Synthesis and Cardiotonic Activity of Pyrimido[5,4-*b*][1,4]oxazinones and 1,4-Dioxino[2,3-*d*]pyrimidines

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The new pyrimido[5,4-*b*][1,4]oxazinones **4a-c** and **6a,b**, **7a,c** were obtained from 6-amino-2,3-dimethyl-4(3*H*)-pyrimidone (**1**) and 4-substituted pyrimido[5,4-*b*][1,4]oxazinones **5**, **7a**, respectively, while derivatives **8a-e** of the novel ring system 1,4-dioxino[2,3-*d*]pyrimidine were prepared starting from **2b**.

Compounds **4a**, **4c** and **7a** showed positive inotropic effect.

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In the recent years, the search for novel cardiotonics of non-glycoside type has attracted attention to some classes of heterocyclic compounds.

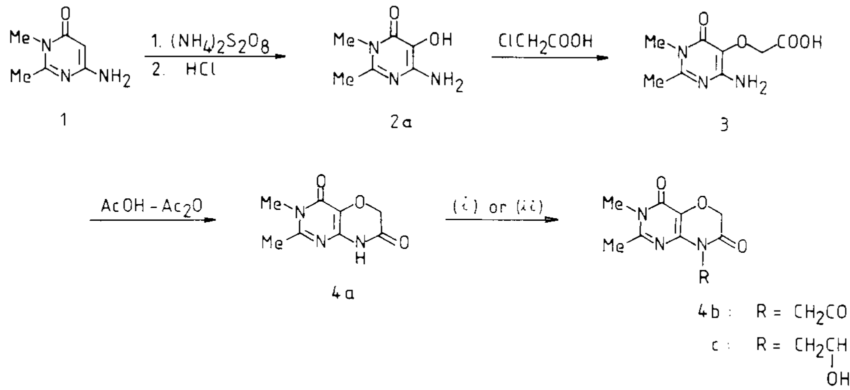
Previous papers from our laboratory [1,2] have described two novel groups of positive inotropic agents, however, none of which could have selected for further development because of their poor absorption. More recently, we have reported [3] that pyrimido[5,4-*b*][1,4]oxazinones characterized by alkylenediamine moiety in the 4-position possess strong and long lasting positive inotropic effect by both oral and intravenous administration. One compound of this series, namely 2-methyl-4-(2-morpholinoethylamino)-6,7-dihydropyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one fumarate, has been investigated as a potential drug candidate for the treatment of congestive heart failure in a detailed study [4]. These findings prompted us to prepare other derivatives and 1,4-dioxino analogs of the parent pyrimido[5,4-*b*][1,4]oxazine.

The synthesis of pyrimido[5,4-*b*][1,4]oxazin-4,7(3*H*,8*H*)-diones was achieved as shown in Scheme I. Thus, 6-amino-2,3-dimethylpyrimidine-4(3*H*)-one (**1**) was converted to its 5-hydroxy derivative **2a** by Elbs oxidation using ammonium persulfate [5]. Compound **2a** was then treated with chloroacetic acid to give the pyrimidin-5-yloxyacetic acid derivative **3** which on heating with a mixture of acetic anhydride and acetic acid cyclized to the desired 2,3-dimethyl-6,7-dihydropyrimido[5,4-*b*][1,4]oxazin-4,7(3*H*,8*H*)-dione (**4a**). The 8-substituted derivatives **4b** and **4c** were subsequently produced by alkylation of **4a**, with ethyl chloroacetate in 2-butanone or with glycidol in the presence of tetrabutylammonium bromide as catalyst, respectively.

The 4-aminoalkoxy- and 4-aminoalkylthiopyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-ones **6a** and **7a** were prepared by S$_N$Ar reaction of **5** with the appropriate aminoalkanol and thiol, respectively, whereas **6b** was obtained from **6a** with glycidol. Oxidation of **7b** with hydrogen peroxide in acetic acid gave the 4-methylsulfonyl derivative **7c** (Scheme II).

