Tautomerism of guanidines studied by ^{15}N NMR: 2-hydrazono-3-phenylquinazolin-4(3*H*)-ones and related compounds†

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2-Hydrazono-3-phenylquinazolin-4(3*H*)-ones **11a–i** are shown by ^{15}N NMR to exist in DMSO solution predominantly as the imino tautomers **B** and not the amino tautomers **A**. 2-Hydrazino-benzimidazole derivative **12** and 2-hydrazino-4,6-dimethylpyrimidine derivative **13** were found to exist predominantly as the amino tautomers.

Introduction

The tautomeric equilibria of heterocycles are of supreme importance in understanding the function of numerous biologically important components of living systems.[1] Thus the genetic code could only be deciphered after the dominant structures of the nucleotide bases were correctly represented. Moreover, it is now realized that the whole basis of evolution depends on the occurrence of minor proportions of the less stable nucleotide base tautomers which cause advantageous genetic mistakes.[2]

The tautomeric equilibria of heterocycles have been investigated extensively[3–6] and the following major trends are now clear as illustrated by Fig. 1: (i) most aminohetero-aromatic compounds exist predominantly in the amino form *cf.* **1** (and not the imino form *cf.* **2**) under normal conditions (aqueous solution or the crystalline state); (ii) under these conditions most (although not all) hydroxyheteroaromatic compounds exist predominantly in the tautomeric carbonyl form (for example 2-hydroxypyridine **3** and 4-hydroxypyridine **5** exist as 2-pyridone **4** and 4-pyridone **6** respectively); (iii) mercapto derivatives of 6-membered heteroaromatics tend to follow their hydroxy analogs and exist as thiones, *e.g.* **8**, and not as mercapto derivatives, *e.g.*, **7**. In contrast mercapto derivatives of five-membered heterocyclic rings exist as mercaptans (following the amino analogs); (iv) methyl groups and most substituted methyl substituents exist very largely in the methyl tautomer *e.g.* **9** and not in the possible methylene tautomer *e.g.* **10** which is far less stable.

Knowledge of the tautomerism of potential drugs is relevant to the modeling of their interaction with a receptor since different tautomers have different affinities for the receptor. It is thus also important in the tuning of a desired pharmacological activity.

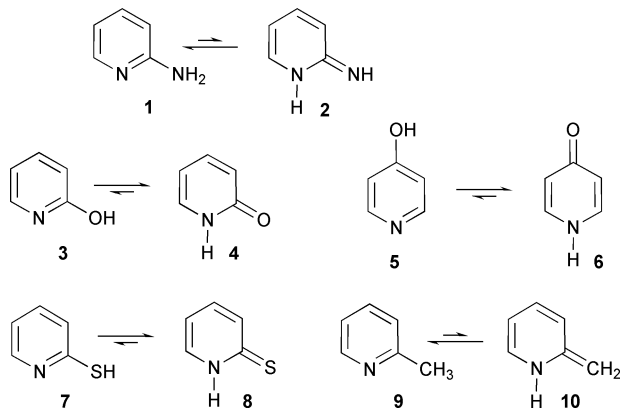

Fig. 1 Dominant tautomeric forms of amino-, hydroxy-, mercapto-, and methyl-pyridines.

The present paper discusses the tautomeric equilibrium of a set of 2-hydrazono-3-phenyl-3*H*-quinazolin-4-ones **11a–i**, all representatives of a group of compounds of intense current interest in the development of commercial drugs with analgesic and anti-inflammatory activity,[7–10] as well as the tautomerism of related 2-hydrazinobenzimidazole **12**, and 2-hydrazinopyrimidine **13** derivatives (Fig. 2).

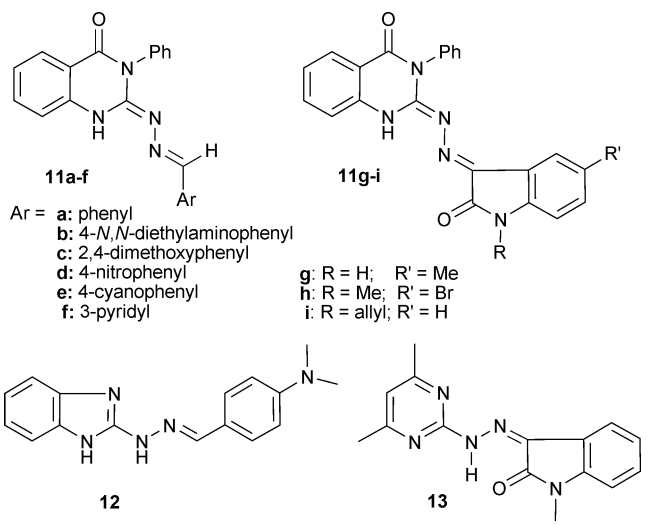

Fig. 2 Compounds under investigation.

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Tautomeric equilibria can depend significantly on the nature of the medium. There are two major inferences. Firstly, the dielectric constant of the medium is important and of course this can range from very low for the vapor phase and nonpolar solvents (favoring the tautomeric form with the lowest dipole moment) to very high for certain polar solvents (favoring the form with the highest dipole moment). The second major effect of the medium is the hydrogen bonding donor and acceptor ability of the solvent/medium, which can interact differently with different tautomeric forms. In the present paper we are dealing with equilibrium positions in DMSO as a solvent. Given the poor solubility of these compounds in water, this is probably the best medium to use for comparisons with biological systems.

Compounds **11a–i**, **12** and **13** could exist in two tautomeric forms, amino forms **A** and imino forms **B**, as shown in Fig. 3 for **11a–f**.

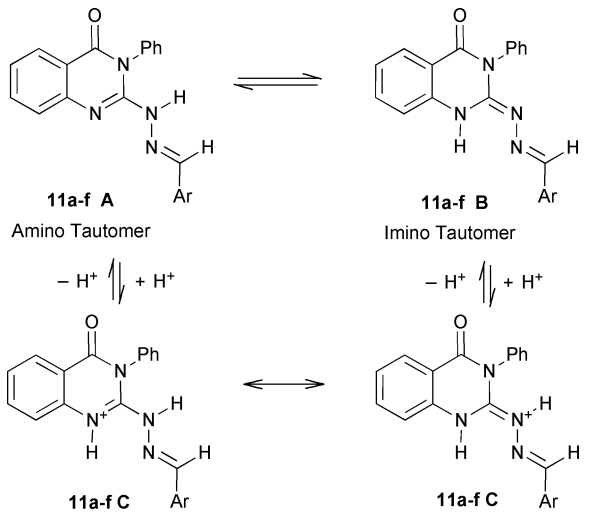


Fig. 3 Tautomers **A** and **B** of 2-hydrazino-3-phenylquinazolin-4(3*H*)-ones **11a–i** and their common cation **C**.

Apparently there has been no previous discussion published of the tautomerism of 2-hydrazinoquinazolin-4(3*H*)-ones **11**. The 404 hits for substructure **11** in a Beilstein search are depicted in the presumed amino form **11A** and none in the imino form **11B**. However, no supporting evidence such as interatomic distances or angles from solid state crystallographic data has been provided for their existence in the amino form **A**.

The tautomerism of 2-hydrazinopyrimidin-4(3*H*)-ones **14** (Fig. 4) has not been studied either. Derivatives of **14** are usually represented in the amino form **14A** (308 Beilstein hits). The 18 hits for the alternative imino **14B** form were perhaps due to the fact that they represent compounds synthesized from uracil.

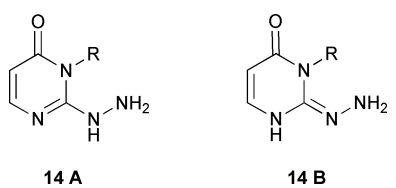


Fig. 4 Tautomers of 2-hydrazinopyrimidin-4(3*H*)-ones.

