SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF FLUORINE-CONTAINING DERIVATIVES OF 1,2,3,4-TETRAHYDROPYRIMIDINE

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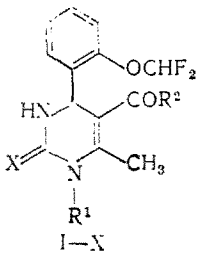
Derivatives of 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid exhibit antitumor and antiviral activity [5, 7]. We were the first to find that amides and β-aminoethyl esters of this acid manifest hypotensive and coronary dilatory properties [1, 3]. As part of our search for new effective cardiovascular agents we synthesized previously unknown esters of 1,2,3,4-tetrahydropyrimidine-5-carboxylic acid that contain fluorinated groups in the aryl substituent (I-X). The fluorine-containing tetrahydropyrimidines were obtained by a modified Biginelli condensation [4], starting with urea or its derivatives, acetoacetic acid esters or acetylacetone, and o-difluoromethoxybenzaldehyde.



I—X

X = O (I—VIII), S (IX, X); R^1 = H (I, III—V, VII, IX), CH_3 (II, VI, VIII), C_6H_5 (X); R^2 = CH_3 (III), OCH_3 (I, II), OC_2H_5 (IV, IX, X), i-C_3H_7O (V, VI), i-$C_5H_{11}O$ (VII, VIII)

The synthesized tetrahydropyridines are colorless crystals. As opposed to the tetrahydropyrimidines I, III-V, VII, and IX that are unsubstituted in position 1, the UV-spectra of the 2-oxo-5-carboxylic acid esters (II, VI, VIII, and X) exhibited a bathochromic shift [(Δ) 9 and 27 respectively) of the longwave maximum. The insertion of an acetyl group into position 5 also yielded a bathochromic shift of the longwave maximum [(Δ) 17 nm] as opposed to the complex ester group.

The structure of the tetrahydropyrimidines was also confirmed by IR- and PMR spectra (Table 1).

In the course of examining the biological activity of the synthesized compounds we found that they exhibited a certain coronary dilatory and hypotensive activity (Table 2).

At a dose of 0.1 mg/kg compound I did not significantly affect minute blood volume, but the dp/dt did increase and there was a short-term increase (by 25%) in the coronary blood flow rate. Compound II markedly increased coronary flow rate within a period of 30-60 min (at doses of 0.01 and 0.1 mg/kg). Thus, the coronary circulatory effect exhibited by compound II was found to last 10 to 12 times longer than that of the N-substituted tetrahydropyrimidine I.

The replacement of a complex ester group in position 5 by an acetyl group (compounds I and II) did not significantly affect coronary flow and minute volume. The replacement of a methoxy group by an ethoxy group (compounds I and IV) also did not have any significant effect. The isopropyl ester of carboxylic acid V significantly increased coronary circulation, but the effect was short-lived. At the same time we also observed intensive negative inotropic activity.

In contrast to the methyl esters of 5-carboxylic acid I and II, the N-methyltetrahydropyrimidine compound VI had a lesser effect on blood supply and minute volume than did the N-unsubstituted compound V. The isoamyl ester VII increased coronary flow, but did not affect minute volume and the dp/dt. Compound VII had a basically relaxant effect on cardiac vessels. When its dose was increased it exhibited a stronger vasodilator effect that lasted for a shorter period.

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TABLE 1. Derivatives of 6-Methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid

Compound	Yield, %	R_f (system)	mp, °C	Found, %			Empirical formula	Calculated, %			Spectra		
				C	H	N		C	H	N	UV λ_{max}, nm (log ε)	IR, ν, cm^{-1}	PMR δ ppm
I	63,8	0,88 (1) 0,13 (2)	181—182	54,0	4,8	9,0	$C_{11}H_{14}F_2N_2O_4$	53,8	4,5	9,0	226 (3,9), 285 (3,9)	1640, 1698, 3117, 3231, 3356	2,25 s (6-CH_3); 3,56 s (OCH_3); 5,65g (4-H); 6,74 t (CHF_2) J = 74Hz ; 6,96g (3-NH); 7,24 m (ArH); 9,1s (1-NH)
II	68,2	0,3 (2)	176—177	54,8	4,6	8,1	$C_{16}H_{16}F_2N_2O_4$	55,2	4,9	8,6	224 (4,0), 294(5,0)	1635, 1690, 3095, 3228	2,62s (6-CH_3); 3,23 s(N-CH_3); 3,6s (O—CH_3); 5,6g (3-NH); 5,77g (4-H); 6,6 t(CHF_2), J = 73,5Hz; 7,18m(ArH)
III	49,7	0,16 (2)	165—166	57,3	4,4	10,2	$C_{11}H_{11}F_2N_2O_3$	56,7	4,7	9,5	233 (3,8), 302 (3,9)	1646, 1702, 3086, 3220, 3291	2,0 s (6-CH_3); 2,33 s (OCH_3); 5,64g (3-NH); 5,81g (4-H); 6,59 t (CHF_2); J = 73,5Hz; 8,06s (1-NH)
IV	38,8	0,31 (2) 0,91 (1)	155—156	55,4	4,9	8,4	$C_{15}H_{16}F_2N_2O_4$	55,2	4,9	8,6	225 (4,1), 285 (4,1)	1636, 1697, 3120, 3234, 3351	1,07 t (CH_3—Et); 2,42s (6-CH_3); 4,02q (CH_2—Et); 5,56g (3-NH); 5,74g (4-H); 6,55 t (CHF_2); J = 74Hz; 7,19m (ArH), 8,29 (1-NH).
V	66,0	0,08 (4) 0,83 (1)	95—97	56,5	5,5	7,9	$C_{16}H_{18}F_2N_2O_4$	56,5	5,3	8,2	225 (4,1), 285 (4,1)	1647, 1674, 1705, 3120, 3252	0,95 (CH_3—Pp); 1,44m(CH_2—Pp); 2,27s (6-CH_3); 3,92 t (CH_2—O); 5,75g (4-H); 5,92g (3-NH), 6,54 t (CHF_2)
VI	52,8	0,75 (2)	142—143	57,4	5,2	7,8	$C_{17}H_{20}F_2N_2O_4$	57,6	5,7	7,9	226 (4,0), 293 (4,0)	1627, 1682, 1700, 3100, 3234	0,71 t (CH_3—Pr); 1,46q (CH_2—Pr); 2,63s (6-CH_3); 3,22 s (N—CH_3); 3,92 t (OCH_2); 5,73m (4-H, 3-NH); 6,6 t (CHF_2), J = 73,5 Hz 7,2m (Ar—H)
VII	38,6	0,11 (4) 0,86 (1)	120—121	57,8	6,4	7,3	$C_{18}H_{22}F_2N_2O_4$	58,5	6,3	7,6	223 (4,3), 285 (4,3)	1640, 1690, 1707, 3121, 3250, 3548	0,75m (CH_3—Am); 1,28m(CH_2—C); 2,40s (6-CH_3); 3,96 t (CH_2O); 5,75 broad s(4-H, 3 NH), 6,55g (CHF_2), J = 73,5 Hz 7,17 (ArH); 8,75 s (1-NH).
VIII	48,8	0,80 (2)	129—130	60,8	6,3	7,6	$C_{19}H_{24}F_2N_2O_4$	59,7	6,3	6,3	226 (4,1), 293 (4,1)	1630, 1690 3103, 3220	0,73m (CH_3—Am); 1,32m(CH_2—Am); 2,40s (6-CH_3); 3,22 s (N—CH_3); 4,0 t (CH_2O); 5,6g (3-NH); 5,7 g(4-H); 6,5 t(CHF_2), J = 74 Hz
IX	70,0	0,65 (4)	193—194	52,3	4,8	7,9	$C_{15}H_{16}F_2N_2O_3S$	52,6	4,7	8,2	205 (4,3), 289 (4,2)	1610, 1665, 3180, 3290	0,96 t (CH_3—Et); 2,24 s(6-CH_3); 3,84 q(CH_2—Et); 5,44g (4-H); 7,04 (CHF_2), J = 73,9Hz; 9,37g (3-NH); 10,22s (1-NH)
X	60,7	0,30 (4)	153—154	60,2	5,0	6,9	$C_{21}H_{20}F_2N_2O_3S$	60,3	4,8	7,6	206 (4,8), 310 (4,6)	1630, 1710 3180	0,99 t (CH_3—Et); 1,82s (6-CH_3); 3,93q (CH_2—Et); 5,62g (4-H) 7,13 t (CHF_2); J = 73,2Hz

Note. System 1) methanol—acetone—water (2:8:1), system 2) chloroform—hexane—ethyl-acetate (1:1:1), system 3) hexane—isopropanol (3:1), system 4) chloroform—hexane—acetone (9:7:1). PMR spectra of IX-X recorded in DMSO-d_6.

There were no significant changes in the compounds' properties when an oxygen atom was replaced by a sulfur atom in position 2 of the tetrahydropyrimidine ring. Compound X with a phenyl substituent on the nitrogen atom in position 1 induced a prolonged increase in coronary circulation rate when administration at a dose of 0.1 mg/kg. Compounds IX and X manifested negative inotropic activity.

Compounds I-IV had practically no effect on systolic arterial pressure in acute experiments in anesthetized cats and spontaneously hypertensive rats (SHR). The N-substituted tetrahydropyrimidine, compound II, induced a hypotensive response in acute experiments (at a dose of 0.1 mg/kg). The tetrahydropyrimidines V-VIII with a longer alkyl chain in position 5 induced a hypotensive response in SHR. The 2-thio-1,2,3,4-tetrahydropyrimidines IX-X had little effect on arterial pressure.

