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SYNTHESIS OF 3-{3-[(4-METHYLCYCLOHEX-3-ENYL-CARBONYL)AMINO]-4-OXO-3,4-DIHYDROQUINAZOLIN-2-YL}PROPANOIC ACID ANILIDES

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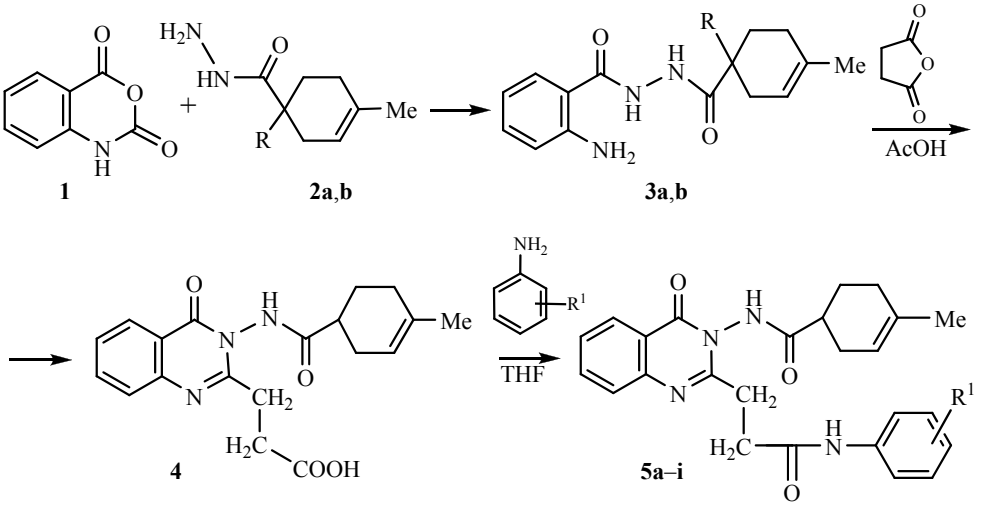
With the aim of discovering potential diuretic agents amongst quinazoline anilides we have prepared anilides of 3-{3-[(4-methylcyclohex-3-enylcarbonyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}propanoic acid. Optimal conditions for obtaining of the starting acid have been established, and anilides have been synthesized by the mixed anhydrides method.

Keywords: anilides, hydrazides, mixed anhydrides, propionic acid, quinazolines, succinic anhydride.

Recently [1, 2] the synthesis of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides has been reported which possess high diuretic activity and are undergoing extended pharmacological study. Thanks to the structural similarity of quinoline and quinazoline compounds the anilides of 3,4-dihydro-quinazolinylpropanoic acids may be of interest as potential diuretics.



1 **2a**,**b** **3a**,**b** **4** **5a–i**

2, 3 a R = H, **b** R = COOH;
5 a R^1 = 2-Cl, **b** R^1 = 2-CF_3, **c** R^1 = 4-OMe, **d** R^1 = 3-Cl, **e** R^1 = 4-NO_2,
f R^1 = 4-COMe, **g** R^1 = 2,4-Me_2, **h** R^1 = 2-OMe, **i** R^1 = 4-Br

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TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **5a-i**

Compound	Empirical formula	Found, % / Calculated, %			Mp*, °C	Yield, %
		C	H	N		
5a	$C_{25}H_{25}ClN_4O_3$	64.36 / 64.58	5.34 / 5.42	11.97 / 12.05	225-227	80
5b	$C_{26}H_{25}F_3N_4O_3$	62.67 / 62.64	5.07 / 5.05	11.31 / 11.24	185-186	82
5c	$C_{26}H_{28}N_4O_4$	67.55 / 67.81	6.16 / 6.13	12.04 / 12.17	194-195	75
5d	$C_{25}H_{25}ClN_4O_3$	64.51 / 64.58	5.42 / 5.42	11.96 / 12.05	187-189	77
5e	$C_{25}H_{25}N_5O_5$	62.97 / 63.15	5.25 / 5.30	14.51 / 14.73	188-192	52
5f	$C_{27}H_{28}N_4O_4$	68.40 / 68.63	6.00 / 5.97	11.68 / 11.86	204-206	62
5g	$C_{27}H_{30}N_4O_3$	70.55 / 70.72	6.55 / 6.59	12.22 / 12.22	217-219	53
5h	$C_{26}H_{28}N_4O_4$	67.91 / 67.81	5.99 / 6.13	11.77 / 12.17	170-172	75
5i	$C_{25}H_{25}BrN_4O_3$	58.81 / 58.95	4.92 / 4.95	10.73 / 11.00	222-224	68

*Recrystallization solvents: ethanol (compounds **5a,c-e**), ethyl acetate (compounds **5b,g**), ethanol-water (compound **5i**).

