

-1-

BENZOTHIAZINE DIOXIDES AS ENDOTHELIN ANTAGONISTS

BACKGROUND OF THE INVENTION

5

The present invention relates to novel 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 compounds of the present invention are antagonists of endothelin useful in treating elevated levels of endothelin, acute and chronic renal failure, essential renovascular malignant and pulmonary hypertension, cerebral infarction and cerebral ischemia, cerebral vasospasm, cirrhosis, septic shock, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrhythmias, asthma, preeclampsia, atherosclerotic disorders including Raynaud's disease and restenosis, angina, cancer, benign prosthetic hyperplasia, ischemic disease, gastric mucosal damage, hemorrhagic shock, ischemic bowel disease, and diabetes.

Also, the compounds will be useful in cerebral ischemia or cerebral infarction resulting from a range of conditions such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, head injury, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery, and cerebral trauma.

Several studies have been reported with both peptide and non-peptide ET antagonists showing efficacy in various models of subarachnoid hemorrhage (SAH). For example, BQ-123-prevents early cerebral vasospasm following SAH in various rat (Clozel M, et al., Life Sci. 1993;52:825) and rabbit (Lee KS, et al., Cerebral

-2-

Vasospasm 1993:217; and Neurosurgery 1994; 34:108) models. FR 139317 significantly inhibited the vasoconstriction of the basilar artery after 7 days in a canine two-hemorrhage model of SAH (Nirei H, et al., Life Sci. 1993;52:1869). BQ-485 also significantly inhibited the vasoconstriction of the basilar artery after 7 days in a canine two-hemorrhage model of SAH (Yano, et al., Biochem Biophys. Res Commun. 1993; 195:969). Ro 46-2005 (Clozel M, et al., Nature 1993;365:759) has been shown to prevent early cerebral vasospasm following SAH in the rat with no significant effect on systemic arterial blood pressure. Treatment with Ro 47-0203-Bosentan (Clozel et al., Circulation 1993;88(4) part 2:0907) to rabbits with SAH had a 36 ± 7% reduction of basilar artery cross-sectional area compared to sham rabbits. All of these studies show in vivo efficacy of endothelin antagonists in cerebral vasospasm resulting from SAH.

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).

Endothelin is involved in many human disease states.

Several in vivo studies with ET antibodies have been reported in disease models. Left coronary artery ligation and reperfusion to induce myocardial infarction in the rat heart, caused a 4- to 7-fold increase in endogenous endothelin levels. Administration of ET antibody was reported to reduce the size of the infarction in a dose-depending manner (Watanabe T, et al., "Endothelin in Myocardial Infarction," Nature (Lond.) 1990;344:114). Thus, ET

- 3 -

may be involved in the pathogenesis of congestive heart failure and myocardial ischemia (Margulies KB, et al., "Increased Endothelin in Experimental Heart Failure," Circulation 1990;82:2226).

5 Studies by Kon and colleagues using anti-ET antibodies in an ischemic kidney model, to deactivate endogenous ET, indicated the peptide's involvement in acute renal ischemic injury (Kon V, et al., "Glomerular Actions of Endothelin In Vivo," J Clin Invest
10 1989;83:1762). In isolated kidneys, preexposed to specific antiendothelin antibody and then challenged with cyclosporine, the renal perfusate flow and glomerular filtration rate increased, while renal resistance decreased as compared with isolated kidneys
15 preexposed to a nonimmunized rabbit serum. The effectiveness and specificity of the anti-ET antibody were confirmed by its capacity to prevent renal deterioration caused by a single bolus dose (150 pmol) of synthetic ET, but not by infusion of angiotensin II,
20 norepinephrine, or the thromboxane A₂ mimetic U-46619 in isolated kidneys (Perico N, et al., "Endothelin Mediates the Renal Vasoconstriction Induced by Cyclosporine in the Rat," J Am Soc Nephrol 1990;1:76).

 Others have reported inhibition of ET-1 or
25 ET-2-induced vasoconstriction in rat isolated thoracic aorta using a monoclonal antibody to ET-1 (Koshi T, et al., "Inhibition of Endothelin (ET)-1 and ET-2-Induced Vasoconstriction by Anti-ET-1 Monoclonal Antibody," Chem Pharm Bull 1991;39:1295).

30 Combined administration of ET-1 and ET-1 antibody to rabbits showed significant inhibition of the blood pressure (BP) and renal blood flow responses (Miyamori I, et al., Systemic and Regional Effects of Endothelin in Rabbits: Effects of Endothelin
35 Antibody," Clin Exp Pharmacol Physiol 1990;17:691).

-4-

Other investigators have reported that infusion of ET-specific antibodies into spontaneously hypertensive rats (SHR) decreased mean arterial pressure (MAP), and increased glomerular filtration rate and renal blood flow. In the control study with normotensive Wistar-Kyoto rats (WKY) there were no significant changes in these parameters (Ohno A, "Effects of Endothelin-Specific Antibodies and Endothelin in Spontaneously Hypertensive Rats," J Tokyo Women's Med Coll 1991;61:951).

In addition, elevated levels of endothelin have been reported in several disease states (see Table I below).

Burnett and co-workers recently demonstrated that exogenous infusion of ET (2.5 ng/kg/Ml) to anesthetized dogs, producing a doubling of the circulating concentration, did have biological actions (Lerman A, et al., "Endothelin has Biological Actions at Pathophysiological Concentrations," Circulation 1991;83:1808). Thus heart rate and cardiac output decreased in association with increased renal and systemic vascular resistances and antinatriuresis. These studies support a role for endothelin in the regulation of cardiovascular, renal, and endocrine function.

In congestive heart failure in dogs and humans, a significant 2- to 3-fold elevation of circulating ET levels has been reported (Rodeheffer RJ, et al., "Circulating Plasma Endothelin Correlates With the Severity of Congestive Heart Failure in Humans," Am J Hypertension 1991;4:9A).

The distribution of the two cloned receptor subtypes, termed ET_A and ET_B, have been studied extensively (Arai H, et al., Nature 1990;348:730, Sakurai T, et al., Nature 1990;348:732). The ET_A, or vascular smooth muscle receptor, is widely distributed

-5-

in cardiovascular tissues and in certain regions of the brain (Lin HY, et al., Proc Natl Acad Sci 1991;88:3185). The ET_B receptor, originally cloned from rat lung, has been found in rat cerebellum and in endothelial cells, although it is not known if the ET_B receptors are the same from these sources. The human ET receptor subtypes have been cloned and expressed (Sakamoto A, et al., Biochem Biophys Res Chem 1991;178:656, Hosoda K, et al., FEBS Lett 1991;287:23). The ET_A receptor clearly mediates vasoconstriction and there have been a few reports implicating the ET_B receptor in the initial vasodilatory response to ET (Takayanagi R, et al., FEBS Lett 1991;282:103). However, recent data has shown that the ET_B receptor can also mediate vasoconstriction in some tissue beds (Panek RL, et al., Biochem Biophys Res Commun 1992;183(2):566).

A recent study showed that selective ET_B agonists caused only vasodilation in the rat aortic ring, possibly through the release of EDRF from the endothelium (ibid). Thus, reported selective ET_B agonists, for example, the linear analog ET[1,3,11,15-Ala] and truncated analogs ET[6-21,1,3,11,15-Ala], ET[8-21,11,15-Ala], and N-Acetyl-ET[10-21,11,15-Ala] caused vasorelaxation in isolated, endothelium-intact porcine pulmonary arteries (Saeki T, et al., Biochem Biophys Res Commun 1991;179:286). However, some ET analogs are potent vasoconstrictors in the rabbit pulmonary artery, a tissue that appears to possess an ET_B, nonselective type of receptor (ibid).

Plasma endothelin-1 levels were dramatically increased in a patient with malignant hemangioendothelioma (Nakagawa K, et al., Nippon Hifuka Gakkai Zasshi 1990;100:1453-1456).

-6-

The ET receptor antagonist BQ-123 has been shown to block ET-1-induced bronchoconstriction and tracheal smooth muscle contraction in allergic sheep providing evidence for expected efficacy in bronchopulmonary diseases such as asthma (Noguchi, et al., Am Rev Respir Dis 1992;145(4 Part 2):A858).

Circulating endothelin levels are elevated in women with preeclampsia and correlate closely with serum uric acid levels and measures of renal dysfunction. These observations indicate a role for ET in renal constriction in preeclampsia (Clark BA, et al., Am J Obstet Gynecol 1992;166:962-968).

Plasma immunoreactive endothelin-1 concentrations are elevated in patients with sepsis and correlate with the degree of illness and depression of cardiac output (Pittett J, et al., Ann Surg 1991;213(3):262).

In addition the ET-1 antagonist BQ-123 has been evaluated in a mouse model of endotoxic shock. This ET_A antagonist significantly increased the survival rate in this model (Toshiaki M, et al., 20.12.90. EP 0 436 189 A1).

Endothelin is a potent agonist in the liver eliciting both sustained vasoconstriction of the hepatic vasculature and a significant increase in hepatic glucose output (Gandhi CB, et al., Journal of Biological Chemistry 1990;265(29):17432). In addition increased levels of plasma ET-1 have been observed in microalbuminuric insulin-dependent diabetes mellitus patients indicating a role for ET in endocrine disorders such as diabetes (Collier A, et al., Diabetes Care 1992;15(8):1038).

ET_A antagonist receptor blockade has been found to produce an antihypertensive effect in normal to low renin models of hypertension with a time course similar to the inhibition of ET-1 pressor responses (Basil MK, et al., J Hypertension 1992;10(Suppl 4):S49). The

-7-

endothelins have been shown to be arrhythmogenic, and to have positive chronotropic and inotropic effects, thus ET receptor blockade would be expected to be useful in arrhythmia and other cardiovascular disorders (Han S-P, et al., Life Sci 1990;46:767).

The widespread localization of the endothelins and their receptors in the central nervous system and cerebrovascular circulation has been described (Nikolov RK, et al., Drugs of Today 1992;28(5):303-310). Intracerebroventricular administration of ET-1 in rats has been shown to evoke several behavioral effects. These factors strongly suggest a role for the ETs in neurological disorders. The potent vasoconstrictor action of ETs on isolated cerebral arterioles suggests the importance of these peptides in the regulation of cerebrovascular tone. Increased ET levels have been reported in some CNS disorders, i.e., in the CSF of patients with subarachnoid hemorrhage and in the plasma of women with preeclampsia. Stimulation with ET-3 under conditions of hypoglycemia have been shown to accelerate the development of striatal damage as a result of an influx of extracellular calcium. Circulating or locally produced ET has been suggested to contribute to regulation of brain fluid balance through effects on the choroid plexus and CSF production. ET-1 induced lesion development in a new model of local ischemia in the brain has been described.

Circulating and tissue endothelin immunoreactivity is increased more than twofold in patients with advanced atherosclerosis (Lerman A, et al., New England J Med 1991;325:997-1001). Increased endothelin immunoreactivity has also been associated with Buerger's disease (Kanno K, et al., J Amer Med Assoc 1990;264:2868) and Raynaud's phenomenon (Zamora MR, et al., Lancet 1990;336:1144-1147).

-8-

An increase of circulating endothelin levels was observed in patients that underwent percutaneous transluminal coronary angioplasty (PTCA) (Tahara A, et al., Metab Clin Exp 1991;40:1235-1237).

5 Increased plasma levels of endothelin have been measured in rats and humans (Stewart DJ, et al., Ann Internal Medicine 1991;114:464-469) with pulmonary hypertension.

10 Elevated levels of endothelin have also been measured in patients suffering from ischemic heart disease (Yasuda M, et al., Amer Heart J 1990;119:801-806) and either stable or unstable angina (Stewart JT, et al., Br Heart J 1991;66:7-9).

15 Infusion of an endothelin antibody 1 hour prior to and 1 hour after a 60-minute period of renal ischaemia resulted in changes in renal function versus control. In addition, an increase in glomerular platelet-activating factor was attributed to endothelin (Lopez-Farre A, et al., J Physiology 1991;444:513-522).

20 In patients with chronic renal failure as well as in patients on regular hemodialysis treatment, mean plasma endothelin levels were significantly increased (Stockenhuber F, et al., Clin Sci (Lond) 1992;82:255-258).

25 Local intra-arterial administration of endothelin has been shown to induce small intestinal mucosal damage in rats in a dose-dependent manner (Mirua S, et al., Digestion 1991;48:163-172). Furthermore, it has been shown that an anti-ET-1 antibody reduced ethanol-induced vasoconstriction in a concentration-

30 dependent manner (Masuda E, et al., Am J Physiol 1992;262:G785-G790). Elevated endothelin levels have been observed in patients suffering from Crohn's disease and ulcerative colitis (Murch SH, et al.,

35 Lancet 1992;339:381-384).

-9-

Recently at the 3rd International Conference on Endothelin, Houston, Texas, February 1993, the nonpeptide endothelin antagonist RO 46-2005 has been reported to be effective in models of acute renal ischemia and subarachnoid hemorrhage in rats (Clozel M, et al., "Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist," Nature 1993;365:759). A related benzene sulphonamide, namely Bosentan, has also been demonstrated to be useful in the treatment of congestive heart failure. ("Role of endothelin in the maintenance of blood pressure in conscious rats with chronic heart failure cute effects of Bernd M, Hess P, Maire J-P, Clozel M, Clozel J-P, Circulation 1994;90(5):2510-2518). In addition, the ET_A antagonist BQ-123 has been shown to prevent early cerebral vasospasm following subarachnoid hemorrhage (Clozel M, Watanabe H, Life Sci 1993;52:825-834).

Most recently an ET_A selective antagonist demonstrated an oral antihypertensive effect (Stein PD, et al., "The Discovery of Sulfonamide Endothelin Antagonists and the Development of the Orally Active ET_A Antagonist 5-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide," J Med Chem 1994;37:329-331).

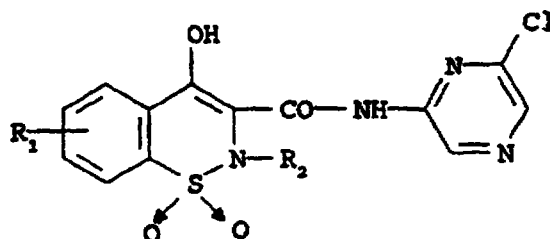
Furthermore, a specific ET_A/ET_B receptor antagonist (see WO93 08799A1 and Elliott JD, et al., J Med Chem 1994;37:1553-7) has demonstrated reduced neointimal formation after angioplasty (Douglas SA, et al., Circ Res 1994;75:190-7).

This specific ET_A/ET_B receptor antagonist, SB 209670, has been demonstrated to be beneficial in ischemia-induced acute renal failure (Brooks DP, et al., "Nonpeptide endothelin receptor antagonists. III. Effect of SB 209670 and BQ123 on acute renal

-10-

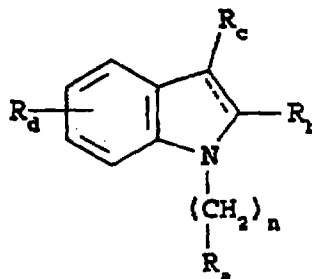
failure in anesthetized dogs," J Pharmacol Exp Ther 1994;271(2):769-975).

United States Patent 4,533,664 covers compound of the formula



wherein R_1 is H, Me, MeO, F, or Cl; and R_2 is H, Me, Et, or n-Pr. The compounds are taught as useful as antithrombotic agents.

