under evaluation in the main official medicine registration offices. Thus, the clinical relevance of tafamidis still needs to be clarified.

Despite the considerable effort that has been made in the field, there is to date no effective pharmacological therapy for the treatment of FAP. It is therefore desirable to provide alternative compounds for the treatment of FAP and other transthyretin-associated amyloidosis.

SUMMARY OF THE INVENTION

The present invention is defined by the appended claims.

The inventors have surprisingly found that catechol-O-methyltransferase (COMT) inhibitors are useful for the prevention and/or treatment of TTR-associated amyloidosis.

As shown in the examples below, the COMT inhibitor tolcapone has a high inhibiting activity against TTR amyloid formation. The good inhibitory activity of tolcapone is revealed by its low IC_{50} and high percent amyloidosis reduction (RA%) values.

Thus, a first aspect of the present invention relates to a COMT inhibitor for use in the prevention and/or treatment of TTR-associated amyloidosis. ~~This aspect can be reformulated as use of a COMT inhibitor for the preparation of a medicament for the prevention and/or treatment of a TTR-associated amyloidosis.~~

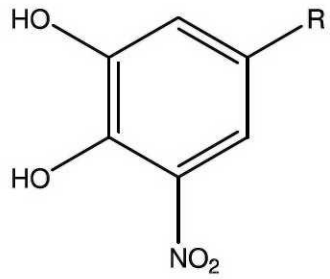
It also forms part of the disclosure~~invention~~ a method for the prevention and/or treatment of a TTR-associated amyloidosis comprising administering a COMT inhibitor formula (I) to a subject in need thereof. In a particular embodiment, the subject in need of the prevention and/or treatment is a mammal, including a human. In a further preferred embodiment, the mammal is a human.

As compared to tafamidis, which is so far the most advanced pharmacological compound for FAP treatment, tolcapone has a four fold lower IC_{50} *in vitro*, which means that the concentration of tolcapone needed to inhibit 50% of TTR fibril formation is much lower than that of tafamidis (see examples below). The examples below additionally demonstrate that tolcapone binds to TTR and prevents TTR-induced cytotoxicity to a greater extent than tafamidis.

According to these results, tolcapone is more effective in reducing TTR fibril formation than the reference tafamidis compound. In addition to preventing TTR fibril formation, the inventors have found that tolcapone exhibits an important disruption activity over existing TTR fibrils. The results presented below demonstrate that tolcapone's TTR fibril disruption activity is higher than that of tafamidi's.

COMT inhibitors are well known in the state of the art as compounds that inhibit the action of catechol-O-methyl transferase, an enzyme that is involved in degrading neurotransmitters (Mannisto and Kaakkola, *Pharm. Rev.*, 1999, vol 51, p. 593-628). COMT inhibitor activity can be determined by methods known in the art, for instance the method disclosed in Zürcher *et al* (*Biomedical Chromatography*, 1996, vol. 10, p. 32-36). COMT inhibitors are well known in the art of pharmacology for the treatment of Parkinson's disease in conjunction with dopaminergic agents such as L-DOPA.

Several COMT inhibitors have been described. Tolcapone, entacapone, and nitecapone belong to the so called "second generation COMT inhibitors", which have been shown to be potent, highly selective, and orally active COMT inhibitors. Nitrocatechol is the key structure in these molecules (*Pharm. Rev.*, 1999, vol 51, p. 593-628, *supra*). Thus, in one embodiment the COMT inhibitor for use in the prevention and/or treatment of TTR-associated amyloidosis is a nitrocatechol compound. In a particular embodiment, the nitrocatecol compound with~~has~~ the following formula I



(Formula I)

