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N′-(3-Amino-1*H*-isoindol-1-ylidene)-R-carbohydrazides and Their Amide-Type Isomerism

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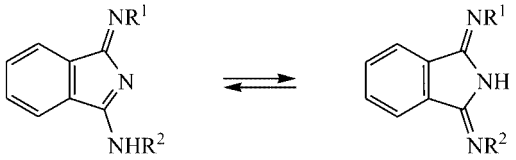
A series of *N′*-(3-amino-1*H*-isoindol-1-ylidene)alkyl(aryl,heteroaryl)carbohydrazides have been synthesized in good yields and their structure and conformational behavior in the solid state and in solution have been studied by X-ray crystallography, NMR spectroscopy, and quantum calculations. (*E*)/(*Z*) amide-type isomerism and the dependence of the isomeric ratio upon steric effects and solvent polarity are discussed. The thermodynamic parameters of (*E*) ⇄ (*Z*) isomerization were determined by ^{1}H NMR dynamic spectroscopy.

Introduction

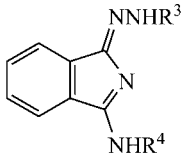
1-Imino-1*H*-isoindol-3-amine, or 3-amino-1-imino-1*H*-isoindole (**1**), usually known as 1,3-diiminoisoindoline, is a key compound in phthalocyanine synthesis and one of the most important feedstocks for phthalogen dyestuffs.[1,2] Its derivatives have been studied mostly from the point of view of their use as dyestuffs or metal-chelating agents, but very little data concerning their biological activities can be found in the literature.

Some papers reporting on the investigation of 1,3-disubstituted 1,3-diiminoisoindolines as potential C3a antagonists have recently been published.[3] Another publication describes the in vivo activity of compounds similar to 3-amino-1-imino-1*H*-isoindole in a carrageenan-induced edema assay in mice.[4]

The derivatives of 1-imino-1*H*-isoindol-3-amine (**1**) that have been described in the literature mostly contain aliphatic or aromatic residues on one (**2**) or two (**3**) of the exocyclic nitrogen atoms but a few of them contain hydrazide moieties. 3-Amino-1*H*-isoindol-1-one hydrazone (**4**), a monohydrazine analog of **1**,[5] and some of its *N*-acyl derivatives **5**–**7**[6,7] are among them.



1 $R^1 = R^2 = H$
2 R^2 = Alk or Ar, $R^2 = H$
3 $R^1 = R^2$ = Alk or Ar



4 $R^3 = R^4 = H$
5 R^3 = C(O)R, $R^4 = H$
6 $R^3 = C(O)CH_3$, $R^4 = NHC(O)CH_3$
7 $R^3 = R^4 = C(O)CH_3$

These derivatives are of great potential interest owing to a combination in their structures of an isoindole nucleus and a pharmacophoric hydrazide group since some acid hydrazides are known to have strong therapeutic effects and can offer efficient antitubercular treatment.[8]

Compounds **5**, which can be considered as mono-*N*-acylated derivatives of 3-amino-1*H*-isoindol-1-one hydrazone (**4**), are, however, not available by direct acylation owing to the presence of multiple reaction centers in the molecule at which the acylation could take place.

Monosubstituted derivatives **5** having only one hydrazide residue have been formed by the Bayer method[6] from 1-imino-1*H*-isoindol-3-amine (**1**) and hydrazides of nicotinic and pyromucic acids. As claimed in a patent,[9] the reaction of phthalonitrile with acetic acid hydrazide leads to the for-

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mation of disubstituted isoindole derivatives **6** possessing two hydrazide moieties. Analogous *N*,*N*′-diacetylated 3-amino-1*H*-isoindol-1-one hydrazone (**7**) is also available by acetylation of **4** with acetic acid anhydride.[7] The starting material, 3-amino-1*H*-isoindol-1-one hydrazone (**4**), can be synthesized by alkoxide-catalyzed addition of hydrazine to phthalonitrile.[5] The reaction of 1-imino-1*H*-isoindol-3-amine (**1**) with hydrazine hydrate leads to either 1,4-diaminophthalazine by ring expansion or under more drastic conditions (in boiling butanol) 1,4-dihydrazinophthalazine, as in the well-known phthalimide hydrazinolysis.[2,5,10]

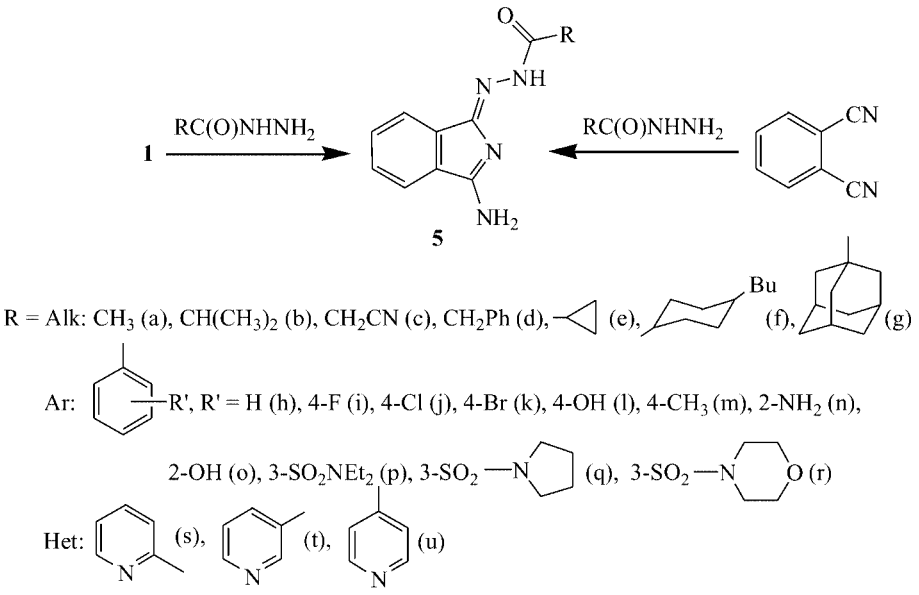
In this paper we describe an easy and efficient synthesis of a series of hydrazide derivatives of 1-imino-1*H*-isoindol-3-amine **5**. These compounds can display three tautomeric forms **A**, **B**, or **C** (see Figure 1) and they can exist as (*Z*) and (*E*) isomers around the C=N, N–N, and N–CO bonds. Furthermore, the NMR spectra of these compounds have allowed various ratios of two isomers to be distinguished; from these observations the interesting problem of resonance assignment has become apparent. In this paper we report on an investigation of the structural and conformational behavior of these compounds by conformational, crystallographic, and theoretical methods.

Results and Discussion

In this work we attempted to extend our investigations on the synthesis and structure determination of hydrazide derivatives of 1-imino-1*H*-isoindol-3-amine (**1**). We have examined the two known synthetic pathways that can lead to the desired compounds **5** starting from **1** as well as its precursor phthalonitrile (Scheme 1, Table 1).

Use of the Bayer method[6] allowed the synthesis of a series of *N*′-(3-amino-1*H*-isoindol-1-ylidene)alkyl(aryl,heteroaryl)carbohydrazides **5** in good yields starting from unsubstituted 1-imino-1*H*-isoindol-3-amine (**1**) and a wide range of acid hydrazides.

We have demonstrated that such compounds could, in addition, be easily obtained in high yields by using a published procedure[9] starting from phthalonitrile and the corresponding hydrazide in methanol in the presence of catalytic amounts of potassium or sodium hydroxide. The sec-



Scheme 1.

