Completely dissimilar: The reactivity of 1-unsubstituted 3-chloroquinoline-2,4-diones with ethylene diamine and ethanolamine to form new molecular rearrangements

Antonin Klásek,*a Antoní Lyčka,b and Michal Rouchala

a Department of Chemistry, Faculty of Technology, Tomas Bata University, CZ-762 72 Zlín, Czech Republic
b University of Hradec Králové, Faculty of Science, Rokitanského 62, CZ-500 03 Hradec Králové 3, Czech Republic
E-mail: klasek@ft.utb.cz

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Abstract

3-Chloroquinoline-2,4-diones react with ethanolamine to give 3-hydroxyethylaminoquinoline-2,4-diones. By reacting with isothiocyanic acid, these compounds cyclize to form thioxoimidazo derivatives. If a benzyl group is attached to carbon atom C-3, it is cleaved off. Simultaneously, molecular rearrangement proceeds through the formation of compounds with quinazoline skeletons. However, when using ethylene diamine, the compounds are subject to new types of molecular rearrangement leading to the formation of new quinazoline derivatives.

Keywords: α-Aminoketones, indolones, quinazolinones, quinolinediones, rearrangement
**Introduction**

Many biologically active compounds contain the amino functional groups. In the quinolinediones series, which is our particular area of interest, we managed to prepare 3-amino derivatives using 3-chloroquinolinediones and ammonium salts or primary amines.\(^1\) Prior to the publication of our results, only two 3-aminoquinolinediones were previously known. The first 3-aminoquinolinedione was prepared by acid hydrolysis of the corresponding 3-acetamido derivative, which was obtained by rearranging the 6-chloro-4-hydroxy-3-imino-1-methyl-4-o-phenyl-3,4-dihydro-1H-quinolin-2-one molecule.\(^2\) The ammonolysis of 3-chloroquinolinediones with aqueous ammonia led to formation of only one product bearing the 3-benzyl substituent at the C-3 atom.\(^3\)

The biological activity of 3-aminoquinoline-2,4-diones was described for 3-amino-3-(4-fluorophenyl)-1H-quinoline-2,4-dione, which is effective against oxidative stress-related diseases\(^4\) and inhibits cisplatin-induced hearing loss by the suppressing the reactive oxygen species.\(^5,6\) A similar effect was exhibited by 3-amino-6-fluoro-3-(4-fluoro-phenyl)-1H-quinoline-2,4-dione.\(^4\)

We discovered that 3-aminoquinolinediones are subject to molecular rearrangement through their reactions with isocyanic acid, forming from urea in boiling acetic acid. By using this synthetic method, new imidazoquinazolinediones, 3-acylureidoindolones, *spiro*-imidazolidine-inolediones and dihydro-imidazoquinolones were prepared.\(^7,8\) We also found that the preferable sources of isocyanic and isothiocyanic acids are sodium cyanate and potassium thiocyanate, respectively, both in acetic acid. Under these conditions, more types of new heterocycles were prepared, *e.g.*, thioureidooxindoles, *spiro*-oxindoles, dihydromidazoquinolones and their sulfur analogues.\(^9\)

In order to discover the influence of other substituents in the amine molecule, we chose to use ethanolamine, as it is an as easily available and inexpensive compound. In our earlier paper,\(^10\) we described its reaction with 3-chloroquinoline-2,4-diones. In line with our expectations, N-substituted compounds 2 were obtained and their reaction with isocyanic acid afforded three new types of heterocycles.

In this paper, we describe the analogous reactions, however, beginning with 1-unsubstituted 3-chloroquinoline-2,4-diones 1 and ethylene diamine (EDA) or ethanolamine (EA).

**Results and Discussion**

Compounds 2b-2d were prepared according to literature\(^1\) new compound 2a was prepared now. For NMR data of compound 2a see Table 1. The reaction of 1-substituted 3-(2-hydroxyethylamino)quinoline-2,4-diones (2a-d) with isothiocyanic acid was carried out using potassium thiocyanate in acetic acid. Four different compounds 3 – 6 were isolated (Scheme 1, NMR Table 1). Compound 3c and 6d were created by adding HNCS to the corresponding compounds 2c and 2d without rearrangement. Compound 4c is the product of the debenzylation of 3c. Previous studies have shown the easy debenzylation of compounds bearing a benzyl group in position 3.\(^9,11\) Compounds 5a, 5b and 5d are products of a molecular rearrangement of compounds 2, in which the quinolone ring opens to form an intermediate isocyanate, before subsequently closing and forming a quinazoline ring. Compounds 5 are structurally similar to compounds prepared in previous studies\(^9\) and their structure was established on the basis of 2D-NMR experiments (see Table 2).
Scheme 1. Reaction of 3-chloroquinolinediones with ethanolamine and ethylene diamine.

