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α-(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-diazines. Part 1: Synthesis and stereochemistry. Extension to *s*-triazine series

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Abstract—The general and efficient synthesis of the title compounds, consisting of the (selective) replacement of chlorine in commercial α-chlorodiazines and cyanuryl chloride by the 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy group (Williamson method) is described. The stereochemistry of this new series of derivatives is analysed in terms of different conformational chirality exhibited in solution (^{1}H NMR) versus solid state (X-ray diffractometry), *meso* against chiral forms, respectively. In solid state, the inclusion capacity of some chiral networks as well as their supramolecular aggregation is pointed out. A good correlation between rotameric behaviour of the *c*-5-di(*s*-tri)-diazinyloxymethyl group in the two states is found.

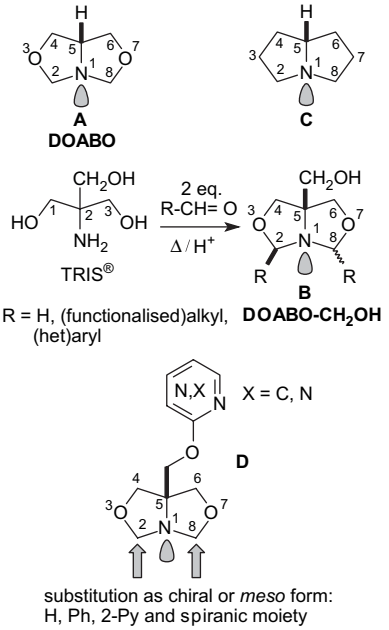
1. Introduction

The 3,7-dioxa-1-azabicyclo[3.3.0]octane heterocyclic saturated system **A** is readily available by double cyclocondensation between TRIS® (2-amino-2-hydroxymethyl-1,3-propandiol) and carbonyl compounds, yielding 5-hydroxymethyl-3,7-dioxa analogous **B** of the core alkaloid, namely *pyrrolizidine* **C** (Scheme 1).[1–4]

A series of various *C*-substituted compounds, having **A** as their basic skeleton, have been shown to have high biological interest: fertilisers, biocides, pesticides and anticancer agents.[5–14]

Although focused mainly on applied research, only few of the results reported previously validated this class as appropriate for further functionalisation.

A method for direct substitution at the carbon ring is still unknown. Functionality was ensured classically by the a priori selection of the substituted starting carbonyl compound, usually an aldehyde (Scheme 1). Thus, only compounds **A** bearing a hydroxymethyl group at C-5 were mentioned to be suitable for functionalisation at this site by acylation,[3–5,7,8,12,15] thionation[16] and, recently, by Dess–Martin oxidation.[13] Depending on the new group linked at C-5, the reported structures are of pharmaceutical[7,8,12,13] and



Scheme 1.

Keywords: Diazines; *s*-Triazines; Oxazolidines; NMR; Chirality; X-ray diffractometry.
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lately, of supramolecular interest as O-, N-, O-protected forms of TRIS®.[17]

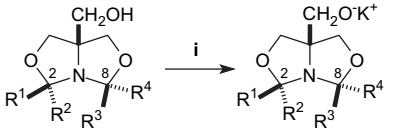
Following on from our developments in the synthesis and stereochemistry of substituted 3,7-DiOxa-*r*-1-AzaBicyclo[3.3.0]-*c*-5-Octanes (hereafter throughout abbreviated as DOABO, Scheme 1),[†,18–20] we recently established that some compounds of type **B** (Scheme 1, R=H, Ph) can be easily converted into 5-alkoxymethyl derivatives, via potassium alkoxides, in much milder conditions than those used earlier by Broadbent in 1976 (Williamson method).[7,20] Not only they were efficient nucleophiles against aliphatic halo compounds, but in a single testing example, against an α-chloro-π-deficient system such as 2,6-dichloropyrazine.[20]

An extension of this result required a larger series of competent substrates. Referring to our previous data about the selective (or exhaustive) nucleophilic replacement of chlorine in certain π-deficient systems,[20,26,27] we considered α-chlorodiazines and cyanuryl chloride as a challenging choice for investigating more elaborated building blocks with potential biological and/or supramolecular interest. Hence, we wish to report here the synthesis and stereochemistry of a new class as 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxydi(*s*-tri)azines **D** (Scheme 1).

2. Results and discussion

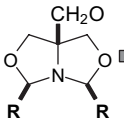
2.1. Synthesis of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-di(*s*-tri)azines

The known DOABO derivatives **1a**–**e**[19,20] were reacted with potassium hydride in conditions depicted in Scheme 2.



i: 1.05 eq. KH / THF / 40 °C / 1.0 - 1.5 hrs.

a: R^1- R^4 = H
b-*cis*: R^1 = R^3 = Ph, R^2 = R^4 = H
b-*trans*: R^1 = R^4 = Ph, R^2 = R^3 = H
c: R^1 = Ph, R^2 - R^4 = H
d-*trans* + **d**-*cis*:
R^1,R^2 = CH_2CH_2[CH(*t*-Bu)]CH_2CH_2,
R^3 = R^4 = H
e: R^1 = R^3 = 2-Py, R^2 = R^4 = H



Abbreviations:
R = H: (2H)DOABO-CH_2O
R = Ph: (2Ph)DOABO-CH_2O

Scheme 2.

† Stereochemical descriptor ***r*** (reference) is used in order to simplify discussion arising from the basic stereochemistry of this molecule as *cis* fused double oxazolidine system, the lone pair at N-1 being the fiducial substituent.[21] This spatial arrangement, together with the absence of pyramidal inversion at N-1 are already well documented.[7,11,18–20,22–25]

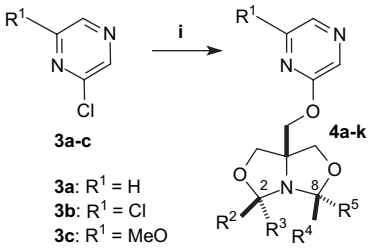
Chiral **1b**-*trans*, **1c**, **1d**-*trans* and **1d**-*cis* were used as racemates.

The study of the reaction between potassium alkoxides **2a**–**e** and α-chlorodiazines was performed using the following protocol:

(i) For exhaustive substitution of chlorine, 1.05×*n* equivalents of **2a**–**e**/equivalent of diazine possessing '*n*' chlorine atoms were used.
(ii) For selective substitution of chlorine, 1 equiv of **2a**–**e**/equivalent of chlorine to be replaced was used.

All syntheses were systematically TLC monitored.

Series of new compounds **4a**–**k** were prepared starting from the α-chloropyrazines **3a**–**c** (Scheme 3, Table 1).



i: **2a-e** / THF, *T*(°C), t (hrs.)

Scheme 3.

Only **2a** exhibited a 'methoxide-like reactivity' regarding yields and selectivity (entries 1, 7, 9 and 10). Indeed, in a competitive experiment, equimolar amounts of 2-chloropyrazine **3a**/**2a**/potassium methoxide gave, in identical conditions (entry 1), the equimolar ratio between 2-methoxypyrazine and **4a**. When **2b**-*cis*, **2b**-*trans*, **2c** and **2e** having C-2, (-8) (di)substituted DOABO units with (het)aryl groups were used as nucleophiles, the yields decreased slightly, **4a** (85%) versus **4b**-*cis* (79%) versus **4b**-*trans* (69%), or strongly, **4a** versus **4c** (48%) and **4e** (44%). The unfavourable influence of substitution at C-2, -8 was best illustrated when the results of the one-pot replacement of the two chlorine atoms in 2,6-dichloropyrazine, **2b**-*cis* versus **2a** (entries 8 and 10) were compared. Treatment of **3b** with 2.1 equiv of **2b**-*cis* yielded a complex mixture of monochloro derivative **4g**, the (2Ph)DOABO–CH_2O substituting pyrazinone **4h** (issued most probably from the partial hydrolysis of **4g** during the aqueous work-up) and, in traces only, the desired product **4i**. Using **2a** as nucleophile, compound **4k** was obtained in a clean procedure as described in a previous publication of our laboratory.[20]

The non-separable mixture of DOABO-spiranic derivatives **1d**-*trans*/**1d**-*cis* (96:4) (Scheme 2) afforded the corresponding **4d**-*trans*/**4d**-*cis* as 96:4 ratio, respectively, in the crude product and 75:25 after crystallisation from ligroin.

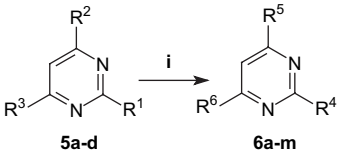
Next, the α-chloropyrimidines **5a**–**d** produced the series **6a**–**m** (Scheme 4, Table 2).

With **2a** as nucleophile, both one-pot exhaustive (entries 2, 4 and 6) and selective substitutions (entries 3, 5 and 7) were

Table 1. Results in the synthesis of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-pyrazines (preparation of compounds **4a–k**)

Entry	Nucleophile→Compd	R^1	R^2	R^3	R^4	R^5	*T* (°C)	*t* (h)	Yield (%)
1	**2a**→**4a**	H	H	H	H	H	40	16	85
2	**2b**-*cis*→**4b**-*cis*	H	Ph	H	Ph	H	60	20	79
3	**2b**-*trans*→**4b**-*trans*	H	Ph	H	H	Ph	50	14	69
4	**2c**→**4c**	H	Ph	H	H	H	65	11	48
5	**2d**-*trans*→**4d**-*trans*	H	$CH_2CH_2[CH(t\text{-Bu})]CH_2CH_2$		H	H	65	2	46[a]
	2d-*cis*→**4d**-*cis*						rt	12	16[a]
6	**2e**→**4e**	H	2-Py	H	2-Py	H	rt	5	44
							35	18	
7	**2a**→**4f**	Cl	H	H	H	H	rt	6	83[b]
8	**2b**-*cis*→**4g**	Cl	Ph	H	Ph	H	65	52	34[c]
	→**4h**	OH	Ph	H	Ph	H			17[c]
	→**4i**	(2Ph)DOABO–CH_2O	Ph	H	Ph	H			6[c]
9	**2a**→**4j**	MeO	H	H	H	H	65	24	33
10	**2a**→**4k**	(2H)DOABO–CH_2O	H	H	H	H	65	3	76[d]
							rt	14	

[a] Isolated as a non-separable mixture of diastereomers **4d**-*trans*/**4d**-*cis* 75:25 (bridged N-1 and *t*-Bu groups as references) as deduced from the ^{1}H NMR spectrum of the crystallised material.
[b] Selectivity as 89:11 **4f**/**4k** in the ^{1}H NMR spectrum of the crude reaction mixture.
[c] As partial conversions of **3b** into **4g–i**.
[d] Starting directly from **3b** without isolation of the intermediate **4f**.



Scheme 4.

performed with good yields. The depicted (regio)selectivities could be ensured in very mild conditions only. Surprisingly (entry 7), the regioisomer **6h** was largely dominant against the expected **6i** as confirmed by the NMR spectra of the pure isolated **6h**, which clearly displayed equal intensity of signals for two magnetically non-equivalent DOABO–CH_2O groups. Their individual assignment, as well as for the **6b** analogous (entry 2), was performed by high-resolution ^{1}H NMR experiments, 2D ^{1}H–^{1}H (COSY and TOWNY),[28,29] ^{1}H–^{13}C (HSQC[30,31] and HMBC[32,33]), ROESY[34,35] and NOESY.[36,37]

As in the α-chloropyrazine series, the use of **2b**-*cis* gave different results (entries 8 and 9): complete replacement of chlorine in dichloropyrimidines was possible only in the 2,4-regioisomer (**5b**→**6k**) with medium yield. In identical conditions, starting from 4,6-dichloropyrimidine **5c**, the separable mixture of **6l** and **6m** was obtained, suggesting that the second substitution of chlorine in **6m** was difficult.

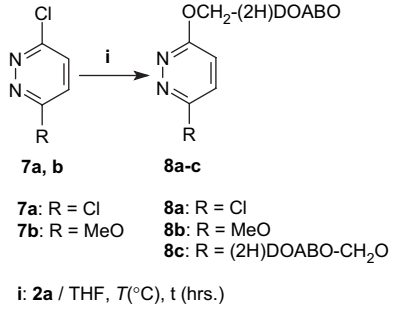
In the α-chloropyridazine series (Scheme 5, Table 3), we limited our investigation to the reactivity of **2a** exclusively.

Compounds **8a–c** were prepared, supporting the validity of our synthetic findings.

Table 2. Results in the synthesis of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-pyrimidines (preparation of compounds **6a–m**)

Entry	Reaction	R^4	R^5	R^6	*T* (°C)	*t* (h)	Yield (%)
1	**5a**→**6a**	(2H)DOABO–CH_2O	H	H	65	4	60
2	**5b**→**6b**	(2H)DOABO–CH_2O	(2H)DOABO–CH_2O	H	40	6	80
3	**5b**→**6c**	Cl	(2H)DOABO–CH_2O	H	−78→rt	24	63 (71[a])
	→**6d**	(2H)DOABO–CH_2O	Cl	H			(23[a])
4	**5c**→**6e**	H	(2H)DOABO–CH_2O	(2H)DOABO–CH_2O	45	24	81
5	**5c**→**6f**	H	(2H)DOABO–CH_2O	Cl	−78→rt	19	63 (82[b])
6	**5d**→**6g**	(2H)DOABO–CH_2O	(2H)DOABO–CH_2O	(2H)DOABO–CH_2O	65	21	58
7	**5d**→**6h**	(2H)DOABO–CH_2O	(2H)DOABO–CH_2O	Cl	−78→rt	22	76 (86[c])
	→**6i**	Cl	(2H)DOABO–CH_2O	(2H)DOABO–CH_2O			(8[c])
	→**6j**	Cl	(2H)DOABO–CH_2O	Cl			(6[c])
8	**5b**→**6k**	(2Ph)DOABO–CH_2O	(2Ph)DOABO–CH_2O	H	65	21	58
9	**5c**→**6l**	H	(2Ph)DOABO–CH_2O	(2Ph)DOABO–CH_2O	65	21	31[d]
	→**6m**	H	(2Ph)DOABO–CH_2O	Cl			23[d]

[a] Regioselectivity according to the ^{1}H NMR spectrum of the crude reaction mixture: 6% unreacted **5b**.
[b] 18% **6e** according to the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Regioselectivity according to the ^{1}H NMR spectrum of the crude reaction mixture.
[d] Partial conversions of **5c**.



Scheme 5.

Table 3. Results in the synthesis of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-pyridazines (preparation of compounds **8a–c**)

Compd	R	*T* (°C)	*t* (h)	Yield (%)
8a	Cl	40	4	86 (96[a])
8b	MeO	65	18	51
8c	(2H)DOABO–CH_2O	40	3	78 (90[b])

[a] Selectivity according to the ^{1}H NMR spectrum of the crude reaction mixture: 4% **8c**.
[b] Starting directly from **7a** without isolation of the intermediate **8a**; content according to the ^{1}H NMR spectrum of the crude reaction mixture: 10% **8a**.

Finally, the nucleophilicity of the alkoxides based on **1a** and **1b**-*cis* was comparatively explored against a more π-deficient system, cyanuryl chloride. Based on the literature data reporting the reaction between alcohols and cyanuryl chloride in neutral or basic conditions,[38–41] the chemistry followed is depicted in Scheme 6. The results are summarised in Table 4.

The target compounds were the trisubstituted *s*-triazines **10a** and **10b** in a one-pot synthesis.

