

LINEAR AND MONOCYCLIC ENDOTHELIN ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to novel linear and monocyclic antagonists of endothelin useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. More particularly, the novel compounds of the present invention are antagonists of endothelin useful in controlling hypertension, myocardial infarction, metabolic, endocrinological, and neurological disorders, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrhythmias, asthma, acute renal failure, preeclampsia, and diabetes.

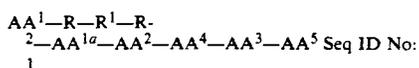
Endothelin-1 (ET-1), a potent vasoconstrictor, is a 21 amino acid bicyclic peptide that was first isolated from cultured porcine aortic endothelial cells. Endothelin-1, is one of a family of structurally similar bicyclic peptides which include; ET-2, ET-3, vasoactive intestinal contractor (VIC), and the sarafotoxins (SRTXs). The unique bicyclic structure and corresponding arrangement of the disulfide bridges of ET-1, which are the same for the endothelins, VIC, and the sarafotoxins, has led to significant speculation as to the importance of the resulting induced secondary structure to receptor binding and functional activity. ET-1 analogues with incorrect disulfide pairings exhibit at least 100-fold less vasoconstrictor activity. The flexible C-terminal hexapeptide of ET-1 has been shown to be important for binding to the ET receptor and functional activity in selected tissues. Additionally, the C-terminal amino acid (Trp-21) has a critical role in binding and vasoconstrictor activity, since ET[1-20] exhibits approximately 1000-fold less functional activity.

Cody, W. L., et al, Abstract, Second International Conference on Endothelin, Tsukuba, Japan, Dec. 9, 1990, and Johansen, N. L., et al, Peptides 1990, Proceedings of the Twenty First European Peptide Symposium, edited by Giralt, E. and Andreu, D., pages 680-681, Escom Science Publishers B.V. (1990) disclosed various monocyclic analogs of ET-1, none of which exhibited any functional vasoconstricting activity.

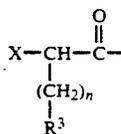
However, we have surprisingly and unexpectedly found that a series of linear and monocyclic analogs of ET-1 are antagonists of endothelin.

SUMMARY OF THE INVENTION

Accordingly, the present invention is a compound of Formula I



wherein
AA¹ is



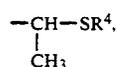
wherein

X is

hydrogen,
alkyl,
alkenyl,
alkynyl,
cycloalkyl,
heterocycloalkyl,
aryl, or
heteroaryl,

n is zero or an integer of 1, 2, 3, 4, 5, or 6,

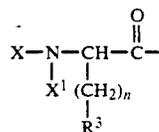
R³ is —S—R⁴, wherein R⁴ is as defined hereinafter,



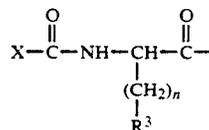
wherein R⁴ is as defined hereinafter,

—C(CH₃)₂—S—R⁴, wherein R⁴ is

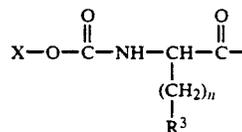
hydrogen,
alkyl, cycloalkyl, aryl, heteroaryl, or R⁴ is absent when AA¹ is covalently linked to AA^{1a} through a disulfide bridge,



wherein X and X¹ are each the same or different and each is as defined above for X or X¹ is Asp-Lys Glu and n and R³ are as defined above,



wherein X, n, and R³ are as defined above, or



wherein X, n, and R³ are as defined above;

R is absent or is one to four amino acids selected from the group consisting of:

Ala,
Arg,
Asn,
Asp,
Cys,
Glu,
Gln,
Gly,