For example, the non-selective inhibition of COXs by NSAIDs may give rise to gastrointestinal side-effects and affect platelet and renal function. Even the selective inhibition of COX-2 by coxibs, whilst reducing such gastrointestinal side-effects, is believed to give rise to cardiovascular problems.

An alternative treatment of inflammatory diseases that does not give rise to the above-mentioned side effects would thus be of real benefit in the clinic. In particular, a drug that preferably inhibits the transformation of PGH_2 to the pro-inflammatory mediator PGE_2 selectively might be expected to reduce the inflammatory response in the absence of a corresponding reduction of the formation of other, beneficial arachidonic acid metabolites. Such inhibition would accordingly be expected to alleviate the undesirable side-effects mentioned above.

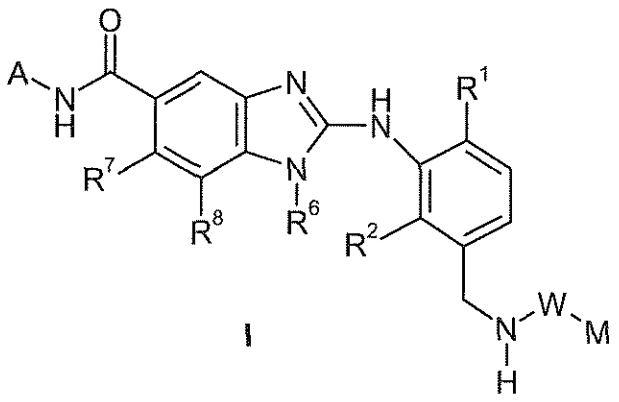
PGH_2 may be transformed to PGE_2 by prostaglandin E synthases (PGES). Two microsomal prostaglandin E synthases (mPGES-1 and mPGES-2), and one cytosolic prostaglandin E synthase (cPGES) have been described. mPGES-1 is proposed to be closely linked to COX-2 and both enzyme's are upregulated during e.g. inflammation. Thus agents that are capable of inhibiting the action of mPGES-1 and thereby reducing the formation of PGE_2 are likely to be of benefit for the treatment of inflammation and more general acute and chronic pain conditions

Benzimidazole and imidazopyridine derivatives with mPGES-1 inhibitory activity are disclosed in WO 2010/034796, WO 2010/034797, WO 2010/034798, WO 2010/034799.

PCT/EP2010/052799 describes a broad class of different 2-arylamino benzimidazoles in which the aryl group bears a particular side chain.

SUMMARY

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



I

in which

R^1 and R^2 independently represent halo, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

W represents -C(O)-, -C(O)O-, which groups are bound to the nitrogen of the –NH- moiety via the carbon atom;

M represents

-C_{1-6}alkyl, -C_{3-7}cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, -NH_2, -NH(C_{1-2}alkyl), -N (C_{1-2}alkyl)$_2$, -OC_{1-3}alkyl, -C_{1-5}alkyl, -C_{3-4}cycloalkyl, in which latter three groups the alkyl or cycloalkyl groups are optionally substituted by one or more fluorine atoms;

or

oxetanyl-, tetrahydrofuranyl-, tetrahydropyranyl-, azetidinyl-, pyrrolidinyl-, piperidinyl-, all of which groups are optionally substituted by one or more substituents selected from fluoro, -CN, -C_{1-3} alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

or

phenyl-, pyridyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, oxazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from halo, -CN or -C_{1-3}alkyl, which latter alkyl group is optionally further substituted by one or more fluorine atoms;

R^8 represents –H, halogen, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

R^6 represents –H, -C_{1-5}alkyl, -C_{3-5}cycloalkyl-C_{0-2}alkyl, in which latter three groups the alkyl or cycloalkyl fragments are optionally substituted by one or more fluorine atoms;

R^7 represents halo, C_{1-5}alkyl-O-, C_{3-7}cycloalkyl-C_{0-2}alkyl-O-, 4-7-membered heterocycloalkyl-C_{0-2}alkyl-O-, in which latter three groups the alkyl, cycloalkyl or heterocycloalkyl fragments are optionally substituted by one or more substituents selected from -F and -OC_{1-3}alkyl which latter alkyl group is optionally further substituted by one or more fluorine atoms;

A	represents C_{1-8} alkyl-, phenyl-, indanyl-, naphthyl-, 1,2,3,4-tetrahydronaphthyl-, pyridyl-, thienyl-, benzothienyl-, pyrrolyl-, indolyl-pyrazolyl-, indazolyl-, thiazolyl-, benzothiazolyl-, oxazolyl-, benzooxazolyl-, isoxazolyl-, benzisoxazolyl-, phenyl-C_{1-3}alkyl-, thienyl-C_{1-3}alkyl-, pyridyl-C_{1-3}alkyl-, C_{3-7}cycloalkyl-C_{0-3}alkyl-, oxetanyl-C_{0-3}alkyl-, tetrahydrofuranyl-C_{0-3}alkyl, tetrahydropyranyl-C_{0-3}alkyl, in which groups the alkyl-, cycloalkyl- and heterocycloalkyl fragments are optionally substituted by one or more substituents selected from R^{9a} and the aryl and heteroaryl fragments are optionally substituted by one or more substituents selected from R^{9b};
each R^{9a}	independently represents -F, -Cl, -C_{1-3}alkyl which is optionally substituted by one or more substituents selected from -F, -OC_{1-3} alkyl;
each R^{9b}	represents independently -halo, -CN; -C_{1-3} alkyl which is optionally substituted by one or more fluorine atoms;

