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A Simple Procedure for Synthesis of Biological Active 4-oxo-4-(quinolin-8-yloxy)but-2-enoic acid

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Abstract

The article is devoted to research on the synthesis of hydroxyquinoline derivative based on 8-oxyquinoline and maleic anhydride. Analysis of available literature was carried out, some drugs were found that are produced based on hydroxyquinoline derivatives and have antiprotozoal, antimicrobial and antiseptic effects, used alone or in combination with other active substances. A technique has been developed for the synthesis of a new derivative in the medium of petroleum distillate using sulfuric acid as a catalyst. A water-soluble ester of 8-oxyquinoline and maleic acid was obtained in good yield (95%), the structure of which was established based on UV, IR and NMR spectroscopy. By analogy with other oxyquinoline derivatives and the results of prediction bioactivity in the PASS program, the obtained derivative may be characterized by antifungal (antiseborrheic) action. It was determined its antibacterial properties at a concentration of 20.0–10.0 mg/cm^3 as well as a significant antioxidant activity which is a useful biological property to expand the range of its application.

1. Introduction

Drugs belonging to the group of oxyquinoline derivatives have significant antimicrobial activity. They are highly effective in acute bacterial infections, including diseases that are difficult to treat with other antimicrobial agents. The greatest activity of drugs is manifested against gram-positive, as well as some gram-negative bacteria and protozoa [1].

The antimicrobial effect of drugs in this group is based on the selective inhibition of microbial cell DNA synthesis. In addition, they reduce the activity of some intracellular enzymes of microorganisms, which results in disruption of the functioning microbial cell genetic apparatus and changes in structures associated with the implementation of pathogenicity factors. Additionally, the permeability of cell wall membranes changes under the influence of microorganisms. The drugs of this group are used as chemotherapeutic and antiseptic agents also [1].

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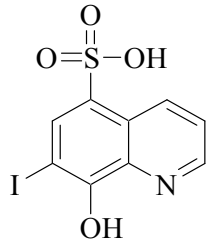
In terms of some properties and practical use, oxyquinoline preparations differ from each other. The most significant differences are observed in their pharmacokinetics. So, the antiprotozoal agent "Chiniofon" (active ingredient 8-hydroxy-7-iodine-5-quinoline sulfonic acid (1)) is absorbed to a small extent from the gastrointestinal tract. As a result, when administered orally, it accumulates in the intestinal lumen in high concentrations. Some drugs from the number of hydroxyquinolines, for example, the antimicrobial agents "Nitroxoline" (active ingredient 5-nitro-8-quinolinol (2)) and "Oxolinic acid" (active ingredient 5-ethyl-8-oxo-5,8-dihydro[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid (3)), after ingestion, are easily absorbed from the gastrointestinal tract into the bloodstream and are mainly excreted from the body in the urine unchanged.

Due to the indicated differences in pharmacokinetics, oxyquinoline preparations which are poorly absorbed from the gastrointestinal tract are more effective in intestinal infections, while well absorbed ones are mainly used in urinary tract infections.



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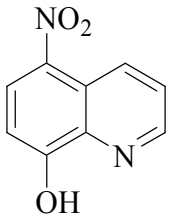

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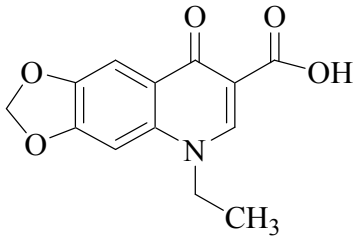

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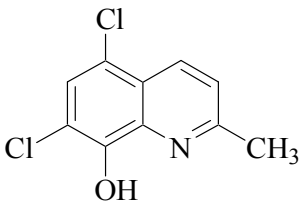
Indications for the use of individual oxyquinoline drugs are not the same. For example, "Chiniofon" is used mainly for the treatment of amoebic dysentery and sometimes in the complex therapy of ulcerative colitis. "Nitroxoline" and "Oxolinic acid" are used for pyelitis, pyelonephritis, cystitis, urethritis, prostatitis, and for the prevention of infectious complications after kidney and urinary tract surgery or after diagnostic procedures (urinary tract catheterization, cystoscopy). 5,7-Dichloro-2-methyl-8-quinolinol (4) which is the active ingredient in the antimicrobial agent "Chlorquinaldol" also inhibits the growth of opportunistic microorganisms in dysbacteriosis, it is not absorbed in the intestine and does not affect its normal microflora [2, 3].

