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SUBSTITUTED (3*H*-QUINAZOLINE-4-YLIDEN)HYDRAZINES IN REACTION WITH MALEIC ACID ANHYDRIDE

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Substituted (3H-quinazoline-4-yliden)hydrazines with maleic acid anhydride and the corresponding hydrazides in glacial acetic acid form 2-(3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic acids or 1-[(3H-quinazoline-4-yliden)amino]pyrrol-2,5-diones. The electron effects of substituents in the aromatic ring do not affect the direction of heterocyclization, but the effect of substituents at the 2 position of the quinazoline system of the pyrimidine ring does it noticeably.

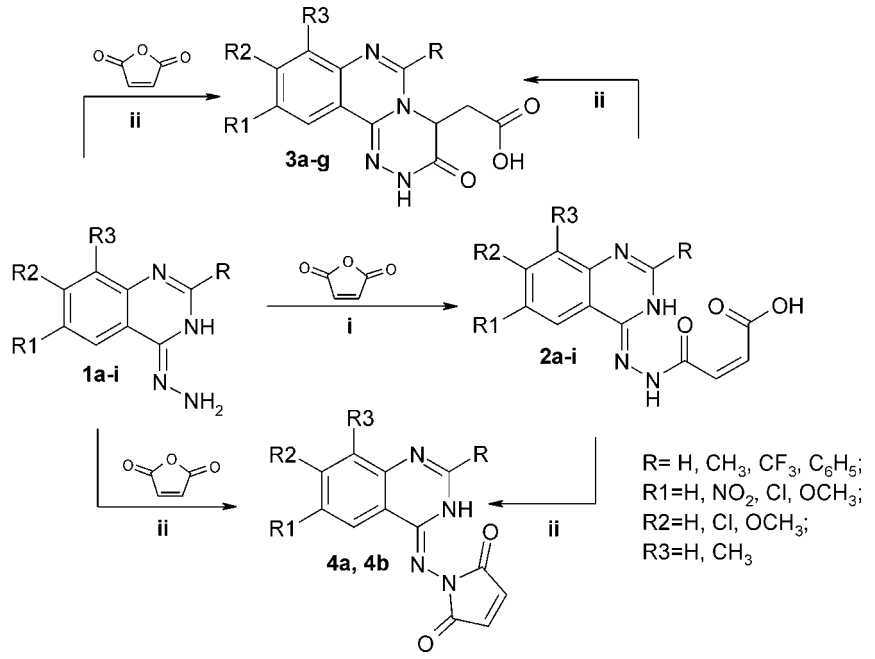
ЗАМІЩЕНІ (3Н-ХІНАЗОЛІН-4-ІЛІДЕН)ГІДРАЗИНИ В РЕАКЦІЇ З МАЛЕЇНОВИМ АНГІДРИДОМ
С.І.Коваленко, О.В.Кривошей
Заміщені (3Н-хіназолін-4-іліден)гідразину з малеїновим ангідридом та відповідні гідразиди в льодяній оцтовій кислоті формують 2-(3,4-дигідро-3-оксо-2Н-[1,2,4]тріазино[4,3-с]хіназолін-4-іл)оцтові кислоти або 1-[(3Н-хіназолін-4-іліден)аміно]пірол-2,5-діони. На напрямок перебігу реакції гетероциклізації не впливають електронні ефекти замісника в ароматичному циклі, але суттєво впливають електронні ефекти замісника 2 положення піримідинового циклу хіназолінової системи.

ЗАМЕЩЕННЫЕ (3Н-ХИНАЗОЛИН-4-ИЛИДЕН)ГИДРАЗИНЫ В РЕАКЦИИ С МАЛЕИНОВЫМ АНГИДРИДОМ
С.И.Коваленко, О.В.Кривошей
Замещенные (3Н-хиназолин-4-илиден)гидразина с малеиновым ангидридом и соответствующие гидразиды в ледяной уксусной кислоте формируют 2-(3,4-дигидро-3-оксо-2Н-[1,2,4]триазино[4,3-с]хиназолин-4-ил)уксусные кислоты или 1-[(3Н-хиназолин-4-илиден)амино]пиррол-2,5-дионы. На направление протекания реакции гетероциклизации не влияют электронные эффекты заместителей в ароматическом цикле, зато существенно влияют электронные эффекты заместителя 2 положения пиримидинового цикла хиназолиновой системы.

It's known, that maleic acid anhydride as dielectrophil synton equivalent $[C_2]^{2+}$ could form aminoimide cycles or heterocyclic systems with α-hydrazines [1, 2]. According to literature data [2], (3*H*-quinazoline-4-yliden)hydrazine reacts with maleic anhydride in narrow term through tandemic reaction, namely by acylation with subsequent nucleophilic cycloaddition to double bond, with production of (3-oxo-3,4-dihydro-2*H*-[1,2,4]triazino[4,3-*c*]quinazoline-4-yl)acetic acids. In view of aforementioned facts, the investigation of substituted (3H-quinazoline-4-yliden)hydrazines interaction with maleic acid anhydride and substitutes' effects on reaction direction, appeared to be interesting.

We established that reaction of starting substances ***1a-i*** with maleic acid anhydride in alcohols at room temperature or for 30 minutes at 40-60№C resulted derivatives of maleic acid (3*H*-quinazoline-4-yliden) hydrazide (***2a-i***). Reflux of starting substances ***1a, 1b, 1f-i*** in presence of maleic anhydride in glacial acetic acid was accompanied by heterocyclisation with formation of acetic acid (3-oxo-3,4-dihydro-2*H*-[1,2,4] triazino[4,3-*c*]quinazoline-4-yl) derivatives (***3a-3g***, Scheme). In case of maleic acid anhydride reaction with substances ***1c*** and ***1d***, heterocyclisation had other direction and proper 1-[(2-R-3H-quinazoline-4-yliden)amino]pyrrol-2,5-dions were obtained (***4a, 4b***, Scheme) in above-mentioned reaction conditions. It's important to notice that in such conditions hydrazides ***2a-i*** reacted in the same way (Scheme).

