СИНТЕЗ ТА АНАЛІЗ БІОЛОГІЧНО АКТИВНИХ РЕЧОВИН

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SYNTHESIS OF A NEW QUINAZOLINONE DERVATIVES BASED ON 2-(4-OXO-3,4-DIHYDRO-3-QUINAZOLINYL) ACETOHYDRAZIDE

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By acetylation of 2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide with anhydrides and chloroanhydrides of mono- and dicarboxylic acids the corresponding derivatives containing two active pharmacophores — the quinazolinone nucleus combined with the fragments of carboxylic acids derivatives — in the structure have been obtained.

One of the most frequently encountered heterocyclic compounds in medicinal chemistry is 4(3*H*)-quinazolinone with wide applications like calcium channel antagonist, anticonvulsant, antidiabetic, anti-tumor, antimicrobial, antihistaminic activities and so many other uses [3-10]. Special interest for purposeful synthesis of biologically active compounds represents obtaining of structures which would combine two pharmacophoric fragments with anticipated biological activity One of perspective directions is the combination of qunazolinone heterocycle and derivatives of dicarboxylic acids, that positively affects on pharmacological effects [1, 2].

2-(4-Oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (1) was tried to be acylated by diethyloxalate in ethanol but the desired product was not achieved. In contrast, it was acylated by using of diethyl oxalate in acetic acid under reflux for 1 hour but the unexpected bis-product namely N,N'-di[2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetyl] ethanediohydrazide (2) was obtained. So, we have used another reagent namely ethyl oxalyl chloride in acetic acid in the presence of triethyl amine to afford the required derivative i.e. N-ethyloxalyl-(4-oxo-3,4-dihydro-3-quinazolinyl)acetohydrazide (3). Furthermore, compound (3) was reacted with hydrazine hydrate in ethanol obtaining N-(dicarbonylhydrazido)-2-(4-oxo-3,4-dihydro-3-quinazolinyl)acetohyd razide (4; scheme 1).

Compound (1) was subjected to acetylation by using acetyl (benzyl) chloride in acetic acid in the presence of triethyl amine resulting in N-acetyl(benzoyl)-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (5). In addition to the previous acylations, compound (1) was taken place by using of succinic anhydride. Initially, reaction was carried out in acetic acid with heating and formation of a mixture of two products of N-succinimido-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetamide (6) and N-succinyl-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetamide (7). But, in case of mixing compound (11) with succinic anhydride in ethyl acetate, the affording product was only compound (7). What's more, compound (7) was subjected to cyclodehydration by using acetic anhydride and formation compound (6) in a good yield only.

