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SYNTHESIS AND THE ANTIMICROBIAL ACTIVITY OF 3-(2-METHYL-4-OXO-1,4-DIHYDROQUINOLINE-3-YL) PROPANOIC ACIDS

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Key words: quinolone-4-one; 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acid; structure-activity relationship; antimicrobial activity

In order to reveal the possible regularities of the structure–activity relationship the derivatives of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acid having various substituents in α-position of the acidic moiety of propanoic acid such as alkyl, carboxyl, acyl and acetamide substituents have been synthesized. The synthesis of the target compounds has been carried out using 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one as a versatile alkylating reagent. Its interaction with methylene active substances allowed to obtain monoalkyldicarbonyl compounds, which further hydrolysis gave the derivatives of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3yl)propanoic acid. The structures of the compounds obtained have been confirmed by the data of ^{1}H NMR and elemental analysis. The results of the screening performed by the agar diffusion method have shown different levels of the antimicrobial activity. For two compounds – 1,3-diethoxy-2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-1,3-dioxopropan-2-yl-carbamic acid and 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoic acid a moderate broad-spectrum activity has been found in the screening method. The results of the research have shown the perspectiveness of further search for novel antibacterial agents based on 4-quinolon-3-yl-propanoic acids, therefore, it is necessary to expand the range of the compounds with this scaffold.

СИНТЕЗ ТА АНТИМІКРОБНА АКТИВНІСТЬ 3-(2-МЕТИЛ-4-ОКСО-1,4-ДИГІДРОХІНОЛІН-3-ІЛ)ПРОПАНОВИХ КИСЛОТ

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***Ключові слова**: гідрохінолін-4-он; 3-(2-метил-4-оксо-1,4-дигідрохінолін-3-іл)пропанова кислота; зв'язок структура – дія; антимікробна активність*

З метою виявлення можливих закономірностей зв'язку структура – дія були синтезовані похідні 3-(2-метил-4-оксо-1,4-дигідрохінолін-3-іл)пропанової кислоти з різними замісниками в α-положенні залишку пропанової кислоти – алкільними, карбоксильними, ацильними та ацетамідними. Синтез цільових сполук проводили з використанням 3-диметиламінометил-2-метил-1,4-дигідрохінолін-4-ону в якості зручного алкілуючого реагента. Його взаємодією з метиленактивними речовинами були одержані моноалкілдикарбонільні сполуки, подальший гідроліз яких приводив до похідних 3-(2-метил-4-оксо-1,4-дигідрохінолін-3-іл)пропанової кислоти. Структури отриманих сполук були підтверджені на основі даних ^{1}H ЯМР та елементного аналізу. За результатами скринінгу, виконаного методом дифузії в агар, виявлені різні рівні антимікробної активності для досліджуваних речовин. Проте дві сполуки: 1,3-діетокси-2-[(2-метил-4-оксо-1,4-дигідрохінолін-3-іл)метил]-1,3-діоксопропан-2-іл карбамінова кислота та 3-(2-метил-4-оксо-1,4-дигідрохінолін-3-іл)пропанова кислота показали помірну активність широкого спектра дії. Проведені дослідження показали перспективність подальшого пошуку потенційних антибактеріальних агентів на основі 4-хінолон-3-іл-пропанової кислоти, для чого необхідно розширити діапазон сполук, що містять даний скаффолд.

СИНТЕЗ И АНТИМИКРОБНАЯ АКТИВНОСТЬ 3-(2-МЕТИЛ-4-ОКСО-1,4-ДИГИДРОХИНОЛИН-3-ИЛ)ПРОПАНОВЫХ КИСЛОТ

В.А.Зубков, Т.П.Осолодченко, Н.И.Рущак, О.Л.Каменецкая, О.В.Кизь

***Ключевые слова**: хинолин-4-он; 3-(2-метил-4-оксо-1,4-дигидрохинолин-3-ил)пропановая кислота; связь структура – действие; антимикробная активность*

