SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF COUMARIN-CONTAINING IMIDAZOLES

P. I. Yagodinets,[1] O. V. Skripskaya,[1] I. N. Chernyuk,[1] V. D. Bezverkhnii,[1] L. I. Vlasik,[1] and V. G. Sinchenko[1]

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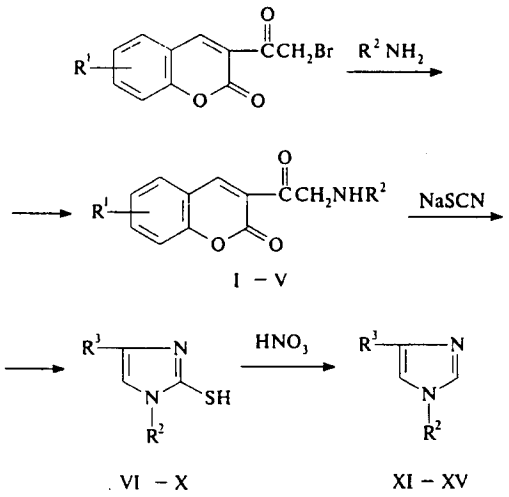
Developing the study of synthesis and biological activity of heterocyclic coumarin derivatives [1], we synthesize coumarin-containing imidazoles and analyze their antimicrobial properties.

Arylaminoketones (I – V) synthesized by the reaction of 3-(ω-bromoacetyl)coumarins [1] with substituted amines are used as starting compounds.



I – V

VI – X XI – XV

R^1 = H (I – III), 5,6-benzo (IV – V);
R^2 = 4-MeC_6H_4 (I, IV, VI, IX, XI, XIV), 4-$MeOC_6H_4$ (II, V, VII, X, XII, XV), β-$C_{10}H_7$ (III, VIII, XIII);
R^3 = 3-coumarinyl (VI – VIII, XI – XIII), 5,6-benzo-3-coumarinyl (IX, X, XIV, XV)

Arylaminoketones I – V react with sodium thiocyanate in boiling methanol in the presence of hydrochloric acid to yield 1-aryl-2-mercapto-4-(R-3-coumarinyl)imidazoles (VI – X). Treatment of compounds VI – X with 15% nitric acid results in oxidation of the mercapto group in imidazole ring, thus yielding 1,4-substituted imidazoles (XI – XV); no introduction of the nitro group into the imidazole ring is observed under these conditions.

The presence of the imidazole ring in compounds VI – X is confirmed by the characteristic bands in their IR spectra at 1575, 1265, 1105, 940, 915, and 740 cm^{-1} [2]. Oscillations of C–S bond are obserwed at 620 – 660 cm^{-1}. The absorption band of the lactone carbonyl group at 1710 – 1730 cm^{-1} in these spectra indicate that the coumarin structure persists.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded on an IKS-29 spectrophotometer for pastes in Vaseline oil. The characteristics of the synthesized compounds are presented in Table 1. The purity of the products was monitored by TLC on Silufol UV-254 plates in the chloroform – ethanol system (1 : 1), and visualization was carried out in UV-light. The elemental analysis data are consistent with the calculated values.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C (solvent for crystallization)	Empirical formula
I	68	156 – 158 (toluene)	$C_{18}H_{15}NO_3$
II	58	136 – 138 (toluene)	$C_{18}H_{15}NO_4$
III	91	178 – 180 (toluene)	$C_{21}H_{15}NO_3$
IV	87	173 – 175 (toluene)	$C_{22}H_{17}NO_3$
V	79	158 – 160 (toluene)	$C_{22}H_{17}NO_4$
VI	82	280 – 283 (DMF – ethanol)	$C_{19}H_{14}N_2O_2S$
VII	86	260 – 263 (DMF – ethanol)	$C_{19}H_{14}N_2O_3S$
VIII	89	307 – 310 (DMF – ethanol)	$C_{22}H_{14}N_2O_2S$
IX	80	> 320 (DMF)	$C_{23}H_{16}N_2O_2S$
X	92	> 320 (DMF – ethanol)	$C_{23}H_{16}N_2O_3S$
XI	90	179 – 180 (ethanol)	$C_{19}H_{14}N_2O_2$
XII	84	148 – 150 (ethanol)	$C_{19}H_{14}N_2O_3$
XIII	88	228 – 231 (ethanol)	$C_{22}H_{14}N_2O_2$
XIV	86	145 – 148 (ethanol)	$C_{23}H_{16}N_2O_2$
XV	82	127 – 130 (ethanol)	$C_{23}H_{16}N_2O_3$

[1] Research Institute of Medico-Ecological Problems of the Ukrainian Ministry of Health Protection, Chernovtsy, Ukraine.