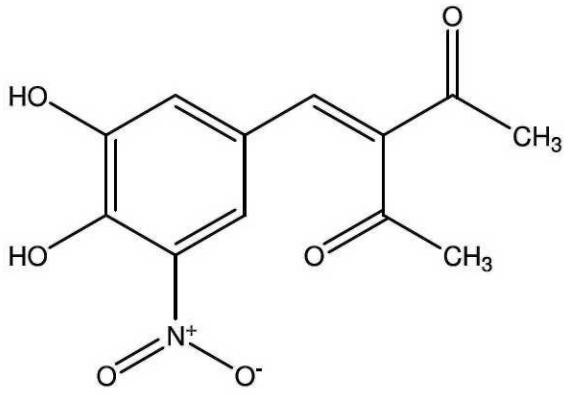
or a pharmaceutically acceptable salt thereof, wherein R= -C(O)-PhCH$_3$, -~~CH=C(N)-C(O)-NEt$_2$ or -CH=C(O)(CH$_3$)-C(O)(CH$_3$).~~ CH=C(CN)-C(O)-NEt$_2$ or -CH=C(C(O)CH$_3$)$_2$.

In another embodiment of the first aspect of the invention the COMT inhibitor is tolcapone, entacapone or nitecapone, or pharmaceutically acceptable salts

clinical trials. As such, these compounds have an acceptable safety profile for human use and good bioavailability. Their safety profile in conjuction with their high inhibitory activity against TTR fibril formation render the COMT inhibitors highly promising drugs for the prevention and/or treatment of TTR-associated amyloidosis.

Additionally, since these compounds have already been subjected to clinical trials for the treatment of human disease, the clinical poof-of-concept is less risky (and faster) to achieve when compared with classical development of new chemical entities. In this sense, it is important to highlight that considerable fewer experimentation needs to be done in human beings and animals, subsequently implying lower developmental costs and, more importanly, less sufferings to humans and animals.

In another embodiment of the first aspect of the invention the COMT inhibitor is nitecapone, or a pharmaceutically acceptable salt thereof. Nitecapone (formula IV) is a compound with molecular mass of 265.21. Its empirical formula is $C_{12}H_{11}NO_6$, the chemical name 3-[(3,4-Dihydroxy-5-nitrophenyl)methylene]-2,4-pentanedione, and CAS reference number 116313-94-1.



(Formula IV)

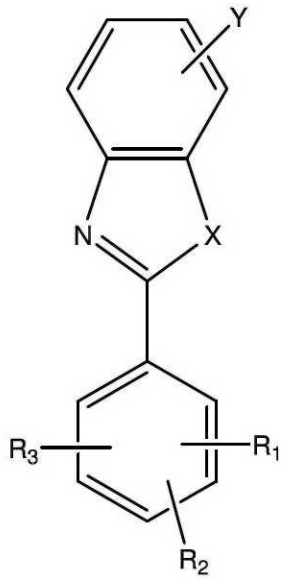
In a preferred embodiment of the invention the TTR-associated amyloidosis is FAP. In another embodiment the TTR-associated amyloidosis is senile systemic amyloidosis. In another embodiment the TTR-associated amyloidosis is familial amyloid cardiomyopathy. In yet another embodiment the TTR-associated amyloidosis is leptomeningeal amyloidosis.

COMT inhibitors~~, such as those~~ defined above can be used either alone or in

combination with other therapeutic agents for the prevention and/or treatment of TTR-associated amyloidosis. Thus, in a second aspect, the invention refers to a combination of a COMT inhibitor of formula (I) and an additional therapeutic agent for use in the prevention and/or treatment of a TTR-associated amyloidosis. ~~This embodiment can be reformulated as a combination of a COMT inhibitor and an additional therapeutic agent for the prevention and/or treatment of a TTR-associated amyloidosis.~~ Further, it also forms part of the ~~invention~~ disclosure a method for the prevention and/or treatment of a transthyretin-associated amyloidosis which comprises administering to a subject in need thereof a combination of a COMT inhibitor of formula (I) and an additional therapeutic agent. ~~Non-limiting examples~~Examples of additional therapeutic agents for use in the second aspect of the invention are another COMT inhibitor, a benzoxazole derivative of formula (V), iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and epigallocatechin-3-gallate (EGCG). ~~Preferably, the~~ The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. The skilled person will understand that pharmaceutically acceptable salts of the above mentioned additional therapeutic agents can also be used in the combination of the second aspect of the invention.

