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Novel amides containing quinoline-4-one moeity: Synthesis and *In silico* prediction their biology activity

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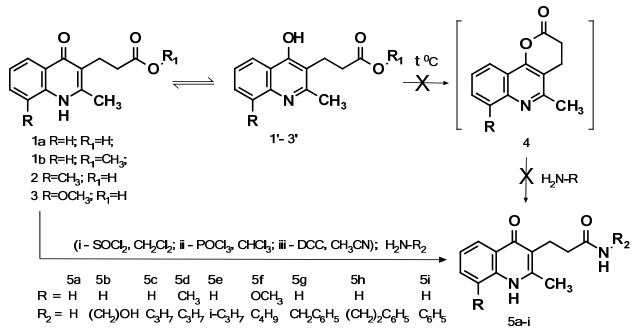
Abstract
To extend the molecular diversity of the derivatives of 3-alkyl carboxylic acids of quinolin-4-ones were synthesized a series of new amides 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl) propanoic acids. The final compounds were obtained by several ways. When acids were activated by standard activators, the highest yield of amide was observed by using $SOCl_2$. Direct aminolysis of esters of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl) propanoic acids can be realized when their structures have electron withdrawing group in the α- position alkylcarbonyl chain.

Keywords: 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl) propanoic acids, amides, PASS prediction.

1. Introduction
Quinolines show a wide variety of biological activities, and rightfully occupy a position of privileged scaffolds in the modern medicinal chemistry. The concept of privileged structures was first used *Evans* [1], and today it represents molecular scaffolds with versatile binding properties, such that a single scaffold is able to provide potent and selective ligands for a range of different biological targets through modification of functional groups [2]. A special place among quinoline belongs to quinolin-4-ones which also have the status of privileged and multivalent scaffold in drug discovery. Of course, the first of all quinolone-4-ones are one of the largest classes of antimicrobial agents used worldwide. The successful development of the quinolone antibiotics began in 1962 and has been going on for over 50 years. There are currently 4th generation fluoroquinolone antibiotics [3]. These drugs have shown themselves in the fight against multi-drug-resistant tuberculosis (MDR-TB) and currently, fluoroquinolones are approved as second-line drugs by the WHO to treat tuberculosis and their use is increasing [4]. In addition to the antimicrobial activity of quinolone-4-ones are known many other biological activities, and they can to be like antitumor, anxiolytic, anti-ischemic, antiviral agents etc. [5-8].
It should be noted that at present, despite the large array of studied derivatives of 4-quinolone-3-carboxylic acid, there is a significant gap in the study of their closest structural analogues - 4-quinolone-3-alkyl carboxylic acids. One of the areas of our research interests is comprehensive investigations of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acids as a new prospectively quinolone scaffolds having pharmacological potential [9-10]. In this work, we pay our attention to methods of synthesis and computer evaluation of the biological activity of amides of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl) propanoic acids.

2. Results and Discussion: Amide bond formation is one of the most important and regularly utilized reactions in organic synthesis and pharmaceutical R&D. For example, amides are present in more than 50% of reported medicinal compounds and it is used in the synthesis of 65% of the drug candidates examined [11].
Although the direction conversion of esters to amides is potentially a useful synthetic operation, but the practical application of this method has been limited for a number of reasons very often. In general, aminolysis of esters requires high temperatures and/or long reaction times and the strong alkali metal catalysts [12].
Structures of quinolin-4-ones may exist as 4-oxo/4-hydroxy tautomers (scheme 1).

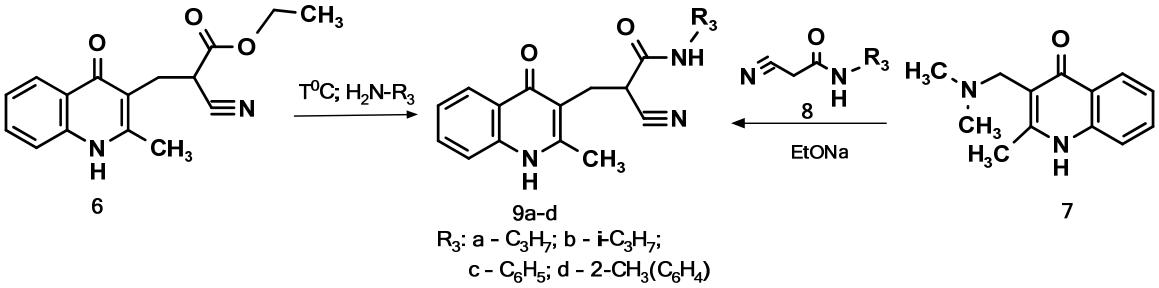
Scheme 1



Normally quinolin-4-ones are in the form of 4-oxo tautomer, but this equilibrium may be established at a high temperature in the reaction. For similar compounds - 3-alkylcarboxylic acid 4-hydroxy-quinolin-2-ones *Ukrainets* [13] described the formation of cyclic lactone, which acted as a highly reactive acylating agent. However, in this case no thermolysis at a high temperature nor prolonged boiling in DMF in the presence of amines do not lead to the desired result, and in all cases of the reaction medium were isolated starting compounds – acids 1a, 2,3, and methyl ester 1b. Amides 5a-i could be synthesized by standard methods of activation of the carboxylic group in the acids 1a, 2,3 (halogenating reagents and DCC) and the highest yields of the final products were obtained using thionyl chloride in methylene chloride solution.