15 Copending application United States Serial Number 08/339,381 filed November 14, 1994, covers endothelin antagonists of formula



wherein

25 --- denotes an optional bond;

n is 0-4;

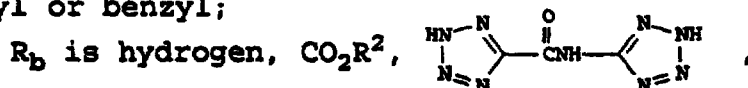
R_a is hydrogen, alkyl of 1-4 carbon atoms or cycloalkyl, phenyl or naphthyl, in which the phenyl or naphthyl group is substituted by methylenedioxy and further unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, OR, NRR^1 , SR, NO_2 , N_3 , COR, CO_2R , $CONRR^1$, SO_2NRR^1 , SO_2R , CN, CF_3 , CF_2CF_3 , CHO, $OCOCH_3$, $B(OH)_2$, phenyl, $NH(CH_2)_mCO_2R$, $S(CH_2)_mCO_2R$, $O(CH_2)_mCO_2R$, $O(CH_2)_mOR$, $NH(CH_2)_mOR$ and $S(CH_2)_mOR$, in which m is 1, 2 or 3, and R and R^1 are each

30

35

-11-

independently hydrogen, alkyl of 1-4 carbon atoms, phenyl or benzyl;



5 SO_3R , PO_3H , $B(OH)_2$, $CONR^1R^2$, $SO_2NR^1R^2$, or

 $-CNHSO_2R^2$, in which R^1 is as defined above and R^2 is hydrogen, alkyl of 1-6 carbon atoms, CF_3 , $-CF_2CF_3$, phenyl or benzyl in which phenyl or the phenyl portion of the benzyl group is unsubstituted or substituted by one or more substituents as defined above;

R_c is $S(O)_p$ -phenyl, in which p is 0, 1 or 2, and phenyl is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, OR, NRR^1 , SR, NO_2 , N_3 , COR, CO_2R , $CONRR^1$, SO_2NRR^1 , SO_2R , CN, CF_3 , CF_2CF_3 , CHO, $OCOCH_3$, $B(OH)_2$, methylenedioxy, $NH(CH_2)_mCO_2R$, $S(CH_2)_mCO_2R$, $O(CH_2)_mCO_2R$, $O(CH_2)_mOR$, $NH(CH_2)_mOR$ and $S(CH_2)_mOR$, in which m , R and R^1 are as defined above, and

R_d is one to four independent substituents selected from hydrogen, alkyl of 1-7 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, cycloalkyl, phenyl, $C(O)$ -phenyl, $X(CH_2)_n$ -phenyl, $X-(CH_2)_n$ -naphthyl, in which X is 0, NH or $S(O)_p$, methylenedioxy, OR, NRR^1 , SR, NO_2 , N_3 , COR, CO_2R , $CONRR^1$, SO_2NRR^1 , SO_2R , CN, CF_3 , CF_2CF_3 , CHO, $OCOCH_3$, $B(OH)_2$, phenyl, $NH(CH_2)_mCO_2R$, $S(CH_2)_mCO_2R$, $O(CH_2)_mCO_2R$, $O(CH_2)_mOR$, $NH(CH_2)_mOR$, $S(CH_2)_mOR$, in which m is 1, 2 or 3 and R and R^1 are each independently hydrogen, alkyl of 1-4 carbon atoms, phenyl or benzyl and where n and p are as defined above and phenyl is unsubstituted or substituted as defined above, or a pharmaceutically acceptable acid addition or base salt thereof.

35 Some of the compounds of Formula I are capable of further forming both pharmaceutically acceptable acid

-12-

addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from
5 nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-
10 substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate,
15 dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate,
20 dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate
25 (see, for example, Berge SM, et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a
30 sufficient amount of the desired acid to produce the salt in the conventional manner.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples
35 of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable

-13-

amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge SM, et al.,
 5 "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the
 10 salt in the conventional manner.

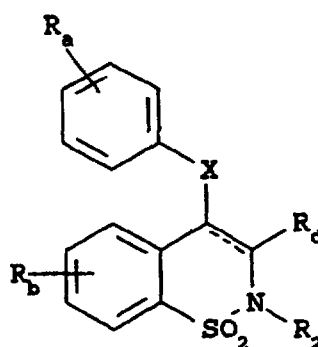
Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are
 15 equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

SUMMARY OF THE INVENTION

20

The present invention is compounds of formula

25

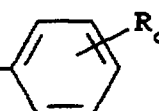


I

30

or a pharmaceutically acceptable acid addition or base salt thereof wherein:

35

R_2 is H, $(CH_2)_n$ -, alkyl of from 1 to

7 carbons, $(CH_2)_n$ -cycloalkyl of from 3 to 8 carbons;

-14-

R_a and R_c are each 1 to 5 substituents and R_b is from 1 to 4 substituents independently selected from:

- hydrogen,
alkyl of from 1 to 7 carbons,
5 alkenyl of from 2 to 7 carbons,
alkynyl of from 2 to 7 carbons,
cycloalkyl of from 3 to 8 carbons,
phenyl,
C(O)-phenyl,
10 methylenedioxy,
ethylenedioxy,
OR,
NRR₁,
SR₁,
15 NO₂,
N₃,
COR,
CO₂R,
Cl,
20 Br,
F,
I,
CONRR₁,
SO₂NRR₁,
25 SO₂R,
CN,
CF₃,
CF₂CF₃,
CHO,
30 OCOR,
B(OH)₂,
NH(CH₂)_pCO₂R,
S(CH₂)_pCO₂R,
O(CH₂)_pCO₂R,
35 O(CH₂)_pOR,
NH(CH₂)_pOR,

-15-

$S(CH_2)_pOR$, or

wherein R and R_1 are each independently selected from hydrogen,

alkyl of from 1 to 6 carbon atoms,

5 alkenyl of from 2 to 7 carbon atoms,

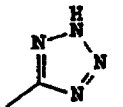
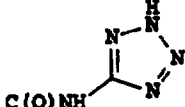
alkynyl of from 2 to 7 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

phenyl or benzyl wherein the phenyl or benzyl ring is substituted by 1 or more hydrogen, methoxy, and

10 methylenedioxy substituents;

R_d is H, CO_2R , SO_3R , PO_3R , $B(OH)_2$, $CONRR_1$, SO_2NRR_1 ,

$C(O)NHSO_2R_1$,  , or  ;

15 n is an integer of from 0 to 2;

p is an integer of from 1 to 4;

--- indicates a single or double bond; and

X is $(CH_2)_n$, O, NR, or $S(O)_n$.

Elevated levels of endothelin have been postulated to be involved in a number of pathophysiological states including diseases associated with the cardiovascular system as well as various metabolic and endocrinological disorders. As antagonists of endothelin, the compounds of Formula I are useful in the treatment of essential, renovascular, malignant, and pulmonary hypertension, cerebral infarction, diabetes, cerebral vasospasm, cirrhosis, septic shock, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrhythmias, asthma, chronic and acute renal failure, preeclampsia, atherosclerotic disorders including Raynaud's disease and restenosis, angina, cancer, benign prosthetic hyperplasia, ischemic disease, gastric mucosal damage, hemorrhagic shock, and ischemic bowel disease. Particularly, the compounds of

35

-16-

Formula I are useful in treating subarachnoid hemorrhage, hypertension, congestive heart failure, and cerebral ischemia and/or cerebral infarction resulting from a range of conditions such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, head injury, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as drowning, pulmonary surgery and cerebral trauma.

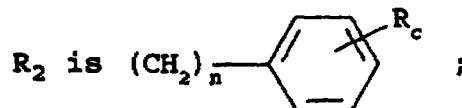
A still further embodiment of the present invention is a pharmaceutical composition for administering a therapeutically effective amount of a compound of Formula I in a mixture with a pharmaceutically acceptable carrier in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to novel intermediates used for the production of compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention are novel benzothiazine dioxides derivatives of Formula I above.

Preferred compounds of the instant invention are those of Formula I wherein



R_a and R_c are each 1 to 5 substituents and R_b is 1 to 4 substituents independently selected from:

hydrogen,
alkyl of from 1 to 3 carbons,
methylenedioxy,
ethylenedioxy,
OH,
methoxy,

-17-

propyloxy,
benzyloxy,
Cl, Br, F, I,
O(CH₂)_n-cycloalkyl of from 3 to 8 carbon atoms,
5 O(CH₂)_pCO₂H,

Rd is CO₂H,

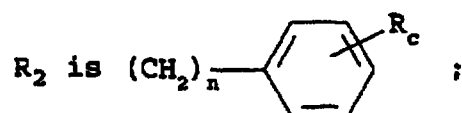
n is an integer of from 0 to 1,

p is an integer of from 1 to 4,

--- indicates a double bond, and

10 X is (CH₂)_n, NH, S, SO, or SO₂.

More preferred compounds of the invention are those of Formula I wherein



R_a and R_c are each independently 1 to 5 substituents selected from, hydrogen, methoxy, OH, and Cl;

R_b is independently 1 to 5 substituents selected from, hydrogen, methoxy, propyloxy, OH, and Cl;

20 R_a, R_b, R_c may also independently be 0 to 2 methylenedioxy or ethylenedioxy substituents,

Rd is CO₂H,

n is 0 or 1,

--- indicates a double bond, and

25 X is (CH₂)_n or S.

Particularly preferred compounds of the instant invention are those of Formula I selected from

4-Benzo[1,3]dioxol-5-yl-2-methyl-1,1-dioxo-1,2-dihydro-1λ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,
30

4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1λ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

35 4-Benzo[1,3]dioxol-5-yl-2-benzyl-1,1-dioxo-1,2-dihydro-1λ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

-18-

- 4-Benzo[1,3]dioxol-5-yl-2-(4-methoxy-benzyl)-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,
- 5 4-Benzo[1,3]dioxol-5-yl-1,1-dioxo-
2-(3,4,5-trimethoxy-benzyl)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 4-Benzo[1,3]dioxol-5-yl-2-(2-carboxymethoxy-
4-methoxy-benzyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 10 4-Benzo[1,3]dioxol-5-yl-2-(6-chloro-
benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 4-Benzo[1,3]dioxol-5-yl-2-(7-methoxy-
benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 15 2-Benzo[1,3]dioxol-5-ylmethyl-4-(3,4-dimethoxy-
phenyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-
4-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 20 N-(4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-
5-ylmethyl-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carbonyl)-
- 25 benzenesulfonamide,
- 2-Benzo[1,3]dioxol-5-ylmethyl-4-(3-methoxy-
phenyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-
5-ylmethyl-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 30 4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-
5-ylmethyl-6-methoxy-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,

- 8-Benzo[1,3]dioxol-5-yl-6-benzo[1,3]dioxol-5-ylmethyl-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid,
4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-methyl-
5 1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-5-ylsulfanyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
10 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-benzyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-(4-methoxybenzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
15 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-1,1-dioxo-2-(3,4,5-trimethoxybenzyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-(carboxymethoxy-4-methoxybenzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
20 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-(6-chlorobenzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
25 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-(7-methoxybenzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
2-Benzo[1,3]dioxol-5-ylmethyl-4-(3,4-dimethoxyphenylsulfanyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
30 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-4-(3,4,5-trimethoxyphenylsulfanyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
35 N-(4-Benzo[1,3]dioxol-5-ylsulfanyl)-2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-

-20-

1 λ ⁶-benzo[e][1,2]thiazine-3-carbonyl)-
benzenesulfonamide,

2-Benzo[1,3]dioxol-5-ylmethyl-4-(3-methoxy-
phenylsulfanyl)-1,1-dioxo-1,2-dihydro-

5 1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-
1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-
10 5-ylsulfanyl)-6-methoxy-1,1-dioxo-1,2-dihydro-
1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

6-Benzo[1,3]dioxol-5-ylmethyl-8-(benzo[1,3]dioxol-
5-ylsulfanyl)-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ ⁶-thia-
6-aza-cyclopenta[b]naphthalene-7-carboxylic acid,

15 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-isobutyl-
1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-
3-carboxylic acid,

2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-7-methoxy-1,1-dioxo-1,2-dihydro-
20 1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

2-Benzo[1,3]dioxol-5-ylmethyl-4-(2,3-dihydro-
benzo[1,4]dioxin-6-ylsulfanyl)-1,1-dioxo-1,2-dihydro-
1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-(2,3-dihydro-
25 benzo[1,4]dioxin-6-ylmethyl)-1,1-dioxo-1,2-dihydro-
1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

4-(Benzo[1,3]dioxol-5-ylsulfanyl)-
2-cyclohexylmethyl-1,1-dioxo-1,2-dihydro-
1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

30 2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-1,1-dioxo-1,2-dihydro-
1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-
35 1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid,

-21-

2,4-Bis-benzo[1,3]dioxol-5-yl-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid,

5 2,4-Bis-benzo[1,3]dioxol-5-yl-6,7-dimethoxy-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,

4-Benzo[1,3]dioxol-5-yl-2-(2-chloro-benzyl)-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,

10 2-Benzo[1,3]dioxol-5-ylmethyl-4-(4-chloro-
2,6-dimethoxy-phenyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,

4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-(2-chloro-
benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
15 thiazine-3-carboxylic acid,

2-Benzo[1,3]dioxol-5-ylmethyl-4-(4-chloro-
2,6-dimethoxy-phenylsulfanyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,

4-(Benzo[1,3]dioxol-5-yl)-2-isobutyl-1,1-dioxo-
20 1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid,

2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-
5-yl)-7-methoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e]-
[1,2]thiazine-3-carboxylic acid,

25 2-Benzo[1,3]dioxol-5-ylmethyl-4-(2,3-dihydro-
benzo[1,4]dioxin-6-yl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,

4-(Benzo[1,3]dioxol-5-yl)-2-(2,3-dihydro-
benzo[1,4]dioxin-6-ylmethyl)-1,1-dioxo-1,2-dihydro-
30 1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid, and

4-(Benzo[1,3]dioxol-5-yl)-2-cyclohexylmethyl-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid.

Novel intermediates useful in the preparation of
35 the final products are:

-22-

2-Methyl-1,1-dioxo-4-(trifluoro-methane-sulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

5 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

10 2-Benzyl-1,1-dioxo-4-(trifluoro-methane-sulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

2-(4-Methoxy-benzyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

15 1,1-Dioxo-4-(trifluoro-methanesulfonyloxy)-2-(3,4,5-trimethoxy-benzyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

20 2-(2-Ethoxycarbonyl-methoxy-4-methoxy-benzyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

2-(6-Chloro-benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

25 2-(7-Methoxy-benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

30 2-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

35 2-Benzo[1,3]dioxol-5-ylmethyl-6-methoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

-23-

6-Benzo[1,3]dioxol-5-ylmethyl-5,5-dioxo-
8-(trifluoro-methanesulfonyloxy)-5,6-dihydro-1,3-dioxo-
5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic
acid methyl ester,

5 2-Benzo[1,3]dioxol-5-ylmethyl-7-methoxy-1,1-dioxo-
4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo-
[e][1,2]thiazine-3-carboxylic acid methyl ester,

2-Benzo[1,3]dioxol-5-ylmethyl-6-propyloxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
10 1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
ester,

2-Benzo[1,3]dioxol-5-ylmethyl-7-propyloxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
15 ester,

2-Benzo[1,3]dioxol-5-ylmethyl-7-benzyloxy-
6-methoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,

20 2-Benzo[1,3]dioxol-5-ylmethyl-6-benzyloxy-
7-methoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,

2-Benzo[1,3]dioxol-5-ylmethyl-6,7,8-trimethoxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
25 1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
ester,

2-Benzo[1,3]dioxol-5-ylmethyl-5,6,7,8-tetra-
methoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
30 1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,

2-Cyclohexylmethyl-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e]-
[1,2]thiazine-3-carboxylic acid methyl ester,

-24-

- 2-Cyclopentylmethyl-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e]-[1,2]thiazine-3-carboxylic acid methyl ester,
- 2-(2-Chloro-benzyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e]-[1,2]thiazine-3-carboxylic acid methyl ester,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,
- 2-Benzo[1,3]dioxol-5-yl-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e]-[1,2]thiazine-3-carboxylic acid methyl ester,
- 2-Benzo[1,3]dioxol-5-yl-6,7-dimethoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,
- 2-Benzo[1,3]dioxol-5-yl-6-methoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,
- 2-Benzo[1,3]dioxol-5-yl-7-methoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,
- 2-Benzo[1,3]dioxol-5-yl-6-propyloxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,
- 2-Benzo[1,3]dioxol-5-yl-7-propyloxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,
- 6-Benzo[1,3]dioxol-5-yl-5,5-dioxo-8-(trifluoro-methanesulfonyloxy)-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid methyl ester,
- 2-Isobutyl-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester,

-25-

(5,6,7-Trimethoxy-1,1,3-trioxo-1,3-dihydro-
1 λ^6 -benzo[d]isothiazol-2-yl)-acetic acid methyl ester,
2-Benzo[1,3]dioxol-5-yl-5,6-dimethoxy-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[d]isothiazol-3-one, and
5 2-Benzo[1,3]dioxol-5-yl-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[d]isothiazol-3-one.