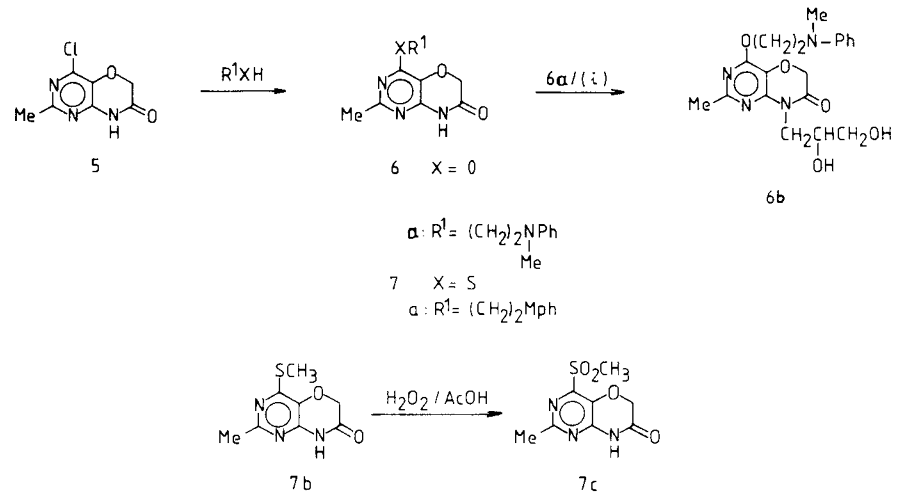
The synthesis of derivatives of the novel ring system 1,4-dioxino[2,3-*d*]pyrimidine was achieved according to Scheme III. Treatment of **2b** with dibromoethane in aqueous sodium hydroxyde afforded 4-amino-2-methyl-6,7-dihydro-1,4-dioxino[2,3-*d*]pyrimidine (**8a**) and no evidence of formation of the corresponding dihydropyrimido[5,4-*b*][1,4]oxazine was observed. On reacting **8a** with diethyl ethoxymethylenemalonate at 120°, the aminomethylenemalonate **8e** was obtained. Acylation of **8a** with acetic anhydride or isocyanates led to the 4-acetylamino derivative **8b**

Scheme I



(i) $ClCH_2COOEt$ / K_2CO_3 ; (ii) glycidol/ $Bu_4N^+Br^-$

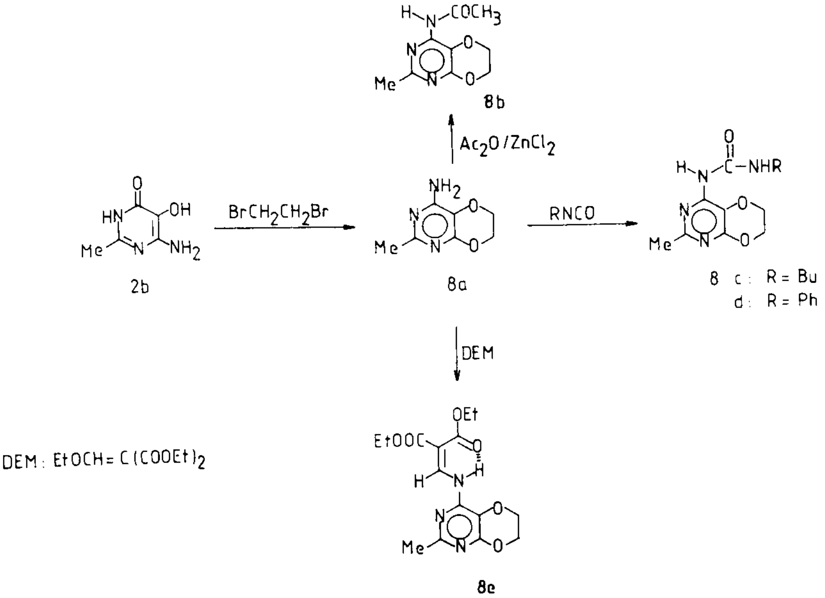
Scheme II



Mph : morpholino

(i) glycidol / $Bu_4N^+Br^-$

Scheme III



DEM: EtOCH=C(COOEt)₂

and the urea derivatives **8c,d**, respectively, in moderate-to-good yields.

