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Competition between cyclisation and bisimine formation in the reaction of 1,3-diaminopropanes with aromatic aldehydes

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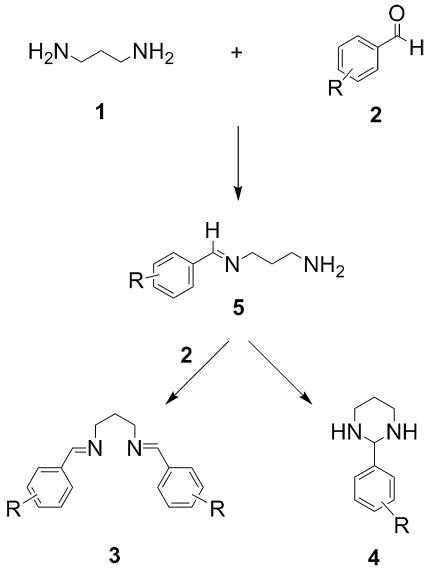
ABSTRACT

Condensation of 1,3-diamines with aldehydes or ketones gives rise to two major products, the hexahydropyrimidine and the bisimine. Experimental studies of the reaction between a range of aromatic aldehydes and 1,3-diaminopropane or 1,3-diamino-2-propanol establish that the hexahydropyrimidine is favoured by the less nucleophilic amine and by the presence of electron withdrawing groups on the aryl ring of the aldehyde. Calculations indicate that the electronic nature of this aryl ring substituent influences both the relative thermodynamic stability of the final products and the reactivity of the aldehyde as an electrophile.

1. Introduction

Condensation of 1,3-diamines with aldehydes and ketones is a well documented reaction. In particular, syntheses of multidentate ligands for metal complexes frequently employ the reaction of 1,3-diaminopropane (**1**) with benzaldehydes (**2**).[1–4] However, two potential products may result from this reaction (Scheme 1), the bisimine (**3**) and the hexahydropyrimidine (**4**). Initially the monoimine (**5**) or analogous monoiminium ion (**5**H$^+$) forms and this intermediate can subsequently react with another molecule of aldehyde to furnish the bisimine **3** as the final product. Alternatively, the free amino group of the monoimine may attack the imine carbon in a 6-*endo*-*trig* ring closure[5] to yield the hexahydropyrimidine **4**.

Historically, aromatic carbonyl compounds have been used to make bisimines whilst aliphatic carbonyl compounds have been employed in the synthesis of hexahydropyrimidines.[6,7] Interest in 2-arylhexahydropyrimidines often only develops after their initial appearance as unwanted side-products in the course of imine synthesis,[8–10] and most modern studies of hexahydropyrimidines are devoted to characterising the ring-chain tautomerism in these



Scheme 1. Possible products from the condensation reaction of 1,3-diaminopropane (**1**) with benzaldehydes (**2**).

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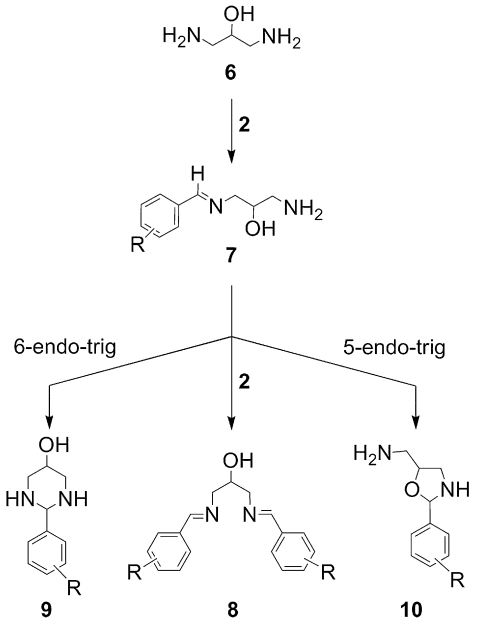
and related 1,3-diheterocyclic systems.[11–17] Factors influencing the product distribution from the reaction of 1,3-diaminopropane (**1**) with benzaldehydes have been elucidated to some extent. It has been shown that an equimolar reaction of the diamine **1** with various aryl aldehydes gives a mixture of hexahydropyrimidine (**4**) and monoimine (**5**) and that the ratio of products formed depends upon both electronic and steric factors.[9,11]

We were interested in probing the influence of intramolecular hydrogen bonding in determining the conformations of a range of 5-hydroxyhexahydropyrimidines.[18] Our early synthetic efforts towards 2-arylhexahydropyrimidines frequently gave complex and inseparable product mixtures. We therefore turned our attention to investigating the reactions of 1,3-diamino-2-propanol (**6**, Scheme 2) and 1,3-diaminopropane (**1**) with a series of benzaldehydes (**2a**–**j**, Table 1) to establish the type of products formed and examine the factors that influence the product distribution in these reactions.



Scheme 2. Possible products from the condensation reaction of 1,3-diamino-2-propanol (**6**) with benzaldehydes (**2**).

Table 1
Composition[a] of the crude products derived from the equimolar reactions of the diamines **1** and **6** with the aromatic aldehydes **2a**–**j**

Aldehyde	Reaction with **1**		Reaction with **6**[b]	
	%**4**	%**3**	%**9**	%**8**
2a *p*-Nitrobenzaldehyde	70[c]	30	80	7
2b *p*-Cyanobenzaldehyde	81[c]	19	75	8
2c *p*-Bromobenzaldehyde	68[c]	32	69	10
2d *p*-Chlorobenzaldehyde	0	100	57	21
2e Benzaldehyde	52	48	70	10
2f *p*-Methylbenzaldehyde	11	48	60	20
2g *p*-Methoxybenzaldehyde	0	100	38	32
2h *p*-Hydroxybenzaldehyde	57	43	46	8[d]
2i *o*-Hydroxybenzaldehyde	0	100	0	65
2j 2-Pyridine carboxaldehyde	82[c]	18	100	0

[a] Determined from the relative integral values of singlets from the protons attached to C2 of the hexahydropyrimidines and the benzylidene protons of the imines in the ^{1}H NMR spectrum acquired in $CDCl_3$ (300 MHz, 298 K).

[b] The percentage of monoimine present in these mixtures makes sum of the stated values up to 100%.

[c] The ^{1}H NMR spectrum of these compounds in $CDCl_3$ (300 MHz, 298 K) showed a trace of monoimine present.

[d] The ^{1}H NMR spectrum of this mixture was obtained in DMSO-d_6 (300 MHz, 298 K) and showed that the crude reaction mixture also contained unreacted aldehyde.

