from G^{2c};

each G^{2c} independently represents halo, R^{a4} , $-CN$, $-A^{a3}-C(Q^{a3})R^{b4}$, $-A^{b3}-C(Q^{b3})N(R^{c4})R^{d4}$, $-A^{c3}-C(Q^{c3})OR^{e4}$, $-A^{d3}-S(O)_qR^{f4}$, $-A^{e3}-S(O)_qN(R^{g4})R^{h4}$, $-A^{f3}-S(O)_qOR^{i4}$, $-N_3$, $-N(R^{j4})R^{k4}$, $-N(H)CN$, $-NO_2$, $-ONO_2$, $-OR^{l4}$ or $-SR^{m4}$;

5 each Q^{a3} to Q^{c3} independently represents $=O$, $=S$, $=NR^{n4}$ or $=N(OR^{o4})$;

each A^{a3} to A^{f3} independently represents a single bond, $-N(R^{p4})-$ or $-O-$;

10 each R^{a4} and R^{f4} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^{3a} , or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} ;

15 each R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{i4} , R^{j4} , R^{k4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} and R^{p4} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^{3a} or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} , or any of R^{c4} and R^{d4} , R^{g4} and R^{h4} and/or R^{j4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring 20 optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^{3b} ;

each G^{3a} and G^{3b} independently represents halo, R^{a5} , $-CN$, $-N(R^{b5})R^{c5}$, $-OR^{d5}$, $-SR^{e5}$ or $=O$;
each R^{a5} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl)
25 each optionally substituted by one or more groups independently selected from G^4 ;

each R^{b5} , R^{c5} , R^{d5} and R^{e5} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more groups independently selected from G^4 , or
30 each R^{b5} and R^{c5} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^4 ;

35 each G^4 independently represents halo, R^{a6} , $-CN$, $-N(R^{b6})R^{c6}$, $-OR^{d6}$ or $=O$;

each R^{a6} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro;

each R^{b6} , R^{c6} and R^{d6} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro; and/or (e.g. and)

each p and q independently represents 1 or 2.

More particular compounds the invention that may be mentioned include those in which:

10

X represents C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl (e.g. C_{1-4} alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

15 Y represents R^{a3} ;

R^{a3} represents aryl optionally substituted by one or more (e.g. one or two) groups independently selected from G^{2c} ;

20 each G^{2c} independently represents halo, R^{a4} , $-CN$, $-A^{a3}-C(O)R^{b4}$, $-A^{b3}-C(O)N(R^{c4})R^{d4}$, $-A^{c3}-C(O)OR^{e4}$, $-A^{d3}-S(O)_qR^{f4}$, $-A^{e3}-S(O)_qN(R^{g4})R^{h4}$, $-N(R^{i4})R^{k4}$ or $-OR^{l4}$;

each A^{a3} to A^{c3} independently represents a single bond or $-N(R^{p4})-$;

25 each R^{a4} and R^{f4} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro;

each R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{j4} , R^{k4} , R^{l4} and R^{p4} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro, or

30

any of R^{c4} and R^{d4} , R^{g4} and R^{h4} and/or R^{j4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^{3b} ;

35

each G^{3b} independently represents fluoro, R^{a5} or $=O$;

each R^{a4} independently represents C_{1-3} alkyl optionally substituted by one or more fluoro; and/or (e.g. and)

each p and q independently represents 1 or 2.

5

Yet more particular compounds of the invention that may be mentioned include those in which:

10 X represents C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl (e.g. C_{1-4} alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

Y represents R^{a3} ;

15 R^{a3} represents aryl optionally substituted by G^{2c} ;

G^{2c} represents halo, R^{a4} , -CN, -C(O)N(R^{c4}) R^{d4} , -C(O)OR^{e4}, -S(O)₂R^{f4}, -S(O)₂N(R^{g4}) R^{h4} , -N(R^{j4}) R^{k4} or -OR^{l4};

20 each R^{a4} and R^{f4} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro; and/or (e.g. and)

each R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{j4} , R^{k4} , R^{l4} and R^{l4} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro.

25

Even more particular compounds of the invention that may be mentioned include those in which each G^{2c} represents fluoro, chloro, -CH₃, -CF₃, -CN, -C(O)NH₂, -C(O)OCH₃, -N(CH₃)₂ or -OCH₃.

30 Particular compounds of the invention that may be mentioned include those in which:

X represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl, such as C_{1-4} alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

35

Y represents R^{a2} ;

R^{a2} represents heteroaryl optionally substituted by one or more groups independently selected from G^{2d};

each G^{2d} independently represents halo, R^{a4}, -CN, -A^{a3}-C(Q^{a3})R^{b4}, -A^{b3}-C(Q^{b3})N(R^{c4})R^{d4},
 5 -A^{c3}-C(Q^{c3})OR^{e4}, -A^{d3}-S(O)_qR^{f4}, -A^{e3}-S(O)_qN(R^{g4})R^{h4}, -A^{f3}-S(O)_qORⁱ⁴, -N₃, -N(R^{j4})R^{k4},
 -N(H)CN, -NO₂, -ONO₂, -OR^{l4} or -SR^{m4};

each Q^{a3} to Q^{c3} independently represents =O, =S, =NRⁿ⁴ or =N(OR^{o4});

10 each A^{a3} to A^{c3} independently represents a single bond, -N(R^{p4})- or -O-;

each R^{a4} and R^{f4} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G^{3a},
 or heterocyclyl optionally substituted by one or more groups independently selected from
 15 G^{3b};

each R^{b4}, R^{c4}, R^{d4}, R^{e4}, R^{g4}, R^{h4}, Rⁱ⁴, R^{j4}, R^{k4}, R^{l4}, R^{m4}, Rⁿ⁴, R^{o4} and R^{p4} independently represents H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G^{3a}, or heterocyclyl
 20 optionally substituted by one or more groups independently selected from G³, or
 any of R^{c4} and R^{d4}, R^{g4} and R^{h4} and/or R^{j4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^{3b};

25

each G^{3a} and G^{3b} independently represents halo, R^{a5}, -CN, -N(R^{b5})R^{c5}, -OR^{d5}, -SR^{e5} or =O;
 each R^{a5} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G⁴;

30 each R^{b5}, R^{c5}, R^{d5} and R^{e5} independently represents H, or C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) each optionally substituted by one or more groups independently selected from G⁴, or

each R^{b5} and R^{c5} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further
 35 heteroatom and which ring optionally is substituted by one or more groups independently selected from G⁴;

each G^4 independently represents halo, R^{a6} , $-CN$, $-N(R^{b6})R^{c6}$, $-OR^{d6}$ or $=O$;

each R^{a5} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro;

5

each R^{b6} , R^{c6} and R^{d6} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro; and/or (e.g. and)

each p and q independently represents 1 or 2.

10

More particular compounds of the invention that may be mentioned include those in which:

X represents C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl (e.g. C_{1-4} alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

15

Y represents R^{a3} ;

R^{a3} represents heteroaryl optionally substituted by one or more (e.g. one or two) groups independently selected from G^{2d} ;

20

each G^{2d} independently represents halo, R^{a3} , $-CN$, $-A^{a3}-C(O)R^{b4}$, $-A^{b3}-C(O)N(R^{c4})R^{d4}$, $-A^{c3}-C(O)OR^{e4}$, $-A^{d3}-S(O)_qR^{f4}$, $-A^{e3}-S(O)_qN(R^{g4})R^{h4}$, $-N(R^{i4})R^{k4}$ or $-OR^{l4}$;

25

each A^{a3} to A^{c3} independently represents a single bond or $-N(R^{p4})-$;

each R^{a4} and R^{f4} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro;

30

each R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{j4} , R^{k4} , R^{l4} and R^{p4} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro, or

any of R^{c4} and R^{d4} , R^{g4} and R^{h4} and/or R^{j4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^{3b} ;

35

each G^{3b} independently represents fluoro, R^{a5} or $=O$;

each R^{a5} independently represents C_{1-3} alkyl optionally substituted by one or more fluoro; and/or (and)

5

each p and q independently represents 1 or 2.

Yet more particular compounds of the invention that may be mentioned include those in which:

10

X represents C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl (e.g. C_{1-4} alkyl) each optionally substituted by Y (e.g. X is unsubstituted or, in certain embodiments, substituted by at least one Y, such as wherein X is substituted by one Y);

15

Y represents R^{a3} ;

R^{a3} represents heteroaryl optionally substituted by G^{2d} ;

20

G^{2d} represents halo, R^{a4} , $-CN$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-S(O)_2R^{f4}$, $-S(O)_2N(R^{g4})R^{h4}$, $-N(R^{i4})R^{k4}$ or $-OR^{l4}$;

each R^{a4} and R^{f4} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro; and/or (e.g. and)

25

each R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{i4} , R^{k4} , R^{l4} and R^{l4} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl) each optionally substituted by one or more fluoro.

Even more particular compounds of the invention that may be mentioned include those in which:

30

R^{a3} represents heteroaryl (e.g. furanyl (e.g. 2-furanyl) or pyrazinyl) optionally substituted (e.g. unsubstituted) by G^{2d} ; and/or (e.g. and)

G^{2d} represents fluoro, chloro or C_{1-3} alkyl (e.g. $-CH_3$).

35

Particular compounds of the invention that may be mentioned include those in which R^1 , R^2 and R^3 each independently represent H, halo (e.g. chloro or fluoro, such as chloro), R^{a1} ,

$-N(R^{j1})R^{k1}$, $-OR^{l1}$ or $-SR^{m1}$ (such as H, halo (e.g. chloro or fluoro, such as chloro), R^{a1} , $-N(R^{j1})R^{k1}$ or $-OR^{l1}$).

More particular compounds of the invention that may be mentioned include those in which:

5

each R^{a1} and R^{f1} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^{1a} , or heterocyclyl optionally substituted by one or more groups independently selected from G^{1b} ; and

10

each R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{g1} , R^{h1} , R^{i1} , R^{j1} , R^{k1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} and R^{p1} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^{1a} or heterocyclyl optionally substituted by one or more groups independently selected from G^{1b} ; or

15

any of R^{c1} and R^{d1} , R^{g1} and R^{h1} and/or R^{j1} and R^{k1} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from halo, and C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl each optionally substituted by one or more halo, and =O.

20

Yet more particular compounds of the invention that may be mentioned include those in which:

25

R^1 represents halo (e.g. chloro), $-N(R^{j1})R^{k1}$, $-OR^{l1}$ or $-SR^{m1}$ (e.g. halo, $-N(R^{j1})R^{k1}$ or $-OR^{l1}$);

each R^2 and R^3 each independently represent H, halo, R^{a1} , $-N(R^{j1})R^{k1}$, $-OR^{l1}$ or $-SR^{m1}$ (e.g. H, halo, R^{a1} , $-N(R^{j1})R^{k1}$ or $-OR^{l1}$); and/or (e.g. and)

30

each R^{a1} , R^{j1} , R^{k1} , R^{l1} and R^{m1} independently represent C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl (e.g. C_{1-6} alkyl, such as $-CH_3$) each optionally substituted by one or more fluoro.

In particular embodiments that may be mentioned, only R^{c1} and R^{d1} , and/or R^{g1} and R^{h1} may alternatively be linked together in the manner described herein.

35

For example, compounds of formula I (i.e. compounds of the invention) that may be mentioned include those in which:

R¹ represents -N(R^{j1})R^{k1} or -OR^{l1};

each R² and R³ each independently represent H or -N(R^{j1})R^{k1}, -OR^{l1}, or heterocyclyl
5 optionally substituted by one G^{1b};

each R^{j1} and R^{k1} independently represents H or C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl),
or R^{j1} and R^{k1} are linked together to form, along with the nitrogen atom to which they are
10 attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom
and which ring optionally is substituted by one or more groups independently selected from
C₁₋₃ alkyl;

each R^{l1} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl)
15 each optionally substituted by one or more fluoro (e.g. so forming a -CH₃, -CHF₂ or -CF₃
group); and/or (and)

G^{1b} represents C₁₋₃ alkyl and =O.

20 Further compounds of the invention that may be mentioned include those in which R² and
R³ each independently represent H, halo (e.g. fluoro or chloro, such as chloro),
-N(R^{j1})R^{k1} or -OR^{l1}.

In particular, compounds of the invention that may be mentioned include those in which:

25 R¹ represents halo (e.g. chloro), -N(R^{j1})R^{k1} or -OR^{l1};

each R² and R³ each independently represent H, halo (e.g. chloro), -N(R^{j1})R^{k1} or
-OR^{l1};

30 each R^{l1} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl)
optionally substituted by one or more fluoro (such as -CH₃, -CHF₂ or -CF₃ group) group);
and/or (e.g. and)

35 each R^{j1} and R^{k1} independently represent C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆
alkyl) optionally substituted by one or more fluoro (such as a -CH₃ group).

For example, particular compounds the invention that may be mentioned include those in which:

R¹ represents -OR¹¹;

5

each R² and R³ each independently represent H or -OR¹¹; and/or (and)

each R¹¹ independently represents C₁₋₆ alkyl (e.g. -CH₃) optionally substituted by one or more fluoro (e.g. so forming -CF₃).

10

Particular compounds of the invention that may be mentioned include those in which each of R² and R³ represent H.

For example, in particular embodiments, there is provided compounds of the invention wherein:

15

R² and R³ represent H; and/or (e.g. and)

R¹ represents -OC₁₋₆ alkyl optionally substituted by one or more fluoro (e.g. -OCH₃).

20

In a further embodiment, there is provided compounds of the invention wherein:

R² and R³ represent H; and/or (e.g. and)

25

R¹ represents halo (e.g. chloro), -N(CH₃)₂, or -OCH₃.

In a yet further embodiment, there is provided compounds of the invention wherein:

30

R² and R³ represent H; and/or (e.g. and)

R¹ represents -OCH₃.

As indicated herein above, particular features and embodiments as described herein may be combined without departing from the teaching of the invention.

35

For example, in a particular embodiment of the invention (e.g. a particular embodiment of the first aspect of the invention), there is provided compounds of the invention wherein:

5 X represents unsubstituted C₁₋₁₂ alkyl, C₁₋₁₂ alkenyl or C₁₋₁₂ alkynyl (e.g. a C₂₋₈ alkyl, including cyclic or part cyclic C₃₋₆ alkyl);

R¹ represents halo, -N(R^{j1})R^{k1} or -OR^{l1}; and

10 each R² and R³ independently represents H, halo, R^{a1}, -N(R^{j1})R^{k1} or -OR^{l1}.

In a particular embodiments of the invention that may be mentioned, there is provided compounds of the invention wherein:

15 X represents an unsubstituted C₂₋₈ alkyl group;

X represents an unsubstituted cyclic or part cyclic C₃₋₆ alkyl group;

20 X represents C₁₋₄ alkyl substituted with a heterocyclyl group as defined in formula I (including all features and embodiments thereof);

X represents C₁₋₄ alkyl substituted with an aryl group as defined in formula I (including all features and embodiments thereof);

25 X represents C₁₋₄ alkyl substituted with a monocyclic heteroaryl group as defined in formula I (including all features and embodiments thereof);

X represents C₁₋₄ alkyl substituted with a five membered heteroaryl group as defined in formula I (including all features and embodiments thereof);

30 X represents C₁₋₄ alkyl substituted with a six membered heteroaryl group as defined in formula I (including all features and embodiments thereof); or

35 X represents C₁₋₄ alkyl substituted with a bicyclic heteroaryl group as defined in formula I (including all features and embodiments thereof).

