Study of anthranilate cyclisation to 2-hydroxymethyl-2,3-dihydroquinazolin-4(1H)-ones and an alternative synthetic route

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Abstract
Applicability of the previously described rearrangement of 2-oxo-2-phenylethyl 2-aminobenzoate leading to 2-phenyl-2-hydroxymethyl-2,3-dihydroquinazolin-4(1H)-one has been studied. To test the limits of the reaction, various starting compounds such as 2-oxopropyl 2-aminobenzoate, 2-oxo-2-phenylethyl 2-aminobenzoate and 3,3-dimethyl-2-oxobutyl 2-aminobenzoate as well as some of their corresponding N-methyl and N-phenyl analogues were used. The structure-reactivity dependence was observed giving the expected products only in specific cases and in limited yields. Structure of the dihydroquinazolin-4(1H)-one skeleton was unambiguously confirmed with use of X-ray analysis of two selected compounds. Finally, an alternative way for the preparation of the desired derivatives was developed.

Keywords: Dihydroquinazolinone, rearrangement, X-ray, condensation

Introduction

2,2-Disubstituted-2,3-dihydroquinazolin-4(1H)-ones belong to relatively low frequently studied derivatives of quinazoline. The most common way of their preparation is based on the condensation of anthranilamide with oxo-compounds which allows synthesis of various dihydroquinazolinones depending on the substitution of the starting ketone.1-6 Regarding the biological properties, dihydroquinazolinones have been studied very rarely, nevertheless some interesting effects were described (for instance inhibition of tyrosine kinases,7,8 inhibition of inosine 5’-monophosphate dehydrogenase9 or diuretic activity10) which proves the promising pharmacological potential of such compounds. In 2000 a paper describing an interesting use of
2-oxo-2-phenylethyl 2-aminobenzoate for the preparation of dihydroquinazolinone derivative was published. The mentioned ester was heated in acetic acid in a presence of ammonium acetate giving the 2-hydroxymethyl-2-phenyl-2,3-dihydroquinazolin-4(1H)-one instead of the expected 2-(2-aminophenyl)-4-phenyloxazole. When methylammonium acetate was used instead, the corresponding 3-N-methyl derivative was obtained. The rearrangement represents very simple way of the appropriate dihydroquinazolinones preparation whereas any other method of their synthesis has not been described so far. In this article we focus on the application of the reaction to a one-step preparation of 1,2,3-substituted-2-hydroxymethyl-dihydroquinazolinones including unambiguous confirmation of their structure with use of X-ray analysis. Additionally, we offer an alternative synthesis which can serve as a complementary method for the preparation of the target derivatives.

**Results and Discussion**

To study the mentioned rearrangement in terms of its applicability for the preparation of 1,2,3-substituted-2-hydroxymethyl-dihydroquinazolinones we used a set of various anthranilic acid esters: 2-oxopropyl 2-aminobenzoate 1a, 2-oxopropyl 2-(methylamino)aminobenzoate 1b, 2-oxopropyl 2-anilinobenzoate 1c, 2-oxo-2-phenylethyl 2-(methylamino)benzoate 1d, 2-oxo-2-phenylethyl 2-anilinobenzoate 1e and 3,3-dimethyl-2-oxobutyl 2-aminobenzoate 1f. First we tested the reaction of the above mentioned anthranilates with ammonium acetate.

![Scheme 1. Outcome of the anthranilates cyclisation reactions.](image)

The esters 1a, 1c, 1d and 1f afforded after short time the desired dihydroquinazolinones 2a, 2c, 2d and 2f without presence of any side-product, however, in some cases their yields were diminished during the isolation from the reaction mixture due to the solubility of the crude products in water and their subsequent problematic crystallization (especially 2a). The
conversion of 1b was significantly slower giving the final product 2b accompanied with its O-acetyl derivative 2b', both compounds were successfully separated with use of the column chromatography. Reaction of 2-oxo-2-phenylethyl 2-anilinobenzoate 1e had to be performed at more elevated temperature (120 °C) to dissolve the starting material. The reaction afforded the corresponding derivative 2e only as a part of a mixture of six compounds and due to its low content (15%, LC-MS traces) a column separation has not been performed.

