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# FIRST EXAMPLE OF SELECTIVE NUCLEOPHILICITY OF 1-AZA-5-HYDROXYMETHYL-3,7-DIOXABICYCLO[3.3.0]OCTANES IN ALKOXIDE FORM

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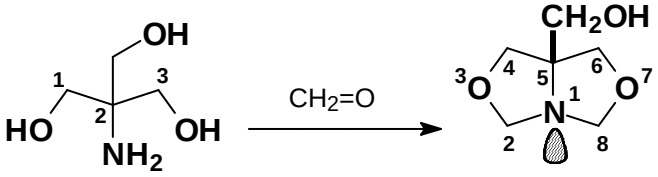
**ABSTRACT.** A rapid and efficient synthesis consisting in the exploit of the nucleophilicity of 1-aza-3,7-dioxabicyclo[3.3.0]octane-5-yl-methoxy group in alkoxide form against reactive halo compounds and masked imidoyl chlorides (as chlorinated π deficient systems) is described. First reaction conditions depending on the halogen and other leaving groups, together with (regio) selectivity of the substitution are discussed.

## 1. INTRODUCTION

The 1-aza-3,7-dioxabicyclo[3.3.0]octane heterocyclic saturated system is known since 1945 when, starting from TRIS® (α,α,α-trimethylolaminomethane) **1** and formaldehyde, the first synthesis of the parent term, having a hydroxymethyl group linked at position C-5 of the skeleton, was reported by Senkus (**Scheme 1**).[1]




**1** **2a**
**5-HOCH$_2$-ADBO**

**Scheme 1**

After the elucidation of this type of structure by chemical methods (Senkus and Pierce),[2-4] a large series of substituted C-2(8), -4(6), -5 derivatives with claimed biological activity were prepared.

The reason for this dedicated attention appears stimulated by the ease of the synthesis: direct cyclocondensation between *C*-substituted 2-amino-1,3-propanediols (better known by their trivial name issued from the pharmaceutical chemistry as *serinols*) and a great variety of carbonyl compounds.[5-20] Though determined mainly on applied research, only minor importance was paid to different functionalisation of 1-aza-3,7-dioxabicyclo[3.3.0]octanes, seen as:

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**i)** *cis* fused double 1,3-oxazolidine systems.

**ii)** 3,7-dioxa-analogues of the core alkaloid, namely pyrrolizidine.[21]

Direct substitution at the carbon ring is still unknown.

Since the period of '50's, only azadioxabicyclooctanes bearing at C-5 a hydroxymethyl group (optionally C-2, -8 substituted derivatives of **2a**, **Scheme 1**) seemed to be suitable to additional functionalisation by predictable methods (*e.g.* $CH_2O$-acylation,[3-5,7,8,12,22] thionation[23] and more recently, by Dess-Martin oxidation[13]). The prepared structures are all reported to be of pharmaceutical interest.[7,8,12,13,24]

Succeeding to our recent findings in the field of stereochemistry of substituted 1-**A**za-3,7-**D**ioxa**B**icyclo[3.3.0]**O**ctanes[6,15,16,25] (hereafter throughout abbreviated simply as **ADBO**) we were paying attention to its C-5 advanced functionalisation. Thus, we considered the parent compound of the 5-hydroxymethyl derivatives, *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane[*] **5-HOCH$_2$-ADBO, 2a** (**Scheme 1**) as well as its *c*-2, *c*-8-diphenyl analogue **2b** to be convertible to 5-alkoxymethyl derivatives *via* the corresponding alkoxides. To our knowledge, this reaction was but once reported by Broadbent in 1976 (deprotonation with sodium metal in refluxing THF).[7] In order to test their nucleophilicity, we needed a larger coherent series of compounds.

Based on our earlier results relating to selective (or exhaustive) nucleophilic replacement of chlorine in certain $\pi$-deficient systems,[27,28] we focused on chlorodiazines (*e.g.* chloropyrimidines): indeed, they were seen in the above circumstance as masked imidoyl chlorides including their well known use as building blocks for structures possessing biological properties.

In this paper, the introductory synthetic and structural results are discussed.

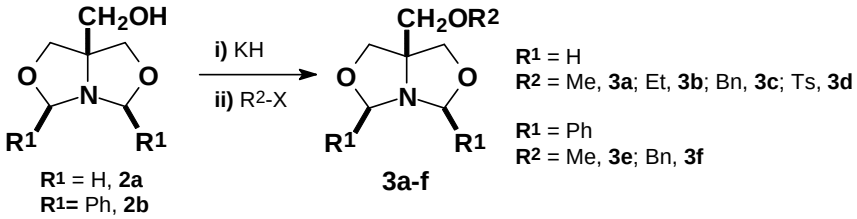
## 2. RESULTS AND DISCUSSION

### 2.1. Synthesis of 5-Alkoxymethyl derivatives of 1-aza-3,7-dioxabicyclo [3.3.0]octane

In order to obtain the title compounds, we first converted **2a** and its *cis*-C-2, -8 diphenyl analogue **2b** into their potassium alkoxides upon treatment with potassium hydride in a nearly stoichiometric ratio. This reagent was able to provide, in a much milder conditions than previously reported by Broadbent,[7] an efficient nucleophile against reactive halo-compounds (**Scheme 2**).

Only the potassium alkoxides of **2a**, **2b** exhibited the desired reactivity. The less basic sodium hydride (also tested) appeared to us not useful since deprotonation only partially occurred. We mention the strong by unexpected nucleophilicity of potassium alkoxide of **2a** proved by the synthesis of the 5-tosyloxymethyl derivative **3d**. Thus, although our initial attempt was to obtain dimeric etheral forms of **2a** [*e.g.* possessing a linkage as O-$(CH_2)_n$-O n=1, 2], its reaction as *O*-potassium form with 1,2-ethylene glycol ditosylate (2:1 molar ratio respectively) afforded the *O*-tosylderivative **3d** in good yield (hence, the $\beta$-tosylethoxide was the leaving group). In a "traditional" route, by using tosylchloride as electrophile, **3d** was isolated with a comparable yield (**Scheme 2**).

