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Substituent effects in the ring-chain tautomerism of 4-aryl-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines

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Dedicated to Professor Alajos Kálmán on the occasion of his 70th birthday

Abstract—By condensation of 1-(2′-aminoethyl)-1,2,3,4-tetrahydroisoquinoline derivatives with substituted benzaldehydes, 1,6-unsubstituted and diastereomers of 1-methyl- or 6-methyl-substituted 4-aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines were prepared. The ring-chain tautomeric equilibria of most of these compounds in $CDCl_3$ at 300 K were found to be shifted nearly totally towards either the cyclic or the open tautomeric forms, while the (6*R**,11b*R**)-6-methyl substituted compounds proved to be three-component tautomeric mixtures, the equilibria of which could be characterized by a Hammett-type equation. The conformational equilibria of the cyclic forms turned out to be strongly influenced by the 1- and 6-methyl substituents and the configurations of the substituted carbons (C-1 or C-6 and C-4) relative to C-11b.

1. Introduction

Ring-chain tautomerism, the reversible intramolecular addition of a hydroxy, mercapto or amino group to a C=N double bond, is a characteristic phenomenon for saturated, *N*-unsubstituted, five- and six-membered 1,3-*X*,*N* heterocycles (X=O, S, NR). It is often exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry.[1,2]

Substituent effects influencing the ring-chain tautomeric process have been studied thoroughly in recent decades. For the tautomeric equilibria of oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2, in both the liquid and the gas phase, a linear Hammett-type correlation was found between the log *K* (*K*=[ring]/[chain]) values of the equilibria and the electronic character (σ^+) of the substituents X on the 2-phenyl group (Eq. 1). The value of ρ in Eq. 1 was found to be characteristic of the ring system and dependent on the temperature and the nature of the solvent.[1,2]

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \quad (1)$$

Recent studies on 2-aryl-substituted imidazolidines,[3,4] hexahydropyrimidines,[5–7] 1,2,3,4-tetrahydro quina zolines,[6,8] perhydroquinazolines[9] and 3-arylhexahydroimidazo[5,1-*a*]- and -[1,5-*b*]isoquinolines[10] led to the conclusion that, similarly to their 1,3-*O*,*N* analogues, the ring-chain tautomeric equilibria of these compounds could likewise be characterized by Eq. 1. Complex 1,3-*N*,*N* heterocyclic tautomeric mixtures containing regioisomeric open and/or diastereomeric cyclic forms could also be characterized by Eq. 1.[7,9,10] For *N*-substituted 2-aryl-1,3-*N*,*N* heterocycles, the tautomeric process and the values of ρ and $\log K_{X=H}$ in Eq. 1 were found to be dependent on the steric and electronic characters of the substituent on the nitrogen. In contrast with the 1,3-*O*,*N* analogues, the value of ρ did not prove to be characteristic of the 1,3-*N*,*N* ring system.[2]

As a continuation of our previous studies on the ring-chain tautomerism of five- and six-membered 1,3-*N*,*N* heterocycles[2] and stereochemical investigations on 1,2,3,4-tetrahydro isoquinoline-condensed 1,3- and 1,2,3-heterocycles,[11] our primary present aim was to determine the influence of the substituents and the relative configuration of the substituted carbon atoms on the ring-chain tautomeric character and the conformation of 4-aryl-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines. In the knowledge of the significant substituent effects on both the ring-chain tautomeric and conformational equilibria of saturated 1,3-heterocycles,[2,12] a further aim was to study the consequences of methyl substitution at positions 1 and 6 of the hexahydropyrimido[6,1-*a*]isoquinoline ring system.

Keywords: Diamines; Isoquinolines; Hexahydropyrimidines; Ring-chain tautomerism; Conformation.
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2. Results and discussion

2.1. Synthesis

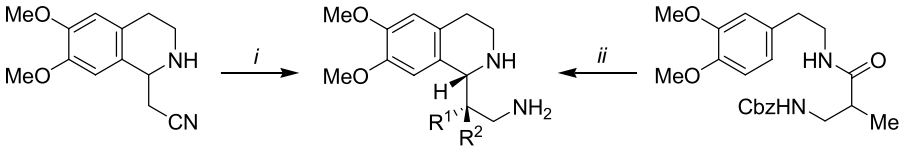
For the synthesis of the target hexahydropyrimido[6,1-*a*] isoquinolines, the appropriate 1-(2′-aminoethyl)-1,2,3,4-tetrahydroisoquinolines bearing a methyl substituent at either position 3 or position 1′ of the side-chain were required. The usual methods applied earlier for the synthesis of 1-aminoalkyl-1,2,3,4-tetrahydroisoquinolines involve reduction of the corresponding isoquinolines bearing nitrogen-containing functional groups (nitrile, carboxamide or nitro) in the side-chain and procedures based on the Bischler–Napieralski or Pictet–Spengler ring-closures, using the appropriate *N*-protected amino acids or amino aldehydes,[13] both of which were utilized in the preparation of the 1′- or 3-methyl-substituted tetrahydroisoquinoline diamines.

The unsubstituted diamine **2a** was obtained by the catalytic hydrogenation of 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylacetonitrile (**1**)[14] (Scheme 1). The 1′-methyl-substituted tetrahydroisoquinoline diamine diastereomers (**2b**,**c**) were prepared via a highly diastereoselective, four-step process, starting from 3-benzyloxycarbonylamino-2-methyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]propanamide (**3**). The formation of either the (1*R**,1′*S**) (**2b**) or the (1*R**,1′*R**) isomer (**2c**) as major product was found to be dependent on the sequence of reduction and deprotection steps applied.[15]

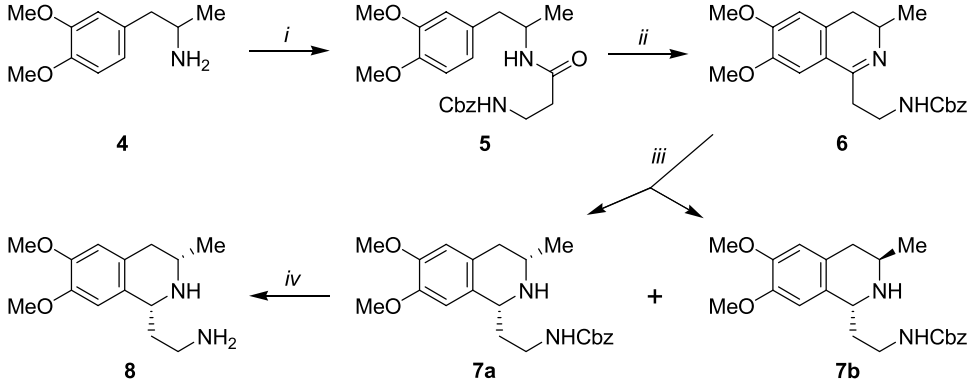
The 3-methyl-substituted tetrahydroisoquinoline diamine diastereomers (**8** and **11**) were prepared using different synthetic pathways. (1*R**,3*S**)-1-(2′-aminoethyl)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (**8**) was obtained by applying a procedure analogous to that used for the synthesis of **2b**. In the $NaBH_4$ reduction of dihydroisoquinoline **6**, obtained in two steps from *N*-protected β-alanine and α-methylhomoveratrylamine (**4**), a 12:1 mixture of tetrahydroisoquinoline isomers (1*R**,3*S**)-**7a** and (1*R**,3*R**)-**7b** was formed, from which **7a** was obtained by crystallization and was converted into the pure (1*R**,3*S**) diamine diastereomer **8** by removal of the Cbz group (Scheme 2). The *cis* selectivity of the reduction can be rationalized by the steric effect of the 3-methyl group, which directs the hydride attack to the sterically less hindered side, resulting in **7a** as the main product.[16–18] The relative configuration (1*R**,3*S**) of **8** was deduced from the NOE data on H-1 and H-3.