Many oxyquinoline preparations are used externally as antiseptics because they have a broad spectrum of antimicrobial activity. So, "Chiniofon" as an antiseptic is used to treat purulent wounds, ulcers, burns and for washing and douching in gynecological and urological practice. 5-Chloro-7-iodoquinolin-8-ol (5) which is the active ingredient in antibacterial and antiprotozoal agents "Enteroseptol" and "Clioquinol" is one of the components in several official ointments (for example, ointment "Dermozolone") using for treatment of infected eczema, pustular and fungal skin diseases. The active ingredient of agent "Chinosol" – hydroxyquinoline sulfate (6) can be used for disinfecting hands, douching, washing wounds and ulcers, etc. In addition, it has a spermicidal effect, and therefore it is used as a contraceptive (for example, as a component in official vaginal suppositories "Contraceptin T") [1, 2].



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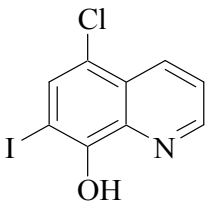

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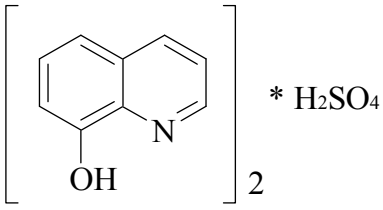


(6)

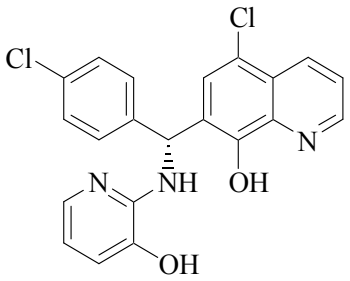
The authors of [4] found that 7-{(4-chlorophenyl)[(3-hydroxypyridin-2-yl)amino]methyl} quinolin-8-ol (adaptaqin) (7) is a specific inhibitor prolyl hydroxylase enzyme and exhibits neuroprotective properties in cell models of oxidative stress as well as in hemorrhagic stroke model *in vivo*.

There is shown in [5] that pyranoquinoline derivatives (8a-d) have a remarkable inhibitory effect on the growth of the majority of the tested bacterial strains compared to the standard antibiotic (penicillin G).

Nineteen new quinoline derivatives which were prepared via the Mannich reaction evaluated for their antibacterial activities against both Gram-positive and Gram-negative bacteria. Among them, compounds (9a,b), (10) and quinolone coupled hybrid exerted the potential effect against most of the tested bacterial strains [6].

Comparative investigation of the bactericidal activity of initial hydroxyquinolines (10a-c) and their glycosaminides (11a-c) show that free hydroxyquinolines had higher ones. But the authors think that conclusion about the negative effect of glycosylation on the medicobiological properties of 8-hydroxyquinolines observed in experiments *in vitro* may be premature because the data are found in the literature regarding the cleavage of a series of aryl-O-β-D-glucosaminides by the enzyme β-D-glucosaminidase in the organisms of mammals and the oxyquinoline glucosaminidines may be also involved in this process [7].

In research [8], antibacterial and antifungal activities of succinimido(2-aryl-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl) acetates (12a-e) have been evaluated. All the compounds have shown significant inhibition of bacterial and fungal growth as compared to the standard (amicacin). Among them, compound (12b) is highly active against *Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus faecalis*, *Klebsiella pneumonia* and *Pseudomonas aeuroginosa* [8].



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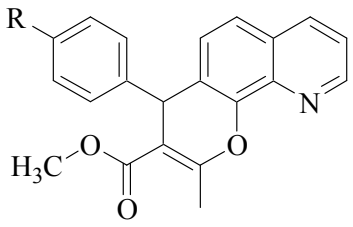
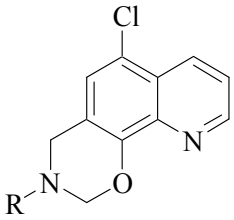


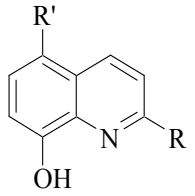
R = Cl; OCH_3; NO_2; H

(8a-d)



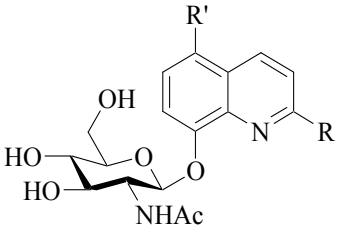
R = CH_2CH_2CN; CH_2OCOCH_3

(9a,b)



