Synthesis, Structure of Zwitterionic 2-Amino-*N*′-(imidazolidin-2-ylidene) benzohydrazides, and Their Transformation into 3-(Imidazolidin-2-ylideneamino)quinazolin-4(1*H*)-one Derivatives

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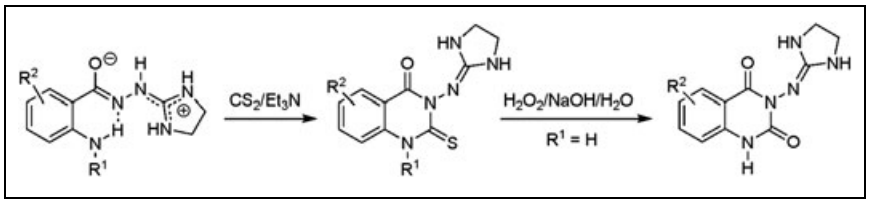

The reaction of 2-chloro-4,5-dihydroimidazole (**5**) with 2-aminobenzohydrazides **6a–e** led to the formation of 2-amino-*N*′-(imidazolidin-2-ylidene)benzohydrazides as zwitterions **7a–e**, which on treatment with carbon disulfide in the presence of triethylamine afforded 3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **8a–e**. Compounds **8a–d** were further converted into the corresponding 3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H*,3*H*)-diones **9a–d** using hydrogen peroxide–sodium hydroxide solution. The structures of the compounds prepared were established by elemental analyses, IR and NMR spectra as well as X-ray crystallographic analyses of **7e** and **9a**.

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INTRODUCTION

Over the years, quinazolin-4(1*H*)-one derivatives have been investigated because of their broad pharmacological potential. They act as central nervous system depressant [1], anticonvulsant [2], anti-inflammatory [3, 4], antidiabetic [5], antibacterial [6–8], anticancer [9–11], and antihypertensive agents [12–15]. For example, Ketanserin **1** has been found to possess antihypertensive activity mediated *via* α_1-adrenoreceptor and 5-HT_{2A} receptor antagonism [12], while 3-aryl-2,4-quinazolinediones **2** have been reported to exhibit cytotoxicity on the colon cancer Col2 cell line [9]. In addition, 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **3** has been shown to act as inhibitor of inosine monophosphate dehydrogenase II, which plays a role in systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and organ transplant rejection [16] (Fig. 1).

On the other hand, 2-iminoimidazolidine derivatives interacting with α-adrenergic and/or imidazoline receptors [17] are known to mediate a variety of biological actions including lowering blood pressure, sedation, anxiety reduction, analgesia, hypothermia, decreased salivary secretion, mydriasis, and lowering intraocular pressure. Iminoimidazolidines are also useful as antineoplastic agents [18]. Moreover, various *N*′-(imidazolidin-2-ylidene) hydrazides were synthesized and tested for their antibacterial [19], anticancer [20], hypotensive [21], or diuretic and saluretic [22] activities.

In continuation of our research program aimed at the synthesis of imidazoline-containing compounds as potential antihypertensive [23, 24] or anticancer agents [25, 26], this study deals with the synthesis of 2-amino-*N*′-(imidazolidin-2-ylidene)benzohydrazides and their transformation into 3-(imidazolidin-2-ylideneamino)quinazolin-4(1*H*)-one derivatives **4** (Fig. 1).

RESULTS AND DISCUSSION

Our research started with the reaction between 2-chloro-4,5-dihydroimidazole (**5**) and 2-aminobenzohydrazides **6a**–**e** in dichloromethane at ambient temperature, which afforded the desired 2-amino-*N*′-(imidazolidin-2-ylidene) benzohydrazides as zwitterions **7a–e** in 26–41% yields (Scheme 1).

We proposed that the first step of the reaction sequence is the formation of 2-amino-*N*′-(imidazolidin-2-ylidene) benzohydrazide **A** that undergoes amide-imidic acid tautomerism leading to imidic acid tautomer **B**. Then, 1,4-proton transfer from the hydroxyl group to the guanidine moiety forms the final product **7** (Scheme 1).

It should be noted that 2-amino-*N*′-(imidazolidin-2-ylidene)benzohydrazides **7a**, **7c**, and **7e** were obtained previously by reacting the corresponding 2-aminobenzohydrazides with 2-methylthio-4,5-dihydroimidazole hydrochloride [21]. However, infrared and nuclear magnetic resonance spectroscopic data for compounds **7a**, **7c**, and **7e** have not been reported previously in chemical literature. Therefore, the known 2-amino-*N*′-(imidazolidin-2-ylidene)

