Synthesis and Some Properties of New 5-Hydroxy-2-[(hetarylthio)methyl]-4H-pyran-4-ones

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Received July 10, 2021; revised July 28, 2021; accepted July 29, 2021

Abstract—The reaction of 2-thioxoazines with chlorokojic acid in the presence of KOH in DMF led to the formation of new hybrid molecules containing fragments of kojic acid and azaheterocycle linked by the SCH₂ spacer. *In silico* prediction of bioavailability parameters was carried out, possible protein targets were predicted by the protein ligand docking method.

Keywords: chlorokojic acid, 3-cyanopyridine-2(1H)-thiones, 2-thioxo-1,2-dihydroquinoxalines, S-alkylation, calculated biological activity

DOI: 10.1134/S107036322109005X

Kojic acid **1** (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) is widely used in the pharmaceutical industry, agrochemistry, cosmetology [1–5], and as a ligand for complex compounds [6] and building blocks for construction of biologically active heterocyclic molecules [7–9]. Being one of the most studied and available non-toxic tyrosinase inhibitors [10, 11], kojic acid as a bioactive molecule is not devoid of disadvantages, among which should be noted the lack of stability during storage and a relatively low inhibitory activity. For this reason, in recent years, the direction of the γ -pyrones chemistry devoted to the preparation of conjugates of kojic acid or other derivatives functionalized at C⁶OH groups has been developed [12–18]. Among the new effective tyrosinase inhibitors, it is worth noting a number of hybrid molecules combining a kojic acid residue and an aryl/hetaryl moiety – for example, Mannich base **2** [18], 1,2,3-triazole derivatives **3** [19, 20], substituted thiophenol **4** [21] or 4-amino-1,2,4-triazoles **5** [22] (Scheme 1). In addition, a number of hybrid structures with a kojic acid motif are known, demonstrating a different spectrum of biological action. Thus, functionalization with a kojic acid was used to create ¹⁰B-labeled derivatives of dodecaboranethiol

6 for boron neutron capture therapy of cancer [23]. Compound ML221 **7** is a highly effective antagonist of the APJ apelin receptor with possible use in the therapy of cardiovascular diseases [24] (Scheme 1). Pivalic acid esters **8** have been shown to be effective inhibitors of neutrophil elastase suitable for the treatment of inflammatory lung diseases [25], while piperazine derivatives **9** exhibit anti-tuberculosis [26] and anticancer [27] effects. According to patent data [28], 2-mercaptoimidazoline derivatives **10** exhibit antibacterial activity.

One of the most accessible methods of functionalization of kojic acid is its transformation into bromo- or chlorokojic acid **11**, with further replacement of the halogen atom by various nucleophiles such as thioureas [28–33], alkyl mercaptans [29, 30, 34], thiophenols [21, 35], sodium arylsulfonates [36], alkali metal thiocyanates [36–39], S-glycosylisothiuronium salts [40], various mercaptoazoles [22, 25, 28, 29, 41], 2-mercaptopyrimidines [24, 42], 2-mercaptoquinazolines [43, 44], mono- and dithiophosphates [45, 46]. Many of the compounds obtained in this way are of interest for agrochemistry as growth regulators and herbicides comparable in efficiency to Fluazifop-P [29], or

Scheme 1.

as insecticides [45, 46]. In general, the analysis of literature data allows us to conclude that the reaction of halokojic acids with heterocyclic *S*-nucleophiles has been relatively little studied. For example, the reaction of 5-hydroxy-2-chloromethyl-4*H*-pyran-4-one with available 3-cyanopyridine-2(1*H*)-thiones and tautomeric mercaptans (for review works, see [47–54]) widely used in heterocyclic synthesis have not been reported earlier. At the same time, the target products can be of interest as promising pharmaceuticals, agrochemicals and reagents for fine organic synthesis.

We performed the reaction of some active *S*-nucleophiles of the azaheterocyclic series with chlorokojic acid **11** (Hlg = Cl). It was found that 2-thioxopyridines **12a**, **12b** react with chloride **11** in the presence of 1 equiv. of 10% aqueous KOH with the formation of previously unknown hybrid molecules **13a**,

13b containing kojic acid and nicotinonitrile fragments (Scheme 2). Under similar conditions, 2-thioxo-1,2-dihydroquinoxaline **14** was converted to compound **15** in 28% yield.