The presence of acceptor groups in α-position of 3- (2-methyl-4-oxo-1,4-dihydroquinoline-3-yl) propanoic acids leads to activation of the carbonyl group, and it is sufficient to conduct the direct aminolysis of ethyl ester 6 under thermolysis conditions at temperature 180-200 ^{0}C or prolonged refluxing in DMF during 6-18 hours (scheme 2).

Scheme 2



Amides of 2-cyano-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl) propanoic acid 9a-d can be obtained also in another way - by alkylation of 3-[(dimethylamino)methyl]-2-methyl-1,4-dihydroquinolin-4-one 7 of the corresponding amides of cyanoacetic acid 8 under mild conditions. This synthesis method is more preferred in those cases where reactive amines are volatile or thermolabile substances.

Prediction of possible spectrum of biological activity of the synthesized compounds was performed using the internet version of PASS and Pharma Expert [14]. According to these data, the value of Pa (probability "to be active") for several pharmacological activities are in the middle range of values 0.5-0.7 and test compounds can behave as plastoquinol-plastocyanin reductase inhibitors, ubiquinol-cytochrome-c reductase inhibitors, 5-hydroxytryptamine release inhibitors and show antihypertensive activity as well as antihypoxic.

3. Materials and Methods: Melting points were determined in open capillary tubes and are 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 internal standard. Elemental analysis was performed on an Elementar Vario EI elemental analyzer.

Compounds 1a-b, 2,3,6,7 were synthesized by the methods described in our previous works [9-10]

General methods of synthesis of amides 5a-i

0.46g. (2.0 Mmol) 3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl) propanoic acid 1a was suspended in 20 ml. methylene chloride and to the reaction mixture was carefully added dropwise 0.36g. (3.0 mmol) SOCl2. and continue to stirring it for two hours at room temperature. Upon cooling, to the reaction mixture was added dropwise 3.0 mmol of the corresponding amine, 0.35g. triethylamine, and left for 3 hours at room temperature. The mixture was diluted with 50 ml. water and acidified with 0.5 M HCl to pH 4-5. The organic layer was separated, the solvent was evaporated under reduced pressure. The residue is crystallized from a suitable solvent.

3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanamide 5a. Yield - 0.39g (84%). m.p. – 252-254 °C. ^{1}H NMR δ, ppm - 11.38 (s, 1H), 8.03 (dd, J = 8.1, 1.4 Hz, 1H), 7.65 – 7.37 (m, 2H), 7.32 – 7.13 (m, 2H), 6.67 (s, 1H), 2.76 – 2.61 (m, 2H), 2.55 – 2.33 (m, 3H), 2.20 (dd, J = 8.4, 6.8 Hz, 2H); Anal.Calcd for $C_{13}H_{14}N_2O_2$; C, 67.81; H, 6.13; N, 12.17; found: C, 67.71; H, 6.12; N, 12.15.

N-(2-hydroxyethyl)-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanamide 5b. Yield - 0.38g (70%). m.p. – 250-251 °C. ^{1}H NMR δ, ppm - 8.10 – 7.90 (m, 2H), 7.62 – 7.37 (m, 2H), 7.20 (ddd, J = 8.2, 6.5, 1.6 Hz, 1H), 3.33 (t, J = 6.1 Hz, 3H), 3.06 (q, J = 5.9 Hz, 2H), 2.69 (t, J = 7.5 Hz, 2H), 2.55 – 2.14 (m, 4H); Anal.Calcd for $C_{15}H_{18}N_2O_3$; C, 65.68; H, 6.61; N, 10.21; found: C, 65.56; H, 6.60; N, 10.20

3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-propylpropanamide 5c. Yield - 0.37g (68%). m.p. – 243-245 °C. ^{1}H NMR δ, ppm - 8.04 (dd, J = 8.0, 1.5 Hz, 1H), 7.81 (t, J = 5.6 Hz, 1H), 7.64 – 7.38 (m, 2H), 7.22 (t, J = 7.4 Hz, 1H), 2.95 (q, J = 6.6 Hz, 2H), 2.78 – 2.48 (m, 2H), 2.39 (s, 3H), 2.23 (t, J = 7.5 Hz, 2H), 1.34 (h, J = 7.3 Hz, 2H), 0.75 (t, J = 7.4 Hz, 3H); Anal.Calcd for $C_{16}H_{20}N_2O_2$; C, 70.56; H, 7.40; N, 10.29; found: C, 70.42; H, 7.38; N, 10.27