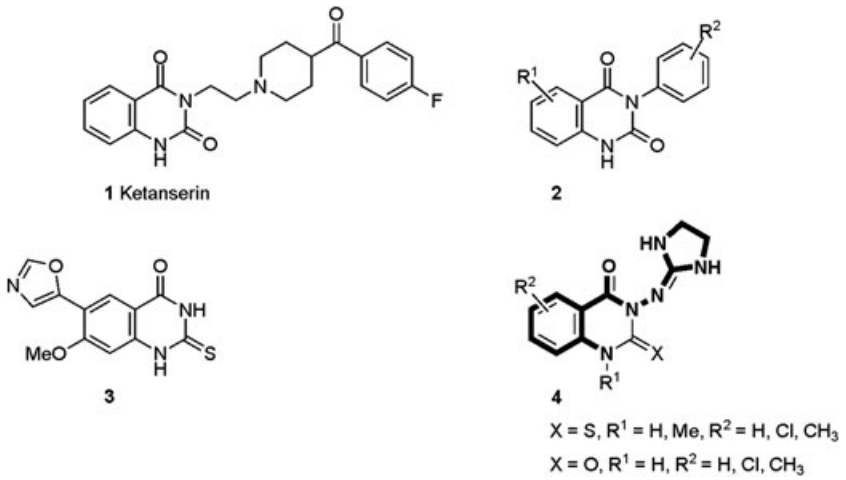
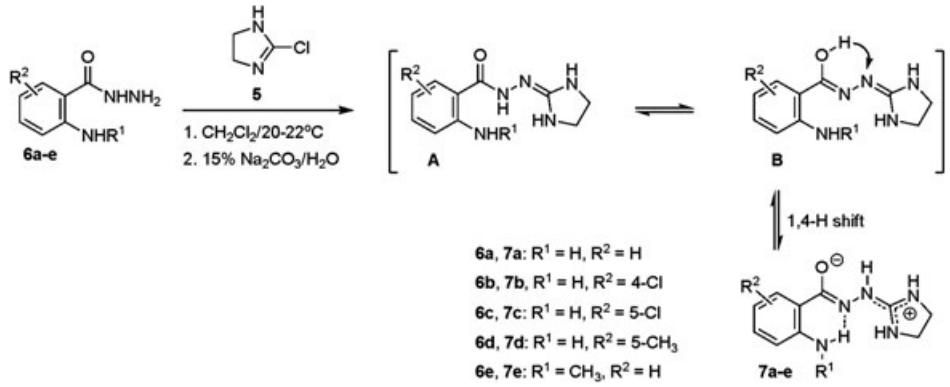


Figure 1. Structures of quinazolin-4(1*H*)-one derivatives **1–4**.

Scheme 1 Synthesis of zwitterionic 2-amino-*N*′-(imidazolidin-2-ylidene)benzohydrazides 7**a–e**.



benzohydrazides **7a**, **7c**, and **7e** as well as the novel derivatives **7b** and **7d** were characterized by IR and NMR spectroscopies.

The IR spectra of compounds **7a–e** exhibited characteristic absorptions at 1705–1690 cm^{-1} corresponding to the carbon–nitrogen stretching vibrations of the imidate moiety. These values agree well with the imidate C═N stretching frequency (1704–1645 cm^{-1}) [27–29].

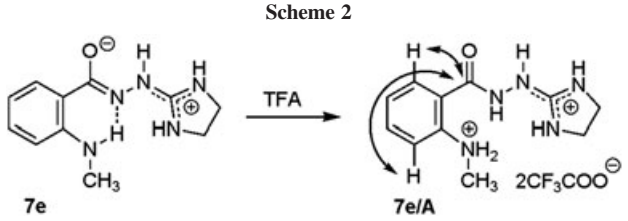
The ^1H NMR spectrum of **7e** recorded in DMSO-d_6 revealed a doublet at 2.77 ppm due to CH_3 protons of the methylamino group and a singlet at 3.44 ppm attributable to the methylene protons of the imidazoline moiety. The aromatic protons appeared as three separate multiplets at 7.68, 7.19–7.09, and 6.53–6.46 ppm, while the NH proton of the methylamino group occurred as a broad signal at 7.80 ppm. Apparently due to prototropic process, the signals of the protons attached to the nitrogen atoms of the guanidine moiety were not observed.

The assignment of the ^{13}C NMR spectrum of **7e** was based on the analysis of 2D NMR spectra (heteronuclear single quantum coherence and heteronuclear multiple bond coherence). In the ^{13}C NMR spectrum of **7e**, the imidazoline C4 and C5 carbon atoms appeared as a sharp signal at 42.4 ppm, whereas the carbon resonance of the imidazoline C2 carbon atom was found as a broad signal at 158.9 ppm. Moreover, the carbon resonance at 165.0 ppm, which showed a long-range correlation to the C3-H proton at 6.52 ppm, was assigned to carbonyl group.

Further confirmation is provided by the analysis of ^1H and ^{13}C NMR spectra recorded in DMSO-d_6 with addition of TFA. Protonation of the charged amide moiety of **7e** on treatment with TFA, as illustrated in Scheme 2, allowed us to clarify the NMR spectra.

Some new features were seen in the ^1H NMR spectrum of the protonated compound **7e/A**: two broad signals attributable to the protons attached to the endocyclic nitrogen

Scheme 2



atoms of the imidazoline moiety appeared at 8.84 and 8.61 ppm and the proton of the HN-C═O group occurred as a singlet at 10.5 ppm.

As in **7e**, the assignment of ^{13}C NMR spectrum of **7e/A** was also based on the analysis of one-bond and long-range coupling carbon–proton shift correlations. In the ^{13}C NMR spectrum of **7e/A**, the imidazoline C4 and C5 carbon atoms appeared as a broad signal at 43.0 ppm, while the imidazoline C2 carbon atom gave rise to a sharp signal at 161.4 ppm. Furthermore, the signal of the carbon atom of the HN-C═O group appeared at 169.1 ppm and this resonance showed long-range correlations to C6-H (δ 7.68 ppm) and C3-H (δ 6.70 ppm) protons (Scheme 2).

