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(54) Titre : UTILISATION DE 4-(4-FLUORO-2-METHOXYPHENYL)-N-{3-[(S-METHYLSULFONIMIDOYL)METHYL]PHENYL}-1,3,5-TRIAZIN-2-AMINE POUR LE TRAITEMENT DU MYELOME MULTIPLE
(54) Title: USE OF 4-(4-FLUORO-2-METHOXYPHENYL)-N-{3-[(S-METHYLSULFONIMIDOYL)METHYL]PHENYL}-1,3,5-TRIAZIN-2-AMINE FOR TREATING MULTIPLE MYELOMA

(57) **Abrégé/Abstract:**

The present invention relates to the use of 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A), more particularly (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A'), for treating multiple myeloma.



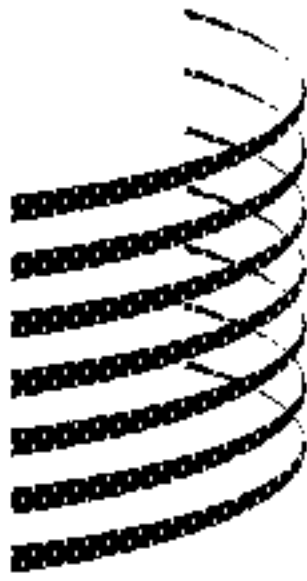
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- (54) Title: USE OF 4-(4-FLUORO-2-METHOXYPHENYL)-N-{3-[(S-METHYLSULFONIMIDOYL)METHYL]PHENYL}-1,3,5-TRIAZIN-2-AMINE FOR TREATING MULTIPLE MYELOMA
- (57) Abstract: The present invention relates to the use of 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A), more particularly (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A'), for treating multiple myeloma.

Use of 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine for treating multiple myeloma

- 5 The present invention relates to the use of 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A), more particularly (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A'), for treating multiple myeloma.
- 10 The family of cyclin-dependent kinase (CDK) proteins consists of members that are key regulators of the cell division cycle (cell cycle CDK's), that are involved in regulation of gene transcription (transcriptional CDK's), and of members with other functions. CDKs require for activation the association with a regulatory cyclin subunit. The cell cycle CDKs CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclinE, CDK4/cyclinD, and CDK6/cyclinD get activated in a sequential order to drive a cell
- 15 into and through the cell division cycle. The transcriptional CDKs CDK9/cyclin T and CDK7/cyclin H regulate the activity of RNA polymerase II via phosphorylation of the carboxy-terminal domain (CTD). Positive transcription factor b (P-TEFb) is a heterodimer of CDK9 and one of four cyclin partners, cyclin T1, cyclin K, cyclin T2a or T2b.
- 20 Whereas CDK9 (NCBI GenBank Gene ID 1025) is exclusively involved in transcriptional regulation, CDK7 in addition participates in cell cycle regulation as CDK-activating kinase (CAK). Transcription of genes by RNA polymerase II is initiated by assembly of the pre-initiation complex at the promoter region and phosphorylation of Ser 5 and Ser 7 of the CTD by CDK7/cyclin H. For a major fraction of genes RNA polymerase II stops mRNA transcription after it moved 20-40
- 25 nucleotides along the DNA template. This promoter-proximal pausing of RNA polymerase II is mediated by negative elongation factors and is recognized as a major control mechanism to regulate expression of rapidly induced genes in response to a variety of stimuli (Cho et al., Cell Cycle **2010**, 9, 1697). P-TEFb is crucially involved in overcoming promoter-proximal pausing of RNA polymerase II and transition into a productive elongation state by phosphorylation of Ser 2 of the CTD as well as by
- 30 phosphorylation and inactivation of negative elongation factors.

Activity of P-TEFb itself is regulated by several mechanisms. About half of cellular P-TEFb exists in an inactive complex with 7SK small nuclear RNA (7SK snRNA), La-related protein 7 (LARP7/PIP7S) and hexamethylene bis-acetamide inducible proteins 1/2 (HEXIM1/2, He et al., Mol. Cell **2008**, 29, 588). The remaining half of P-TEFb exists in an active complex containing the bromodomain protein Brd4 (Yang et al., Mol. Cell **2005**, 19, 535). Brd4 recruits P-TEFb through interaction with acetylated

histones to chromatin areas primed for gene transcription. Through alternately interacting with its positive and negative regulators, P-TEFb is maintained in a functional equilibrium: P-TEFb bound to the 7SK snRNA complex represents a reservoir from which active P-TEFb can be released on demand of cellular transcription and cell proliferation (Zhou & Yik, Microbiol. Mol. Biol. Rev. **2006**, 70, 646).

5 Furthermore, the activity of P-TEFb is regulated by posttranslational modifications including phosphorylation/de-phosphorylation, ubiquitination, and acetylation (reviewed in Cho et al., Cell Cycle **2010**, 9, 1697).

Deregulated CDK9 kinase activity of the P-TEFb heterodimer is associated with a variety of human
10 pathological settings such as hyper-proliferative diseases (e.g. cancer), virally induced infectious diseases or cardiovascular diseases.

Cancer is regarded as a hyper-proliferative disorder mediated by a disbalance of proliferation and cell death (apoptosis). High levels of anti-apoptotic Bcl-2-family proteins are found in various human
15 tumours and account for prolonged survival of tumour cells and therapy resistance. Inhibition of P-TEFb kinase activity was shown to reduce transcriptional activity of RNA polymerase II leading to a decline of short-lived anti-apoptotic proteins, especially Mcl-1 and XIAP, reinstalling the ability of tumour cells to undergo apoptosis. A number of other proteins associated with the transformed tumour phenotype (such as Myc, NF-kB responsive gene transcripts, mitotic kinases) are either short-lived
20 proteins or are encoded by short-lived transcripts which are sensitive to reduced RNA polymerase II activity mediated by P-TEFb inhibition (reviewed in Wang & Fischer, Trends Pharmacol. Sci. **2008**, 29, 302).

Many viruses rely on the transcriptional machinery of the host cell for the transcription of their own
25 genome. In case of HIV-1 RNA polymerase II gets recruited to the promoter region within the viral LTR's. The viral transcription activator (Tat) protein binds to nascent viral transcripts and overcomes promoter-proximal RNA polymerase II pausing by recruitment of P-TEFb which in turn promotes transcriptional elongation. Furthermore, the Tat protein increases the fraction of active P-TEFb by replacement of the P-TEFb inhibitory proteins HEXIM1/2 within the 7SK snRNA complex. Recent
30 data have shown that inhibition of the kinase activity of P-TEFb is sufficient to block HIV-1 replication at kinase inhibitor concentrations that are not cytotoxic to the host cells (reviewed in Wang & Fischer, Trends Pharmacol. Sci. **2008**, 29, 302). Similarly, recruitment of P-TEFb by viral proteins has been reported for other viruses such as B-cell cancer-associated Epstein-Barr virus, where the nuclear antigen EBNA2 protein interacts with P-TEFb (Bark-Jones et al., Oncogene **2006**, 25, 1775),

and the human T-lymphotropic virus type 1 (HTLV-1), where the transcriptional activator Tax recruits P-TEFb (Zhou et al., J. Virol. **2006**, 80, 4781).

Cardiac hypertrophy, the heart's adaptive response to mechanical overload and pressure
5 (hemodynamic stress e.g. hypertension, myocardial infarction), can lead, on a long term, to heart failure and death. Cardiac hypertrophy was shown to be associated with increased transcriptional activity and RNA polymerase II CTD phosphorylation in cardiac muscle cells. P-TEFb was found to be activated by dissociation from the inactive 7SK snRNA/HEXIM1/2 complex. These findings suggest pharmacological inhibition of P-TEFb kinase activity as a therapeutic approach to treat cardiac
10 hypertrophy (reviewed in Dey et al., Cell Cycle **2007**, 6, 1856).

In summary, multiple lines of evidence suggest that selective inhibition of the CDK9 kinase activity of the P-TEFb heterodimer (= CDK9 and one of four cyclin partners, cyclin T1, cyclin K, cyclin T2a or T2b) represents an innovative approach for the treatment of diseases such as cancer, viral diseases,
15 and/or diseases of the heart. CDK9 belongs to a family of at least 13 closely related kinases of which the subgroup of the cell cycle CDK's fulfils multiple roles in regulation of cell proliferation. Thus, co-inhibition of cell cycle CDK's (e.g. CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclinE, CDK4/cyclinD, CDK6/cyclinD) and of CDK9 is expected to impact normal proliferating tissues such as intestinal mucosa, lymphatic and hematopoietic organs, and reproductive organs. To maximize the therapeutic
20 margin of CDK9 kinase inhibitors, molecules with high selectivity towards CDK9 are therefore required.

CDK inhibitors in general as well as CDK9 inhibitors are described in a number of different publications: WO2008129070 and WO2008129071 both describe 2,4 disubstituted aminopyrimidines as CDK
25 inhibitors in general. It is also asserted that some of these compounds may act as selective CDK9 inhibitors (WO2008129070) and as CDK5 inhibitors (WO2008129071), respectively, but no specific CDK9 IC₅₀ (WO2008129070) or CDK5 IC₅₀ (WO200812971) data is presented.

WO2008129080 discloses 4,6 disubstituted aminopyrimidines and demonstrates that these compounds show an inhibitory effect on the protein kinase activity of various protein kinases, such as CDK1,
30 CDK2, CDK4, CDK5, CDK6 and CDK9, with a preference for CDK9 inhibition (example 80).

EP1218360 B1 describes triazin derivatives as kinase inhibitors, but does not disclose potent or selective CDK9 inhibitors.

WO2008079933 discloses aminopyridine and aminopyrimidine derivatives and their use as CDK1,
35 CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8 or CDK9 inhibitors.

WO2011012661 describes aminopyridine derivatives useful as CDK inhibitors.

Wang et al. (Chemistry & Biology **2010**, 17, 1111-1121) describe 2-anilino-4-(thiazol-5-yl)pyrimidine transcriptional CDK inhibitors, which show anticancer activity in animal models.

