Synthesis of New Tricyclic Ring Systems Containing the Pyrimido[5,4-*b*][1,4]oxazine Skeleton

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Synthesis of derivatives **4** and **6** of two novel tricyclic ring systems, 1,2,4-triazolo[3,4-*c*]pyrimido[5,4-*b*][1,4]oxazine and imidazo[1,2-*c*]pyrimido[5,4-*b*][1,4]oxazine, respectively is described. Although the parent pyrimido[5,4-*b*]oxazines possess positive inotropic activity, the tricyclic compounds are practically inactive.

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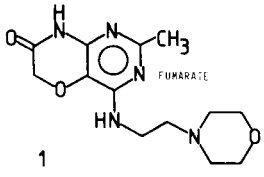
In the course of our program focused on the synthesis of potentially cardiotonic compounds of non-glycoside type [1,2], we have discovered that some members of pyrimido-[5,4-*b*][1,4]oxazines exert a strong and long lasting positive inotropic effect [3,4]. One of these compounds, GYKI-12735 (**1**), has been selected for further development as a promising agent for the treatment of congestive heart failure [5].



(GYKI - 12735)

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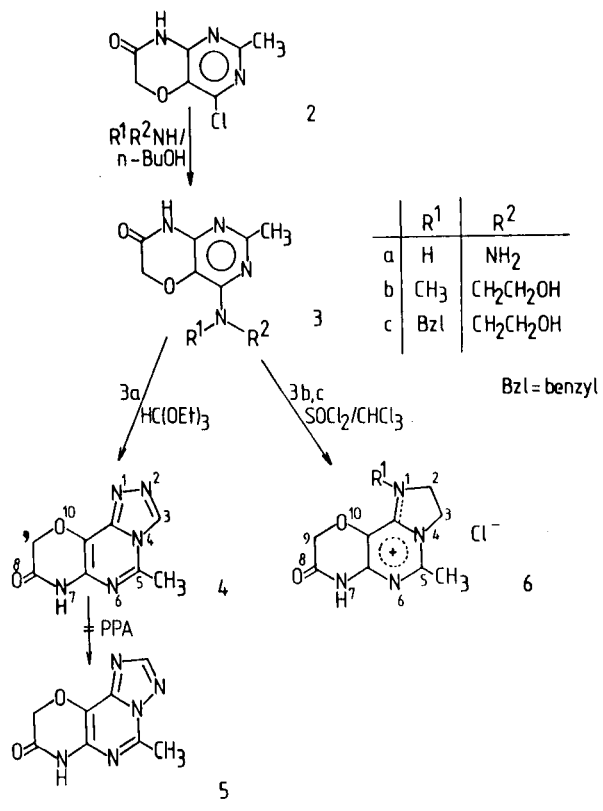
In order to fully evaluate the contribution of the pyrimidine moiety to the inotropic activity we have also synthesized some novel fused triazolo and dihydroimidazo derivatives of the parent system.

The appropriate starting materials, the 4-hydrazino **3a** and 4-(2-hydroxyethylamino) **3b,c** derivatives, respectively, were prepared following the earlier described procedure [3] from 4-chloro-6,7-dihydro-2-methylpyrimido-[5,4-*b*][1,4]oxazin-7(8*H*)-one (**2**) [6] with hydrazine hydrate or the appropriate 2-aminoethanol, respectively, in 1-butanol at 110°.

Compound **3a** was then converted to the fused triazole **4** by treatment with triethyl orthoformate under reflux (Scheme 1).

Scheme 1



	R^1	R^2
a	H	NH_2
b	CH_3	CH_2CH_2OH
c	Bzl	CH_2CH_2OH

Bzl = benzyl

It is well known that in the synthesis of triazoles of type **4**, the formation of the isomers of type **5** by Dimroth rearrangement has to be taken into consideration, also. For decision between such isomers, the chemical shift of the triazole proton is of diagnostic value: if $\delta H^{rr} > 8.7$ ppm, the constitution of type **5** can be excluded [7]. In our case the H-3 signal appeared as a singlet at 9.40 ppm so proving unambiguously the annellation of type **4**. The rearrangement was not achieved either by heating of **4** with polyphosphoric acid at 120° for one hour.

On treatment of **3b,c** with thionyl chloride in chloroform, the desired fused dihydroimidazole derivatives **6b** and **6c**, respectively, were formed in good yield. In the ^1H nmr spectrum of **6b,c** signals due to the imidazole protons appeared as two virtual triplets in the range δ 3.9-4.7 ppm being characteristic for dihydroimidazopyrimidines [8]. The constitution of **6b** and **6c** was also confirmed by DNOE experiments. Irradiation of the resonance of the triplets at 4.60 and 4.70 ppm, respectively, gave positive enhancement for the signal of 5-methyl group. On the contrary, irradiation of the triplet at 4.00 ppm in derivative **6b** and 3.95 ppm in **6c**, respectively, resulted in a positive NOE on the signal of the *N*-methyl and benzylic methylene groups, respectively.