For the avoidance of doubt, in a particular embodiments of the invention, there is provided compounds of the invention wherein R² and R³ represent H and R¹ represents:

-OR^{l1} (e.g. -OCH₃);
 -N(R^{j1})R^{k1} (e.g. -N(CH₃)₂); or
 chloro.

- 5 For the avoidance of doubt, the skilled person will understand that each G^{3c} and G^{3d} may be construed relative to G^{3a} and G^{3b} in the same manner as the corresponding G^{2c} and G^{2d} groups are construed relative to G^{2a} and G^{2b}, i.e. such that:

G^{3c} and G^{3d} independently representing halo, R^{a5}, -CN, -A^{a4}-C(Q^{a4})R^{b5},
 -A^{b4}-C(Q^{b4})N(R^{c5})R^{d5}, -A^{c4}-C(Q^{c4})OR^{e5}, -A^{d5}-S(O)_qR^{f5}, -A^{e4}-S(O)_qN(R^{g5})R^{h5},
 10 -A^{f4}-S(O)_qORⁱ⁵, -N₃, -N(R^{j5})R^{k5}, -N(H)CN, -NO₂, -ONO₂, -OR^{l5} or -SR^{m5},

each Q^{a4} to Q^{c4} independently represents =O, =S, =NRⁿ⁵ or =N(OR^{o5});

each A^{a4} to A^{f4} independently represents a single bond, -N(R^{p5})- or -O-;

with each R^{f5} to R^{p5} independently representing H, or C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl
 each optionally substituted by one or more groups independently selected from G⁴, or with
 15 each R^{g5} and R^{h5}, and R^{j5} and R^{k5} being linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G⁴.

- 20 Particular compounds of the invention (including compounds of formula I and all embodiments and particular forms thereof) that may be mentioned include the compounds of the examples as provided herein, or a pharmaceutically acceptable salt thereof.

Where an example compound is indicated to have been obtained in a particular salt form,
 25 the skilled person will understand that particular compounds of the invention that may be mentioned include the free base or free acid (as appropriate) of that compound, and *vice versa*. Further, where an example compound is indicated to have been obtained in a particular salt form, particular compounds of the invention that may be mentioned include other (i.e. different) pharmaceutically acceptable salts of that compound.

30

Thus, for the avoidance of doubt, particular compounds of the invention that may be mentioned include:

2-benzylsulfonyl-6-methoxy-3-nitropyridine;

- 2-cyclopentylsulfonyl-6-methoxy-3-nitropyridine;
 2-hexylsulfonyl-6-methoxy-3-nitropyridine;
 2-benzylsulfonyl-6-chloro-3-nitropyridine;
 6-chloro-2-(cyclopentylsulfonyl)-3-nitropyridine;
 5 6-chloro-2-(hexylsulfonyl)-3-nitropyridine;
 2-benzylsulfonyl-6-dimethylamino-3-nitropyridine;
 2-cyclopentylsulfonyl-6-dimethylamino-3-nitropyridine;
 6-dimethylamino-2-hexylsulfonyl-3-nitropyridine;
 2-(ethylsulfonyl)-6-methoxy-3-nitropyridine;
 10 2-(isopropylsulfonyl)-6-methoxy-3-nitropyridine;
 6-methoxy-3-nitro-2-(octylsulfonyl)pyridine;
 2-(cyclopropylsulfonyl)-6-methoxy-3-nitropyridine;
 6-methoxy-3-nitro-2-((5,5,5-trifluoropentyl)sulfonyl)pyridine;
N-(2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethyl)acetamide;
 15 methyl 3-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)propanoate;
 3-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)propan-1-ol;
 6-methoxy-3-nitro-2-((2-(piperidin-1-yl)ethyl)sulfonyl)pyridine;
 2-((2-chlorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine;
 2-((3-chlorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine;
 20 2-((4-chlorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine;
 2-((4-fluorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine;
 6-methoxy-2-((4-methylbenzyl)sulfonyl)-3-nitropyridine;
 6-methoxy-2-((4-methoxybenzyl)sulfonyl)-3-nitropyridine;
 6-methoxy-3-nitro-2-((4-(trifluoromethoxy)benzyl)sulfonyl)pyridine;
 25 6-methoxy-3-nitro-2-(phenethylsulfonyl)pyridine;
 6-methoxy-3-nitro-2-((3-phenylpropyl)sulfonyl)pyridine;
 6-methoxy-3-nitro-2-((2-phenoxyethyl)sulfonyl)pyridine;
 2-((furan-2-ylmethyl)sulfonyl)-6-methoxy-3-nitropyridine; and
 2-(2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethyl)pyrazine,
 30 and pharmaceutically acceptable salts thereof.

Compositions and medical uses

- 35 As discussed hereinbefore, compounds of the invention, and therefore compositions and kits comprising the same, are useful as pharmaceuticals.

According to a second aspect of the invention there is provided a compound of the invention, as hereinbefore defined (i.e. in the first aspect of the invention, including all embodiments and particular features therein, but without the provisos), for use as a pharmaceutical. Further, there is provided a compound of the invention, as hereinbefore defined, for use in medicine.

In a particular embodiment of the second aspect of the invention, the compound of the invention is a compound of the invention but with proviso (B) (i.e. including proviso (B) as defined in the first aspect of the invention).

In a particular embodiment of the second aspect of the invention, the compound of the invention is a compound of the first aspect of the invention (i.e. including the provisos).

As indicated herein, compounds of the invention may be of particular use in treating cancers.

Thus, in a third aspect of the invention, there is provided a compound of the invention, as hereinbefore defined (i.e. in the first aspect of the invention, including all embodiments and particular features therein, but without the provisos), for use in the treatment of cancer.

In an alternative third aspect of the invention, there is provided the use of a compound of the invention, as hereinbefore defined, in the manufacture of a medicament for the treatment of cancer.

In a further alternative third aspect of the invention, there is provided a method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the invention.

In a particular embodiment of the third aspect of the invention, the compound of the invention is a compound of the invention but with proviso (B) (i.e. including proviso (B) as defined in the first aspect of the invention).

In a particular embodiment of the third aspect of the invention, the compound of the invention is a compound of the first aspect of the invention (i.e. including the provisos).

The skilled person will understand that references to the treatment of a particular condition (or, similarly, to treating that condition) take their normal meanings in the field of medicine.

In particular, the terms may refer to achieving a reduction in the severity of one or more clinical symptom associated with the condition. For example, in the case of a cancer, the term may refer to achieving a reduction of the amount of cancerous cells present (e.g. in the case of a cancer forming a solid tumour, indicated by a reduction in tumour volume).

5

As used herein, references to patients will refer to a living subject being treated, including mammalian (e.g. human) patients.

As used herein, the term effective amount will refer to an amount of a compound that confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of and/or feels an effect).

Although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the active compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the invention.

As used herein, references to prodrugs will include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time, following enteral or parenteral administration (e.g. oral or parenteral administration). All prodrugs of the compounds of the invention are included within the scope of the invention.

Furthermore, certain compounds of the invention may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds of the invention that possess pharmacological activity as such. Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the active compounds of the invention to which they are metabolised), may also be described as "prodrugs".

35

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds that possess pharmacological activity.

- 5 Without wishing to be bound by theory, it is believed that compounds of the invention wherein n represents 1 may be metabolised *in vivo* to form corresponding compounds of the invention wherein n represents 2.

- As indicated herein, the compounds of the invention may be useful in the treatment of
10 cancer (i.e. particular cancers).

Particular cancers that may be mentioned include those selected from the group comprising:

- 15 soft tissue cancers, such as sarcoma (e.g. angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma;

- lung cancers, such as bronchogenic carcinoma (e.g. squamous cell, undifferentiated small
20 cell, undifferentiated large cell, adenocarcinoma), alveolar (or bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, including non-small cell lung cancer;

- gastrointestinal cancers: such as esophageal cancers (e.g. squamous cell carcinoma,
25 adenocarcinoma, leiomyosarcoma, lymphoma), stomach cancers (e.g. carcinoma, lymphoma, leiomyosarcoma), pancreatic cancers (e.g. ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel cancers (e.g. adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel cancers (e.g. adenocarcinoma,
30 tubular adenoma, villous adenoma, hamartoma, leiomyoma);

- genitourinary tract cancers, such as cancer of the kidney (e.g. adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (e.g. squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (e.g. adenocarcinoma,
35 sarcoma), testis (e.g. seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

liver cancers, such as hepatoma (e.g. hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;

5 bone cancers, such as osteogenic sarcoma (e.g. osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (e.g. reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (e.g. osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

10

cancers of the head and/or nervous system, such as cancer of the skull (e.g. osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (e.g. meningioma, meningiosarcoma, gliomatosis), brain (e.g. astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord (e.g. neurofibroma, meningioma, glioma, sarcoma);

15

gynecological cancers, such as cancers of the uterus (e.g. endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (e.g. ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), cancers of the vulva (e.g. squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (e.g. clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma)), fallopian tubes (e.g. carcinoma);

25

haematologic cancers, such as cancers of the blood and bone marrow (e.g. myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma);

30

skin cancers, such as malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids; neurofibromatosis and Adrenal glands; and

35

neuroblastomas.

As used herein, references to cancerous cells and the like will include references to a cell afflicted by any one of the above identified conditions.

5 More particular cancers that may be mentioned include those corresponding to the cell lines used in the examples provided herein.

For example, particular cancers that may be mentioned include breast cancer (such as mammary adenocarcinoma, e.g. metastatic mammary adenocarcinoma) and/or glioblastoma (such as glioblastoma multiform).

10

More particular cancers that may be mentioned include:

head and neck cancer (such as throat cancer, e.g. pharyngeal squamous cell carcinoma);
colon cancer (such as colorectal carcinoma);
15 skin cancer (such as epidermoid (skin) carcinoma);
gastrointestinal cancers (such as pancreatic cancer, e.g. pancreatic ductal carcinoma);
breast cancer (such as mammary adenocarcinoma, e.g. metastatic mammary adenocarcinoma);
lung cancer (such as carcinoma); and
20 haematologic cancers (such as leukemia, e.g. acute monocytic leukemia).

In particular embodiments, the cancer is a solid tumor cancer.

25 In more particular embodiments, the cancer is selected from pancreatic cancer, ovarian cancer and colorectal cancer.

For example, in certain embodiments, the cancer is selected from colorectal cancer (including those processing Ras mutations), small cell lung cancer, non-small cell lung cancer (NSCLC), and glioma.

30

In other embodiments, the cancer is selected from non-small cell lung cancer, ovarian cancer, metastatic breast cancer, pancreatic cancer, hepatobiliary cancer (including hepatocellular cancer, bile duct cancer and cholangiocarcinoma), and gastric cancer.

35 In further embodiments, the cancer is selected from colorectal cancer (including Ras mutations), small cell lung cancer, non-small cell lung cancer, ovarian cancer, hepatobiliary cancer (including hepatocellular cancer, bile duct cancer and

cholangiocarcinoma), gastric cancer, testicular cancer, and head and neck squamous cell carcinoma.

5 In certain embodiments of the present invention, the cancer is selected from leukemia (including acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and chronic lymphoid leukemia), lymphoma (including mantle cell lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma), and prostate cancer

10 The skilled person will understand that treatment with compounds of the invention may further comprise (i.e. be combined with) further treatment(s) for the same condition. In particular, treatment with compounds of the invention may be combined with means for the treatment of cancer, such as treatment with one or more other therapeutic agent that is useful in the in the treatment of cancer and/or one or more physical method used in the treatment of cancer (such as treatment through surgery), as known to those skilled in the
15 art.

In particular, treatment with compounds of the invention may be performed in patients who are being or have been (i.e. as part or of a treatment for the same condition, such as within a month of treatment with compounds of the invention, such as within two weeks, e.g.
20 within a week or, particularly, on the same day) treated with a therapeutic agent or physical method that is capable of causing (e.g. can be demonstrated to cause) an increase in reactive oxygen species.

For the avoidance of doubt, the skilled person will understand that therapeutic agents or
25 physical methods capable of causing (e.g. can be demonstrated to cause) an increase in reactive oxygen species may not necessarily be effective treatments *per se*, but will become effective when used in combination with compounds of the invention.

For the avoidance of doubt, the skilled person will understand that compounds of the
30 invention may also be used in combination with one or more other therapeutic agent that is useful in the in the treatment of cancer and/or one or more physical method used in the treatment of cancer (such as treatment through surgery) wherein such methods do not cause an increase in reactive oxygen species.

35 In particular, treatment with compounds of the invention may be performed in patients who are being or have been treated with radiotherapy.

Thus, there is also provided:

a method of treating cancer in a patient in need thereof wherein the patient is administered a therapeutically effective amount of a compound of the invention in combination with
5 treatment by radiotherapy (i.e. concomitantly or sequentially); and

a compound of the invention for use in treating cancer in a patient who is also being treated with radiotherapy.

10 Compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, intranasally, topically, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

15 Compounds of the invention may be administered alone or may be administered by way of known pharmaceutical compositions/formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

20 According to a fourth aspect of the invention there is thus provided a pharmaceutical composition/formulation comprising a compound of the invention as hereinbefore defined (i.e. in the first aspect of the invention, including all embodiments and particular features therein, but without the provisos), and optionally (e.g. in admixture with) one or more pharmaceutically acceptable adjuvant, diluent and/or carrier.

25

In a particular embodiment of the fourth aspect of the invention, the compound of the invention is a compound of the invention but with proviso (B) (i.e. including proviso (B) as defined in the first aspect of the invention).

30 In a particular embodiment of the fourth aspect of the invention, the compound of the invention is a compound of the first aspect of the invention (i.e. including the provisos).

The skilled person will understand that references herein to compounds of the invention being for particular uses (and, similarly, to uses and methods of use relating to compounds
35 of the invention) may also apply to pharmaceutical compositions comprising compounds of the invention as described herein.

Compounds of the invention may be administered in the form of tablets or capsules, e.g. time-release capsules that are taken orally. Alternatively, the compounds of the invention may be in a liquid form and may be taken orally or by injection. The compounds of the invention may also be in the form of suppositories, or, creams, gels, and foams e.g. that can be applied to the skin. In addition, they may be in the form of an inhalant that is applied nasally or *via* the lungs.

The skilled person will understand that compounds of the invention may act systemically and/or locally (i.e. at a particular site).

Compounds of the invention may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form. Alternatively, particularly where compounds of the invention are intended to act locally, compounds of the invention may be administered topically.

