DOI 10.1007/s11094-015-1337-2
Pharmaceutical Chemistry Journal, Vol. 49, No. 9, December, 2015 (Russian Original Vol. 49, No. 9, September, 2015)

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1-[2-(4-AMINOSULFONYLPHENYL)ETHYL]-5-ARYL-4-AROYL-3-HYDROXY-3-PYRROLIN-2-ONES

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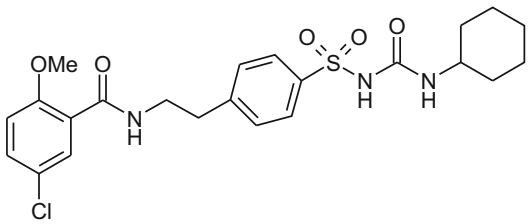
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 49, No. 9, pp. 32 – 34, September, 2015.

Original article submitted July 5, 2014.

Reaction of the methyl esters of aroylpyruvic acids with mixtures of 4-(2-aminoethyl)benzenesulfonamide and an aromatic aldehyde was used to synthesize 1-[2-(4-aminosulfonylphenyl)ethyl]-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones. The structures of these compounds were verified by IR and ^{1}H NMR spectroscopy and mass spectrometry. Their antibacterial activity was studied.

Keywords: 1-[2-(4-aminosulfonylphenyl)ethyl]-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones, synthesis, antibacterial activity.

The synthesis of new heterocyclic systems containing pharmacophore groups constitutes a potential direction in organic chemistry. Previous investigations produced 3-hydroxy-3-pyrrolin-2-ones containing sulfamide groups, namely, the 4-aminosulfonylphenyl and 4-guanylsulfonylphenyl fragments [1, 2]. With the aim of seeking new biologically active substances, we investigated the possibility of preparing tetrahydropyrrol-2,3-diones containing an aminosulfonylphenylethyl group at position 1, this being present in the known drug glibenclamide (Maninyl).



Glibenclamide (Maninyl) is the main of the second-generation antidiabetic agents, and also has antidiuretic and hypocholesterolemic actions, and decreases platelet aggregation [3].

The target 1-[2-(4-aminosulfonylphenyl)ethyl]-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones (I – IX) were synthesized using a three-component reaction of the methyl esters of aroylpyruvic acids with mixtures of 4-(2-aminoethyl)-benzenesulfonamide and an aromatic aldehyde.

Reactions were run with brief boiling of equimolar quantities of starting reagents in 1,4-dioxane medium.

Compounds I – IX were crystalline substances which were white or light yellow in color, soluble in DMF and DMSO and, with heating, in glacial acetic acid, acetonitrile,

TABLE 1. Physicochemical Properties of Compounds I – IX

Compound	Yield, %	mp, °C	Atomic formula	$[M]^+$
I	61	185 – 187	$C_{29}H_{30}N_2O_8S$	
II	63	245 – 247	$C_{25}H_{20}Br_2N_2O_5S$	618, 620, 622
III	70	251 – 253	$C_{25}H_{20}BrClN_2O_5S$	
IV	74	236 – 238	$C_{25}H_{20}BrN_3O_7S$	
V	64	240 – 242	$C_{25}H_{20}F_2N_2O_5S$	498
VI	54	236 – 238	$C_{25}H_{20}BrFN_2O_5S$	558, 560
VII	73	218 – 220	$C_{27}H_{25}BrN_2O_7S$	600, 602
VIII	67	206 – 208	$C_{25}H_{20}BrN_3O_7S$	
IX	61	210 – 212	$C_{26}H_{23}BrN_2O_6S$	570, 572

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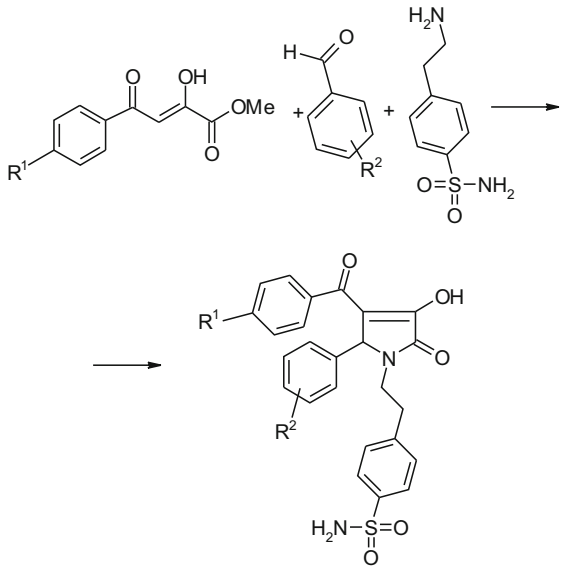
and dioxane, poorly soluble in ethanol, and insoluble in water. The physicochemical characteristics of compounds I – IX are shown in Table 1.



R^1 = C_2H_5O (I), Br (II – IV, VI – IX), F (V);R^2 = 2,5-$(CH_3O)_2$ (I), 4-Br (II), 4-Cl (III), 3-NO_2 (IV), 4-F (V), 3-F (VI), 2,4-$(CH_3O)_2$ (VII), 2-NO_2 (VIII), 2-CH_3O (IX).

The structures of the compounds synthesized here were confirmed by ^{1}H NMR and IR spectroscopy and mass spectrometry.

The IR spectra of compounds I – IX contained bands corresponding to stretch vibrations of the NH^2 group at 3456 – 3280 cm^{-1}, the hydroxyl group at 3140 – 3100 cm^{-1}, the lactam carbonyl at 1688 – 1664 cm^{-1}, the ketone carbonyl at 1632 – 1616 cm^{-1}, and the SO^2 group at two ranges, 1380 – 1344 and 1168 – 1160 cm^{-1}.

