

activation or to increased cell proliferation and cell adhesion. As a consequence, formation of endothelial dysfunction, atherosclerosis, hypertension, stable or unstable angina pectoris, thrombosis, myocardial infarction, strokes or erectile dysfunction results. Pharmacological stimulation of sGC offers a possibility to normalize cGMP production and therefore may make possible the treatment and/or prevention of such disorders.

For the pharmacological stimulation of the sGC, use has been made of compounds whose activity is based on an intermediate NO release, for example organic nitrates. The drawback of this treatment is the development of tolerance and a reduction of activity, and the higher dosage which is required because of this.

Various sGC stimulators which do not act via NO release were described by Vesely in a series of publications. However, the compounds, most of which are hormones, plant hormones, vitamins or natural compounds such as, for example, lizard poisons, predominantly only have weak effects on the cGMP formation in cell lysates. D. L. Vesely, Eur. J. Clin. Invest., vol.15, 1985, p. 258; D. L. Vesely, Biochem. Biophys. Res. Comm., vol. 88, 1979, p.1244. A stimulation of heme-free guanylate cyclase by protoporphyrin IX was demonstrated by Ignarro et al., Adv. Pharmacol., vol. 26, 1994, p. 35. Pettibone et al., Eur. J. Pharmacol., vol. 116, 1985 p. 307, described an antihypertensive action of diphenyliodonium hexafluorophosphate and attributed this to a stimulation of sGC. According to Yu et al., Brit. J. Pharmacol., vol. 114, 1995, p.1587, isoliquiritigenin, which has a relaxing action on isolated rat aortas, also activates sGC. Ko et al., Blood vol. 84, 1994, p. 4226, Yu et al., Biochem. J. vol. 306, 1995, p. 787, and Wu et al., Brit. J. Pharmacol. vol. 116, 1995, p. 1973, demonstrated a sGC-stimulating activity of 1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole and demonstrated an antiproliferative and thrombocyte-inhibiting action. Pyrazoles and fused pyrazoles which exhibit a sGC-stimulating activity are described in European Patent No. 908,456 and German Patent Application No. 19,744,027.

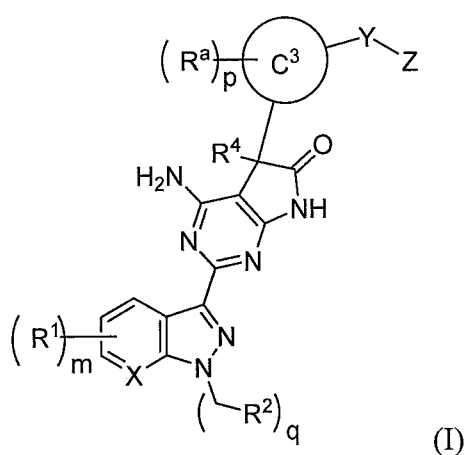
It has now been found that the compounds of the present invention effect a strong activation of soluble guanylate cyclase and are therefore may be suitable for the therapy and prophylaxis of disorders which are associated with a low cGMP level.

SUMMARY

The present disclosure relates to compounds which activate soluble guanylate cyclase and may be valuable pharmaceutically active compounds for the therapy and prophylaxis of diseases, for example for cardiovascular diseases such as hypertension, heart failure, pulmonary

(I)

In one aspect, there is provided a compound of the Formula (I)



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(iv.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 2 heteroatoms selected from N, O, or S;

wherein ring C2 is unsubstituted or substituted by 1 to 3 moieties independently selected from halo, cyano, C1-C3 alkyl, -O-C1-C3 alkyl, or oxo;

5 R4 is C1-C6 alkyl, CF3, or C3-C6 cycloalkyl;

ring C3 is:

(a.) phenyl;

(b.) a 5- or 6-membered monocyclic heteroaryl or a 9- to 10-membered bicyclic heteroaryl containing 1 to 3 heteroatoms selected from N, O, or S;

10 (c.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 3 heteroatoms selected from N, O, or S; or

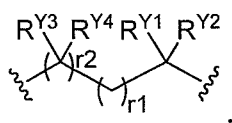
(d.) C3-C6 cycloalkyl;

each Ra is independently selected from halo, cyano, C1-C3 alkyl, -O-C1-C3 alkyl, oxo, or hydroxy;

