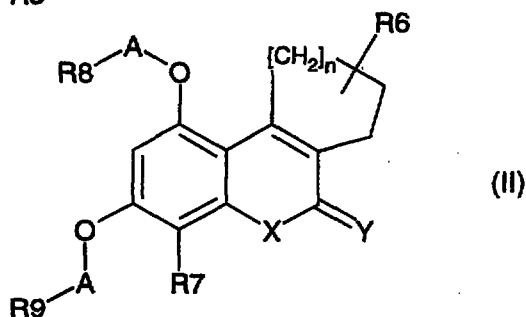
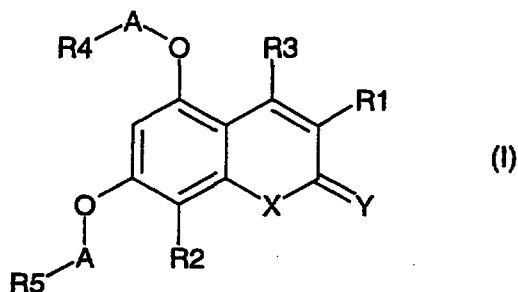


BIETHERS OF 1-OXA, AZA AND THIANAPHTHALEN-2-ONES AS PHOSPHOLAMBAN INHIBITORS

The present invention relates to new therapeutically active compounds and salts and esters thereof as well as new intermediates. The invention also relates to pharmaceutical compositions containing these compounds as active ingredients. The compounds of the invention have phospholamban inhibiting properties and are useful in the treatment of heart failure and stunned myocardium.

Compounds of the present invention have the structure represented by formulae (I) or (II):



in which

R₁ is hydrogen, alkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl, halogenalkyl, alkoxy, COR₁₀, CONR₁₀R₁₁, OR₁₀, S(O)_mR₁₀, NR₁₀COR₁₁ or NR₁₀R₁₁, where R₁₀ is hydrogen, alkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl, halogenalkyl, alkoxy or hydroxy and R₁₁ is hydrogen, alkyl, aryl, arylalkyl, alkoxy, aryloxy, hydroxy or acyl, or in case where X is NR₁₁, can R₁ also be carboxylalkyl,

R₆ is hydrogen, alkyl, alkenyl, aryl, arylalkyl,

R₂ and R₇ mean hydrogen, alkyl, aryl, arylalkyl, alkenyl, COR₁₀, CONR₁₀R₁₁, halogen, trifluoromethyl, nitro or cyano, where R₁₀ and R₁₁ are defined as above,

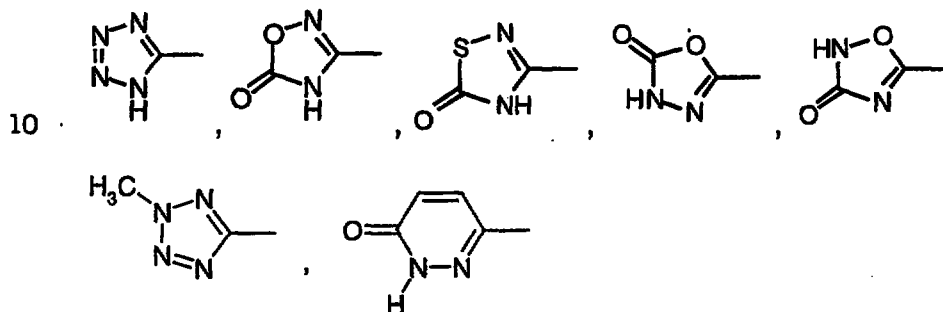
R₃ is hydrogen, alkyl, aryl or arylalkyl,

- 5 A means alkyl or substituted alkyl,
m is 0-2 and n is 1-3,

Y means O, NR₁₁ or S, where R₁₁ is the same as above,

X means O, NR₁₁ or S, where R₁₁ is the same as above,

R₄, R₅, R₈ and R₉ mean independently one of the following groups:



- or in case where X is NR₁₁, can R₄, R₅, R₈ and R₉ also
15 independently mean HOOC-, R₁₂OOC-, H₂NCO- or HOHNCO- wherein
R₁₂ means alkyl, arylalkyl or aryl,
and wherein each aryl residue defined above by itself or as part of another
group may be substituted,
and pharmaceutically acceptable salts and esters thereof.

- 20 In one class of preferred compounds and pharmaceutically acceptable
salts and esters thereof are compounds of formula (I) wherein R₂ is
hydrogen. In a subclass of this class of compounds and pharmaceutically
acceptable salts and esters thereof R₁ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl,
C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ halogenalkyl or C₁₋₆
25 alkoxy. In a group of this subclass of compounds and pharmaceutically
acceptable salts and esters thereof, Y is O or S, preferably O; and X is O. In
another group of this subclass of compounds and pharmaceutically
acceptable salts and esters thereof, Y is O or S, preferably O; and X is
NR₁₁, where R₁₁ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl, C₁₋₆
30 alkoxy, C₆₋₁₀ aryloxy, hydroxy, C₁₋₆ alkanoyl or C₁₋₆ carboxyalkyl. In a
subgroup of these group of compounds and pharmaceutically acceptable
salts and esters thereof, R₃ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, or C₇₋₁₂
arylalkyl, preferably C₁₋₆ alkyl, most preferably methyl. In a family of these

subgroups of compounds and pharmaceutically acceptable salts and esters thereof, A is preferably straight-chain or branched C₁₋₄ alkylene.

In another preferred class of compounds and pharmaceutically acceptable salts and esters thereof, compounds have formula (II) wherein
5 R₇ is hydrogen. In a subclass of this class of compounds and pharmaceutically acceptable salts and esters thereof R₆ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl; and n is 1, 2 or 3, preferably 1 or 2. In a group of this subclass of compounds and pharmaceutically acceptable salts and esters thereof, Y is O or S, preferably O; and X is O. In another group of
10 this subclass of compounds and pharmaceutically acceptable salts and esters thereof, Y is O or S, preferably O; and X is NR₁₁, where R₁₁ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl, C₁₋₆ alkoxy, C₆₋₁₀ aryloxy, hydroxy, C₁₋₆ alkanoyl or C₁₋₆ carboxyalkyl. In a subgroup of these group of compounds and pharmaceutically acceptable salts and esters
15 thereof, A is preferably straight-chain or branched C₁₋₄ alkylene.

Each aryl residue in each of these preferred classes of compounds, by itself or as part of another group, may be substituted by 1 to 3, preferably 1 or 2, most preferably one of fluorine, chlorine, bromine, iodine, trifluoromethyl, amino, C₁₋₄ alkyl, C₁₋₄ alkoxy, phenyl, naphthyl, halophenyl,
20 halonaphthyl, benzyl, phenethyl, halobenzyl, halophenethyl, naphthylmethyl, naphthylethyl, C₄₋₇ cycloalkyl, C₁₋₄ alkyl (C₄₋₇)cycloalkyl, hydroxy, mono-(C₁₋₄)alkylamino, di-(C₁₋₄)alkylamino, C₁₋₆ alkanoylamino, phenylcarbonylamino, naphthylcarbonylamino nitro, cyano, thiol, or C₁₋₆ alkylthio.

25 Brief description of the drawings

FIG. 1A shows the effect of the compound of Example 1c (50 and 100 μ M) on the Ca²⁺ uptake rate into the cardiac muscle SR vesicles.

FIG. 1B shows the effect of the compound of Example 1c (50 and 100 μ M) on the Ca²⁺ uptake rate into the fast skeletal muscle SR vesicles.

30 FIG. 2A shows the development of stunned myocardium and the subsequent decrease in the left ventricular systolic pressure.

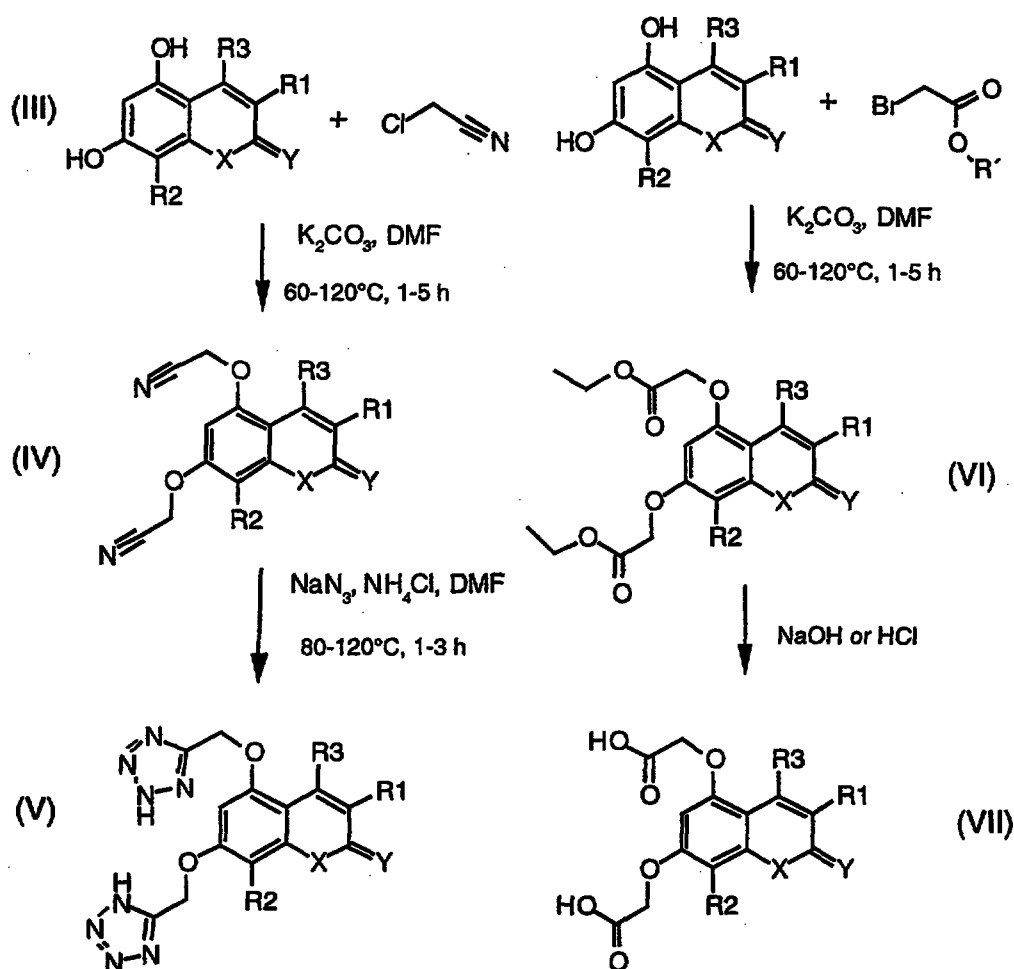
FIG. 2B shows the complete inhibition of the development of stunned myocardium by the compound of Example 8g.

35 The compounds of the invention can be prepared from the 1,3-dihydroxy substituted heteroaromatics by alkylation of the dihydroxy

compounds by suitable alkylating agents, for example by chloroacetonitrile or bromoacetic ester according to the following Scheme 1, wherein R_1 , R_2 , R_3 , X and Y are the same as defined above, R' is a protecting group for the hydroxyl, e.g. methyl, benzyl or tetrahydropyranyl.

5

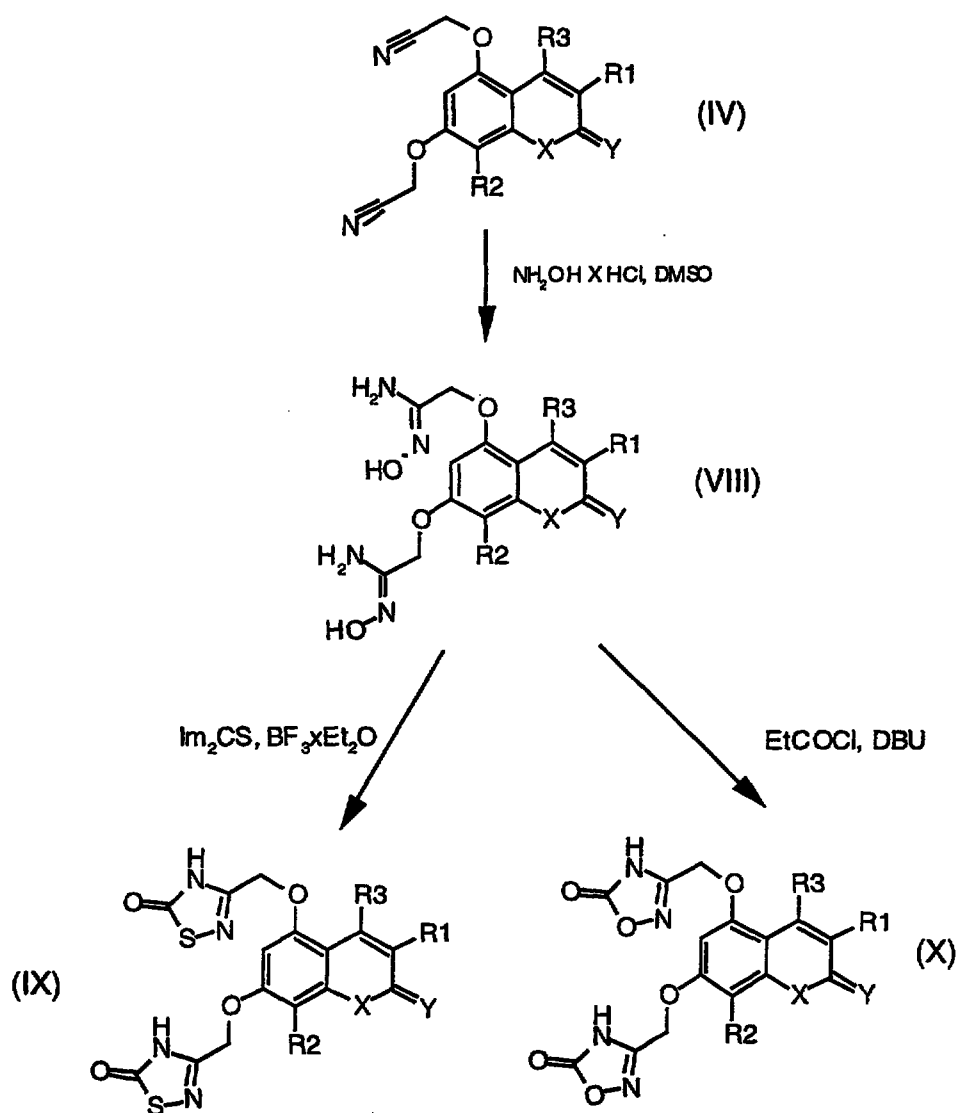
SCHEME 1



10 The cyano compound (IV) described above is used to prepare the 1,2,4-oxadiazole and 1,2,4-thiadiazole derivatives using the methods described in J. Med. Chem. 1996, 39, 5228-5235.

The syntheses are shown in Scheme 2, wherein R_1 , R_2 , R_3 , X and Y are the same as defined above.

