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SYNTHESIS OF PURINE-ACRIDINE HYBRID MOLECULES RELATED TO ARTIFICIAL ENDONUCLEASES

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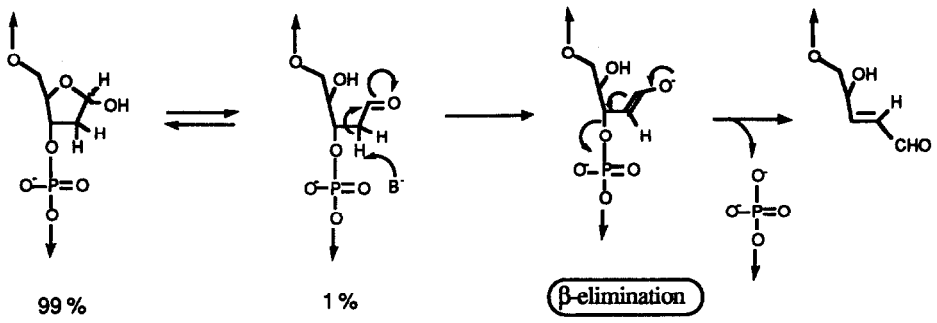
Abstract: In the course of a program devoted to the synthesis of artificial endonucleases, we have previously reported a series of hybrid molecules in which a purine is linked to an intercalating drug by a polyamino chain. These molecules recognize and cleave selectively abasic sites in DNA with very high efficiency. In order to get insight into the mechanism of recognition and cleavage, we have prepared a new series of molecules in which the purine is linked to an amino-acridine by an aliphatic chain containing amido or/and amino groups. The key intermediates are α-halo-ω-amino polyaza chains which may be of general use as linkers in bioconjugate chemistry.

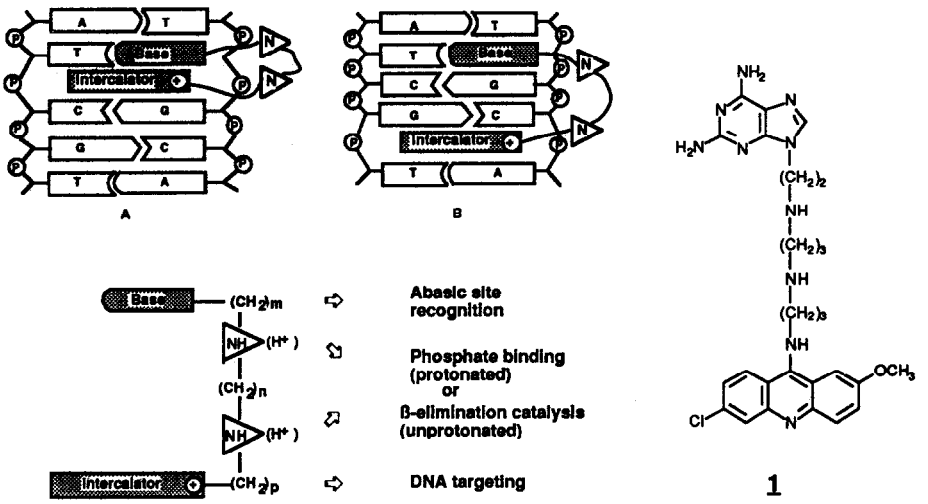
Abasic site formation (i.e. loss of a nucleic base) is the most common lesion produced in DNA. Abasic sites (apurinic/apyrimidinic sites or AP-sites) are formed by chemical modifications induced by DNA damaging agents such as bleomycin, alkylating agents, or by ionizing radiations. They also form spontaneously in the cell by hydrolysis of the N-glycosidic bond with an appreciable frequency (10 000 lesions per cellular cycle[1]). They are also produced enzymatically by action of DNA-glycosylases that remove modified or abnormal bases. *In vitro* abasic sites are generated by warming DNA in diluted acidic medium. The abasic site is an equilibrium mixture between different forms: the hemi-acetals, the aldehyde and the hydrated aldehyde. The aldehydic form represents only 1% of the total[2]. If unrepaired, abasic sites are mutagenic or even lethal for the cells. The first step of the repair process *in vivo* implies cleavage of the damaged DNA strand at the abasic site, according to two possible pathways, (i) AP-endonucleases such as endonuclease IV cleave by hydrolysis of the phosphodiester bond, (ii) AP-lyases such as UV endonuclease V or endonuclease III cleave by a β-elimination reaction[3] (Scheme 1).

A few chemicals (simple polyamines[4], amino-ellipticine[5] or a tripeptide Lysyl-Tryptophyl-Lysyl[6]) have been reported to catalyse this β-elimination process *in vitro*.



Scheme 1

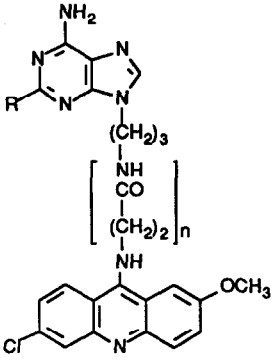
We have previously described[7] new tailor-made molecules designed to mimic endonuclease of the AP-lyase type, i.e. molecules that recognize and cleave the abasic sites by a β-elimination process (Scheme 2). These molecules are made of three parts: an intercalating drug (aminoacridine) for DNA affinity, a nucleic base (adenine or 2,6-diaminopurine) for abasic site recognition and a linker (aliphatic chain containing secondary amines) endowed with both a binding function and a base catalysis function.



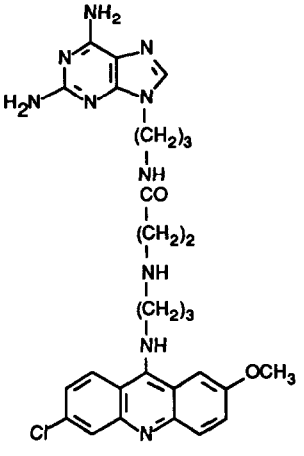
Scheme 2

We have shown that these molecules are able to selectively recognize and cleave Ap-site containing DNA a very low concentration (10^{-9} M). They are totally inactive on normal DNA. The three parts of the molecules are necessary to the activity[8]. The most efficient molecules such as **1** possess two secondary aliphatic amines in the chain. In the postulated mode of action, one of the two amine functions is protonated at physiological pH and increases DNA affinity by interacting with the phosphate backbone, while the second amine, with a lower pK[9] reacts as a free base to promote hydrogen-abstraction and induces β-elimination of the phosphate. To optimise these artificial nucleases it is necessary to understand in the detail the role and importance of each part of the

molecules in this mechanism. In order to investigate the effect of the two secondary aliphatic amines in the linking chain[10] we have prepared a new series of molecules (Scheme 3) in which we have replaced one or both amino groups by amido functions. We report here the synthesis of molecules **2-7** and give some indications on their cleavage activity.



