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Tuning of Chemo- and Regioselectivities in Multicomponent Condensations of 5-Aminopyrazoles, Dimedone, and Aldehydes

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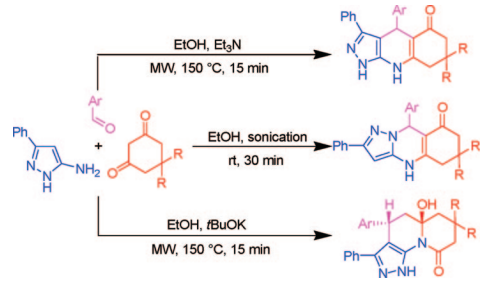

Regio- and chemoselective multicomponent protocols for the synthesis of 1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones, 5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8-ones, and 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones starting from 5-amino-3-phenylpyrazole, cyclic 1,3-dicarbonyl compounds and aromatic aldehydes are described. Whereas the three-component coupling in ethanol under reflux conditions provides mixtures of pyrazoloquinolinones and pyrazoloquinazolinones, the condensation can be successfully tuned toward the formation pyrazoloquinolinones (Hantzsch-type dihydropyridines) by performing the reaction at 150 °C in the presence of triethylamine base applying sealed vessel microwave or conventional heating. On the other hand, using sonication at room temperature under neutral conditions favors the formation of the isomeric pyrazoloquinazolinones (Biginelli-type dihydropyrimidines). These products are also obtained when the three-component condensation is executed in the presence of trimethylsilylchloride as reaction mediator at high temperatures. A third reaction pathway leading to pyrazoloquinolizinones in a ring-opening/recyclization sequence can be accessed by switching from triethylamine to a more nucleophilic base such as sodium ethoxide or potassium *tert*-butoxide. The reaction mechanism and intermediates leading to these three distinct tricyclic condensation products are discussed.

Introduction

Control of selectivity, for example, chemo- and regioselectivity, is among the most important objectives in organic chemistry. For multicomponent reactions involving the simultaneous molecular interaction of three or more components, the issue of selectivity is of particular significance due to the high probability of several potential parallel reaction pathways leading to different product classes.[1] Many different process parameters such as temperature, pressure, solvent, catalyst type, as well as kinetic or thermodynamic control, and other factors can be utilized to modulate the selectivity of synthetic transformations.[2]

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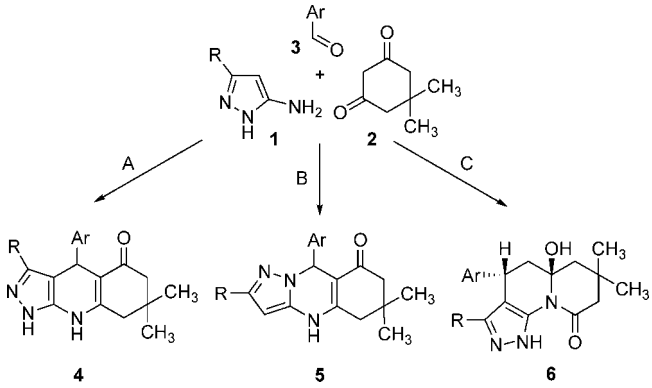

FIGURE 1. Different reaction pathways for the condensation of 5-aminopyrazoles, aldehydes, and 1,3-cyclic diketones.

In addition to these classical reaction parameters, the use of microwave irradiation[3] or sonication[4] has provided additional opportunities to execute reactions and to tune selectivities in organic synthesis.

A challenging example in this context are multicomponent condensation reactions of 5-aminopyrazoles **1** with cyclic 1,3-diketones **2** and aromatic aldehydes **3**, which in general can lead to the formation of several different tricyclic reaction products (Figure 1, **4**−**6**) due to the presence of at least three nonequivalent nucleophilic reaction centers in the aminopyrazole building block **1** (N1, C4, and NH_2).[5,6] The resulting partially hydrogenated azoloazines belong to a class of interesting target structures owing to their specific role in several biological processes and their diverse physiological activities.[7] The pyrazole ring itself constitutes a key structural motif in numerous biologically active compounds,[8] among them such prominent drug molecules as Viagra, Celebrex and many others. Therefore, these MCRs have recently attracted the interest of the synthetic community and several reports have already discussed the formation of isomeric reaction products of type **4** or **5** from these three-component condensations (Figure 1).[5] It has been found that in the case of 1- and 4-substituted 5-aminopyrazoles this MCR typically leads to the formation of either pyrazoloquinolinone (path A)[5b,c] or pyrazoloquinazolinone (path B)[6] heterocycles, respectively. In contrast, the behavior of 1,4-unsubstituted 5-aminopyrazoles is somewhat ambiguous. For example, it has been reported[5b,c] that in a three-component condensation with cyclic 1,3-diketones and aldehydes, 3-methyl-5-aminopyrazole forms exclusively pyrazoloquinolinones of type **4** (path A), while 3-aryl-substituted 5-aminopyrazoles can yield both pyrazoloquinolinones **4** (path A)[5b] and pyrazoloquinazolinones **5** (path B)[5d] or mixtures of both heterocyclic systems. Several different reaction pathways for related cyclocondensation processes involving 5-aminopyrazoles, pyruvic acids and aromatic aldehydes leading to bicyclic pyrazolo[3,4-*b*]pyridines, pyrazolo[1,5-*a*]pyrimidines, and pyrazolo[3,4-*b*]pyridines were also recently described.[9]

In this article we detail our efforts[6] in tuning the three-component condensation of 5-aminopyrazoles, aromatic aldehydes, and cyclic 1,3-diketones to selectively yield three distinct reaction products: pyrazolo[3,4-*b*]quinolin-5-ones **4**, pyrazolo[5,1-*b*]quinazolin-8-ones **5**, and pyrazolo[4,3-*c*]quinolizin-9-ones **8** (Figure 1). These tricyclic heterocycles can be obtained in moderate to good isolated yields by specific variation of both catalyst type and reaction temperature employing either rapid microwave flash heating or sonication as alternative energy sources.

Results and Discussion

Our initial investigations involving the condensation of 5-amino-3-phenylpyrazole **1**, 1,3-diketones **2a,b**, and aromatic aldehydes **3a**−**g** in refluxing ethanol at ∼80 °C confirmed that, in agreement with previously published data,[5b,d] the experimental outcome in these MCR processes is rather unpredictable. Although in some instances pure Hantzsch-type dihydropyridine derivatives were isolated (path A), in most cases the formation of mixtures of both possible regioisomers **4** and **5** in varying ratios was observed (Figure 1). We therefore first attempted to elaborate reaction conditions that would allow the selective and preparatively useful generation of either pyrazoloquinolinones **4** or pyrazoloquinazolinones **5** in a one-pot fashion avoiding chromatographic separation of the two isomers.

By using controlled microwave heating in sealed vessels,[3] it was quickly established that an increase of the reaction

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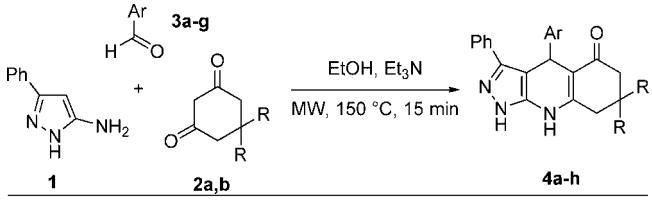
TABLE 1. Microwave-Assisted Synthesis of 4-Aryl-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-xones 4a−h (Figure 1, Path A)



1 2a,b 4a-h

entry	1,3-diketone (R)		aldehyde (Ar)		product	yield[a] (%)
1	**2a**	Me	**3a**	C_6H_5	**4a**	85
2	**2a**	Me	**3b**	4-MeC_6H_4	**4b**	86
3	**2a**	Me	**3c**	4-$MeOC_6H_4$	**4c**	76
4	**2a**	Me	**3d**	4-BrC_6H_4	**4d**	91
5	**2a**	Me	**3e**	4-$NO_2C_6H_4$	**4e**	83
6	**2a**	Me	**3f**	2-$CF_3C_6H_4$	**4f**	86
7	**2b**	H	**3b**	4-MeC_6H_4	**4g**	70
8	**2b**	H	**3g**	4-FC_6H_4	**4 h**	85

[a] Isolated yield of pure product after recrystallization.

temperature to above the boiling point of ethanol favors the formation of the dihydropyridine type heterocycle (pyrazoloquinolinones **4**, path A). Similarly it was found that introducing a base such as a tertiary amine (*N*-methylmorpholine or triethylamine) increased the overall yield in this MCR process. Based on these empirical observations a thorough optimization of reaction conditions ultimately led to a 150 °C microwave-assisted procedure that enabled the more or less exclusive formation of 4-aryl-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones **4a−h** in excellent yields (70−91%) (Table 1). The optimum conditions involved dissolving an equimolar mixture of the three starting materials in ethanol, addition of 1.2 equiv of triethylamine, followed by heating in a sealed microwave vial at 150 °C for 15 min (7−8 bar pressure). Shorter reaction times (5−10 min) were tolerated in some cases; however, for example with *ortho*-substituted benzaldehydes, isolated product yields were reduced (**4d,f,h**). The same correlation was observed for lower reaction temperatures (120−140 °C). After recrystallization from an ethanol/water mixture (1:1) the desired pyrazoloquinolinones **4a−h** exhibited >98% purity by NMR, and HPLC analysis and did not require further purification.