The ^{1}H NMR spectra of compounds I – IX contained signals from aromatic protons and sulfamide group protons as a multiplet at 6.45 – 8.26 ppm, a singlet at 5.41 – 6.11 ppm from the methine proton in position 5 of the heterocycle, two multiplets from protons of the enantiomeric methylene group at position 1 of the aliphatic chain at 2.88 – 3.13 ppm ($C^1H_A\underline{H}_B$) and 3.80 – 3.94 ppm ($C^1\underline{H}_AH_B$), a multiplet from two methylene group protons in position 2 of the aliphatic chain at 2.73 – 2.93 ppm, and a broad singlet from the enol hydroxy at position 3 of the heterocycle at 11.50 – 12.10 ppm. The absence of a signal from the proton of the enol hydroxyl at position 3 of the heterocycle in some ^{1}H NMR spectra was probably due to significant broadening due to exchange processes. The spectral characteristics of the compounds are presented in Table 2.

The mass spectra of compounds II, V – VII, and IX showed a molecular ion peak (Table 1) and peaks corresponding to ion fragments confirming the structure. The presence of bromine atoms in the molecular structures of compounds II, VI, VII, and IX caused the molecular peak to form a doublet of ion peaks with a 2-unit difference in mass [4].

EXPERIMENTAL CHEMICAL SECTION

IR spectra were recorded on a Specord M-80 as pastes in Vaseline grease. ^{1}H NMR spectra were recorded on a Bruker DRX 500 instrument (working frequency 500.13 MHz) and a Bruker AM-300 (300 MHz) instrument, with DMSO-d^6 as solvent and TMS as internal standard. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument with an ionization energy of 70 eV. Elemental analysis data obtained

TABLE 2. Spectral Characteristics of Compounds I – IX

Compound	^{1}H NMR spectrum, δ, ppm							IR Spectrum, ν, cm^{-1}				
	$C^{(2)}H_2$ (m)	$C^{(1)}H_A\underline{H}_B$ (m)	$C^{(1)}\underline{H}_AH_B$ (m)	$C^{(5)}H$ (s)	Ar and SO_2NO_2 (m)	OH (broad s)	Other protons	NH_2	OH	C=O lact.	C=O ket.	SO_2
I	2.82	2.92	3.94	5.74	6.68 – 7.69	11.50	1.30 (t) $C\underline{H}_3CH_2O$, 4.00 (q) $CH_3C\underline{H}_2O$, 3.57 (s) CH_3O 3.75 (s) CH_3O	3380 3280	3140	1672	1616	1380 1160
II	2.83	2.91	3.86	5.41	6.95 – 7.68	-	-	3424 3352	3120	1676	1628	1344 1164
III	2.82	2.92	3.85	5.42	6.96 – 7.92	12.00	-	3408 3296	3104	1688	1632	1352 1168
IV	2.86	2.98	3.88	5.66	7.22 – 8.26	-	-	3400 3320	3104	1672	1628	1352 1164
V	2.82	2.90	3.89	5.50	7.13 – 7.79	11.92	-	3456 3352	3120	1664	1616	1348 1164
VI	2.82	2.91	3.89	5.51	7.11 – 7.73	12.10	-	3408 3288	3120	1672	1628	1344 1164
VII	2.74	2.89	3.80	5.64	6.45 – 7.74	11.75	3.73 (s) CH_3O 3.83 (s) CH_3O	3416 3296	3112	1684	1632	1344 1164
VIII	2.93	3.13	3.93	6.11	7.30 – 7.94	-	-	3360 3300	3112	1672	1632	1348 1164
IX	2.73	2.88	3.81	5.83	6.88 – 7.73	11.80	3.84 (s) CH_3O	3380 3285	3100	1684	1624	1376 1164

TABLE 3. Antibacterial Activity of Compounds I – IX

Compound	MIC, μg/ml	
	St. aureus ATCC 6538-P	*E. coli* ATCC 25922
I	1000	1000
II	250	500
III	500	500
IV	500	500
V	1000	1000
VI	500	500
VII	500	500
VIII	1000	500
IX	1000	1000
Furacillin	250	125
Chloramine B	500	250

on a Perkin Elmer 2400 instrument were consistent with calculated values. The melting temperatures of the compounds synthesized here were determined using an M-565 melting point apparatus.

1-[2-(4-Aminosulfonylphenyl)ethyl]-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones (I – IX). A solution of 0.01 mol of 4-(2-aminoethyl)benzenesulfonamide and 0.01 mol of aromatic aldehyde in 5 – 10 ml of dioxane was supplemented with a solution of 0.01 mol of aroylpyruvic acid methyl ester in 5 – 10 ml of dioxane. The reaction mix was boiled for 5 min. The resulting precipitate was collected by filtration and recrystallized from dioxane.

EXPERIMENTAL BIOLOGICAL SECTION

The antibacterial activity of study compounds I-IX against test strains of *Staph. aureus* ATCC 6538-P and *E. coli* ATCC 25922 was assessed by twofold serial dilutions in liquid nutritive medium with a bacterial load of 250,000 cells/ml of solution [5]. The active dose was taken as the minimum inhibitory concentration (MIC). MIC values were determined in terms of the absence of signs of growth on nutritive medium and the last tube with delayed growth (transparent solution) corresponded to the MIC of the compound against the strain concerned. The bacteriostatic effects of the compounds synthesized here were compared with those of furacillin and chloramine B. Test results are shown in Table 3.

Studies of the antibacterial activity of the study compounds showed that compounds II – IV, VI, and VII were active at the level of furacillin and chloramine B against *Staph. aureus* ATCC 6538-P.

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