Structure of the obtained compounds was confirmed by a complex of spectral data. The IR spectra of compounds **13** and **15** show an absorption band at 1646–1649 cm^{−1}, corresponding to stretching vibrations of the conjugated carbonyl group of γ -pyrone, as well as a broad band at 3226–3253 cm^{−1} (O–H). The spectra of compounds **13a**, **13b** also show an absorption band in the range of 2218–2223 cm^{−1} (conjugated cyano group). The ¹H NMR spectra of compounds **13** and **15** exhibit singlets at 4.47–4.64 ppm (SCH₂), as well as signals of the 5-hydroxypyran-4-one fragment at 6.47–6.59 (H³), 8.01–8.09 (H⁶), and 9.11–9.15 ppm (OH). The ¹³C NMR spectra of compounds **13** and **15** contain characteristic

Scheme 2.

signals at 30.8–31.6 (SCH₂), 112.1–112.9 (C³-pyran), 139.6–139.8 (C⁶-pyran), 143.5–145.8 (C⁵-pyran), 163.1–163.8 (C²-pyran), and 173.6 ppm (C=O).

In the context of the known biological activity of kojic acid derivatives [7–11], nicotinonitriles, and quinoxalines (for recent reviews see [55–58] and [59–67], respectively), it seemed appropriate to perform a preliminary *in silico* study of possible targets, ADMET parameters, and the bioavailability criteria for new hybrid molecules. Analysis of the structures for compliance with the “Lipinski’s rule of five” [molecule mass (MW) ≤ 500, *cLogP* ≤ 5.0, TPSA ≤ 140 Å², number of hydrogen bond acceptors ≤ 10, donors ≤ 5] [68–70] was carried out using the OSIRIS Property Explorer software service [71]. The following parameters were calculated: *cLogP* (logarithm of the partition coefficient between *n*-octanol and water $\log(c_{\text{octanol}}/c_{\text{water}})$), solubility ($\log S$), Topological Polar Surface Area (TPSA), a number of toxicological characteristics such as risks of side effects

(mutagenic, oncogenic, reproductive effects), the drug-likeness parameter, as well as the overall assessment of the pharmacological potential of the compound (drug score). The calculated data are presented in Table 1.

The *cLogP* value for all the studied structures indicates probable good absorption and permeability [68–70]. At the same time, for all the compounds, the $\log S$ value < –4.0 indicates low solubility (less than 1 × 10^{–4} mol/L). The molecular weights of all the compounds and the TPSA parameter met the criteria for oral bioavailability. The studied compounds show a moderate risk of oncogenic action associated with the presence of a 5-hydroxypyran-4-one fragment. However, the total predicted values of the drug score are rather high. To predict the ADMET parameters (Absorption, Distribution, Metabolism, Excretion, Toxicity) and probable targets, the SwissADME [72] and GUSAR [73] software packages were also used. The results are shown in Table 2. In general, the assessment of acute toxicity

Table 1. Toxicity risks and physico-chemical parameters of compounds **13a**, **13b**, **15** predicted by OSIRIS Property Explorer

Compound	Toxicity risk ^a				Physico-chemical parameters					
	A	B	C	D	<i>cLogP</i>	$\log S$	MW	TPSA	drug-likeness	drug score
13a	–	±	–	–	3.81	–6.86	412	108.5	–2.83	0.18
13b	–	±	–	–	5.02	–8.34	480	108.5	–1.53	0.14
15	+	±	–	+	2.69	–4.62	392	106.8	1.93	0.31

^a The sign “+” indicates a high risk of toxicity, “±”—a moderate risk, “–”—no toxicity. A—Mutagenicity, B—carcinogenicity, C—irritant effect, D—reproductive effects.