С целью выявления возможных закономерностей связи структура – действие были синтезированы производные 3-(2-метил-4-оксо-1,4-дигидрохинолин-3-ил)пропановой кислоты с различными заместителями в α-положении остатка пропановой кислоты – алкильными, карбоксильными, ацильными и ацетамидными. Синтез целевых соединений был осуществлен с использованием 3-диметиламинометил-2-метил-1,4-дигидрохинолин-4-она в качестве удобного алкилирующего реагента. Его взаимодействие с метиленактивными веществами позволило получить моноалкилдикарбонильные соединения, последующий гидролиз которых давал производные 3-(2-метил-4-оксо-1,4-дигидрохинолин-3-ил)пропановой кислоты. Структуры полученных соединений были подтверждены на основе данных ^{1}H ЯМР и элементного анализа. По результатам скрининга, выполненного методом диффузии в агар, выявлены различные уровни антимикробной активности для исследуемых веществ. Однако два соединения: 1,3-диэтокси-2-[(2-метил-4-оксо-1,4-дигидрохинолин-3-ил)метил]-1,3-диоксопропан-2-ил карбаминовая кислота и 3-(2-метил-4-оксо-1,4-дигидрохинолин-3-ил)пропановая кислота показали умеренную активность широкого спектра действия. Проведенные исследования показали перспективность дальнейшего поиска потенциальных антибактериальных агентов на основе 4-хинолон-3-ил-пропановой кислоты, для чего необходимо расширить диапазон соединений, содержащих данный скаффолд.

The discovery of antibiotics was one of the most significant events in the history of medicine which had led to significantly increase of the human life expectancy. Together with vaccination and public health measures, antibiotics have played an important role in the drastic reduction of the mortality rate from infectious diseases [1]. However, from the first application of penicillin in practical medicine, humanity was faced with the serious problem of the antimicrobial resistance (AMR) occurrence. In consequence, after using any new antibiotics for the first time cases of clinically significant resistance to these drugs developed by microorganisms in a relatively short period of time were identified (Fig. 1) [2].

In recent decades, the problem of AMR has rapidly escalated and became global. The number of registered cases of AMR increased in hundreds of times. In addition to the natural ability of microorganisms to acquire antibiotics resistance, anthropogenic factors such as the irrational and uncontrolled overuse of antibiotics in medicine and agriculture, as well as the absence of introduction of new drugs in the last 30 years have been added [3]. The World Health Organization (WHO) emphasizes that "the antimicrobial resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill" [4]. Therefore, the research aimed at finding new antimicrobial agents is a priority task of modern medicinal chemistry.

Fluoroquinolones are broad-spectrum antibacterials based on the structure of nalidixic acid – the first active agent in this class of compounds [5]. The fluoroquinolone antibiotic class has evolved through four subsequent generations, each loosely defined by either structural modifications, ability to overcome resistant mutant bacteria, or the type of bacterial infection targeted [6, 7]. However, it should be noted that the bacterial resistance exists currently in the fourth-generation fluoroquinolone antibiotics, including moxifloxacin [8].

The general mechanism of action of the fluoroquinolone class is inhibition of type II topoisomerases DNA gyrase or topoisomerase IV (topoIV). Quinolo-

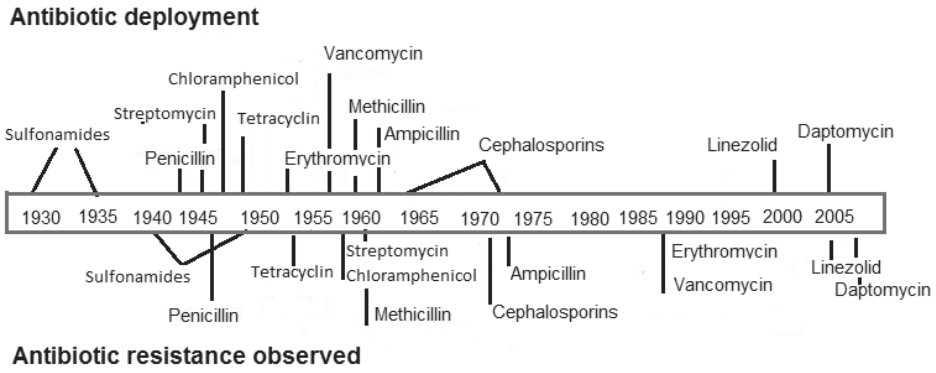


Fig. 1. The timeline showing the year of discovery of antibiotics (upper scale) and the year when resistance to antibiotics was revealed (lower scale).