R = H	n = 1	**2**
R = NH_2	n = 1	**3**
R = H	n = 2	**4**
R = NH_2	n = 2	**5**



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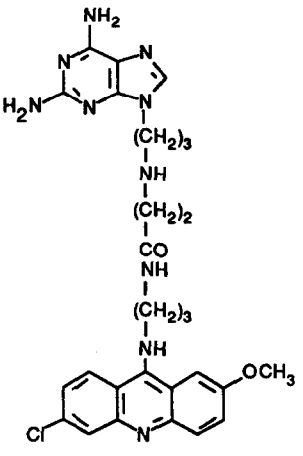

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Scheme 3

RESULTS AND DISCUSSION

All new molecules prepared possess the same chloro-methoxy-9-aminoacridine unit as intercalator chosen for its high DNA affinity.

In compounds **2-5** which contain only amido functions in the chain, the adenine and 2,6-diaminopurine derivatives have been prepared. In compounds **6** and **7**, bearing one amine and one amide in the chain ("mixed" chains), we introduced 2,6-diaminopurine as nucleic base analog. As a matter of fact, we had previously observed that this non-natural base was more effective than adenine both for DNA affinity and AP-site cleavage activity[7].

The target molecules **4-7** possess the general formula Base-$(CH_2)_m$-X-$(CH_2)_n$-Y-$(CH_2)_p$-NHAcr where m, n, p = 2 or 3 and X, Y, are amino or amido functions. The bases, adenine or diaminopurine are readily alkylated at the N-9 position and can thus be introduced as nucleophiles. The 9-aminoacridine moiety on the other hand is generally obtained by nucleophilic aromatic substitution at carbon 9 by a primary amine. We thus selected a general versatile strategy involving the synthesis of the polyfunctionalized chains Cl-$(CH_2)_m$-X-$(CH_2)_n$-Y-$(CH_2)_p$-NH_R **13, 17, 20** bearing an halogen atom at one end, a protected primary amino group at the other end and including amido or protected secondary amino groups. These chains were used to alkylate the purines at their N-9 positions and, after deprotection of the primary amino groups, the acridine nucleus was introduced in a last step.

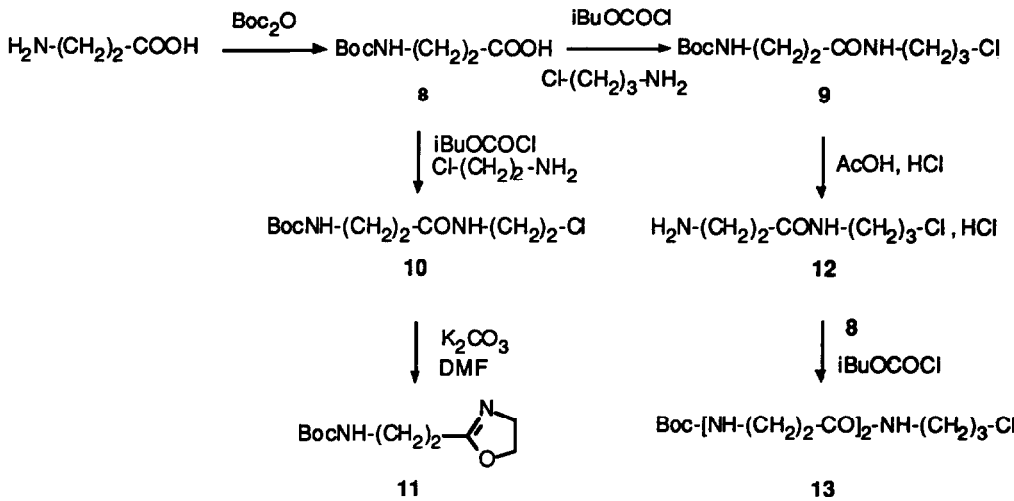
The same route was used to prepare molecules **2** and **3** by introducing sequentially the purine and the acridine onto the already reported **9**.

1) Synthesis of chains 9 and 13:

Chain **9** was obtained as described by DAS et al.[11] Condensation of N-Boc protected ß-alanine **8** with 3-chloropropylamine using isobutylchloroformiate as coupling agent afforded compound **9** with 83 % yield, which was used as a linker to prepare molecules **2** and **3**.

Protected β-alamine **8** was also coupled with 2-chloroethylamine in the same conditions. However the resulting derivative **10** could not be used further to prepare the corresponding hybrid molecule. In the basic conditions used to introduce the purine ring, i.e. sodium hydride or potassium carbonate in DMF, **10** is rapidly transformed into the oxazoline **11**. The ^{1}H nmr spectra of compounds **10** and **11** differ by the absence of one N-H signal for **11** and by modification of the AA'BB' spectrum corresponding to the chloroethyl group in **10** and the oxazoline hydrogens in **11**. The formation of oxazoline ring such as **11** from a β-halogenoamide is a rapid intramolecular process[12].

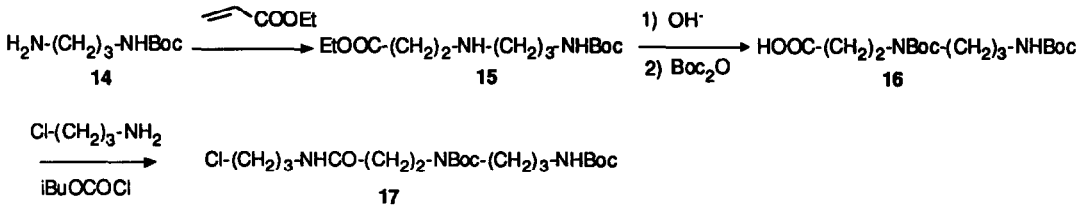
To prepare compound **13** which possesses a longer chain, we repeated the coupling reaction. After deprotection of the primary amino group in **9** in acidic condition (1N hydrochloric acid in acetic acid), a new amido linkage was created by reacting **12** with a second N-Boc protected β-alanine molecule **8**. We thus obtained the functionalized chain **13** with an overall yield of 38 % starting from **8**.