The (1*R**,3*R**) diamine diastereomer **11** was prepared by $LiAlH_4$ reduction of (1*R**,3*R**)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetamide (**10**), which was obtained in a highly diastereoselective two-step procedure[16,17] (monoethyl malonate addition and subsequent amidation) from 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**9**) (Scheme 3).

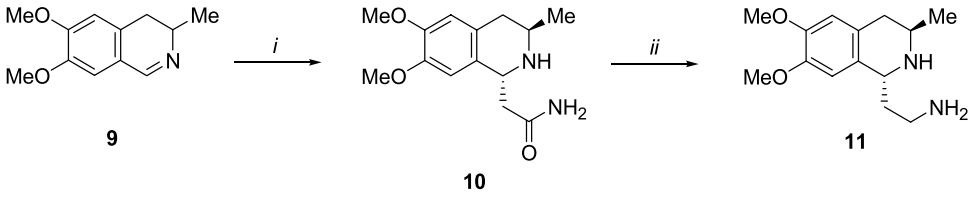
Condensations of diamines **2a–c**, **8** and **11** with equivalent amounts of *p*-nitro- and *p*-(dimethylamino)benzaldehyde resulted in model hexahydropyrimido[6,1-*a*]isoquinoline compounds **12–16** mainly as crystalline products (Scheme 4). In the knowledge of the strong influence of the electronic effects of the aromatic substituents on the ring-chain tautomeric behaviour of 1,3-*X*,*N* heterocyclic compounds,[1,2] aromatic aldehydes were chosen according to their opposite electronic character, which favour the predominance of either the cyclic (in the case of *p*-NO_2) or the open (in the case of *p*-NMe_2) form.



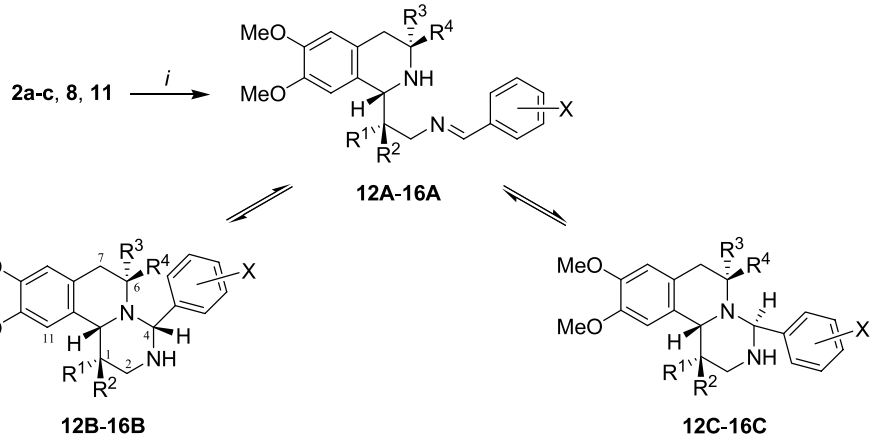
Scheme 1. Reagents and conditions: (i) see Ref. 14 (**1**→**2a**); (ii) see Ref. 15 (**3**→**2b**,**c**).



Scheme 2. Reagents and conditions: (i) ClCOOEt, *N*-Cbz-β-alanine, toluene, −10 °C, △, 5 min, 84%; (ii) $POCl_3$, $CHCl_3$, △, 3 h, 78%; (iii) $NaBH_4$, MeOH, 0 °C, 3 h, then rt, 3 h, **7a**:**7b**=12:1, 82% (**7a**); (iv) 1. 33% HBr in AcOH, rt, 30 min, 2. NaOH, 74%.



Scheme 3. Reagents and conditions: (i) see Ref. 17; (ii) $LiAlH_4$, THF, reflux, 7 h, 82%.



Scheme 4. Reagents and conditions: (i) XC_6H_4CHO, MeOH, rt, 1 h, 43–100%. (For the meanings of R^1–R^4 and X, see Table 1).

2.2. Ring-chain tautomerism

Quantitative studies on the ring-chain tautomeric equilibria of 2-aryl-substituted 1,3-*X*,*N* heterocycles (X=O, S, NR) are based on the integration of the well-separated X-C*H*Ar-N (ring) and N=C*H*Ar (chain) proton singlets in the ^{1}H NMR spectra.[1,2] The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equilibria of **12**–**16** were determined by this method (Table 1). The ^{1}H NMR ($CDCl_3$, 300 K) spectroscopic data on the 1-unsubstituted and 1-methyl-substituted model compounds (**12**–**14**) revealed that, independently of the electronic character of the aromatic substituents and the presence of the methyl group at position 1, their tautomeric equilibria were shifted totally towards the cyclic forms (**B** and **C**). The NOESY spectra unequivocally showed that the major ring forms in the tautomeric equilibria of **12**–**14** contain H-4 and H-11b in the *cis* position (**B**). The proportion of the minor cyclic tautomer, possessing H-4 and H-11b in the *trans* position (**C**), was found to be increased in (1*R**,11b*R**)-1-methylhexahydropyrimido[6,1-*a*]isoquinoline **14**.

The 6-methyl substitution caused a dramatic change in the tautomeric ratios. For (6*S**,11b*R**)-6-methyl-substituted hexahydropyrimido[6,1-*a*]isoquinolines **15**, the tautomeric equilibrium was found to be shifted entirely towards the open tautomer (**A**), even in **15a**, which bears an electron-withdrawing *p*-nitro substituent on the aromatic ring.