A much greater dependence with respect to the starting **1a** or **1b**-*cis* and their deprotonated forms was observed. Thus, **2a** was efficient only in disubstitution of chlorine with poor yield (**9a**, entry 1). No intermediate of type monoalkoxy was detected. In contrast, the use of its lithium alkoxide **2f** (entry 2) permitted rapidly the optimisation of the synthesis towards the desired **10a** in gentle and clean reproducible conditions. The mass spectra of **9a** and **10a** (ESI and FAB$^+$, respectively) fully confirmed the envisaged structures.

Table 4. Results in the synthesis of 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy-*s*-triazines (preparation of compounds **9a**, **b**, **10a**, **b**)

Entry	Starting material	Nucleophile	*T* (°C)	*t* (h)	Results	
					Compounds	Yield (%)
1	**1a**	**2a**	65	36	**9a**	34
2		**2f**	−78→rt	20	**10a**	82
3	**1b**-*cis*	**2b**-*cis*	0	1	**10b** (51);	37
			65	40	**9b** (10); **1b**-*cis* (39)[a]	
4		**2g**-*cis*	−60→rt	20	**10b** (46);	29
			rt	48	**9b** (8);	
			65	4	**1b**-*cis* (46)[a]	

[a] Contents according to the ^{1}H NMR spectra of the crude reaction mixtures.

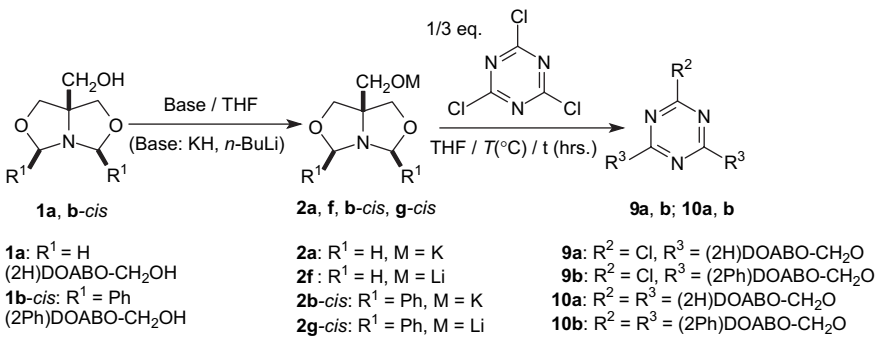
Starting from **1b**-*cis*, its potassium alkoxide **2b**-*cis* rather than **2g**-*cis* gave this time a slightly higher content of the trisubstituted product **10b** in the crude reaction mixture (entries 3 and 4). The bias between **9b** and **10b** was solved by MS-(FAB$^+$) spectrometry. With the isolated **9a**, **10a**, **9b** and **10b** in our hands, the content of the crude reaction mixtures (Table 4) based on their ^{1}H NMR spectra was determined.

2.2. Stereochemistry of α-(3,7-dioxa-*r*-1-azabicyclo-[3.3.0]oct-*c*-5-ylmethoxy)-di(*s*-tri)azines

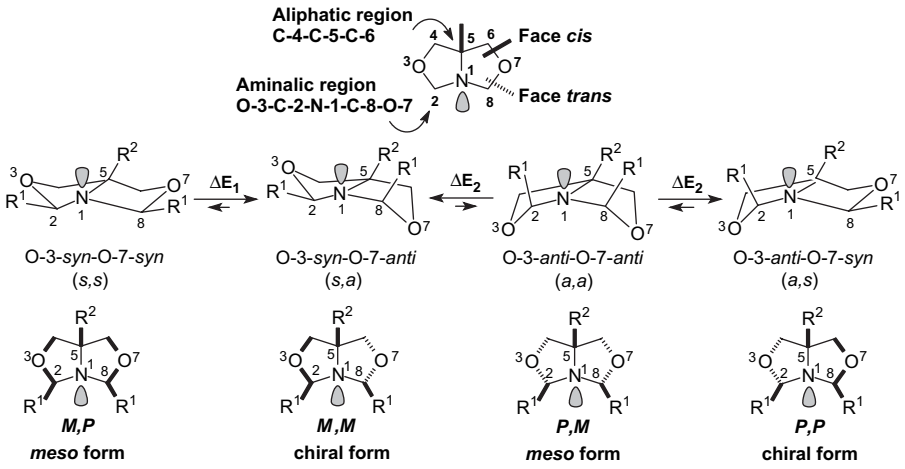
2.2.1. Conformational considerations. As pyrrolizidine **C** (Scheme 1), the skeleton of its 3,7-dioxa analogous **A** is heterofacial. All its (hetero)atoms are prostereogenic centres.[20] Except H-5, the substitution of any of the hydrogen atoms generates configurational chirality. We earlier described in detail this stereochemistry.[19,20]

The basic molecule itself **A**, a *cis* fused double oxazolidine system, as well as its *c*-C-5-achiral monosubstituted derivatives (e.g., **B**, R=H), can exist in a number of flexible conformations upon pseudorotation occurring at each oxazolidine ring. Few experimental studies confirmed this flipping,[19,20,23] presumably because determining the frozen conformation in solution is a quite difficult task, for example, in the case of compounds **1a** and **1b**-*cis* (Scheme 2).

Our previous results of the ab initio RHF/6-31G* calculations[20] in gas phase and solvation models predicted that



Scheme 6.



Type of structure	Configuration	ΔE_1 (kJ/mol)[a]	ΔE_2 (kJ/mol)[a]
R^1 = H; R^2 = CH_2OH (**1a**), MOM	Achiral	-18.87	-5.48
R^1 = Ph; R^2 = CH_2OH (**1b**-*cis*), MOM	Non-chiral (*meso* form) 1*r*,2*R*,5*s*,8*S*	-14.86	-8.54

[a]Typical ΔE values in vacuum and gas phase.[19,20]

Scheme 7.

the DOABO skeleton could be involved in three different conformational equilibriums depicted in Scheme 7.

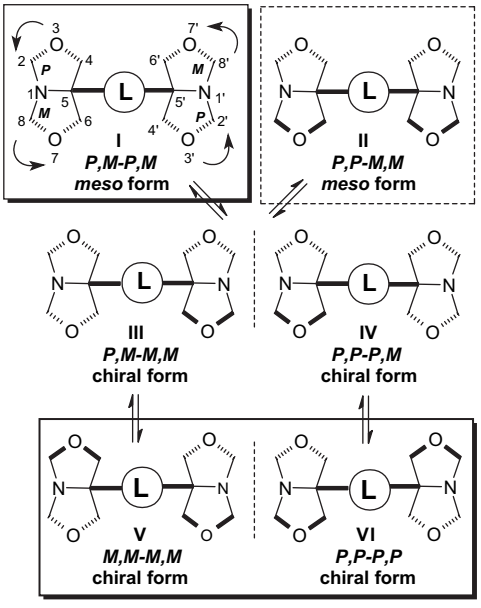
Calculation suggested an oriented flexibility of the bicycle, ascertained as a single oxazolidine ring inversion/equilibrium. It occurs regardless of the configurational nature, achiral or non-chiral, of the structure. The four stereoisomers were discriminated based on the sense of puckering in the two oxazolidine rings, *syn*/*anti* O-3/O-7, revealed as fused *O*-envelope conformers. The lone pair at N-1 was the fiducial substituent for the descriptors *syn*/*anti*. The substitution test shows that the steric relationships between homofacial protons, aminalic H-2, -8 or aliphatic H-4, -6, are different in the two types of conformers, enantiotopic in diastereomeric *meso* forms (*s*,*s*) or (*a*,*a*) but diastereotopic in chiral forms (*a*,*s*) or (*s*,*a*).

Next, in order to designate enantiomeric and *meso* form conformations, the two torsion angles in the aminalic part of the skeleton, C-5–N-1–C-2–O-3 and C-5–N-1–C-8–O-7, were selected and defined by using the helicity rules descriptors *M* and *P*.

As shown in Scheme 7, the occurrence of the *meso* (*M*,*P*) conformer can be reasonably ruled out since it was found much less stable than the alternative *meso* (*P*,*M*) diastereomer and the chiral conformers $(M,M) \equiv (P,P)$. Only the equilibriums $(M,M) \leftrightarrows (P,M) \leftrightarrows (P,P)$, consisting of two diastereomeric inversions and, overall, an enantiomeric interconversion, are to be considered. However, the magnitude of the corresponding ΔE_2 values precluded an a priori assignment of the frozen conformation in gas phase as well as in solution.[20]

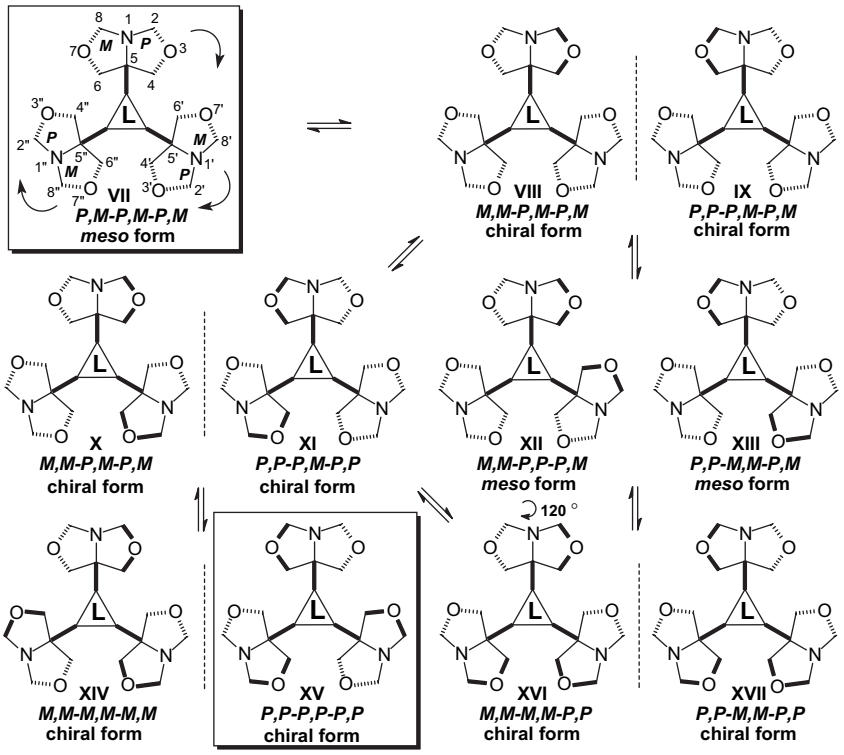
These results, issued from an apparently restrictive rotation about the C–O–C bonds only, were proved by our inspection of some earlier X-ray crystallographically determined structures in this class.[20,24,25]

For the present work, we enlarged the analysis to compounds comprising two, even three identical DOABO units tied together by an achiral linker **L** (Schemes 8 and 9).[‡] Obviously, the linker should be highly symmetric, i.e., C_{nh}, C_{nv} groups, such as di(tri)methoxy-di(*s*-tri)azine fragments. They are statistically achiral, considering the angular geometry of the –O–CH_2– sequence. The last one can promote a preferred rotamerism, as we will mention later.



Scheme 8.

[‡] In Schemes 8 and 9, the DOABO homomorphic substitution at C-2, -8 was omitted for the reason of simplicity.



Scheme 9.

The stereoisomerism depicted in Schemes 8 and 9 is exacerbated although, by neglecting all the DOABO *meso*-(*M*,*P*) type forms (Scheme 7), the conformational analysis is simplified.

In this purpose, we applied our previous proposal, namely *local stereochemistry*, referring to compounds possessing only one DOABO unit (Scheme 7) and *global stereochemistry* defining molecules built on two or three DOABO units (Schemes 8 and 9).[20] In this approach, 'dimeric' DOABO derivatives can exist as two *global meso* forms, **I** and **II**, and four *global* chiral forms, two racemates **III–IV** and **V–VI**. 'Trimeric' DOABO derivatives, the *s*-triazines **10a**, **10b**, provide three *global meso* forms, **VII**, **XII** and **XIII**, and eight *global chiral* forms, four racemates, **VIII–IX**, **X–XI**, **XIV–XV** and **XVI–XVII**. The common feature is that each conformer **I**→**VI** and **VII**→**XVII** can be generated, step by step, in a single oxazolidine ring inversion/equilibrium, following the pathways depicted in Schemes 8 and 9.

2.2.2. Determining the stereochemistry in solution by ^{1}H DNMR. A stereochemical analysis, focused on compounds **4a**, **4k**, **6e**, **6l**, **10a** and **10b**, was carried out by ^{1}H DNMR at low temperature (293–173 K) in THF-d_8 on 400 MHz timescale. The results obtained prompted us to discuss the behaviour of the two building heterocyclic systems separately.

2.2.2.1. Conformational analysis of the DOABO counterparts. In Table 5, the main chemical shifts at room temperature (T_i), at coalescence ($T_{coales.}$) and at the lowest temperature (T_{calcd}) are collected. The last one was used for calculation of the rate constant at coalescence (k_c) and the free enthalpy of activation ($\Delta G^{\neq}$) of DOABO ring inversion. These two parameters were available by applying the Eyring equations (Eqs. 1 and 2).[21,42]

$$k_c = 2.22\left(\Delta\nu^2 + 6J^2\right)^{0.5} \ [s^{-1}] \tag{1}$$

$$\Delta G^{\neq} = 19.14\, T_c(10.32 + \log T_{coales.}/k_c) \ [J/mol] \tag{2}$$

The results are listed in Table 6. They refer throughout to a single oxazolidine ring inversion/equilibrium placed in different environments, created by the number of DOABO units (1–3)/compound.

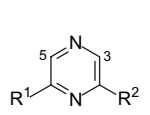
The ^{1}H DNMR behaviour of the simplest compound, **4a**, is shown in Figure 1.

We assigned the spectral shape above the coalescence point as to refer to the fast conformational interconversion involving the exchanging sites illustrated in Scheme 7 (Eq. 3):

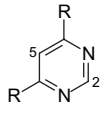
$$\mathbf{4a}\ (M,M) \leftrightarrows \mathbf{4a}\ (P,M) \leftrightarrows \mathbf{4a}\ (P,P) \tag{3}$$

Both equilibriums were seen as first-order reactions and equally populated. Consequently, the k_c value was approximated to be the same for the forward and the reverse processes. The supporting reason is that the calculated ΔE_2 values, chiral versus *meso* form (Scheme 7), were small enough. Since the temperature of coalescence was revealed to be the same for both the aminalic and aliphatic methylenes (Fig. 1), we concluded that these two 'internal clocks' were

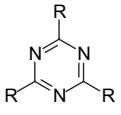
Table 5. Relevant ^{1}H DNMR data [δ (ppm) in THF-d_8] of compounds **4a**, **4k**, **6e**, **6l**, **10a** and **10b**



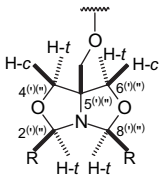
4a: R^1 = H, R^2 = (2H)DOABO-CH_2O
4k: R^1 = R^2 = (2H)DOABO-CH_2O



6e: R = (2H)DOABO-CH_2O
6l: R = (2Ph)DOABO-CH_2O



10a: R = (2H)DOABO-CH_2O
10b: R = (2Ph)DOABO-CH_2O



R = H-*c*, (2H)DOABO-CH_2O
R = Ph, (2Ph)DOABO-CH_2O

Compd	T_i (K)	δ		δ		δ[d]
	$T_{coales.}$ (K)	Aminalic methylenes[b]		Aliphatic methylenes[c]		Heteroaromatic
	T_{calcd} (K)[a]	H-2(8)$^{(r)(n)}$-*c*	H-2(8)$^{(r)(n)}$-*t*	H-4(6)$^{(r)(n)}$-*c*	H-4(6)$^{(r)(n)}$-*t*	
4a	293	4.42	4.40	3.84	3.81	H-3: 8.20
	268	4.41		3.83		H-3: 8.21
	253	4.42	4.40	3.84	3.82	H-3: 8.23
4k	293	4.42	4.40	3.84	3.81	H-3, -5: 7.78
	263	4.41		3.82		H-3, -5: 7.79
	183	4.45	4.38	3.88	3.81	H-3, -5: 7.85
6e	293	4.39	4.38	3.78	3.76	H-5: 6.12
	273	4.39		3.77		H-5: 6.15
	173	4.45	4.35	3.85	3.76	H-5: 6.35
10a	293	4.40	4.38	3.78		—
	273	4.39		3.80	3.78	—
	213	4.43	4.37	3.84	3.76	—
6l	293	—	5.59	4.00	3.91	H-5: 5.75
	173	—	5.58	3.96	3.96	H-5: 6.12
10b	293	—	5.58	3.98	3.92	—
	233	—	5.58	3.96		—
	193	—	5.58	3.99	3.94	—

[a] Temperature at which the parameters $\Delta\nu$ and ^2J were extracted from the spectrum and used for calculation of parameters k_c and $\Delta G^{\neq}$ (see Table 6).
[b] Doublets with ^2J=5.2–5.6 Hz and singlets in **6l**, **10b** above T_i and below $T_{coales.}$.
[c] Doublets with ^2J=8.4–9.0 Hz.
[d] Protons having *ortho* relationships with DOABO–CH_2O groups.

synchronised. They provided similar $\Delta G^{\neq}$ values (Table 6, entry 1).[21]

Below coalescence, we ascertained the spectral appearance to depict the (2H)DOABO unit in **4a** as frozen *meso*-(*P*,*M*) conformer (C_s symmetry, Scheme 7) because the homofacial aminalic (or aliphatic) protons were isochronous, hence enantiotopic (e.g., H-2-*c* vs H-8-*c*, etc.).