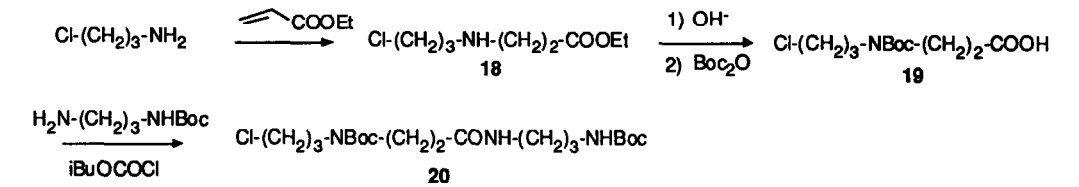
2) Synthesis of the "mixed" chains 17 and 20:

Many polyamines have been reported in the literature[13]. To our knowledge only a few halogenated polyamines have been described[14,11], none of them however containing both amino and amido functions in the middle of the chains. To prepare the desired chains **17** and **20**, the same basic reactions were used in two

different sequences. In the case of chain **17**, the monoprotected diaminopropane **14**[15] was reacted with ethylacrylate in a Michael-type reaction to give **15**. After basic hydrolysis of the ethyl ester and protection of the secondary amino function, the resulting **16** was coupled with chloropropylamine using isobutylchloroformate as coupling agent to give the protected α-chloro-ω-amino chain **17**.

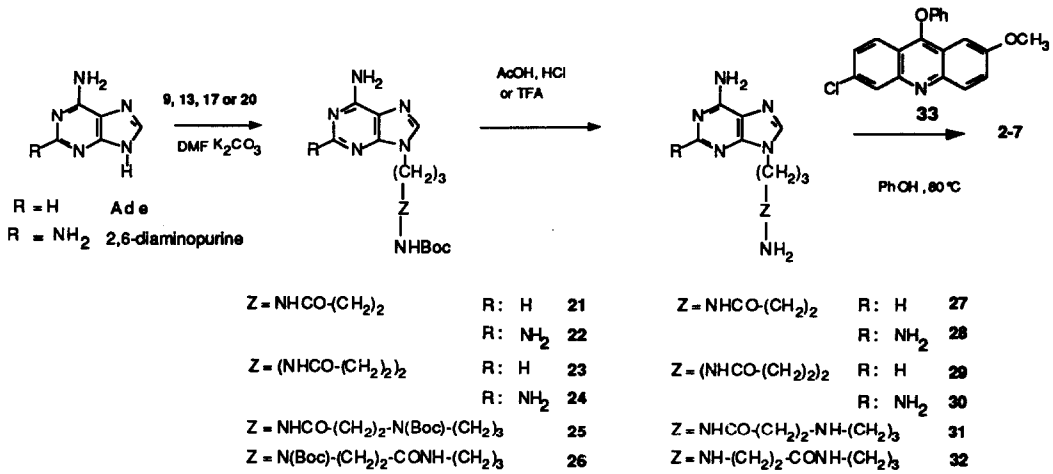


To prepare the alternate amino-amido chain **20**, 3-chloropropylamine was added to ethylacrylate giving the intermediate **18**. Basic hydrolysis of the ethylester followed by protection of the secondary amine yielded the acid **19** which was reacted with the monoprotected diaminopropane **14** in the presence of isobutylchloroformate to form the amido linkage of the chain derivative **20**. It should be noticed that the Michael-type reaction of a primary amine with ethylacrylate[16] in stoechiometric conditions gives only the secondary amine with fairly good yields (80-85%). The functionalized chains **17** and **20** were obtained with 45 and 59 % overall yields respectively.



3) Introduction of the purine and acridine rings :

The purines (adenine or 2,6-diaminopurine) were alkylated with the newly synthesized chains **9**, **13**, **17** or **20**. In the conditions used (DMF, sodium hydride or sodium carbonate, room temperature), we did not observe any reaction at the N-7 position of the purine[17]. The reaction occurs selectively at the N-9 position to give the Boc protected intermediates **21-26**. The yields are higher in the 2,6-diaminopurine series (70-76 % for **22** and **24**) than in the adenine series (38-40 % for **21** and **23**).



Z = $NHCO-(CH_2)_2$	R: H	21	Z = $NHCO-(CH_2)_2$	R: H	27
	R: NH_2	22		R: NH_2	28
Z = $(NHCO-(CH_2)_2)_2$	R: H	23	Z = $(NHCO-(CH_2)_2)_2$	R: H	29
	R: NH_2	24		R: NH_2	30
Z = $NHCO-(CH_2)_2-N(Boc)-(CH_2)_3$		25	Z = $NHCO-(CH_2)_2-NH-(CH_2)_3$		31
Z = $N(Boc)-(CH_2)_2-CONH-(CH_2)_3$		26	Z = $NH-(CH_2)_2-CONH-(CH_2)_3$		32

After hydrolysis of the Boc protecting groups in acidic medium (1N hydrochloric acid in acetic acid), the acridine nucleus was introduced by reaction of the primary amino groups of compounds **27-32** with phenoxyacridine **33**[18] to give the final compounds **2-7**. The reaction was performed in phenol under nitrogen. The yields for this last step were about 50 %. The purification of the final compounds **2-7** happened to be difficult due to the high polarity of the products. They were generally obtained in a pure state by precipitation in acetone and crystallizations in acidic methanol. In one case, for compound **6**, a further purification on silica gel was necessary.

CONCLUSION

We have prepared a series of molecules **2-7** in which purines are bridged to acridines through linkers including amido and amino junctions. The synthetic route which was selected implies preparation of the linkers at the initial stage followed by introduction of the two aromatic moieties. The linkers **9, 13, 17** and **20** were obtained in good yields and prooved to be convenient and versatile for adding sequentially the nucleic base as a nucleophile and the acridine moiety by nucleophilic aromatic substitution. Polyamine linkers have been widely reported in the literature[12,13]. Such new linkers as **13, 17** and **20** possessing amido group(s) in the chain and halogen and amine at the extremities may be of general use in preparing bioconjugates involving biopolymers with small reporter molecules (dyes, haptens...) or in the design of heterobifunctional crosslinking reagents[19].

The hybrid molecules **2-7** are analogs of the nuclease mimic **1** which has been shown to recognize and cleave abasic sites in DNA with high selectivity and efficiency. Scheme 2 represents two possible modes of interaction which point to the postulated role of the two amino functions in the linking chain, one of them being essentially protonated and having a binding function with the negatively charged phosphates of DNA, the other amine, as a consequence of pK decrease well known in polyamines, is essentially unprotonated and acts as a basic catalysts to abstract hydrogen and trigger the DNA strand-break by β-elimination of the phosphate. The acridine and the base either stack intramolecularly in the abasic pocket (A) or "bisintercalate" with one or two base pairs to separate them (B).