The tautomerism of the compounds **11a–i**, **12**, and **13** under investigation each involves a guanidine moiety **15**. In substituted guanidines **15a–c** (Fig. 5), the most stable tautomer is **15a** with the double bond attached to the nitrogen carrying the most electron-attracting substituent (*e.g.* R = NO_2, CN, -SO_2-C_6H_4-NH_2).[11]

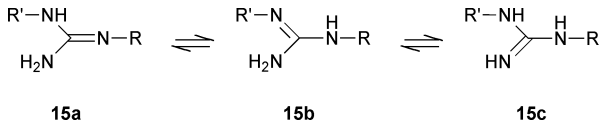


Fig. 5 Tautomers of disubstituted guanidines.

This can be rationalized by realizing that of the two exchangeable protons in the common cation (**11a–f C** in Fig. 3) the hydrogen attached to the most electronegative nitrogen is the most acidic. The experimental evidence for such tautomerism of guanidines includes ^{15}N NMR[12] and crystal structures.[13] When two of the guanidine nitrogens are part of an aromatic system, the 'most aromatic' tautomer is usually favored. The tautomerism of 2-aminopyrimidines has been studied extensively; both experimental data (low temperature IR spectroscopy)[14] and semiempirical and *ab initio* calculations[15,16] confirm the 2-amino tautomer as the most stable. Spectroscopic studies (UV, IR and ^{1}H NMR) of *N*-substituted-2-pyrimidinamine **16** (R = H, NO_2) show that neither the phenyl[17] nor the 2,4,6-trinitrophenyl[18] is electronegative enough to shift the equilibrium from the amino form **16a** to the imino form **16b** (Fig. 6).

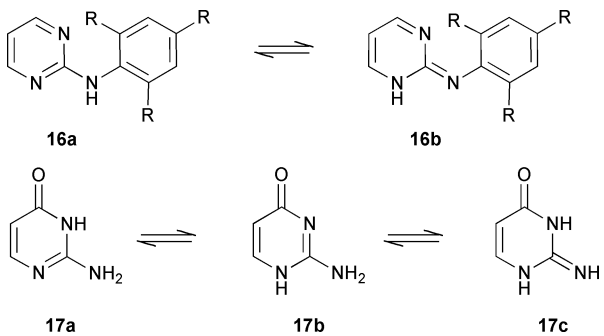


Fig. 6 Tautomers of 2-pyrimidinamine and of isocytosine.

2-Amino-3*H*-pyrimidin-4-one **17** (isocytosine), which was studied extensively, both experimentally[19–21] and computationally,[22] exists in aqueous solution mainly as 2-amino-3*H*-pyrimidin-4-one **17a** with some 2-amino-1*H*-pyrimidin-4-one **17b**. Calculations suggest the 2-imino form **17c**, not detected experimentally, is 5.6 kcal/mol less stable in aqueous solution than the 2-amino form **17b**.

The tautomerism of 2-hydrazinopyrimidine has apparently not been studied. 2-Quinolylhydrazones **18** (Fig. 7) exist in solution predominantly in the amino form **18a**, although the imino form was also detected.[23–25] In the solid state compounds **18** were found

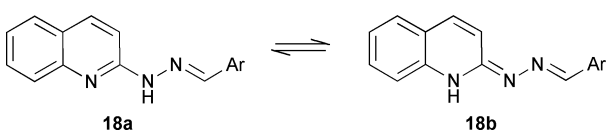


Fig. 7 Tautomeric forms of 2-quinolylhydrazones **18**.

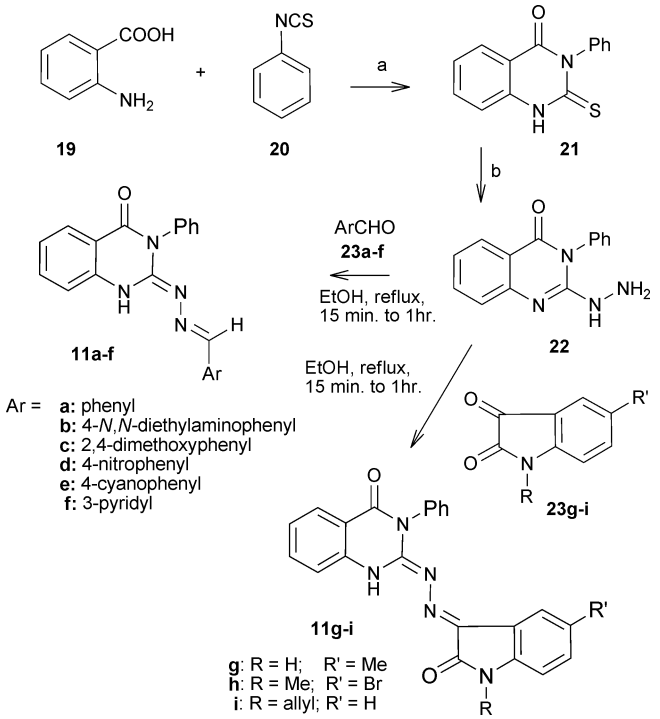
in the amino form when Ar = thienyl or 5-chlorothienyl and in the imino form when Ar = 5-bromo-2-thienyl.[26]

We aimed in the present work to identify the tautomeric preferences of the title compounds **11a–i**, **12**, **13**. The literature data presented above support both the 'most aromatic' amino form **A** and the imino form **B** which has the double bond on the most electronegative nitrogen. Since the two tautomeric forms differ in the protonation of two different nitrogens, ^{15}N NMR is the method of choice as a large difference in the chemical shifts of the alternative structures is expected. Measurement of the ^{15}N chemical shifts at natural abundance is now facile, with the advent of indirect detection and pulsed field gradients.[27,28]

Results and discussion

Syntheses

Products **11a–i** were prepared eventually by the literature procedure described in Scheme 1.[29]

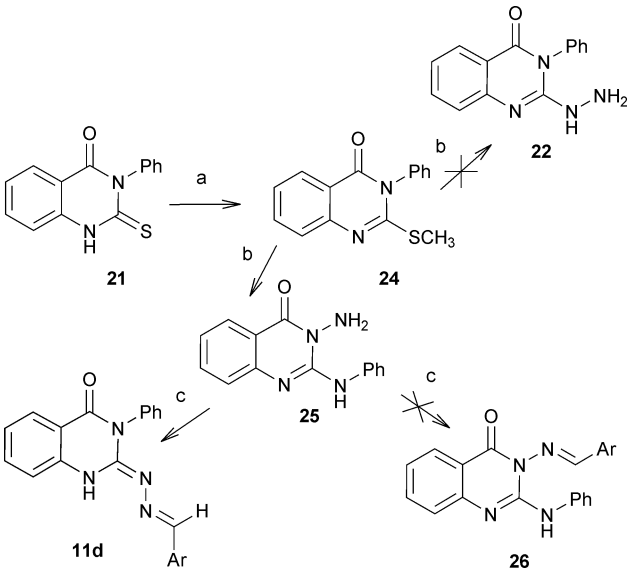


Scheme 1 Reagents and conditions: (a) EtOH, reflux 2 h; (b) *n*-BuOH, $N_2H_4{\cdot}H_2O$, reflux, 2 h.

Compounds **12** and **13** were prepared by condensing 2-hydrazino-1*H*-benzimidazole and 2-hydrazino-4,6-dimethylpyrimidine with 4-(dimethylamino)benzaldehyde and 1-methyl-1*H*-indole-2,3-dione respectively.

