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

NI Ruschak, VO Zubkov and IS Gritsenko

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 SOCl₂. 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).
reaction mixture was added dropwise 3.0 mmol of the chlorides and to the reaction mixture was carefully added yl) propanoic acid 1a was suspended in 20 ml. methylene chloride in methylene chloride solution.

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 [9-10] described in our previous works [9-10]Compounds 1a-b, 2,3,6,7 were synthesized by the methods of 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 (1H NMR) spectra were recorded on Varian Mercury VX-200 (200 MHz) in DMSO-δ6 using tetramethylsilane [(CH3)4Si] as internal standard. Elemental analysis was performed on an Elementar Vario EL elemental analyzer.

Compounds 1a-b, 2,3,6,7 were synthesized by the methods described in our recent 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 then added dropwise 0.36g. (3.0 mmol) SOCl2. After two hours at room temperature. Upon cooling, in 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. 1H 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 C16H20N2O2; C, 70.56; H, 7.40; N, 12.15; found: C, 70.42; H, 7.38; N, 10.27

N-(2-hydroxyethyl)-3-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-N-propylpropanamide 5b. Yield - 0.38g (70%). m.p. – 250-251 °C. 1H NMR δ, ppm - 11.38 (s, 1H), 8.03 (dd, J = 8.1, 1.4 Hz, 1H), 7.62 – 7.37 (m, 2H), 7.20 (dd, 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 C16H25N2O2; 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. – 240-245 °C. 1H NMR δ, ppm - 11.20 (s, 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 C16H25N2O2; 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

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.
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-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-N-propylacetamide 9a. Yield – Method A 0.32g (53%); m.p. – 257-258 °C. 1H 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, 4H), 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 C17H19N3O2; C, 68.67; H, 6.44; N, 14.13; found: C, 68.61; H, 6.43; N, 14.10

2-cyano-2-[2-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-N-(propan-2-yl)acetamide 9b. Yield – Method A 0.39g (59%); m.p. – 268-270 °C. 1H NMR δ, ppm - 11.41 (s, 1H), 10.50 (s, 1H), 8.08 (d, 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 C21H21N3O2; C, 72.49; H, 5.17; N, 12.68; found: C, 72.42; H, 5.16; N, 12.66

2-cyano-2-[2-(2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl]-N-(2-phenethyl)propanamide 9c. Yield – Method A 0.36g (62%); m.p. – 265-267 °C. 1H 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 C21H21N3O2; 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.

5. References