Preliminary experiments indicate that all new molecules bind to DNA[20]. Molecules **2-5** which possess only amido functions in the chain do not cleave abasic sites, which fits to the scheme. The most interesting result is that the two molecules **6** and **7** which differ by the position of the amido and amino functions in the chain exhibit identical affinity for DNA and more surprisingly identical cleavage activity. This result is rather in favour of an interaction scheme of type A, in which both nitrogens can be in close proximity to the hydrogen to be abstracted at the abasic site. Further studies are in progress to precise this postulated reaction scheme.

EXPERIMENTAL SECTION

General procedures. All solvents or reagents were of reagent-grade quality and were used without further purification. Analytical TLC was performed on 0.2-mm silica 60 coated aluminium foils with F-254 indicator. Analytical HPLC was performed on a Waters equipment (two M-510 pumps, solvent gradient M680) with UV detection (M490 and diode array 990). Reverse phase μ-Bondapak C-18 (Millipore-Waters) was used with a methanol-water pH 2.5 gradient, flow 2 ml/mn. Melting points were measured on a Totoli apparatus and are uncorrected. ^{1}H nmr spectra were recorded on Bruker WP80, AM200 and AM400 spectrometers. Spectra were referenced to the residual proton solvent peak. Coupling constants are reported in Hz. Infrared spectra were recorded on Perkin-Elmer 298 and 1320 spectrometers. Mass spectra were recorded on Varian MAT311 and AET MS30. Elemental analysis were performed by "Service Central de Microanalyse du CNRS".

N-(3-chloropropyl)-3-(tert-butoxycarbonylamino)-propionamide 9

To a solution of **8**[21] (5 g, 26.4 mmol) and triethylamine (3.65 mL, 26.4 mmol) in THF (70 mL), cooled in an ice-bath and kept under nitrogen, was added isobutylchloroformiate (3.4 mL, 26.4 mmol). After 5 min. of stirring, was added a mixture of 3-chloropropylamine hydrochloride (3.7 g, 28.87 mmol) and triethylamine (3.7 mL, 26.4 mmol) in DMF (10 mL). Stirring was continued for an extra 30 min. at room temperature, then the solvent was evaporated to dryness under reduced pressure. The resulting gum was extracted with methylene chloride, washed successively with a saturated sodium carbonate solution and saturated sodium chloride solution and finely dried over magnesium sulfate. Evaporation of the solvent gave an oily residu that crystallises from a diethylether-hexane mixture (5.8 g, 83 % yield). mp: 79-81°C. ir: (Nujol): 3380, 1690, 1660, 1540, 1300, 1250, 1180, 1070, 1020, 930, 880 cm^{-1}. nmr: (60 MHz, $CDCl_3$); δ ppm = 6.15 (1H, s, NH); 4.80 (1H, s, NH); 3.40 (6H, m, $3CH_2$); 2.35 (2H, t, CH_2); 1.95 (2H, quint, $CH_2CH_2CH_2$); 1.40 (9H, s, $C(CH_3)_3$). ms: (EI); M = 264; m/z: 264 (M^+); 229 (M^+-Cl); 208 (M^+-$C(CH_3)_3$); 191 (M^+-O $C(CH_3)_3$); 129; 94; 57.

N-(2-chloroethyl)-3-(tert-butoxycarbonylamino)-propionamide 10

Compound **10** was prepared as described for compound **9** with 85 % yield by reaction of 2-ethylamine hydrochloride with compound **8**. mp: 87-89°C. ir: (KBr): 3340, 2980, 1690, 1660, 1530, 1450, 1390, 1370, 1340, 1280, 1240, 1170, 1100, 1050, 970, 870 cm^{-1}. nmr: (80 MHz, $CDCl_3$); δ ppm = 6.05 (1H, s, NH); 5.00 (1H, s, NH); 3.60-3.20 (6H, m, $3CH_2$); 2.45 (2H, t, CH_2CO); 1.40 (9H, s, $C(CH_3)_3$). ms: (CI, NH_3, isobutane); M = 250.5; m/z: 251 (M^++H); 215 (M^+-Cl); 195 (M^+-$C(CH_3)_3$); 177 (M^+-O $C(CH_3)_3$); 151 (M^+-COO $C(CH_3)_3$).

N-(3-chloropropyl)-3-aminopropionamide hydrochloride 12

Hydrochloric acid (4 mL) was added to a solution of compound **9** (4.4 g, 16.6 mmol) in methanol (20 mL). After stirring overnight at room temperature, the solvent was evaporated and the oily compound was triturated in acetone. Compound **12** was obtained as a gum (2.7 g, 80 % yield). ir: (Nujol): 3300, 1650, 1560, 1260, 1230, 1160, 960, 920 cm^{-1}. nmr: (60 MHz, D_2O); δ ppm = 3.80-3.20 (6H, m, $3CH_2$); 2.70 (2H, t, CH_2); 2.0 (2H, quint, $CH_2CH_2CH_2$). ms: (EI); M = 165; m/z: 165 (M^+); 148 (M^+-NH_2); 135 (M^+-CH_2NH_2); 127 (M^+-Cl); 112 (M^+-CH_2Cl); 99 (M^+-$(CH_2)_2Cl$); 84 (M^+-$(CH_2)_3Cl$).

N-(3-chloropropyl)-3-[(tert-butoxycarbonylamino)-propionamido]propionamide 13

We repeated the procedure described for **9**, starting from compounds **12** and **8**. Compound **13** was obtained with 56 % yield. mp: 134-137°C. ir: (KBr): 3320, 3080, 2980, 2940, 1680, 1650, 1530, 1450, 1390, 1370, 1350, 1290, 1250, 1170, 1110, 1050, 870 cm^{-1}. nmr: (200 MHz, $CDCl_3$); δ ppm = 6.40 (1H, s, NH); 6.00 (1H, s, NH); 5.10 (1H, s, NH); 3.60-3.20 (8H, m, $4CH_2$); 2.25 (4H, m, $2CH_2$); 1.95 (2H, quint, $CH_2CH_2CH_2$); 1,35 (9H, s, $C(CH_3)_3$). ms: (EI); M = 335; m/z: 335 (M^+); 299 (M^+-Cl); 279 (M^+-$C(CH_3)_3$); 264 (M^+-$OC(CH_3)_3$); 229 (M^+-$CONH(CH_2)_3Cl$); 220 (M^+-$NHCOOC(CH_3)_3$, 30); 205 (M^+-$CH_2NHCOOC(CH_3)_3$); 191 (M^+-$(CH_2)_2NHCOOC(CH_3)_3$); 165 (M^+-$CO(CH_2)_2NHCOOC(CH_3)_3$).