In one embodiment of the second aspect of the invention it is provided a combination of a COMT inhibitor of formula (I) ~~and~~ an additional therapeutic agent selected from the group consisting of another COMT inhibitor, a benzoxazole derivative of formula (V), and iododiflunisal for use in the prevention and/or treatment of transthyretin-associated amyloidosis. ~~Preferably, the~~The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention.

Benzoxazole derivatives are disclosed in the international patent application WO2005113523 as compounds that stabilize the native state of TTR, thereby inhibiting protein misfolding. In ~~one~~ accordance with ~~embodiment of~~ the second aspect of the invention, the benzoxazole derivatives are compounds of formula V:



(Formula V)

or a pharmaceutically acceptable salt thereof, wherein:
Y is COOR, tetrazolyl, CONHOR, $B(OH)_2$ or OR;
X is O; and
R^1, R^2 and R^3 are each independently selected from hydrogen, halo, OR, $B(OH)_2$ or CF_3, and
wherein R is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 cycloalkyl, C_1-C_6 heterocyclyl, phenyl, xylyl, naphthyl, thienyl, indolyl or pyridyl.

In ~~a particular embodiment of~~accordance with the second aspect of the invention the COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention and the additional therapeutic agent is a benzoxazole derivative of formula V or a pharmaceutically acceptable salt thereof as defined above.

In another embodiment of the second aspect of the invention the benzoxazole derivative is a compound of formula VI

therapeutic agent is iododiflunisal. In a particular embodiment the COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention and the additional therapeutic agent is iododiflunisal. In another particular embodiment the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof and the additional therapeutic agent is iododiflunisal.

In another particular embodiment, the COMT inhibitor is combined with another COMT inhibitor. ~~Preferably, the~~The COMT inhibitors are nitrocatechol compounds of formula I or pharmaceutically acceptable salts thereof as defined for the first aspect of the invention. For instance, the invention provides a combination of tolcapone and entacapone for the prevention and/or treatment of a TTR-associated amyloidosis.

In a further embodiment of the second aspect of the invention it is provided a combination of a COMT inhibitor of formula (I) and an additional therapeutic agent selected from the group consisting of diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and EGCG for use in the prevention and/or treatment of a TTR-associated amyloidosis. EGCG is a the main and most significant polyphenol in green tea. In the sense of the present invention, EGCG can be used as an isolated compound or forming part of a plant extract, particularly a tea extract. ~~Preferably, the~~ The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. More preferably the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof. A particular embodiment provides a combination of tolcapone or a pharmaceutically acceptable salt thereof and EGCG for use in the prevention and/or treatment of a TTR-associated amyloidosis.

As will be apparent to the skilled in the art, the combination of the present invention is effective not only when the active ingredients are used in a single composition, but also when used in two different compositions, either administered simultaneously, sequentially or separately after a certain period of time. Furthermore, the skilled in the art will understand that the COMT inhibitor can be prescribed to be used together with the other active ingredient in a combination therapy in order to prevent and/or treat a transthyretin-associated amyloidosis, and viceversa.

Thus, a third aspect of the present invention provides a COMT inhibitor of formula (I) for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with an additional therapeutic agent. ~~This embodiment may be reformulated as use of a COMT inhibitor for the preparation of a medicament for the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with an additional therapeutic agent.~~ It also forms part of the ~~invention~~ disclosure a method for the prevention and/or treatment of a transthyretin-associated amyloidosis which comprises administering to a subject in need thereof a COMT inhibitor of formula (I) in combination with an additional therapeutic agent.

~~Non-limiting examples~~Examples of additional therapeutic agents for use in the third aspect of the invention are another COMT inhibitor, a benzoxazole derivative of formula (V), iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and EGCG. Preferably, the COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. The skilled person will understand that pharmaceutically acceptable salts of the above mentioned additional therapeutic agents can also be used in the combination therapy of the third aspect of the invention.

In one embodiment of the third aspect of the invention it is provided a COMT inhibitor of formula (I) for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with an additional therapeutic agent selected from the group consisting of another COMT inhibitor, a benzoxazole derivative of formula (V), and iododiflunisal. Preferably, the COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention.