The results of the reactions of chloro-derivatives 1a-d with ethylene diamine were surprising. We obtained two types of compounds that did not react with isocyanic and isothiocyanic acids, contrary to previous studies. From their 2D-NMR spectra (see Tables 2 and 3), the structures of 7 and 8 were established. A key piece of information concerning the constitution of compounds 7 was obtained from the $^1$H-$^{15}$N HMBC spectra, where a correlation of the CON(1)H proton with $^3$N(3)- nitrogen typical of NH-X-N fragments was detected. $^{13}$C Chemical shifts of C(O)NH in compounds 1 were shifted to ca. 150 ppm, characteristic of a urea fragment (-N-C(=O)-N-) in the compounds 7. Moreover, correlations of the second carbonyl group (C(4)=O) with aromatic protons from peri- position (H-5) were observed in gs $^1$H-$^{13}$C HMBC spectra. The last correlation from the peri position was missing in from $^1$H-$^{13}$C HMBC spectrum of compound 8d, where a correlation of this proton with quaternary carbon 10b was observed. Through-space interactions of H-10 proton with ortho and meta protons of phenyl group were detected in the NOESY spectrum of compound 8d. Correlations were also found in the C$_6$H$_5$CO fragment, both in the $^1$H-$^{13}$C HMQC and $^1$H-$^{13}$C HMBC spectra.
To the best of our knowledge, compound 8, as well as its analogues bearing an acyl group in position 10b, have not been described in the literature. Compounds 7 are also unknown, but many of their analogues containing modified amino groups are constituents of serotonin antagonists, e.g., ketanserin. They are also a part of dsDNA binding unnatural oligopeptides.

Our proposal of the reaction mechanism is shown (Scheme 2). We assumed, that this unprecedented rearrangement of compounds 1 is caused by the presence of ethylene diamine, which is much more basic then ethanolamine. One of the reaction product (8d) contains an imidazolidine ring. The presence of both nitrogen atoms at one quaternary carbon atom is only possible when the entire of ethylene diamine molecule is added to the carbonyl group. However, formerly must be removed the halogen atom to the prevention of nucleophilic substitution at C-3 atom. The formation of 3-hydroxyquinolinedione as the first intermediate is unsurprising, as its conversion to intermediate A. The following base catalyzed opening of the ring B leads to the formation of isocyanate intermediate B, which after the intramolecular addition of an NH group produces rearranged minor product 8d. The reaction way to major products 7a-d is different. We assumed, that the substitution of ethylene diamine for a chlorine atom in 1a-d following cyclization leads to intermediate C, which is a common reaction in the chemistry of quinolinediones. By the addition of a molecule of water originates intermediate D. It is possible, that this intermediate arises directly from 2a-d. The base catalyzed opening of the ring B in intermediate D and, along with the addition of water, leads to intermediate E, which cyclizes to form the major products 7a-d.

The experiments relating to the hydrolysis of compounds 7 were unsuccessful. Using aqueous sodium hydroxide, only non-separable mixtures of compounds were obtained. The same results were obtained using non-aqueous conditions, or using sodium peroxide as a mild hydrolysing agent. On the other hand, we were successful in reducing ketone 8d. Compound 8d was reduced by NaBH₄ to give compound 9d. The carbonyl group from the C₆H₅CO fragment disappeared in the ¹³C NMR spectrum and new resonance signals were detected in compound 9d at 77.3 and 74.7 ppm, respectively. Those belonged to two CHOH moieties (diastereoisomers as a consequence of two stereogenic centers existing in compound 9d). Through-space interactions of –CH(–)O- protons with OH and NH protons, as well as ortho protons of phenyl groups, were detected in the NOESY spectrum of compound 9d. However, the results of NOESY were multivalent, because the conformation is not fixed. As a consequence of the free rotation around C(q)-CHOH, protons of both diastereoisomers can be located side- by -side. The constitution of compound 9d retrospectively confirms the constitution of compound 8d. The data for ¹H, ¹³C and ¹⁵N NMR are shown in Tables 2 and 3.

Scheme 2. Proposed mechanism for the rearrangement of compound 2d.
### Table 1. $^1$H, $^{13}$C and $^{15}$N NMR data (δ, ppm) of compounds 2a, 3c, 4c and 6d in DMSO-$d_6$