2-tert-butoxycarbonylaminoethyl-oxazoline 11

A mixture of compound **10** (0.05 g, 0.2 mmol) and potassium carbonate (0.04 g, 0.4 mmol) in DMF (1 mL) was stirred at 70°C under nitrogen for 5 h.The solvent was then evaporated and the residue dissolved in dichloromethane. After filtration, the solvent was evaporated again and title compound **11** was obtained as an oil. ir: (Film): 3340, 2960, 1660, 1500, 1380, 1360, 1270, 1240, 1170, 1090, 980, 860 cm^{-1}. ^1H nmr: (200 MHz, $CDCl_3$); δ ppm = 5.22 (1H, s, BocNH); 4.16 (m, 2H); 3.76 (m, 2H); 3.34 (2H, q, CH_2NH); 2.39 (2H, t, CH_2); 1.36 (9H, s, $C(CH_3)_3$). ^{13}C nmr ($CDCl_3$): δ ppm = 166.7, 155.6, 79.0, 617.1, 54.1, 36.6, 28.3, 28.2. ms: (CI, ammoniac, isobutane); M = 214; m/z: 215 $(M+1)^+$; 159, 158 (M^+-$C(CH_3)_3$), 141 (M^+-$OC(CH_3)_3$), 113 (M^+-$CCOOC(CH_3)_3$); hrms (FAB+): m/z $(M+H)^+$ Calcd for $C_{10}H_{19}N_2O_3$ 215.1395; Found 215.1405.

6-amino-9-[3-(3-(tert-butoxycarbonylamino)-propionamido)propyl]-9H-purine 21

Sodium hydride (0.1 g, 2 mmol) was added to a suspension of adenine (0.263 g, 1.75 mmol) in dry DMF (10 mL). The mixture was stirred at room temperature under nitrogen for 30 min. before addition of a solution of compound **9** (0.480g, 1.75 mmol) in dry DMF (5 mL) containing a catalytic amount of tetrabutylammonium iodide. The solution was then stirred at 70°C during 48 h. After filtration, the solvent was evaporated under reduced pressure. The oily residue was extracted with ethylacetate, dried with sodium sulfate and evaporated. We obtained again an oil that was crystallised in a mixture of methanol and diethylether to give a white powder (0.25 g, 40 % yield). mp: 131-133°C. ir: (KBr): 3320, 2950, 1690, 1640, 1590, 1510, 1460, 1390, 1360, 1240, 1160, 1070, 1030, 970, 860, 770 cm^{-1}. nmr: (80 MHz, DMSO d_6); δ ppm = 8.10 (2H, s, Ade-C_2H and Ade-C_8H); 7.80 (1H, s, NHCO); 7.10 (2H, s, NH_2); 6.70 (1H, s, NHCO); 4.10 (2H, t, Ade-CH_2); 3.05 (4H, m, $2CH_2NH$); 2.15 (2H, t, CH_2CO); 1.85 (2H, quint, $CH_2CH_2CH_2$); 1.25 (9H, s, $C(CH_3)_3$). ms: (CI, ammoniac, isobutane); M = 363; m/z: 364 $(M+1)^+$; 308 (M^+-$C(CH_3)_3$); 264 (M^+-$COOC(CH_3)_3$). uv: (H_2O); λ_{max} (ε): 262 (10610) nm. Anal. Calc. for $C_{16}H_{25}N_7O_3$, H_2O: C, 50.38; H, 7.13; N, 25.70. Found: C, 50.35; H, 7.21; N, 25.67.

2,6-diamino-9-[3-(3-(tert-butoxycarbonylamino)-propionamido)propyl]-9H-purine 22

Title compound **22** was prepared as described for compound **21** with 71 % yield. mp: 165-169°C. ir: (Nujol): 3320, 3160, 1690, 1660, 1600, 1520, 1250, 1210, 1160, 1080, 1050, 980, 850 cm^{-1}. nmr: (80 MHz, DMSO d_6); δ ppm = 7.90 (1H, s, NH); 7.70 (1H, s, DAP-C_8H) ; 6.55 (3H, s, NH_2 and NH); 5.70 (2H, s, NH_2); 3.90 (2H, t, DAP-CH_2); 3.45-2.85 (4H, m, $2CH_2$); 2.20 (2H,t, CH_2); 1.80 (2H, quint, $CH_2CH_2CH_2$); 1.30 (9H, s, $C(CH_3)_3$). ms: (EI); M = 378; m/z: 378 (M^+); 305 (M^+-$OC(CH_3)_3$); 279 (M^+-$COOC(CH_3)_3$); 234 (M^+-$(CH_2)_2$ NH $COOC(CH_3)_3$); 207 (DAP-$(CH_2)_3NH^+$); 177 (DAP-$(CH_2)_2^+$); 164 (DAP-CH_2^+); 150 (DAP^+).

6-amino-9-[3-(3-(3-(tert-butoxycarbonylamino)-propionamido)propionamido)propyl]-9H-purine 23

A suspension of adenine (0.225g, 1.5 mmol) and sodium hydride (0.075 g, 1.5 mmol) in dry DMF (7 mL) was stirred at room temperature for 30 min. Then a mixture of compound **13** (0.068 g, 2 mmol) and a catalytic amount of tetrabutylammonium iodide in DMF was added and the resulting solution was stirred at 80°C for 24 h. After filtration and evaporation of the solvent, the resulting oil was dissolved in the minimum amount of methanol and compound **23** was precipitated by adding diethylether (0.25 g, 38 % yield). mp: 175-182°C. ir: (KBr): 3310, 3120, 2980, 2920, 1670, 1635, 1600, 1565, 1530, 1460, 1420, 1360, 1330, 1300, 1250, 1100, 1050, 1000, 940, 900, 870, 790 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 8.15 (2H, s, Ade-C_2H and Ade-C_8H); 4.25 (2H, t, Ade-CH_2); 3.40 (2H, t, CH_2); 3.25 (4H, m, $2CH_2$); 2.35 (4H, m, $2CH_2$); 2.10 (2H, m, $CH_2CH_2CH_2$); 1.35 (9H, s, $C(CH_3)_3$). ms: (CI, NH_3, isobutane); M = 434; m/z: 435 (M^++H) ; 364 (M^+-$OC(CH_3)_3$); 335 (M^+-$COOC(CH_3)_3$); 318 (M^+-NHCOO $C(CH_3)_3$). uv: (H_2O); λ_{max} (ε): 261 (15460) nm. Anal.: Calcd. for $C_{19}H_{30}N_8O_4$, H_2O: C, 50.43; H, 7.13; N, 24.76. Found: C, 50.45; H, 7.04; N, 24.50.

