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

V.O.Zubkov, N.I.Ruschak*, O.L.Kamenetska, I.S.Gritsenko

National University of Pharmacy
53, Pushkinska str., Kharkov, 61002, Ukraine. E-mail: vadim.zubkov@gmail.com
* Ivano-Frankivsk National Medical University

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, ChemBl и 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 ChemBl_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).
3-Substituted quinolones are attractive targets in medicinal chemistry over the past decades. It is connected with their ability to exhibit different types of 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-dihydroquinolin-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.](image-url)

<table>
<thead>
<tr>
<th>Reference structure:</th>
<th>PubChem Compound</th>
<th>ChEMBL_20</th>
<th>SPRESIweb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CID 73182817</td>
<td>67.25 million compounds</td>
<td>1.46 million compounds</td>
<td>5.68 million compounds</td>
</tr>
<tr>
<td>Similarity threshold &gt;= 85%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHEMBL474651</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spresi RegNo: 0289308-000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarity – 75.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarity – 70.02%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table
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 quinolaxine-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 biological 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
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 (\(^1\)H NMR) spectra were recorded on a Varian Mercury VX-200 (200 MHz) in DMSO-\(d_6\) using tetramethylsilane \([\text{CH}_3]_4\text{Si}\) as an internal standard. Elemental analysis was performed on an Elementar Vario El 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. \(^1\)H NMR, \(\delta\), 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, \(J = 14.0, 8.1, 2H\)), 2.45 (s, 3H), 1.18 (t, \(J = 7.1\) Hz, 3H). Anal. Calcd for C\(_{16}\)H\(_{16}\)NO\(_3\): 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. \(^1\)H NMR, \(\delta\), 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 C\(_{17}\)H\(_{19}\)NO\(_4\): 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 \(^1\)H 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]methyl}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. \(^1\)H NMR, \(\delta\), 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), 2.45 (s, 3H), 1.18 (t, \(J = 7.1\) Hz, 3H). Anal. Calcd for C\(_{15}\)H\(_{20}\)N\(_2\)O\(_4\): C, 67.64; H, 6.37; N, 9.85; found: C, 67.59; H, 5.67; N, 9.87.

Compounds 2b, c were synthesized by the same procedure.
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 quinoline substituents. By the example of condensation with hydrazine hydrate the synthesis of new derivatives of 2-methyl-3-[[(2-oxo-1,4-dihydropyrazol-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-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. Filtrate 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), 9.06 (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 C19H13N3O3: C, 55.44; H, 6.65; N, 23.09; found: C, 55.33; H, 5.66; N, 20.78.

2-(methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]pyrazolidine-3,5-dione. 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-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. Filtrate 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), 9.06 (s, 1H), 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 C19H13N3O3: C, 61.99; H, 4.83; N, 15.49; found: C, 61.89; H, 4.84; N, 13.63.

Conclusions

References