Thus, in a particular embodiment, the pharmaceutical formulation is provided in a pharmaceutically acceptable dosage form, including tablets or capsules, liquid forms to be taken orally or by injection, suppositories, creams, gels, foams, or inhalants (e.g. to be applied intranasally). For the avoidance of doubt, in such embodiments, compounds of the invention may be present as a solid (e.g. a solid dispersion), liquid (e.g. in solution) or in other forms, such as in the form of micelles.

In more particular embodiments, the pharmaceutical formulation is provided the form of a tablets or capsules, liquid forms to be taken orally or by injection (e.g. a form suitable for intravenous injection). In particular, injection may take place using conventional means, and may include the use of microneedles.

Depending on e.g. potency and physical characteristics of the compound of the invention (i.e. active ingredient), pharmaceutical formulations that may be mentioned include those in which the active ingredient is present in at least 1% (or at least 10%, at least 30% or at least 50%) by weight. That is, the ratio of active ingredient to the other components (i.e. the addition of adjuvant, diluent and carrier) of the pharmaceutical composition is at least 1:99 (or at least 10:90, at least 30:70 or at least 50:50) by weight.

As described herein, compounds of the invention may also be combined with one or more other (i.e. different, e.g. agents other than compounds of formula I) therapeutic agents that

are useful in the treatment of cancer. Such combination products that provide for the administration of a compound of the invention in conjunction with one or more other therapeutic agent may be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the one or more other therapeutic agent).

Thus, according to a fifth aspect of the invention, there is provided a combination product comprising:

- (A) a compound of the invention, as hereinbefore defined (i.e. in the first aspect of the invention, including all embodiments and particular features therein, but without the provisos); and
 - (B) one or more other therapeutic agent that is useful in the treatment of cancer,
- wherein each of components (A) and (B) is formulated in admixture, optionally with one or more a pharmaceutically-acceptable adjuvant, diluent or carrier.

In a sixth aspect of the invention there is provided a kit-of-parts comprising:

- (a) a pharmaceutical formulation as hereinbefore defined (i.e. in the fourth aspect of the invention); and
 - (b) one or more other therapeutic agent that is useful in the treatment of cancer, optionally in admixture with one or more pharmaceutically-acceptable adjuvant, diluent or carrier,
- which components (a) and (b) are each provided in a form that is suitable for administration in conjunction (i.e. concomitantly or sequentially) with the other.

In a particular embodiment of the fifth and sixth aspects of the invention, the compound of the invention is a compound of the invention but with proviso (B) (i.e. including proviso (B) as defined in the first aspect of the invention).

30

The skilled person will understand that compounds of the invention, and pharmaceutically-acceptable salts thereof, may be administered (for example, as formulations as described hereinabove) at varying doses, with suitable doses being readily determined by one of skill in the art. Oral, pulmonary and topical dosages (and subcutaneous dosages, although these dosages may be relatively lower) may range from between about 0.01 µg/kg of body weight per day (µg/kg/day) to about 200 µg/kg/day, preferably about 0.01 to about 10 µg/kg/day, and more preferably about 0.1 to about 5.0 µg/kg/day. For example, when

administered orally, treatment with such compounds may comprise administration of a formulations typically containing between about 0.01 µg to about 2000 mg, for example between about 0.1 µg to about 500 mg, or between 1 µg to about 100 mg (e.g. about 20 µg to about 80 mg), of the active ingredient(s). When administered intravenously, the most preferred doses will range from about 0.001 to about 10 µg/kg/hour during constant rate infusion. Advantageously, treatment may comprise administration of such compounds and compositions in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily (e.g. twice daily with reference to the doses described herein, such as a dose of 10 mg, 20 mg, 30 mg or 40 mg twice daily).

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Preparation of compounds/compositions

Pharmaceutical compositions/formulations, combination products and kits as described herein may be prepared in accordance with standard and/or accepted pharmaceutical practice.

Thus, in a further aspect of the invention there is provided a process for the preparation of a pharmaceutical composition/formulation, as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, with one or more pharmaceutically-acceptable adjuvant, diluent or carrier.

In further aspects of the invention, there is provided a process for the preparation of a combination product or kit-of-parts as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable salt thereof with the other therapeutic agent that is useful in the treatment of cancer, and at least one pharmaceutically-acceptable adjuvant, diluent or carrier.

As used herein, references to bringing into association will mean that the two components are rendered suitable for administration in conjunction with each other.

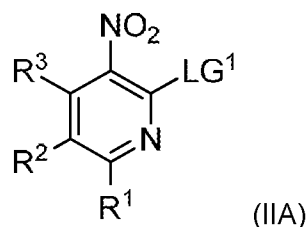
Thus, in relation to the process for the preparation of a kit of parts as hereinbefore defined, by bringing the two components “into association with” each other, we include that the two components of the kit of parts may be:

- (i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or
- (ii) packaged and presented together as separate components of a “combination pack” for use in conjunction with each other in combination therapy.

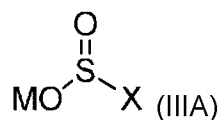
Compounds of the invention as described herein may be prepared in accordance with techniques that are well known to those skilled in the art, such as those described in the examples provided hereinafter.

According to a seventh aspect of the invention there is provided a process for the preparation of a compound of the first aspect of the invention as hereinbefore defined (i.e. a compound of the invention but including the proviso), which process comprises:

- (i) where n represents 2, reaction of a compound of formula IIA

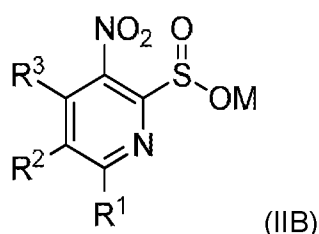


wherein R^1 , R^2 and R^3 are as defined herein (i.e. for compounds of the invention, or any particular feature or embodiment thereof) and LG^1 represents a suitable leaving group (such as halo, e.g. chloro), with a compound of formula IIIA

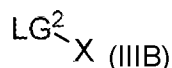


wherein X is as defined herein (i.e. for compounds of the invention, or any particular feature or embodiments thereof) and M represents an alkali metal ion (such as a Na ion), in the presence of a suitable acid (such as a concentrated acid, e.g. a concentrated mineral acid, for example concentrated HCl, e.g. concentrated aqueous HCl) and in the presence of a suitable solvent (such as a polar organic solvent, e.g. *N,N'*-dimethylacetamide, *N,N'*-dimethylformamide or tetrahydrofuran), and optionally in the presence of a suitable phase transfer catalyst (such as a quaternary ammonium salt, e.g. *tetra*-butyl ammonium chloride);

- (ii) where n represents 2, reaction of a compound of formula IIB



- wherein R¹, R² and R³ are as defined herein (i.e. for compounds of the invention, or any particular feature or embodiments thereof) and M represents an alkali metal ion (such as a Na ion), with a compound of formula IIIB



- wherein X is as defined herein in formula I (i.e. for compounds of the invention, or any particular feature or embodiments thereof) and LG² represents a suitable leaving group (such as halo, e.g. chloro), in the presence of a suitable acid (such as a concentrated acid, e.g. a concentrated mineral acid, for example concentrated HCl, e.g. concentrated aqueous HCl) and in the presence of a suitable solvent (such as a polar organic solvent, e.g. *N,N'*-dimethylacetamide, *N,N'*-dimethylformamide or tetrahydrofuran), and optionally in the presence of a suitable phase transfer catalyst (such as a quaternary ammonium salt, e.g. *tetra*-butyl ammonium chloride);

- (iii) where n represents 2, reaction of a compound of formula IIA as hereinbefore defined with a compound of formula IIIA as hereinbefore defined, in the presence of a suitable metal halide (such as a suitable metal iodide, e.g. CuI, or a suitable metal bromide, e.g. CuBr; which metal halide may be present in excess, such as in amount corresponding

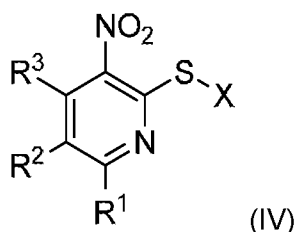
to at least 2 molar equivalents of the compound of formula IIA and/or the compound of formula IIIA) and in the presence of a suitable solvent (such as a polar organic solvent, e.g. *N,N'*-dimethylacetamide, *N,N'*-dimethylformamide, tetrahydrofuran or 3-dimethyl-2-imidazolidinone), under conditions known to those skilled in the art;

5

(iv) where n represents 2, reaction of a compound of formula IIB as hereinbefore defined with a compound of formula IIIB as hereinbefore defined, in the presence of a suitable metal halide (such as a suitable metal iodide, e.g. CuI, or a suitable metal bromide, e.g. CuBr; which metal halide may be present in excess, such as in amount corresponding to at least 2 molar equivalents of the compound of formula IIB and/or the compound of formula IIIB) and in the presence of a suitable solvent (such as a polar organic solvent, e.g. *N,N'*-dimethylacetamide, *N,N'*-dimethylformamide, tetrahydrofuran or 3-dimethyl-2-imidazolidinone), under conditions known to those skilled in the art;

10

15 (v) reaction of a compound of formula IV

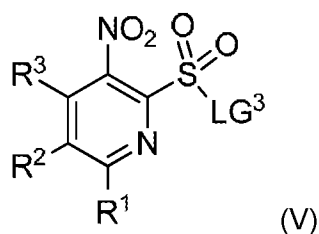


wherein R¹ to R³ and X are as defined herein (i.e. for compounds of the invention, or any particular feature or embodiments thereof), with a suitable oxidising agent (i.e. an oxidising agent chosen and used in a manner as required to achieved the desired degree of oxidation; such as a hypochlorite salt, e.g. sodium hypochlorite, a peroxymonosulfate salt, e.g. potassium peroxymonosulfate (Oxone), a percarboxylic acid, e.g. *meta*-chloroperoxybenzoic acid (mCPBA), or potassium permanganate) in the presence of a suitable solvent (such as a polar organic solvent, e.g. *N,N'*-dimethylacetamide, *N,N'*-dimethylformamide or tetrahydrofuran), and optionally in the presence of water, under conditions known to those skilled in the art;

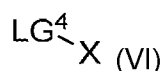
25

(vi) where n represents 2, reaction of a compound of formula V

30



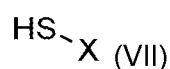
wherein R^1 , R^2 and R^3 are as defined herein (i.e. for compounds of the invention, or any particular feature or embodiments thereof) and LG^3 represents a suitable leaving group (such as halo, e.g. chloro) with a compound of formula VI



wherein X is as defined herein (i.e. for compounds of the invention, or any particular feature or embodiments thereof) and LG^4 represents a suitable leaving group (such as a boronic acid), in the presence of a suitable catalyst (such as a suitable metal halide, e.g. CuBr, or phenanthroline) and in the presence of a suitable solvent (such as an organic solvent, e.g. dichloromethane or dichloroethane).

Compounds of formulae IIA, IIB, IIIA, IIIB, IV, V and VI are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions. In this respect, the skilled person may refer to *inter alia* "Comprehensive Organic Synthesis" by B. M. Trost and I. Fleming, Pergamon Press, 1991. Further references that may be employed include "Heterocyclic Chemistry" by J. A. Joule, K. Mills and G. F. Smith, 3rd edition, published by Chapman & Hall, "Comprehensive Heterocyclic Chemistry II" by A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, 1996 and "Science of Synthesis", Volumes 9-17 (Heteroarenes and Related Ring Systems), Georg Thieme Verlag, 2006.

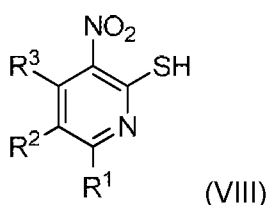
In particular, compounds of formula IV may be prepared by reaction of a compound of formula VII



wherein X is as defined herein (i.e. for compounds of the invention, or any particular feature or embodiments thereof), with a compound of formula IIA as herein before defined, under

conditions known to those skilled in the art, such as in the presence of a suitable base (such as a metal carbonate, e.g. potassium carbonate, a metal hydroxide, e.g. sodium hydroxide, or an amine base, e.g. triethyl amine), and in the presence of a suitable solvent (such as a polar organic solvent, e.g. *N,N*-dimethylacetamide, *N,N*-dimethylformamide or tetrahydrofuran, or a mixture of a polar organic solvent and water), under conditions known to those skilled in the art.

Similarly, compounds of formula IV may be prepared by reaction of a compound of formula VIII



wherein R^1 , R^2 and R^3 are as defined herein (i.e. for compounds of the invention, or any particular feature or embodiments thereof), with a compound of formula IIIB as described herein, under conditions known to those skilled in the art (for example, where the R^4 groups present in the compound of formula IIIB are not sufficiently electron withdrawing, the reaction may be performed in the presence of a suitable catalyst, such as palladium(II) acetate or copper oxide, in which case the suitable base may be an alkali metal *tert*-butoxide, such as $K^t\text{-OBu}$).

Similarly, compounds of formulae VII and VIII are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions.

The substituents R^1 to R^3 and Y, as hereinbefore defined, may be modified one or more times, after or during the processes described above for preparation of compounds of formula I by way of methods that are well known to those skilled in the art. Examples of such methods include substitutions, reductions, oxidations, dehydrogenations, alkylations, dealkylations, acylations, hydrolyses, esterifications, etherifications, halogenations and nitrations. The precursor groups can be changed to a different such group, or to the groups defined in formula I, at any time during the reaction sequence. The skilled person may also refer to "*Comprehensive Organic Functional Group Transformations*" by A. R.

Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon Press, 1995 and/or "*Comprehensive Organic Transformations*" by R. C. Larock, Wiley-VCH, 1999.

5 Compounds of the invention may be isolated from their reaction mixtures and, if necessary, purified using conventional techniques as known to those skilled in the art. Thus, processes for preparation of compounds of the invention as described herein may include, as a final step, isolation and optionally purification of the compound of the invention (e.g. isolation and optionally purification of the compound of formula I).

10 It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups. The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

15 Protecting groups may be applied and removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques. The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing
20 the synthesis. The use of protecting groups is fully described in "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

In a further aspect of the invention, there is provided a compound of formula IV as defined herein (i.e. wherein R^1 , R^2 , R^3 and X are as defined herein, including all particular features
25 and embodiments thereof), or a pharmaceutically acceptable salt thereof.

Particular compounds of formula IV that may be mentioned include those prepared in the examples provided herein, and pharmaceutically acceptable salts thereof.

30 Compounds of the invention may have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art,
35 whether for use in the above-stated indications or otherwise. In particular, compounds of the invention may have the advantage that they are more efficacious and/or exhibit advantageous properties *in vivo*.

Without wishing to be bound by theory, it is thought that inhibition of thioredoxin reductase is obtained by the utilization of strong electrophilicity of small molecule inhibitors in combination with a pronounced inherent nucleophilicity of NADPH-reduced, but not oxidized, thioredoxin reductase, resulting in selective and potent inhibition of said enzyme without major targeting of other cellular pathways or enzymes.

Moreover, it is thought that normal non-cancerous cells may survive without a functional cytosolic thioredoxin reductase enzyme because of maintained function of the glutathione system, while cancer cells cannot survive upon specific inhibition of cytosolic thioredoxin reductase.