| Position | 2a $\delta_H$ | 2a $\delta_C$ | 3c $\delta_H$ | 3c $\delta_C$ | 4c $\delta_H$ | 4c $\delta_C$ | 6d $\delta_H$ | 6d $\delta_C$ |
|----------|----------------|--------------|---------------|--------------|---------------|--------------|--------------|--------------|
| 1        | 10.90          | -248.4$^a$   | 9.19          | -236.9$^{acb}$ | 13.8          | -222.3$^{a,e}$ | 9.40         | –            |
| 2        | –              | 173.1        | –             | 181.4        | –             | 152.9        | –            | 184.2        |
| 3        | –              | 68.8         | –             | -256.2$^a$   | –             | -220.5$^a$   | –            | –            |
| 3a       | –              | –            | 72.8          | –            | 109.5         | –            | 78.5         |
| 4        | –              | 196.3        | –             | 168.4        | –             | 166.9        | –            | 168.2        |
| 4a       | –              | 118.5        | –             | –            | –             | –            | –            | –            |
| 5        | 7.76           | 127.0        | 10.29         | -243.9$^{a,c}$ | 11.93         | -232.4$^{a,f}$ | 10.21        | –            |
| 5a       | –              | –            | –             | 134.0        | –             | 136.2        | –            | 134.6        |
| 6        | 7.11           | 122.6        | 6.37          | 114.3        | 7.41          | 116.0        | 6.99         | 115.3        |
| 7        | 7.60           | 136.2        | 6.95          | 129.0        | –             | –            | 7.33         | 128.9        |
| 8        | 7.09           | 116.3        | 6.90          | 122.2        | 7.26          | 122.4        | 7.01         | 122.8        |
| 8a       | –              | 141.7        | –             | –            | –             | –            | –            | –            |
| N$^b$HCH$_2$ | 2.39       | 46.7         | –             | –            | –             | –            | –            | –            |
| CH$_2$O  | 3.41           | 61.0         | –             | –            | –             | –            | –            | –            |
| 9        | –              | –            | 7.55          | 126.0        | 8.03          | 121.6        | 7.50         | 127.7        |
| 9a       | –              | –            | –             | 122.1        | –             | 118.3        | –            | 121.4        |
| 9b       | –              | –            | 85.8          | –            | 132.6         | –            | 87.1         |
| OH       | –              | –            | 6.16          | –            | –             | –            | 6.76         | –            |
| NCH$_2$  | –              | –            | 4.03          | 46.9         | 4.55          | 46.3         | 3.99         | 48.8         |
| CH$_2$   | –              | –            | 3.73          | 59.2         | 3.72          | 58.5         | 3.67         | 58.4         |
| OH       | 4.48           | –            | 4.66          | –            | –             | –            | 4.57         | –            |
| 1(R)     | 1.37           | 25.2         | 3.37          | 36.1         | –             | –            | –            | 131.9        |
| 2(R)     | –              | –            | –             | 132.5        | –             | –            | 7.33         | 128.0        |
| 3(R)     | –              | –            | 7.05          | 127.1        | –             | –            | 7.33         | 128.0        |
| 4(R)     | –              | –            | 6.90          | 130.5        | –             | –            | 7.33         | 131.5        |
| 5(R)     | –              | –            | 6.93          | 126.6        | –             | –            | –            | –            |

$^a\delta^{(15)N}$.  $^b\delta^{(15)N} = -338.4$.  $^cJ^{(15)N, H} = 88.8$ Hz.  $^dJ^{(15)N, H} = 95.6$ Hz.  $^eJ^{(15)N, H} = 96.9$ Hz.  $^fJ^{(15)N, H} = 88.9$ Hz.

### Conclusions

In conclusion, N-unsubstituted 3-chloroquinolininediones 1 reacts with ethanolamine to give 3-hydroxyethylaminoquinolinediones 2. These compounds cyclize with isothiocyanic acid to form thioxoimidazo derivatives. If a benzyl group is attached to carbon atom C-3, it is cleaved off owing to the high acidity of isothiocyanic acid. Simultaneously, molecular rearrangement proceeds under the formation of a quinazoline skeleton. However, when using the more basic ethylene diamine, compounds 1 are subject to new types of molecular rearrangement leading to the new quinazoline derivatives 7 and 8.
This paper’s significant contribution has been the discovery of these two new compounds, which can be used in synthetic organic chemistry. Compounds 4 and 5 can also be used as a precursor in the preparation of hard blocks in order to modify the polymeric properties, e.g., enhanced thermostability or reduced combustibility.16

Table 2. $^1$H, $^{13}$C and $^{15}$N NMR data (δ, ppm) of compounds 5a, 5b, 5d, 8d and 9d in DMSO-$d_6$