In the compounds of Formula I, the term "alkyl"
means a straight or branched hydrocarbon radical having
from 1 to 12 carbon atoms unless otherwise specified
10 and includes, for example, methyl, ethyl, n-propyl,
isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl,
allyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl,
n-decyl, undecyl, and dodecyl.

The term "alkenyl" means a straight or branched
15 hydrocarbon radical having from 2 to 12 carbon atoms
unless otherwise specified and having at least one
double bond in the carbon atom chain and includes, for
example, 1-ethene, 1-propene, 2-methyl-1-propene,
1-butene, 2-butene, 1-pentene, 2-pentene, 2-methyl-
20 1-butene, 3-methyl-1-butene, 3-methyl-2-butene,
1-hexene, 1-heptene, 1-octene, 1-nonene, 1-decene,
1-undecene, 1-dodecene, and the like.

The term "alkynyl" means a straight or branched
hydrocarbon radical having from 2 to 12 carbon atoms
25 unless otherwise specified and having at least one
triple bond in the carbon atom chain and includes, for
example, 1-ethyne, 1-propyne, 1-butyne, 3-methyl-
1-butyne, 1-pentyne, 2-pentyne, 1-hexyne, and the like.

The term "cycloalkyl" means a saturated
30 hydrocarbon ring which contains from 3 to 12 carbon
atoms unless otherwise specified, for example,
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, and adamantyl.

"Halogen" is fluorine, chlorine, bromine or
35 iodine.

-26-

Some of the compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

5 Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the
10 salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include
15 sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate,
20 succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like.
25 Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge SM, et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

30 The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner.

35 Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of

-27-

metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example Berge SM, et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention, possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate diastereomeric mixtures thereof.

The compounds of Formula I are valuable antagonists of endothelin. The tests employed indicate that compounds of the invention possess endothelin antagonist activity. Thus, the compounds were tested for their ability to inhibit [¹²⁵I]-ET-1([¹²⁵I]-Endothelin-1) binding in a receptor assay. Selected compounds were also tested for antagonist activity by inhibition of ET-1 stimulated arachidonic acid release and ET-1 stimulated vasoconstriction. The following testing procedures were used (Doherty AM, et al., "Design of C-Terminal Peptide Antagonists of Endothelin: Structure-Activity Relationships of ET-1

-28-

[16-21, D-His¹⁶]", Bioorganic and Medicinal Chemistry Letters 1993;3:497-502).

Radioligand Binding Assays

5 The following cultured cells were used in binding experiments: rabbit renal artery vascular smooth muscle cells (ERBA-A), Ltk-cells expressing recombinant human ET_AR (HERBA-A), and CHO-K1 cells expressing recombinant human ET_BR (HERBA-B).

10 Membranes were prepared from cultured cells by lysing cells in cold lysis buffer (5 mM HEPES, 2 mM EDTA, pH 7.4) and homogenizing with a Dounce "A" homogenizer. The homogenate was centrifuged at 30,000 × g for 20 minutes at 4°C. Membrane pellets
15 were suspended in cold buffer containing 20 mM Tris, 2 mM EDTA, 200 μM Pefabloc, 10 μM phosphoramidon, 10 μM leupeptin, 1 μM pepstatin at pH 7.4 and frozen at -80°C until use. Membranes were thawed and homogenized with a Brinkmann Polytron then diluted in tissue buffer
20 containing 20 mM Tris, 2 mM EDTA, 200 μM Pefabloc, and 100 μM bacitracin (pH 7.4). Radioligand and competing ligands were prepared in binding buffer containing 20 mM Tris, 2 mM EDTA, and 0.1% BSA.

 Competing binding assays were initiated by
25 combining membranes, [125I]-ET-1 (40 pM) and the competing ligand in a final volume of 250 μL and incubating for 2 hours at 37°C. The assay was terminated by filtration over Whatman GF/B filters which were presoaked with 50 mM Tris, pH 7.4 containing
30 0.2% BSA and 100 μM bacitracin. Nonspecific binding was defined as binding in the presence of 100 nM ET-1.

-29-

IN VITRO INHIBITION OF ET-1 STIMULATED ARACHIDONIC ACID
RELEASE (AAR) IN CULTURED RABBIT VASCULAR SMOOTH MUSCLE
CELLS (ET_A) BY THE COMPOUNDS OF THE INVENTION

5 Antagonist activity is measured by the ability of
added compounds to reduce endothelin-stimulated
arachidonic acid release in cultured vascular smooth
muscle cells. [³H]Arachidonic Acid Loading Media (LM)
is DME/F12 + 0.5% FCS × 0.25 mCi/mL [³H] arachidonic
10 acid (Amersham). Confluent monolayers of cultured
rabbit renal artery vascular smooth muscle cells were
incubated in 0.5 mL of the LM over 18 hours, at 37°C,
in 5% CO₂. The LM was aspirated and the cells were
washed once with the assay buffer (Hank's BSS + 10 mM
15 HEPES + fatty acid-free BSA (1 mg/mL)), and incubated
for 5 minutes with 1 mL of the prewarmed assay buffer.
This solution was aspirated, followed by an additional
1 mL of prewarmed assay buffer, and further incubated
for another 5 minutes. A final 5-minute incubation was
20 carried out in a similar manner. The same procedure
was repeated with the inclusion of 10 μL of the test
compound (1 nM to 1 μM) and 10 μL ET-1 (0.3 nM) and the
incubation was extended for 30 minutes. This solution
was then collected, 10 mL of scintillation cocktail was
25 added, and the amount of [³H] arachidonic acid was
determined in a liquid scintillation counter.

IN VITRO ANTAGONISM OF ET-1 STIMULATED VASOCONSTRICTION
30 (VERA-A) IN THE RABBIT FEMORAL ARTERY (ET_A) AND
SARAFOTOXIN 6c STIMULATED VASOCONSTRICTION IN THE
RABBIT PULMONARY ARTERY (ET_B)

Male New Zealand rabbits were killed by cervical
35 dislocation and exsanguination. Femoral and pulmonary
arteries were isolated, cleaned of connective tissue,

-30-

and cut into 4-mm rings. The endothelium was denuded by placing the rings over hypodermic tubing (32 gauge for femoral rings and 28 gauge for pulmonary rings, Small Parts, Inc., Miami, Florida) and gently rolling them. Denuded rings were mounted in 20 mL organ baths containing Krebs-bicarbonate buffer (composition in mM: NaCl, 118.2; NaHCO₃, 24.8; KCl, 4.6; MgSO₄ 7H₂O, 1.2; KH₂PO₄, 1.2; CaCl₂ 2H₂O; Ca-Na₂ EDTA, 0.026; dextrose, 10.0), that was maintained at 37°C and gassed continuously with 5% CO₂ in oxygen (pH 7.4). Resting tension was adjusted to 3.0 g for femoral and 4.0 g pulmonary arteries; the rings were left for 90 minutes to equilibrate. Vascular rings were tested for lack of functional endothelium (i.e., lack of an endothelium-dependent relaxation response to carbachol (1.0 nM) in norepinephrine (0.03 nM) contracted rings. Agonist peptides, ET-1 (femoral), and S6c (pulmonary), were cumulatively added at 10-minute intervals. The ET antagonists were added 30 minutes prior to adding the agonist.

The data in Table I below show the endothelin receptor binding activity of representative compounds of the instant invention.

-31-

TABLE I

Example	HERBAA (IC ₅₀ , μM)	AAR (IC ₅₀ , μM)	VERAA (pA2)	HERBAB (IC ₅₀ , μM)
	24	11		>25
	25	1.7		>25
5	26	0.3		3.1
	27	0.16		4.6
	29	0.17		4.7
	30	1.8		4.9
	31	0.055	1.3	0.38
10	32	0.3		4.7
	33	0.72		3.6
	35	3		>25
	41	0.1		25
	42	0.066	1.2	5.4
15	43	0.12		12
	44	0.4		2.3
	45	0.2		12
	46	0.51		22
	48	0.23		8.2
20	49	0.51		8.7
	50	0.3		3.5

25 The compounds of Formula I may be prepared by several methods. These methods are illustrated by way of Scheme 1 through 12 and in a detailed manner by way of illustration in the example section of the specification.

30 Scheme 1 illustrates a procedure used for preparing alkoxy substituted saccharins. The 1,2-benzisothiazol-3(2H)-one (Burri KF. [4+2] Additions with Isothiazol-3(2H)-one 1,1-dioxide. Helv Chim Acta 1990;73:69-80) is alkylated with an alkyl
35 halide, typically propyl iodide, in the presence of a base, typically cesium carbonate in a dipolar aprotic solvent at room temperature. Treatment with acid, typically trifluoroacetic acid at reflux for several days affords the intermediate 6-propyloxysaccharin.

40 Scheme 2 outlines a procedure for the preparation of appropriately substituted benzothiazine dioxides by way of the corresponding anthranilic acid. Diazotization of the aniline in acid is accomplished typically by treatment with aqueous sodium nitrite.

-32-

Sulfur dioxide and copper (II) chloride are then added and the mixture stirred at room temperature for several days in which time the o,o'-dithiodibenzoic acid, methyl ester precipitates (Meerwein Chem Ber 1957;90:847). An alternative procedure for the preparation of substituted o,o'-dithiodibenzoic acids involves the treatment of the diazotized anthranilic acid with potassium ethyl xanthate, basic hydrolysis and air oxidation as described in (Katz L, Karger LS, Scroeder W, Cohen M. Hydrazine Derivatives. I. Benzalithio- and Bisbenzaldithio-Salicylhydrazides. J Org Chem 1953;18:1380-1402). The disulphide is converted to the sulphonyl chloride by treatment with sulfuryl chloride and potassium nitrate at room temperature (Park YJ, Shin HH, Kim YH. Convenient One-Pot Synthesis of Sulfonyl Chlorides from Thiols Using Sulfuryl Chloride and Metal Nitrate. Chem Lett 1992:1483-1486). Addition of glycine methyl ester and base, typically triethylamine, affords after several hours the corresponding sulphonamide. Treatment of this adduct with sodium methoxide in DMF and acidification with aqueous HCl affords the required benzothiazine dioxide intermediate.

Scheme 3 demonstrates the method employed for the conversion of a saccharin derivative to the corresponding benzothiazine dioxide. Briefly, the saccharin derivative is N-alkylated with methyl bromoacetate in DMF employing sodium hydride as a base. The adduct is rearranged to the corresponding benzothiazine dioxide by treatment with sodium methoxide in DMF at room temperature.

Scheme 4 demonstrates an alternative procedure for preparing the requisite benzothiazine dioxide intermediate. In this situation treatment of the sulphonyl chloride with an appropriately substituted aniline affords the sulphonamide which upon warming

-33-

affords the N-substituted saccharin. Addition of methyl chloroacetate and sodium hydride results in the isolation of the intermediate benzothiazine dioxide.

5 Scheme 5 the intermediate benzothiazine dioxide is benzylated typically with (3,4-methylenedioxy)benzyl chloride in DMF in the presence of a base typically sodium hydride. The N-benzylated adduct is treated with trifluoromethanesulphonic anhydride and pyridine in methylene chloride at room temperature for about
10 1 hour. This intermediate is used directly in the subsequent reactions.

 Scheme 6 illustrates the procedure employed for the synthesis of 4-arylsulfanyl benzothiazine dioxides. Typically sodium (3,4-methylenedioxy)phenyl thiolate is
15 added to a solution of the vinyl triflate in DMF. The adduct is isolated by chromatography and saponified with aqueous lithium hydroxide.

 Scheme 7 illustrates the procedure employed for the synthesis of 4-aryl benzothiazine dioxides. Typically (3,4-methylenedioxy)phenyl boronic acid is
20 employed in a palladium mediated cross coupling reaction with the corresponding vinyl triflate. The adduct is isolated by chromatography and saponified with aqueous lithium hydroxide.

25 Scheme 8 depicts the procedure for derivatization the 3-carboxylic acid of the parent benzothiazine dioxide. The acid is activated with a carbodiimide, typically 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and coupled with a sulphonamide to afford
30 the corresponding carbonyl-arylsulphonamide. Similarly activation with carbonyl diimidazole and addition of aqueous ammonia provides the corresponding amide. This amide is dehydrated with trichloroacetyl chloride and triethylamine to afford the corresponding nitrile.
35 Addition of sodium azide and ammonium chloride to the nitrile in DMF and several hours at elevated

-34-

temperature, typically 100°C, affords the corresponding tetrazole.

Scheme 9 is an alternate procedure for the preparation of the required benzothiazine dioxides. In this situation the saccharin is N-alkylated by the addition of a base, typically sodium hydride and the addition of the alkylating agent, typically (3,4-methylenedioxy)benzyl chloride. Ring expansion by the addition of chloro methylacetate and NaH, in a dipolar aprotic solvent, such as DMSO, affords the N-alkylated benzothiazine dioxide.

Scheme 10 is an alternate procedure used to prepare substituted saccharins and hence the corresponding benzothiazine dioxide. In this situation the ortho-methyl sulphonyl chloride product is isolated upon treatment of the parent toluene derivative with chlorosulphonic acid. Oxidation to the corresponding benzoic acid is achieved with aqueous permanganate. The acid chloride and sulphonyl chloride are prepared upon treatment with phosphorus pentachloride. Addition of ammonium hydroxide affords the corresponding saccharin.

