

SYNTHESIS AND *IN SILICO* SCREENING OF NOVEL 2-METHYLQUINOLINE-4-ONES BOUND WITH THE PYRAZOL-5-ONES MOIETY

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Key words: 2-methyl-1,4-dihydroquinoline-4-one; pyrazol-5-one; Mannich base; molecular similarity

The 1,3-dicarbonyl derivatives of 2-methyl-1,4-dihydroquinoline-4-one have been synthesized by alkylation of methylene active compounds with 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one. These compounds are the convenient starting material for creating the new chemical libraries in the series of 3-heteryl substituted 2-methyl-1,4-dihydroquinoline-4-ones. In this work the examples of the synthesis of new quinolone-pyrazolone systems are presented. Their condensation with hydrazine hydrate resulted in the new derivatives of 2-methyl-3-[(5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-1,4-dihydroquinolin-4-ones. The estimation of novelty of the compounds obtained in such chemical databases as PubChem, ChemBI u Spresi has shown that these substances are not present in these sources, and the chemical scaffold – quinolone bound via the methylene bridge with azoles is new. Determination of 2D similarity of the compounds synthesized by standard molecular descriptors with the biologically active structures in the ChemBI_20 database has shown the uniqueness of a new quinolone scaffold and the potential anti-inflammatory activity for compounds of this series. The molecular similarity has been determined using the ChemAxon software (JKlustor, Instant JChem).

СИНТЕЗ І КОМП'ЮТЕРНИЙ СКРИНІНГ НОВИХ 2-МЕТИЛХІНОЛІН-4-ОНІВ, ЗВ'ЯЗАНИХ З ПІРАЗОЛОН-5-ООНОВИМ ФРАГМЕНТОМ

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Ключові слова: 2-метил-1,4-дигідрохінолін-4-он; піразол-5-он; основа Маніха; молекулярна подібність
Алкилуванням 3-диметиламінометил-2-метил-1,4-дигідрохінолін-4-оном метиленактивних сполук були синтезовані 1,3-дикарбонільні похідні 2-метил-1,4-дигідрохінолін-4-ону. Дані сполуки є зручним стартовим матеріалом для створення хімічних бібліотек в ряду 3-гетерилзаміщених 2-метил-1,4-дигідрохінолін-4-онів. У роботі наведені приклади синтезу нових хінолон-піразолонових систем. Конденсацією алкілованих метиленактивних сполук з гідразин гідратом отримані нові похідні 2-метил-3-[(5-оксо-4,5-дигідро-1H-піразол-4-іл)метил]-1,4-дигідрохінолін-4-онів. Проведена оцінка новизни отриманих сполук за хімічними базами PubChem, ChemBI і Spresi показала, що дані сполуки зовсім не представлені в цих джерелах; а хімічний скафолд – хінолон, з'єднаний через метиленовий місток з азолами, є новим. Визначення 2D схожості синтезованих речовин за стандартними молекулярними дескрипторами з біологічно активними структурами бази даних ChemBI_20 показало унікальність і перспективність нового хінолонового скафолда в дизайні лікарських речовин, а також імовірність прояву протизапальної активності серед сполук даного ряду. Молекулярну схожість було визначено за допомогою програмного забезпечення ChemAxon (JKlustor, Instant JChem).

СИНТЕЗ И КОМПЬЮТЕРНЫЙ СКРИНИНГ НОВЫХ 2-МЕТИЛХИНОЛИН-4-ОНОВ, СВЯЗАННЫХ С ПИ-РАЗОЛ-5-ООНОВЫМ ФРАГМЕНТОМ

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Ключевые слова: 2-метил-1,4-дигидрохинолин-4-он; пиразол-5-он; основание Манниха; молекулярное подобие