SCHEME 2

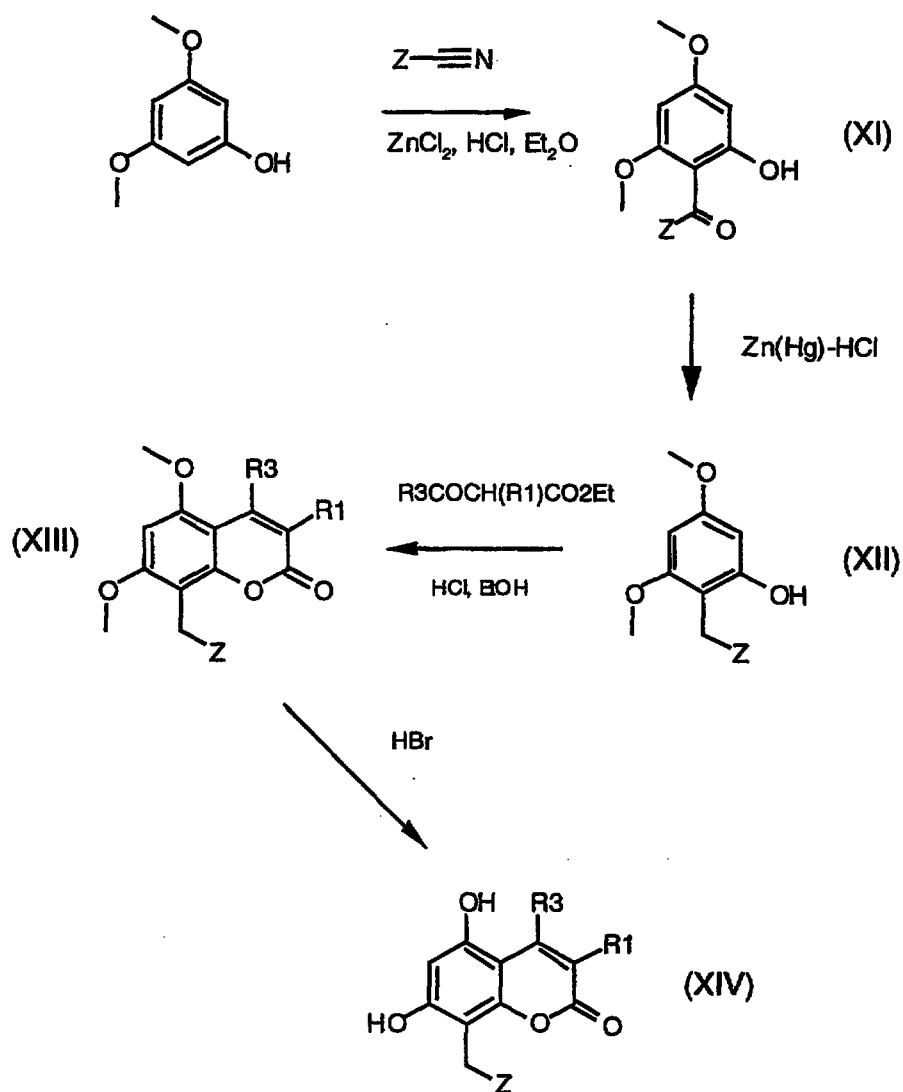


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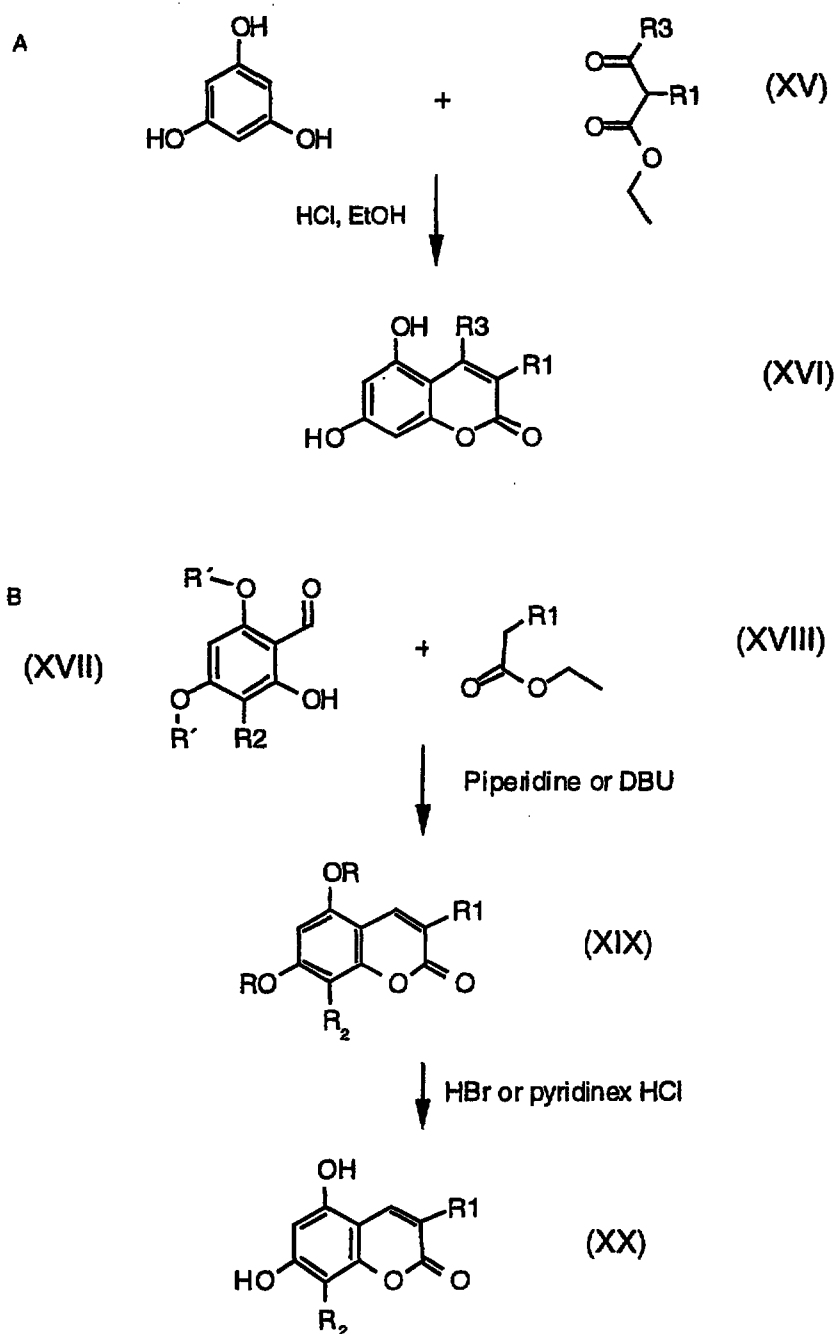
The other heterocyclics as groups R₄, R₅, R₈ and R₉ are prepared as described in Bioorg. Med. Chem. Lett., 1994, 4, 45-50.

The dihydroxyaromatics (III) are made by use of the literature methods. The coumarins (XIV), (XVI) and (XX) are made by the use of the
 10 Knoevenagel condensation or von Pechmann reaction as presented in Scheme 3 and 4, where R₁, R₂ and R₃, are the same as defined above, Z is alkyl, aryl, arylalkyl or alkenyl and R' is a protecting group for the hydroxyls e.g. methyl, benzyl or tetrahydropyranyl.

SCHEME 3.



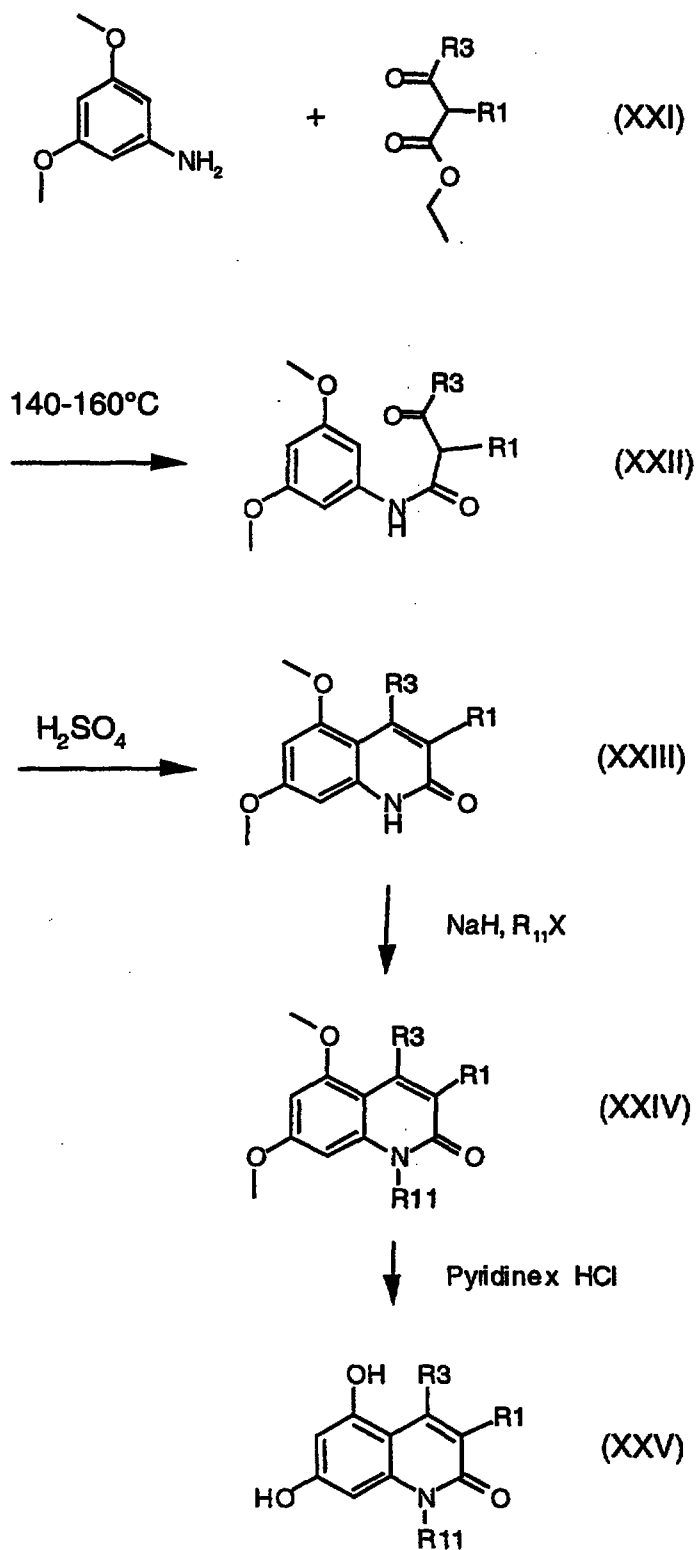
SCHEME 4.



5

The quinolinones are prepared by the Knorr reaction as described in Scheme 5, wherein R₁, R₁₁ and R₃ are the same as defined above, X is a halogen.

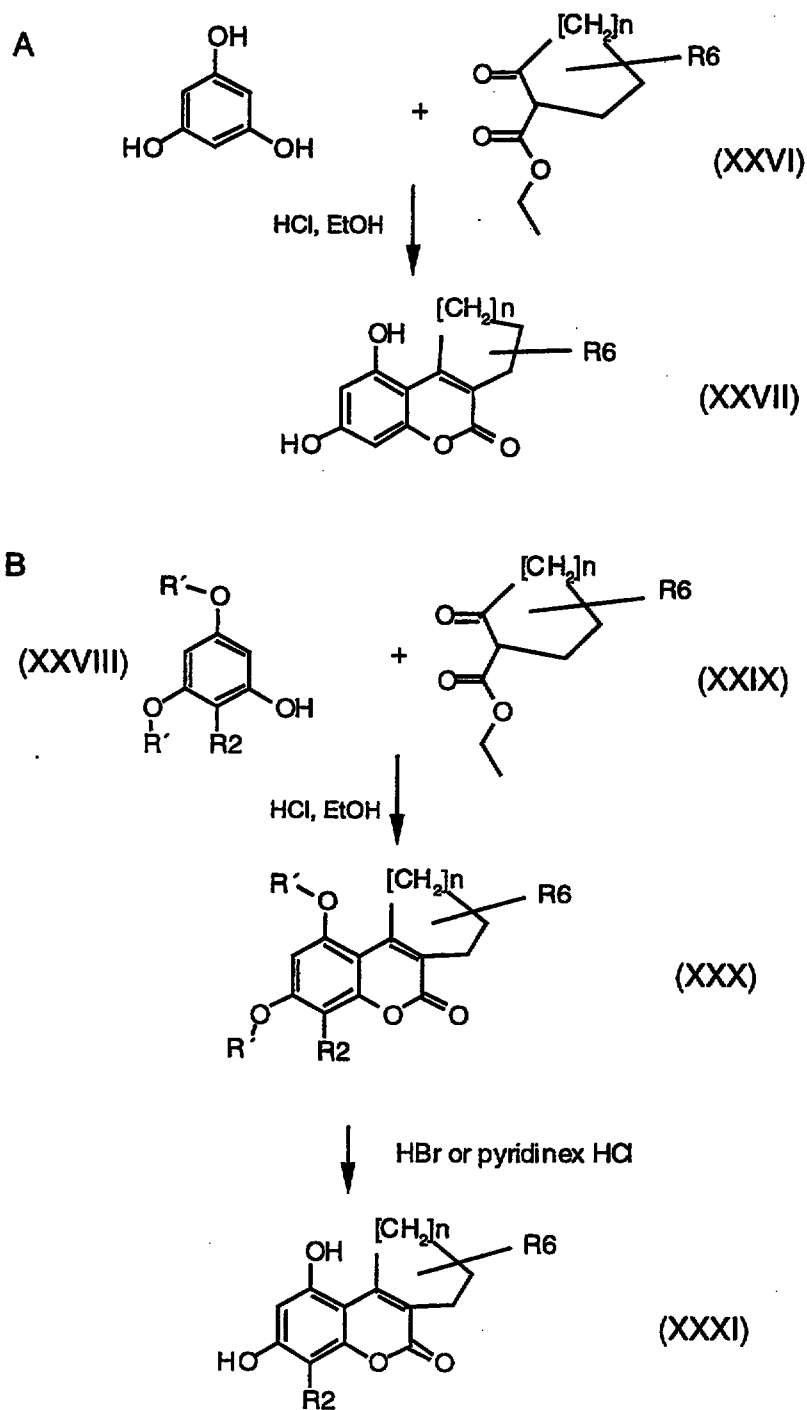
SCHEME 5.



The cyclic compounds (II) can be prepared correspondingly from compound (XXXI) which can be prepared according to the Scheme 6, wherein R₂ and R₆ are the same as defined above, R' is a protecting group for the hydroxyls e.g. methyl, benzyl or tetrahydropyranyl.

5

SCHEME 6.



Cyclic quinolinone compounds (II) can be prepared correspondingly from (XXVI) using Scheme 5.

Salts and esters of the compounds, when applicable, may be prepared by known methods. Physiologically acceptable salts are useful as active medicaments, however, preferred are the salts with alkali or alkaline earth metals. Physiologically acceptable esters are also useful as active medicaments. Examples are the esters with aliphatic or aromatic alcohols.

The term "alkyl" as employed herein by itself or as part of another group includes both straight, branched and cyclized chain radicals of up to 18 carbon atoms, preferably 1 to 8 carbon atoms, most preferably 1 to 4 carbon atoms. The term "lower alkyl" as employed herein by itself or as part of another group includes straight, branched and cyclized chain radicals of 1 to 7, preferably 1 to 4, most preferably 1 or 2 carbon atoms. Specific examples for the alkyl and lower alkyl residues, respectively, are methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, octyl, decyl and dodecyl including the various branched chain isomers thereof.

The term "acyl" as employed herein by itself or as part of another group refers to an alkylcarbonyl or alkenylcarbonyl group, the alkyl and alkenyl groups being defined above.

The term "aryl" as used herein by itself or as part of another group refers to a monocyclic or bicyclic group containing from 6 to 10 carbon atoms in the ring portion. Specific examples for aryl groups are phenyl, naphthyl and the like. "Aroyl" means in a corresponding way an arylcarbonyl group.

The term "alkoxy" as employed herein by itself or as part of another group includes an alkyl group as defined above linked to an oxygen atom. "Aryloxy" means in a corresponding way an aryl group linked to an oxygen atom.

The term "substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine or trifluoromethyl group, amino, alkyl, alkoxy, aryl, alkyl-aryl, halogen-aryl, cycloalkyl, alkylcycloalkyl, hydroxy, alkylamino, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, or alkylthio substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2, most preferably 1 of the above mentioned substituents.

Compounds of the invention may be administered to a patient in therapeutically effective amounts which range usually from about 0.1 to 500 mg per day depending on the age, weight, condition of the patient, administration route and the phospholamban inhibitor used. The compounds of the invention can be formulated into dosage forms using the principles known in the art. It can be given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, dragees, capsules, suppositories, emulsions, suspensions or solutions. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used. The compositions containing the active compound can be given enterally or parenterally, the oral route being the preferred way. The contents of the active compound in the composition is from about 0.5 to 100 %, preferably from about 0.5 to about 20 %, per weight of the total composition.

EXPERIMENTS

Experiment 1. Effect on calcium uptake into the SR vesicles prepared from cardiac and fast skeletal muscle

The inhibitory effect of a given compound on phospholamban can be demonstrated by measuring the effect of the compound on calcium uptake into the SR vesicles prepared from cardiac tissue and into SR vesicles prepared from fast skeletal muscle (psoas m.). Both kind of SR vesicles contain Ca^{2+} -ATPase but the vesicles from the fast skeletal muscle do not contain phospholamban (Hoh JFY, "Muscle fiber types and function", Current Opinion in Rheumatology, 4:801-808, 1992). An increase in the calcium uptake into the SR vesicles prepared from cardiac tissue but not into the SR vesicles prepared from fast skeletal muscle indicates that the compound relieves the inhibitory effect of phospholamban on SR Ca^{2+} -ATPase and thus acts as a phospholamban inhibitor. Since phospholamban represses both the rates of relaxation and contraction in the mammalian heart through its inhibitory effects on the cardiac SR Ca^{2+} -ATPase, a

compound relieving these effects is potentially useful in the treatment of heart failure.

Method

Guinea pigs (10-12) were decapitated. Their hearts or the psoas
5 muscles were excised, washed in ice-cold 0.9 % NaCl and cut into pieces in
a buffer containing 20 mM Tris-maleate, 0.3 M sucrose, pH 7.0. Thereafter
tissue pieces were homogenized with Polytron and further with Potter (10
strokes). The homogenate was centrifugated at 1000 g for 15 min at 4 °C.
The supernatant was collected and the pellet was resuspended into 5 ml of
10 the buffer (20 mM Tris-maleate, 0.3 M sucrose, pH 7.0) and recentrifugated
at 1000 g for 10 min at 4 °C. The obtained supernatant was combined with
the earlier collected supernatant and centrifugated once again at 10 000 g
for 20 min at 4 °C. The final supernatant was filtered into a bottle equipped
with a magnetic stirrer. KCl was added to the filtered supernatant to achieve
15 the final concentration of 0.6 M (at 4 °C). The obtained solution was
centrifugated at 100 000 g for 60 min at 4 °C. The pellet was suspended in 5
ml of the buffer containing 20 mM Tris-maleate, 0.3 M sucrose, pH 7.0 and
centrifugated at 100 000 g for 60 min at 4 °C. The obtained pellet was
suspended in 5 ml of buffer containing 20 mM Tris-maleate, 0.3 M sucrose,
20 0.1 M KCl, pH 7.0 and stored at -80 °C until use. The protein concentration
was also measured in order to standardise the separately prepared vesicle
preparations.

In the calcium uptake assay, the fluorescent indicator, fluo-3 was
used to detect the decrease of the extravesicular Ca^{2+} -concentration, when
25 the SR Ca^{2+} -ATPase was transferring Ca^{2+} from the extravesicular space
into the SR-vesicles.

The SR-vesicles obtained above (50 µg protein/ml) were pre-
incubated with or without the test compound at 37 °C for 5 min in the assay
buffer containing 40 mM imidazole, 95 mM KCl, 5 mM NaN_3 , 5 mM MgCl_2 ,
30 0.5 mM EGTA, 5 mM potassium oxalate, 2 µM ruthenium red, 5 µM fluo-3,
pH 7.0. The free calcium was adjusted to 0.1 µM or to 0.04 µM by CaCl_2 .
The reaction was initiated by adding ATP (5 mM). The final reaction volume
was 1.5 ml. The fluorescence of reaction mixture was measured for 3 min by
using the excitation and emission wavelengths of 510 nm and 530 nm,
35 respectively.

Results

Figures 1A and 1B show the effect of the compound of Example 1c (50 and 100 μM) on the Ca^{2+} uptake rate into the cardiac (A) and fast skeletal muscle (B) SR vesicles. It can be seen that the compound of the invention accelerated the calcium uptake into the cardiac SR vesicles but did not change the calcium uptake into the SR vesicle prepared from the fast skeletal muscle.

Table 1 shows the effects of various other phospholamban inhibitors of formula (I) or (II) on the Ca^{2+} uptake rate into the cardiac (A) and fast skeletal muscle (B) SR vesicles. The experiments were carried out at 0.1 μM and 0.04 μM free calcium concentrations, respectively.

TABLE 1. Stimulation (%) of the Ca^{2+} uptake into the vesicle preparations obtained from the ventricular myocardium (A) and fast skeletal muscle (B) of the guinea-pig heart.