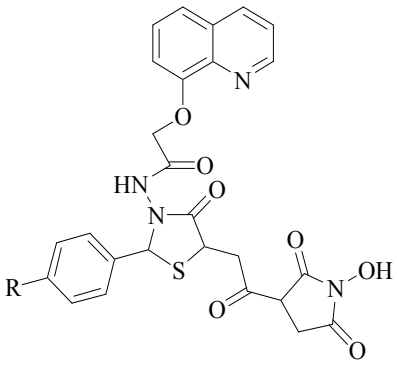
a) R = H; R' = Cl
b) R = CH_3; R' = H
c) R = R' = H

(10a-c)



a) R = R' = H
b) R = CH_3; R' = H
c) R = H; R' = Cl

(11a-c)



R = H; Cl; OCH_3; CH_3; $N(CH_3)_2$

(12a-e)

In connection with the above, scientific research in the field of oxyquinoline derivatives synthesis is currently very relevant. According to the results of the patent-information search, no derivatives were found that are products of 8-oxyquinoline and maleic anhydride interaction, which confirms the scientific novelty of this study. In the present study, we have synthesized a new compound based on them and its structure was elucidated based on of IR, UV and NMR spectral data.

2. Experimental part

2.1. Materials and instrumentation

8-Oxyquinoline (C_9H_7ON, purity 99%), maleic anhydride ($C_4H_2O_3$, purity 98%), sulfuric acid (H_2SO_4 reagent grade, 95%, GOST 4204-77), petroleum distillate (boiling range 70–100 °C), ethyl acetate ($C_4H_8O_2$, 99%, GOST 8981-78). All reagents were used without additional purification.

The melting point was determined by the capillary method on a MPA100 OptiMelt (Melting Point System MP30).

UV spectrum was recorded on a Shimadzu UV-1800 spectrometer in H_2O and on a Cary 60 spectrometer in ethanol.

IR spectrum was recorded on a Nicolet 6700 FT-IR spectrometer in KBr disks.

^1H and ^{13}C NMR, COSY (^1H-^1H), HMQC and HMBC (^1H-^{13}C) spectra were recorded on a JNM-ECA Jeol 400 spectrometer with a frequency of 399.78 Hz for protons and 100.53 Hz for carbon atoms at room temperature in deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts were measured relative to residual protons or carbon atoms DMSO-d_6.

2.2. The procedure for the synthesis

In a 0.5 L three-necked flask equipped with a mechanical stirrer with a mercury seal and a dropping funnel, 100 mL of petroleum distillate and

5 g of oxyquinoline were loaded. Maleic anhydride was dissolved in 20 mL of ethyl acetate and added to the reaction mixture under constant stirring. Then the reaction mass was heated under stirring to a temperature of 90–100 °C and 1.5 mL of concentrated sulfuric acid was added dropwise through a dropping funnel. A yellow reaction product insoluble in an organic solvent was formed. The synthesis time was 2 h.

After the completion of the process, 100 mL of distilled water was poured into the flask. As a result transition of products into the aqueous phase, the organic layer became colorless. The mixture was placed in a separating funnel for the separation of layers. The aqueous layer was poured off and dried in a vacuum drying oven at a temperature of 60 °C and a vacuum of minus 0.8 MPa. After drying, a yellow-green precipitate with a needle-like structure formed in a porcelain evaporating dish. For purification, the resulting substance was washed twice with hexane (2×50 mL). The product yield was 95%.

4-Oxo-4-(quinolin-8-yloxy)but-2-enoic acid (15) (ester of 8-oxyquinoline and maleic acid). Yield 95%. Yellow-green needle crystals. M.p. 110–115 °C. IR (KBr, ν, cm^{-1}): 1702 (C=O), 1623 (C=C), 1599, 1548, 1490, 1428, 1400, 1348, 1316, 1258, 1213, 1143, 1096, 881, 867, 831. UV (λ, nm; C_2H_5OH): 203 (lg ε 1.626) and 242 (lg ε 1.696). ^1H NMR (399.78 MHz, δ, ppm, J, Hz, DMSO-d_6): 8.95 br.s 1H (H-1), 7.8-7.88 m 1H (H-2), 8.81 d 1H (H-3, J=8.0 Hz), 7.54-7.62 m 2H (H-5 and H-6), 7.27-7.33 m 1H (H-7), 6.45 br.s 1H (OH). ^{13}C NMR (100.53 MHz, δ, ppm, DMSO-d_6): 146.18 (C-1), 122.75 (C-2), 143.34 (C-3), 129.94 (C-4), 118.78 (C-5), 129.94 (C-6), 114.94 (C-7), 150.52 (C-8), 132.60 (C-9), 167.31 (C-10, C-13), 130.86 (C-11, C-12).