Алкилированием 3-диметиламинометил-2-метил-1,4-дигидрохинолин-4-оном метиленактивных соединений были синтезированы 1,3-дикарбонильные производные 2-метил-1,4-дигидрохинолин-4-она. Данные соединения являются удобным стартовым материалом для создания библиотек в ряду 3-гетерилзамещенных 2-метил-1,4-дигидрохинолин-4-онов. В работе приведены примеры синтеза новых хинолон-пиразолоновых систем. Конденсацией алкилированных метиленактивных соединений с гидразин гидратом получены новые производные 2-метил-3-[(5-оксо-4,5-дигидро-1H-пиразол-4-ил)метил]-1,4-дигидрохинолин-4-онов. Проведенная оценка новизны полученных соединений по химическим базам PubChem, ChemBI и Spresi показала, что данные соединения совсем не представлены в этих источниках, а химический скафолд – хинолон, соединенный через метиленовый мостик с азолами, является новым. Определение 2D подобия синтезированных соединений по стандартным молекулярным дескрипторам с биологически активными структурами базы данных ChemBI_20 показало уникальность и перспективность нового хинолонового скафолда в дизайне лекарственных веществ, а также вероятность проявления противовоспалительной активности среди соединений данного ряда. Молекулярное подобие было определено с помощью программного обеспечения ChemAxon (JKlustor, Instant JChem).

3-Substituted quinolones are attractive targets in medicinal chemistry over the past decades. It is connected with their ability to exhibit different types of the biological activity, and there are many successful stories of creation of medicines on their basis [1-3]. It was discovered earlier that 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-ones could be effective alkylating agents in the reactions with N- and C-nucleophiles [4-5]. In continuation of our previous research efforts of increasing the molecular diversity of 3-substituted quinolones with various biologically important moieties it has been decided to expand the range of active methylene compounds using their reaction with 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one, and then make some heterocyclization on the basis of the resulting products.

It is well known that 1,3-dicarbonyl compounds are convenient reagents in the synthesis of various 5- and 6-membered heterocycles according to the "2 + 3" and "3 + 3" strategies [6]. In relation to the objects of our studies, the molecular diversity expansion can be carried out as shown in Fig. 1. In this work the synthesis of new quinolone-pyrazol systems bound via the methylene group, namely derivatives of 2-methyl-3-[(5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-1,4-dihydroquinolin-4-ones is presented.

To estimate the novelty of the compounds planned to synthesize the literature search and structural web-search in such chemical databases as PubChem, ChemBl and Spresi were conducted at first [7-9]. The results obtained have shown that currently such compounds are not present in these chemical databases. As an example, the structures of the most similar substances according to 2D similarity methods with the Tanimoto coefficient for 3-[(3-amino-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-2-methyl-1,4-dihydroquinolin-4-one are given in Table.

The next step of our chemoinformatic studies was the preliminary estimation of the pharmacological potential of 2-methyl-3-[(5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-1,4-dihydroquinoline-4-ones. To achieve this purpose, the sdf ChemBl_20 database was chosen. This database is one of the most powerful tool of chemo- and bioinformatics and currently contains 1.463.270 distinct compounds, 13.520.737 activities, and 59.610 source documents. The platform of ChemAxon under free academic license was used as a software. The 2D similarity method was used, and considering the vast number of compounds in ChemBl-20, the clustering of the data was carried out by Bemis-Murcko algorithm. JKlustor was used for clustering and diversity analysis of chemical sets, JChem 15.2.23.0, 2015, ChemAxon (<http://www.chemaxon.com>). The search

