

expansion of white adipose tissue. An sGC activator was shown to enhance lipid uptake into brown adipose tissue which combusts energy to produce heat and was also shown to induce weight loss in a model of established obesity in mice (L.S. Hoffmann, et al., 2015, Nature Communications, 6, Article number 7235). This study suggests that sGC activators would be useful in treatment of obesity.

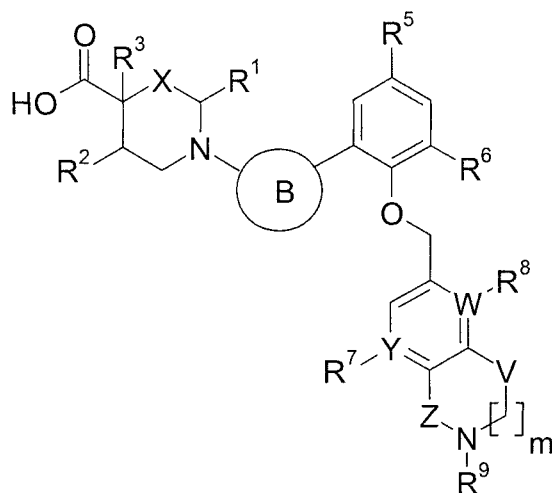
In a mouse model of estrogen deficiency-induced osteoporosis, a sGC activator significantly improved trabecular bone microarchitecture with an effect size similar to estrogen replacement therapy (J. Joshua et al., 2014, Endocrinology, 155, 4720-4730). The study also found that the sGC activator increased osteoblast number and activity with little effect on osteoclast numbers. These results suggest that sGC activators would be useful in treating osteoporosis.

The above studies provide evidence for the use of sGC activators to treat cardiovascular diseases including hypertension, atherosclerosis, peripheral artery disease, restenosis, myocardial infarction, stroke, heart failure, coronary vasospasm, cerebral vasospasm, ischemia/reperfusion injury, thromboembolic pulmonary hypertension, pulmonary arterial hypertension, stable and unstable angina, thromboembolic disorders. Additionally, sGC activators have the potential to treat renal disease, diabetes, glaucoma, obesity, osteoporosis, fibrotic disorders including those of the skin, liver, kidney and lungs, urologic disorders including overactive bladder, benign prostatic hyperplasia, and erectile dysfunction, and neurological disorders including Alzheimer's disease, Parkinson's disease, as well as neuropathic pain. Treatment with sGC activators may also provide benefits in inflammatory disorders such as psoriasis, multiple sclerosis, arthritis, asthma, ulcerative colitis, Crohn's disease and chronic obstructive pulmonary disease.

BRIEF SUMMARY

The present disclosure provides novel compounds which activate or potentiate sGC and are thus useful for treating a variety of diseases and disorders that can be alleviated by sGC activation or potentiation including cardiovascular, inflammatory and renal diseases.

In one aspect, the disclosure provides a compound of the formula I



I,

wherein:

X is CHR^4 or a bond;

Y is C or N;

W is C or N, provided that Y and W are not both N;

V is $-\text{C}(\text{R}^{11})(\text{R}^{12})-$ or $-\text{OCH}_2-$, provided that if V is $-\text{OCH}_2-$, then Z is $-\text{CH}_2-$, Y and W are both C;

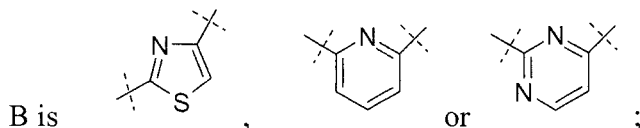
Z is $-\text{CH}_2-$, $-\text{C}(\text{R}^{10})_2\text{CH}_2-$ or $-\text{C}(\text{O})-$;

R^1 is H, Me, or $-\text{CH}_2\text{OMe}$;

R^2 is H, $-\text{OMe}$ or $-\text{OEt}$;

R^3 is H or R^2 and R^3 together with the carbons they are bonded to form a fused 3-membered ring;

R^4 is H or R^2 and R^4 form a 2-carbon alkylidene bridge or R_1 and R_4 together with the piperidine ring they are bonded to may form an octahydropyrano[3,2-b]pyridine ring;



R^5 and R^6 are independently selected from H, Me, F, Cl and CF_3 ;

R^7 is H, Me, Et, -OMe, CN, F, or $-CH_2OMe$ or is not present when Y is N;

R^8 is H, Me or F or is not present when W is N;

R^9 is H or C_{4-6} cycloalkyl, optionally substituted with one to two F, or R^9 is $-(CH_2)_n$

heterocyclyl, wherein the heterocyclyl is selected from tetrahydropyranyl, tetrahydrofuranyl, oxetanyl and [1,4]-dioxanyl or $-CH(R_{10})$ heteroaryl, wherein the heteroaryl is selected from the group consisting of pyrazine, imidazole, pyridyl and isoxazolyl and wherein the heteroaryl is optionally substituted with a methyl group;

each R^{10} is independently H or Me;

R^{11} is H or Me;

R^{12} is H or Me;

m is 0 or 1, provided that if m is 0, Z is $-CH_2-$, V is $-C(R^{11})(R^{12})-$ and R^{11} and R^{12} are both H; and

n is 0 or 1;

or a salt thereof.

In another aspect, the disclosure provides the disclosed compounds for use as medicaments. In another aspect, the disclosure provides the disclosed compounds for use in the treatment of a disease or disorder that can be alleviated by sGC activation or potentiation. In another aspect, the disclosure provides the use of the disclosed compounds for the manufacture of a medicament for the treatment of a disease or disorder that can be alleviated by sGC activation or potentiation.

In another aspect, the disclosure provides pharmaceutical compositions comprising the disclosed compounds and a pharmaceutically acceptable excipient or carrier. There is also provided methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

The present disclosure provides activators of soluble guanylate cyclase having solubility properties consistent with acceptable pharmacokinetic properties. As is known in the art, poorly soluble compounds may suffer from poor human exposure. The compounds of the present disclosure would be expected to have exposure properties consistent with being a suitable drug.

The present disclosure provides compounds with metabolic stability properties consistent with acceptable pharmacokinetic properties. As is known in the art, compounds having poor metabolic stability may not readily achieve desirable therapeutic levels. The compounds of the present disclosure would be expected to have metabolic stability properties consistent with being a suitable drug.

DETAILED DESCRIPTION OF THE INVENTION

In an embodiment (1), there are provided compounds of the formula I

m is 1;

or a salt thereof.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable excipient or carrier.

12. A compound according to any one of claims 1 to 10 for use as a medicament.

13. A compound according to any one of claims 1 to 10 for use in the treatment of a disease or disorder that can be alleviated by sGC activation or potentiation

14. Use of a compound according to any one of claims 1-10 for the manufacture of a medicament for the treatment of a disease or disorder that can be alleviated by sGC activation or potentiation.

15. The use according to claim 14 wherein the disease or disorder is selected from a cardiovascular disease, inflammatory disease, hepatic fibrotic disorder, skin fibrotic disorder, renal fibrotic disorder, pulmonary fibrotic disorder and cardiac fibrotic disorder.

16. The use according to claim 14 wherein the disease is selected from renal disease, diabetes, glaucoma, muscular dystrophy, urologic disorders including overactive bladder, benign prostatic hyperplasia, erectile dysfunction, and neurological disorders including Alzheimer's disease, dementia, Parkinson's disease and neuropathic pain.

17. The use according to claim 14 wherein the disease is diabetic nephropathy.