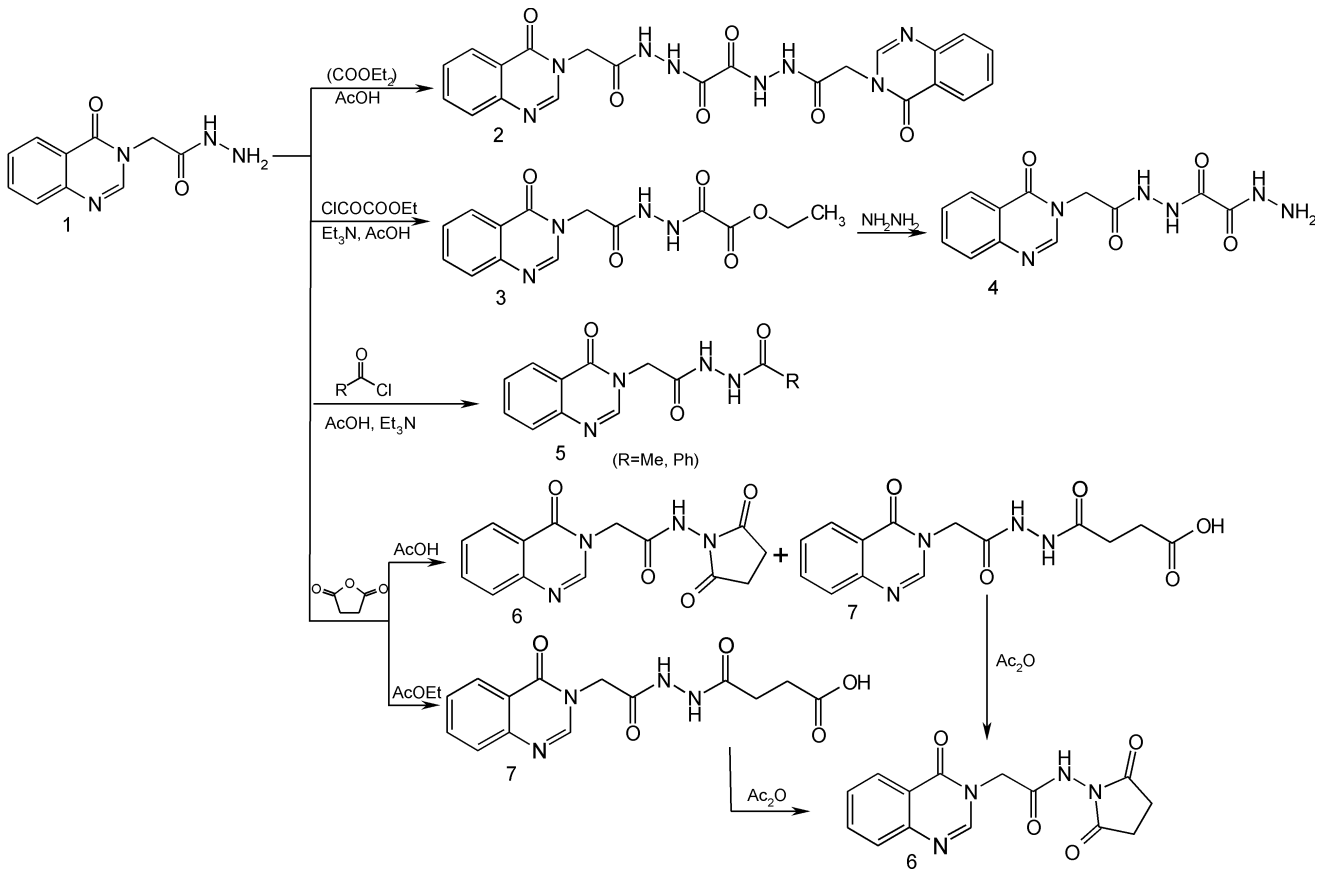
Also acyclic anthranilamide (8) was acylated by using succinic anhydride in acetic acid and obtaining *N*-(phenyl hydrazidoacetyl)-N'-succinamido anthranilamide (10; scheme 2).

In addition compound (9) was subjected to acylation by using succinic anhydride in ethyl acetate yielding N-(*o*-succinylaminobenzoyl) methyl glycinate (11).

Experimental Methods

^{1}H NMR spectra were registered on a spectrophotometer Varian M200, operating frequency 200 MHz, from solutions in DMSO-d_6 with TMS as internal reference.

N,N'-Di[2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetyl] ethanediohydrazide (2). To a mixture of 0.01 mole (2.18 g) of 2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (1) and 10 ml of acetic acid, 0.01 mole (1.68 ml) of diethyl oxalate was added, heated for 30 min and left to the next day. The formed product was filtered off, dried, recrystallized from acetic. Yield — 58%. M.p. — 260-262°C; ^{1}H NMR, δ, ppm: 4.70 s (4H,CH_2+CH_2), 7.5 t (2H, ArH), 7.65 d (2H, ArH), 7.85 t (2H,ArH), 8.10 d (2H,ArH), 8.25 s (2H,C-2 H quinazolinone), 9.65 d (2H,NH), 10.40 d (2H,NH).