2. Results and discussion

2.1. Experimental product ratios

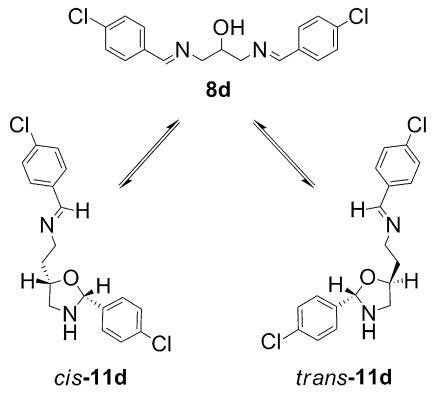
The diamines **1** and **6** were reacted with a series of variously substituted benzaldehydes (**2a**–**j**) in 1:1 and 1:2 (amine/aldehyde) molar ratios (Schemes 1 and 2) and the distribution of products from their condensation reactions was determined. Heating the diamines and aldehydes in a methanolic solution at reflux provided crude products from the condensation reaction. Attempts to isolate products from the reaction mixtures were unsuccessful, and consequently preliminary characterisation of the bisimines and hexahydropyrimidines in the crude reaction mixtures was accomplished through comparison with the ^{1}H NMR spectra of the bisimines derived from *o*-hydroxybenzaldehyde (**3i** and **8i**),[19,20] as well as hexahydropyrimidine[6,18] and 5-hydroxyhexahydropyrimidine.[18,21] Characterisation of the products derived from 1,3-diamino-2-propanol (**6**, Scheme 2) was also facilitated by comparison of their ^{1}H NMR spectra with those obtained for the crude products from the reaction of **6** and **2j**, where the sole product obtained was a mixture of *cis*- and *trans*-5-hydroxy-2-(2′-pyridinyl)hexahydropyrimidine (**9j**). Product ratios in the crude reaction mixtures were determined from the ^{1}H NMR spectra in $CDCl_3$ via integration values of the well-separated singlets arising from the proton/s on C2 of the hexahydropyrimidines (4–5 ppm) and the azomethine proton (8.0–8.5 ppm, see Supplementary data). The ^{1}H NMR spectra of the crude reaction products contained no signals from unreacted diamine. In all cases, examination of the EI mass spectra of the crude reaction products showed no peaks with greater *m*/*z* than the expected parent ion for the bisimine.

Reaction of the diamine **1** with two molar equivalents of various aldehydes (**2a**–**j**) almost exclusively yielded the bisimines **3a**–**j**. The ^{1}H and ^{13}C NMR spectra of bisimines derived from **2a**–**i** indicated that the compounds were pure and data obtained for known compounds compared well to available literature values. Condensation of **1** with the pyridyl derivative **2j** in a 1:2 (amine/aldehyde) molar ratio yielded a crude reaction mixture containing a significant proportion (34%) of hexahydropyrimidine **4j** as well as the aldehyde **2j** and bisimine **3j**. The production of a substantial amount of hexahydropyrimidine in this reaction is most likely a consequence of the electron withdrawing nature of the pyridyl ring (see below).

Condensation of the diaminoalcohol **6** with two molar equivalents of aldehydes **2a**–**j** also gave the bisimine as the major product. However, in the ^{1}H NMR spectra of the crude reaction mixtures from the reaction of **6** with **2a**, **2b** and **2e**, traces of the *cis* and *trans* hydroxyhexahydropyrimidines (**9**) and the associated aldehydes were also observed. None of the ^{1}H NMR spectra of the crude reaction mixtures from **6** contained signals attributable to the aminomethyloxazolidines (**10a**–**j**). The amino group is more nucleophilic than the hydroxyl group and a 6-*endo*-*trig* ring closure is more favourable than the 5-*endo*-*trig* route therefore this result was predictable. Again, the aldehyde **2j** gave an anomalous result and the ^{1}H NMR spectrum of this crude reaction product showed a largely uncharacterisable mixture of compounds, including the bisimine **8j** and the diastereomeric pair of 5-hydroxyhexahydropyrimidines, *cis*- and *trans*-**9j**. The ^{1}H NMR spectra of the crude reaction products in $CDCl_3$ also contained a number of minor signals unrelated to the starting materials (**6**, **2**), bisimines (**8**) or 5-hydroxyhexahydropyrimidines (**9**). These extraneous signals, which consistently included two prominent singlets between 5 and 6 ppm, occurred at varying intensities in crude reaction mixtures for **8a**–**8g** but were absent from those derived from the hydroxy benzaldehydes **2h** and **2i**.

Additional NMR investigations of *N*,*N*′-bis(*p*-nitrobenzylidene)-1,3-diamino-2-propanol (**8a**) and *N*,*N*′-bis(*p*-chlorobenzylidene)-1,3-

diamino-2-propanol (**8d**) revealed these that extra signals are not present in the ^{1}H NMR spectrum obtained in deuterated DMSO (400 MHz, 303 K); the only signals observed in this solvent were those expected for the bisimine (see Supplementary data). This result suggests the extra signals observed in $CDCl_3$ (400 MHz, 303 K) originate from products formed as the β-hydroxybisimine **8** undergoes ring-chain tautomerism. Formation of the oxazolidine is a disfavoured 5-*endo*-*trig* process according to Baldwin's rules,[5] however breakdown of these rules in the β-hydroxyimine-oxazolidine system has been reported.[22] Intramolecular attack by the hydroxyl group at either imine moiety would result in formation of a mixture the *cis*- and *trans*-5-[*N*-(*p*-chlorobenzylidene)aminomethyl]-2-(*p*-chlorophenyl)oxazolidine (Scheme 3, **11d**). Inhibition of the tautomeric interconversion in deuterated DMSO, as seen for compounds **8a** and **8d**, occurs through hydrogen bonding between the solvent and the hydroxyl group, an observation previously noted in related systems.[23] The downfield shift of the phenolic proton (13.05 ppm), in $CDCl_3$ indicates that the imine groups of the *o*-hydroxy bisimine **8i** are engaged in resonance-assisted intramolecular hydrogen bonds, typical of these compounds.[24] Competition from this intramolecular hydrogen bonding most likely hampers attack at the imine thereby preventing ring-chain tautomerism in this molecule.



Scheme 3. Possible ring-chain tautomeric equilibrium of compound **8d**.

^{1}H NMR spectra of **8d** obtained immediately following dissolution of the sample in $CDCl_3$ showed that the formation of the oxazolidines **11d** was quite rapid (<5 min). No measurable change was observed in the ratio of **8d**, *cis*-**11d** and *trans*-**11d** after 24 h, although a set of minor signals unrelated to these products became apparent in the ^{1}H NMR spectrum acquired in $CDCl_3$, these were also not observed in the spectrum obtained in DMSO-d_6. A number of key features and relationships in the ^{1}H and ^{13}C NMR spectra of **8d** provide evidence for the presence of the dia stereomeric pair of oxazolidines *cis*-**11d** and *trans*-**11d** as summarised in Table S1 (see Supplementary data). Significantly, the singlets observed at 5.38 and 5.55 ppm arise from protons bonded to carbons with shifts of 93.0 and 92.1 ppm, respectively, typical shifts observed for carbons in an O–C–N fragment.[25] Unfortunately, the presence of numerous overlapping signals, particularly in the aromatic region of the spectra, precluded definitive identification of the minor products.

