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The preparation and the physico-chemical characterization of 2*H*-pyrido[2,3-*e*]-1,3-oxazine-2,4(3*H*)-diones, 2*H*-pyrido[4,3-*e*]-1,3-oxazine-2,4(3*H*)-diones, 2*H*-pyrido[4,3-*e*]-1,3-oxazin-4(3*H*)-ones, 2*H*-thieno[2,3-*e*]-1,3-oxazin-4(3*H*)-ones and 2*H*-thieno[3,4-*e*]-1,3-oxazine-2,4(3*H*)-diones are reported.

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Introduction.

Organic nitrates have been in therapeutic use for the treatment of angina pectoris for over a century and during the last decade, the search for new organic nitro esters with reduced side-effects and improved oral bioavailability has greatly intensified [1]. During our studies for new organic nitrates with a different profile than glyceryl trinitrate (GTN), we discovered a new class of compounds, such as **1** [2] and **2** [3] (Figure 1), which are characterized by a coronary vascular selectivity greater than GTN and good oral activity. ITF 296 is now under clinical evaluation.

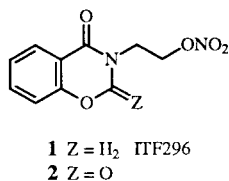


Figure 1

In order to verify if the benzoxazinone system was particular for the activity, we decided to substitute the aromatic ring with an heteroaromatic one (Figure 2).

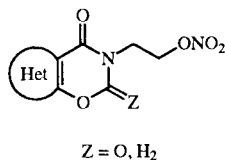


Figure 2

Chemistry.

The synthesis of compounds **7a**, **7b** and **7c** is reported in Scheme 1. The treatment of methyl esters **3a** [4] or **3b** [5] with ethanolamine at 170° [6] gave the corresponding 2-hydroxyethylamides **4a** or **4b** which were directly con-

verted into the chloro derivatives **5a** and **5b** with thionyl chloride without further purification. The cyclization of these compounds with 1,1'-carbonyldiimidazole gave fused bicyclic systems **6a** and **6b**, instead the cyclization of **5b** with paraformaldehyde under acidic condition, using a modification of the procedure previously described [7] gave 2*H*-pyrido[4,3-*e*]-1,3-oxazin-4(3*H*)-one system **6c**. The three chloro derivatives **6a**, **6b** and **6c** were converted into the target compounds **7a**, **7b** and **7c** by treatment with silver nitrate in refluxing acetonitrile [8]. The analytical data of compounds **6a-c** and **7a-c** are reported in Table 1.