15 Y is:

(a.) a bond;

(b.) a group of the formula

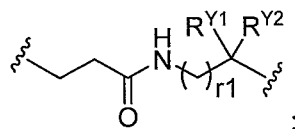


wherein RY1 and RY2 are independently H, C1-C3 alkyl, hydroxy, fluoro, C1-C3 hydroxyalkyl, or amino; or alternatively RY1 and RY2, together with the carbon atom to which they are

20 attached form a C3-C6 cycloalkyl;

RY3 and RY4 are independently H, C1-C3 alkyl, hydroxy, fluoro, or C1-C3 hydroxyalkyl; or alternatively RY3 and RY4, together with the carbon atom to which they are attached form a C3-C6 cycloalkyl;

(c.) a group of the formula

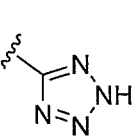
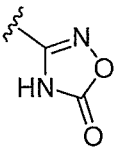
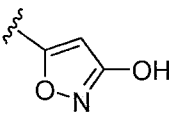


25 (d.) ring AH, wherein ring AH is C3-C6 cycloalkyl or phenyl, wherein ring AH is unsubstituted or substituted by 1 to 3 moieties independently selected from halo or C1-C3 alkyl;

(e.) a group -CH=CH-; or

(f.) a group

Z is:

- (a.) $-\text{CO}_2\text{H}$; (b.) $-\text{C}(\text{O})\text{N}(\text{H})\text{OH}$; (c.) ; (d.) ; (e.) ;
- (f.) $-\text{SO}_3\text{H}$; (g.) $-\text{P}(=\text{O})(\text{OH})_2$; or (h.) $-\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$;
- the subscript m is 0, 1, or 2;
- 5 the subscript p is 0, 1, 2, or 3;
- the subscript q is 0 or 1;
- the subscript r1 is 0, 1, 2, 3, or 4; and
- the subscript r2 is 0 or 1.

The disclosure furthermore relates to processes for preparing compounds of Formula (I),
10 to the use of such compounds for the therapy and prophylaxis of the above mentioned diseases
and for preparing compounds for this purpose, and to pharmaceutical compositions which
comprise compounds of Formula (I).

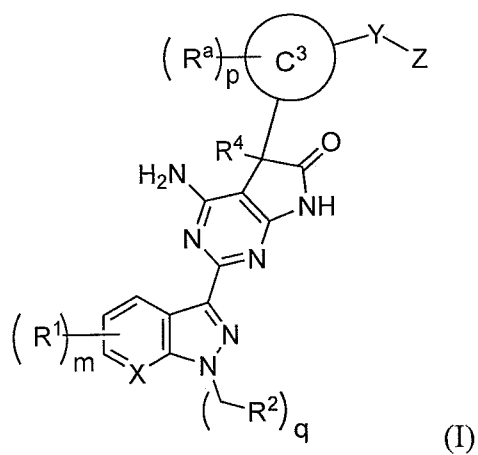
In another aspect, there is provided a pharmaceutical composition comprising the
compound as defined herein or a pharmaceutically acceptable salt thereof, and a
15 pharmaceutically acceptable carrier.

In another aspect, there is provided a compound as defined herein, or a pharmaceutically
acceptable salt thereof, for use in therapy

In another aspect, there is provided the use of the compound as defined herein, or a
pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for treating
20 a condition selected from cardiovascular disease, endothelial dysfunction, diastolic dysfunction,
atherosclerosis, hypertension, heart failure, pulmonary hypertension (WHO groups I, II, III, IV),
angina pectoris, thrombosis, restenosis, myocardial infarction, stroke, cardiac insufficiency,
fibrosis, pulmonary hypertonia, erectile dysfunction, asthma, acute respiratory distress syndrome
(ARDS), chronic kidney disease, cystic fibrosis, sickle cell anemia, scleroderma, Raynaud's
25 Syndrome, diabetes, diabetic retinopathy, cirrhosis of the liver, chronic obstructive pulmonary
disease (COPD), acute lung injury, pulmonary fibrosis, or interstitial lung disease.

DETAILED DESCRIPTION OF THE INVENTION

In embodiment no. 1, the present invention provides a compound having structural Formula (I):



(I)

5 or a pharmaceutically acceptable salt thereof, wherein:

X is C(H) or N;

each R^1 is independently halo, hydroxy, C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl or $-O$ - C_1 - C_3 alkyl;

3-{4-[4-amino-2-(1-butyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

4-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

4-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

2-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-cyanophenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoic acid; or

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-hydroxyphenyl)propanoic acid.

18. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is:

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

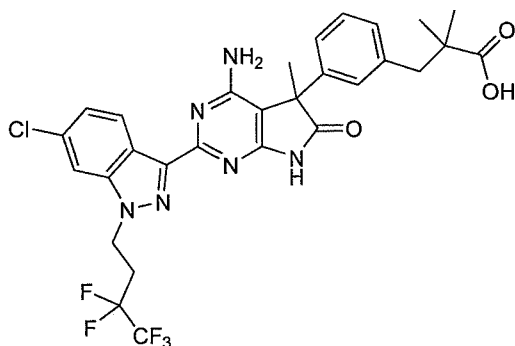
3-{2-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[1-(2,3-difluorobenzyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid; or

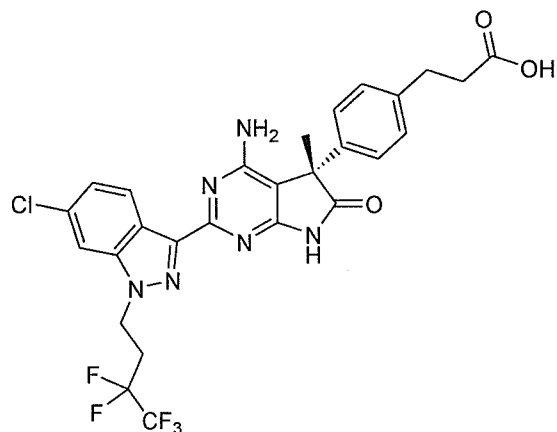
3-(2-{4-amino-2-[1-(cyclohexylmethyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid.

19. The compound of claim 1, which is



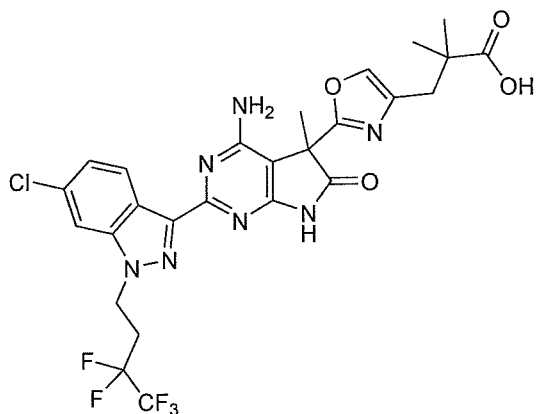
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1, which is



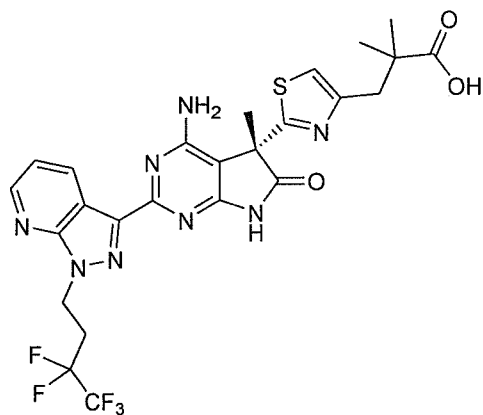
or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1, which is



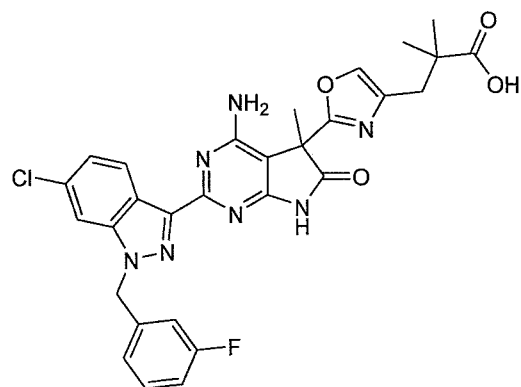
or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1, which is