Spectral data of all synthesized substances proved the reaction direction and deduce their structures. Thus, FTIR spectra of substances **2.1-2.9** had characteristic bands, due to associate vibrations of ν_{NH} and ν_{OH} at 3546-3064 cm^{-1} and, what was important, had characteristic band shape of dimers at 2634-2345 cm^{-1} (except for substances **2.1, 2.4, 2.5, 2.8**). Stretching vibration of CO and wide band of middle rate out-of-plane deformation of OH...O were demonstrated at 1914-1681 cm^{-1} and 989-846 cm^{-1} correspondingly.



(i) EtOH or i-PrOH or dioxane, r.t. 12h or 60-80°C 30 min; (ii) AcOH, reflux, 2-3h.

Scheme

In addition, substances **2.1-2.9** were characterized by stretching vibration at 1665-1625 cm^{-1} (amide I), 1611-1518 cm^{-1} (amide II), $\nu_{C=C}$ of aromatic ring at 1589-1468 cm^{-1} and intensive $\gamma_{=CH}$ at 771-666 cm^{-1} (*cis*-isomer) and γ_{CH} at 846-771 cm^{-1} [3]. FTIR spectra of acids **3.1-3.7** were characterized by associate vibrations of ν_{NH} and ν_{OH} at 3444-3011 cm^{-1}, characteristic shaped peaks at 2784-2469 cm^{-1}, frequencies of ν_{CO} at 1738-1706 cm^{-1} and $\gamma_{(OH...O)}$ at 992-917 cm^{-1}. Stretching vibration of carbonyl group of lactam fragment, shown at 1712-1662 cm^{-1}, $\nu_{C=C}$ — at 1643-1468 cm^{-1} and intensive out-of-plane deformation of aromatic rings CH — at 846-771 cm^{-1} were revealed for substances **3.1-3.7**. It is important to mark that substances **4.1** and **4.2** unlike aforementioned compounds have high rate lactam ν_{CO} at 1730-1729 cm^{-1}. Band ν_{NH} was demonstrated at 3291-3256 cm^{-1} and at 3101-3066 cm^{-1}, which was the combination of ν_{CO} and γ_{NH} frequencies.

^{1}H NMR spectra of substances ***2a-i*** were characterized by non equivalent CH=CH doublets, which were in *cis*-configuration like starter maleic acid anhydride, accordingly to J = 12.1-12.5 Hz and broadened proton singlets of NH-, NHCO- and COOH-groups in low field. The basic difference of substances ***3a-g*** from substances ***2a-g*** was appearance of characteristic proton triplet of H(4) at 5,08-5.02 ppm (J = 4.7-5.6 Hz), doublet of CH_2-group at 2,71-2.98 ppm (J = 4.7-5.2 Hz) and two broadened low field proton singlets of NH and COOH groups at 11.14-10.81 and 13.09-11.73 ppm accordingly [2]. Two magnetic equivalent protons signals of pyrrol in aromatic part of spectrum appeared for compound ***4a*** (7.33 ppm) and ***4b*** (7.88 ppm). Besides that, synthesized substances were characterized by quinazoline ring signals, which had classic magnetic shifts influenced by substituents.

In LC-MS spectra of synthesized substances ***2a-i***, ***3a-g***, ***4a***, ***4b*** were observed high rate peaks of protonated molecular ions. Ion $[MH - COOH]^+$ was presented in spectra of acids ***3a***, ***3b***, ***3f***, besides $[MH]^+$.

EI-MS of synthesized substances additionally confirm their structure. So, spectra of substances ***2a-i*** were characterized by low rate molecular ion signals in difference from compounds ***3a-g***. It is important to notice that molecular ions for substances ***2f***, ***2g***, ***3f***, ***3g*** was dehydrate, but substances ***2c***, ***2d*** alternatively lost the molecule of water in process of conducting the experiment (direct input of substance) and formed molecular ions with m/z 308 (29,5%) and 316 (100%) consequently. The basic stages of fragmentation of derivatives **2a-i** were related to formation of fragment ions $[M - H_2O]^+$, $[M - COOH]^+$, $[M - C(O)CH{=}CHCOOH]^+$, $[M - NHCOCH{=}CHCOOH]^+$ and $[M - {=}NNHCOCH{=}CHCOOH]^+$ [4]. Besides latter fragmentation, substances **2c** and **2d** had characteristic destruction, giving stable ions CF_3^+ with *m/z* 69 (26,7%) and $C_6H_5CHN^+$ with *m/z* 103 (85,2%) [4].

For acids ***3a-g*** in EI-MS spectra the characteristic steps were formation of ions $[M - H_2O]^+$, $[M - COOH]^+$, $[M - CH_2COOH]^+$, fragmentation of molecules by the bonds C(11b)—N(1) and N(5)—C(4) resulting ions, mass of which responded to calculated mass of substituted quinazolines [2]. Then, fragmentation of substance ***4b***, in contrast to ***2d***, related to the break of bond N(1)pyrrol-N(4)quinazoline and education of the ion with *m/z* 221 (100%), which subsequently lost the molecule of nitrogen of and defragmentated by C(8a)-N(1) and C(2)-N(3)of quinazoline cycle with formation of alternative ions $C_7H_7N^+$ and $C_7H_5N^+$ with *m/z* 105 and 103 accordingly. Its worth mentioning that substance ***4a*** demonstrated the most intensive ion $C_2HF_3^+$ with *m/z* 82 (100%), in difference of substance ***2c***.