The cyclisation with methylammonium acetate has shown to be significantly more complicated. Only in the case of 1a and 1d the corresponding dihydroquinazolinones 3a and 3d were obtained in a reasonable yield. The conversion of 1b and 1e did not furnish the corresponding dihydroquinazolinones 3b and 3e but formation of a mixture of unknown compounds was detected (LC-MS traces). Esters 1c and 1f afforded the target dihydroquinazolinones only as a part of complex mixtures without reasonable chance for their separation.

The results obtained from the cyclisation reactions illustrate that the method can be generally applicable for the preparation of the corresponding 2-hydroxymethyl-1,3-substituted dihydroquinazolinones but it is not versatile. The cyclisation does not work for derivatives with both sterically hindered positions 1 and 2 (the starting anthranilate 1e). Except this single case the method seems to be versatile for the preparation of N3-unsubstituted dihydroquinazolinones 2, although some of the products were obtained in a limited yield. The cyclisation of esters with methylammonium acetate afforded the products 3 only for the specific combination of substituents hence its use for the preparation of such compounds is significantly limited. Theoretically the method is applicable also for the preparation of the corresponding O-acetyl derivatives (e.g. isolation of 2b') when the reaction time is prolonged, but such procedure leads to formation of another impurities and affect negatively purity/yield of the target compounds. Comparison of the anthranilates 1 reactivity is summarized in Table 1.

Table 1. Comparison of the starting compounds 1 reactivity

<table>
<thead>
<tr>
<th>Product</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Reaction time (min.)</th>
<th>Yield (purified)</th>
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<tr>
<td>2a</td>
<td>H</td>
<td>CH3</td>
<td>H</td>
<td>90</td>
<td>27</td>
</tr>
<tr>
<td>2b</td>
<td>CH3</td>
<td>CH3</td>
<td>H</td>
<td>180</td>
<td>19</td>
</tr>
<tr>
<td>2b'</td>
<td>CH3</td>
<td>CH3</td>
<td>H</td>
<td>180</td>
<td>20</td>
</tr>
<tr>
<td>2c</td>
<td>C6H5</td>
<td>CH3</td>
<td>H</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>2d</td>
<td>CH3</td>
<td>C6H5</td>
<td>H</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>2e</td>
<td>C6H5</td>
<td>C6H5</td>
<td>H</td>
<td>90 Complex mixture</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>H</td>
<td>(CH3)3C</td>
<td>H</td>
<td>50</td>
<td>73</td>
</tr>
<tr>
<td>3a</td>
<td>H</td>
<td>CH3</td>
<td>CH3</td>
<td>60</td>
<td>73</td>
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Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>CH₃</th>
<th>CH₃</th>
<th>CH₃</th>
<th>60</th>
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<tr>
<td>3b</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>60</td>
<td>Not detected</td>
</tr>
<tr>
<td>3c</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>CH₃</td>
<td>60</td>
<td>Not detected</td>
</tr>
<tr>
<td>3d</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>150</td>
<td>41</td>
</tr>
<tr>
<td>3e</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>60</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3f</td>
<td>H</td>
<td>(CH₃)₃C</td>
<td>CH₃</td>
<td>60</td>
<td>Complex mixture</td>
</tr>
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</table>

In the original paper, the course of the anthranilate cyclisation has been confirmed only with help of NMR characterization of the single prepared product. We managed to prepare two target dihydroquinazolinones in a sufficient crystalline form for X-ray studies and we offer the full structure elucidation of derivatives 3d and 2b' (Figure 1). These compounds were isolated in their racemic form, but crystals selected for X-ray structure confirmation were assigned as S-isomers for both derivatives. A molecule geometry of derivative 3d shows the distortion of the phenyl ring which leads to the possibility of atropoisomerism when the substitution of the phenyl ring at positions 2,6 is different and substituents at nitrogens N₁ and N₃ are bulky. This fact renders possible in some derivatives the formation of four isomers. Although the study of stereochemistry was not the objective of this work, it will have to be solved when the compounds exhibit any interesting biological activity.

