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SYNTHESIS AND HYPOTENSIVE ACTIVITY OF NOVEL STYRYL DERIVATIVES BASED ON ETHYL-4-(4-METHOXYPHENYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE

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Three-component condensation of thiourea, ethyl acetoacetic ester, and anisaldehyde was performed to synthesize ethyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. This compound interacted with aromatic aldehydes to yield the corresponding styryl derivatives. The hypotensive activity of the compounds synthesized here was assessed.

Keywords: Biginelli reaction, three-component condensation, carboxylates, styryl derivatives of carboxylates, hypotensive activity.

Derivatives of 3,4-dihydryopyrimidin-2(1H)-ones (thiones) obtained by three-component condensation using the Biginelli reaction [1 – 3] are some of the most interesting objects of chemical, physicochemical, and biological studies. This is due mainly to the structural similarity between 3,4-dihydropyrimidin-2(1H)-ones (thiones) and known calcium channel blockers, i.e., dihydropyrimidines (nifedipine, verapamil, amlodipine, isradipine, lacidipine, felodipine, Adalat SL, Isoptin SR), which suggests that they should have antihypertensive properties. Compounds of this series include substances which also have other types of pharmacological activity: anticancer [4], antibacterial [5], analgesic [6], antiviral [7], antioxidant [8], etc. Some compounds are currently undergoing clinical trials as anticancer substances and agents for the treatment of AIDS [9].

Further studies of such "lead" compounds for targeted synthesis of novel biologically active compounds have potential.

The aim of the present work was to synthesize I and its novel styryl derivatives II-IV and to study their hypotensive properties to identify changes in the hypotensive activity of I resulting from introduction of styryl radicals with different substituents into position 6.

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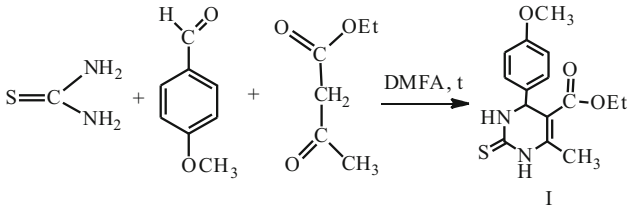
Starting compound I was synthesized by three-component condensation of thiourea, ethyl acetoacetic, ester, and anisaldehyde using the Biginelli reaction with convection heating in dimethylformamide (DMF) using scheme 1.

Scheme 1



I

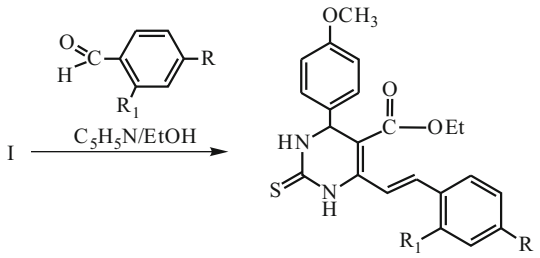
Compounds II-IV were synthesized by condensation of I with the following aromatic aldehydes: *p*-methoxybenzaldyde, *p*-nitrobenzaldehyde, and *o*-chlorobenzaldehyde. Reactions were run in ethanol with boiling for 7 – 8 h in the presence of catalytic quantities of pyridine as shown in Scheme 2.

All the compounds synthesized here were chromatographically pure crystalline substances identified by elemental analysis and IR and ^{1}H NMR spectroscopy data. Yields and physicochemical data for compounds I-IV are presented in Table 1.

The IR spectra of compounds I-IV contained bands for stretch vibrations at 1328 cm^{-1} (C=S-), 1650 cm^{-1} (C=O-), 3150 – 3200 cm^{-1} (NH-), and 2850 cm^{-1} (OCH_3-). Compounds II-IV showed additional bands at 1675 – 1630 cm^{-1}

(-C=C-), while compound III had a band at 1500 cm^{-1} (NO_2-) and compound IV had an additional band at 850 cm^{-1} (Cl^-).

Scheme 2



II – IV

R=OCH_3, R_1=H (II); R=NO_2, R_1=H (III); R=H, R_1=Cl (IV).

The ^{1}H NMR spectra of styryl derivatives II-IV lacked the methyl group singlet from the C(6) atom of the pyrimidinyl ring present in the ^{1}H NMR spectrum of the initial carboxylate I but included additional signals at 6.90 – 7.90 ppm from the aromatic protons of the second phenyl ring and the vinyl protons of the styryl group. Thus, the ^{1}H NMR spectrum of compound II in the strong-field region showed resonance of the ethoxy group methyl moiety protons at 1.12 ppm as a triplet, while the methylene protons of this group appeared as a quartet at 4.05 ppm. Two intense singlets were seen at 4.72 and 4.88 ppm, typical of the two methoxy groups of the aromatic rings, and the aromatic α and β protons of the two phenyl rings were seen at 6.90 and 7.13 ppm as two doublets. The signal from the C(4) proton in the pyrimidine ring was at 5.12 ppm as a doublet. In the weak-field area, at 7.86 and 7.88 ppm, vinyl protons resonated as two doublets. Protons at nitrogen atoms N(1)-H and N(3)-H were seen at 10.35 and 9.56 ppm respectively as two singlets.