Our initial attempt to prepare compound **22** following the previously reported procedure[7,9,30–34] described in Scheme 2 gave instead 3-amino-2-anilino-4(3*H*)-quinazolinone **25**. There is a single literature report[29] of **25**, in which this compound was characterized only by melting point and elemental analysis.

Our proof for the structure of compound **25** is based on its NMR data. The nitrogen that couples with the *ortho* protons of the phenyl ring was at 102.2 ppm and carried the proton at 9.36 ppm. This proton couples with carbons C1′ and C5a′ (for numbering



Scheme 2 Reagents and conditions: (a) $(CH_3O)_2SO_2$, 2% ethanolic sodium hydroxide, rt, 1 h; (b) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 20 h; (c) EtOH, **23d**, reflux, 7 h.

see Experimental), and with three nitrogens at 187.5, 165.5, and 64.3. The nitrogen at 187.5 ppm was assigned to N1, because it couples with H8. The nitrogen at 64.3 has the chemical shift of an amino group and it carries two protons at 5.71. These latter protons couple with the nitrogen at 165.5 (N3 in **25**) and with two carbons, C4 and another one assigned as C2.

Compound **25** reportedly[29] condensed with benzaldehydes to give the corresponding Schiff's base **26** (Scheme 2). In our case **25** with *p*-nitrobenzaldehyde (**23d**), gave compound **11d** instead of the corresponding **26d**. The reaction was much slower than in the case of **22**.

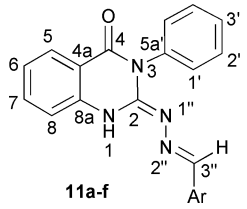
Tautomerism and NMR

^{1}H and ^{13}C chemical shifts were assigned based on the ^{1}H–^{1}H, and one-bond and long-range ^{1}H–^{13}C couplings, seen in the gDQCOSY, gHMQC and gHMBC spectra. They are presented in Tables 1, 2, 4 and 5.

A typical assignment started with identifying the sequence H5–H8 in the gDQCOSY spectrum. H5 and C4 would then be assigned by their cross-peak in the gHMBC spectrum. The ^{1}H–^{13}C gHMBC spectrum of **11b** is presented in Fig. 8. Cross-peaks of C4a with H6 and H8, and of C8a with H5 and H7 reveal these quaternary carbons. The phenyl protons, H1′–H3′ can be assigned from their intensity and coupling pattern. C5a′ couples with H2′.

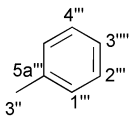
In 2-hydrazono-3-phenyl-3*H*-quinazolin-4-ones, **11a–f**, H3″, the singlet on a carbon at *ca.* 150 ppm couples with C1‴ and C5a‴. Other cross-peaks in the gHMBC spectrum were then used to complete the assignments on the substituted benzylidene moiety C1‴–C5a‴.

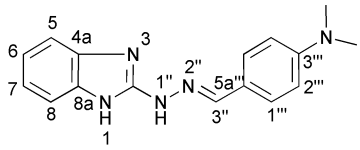
In 2-[*N*′-(2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazono]-3-phenyl-3*H*-quinazolin-4-ones **11h**,**i** having a substituent on N1‴, the α substituent protons couple with C7a‴. Carbon C7a‴ also couples with H6‴ and H4‴ which can be discriminated based on their multiplicity. Other cross-peaks in the gHMBC spectrum were then used to complete the assignments on the



11a-f

Ar = **a**: phenyl
b: 4-*N*,*N*-diethylaminophenyl
c: 2,4-dimethoxyphenyl
d: 4-nitrophenyl
e: 4-cyanophenyl
f: 3-pyridyl





12

Table 1 ^{1}H chemical shifts (ppm) in compounds **11a–f**, **12**, **21**, **22** and **24**

	Position													
Compd.	1	5	6	7	8	1′	2′	3′	3″	1‴	2‴	3‴	4‴	5‴
11a	10.61	7.91	7.16	7.69	7.69	7.34	7.49	7.40	8.07	7.93	7.41	7.38	7.41	7.93
11b	10.41	7.88	7.11	7.63	7.64	7.31	7.48	7.40	7.87	7.68	6.64	3.37, 1.09[a]	6.64	7.68
11c	nm[b]	8.00	7.37	7.83	8.04	7.49	7.61	7.59	8.59	3.80	6.60	3.83	6.65	8.38
11d	nm	7.97	7.22	7.72	7.72	7.36	7.52	7.44	8.19	8.16	8.21	—	8.21	8.16
11e	10.83	7.96	7.22	7.72	7.72	7.36	7.52	7.44	8.16	8.11	7.86	—	7.86	8.11
11f	10.68	7.94	7.18	7.70	7.70	7.35	7.50	7.42	8.12	9.09	—	8.55	7.43	8.31
12	nm	7.40	7.16	7.16	7.40	—	—	—	8.19	7.68	6.74	2.96	6.74	7.68
21	13.03	7.96	7.35	7.78	7.46	7.29	7.50	7.42	—	—	—	—	—	—
22[c]	8.87[d]	8.50	7.29	7.79	7.88	7.53	7.43	7.29	—	—	—	—	—	—
24	2.50[e]	8.10	7.49	7.84	7.65	7.47	7.58	7.58	—	—	—	—	—	—

[a] CH_2 and CH_3, correspondingly. [b] Not measured. [c] Measured in pyridine-d_5 at −30 °C. [d] H1″. [e] CH_3S in position 2.

Table 2 ^{13}C chemical shifts (ppm) in compounds **11a–f**, **12**, **21**, **22** and **24**

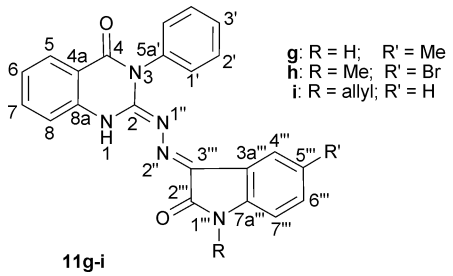
	Position																			
Compd.	2	4	4a	5	6	7	8	8a	1′	2′	3′	5a′	3″	1‴	2‴	3‴	4‴	5‴	5a‴	Other
11a	152.2	161.3	115.1	128.0	122.6	135.8	116.4	140.6	129.9	129.5	128.7	137.1	153.9	128.5	129.0	130.3	129.0	128.5	135.9	—
11b	150.6	161.3	114.9	128.1	122.1	135.7	116.2	140.8	130.0	129.6	128.6	137.3	154.5	130.3	111.4	149.3	111.4	130.3	122.6	44.4 (CH_2), 13.2 (CH_3)
11c	nm[a]	160.4	116.0	128.0	124.9	136.4	118.0	139.4	130.0	130.4	130.4	134.2	149.7	160.5	98.6	164.0	107.3	129.4	114.9	56.4 (CH_3O-1‴); 56.3 (CH_3O-3‴)
11d	nm	161.2	115.9	128.2	123.0	135.8	116.8	140.3	129.9	129.5	128.6	137.0	151.5	129.2	124.2	148.4	124.2	129.2	142.3	—
11e	nm	161.3	115.4	128.1	122.9	135.8	116.7	140.4	129.9	129.5	128.7	136.9	152.0	128.9	132.9	112.1	132.9	128.9	140.4	119.5 (CN)
11f	nm	161.4	115.3	128.1	122.7	135.8	116.4	140.5	129.9	129.5	128.6	137.0	151.0	149.8	—	150.7	124.3	135.1	131.7	—
12	nm	—	133.5	112.6	122.7	122.7	112.6	133.5	—	—	—	—	147.0	129.1	112.3	152.1	112.3	129.1	122.2	40.5 (CH_3)
21	nm	160.5	116.9	128.1	125.0	136.3	116.4	140.3	129.7	129.6	128.8	140.0	—	—	—	—	—	—	—	—
22[b]	nm	163.1	118.7	128.0	122.9	135.4	125.8	150.9	130.2	130.8	130.0	136.0	—	—	—	—	—	—	—	—
24	158.7	161.5	120.3	127.3	126.5	135.6	126.8	148.1	130.1	130.7	130.0	137.0	—	—	—	—	—	—	—	15.7 (CH_3)

[a] Not measured. [b] Measured in pyridine-d_5 at −30 °C.