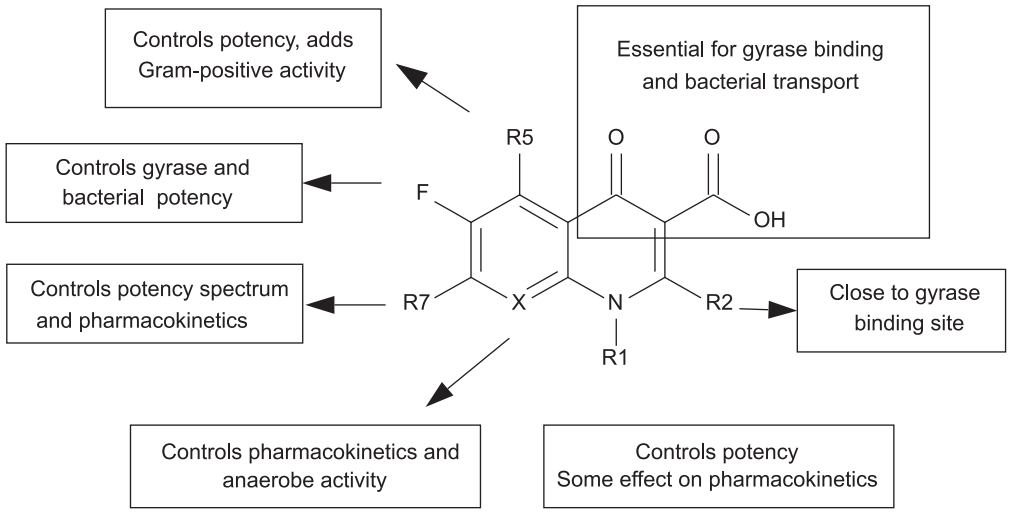


Fig. 2. The structure–activity relationship for fluoroquinolone antibiotics.

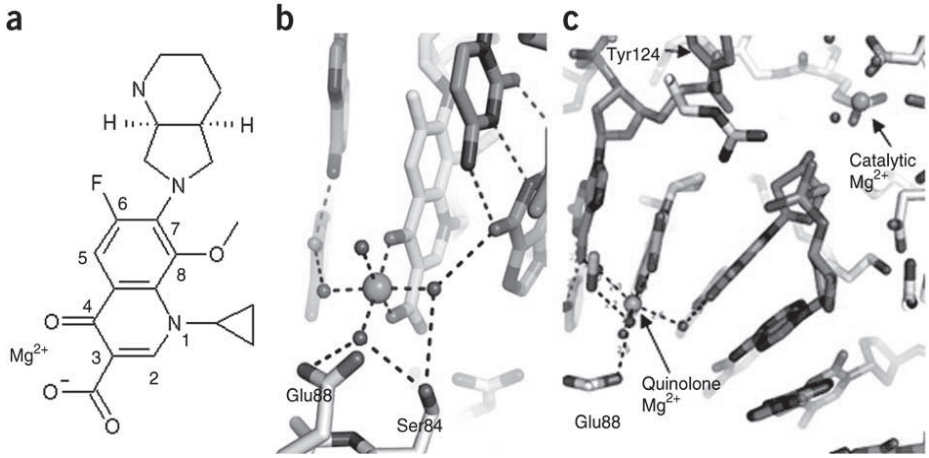
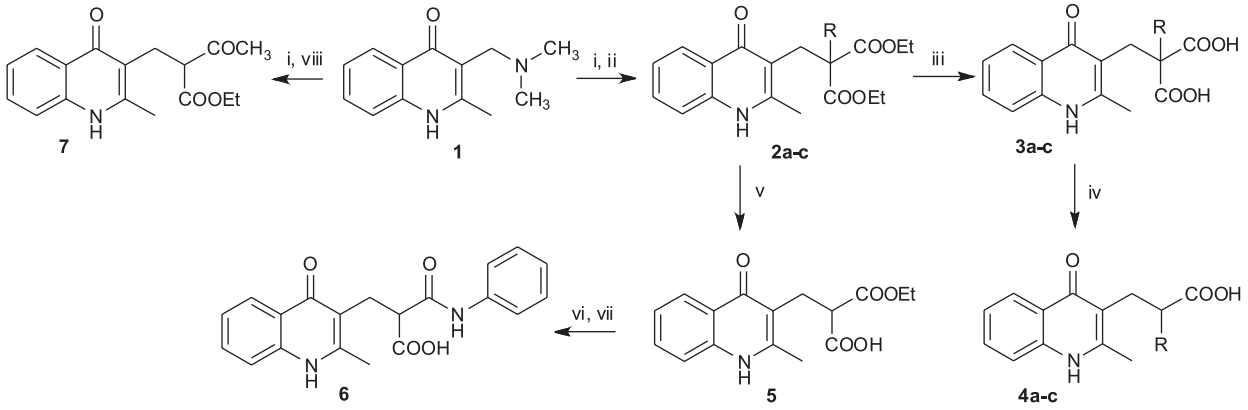


Fig. 3. (**a**) The structure of moxifloxacin with Mg^{2+} ion. (**b**) Moxifloxacin in the complex with ParE28-ParC58 and DNA at 3.27 Å. (**c**) The quinolone-bound Mg^{2+} is 14.5 Å from the 'Y site' catalytic Mg^{2+}.