In a particular embodiment of the third aspect of the invention, the additional therapeutic agent is another COMT inhibitor. Preferably, the COMT inhibitors are nitrocatechol compounds of formula I or pharmaceutically acceptable salts thereof as defined for the first aspect of the invention. For example, the invention provides tolcapone for the prevention and/or treatment of a TTR-associated amyloidosis in combination with entacapone. In another particular embodiment, the additional therapeutic agent is a benzoxazole derivative of formula (V).

~~Preferably, said~~ Said benzoxazole derivative is a compound of formula V or VI or pharmaceutical salts thereof as defined for the second aspect of the invention. For example, the invention provides a COMT inhibitor of formula (I) for the prevention and/or treatment of a TTR-associated amyloidosis in combination with tafamidis. ~~Preferably, the~~The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. More preferably the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof. Thus the invention provides tolcapone for the prevention and/or treatment of a TTR-associated amyloidosis in combination with tafamidis. In yet another embodiment, the additional therapeutic agent is iododiflunisal. In yet another embodiment, the additional therapeutic agent is iododiflunisal and the COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. The invention thus provides tolcapone or a pharmaceutically acceptable salt thereof for the prevention and/or treatment of a TTR-associated amyloidosis in combination with iododiflunisal.

In a further embodiment of the third aspect of the invention it is provided a COMT inhibitor of formula (I) for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with an additional therapeutic agent selected from the group consisting of diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and EGCG for use in the prevention and/or treatment of a TTR-associated amyloidosis. ~~Preferably, the~~The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. More preferably the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof. In a particular embodiment the invention provides tolcapone or a pharmaceutically acceptable salt thereof for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with EGCG.

A fourth aspect of the invention provides a therapeutic agent selected from the group consisting of a benzoxazole derivative of formula (V), iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and EGCG, for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with a COMT inhibitor. ~~Preferably, the~~ The COMT inhibitor is

a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. The skilled person will understand that pharmaceutically acceptable salts of the above mentioned therapeutic agents can also be used in the combination therapy of the fourth aspect of the invention.

In one embodiment of the fourth aspect of the invention it is provided a therapeutic agent selected from the group consisting of a benzoxazole derivative of formula (V) and iododiflunisal for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with a COMT inhibitor. ~~Preferably, the~~The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention.

In a particular embodiment of the fourth aspect of the invention, the therapeutic agent is a benzoxazole derivative~~. Preferably, said benzoxazole derivative is a compound~~ of formula V or VI or pharmaceutical salts thereof as defined for the second aspect of the invention. For example, the invention provides tafamidis for the prevention and/or treatment of TTR-associated amyloidosis in combination with a COMT inhibitor. ~~Preferably, the~~The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. More preferably the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof. Thus the invention provides tafamidis for the prevention and/or treatment of a TTR-associated amyloidosis in combination with tolcapone or a pharmaceutically acceptable salt thereof. In yet another embodiment, the therapeutic agent is iododiflunisal. In yet another embodiment, the additional therapeutic agent is iododiflunisal and the COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. The invention provides iododiflunisal for the prevention and/or treatment of a TTR-associated amyloidosis in combination with tolcapone or a pharmaceutically acceptable salt thereof.

In a further embodiment of the fourth aspect of the invention it is provided a therapeutic agent selected from the group consisting of diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and EGCG for use in the prevention

and/or treatment of transthyretin-associated amyloidosis in combination therapy with a COMT inhibitor. ~~Preferably, the~~The COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention. More preferably, the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof. A particular embodiment provides EGCG for use in the prevention and/or treatment of a TTR-associated amyloidosis in combination therapy with tolcapone or a pharmaceutically acceptable salt thereof.

Additionally, the COMT inhibitor can be used as adjuvant treatment before and/or after liver transplant in a patient with a TTR-associated amyloidosis. ~~Preferably, said~~Said COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention.

The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a COMT inhibitor of formula (I) together with pharmaceutically acceptable excipients and/or carriers for the prevention and/or treatment of a TTR-associated amyloidosis. ~~Preferably, said~~Said COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention.

The expression "therapeutically effective amount", also referred as “dose”, refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease which is addressed. The particular dose of compound administered according to this invention will be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations.