The tautomeric ratios determined for (6*R**,11b*R**) 6-methyl-substituted 4-(*p*-nitrophenyl)- (**16a**) and 4-[*p*-(dimethylamino)phenyl]hexahydropyrimido[6,1-*a*]isoquinoline (**16g**) suggested that the ring-chain equilibrium of this model compound was sensitive to the electronic effects of the 4-aryl substituents (Table 1). Accordingly, a full set of 4-(X-phenyl)-substituted derivatives was prepared, with substituent X exhibiting different electronic characters (**16a**–**g**). In consequence of the very similar NMR spectroscopic characteristics of **16a**–**g**, the relative configurations of the major (**B**) and minor (**C**) ring-closed tautomers were determined only for **16a**. The proportion of the minor cyclic form (**C**) was found to be decreased to below the limit of detection in the event of strongly electron-donating 4-aryl substituents (*p*-OMe and *p*-NMe_2).

Data on **16a** and **16g** were chosen to illustrate the ^{1}H NMR spectra of this type of prepared tautomeric compound (see Section 4). 4-Aryl substituents did not change the sequence of the chemical shifts of the characteristic N–C*H*Ar–N and N=C*H*Ar protons. The configuration of the azomethine double bond was found to be *E*, according to the NOE interaction observed between H-2 and N=C*H*.

When Eq. 1 was applied to the log K_X values (K_X=[ring]/[chain]) of **16a**–**g**, good linear correlations were obtained versus the Hammett–Brown parameter σ^+ of the substituent X on the 4-phenyl group, for both the *cis*-chain (**B**⇌**A**) and the *trans*-chain (**C**⇌**A**) equilibria (Fig. 1 and Table 2).

The data in Table 2 show that both the slope (ρ) and the intercept (log $K_{X=H}$) of the regression line were strongly influenced by the relative configuration of C-4 and C-11b. A comparison of the intercepts in Table 2, which indicate the stability of the given cyclic form,[1,2] indicates, that the attached tetrahydroisoquinoline ring makes both cyclic forms of **16** more stable than the corresponding monocyclic analogue 2-aryl-1-isopropylhexahydropyrimidine (**17B**). The difference in the values of ρ for the *cis*-chain (**16B**⇌**16A**) and *trans*-chain (**16C**⇌**16A**) equilibria, which reflects the difference in the sensitivities of the

Table 1. Proportions (%) of tautomeric forms (**A**, **B** and **C**) in tautomeric equilibria for compounds **12–16** ($CDCl_3$, 300 K)

Comp.	R^1	R^2	R^3	R^4	X	σ^+	**A**	**B**	**C**
12a	H	H	H	H	*p*NO_2	0.79	0	92.6	7.4
12b	H	H	H	H	*p*NMe_2	−1.7	0	100	0
13a	Me	H	H	H	*p*NO_2	0.79	0	100	0
13b	Me	H	H	H	*p*NMe_2	−1.7	0	100	0
14a	H	Me	H	H	*p*NO_2	0.79	0	65.4	34.6
14b	H	Me	H	H	*p*NMe_2	−1.7	0	81.3	18.7
15a	H	H	Me	H	*p*NO_2	0.79	100	0	0
15b	H	H	Me	H	*p*NMe_2	−1.7	100	0	0
16a	H	H	H	Me	*p*NO_2	0.79	10.7	74.7	14.6
16b	H	H	H	Me	*m*Br	0.405	17.6	75.4	7.0
16c	H	H	H	Me	*p*Br	0.15	24.1	69.2	6.7
16d	H	H	H	Me	H	0	31.4	64.9	3.7
16e	H	H	H	Me	*p*Me	−0.311	40.8	57.2	2.0
16f	H	H	H	Me	*p*OMe	−0.778	54.9	45.1	0
16g	H	H	H	Me	*p*NMe_2	−1.7	79.4	20.6	0

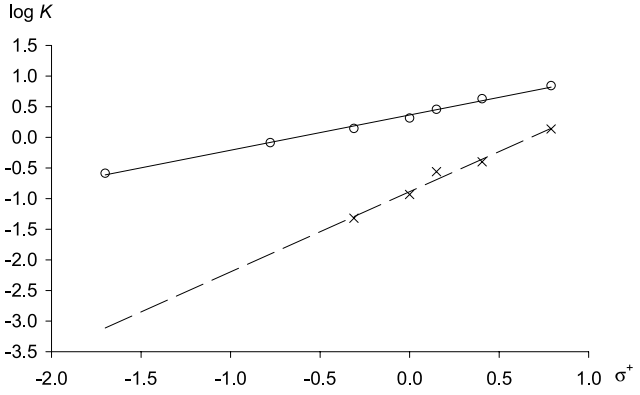


Figure 1. Plots of log K_X for **16B** (○) and **16C** (×) versus Hammett–Brown parameter σ^+.

reactions to electron supply or withdrawal, was found to be considerable higher ($\Delta\rho=0.94$) than that observed for the ring-chain tautomeric equilibria of the analogous 3-aryl-hexahydroimidazo[5,1-*a*]isoquinolines ($\Delta\rho=0.04$).[2,10] The different values of ρ for the *cis*-chain (**16B**⇌**16A**) and *trans*-chain (**16C**⇌**16A**) equilibria can probably be rationalized by the different hyperconjugative (anomeric) effects[10] in **16B** and **16C**, possessing different predominant B/C ring connections (see Section 2.3). The polarization along all the single bonds associated with C-4 changes the extent of the orbital overlaps between the nitrogen lone pairs and the antibonding orbitals. Because of the dihedral angles between the interacting orbitals ($n_N-\sigma^*_{C\text{-}Ar}=-66.9$ and 67.9), the hyperconjugative effect is higher in **16B**, containing *trans*-connected rings B/C, than that in **16C**, with a predominant *cis*[1] conformation ($n_N-\sigma^*_{C\text{-}Ar}=-167.9$ and 37.3).

The substantial increase in the proportions of the open tautomers for the equilibria of **15** and **16**, as compared with the tautomeric ratios for **12–14**, can be rationalized by the increased steric hindrance of the *N*-substituent caused by the 6-methyl group. Earlier data on the ring-chain tautomeric equilibria of 1,3-*N*,*N*-heterocycles indicated that the proportion of the ring-closed form decreases with increasing bulkiness of the *N*-substituent.[2]

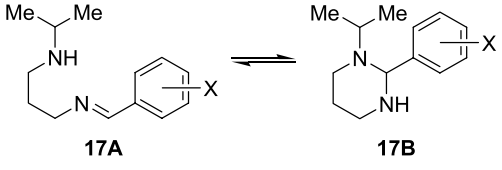
2.3. Conformations

The stereostructure of tetrahydroisoquinoline-fused six-membered saturated heterocycles can be described by a conformational equilibrium of *cis*[1]–*trans*–*cis*[2] type. In the *trans* structure, the B/C hetero rings are *trans*-connected, with H-11b and the N-5 lone pair *trans-diaxial*. In the two other configurations, the hetero rings are *cis*-connected, where in the *cis*[1] conformation C-1 is in the inside, while in the *cis*[2] conformation C-1 is in the outside position (Fig. 2).[19] The conformational equilibria of 1-, 2- and 4-substituted saturated 1,3-oxazino[4,3-*a*]-,[11] 1,2,3-oxathiazino[4,3-*a*]-[20] and 1,3,2-oxazaphosphorino [4,3-*a*]isoquinolines[21] and 1,3,2-diazaphosphorino[6,1-*a*]isoquinolines[15] have been thoroughly studied, but fewer data are available on the analogous hexahydropyrimido[6,1-*a*]isoquinolines. A slight predominance of the conformer with *trans*-connected B/C

Table 2. Linear regression data on compounds **16** and 2-aryl-1-isopropylhexahydropyrimidines (**17**)

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a]	Correlation coefficient
16A⇌**16B**	7	0.36(5)	0.57(6)	0.995
16A⇌**16C**	5	1.30(9)	−0.88(6)	0.982
17A⇌**17B**[b]	6	0.77(3)	−1.04(4)	0.985

[a] Standard deviations are given in parentheses.
[b] Data from Ref. 6.