Scheme 1

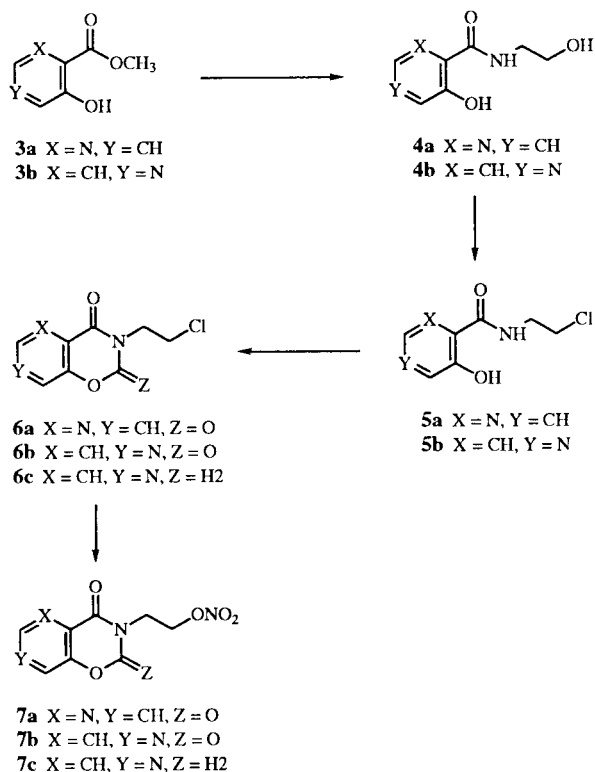


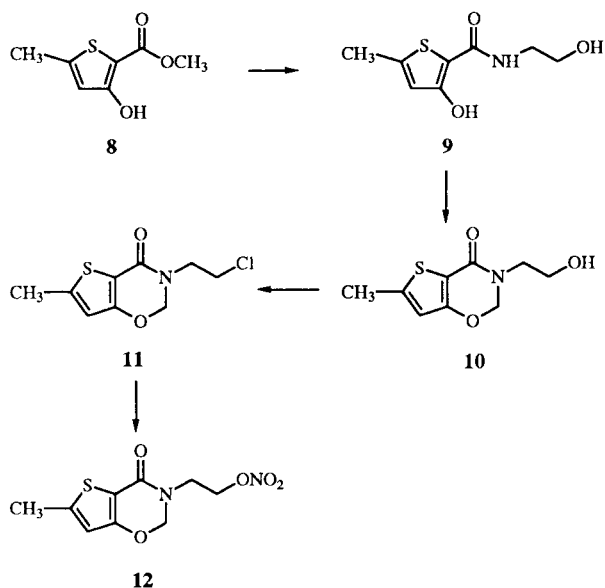
Table 1
Analytical Data for Compounds **6a-c** and **7a-c**

Compound	Mp °C [a]	¹ H-NMR (200 MHz, DMSO-d ₆)	Molecular Formula	Analysis, % (Calcd./Found)			
				C	H	N	Cl
6a	136-138	8.70 (1H, dd), 7.97 (1H, dd), 7.89 (1H, dd), 4.10 (2H, t), 3.85 (2H, t)	C ₉ H ₇ ClN ₂ O ₃	47.80 47.91	3.11 3.08	12.36 12.21	15.65 15.36
6b	139-140	8.89 (1H, s), 8.68 (1H, d), 7.92 (1H, d), 4.27 (2H, t), 3.87 (2H, t)	C ₉ H ₇ ClN ₂ O ₃	47.80 47.94	3.11 3.05	12.36 12.25	15.65 15.37
6c	154-156	8.55 (1H, s), 8.46 (1H, d), 7.73 (1H, d), 5.53 (2H, s), 3.91 (4H, s)	C ₉ H ₉ ClN ₂ O ₂	50.83 50.97	4.27 4.30	13.18 13.19	16.67 16.53
7a	105-107	8.72 (1H, dd), 7.99 (1H, dd), 7.87 (1H, dd), 4.79 (2H, t), 4.30 (2H, t)	C ₉ H ₇ N ₃ O ₆	42.70 42.70	2.79 2.76	16.60 16.51	
7b	98-99	8.92 (1H, s), 8.70 (1H, d), 7.94 (1H, d), 4.78 (2H, m), 4.23 (2H, m)	C ₉ H ₇ N ₃ O ₆	42.70 42.77	2.79 2.69	16.60 16.48	
7c	79-80	8.55 (1H, s), 8.45 (1H, d), 7.72 (1H, d), 5.50 (2H, s), 4.74 (2H, m), 3.89 (2H, m)	C ₉ H ₉ N ₃ O ₅	45.19 45.37	3.79 3.86	17.57 17.42	

[a] Crystallization solvent, ethyl ether.

