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Title: DIARYL UREA FOR TREATING DIABETIC NEUROPATHY

Abstract: The present invention relates to pharmaceutical compositions for treating diabetic neuropathy comprising 4-[4-{3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxo}-pyridine-2-carboxylic acid methylamide optionally combined with at least one additional therapeutic agent.
DIARYL UREA FOR TREATING DIABETIC NEUROPATHY

The present invention relates to pharmaceutical compositions for treating diabetic neuropathy comprising 4-{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide optionally combined with at least one additional therapeutic agent.

Diaryl urea compounds e.g. 4-{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide as described e.g. in US 20050038080 are potent anti-cancer and anti-angiogenic agents that possess various activities, including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or fTl-3 kinase signaling molecules. These diaryl urea compounds have been previously characterized as having various activities, including for inhibiting the Raf/MEK/ERK pathway, raf kinase, p38 kinase, VEGFR kinase, PDGFR kinase. These activities and their use in treating various diseases and conditions are disclosed in, e.g., WO 2005/009961.

Diabetic neuropathy also called painful diabetic neuropathy is a common diabetes related phenomenon. Pain as syndrome of neuropathy may be seen in as many as one third of all patients with diabetes. Neuropathic pain is difficult to manage and the available treatment options rarely provide total relief (CF. Corbett, The Diabetes Educator, Vol. 31, 2005, 4, 523-540). Its cause is unclear and it does not respond well to traditional pain therapies (R.A. Malik (2003) Treat. Endocrinol. 2(6), 339-400).

Recent advancements in the diagnosis of neuropathic pain include methods that can distinguish between neuropathic and non-neuropathic pain. In the absence of treatment, nerve damage may progress while pain diminishes. Symptom management treatment is available and includes the use of analgesics (NSAIDs), antidepressants (e.g. selective serotonin reuptake inhibitors, tricyclic antidepressants), anticonvulsants, capsicain topical cream, nexiletine, as well as physical or mechanical therapy such as electrical stimulation, acupuncture, magnet therapy or topical use of polyurethane films.

As demonstrated recently (S.A Price et al. (2004) Diabetes, 53, 1851-1856) treatment of diabetic animals with SB 239063, fidarestat or insulin prevent reduction in both motory and sensory nerve conduction velocity. Reduced nerve conduction velocity (NCV) is an established hallmark of diabetic neuropathy.

The present invention provides pharmaceutical compositions for treating diabetic neuropathy comprising a compound of formula I and optionally at least one further therapeutic agent.

The present invention provides a therapeutic method which do not only reduce the neuropathic pain of patients more effectively compared to current therapies but also provides a therapeutic
method for the reconstitution of nerve functions. The therapeutic method according to the
invention is superior to current therapies. Therefore the present invention can be used e.g. by
administering a diaryl urea compound of formula I and optionally a further therapeutic agent,
pharmaceutically-acceptable salts thereof, and derivatives thereof, etc.

The compounds with the structure of formula I, pharmaceutically acceptable salts, polymorphs,
solvates, hydrates metabolites and prodrugs thereof, including diastereoisomeric forms (both
isolated stereoisomers and mixtures of stereoisomers) are collectively referred to herein as the
"compounds of formula I".

Formula (I) is as follows:

![Chemical Structure](image)

where the plural form of the word compounds, salts, and the like, is used herein, this is taken to
mean also a single compound, salt, or the like.

The present invention also relates to useful forms of the compounds as disclosed herein, such as
pharmaceutically acceptable salts, metabolites and prodrugs. The term "pharmaceutically
acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a
compound of the present invention. For example, see S. M. Berge, et al. "Pharmaceutical Salts," J.
Pharm. Sci. 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting
the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for
example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor
sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable
salts also include those in which the main compound functions as an acid and is reacted with an
appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline
salts. Those skilled in the art will further recognize that acid addition salts of the claimed
compounds may be prepared by reaction of the compounds with the appropriate inorganic or
organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal
salts are prepared by reacting the compounds of the invention with the appropriate base via a
variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts
and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecyl-sulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, trifluoromethanesulfonate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aryl or aralkyl halides like benzyl and phenethyl bromides and others monosubstituted aralkyl halides or polysubstituted aralkyl halides.