[*] Stereochemical descriptors ***r*** (reference) and ***c*** (*cis*) are used according to I.U.P.A.C. 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 is the fiducial substituent).[26] This spatial arrangement, together with the absence of any pyramidal inversion at N-1 are already very well documented.[7,11,14-17,25]




**i)** 1.00:1.05 molar ratio **2a** (**2b**) : KH;1.5 - 2.0 hrs. at 40°C in anh. THF
**ii)** 1.10:1.00 molar ratio $R^2$-X : **2a** (**2b**) in anh.THF.

| Compound | $R^2$-X | Yield (%) |
|---|---|---|
| **3a** | MeI | 45 |
| **3b** | EtI | 66 |
| **3c** | BnBr | 50 |
| **3d** | TsO-$CH_2$-$CH_2$-OTs | 75 |
| | TsCl | 67 |
| **3e** | MeI | 50 |
| **3f** | BnBr | 50 |

**Scheme 2**

No reaction occurred with diiodomethane. No elimination product we detected during the synthesis of **3b**.

All new ethers **3a-f** revealed convincing NMR spectra for the envisaged structures. We note however that the $^1$H NMR experiments performed at low temperature (toluene-$d_8$) evidenced no modification of the signals (not discussed in this paper); that is, all compounds **3a-f** were more flipping structures than their starting materials (**2a**, **2b**).

### 2.2. Synthesis of 5-pyrimidinyloxymethyl derivatives of 1-aza-3,7-dioxabicyclo[3.3.0]octane

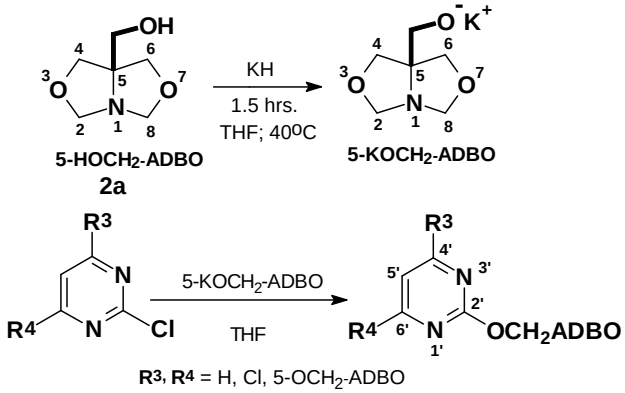
Encouraged by these results in the aliphatic series, the same tactic was straightforward in chlorodiazines series. The preliminary data are presented below regarding (poly)chloropyrimidines. They exhibited useful and comparable reactivity (**Scheme 3**, **Table 1**). Both complete and selective substitutions were examined.

As accepted, reasonably poor reactivity of the chlorine linked at position C-2' (numbering according to pyrimidine) was observed (preparation of the compound **4a**); additional chlorine atoms in the molecule facilitated exhaustive substitution, leading to the compounds **4b**, **4d** and **4g** (in **Table 1** overall yields as isolated material by simple crystallisation are given).

Some problems arose when selective substitutions were attempted.

Thus, 2',4'-dichloropyrimidine showed weaker aptitude against selective monosubstitution than its 4',6'-regioisomer (compounds **4c** and **4e** respectively) although yields appeared identical: thus, for **4c**, the regioselectivity was initially about 2:1 (substitution at C-4' *vs.* C-2', 6 hrs. at 65°C). Repeated failures we encountered in order to separate the regioisomers since they exhibited more or

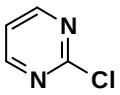
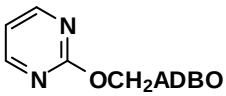
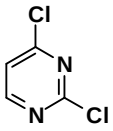
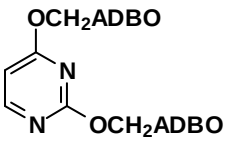
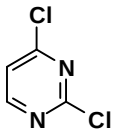
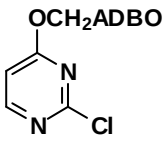
less the same $R_f$ values on a large scale of mixtures of eluents. That is, we had to find conditions in order to more favour C-4' *vs.* C-2' substitution in 2',4'-dichloropyrimidine. They were found by cooling the potassium alkoxide of the starting **2a** as THF suspension at -78°C before adding the 2',4'-dichloropyrimidine. Then, the reaction mixture was very gently let to reach the room temperature. The content of the major regioisomer **4c** was this time about 75% (revealed by the $^1$H NMR spectrum of the crude reaction mixture). This allowed the separation of pure major **4c** by simple crystallisation.