- 5 WO2004009562 discloses substituted triazine kinase inhibitors. For selected compounds CDK1 and CDK 4 test data, but no CDK9 data is presented.

WO2004072063 describes heteroaryl (pyrimidine, triazine) substituted pyrroles as inhibitors of protein kinases such as ERK2, GSK3, PKA or CDK2.

- 10 WO2010009155 discloses triazine and pyrimidine derivatives as inhibitors of histone deacetylase and/or cyclin dependent kinases (CDKs). For selected compounds CDK2 test data is described.

WO2003037346 (corresponding to US7618968B2, US7291616B2, US2008064700A1, US2003153570A1) relates to aryl triazines and uses thereof, including to inhibit lysophosphatidic acid acyltransferase beta (LPAAT-beta) activity and/or proliferation of cells such as tumour cells.

- 15 WO2008025556 describes carbamoyl sulfoximides having a pyrimidine core, which are useful as kinase inhibitors. No CDK9 data is presented.

WO2002066481 describes pyrimidine derivatives as cyclin dependent kinase inhibitors CDK9 is not mentioned and no CDK9 data is presented.

- 20 WO2008109943 concerns phenyl aminopyri(mi)dine compounds and their use as kinase inhibitors, in particular as JAK2 kinase inhibitors. The specific examples focus on compounds having a pyrimidine core.

WO2009032861 describes substituted pyrimidinyl amines as JNK kinase inhibitors. The specific examples focus on compounds having a pyrimidine core.

- 25 WO2011046970 concerns amino-pyrimidine compounds as inhibitors of TBKL and/or IKK epsilon. The specific examples focus on compounds having a pyrimidine core.

- 30 WO2012160034 the compounds of the present invention. It is disclosed the compounds inhibit the cell proliferation of HeLa cells (cervical cancer), HeLa/MaTu/ADR cells (cervical cancer), NCI-H460 cells (non-small cell lung cancer), DU145 cells (hormone-independent human prostate cancer), Caco-2 cells (colorectal cancer) and B16F10 cells (melanoma).

The object of the present invention is to improve the treatment of multiple myeloma.

Treatment of multiple myeloma

- Multiple myeloma is characterised by clonal proliferation of malignant plasma cells in the bone marrow and, depending on disease stage, is typically accompanied by the secretion of monoclonal immunoglobulins, hypercalcaemia, anaemia and bone damage. The transformation of premalignant plasma cells is a multistep process involving many genetic and microenvironmental changes that support tumour cell growth and survival (Palumba A et al. Multiple Myeloma. N Engl J Med 2011;364:1046-60; Hideshima T et al. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nat Rev Cancer 2007;7:585-98).
- Conventional therapies for multiple myeloma have included the use of alkylating agents (e.g. melphalan), anthracyclines, and corticosteroids. Over the past two decades, high-dose cytotoxic therapy, followed by autologous stem cell transplantation, has been the standard frontline consolidative therapy for newly diagnosed multiple myeloma patients, leading to a modest increase in overall survival (4–5 years) (Hideshima T et al. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nat Rev Cancer 2007;7:585-98). However, the clinical management of multiple myeloma is very challenging, in particular for a patient with relapsed/refractory disease, and is dependent on cytogenetic status, disease burden (e.g. renal failure and bone fractures), in addition to the patient's age and response to previous treatments. Thus, autologous stem cell transplantation is not always an option for every patient (Usmani SZ et al. Novel Drug Combinations for the Management of Relapsed/Refractory Multiple Myeloma. Clin Lymphoma Myeloma Leuk 2013;14 Suppl:S71-7).

- The introduction of novel agents including immunomodulatory/anti-angiogenic drugs (thalidomide, pomalidomide and lenalidomide), proteasome inhibitors (bortezomib and carfilzomib), and liposome-encapsulated doxorubicin (Doxil), have further raised the debate on the role of autologous stem cell transplant therapy for multiple myeloma (Richardson PG et al. Early or delayed transplantation for multiple myeloma in the era of novel therapy: does one size fit all? Hematology Am Soc Hematol Educ Program 2014;(1):255-61). The anti-tumour activity of these drugs arises from the disruption of multiple signalling pathways that support the growth, proliferation, and survival of myeloma cells; Proteasome inhibition stimulates multiple apoptotic pathways, including inhibition of nuclear factor κ B (NF- κ B) signaling (Adams J. The proteasome: a suitable antineoplastic target. Nat Rev Cancer 2004;4:349-60); Immunomodulatory drugs stimulate apoptosis and inhibit angiogenesis, adhesion, and cytokine circuits and stimulate an enhanced host immune response to myeloma cells (Quach H et al. Mechanism of action of immunomodulatory drugs (IMiDs) in multiple myeloma. Leukemia 2010;24:22-32). These novel agents have been incorporated successfully as induction regimens before transplantation, and as both consolidation (2-4 cycles of drug combinations) and maintenance therapy

(continuous therapy with a single agent until disease progression) to significantly improve progression-free and overall survival. The efficacy of these novel therapeutics has also led to investigations into delaying autologous stem cell transplantation in the treatment of multiple myeloma (Richardson PG et al. Early or delayed transplantation for multiple myeloma in the era of novel therapy: does one size fit all? Hematology Am Soc Hematol Educ Program 2014;(1):255-61). However, toxic effects, in particular in consolidation therapy, have been associated with these agents and include peripheral neuropathy, infection and hyperglycaemia. Thus, less intensive approaches that limit toxic effects or prevent treatment interruption are needed in patients over 75 years of age and/or with coexisting conditions (Palumba A et al. Multiple Myeloma. N Engl J Med 2011;364:1046-60).

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Other drugs, such as histone deacetylase inhibitors (vorinostat, panobinostat) or monoclonal antibodies elotuzumab (anti-CS1), daratumumab (anti-CD38), SAR650984 (anti-CD38) and MOR03087 (anti-CD38) are currently under investigation in clinical trials and may improve the prospect of a nontransplantation approach and reduce acute toxicity or long-term complications, inherent to high-dose alkylation, and melphalan exposure in particular (Munshi NC et al. New Strategies in the Treatment of Multiple Myeloma. Clin Cancer Res. 2013;19(13):3337-44).

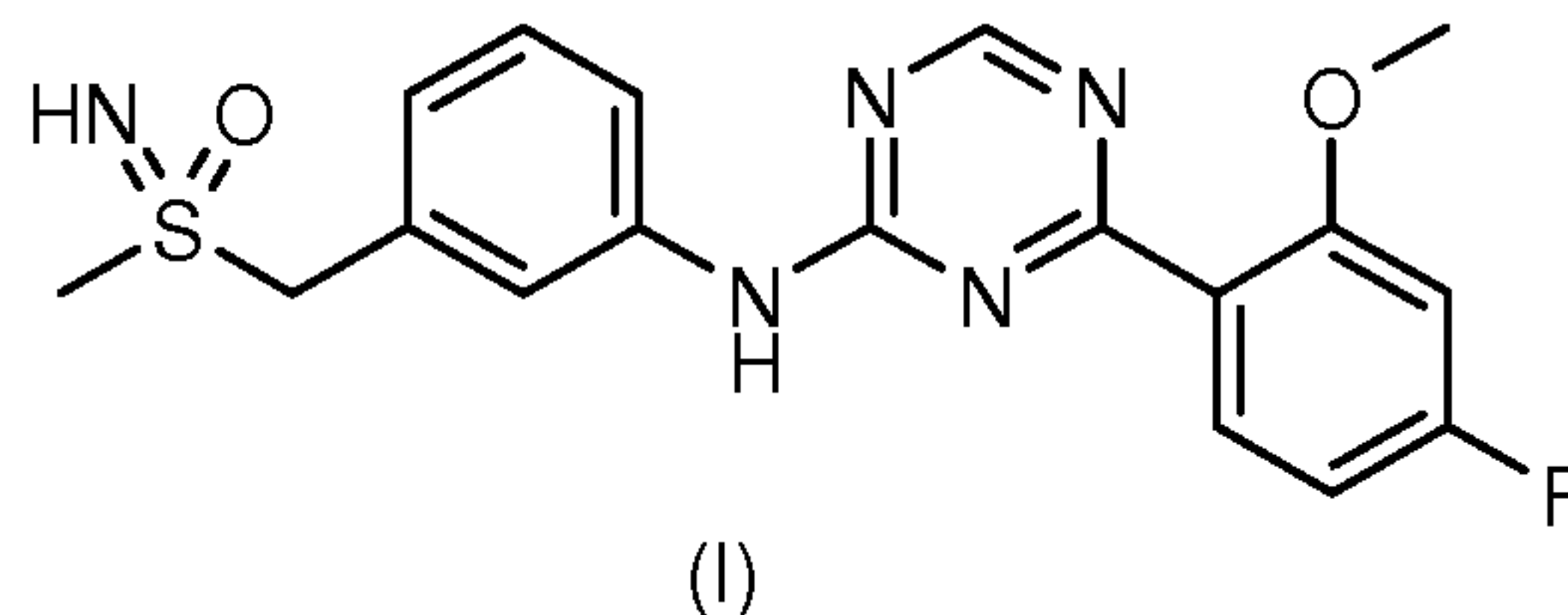
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Due to the genetic heterogeneity of multiple myeloma and the multitude of oncogenes and signalling pathways that drive disease progression (De la Puente P et al. Molecularly Targeted Therapies in Multiple Myeloma. Leuk Res Treatment 2014;976567; Palumba A et al. Multiple Myeloma. N Engl J Med 2011;364:1046-60), continuing preclinical studies are aiming to further delineate the specific pathophysiological mechanisms involved. These studies have led to several investigations into cell cycle inhibitors as therapeutic targets with the aim to enhance tumour cytotoxicity, prevent drug resistance, increase tolerability and to improve patient outcome (Delmore JE et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011;146:904-17; Gojo I et al. The cyclin-dependent kinase inhibitor flavopiridol induces apoptosis in multiple myeloma cells through transcriptional repression and down-regulation of Mcl-1. Clin Cancer Res 2002;8:3527-38; Conroy A et al. SNS-032 is a potent and selective CDK 2, 7 and 9 inhibitor that drives target modulation in patient samples. Cancer Chemother Pharmacol 2009;64:723-32; Santo L et al. AT7519, A novel small molecule multi-cyclin-dependent kinase inhibitor, induces apoptosis in multiple myeloma via GSK-3beta activation and RNA polymerase II inhibition. Oncogene 2010;29(16):2325-36).