Examples

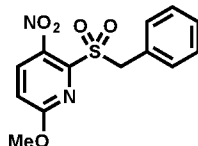
The invention is illustrated by way of the following examples, in which the following abbreviations may be employed.

aq	aqueous
BSA	bovine serum albumin
20 conc	concentrated
DMA	<i>N,N'</i> -dimethylacetamide
DMF	<i>N,N'</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DTNB	5,5'-dithio-bis-(2-nitrobenzoic acid)
25 EDTA	ethylenediaminetetraacetic acid
GSSG	glutathione disulfide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
mCPBA	<i>meta</i> -chloroperbenzoic acid
30 NADPH	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic resonance
PBS	phosphate buffered saline
rt	room temperature

Starting materials and chemical reagents specified in the syntheses described below are commercially available from a number of suppliers, such as Sigma Aldrich.

In the event that there is a discrepancy between nomenclature and the structure of compounds as depicted graphically, it is the latter that presides (unless contradicted by any experimental details that may be given and/or unless it is clear from the context). The names of the final compounds may be translated to the structures e.g. using ChemBioDraw Ultra 14.

Example 1: 2-Benzylsulfonyl-6-methoxy-3-nitropyridine



(a) 2-(Benzyldithio)-6-methoxy-3-nitropyridine

A mixture of 2-chloro-6-methoxy-3-nitropyridine (0.20 g, 1.06 mmol), benzylmercaptan (0.14 mL, 1.17 mmol), K₂CO₃ (0.18 g, 1.29 mmol) and DMF (1 mL) was stirred at rt for 3 h. The mixture was poured into water and filtered to give the sub-title compound (0.29 g, 98 %).

(b) 2-Benzylsulfonyl-6-methoxy-3-nitropyridine

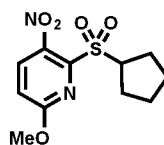
NaOCl (aq, 10%, 1.36 mL, 2.29 mmol) was added dropwise to a stirred mixture of 2-(benzyldithio)-6-methoxy-3-nitropyridine (0.29 g, 1.04 mmol), glacial acetic acid (0.08 mL, 1.34 mmol) and DMF (1 mL) at rt. The mixture was stirred at rt for 14 h and poured into water. The pH was adjusted to ~9 with aq NaOH (20% (w/v)). After stirring for 5 s the mixture was filtered through a cotton plug and washed with water. The plug was rinsed with dichloromethane and the dichloromethane was evaporated to give the title compound as an oil (0.02 g, 6 %).

¹H NMR (400 MHz, CDCl₃) δ 8.08-8.04 (1H, m), 7.41-7.30 (5H, m), 7.02-6.98 (1H, m), 4.83 (2H, s), 3.97 (3H, s);

¹³C-NMR (100 MHz, CDCl₃) δ 163.9, 148.4, 136.2, 131.5, 129.3, 128.9, 126.5, 115.7, 60.2, 55.6;

ESI-MS: 309 [M+H]⁺.

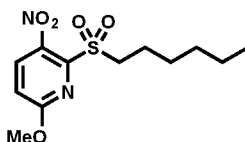
Example 2: 2-Cyclopentylsulfonyl-6-methoxy-3-nitropyridine



The title compound was prepared in accordance with the procedure in Example 1, Steps (a) and (b) from 2-chloro-6-methoxy-3-nitropyridine and cyclopentylmercaptan. The compound was purified by chromatography.

^1H NMR (400 MHz, CDCl_3) δ 8.12-8.07 (1H, m), 7.06-7.00 (1H, m), 4.39-4.29 (1H, m), 4.08 (3H, s), 2.25-2.14 (2H, m), 2.08-1.97 (2H, m), 1.91-1.80 (2H, m), 1.74-1.62 (2H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ 164.0, 149.2, 136.4, 115.4, 77.2, 61.4, 55.5, 27.4, 26.3; ESI-MS: 287 $[\text{M}+\text{H}]^+$.

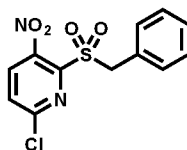
Example 3: 2-Hexylsulfonyl-6-methoxy-3-nitropyridine



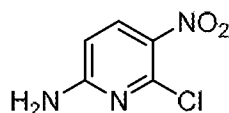
The title compound was prepared in accordance with the procedure in Example 1, Steps (a) and (b) from 2-chloro-6-methoxy-3-nitropyridine and hexyl mercaptan.

^1H NMR (400 MHz, CDCl_3) δ 8.16-8.12 (1H, m), 7.07-7.04 (1H, m), 4.08 (3H, s), 3.59-3.54 (2H, m), 1.92-1.82 (2H, m), 1.52-1.41 (2H, m), 1.36-1.26 (4H, m), 0.92-0.84 (3H, m). ^{13}C -NMR (100 MHz, CDCl_3) δ 164.1, 149.2, 136.6, 115.6, 55.6, 55.5, 53.5, 31.3, 28.3, 22.4, 22.2, 14.0; ESI-MS: 303 $[\text{M}+\text{H}]^+$.

Example 4: 2-Benzylsulfonyl-6-chloro-3-nitropyridine

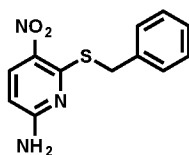


(a) 6-Chloro-5-nitropyridin-2-amine



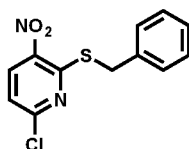
Conc. HNO₃ (2.39 mL, 35.00 mmol) was added dropwise to a mixture of conc H₂SO₄ (56 mL, 1050 mmol) and 6-chloropyridin-2-amine (3.00 g, 23.34 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h and poured into ice-water. The mixture was extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by chromatography to give the sub-title compound (1.38 g, 34 %).

(b) 6-(Benzylthio)-5-nitropyridin-2-amine



A mixture of 6-chloro-5-nitropyridin-2-amine (0.26 g, 1.50 mmol), benzylmercaptan (0.19 mL, 1.65 mmol), K₂CO₃ (0.25 g, 1.83 mmol) and DMF (2.1 mL) was stirred at 80 °C for 3.5 h. The mixture was poured into water and extracted with CH₂Cl₂ (3x15 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was dissolved in CH₂Cl₂, and the product was precipitated by addition of hexane to give the sub-title compound (0.32 g, 83 %).

(c) 2-(Benzylthio)-6-chloro-3-nitropyridine



Isoamyl nitrite (0.30 mL, 2.23 mmol) was added to a stirred mixture of 5-nitro-6-(pyridin-2-ylthio)pyridin-2-amine (0.29 g, 1.12 mmol), CuCl₂ (0.30 g, 2.24 mmol) and MeCN (5 mL) at rt. The mixture was stirred at 60 °C for 14 h, poured into acidic water (1N HCl, 4 mL) and extracted with EtOAc (3x15 mL). The combined organic layers were washed with saturated aq NaHCO₃ (10 mL), brine (10 mL) and dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by chromatography to give the sub-title compound (0.11 g, 36 %).

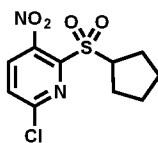
(d) 2-Benzylsulfonyl-6-chloro-3-nitropyridine

mCPBA (0.11 g, 0.45 mmol) was added in portions to a stirred mixture of 6-chloro-3-nitro-2-(pyridin-2-ylthio)pyridine (0.06 g, 0.20 mmol) and CH₂Cl₂ (7 mL) at 0 °C. The mixture was stirred at rt for 60 h and poured into saturated aq Na₂S₂O₃ (3 mL) at 0 °C. The phases were separated and the organic layer extracted with saturated aq NaHCO₃ (2x5 mL) and brine (5 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated. The crude mixture was purified by chromatography to give the title compound (0.05 g, 71 %).

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.43 – 7.41 (m, 2H), 7.37 – 7.32 (m, 3H), 4.85 (s, 2H).

¹³C-NMR (100 MHz, CDCl₃) δ 153.1, 150.0, 144.6, 136.0, 131.7, 129.4, 129.1, 129.0, 126.1, 59.7;

ESI-MS: 313 [M+H]⁺.

Example 5: 6-Chloro-2-(cyclopentylsulfonyl)-3-nitropyridine

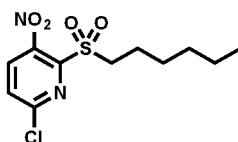
20

The title compound was prepared in accordance with the procedure in Example 4, Steps (a) to (d), from 6-chloropyridin-2-amine and cyclopentylmercaptan

¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 4.31 (tt, J = 9.0, 6.8 Hz, 1H), 2.21 – 2.10 (m, 2H), 2.10 – 1.99 (m, 2H), 1.90 – 1.79 (m, 2H), 1.76 – 1.63 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃) δ 153.2, 150.7, 144.6, 135.9, 128.8, 61.8, 27.3, 26.3;

ESI-MS: 291 [M+H]⁺.

Example 6: 6-Chloro-2-(hexylsulfonyl)-3-nitropyridine

30

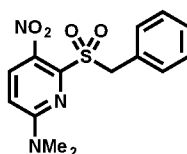
The title compound was prepared in accordance with the procedure in Example 4, Steps (a) to (d), from 6-chloropyridin-2-amine and hexylmercaptan.

^1H NMR (300 MHz, CDCl_3) δ 8.18 (d, $J = 8.5$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 3.63 – 3.51 (m, 2H), 1.96 – 1.79 (m, 2H), 1.55 – 1.40 (m, 2H), 1.35 – 1.29 (m, 4H), 0.95 – 0.82 (m, 3H);

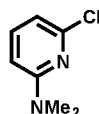
^{13}C -NMR (75 MHz, CDCl_3) δ 153.4, 150.6, 144.2, 136.1, 129.1, 53.5, 31.2, 28.1, 22.4, 22.0, 14.0;

ESI-MS: 307 $[\text{M}+\text{H}]^+$.

10 Example 7: 2-Benzylsulfonyl-6-dimethylamino-3-nitropyridine

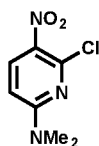


15 (a) 6-Chloro-*N,N*-dimethylpyridin-2-amine



A mixture of 2,6-dichloropyridine (2.20 g, 14.9 mmol) and DMF (11.5 mL, 148.7 mmol) was heated under microwave irradiation at 180 °C for 1 h. The mixture was poured into water and extracted with EtOAc (3x30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography to give the sub-title compound (2.12 g, 91 %).

25 (b) 6-Chloro-*N,N*-dimethyl-5-nitropyridin-2-amine

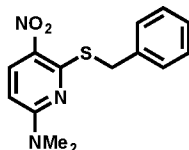


Conc HNO_3 (0.9 mL, 13.52 mmol) was added dropwise to a mixture of conc H_2SO_4 (32.4 mL, 608.6 mmol) and 6-chloro-*N,N*-dimethylpyridin-2-amine (2.12 g, 13.5 mmol) at 0 °C.

30 The mixture was stirred at 0 °C for 1.5 h and poured into ice-water. The mixture was

extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were washed with saturated aq Na_2CO_3 , dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography to give the sub-title compound (0.89 g, 33 %).

5 (c) 6-(Benzylthio)-*N,N*-dimethyl-5-nitropyridin-2-amine



A mixture of 6-chloro-*N,N*-dimethyl-5-nitropyridin-2-amine (0.15 g, 0.74 mmol), benzylmercaptan (0.10 mL, 0.82 mmol), K_2CO_3 (0.13 g, 0.91 mmol) and DMF (1 mL) was stirred at 80 °C for 1 h. The mixture was poured into water, the precipitate was collected, washed with water and dried to give the sub-title compound (0.20 g, 93 %).

15 (d) 6-Dimethylamino-3-nitro-2-(pyridin-2-ylsulfonyl)pyridine

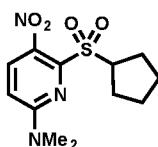
mCPBA (0.36 g, 1.52 mmol) was added in portions to a stirred mixture of 6-(benzylthio)-*N,N*-dimethyl-5-nitropyridin-2-amine (0.20 g, 0.69 mmol) and CH_2Cl_2 (8 mL) at 0 °C. The mixture was stirred at rt for 5 h and poured into saturated aq K_2CO_3 (5 mL). The phases were separated and the aq layer extracted with CH_2Cl_2 . The combined organic phases were washed with saturated aq $\text{Na}_2\text{S}_2\text{O}_5$ and NaHSO_3 mixture, dried over anhydrous Na_2SO_4 and concentrated. The residue was recrystallized from $\text{H}_2\text{O}/\text{EtOH}$ (1:9) to give the title compound (0.15 g, 69 %).

^1H NMR (400 MHz, CDCl_3) δ 8.09 (1H, d, J = 9.3 Hz), 7.47-7.41 (2H, m), 7.37-7.32 (3H, m), 6.58 (1H, d, J = 9.3 Hz), 4.87 (2H, s), 3.20 (6H, s);

25 ^{13}C -NMR (100 MHz, CDCl_3) δ 158.0, 151.6, 135.8, 131.8, 129.0, 128.8, 127.1, 107.4, 59.3, 38.7;

ESI-MS: 332 $[\text{M}+\text{H}]^+$.

Example 8: 2-Cyclopentylsulfonyl-6-dimethylamino-3-nitropyridine



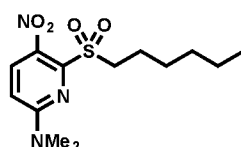
The title compound was prepared in accordance with the procedure in Example 7, Steps (a) to (d), from 2,6-dichloropyridine and cyclopentylmercaptan. The compound did not precipitate and was instead purified by chromatography.

¹H NMR (400 MHz, CDCl₃) δ 8.09 (1H, d, J = 9.3 Hz), 6.59 (1H, d, J = 9.3 Hz), 4.44 (1H, tt, J = 9.1, 6.7 Hz), 3.23 (6H, s), 2.21-2.11 (2H, m), 2.09-1.98 (2H, m), 1.89-1.78 (2H, m), 1.71-1.59 (2H, m);

¹³C-NMR (100 MHz, CDCl₃) δ 158.0, 151.9, 135.8, 107.1, 60.8, 38.6, 27.7, 26.3;

ESI-MS: 300 [M+H]⁺.

10 Example 9: 6-Dimethylamino-2-hexylsulfonyl-3-nitropyridine



The title compound was prepared in accordance with the procedure in Example 7, Steps (a) to (d), from 2,6-dichloropyridine and hexylmercaptan. The compound did not precipitate and was instead purified by chromatography.