Table 1. Preparation of *N*′-(3-amino-1*H*-isoindol-1-ylidene)alkyl(aryl,heteroaryl)carbohydrazides **5**.

Compound	Method[a]	Yield [%]	Isomer[b]	Compound	Method[a]	Yield [%]	Isomer[b]
5a	A/B	93/90	(*Z*) + (*E*)	**5l**	A	89	(*Z*)
5b	B	96	(*Z*) + (*E*)	**5m**	A/B	76/72	(*Z*)
5c	A/B	32/28	(*Z*) + (*E*)	**5n**	A/B	88/83	(*Z*)
5d	A/B	75/78	(*Z*) + (*E*)	**5o**	A	94	(*Z*)
5e	A	78	(*Z*) + (*E*)	**5p**	A	78	(*Z*) + (*E*)
5f	B	98	(*Z*) + (*E*)	**5q**	A	72	(*Z*) + (*E*)
5g	A	96	(*Z*)	**5r**	A	78	(*Z*) + (*E*)
5h	A/B	94/91	(*Z*)	**5s**	B	90	(*Z*)
5i	B	71	(*Z*)	**5t**	B	84	(*Z*) + (*E*)
5j	B	88	(*Z*)	**5u**	B	90	(*Z*) + (*E*)
5k	B	85	(*Z*)	–	–	–	–

[a] Method A: **1**, acid hydrazide, MeOH or EtOH, reflux. Method B: phthalonitrile, acid hydrazide, MeOH or EtOH, catalytic amount of KOH or NaOH, reflux. [b] Determined by NMR spectroscopy.

ond method seems to be more convenient as it allows target compounds to be synthesized directly from phthalonitrile and does not involve 1-imino-1*H*-isoindol-3-amine (**1**) as an intermediate product.

Selectivity is the main advantage of this reaction, which, irrespective of the reaction conditions used [excess of the acid hydrazide, the nature of the substituents (alkyl, aryl, or heteroaryl)], leads to the formation of monosubstituted *N′*-(3-amino-1*H*-isoindol-1-ylidene)alkyl(aryl,heteroaryl)-carbohydrazides **5**, in contrast to the results of experiments previously described by Titkov et al.[9]

Moreover, an attempted substitution of the free amino group of **5a** by the action of a primary amine (benzylamine or 4-bromoaniline) in boiling MeOH or DMF failed. Such a result is different to that observed for the reaction of compounds **1** or phthalonitrile with primary aromatic amines: Depending on the amount of amine used, mono-*N*-substituted derivatives **2** as well as *N*,*N′*-disubstituted ones **3** may be obtained.[2,11]

Hydrazide derivatives **5** as well as the parent 1-imino-1*H*-isoindol-3-amine (**1**) are potential tautomeric systems that exhibit a so-called N–C–N–C–N pentade. In compounds **5**, 1,3- or 1,5-proton shifts can take place such that these compounds may exist in three tautomeric forms: 3-amino-1*H*-isoindol-1-one hydrazone **A**, 3-iminoisoindolin-1-one hydrazone **B** and hydrazide **C** (Figure 1). Moreover, (*Z*)/(*E*) isomerism could be observed in these molecules owing to the presence of an exocyclic C=N bond and the *N*-acyl hydrazone fragment may exhibit an amide-type isomerism.[12–15]

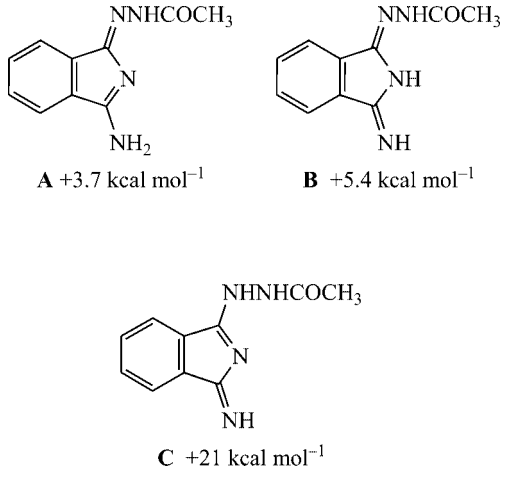


Figure 1. Results of quantum calculations of the possible tautomeric forms of compound **5a**.

For the first time we have examined the structures of the synthesized compounds in the solid state by X-ray diffraction. We demonstrated that in the solid state all of these compounds exist in one tautomeric form **A** with a (*Z*) orientation of the hydrazide residue at the exocyclic C=N bond and a (*Z*) orientation of the *N*-acyl hydrazone fragment irrespective of the substituent R (aliphatic, aromatic, or heteroaromatic, Figure 2).

The results of quantum calculations undertaken on compound **5a** (R = CH_3) are listed in Figure 1 and Figure 3. The data in Figure 1 allow the energies of the tautomeric

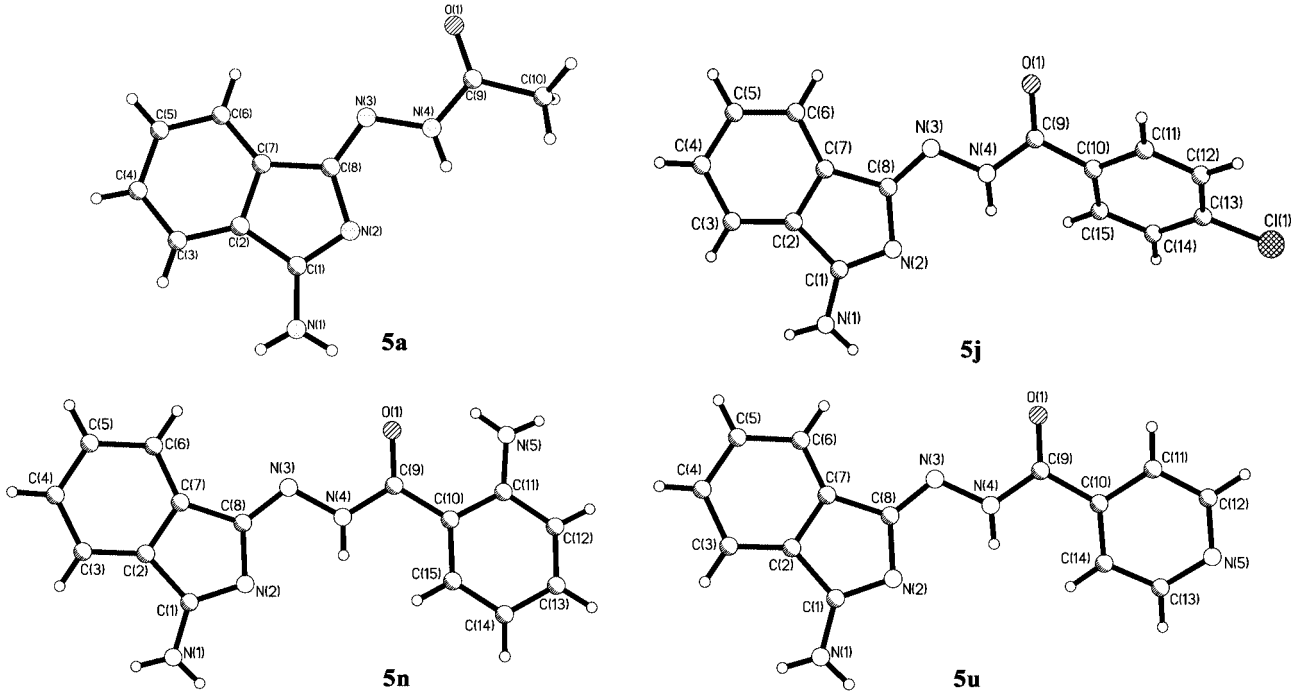


Figure 2. Molecular structures of **5a**, **5j**, **5n**, and **5u** as determined by X-ray diffraction.

forms to be compared and Figure 3 the energies of the isomeric forms. All energies are listed relatively to the lowest energy form.