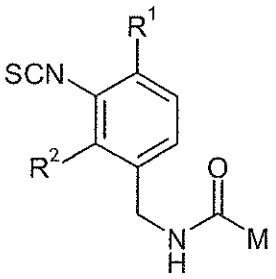
or a salt thereof.

In a second aspect, there is provided a compound as defined above for use as a medicament.

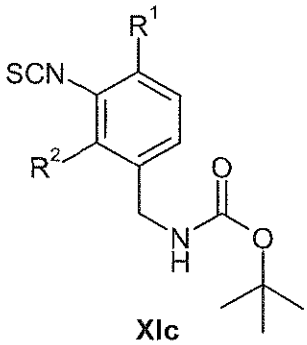
In a third aspect, there is provided a pharmaceutical composition comprising at least one compound as defined above or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

In a fourth aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of inflammatory diseases and/or associated conditions, in particular pain.

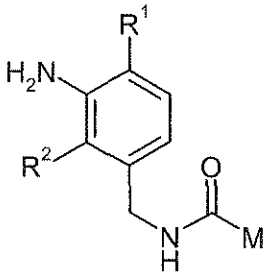
In a fifth aspect, there is provided an intermediate of formula **XIb, XIc, XVIIb, XVIIc, XIX or XX**



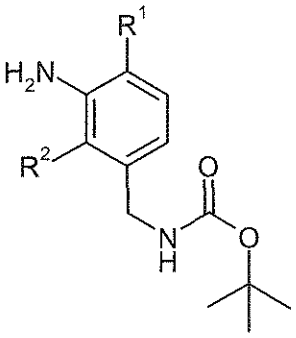
XIb



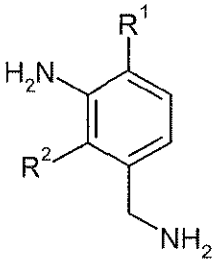
XIc



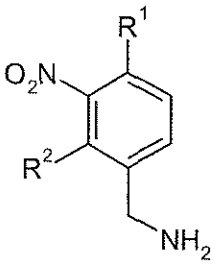
XVIIb



XVIIc



XIX



XX

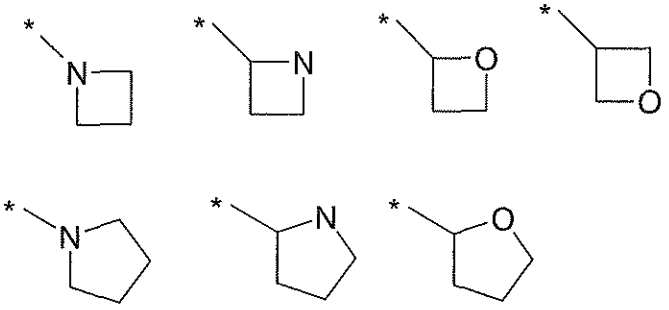
in which

R^1 and R^2 independently represent –chloro, fluoro or $-CH_3$;

M represents

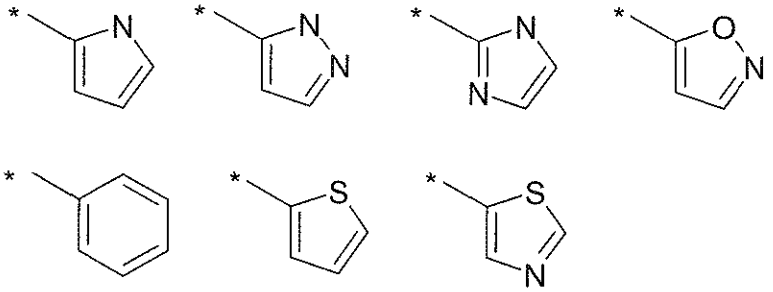
methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, cyclopentyl, all of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CF_3$;

or is selected from the following groups



all of which groups are optionally substituted by one or more substituents selected from -F, $-CH_3$, or $-CF_3$;

or is selected from the following groups



all of which groups are optionally substituted by one or more substituents selected from -F, -Cl, $-CH_3$, or $-CF_3$.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a selection from the general formula of PCT/EP2010/052799 providing compounds that unexpectedly show improved activity in a cell based pharmacological assay.

Compounds with a similar affinity for the mPGES-1 enzyme as measured in the enzyme assay may have different potencies in the cell-based assay.

Data from a cell based pharmacological assay when compared with data from an enzyme assay are considered to allow for a better predictibility and estimation of therapeutic effective concentrations/doses. Compounds of the present invention show high potency in both assays. Consequently, they are likely to be more suitable for the in-vivo use.