Thus it was established, that (3N-quinazoline-4-yliden)hydrazine substituted with maleic anhydride or proper hydrazides in glacial acetic acid resulted (3-oxo-3,4-dihydro-2*H*-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic acids or 1-[(2-R-3*H*-quinazoline-4-yliden) amino]pyrrol-2,5-dions. Electronic effects of aromatic cycle substituents did not influence on heterocyclisation direction , but substituents in 2 position of pyrimidine cycle of the quinazoline system affected substantially.

Experimental

4-Hydrazinoquinazoline derivatives (**1a-i**) were prepared as reported [5, 6]. Other starting materials were commercially available and used without additional purification. All melting points were determined in open capillary tubes in a Thiele's apparatus. IR-spectra (4000-600 cm^{-1}) were recorded on a Bruker ALPHA FT-IR spectrometer using a module for measuring attenuated total reflection (ATR). ^{1}H NMR-spectra were recorded on a Varian-Mercury 400 (400 MHz) spectrometers with $SiMe_4$ as internal standard in DMSO-d_6 solution. LC-MS were recorded using chromatography/mass spectrometric system which consists of high-performed liquid chromatograph "Agi1ent 1100 Series" equipped with diode-matrix and mass-selective detector "Agi1ent LC/MSD SL" (atmospheric pressure chemical ionization — APCI). Electron impact mass spectra (EI-MS) were recorded on a Varian 1200 L instrument at 70 eV. The purity of all obtained compounds was checked by ^{1}H NMR and LC-MS.

Maleic Acid (3H-quinazolin-4-ylidene)hydrazide derivatives (2a-i), General Procedures. Maleic acid anhydride (0,98 g, 10 mmol) was added to a mixture of **1a-i** (10 mmol) in a ethanol or 2-propanol (20 mL). The resulting mixture was stirred at room temperature for 12 h or heated at 40°C for 1 h. Precipitate was filtered, washed well with ethanol and propanol-2 and dried.

Maleic Acid (3*H*-quinazolin-4-ylidene)hydrazide (2a). Yield — 93,8%; m.p. — 252-254°C; IR (cm^{-1}): 3271, 3042, 1703, 1622, 1580, 1525, 1469, 1445, 1409, 1371, 1319, 1242, 1198, 1155, 1129, 1108, 1065, 1020, 1005, 920, 903, 846, 814, 785, 753, 720, 683, 640; ^{1}H NMR: δ = 6.88, 6.23 (d, 1H, CH=CH, *J* = 12.5), 7.34 (m, 2H, H-6,8), 7.59 (t, 1H, *J* = 7.8, H-7), 8.03 (m, 2H, H-2,5), 10.16 (br. s, 1H, NHCO), 11.71 (br. s, 1H, NH), 12.07 (br. s, 1H, COOH); LC-MS: *m/z* = 259 (MH^+); MS (EI): *m/z* = 259 (4.4), 258 (29.8), 240 (20.5), 213 (40.6), 212 (49.1), 199 (17.2), 196 (17.3), 195 (36.8), 170 (15.5), 168 (6.3), 161 (8.8), 160 (100.0), 159 (27.4), 145 (10.5), 144 (7.7), 131 (13.0), 130 (39.8), 129 (43.4), 118 (14.6), 117 (6.1), 116 (5.7), 115 (9.7), 114 (6.6), 105 (5.1), 104 (11.7), 103 (72.2), 102 (41.8), 98 (15.0), 90 (7.7), 89 (7.1), 88 (10.7), 87 (7.0), 85 (35.1), 83 (48.8), 82 (10.7), 81 (7.1), 77 (12.3), 76 (21.2), 75 (9.8), 73 (9.4), 71 (16.8), 70 (6.7), 64 (7.6), 63 (6.8), 60 (9.3), 57 (20.5), 55 (18.1), 54 (60.9), 53 (7.2), 51 (15.4), 50 (7.9), 45 (11.3), 43 (7.2); Anal. calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.78; H, 3.95; N, 21.74.

Maleic Acid (2-methyl-3*H*-quinazoline-4-ylidene) hydrazide (2b). Yield — 58,48%; m.p. — 246-248°C; IR (cm^{-1}): 3416, 3262, 3223, 3177, 3064, 3008, 2921, 2870, 1914, 1699, 1631, 1611, 1589, 1537, 1470, 1445, 1386, 1358, 1330, 1259, 1246, 1211, 1137, 1055, 1014, 989, 908, 870, 859, 847, 835, 767, 722, 689, 677, 636; ^{1}H NMR: δ = 6.93, 6.23 (d, 1H, CH=CH, *J* = 12.5), 7.22 (m, 2H, H-6,8), 7.55 (t, 1H, *J* = 7.6, H-7), 7.96 (d, 1H, H-5, *J* = 7.9), 10.18 (s, 1H, NHCO), 11.48 (s, 1H, NH), 11.87 (s, 1H, COOH); LC-MS: *m/z* = 273 (MH^+); MS (EI): *m/z* = 273 (2.3), 272 (12.7), 255 (7.2), 254 (35.7), 227 (10.2), 213 (6.5), 210 (12.0), 209 (54.3), 185 (12.8), 184 (7.5), 175 (16.0), 174 (100.0), 173 (20.1), 160 (9.8), 159 (54.9), 145 (26.6), 144 (32.5), 143 (55.0), 129 (14.7), 119 (14.2), 118 (11.2), 117 (11.4), 116 (10.2), 103 (40.8), 102 (38.3), 98 (19.7), 91 (5.1), 90 (17.3), 89 (5.8), 77 (5.9), 76 (11.6), 75 (9.4), 64 (7.4), 63 (9.1), 57 (23.6), 55 (6.2), 54 (71.5), 53 (5.4), 51 (6.8), 44 (7.0); Anal. calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.38; H, 4.45; N, 20.54.