The starting 3-{3-[(4-methylcyclohex-3-enylcarbonyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}propanoic acid (**4**) was prepared by different methods. The first of these was the decarboxylation of the earlier described [3] *N*'-cyclohexenylcarbonyl-substituted 2-aminobenzoic acid hydrazide **3b** with subsequent reaction of the formed *N*,*N*'-diacylhydrazine **3a** with succinic anhydride in acetic acid (method A). The second method consists of a condensation of isatoic anhydride (**1**) with the hydrazide **2a** and treatment of the compound **3a** formed with succinic anhydride under the same conditions (method B). The third method is a direct reaction of the *N*,*N*'-diacylhydrazine **3b** with succinic anhydride in acetic acid (method C) and deserves attention because it does not demand an initial decarboxylation.

Despite the number of stages being optimal for method C, preference should be given to method A since the target acid **4** can be prepared in the best yield and with purity sufficient for carrying out the subsequent stage without additional purification.

The method of mixed anhydrides known in peptide synthesis was used for preparation of anilides **5a-i**. The majority of the anilides are formed in good yield (Table 1). Exceptions are the anilides **5e** and **5g** since colored side products were observed in the course of their synthesis.

The structure of the synthesized compounds was confirmed by the elemental analytical data and by ^{1}H NMR spectra in which the proton signals of all the fragments are found in regions which are characteristic for them (Table 2).