| Position | 5a | 5b | 5d | 8d | 9d major $^i$ | 9d minor $^i$ |
|----------|----|----|----|----|--------------|--------------|
| δH       | δC | δH | δC | δH | δC           | δH           | δC           | δH | δC           |
| 1        | –  | 122.0 | –  | 126.1 | –  | 127.9 | 4.40 | -318.7 $^a$ | 3.20 | -322.8 $^a$ | n.o. | –  | 323.2 $^a$ |
| 2        | –  | –  | –  | -203.6 $^a$ | –  | -204.4 $^a$ | 3.34 | 43.3 | 3.61 | 45.5 | 3.56 | 45.4 |
| 3        | –  | 160.0 | –  | 160.1 | –  | 160.2 | 3.51 | 43.7 | 3.18 | 43.2 | 3.13 | 42.4 |
| 4        | –  | –  | –  | -203.6 $^a$ | –  | -203.0 $^a$ | -275.7 $^a$ | -277.4 $^a$ | –  | –  | 276.9 $^a$ |
| 5        | –  | 144.8 | –  | 144.7 | –  | 144.8 | –  | 150.8 | –  | 151.3 | –  | 151.0 |
| 6        | 10.96 | –  | 11.01 | -262.1 $^{ab}$ | 11.15 | -261.7 $^{ac}$ | 9.48 | -270.4 $^{ad}$ | 8.96 | -271.2 $^{ag}$ | 8.75 | -  | 271.7 $^{ah}$ |
| 6a       | –  | 134.0 | –  | 134.0 | –  | 134.3 | –  | 137.9 | –  | 137.7 | –  | 137.5 |
| 7        | 7.03 | 114.9 | 7.08 | 115.0 | 7.05 | 115.2 | 6.84 | 114.1 | 6.64 | 112.8 | 6.56 | 112.5 |
| 8        | 7.24 | 128.1 | 7.29 | 128.2 | 7.22 | 127.9 | 7.16 | 129.6 | 7.06 | 128.3 | 7.08 | 128.4 |
| 9        | 7.09 | 123.0 | 7.15 | 123.2 | 6.79 | 122.6 | 6.82 | 121.2 | 6.72 | 119.8 | 6.82 | 120.0 |
| 10       | 7.71 | 122.2 | 7.63 | 121.8 | 6.56 | 121.2 | 7.33 | 126.6 | 6.68 | 126.6 | 7.10 | 126.9 |
| 10a      | –  | 112.9 | –  | 112.6 | –  | 112.2 | –  | 117.5 | –  | 120.9 | –  | 119.9 |
| 10b      | –  | 118.8 | –  | 118.8 | –  | 120.2 | –  | 86.4 | –  | 83.0 | –  | 82.9 |
| 1'(R)    | 2.59 | 11.2 | 3.04 | 23.6 | –  | 124.5 | –  | 195.5 $^e$ | 4.57 $^i$ | 77.3 $^i$ | 4.53 $^i$ | 74.7 $^i$ |
| 2'(R)    | –  | –  | 1.57 | 29.6 | 7.65 | 128.8 | –  | 134.3 $^i$ | –  | 140.9 $^f$ | –  | 140.3 $^f$ |
| 3'(R)    | –  | –  | 1.46 | 21.9 | 7.59 | 131.5 | 8.24 | 129.8 $^f$ | 6.98 | 127.8 $^f$ | 6.83 | 127.6 $^f$ |
| 4'(R)    | –  | –  | 0.97 | 13.7 | 7.65 | 129.6 | 7.42 | 128.3 $^f$ | 7.12 | 126.6 $^f$ | 7.06 | 126.9 $^f$ |
| N(2)     | 4.23 | 46.2 | 4.21 | 46.1 | 3.91 | 46.2 | 7.54 | 132.8 $^f$ | 7.18 | 126.7 $^f$ | 7.14 | 127.0 $^f$ |
| CH       | 2    | OC | 3.70 | 57.6 | 3.75 | 57.4 | 3.58 | 56.6 | –  | –  | –  | –  |
| H2       | OH | 4.98 | –  | 4.97 | –  | 4.83 | –  | –  | 5.60 | –  | 5.33 | –  |

$^a$ δ($^{15}$N). $^b$ $^1$J($^{15}$N, H) = 91.5 Hz. $^c$ $^1$J($^{15}$N, H) = 90.2 Hz. $^d$ $^1$J($^{15}$N, H) = 92.6 Hz. $^e$ C=O $^f$ -C$_6$H$_5$. $^g$ $^1$J($^{15}$N, H) = 92.5 Hz. $^h$ $^1$J($^{15}$N, H) = 92.2 Hz. $^i$ diastereoisomeric ratio 1 : 0.34. $^j$ CHOH
**Experimental Section**

**General.** Melting points were determined on a Kofler block. IR (KBr) spectra were recorded on a Smart OMNI-Transmission Nicolet iS10 spectrophotometer. The $^1$H, $^{13}$C, and $^{15}$N NMR spectra were recorded on a Bruker Avance III HD 500 spectrometer (500.13 MHz for $^1$H, 125.76 MHz for $^{13}$C, and 50.68 MHz for $^{15}$N) in DMSO-$d_6$. $^1$H and $^{13}$C chemical shifts are given on the $\delta$ scale (ppm) and are referenced to internal TMS ($\delta = 0.0$). $^{15}$N chemical shifts were referred to external neat CH$_3$NO$_2$ in a co-axial capillary ($\delta = 0.0$). All 2D experiments (gradient-selected (gs)-COSY, gs-TOCSY, gs-NOESY, gs-HMQC, gs-HMQC-TOCSY, gs-HMQC-RELAY, gs-HMBC) were performed using manufacturer’s software (TOPSPIN 3.5). The electrospray mass spectra (ESI-MS) were recorded using an amaZon X ion-trap mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an electrospray ion source. All experiments were conducted in both positive and negative polarity mode. Individual samples (with a concentration of 500 ng mL$^{-1}$) were infused into the ESI source as methanol/water (1:1, v/v) solutions via a syringe pump with a constant flow rate of 3 μL·min$^{-1}$. The other instrumental conditions were as follows: electrospray voltage of ±4.2 kV, capillary exit voltage of ±140 V, drying gas temperature of 220 °C, drying gas flow of 6.0 dm$^3$·min$^{-1}$, nebulizer pressure of 8.0 psi. Nitrogen was used as the nebulizing and drying gases for all experiments. Tandem mass spectra were collected using collision-induced dissociation (CID) with He as the collision gas after isolating of the required ions. Column chromatography was carried out on silica gel (Merck, grade 60, 70–230 mesh) using successive mixtures of chloroform/ethanol (in ratios from 99:1 to 8:2) (S1), or benzene/ethyl acetate (in ratios from 99:1 to 8:2) (S2). Reactions as well as the course of separation and also the purity of all substances were monitored by TLC (elution systems benzene/ethyl acetate (4:1) (S3), chloroform/ethanol (9:1 and 1:1) (S4 and S5), and chloroform/ethyl acetate (7:3) (S6) on Alugram® SIL G/UV254 foils (Macherey-Nagel). Elemental analyses (C, H, N) were performed using a EA Flash EA 1112 Elemental Analyzer (Thermo Fisher Scientific).