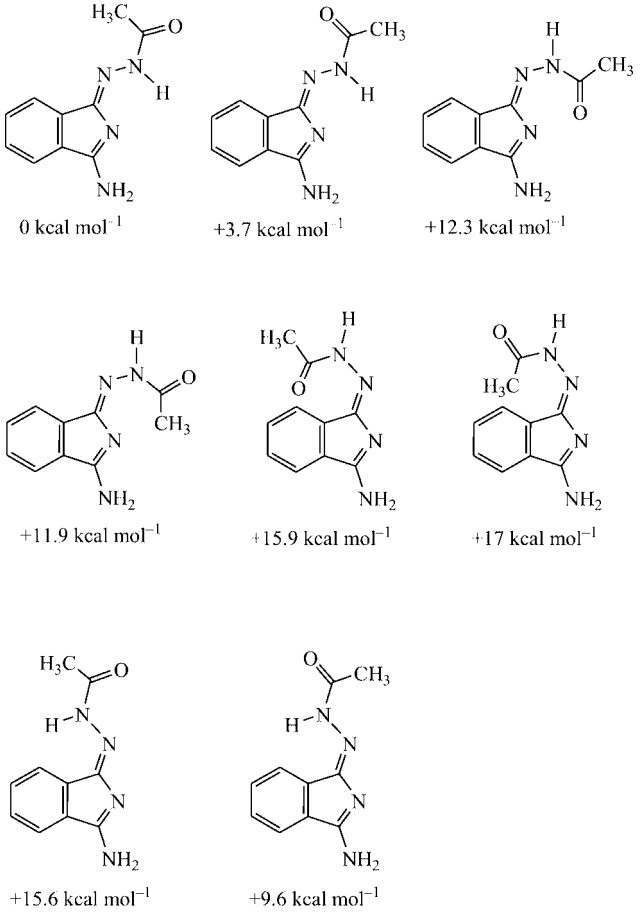


Figure 3. Comparison of the energies of the isomeric forms of compound **5a**.

From Figure 1 it can be seen that the tautomeric form **A** encountered in the solid state is also the most stable in vacuo according to the calculations. The tautomeric form **B** has a slightly higher energy and is not too disfavored. The tautomeric form **C** is extremely unfavorable.

From Figure 3 it can be seen that of the eight isomers, the first two are significantly more stable than the other six. They exhibit the (*Z*) form around C=N bond, as found in the solid state by X-ray diffraction; in **5a**, the (*E*) form of the NCO bond is actually the most stable.

Analysis of the X-ray geometrical parameters of substituted 3-amino-1*H*-isoindol-1-one hydrazones reveals significant redistribution of electron density within the N(1)–C(1)–N(2) fragment. In **5j** and **5n** the formal single N(1)–C(1) and double C(1)–N(2) bonds almost have the same lengths [1.316(6) and 1.312(6) Å for **5j**; 1.323(3) and 1.324(3) Å for **5n**]. In the case of **5a** and **5u** the single N(1)–C(1) bond [1.315(2) and 1.311(4) Å] is even shorter than the double C(1)–N(2) bond [1.333(2) and 1.340(4) Å]. For comparison, the average values[16] of single C(sp^2)–NH_2 and double N=C(sp^2) bonds are 1.43 and 1.28 Å, respectively. This clearly indicates that in the crystal phase compounds **5** exhibit structures containing delocalized bonds that are hybrids of **A** and **A′** with a considerable contribution of the bipolar resonant form **A′** to the overall structure of the molecules (Figure 4).

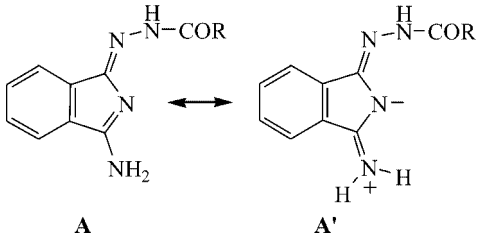


Figure 4. Resonant forms of compounds **5**.

Quantum calculations show the same trends in bond lengths. The (*Z*) form of compound **5a** for instance has a bond length of 1.35 Å for N(1)–C(1) and 1.31 Å for N(2)–C(1). Moreover, Figure 5 shows a representation of the electrostatic potential created by the molecule as mapped on an isodensity surface. The electrostatic potential on N(1) is remarkably high, corresponding to an electrophilic electron-poor nitrogen atom, whereas it is remarkably low on N(2), corresponding to a nucleophilic electron-rich nitrogen atom. This electrostatic potential diagram of the molecule is consistent with a significant contribution of the mesomeric form **A′** to the electronic description of the molecule and its consequences on bond lengths.

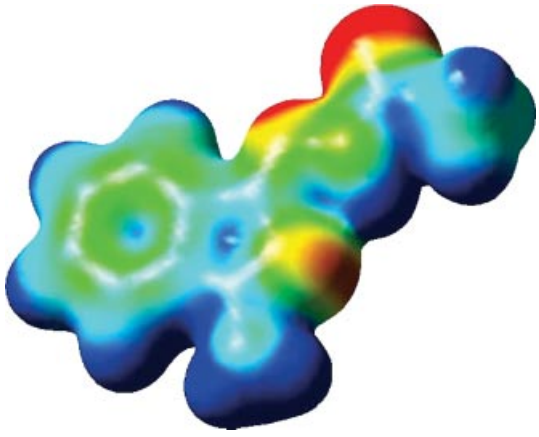


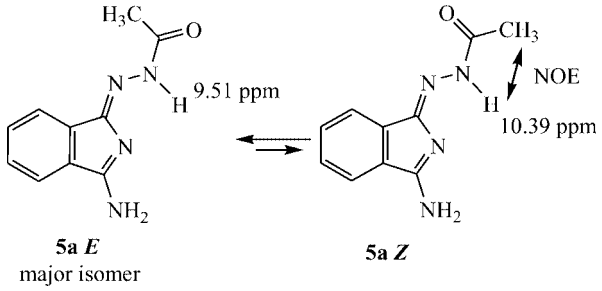
Figure 5. Electrostatic potential diagram of molecule **5a**.

In **5n** the carbonyl C(9)–O(1) bond length is 1.246(3) Å. This value is intermediate between the mean values of double C=O bonds (1.22 Å) and delocalized C–O⁻ bonds in carboxylate anions (1.26 Å). So far, one can assume the presence of partial negative charge localized on the carbonyl oxygen atom. This agrees well with the electron-donating properties of the 2-aminophenyl substituent since, in the case of **5a**, **5j**, and **5u**, no elongation of the carbonyl bond is observed [the values are 1.225(2), 1.221(6), and 1.221(4) Å, respectively].

As has already been pointed out, the exocyclic C=N double bond of compounds **5** in solution can display configurational (*Z*)/(*E*) isomerism whilst the *N*-acyl hydrazone

residue can exhibit conformational (*Z*)/(*E*) amide-type isomerism.