2-4 a) R = H; 2b) R = $NHCOCH_3$; 2c) R = Bn

i - CH_3**I**; **ii** - R-$CH_2COOC_2H_5$, EtONa; **iii** - aq. NaOH, AcOH; **iv** - aq HBr; **v** - KOH, AcOH; **vi** - $SOCl_2$, $PhNH_2$; **vii** - aq. NaOH, AcOH; **viii** - $CH_3COCH_2COOC_2H_5$, EtONa.

Scheme 1

nes are capable to inhibit DNA synthesis that results in fragmented DNA and leads to the rapid bacterial cell death [9, 10]. For a long time the mechanism of action of fluoroquinolone antibiotics has not been well understood. In the middle of the 90s of the last century the structure-activity relationship was determined based upon experimental data. It has become a firm foundation for all subsequent modifications of the quinoline scaffold (Fig. 2) [11].

It is suggested that the carbonyl group in position 4 of the quinolone cycle and the carboxyl group at C-3 play the key role in the mechanism of action of fluoroquinolones; moreover, in SAR it has been stated that no modifications are possible without loosing of the pharmacological effect. In addition, the X-ray study of the complex moxifloxacin with topoisomerase and DNA has shown that binding of fluoroquinolones occurs in a more complicated way with the participation of Mg^{2+} cation, which coordinates the carbonyl and carboxyl groups of quinolone and four water molecules (Fig. 3) [12].

Taking into account the latest data of the key role of magnesium in the cation complex forming quinolone-topoisomerase-DNA the molecular modelling (force field MMFF94) for 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acid with cation Mg^{2+} was carried out. The possibility of forming a strong complex between them was shown. Thus, the aim of this study was to elucidate the structure–antimicrobial activity relationship of various derivatives of quinolone-3-propanoic acid with the structures different from the generally accepted model of SAR quinolone antibiotics.

In order to reveal the possible regularities of the structure–activity relationship, within our assumed hypothesis on likelihood of the antimicrobial activity of quinolones with the carboxyl group bonded to the cycle via an alkyl linker our task was to synthesize derivatives of 3-(2-methyl-4-oxo-1, 4-dihydroquinoline-3-yl) propanoic acid having various substituents in α-position of the carboxylic group.

The synthesis of the target compounds was carried out according to Schemes 1 and 2. As the starting material 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one **1** was used, its quaternization with methyl iodide allowed to obtain an effective alkylating agent [13, 14].

The alkylation of malonic (**ii**) and acetoacetic ester (**vii**) was performed to form compounds **2a-c** and **7** without further isolation **1** from the reaction medium. Compounds **3a-c** and **4-a-c** were obtained using the procedure previously known [13]. Monoacid **5** was obtained using the reaction of dimethyl 2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl) malonate **2a** with the equimolar amount of potassium hydroxide, followed by acidification of the reaction medium with acetic acid. For the synthesis of 2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-3-oxo-3-(phenylamino)propanoic acid **6** there were the following successive stages: obtaining of anilide monoacid **5** using thionyl chloride, and the alkaline hydrolysis of the ester group. Esters **8a-c** were prepared by reaction of acid **4a** with the 3-fold excess of the corresponding alcohols in the presence of thionyl chloride.

The structures of all compounds obtained were confirmed by the data of ^{1}H NMR spectroscopy and elemental analysis.

The antimicrobial activity of the compounds obtained was evaluated by the agar diffusion screening method ("well method") (Table 1) [15, 16].

The results obtained showed that the compounds synthesized had different levels of the antimicrobial activity, but two compounds **2b** and **4a** in the screening method showed a moderate activity against all microorganisms, including *Candida albicans*. Notably, 3- (2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acid **4a** was the compound that showed the best spectrum of the antimicrobial activity of the sample. This fact agrees with our hypothesis of probability of antimicrobial active compounds, which are not related to the fluoroquinolone scaffold, but have the structural similarity with them and capable of forming a complex with Mg^{2+} cation.