3-Hydroxyethylamino-3-methylquinoline-2,4-dione (2a). Compound was prepared in 45% yield from 1a by the procedure described in Ref.10. Colorless solid, mp 120-129 °C (benzene); IR: 3312, 3135, 3073, 2981, 1682, 1602, 1495, 1448, 1404, 1311, 1240, 1191, 1137, 1097, 960, 887, 788, 760, 695, 665, 527, 467 cm$^{-1}$. ESI-MS (pos.) m/z (%): 491.3 [2·M+Na]$^+$ (42), 257.0 [M+K]$^+$ (78), 235.0 [M+Na]$^+$ (100). ESI-MS (neg.) m/z (%): 232.8 [M-H]$^-$(100). For C$_{12}$H$_{14}$N$_2$O$_3$ (234.25) calcd.: C 61.53, H 6.02, N 11.96; found: C 61.50, H 6.15, N 11.75.

**General procedure for the reaction of compounds 2 with isothiocyanic acid.** The solution of compound 2 (1 mmol) and potassium thiocyanate (6 mmol) in AcOH (3 mL), was stirred for 4 h at 50 °C. The solution was poured onto crushed ice (60 mL), the resulting precipitate was filtered with suction and crystallized. In the case of oily product, the mixture was extracted with chloroform (3 x 20 mL), the collected extracts were evaporated to dryness and chromatographed on silica gel column.

3a-Benzyl-9b-hydroxy-3-(2-hydroxyethyl)-2-thioxo-3a,5,9b-tetrahydro-1H-imidazo[4,5-c]quinolin-4(2H)-one (3c). Compound was prepared from 2c in 9% yield. Colorless solid, mp 236-246 °C (ethyl acetate). IR: 3199, 2997, 2931, 1682, 1602, 1495, 1479, 1448, 1404, 1311, 1240, 1191, 1137, 1097, 1069, 1010, 960, 868, 835, 763, 749, 702, 670, 627, 598, 563, 546, 529 cm$^{-1}$. ESI-MS (pos.) m/z (%): 761.2 [2·M+Na]$^+$ (23), 408.1 [M+K]$^+$ (14), 392.0 [M+Na]$^+$ (100). ESI-MS (neg.) m/z (%): 737.0 [2·M-H]$^-$ (25), 403.9 [M+Cl]$^-$ (18), 367.9 [M-H]$^-$ (100). For C$_{19}$H$_{19}$N$_3$O$_3$S (369.44) calcd. C 61.77, H 5.18, N 11.37, S 8.68; found: C 61.99, H 5.16, N 11.33, S 8.54.

3-(2-Hydroxyethyl)-2-thioxo-2,3-dihydro-1H-imidazo[4,5-c]quinolin-4(5H)-one (4c). Compound was prepared from 2c in 16% yield. Yellowish solid, mp > 330 °C (methanol). IR: 3418, 3109, 3000, 2891, 2682, 1658, 1613,
1571, 1521, 1502, 1464, 1440, 1422, 1373, 1346, 1287, 1259, 1196, 1151, 1051, 1035, 978, 877, 854, 788, 757, 685, 604, 537 cm\(^{-1}\). ESI-MS (pos.) \(m/z\): 545.1 [2·M+Na\(^+\)] (9), 284.0 [M+Na\(^+\)] (100). ESI-MS (neg.) \(m/z\): 542.9 [2·M-2H+Na\(^-\)] (11), 259.8 [M-H\(^-\)] (100). Calcd. for C\(_{12}H_{11}N_2O_2S\) (261.30) C 55.16, H 4.24, N 16.08, S 12.27; found: C 55.30, H 4.10, N 15.97, S 12.06.