2.3. Antioxidant activity testing

Antioxidant activity was studied using the method of cathodic stripping voltammetry. Voltammograms of cathode electrochemical reduction of oxygen were registered using a voltammetric analyzer "STA" (ITM LLC, Russia) according to the method given in [9].

Constant-current mode of cathode voltammetry was used, the rate of potential sweep 30 mV/s in the range from 0.0 to –0.6 V, time of stirring 20 s, time of soothing 10 s. The electrochemical cell consisted of a glass beaker with the background electrolyte (10 mL) and 3 electrodes immersed: a mercury-film (indicating electrode), a silver chloride (reference electrode), and a silver chloride (auxiliary electrode). As a background solution, the alcohol solution of sodium perchlorate was used.

Starting solutions with 0.1 g/mL concentration of the studied compounds were prepared by dissolution of the specimen of 0.0500 g in 5 mL of ethanol. For measurements, aliquots of 0.5 mL were taken. Three parallel determinations were carried out, and the kinetic criterion of antioxidant activity K (μmol/L·min) was calculated, which reflects the number of oxygen forms that reacted with the sample over a certain time.

2.4. Antibacterial activity testing

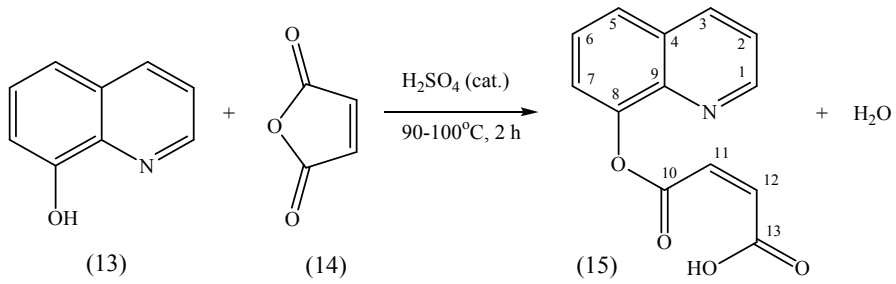
Antibacterial properties of samples were determined by assessing their minimum inhibitory concentration against *Escherichia coli* and *Streptococcus pyogenes* according to the method presented in the patent [10]. Microbial growth was monitored visually by changing the turbidity in a medium. The minimum bactericidal concentration (mg/cm^3) was taken as the one at which the growth of microorganisms began to be suppressed. Lithium ascorbate was used as a reference sample.

3. Results and discussion

Due to the presence of a phenolic hydroxyl group and heterocyclic nitrogen in the 8-oxyquinoline (13) structure, it can form stable five-membered chelate rings with many elements, which determines its chemical-analytical properties. So, 8-oxyquinoline (13) is a poorly selective group reagent due to its ability to form crystalline intracomplex salts (chelates) with more than 40 metal cations, many of which are poorly soluble in aqueous solutions (acetic acid, ammonia, etc.). It is used in practice for the determination and separation of some metals (Al, Zn, Cd, Mg, etc.). Wherein, hydroxychniolinates of various metals differ in color and can be determined photometrically, and their good solubility in chloroform is used for the extraction-photometric determination. Some hydroxyquinolinates (for example, $(C_9H_6ON)_2Cu$) are used as fungicides and antiseptics of amoebocidal action and external application. The complex of 8-hydroxyquinoline with aluminum is used for the manufacture of organic light-emitting diodes (OLEDs), and variations of substituents in the quinoline core make it possible to obtain materials with different luminescent properties [2].

Due to high reactivity and presence of two functional groups, chemical properties of maleic anhydride (14) are extremely diverse. When maleic anhydride (14) interacts with water, maleic acid is formed (cis-$HO_2CCH=CHCO_2H$), and with alcohols (R-OH) – partial esters (cis-$HO_2CCH=CHCO_2R$). It is a very active dienophile in Diels-Alder reactions, reacts with abietic acid and its esters [11].