Maleic Acid (2-trifluoromethyl-3H-quinazoline-4-ylidene)hydrazide (2c). Yield — 79,75%; m.p. — 240-242°C; IR (cm^{-1}): 3546, 3272, 3219, 3002, 2955, 2378, 2345, 2311, 2187, 1715, 1590, 1555, 1519, 1501, 1465, 1431, 1404, 1379, 1335, 1313, 1275, 1255, 1206, 1191, 1176, 1137, 1127, 987, 962, 898, 852, 817, 771, 740, 666, 636; ^{1}H NMR: δ = 6.47, 6.40 (d, 1H, CH=CH, *J* = 12.1), 7.75 (t, 1H, ^3J = 7.3, ^4J = 2.2, H-7), 7.95 (m, 2H, H-6,8), 8.43 (d, 1H, *J* = 8.2, H-5), 10.82 (br. s, 2H, NH, NHCO), 12.93 (br. s, 1H, COOH); LC-MS: *m/z* = 327 (MH^+), 309 ($MH^+ - H_2O$); MS (EI): *m/z* = 309 (4.3), 308 (29.5), 281 (8.5), 228 (32.8), 227 (7.4), 208 (5.2), 195 (18.2), 189 (5.4), 152 (10.0), 130 (12.3), 129 (100.0), 103 (30.7), 102 (30.6), 98 (10.5), 90 (9.5), 69 (26.7), 64 (5.7), 63 (5.4), 54 (9.0); Anal. calcd. for $C_{13}H_9F_3N_4O_3$: C, 47.86; H, 2.78; F, 17.47; N, 17.17. Found: C, 47.85; H, 2.82; F, 17.48; N, 17.21.

Maleic Acid (2-phenyl-3H-quinazoline-4-ylidene) hydrazide (2d). Yield — 77,08%; m.p. — 203-205°C; IR (cm^{-1}): 3278, 3219, 3173, 3116, 3068, 2977, 1704, 1621, 1518, 1468, 1454, 1434, 1401, 1361, 1338, 1286, 1205, 1188, 1155, 1126, 1105, 1060, 1020, 1009, 950, 910, 831, 793, 749, 701, 666, 651, 640, 629; ^{1}H NMR: δ = 6.94, 6.37 (d, 1H, CH=CH, *J* = 12.5), 7.53 (m, 5H, H-2′, 3′, 4′, 5′, 6′ Ph), 8.38-7.72 (m, 4H, H-6, 8, 7, 5), 10.58 (br. s, 1H, NHCO), 11.55 (br. s, 1H, NH), 11.92 (br. s, 1H, COOH); MS (EI): *m/z* = 318 (2.8), 317 (17.2), 316 (100.0), 289 (9.5), 272 (15.6), 271 (9.9), 247 (16.8), 245 (11.9), 222 (16.4), 221 (74.8), 220 (13.4), 191 (7.1), 180 (9.8), 151 (13.7), 150 (5.3), 129 (21.2), 119 (8.9), 118 (9.2), 104 (52.1), 103 (85.2), 102 (52.2), 100 (6.1), 99 (11.5), 98 (33.4), 91 (12.7), 90 (15.5), 77 (5.4), 69 (7.7), 63 (18.3), 57 (9.0); Anal. calcd. for $C_{18}H_{14}N_4O_3$: C, 64.67; H, 4.22; N, 16.76. Found: C, 64.69; H, 4.25; N, 16.81.

Maleic Acid (6-nitro-3H-quinazoline-4-ylidene)hydrazide (2e). Yield — 90,23%; m.p. — 244-248°C; IR (cm^{-1}): 3290, 3227, 3186, 3106, 3029, 1712, 1665, 1622, 1565, 1555, 1536, 1503, 1472, 1416, 1387, 1335, 1295, 1249, 1210, 1166, 1134, 1094, 1028, 939, 913, 851, 837, 800, 779, 763, 746, 678, 657, 620, 604; ^{1}H NMR: δ = 6.84, 6.27 (d, 1H, CH=CH, *J* = 12.7), 7.41 (d, 1H, *J* = 8.7, H-8), 8.06 (s, 1H, H-2), 8.34 (d, 1H, *J* = 8.7, H-7), 8.66 (s., 1H, H-5), 10.12 (s, 1H, NHCO), 11.65 (s, 1H, NH), 12.21 (br. s, 1H, COOH); LC-MS: *m/z* = 302 (M — H); MS (EI): *m/z* = 303 (15.6), 246 (16.9), 285 (6.6), 258 (9.0), 257 (27.8), 241 (6.1), 240 (4.7), 215 (8.5), 206 (6.6), 205 (100.0), 198 (9.4), 188 (14.4), 175 (13.5), 174 (4.6), 159 (5.6), 158 (11.1), 148 (14.0), 143 (7.5), 142 (22.4), 132 (5.2), 130 (6.9), 129 (3.9), 128 (12.4), 117 (5.4), 116 (6.9), 115 (14.6), 105 (17.4), 103 (10.9), 102 (33.5), 101 (16.9), 98 (13.8), 87 (4.7), 83 (7.5), 82 (15.3), 77 (5.5), 76 (9.1), 75 (19.9), 74 (4.9), 71 (6.8), 55 (10.4), 54 (85.5), 50 (5.4), 45 (5.3), 44 (7.5); Anal. calcd. for $C_{12}H_9N_5O_5$: C, 47.53; H, 2.99; N, 23.10. Found: C, 47.59; H, 3.05; N, 23.18.