The optimized microwave conditions were also applicable to closely related MCRs involving 3-methylpyrazole as building blocks to yield the corresponding 4-aryl-3,7,7-trimethyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones (Figure 1, **4**, R = Me) in good yield (data not shown). However, in this case the regioselective formation of Hantzsch-type dihydropyridines can also be achieved using conventional reflux conditions.[5b,c]

To establish if the selective formation of the dihydropyridine isomers of type **4** was somehow specifically connected to microwave irradiation[3] or merely a result of the higher reaction temperature, a set of comparison experiments was conducted at 150 °C for both microwave and oil bath procedures. For this purpose a commercially available setup was employed which allows the use of the identical sealed glass vial both in an oil bath and microwave experiment in combination with internal reaction temperature measurement involving fiber-optic sensors (see Supporting Information for details and heating profiles).[10] Using the condensation of amine **1**, dimedone **2a**, and aldehyde **3c** as a model reaction, it was demonstrated that this reaction heated in an oil bath to the same target temperature of 150 °C also led exclusively to pyrazoloquinolinone **4c**, similar to the experiment carried out under microwave irradiation. Both the isolated pure product yields (74% vs 76%) and the HPLC traces of the crude reaction mixtures were virtually identical. Therefore, the effect of microwave heating in changing the selectivity of this MCR process in comparison to the oil bath reflux experiment can be explained by the higher reaction temperature (150 vs 80 °C) and can thus be classified as a purely thermal effect.[3]

The increase in the ratio of dihydropyridine versus dihydropyrimidine products (Figure 1) on going to higher temperatures indicates that the Hantzsch-type dihydropyridines **4** (pyrazoloquinolinones, path A) are probably the thermodynamically controlled reaction products in this transformation.[11] Conversely, this may suggest that Biginelli-type dihydropyrimidines **5** (pyrazoloquinazolinones, path B) are the kinetically preferred regioisomers, and that their formation would therefore be favored at a lower temperature. However, simple stirring of the reaction mixture at room temperature was ineffective and did not give any of the desired reaction products due to, in part, the low solubility of the starting materials in ethanol, especially aminopyrazole **1** and aldehydes **3d,e,i**, under these conditions.

As already emphasized in the introduction, ultrasound-promoted synthesis (sonication) is widely used today to promote organic reactions and can be effectively employed for both low and high temperature processes.[4] According to the currently accepted theory there is no direct interaction between matter, its vibrational or electronic levels, and ultrasonic waves.[4] The application of ultrasound in organic synthesis results in beneficial effects mainly based on improved mass transfer through cavitation phenomena.[4] Our recent experience in this field confirms that sonication can often be utilized for otherwise sluggish room temperature organic transformations, including multicomponent reactions.[12] Indeed, sonication of a mixture of 5-amino-3-phenylpyrazole **1**, cyclic 1,3-diketones **2a,b**, and aldehydes **3a-e,h** in ethanol at room temperature under neutral conditions for 30 min provided the desired 9-aryl-2-phenyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-ones **5a−h** in moderate to good yield (51−70%). In most of the cases the isolated dihydropyrimidine products were obtained in pure form not contaminated by their pyrazoloquinolinone regioisomers **4** (Table 2). It was established that the optimal synthetic procedure involved sonication of an equimolar mixture of the starting materials in ethanol in a standard ultrasonic bath producing irradiation at 44.2 kHz in a round-bottom flask for 30 min. During this period of time only a slight increase in the bulk bath temperature was observed, whereas longer sonication (40−60 min) led to an increase of the ultrasonic bath temperature to 40−50 °C. In most instances the desired pyrazoloquinazolinones **5** precipitated directly from the reaction mixture as solids, which were subsequently removed by simple filtration (Table 2).

The work up procedure for pyrazoloquinazolinones **5g,h** resulting from 1,3-cyclohexanedione **2b** was somewhat more elaborate and involved evaporation and crystallization of the

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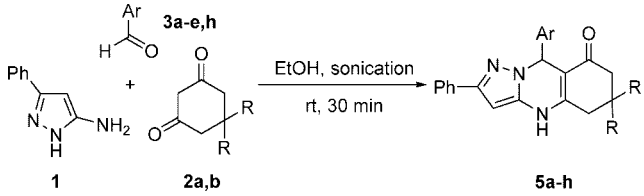
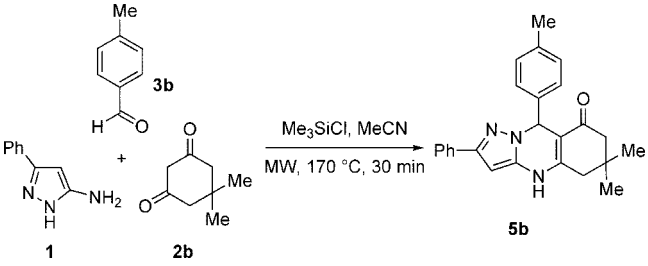
TABLE 2. Ultrasound-Promoted Synthesis of 9-Aryl-6,6-dimethyl-2-phenyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*] quinazolin-8(4*H*)-ones 5a−h (Figure 1, Path B)



entry	1,3-diketone (R)		aldehyde (Ar)		product	yield[a] (%)
1	**2a**	Me	**3a**	C_6H_5	**5a**	67
2	**2a**	Me	**3b**	4-MeC_6H_4	**5b**	56
3	**2a**	Me	**3c**	4-$MeOC_6H_4$	**5c**	61
4	**2a**	Me	**3d**	4-BrC_6H_4	**5d**	70
5	**2a**	Me	**3e**	4-$NO_2C_6H_4$	**5e**	54
6	**2a**	Me	**3 h**	2-$MeOC_6H_4$	**5f**	60
7	**2b**	H	**3d**	4-BrC_6H_4	**5g**	51
8	**2b**	H	**3e**	4-$NO_2C_6H_4$	**5 h**	54

[a] Isolated yield of pure product after crystallization from the reaction mixture.

SCHEME 1



resulting crude oil with acetonitrile. The purity of the target compounds **5a**−**h** obtained after direct crystallization from the reaction mixture was generally very high (>98% by ^{1}H NMR and HPLC), although in some cases (**5g**,**h**) minor impurities of up to 10% of the pyrazoloquinolinone isomers **4** were observed. A reduction of the reaction temperature by addition of ice to the ultrasound bath did not influence the selectivity for dihydropyrimidine formation but rather led to incomplete conversions resulting in products contaminated with starting materials.