Finally, the structural proof was also furnished by X-ray crystal structure analysis of **7e** (Fig. 2).

The molecule **7e** exists in crystals in a zwitterionic form with a positive charge located at the protonated guanidine fragment and the negative charge located at the deprotonated amide group. The shape of the molecule results to a large extent from the intramolecular N2-H···N7 hydrogen bond (Scheme 1 and Fig. 2).

The length of 1.316(1) Å of the exocyclic C2-N6 bond in the guanidine fragment indicates its more pronounced double-bond character than that of the two endocyclic C-N bonds of 1.333(1) and 1.349(1) Å. The sums of the bond angles around N1 and N3 equal to 353° and 350°, respectively, point to the sp^2 hybridization state of these N atoms, each bearing a partial positive charge. Analogously, the negative charge is spread over the anionic O1-C8-N7 fragment as can be guessed from the C8-O1 and C8-N7 bond lengths of 1.293(1) and 1.322(1) Å, respectively. In **7e**, the amide C-O bond is substantially lengthened when compared with a double C═O bond in benzoylhydrazones (1.203–1.229 Å), whereas formally single C_{sp2}-N bond of the O═C-N group is significantly shorter than the values 1.350–1.356 Å reported for benzoylhydrazones [30, 31].

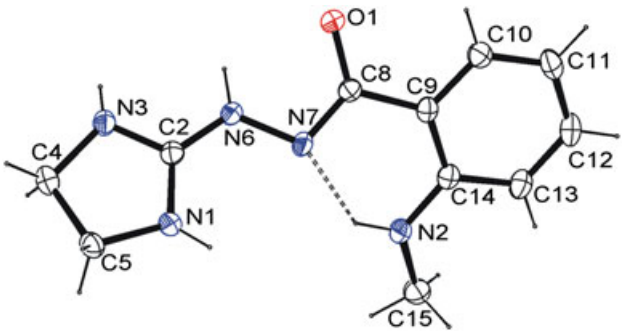


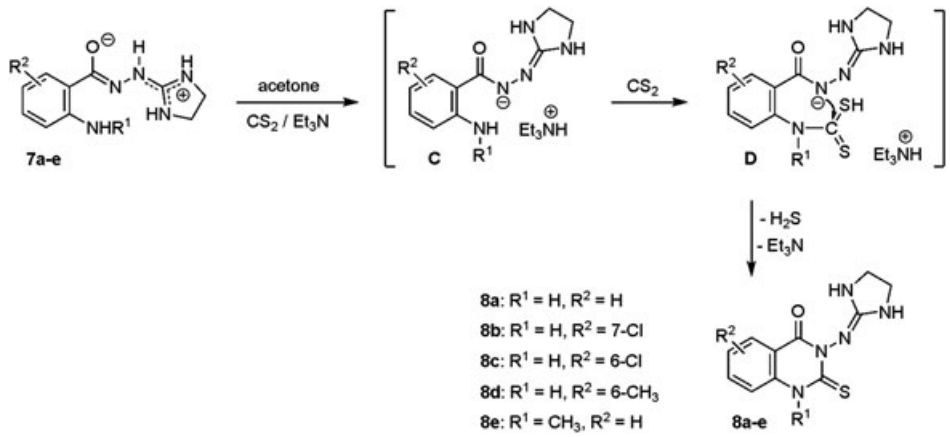
Figure 2. View of the molecular structure of **7e** with displacement ellipsoids drawn at the 50% probability level. Intramolecular hydrogen bond is shown with a dashed line.

Further reactions of compounds **7a–e** with an excess of carbon disulfide in anhydrous acetone at ambient temperature, in the presence of triethylamine gave 3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **8a–e**, as illustrated in Scheme 3.

The mechanism of the reaction pathway was not investigated but it can be explained as follows. First, in the presence of Et_3N, the zwitterion **7** may form triethylammonium salt **C**, which then reacts with carbon disulfide to give dithiocarbamic acid derivative **D**. The later intermediate can subsequently undergo an intramolecular cyclocondensation with evolution of H_2S giving rise to the formation of the final product **8** (Scheme 3).

The structures **8a–e** were in accordance with ^{1}H and ^{13}C NMR spectroscopic data as illustrated for the representative example **8a**. The four methylene protons of the imidazolidine moiety were seen as two distinct multiplets at 3.37–3.34 and 3.29–3.26 ppm; the signals of two protons attached to the endocyclic nitrogen atoms of the imidazolidine appeared at 6.64 and 6.57 ppm, and the signal of the HN-C═S proton appeared at 12.59 ppm. In the ^{13}C NMR spectrum, chemical value shift at 158.1 ppm attributable to the carbon atom of the exocyclic C═N double bond is in agreement with those found for the related 2-iminoimidazolidine derivatives [32].

Scheme 3 Synthesis of 3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **8a–e**.



Furthermore, the carbon resonances at 174.6 and 164.4 ppm were assigned to the carbon atoms of the thiocarbonyl and carbonyl groups, respectively.