Table 1 shows the compositions of the crude products from the equimolar reactions of selected benzaldehydes (**2a**–**j**) with 1,3-diaminopropan-2-ol (**6**) and 1,3-diaminopropane (**1**). Without exception, the experimental results showed that the reaction of benzaldehydes with electron donating substituents favoured bisimine products and benzaldehydes with electron withdrawing substituents favoured the formation of the hexahydropyrimidines. For example, the crude mixtures from the equimolar reactions of diaminopropane **1** with *p*-chloro-, *p*-methoxy- and *o*-hydroxy benzaldehyde (**2d**, **2g** and **2i**) gave the bisimine as the sole product, whilst the reaction with *p*-nitrobenzaldehyde (**2a**) and *p*-cyanobenzaldehyde (**2b**) formed the hexahydropyrimidine in yields of 70 and 81%, respectively. The same trend was observed in the reactions with the diaminoalcohol **6**, although, often substantially more heterocycle was produced in reactions with **6**. Both *cis* and *trans* hydroxyhexahydropyrimidine **9** were present in the crude product mixtures isolated from the reaction of **6** with **2a**–**h** and **2j**. In all cases, the *cis* isomer was the major hydroxyhexahydropyrimidine observed and constituted 60–80% of the hexahydropyrimidine yield, however no correlation was observed between *cis*/*trans* ratios and the electronic nature of the aryl substituent. The ^{1}H NMR spectra of the crude products from the reactions of the diaminoalcohol **6** with all benzaldehydes except **2j** also showed evidence of the monoimine, particularly when an electron donating group was present in the benzaldehyde. An anomalous result obtained in the reaction of *p*-hydroxybenzaldehyde **2h** with **6** is possibly a result of a competing acid–base reaction with the phenol. The ^{1}H NMR spectrum of this crude reaction mixture showed that a large amount of aldehyde was still present. As expected from results obtained in the corresponding reactions of **6** with 2 mol of aldehyde, none of the ^{1}H NMR spectra of the crude reaction mixtures from the equimolar reactions contained signals attributable to the aminomethyloxazolidines (**10a**–**j**).

2.2. Heats of formation

Whilst the results described above displayed obvious trends, it was apparent from the various anomalies that there were a number of factors influencing product distribution. Molecular modelling techniques permitted further examination of these factors. The thermodynamic stabilities of the observed products were explored using the calculated heats of formation (ΔH_f) of the possible products at the semi-empirical (AM1) level (Tables 2 and 3). Table 2 presents calculated results for products formed in the reaction of 1,3-diaminopropane (**1**) with the benzaldehydes **2a**–**j**. Some general trends are apparent in these results. In most cases, the bisimine (**3**) is higher in energy than the corresponding monoimine (**5**) or hexahydropyrimidine (**4**), whereas **4** and **5** are of similar energies. The ΔH_f of a compound depends to some extent upon the molecular weight, which possibly contributes to the higher ΔH_f of the bisimines. However, variations in molecular weights do not explain why the differences in the heat of formation between the bisimines and the monoimines ($\Delta\Delta H_f$ **3**–**5**) show such a wide variation.

Table 2
The calculated heats of formation (ΔH_f)[a] for the monoimines **5a**–**j**, bisimines **3a**–**j** and hexahydropyrimidines **4a**–**j** and the calculated differences in heats of formation ($\Delta\Delta H_f$)[b] between the intermediate **5a**–**j** and the potential products **3a**–**j** and **4a**–**j**

Derivative	ΔH_f (kJ mol^{-1})			$\Delta\Delta H_f$[b] (kJ mol^{-1})	
	5[c]	**4**	**3**[c]	**4**–**5**	**3**–**5**
a	154	155	384	1	230
b	274	250	613	−25	338
c	158	162	392	4	234
d	107	89	292	−19	185
e	142	118	342	−23	200
f	105	110	287	6	182
g	−23	−17	32	6	55
h	−45	−67	−27	−22	19
i	−44	−69	−25	−25	19
j	194	165	444	−29	250

[a] Modelled at the semi-empirical level (AM1).
[b] $\Delta\Delta H_f$=ΔH_f (product)−ΔH_f (monoimine).
[c] All imine bonds were modelled in the *anti* configuration.

Table 3
The calculated heats of formation (ΔH_f)[a] for the monoimines **7a–j**, bisimines **8a–j**, *cis* and *trans*-5-hydroxyhexahydropyrimidines **9a–j**, the *cis*- and *trans*-5-aminomethyloxazolidines **10a–j** and the calculated differences in heats of formation ($\Delta\Delta H_f$)[b] between the intermediate **7a–j** and the potential products **8a–j**, *cis*-**9a–j** and *trans*-**10a–j**

Derivative	ΔH_f (kJ mol^{-1})						$\Delta\Delta H_f$[b] (kJ mol^{-1})		
	7[c,d]	**8**[c]	*cis*-**9**	*trans*-**9**	*cis*-**10**	*trans*-**10**	**8–7**	*cis*-**9–7**	*trans*-**10–7**
a	−43	192	−41	−32	−31	−36	235	2	7
b	83	423	57	62	85	81	340	−26	−2
c	−40	199	−35	−27	−26	−30	239	4	10
d	−76	98	−100	−105	−77	−81	174	−24	−5
e	−53	157	−75	−70	−46	−60	210	−22	−7
f	−94	93	−88	−79	−79	−83	186	6	11
g	−221	−163	−215	−206	−206	−210	58	6	11
h	−239	−216	−261	−256	−233	−236	23	−23	2
i	−238	−197	−260	−256	−233	−234	41	−23	3
j	2	257	−26	−23	−4	−7	255	−29	−9

[a] Modelled at the semi-empirical level (AM1).
[b] $\Delta\Delta H_f$=ΔH_f (product)−ΔH_f (monoimine).
[c] All imine bonds were modelled in the *anti* configuration.
[d] Monoimines were modelled as the *R* stereoisomer.

Table 3 shows the differences in ΔH_f values ($\Delta\Delta H_f$) for the monoimines (**7**) and the corresponding hydroxyhexahydropyrimidines (**9**), aminomethyloxazolidines (**10**) and bisimines (**8**) for the reactions with the diaminoalcohol **6**. The most obvious trend is the increase in the difference in the ΔH_f of the bisimines ($\Delta\Delta H_f$ **8–7**) with an increase in the electron withdrawing nature of the aldehyde ring substituent. The hexahydropyrimidines *cis*-**9a–j** and *trans*-**9a–j** do not show this trend; conversely, they are of comparable energy to the monoimine **7**. In the reactions of *p*-nitrobenzaldehyde (**2a**) with **6**, for example, the difference in energy between the hexahydropyrimidine *cis*-**9a** and the monoimine **7a** is 2 kJ mol^{-1}, but the difference in ΔH_f between the associated bisimine **8a** and the monoimine **7a** is 235 kJ mol^{-1}. By comparison, the differences found in the reaction of **6** with *o*-hydroxybenzaldehyde (**2i**) are significantly smaller; the difference in ΔH_f of the hexahydropyrimidine *cis*-**9i** and the monoimine **7i** is −23 kJ mol^{-1} and that of the bisimine **8i** is 41 kJ mol^{-1}.

These results indicate that the ΔH_f of the product can influence the product distribution seen in the crude mixtures. Qualitatively, we observe that the higher the difference in the heat of formation ($\Delta\Delta H_f$) between the monoimine/hexahydropyrimidine and the bisimine, the less favourable it is for the bisimine to form. Conversely, the closer in energy the heats of formation are, the more likely it is that the bisimine will form. However, results from experimental product distributions (Table 1) and the relative ΔH_f of the products (Tables 2 and 3) shows that the formation of the hexahydropyrimidine product depends mostly upon the nature of the substituent attached to the benzaldehyde ring.