Figure 1. ORTEP views of compounds 3d and 2b' displaying the thermal ellipsoids at 40% probability.

As mentioned before, the cyclisation of anthranilates 1 can be considered as the method theoretically applicable also for the preparation of O-acetyl derivatives of the products 2 (see the preparation of 2b'). As the alternative method for the preparation of such compounds we developed a complementary synthesis of appropriate dihydroquinazolinones (both N₁ and N₃
unsubstituted) based on the condensation of anthranilamide with oxo-compounds. To prepare the desired products, 2-oxo(alkyl) acetates were used giving the target dihydroquinazolinones as the corresponding O-acetyl derivatives. The method was successfully tested for 2-oxopropyl acetate 4a, 2-oxo-2-phenylethyl acetate 4b, 2-(4-methoxyphenyl)-2-oxoethyl acetate 4c and 2-(4-nitrophenyl)-2-oxoethyl acetate 4d (Scheme 2).


The dihydroquinazolinones 5a-d were obtained in very good yield which proves the method is generally applicable for the simple preparation of such derivatives substituted at position 2 with alkyls or aryls that contain both electron-donating and electron-withdrawing functional groups. The reaction of anthranilamide with 3,3-dimethyl-2-oxobutyl acetate 4e was unsuccessful probably due to a sterical hindrance of a carbonyl group with a t-butyl skeleton but similar derivatives can be synthesized with use of the anthranilates cyclisation method (see the preparation of the compound 2f). The reactivity of the starting material 4 is summarized in Table 2. The condensation method can also generally afford the compounds 2 via basic hydrolysis of the derivatives 5. An illustrative example is given when dihydroquinazolinone 6c was prepared by the simple hydrolysis of 5c with methanolic potassium hydroxide in almost quantitative yield.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Reaction time (min.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>CH₃</td>
<td>300</td>
<td>80</td>
</tr>
<tr>
<td>5b</td>
<td>C₆H₅</td>
<td>250</td>
<td>75</td>
</tr>
<tr>
<td>5c</td>
<td>4-MeOC₆H₅</td>
<td>420</td>
<td>70</td>
</tr>
<tr>
<td>5d</td>
<td>4-NO₂C₆H₅</td>
<td>420</td>
<td>65</td>
</tr>
<tr>
<td>5e</td>
<td>(CH₃)₃C</td>
<td>420</td>
<td>Not detected</td>
</tr>
</tbody>
</table>
Conclusions

Various 2-hydroxymethyl-2-substituted-2,3-dihydroquinazolin-4(1H)-ones or their O-acetyl derivatives can be prepared via anthranilate cyclisation or anthranilamide condensation with 2-oxo(alkyl) acetates. The latter method is more simple and furnishes the target derivatives in higher yields. However, its use for the preparation of diverse dihydroquinazolinone in terms of their variable substitution of the quinazoline moiety as well as the substitution of the nitrogen atoms is limited by the availability of appropriate anthranilamides. In contrast, the substituted anthranilates represent very easily available starting materials. Hence both strategies can be considered as complementary methods for the preparation of the desired compounds.

