JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Azine-Hydrazone Tautomerism of Guanylhydrazones: Evidence for the Preference Toward the Azine Tautomer

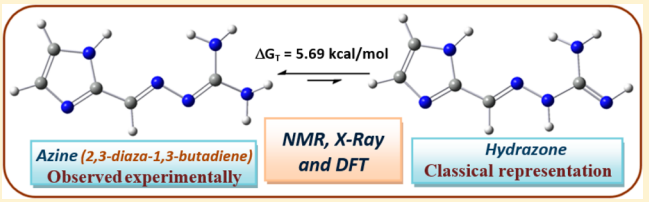
Sumit S. Chourasiya,[†] Deepika Kathuria,[†] Sampada S. Nikam,[†] Ashok Ramakrishnan,[†] Sadhika Khullar,[‡] Sanjay K. Mandal,*[,‡] Asit K. Chakraborti,*[,†] and Prasad V. Bharatam*[,†]

[†]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar 160 062, Punjab, India

[‡]Department of Chemical Sciences, Indian Institute of Science Education and Research, Mohali Sector 81, S.A.S. Nagar 140 306, Punjab, India

Supporting Information

ABSTRACT: Guanylhydrazones have been known for a long time and have wide applications in organic synthesis, medicinal chemistry, and material science; however, little attention has been paid toward their electronic and structural properties. Quantum chemical analysis on several therapeutically important guanylhydrazones indicated that all of them prefer the azine tautomeric state (by about 3−12 kcal/mol). A set of simple and conjugated azines were designed using quantum chemical methods, whose tautomeric preference toward the azine tautomer is in the range of 3−8 kcal/mol. Twenty new azines were synthesized and isolated in their neutral state. Variable temperature NMR study suggests existence of the azine tautomer even at higher temperatures with no traces of the hydrazone tautomer. The crystal structures of two representative compounds confirmed that the title compounds prefer to exist in their azine tautomeric form.



INTRODUCTION

Guanylhydrazones also known as amidinohydrazones are a class of compounds obtained by the condensation of oxo compounds (aldehyde/ketone) with aminoguanidine, known in the literature for more than 50 years.[1] Guanylhydrazones have been reported to possess antiprotozoal,[2,3] antibacterial,[4] antimalarial,[3,5] trypanocidal,[6] antisecretory,[7] antidiarrheal,[7] anticoagulant,[8,9] antihypertensive,[10−13] antiviral,[14] antileukemic,[15] cardiotonic,[16] and anticancer[17−21] activities. Recently, guanylhydrazones have been reported to inhibit Chk, a novel target for cancer.[22−26] Apart from their medicinal importance, guanylhydrazones are also useful as building blocks for the synthesis of heterocycles,[27,28] and recently furoxan derivatives of guanylhydrazones have been reported as thermally stable energetic material.[29]

Surprisingly, in spite of their use in organic synthesis and potential biological applications, very little is known about their structure and tautomeric preferences. These compounds can undergo 1,3-H shift to exhibit the azine⇋hydrazone tautomerism.[30] Only a few studies have paid attention to the structure and tautomeric preferences of guanylhydrazones. These studies include (i) the crystal and molecular structure of the free base of the antileukemic agent glyoxal *bis* (amidinohydrazones),[31] (ii) the crystal and conformational analysis of guanabenz (GBZ) free base,[32] (iii) the structure of guanylhydrazones derived from aromatic aldehydes (NMR,[33,34] X-ray[34]), and (iv) the crystal structure of 2-(1-phenylethylideneamino)-guanidine.[35] All these studies reported the presence of azine (2,3-diaza-1,3-butadiene) tautomer (**A**) in solution as well as in the solid state. These crystal structures indicate that guanylhydrazones should be represented as azines. However, they are mostly being represented in their "classical" hydrazone form (**B**) (Figure 1). The most probable reason for this misrepresentation could be that in many cases the salts (hydrochloride or bicarbonate) of guanylhydrazones were synthesized and used for their biological activity. Protonation of the azine and hydrazone tautomers leads to the same structure (**C**).[30]

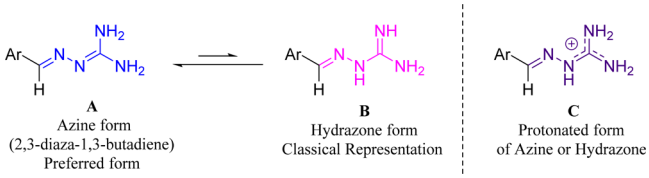


Figure 1. Two possible tautomeric forms (**A** and **B**) of guanylhydrazones along with their protonated form (**C**).

The free base of guanylhydrazones cannot be ignored since the available literature on the biological activity of guanylhydrazone hydrochloride suggested the existence of considerable proportion (~16%) of free base at physiological temperature (37 °C) and pH (7.4).[31,32] Moreover, in many reports, wherein the enzymatic activity of the guanylhydrazones is reported, the

Received: May 25, 2016
Published: August 5, 2016

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

inhibitory action of these compounds was interpreted with the help of molecular modeling studies.[22,36] For example, Qian et al. reported guanylhydrazones as anticancer agents targeting tubulin, and during molecular docking studies, they have used hydrazone tautomer instead of azine tautomer as a neutral ligand.[36] Recently, NSC109555, the sole lead chemotype from HTS of 100 000 compounds has been reported as Chk2 inhibitor.[22−26] Molecular modeling studies were carried out to predict the binding pose, in which case the hydrazone tautomer as a neutral ligand was considered rather than the azine tautomer.[22] This can potentially mislead the interpretation of interactions with the target enzymes. Similarly, it may lead to a mistaken information about the structure activity relationship (SAR) by considering the wrong pharmacophoric feature, i.e., hydrazone instead of azine.

Consideration of the energetically preferred azine tautomer of guanylhydrazone under neutral condition will open many new opportunities for exploring these compounds as substrates for the various crisscross cycloaddition reactions and/or in the synthesis of heterocyclic rings, such as 1,2,4-triazoles,[27,37] oxadiazoles,[38] isoquinolines,[39−41] etc. It is also worth noting that azines can be involved in N−N cleavage chemistry[39−42] and in exchange reactions of the ═N−N═ group with an azo group.[43] Similarly, conjugation in such azines can be studied since previous studies identified conjugation stopper[44] and conjugation switch properties[45] as characteristics of azines. The push−pull effect,[46,47] liquid crystals,[48,49] nonlinear optics,[50] optoelectronics,[51] etc., are properties which are exhibited by azines but not by hydrazones. Hence, it is very important to consider both the tautomers separately. In this article, we report the quantum chemical studies, synthesis, and structural analysis of two series of neutral guanylhydrazones (Figure 2). The structures of two such examples were established as azines through quantum chemical and spectral studies and confirmed by single crystal X-ray diffraction studies.

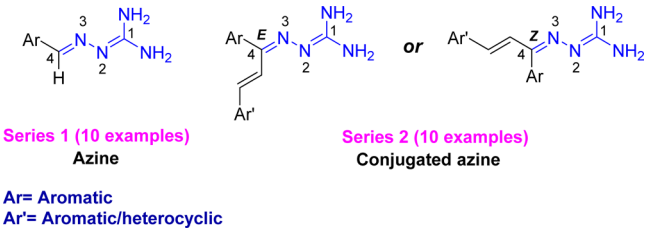


Figure 2. Guanylhydrazones considered in this study in their preferred azine form. *E*/*Z* isomers are expected for compounds in series 2. Based on the known literature *E*/*Z* isomers are not generally expected for compounds in series 1.

RESULTS AND DISCUSSION

A. Quantum Chemical Studies. This work was initiated by calculating the azine⇌hydrazone tautomeric energy difference in a few important guanylhydrazones listed in Figure 3. In all these cases it was found that the global minimum tautomer is in the azine form (**A**). In literature, they were reported in the salt form but are represented (e.g., in ZINC database)[52] in the form of hydrazone tautomer (**B**) in the neutral state.

Due to the presence of C4═N3 double bond in these guanylhydrazones (Figure 3), all these compounds may exhibit *E*/*Z* isomerism and hence the energy differences between the *E* and Z isomers of global minimum tautomer (azine) were also estimated (Table SI-2). In most of these cases, the *E* isomer was found to be more stable than the *Z* isomer (0.49−6.35 kcal/mol) except in the case of compounds **VIII** and **X** where the *Z* isomer was found to be marginally more stable (0.43−1.90 kcal/mol). Hence, the azines **I**−**XIV** in Figure 3 have been represented in the energetically most stable geometrical isomeric state.