8-Oxyquinoline (13) and maleic anhydride (14) interact in the presence of concentrated sulfuric acid (as a catalyst) according to the following scheme:



(13) (14) (15)

The resulting substance (15) has a melting point of 110–115 °C. It is insoluble in non-polar solvents, but readily soluble in distilled water, ethanol, and methanol.

In UV spectrum (λ, nm; C_2H_5OH) of (15), there are intense absorption maxima at 203 (lg ε 1.626) and 242 (lg ε 1.696), which refer to the π–π* transition of electrons in the aromatic system (as in benzene and pyridine).

In IR spectrum (KBr, ν, cm^{-1}), there are absorption bands at 1702 (C=O), 1623 (C=C), 1599 and 1490 (C-C arom), 1548 (C=N), 1428, 1400, 1348, 1316 (C-O), 1258, 1213, 1143, 1096, 881, 867, 831.

^{1}H NMR spectrum of compound (15) is characterized by the presence of signals in the downfield region at 7.27-7.33 m (1H, H-7), 7.54-7.62 m (2H, H-5 and H-6), 7.84-7.88 m (1H, H-2), 8.81 d (1H, H-3, J=8.0 Hz) and 8.95 s (1H, H-1) ppm which are referred to the protons of oxyquinoline fragment (Table). H-11 and H-12 protons of unsaturated carbon bond in the maleic fragment have appeared as a singlet two-proton signal at 6.23 ppm. The carboxyl proton at C-13 appeared as a broadened singlet at 6.45 ppm.

In ^{13}C NMR spectrum of compound (15), signals of oxyquinoline fragment are observed at 114.94 (C-7), 118.78 (C-5), 122.75 (C-2), 129.94 (C-6, C-4), 132.60 (C-9), 143.34 (C-3), 146.18 (C-1) and 150.52 (C-8) ppm (Table). Carbon atoms of the maleic fragment appeared at 167.31 ppm (carboxylate carbons C-10 and C-13) and 130.86 ppm (carbons C-11 and C-12 of double bond).

The structure of compound (15) was also confirmed by two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), which makes it possible to establish homo- and heteronuclear spin-spin coupling. Correlations observed in the molecule (15) are shown in Fig. 1.

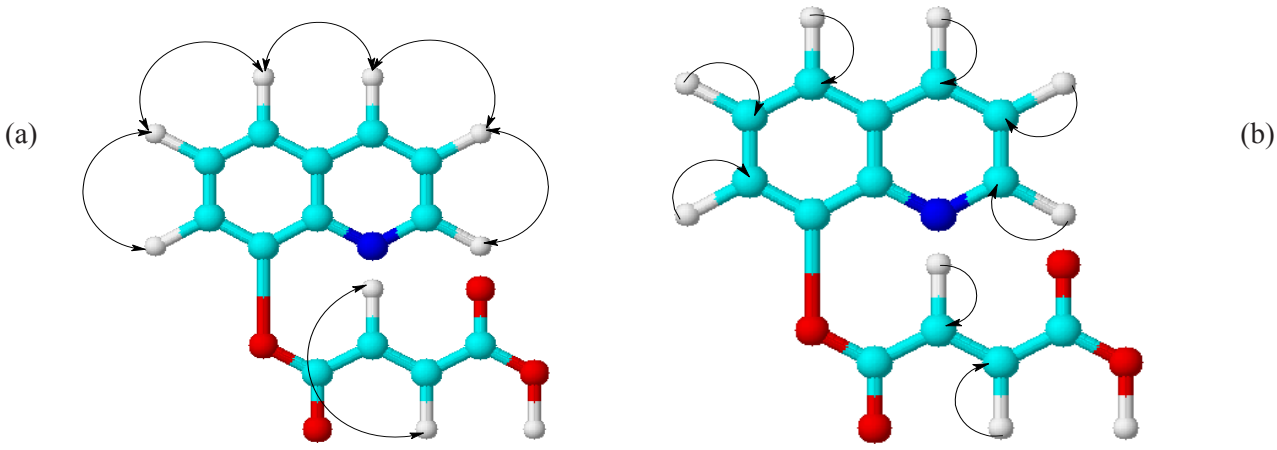


Fig. 1. Correlations observed in two-dimensional NMR spectra of molecule (15): (a) – COSY (^{1}H-^{1}H); (b) – HMQC (^{1}H-^{13}C).