Maleic Acid (6-chloro-3H-quinazoline-4-ylidene) hydrazide Dihydrate (2f). Yield — 60,80%; m.p. — 222-224°C; IR (cm^{-1}): 3163, 3058, 2994, 2907, 2634, 1703, 1659, 1617, 1553, 1516, 1469, 1411, 1386, 1322, 1273, 1208, 1187, 1155, 1135, 1093, 1080, 1068, 1048, 1011, 939, 900, 847, 837, 813, 765, 694, 686, 663, 625; ^{1}H NMR: δ = 6.61, 6.26 (d, 1H, CH=CH, *J* = 12.7), 7.54 (d, 1H, *J* = 8.7, H-8), 7.79 (d, 1H, ^3J = 8.7, ^4J = 2.4, H-7), 7.96 (s, 1H, H-2), 8.36 (s., 1H, H-5), 10.24 (br. s, 1H, NHCO), 11.14 (br. s, 1H, NH), 11.67 (br. s, 1H, COOH); MS (EI): *m/z* = 332 (3.2), 331 (13.1), 330 (5.5), 329 (24.6), 294 (3.1), 274 (5.9), 246 (8.4), 233 (4.7), 212 (7.1), 206 (36.3), 205 (9.2), 204 (100.0), 179 (15.9), 177 (7.1), 154 (7.6), 152 (25.1), 150 (11.0), 124 (6.7), 115 (11.4), 114 (25.5), 112 (31.7), 111 (5.4), 90 (4.8), 89 (5.0), 88 (13.2), 87 (16.6), 86 (5.2), 85 (18.8), 84 (5.7), 83 (21.0), 82 (19.7), 62 (5.3), 57 (6.3), 55 (13.4), 54 (30.4), 50 (5.7); Anal. calcd. for $C_{12}H_9ClN_4O_3 \times 2H_2O$: C, 43.99; H, 3.99; Cl, 10.79; N, 17.04. Found: C, 43.95; H, 3.98; Cl, 10.79; N, 17.06.

Maleic Acid (7-chloro-3H-quinazoline-4-ylidene) hydrazide Dihydrate (2g). Yield — 68,70%; m.p. — 236-238°C; IR (cm^{-1}): 3162, 3118, 3064, 3005, 2966, 2788, 2618, 1694, 1650, 1614, 1548, 1518, 1471, 1454, 1404, 1387, 1332, 1273, 1209, 1168, 1133, 1091, 1038, 1011, 920, 892, 874, 840, 813, 787, 751, 676, 648; 1H NMR: δ = 6.78, 6.28 (d, 1H, CH=CH, *J* = 12.5), 7.48 (d, 1H, *J* = 7.9, H-5), 7.53 (s, 1H, H-8), 8.06 (d, 1H, *J* = 8.2, H-6), 8.17 (s, 1H, H-2), 10.1 (s, 1H, NHCO), 10.99 (br. s, 1H, NH), 11.54 (br. s, 1H, COOH); MS (EI): *m/z* = 332 (6.3), 331 (15.3), 330 (21.6), 329 (21.6), 328 (14.8), 294 (31.6), 293 (19.2), 292 (100.0), 290 (5.1), 288 (10.5), 225 (5.9), 221 (5.0), 207 (8.9), 206 (19.0), 204 (11.2), 202 (5.8), 195 (26.3), 194 (22.0), 179 (22.9), 167 (6.3), 166 (30.7), 165 (14.5), 164 (27.9), 163 (49.6), 143 (9.1), 141 (6.2), 140 (8.4), 139 (5.9), 138 (13.6), 137 (21.0), 136 (27.7), 123 (7.0), 115 (9.4), 114 (5.9), 111 (6.7), 110 (8.5), 104 (11.2), 102 (9.2), 100 (12.8), 99 (10.4), 87 (8.2), 85 (27.7), 83 (7.6), 82 (27.2), 80 (5.1), 79 (7.5), 76 (10.7), 75 (9.2), 74 (10.7), 73 (7.6), 71 (9.9), 69 (11.5), 68 (6.3), 62 (5.8), 55 (23.2), 54 (10.2), 50 (6.6), 45 (17.1), 44 (17.0), 43 (30.2); Anal. calcd. for $C_{12}H_9ClN_4O_3 \times 2H_2O$: C, 43.99; H, 3.99; Cl, 10.79; N, 17.04. Found: C, 43.98; H, 3.97; Cl, 10.79; N, 17.04.

Maleic Acid (8-methyl-3H-quinazoline-4-ylidene) hydrazide (2h). Yield — 85,71%; m.p. — 224-226°C; IR (cm^{-1}): 3265, 1703, 1627, 1585, 1564, 1520, 1453, 1410, 1363, 1326, 1251, 1185, 1163, 1131, 1077, 1005, 912, 846, 800, 753, 721, 690, 642; ^{1}H NMR: δ = 2.48 (s., 3H, CH_3), 6.25 (d, 1H, CH=C*H*-COOH, *J* = 12.5), 7.31 (m, 2H, CH=C*H*-COOH, H-6), 7.54 (d, 1H, *J* = 7.8, H-7), 7.93 (d, 1H, *J* = 7.8, H-5), 8.39 (s, 1H, H-2), 10.33 (br. s, 1H, NHCO), 11.53 (br. s, 1H, NH); LC-MS: *m*/z = 273 (MH^+); MS (EI): *m/z* = 273 (2.2), 272 (9.5), 254 (15.3), 227 (15.1), 226 (20.0), 213 (12.2), 175 (6.7), 174 (100.0), 173 (8.8), 159 (19.1), 158 (5.2), 156 (10.2), 144 (12.9), 143 (24.2), 131 (17.2), 130 (5.4), 129 (5.2), 116 (7.0), 104 (5.6), 103 (11.5), 102 (5.3), 99 (5.7), 98 (7.5), 90 (5.4), 89 (13.0), 54 (6.2); Anal. calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.36; H, 4.43; N, 20.59.