Both acylation and alkylation of other 4-aminopyrimidines have been well documented. It was stated that the reaction of 4-amino-2,6-dimethylpyrimidine with chloroacetic anhydride gave the 4-chloroacetylamino derivative [6], whereas 4-aminopyrimidines, when treated with methyl iodide, underwent *endo-N*-methylation either at *N*-1 or *N*-3 depending on the substituent at position-6 [7]. Similarly, when 8-bromo-9-methyladenine was reacted with methyl iodide, the corresponding 1-methylated product was formed, *i.e.* also in this case, nuclear methylation took place [8].

In our compounds, the *exo-N* position of the substituent was proved by ^1H nmr data. In the case of **8e**, the N*H* signal has a chemical shift of δ 15.8 ppm and shows a splitting of 13 Hz due to the coupling with the methylene proton. These facts are in agreement with the hydrogen-bonded structure of **8e** as shown in Scheme III. The chemical shifts of the 2-methyl signals in **8b-e** are within a narrow range (Table 1) supporting the analogous constitution, *i.e.* the *exo-N*-substitution, for **8b-d**, as well. Obviously, in the cases of *N*-1 and/or *N*-3 substitutions, these signals should differ from that of **8e** to a much higher extent. The analytical data of these compounds are summarized in Table 2.

Table 1

^{1}H NMR (deuteriochloroform, δ ppm) Data of Compounds **8a-e**

Compound	CH_3 (s) 3H	OCH_2 (m) 4H	4-NH (br s) 1H	Other signals (J, Hz)
8a	2.35	4.3	5.17 [a]	
8b	2.47	4.3	7.7	2.54 (s, 3H, NHCO-CH_3)
8c	2.45	4.3	9.2	0.97 (t, 6, 3H, CH_3CH$_2$), 1.53 (m, 4H, CH$_2$CH$_2$), 3.35 (q, 2H, NHCH_2)
8d	2.57	4.3	11.6	7.2 (s, 1H, NH), 7.0-7.7 (m, 5H, Ph–H)
8e	2.48	4.4	15.8 [b]	1.35 (t, 7, 3H, CH$_2$CH_3), 1.37 (t, 7, 3H, CH$_2$CH_3), 4.22 (q, 2H, CH_2CH$_3$), 4.30 (q, 2H, CH_2-CH$_3$), 9.00 (d, 13, 1H, CH)

[a] Singlet of 2H intensity. [b] Doublet (J = 13 Hz).

The inotropic effect of novel derivatives was investigated as described earlier [1]. Of compounds tested, **4a** and **4c** showed a moderate activity whereas **8a-e** were practically inactive. Compound **7a** possessed remarkable positive inotropic effect.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. The ir spectra were recorded in potassium bromide pellets on a Bruker IFS 85 spectrometer, ^{1}H nmr spectra were measured on a Varian EM 390 spectrometer using TMS as internal reference and DMSO-d$_6$ as solvent unless otherwise stated.

Syntheses of compounds **1** [9], **2b** [5], **5** [10], **7b** [11], 2-*N*-methyl-*N*-phenylaminoethanol [12] and 2-morpholinoethanethiol [13] were performed to the quoted literature.

6-Amino-5-hydroxy-2,3-dimethylpyrimidin-4(3*H*)-one (**2a**).