In order to explore the effect of substitutions and extended conjugation on tautomeric energy differences in the designed molecules (series 1 and 2), ΔG_T was calculated using quantum chemical method (Table 1). In all cases, the azine tautomers are more stable than the corresponding hydrazone tautomers by 3−8 kcal/mol. Compounds containing an electron donating methoxy groups on the phenyl ring showed relatively lower ΔG_T (**19** and **20**) whereas compounds containing electron withdrawing groups such as chloro, fluoro, and nitro showed relatively higher ΔG_T (**11**, **16**, and **17**). Even under implicit solvent conditions (DMSO and H_2O), the preference is for the azine tautomers (Table SI-3). For compounds in series 1 and series 2, two geometrical isomers (*E*/*Z*) are possible with reference to the newly formed C4═N3 double bond. The crystal structure data of compounds **4** and **14** showed *E* geometry across C4═N3 double bond (*vide infra*). The ΔG_T values given in Table 1 are after employing the *E* geometrical isomer in all cases. The ΔG_{EZ} values (the difference between the *E* and *Z* isomers) were estimated using quantum chemical methods, the results are provided in Table SI-4.

B. Synthesis and Spectral Analysis. The conventional method for the synthesis of guanylhydrazones involves the condensation of the carbonyl compounds (aldehyde/ketone) with aminoguanidine hydrochloride in ethanol under reflux to give the desired hydrochloride salt.[7,53] The neutralization of the salts can be carried out to afford the guanylhydrazone free bases;[34] however, many workers did not report this neutralization step. In this work, the same reaction is carried out in the presence of aqueous NaOH to produce the compounds **1**−**10** directly in their neutral form, as precipitates (Scheme 1). Several advantages were noticed, though the modification is very nominal—(i) the green reaction conditions (aqueous solvent instead of organic solvent), (ii) the reaction is completed within an hour, whereas the conventional method required more than 6 h, (iii) the reaction can be carried out at room temperature, instead of reflux (∼80 °C), and (iv) in the conventional method, during neutralization, some loss of the product was noticed, which is avoided during the single step procedure. The neutral compounds (**11**−**20**) in series 2 (Scheme 2) were obtained by the neutralization of **11**−**20**·HCl. The salts (**11**−**20**·HCl) were synthesized using conventional method from chalcones which were obtained employing reported methods.[36,54−57] The direct synthesis of **11**−**20** using the above-defined method (as in compounds of series 1) is not applicable because the reaction of α,β-unsaturated ketones, under basic conditions, is known to yield cyclized products.[58,59]

During neutralization, two geometrical isomers (*E* and *Z*) across the newly formed −C═N bond have been observed in two of the compounds, i.e., **12** and **18** in the ratio of 2:1 (*E*:*Z*) (calculated from integration of proton signals). It is important to note that the compounds **2**, **7**, **8**, and **11** were previously reported in their hydrochloride salt.[36,60−62]

All the synthesized compounds were characterized by NMR, IR, and mass spectroscopy techniques. The most convincing evidence for the presence of the azine tautomer in the synthesized compounds is obtained from the ^{1}H NMR in

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

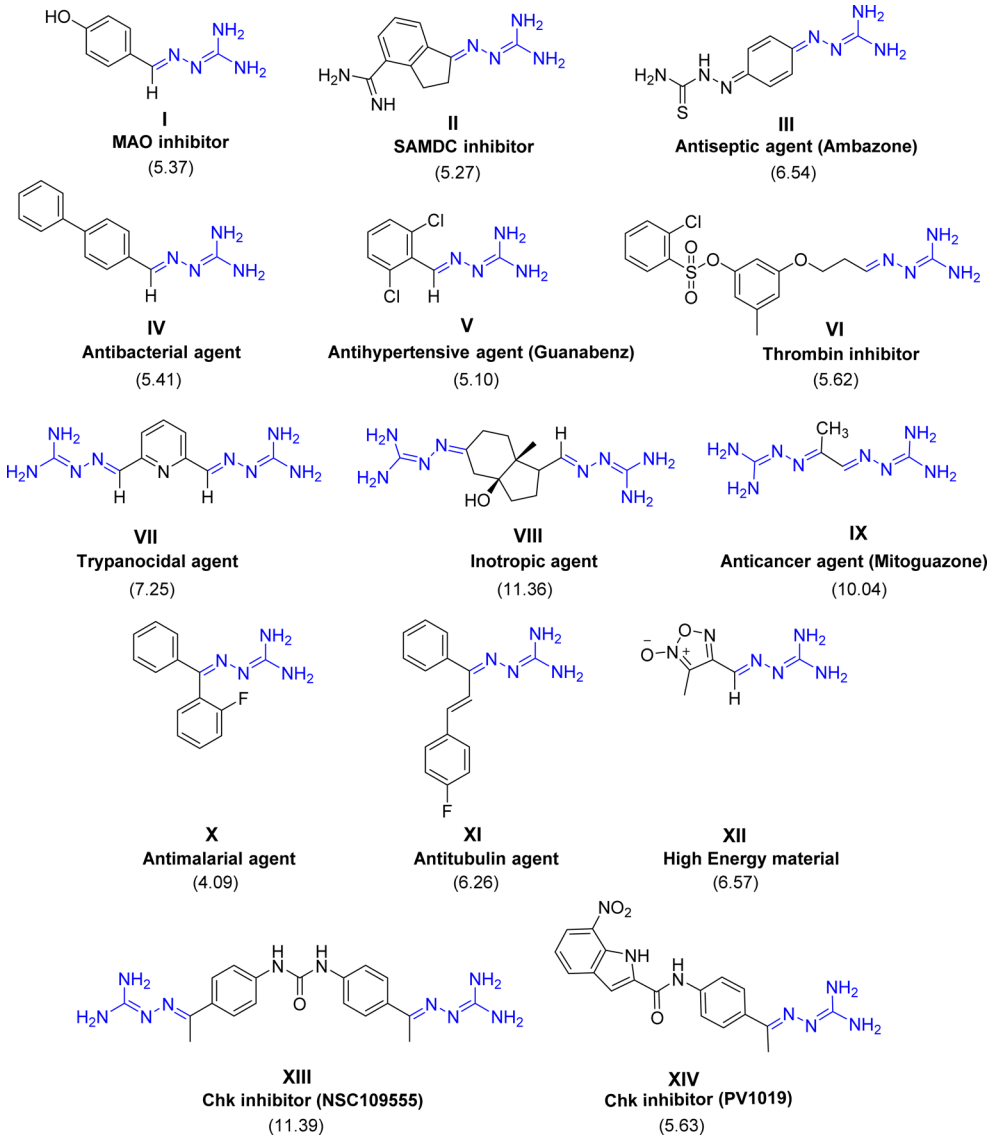


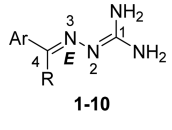
Figure 3. 2D structures of several important azine derivatives. In the literature all of these compounds were represented as guanylhydrazone derivatives. In this figure, they are given in their energetically preferred azine tautomeric representation (values in parentheses indicate the azine⇋hydrazone tautomeric energy difference, ΔG_T in kcal/mol, where T represents tautomer, calculated at B3LYP/6-311++G(d,p) level). Absolute Gibbs free energy and the optimized 3D structures are given in Supporting Information (Table SI-1).

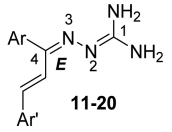
solution.[63] In dimethyl sulfoxide-d_6, the ^{1}H NMR spectrum of the synthesized free bases **1**−**20** exhibited two slightly broadened singlets (at ∼5.4−6.5 ppm). The broad peaks were due to the protons bound to the nitrogen atoms and were confirmed by deuterium exchange study (Figure SI-1). The consistent pattern and the intensity ratio (1:1) of the broad peaks in **1**−**20** can be explained by assuming that the compounds carry two terminal NH_2 groups which are chemically nonequivalent and thus would be expected to have different chemical shifts. They are chemically nonequivalent because of the presence of hydrogen-bond interactions between the hydrogen atoms of guanidinyl group and an imino N3 atom (Figure 2). In the case of hydrazone and its salt, the −NH proton appears in the range of 11−14 ppm in ^{1}H NMR.[64−67] This was found to be true in all the salts (Scheme 2) prepared during this work. After neutralization, disappearance of −NH proton in the region 11−14 ppm in ^{1}H NMR and an existence of two broad singlets of $-NH_2$ at 5.5−6.5 ppm confirms the formation of the azine at room temperature.