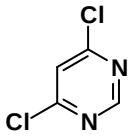
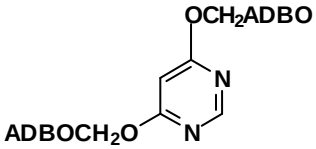
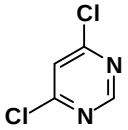
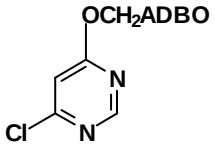
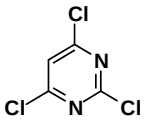
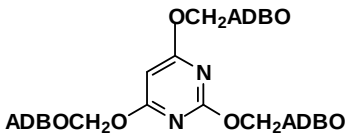
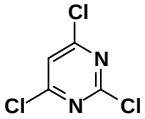
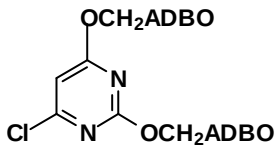



**Scheme 3**

**Table 1**

Results of the synthesis in the chloropyrimidine series;
preparation of the compounds **4a-g**

| **Starting material** | **Molar Ratio** Diazine: KH:**2a** | **Time** (hrs.) | **Temp.** (°C) | **Main Products and Yields** (%) |
|---|---|---|---|---|
|  | 1.00:1.10:1.05 | 4 | 70 |  **4a - 60** |
|  | 1.00:2.00:2.00 | 6 | 40 |  **4b - 80** |
|  | 1.00:1.00:1.00 | 24 | -78→r.t. |  **4c – 63** |

| **Starting material** | **Molar Ratio** Diazine: KH:**2a** | **Time** (hrs.) | **Temp.** ($^{o}$C) | **Main Products and Yields** (%) |
|---|---|---|---|---|
|  | 1.00:2.15:2.05 | 24 | 45 |  **4d** - **81** |
|  | 1.00: 1.05:1.00 | 19 | -78→r.t. |  **4e** - **63** |
|  | 1.00:3.15:3.00 | 21 | 65 |  **4f** - **58** |
|  | 1.00:2.00:2.00 | 22 | -78→r.t |  **4g** - **76** |

The same strategy performed on 4',6'-dichloropyrimidine provided the chemioselectivity (mono- *vs.* disubstitution) as 82:18 **4e** : **4d**.

The above protocol was then repeated in the case of the synthesis of disubstituted compound **4g** and excellent regioselectivity and yield were again obtained. It must be observed the unexpected orientation of the second substitution in 2',4',6'-trichloropyrimidine (at C-2' in lieu of C-6'), fully confirmed by the NMR spectra of **4g**: two different 5-$OCH_2$-ADBO environments with equal intensity of all typical $^{1}H$ and $^{13}C$ NMR signals respectively were displayed.

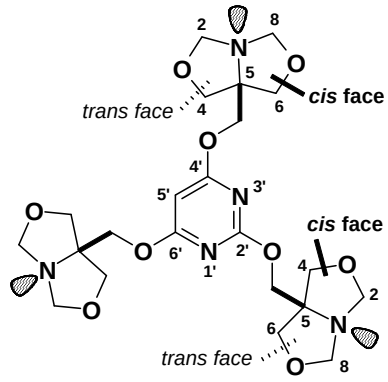
In the end, we note a general valid remark regarding the separation of this class of compounds: flash chromatography on silica gel could be successfully used only if the difference between the number of ADBO units linked to the pyrimidine skeleton was at least 1 for the components of the mixture: decreasing $R_f$ values as starting chloropyrimidine > ADBO-monosubstituting- > ADBO-disubstituting- ≈ 5-$HOCH_2$-ADBO > ADBO-trisubstituting pyrimidine were constantly observed in each case.

All compounds **4a-g** provided NMR spectra consistent with the depicted structures. We note their common stereochemistry connected to the heterofacial character of the ADBO skeleton: they were rotamers in which the π-deficient diatropic ring was oriented as to deshield the *cis* protons with respect to the *trans* ones in the

ADBO motif. Consequently, the geminal anisochrony in the aliphatic part of the bicyle [H-4(6)-*c vs.* H-4(6)-*t*, Δδ, ppm.] was revealed only by A.S.I.S. (***A**romatic **S**olvent **I**nduced **S**hifts*) phenomena (see **Figures 1**, **2** and **EXPERIMENTAL** for the compound **4f**).[29,30]

### 3. CONCLUSION

1-Aza-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octanes can be easily functionalised at position C-5 *via* potassium alkoxides upon treatment with various reactive halo compounds and selected π-deficient systems, such as (poly)chloropyrimidines. The reaction can be carried out with good to excellent yields, chemio- and regioselectivities respectively. The synthetic protocol is simple, in mild conditions and very efficient.