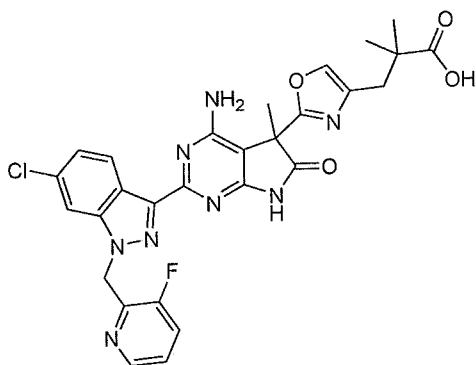
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1, which is



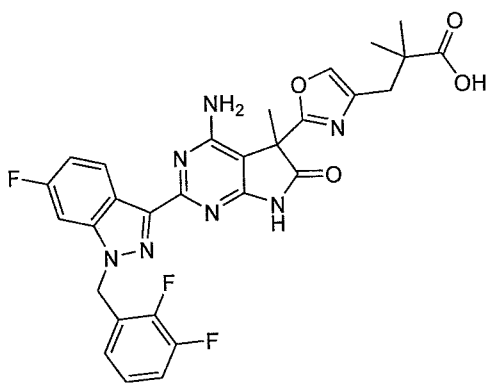
or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1, which is



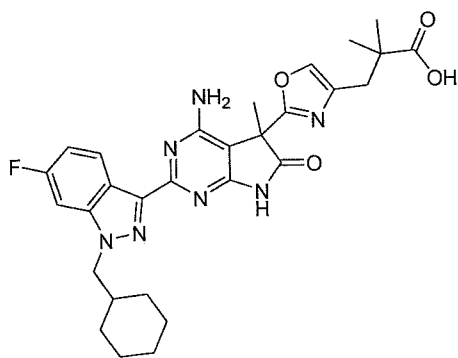
or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1, which is



or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1, which is



or a pharmaceutically salt thereof.