2-[2-Hydroxyethyl]-1-methyl-3-thioxo-2,3-dihydroimidazo[1,5-c]quinazolin-5(6H)-one (5a). Compound was prepared from 2a in 49% yield. Yellowish solid, mp 290-294 °C (acetic acid). IR: 3389, 3225, 3166, 3101, 3070, 2998, 2938, 1721, 1642, 1612, 1589, 1492, 1453, 1376, 1357, 1303, 1263, 1224, 1159, 1133, 1093, 1053, 917, 863, 832, 817, 760, 740, 699, 666, 565, 524 cm\(^{-1}\). ESI-MS (pos.) \(m/z\): 573.1 [2·M+Na\(^+\)] (81), 314.0 [M+K\(^+\)] (14), 298.0 [M+Na\(^+\)] (100). ESI-MS (neg.) \(m/z\): 571.0 [2·M-2H+Na\(^-\)] (12), 273.8 [M-H\(^-\)] (100). For C\(_{13}H_{13}N_3O_2S\) (275.33) calcd. C 56.17, H 4.76, N 15.26, S 11.65; found: C 56.55, H 4.72, N 14.99, S 11.49.

**Table 3.** \(^1\)H, \(^13\)C and \(^15\)N NMR data of compounds 7a-d in DMSO-\(d_6\)

|        | \(\delta_H\) | \(\delta_C\) | \(\delta_H\) | \(\delta_C\) | \(\delta_H\) | \(\delta_C\) | \(\delta_H\) | \(\delta_C\) |
|--------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 7a     |             |             |             |             |             |             |             |             |
| 7b     |             |             |             |             |             |             |             |             |
| 7c     |             |             |             |             |             |             |             |             |
| 7d     |             |             |             |             |             |             |             |             |
| 1      | 11.28       | -261.4      | 11.39       | -260.2      | 11.37       | -261.2      | 11.43       | -261.2      |
| 2      |             | 150.4       |             | 150.4       |             | 150.4       |             | 150.4       |
| 3      |             | -224.7      |             | -222.6      |             | -222.6      |             | -222.6      |
| 4      |             |             |             | 162.2       |             | 162.7       |             | 162.7       |
| 4a     |             |             |             | 115.0       |             | 114.0       |             | 114.0       |
| 5      | 7.92        | 127.4       | 7.90        | 127.4       | 7.93        | 127.4       | 7.92        | 127.4       |
| 6      | 7.19        | 122.4       | 7.18        | 122.4       | 7.16        | 122.4       | 7.18        | 122.4       |
| 7      | 7.64        | 134.9       | 7.64        | 134.9       | 7.64        | 134.9       | 7.64        | 134.9       |
| 8      | 7.16        | 114.0       | 7.15        | 115.0       | 7.16        | 115.0       | 7.15        | 115.0       |
| 8a     |             | -139.5      |             | -139.6      |             | -139.5      |             | -139.6      |
| N(3)CH\(_2\) | 3.95      | 39.8        | 3.96        | 39.9        | 3.97        | 39.8        | 4.11        | 40.0        |
| CH\(_2\) | 3.29      | 36.4        | 3.31        | 36.2        | 3.34        | 36.4        | 3.35        | 37.2        |
| NH     | 7.92        | 267.6\(^{a,b}\) | 7.86        | 267.6\(^{a,c}\) | 8.13        | -           | 8.56        | -272.8\(^{d}\) |
| C=O    |             | 169.4       |             | 172.3       |             | 170.3       |             | 166.6       |
| 1'(R\(^2\)) | 1.71      | 22.6        | 1.94        | 35.2        | 3.31        | 42.3        |             | 134.9       |
| 2'(R\(^2\)) |             | 1.37        | 27.3        | -            | 136.3       | 7.71        | 127.2       |             |
| 3'(R\(^2\)) |             | 1.16        | 21.8        | 7.16        | 128.1       | 7.42        | 128.2       |             |
| 4'(R\(^2\)) |             | 0.79        | 13.8        | 7.23        | 129.1       | 7.48        | 131.0       |             |
| 5'(R\(^2\)) |             |             |             | 7.16        | 126.2       |             |             |             |

\(^{a}\) \(\delta^{(15\text{N})}\) \(^{b}\) \(\delta^{(15\text{N}, 1\text{H})} = 91.8\) Hz \(^{c}\) \(\delta^{(15\text{N}, 1\text{H}}) = 91.7\) Hz \(^{d}\) \(\delta^{(15\text{N}, 1\text{H})} = 91.8\) Hz