	Compound of Example No. (100 μM)	The stimulation (%) of Ca^{2+} uptake	
		A	B
20	3c**	51	0
	2c	26	-1
	7c	5	-17
	8g*	18	0
25	11b	28	nd
	12	32	nd
	13d***	23	nd
	14c*	18	nd
	18e	13	nd
30	21	11	nd
	23****	20	nd

*10 μM , **20 μM , ***50 μM , ****5 μM

nd=not determined

Experiment 2. The effects on the left ventricular pressure derivatives

Method

Guinea-pigs of either sex weighing 300-400 g were used in the study. After the guinea-pig was sacrificed by a blow on the skull and decapitated the heart was rapidly excised. The heart was then rinsed in cold oxygenated perfusion buffer. A cannula was inserted into the aorta and secured with a ligature. Retrograde perfusion began as soon as the heart was placed in a thermostatically controlled moist chamber of the Langendorff apparatus. Modified Tyrode solution (37 °C), equilibrated in a thermostatically controlled bulb oxygenator with carbogen (95 % O₂ and 5% CO₂) was used as a perfusion buffer. The composition of the Tyrode solution was (in mM): NaCl 135; MgCl₂ x 6H₂O 1; KCl 5; CaCl₂ x 2H₂O 2; NaHCO₃ 15; Na₂HPO₄ x 2H₂O 1; glucose 10; pH 7.3-7.4. The experiments were carried out under constant pressure condition (50 mmHg). After a short prestabilization (10 min) a latex balloon (size 4) was carefully placed into the left ventricle through the left pulmonary vein and the left atrium. The latex balloon was attached to a stainless-steel cannula coupled with a pressure transducer. The latex balloon, the cannula and the chamber of the pressure transducer were filled with ethylene glycol / water (1:1) mixture avoiding any air-bubble. The isovolumetric left ventricular pressure was recorded through the pressure transducer. At the beginning of the experiment, the volume of the balloon was adjusted to obtain a diastolic pressure of approximately 5 mmHg. Before starting the experiment, the heart was allowed to stabilise further for 30 - 50 min with vehicle (0.1% DMSO) in the perfusion buffer.

After 15 min baseline recording various concentrations of the test compound were added to the perfusion buffer at 15 min intervals. The concentration range of 0.3 - 30 µM was tested. The vehicle concentration (0.1% DMSO) was kept constant throughout the experiment.

Results

The EC₅₀ values and maximum effects (% change from baseline) of various compounds of the invention on left ventricular systolic pressure are given in Table 2.

TABLE 2. The EC₅₀ values and maximum effects (% change from baseline) on left ventricular systolic pressure.

5	Compound of Example No.	EC ₅₀ (μ M)	maximum effect (%)
	1c	9	+52 at 30 μ M
	3c	4	+63 at 10 μ M
10	5c	>10	+14 at 30 μ M
	6c	0.5	+25 at 10 μ M
	7c	2.5	+29 at 10 μ M
	8g	2	+64 at 10 μ M
	9d	5	+50 at 30 μ M
15	12	5	+22 at 10 μ M
	13d	10	+48 at 30 μ M
	14c	1.5	+25 at 10 μ M
	15c	3	+37 at 10 μ M
	16c	10	+57 at 30 μ M
20	18e	10	+35 at 30 μ M
	19e	6	+39 at 30 μ M

Experiment 3. Effect on the development of stunned myocardium in
25 isolated guinea-pig Langendorff heart

Method

Guinea-pigs of either sex weighing 300-400 g were used in the study. After the guinea-pig was sacrificed by a blow on the skull and decapitated
30 the heart was rapidly excised. The heart was then rinsed in oxygenated perfusion buffer. A cannula was inserted into the aorta and secured with a ligature. Retrograde perfusion began as soon as the heart was placed in a thermostatically controlled moist chamber of the Langendorff apparatus. Modified Tyrode solution (37 °C), equilibrated in a thermostatically controlled
35 bulb oxygenator with carbogen (95 % O₂ and 5% CO₂) was used as a perfusion buffer. The composition of the Tyrode solution was (in mM): NaCl 135; MgCl₂ x 6H₂O 1; KCl 5; CaCl₂ x 2H₂O 2; NaHCO₃ 15; Na₂HPO₄ x 2H₂O 1; glucose 10; pH 7.3-7.4. The experiments were carried out under constant pressure condition (50 mmHg). After a short prestabilization (10
40 min) a latex balloon attached through the stainless-steel cannula to a pressure transducer was carefully placed into the left ventricle through the left pulmonary vein and the left atrium. The latex balloon, the cannula and

the chamber of the pressure transducer were filled with ethylene glycol / water (1:1) mixture avoiding any air-bubble. The isovolumetric left ventricular pressure was recorded through the pressure transducer. At the beginning of the experiment, the volume of the balloon was adjusted to obtain the end-diastolic pressure of approximately 5 mmHg. Before starting the experiment, the spontaneously beating heart was allowed to stabilise further for 30 - 50 min with vehicle (0.1% DMSO) in the perfusion buffer.

After 15 min baseline recordings compound of Example 8g (10 μ M) was added to the perfusion buffer. The heart was 15 min later exposed to the 8 minute period of global ischemia followed by reperfusion. This procedure was then repeated twice at 35 min intervals. Another series of experiments was performed with vehicle instead of compound of Example 8g. The vehicle concentration (0.1% DMSO) was kept constant throughout the experiments. The baseline value was the average of the two minute recordings obtained just before compound of Example 8g or vehicle was added to the perfusion buffer. The preischemia values were the average of the two minute recordings obtained just before each ischemia period and the reperfusion values were the average of the two minute recordings obtained at 8 min during each reperfusion period.

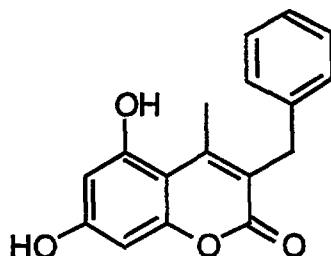
The results are shown in Figures 2 A and B. Figure 2A shows the development of stunned myocardium and the subsequent decrease in the left ventricular systolic pressure in the control group. Figure 2B shows that the phospholamban inhibitor of Example 8g completely inhibited the development of stunned myocardium. Givens are mean $\pm$ SEM of 2-3 experiments.

EXAMPLES

Example 1. Preparation of 3-Benzyl-5,7-bis[(1H-tetrazol-5-yl)-methoxy]-4-methyl-2H-1-benzopyran-2-one

a) 3-Benzyl-5,7-dihydroxy-4-methyl-2H-1-benzopyran-2-one

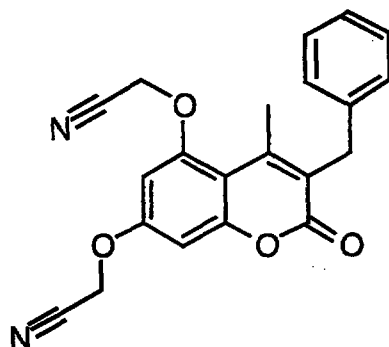
17



A solution of phloroglucinol dihydrate (20 g) and ethyl 2-benzylaceto-
acetate (27.5 ml) in ethanol (320 ml) was treated with dry HCl at 0°C for five
hours and the solution was kept at that temperature overnight. The yellow
5 solution was concentrated and triturated with water, the solids filtered,
washed with water and dried. The resulting hydrate was thrice evaporated to
dryness from toluene, triturated with petroleum ether (bp. 40-60°C) and
filtered. Yield 33,4 g (96 %). Melting point 258-260 °C.

¹H-NMR (DMSO-d₆, 400MHz): 2.525 (s, 3H, CH₃), 3.887 (s, 2 H,
10 CH₂Ph), 6.171 (d, 1H, J = 2,4 Hz), 6.274 (d, 1H, J = 2,4 Hz), 7.167-7.279
(m, 5H, Ph), 10.2 (s, 1H, OH), 10.47 (s, 1H, OH).

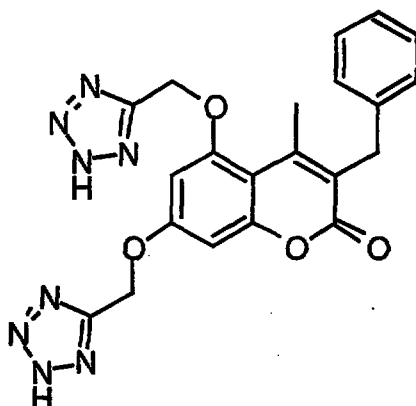
b) 3-Benzyl-5,7-bis(cyanomethoxy)-4-methyl-2H-1-benzopyran-2-one



Chloroacetonitrile (6.86 g), potassium carbonate (23.9 g) and 12.2 g of
15 the product from example 1a were stirred in 120 ml of DMF at 100°C under
nitrogen for two hours. The reaction mixture was cooled and poured into ice
water. The solids were filtered and washed with water. Yield 13.8 g (88 %).
Melting point 147-154°C.

¹H-NMR (DMSO-d₆, 400MHz): 2.525 (s, 3H, CH₃), 3.969 (s, 2H,
20 CH₂Ph), 5.307 (s, 2H, OCH₂CN), 5.314 (s, 2H, OCH₂CN), 6.814 (d, 1 H, J =
2.5 Hz), 6.940 (d, 1H, J = 2.5 Hz), 7.18-7.292 (m, 5H, Ph).

c) 3-Benzyl-5,7-bis[(1*H*-tetrazol-5-yl)methoxy]-4-methyl-2*H*-1-benzopyran-2-one

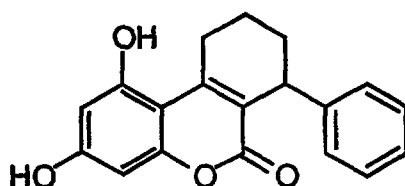


The product from example 1b (1 g), sodium azide (0.42 g) and ammonium chloride (0.34 g) were stirred in DMF (5 ml) under nitrogen at 100 °C for 5 hours. The reaction mixture was allowed to cool down and then poured into ice water. The pH of the solution was adjusted to 10-11 and then the solution either extracted once with ethyl acetate or filtered through CELITE. The solution was acidified to pH 2 with hydrochloric acid, kept at 5°C and filtered. Yield 0.96 g (81 %). Melting point 229-233°C.

¹H-NMR (DMSO-d₆, 400MHz): 2.468 (s, 3H, CH₃), 3.937 (s, 2H, CH₂Ph), 5.596 (s, 2H, OCH₂Tet), 5.602 (s, 2H, OCH₂Tet), 6.832 (d, 1H, J = 2.4 Hz), 6.851 (d, 1H, J = 2.4 Hz), 7.171-7.283 (m, 5H, Ph).

Example 2. Preparation of 7,8,9,10-Tetrahydro-1,3-bis[(1*H*-tetrazol-5-yl)methoxy]-7-phenyl-6*H*-dibenzo[b,d]pyran-6-one

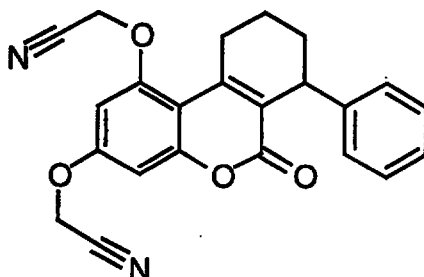
a) 7,8,9,10-Tetrahydro-1,3-dihydroxy-7-phenyl-6*H*-dibenzo[b,d]pyran-6-one



A solution of phloroglucinol (0.7 g) and 2-ethoxycarbonyl-3-phenylcyclohexanone (1.5 g) in ethanol was treated with dry HCl as described in example 1a. The product was first recrystallized from ethanol-water (1:1) and then triturated with ether. Yield 0.61 g.

$^1\text{H-NMR}$ (DMSO- d_6 , 400MHz): 1.38-1.52 (m, 1H), 1.57-1.66 (m, 1H), 1.69-1.78 (m, 1H), 1.86-1.96 (m, 1H), 2.9-3.02 (m, 1H), 3.3-3.4 (m, 1H), 4.050 (b, 1H), 6.157 (d, 1H, $J = 2.4$ Hz), 6.297 (d, 1H, $J = 2.4$ Hz), 7.076-7.265 (m, 5H), 10.153 (s, 1H), 10.456 (s, 1H).

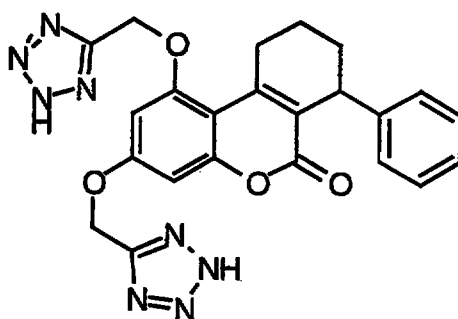
- 5 b) 7,8,9,10-Tetrahydro-1,3-bis(cyanomethoxy)-7-phenyl-6H-dibenzo[b,d]pyran-6-one



- 10 The product from example 2a (0.5 g) was treated with chloroacetonitrile (0.25 g) and potassium carbonate (1.12g) in DMF (5 ml) as described in example 1b. Yield 0.6 g.

$^1\text{H-NMR}$ (DMSO- d_6 , 400MHz): 1.38-1.58 (m, 1H), 1.6-1.7 (m, 1H), 1.7-1.76 (m, 1H), 1.89-1.99 (m, 1H), 2.9-3.03 (m, 1H), 3.2-3.28 (m 1H), 4.111(b, 1H), 5.314 (s, 2H), 5.349 (s, 2H), 6.840 (d, 1H, $J = 2.5$ Hz), 6.925 (d, 1H, $J = 2.5$ Hz), 7.108-7.274 (m, 5H).

- 15 c) 7,8,9,10-Tetrahydro-1,3-bis[(1H-tetrazol-5-yl)methoxy]- 7-phenyl-6H-dibenzo[b,d]pyran-6-one

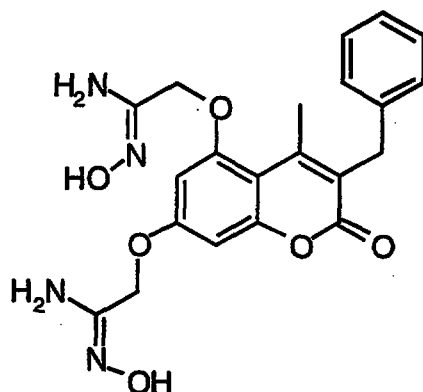


- 20 The product from example 2b (0.6 g) was treated with sodium azide (0.2 g) and ammonium chloride (0.17 g) in DMF (5 ml) as in example 1c. The product was recrystallized from a mixture of DMF, ethanol and water (approximately 1:2:3). Yield 0.41 g. Melting point: 153-154°C.

¹H-NMR (DMSO-d₆, 400MHz): 1.38-1.5 (m, 1H), 1.5-1.6 (m, 1H), 1.69-1.76 (m, 1H), 1.87-1.96 (m, 1H), 2.9-3.05 (m, 1H), 3.2-3.3 (m, 1H), 4.094 (b, 1H), 5.602 (s, 2H), 5.643 (s, 2H), 6.832 (d, 1H, J = 2.3 Hz), 6.851 (d, 1H, J = 2.3 Hz), 7.089-7.212 (m, 5H).

- 5 Example 3. Preparation of 3-Benzyl-5,7-bis[(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)-methoxy]-4-methyl-2H-1-benzopyran-2-one

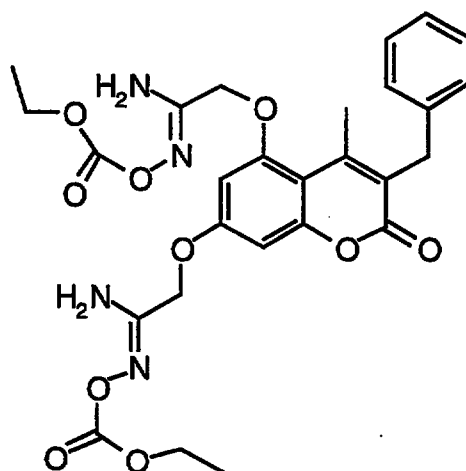
a) 3-Benzyl-5,7-bis[(hydroxyamidino)methoxy]-4-methyl-2H-1-benzopyran-2-one



- 10 Triethylamine (1.94 ml) was added to a suspension of hydroxylamine hydrochloride (0.97 g) in DMSO (2 ml) and the resulting mixture stirred at room temperature for thirty minutes. The crystals were filtered and washed with THF. The filtrate was concentrated and the product from example 1b (0.5 g) added. This solution was kept at 75 °C overnight. The reaction
15 mixture was treated with ice water, the pH adjusted to 11 and the solids filtered, washed with water, and dried. Yield 0.5 g. Melting point: 155-160°C.

- 20 ¹H-NMR (DMSO-d₆, 400MHz): 2.56 (s, 3H, CH₃), 3.938 (s, 2H), 4.466 (s, 2H), 4.486 (s, 2H), 5.565 (s, H, NH₂), 5.709 (s, 2H, NH₂), 6.658 (d, 1H, J = 2.4 Hz), 6.692 (d, 1H, J = 2.4 Hz), 7.168-7.284 (m, 5H, Ph), 9.346 (s, 1H, OH), 9.362 (s, 1H, OH).

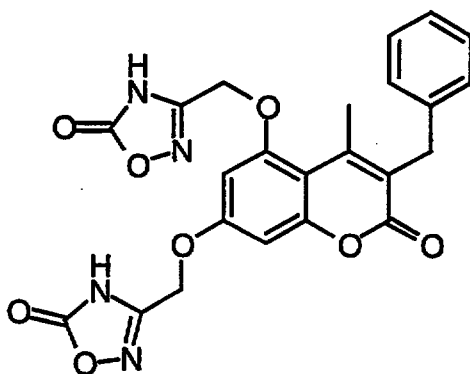
b) 3-Benzyl-5,7-bis[(ethoxycarbonyloxyamidino)methoxy]-4-methyl-2H-1-benzopyran-2-one



Ethyl chloroformate (0.45 ml) was added to a solution of the product from example 3a (1 g) and pyridin (0.38 ml) in DMF (5 ml) at 0°C. The reaction mixture was kept at that temperature for an additional 30 minutes and then ice water added. The solids were filtered and washed with water. Yield 1.63 g. Melting point 87-92°C.