Hence the mixed anhydride method gave the 3-{3-[(4-methylcyclohex-3-enylcarbonyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}propanoic acid anilides from the corresponding acid and substituted anilines. The best method for preparing the starting acid proved to be the decarboxylation of the *N*'-cyclohexenylcarbonyl-substituted 2-aminobenzoic acid hydrazide in pyridine and treatment of the *N*,*N*'-diacylhydrazine formed with succinic anhydride in acetic acid.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds **5a-i**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
5a	1.65 (3H, br. s, CH_3); 1.67-2.12 (4H, m, $2CH_2$); 2.12-2.30 (2H, m, CH_2); 2.44-2.69 (2H, m, CH_2); 2.72-2.98 (2H, m, CH_2); 3.04-3.26 (1H, m, CH); 5.42 (1H, br. s, =CH); 7.07 (1H, d, *J* = 8.1, H Ar); 7.31 (1H, t, *J* = 8.1, H Ar); 7.41-7.49 (1H, m, H Ar); 7.52-7.60 (2H, m, H Ar); 7.77-7.90 (2H, m, H Ar); 8.10 (1H, d, *J* = 7.3, H Ar); 10.30 (1H, s, NH); 11.10 (1H, s, NH)
5b	1.63 (3H, br. s, CH_3); 1.86-2.28 (4H, m, $2CH_2$); 2.14-2.28 (2H, m, CH_2); 2.40-2.70 (2H, m, CH_2); 2.98-3.21 (2H, m, CH_2); 3.23-3.35 (1H, m, CH); 5.40 (1H, br. s, =CH); 7.28 (1H, d, *J* = 7.3, H Ar); 7.45-7.62 (3H, m, H Ar); 7.69-7.89 (2H, m, H Ar); 8.11 (2H, d, *J* = 7.3, H Ar); 10.45 (1H, s, NH); 11.05 (1H, s, NH)
5c	1.64 (3H, br. s, CH_3); 1.88-2.00 (4H, m, $2CH_2$); 2.20-2.49 (2H, m, CH_2); 2.49-2.81 (2H, m, CH_2); 2.81-3.00 (2H, m, CH_2); 3.05-3.16 (1H, m, CH); 3.62 (3H, s, CH_3O); 5.41 (1H, br. s, =CH); 6.68 (1H, d, *J* = 10.8, H Ar); 7.14-7.29 (1H, m, H Ar); 7.39 (2H, t, *J* = 8.1, H Ar); 7.96-8.20 (3H, m, H Ar); 8.61 (1H, s, H Ar); 9.95 (1H, s, NH); 11.04 (1H, s, NH)
5d	1.67 (3H, br. s, CH_3); 1.89-2.16 (4H, m, $2CH_2$); 2.17-2.35 (2H, m, CH_2); 2.53-2.92 (2H, m, CH_2); 2.93-3.10 (2H, m, CH_2); 3.27-3.30 (1H, m, CH); 5.46 (1H, br. s, =CH); 6.40 (1H, d, *J* = 8.1, H Ar); 6.49-6.63 (1H, m, H Ar); 7.13-7.53 (2H, m, H Ar); 7.68 (1H, d, *J* = 9.9, H Ar); 7.98 (1H, d, *J* = 8.0, H Ar); 8.16 (1H, t, *J* = 8.1, H Ar); 8.6 (1H, s, H Ar); 11.13 (1H, s, NH); 12.44 (1H, s, NH)
5e	1.62 (3H, br. s, CH_3); 2.20-2.32 (4H, m, $2CH_2$); 2.49-2.52 (2H, m, CH_2); 2.56-2.81 (2H, m, CH_2); 2.84-2.88 (2H, m, CH_2); 3.30-3.36 (1H, m, CH); 5.42 (1H, br. s, =CH); 7.51-7.60 (1H, m, H Ar); 7.58 (1H, d, *J* = 8.0, H Ar); 7.83-7.92 (3H, m, H Ar); 8.10 (1H, d, *J* = 8.0, H Ar); 8.32 (2H, d, *J* = 8.0, H Ar); 10.74 (1H, s, NH); 11.03 (1H, s, NH)
5f	1.65 (3H, br. s, CH_3); 1.66-1.74 (1H, m) and 1.95-2.10 (3H, m, $2CH_2$); 2.12-2.27 (2H, m, CH_2); 2.51 (3H, s, $COCH_3$); 2.58-2.67 (1H, m) and 2.78-2.97 (3H, m, $2CH_2$); 3.10-3.19 (1H, m, CH); 5.40 (1H, br. s, =CH); 7.51 (1H, t, *J* = 7.3, H Ar); 7.54 (1H, d, *J* = 8.0, H Ar); 7.72 (2H, d, *J* = 8.7, H Ar); 7.81 (1H, t, *J* = 7.3, H Ar); 7.90 (2H, d, *J* = 8.7, H Ar); 8.10 (1H, d, *J* = 8.0, H Ar); 10.43 (1H, s, NH); 11.03 (1H, s, NH)
5g	1.59 (3H, br. s, CH_3); 1.88-2.05 (4H, m, $2CH_2$); 2.22-2.27 (2H, m, CH_2); 2.35-2.40 (6H, m, $2CH_3$); 2.52-2.54 (2H, m, CH_2); 2.66-2.70 (2H, m, CH_2); 3.03-3.10 (1H, m, CH); 5.36 (1H, br. s, =CH); 6.60 (1H, br. s, H Ar); 7.16 (2H, s, H Ar); 7.47 (1H, t, *J* = 7.0, H Ar); 7.53 (1H, d, *J* = 7.8, H Ar); 7.80 (1H, t, *J* = 7.0, H Ar); 8.15 (1H, d, *J* = 7.8, H Ar); 9.86 (1H, s, NH); 10.97 (1H, s, NH)
5h	1.61 (3H, br. s, CH_3); 1.87-2.25 (4H, m, $2CH_2$); 2.48-2.62 (2H, m, CH_2); 2.68-2.81 (2H, m, CH_2); 2.82-2.95 (2H, m, CH_2); 3.02-3.13 (1H, m, CH); 3.78 (3H, br. s, CH_3O); 5.36 (1H, br. s, =CH); 6.81 (1H, t, *J* = 7.4, H Ar); 6.94-7.04 (2H, m, H Ar); 7.48 (1H, t, *J* = 7.4, H Ar); 7.59 (1H, d, *J* = 7.8, H Ar); 7.80 (1H, t, *J* = 7.0, H Ar); 7.87 (1H, d, *J* = 7.8, H Ar); 8.05 (1H, d, *J* = 7.0, H Ar); 9.18 (1H, s, NH); 10.97 (1H, s, NH)
5i	1.59 (3H, br. s, CH_3); 1.90-2.06 (4H, m, $2CH_2$); 2.12-2.27 (2H, m, CH_2); 2.48-2.60 (2H, m, CH_2); 2.69-2.87 (2H, m, CH_2); 3.02-3.16 (1H, m, CH); 5.32 (1H, br. s, =CH); 7.42 (2H, d, *J* = 9.0, H Ar); 7.48 (1H, t, *J* = 7.8, H Ar); 7.52 (3H, m, H Ar); 7.77-7.82 (1H, m, H Ar); 8.07 (1H, d, *J* = 7.8, H Ar); 10.18 (1H, s, NH); 10.98 (1H, s, NH)