The expression "pharmaceutically acceptable excipients and/or carriers" refers to pharmaceutically acceptable materials, compositions or vehicles. Each component must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the pharmaceutical composition. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response,

Thus, the dose of COMT inhibitor to be administered can be between 0.1 and 16000 mg/day, or between 0.1 and 12000 mg/day, or between 0.1 and 10000 mg/day, or between 0.1 and 5000 mg/day, or between 0.1 and 3000 mg/day. In a particular embodiment, the dose of COMT inhibitor to be administered is between 1 and 3000 mg/day. In another embodiment, the dose is between 1 and 2000 mg/day. Preferably, the COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof as defined for the first aspect of the invention.

Throughout the description and claims the word "comprise" and variations of the word, are not intended to exclude other technical features, additives, components, or steps. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples are provided by way of illustration~~, and they are not intended to be limiting of the present invention. Furthermore, the present invention covers all possible combinations of particular and preferred embodiments described herein~~.

BRIEF DESCRIPTION OF THE FIGURES

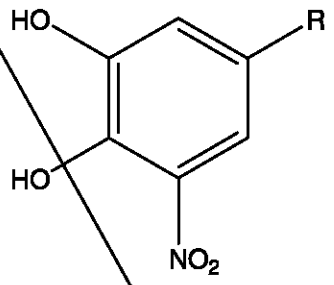
Figure 1. Assay of competition with T4 for the binding to TTR wild type (WT) by gel filtration: Curves of T4 displacement from TTR WT by different compounds. Y axis: Amount of TTR-bound T4 / total T4; X-axis: log10 concentration of compound (molar units). Values correspond to a representative experiment done in duplicates, represented as average +/- standard deviation. Test compounds: Thyroxine (T4), Tolcapone (SOM), Tafamidis (TAF), and (-)-epigallocatechin-3-gallate (EGCG).

Figure 2. TTR tetrameric stability in the presence of different compounds by IEF: Plasma from control individuals (C) and from familial amyloid polyneuropathy patients carrying V30M mutation (V30M) was treated with test compounds Tafamidis (T); tolcapone (S); epigallocatechin-3-gallate (EGCG) or left untreated (nt); and subjected to IEF under semidenaturing conditions as described in the text. The ratio of TTR tetramer / total TTR for each condition was calculated and represented as average +/- sem (standard error of the

CLAIMS

1. A catechol-O-methyltransferase (COMT) inhibitor for use in the prevention and/or treatment of transthyretin-associated amyloidosis.

2. The catechol-O-methyltransferase (COMT) inhibitor for use according to claim 1, wherein said COMT inhibitor is a nitrocatechol compound of formula I or a pharmaceutically acceptable salt thereof;



(Formula I)

wherein R= -C(O)-PhCH$_3$, -CH=C(N)-C(O)-NEt$_2$ or -CH=C(O)(CH$_3$)-C(O)(CH$_3$).

3. The catechol-O-methyltransferase (COMT) inhibitor for use according to claim 2, wherein the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof.

4. The catechol-O-methyltransferase (COMT) inhibitor for use according to any of the claims 1-3, wherein the transthyretin-associated amyloidosis is familial amyloid polyneuropathy.

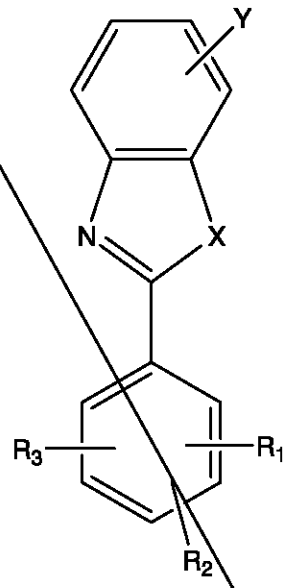
5. The catechol-O-methyltransferase (COMT) inhibitor for use according to any of the claims 1-3, wherein the transthyretin-associated amyloidosis is senile systemic amyloidosis.

6. The catechol-O-methyltransferase (COMT) inhibitor for use according to any of the claims 1-3, wherein the transthyretin-associated amyloidosis is leptomeningeal amyloidosis.