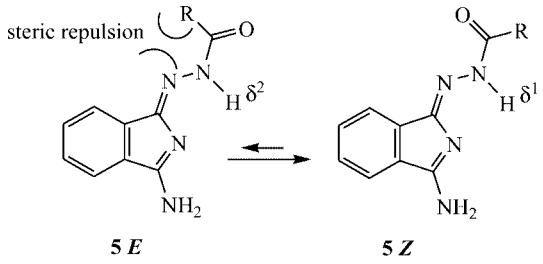
Two sets of signals were observed in the ^{1}H NMR spectrum of compound **5a** for the methyl group and the NH proton of the hydrazone moiety indicating the existence of two forms in a ratio of 1:1.12. A NOESY experiment was performed to assign the resonances of these two populations: In contrast with the major isomer, a strong NOE effect between the CH_3 and the NH proton of the minor isomer was observed. This result indicates the exclusive occurrence of (*Z*)/(*E*) amide isomerism, precluding isomerism around the C=NN bond, and permits us to propose an (*E*) conformation for the major isomer (Scheme 2), as predicted by quantum calculations in vacuo. Note that, in accord with previously described studies, the NMR signal of the hydrazide NH proton occupying the position *syn* to the carbonyl oxygen [the (*E*) isomer] is shifted upfield.



Scheme 2.

A resonance assignment based on the chemical shifts of the NH protons was performed for compounds **5b**–**f** which exhibit two sets of signals in their NMR spectra and compounds **5p**–**r**, **5t**, and **5u** which exhibit two sets of NH proton signals, the downfield NH signal being associated with the (*Z*) isomer (Table 2). From this assignment it is clear that the proportion of the (*E*) conformer decreases with increasing size of the R group, the (*Z*) conformer being favored by lower steric repulsion. In the rest of the series (compounds **5g**–**o** and **5s**, which bear aromatic or hindered alkyl groups), a single isomer was detected in the NMR spectra, which was assigned to the (*Z*) isomer.

Quantum calculations have also been undertaken on the (*E*) and (*Z*) isomers of compound **5g** (R = adamantyl). In this compound, the (*E*) isomer is the most stable, as in compound **5a** (R = CH_3). But the difference in energy between the most stable (*E*) isomer and the less stable (*Z*) isomer is less than in compound **5a**: For compound **5g**, it is 1.6 kcal mol^{-1}, whereas for compound **5a**, it is 3.7 kcal mol^{-1}. Thus a bulkier substituent like adamantyl tends to relatively favor the (*Z*) isomer compared with a smaller substituent like methyl (Scheme 3).



Scheme 3.

We have also found that solvent polarity dramatically influences the ratio of (*Z*)/(*E*) amide conformers. The (*Z*)/(*E*) ratio for three compounds (**5a**, **5d**, and **5f**) in mixtures of [D$_6$]DMSO/$CDCl_3$ are given in Table 3. In a polar solvent ([D$_6$]DMSO), the equilibrium was significantly shifted towards the (*Z*) form. This is supported by the fact that the (*Z*) form possesses a higher dipole moment, as calculated by quantum calculations: The dipole moments of the (*Z*) and (*E*) isomers of compound **5a** are, respectively, 7.07 and 6.69 D. Thus, the (*Z*) form is certainly more stabilized by polar solvents than the (*E*) form.[14]

Table 3. Influence of solvent polarity on the (*Z*)/(*E*) isomeric ratio of compounds **5a**, **5d**, and **5f**.

	(*Z*)/(*E*) ratio		
[D$_6$]DMSO/$CDCl_3$	1:0	1:1	1:3
5a	1:1.12	1:1.40	1:1.77
5d	1:0.67	1:0.91	1:1.20
5f	1:0.52	1:0.57	1:0.78

Interestingly, the observation of two singlets in the ^{1}H NMR spectra [or three in the case of **5a**–**f** because of (*Z*)/(*E*) isomerism] due to NH_2 proton signals indicates the important contribution of the mesomeric form **A′** to the overall structure in solution, as also observed in the solid state (Figure 4).

To estimate the rotational energy barrier of the hydrazide C–NN bonds, temperature-dependent ^{1}H NMR spectra were recorded for compounds **5a** and **5d**–**f**. The spectra collected for **5a** in [D$_6$]DMSO from 297 to 363 K are shown in Figure 6 (for the other compounds, see the Supporting Information). On heating compound **5a**, gradual signal-broadening occurred; methyl group signal coalescence was observed at 348 K whilst coalescence of the hydrazide protons occurred at a higher temperature (358 K). Upon cooling all signals reappeared and thus the assignments were confirmed as being due to (*Z*)/(*E*) isomeric absorption.

From the NMR spectroscopic data, it was possible to determine the (*Z*)/(*E*) ratio at different temperatures

Table 2. ^{1}H NMR chemical shifts of NH–N= protons for compounds **5** in [D$_6$]DMSO and (*Z*)/(*E*) assignment.

	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5p**	**5q**	**5r**	**5t**	**5u**
δ^1 [ppm]	10.39	10.28	10.89	10.59	10.70	10.07	10.83	10.87	10.89	10.84	10.81
δ^2 [ppm]	9.51	9.42	10.05	9.62	9.61	9.36	10.09	10.12	10.16	10.16	10.23
(*Z*)/(*E*)	0.89	1.78	1.56	1.49	1.42	1.92	11.1	11.1	14.3	14.3	12.5