Maleic Acid (6,7-dimethoxy-3H-quinazoline-4-ylidene)hydrazide (2i). Yield — 80,00%; m.p. — 232-236°C; IR (cm^{-1}): 3289, 3155, 3114, 2975, 2840, 1681, 1625, 1568, 1503, 1439, 1361, 1278, 1227, 1166, 1148, 1085, 1050, 1020, 949, 935, 880, 845, 769, 753, 738, 703, 651, 629; ^{1}H NMR: δ = 3.86 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 6.68, 6.31 (d, 1H, CH=CH, *J* = 12.5), 7.09 (s, 1H, H-8), 7.66 (s, 1H, H-5), 8.44 (s, 1H, H-2), 10.81 (br. s, 1H, NHCO), 11.72 (br. s, 1H, NH); LC-MS: *m/z* = 319 (MH^+); MS (EI): *m/z* = 318 (1.1), 300 (9.7), 221 (5.4), 220 (100.0), 205 (20.9), 190 (8.2), 189 (11.1), 187 (5.3), 175 (5.8), 173 (7.2), 147 (7.0), 120 (11.5), 117 (5.3), 87 (6.8), 85 (8.6), 83 (14.0), 54 (46.1), 53 (5.2); Anal. calcd. for $C_{14}H_{14}N_4O_5$: C, 58.83; H, 4.43; N, 17.60. Found: C, 58.86; H, 4.45; N, 17.69.

2-(3,4-Dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c] quinazoline-4-yl)acetic Acid Derivatives (3a-3g), General Procedures

Method A. Maleic acid anhydride (1,47 g, 10,5 mmol) was added to a solution of **1a, 1b, 1f-i** (10 mmol) in a glacial acetic acid (10-15 mL) and the resulting mixture was refluxed with stirring for 3-6 h. Solvent was evaporated in vacuum. The resulting precipitate was mixed with ethanol, filtered, washed well with ethanol and dried. If necessary, additional purification could be achieved by recrystallization from glacial acetic acid.

Method B. A mixture of **2a, 2b, 2d, 2f** (10 mmol) and 10-15 mL glacial acetic acid was refluxed with stirring for 3-6 h. Further work-up as in method A afforded proper substances.

2-(3,4-Dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c] quinazoline-4-yl)acetic acid (3a). Yield —77,2% (me-

thod A), 84,3% (method B); m.p. — 266-268°C; IR (cm^{-1}): 3147, 3015, 2846, 2756, 2722, 2580, 2503, 1728, 1711, 1643, 1629, 1502, 1480, 1463, 1448, 1414, 1368, 1329, 1291, 1271, 1214, 1189, 1152, 1089, 1041, 983, 957, 917, 887, 869, 827, 802, 790, 761, 705, 694, 662, 649; ^{1}H NMR: δ = 2.93 (d, 2H, *J* = 4.8, CH_2), 5.06 (t, 1H, *J* = 4.9, H-4), 7.4 (m, 2H, H-8,10), 7.56 (t, 1H, ^3J = 7.6, ^4J = 1.5, H-9), 7.87 (s, 1H, H-6), 7.88 (d, 1H, *J* = 7.6, H-11), 10.96 (s, 1H, NH), 13.09 (br. s, 1H, COOH); LC-MS: *m/z* = 257 (M — H), 213 (M — COOH); MS (EI): *m/z* (%) = 259 (12.5), 258 (100.0), 200 (6.5), 199 (58.5), 171 (18.1), 130 (19.0), 129 (56.7), 103 (21.2), 102 (32.2), 76 (11.1), 75 (6.7). Anal. calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.85; H, 3.96; N, 21.64.

2-[(6-Methyl-3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic Acid (3b). Yield — 50,31% (method A), 74,3% (method B); m.p. —212-214°C; IR (cm^{-1}): 3135, 3011, 2890, 1738, 1629, 1529, 1464, 1433, 1391, 1362, 1298, 1270, 1231, 1180, 1093, 1044, 992, 952, 864, 811, 775, 722, 655; ^{1}H NMR: δ = 2.46 (s, 3H, CH_3), 2.71 (d, , 2H, *J* = 5.2, CH_2), 5.07 (t, 1H, *J* = 5.6, H-4), 7.3 (m, 2H, H-8,10), 7.49 (t, 1H, *J* = 7.6, H-9), 7.84 (d, 1H, *J* = 7.2, H-11), 11.09 (s, 1H, NH); LC-MS: *m/z* = 273 (MH^+), 227 (M — COOH); MS (EI): *m/z* (%) = 272 (63.5), 254 (28.1), 227 (9.2), 213 (7.5), 209 (15.8), 198 (10.4), 185 (12.2), 160 (13.3), 159 (100.0), 145 (5.2), 144 (28.6), 143 (59.0), 129 (9.5), 119 (15.5), 118 (5.0), 117 (7.3), 103 (24.1), 102 (45.1), 90 (9.4), 77 (7.0), 76 (14.9), 75 (8.3), 63 (7.2), 51 (5.7), 50 (5.9), 44 (10.9). Anal. calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 20.56. Found: C, 55.83; H, 3.92; N, 20.54.

2-(8-Methyl-3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic Acid (3c). Yield — 65,71% (method A); m.p. — 246-248°C; IR (cm^{-1}): 3198, 3070, 2919, 2849, 2520, 1706, 1665, 1628, 1575, 1474, 1420, 1371, 1298, 1253, 1215, 1191, 1121, 1088, 1062, 1037, 969, 956, 928, 912, 885, 874, 842, 798, 762, 712, 674, 642, 613; ^{1}H NMR: δ = 2.90 (d, 2H, *J* = 4.9, CH_2), 3.54 (s, 3H, CH_3), 5.03 (t, 1H, *J* = 5.0, H-4), 7.23 (t, 1H, *J* = 7.8, H-10), 7.39 (d, 1H, *J* = 7.8, H-9), 7.72 (d, 1H, *J* = 7.8, H-11), 7.7 (s, 1H, H-6), 10.89 (s, 1H, NH), 12.57 (br. s, 1H, COOH); LC-MS: *m/z* = 273 (MH^+); MS (EI): *m/z* = 273 (18.5), 272 (93.0), 254 (14.9), 227 (16.7), 226 (100.0), 214 (10.7), 213 (96.3), 186 (10.1), 185 (24.0), 184 (10.0), 159 (10.8), 158 (8.4), 155 (5.4), 131 (12.7), 129 (8.6), 127 (5.9), 103 (6.7), 102 (7.3), 90 (14.8), 89 (34.0), 71 (9.6), 69 (5.3), 63 (10.6), 62 (5.8), 57 (5.3); Anal. calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.32; H, 4.46; N, 20.57.