**4f**

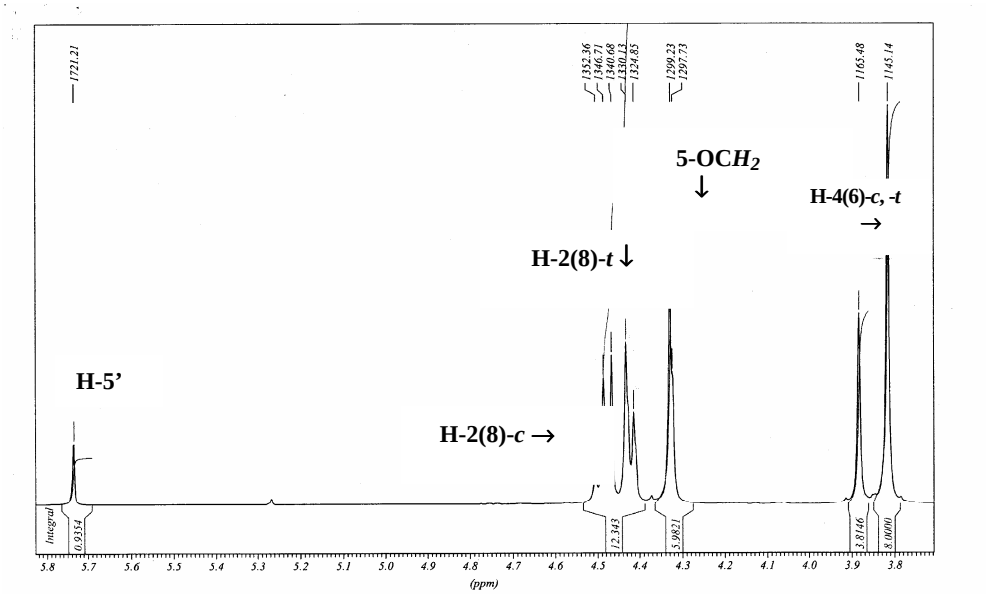



**Figure 1.** *$^1$H NMR spectrum of the compound **4f** (300 MHz, $CDCl_3$)*

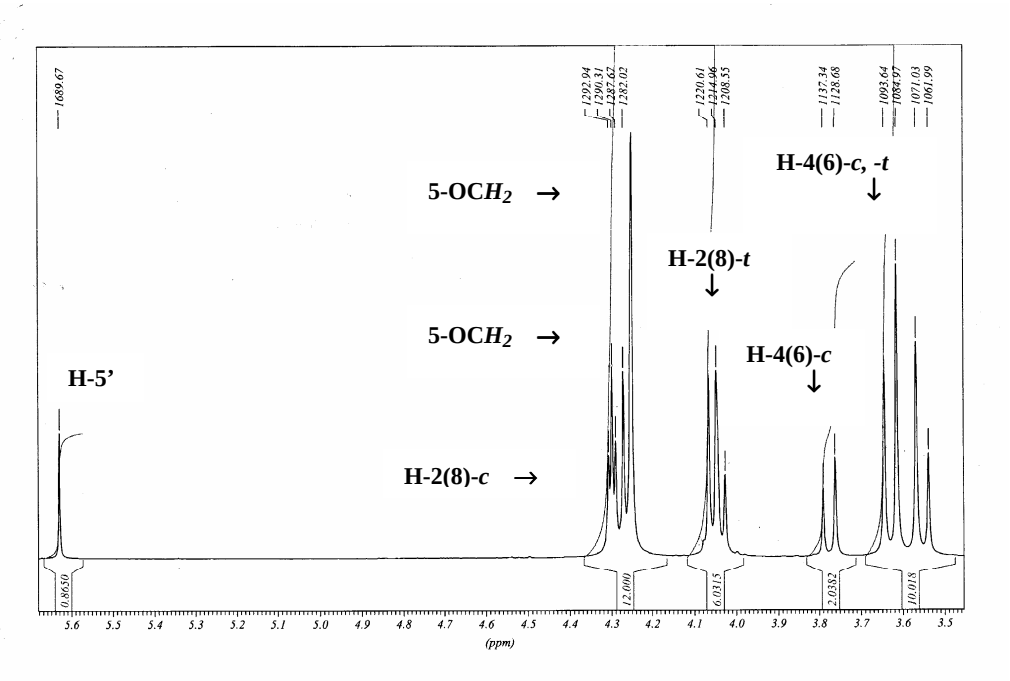



**Figure 2.** *$^{1}$H NMR spectrum of the compound 4f (300 MHz, $C_6D_6$)*

## 4. EXPERIMENTAL

### General

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

Current NMR spectra were recorded on Brucker® AM300 instrument operating at 300 and 75 MHz for $^{1}$H and $^{13}$C nuclei respectively. For the compound **4b**, Brucker® DMX 500 instrument was used operating at 500 and 125 MHz for $^{1}$H and $^{13}$C nuclei respectively. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak, throughout re-calibrated for $CDCl_3$ or $C_6D_6$. All NMR spectra were measured in anhydrous commercially available deuterated solvents. All chemical shifts (δ) values are given throughout in ppm; all coupling patterns (*J*) values are given throughout in Hz.

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® 16 PC FT-IR spectrometer. Only relevant absorptions are listed [throughout in $cm^{-1}$: weak (w), medium (m) or (s) strong]. Mass spectra (MS) were recorded on an ATI-Unicam Automass® apparatus, fitted (or not) with a GC-mass coupling (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL $min^{-1}$).

All syntheses were performed under dry nitrogen atmosphere. THF was freshly distilled from Na/benzophenone prior to use. All solvents and starting materials were of commercial quality. The starting materials **2a** and **2b** were prepared according to literature[1] and our improved protocol.[16]

**General procedure for the preparation of the compounds 3a-f**

In freshly distilled THF (50 mL) and under nitrogen atmosphere, potassium hydride (for the synthesis of compounds **3a-c**: 1.400 g as 30% oily suspension, 0.421 g 100%, 10.50 mmol; for the synthesis of compounds **3e** and **3f**: 0.683 g as 30% oily suspension, 0.205 g 100%, 5.12 mmol) was suspended with stirring. Fine powdered *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane **2a** (1.450 g, 10.00 mmol) [or *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*c*-8-diphenyl-bicyclo[3.3.0]octane **2b** (1.450 g, 4.88 mmol)] was one pot added at room temperature. The resulted suspension was warmed at 40°C for 1.5-2.0 hrs. (until no more hydrogen was formed) then cooled at room temperature to afford a fine white clear suspension. The corresponding electrophile (for the synthesis of compounds **3a–c** 11.00 mmol; for the synthesis of compounds **3e** and **3f** 5.37 mmol) was one pot added as freshly distilled THF solution (10 mL) at room temperature. The reaction mixture was warmed at 55-60°C for 10-15 min., then let to gently cool and kept with stirring at room temperature over night (12-24 hrs.). The TLC monitoring indicated the starting materials (**2a** and **2b**) absent or in small traces only (double visualisation: first UV 254 nm for the compounds **3c**, **3e** and **3f** then $I_2$ bath; single visualisation in $I_2$ bath for the compounds **3a** and **3b**). During condensation, the reaction mixture turned brown and potassium halide was formed abundantly. 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 x 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 purified by flash column chromatography or directly crystallised from an appropriate solvent to yield the title compounds **3a-f**.