3-(2,8-dimethyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-propylpropanamide 5d. Yield - 0.43g (75%). m.p. – 241-242

°C. ^{1}H NMR δ, ppm - 10.10 (s, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 3.24 (d, J = 9.0 Hz, 2H), 2.73 (t, J = 7.7 Hz, 2H), 2.41 (d, J = 7.4 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H); Anal.Calcd for $C_{17}H_{22}N_2O_2$; C, 71.30; H, 7.74; N, 9.78; found: C, 71.19; H, 7.73; N, 9.77

3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-(propan-2-yl)propanamide 5e. Yield - 0.39g (71%). m.p. – 245-247 °C. ^{1}H NMR δ, ppm - 11.39 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.71 – 7.37 (m, 3H), 7.31 – 7.14 (m, 1H), 3.88 – 3.68 (m, 1H), 2.67 (t, J = 7.7 Hz, 2H), 2.55 – 2.34 (m, 7H), 2.17 (t, J = 7.5 Hz, 2H), 0.97 (d, J = 6.6 Hz, 6H); Anal.Calcd for $C_{16}H_{20}N_2O_2$; C, 70.56; H, 7.40; N, 10.29; found: C, 70.45; H, 7.39; N, 10.28

N-butyl-3-(8-methoxy-2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanamide 5f. Yield - 0.42g (67%). m.p. – 238-239 °C. ^{1}H NMR δ, ppm - 10.76 (s, 1H), 7.60 (t, J = 4.8 Hz, 1H), 7.16 (d, J = 4.7 Hz, 2H), 3.94 (d, J = 6.2 Hz, 5H), 2.71 (t, J = 7.8 Hz, 2H), 2.57 – 2.34 (m, 1H), 1.47 (p, J = 6.6 Hz, 2H), 1.20 (dt, J = 14.5, 7.3 Hz, 2H), 0.80 (t, J = 7.2 Hz, 3H); Anal.Calcd for $C_{18}H_{24}N_2O_3$; C, 68.33; H, 7.65; N, 8.85; found: C, 68.23; H, 7.64; N, 8.84

N-benzyl-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanamide 5g. Yield - 0.49g (76%). m.p. – 242-244 °C. ^{1}H NMR δ, ppm - 11.31 (s, 1H), 8.24 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.76 – 7.36 (m, 3H), 7.31 – 7.04 (m, 5H), 4.22 (d, J = 5.9 Hz, 2H), 3.02 – 2.66 (m, 2H), 2.37 (d, J = 7.2 Hz, 4H); Anal.Calcd for $C_{20}H_{20}N_2O_2$; C, 74.98; H, 6.29; N, 8.74; found: C, 74.87; H, 6.28; N, 8.73

3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-(2-phenylethyl)propanamide 5h. Yield - 0.52g (78%). m.p. – 236-238 °C. ^{1}H NMR δ, ppm - 11.38 (s, 1H), 8.04 (dd, J = 8.2, 1.5 Hz, 1H), 7.88 (t, J = 5.5 Hz, 1H), 7.66 – 7.38 (m, 2H), 7.32 – 7.00 (m, 6H), 3.30 – 3.10 (m, 2H), 2.77 – 2.32 (m, 9H), 2.22 (t, J = 7.5 Hz, 2H); Anal.Calcd for $C_{21}H_{22}N_2O_2$; C, 75.42; H, 6.63; N, 8.38; found: C, 75.34; H, 6.62; N, 8.37

3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-phenylpropanamide 5i. Yield - 0.44g (72%). m.p. – 250-251 °C. ^{1}H NMR δ, ppm - 11.41 (s, 1H), 9.89 (s, 1H), 8.06 (dd, J = 8.2, 1.4 Hz, 1H), 7.65 – 7.14 (m, 7H), 6.98 (t, J = 7.3 Hz, 1H), 2.77 (q, J = 8.8, 8.1 Hz, 2H), 2.45 (d, J = 11.4 Hz, 4H); Anal.Calcd for $C_{19}H_{18}N_2O_2$; C, 74.49; H, 5.92; N, 9.14; found: C, 74.39; H, 5.91; N, 9.13

General methods of synthesis of amides 9a-d

Method A: 0.57g (2.0 Mmol) ethyl 2-cyano-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)propanoate 6 and 2.5 mmol of the corresponding amine in 10 ml of DMF was heated under reflux during 8-16 hours. The reaction mixture diluted with 100 ml. water and acidified with 0.5 M HCl to pH 4-5. The precipitate was filtered and crystallized from a suitable solvent.