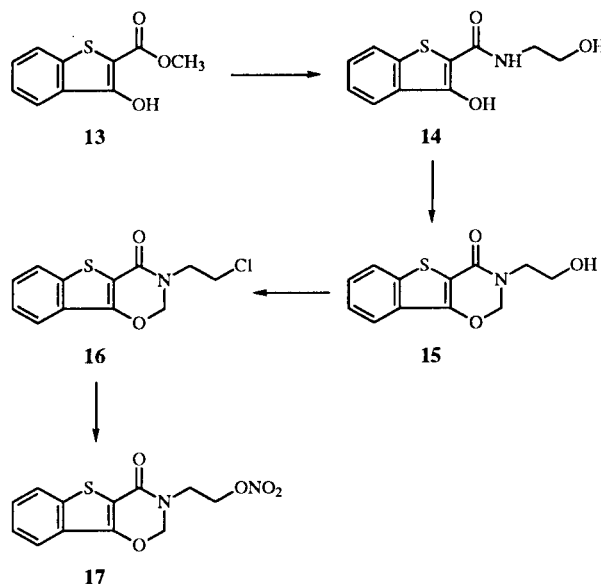
For the preparation of 6-methyl-3-(2-nitrooxyethyl)-2*H*-thieno[2,3-*e*]-1,3-oxazin-4(3*H*)-one **12** and 3-(2-nitrooxyethyl)-2*H*-benzothieno[2,3-*e*]-1,3-oxazin-4(3*H*)-one **17** we had to modify the synthesis (Scheme 2 and 3) because of the instability of compounds **9** and **14**, which were prepared following the same procedure as described above, under the strong condition of the chlorination reaction. So we cyclized the molecule first with paraformaldehyde under acidic condition, giving compounds **10** and **15**, and then transformed the hydroxy group to chlorine with thionyl chloride yielding compounds **11** and **16**. The treatment of chloro derivatives **11** and **16** with silver nitrate gave the final nitro esters **12** and **17**.

Scheme 2



Due to the high instability of the 4-hydroxythiophene-3-carboxylic acid system, for the synthesis of nitroester

Scheme 3



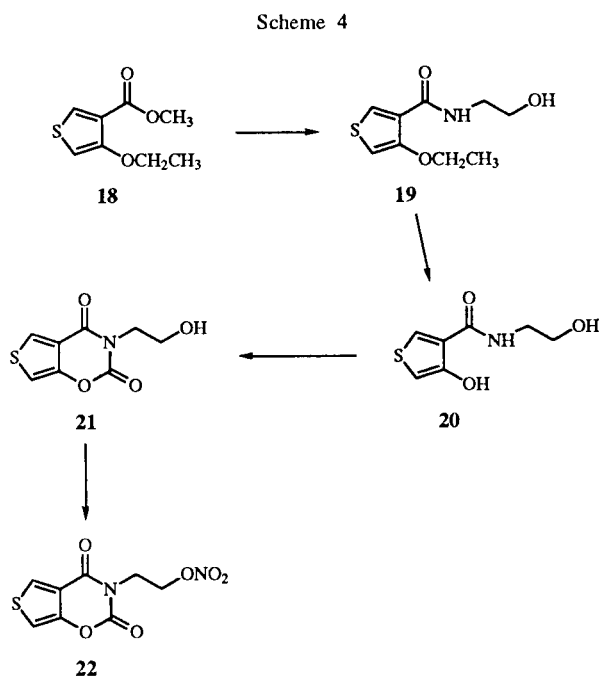
22 we had to change the whole synthetic pathway (Scheme 4). First we protected the hydroxy group as ethyl ether, so starting from ethyl 4-ethoxythiophene-3-carboxylate **18** [9] we obtained *N*-(2-hydroxyethyl)-4-hydroxythiophene-3-carboxamide **20** after treatment with ethanolamine followed by deprotection with boron tribromide at room temperature. Using all our cyclization conditions, we were not able to cycle compound **20** with paraformaldehyde, so we decided to use 1,1'-carbonyldiimidazole yielding 3-(2-hydroxyethyl)-2*H*-thieno[3,4-*e*]-1,3-oxazine-2,4(3*H*)-dione **21**. Compound **21** was unstable under the chlorination reaction, so we had to convert the alcohol directly to the nitroester **22** using tetrabutylammonium nitrate as nitrate donor, and trifluoromethanesulfonic anhydride for the activation of the