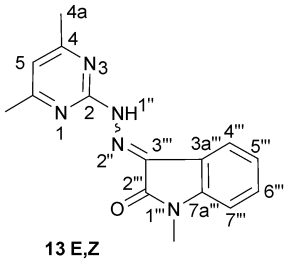
Table 3 ^{15}N chemical shifts (ppm) in compounds **11a–f**, **12**, **21**, **22** and **24**. Protons which couple to a ^{15}N are given in parentheses

	Position				
Compd.	1	3	1″	2″	Other
11a	100.4 (H8)	151.9 (H1′)	247.0 (H3″)	346.0 (H3″ 45)	—
11b	99.7 (H1, H8)	151.3 (H1″)	247.2 (H3″)	329.1 (H3″)	78.8 (H2‴, CH_2)
11c[a]	110.5 (H8)	156.3 (H1′)	nm	318.5 (H3″)	—
11d	113.9 (H8)	157.2 (H1′)	251.7 (H3″)	369.2 (H3″)	372.9 (H2‴)
11e[a]	nm[b]	157.1 (H1′)	251.1 (H3″)	361.2 (H3″)	—
11f	104.4 (H8)	156.4 (H1′)	251.2 (H3″)	354.7 (H3″)	318.2 (H1‴, H3‴, H4‴)
12	136.3 (H7,H8)	136.3 (H4,H5)	142.9 (H3″)	305.1 (H3″, H1‴)	55.5 (H2‴, CH_3)
21	150.9 (H1, H8)	191.1 (H1, H1′)	—	—	—
22[c]	183.9 (H8, H1″)	161.4 (H1′)	106.5 (H1″)	62.7 (H1″)	—
24	230.6 (H8)	180.6 (H1′)	—	—	—

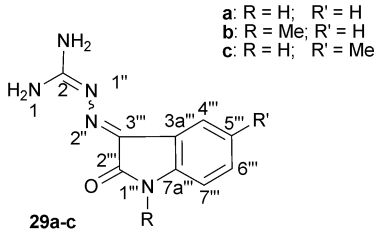
[a] Measured at 70 °C. [b] Not measured. [c] Measured in pyridine-d_5 at −30 °C.



11g-i



13 E,Z



29a-c

Table 4 ^{1}H chemical shifts (ppm) in compounds **11g–i** and **13**

	Position												
Compd.	1	5	6	7	8	1′	2′	3′	1‴	4‴	5‴	6‴	7‴
11g	11.70	7.99	7.27	7.75	7.75	7.45	7.60	7.53	10.42	6.81	1.97a	6.93	6.63
11h	11.76	8.01	7.33	7.77	7.87	7.45	7.60	7.55	3.14[a]	7.11	—	7.39	6.90
11i	11.80	8.03	7.29	7.75	7.86	7.45	7.60	7.55	[b]	6.94	6.59	7.19	6.85
13 (*E*)[c]	10.59[d]		6.86 (CH), 2.40 (CH_3)			—	—	—	3.19[a]	8.06	7.10	7.40	7.04
13 (*Z*)[c]	12.80[d]		6.85 (CH), 2.38 (CH_3)			—	—	—	3.24[a]	7.58	7.12	7.37	7.08

[a] CH_3. [b] 4.34 ($CH_2\alpha$), 5.83 (CHβ), 5.09 ($CH_2\gamma$, H-*cis* to Hβ), 5.12 ($CH_2\gamma$, H-*trans* to Hβ). [c] At 70 °C. [d] H1″.

Table 5 ^{13}C chemical shifts (ppm) in compounds **11g–i**, **13** and **29a–c**

	Position																			
Compd.	2	4	4a	5	6	7	8	8a	1′	2′	3′	5a′	2‴	3‴	3a‴	4‴	5‴	6‴	7‴	7a‴	Other
11g	nm[a]	161.2	116.1	128.0	123.8	136.1	117.2	140.0	129.6	129.9	129.3	137.3	166.8	144.8	118.2	128.0	131.0	131.9	109.0	141.0	21.3 (CH_3)
11h	nm	161.2	116.3	128.0	124.1	136.0	117.8	139.8	129.2	129.9	129.9	136.9	164.1	142.2	114.6	129.0	118.8	133.6	109.0	143.2	25.9 (CH_3)
11i	nm	161.2	116.3	128.1	123.9	138.0	117.6	140.0	129.6	130.0	128.8	137.0	164.9	nm	117.6	127.7	122.3	131.1	107.5	143.5	41.9 (Cα), 132.8 (Cβ), 117.2 (Cγ)
13 (*E*)[b]	nm	168.6	24.1	115.4	—	—	—	—	—	—	—	—	164.6	nm	116.2	125.5	122.7	131.7	107.4	144.5	—
13 (*Z*)[b]	nm	168.8	24.0	115.4	—	—	—	—	—	—	—	—	161.9	131.7	120.7	120.1	123.4	130.4	108.6	143.0	—
29a (*E*)[c]	—	—	—	—	—	—	—	—	—	—	—	—	166.8	134.6	118.9	125.5	120.8	128.1	109.0	140.7	—
29a (*Z*)[c]	—	—	—	—	—	—	—	—	—	—	—	—	158.9	132.2	124.3	118.5	120.6	127.1	109.0	139.6	—
29b (*E*)[c]	—	—	—	—	—	—	—	—	—	—	—	—	165.1	133.8	118.0	125.2	121.3	128.0	107.5	141.9	—
29b (*Z*)[c]	—	—	—	—	—	—	—	—	—	—	—	—	156.9	130.8	123.4	118.0	120.9	126.8	107.4	140.7	—
29c (*E*)[c]	—	—	—	—	—	—	—	—	—	—	—	—	166.8	134.8	118.9	126.1	129.4	128.4	108.6	138.5	—

[a] Not measured. [b] At 70 °C. [c] From ref. 40.

Table 6 ^{15}N chemical shifts (ppm) in compounds **11g–i** and **13**. Protons which couple to a ^{15}N are given in parentheses

	Position				
Compd.	1	3	1″	2″	1‴
11g	104.2 (H8)	156.7 (H1′)	nm[a]	377.6 (H1‴)	133.0 (H1‴, H7‴)
11h	109.4 (H8)	161.8 (H1′)	nm	nm	131.8 (CH_3, H7‴)
11i	105.1 (H8)	157.5 (H1′)	nm	nm	136.2 ($CH_2\alpha$, CHβ, H7‴)
13 (*E*)[b]	254.2 (CH_3)	nm	nm	nm	—
13 (*Z*)[b]	252.4 (CH_3, CH, NH)	164.3 (NH, CH)	340.0 (NH, H7‴)	133.1 (CH_3, H7‴, H6‴)	—

[a] Not measured. [b] At 70 °C.

substituted indole moiety C1‴–C7a‴. In compound **11g**, lacking the substituent on N1‴, H7‴ is the proton on a carbon at *ca.* 110 ppm.

A sharp signal of the exchangeable proton in compound **11b** afforded cross-peaks with C8, C8a, C4a and with another quaternary carbon, assigned as C2 (Fig. 8). This indicates that this exchangeable proton is linked to N1, meaning that **11b** is present in DMSO solution mainly as the imino tautomer. The chemical shift of C8, at *ca.* 117 ppm, further supports this assignment of tautomerism. Final proof for the imino tautomer comes from the one-bond cross-peak in the ^{1}H–^{15}N CIGAR spectrum (Fig. 9) between the exchangeable proton and the nitrogen at 99.7 ppm, which is N1, because it displays a long-range coupling with H8.