A solution of ammonium persulfate (9.22 g, 40 mmoles) in water (18 ml) was added to **1** (4.30 g, 31 mmoles) in 3*N* sodium hydroxide (60 ml) with stirring. After 2 hours at room temperature, the mixture was acidified with 12*N* hydrochloric acid and cooled. The crude sulfate ester of **2a** was filtered off and washed with

Table 2

Physical and Analytical Data of Compounds **2a**, **3**, **4a-c**, **6a-c**, **7a**, **7c**, **8a-e**

Compound	mp (°C) (Crystallized from)	Yield (%)	Molecular Formula	Analysis (%) (Found/Calcd.) C	H	N	S
2a	>260 (ethanol)	27	$C_{16}H_9N_3O_2$ (155.16)	46.28 46.44	6.13 5.85	26.92 27.08	
3	>260 (50% ethanol)	48	$C_{18}H_{11}N_3O_4$ (213.19)	45.12 45.07	5.32 5.20	19.54 19.71	
4a	>260 (ethanol)	66	$C_8H_9N_3O_3$ (195.18)	49.17 49.23	4.82 4.65	21.35 21.53	
4b	150-152 (2-butanone)	52	$C_{12}H_{15}N_3O_5$ (281.26)	51.38 51.24	5.26 5.38	14.85 14.94	
4c	164-165 (50% ethanol)	63	$C_{11}H_{15}N_3O_5$ (269.25)	49.50 49.06	5.85 5.65	15.41 15.61	
6a	154-155 (ethanol)	52	$C_{16}H_{18}N_4O_3$ (314.34)	60.92 61.13	5.82 5.77	17.65 17.83	
6b	105-106 (2-propanol)	97	$C_{19}H_{24}N_4O_5$ (388.41)	58.70 58.75	6.27 6.23	14.62 14.43	
7a	148-149 (ethanol)	37	$C_{13}H_{18}N_4O_3S$ (310.37)	50.27 50.30	5.65 5.85	18.19 18.05	10.45 10.33
7c	203-204 (ethanol)	49	$C_8H_9N_3O_4S$ (243.25)	39.45 39.50	3.65 3.73	17.12 17.28	13.31 13.18
8a	167-170 (ethanol)	42	$C_7H_9N_3O_2$ (167.17)	50.02 50.29	5.65 5.43	25.02 25.14	
8b	168-169 (2-propanol)	65	$C_9H_{11}N_3O_3$ (209.20)	51.55 51.67	5.40 5.30	20.01 20.09	
8c	102-104 (ethanol)	74	$C_{12}H_{18}N_4O_3$ (266.30)	54.23 54.12	6.69 6.81	21.00 21.04	
8d	214-215 (acetone)	42	$C_{14}H_{14}N_4O_3$ (286.29)	58.53 58.73	4.98 4.93	19.27 19.57	
8e	160-162 (ethanol)	81	$C_{15}H_{19}N_3O_6$ (337.33)	53.61 53.41	5.42 5.68	12.55 12.46	

cold water. Then, it was added to 5*N* hydrochloric acid (10 ml) and the mixture was heated under reflux for 20 minutes. The reaction mixture was basified with ammonia solution in water (d, 0.91) to *p*H = 8 and left at 5° overnight. The title product was isolated by suction and recrystallization.

This compound had ir: ν C=O 1668, 1637 cm^{-1}; ^{1}H nmr: δ 2.37 (s, 3H, 2-CH_3), 3.40 (s, 3H, N-CH_3).

6-Amino-2,3-dimethyl-4-oxo-3,4-dihydropyrimidin-5-yloxyacetic Acid (**3**).

Chloroacetic acid (5.48 g, 58 mmoles) was added to **2a** in a solution of sodium hydroxide (7.28 g, 180 mmoles) in water (75 ml) with stirring. After 3 hours at 80°, the cooled mixture was filtered. The solid was dissolved in water (80 ml) and the solution was acidified with 12*N* hydrochloric acid to *p*H = 2. The precipitate was was filtered off and recrystallized.

This compound had ir: ν C=O 1643 cm^{-1}; ^{1}H nmr: δ 2.37 (s, 3H, 2-CH_3), 3.37 (s, 3H, N-CH_3), 4.43 (s, 2H, CH_2).

2,3-Dimethyl-6,7-dihydropyrimido[5,4-*b*][1,4]oxazin-4,7-(3*H*,8*H*)-dione (**4a**).

Compound **3** (1.09 g, 5 mmoles) was added to a mixture of acetic anhydride (1 ml) and acetic acid (5 ml). After heating for 3 hours under reflux, the cooled reaction mixture was filtered. The crude product was purified by recrystallization.