Table 2
Analytical Data for Compounds 12, 17 and 22

Compound	Mp °C [a]	¹ H-NMR (200 MHz, DMSO-d ₆)	Molecular Formula	Analysis, % (Calcd./Found)			
				C	H	N	Cl
12	87-89	6.71 (1H, s), 5.41 (2H, s), 4.67 (2H, t), 3.79 (2H, t), 2.48 (3H, s)	C ₉ H ₁₀ N ₂ O ₅ S	41.86 41.93	3.90 3.98	10.85 10.81	12.41 12.50
17	88-89	8.07 (1H, dd), 7.85 (1H, dd), 7.56 (2H, m), 5.66 (2H, s), 4.74 (2H, t), 3.90 (2H, t)	C ₁₂ H ₁₀ N ₂ O ₅ S	48.98 49.03	3.42 3.50	9.52 9.50	10.89 10.96
22	110-113	8.57 (1H, d), 7.49 (1H, d), 4.75 (2H, t), 4.22 (2H, t)	C ₈ H ₆ N ₂ O ₆ S	37.21 37.49	2.34 2.41	10.85 10.64	12.42 12.23

[a] Crystallization solvent, *n*-hexane.

hydroxy group [10]. The analytical data of compounds 12, 17 and 22 are reported in Table 2. All nitroesters synthesized were tested but none of these were active showing that the aromatic system was necessary for the anti-anginal activity.



EXPERIMENTAL

General.

Melting points were determined on a Buchi 530 apparatus in glass capillary tubes and were uncorrected. Thin-layer chromatography was performed on silica gel glass backed plates (5719) purchased from E. Merck & Co., and flash chromatography was performed on silica gel 60 (230-400 mesh ASTM) (E. Merck & Co). The ¹H-nmr spectra were recorded at room temperature on a Varian CFT-20 (80 MHz) or a Varian Gemini 200 (200 MHz) spectrometer and the chemical shifts are given in ppm (δ) refer-

enced to the DMSO-d₆ (2.50 ppm). Elemental analyses were carried out on a Perkin Elmer 240. The analytical data of compounds 6a-c, 7a-c, 12, 17 and 22 are reported in Tables 1 and 2.

N-(2-Hydroxyethyl)-3-hydroxypyridine-2-carboxamide (4a).

Ethanolamine (25 g, 163 mmol) and methyl-3-hydroxypyridine-2-carboxylate (3a) [4] (10 g, 163 mmol) were heated at 170° while the formed methanol was distilled away. After 3 hours the mixture was cooled to room temperature and the crude product (29.6 g) was used immediately for the next step without further purification; ¹H-nmr (80 MHz, DMSO-d₆): δ 9.00 (1H, bt), 8.16 (1H, dd), 7.56 (1H, t), 7.43 (1H, dd), 4.86 (1H, bs), 3.56 (4H, m).

N-(2-Hydroxyethyl)-3-hydroxypyridine-4-carboxamide (4b) was synthesized following the same procedure as described above starting from methyl-3-hydroxypyridine-4-carboxylate (3a) [5] yielding 4b which was used immediately for the next step without further purification; ¹H-nmr (80 MHz, DMSO-d₆): δ 8.99 (1H, bt), 8.37 (1H, s), 8.16 (1H, d), 7.78 (1H, d), 4.88 (1H, bs), 3.57 (2H, t), 3.40 (2H, q).

N-(2-Chloroethyl)-3-hydroxypyridine-2-carboxamide (5a).

A solution of thionyl chloride (14.4 ml, 197 mmol) in chloroform (70 ml) was added to a solution of alcohol 4a (29.6 g, 163 mmol) in chloroform (70 ml) at 0°. The reaction mixture was heated to 60° for 4 hours, then the mixture was cooled to room temperature and washed with a 5% aqueous solution of sodium bicarbonate (2 x 200 ml). The aqueous solution was saturated with sodium chloride and extracted with chloroform. The combined organic phases were dried with sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (eluent chloroform-acetone 95:5) yielding 25.7 g of pure 5a (78%, mp 42-44°, ethyl ether); ¹H-nmr (80 MHz, DMSO-d₆): δ 9.26 (1H, bt), 8.13 (1H, dd), 7.50 (1H, t), 7.43 (1H, dd), 3.76 (4H, m).