In the same way, at room temperature, the DOABO units in polysubstituted analogues **4k**, **6e**, **6l**, **10a** and **10b** were magnetically equivalent and flipping structures (Table 5). However, upon cooling, only in diazines **4k**, **6e** and *s*-triazine **10b** did the (2H)DOABO signals expose a single clear point of coalescence followed by a new relevant splitting as (AB)→(A_2)→(AB) systems. For **4k** and **6e** only, it was again possible to double-check the calculation of k_c and $\Delta G^{\neq}$, the values arising from the identical evolution of the aminalic and aliphatic methylenes (Table 6, entries 2 and 3). The calculated energetic barriers of compounds **4a**, **4k** and **6e** agree with the literature data.[43]

The ^{1}H DNMR spectra of the *s*-triazine **10a** displayed two points of coalescence, 293 K (aliphatic methylenes)

Table 6. ^{1}H DNMR data, k_c (s^{-1}) and $\Delta G^{\neq}$ (kJ/mol) values of DOABO oxazolidine ring inversion in compounds **4a**, **4k**, **6e**, **6l**, **10a** and **10b**

Entry	Compd	Oxazolidine ring inversion data											
		Aminalic zone: H-2(8)$^{(r)(n)}$-*c* versus -*t*						Aliphatic zone: H-4(6)$^{(r)(n)}$-*c* versus -*t*					
		$T_{coales.}$ (K)	T_{calcd}[a] (K)	$\Delta\nu$ (Hz)	^2J (Hz)	k_c[b] (s^{-1})	$\Delta G^{\neq}$ (kJ/mol)	$T_{coales.}$ (K)	T_{calcd}[a] (K)	$\Delta\nu$ (Hz)	^2J (Hz)	k_c[b] (s^{-1})	$\Delta G^{\neq}$ (kJ/mol)
1	**4a**	268	253	6.8	5.6	68.0	56.0	268	253	9.0	9.0	105.7	55.0
2	**4k**	263	183	28.8	5.2	139.8	53.3	263	183	29.0	8.6	159.1	53.1
3	**6e**	273	173	38.1	5.4	179.1	54.9	273	173	37.9	8.7	192.9	54.7
4	**10a**	273	213	23.0	5.4	117.3	55.8	293	213	29.4	8.9	162.5	59.3
5	**6l**	—	—	—	—	—	—	173	—	—	—	—	—
6	**10b**	—	—	—	—	—	—	233	193	19.9	9.1	132.8	47.1

[a] Temperature at which the parameters $\Delta\nu$ and ^2J were extracted from the spectrum and used for calculations.
[b] The k_c values issued by applying Eq. 1 were multiplied by 2 since the DOABO system is a double oxazolidine structure.[21,42]

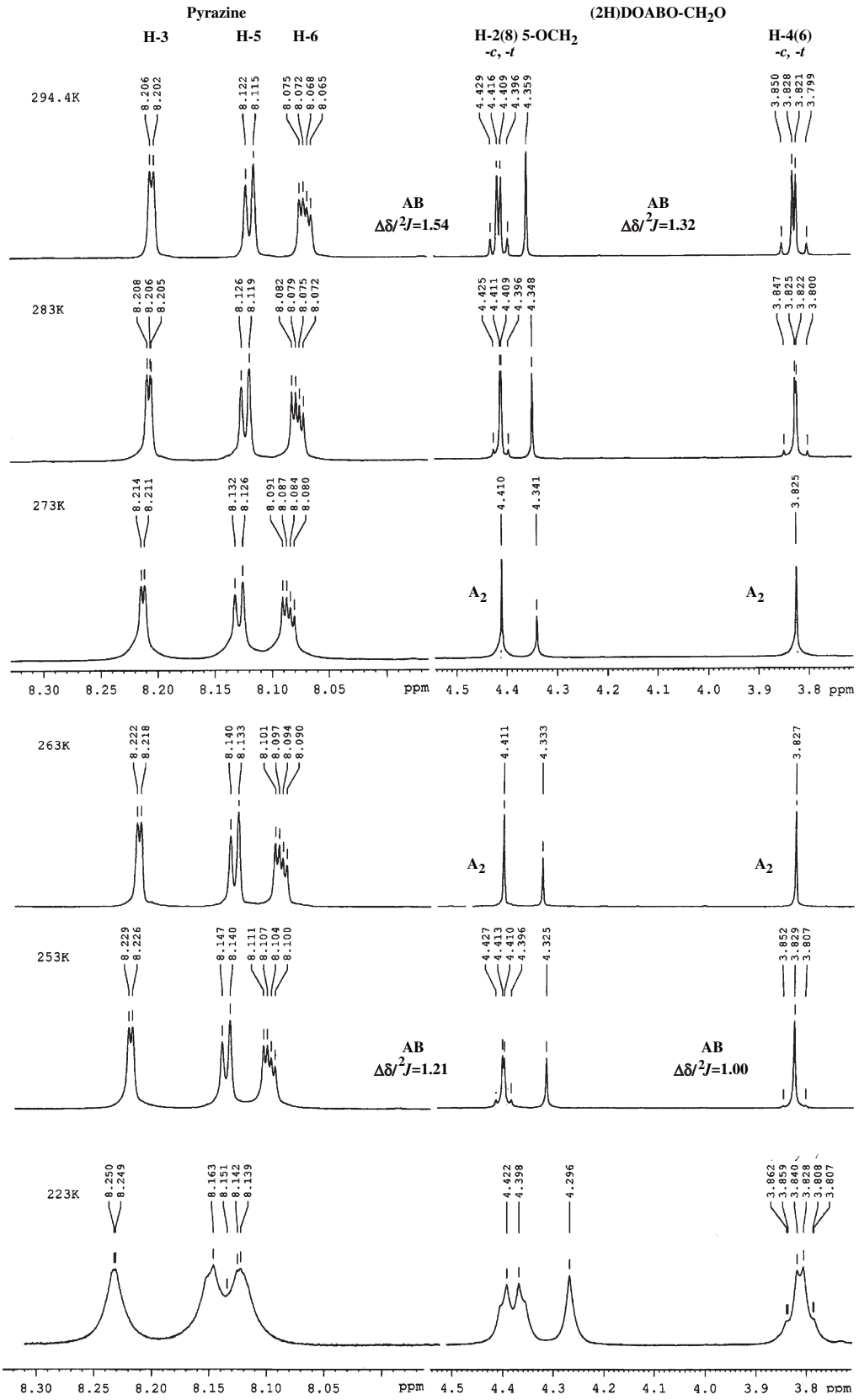


Figure 1. ^{1}H DNMR spectra of compound **4a** (400 MHz, THF-d_8).

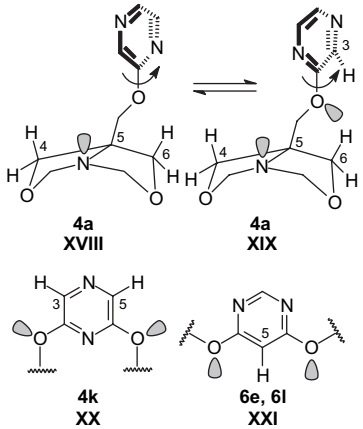
and 273 K (aminalic methylenes) providing two notably different $\Delta G^{\neq}$ values (Table 6, entry 4). The $\Delta G^{\neq}$ value issued from the analysis of the aliphatic methylenes was more credible because the difference $\Delta T = T_{\text{coales.}} - T_{\text{calcd}}$ was greater (80 K) at C-4(6)$^{(I)(II)}$ than at C-2(8)$^{(I)(II)}$ (60 K).[42] The higher $\Delta G^{\neq}$ value of the oxazolidine ring inversion in

10a should be plausible since, as a trisubstituted structure, it was the most crowded term in the series of (2H)DOABO–CH_2O group containing **4a**, **4k** and **6e**.

Nevertheless, in the case of a more crowded compound than **10a**, (2Ph)DOABO–CH_2O groups trisubstituting the *s*-triazine **10b**, the results of the DNMR experiments had to be compared with those of **6l** possessing two *meta* related (2Ph)DOABO–CH_2O groups. Thus, **6l** presented but coalescence of the methylenes C-4(6)$^{(\prime)}$ at the limit of the temperature domain, 173 K (Tables 5 and 6, entry 5) preventing us to assign its rigid conformation. That is, pyrimidine **6l** behaved like simpler (2Ph)DOABO–CH_2OR (R=H, Et, Me) derivatives.[19,20] In contrast, the *s*-triazine **10b** reached coalescence at 233 K (Table 6, entry 6).[§] The corresponding $\Delta G^{\neq}$ value was, however, the smallest in the entire series under investigation, in agreement with our earlier results referring to the faster flipping aptitude of the structures (2Ph)DOABO against (2H)DOABO, for example, **1b**-*cis* against **1a**.[20]

Just below coalescence, the compounds **4k**, **6e**, **10a** and **10b** were established as frozen double or triple *local meso* (*P*,*M*) form DOABO conformers building *global meso* forms of type **I** (Scheme 8, **4k** and **6e**) and of type **VII** (Scheme 9, **10a**, **10b**). The isochronous aminalic or aliphatic homofacial protons, which were found enantiotopic (Table 5), motivate this conclusion.

2.2.2.2. Rotameric behaviour of the *c*-5$^{(\prime)}$-di(*s*-tri)-azinyloxymethyl sequence. In the case of compound **4a** only (Table 6, entry 1), for the calculation we had to use spectral values $\Delta\nu$ and ^2J not well below the coalescence[21,42] because a subsequent process occurred (Fig. 1). Besides the broadening of all signals, an unexpected multiplicity of those of methylenes C-4(6) appeared. The slow rotation of pyrazine ring about the C-2(pyrazine)–O bond might be responsible for generating two distinct populations of rotamers **4a XVIII** and **4a XIX** (Scheme 10).



Scheme 10.

[§] The *s*-triazines **10a** and **10b** were the two cases in which, at the limit of the temperature domain, 173 K, the non-equivalence between DOABO units was displayed but the spectral appearances were not appropriate for pertinent assignments.

This rotamerism could explain the observed splitting at C-4(6) as two partially overlapping AB systems. In addition, the resonance of the pyrazine proton H-3 was significantly shifted downfield from 8.20 (294 K) to 8.29 ppm (183 K) presumably because of its statistical coplanarity with one of the lone pairs of the exocyclic oxygen (rotamer **4a XIX**). We entitled this spatial arrangement s-*trans out* bisectional rotamer with reference to the orientation of the pyrazin-2-yloxymethyl fragment against the bicycle DOABO.

By decreasing the temperature (Table 5), deshielding of the diazine protons *ortho* to the CH_2O linkage in **4k**, **6e** and even in the still flipping **6l** was observed as well. If so, the same nearly coplanar s-*trans out* bisectional conformation could expose these protons to the deshielding proximity of one of the lone pairs of the oxygen atoms in the CH_2O connectivity as rotamers of types **XX** and **XXI**. Accordingly, at low temperature, as for **4a**, our conclusion designates diazines **4k**, **6e** and **6l** to be statistically also s-*trans out* bisectional rotamers.

2.2.3. Determining the stereochemistry in solid state by X-ray diffractometry. Compounds **4b**-*cis*, **4c**, **4k**, **6l** and **10b** supplied crystals suitable for study by X-ray diffractometry. Their crystallographically determined structures are depicted in Figures 2–6. The relevant bond angles and bond lengths are collected in Tables 7 and 8, respectively.

2.2.3.1. Local stereochemistry as frozen conformation and blocked rotamerism (Scheme 11, Table 7). Inspection of all ORTEP diagrams showed exclusively the chiral O-*syn*-O-*anti* opposite orientation of the two *cis* fused oxazolidine rings as *O*-envelope conformers. Indeed, the corresponding torsion angles are small enough, ranging between 0.19 and 7.2°. The torsion angles in the aminalic zone, used to assign the conformational chirality of the DOABO skeleton (Schemes 7 and 11), are noteworthy, 16.8–28.9° in O-3$^{(\prime)(\prime\prime)}$-*syn* rings and 21.3–28.0° in O-7$^{(\prime)(\prime\prime)}$-*anti* rings.

The torsion angles describing the rotamerism of the *c*-5$^{(\prime)(\prime\prime)}$-di(*s*-tri)azinyloxymethyl motif point to its almost coplanar, bisectional, s-*trans* and *out* arrangement with respect to the medium plane of the bicycle. The most significant deviations from coplanarity, 13–17°, are observed regarding the s-*trans* conformation of the bulky substituents about the bonds C-9$^{(\prime)(\prime\prime)}$–O-10$^{(\prime)(\prime\prime)}$. The rest of deviations are considerably smaller, 0.2–6.0°.

None of the above assignments was mandatory to the presence of phenyl groups linked in positions *pseudo*-equatorial-bisectional at C-2$^{(\prime)(\prime\prime)}$ and *pseudo*-axial-orthogonal at C-8$^{(\prime)(\prime\prime)}$.