17A **17B**

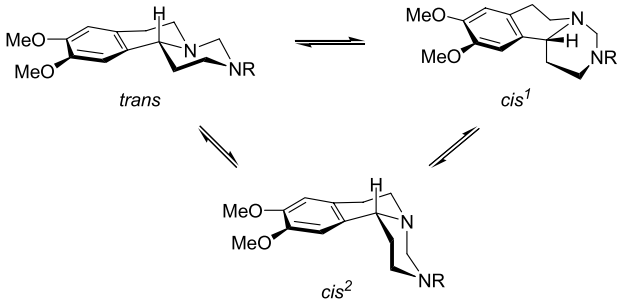


Figure 2. Possible steric structures of 1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines.

rings was found for the conformational equilibrium of the 3-methyl-substituted parent compound in $CDCl_3$.[22]

Conformational analysis of the prepared hexahydropyrimido[6,1-*a*]isoquinolines was performed only for the 4-(*p*-nitrophenyl)-substituted derivatives, which contain the cyclic tautomers in the highest proportions. To determine the mode of connection of the B/C rings ^{1}H NMR spectroscopic methods were used, since the geometries of the B/C ring connections of *cis*[1] or *cis*[2] or *trans* type produce different patterns of cross-peaks derived from the 1,3-diaxial protons in the NOESY spectra. While the stereostructure of the major cyclic forms (**B**) of the prepared model compounds could be determined in each case (**12a**–**14a** and **16a**), the relatively low abundance of the minor cyclic form (**C**) meant that its conformational analysis could be performed only for **14a**.

For **12aB** and **13aB**, the NOESY spectra showed H-11b–H-6_{ax}, H-11b–H-4, and H-4–H-6_{ax} NOE cross-peaks, which are typical for a B/C *trans*-arranged ring junction with an equatorial aromatic substituent. For **14aB**, however, the NOESY spectrum revealed H-1–H-6_{ax}, H-11b–H-2_{ax} and H-11b–H-4 NOE cross-peaks, which unequivocally proved the *cis*[1] connection of the B/C rings. For **14aC**, the NOESY cross-peaks for H-11b with H-2_{ax}, H-6_{ax} and the *ortho* protons of the 4-(*p*-nitrophenyl) substituents pointed to a *trans* B/C ring junction with an axial aromatic substituent. The NOESY cross-peaks for the (6*R**,11b*R**)-6-methyl-substituted C-4 epimeric model compounds (**16aB** and **16aC**) could be characterized by different B/C ring junctions: *trans* for **16aB** (NOESY cross-peaks: H-11b-H-2_{ax}, H-11b-H-4 and H-4-Me-6_{ax}), and *equatorial* and *cis*[1] for **16aC** (NOESY cross-peaks: H-11b–H-2_{ax}, H-4–Me-6_{ax}) with an *axial* 4-(*p*-nitrophenyl) substituent.

The structures of the C-4 epimers of **14a** and **16a** were confirmed by molecular modelling. The conformational protocol comprised a stochastic search, using the Merck Molecular Force Field (MMFF94). Figure 3 depicts the typical minimum-energy molecular structures for **14aB** and **14aC** and for **16aB** and **16aC**. The steric hindrance between H-11 and the 1-methyl group (for **14aB**), or between the 6-methyl and 4-(*p*-nitrophenyl) groups (for **16aC**), makes the predominant conformation with *trans*-arranged B/C rings unfavourable and shifts the conformational equilibrium towards the *cis*[1] structure.

3. Conclusions

Both the ring-chain tautomeric and conformational equilibria of 4-aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines proved to be sensitive to the effects of the methyl substituents at position 1 or 6 and the configurations of the substituted carbons (C-1 or C-6 and C-4) relative to C-11b. For the 1,6-unsubstituted parent compound **12**, NMR spectroscopic investigations revealed the predominance of the ring form **B** (*cis* H-4 and H-11b) with a *trans* B/C anellated conformation in $CDCl_3$ at 300 K. (1*R**,11b*R**)-1-Methyl substitution (**14**) caused changes in the ratios of the C-4 epimeric ring-closed tautomers (**B** and **C**). 6-Methyl substitution resulted in dramatic decreases in the ratios of the ring-closed forms, leading either to a total shift of the equilibrium towards the open forms (**A**) for the 6*S**,11b*R** isomers (**15**) or to the existence of three-component tautomeric equilibria for the 6*R**,11b*R** compounds (**16**), which could be characterized by a

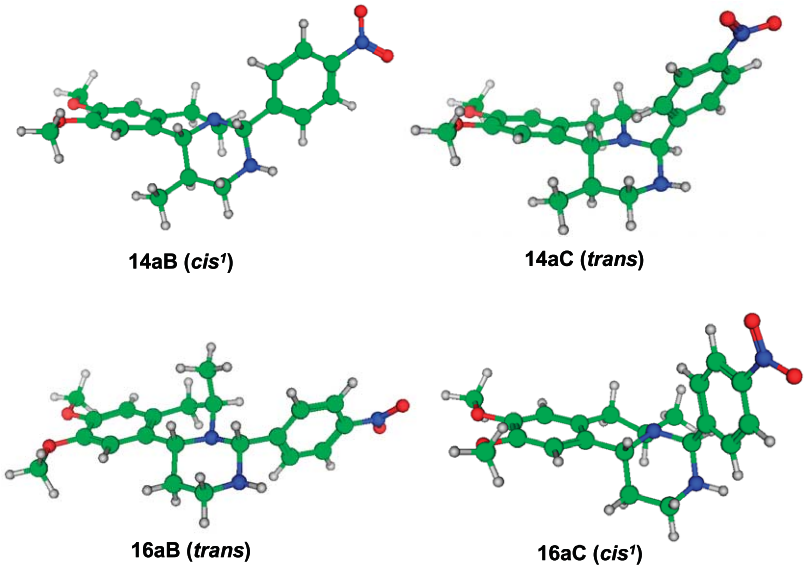


Figure 3. Typical minimum-energy structures for **14aB** and **14aC** and for **16aB** and **16aC**.