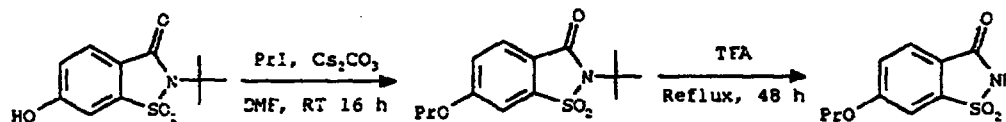
Scheme 11 illustrates a procedure employed for the synthesis of substituted 2H-1,2-benzothiazine-3-carbonitrile, 4-hydroxy-, 1,1-dioxide and the subsequent steps required for conversion to the compounds of Formula 1. In this situation the arylsulphonyl chloride is converted to the cyanoacetic sulphonamide by the addition of amino acetonitrile. This sulphonamide is treated with sodium methoxide to afford the required benzothiazine dioxide, upon acidic workup (for an alternative procedure see 1,2-Benzothiazine derivative. ES 508671A1 Foguet Ambros, Rafael, Ortiz Hernandez, Jose Alfonso). This intermediate is benzylated and derivatized to afford the corresponding 4-aryl and 4-arylsulfanyl products by the conditions

-35-

previously described. The nitrile is then either hydrolyzed to afford the corresponding amide and ultimately the carboxylic acid. The tetrazole is generated by the reaction with tributyltin azide or ammonium chloride and sodium azide in DMF.

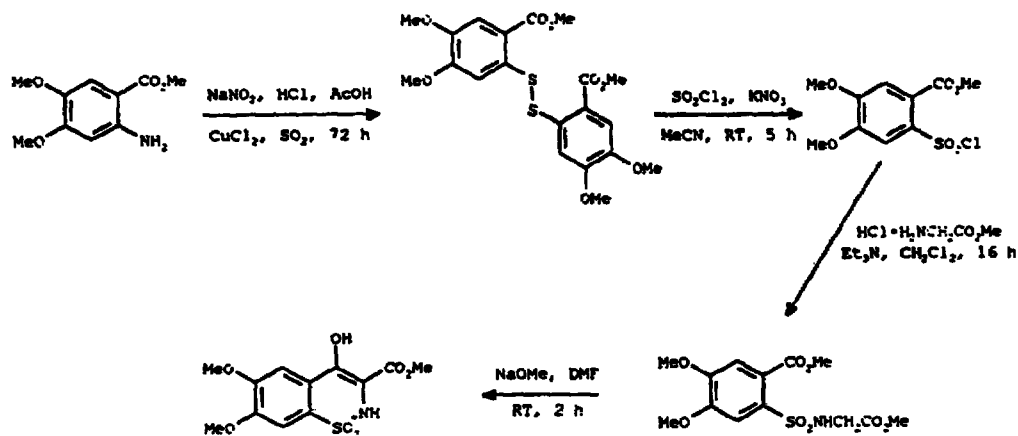
Scheme 12 depicts a procedure for preparing benzoisothiazol-3-one dioxides, and hence the corresponding benzothiazine dioxides, by oxidation of the corresponding 1,2-benzoisothiazol-3-ones (see Bambas LL. "The Chemistry of Heterocyclic Compounds"; Weissburger A. Wiley-Interscience: New York, 1952;4:225-227 and Davis M. Adv Heterocycl Chem 1972;14:43). Reaction of diazotized anthranilic acids with potassium ethyl xanthate followed by hydrolysis, typically with potassium hydroxide, and oxidation, typically with iodine, affords the corresponding 2,2'-dithiosalicylic acid. Addition of thionyl chloride and glycine methyl ester affords the corresponding amide which was cyclized to the 1,2-benzothiazol-3-ones. Oxidation of the 1,2-benzoisothiazol-3-one to the benzoisothiazol-3-one 1,1-dioxide was achieved with peracetic acid. (Gialdi F, et al., Farmaco Ed Sci 1961;16:509-526).

SCHEME 1

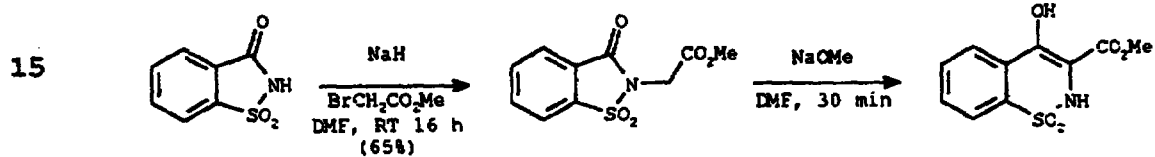


- 36 -

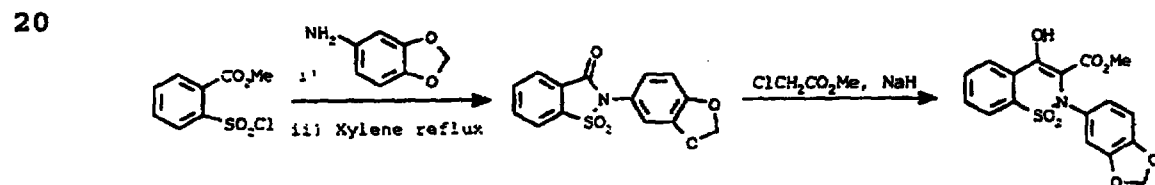
SCHEME 2



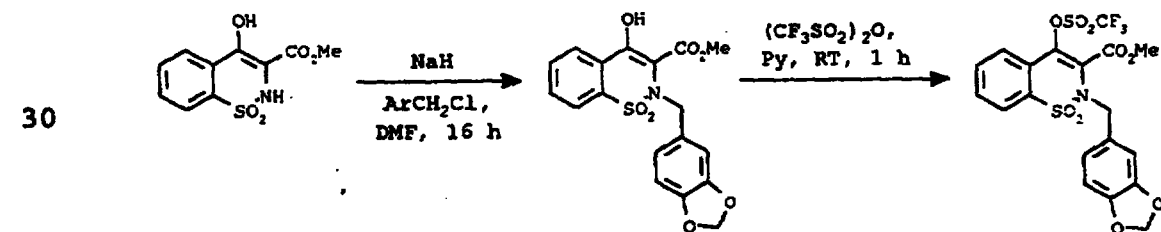
SCHEME 3



SCHEME 4

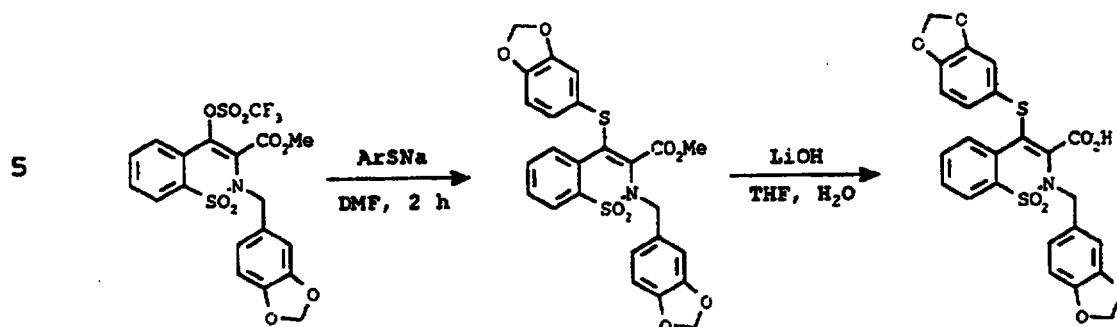


SCHEME 5

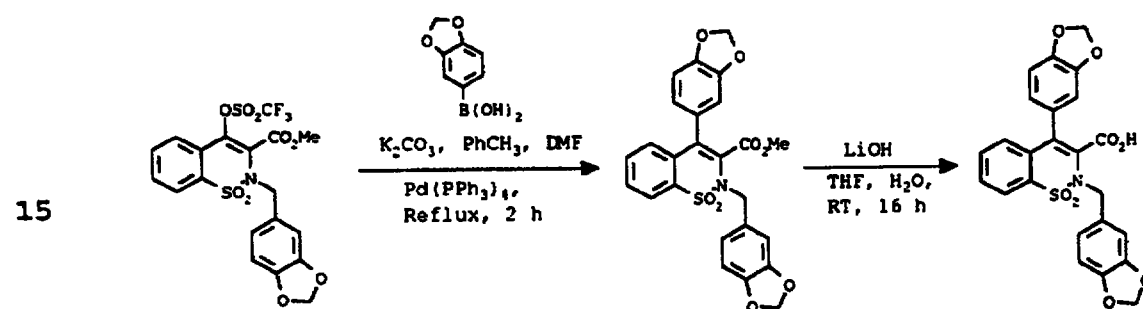


- 37 -

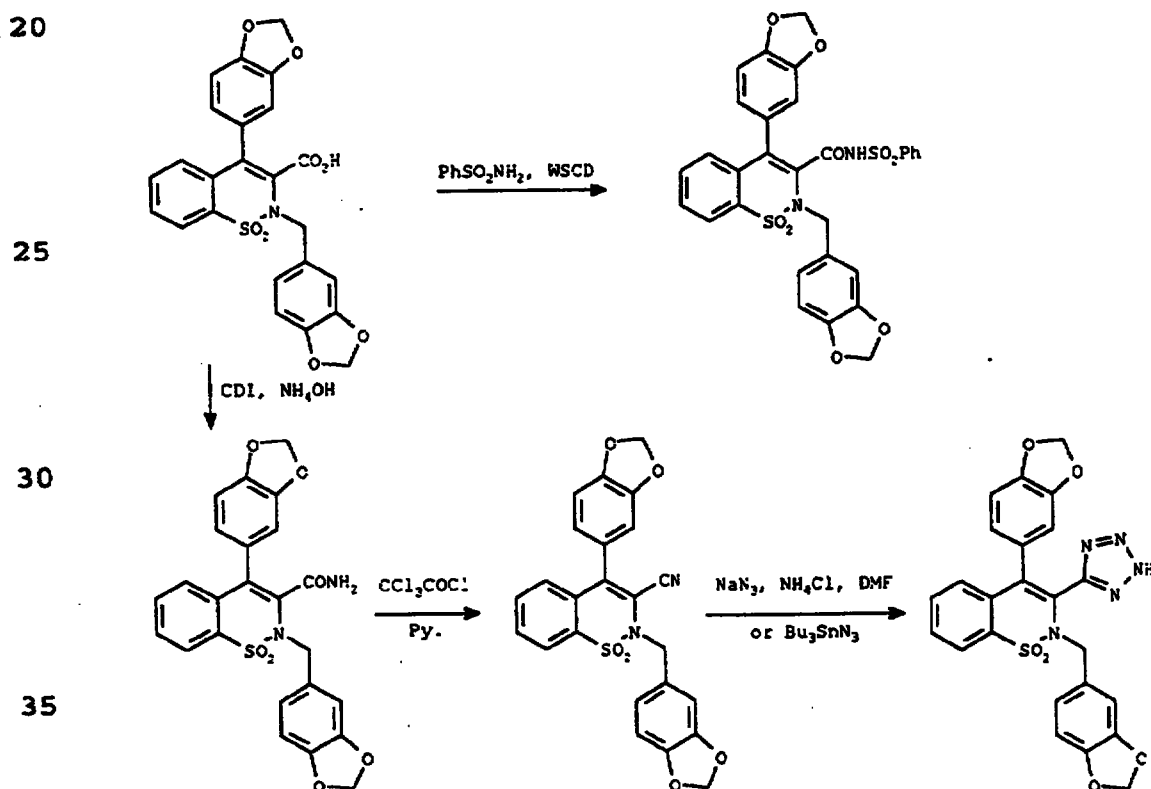
SCHEME 6



SCHEME 7

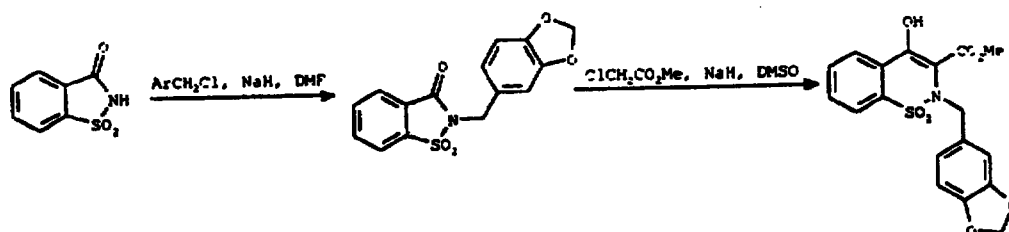


SCHEME 8

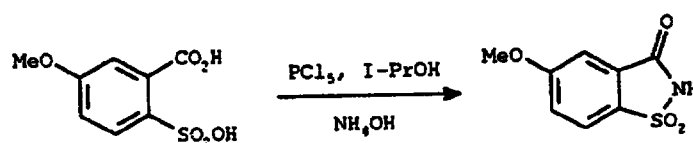
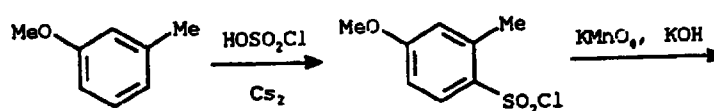


- 38 -

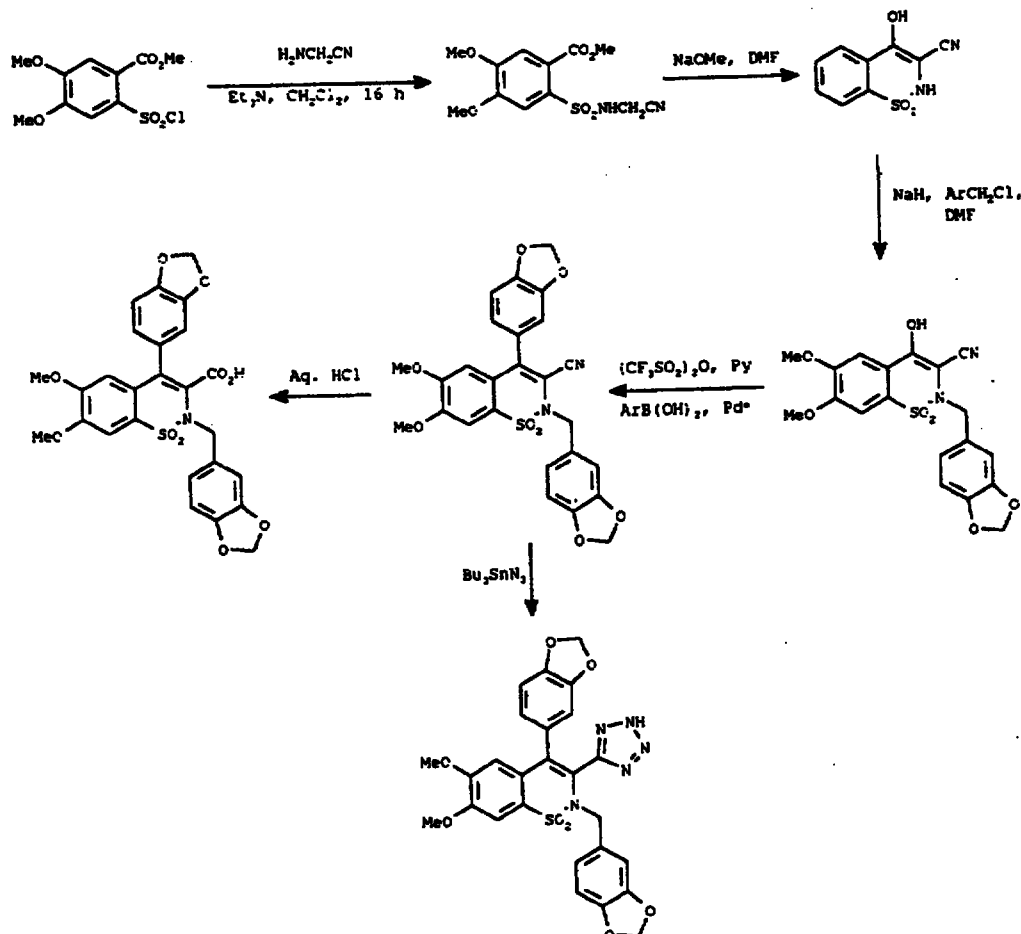
SCHEME 9



SCHEME 10

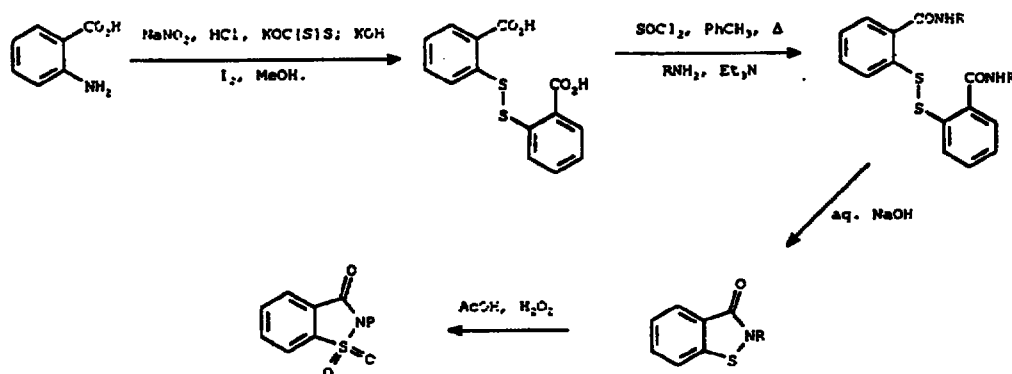


SCHEME 11



- 39 -

SCHEME 12



The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

-40-

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

5 In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

10 The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is
15 intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly,
20 cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa
25 butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

30 Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

35 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water

-41-

and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

5 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

10 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors,
15 stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

 The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is
20 subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or
25 ampoules. Also, the unit dosage form can be a capsule, table, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

 The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to
30 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

 In therapeutic use as antagonists of endothelin,
35 the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage

-42-

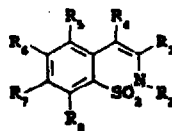
of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 10 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the preferred methods for preparing the compounds of the invention.