Table
NMR spectra of compound (15) in DMSO-d_6

No atom	δ_C	δ_H	COSY	HMQC
1	146.18 =CH	8.95 s 1H	$H^1 – H^2$ (8.95; 7.83)	$H^1 – C^1$ (8.95; 146.18)
2	122.75 =CH	7.84-7.88 m 1H	$H^2 – H^1$ (7.83; 8.95) $H^2 – H^3$ (7.83; 8.80)	$H^2 – C^2$ (7.83; 122.76)
3	143.34 =CH	8.81 d J=8.0 Hz 1H	$H^3 – H^2$ (8.80; 7.83)	$H^3 – C^3$ (8.80; 143.36)
4	129.94 C_{aryl}	-	-	-
5	118.78 C_{aryl} –H	7.54-7.62 m 2H (overlap with H^6)	$H^5 – H^6$ (7.60; 7.60)	$H^5 – C^5$ (7.57; 118.80)
6	129.94 C_{aryl} –H	7.54-7.62 m 2H (overlap with H^5)	$H^6 – H^7$ (7.60; 7.28) $H^6 – H^5$ (7.60; 7.60)	$H^6 – C^6$ (7.56; 129.94)
7	114.94 C_{aryl} –H	7.27-7.33 m 1H	$H^7 – H^6$ (7.28; 7.60)	$H^7 – C^7$ (7.28; 114.96)
8	150.52 C_{aryl} –O	-	-	-
9	132.60 C_{aryl}	-	-	-
10	167.31 C=O	-	-	-
11	130.86 =CH	6.23 s 2H (overlap with H^{12})	-	$H^{11} – C^{11}$ (6.21; 130.81)
12	130.86 =CH	6.23 s 2H (overlap with H^{11})	-	$H^{12} – C^{12}$ (6.21; 130.81)
13	167.31 C=O	6.45 br.s -OH	-	-

In COSY spectrum (^{1}H-^{1}H) of compound (15), spin-spin correlations through three bonds are observed for protons of neighboring methine groups of oxyquinoline fragment H7-H5,6 (7.28, 7.60 and 7.60, 7.28), H2-H3 (7.83, 8.80 and 8.80, 7.83) and H2-H1 (7.83, 8.95 and 8.95, 7.83) ppm (Table).

Using HMQC spectroscopy (^{1}H-^{13}C), one-bond heteronuclear coupling were established for the following proton-carbon pairs present in the compound (15): H11,12-C11,12 (6.21, 130.93), H7-C7 (7.28, 114.96), H5-C5 (7.57, 118.80), H6-C6 (7.56, 129.94), H2-C2 (7.83, 122.76), H3-C3 (8.80, 143.36) and H1-C1 (8.95, 146.18) ppm (Table).

By analogy with other oxyquinoline derivatives, the antifungal effect may be characteristic of the ester of 8-oxyquinoline and maleic acid (15). In particular, antiseborrheic activity was predicted for it with Pa = 0.885 and Pi = 0.005 in the PASS program (see Supporting information).

The results of testing antibacterial properties against cultures of *E. coli* and *Str. pyogenes* by serial dilutions in the meat-peptone broth method [10] indicated that the synthesized sample (15) exhibits bactericidal properties at doses of 20.0–10.0 mg/cm^3.

The results of determining the antioxidant activity by stripping voltammetry showed method [9] that the synthesized ester of 8-oxyquinoline and maleic acid (15) exhibits antioxidant properties (K = 2.56 μmol/L·min), significantly superior to those of dihydroquercetin (K = 0.68 μmol/L·min). In this regard, a more detailed study of the biological activity spectrum of compound (15) and its extended comparison with known drugs are promising. Antioxidant activity in this case can be considered a useful biological property that expands the range of its application.

4. Conclusion

Thus, a product of the interaction of oxyquinoline and maleic anhydride was obtained in good yield (95%), which is a new water-soluble oxyquinoline derivative. The structure of compound (15) was proved by IR, UV and NMR spectroscopy as 4-oxo-4-(quinolin-8-yloxy)but-2-enoic acid. By analogy with other oxyquinoline derivatives and prediction of its biological activity in the PASS program, the antifungal (antiseborrheic) effect may be characteristic of an ester of 8-oxyquinoline and maleic acid. It exhibits antibacterial properties at a concentration of 20.0–10.0 mg/cm^3 as well as

a significant antioxidant activity which is a useful biological property to expand the range of its application. Its good solubility in water contributes to bioavailability and is of great importance for the production of drugs based on it.

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