Table 2. Calculated ADMET parameters for compounds **13a**, **13b**, and **15**^a

Comp. no.	Penetration through BBB	Gastrointestinal absorption	Inhibition of cytochromes P450					Acute toxicity (rats), LD ₅₀ [log (mmol/kg)/(mg/kg)] ^b		
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	IP	IV	Oral
13a	–	+	+	+	+	+	+	<u>0.215</u> 677.4	<u>–0.429</u> 153.7	<u>0.472</u> 1224.0
13b	–	–	+	+	+	–	+	<u>0.167</u> 706.5	<u>–0.484</u> 157.8	<u>0.728</u> 2571.0
15	–	+	+	+	+	+	+	<u>–0.007</u> 385.9	<u>–0.423</u> 148.2	<u>0.716</u> 2040.0

^a The sign “+” or “–” indicates the presence or absence of the effect.

^b IP (IntraPeritoneal)—intraperitoneal administration, IV (IntraVenous)—intravenous administration, Oral—oral administration.

allows all the studied compounds to be classified as IV and V hazard classes according to the OECD criteria [74]. For these compounds, an inhibitory effect on a wide range of cytochrome P450 isoforms is postulated.

Possible protein targets for the obtained compounds were predicted using the new Galaxy Sagittarius protein ligand docking protocol [75] based on the GalaxyWeb web server [76, 77]. The 3D joint structures were pre-optimized by molecular mechanics in an MM2 force field to optimize geometry and minimize energy. Docking using the GalaxySagittarius protocol was performed in the Binding compatability prediction and Re-ranking using docking modes. Table 3 shows the results of docking for each of compounds **13a**, **13b**, **15** for 10 target-ligand complexes with the minimum free binding energy ΔG_{bind} and the best estimate of the protein-ligand interaction. Predicted protein targets are specified using ID-identifiers in the Protein Data Bank (PDB) and in the UniProt database. As one can see from the Table 3, common receptors for compounds **13a**, **13b**, and **15** are RPA (Replication Protein A, PDB ID 4luv) phosphoprotein responsible for DNA replication and repair in eukaryotes, 3-phosphoinositol-dependent protein kinase-1 (PDK1, PDB ID 4rqv), and apoptosis regulator Mcl-1 (PDB ID 6qfq) (Fig. 1). Thus, 5-hydroxy-2-[(hetarylthio)methyl]-4*H*-pyran-4-ones **13a**, **13b**, and **15** can be considered as promising objects for screening in order to search for new agents for the treatment and therapy of oncological diseases.

In conclusion, we developed a convenient method for the preparation of previously unknown 5-hydroxy-2-[(hetarylthio)methyl]-4*H*-pyran-4-ones by the reaction of 2-thioxonicotinonitrile and 2-thioxo-1,2-dihydroquinoxaline derivatives with 5-hydroxy-2-chloromethyl-4*H*-pyran-4-one (chlorokojic acid). The results of *in silico* experiments on the assessment of probable protein targets, toxicity, and bioavailability parameters make it possible to consider the obtained compounds as promising objects for the development of new drugs with antitumor action.

EXPERIMENTAL

IR spectra were registered on a Bruker Vertex 70 spectrometer with an ATR attachment. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III HD 400 MHz instrument (400.17 and 100.63 MHz, respectively) in a DMSO-*d*₆ solution. Chromato-mass spectra were recorded on a Bruker Customer MicroTOF instrument in the range of *m/z* 50–1200, the method of ionization was electrospray (ESI). Elemental analysis was performed on an Elementar vario Micro cube instrument. The individuality of the obtained samples was controlled by TLC on Sorbfil-A plates (LLC Imid, Krasnodar), eluent was acetone–hexane mixture (1 : 1) or ethyl acetate, visualized with iodine vapors or UV light.

The starting 3-cyanopyridine-2(1*H*)-thiones **12a**, **12b** [80, 81] and 2-thioxo-1,2-dihydroquinoxaline **14** [82] were obtained according to the known methods.

