New DDAH inhibitors

General information

The versatility of nitric oxide (NO) as physiological mediator makes the balanced regulation of its formation vital. An impaired NO availability results in hypertonia and cardiovascular and erectile dysfunction. On the other hand, NO overproduction is also associated with a number of pathophysiological conditions such as cardiogenic shock, septic shock, stroke, pain, migraine, neurodegenerative diseases (e.g. Alzheimer's disease), rheumatoid arthritis, chronic inflammation, diabetes and meningitis.

Despite the many efforts towards using the direct inhibition of NO-synthase for the therapy of these pathophysiological conditions, to date none of the tested substances has been approved as a pharmaceutical product.

The inhibition of dimethylarginine dimethylaminohydrolase (DDAH) represents a promising new pharmaceutical strategy to indirectly affect NO formation by elevating N^{ω}-methylated L-arginine levels. DDAH inhibition may thus be useful for the therapy of pathophysiological conditions associated with NO overproduction, as well as be a pharmaceutical strategy to reduce angiogenesis associated with tumors, arthritis and diabetic retinopathy.

State of the art

At present, several L-arginine derivatives have been identified as inhibitors for the human DDAH-1, N^{ω}-(2-methoxyethyl)-L-arginine being the most potent representative. However, the known L-arginine analogues have disadvantageous pharmacokinetic profiles resulting mainly from their amino acid structure, since these are present as zwitterions at physiological pH values. The amine function is protonated and thus positively charged, whereas the carboxyl function is deprotonated and thus negatively charged. Charged molecules are only moderately taken in by the gastrointestinal tract, since they are not able to diffuse through the lipophilic gastrointestinal membranes.

The invention

The new inhibitors of DDAH have a single amine function simultaneously displaying the same activity as the most potent known inhibitors without the pharmacokinetically disadvantageous zwitterion profile.

Utilisation concept

Licensing/selling of this invention is sought to a company that will produce, bring to market and distribute the described DDAH inhibitors. If desired PVA SH GmbH will further assist by arranging contact with the inventors.

Contact

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