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It has now been found that the compound 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A, formula (I)),



Compound A

more particularly

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A'),

acts in specific tumour types which had previously not yet been contemplated, viz. multiple myeloma.

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) is a selected sulfoximine-substituted anilinopyrimidine derivative which can be separated into two stereoisomers, viz.:

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A') and

(-)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A'').

Compound A' is preferred and is in clinical development as BAY1143572.

Where compound A is mentioned below, both the pure stereoisomers A' and A'', and also any mixture of these two, are meant thereby.

The present invention is directed to the use of

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) or one of its physiologically acceptable salts or enantiomers,

more particularly

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A') or one of its physiologically acceptable salts,

for the treatment and/or prophylaxis of multiple myeloma.

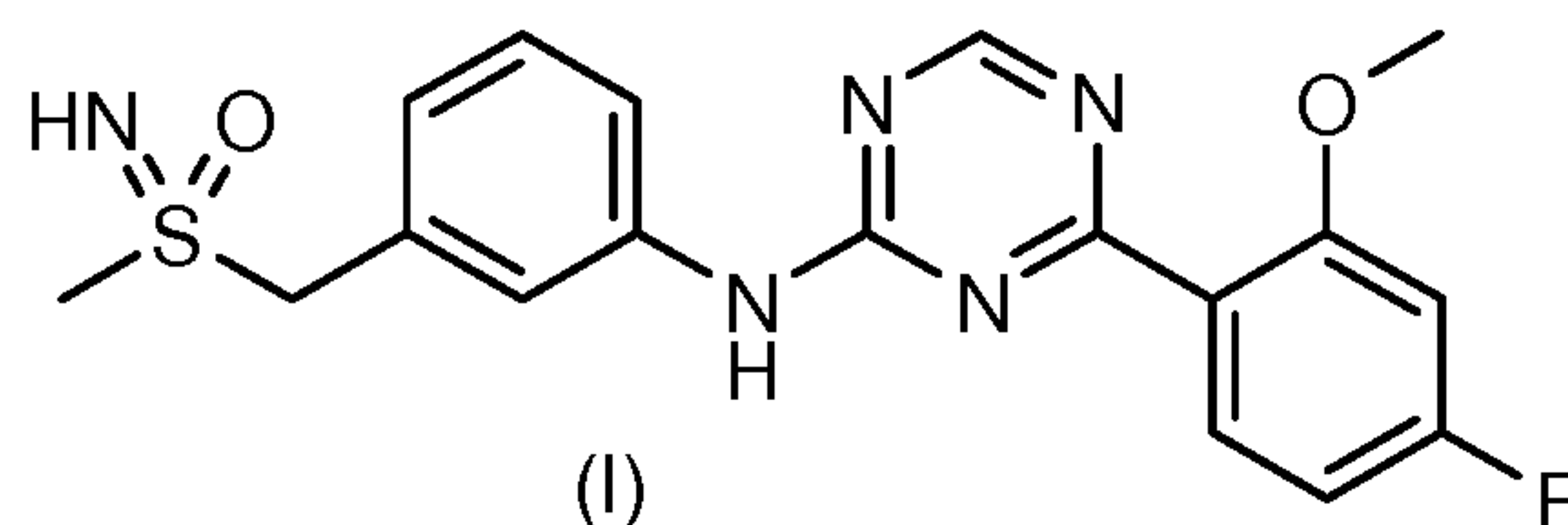
The present application is further directed to the use of

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts or enantiomers, more particularly

- 5 (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts, for preparing a medicament for treating multiple myeloma.

Another aspect of the present invention is the

- 10 use of 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) according to formula (I) or one of its physiologically acceptable salts or enantiomers

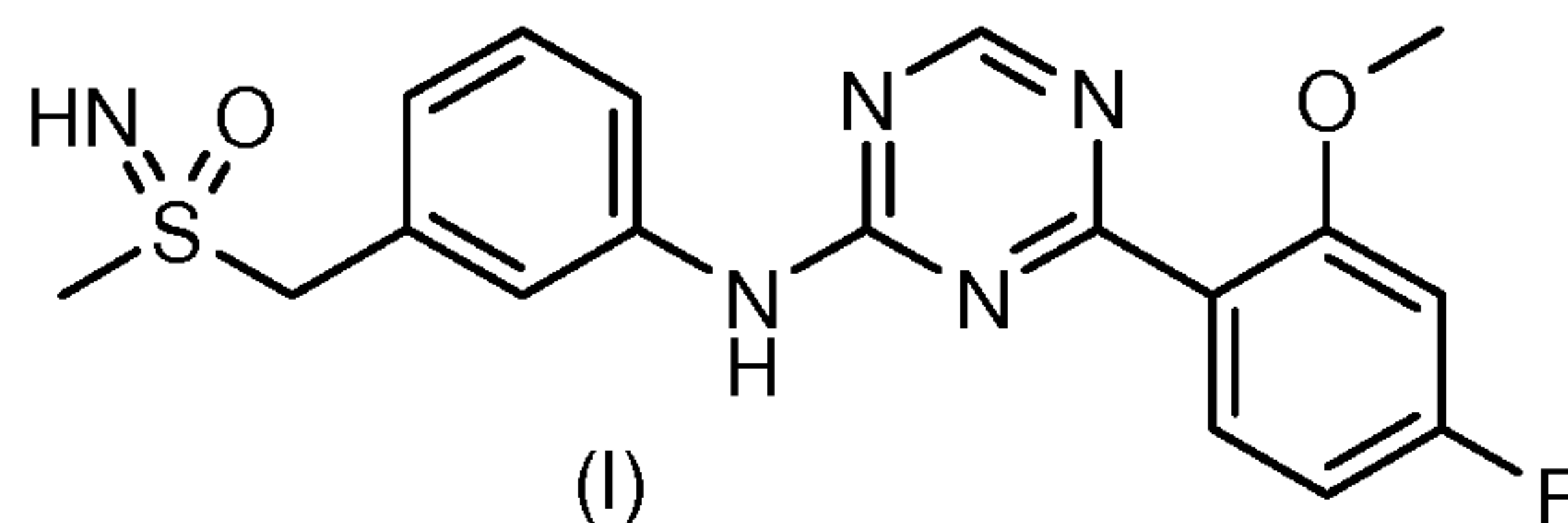


more particularly

- 15 (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is manufactured for treating multiple myeloma.

- 20 The present application further provides

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine of formula I (compound A) or one of its physiologically acceptable salts or enantiomers

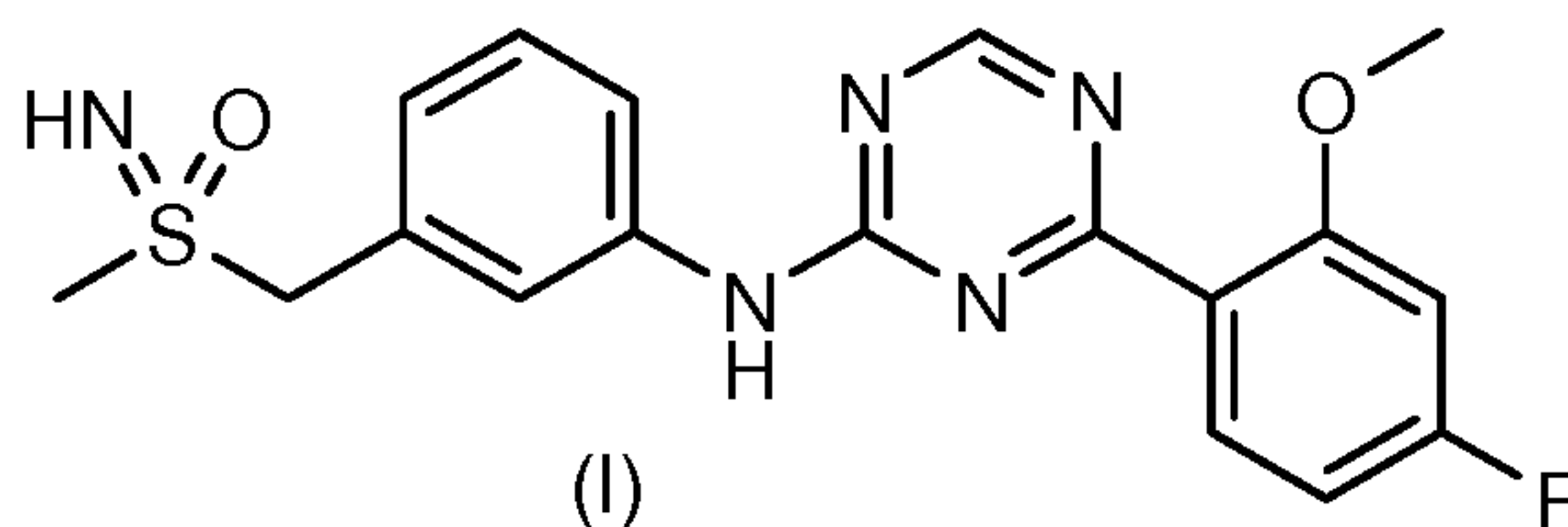


more particularly

- 25 (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts, for the use of treating multiple myeloma.

