These convergent findings indicate that the inhibition of BACE1 may be a therapeutic target for the treatment of AD as well as disorders for which the reduction of Aβ deposits is beneficial.

At the 2012 Alzheimer's Association International Conference in Vancouver, several drug developers announced their BACE1 inhibitors in clinical trials. Eli Lilly scientists reported preclinical research on LY2886721 which had entered a Phase II study. Merck presented a series of posters detailing the Phase I studies of its BACE inhibitor, MK-8931, and announced the start of separate Phase III studies which will test the compound for two years in people with prodromal Alzheimer's disease. Numerous patent applications directed to BACE1 inhibitors have been published over the past several years.

AstraZeneca announced the discovery of AZD3839, a potent and selected BACE1 inhibitor clinical candidate for the treatment of AD (Jeppsson, F., et al. JBC, 2012, 287, 41245-41257) in October 2012. The effort which led to the discovery of AZD3839 was further described in Ginman, T., et al. Journal of Medicinal Chemistry, 2013, 56, 4181-4205. The Ginman publication describes the issues which were overcome in connection with the discovery and identification of AZD3839. These issues related to poor blood brain barrier penetration and P-glycoprotein mediated efflux of the compounds resulting in lack of brain exposure.

The Ginman manuscript hypothesized that the differences would largely be due to the core structures and Structure Activity Relationship data was provided wherein the in vitro properties on the reported compounds were given into four tables according to core sub-types. In table 4, a series of amidine containing compounds are described that were considered interesting from an activity perspective. However, the data suggests that the amidine containing core did not exhibit a favourable blood brain barrier permeability profile.

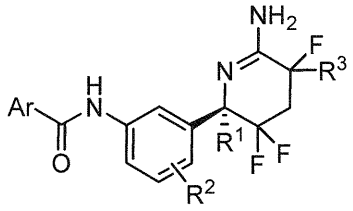
Researchers from Hoffmann-La Roche and Siena Biotech also reported the discovery of amidine containing compounds (Woltering, T. J., et al. Bioorg. Med. Chem. Lett. 2013, 23, 4239-4243). These compounds (compounds 17 and 18 in the paper) were found not to have any in vivo effect (lack of Aβ40 reduction in brain in wild type mice).

SUMMARY OF THE INVENTION

Contrary to the teachings of Ginman, et al. and Woltering, T. J., et al., the inventors have discovered a series of amidine compounds which are brain penetrant and are thus able to inhibit BACE1 in the brain after peripheral dose of said compounds. Accordingly, the present ~~invention~~ disclosure relates to novel compounds

having BACE1 inhibitory activity, to their preparation, to their medical use and to medicaments comprising them.

An objective of the present ~~invention~~ disclosure is to provide compounds that inhibit BACE1. Accordingly, in one aspect, the present ~~invention~~ disclosure relates to compounds of Formula I.



Formula I

Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, isothiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, furazanyl and 1,2,4-thiadiazolyl and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy;

R^1 is C_1-C_3 alkyl or C_1-C_3 fluoroalkyl;

R^2 is hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl; and

R^3 is C_1-C_3 alkyl; or a pharmaceutically acceptable salt thereof.

The present ~~invention~~ disclosure further provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier.

The present ~~invention~~ disclosure provides a method of treating a subject suffering from Alzheimer's disease comprising administering to the subject a therapeutically effective amount of a compound of Formula I.

The present ~~invention~~ disclosure is directed to the use of a compound as defined in Formula I for the manufacture of a medicament for treating Alzheimer's disease.

Further embodiments of the ~~invention~~ present disclosure are provided immediately below:

In one embodiment, the compound is of formula Ia

In one embodiment, Ar is optionally substituted 1,2,4-oxadiazolyl.

In one embodiment, Ar is optionally substituted furazanyl.

In one embodiment, Ar is optionally substituted 1,2,4-thiadiazolyl.

In separate embodiments of the ~~invention~~present disclosure, the compound is selected from one of the exemplified compounds disclosed in the Experimental Section.

In another aspect,~~A separate embodiment~~ the present disclosure is directed to a pharmaceutical composition comprising the compound as disclosed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Another embodiment is directed to a method of treating Alzheimer's disease comprising administering a therapeutically effective amount of the compound.

In ~~Y~~yet another ~~embodiment~~ aspect, the present disclosure is directed to a use of a compound as disclosed herein for the manufacture of a medicament for treating Alzheimer's disease.

In another aspect~~One embodiment~~, the present disclosure is related to a compound as disclosed herein for use in therapy.

In ~~Y~~yet another ~~embodiment~~ aspect, the present disclosure is directed to a compound as disclosed herein for use in the treatment of Alzheimer's disease.

Included also in this ~~invention~~ disclosure are isotopically labelled compounds, which are identical to those claimed in formula I, where one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present disclosure ~~invention~~ include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl and ^{125}I, respectively. Compounds of the present disclosure~~invention~~, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this ~~invention~~disclosure. Certain isotopically labelled compounds of the ~~invention~~present disclosure, such as those with radioactive isotopes incorporated including but not limited to ^{3}H and ^{14}C, are useful in drug and/or substrate tissue distribution assays.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the two molecules in the asymmetric unit as found in the crystal structure. The X-ray method used cannot distinguish between hydrogen (^{1}H) and deuterium (D or ^{2}H). Hence , the deuterium atoms in the *d3*-methoxy group are depicted as hydrogen.

~~12. A method of treating Alzheimer's disease comprising administering a therapeutically effective amount of the compound of anyone of claims 1-10.~~

~~13.~~12. A use of a compound of anyone of claims 1-10 for the manufacture of a medicament for treating Alzheimer's disease.

~~14.~~13. A compound according to anyone of claims 1-10 for use in therapy.

~~15.~~14. A compound according to anyone of claims 1-10 for use in the treatment of Alzheimer's disease.