In addition to our investigations involving the selective formation of pyrazoloquinazolinones at ambient conditions using sonication, we also attempted to influence the selectivity in this process using acidic catalysts, more commonly used to aid Biginelli-type dihydropyrimidine synthesis.[13] As a model reaction for these studies the synthesis of pyrazoloquinazolinone **5b** was chosen (Table 2). When using a 1:1:1 ratio of starting materials **1a**, **2b**, and **3b** and catalytic amounts of hydrochloric acid at 150−170 °C for 15−40 min (microwave irradiation), mixtures containing both the pyrazoloquinolinone **4b** and the isomeric pyrazoloquinazolinone **5b** were obtained, along with unidentified byproducts. However, by variation of the molar ratio of starting materials in this MCR a higher selectivity for the formation of pyrazoloquinazolinone **5b** could be obtained. For example, the condensation of 5-amino-3-phenylpyrazole **1**, dimedone (**2b**) and *p*-tolualdehyde (**3b**) in a molar ratio of 2:2:1 at 150 °C for 30 min using hydrochloric acid as a catalyst provided an increased selectivity for the formation of the pyrazoloquinazolinone isomer **5b** (**5b**:**4b** = 80:20 by HPLC analysis at 254 nm). When employing 0.4 equiv of trimethylsilylchloride as a reaction mediator in combination with acetonitrile as solvent,[13] we were pleased to see nearly full conversion of the starting materials into pyrazoloquinazolinone **5b** after 30 min at 170 °C (10−11 bar pressure), with only minor amounts of **4b** byproduct being formed according to HPLC analysis of the crude reaction mixture (<10%) (Scheme 1). After recrystallization of the crude reaction product from 2-propanol/water pyrazoloquinazolinone **5b** was obtained consistently in >75% yield and analytical purity (HPLC, ^{1}H NMR) on a gram scale.

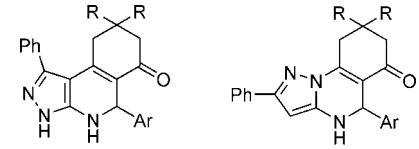


FIGURE 2. Possible angular structural isomers of condensation products **4** and **5**.

Using 5-amino-3-methylpyrazole as a starting material, the corresponding 9-aryl-2-methyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-ones (Figure 1, **5**, R = Me) can not be obtained by either the sonication or acid-mediated protocols described above. Due to the reduced sterical hindrance of the C4 center in 5-amino-3-methylpyrazole (Ph versus Me), the formation of Hantzsch-type dihydropyridines is apparently strongly favored in the case of a methyl substituent at C3 of the pyrazole ring.[5b,c]

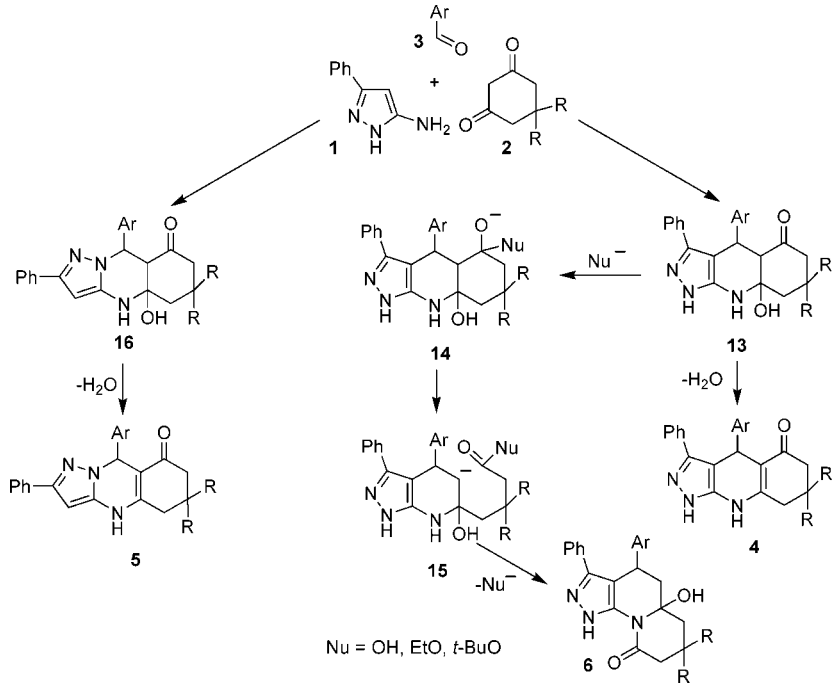
The structures of heterocycles of type **4** and **5** were established by elemental analyses in combination with MS and NMR spectroscopic data. The ^{1}H NMR spectra of 4-aryl-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones **4a**−**h** exhibit the following signals: characteristic multiplets for the aromatic rings (6.6−8.0 ppm), a singlet for the dihydropyridine CH proton (∼5.3 ppm), four doublets for the two CH_2 groups of the cyclohexenone ring, a sharp singlet for the pyridine NH at ∼10 ppm, and a broad singlet for the pyrazole NH at 12.5 ppm, as well as signals resulting from the other functional groups present. Spectra for 9-aryl-2-phenyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-ones **5a**−**h** contained analogous sets of signals, apart from the absence of the pyrazole NH singlet and the appearance of a sharp singlet at (6.1−6.3 ppm) assigned to the pyrazole CH proton. In principle, for both types of linear tricyclic heterocycles alternative angular structures **7** and **8** can be envisaged[14] (Figure 2). Importantly, our earlier experience with closely related structures has demonstrated a distinct dependence of the chemical shift of the amino group in the ^{1}H NMR spectrum on its position in the dihydroazine fragment.[15] Linear structures like **4** and **5** exhibit a signal for the NH proton at 9.5−10.5 ppm, whereas in the case of angular structures similar to **7** and **8** this signal

(13) Matloobi, M.; Kappe, C. O. *J. Comb. Chem* **2007**, *9*, 275, and references therein.

(14) (a) Chebanov, V. A.; Desenko, S. M. *Curr. Org. Chem.* **2006**, *10*, 297. (b) Desenko, S. M.; Orlov, V. D. *Azaheterocycles Based on Aromatic Unsaturated Ketones*; Folio: Kharkov, 1998.

(15) (a) Lipson, V. V.; Desenko, S. M.; Shirobokova, M. G.; Borodina, V. V. *Khim. Geterotsikl. Soedin.* **2003**, *39*, 1383; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2003**, *39*, 1213. (b) Desenko, S. M.; Orlov, V. D.; Estrada, J. *Khim. Geterotsikl. Soedin.* **1990**, *26*, 999; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1990**, *26*, 839. (c) Desenko, S. M.; Orlov, V. D.; Getmanskii, N. V.; Shishkin, O. V.; Lindeman, S. V.; Struchkov, Yu. T. *Khim. Geterotsikl. Soedin.* **1993**, *29*, 481; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1993**, *29*, 406. (d) Chebanov, V. A.; Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Kappe, C. O. *J. Comb. Chem.* **2006**, *8*, 427.

SCHEME 2. Possible Reaction Mechanism for Formation of Tricyclic Heterocycles 4−6 from 5-Amino-3-phenylpyrazole 1, Cyclic 1,3-Diketones 2, and Substituted Benzaldehydes 3

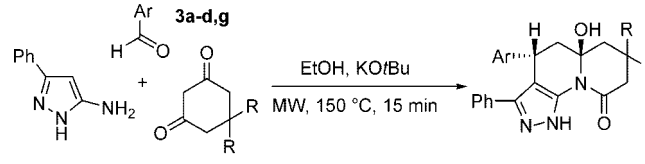


was strong-field shifted by 2−3 ppm. As a further confirmation, no NOE and COSY correlations in the structures of type **4** and **5** were found between the CH and the NH group in the azine moiety.

The extensive optimization studies performed in the quest for a regioselective synthesis of pyrazolo[3,4-*b*]quinolin-5-ones **4** and the search for the most favorable catalyst for this transformation resulted in the unexpected discovery of a novel MCR pathway involving the formation of hitherto undisclosed pyrazolo[4,3-*c*]quinolizin-9-one products of type **6** (Figure 1, Path C).[6] It was established that microwave-assisted condensation (ethanol, 150 °C, 15 min) of 5-amino-3-phenylpyrazole **1** with cyclic 1,3-diketones **2a,b** and substituted benzaldehydes **3a−d,g** in the presence of an equimolar amount of sodium ethoxide or potassium hydroxide base (as opposed to triethylamine) led to these novel heterocycles whose structures were confirmed on the basis of X-ray analyses.[6] These tricyclic products **6** do not result from dihydropyridines **4** since treatment of pyrazolo[3,4-*b*]quinolin-5-ones **4** with sodium ethoxide under microwave conditions at 150 °C did not provide any trace of pyrazolo[4,3-*c*]quinolizin-9-ones **6**, with only unchanged starting material being recovered. Therefore, this unique MCR must apparently involve ring-opening and recyclization of the cyclic 1,3-diketone fragment as the key step, before formation of a Hantzsch-type dihydropyridine ring occurs (see Scheme 2).