CC(C)(C)C[C@@H]1C(=O)Nc2c(N)nnc2C3=C(N1)C(=C4C(=C(C=C3)N)C(=C5C(=C(C=C4)N)C(=C6C(=C(C=C5)N)C(=C7C(=C(C=C6)N)C(=C8C(=C(C=C7)N)C(=C9C(=C(C=C8)N)C(=C10C(=C(C=C9)N)C(=C11C(=C(C=C10)N)C(=C12C(=C(C=C11)N)C(=C13C(=C(C=C12)N)C(=C14C(=C(C=C13)N)C(=C15C(=C(C=C14)N)C(=C16C(=C(C=C15)N)C(=C17C(=C(C=C16)N)C(=C18C(=C(C=C17)N)C(=C19C(=C(C=C18)N)C(=C20C(=C(C=C19)N)C(=C21C(=C(C=C20)N)C(=C22C(=C(C=C21)N)C(=C23C(=C(C=C22)N)C(=C24C(=C(C=C23)N)C(=C25C(=C(C=C24)N)C(=C26C(=C(C=C25)N)C(=C27C(=C(C=C26)N)C(=C28C(=C(C=C27)N)C(=C29C(=C(C=C28)N)C(=C30C(=C(C=C29)N)C(=C31C(=C(C=C30)N)C(=C32C(=C(C=C31)N)C(=C33C(=C(C=C32)N)C(=C34C(=C(C=C33)N)C(=C35C(=C(C=C34)N)C(=C36C(=C(C=C35)N)C(=C37C(=C(C=C36)N)C(=C38C(=C(C=C37)N)C(=C39C(=C(C=C38)N)C(=C40C(=C(C=C39)N)C(=C41C(=C(C=C40)N)C(=C42C(=C(C=C41)N)C(=C43C(=C(C=C42)N)C(=C44C(=C(C=C43)N)C(=C45C(=C(C=C44)N)C(=C46C(=C(C=C45)N)C(=C47C(=C(C=C46)N)C(=C48C(=C(C=C47)N)C(=C49C(=C(C=C48)N)C(=C50C(=C(C=C49)N)C(=C51C(=C(C=C50)N)C(=C52C(=C(C=C51)N)C(=C53C(=C(C=C52)N)C(=C54C(=C(C=C53)N)C(=C55C(=C(C=C54)N)C(=C56C(=C(C=C55)N)C(=C57C(=C(C=C56)N)C(=C58C(=C(C=C57)N)C(=C59C(=C(C=C58)N)C(=C60C(=C(C=C59)N)C(=C61C(=C(C=C60)N)C(=C62C(=C(C=C61)N)C(=C63C(=C(C=C62)N)C(=C64C(=C(C=C63)N)C(=C65C(=C(C=C64)N)C(=C66C(=C(C=C65)N)C(=C67C(=C(C=C66)N)C(=C68C(=C(C=C67)N)C(=C69C(=C(C=C68)N)C(=C70C(=C(C=C69)N)C(=C71C(=C(C=C70)N)C(=C72C(=C(C=C71)N)C(=C73C(=C(C=C72)N)C(=C74C(=C(C=C73)N)C(=C75C(=C(C=C74)N)C(=C76C(=C(C=C75)N)C(=C77C(=C(C=C76)N)C(=C78C(=C(C=C77)N)C(=C79C(=C(C=C78)N)C(=C80C(=C(C=C79)N)C(=C81C(=C(C=C80)N)C(=C82C(=C(C=C81)N)C(=C83C(=C(C=C82)N)C(=C84C(=C(C=C83)N)C(=C85C(=C(C=C84)N)C(=C86C(=C(C=C85)N)C(=C87C(=C(C=C86)N)C(=C88C(=C(C=C87)N)C(=C89C(=C(C=C88)N)C(=C90C(=C(C=C89)N)C(=C91C(=C(C=C90)N)C(=C92C(=C(C=C91)N)C(=C93C(=C(C=C92)N)C(=C94C(=C(C=C93)N)C(=C95C(=C(C=C94)N)C(=C96C(=C(C=C95)N)C(=C97C(=C(C=C96)N)C(=C98C(=C(C=C97)N)C(=C99C(=C(C=C98)N)C(=C100C(=C(C=C99)N)C(=C101C(=C(C=C100)N)C(=C102C(=C(C=C101)N)C(=C103C(=C(C=C102)N)C(=C104C(=C(C=C103)N)C(=C105C(=C(C=C104)N)C(=C106C(=C(C=C105)N)C(=C107C(=C(C=C106)N)C(=C108C(=C(C=C107)N)C(=C109C(=C(C=C108)N)C(=C110C(=C(C=C109)N)C(=C111C(=C(C=C110)N)C(=C112C(=C(C=C111)N)C(=C113C(=C(C=C112)N)C(=C114C(=C(C=C113)N)C(=C115C(=C(C=C114)N)C(=C116C(=C(C=C115)N)C(=C117C(=C(C=C116)N)C(=C118C(=C(C=C117)N)C(=C119C(=C(C=C118)N)C(=C120C(=C(C=C119)N)C(=C121C(=C(C=C120)N)C(=C122C(=C(C=C121)N)C(=C123C(=C(C=C122)N)C(=C124C(=C(C=C123)N)C(=C125C(=C(C=C124)N)C(=C126C(=C(C=C125)N)C(=C127C(=C(C=C126)N)C(=C128C(=C(C=C127)N)C(=C129C(=C(C=C128)N)C(=C130C(=C(C=C129)N)C(=C131C(=C(C=C130)N)C(=C132C(=C(C=C131)N)C(=C133C(=C(C=C132)N)C(=C134C(=C(C=C133)N)C(=C135C(=C(C=C134)N)C(=C136C(=C(C=C135)N)C(=C137C(=C(C=C136)N)C(=C138C(=C(C=C137)N)C(=C139C(=C(C=C138)N)C(=C140C(=C(C=C139)N)C(=C141C(=C(C=C140)N)C(=C142C(=C(C=C141)N)C(=C143C(=C(C=C142)N)C(=C144C(=C(C=C143)N)C(=C145C(=C(C=C144)N)C(=C146C(=C(C=C145)N)C(=C147C(=C(C=C146)N)C(=C148C(=C(C=C147)N)C(=C149C(=C(C=C148)N)C(=C150C(=C(C=C149)N)C(=C151C(=C(C=C150)N)C(=C152C(=C(C=C151)N)C(=C153C(=C(C=C152)N)C(=C154C(=C(C=C153)N)C(=C155C(=C(C=C154)N)C(=C156C(=C(C=C155)N)C(=C157C(=C(C=C156)N)C(=C158C(=C(C=C157)N)C(=C159C(=C(C=C158)N)C(=C160C(=C(C=C159)N)C(=C161C(=C(C=C160)N)C(=C162C(=C(C=C161)N)C(=C163C(=C(C=C162)N)C(=C164C(=C(C=C163)N)C(=C165C(=C(C=C164)N)C(=C166C(=C(C=C165)N)C(=C167C(=C(C=C166)N)C(=C168C(=C(C=C167)N)C(=C169C(=C(C=C168)N)C(=C170C(=C(C=C169)N)C(=C171C(=C(C=C170)N)C(=C172C(=C(C=C171)N)C(=C173C(=C(C=C172)N)C(=C174C(=C(C=C173)N)C(=C175C(=C(C=C174)N)C(=C176C(=C(C=C175)N)C(=C177C(=C(C=C176)N)C(=C178C(=C(C=C177)N)C(=C179C(=C(C=C178)N)C(=C180C(=C(C=C179)N)C(=C181C(=C(C=C180)N)C(=C182C(=C(C=C181)N)C(=C183C(=C(C=C182)N)C(=C184C(=C(C=C183)N)C(=C185C(=C(C=C184)N)C(=C186C(=C(C=C185)N)C(=C187C(=C(C=C186)N)C(=C188C(=C(C=C187)N)C(=C189C(=C(C=C188)N)C(=C190C(=C(C=C189)N)C(=C191C(=C(C=C190)N)C(=C192C(=C(C=C191)N)C(=C193C(=C(C=C192)N)C(=C194C(=C(C=C193)N)C(=C195C(=C(C=C194)N)C(=C196C(=C(C=C195)N)C(=C197C(=C(C=C196)N)C(=C198C(=C(C=C197)N)C(=C199C(=C(C=C198)N)C(=C200C(=C(C=C199)N)C(=C201C(=C(C=C200)N)C(=C202C(=C(C=C201)N)C(=C203C(=C(C=C202)N)C(=C204C(=C(C=C203)N)C(=C205C(=C(C=C204)N)C(=C206C(=C(C=C205)N)C(=C207C(=C(C=C206)N)C(=C208C(=C(C=C207)N)C(=C209C(=C(C=C208)N)C(=C210C(=C(C=C209)N)C(=C211C(=C(C=C210)N)C(=C212C(=C(C=C211)N)C(=C213C(=C(C=C212)N)C(=C214C(=C(C=C213)N)C(=C215C(=C(C=C214)N)C(=C216C(=C(C=C215)N)C(=C217C(=C(C=C216)N)C(=C218C(=C(C=C217)N)C(=C219C(=C(C=C218)N)C(=C220C(=C(C=C219)N)C(=C221C(=C(C=C220)N)C(=C222C(=C(C=C221)N)C(=C223C(=C(C=C222)N)C(=C224C(=C(C=C223)N)C(=C225C(=C(C=C224)N)C(=C226C(=C(C=C225)N)C(=C227C(=C(C=C226)N)C(=C228C(=C(C=C