2.2.3.2. Stereoelectronic effects creating local chirality (Scheme 11, Table 8). In the O-7$^{(\prime)(\prime\prime)}$-*anti* oxazolidine rings, the contraction of the bonds N-1$^{(\prime)(\prime\prime)}$–C-8$^{(\prime)(\prime\prime)}$ versus N-1$^{(\prime)(\prime\prime)}$–C-5$^{(\prime)(\prime\prime)}$ (selected as reference), found significant in all compounds, around 0.030 Å, has been recently explained by Pavia[25] and then by us[20] in terms of the hyperconjugative interaction (*endo*-anomeric effect)[25] involving the orbitals lpN-1$^{(\prime)(\prime\prime)}$ax. (donor)→σ*C-8$^{(\prime)(\prime\prime)}$–O-7$^{(\prime)(\prime\prime)}$ (acceptor). This stereoelectronic effect is due to their near antiperiplanar position created by the frozen oxazolidine

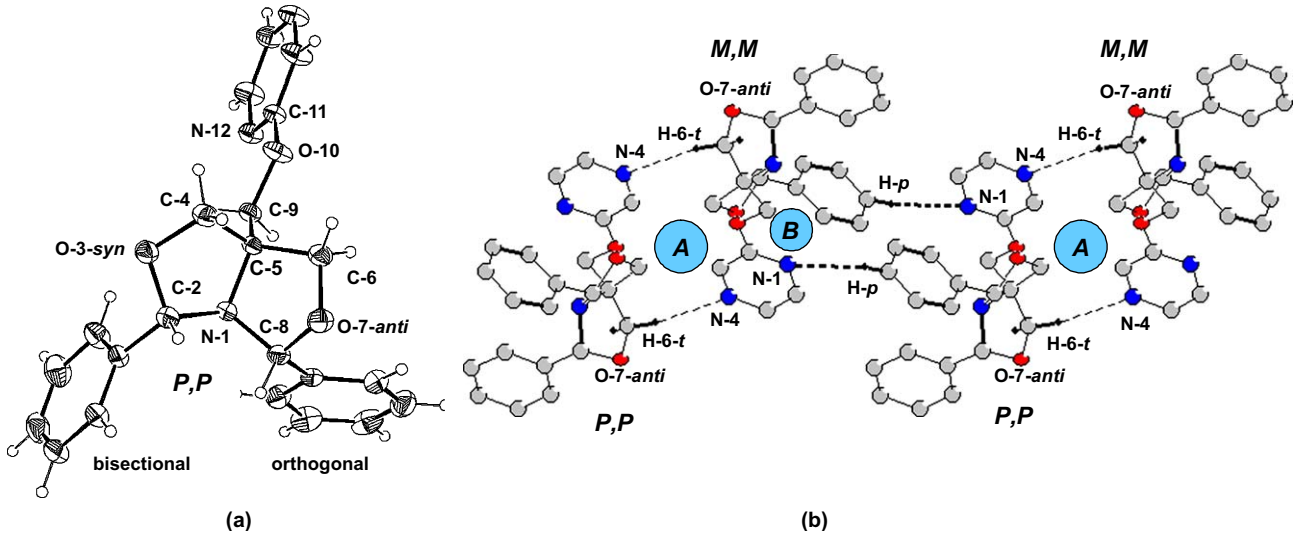


Figure 2. (a) The X-ray crystallographically determined structure of compound **4b**-*cis*; (b) the non-bonding interactions in the elementary cell.

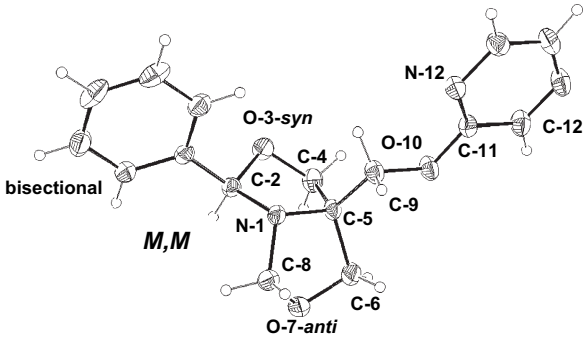


Figure 3. The X-ray crystallographically determined structure of compound **4c**.

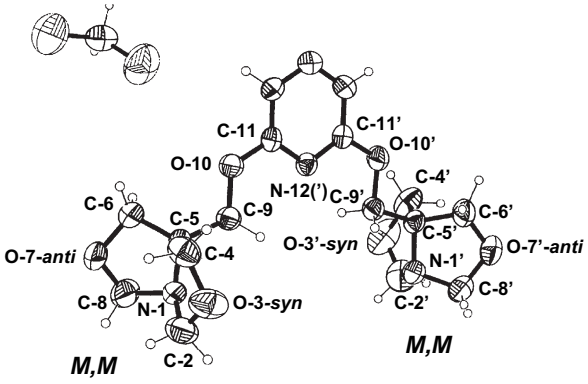
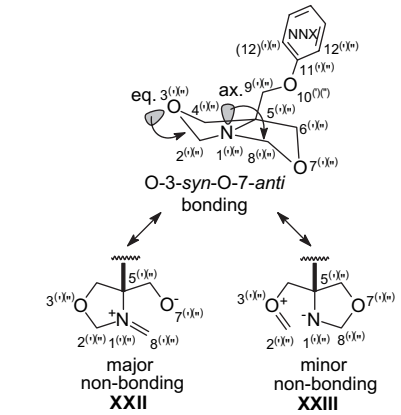


Figure 4. The X-ray crystallographically determined structure of compound *chiral* **4k**.

O-*anti*-envelope conformation. For example, in the case of compound **4k**, we lately estimated the energy of this delocalisation, $E_{del.}$=38.42 kJ/mol (NBO method).[20] The corresponding major non-bonding structure **XXII** suggests the increased basicity of the O-$7^{(\prime)(\prime\prime)}$-*anti* atom.

In the O-$3^{(\prime)(\prime\prime)}$-*syn* oxazolidine rings, a second noticeable contraction was detected this time regarding the bonds



Scheme 11.

O-$3^{(\prime)(\prime\prime)}$–C-$2^{(\prime)(\prime\prime)}$. They were shorter than O-$7^{(\prime)(\prime\prime)}$–C-$8^{(\prime)(\prime\prime)}$ with about 0.17 Å, covering however a larger domain of fluctuation, 0.05–0.050 Å. As above, this contraction originates in the O-*syn*-envelope geometry of the ring favouring the close to antiperiplanar arrangement of the orbitals lpO-$3^{(\prime)(\prime\prime)}$eq.→σ*C-$2^{(\prime)(\prime\prime)}$–N-$1^{(\prime)(\prime\prime)}$, hence the second as weaker delocalising interaction (e.g., E_{del}=30.93 kJ/mol in **4k**[20]). The matching minor non-bonding structures **XXIII** reveal a decreased basicity of the O-$3^{(\prime)(\prime\prime)}$-*syn* atom.

We concluded that the chirality of the DOABO skeleton was, in fact, the major consequence of the cross *endo*-anomeric effect, consisting in two and identically oriented delocalisation in the *syn–anti* aminalic part of the bicycle. The different basicity of the intracyclic oxygen atoms could be of practical interest, as already outlined in the literature in the case of the starting material **1b**-*cis*.[44,45]

2.2.3.3. Global stereochemistry and supramolecular interactions. In solid state, the essential characteristic of polysubstituted compounds **4k**, **6l** and **10b** was their crystallisation as *global chiral* forms. The same sense of chirality is exposed by the DOABO groups in duplicate (**4k**, **6l**), even in triplicate (**10b**) (Figs. 4–6).

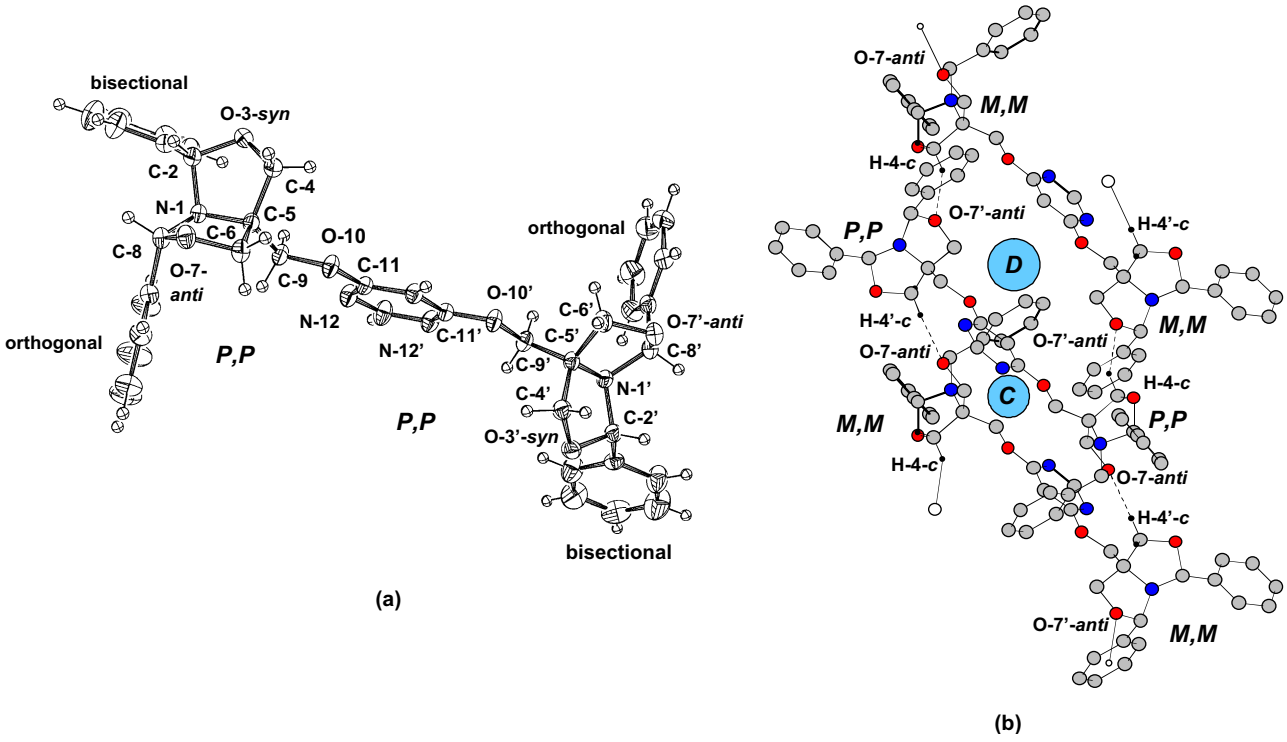


Figure 5. (a) The X-ray crystallographically determined structure of compound **6l**; (b) the non-bonding interactions in the network.

The network of **4k** consisted in *global chiral* form units of type **V** (Scheme 8) in a high occupation factor, 0.87 and *global meso* form units (not depicted, type **II**, Scheme 8) in a low occupation factor, 0.13. As shown in Figure 4, **4k** was a non-stoichiometric solvate of dichloromethane. The solvent, located in the channels of the network, had an occupation factor of 0.96. The dominant incidence of *global chiral* against *meso* form units appeared to us mandatory to the inclusion aptitude of *chiral* **4k**. Indeed, the alternative *meso* **4k** structure exhibited strong geometric distortions, discussed previously by us,[20] hence, lower inclusion ability. Moreover, the entire network was stable only in the presence of the solvent.

Stronger dichloromethane incorporating capacity manifested the network of the *s*-triazine **10b** (Fig. 6), found as triple chiral form of type **XV** (Scheme 9). It was ascertained to be a stable equimolar adduct with dichloromethane (omitted in Fig. 6 for the reason of simplicity).

Important non-bonding interactions were identified in the networks of compounds **4b**-*cis* and **6l**.

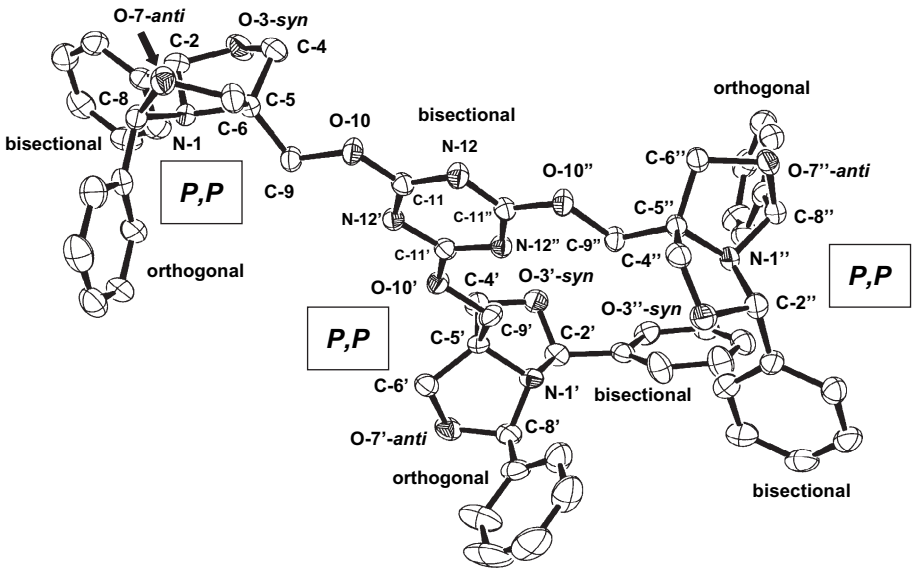


Figure 6. The X-ray crystallographically determined structure of compound **10b**.

Table 7. Relevant torsion angles (°) of compounds **4b**-*cis*, **4c**, **4k**, **6l** and **10b**

Torsion angles	Compound				
	4b-*cis*	**4c**	*chiral* **4k**[a]	**6l**	**10b**
Oxazolidines O-envelope conformation					
O-3$^{(r)(n)}$-syn rings					
C-4–C-5–N-1–C-2	+1.3(2)	−1.46(16)	−6.8(3)	−0.26(13)	−4.1(3)
C-4′–C-5′–N-1′–C-2′	—	—	−7.2(3)	−0.19(13)	+3.8(3)
C-4″–C-5″–N-1″–C-2″	—	—	—	—	+4.1(3)
O-7$^{(r)(n)}$-anti rings					
C-6–C-5–N-1–C-8	−1.6(2)	+1.17(18)	−2.8(3)	−4.07(13)	−4.5(3)
C-6′–C-5′–N-1′–C-8′	—	—	−3.8(3)	−2.54(14)	−1.6(3)
C-6″–C-5″–N-1″–C-8″	—	—	—	—	−0.9(3)
DOABO units conformational chirality					
O-3$^{(r)(n)}$-syn rings					
C-5–N-1–C-2–O-3	+23.3(2) *P*	−24.37(16) *M*	−18.6(3) *M*	+23.80(14) *P*	+28.9(3) *P*
C-5′–N-1′–C-2′–O-3′	—	—	−16.8(4) *M*	+24.09(14) *P*	+20.9(3) *P*
C-5″–N-1″–C-2″–O-3″	—	—	—	—	+22.3(3) *P*
O-7$^{(r)(n)}$-anti rings					
C-5–N-1–C-8–O-7	+24.0(2) *P*	−26.31(18) *M*	−21.6(4) *M*	+27.60(13) *P*	+28.0(3) *P*
C-5′–N-1′–C-8′–O-7′	—	—	−21.3(4) *M*	+26.24(13) *P*	+25.7(3) *P*
C-5″–N-1″–C-8″–O-7″	—	—	—	—	+24.8(3) *P*
Coplanarity of the c-5$^{(r)(n)}$-di(s-tri)azinyloxymethyl sequences					
N-1–C-5–C-9–O-10	−176.93(17)	+177.68(14)	+173.96(19)	−177.10(10)	−176.0(2)
N-1′–C-5′–C-9′–O-10′	—	—	174.78(19)	−175.54(11)	−176.9(2)
N-1″–C-5″–C-9″–O-10″	—	—	—	—	−174.2(2)
C-5–C-9–O-10–C-11	−172.91(19)	+167.01(15)	+178.57(19)	−168.55(11)	−163.9(3)
C-5′–C-9′–O-10′–C-11′	—	—	+178.2(2)	−163.21(11)	−173.4(3)
C-5″–C-9″–O-10″–C-11″	—	—	—	—	−179.3(3)
C-9–O-10–C-11–N-12	−3.3(3)	−2.5(2)	−6.1(3)	−4.77(19)	−178.0(3)
C-9′–O-10′–C-11′–N-12′	—	—	+3.2(3)	−2.82(19)	−176.7(3)
C-9″–O-10″–C-11″–N-12″	—	—	—	—	−0.2(4)

[a] For the *meso* form **4k** see text and Ref. 20.