It has been reported that 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones can undergo oxidative desulfurization using hydrogen peroxide–sodium hydroxide solution or concentrated sulfuric acid in DMSO to afford quinazoline-2,4(1*H,3H*)-diones [33–35]. In accordance with the known procedure [33], treatment of 3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **8a–d** with 30% aqueous H_2O_2 solution in 2% aqueous NaOH solution at room temperature gave the expected 3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H,3H*)-diones **9a–d** (Scheme 4).

The structures of compounds **9a–d** were confirmed by spectroscopic data presented in Experimental section. For example, the ^{1}H NMR spectrum of 3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H,3H*)-dione (**9a**) revealed characteristic singlet of the HN-C═O proton at 11.16 ppm. In the ^{13}C NMR, the carbonyl C4═O and the cyclic ureido C2═O signals, respectively, at 165.6 and 150.2 ppm are also consistent with the proposed structure.

The structure of **9a** was further confirmed by X-ray crystallographic analysis (Fig. 3).

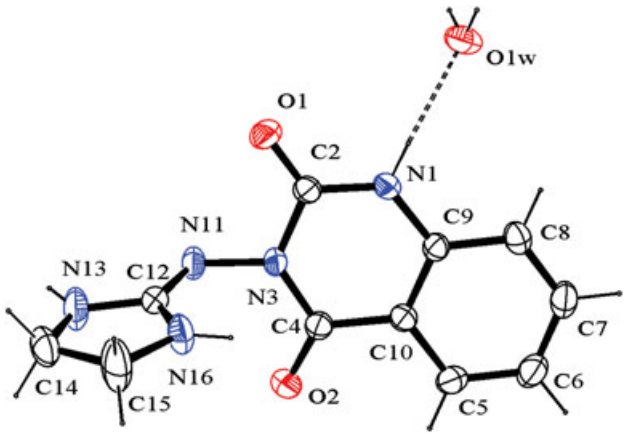


Figure 3. View of the molecular structure of **9a** with displacement ellipsoids drawn at the 50% probability level. Hydrogen bond is shown with a dashed line.

CONCLUSIONS

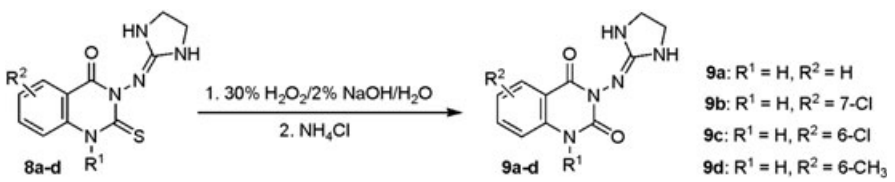
We have found that 2-chloro-4,5-dihydroimidazole (**5**) reacts with 2-aminobenzohydrazides **6a–e** to give zwitterionic 2-amino-*N*′-(imidazolidin-2-ylidene)benzohydrazides **7a–e**. These compounds undergo cyclocondensation reaction with carbon disulfide to afford 3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **8a–e**. The oxidative desulfurization of compounds **8a–d** with hydrogen peroxide–sodium hydroxide solution furnishes 3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H,3H*)-diones **9a–d**.

EXPERIMENTAL

Melting points were determined on a Bűchi SMP 20 apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrophotometer for potassium bromide pellets and frequencies are expressed in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 or Varian Unity 500 spectrometers. Two-dimensional NMR experiments were carried out on a Varian Unity Plus 500 spectrometer. Chemical shifts (δ) were measured relative to the residual solvent signal at 2.50 and 39.5 ppm (DMSO-d_6). Preparative thin-layer chromatography was performed on precoated silica gel plate (Merck 60 PF_{254} containing gypsum, 0.2 mm) using Chromatotron apparatus (Harrison Research Inc., Palo Alto, CA). The results of elemental C, H, N analyses of all prepared compounds were within ±0.4% of the theoretical values. 2-Chloro-4,5-dihydroimidazole (**5**) was obtained according to procedure described by Trani and Bellasio [36]. The 2-aminobenzohydrazides (**6a**) [37], (**6b**) [38], (**6c**) [39], (**6d**) [40], and (**6e**) [41] were prepared as reported.

Synthesis of zwitterionic 2-amino-*N*′-(imidazolidin-2-ylidene) benzohydrazide (7a). A solution of 2-chloro-4,5-dihydroimidazole (**5**) (2.5 g, 24.7 mmol) in CH_2Cl_2 (30 mL) was treated with equimolar amount of 2-aminobenzohydrazide (**6a**) (3.73 g, 24.7 mmol) and then was stirred at rt for 6 h. The solid that precipitated was collected by filtration, washed with CH_2Cl_2, dried and suspended in water. The resulting suspension was made alkaline with 15% aqueous Na_2CO_3 solution (pH 10–10.5) and extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were dried over anhydrous Mg_2SO_4, filtered and evaporated to dryness. The crude product thus obtained was purified by crystallization from acetonitrile to give 2.02 g (37.0%) of **7a** as a white solid, mp 211–214°C; IR (KBr): ν 3450, 3405 (NH_2), 3350–2700 (max: 3350, 3190, 2955, 2880 $NH^{\oplus}$, CH), 1690 (CN), 1660, 1615, 1580 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.60 (d, J = 7.8 Hz, 1H, CH-aromat.), 7.07–7.00 (m, 1H, CH-aromat.), 6.64 (d, J = 8.1 Hz, 1H, CH-aromat.), 6.50–6.42 (m, 1H, CH-aromat.), 6.27 (s, 2H, NH_2), 3.43 (s, 4H, 2× CH_2, imidaz.); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.2 (NCO), 160.0 (br s, C2-imidaz.), 148.8 (1C), 130.1 (1C), 128.9 (1C), 115.8 (1C), 114.5 (2C),

Scheme 4 Synthesis of 3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H*,3*H*)-diones **9a–d**.