This compound had ir: ν C=O 1709, 1661 cm^{-1}; ^{1}H nmr: δ 2.41 (s, 3H, 2-CH_3), 3.40 (s, 3H, N-CH_3), 4.47 (s, 2H, 6-CH_2).

8-Ethoxycarbonylmethyl-2,3-dimethyl-6,7-dihydropyrimido-[5,4-*b*][1,4]oxazin-4,7(3*H*,8*H*)-dione (**4b**).

Compound **4a** (1.95 g, 10 mmoles) was added to a mixture of ethyl chloroacetate (1.23 g, 10 mmoles) and anhydrous potassium carbonate (1.52 g, 11 mmoles) in 2-butanone (30 ml) with stirring. The reaction mixture was heated under reflux for 4.5 hours and then filtered. The filtrate was left to stand at 5° for a night and the precipitate was filtered off. The crude product was purified by recrystallization.

This compound had ir: ν C=O 1747, 1709, 1668 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.28 (t, 3H, $CH_2C\mathit{H}_3$), 2.47 (s, 3H, 2-CH_3), 3.52 (s, 3H, N-CH_3), 4.18 (q, 2H, $C\mathit{H}_2CH_3$), 4.68 (s, 4H, $C\mathit{H}_2$COOEt+, 6-CH_2).

8-(2,3-Dihydroxypropyl)-2,3-dimethyl-6,7-dihydropyrimido[5,4-*b*]-[1,4]-oxazin-4,7(3*H*,8*H*)-dione (**4c**).

Compound **4a** (1.95 g, 10 mmoles) was added to a mixture of freshly distilled glycidol (1.48 g, 20 mmoles) and tetrabutylammonium bromide (0.32 g, 1 mmole) in anhydrous benzene (40 ml) with stirring. The reaction mixture was heated under reflux for 6 hours and filtered. The crude product was recrystallized.

This compound had ir: ν C=O 1709, 1661 cm^{-1}; ^{1}H nmr: δ 2.47 (s, 3H, 2-CH_3), 3.32 (m, 2H, NCH_2), 3.43 (s, 3H, N-CH_3), 3.75-4.05 (m, 5H, CH_2CHCH_2), 4.55 (t, 1H, $CH_2O\mathit{H}$), 4.60 (s, 2H, 6-CH_2), 4.76 (d, 1H, $CHO\mathit{H}$).

2-Methyl-4-(2-*N*-methyl-*N*-phenylaminoethyl)-6,7-dihydropyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one (**6a**).

A solution of 2-*N*-methyl-*N*-phenylaminoethanol (3.02 g, 20 mmoles) in dimethyl formamide (6 ml) was added dropwise at 10° to a mixture of sodium hydride (as 50% oil dispersion, 1.00 g, 22 mmoles) in dimethyl formamide (10 ml) with stirring. After 10 minutes at this temperature, compound **5** (2.00 g, 10 mmoles) was added to the mixture. The reaction mixture was stirred at room temperature for 1 hour and then heated at 85° for 9 hours. The solvent was removed *in vacuo* the residue was taken up in water (20 ml) and extracted with chloroform (4 x 50 ml). The organic layer was dried and evaporated. The crude product was recrystallized.

This compound had ms: m/z (%) 157 (3), 133 (100), 132 (45), 120 (98).

8-(2,3-Dihydroxypropyl)-2-methyl-4-(2-*N*-methyl-*N*-phenylaminoethyl)-6,7-dihydropyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one (**6b**).

This compound was prepared from **6a** by the same procedure as described for **4c**.

This compound had ir: ν C=O 1707 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.48 (s, 3H, 2-CH_3), 2.98 (s, 3H, NCH_3), 3.72 (t, 2H, $NC\mathit{H}_2CH_2$), 3.1-4.6 (m, 7H, 8-subst.), 4.60 (t, 2H, OCH_2), 4.63 (s, 2H, 6-CH_2), 6.65 (m, 3H, *o,p*-PhH), 7.20 (m, 2H, *m*-PhH).