The elementary cell of **4b**-*cis* was a tetramer (Fig. 2b), based on two different types of intermolecular interactions (**a**) and (**b**). The interatomic distances that we associated to these interactions are: (**a**) H-6-*t*(DOABO)···N-4(pyrazine) 2.550(3) Å and N-1(pyrazine)···H-*para*(C-2-*pseudo*-equatorial-bisectional phenyl ring) 2.636(2) Å. They are smaller than the corresponding sum of the van der Waals radii (ΣvdW N···H) 2.74 Å.[46] The interactions (**a**) close two

Table 8. Relevant bond lengths (Å) of compounds **4b**-*cis*, **4c**, **4k**, **6l** and **10b**

Compd	N-1–C-5	N-1–C-8		O-7–C-8	O-3–C-2	
	N-1′–C-5′	N-1′–C-8′		O-7′–C-8′	O-3′–C-2′	
	N-1″–C-5″	N-1″–C-8″		O-7″–C-8″	O-3″–C-2″	
	Length		Contraction[a]	Length		Contraction[b]
	O-7$^{(r)(n)}$-anti ring			*O-3$^{(r)(n)}$-syn ring*		
4b-*cis*	1.486(3)	1.460(3)	−0.026	1.425(3)	1.416(3)	−0.009
4c	1.491(2)	1.455(2)	−0.036	1.427(2)	1.416(2)	−0.011
chiral	1.493(3)	1.448(4)	−0.045	1.403(4)	1.398(4)	−0.005
4k[c]	1.480(3)	1.454(4)	−0.026	1.405(4)	1.355(5)	−0.050
6l	1.4890(17)	1.4579(18)	−0.0311	1.4411(18)	1.4227(17)	−0.0187
	1.4908(17)	1.4648(18)	−0.026	1.4391(17)	1.4172(17)	−0.0219
10b	1.483(4)	1.462(4)	−0.021	1.438(4)	1.421(4)	−0.017
	1.491(4)	1.465(4)	−0.026	1.437(5)	1.420(4)	−0.017
	1.486(4)	1.464(4)	−0.022	1.434(4)	1.427(4)	−0.007

[a] With respect to N-1$^{(r)(n)}$–C-5$^{(r)(n)}$.
[b] With respect to O-7$^{(r)(n)}$–C-8$^{(r)(n)}$.
[c] For the *meso* **4k** see text and Ref. 20.

identical cavities ***A***, meanwhile the interactions (**b**) lock the central cavity ***B***. Two **4b**-*cis* partners, having an opposite sense of chirality of the DOABO groups, are the building blocks of each cavity.

The network of compound **6l** was a polymeric structure (Fig. 5b) in which the non-bonding interactions between the **6l** units are of the same type H-4′-*c*···O-7-*anti* 2.464(1) Å and H-4-*c*···O-7′-*anti* 2.449(1) Å (ΣvdW O···H 2.60 Å).[46] Their magnitude is slightly different since the two DOABO groups in monomeric **6l** are geometrically not quite identical (Tables 7 and 8). Consequently, two cavities labelled ***C*** and ***D*** are observed, comprising each two **6l** units with a reverse sense of the *global chirality* one against the other.

3. Conclusions

Twenty-two examples demonstrate the Williamson procedure to be as general as simple methodology starting from *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octanes in reaction with α-chlorodiazines and cyanuryl chloride. The nucleophilicity of the DOABO–CH_2OH reagents in alkoxide form depends on the type of substituents at positions C-2, -8 of the bicycle and the cation against the π-deficiency of the substrates. A large variety of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-di(*s*-tri)azines is available in good yields and selectivity. The conformation analysis of some structures by X-ray diffractometry and ^{1}H DNMR indicates exclusively a chiral against *meso* form frozen conformation of the DOABO skeleton in solid state versus solution, respectively. The cross *endo*-anomeric effect in the aminalic O–C–N–C–O DOABO sequence is responsible for the chiral conformation in solid state. The rotamerism of the *c*-5-di(*s*-tri)azinyloxymethyl group against bicycle is bisectional and s-*trans out* oriented both in solution and solid state. In solid state, an inclusion aptitude of the solvent by the chiral networks is found as well as non-bonding interaction creating specific self-assembly.

The attempt at exploiting these findings in synthesis will be discussed in part II of our report.

4. Experimental

Melting points are uncorrected; they were carried out on a ELECTROTHERMAL® 9100 apparatus.

Current NMR spectra were recorded on a Brucker® AM300 (300 MHz ^{1}H, 75 MHz ^{13}C) instrument. The NMR analysis of the compounds **6b** and **6h** was also carried out on a Brucker® DMX500 (500 MHz ^{1}H, 125 MHz ^{13}C) instrument. ^{1}H DNMR analysis of compounds **4a**, **4k**, **6e**, **6l**, **10a** and **10b** was carried out on a Brucker® AM400 (400 MHz ^{1}H, 100 MHz ^{13}C) instrument. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on silica gel Si 60 (40–63 μm, Merck®). IR spectra were performed on a Perkin–Elmer® Paragom FTIR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or strong (s)]. Mass spectra (MS) were recorded on an ATI-Unicam Automass® apparatus, fitted (or not) with a GC-mass coupling. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. All syntheses were performed under dry nitrogen atmosphere. THF was freshly distilled from Na/benzophenone prior to use. All other solvents and starting materials were of commercial quality.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC: compound **4b**-*cis* CCDC 283623. Unit cell parameters: *a* 13.0640(11), *b* 8.8414(7), *c* 17.2561(14); space group *P*1 21/*c* 1(14). Compound **4c** CCDC 283622. Unit cell parameters: *a* 5.9105(11), *b* 18.196(3), *c* 14.199(3); space group *P*2(1)/*n*. Compound **4k** CCDC 199978. Unit cell parameters: *a* 12.251, *b* 11.072, *c* 15.243; space group *P*2(1)/*n*. Compound **6l** CCDC 238894. Unit cell parameters: *a* 27.3536(3), *b* 11.8334, *c* 23.7369(3); space group *C*2/*c*. Compound **10b** CCDC 272371. Unit cell parameters: *a* 8.9574(2), *b* 12.2323(2), *c* 24.6520(4); space group *P*-1. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

The synthesis of compounds **1a–e** and **4k** we discussed elsewhere.[19,20]

4.1. General procedure for the preparation of compounds 4a–j, 6a–m and 8a–c

In a 100 mL three-necked round bottom flask, potassium hydride (1.000 g as 30% oily suspension, 0.300 g 100%, 7.48 mmol) was rapidly introduced and washed with stirring three times with dry ligroin (optionally pentane, hexane) (30 mL). THF (50 mL) was then introduced with stirring to yield a fine grey suspension. Fine powdered *c*-5-hydroxymethyl-3,7-dioxa-1-azabicyclo[3.3.0]-*c*-5-octanes **1a–e** (7.12 mmol, Scheme 2) was added and the mixture was heated at 40 °C for 1.0–1.5 h (room temperature in the case of **1e**) until no more hydrogen was formed and a fine suspension was obtained. For the synthesis attempting at complete substitution of chlorine [compounds **4a**, **4b**-*cis*, **4b**-*trans*, **4c**, **4d**-*trans*, **4d**-*cis*, **4e**, **4j** (Table 1), **6a**, **6b**, **6e**, **6g**, **6k**, **6l** (Table 2), **8b**, **8c** (Table 3)] the corresponding α-chlorodiazine (6.78/*n* mmol, *n*=number of chlorine atoms to be replaced) was rapidly injected as THF (10 mL) solution, at room temperature (see Tables 1–3 for temperatures and time reaction). For selective substitution of chlorine, in the case of compounds **6c**, **6f** and **6h** the reaction mixture was cooled to −78 °C prior to the addition by injection of the corresponding stoichiometric amount of α-chloropyrimidine as THF (10 mL) solution. Then, it was allowed to slowly reach room temperature. For selective substitution of chlorine in the case of compounds **4f** and **8a**, stoichiometric amounts of α-chlorodiazine were used (conditions as temperature and time reaction are given in Tables 1 and 3). TLC monitoring was performed until the starting materials were absent or in small traces only. Double visualisation was required if **2a** was the nucleophile (Scheme 2): first UV 254 nm then I_2 bath, for the detection of **1a**. During condensation, the reaction mixture turned coloured and

potassium chloride was formed. The reaction was quenched at room temperature with water (100 mL) and dichloromethane (100 mL) with vigorous stirring. After separation, the organic layer was washed with water (about 3×50 mL) to pH=7.5–8.0 then dried over $MgSO_4$. After filtering, the organic solution was evaporated under vacuum to dryness to yield the crude product, which was directly crystallised from an appropriate solvent or purified by flash column chromatography to yield the title compounds.

4.1.1. 2-[(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)-methoxy]-pyrazine (4a). Yield 85%. Yellowish crystalline powder, mp 128–129 °C (pentane) [Found: C, 53.50; H, 6.09; N, 18.55. $C_{10}H_{13}N_3O_3$ requires: C, 53.81; H, 5.87; N, 18.82%]. R_f (75% ligroin/acetone) 0.40. ν_{max} (film NaCl) 2868 (m), 1524 (s), 1465 (m), 1413 (s), 1361 (m), 1289 (s), 1134 (m), 1032 (s), 1002 (s), 915 (s), 832 (m), 692 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.19 (1H, d, *J*=1.5 Hz, H-3), 8.09 (1H, d, *J*=3.0 Hz, H-5), 8.01 (1H, dd, *J*=3.0, 1.5 Hz, H-6); *DOABO–CH₂O*: 4.47 (2H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.41 (2H, d, *J*=5.7 Hz, H-2, -8-*t*), 4.33 (2H, s, 5-OCH_2), 3.83 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 160.1 (1C, C-2), 140.9 (1C, C-6), 137.5 (1C, C-3), 136.1 (1C, C-5); *DOABO–CH₂O*: 88.6 (2C, C-2, -8), 74.4 (2C, C-4, -6), 71.9 (1C, C-5), 69.0 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): 223 (6), 178 (14), 163 (13), 114 (100), 98 (17), 86 (9), 68 (26), 58 (11), 42 (18), 41 (59).

4.1.2. 2-[(*c*-2,*c*-8-Diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4b-*cis*). Yield 79%. Yellowish crystalline powder, mp 134–136 °C (flash column chromatography, eluent ligroin/AcOEt 3:1 v/v) [Found: C, 70.17; H, 5.94; N, 10.95. $C_{22}H_{21}N_3O_3$ requires C, 70.38; H, 5.64; N, 11.19%]. R_f (75% ligroin/AcOEt) 0.56. ν_{max} (film KBr) 2877 (s), 1586 (m), 1540 (s), 1418 (s), 1388 (m), 1312 (s), 1135 (s), 1065 (s), 932 (s), 834 (s), 800 (m), 763 (s), 738 (s), 696 (s), 617 (m), 537 (m), 499 (w), 465 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.09 (1H, d, *J*=2.6 Hz, H-5), 8.04 (1H, s, H-3), 8.01 (1H, dd, *J*=2.6, 1.3 Hz, H-6), 7.52 (4H, d, *J*=6.0 Hz, Ph), 7.36–7.30 (6H, m, Ph); *DOABO–CH₂O*: 5.61 (2H, s, H-2, -8-*t*), 4.27 (2H, s, 5-OCH_2), 4.10 (2H, d, *J*=9.0 Hz, H-4, -6-*c*), 4.00 (2H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 160.1 (1C, C-2), 140.8 (1C, C-6), 139.7 (2C, Cq., Ph), 137.4 (1C, C-3), 136.1 (1C, C-5), 129.0 (2C, CH, Ph), 128.7 (4C, CH, Ph), 127.6 (4C, CH, Ph); *DOABO–CH₂O*: 97.8 (2C, C-2, -8), 73.6 (2C, C-4, -6), 73.3 (1C, C-5), 70.2 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^+) 375 (<1), 269 (30), 173 (100), 155 (33), 128 (21).

4.1.3. 2-[(*c*-2,*t*-8-Diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4b-*trans*). Yield 69%. Yellowish crystalline powder, mp 144–145 °C (pentane) [Found: C, 70.17; H, 5.94; N, 10.95. $C_{22}H_{21}N_3O_3$ requires C, 70.38; H, 5.64; N, 11.19%]. R_f (75% ligroin/AcOEt) 0.75. ν_{max} (film KBr) 2859 (m), 1579 (m), 1528 (s), 1412 (s), 1309 (s), 1291 (s), 1265 (m), 1090 (s), 1060 (s), 1038 (m), 1028 (w), 839 (m), 760 (s), 731 (s) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.48, 8.40, 8.34 (3H, s, H-3, -5, -6), 7.59–7.52 (2H, m, Ph), 7.48–7.33 (6H, m, Ph), 7.27–7.24 (2H, m, Ph); *DOABO–CH₂O*: 5.86 (1H, s, H-8-*c*), 5.49 (1H, s, H-2-*t*), 4.80 (1H, d, *J*=11.1 Hz, 5-OCH_2), 4.76 (1H, d, *J*=11.1 Hz, 5-OCH_2), 4.52 (1H, d, *J*=9.0 Hz, H-4-*c*), 4.48 (1H, d, *J*=9.0 Hz, H-6-*c*), 4.15 (2H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 160.1 (1C, C-2), 141.0 (1C, C-6), 140.2 (1C, Cq., Ph), 137.5 (1C, C-3), 136.2 (1C, C-5), 134.5 (1C, Cq., Ph), 128.9 (1C, CH, Ph), 128.5 (1C, CH, Ph), 128.4 (2C, CH, Ph), 128.1 (2C, CH, Ph), 127.6 (2C, CH, Ph), 127.5 (2C, CH, Ph); *DOABO–CH₂O*: 94.7, 93.6 (2C, C-2, -8), 75.3, 73.6 (2C, C-4, -6), 72.9 (1C, C-5), 69.9 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^+) 375 (<1), 266 (100), 239 (40), 192 (5), 177 (10), 160 (30), 105 (50), 77 (45), 51 (20).

4.1.4. 2-[(*c*-2-Phenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4c). Yield 48%. White crystalline powder, mp 79–81 °C (flash column chromatography, eluent ligroin/AcOEt 2:1 v/v) [Found: C, 63.91; H, 6.02; N, 13.74. $C_{16}H_{17}N_3O_3$ requires C, 64.20; H, 5.72; N, 14.04%]. R_f (67% ligroin/AcOEt) 0.58. ν_{max} (film KBr) 3065 (m), 2860 (m), 1834 (w), 1580 (m), 1531 (s), 1471 (m), 1413 (s), 1305 (m), 1174 (m), 1106 (s), 1034 (m), 909 (s), 856 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.22 (1H, d, *J*=1.3 Hz, H-3), 8.14 (1H, d, *J*=2.6 Hz, H-5), 8.07 (1H, dd, *J*=2.6, 1.3 Hz, H-6), 7.52–7.49 (2H, m, Ph), 7.39–7.34 (3H, m, Ph); *DOABO–CH₂O*: 5.24 (1H, s, H-2-*t*), 4.57 (1H, d, *J*=7.0 Hz, H-8-*c*), 4.50 (1H, d, *J*=10.0 Hz, 5-OCH_2), 4.40 (1H, d, *J*=8.9 Hz, H-4-*c*), 4.37 (1H, d, *J*=10.0 Hz, 5-OCH_2), 4.30 (1H, d, *J*=7.0 Hz, H-8-*t*), 4.06 (1H, d, *J*=9.0 Hz, H-6-*c*), 3.83 (1H, d, *J*=8.9 Hz, H-4-*t*), 3.70 (1H, d, *J*=9.0, H-6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 160.2 (1C, C-2), 140.9 (1C, C-6), 139.5 (1C, Cq., Ph), 137.5 (1C, C-3), 136.2 (1C, C-5), 129.5 (1C, CH, Ph), 128.8 (2C, CH, Ph), 127.8 (2C, CH, Ph); *DOABO–CH₂O*: 99.2 (1C, C-2), 88.2 (1C, C-8), 75.4 (1C, C-4), 73.6 (1C, C-6), 72.5 (1C, C-5), 69.7 (1C, 5-OCH_2). MS (ES^+); *m/z* (rel int. %): (M^++1) 300 (39), 223 (2), 204 (100), 194 (36).