2,6-diamino-9-[3-(3-(3-(tert-butoxycarbonylamino)-propionamido)propionamido)propyl]-9H-purine 24

Potassium carbonate (1 g, 7.5 mmol) and compound **13** (0.85 g, 2.5 mmol) were suscessively added to a suspension of 2,6-diaminopurine (0.5 g, 2.5 mmol) in DMF (50 mL). The mixture was stirred at 80°C under nitrogen for 24 h. After filtration and evaporation of the solvent, the resulting oil was dissolved in acetone and compound **24** was precipitated with diethylether (0.85 g, 76 % yield). mp: 120-123°C. ir: (KBr): 3320, 3200, 2950, 1680, 1640, 1600, 1530, 1470, 1450, 1410, 1370, 1340, 1280, 1250, 1170, 1050, 870 cm^{-1}. nmr: (80 MHz, DMSO d_6); δ ppm = 7.90 (2H, s, 2NH); 7.65 (1H, s, DAP-C_8H); 6.55 (3H, s, NH and NH_2); 5.70 (2H, s, NH_2); 3.85 (2H, t, DAP-CH_2); 3.05 (6H, m, $3CH_2$); 2.20 (4H, m, $2CH_2$); 1.75 (2H, quint, $CH_2CH_2CH_2$); 1.30 (9H, s, $C(CH_3)_3$). ms: (CI, NH_3, isobutane); M = 449; m/z: 450 (M^++H); 379 (M^+-$C(CH_3)_3$); 217 (M^+-DAP$(CH_2)_3$ NHCO); 185 (M^+-DAP$(CH_2)_3$ $NH(CH_2)_2$). uv: (H_2O); λ_{max} (ε): 281 (11318); 255 (9093); 215 (32335) nm. Anal. Calcd for $C_{19}H_{31}N_9O_4$, H_2O: C, 48.81; H, 7.11; N, 26.96. Found: C, 48.83; H, 6.94; N, 27.55.

6-amino-9-[3-(3-aminopropionamido)propyl]-9H-purine hydrochloride 27

Compound **21** (0.06 g, 0.16 mmol) dissolved in 1N solution of hydrochloric acid in acetic acid (3 mL) was stirred at room temperature for 1h. After evaporation of the solvent under reduced pressure, the gum was dissolved in methanol and precipitated by adding diethylether. Title compound **27** was obtained as the hydrochloride (0.05 g, 95 % yield). mp: 190-193°C. ir: (KBr): 3060, 1690, 1660, 1600, 1550, 1520, 1450,

1410, 1340, 1230, 1220, 1110, 870 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 8.35 (2H, s, Ade-C_2H and Ade-C_8H); 4.35 (2H, t, Ade-CH_2); 3.25 (4H, m, $2CH_2$); 2.65 (2H, t, CH_2-CO); 2.15 (2H, quint, $CH_2CH_2CH_2$). ms: (FAB (+), NBA); M = 263; m/z: 264 (M^++H). uv: (H_2O); λ_{max} (ε): 262 (12360) nm.

9-[3-(3-aminopropionamido)propyl]-2,6-diamino-9H-purine hydrochloride 28

Compound **28** was prepared as described for compound **27** with 84 % yield. mp: 230°C (dec.). ir: (Nujol): 3320, 3160, 1710, 1660, 1610, 1250, 1230, 1210, 1180, 1100, 850 cm^{-1}. nmr: (80 MHz, DMSO d_6); δ ppm = 8.90 (2H, s, NH_2); 8.45 (1H, t, NH); 8.25 (1H, s, DAP-C_8H); 8.15 (2H, s, NH_2); 4.05 (2H, t, DAP-CH_2); 3.00 (4H, m, $2CH_2$); 2.50 (2H, m, CH_2); 1.90 (2H, m, CH_2). ms: (CI, NH_3, isobutane); M = 278; m/z: 279 (M^++H); 262 (M^+-NH_2); 208 (M^+-$CO(CH_2)_2NH_2$); 191 (DAP $(CH_2)_3^+$); 151 (DAP$^+$). uv: (H_2O); λ_{max} (ε): 280 (11340); 255 (29430) nm.

6-amino-9-[3-(3-(3-aminopropionamido)propionamido)-propyl]-9H-purine hydrochloride 29

Compound **29** was prepared as described for compound **27** with 95 % yield. mp: 235-240°C. ir: (KBr): 3260, 3100, 1680, 1650, 1620, 1590, 1520, 1450, 1400, 1340, 1310, 1230, 1210, 1130, 960, 890, 860, 730, 710 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 8.25 (2H, s, Ade-C_2H and Ade-C_8H); 4.30 (2H, t, Ade-CH_2); 3.40 (2H, t, CH_2); 3.20 (4H, m, $2CH_2$); 2.65 (2H, t, CH_2) ; 2.35 (2H, t, CH_2); 2.10 (2H, quint, $CH_2CH_2CH_2$). ms: (FAB (+), glycerol); M = 334; m/z: 335 (M^++H). uv: (H_2O); λ_{max} (ε): 261 (12870) nm.

9-[3-(3-(3-aminopropionamido)propionamido)propyl]-2,6-diamino-9H-purine hydrochloride 30

Compound **30** was prepared as described for compound **27** with 70 % yield. mp: 235-238°C.ir: (KBr): 3140, 1630, 1530, 1440, 1380, 1220, 1090, 1060, 980, 950, 850, 760, 700, 650 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 7.95 (1H, s, DAP-C_8H); 4.15 (2H, t, DAP-CH_2); 3.40 (2H, t, CH_2); 3.20 (4H, m, $2CH_2$); 2,65 (2H, t, CH_2); 2.40 (2H, t, CH_2); 2.05 (2H, quint, $CH_2CH_2CH_2$). ms: (FAB (+), glycerol); M = 349; m/z: 350 (M^++H); 333 (M^+-NH_2); 277 (M^+-$CO(CH_2)_2$ NH_2). uv: (H_2O); λ_{max} (ε): 280 (5600); 255 (4700); 215 (14540) nm.