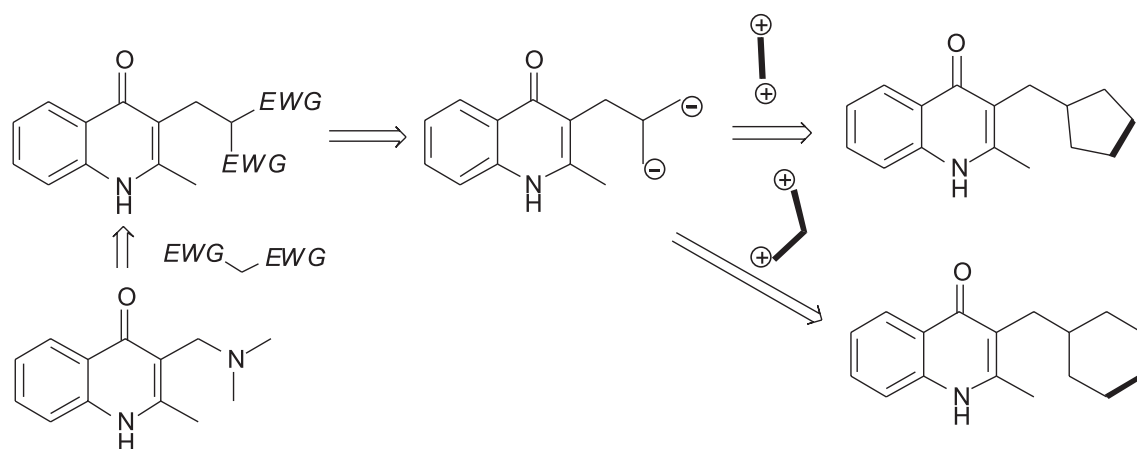


Fig. 1. The "2 + 3" and "3 + 3" strategies for the synthesis of new heterocycles of quinolin-4-ones derivatives.

Table

Reference structure:	PubChem Compound 67.25 million compounds	ChEMBL_20 1.46 million compounds	SPRESIweb 5.68 million compounds
	CID 73182817 Similarity threshold $\geq 85\%$	CHEMBL474651 Similarity – 75.03	Spresi RegNo: 0289308-000 Similarity – 70.02%

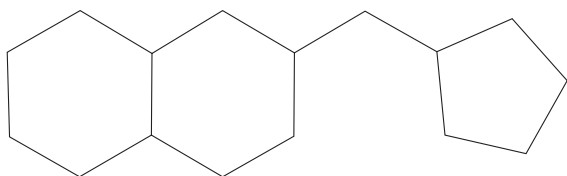


Fig. 2. Bemis-Murcko scaffold describing the compounds synthesized.

of the graph scaffold describing the compounds synthesized (Fig. 2) among Bemis and Murcko frameworks of the ChemBl database has shown that there are 1167 substances that correspond to this parameter.

For structure database management, search and analysis of data the Instant JChem software was used (Instant JChem 15.2.23.0, 2015, ChemAxon, <http://www.chemaxon.com>). To determine the molecular similarity, standard 2D molecular descriptors calculated using Instant JChem were applied.

Data analysis and visualization were carried out by constructing combinations of all possible scatter plots and radar charts. As a result, it has been found that the most similar compound is 3-substituted quinoxaline-2-one, CHEMBL2263312 (Fig. 3) that exhibits the anti-inflammatory activity on the carrageenan-induced rat paw edema model [10].

Thus, the data analysis of 2D similarity of 2-methyl-3-[(5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-1,4-dihydroquinoline-4-ones with distinct compounds from the ChemBl database has shown that the bio-

logical activity of this scaffold has not been studied yet, and for more accurate determination of similarity with the known ligands it is necessary to perform the 3D ligand-based virtual screening for these compounds.

The synthesis of the target compounds **3a**, **b**, and **6** was carried out as shown in Scheme. At first, the active methylene compounds – ethyl cyanoacetate, ethyl acetoacetate and diethyl malonate were alkylated with 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one **1** with good yields using the method recently described [5]. The preliminary quaternization of 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one with methyl iodide allows to alkylate the activated C-nucleophiles under mild conditions and in good yields. In this study we did not isolate the intermediate quaternized quinolone salt from the reaction medium, the one-pot synthesis was performed to yield the resulting products **2a-c**. Then condensation of compounds **2a**, **b** with hydrazine hydrate and further intramolecular cyclization *in situ* to the corresponding derivatives of pyrazole-5-ones was carried out [11].

In the case of alkylated diethylmalonate **2c** the synthesis of the target pyrazolidine-3,5-dione **6** was conducted somewhat differently using the method described by *Metwally et al.* [12]. Condensation of the substituted diethylmalonate **2c** with hydrazine hydrate occurred ambiguously and led to formation of the mixture of mono- **5** and dihydrazide **6** in the