4.1.5. 2-{[2-(*t*-4-*tert*-Butylspirocyclohexyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl]methoxy}-pyrazine (4d-*trans*) (46%) and 2-{[2-(*c*-4-*tert*-butylspirocyclohexyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl]methoxy}-pyrazine (4d-*cis*). Yield 16%. Non-separable two-component mixture (**4d**-*trans*/**4d**-*cis* 75:25) as yellow crystalline powder, mp 103–105 °C (ligroin) [Found: C, 65.79; H, 8.19; N, 11.85. $C_{19}H_{29}N_3O_3$ requires: C, 65.68; H, 8.41; N, 12.09%]. R_f (75% ligroin/acetone) 0.60. ν_{max} (film NaCl) 2940 (s), 2857 (m), 1529 (s), 1465 (m), 1408 (s), 1284 (s), 1080 (w), 1005 (m), 909 (w) cm^{-1}. Diastereomer **4d**-*trans*: δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.21 (1H, s, H-3), 8.11 (1H, d, *J*=3.0 Hz, H-5), 8.03 (1H, d, *J*=2.6 Hz, H-6); *DOABO–CH₂O*: 4.79 (1H, d, *J*=7.5 Hz, H-8-*c*), 4.42 (1H, d, *J*=10.6 Hz, 5-OCH_2), 4.29 (1H, d, *J*=10.6 Hz, 5-OCH_2), 4.15 (1H, d, *J*=7.5 Hz, H-8-*t*), 4.04 (1H, d, *J*=9.2 Hz, H-4-*c*), 3.86 (1H, d, *J*=9.2 Hz, H-4-*t*), 3.77 (1H, d, *J*=8.7 Hz, H-6-*c*), 3.65 (1H, d, *J*=8.7 Hz, H-6-*t*); 1.97–1.79 (2H, m, spirocyclohexyl), 1.77–1.67 (1H, m, spirocyclohexyl), 1.60–1.45 (2H, m, spirocyclohexyl), 1.44–1.15 (3H, m, spirocyclohexyl), 1.03–0.89 (1H, m, spirocyclohexyl), 0.81 [9H, s, $C(CH_3)_3$]; δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 160.3 (1C, C-2), 140.8 (1C, C-6), 137.4 (1C, C-3), 136.2 (1C, C-5); *DOABO–CH₂O*: 98.1 (1C, C-2), 82.0 (1C, C-8), 73.8 (1C, C-6), 72.0 (1C, C-5),

71.6 (1C, C-4), 69.7 (1C, 5-OCH_2), 47.5 (1C, CH, spirocyclohexyl), 38.5, 32.7, 32.2, 24.7 (4C, CH_2, spirocyclohexyl), 28.0 [3C, C(CH_3)$_3$], 24.5 [1C, $C(CH_3)_3$]. Diastereomer **4d**-*cis*: δ_H (300 MHz $CDCl_3$ only distinct peaks are listed) *heteroaromatic*: 8.09 (1H, s, H-5), 8.01 (1H, s, H-6); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 136.3 (1C, C-5); *DOABO–CH_2O*: 96.2 (1C, C-2), 68.4 (1C, 5-OCH_2), 47.3 (1C, CH, spirocyclohexyl), 37.8 (1C, CH_2, spirocyclohexyl). MS (EI, 70 eV); *m*/*z* (rel int. %): (M^+) 348 (50), 334 (11), 318 (27), 292 (13), 252 (100), 234 (15), 222 (35), 194 (50), 165 (7), 152 (9), 98 (70).

4.1.6. 2-{[*c*-2,*c*-8-Bis(pyridin-2-yl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl]methoxy}-pyrazine (4e). Yield 44%. Yellow crystalline powder, mp 89–90 °C (pentane) [Found: C, 63.44; H, 5.17; N, 18.26. $C_{20}H_{19}N_5O_3$ requires C, 63.65; H, 5.07; N, 18.56%]. R_f (100% acetone) 0.65. ν_{max} (film KBr) 3058 (m), 2863 (m), 15890 (s), 1534 (s), 1441 (m), 1414 (s), 1298 (s), 1129 (s), 1081 (s), 992 (s), 924 (m), 841 (m), 781 (s), 709 (m), 659 (m), 622 (m), 608 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.56 (2H, d, *J*=4.2 Hz, H-6, Py), 8.09 (1H, d, *J*=1.9 Hz, H-5, pyrazine), 8.05 (1H, s, H-3, pyrazine), 8.00 (1H, s, H-6, pyrazine), 7.65 (2H, dd as t, *J*=7.5, 7.5 Hz, H-4, Py), 7.54 (2H, d, *J*=7.9 Hz, H-3, Py), 7.20 (2H, dd as t, *J*=5.7, 6.0 Hz, H-5, Py); *DOABO–CH_2O*: 5.79 (2H, s, H-2, -8-*t*), 4.31 (2H, s, 5-OCH_2), 4.25 (2H, d, *J*=9.0 Hz, H-4, -6-*c*), 4.07 (2H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 160.1 (1C, C-2, pyrazine), 159.2 (2C, C-2, Py), 149.6 (2C, C-6, Py), 140.8 (1C, C-6, pyrazine), 137.4 (1C, C-3, pyrazine), 137.0 (2C, C-4 Py), 136.1 (1C, C-5, pyrazine), 123.6 (2C, C-5, Py), 121.7 (2C, C-3, Py); *DOABO–CH_2O*: 98.4 (2C, C-2, -8), 73.5 (1C, C-5), 73.4 (2C, C-4, -6), 69.8 (1C, 5-OCH_2). MS (EI, 70 eV); *m*/*z* (rel int. %): (M^++1) 378 (62), 282 (83), 272 (19), 252 (18), 214 (13), 175 (100), 165 (23), 159 (42), 145 (37).

4.1.7. 2-Chloro-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4f). Yield 83%. Pale yellowish crystalline powder, mp 88–89 °C (flash column chromatography; eluent ligroin/acetone 3.5:1 v/v) [Found: C, 46.88; H, 4.51; N, 16.50. $C_{10}H_{12}N_3O_3Cl$ requires: C, 46.61; H, 4.69; N, 16.31%]. R_f (78% ligroin/acetone) 0.45. ν_{max} (film NaCl) 2857 (w), 2366 (w), 1563 (m), 1525 (s), 1409 (s), 1364 (m), 1309 (s), 1177 (s), 1093 (w), 1000 (m), 928 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.13 (1H, s, H-5), 8.11 (1H, s, H-3); *DOABO–CH_2O*: 4.48 (2H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.42 (2H, d, *J*=5.7 Hz, H-2, -8-*t*), 4.35 (2H, s, 5-OCH_2), 3.83 (4H, s, H-4, -6-*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 159.1 (1C, C-6), 145.7 (1C, C-2), 136.3 (1C, C-3), 133.3 (1C, C-5); *DOABO–CH_2O*: 88.6 (2C, C-2, -8), 74.3 (2C, C-4, -6), 71.8 (1C, C-5), 69.8 (1C, 5-OCH_2). MS (EI, 70 eV); *m*/*z* (rel int. %): (M^+) 257 (<1), 212 (6), 197 (10), 192 (4), 169 (4), 128 (6), 114 (100), 98 (20), 86 (10), 68 (24), 58 (9), 41 (52).

4.1.8. 2-Chloro-6-[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4g). White crystalline powder (as 34% conversion of **3b**, Table 1, entry 8), mp 128–129 °C (flash column chromatography, eluent ligroin/AcOEt 2:1 v/v) [Found: C, 64.59; H, 4.60; N, 10.51. $C_{22}H_{20}N_3O_3Cl$ requires: C, 64.47; H, 4.92; N, 10.25%]. R_f (67% ligroin/AcOEt) 0.35. ν_{max} (film KBr) 3060 (m), 2990 (m), 2878 (s), 1568 (s), 1528 (s), 1435 (s), 1409 (s), 1309 (s), 1209 (s), 1179 (s), 1131 (s), 1091 (s), 1064 (s), 1006 (s), 949 (m), 923 (s), 961 (s), 762 (s), 736 (s), 697 (s), 637 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)-aromatic*: 8.14 (1H, s, H-5), 7.89 (1H, s, H-3), 7.54–7.52 (4H, m, Ph), 7.40–7.31 (6H, m, Ph); *DOABO–CH_2O*: 5.63 (2H, s, H-2, -8-*t*), 4.30 (2H, s, 5-OCH_2), 4.10 (2H, d, *J*=9.0 Hz, H-4, -6-*c*), 4.00 (2H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 159.0 (1C, C-6), 145.7 (1C, C-2), 139.5 (2C, Cq., Ph), 136.1 (1C, C-3), 133.3 (1C, C-5), 129.0 (2C, CH, Ph), 128.8 (4C, CH, Ph), 127.5 (4C, CH, Ph); *DOABO–CH_2O*: 97.9 (2C, C-2, -8), 73.4 (2C, C-4, -6), 73.2 (1C, C-5), 70.6 (1C, 5-OCH_2). MS (EI, 70 eV); *m*/*z* (rel int. %): (M^+-1) 408 (<1), 267 (22), 266 (100), 160 (10), 105 (28).

4.1.9. 6-[(*c*-2,*c*-8-Diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-1*H*-pyrazin-2-one (4h). White crystalline powder (as 17% conversion of **3b**, Table 1, entry 8), mp 199–201 °C (flash column chromatography, eluent ligroin/AcOEt 1:1 v/v [Found: C, 67.42; H, 5.63; N, 10.46. $C_{22}H_{21}N_3O_4$ requires: C, 67.51; H, 5.41; N, 10.74%]. R_f (50% ligroin/AcOEt) 0.60. ν_{max} (film KBr) 3062 (m), 2978 (m), 2877 (s), 2442 (s), 1822 (s), 1612 (s), 1537 (s), 1449 (s), 1376 (s), 1315 (s), 1269 (s), 1188 (s), 1135 (s), 1091 (s), 921 (s), 836 (s), 757 (s), 732 (s), 695 (s) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 7.77 (1H, s, H-5), 7.62 (1H, s, H-3), 7.52–7.50 (4H, m, Ph), 7.36–7.27 (6H, m, Ph), 7.03 (1H, br s, NH); *DOABO–CH_2O*: 5.60 (2H, s, H-2, -8-*t*), 4.17 (2H, s, 5-OCH_2), 4.08 (2H, d, *J*=9.0 Hz, H-4, -6-*c*), 3.98 (2H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 158.1 (1C, C-2), 157.0 (1C, C-6), 139.6 (2C, Cq., Ph), 129.1 (2C, CH., Ph), 128.8 (4C, CH., Ph), 127.6 (4C, CH., Ph), 125.3 (1C, C-3), 124.2 (1C, C-5); *DOABO–CH_2*: 97.7 (2C, C-2, -8), 73.6 (2C, C-4, -6), 73.2 (1C, C-5), 70.5 (1C, 5-OCH_2); MS (EI, 70 eV); *m*/*z* (rel int. %): (M^+) 391 (<5), 285 (50), 179 (15), 174 (100), 155 (13), 128 (17).

4.1.10. 2,6-Bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4i). White crystalline powder (as 8% conversion of **3b**); this compound was isolated only as a non-separable mixture (38%) with **4h** (62%) during the work-up by flash column chromatography of the reaction between **3b** and **2b**-*cis* (Table 1, entry 8). δ_H (300 MHz $CDCl_3$) only distinct peaks are listed as *DOABO–CH_2O*: 5.63 (4H, s, H-2, -8-*t*), 4.15 (4H, s, 5-, 5′-OCH_2), 4.07 (4H, d, *J*=9.1 Hz, H-4, -4′, -6, -6′-*c*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 139.7 (4C, Cq., Ph), 125.0 (2C, C-3, -5); *DOABO–CH_2O*: 73.2 (4C, C-4, -4′ -6, -6′). MS (EI, 70 eV); *m*/*z* (rel int. %): (M^+) 670 (<1).

4.1.11. 6-Methoxy-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4j). Yield 33%. White crystalline powder, mp 99–100 °C (flash column chromatography, eluent ligroin/acetone 3.5:1 v/v) [Found: C, 52.30; H, 6.09; N, 16.76. $C_{11}H_{15}N_3O_4$ requires: C, 52.17; H, 5.97; N, 16.59%]. R_f (78% ligroin/acetone) 0.76. ν_{max} (film KBr) 3076 (w), 2859 (m), 1590 (m), 1540 (s), 1414 (s), 13223 (s), 1270 (s), 1182 (s), 1034 (s), 941 (s), 843 (s), 720 (w), 679 (s), 623 (w), 489 (m), 458 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 7.78, 7.75 (2H, s, H-3, -5); *DOABO–CH_2O*: 4.50 (2H, d, *J*=5.5 Hz, H-2, -8-*c*),

4.44 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.33 (2H, s, 5-OCH_2), 3.90 (3H, s, –OCH_3), 3.87 (4H, s, H-4, -6-*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 159.2, 158.4 (2C, C-2, -6), 125.8, 124.9 (2C, C-3, -5); *DOABO–CH_2O*: 88.5 (2C, C-2, -8), 74.6 (2C, C-4, -6), 71.9 (1C, C-5), 69.2 (1C, 5-OCH_2), 54.0 (1C, –OCH_3). MS (EI, 70 eV); *m/z* (rel int. %): (M^+) 253 (<1), 127 (100), 97 (18).

4.1.12. 2-[(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)-methoxy]-pyrimidine (6a). Yield 60%. White crystalline powder, mp 107–109 °C (pentane) [Found: C, 53.59; H, 5.61; N, 19.13. $C_{10}H_{13}N_3O_3$ requires: C, 53.80; H, 5.87; N, 18.82%]. R_f (75% ligroin/acetone) 0.40. ν_{max} (film NaCl) 2858 (w), 1569 (s), 1431 (s), 1332 (s), 1300 (m), 1137 (w), 1021 (s), 925 (m), 814 (w), 682 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.44 (2H, d, *J*=4.9 Hz, H-4, -6), 6.90 (1H, dd as t, *J*=4.9, 4.9 Hz, H-5); *DOABO–CH_2O*: 4.45 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.38 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.35 (2H, s, 5-OCH_2), 3.87 (2H, d, *J*=9.4 Hz, H-4, -6-*c*), 3.84 (2H, d, *J*=9.4 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 165.2 (1C, C-2), 159.7 (2C, C-4, -6), 115.8 (1C, C-5); *DOABO–CH_2O*: 88.5 (2C, C-2, -8), 74.7 (2C, C-4, -6), 71.7 (1C, C-5), 70.6 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^+-1) 222 (10), 206 (12), 176 (14), 148 (8), 128 (100), 109 (16), 98 (11).