Anal. Calcd. for C₈H₉ClN₂O₂: C, 47.89; H, 4.52; Cl, 17.67; N, 13.97. Found: C, 48.02; H, 4.45; Cl, 17.73; N, 13.93.

N-(2-Chloroethyl)-3-hydroxypyridine-4-carboxamide (5b) was synthesized following the same procedure as described above starting from 4b yielding 5b (70%, mp 111-112°, ethyl ether); ¹H-nmr (80 MHz, DMSO-d₆): δ 9.04 (1H, bt), 8.63 (1H, s), 8.33 (1H, d), 8.05 (1H, d), 3.70 (4H, s).

Anal. Calcd. for C₈H₉ClN₂O₂: C, 47.89; H, 4.52; Cl, 17.67; N, 13.97. Found: C, 47.99; H, 4.41; Cl, 17.63; N, 13.90.

3-(2-Chloroethyl)-2*H*-pyrido[2,3-*e*]-1,3-oxazine-2,4(3*H*)-dione (6a).

A solution of 1,1'-carbonyldiimidazole (2.4 g, 14 mmol) in chloroform (50 ml) was added slowly to a solution of **5a** (2.4 g, 12 mmol) in chloroform (50 ml), then the mixture was stirred overnight at room temperature. The mixture was then washed with brine, the organic phase was dried with sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (eluent chloroform-acetone 9:1) yielding 2.8 g of pure **6a** (76%).

3-(2-Chloroethyl)-2H-pyrido[4,3-*e*]-1,3-oxazine-2,4(3H)-dione (**6b**) was synthesized following the same procedure as described above starting from **5b** yielding **6b** (82%).

3-(2-Chloroethyl)-2H-pyrido[4,3-*e*]-1,3-oxazin-4(3H)-one (**6c**).

Paraformaldehyde (4 g, 131 mmol) was added to a solution of **5b** (3.1 g, 13 mmol) and *p*-toluenesulfonic acid (2.5 g, 13 mmol) in acetic acid (65 ml) and the reaction mixture was heated to reflux for 3 hours. Then the mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude was dissolved in chloroform and 1*N* aqueous solution of sodium hydroxide. The phases were separated and the aqueous solution was extracted with chloroform. The combined organic phases were dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (eluent chloroform-acetone 8:2) yielding 2.3 g of pure **6c** (80%).

3-(2-Nitrooxyethyl)-2H-pyrido[2,3-*e*]-1,3-oxazine-2,4(3H)-dione (**7a**).

A solution of **6a** (2 g, 9 mmol) and silver nitrate (6 g, 35 mmol) in acetonitrile (70 ml) was heated to reflux for 4 hours. Then the mixture was cooled to room temperature and salts were filtered off and the solvent was removed under reduced pressure. The crude product was dissolved in chloroform and the organic phase was washed with water, dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (eluent chloroform-acetone 9:1) yielding 1 g of pure **7a** (44%).

3-(2-Nitrooxyethyl)-2H-pyrido[4,3-*e*]-1,3-oxazine-2,4(3H)-dione (**7b**) was synthesized following the same procedure described above starting from **6b** yielding **7b** (50%).

3-(2-Nitrooxyethyl)-2H-pyrido[4,3-*e*]-1,3-oxazin-4(3H)-one (**7c**) was synthesized following the same procedure described above starting from **6c** yielding **7c** (43%).

N-(2-Hydroxyethyl)-3-hydroxy-5-methylthiophen-2-carboxamide (**9**).