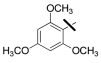
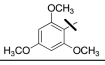
Variable temperature ^{1}H NMR of compound **14** was recorded and it was found that at higher temperature (70 °C), (because of the breaking of hydrogen bond interactions between hydrogen atom of guanidinyl group and an imino N3) the two $-NH_2$ peaks become equivalent and thus give rise to broad singlet of four protons. Even at 70 °C, the characteristic −NH peak of the hydrazone tautomer in the range of 11−14 ppm did not appear (Figure 4). This indicates that no traces of hydrazone tautomer can be identified even at higher temperature and hence confirm that under experimental condition only the azine tautomer exists. The quantum chemical studies were carried out for further exploration. Though azine⇋hydrazone tautomerism was not observed even at higher temperature, thermal isomerization may be possible in compound **14** due to the presence of two imine groups. Three different mechanisms of *E*/*Z* isomerization, i.e., pure inversion, pure rotation, or intermediate mechanism, were proposed earlier in the literature.[68−71] In order to explore the mechanism of thermal isomerization in the case of azine **14**, we

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

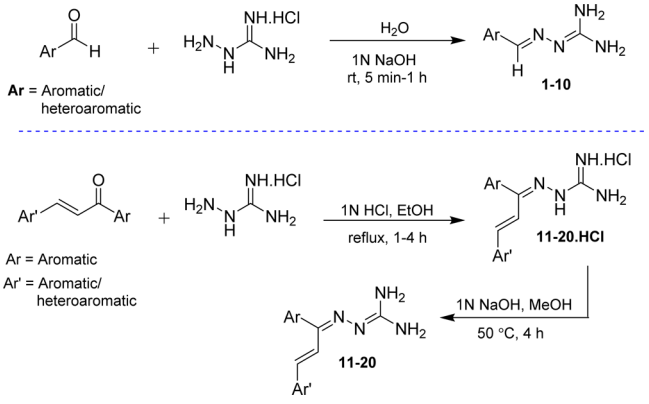
Table 1. Influence of Substituents on the Energy Difference (ΔG_T in kcal/mol) Between the Azine and the Hydrazone Tautomers (1−20) with Azine Structure Taken as a Base



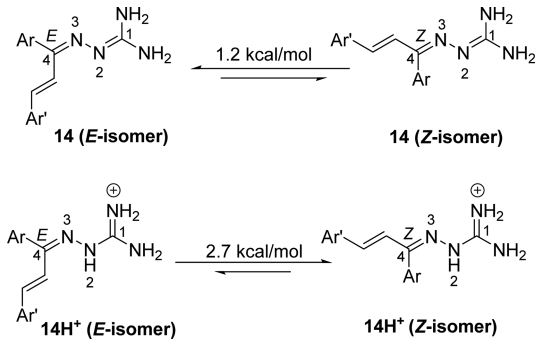


Compd	Ar	R	ΔG_T	Compd	Ar	Ar'	ΔG_T
V		H	5.96				
1		H	5.40	11			6.25
2		H	5.00	12			5.51
3		H	5.50	13			5.65
4		H	5.69	14			5.62
5		H	5.90	15			5.72
6		H	4.84	16			8.43
7		H	6.04	17			6.35
8		CH_3	6.21	18			6.43
9		H	5.74	19			3.72
10		H	5.55	20			4.04

Scheme 1. Synthesis of Azines 1−20



Scheme 2. ΔG_{EZ} Values Across N3−C4 Bond in Compounds 14 and $14H^+$ Calculated at B3LYP/6-311++G(d,p) Level of Theory



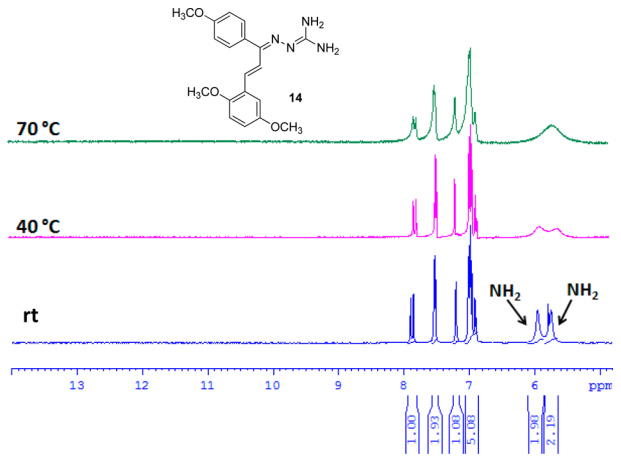


Figure 4. Variable temperature ^{1}H NMR of compound **14**.

calculated the N-inversion barriers for N2 and N3 imine nitrogen centers in the gas phase. The inversion barrier for N2 and N3 nitrogen centers were found to be 22.7 and 38.7 kcal/mol, respectively. Based on the angle α (C−N−N) in the ground (α_G) and in the transition (α_T) states, the percentage of inversion and rotation mechanism associated with thermal isomerization were estimated using the following eq 1[72]

$$\beta_I = \frac{(\alpha T - \alpha G) \times 100}{180 - \alpha G} \quad (1)$$

where β_I is percent of inversion mechanism, α_G = CNN bond angle in the ground state, α_G = 112°, αT = CNN bond angle in the transition state, α_{GN2} = 146.3°, and α_{GN3} = 160.6°. The

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

percentage of rotation mechanism, β_R, can be obtained by subtracting β_I from 100.

The β_I for N2 nitrogen was found to be 50% indicating that the N2 nitrogen is associated with mixed inversion and C=N rotation. The β_I for N3 was found to be ~70% (a table comparing energy barriers and structural parameters in ground state and transition state of azine **14** is given in Table SI-5). Thus, at 70 °C, it is possible that the compound **14** may undergo 2-fold nitrogen inversion across the N2 and N3 nitrogen centers.

The ^{13}C NMR chemical shifts were estimated using the GIAO method for both the azine and the hydrazone tautomers of compounds **1**–**20**. The characteristic signal to distinguish the tautomers is due to C1 carbon which was observed in the range of 159–162 ppm in all of the synthesized compounds. The NMR simulation study of compounds in series 1 revealed that in case of the hydrazone tautomer, the calculated chemical shift for the C1 carbon is appearing in the range of 154–157 which is far from the experimentally observed C1 chemical shift. However, in the case of the azine tautomer, the calculated ^{13}C NMR of azine tautomer, the chemical shift for C1 carbon is appearing in the range of 159–164 which is very close to the experimental values (Table 2). A similar clear distinction was not observed for compounds in series 2 (Table SI-6).

Table 2. Comparison of Experimental and Theoretical ^{13}C NMR Chemical Shift Values (ppm) for the Azine and the Hydrazone Tautomers of Compounds 1–10

	^{13}C NMR, C1 (calculated, gas phase)		
compd	hydrazone	azine	^{13}C NMR, C1 (observed) experimental
1	156.9	163.1	161.0
2	153.9	159.3	162.2
3	157.4	164.0	161.7
4	156.6	162.2	161.5
5	157.0	163.0	161.7
6	154.2	159.0	161.7
7	157.7	161.3	160.1
8	156.5	162.8	160.5
9	156.3	162.7	161.9
10	154.5	164.0	162.4

Crystal Structure Analysis. In order to confirm the structural features of the synthesized compounds, single crystals of compounds **4** and **14**, obtained by slow evaporation of their methanol solutions, were studied by X-ray diffractometry.[73,74] The analysis of single crystal structures reveals that **4** and **14** contain free terminal NH_2 groups and exist in *s*-trans form across the N–N single bond (Figure SI-3 and SI-4). The geometrical parameters from the crystal structures of **4** and **14** indicate that the synthesized compounds are in the azine tautomeric state (Figure 5). The important geometrical parameters of **4** and **14** are given in Table 3. The molecular geometries of compounds **4** and **14** are also consistent with the ^{1}H NMR spectrum, which shows a characteristic azine $-NH_2$ signal at 5.5–6.5 ppm. The geometrical parameters obtained from quantum chemical analysis and X-ray diffraction are quite comparable (Table 3), the small differences are due to the packing forces (which are governed by intermolecular interaction) in the solid state.

Table 3. Important Geometrical Parameters of 4 and 14[a]

	4		**14**	
parameters	DFT	X-ray	DFT	X-ray
bond lengths				
C1–N2	1.301	1.327	1.302	1.330
C4–N3	1.285	1.278	1.302	1.306
N2–N3	1.381	1.385	1.380	1.386
bond angles				
C1–N2–N3	112.89	110.37	111.58	111.22
C4–N3–N2	114.07	116.68	116.98	116.08
dihedral angles				
C1–N2–N3-C4	175.67	179.74	174.125	161.86
C5–C4–N3-N2	179.32	178.77	2.84	6.40

[a]Comparison between the XRD data and DFT (B3LYP/6-311++G(d,p)) data is listed. Distances are in Å and angles are in degree (deg).

According to the quantum chemical data, compound **4** prefers a *Z* geometrical isomer in gas phase condition by a marginal ΔG_{EZ} value (0.75 kcal/mol, see Supporting Information, Table SI-4). But in the crystal structure, the intermolecular hydrogen bonds ensure that the *E* isomer is the preferred geometrical isomer. The crystal structure of the corresponding hydrochloride salt of compound **14**[75] is provided in the Supporting Information (Figure-SI-5).