42.7 (C4, C5-imidaz.). *Anal*. Calcd. for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.58; H, 5.61; N, 31.97.

General procedure for the preparation of zwitterionic 2-amino-*N′*-(imidazolidin-2-ylidene)benzohydrazides (7b–e). The reaction of 2-chloro-4,5-dihydroimidazole (**5**) (2.5 g, 24.7 mmol) in CH_2Cl_2 (30 mL) with equimolar amount of the appropriate 2-aminobenzohydrazide **6b–e** (24.7 mmol) was carried out according to the procedure described above for **7a** except the extraction with CH_2Cl_2. The crude product thus obtained was purified by crystallization from a suitable solvent. In this manner, the following compounds were obtained.

Zwitterionic 2-amino-4-chloro-*N′*-(imidazolidin-2-ylidene) benzohydrazide (7b). Yield 2.24 g (36.0%). White solid, mp 230–232°C (dec, DMF); IR (KBr): ν 3445, 3390 (NH_2), 3330–2850 (max: 3290, 3100, 2970, 2890 $NH^{\oplus}$, CH), 1700 (CN), 1650, 1600, 1560 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.68 (br s, 1H, CH-aromat.), 7.02 (br s, 1H, NH), 6.65 (s, 3H, CH-aromat. and NH_2), 6.48–6.40 (m, 1H, CH-aromat.), 3.45 (s, 4H, 2× CH_2, imidaz.). *Anal*. Calcd. for $C_{10}H_{12}ClN_5O$: C, 47.34; H, 4.77; N, 27.61. Found: C, 47.01; H, 4.32; N, 27.55.

Zwitterionic 2-amino-5-chloro-*N′*-(imidazolidin-2-ylidene) benzohydrazide (7c). Yield 1.65 g (26.4%). White solid, mp 208–210°C (dec, DMF/MeOH); IR (KBr): ν 3473, 3330 (NH_2), 3250–2830 (max: 3235, 2900, 2830 $NH^{\oplus}$, CH), 1695 (CN), 1604, 1565 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.71 (br s, 1H, CH-aromat.), 6.96 (br s, 1H, CH-aromat.), 6.63 (d, J = 7.3 Hz, 1H, CH-aromat.), 6.50 (br s, 2H, NH_2), 3.64 (br s, 4H, 2× CH_2, imidaz.); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.9 (NCO), 157.5 (br s, C2-imidaz.), 147.3, 128.8, 128.6, 120.0, 117.6, 117.1 (6C), 42.8 (C4, C5-imidaz.). *Anal*. Calcd. for $C_{10}H_{12}ClN_5O$: C, 47.34; H, 4.77; N, 27.61. Found: C, 47.42; H, 4.83; N, 27.97.

Zwitterionic 2-amino-*N′*-(imidazolidin-2-ylidene)-5-methylbenzohydrazide (7d). Yield 2.13 g (37.0%). White solid, mp 226–228°C (dec, acetonitrile); IR (KBr): ν 3475, 3325 (NH_2), 3300–2800 (max: 3225, 2900, 2825 $NH^{\oplus}$, CH), 1695 (CN), 1620, 1575 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.40 (s, 1H, 6-H, CH-aromat.), 6.84 (d, J = 8.1 Hz, 1H, 3-H, CH-aromat.), 6.53 (d, J = 8.1 Hz, 1H, 4-H, CH-aromat.), 6.01 (br s, 2H, NH_2), 3.40 (s, 4H, 2× CH_2, imidaz.), 2.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.0 (NCO), 159.8 (br s, C2-imidaz.), 146.2, 130.6, 128.8, 122.5, 117.4, 115.8 (6C), 42.4 (C4, C5-imidaz.), 20.2 (CH_3). *Anal*. Calcd. for $C_{11}H_{15}N_5O$: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.31; H, 6.13; N, 29.70.

Zwitterionic *N′*-(imidazolidin-2-ylidene)-2-(methylamino) benzohydrazide (7e). Yield 2.36 g (41.0%). White solid, mp 221–223°C (dec, DMF); IR (KBr): ν 3350–2810 (max: 3310, 3210, 3030, 2905, 2815 NH, $NH^{\oplus}$, CH), 1700 (CN), 1605, 1580 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.80 (br s, 1H, NHCH$_3$), 7.68 (br s, 1H, 6-H, CH-aromat.), 7.19–7.09 (m, 1H, 4-H, CH-aromat.), 6.52 (d, J = 7.8 Hz, 1H, 3-H, CH-aromat.), 6.48 (t, 1H, 5-H, CH-aromat.), 3.44 (s, 4H, 2× CH_2, imidaz.), 2.77 (d, J = 4.4 Hz, 3H, NHCH$_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.0 (NCO), 158.9 (br s, C2-imidaz.), 149.1, 130.2, 128.8, 118.1, 113.6, 109.4 (6C), 42.4 (C4, C5-imidaz.), 29.5 (CH_3). *Anal*. Calcd. for $C_{11}H_{15}N_5O$: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.86; H, 6.71; N, 30.10.