4.1.13. 2,4-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6b). Yield 80%. White crystalline powder, mp 136–137 °C (pentane) [Found: C, 52.61; H, 6.01; N, 15.58. $C_{16}H_{22}N_4O_6$ requires: C, 52.45; H, 6.05; N, 15.29%]. R_f (75% ligroin/acetone) 0.20. ν_{max} (film NaCl) 2590 (w), 2863 (w), 1585 (s), 1449 (m), 1416 (s), 1336 (m), 1274 (m), 1181 (w), 1098 (s), 1021 (m), 928 (m), 749 (w) cm^{-1}. δ_H (500 MHz benzene-d_6) *heteroaromatic*: 8.05 (1H, d, *J*=6.0 Hz, H-6), 6.15 (1H, d, *J*=6.0 Hz, H-5); *DOABO–CH_2O linked at C-2*: 4.40 (2H, s, 5-OCH_2), 4.30 (2H, d, *J*=5.3 Hz, H-2, -8-*c*), 4.05 (2H, d, *J*=5.3 Hz, H-2, -8-*t*), 3.77 (2H, d, *J*=8.7 Hz, H-4, -6-*c*), 3.64 (2H, d, *J*=8.7 Hz, H-4, -6-*t*); *DOABO–CH_2O linked at C-4*: 4.23 (2H, d, *J*=5.3 Hz, H-2, -8-*c*), 4.21 (2H, s, 5-OCH_2), 4.04 (2H, d, *J*=5.3 Hz, H-2, -8-*t*), 3.56 (2H, d, *J*=8.9 Hz, H-4, -6-*c*), 3.51 (2H, d, *J*=8.9 Hz, H-4, -6-*t*); δ_C (125 MHz benzene-d_6) *heteroaromatic*: 171.1 (1C, C-4), 165.5 (1C, C-2), 158.9 (1C, C-6), 102.3 (1C, C-5); *DOABO–CH_2O linked at C-2*: 88.1 (2C, C-2, -8), 74.3 (2C, C-4, -6), 72.7 (1C, C-5), 70.7 (1C, 5-OCH_2); *DOABO–CH_2O linked at C-4*: 88.2 (2C, C-2, -8), 73.9 (2C, C-4, -6), 71.5 (1C, C-5), 69.2. (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): 366 (<1), 238 (6), 208 (6), 128 (68), 114 (100), 98 (14), 68 (27), 42 (32), 41 (60).

4.1.14. 2-Chloro-4-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6c). Yield 63%. White crystalline powder, mp 139–140 °C (dichloromethane/pentane 1:2 v/v) [Found: C, 46.80; H, 4.81; N, 16.65. $C_{10}H_{12}N_3O_3Cl$ requires: C, 46.61; H, 4.69; N, 16.31%]. R_f (75% ligroin/acetone) 0.50. ν_{max} (film NaCl) 2857 (w), 1636 (s), 1582 (s), 1545 (m), 1446 (m), 1327 (s), 1230 (m), 1102 (w), 1017 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.30 (1H, d, *J*=5.7 Hz, H-6), 6.67 (1H, d, *J*=5.7 Hz, H-5); *DOABO–CH_2O*: 4.47 (2H, d, *J*=5.3 Hz, H-2, -8-*c*), 4.42 (2H, d, *J*=5.3 Hz, H-2, -8-*t*), 4.40 (2H, s, 5-OCH_2), 3.81 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 170.4 (1C, C-4), 160.6 (1C, C-2), 159.5 (1C, C-6), 107.4 (1C, C-5); *DOABO–CH_2O*: 88.6 (2C, C-2, -8), 74.2 (2C, C-4, -6), 71.7 (1C, C-5), 69.9 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): 257 (<1), 212 (9), 197 (12), 169 (11), 114 (100), 86 (10), 68 (14), 58 (11), 42 (16), 41 (50).

4.1.15. 4-Chloro-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6d). Yield 23%. This compound was identified as side product in the synthesis of the compound **6c** (Table 2). Its identity was established according to NMR spectra performed on the crude reaction mixture together with the residue of the column chromatography (**6c+6d**) after isolation of the pure **6c**. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.36 (1H, d, *J*=5.3 Hz, H-6), 7.00 (1H, d, *J*=5.3 Hz, H-5); *DOABO–CH_2O*: 4.49 (2H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.44 (2H, d, *J*=5.7 Hz, H-2, -8-*t*), 4.40 (2H, s, 5-OCH_2), 3.88 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 165.0 (1C, C-2), 163.0 (1C, C-4), 160.4 (1C, C-6), 115.9 (1C, C-5); *DOABO–CH_2O*: 88.6 (2C, C-2, -8), 74.6 (2C, C-4, -6), 71.6 (1C, C-5), 71.2 (1C, 5-OCH_2).

4.1.16. 4,6-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6e). Yield 81%. White crystalline powder, mp 146–148 °C (pentane) [Found: C, 52.70; H, 5.88; N, 14.98. $C_{16}H_{22}N_4O_6$ requires: C, 52.45; H, 6.05; N, 15.29%]. R_f (75% ligroin/acetone) 0.35. ν_{max} (film NaCl) 2950 (w), 2858 (m), 1593 (s), 1563 (s), 1457 (m), 1421 (m), 1341 (m), 1195 (m), 1137 (m), 1095 (m), 1039 (s), 933 (m), 674 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.38 (1H, s, H-2), 6.08 (1H, s, H-5); *DOABO–CH_2O*: 4.49 (4H, d, *J*=5.7 Hz, H-2, -2′, -8, -8′-*c*), 4.44 (4H, d, *J*=5.7 Hz, H-2, -2′, -8, -8′-*t*), 4.38 (4H, s, 5-, 5′-OCH_2), 3.84 (8H, s, H-4, -4′, -6, -6′, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 171.0 (2C, C-4, -6), 157.8 (1C, C-2), 91.4 (1C, C-5); *DOABO–CH_2O*: 88.6 (4C, C-2, -2′, -8, -8′), 74.4 (4C, C-4, -4′, -6, -6′), 71.9 (2C, C-5, -5′), 69.4 (2C, 5-, 5′-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^++1) 367 (<1), 274 (3), 252 (2), 168 (8), 128 (100), 98 (4).

4.1.17. 4-Chloro-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6f). Yield 63%. White crystalline powder, mp 118–119 °C (flash column chromatography, eluent ligroin/acetone 3:1 v/v) [Found: C, 46.33; H, 5.02; N, 16.59. $C_{10}H_{12}N_3O_3Cl$ requires: C, 46.61; H, 4.69; N, 16.31%]. R_f (75% ligroin/acetone) 0.60. ν_{max} (film NaCl) 2956 (w), 2884 (s), 1574 (s), 1546 (s), 1454 (s), 1387 (w), 1343 (s), 1314 (m), 1264 (w), 1213 (w), 1140 (m), 1094 (s), 1040 (s), 1007 (s), 981 (m), 868 (w), 749 (s), 678 (w). δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.50 (1H, s, H-2), 6.74 (1H, d, *J*=0.8 Hz, H-5); *DOABO–CH_2O*: 4.44 (2H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.38 (2H, d, *J*=5.7 Hz, H-2, -8-*t*), 4.38 (2H, s, 5-OCH_2), 3.78 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 170.2 (1C, C-6), 161.3 (1C, C-4), 158.5 (1C, C-2), 108.2 (1C, C-5); *DOABO–CH_2O*: 88.5 (2C, C-2, -8), 74.2 (2C, C-4, -6), 71.7 (1C, C-5), 69.8 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^+-1) 256 (2), 240 (8), 210 (7), 128 (100), 98 (7).

4.1.18. 2,4,6-Tris[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6g). Yield 58%. Yellowish crystalline powder, mp 188–189 °C (pentane/dichloromethane, 2:1 v/v) [Found: C, 51.53; H, 6.45; N, 14.11. $C_{22}H_{31}N_5O_9$

requires: C, 51.86; H, 6.13; N, 13.75%]. R_f (50% ligroin/acetone) 0.50. ν_{max} (film NaCl) 2857 (s), 1600 (s), 1405 (m), 1382 (s), 1325 (m), 1192 (w), 1095 (w), 923 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 5.74 (1H, s, H-5); *DOABO–CH_2O linked at C-2*: 4.50 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.42 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.325 (2H, s, 5-OCH_2), 3.88 (4H, s, H-4, -6, -*c*, -*t*); *DOABO–CH_2O linked at C-4, -6*: 4.48 (4H, d, *J*=5.5 Hz, H-2, -2′, -8, -8′-*c*), 4.42 (4H, d, *J*=5.3 Hz, H-2, -2′, -8, -8′-*t*), 4.331 (4H, s, 5-, 5′-OCH_2), 3.82 (8H, s, H-4, -4′, -6, -6′, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 172.4 (2C, C-4, -6), 164.3 (1C, C-2), 84.9 (1C, C-5); *DOABO–CH_2O linked at C-2*: 88.3 (2C, C-2, -8), 74.7 (2C, C-4, -6), 71.6 (1C, 5-OCH_2), 70.8 (1C, C-5); *DOABO–CH_2O linked at C-4, -6*: 88.6 (4C, C-2, -2′, -8, -8′), 74.4 (4C, C-4, -4′, -6, -6′), 71.8 (2C, 5-, 5′-OCH_2), 69.4 (2C, C-5, -5′). MS (EI, 70 eV); *m/z* (rel int. %): 510 (8), 297 (<1), 256 (<1), 197 (4), 158 (4), 128 (100), 98 (4).

4.1.19. 4-Chloro-2,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]-oct-*c*-5-yl)methoxy]-pyrimidine (6h). Yield 76%. White crystalline powder, mp 142–144 °C (flash column chromatography, eluent ligroin/acetone 2:1 v/v) [Found: C, 48.31; H, 4.99; N, 14.19. $C_{16}H_{21}N_4O_6Cl$ requires: C, 47.95; H, 5.28; N, 13.98%]. R_f (66% ligroin/acetone) 0.45. ν_{max} (film NaCl) 2852 (s), 1635 (w), 1577 (s), 1416 (m), 1325 (m), 1137 (m), 1093 (m), 1023 (m), 917 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 6.43 (1H, s, H-5); *DOABO–CH_2O linked at C-2*: 4.49 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.42 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.38 (2H, s, 5-OCH_2), 3.87 (4H, s, H-4, -6, -*c*, -*t*); *DOABO–CH_2O linked at C-6*: 4.48 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.41 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.35 (2H, s, 5-OCH_2), 3.81 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 171.9 (1C, C-6), 164.4 (1C, C-2), 162.4 (1C, C-4), 101.6 (1C, C-5); *DOABO–CH_2O*: 88.5 and 88.4 (4C, C-2, -8), 74.5, 74.2 (4C, C-4, -6), 71.7, 71.6 (2C, C-5), 71.2, 70.1 (2C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^+-1) 400 (5), 365 (5), 128 (100), 98 (7).

4.1.20. 2-Chloro-4,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]-oct-*c*-5-yl)methoxy]-pyrimidine (6i). Yield 8%. This compound was identified as side product in the synthesis of the compound **6h** (Table 2). Its identity was established according to NMR spectra performed on the crude reaction mixture together with the residue of the column chromatography (**6i+6h**) after isolation of the pure **6h**. δ_H (300 MHz $CDCl_3$ *only distinct peaks are listed*) *heteroaromatic*: 5.96 (1H, s, H-5); *DOABO–CH_2O*: 4.43 (2H, d, *J*=5.3 Hz, H-2, -2′, -8, -8′, -*c*, -*t*), 4.33 (4H, s, 5-, 5′-OCH_2), 3.77 (4H, s, H-4, -4′, -6, -6′, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 171.8.0 (2C, C-4, -6); *DOABO–CH_2*: 88.6 (4C, C-2, -2′, -8, -8′), 71.6 (2C, C-5, -5′).

4.1.21. 2,4-Dichloro-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]-oct-*c*-5-yl)methoxy]-pyrimidine (6j). White crystalline powder (6% side product in the synthesis of **6h**), mp 117–119 °C (flash column chromatography, eluent ligroin/acetone 2:1 v/v) [Found: C, 40.89; H, 4.15; N, 14.58. $C_{10}H_{11}N_3O_3Cl_2$ requires: C, 41.12; H, 3.80; N, 14.39%]. R_f (66% ligroin/acetone) 0.70. ν_{max} (film NaCl) 2857 (w), 1579 (s), 1528 (s), 1423 (w), 1367 (m), 1272 (m), 1119 (m), 1020 (s), 909 (w), 824 (m), 754 (w), 672 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 6.72 (1H, s, H-5); *DOABO–CH_2O*: 4.48 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.43 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.43 (2H, s, 5-OCH_2), 3.82 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 171.1 (1C, C-6), 162.1 (1C, C-2), 160.0 (1C, C-4), 106.7 (1C, C-5); *DOABO–CH_2O*: 88.6 (2C, C-2, -8), 74.2 (2C, C-4, -6), 71.7 (1C, C-5), 70.6 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): 292 (3), 128 (100), 98 (10).

4.1.22. 2,4-Bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6k). Yield 58%. White crystalline powder, mp 168–170 °C (pentane) [Found: C, 71.52; H, 5.94; N, 8.07. $C_{40}H_{38}N_4O_6$ requires C, 71.63; H, 5.71; N, 8.35%]. R_f (75% ligroin/AcOEt) 0.30. ν_{max} (film KBr) 2874 (m), 1954 (w), 1591 (s), 1571 (s), 1450 (m), 1414 (m), 1331 (m), 1210 (m), 1098 (s), 1011 (m), 927 (m), 818 (s), 698 (s), 643 (w), 522 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.08 (1H, d, *J*=5.8 Hz, H-6), 7.55–7.50 (8H, m, Ph), 7.36–7.28 (12H, m, Ph), 6.15 (1H, d, *J*=5.8 Hz, H-5); *DOABO–CH_2O linked at C-2*: 5.61 (2H, s, H-2, -8-*t*), 4.26 (2H, s, 5-OCH_2), 4.14 (2H, d, *J*=9.2 Hz, H-4, -6-*c*), 4.02 (2H, d, *J*=9.2 Hz, H-4, -6-*t*); *DOABO–CH_2O linked at C-4*: 5.60 (2H, s, H-2, -8-*t*), 4.23 (2H, s, 5-OCH_2), 4.04 (2H, d, *J*=9.0 Hz, H-4, -6-*c*), 3.95 (2H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 171.0 (1C, C-4), 164.9 (1C, C-2), 158.9 (1C, C-6), 139.7, 139.6 (4C, Cq., Ph), 129.0, 128.9 (4C, CH, Ph), 128.8, 128.7 (8C, CH, Ph), 127.6, 127.5 (8C, CH, Ph), 102.6 (1C, C-5); *DOABO–CH_2O*: 97.9, 97.6 (4C, C-2, -8), 73.9, 73.5 (4C, C-4, -6), 73.10, 73.07 (2C, C-5), 71.8, 70.2 (2C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): 708 (20), 692 (100), 670 (10), 564 (5), 451 (6), 435 (22), 413 (10), 348 (5).

4.1.23. 4,6-Bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6l). Yield 31%. White crystalline powder, mp 176–178 °C (flash column chromatography, eluent ligroin/AcOEt 3:1 v/v) [Found: C, 71.53; H, 5.93; N, 8.07. $C_{40}H_{38}N_4O_6$ requires C, 71.63; H, 5.71; N, 8.35%]. R_f (75% ligroin/AcOEt) 0.59. ν_{max} (film KBr) 2876 (m), 1595 (s), 1455 (s), 1430 (m), 1314 (w), 1256 (s), 1166 (m), 1089 (m), 989 (w), 921 (m), 838 (s), 752 (m), 694 (m), 470 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.30 (1H, s, H-2), 7.52–7.49 (8H, m, Ph), 7.38–7.29 (12H, m, Ph), 5.71 (1H, s, H-5); *DOABO–CH_2O*: 5.59 (4H, s, H-2, -2′, -8, -8′-*t*), 4.23 (4H, s, 5-, 5′-OCH_2), 4.05 (4H, d, *J*=9.0 Hz, H-4, -4′, -6, -6′-*c*), 3.95 (4H, d, *J*=9.0 Hz, H-4, -4′, -6, -6′-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 170.8 (2C, C-4, -4′ -6, -6′), 157.8 (1C, C-2), 139.6 (4C, Cq., Ph), 129.0 (4C, CH, Ph), 128.8 (8C, CH, Ph), 127.6 (8C, CH, Ph); *DOABO–CH_2O*: 97.8 (4C, C-2, -2′, -8, -8′), 73.6 (4C, C-4, -4′, -6, -6′), 73.2 (2C, C-5, -5′), 70.7 (2C, 5-, 5′-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^+) 670 (31), 692 (14), 564 (9), 280 (100).