2-(9-Chloro-3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic Acid (3d). Yield — 43,84% (method A), 74,3% (method B); m.p. — 294-296°C; IR (cm^{-1}): 3023, 2917, 2848, 2773, 2723, 2580, 2469, 1728, 1711, 1643, 1631, 1596, 1555, 1503, 1473, 1447, 1433, 1402, 1362, 1325, 1288, 1271, 1213, 1189, 1097, 1084, 1037, 1005, 964, 920, 890, 841, 822, 788, 757, 708, 647, 629; ^{1}H NMR: δ = 2.92 (d, 2H, *J* = 5.0, CH_2), 5.03 (t, 1H, *J* = 4.7, H-4), 7.37 (d, 1H, *J* = 8.2, H-10), 7.41 (s, 1H, H-7), 7.83 (s, 1H, H-6), 7.88 (d, 1H, *J* = 8.2, H-11), 10.98 (s, 1H, NH), 11.73 (br. s, 1H, COOH); MS (EI): *m/z* = 295 (3.9), 294 (35.5), 293 (11.9), 292 (100.0), 235 (22.3), 234 (6.6), 233 (58.7), 207 (8.0), 206 (7.6), 205 (19.8), 138 (8.0), 137 (13.7), 136 (9.5), 114 (5.6), 110 (5.5), 109 (9.1), 87 (5.2), 75 (5.1), 55 (15.6), 45 (9.6); Anal. calcd. for $C_{12}H_9ClN_4O_3$: C, 49.25; H, 3.10; Cl, 12.11; N, 19.14. Found: C, 49.23; H, 3.15; Cl, 12.13; N, 19.12.

2-(10-Chloro-3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic Acid Dihydrate (3e). Yield — 50,82% (method A); m.p. — 280-282°C; IR (cm^{-1}): 3444, 3331, 3152, 3031, 2920, 2850, 2782, 2733, 2584, 2511, 2476, 2350, 1728, 1712, 1643, 1633, 1610, 1568, 1555, 1505, 1473, 1453, 1427, 1410, 1364, 1319, 1309, 1273, 1254, 1213, 1154, 1132, 1103, 1080, 1042, 1007, 960, 917, 881, 828, 812, 791, 763, 714, 655, 642; ^{1}H NMR: δ = 2.92 (d, 2H, *J* = 4.7, CH_2), 5.04 (t, 1H, *J* = 4.7, H-4), 7.39 (d, 1H, *J* = 8.7, H-8), 7.56 (d.d, 1H, ^3J = 8.7, ^4J = 2.4, H-9), 7.79 (d.d, 1H, ^4J = 2.4, H-11), 7.81 (s, 1H, H-6), 11.0 (s, 1H, NH), 11.73 (br. s, 1H, COOH); MS (EI): *m/z* = 333 (5.1), 332 (5.8), 331 (33.0), 330 (12.2), 329 (63.5), 328 (6.9), 294 (18.5), 292 (52.4), 248 (6.1), 247 (5.7), 246 (24.6), 233 (26.3), 205 (6.3), 165 (7.8), 164 (5.7), 163 (17.5), 152 (5.0), 139 (5.6), 138 (14.2), 137 (7.1), 136 (8.4), 112 (100.0), 100 (5.9), 87 (5.9), 84 (5.0), 83 (7.9), 82 (53.5), 57 (6.2), 55 (34.9), 54 (11.7), 43 (6.3); Anal. calcd. for $C_{12}H_9ClN_4O_3 \times 2H_2O$: C, 43.99; H, 3.99; Cl, 10.79; N, 17.04. Found: C, 43.96; H, 3.99; Cl, 10.78; N, 17.04.

2-(10-Nitro-3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic Acid (3f). Yield — 60,07% (method A); m.p. — 264-266°C; IR (cm^{-1}): 3320, 3029, 2784, 1731, 1711, 1642, 1601, 1568, 1524, 1502, 1468, 1454, 1437, 1414, 1384, 1366, 1337, 1309, 1292, 1274, 1221, 1191, 1143, 1106, 1093, 1059, 1041, 971, 919, 903, 846, 800, 763, 742, 712, 655, 629; ^{1}H NMR: δ = 2.98 (d, 2H, *J* = 4.9, CH_2), 5.08 (t, 1H, *J* = 4.9, H-4), 7.54 (d, 1H, *J* = 8,9, H-8), 7.97 (s, 1H, H-6), 8.29 (d.d, 1H, ^3J = 8.9, ^4J = 2.6, H-9), 8.55 (d, 1H, ^4J = 2.7, H-11), 11.14 (s, 1H, NH), 12.26 (br. s, 1H, COOH); LC-MS: *m/z* = 304 (MH^+); MS (EI): *m/z* = 304 (9.2), 303 (100.0), 216 (6.4), 215 (6.6), 213 (10.3), 212 (43.7), 211 (14.1), 198 (11.6), 186 (5.9), 183 (5.8), 170 (7.4), 159 (5.1), 158 (9.4), 155 (6.2), 148 (6.6), 130 (9.5), 129 (9.3), 128 (39.3), 117 (6.5), 116 (6.2), 103 (9.1), 102 (25.6), 101 (28.9), 99 (8.2), 98 (6.8), 90 (6.1), 88 (7.5), 73 (5.0), 71 (5.9), 64 (6.7), 63 (6.2), 57 (6.0), 55 (6.3), 43 (5.0); Anal. calcd. for $C_{12}H_9N_5O_5$: C, 47.53; H, 2.99; N, 23.10. Found: C, 47.55; H, 3.00; N, 23.12.