Ethanolamine (18.6 ml, 309 mmol) and methyl 3-hydroxy-5-methylthiophene-2-carboxylate (**8**) [11] (17.8 g, 103 mmol) were heated at 170° for 1 hour. Then the mixture was cooled to room temperature and dissolved with dichloromethane and sodium chloride saturated 1*N* solution of hydrochloric acid. The two phases were separated and the organic phase was washed with brine, dried with sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (eluent chloroform-acetone 8:2) yielding 10 g of pure **9** as low melting solid (48%); ¹H-nmr (80 MHz, DMSO-*d*₆): δ 7.63 (1H, bt), 6.50 (1H, s), 4.80 (1H, bs), 3.76-3.20 (4H, m), 2.43 (3H, s).

Anal. Calcd. for C₈H₁₁NO₃S: C, 47.74; H, 5.51; N, 6.96; S, 15.93. Found: C, 47.91; H, 5.48; N, 6.79; S, 15.67.

N-(2-Hydroxyethyl)-3-hydroxybenzothiophene-2-carboxamide (**14**) was synthesized following the same procedure

described above starting from methyl 3-hydroxybenzothiophenecarboxylate **13** [12] yielding **14** as low melting solid (85%); ¹H-nmr (80 MHz, DMSO-*d*₆): δ 8.26 (1H, bt), 7.97 (2H, m), 7.46 (2H, m), 4.66 (1H, bs), 3.70-3.30 (4H, m).

Anal. Calcd. for C₁₁H₁₁NO₃S: C, 55.68; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.85; H, 4.58; N, 5.68; S, 13.33.

6-Methyl-3-(2-hydroxyethyl)-2H-thieno[2,3-*e*]-1,3-oxazin-4(3H)-one (**10**).

Paraformaldehyde (6.3 g, 210 mmol) and acetic acid (2.4 ml, 42 mmol) were added to a suspension of **9** (8.5 g, 42 mmol) in chloroform (80 ml). The reaction mixture was saturated with hydrogen chloride gas and stirred at room temperature for 15 minutes. The solution obtained was washed with water, dried with sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (eluent chloroform-acetone 8:2) yielding 3.15 g of pure **10** as amorphous solid (35%); ¹H-nmr (80 MHz, DMSO-*d*₆): δ 6.68 (1H, s), 5.37 (2H, s), 4.85 (1H, bs), 3.50 (4H, m), 2.47 (3H, s).

Anal. Calcd. for C₉H₁₁NO₃S: C, 50.69; H, 5.20; N, 6.57; S, 15.03. Found: C, 50.47; H, 5.15; N, 6.44; S, 14.86.

3-(2-Hydroxyethyl)-2H-benzothiopheno[2,3-*e*]-1,3-oxazin-4(3H)-one (**15**).

Paraformaldehyde (3.74 g, 124 mmol), compound **14** (7.9 g, 31 mmol) and *p*-toluenesulfonic acid (590 mg, 3.1 mmol) in toluene (130 ml) were heated to reflux for 2 hours. Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with water, dried with sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (eluent ethyl acetate-*n*-hexane 8:2) yielding 1.5 g of pure **15** as amorphous solid (20%); ¹H-nmr (80 MHz, DMSO-*d*₆): δ 8.07-7.36 (4H, m), 5.56 (2H, s), 4.86 (1H, bs), 3.50 (4H, m).

Anal. Calcd. for C₁₂H₁₁NO₃S: C, 57.81; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.58; H, 4.33; N, 5.67; S, 12.75.

6-Methyl-3-(2-nitrooxyethyl)-2H-thieno[2,3-*e*]-1,3-oxazin-4(3H)-one (**12**).

Thionyl chloride (1.2 ml, 17 mmol) was added to a suspension of alcohol **10** (3 g, 14 mmol) in chloroform (40 ml). The reaction mixture was heated to reflux for 3 hours, then it was cooled at room temperature, washed with water and dried with sodium sulfate and the solvent was removed under reduced pressure. The crude chloro derivative **11** was then dissolved in acetonitrile (80 ml) and silver nitrate (5.3 g, 31 mmol) was added and the solution was heated to reflux for 4 hours. Then the mixture was cooled to room temperature and salts were filtered off and the solvent was removed under reduced pressure. The crude material was dissolved in chloroform and the organic phase was washed with water, dried with sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (eluent *n*-hexane-ethyl acetate 7:3) yielding 1.8 g of pure **12** (49%).