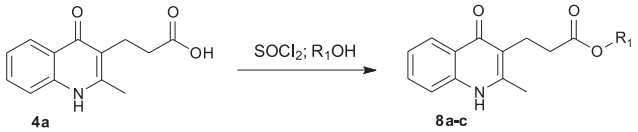
For the most promising compounds **2b** and **4a** the minimum inhibitory concentration (MIC) was determined by the serial dilution method (Table 2).

The results have shown the low level of the antimicrobial activity of the test compounds, which is not quite consistent with the screening data. Thus, in order to completely confirm or refute the hypothesis of development of new antibiotics on the basis of 3-(4-quinolone-yl)propanoic acid it is necessary to expand the range of the compounds with this scaffold.

Experimental Part

Chemistry

Melting points were determined in open capillary tubes and were uncorrected. The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Mercury VX-200 (200 MHz) in DMSO-D_6 using tetramethylsilane [$(CH_3)_4Si$] as an internal standard. Elemental analysis was performed on an Elementar Vario EI elemental analyzer.



8 a) R = Me; b) R = Pr; c) R = i-Pr

Scheme 2

3-Dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one **1**, diethyl 2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)malonate **2a**, diethyl 2-benzyl-2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl) methyl)malonate **2c**, 2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)malonic acid **3a**, 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoic acid **4a** and 2-benzyl-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl) propanoic acid **4c** were obtained using the method previously described [13]. Ethyl 2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-3-oxobutanoate **7** was obtained using the method previously described [14].

Diethyl 2-acetamido-2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)malonate 2b. To 1.08 g (5 mmol) of 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one in 20 ml in absolute ethanol add 0.5 ml (8 mmol) of methyl iodide, and stir the mixture at room temperature for 7 h. Then raise the temperature to 60°C, and keep the mixture under this temperature for an hour. Cool the solution to room temperature, then add 1.09 g (5 mmol) of 1,3-diethyl-2-acetamidopropanedioate, and with vigorous stirring by portions the solution of sodium ethylate prepared from 0.12 g of metal sodium (5.3 mmol) and 10 ml of absolute ethanol. Reflux the reaction mixture until disappearance of trimethylamine. Add water to the mixture, and acidify the solution to pH 5. Filter the resulting precipitate, wash and recrystallize from ethanol. Yield – 1.67 g (86%). M.p. – 264-266°C. ^{1}H NMR – δ, ppm – 11.45 (s, 1H), 8.28 (s, 1H), 7.98 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.66-7.37 (m, 2H), 7.22 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 4H), 2.24 (s, 3H), 1.83 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 6H). Anal. Calcd for $C_{20}H_{24}N_2O_6$; C, 61.85; H, 6.23; N, 7.21; found: C, 61.74; H, 6.24; N, 7.23.

2-Acetamido-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoic acid 4b. Heat 1.0 g (2.6 mmol) of diethyl 2-acetamido-2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)malonate 2b in 15 ml 50% solution of H2SO4 with 2 ml of THF at 110-120°C for 6 h. To the reaction mixture add the solution of NaOH to adjust the alkaline medium (pH 4). Filter the resulting precipitate, wash and recrystallize from DMF. Yield – 0.52 g (70%). M.p – 285-287°C. 1H NMR – δ, ppm – 12.49 (s, 1H), 11.60 (s, 1H), 8.32 (d, J = 7.0 Hz, 1H), 8.06 (dd, J = 8.1, 1.5 Hz, 1H), 7.69-7.41 (m, 2H), 7.27 (ddd, J = 8.1, 6.7, 1.3 Hz, 1H), 4.41-4.20 (m, 1H), 3.02-2.72 (m, 2H), 2.39 (s, 3H), 1.76 (s, 3H). Anal. Calcd for $C_{15}H_{16}N_2O_4$; C, 62.49; H, 5.59; N, 9.72; found: C, 62.37; H, 5.60; N, 9.75.