Experimental Section

General. Melting points were determined on a Boetius stage and are uncorrected. The LC-MS analyses were carried out on UHPLC-MS system consisting of UHPLC chromatograph Accela with photodiode array detector and triple quadrupole mass spectrometer TSQ Quantum Access (both Thermo Scientific, CA, USA), using Nucleodur Gravity C18 column at 30 °C and flow rate of 800 µL/min (Macherey-Nagel, 1.8 µm, 2.1 x 50 mm, Germany). Mobile phase was (A) 0.1% ammonium acetate in water, and (B) 0.1% acetonitrile, linearly programmed from 10% to 80% B over 2.5 min, kept for 1.5 min. The column was re-equilibrated with 10% of solution B for 1 min. The APCI source operated at discharge current of 5 µA, vaporizer temperature of 400°C and capillary temperature of 200 °C. NMR ¹H/¹³C spectra were obtained on a Varian UnityPlus (299.89 MHz, ¹H) instrument. NMR spectra were recorded at ambient temperature (21 °C) in DMSO-d₆ solutions and referenced to the resonance signal of DMSO. Chemical shifts δ are reported in ppm and coupling constants J in Hz. Elemental analysis was performed on EA 1108 Elemental Analyser (Fisons Instrument).

General procedure for preparation 2,3-dihydroquinazolin-4(1H)-ones (2)
Compound 1 (0.01 mol) was added to the solution of ammonium acetate (0.1 mol) in acetic acid (12 mL) at temperature 50 °C and gradually heated. After reaching 90 °C, the stirred mixture was kept at this temperature (for reaction time see the discussion part). Then the reaction mixture was cooled to a laboratory temperature and cold water (40 mL) was added. Product 2f precipitated as a solid which was removed by filtration and dried. Products 2a, 2c and 2d precipitated as an oil which was extracted with ethylacetate (4 x 20 mL), organic layer was washed with saturated aqueous sodium bicarbonate solution and evaporated in vacuo to dryness. Honey-like residue was then treated with diethyl ether and cooled to −15 °C. After cooling overnight a solid was obtained which was removed by filtration, washed with diethyl ether and dried. Compounds 2b and 2b' were separated by column chromatography (silicagel) eluting ethyl acetate.
2-Hydroxymethyl-2-methyl-2,3-dihydroquinazolin-4(1H)-one (2a). Yield 27%, mp 121-125 °C (ethylacetate/diethylether); MS [M+H]+ = 193.07. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.32 (s, 3 H) 3.33 - 3.45 (m, 2 H) 5.11 (br. s., 1 H) 6.53 - 6.72 (m, 3 H) 7.18 (t, J=7.68 Hz, 1 H) 7.54 (d, J=7.68 Hz, 1 H) 7.78 (s, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 24.2, 66.5, 69.2, 113.7, 114.1, 116.0, 126.9, 133.0, 146.9, 162.9. Anal. Calcd for C10H12N2O2: C, 62.49; H, 6.29; N 14.57. Found: C, 62.36; H, 6.26; N, 14.29.

1,2-Dimethyl-2-hydroxymethyl-2,3-dihydroquinazolin-4(1H)-one (2b). Yield 19%, mp 123-126 °C (ethylacetate); MS [M+H]+ = 207.07. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.41 (s, 3 H) 2.84 (s, 3 H) 3.38 - 3.52 (m, 2 H) 5.03 (t, J=4.85 Hz, 1 H) 6.65 - 6.75 (m, 2 H) 7.34 (td, J=7.78, 1.65 Hz, 1 H) 7.65 (dd, J=7.50, 1.46 Hz, 1 H) 7.91 (s, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 31.2, 65.2, 73.5, 111.8, 115.6, 116.1, 126.9, 133.5, 147.8, 162.6. Anal. Calcd: for C11H14N2O: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.01; H, 6.79; N, 13.39.

1,2-Dimethyl-2-acetoxyethyl-2,3-dihydroquinazolin-4(1H)-one (2b'). Yield 20%, mp 131-134 °C (ethanol), MS [M+H]+ = 249.05. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.52 (s, 3 H) 1.68 (s, 3 H) 2.81 (s, 3 H) 3.85 (d, J=11.53 Hz, 1 H) 4.34 (d, J=11.53 Hz, 1 H) 6.66 - 6.79 (m, 2 H) 7.30 - 7.42 (m, 1 H) 7.68 (dd, J=7.59, 1.56 Hz, 1 H) 8.19 (s, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 20.0, 23.0, 30.8, 66.0, 72.1, 111.6, 115.6, 116.6, 126.8, 145.7, 162.6, 169.7. Anal. Calcd.: for C13H16N2O2: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.80; H, 6.81; N, 11.15.