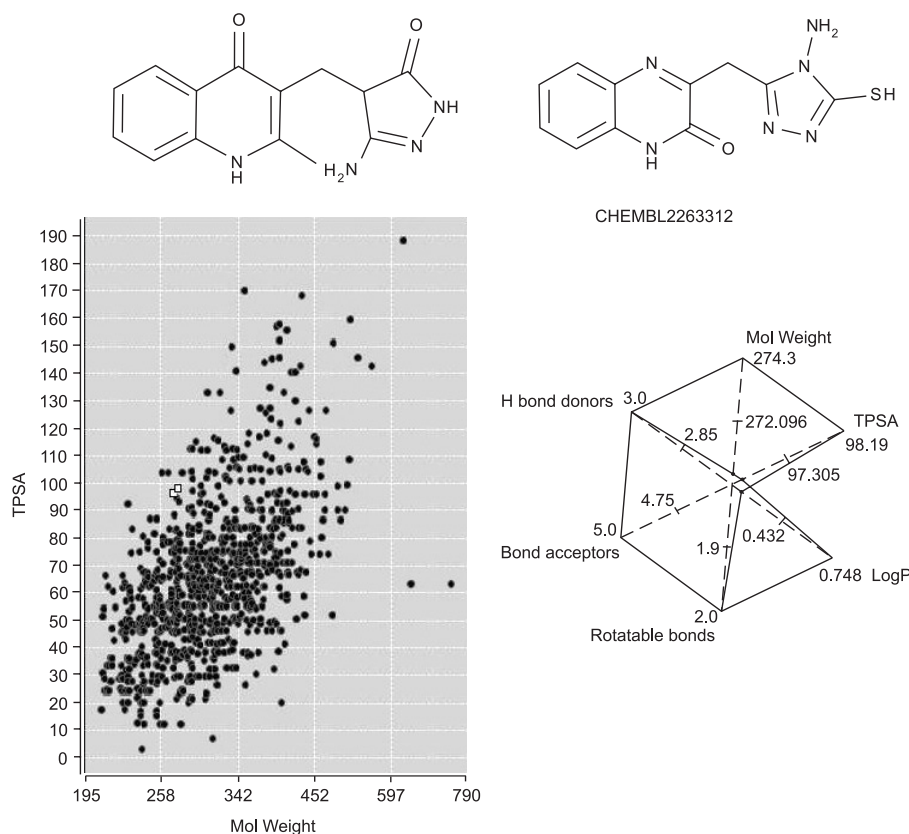
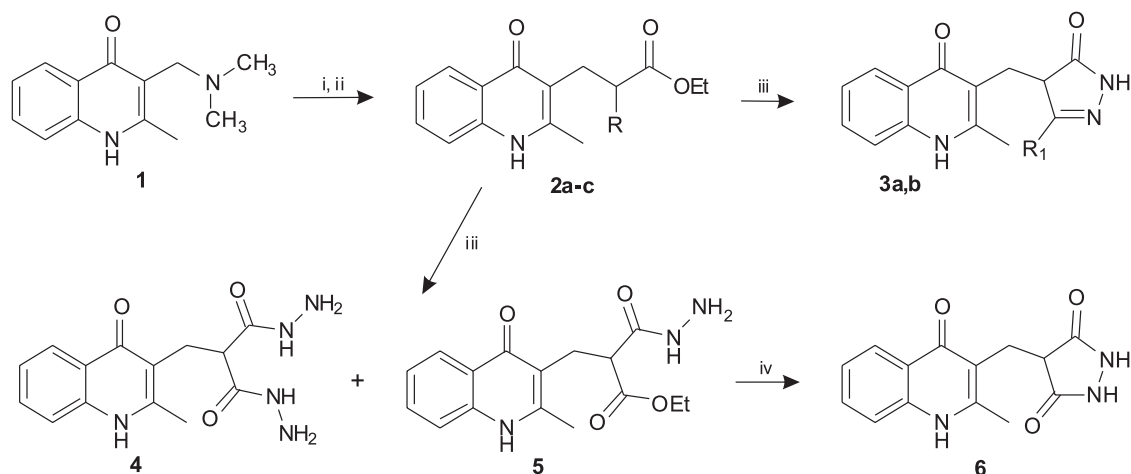


Fig. 3. A graphical representation of the most similar structure from the ChemBl database with the compound studied.



2a) R = CN; 2b) R = COCH₃; 2c) R = COOC₂H₅

3a) R₁ = NH₂; 3b) R₁ = CH₃

i - CH₃I; ii - R-CH₂COOC₂H₅, EtONa; iii - NH₂NH₂·xH₂O; iv - EtONa

Scheme

ratio of approximately 80:20. These products were separated quite easily due to their different solubility in ethanol. The subsequent intramolecular cyclization of monohydrazide **5** in the presence of sodium ethylate led to formation of pyrazolidine-3,5-dione with a good yield.