The X-ray structure of compound **11b** (Fig. 10) unambiguously demonstrated the imino tautomer in the solid state.[35]

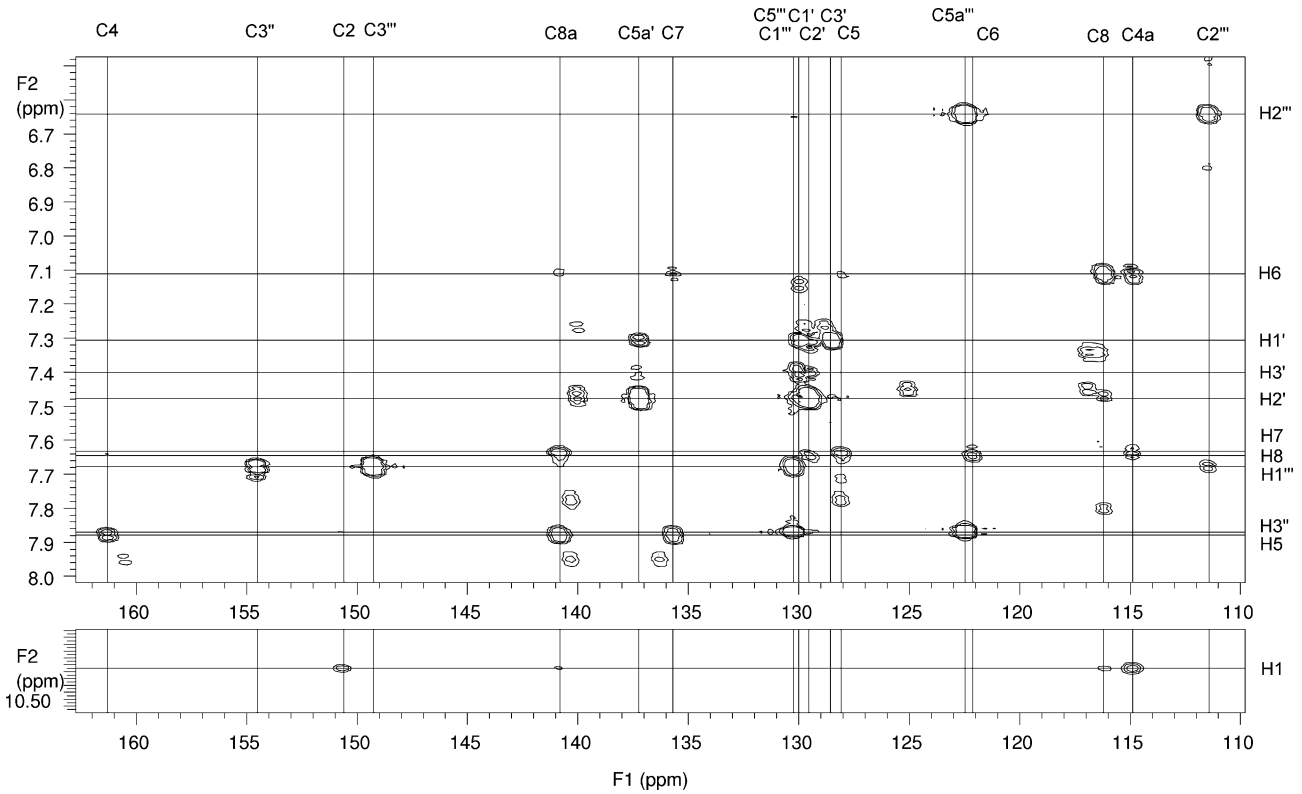


Fig. 8 Expansions of the ^{1}H–^{13}C gHMBC spectrum of compound **11b**.

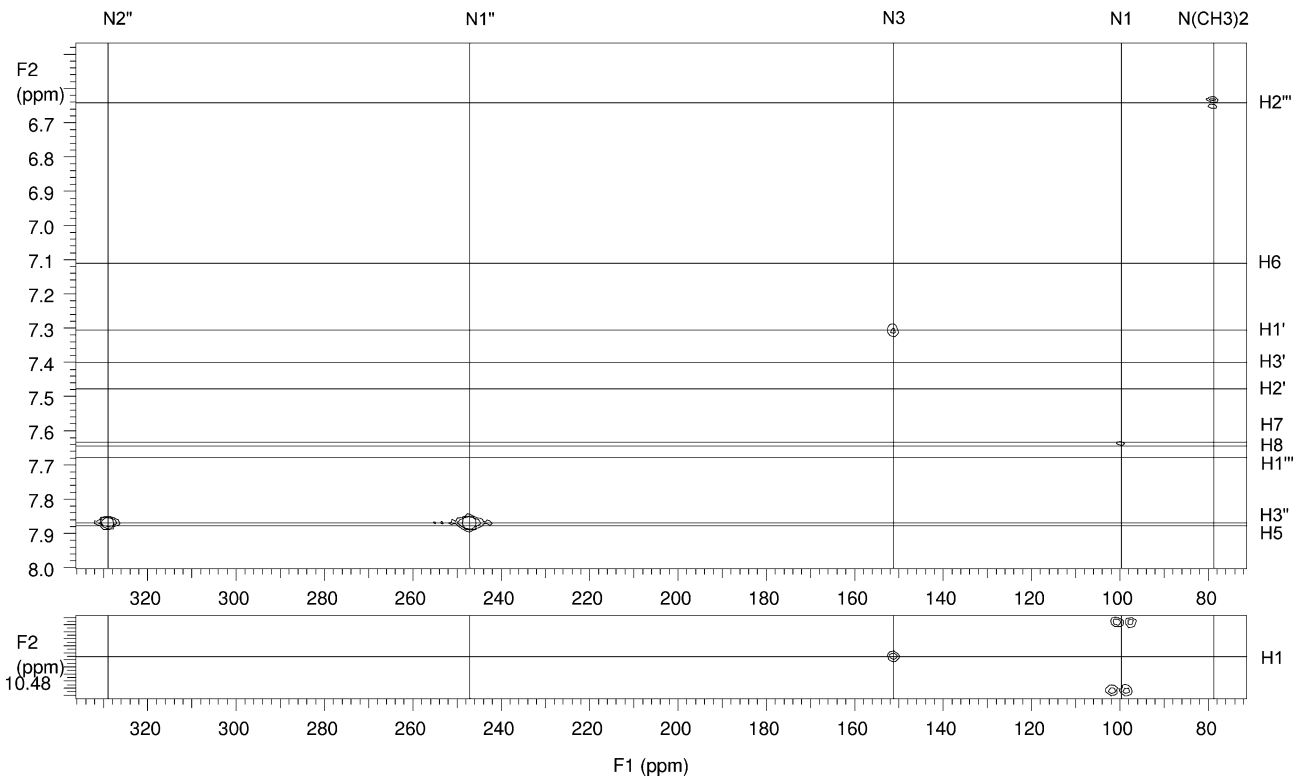


Fig. 9 Expansions of the ^{1}H–^{15}N CIGAR spectrum of compound **11b**.