or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising the compound of any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, further comprising one or more additional active agents is selected from an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a neutral endopeptidase inhibitor, an aldosterone antagonist, a renin inhibitor, an endothelin receptor antagonist, an aldosterone synthase inhibitor, a phosphodiesterase-5 inhibitor, a vasodilator, a calcium channel blocker, a potassium channel activator, a diuretic, a sympatholytic, a beta-adrenergic blocking drug, an alpha adrenergic

blocking drug, a central alpha adrenergic agonist, a peripheral vasodilator, a lipid lowering agent or a metabolic altering agent.

30. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for use in therapy.

31. The use of the compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for treating a condition selected from cardiovascular disease, endothelial dysfunction, diastolic dysfunction, atherosclerosis, hypertension, heart failure, pulmonary hypertension (WHO groups I, II, III, IV), angina pectoris, thrombosis, restenosis, myocardial infarction, stroke, cardiac insufficiency, fibrosis, pulmonary

hypertonia, erectile dysfunction, asthma, acute respiratory distress syndrome (ARDS), chronic kidney disease, cystic fibrosis, sickle cell anemia, scleroderma, Raynaud's Syndrome, diabetes, diabetic retinopathy, cirrhosis of the liver, chronic obstructive pulmonary disease (COPD), acute lung injury, pulmonary fibrosis, or interstitial lung disease.

32. The use according to claim 31, wherein said condition is pulmonary hypertension.

33. The use according to claim 31, wherein said condition is heart failure.