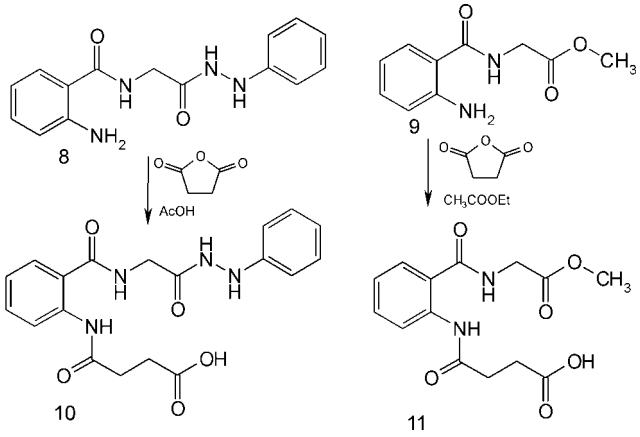
Scheme 1

N-Ethyloxalyl-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (3). To a mixture of 0.01 mole (2.18 g) of 2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (1) and 10 ml of acetic acid 0.01 mole (1.44 ml) of triethylamine was added droply. To that mixture, 0.01 mole (1.2 ml) of ethyl oxalyl chloride was added gradually and the mixture was heated for 60 min. The mixture was cooled, diluted with water and the precipitate was filtered off, dried and recrystallized from acetic acid. Yield — 75%. M.p. — 279-280°C; ^{1}H NMR, δ, ppm: 1.20 t (3H, CH_3), 4.30 q (2H, $\underline{CH_2}CH_3$), 4.7 s (2H, CH_2CO), 7.40 t (1H, ArH), 7.60 d (1H, ArH), 7.90 t (1H, ArH), 8.1 d (1H, ArH), 8.4 s (1H, C-2 H quinazolinone), 10.60 d (1H, $CH_2CO\underline{NH}$), 11.00 d (1H, $NH\underline{NH}CO$).

N-(Dicarbonylhydrazido)-2-(4-oxo-3,4-dihydro-3-quinazolinyl) aceto-hydrazide (4). A mixture of 0.01 mole (3.56 g) of *N*-ethyloxalyl-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (3) and 0.01 mole (0.48 ml) of hydrazine hydrate was stirred in 15 ml ethanol for 6 hours. The precipitate was filtered off, dried and recrystallized from ethanol. Yield — 47-50%. M.p. — 297-299°C; ^{1}H NMR, δ, ppm: 4.30 d (2H, NH_2), 4.80 s (2H, CH_2), 7.40 t (1H, ArH), 7.70 d (1H, ArH), 7.90 t (1H, ArH), 8.10 d (1H, ArH), 8.40 s (1H, C-2 H quinazolinone), 9.5 m (3H, $\underline{NH}NH+\underline{NH}NH_2$).

N-Acetyl-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (5a). 0.01 mole (2.18 g) of 2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (1) was dissolved in 10 ml of acetic acid with little heating. Droply 0.01 mole (1.44 ml) of triethylamine was added. Then 0.01 mole (0.69 ml) of acetyl chloride was added to the mixture and stirred for 5 hours. The mixture was diluted with water, left for 24 hours and the precipitate was filtered off, dried, recrystallized from acetic. Yield — 45%. M.p. — 240-242°C; ^{1}H NMR, δ, ppm: 1.70 s (3H, CH_3), 4.70 s (2H, CH_2), 7.20 t (1H, ArH), 7.40 d (1H, ArH), 7.70 t (1H, ArH), 7.90 d (1H, ArH), 8.30 s (1H, C-2 H quinazolinone), 9.70 d (1H, $NH\underline{NH}CO$), 10.10 d (1H, $CO\underline{NH}NH$).

Compound (5b) was obtained similarly.



Scheme 2

N-Benzoyl-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (5b). Yield — 95%. M.p. — 258-261°C; ^{1}H NMR, δ, ppm: 4.80 s (2H, CH_2), 7.10 m (4H, ArH), 7.30 d (1H, ArH), 7.50 m (3H, ArH), 7.90 d (1H, ArH), 8.60 s (1H, C-2 H quinazolinone), 10.5 d (2H, NHNH).

N-Succinyl-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetamide (7). To a mixture of 0.01 mole (2.18 g) of 2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetohydrazide (1) and 0.01 mole (1 g) of succinic anhydride 15 ml of AcOEt was added. The mixture was stirred for 5 hours then filtered off and the precipitate was recrystallized from acetic. Yield — 67%. M.p. — 220-222°C; ^{1}H NMR, δ, ppm: 2.75 m (4H, CH_2CH_2), 4.90 s (2H, CH_2CO), 7.35 t (1H, ArH), 7.60 d (1H, ArH), 7.85 t (1H, ArH), 8.10 d (1H, ArH), 8.3 s (1H, C-2 H quinazolinone), 9.7 d (1H, NHNHCO), 10.2 d (1H, CONHNH), 12.0 s (1H, COOH).