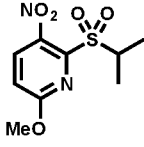
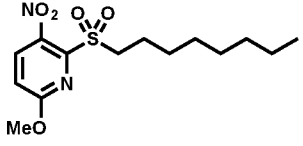
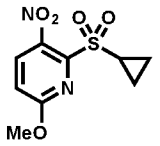
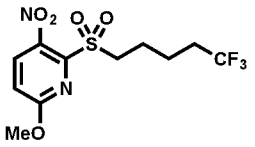
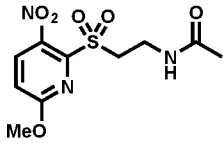
¹H NMR (400 MHz, CDCl₃) δ 8.13 (1H, d, J = 9.4 Hz), 6.61 (1H, d, J = 9.3 Hz), 3.61-3.56 (2H, m), 3.23 (6H, s), 1.94-1.84 (2H, m), 1.51-1.40 (2H, m), 1.36-1.27 (4H, m), 0.91-0.84 (3H, m);

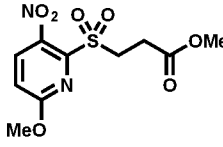
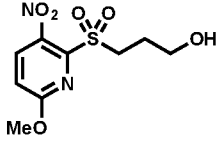
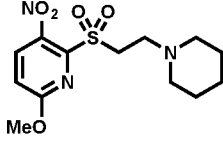
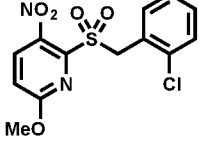
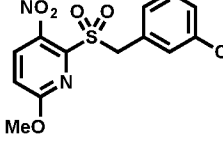
¹³C-NMR (100 MHz, CDCl₃) δ 158.1, 151.9, 136.0, 107.3, 53.3, 38.7, 31.4, 28.5, 22.5, 22.5, 14.1;

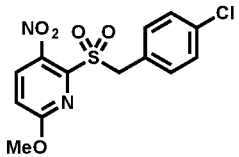
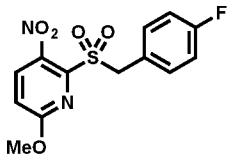
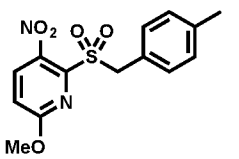
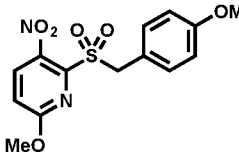
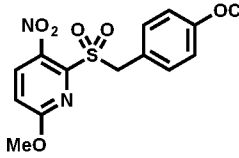
ESI-MS: 316 [M+H]⁺.

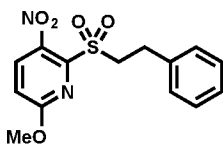
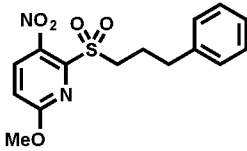
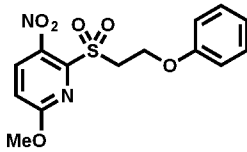
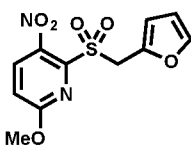
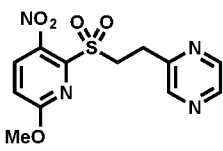
The following example compounds were prepared from 2-chloro-6-methoxy-3-nitropyridine and the appropriate alkylthiol in accordance with the procedure in Example 1, Step a, and Example 4, Step d.

Ex.	Chemical structure	MS [m/z (M+H) ⁺]
	Name	
	¹ H-NMR [solvent, δ]	
10		MS [m/z (M+H) ⁺ =(Calculated for C ₈ H ₁₀ N ₂ O ₅ S+H: 247.04) found: 247.1]

	2-(ethylsulfonyl)-6-methoxy-3-nitropyridine	
	¹ H-NMR [DMSO- <i>d</i> ₆ , δ 8.48 (d, <i>J</i> = 9 Hz, 1H), 7.36 (d, <i>J</i> = 9 Hz, 1H), 4.02 (s, 3H), 3.72-3.67 (m, 2H), 1.26 (t, <i>J</i> = 7 Hz, 3H)]	
11		MS [m/z (M+H) ⁺ =(Calculated for C ₉ H ₁₂ N ₂ O ₅ S+H: 261.06) found: 261.1]
	2-(isopropylsulfonyl)-6-methoxy-3-nitropyridine	
12	¹ H-NMR [CDCl ₃ , δ 8.04 (d, <i>J</i> = 9 Hz, 1H), 7.03 (d, <i>J</i> = 9 Hz, 1H), 4.07-4.06 (m, 4H), 1.43 (d, <i>J</i> = 7 Hz, 6H)]	
		MS [m/z (M+H) ⁺ =(Calculated for C ₁₄ H ₂₂ N ₂ O ₅ S+H: 331.13) found: 331.2]
13	6-methoxy-3-nitro-2-(octylsulfonyl)pyridine	
	¹ H-NMR [CDCl ₃ , δ 8.13 (d, <i>J</i> = 9 Hz, 1H), 7.04 (d, <i>J</i> = 8 Hz, 1H), 4.07 (s, 3H), 3.56 (t, <i>J</i> = 8 Hz, 2H), 1.89-1.86 (m, 2H), 1.46-1.44 (m, 2H), 1.27-1.25 (m, 8H), 0.86 (m, 3H)]	
13		MS [m/z (M+H) ⁺ =(Calculated for C ₉ H ₁₀ N ₃ O ₅ S+H: 259.04) found: 259.1]
	2-(cyclopropylsulfonyl)-6-methoxy-3-nitropyridine	
14	¹ H-NMR [DMSO- <i>d</i> ₆ , δ 8.48 (d, <i>J</i> = 9 Hz, 1H), 7.35 (d, <i>J</i> = 9 Hz, 1H), 4.04 (s, 3H), 3.27-3.23 (m, 1H), 1.24-1.22 (m, 2H), 1.16-1.15 (m, 2H)]	
		MS [m/z (M+H) ⁺ =(Calculated for C ₁₁ H ₁₃ F ₃ N ₂ O ₅ S+H: 343.06) found: 342.8]
15	6-methoxy-3-nitro-2-((5,5,5-trifluoropentyl)sulfonyl)pyridine	
	¹ H-NMR [DMSO- <i>d</i> ₆ , δ 8.48 (d, <i>J</i> = 9 Hz, 1H), 7.37 (d, <i>J</i> = 9 Hz, 1H), 4.02 (s, 3H), 3.76 (t, <i>J</i> = 8 Hz, 2H), 2.34-2.24 (m, 2H), 1.78-1.77 (m, 2H), 1.65-1.63 (m, 2H)]	
15		MS [m/z (M+H) ⁺ =(Calculated for C ₁₀ H ₁₃ N ₂ O ₆ S+H: 304.06) found: 304.2]
	2-(acetamidosulfonyl)-6-methoxy-3-nitropyridine	

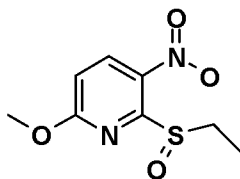
	<i>N</i> -(2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethyl)acetamide	
	¹ H-NMR [DMSO- <i>d</i> ₆ , δ 8.48 (d, <i>J</i> = 9 Hz, 1H), 8.06-8.04 (m, 1H), 7.35 (d, <i>J</i> = 9 Hz, 1H), 4.05 (s, 3H), 3.86 (t, <i>J</i> = 7 Hz, 2H), 3.45 (q, <i>J</i> = 7 Hz, 2H), 1.69 (s, 3H)]	
16		MS [m/z (M+H) ⁺ =(Calculated for C ₁₀ H ₁₂ N ₂ O ₇ S+H: 305.05) found: 305.1]
	methyl 3-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)propanoate	
	¹ H-NMR [DMSO- <i>d</i> ₆ , δ 8.49 (d, <i>J</i> = 9 Hz, 1H), 7.37 (d, <i>J</i> = 9 Hz, 1H), 4.01-3.97 (m, 5H), 3.59 (s, 3H), 2.84 (t, <i>J</i> = 7 Hz, 2H)]	
17		MS [m/z (M+H) ⁺ =(Calculated for C ₉ H ₁₂ N ₂ O ₆ S+H: 277.05) found: 277.1]
	3-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)propan-1-ol	
	¹ H-NMR [CDCl ₃ , δ 8.15 (d, <i>J</i> = 9 Hz, 1H), 7.05 (d, <i>J</i> = 9 Hz, 1H), 4.08 (s, 3H), 3.85-3.73 (m, 4H), 2.17-2.14 (m, 2H), 1.61-1.58 (m, 1H)]	
18		MS [m/z (M+H) ⁺ =(Calculated for C ₁₃ H ₁₉ N ₃ O ₅ S+H: 330.11) found: 330.2]
	6-methoxy-3-nitro-2-((2-(piperidin-1-yl)ethyl)sulfonyl)pyridine	
	¹ H-NMR [CDCl ₃ , δ 8.07 (d, <i>J</i> = 9 Hz, 1H), 7.03 (d, <i>J</i> = 9 Hz, 1H), 4.09 (s, 3H), 3.76 (t, <i>J</i> = 7 Hz, 2H), 2.85 (t, <i>J</i> = 7 Hz, 2H), 2.31 (broad s, 4H), 1.27 (broad s, 6H)]	
19		MS [m/z (M+H) ⁺ =(Calculated for C ₁₃ H ₁₁ ClN ₂ O ₅ S+H: 343.02) found: 342.8]
	2-((2-chlorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine	
	¹ H-NMR [DMSO- <i>d</i> ₆ , δ 8.48 (d, <i>J</i> = 9 Hz, 1H), 7.55 - 7.37 (m, 5H), 5.19 (s, 2H), 3.94 (s, 3H)]	
20		MS [m/z (M+H) ⁺ =(Calculated for C ₁₃ H ₁₁ ClN ₂ O ₅ S+H: 343.02) found: 343.0]
	2-((3-chlorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine	

	¹H-NMR [DMSO- <i>d</i> ₆ , δ 8.46 (d, J = 9 Hz, 1H), 7.49 - 7.28 (m, 5H), 5.11 (s, 2H), 4.05 (s, 3H)]	
21		MS [m/z (M+H) ⁺ =(Calculated for C ₁₃ H ₁₁ ClN ₂ O ₅ S+H: 343.02) found: 343.0]
	2-((4-chlorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine	
	¹H-NMR [CDCl ₃ , δ 8.09 (d, J = 9 Hz, 1H), 7.33 (s, 4H), 7.02 (d, J = 9 Hz, 1H), 4.79 (s, 2H), 4.00 (s, 3H)]	
22		MS [m/z (M+H) ⁺ =(Calculated for C ₁₃ H ₁₁ FN ₂ O ₅ S+H: 327.05) found: 327.0]
	2-((4-fluorobenzyl)sulfonyl)-6-methoxy-3-nitropyridine	
	¹H-NMR [CDCl ₃ , δ 8.09 (d, J = 9 Hz, 1H), 7.42-7.37 (m, 2H), 7.08 - 6.98 (m, 3H), 4.79 (s, 2H), 4.00 (s, 3H)]	
23		MS [m/z (M+H) ⁺ =(Calculated for C ₁₄ H ₁₄ N ₂ O ₅ S+H: 323.07) found: 323.2]
	6-methoxy-2-((4-methylbenzyl)sulfonyl)-3-nitropyridine	
	¹H-NMR [CDCl ₃ , δ 8.06 (d, J = 9 Hz, 1H), 7.28-7.24 (m, 2H), 7.13 (d, J = 8 Hz, 2H), 6.99 (d, J = 9 Hz, 1H), 4.78 (s, 2H), 3.99 (s, 3H), 2.32 (s, 3H)]	
24		MS [m/z (M+H) ⁺ =(Calculated for C ₁₄ H ₁₄ N ₂ O ₆ S+H: 339.07) found: 339.2]
	6-methoxy-2-((4-methoxybenzyl)sulfonyl)-3-nitropyridine	
	¹H-NMR [CDCl ₃ , δ 8.08 (d, J = 9 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 6.99 (d, J = 9 Hz, 1H), 6.86 (d, J = 8 Hz, 2H), 4.77 (s, 2H), 4.01 (s, 3H), 3.79 (s, 3H)]	
25		MS [m/z (M+H) ⁺ =(Calculated for C ₁₄ H ₁₁ F ₃ N ₂ O ₆ S+H:393. 04) found: 392.8]
	6-methoxy-3-nitro-2-((4-(trifluoromethoxy)benzyl)sulfonyl)pyridine	

	¹H-NMR [DMSO- <i>d</i> ₆ , δ 8.46 (d, <i>J</i> = 9 Hz, 1H), 7.50 -7.46 (m, 3H), 7.43-7.35 (m, 3H), 5.13 (s, 2H), 4.03 (s, 3H)]	
26		MS [m/z (M+H) ⁺ =(Calculated for C ₁₄ H ₁₄ N ₂ O ₅ S+H: 323.07) found: 323.1]
	6-methoxy-3-nitro-2-(phenethylsulfonyl)pyridine	
	¹H-NMR [CDCl ₃ , δ 8.11 (d, <i>J</i> = 9 Hz, 1H), 7.30 -7.15 (m, 5H), 7.00 (d, <i>J</i> = 9 Hz, 1H), 4.03 (s, 3H), 3.90-3.86 (m, 2H), 3.22-3.18 (m, 2H)]	
27		MS [m/z (M+H) ⁺ =(Calculated for C ₁₅ H ₁₆ N ₂ O ₅ S+H: 337.07) found: 337.1]
	6-methoxy-3-nitro-2-((3-phenylpropyl)sulfonyl)pyridine	
	¹H-NMR [DMSO- <i>d</i> ₆ , δ 8.46 (d, <i>J</i> = 9 Hz, 1H), 7.34 (d, <i>J</i> = 9 Hz, 1H), 7.32 - 7.15 (m, 5H), 3.90 (s, 3H), 3.67 (t, <i>J</i> = 7 Hz, 2H), 2.73 (t, <i>J</i> = 7 Hz, 2H) 1.99-1.95 (m, 2H)]	
28		MS [m/z (M+H) ⁺ =(Calculated for C ₁₄ H ₁₄ N ₂ O ₆ S+H: 339.07) found: 338.8]
	6-methoxy-3-nitro-2-((2-phenoxyethyl)sulfonyl)pyridine	
	¹H-NMR [CDCl ₃ , δ 8.15 (d, <i>J</i> = 9 Hz, 1H), 7.21 (d, <i>J</i> = 8 Hz, 2H), 7.02 (d, <i>J</i> = 9 Hz, 1H), 6.95 (t, <i>J</i> = 7 Hz, 1H), 6.62 (d, <i>J</i> = 8 Hz, 2H), 4.50 (t, <i>J</i> = 6 Hz, 2H), 4.10 (t, <i>J</i> = 6 Hz, 2H), 3.87 (s, 3H)]	
29		MS [m/z (M+H) ⁺ =(Calculated for C ₁₁ H ₁₀ N ₂ O ₆ S+H: 299.04) found: 299.0]
	2-((furan-2-ylmethyl)sulfonyl)-6-methoxy-3-nitropyridine	
	¹H-NMR [CDCl ₃ , δ 8.13 (d, <i>J</i> = 9 Hz, 1H), 7.36 (s, 1H), 7.02 (d, <i>J</i> = 9 Hz, 1H), 6.48 (s, 1H), 6.35 (s, 1H), 4.96 (s, 2H), 4.07 (s, 3H)]	
30		MS [m/z (M+H) ⁺ =(Calculated for C ₁₂ H ₁₂ N ₄ O ₅ S+H: 325.06) found: 325.1]

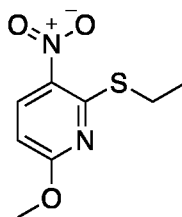
	2-(2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethyl)pyrazine
	¹ H-NMR [DMSO- <i>d</i> ₆ , δ 8.62 (s, 1H), 8.53-8.50 (m, 1H), 8.49-8.46 (m, 2H), 7.33 (d, <i>J</i> = 9 Hz, 1H), 4.20 (t, <i>J</i> = 7 Hz, 2H), 3.99 (s, 3H), 3.32-3.27 (m, 2H)]

Example 31: 2-Ethanesulfinyl-6-methoxy-3-nitro-pyridine



5

(a) 2-Ethanesulfanyl-6-methoxy-3-nitro-pyridine



10 To a solution of 6-methoxy-2-chloro-3-nitro pyridine (5 g, 26.59 mmol) in dimethylformamide (50 mL) was added potassium carbonate (4.44 g, 31.95 mmol) and ethane thiol (1.81g, 29.25 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature. Progress of reaction was monitored by LCMS. The reaction mixture was quenched with ice cold water (35 mL) where in solid precipitated from
15 the reaction mixture. The solid were filtered and washed with ice cold water (3 x 30 mL) and was dried under reduced pressure affording the the sub-title compound as a yellow solid (4.8 g, 84.24%).