7. The catechol-O-methyltransferase (COMT) inhibitor for use according to any of the claims 1-3, wherein the transthyretin-associated amyloidosis is

familial amyloid cardiomyopathy.

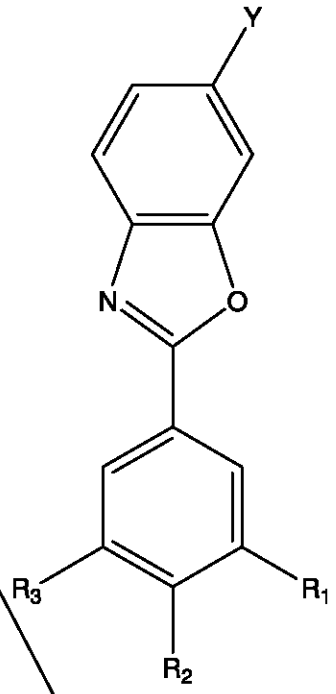
8. A catechol-O-methyltransferase (COMT) inhibitor for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with an additional therapeutic agent selected from the group consisting of another COMT inhibitor, a benzoxazole derivative, iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and epigallocatechin-3-gallate, wherein the benzoxazole derivative is a compound of formula V



(formula V)

or a pharmaceutically acceptable salt thereof, wherein:
Y is COOR, tetrazolyl, CONHOR, $B(OH)_2$ or OR;
X is 0; and
R^1, R^2 and R^3 are each independently selected from hydrogen, halo, OR, $B(OH)_2$ or CF_3, and wherein
R is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 cycloalkyl, C_1-C_6 heterocyclyl, phenyl, xylyl, naphthyl, thienyl, indolyl or pyridyl.

9. The catechol-O-methyltransferase (COMT) inhibitor for use according to claim 8, wherein the benzoxazole derivative is a compound of formula VI



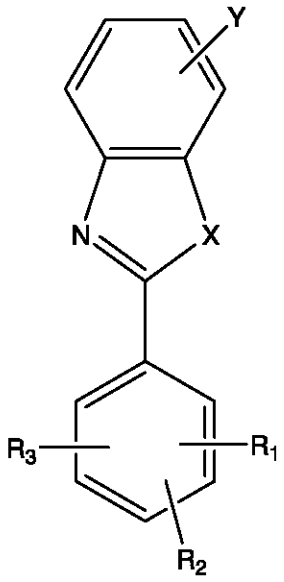
Formula VI

or a pharmaceutically acceptable salt thereof, wherein:
Y is COOH, or OH; and
R^1, R^2 and R^3 are each independently selected from hydrogen, halo, OH, $B(OH)_2$ or CF_3.

10. The catechol-O-methyltransferase (COMT) inhibitor for use according to any one of the claims 8-9, wherein the benzoxazole derivative is tafamidis.

11. The catechol-O-methyltransferase (COMT) inhibitor for use according to any of the claims 1-10, wherein the COMT inhibitor is administered as an injectable dosage form, as an oral dosage form or as a controlled release dosage form.

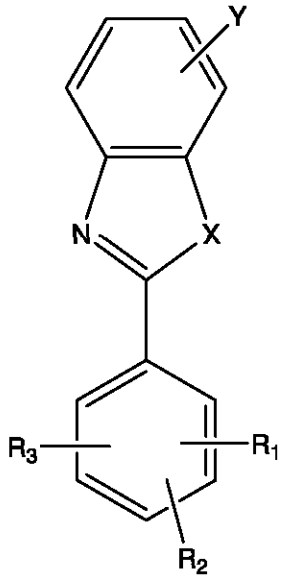
12. A combination of a catechol-O-methyltransferase (COMT) inhibitor and an additional therapeutic agent selected from the group consisting of another COMT inhibitor, a benzoxazole derivative, iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and epigallocatechin-3-gallate, for use in the prevention and/or treatment of transthyretin-associated amyloidosis, wherein the benzoxazole derivative is a compound of formula V



(formula V)

or a pharmaceutically acceptable salt thereof, wherein:
Y is COOR, tetrazolyl, CONHOR, $B(OH)_2$ or OR;
X is 0; and
R^1, R^2 and R^3 are each independently selected from hydrogen, halo, OR, $B(OH)_2$ or CF_3, and wherein
R is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 cycloalkyl, C_1-C_6 heterocyclyl, phenyl, xylyl, naphthyl, thienyl, indolyl or pyridyl.