The present invention is also directed to

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine of formula I (compound A) or one of its physiologically acceptable salts or enantiomers



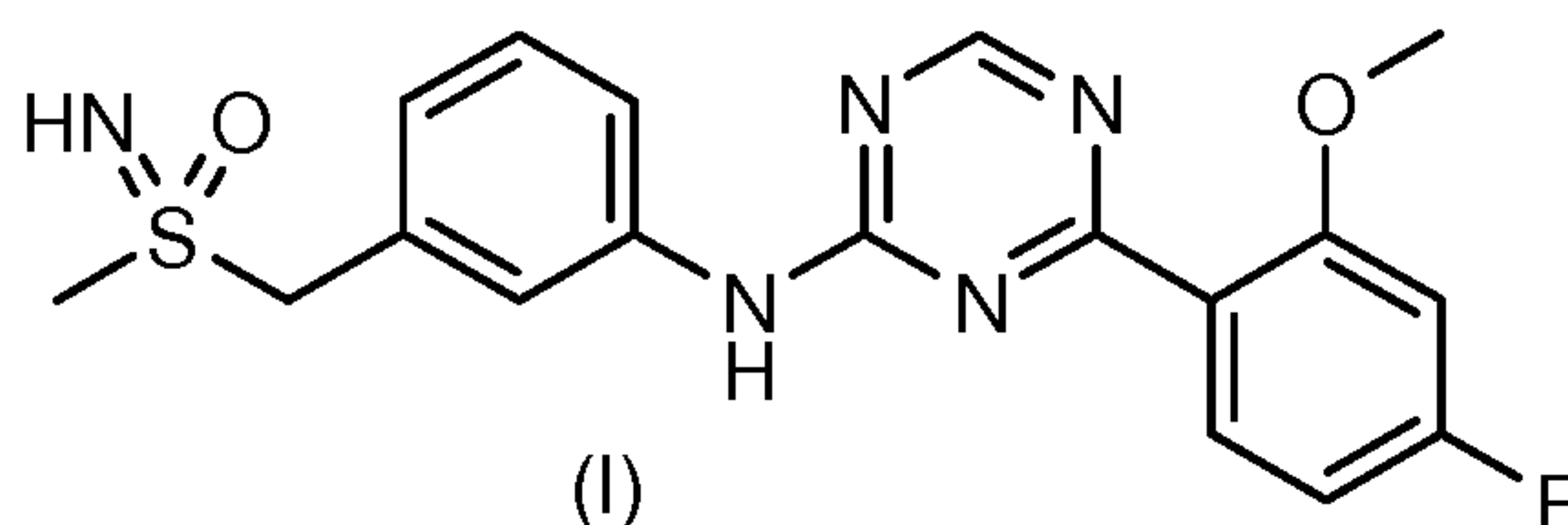
5 more particularly

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts

for the use in a method of treatment and/or prophylaxis of multiple myeloma.

10 Another aspect of the present invention is a method of treatment and/or prophylaxis of multiple myeloma using an effective amount of

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) of formula I or one of its physiologically acceptable salts or enantiomers



15 more particularly

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) or one of its physiologically acceptable salts.

The present application further provides pharmaceutical compositions comprising

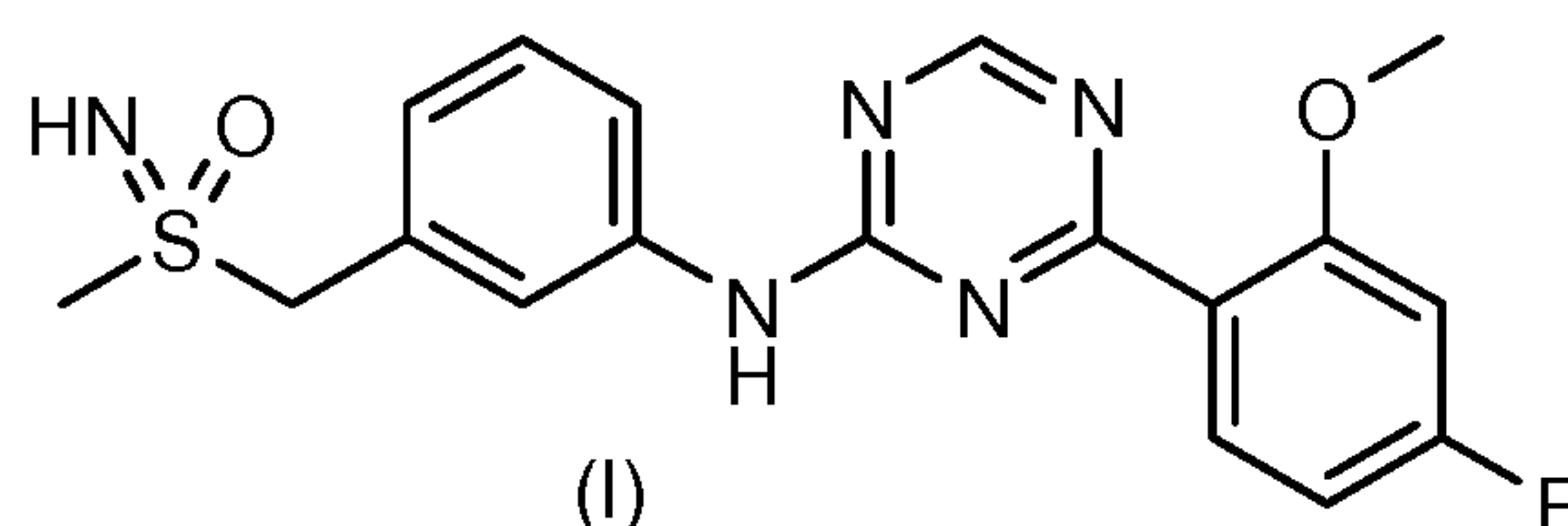
20 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts or enantiomers,

more particularly

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts,

25 for treating multiple myeloma.

The present invention is also directed to pharmaceutical compositions comprising 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) of formula I or one of its physiologically acceptable salts or enantiomers



5 more particularly

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) or one of its physiologically acceptable salts

and at least one inert, nontoxic, pharmaceutically suitable adjuvant for the treatment and/or prophylaxis of multiple myeloma.

10

The present application further provides combinations of

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) or one of its physiologically acceptable salts or enantiomers,

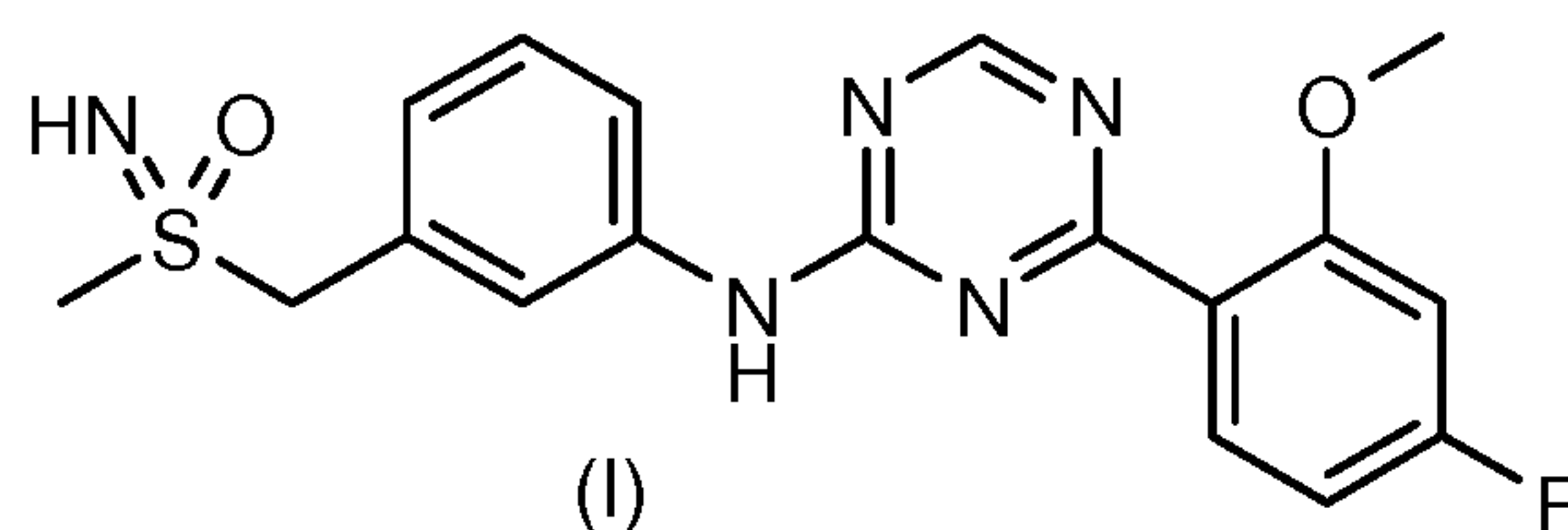
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15 (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) or one of its physiologically acceptable salts,

with at least one further active ingredient for treating multiple myeloma.

The present invention is also directed to pharmaceutical combinations comprising

20 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) of formula I or one of its physiologically acceptable salts or enantiomers



more particularly

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (compound A) or one of its physiologically acceptable salts,

25

and at least one or more further active ingredients for the treatment and/or prophylaxis of multiple myeloma.

The use of the physiologically tolerable salts of compound A should likewise be considered to be covered by the present invention.

- Physiologically safe salts of compound A encompass acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, 5 phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.
- 10 Physiologically safe salts of compound A also encompass salts of customary bases, such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having from 1 to 16 C atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, 15 dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.

The present invention further provides drugs containing compound A and at least one or more further active ingredients for treating multiple myeloma.

- 20 Compound A may have systemic and/or local activity. For this purpose, it can be administered in a suitable manner, such as, for example, orally, parenterally, via the pulmonary route, nasal, sublingually, lingually, buccally, rectally, vaginally, dermally, transdermally, conjunctivally, otically or as an implant or stent.

- 25 For these administration routes, compound A according to the invention may be administered in suitable administration forms.