Solvates for the purposes of the invention are those forms of the compounds where solvent molecules form a complex in the solid state and include, but are not limited to for example ethanol and methanol. Hydrates are a specific form of solvates, where the solvent molecule is water.

Certain pharmacologically active agents can be further modified with labile functional groups that are cleaved after in vivo administration to furnish the parent active agent and the pharmacologically inactive derivatizing group. These derivatives, commonly referred to as prodrugs, can be used, for example, to alter the physicochemical properties of the active agent, to target the active agent to a specific tissue, to alter the pharmacokinetic and pharmacodynamic properties of the active agent, and to reduce undesirable side effects. Prodrugs of the invention include, e.g., the esters of appropriate compounds of this invention that are well-tolerated, pharmaceutically acceptable esters such as alkyl esters including methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters. Additional esters such as phenyl-C1-C4 alkyl may be used, although methyl ester is preferred.

Methods which can be used to synthesize other prodrugs are described in the following reviews on the subject, which are incorporated herein by reference for their description of these synthesis methods:
The metabolites of the compounds of this invention include oxidized derivatives of the compounds of formula I, wherein one or more of the nitrogens are substituted with a hydroxy group; which includes derivatives where the nitrogen atom of the pyridine group is in the oxide form, referred to in the art as 1-oxo-pyridine or has a hydroxy substituent, referred to in the art as 1-hydroxy-pyridine.

General Preparative Methods

The compounds of the invention may be prepared by use of known chemical reactions and procedures as described e.g. in the following published international application WO 2005/009961.

Further therapeutic agents

The compounds of formula I according to the present invention can be combined with further therapeutic agents such as analgesics, anti-depressants, anti-diabetics, glucose controlling agents, neuroprotective agents, anticonvulsants, anesthesics, anti-inflammatory agents or capsaicin.
Examples of analgesics include, but are not limited to, NSAID (non-steroidal antiinflammatory drugs), COX-I- or COX-2-inhibitors etc..

Examples of NSAID include, but are not limited to, e.g. aceclofenac, acetaminophen, o-acetyl salicylic acid, alclofenac, amprofen, amfenac, ampiroxicam, antolfmetingualc, anirolac, antrafenin, azapropazon, benorilat, bermoprofen, bindarit, bromfenac, bucloxaure, bucolom, bufexamac, bumadizon, butibufen, butixirat, carbasalat calcium, carprofen, cinmetacin, cinnoxicam,clidanac, clobuzarit, deboxamet, dexibuprofen, dextetroprofen, diclofenac, diflunisal, eltenac, enfenamsaure, etersalat, etodolac, etofenamat, feclobuzon, felbinac, fentiazac, fepradinol, flobufen, floctafenin, flunoxaprofen, flunoxaprofen, flurbiprofen axetil, furfenac, furprofen, glucametacin, ibufenac, ibuprofen, indobufen, indometacin, indometazin franesil, indoprofen, ketoprofen, ketorolac, lobenzarit, lonazolac, lornoxicam,loxoprofen, mafenam acid, meloxicam, mesalazin, mofezolac, nabumeton, naproxen, niflumic, olsalazin, oxaprozin, pelubiprofen, phenylbutazon, pimeprofen, pirazolac, piroxicam, pirprofen, pranoprofen, prifelon, prinomid, proglumetacin, proquazone, protizin acid, romazarit, salicylamide, salicylic acid, salmisten, salnacedin, salosalat, sulindac, suprofen, talniflumat, tenidap, tenosal, tenoxicam, tepoxalin, tiaprofensaire, tiaramid, tiltroprofen arbamel, timegadin, tinoridin, tolfenam acid, toletin, ufenamat, ximoprofen, zaltoprofen and zoliprofen.

Preference is given to an NSAID selected from the group consisting of acetaminophen, o-acetyl salicylic acid, clidanac, diclofenac, flurbiprofen, ibuprofen, ketoprofen and sulindac. More preferably o-acetyl salicylic acid is used as NSAID.

Examples of anesthesics include, but are not limited to, e.g. melixetine, lidocaine and benzocaine. Preference is given to melixetine.

