SYNTHESIS OF NEW 3-SUBSTITUTED DERIVATIVES OF 7-AZACOUMARINES

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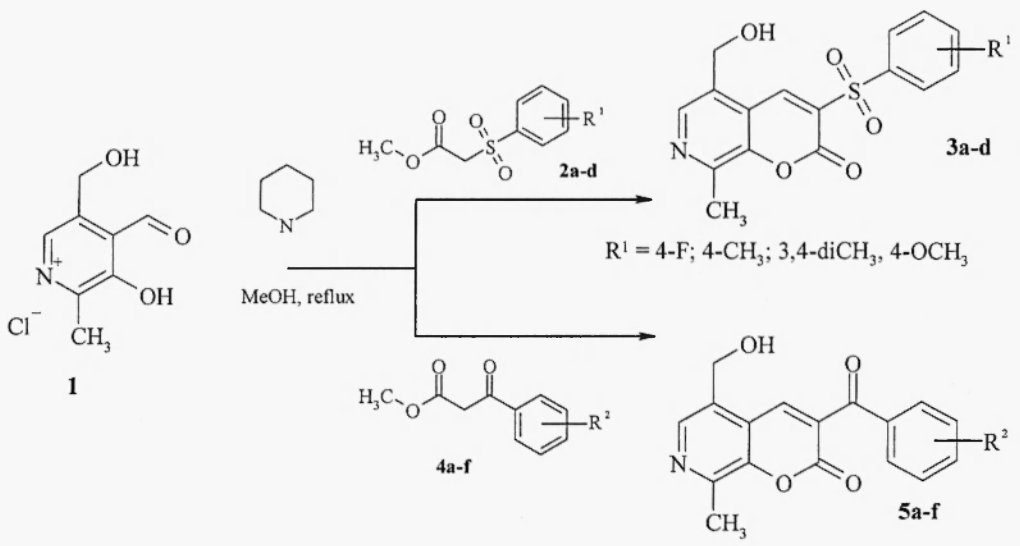
Abstract: New 3-arylsulfonyl/3-aroyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-ones were prepared by reaction of pyridoxal hydrochloride with methyl arylsulfonylacetate or methyl arylacetoacetate under Knoevenagel condensation. The structure of obtained compounds was determined through a complete ^{1}H NMR analysis. Antibacterial and antifungal activities of the synthesized compounds were studied. Most of the obtained compounds demonstrated significant activity against bacterial or fungal strains (MIC in the range of 12.5 – 50.0 μg/mL).

Introduction

2*H*-Pyrano[2,3-*c*]pyridin-2-ones-7-azacoumarines have not been studied enough especially concerning their physiological action. However it is known that the compounds with coumarine-fragment posses a wide range of biological activities and are widely used in medicine. In view of this the 7-azaanalogues of coumarines attracted us as a potential class of biological active substances (1 – 3). *Bruffola and collaborators* (4) isolated 5-hydroxymethyl-8-methyl-3-phenylsulfonylpyrano[2,3-*c*]pyridin-2-one by the reaction of pyridoxal hydrochloride with phenylsulfonylacetonitrile in water medium. Application of methyl arylsulfonylacetates or methyl arylacetoacetates in the reaction allowed us to increase the number of target products and to obtain 3-arylsulfonyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-ones and novel 3-aroyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-ones respectively. The suggested method is rather simple and convenient for synthesis of the substituted policyclic heterocycles with potential pharmacological activity.

Results and Discussions

Synthesis. 3-Arylsulfonyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-ones **3** and 3-aroyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2ones **5** were obtained according to **Scheme-1**.