2.3. The nature of the aldehyde

The presence of electron donating groups, such as the hydroxy group, on the aryl ring appears to facilitate formation of the imine (both bis and mono). When the benzaldehyde has an electron withdrawing substituent, the formation of the hexahydropyrimidine is favoured, as observed for the reactions with the *p*-nitro- and *p*-cyanobenzaldehyde (**2a** and **2b**). To gain further insight into this phenomenon, we next compared the percentage of hexahydropyrimidine (**4a–h** and **9a–h**) formed in reactions of the *para* substituted benzaldehydes (**2a–h**) with a more quantitative measure of the electronic effect of the benzaldehyde substituents, Hammett substituent constants[26,27] (see Supplementary data). For each diamine, plots of the percentage of heterocycle formed against Hammett constant (σ_p) showed the same clear trends but no quantitative correlation; increasing the electron withdrawing nature of the aryl ring substituent increased the amount of hexahydropyrimidine formed. A plot of the percentage of 5-hydroxyhexahydropyrimidine (**9**) formed against σ_p^+, a Hammett constant corrected for resonance effects, showed this same trend but with improved correlation (R^2=0.86). However, the same plot for product **4** from 1,3-diaminopropane (**1**) showed no quantitative correlation.

Whether the imine or iminium ion intermediate undergoes an intramolecular cyclisation reaction to form the hexahydropyrimidine, or reacts with another molecule of benzaldehyde to give the bisimine, may be related to the comparative reactivities of the electrophilic carbon atoms in the intermediate and the benzaldehyde. To investigate this further, the energies of the frontier molecular orbitals (FMOs) of benzaldehydes with a range of substituents (**2a–j**) were calculated at ab initio level using the 6-311G* basis set (Table 4). The energy of the LUMO (E_{LUMO}) as well as the normalised E_{LUMO} (E_{LUMO}×LUMO coefficient at the carbonyl carbon), and the partial charge on the carbonyl carbon all decrease in a linear relationship with increasing electron withdrawing nature of the substituent as measured using σ_p (R^2=0.97, 0.98 and 0.98, respectively). Comparison of these values to σ_p^+ gave poorer correlations (R^2=0.88, 0.92 and 0.93, respectively).

A normalised E_{LUMO} was calculated to account for the difference in E_{LUMO} for the individual molecules as it is not strictly correct to directly compare coefficients of atoms in different molecules.[28,29] This measure is related to the density of the E_{LUMO} on the carbonyl carbon. The same general trend, but no linear correlation, was observed between the calculated E_{LUMO} and normalised E_{LUMO} values and the percentage of heterocycle (**4a–j** and **9a–j**) formed. The reactions of benzaldehydes with lower E_{LUMO} values gave more 2-arylhexahydropyrimidine product, in accord with the fact that decreased E_{LUMO} and increased substituent electron withdrawing effect are associated. Likewise, the same general trend, but no linear correlation, was observed when relating the partial charge on the carbonyl carbon to the percentage heterocycle formed in the reactions with 1,3-diaminopropane. Interestingly, a linear relationship was observed (R^2=0.92) between the partial charge on the carbonyl carbon of the aldehyde (**2a–j**), including 2-pyridine carboxaldehyde (**2j**) and *o*-hydroxybenzaldehyde (**2i**), and the yield of the heterocycle (**9a–j**) in the reactions with 1,3-diamino-2-propanol (**6**). The same plot for the percentage of hexahydropyrimidine **4** formed in the reaction with 1,3-diaminopropane (**1**) showed no quantitative correlation.

The reactions of (**2j**) and *o*-hydroxybenzaldehyde (**2i**) gave extreme results. The reaction of *o*-hydroxybenzaldehyde with the diaminoalcohol **6** gave only bis- or monoimine (**8i**, **7i**) in the equimolar reaction, whilst the 2-pyridine carboxaldehyde yielded only the hexahydropyrimidine (**9j**). Additional effects due to the *ortho* substituent/endocyclic heteroatom are likely to influence the product outcomes in the reactions of these aldehydes. For example, imines derived from *o*-hydroxybenzaldehyde are known to gain

Table 4
Computed total energies,[a] partial charges on the aldehyde carbonyl carbon,[b] LUMO energies (E_{LUMO}), LUMO coefficients,[c] calculated values for the normalised E_{LUMO} (E_{LUMO} norm)[d] and HOMO–LUMO band gaps[e] for the aldehydes **2a**–**j** after ab initio geometry optimization

Aldehyde	E (10^4 kJ mol^{-1})	Charge on the carbonyl carbon	E_{LUMO} (kJ mol^{-1})	LUMO coefficient	E_{LUMO} norm (kJ mol^{-1})	HOMO–LUMO band gap (10^3 kJ mol^{-1})
2a	−144	0.542	62	0.353	22	1.07
2b	−114	0.543	100	0.431	43	1.08
2c	−765	0.547	169	0.527	89	1.09
2d	−211	0.548	173	0.532	92	1.10
2e	−90	0.549	206	0.555	114	1.13
2f	−100	0.550	217	0.543	118	1.11
2g	−120	0.552	238	0.607	144	1.09
2h	−110	0.552	235	0.607	143	1.10
2i[f]	−110	0.564	192	0.595	114	1.05
2j	−94	0.533	185	0.491	92	1.14

[a] Calculated at the HF/6-311G* level.
[b] Natural atomic charge of the carbonyl carbon.
[c] LUMO coefficient at the carbonyl carbon; the absolute value of the sum of all coefficients; dominated by pz.
[d] LUMO coefficient multiplied by E_{LUMO}.
[e] Energy difference between the HOMO and the LUMO.
[f] Values are for the conformation with an internal hydrogen bond.

extra stabilisation from a strong resonance-assisted hydrogen bond.[24,30] The extra stability gained by the intramolecular hydrogen bond may be a factor in why no hexahydropyrimidine forms in the reaction with *o*-hydroxybenzaldehyde when hexahydropyrimidine is observed in the reaction with *p*-hydroxybenzaldehyde. Two different conformations of *o*-hydroxybenzaldehyde were modelled here. In one conformation, the substituents were arranged in such a way that an internal hydrogen bond could be formed, in the other conformation the carbonyl oxygen and the hydroxyl hydrogen were turned away from one another. The former conformation had the lower total energy, lower E_{LUMO} and band gap, as well as larger LUMO coefficient, normalised E_{LUMO}, and a more positive charge on the carbonyl carbon than the latter conformation. For all these reasons, the conformation with the intramolecular hydrogen bond was used here as the representative conformation.