The crystal structure of **14**·HCl (Figure SI-5) indicates *E* geometry across N3–C4 bond, which is different from the crystal structure of guanidine derivative reported earlier as *Z* isomer.[36] The ΔG_{EZ} in **14** is 1.20 kcal/mol (in favor of *E*

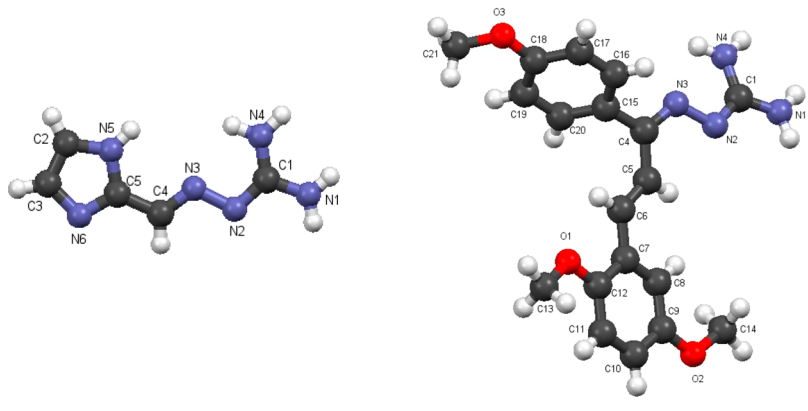


Figure 5. 3D solid state structures of **4** (left) and **14** (right) determined by the single crystal X-ray diffraction method.

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574–7583

isomer) and ΔG_{EZ} in **14**·HCl is 2.72 kcal/mol (in favor of *Z* isomer) calculated using B3LYP with 6-311++G(d,p) basis set (Scheme 2, Table SI-7). The observed structural differences and the small energy differences indicate that **11**−**20** can possibly show polymorphism originating from geometrical isomerism.

CONCLUSIONS

Several guanylhydrazones have been reported in literature. Recent quantum chemical studies reported that these compounds should be considered as azines rather than hydrazones. To verify this dichotomy, two series of azines (with and without extended conjugation) were synthesized. The quantum chemical calculations, NMR, and XRD data clearly suggest that the azine tautomer is the preferred tautomeric state of this class of compounds. Although, the tautomeric energy difference is small (3−8 kcal/mol), the NMR data up to 70 °C showed only the azine tautomer without any traces of hydrazone tautomer. Thus, in the case of guanylhydrazones, we should consider only the azine tautomer in all future studies. In the organic and medicinal chemistry literature, these compounds are generally represented in their hydrazone form, but this study shed light on its structural features and suggests that the correct tautomer (azine) should be considered in medicinal chemistry as well as in organic chemistry. The modified synthetic strategy adopted in this work carries the additional advantage of direct access of the preparation of neutral azines.

EXPERIMENTAL SECTION

Computational Methods. The quantum chemical calculations were performed using the Gaussian 09[76] suite of programs. Geometry optimization of compounds **I-XIV** and **1**−**20** was performed by DFT[77] using B3LYP[78] method. The basis set used was 6-311++G(d,p). To estimate the effect of the solvent, we employed the self-consistent reaction field theory (SCRF) polarizable continuum model (IEFPCM),[79] as implemented in Gaussian09, at the B3LYP/6-311++G(d,p) level of theory. Frequency calculations were carried out on all the structures to verify stationary point with zero negative frequency. NMR calculations were performed by using the GIAO method.[80,81]

Chemistry. The reagents and chemicals required for the study were procured and were used as such without further purification unless otherwise mentioned. The progress of the reaction was monitored by thin layer chromatography (TLC) performed on silica gel aluminum plates and visualization was done by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz spectrometer respectively, with TMS as an internal standard. The ^{1}H NMR and ^{13}C NMR spectra were recorded for DMSO-d_6 at 2.50 and 39.51 ppm, respectively. Chemical shifts (δ) are reported in part per million (ppm). Coupling constants (J) were reported in hertz (Hz). The abbreviations used to characterize the signals are as follows: s = singlet, m = multiplet, d = doublet, br s = broad singlet, dd = doublet of doublet, t = triplet. High resolution mass spectra were taken using ESI-TOF method. Mass spectra were recorded using ESI mode. Melting points were determined by using melting point apparatus.

*General Procedure for the Synthesis of Azines (**1**−**10**).* To the substituted carboxaldehyde and aminoguanidine hydrochloride in H_2O was added 1N NaOH (2 mL) and the reaction mixture was stirred for 5 min−1 h, until precipitate is formed. The resultant precipitate was filtered and dried to afford the desired azines **1**−**10** in 63 to 96% yields.

*(E)-4-([1,1′-Biphenyl]-4-yl)-1,1-diamino-2,3-diazabuta-1,3-diene (**1**).* White solid (420 mg, 81%). mp 235−237 °C; IR (KBr, cm^{-1}): 3358, 1663, 1538, 1148; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.36 (s, 1H), 5.95 (br s, 2H), 5.53 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 143.2, 140.2, 139.6, 136.6, 129.4, 127.8, 127.2, 127.0, 126.9; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{14}H_{15}N_4$ 239.1296; Found 239.1283.

*(E)-4-(2-Chloroquinolin-3-yl)-1,1-diamino-2,3-diazabuta-1,3-diene (**2**).* Yellow solid (440 mg, 82%). mp 217−220 °C; IR (KBr, cm^{-1}): 3477, 1616, 1519, 1137; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.30 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 6.29 (br s, 2H), 5.81 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 146.5, 137.0, 134.2, 130.7, 129.1, 128.5, 128.1, 127.9, 127.8; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{11}H_{11}ClN_5$ 248.0703; Found 248.0699.

*(E)-4-(4-(Dimethylamino)-2-nitrophenyl)-1,1-diamino-2,3-diazabuta-1,3-diene (**3**).* Brown solid (472 mg, 87%). mp 170−173 °C; IR (KBr, cm^{-1}): 3361, 1602, 1519, 1371; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 8.04 (d, J = 12 Hz, 1H), 7.05 (d, J = 4 Hz, 1H), 6.98 (dd, J = 8.8, 2.5 Hz, 1H), 6.49 (br s, 4H), 2.99 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 150.5, 149.5, 139.5, 129.2, 116.6, 116.3, 105.8, 23.7; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{10}H_{15}N_6O_2$ 251.1256; Found 251.1250.

*(E)-4-(1H-Imidazol-2-yl)-1,1-diamino-2,3-diazabuta-1,3-diene (**4**).* Yellow solid (315 mg, 96%). mp 200−203 °C; IR (KBr, cm^{-1}): 3378, 1621, 1538, 1144; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.06 (s, 2H), 6.49 (br s, 2H), 6.02 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.8, 161.6, 146.2, 133.4; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_5H_8N_6Na$ 175.0708; Found 175.0708.

*4-(1,2,3-Thiadiazol-4-yl)-1,1-diamino-2,3-diazabuta-1,3-diene (**5**).* White solid (174 mg, 96%). mp 180−183 °C; IR (KBr, cm^{-1}): 3407, 1634, 1541, 1159; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.68 (s, 1H), 5.97 (br s, 2H), 5.90 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 161.5, 133.8, 131.8; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_4H_7N_6S$ 171.0452; Found 171.0450.

*(E)-4-(Benzofuran-2-yl)-1,1-diamino-2,3-diazabuta-1,3-diene (**6**).* Yellow solid (120 mg, 86%). mp 205−207 °C; IR (KBr, cm^{-1}): 3410, 1599, 1525, 1158; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.16−7.32 (m, 2H), 7.02 (s, 1H), 6.02 (br s, 2H), 5.81 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 154.6, 154.7, 133.2, 129.0, 124.9, 123.5, 121.4, 111.3, 104.8; HRMS (ESI-TOF) m/z: [M]$^+$ Calcd for $C_{10}H_{11}N_4O$ 203.0932; Found 203.0929.

*(E)-4-(1H-Pyrrol-2-yl)-1,1-diamino-2,3-diazabuta-1,3-diene (**7**).* Yellow solid (120 mg, 77%). mp 195−197 °C; IR (KBr, cm^{-1}): 3402, 1622, 1440, 1278; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (br s, 1H), 7.02 (s, 1H), 6.85 (s, 1H), 6.24 (s, 1H), 6.08 (s, 1H), 5.89 (br s, 2H), 5.57 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 133.9, 130.2, 118.9, 111.1, 108.4; HRMS (ESI-TOF) m/z: [M]$^+$ Calcd for $C_6H_9N_5$ 151.0858; Found 151.0880.

*(E)-4-(4-(1H-Imidazol-1-yl)phenyl)-1,1-diamine-2,3-diaza-1,3-pentadiene (**8**).* Yellow solid (330 mg, 63%). mp 208−210 °C; IR (KBr, cm^{-1}): 3439, 1651, 1520, 1166; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.77 (t, J = 4, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.11 (s, 1H), 5.94 (br s, 2H), 5.54 (br s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.8, 159.6, 146.9, 139.2, 135.8, 130.1, 127.1, 120.4, 118.0, 13.5; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{12}H_{15}N_6$ 243.1358; Found 243.1347.