- Suitable for oral administration forms which function according to the prior art and deliver compound 30 A of the invention rapidly and/or in a modified manner and which comprise compound A according to the invention in crystalline and/or amorphised and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example with coatings which are resistant to gastric juice or dissolve with a delay or are insoluble and control the release of the compound of the invention), tablets which disintegrate rapidly in the oral cavity, or films/wafers, films/lyophilisates, capsules (for example hard 35 or soft gelatine capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms which are suitable for parenteral administration are, inter alia, preparations for
 5 injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia power inhalers, nebulizers], nasal drops, solutions, sprays; tablets, films/wafers or capsules,
 10 to be administered lingually, sublingually or buccally, suppositories, preparations for the eyes and the ears, eye baths, ocular insert, ear drops, ear powders, ear-rinses, ear tampons, vaginal capsules, aqueous suspensions (lotions, mixturae agitandae), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

15 Compound A can be converted into the stated administration forms. This can be affected in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable adjuvants. These adjuvants include, inter alia,

- fillers and excipients (for example cellulose, microcrystalline cellulose, such as, for example, Avicel®, lactose, mannitol, starch, calcium phosphate such as, for example, Di-Cafos®),
 20
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat)
- solvents (for example water, ethanol, Isopropanol, glycerol, propylene glycol, medium chain-
 25 length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulphate, lecithin, phospholipids, fatty alcohols such as, for example, Lanette®, sorbitan fatty acid esters such as, for example, Span®, polyoxyethylene sorbitan fatty acid esters such as, for example, Tween®, polyoxyethylene fatty acid glycerides such as, for example, Cremophor®,
 30 polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers such as, for example, Pluronic®),
- buffers and also acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine)
- 35 • isotonicity agents (for example glucose, sodium chloride),

- adsorbents (for example highly-disperse silicas)
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidon, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids such as, for example, Carbopol®, alginates, gelatine),
- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate such as, for example, Explotab®, cross- linked polyvinylpyrrolidon, croscarmellose-sodium such as, for example, AcDiSol®),
- flow regulators, lubricants, glidant and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas such as, for example, Aerosil®),
- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones such as, for example, Kollidon®, polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropylmethylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®),
- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates such as, for example, Eudragit®, polyvinylpyrrolidones such as, for example, Kollidon®, polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticisers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to medicaments which comprise at least one compound according to the invention, conventionally together with one or more inert, non-toxic, pharmaceutically suitable adjuvants, and to their use for the above mentioned purposes.

Dosage and treatment regimen

The dosage and the treatment regimen can and must be varied depending on the carcinoma type and the treatment goal.

5

The daily dose is generally between 20 mg and 850 mg and can be divided into a plurality of identical or different dosage units, preferably 2 which can be taken simultaneously or according to a certain time schedule.

10 In particular the daily dose is between 30 mg and 500 mg and can be divided into a plurality of identical or different dosage units, preferably 2 which can be taken simultaneously or according to a certain time schedule.

15 A preferred daily dose is between 20 mg and 400 mg and can be divided into a plurality of identical or different dosage units, preferably 2 which can be taken simultaneously or according to a certain time schedule.

20 More particularly, the daily dose is between 40 mg and 300 mg and can be divided into a plurality of identical or different dosage units, preferably 2 which can be taken simultaneously or according to a certain time schedule.

A more preferred daily dose is between 20 mg and 200 mg and can be divided into a plurality of identical or different dosage units, preferably 2 which can be taken simultaneously or according to a certain time schedule.

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An even more preferred daily dose is between 50 mg and 180 mg and can be divided into a plurality of identical or different dosage units, preferably 2 which can be taken simultaneously or according to a certain time schedule.

30 This applies both to monotherapy and to combination therapy with other anti-hyperproliferative, cytostatic or cytotoxic substances, the combination therapy possibly requiring a reduction in dose.

The treatment can be carried out in regularly repeated cycles. Treatment cycles may have varying duration, such as 21 days or 28 days, whereby dosing is given continuously, or intermittently.

35 Preferred is a cycle length of 28 days, whereby dosing is given continuously, or intermittently.

Continuous schedules involve daily dosing, for example, 21 daily doses in a 21-day cycle, or 28 daily doses in a 28-day cycle. A preferred continuous schedule is 28 daily doses in a 28 daily cycle.

Intermittent schedules involve a period of treatment followed by a period of non-treatment, for example in a cycle of 21 days, or a cycle of 28 days. A preferred cycle duration for an intermittent schedule is 28 days.

The period of treatment may be repeated more than once in a given treatment cycle.

The period of treatment may be for example 1 to 21 days, more preferably 3 to 14 days.

An even more preferred intermittent schedule involves treatment for 3 days followed by non-treatment for 4 days, repeated every week in such a way that a 28-day treatment cycle is completed.

Treatment is successful when there is at least disease stabilization and the adverse effects occur to an extent which is easily treatable, but at least easily acceptable. Thus the number of cycles of treatment applied may vary from patient to patient, according to treatment response and tolerability.

Treatment is successful when there is at least disease stabilization and the adverse effects occur to an extent which is easily treatable, but at least easily acceptable.

Compound A can be used on its own or, if required, in combination with one or more other pharmacologically effective substances, provided said combination does not lead to undesired and unacceptable adverse effects. The present invention therefore further provides drugs containing compound A according to the invention and one or more further active ingredients, in particular for treating and/or preventing the above-mentioned diseases.

For example, compound A can be combined with known anti-hyperproliferative, cytostatic or cytotoxic substances for treating cancers. The combination compound A according to the invention with other substances in use for cancer therapy or else with radiotherapy is especially advisable.

Examples of suitable active ingredients for combination purposes include:

abraxane, afinitor, aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzemet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice-BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulphate, broxuridine, bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone,

celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, clodronic acid, cyclophosphamide,
 cytarabine, dacarbazine, dactinomycin, daunoxome, decadron, decadron phosphate, delestrogen,
 denileukin diftitox, depo-medrol, deslorelin, dexrazoxane, diethylstilbestrol, diflucan, docetaxel,
 doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin,
 5 epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine sodium phosphate, ethinyl
 estradiol, ethylol, etidronic acid, etopophos, etoposide, fadrozole, fareston, filgrastim, finasteride,
 fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil
 (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard,
 gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron hydrochloride, histrelin, hycamtin,
 10 hydrocortone, erythro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin,
 ifosfamide, interferon alpha, interferon alpha 2, interferon alpha 2 α , interferon alpha 2 β , interferon
 alpha n1, interferon alpha n3, interferon beta, interferon gamma 1 α , interleukin 2, intron A, iressa,
 irinotecan, kytril, lapatinib, lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate,
 levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol,
 15 mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest,
 6-mercaptopurine, mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane,
 mitoxantrone, modrenal, myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex,
 NSC-631570, OCT-43, octreotide, ondansetron hydrochloride, orapred, oxaliplatin, paclitaxel,
 pediapred, pegaspargase, pegasys, pentostatin, picibanil, pilocarpine hydrochloride, pirarubicin,
 20 plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine,
 procrit, raltitrexed, RDEA119, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide,
 salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, streptozocin,
 strontium-89 chloride, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin,
 temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin,
 25 tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall,
 trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin,
 vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin stimalamer,
 zofran; ABI-007, acolbifene, actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane,
 atrasentan, BAY 43-9006 (sorafenib), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol,
 30 cyproterone acetate, decitabine, DN-101, doxorubicin MTC, dSLIM, dutasteride, edotecarin,
 eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-
 166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone, keyhole limpet
 hemocyanin, L-651582, lanreotide, lasofoxifene, libra, lonafarnib, miproxifen, minodronate, MS-209,
 liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS,
 35 osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549,
 raloxifene, ranpirnase, 13-cis-retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin,

thymosin alpha 1, tiazofurin, tipifarnib, tirapazamine, TLK-286, toremifene, transMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid, and also combinations thereof.

- 5 In a preferred embodiment, compound A of the present invention can be combined with the following active ingredients:

131I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, arglabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, BAY 80-6946, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane, fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gentuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, interferon alpha, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melphalan, mepitiothane, mercaptopurine, methotrexate, methoxsalen, methyl aminolevulinate, methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, ofatumumab, omeprazole, oprelvekin, oxaliplatin, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, pamidronic acid, panitumumab, pazopanib, pegaspargase, PEG-epoetin beta (methoxy-PEG-epoetin beta), pegfilgrastim, peginterferon alfa 2b, pemetrexed, pentazocine, pentostatin, peplomycin, perfosfamide, picibanil, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polysaccharide-K, porfimer sodium, pralatrexate, prednimustine, procarbazine, quinagolide, radium-223 chloride, raloxifene, raltitrexed, ranimustine, razoxane, refametinib, regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, sargramostim, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, streptozocin, sunitinib,

talaporfin, tamibarotene, tamoxifen, tasonermin, teceleukin, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, trilostane, triptorelin, trofosfamide, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Promisingly, compound A can also be combined with biological therapeutics such as antibodies (e.g. avastin, rituxan, erbitux, herceptin, cetuximab) and recombinant proteins.

Compound A can also achieve positive effects in combination with other therapies directed against angiogenesis, such as, for example, with avastin, axitinib, regorafenib, recentin, sorafenib or sunitinib. Combinations with inhibitors of the proteasome and of mTOR and also antihormones and steroidal metabolic enzyme inhibitors are especially useful because of their favourable profile of adverse effects.

In general, the combination of compound A with other cytostatic or cytotoxic agents makes it possible to pursue the following goals:

- improved efficacy in slowing the growth of a tumour, in reducing tumour burden or even in completely eliminating it in comparison with treatment using an individual active ingredient;
- the possibility of employing the chemotherapeutics used in a lower dosage than in the case of monotherapy;
- the possibility of a more tolerable therapy with fewer adverse effects in comparison with individual administration;
- the possibility of treating a broader spectrum of tumour diseases;
- achieving a higher response rate to the therapy;
- longer patient survival time in comparison with current standard therapy.