Lower values for LUMO coefficients and normalised E_{LUMO} on benzaldehydes with electron withdrawing substituents are counter-intuitive and result from delocalisation of the LUMO. The pictorial representations of the LUMOs for *p*-nitrobenzaldehyde (**2j**) and *p*-hydroxybenzaldehyde (**2h**; see Supplementary data) illustrate this. The density of the LUMO on the carbonyl group of *p*-hydroxybenzaldehyde is much greater than that on the carbonyl of the *p*-nitrobenzaldehyde. The *p*-nitrobenzaldehyde molecule also has a more evenly distributed LUMO. A consequence of this delocalisation is enhanced stability and hence a lower E_{LUMO} for the LUMO of benzaldehydes with electron withdrawing substituents. Similar results were obtained when calculations were performed at a lower level of theory (HF/6-31G*, data not shown).

The energy difference between the LUMO and HOMO (HOMO–LUMO band gap) was calculated because it is related to the stability and therefore the reactivity of a compound. However, the HOMO–LUMO band gaps showed little variation in this work and no apparent correlation with Hammett constants or with the relative amounts of heterocycle formed.

Altered reactivity of the benzaldehyde would change the kinetics for the formation of the intermediate imine/iminium ion. Benzaldehydes with electron withdrawing substituents are more amenable to attack by a nucleophile because they have a more stable LUMO. This should result in an increased rate of imine formation, as is seen in other imine forming reactions. For example, it has been shown that the presence of an electron donating group in the *para* position of benzaldehydes decreases the rate of imine formation in the reaction with anilines to form the Schiff base.[31] A number of proposed intermediate monoimine/monoiminium ions were built to investigate their FMOs. These structures were subjected to a conformation search and the geometry of three conformers (chosen to be as different as possible) was optimised at ab initio (HF/6-31G*) level. In this case, the computed values gave no insight into the reactivity of the monoimines, as the energy differences calculated for the different conformations were sometimes large enough to be greater than the energy differences between the individual molecules. Also, the calculated values for the E_{LUMO}, E_{HOMO} and the LUMO coefficients[32] depended upon the conformation adopted by the aliphatic chain of the monoimines/monoiminium ions. In contrast, the benzaldehydes, which are rather rigid molecules, did not present this problem.

The effect of the amine structure on the imine/heterocycle ratio was not investigated. The propanediamines are highly flexible and conformationally complex,[33] resulting in difficulties when modelling the FMOs. The low energy barriers between the conformations mean that the LUMO coefficients would be unreliable. Hydrogen bonding further complicates the matter as both the terminal amino and the hydroxyl group have the potential to hydrogen bond.

3. Conclusion

The investigations discussed above, both experimental and computational, demonstrate an identical trend and indicate that two factors influence the product ratios formed in the reaction of the diaminopropanes **1** and **6** with benzaldehydes, namely the electronic nature of the aryl ring substituent and the substituent group on the carbon 2 of the amine nucleophile. Experimental evidence shows that hexahydropyrimidine formation is favoured by the less nucleophilic amine and by the presence of electron withdrawing groups on the aryl ring of the aldehyde. Calculations show that the electronic nature of this aryl ring substituent influences both the relative thermodynamic stability of the final products and the reactivity of the aldehyde as an electrophile.

The differences between calculated ΔH_f values for the bisimine and the hexahydropyrimidine are related to the nature of the benzaldehyde substituent and can explain experimental observations. The thermodynamic stability of the hexahydropyrimidines formed in reactions with electron donating substituents is similar to that of the analogous bisimines. However, the difference in heat of formation ($\Delta\Delta H_f$) between the bisimine and the hexahydropyrimidine increases with increasing electron withdrawing nature of the substituent. The relative stability of the bisimine decreases with increasing electron withdrawing ability of the substituent making the formation of the hexahydropyrimidine more favourable with

increasing electron withdrawing nature of the substituent. This trend is mirrored by experimental observations.

Increased hexahydropyrimidine formation with an increase in electron withdrawing nature of the benzaldehyde substituent can also be attributed to perturbation of the FMOs of the benzaldehyde. Electron withdrawing groups in the *para* position of the benzaldehyde lead to stabilisation of the LUMO; the more stable the LUMO, the higher the percentage of hexahydropyrimidine. The increased stability of the LUMO is due to it becoming more delocalised and hence lower in energy. These results do not demonstrate why a more stable LUMO in the aldehyde encourages the formation of a hexahydropyrimidine rather than a bisimine. It is possible that the stabilising effect of an electron withdrawing substituent on the LUMO is more pronounced for the monoimines, making them more susceptible to intramolecular nucleophilic attack, however we have no evidence to support this because of the conformational flexibility of the monoimines.

4. Experimental

4.1. General

Benzaldehyde, 1,3-diaminopropane and 2-pyridine carboxaldehyde were purified and/or distilled before use.[34] All other aldehydes were used as received from freshly opened containers. $CDCl_3$ was pre-dried over $NaSO_4$ and stored over 4 Å molecular sieves. DMSO-d_6 was dried by vacuum distillation from CaH_2. NMR spectra were acquired at 300 (^{1}H NMR) and 75 MHz (^{13}C NMR) on a Varian Mercury 300 spectrometer or at 500 (^{1}H NMR) and 126 MHz (^{13}C NMR) on a Varian Inova 500 spectrometer at a probe temperature of 298 K. NMR spectra obtained at 400 MHz (^{1}H NMR) were acquired on a Bruker Avance III spectrometer at a probe temperature of 303 K. NMR spectra are referenced to TMS or the residual solvent peak. Hydrogen and carbon assignments were made using standard NOE, APT, DEPT, gCOSY, gHSQC and gHMBC spectroscopic techniques. Low resolution EI mass spectra (LREI-MS) between 100 and 700 amu were determined on a Shimadzu QP5050 spectrometer. High resolution EI mass spectra (HREI-MS) were determined on VG Autospec spectrometer operating at 70 eV with a source temperature of 250 °C and were referenced with perfluorokerosene. Melting points were determined on a Gallenkamp capillary or Reichert hot-stage melting point apparatus and are uncorrected. Infrared spectra were measured on a Nicolet Avatar 360 FTIR spectrometer; samples were deposited on a Ge crystal for IR spectrum acquisition. Characterisation data is reported only for compounds that gave well-resolved, unambiguous signals in their ^{1}H NMR spectrum (compounds **3a**–**i**, **8a**, **8c**–**g**, **8i**, **9a** and **9j**). Geminal protons that give well-separated signals are denoted as H^A and H^B; the proton with the most downfield signal is designated as H^A. The ^{1}H NMR spectra of compounds **8a**, **8c**–**g** and **8i** exhibited a small allylic coupling (~1 Hz) between the azomethine proton (N=C*H*) and the protons on C1/C3, which resulted in the N=C*H* signal appearing as a broad singlet/unresolved triplet (br s/t).

4.2. Competitive reactions

One molar equivalent of the aldehyde (**2a**–**j**) in methanol (15 mL) was added dropwise to a stirred solution of **1** (0.1 g, 1.35 mmol) or **6** (0.1 g, 1.10 mmol) in methanol (15 mL). The mixture was heated at reflux for 2 h and the solvent removed under vacuum. Residues were lyophilised to remove residual water from the crude product mixtures before analysis. Synthesis of the imines was accomplished under the same conditions using 2 M equiv of the aldehyde. ^{1}H NMR spectra of the crude mixtures were acquired in $CDCl_3$ with the exception of the crude products derived from **2h**, which were obtained in DMSO-d_6 because of their low solubility in $CDCl_3$. Product ratios for the crude reaction mixtures were determined from the ^{1}H NMR integrals of the imine CH protons for the mono- and bisimines, the methine proton (H^2) for the hexahydropyrimidine and when necessary, the CHO proton of the aldehyde (see Supplementary data).