20

- 43 -

Example/Structure Table



5

10

15

20

25

30

35

40

45

50

Example	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈
24		CO ₂ H		H	H	H	H
25	Me	CO ₂ H		H	H	H	H
26		CO ₂ H		H	H	H	H
27		CO ₂ H		H	H	H	H
28		CO ₂ H		H	H	H	H
29		CO ₂ H		H	H	H	H
30		CO ₂ H		H	H	H	H

- 44 -

Example/Structure Table

Example	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈
5 31		CO ₂ H		H	H	H	H
10 32		CO ₂ H		H	H	H	H
15 33		CO ₂ H		H	H	H	H
20 34		CO ₂ H		H	H	H	H
25 35		CONH SO ₂ Ph		H	H	H	H
30 36		CO ₂ H		H	H	H	H
35 37		CO ₂ H		H	MeO	MeO	H
40 38		CO ₂ H		H	MeO	H	H

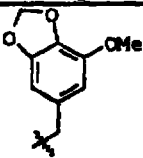
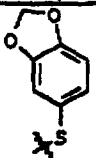
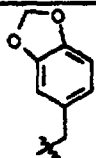
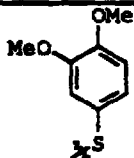
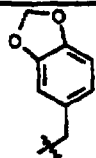
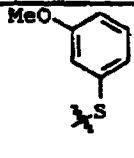
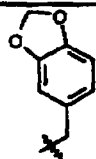
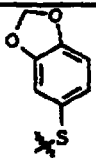
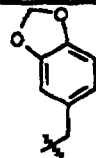
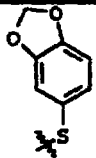
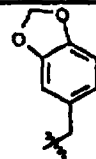
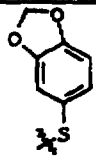
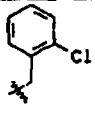
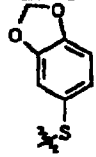
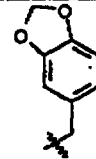
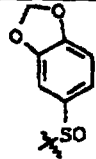
-45-

Example/Structure Table

	Example	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈
5	39		CO ₂ H		H	-OCH ₂ O-		H
10	40		CO ₂ Me		H	H	H	H
15								
20	41	Me	CO ₂ H		H	H	H	H
25	42		CO ₂ H		H	H	H	H
30								
35	43		CO ₂ H		H	H	H	H
40	44		CO ₂ H		H	H	H	H
45	45		CO ₂ H		H	H	H	H
50								
55	46		CO ₂ H		H	H	H	H

-46-

Example/Structure Table

Example	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈
47		CO ₂ H		H	H	H	H
48		CO ₂ H		H	H	H	H
49		CO ₂ H		H	H	H	H
50		CO ₂ H		H	MeO	MeO	H
51		CO ₂ H		H	MeO	H	H
52		CO ₂ H		H	-OCH ₂ O-		H
53		CO ₂ H		H	H	H	H
54		CO ₂ H		H	H	H	H

-47-

EXAMPLE 1

1,2-Benzisothiazole-2(3H)-acetic acid, 3-oxo-, methyl ester, 1,1-dioxide

To a solution of saccharin (40 g, 0.218 mol) in DMF (100 mL) at 0°C was added sodium hydride (8.73 g, 60%, 0.218 mol). After 15 minutes methyl bromoacetate (20.7 mL, 0.218 mol) was added and the mixture was stirred at room temperature for 18 hours. Diluted with dichloromethane (250 mL) and washed with saturated sodium bicarbonate (2 x 180 mL), water (100 mL), brine (2 x 150 mL). Dried organic phase with magnesium sulfate, removed solvent in vacuo, and crystallized product from hot ethanol to give the title compound (36.3 g, 65%).

Analysis calc'd for $C_{10}H_9N_1O_5S_1$:

C, 47.06; H, 3.55; N, 5.49;

Found: C, 47.02; H, 3.68; N; 5.37.

MS (CI) m/e 256.

Svoboda J, Palecek J, Dedek V. Phase transfer catalysed N-substitution of 2H-1,2-benzisothiazolin-3-one 1,1-dioxide. Collect Czech Chem Commun 1986;51(6):1304-1310.

EXAMPLE 2

4-Hydroxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]-thiazine-3-carboxylic acid methyl ester

To methanol (100 mL) was added sodium (5.4 g, 0.23 mol) portionwise. Once all the sodium had dissolved the solution was concentrated in vacuo and the final traces of methanol were removed under high vacuum. The sodium methoxide was suspended in dry DMF (65 mL). Dissolved 1,2-Benzisothiazole-2(3H)-acetic acid, 3-oxo-, methyl ester, 1,1-dioxide (20 g, 0.078 mol) in DMF (30 mL), cooled to 0°C, and added the freshly prepared sodium methoxide suspension over 7 minutes. Stirred solution at 0°C for 30 minutes.

-48-

Added 1N HCl (430 mL) to reaction via addition funnel, collected and washed precipitate with water. Dried precipitate at 52°C under vacuum overnight to give the title compound (13.6 g, 68%);

5 Analysis calc'd for $C_{10}H_9N_1O_5S_1$:

C, 47.06; H, 3.55; N, 5.49;

Found: C, 47.11; H, 3.67; N; 5.16.

MS (CI) m/e 256.

10 Svoboda J, Palecek J, Dedek V. The Synthesis of substituted 2H-1,2-benzothiazines 1,1-dioxides. Collect Czech Chem Commun 1986;51(5):1133-1139.

EXAMPLE 3

15 2-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester

To 4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester (1.48 g, 5.84 mmol) in DMF (10 mL) was added sodium hydride (0.257 g, 60%, 6.4 mmol) and the mixture stirred for 5 minutes. 3,4-methylenedioxymethyl chloride (2.2 g, 50 wt.% in dichloromethane, 6.4 mmol) was added and the mixture stirred at room temperature for 18 hours. Diluted with ethyl acetate (100 mL), washed with water (2 x 80 mL), brine (80 mL), dried over magnesium sulfate, removed solvent in vacuo, and crystallized from ethyl acetate/heptane to give the title compound (1.63 g, 72%);

25 Analysis calc'd for $C_{18}H_{15}N_1O_7S_1$:

30 C, 55.52; H, 3.88; N, 3.60;

Found: C, 55.45; H, 3.72; N; 3.49.

MS (CI) m/e 389.

EXAMPLE 4

35 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[d]isothiazol-3-one

-49-

To saccharin (5.0 g, 0.0273 mol) in DMF (10 mL) was added NaH (1.15 g, 60% in oil, 0.0288 mol) with ice bath cooling. After stirring for 10 minutes. a solution of 3,4-methylenedioxybenzyl chloride in methylene chloride, 50% by weight, (10 g, 0.0293 mol) was added and the mixture stirred for 16 hours. The mixture was diluted with ethyl acetate (200 mL) containing 10% methylene chloride and washed with 1N HCl (2 x 100 mL). The organic phase was washed with brine and dried over MgSO_4 . The mixture was concentrated until crystals were apparent. After standing for 16 hours the product was collected by filtration (4.2 g, 49%);

Analysis calc'd for $\text{C}_{15}\text{H}_{11}\text{N}_1\text{O}_5\text{S}_1$:

15 C, 56.78; H, 3.49; N, 4.41;
Found: C, 56.26; H, 3.50; N, 4.56.
MS (CI) m/e 317.

EXAMPLE 5

20 2-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester (Alternative procedure)

To 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[d]isothiazol-3-one (1.115 g, 3.517 mmol) in DMSO (6 mL) was added methyl 2-chloroacetate (0.61 mL, 6.96 mmol). The mixture was heated to 40°C and sodium hydride (0.562 g, 60% in oil, 14 mmol) was added slowly over 1 hour. The mixture was maintained at 40°C for 3h and then cooled to room temperature and diluted with 1N HCl (100 mL). The mixture was extracted with ethylacetate (2 x 100 mL) and the organic phase washed with brine and dried over MgSO_4 . Chromatography, silica gel, eluant CHCl_3 , and crystallization from methylene chloride/hexane afforded

35 the required product (0.596 g, 44%);

-50-

Analysis calc'd for $C_{18}H_{15}N_1O_7S_1$:

C, 55.52; H, 3.88; N, 3.60;

Found: C, 55.62; H, 3.85; N, 3.52.

MS (CI) m/e 389.

5

EXAMPLE 6

2-tert-Butyl-1,1-dioxo-6-propyloxy-1,2-dihydro-
1 λ ⁶-benzo[d]isothiazol-3-one

To a solution of 2-tert-butyl-6-hydroxy-1,1-dioxo-
1,2-dihydro-1 λ ⁶-benzo[d]isothiazol-3-one (0.454 g,
1.78 mmol) in DMF (10 mL) was added cesium carbonate
(1.16 g, 3.56 mmol) and the mixture stirred for
10 minutes. 1-iodopropane (0.26 mL, 2.67 mmol) was
added and the mixture stirred for 16 hours. Added
ethylacetate (100 mL) and water (50 mL). The organic
layer was washed with brine and then dried over $MgSO_4$.
Concentration in vacuo afforded the required product
(0.526 g, 99%). A portion was crystallized from ether/
hexane to afford long colorless needles;

20 Analysis calc'd for $C_{14}H_{19}N_1O_4S_1$:

C, 56.55; H, 6.44; N, 4.71;

Found: C, 56.72; H, 6.46; N, 4.66.

MS (CI) m/e 298.

25

EXAMPLE 7

1,1-Dioxo-6-propyloxy-1,2-dihydro-1 λ ⁶-benzo[d]-
isothiazol-3-one

A solution of 2-tert-butyl-1,1-dioxo-6-propyloxy-
1,2-dihydro-1 λ ⁶-benzo[d]isothiazol-3-one (0.346 g,
1.165 mmol) in trifluoroacetic acid (10 mL) was
refluxed for 48 hours. NMR of the reaction mixture
revealed quantitative deprotection. The mixture was
concentrated in vacuo and crystallized from methylene
chloride, methanol and hexane, to afford the required
product (0.130 g, 46%);

35

-51-

Analysis calc'd for $C_{10}H_{11}N_1O_4S_1$:

C, 49.78; H, 4.60; N, 5.81;

Found: C, 49.61; H, 4.49; N, 5.80.

MS (CI) m/e 242.

5

EXAMPLE 8

5-Methoxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[d]isothiazol-3-oneAnalysis calc'd for $C_8H_7N_1O_4S_1$:

10 C, 45.07; H, 3.31; N, 6.57;

Found: C, 45.23; H, 3.31; N, 6.52.

MS (CI) m/e 213.

Prepared according to Scheme 10 and the method of

Haworth RB, Lapworth A. "Sulphonation of m-cresol and

15 its methyl ether". J Chem Soc 1924-1299.

EXAMPLE 9

2-Benzo[1,3]dioxol-5-ylmethyl-5-methoxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[d]isothiazol-3-one

20 Prepared according to Example 3;

Analysis calc'd for $C_{16}H_{13}N_1O_6S_1$:

C, 55.33; H, 3.77; N, 4.03;

Found: C, 55.31; H, 3.81; N, 3.89.

MS (CI) m/e 347.

25

EXAMPLE 10

(5-Methoxy-1,1,3-trioxo-1,3-dihydro-1 λ ⁶-benzo[d]isothiazol-2-yl)-acetic acid methyl ester

Prepared according to Example 1;

30 Analysis calc'd for $C_{11}H_{11}N_1O_6S_1$:

C, 46.31; H, 3.89; N, 4.91;

Found: C, 45.93; H, 3.90; N, 4.78.

MS (CI) m/e 286.

-52-

EXAMPLE 11

Benzoic acid, 2,2'-dithiobis[4,5-dimethoxy-, dimethyl ester

To a suspension of methyl 2-amino-4,5-dimethoxy-benzoate (1.50 g, 7.11 mmol) in acetic acid (10 mL) and conc. HCl (13 mL) at an internal temperature of 1-3°C was slowly added a solution of sodium nitrite (0.55 g, 7.97 mmol) in water (5 mL); the solid went into solution upon the final addition of the aqueous sodium nitrite. The solution was stirred for an additional 30 minutes. and then sulphur dioxide was bubbled through the cold solution for 30 minutes. Cupric chloride dihydrate (0.471 g, 2.76 mmol) in water (5 mL) was added and the green mixture allowed to warm to room temperature over 48 hours. Filtration and washing with water (3 x 100 mL) afforded the required product as a white solid (0.800 g, 49%).

Analysis calc'd for $C_{20}H_{22}O_8S_2$:

C, 52.85; H, 4.88;

Found: C, 52.64; H, 4.89.

MS (CI) m/e 454.

EXAMPLE 12

1,3-Benzodioxole-5-carboxylic acid, 6,6'-dithiobis-, dimethyl ester

Prepared according to the procedure of Example 11 from 6-amino-benzo[1,3]dioxole-5-carboxylic acid methyl ester. Crystallized from methylene chloride/hexane;

Analysis calc'd for $C_{18}H_{14}O_8S_2$:

C, 51.18; H, 3.34;

Found: C, 51.04; H, 3.33.

MS (CI) m/e 422.