13. A therapeutic agent selected from the group consisting of a benzoxazole derivative, iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and epigallocatechin-3-gallate, for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with a catechol-O-methyltransferase (COMT) inhibitor, wherein the benzoxazole derivative is a compound of formula V



(formula V)

or a pharmaceutically acceptable salt thereof, wherein:

Y is COOR, tetrazolyl, CONHOR, $B(OH)_2$ or OR;

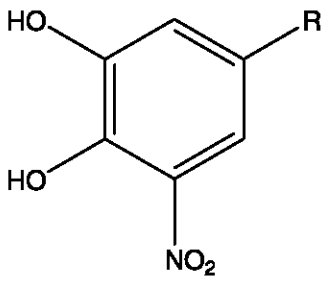
X is 0; and

R^1, R^2 and R^3 are each independently selected from hydrogen, halo, OR, $B(OH)_2$ or CF_3, and wherein

R is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 cycloalkyl, C_1-C_6 heterocyclyl, phenyl, xylyl, naphthyl, thienyl, indolyl or pyridyl.

CLAIMS

1. A catechol-O-methyltransferase (COMT) inhibitor of formula I or a pharmaceutically acceptable salt thereof



(Formula I)

wherein R is selected from the group consisting of -C(O)-PhCH$_3$, -CH=C(CN)-C(O)-NEt$_2$ and -CH=C(C(O)CH$_3$)$_2$,
for use in the prevention and/or treatment of transthyretin-associated amyloidosis.

2. The catechol-O-methyltransferase (COMT) inhibitor for use according to claim 1, wherein the COMT inhibitor is tolcapone or a pharmaceutically acceptable salt thereof.

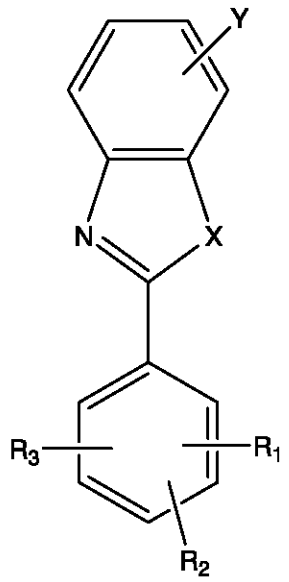
3. The catechol-O-methyltransferase (COMT) inhibitor for use according to any one of claims 1 or 2, wherein the transthyretin-associated amyloidosis is familial amyloid polyneuropathy.

4. The catechol-O-methyltransferase (COMT) inhibitor for use according to any one of claims 1 or 2, wherein the transthyretin-associated amyloidosis is senile systemic amyloidosis.

5. The catechol-O-methyltransferase (COMT) inhibitor for use according to any one of claims 1 or 2, wherein the transthyretin-associated amyloidosis is leptomeningeal amyloidosis.

6. The catechol-O-methyltransferase (COMT) inhibitor for use according to any one of claims 1 or 2, wherein the transthyretin-associated amyloidosis is familial amyloid cardiomyopathy.

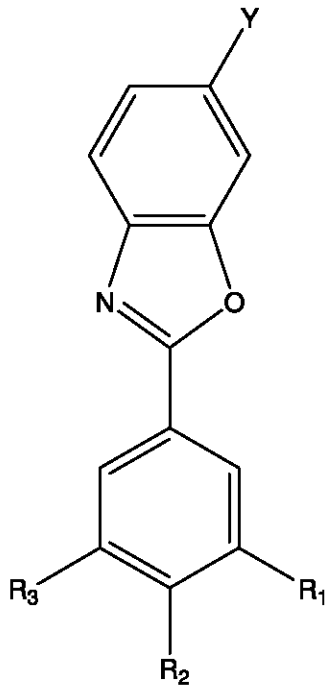
7. A catechol-O-methyltransferase (COMT) inhibitor as defined in claim 1 for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with an additional therapeutic agent selected from the group consisting of another COMT inhibitor as defined in claim 1, a benzoxazole derivative, iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and epigallocatechin-3-gallate, wherein the benzoxazole derivative is a compound of formula V



(formula V)

or a pharmaceutically acceptable salt thereof, wherein:
Y is selected from the group consisting of COOR, tetrazolyl, CONHOR, $B(OH)_2$ and OR;
X is O; and
R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, OR, $B(OH)_2$ and CF_3, and wherein
R is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 cycloalkyl, C_1-C_6 heterocyclyl, phenyl, xylyl, naphthyl, thienyl, indolyl and pyridyl.