Hammett-type equation. For **14a** and **16a**, steric hindrance between the substituents resulted in different predominant conformations (*cis*[1] for **14aB** and **16aC**; *trans* for **14aC** and **16aB**) for the C-4 epimeric ring forms (**B** and **C**).

4. Experimental

4.1. General

The ^{1}H NMR spectra were recorded in $CDCl_3$ or in D_2O solutions at 300 K on a Bruker AVANCE DRX 400 spectrometer at 400.13 MHz (^{1}H NMR) and at 100.03 MHz (^{13}C NMR). Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to DSS (D_2O) as internal standards; multiplicites were recorded as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), ddd (double double doublet), dt (double triplet), t (triplet), q (quartet) and m (multiplet). In the cases of **12–16**, the solutions were left to stand at ambient temperature for 1 day for the equilibria to be established before the ^{1}H NMR spectra were run. IR spectra were run in KBr discs on a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer controlled by GRAMS Analyst for PE 1000 3.01A software. Mass spectra were recorded on a Finnigan MAT 95S instrument, using electron impact ionization. Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected.

Compounds **2a–c**,[14,15] **4**[23] and **10**[17] were prepared according to known procedures.

4.1.1. 3-Benzyloxycarbonylamino-*N*-[1-methyl-2-(3,4-dimethoxyphenyl)ethyl]propanamide (5). To a stirred and ice-salt bath-cooled solution of *N*-benzyloxycarbonyl-β-alanine (11.16 g, 0.05 mol) and triethylamine (5.06 g, 0.05 mol) in anhydrous toluene (150 mL), ethyl chloroformate (5.43 g, 0.05 mol) was added dropwise at a rate low enough to keep the internal temperature below −10 °C. After 5 min, a solution of 1-methyl-2-(3,4-dimethoxyphenyl)ethylamine (**4**) (9.76 g, 0.05 mol) in CH_2Cl_2 (60 mL) was added dropwise, the internal temperature being kept below 0 °C. When the addition was complete, the reaction mixture was heated under reflux for 5 min. The mixture was allowed to cool down to room temperature and $CHCl_3$ (300 mL) was added. The mixture was next washed with saturated $NaHCO_3$ solution (3×75 mL) and water (2×75 mL), and then dried (Na_2SO_4), and the solvent was removed in vacuo to give a crude oily (**2**) product, which crystallized on treatment with Et_2O. The crystals were filtered off, washed with Et_2O and recrystallized from EtOAc.

Compound **5**. A white solid; yield: 16.75 g (84%); mp 107–108 °C; [found: C, 65.76; H, 6.98; N, 7.05. $C_{22}H_{28}N_2O_5$ requires C, 65.98; H, 7.05; N, 6.99%]; ν_{max} 3335, 1690, 1636, 1542, 1262 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 1.10 (3H, d, J=6.6 Hz, CH_3), 2.28–2.41 (2H, m, COCH_2), 2.60 (1H, dd, J=13.6, 7.4 Hz, ArCH_2), 2.76 (1H, dd, J=13.6, 5.9 Hz, ArCH_2), 3.44 (2H, q, J=6.0 Hz, NCH_2), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.15–4.27 (m, 1H, NCH), 5.09 (2H, s, OCH_2), 5.38 (1H, bs, NH), 5.45 (1H, d, J=6.8 Hz, NH), 6.66–6.71 (2H, m, C$_6H_3$), 6.77 (1H, d, J=8.2 Hz, C$_6H_3$), 7.28–7.38 (5H, m, C$_6H_5$); MS m/z 400 [M+1]$^+$.

4.1.2. 1-[2′-(Benzyloxycarbonylamino)ethyl]-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (6). To a stirred solution of the propanamide (**2**, 16.02 g, 0.04 mol) in dry $CHCl_3$ (300 mL), $POCl_3$ (18.40 g, 0.12 mol) was added. The mixture was heated under reflux for 3 h, and then evaporated in vacuo. The oily residue was dissolved in water (250 mL) under gentle warming, and the solution was cooled and extracted with EtOAc (2×75 mL). The aqueous phase was made alkaline with 25% NaOH solution with cooling, and extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a crystalline product, which was filtered off and washed with Et_2O. This crude product was used in the next step without further purification.

Compound **6**. Yield: 11.98 g (78%). An analytical sample of **6** was recrystallized from MeOH to give beige needles, mp 128–130 °C; [found: C, 68.91; H, 6.87; N, 7.48. $C_{22}H_{26}N_2O_4$ requires C, 69.09; H, 6.85; N, 7.32%]; ν_{max} 3192, 2956, 1701, 1517, 1280 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 1.33 (3H, d, J=6.8 Hz, CH_3), 2.38 (1H, dd, J=15.6, 12.3 Hz, 4-CH_2), 2.65 (1H, dd, J=15.6, 5.4 Hz, 4-CH_2), 2.77–2.96 (2H, m, 1′-CH_2), 3.49–3.67 (3H, m, 3-CH, 2′-CH_2), 3.91 (6H, s, 2×OCH_3), 5.09 (2H, s, OCH_2), 5.70 (1H, bs, NH), 6.66 (1H, s, C$_6H_2$), 7.01 (1H, s, C$_6H_2$), 7.27–7.38 (5H, m, C$_6H_5$); MS m/z 382 [M+1]$^+$.

4.1.3. (1*R,3*S**)-1-[2′-(Benzyloxycarbonylamino)ethyl]-3-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7a).** To a stirred and ice-cooled solution of dihydroisoquinoline **6** (11.47 g, 30 mmol) in MeOH (250 mL), $NaBH_4$ (3.40 g, 90 mmol) was added in small portions. The resulting mixture was stirred for 3 h with ice-water bath cooling and for 3 h without, and then evaporated in vacuo. The residue was dissolved in 5% HCl (250 mL), and the solution was made alkaline with 20% NaOH while cooled, and then extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give an oily product, containing diastereomers **7a** and **7b** in a 12:1 ratio. The oil crystallized on treatment with *n*-hexane. The crystalline product, which was filtered off and washed with *n*-hexane, proved to be diastereomerically pure **7a**. The crude crystalline product was used in the next step without further purification.

Compound **7a**. Yield: 9.46 g (82%). An analytical sample of **7a** was recrystallized from Et_2O to give a white solid, mp 69–72 °C; [found: C, 67.80; H, 6.97; N, 7.59. $C_{22}H_{28}N_2O_4$ requires C, 68.73; H, 7.34; N, 7.29%]; ν_{max} 3346, 1687, 1532, 1247, 1094 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 1.19 (3H, d, J=6.0 Hz, CH_3), 1.82–1.92 (1H, m, 1′-CH_2), 2.04–2.14 (1H, m, 1′-CH_2), 2.45 (1H, dd, J=15.5, 10.7 Hz, 4-CH_2), 2.56 (1H, dd, J=15.5, 2.9 Hz, 4-CH_2), 2.85–2.95 (1H, m, 2′-CH_2), 3.26–3.35 (2H, m, 3-CH, 2′-CH_2), 3.80 (6H, s, 2×OCH_3), 4.13–4.19 (1H, m, 1-CH), 5.05 (2H, s, OCH_2), 6.13 (1H, bs, NH), 6.52 (1H, s, C$_6H_2$), 6.61 (1H, s, C$_6H_2$), 7.23–7.35 (5H, m, C$_6H_5$); MS m/z 384 [M+1]$^+$.