6-amino-9-[3-(3-(6-chloro-2-methoxyacridin-9-yl)amino-propionamido)propyl]-9H-purine hydrochloride 2

Compound **27** (0.12 g, 0.36 mmol) and 6-chloro-2-methoxy-9-phenoxyacridine **33** (0.20 g, 0.60 mmol) were stirred together in phenol (4 ml) heated at 80°C under nitrogen for 1h. The solution was then poured in a large volume of acetone to precipitate the desired compound **2**. After filtration, the compound was crystallized in acidic methanol (0.08 g, 45 % yield). mp: 235°C. ir: (KBr): 3250, 3090, 3050, 2960, 2870, 1685, 1625, 1590, 1550, 1520, 1495, 1465, 1450, 1415, 1400, 1375, 1345, 1310, 1295, 1270, 1240, 1230, 1185, 1165, 1140, 1115, 1095, 1030, 955, 930, 890, 850, 835, 765 cm^{-1}. nmr: (200 MHz, TFA d); δ ppm = 8.95 and 8.30 (2H, 2s, Ade-C_2H and Ade-C_8H); 7.85 (1H, d, Acr-C_8H); 7.40-7.00 (5H, m, Acr-H); 4.25 (2H, m, CH_2); 4.10 (2H, m, CH_2); 3.60 (3H, s, OCH_3); 3.10 (2H, m, CH_2); 2.65 (2H, m, CH_2); 1.95 (2H, m, CH_2). ms: (FAB(+), thioglycerol); M = 504; m/z: 505 (M^++H). uv: (H_2O); λ_{max} (ε): 423 (9240); 345 (5520); 278 (59030) nm. Anal. Calcd for $C_{25}H_{25}N_8O_2Cl$, 2HCl, 1.5H_2O: C, 49.65; H, 5.00; N, 18.52. Found: C, 49.98; H, 4.95; N, 18.49.

9-[3-(3-(6-chloro-2-methoxy-2-acridin-9-yl)amino-propionamido)propyl]-2,6-diamino-9H-purine hydrochloride 3

Compound **3** was prepared as described for compound **2** with 85 % yield. mp: 207-212°C (dec.).ir: (KBr): 3280, 3040, 1800, 1695, 1650, 1630, 1595, 1530, 1500, 1480, 1455, 1425, 1370, 1350, 1265, 1245, 1190, 1170, 1095, 1030, 935, 835, 760 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 8.05 (1H, d, Acr-C_8H); 7.60-7.05 (7H, m, DAP-C_8H and AcrH); 4.30 (2H, t, DAP-CH_2); 3.80 (3H, s, OCH_3); 3.35 (2H, t, CH_2NH); 3.25 (2H, t, CH_2NH); 2.80 (2H, t, CH_2 CO); 1.75 (2H, quint, $CH_2CH_2CH_2$). ms: (FAB (+), glycerol); M = 519; m/z = 520 (M^++H). uv: (EtOH); λ_{max} (ε): 442 (12040); 421 (12520); 340 (5043); 276 (73260); 215 (56610) nm. Anal. Calcd for $C_{25}H_{26}N_9O_2Cl$, 3HCl, 1.5H_2O: C, 45.75; H, 4.91; N, 19.20. Found: C, 45.85; H, 5.07; N,19.03.

6-amino-9-[3-(3-(3-(6-chloro-2-methoxyacridin-9-yl)amino-propionamido)propionamido) propyl]-9H-purine hydrochloride 4

Compound **4** was prepared as described for compound **2** with 55 % yield. mp: 154°C. ir: (KBr): 3250, 3060, 1690, 1650, 1630, 1590, 1555, 1500, 1430, 1410, 1360, 1270, 1245, 1085, 1025, 930, 840, 760 cm^{-1}. nmr: (200 MHz, TFA d); δ ppm = 9.00 and 8.30 (2H, 2s, Ade-C_2H and Ade-C_8H); 7.85 (1H, d, Acr-C_8H); 7.40-7.10 (5H, m, Acr-H); 4.20 (4H, m, $2CH_2$); 3.60 (3H, s, OCH_3); 3.20 (4H, m, $2CH_2$); 2.70-2.30 (4H, m, $2CH_2$); 1.95 (2H, m, CH_2). ms: (FAB (+), thioglycerol); M =575.5; m/z: 576 (M^++H). uv: (H_2O); λ_{max} (ε): 423 (5570); 344 (2810); 279 (31310) nm. Anal. Calcd for $C_{28}H_{30}N_9O_3$, 3HCl, 2H_2O: C, 46.61; H, 5.17; N, 17.47. Found: C, 46.49; H, 5.33; N, 17.78.

9-[3-(3-(3-(6-chloro-2-methoxyacridin-9-yl)amino-amino-propionamido)propionamido) propyl]-2,6-diamino-9H-purine hydrochloride 5

Compound **5** was prepared as described for compound **3** with 57 % yield. mp: 167-172°C (dec.). ir: (KBr): 3260, 3080, 2940, 1690, 1630, 1585, 1500, 1470, 1440, 1420, 1390, 1360, 1270, 1250, 1185, 1170, 1120, 1090, 1025, 980, 935, 865, 835, 760 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 7.95 (1H, d, Acr-C_8H); 7.45-7.15 (7H, m, DAP-C_8H and Acr-H); 4.20 (2H, t, DAP-CH_2); 3.90 (3H, s, OCH_3); 3.60 (4H, m, $2CH_2$); 3.10 (2H, t, CH_2); 2.90 (2H, t, CH_2); 2.45 (2H, t, CH_2); 1.75 (2H, quint, $CH_2CH_2CH_2$). ms: (FAB (+), thioglycerol); M = 590.5; m/z: 591 (M^++H). uv: (EtOH); λ_{max} (ε): 421 (11550); 340 (4600); 276 (67180); 214 (52260) nm. Anal. Calcd for $C_{28}H_{31}N_{10}O_3Cl$, 3HCl, 1.5H_2O: C, 46.23; H, 5.13; N, 19.25. Found: C, 46.35; H, 5.53; N, 18.76.

Ethyl-4-aza-7-tert-butoxycarbonylaminoheptanoate 15

A mixture of **14** (0.87 g, 5 mmol) and ethylacrylate (0.5 mL, 5 mmol) in ethanol (10 mL) was stirred at room temperature for 48 h. After evaporation of the solvent, the resulting oil was triturated in diethylether to give **15** as a white powder (1.1 g, 80 % yield). mp: 125-130°C.ir: (KBr) 3340, 2980, 2930, 1700, 1520, 1450, 1390, 1360, 1270, 1250, 1170, 1040, 1020, 855, 775 cm^{-1}. nmr: (80 MHz, $CDCl_3$); δ ppm = 5.05 (1H, s, NH CO); 4.15 (2H, q, CH_2CH_3); 3.15 (2H, m, CH_2); 2.60 (6H, m, $3CH_2$); 1.60 (3H, m, NH and CH_2); 1.40 (9H, s, $C(CH_3)_3$); 1.20 (3H, t, CH_2-CH_3). ms: (FAB(+), glycerol); M = 274; m/z: 275 (M^++H); 230 (M^+-OCH_2CH_3); 219 (M^+-$C(CH_3)_3$); 175 (M^+-$COOC(CH_3)_3$); 144 (M^+-$CH_2NHCOOC(CH_3)_3$); 30 (M^+-$(CH_2)_2NHCOOC(CH_3)_3$).