*(E)-4-(Thiazol-2-yl)1,1-diamino-2,3-diazabuta-1,3-diene (**9**).* Yellow solid (138 mg, 76%). mp 190−193 °C; IR (KBr, cm^{-1}): 3435, 1618, 1532, 1145; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s., 1H), 7.84 (s, 1H), 7.45 (s 1H), 6.00 (br s, 2H), 5.93 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 161.9, 143.5, 137.3, 119.1; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_5H_8N_5S$ 170.0500; Found 170.0500.

*(E)-4-(Benzo[d]thiazol-2-yl) 1,1-diamino-2,3-diazabuta-1,3-diene (**10**).* Yellow solid (120 mg, 86%). mp 215−218 °C; IR (KBr, cm^{-1}): 3413, 1618, 1490, 1141; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.97 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 7.45 (t, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H) 6.20 (br s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.6, 162.5, 153.9, 136.7, 133.9, 126.6, 125.6, 122.6, 122.3; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_9H_{10}N_5S$ 220.0656; Found 220.0647.

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

*General Procedure for the Synthesis of Conjugated Azines (**11**−**20**).* Conjugated azines **11**−**20** were synthesized from substituted chalcones and aminoguanidine hydrochloride by adopting conventional synthesis. The substituted chalcones were in turn prepared by treating substituted acetophenone with substituted aldehydes using 10% NaOH in ethanol at room temperature for 2−72 h. These chalcones (1 mmol) and aminoguanidine HCl (1 mmol) in ethanol (2 mL) were refluxed in the presence of conc. HCl (0.2 mL). The completion of reaction was monitored by TLC (1−4 h). The reaction mixture was subjected to rota evaporation and recrystallized using ethyl acetate/acetone/hexane to obtain **11**−**20**·HCl in the yield of 63−95%. The recrystallized salts were neutralized by treating with 1N NaOH in methanol at 50 °C for 4 h. The reaction mixture was concentrated by evaporation under reduced pressure, and the aqueous residue was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to obtain neutral conjugated azines **11**−**20** in the yield of 73−95%.

*(3E,5E)-6-(4-Chlorophenyl)-4-(phenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**11**).* Yellow solid (65 mg, 73%). mp 170−173 °C; IR (KBr, cm^{-1}): 3468, 1617, 1530, 1255; ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 16 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.51 (d, J = 8 Hz, 2H), 7.33−7.42 (m, 5H), 6.75 (d, J = 16 Hz, 1H), 5.96 (br s, 2H), 5.80 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 162.8, 160.7, 149.4, 139.5, 136.7, 132.7, 131.6, 129.2, 128.9, 128.7,128.4, 127.9, 122.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{16}ClN_4$ 299.1063; Found 299.1058.

*(E)-2-((E)-1,3-Bis(4-methoxyphenyl)allylidene)-hydrazinecarboximidamide Hydrochloride (**12**·HCl).* Cream solid (280 mg, 70%). mp 180−183 °C; IR (KBr, cm^{-1}): 3445, 1687, 1593, 1235; ^1H NMR (400 MHz, $CDCl_3$) δ 11.74 (br s, 2H), 7.97 (br s, 2H), 7.68 (d, J = 8 Hz, 2H), 7.54 (d, J = 16 Hz, 1H), 7.47 (d, J = 12 Hz, 2H), 6.94 (d, J = 8 Hz, 2H), 6.88 (d, J = 8 Hz, 2H), 6.87 (d, J = 16 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 156.4, 154.6, 142.6, 130.7, 130.0, 128.9, 128.2, 115.8, 114.2, 113.7, 55.4, 55.3; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{18}H_{21}N_4O_2$ 325.1659; Found 325.1653.

*(3E,5E)-6-(4-Methoxyphenyl)-4-(4-methoxyphenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**12**); Mixture of E and Z Isomers (2:1).* Yellow solid (88 mg, 89%). mp 153−155 °C; IR (KBr, cm^{-1}): 3448, 1607, 1503, 1245; ^1H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 16 Hz, 1H), 7.53 (d, J = 8 Hz, 2H), 7.48 (d, J = 12 Hz, 2H), 7.39 (d, J = 8 Hz, 1H), 7.19 (d, J = 8 Hz, 1H), 7.06 (d, J = 16 Hz, 1H), 7.01−6.98 (m, 5H), 6.93 (d, J = 8 Hz, 1H), 6.71 (d, J = 16 Hz, 1H), 6.21 (d, J = 16 Hz, 0.5H), 5.98 (br s, 1H), 5.89 (br s, 2H), 5.69 (br s, 2H), 5.50 (br s, 1H), 3.85 (s, 5 H), 3.83 (s, 3H), 3.80 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) 160.1, 159.7, 159.3, 159.1, 158.6, 150.4, 133.1, 132.0, 130.8, 130.5, 130.2, 128.5, 127.9, 119.7, 114.6, 114.7, 113.8, 113.7, 55.6, 55.5, 55.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_4O_2$ 325.1664; Found 325.1659.

*(E)-2-((E)-1-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-allylidene)hydrazine Carboximidamide Hydrochloride (**13**·HCl).* Cream solid (400 mg, 95%). mp 172−175 °C; IR (KBr, cm^{-1}): 3460, 1570, 1413, 1254; ^1H NMR (400 MHz, DMSO-d_6) δ 11.91 (br s, 1H), 7.75 (br s, 3H), 7.66 (d, J = 12 Hz, 1H), 7.64 (d, J = 16 Hz, 2H), 7.16 (s, 2H), 7.04 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 16 Hz, 1H), 3.84 (s, 6H), 3.82 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz DMSO-d_6) δ 160.3, 155.8, 152.9, 152.6, 141.1, 138.7, 130.8, 130.5, 128.3, 117.5, 113.7, 105.6, 60.0, 56.2, 55.2; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{20}H_{25}N_4O_4$ 385.1870; Found 385.1868.

*(3E,5E)-4-(4-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**13**).* Yellow solid (80 mg, 89%). mp 148−151 °C; IR (KBr, cm^{-1}): 3434, 1634, 1463, 1125; ^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 16 Hz, 1H), 7.54 (d, J = 9.56 Hz, 2H), 7.01 (d, J = 8 Hz, 2H), 6.86 (s, 2H), 6.73 (d, J = 16.7 Hz, 1H), 5.93 (br s, 2H), 5.71 (br s, 2H), 3.86 (s, 6H), 3.85 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.2, 159.3, 153.5, 149.8, 138.1, 133.5, 132.2, 130.2, 121.3, 113.8, 104.5, 60.6, 60.2, 56.4, 55.6 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{25}N_4O_4$ 385.1875; Found 385.1861.

*(E)-2-((E)-3-(2,5-Dimethoxyphenyl)-1-(4-methoxyphenyl)-allylidene)hydrazinecarboximid Amide Hydrochloride (**14**·HCl).* Yellow solid (234 mg, 66%). mp 168−170 °C; IR (KBr, cm^{-1}): 3469, 1682, 1513, 1249; ^1H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 7.78 (br s, 3H), 7.69 (d, 1H), 7.64 (d, J = 16 Hz, 1H), 7.60 (d, J = 8 Hz, 2H), 7.18 (d, J = 16 Hz, 1H), 7.03 (d, J = 8 Hz, 2H), 6.96−6.97 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H): ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 156.4, 153.9, 152.0,135.3, 131.1, 128.9, 124.7, 118.7, 118.1, 114.1, 113.5, 56.6, 56.4, 55.7; LC-MS (ESI) m/z: $[M]^+$ Calcd for $C_{19}H_{23}N_4O_3$ 355.1770; Found 355.14.

*(3E,5E)-6-(2,5-Dimethoxyphenyl)-4-(4-methoxyphenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**14**).* Yellow solid (80 mg, 88%). mp 155−158 °C; IR (KBr, cm^{-1}): 3436, 1626, 1509, 1246; ^1H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 16 Hz, 1H), 7.48 (d, J = 8 Hz, 2H), 7.13 (d, J = 2.8 Hz, 1H), 6.96−6.84 (m, 5H), 5.89 (br s, 2H), 5.71 (br s, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.2, 159.4, 153.8, 151.4, 150.9, 131.8, 130.3, 127.9, 126.7, 121.7, 115.3, 13.9, 113.2, 111.3, 60.5, 56.5, 55.9, 55.6; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{19}H_{23}N_4O_3$ 355.1770; Found 355.1757.