Table 1

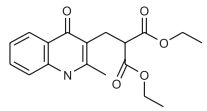
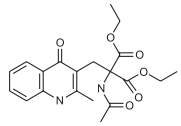
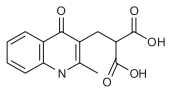
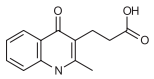
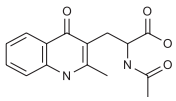
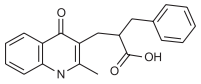
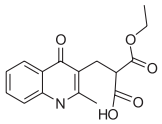
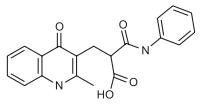
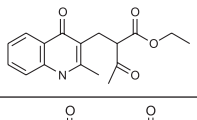
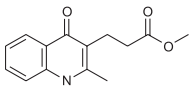
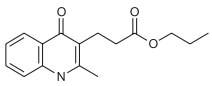
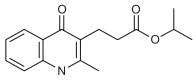
Compound	Structure	Diameter of the growth inhibition zone in mm The number of the repeated experiments n = 3					
		Staphylococcus aureus ATCC 25923	*Escherichia coli* ATCC 25922	*Proteus Vulgaris* ATCC 4636	*Pseudomonas aeruginosa* ATCC 27853	*Basillus Subtilis* ATCC 6633	*Candida aibicans* ATCC 653/885
2a		14, 14, 15	15, 14, 13	growth	growth	21, 22, 20	growth
2b		18, 17, 18	18, 17, 18	15, 14, 14	15, 14, 15	25, 24, 25	18, 17, 17
3a		15, 14, 15	14, 15, 14	growth	growth	22, 21, 22	growth
4a		17, 18, 17	16, 18, 17	15, 14, 15	14, 15, 14	25, 24, 26	17, 16, 17
4b		15, 15, 16	15, 15, 14	growth	growth	20, 21, 22	growth
4c		16,15, 17	15, 16, 15	growth	growth	20, 21, 20	growth
5		14, 13, 14	14, 14, 15	growth	growth	22, 23, 22	growth
6		14, 15, 15	14, 14, 14	growth	growth	23, 23, 22	14, 13, 14
7		15, 15, 14	14, 15, 14	growth	growth	22, 21, 22	growth
8a		13, 14, 14	14, 15, 14	12, 12, 13	13, 14, 13	21, 21, 22	growth
8b		13, 14, 15	14, 14, 13	12, 13, 12	12, 13, 12	22, 20, 20	growth
8c		15, 15, 14	14, 14, 13	growth	growth	21, 21, 22	growth

Table 2

Compound	The antibacterial activity of the samples (MIC, mg/ml) by the serial dilution method					
	Staphylococcus aureus ATCC 25923	*Escherichia coli* ATCC 25922	*Proteus Vulgaris* ATCC 4636	*Pseudomonas aeruginosa* ATCC 27853	*Basillus Subtilis* ATCC 6633	*Candida aibicans* ATCC 653/885
2b	100-150	125-175	> 500	> 500	50-100	150-200
4a	100-125	125-150	> 500	> 500	50-100	150-200

3-Ethoxy-2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-3-oxopropanoic acid 5. To 0.67 g (2 mmol) of diethyl 2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)malonate **2a** add 0.12 g of potassium hydroxide dissolved in 15 ml of ethanol. Stir the reaction mixture at room temperature for 3 h. Evaporate the solvent under the pressure, acidify the residue with 1M acetic acid. Filter the resulting precipitate, wash and recrystallize from ethanol. Yield – 0.36 g (60%). M.p. – 263-265°C decomp. ^{1}H NMR – δ, ppm – 11.49 (s, 1H), 8.02 (dd, J = 8.1, 1.5 Hz, 1H), 7.67-7.38 (m, 2H), 7.25 (ddd, J = 8.0, 6.8, 1.3 Hz, 1H), 4.14-3.80 (m, 3H), 2.93 (dd, J = 7.4, 5.6 Hz, 2H), 2.39 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H). Anal. Calcd for $C_{16}H_{17}NO_5$; C, 63.36; H, 5.65; N,4.62; found: C, 63.26; H, 5.66; N, 4.57.

2-((2-Methyl-4-oxo-1,4-dihydroquinolin-3-yl) methyl)-3-oxo-3-(phenylamino)propanoic acid 6. To 0.3 g (1 mmol) of 3-ethoxy-2-((2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-3-oxopropanoic acid **5** in 20 ml chloroform add 0.18 g (1.5 mmol) of thionyl chloride while cooling and stirring. Stir the reaction mixture for 4 h at room temperature, and then add dropwise 0.23 g (2.5 mmol) of aniline, leave the mixture overnight. Evaporate the solvent under the pressure until dryness. To the residue add 20 ml of 5M NaOH and reflux for 1 h. After acidification with dilute HCl solution filter the precipitate formed and recrystallize from butanol-1. Yield – 0.52 g (70%). M.p. – 294-296°C decomp. ^{1}H NMR – 11.41 (s, 1H), 10.13 (s, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.65-7.36 (m, 4H), 7.24 (td, J = 7.7, 2.6 Hz, 3H), 6.99 (t, J = 7.3 Hz, 1H), 4.05 (m, 3H), 3.28-2.82 (m, 2H), 2.39 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H). Anal. Calcd for $C_{20}H_{18}N_2O_4$; C,68.56; H, 5.18; N,8.00; found: C, 68.70; H, 5.19; N, 8.02.