1-Butyl-2-(2-hydroxyethyl)-3-thioxo-2,3-dihydroimidazo[1,5-c]quinazolin-5(6H)-one (5b). Compound was prepared from 2b in 42% yield. Yellowish solid, mp 241-245 °C (ethyl acetate); IR: 3371, 3143, 3099, 3062, 2993, 2932, 2887, 1726, 1633, 1615, 1592, 1494, 1461, 1431, 13988, 1289, 1279, 1239, 1204, 1155, 1135, 1092, 1063, 1017, 964, 861, 824, 791, 752, 741, 663, 574, 564 cm\(^{-1}\). ESI-MS (pos.) \(m/z\): 657.2 [2·M+Na\(^+\)] (37), 495.6 [3·M+H+K\(^+\)] (16), 356.0 [M+K\(^+\)] (12), 340.0 [M+Na\(^+\)] (100), 318.1 [M+H\(^+\)] (6). ESI-MS (neg.) \(m/z\): 655.1 [2·M-2H+Na\(^-\)] (6), 315.9 [M-H\(^-\)] (100). For C\(_{15}H_{19}N_3O_2S\) (317.41) calcd. C 60.54, H 6.03, N 13.24, S 10.10; found: C 60.46, H 6.02, N 13.25, S 10.22.
2-(2-Hydroxyethyl)-1-phenyl-3-thioxo-2,3-dihydroimidazo[1,5-c]quinazolin-5(6H)-one (5d). Compound was prepared from 2d in 26% yield besides 6d. Yellowish solid, mp 248-252 °C (ethyl acetate). IR: 3378, 3254, 3206, 2994, 2930, 2876, 1732, 1645, 1616, 1591, 1485, 1443, 1380, 1325, 1296, 1262, 1232, 1186, 1125, 1080, 1047, 1022, 928, 846, 789, 745, 709, 669, 585, 506 cm⁻¹. ESI-MS (pos.) m/z (%): 697.1 [2-M+Na]⁺ (22), 525.6 [3-M+H+K]⁺ (9), 376.0 [M+K]⁺ (12), 360.0 [M+Na]⁺ (100). ESI-MS (neg.) m/z (%): 695.0 [2-M-2+H+Na]⁻ (7), 335.9 [M-H]⁻ (100). For C₁₈H₁₅N₃O₂S (337.40) calcd.: C 64.08, H 4.48, N 12.45, S 9.50; found: C 64.25, H 4.39, N 12.26, S 9.39.

3-(2-hydroxyethyl)-3a-phenyl-2-thioxo-3,3a-dihydro-2H-imidazo[4,5-c]quinolin-4(5H)-one (6d). Compound was prepared from 2d in 8% yield besides 6d. Colorless solid, mp 232-236 °C (ethyl acetate); IR: 3426, 3204, 2993, 2930, 1731, 1680, 1599, 1485, 1445, 1401, 1366, 1246, 1196, 1157, 1140, 1079, 1037, 1005, 977, 949, 936, 901, 788, 760, 745, 698, 652, 588, 558, 518 cm⁻¹. ESI-MS (pos.) m/z (%): 697.2 [2-M+Na]⁺ (8), 525.6 [3-M+H+K]⁺ (9), 376.0 [M+K]⁺ (13), 360.0 [M+Na]⁺ (100), 338.1 [M+H]⁺ (13). ESI-MS (neg.) m/z (%): 695.0 [2-M-2+H+Na]⁻ (6), 335.9 [M-H]⁻ (100). For C₁₈H₁₅N₃O₂S (337.40) calcd.: C 64.08, H 4.42, N 12.20, S 9.45.

General procedure for the reaction of chloroderivatives 1a-d with ethyline diamine. To a solution of compound 1 (20 mmol) in DMF (125 mL) was added potassium carbonate (45 mmol) and ethyline diamine (1.6 mL, 2.4 mmol). The mixture was stirred at rt for 4 h, then poured onto crushed ice (1000 mL) and extracted with chloroform (10 x 40 mL). Collected extracts were evaporated to dryness and crystallized from propionate solvent or chromatographed on silica gel column.

N-(2-(2,4-Dioxo-1,2-dihydroquinazolin-3(4H)-yl)ethyl)acetamide (7a). Compound was prepared from 1a in 52% yield. Colorless solid, mp 271-281 °C (ethanol). IR: 3293, 3090, 2999, 2936, 1712, 1655, 1603, 1567, 1491, 1454, 1409, 1380, 1341, 1283, 1266, 1234, 1177, 1163, 1108, 1047, 1026, 927, 819, 765, 694, 682, 666, 634, 599, 539, 466 cm⁻¹. ESI-MS (pos.) m/z (%): 517.2 [2-M+Na]⁺ (71), 286.0 [M+K]⁺ (11), 270.0 [M+Na]⁺ (100). ESI-MS (neg.) m/z (%): 515.0 [2-M-2+H+Na]⁻ (6), 245.8 [M-H]⁻ (100). For C₁₂H₁₃N₃O (247.25) calcd.: C 58.29, H 5.30, N 16.99; found: C 58.26, H 5.41, N 16.91.

N-(2-(2,4-Dioxo-1,2-dihydroquinazolin-3(4H)-yl)ethyl)pentanamide (7b). Compound was prepared from 1b in 36% yield. Colorless solid, mp 208-210 °C (benzene). IR: 3309, 3198, 3074, 2936, 1715, 1671, 1548, 1518, 1493, 1455, 1432, 1407, 1374, 1653, 1330, 1278, 1231, 1172, 1123, 1052, 1028, 940, 868, 824, 756, 694, 680, 597, 560, 528 cm⁻¹. ESI-MS (pos.) m/z (%): 601.3 [2-M+Na]⁺ (35), 328.1 [M+K]⁺ (13), 312.1 [M+Na]⁺ (100), 309.1 [2-M+H+K]⁺ (12), 290.1 [M+H]⁺ (5). ESI-MS (neg.) m/z (%): 599.1 [2-M-2+H+Na]⁻ (6), 287.9 [M-H]⁻ (100). For C₁₅H₁₉N₃O₃ (289.33) calcd.: C 62.27, H 6.62, N 14.52; found: C 62.00, H 6.60, N 14.38.