*(E)-2-((E)-3-(4-(Benzyloxy)phenyl)-1-(4-methoxyphenyl)-allylidene)hydrazine Carboximidamide Hydrochloride (**15**·HCl).* White solid (280 mg, 71%). mp 180−182 °C; IR (KBr, cm^{-1}): 3246, 3158, 1604, 1509, 1244; ^1H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 7.74 (d, J = 8.8 Hz, 5H), 7.61 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 3H), 7.40 (d, J = 16 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 16 Hz, 1H), 5.17 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 160.0, 156.3, 153.5, 141.2, 137.2, 131.0, 128.9, 128.7, 128.3, 128.1, 116.5, 115.6, 114.2, 69.8, 55.8; LC-MS (ESI) m/z: $[M]^+$ Calcd for $C_{24}H_{25}N_4O_2$ 401.1977; Found 401.24.

*(3E,5E)-6-(4-(Benzyloxy)phenyl)-4-(4-methoxyphenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**15**).* Yellow solid (82 mg, 90%). mp 160−162 °C ; IR (KBr, cm^{-1}): 3435, 1633, 1508, 1247; ^1H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 16 Hz, 1H), 7.48−7.31 (m, 9H), 7.01 (d, J = 8 Hz, 2H), 6.94 (d, J = 8 Hz, 2H), 6.65 (d, J = 16 Hz, 1H), 5.84 (br s, 2H), 5.65 (br s, 2H), 5.12 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.1, 159.3, 158.8, 137.4, 132.9, 130.5, 130.2, 128.9, 128.5, 128.3, 119.9, 115.6, 113.8, 69.7, 55.6; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{25}N_4O_2$ 401.1977; Found 401.1960.

*(E)-2-((E)-1-(4-Methoxyphenyl)-3-(3-nitrophenyl)allylidene)-hydrazinecarboximidamide Hydrochloride (**16**·HCl).* Yellow solid (250 mg, 86%). mp 163−165 °C ; IR (KBr, cm^{-1}): 3507, 1610, 1509, 1251; ^1H NMR (400 MHz, DMSO-d_6) δ 11.58 (br s, 1H), 8.58 (s, 1H), 8.30 (d, J = 7.84 Hz, 1H), 8.23 (dd, J = 4, 8.24 Hz, 1H), 7.74 (br s, 3H), 7.73 (d, J = 8 Hz, 1H), 7.69 (d. J = 8.88 Hz, 2H), 7.66 (d, J = 16 Hz, 1H), 7.08 (d, J = 16.36 Hz, 1H), 7.02 (d, J = 9.76 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 156.2, 152.3, 148.7, 138.7, 137.7, 134.7, 130.9, 130.7, 128.4, 124.2, 122.9, 121.7, 114.3, 55.8; LC-MS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{18}N_5O_3$ 340.1409; Found 340.16.

*(3E,5E)-4-(4-Methoxyphenyl)-6-(3-nitrophenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**16**).* Brown solid (77 mg, 86%). mp 142−143 °C; IR (KBr, cm^{-1}): 3434, 1626, 1414, 1254; ^1H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.12 (dd, J = 8 Hz, 2 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 7.97 (d, J = 16 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 7.53 (d, J = 16 Hz, 2H), 6.96 (d, J = 8 Hz, 2H), 6.92 (d, J = 16 Hz, 1H), 6.07 (br s, 4H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 159.6, 149.1, 148.7, 139.5, 133.7, 132.0, 131.2, 130.6, 130.3, 123.8, 122.9, 121.3, 113.9, 55.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_5O_3$ 340.1409; Found 340.1396.

*(E)-2-((E)-3-(4-Fluorophenyl)-1-(4-methoxyphenyl)allylidene)-hydrazinecarboximidamide Hydrochloride (**17**·HCl).* Cream solid (278 mg, 89%). mp 133−135 °C; IR (KBr, cm^{-1}): 3449, 1624, 1508, 1256; ^1H NMR (400 MHz, DMSO-d_6) δ 11.78 (s,1H), 7.86−7.89 (m, 2H), 7.82 (br s, 3H), 7.63 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 16.4 Hz, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 16.4 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 159.2, 158.0, 154.9 (d, 1JC-F = 274.5 Hz), 141.7, 137.9, 131.0, 130.2,

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

127.1,119.5, 118.5, 117.3, 115.6, 114.9, 55.7; LC-MS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{18}FN_4O$ 313.1464; Found 313.09.

*(3E,5E)-6-(4-Fluorophenyl)-4-(4-methoxyphenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**17**).* Brown solid (89 mg, 89%). mp 118−120 °C; IR (KBr, cm^{-1}): 3466, 1604, 1508, 1249; ^1H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 16 Hz, 1H), 7.47−7.39 (m, 4H), 7.10 (t, J = 8 Hz, 2H), 6.85 (d, J = 8, 2H), 6.63 (d, J = 16 Hz, 1H), 5.81 (s, 2H), 5.64 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3 (d, 1JC-F = 244 Hz), 160.3, 159.3, 149.4, 134.2 (JC−C−C-C-F = 3 Hz), 132.0, 131.8, 130.1, 129.0, 128.9, 121.9, 116.2, 115.9, 113.8, 55.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}FN_4O$, 313.1464; Found 313.1450.

*(E)-2-((E)-3-(1H-Imidazol-2-yl)-1-(4-methoxyphenyl)allylidene)-hydrazinecarboximidamide Hydrochloride (**18**·HCl).* Cream solid (290 mg, 74%). mp 198−201 °C; IR (KBr, cm^{-1}): 3504, 1610, 1509, 1251; ^1H NMR (400 MHz, DMSO-d_6) δ 11.56 (br s, 1H), 7.91 (br s, 3H), 7.75−7.82 (m, 5H), 7.02 (d, J = 8 Hz, 2H), 6.89 (d, J = 16 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 156.2, 150.3, 141.7, 130.5, 128.2, 127.3, 121.6, 121.3, 114.4, 55.8;LC-MS (ESI) m/z: $[M]^+$ Calcd for $C_{14}H_{17}N_6O$ 285.1463; Found 285.05.

*(3E,5E)-6-(1H-Imidazol-2-yl)-4-(4-methoxyphenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**18**); Mixture of E and Z Isomers (2:1).* Brown solid (88 mg, 95%). mp 180−183 °C; IR (KBr, cm^{-1}): 3362, 1608, 1509, 1246; ^1H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 2H), 7.90 (d, J = 16 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.23 (d, J = 16 Hz, 1H), 7.21−6.94 (m, 6H), 6.56 (d, J = 16 Hz, 1H), 6.03 (d, J = 16 Hz, 1H), 5.92 (br s, 2H), 5.64 (br s, 3H), 3.77 (s, 5H); ^{13}C NMR (100 MHz, DMSO-d_6); 160.3, 159.3, 158.6, 158.1,151.4, 149.5, 147.7, 145.9, 131.8,130.8, 130.1,122.4, 122.0, 113.9, 113.8, 55.6, 55.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}N_6O$ 285.1463; Found 285.1477.

*(E)-2-((E)-3-(2,4,6-Trimethoxyphenyl)-1-(phenyl)allylidene)-hydrazinecarboximidamide Hydrochloride (**19**·HCl).* Orange solid (136 mg, 66%). mp 175−178 °C; IR (KBr, cm^{-1}): 3401, 1616, 1446, 1249; ^1H NMR (400 MHz, DMSO-d_6) δ 11.17 (br s, 1H), 7.77 (br s, 3H), 7.60 (d, J = 8 Hz, 2H), 7.55 (d, J = 16 Hz, 1H), 7.45−7.48 (m, 3H), 7.07 (d, J = 16 Hz, 1H), 6.28 (s, 2H), 3.83 (s, 3H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) 162.8, 160.6, 156.5, 156.3, 137.1, 133.7, 129.8, 128.7, 117.8, 105.7, 91.3, 56.5, 55.9; LC-MS (ESI) m/z: $[M]^+$ Calcd for $C_{19}H_{23}N_4O_3$ 355.1770; Found 355.21.

*(3E,5E)-6-(2,4,6-Trimethoxyphenyl)-4-(phenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**19**).* Yellow solid (80 mg, 88%). mp 153−155 °C; IR (KBr, cm^{-1}): 3421, 1626, 1436, 1219; ^1H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 16 Hz, 1H), 7.60 (d, J = 8 Hz, 2H), 7.37−7.45 (m, 3H), 6.87 (d, J = 16 Hz, 1H), 6.30 (s, 2H), 5.92 (br s, 2H), 5.70 (br s, 2H), 3.86 (s, 3H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 159.8, 159.5, 152.8, 139.9, 129.2, 128.2, 127.8, 125.2, 123.1, 107.4, 91.3, 60.2, 56.2, 55.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{23}N_4O_3$ 355.1770; Found 355.1754.