Furthermore, compound A according to the invention can also be used in connection with radiotherapy and/or a surgical intervention.

Examples

1. Preparation of Compound A

5 Compound A' was prepared according to the procedure described in example 4 of WO2012/160034.

2. Proliferation Assay

Table 1: List of the cell lines investigated and results of the proliferation assays.

	Example	Compound A'
Tumour indication	Cell line	IC₅₀ [nmol/l]
Multiple myeloma	EJM	200
Multiple myeloma	JJN3	330
Multiple myeloma	OPM-2	600
Multiple myeloma	NCI-H929	237

10

After 72 hours of incubation with the substance

3. In Vivo Experiments

The aim of the present experiments was to assess the *in vivo* efficacy and tolerability of
15 Compound A' in monotherapy in the NCI-H929 multiple myeloma xenograft model subcutaneously
implanted into NOD/SCID mice.

3.1 Acronyms and Abbreviations

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Table 2: Acronyms and abbreviations.

BW	Body weight
BW ₀	Individual body weight at day 0
BW _x	Individual body weight at day X
BWL	Body weight loss
n/a	Not applicable
NOD/SCID	Non obese diabetic / severe combined immunodeficiency
p.o.	Per os, orally
T/C	Treatment to control ratio
RTV	Relative tumour volume

3.2 Design

In vivo efficacy was determined in female NOD/SCID mice bearing subcutaneous multiple myeloma NCI-H929 xenografts. Compound A' was assessed at one dose level in monotherapy. Anti-tumour activity and tolerability of the treated group was assessed using the vehicle control group as a reference.

Group ID	Therapy	Total Daily Dose [mg/kg/day]	Schedule [Dosing days]	Appl. Route	No. of Animals
1	Vehicle	10 mL/kg/day	1-17	p.o.	12
2	Compound A'	25	1-28	p.o.	12

3.3 Experimental Procedures

3.3.1. Specific Animal Information

Mouse strain, sex: NOD/SCID, female
Animals supplied by: Harlan

Total number of mice

Efficacy test (implanted / randomised): 78 / 24

Approximate age at implantation: 5-7 weeks

Approximate age at randomisation: 8-10 weeks

Housing conditions

The animals were housed in individually ventilated cages. The animals were monitored twice daily. All materials were autoclaved prior to use. Food and water were provided ad libitum.

3.3.2 Tumour Information

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3.3.2.1 Characterization of Test Tumours

The tumour model used in this study was derived from a commercially available cell line NCI-H929.

3.3.2.2 Tumour Implantation

30

Multiple myeloma tumour fragments, derived from the NCI-H929 cell line, were obtained from xenografts in serial passage in nude mice and placed in PBS containing 10% penicillin/streptomycin. Tumour fragments (one fragment per animal; 3-4 mm edge length) were then subcutaneously implanted in the flank of NOD/SCID recipient mice under isoflurane anaesthesia.

3.3.3 Randomisation

Animals and tumour implants were monitored daily until the maximum number of implants showed clear signs of beginning solid tumour growth. At randomisation, the volume of growing tumours was initially determined. Animals bearing one tumour of a volume of 50 - 250 mm³, preferably 80 – 200 mm³, were distributed in experimental groups according to the study protocol, considering a comparable median and mean of group tumour volume of approximately 100 – 120 mm³. The result of the randomisation was documented and maintained with the experimental data. Animals not randomised were euthanised. The day of randomisation is designated as day 0 of an experiment.

10 3.3.4. Test Reagents

Vehicle: 80% (m/V) PEG400 in water for injection

Compound A': preparation of a dosing solution (2.5 mg/ml) once weekly by diluting the Compound A' powder at 0.25% (w/v) in vehicle; dosing solution stored at 4°C; dosing volume 10 mL/kg.

15 3.3.5. Observations and Calculations

3.3.5.1 Mortality

Mortality checks were conducted daily during routine monitoring.

20 3.3.5.2 Body Weight

Mice were weighed twice a week. Relative body weights of individual mice in % were calculated by dividing the individual body weight on day X (BW_X) by the individual body weight on day 0 (BW₀) multiplied by 100 according to the formula:

$$25 \quad \text{Relative Body Weight (Day}_x\text{) [\%]} = \frac{BW_x}{BW_0} \times 100$$

Group median relative body weights were calculated as well, considering only the weights of mice that were alive on the day in question.

3.3.5.3 Tumour Volume

The tumour volumes were determined by two-dimensional measurement with a caliper on the day of randomisation (day 0) and then twice weekly (i.e. on the same days on which mice were weighed).

35 Tumour volumes were calculated according to the formulas:

$$\text{Tumour volume} = (a \times b^2) \times 0.5$$

where a represents the largest and b the perpendicular tumour diameter.

Relative volumes of individual tumours (RTVs) for Day x were calculated by dividing the absolute individual tumour volume on Day x (T_x) by the absolute individual tumour volume of the same tumour on Day 0 (T_0) multiplied by 100%:

5 $RTV_x [\%] = (T_x / T_0) \times 100$

3.3.5.4 Anti-tumour Activity

Anti-tumour activity was evaluated as maximum tumour volume inhibition versus the vehicle control group.

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3.3.5.5 Tumour Inhibition, Test/Control Value in %

Tumour inhibition for a particular day (T/C in %) was calculated from the ratio of the median RTV values of test versus control groups multiplied by 100.

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$T/C (\text{Day } x) [\%] = \frac{\text{Median relative tumour volume of the test group on Day}_x}{\text{Median relative tumour volume of the control group on Day}_x} = 100$

The minimum (or optimum) T/C% value recorded for a particular test group during an experiment represents the maximum anti-tumour activity for the respective treatment. T/C values were calculated if at least 50% of the randomized animals in the treated group were alive on the day in question.

20

3.3.5.6 Efficacy Criteria

Group optimum T/C values (in %) were used for activity rating as follows:

Table 3: Efficacy criteria.

-	Inactive	$T/C \geq 65\%$
+/-	Borderline activity	$50\% \leq T/C < 65\%$
+	Moderate activity	$25\% \leq T/C < 50\%$
++	High activity	$10\% \leq T/C < 25\%$
+++	Very high activity	$5\% \leq T/C < 10\%$
++++	Complete remission	$T/C < 5\%$

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3.4 Results

3.4.1 Anti-tumour Efficacy of Compound A' in Xenograft-bearing Mice

Compound A' was assessed at one dose level in the NCI-H929 multiple myeloma xenograft model subcutaneously implanted into NOD/SCID mice.

High anti-tumour activity was observed with Compound A' in the NCI-H929 xenograft model with a minimum T/C value of 5.5%. NCI-H929 tumour growth was significantly reduced by Compound A' treatment as compared to the respective vehicle control group and determined by the non-parametric Mann-Whitney-Wilcoxon U-test.

Table 4: Summary of anti-tumour efficacy of Compound A'.

Group ID	Therapy	Dose Level [mg/kg/day]	Schedule	Min. T/C [%] (Day)	Activity Rating
NCI-H929					
1	Vehicle	10 mL/kg/day	1-17	n/a	n/a
2	Compound A'	25	1-28	5.5 (17)	+++

* Vehicle, 80% PEG400 in water for injection

In conclusion, these data indicate significant and meaningful anti-tumour activity of Compound A' in patients with multiple myeloma.

3.4.2. Survival and Body Weight Changes

No or minor group median BWLs $\leq 2.7\%$ was observed. Survival rates $\geq 83\%$ were observed for all groups in this study.

In conclusion, Compound A' showed an acceptable tolerability profile in multiple myeloma xenograft-bearing mice.

3.5. Summary and Conclusion

The *in vivo* efficacy and tolerability of BHC's investigational compound Compound A' was assessed in monotherapy in the NCI-H929 multiple myeloma xenograft model. NCI-H929 tumour fragments, obtained from serial passage in nude mice, were implanted subcutaneously into female NOD/SCID mice. Compound A' was administered orally at one dose level (25 mg/kg/day) in monotherapy once daily and treatment was started once subcutaneous tumours were established. A vehicle-treated control group was included in each experiment. Group size consisted of 12 mice per group. Anti-tumour activity (tumour

growth inhibition) and tolerability of treatment group was assessed using the vehicle control group as a reference.

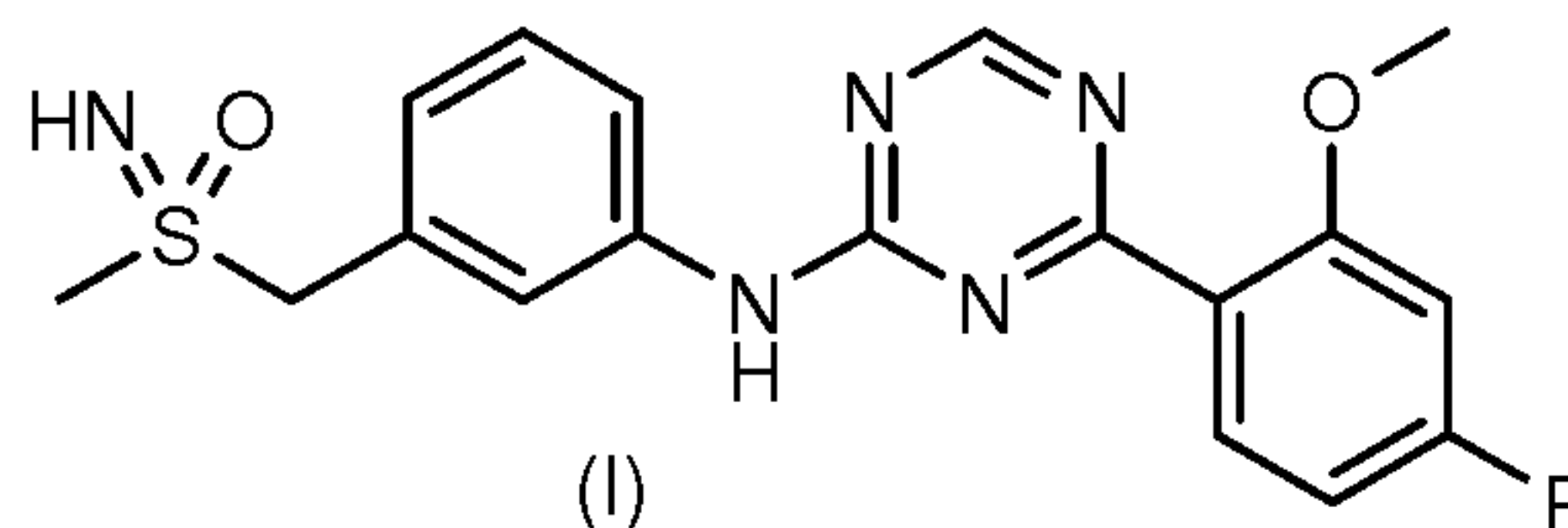
5 High anti-tumour activity was observed in the NCI-H929 tumour xenograft model with a minimum T/C value of 5.5 %. NCI-H929 tumour growth was significantly attenuated by Compound A' treatment as compared to the respective vehicle control group (Mann-Whitney-Wilcoxon U-test). No or minor group median BWLs $\leq 2.7\%$ was observed.

