HIGHLY SELECTIVE INHIBITORS OF ADAMS ACTIVITY

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Invention

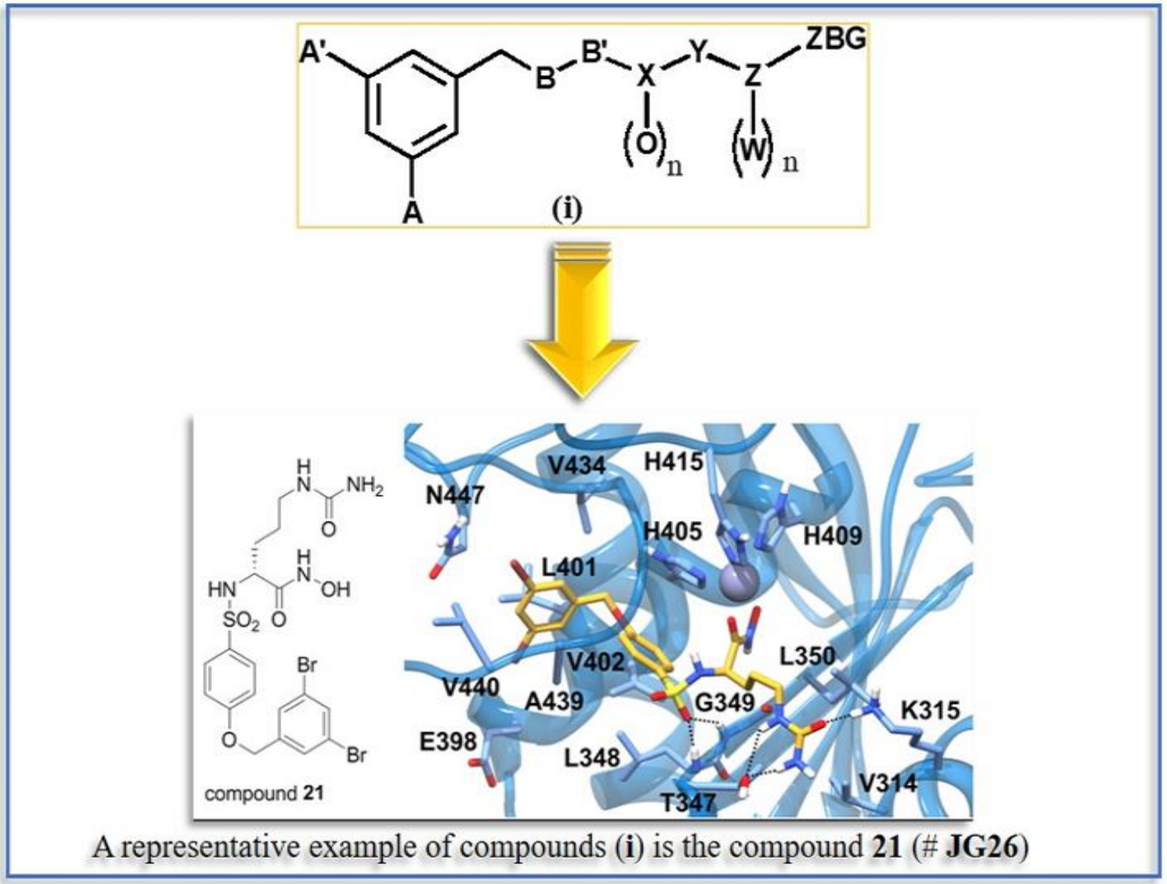
The invention concerns the development of appropriately designed and synthesized chemical entities that **selectively exert their activity on ADAMs**, **A Disintegrin And Metalloproteinase (ADAM) enzyme**.

ADAM proteins are a biologically diverse group of proteins that play numerous roles in the cells interactions with the surrounding microenvironment. Many ADAM proteins have been implicated in neoplastic processes.

An appropriate combination of the molecular structure substituents on the molecular scaffold is able to confer suitable features able to strongly discriminate their selectivity between some sheddases, such as TACE (ADAM17), and other antitarget proteases (MMPs, other ADAMs and ADAMTS). In this range of action, the absence of selectivity would cause a serious of side effects and/or aggravation of diseases correlated with their expression.

The aim of the patented invention is to obtain a pharmaceutical solution, that can provide appreciable therapeutic safety compared to the state of the art. The advantage of this invention is related, in fact, to the high potency and selectivity of action, low toxicity and good bioavailability of molecules of general formula (i), shown in the figure.

Drawings
& pictures



A representative example of compounds (**i**) is the compound **21** (# **JG26**)

Industrial applications

POSSIBLE APPLICATIONS

- Therapy or diagnosis in immunology, for anti-sheddase activity that modulates immune system cells (NK/T cells);
- Therapy or diagnosis of cancers, cardiovascular diseases, rheumatoid arthritis, viral/bacterial infections, angio-/lympho-angiogenesis, neurodegeneration.

ADVANTAGES

- High selectivity for ADAM17 with increased therapeutic safety and reduced pro-carcinogenic effects;
- Excellent bioavailability and low cytotoxicity;
- Simple synthetic preparation and/or diagnostic labeling;
- Shedding modulation of TNFA, TGF-A, EGFR, ERBB, HER3, ALCAM, CD16, MICA/-B.

Possible developments

The new synthetic compounds inhibit ADAM17 (TACE) activity in the nanomolar range and are simultaneously inactive on various metalloproteases (MMPs), thus being of particular relevance.

The new molecules promise a significantly higher therapeutic safety profile than those already known in the state of the art. This profile is achieved by the absence of inhibitory activity on other zinc proteases, defined as therapeutic antitargets. It is emphasized that, in the past, nonspecific inhibition of these antitarget proteases has been the main cause of therapeutic failure of MMPs inhibitors. Targeted action on the therapeutic target achievable only through the use of the compounds of the present invention (i.e., compound 21) may lead to **reduced drug doses administered, elimination of pro-carcinogenic effects** due to nonselective inhibition of antitarget proteases, **limitations of toxic effects, and fewer side effects in long-term treatments**.

The inventors are open to undertake future collaborations to increase the technological readiness level of the invention and expand innovative drug opportunities, considering licensing or transferring for further development and commercialization by interested pharmaceutical companies.

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