Thieno[2,3-B]Pyridine Derivatives as Epac Inhibitors and their pharmaceutical uses.

KEYWORDS

- EXCHANGE PROTEINS DIRECTLY ACTIVATED BY cAMP (EPAC)
- cAMP
- CARDIAC DISEASES
- CARDIOPROTECTIVE ACTIVITY
- CARDIOMYOCYTE HYPERTROPHY

AREA

- PHARMACEUTICAL

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Patent Type
Patent for invention.

Co-Ownership
Sapienza University of Rome 50%, Sapienza Università di Roma 22,50%, Institut National de la Santé et de la Recherche Médicale (INSERM) 38,75%, Universitè Paris Sud 11,25%, Universitè de Toulouse III, Paul Sabatier 27,5%.

Inventors
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Industrial & Commercial Reference
The patent is for the pharmaceutical industries, these compounds are a novelty for the heart failure treatment.

Time to Market
The patent is ready for the market. Further studies are crucial for the evaluation of safety and bioavailability of the compounds. TLR3-TLR4 Technology validated in lab.

Availability
Cession, Research, Development, Experimentation, Collaboration.

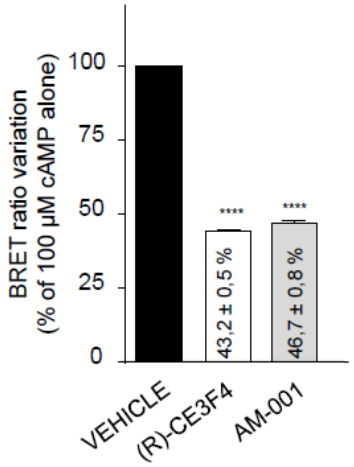

Fig. 1 BRET assay. AM-001, (R)-CE3F4 (20 µM) or vehicle were added to the cell extract before addition of cAMP (100 µM), and BRET ratios (mean±S.E.M from 3 wells) were measured and plotted as percent variations 5 in BRET ratios relative to no-inhibitor control value.

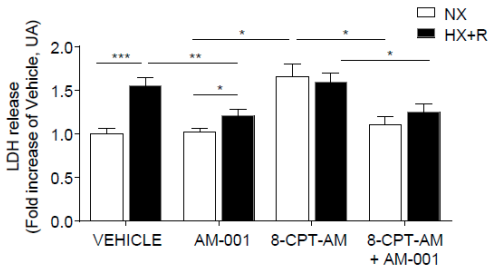

Fig. 2 Isolated adult cardiomyocytes were pretreated or not with AM-001 (20 µM, 30 min), stimulated or not with 8-CPT-AM (10 µM, 30 min), and subjected to normoxia (NX) or hypoxia-reoxygenation (HX+R) treatment. Cell viability was determined by lactate dehydrogenase (LDH) release in under NX or HX+R conditions (n=6).

Abstract
Recent studies reported that Epac1-deficient mice were protected against various forms of cardiac stress.
We identified the Thieno[2,3-B]Pyridine derivatives as EPAC1 inhibitors that confirmed the beneficial for the treatment of cardiac diseases by these inhibitors.
The compounds have the advantage to be selective for the EPAC isoforms.
Our finding on the cardioprotective effect of Thieno[2,3-B]Pyridine derivatives in a preclinical model of myocardial I/R injury, highlights the therapeutic potential in cardiac ischemia.
Our data also showed that the compounds were helpful in chronic treatment in a mouse model of cardiac remodeling induced by sustained activation of β-ARs.

Publications

- Identification of a pharmacological inhibitor of Epac1 that protects the heart against acute and chronic models of cardiac stress. Cardiovascular Research. 2019. https://doi.org/10.1093/cvr/cvz076

Thieno[2,3-B]Pyridine Derivatives as Epac Inhibitors and their pharmaceutical uses.

Technical Description

Thus it was reported the advantage of the EPAC1 inhibition in the therapy of many cardiac stress we used the Epac1-BRET sensing assay for searching for non-cyclic nucleotide Epac1 modulators.
The thieno[2.3-b]pyridine derivatives, were identified as non-competitive inhibitor of Epac1. The compounds have no antagonist effect on Epac2 or protein kinase A (PKA) activity. In addition, we found that AM-001 inhibited Epac1-dependent deleterious effects such as cardiomyocyte hypertrophy and death.
Importantly, the compounds mediated inhibition of Epac1 reduces infarct size after mouse myocardial I/R injury.
Finally, AM-001 attenuates cardiac hypertrophy, inflammation and fibrosis, and improves cardiac function during chronic β- adrenergic receptor (β-AR) activation with isoprenaline in mice.

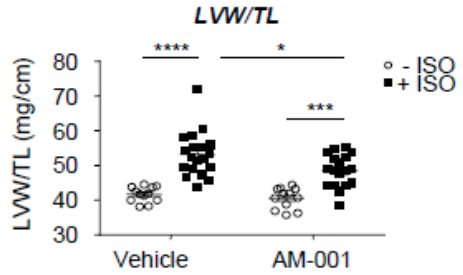

Fig. 3 LVW/TL ratios of mice after 14 days of treatment with vehicle or AM-001.

Technologies & Advantages

Pharmaceutical manipulation of cAMP levels exerts beneficial effects through the regulation of the EPAC and PKA pathway. Recent attention has turned to the specific regulation of EPAC isoforms as a more targeted approach to cAMP-based therapies.
Drugs that target the cAMP system are currently prescribed for a range of diseases, including β2-adrenoceptor agonists such as salbutamol, for the treatment of asthma.
The challenge now is to specifically target cAMP signaling in a pathway-specific manner to reduce the side effects. To fix this point we identify a selective EPAC1 antagonist which proved to be useful in animal model for the treatment of myocardial I/R injury, highlights the therapeutic potential in cardiac ischemia and in the cardiac remodeling induced by activation of β-ARs.
At the state of the art these compounds represent a novelty for the treatment of the heart failure.
The already reported EPAC1 antagonist are analogues of the substrate cAMP which are far to be classified as drug-like. The beneficial effect of the inhibition of the EPAC1 by the reported compounds was also confirmed in animal model.

Applications

The application of the compounds reported in the patent application is in the field of medicinal chemistry.

The compounds are selective antagonist of the EPAC1 enzyme, thus they may be used as therapeutic tool in the diseases EPAC1 dependent such as cardiac arrhythmia and heart failure.

The advantages of the EPAC1 inhibitors instead of drugs already approved for these pathological conditions is the higher therapeutic index.
Furthermore, nowadays there are not compounds used in therapy that target EPAC1 despite there are many drugs that act modifying the level of the EPAC substrate thus doing the EPAC pathway a validated target.

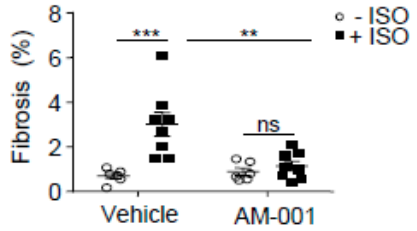

Fig. 4 The bar graph shows the quantification of fibrosis (n=6–8 per group).

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