Scheme-1

Initial methyl arylsulfonylacetates **2** were prepared by interaction of methyl chloroacetate with sodium arylsulfonates in DMF (5). The methyl arylacetoacetates **4** were prepared by Claisen condensation of acetophenones with dimethylcarbonate. The reaction of pyridoxal hydrochloride **1** with methyl arylsulfonylacetates **2a-d** afforded 3-arylsulfonyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-ones **3a-d**. Methyl arylacetoacetates **4a-f** in the same condition gave the novel 3-aroyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridin-2-ones **5a-f**. The condensation was conducted under reflux in methanol in presence of piperidine excess for 20 – 40 minutes. Products of these reactions were obtained as crystals after the cooling of reaction mixture.

The purity and individuality of the obtained compounds were determined by thin layer chromatography (TLC) in system of solvents $CHCl_3$: NEt_3 : MeOH (90:5:5). The structure of compounds was assigned on the basis of complete analysis of IR-, ^{1}H NMR and MS spectra.

^{1}H NMR spectra of compounds **3** and **5** showed characteristic signals from protons of the substituted pyrano[2,3-*c*]pyridin-2-one heterocycle system in the range of δ 8.36 – 9.10 ppm (s, 1H, H-4) and δ 8.36 – 8.43 ppm (s, 1H, H-6). All these spectra also contained signals of methyl group (singlet at 2.48 – 2.61 ppm) and signals of aromatics cycle.

Hydroxymethyl substituent's signal in some spectra appeared as resonances of methylene fragment (doublet at 4.72 – 4.83 ppm) and hydroxyl group (triplet at 5.48 – 5.70 ppm), sometimes the OH-resonance disappeared caused by deuterium-exchange with DMSO-d_6.

Antibacterial and antifungal activity. All the synthesized 3-substituted 2*H*-pyrano[2,3-*c*]pyridines were submitted for preliminary evaluation of their *in vitro* activity against *P. aeruginosa*, *S. aureus*, *E. coli*, *P. vulgaris*, *B. anthracoides* and antimycotic activity against *C. albicans*. The antimicrobial activity was determined by double dilution method (6). In general, most of obtained compounds were demonstrated significant activity against Gram-positive or Gram-negative microorganisms with MIC in the range of 12.5 – 50.0 μg/mL.

Experimental

General Information. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). IR spectra were recorded on Specord M80 spectrometers in KBr. ^{1}H NMR spectra were recorded on Varian Gemini-300 spectrometer in DMSO-d_6 using TMS as an internal standard.

Elemental analysis were within ± 0.4% of the theoretical value.

General Procedure for Synthesis of 3-arylsulfonyl-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c]pyridin-2-ones 3a-d.
A mixture of pyridoxal hydrochloride **1** (1.02 g, 5 mmol) and corresponding methyl arylsulfonylacetates **2a-d** (5 mmol) was dissolved at heating (30 – 40°C) in 50 mL of absolute methanol. To the obtained solution piperidine (0.05 g, 6 mmol) was added and refluxed during 20 – 40 min. The reaction mixture was cooling until the precipitate was formed. The precipitate was filtered off and recrystallized from methanol or its mixture with water.

3-(4-Fluorophenysulfonyl)-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c]pyridin-2-one ***3a.*** Yield: 72%, m.p.: 234°C (dec.); ^{1}H NMR, δ, ppm: 2.50 (s, 3H, CH_3), 4.83 (d, J = 6.4 Hz, 2H, -CH_2-), 5.70 (t, J = 7.4 Hz, 1H, OH), 7.50 (t, J = 10.4 Hz, 2H, H-2',6'), 8.10 (m, 2H, H-3',5'), 8.41 (s, 1H, H-6), 9.10 (s, 1H, H-4).
Anal. calcd for $C_{16}H_{12}NO_5FS$: C, 55.02, H, 3.46, N, 4.01; found: C, 55.02, H, 3.45, N, 4.00.