***r*-1-Aza-*c*-5-methoxymethyl-3,7-dioxabicyclo[3.3.0]octane (3a)** (45%) yellowish oil (flash column chromatography, eluent pentane : acetone 1:1 v/v); [Found: C, 52.55; H, 8.50; N, 9.11. $C_7H_{13}NO_3$ requires C, 52.81; H, 8.23; N, 8.80%]; $R_f$ (50% pentane/ acetone) 0.70; $\nu_{max}$ ($CH_3Cl$ film) 2921 (s), 2857 (m), 1737 (w), 1470 (w), 1387 (w), 1263 (w), 1120 (w), 1074.3 (w), 1019 (w), 798 (w) $cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) 4.42 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.38 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 3.75 (4H, s, H-4, -6, -*c*, -*t*), 3.40 (2H, s, 5-OC*H*$_2$), 3.34 (3H, s, OC*H*$_3$); $\delta_C$ (75 MHz $CDCl_3$) 88.5 (2C, C-2, -8), 76.4 (1C, 5-*C*$H_2$O), 74.7 (2C, C-4, -6), 72.2 (1C, C-5), 59.9 (1C, O*C*$H_3$). MS (CI, $CH_4$); m/z (rel. int.): 149 (55), 129 (8), 97 (18), 79 (18), 57 (100).

***r*-1-Aza-*c*-5-ethoxymethyl-3,7-dioxabicyclo[3.3.0]octane (3b)** (66%) yellowish oil (flash column chromatography, eluent pentane : $Et_2O$ 2:1 v/v); [Found: C, 55.2; H, 9.1; N, 8.3. $C_8H_{15}NO_3$ requires C, 55.47; H, 8.73; N, 8.09%]; $R_f$ (66% pentane/$Et_2O$) 0.80; $\nu_{max}$ ($CH_3Cl$ film) 2975 (m), 2932 (s), 2863 (s), 1653 (w), 1636 (w), 1465 (m), 1445 (w), 1374 (m), 1363 (m), 1352 (m), 1274 (m), 1176 (s), 1157 (s), 1110 (s), 1045 (s), 1022 (s), 929 (s), 877 (m) $cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) 4.33 (2H, d, *J*=5.3 Hz, H-2, -

8-*t*), 4.29 (2H, d, *J*=5.3 Hz, H-2, -8-*c*), 3.67 (4H, s, H-4, -6, -*c*, -*t*), 3.40 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 3.37 (2H, s, 5-OC*H*$_2$), 1.06 (3H, t, *J*=7.0 Hz, -CH$_2$C*H*$_3$); $\delta_C$ (75 MHz $CDCl_3$) 88.4 (2C, C-2, -8), 74.8 (2C, C-4, -6), 74.2 (1C, 5-O*C*H$_2$), 72.2 (1C, C-5), 67.4 (1C, *C*H$_2$CH$_3$), 15.3 (1C, CH$_2$*C*H$_3$). MS (CI, $CH_4$); m/z (rel. int.): 174(70) [M$^+$+1], 128 (25), 114 (100), 99 (7), 86 (15), 58 (25).

***r*-1-Aza-*c*-5-benzyloxymethyl-3,7-dioxabicyclo[3.3.0]octane (3c)** (50%) yellowish oil (flash column chromatography; $Et_2O$ : heptane 3.5:1.0 v/v); [Found: C, 66.59; H, 7.15; N, 6.22. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.28; N, 5.95%]; $R_f$ (78% $Et_2O$/heptane) 0.65; $\nu_{max}$ ($CH_3Cl$ film) 2939 (s), 2866 (s), 1502 (w), 1461 (m), 1364 (m), 1286 (w), 1217 (m), 1189 (m), 1102 (s), 1051 (s), 1036 (s), 936 (s), 798 (w), 756 (s), 706 (s) cm$^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) 7.34 – 7.28 (5H, m, Ph), 4.53 (2H, s, OC*H*$_2$Ph), 4.44 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.40 (2H, d, *J* = 5.5 Hz, H-2, -8-*c*), 3.80 (4H, s, H-4, -6, -*c*, -*t*), 3.50 (2H, s, 5-OC*H*$_2$); $\delta_C$ (75 MHz $CDCl_3$) 138.2 (1C, Cq, arom.), 128.9 (1C, *C*H arom.), 128.2 (2C, *C*H arom.), 128.1 (2C, *C*H arom.), 88.5 (2C, C-2, -8), 75.0 (2C, C-4, -6), 74.1 (1C, O*C*H$_2$Ph), 73.9 (1C, 5-O*C*H$_2$), 72.3 (1C, C-5). MS (CI, $CH_4$); m/z (rel. int.): 236 (100) [M$^+$+1], 158 (10), 129 (29), 114 (96), 91 (90), 58 (36).

***r*-1-Aza-3,7-dioxa-*c*-5-tosyloxymethylbicyclo[3.3.0]octane (3d)** (70%) yellowish crystalline powder, mp 124–125 $^oC$ (direct crystallisation from $Et_2O$); [Found: C, 51.81; H, 6.05; N, 4.98. $C_{13}H_{17}NSO_5$ requires C, 52.16; H, 5.72; N, 4.68%]; $R_f$ (78% $Et_2O$/ heptane) 0.65; $\nu_{max}$ ($CH_3Cl$ film) 2856 (w), 1636 (s), 1357 (m), 1186 (m), 1166 (s), 1135 (w), 1045 (m), 971 (m), 927 (w), 840 (m) cm$^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) 7.77 (2H, d, *J*=8.1 Hz, Ts), 7.35 (2H, d, *J*=8.1 Hz, Ts), 4.38 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.33 (2H, d, *J* = 5.5 Hz, H-2, -8-*c*), 3.99 (2H, s, 5-OC*H*$_2$), 3.73 (2H, d, *J*=9.2 Hz, H-4, -6-*t*), 3.70 (2H, d, *J*=9.2 Hz, H-4, -6-*c*), 2.44 (3H, s, C*H*$_3$); $\delta_C$ (75 MHz $CDCl_3$) 145.7 (1C, Cq, Ts), 132.7 (1C, Cq, Ts), 130.4 (2C, *C*H, Ts), 128.4 (2C, *C*H, Ts), 88.2 (2C, C-2, -8), 74.0 (2C, C-4, -6), 72.5 (1C, 5-O*C*H$_2$), 71.3 (1C, C-5), 22.1 (1C, *C*H$_3$). MS (CI, $CH_4$); m/z (rel. int.): 300 (3) [M$^+$+1], 146 (40), 128 (100), 93 (22), 65 (17).