2-Methyl-1-phenyl-2-hydroxymethyl-2,3-dihydroquinazolin-4(1H)-one (2c). Yield 52%, mp 231-233 °C (2-methoxyethanol), MS [M+H]+ = 269.05. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.17 (s, 3 H) 3.36 - 3.58 (m, 2 H) 5.29 (t, J=5.58 Hz, 1 H) 5.98 (d, J=8.23 Hz, 1 H) 6.69 (t, J=7.41 Hz, 1 H) 7.06 - 7.18 (m, 1 H) 7.29 - 7.57 (m, 5 H) 7.71 (dd, J=7.68, 1.46 Hz, 1 H) 8.11 (s, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 32.9, 64.3, 77.8, 111.8, 115.4, 116.3, 126.8, 127.2, 127.9, 128.2, 133.8, 142.6, 148.0, 162.8. Anal. Calcd: for C16H16N2O2: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.77; H, 6.10; N, 10.31.

1-Methyl-2-hydroxymethyl-2-phenyl-3-dihydroquinazolin-4(1H)-one (2d). Yield 67%, mp 62-64 °C (ethanol), MS [M+H]+ = 269.06. 1H NMR (300 MHz, DMSO-d6) δ ppm 2.88 (s, 3 H) 3.87 - 4.11 (m, 2 H) 5.26 (t, J=5.40 Hz, 1 H) 6.69 (t, J=7.23 Hz, 1 H) 6.78 (d, J=8.23 Hz, 1 H) 7.23 - 7.47 (m, 6 H) 7.64 (d, J=7.68 Hz, 1 H) 8.30 (s, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 32.8, 64.2, 77.7, 111.7, 115.3, 116.1, 126.7, 127.1, 127.8, 128.1, 136.7, 142.5, 147.9, 162.7. Anal. Calcd: for C16H16N2O2: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.80; H, 6.19; N, 10.60.

2-Hydroxymethyl-2-t-butyl-2,3-dihydroquinazolin-4(1H)-one (2f). Yield 73%, mp 238-242 °C (2-methoxyethanol); MS [M+H]+ = 235.08. 1H NMR (300 MHz, DMSO-d6) δ ppm 0.93 (s, 9 H) 3.52 (d, J=5.49 Hz, 2 H) 4.67 (t, J=5.58 Hz, 1 H) 6.34 (s, 1 H) 6.47 (t, J=7.41 Hz, 1 H) 6.72 (d, J=8.23 Hz, 1 H) 7.13 (t, J=7.68 Hz, 1 H) 7.36 (s, 1 H) 7.48 (d, J=7.68 Hz, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 24.8, 40.7, 63.9, 76.3, 111.9, 113.1, 114.7, 126.6, 132.9, 148.6, 163.1. Anal. Calcd.: for C13H18N2O2: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.85; H, 7.55; N, 11.74.
General procedure for preparation 2,3-dihydroquinazolin-4(1H)-ones (3)

Compound 1 (0.01 mol) was added to the solution of methylammonium acetate (0.1 mol) in acetic acid (12 mL) at temperature 50 °C and gradually heated. After reaching 90 °C, the stirred mixture was kept at this temperature (for reaction time see the discussion part). Then the reaction mixture was cooled to room temperature and cold water (40 mL) was added. Product 3a precipitated as a solid which was removed by filtration and dried. Product 3d precipitated as an oil which was extracted with of ethyl acetate (4 x 20 mL), organic layer was washed with saturated aqueous sodium bicarbonate solution and evaporated in vacuo to dryness. Honey-like residue was then treated with diethyl ether and cooled to –15 °C. A solid was obtained which was removed by filtration, washed with diethyl ether and dried.