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.49 (d, *J*= 9.0 Hz, 1H), 6.75 (d, *J*= 9.0 Hz, 1H), 4.04 (s, 3H), 3.21 (q, *J*= 7.3 Hz, 2H), 1.34 (t, *J*= 7.3 Hz, 3H);

20 LCMS [*m/z* (*M*+*H*)⁺] 215 (MW calc = 214) *R*_t = 1.69

(b) 2-Ethanesulfinyl-6-methoxy-3-nitro-pyridine

To a solution of the compound obtained from step (a) (4.8g, 22.42 mmol) in
25 dichloromethane (100 mL) was added *m*-chloro per benzoic acid (8.84 g, 51.40 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. Progress of reaction was monitored by LCMS. The reaction mixture was diluted with

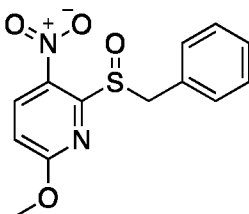
dichloromethane (20 mL) and washed with saturated sodium sulphite solution (2 x 80 mL) followed by brine (1 x 80 mL). The organic layer was dried over anhydrous sodium sulphate and was evaporated under reduced pressure to give the crude product which was purified by column chromatography eluting with 80% ethyl acetate in hexane affording the title compound as a yellow solid (2.6 g, 60.61%).

^1H NMR (DMSO- d_6 , 400 MHz) δ 8.55 (d, J = 8.9 Hz, 1H), 7.16 (d, J = 8.9 Hz, 1H), 4.08 (s, 3H), 3.26-3.18 (m, 1H), 2.97-2.88 (m, 1H), 1.23 (t, J = 7.3 Hz, 3H)

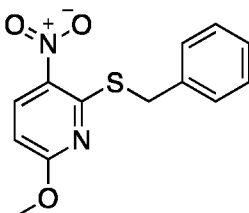
MS [m/z ($M+H$) $^+$] 231 (MW calc = 230), R_t = 1.66

HPLC purity at λ =220nm: 99.38%.

Example 32: 2-Benzylsufinyl-6-methoxy-3-nitro-pyridine



(a) 2-Benzylsulfanyl-6-methoxy-3-nitro-pyridine



To a solution of 6-methoxy-2-chloro-3-nitro pyridine (5.0 g, 26.59 mmol) in dimethylformamide (20 mL) was added potassium carbonate (4.441g, 32.181 mmol) and benzyl mercaptan (3.595g, 28.98 mmol) at room temperature. The reaction mixture was stirred for overnight at room temperature. Progress of reaction was monitored by LCMS. The reaction mixture was quenched with ice cold water (30 mL) and was extracted with ethyl acetate (300 mL). The organic layer was washed with water (3 x 50 mL) followed by brine (1 x 50 mL). The organic layer was dried over anhydrous sodium sulphate and was evaporated under reduced pressure to give the crude product which was purified by column chromatography eluting with 2% ethyl acetate in hexane affording the sub-title compound as pale yellow solid (3.2 g, 43.55%).

^1H NMR (DMSO- d_6 , 400 MHz) δ 8.51 (d, J = 8.96 Hz, 1H), 7.44 (d, J = 7.3 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.29-7.26 (m, 1H), 6.77 (d, J = 8.96 Hz, 1H), 4.52 (s, 2H), 4.01 (s, 3H); LCMS [m/z ($M+H$) $^+$] 277 (MW calc = 276); R_t = 1.83

5 (b) 2-Benzylsulfinyl-6-methoxy-3-nitro-pyridine

To a solution of 2-benzylsulfinyl-6-methoxy-3-nitro-pyridine (2.0 g, 72.46 mmol) in dichloromethane (30 mL) was added *m*-chloro per benzoic acid (1.87 g, 10.87 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight.

10 Progress of reaction was monitored by LCMS. The reaction mixture was diluted with dichloromethane (15 mL) and washed with saturated sodium sulphite solution (2 x 10 mL) followed by brine (1 x 20 mL). The organic layer was dried over anhydrous sodium sulphate and was evaporated under reduced pressure to give the crude product which was purified by column chromatography eluting with 40% ethyl acetate in hexane affording the

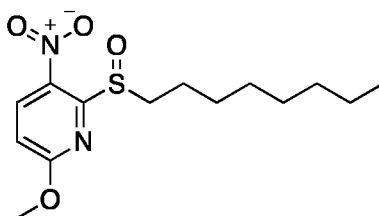
15 title compound as yellow solid (2.0 g, 94.42%).

^1H NMR (DMSO- d_6 , 400 MHz) δ 8.56 (d, J = 8.9 Hz, 1H), 7.33-7.31 (m, 3H), 7.21-7.20 (m, 2H), 7.13 (d, J = 8.96 Hz, 1H), 4.52 (d, J = 12.8 Hz, 1H), 4.09 (d, J = 12.8 Hz, 1H), 3.90 (s, 3H);

LCMS [m/z ($M+H$) $^+$] 293 (MW calc = 292); R_t = 1.74;

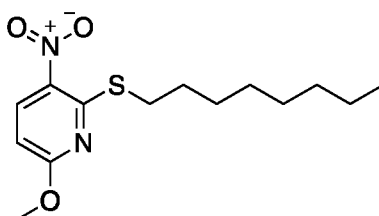
20 HPLC purity at λ =220nm: 98.98%.

Example 33: 6-Methoxy-3-nitro-2-octylsulfinyl-pyridine



25

(a) 6-Methoxy-3-nitro-2-octylsulfinyl-pyridine



To a solution of 6-methoxy-2-chloro-3-nitro pyridine (10 g, 53.191 mmol) in dimethylformamide (50 mL) was added potassium carbonate (8.8 g, 63.829 mmol) and octane-1-thiol (8.54 g, 58.51 mmol) at room temperature. The reaction mixture was stirred for 12 hours at room temperature. Progress of reaction was monitored by LCMS. The reaction mixture was quenched with ice cold water (100 mL) and was extracted with ethyl acetate (200 mL). The organic layer was washed with water (3 x 75 mL) followed by brine (1 x 50 mL). The organic layer was dried over anhydrous sodium sulphate and was evaporated under reduced pressure to give the crude product which was purified by column chromatography eluting with 10% ethyl acetate in hexane affording the sub-title compound as yellow solid (13 g, 82%).

¹H NMR (DMSO-d₆, 400 MHz) δ 8.48 (d, J= 9.0 Hz, 1H), 6.74 (d, J= 9.0 Hz, 1H), 4.02 (s, 3H), 3.18 (t, J= 7.4 Hz, 2H), 1.75-1.65 (m, 2H), 1.42-1.35 (m, 2H), 1.3-1.2 (m, 8H), 0.86-0.83 (m, 3H);

¹³C NMR (DMSO-d₆, 100 MHz) δ 164.0, 158.0, 137.3, 135.8, 106.4, 54.5, 31.1, 30.0, 28.57, 28.52, 28.38, 21.9, 13.8;

LCMS [m/z (M+H)⁺] 299 (MW calc = 298) R_t = 2.12

(b) 6-Methoxy-3-nitro-2-octylsulfinyl-pyridine

To a solution of 6-methoxy-3-nitro-2-octylsulfinyl-pyridine (600 mg, 2.013 mmol) in dichloromethane (10 mL) was added m-chloro per benzoic acid (519 mg, 3.020 mmol) at 0°C. The reaction mixture was stirred at room temperature for 4 hours. Progress of reaction was monitored by LCMS. The reaction mixture was quenched with sodium sulphite and sodium bicarbonate (1:1) solution for 20 minutes. The reaction mixture was extracted with dichloromethane (3x30 mL) and combined organic layer was washed with brine (1 x 20 mL). The organic layer was separated and dried over anhydrous sodium sulphate and was evaporated under reduced pressure to give the crude product which was purified by column chromatography eluting with 50% ethyl acetate in hexane affording the title compound as brown sticky liquid (430 mg, 68%).

¹H NMR (DMSO-d₆, 400 MHz) δ 8.54 (d, J= 8.9 Hz, 1H), 7.15 (d, J= 8.9 Hz, 1H), 4.08 (s, 3H), 3.20-3.13 (m, 1H), 2.87-2.81 (m, 1H), 1.86-1.79 (m, 1H), 1.70-1.67 (m, 1H), 1.45-1.40 (m, 2H), 1.29-1.21 (m, 8H), 0.88-0.81 (m, 3H);

¹³C NMR (DMSO-d₆, 100 MHz) δ 165.8, 161.6, 137.2, 136.8, 112.5, 55.1, 53.8, 31.0, 28.44, 28.4, 27.7, 22.4, 21.9, 13.7;

MS [m/z (M+H)⁺] 315 (MW calc = 314); R_t = 1.92;

HPLC purity at λ=220nm: 99.80%.

Biological Examples

Biological Example 1: Inhibition of recombinant TrxR1 and GR

- 5 Small molecule inhibition of recombinant thioredoxin reductase 1 (TrxR1) and glutathione reductase (GR) was examined in 96-well plate format. 30nM TrxR1 was incubated in the presence of 250μM NADPH, 0.1mg/ml BSA, and various concentrations of compound (1% DMSO final) in 50mM Tris (pH 7.5) and 2mM EDTA buffer for 15 minutes. Following the incubation period, 2mM DTNB was added to each well and the change in O.D. at 412nm
- 10 was followed. Percent activity was determined using DMSO vehicle and no TrxR1 (blank) controls. 2nM GR was incubated in the presence of 250μM NADPH, 0.1mg/ml BSA, and various concentrations of compounds (1% DMSO final) in 50mM Tris (pH 7.5) and 2mM EDTA buffer for 15 minutes. Following the incubation period, 1mM GSSG was added to each well and the change in O.D. at 340nm was followed. Percent activity was determined
- 15 using DMSO vehicle and no GR (blank) controls.

Using the assays described in Biological Example 1, the following IC₅₀ values were obtained. The results obtained are provided in Table 1 below.

Example #	TrxR Assay IC ₅₀ (nM)	GR Assay IC ₅₀ (μM)
1	18.2	>100μM
2	1030	>100μM
3	489	>100μM
4	39.2	18.1
5	181	60.5
6	56.0	8.76
7	276	>100μM
8	188	>100μM
9	333	>100μM
10	124	>100μM
11	204	>100μM
12	12.3	>100μM
13	160	>100μM
14	96.9	>100μM
15	122	>100μM
16	60.6	>100μM
17	103	>100μM
18	1.52	>100μM

19	7.60	>100μM
20	7.16	>100μM
21	4.35	>100μM
22	5.05	>100μM
23	14.51	>100μM
24	25.3	>100μM
25	1.03	>100μM
26	18.8	>100μM
27	7.33	>100μM
28	20.3	>100μM
29	6.78	>100μM
30	66.9	>100μM
31	131.3	>100μM
32	76.5	-
33	500	85.4

Biological Example 2: Head and neck cancer cell viability assay

5 FaDu cells were plated 2000 cells/well in 96-well black optical plates in the presence of 10% FBS media containing 25nM selenite. The following day cells were treated with various concentrations of the compound of Example 1 (0.1% DMSO final) and incubated for 72hrs. After the incubation Cell-Quanti Blue reagent was added to each well and incubated for additional 3hrs. Fluorescence was read ex:530nm/em:590nm, and percent of viability was determined using DMSO vehicle and no cell (blank) controls.

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Using the assays described in Biological Example 2, the following IC₅₀ values were obtained. The results obtained are provided in Table 2 below.

Example #	FaDu Cell IC ₅₀ (μM)
1	0.28
2	3.65
3	0.45
4	0.66
5	1.01
6	0.71
7	2.88
8	6.97
9	12.69

Biological Example 3: Breast cancer cell viability assay

- MDA-MB-231 cells were plated 2000 cells/well in 96-well black optical plates in the presence of 10% FBS media containing 25nM selenite. The following day cells were treated with various concentrations of compounds (0.1% DMSO final) and incubated for 72hrs. After the incubation Alamar Blue reagent was added to each well and incubated for additional 3hrs. Fluorescence was read ex:530nm/em:590nm, and percent of viability was determined using DMSO vehicle and no cell (blank) controls.
- Using the assays described in Biological Example 3, the following IC₅₀ values were obtained. The results obtained are provided in Table 3 below.

Example #	MDA-MB-231 Cell viability IC ₅₀ (μM)
1	3.81
10	2.95
12	4.51
14	5.6
15	11.36
16	8.09
17	12.46
19	1.8
20	3.2
21	4.1
22	1.85
24	3.5
26	5.22
27	7.13
28	5.24
29	4.36
30	2.66

Biological Example 4: Cancer cell viability assay

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Breast cancer and glioblastoma cell lines were plated 4000 cells/well in 96-well plates in the presence of 10% FBS media. The following day cells were treated with various concentrations of the example compounds (0.1% DMSO final) and incubated for 72hrs.

After the incubation An MTT assay was performed to access cell viability. Percent of viability was determined using DMSO vehicle and no cell (blank) controls.

Using the assays described in Biological Example 4, the following IC₅₀ values were obtained. The results obtained are provided in Table 4 below.

Example #	U-87 MG IC50 (μM)	MDA-MB-231 IC50 (μM)	MDA-MB-468 IC50 (μM)
1	6.11	1.8	2.89
10	5.95	5.12	3.16
11	6	7.1	4.9
13	6.92	5.91	4.68
14	7.52	7.73	3.88
15	16.27	18.4	5.47
16	5.23	4.9	3.9
17	19.53	>33μM	9.77
31	6.22	3.51	3.23
32	2.48	1.42	0.64
33	9.25	3.84	1.85

Biological Example 5: *In vivo* mouse study

Athymic nude mice were inoculated orthotopically with 5x10⁶ MDA-MB-231 breast cancer cells into the mammary fat pad, and randomized for treatment when tumors reached an average volume of 80-120 mm³ (N=12 in each group).

Mice were either treated with 25 mg/kg of the compound of Example 10 via intravenous injection (IV) or intraperitoneal injection (IP), or with vehicle alone by intravenous injection, once a day for the first five days, followed by two days of no treatment, then three times per week for two weeks and four days totaling 12 doses.