4.1.24. 4-Chloro-6-[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (6m). Yield 23%. Yellowish crystalline powder, mp 145–147 °C (flash column chromatography, eluent ligroin/AcOEt 3:1 v/v) [Found: C, 64.32; H, 5.14; N, 10.19. $C_{22}H_{20}N_3O_3Cl$ requires C, 64.47; H, 4.92; N, 10.25%]. R_f (75% ligroin/AcOEt) 0.80. ν_{max} (film KBr) 3091 (m), 2874 (m), 1573 (s), 1454 (s), 1334 (m), 1258 (m), 1213 (m), 1088 (s), 1009 (s), 931 (w), 871

(w), 804 (m), 753 (s), 696 (s), 535 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.50 (1H, s, H-2), 7.51–7.48 (4H, m, Ph), 7.37–7.28 (6H, m, Ph), 6.53 (1H, s, H-5); *DOABO–CH_2O*: 5.60 (2H, s, H-2, -8-*t*), 4.33 (2H, s, 5-OCH_2), 4.06 (2H, d, *J*=9.0 Hz, H-4, -6-*c*), 3.96 (2H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 170.0 (1C, C-6), 161.3 (1C, C-4), 158.5 (1C, C-2), 139.5 (2C, Cq., Ph), 129.1 (2C, CH, Ph), 128.8 (4C, CH, Ph), 127.5 (4C, CH, Ph), 108.2 (1C, C-5); *DOABO–CH_2O*: 97.8 (2C, C-2, -8), 73.4 (2C, C-4, -6), 73.1 (1C, C-5), 70.8 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): (M^++1) 410 (4), 386 (<1), 304 (100), 280 (42), 174 (98), 156 (23), 129 (11), 91 (18).

4.1.25. 3-Chloro-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazine (8a). Yield 86%. White crystalline powder, mp 130–132 °C (pentane) [Found: C, 46.33; H, 5.03; N, 16.13. $C_{10}H_{12}N_3O_3Cl$ requires: C, 46.61; H, 4.66; N, 16.31%]. R_f (75% ligroin/acetone) 0.50. ν_{max} (film NaCl) 2852 (w), 2082 (w), 1643 (s), 1441 (m), 1310 (w), 1101 (m), 1044 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 7.37 (1H, d, *J*=9.0 Hz, H-4), 6.97 (1H, d, *J*=9.0 Hz, H-5); *DOABO–CH_2O*: 4.54 (2H, s, 5-OCH_2), 4.50 (2H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.45 (2H, d, *J*=5.7 Hz, H-2, -8-*t*), 3.86 (4H, s, H-4, -6, -*c*, -*t*). δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 164.4 (1C, C-6), 152.0 (1C, C-3), 131.4 (1C, C-4), 120.4 (1C, C-5); *DOABO–CH_2O*: 88.7 (2C, C-2, -8), 74.3 (2C, C-4, -6), 71.9 (1C, C-5), 70.4 (1C, 5-OCH_2). MS (EI, 70 eV); *m/z* (rel int. %): 257 (<1), 212 (13), 199 (8), 169 (15), 127 (15), 114 (100), 97 (19), 68 (26), 58 (13), 42 (30), 41 (76).

4.1.26. 6-Methoxy-3-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazine (8b). Yield 51%. White crystalline powder, mp 117–119 °C (dichloromethane/pentane 1:2 v/v) [Found: C, 51.89; H, 6.25; N, 16.91. $C_{11}H_{15}N_3O_4$ requires: C, 52.17; H, 5.97; N, 16.59%]. R_f (75% ligroin/acetone) 0.30. ν_{max} (film NaCl) 2360 (w), 1630 (s), 1476 (m), 1384 (s), 1268 (m), 1036 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 6.92 (2H, s, H-4, -5); *DOABO–CH_2O*: 4.51 (2H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.48 (2H, s, 5-OCH_2), 4.46 (2H, d, *J*=5.7 Hz, H-2, -8-*t*); 4.01 (3H, s, OCH_3), 3.86 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 162.6, 161.9 (2C, C-3, -6), 122.0, 121.6 (2C, C-4, -5); *DOABO–CH_2O*: 88.8 (2C, C-2, -8), 74.5 (2C, C-4, -6), 72.0 (1C, C-5), 69.7 (1C, 5-OCH_2), 55.0 (1C, OCH_3). MS (EI, 70 eV); *m/z* (rel int. %): 253 (<1), 223 (9), 208 (20), 195 (18), 165 (25), 140 (13), 139 (16), 128 (20), 127 (26), 114 (100), 98 (26), 97 (20), 80 (13), 68 (46), 54 (24), 42 (40), 41 (95).

4.1.27. 3,6-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazine (8c). Yield 78%. White crystalline powder, mp 195–197 °C (dichloromethane/pentane 1:2 v/v) [Found: C, 52.75; H, 5.85; N, 15.55. $C_{16}H_{22}N_4O_6$ requires: C, 52.45; H, 6.05; N, 15.29%]. R_f (75% ligroin/acetone) 0.30. ν_{max} (film NaCl) 2868 (w), 2361 (w), 1467 (m), 1446 (s), 1267 (s), 1137 (w), 1039 (s), 920 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 7.24 (2H, s, H-4, -5); *DOABO–CH_2O*: 4.80 (4H, d, *J*=5.7 Hz, H-2, -2′, -8, -8′-*c*), 4.76 (4H, s, 5-, 5′-OCH_2), 4.75 (4H, d, *J*=5.7 Hz, H-2, -2′, -8, -8′-*t*), 4.16 (8H, s, H-4, -4′, -6, -6′, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 162.1 (2C, C-3, -6), 121.9 (2C, C-4, -5); *DOABO-CH_2O*: 88.7 (4C, C-2, -2′, -8, -8′), 74.5 (4C, C-4, -4′, -6, -6′), 71.9 (2C, 5-, 5′-OCH_2), 69.8 (2C, C-5, 5′). MS (EI, 70 eV); *m/z* (rel int. %): (M^++Na) 389 (14), (M^+−1) 365 (4), 168 (4), 128 (100), 98 (5).

4.2. Preparation of compound 9a

To a suspension in THF (50 mL) of **2a** (prepared from **1a**, 1.450 g, 10.0 mmol and potassium hydride 1.337 g as 30% KH in mineral oil suspension, 0.401 g 100%, 10.0 mmol, Scheme 2), cyanuryl chloride (0.571 g, 3.1 mmol) was added as THF (20 mL) solution. The reaction mixture was heated at 65 °C for 36 h. with vigorous stirring, until the starting **1a** was absent (TLC monitoring, eluent ligroin/acetone 2:1 v/v). The reaction was quenched with isopropanol (1 mL) with stirring for additional 30 min. The mineral compounds were filtered off and washed with excess of THF. The combined THF solution was evaporated under vacuum to dryness to provide the crude product as yellow oil. Purification by flash column chromatography (eluent ligroin/acetone 2:1 v/v visualisation in I_2-bath) afforded the desired **9a** as a yellowish crystalline powder: 0.420 g (34% yield).

4.2.1. 2-Chloro-4,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]-oct-*c*-5-yl)methoxy]-*s*-triazine (9a). Yield 34%. Yellowish crystalline powder, mp 91.8–93.4 °C (flash column chromatography, eluent ligroin/acetone 2:1 v/v) [Found: C, 44.91; H, 5.19; N, 17.63. $C_{15}H_{20}N_5O_6Cl$ requires: C, 44.84; H, 5.02; N, 17.43%]. R_f 0.75 (66% ligroin/acetone). ν_{max} (KBr) 2971 (m), 2868 (s), 1731 (s), 1390 (m), 1252 (s), 1138 (m), 1038 (s), 926 (s), 885 (w), 792 (m), 673 (s), 610 (s), 505 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) 4.39 (4H, s, H-2, -2′, -8, -8′-*c*), 4.37 (4H, s, H-2, -2′, -8, -8′-*t*), 4.06 (4H, s, 5-, 5′-OCH_2), 3.73 (4H, d, *J*=9.0 Hz, H-4, -4′, -6, -6′-*c*), 3.68 (4H, d, *J*=9.0 Hz, H-4, -4′, -6, -6′-*t*); δ_C (75 MHz $CDCl_3$) 171.0 (3C, C-2, -4, -6 *s*-triazine), 88.6 (4C, C-2, -2′, -8, -8′), 74.2 (4C, C-4, -4′, -6, -6′), 71.5 (2C, C-5, -5′), 66.9 (2C, 5-, 5′-OCH_2). MS (EI), *m/z* (rel int. %) (M^++1) 402 (<1), 324 (38), 256 (57), 145 (58), 127 (100).

4.3. Preparation of compound 10a

A solution of *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo-[3.3.0]octane **1a** (0.740 g, 5.10 mmol) in THF (25 mL) was cooled at −78 °C with stirring, then *n*-BuLi (1.6 M in hexane, 3.35 mL, 5.35 mmol) was injected to provide a clear white fine suspension. After 20 min, cyanuryl chloride (0.320 g, 1.70 mmol) was injected as THF (15 mL) solution. The reaction mixture was allowed to slowly reach room temperature (20 h) with vigorous stirring then quenched with water (5 mL). The reaction mixture was evaporated to dryness, then water (50 mL) and dichloromethane (50 mL) were added with stirring. After separation, the dichloromethane solution was washed with water to neutrality and then dried over $MgSO_4$. After filtering, the organic solution was concentrated in vacuum to provide the crude product, which was taken with Et_2O to yield the compound **10a** as white crystalline powder: 0.720 g (82% yield).

4.3.1. 2,4,6-Tris[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-*s*-triazine (10a). Yield 82%. White crystalline powder, mp 238.9–239.5 °C (Et_2O) [Found: C, 49.44; H,

5.98; N, 16.44. $C_{21}H_{30}N_6O_9$ requires: C, 49.41; H, 5.92; N, 16.46%]. R_f (50% ligroin/acetone) 0.30. ν_{max} (KBr) 3444 (m), 2969 (w), 2858 (s), 1589 (s), 1414 (s), 1334 (s), 1189 (m), 1141 (m), 1096 (s), 1044 (s), 1028 (s), 943 (m), 807 (s), 750 (m), 718 (w), 676 (m), 572 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) 4.49 (6H, d, J=5.6 Hz, H-2, -2′, -2″, -8, -8′, -8″-*c*), 4.42 (6H, d, J=5.6 Hz, H-2, -2′, -2″, -8, -8′, -8″-*t*), 4.41 (6H, s, 5-, 5′-, 5″-OCH_2), 3.85 (12H, s, H-4, -4′, -4″, -6, -6′, -6″-*c*, -*t*); δ_C (75 MHz $CDCl_3$) 173.3 (3C, C-2, -4, -6 *s*-triazine), 88.5 (6C, C-2, -2′, -2″, -8, -8′, -8″), 74.3 (6C, C-4, -4′, -4″, -6, -6′, -6″), 71.5 (3C, 5-, 5′-, 5″-OCH_2), 71.3 (3C, C-5, -5′, -5″); MS (ESI), *m*/*z* (rel int. %) (M^+-1+Na^+) 532 (100), (M^+) 511 (40), 384 (10).

4.4. Preparation of compounds 9b and 10b

To a suspension in THF (50 mL) of **2b**-*cis* (prepared from **1b**-*cis*, 1.480 g, 5.0 mmol and potassium hydride 0.668 g as 30% KH in mineral oil suspension, 0.200 g 100%, 5.0 mmol, Scheme 2), cyanuryl chloride (0.302 g, 1.64 mmol) was rapidly added as THF (30 mL) solution. The reaction mixture was slowly heated at 65 °C for 40 h with vigorous stirring, until the starting **1b**-*cis* was present in traces only (TLC monitoring, eluent ligroin/acetone 3.5:1 v/v, visualisation in UV-254 nm). The reaction was quenched with water (50 mL) and dichloromethane (125 mL) with stirring for additional 30 min. After separation, the aqueous layer was extracted with dichloromethane (3×25 mL) and the combined dichloromethane solution was washed with water to neutrality. After drying on $MgSO_4$, the organic solution was evaporated under vacuum to yield 1.10 g of the crude reaction mixture. Purification by flash column chromatography (eluent ligroin/acetone 3.5:1 v/v visualisation in UV-254 nm) afforded the following fractions: 0.137 g recovered **1b**-*cis*; 0.370 g desired **10b** as a white crystalline powder. The column was then completely eluted with pure acetone to afford 0.310 g mixture **10b** (66%)+**9b** (34%), according to the ^1H NMR spectrum.

4.4.1. 2-Chloro-4,6-bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-triazine (9b). Yield 8%. δ_H (300 MHz $CDCl_3$) as detected from the mixture with **10b**: 5.59 (4H, s, H-2, -8-*t*), 4.31 (4H, s, 5-, 5′-OCH_2), 4.06 (4H, d, J=9.2 Hz, H-4, -4′, -6, -6′-*c*), 3.98 (4H, d, J=9.2 Hz, H-4, -4′, -6, -6′-*t*); δ_C (75 MHz $CDCl_3$), 171.8 (3C, C-2, -4, -6 *s*-triazine), 139.3 (4C, Cq., Ph), 127.5 (8C, CH, Ph). MS (FAB^+), *m*/*z* (rel int. %) (M^+-1) 704 (20).

4.4.2. 2,4,6-Tris[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-*s*-triazine (10b). Yield 37%. White crystalline powder, mp 162.5–164.2 °C (flash column chromatography, eluent ligroin/acetone 3.5:1 v/v) [Found: C, 70.61; H, 5.70; N, 8.44. $C_{57}H_{54}N_6O_9$ requires: C, 70.80; H, 5.63; N, 8.69%] R_f (78% ligroin/acetone) 0.40. ν_{max} (KBr) 3063 (w), 2871 (m), 1571 (s), 1417 (s), 1334 (s), 1210 (m), 1131 (s), 1088 (m), 1068 (m), 922 (m), 820 (w), 762 (m), 735 (s), 698 (s) cm^{-1}. δ_H (300 MHz $CDCl_3$) 7.51 (12H, m, Ph), 7.32–7.26 (18H, m, Ph), 5.59 (6H, s, H-2, -2′, -2″, -8, -8′, -8″-*t*), 4.24 (6H, s, 5-, 5′-, 5″-OCH_2), 4.06 (6H, d, J=9.2 Hz, H-4, -4′, -4″, -6, -6′ -6″-*c*), 3.98 (6H, d, J=9.2 Hz, H-4, -4′, -4″, -6, -6′, -6″-*t*); δ_C (75 MHz $CDCl_3$) 172.9 (3C, C-2, -4, -6 *s*-triazine), 139.5 (6C, Cq., Ph), 129.1 (6C, CH, Ph), 128.8 (12C, CH, Ph), 127.5 (12C, CH, Ph), 97.6 (6C, C-2, -2′, -2″, -8, -8′, -8″), 73.6 (6C, C-4, -4′, -4″, -6, -6′, -6″), 72.8 (3C, 5-, 5′-, 5″-OCH_2), 72.2 (3C, C-5, -5′, -5″); MS (FAB^+), *m*/*z* (rel int. %) (M^++1) 967.9 (100).

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