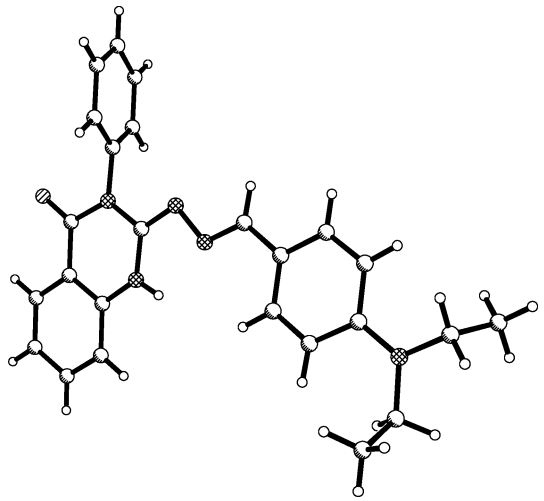


Fig. 10 X-ray structure of **11b**.

There is one more long-range cross-peak of the exchangeable proton in the ^{1}H–^{15}N CIGAR spectrum of **11b**, with one of the nitrogens three bonds away, which was assigned as N3 (151.3 ppm), because it also couples with H1′.

N1″ and N2″ both couple with H3″ only, therefore, they could not be discriminated based on their couplings with protons. Their chemical shifts, 329.1 and 247.2 ppm, are different enough however to allow for the assignment based on chemical shifts seen in related compounds. Particularly interesting is the example presented in Fig. 11, from the work of Bedford, Taylor and Webb,[36] of heterocycles that have the same sequence of nitrogen atoms as in aminoguanidines, in the amino form in **27**, and in the imino form in **28**. Based on the ^{15}N chemical shifts in compound **28**, the signal at 247.2 ppm was assigned to N1″, and the signal at 329.1 ppm to N2″.

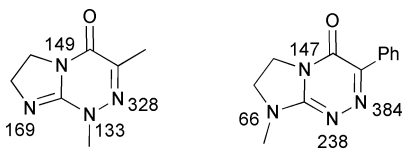


Fig. 11 ^{15}N chemical shifts in related heterocycles from ref. 36.

The heterocycles in Fig. 11 demonstrate that the chemical shifts of N1 and N1″ are good reporters of the amino–imino tautomerism of 2-hydrazono-3-phenyl-3*H*-quinazolin-4-ones, as a difference of *ca.* 100 ppm is to be expected in the two tautomers. The value of 99.7 ppm for N1 in **11b** is in the range found for N1 in a series of 2,3-dihydro-1*H*-quinazolin-4-ones, 92–100 ppm; in a series of quinazolin-4(3*H*)-ones N1 was at 253–270 ppm. In both series, N3 was at 140–190 ppm.[37]

Of all the compounds taken into this study, **11a** and **11b** were the only ones in which the signal of the exchangeable proton was sharp enough to afford cross-peaks in the ^{1}H–^{13}C gHMBC spectrum. Cross-peaks with C4a, C8 and C8a identified the imino tautomer. A cross-peak with C3‴ would have been a proof for the amino tautomer. For all of the other compounds, exchange with water or between tautomeric forms broadens the signal of the exchangeable proton too much for it to display any couplings with carbons or with nitrogens. In all of these cases, the tautomerism was assigned based solely on ^{15}N chemical shifts.

In both 2-hydrazono-3-phenyl-3*H*-quinazolin-4-ones **11a–f** and in the 2-[*N*′-(2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazono]-3-phenyl-3*H*-quinazolin-4-ones **11g–i**, N1 displayed a cross-peak with H8 in the CIGAR spectrum. The range of chemical shifts for N1 was 100–114 ppm (Tables 3 and 6). In the first series, the chemical shift of N1″ was detected through the coupling between N1″ and H3″. The values for N1″ chemical shifts were 247–251 ppm. These chemical shifts identify the imino form as the prevalent tautomer in solution for compounds **11a–i**. The N1 chemical shift is expected to depend mainly on the position of the tautomeric equilibrium, and could be used to estimate this position, if values in the two tautomers are known.

When the guanidine is part of a more aromatic structure, the amino form would prevail. This is demonstrated by compounds **12** and **13**. In **12**, rapid exchange of the proton between N1 and N3 (numbering relative to the aminoguanidine moiety, as in **11a–i**) produced an AA′XX′ pattern for the signals of H5–H8. The NH protons were in fast exchange with the residual water in DMSO-d_6, and did not produce a separate signal. The chemical shift of N1, N3 was revealed by coupling with H5, H8; cross-peaks with H3″ revealed N1″ and N2″. The chemical shifts in the pair N1″, N2″, (142.9, 305.1) were closer to the values in **27** (133, 328) than to the values in **28** (238,384), indicating that compound **12** is present in DMSO solution predominantly in the amino form. The chemical shift of the azole nitrogen cannot be used for the assignment of the tautomerism, at least in the presence of fast exchange. The value in **12**, 136.3 ppm, is closer to the value for N1 in 1-methyl-2-amino-benzimidazole (134.6 ppm), than to their average (N3 is at 191.9 ppm), which would suggest that **12** is in the imino form. However, in 1-methyl-benzimidazole N1 and N3 are at 143.8 and 243.9 ppm, correspondingly, while in benzimidazole, the equivalent nitrogens are at 143.2 ppm.[38]

Compound **13** did not dissolve in DMSO-d_6 at room temperature, but it did at 70 °C. About 30 minutes after dissolution, the proton spectrum of **13** displayed the signals of two compounds, in a ratio 2:1. ^{1}H–^{13}C correlations indicated that both compounds contain the 4,6-dimethylpyrimidine and the 1,3-dihydro-indole-2-one moieties. After one day, the sample consisted entirely of what was initially the minor compound. Correlations to the methyl protons identified the pyrimidine nitrogens at 254.2 and 252.4 ppm in the initially major and minor compounds, correspondingly (Table 6). These values are comparable to the one in 2-amino-4,6-dimethylpyrimidine, at 242 ppm,[39] indicating that both isomers are in the amino form. Further evidence comes in the case of the initially minor compound, which displayed a sharp signal for the exchangeable proton at 12.80. This proton is on the nitrogen at 164.3, and displays long-range couplings with the nitrogens at 252.4 and 340.0 ppm. Being both the amino tautomers, these two isomers have to differ in the configuration of the C3‴=N2″ double bond. The sharp, deshielded signal of the NH proton in the initially minor compound suggests an intramolecular hydrogen bond, possible only in the *Z* isomer. Some of the signals in the other isomer, *E*, are broadened, particularly H4‴ and the pyrimidine CH. This has to do with restricted rotation. The bonds to be considered as having partial double bond character are C2–N1″ and N1″–N2″. Restricted rotation about C2-N1″ would produce broadening of the signals of the methyl groups in the

4,6-dimethylpyrimidine moiety, but not of the pyrimidine CH or of H4‴. Broadening of these latter signals is due to restricted rotation about the N1″–N2″ bond (Fig. 12). The assignment of the *Z* and *E* isomers was also confirmed by ^{13}C chemical shifts, as described further on.

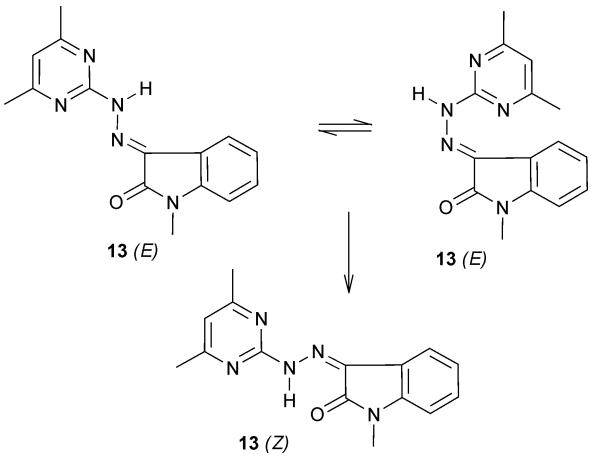


Fig. 12 Isomers/rotamers of compound **13**.