8. The catechol-O-methyltransferase (COMT) inhibitor for use according to claim 7, wherein the benzoxazole derivative is a compound of formula VI



Formula VI

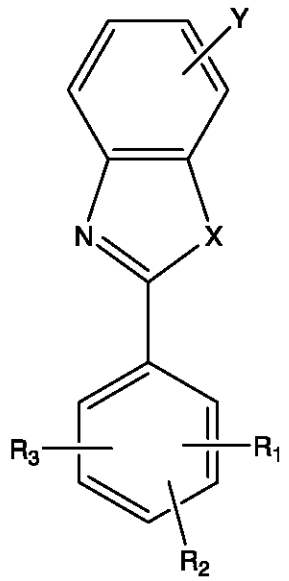
or a pharmaceutically acceptable salt thereof, wherein:
Y is selected from the group consisting of COOH, and OH; and
R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, OH, $B(OH)_2$ and CF_3.

9. The catechol-O-methyltransferase (COMT) inhibitor for use according to any one of claims 7 or 8, wherein the benzoxazole derivative is tafamidis.

10. The catechol-O-methyltransferase (COMT) inhibitor for use according to any of claims 1-9, wherein the COMT inhibitor is administered as an injectable dosage form, as an oral dosage form or as a controlled release dosage form.

11. A combination of a catechol-O-methyltransferase (COMT) inhibitor as defined in claim 1 and an additional therapeutic agent selected from the group consisting of another COMT inhibitor as defined in claim 1, a benzoxazole derivative, iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and epigallocatechin-3-gallate, for use in the prevention and/or

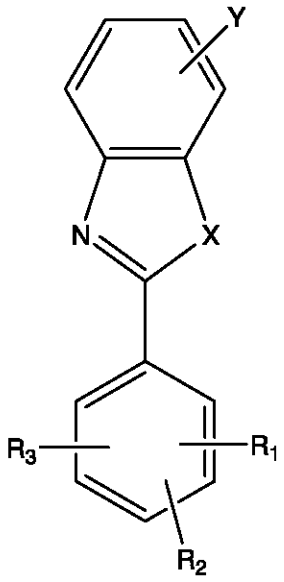
treatment of transthyretin-associated amyloidosis, wherein the benzoxazole derivative is a compound of formula V



(formula V)

or a pharmaceutically acceptable salt thereof, wherein:
Y is selected from the group consisting of COOR, tetrazolyl, CONHOR, $B(OH)_2$ and OR;
X is O; and
R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, OR, $B(OH)_2$ and CF_3, and wherein
R is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 cycloalkyl, C_1-C_6 heterocyclyl, phenyl, xylyl, naphthyl, thienyl, indolyl and pyridyl.

12. A therapeutic agent selected from the group consisting of a benzoxazole derivative, iododiflunisal, diflunisal, resveratrol, tauroursodeoxycholic acid, doxocycline and epigallocatechin-3-gallate, for use in the prevention and/or treatment of transthyretin-associated amyloidosis in combination therapy with a catechol-O-methyltransferase (COMT) inhibitor as defined in claim 1, wherein the benzoxazole derivative is a compound of formula V



(formula V)

or a pharmaceutically acceptable salt thereof, wherein:

Y is selected from the group consisting of COOR, tetrazolyl, CONHOR, $B(OH)_2$ and OR;

X is O; and

R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, OR, $B(OH)_2$ and CF_3, and wherein

R is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 cycloalkyl, C_1-C_6 heterocyclyl, phenyl, xylyl, naphthyl, thienyl, indolyl and pyridyl.