Methyl 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoate 8a. To 0.46 g (2 mmol) of 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoic acid **4a** in 20 ml chloroform add 0.48 g (4 mmol) of thionyl chloride while cooling and stirring. Stir the reaction mixture for 2 h at room temperature, and then add 0.2 g of methanol, boil the mixture for 3 h. Evaporate the solvent under the pressure until dryness. Treat the residue with 10% solution of $NaHCO_3$. Filter the precipitate formed and recrystallize from methanol. Yield – 0.52 g (88%). M.p – 258-259°C. ^{1}H NMR – 11.43 (s, 1H), 8.02 (dd, J = 8.1, 1.5 Hz, 1H), 7.65-7.38 (m, 2H), 7.23 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 3.56 (s, 3H), 2.72 (dd, J = 8.6, 6.7 Hz, 2H), 2.48 (m, 2H), 2.39 (s, 3H). Anal. Calcd for $C_{14}H_{15}NO_3$; C, 68.56; H, 6.16; N,5.71; found: C, 68.45; H, 6.17; N, 5.72.

Compounds **8b, c** were synthesized by the same procedure.

Propyl 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoate 8b. Crystd. from n-propanol. Yield – 0.41 g (76%). M.p. – 246-247°C. ^{1}H NMR – 11.41 (s, 1H), 8.03 (dd, J = 8.0, 1.4 Hz, 1H), 7.66-7.38 (m, 2H), 7.23 (ddd, J = 8.0, 6.6, 1.3 Hz, 1H), 3.94 (t, J = 6.6 Hz, 2H), 2.73 (dd, J = 8.6, 6.6 Hz, 2H), 2.49 (m, 2H), 2.40 (s, 3H), 1.53 (h, J = 7.2 Hz, 2H), 0.82 (t, J = 7.4 Hz, 3H). Anal. Calcd for $C_{16}H_{19}NO_3$; C, 70.31; H, 7.01; N,5.12; found: C, 70.18; H, 7.02; N, 5.14.

Isopropyl 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoate 8c. Crystd. from propanol-2. Yield – 0.39 g (71%). M.p. – 240-242°C. ^{1}H NMR – 11.41 (s, 1H), 8.03 (dd, J = 8.1, 1.5 Hz, 1H), 7.66-7.38 (m, 2H), 7.24 (t, J = 7.4 Hz, 1H), 4.85 (p, J = 6.2 Hz, 1H), 2.71 (dd, J = 8.9, 6.5 Hz, 2H), 2.49 (m, 2H), 2.40 (s, 3H), 1.13 (d, J = 6.3 Hz, 6H). Anal. Calcd for $C_{16}H_{19}NO_3$; C, 70.31; H, 7.01; N,5.12; found: C, 70.13; H, 7.00; N, 5.09.

The study of the antimicrobial activity

According the WHO recommendations such test strains as *Staphylococcusaureus ATCC 25923, Escherichia coli ATCC 25922, Pseudomonasaeruginosa ATCC 27853, Basillussubtilis ATCC 6633, Proteusvulgaris ATCC 4636, Candidaalbicans ATCC 885/653* were used [15, 16].

The microbial suspension was prepared using a Densi-La-Meter device (PLIVA-Lachema, CzechRepublic; wavelenght 540 nm) according to the instructions to the device and news letters about innovations in the Healthcare system (No.163-2006 "Standardization of preparation of microbial suspensions", Kiev). Synchronization of cultures was carried out using a low temperature (4°C). The 18-24-hour old culture of the microorganisms tested was used. The bacterial suspension was inoculated onto the entire surface of Mueller-Hinton agar ("HIMediaLaboratories Pvt. Ltd India"). For *Candida albicans* agar Saburo ("HIMediaLaboratories Pvt. Ltd India") was used. The bacterial concentration was 10^7 CFU/ml (determined by McFarland standard).