4.1.4. (1*R,3*S**)-1-(2′-Aminoethyl)-3-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrobromide**

(8·2HBr). A mixture of compound **7a** (7.69 g, 20 mmol) and 33% HBr in AcOH (25 mL) was heated gently in a flask equipped with a $CaCl_2$ tube, with occasional shaking, until all of the substance had dissolved. The bubbling solution was left to stand at ambient temperature for 30 min, and Et_2O (25 mL) was then added. The yellow crystals of the dihydrobromide of **8** which formed were filtered off, washed with a mixture of MeOH and Et_2O, dried and recrystallized from 90% MeOH–Et_2O.

Compound **8**·2HBr. White crystals; yield: 6.10 g (74%); mp 250–252 °C; [found: C, 40.97; H, 5.76, N, 6.89. $C_{14}H_{24}Br_2N_2O_2$ requires C, 40.80, H, 5.87; N, 6.80%]; ν_{max} 3410, 1613, 1522, 1256, 1009 cm^{-1}; ^1H NMR δ (D_2O) 1.57 (3H, d, $J=6.6$ Hz, CH_3), 2.48–2.72 (2H, m, 1′-CH_2), 2.96–3.10 (2H, m, 4-CH_2), 3.20–3.37 (2H, m, 2′-CH_2), 3.57–3.68 (1H, m, 3-C*H*), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.81–4.85 (1H, m, 1-C*H*), 6.94 (1H, s, C_6H_2), 6.96 (1H, s, C_6H_2); MS *m/z* 250 $[M+1]^+$.

4.1.5. (1*R,3*R**)-1-(2′-Aminoethyl)-3-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride (11·2HCl).** To a stirred and cooled suspension of $LiAlH_4$ (3.42 g, 90 mmol) in dry THF (120 mL), (1*R**,3*R**)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetamide (**10**)[17] (7.93 g, 30 mmol) was added in small portions. The mixture was stirred and refluxed for 4 h and then cooled, and the excess of $LiAlH_4$ was decomposed by the addition of a mixture of water (6.8 mL) and THF (30 mL). The inorganic salts were filtered off and washed with EtOAc (3×50 mL). The combined organic filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give an oily product, which was converted to the crystalline dihydrochloride of **11** by treatment of its solution in MeOH with an excess of 22% ethanolic HCl and Et_2O. The crystalline dihydrochloride of **11** was filtered off, dried and recrystallized from MeOH–H_2O–Et_2O.

Compound **11**·2HCl. A white solid, yield: 4.37 g (45%); mp 240–245 °C; [found: C, 51.97; H, 7.56, N, 8.74. $C_{14}H_{24}Cl_2N_2O_2$ requires C, 52.02, H, 7.48; N, 8.67%]; ν_{max} 3157, 1618, 1521, 1259, 1117 cm^{-1}; ^1H NMR δ (D_2O) 1.54 (3H, d, $J=6.3$ Hz, CH_3), 2.43–2.49 (2H, m, 1′-CH_2), 2.88 (1H, dd, $J=10.0$, 17.5 Hz, 4-CH_2), 3.24–3.35 (3H, m, 2′-CH_2, 4-CH_2), 3.90 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.94–3.98 (1H, m, 3-C*H*), 4.75 (1H, t, $J=6.5$ Hz, 1-C*H*), 6.90 (1H, s, C_6H_2), 6.97 (1H, s, C_6H_2); MS *m/z* 250 $[M+1]^+$.

Pure diamine bases **8** and **11** were obtained from the above dihydrohalides by alkaline treatment (20% NaOH), extraction (CH_2Cl_2) and evaporation under reduced pressure. The free bases were dried in a vacuum desiccator for 24 h before further transformations.

4.2. General procedure for the preparation of 4-Aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (12–16)

To a solution of the corresponding tetrahydroisoquinoline diamine (**2a–c**, **8** and **11**) (3 mmol) in absolute MeOH (25 mL), an equivalent amount of aromatic aldehyde was added (for liquid aldehydes, a freshly distilled sample was used), and the mixture was allowed to stand at ambient temperature for 1 h. The solvent was then evaporated off and the oily product crystallized on treatment with Et_2O or *n*-hexane. The crystalline products (**12a**,**b**, **13a**,**b**, **14a**,**b**, **15a**,**b** and **16a**,**c**,**d**,**e**,**g**) were filtered off and recrystallized. In the cases of **16b** and **16f**, the evaporation was repeated after the addition of toluene (10 mL), and the oily products (obtained in nearly quantitative yields) were dried in a vacuum desiccator for 24 h. The NMR spectrum proved that the purity of these compounds was >95%.

In consequence of the small relative concentrations, only the characteristic N–C*H*Ar–N and N=C*H*Ar protons are listed for the detectable minor tautomeric forms of **12a**,**b**, **13a**,**b**, **14b** and **15a**,**b**; a full NMR characterization is given for **12aB**, **13aB**, **14aB**, **14aC** and **15aA**. With regard to the similarities in the ^1H NMR data for **16a–g**, the full spectra of the major tautomers are described only for two representatives of this set of compounds (**16aB** and **16gA**). The protons of the open form (**A**) are numbered according to the corresponding protons of the 1,3,4,6,7,11b-hexahydro-2*H*-[6,1-*a*]isoquinoline ring forms (**B** and **C**).

4.2.1. Compound 12a. Beige crystals; yield: 0.83 g (75%); mp: 150–151 °C (*i*Pr_2O–EtOAc); [found: C, 65.25; H, 6.13; N, 11.48. $C_{20}H_{23}N_3O_4$ requires C, 65.03; H, 6.28; N, 11.37%]; ν_{max} 2910, 1520, 1224, 1099, 745 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.77 (1H, dd, $J=4.3$, 12.6 Hz, H-1), 2.18–2.30 (2H, m, H-1, H-6), 2.54 (1H, dt, $J=3.8$, 16.1 Hz, H-7), 2.66–2.74 (1H, m, H-6), 2.88 (1H, dd, $J=2.8$, 16.1 Hz, H-7), 3.37 (1H, ddd, $J=1.3$, 4.0, 13.4 Hz, H-2), 3.70 (1H, d, $J=$ 10.6 Hz, H-11b), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.40 (1H, s, H-4), 6.58 (1H, s, H-8), 6.71 (1H, s, H-11), 7.68–7.74 (2H, m, Ar), 8.22–8.26 (2H, m, Ar), ^{13}C NMR δ ($CDCl_3$) 29.5, 32.4, 46.4, 46.6, 56.6, 56.8, 62.8, 81.1, 108.8, 112.2, 124.7, 127.4, 128.9, 130.6, 148.4 (3×), 149.9 (tautomeric form **B**); 4.92 (1H, s, 4-H) (tautomeric form **C**); MS *m/z* 369 $[M+1]^+$.