EXAMPLE 13

2-Chlorosulfonyl-4,5-dimethoxy-benzoic acid methyl ester

-53-

To a suspension of benzoic acid, 2,2' dithiobis 4,5-dimethoxy-, dimethyl ester (0.170 g, 0.374 mmol) in acetonitrile (4 mL) at 0°C was added potassium nitrate (0.095 g, 0.940 mmol) and then sulfonyl chloride (0.075 mL, 0.934 mmol) dropwise. A yellow solution formed briefly which was replaced rapidly by a heavy precipitate. The mixture was stirred for 1 hour at 0°C and then for 4 hours at room temperature. Saturated NaHCO₃ aq. (10 mL) and ethylacetate (50 mL) were added. The organic fraction was washed with brine and dried over MgSO₄. Crystallization from ethylacetate/hexane afforded the required product (0.119 g, 54%); Analysis calc'd for C₁₀H₁₁O₆S₁Cl₁:
C, 40.76; H, 3.76;
Found: C, 40.79; H, 3.74.
MS (CI) m/e 294.

EXAMPLE 14

6-Chlorosulfonyl-benzo[1,3]dioxole-5-carboxylic acid methyl ester

Prepared according to the method of Example 13 from 1,3-benzodioxole-5-carboxylic acid, 6,6'-dithiobis-, dimethyl ester.
Analysis calc'd for C₉H₇O₆S₁Cl₁:
C, 38.79; H, 2.53.
Found: C, 39.19; H, 2.42.
MS (CI): m/e 287.

EXAMPLE 15

4,5-Dimethoxy-2-(methoxycarbonylmethyl-sulfamoyl)-benzoic acid methyl ester

To a solution of 2-Chlorosulfonyl-4,5-dimethoxy-benzoic acid methyl ester (0.100 g, 0.339 mmol) in methylene chloride (5 mL) was added triethylamine (0.28 mL, 2.012 mmol) and methyl glycinate.HCl (0.128 g, 1.02 mmol). The mixture was stirred for

-54-

2 hours and then diluted with ethyl acetate (50 mL) and 1N HCl (50 mL). The organic fraction was washed with brine and dried over MgSO_4 . Crystallization from methylene chloride hexane affords the title compound (0.092 g, 78%);

Analysis calc'd for $\text{C}_{13}\text{H}_{17}\text{N}_1\text{O}_8\text{S}_1$:

C, 44.95; H, 4.93; N, 4.03;

Found: C, 44.91; H, 4.81; N, 4.09.

MS (CI) m/e 347.

10

EXAMPLE 16

6-(Methoxycarbonylmethyl-sulfamoyl)-benzo[1,3]dioxole-5-carboxylic acid methyl ester

Prepared according to the method of Example 15, from 6-Chlorosulfonyl-benzo[1,3]dioxole-5-carboxylic acid methyl ester;

Analysis calc'd for $\text{C}_{12}\text{H}_{13}\text{N}_1\text{O}_8\text{S}_1$:

C, 43.51; H, 3.96; N, 4.23;

Found: C, 43.41; H, 3.71; N, 3.99.

MS (CI) m/e 331.

15

20

EXAMPLE 17

4-Hydroxy-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester

To a solution of 4,5-dimethoxy-2-(methoxycarbonylmethyl-sulfamoyl)-benzoic acid methyl ester (0.555 g, 1.60 mmol) in dry DMF (3 mL) was added dry and freshly prepared sodium methoxide (0.345 g, 6.39 mmol). A red colour was generated upon the addition of the sodium methoxide. The mixture was stirred for 45 minutes. and then diluted with 1N HCl (100 mL). The pale yellow solid that precipitated was collected and washed with water (0.341 g, 68%);

25

30

-55-

Analysis calc'd for $C_{12}H_{13}N_1O_7S_1$:

C, 45.71; H, 4.16; N, 4.44;

Found: C, 45.67; H, 4.14; N, 4.40.

MS (CI) m/e 316.

5

EXAMPLE 18

8-Hydroxy-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid methyl ester

10

Prepared according to Example 17 from

6-(methoxycarbonylmethyl-sulfamoyl)-benzo[1,3]dioxole-5-carboxylic acid methyl ester;

Analysis calc'd for $C_{11}H_9N_1O_7S_1$:

C, 44.15; H, 3.03; N, 4.68;

15

Found: C, 44.14; H, 2.87; N, 4.24.

MS (CI) m/e 299.

EXAMPLE 19

20

2-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester

25

Prepared according to the method of Example 3 from 4-hydroxy-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester;

Analysis calc'd for $C_{20}H_{19}N_1O_9S_1$:

C, 53.45; H, 4.26; N, 3.12;

Found: C, 53.27; H, 4.23; N, 3.01.

MS (CI) m/e 449.

30

EXAMPLE 20

6-Benzo[1,3]dioxol-5-ylmethyl-8-hydroxy-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]-naphthalene-7-carboxylic acid methyl ester

35

Prepared according to the method of Example 3 from 8-hydroxy-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-

-56-

6-aza-cyclopenta[b]naphthalene-7-carboxylic acid methyl ester;

Analysis calc'd for $C_{19}H_{15}N_1O_3S_1$:

C, 52.66; H, 3.49; N, 3.23;

5 Found: C, 52.93; H, 3.81; N, 3.17.

MS (CI) m/e 433.

EXAMPLE 21

10 2-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-6-methoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester

Prepared according to the method of Example 3 from 4-hydroxy-6-methoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester;

15 Analysis calc'd for $C_{19}H_{17}N_1O_8S_1$:

C, 54.41; H, 4.09; N, 3.34;

Found: C, 54.22; H, 4.15; N, 3.26.

MS (CI) m/e 419.

20

EXAMPLE 22

2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-4-(trifluoromethanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester

25 A solution of benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester (0.40 g, 1.03 mmol) and pyridine (0.42 mL, 5.14 mmol) in methylene chloride (5 mL) at 0°C and under N_2 was treated with trifluoromethanesulfonic anhydride (0.21 mL, 1.23 mmol) and the reaction mixture stirred at 0°C for 2 hours. The solution was diluted with ethyl acetate, washed with 1N HCl (2x), brine, dried over magnesium sulfate, and the solvent evaporated.

30

35 Drying under high vacuum overnight afforded the crude triflate. This was passed through a pad of silica gel

-57-

eluted with hexane/ ethyl acetate 1:1; evaporation and drying under high vacuum afforded the title compound; Analysis calc'd for $C_{19}H_{14}NO_9S_2F_3$:

C, 43.77; H, 2.71; N, 2.69;

5 Found: C, 44.15; H, 2.84; N, 2.59.

MS(CI) m/e 521.

EXAMPLE 23

10 Methyl 2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-
4-(3,4,5-trimethoxyphenyl)-1,2-dihydro-1 λ ⁶-benzo[e]
[1,2]thiazine-3-carboxylate

2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-
4-(trifluoromethanesulfonyloxy)-1,2-dihydro-
1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl
15 ester was taken up in toluene/ DMF (10 mL/2 mL) and
treated with (3,4,5-trimethoxy)phenylboronic acid
(0.35 g, 1.65 mmol), potassium carbonate (0.23 g,
1.67 mmol), and $Pd^0(PPh_3)_4$ (0.19 g, 0.16 mmol). The
reaction mixture was heated to reflux for 2 hours,
20 cooled to room temperature, diluted with ethyl acetate,
washed with sat. aq. $NaHCO_3$, brine, dried over
magnesium sulfate, and the solvent evaporated. The
residue was purified by silica gel chromatography
eluting with hexane/ ethyl acetate 1:1. The resulting
25 oil was treated with diethyl ether, the precipitated
solid collected, and dried to give the product as an
off-white solid;

Analysis calc'd for $C_{27}H_{25}N_1O_9S_1$:

C, 59.42; H, 4.41; N, 2.67;

30 Found: C, 59.04; H, 4.42; N, 2.48.

MS (CI) m/e 539, mp 182-183°C.

-58-

EXAMPLE 24

2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

5 A solution of methyl 2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylate (0.28 g, 0.05 mmol) in THF/methanol/water (10 mL/3 mL/3 mL) was treated with lithium hydroxide
10 (0.33 g, 7.78 mmol) and the reaction mixture stirred at room temperature overnight. The solution was diluted with ethyl acetate, washed with 1N HCl, brine, dried over magnesium sulfate, and the solvent evaporated. The foam was crystallized from methylene
15 chloride/isopropyl ether;
MS(CI) m/e 525.

EXAMPLE 25

20 4-Benzo[1,3]dioxol-5-yl-2-methyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

 Prepared according to the method of Example 23, from 2-methyl-1,1-dioxo-4-(trifluoromethane-sulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester, and saponification
25 according to the method of Example 24;
Analysis calc'd for C₁₇H₁₃NO₆S:
 C, 56.82; H, 3.65; N, 3.90;
Found: C, 56.68; H, 3.69; N, 3.79.
MS(CI) m/e 359, mp 204.0-205.0°C.

30

EXAMPLE 26

4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

35 Prepared according to the method of Example 23, from 2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-

-59-

4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
ester, and saponification according to the method of
Example 24;

5 MS (CI) m/e 479, mp 229-230°C.

EXAMPLE 27

4-Benzo[1,3]dioxol-5-yl-2-benzyl-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

10 Prepared according to the method of Example 23,
from 2-benzyl-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester, and
saponification according to the method of Example 24;
15 MS (CI) m/e 435.

EXAMPLE 28

4-Benzo[1,3]dioxol-5-yl-2-(4-methoxy-benzyl)-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

20 Prepared according to the method of Example 23,
from 2-(4-methoxy-benzyl)-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester, and
saponification according to the method of Example 24;
25 MS (CI) m/e 465, mp 200-201°C.

EXAMPLE 29

4-Benzo[1,3]dioxol-5-yl-1,1-dioxo-2-(3,4,5-trimethoxy-
benzyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
30 3-carboxylic acid

Prepared according to the method of Example 23,
from 1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
2-(3,4,5-trimethoxy-benzyl)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
35 ester, and saponification according to the method of
Example 24;

-60-

Analysis calc'd for $C_{26}H_{23}NO_9S$:

C, 59.42; H, 4.41; N, 2.67;

Found: C, 56.23; H, 4.38; N, 2.40; H_2O , 4.42.

MS(CI) m/e 525, mp 211.0-212.0°C.

5

EXAMPLE 30

4-Benzo[1,3]dioxol-5-yl-2-(2-carboxymethoxy-4-methoxy-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e]-[1,2]thiazine-3-carboxylic acid

10 Prepared according to the method of Example 23, from 2-(2-ethoxycarbonyl-methoxy-4-methoxy-benzyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester, and saponification according to the method of

15 Example 24;

Analysis calc'd for $C_{26}H_{21}NO_{10}S$:

C, 57.88; H, 3.92; N, 2.60;

Found: C, 57.62; H, 3.90; N, 2.54.

MS(CI) m/e M-C10H11O4 = 345, mp 192.0-192.0°C.

20

EXAMPLE 31

4-Benzo[1,3]dioxol-5-yl-2-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]-thiazine-3-carboxylic acid

25 Prepared according to the method of Example 23, from 2-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester, and saponification according to the method of

30 Example 24;

MS (CI) m/e 513.

EXAMPLE 32

4-Benzo[1,3]dioxol-5-yl-2-(7-methoxy-benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]-thiazine-3-carboxylic acid

35

-61-

Prepared according to the method of Example 23,
from 2-(7-methoxy-benzo[1,3]dioxol-5-ylmethyl)-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
5 ester, and saponification according to the method of
Example 24;
MS (CI) m/e 509, mp 181-182°C.

EXAMPLE 33

10 2-Benzo[1,3]dioxol-5-ylmethyl-4-(3,4-dimethoxy-phenyl)-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid

Prepared according to the method of Example 23,
from 2-(benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-
15 4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
ester with 3,4-dimethoxyphenyl boronic acid, and
saponification according to the method of Example 24;
MS (CI) m/e 495, mp 267-268°C.

20

EXAMPLE 34

4-Benzo[2,3]dioxol-5-yl-2-(2-chloro-benzyl)-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 24,
25 from 2-(2-chloro-benzyl)-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester, and
saponification according to the method of Example 24;
Analysis calc'd for C₂₃H₁₆N₁O₆S₁Cl₁:
30 C, 58.79; H, 3.43; N, 2.84;
Found: C, 58.53; H, 3.61; N, 2.84.
MS (CI) m/e 470.

-62-

EXAMPLE 35

N-(4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carbonyl)-benzenesulfonamide

5 To a solution of 4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid (0.25 g, 0.56 mmol) in methylene chloride (5 mL) was added benzene sulfonamide (0.10 g, 0.65 mmol),
10 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.12 g, 0.65 mmol) and dimethylaminopyridine (0.05 g). The mixture was stirred for 3 days and then diluted with ethylacetate (50 mL) and water (20 mL). The organic phase was
15 washed with brine, dried over MgSO₄ and evaporated in vacuo. Silica gel chromatography, eluant methylene chloride/ ethylacetate afforded the title compound (0.15 g, 46%).
MS(CI) m/e 618.

20

EXAMPLE 36

2-Benzo[1,3]dioxol-5-yl-4-(3-methoxy-phenyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid

 Prepared according to the method of Example 23;
25 from 2-(benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester with 3-methoxyphenyl boronic acid, and saponification according to the method of Example 24;
30 Analysis calc'd for C₂₇H₂₇N₂O₇S₂:
 C, 61.93; H, 4.11; N, 3.01;
Found: C, 61.50; H, 4.40; N, 2.90.
MS (CI) m/e 465.

-63-

EXAMPLE 37

4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e]-[1,2]thiazine-3-carboxylic acid

- 5 Prepared according to the method of Example 23, from 2-benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester, and saponification according to the method of
- 10 Example 24;
- Analysis calc'd for C₂₆H₂₁N₁O₁₀S₁:
- C, 57.88; H, 3.92; N, 2.60;
- Found: C, 57.64; H, 3.94; N, 2.51.
- MS (CI) m/e 539.

15

EXAMPLE 38

4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-6-methoxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]-thiazine-3-carboxylic acid

- 20 Prepared according to the method of Example 23, from 2-benzo[1,3]dioxol-5-ylmethyl-6-methoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester, and saponification according to the method of
- 25 Example 24;
- Analysis calc'd for C₂₅H₁₉N₁O₉S₁:
- C, 58.94; H, 3.76; N, 2.75;
- Found: C, 58.63; H, 3.86; N, 2.64.
- MS (CI) m/e 509.

30

EXAMPLE 39

8-Benzo[1,3]dioxol-5-yl-6-benzo[1,3]dioxol-5-ylmethyl-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ ⁶-thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid

- 35 Prepared according to the method of Example 23, from 6-benzo[1,3]dioxol-5-ylmethyl-5,5-dioxo-

-64-

8-(trifluoro-methanesulfonyloxy)-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid methyl ester, and saponification according to the method of Example 24;

5 Analysis calc'd for C₂₅H₁₇N₁O₁₀S₁:

C, 57.36; H, 3.27; N, 2.68;

Found: C, 56.95; H, 3.52; N, 2.53.

MS (CI) m/e 523.

10

EXAMPLE 40

2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-5-ylsulfanyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e]-[1,2]thiazine-3-carboxylic acid methyl ester

To 2-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester in dichloromethane (6 mL) and pyridine (0.65 mL, 7.75 mmol) was added trifluoromethanesulfonic anhydride (0.32 mL, 1.71 mmol). This mixture was stirred at room temperature for 30 minutes. Diluted with ethyl acetate (100 mL), washed with 1N HCl (2 x 50 mL), brine (50 mL), dried with magnesium sulfate and then evaporated in vacuo to afford the crude 2-benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester. A solution of this ester, in DMF (3 mL), was added to sodium 1,3-benzodioxole-5-thiolate (0.31 g, 2.0 mmol) {prepared by dissolving 1,3-benzodioxole-5-thiol (0.31 g, 2.0 mmol) in DMF (3 mL) and stirring with sodium hydride (0.081 g, 2.0 mmol) for 5 minutes} in DMF (3 mL). After stirring at room temperature for 16 hours the mixture was diluted with ethyl acetate (100 mL), washed with 1N NaOH (2 x 50 mL), brine (50 mL), dried with magnesium sulfate, and evaporated in vacuo. Silica gel column chromatography eluting

-65-

with 25% ethyl acetate in hexane afforded the title compound as a foam (0.64 g, 79%);

Analysis calc'd for $C_{25}H_{19}N_1O_8S_2$:

C, 57.14; H, 3.64; N, 2.67;

5 Found: C, 56.93; H, 3.93; N, 2.51.

MS (CI) m/e 525.