NMR analysis of compound 7e/A. ^1H NMR (500 MHz, DMSO-d_6 + TFA): δ 10.55 (br s, 2H, $NH_2^{\oplus}$), 10.38 (s, 1H, HN-C=O), 8.84 (br s, 1H, $NH^{\oplus}$), 8.61 (br s, 1H, $NH^{\oplus}$), 7.68 (d, J = 7.3 Hz, 1H, 6-H, CH-aromat.), 7.37 (t, 1H, 4-H, CH-aromat.), 6.70 (d, J = 7.4 Hz, 1H, 3-H, CH-aromat.), 6.60 (t, 1H, 5-H, CH-aromat.), 3.66 (br s, 4H, 2× CH_2, imidaz.), 2.80 (s, 3H, NHCH$_3$); ^{13}C NMR (125 MHz, DMSO-d_6 + TFA): δ 169.1 (HN-C=O), 161.4 (C2-imidaz.), 150.7, 133.9, 129.1, 114.1, 111.4, 111.1 (6C), 43.0 (br s C4, C5-imidaz.), 29.3 (CH_3).

General procedure for the preparation of 3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones (8a–e). To a stirred mixture of the appropriate *N′*-(imidazolidin-2-ylidene)benzohydrazide **7a–e** (8.9 mmol) and Et_3N (1.24 mL, 0.9 g, 8.9 mmol) in anhydrous acetone (20 mL) carbon disulfide (6.23 g, 82.0 mmol) was added dropwise. After stirring for 48–72 h at rt (until H_2S had ceased), the solid that precipitated was filtered off, washed with acetone and dried. Then, the crude product thus obtained was treated with hot anhydrous methanol (1:20). The insoluble solid was separated by suction, washed with hot methanol, and dried to give pure compounds **8a–c**, **e**. The product **8d** was purified by crystallization from DMF/MeOH.

3-(Imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (8a). Yield 1.36 g (69.7%). White solid, mp 284–286°C (dec); IR (KBr): ν 3375, 3220 (NH), 1675 (C=O), 1625 (C=N), 1215 (C=S) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.59 (s, 1H, HN-C=S), 7.90 (d, J = 7.8 Hz, 1H, CH-aromat.), 7.67 (t, 1H, CH-aromat.), 7.37 (d, J = 8.3 Hz, 1H, CH-aromat.), 7.26 (t, 1H, CH-aromat.), 6.64 (s, 1H, NH), 6.52 (s, 1H, NH), 3.37–3.34 (m, 2H, CH_2, imidaz.), 3.29–3.26 (m, 2H, CH_2, imidaz.); ^{13}C NMR (50 MHz, DMSO-d_6) δ 174.6 (CS), 164.4 (CO), 158.1 (C2-imidaz.), 139.2, 134.4, 127.3, 123.6, 116.8, 115.5 (6C), 42.3 (C4, C5-imidaz.). *Anal*. Calcd. for $C_{11}H_{11}N_5OS$: C, 50.56; H, 4.24; N, 26.80. Found: C, 50.32; H, 4.01; N, 26.53.

7-Chloro-3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (8b). Yield 2.1 g (79.8%). White solid, mp 255–257°C (dec); IR (KBr): ν 3385, 3235 (NH), 1665 (C=O), 1630 (C=N), 1205 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 12.59 (br s, 1H, HN-C=S), 7.89 (d, J = 8.5 Hz, 1H, 5-H, CH-aromat.), 7.37 (s, 1H, 8-H, CH-aromat.), 7.28 (dd, $J_{6,8}$ = 1.6 Hz, $J_{6,5}$ = 8.5 Hz, 1H, 6-H, CH-aromat.), 6.68 (br s, 1H, NH), 6.56 (br s, 1H, NH), 3.33–3.16 (m, 4H, 2× CH_2, imidaz.); ^{13}C NMR (50 MHz, DMSO-d_6) δ 174.9 (CS), 164.4 (CO), 157.5 (C2-imidaz.), 140.2, 138.9, 129.5, 123.7, 115.7, 114.8 (6C), 42.3 (C4, C5-imidaz.). *Anal*. Calcd. for $C_{11}H_{10}ClN_5OS$: C, 44.67; H, 3.41; N, 23.68. Found: C, 44.32; H, 3.17; N, 23.39.

6-Chloro-3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (8c). Yield 1.82 g (69.2%). White solid, mp 310–312°C (dec); IR (KBr): ν 3395, 3210 (NH), 1670 (C=O), 1625 (C=N), 1215 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 12.70 (br s, 1H, HN-C=S), 7.82 (d, $J_{5,7}$ = 2.4 Hz, 1H, 5-H, CH-aromat.), 7.72 (dd, $J_{7,5}$ = 2.4 Hz, $J_{7,8}$ = 8.8 Hz, 1H, 7-H, CH-aromat.), 7.38 (d, $J_{8,7}$ = 8.8 Hz, 1H, 8-H, CH-aromat.), 6.63 (br s, 1H, NH), 6.52 (br s, 1H, NH), 3.30 (br s, 4H, 2× CH_2); ^{13}C NMR (50 MHz, DMSO-d_6) δ 174.6 (CS), 163.7 (CO), 157.2 (C2-imidaz.), 138.1, 134.7, 127.7, 126.2, 118.1, 117.9 (6C), 42.4 (C4, C5-imidaz.). *Anal*. Calcd. for $C_{11}H_{10}ClN_5OS$: C, 44.67; H, 3.41; N, 23.68. Found: C, 44.82; H, 3.71; N, 23.94.