5-Hydroxymethyl-8-methyl-3-(4-methylphenysulfonyl)-2H-pyrano[2,3-c]pyridin-2-one **3b**. Yield: 74%, m.p.: 213-214°C; ^{1}H NMR, δ, ppm: 2.40 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.82 (s, 2H, -CH_2-), 5.40 (br.s, OH in change), 7.45 (d, J = 9.3 Hz, 2H, H-2',6'), 7.92 (d, J = 9.3 Hz, 2H, H-3',5'), 8.43 (s, 1H, H-6), 9.08 (s, 1H, H-4).
Anal. calcd for $C_{17}H_{15}NO_5S$: C, 59.12, H, 4.38, N, 4.06; found: C, 59.10, H, 4.40, N, 4.05.

3-(3,4-Dimethylphenysulfonyl)-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c]pyridin-2-one **3c**. Yield: 81%, m.p.: 226-227°C; ^{1}H NMR, δ, ppm: 2.28 (s, 6H, 2CH_3), 2.48 (s, 3H, CH_3), 4.85 (s, 2H, -CH_2-), 5.55 (t, J = 8.2 Hz, 1H, OH), 7.39 (d, J = 8.2 Hz, 1H, H-6'), 7.70 (d, J = 9.8 Hz, 1H, H-5'), 7.75 (s, 1H, H-2'), 8.40 (s, 1H, H-6), 9.08 (s, 1H, H-4).
Anal. calcd for $C_{18}H_{17}NO_5S$: C, 60.16, H, 4.77, N, 3.90; found: C, 60.15, H, 4.76, N, 3.89.

5-Hydroxymethyl-8-methyl-3-(4-methoxyphenysulfonyl)-2H-pyrano[2,3-c]pyridin-2-one **3d**. Yield: 69%, m.p.: 238-239°C; ^{1}H NMR, δ, ppm: 2.49 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.83 (s, 2H, -CH_2-), 5.68 (br.s, 1H, OH), 7.16 (d, J = 9.3 Hz, 2H, H-2',6'), 7.95 (d, J = 9.3 Hz, 2H, H-3',5'), 8.40 (s, 1H, H-6), 9.02 (s, 1H, H-4).
Anal. calcd for $C_{17}H_{15}NO_6S$: C, 56.50, H, 4.18, N, 3.88; found: C, 56.50, H, 4.20, N, 3.90.

General Procedure for Synthesis of 3-aroyl-5-hydroxymethyl-8-methyl-2H-pyrano[3,2-c]pyridin-2-ones **5a-f**.

A mixture of pyridoxal hydrochloride **1** (1.02 g, 5 mmol) and corresponding methyl arylacetoacetate **4a-f** (5 mmol) was dissolved at heating (30 – 40°C) in 50 mL of absolute methanol. To the obtained solution piperidine (0.05 g, 6 mmol) was added and refluxed during 30 – 45 min. The reaction mixture was cooling and diluted with 50 mL of water. The precipitate was filtered off and recrystallized from methanol or its mixture with water.

3-Benzoyl-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c]pyridin-2-one **5a**. Yield: 71%, m.p.: 198-199°C; ^{1}H NMR, δ, ppm: 2.60 (s, 3H, CH_3), 4.75 (d, J = 6.5 Hz, 2H, -CH_2-), 5.50 (t, J = 5.1 Hz, OH), 7.54 (t, J = 7.3 Hz, 2H, H-3',5'), 7.71 (m, 1H, H-4'), 7.98 (dd, J = 6.5 Hz, J = 1.7 Hz, 2H, H-2',6'), 8.39 (s, 1H, H-6), 8.46 (s, 1H, H-4).
Anal. calcd for $C_{17}H_{13}NO_4$: C, 69.15, H, 4.44, N, 4.74; found: C, 69.14, H, 4.43, N, 4.76.

5-Hydroxymethyl-8-methyl-3-(4-methylbenzoyl)-2H-pyrano[2,3-c]pyridin-2-one **5b**. Yield: 83%, m.p.: 218-220°C; ^{1}H NMR, δ, ppm: 2.40 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.75 (d, J = 6.4 Hz, 2H, -CH_2-), 5.50 (t, J = 6.1 Hz, OH), 7.35 (d, J = 8.8 Hz, 2H, H-3',5'), 7.87 (d, J = 8.9 Hz, 2H, H-2',6'), 8.38 (s, 1H, H-6), 8.42 (s, 1H, H-4).
Anal. calcd for $C_{18}H_{15}NO_4$: C, 69.89, H, 4.89, N, 4.53; found: C, 69.87, H, 4.86, N, 4.56.