Table 3. Results of prediction of protein-ligand interaction for compounds **13a**, **13b**, **15**

Compound	PDB ID	UniProt ID	Predock score	Free energy, kcal/mol (Docking score)	Overall assessment of protein ligand interaction
13a	4luv	P27694	0.283	−18.510	0.422
	5l7h	P08235	0.183	−27.591	0.390
	5dx4	O60885	0.181	−24.010	0.361
	2yek	P25440,P25440	0.144	−25.314	0.334
	6qfq	Q07820	0.144	−25.224	0.333
	2vv2	P37231	0.124	−26.546	0.323
	3zk6	Q07817,Q07817	0.113	−26.689	0.313
	4kiq	Q16539	0.120	−24.931	0.307
	6azv	P14902,P14902	0.092	−28.363	0.305
	4rqv	O15530	0.140	−21.431	0.301
13b	4luv	P27694	0.263	−18.691	0.403
	4rqv	O15530	0.229	−20.030	0.379
	6icj	P37231	0.151	−26.877	0.352
	4mdn	Q00987	0.160	−24.357	0.342
	5nkh	P29317	0.135	−23.493	0.311
	6qfq	Q07820	0.104	−26.915	0.306
	5nxd	P53671,P53671	0.075	−30.235	0.302
	4rak	P55055	0.104	−26.374	0.302
	5yxl	Q96R11	0.077	−29.239	0.297
	4tpw	P06730	0.127	−21.695	0.290
15	5d3s	O60885	0.292	−21.774	0.455
	4alg	P25440	0.201	−22.203	0.367
	5l7e	P08235	0.159	−23.347	0.334
	4luv	P27694	0.211	−15.684	0.328
	2yw5	Q15059	0.168	−20.611	0.322
	6s56	Q6PL18	0.148	−20.850	0.304
	5o2d	Q460N5	0.108	−24.657	0.293
	3l3z	P10275,Q9Y6Q9	0.098	−25.460	0.289
	6qfq	Q07820	0.112	−22.685	0.282
	5ugm	P37231	0.087	−25.772	0.280

Chlorokojic acid **11** was prepared by treating commercial kojic acid with thionyl chloride [83].

General procedure for the synthesis of 5-hydroxy-2-[(hetarylthio)methyl]-4H-pyran-4-ones 13a, 13b, 15. The appropriate 2-thioxonicotinonitrile **12** or thione **14** (2 mmol) was suspended in 2 mL of DMF, then an aqueous 10% KOH solution (1.03 mL, 2 mmol, *d* 1.09 g/mL) was added. The resulting suspension was stirred at room temperature until dissolved, then through a paper filter it was added dropwise to a solution of 321 mg (2 mmol) of chlorokojic acid **11** in 0.5 mL of DMF. The resulting mixture was stirred for 30 min. The

formed precipitate was filtered off, washed with 50% ethanol, and dried at 60°C.

2-[(5-Hydroxy-4-oxo-4H-pyran-2-yl)methylthio]-4,6-diphenylnicotinonitrile (13a). Yield 75%, pale brown powder. IR spectrum, ν , cm^{-1} : 1647 (C=O), 2218 (C≡N), 3239 (O–H). ^1H NMR spectrum, δ , ppm: 4.64 s (2H, SCH₂), 6.50 s (1H, H³_{pyran}), 7.53–7.59 m (6H, H-Ph), 7.74–7.77 m (2H, H-Ph), 7.96 s (1H, H⁵-Py), 8.09 s (1H, H⁶_{pyran}), 8.24–8.26 m (2H, H-Ph), 9.15 br. s (1H, OH). ^{13}C DEPTQ NMR spectrum, δ_{C} , ppm: 30.8 (SCH₂), 103.1 (C–C≡N), 112.2* (C³H, pyran), 115.5 (C≡N), 116.9* (C⁵, Py), 127.6* (2C, CH, Ph), 128.7* (2C, CH, Ph), 128.9* (2C, CH, Ph), 129.0* (2C, CH, Ph), 130.2* (C⁴H, Ph),

Fig. 1. Predicted structures of protein-ligand complexes for compound **13a** and phosphoprotein RPA (PDB ID 4luv) (a), compound **13a** and protein Mcl-1 (PDB ID 6qfq) (b), compound **13b** and protein kinase PDK1 (PDB ID 4rqv) (c), quinoxaline **15** and phosphoprotein RPA (PDB ID 4luv) (d) (obtained using the Galaxy Sagittarius protocol). Molecular graphics were visualized using the UCSF Chimera software package [78, 79].