¹H-NMR (DMSO-d₆, 400MHz): 1.215-1.256 (m, 6H), 2.553 (s, 3H), 3.947 (s, 2H), 4.140-4.198 (m, 4H), 4.566 (s, 2H), 4.599 (s, 2H), 6.688 (d, 1H, J = 2.4 Hz), 6.718 (d, 1H, J = 2.4 Hz), 6.792 (b, 2H, NH₂), 6.818 (b, 2H, NH₂), 7.171-7.285 (m, 5H).

c) 3-Benzyl-5,7-bis[(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)-methoxy]-4-methyl-2H-1-benzopyran-2-one



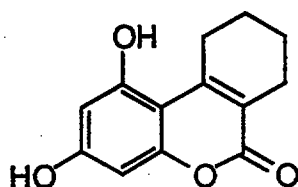
The product from the previous example (1.5 g) and DBU (0.8 ml) in DMF (5 ml) was stirred at room temperature overnight. The reaction mixture was treated with ice water and acidified. The solids were filtered and washed with water. The resulting solid mass was taken in 0.1 N sodium hydroxide

solution, treated with activated carbon and finally acidified. Yield 0.64 g.
Melting point: 130-136°C.

¹H-NMR (DMSO-d₆, 400MHz): 2.524 (s, 3H), 3.954 (s, 2H), 5.187 (s, 2H), 5.215 (s, 2H), 6.748 (d, 1H, J = 2.4 Hz), 6.834 (d, 1H, J = 2.4 Hz),
5 7.158-7.289 (m, 5H), 12.8 (b, 2H).

Example 4. Preparation of 7,8,9,10-Tetrahydro-bis[(1H-tetrazol-5-yl)methoxy]-1,3-dihydroxy-6H-dibenzo[b,d]pyran-6-one

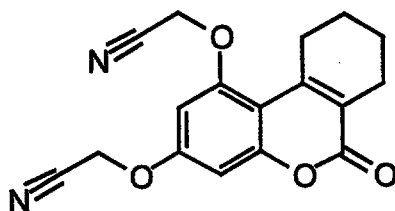
a) 7,8,9,10-Tetrahydro-1,3-dihydroxy-6H-dibenzo[b,d]pyran-6-one



10 Phloroglucinol (1 g) and ethyl 2-oxocyclohexane carboxylate (1.32 g) were stirred in 75 % sulfuric acid (10 ml) overnight, the mixture poured into ice water and filtered. Yield: 1.55 g.

¹H-NMR (DMSO-d₆, 400MHz): 1.65 (b, 4H), 2.345 (b, 2H), 3.037 (b, 2H), 6.138 (d, 1H, J = 2.4 Hz), 6.245 (d, 1H, J = 2.4 Hz), 10.069 (b, 1H, OH),
15 10.322 (s, 1H, OH).

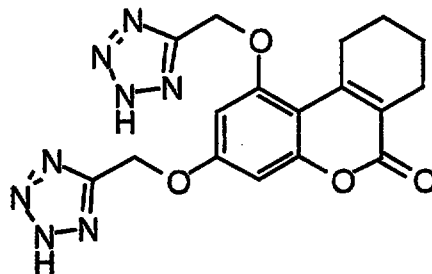
b) 7, 8, 9, 10-Tetrahydro-bis(cyanomethoxy)-1,3-dihydroxy-6H-dibenzo[b,d]pyran-6-one



The product from the previous example (0.5 g), chloroacetonitrile
20 (0.34 g) and potassium carbonate (1.5 g) in DMF (5 ml) were reacted as in example 1b. Yield: 0.44 g.

¹H-NMR (DMSO-d₆, 400MHz): 1.68 (b, 4H), 2.41 (b, 2H), 3.00 (b, 2H), 5.297 (s, 2H), 5.309 (s, 2H), 6.797 (d, 1H, J = 2.4 Hz), 6.899 (d, 1H, J = 2.4 Hz).

c) 7,8,9,10-Tetrahydro-bis[(1*H*-tetrazol-5-yl)methoxy]-1,3-dihydroxy-6*H*-dibenzo[*b,d*]pyran-6-one

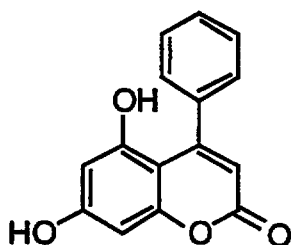


The product from the previous example (0.4 g) was treated with sodium azide (0.18 g) and ammonium chloride (0.14 g) in DMF (2.5 ml) as in example 1c. The product was recrystallized from ethanol-DMF (1:1). Yield 0.17 g. Melting point 283-286°C.

¹H-NMR (DMSO-*d*₆, 400MHz): 1.626 (b, 4H), 2.393 (b, 2H), 2.971 (b, 2H), 5.583 (s, 2H), 5.599 (s, 2H), 6.811 (s, 2H).

Example 5. Preparation of 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-4-phenyl-2*H*-1-benzopyran-2-one

a) 5,7-Dihydroxy-4-phenyl-2*H*-1-benzopyran-2-one

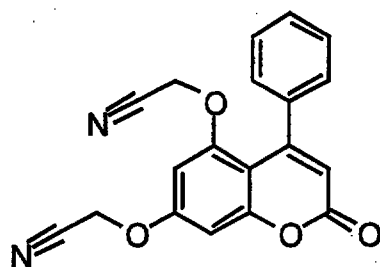


A solution of phloroglucinol (2.00 g) and ethyl benzoylacetate (3.05 g) in ethanol (30 ml) was treated with dry HCl as described in example 1a. The product was recrystallized from ethanol-water (1:1). Yield 3.0 g (75 %).

¹H-NMR (DMSO-*d*₆, 300 MHz): 5.739 (s, 1H, CH=C), 6.155 (d, 1H, J = 2.3 Hz), 6.263 (d, 1H, J = 2.3 Hz), 7.305-7.381 (m, 5H, Ph), 10.084 (s, 1H, OH), 10.368 (s, 1H, OH).

b) 5,7-Bis(cyanomethoxy)-4-phenyl-2*H*-1-benzopyran-2-one

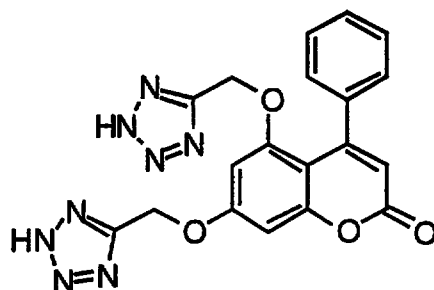
24



The product from previous example (1.00 g) was treated with chloroacetonitrile (0.62 g) and potassium carbonate (2.72 g) in DMF (5 ml) as described in example 1b. The reaction mixture was poured into ice water and the mixture extracted with ethyl acetate. Ethyl acetate was washed with 1 M NaOH, dried with sodium sulfate and evaporated. The product was recrystallized from isopropanol. Yield 0.41 g (31 %).

¹H-NMR (DMSO-d₆, 300 MHz): 4.845 (s, 2H, OCH₂CN), 5.344 (s, 2H, OCH₂CN), 6.086 (s, 1H, CH=C), 6.770 (d, 1H, J = 2.4 Hz), 7.040 (d, 1H, J = 2.4 Hz), 7.320-7.443 (m, 5H, Ph).

c) 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-4-phenyl-2*H*-1-benzopyran-2-one

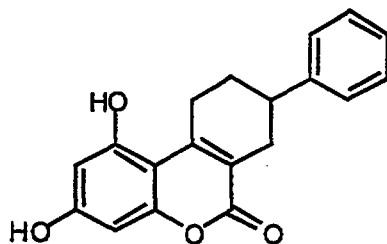


The product from previous example (0.40g) was treated with sodium azide (0.16 g) and ammonium chloride (0.14 g) in DMF (2 ml) at 100 °C for 2 hours. The product was isolated as described in example 1c. Yield: 0.40 g (79 %). Melting point 222-224 °C.

¹H-NMR (DMSO-d₆, 400 MHz): 5.148 (s, 2H, OCH₂Tet), 5.649 (s, 2H, OCH₂Tet), 5.968 (s, 1H, CH=C), 6.811 (d, 1H, J = 2.3 Hz), 6.962 (d, 1H, J = 2.3 Hz), 6.994-7.185 (m, 5H, Ph).

Example 6. Preparation of 7,8,9,10-Tetrahydro-1,3-bis[(1*H*-tetrazol-5-yl)methoxy]-8-phenyl-6*H*-dibenzo[b,d]pyran-6-one

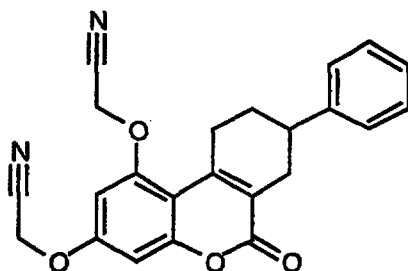
a) 7,8,9,10-Tetrahydro-1,3-dihydroxy-8-phenyl-6*H*-dibenzo[b,d]pyran-6-one



A solution of phloroglucinol (1.56 g) and ethyl 2-oxo-5-phenylcyclohexane-carboxylate (2.52 g) in ethanol (25 ml) was treated with dry HCl as described in example 1a. The precipitate was filtered and washed with water and EtOH. Yield 1.0 g (32 %).

¹H-NMR (DMSO-d₆, 400 MHz): 1.72-1.82 (m, 1H), 2.01 (b, 1H), 2.317-2.387 (m, 1H), 2.707-2.763 (m, 1H), 2.830 (b, 1H), 3.041 (b, 1H), 3.35 and 3.40 (b, 1H), 6.174 (d, 1H, J = 2.3 Hz), 6.277 (d, 1H, J = 2.3 Hz), 7.200-7.350 (m, 5H, Ph), 10.131 (s, 1H, OH), 10.401 (s, 1H, OH).

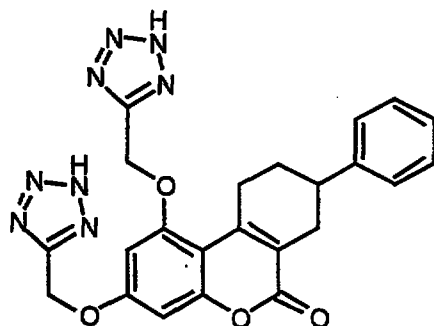
b) 7,8,9,10-Tetrahydro-1,3-bis(cyanomethoxy)-8-phenyl-6*H*-dibenzo[b,d]pyran-6-one



The product from previous example (1.0 g) was treated with chloroacetonitrile (0.57 g) and potassium carbonate (1.0 g) in DMF (5 ml) as described in example 1b. DMF was evaporated and residue dissolved in EtOAc. Ethyl acetate was washed with 1 M NaOH, dried with sodium sulfate and evaporated. The product was recrystallized from acetone-isopropanol (1:3). Yield 0.50 g (40 %).

¹H-NMR (DMSO-d₆, 300 MHz): 1.75-1.88 (m, 1H), 2.05 (b, 1H), 2.38-2.48 (m, 1H), 2.77-2.85 (m, 1H), 2.90 (b, 1H), 3.07 (b, 1H), 3.22 and 3.28 (b, 1H), 5.316 (s, 2H, OCH₂CN), 5.331 (s, 2H, OCH₂CN), 6.829 (d, 1H, J = 2.5 Hz), 6.939 (d, 1H, J = 2.5 Hz), 7.210-7.380 (m, 5H, Ph).

c) 7,8,9,10-Tetrahydro-1,3-bis[(1*H*-tetrazol-5-yl)methoxy]-8-phenyl-6*H*-dibenzo[b,d]pyran-6-one

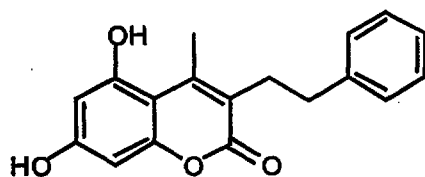


The product from previous example (0.30 g) was treated with sodium azide (0.10 g) and ammonium chloride (0.09 g) in DMF (2 ml) at 100 °C for 3.5 hours. The product was isolated in the same manner as in example 1c. Yield 0.30 g (82 %). Melting point 235-245 °C.

¹H-NMR (DMSO-d₆, 400 MHz): 1.70-1.80 (m, 1H), 1.96 (b, 1H), 2.38-2.446 (m, 1H), 2.836 (m, 2H), 3.052 (b, 1H), 3.252 and 3.301 (b, 1H), 5.604 (s, 2H, OCH₂CN), 5.632 (s, 2H, OCH₂CN), 6.827 (d, 1H, J = 2.5 Hz), 6.858 (d, 1H, J = 2.5 Hz), 7.209-7.351 (m, 5H, Ph).

Example 7. Preparation of 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-4-methyl-3-(2-phenylethyl)-2*H*-1-benzopyran-2-one

a) 5,7-Dihydroxy-4-methyl-3-(2-phenylethyl)-2*H*-1-benzopyran-2-one

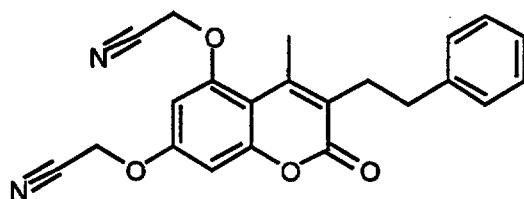


A solution of phloroglucinol (0.87 g) and ethyl 2-(2-phenylethyl)-acetoacetate (1.62 g) in ethanol (30 ml) was treated with dry HCl as described in example 1a. Yield: 1.77 g (87 %). Melting point 248-252 °C.

¹H-NMR (DMSO-d₆, 300 MHz): 2.413 (s, 3H, CH₃), 2.652-2.782 (m, 4H, CH₂CH₂), 6.151 (d, 1H, J = 2.4 Hz), 6.256 (d, 1H, J = 2.4 Hz), 7.183-7.304 (m, 5H, Ph), 10.137 (s, 1H, OH), 10.369 (s, 1H, OH).

b) 5,7-Bis(cyanomethoxy)-4-methyl-3-(2-phenylethyl)-2*H*-1-benzopyran-2-one

27

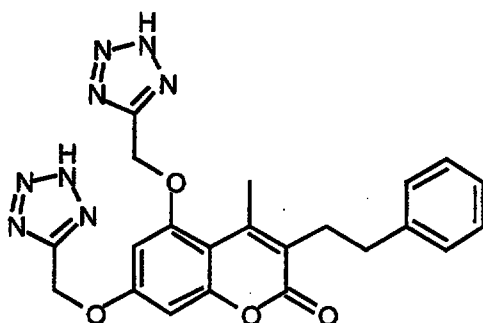


The product from previous example (0.90 g) was treated with chloroacetonitrile (0.48 g) and potassium carbonate (2.1 g) in DMF (5 ml) at 100 °C for 0.5 hours. The product was isolated as described in example 1b.

5 Yield 1.00 g (88 %). Melting point 179-183 °C.

¹H-NMR (DMSO-d₆, 300 MHz): 2,384 (s, 3H, CH₃), 2.699-2,754 (m, 2H, CH₂CH₂), 2.805-2.841 (m, 2H, CH₂CH₂), 5,302 (s, 4H, OCH₂CN), 6,790 (d, 1H, J = 2.5 Hz), 6.909 (d, 1H, J = 2.5 Hz), 7.190-7.307 (m, 5H, Ph).

c) 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-4-methyl-3-(2-phenylethyl)-2*H*-
10 1benzopyran-2-one



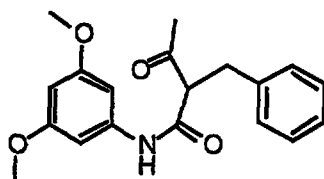
The product from previous example (0.40g) was treated with sodium azide (0.15 g) and ammonium chloride (0.12 g) in DMF (2 ml) at 100 °C for 2.5 hours. The product was isolated as described in example 1c. Yield 0.385
15 g (78 %). Melting point 248-250 °C.

¹H-NMR (DMSO-d₆, 400 MHz): 2.368 (s, 3H, CH₃), 2.668-2.707 (m, 2H, CH₂CH₂), 2.783-2.822 (m, 2H, CH₂CH₂), 5.593 (s, 2H, OCH₂Tet), 5.604 (s, 2H, OCH₂Tet), 6.819 (d, 1H, J = 2.3 Hz), 6.834 (d, 1H, J = 2.3 Hz), 7.161-7.291 (m, 5H, Ph).

20 Example 8. Preparation of 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-1,3-dibenzyl-4-methyl-2(1*H*)-quinolinone

a) 2-Benzyl-3-oxobutanoic acid 3,5-dimethoxyanilid

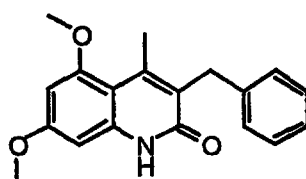
28



3,5-Dimethoxyaniline (5 g) was added in portions to a preheated (160 °C) ethyl 2-benzyl acetoacetate (15 ml) under nitrogen and kept at that temperature for 60 minutes. The cooled solution was diluted with heptane-ethyl ether and filtered. Yield 5.2 g (49 %).

¹H-NMR (DMSO-d₆, 300 MHz): 2.183 (s, 3H), 3.069 (d, 2H, J = 7.2 Hz), 3.923 (t, 1H, J = 7.2 Hz), 6.616 (dd, 1H, J = 2.3 Hz), 6.765 (d, 2H, J = 2.3 Hz), 7.13- 7.3 (m, 5H), 10.123 (s, 1H).

b) 3-Benzyl-5,7-dimethoxy-4-methyl-2(1H)-quinolinone

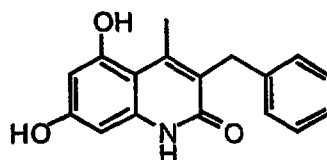


10

The product from the previous example (1.2 g) was added to a preheated (85 °C) methanesulfonic acid (3.5 ml) and kept at that temperature for 15 minutes. The solution was allowed to cool and then treated with ice water. The product was filtered, washed with sodium bicarbonate and water. Yield 1.08 g (95 %).

¹H-NMR (300 MHz): 2.486 (s, 3H), 3.785 (s, 3H), 3.808 (s, 3H), 3.985 (s, 2H), 6.315 (d, 1H, J = 2.4 Hz), 6.472 (d, 1H, J = 2.4 Hz), 7.1-7.3 (m, 5 H), 11.52 (s, 1H).

c) 3-Benzyl-5,7-dihydroxy-4-methyl-2(1H)-quinolinone



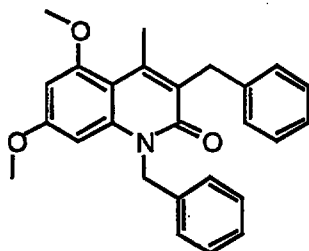
20

The product from the previous example (1 g) was refluxed under nitrogen in pyridine hydrochloride (5 g) for twenty minutes. The reaction

mixture was treated with water and the product filtered. Yield 0.9 g (100 %).
Melting point: 307 - 312 °C.