Table 1

Physical and Analytical Data of Compounds **3a,c**, **4**, **6b** and **6c**

Compound No.	mp (°C) (crystallized from)	Yield (%)	Molecular formula	Analysis (%) (Found/Calcd.) C	H	N	Cl
3a	264-266 (ethanol)	56	$C_7H_9N_5O_2$ (195.18)	42.88 43.07	4.75 4.65	35.45 35.90	
3b	150-151 (ethanol)	92	$C_{10}H_{14}N_4O_3$ (238.24)	50.65 50.41	5.68 5.92	23.38 23.52	
3c	135-137 (2-propanol)	75	$C_{16}H_{18}N_4O_3$ (314.33)	61.02 61.13	5.83 5.77	17.60 17.82	
4	>300 (DMF)	95	$C_8H_7N_5O$ (205.18)	46.42 46.83	3.71 3.44	33.81 34.14	
6b	284-287 (2-propanol)	87	$C_{10}H_{13}ClN_4O_2$ (256.69)	46.69 46.79	5.32 5.11	21.65 21.83	13.38 13.81
6c	266-268 (2-propanol)	92	$C_{16}H_{17}ClN_4O_2$ (332.79)	57.62 57.74	5.43 5.15	16.59 16.84	10.42 10.66

The properties of these compounds are summerized in Table 1.

While compounds **3a-c** showed moderate-to-good positive inotropic effect, all fused tricyclic derivatives **4**, **6b** and **6c** were practically inactive. This fact demonstrates the importance of the availability of the pyrimidine ring nitrogen of compounds of type **3** for potent positive inotropic activity.

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. The ^1H nmr spectra were recorded (in DMSO-d_6) on a Bruker AC-250 spectrometer at 250.13 MHz with TMS as the internal standard.

General Method for the Preparation of 6,7-Dihydro-2-methylpyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one Derivatives **3a-c** [3].

Hydrazine hydrate, 2-benzyl- or 2-methylaminoethanol (0.25 mole), respectively, in 1-butanol (40 ml) was added dropwise to a stirred solution of 4-chloro-6,7-dihydro-2-methylpyrimido[5,4-*b*][1,4]oxazin-7(8*H*)-one (**2**) (0.10 mole) in 1-butanol (100 ml) at reflux temperature. After heating for a half (for **3a**) or twelve hours (for **3b,c**), the product was isolated either by suction for **3a** or by work up as follows for **3b,c**. The solvent was evaporated under *vacuo* and water was added to the residue. The precipitate was filtered and recrystallized.

8,9-Dihydro-5-methyl-1,2,4-triazolo[3,4-*c*]pyrimido[5,4-*b*][1,4]-oxazin-8(7*H*)-one (**4**).

A mixture of 1.95 g (0.01 mole) of **3a** and an excess of triethyl orthoformate (10 ml) was heated under reflux until tlc shows absence of starting material (*ca.* 2 hours). The precipitate was filtered, washed with ethanol and recrystallized. This compound had ir: ν C=O 1707 (amide-I) cm^{-1}; ^1H nmr: δ 2.79 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 9.40 (s, 1H, 3-CH), 11.35 (s, 1H, NH).

General Method for the Preparation of 2,3,8,9-Tetrahydro-5-methyl-8-oxo-7*H*-imidazo[1,2-*c*]pyrimido[5,4-*b*][1,4]oxazinium Chloride Derivatives **6b,c**.

A solution of **3b** or **3c** (0.01 mole) in chloroform (10 fold by volume), respectively, was treated with thionyl chloride (0.015 mole). After a slightly exothermic reaction took place, the reaction mixture was heated under reflux for two hours. The product was separated either by suction for **6b** or by work up as follows for **6c**. The solution was concentrated under reduced pressure, the residue was treated with diethyl ether and the precipitate was filtered.

2,3,8,9-Tetrahydro-1,5-dimethyl-8-oxo-7*H*-imidazo[1,2-*c*]pyrimido-[5,4-*b*][1,4]oxazinium chloride (**6b**).

This compound had ir: ν HN^+ 3040-2600, ν C=O 1720, ν C=N 1664 cm^{-1}; ^1H nmr: δ 2.50 (s, 3H, 5-CH_3), 3.30 (s, 3H, 1-CH_3), 4.00 (t (J = 9 Hz), 2H, 2-CH_2); 4.70 (t, 2H, 3-CH_2), 4.80 (s, 2H, 9-CH_2), 12.0 (br s, 1H, NH).

1-Benzyl-2,3,8,9-tetrahydro-5-methyl-8-oxo-7*H*-imidazo[1,2-*c*]-pyrimido[5,4-*b*][1,4]oxazinium Chloride (**6c**).

This compound had ir: ν HN^+ 3200-2600, ν C=O 1713, ν C=N 1655 cm^{-1}; ^1H nmr: δ 2.55 (s, 3H, 5-CH_3) 3.95 (t(9), 2H, 2-CH_2), 4.60 (t(9), 2H, 3-CH_2), 4.80 (s, 2H, 9-CH_2), 5.00 (s, 2H, Ph-CH_2), 7.50 (s, 5H, Ph-H); 12.1 (br s, 1H, NH).

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