4.3. Characterisation data for the isolated hexahydropyrimidines

*4.3.1. 5-Hydroxy-2-(4′-nitrophenyl)hexahydropyrimidine (**9a**).* The crude product was crystallised from methanol to yield a pale tan solid (0.19 g, 77%). The ^{1}H NMR spectrum of **9a** in $CDCl_3$ showed that the reaction product was a 3:1 mixture of *cis* (major) and *trans* (minor) isomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70 (br s, 3H, OH and NH), 2.78 (dd, J=11, 9 Hz, 2H, *trans* axial H4 and H6), 3.16 (dd, J=11, 2 Hz, 2H, *cis* equatorial H4 and H6), 3.20 (dd, J=11, 2 Hz, 2H, *cis* axial H4 and H6), 3.36 (dd, J=11, 4 Hz, 2H, *trans* equatorial H4 and H6), 3.65 (m, 1H, *trans* H5), 3.68 (m, 1H, *cis* H5), 4.63 (s, 1H, *trans* H2), 4.69 (s, 1H, *cis* H2), 7.72 (overlapping m, 2H+2H, *cis* and *trans* ArH), 8.22 (overlapping m, 2H+2H, *cis* and *trans* ArH). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 39.5, 39.7, 50.5, 52.7, 62.2, 70.4, 71.6, 122.9, 123.0, 128.0, 128.1, 146.6, 146.7, 150.1, 150.2. LREI-MS m/z 222 ($[M-H]^+$); HREI-MS m/z calcd for $[M-H]^+$ $C_{10}H_{12}N_3O_3$: 222.0879, found: 222.0884. IR (ν, cm^{-1}) 3242 (N–H), 3073 (OH), 1510 and 1345 (N=O).

*4.3.2. 5-Hydroxy-2-(2′-pyridinyl)hexahydropyrimidine (**9j**).* The crude product was a colourless oil that solidified on standing in a desiccator over P_2O_5. The ^{1}H NMR spectrum showed that the reaction product was essentially a 3:2 mixture of *cis* (major) and *trans* (minor) isomers (0.19 g, quant.). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (br s, 3H, OH and NH), 2.76 (dd, J=10.3, 9.9 Hz, 2H, *trans* axial H4 and H6), 3.17 (dd, J=14, 1 Hz, 2H, *cis* H4 and H6), 3.22 (dd, J=14, 2 Hz, 2H, *cis* H4 and H6), 3.37 (dd, J=10.3, 4.5 Hz, 2H, *trans* equatorial H4 and H6), 3.62 (overlapping m, 1H+1H, *cis* and *trans* H5), 4.55 (s, 1H, *trans* H2), 4.67 (s, 1H, *cis* H2), 7.20–7.24 (overlapping m, 1H+1H, *cis* and *trans* H4′), 7.42 (d, J=8 Hz, 1H, *trans* H6′), 7.45 (d, J=8 Hz, 1H, *cis* H6′), 7.66–7.71 (overlapping m, 1H+1H, *cis* and *trans* H5′), 8.54 (d, J=9 Hz, 1H, *cis* H3′), 8.55 (d, J=9 Hz, 1H, *trans* H3′). ^{13}C NMR ($CDCl_3$ 126 MHz) *cis* isomer δ 51.6 (C4 and C6), 63.0 (C5), 73.9 (C2), 121.4 (C6′), 123.33 (C4′), 137.2 (C5′), 149.3 (C3′), 159.5 (C1′), *trans* isomer δ 52.5 (C4 and C6), 65.8 (C5), 73.0 (C2), 121.8 (C6′), 123.28 (C4′), 137.1 (C5′), 149.4 (C3′), 159.2 (C1′). LREI-MS m/z 179 ($[M]^+$); HREI-MS m/z calcd for $[M-H]^+$ $C_9H_{12}N_3O$: 178.0975, found: 178.0980. IR (ν, cm^{-1}) 3278 (br, OH and NH).

4.4. Characterisation data for the isolated bisimines

*4.4.1. N,N′-Bis(p-nitrobenzylidene)-1,3-diaminopropane (**3a**).* The crude product was crystallised from acetonitrile to afford pale yellow crystals (0.43 g, 93%), mp 202–204 °C (lit.[35] 197–201 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (m, 2H, H2), 3.80 (dt, J=7, 1 Hz, 4H, H1 and H3), 7.88 (d, J=9 Hz, 4H, ArH), 8.25 (d, J=9 Hz, 4H, ArH), 8.39 (s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.9, 59.3, 123.8, 128.6, 141.5, 148.9, 158.9. LREI-MS m/z 340 ($[M]^+$); HREI-MS m/z calcd for $[M]^+$ $C_{17}H_{16}N_4O_4$: 340.1172, found: 340.1166. IR (ν, cm^{-1}) 1644 (C=N), 1511 and 1342 (N=O).

*4.4.2. N,N′-Bis(p-cyanobenzylidene)-1,3-diaminopropane (**3b**).* The crude product was crystallised from petroleum spirit to give colourless crystals (0.38 g, 95%), mp 163–164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (m, 2H, H2), 3.76 (dt, J=7, 1 Hz, 4H, H1 and H3), 7.68 (d, J=8 Hz, 4H, ArH), 7.81 (d, J=8 Hz, 4H, ArH), 8.32 (br s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.8, 59.1, 113.7, 118.3, 128.3, 132.2, 139.8, 159.2. LREI-MS m/z 300 ($[M]^+$); HREI-MS m/z calcd for

$[M]^+$ $C_{19}H_{16}N_4$: 300.1374, found: 300.1372. IR (ν, cm^{-1}) 1642 (C=N), 2223 (C≡N).

*4.4.3. N,N′-Bis(p-bromobenzylidene)-1,3-diaminopropane (**3c**).* The crude product was crystallised from petroleum spirit to give colourless crystals (0.52 g, 95%), mp 73.7–74.5 °C (lit.[11] 45 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01 (m, 2H, H2), 3.70 (dt, J=7, 1 Hz, 4H, H1 and H3), 7.52 (d, J=9 Hz, 4H, ArH), 7.57 (d, J=9 Hz, 4H, ArH), 8.22 (br s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 31.8, 59.1, 124.9, 129.4, 131.8, 135.1, 160.0. LREI-MS m/z 406/408/410 ($[M]^+$/$[M+2]^+$/$[M+4]^+$); HREI-MS m/z calcd for $[M]^+$ $C_{17}H_{16}N_2{}^{79}Br_2$: 405.9680; found: 405.9697. IR (ν, cm^{-1}) 1644 (C=N).