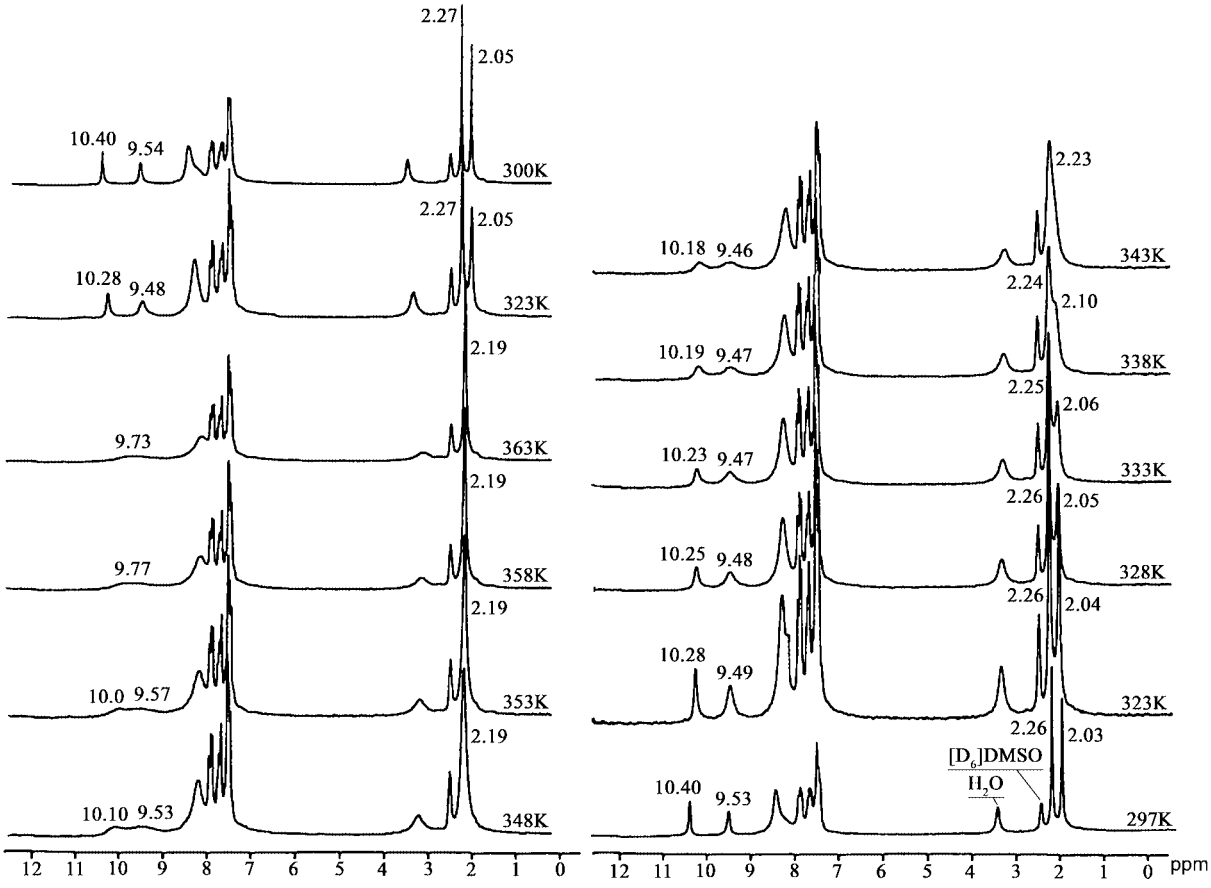


Figure 6. Temperature-dependent ^{1}H NMR (100 MHz, [D$_6$]DMSO) spectra of compound **5a**.

Table 4. Thermodynamic parameters for compounds **5a** and **5d**–**f** ([D$_6$]DMSO/CDCl$_3$, 1:1).

5	(*Z*)/(*E*) (245 K)	(*Z*)/(*E*) (298 K)	(*Z*)/(*E*) (341 K)	$\Delta S°$ [J mol^{-1} K^{-1}]	$\Delta H°$ [kJ mol^{-1}]	$T\Delta S°$ [kJ mol^{-1}]	$\Delta G°$ (298 K) [kJ mol^{-1}]
a	1:0.76	1:1.35	1:2.03	–26.3	–7.10	–7.83	0.73
d	1:0.53	1:0.94	1:1.19	–20.8	–6.44	–6.19	–0.24
e	1:0.38	1:0.92	1:1.49	–32.7	–10.12	–9.74	–0.38
f	1:0.31	1:0.57	1:0.72	–15.9	–6.23	–4.73	–1.49

and thus the thermodynamic parameters of the reaction (*E*) ⇄ (*Z*) for compounds **5a** and **5d**–**f** (see Table 4).

From these data, it appears that $\Delta G°$ values increase with decreasing steric hindrance of the R substituent: The largest free energy value was observed for the most hindered 4-butylcyclohexyl derivative **5f** [$\Delta G°$ (298 K) = –1.49 kJ mol^{-1}], whereas for the methyl derivative **5a**, $\Delta G°$ was positive [$\Delta G°$ (298 K) = +0.73 kJ mol^{-1}]. Thus, these results show that in a given solvent, steric factors are mainly responsible for determining which isomer predominates.

Conclusions

In this study we have prepared a series of *N*′-(3-amino-1*H*-isoindol-1-ylidene)alkyl(aryl,hetaryl)carbohydrazides **5** in good yield. We have shown that, in solution as well as in the solid state and in vacuo, as probed by quantum calculations, compounds **5** exist in one tautomeric form, that of 3-amino-1*H*-isoindol-1-one hydrazone **A**, which has a structure containing a delocalized bond with a considerable contribution of the bipolar resonant form **A**′ to the overall structure of the molecule. This view is supported by the bond-length and electrostatic-potential analyses. In the solid state, compounds **5** adopt a (*Z*) configuration of the hydrazide residue at the exocyclic C=N bond and a (*Z*) amide conformation, irrespective of the nature of the R substituent, whereas in vacuo the (*E*) amide conformation is favored for the calculated compounds. In solution, NMR spectroscopic data revealed a very pronounced (*E*)/(*Z*) amide-type isomerism for the aliphatic derivatives of **5**. The (*E*)/(*Z*) isomeric ratio depends upon two factors: Steric effects and solvent polarity. Thus, with increasing solvent polarity or size of the substituent R in the *N*-acyl hydrazone residue the proportion of the (*E*) conformer decreased. This is in a good agreement with theoretical studies which show the influence of the dipole moment and the

steric hindrance of the R substituent on the (*E*)/(*Z*) ratio. The rotational barriers around the NN–C(O) bond were estimated by ^{1}H NMR dynamic spectroscopy.

Experimental Section

General: ^{1}H NMR spectra (in [D$_6$]DMSO) were recorded with Bruker WP-100 SY (100 MHz for ^{1}H), Bruker Avance 300 (300 MHz for ^{1}H), and Mercury Varian (400 MHz for ^{1}H) spectrometers with tetramethylsilane as an internal standard. ^{13}C NMR spectra (in [D$_6$]DMSO) were recorded with a Mercury Varian (100 MHz for ^{13}C) spectrometer with the tetramethylsilane residual peak as a standard. TLC analyses were performed on silica gel coated aluminium sheets (Silufol UV-254) and visualized with UV light. Melting points were measured with a Boetius microscope hotplate apparatus and are uncorrected. Solvents were of commercial quality and were used without further purification.

X-ray Crystallography: The crystal data, details of their collection, and refinement procedures are given in Table 5. All measurements were performed at 20 °C on a Siemens P3/PC diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.17073 Å) 2θ scans, $2\theta_{max}$ = 50°. The structures were solved by direct methods and refined by full-matrix least-squares techniques on all F^2 data using the SHELX-97 package.[17] All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed in calculated positions and included in the refinement as a riding-model approximation with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl, hydroxy, and water hydrogen atoms and n = 1.2 for the remaining hydrogen atoms). The values of selected geometrical parameters are listed in the Table 6.

CCDC-294129 to -294132 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 6. Selected geometrical parameters [Å, °] for compounds **5a**, **5j**, **5n**, and **5u**.

Compound	**5a**	**5j**	**5n**	**5u**
N(1)–C(1)	1.315(2)	1.316(6)	1.323(3)	1.311(4)
C(1)–N(2)	1.333(2)	1.312(6)	1.324(3)	1.340(4)
N(2)–C(8)	1.395(2)	1.394(6)	1.392(3)	1.389(4)
C(8)–N(3)	1.294(2)	1.299(6)	1.300(3)	1.287(4)
N(3)–N(4)	1.383(2)	1.376(5)	1.385(3)	1.370(4)
N(4)–C(9)	1.346(2)	1.335(6)	1.351(3)	1.339(4)
C(9)–O(1)	1.225(2)	1.221(6)	1.246(3)	1.221(4)
N(2)–C(8)–N(3)–N(4)	0.6(3)	–0.3(9)	–2.6(4)	–0.3(5)
C(8)–N(3)–N(4)–C(9)	175.21(18)	–171.5(6)	177.8(2)	–176.0(3)
N(3)–N(4)–C(9)–O(1)	–0.4(3)	1.9(9)	–7.6(4)	1.8(6)

Computational Details: All calculations have been performed at the CINES calculation center with the Gaussian 03 version B5 package,[18] with default conditions. The geometry optimization of compound **5a** has been performed in three tautomeric forms (as shown in Figure 1) and eight isomeric forms (as shown in Figure 3) using the B3LYP/6-31G(d,p)[19,20] density functional level of theory. Compound **5g** has been optimized in two isomeric (*Z*) and (*E*) forms. Minima were checked successfully for consistent positive vibration frequencies.