4.2.2. Compound 12b. Beige crystals; yield: 0.62 g (56%); mp: 100–103 °C (*i*Pr_2O); [found: C, 72.21; H, 8.02; N, 11.31. $C_{22}H_{29}N_3O_2$ requires C, 71.90; H, 7.95; N, 11.43%]; ν_{max} 2938, 1610, 1517, 1253, 820 cm^{-1}; ^1H NMR δ ($CDCl_3$) 4.15 (N–C*H*Ar–N) (tautomeric form **B**); MS *m/z* 367 $[M+1]^+$.

4.2.3. Compound 13a. Orange-yellow crystals; yield: 0.49 g (43%); mp: 86–90 °C (*n*-hexane); [found: C, 66.02; H, 6.45; N, 10.88. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; ν_{max} 2964, 1519, 1343, 1133, 861 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.02 (3H, d, $J=6.8$ Hz, CH_3), 2.12 (1H, ddd, $J=3.3$, 11.8 Hz, H-6), 2.31–2.43 (2H, m, H-1, H-7), 2.54–2.61 (1H, m, H-6), 2.83–2.93 (1H, m, H-7), 3.10 (1H, dd, $J=1.3$, 13.6 Hz, H-2), 3.28 (1H, dd, $J=3.3$, 13.6 Hz, H-2), 3.72 (1H, s, H-11b), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.22 (1H, s, H-4), 6.56 (1H, s, H-8), 6.69 (1H, s, H-11), 7.68–7.74 (2H, m, Ar), 8.22–8.28 (2H, m, Ar), ^{13}C NMR δ ($CDCl_3$) 12.6, 29.5, 32.7, 48.3, 52.5, 56.5, 56.8, 66.4, 82.1, 108.4, 112.0, 124.8, 128.7, 129.3, 148.0 (2×), 148.5, 150.6 (tautomeric form **B**); 4.87 (H-4) (tautomeric form **C**); MS *m/z* 383 $[M+1]^+$.

4.2.4. Compound 13b. Pale-yellow crystals; yield: 0.80 g (70%); mp: 129–131 °C (*n*-hexane); [found: C, 72.26; H,

8.30; N, 10.89. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; ν_{max} 2904, 1611, 1249, 1131, 820 cm^{-1}; ^1H NMR δ ($CDCl_3$) 4.00 (N–C*H*Ar–N) (tautomeric form **B**); MS *m/z* 381 $[M+1]^+$.

4.2.5. Compound 14a. Yellow crystals; yield: 0.75 g (65%); mp: 147–149 °C (EtOH); [found: C, 65.50; H, 6.38; N, 10.73. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; ν_{max} 2910, 1513, 1350, 1123, 834 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.99 (3H, d, $J=6.3$ Hz, CH_3), 1.99–2.13 (2H, m, H-1), 2.37 (1H, dd, $J=7.3$, 11.3 Hz, H-2), 2.64 (1H, dd, $J=4.0$, 16.1 Hz, H-7), 2.75–2.98 (2H, m, H-2, H-7), 3.06 (1H, ddd, $J=4.3$, 11.3 Hz, H-6), 3.36 (1H, dd, $J=4.3$, 13.1 Hz, H-2), 3.77–3.81 (1H, m, H-11b), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.12 (1H, s, H-4), 6.62 (2H, s, H-8, H-11), 7.72–7.78 (2H, m, Ar), 8.17–8.24 (2H, m, Ar), ^{13}C NMR δ ($CDCl_3$) 17.4, 29.2, 29.8, 36.7, 54.9, 56.2 (2×), 67.2, 78.0, 112.1, 112.5, 123.8, 127.1, 128.4, 129.2, 146.5, 148.2 (3×) (tautomeric form **B**); ^1H NMR δ ($CDCl_3$) 0.85 (3H, d, $J=6.6$ Hz, CH_3), 1.99–2.13 (1H, m, H-1), 2.50 (1H, dd, $J=10.3$, 13.9 Hz, H-6), 2.75–2.98 (3H, m, H-2, H-6, H-7), 3.08–3.16 (1H, m, H-7), 3.49 (1H, d, $J=9.6$ Hz, H-11b), 3.60 (1H, ddd, $J=4.8$, 10.8 Hz, H-2), 3.79 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.89 (1H, s, H-4), 6.46 (2H, s, H-8), 6.67 (2H, s, H-11), 7.92–7.98 (2H, m, Ar), 8.17–8.24 (2H, m, Ar), ^{13}C NMR δ ($CDCl_3$) 17.5, 28.9, 30.3, 45.7, 48.6, 56.4, 56.5, 59.7, 76.0, 112.1, 112.2, 124.0, 127.0, 128.7, 129.3, 147.8, 148.2, 148.4, 148.9 (tautomeric form **C**); MS *m/z* 383 $[M+1]^+$.

4.2.6. Compound 14b. White crystals; yield: 0.49 g (43%); mp: 123–125 °C (*i*Pr_2O); [found: C, 72.08; H, 8.03; N, 10.81. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; ν_{max} 2929, 1519, 1225, 1125, 812 cm^{-1}; ^1H NMR δ ($CDCl_3$) 4.99 (N–C*H*Ar–N) (tautomeric form **B**); 4.70 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 381 $[M+1]^+$.

4.2.7. Compound 15a. A pale-beige solid; yield: 0.72 g (63%); mp: 108–109 °C (*n*-hexane–Et_2O); [found: C, 65.59; H, 6.41; N, 11.10. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; ν_{max} 2860, 1517, 1350, 1219, 855 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.24 (3H, d, $J=6.3$ Hz, CH_3), 2.03–2.14 (1H, m, H-1), 2.36–2.51 (2H, m, H-1, H-7), 2.62 (1H, dd, $J=3.3$, 15.9 Hz, H-7), 2.94–3.05 (1H, m, H-6), 3.75–3.92 (8H, m, 2×H-2, 2×OCH_3), 4.27 (1H, d, $J=7.3$ Hz, H-11b), 6.55 (1H, s, H-8), 6.71 (1H, s, H-11), 7.84–7.90 (2H, m, Ar), 8.24–8.30 (2H, m, Ar), 8.35 (1H, s, N=C*H*Ar), ^{13}C NMR δ ($CDCl_3$) 23.1, 37.7, 38.4, 49.3, 55.7, 56.2, 56.5, 58.9, 108.9, 112.0, 124.3, 128.5, 129.1, 130.3, 142.0, 147.7, 159.4 (tautomeric form **A**); MS *m/z* 383 $[M+1]^+$.