Xenograft tumor volume was assessed using caliper measurements for 25 days. The results obtained are provided in Figure 1.

Biological Example 6: *In vivo* mouse study

Athymic nude mice were inoculated orthotopically with 5x10⁶ MDA-MB-231 breast cancer cells into the mammary fat pad, and randomized for treatment when tumors reached an average volume of 80-120 mm³ (N=12 in each group).

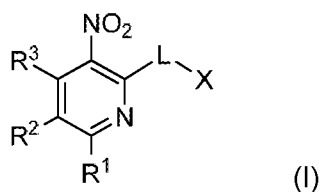
Mice were either treated with 10 mg/kg of the compound of Example 10, 10 mg/kg of the compound of Example 12, or 5 mg/kg of the compound of Example 31 via intravenous injection, or with the respective vehicle via intravenous injection, once a day using a 5 day on, two day off (5/2) dosing regimen for the duration of the experiment.

5

Xenograft tumor volume was assessed using caliper measurements for 25 days. The results obtained are provided in Figure 2.

Claims

1. A compound of formula I



or a pharmaceutically acceptable salt thereof, wherein:

L represents $-S(O)_n-$;

n represents 2 or 1;

X represents C_{1-12} alkyl, C_{2-12} alkenyl or C_{2-12} alkynyl each optionally substituted by one or more groups independently selected from Y;

R^1 represents halo, $-N(R^{j1})R^{k1}$, $-OR^{l1}$ or $-SR^{m1}$;

R^2 and R^3 each independently represent H, halo, R^{a1} , $-CN$, $-A^{a1}-C(Q^{a1})R^{b1}$, $-A^{b1}-C(Q^{b1})N(R^{c1})R^{d1}$, $-A^{c1}-C(Q^{c1})OR^{e1}$, $-A^{d1}-S(O)_pR^{f1}$, $-A^{e1}-S(O)_pN(R^{g1})R^{h1}$, $-A^{f1}-S(O)_pOR^{i1}$, $-N_3$, $-N(R^{j1})R^{k1}$, $-N(H)CN$, $-NO_2$, $-ONO_2$, $-OR^{l1}$ or $-SR^{m1}$;

each A^{a1} to A^{f1} independently represents a single bond, $-N(R^{p1})-$ or $-O-$;

each Q^{a1} to Q^{c1} independently represents $=O$, $=S$, $=NR^{n1}$ or $=N(OR^{o1})$;

each R^{a1} and R^{f1} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^{1a} , heterocyclyl optionally substituted by one or more groups independently selected from G^{1b} , aryl optionally substituted by one or more groups independently selected from G^{1c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{1d} ;

each R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{g1} , R^{h1} , R^{i1} , R^{j1} , R^{k1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} and R^{p1} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or

more groups independently selected from G^{1a} , heterocyclyl optionally substituted by one or more groups independently selected from G^{1b} , aryl optionally substituted by one or more groups independently selected from G^{1c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{1d} ;

5

any of R^{c1} and R^{d1} , R^{g1} and R^{h1} and/or R^{j1} and R^{k1} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^{1b} , C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl each optionally substituted by one or more G^{1a} , and =O;

10

each G^{1a} and G^{1b} independently represents halo, -CN, $-N(R^{a2})R^{b2}$, $-OR^{c2}$, $-SR^{d2}$ or =O;

each R^{a2} , R^{b2} , R^{c2} and R^{d2} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more fluoro; or

15

R^{a2} and R^{b2} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from fluoro and C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl each optionally substituted by one or more fluoro;

20

each Y independently represents halo, R^{a3} , -CN, $-A^{a2}-C(Q^{a2})R^{b3}$, $-A^{b2}-C(Q^{b2})N(R^{c3})R^{d3}$, $-A^{c2}-C(Q^{c2})OR^{e3}$, $-A^{d2}-S(O)_qR^{f3}$, $-A^{e2}-S(O)_qN(R^{g3})R^{h3}$, $-A^{f2}-S(O)_qOR^{i3}$, $-N_3$, $-N(R^{j3})R^{k3}$, $-N(H)CN$, $-NO_2$, $-ONO_2$, $-OR^{l3}$, $-SR^{m3}$ or =O;

25

each Q^{a2} to Q^{c2} independently represents =O, =S, $=NR^{n3}$ or $=N(OR^{o3})$;

each A^{a2} to A^{f2} independently represents a single bond, $-N(R^{p3})-$ or $-O-$;

30

each R^{a3} independently represents heterocyclyl optionally substituted by one or more groups independently selected from G^{2b} , aryl optionally substituted by one or more groups independently selected from G^{2c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{2d} ;

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each R^{f3} independently represents C_{1-6} alkyl optionally substituted by one or more groups independently selected from G^{2a} , heterocyclyl optionally substituted by one or more groups

independently selected from G^{2b} , aryl optionally substituted by one or more groups independently selected from G^{2c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{2d} ;

- 5 each R^{b3} , R^{c3} , R^{d3} , R^{e3} , R^{g3} , R^{h3} , R^{i3} , R^{j3} , R^{k3} , R^{l3} , R^{m3} , R^{n3} , R^{o3} and R^{p3} independently represents H, C_{1-6} alkyl optionally substituted by one or more groups independently selected from G^{2a} , heterocyclyl optionally substituted by one or more groups independently selected from G^{2b} , aryl optionally substituted by one or more groups independently selected from G^{2c} , or heteroaryl optionally substituted by one or more groups
10 independently selected from G^{2d} ; or

- any two R^{c3} and R^{d3} , R^{g3} and R^{h3} and/or R^{j3} and R^{k3} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one
15 or more groups independently selected from heterocyclyl optionally substituted by one or more groups independently selected from G^{2b} , aryl optionally substituted by one or more groups independently selected from G^{2c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{2d} , and =O;

- 20 each G^{2a} independently represents halo, -CN, $-N(R^{j4})R^{k4}$, $-OR^{l4}$, $-SR^{m4}$ or =O;

each G^{2b} independently represents halo, R^{a4} , -CN, $-N(R^{j4})R^{k4}$, $-OR^{l4}$, $-SR^{m4}$ or =O;

- each G^{2c} and G^{2d} independently represents halo, R^{a4} , -CN, $-A^{a3}-C(Q^{a4})R^{b4}$,
25 $-A^{b3}-C(Q^{b3})N(R^{c4})R^{d4}$, $-A^{c3}-C(Q^{c3})OR^{e4}$, $-A^{d3}-S(O)_qR^{f4}$, $-A^{e3}-S(O)_qN(R^{g4})R^{h4}$,
 $-A^{f3}-S(O)_qOR^{i4}$, $-N_3$, $-N(R^{j4})R^{k4}$, $-N(H)CN$, $-NO_2$, $-ONO_2$, $-OR^{l4}$ or $-SR^{m4}$;

each Q^{a3} to Q^{c3} independently represents =O, =S, $=NR^{n4}$ or $=N(OR^{o4})$;

- 30 each A^{a3} to A^{f3} independently represents a single bond, $-N(R^{p4})-$ or $-O-$;

- each R^{a4} and R^{f4} independently represents C_{1-6} alkyl optionally substituted by one or more groups independently selected from G^{3a} , heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} , aryl optionally substituted by one or more groups
35 independently selected from G^{3c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{3d} ;

each R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{g4} , R^{h4} , R^{i4} , R^{j4} , R^{k4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} and R^{p4} independently represents H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^{3a} or heterocyclyl optionally substituted by one or more groups independently selected from G^{3b} , aryl optionally substituted by one or more groups independently selected from G^{3c} , or heteroaryl optionally substituted by one or more groups independently selected from G^{3d} ; or

any of R^{c4} and R^{d4} , R^{g4} and R^{h4} and/or R^{i4} and R^{k4} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected G^{3b} ;

each G^{3a} and G^{3b} independently represents halo, R^{a5} , $-CN$, $-N(R^{b5})R^{c5}$, $-OR^{d5}$, $-SR^{e5}$ or $=O$;

each R^{a5} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^4 ;

each R^{b5} , R^{c5} , R^{d5} and R^{e5} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more groups independently selected from G^4 ;
or

each R^{b5} and R^{c5} are linked together to form, together with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups independently selected from G^4 ;

each G^4 independently represents halo, R^{a6} , $-CN$, $-N(R^{b6})R^{c6}$, $-OR^{d6}$ or $=O$;

each R^{a6} independently represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more fluoro;

each R^{b6} , R^{c6} and R^{d6} independently represents H, or C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl each optionally substituted by one or more fluoro; and

each p and q independently represents 1 or 2,

with the provisos that the compound of formula I does not represent:

(A)

- 2-((1-chloropropan-2-yl)sulfonyl)-6-methoxy-3-nitropyridine,
 2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethane-1-sulfonamide,
 5 2-((2-chloroethyl)sulfonyl)-6-methoxy-3-nitropyridine,
 2-((4-chlorobutan-2-yl)sulfonyl)-6-methoxy-3-nitropyridine,
 2-((6-methoxy-3-nitropyridin-2-yl)sulfonyl)ethane-1-sulfonyl chloride,
 2-((3-chloro-2-methylpropyl)sulfonyl)-6-methoxy-3-nitropyridine,
 2-((3-chloropropyl)sulfonyl)-6-methoxy-3-nitropyridine,
 10 6-methoxy-3-nitro-2-(vinylsulfonyl)pyridine,
 6-methoxy-2-(methylsulfonyl)-3-nitropyridine,
 6-(2,6-dichloro-4-(trifluoromethyl)phenoxy)-2-(methylsulfonyl)-3-nitropyridine,
 6-(2,6-dichloro-4-(trifluoromethoxy)phenoxy)-2-(methylsulfonyl)-3-nitropyridine, or
 6-(2,6-dichloro-4-(trifluoromethyl)phenoxy)-2-(ethylsulfonyl)-3-nitropyridine;

15

or

(B)

2-(butylsulfinyl)-3-nitro-pyridine;

20

or

(C)

- 3-[(3-nitro-2-pyridinyl)sulfinyl]-2-propenoic acid methyl ester,
 25 3-[(3-nitro-2-pyridinyl)sulfinyl]-2-propenoic acid ethyl ester,
 6-[(2-methylpropyl)sulfinyl]-5-nitro-2-methanesulfonate-2-pyridinol,
 3-chloro-2-[(6-chloro-3-nitro-2-pyridinyl)sulfinyl]-benzoic acid ethyl ester,
 3-nitro-2-[(4-piperidinylmethyl)sulfinyl]-pyridine,
 3-nitro-2-[(3-pyrrolidinylmethyl)sulfinyl]-pyridine,
 30 3-nitro-2-[(3-piperidinylmethyl)sulfinyl]-pyridine,
 3-nitro-2-[(2-pyrrolidinylmethyl)sulfinyl]-pyridine,
 3-nitro-2-[(2-piperidinylmethyl)sulfinyl]-pyridine,
 4-[(3-nitro-2-pyridinyl)sulfinylmethyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester,
 3-[(3-nitro-2-pyridinyl)sulfinylmethyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester,
 35 3-[(3-nitro-2-pyridinyl)sulfinylmethyl]-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl
 ester,
 2-[(3-nitro-2-pyridinyl)sulfinylmethyl]-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester,

2-[[[(3-nitro-2-pyridinyl)sulfinyl]methyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester,
6-[2,6-dichloro-4-(trifluoromethoxy)phenoxy]-2-(methylsulfinyl)-3-nitro-pyridine, or
6-[2,6-dichloro-4-(trifluoromethyl)phenoxy]-2-(ethylsulfinyl)-3-nitro-pyridine.

5 2. A compound as claimed in Claim 1, wherein X represents C₁₋₈ alkyl, C₂₋₈ alkenyl or C₂₋₈ alkynyl.

3. A compound as claimed in Claim 1 or Claim 2, wherein when X represents C₁ alkyl X is substituted with at least one Y group.

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4. A compound as claimed in any one of Claims 1 to 3, wherein each Y independently represents halo, R^{a3}, -CN, -C(O)N(R^{c3})R^{d3}, -N(R^{p3})C(O)R^{b3}, -C(O)OR^{e3}, -N(R^{j3})R^{k3}, -OR^{l3}, -SR^{m3} or =O.

15 5. A compound as claimed in any one of Claims 1 to 4, wherein each Y independently represents halo, R^{a3}, -C(O)N(R^{c3})R^{d3}, -N(H)C(O)R^{b3}, -C(O)OR^{e3}, -N(R^{j3})R^{k3} or -OR^{l3}.

6. A compound as claimed in any one of Claims 1 to 5, wherein:

R¹ represents halo, -N(R^{j1})R^{k1}, -OR^{l1} or -SR^{m1}; and/or

20 R² and R³ each independently represent H, halo, R^{a1}, -N(R^{j1})R^{k1}, -OR^{l1} or -SR^{m1}.

7. A compound as claimed in any one of Claims 1 to 6, wherein each R^{a1}, R^{j1}, R^{k1}, R^{l1} and R^{m1} independently represent C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl each optionally substituted by one or more fluoro.

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8. A compound as claimed in any one of Claims 1 to 7, wherein:

R¹ represents halo, -N(R^{j1})R^{k1} or -OR^{l1}; and/or

R² and R³ each independently represent H, halo, R^{a1}, -N(R^{j1})R^{k1} or -OR^{l1}.

30 9. A compound as claimed in any one of Claims 1 to 8, wherein each R^{a1}, R^{j1}, R^{k1}, R^{l1} and R^{m1} independently represent C₁₋₆ alkyl optionally substituted by one or more fluoro.

10. A compound as claimed in any one of Claims 1 to 9, wherein:

35 R¹ represents halo, -N(R^{j1})R^{k1} or -OR^{l1};

R² and R³ each independently represent H, halo (e.g. chloro), -N(R^{j1})R^{k1} or -OR^{l1};

each R^{l1} independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) optionally substituted by one or more fluoro (such as methyl, difluoromethyl, trifluoromethyl group); and/or (e.g. and)

5

each R^{j1} and R^{k1} independently represent C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl (e.g. C₁₋₆ alkyl) optionally substituted by one or more fluoro (such as a methyl group).

11. A compound as claimed in any one of Claims 1 to 10, wherein R¹ represents a group other than H.

10

12. A compound as claimed in any one of Claims 1 to 10, wherein:

R² and R³ represent H; and/or

15

R¹ represents halo, -N(CH₃)₂ or -OCH₃.

13. A compound as defined in any one of Claims 1 to 12 but without provisos (A) and (C) for use as a pharmaceutical.

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14. A compound as defined in any one of Claims 1 to 12 but without provisos (A) and (C) for use in the treatment of cancer.

15. The use of a compound as defined in any one of Claims 1 to 12 but without provisos (A) and (C) for the manufacture of a medicament for the treatment of cancer.

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16. A method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a compound as defined in any one of Claims 1 to 12 but without provisos (A) and (C).