5-Hydroxymethyl-8-methyl-3-(4-methoxybenzoyl)-2H-pyrano[2,3-c]pyridin-2-one **5c**. Yield: 79%, m.p.: 197-198°C; ^{1}H NMR, δ, ppm: 2.61 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.72 (d, J = 6.3 Hz, 2H, -CH_2-), 5.50 (t, J = 5.8 Hz, OH), 7.06 (d, J = 8.6 Hz, 2H, H-3',5'), 7.94 (d, J = 8.8 Hz, 2H, H-2',6'), 8.37 (s, 2H, H-4,6).
Anal. calcd for $C_{18}H_{15}NO_5$: C, 66.46, H, 4.65, N 4.31; found: C, 66.45, H, 4.65, N, 4.30.

3-(4-Ethoxybenzoyl)-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c]pyridin-2-one **5d**. Yield: 76%, m.p.: 218-220°C; ^{1}H NMR, δ, ppm: 1.34 (t, J = 5.8 Hz, 3H, CH_2CH_3), 2.60 (s, 3H, CH_3), 4.12 (q, J = 6.5 Hz, 2H, CH_2CH_3), 4.75 (d, J = 6.4 Hz, 2H, -CH_2-), 5.50 (t, J = 6.5 Hz, OH), 7.03 (d, J = 9.2 Hz, 2H, H-3',5'), 7.92 (d, J = 9.1 Hz, 2H, H-2',6'), 8.36 (s, 2H, H-4,6).
Anal. calcd for $C_{19}H_{17}NO_5$: C, 67.25, H, 5.05, N, 4.13; found: C, 67.24, H, 5.03, N, 4.13.

3-(4-Fluorobenzoyl)-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c]pyridin-2-one **5e**. Yield: 63%, m.p.: 232-234°C; ^{1}H NMR, δ, ppm: 2.60 (s, 3H, CH_3), 4.75 (d, J = 6.2 Hz, 2H, -CH_2-), 5.50 (t, J = 6.3 Hz, OH), 7.37 (t, J = 8.7 Hz, 2H, H-3',5'), 8.08 (m, 2H, H-2',6'), 8.39 (s, 1H, H-6), 8.45 (s, 1H, H-4).
Anal. calcd for $C_{17}H_{12}FNO_4$: C, 65.18, H, 3.86, N, 4.47; found: C, 65.16, H, 3.88, N, 4.47.

5-Hydroxymethyl-8-methyl-3-(3-4-methylendioxybenzoyl)-2H-pyrano[2,3-c]pyridin-2-one 5f. Yield: 81%, m.p.: 242-244°C; ^{1}H NMR, δ, ppm: 2.61 (s, 3H, CH_3), 4.82 (d, J = 6.2 Hz, 2H, -CH_2-), 5.48 (t, J = 6.2 Hz, OH), 6.15 (s, 2H, CH_2), 7.05 (d, J = 9.1 Hz, 1H, H-5'), 7.50 (s, 1H, H-2'), 7.60 (d, J = 9.0 Hz, 1H, H-6'), 8.37 (s, 2H, H-4,6).
Anal. calcd for $C_{18}H_{13}NO_6$: C, 63.72, H, 3.86, N, 4.13; found: C, 63.72, H, 3.85, N, 4.11.

Conclusions

A facile approach to 3-arylsulfonyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[3,2-*c*]pyridin-2-ones and 3-aroyl-5-hydroxymethyl-8-methyl-2*H*-pyrano[3,2-*c*]pyridin-2-ones has been developed. A series of novel compounds were synthesized and characterized, and most of them proved to be potent antibacterial or antifungal agents.

References and Notes

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