2,3-Dimethyl-2-hydroxymethyl-2,3-dihydroquinazolin-4(1H)-one (3a).
 Yield 73%, mp 182-185 °C (ethanol), MS [M+H]+ = 207.08. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.43 (s, 3 H) 2.96 (s, 3 H) 3.46 (dd, J = 5.58, 3.57 Hz, 2 H) 5.12 (t, J = 5.67 Hz, 1 H) 6.57 - 6.70 (m, 3 H) 7.16 - 7.24 (m, 1 H) 7.57 (d, J = 7.68 Hz, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 22.1, 27.4, 64.4, 73.1, 113.9, 114.0, 116.3, 127.2, 132.7, 146.1, 162.4. Anal. Calcd: for C11H14N2O2: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.96; H, 7.05; N, 13.79.

1,3-Dimethyl-2-phenyl-2-hydroxymethyl-2,3-dihydroquinazolin-4(1H)-one (3d).
 Yield 41%, mp 230-235 °C (2-methoxyethanol), MS [M+H]+ = 283.08. 1H NMR (300 MHz, DMSO-d6) δ ppm 2.52 (s, 3 H) 2.57 (s, 3 H) 4.17 (d, J = 5.49 Hz, 2 H) 5.29 (t, J = 5.40 Hz, 1 H) 6.60 - 6.75 (m, 2 H) 7.26 - 7.50 (m, 4 H) 7.50 - 7.59 (m, 2 H) 7.72 (d, J = 7.50 Hz, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 30.7, 33.3, 60.2, 82.8, 110.7, 114.2, 116.0, 127.0, 127.5, 128.5, 128.6, 133.3, 140.7, 147.5, 162.1. Anal. Calcd: for C17H18N2O2: C, 72.31; H, 6.43; N, 9.92. Found: C, 71.99; H, 6.65; N, 10.24.

General procedure for preparation 2-acetoxymethyl-2,3-dihydroquinazolin-4(1H)-ones (5)

Anthranilamide (11 mmol) and 2-oxopropyl acetate 4 (11 mmol) were dissolved in toluene (50 mL) and 20 mg of p-toluenesulfonic acid was added. The reaction mixture was refluxed (for reaction time see the discussion part), then evaporated in vacuo to dryness. Solid material was stirred with diethyl ether, filtered off and dried.

2-Acetoxymethyl-2-methyl-2,3-dihydroquinazolin-4(1H)-one (5a).
 Yield 80%, mp 135-139 °C, MS [M+H]+ = 235.08. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.32 (s, 3 H) 2.01 (s, 3 H) 3.30 - 3.41 (m, 2 H) 6.50 - 6.70 (m, 3 H) 7.20 (t, J = 7.60 Hz, 1 H) 7.48 (d, J = 7.60 Hz, 1 H) 7.80 (s, 1 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 21.0, 23.9, 65.0, 70.5, 112.7, 116.1, 116.7, 126.6, 136.5, 147.8, 162.4, 170. Anal. Calcd: for C12H14N2O3: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.32; H, 6.40; N, 11.89.

2-Acetoxymethyl-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (5b).
 Yield 75%, mp 140-146 °C (ethanol/diethyl ether, lit.), MS [M+H]+ = 297.05 1H NMR (300 MHz, DMSO-d6) δ ppm 8.81 (s, 1 H) 7.69 - 7.45 (m, 5 H) 7.43 - 7.15 (m, 4 H) 6.86 (d, J = 8.1 Hz, 1 H) 6.61 (t, J = 7.4 Hz, 1 H) 4.33 (d, J = 11.5 Hz, 1 H) 4.14 (d, J = 11.5 Hz, 1 H) 2.01 (s, 3 H). 13C NMR (75 MHz, DMSO-d6) δ ppm 169.9, 163.3, 146.6, 143.1, 133.4, 128.0, 127.9, 127.0, 126.1,
117.0, 114.5, 114.4, 71.9, 67.5, 20.6. Anal. Calcd: for C_{17}H_{16}N_{2}O_{3}: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.51; H, 5.15; N, 9.28.