¹H-NMR (300 MHz): 2.503 (s, 3H), 3.942 (s, 2H), 6.102 (d, 1H, J = 2.3 Hz), 6.187 (d, 1H, J = 2.3 Hz), 7.1-7.25 (m, 5H), 9.725 (s, 1H), 9.984 (s, 1H), 11.285 (s, 1H).

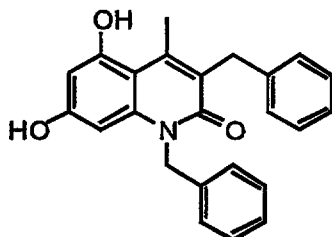
d) 1,3-Dibenzyl-5,7-dimethoxy-4-methyl-2(1H)-quinolinone



The product from the example 8b (1 g), potassium t-butoxide (0.62 g) and benzyl bromide (0.68 ml) were stirred in DMSO (10 ml) at 60 °C for 4 hours. The reaction mixture was treated with water, extracted with toluene and evaporated. The product was triturated with ethyl ether and filtered. Yield 0.5 g (39 %).

¹H-NMR (400 MHz): 2.537 (s, 3H), 3.708 (s, 3H), 3.826 (s, 3H), 4.124 (s, 2H), 5.56 (b, 2H), 6.413-6.434 (m, 2H), 7.154- 7.332 (m, 10H).

e) 1,3-Dibenzyl-5,7-dihydroxy-4-methyl-2(1H)-quinolinone.

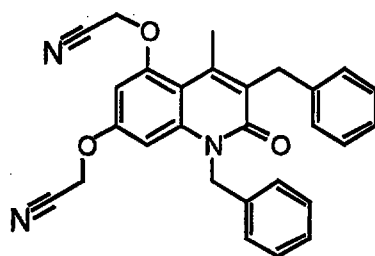


The product from the previous example (2 g) was treated with pyridine hydrochloride (10 g) as described in example 8c. The product was extracted with ethyl acetate and evaporated. Yield 1,4 g (75 %).

¹H-NMR (400 MHz): 2.570 (s, 3H), 4.076 (s, 2H), 5.450 (b, 2H), 6.135 (d, 1H, J = 2.2 Hz), 6.199 (d, 1H, J = 2.2 Hz), 7.128 - 7.333 (m, 10 H), 9.83 (b, 1H), 10.166 (s, 1H).

f) 5,7-Bis(cyanomethoxy)-1,3-dibenzyl-4-methyl-2(1H)-quinolinone.

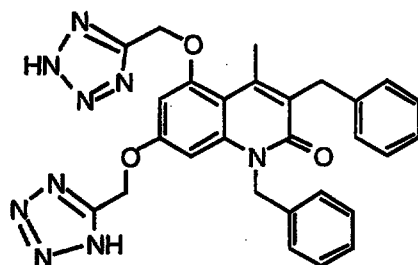
30



The product from the previous example (1.4 g) was treated with chloroacetonitrile (0.76 g) and K_2CO_3 (2.5 g) in DMF (20 ml) as described in example 1b. Yield 1.5 g (89 %).

5 1H -NMR (400 MHz): 2.555 (s, 3H), 4.146 (s, 2H), 5.214 (s, 2H), 5.275 (s, 2H), 5.578 (s, 2H), 6.735 (s, 2H), 7.13-7.33 (m, 10H).

g) 5,7-Bis[(1H-tetrazol-5-yl)methoxy]-1,3-dibenzyl-4-methyl-2(1H)-quinolinone.

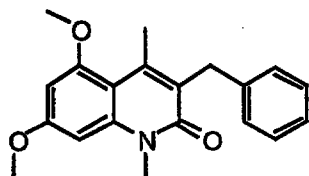


10 The product from the previous example (1.3 g) was treated with sodium azide (0.41 g) and ammonium chloride (0.34 g) as described in example 1c. Yield: 0.69 g (45 %).

1H -NMR (400 MHz): 2.471 (s, 3H), 4.113 (s, 2H), 5.477 (s, 2H), 5.55 (b, 2H), 5.574 (s, 2H), 6.670 (d, 1H, $J = 2.1$ Hz), 6.775 (d, 1H, $J = 2.1$ Hz),
15 7.13-7.32 (m, 10 H).

Example 9. Preparation of 5,7-Bis[(1H-tetrazol-5-yl)methoxy]-3-benzyl-1,4-dimethyl-2(1H)-quinolinone.

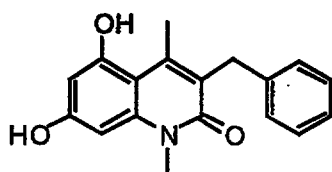
a) 3-Benzyl-5,7-dimethoxy-1,4-dimethyl-2(1H)-quinolinone.



The product from example 8b (0.5 g), t-BuOK (0.2 g) and methyl iodide (0.4 ml) were stirred in DMSO (5 ml) at 35 °C for two days. The reaction mixture was treated with water and extracted with toluene. The product was purified by column chromatography using toluene-ethyl acetate-acetic acid 8 : 2: 1 as the eluent. Yield 0.24 g (46 %).

¹H-NMR (300 MHz): 2.51 (s, 3H), 3.632 (s, 2H), 3.846 (s, 3H), 3.896 (s, 3H), 4.047 (s, 2H), 6.468 (d, 1H, J = 2.3 Hz), 6.558 (d, 1H, J = 2.3 Hz), 7.1-7.26 (m, 5H).

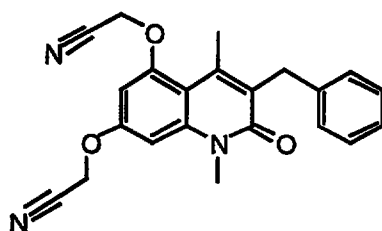
b) 3-Benzyl-5,7-dihydroxy-1,4-dimethyl-2(1H)-quinolinone.



The product from the previous example (0.2 g) was treated with pyridine hydrochloride (2 g) as described in example 8c and the product extracted with ethyl acetate. Yield 0.16 g (89 %).

¹H-NMR (400 MHz): 2.567 (s, 3H), 3.515 (s, 3H), 4.005 (s, 2H), 6.244 (d, 1H, J = 2.3 Hz), 6.268 (d, 1H, J = 2.3 Hz), 7.08-7.25 (m, 5H), 9.879 (s, 1H), 10.113 (s, 1H).

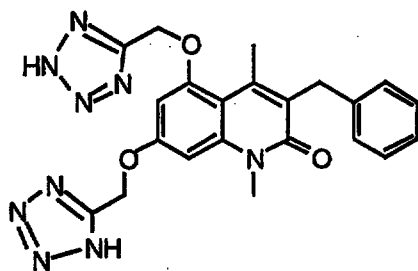
c) 5,7-Bis(cyanomethoxy)-3-benzyl-1,4-dimethyl-2(1H)-quinolinone.



The product from the previous example (0.15 g), chloroacetonitrile (0.08 g) and K₂CO₃ (0.28 g) were reacted in DMF (2 ml) as described in example 1b. Yield 0.16 g (84 %).

¹H-NMR (400 MHz): 2.524 (s, 3H), 3.658 (s, 3H), 4.079 (s, 2H), 5.292 (s, 2H), 5.379 (s, 2H), 6.766 (d, 1H, J = 2.3 Hz), 6.855 (d, 1H, J = 2.3 Hz), 7.13-7.24 (m, 5H).

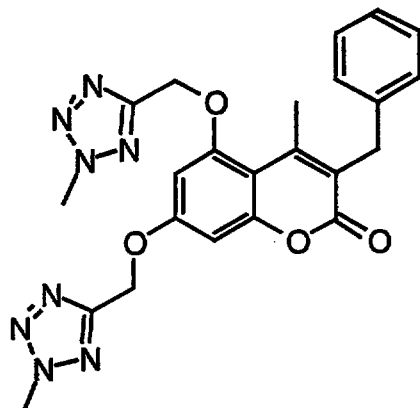
d) 5,7-Bis[(1H-tetrazol-5-yl)methoxy]-3-benzyl-1,4-dimethyl-2(1H)-quinolinone.



The product from the previous example (0.15 g) was treated with
 5 NaN₃ (57 mg) and NH₄Cl (47 mg) in DMF (2 ml) as described in example
 1c. Yield 0.115 g. Melting point: 250-253°C.

¹H-NMR (400 MHz): 2.451 (s, 3H), 3.649 (s, 3H), 4.042 (s, 2H),
 6.792 (d, 1H, J = 2.2 Hz), 6.833 (d, 1H, J = Hz), 7.1-7.25 (m, 5H).

Example 10. Preparation of 3-Benzyl-5,7-bis[(2-methyl-1H-tetrazol-5-yl)methoxy]-4-methyl-2H-1-benzopyran-2-one and the three isomers.
 10

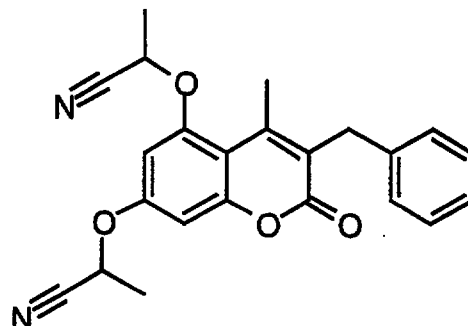


0.07 ml of methyl iodide was added to a solution of 0.2 g of the
 product from example 1c and 0.31 g of K₂CO₃ in 2 ml of DMF and the
 mixture stirred at room temperature for 4 hours. The reaction mixture was
 15 poured into ice water and filtered. Yield 0.2 g as a mixture of four
 regioisomers, melting point 71-76°C.

¹H-NMR (DMSO-d₆, 400MHz): 2.47 (s, CH₃), 2.48 (s, CH₃), 3.93 (s,
 CH₂Ph), 4.11 (s, NCH₃), 4.12 (s, NCH₃), 4.15 (s, NCH₃), 4.38 (s, NCH₃),
 4.40 (s, NCH₃), 5.51 (s, OCH₂), 5.52 (s, OCH₂), 5.62 (s, OCH₂), 5.67 (s,
 20 OCH₂), 6.84-6.91 (m, 2H), 7.16-7.28 (m, 5H, Ph).

Example 11. Preparation of 3-Benzyl-5,7-bis[1-(1 *H*-tetrazol-5-yl)ethoxy]4-methyl-2 *H*-1-benzopyran-2-one, mixture of stereoisomers

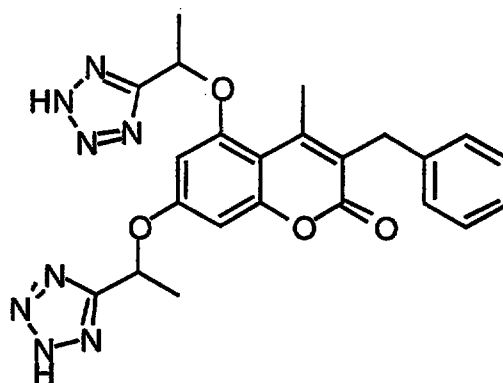
a) 3-Benzyl-5,7-bis-[(1-cyano)ethoxy]-4-methyl-2 *H*-1-benzopyran-2-one



- 5 The product from example 1a (1 g), 2-chloropropionitrile (0.7 g) and potassium carbonate (2 g) were heated in DMF (15 ml) under nitrogen at 110°C for sixty minutes. The mixture was treated with water, filtered and washed with 1 N NaOH and water. Yield 1.2 g.

- 10 ¹H-NMR (DMSO-d₆, 300MHz): 1.74-1.78 (t + t, 6 H, CH-CH₃), 2.53 (s, 3 H), 3.97 (s, 2H), 5.58-5.66 (m, 2H, CH-CH₃), 6.87 (m, 1H), 6.99 (d, 1H), 7.18-7.31 (m, 5H).

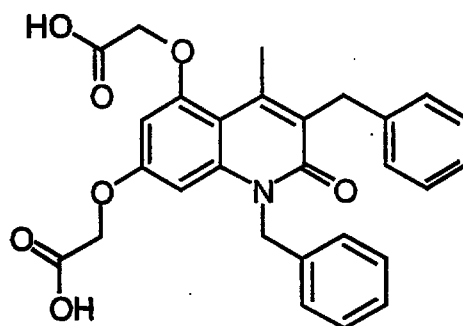
b) 3-Benzyl-5,7-bis[1-(1 *H*-tetrazol-5-yl)ethoxy]4-methyl-2 *H*-1-benzopyran-2-one, mixture of stereoisomers.



- 15 The product from the previous example (0.5 g), sodium azide (0.18 g) and ammonium chloride (0.15 g) were heated in DMF (7 ml) at 100 °C for 90 minutes. The product was treated with water, extracted with ethyl acetate and evaporated. Yield 0.57 g. Melting point 91-104°C.

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz): 1.69-1.77 (m, 6 H, CH-CH₃), 2.54 (s, 3H), 3.94 (s, 2H), 6.10-6.17 ((m, 2H, CH-CH₃), 6.65 (dd, 1H), 6.74 (dd, 1H), 7.13-7.30 (m, 5H).

Example 12. Preparation of 5,7-Bis(carboxymethoxy)-1,3-dibenzyl-4-methyl-2(1H)-quinolinone

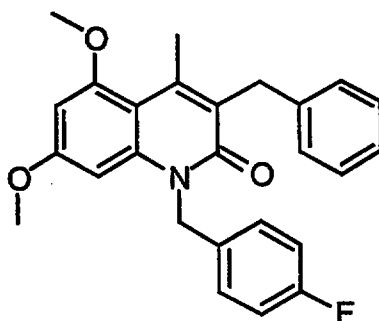


The product from example 8f (0.2 g) was refluxed in a solution of concentrated hydrochloric acid (3 ml) and acetic acid (2 ml) for one hour. The product was filtered at 25 °C. Yield 0.14 g.

$^1\text{H-NMR}$ (300 Mhz, DMSO-d_6): 2.63 (s, CH₃), 4.14 (s, 2H, CH₂Ph), 4.66 (s, 2 H, OCH₂COOH), 4.79 (s, 2H, OCH₂COOH), 5.53 (s, 2H, NCH₂Ph), 6.41 (d, 1H, J = 2.2 Hz), 6.45 (d, 1H, J = 2.2 Hz), 7.13-7.34 (m, 10 H, Ph).

Example 13. Preparation of 3-Benzyl-5,7-bis[(1H-tetrazol-5-yl)methoxy]-1-(4-fluorobenzyl)-4-methyl-2(1H)-quinolinone

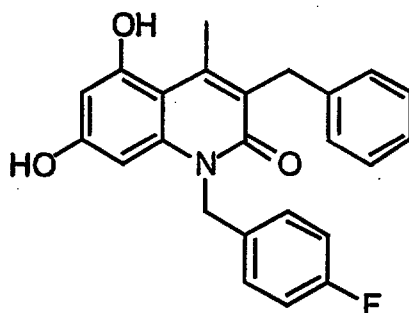
a) 1-Benzyl-5,7-dimethoxy-3-(4-fluorobenzyl)-4-methyl-2(1H)-quinolinone



The product from example 8b (2 g), potassium -tert-butoxide (0.87 g) and 4-fluorobenzylchloride (1.12 g) were heated in DMSO (20 ml) at 60 °C for three hours as in example 8d. Yield 1.28 g.

¹H-NMR (400 Mhz, DMSO-d₆): 2.53 (s, 3H), 3.73 (s, 3H), 3.83 (s, 3H), 5.55 (s, 2H), 6.43 (s, 2H), 7.12-7.2 (m, 5 H), 7.26-7.28 (m, 4H).

b) 3-Benzyl-5,7-dihydroxy-1-(4-fluorobenzyl)-4-methyl-2(1H)-quinolinone



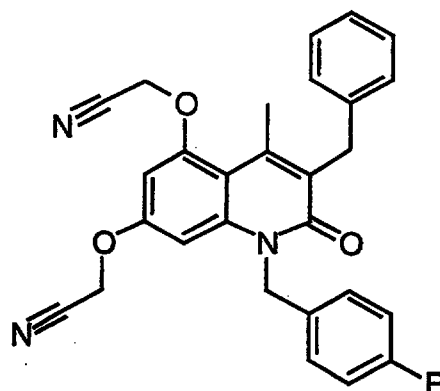
5

The product from previous example (1.25 g) were heated in pyridine hydrochloride (12.5 g) at about 225 °C for 9 minutes. Yield 1 g.

¹H-NMR (300 Mhz, DMSO-d₆): 2.56 (s, 3H), 4.07 (s, 2H), 5.4 (b, 2H), 6.13 (d, 1H, J = 2.1 Hz), 6.20 (d, 1H, J = 2.1 Hz), 7.12-7.28 (m, 9H), 9.88 (s, 1H), 10.22 (s, 1H).

10

c) 3-Benzyl-5,7-Bis(cyanomethoxy)-1-(4-fluorobenzyl)-4-methyl-2(1H)-quinolinone

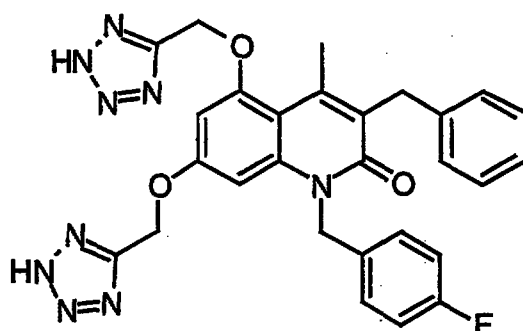


The product from the previous example (1 g), ClCH₂CN (0.43 g) and K₂CO₃ (1.42 g) were heated in DMF (8 ml) at 120 °C for one hour. Yield 0.94 g.