General Procedure A. Preparation of *N′*-(3-Amino-1*H*-isoindol-1-ylidene)alkyl(aryl,hetaryl)carbohydrazides 5 from 1-Imino-1*H*-isoindol-3-amine (1): 1-Imino-1*H*-isoindol-3-amine (1.452 g, 10 mmol) was dissolved in methanol or ethanol (30–35 mL) and then the appropriate carboxylic acid hydrazide (10 mmol) was added. The mixture was refluxed for 4–5 h until all ammonia had been eliminated. After cooling the precipitate formed was filtered, washed with methanol or ethanol, and dried in vacuo.

General Procedure B. Preparation of Compounds 5 from Phthalonitrile: The appropriate carboxylic acid hydrazide (10 mmol) was added to phthalonitrile (1.281 g, 10 mmol) in methanol or ethanol (30–35 mL). The mixture was heated to dissolve the starting mate-

Table 5. Crystal data for compounds **5a**, **5j**, **5n**, and **5u**.

Compound	**5a**	**5j**	**5n**	**5u**
Empirical formula	$C_{10}H_{10}N_4O{\cdot}CH_3OH{\cdot}H_2O$	$C_{15}H_{11}ClN_4O{\cdot}CH_3OH{\cdot}H_2O$	$C_{14}H_{11}N_5O{\cdot}H_2O$	$C_{15}H_{13}N_5O{\cdot}H_2O$
Formula weight	252.28	348.79	283.29	297.32
Crystal system	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$	$Pbcn$
a [Å]	7.641(3)	7.385(2)	6.750(1)	11.879(3)
b [Å]	13.319(6)	16.062(6)	16.718(3)	13.204(2)
c [Å]	13.442(5)	14.118(5)	11.735(2)	18.463(6)
α [°]	90	90	90	90
β [°]	105.92(2)	99.57(2)	94.63(2)	90
γ [°]	90	90	90	90
Cell volume [Å^3]	1315.5(9)	1651(1)	1319.9(4)	2896(1)
Z	4	4	4	8
D_{calc} [g cm^{-1}]	1.274	1.403	1.426	1.364
μ [mm^{-1}]	0.10	0.25	0.10	0.10
Range of h, k, l	0–9, 0–15, –15–15	0–8, 0–19, –16–16	0–8, 0–19, –13–13	0–14, 0–15, 0–22
Reflections measured	2434	3054	2017	2500
Reflections unique (R_{int})	2261 [0.024]	2823 [0.098]	1867 [0.052]	2500
Number of observed reflections	1391	941	1211	1229
Number of parameters refined	166	218	190	200
S	0.93	0.85	0.94	0.85
R, wR [$I > 2\sigma(I)$]	0.041, 0.104	0.084, 0.173	0.074, 0.197	0.048, 0.098
R, wR (all data)	0.100, 0.112	0.310, 0.204	0.109, 0.214	0.159, 0.113
Largest diff. peak and hole [e Å^{-1}]	0.13, –0.17	0.22, –0.22	0.25, –0.29	0.19, –0.23