2-Acetoxymethyl-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (5c). Yield 70 %, mp 88-90 °C, MS [M+H]^+ = 327.08. \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) ppm 8.75 (s, 1 H), 7.65 - 7.40 (m, 4 H), 7.23 (t, \(J = 7.4 \text{ Hz, 1 H}\), 6.97 - 6.79 (m, 3 H), 6.62 (t, \(J = 7.4 \text{ Hz, 1 H}\), 4.31 (d, \(J = 11.3 \text{ Hz, 1 H}\), 4.12 (d, \(J = 11.5 \text{ Hz, 1 H}\), 3.70 (s, 3 H), 2.01 (s, 3 H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) ppm 170.0, 163.4, 158.8, 146.7, 134.9, 133.3, 127.4, 127.0, 117.0, 114.5, 114.5, 113.4, 71.7, 67.6, 55.0, 20.6. Anal. Calcd: for C\(_{18}\)H\(_{18}\)N\(_2\)O\(_4\): C, 66.25; H, 5.56; N, 8.58. Found: C, 65.89; H, 5.36; N, 8.30.

2-Acetoxymethyl-2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (5d). Yield 65 %, mp 116-118 °C, MS [M+H]^+ = 341.76. \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) ppm 9.01 (s, 1 H), 8.23 (d, \(J = 8.8 \text{ Hz, 2 H}\), 7.91 - 7.74 (m, 4 H), 7.58 - 7.45 (m, 1 H), 7.34 - 7.21 (m, 1 H), 6.89 (d, \(J = 7.9 \text{ Hz, 1 H}\), 6.65 (t, \(J = 7.1 \text{ Hz, 1 H}\), 4.40 (d, \(J = 11.3 \text{ Hz, 1 H}\), 4.21 (d, \(J = 11.3 \text{ Hz, 1 H}\), 2.00 (s, 3 H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) ppm 169.8, 163.1, 150.6, 147.2, 146.1, 133.7, 127.7, 127.1, 123.3, 117.6, 114.6, 114.4, 71.9, 67.1, 20.5. Anal. Calcd: for C\(_{17}\)H\(_{15}\)N\(_3\)O\(_5\): C, 59.82; H, 4.43; N, 12.31. Found: C, 59.22; H, 4.14; N, 12.11.

Preparation of 2-hydroxymethyl-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (6c). Compound 5c (0.09 mmol) was added to the solution of potassium hydroxide (0.14 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under the reduced pressure and the residue was suspended in 5% aqueous solution of acetic acid (10 mL). The white solid was filtrated, washed with water (30 mL) and dried. Yield 94 %, mp 190-192 °C, MS [M+H]^+ = 285.07. \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) ppm 8.41 (s, 1 H), 7.54 - 7.34 (m, 4 H), 7.17 (t, \(J = 8.4 \text{ Hz, 1 H}\), 6.94 - 6.78 (m, 3 H), 6.56 (t, \(J = 7.1 \text{ Hz, 1 H}\), 5.04 (s, 1 H), 3.68 (s, 3 H), 3.60 (s, 2 H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) ppm 163.6, 158.4, 147.2, 136.4, 133.1, 127.5, 127.0, 116.5, 114.7, 114.6, 113.0, 73.3, 67.8, 54.9. Anal. Calcd: for C\(_{16}\)H\(_{16}\)N\(_2\)O\(_3\): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.29; H, 5.51; N, 9.73.