15

¹H-NMR (300 Mhz, DMSO-d₆): 2.55 (s, 3H), 4.14 (s, 2H), 5.25 (s, 2H), 5.28 (s, 2H), 5.57 (s, 2H), 6.74 (s, 2H, ArH), 7.1 -7.3 (m, 9H).

d) 3-Benzyl-5,7-bis[(1H-tetrazol-5-yl)methoxy]-1-(4-fluorobenzyl)-4-methyl-2(1H)-quinolinone

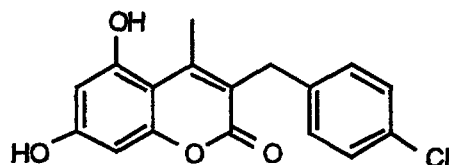


The product from the previous example (0.5 g), sodium azide (0.14 g) and ammonium chloride (0.12 g) were heated in DMF (5 ml) at 120 °C for 90 min. The product was triturated with acetonitrile. Yield 0.28 g. Melting point: 126-132 °C.

¹H-NMR (300 Mhz, DMSO-d₆): 2.48 (s, 3H), 4.11 (s, 2H), 5.51 (s, 2H), 5.55 (s, 2H), 5.58 (s, 2H), 6.67 (d, 1H, J = 2.1 Hz), 6.78 (d, 1H, J = 2.1 Hz).

Example 14. Preparation of 5,7-Bis[(1H-tetrazol-5-yl)methoxy]-3-(4-chlorobenzyl)-4-methyl-2H-1-benzopyran-2-one

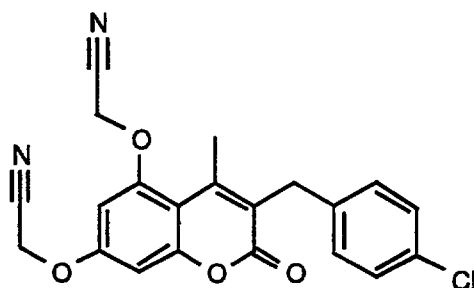
a) 3-(4-Chlorobenzyl)-5,7-dihydroxy-4-methyl-2H-1-benzopyran-2-one



A solution of phloroglucinol (1.57 g) and ethyl 2-(4-chlorobenzyl)-acetoacetate (3.18 g) in ethanol (25 ml) was treated with dry HCl at 0 °C for 1.5 hours and the solution was kept at that temperature overnight. Solvent was evaporated and the precipitate triturated with water. Yield 3.87 g (98 %). Melting point 270-278 °C.

¹H-NMR (DMSO-d₆, 300 MHz): 2.52 (s, 3H, CH₃), 3.87 (s, 2H, CH₂), 6.17 (d, 1H, J = 2.4 Hz), 6.28 (d, 1H, J = 2.4 Hz), 7.18-7.34 (m, 4H, Ph), 10.21 (s, 1H, OH), 10.48 (s, 1H, OH).

b) 5,7-Bis(cyanomethoxy)-3-(4-chlorobenzyl)-4-methyl-2H-1-benzopyran-2-one

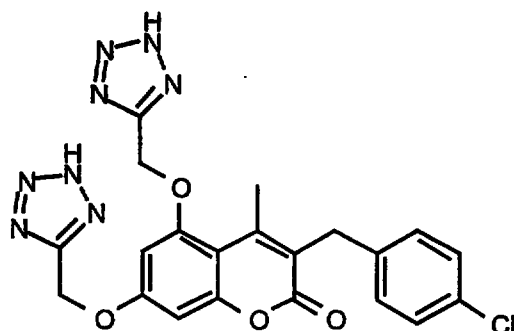


The product from the previous example (1.00 g), chloroacetonitrile (0.50 g) and potassium carbonate (2.18 g) were heated in DMF (5 ml) at 100 °C for 30 minutes. The product was isolated as described in example 1b.

5 Yield 0.90 g (72 %).

¹H-NMR (DMSO-d₆, 300 MHz): 2.52 (s, 3H, CH₃), 3.95 (s, 2H, CH₂), 5.308 (s, 2H, OCH₂CN), 5.312 (s, 2H, OCH₂CN), 6.81 (d, 1H, J = 2.5 Hz), 6.94 (d, 1H, J = 2.5 Hz), 7.22-7.33 (m, 4H, Ph).

c) 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-3-(4-chlorobenzyl)-4-methyl-2*H*-
10 1-benzopyran-2-one



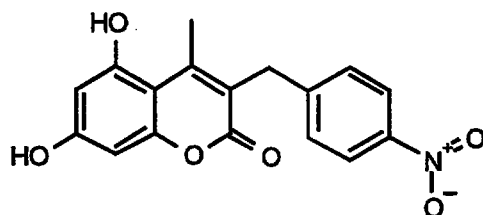
The product from the previous example (0.40 g), sodium azide (0.14 g) and ammonium chloride (0.11 g) were heated in DMF (2 ml) at 100 °C for 2 hours. The product was isolated as in example 1c. Yield 0.40 g (82 %).

15 ¹H-NMR (DMSO-d₆, 300 MHz): 2.46 (s, 3H, CH₃), 3.92 (s, 2H, CH₂), 5.602 (s, 2H, OCH₂Tet), 5.609 (s, 2H, OCH₂Tet), 6.83 (d, 1H, J = 2.5 Hz), 6.85 (d, 1H, J = 2.5 Hz), 7.20-7.33 (m, 4H, Ph).

Example 15. Preparation of 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-3-(4-nitrobenzyl)-4-methyl-2*H*-1-benzopyran-2-one
20

a) 5,7-Dihydroxy-4-methyl-3-(4-nitrobenzyl)-2*H*-1-benzopyran-2-one

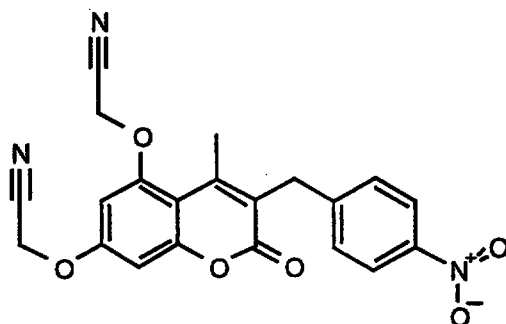
38



A solution of phloroglucinol (0.48 g) and ethyl 2-(4-nitrobenzyl)aceto-
acetate (1.00 g) in ethanol (150 ml) was treated with dry HCl at 0 °C for 7.5
hours and the solution was kept at that temperature overnight. Solvent was
5 evaporated and the precipitate triturated with water. Yield 0.63 g (51 %).
Melting point 280-285 °C.

¹H-NMR (DMSO-d₆, 300 MHz): 2.53 (s, 3H, CH₃), 4.03 (s, 2H, CH₂),
6.19 (d, 1H, J = 2.4 Hz), 6.29 (d, 1H, J = 2.4 Hz), 7.40-7.51 and 8.11-8.17
(m, 4 H, Ph), 10.25 (s, 1H, OH), 10.52 (s, 1H, OH).

10 b) 5,7-Bis(cyanomethoxy)-3-(4-nitrobenzyl)-4-methyl-2H-1-
benzopyran-2-one

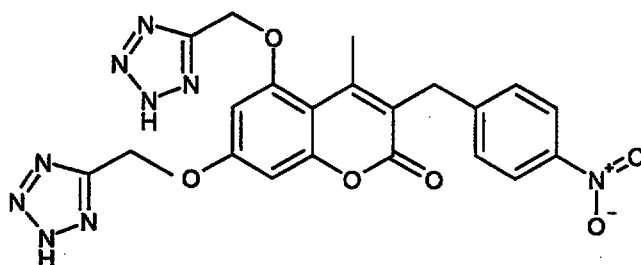


The product from the previous example (0.57 g), chloroacetonitrile
(0.27 g) and potassium carbonate (1.20 g) were heated in DMF (2 ml) at 100
15 °C for 50 minutes. The product was isolated as described in example 1b.
Yield 0.47 g (67 %). Melting point 178-185 °C.

¹H-NMR (DMSO-d₆, 400 MHz): 2.53 (s, 3H, CH₃), 4.11 (s, 2H, CH₂),
5.319 (s, 2H, OCH₂CN), 5.323 (s, 2H, OCH₂CN), 6.83 (d, 1H, J = 2.4 Hz),
6.96 (d, 1H, J = 2.4 Hz), 7.48-7.53 and 8.12-8.16 (m, 4H, Ph).

c) 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-3-(4-nitrobenzyl)-4-methyl-2*H*-1-benzopyran-2-one

5



The product from the previous example (0.38 g), sodium azide (0.12 g) and ammonium chloride (0.11 g) were heated in DMF (3 ml) at 100 °C for 2 hours. The product was isolated as described in example 1c. Yield 0.25 g (54 %). Melting point 240-244 °C.

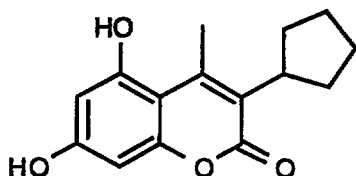
10

¹H-NMR (DMSO-*d*₆, 400 MHz): 2.47 (s, 3H, CH₃), 4.08 (s, 2H, CH₂), 5.611 (s, 2H, OCH₂Tet), 5.623 (s, 2H, OCH₂Tet), 6.85 (d, 1H, *J* = 2.4 Hz), 6.87 (d, 1H, *J* = 2.4 Hz), 7.46-7.50 and 8.12-8.16 (m, 4H, Ph).

Example 16. Preparation of 5,7-Bis[(1*H*-tetrazol-5-yl)methoxy]-3-cyclopentyl-4-methyl-2*H*-1-benzopyran-2-one

15

a) 3-Cyclopentyl-5,7-dihydroxy-4-methyl-2*H*-1-benzopyran-2-one



A solution of phloroglucinol (2.00 g) and ethyl 2-cyclopentylacetoacetate (3.14 g) in ethanol (40 ml) was treated with dry HCl at 0 °C for 2.5 hours and the solution kept at that temperature overnight. Solvent was evaporated and the precipitate purified with flash chromatography eluting with toluene-EtOAc-AcOH (8:1:1). Yield 1.22 g (29 %).

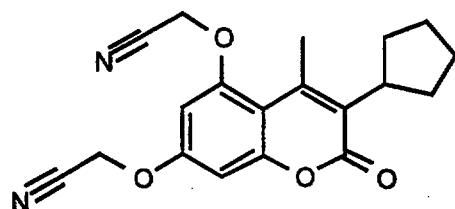
20

¹H-NMR (DMSO-*d*₆, 300 MHz): 1.50-1.88 (m, 8H, -(CH₂)₄-), 2.57 (s, 3H, CH₃), 3.25 (m, 1H, CH), 6.11 (d, 1H, *J* = 2.4 Hz), 6.25 (d, 1H, *J* = 2.4 Hz), 10.25 (b, 2H, OH).

25

b) 5,7-Bis(cyanomethoxy)-3-cyclopentyl-4-methyl-2*H*-1-benzopyran-2-one

40

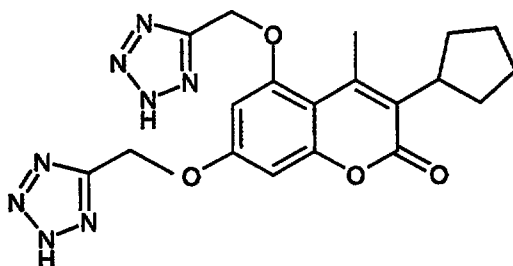


The product from the previous example (0.50 g), chloroacetonitrile (0.31 g) and potassium carbonate (0.61 g) were heated in DMF (2 ml) at 80 °C for 40 minutes. The product was isolated as described in example 1b.

5 Yield 0.56 g (86 %).

¹H-NMR (DMSO-d₆, 300 MHz): 1.55-1.90 (m, 8H, -(CH₂)₄-), 2.56 (s, 3H, CH₃), 3.37 (m, 1H, CH), 5.29 (s, 2H, OCH₂CN), 5.31 (s, 2H, OCH₂CN), 6.75 (d, 1H, J = 2.5 Hz), 6.88 (d, 1H, J = 2.5 Hz).

c) 5,7-Bis[(1H-tetrazol-5-yl)methoxy]-3-cyclopentyl-4-methyl-2H-1-benzopyran-2-one
10



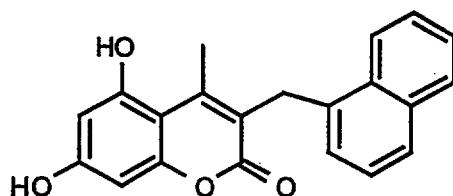
15 The product from the previous example (0.30 g), sodium azide (0.13 g) and ammonium chloride (0.11 g) were heated in DMF (1 ml) at 100 °C for 1.5 hours. The product was isolated as described in example 1c. Yield 0.30 g (80 %). Melting point 248-252 °C.

20 ¹H-NMR (DMSO-d₆, 400 MHz): 1.53-1.89 (m, 8H, -(CH₂)₄-), 2.51 (s, 3H, CH₃), 3.34 (m, 1H, CH), 5.59 (s, 2H, OCH₂Tet), 5.61 (s, 2H, OCH₂Tet), 6.80 (s, 2H).

Example 17. Preparation of 5,7-Bis[(1H-tetrazol-5-yl)methoxy]-4-methyl-3-(1-naphthylmethyl)-2H-1-benzopyran-2-one

a) 5,7-dihydroxy-4-methyl-3-(1-naphthylmethyl)-2H-1-benzopyran-2-one
25 one

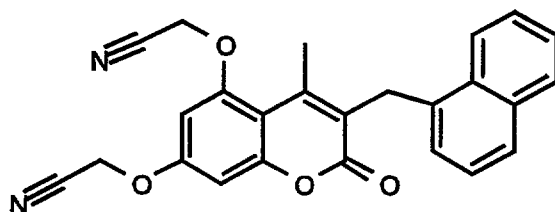
41



- A solution of phloroglucinol (0.47 g) and ethyl 2-(1-naphthylmethyl)-acetoacetate (1.00 g) in ethanol (20 ml) was treated with dry HCl at 0 °C for 3 hours and the solution kept at that temperature overnight. Solvent was
 5 evaporated and the precipitate triturated with water and recrystallized from isopropanol-water (1:1). Yield 0,96 g (78 %). Melting point 275-280 °C.

¹H-NMR (DMSO-d₆, 400 MHz): 2.45 (s, 3H, CH₃), 4.32 (s, 2H, CH₂), 6.23 (d, 1H, J = 2.5 Hz), 6.32 (d, 1 H, J = 2.5 Hz), 6.97-8.25 (m, 7H, Naph), 10.26 (s, 1H, OH), 10.53 (s, 1H, OH).

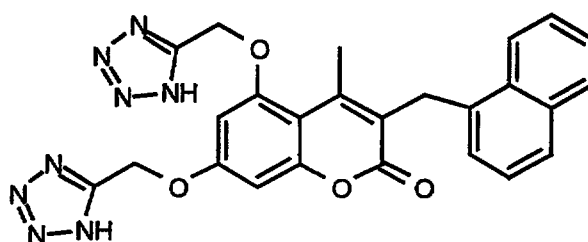
- 10 b) 5,7-Bis(cyanomethoxy)-4-methyl-3-(1-naphthylmethyl)-2H-1-benzopyran-2-one



- The product from the previous example (0.80 g), chloroacetonitrile (0.36 g) and potassium carbonate (0.66 g) were heated in DMF (4 ml) at 100 °C for 1
 15 hour. The product was isolated as in example 1b. Yield 0.30 g (30 %).

¹H-NMR (DMSO-d₆, 300 MHz): 2.45 (s, 3H, CH₃), 4.40 (s, 2H, CH₂), 5.34 (s, 2H, OCH₂CN), 5.36 (s, 2H, OCH₂CN), 6.86 (d, 1H, J = 2.5 Hz), 7.010 (d, 1H, J = 2.5 Hz), 7.016-8.27 (m, 7H, Naph).

- 20 c) 5,7-Bis[(1H-tetrazol-5-yl)methoxy]-4-methyl-3-(1-naphthylmethyl)-2H-1-benzopyran-2-one

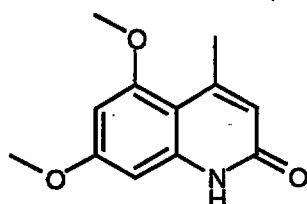


The product from the previous example (0.25 g), sodium azide (0.080 g) and ammonium chloride (0.072 g) were heated in DMF (2 ml) at 100 °C for 2.5 hours. The product was isolated as described in example 1c. Yield 0.11 g (36 %). Melting point 164-174 °C.

- 5 ¹H-NMR (DMSO-d₆, 300 MHz): 2.40 (s, 3H, CH₃), 4.37 (s, 2H, CH₂), 5.63 (s, 2H, OCH₂Tet), 5.65 (s, 2H, OCH₂Tet), 6.87 (d, 1H, J = 2.5 Hz), 6.92 (d, 1H, J = 2.5 Hz), 6.98-8.26 (m, 7H, Naph).

Example 18. Preparation of 1-Benzyl-5,7-bis-[(1H-tetrazol-5-yl)-methoxy]-4-methyl-2(1H)-quinolinone

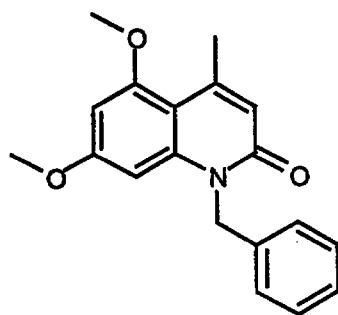
- 10 a) 5,7-Dimethoxy-4-methyl-2(1H)-quinolinone



- 15 *tert*-Butyl acetoacetate (1.58 g) was heated to 120 °C and 3,5-dimethoxyaniline (1.53 g) dissolved in xylene (4 ml) was added. The mixture was heated at 120-130 °C for 20 minutes and then cooled to room temperature. Methanesulfonic acid (2 ml) was added and the mixture was stirred at ambient temperature for 10 minutes. Water (40 ml) was added and the precipitate filtered and dried. Yield 1.31 g (60 %).

- 20 ¹H-NMR (DMSO-d₆, 300 MHz): 2.50 (s, 3H, CH₃), 3.79 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 6.03 (s, 1H, CH=C), 6.31 (d, 1H, J = 2.3 Hz), 6.45 (d, 1H, J = 2.3 Hz), 11.4 (b, 1H, NH).