The product yields in this MCR typically were in the range of 32−45% using sodium ethoxide as a base.[6] The formation of pyrazolo[4,3-*c*]quinolizin-9-ones **6** in yields up to 75% was possible, however, when 2 equiv of the 1,3-diketone building block and sodium ethoxide or potassium *tert*-butoxide were employed (Table 3). Based on these observations it appears that this three-component reaction involves the initial formation of Michael adducts of type **9** (Figure 3) derived from condensation

TABLE 3. Microwave-Assisted Synthesis of 4-Aryl-5a-hydroxy-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones 6a−i (Figure 1, Path C)



1 2a,b 6a-i

entry	1,3-diketone (R)		aldehyde (Ar)		product	yield[a] (%)
1	**2a**	Me	**3a**	C_6H_5	**6a**	60
2	**2a**	Me	**3b**	4-MeC_6H_4	**6b**	75
3	**2a**	Me	**3c**	4-$MeOC_6H_4$	**6c**	65
4	**2a**	Me	**3d**	4-BrC_6H_4	**6d**	70
5	**2a**	Me	**3g**	4-FC_6H_4	**6e**	38
6	**2b**	H	**3a**	C_6H_5	**6f**	58
7	**2b**	H	**3b**	4-MeC_6H_4	**6g**	60
8	**2b**	H	**3c**	4-$MeOC_6H_4$	**6 h**	58
9	**2b**	H	**3d**	4-BrC_6H_4	**6i**	59

[a] Isolated yield of pure product after recrystallization.

of the aldehyde and 1,3-diketone components. This assumption was supported by the spectroscopic (^{1}H NMR) identification of intermediate **9** in the crude reaction mixture. Additional evidence was also obtained by subjecting independently synthesized Michael adduct **9**[16] to the standard reaction conditions in the presence of 5-amino-3-phenylpyrazole **1**. This fact allowed us to elaborate two additional one-pot, two-step reaction protocols that in some instances produced higher product yields.[6] One of these involved the initial in situ formation of Michael adducts **9** via precondensation of the cyclic 1,3-diketone with the appropriate aldehyde and subsequent addition of the 5-aminopyrazole to the reaction mixture. Alternatively, it was found that precondensation of 5-aminopyrazole **1** with dimedone in ethanol (probably leading to hemiacetal **10**, Figure 3) in the

(16) (a) Jin, T.-S.; Zhang, J.-S.; Wang, A.-Q.; Li, T.-S. *Synth. Commun.* **2005**, *35*, 2339. (b) Shi, D.; Wang, Y.; Lu, Z.; Dai, G. *Synth. Commun.* **2000**, *30*, 713.
(17) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.

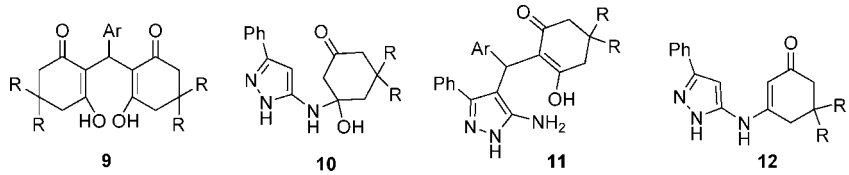


FIGURE 3. Possible reaction intermediates for pathways A, B, and C.

presence of sodium ethoxide followed by addition of the appropriate aldehyde also led to the formation of target structures **6**.[6]

A thorough investigation of the multicomponent pathway leading to pyrazoloquinolizin-9-ones **6** (Figure 1, Table 3) revealed several additional important facts. Treatment of 5-amino-3-phenylpyrazole **1** with cyclic diketones **2a,b** and substituted benzaldehydes **3a**−**d,g** in the presence of sodium ethoxide or potassium *tert*-butoxide in ethanol at reflux temperature (∼80 °C) provided only Hantzsch-type dihydropyridines **4** without any trace of the pyrazoloquinolizin-9-ones **6** (the reaction using nucleophilic bases such as sodium ethoxide or potassium *tert*-butoxide is however much slower compared to using triethylamine as a base, see Table 1). It is therefore apparent that this pathway requires a high temperature (150 °C) and is not a simple consequence of the change to a different and more nucleophilic base. HPLC monitoring of the reaction mixture at 150 °C under microwave conditions demonstrates that in essence a mixture of pyrazoloquinolin-5-ones **4** (path A) and pyrazoloquinolizin-9-ones **6** (path C) is obtained under these conditions. Depending on the individual building blocks the ratio between the two reaction products varies, however, the isolation protocol favors the crystallization of the less soluble pyrazoloquinolizin-9-ones **6** from the crude reaction mixture which therefore allows the isolation of these structures in a very efficient and chromatography-free way (see Experimental Section).

Similar to the control studies described above for the formation of Hantzsch-type dihydropyridines under microwave and oil bath conditions, also in the case of pyrazoloquinolizin-9-ones **6** it was demonstrated by an experiment involving the formation of tricyclic structure **6b** from aminopyrazole **1**, aldehyde **3b**, and dimedone **2a** using conventional heating to 150 °C that there was no difference between microwave heating and conventional heating using an appropriate experimental setup.[10]

While detailed mechanistic studies on these three-component reactions were not pursued in the present work, an overall mechanistic rational for all three distinct pathways (A, B, and C) is presented in Scheme 2. For paths A and C the mechanism most likely involves the initial base-catalyzed formation of Michael adduct **9** (Figure 9), which subsequently reacts with aminopyrazole **1** to furnish the tricyclic intermediates **13**. The formation of these intermediates may occur either by (i) nucleophilic addition of the NH_2-group of the aminopyrazole to one of the carbonyl centers in adduct **9** and concomitant elimination of one molecule of cyclic diketone **2**, or (ii) via nucleophilic substitution of the diketone moiety in adduct **9** by 5-aminopyrazole. Path B (Biginelli-type condensation) may proceed via the tricyclic intermediate **16** but we cannot exclude other mechanistic pathways, for example the involvement of hemiacetal **10**[17] or Michael adduct **11** (Figure 3).

Elimination of water from the intermediates **13** and **16** may lead to the formation of the classical Hantzsch-type dihydropyridine **4** (path A) and Biginelli-type dihydropyrimidine **5** (path B). However, water elimination may also proceed at an earlier stage from hemiacetal **10** to furnish enamine **12** (Figure 3). In the presence of a strong base at high temperatures however, the cyclic 1,3-dicarbonyl fragment in **13**, after nucleophilic attack of the base to the carbonyl group, apparently undergoes ring opening (**14** → **15**) in accordance with previously reported mechanisms for the cleavage of β-diketones.[18] In the particular case reported here, the intermediate **14** is able to efficiently recyclize to provide the observed fused quinolizinones **6** (path C).[19]

Conclusions

As demonstrated in the present article, temperature in combination with the choice of catalyst is the main factor in controlling the direction of the investigated multicomponent reaction. Under ambient and neutral conditions the reaction between 5-amino-3-phenylpyrazole **1**, cyclic diketones **2**, and aromatic aldehydes **3** proceeds via the formation of the kinetically controlled intermediate **16** yielding Biginelli-type dihydropyrimidine **5** (path B). Increase of the reaction temperature in combination with added triethylamine base allows the reaction to proceed via the thermodynamically controlled tricycle **13**. The critical step in distinguishing between paths A and C is the further transformation of the tricyclic intermediate **13**. In addition to the temperature factor, the nature of the catalyst and its relative basicity and nucleophilicity plays an important role. Tertiary bases such as triethylamine or *N*-methylmorpholine are not capable to act as nucleophiles and therefore cannot react with the carbonyl group in **13**, leading to an opening of the cyclic diketone ring structure. Strong bases of relatively small size (hydroxide, methoxide) lead either to mixtures, containing both pyrazoloquinolizinones **6** and pyrazoloquinolinones **4**, or to pure pyrazoloquinolinones depending on the reaction conditions. Using sodium ethoxide in most cases avoids the formation of large amounts of pyrazoloquinolinones **4**, whereas sterically bulky potassium *tert*-butoxide was found as the best base to promote path C in this MCR. While sealed vessel microwave heating has aided in the rapid screening and optimization of the reaction conditions, the observed effects could also be achieved in an oil bath under carefully controlled conditions.