***r*-1-Aza-*c*-5-methoxymethyl-*c*-2-*c*-8-diphenyl-3,7-dioxabicyclo[3.3.0]octane (3e)** (50%) yellowish crystalline powder, mp 73–74 $^oC$ (flash column chromatography, eluent pentane : $Et_2O$ 1:1 v/v) [Found: C, 73.55; H, 7.11; N, 4.41. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.80; N, 4.52%]; $R_f$ (50% pentane/$Et_2O$) 0.75; $\nu_{max}$ ($CH_3Cl$ film) 2995 (m), 2884 (s), 1466 (m), 1392 (m), 1314 (w), 1199 (m), 1111 (s), 927 (m), 701 (s) cm$^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) 7.44 – 7.42 (4H, m, Ph), 7.30 – 7.22 (6H, m, Ph), 5.47 (2H, s, H-2, -8-*t*), 3.96 (2H, d, *J* = 9.0 Hz, H-4, -6-*c*), 3.80 (2H, s, H-4, -6-*t*), 3.27 (2H, s, 5-OC*H*$_2$), 3.17 (3H, s, OC*H*$_3$); $\delta_C$ (75 MHz $CDCl_3$) 140.1 (2C, Cq., Ph); 128.9 (2C, *C*H arom.), 128.7 (4C, *C*H. Arom.), 128.6 (4C, *C*H arom.), 97.5 (2C, C-2, -8), 78.0 (1C, 5-*C*H$_2$O), 74.0 (2C, C-4, -6), 73.5 (1C, C-5), 59.8 (1C, O*C*H$_3$). MS (CI, $CH_4$); m/z (rel. int.): 312 (7) [M$^+$+1], 266 (95), 234 (42), 206 (100), 160 (20), 105 (50), 77 (46), 51 (34).

***r*-1-Aza-*c*-5-benzyloxymethyl-*c*-2-*c*-8-diphenyl-3,7-dioxabicyclo[3.3.0]octane(3f)** (50%) yellowish crystalline powder, mp 84–85 $^oC$ (flash column chromatography; eluent $Et_2O$ : heptane 1.5:1.0 v/v); [Found: C, 77.81; H, 6.88; N, 3.44. $C_{25}H_{25}NO_3$ requires C, 77.49; H, 6.50; N, 3.61%]; $R_f$ (60% $Et_2O$/heptane) 0.70; $\nu_{max}$ ($CH_3Cl$ film) 3041 (w),

2866 (m), 1457 (m), 1203 (m), 1097 (s), 1033 (m), 742.8 (s), 701 (s) $cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) 7.41 – 7.39 (4H, m, Ph), 7.26 – 7.11 (11H, m, Ph), 5.46 (2H, s, H-2, -8-*t*), 4.32 (2H, s, OC*H*$_2$Ph), 3.98 (2H, d, *J* = 9.0 Hz, H-4, -6-*c*), 3.82 (2H, d, *J*=9.0 H-4, -6-*t*), 3.67 (2H, s, 5-OC*H*$_2$); $\delta_C$ (75 MHz $CDCl_3$) 140.1 (2C, Cq., Ph); 138.4 (1C, Cq., Ph), 128.9 (2C, *C*H arom.), 128.8 (2C, *C*H arom.), 128.7 (4C, *C*H arom.), 128.1 (1C, *C*H arom.), 127.9 (2C, *C*H arom.), 127.6 (4C, *C*H arom.), 97.6 (2C, C-2, -8), 75.5 (1C, O*C*H$_2$Ph), 74.1 (2C, C-4, -6), 73.9 (1C, 5-O*C*H$_2$), 73.6 (1C, C-5). MS (CI, $CH_4$); m/z (rel. int.): 388 (99) [$M^+$+1], 266 (15), 91 (50).

**Typical procedure for the preparation of the compounds 4a-g**

At room temperature, in a perfectly dried 100 mL three necked round bottom flask and under nitrogen atmosphere, potassium hydride (1.000 g as 30% oily suspension, 0.300 g 100%, 7.48 mmol) was rapidly introduced and washed three times with dry ligroine (optionally pentane, hexane) (30 mL): each time about 5 min. stirring and 5 min. complete decanting. Dry and freshly distilled THF (50 mL) was then introduced with stirring to yield a fine grey suspension. Fine powdered 1-aza-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane 5-HOCH$_2$-ADBO **2a** (1.085 g-0.987 g, 7.48-6.80 mmol, see **Table 1**) was added and the reaction mixture was heated at 40-45$^o$C for 1.0-1.5 hrs. until no more hydrogen was formed and a white fine suspension was obtained. For the synthesis of the compounds **4a**, **4b**, **4d** and **4f** the corresponding (poly)chloropyrimidine was rapidly injected as dry and freshly distilled THF (10 mL) solution, at room temperature (see **Table 1** for specific molar ratios, temperatures and time reaction). For selective substitution, in the case of compounds **4c**, **4e** and **4g** the reaction mixture was cooled at -78$^o$C prior the addition by injection of the corresponding chloropyrimidine as dry and freshly distilled THF (10 mL) solution. Then, it was let to reach very gently the room temperature. The TLC monitoring was performed systematically until the starting materials were absent or in small traces only. Double visualisation is required: first UV 254 nm for detection of the (di)azines then $I_2$ bath, for 5-HOCH$_2$-ADBO **2a** detection. During condensation, the reaction mixture turned coloured and potassium chloride was formed abundantly. The reaction was carefully quenched at room temperature with water (100 mL) and dichloromethane (100 mL) with vigorous stirring. After separation, the organic layer was colourless or very pale yellow. It was washed with water (about 3x50 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 as a solid (usually already crystalline mass). The crude NMR spectra were performed by using this material. The title pure compounds **4a-g** were isolated by direct crystallisation or flash column chromatography as indicated below.