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury BB instrument (200 MHz) using DMSO-d_6 with TMS as internal standard. The purity of the compounds synthesized was monitored by TLC on Merck Silica Gel 60 F_{254} plates in a chloroform–ethanol (9:1) solvent system.

3-{3-[(4-Methylcyclohex-3-enylcarbonyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}propanoic acid (4). A. Compound **3b** [3] (3.17 g, 0.01 mol) was refluxed in pyridine (25 ml) for 3 h. The product was cooled, poured into water, filtered, and the residue on the filter was washed with ethanol and dried to give the *N*,*N*'-di-

acylhydrazine **3a** (2.46 g, 90%). An equimolar amount of succinic anhydride and glacial acetic acid (15 ml) were added, and the mixture was refluxed for 6 h. One third of the solvent was evaporated off, and the precipitate formed was filtered. Recrystallization from glacial acetic acid gave acid **4** (2.62 g, 82% calculated on compound **3a**). Mp 201-202ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.63 (3H, br. s, CH_3); 1.89-2.08 (2H, m, CH_2); 2.13-2.26 (2H, m, CH_2); 2.38-2.56 (4H, m, $2CH_2$); 2.60-2.82 (2H, m, CH_2); 2.93-3.13 (1H, m, CH); 5.40 (1H, br. s, =CH); 7.25 (1H, t, *J* = 8.0, H Ar); 7.63 (1H, d, *J* = 8.0, H Ar); 7.84 (1H, t, *J* = 8.0, H Ar); 8.09 (1H, d, *J* = 8.0, H Ar); 11.02 (1H, br. s, NH)); 12.18 (1H, s, COOH). Found, %: C 64.02; H 5.96; N 11.63. $C_{19}H_{21}N_3O_4$. Calculated, %: C 64.21; H 5.96; N 11.82.

B. Hydrazide **2a** [3] (3.10 g, 0.02 mol) and an equimolar amount of isatoic anhydride (**1**) were refluxed in ethanol (30 ml) for 5 h. The mixture was cooled and the precipitate formed was filtered off and recrystallized from ethanol to give compound **3a** (3.83 g, 60%) which was then treated with an equimolar amount of succinic anhydride in the conditions reported above. The acid **4** (2.88 g, 58% calculated on compound **3a**) was obtained with analytical data corresponding to acid **4** prepared by method A.

C. Compound **3b** [3] (3.17 g, 0.01 mol) and an equimolar amount of succinic anhydride were refluxed in glacial acetic acid (25 ml) for 10 h. The product was cooled, left for 5-6 h, and filtered. Recrystallization from glacial acetic acid gave acid **4** (1.14 g, 32%). The analytical data for acid **4** corresponded to that for the acid prepared by method A.

3-{3-[(4-Methylcyclohex-3-enylcarbonyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}propanoic Acid Anilides (5a-i). Triethylamine (0.14 g, 0.001 mol) was added with stirring to a mixture of the acid **4** (0.36 g, 0.001 mol) and dry tetrahydrofuran (6 ml). The mixture was cooled to -10ºC and ethyl chloroformate (0.08 ml, 0.001 mol) was added. After holding the mixture at this temperature for about 20 min, an equimolar amount of the corresponding aniline was added and stirring was continued at room temperature for another 6 h. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with 2% citric acid solution and then 5% solution of sodium bicarbonate, and dried over anhydrous magnesium sulfate. The solution was filtered, ethyl acetate was distilled off, and the residue was recrystallized if needed. The recrystallization solvents, yields, and elemental analytical data for the anilides **5a-i** are given in Table 1.

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