Experimental Part

Melting points were determined in open capillary tubes and were uncorrected. The proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Varian Mercury VX-200 (200 MHz) in DMSO-D₆ using tetramethylsilane [(CH₃)₄Si] as an internal standard. Elemental analysis was performed on an Elementar Vario EI elemental analyzer.

3-Dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one **1** was obtained using the method [4].

Ethyl 2-cyano-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoate 2a. To 1.08 g (5 mmol) of 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one in 20 ml of absolute ethanol add 0.5 ml (8 mmol) of methyl iodide and stir the mixture at room temperature for 15 hours. Then raise the temperature to 60°C and allow to stand for an hour. Cool the solution to room temperature, add 0.6 g (5.3 mmol) of ethyl cyanoacetate, and while mixing thoroughly add 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 no trimethylamine is evolved. Add water, acidify the mixture to pH 5. Filter the precipitate obtained, wash and recrystallize from ethanol. Yield – 1.03 g (76%). M.p. – 211-213°C. ¹H NMR – δ, ppm – 11.57 (s, 1H), 8.04 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.61 (ddt, *J* = 9.2, 4.3, 2.1 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.38-7.17 (m, 1H), 4.38 (dd, *J* = 8.9, 6.7 Hz, 1H), 4.16 (q, *J*

7.1 Hz, 2H), 3.13 (td, *J* = 14.0, 8.1 Hz, 2H), 2.45 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). Anal. Calcd for C₁₆H₁₆N₂O₃; C, 67.59; H, 5.67; N, 9.85; found: C, 67.73; H, 5.68; N, 9.87.

Compounds **2b, c** were synthesized by the same procedure.

Ethyl 2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-3-oxobutanoate 2b. The compound was recrystallized from ethanol. Yield – 0.92 g (64%). M.p. – 148-150°C. ¹H NMR, δ, ppm, 11.47 (s, 1H), 8.02 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.25 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 4.17-3.92 (m, 3H), 2.89 (qd, *J* = 13.8, 7.3 Hz, 2H), 2.39 (s, 3H), 2.17 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). Anal. Calcd for C₁₇H₁₉NO₄; C, 67.76; H, 6.36; N, 4.65; found: C, 67.64; H, 6.37; N, 3.39.

1,3-Diethyl 2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]propanedioate 2c. The compound was recrystallized from ethanol. Yield – 1.14 g (69%). The melting point and data of ¹H NMR spectra coincide with those given in the work [5].

3-[(3-Amino-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-2-methyl-1,4-dihydroquinolin-4-one 3a. Dissolve 0.5 g (1.76 mmol) of ethyl 2-cyano-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl) propanoate **2a** while stirring in 5 ml ethanol. Add dropwise 0.1 g (2.06 mmol) of hydrazine hydrate to the resulting solution and stir at 70°C for 16 hours. Evaporate the solvent under reduced pressure. Treat the residue with water and 3 ml 1 M of acetic acid. Filter the precipitate obtained, wash and recrystallize from dimethylformamide. Yield – 0.34 g (72%). M.p. > 300°C. ¹H NMR – δ, ppm 11.62 (s, 1H), 9.49 (s, 1H), 8.04 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.3, 6.7, 1.5 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 4.42 (s, 2H), 3.99 (t, *J* = 7.6 Hz, 1H), 2.98 (dd, *J* = 7.6, 2.7 Hz,

2H), 2.44 (s, 3H). Anal. Calcd for $C_{14}H_{14}N_4O_2$; C, 62.21; H, 5.22; N, 20.73; found: C, 62.05; H, 5.21; N, 23.42.

2-Methyl-3-[(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-1,4-dihydroquinolin-4-one 3b was prepared by the same procedure and under the same conditions using ethyl 2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-3-oxobutanoate **2b** and hydrazine hydrate. Yield – 0.46 g (57%). M.p. > 300°C. 1H NMR δ , ppm – 11.56 (s, 1H), 9.11 (s, 1H), 8.01 (dd, $J = 7.4, 1.6$ Hz, 1H), 7.43 (td, $J = 7.4, 1.5$ Hz, 1H), 7.39 (td, $J = 7.5, 1.6$ Hz, 1H), 7.20 (dd, $J = 7.5, 1.5$ Hz, 1H), 3.87 (t, $J = 8.0$ Hz, 1H), 2.95 (m, 2H), 2.43 (s, 3H), 2.04 (s, 3H). Anal. Calcd for $C_{15}H_{15}N_3O_2$; C, 66.90; H, 5.61; N, 15.60; found: C, 67.02; H, 5.60; N, 17.63.

