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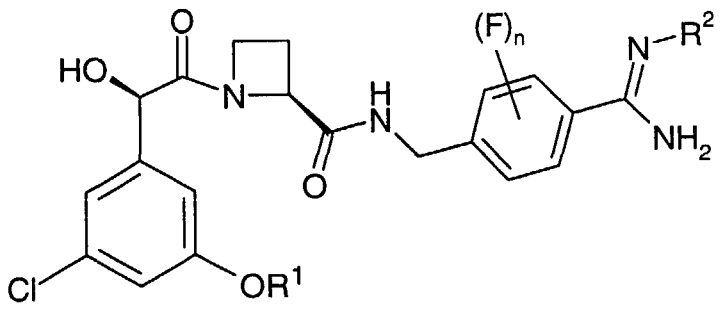
[Continued on next page]

(54) Title: IMMEDIATE RELEASE PHARMACEUTICAL FORMULATION



(I)

(57) Abstract: According to the present invention there is provided an immediate release pharmaceutical formulation comprising, as active ingredient, a compound of formula (I), wherein R_1 represents C?1-2#191 alkyl substituted by one or more fluoro substituents;R_2 represents hydrogen, hydroxy, methoxy or ethoxy; andn represents 0, 1 or 2;or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable diluent or carrier; provided that when the active ingredient is other than in the form of a salt the formulation does not solely contain:• a solution of one active ingredient and water;• a solution of one active ingredient and dimethylsulphoxide; or• a solution of one active ingredient in a mixture of ethanol : PEG 660 12-hydroxy stearate : water 5:5:90; such formulations being of use for the treatment of a cardiovascular disorder.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

IMMEDIATE RELEASE PHARMACEUTICAL FORMULATION

This invention relates to a novel immediate release pharmaceutical formulation that provides for the delivery of particular pharmaceuticals, to the manufacture of such a formulation, and to the use of such a formulation in the treatment or prevention of thrombosis.

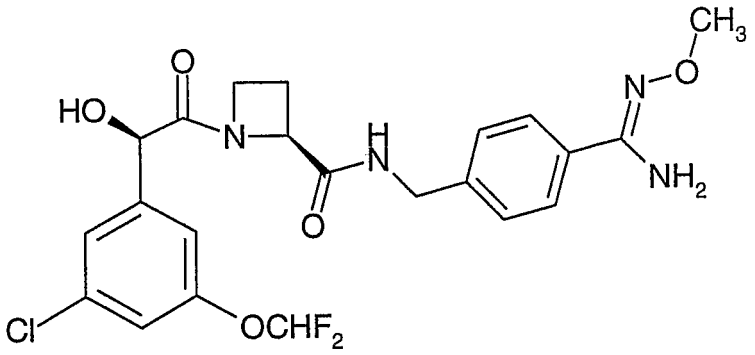
It is often desirable to formulate pharmaceutically active compounds for immediate release following oral and/or parenteral administration with a view to providing a sufficient concentration of drug in plasma within the time-frame required to give rise to a desired therapeutic response.

Immediate release may be particularly desirable in cases where, for example, a rapid therapeutic response is required (for example in the treatment of acute problems), or, in the case of parenteral administration, when peroral delivery to the gastrointestinal tract is incapable of providing sufficient systemic uptake within the required time-frame.

In the case of the treatment or prophylaxis of thrombosis, immediate release formulations may be necessary to ensure that a sufficient amount of drug is provided in plasma within a relatively short period of time to enable quick onset of action. Immediate release formulations are also typically simpler to develop than modified release formulations, and may also provide more flexibility in relation to the variation of doses that are to be administered to patients. Immediate release formulations are superior when multiple doses are not required and where it is not necessary to keep the plasma concentration at a constant level for an extended time.