Experimental Section

4-Aryl-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones (4a−**h).**

General Procedure (Table 1). A mixture of 5-amino-3-phenylpyrazole **1** (1.30 mmol, 1 equiv), cyclic 1,3-diketone **2a,b** (1.30 mmol, 1 equiv), the appropriate aromatic aldehyde **3a**−**g** (1.3 mmol, 1 equiv), triethylamine (1.56 mmol, 1.2 equiv), and 3 mL of ethanol contained in a sealed microwave vial was heated in a

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single mode microwave reactor at 150 °C for 15 min with magnetic stirring. After cooling to ambient conditions by compressed air, 4 mL of a EtOH−H_2O mixture (1:1) was added to the crude reaction mixture and heated to 50−60 °C with vigorous stirring. After cooling the precipitate was removed by filtration, washed with EtOH−H_2O (1:1), and dried at room temperature to produce the desired pyrazoloquinolinone **4a**−**g** in >98% purity (^{1}H NMR and HPLC).

7,7-Dimethyl-3,4-diphenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-ones (4a). Yield 85%, mp >300 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.82 (s, 3H), 0.98 (s, 3H), 1.92 (d, 1H, J = 16.3 Hz), 2.14 (d, 1H, J = 16.3 Hz), 2.33 (d, 1H, J = 16.3 Hz), 2.45 (d, 1H, J = 16.3 Hz), 5.31 (s, 1H), 6.86−7.17 (m, 5H), 7.19−7.43 (m, 3H), 7.45−7.57 (m, 2H), 9.91 (br s, 1H), 12.55 (br s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 27.0, 29.45, 32.42, 35.67, 41.37, 50.9, 56.55, 103.8, 108.3, 125.8, 126.4, 127.9, 128.1, 128.3, 129.2, 130.0, 137.8, 148.04, 148.6, 152.6, 193.2; MS (EI, 70 eV) *m*/*z* 369 (M, 19), 292 (93), 293 (18). Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 77.92; H, 6.25; N, 11.41.

7,7-Dimethyl-4-(4-methylphenyl)-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-one (4b). Yield 86%, mp 207−209 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.84 (s, 3H), 0.99 (s, 3H), 1.95 (d, 1H, J = 16.9 Hz), 2.12 (s, 3H), 2.15 (d, 1H, J = 16.9 Hz), 2.35 (d, 1H, J = 16.9 Hz), 2.48 (d, 1H, J = 16.9 Hz), 5.31 (s, 1H), 6.89 (d, 2H, J = 8.0 Hz), 7.01 (d, 2H, J = 8.0 Hz), 7.22−7.31 (m, 1H), 7.32−7.42 (m, 2H), 7.49−7.58 (m, 2H), 9.91 (s, 1H), 12.56 (br s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 20.8, 26.2, 28.7, 31.6, 34.0, 40.6, 50.1, 103.2, 107.8, 110.5, 125.6, 127.5, 128.1, 128.4, 139.5, 151.6, 156.6, 192.5; MS (EI, 70 eV) *m*/*z* 383 (M, 60), 384 (M^+, 25), 292 (100), 293 (20). Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.15; H, 6.54; N, 11.11.

7,7-Dimethyl-4-(4-methoxyphenyl)-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-one (4c). Yield 76%, mp 183−186 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.83 (s, 3H), 0.99 (s, 3H), 1.95 (d, 1H, J = 16.3 Hz), 2.14 (d, 1H, J = 16.3 Hz), 2.35 (d, 1H, J = 16.3 Hz), 2.47 (d, 1H, J = 16.3 Hz), 3.60 (s, 3H), 5.28 (s, 1H), 6.65 (d, 2H, J = 8.6 Hz), 7.00 (d, 2H, J = 8.6 Hz), 7.23−7.33 (m, 1H), 7.33−7.42 (m, 2H), 7.46−7.59 (m, 2H), 9.89 (s, 1H), 12.56 (br s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 27.0, 29.4, 32.48 34.7, 41.3, 50.9, 55.2, 104.0, 108.6, 113.4, 126.3, 128.3, 128.8, 129.2, 130.1, 137.6, 140.3, 148.6, 152.4, 157.4, 193.3; MS (EI, 70 eV) *m*/*z* 399 (M, 58), 400 (M^+, 15), 292 (100), 293 (19). Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; Í, 6.31; N, 10.52. Found: C, 75.01; Í, 6.28; N, 10.41.

4-(4-Bromophenyl)-7,7-dimethyl-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-one (4d). Yield 91%, mp 195−197 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.83 (s, 3H), 0.99 (s, 3H), 1.96 (d, 1H, J = 16.3 Hz), 2.16 (d, 1H, J = 16.3 Hz), 2.36 (d, 1H, J = 16.5 Hz), 2.48 (d, 1H, J = 16.5 Hz), 5.33 (s, 1H), 7.06 (d, 2H, J = 8.6 Hz), 7.23−7.33 (m, 3H), 7.33−7.43 (m, 2H), 7.47−7.55 (m, 2H), 10.00 (s, 1H), 12.63 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 27.0, 29.4, 32.4, 35.4, 41.3, 50.8, 103.2, 107.7, 118.8, 126.4, 128.4, 129.2, 129.8, 130.2, 130.9, 138.0, 147.3, 148.4, 152.8, 193.2; MS (EI, 70 eV) *m*/*z* 447 (M^-, 21), 448 (M, 8), 449 (M^+, 24), 292 (100), 293 (19). Anal. Calcd for $C_{24}H_{22}BrN_3O$: C, 64.29; H, 4.95; Br, 17.82; N, 9.37. Found: C, 64.10; H, 4.88; Br, 17.65; N, 9.21.

7,7-Dimethyl-4-(4-nitrophenyl)-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-one (4e). Yield 83%, mp 196−198 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.83 (s, 3H), 0.99 (s, 3H), 1.96 (d, 1H, J = 15.9 Hz), 2.16 (d, 1H, J = 15.9 Hz), 2.39 (d, 1H, J = 16.3 Hz), 2.55 (d, 1H, J = 16.3 Hz), 5.50 (s, 1H), 7.23−7.31 (m, 1H), 7.32−7.42 (m, 4H), 7.44−7.54 (m, 2H), 7.92−8.00 (m, 2H), 10.13 (s, 1H), 12.70 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 27.0, 29.3, 32.4, 36.2, 41.3, 50.7, 102.5, 106.9, 123.4, 126.5, 128.5, 129.2, 129.2, 129.6, 138.4, 145.8, 148.2, 153.3, 155.3, 193.2; MS (EI, 70 eV) *m*/*z* 414 (M, 34), 415 (M^+, 12), 292 (100), 293 (17). Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.29; H, 5.18; N, 13.58.

7,7-Dimethyl-3-phenyl-4-[2-(trifluoromethyl)phenyl]-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-one (4f). Yield 86%, mp 247−250 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.86 (s, 3H), 0.99 (s, 3H), 1.89 (d, 1H, J = 15.9 Hz), 2.11 (d, 1H, J = 15.9 Hz), 2.39 (d, 1H, J = 16.6 Hz), 2.52 (d, 1H, J = 16.6 Hz), 5.69 (s, 1H), 7.04−7.13 (m, 2H), 7.15−7.22 (m, 1H), 7.23−7.31 (m, 4H), 7.33−7.36 (m, 1H), 7.36−7.45 (m, 1H), 9.99 (s, 1H), 12.43 (br s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 27.1, 29.3, 32.4, 41.5, 50.9, 103.8, 108.2, 126.3, 126.6, 127.9, 128.6, 130.0, 131.6, 132.0, 139.6, 147.6, 147.7, 152.8, 193.0; MS (EI, 70 eV) *m*/*z* 437 (M, 22), 438 (M^+, 8), 292 (100), 293 (18). Anal. Calcd for $C_{25}H_{22}F_3N_3O$: C, 68.64; H, 5.07; N, 9.61. Found: C, 68.45; H, 4.98; N, 9.72.