*(E)-2-((E)-1-(4-Chlorophenyl)-3-(2,4,6-trimethoxyphenyl)-allylidene)hydrazine carboximidamide Hydrochloride (**20**.HCl).* Cream solid (136 mg, 63%). mp 180−183 °C ; IR (KBr, cm^{-1}): 3459, 1545, 1487, 1135; ^1H NMR (400 MHz, DMSO-d_6) 11.04 (s, 1H), 7.77 (br s, 3H), 7.67 (d, J = 8 Hz, 3H), 7.53 (d, J = 8 Hz, 2H), 7.48 (d, J = 16 Hz, 1H), 7.05 (d, J = 16 Hz, 1H), 6.29 (s, 2H), 3.83 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 160.1, 155.8, 154.4, 135.4, 134.2, 133.0, 131.0, 128.2, 116.9 105.0, 90.8, 56.0, 55.4; LC-MS (ESI) m/z: $[M]^+$ Calcd for $C_{19}H_{22}ClN_4O_3$ 389.1380; Found 389.87.

*(3E,5E)-6-(2,4,6-Trimethoxyphenyl)-4-(4-chlorophenyl)-1,1-diamino-2,3-diaza-1,3,5-hexatriene (**20**).* Yellow solid (69 mg, 75%). mp 168−170 °C ; IR (KBr, cm^{-1}): 3450, 1575, 1457, 1125; ^1H NMR (400 MHz, DMSO-d_6) 7.96 (d, J = 16 Hz, 1H), 7.62 (d, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 2H), 6.85 (d, J = 16 Hz, 1H), 6.30 (s, 2H), 5.90 (br s, 2H), 5.66 (br s, 2H), 3.86 (s, 3H), 3.83 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 160.1, 159.6, 138.9, 132.2, 130.8, 128.3, 125.0, 122.9, 107.3, 91.3, 56.2, 55.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}ClN_4O_3$ 389.1380; Found 389.1367.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01258.

^1H NMR and ^{13}C NMR spectra for the synthesized azines (**1**−**20**), VT-^1H NMR spectra of compound **4**, deuterated NMR of compounds **4** and **14**, Cartesian coordinates and absolute energies of the optimized geometry of all synthesized azines, and reported biologically active molecules (PDF)

Complete crystallographic data of **4**, **14**·CH_3OH, and **14**·HCl (CCDC No. 1473843, 1473844, and 1473846) (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*Email: sanjaymandal@iisermohali.ac.in; Telephone:+91-172-2214682

*Email: akchakraborti@niper.ac.in; Telephone:+91-172-2214682

*Email: pvbharatam@niper.ac.in; Telephone:+91-172-2214682

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.S.C. acknowledges the Physical Chemistry division and D. K. acknowledges the INSPIRE division of Department of Science and Technology (DST), New Delhi, India for financial support. The X-ray facility at IISER Mohali is gratefully acknowledged. Authors are thankful to the reviewers of this article for their valuable suggestions.

■ REFERENCES

(1) Lieber, E.; Smith, G. B. L. *Chem. Rev.* **1939**, *25*, 213−271.

(2) Sundberg, R. J.; Dahlhausen, D. J.; Manikumar, G.; Mavunkel, B.; Biswas, A.; Srinivasan, V.; Musallam, H. A.; Reid, W. A.; Ager, A. L. *J. Med. Chem.* **1990**, *33*, 298−307.

(3) DoAmaral, J. R.; Blanz, E. J.; French, F. A. *J. Med. Chem.* **1969**, *12*, 21−25.

(4) Cavallini, G.; Massarani, E.; Nardi, D.; Mauri, L.; Mantegazza, P. *J. Med. Pharm. Chem.* **1961**, *4*, 177−182.

(5) French, F. A.; DoAmaral, J. R.; Blanz, E. J.; French, D. A. *J. Med. Chem.* **1971**, *14*, 862−866.

(6) Ulrich, P.; Cerami, A. *J. Med. Chem.* **1984**, *27*, 35−40.

(7) Pitzele, B. S.; Moormann, A. E.; Gullikson, G. W.; Albin, D.; Bianchi, R. G.; Palicharla, P.; Sanguinetti, E. L.; Walters, D. E. *J. Med. Chem.* **1988**, *31*, 138−144.

(8) Desideri, N.; Sestili, I.; Manarini, S.; Cerletti, C.; Stein, M. L. *Eur. J. Med. Chem.* **1991**, *26*, 455−460.

(9) Soll, R. M.; Lu, T.; Tomczuk, B.; Illig, C. R.; Fedde, C.; Eisennagel, S.; Bone, R.; Murphy, L.; Spurlino, J.; Salemme, F. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1−4.

(10) Cavé, C.; Galons, H.; Miocque, M.; Rinjard, P.; Tran, G.; Binet, P. *Eur. J. Med. Chem.* **1994**, *29*, 389−392.

(11) George, T.; Kaul, C.; Grewal, R. S.; Mehta, D. V. *J. Med. Chem.* **1971**, *14*, 909−913.

(12) Sevillano, L. G.; Melero, C. P.; Caballero, E.; Tomé, F.; Lelièvre, L. G.; Geering, K.; Crambert, G.; Carrón, R.; Medarde, M.; San Feliciano, A. *J. Med. Chem.* **2002**, *45*, 127−136.

(13) Mutschler, E.; Springer, J.; Wassermann, O. *Biochem. Pharmacol.* **1970**, *19*, 9−15.

(14) Foye, W. O.; Almassian, B.; Eisenberg, M. S.; Maher, T. J. *J. Pharm. Sci.* **1990**, *79*, 527−530.