3-(2-Nitrooxyethyl)-2H-benzothiopheno[2,3-*e*]-1,3-oxazin-4(3H)-one (**17**) was synthesized following the same procedure as described above starting from alcohol **15** yielding **17** (47%).

N-(2-Hydroxyethyl)-4-ethoxythiophene-3-carboxamide (**19**).

Ethanolamine (6 ml, 100 mmol) was added to ethyl 4-ethoxythiophene-3-carboxylate (**18**) [9] (5.75 g, 29 mmol)

and the reaction mixture was stirred at room temperature for 4 days. The crude product (6.18 g) was used immediately for the next step without further purification; ^1H -nmr (200 MHz, deuteriochloroform): δ 8.07 (1H, d), 7.93 (1H, bt), 6.30 (1H, d), 4.12 (2H, q), 3.79 (2H, t), 3.58 (2H, q), 1.49 (3H, t).

N-(2-Hydroxyethyl)-4-hydroxythiophene-3-carboxamide (**20**).

A solution of ether **19** (4 g, 18 mmoles) in dichloromethane (40 ml) was slowly added to a 1M solution of boron tribromide in dichloromethane (36 ml, 36 mmoles). The reaction mixture was stirred at room temperature for 24 hours, then the solvent was evaporated under reduced pressure and the crude material was dissolved in ethyl acetate and brine. The two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with sodium sulfate and the solvent was removed under reduced pressure yielding 3.17 g of crude **20** as a yellow oil (90%) which was used immediately for the next step without further purification; ^1H -nmr (200 MHz, DMSO- d_6): δ 8.42 (1H, bt), 8.10 (1H, d), 6.48 (1H, d), 3.52 (2H, t), 3.35 (2H, q).

3-(2-Hydroxyethyl)-2H-thieno[3,4-*e*]-1,3-oxazine-2,4(3H)-dione (**21**).

A solution of 1,1'-carbonyldiimidazole (5.5 g, 34 mmoles) in THF (10 ml) was added slowly to a solution of **20** (3.17 g, 17 mmoles) in THF (10 ml). The mixture was stirred at room temperature for 1 hour, then it was acidified to pH 1 with 2 N solution of hydrochloric acid and the solution was stirred for 1 hour. The reaction mixture was saturated with sodium chloride and the two phases were separated and the aqueous phase was extracted with fresh THF. The combined organic phases were dried with sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (eluent toluene-methanol 9:1) yielding 1.55 g of pure **21** as amorphous solid (43%); ^1H -nmr (200 MHz, DMSO- d_6): δ 8.51 (1H, d), 7.45 (1H, d), 3.94 (2H, t), 3.59 (2H, t).

Anal. Calcd. for $\text{C}_8\text{H}_6\text{NO}_4\text{S}$: C, 45.28; H, 2.85; N, 6.60; S, 15.11. Found: C, 45.45; H, 2.97; N, 6.38; S, 15.06.

3-(2-Nitrooxyethyl)-2H-thieno[3,4-*e*]-1,3-oxazine-2,4(3H)-dione (**22**).

A solution of trifluoromethanesulfonic anhydride (2 ml, 12 mmoles) in dichloromethane (21 ml) was slowly added at -50° to a solution of alcohol **21** (1.3 g, 6 mmoles), tetrabutylammonium nitrate (3.7 g, 12 mmoles) and pyridine (1 ml, 12 mmoles) in dichloromethane-DMF 1:1 (70 ml). The reaction mixture was stirred at -50° for 20 minutes, then the solution was heated at 40° for 1 hour. The mixture was cooled at room temperature, diluted with water and the two phases were separated. The organic phase was washed with 1 N solution of hydrochloric acid, saturated solution of sodium bicarbonate and water, then was dried with sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (eluent *n*-hexane-ethyl acetate 9:1) yielding 230 mg of pure **22** (14%).

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