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TABLE 2. Antimicrobial Activity of Coumarin-Containing Anilides and Imidazoles

Compound	*E. coli* 12	*S. aureus* 209	*P. aeruginosa* 40	*B. subtilis* 39	*C. albicans* 23	*S. cerevisiae*
I	500*	500	250	125	500	125
II	500	250	250	125	500	250
III	i/a	500	250	500	250	62.5
IV	500	250	500	125	500	62.5
V	500	250	500	62.5	250	125
VI	500	500	500	500	500	500
VII	500	500	250	250	500	250
VIII	250	500	500	500	i/a	125
IX	250	500	250	125	i/a	125
X	250	500	125	125	500	125
XI	i/a	250	500	i/a	i/a	125
XII	500	250	i/a	31.25	250	500
XIII	i/a	500	500	500	500	500
XIV	500	250	250	250	500	250
XV	500	250	500	250	250	125

Note. Designation i/a means that the compound is inactive in tested concentration.

* Concentration is given in μg/ml.

3-(4-Methylphenylaminoacetyl)coumarin (I), 3-(4-methoxyphenylaminoacetyl)coumarin (II), 3-(β-naphthylaminoacetyl)coumarin (III), 3-(4-methylphenylaminoacetyl)-5,6-benzocoumarin (IV), 3-(4-methoxyphenylaminoacetyl)-5,6-benzocoumarin (V). 0.01 mole of the corresponding amine was added to a hot solution of 0.005 mole of 3-(ω-bromoacetyl)coumarin or 3-(ω-bromoacetyl)-5,6-benzocoumarin in 15 ml of dry ethanol, and the resulting mixture was refluxed for 20 – 30 min. After cooling the precipitate formed was extracted, washed with ether, and dried.

1-(4-Methylphenyl)-2-mercapto-4-(3-coumarinyl)imidazole (VI), 1-(4-methoxyphenyl)-2-mercapto-4-(3-coumarinyl)imidazole (VII), 1-(β-naphthyl)-2-mercapto-4-(3-coumarinyl)imidazole (VIII), 1-(4-methylphenyl)-2-mercapto-4-(5,6-benzo-3-coumarinyl)imidazole (IX), 1-(4-methoxyphenyl)-2-mercapto-4-(5,6-benzo-3-coumarinyl) imidazole (X). Sodium thiocyanate (0.005 mole) was added to 0.005 mole of corresponding compounds (I – V) in 70 ml of boiling methanol while stirring. Concd. hydrochloric acid (0.52 ml) was then added to the reaction mixture and the resulting mixture was boiled for 3 h. The precipitate formed was filtered off and dried.

1-(4-Methylphenyl)-4-(3-coumarinyl)imidazole (XI), 1-(4-methoxyphenyl)-4-(3-coumarinyl)imidazole (XII), 1-(β-naphthyl)-4-(3-coumarinyl)imidazole (XIII), 1-(4-methylphenyl)-4-(5,6-benzo-3-coumarinyl)imidazole (XIV), 1-(4-methoxyphenyl)-4-(5,6-benzo-3-coumarinyl)- imidazole (XV). A solution of 0.005 mole of compounds (VI – X) in 70 ml of 15% nitric acid was heated with stirring over a period of 1 h. The resulting precipitate was extracted, washed with water, and dried.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity was studied using the method of twofold serial dilution in beef-extract broth (pH 7.2) with respect to *E. coli* 12, *S. aureus* 209, *P. aeruginosa* 40, and *B. subtilis* 39. The minimal inhibiting concentrations for the fungi *C. albicans* 23 and *S. cerevisiae* were determined using the twofold dilution in liquid Sabouraud's medium (pH 5.6) [4]. It was found that the studied compounds exhibit the bacteriostatic effect only in high concentrations (see Table 2). Note that bacteriostatic concentrations of antibiotics (tetracycline, oxytetracycline, and chlorotetracycline) are about 20 μg/ml, and those of chloramphenicol, polymyxin B, and erythromycin are 50, 20, and 5 μg/ml, respectively [5].

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