Examples of anti-depressants include, but are not limited to, e.g. selective serotonin reuptake inhibitors and tricyclic anti-depressants such as duloxetine, trazodone and venlafaxine.

Examples of anticonvulsants include, but are not limited to, e.g. gabapentin, lamotrigine, amitriptyline and pregabalin.

Examples of anti-diabetic agents include, but are not limited to, e.g. insuline, CB-I antagonists such as rimonabant or SLV-319, 5HT uptake inhibitors such as sibutramin, ilpase inhibitors such as orlistat or ALT-962, CNTF agonists such as axokine, DGAT inhibitors such as BAY 74-41 13, DPP IV inhibitors such as vildagliptin, sitagliptin, saxagliptin, LAF-237, MK-0431 or BMS-4771 18, GLP-I analogues such as exenatide, betatropin, BIM-51077, CJC-1 131 or liraglutide, PPAR αγ agonists such as BAY 62-9069, BAY 68-2959, tesaglitazar, muraglitazar, ONO-5129,
LY-510929, LY-519818, GW-677954, TAK-559, navelgitazar or AVE-0847, PPAR γ agonists such as pioglitazone, rosiglitazone, R-483, balaglitazone, rivoglitazone or TAK-654. Preference is given to BAY 74-4113, BAY 62-9069, BAY 68-2959, rimonabant, SLV-319, pioglitazone, rosiglitazone, orlistat, tesaglitazar, muraglitazar and exenatide.

5 **Indications**

The compounds and combinations according to the present invention can be used for manufacture of a medicament for treating diabetic neuropathy. Also the present invention provides methods of treating diabetic neuropathy, comprising administering effective amounts of at least one compound of formula I and optionally at least one further therapeutic agent according to the invention. An "effective amount" is the quantity of the compound that is useful to achieve the desired result, e.g., to treat the disease or condition. Diabetic neuropathy is also known as painful diabetic neuropathy.

**Administration**

Compounds or drug combinations of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosal, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

Preference is given to an oral administration.

Compounds or drug combinations of the present invention can be converted in a known manner into the usual formulations, which may be liquid or solid formulations e.g. without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions.

The combinations of the present invention can be administered at any time and in any effective form. For example, the compounds can be administered simultaneously, e.g., as a single composition or dosage unit (e.g., a pill or liquid containing both compositions), or they can be administered as separate compositions, but at the same time (e.g., where one drug is administered intravenously and the other is administered orally or intramuscularly). The drugs can also be administered sequentially at different times. Agents can be formulated conventionally to achieve the desired rates of release over extended period of times, e.g., 12-hours, 24-hours. This can be achieved by using agents and/or their derivatives which have suitable metabolic half-lives, and/or by using controlled release formulations.
The drug combinations can be synergistic, e.g., where the joint action of the drugs is such that the combined effect is greater than the algebraic sum of their individual effects. Thus, reduced amounts of the drugs can be administered, e.g., reducing toxicity or other deleterious or unwanted effects, and/or using the same amounts as used when the agents are administered alone, but achieving greater efficacy.

Compounds or drug combinations of the present invention can be further combined with any other suitable additive or pharmaceutically acceptable carrier. Such additives include any of the substances already mentioned, as well as any of those used conventionally, such as those described in Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds., 20th edition, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy (Lachman et al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); Encyclopedia of Pharmaceutical Technology (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002). These can be referred to herein as "pharmaceutically acceptable carriers" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic purposes.

In addition, compounds or drug combinations of the present invention can be administered with other active agents or other therapies that are utilized to treat any of the above-mentioned diseases and/or conditions.

Other therapies according to the invention include, but are not limited to, physical or mechanical therapy such as electrical stimulation, acupuncture, magnet therapy or topical use of polyurethane films.

The present invention provides also combinations of at least one compound of Formula I and at least one other therapeutic agent mentioned above useful in treating a disease or disorder. "Combinations" for the purposes of the invention include:

- single compositions or dosage forms which contain at least one compound of Formula I and at least one other therapeutic agent mentioned above;

- combination packs containing at least one compound of Formula I and at least one other therapeutic agent mentioned above to be administered concurrently or sequentially;

- kits which comprise at least one compound of Formula I and at least one other therapeutic agent mentioned above packaged separate from one another as unit dosages or as independent unit dosages, with or without instructions that they be administered concurrently or sequentially; and
-separate independent dosage forms of at least one compound of Formula I and at least one other therapeutic agent mentioned above which cooperate to achieve a therapeutic effect, e.g., treatment of the same disease, when administered concurrently or sequentially.