EXAMPLE 41

10 4-(benzo[1,3]dioxol-5-ylsulfanyl)-2-methyl-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 40, from 4-hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester and saponified according to the method of Example 42;

15

Analysis calc'd for $C_{17}H_{13}N_1O_6S_2$:

C, 52.17; H, 3.35; N, 3.58;

Found: C, 51.94; H, 3.34; N, 3.60.

MS (CI) m/e 391.

20

EXAMPLE 42

2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-5-ylsulfanyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e]-[1,2]thiazine-3-carboxylic acid

25

To 2-benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-5-ylsulfanyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester (0.467 g, 0.89 mmol) in THF:methanol:water (5 mL:2 mL:2 mL) was added LiOH (0.46 g, 19 mmol).

30

Stirred at room temperature for 5 hours, diluted with water (80 mL) and 50% HCl (10 mL) then extracted with chloroform (3 x 80 mL). Dried with magnesium sulfate and removed solvent to afford the title compound as a foam (0.4 g, 88%);

-66-

Analysis calc'd for $C_{24}H_{17}N_1O_8S_2$:

C, 56.35; H, 3.35; N, 2.74;

Found: C, 55.78; H, 3.43; N; 2.58.

MS (CI) m/e 511.

5

EXAMPLE 43

4-(benzo[1,3]dioxol-5-ylsulfanyl)-2-benzyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 40,
10 from 2-benzyl-4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester and saponified according to the method of Example 42;

Analysis calc'd for $C_{23}H_{17}N_1O_8S_2$:

15 C, 59.09; H, 3.67; N, 3.00;

Found: C, 58.74; H, 3.91; N, 2.68.

MS (CI) m/e 467.

EXAMPLE 44

20 4-(benzo[1,3]dioxol-5-ylsulfanyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 40,
from 4-hydroxy-2-(4-methoxy-benzyl)-1,1-dioxo-
25 1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester and saponified according to the method of Example 42;

Analysis calc'd for $C_{24}H_{19}N_1O_7S_2$:

C, 57.94; H, 3.85; N, 2.82;

30 Found: C, 57.97; H, 4.12; N, 2.59.

MS (CI) m/e 498.

EXAMPLE 45

35 4-(benzo[1,3]dioxol-5-ylsulfanyl)-2-(3,4,5-trimethoxy-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

- 67 -

Prepared according to the method of Example 40,
from 4-hydroxy-1,1-dioxo-2-(3,4,5-trimethoxy-benzyl)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester and saponified according to the method of
Example 42;

Analysis calc'd for C₂₆H₂₃N₁O₉S₂:

C, 56.01; H, 4.16; N, 2.51;

Found: C, 55.97; H, 4.47; N, 2.36.

MS (CI) m/e 557.

EXAMPLE 46

4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-(6-chloro-
benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 40,
from 2-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-
4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester and saponified
according to the method of Example 42;

Analysis calc'd for C₂₄H₁₆N₁O₈S₂Cl₁:

C, 52.80; H, 2.95; N, 2.57;

Found: C, 52.91; H, 2.87; N, 2.42.

MS (CI) m/e 544, mp 203-204°C.

EXAMPLE 47

4-(benzo[1,3]dioxol-5-ylsulfanyl)-2-(7-methoxy-
benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 40,
from 2-(7-methoxy-benzo[1,3]dioxol-5-ylmethyl)-
4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester and saponified
according to the method of Example 42;

MS (CI) m/e 541.

- 68 -

EXAMPLE 48

2-Benzo[1,3]dioxol-5-ylmethyl-4-(3,4-dimethoxy-phenylsulfanyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e]-[1,2]thiazine-3-carboxylic acid

5 Prepared according to the method of Example 40, from 4-hydroxy-2-(3,4-dimethoxy-benzyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester and saponified according to the method of Example 42;

10 Analysis calc'd for C₂₅H₂₁N₁O₈S₂:

C, 56.92; H, 4.01; N, 2.65;

Found: C, 57.02; H, 4.10; N; 2.59.

MS (CI) m/e 527.

15

EXAMPLE 49

2-Benzo[1,3]dioxol-5-ylmethyl-4-(3-methoxy-phenylsulfanyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e]-[1,2]thiazine-3-carboxylic acid

20 Prepared according to the method of Example 40, from 2-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester and saponified according to the method of Example 42;

Analysis calc'd for C₂₄H₁₉N₁O₇S₂:

25 C, 57.93; H, 3.85; N, 2.82;

Found: C, 57.73; H, 4.02; N; 2.63.

MS (CI) m/e 497.

EXAMPLE 50

30 2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-5-ylsulfanyl)-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid

35 Prepared according to the method of Example 40, from 2-Benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl

-69-

ester and saponified according to the method of Example 42;

Analysis calc'd for $C_{27}H_{23}N_1O_{10}S_2$:

C, 54.64; H, 3.70; N, 2.45;

5 Found: C, 54.96; H, 4.08; N, 2.09.

MS (CI) m/e 571.

EXAMPLE 51

10 2-Benzo[1,3]dioxol-5-ylmethyl-4-(benzo[1,3]dioxol-5-ylsulfanyl)-6-methoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 40, from 2-benzo[1,3]dioxol-5-ylmethyl-4-hydroxy-6-methoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester and saponified according to the method of Example 42;

15 MS (CI) m/e 541.

EXAMPLE 52

20 6-Benzo[1,3]dioxol-5-ylmethyl-8-(benzo[1,3]dioxol-5-ylsulfanyl)-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid

Prepared according to the method of Example 40, from 6-benzo[1,3]dioxol-5-ylmethyl-8-hydroxy-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid methyl ester and saponified according to the method of Example 42.

25 MS (CI) m/e 555.

EXAMPLE 53

30 4-(Benzo[1,3]dioxol-5-ylsufanyl)-2-(2-chloro-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid

Prepared according to the method of Example 40, from 2-(2-chloro-benzyl)-1,1-dioxo-4-(trifluoromethanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-

35

-70-

thiazine-3-carboxylic acid methyl ester, and saponification according to the method of Example 42; Analysis calc'd for $C_{23}H_{16}N_1O_6S_2Cl_1$:

C, 55.03; H, 3.21; N, 2.79;

5 Found: C, 54.82; H, 3.85; N, 2.46.

MS (CI) m/e 501.

EXAMPLE 54

10 2-(2-Benzo[1,3]dioxol-5-ylmethyl)-4-(benzo[1,3]dioxol-5-ylsufinyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid

Addition of meta-chloro perbenzoic acid (1.1 equiv) to a solution of 2-(2-benzo[1,3]dioxol-5-ylmethyl)-4-(benzo[1,3]dioxol-5-ylsufanyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester in methylene chloride and stirring for 10 minutes affords, upon workup, 2-(2-benzo[1,3]dioxol-5-ylmethyl)-4-(benzo[1,3]dioxol-5-ylsufinyl)-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo[e][1,2]thiazine-3-carboxylic acid methyl ester, which was saponified according to the procedure of Example 42;

Analysis calc'd for $C_{24}H_{17}N_1O_9S_2$:

C, 54.64; H, 3.25; N, 2.66;

Found: C, 54.75; H, 3.38; N, 2.61.

25 MS (CI) m/e 527.

EXAMPLE 55

2-Benzo[1,3]dioxol-5-yl-1,1-dioxo-1,2-dihydro-1 λ ⁶-benzo-[d][isothiazol-3-one

30 To a solution of 3,4-methylenedioxylaniline (9.5 g, 36.5 mmol) and pyridine (3.53 mL, 43.6 mmol) in chloroform (20 mL) at 0°C was added 90% methyl 2-(chlorosulfonyl)benzoate (9.5 g, 36.5 mmol) in 6 portions over 45 minutes. Stirred at room temperature for 3 days. Diluted with ethyl acetate and washed with 1N HCl. After drying over $MgSO_4$ the crude

35

-71-

5 sulphonamide was dissolved in xylenes (100 mL) and treated with pyridine (0.61 mL, 7.64 mmol) and DMAP (0.93 g, 7.64 mmol) and heated to reflux for 18 hours. The reaction mixture was evaporated in vacuo and trituated with 1N HCl. The solid was collected, washed with water, and dried to afford the title compound;

Analysis calc'd for $C_{14}H_9N_1O_5S$:

C, 55.44; H, 2.99; N, 4.62;

10 Found: C, 55.43; H, 3.08; N, 4.70.

MS (CI) m/e 303.

EXAMPLE 56

15 2-Benzo[1,3]dioxol-5-yl-4-hydroxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl ester

To a solution of 2-benzo[1,3]dioxol-5-yl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[d][isothiazol-3-one (2 g, 6.59 mmol) in DMSO (11 mL) was added methyl 20 2-chloroacetate (1.16 mL, 13.2 mmol) and the mixture heated to 40°C. To this was added 60% NaH (1.05 g, 26.4 mmol) in portions over 1 hour. The reaction was maintained at 40°C for a further 3 hours, acidified with 1N HCl, extracted into ethylacetate, washed with 25 brine and dried over $MgSO_4$. Chromatography afforded the required product;

Analysis calc'd for $C_{17}H_{13}N_1O_7S$:

C, 54.40; H, 3.49; N, 3.73;

Found: C, 54.11; H, 3.66; N, 3.60.

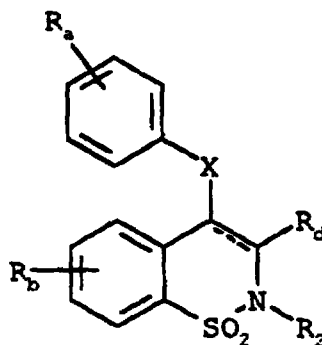
30 MS (CI) m/e 375.



- 72 -

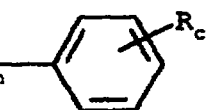
CLAIMS

1. A compound of formula



I

or a pharmaceutically acceptable acid addition or base salt thereof wherein:

R_2 is H, $(CH_2)_n$ -, alkyl of from 1 to

7 carbons, or $(CH_2)_n$ -cycloalkyl of from 3 to 8 carbons;

R_a and R_c are each 1 to 5 substituents and R_b is 1 to 4 substituents independently selected from:

hydrogen,

alkyl of from 1 to 7 carbons,

alkenyl of from 2 to 7 carbons,

alkynyl of from 2 to 7 carbons,

cycloalkyl of from 3 to 8 carbons,

phenyl,

C(O)-phenyl,

methylenedioxy,

ethylenedioxy,

OR,

NRR₁,

SR₁,

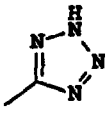
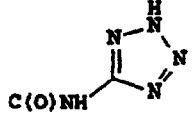
NO₂,

N₃,

COR,



-73-

- 35 Cl,
Br,
F,
I,
CO₂R,
40 CONRR₁,
SO₂NRR₁,
SO₂R,
CN,
CF₃,
45 CF₂CF₃,
CHO,
OCOR,
B(OH)₂,
NH(CH₂)_pCO₂R,
50 S(CH₂)_pCO₂R,
O(CH₂)_pCO₂R,
O(CH₂)_pOR,
NH(CH₂)_pOR, and
S(CH₂)_pOR;
55 wherein R and R₁ are each independently selected
from
hydrogen,
alkyl of from 1 to 6 carbon atoms,
alkenyl of from 2 to 7 carbon atoms,
60 alkynyl of from 2 to 7 carbon atoms,
cycloalkyl of from 3 to 8 carbon atoms,
phenyl or benzyl wherein the phenyl or benzyl
ring is substituted by 1 or more H, methoxy,
and methylenedioxy substituents;
65 R_d is H, CO₂R, CO₃R, PO₄H, B(OH)₂, CONRR₁, SO₂NRR₁,
C(O)NHSO₂R₁, , or  ;
n is an integer of from 0 to 2;
70 p is an integer of from 1 to 4;



-74-

--- indicates a single or double bond; and
X is $(\text{CH}_2)_n$, O, NR, or $\text{S}(\text{O})_n$.

2. A compound according to Claim 1 wherein

R_2 is $(\text{CH}_2)_n$ -, alkyl of from 1 to 5 carbons, or $(\text{CH}_2)_n$ -cycloalkyl of from 5 to 7 carbons;

R_a and R_c are each 1 to 5 substituents and R_b is 1 to 4 substituents selected from:

hydrogen,

alkyl of from 1 to 3 carbons,

methylenedioxy,

ethylenedioxy,

OH,

methoxy,

propyloxy,

benzyloxy,

Cl, Br, F, I

$\text{O}(\text{CH}_2)_n$ -cycloalkyl of from 3 to 8 carbon atoms,

$\text{O}(\text{CH}_2)_p\text{CO}_2\text{H}$,

R_d is CO_2H ,

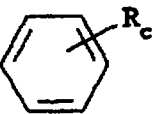
n is an integer of from 0 to 1,

p is an integer of from 1 to 4,

--- indicates a double bond, and

X is $(\text{CH}_2)_n$, NH, S, SO, or SO_2 .