*4.4.4. N,N′-Bis(p-chlorobenzylidene)-1,3-diaminopropane (**3d**).* The crude product was crystallised from petroleum spirit to give leafy white crystals (0.40 g, 95%), mp 65–66 °C (lit.[36,37] 66.0–67.0 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09 (m, 2H, H2), 3.70 (dt, J=7, 1 Hz, 4H, H1 and H3), 7.35 (d, J=8 Hz, 4H, ArH), 7.63 (d, J=8 Hz, 4H, ArH), 8.22 (br s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.9, 59.1, 128.7, 129.1, 134.6, 136.3, 159.7. LREI-MS m/z 318 ($[M]^+$). IR (ν, cm^{-1}) 1644 (C=N).

*4.4.5. N,N′-Bisbenzylidene-1,3-diaminopropane (**3e**)[38,1].* The crude product was isolated as colourless oil that did not require further purification (0.33 g, quant.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (m, 2H, H2), 3.72 (dt, J=7, 1 Hz, 4H, H1 and H3), 7.37–7.42 (m, 6H, ArH), 7.68–7.74 (m, 4H, ArH), 8.28 (br s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.0, 59.2, 127.9, 128.5, 130.4, 136.1, 161.2. LREI-MS m/z 250 ($[M]^+$). IR (ν, cm^{-1}) 1643 (C=N).

*4.4.6. N,N′-Bis(p-methylbenzylidene)-1,3-diaminopropane (**3f**).* The crude product was a white solid that was characterised without further purification (0.37 g, quant.) mp 66.5–68.0 °C (lit.[37] 66 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (m, 2H, H2), 2.31 (s, 6H, CH_3), 3.61 (dt, J=7, 1 Hz, 4H, H1 and H3), 6.90 (d, J=8 Hz, 4H, ArH), 7.64 (d, J=8 Hz, 4H, ArH), 8.16 (br s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 32.1, 59.2, 127.9, 129.2, 133.6, 140.6, 161.0. LREI-MS m/z 278 ($[M]^+$). IR (ν, cm^{-1}) 1646 (C=N).

*4.4.7. N,N′-Bis(p-methoxybenzylidene)-1,3-diaminopropane (**3g**)[1,11,37].* Thecrude product was crystallised from petroleum spirit to give colourless crystals (0.34 g, 90%), mp 81–82 °C (lit.[11] 81 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (m, 2H, H2), 3.66 (dt, J=7, 1 Hz, 4H, H1 and H3), 3.82 (s, 6H, OCH_3), 6.90 (d, J=9 Hz, 4H, ArH), 7.64 (d, J=9 Hz, 4H, ArH), 8.20 (br s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.2, 55.3, 59.2, 113.9, 129.2, 129.4, 160.4, 161.3. LREI-MS m/z 310 ($[M]^+$). IR (ν, cm^{-1}) 1639 (C=N), 1249 (C–O).

*4.4.8. N,N′-Bis(p-hydroxybenzylidene)-1,3-diaminopropane (**3h**).* The crude product was a brown solid that was not purified further (0.37 g, quant.) mp 65–68 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.87 (m, 2H, H2), 3.53 (t, J=7 Hz, 4H, H1 and H3), 6.78 (d, J=8 Hz, 4H, ArH), 7.53 (d, J=8 Hz, 4H, ArH), 8.17 (s, 2H, N=C*H*), 9.65 (br s, 2H, OH). ^{13}C NMR (DMSO-d_6, 126 MHz) δ 32.2, 58.2, 115.4, 127.4, 129.5 159.9, 160.2. LREI-MS m/z 282 ($[M]^+$). HREI-MS m/z calcd for $[M]^+$ $C_{17}H_{18}N_2O_2$: 282.1368; found: 282.1373. IR (ν, cm^{-1}) 1644 (C=N).

*4.4.9. N,N′-Bis(o-hydroxybenzylidene)-1,3-diaminopropane (**3i**).* The crude product was a bright yellow solid (0.38 g, quant.), mp 59.8–60.5 °C (lit.[20] 59 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.11 (m, 2H, H2), 3.71 (dt, J=7, 1 Hz, 4H, H1 and H3), 6.86 (dt, J=7, 2 Hz, 2H, ArH), 6.95 (dd, J=8, 2 Hz, 2H, ArH), 7.22 (dd, J=8, 2 Hz, 2H, ArH), 7.29 (ddd, J=8, 7, 2 Hz, 2H, ArH), 8.35 (s, 2H, N=C*H*), 13.39 (br s, 2H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.7, 56.8, 116.9, 118.5, 118.6, 131.1, 132.1, 160.9, 165.2. LREI-MS m/z 282 ($[M]^+$). IR (ν, cm^{-1}) 1632 (C=N).

*4.4.10. N,N′-Bis(p-nitrobenzylidene)-1,3-diamino-2-propanol (**8a**).* The crude product was crystallised from ethyl acetate to afford **8a** as pale tan crystals (0.38 g, 98%), mp 137–138 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.67 (d, J=4 Hz, 1H, O*H*), 3.84 (ddd, J=11, 7, 1 Hz, 2H, $H1^B$ and $H3^B$), 3.94 (ddd, J=11, 5, 1 Hz, 2H, $H1^A$ and $H3^A$), 4.29 (m, 1H, H2), 7.90 (d, J=9 Hz, 4H, ArH), 8.25 (d, J=9 Hz, 4H, ArH), 8.44 (br s/t, 2H, N=C*H*). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.69 (ddd, J=12, 6, 1 Hz, 2H, H^{1B} and H^{3B}), 3.88 (ddd, J=12, 5, 1 Hz, 2H, $H1^A$ and $H3^A$), 4.12 (m, 1H, H2), 4.95 (d, J=6 Hz, 1H, OH), 8.03 (d, J=9 Hz, 4H, ArH), 8.30 (d, J=9 Hz, 4H, ArH), 8.51 (s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.9, 70.8, 123.8, 128.8, 141.1, 149.1, 160.7. LREI-MS m/z 356 ($[M]^+$). HREI-MS m/z calcd for $[M]^+$ $C_{17}H_{16}N_4O_5$: 356.1121, found: 356.1120. IR (ν, cm^{-1}) 1649 (C=N), 1525 and 1320 (N=O).

*4.4.11. N,N′-Bis(p-bromobenzylidene)-1,3-diamino-2-propanol (**8c**).* The crude product was a colourless solid (0.46 g, quant.), mp 137–139 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80 (br s, residual H_2O and OH), 3.73 (ddd, J=11, 7, 1 Hz, 2H, $H1^B$ and $H3^B$), 3.83 (ddd, J=11, 5, 1 Hz, 2H, $H1^A$ and $H3^A$), 4.21 (m, 1H, H2), 7.53 (d, J=8 Hz, 4H, ArH), 7.59 (d, J=8 Hz, 4H, ArH), 8.28 (br s/t, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.8, 70.9, 125.2, 129.5, 131.8, 134.7, 161.7. LREI-MS m/z 421/423/425 ($[M-H]^+$/$[(M+2)-H]^+$/$[(M+4)-H]^+$); HREI-MS m/z calcd for $[M-H]^+$ $C_{17}H_{15}N_2O^{79}Br_2$: 420.9551, found: 420.9553. IR (ν, cm^{-1}) 1648 (C=N), 3268 (OH).