3-(Imidazolidin-2-ylideneamino)-6-methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (8d). Yield 1.32 g (53.9%). White solid, mp 298–301°C (dec); IR (KBr): ν 3370, 3205 (NH), 1670 (C= O), 1630 (C= N), 1215 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 12.53 (br s, 1H, HN-C=S), 7.70 (s, 1H, CH-aromat.), 7.49 (d, J = 7.8 Hz, 1H, CH-aromat.), 7.27 (d, J = 9.4 Hz, 1H, CH-aromat), 6.56 (br s, 1H, NH), 6.50 (br s, 1H, NH), 3.35–3.29 (m, 4H, 2× CH_2, imidaz.), 2.35 (s, 3H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 174.1 (CS), 164.5 (CO), 158.0 (C2-imidaz.), 137.2, 135.5, 133.0, 126.6, 116.6, 115.5 (6C), 42.3 (C4, C5-imidaz.), 20.7 (CH_3). *Anal*. Calcd. for $C_{12}H_{13}N_5OS$: C, 52.35; H, 4.76; N, 25.44. Found: C, 52.01; H, 4.41; N, 25.14.

3-(Imidazolidin-2-ylideneamino)-1-methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (8e). Yield 1.15 g (46.9%). White solid, mp 232–234°C (dec); IR (KBr): v 3370, 3190 (NH), 1700 (C═O), 1625 (C═N), 1225 (C═ S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 8.05 (d, J = 7.8 Hz, 1H, CH-aromat.), 7.79 (t, 1H, CH-aromat.), 7.60 (d, J = 8.4 Hz, 1H, CH-aromat.), 7.38 (t, 1H, CH-aromat.), 6.54 (br s, 1H, NH), 6.50 (br s, 1H, NH), 4.10 (s, 3H, CH_3), 3.35–3.20 (m, 4H, 2× CH_2, imidaz.). *Anal.* Calcd. for $C_{12}H_{13}N_5OS$: C, 52.35; H, 4.76; N, 25.44. Found: C, 52.13; H, 4.43; N, 25.34.

Synthesis of 3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H*,3*H*)-dione monohydrate (9a). To a stirred suspension of **8a** (1.0 g, 3.83 mmol) in 2% aqueous NaOH solution (20 mL) 30% aqueous H_2O_2 solution (6 mL) was added dropwise at 0–5°C temperature. After 20 min, the cooling bath was removed and the stirring was continuing for 2 h at rt. Then, NH_4Cl (2.0 g, 37.0 mmol) was added and the reaction mixture was stirred at rt for an additional 24 h. The precipitate was filtered off, dried, and chromatographed on silica gel with use of Chromatotron apparatus (AcOEt:MeOH, 90:10 v/v, as the mobile phase). The crude product thus obtained was purified by crystallization from EtOH to give 0.15 g (15.0%) of **9a** as a white solid, mp 252–253°C (dec). IR (KBr): v 3385, 3295 (NH), 1715, 1665 (C═O), 1615 (C═N), 1490, 1445 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 11.16 (br s, 1H, HN-C═O), 7.89–7.85 (m, 1H, CH-aromat.), 7.58–7.54 (m, 1H, CH-aromat.), 7.15–7.12 (m, 2H, CH-aromat.), 6.59 (s, 1H, NH), 6.41 (br s, 1H, NH), 3.31 (br s, 4H, 2× CH_2, imidaz.); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.6 (C4═O), 163.0 (C2-imidaz.), 150.2 (C2═O), 139.6, 134.4, 127.8, 122.3, 115.7, 115.4 (6C), 42.8, 42.7 (C4, C5-imidaz.). *Anal.* Calcd. for $C_{11}H_{11}N_5O_2 \cdot H_2O$: C, 50.19; H, 4.98; N, 26.60. Found: C, 49.81; H, 4.63; N, 26.43.

General procedure for the preparation of 3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H*,3*H*)-diones (9b–d). The reaction of the appropriate 3-(imidazolidin-2-ylideneamino)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **8b–d** with 30% aqueous H_2O_2 solution in 2% aqueous NaOH solution was carried out according to the procedure described above for **9a**, except the silica gel chromatography. The crude product thus obtained was purified by treatment with hot anhydrous methanol (1:20) in the case of **9b** or by crystallization from a suitable solvent in the case of **9c–d**.

