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ANTI-INFLAMMATORY AND ANTIAGGREGATION ACTIVITY OF 11-DEOXYPROSTAGLANDIN E_1 ANALOGS

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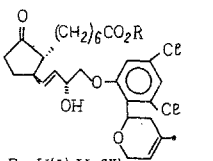
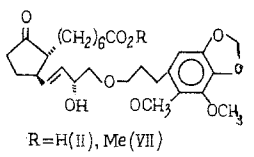
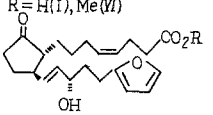
UDC 615.357:577.175.859].07

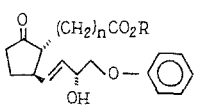
Inflammation, as a complex reaction of the organism to injury, lies at the basis of many diseases. One of the components of the inflammatory reaction is an impairment of blood clotting.

It is known that prostaglandins (PG) play an important role in the development of inflammation. At the same time, there are experimental data indicating that they have an antiphlogistic effect [4]. The aim of this work was to study the influence of analogs of 11-deoxy-PGE_1 (I-V) on inflammatory edema and platelet aggregation. Compounds I-V were produced by saponification of methyl esters of VI-X with an aqueous methanol solution of KOH [1, 5].









R=H, n=10(IV); R=H, n=6(V); R=Me, n=10(IX); R=Me, n=6(X)

EXPERIMENTAL (CHEMICAL)

Silufol plates were used for thin-layer chromatographic analysis, with a mixture of $CHCl_3$–ethanol or benzene–alcohol, 10:1, as the mobile phase.

General Procedure of Hydrolysis of 11-Deoxy-PGE_1 Esters (VI-X). A solution of 0.04 g KOH in 2 ml of water was added to a solution of 0.2 g of the corresponding ester in 5 ml of methanol, and the mixture was mixed at room temperature for 2 h. After the methanol was distilled off, the residue was acidified with 1 N HCl and extracted with ethyl acetate. The combined extracts were washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, evaporated, and 0.16-0.19 g of acid was obtained in the form of a colorless oil, individual according to the TLC data.

EXPERIMENTAL (PHARMACOLOGICAL)

The antiinflammatory action of 11-deoxy-PGE_1 analogs was studied on noninbred white mice weighing 16-18 g on a model of carrageenan and formalin inflammation (1% carrageenan solution were injected under the aponeurosis of one of the hind paws in amounts of 0.05 ml). The compounds studied were injected subcutaneously in doses of 10, 50, and 100 μg/kg. The antiinflammatory effect was judged according to the average percent inhibition of inflammation.

Institute of Organic Chemistry, Urals Branch, Russian Academy of Sciences, Ufa. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 26, Nos. 9-10, pp. 76-77, September-October, 1992. Original article submitted September 12, 1991.

0009-150X/92/0910-0759$12.50

TABLE 1. Influence of 11-Deoxy-PGE_1 Analogs on Edema of Mouse Paws, Induced by Carrageenan and Formalin

Compound	Dose, μg/kg	Inhibition of edema (in %)	
		carrageenan	formalin
I	10	42,3±4,2	30,9±3,1
	50	44,5±3,9	36,1±2,8
	100	46,9±3,1	34,5±3,3
II	10	30,1±2,9	29,7±2,3
	50	28,9±2,6	25,1±3,0
	100	50,8±1,7	37,3±3,2
III	10	37,6±4,1	37,0±4,1
	50	30,4±4,7	30,4±4,7
	100	31,1±4,9	31,1±4,9
IV	10	36,3±3,7	27,6±2,5
	50	34,9±5,6	20,9±1,5
	100	36,5±3,1	36,3±4,2
V	10	—	38,6±3,5
	50	—	35,1±4,5
	100	27,7±4,9	31,2±5,8

TABLE 2. Influence of 11-Deoxy-PGE_1 Analogs on Platelet Aggregation Induced by ADP and Ristomycin

Compound	Aggregation induced by	
	ADP	ristomycin
I	↓42,3±4,7	↓16,2±2,0
II	↓20,0±2,5	↓16,8±2,0
III	↓ 4,1±0,39	↓ 7,8±0,91
IV	↑6,5±0,78	↑11,3±2,1
V	↓8,1±1,0	↓18,1±3,0

Notes. ↓) percent inhibition of platelet aggregation; ↑) percent increase in platelet aggregation.

The antiinflammatory action of 11-deoxy-PGE_1 analogs was compared with the activity of a highly effective antiphlogistic – voltaren, taken in a dose of 8 mg/kg (ED_{50}). Platelet aggregation was determined by the Born method [3]. Platelet aggregation was induced with ADP (from Reanal) in a final concentration of 2 μM and ristomycin in a concentration of 1.67 mg/ml. The preparations were studied in a $1 \cdot 10^{-6}$ M dilution. The acute toxicity of 11-deoxy-PGE_1 analogs was studied on mice in a single intravenous injection. The parameters of the acute toxicity were determined according to Litchfield and Wilcoxon [2]. The results were treated statistically using the Student criterion.

In the group of 11-deoxy-PGE_1 analogs IV and V the chain length has no effect on the toxicity. However, replacement of the phenyl ring by furan in the ω-chain (compounds III and V) leads to a 2.5-5-fold decrease in toxicity. Thus, LD_{50} was 37.0 (40.4-35.6) mg/kg for I, 40.0 (41.6-38.5) for II, 100.0 (110.0-90.9) for III, 20 (33.0-12.1) for IV, and 27.0 (28.2-25.9) for V.

In all the doses investigated, the 11-deoxy-PGE_1 analogs have an antiinflammatory effect on both models of inflammation. However, compound V in doses of 10 and 50 μg/kg was ineffective on models of carrageenan inflammation (Table 1).

One of the most effective inhibitors of platelet aggregation is PGE_1. Our investigations showed that not all 11-deoxy-PGE_1 analogs exhibit an antiaggregation effect. Thus, compounds I and II in a final concentration of $1 \cdot 10^{-6}$ M inhibited reversible platelet aggregation induced by ADP by 42.3 and 20.0%, respectively (Table 2). The antiaggregation effect of these compounds was also observed on another model of platelet aggregation. The introduction of furan rings (compound III) and a phenoxy-substituent (compounds IV and V) into the ω-chain of PG leads to a significant weakening of the investigated activity.

Thus, by modifications of the chemical structure of 11-deoxy-PGE_1 analogs it is possible to change both the toxicity of the compounds and their biological activity.

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