Preparation of 2-(4-nitrophenyl)-2-oxoethyl acetate (4d). Sodium acetate (2 mmol) was suspended in DMF (2 mL). After 10 minutes 2-bromo-1-(4-nitrophenyl)ethanone (1 mmol) was added. The reaction mixture was stirred at 50 °C for 3 h, then cold water (20 mL) was added. The precipitated material was filtrated, washed with cold water and dried. Yield 89 %, mp 116-118 °C, MS [M-H]^− = 222.98. \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) ppm 8.37 (d, \(J = 9.0 \text{ Hz, 2 H}\), 8.20 (d, \(J = 9.0 \text{ Hz, 2 H}\), 5.53 (s, 2 H), 2.16 (s, 3 H). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) ppm 192.3, 169.8, 150.2, 138.4, 129.2, 123.9, 66.6, 20.2. Anal. Calcd: for C\(_{10}\)H\(_9\)NO\(_5\): C, 53.82; H, 4.06; N, 6.28. Found: C, 54.19; H, 4.31; N, 6.55.

X-ray structure determinations
Crystal data of the compounds 3d and 2b' were collected on a Nonius Kappa CCD diffractometer using graphite monochromated Mo Kα radiation (\(\lambda = 0.7107 \text{ Å}\)) at room temperature (295 K). Data sets were integrated with the Denzo-SMN package \(^{12}\) and corrected for Lorentz-polarization effects. The structures were solved by direct methods (SIR97) \(^{13}\) and
refined by full-matrix least square methods with all non-hydrogen atoms anisotropic and hydrogens isotropic. All calculations were performed using SHELXL-97 and PARST implemented in WINGX system of programs.

3d. C_{17}H_{16}N_{2}O_{2}, M = 282.33, Monoclinic, P2_1/c (N. 14), a = 7.4955(2) Å, b = 9.3824(3) Å, c = 21.5365(6) Å, β = 99.425(2)°, V = 1494.13(7) Å^3, Z = 4, D_c = 1.255 g cm^{-3}, µ = (Mo-Kα) = 0.83 cm^{-1}, 3487 independent reflections, θ ≤ 28.00°, 2441 observed reflections [I ≥ 2σ(I)], R_1 = 0.0542 (observed reflections), wR_2 = 0.1501 (all reflections), GOF = 1.035, 262 parameters. The molecules, in the crystals, are linked in couples by means of intermolecular O2-H2…O1 hydrogen bond: [ O2…O1(1-x,2-y,1-z) = 2.712(2) Å, H2…O2 = 1.79(3) Å, O2-H2…O1 = 167(2)°].

2b'. C_{13}H_{16}N_{2}O_{3}, M = 248.28, Triclinic, P-1 (N. 2), a = 6.8583(2) Å, b = 7.7561(2) Å, c = 13.1478(5) Å, α = 86.263(1)°, β = 88.069(1)°, γ = 64.993(2)°, V = 632.45(3) Å^3, Z = 2, D_c = 1.304 g cm^{-3}, µ = (Mo-Kα) = 0.94 cm^{-1}, 2971 independent reflections, θ ≤ 28.00°, 2304 observed reflections [I ≥ 2σ(I)], R_1 = 0.0437 (observed reflections), wR_2 = 0.1218 (all reflections), GOF = 1.030, 227 parameters. The molecules, in the crystals, are linked in couples by means of intermolecular N1-H1…O1 hydrogen bond: [ N1…O1(1-x,1-y,2-z) = 2.888(2) Å, H1…O2 = 1.99(2) Å, O2-H2…O1 = 177(2)°].

Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 775090-775091. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, Union Road, Cambridge, CB2 1EZ, UK [fax: (+44)1223-336033, e-mail: deposit@ccdc.cam.ac.uk]

Acknowledgements

This project was supported in part by the Ministry of Education, Youth and Sport of the Czech Republic (grants MSM6198959216 and ME09057) and FM EEA/Norska (A/CZ0046/1/0022). Infrastructural part of this project (Institute of Molecular and Translational Medicine) was supported from the Operational Programme Research and Development for Innovations (project CZ.1.05/2.1.00/01.0030).

References