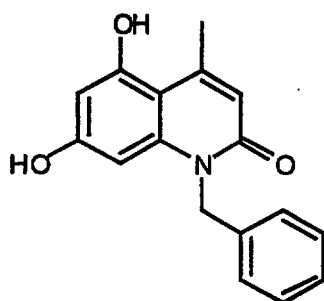
b) 1-Benzyl-5,7-dimethoxy-4-methyl-2(1H)-quinolinone



The product from the previous example (1.20 g) was suspended to DMSO (15 ml) and *t*-BuOK (0.68 g) and benzylbromide (1.03 g) were added. Reaction mixture was stirred at ambient temperature overnight. Water was added and the product extracted to EtOAc. EtOAc was dried and evaporated to dryness. The product was recrystallized from toluene. Yield 0.80 g (47 %).

¹H-NMR (DMSO-d₆, 300 MHz): 2.55 (d, 3H, J = 1.1 Hz, CH₃), 3.71 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 5.48 (b, 2H, NCH₂), 6.29 (d, 1H, J = 1.1 Hz, CH=C), 6.4 (s, 2H), 7.18-7.33 (m, 5H, Ph).

c) 1-Benzyl-5,7-dihydroxy-4-methyl-2(1H)-quinolinone



10

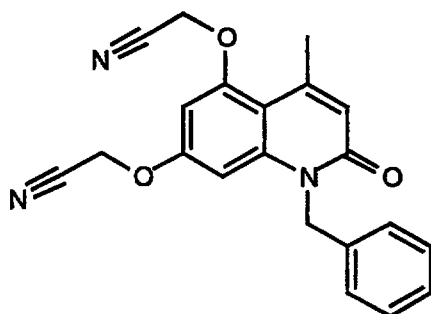
The product from the previous example (0.69 g) was dissolved to CH₂Cl₂ (14 ml) and the reaction mixture cooled to -20 °C. BBr₃ (2.4 g) in CH₂Cl₂ (1M solution) was added and the mixture was allowed to warm to ambient temperature during the night. The precipitate was filtered, washed with CH₂Cl₂ and dissolved to EtOAc. EtOAc was washed with dilute HCl, dried and evaporated to dryness. Yield 0.34 g (54 %).

15

¹H-NMR (DMSO-d₆, 300 MHz): 2.56 (d, 3H, J = 1.0 Hz, CH₃), 5.33 (b, 2H, NCH₂), 6.11 (d, 1H, J = 2.1 Hz), 6.13 (d, 1H, J = 1.0 Hz, CH=C), 6.17 (d, 1H, J = 2.1 Hz), 7.12-7.34 (m, 5H, Ph), 9.90 (b, 1H, OH), 10.22 (s, 1H, OH).

20

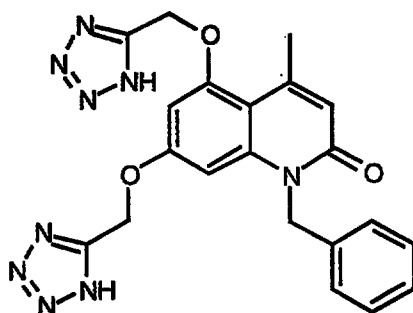
d) 1-Benzyl-5,7-bis(cyanomethoxy)-4-methyl-2(1H)-quinolinone



The product from the previous example (0.34 g), chloroacetonitrile (0.13 g) and potassium carbonate (0.34 g) were heated in DMF (2 ml) at 100 °C for 1.5 hours. Water was added and the precipitate filtered and dried. The product was recrystallized from isopropanol. Yield 0.20 g (46 %).

- 5 $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): 2.57 (s, 3H, CH_3), 5.22 (s, 2H, OCH_2CN), 5.30 (s, 2H, OCH_2CN), 5.50 (b, 2H, NCH_2), 6.42 (s, 1H, $\text{CH}=\text{C}$), 6.70 (d, 1H, $J = 2.1$ Hz), 6.73 (d, 1H, $J = 2.1$ Hz), 7.21-7.32 (m, 5H, Ph).

e) 1-Benzyl-5,7-bis-[(1*H*-tetrazol-5-yl)methoxy]-4-methyl-2(1*H*)-quinolinone



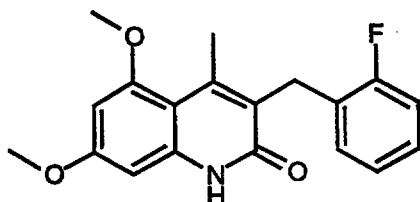
10

The product from the previous example (0.20 g), sodium azide (0.072 g) and ammonium chloride (0.060 g) were heated in DMF (2 ml) at 100 °C for 3 hours. The product was isolated as described in example 1c. Yield 0.21 g (85 %). Melting point 246-249 °C.

- 15 $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): 2.50 (s, 3H, CH_3), 5.48 (b, 4H, OCH_2Tet , NCH_2), 5.60 (s, 2H, OCH_2Tet), 6.34 (s, 1H, $\text{CH}=\text{C}$), 6.64 (d, 1H, $J = 1.9$ Hz), 6.77 (d, 1H, $J = 1.9$ Hz), 7.18-7.32 (m, 5H, Ph).

Example 19. Preparation of 1-Benzyl-5,7-bis[1*H*-tetrazol-5-yl)methoxy]-3-(2-fluorobenzyl)-4-methyl-2(1*H*)-quinolinone

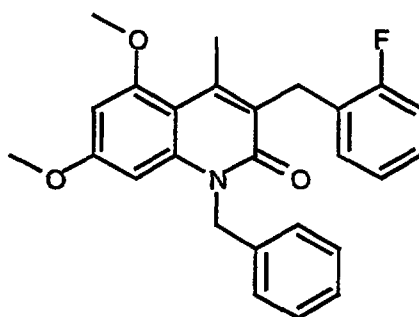
- 20 a) 5,7-Dimethoxy-3-(2-fluorobenzyl)-4-methyl-2(1*H*)-quinolinone



Ethyl 2-(2-fluorobenzyl)acetoacetate (2.5 g) in xylene (1 ml) was heated to 150 °C and 3,5- dimethoxyaniline (1.46 g) in xylene (4 ml) was added in small portions during 30 minutes. The reaction mixture was heated at 160 °C for 3 hours and then cooled to room temperature. Methanesulfonic acid (1.7 ml) was added and the mixture was stirred at ambient temperature for 30 minutes. Water was added and the precipitate filtered and dried. The product was triturated with warm ethanol. Yield 0.64 g (21 %).

¹H-NMR (DMSO-d₆, 300 MHz): 2.45 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 3.97 (s, 2H), 6.33 (d, 1H, J = 2.4 Hz), 6.48 (d, 1H, J = 2.4 Hz), 6.90-7.25 (m, 4H), 11.61 (s, 1H).

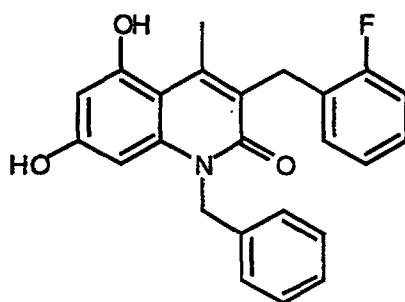
b) 1-Benzyl-5,7-dimethoxy-3-(2-fluorobenzyl)-4-methyl-2(1H)-quinolinone



The product from the previous example (0.62 g) was treated with *t*-BuOK (0.23 g) and benzylbromide (0.36 g) in DMSO (12 ml) at 60 °C for 2.5 hours. The product was isolated as described in example 18b. Yield 0.39 g (49 %).

¹H-NMR (DMSO-d₆, 400 MHz): 2.51 (s, 3H), 3.72 (s, 3H), 3.84 (s, 3H), 4.11 (s, 2H), 5.55 (b, 2H), 6.433 (d, 1H, J = 2.1 Hz), 6.443 (d, 1H, J = 2.1 Hz), 6.97-7.33 (m, 9H).

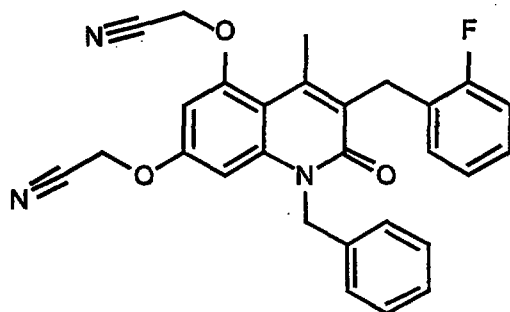
c) 1-Benzyl-5,7-dihydroxy-3-(2-fluorobenzyl)-4-methyl-2(1H)-quinolinone



The product from the previous example (0.34 g) was treated with BBr₃ (8.48 g) in CH₂Cl₂ (7 ml) as described in example 18c. Yield 0.30 g (82 %).

¹H-NMR (DMSO-d₆, 400 MHz): 2.55 (s, 3H), 4.06 (s, 2H), 5.40 (b, 2H), 6.13 (d, 1H, J = 2.1 Hz), 6.22 (d, 1H, J = 2.1 Hz), 6.97-7.33 (m, 9H), 10.3 (b, 2H).

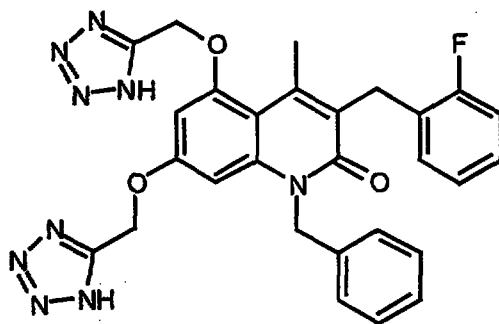
- 5 d) 1-Benzyl-5,7-bis(cyanomethoxy)-3-(2-fluorobenzyl)-4-methyl-2(1H)-quinolinone



- 10 The product from the previous example (0.21 g), chloroacetonitrile (0.086 g) and potassium carbonate (0.37 g) were heated in DMF (2 ml) at 100 °C for 2 hours. The product was isolated as described in example 1b. Yield 0.18 g (71 %).

¹H-NMR (DMSO-d₆, 400 MHz): 2.53 (s, 3H), 4.13 (s, 2H), 5.23 (s, 2H), 5.29 (s, 2H), 5.57 (b, 2H), 6.746 (d, 1H, J = 2.3 Hz), 6.756 (d, 1H, J = 2.3 Hz), 7.00-7.32 (m, 9H).

- 15 e) 1-Benzyl-5,7-bis[1H-tetrazol-5-yl)methoxy]-3-(2-fluorobenzyl)-4-methyl-2(1H)-quinolinone

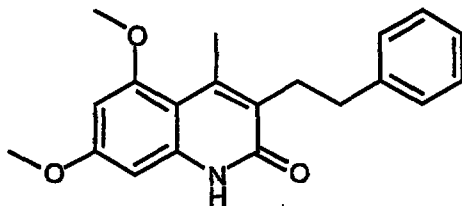


- 20 The product from the previous example (0.17 g), sodium azide (0.051 g) and ammonium chloride (0.042 g) were heated in DMF at 100 °C for 3 hours. The product was isolated as described in example 1c. Yield 0.17 g (85 %). Melting point 135-140 °C.

$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): 2.46 (s, 3H), 4.10 (s, 2H), 5.48 (s, 2H), 5.51 (b, 2H), 5.59 (s, 2H), 6.68 (d, 1H, $J = 2.2$ Hz), 6.79 (d, 1H, $J = 2.2$ Hz), 6.99-7.32 (m, 9H).

Example 20. Preparation of 1-Benzyl-5,7-bis[1*H*-tetrazol-5-yl]-methoxy]-4-methyl-3-(2-phenylethyl)-2(1H)-quinolinone

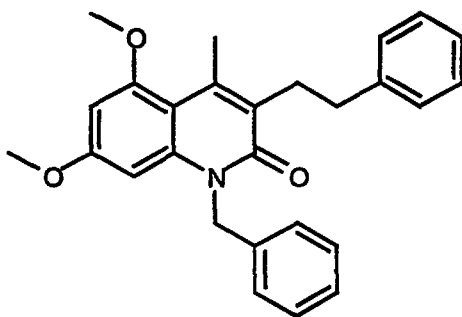
a) 5,7-Dimethoxy-4-methyl-3-(2-phenylethyl)-2(1H)-quinolinone



Ethyl 2-(2-phenylethyl)acetoacetate (2.70 g) in xylene (5 ml) was treated with 3,5-dimethoxyaniline (1.60 g) at 150 °C as described in example 19a. Methanesulfonic acid (4.0 ml) was added at room temperature and the mixture heated at 80 °C for 1 hour. The product was isolated as described in example 19a. Yield 1.38 g (41 %).

$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): 2.45 (s, 3H), 2.64-2.68 (m, 2H), 2.82-2.86 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 6.30 (d, 1H, $J = 2.3$ Hz), 6.45 (d, 1H, $J = 2.3$ Hz), 7.18-7.30 (m, 5H), 11.45 (s, 1H).

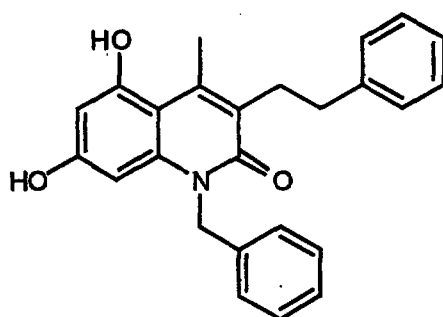
b) 1-Benzyl-5,7-dimethoxy-4-methyl-3-(2-phenylethyl)-2(1H)-quinolinone



The product from the previous example (0.61 g), *t*-BuOK (0.24 g) and benzylbromide (0.36 g) were heated in DMSO (12 ml) at 60 °C for 2 hours. The product was isolated as described in example 18b. Yield 0.31 g (40 %).

¹H-NMR (DMSO-d₆, 400 MHz): 2.51 (s, 3H), 2.73-2.77 (m, 2H), 2.96-3.00 (m, 2H), 3.70 (s, 3H), 3.83 (s, 3H), 5.55 (b, 2H), 6.40 (s, 2H), 7.17-7.33 (m, 10 H).

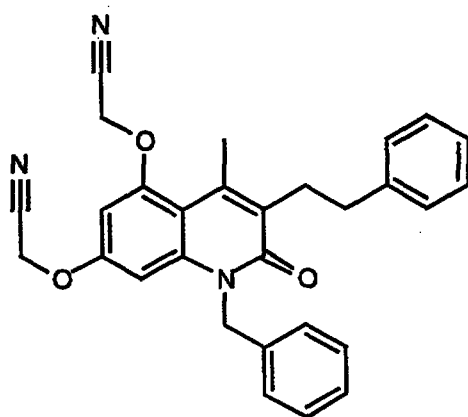
5 c) 1-Benzyl-5,7-dihydroxy-4-methyl-3-(2-phenylethyl)-2(1H)-quinolinone



The product from the previous example (0.31 g) was treated with BBr₃ (0.75 g) in CH₂Cl₂ (5 ml) as in example 18c. Yield 0.26 g (89 %).

10 ¹H-NMR (DMSO-d₆, 300 MHz): 2.56 (s, 3H), 2.69-2.75 (m, 2H), 2.90-2.95 (m, 2H), 5.39 (b, 2H), 6.08 (d, 1H, J = 2.0 Hz), 6.19 (d, 1H, J = 2.0 Hz), 7.11-7.33 (m, 10H), 10.2 (b, 2H).

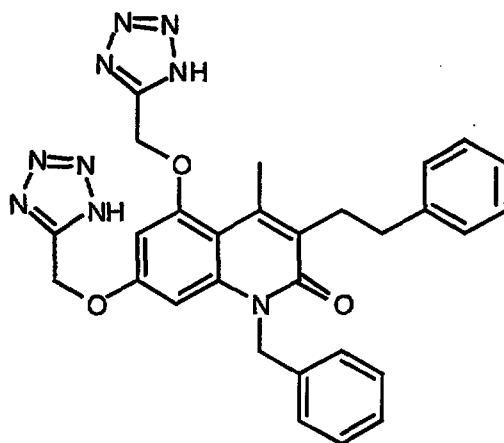
d) 1-Benzyl-5,7-bis(cyanomethoxy)-4-methyl-3-(2-phenylethyl)-2(1H)-quinolinone



15 The product from the previous example (0.22 g), chloroacetonitrile (0.091 g) and potassium carbonate (0.39 g) were heated at 100 °C for 2 hours. The product was isolated as in example 1b. Yield 0.20 g (76 %).

$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): 2.50 (s, 3H), 2.73-2.77 (m, 2H), 2.98-3.02 (m, 2H), 5.21 (s, 2H), 5.29 (s, 2H), 5.56 (b, 2H), 6.70 (d, 1H, $J = 2.1$ Hz), 6.72 (d, 1H, $J = 2.1$ Hz), 7.18-7.33 (m, 10H).

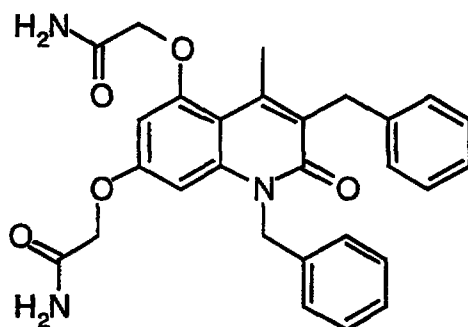
e) 1-Benzyl-5,7-bis[1*H*-tetrazol-5-yl]methoxy-4-methyl-3-(2-phenylethyl)-2(1*H*)-quinolinone



The product from the previous example (0.19 g), sodium azide (0.057 g) and ammonium chloride (0.047 g) were heated in DMF at 100 °C for 3 hours. The product was isolated as described in example 1c. Yield 0.18 g (78 %). Melting point 215-218 °C.

$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): 2.46 (s, 3H), 2.70-2.74 (m, 2H), 2.95-2.99 (m, 2H), 5.47 (s, 2H), 5.54 (b, 2H), 5.57 (s, 2H), 6.64 (d, 1H, $J = 2.0$ Hz), 6.77 (d, 1H, $J = 2.0$ Hz), 7.16-7.33 (m, 10H).

Example 21. Preparation of 5,7-Bis(aminocarbonylmethoxy)-1,3-dibenzyl-4-methyl-2(1*H*)-quinolinone.