4-(4-Methylphenyl)-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-one (4g). Yield 70%, mp >310 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 1.61−1.78 (m, 1H), 1.78−1.82 (m, 1H), 2.12 (s, 3H), 2.14−2.27 (m, 2H), 2.50−2.60 (m, 2H), 5.35 (s, 1H), 6.83−6.93 (m, 2H), 6.89 (d, 2H, J = 8.0 Hz), 7.00 (d, 2H, J = 8.0 Hz), 7.23−7.31 (m, 1H), 7.33−7.42 (m, 2H), 7.47−7.57 (m, 2H), 9.93 (s, 1H), 12.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 21.0, 21.4, 28.1, 35.0, 37.4, 103.8, 109.8, 126.3, 127.8, 128.3, 129.2, 130.0, 134.7, 137.6, 145.3, 148.6, 154.4, 193.6; MS (EI, 70 eV), *m*/*z* 355 (M, 37), 356 (M^+, 10), 264 (M, 100). Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.95; H, 5.98; N, 11.60.

4-(4-Fluorophenyl)-3-phenyl-1,4,6,7,8,9-hexahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5-one (4h). Yield 85%, mp >300 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 1.73−1.89 (m, 2H), 2.14−2.18 (m, 2H), 2.53−2.56 (m, 2H), 5.36 (s, 1H), 6.75−6.95 (m, 2H), 6.97−7.18 (m, 2H), 7.19−7.40 (m, 3H), 7.40−7.55 (m, 2H), 9.96 (s, 1H), 12.59 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 21.4, 28.1, 34.9, 37.4, 56,5, 103.5, 109.4, 114.7, 114.9, 126.4, 128.4, 129.2, 129.6, 129.7, 129.9, 137.8, 144.4, 144.4, 148.5, 154.6, 159.6, 161.5, 193.7; MS (EI, 70 eV), *m*/*z* 359 (M, 39), 360 (M^+, 9), 264 (100). Anal. Calcd for $C_{22}H_{18}FN_3O$: C, 73.52; H, 5.05; N, 11.69. Found: C, 73.33; H, 4.95; N, 11.77.

9-Aryl-2-phenyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-ones (5a−h).

General Procedure (Table 2). A mixture of 5-amino-3-phenylpyrazole **1** (1.30 mmol, 1 equiv), cyclic 1,3-diketone **2a,b** (1.30 mmol, 1 equiv), the appropriate aromatic aldehyde **3a**−**e,h** (1.3 mmol, 1 equiv), and 2 mL of ethanol was sonicated in a standard ultrasonic bath (44.2 kHz) at room temperature for 30 min in a 5 mL round-bottom flask equipped with condenser. The precipitates formed were removed by filtration, washed with EtOH-H_2O (1:1) and dried at room temperature to produce the desired pyrazoloquinazolinones **5a**−**h**. The work up procedure for pyrazoloquinazolinones **5g,h** involved evaporation under reduced pressure and crystallization of the resulting crude oil with acetonitrile at room temperature. The purity of pyrazoloquinazolinones **5a**−**h** was >98% (^{1}H NMR and HPLC).

2,9-Diphenyl-6,6-dimethyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-one (5a). Yield 67%, mp 202−204 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.91 (s, 3H), 1.03 (s, 3H), 2.07 (d, 1H, J = 16.2 Hz), 2.17 (d, 1H, J = 16.2 Hz), 2.44 (d, 1H, J = 17.2 Hz), 2.58 (d, 1H, J = 17.2 Hz), 6.17 (s, 2H), 7.09−7.40 (m, 8H), 7.62−7.75 (m, 2H), 10.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 27.2, 29.2, 32.6, 50.4, 58.0, 85.9, 105.4, 125.5, 127.1, 127.7, 128.2, 128.6, 128.9, 133.6, 138.8, 143.4, 149.7, 150.7, 192.8; MS (EI, 70 eV) *m*/*z* 369 (M, 100), 368 (M^-, 32), 292 (99), 159 (37). Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.13; H, 6.48; N, 11.07.

6,6-Dimethyl-9-(4-methylphenyl)-2-phenyl-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazolin-8-one (5b). Yield 56%, mp 228−230

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°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.92 (s, 3H), 1.03 (s, 3H), 2.01 (d, 1H, J = 16.2 Hz), 2.22 (d, 1H, J = 16.2 Hz), 2.18 (s, 3H), 2.42−2.57 (m, 2H), 6.13 (s, 1H), 6.15 (s, 1H), 6.90−7.12 (m, 4H), 7.18−7.40 (m, 3H), 7.60−7.55 (m, 2H), 10.48 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.1, 27.2, 29.2, 32.6, 50.4, 57.8, 85.9, 105.5, 125.5, 127.1, 128.1, 128.9, 129.1, 133.6, 136.8, 138.7, 140.6, 149.6, 150.6, 192.8; MS (EI, 70 eV) *m*/*z* 383 (M, 100), 382 (M^-, 29), 292 (34). Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.45; H, 6.40; N, 10.81.

6,6-Dimethyl-9-(4-methoxylphenyl)-2-phenyl-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazolin-8-one (5c). Yield 61%, mp 193−195 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.93 (s, 3H), 1.04 (s, 3H), 2.02 (d, 1H, J = 16.1 Hz), 2.23 (d, 1H, J = 16.1 Hz), 2.43 (d, 1H, J = 16.9 Hz), 2.56 (d, 1H, J = 16.9 Hz), 3.65 (s, 3H), 6.12 (s, 1H), 6.14 (s, 1H), 6.73−6.85 (m, 2H), 7.00−7.13 (m, 2H), 7.18−7.41 (m, 3H), 7.62−7.74 (m, 2H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 27.3, 29.2, 32.6, 50.4, 55.5, 57.5, 85.8, 105.5, 113.9, 125.5, 128.1, 128.3, 128.9, 133.6, 135.7, 138.7, 149.5, 150.5, 158.8, 192.8; MS (EI, 70 eV) *m*/*z* 399 (M, 100), 400 (M^+, 15), 292 (20). Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found: C, 75.55; H, 6.21; N, 10.36.

9-(4-Bromophenyl)-6,6-dimethyl-2-phenyl-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazolin-8-one (5d). Yield 70%, mp 256−258 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.91 (s, 3H), 1.04 (s, 3H), 2.02 (d, 1H, J = 16.3 Hz), 2.22 (d, 1H, J = 16.3 Hz), 2.42 (d, 1H, J = 16.4 Hz), 2.57 (d, 1H, J = 16.4 Hz), 6.17 (s, 1H), 6.19 (s, 1H), 7.04−7.17 (m, 2H), 7.18−7.39 (m, 3H), 7.39−7.53 (m, 2H), 7.60−7.79 (m, 2H), 10.58 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 27.4, 29.1, 32.6, 50.4, 57.6, 86.1, 104.9, 120.8, 125.6, 128.2, 128.9, 129.3, 131.5, 133.6, 138.8, 142.8, 149.8, 151.0, 192.8; MS (EI, 70 eV) *m*/*z* 447 (M, 53), 448 (M^+, 25), 449 (M^{2+}, 50), 292 (33). Anal. Calcd for $C_{24}H_{22}BrN_3O$: C, 64.29; Í, 4.95; Br, 17.82; N, 9.37. Found: C, 64.01; Í, 4.49; Br, 17.66; N, 9.24.

6,6-Dimethyl-9-(4-nitrophenyl)-2-phenyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8-one (5e). Yield 54%, mp 193−195 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.90 (s, 3H), 1.04 (s, 3H), 2.02 (d, 1H, J = 16.3 Hz), 2.23 (d, 1H, J = 16.3 Hz), 2.44 (d, 1H, J = 16.9 Hz), 2.59 (d, 1H, J = 16.9 Hz), 6.24 (s, 1H), 6.32 (s, 1H), 7.20−7.50 (m, 5H), 7.62−7.76 (m, 2H), 8.06−8.20 (m, 2H), 10.13 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 27.4, 29.0, 32.6, 50.4, 57.7, 86.4, 104.4, 123.9, 125.7, 128.3, 128.5, 128.9, 133.4, 138.9, 147.2, 150.2, 150.4, 151.3, 192.8; MS (EI, 70 eV) *m*/*z* 414 (M, 100), 415 (M^+, 30), 416 (M + 2, 62), 292 (65). Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.36; H, 5.20; N, 13.66.