Scale up of the synthesis: 0.800-1.500 g **5-HOCH$_2$-ADBO**, **2a**.

**2-{*r*-1-Aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrimidine (4a)** (60%) yellow crystalline powder, mp 107-109 $^o$C (crystallisation from pentane); [Found: C, 53.59; H, 5.61; N, 19.22. $C_{10}H_{13}N_3O_3$ requires: C, 53.81; H, 5.87; N, 18.92%]; $R_f$ (75% ligroine/acetone) 0.40; $\nu_{max}$ (film NaCl) 2858 (w), 1569 (s), 1431 (s), 1332 (s), 1300 (m), 1137 (w), 1021 (s), 925 (m), 814 (w), 682 (w) $cm^{-1}$. $\delta_H$ (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); *alicyclic*: 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-OC*H*$_2$), 3.87 (2H, d, *J* =9.4 Hz, H-4, -6-*c*), 3.84 (2H, d, *J*=9.4 Hz, H-4, -6-*t*); $\delta_C$ (75 MHz $CDCl_3$) *heteroaromatic*: 165.2 (1C, C-2), 159.7 (2C, C-4, -6), 115.8 (1C, C-5); *alicyclic*: 88.5 (2C, C-2, -8), 74.7 (2C, C-4, -6), 71.7 (1C, C-5), 70.6 (1C, 5-O*C*H$_2$). MS (EI, 70 eV); m/z (rel. int. %): 222 (10) [$M^+$-1], 206 (12), 176 (14), 148 (8), 128 (100), 109 (16), 98 (11).

**2,4-Bis{*r*-1-aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrimidne (4b)** (80%) white crystalline powder, mp 136-137 $^oC$ (crystallisation from 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% ligroine/acetone) 0.20; $\nu_{max}$ (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) $cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) *heteroaromatic*: 8.15 (1H, d, *J*=5.7 Hz, H-6), 6.35 (1H, d, *J*=5.7 Hz, H-5); *alicyclic linkage at C-2*: 4.46 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.40 (2H, d, *J*=5.5 Hz, H-2, -8-*t*), 4.35 (2H, s, 5-OC*H*$_2$), 3.86 (4H, s, H-4, -6, -*c*, -*t*); *alicyclic linkage at C-4*: 4.45 (2H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.39 (2H, d, *J* =5.5 Hz, H-2, -8-*t*), 4.33 (2H, s, 5-OC*H*$_2$), 3.80 (4H, s, H-4, -6, -*c*, -*t*); $\delta_C$ (75 MHz $CDCl_3$) *heteroaromatic*: 171.1 (1C, C-4), 165.0 (1C, C-2), 159.4 (1C, C-6), 102.6 (1C, C-5); *alicyclic*: 88.6 and 88.4 (4C, C-2, -8), 74.7 and 74.3 (4C, C-4, -6), 71.7 and 70.7 (2C, 5-O*C*H$_2$), 69.3 and 68.3 (2C, C-5); $\delta_H$ (500 MHz $C_6D_6$) *heteroaromatic*: 8.05 (1H, d, *J* =6.0 Hz, H-6), 6.15 (1H, d, *J*=6.0 Hz, H-5); *alicyclic linkage at C-2*: 4.40 (2H, s, 5-OC*H*$_2$), 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*); *alicyclic linkage at C-4*: 4.23 (2H, d, *J*=5.3 Hz, H-2, -8-*c*), 4.21 (2H, s, 5-OC*H*$_2$), 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*); $\delta_C$ (125 MHz $C_6D_6$) *heteroaromatic*: 171.1 (1C, C-4), 165.5 (1C, C-2), 158.9 (1C, C-6), 102.3 (1C, C-5); *alicyclic linkage at C-2*: 88.1 (2C, C-2, -8), 74.3 (2C, C-4, -6), 72.7 (1C, C-5), 70.7 (1C, 5-O*C*H$_2$); *alicyclic linkage at C-4*: 88.2 (2C, C-2, -8), 73.9 (2C, C-4, -6), 71.5 (1C, C-5), 69.2. (1C, 5-O*C*H$_2$) MS (EI, 70 eV); m/z (rel. int. %): 366 (<1) [$M^+$], 238 (6), 208 (6), 128 (68), 114 (100), 98 (14), 68 (27), 42 (32), 41 (60).