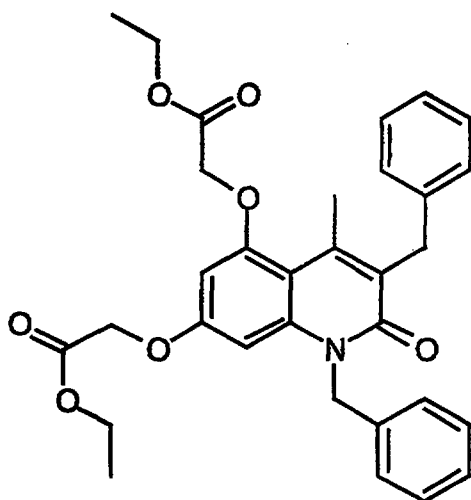


The mixture of 5,7-dihydroxy-1,3-dibenzyl-4-methyl-2(1*H*)-quinolinone (0.5 g), potassium carbonate (0.9 g) and 2-chloroacetamide (0.25 g) in DMF (6.5 ml) were reacted at 100 °C for two hours. The reaction mixture was

treated with ice water and filtered. The product was triturated with hot ethanol. Yield: 0.32 g. Melting point 252-253°C.

- ¹H-NMR (400 MHz, DMSO-d₆): 2.63 (s, 3H, CH₃), 4.13 (s, 2H, PhCH₂), 4.37 (s, 2H, OCH₂), 4.55 (s, 2H, OCH₂), 5.54 (s, 2H, NCH₂Ph),
5 6.40 (d, 1H, J = 2 Hz, ArH), 6.53 (d, 1H, J = 2 Hz, ArH), 7.13-7.33 (m, 10 H, Ph), 7.44 (d, 2H, J = 65 Hz, CONH₂), 7.47 (d, 2H, J = 68 Hz, CONH₂).

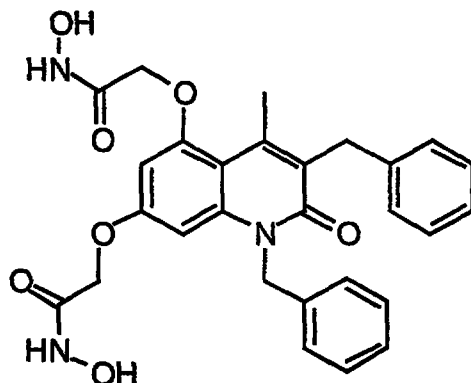
Example 22. Preparation of 5,7-Bis(ethoxycarbonylmethoxy)-1,3-dibenzyl-4-methyl-2(1H)-quinolinone.



- 10 The mixture of 5,7-dihydroxy-1,3-dibenzyl-4-methyl-2(1H)-quinolinone (1 g), ethyl 2-bromoacetate (0.63 ml) and potassium carbonate (1.49 g) in DMF (5 ml) was heated under nitrogen at 110 °C for three hours, poured into ice water and filtered. The resulting solid material was triturated with ether and filtered again. Yield: 1.03 g, melting point 113-116 °C.

- 15 ¹H-NMR (400 MHz, DMSO-d₆): 1.15 (t, 3H, CH₃CH₂, J = 7.1 Hz), 1.20 (t, 3H, CH₃CH₂, J = 7.1 Hz), 2.63 (s, 3H, CH₃), 4.03 (q, 2H, CH₂CH₃, J = 7.1 Hz), 4.13 (s, 2H, CH₂Ph), 4.17 (q, 2H, CH₂CH₃, J = 7.1 Hz), 4.78 (s, 2H, OCH₂), 4.90 (s, 2H, OCH₂), 6.41 (d, 1H, J = 2.2 Hz), 6.44 (d, 1H, J = 2.2 Hz), 7.13-7.33 (m, 10 H, Ph).

Example 23. Preparation of 5,7-Bis(hydroxyaminocarbonylmethoxy)-1,3-dibenzyl-4-methyl-2(1H)-quinolinone

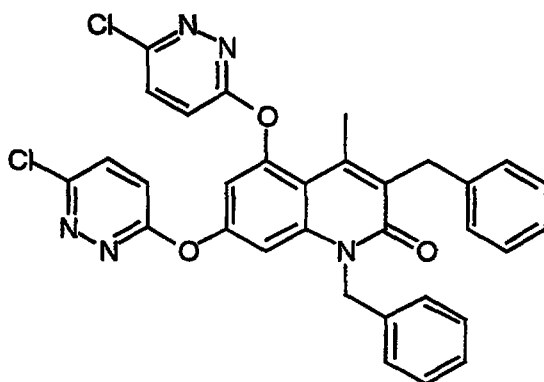


The product from the previous example (0.3 g), hydroxylamine
 5 hydrochloride (0.32 g) and 5 N NaOH (1.05 ml) were reacted in ethanol (8 ml) at 50 °C for six hours. The reaction mixture was treated with water and made basic (pH 10) and filtered. The filtrate was acidified to pH 2 and filtered. Yield: 0.2 g, melting point 121-127°C.

¹H-NMR (400 MHz, DMSO-d₆): the tautomeric forms of hydroxamic
 10 acid are seen in OCH₂-signals: 2.63 (s, 3H, CH₃), 4.13 (s, 2H, CH₂Ph), 4.41 (s, 2H, OCH₂), 4.54 (s, 2H, OCH₂), 4.64 (s, 2H, HON=C(OH)CH₂O), 4.65 (s, 2H, HON=C(OH)CH₂O), 4.77 (s, 2H, HON=C(OH)CH₂O), 4.78 (s, 2H, HON=C(OH)CH₂O), 5.54 (s, 2H, NCH₂Ph), 6.38-6.54 (m, 2H, ArH), 7.14-7.34 (m, 10 H, Ph), 9.05 (b, 2H, NOH), 10.84 (s, 1H, HONHCO), 10.88 (s,
 15 1H, HONHCO).

Example 24. Preparation of 5,7-Bis-[1-(6-hydroxypyridazinyl)]oxy-1,3-dibenzyl-4-methyl-2(1H)-quinolinone

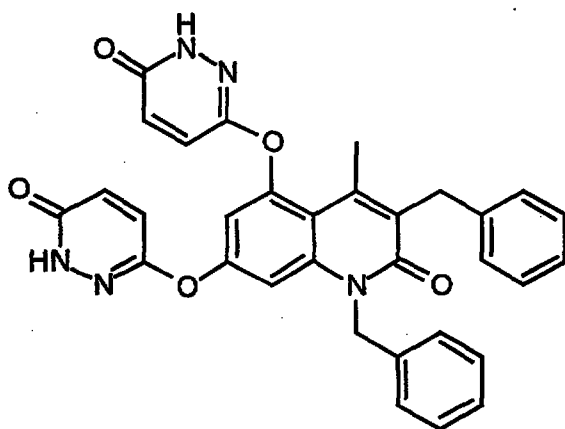
a) 5,7-Bis-[1-(6-chloropyridazinyl)]oxy-1,3-dibenzyl-4-methyl-2(1H)-quinolinone



A mixture of 1,3-dibenzyl-5,7-dihydroxy-4-methyl-2(1H)-quinolinone (0.5 g), 3,6-dichloropyridazine (0.83 g) and potassium carbonate (0.75 g) in DMF (12,5 ml) was stirred at 80 °C for 4 hours. The reaction mixture was treated with water at pH 8 and filtered. The solids were recrystallized from ethanol-DMF (2:1). Yield 0.5 g. Melting point 208-218°C.

¹H-NMR (DMSO-*d*₆, 300 MHz): 2.43 (s, 3H, CH₃), 4.16 (s, 2H, CH₂Ph), 5.58 (s, 2H, NCH₂Ph), 7.09-7.33 (m, 12H, ArH + Ph), 7.55 (d, 1H, PyridH, J = 9,2 Hz), 7.70 (d, 1H, PyridH, J = 9,2 Hz), 7.93 (d, 1H, PyridH, J = 9,2 Hz), 7.98 (d, 1H, PyridH, J = 9,2 Hz).

b) 5,7-Bis -[1-(6-hydroxypyridazinyl)]oxy-1,3-dibenzyl-4-methyl-2(1H)-quinolinone

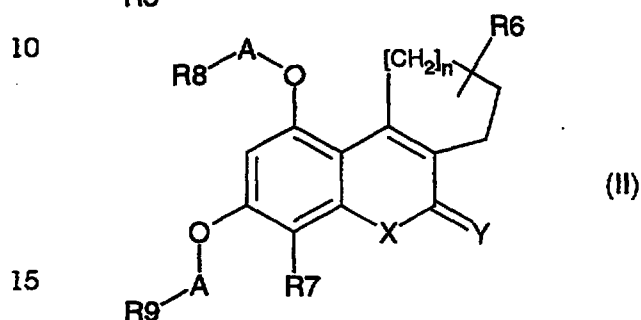
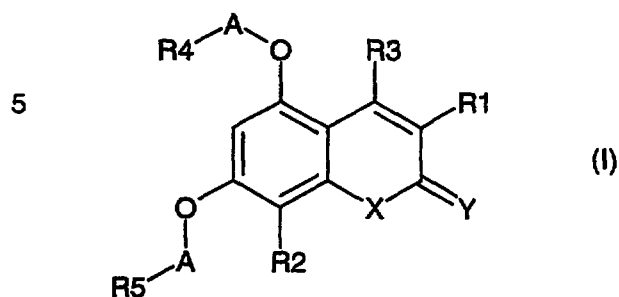


The product from the previous example (0.2 g) and potassium acetate (0.13 g) in acetic acid (5 ml) were refluxed for 4 hours. The mixture was evaporated, treated with water at pH 10 and filtered. The filtrate was acidified to pH 6 and filtered. Yield 70 mg.

¹H-NMR (DMSO-*d*₆, 300 MHz): 2.47 (s, 3H, CH₃), 4.15 (s, 2H, CH₂Ph), 5.55 (s, 2H, NCH₂), 6.93- 7.34 (m, 15 H, PyridH + ArH + Ph), 7.47 (d, 1H, J = 10 Hz), 12.25 (s, 1H, NH), 12.38 (s, 1H NH).

CLAIMS

1. Compounds of formula (I) or (II):



in which

R₁ is hydrogen, alkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl,
 20 halogenalkyl, alkoxy, COR₁₀, CONR₁₀R₁₁, OR₁₀, S(O)_mR₁₀,
 NR₁₀COR₁₁ or NR₁₀R₁₁, where R₁₀ is hydrogen, alkyl, alkenyl, aryl,
 arylalkyl, hydroxyalkyl, halogenalkyl, alkoxy or hydroxy and R₁₁ is hydrogen,
 alkyl, aryl, arylalkyl, alkoxy, aryloxy, hydroxy or acyl, or in case where X is
 NR₁₁, can R₁ also be carboxylalkyl,

25 R₆ is hydrogen, alkyl, alkenyl, aryl, arylalkyl,

R₂ and R₇ mean hydrogen, alkyl, aryl, arylalkyl, alkenyl, COR₁₀,
 CONR₁₀R₁₁, halogen, trifluoromethyl, nitro or cyano, where R₁₀ and R₁₁
 are defined as above,

R₃ is hydrogen, alkyl, aryl or arylalkyl,

30 A means alkyl or substituted alkyl,

m is 0-2 and n is 1-3,

Y means O, NR₁₁ or S, where R₁₁ is the same as above,

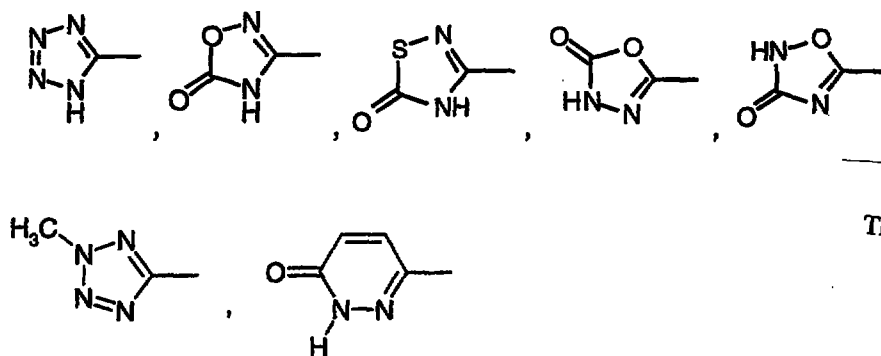
X means O, NR₁₁ or S, where R₁₁ is the same as above,

R₄, R₅, R₈ and R₉ mean independently one of the following groups:

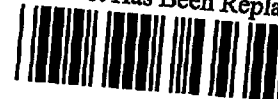
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This Sheet Has Been Replaced



5

or in case where X is NR₁₁, can R₄, R₅, R₈ and R₉ also independently mean HOOC-, R₁₂OOC-, H₂NCO- or HOHNCO-, wherein R₁₂ means alkyl, arylalkyl or aryl, and wherein each aryl residue defined above by itself or as part of another group may be substituted, and pharmaceutically acceptable salts and esters thereof, provided that the compound of formula (I) is not 3-benzyl-5,7-bis((1H-tetrazol-5-yl)-methoxy)-4-methyl-2H-1-benzopyran-2-one.

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2. A compound of claim 1 wherein said compound has formula (I) and R₂ is hydrogen.

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3. A compound of claim 2 wherein R₁ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ halogenalkyl or C₁₋₆ alkoxy.

4. A compound of claim 3 wherein Y is O or S, and X is O.

25

5. A compound of claim 3 wherein Y is O or S; and X is NR₁₁, where R₁₁ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl, C₁₋₆ alkoxy, C₆₋₁₀ aryloxy, hydroxy, C₁₋₆ alkanoyl or C₁₋₆ carboxyalkyl.

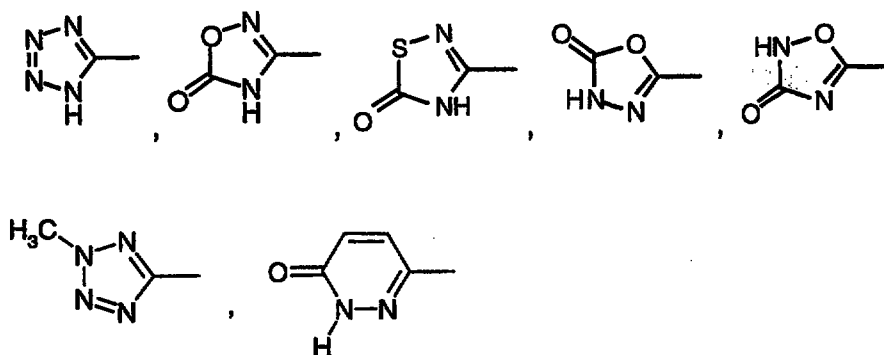
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6. A compound of claim 5, wherein R₃ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, or C₇₋₁₂ arylalkyl.

7. A compound of claim 6, wherein R₃ is C₁₋₆ alkyl.

8. A compound of claim 7, wherein A is straight-chain or branched C₁₋₄ alkylene and R₄ and R₅ are each





- 5 ; or where X is NR₁₁, then R₄ and R₅ can also be HOOC-, R₁₂OOC-, H₂NCO- or HOHNCO-, where R₁₂ is C₁₋₆ alkyl, C₆₋₁₀ aryl, or C₇₋₁₂ arylalkyl.

9. A compound of claim 1, wherein said compound has formula (II) and
10 R₇ is hydrogen.

10. A compound of claim 9, wherein R₆ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl; and n is 1, 2 or 3.

- 15 11. A compound of claim 10, wherein Y is O or S, and X is O.

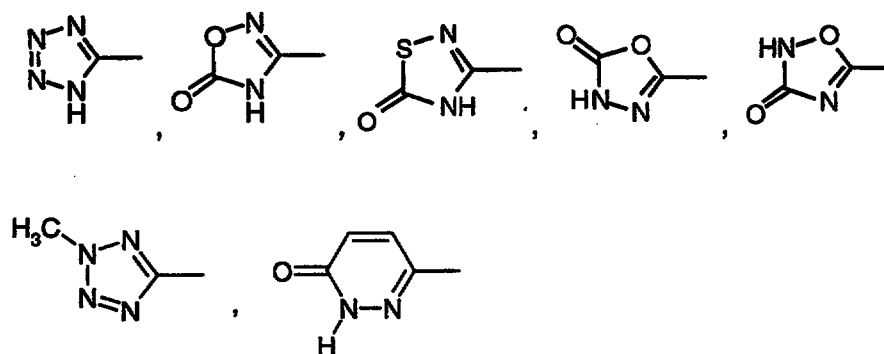
12. A compound of claim 10, wherein Y is O or S; and X is NR₁₁, where R₁₁ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ arylalkyl, C₁₋₆ alkoxy, C₆₋₁₀ aryloxy, hydroxy, C₁₋₆ alkanoyl or C₁₋₆ carboxyalkyl.

20

13. A compound of claim 11, wherein A is straight-chain or branched C₁₋₄ alkylene.

14. A compound of claim 13, wherein R₄ and R₅ are each

25



; or where X is NR₁₁, then R₄ and R₅ can also be HOOC-, R₁₂OOC-, H₂NCO- or HOHNCO-, where R₁₂ is C₁₋₆ alkyl, C₆₋₁₀ aryl, or C₇₋₁₂ arylalkyl.

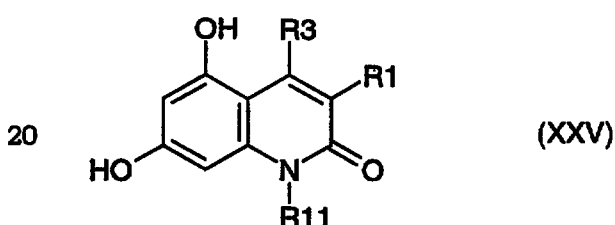
5 15. A pharmaceutical composition comprising a compound of claim 1 as an active ingredient together with pharmaceutically acceptable carrier.

16. A method of treating heart failure comprising administering to a subject in need thereof a therapeutically effective amount of a compound of
10 claim 1.

17. A method for the treatment and prevention of stunned myocardium comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

15

18. A compound of formula (XXV):



wherein R₁ is hydrogen, alkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl,
25 halogenalkyl, alkoxy, COR₁₀, CONR₁₀R₁₁, OR₁₀, S(O)_mR₁₀, NR₁₀COR₁₁ or NR₁₀R₁₁, where R₁₀ is hydrogen, alkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl, halogenalkyl, alkoxy or hydroxy and R₁₁ is hydrogen, alkyl, aryl, arylalkyl, alkoxy, aryloxy, hydroxy or acyl, or carboxylalkyl,

R₃ is hydrogen, alkyl, aryl or arylalkyl,

30 R₁₁ is hydrogen, alkyl, aryl, arylalkyl, alkoxy, aryloxy, hydroxy or acyl, or carboxylalkyl,

and wherein each aryl residue defined above by itself or as part of another group may be substituted.