EXPERIMENTAL CHEMICAL SECTION

IR spectra were taken on an Avatar-320 spectrometer (Nicolet) in KBr tablets. ^{1}H NMR spectra were recorded on a Bruker DRX500 spectrometer at a frequency of 500 MHz in $CDCl_3$ and DMSO-d_6 solutions relative to the internal standard TMS (measurement error ± 0.05 ppm). Meting temperatures were measured on a Boetius apparatus (measurement error ± 0.1°C. TLC analysis was performed on Silufol UV-254 and Sorbfil plates; the eluant was ethyl acetate and hexane (1:1) and plates were developed in iodine vapor. Yields and physicochemical values of compounds I-IV are shown in Table 1. Elemental analysis data were consistent with calculated values.

TABLE 1. Yields and Physicochemical Properties of Compounds I-IV.

Compound	Yield, %	T_m, °C	R_f *	Molecular formula
I	40.0	159 – 160	0.55	$C_{14}H_{18}N_2O_3S$
II	42.6	98 – 101	0.57	$C_{23}H_{24}N_2O_4S$
III	72.8	134 – 136	0.5	$C_{22}H_{21}N_3O_5S$
IV	54.3	154 – 155	0.53	$C_{22}H_{21}ClN_2O_3S$

* Eluent: ethyl acetate:hexane (1:1)

Ethyl-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (I). A mixture of 6.8 g (0.05 mol) of anisaldehyde, 6.5 g (0.05 mol) of ethyl acetoacetic ester, and 4.5 g (0.06 mol) of thiourea in 10 ml of absolute DMF was boiled in a reflex condenser for 20 h. The reaction mix was cooled and poured into a vessel containing iced water. The resulting precipitate was triturated under water, collected by filtration, dried, and purified by recrystallization from a mixture of 2-propanol and acetonitrile (1:1).

Ethyl-(4-methoxyphenyl)-6-[2-(4-methoxyphenyl)-vinyl]-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (II). compound I (0.5 g, 0.0016 mol) was dissolved in hot ethanol and 0.21 g (0.0016 mol) of anisaldehyde was added. The mixture was supplemented with a few drops of pyridine and boiled for 7 – 8 h in a reflux condenser. Cooling of the reaction mix was accompanied by precipitation of crystals, which were collected by filtration and dried.

Ethyl-(4-methoxyphenyl)-6-[2-(4-nitrophenyl)-vinyl]-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (III)

TABLE 2. Effects of Compounds I-IV on Systolic Arterial Blood Pressure (SBP) in Anesthetized Rats.

Compound, 10 mg/kg	Initial SBP, mmHg, $M \pm m$	Change in SBP, % of baseline*	
		30 min	60 min
Control (physiological saline)	127.3 ± 3.4	– 4.2 ± 3.0	– 1.0 ± 1.5
Papaverine hydrochloride	125.3 ± 4.5	– 5.5 ± 5.1	– 9.8 ± 6.5
I	132.4 ± 2.0	– 7.1 ± 4.7	– 10.0 ± 3.5
II	132.3 ± 3.5	– 8.1 ± 1.5	– 13.2 ± 3.5
III	138.2 ± 4.7	– 14.1 ± 3.8	– 18.2 ± 3.5
IV	134.3 ± 6.2	– 13.1 ± 4.4	– 17.2 ± 3.5

and ethyl-(4-methoxyphenyl)-6-[2-(2-chlorophenyl)-vinyl)-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (IV) were prepared by a method analogous to that used for II.

EXPERIMENTAL BIOLOGICAL SECTION

The hypotensive activity of compounds I-IV was studied as described by Gatsur [10] for assessment of the actions of compounds I-IV on systolic arterial blood pressure (SBP) in anesthetized white rats. Male rats aged 200 – 240 g were anesthetized with Nembutal (40 mg/kg, i.p.). Physiological saline in the control series, the reference agent in the standard series, and the study compounds in the experimental series were given i.v. after warming to 37°C. SBP was measured using a mercury manometer in the femoral artery. Arterial pressure was recorded before and after administration of aqueous solutions of compounds I-IV as percentages of baseline. The standard was papaverine hydrochloride, which was given at a dose of 10 mg/kg. Five animals were used in each series. The doses of the standard agent and the study compounds were selected in terms of their effects. Results were processed statistically using Student's t test [11]. Effects were regarded as significant at $p \leq 0.05$. Experimental results were analyzed statistically and are presented in Table 2.

Experiments showed clear hypotensive activity with compounds at 10 mg/kg given i.v. Changes in SBP were biphasic in nature, with a significant drop in SBP followed by some increase after 5 min, after which there was a second, long-lasting wave of decreased arterial pressure. Dose studies showed that no additional significant positive effects were obtained with doses of greater than 10 mg/kg (i.e., at 25 and 50 mg/kg).

The results obtained here show that compounds I-IV had moderate hypotensive actions, which were greater than the activity of the standard. Introduction of styryl groups with different substituents at position 6 of molecule I had significant effects on the increase in the hypotensive activity of starting compound I. Comparative evaluation of the data on the hypotensive activity of styryl derivatives II-IV showed significant increases in effects on systolic arterial pressure with styryl derivative III, which was linked with the presence of a nitro group in the molecule.

Thus, these results confirm the potential of the search for novel hypotensive agents among this class of compounds.

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