The dosage of each agent of the combination can be selected with reference to the other and/or the type of disease and/or the disease status in order to provide the desired therapeutic activity. For example, the active agents in the combination can be present and administered in a fixed combination. "Fixed combination" is intended here to mean pharmaceutical forms in which the components are present in a fixed ratio that provides the desired efficacy. These amounts can be determined routinely for a particular patient, where various parameters are utilized to select the appropriate dosage (e.g., type of disease, age of patient, disease status, patient health, weight, etc.), or the amounts can be relatively standard.

The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

Preference is given to an amount of the compound of formula I from 20 to 2000 mg, preferably from 40 to 800 mg, more preferably from 50 to 600 mg.

Particular preference is given to an amount of 4-[4-[[3-(4-chloro-3-trifluoromethyl)phenyl]-ureido]-3-fluorophenoxy]-pyridine-2-carboxylic acid methylamide in the pharmaceutical composition from 20 to 3000 mg, preferably from 50 to 1500, more preferably from 60 to 1000 mg.

In another embodiment of the invention the compound of formula I is administered in combination with at least one further therapeutic agent in an amount that those of ordinary skill in the art can determine by their professional judgement.

The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route. With each administration the number of tablets or capsules taken in at the same time should not exceed two.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behavior toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified
has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

The combination can comprise effective amounts of at least one compound of Formula I and at least one other therapeutic agent mentioned above, which achieves a greater therapeutic efficacy than when either compound is used alone. The combination can be useful to treat diabetic neuropathy, where the therapeutic effect is not observed when the agents are used alone, or where an enhanced effect is observed when the combination is administered.

The relative ratios of each compound in the combination can also be selected based on their respective mechanisms of action and the disease biology. The relative ratios of each compound can vary widely and this invention includes combinations for treating diabetic neuropathy where the amounts of the formula I compound and the other therapeutic agent can be adjusted routinely such that either is present in higher amounts.

The release of one or more agents of the combination can also be controlled, where appropriate, to provide the desired therapeutic activity when in a single dosage form, combination pack, kit or when in separate independent dosage forms.

Preference is given to a combination comprising a compound of formula I and at least one NSAID. More preferably a combination comprising 4-[4-{3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy]-pyridine-2-carboxylic acid methylamide and at least one NSAID is used. Most preferably a combination comprising 4-[4-{3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy]-pyridine-2-carboxylic acid methylamide and o-acetylsalicylic acid is used.
What we claim:

1. Use of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof, for manufacture of a medicament for treatment of diabetic neuropathy,

2. Combination comprising at least one compound of formula I as defined in claim 1 and at least one therapeutic agent selected from the group consisting of analgesics, anti-depressants, anti-diabetics, glucose controlling agents, neuroprotective agents, anti-convulsants, anesthetics, anti-inflammatory agents and capsaicin.

3. Combination of claim 2 wherein the further therapeutic agent is an NSAID or an anti-diabetic agent.

4. Combination of claim 3 wherein the further therapeutic agent is o-acetylsalicylic acid.

5. Use of the combination of any of claims 2 to 4 for manufacture of a medicament for treatment of diabetic neuropathy.

6. Pharmaceutical composition comprising a combination as defined in any of claims 2 to 4.


8. A method for treating diabetic neuropathy in a subject in need thereof comprising administering effective amounts of a compound of formula I or a pharmaceutically acceptable salt, polymorph, solvate, hydrate, metabolite, prodrug or diastereoisomeric form thereof

wherein said compound of formula I is:
The method of claim 8 wherein the compound of formula I is combined with at least one therapeutic agent selected from the group consisting of analgesics, anti-depressants, anti-diabetics, glucose controlling agents, neuroprotective agents, anticonvulsants, anesthetics, anti-inflammatory agents and capsaicin.