Thus, most of the investigated tetrahydropyrimidines did not significantly affect systematic arterial pressure in either anesthetized or non-anesthetized (SHR) animals. Compounds V-VI induced a strong cardiodepressive reaction accompanied by a pronounced increase in peripheral resistance.

All of the investigated compounds had a comparatively low degree of acute toxicity, i.e., LD_{50} > 100 mg/kg.

EXPERIMENTAL CHEMICAL PART

IR-spectra were read on a Perkin-Elmer 580 B instrument in the form of a suspension of Nujol. UV-spectra were recorded on a Specord UV-vis instrument in ethanol (with $5 \cdot 10^{-5}$ moles). PMR spectra were recorded on a WH 90/DC (90 MHz) in a $CDCl_3$ solution with tetramethylsilane as the internal standard. The reaction was monitored by TLC on Silufol UV-254 plates.

N-methyl-2-oxo-4-(o-difluoromethoxyphenyl)-5-methoxycarbonyl-6-methyl-1,2,3,4-tetrahydropyrimidine (VI). A mixture of 2.83 g (0.0016 mole) of o-difluoromethoxybenzaldehyde, 1.2 g (0.0016 mole) of methylurea, and 1.9 g (0.0016 mole) of methyl acetoacetate was boiled for 8 h in 10 ml of ethanol in the presence of several drops of concentrated HCl. A precipitate formed upon cooling and the resultant product was crystallized from ethanol (see Table 1).

TABLE 2. Effect of Tetrahydropyrimidine Derivatives on Hemodynamics

Compound	Dose, mg/kg (iv)	Arterial pressure, %		Coronary flow increase		Blood minute volume, %	dp/dt, %
		cats	spontaneously hypertensive rats (10 mg/kg ip)	effect, %	duration, min		
I	0,01	12↓		9	3	7↑	3↑
	0.1	—	6↓	25	5	—	25↑
	1,0	8↑		25	8	50↓	75↓
II	0,01	5↑		20	30	36↑	11↑
	0,1	35↓	—	30	60	47↑	7↑
III	0.01	—	—	...	...	5↓	5↑
	0,1	—		16	13	22↓	16↑
	1,0	—		10	5	—	18↓/22↑
IV	0,01	—	—	—	—	...	5↑
	0.1	11↓		12	8	5↑	10↑
	1,0	13↓		32	21	20↓	20↓
V	0.01	18↓		29	5	14↓	20↓
	0,1	10↓	15↓	44	10	74↓	89↓
	1,0	—		84	5	...	...
VI	0,01	—		—	—	—	—
	0,1	5↓	14↓	11	6	32↓	15↑
	1,0	17↓		13	5	55↓	—
VII	0,01	6↑	14↓	25	8	—	—
	0.1	9↑		45	22	—	—
VIII	0.1	—	—	20	25	18↓	7↑
	1,0	10↓		67	5	9↓	17↑
IX	0.01	8↓	11↓	—	—	9↑	—
	0.1	16↓		7	20	25↓	—
X	0.01	21↓	13↓	—	—	10↓	—
	0.1	11↓		24	30	25↓	—

Note. Averages are given for five tests.

The remaining tetrahydropyrimidines were obtained in a similar fashion. The duration of the condensation reaction with thiourea was 3 h.

EXPERIMENTAL PHARMACOLOGICAL PART

The experiments were conducted on Chlorazol-anesthetized (90 mg/kg ip) cats of both sexes, weighing 2.4-3.7 kg. Systemic arterial pressure was recorded electromanometrically from the common carotid with the aid of a MRI-0.5 sensor (Nikon Koden, Japan).

Changes in coronary volume flow rate were evaluated by the amount of effluent blood from the coronary venous sinus in accordance with the N. V. Kaverina method [2]. Minute blood volume was recorded by electromagnetic flow meter (MFV-1200 Nihon Koden flow meter) by attaching the sensor to the ascending segment of the aortic arch. The recordings were made on an RP-6000 polygraph (Nihon Koden).

The test substances were administered iv through a cannula tied to the femoral vein. The compounds were dissolved in a 50% solution of dimethylacetamide for the iv injections.

The effect the test substances had on systolic arterial pressure was examined in the experiments on alert Okamoto Aoki pedigree SHR [6]. We used rats of both sexes aged six to nine months and weighing 180 to 210 g. Systolic arterial pressure was measured by a pneumatic impulse transducer by attaching a cuff to the tail of the rats after they were warmed for 5 min in a chamber at 45°C. Arterial pressure was recorded on a physiograph (Narco Bio Systems, USA). The compounds were administered into the stomach at a dose of 10 mg/kg in the form of an aqueous suspension which was prepared with Tween 80.

Acute toxicity was assayed upon ip administration in white nonpedigree mice weighing 18 to 23 g. Reference lethal doses were determined in three mice. The mice were observed for 10 days after the administration of the test substance and toxic effects and lethal outcomes were recorded.

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