Method B: To 1.08 g (5 mmol) of 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-one **7** in 20 ml of absolute ethanol was added 0.5 ml (8 mmol) of methyl iodide and the mixture stirred at room temperature for 15 hours. Then the temperature was raised to 60 ºC and maintained for an hour. The solution was cooled to room temperature, upon which was added (5 mmol) of corresponding amides of cyanoacetate 8 under vigorous stirring, a solution of sodium ethylate, which is prepared from 0.12 g metal sodium (5.3 mmol) and 10 ml of absolute ethanol. The reaction mixture was refluxed until no trimethylamine evaluated. Water was added, the mixture acidified to pH 5. The resulting precipitate was filtered, washed and recrystallized from a suitable solvent

2-cyano-2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-N-propylacetamide 9a. Yield – Method A 0.40g (67%); Method B 0.31g (52%). m.p. – 262-264 °C. ^{1}H NMR δ, ppm - 11.53 (s, 1H), 8.37 (t, J = 5.6 Hz, 1H), 8.05 (dd, J = 8.1, 1.5 Hz, 1H), 7.70 – 7.41 (m, 2H), 7.28 (ddd, J = 8.0, 6.7, 1.3 Hz, 1H), 4.13 – 3.96 (m, 1H), 3.17 – 2.78 (m, 4H), 2.48 (p, J = 1.8 Hz, 3H), 1.30 (h, J = 7.3 Hz, 2H), 0.68 (t, J = 7.4 Hz, 3H); Anal.Calcd for $C_{17}H_{19}N_3O_2$; C, 68.67; H, 6.44; N, 14.13; found: C, 68.57; H, 6.43; N, 14.11

2-cyano-2-[(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-N-(propan-2-yl)acetamide 9b. Yield – Method A 0.32g (53%); m.p. – 257-258 °C. ^{1}H NMR δ, ppm - 11.58 (s, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.70 – 7.41 (m, 2H), 7.28 (t, J = 7.4 Hz, 1H), 3.99 (t, J = 7.7 Hz, 1H), 3.77 (q, J = 6.8 Hz, 1H), 2.97 (d, J = 7.7 Hz, 2H), 2.55 – 2.33 (m, 5H), 0.96 (dd, J = 18.3, 6.6 Hz, 6H); Anal.Calcd for $C_{17}H_{19}N_3O_2$; C, 68.67; H, 6.44; N, 14.13; found: C, 68.61; H, 6.43; N, 14.10

2-cyano-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-phenylpropanamide 9c. Yield – Method A 0.32g (48%); Method B 0.39g (59%). m.p. – 268-270 °C. ^{1}H NMR δ, ppm - 10.50 (s, 1H), 8.08 (dd, J = 8.1, 1.5 Hz, 1H), 7.70 – 7.41 (m, 4H), 7.40 – 7.21 (m, 3H), 7.08 (t, J = 7.3 Hz, 1H), 4.42 – 4.24 (m, 1H), 3.34 (d, J = 12.5 Hz, 4H), 3.10 (d, J = 7.5 Hz, 2H), 2.48 (dd, J = 3.4, 1.7 Hz, 3H); Anal.Calcd for $C_{20}H_{17}N_3O_2$; C, 72.49; H, 5.17; N, 12.68; found: C, 72.42; H, 5.16; N, 12.66

2-cyano-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-(2-methylphenyl)propanamide 9d. Yield – Method A 0.36g (62%). m.p. – 265-267 °C. ^{1}H NMR δ, ppm - 11.65 (s, 1H), 9.87 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.71 – 7.43 (m, 2H), 7.38 – 7.03 (m, 5H), 4.51 – 4.25 (m, 1H), 3.11 (d, J = 7.6 Hz, 2H), 2.55 – 2.40 (m, 6H), 1.98 (s, 3H); Anal.Calcd for $C_{21}H_{19}N_3O_2$; C, 73.03; H, 5.54; N, 5.54; found: C, 72.96; H, 5.53; N, 5.53

4. Conclusions

New alkyl and arylamides of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl)propanoic acids have been synthesized by several methods with high yields. Studied the reactivity of the starting compounds with amines under conditions of thermolysis reaction. It is shown that the presence of the nitrile group in the alkylcarbonyl chain promotes the direct amidation of esters of 3-(2-methyl-4-oxo-1,4-dihydroquinoline-3-yl) propanoic acids. The synthesized amides are the perspective scaffold for the future synthesis of various heterocyclic systems with quinolone substituents. Computer-aided prediction (PASS) has shown the ability to have these amides biological activity as inhibitors of oxidative enzymes.

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