Discrimination between compounds **22** and **25** was possible only based on the ^{15}N NMR data. The ^{1}H–^{15}N correlations are presented in the experimental part for **25** and in Table 3 for **22**. N1 was identified in both compounds by its cross-peak with H8 in the CIGAR-gHMBC spectrum. Chemical shift values for N1 of 183.9 ppm in **22** and 188.0 ppm in **25** demonstrate that these compounds are both present in solution predominantly as the amino tautomer. This is to be expected for **25**, in which the exocyclic guanidine nitrogen does not carry another nitrogen. The preference for the amino tautomer of **22** is surprising, considering that its derivatives **11a–i** prefer the imino form, and can be explained by the greater electronegativity of N2″ in the latter compounds. The substituents on N1″ could be used to control the tautomeric equilibrium of 2-hydrazino-3-substituted-quinazolin-4(3*H*)-ones and related compounds, in order to fine tune their pharmacological and optical properties.

Stereochemistry of the C=N bonds

The barrier to rotation about a C=N bond is smaller than that about a C=C bond, and decreases with the electronegativity of the substituents on the N atom. In hydrazones, often the *E* and *Z* forms equilibrate in a matter of hours or days.[40] NOe experiments when both forms were available identified the isomers and demonstrated that ^{13}C chemical shifts can be diagnostic for the stereochemistry. Particularly, carbons *alpha* to the C=N carbons are shifted upfield when *syn* to the vicinal nitrogen, relative to the situation when they are *anti.* This is the *gamma* effect and it is due to steric compression.

The *E–Z* pairs of the related isatin guanylhydrazones[41] **29a** and **29b** (Table 5) display ^{13}C chemical shift differences of *ca.* 6 ppm in positions 2‴, 3a‴ and 4‴. The ^{13}C chemical shifts of these positions in **11g–i** demonstrate the *E* configuration for the C3‴=N2″ double bond in these compounds. The chemical shifts of the same positions in **13** *(E)* and **13** *(Z)* confirm the assignment.

The X-ray structure of **11b** (Fig. 10) shows the *E* configuration of the C3‴=N2″ double bond. Since this is the expected configuration of hydrazones of aldehydes[40] it is reasonable to assume it for all of the compounds **11a–f**.

The C2 =N1″ double bond is in the *E* configuration in **11b**. The same configuration is expected for all of **11a–i**, because the 2-hydrazono-3-phenyl-3*H*-quinazolin-4-one moiety is common to all of these compounds. The *Z* configuration would be higher in energy due to the steric hindrance between the phenyl in position 3 and N2″. Besides, there is a hydrogen bond between H1 and N2″, which stabilizes the *E* form.

Conclusions

^{15}N NMR is a powerful technique for the elucidation of tautomerism involving protonation of a nitrogen atom, since a large chemical shift difference, *ca.* 100 ppm, is expected for that nitrogen between the two tautomeric forms. ^{15}N chemical shifts can be measured by indirect detection, through coupling of the nitrogen reporter of tautomerism with non-exchangeable protons 2 or 3 bonds away. On typical samples of 15–30 mg, at natural abundance of ^{15}N, the total experiment time was a couple of hours.

2-(2-Substituted-methylenehydrazinyl)-3-phenylquinazolin-4(3*H*)-ones (**11a–i**) in DMSO solution were found to be predominantly in the imino form, following the tautomeric preferences of the aminoguanidines.

2-Hydrazino-3-phenyl-3*H*-quinazolin-4-one (**22**) itself is in the amino form, demonstrating that the terminal nitrogen in the hydrazine moiety has to be involved in a double bond for the imino form to prevail.

When the 3,4-dihydro-4-oxo-3-phenylquinazolin-2-yl moiety of **11a–i** is replaced by a more aromatic one, as benzimidazol-2-yl in **12** or 4,6-dimethylpyrimidin-2-yl in **13**, the amino tautomer dominates the equilibrium in DMSO solution.

Experimental

General

Melting points were determined on a capillary point apparatus equipped with a digital thermometer.

The NMR spectra were recorded on a Varian Inova instrument, operating at 500 MHz for ^{1}H, 125 MHz for ^{13}C and 50 MHz for ^{15}N, equipped with a three channel, 5 mm, indirect detection probe, with z-axis gradients. The solvent was DMSO-d_6, and the temperature was 25 °C, unless specified otherwise. The chemical shifts for ^{1}H and ^{13}C were referenced to the residual solvent signal, 2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C, on the tetramethylsilane scale. The chemical shifts for ^{15}N were referenced to $\Xi = 10.1328898$, corresponding to 0 for neat ammonia. On the Ξ scale the frequency of protons in tetramethylsilane is 100.0000000 MHz. For conversion to the neat nitromethane scale, subtract 381.7 ppm.[27]

^{1}H spectra were acquired in one transient, with a 90° pulse, no relaxation delay and an acquisition time of 5 s, over a spectral window from 16 to –2 ppm. The FID was zero-filled to 131072 points prior to Fourier transform.

Typically, ^{1}H–^{13}C gHMBC spectra were acquired in 2048 points in *f2*, on a spectral window from 6.5 to 11 ppm, and 1 s relaxation

delay. In *f1*, 256 increments were acquired in 1 transient over a spectral window from 110 to 170 ppm, then the corresponding FID's were zero-filled twice prior to the second Fourier transform.

^{1}H–^{15}N CIGAR-gHMBC spectra were acquired with a pulse sequence optimized for ^{15}N, as decribed in ref. 42. 2048 points were acquired in *f2*, over a spectral window typically from 6.5 to 11 ppm, with 1 s relaxation delay. 1024 increments were acquired in *f1*, on a spectral window from 0 to 400 ppm, and the corresponding FID was zero-filled twice prior to Fourier transform. The accordion delay was optimized for a value of ^{1}H–^{15}N coupling constants between 3 and 10 Hz. The number of transients per increment was between 4 and 64, depending on the concentration of the sample. Total experiment time was in most cases, *ca.* 2 h.

Preparation of 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (21). Anthranilic acid (1.37 g, 0.01 mol) and phenylisothiocyanate (1.35 g, 0.01 mol) were refluxed in 50 mL ethanol for 2 hours. The solid obtained was filtered off and purified by crystallization from DMF: white microcrystals (2.03 g, 80%), m.p. 313–315 °C [Lit. m.p. 300 °C].[29] Anal. Calcd. for $C_{14}H_{10}N_2OS$ (254.31): C, 66.12; H, 3.96; N, 11.02. Found: C, 66.11; H, 3.78; N, 10.94.

Preparation of 2-hydrazino-3-phenylquinazolin-4(3*H*)-one (22). A mixture of 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **21** (0.25 g, 1 mmol) and hydrazine hydrate (99%, 0.05 g, 10 mmol) was refluxed in butanol for 3 h. After the reaction was cooled down, a white precipitate was separated. This precipitate was recrystallized from *n*-butanol to give the desired product in 79% yield (0.20 g, 0.8 mmol). White needles, m.p. 193–195 °C [Lit. m.p. 202–203 °C].[29] Anal. Calcd. for $C_{14}H_{12}N_4O$ (252.28): C, 66.65; H, 4.79; N, 22.21. Found: C, 66.27; H, 4.70; N, 21.96.

General procedure for preparing compounds 11a–i

2-Hydrazinyl-3-phenylquinazolin-4(3*H*)-one **22** (0.25 g, 1 mmol) was heated under reflux in ethanol (25 mL) for 15 min. to 1 h with 1 mmol of the corresponding aldehyde or ketone **23a–i**. The precipitate formed was collected and crystallized from the appropriate solvent to give the desired products in quantitative yields.