10 In conclusion, these data indicate significant and meaningful anti-tumour activity of Compound A' in patients with multiple myeloma.

Claims

1. Use of

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine according to formula (I) or one of its physiologically acceptable salts or enantiomers



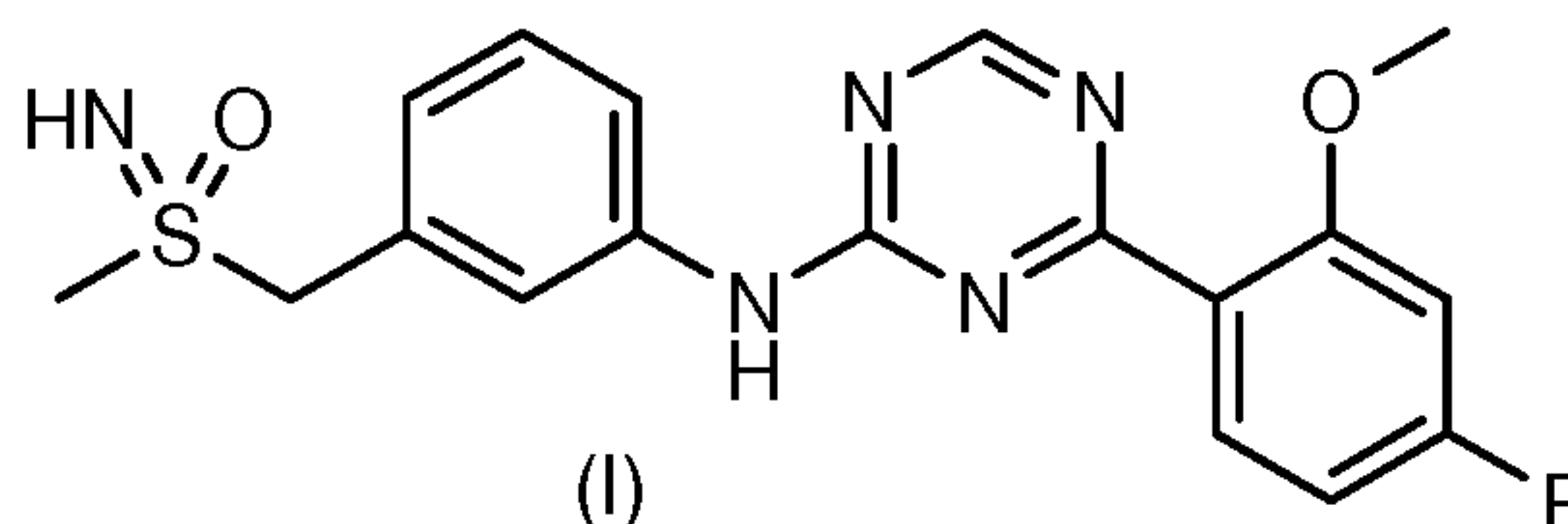
in the manufacture of a medicament for treating cancer in a subject,
wherein the medicament is manufactured for treating multiple myeloma.

2. Use of a compound of formula (I) according to claim 1,
wherein the enantiomer

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts is used.

3. Compound

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine of formula I or one of its physiologically acceptable salts or enantiomers



for the use of treating multiple myeloma.

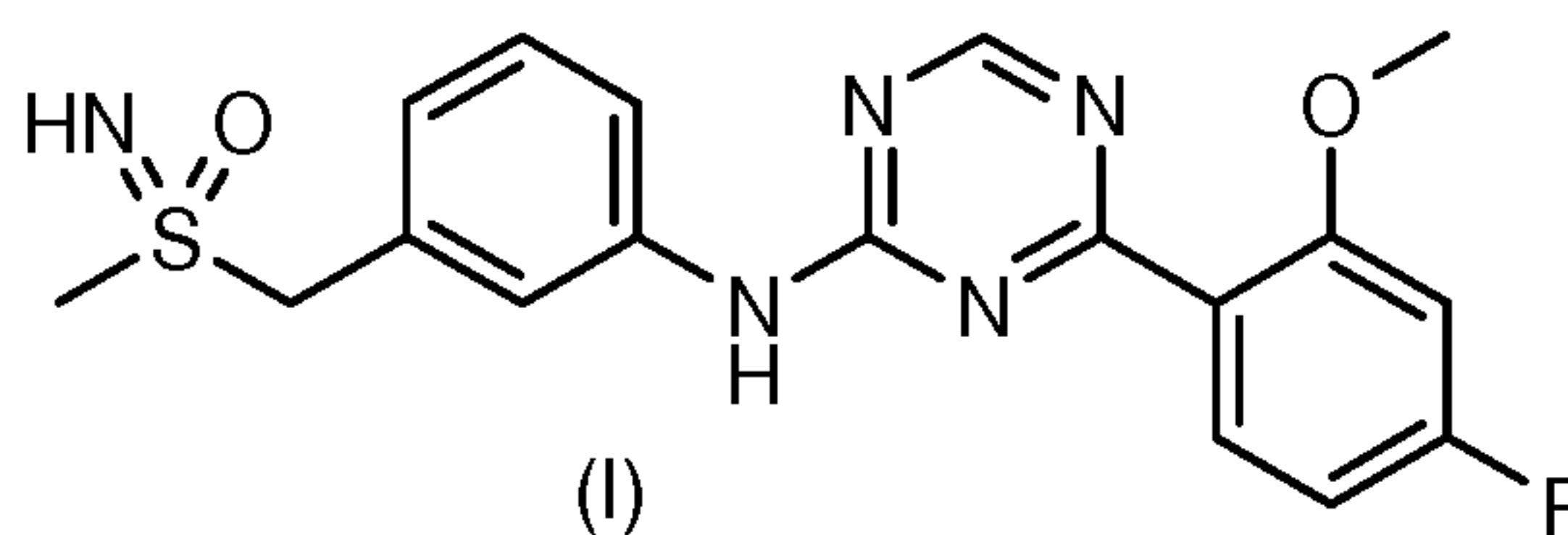
4. Compound according to claim 3, wherein the enantiomer

(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts is used.

5. Compound

4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine of formula I or one of its physiologically acceptable salts or enantiomers

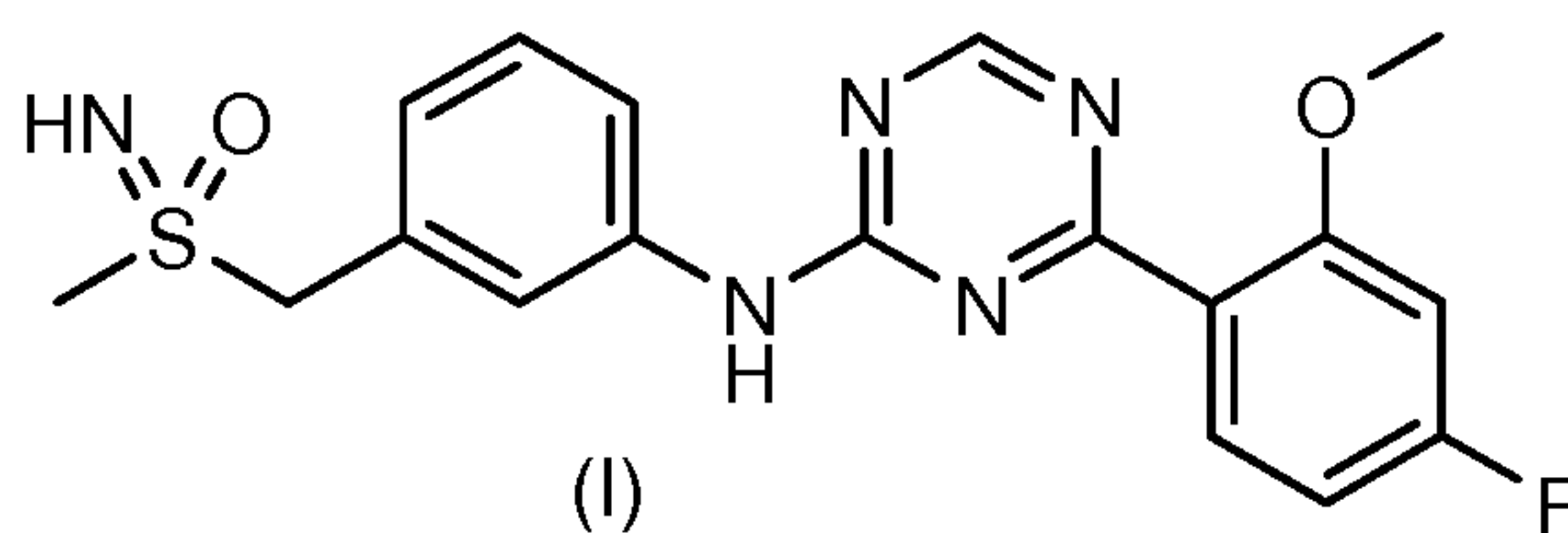
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for the use in a method of treatment and/or prophylaxis of multiple myeloma.