Ethyl 2-(hydrazinecarbonyl)-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoate 5. To the solution of 0.95 g (3.16 mmol) of 1,3-diethyl 2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]propanedioate **2c** in 10 ml of ethanol add 0.15 g (3 mmol) of hydrazine hydrate. Stir the mixture at room temperature for 12 hours, separate dihydrazide **4** (0.13 g) by filtration. After evaporating the filtrate and treating the residue successively with methylene chloride and isopropanol obtain monohydrazide **5** and recrystallize from ethanol. Yield – 0.62 g (55%). M.p. – 194-196°C. 1H NMR δ , ppm – 11.40 (s, 1H), 9.06 (s, 1H), 8.03 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.58 (ddd, $J = 8.3, 6.8, 1.6$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.23 (ddd, $J = 8.2, 6.8, 1.5$ Hz, 1H), 4.15-3.90 (m, 3H), 2.99-2.85 (m, 2H), 2.42 (s, 3H), 1.06 (t, $J = 7.1$ Hz, 3H). Anal. Calcd for $C_{16}H_{19}N_3O_4$; C, 60.56; H, 6.03; N, 13.24; found: C, 60.46; H, 6.04; N, 11.65.

2-[(2-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]propanedihydrazide 4. Yield – 0.13 g (12%). M.p. – 281-283°C. 1H NMR δ , ppm – 11.45 (s, 1H), 10.32 (br, s, 4H), 9.06 (s, 1H), 9.01 (s, 1H), 8.02 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.58 (ddd, $J = 8.3, 6.8, 1.5$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.22 (ddd, $J = 8.2, 6.8, 1.4$ Hz,

1H), 3.94 (t, $J = 7.9$ Hz, 1H), 2.91 (m, 2H), 2.41 (s, 3H). Anal. Calcd for $C_{14}H_{17}N_5O_3$; C, 55.44; H, 5.65; N, 23.09; found: C, 55.33; H, 5.66; N, 20.78.

4-[(2-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]pyrazolidine-3,5-dione 6. Add slowly the solution of sodium ethylate prepared from 0.04 g (1.73 mmol) of sodium metal and 5 ml of absolute ethanol dropwise to a cold solution of 0.05 g (1.58 mmol) of 2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]propanedihydrazide **4** in 10 ml of absolute ethanol. Leave the reaction mixture overnight in the refrigerator, then stir at room temperature for 6 hours and filter. Add 5 ml of 1 M acetic acid to the filtrate. Filter the precipitate obtained, wash and recrystallize from the mixture of solvents DMF – EtOH. Yield – 0.22 g (51%). M.p. > 300°C. 1H NMR δ , ppm – 11.60 (s, 1H), 10.26 (br, s, 2H), 8.02 (dd, $J = 8.1, 1.3$ Hz, 1H), 7.60 (ddd, $J = 8.3, 6.7, 1.4$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.27 (t, $J = 7.8$ Hz, 1H), 4.02 (t, $J = 7.6$ Hz, 1H), 2.97 (dd, $J = 7.6, 2.7$ Hz, 2H), 2.44 (s, 3H). Anal. Calcd for $C_{14}H_{13}N_3O_3$; C, 61.99; H, 4.83; N, 15.49; found: C, 61.89; H, 4.84; N, 13.63.

Conclusions

The new derivatives of 1,3-dicarbonyl 2-methyl-1,4-dihydroquinoline-4-one have been obtained using 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one as the alkylating agent. These compounds are a promising scaffold for the synthesis of various heterocyclic systems with quinolone substituents. By the example of condensation with hydrazine hydrate the synthesis of new derivatives of 2-methyl-3-[(5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methyl]-1,4-dihydroquinolin-4-ones has been shown. Using the tools of chemoinformatics the novelty of these compounds has been shown, and determination of 2D similarity with structures from the ChemBl 20 database has been conducted.

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Надійшла до редакції 30.01.2015 p.