3. A compound according to Claim 1 wherein

R_2 is $(\text{CH}_2)_n$ -, alkyl of from 1 to 5 carbons, or $(\text{CH}_2)_n$ -cycloalkyl of from 5 to 7 carbons;



-75-

- 10 R_a and R_c are each independently 1 to 5 substituents selected from, hydrogen, methoxy, OH, and Cl;
 R_b is independently 1 to 5 substituents selected from hydrogen, methoxy, propyloxy, OH, and Cl;
 R_a , R_b , R_c may also independently be 0 to 2 methylenedioxy or ethylenedioxy substituents,
15 R_d is CO_2H ,
 n is 0 or 1,
--- indicates a double bond, and
 X is $(\text{CH}_2)_n$ or S.
4. A compound according to Claim 1 and selected from
4-Benzo[1,3]dioxol-5-yl-2-methyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
5 4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
4-Benzo[1,3]dioxol-5-yl-2-benzyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
10 acid,
4-Benzo[1,3]dioxol-5-yl-2-(4-methoxy-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
4-Benzo[1,3]dioxol-5-yl-1,1-dioxo-2-(3,4,5-trimethoxy-benzyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
15 4-Benzo[1,3]dioxol-5-yl-2-(2-carboxymethoxy-4-methoxy-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
20 4-Benzo[1,3]dioxol-5-yl-2-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,



- 76 -

- 25 4-Benzo[1,3]dioxol-5-yl-2-(7-methoxy-benzo[1,3]dioxol-5-ylmethyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 30 2-Benzo[1,3]dioxol-5-ylmethyl-4-(3,4-dimethoxy-phenyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 35 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-4-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 40 N-(4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carbonyl)-benzenesulfonamide,
- 45 2-Benzo[1,3]dioxol-5-yl-4-(3-methoxy-phenyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid.,
- 50 4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid.,
- 55 4-Benzo[1,3]dioxol-5-yl-2-benzo[1,3]dioxol-5-ylmethyl-6-methoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 8-Benzo[1,3]dioxol-5-yl-6-benzo[1,3]dioxol-5-ylmethyl-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-7-carboxylic acid,
- 2,4-Bis-benzo[1,3]dioxol-5-yl-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 2,4-Bis-benzo[1,3]dioxol-5-yl-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 4-Benzo[1,3]dioxol-5-yl-2-(2-chloro-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,



- 77 -

- 60 2-Benzo[1,3]dioxol-5-ylmethyl-4-(4-chloro-
2,6-dimethoxy-phenyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
4-(Benzo[1,3]dioxol-5-yl)-2-isobutyl-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
65 3-carboxylic acid,
2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-yl)-6-methoxy-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
70 5-yl)-7-methoxy-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
6-Benzo[1,3]dioxol-5-yl-8-(benzo[1,3]dioxol-
5-yl)-5,5-dioxo-5,6-dihydro-1,3-dioxo-5 λ^6 thia-
6-aza-cyclopenta[b]naphthalene-7-carboxylic acid,
75 2-Benzo[1,3]dioxol-5-ylmethyl-4-(2,3-dihydro-
benzo[1,4]dioxin-6-yl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
4-(Benzo[1,3]dioxol-5-yl)-2-(2,3-dihydro-
benzo[1,4]dioxin-6-ylmethyl)-1,1-dioxo-1,2-di-
80 hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
and
4-(Benzo[1,3]dioxol-5-yl)-2-cyclohexylmethyl-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid.
5. A compound according to Claim 1 and selected from
4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-methyl-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,
5 2-Benzo[1,3]dioxol-5-ylmethyl-
4-(benzo[1,3]dioxol-5-ylsulfanyl)-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid,



-78-

- 10 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-benzyl-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,
- 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-
2-(4-methoxy-benzyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 15 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-1,1-dioxo-
2-(3,4,5-trimethoxy-benzyl)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-
2-(carboxymethoxy-4-methoxy-benzyl)-1,1-dioxo-
20 1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid,
- 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-
2-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
25 3-carboxylic acid,
- 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-
2-(7-methoxy-benzo[1,3]dioxol-5-ylmethyl)-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid.,
- 30 2-Benzo[1,3]dioxol-5-ylmethyl-
4-(3,4-dimethoxy-phenylsulfanyl)-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid,
- 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-
35 4-(3,4,5-trimethoxy-phenylsulfanyl)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
- N-(4-Benzo[1,3]dioxol-5-ylsulfanyl)-
2-benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carbonyl)-
40 benzenesulfonamide.,
- 2-Benzo[1,3]dioxol-5-ylmethyl-4-(3-methoxy-
phenylsulfanyl)-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,



- 79 -

- 2-Benzo[1,3]dioxol-5-ylmethyl-
45 4-(benzo[1,3]dioxol-5-ylsulfanyl)-6,7-dimethoxy-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid.,
2-Benzo[1,3]dioxol-5-ylmethyl-
4-(benzo[1,3]dioxol-5-ylsulfanyl)-6-methoxy-
50 1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,
6-Benzo[1,3]dioxol-5-ylmethyl-
8-(benzo[1,3]dioxol-5-ylsulfanyl)-5,5-dioxo-
5,6-dihydro-1,3-dioxo-5 λ^6 -thia-6-aza-
55 cyclopenta[b]naphthalene-7-carboxylic acid,
4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-isobutyl-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,
2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-
60 1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-6-methoxy-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
65 2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-7-methoxy-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
6-Benzo[1,3]dioxol-5-yl-8-(benzo[1,3]dioxol-
5-ylsulfanyl)-5,5-dioxo-5,6-dihydro-1,3-dioxo-
70 5 λ^6 thia-6-aza-cyclopenta[b]naphthalene-
7-carboxylic acid,
2-Benzo[1,3]dioxol-5-ylmethyl-4-(2,3-dihydro-
benzo[1,4]dioxin-6-ylsulfanyl)-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
75 acid,
4-(Benzo[1,3]dioxol-5-ylsulfanyl)-
2-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-
3-carboxylic acid,



-80-

- 80 4-(Benzo[1,3]dioxol-5-ylsulfanyl)-
2-cyclohexylmethyl-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-1,1-dioxo-1,2-dihydro-
85 1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid, and
2-Benzo[1,3]dioxol-5-yl-4-(benzo[1,3]dioxol-
5-ylsulfanyl)-6,7-dimethoxy-1,1-dioxo-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
4-(Benzo[1,3]dioxol-5-ylsulfanyl)-2-
90 (2-chloro-benzyl)-1,1-dioxo-1,2-dihydro-1 λ^6 -benzo-
[e][1,2]thiazine-3-carboxylic acid,
2-Benzo[1,3]dioxol-5-ylmethyl-4-(4-chloro-
2,6-dimethoxy-phenylsulfanyl)-1,1-dioxo-1,2-di-
hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid,
95 and
2-(2-Benzo[1,3]dioxol-5-ylmethyl)-
4-(benzo[1,3]dioxol-5-ylsufinyl)-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid.
6. A compound named
2-Methyl-1,1-dioxo-4-(trifluoro-methane-
sulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thia-
zine-3-carboxylic acid methyl ester,
5 2-Benzo[1,3]dioxol-5-ylmethyl-1,1-dioxo-
4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
ester,
2-Benzyl-1,1-dioxo-4-(trifluoro-methane-
sulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thia-
zine-3-carboxylic acid methyl ester,
10 2-(4-Methoxy-benzyl)-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester,



- 15 1,1-Dioxo-4-(trifluoro-methanesulfonyloxy)-
2-(3,4,5-trimethoxy-benzyl)-1,2-dihydro-1 λ^6 -benzo-
[e][1,2]thiazine-3-carboxylic acid methyl ester,
2-(2-Ethoxycarbonyl-methoxy-4-methoxy-
benzyl)-1,1-dioxo-4-(trifluoro-methane-sulfonyl-
20 oxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carb-
oxylic acid methyl ester,
2-(6-Chloro-benzo[1,3]dioxol-5-ylmethyl)-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
25 acid methyl ester,
2-(7-Methoxy-benzo[1,3]dioxol-5-ylmethyl)-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-di-
hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,
30 2-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-di-
hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,
2-Benzo[1,3]dioxol-5-ylmethyl-6-methoxy-
35 1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-di-
hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,
6-Benzo[1,3]dioxol-5-ylmethyl-5,5-dioxo-
8-(trifluoro-methanesulfonyloxy)-5,6-dihydro-
40 1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-
7-carboxylic acid methyl ester,
2-Benzo[1,3]dioxol-5-ylmethyl-7-methoxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
45 acid methyl ester,
2-Benzo[1,3]dioxol-5-ylmethyl-6-propyloxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-di-
hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,



- 50 2-Benzo[1,3]dioxol-5-ylmethyl-7-propyloxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-di-
hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,
- 55 2-Benzo[1,3]dioxol-5-ylmethyl-7-benzyloxy-
6-methoxy-1,1-dioxo-4-(trifluoro-methane-sulfonyl-
oxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carb-
oxylic acid methyl ester,
- 60 2-Benzo[1,3]dioxol-5-ylmethyl-6-benzyloxy-
7-methoxy-1,1-dioxo-4-(trifluoro-methane-sulfonyl-
oxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carb-
oxylic acid methyl ester,
- 65 2-Benzo[1,3]dioxol-5-ylmethyl-6,7,8-tri-
methoxy-1,1-dioxo-4-(trifluoro-methane-sulfonyl-
oxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carb-
oxylic acid methyl ester,
- 70 2-Benzo[1,3]dioxol-5-ylmethyl-5,6,7,8-tetra-
methoxy-1,1-dioxo-4-(trifluoro-methane-sulfonyl-
oxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carb-
oxylic acid methyl ester,
- 75 2-Cyclohexylmethyl-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e]-
[1,2]thiazine-3-carboxylic acid methyl ester,
- 2-Cyclopentylmethyl-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester,
- 80 2-(2-Chloro-benzyl)-1,1-dioxo-4-(trifluoro-
methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-
thiazine-3-carboxylic acid methyl ester,
- 2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-1,2-di-
hydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid
methyl ester,
- 85 2-Benzo[1,3]dioxol-5-yl-1,1-dioxo-4-(tri-
fluoro-methanesulfonyloxy)-1,2-dihydro-1 λ^6 -benzo-
[e][1,2]thiazine-3-carboxylic acid methyl ester,



- 2-Benzo[1,3]dioxol-5-yl-6,7-dimethoxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid methyl ester,
- 90 2-Benzo[1,3]dioxol-5-yl-6-methoxy-1,1-dioxo-
4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
ester,
- 95 2-Benzo[1,3]dioxol-5-yl-7-methoxy-1,1-dioxo-
4-(trifluoro-methanesulfonyloxy)-1,2-dihydro-
1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic acid methyl
ester,
- 100 2-Benzo[1,3]dioxol-5-yl-6-propyloxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid methyl ester,
- 105 2-Benzo[1,3]dioxol-5-yl-7-propyloxy-
1,1-dioxo-4-(trifluoro-methanesulfonyloxy)-
1,2-dihydro-1 λ^6 -benzo[e][1,2]thiazine-3-carboxylic
acid methyl ester,
- 110 6-Benzo[1,3]dioxol-5-yl-5,5-dioxo-
8-(trifluoro-methanesulfonyloxy)-5,6-dihydro-
1,3-dioxo-5 λ^6 -thia-6-aza-cyclopenta[b]naphthalene-
7-carboxylic acid methyl ester,
- 115 2-Isobutyl-1,1-dioxo-4-(trifluoro-methane-
sulfonyloxy)-1,2-dihydro-1 λ^6 -benzo[e][1,2]-thia-
zine-3-carboxylic acid methyl ester,
- (5,6,7-Trimethoxy-1,1,3-trioxo-1,3-dihydro-
1 λ^6 -benzo[d]isothiazol-2-yl)-acetic acid methyl
ester,
- 120 2-Benzo[1,3]dioxol-5-yl-5,6-dimethoxy-
1,1-dioxo-1,2-dihydro-1 λ^6 -benzo[d]isothiazol-
3-one, or
- 2-Benzo[1,3]dioxol-5-yl-1,1-dioxo-
1,2-dihydro-1 λ^6 -benzo[d]isothiazol-3-one.



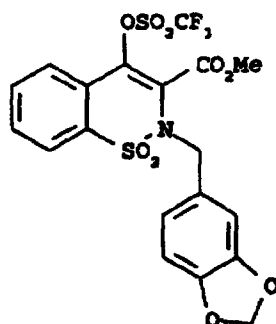
-84-

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in admixture with a pharmaceutically acceptable carrier.
8. A method of inhibiting elevated levels of endothelin comprising administering to a host in need thereof a therapeutically effective amount of a compound of Claim 1 in unit dosage form.
9. A method of treating subarachnoid hemorrhage comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Claim 1 in unit dosage form.
- 5 10. A method of treating essential, renovascular, malignant and pulmonary hypertension comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Claim 1 in unit dosage form.
11. A method of treating congestive heart failure comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Claim 1 in unit dosage form.
- 5 12. A method of treating cerebral ischemia or cerebral infarction comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Claim 1 in unit dosage form.

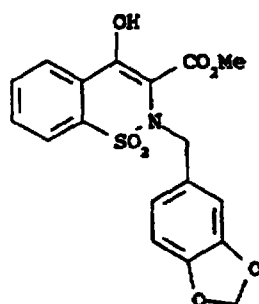


-85-

13. A process of the preparation of key intermediate

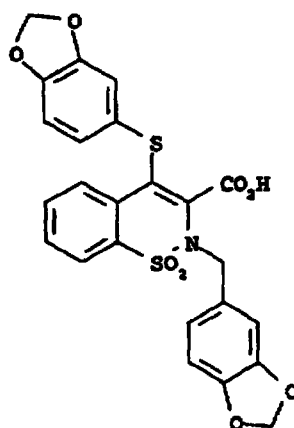


which comprises treating



with trifluoromethanesulphonic anhydride and pyridine in methylene chloride at room temperature for about 1 hour.

14. Process for the preparation of



which comprises adding sodium (3,4-methylenedioxy)phenyl thiolate to a solution of

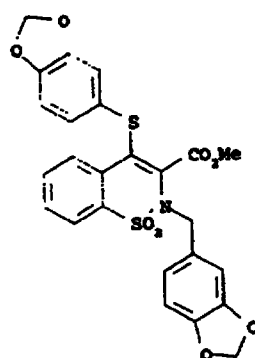
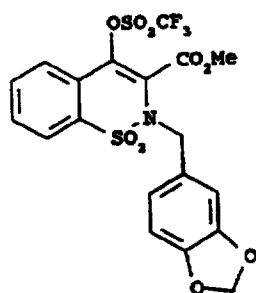


WO 96/26195

PCT/US96/01093

-86-

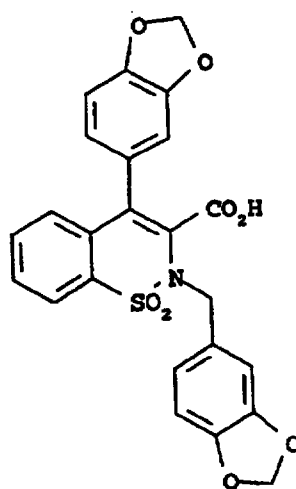
in DMF, isolating the adduct



25

30 by chromatography, and saponifying it with aqueous lithium hydroxide.

15. A process for the preparation of a compound



10

15



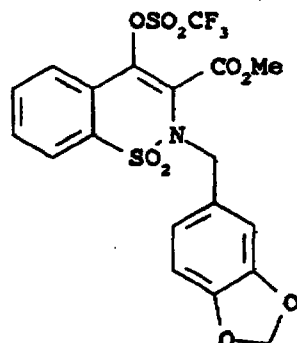
WO 96/26195

PCT/US96/01093

- 87 -

20

which comprises coupling



with

25

(3,4-methylenedioxy)phenyl boronic acid mediated by palladium and isolating the adduct produced by chromatography and saponifying it with aqueous lithium hydroxide.

9704849-0

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 279/02, 417/04, 417/06, 417/12, 417/14, 275/06, A61K 31/54	A1	(11) International Publication Number: WO 96/26195 (43) International Publication Date: 29 August 1996 (29.08.96)
(21) International Application Number: PCT/US96/01093 (22) International Filing Date: 26 January 1996 (26.01.96) (30) Priority Data: 08/393,143 / 21 February 1995 (21.02.95) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors: BERRYMAN, Kent, Alan; 3211 Mc Comb, Ann Arbor, MI 48108 (US). BUNKER, Amy, Mac; 2341 Woodridge Way #2B, Ypsilanti, MI 48197 (US). DOHERTY, Annette, Marian; 106 Tulip Tree Court, Ann Arbor, MI 48103 (US). EDMUNDS, Jeremy, John; 3957 Beech Drive, Ypsilanti, MI 48197 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.	(81) Designated States: AM, AU, BG, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG SI, SK, TJ, UA, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>	
(54) Title: BENZOTHAIAZINE DIOXIDES AS ENDOTHELIN ANTAGONISTS (57) Abstract Novel benzothiazine dioxides which are antagonists of endothelin are described, as well as novel intermediates used in their preparation, methods for the preparation, and pharmaceutical compositions of the same, which are useful in treating elevated levels of endothelin, essential renovascular malignant and pulmonary hypertension, cerebral infarction, cerebral ischemia, congestive heart failure, and subarachnoid hemorrhage.		