rials and then a catalytic amount of sodium (potassium) hydroxide was added. The mixture was refluxed for 4–5 h. After cooling the precipitate formed was filtered, washed with the corresponding alcohol, and dried. In most cases products were obtained in an analytically pure state. If necessary, additional purification could be achieved by recrystallization from methanol, ethanol, or propan-2-ol.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)acetohydrazide (5a):** Yields: 1.88 g (93%, procedure A)/1.81 g (90%, procedure B); m.p. 248–249 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.02 and 2.25 (2 s, 3 H, CH$_3$), 7.48 (t, J = 7.4 Hz, 1 H), 7.52 (t, J = 7.4 Hz, 1 H), 7.68 and 7.71 (2 d, J = 7.4 Hz, 1 H), 7.89 and 7.91 (2 d, J = 7.4 Hz, 1 H), 8.16 and 8.44 (2 br. s, 2 H, NH$_2$), 9.51 and 10.39 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 20.61 and 22.30 (CH$_3$), 120.57, 120.90, 121.93, 121.96, 129.63, 129.70, 131.27, 135.21, 138.43, 139.06, 154.47, 156.40, 165.95, 167.64, 167.81 and 171.02 (C=O) ppm. C$_{10}$H$_{10}$N$_4$O (202.213): calcd. C 59.40, H 4.98, N 27.71; found C 59.21, H 4.80, N 28.02.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-2-methylpropanohydrazide (5b):** Yield: 2.21 g (96%, procedure B); m.p. 130–131 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.06 and 1.10 (2 d, J = 6.8 Hz, 6 H, –(CH$_3$)$_2$), 2.64–2.68 and 3.46–3.49 (2 m, 1 H, CH), 7.49 (t, J = 7.6 Hz, 1 H), 7.54 (t, J = 7.6 Hz, 1 H), 7.69 and 7.71 (2 d, J = 7.6 Hz, 1 H), 7.90 (d, J = 7.6 Hz, 1 H), 8.26 and 8.48 (2 br. s, 2 H, NH$_2$), 9.42 and 10.28 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 19.23 and 19.65 (–(CH$_3$)$_2$), 29.85 and 33.39 (CH), 120.53, 120.88, 121.83, 121.93, 129.64, 129.69, 131.30, 135.17, 138.49, 138.96, 154.21, 156.78, 167.65, 167.73, 172.63 and 177.01 (C=O) ppm. C$_{12}$H$_{14}$N$_4$O (230.266): calcd. C 62.59, H 6.13, N 24.33; found C 62.40, H 5.98, N 24.32.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-2-cyanoacetohydrazide (5c):** Yields: 0.73 g (32%, procedure A)/0.64 g (28%, procedure B); m.p. 130–131 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.97 and 4.25 (2 s, 2 H, CH$_2$), 7.51 (t, J = 7.2 Hz, 1 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.68 and 7.72 (2 d, J = 7.2 Hz, 1 H), 7.91 and 7.93 (2 d, J = 7.2 Hz, 1 H), 8.21 and 8.56 (2 br. s, 2 H, NH$_2$), 10.05 and 10.89 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 24.88 and 25.41 (CH$_2$), 116.74, 120.79, 121.40, 121.46, 122.49, 130.01, 131.44, 135.30, 138.31, 138.85, 155.71, 158.10, 159.10, 165.98, 168.17 and 168.35 (C=O) ppm. C$_{11}$H$_9$N$_5$O (227.222): calcd. C 58.14, H 3.99, N 30.82; found C 58.28, H 4.15, N 30.92.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-2-phenylacetohydrazide (5d):** Yields: 2.09 g (75%, procedure A)/2.17 g (78%, procedure B); m.p. 235–236 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.71 and 4.05 (2 s, 2 H, CH$_2$), 7.21–7.36 (m, 5 H), 7.47–7.59 (m, 2 H), 7.70 and 7.78 (2 d, J = 7.2 Hz, 1 H), 7.92 (d, J = 7.2 Hz, 1 H), 8.21 and 8.50 (2 br. s, 2 H, NH$_2$), 9.62 and 10.59 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 39.38 and 41.73 (CH$_2$), 120.68, 120.91, 121.83, 121.98, 126.95, 127.07, 128.76, 128.89, 129.69, 129.79, 130.09, 131.30, 131.38, 135.20, 136.21, 136.65, 138.48, 139.00, 154.65, 156.94, 166.86, 167.73, 167.88 and 171.38 (C=O) ppm. C$_{13}$H$_{14}$N$_4$O (278.309): calcd. C 69.05, H 5.07, N 20.13; found C 69.08, H 4.90, N 20.12.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)cyclopropanecarbohydrazide (5e):** Yield: 1.78 g (78%, procedure A); m.p. 155–156 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.71–0.88 (m, 4 H), 1.96–1.98 and 2.69–2.72 (2 m, 1 H, CH), 7.48 (t, J = 7.4 Hz, 1 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.69 and 7.72 (2 d, J = 7.4 Hz, 1 H), 7.91 (d, J = 7.4 Hz, 1 H), 8.12 and 8.45 (2 br. s, 2 H, NH$_2$), 9.61 and 10.70 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 7.57, 8.57, 10.35, 13.27, 120.40, 120.87, 121.81, 122.21, 129.57, 129.70, 131.22, 135.20, 138.48, 139.13, 154.73, 156.10, 167.59, 167.74, 169.60 and 173.61 (C=O) ppm. C$_{12}$H$_{12}$N$_4$O (228.250): calcd. C 63.14, H 5.30, N 24.55; found C 62.96, H 5.28, N 24.50.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-4-butylcyclohexanecarbohydrazide (5f):** Yield: 3.19 g (98%, procedure B); m.p. 166–168 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.86–1.77 (m, 9 H), 2.27–2.29 and 3.15–3.16 (2 m, 1 H, CH), 7.49 (t, J = 7.2 Hz, 1 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.71 (d, J = 7.2 Hz, 1 H), 7.91 (d, J = 7.2 Hz, 1 H), 8.36 (br. s, 2 H, NH$_2$), 9.36 and 10.07 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 14.55, 23.01, 29.11, 29.81, 32.49, 37.08, 43.52, 120.53, 120.83, 121.87, 129.62, 131.28, 135.13, 138.85, 138.90, 153.96, 156.60, 167.53, 171.52 and 176.05 (C=O) ppm. C$_{19}$H$_{26}$N$_4$O (326.436): calcd. C 69.91, H 8.03, N 17.16; found C 69.81, H 8.19, N 17.15.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)adamantane-1-carbohydrazide (5g):** Yield: 3.09 g (96%, procedure A); m.p. 265–266 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.68 (br. s, 6 H), 1.86 (br. s, 6 H), 1.99 (br. s, 3 H), 7.51 (t, J = 7.2 Hz, 1 H), 7.55 (t, J = 7.2 Hz, 1 H), 7.72 (d, J = 7.2 Hz, 1 H), 7.91 (d, J = 7.2 Hz, 1 H), 8.55 and 8.61 (2 s, 2 H, NH$_2$), 9.99 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 28.05, 36.51, 39.18, 120.85, 121.99, 129.78, 131.48, 135.24, 138.51, 157.76, 167.68, 172.03 (C=O) ppm. C$_{19}$H$_{22}$N$_4$O (322.404): calcd. C 70.78, H 6.88, N 17.38; found C 70.49, H 6.90, N 17.20.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)benzohydrazide (5h):** Yields: 2.48 g (94%, procedure A)/2.40 g (91%, procedure B); m.p. 260–261 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.51–7.59 (m, 5 H) 7.80 (d, J = 7.2 Hz, 1 H), 7.84 (d, J = 7.6 Hz, 1 H), 7.94 (d, J = 7.2 Hz, 1 H), 8.65 (br. s, 2 H, NH$_2$), 10.60 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 121.07, 122.10, 127.47, 129.40, 130.02, 131.61, 132.35, 134.17, 135.37, 137.50, 158.77, 162.24, 168.05 (C=O) ppm. C$_{15}$H$_{12}$N$_4$O (264.282): calcd. C 68.17, H 4.58, N 21.20; found C 68.24, H 4.70, N 21.09.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-4-fluorobenzohydrazide (5i):** Yield: 2.00 g (71%, procedure B); m.p. 255–256 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.33–7.39 (m, 2 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.8 (d, J = 7.2 Hz, 1 H), 7.91–7.95 (m, 3 H), 8.65 (br. s, 2 H, NH$_2$), 10.62 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 116.21, 116.43, 121.07, 122.08, 130.03, 130.19, 130.73, 131.61, 135.31, 138.49, 158.71, 161.39, 163.39, 165.86, 168.05 (C=O) ppm. C$_{15}$H$_{11}$FN$_4$O (282.273): calcd. C 63.83, H 3.93, N 19.85; found C 63.71, H 4.08, N 19.82.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-4-chlorobenzohydrazide (5j):** Yield: 2.63 g (88%, procedure B); m.p. 273–274 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.53 (t, J = 7.2 Hz, 1 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.59 (d, J = 8.4 Hz, 2 H), 7.79 (d, J = 7.2 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 2 H), 7.93 (d, J = 7.2 Hz, 1 H), 8.65 (br. s, 2 H, NH$_2$), 10.65 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 121.11, 122.08, 129.48 (2′-,3′-,5′-,6′-C), 130.06, 131.62, 132.94, 135.34, 137.07, 138.51, 158.95, 161.38, 168.14 (C=O) ppm. C$_{15}$H$_{11}$ClN$_4$O (298.727): calcd. C 60.31, H 3.71, N 18.76; found C 60.12, H 3.70, N 18.70.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-4-bromobenzohydrazide (5k):** Yield: 2.92 g (85%, procedure B); m.p. 293–294 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.54 (t, J = 7.4 Hz, 1 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.71–7.96 (m, 6 H), 8.69 (br. s, 2 H, NH$_2$), 10.66 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 121.12, 122.15, 126.02, 129.65, 130.10, 131.69, 132.31, 133.27, 135.20, 138.43, 158.58, 161.49, 167.98 (C=O) ppm. C$_{15}$H$_{11}$BrN$_4$O (343.178): calcd. C 52.50, H 3.23, N 16.33; found C 52.41, H 3.17, N 16.22.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-4-hydroxybenzohydrazide (5l):** Yield: 2.49 g (89%, procedure A); m.p. >300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.90 (d, J = 8 Hz, 2 H), 7.52 (t, J =

7.2 Hz, 1 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.72 (d, *J* = 8 Hz, 2 H), 7.78 (d, *J* = 7.2 Hz, 1 H), 7.94 (d, *J* = 7.2 Hz, 1 H), 8.60 (br. s, 2 H, NH_2), 10.21 (br. s, 1 H, OH), 10.49 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 115.40, 121.48, 122.05, 124.62, 128.95, 129.84, 131.50, 135.31, 138.54, 158.00, 161.27, 161.92, 167.81 (C=O) ppm. $C_{15}H_{12}N_4O_2$ (280.282): calcd. C 64.28, H 4.32, N 19.99; found C 64.24, H 4.18, N 20.04.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-4-methylbenzohydrazide (5m):** Yields: 2.10 g (76%, procedure A)/2.00 g (72%, procedure B); m.p. 294–295 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 2.36 (s, 3 H, CH_3), 7.33 (d, *J* = 7.6 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 1 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 2 H), 7.80 (d, *J* = 7.2 Hz, 1 H), 7.95 (d, *J* = 7.2 Hz, 1 H), 8.66 (br. s, 2 H, NH_2), 10.58 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 21.57 (CH_3), 121.04, 122.10, 127.43, 129.90, 131.26, 131.58, 135.30, 138.49, 142.40, 158.38, 162.06, 167.93 (C=O) ppm. $C_{16}H_{14}N_4O$ (278.309): calcd. C 69.05, H 5.07, N 20.13; found C 69.01, H 4.98, N 20.03.