4.2.8. Compound 15b. A pale-beige solid; yield: 0.66 g (58%); mp: 69–72 °C (*n*-hexane-Et_2O); [found: C, 72.60; H, 8.27; N, 11.16. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; ν_{max} 3581, 2904, 1610, 1219, 817 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.12 (N=C*H*Ar) (tautomeric form **A**); MS *m/z* 381 $[M+1]^+$.

4.2.9. Compound 16a. Pale-yellow crystals; yield: 0.91 g (79%); mp: 135–139 °C (*n*-hexane–EtOAc); [found: C, 65.96; H, 6.40; N, 11.09. $C_{21}H_{25}N_3O_4$ requires C, 65.78; H, 6.57; N, 10.96%]; ν_{max} 2927, 1512, 1343, 1108, 999 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.46, ^{13}C NMR δ ($CDCl_3$) 159.3 (tautomeric form **A**); ^1H NMR δ ($CDCl_3$) 0.86 (3H, d, $J=6.6$ Hz, CH_3), 1.70 (1H, ddd, $J=4.5$, 12.8 Hz, H-1), 2.22 (1H, d, $J=15.6$ Hz, H-7), 2.30–2.37 (1H, m, H-1), 2.89–2.93 (1H, m, H-6), 3.02 (1H, ddd, $J=2.8$, 13.4 Hz, H-2), 3.10 (1H, dd, $J=5.5$, 15.6 Hz, H-7), 3.32 (1H, ddd, $J=1.5$, 4.0, 13.4 Hz, H-2), 3.84–3.87 (7H, m, H-11b, 2×OCH_3), 4.50 (1H, s, H-4), 6.55 (1H, s, H-8), 6.71 (1H, s, H-11), 7.65–7.71 (2H, m, Ar), 8.22–8.28 (2H, m, Ar) ^{13}C NMR δ ($CDCl_3$) 10.0, 34.2, 36.1, 45.3, 48.0, 55.5, 56.2, 56.4, 78.6, 108.2, 112.5, 124.6 (2×), 125.7, 129.0, 147.6, 149.6 (3×) (tautomeric form **B**); ^1H NMR δ ($CDCl_3$) 5.24, ^{13}C NMR δ ($CDCl_3$) 69.6 (tautomeric form **C**); MS *m/z* 383 $[M+1]^+$.

4.2.10. Compound 16b. An orange foam; [found: C, 60.72; H, 5.89; N, 6.78. $C_{21}H_{25}BrN_2O_2$ requires C, 60.44; H, 6.04; N, 6.71%]; ν_{max} 2829, 1508, 1250, 1018, 779 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.21 (N=C*H*Ar) (tautomeric form **A**); 4.27 (N–C*H*Ar–N) (tautomeric form **B**); 4.99 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 416 $[M+1]^+$.

4.2.11. Compound 16c. A pale-yellow solid; yield: 0.90 g (72%); mp: 113–116 °C (*n*-hexane–EtOAc); [found: C, 60.17; H, 5.89; N, 6.92. $C_{21}H_{25}BrN_2O_2$ requires C, 60.44; H, 6.04; N, 6.71%]; ν_{max} 2945, 1513, 1248, 1002, 737 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.33 (N=C*H*Ar) (tautomeric form **A**); 4.37 (N-C*H*Ar-N) (tautomeric form **B**); 5.07 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 416 $[M+1]^+$.

4.2.12. Compound 16d. Yellow crystals; yield: 0.77 g (76%); mp: 88–91 °C (*n*-hexane–EtOAc); [found: C, 74.77; H, 7.52; N, 8.40. $C_{21}H_{26}N_2O_2$ requires C, 74.52; H, 7.74; N, 8.28%]; ν_{max} 2921, 1513, 1251, 1108, 794 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.30 (N=C*H*Ar) (tautomeric form **A**); 4.31 (N–C*H*Ar–N) (tautomeric form **B**); 4.97 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 338 $[M+1]^+$.

4.2.13. Compound 16e. Yellow crystals; yield: 0.66 g (62%); mp: 73–75 °C (*n*-hexane); [found: C, 75.12; H, 8.20; N, 7.81. $C_{22}H_{28}N_2O_2$ requires C, 74.97; H, 8.01; N, 7.95%]; ν_{max} 2959, 1514, 1251, 1109, 780 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.35 (N=C*H*Ar) (tautomeric form **A**); 4.37 (N–C*H*Ar–N) (tautomeric form **B**); 5.02 (N–C*H*Ar–N) (tautomeric form **C**); MS *m/z* 352 $[M+1]^+$.

4.2.14. Compound 16f. A yellow oil; [found: C, 72.02; H, 7.51; N, 7.69. $C_{22}H_{28}N_2O_3$ requires C, 71.71; H, 7.66; N, 7.60%]; ν_{max} 2936, 1606, 1248, 1032, 833 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.21 (N=C*H*Ar) (tautomeric form **A**); 4.25 (N–C*H*Ar–N) (tautomeric form **B**); MS *m/z* 368 $[M+1]^+$.

4.2.15. Compound 16g. Yellow crystals; yield: 0.97 g (85%); mp: 111–114 °C (*n*-hexane–EtOAc); [found: C, 72.68; H, 8.07; N, 10.86. $C_{23}H_{31}N_3O_2$ requires C, 72.41; H, 8.19; N, 11.01%]; ν_{max} 2835, 1607, 1517, 1224, 1092 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.18 (3H, d, $J=6.3$ Hz, CH_3), 1.94–2.05 (1H, m, H-1), 2.08–2.08 (1H, m, H-1), 2.39 (1H, dd, $J=10.3$, 16.2 Hz, H-7), 2.66 (1H, dd, $J=3.8$, 16.2 Hz, H-7), 3.01 (6H, s, N(CH_3)$_2$), 3.15–3.27 (1H, m, H-6), 3.69–3.79 (1H, m, H-2), 3.81–3.83 (7H, m, H-2, 2×OCH_3), 4.11 (1H, dd, $J=2.8$, 10.3 Hz, H-11b), 6.53 (1H, s, H-8), 6.60 (1H, s, H-11), 6.67–6.72 (2H, m, Ar), 7.69–7.64 (2H, m, Ar), 8.23 (N=C*H*Ar), ^{13}C NMR δ ($CDCl_3$) 23.0, 37.6, 38.4, 40.6, 42.9, 55.0, 56.2, 56.4, 60.1, 110.2, 111.9, 112.0, 112.5,

124.9, 127.2, 129.8, 131.9, 147.5, 147.6, 152.4, 161.6 (tautomeric form **A**); 4.29 (N–C*H*Ar–N) (tautomeric form **B**); MS *m*/*z* 381 $[M+1]^+$.

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