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17. The compound for use, use or method of Claims 14 to 16, wherein the cancer is selected from the group consisting of:

soft tissue cancers, such as sarcoma, myxoma, rhabdomyoma, fibroma, lipoma and teratoma;

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lung cancers, such as bronchogenic carcinoma, alveolar or bronchiolar carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

- gastrointestinal cancers: such as esophageal cancers, stomach cancers, pancreatic cancers, small bowel cancers, large bowel cancers;
- genitourinary tract cancers, such as cancer of the kidney, bladder and urethra, prostate, testis;
- 5 liver cancers, such as hepatoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;
- bone cancers, such as osteogenic sarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, multiple myeloma, malignant giant cell tumor chordoma, osteochondroma, benign chondroma, chondroblastoma,
- 10 chondromyxofibroma, osteoid osteoma and giant cell tumors;
- cancers of the head and/or nervous system, such as cancer of the skull, meninges, brain, spinal cord;
- gynecological cancers, such as cancers of the uterus, cervix, ovaries, cancers of the vulva, vagina, fallopian tubes;
- 15 haematologic cancers, such as cancers of the blood and bone marrow, Hodgkin's disease, non-Hodgkin's lymphoma;
- skin cancers, such as malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids; neurofibromatosis and adrenal glands; and
- 20 neuroblastomas.

18. The compound for use, use or method of Claims 14 to 17, wherein the cancer is a solid tumor cancer.

- 25 19. A pharmaceutical composition comprising a compound as defined in any one of Claims 1 to 12 but without provisos (A) and (C), and optionally one or more pharmaceutically acceptable adjuvant, diluent and/or carrier.

20. A combination product comprising:

- 30 (A) a compound as defined in any one of Claims 1 to 12 but without provisos (A) and (C); and
- (B) one or more other therapeutic agent that is useful in the treatment of cancer, wherein each of components (A) and (B) is formulated in admixture, optionally with one or more a pharmaceutically-acceptable adjuvant, diluent or carrier.

35

21. A kit-of-parts comprising:

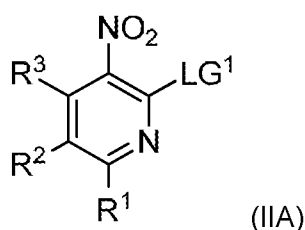
- (a) a pharmaceutical formulation as defined in Claim 19; and

(b) one or more other therapeutic agent that is useful in the treatment of cancer, optionally in admixture with one or more pharmaceutically-acceptable adjuvant, diluent or carrier,

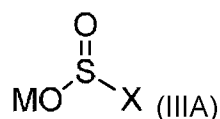
which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

22. A process for the preparation of a compound as defined in any one of Claims 1 to 12, which process comprises:

(i) where n represents 2, reaction of a compound of formula IIA

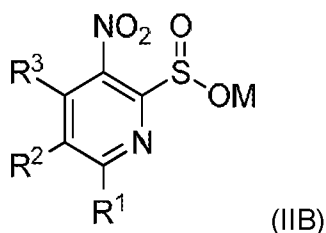


wherein R¹, R² and R³ are as defined in any one of Claims 1 to 12 and LG¹ represents a suitable leaving group, with a compound of formula IIIA

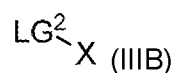


wherein X is as defined in any one of Claims 1 to 12 and M represents an alkali metal ion, in the presence of a suitable acid and in the presence of a suitable solvent, and optionally in the presence of a suitable phase transfer catalyst;

(ii) where n represents 2, reaction of a compound of formula IIB



wherein R¹, R² and R³ are as defined in any one of Claims 1 to 12 and M represents an alkali metal ion, with a compound of formula IIIB

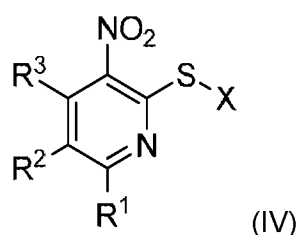


wherein X is as defined in any one of Claims 1 to 12 and LG^2 represents a suitable leaving group, in the presence of a suitable acid and in the presence of a suitable solvent, and optionally in the presence of a suitable phase transfer catalyst;

(iii) where n represents 2, reaction of a compound of formula IIA with a compound of formula IIIA, in the presence of a suitable metal halide and in the presence of a suitable solvent;

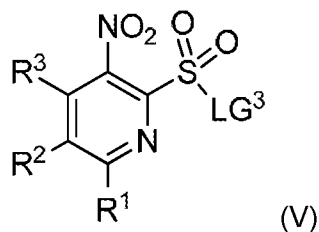
(iv) where n represents 2, reaction of a compound of formula IIB with a compound of formula IIIB, in the presence of a suitable metal halide and in the presence of a suitable solvent;

(v) reaction of a compound of formula IV

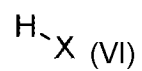


wherein R^1 to R^3 and X are as defined in any one of Claims 1 to 12, with a suitable oxidising agent in the presence of a suitable solvent, and optionally in the presence of water;

(vi) where n represents 2, reaction of a compound of formula V



wherein R^1 , R^2 and R^3 are as defined in any one of Claims 1 to 12 and LG^3 represents a suitable leaving group with a compound of formula VI

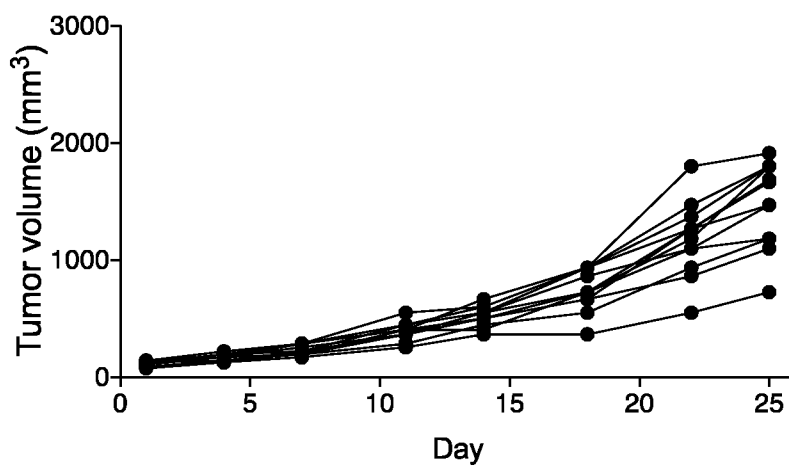


wherein X is as defined in any one of Claims 1 to 12, in the presence of a suitable Lewis
5 acid and in the presence of a suitable solvent.

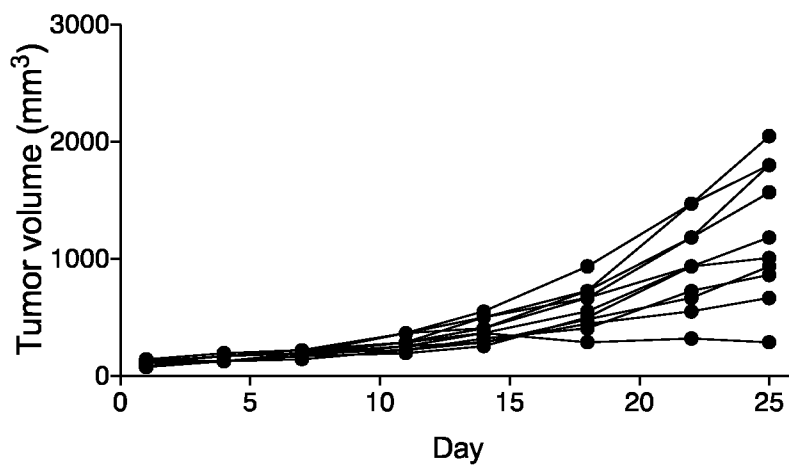
23. A compound, compound for use, use, method, formulation, formulation for use or
process substantially as described herein, with reference to the examples.

1/2

Vehicle



Example 10 IV (TGI: 25%)



Example 10 IP (TGI: 25%)

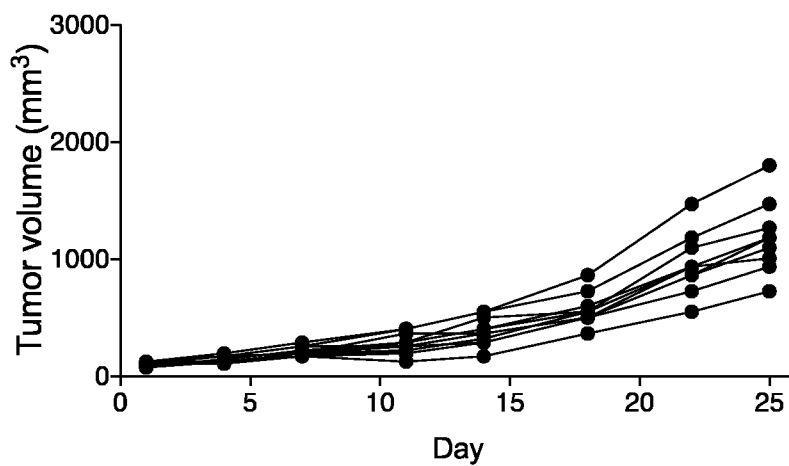


FIGURE 1

2/2

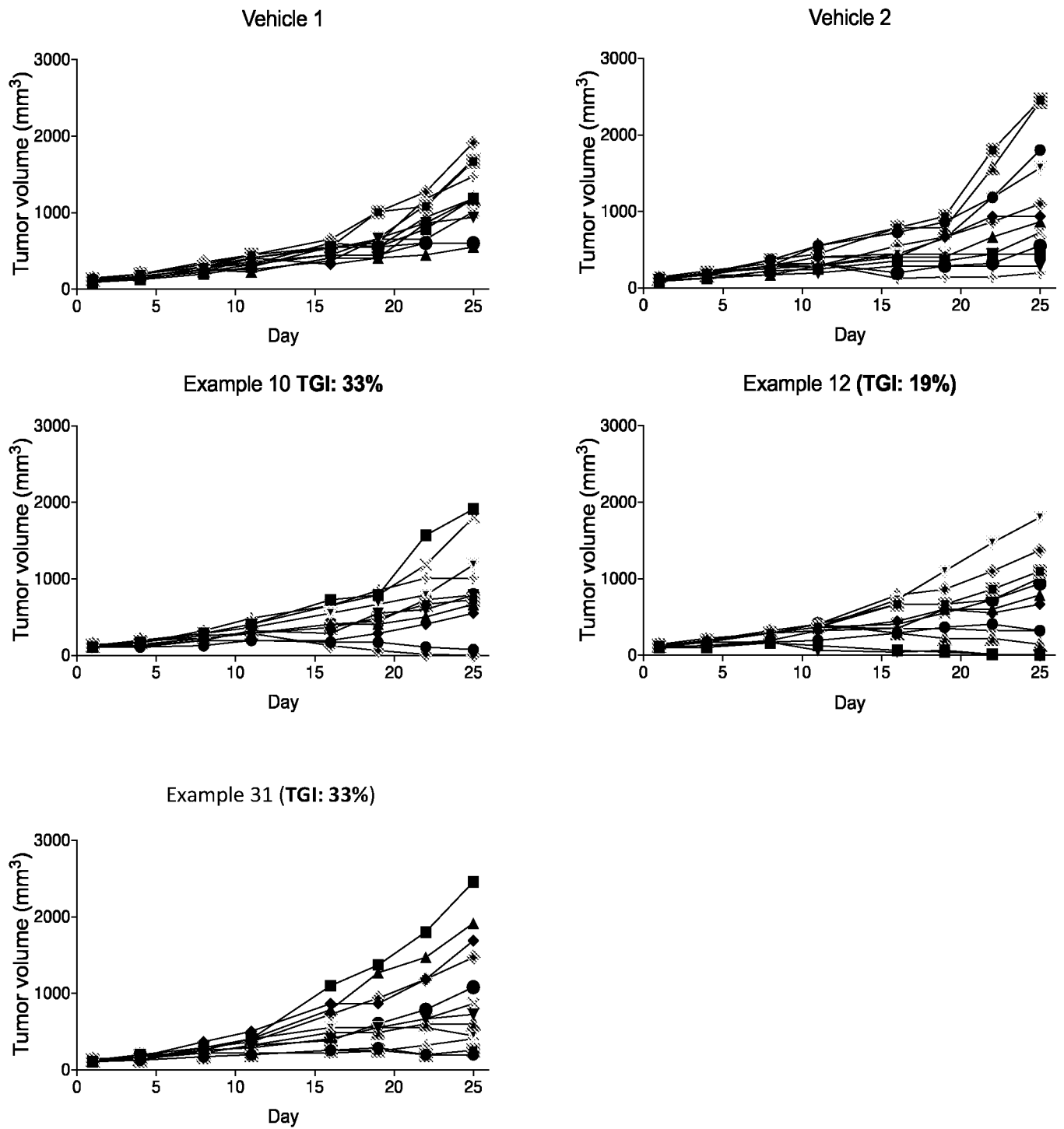


FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/050346

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/71 A61K31/44 C07D401/12 C07D405/12
ADD. A61P35/00

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)

C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 195 31 148 A1 (BASF AG [DE]) 27 February 1997 (1997-02-27) page 63; table 4; compound Ia513 -----	1,3,6, 11,12
A	EP 2 366 691 A1 (BEIJING YILING BIOENGINEERING CO LTD [CN]) 21 September 2011 (2011-09-21) claims 1-5 -----	1-23
A,P	WO 2017/027359 A1 (ARNÉR ELIAS SET JENÖ [SE]; THE USA AS REPRESENTED BY THE SECRETARY DEP) 16 February 2017 (2017-02-16) claims 1-21 -----	1-23



Further documents are listed in the continuation of Box C.



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

14 May 2018

Date of mailing of the international search report

25/05/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Rufet, Jacques

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2018/050346

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-23(partially)
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:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims 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 an 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 claims 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 claims 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-23(partially)

The subject-matter of claims 1 to 23 relates to an extremely large number of possible compounds and pharmaceutical compositions thereof, due to the fact that formula (I) contains so many options, variables, possible permutations and provisos. Support and disclosure within the meaning of Articles 6 and 5 PCT are to be found, however, for only a very small proportion of the compounds claimed, namely the 33 compounds of the examples.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1 to 23 (PCT Guidelines 9.19 and 9.23).

Consequently, the search of claims 1 to 23 was restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae, namely to compounds of formula (I) wherein:

- R1 is always present and represents halo, NRj1Rk1, -ORl1 or -SRm1, wherein Rj1, Rk1, Rl1 or Rm1 represent hydrogen, alkyl, alkenyl or alkynyl optionally substituted by one or more fluoro atom;

- R2 and R3 have the definition given in claim 1;

- L-X has the definition given in claim 1.

It is stressed that all exemplified compounds have been searched.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2018/050346

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			ZA	9607171 B		20-03-1998

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			EP	2366691 A1		21-09-2011
			US	2012071515 A1		22-03-2012
			US	2014073796 A1		13-03-2014
			WO	2010048880 A1		06-05-2010

WO 2017027359	A1	16-02-2017	AU	2016306276 A1		22-02-2018
			CA	2995077 A1		16-02-2017
			KR	20180035904 A		06-04-2018
			WO	2017027359 A1		16-02-2017