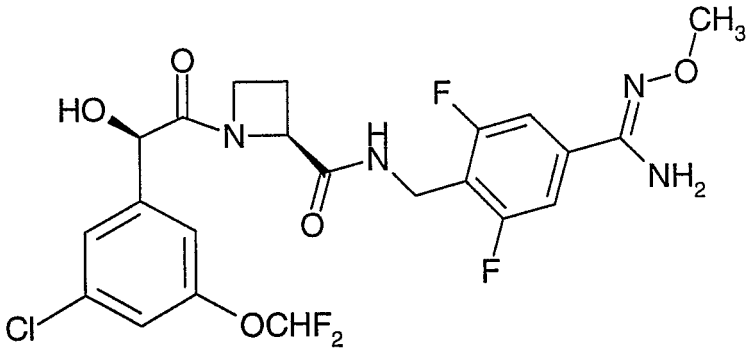
International Patent Application No. PCT/SE01/02657 (WO 02/44145, earliest priority date 01 December 2000, filed 30 November 2001, published 06 June 2002) discloses a number of compounds that are, or are metabolised to compounds which are, competitive inhibitors of trypsin-like proteases, such as thrombin. The following three compounds are amongst those that are specifically disclosed:

(a) Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe):



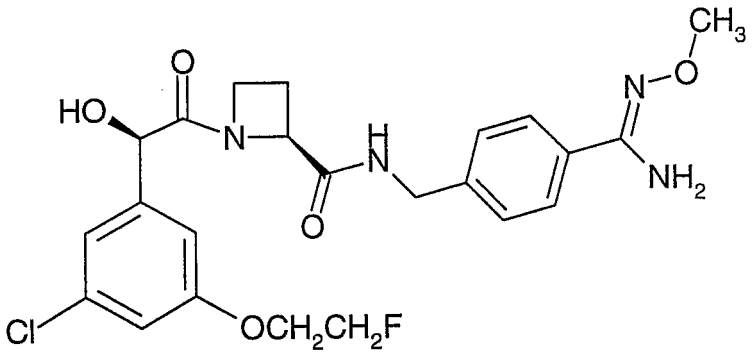
which compound is referred to hereinafter as Compound A;

(b) Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OMe):



which compound is referred to hereinafter as Compound B; and

(c) Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OMe):



which compound is referred to hereinafter as Compound C.

The methoxyamidine Compounds A, B and C are metabolised following oral and/or parenteral administration to the corresponding free amidine compounds, which latter compounds have been found to be potent inhibitors of thrombin. Thus:

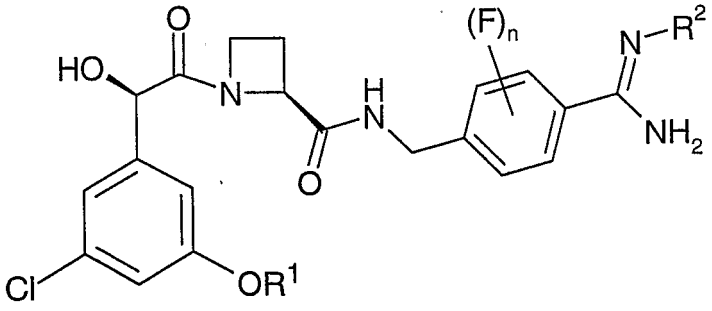
- Compound A is metabolized to Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab (which compound is referred to hereinafter as Compound D) via a prodrug intermediate

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OH) (which compound is referred to hereinafter as Compound G);

- Compound B is metabolized to Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF) (which compound is referred to hereinafter as Compound E) via a prodrug intermediate Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(2,6-diF)(OH) (which compound is referred to hereinafter as Compound H); and,
- Compound C is metabolized to Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab (which compound is referred to hereinafter as Compound F) via a prodrug intermediate Ph(3-Cl)(5-OCH_2CH_2F)-(*R*)CH(OH)C(O)-(*S*)Aze-Pab(OH) (which compound is referred to hereinafter as Compound J).

Processes for the synthesis of Compounds A, B, C, D, E, F, G and J are described in Examples 12, 40, 22, 3, 39, 21, 2 and 31 (respectively) of international patent application No. PCT/SE01/02657. An immediate release formulation of these compounds, or their metabolites has yet to be described in the literature. We have found that the compounds of formula (I) and their salts can be formulated as immediate release pharmaceutical formulations which are easy to administer, for example by oral or parenteral administration.

According to a first aspect of the invention, there is provided an immediate release pharmaceutical formulation comprising, as active ingredient, a compound of formula (I):



(I)

wherein

R^1 represents C_{1-2} alkyl substituted by one or more fluoro substituents;

R^2 represents hydrogen, hydroxy, methoxy or ethoxy; and

n represents 0, 1 or 2;

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