2-Methyl-4-(2-morpholinoethylthio)-6,7-dihydropirimido[5,4-*b*]-[1,4]oxazin-7(8*H*)-one (**7a**).

2-Morpholinoethanethiol (0.73 g, 5 mmoles) was added dropwise to a mixture of sodium hydride (50% oil dispersion, 0.25 g, 5.2 mmoles) in dimethyl formamide (1 ml) with stirring. After 10 minutes, compound **5** was added and the reaction mixture was heated at 120° for 12 hours. The solvent was evaporated *in vacuo* and the residue was taken up in water (10 ml). The solution was acidified with 2*N* hydrochloric acid and extracted with ethyl acetate (4 x 40 ml). The organic layer was dried and evaporated. The crude product was recrystallized.

This compound had ir: ν C=O 1705 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.57 (m, 4H, $N(CH_2)_2$), 2.58 (s, 3H, 2-CH_3), 2.68 (t, 2H, SCH_2), 3.35 (t, 2H, CH_2N), 3.72 (m, 4H, $(CH_2)_2O$), 4.68 (s, 2H, 6-CH_2).

2-Methyl-4-methylsulfonyl-6,7-dihydropyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one (**7c**).

To a solution of **7b** (2.65 g, 12.5 mmoles) in glacial acetic acid (25 ml), 30% hydrogen peroxyde (6.5 ml) was added dropwise. After 3 hours at 75°, water (15 ml) was added to the cooled mixture. The solvent was then evaporated *in vacuo* and the residue recrystallized.

This compound had ir: ν C=O 1751 cm^{-1}; ^{1}H nmr: 2.52 (s, 3H, 2-CH_3), 3.23 (s, 3H, SO_2CH_3), 4.83 (s, 2H, 6-CH_2).

4-Amino-2-methyl-6,7-dihydro-1,4-dioxino[2,3-*d*]pyrimidine (**8a**).

A solution of potassium hydroxyde (3.69 g, 66 mmoles) in water (25 ml) was added to a mixture of **2b** (2.82 g, 20 mmoles) and 1,2-dibromoethane (8.46 g, 45 mmoles) in water (20 ml) with stirring. After 20 hours at reflux, the solvent and excess of 1,2-dibromoethane were removed *in vacuo* and the residue taken up in chloroform. The insoluble was filtered off and the filtrate was washed with 1*N* sodium hydroxyde. The organic layer was dried and evaporated. The crude product was recrystallized.

This compound had ir: ν NH_2 3470, 3285 cm^{-1}.

4-Acetylamino-2-methyl-6,7-dihydro-1,4-dioxino[2,3-*d*]pyrimidine (**8b**).

Acetic anhydride (1.08 g, 10.5 mmoles) was added to a solution of **8a** (1.00 g, 6 mmoles) and zinc chloride (0.10 g, 0.7 mmoles) in dichloromethane (50 ml). After 10 hours at reflux, the solution was washed with water and dried. After evaporation, the crude product was recrystallized.

This compound had ir: ν C=O 1690 cm^{-1}.

Reaction of **8a** with Isocyanates.

The appropriate isocyanate (30 mmoles for **8c** and 20 mmoles for **8d**) was added to a solution of **8a** (1.67 g, 10 mmoles) in dioxane (50 ml) with stirring. After 12 hours at reflux, the product was isolated as follows. The precipitate was filtered off, the filtrate was evaporated and the residue was recrystallized (for **8c**) or the solvent was removed *in vacuo* from the reaction mixture and the crude product was recrystallized (for **8d**).

N-Butyl-*N'*-(2-methyl-6,7-dihydro-1,4-dioxino[2,3-*d*]pyrimidin-4-yl)urea (**8c**).

This compound had ir: ν C=O 1710, 1685 cm^{-1}.

N-Phenyl-*N'*-(2-methyl-6,7-dihydro-1,4-dioxino[2,3-*d*]pyrimidin-4-yl)urea (**8d**).

This compound had ir: ν C=O 1695 cm^{-1}.

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