2-(9,10-Dimethoxy-3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazoline-4-yl)acetic Acid (3g). Yield — 38,38% (method A); m.p. — 264-266°C'; IR (cm^{-1}): 3198, 3069, 2916, 2492, 2377, 2310, 1711, 1662, 1632, 1609, 1553, 1504, 1467, 1417, 1403, 1359, 1297, 1262, 1249, 1227, 1199, 1186, 1170, 1143, 1101, 1043, 1023, 982, 953, 937, 898, 870, 852, 830, 805, 743, 712, 668,

649, 627; ^{1}H NMR: δ = 2.89 (d, 2H, *J* = 4.9, CH_2), 3.80 (s, 3H, 10-OCH_3), 3.82 (s, 3H, 9-OCH_3), 5.02 (t, 1H, *J* = 4.7, H-4), 6.92 (s, 1H, H-8), 7.25 (s, 1H, H-11), 7.73 (s, 1H, H-6), 10.81 (s, 1H, NH), 12.56 (br. s, 1H, COOH); LC-MS: *m/z* = 319 (MH^+); MS (EI): *m/z* = 319 (14.6), 318 (100.0), 272 (7.5), 259 (31.4), 215 (9.1), 190 (5.8), 189 (7.4); Anal. calcd. for $C_{14}H_{14}N_4O_5$: C, 58.83; H, 4.43; N, 17.60. Found: C, 58.82; H, 4.43; N, 17.62.

1-[(3H-Quinazoline-4-ylidene)amino]pirrole-2,5-dione Derivatives (4a-b), General Procedures

Method A. Maleic acid anhydride (1,47 g, 10,5 mmol) was added to a solution of **1c, 1d** (10 mmol) in a glacial acetic acid (10-15 mL) and the resulting mixture was refluxed with stirring for 3 h. Solvent was evaporated in vacuum. The resulting precipitate was mixed with ethanol-aqueous solution and filtered.

Method B. A mixture of **2c, 2d** (10 mmol) and 10-15 mL glacial acetic acid was refluxed with stirring for 3 h. Further work-up as in method A afforded proper substances.

1-[(2-Trifluoromethyl-3H-quinazoline-4-ylidene) amino]pirrole-2,5-diones (4a). Yield — 92,2% (method A); yield — 87,8% (method B); m.p. — 242-242°C (methanol — H_2O); IR (cm^{-1}): 3291, 3101, 1730, 1687, 1619, 1590, 1574, 1527, 1500, 1469, 1433, 1393, 1333, 1257, 1190, 1136, 1074, 1039, 958, 842, 819, 770, 737, 686, 663, 607; ^{1}H NMR: δ = 7.33 (s, 2H, H-3, 4 Pir), 7.86 (t, 1H, ^3J = 7.3, ^4J = 2.2, H-7 Quin), 7.94 (m, 2H, H-6, 8 Quin), 8.44 (d, 1H, ^3J = 8.2, H-5 Quin), 11.39 (s, 1H, NH); LC-MS: *m/z* = 309 (MH^+); MS (EI): *m/z* = 309 (2.7), 308 (45.9), 113 (15.1), 90 (5.1), 85 (7.0), 83 (12.6), 82 (100.0), 55 (10.8), 54 (31.1), 51 (7.7); Anal. calcd. for $C_{13}H_7F_3N_4O_2$: C, 50.66; H, 2.29; F, 18.49; N, 18.18. Found: C, 50.65; H, 2.27; F, 18.48; N, 18.20.

1-[(2-Phenyl-3*H*-quinazoline-4-ylidene)amino] pirrole-2,5-diones (4b). Yield — 83,00% (method A); yield — 77,8% (method B); m.p. — 242-244°C (dioxane — H_2O); IR (cm^{-1}): 3246, 3066, 1730, 1695, 1621, 1604, 1563, 1517, 1468, 1433, 1391, 1362, 1328, 1253, 1206, 1158, 1125, 1030, 1001, 758, 701, 616; ^{1}H NMR: δ = 7.55 (m, 5H, H-2, 3, 4, 5, 6 Ph), 7.88 (s, 2H, H-3, 4 Pir), 8.42-8.2 (m, 4H, H-5, 7, 6, 8 Quin), 10.96 (br. s, 1H, NH); MS (EI): *m/z* = 317 (2.6), 316 (8.2), 262 (8.9), 259 (5.6), 222 (21.5), 221 (100.0), 220 (16.3), 205 (8.1), 105 (22.3), 104 (16.6), 103 (19.0), 102 (20.4), 77 (41.6), 76 (11.7), 75 (5.3), 50 (5.8), 44 (8.0); Anal. calcd. for $C_{18}H_{12}N_4O2$: C, 68.35; H, 3.82; N, 17.71; Found: C, 68.39; H, 3.85; N, 17.71.

References

1. *Palanki M.S.S., Erdman P.E., Manning A.M. et al. // Bioorg. Med. Chem. Lett. — 2000. — Vol. 10(15). — P. 1645-1648.*
2. *Kovalenko S.I., Karpenko A.V., Krivoshey O.V. et al. // Synthetic Communications. — 2007. — №37. — P. 3719-3727.*
3. *Burgi H.-B., Dunitz J.D. // Weinheim. — 1994. — Vol. 2. — P. 741-784.*
4. *Заикин В.Г., Варламов А.В., Микая А.И., Простаков Н.С. Основы масс-спектрометрии органических соединений. — М.: Наука/Интерпериодика, 2001. — 286 с.*
5. *Claesen M., Vanderhaeghe H. // Bull. Soc. Chim. Belg. — 1959. — Vol. 68. — P. 220-224; Chem. Abstr. — 1960. — Vol. 54. — 9939b.*
6. *Armarego W.L.F. — N.-Y.: "Interscience publ. Ltd", 1967.*

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