N-Succinimido-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetamide (6). A mixture of 0.01 mole (3.18 g) of N-succinyl-2-(4-oxo-3,4-dihydro-3-quinazolinyl) acetamide (7) and 5 ml of acetic anhydride was heated under reflux for 60 min. The mixture was cold, diluted with water and the precipitate was formed, filtered off and dried. The product was recrystallized and collected as pale brown crystals. Yield — 78%. M.p. — 311-314°C; ^{1}H NMR, δ, ppm: 1.90-2.35 m (4H, CH_2CH_2), 4.90 s (2H, CH_2CO), 7.35 t (1H, ArH), 7.60 d (1H, ArH), 7.85 t (1H, ArH), 8.10 d (1H, ArH), 8.3 s (1H, C-2 H quinazolinone), 11.00 s (1H, NH).

N-(*o*-Succinylaminobenzoyl) methyl glycinates (10). A mixture of 0.01 mole (2.08 g) of *N*-(*o*-amino benzoyl) methyl glycinate (8) and 0.01 mole (1.00 g) of succinic anhydride was stirred in 10 ml of ethyl acetate for 4 hours. The mixture was diluted with water and the formed precipitate was filtered off and recrystallized from acetic acid. Yield — 56%. M.p. — 100-102°C; ^{1}H NMR, δ, ppm: 2.50 m (4H, CH_2CH_2), 3.60 s (3H, CH_3), 4.00 d (2H, $NHCH_2$), 7.10 t (1H, ArH), 7.45 t (1H, ArH), 7.80 d (1H, ArH), 8.40 d (1H, ArH), 9.15 t (1H, $NHCH_2$), 11.10 s (1H, NHCO), 12.15 s (1H, COOH).

N-(Phenylhydrazidoacetyl)-N'-succinamido anthranilamide (11). A mixture of 0.01 mole (2.84 g) of N-(phenyl hydrazidoacetyl) anthranilamide (9) and 0.01 mole (1 g) of succinic anhydride was heated for 60 min in 15 ml acetic acid. The mixture was cooled, diluted with water, scratched and left overnight. The formed precipitate was filtered off, recrystallized from acetic acid, dried and collected as yellowish white crystals. Yield — 54%. M.p. — 119-122°C; ^{1}H NMR, δ, ppm: 2.50-3.40 m (4H, CH_2CH_2), 3.60 d (2H, $NHCH_2$), 6.55-8.10 m (9H, ArH), 8.55 t (1H, $NHCH_2$), 9.00 (1H, NHPh), 10.10 d (1H, CONHNH), 10.30 s (1H, PhNHCO), 12.10 s (1H, COOH).

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СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ ХИНАЗОЛИНОНА НА ОСНОВЕ 2-(4-ОКСО-3,4-ДИГИДРО-3-ХИНАЗОЛИНИЛ)АЦЕТОГИДРАЗИДА

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Ацилированием 2-(4-оксо-3,4-дигидро-3-хиназолинил)ацетогидразида ангидридами и хлорангидридами моно- и дикарбоновых кислот получены соответствующие производные, содержащие в своей структуре два активных фармакофора — хиназолиноновое ядро, соединенное с фрагментами производных карбоновых кислот.

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СИНТЕЗ НОВИХ ПОХІДНИХ ХІНАЗОЛІНОНУ НА ОСНОВІ 2-(4-ОКСО-3,4-ДИГІДРО-3-ХІНАЗОЛІНІЛ)АЦЕТОГІДРАЗИДУ

Л.А.Шемчук, М.Аль-Асрі Джаміль, Д.В.Левашов, Ю.А.Шенгоф, П.С.Арзуманов

Ацилюванням 2-(4-оксо-3,4-дигідро-3-хіназолініл)ацетогідразиду ангідридами та хлорангідридами моно- та дикарбонових кислот отримано відповідні похідні, що містять у своїй структурі два активних фармакофори — хіназолінонове ядро, поєднане з фрагментами похідних карбонових кислот.