The compounds were introduced to the wells in the form of DMSO solution in the concentrations of 100 μg/ml; the open wells were filled with 0.3 ml of the solution.

Conclusions

Based upon latest data about the mechanism of action of antibacterial fluoroquinolones and occurrence of the antimicrobial resistance the synthesis of various derivatives of quinolone-3-propanoic acid with the structures that are different from the generally accepted model of SAR quinolone antibiotics has been performed, and their structure–antimicrobial activity relationship has been elucidated. Taking into account the latest data of the key role of magnesium in the cation complex forming quinolone-topoisomerase-DNA the molecular modelling for 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acid with Mg^{2+} cation has been carried out.

The derivatives of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acid having substituents in α-position of the acidic moiety of propanoic acid such as alkyl, carboxyl, acyl and acetamide substituents have been synthesized using 3-dimethylaminome-

thyl-2-methyl-1,4-dihydroquinoline-4-one as a versatile alkylating agent.

The results of the antimicrobial activity screening have shown that two compounds – 1,3-diethoxy-2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-1,3-dioxopropan-2-ylcarbamic acid and 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoic acid have a moderate broad-spectrum activity.

References

1. *Esther T. Kok, Miek C. Jong, Barbara Gravendeel, Willem B. Van Leeuwen, Erik W. Baars. Evidence-Based Complementary and Alternative Medicine, Vol. 2015, Article ID 521584, 6 pages, 2015. doi:10.1155/2015/521584.*
2. *Clatworthy A. E., Pierson E., & Hung D. T. Nature Chemical Biology, 2007, Vol. 3(9), pp.541-548. Cited 384 times. doi:10.1038/nchembio.2007.24.*
3. *Laxminarayan R. et al. The Lancet Infectious Diseases, 2015, Vol. 13(12), pp.1057-1098. Cited 214 times. doi: 10.1016/S1473-3099(13)70318-9.*
4. *Antimicrobial resistance, Fact sheet No.194, Updated April 2015, http://www.who.int/mediacentre/factsheets/fs194/en/.*
5. *Andriole Vincent T. Clinical Infectious Diseases, 2005, Vol. 41, pp.113-119. Cited 102 times. doi: 10.1086/428051.*
6. *King D. E., Malone R., Lilley S. H. Am Fam Physician, 2000, Vol. 61(9), pp.2741-2748. Cited 128 times.*
7. *Ball P. J. Antimicrob. Chemother. 2000, Vol. 46, suppl 3, pp.17-24. doi: 10.1093/oxfordjournals.jac.a020889.*
8. *Oldenburg C., Lalitha P., Srinivasan M. etc. Ophthalmic epidemiology, 2013, Vol. 05, pp.20-23. Cited 2 times. doi: 10.3109/09286586.2013.790978.*
9. *Morais Cabral J. H., Jackson A. P., Smith C. V., Shikotra N., Maxwell A., Liddington R. C. Nature, 1997, Vol. 388(6645), pp.903-906. Cited 316 times.*
10. *Maxwell A. Biochemical Society Transactions, 1999, Vol. 27(2), pp.48-53. Cited 117 times.*
11. *Domagala J. M. J. Antimicrob. Chemother, 1994, Vol. 33 (4), pp.685-706. Cited 608 times. doi: 10.1093/jac/33.4.685.*
12. *Wohlkonig A., Chan P. F., Fosberry A. P., Homes P. et al. Nat. Struct. Mol. Biol., 2010, Sep, Vol. 17(9), pp.1152-1153. Cited 80 times. doi: 10.1038/nsmb.1892.*
13. *Zubkov V. O., Tsapko T. O., Gritsenko I. S., Rushchak N. I. Zhurnal organichnoi ta farmatsevtichnoi khimii – Journal of organic and pharmaceutical chemistry, 2011, Vol. 9, No.4, pp.38-41.*
14. *Zubkov V. O., Ruschak N. I., Kamenetska O. L., Gritsenko I. S. Zhurnal organichnoi ta farmatsevtichnoi khimii – Journal of organic and pharmaceutical chemistry, 2015, Vol. 13, No.4, pp.32-36.*
15. *Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. Document M100-S22, 2012, Vol. 32, No.3, CLSI, Wayne, PA, January.*
16. *American Society for Microbiology, Coyle M. B. Manual of Antimicrobial Susceptibility Testing. American Society for Microbiology: Washington, 2005, p.236.*

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