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

(15) Korytnyk, W.; Ghosh, A. C.; Angelino, N.; Dave, C. *J. Med. Chem.* **1973**, *16*, 959−961.
(16) Gelbart, A.; Thomas, R. *J. Med. Chem.* **1978**, *21*, 284−288.
(17) Savini, L.; Chiasserini, L.; Travagli, V.; Pellerano, C.; Novellino, E.; Cosentino, S.; Pisano, M. B. *Eur. J. Med. Chem.* **2004**, *39*, 113−122.
(18) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Lannigan, D.; Smith, J.; Scudiero, D.; Kondapaka, S.; Shoemaker, R. H. *Eur. J. Med. Chem.* **2011**, *46*, 4311−4323.
(19) Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Farruggia, G.; Stefanelli, C.; Masotti, L.; Kunkel, M. W. *J. Med. Chem.* **2006**, *49*, 7897−7901.
(20) Stanek, J.; Caravatti, G.; Capraro, H. G.; Furet, P.; Mett, H.; Schneider, P.; Regenass, U. *J. Med. Chem.* **1993**, *36*, 46−54.
(21) Lober, G.; Hoffmann, H. *Biophys. Chem.* **1990**, *35*, 287−300.
(22) Jobson, A. G.; Cardellina, J. H.; Scudiero, D.; Kondapaka, S.; Zhang, H.; Kim, H.; Shoemaker, R.; Pommier, Y. *Mol. Pharmacol.* **2007**, *72*, 876−884.
(23) Jobson, A. G.; Lountos, G. T.; Lorenzi, P. L.; Llamas, J.; Connelly, J.; Cerna, D.; Tropea, J. E.; Onda, A.; Zoppoli, G.; Kondapaka, S.; Zhang, G.; Caplen, N. J.; Cardellina, J. H.; Yoo, S. S.; Monks, A.; Self, C.; Waugh, D. S.; Shoemaker, R. H.; Pommier, Y. *J. Pharmacol. Exp. Ther.* **2009**, *331*, 816−826.
(24) Lountos, G. T.; Jobson, A. G.; Tropea, J. E.; Self, C. R.; Zhang, G.; Pommier, Y.; Shoemaker, R. H.; Waugh, D. S. *J. Struct. Biol.* **2011**, *176*, 292−301.
(25) Matthews, T. P.; Jones, A. M.; Collins, I. *Expert Opin. Drug Discovery* **2013**, *8*, 621−640.
(26) Lountos, G. T.; Jobson, A. G.; Tropea, J. E.; Self, C. R.; Zhang, G.; Pommier, Y.; Shoemaker, R. H.; Waugh, D. S. *FEBS Lett.* **2011**, *585*, 3245−3249.
(27) Györgydeák, Z.; Holzer, W. *Heterocycles* **1998**, *48*, 1395−1406.
(28) Kurzer, F.; Godfrey, L. E. A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 459−476.
(29) Wu, B.; Yang, H.; Lin, Q.; Wang, Z.; Lu, C.; Cheng, G. *New J. Chem.* **2015**, *39*, 179−186.
(30) Ramakrishnan, A.; Chourasiya, S. S.; Bharatam, P. V. *RSC Adv.* **2015**, *5*, 55938−55947.
(31) Mutikainen, I.; Elo, H.; Tilus, P. *Z. Naturforsch., B: J. Chem. Sci.* **1993**, *48*, 1821−1827.
(32) Diamant, S.; Agranat, I.; Goldblum, A.; Cohen, S.; Atlas, D. *Biochem. Pharmacol.* **1985**, *34*, 491−498.
(33) Holzer, W.; Györgydeák, Z. *Monatsh. Chem.* **1992**, *123*, 1163−1173.
(34) Györgydeák, Z.; Holzer, W.; Mereiter, K. *Monatsh. Chem.* **1999**, *130*, 899−913.
(35) Demir, S.; Dinçer, M.; Sarıpınar, E. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2006**, *62*, o4194−o4195.
(36) Qian, Y.; Zhang, H.-J.; Lv, P.-C.; Zhu, H.-L. *Bioorg. Med. Chem.* **2010**, *18*, 8218−8225.
(37) Boyle, J. T. A.; Grundon, M. F. *Chem. Commun.* **1967**, 1137−1138.
(38) Shafiee, A.; Lalezari, I.; Yalpani, M. *J. Org. Chem.* **1972**, *37*, 2052−2053.
(39) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2014**, *79*, 1025−1031.
(40) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 5750−5753.
(41) Han, W.; Zhang, G.; Li, G.; Huang, H. *Org. Lett.* **2014**, *16*, 3532−3535.
(42) Cohen, R.; Rybtchinski, B.; Gandelman, M.; Shimon, L. J. W.; Martin, J. M. L.; Milstein, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 1949−1952.
(43) Cohen, S. G.; Groszos, S. J.; Sparrow, D. B. *J. Am. Chem. Soc.* **1950**, *72*, 3947−3951.
(44) Lewis, M.; Glaser, R. *J. Org. Chem.* **2002**, *67*, 1441−1447.
(45) McLoughlin, C.; Clyburne, J. A. C.; Weinberg, N. *J. Mater. Chem.* **2007**, *17*, 4304−4308.
(46) Chen, G. S.; Wilbur, J. K.; Barnes, C. L.; Glaser, R. *J. Chem. Soc., Perkin Trans. 2* **1995**, *2*, 2311−2317.
(47) Choytun, D. D.; Langlois, L. D.; Johansson, T. P.; Macdonald, C. L. B.; Leach, G. W.; Weinberg, N.; Clyburne, J. A. C. *Chem. Commun.* **2004**, 1842−1843.
(48) Wei, Q.; Shi, L.; Cao, H.; Wang, L.; Yang, H.; Wang, Y. *Liq. Cryst.* **2008**, *35*, 581−585.
(49) Kodaka, M.; Shah, S. N.; Tomohiro, T.; Chudgar, N. K. *J. Phys. Chem. B* **1998**, *102*, 1219−1223.
(50) Nalwa, H. S.; Kakuta, A.; Mukoh, A. *J. Appl. Phys.* **1993**, *73*, 4743−4745.
(51) Sek, D.; Siwy, M.; Bijak, K.; Grucela-Zajac, M.; Malecki, G.; Smolarek, K.; Bujak, L.; Mackowski, S.; Schab-Balcerzak, E. *J. Phys. Chem. A* **2013**, *117*, 10320−10332.
(52) Irwin, J. J.; Sterling, T.; Mysinger, M. M.; Bolstad, E. S.; Coleman, R. G. *J. Chem. Inf. Model.* **2012**, *52*, 1757−1768.
(53) Fukumoto, S.; Imamiya, E.; Kusumoto, K.; Fujiwara, S.; Watanabe, T.; Shiraishi, M. *J. Med. Chem.* **2002**, *45*, 3009−3021.
(54) Li, J.-T.; Du, C.; Xu, X.-Y.; Chen, G.-F. *Ultrason. Sonochem.* **2012**, *19*, 1033−1038.
(55) Du, C.; Li, J.-T. *E-J. Chem.* **2012**, *9*, 2108−2113.
(56) Bhagat, S.; Sharma, R.; Sawant, D. M.; Sharma, L.; Chakraborti, A. K. *J. Mol. Catal. A: Chem.* **2006**, *244*, 20−24.
(57) Bhagat, S.; Sharma, R.; Chakraborti, A. K. *J. Mol. Catal. A: Chem.* **2006**, *260*, 235−240.
(58) Pizzuti, L.; Martins, P. L. G.; Ribeiro, B. A.; Quina, F. H.; Pinto, E.; Flores, A. F. C.; Venzke, D.; Pereira, C. M. P. *Ultrason. Sonochem.* **2010**, *17*, 34−37.
(59) Oliveira, S.; Pizzuti, L.; Quina, F.; Flores, A.; Lund, R.; Lencina, C.; Pacheco, B. S.; de Pereira, C. M. P.; Piva, E. *Molecules* **2014**, *19*, 5806−5820.
(60) Singh, K.; Verma, V.; Yadav, K.; Sreekanth, V.; Kumar, D.; Bajaj, A.; Kumar, V. *Eur. J. Med. Chem.* **2014**, *87*, 150−158.
(61) Ring, J. R.; Zheng, F.; Haubner, A. J.; Littleton, J. M.; Crooks, P. A. *Bioorg. Med. Chem.* **2013**, *21*, 1764−1774.
(62) Sircar, I.; Moos, W. H.; Morrison, G. C.; Duell, B. L.; Bobowski, G.; Potoczak, R. *Eur. J. Med. Chem.* **1989**, *24*, 349−355.
(63) Elo, H. *Spectrosc. Lett.* **1989**, *22*, 123−160.
(64) Su, X.; Aprahamian, I. *Org. Lett.* **2011**, *13*, 30−33.
(65) Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 4074−4077.
(66) Jeong, M. J.; Park, J. H.; Lee, C.; Chang, J. Y. *Org. Lett.* **2006**, *8*, 2221−2224.
(67) Zheng, J.; Qi, J.; Cui, S. *Org. Lett.* **2016**, *18*, 128−131.
(68) Glaser, R.; Yin, J.; Miller, S. *J. Org. Chem.* **2010**, *75*, 1132−1142.
(69) Coyle, S.; Glaser, R. *J. Org. Chem.* **2011**, *76*, 3987−3996.
(70) Raban, M.; Carlson, E. *J. Am. Chem. Soc.* **1971**, *93*, 685−691.
(71) Prasad, B. V.; Grover, G.; Uppal, P.; Kaur, D. *J. Mol. Struct.: THEOCHEM* **1999**, *458*, 227−237.
(72) Galvex, J.; Guirado, A. *J. Comput. Chem.* **2009**, *31*, 520−531.
(73) Crystal data for **4**: $C_5H_8N_6$, M = 152.17, Orthorhombic, space group *Pbca*, a = 8.309(10) Å, b = n 9.627(11) Å, c = 19.08(2) Å, α = 90°, β = 90°, γ = 90°, V = 1526(3) Å^3, Z = 8, D_c = 1.325 Mg/cm^3, μ (Mo-Kα) = 0.094 mm^{-1}, T = 296(2) K, 11923 reflections collected. Refinement of 1169 reflections (110 parameters) with I > 2σ(I) converged at a final R_1 = 0.043, wR_2 = 0.0533, gof = 1.031.
(74) Crystal data for **14**·CH_3OH: $C_{20}H_{26}N_4O_4$, M = 386.45, Triclinic, space group *P-1*, a = 8.887(17) Å, b = 10.048(19) Å, c = 12.94(2) Å, α = 104.87(2)°, β = 101.59(3)°, γ = 111.32(3)°, V = 983(3) Å^3, Z = 2, D_c = 1.305 Mg/cm^3, μ (Mo-Kα) = 0.092 mm^{-1}, T = 296(2) K, 11768 reflections collected. Refinement of 2460 reflections (258 parameters) with I > 2σ(I) converged at a final R_1 = 0.082, wR_2 = 0.1017, gof = 0.992.
(75) Crystal data for **14**·HCl: $C_{19}H_{23}ClN_4O_3$, M = 390.86, Orthorhombic, space group $P2_12_12_1$, a = 7.4460(13) Å, b = 11.786(2) Å, c = 21.591(4) Å, α = 90°, β = 90°, γ = 90°, V = 1894.8(6) Å^3, Z = 4, D_c = 1.370 Mg/cm^3, μ (Mo-Kα) = 0.229 mm^{-1}, T = 296(2) K, 19415 reflections collected. Refinement of 3053

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583

reflections (247 parameters) with $I > 2\sigma(I)$ converged at a final R_1 = 0.037, wR_2 = 0.0417, gof = 1.041.

(76) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford CT, 2009.

(77) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(78) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789.

(79) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032−3041.

(80) Barfield, M.; Fagerness, P. *J. Am. Chem. Soc.* **1997**, *119*, 8699−8711.

(81) Martins, T. L. C.; Ramalho, T. C.; Figueroa-Villar, J. D.; Flores, A. F. C.; Pereira, C. M. P. *Magn. Reson. Chem.* **2003**, *41*, 983−988.

DOI: 10.1021/acs.joc.6b01258
J. Org. Chem. 2016, 81, 7574−7583