(*E*)-2-((*E*)-Benzylidenehydrazono)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (11a). The product was crystallized from EtOH to give white needles (98%), m.p. 215–217 °C [Lit. m.p. 218 °C].[29] Anal. Calcd. for $C_{21}H_{16}N_4O$ (340.39): C, 74.10; H, 4.74; N, 16.46. Found: C, 74.21; H, 4.63; N, 16.46.

(*E*)-2-((*E*)-(4-(Diethylamino)benzylidene)hydrazono)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (11b). The solid obtained was crystallized from DCM/hexanes to give the desired product as yellow needles (97%), m.p. 202–204 °C. Anal. Calcd. for $C_{25}H_{25}N_5O$ (411.51): C, 72.97; H, 6.12; N, 17.02. Found: C, 72.81; H, 6.12; N, 17.11.

(*E*)-2-((*E*)-(2,4-Dimethoxybenzylidene)hydrazono)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (11c). The solid obtained was filtered off and crystallized from *n*-butanol to give yellow microcrystals (98%), m.p. 257–259 °C. Anal. Calcd. for $C_{23}H_{20}N_4O_3$ (400.44): C, 68.99; H, 5.03; N, 13.99. Found: C, 68.73; H, 5.02; N, 13.79.

(*E*)-2-((*E*)-(4-Nitrobenzylidene)hydrazono)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (11d). The precipitate formed was collected and crystallized from *n*-butanol to give yellow microcrystals (97%), m.p. 275.0–277.0 °C [Lit. m.p. 260–262 °C].[7] Anal. Calcd. for $C_{21}H_{15}N_5O_3 \cdot 1/3\ H_2O$ (391.39): C, 64.44; H, 4.03; N, 17.89. Found: C, 64.66; H, 3.85; N, 17.67.

4-((*E*)-((*E*)-(4-Oxo-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-ylidene)hydrazono)methyl)benzonitrile (11e). The precipitate formed was collected and crystallized from *n*-butanol to give pale yellow microcrystals (90%), m.p. 312–314 °C. Anal. Calcd. for $C_{22}H_{15}N_5O$ (365.40): C, 72.32; H, 4.14; N, 19.17. Found: C, 72.07; H, 3.99; N, 19.03.

(*E*)-3-Phenyl-2-((*E*)-(pyridin-3-ylmethylene)hydrazono)-2,3-dihydroquinazolin-4(1*H*)-one (11f). The precipitate formed was collected and crystallized from *n*-butanol to give white crystals (97%), m.p. 216.0–217.0 °C. Anal. Calcd. for $C_{20}H_{15}N_5O.H_2O$ (359.39): C, 66.84; H, 4.77; N, 19.49. Found: C, 67.04; H, 4.56; N, 19.38.

(*E*)-2-((*E*)-(5-Methyl-2-oxoindolin-3-ylidene)hydrazono)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (11g). The product was crystallized from *n*-butanol to give pale yellow needles (96%), m.p. 348–350 °C [Lit. m.p. not reported].[43] Anal. Calcd. for $C_{23}H_{17}N_5O_2.H_2O$ (413.44): C, 66.82; H, 4.63; N, 16.94. Found: C, 66.66; H, 4.50; N, 16.88.

(*E*)-2-((*E*)-(5-Bromo-1-methyl-2-oxoindolin-3-ylidene)hydrazono)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (11h). The product was crystallized from EtOH to give orange needles (95%), m.p. 363–365 °C. Anal. Calcd. for $C_{23}H_{16}BrN_5O_2$ (474.32): C, 58.24; H, 3.40; N, 14.77. Found: C, 57.98; H, 3.35; N, 14.60.

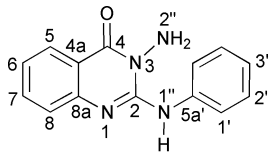
(*E*)-2-((*E*)-(1-Allyl-2-oxoindolin-3-ylidene)hydrazono)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (11i). The product was crystallized from EtOH to give yellow needles (84%), m.p. 242–244 °C. Anal. Calcd. for $C_{25}H_{19}N_5O_2.H_2O$ (474.32): C, 68.33; H, 4.82; N, 15.94. Found: C, 68.79; H, 4.58; N, 15.94.

4-[(2-(1*H*-Benzimidazol-2-yl)hydrazono)methyl]-*N*,*N*-dimethylaniline (12). 2-Hydrazinyl-1*H*-benzoimidazole (0.074 g, 0.5 mmol) was heated under reflux in ethanol (25 mL) with 4-(dimethylamino)benzaldehyde (0.075 g, 0.5 mmol) for 3 h. The precipitate formed was collected and crystallized from EtOH to give brown microcrystals (50%), m.p. 262–264 °C [Lit. m.p. 245 °C].[44] HRMS (ESI) calcd. for $C_{16}H_{17}N_5$ $(MH)^+$ 280.1557, found 280.1557.

3-[2-(4,6-Dimethylpyrimidin-2-yl)hydrazono]-1-methylindolin-2-one (13). 2-Hydrazinyl-4,6-dimethylpyrimidine (0.069 g, 0.5 mmol) was heated under reflux in ethanol (25 mL) with 1-methyl-1*H*-indole-2,3-dione (0.08 g, 0.5 mmol) for 1 h. The precipitate formed was collected and purified by column chromatography using ethyl acetane/hexanes (1:3) as an eluent system. The sharp yellow needle crystals were pure enough for elemental analysis. This compound was obtained in 71% yield and had m.p. 191–193 °C. Anal. Calcd. for $C_{15}H_{15}N_5O \cdot 1/4\ H_2O$ (285.83): C, 63.03; H, 5.47; N, 24.50. Found: C, 63.32; H, 5.39; N, 24.10.

Preparation of 2-(methylsulfanyl)-3-phenyl-4(3*H*)-quinazolinone (24). This compound was prepared according to the literature method.[35] The solid obtained was crystallized from

dichloromethane/diethyl ether to give compound **24** as colorless needles (75%), m.p. 118–120 °C [Lit. m.p. 124–126 °C].[7] Anal. Calcd. for $C_{15}H_{12}N_2OS$ (268.34): C, 67.14; H, 4.51; N, 10.44. Found: C, 67.36; H, 4.50; N, 10.46.



25

Preparation of 3-amino-2-anilino-4(3*H*)-quinazolinone (25)

This compound was prepared according to the literature method.[29] The solid obtained was crystallized from dichloromethane/hexanes to afford compound **25** as colorless prisms (80%), m.p. 153–155 °C [Lit. m.p. 151°C].[29] ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H, H1″), 8.00 (dd, J = 7.9, 1.3 Hz, 1H, H5), 7.93 (dd, J = 8.7, 1.1 Hz, 2H, H1′), 7.65 (ddd, J = 8.5 Hz, 7.2, 1.7, 1H, H7), 7.39 (d, J = 8.1 Hz, 1H, H8), 7.36 (t, J = 8.0 Hz, 2H, H2′), 7.23 (ddd, J = 8.0, 7.9, 1.1 Hz, 1H, H6), 7.07 (tt, J = 7.4, 1.0 Hz, 1H, H3′), 5.72 (s, 2H, H2″). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7 (C4), 148.7 (C2), 148.4 (C8a), 139.3 (C5a'), 134.9 (C7), 129.3 (C2′), 126.8 (C5), 125.8 (C8), 123.6 (C3′), 123.4 (C6), 121.2 (C1′), 118.3 (C4a). ^{15}N NMR (50 MHz, DMSO-d_6) δ 188.0 (N1), 164.4 (N3), 101.9 (N1″), 64.1 (N2″). Anal. Calcd. for $C_{14}H_{12}N_4O$ (252.28): C, 66.65; H, 4.79; N, 22.21. Found: C, 66.45; H, 4.73; N, 22.34.

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