7-Chloro-3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H*,3*H*)-dione (9b). Yield 0.7 g (65.4%). White solid, mp 318–320°C. IR (KBr): v 3410, 3310 (NH), 1715, 1660 (C═O), 1610 (C═N), 1500, 1420 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): 11.32 (br s, 1H, HN-C═O), 7.88 (d, J = 8.8 Hz, 1H, CH-aromat.), 7.20 (d, J = 8.3 Hz, 1H, CH-aromat.), 7.17 (s, 1H, CH-aromat.), 6.71 (br s, 1H, NH), 6.49 (br s, 1H, NH), 3.36–3.29 (m, 4H, 2× CH_2, imidaz.); ^{13}C NMR (50 MHz, DMSO-d_6) δ 161.8 (C4═O), 160.1 (C2-imidaz.), 149.1 (C2═O), 140.5, 139.7, 129.9, 123.0, 114.9, 113.7 (6C), 42.9 (br s, C4, C5-imidaz.). *Anal.* Calcd. for $C_{11}H_{10}ClN_5O_2$: C, 47.24; H, 3.60; N, 25.04. Found: C, 47.08; H, 3.48; N, 25.12.

6-Chloro-3-(imidazolidin-2-ylideneamino)quinazoline-2,4(1*H*,3*H*)-dione (9c). Yield 0.43 g (40.2%). White solid, mp 261–263°C (dec, DMF/MeOH). IR (KBr): v 3410, 3235 (NH), 1730, 1665 (C═O), 1615 (C═N), 1495, 1430 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 11.33 (br s, 1H, HN-C═O), 7.80 (d, $J_{5,7}$ = 2.2 Hz, 1H, 5-H, CH-aromat.), 7.63 (dd, $J_{7,8}$ = 8.7 Hz, $J_{7,5}$ = 2.4 Hz, 1H, 7-H, CH-aromat.), 7.16 (d, $J_{8,7}$ = 8.8 Hz, 1H, 8-H, CH-aromat.), 6.63 (s, 1H, NH), 6.43 (br s, 1H, NH), 3.34 (br s, 4H, 2× CH_2, imidaz.); ^{13}C NMR (50 MHz, DMSO-d_6) δ 165.2 (C4═O), 159.7 (C2-imidaz.), 149.5 (C2═O), 138.0, 133.8, 126.2, 125.8, 117.2, 116.7 (6C), 42.3, 42.2 (C4, C5-imidaz.). *Anal.* Calcd. for $C_{11}H_{10}ClN_5O_2$: C, 47.24; H, 3.60; N, 25.04. Found: C, 46.98; H, 3.34; N, 24.86.

3-(Imidazolidin-2-ylideneamino)-6-methylquinazoline-2,4(1*H*,3*H*)-dione isopropanol solvate (9d). Yield 0.33 g (27.0%). White solid, mp 270–274°C (*i*-PrOH). IR (KBr): v 3350, 3270 (NH), 1720, 1665 (C═O), 1620 (C═N), 1515, 1430 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 11.08 (br s, 1H, HN-C═O), 7.67 (s, 1H, 5-H, CH-aromat.), 7.40 (d, J = 7.8 Hz, 1H, CH-aromat.), 7.04 (d, J = 8.7, 1H, CH-aromat.), 6.55 (s, 1H, NH), 6.40 (br s, 1H, NH), 3.35 (br s, 4H, 2× CH_2), 2.32 (s, 3H, CH_3). *Anal.* Calcd. for $C_{12}H_{13}N_5O_2 \cdot i\text{-}C_3H_7OH$: C, 56.41; H, 6.63; N, 21.93. Found: C, 56.15; H, 6.52; N, 22.24.

X-ray crystal structure analysis. The intensity data for compounds **7e** and **9a** were collected and processed using Oxford Diffraction CrysAlis Software [42]. The structures were solved by direct methods with the program SHELXS-97 [43] and refined by full-matrix least-squares method on F^2 with SHELXL-97 [43].

Crystal data for 7e. $C_{11}H_{15}N_5O$, monoclinic, space group $P2_1/c$, a = 14.3956(5), b = 7.4546(2), c = 10.7744(3) Å, β = 103.572(3)°, V = 1123.95(6) $Å^3$, Z = 4, T = 120 K, d_x = 1.379 g cm^{-3}, μ(Mo Kα) = 0.095 mm^{-1}, 14,182 data were collected up to θ_{max} = 26.36° for a crystal with dimensions 0.5× 0.4× 0.3 mm^3 (R_{int} = 0.0141, R_σ = 0.0078). Final R indices for 2010 reflections with $I > 2\sigma(I)$ and 183 refined parameters are: R_1 = 0.0306, wR_2 = 0.0781 (R_1 = 0.0367, wR_2 = 0.0851 for all 2289 data).

Crystal data for 9a. $C_{11}H_{11}N_5O_2.H_2O$, orthorhombic, space group $Pna2_1$, a = 7.4518(2), b = 14.2418(3), c = 11.3435(3) Å, V = 1203.85(5) $Å^3$, Z = 4, T = 130 K, d_x = 1.453 g cm^{-3}, μ(Cu Kα) = 0.922 mm^{-1}, 6023 data were collected up to θ_{max} = 75.62° for a crystal with dimensions 0.4× 0.3 ×0.3 mm^3 (R_{int} = 0.0126, R_σ = 0.0102). Final R indices for 2209 reflections with $I > 2\sigma(I)$ and 188 refined parameters are: R_1 = 0.0275, wR_2 = 0.0764 (R_1 = 0.0276, wR_2 = 0.0764 for all 2217 data).

Crystallographic data for compounds **7e** and **9a** have been deposited with the Cambridge Crystallographic Data Centre, with the deposition Nos. CCDC 805482–805483.

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