**4-{*r*-1-Aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxy-2-chloroypyrimidne (4c)** (63%) white crystalline powder, mp 139-140 $^oC$ (direct crystallisation from dichloromethane : pentane 1:2 v/v); [Found: C, 47.08; H, 4.81; N, 16.65. $C_{10}H_{12}N_3O_3Cl$ requires: C, 46.61; H, 4.69; N, 16.44%]; $R_f$ (75% ligroine/acetone) 0.50; $\nu_{max}$ (film NaCl) 2857 (w), 1636 (s), 1582 (s), 1545 (m), 1446 (m), 1327 (s), 1230 (m), 1102 (w), 1017 (m) $cm^{-1}$. $\delta_H$ (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); *alicyclic*: 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-OC*H*$_2$), 3.81 (4H, s, H-4, -6, -*c*, -*t*); $\delta_C$ (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); *alicyclic*: 88.6 (2C, C-2, -8), 74.2 (2C, C-4, -6), 71.7 (1C, C-5), 69.9 (1C, 5-O*C*H$_2$). MS (EI, 70 eV); m/z (rel. int. %): 257.5 (<1) [$M^+$], 212 (9), 197 (12), 169 (11), 114 (100), 86 (10), 68 (14), 58 (11), 42 (16), 41 (50).

**4,6-Bis{*r*-1-aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrimidne (4d)** (81%) yellowish crystalline powder, mp 146-148 $^oC$ (direct crystallisation from 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% ligroine/acetone) 0.35; $\nu_{max}$ (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)

$cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) *heteroaromatic*: 8.38 (1H, s, H-2), 6.08 (1H, s, H-5); *alicyclic*: 4.49 (4H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.44 (4H, d, *J* =5.7 Hz, H-2, -8-*t*), 4.38 (4H, s, 5-OC*H*$_2$), 3.84 (8H, s, H-4, -6, -*c*, -*t*); $\delta_C$ (75 MHz $CDCl_3$) *heteroaromatic*: 171.0 (2C, C-4, -6), 157.8 (1C, C-2), 91.4 (1C, C-5); *alicyclic*: 88.6 (4C, C-2, -8), 74.4 (4C, C-4, -6), 71.9 (2C, C-5), 69.4 (2C, 5-O*C*$H_2$); MS (EI, 70 eV); m/z (rel. int. %): 367 (<1) [$M^+$+1], 274 (3), 252 (2), 168 (8), 128 (100), 98 (4).

**6-{*r*-1-Aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxy-4-chloroypyrimidne (4e)** (63%) white crystalline powder, mp 118-119 $^oC$ (flash column chromatography, eluent ligroine : 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% ligroine/acetone) 0.60; $\nu_{max}$ (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) $cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) *heteroaromatic*: 8.50 (1H, s, H-2), 6.74 (1H, d, *J*=0.8 Hz, H-5); *alicyclic*: 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-OC*H*$_2$), 3.78 (4H, s, H-4, -6, -*c*, -*t*); $\delta_C$ (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); *alicyclic*: 88.5 (2C, C-2, -8), 74.2 (2C, C-4, -6), 71.7 (1C, C-5), 69.8 (1C, 5O*C*$H_2$). MS (EI, 70 eV); m/z (rel. int. %): 256.5 (2) [$M^+$-1], 240 (8), 210 (7), 128 (100), 98 (7).

**2,4,6-Tris{*r*-1-aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrimidne (4f)** (58%) yellowish crystalline powder, mp 188-189 $^oC$ (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% ligroine/acetone) 0.50; $\nu_{max}$ (film NaCl) 2857 (s), 1600 (s), 1405 (m), 1382 (s), 1325 (m), 1192 (w), 1095 (w), 923 (m) $cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) *heteroaromatic*: 5.74 (1H, s, H-5); *alicyclic linkage 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-OC*H*$_2$), 3.88 (4H, s, H-4, -6, -*c*, -*t*); *alicyclic linkage at C-4, -6*: 4.48 (4H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.42 (4H, d, *J* =5.3 Hz, H-2, -8-*t*), 4.331 (4H, s, 5-OC*H*$_2$), 3.82 (8H, s, H-4, -6, -*c*, -*t*); $\delta_C$ (75 MHz $CDCl_3$) *heteroaromatic*: 172.4 (2C, C-4, -6), 164.3 (1C, C-2), 84.9 (1C, C-5); *alicyclic linkage at C-2*: 88.3 (2C, C-2, -8), 74.7 (2C, C-4, -6), 71.6 (1C, 5-O*C*$H_2$), 70.8 (1C, C-5); *alicyclic linkage at C-4, -6*: 88.6 (4C, C-2, -8), 74.4 (4C, C-4, -6), 71.8 (2C, 5-O*C*$H_2$), 69.4 (2C, C-5); MS (EI, 70 eV); m/z (rel. int. %): 510 (8) [$M^+$], 297 (<1), 256 (<1), 197 (4), 158 (4), 128 (100), 98 (4).

**2,6-Bis{*r*-1-aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxy-4-chloro pyrimidne (4g)** (76%) white crystalline powder, mp 142-144 $^oC$ (flash column chromatography, eluent ligroine : acetone 2:1 v/v, then recrystallisation from dichloromethane : pentane 1:2 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% ligroine/acetone) 0.45; $\nu_{max}$ (film NaCl) 2852 (s), 1635 (w), 1577 (s), 1416 (m), 1325 (m), 1137 (m), 1093 (m), 1023 (m) 917 (w) $cm^{-1}$. $\delta_H$ (300 MHz $CDCl_3$) *heteroaromatic*: 6.43 (1H, s, H-5); *alicyclic linkage 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-OC*H*$_2$), 3.87 (4H, s, H-4, -6, -*c*, -*t*); *alicyclic linkage 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-OC*H*$_2$), 3.81 (4H, s, H-4, -6, -*c*, -*t*); $\delta_C$ (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); *alicyclic*: 88.5 and 88.4 (4C, C-2, -8), 74.5 and 74.2 (4C, C-4, -6), 71.7 and 71.6 (2C, C-5), 71.2 and 70.1 (2C, 5-O*C*$H_2$); MS (EI, 70 eV); m/z (rel. int. %): 400.5 (5) [$M^+$-1], 365 (5), 128 (100), 98 (7).

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