N-(2-(2,4-Dioxo-1,2-dihydroquinazolin-3(4H)-yl)ethyl)-2-phenylacetamide (7c). Compound was prepared from 1c in 32% yield. Colorless solid, mp 255-258 °C (ethanol). IR: 3307, 3196, 3065, 2909, 1723, 1657, 1608, 1546, 1494, 1453, 1412, 1382, 1339, 1299, 1266, 1247, 1201, 1176, 1160, 1073, 1036, 1025, 952, 834, 790, 758, 732, 703, 692, 665, 561, 533, 523, 464 cm⁻¹. ESI-MS (pos.) m/z (%): 669.2 [2-M+Na]⁺ (19), 362.0 [M+K]⁺ (14), 346.0 [M+Na]⁺ (100). ESI-MS (neg.) m/z (%): 667.1 [2-M-2+H+Na]⁻ (5), 321.9 [M-H]⁻ (100). For C₁₈H₁₇N₃O₃ (323.35) calcd.: C 66.36, H 5.30, N 13.00; found: C 66.22, H 5.36, N 12.92.

N-(2-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)ethyl)benzamide (7d). Compound was prepared from 1d in 7% yield. Colorless solid, mp 249-253 °C (ethyl acetate). IR: 3234, 3064, 3006, 2940, 1721, 1657, 1604, 1579, 1546, 1492, 1453, 1411, 1382, 1339, 1289, 1267, 1232, 1175, 1153, 1060, 1019, 938, 852, 801, 764, 733, 693, 682, 666, 560, 532 cm⁻¹. ESI-MS (pos.) m/z (%): 641.1 [2-M+Na]⁺ (35), 348.0 [M+K]⁺ (14), 322.0 [M+Na]⁺ (100). ESI-MS (neg.) m/z (%): 307.9 [M-H]⁻ (100). For C₁₇H₁₅N₃O₃ (309.32) calcd.: C 66.01, H 4.89, N 13.58; found: C 65.96, H 4.90, N 13.43.
10b-Benzoyl-1,2,3,10b-tetrahydroimidazo[1,2-c]quinazolin-5(6H)-one (8d). Compound was prepared from 1d in 25% yield besides 7d. Colorless solid, mp 217-226 °C (ethyl acetate); IR: 3277, 3196, 3124, 3061, 2982, 2891, 1678, 1597, 1508, 1486, 1478, 1467, 1447, 1331, 1309, 1264, 1228, 1173, 1159, 1131, 1118, 1082, 940, 908, 879, 866, 833, 792, 757, 707, 691, 663, 639 cm⁻¹. ESI-MS (pos.) m/z (%): 609.1 [2·M+Na]+ (27), 587.1 [2·M+H]+ (16), 459.6 [3·M+H+K]+ (10), 332.0 [M+K]+ (8), 316.0 [M+Na]+ (53), 294.0 [M+H]+ (100). ESI-MS (neg.) m/z (%): 291.9 [M–H]– (100).

For C_{17}H_{15}N_{3}O_{2} (293.32) calcd.: C 69.61, H 5.15, N 14.33; found: C 69.62, H 5.25, N 14.27.

Reduction of compound 8d.

10b-(Hydroxy(phenyl)methyl)-1,2,3,10b-tetrahydroimidazo[1,2-c]quinazolin-5(6H)-one (9d). To the solution of compound 8d (0.2051 g, 0.7 mmol) in methanol (10 mL), NaBH₄ (0.029 g, 0.78 mmol) was added during 5 min. After 1 h at rt, the solution was poured onto crushed-ice. Hydrochloric acid (0.5 mL) and, after 10 min, the solution of sodium bicarbonate (6%, 12 mL) were added. The mixture was extracted (8 x 25 mL) of chloroform. Collected extracts were dried with sodium sulfate, evaporated to dryness and crystallized from benzene. 103 mg (50%) of 9d, mp 242-248 °C (benzene) was obtained; IR: 3319, 3285, 3247, 3063, 3031, 2975, 2892, 1666, 1614, 1598, 1510, 1487, 1448, 1337, 1308, 1259, 1200, 1172, 1156, 1135, 1115, 1096, 1058, 1039, 1025, 988, 959, 892, 869, 823, 787, 755, 709, 680, 610, 586, 535 cm⁻¹. ESI-MS (pos.) m/z (%): 318.1 [M+Na]+ (28), 296.1 [M+H]+ (100). For C_{17}H_{17}N_{3}O_{2} (295.34) calcd.: C 69.14, H 5.80, N 14.23; found: C 69.24, H 6.05, N 14.13.

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Author contribution statement: A. K. designed the studies and wrote the manuscript. A. L. and M. R. conducted the experiments.

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