9-(2-Methoxyphenyl)-6,6-dimethyl-2-phenyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-one (5f). Yield 60%, mp 220−222 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.92 (s, 3H), 1.03 (s, 3H), 1.94 (d, 1H, J = 16.5 Hz), 2.19 (d, 1H, J = 16.5 Hz), 2.38 (d, 1H, J = 16.8 Hz), 2.57 (d, 1H, J = 16.8 Hz), 3.68 (s, 3H), 6.06 (s, 1H), 6.35 (s, 1H), 6.74−6.96 (m, 2H), 7.05−7.39 (m, 5H), 7.60−7.70 (m, 2H), 10.42 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 26.9, 29.4, 32.5, 50.6, 54.9, 56.4, 85.2, 104.6, 112.5, 120.5, 125.5, 127.9, 128.9, 129.1, 130.0, 131.3, 133.9, 139.0, 150.0, 157.7, 192.4; MS (EI, 70 eV) *m*/*z* 399 (M, 54), 400 (M^+, 15), 368 (100), 369 (28). Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found: C, 75.12; H, 6.36; N, 10.42.

9-(4-Nitrophenyl)-2-phenyl-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazolin-8-one (5g). Yield 54%, mp 218−220 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.78−2.01 (m, 2H), 2.10−2.29 (m, 2H), 2.50−2.70 (m, 2H), 6.23 (s, 1H), 6.33 (s, 1H), 7.15−7.40 (m, 3H), 7.45 (d, 2H, J = 8.7 Hz), 7.61−7.70 (m, 2H), 8.10 (d, 2H, J = 8.7 Hz), 10.71 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.1, 27.0, 36.7, 57.5, 86.3, 105.4, 123.9, 125.6, 128.3, 128.5, 128.96, 133.3, 138.7, 147.1, 150.4, 151.2, 152.2, 193.3; MS (EI, 70 eV) *m*/*z* 386 (M, 7), 264 (M, 7), 159 (100). Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.01; H, 4.65; N, 14.10.

9-(4-Bromophenyl)-2-phenyl-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazolin-8-one (5h). Yield 51%, mp 178−180 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.71−2.05 (m, 2H), 2.10−2.31 (m, 2H), 2.51−2.72 (m, 2H), 6.17 (s, 2H), 7.11 (d, 2H, J = 8.4 Hz), 7.20−7.38 (m, 3H), 7.43 (d, 2H, J = 8.4 Hz), 7.65−7.75 (m, 2H), 10.34 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.9, 21.2, 26.9, 36.8, 57.4, 85.9, 105.9, 120.8, 125.6, 128.2, 128.9, 129.4, 131.5, 133.5, 138.6, 142.7, 150.8, 151.8, 193.2; MS (EI, 70 eV) *m*/*z* 421 (M^+, 72), 420 (M, 42), 422 (M^-, 19), 264 (100). Anal. Calcd for $C_{22}H_{18}BrN_3O$: C, 62.87; H, 4.32; N, 10.00. Found: C, 62.30; H, 4.10; N, 9.82.

6,6-Dimethyl-9-(4-methylphenyl)-2-phenyl-4,5,6,7,8,9-hexahydropyrazolo[5,1-*b*]quinazolin-8-one (5b) via Trimethylsilylchloride Method (Scheme 1). Into a 20-mL microwave process vial equipped with a magnetic stirring bar were added 10 mL of acetonitrile, 5-phenyl-1*H*-pyrazol-3-amine (1.39 g, 8.74 mmol, 2.0 equiv), and 5,5-dimethyl-1,3-cyclohexanedione (1.23 g, 8.74 mmol, 2.0 equiv), and the mixture was stirred vigorously for 1 min at room temperature to form a suspension. Chlorotrimethylsilane (224 μL, 190 mg, 1.75 mmol, 0.40 equiv) was then dropwise added. After an additional stirring period of 1 min at room temperature, *p*-tolualdehyde (515 μL, 525 mg, 4.37 mmol, 1.0 equiv) was added dropwise. The formed reaction mixture is stirred for additional 2 min, and then the sealed reaction vial was heated at 170 °C for 30 min in a microwace reactor. After the reaction mixture has been processed, the reaction mixture was transferred into a beaker containing a vigorously stirred 300 mL water−ethanol mixture (2:1), containing 160 mg of dissolved NaOH, to adjust the pH to 8−9. The resulting suspension was stirred for an additional 1 h and was then filtered and washed with cold (0 °C) H_2O−EtOH mixture (2:1). The precipitate was dried overnight in a drying oven at 50 °C under atmospheric conditions. The crude product was then recrystallized from 2-propanol−H_2O mixture (2:1), resulting in a 77% yield of 6,6-dimethyl-2-phenyl-9-*p*-tolyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]-quinazolin-8(4*H*)-one (**5b**) as a white powder. Analytical and spectroscopic data were as described above.

4-Aryl-5a-hydroxy-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-ones (6a−i).

General Procedure (Table 3). A mixture of 5-amino-3-phenylpyrazole **1** (0.7 mmol, 1 equiv), 1,3-diketone **2a,b** (1.4 mmol, 2 equiv), the corresponding aromatic aldehyde **3a−d,g** (0.7 mmol, 1 equiv), potassium *tert*-butoxide (1.4 mmol, 2 equiv), and 3 mL of absolute EtOH contained in a sealed microwave vial was heated in a single mode microwave reactor at 150 °C for 15 min with magnetic stirring. After cooling to ambient conditions by compressed air the solvent was removed by evaporation under reduced pressure. The crude solid product mixture was heated (∼ 80 °C) in a 4 mL EtOH−H_2O (1:1) mixture to produce the expected pyrazoloquinolizinones **6a−i** upon cooling.

3,4-Diphenyl-5a-hydroxy-7,7-dimethyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-one (6a). Yield 60%, mp 238−240 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.97 (s, 3H), 1.18 (s, 3H), 1.80 (dd, 1H, J = 11.3 and 13.6 Hz), 1.93 (s, 2H), 2.28 (dd, 1H, J = 6.0 and 13.6 Hz), 2.36 (d, 1H, J = 17.2 Hz), 2.45 (d, 1H, J = 17.2 Hz), 4.43 (dd, 1H, J = 6.0 and 11.3 Hz, 1H), 6.09 (br s, 1H, D_2O-exchangeable), 6.85−7.20 (m, 5H), 7.21−7.42 (m, 3H), 7.52 (m, 2H), 12.57 (br s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 29.0, 29.7, 30.3, 35.5, 48.3, 49.6, 85.0, 103.8, 126.4, 126.4, 127.4, 127.8, 127.9, 128.5, 129.2, 144.3, 148.0, 152.6; MS (EI, 70 eV) *m*/*z* 387 (76), 388 (M^+, 16), 294 (M, 100). Anal. Calcd for $C_{24}H_{25}N_3O2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.13; H, 6.41; N, 10.87.

5a-Hydroxy-4-(4-methylphenyl)-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-one (6b). Yield 75%, mp 265−267 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.96 (s, 3H), 1.17 (s, 3H), 1.77 (dd, 1H, J = 13.6 and 11.3 Hz), 1.89 (d, 1H, J = 15.0 Hz), 1.95 (d, 1H, J = 15.0 Hz), 2.11 (s, 3H), 2.26 (dd, 1H, J = 6.0 and 13.6 Hz), 2.37 (d, 1H, J = 16.3 Hz), 2.46 (d, 1H, J = 16.3 Hz), 4.40 (dd, 1H, J = 6.0 and 11.3 Hz), 6.09 (br s, 1H, D_2O-exchangeable), 6.78−6.99 (m, 4H), 6.99−7.12 (m, 3H), 7.30−7.45 (m, 2H), 12.83 (br s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 21.0, 28.9, 29.7, 30.3, 35.1, 46.7, 48.3, 49.7, 85.0, 126.9,

127.4, 127.8, 127.9, 128.7, 129.1, 135.1, 141.3, 168.4; MS (APCI, 70 eV) *m/z* 403 (26), 402 (M^+, 100), 385 (25). Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.50; H, 6.75; N, 10.50.