131.0* (C⁴H, Ph), 135.5 (C¹, Ph), 136.4 (C¹, Ph), 139.8* (C⁶H, pyran), 145.8 (C⁵, pyran), 154.5 (Py), 158.1 (Py), 160.6 (Py), 163.8 (C², pyran), 173.6 (C=O). Hereinafter, an asterisk denotes signals in antiphase. Mass spectrum, *m/z* (*I*_{rel}, %): 451.05 [*M* + K]⁺ (100), 863.15 [2*M* + K]⁺. Found, %: C 69.77; H 4.06; N 6.90. C₂₄H₁₆N₂O₃S (*M* 412.46). Calculated, %: C 69.89; H 3.91; N 6.79.

2-[(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methyl]thio}-6-phenyl-4-(2,4-dichlorophenyl)nicotinonitrile (13b**). Yield 30%, brown powder. IR spectrum, *v*, cm⁻¹: 1649**

(C=O), 2223 (C≡N), 3226 (O–H). ¹H NMR spectrum, *δ*, ppm: 4.64 s (2H, SCH₂), 6.47 s (1H, H³_{pyran}), 7.52–7.56 m (5H, H-Ar), 7.65–7.66 m (2H, H-Ar), 7.90 d (1H, H-Ar, ⁴*J* 0.9 Гц), 7.99 s (1H, H⁵-Py), 8.01 s (1H, H⁶_{pyran}), 8.22–8.24 m (2H, H-Ar). Signal of the OH group does not appear due to deuterium exchange. ¹³C DEPTQ NMR spectrum, *δ*_C, ppm: 30.8 (SCH₂), 104.6 (C–C≡N), 112.1* (C³H, pyran), 114.5 (C≡N), 117.5* (C⁵, Py), 127.6* (CH, Ar), 127.9* (CH, Ar), 129.1* (CH, Ar), 131.2* (CH, Ar), 132.3* (CH, Ar), 132.5 (Ar), 133.6 (Ar), 135.4 (Ar), 136.1

(Ar), 139.6* (C⁶H, pyran), 145.8 (C⁵, pyran), 151.5 (Py), 158.3 (Py), 160.1 (Py), 163.1 (C², pyran), 173.6 (C=O). Mass spectrum, m/z (I_{rel} , %): 481.50 [$M + Na$]⁺ (100), 985.02 [$2M + Na$]⁺. Found, %: C 59.74; H 3.10; N 5.94. C₂₄H₁₄Cl₂N₂O₃S (M 481.35). Calculated, %: C 59.89; H 2.93; N 5.82.

5-Hydroxy-2-({[3-(4-methoxyphenyl)quinoxalin-2-yl]thio}methyl)-4H-pyran-4-one (15). Yield 28%, brown powder. IR spectrum, ν , cm⁻¹: 1646 (C=O), 3253 (O-H). ¹H NMR spectrum, δ , ppm: 3.85 s (3H, MeO), 4.47 s (2H, SCH₂), 6.59 s (1H, H³_{pyran}), 7.10–7.12 m (2H, H-Ar), 7.72–8.03 m (8H, H-Ar, overlapping with the signal of H⁵_{pyran}), 9.11 s (1H, OH). ¹³C DEPTQ NMR spectrum, δ_C , ppm: 31.6 (SCH₂), 55.3* (MeO), 112.9* (C³H, pyran), 113.9* (CH, Ar), 127.1* (CH, Ar), 128.8* (CH, Ar), 129.0* (CH, Ar), 129.1* (CH, Ar), 130.4* (CH, Ar), 130.5* (CH, Ar), 139.1 (Ar), 139.8* (CH, pyran), 143.5* (C⁵, pyran), 145.7 (Ar), 152.4 (Ar), 152.9 (Ar), 160.6 (Ar), 163.6 (C², pyran), 173.6 (C=O). Found, %: C 64.15; H 4.22; N 7.24. C₂₁H₁₆N₂O₄S (M 392.43). Calculated, %: C 64.27; H 4.11; N 7.14.

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ACKNOWLEDGMENTS

The studies were carried out using the equipment of the Research and Education Center “Diagnostics of the Structure and Properties of Nanomaterials” and the Ecological Analytical Center of the Kuban State University.

FUNDING

This work was financially supported by the Russian Foundation for Basic Research and the Krasnodar Territory Administration (project no. 19-43-230007_r_a), as well as by the

Ministry of Education and Science of the Russian Federation (topic 0795-2020-0031).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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