2-Amino-*N′*-(3-amino-1*H*-isoindol-1-ylidene)benzohydrazide (5n): Yields: 2.46 g (88%, procedure A)/2.32 g (83%, procedure B); m.p. 258–260 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 6.41 (s, 2 H, NH_2), 6.60 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.2 Hz, 1 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.78 (d, *J* = 7.2 Hz, 1 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 8.59 and 8.64 (2 s, 2 H, NH_2), 10.45 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 114.42, 115.82, 117.43, 120.92, 122.05, 127.59, 129.84, 131.50, 132.92, 135.31, 138.51, 150.32, 157.96, 164.25, 167.85 (C=O) ppm. $C_{15}H_{13}N_5O$ (279.297): calcd. C 64.51, H 4.69, N 25.08; found C 64.61, H 4.80, N 25.10.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-2-hydroxybenzohydrazide (5o):** Yield: 2.63 g (94%, procedure A); m.p. 265–266 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 6.81 (t, *J* = 8.4 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 7.23 (t, *J* = 8.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 8.43 (br. s, 2 H, NH_2) ppm. ^{13}C NMR: δ = 116.85, 118.88, 119.15, 120.97, 121.74, 129.44, 131.10, 133.30, 135.28, 139.30, 156.89, 161.89, 163.24, 167.66 (C=O) ppm. $C_{15}H_{12}N_4O_2$ (280.282): calcd. C 64.28, H 4.32, N 19.99; found C 64.18, H 4.30, N 19.97.

3-{[2-(3-Amino-1*H*-isoindol-1-ylidene)hydrazino]carbonyl}-*N*,*N*-diethylbenzenesulfonamide (5p): Yield: 3.11 g (78%, procedure A); m.p. 144–145 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.05 (t, *J* = 6.8 Hz, 6 H, 2 CH_3), 3.21 (q, *J* = 6.8 Hz, 4 H, 2 CH_2), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.8 (d, *J* = 7.6 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.99 (d, *J* = 7.4 Hz, 1 H), 8.11 (d, *J* = 7.4 Hz, 1 H), 8.20 (s, 1 H), 8.65 (br. s, 2 H, NH_2), 10.09 and 10.83 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 14.72 (2 CH_3), 42.50 (2 C, –N(CH_2)$_2$), 121.18, 122.10, 125.86, 130.13, 130.66, 131.58, 135.33, 138.60, 140.83, 159.18, 161.28, 168.22 (C=O) ppm. $C_{19}H_{21}N_5O_3S$ (399.468): calcd. C 57.13, H 5.30, N 17.53; found C 57.22, H 5.18, N 17.42.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-3-(pyrrolidin-1-ylsulfonyl)-benzohydrazide (5q):** Yield: 2.86 g (72%, procedure A); m.p. 158–159 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.66 (br. s, 4 H, –(CH_2)$_2$–), 3.38 (br. s, 4 H, –N(CH_2)$_2$), 7.55 (t, *J* = 7.2 Hz, 1 H), 7.59 (t, *J* = 7.2 Hz, 1 H), 7.77–7.82 (m, 2 H), 7.94 (d, *J* = 7.2 Hz, 1 H), 8.01 (d, *J* = 7.6 Hz, 1 H), 8.17 (d, *J* = 7.6 Hz, 1 H), 8.21 (s, 1 H), 8.64 (br. s, 2 H, NH_2), 10.12 and 10.87 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 25.31 (2 CH_2), 48.48 (2 C, –N(CH_2)$_2$), 121.17, 122.08, 126.38, 130.13, 130.64, 131.65, 132.03, 135.31, 137.23, 138.63, 159.19, 161.33, 168.24 (C=O) ppm. $C_{19}H_{19}N_5O_3S$ (397.452): calcd. C 57.42, H 4.82, N 17.62; found C 57.31, H 4.78, N 17.49.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)-3-(morpholin-4-ylsulfonyl)-benzohydrazide (5r):** Yield: 3.22 g (78%, procedure A); m.p. 178–180 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 2.92 (br. s, 4 H, –N(CH_2)$_2$), 3.65 (br. s, 4 H, –O(CH_2)$_2$), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.81–7.95 (m, 3 H), 8.14 (s, 1 H), 8.2 (d, *J* = 7.4 Hz, 1 H), 8.64 (br. s, 2 H, NH_2), 10.16 and 10.89 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 46.44 (2 C, –N(CH_2)$_2$), 65.81 (2 C, –O(CH_2)$_2$), 121.18, 122.09, 126.78, 130.13, 130.67, 130.98, 131.64, 132.39, 135.33, 135.56, 138.62, 159.25, 161.32, 168.24 (C=O) ppm. $C_{19}H_{19}N_5O_4S$ (413.451): calcd. C 55.19, H 4.63, N 16.94; found C 54.98, H 4.81, N 17.09.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)pyridine-2-carbohydrazide (5s):** Yield: 2.39 g (90%, procedure B); m.p. 288–290 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.54 (t, *J* = 7.6 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.81 (d, *J* = 7.6 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 8.06 (t, *J* = 7.6 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 8.69 (d, *J* = 4.4 Hz, 1 H), 8.65 and 8.86 (2 s, 2 H, NH_2), 11.83 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 121.10, 122.08, 122.76, 127.55, 130.05, 131.60, 132.58, 135.40, 138.54, 138.78, 149.18, 149.87, 159.02, 159.17, 168.27 (C=O) ppm. $C_{14}H_{11}N_5O$ (265.270): calcd. C 63.39, H 4.18, N 26.40; found C 63.28, H 4.19, N 26.20.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)nicotinohydrazide (5t):** Yield: 2.23 g (84%, procedure B); m.p. 238–239 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.53–7.61 (m, 3 H), 7.81 (d, *J* = 6.8 Hz, 1 H), 7.94 (d, *J* = 6.8 Hz, 1 H), 8.22 (d, *J* = 6.8 Hz, 1 H), 8.66 (br. s, 2 H, NH_2), 8.74 (d, *J* = 4.4 Hz, 1 H), 9.03 (s, 1 H), 10.16 and 10.84 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 121.15, 122.08, 124.26, 130.10, 131.62, 135.33, 135.53, 138.58, 149.64, 153.23, 159.11, 161.19, 168.19 (C=O) ppm. $C_{14}H_{11}N_5O$ (265.270): calcd. C 63.39, H 4.18, N 26.40; found C 63.37, H 4.21, N 26.39.

***N′*-(3-Amino-1*H*-isoindol-1-ylidene)isonicotinohydrazide (5u):** Yield: 2.39 g (90%, procedure B); m.p. 264–265 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.54 (t, *J* = 7.2 Hz, 1 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.76 (d, *J* = 4.4 Hz, 2 H), 7.8 (d, *J* = 7.2 Hz, 1 H), 7.94 (d, *J* = 7.2 Hz, 2 H), 8.69 (br. s, 2 H, NH_2), 8.76 (d, *J* = 4.4 Hz, 2 H), 10.23 and 10.81 (2 s, 1 H, NH) ppm. ^{13}C NMR: δ = 121.20, 121.64, 123.13, 130.21, 131.69, 135.40, 138.50, 141.31, 151.03, 159.67, 160.98, 168.36 (C=O) ppm. $C_{14}H_{11}N_5O$ (265.270): calcd. C 63.39, H 4.18, N 26.40; found C 63.32, H 3.98, N 26.24.

Supporting Information: Temperature-dependent ^1H NMR (300 MHz, [D$_6$]DMSO/$CDCl_3$, 1:1) spectra of compounds **5a** and **5d**–**f**.

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