*4.4.12. N,N′-Bis(p-chlorobenzylidene)-1,3-diamino-2-propanol (**8d**).* The crude product was crystallised from ethanol to give a colourless solid (0.35 g, 95%), mp 132–135 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (d, J=4 Hz, 1H, OH), 3.73 (ddd, J=12, 7, 1 Hz, 2H, $H1^B$ and $H3^B$), 3.83 (ddd, J=12, 5, 1 Hz, 2H, $H1^A$ and $H3^A$), 4.22 (m, 1H, H2), 7.36 (d, J=8 Hz, 4H, ArH), 7.66 (d, J=8 Hz, 4H, ArH), 8.29 (br s/t, 2H, N=C*H*). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.58 (dd, J=12, 6 Hz, 2H, $H1^B$ and $H3^B$), 3.77 (dd, J=12, 4 Hz, 2H, $H1^A$ and $H3^A$), 4.04 (m, 1H, H2), 4.83 (d, J=5 Hz, 1H, OH), 7.48 (d, J=8 Hz, 4H, ArH), 7.76 (d, J=8 Hz, 4H, ArH), 8.32 (s, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.8 (C1, C3), 70.9 (C2), 128.8, 129.3, 134.3, 136.7, 161.5 (*C*=N). LREI-MS m/z 333/335/337 ($[M-H]^+$/$[(M+2)-H]^+$/$[(M+4)-H]^+$); HREI-MS m/z calcd for $[M-H]^+$ $C_{17}H_{15}N_2O^{35}Cl_2$: 333.0561, found: 333.0556. IR (ν, cm^{-1}) 1648 (C=N), 3272 (OH).

*4.4.13. N,N′-Bisbenzylidene-1,3-diamino-2-propanol (**8e**)[39,40].* The crude product was a viscous oil that solidified on standing (0.29 g, quant.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.10 (br s, 1H, OH), 3.75 (ddd, J=11, 7, 1 Hz, 2H, $H1^B$ and $H3^B$), 3.85 (ddd, J=11, 5, 1 Hz, 2H, $H1^A$ and $H3^A$), 4.24 (m, 1H, H2), 7.37–7.43 (m, 6H, ArH), 7.70–7.76 (m, 4H, ArH), 8.33 (br s/t, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.9, 70.8, 128.0, 128.7, 130.4, 136.2, 161.3. LREI-MS m/z 266 ($[M]^+$). IR (ν, cm^{-1}) 1644 (C=N).

*4.4.14. N,N′-Bis(p-methylbenzylidene)-1,3-diamino-2-propanol (**8f**).* The crude product was a colourless solid (0.32 g, quant.), mp >250 °C dec ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 6H, 2×CH_3), 2.85 (br s, 1H, OH), 3.72 (ddd, J=11, 7, 1 Hz, 2H, $H1^B$ and $H3^B$), 3.82 (ddd, J=11, 5, 1 Hz, 2H, $H1^A$ and $H3^A$), 4.21 (m, 1H, H2), 7.19 (d, J=8 Hz, 4H, ArH), 7.61 (d, J=8 Hz, 4H, ArH), 8.28 (br s/t, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 64.8, 71.1, 128.1, 129.2, 133.3, 141.0, 162.7. LREI-MS m/z 294 ($[M]^+$), 293 ($[M-H]^+$); HREI-MS m/z calcd for $[M]^+$ $C_{19}H_{22}N_2O$: 294.1732; found: 294.1728. IR (ν, cm^{-1}) 1646 (C=N), 3242 (OH).

*4.4.15. N,N′-Bis(p-methoxybenzylidene)-1,3-diamino-2-propanol (**8g**).* The crude product was a colourless solid that was not purified further (0.32 g, quant.), mp 117–119 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (d, J=4 Hz, 1H, OH), 3.71 (ddd, J=11, 7, 1 Hz, 2H, $H1^B$ and $H3^B$),

3.81 (ddd, J=11, 5, 1 Hz, 2H, H1^A and H3^A), 4.20 (br m, 1H, H2), 3.84 (s, 6H, 2×CH_3), 6.93 (d, J=9 Hz, 4H), 7.72 (d, J=9 Hz, 4H), 8.26 (br s/t, 2H, N=C*H*). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.7, 65.1, 71.4, 114.2, 129.2, 129.9, 161.9, 162.4. LREI-MS m/z 327 ([M]$^+$); HREI-MS m/z calcd for [M]$^+$ $C_{19}H_{22}N_2O_3$: 326.1630; found: 326.1632. IR (ν, cm^{-1}) 1649 (C=N), 3140 (OH).

*4.4.16. N,N′-Bis(o-hydroxybenzylidene)-1,3-diamino-2-propanol (**8i**).* The crude product was a bright yellow solid (0.32 g, quantitative), mp 106–107 °C (lit.[41] 105 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (br s, 1H, C2-O*H*), 3.75 (ddd, J=12, 7, 1 Hz, 2H, H1^B and H3^B), 3.90 (ddd, J=12, 5, 1 Hz, 2H, H1^A and H3^A), 4.28 (m, 1H, H2), 6.87 (ddd, J=8, 7, 1 Hz, 2H, ArH), 6.95 (ddd, J=8, 7, 0.5 Hz, 2H, ArH), 7.25 (dd, J=8, 2 Hz, 2H, ArH), 7.31(ddd, J=8, 7, 2 Hz, 2H, ArH), 8.40 (br s/t, 2H, N=C*H*), 13.05 (br s, 2H, phenyl OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 63.2, 70.5, 116.9, 118.6, 118.7, 131.5, 132.5, 160.9, 167.3. LREI-MS m/z 298 ([M]$^+$). IR (ν, cm^{-1}) 1633 (C=N), 3401 (OH). The spectroscopic data for this compound is consistent with published data.[19]

4.5. Computational methods

4.5.1. Calculation of heats of formation (ΔH_f). All calculations of ΔH_f were performed on an SG Indy workstation using Spartan '02 suite of programs from Wavefunction Inc. (www.wavefun.com).[42] Hexahydropyrimidines **4a–j**, the *cis* and *trans* forms of 5-hydroxyhexa hydropyrimidines **9a–j** and the *cis* and *trans* forms of the aminomethyloxazolidines **10a–j** were built in the chair conformation with the N–H bonds and phenyl rings in the equatorial position. The geometry of each compound was optimised at the semi-empirical level using AM1 theory. Monoimines **5a–j** and **7a–j** and the bisimines **3a–j** and **8a–j** were built with the imine bond in the *anti* conformation. Monoimines **7a–j** were built in the R configuration at C2. A single derivative of each product was built and subjected to a systematic conformational search at the molecular mechanics level using the MMFF94 force field. The three lowest energy conformers of each compound were extracted and geometry optimisation of each model was performed at the semi-empirical level using AM1 theory. The lowest energy conformer after semi-empirical optimisation was then used to build the remaining derivatives and each molecule was then subjected to semi-empirical geometry optimization (AM1 theory).

4.5.2. Calculation of the FMO energies and LUMO coefficients. These calculations were executed using Spartan '06 from Wavefunction Inc.[42] on an IBM X Series Server. The aldehyde was built and its geometry optimised at the molecular mechanics level using the MMFF as implemented in Spartan. A further geometry optimization was then performed at the HF/6-311G* level.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2009.10.060.

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