5a-Hydroxy-4-(4-methoxyphenyl)-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-one (6c). Yield 65%, mp 256−258 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.96 (s, 3H), 1.16 (s, 3H), 1.76 (dd, 1H, J = 11.6 and 13.0 Hz), 1.89 (m, 2H), 2.24 (dd, 1H, J = 6.0 and 13.0 Hz), 2.36 (d, 1H, J = 16.6 Hz), 2.45 (d, 1H, J = 16.6 Hz), 3.58 (s, 3H), 4.38 (dd, 1H, J = 6.0 and 11.6 Hz), 6.04 (br s, 1H, D_2O-exchangeable), 6.55−6.67 (m, 2H), 6.89−6.99 (m, 2H), 7.00−7.12 (m, 3H), 7.30−7.39 (m, 2H), 12.78 (br s, 1H, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 29.0 29.7, 30.3, 34.6, 46.7, 48.4 49.8, 55.3, 85.0, 104.2, 114.0, 127.0, 127.5, 127.8, 128.9, 136.2, 157.8, 168.5; MS (EI, 70 eV) *m/z* 417 (M, 87), 418 (M^+, 26), 399 (30), 398 (56). Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.71; H, 6.57; N, 9.99.

4-(4-Bromophenyl)-5a-hydroxy-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9-one (6d). Yield 70%, mp 258−260 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.95 (s, 3H), 1.16 (s, 3H), 1.75 (dd, 1H, J = 11.3 and 13.0 Hz), 1.87−1.95 (m, 2H), 2.25 (dd, 1H, J = 6.0 and 11.3 Hz), 2.36 (d, 1H, J = 15.9 Hz), 2.45 (d, 1H, J = 15.9 Hz), 4.34 (dd, 1H, J = 6.0 and 13.0 Hz), 6.08 (br s, 1H, D_2O-exchangeable), 6.93−7.38 (m, 9H), 12.76 (br s, 1H, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 28.9, 29.7, 30.3, 35.0, 46.7, 48.3, 49.2, 85.0, 103.4, 119.1, 126.4, 127.1, 127.4, 128.0, 130.2, 131.3, 134.1, 143.8, 168.4; MS (EI, 70 eV) *m/z* 465 (M, 8), 292 (100). Anal. Calcd for $C_{24}H_{24}BrN_3O_2$: C, 61.81; H, 5.19; Br, 17.13; N, 9.01. Found: C, 61.58; H, 5.25; Br, 17.07; N, 9.04.

4-(4-Fluorophenyl)-5a-hydroxy-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9(1*H*)-one (6e). Yield 38%, mp 243−245 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 0.96 (s, 3H), 1.17 (s, 3H), 1.79 (dd, 1H, J = 11.6 and 13.6 Hz), 1.88−1.99 (m, 2H), 2.26 (dd, 1H, J = 6.0 and 13.6 Hz), 2.37 (d, 1H, J = 16.6 Hz), 2.46 (d, 1H, J = 16.6 Hz), 4.45 (dd, 1H, J = 6.0 and 11.6 Hz), 6.09 (s, 1H), 6.80−6.90 (m, 2H), 7.00−7.12 (m, 5H), 7.31 (m, 2H), 12.77 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 29.0, 29.7, 30.3, 34.7, 46.6, 48.3, 49.3, 85.0, 103.7, 115.0, 115.2, 127.0, 127.5, 127.8, 129.7, 134.3, 138.3, 140.3, 146.6, 159.5, 168.5; MS (EI, 70 eV) *m/z* 405 (M, 80), 406 (M^+, 21), 292 (100). Anal. Calcd for $C_{24}H_{24}FN_3O_2$: C, 71.09; H, 5.97; N, 10.36. Found: C, 70.87; H, 6.02; N, 10.39.

3,4-Diphenyl-5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9(1*H*)-one (6f). Yield 58%, mp 285−287 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 1.62−1.73 (m, 1H), 1.79 (dd, 1H, J = 11.3 Hz 13.6 Hz), 1.83−1.98 (m, 2H), 2.08−2.21 (m, 1H), 2.27 (dd, 1H, J = 6.0 and 13.6 Hz), 2.51 (d, 1H, J = 4.0 Hz), 2.56 (d, 1H, J = 4.0 Hz), 4.43 (dd, 1H, J = 6.0 and 11.3 Hz), 6.35 (br s, 1H, D_2O-exchangeable), 6.90−7.19 (m, 8H), 7.28−7.38 (dd, 2H, J = 7.6 and 7.6 Hz), 12.80 (br s, 1H, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 15.4, 33.2, 35.3, 35.7, 48.3, 84.5, 103.6, 126.3, 126.9, 127.5, 127.8, 127.9, 128.5, 134.2, 144.4, 168.6; MS (EI, 70 eV) *m/z* 359 (M, 100), 282 (42). Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.76; H, 5.93; N, 11.72.

5a-Hydroxy-4-(4-methylpenyl)-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9(1*H*)-one (6g). Yield 60%, mp 310−312 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 1.61−1.80 (m, 2H), 1.81−1.97 (m, 2H), 2.10 (s, 3H), 2.14−2.22 (m, 1H), 2.24 (dd, 1H, J = 6.0 and 13.6 Hz), 2.48 (d, 1H, J = 3.6 Hz), 2.51(d, 1H, J = 3.6 Hz), 4.40 (dd, 1H, J = 6.0 and 11.3 Hz), 6.25 (br s, 1H, D_2O-exchangeable), 6.86 (d, 2H, J = 8.0 Hz), 6.94 (d, 2H, J = 8.0 Hz), 6.99−7.11 (m, 4H), 7.31−7.40 (m, 2H), 12.84 (br s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 15.4, 21.0, 33.2, 34.9, 35.8, 48.5, 84.5, 103.7, 126.4, 127.0, 127.4, 127.8, 127.9, 128.5, 129.1, 134.3, 135.0, 141.4, 168.5; MS (EI, 70 eV) *m/z* 373 (M, 100), 374 (M^+, 24), 264 (55). Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.75; H, 6.19; N, 11.28.

5a-Hydroxy-4-(4-methoxyphenyl)-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9(1*H*)-one (6h). Yield 58%, mp 298−300 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 1.60−1.80 (m, 2H), 1.81−1.98 (m, 2H), 2.06−2.20 (m, 2H), 2.23 (dd, 1H, J = 6.0 and 13.9 Hz), 2.52−2.56 (m, 2H), 3.58 (s, 3H), 4.38 (dd, 1H, J = 6.0 and 11.6 Hz), 6.24 (s, 1H), 6.61 (d, 2H, J = 8.6 Hz), 6.96 (d, 2H, J = 8.6 Hz), 7.00−7.10 (m, 3H), 7.35 (m, 2H), 12.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 15.4, 33.2, 34.4, 35.7, 48.5, 55.3, 84.5, 113.9, 126.9, 127.5, 127.8, 128.8, 134.4, 136.0, 136.1, 136.3, 157.7; MS (EI, 70 eV) *m/z* 389 (M, 100), 390 (M^+, 16), 264 (59). Anal. Calcd for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79. Found: C, 70.71; H, 5.90; N, 10.82.

4-(4-Bromophenyl)-5a-hydroxy-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-*c*]quinolizin-9(1*H*)-one) (6i). Yield 59%, mp 252−254 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 1.57−1.81 (m, 2H), 1.82−2.00 (m, 2H), 2.08−2.21 (m, 2H), 2.26 (dd, 1H, J = 6.0 and 13.6 Hz), 2.53−2.59 (m, 2H), 4.45 (dd, 1H, J = 6.0 and 11.3 Hz), 6.33 (br s, 1H, D_2O-exchangeable), 6.96−7.14 (m, 5H), 7.18−7.26 (m, 2H), 7.28−7.38 (m, 2H), 12.78 (br s, 1H, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 15.4, 33.2, 34.8, 35.7, 47.9, 84.5, 103.2, 119.9, 126.3, 127.1, 127.5, 127.9, 128.6, 130.2, 131.3, 143.9, 168.6; MS (EI, 70 eV) *m/z* 437 (M, 33), 438 (M^+, 7), 439 (39), 264 (100). Anal. Calcd for $C_{22}H_{20}BrN_3O_2$: C, 60.28; H, 4.60; Br, 18.23; N, 9.59. Found: C, 60.45; H, 4.65; Br, 18.18; N, 9.63.

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Supporting Information Available: General experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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