6. Compound according to claim 5, wherein the enantiomer
 5 (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonylmethyl)phenyl]-1,3,5-triazin-2-amine or one of its physiologically acceptable salts is used.

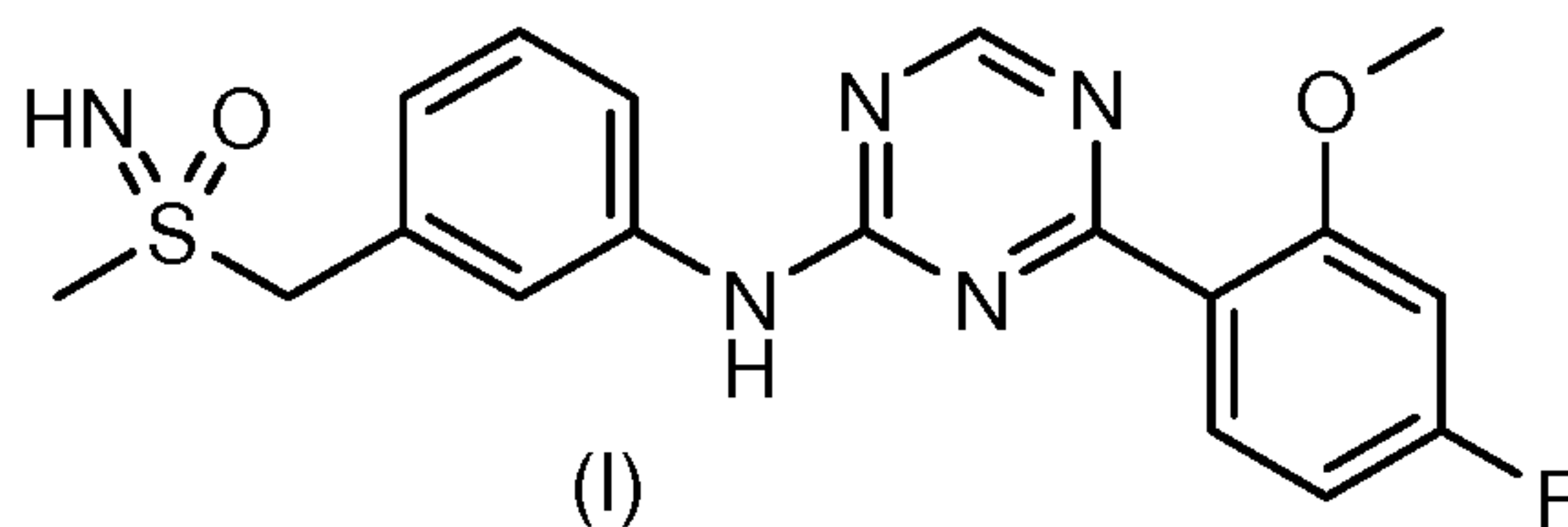
7. Use of
 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonylmethyl)phenyl]-1,3,5-triazin-2-amine of formula I or one of its physiologically acceptable salts or enantiomers
 10



for the treatment and/or prophylaxis of multiple myeloma.

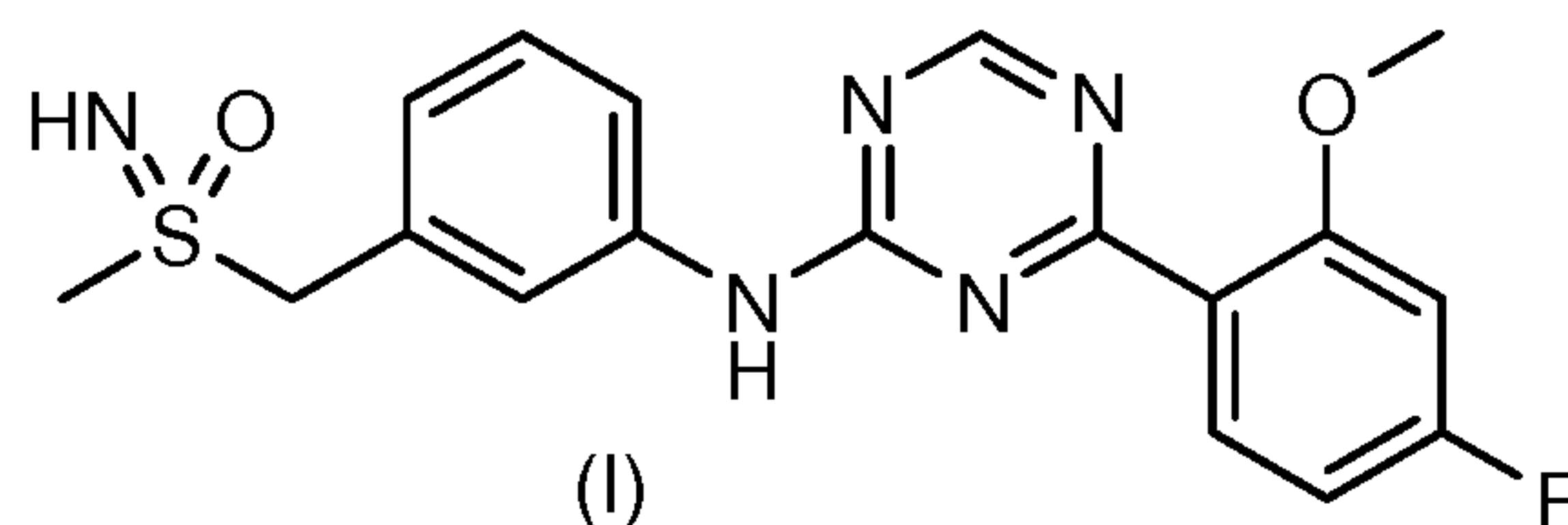
- 15 8. Use of a compound of formula (I) according to claim 7, wherein the enantiomer (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonylmethyl)phenyl]-1,3,5-triazin-2-amine or one of its physiologically acceptable salts is used.

9. Pharmaceutical combination comprising
 20 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonylmethyl)phenyl]-1,3,5-triazin-2-amine of formula I or one of its physiologically acceptable salts or enantiomers



as defined in claim 1 and at least one or more further active ingredients for the treatment and/or prophylaxis of multiple myeloma.

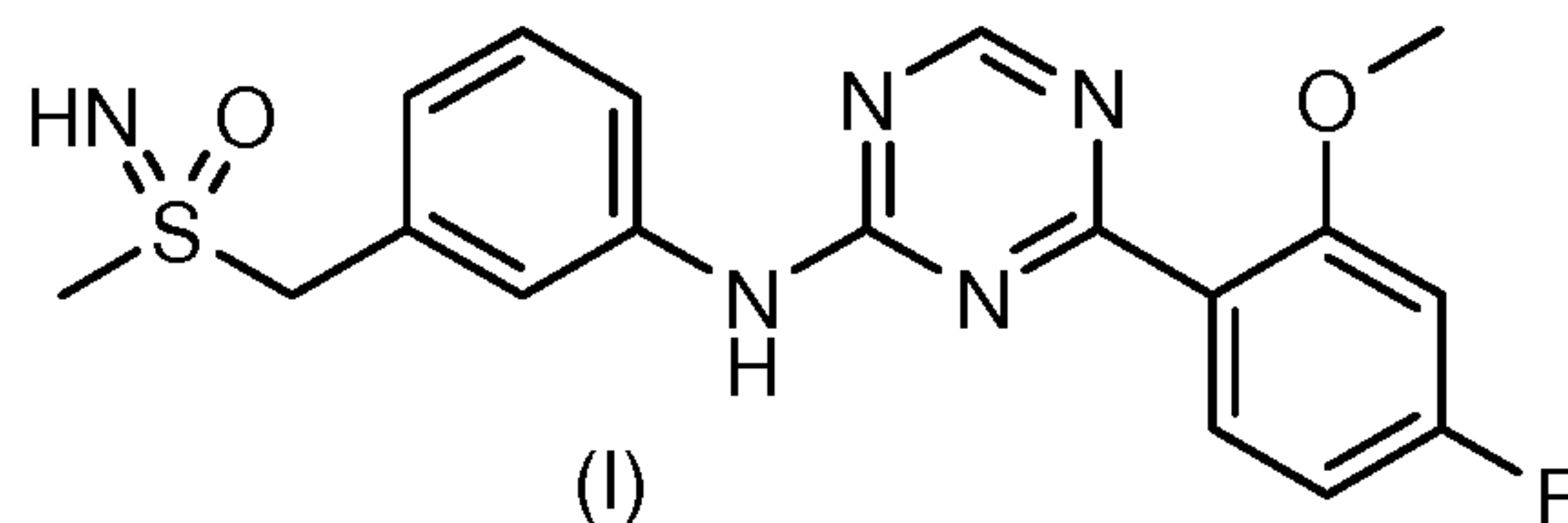
10. Pharmaceutical compositions comprising
4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine of formula I or one of its physiologically acceptable salts or enantiomers



- 5 as defined in claim 1 and at least one inert, nontoxic, pharmaceutically suitable adjuvant for the treatment and/or prophylaxis of multiple myeloma.

11. Pharmaceutical combination or pharmaceutical composition according to claim 10, wherein the enantiomer
10 (+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts is comprised.

12. Method of treatment and/or prophylaxis of multiple myeloma using an effective amount of
15 4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine of formula I or one of its physiologically acceptable salts or enantiomers



- 20 13. Method of treatment according to claim 12, wherein the enantiomer
(+)-4-(4-Fluoro-2-methoxyphenyl)-N-{3-[(S-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine or one of its physiologically acceptable salts is used.