(4,8-diaza-4,8-di-tert-butoxycarbonyl) octanoic acid 16

Ester **15** (0.27 g, 1 mmol), dissolved in a 0.18 N solution of potassium hydroxide in ethanol (5.6 mL), was kept at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the residue triturated in diethylether to give a white powder that was dissolved in a mixture of water (10 mL) and dioxane (2 mL) containing an excess of sodium hydroxide (0.08 g, 2 mmol). Di-tert-butyldicarbonate (0.23 mL, 1.05 mmol) was added to this solution cooled at 0°C, then the solution was stirred 2 h at room temperature. A saturated solution of citric acid was added until the mixture reached pH 4, compound **16** was extracted with dichloromethane. After evaporation of the solvent, it was obtained as an oil (0.264 g, 76 % yield). ir: 3320, 2990, 1800, 1660, 1510, 1470, 1410, 1360, 1300, 1250, 1210, 1160, 1120, 1070, 950, 860, 840, 770, 730 cm^{-1}. nmr: (80 MHz, $CDCl_3$); δ ppm = 5.00 (1H, s, NHCO); 3.20 (6H, m, $3CH_2$); 2.55 (2H, t, CH_2CO); 1.60 (2H, quint, $CH_2CH_2CH_2$); 1.40 (18H, 2s, $2C(CH_3)_3$). ms: (CI, NH_3, isobutane); M = 346; m/z: 347 (M^++H); 291 (M^+-$C(CH_3)_3$); 247 (M^+-$COOC(CH_3)_3$).

N-(3-chloropropyl)-4,8-diaza-4,8-di-tert-butoxycarbonyl-octanamide 17

Compound **17** was prepared as compound **9**, starting from the acid **16** and 3-chloropropylamine. It was obtained as an oil with 74 % yield. ir: (film): 3320, 2940, 1800, 1670, 1540, 1470, 1410, 1360, 1250, 1160, 1070, 1030, 950, 860, 770 cm^{-1}. nmr: (80 MHz, $CDCl_3$); δ ppm = 6.05 (1H, s, NH); 4.80 (1H, s, NH); 3.20 (12H, m, $6CH_2$); 2.40 (2H, t, CH_2CO); 1.80 (4H, m, $2CH_2CH_2CH_2$); 1.40 (18H, s, $2C(CH_3)_3$). ms: (FAB(+), glycérol); M = 421.5; m/z: 422 (M^++H); 386 (M^+-Cl); 322 (M^+-$COOC(CH_3)_3$); 286 (M^+-(Cl+$COOC(CH_3)_3$)); 266 (M^+-($C(CH_3)_3$ + $COOC(CH_3)_3$)).

ethyl 4-aza-7-chloroheptanoate 18

A solution of 3-chloropropylamine hydrochloride (1.3 g, 10 mmol), triethylamine (1.4 mL, 10 mmol) and ethylacrylate (1 mL, 10 mmol) en ethanol (10 mL) was stirred 48 h at room temperature. After evaporation of the solvent, the residue was treated with 0.18 N sodium hydroxide in ethanol (60 mL) and the solvent evaporated again. Trituration in dichloromethane gave a solid which was removed by filtration and the filtrate concentrated, title compound **18** was precipitated by adding diethylether (1.64 g, 85 % yield). mp: 75-78°C. ir: (KBr): 3430, 2940, 2770, 2480, 1725, 1590, 1480, 1450, 1410, 1385, 1365, 1340, 1310, 1220, 1200, 1115, 1030, 975, 940, 860, 800, 660 cm^{-1}. nmr: (200 MHz, $CDCl_3$); δ ppm = 4.15 (2H, q, CH_2CH_3); 3.65 (2H, t, CH_2Cl); 3.25 (2H, t, CH_2NH); 3.15 (2H, t, CH_2NH); 2.95 (2H, t, CH_2CO); 2.35 (2H, quint, $CH_2CH_2CH_2$); 2.10 (1H, s, NH); 1.20 (3H, t, CH_2CH_3). ms: (FAB(+), glycerol); M = 193; m/z: 194 (M^++H); 158 (M^+-Cl); 130 (M^+-$Cl(CH_2)_2$); 106 ($Cl(CH_2)_3$ $NHCH_2^+$).

(4-aza-7-chloro-4-tert-butoxycarbonyl) heptanoic acid 19

Ester **18** was stirred 24 h at room temperature in a 0.37 N solution of sodium hydroxide in ethanol (25 mL). After evaporation of the solvent under reduced pressure, the oily residue was solubilised in 1N sodium hydroxide (25 mL) and the di-tert-butyldicarbonate (2.25 mL, 10 mmol) was added. After 3 h of stirring, the solution was cooled in an ice-bath and the pH brought to 4 with aqueous citric acid. Compound **19** was extracted with dichloromethane and was obtained as an oil after evaporation of the solvent (2 g, 77 % yield). ir: 3400, 2960, 1680, 1470, 1410, 1360, 1280, 1250, 1160, 1115, 930, 870, 850, 770 cm^{-1}. nmr: (80 MHz, $CDCl_3$); δ ppm = 3.45 (6H, m, $3CH_2$); 2.55 (2H, t, CH_2 CO); 1.90 (2H, quint, $CH_2CH_2CH_2$); 1.40 (9H, s, $C(CH_3)_3$). ms:

(FAB(+), glycerol); M = 265.5; m/z: 266 (M^++H); 248 (M^+-OH); 210 (M^+-$C(CH_3)_3$); 192 (M^+-$OC(CH_3)_3$); 166 (M^+-$COOC(CH_3)_3$).

4-aza-7-chloro-4-tert-butoxycarbonyl-N-(3-tert-butoxycarbonylaminopropyl) heptanamide 20

Compound **20** was prepared as described for **9**, starting from compounds **14** and **19** with 90 % yield. ir: 3320, 2960, 2920, 1680, 1520, 1470, 1410, 1390, 1360, 1270, 1250, 1160, 1115, 1030, 850, 770 cm^{-1}. nmr: (80 MHz, $CDCl_3$); δ ppm = 6.50 (1H, s, NH); 4.70 (1H, s, NH); 3.55-3.00 (10H, m, $5CH_2$); 2.40 (2H, t, CH_2CO); 2.05-1.50 (4H, m, $2CH_2CH_2CH_2$); 1.40 (18H, s, $2C(CH_3)_3$). ms: (FAB(+), glycerol); M = 421.5; m/z: 422 (M^++H); 351 (M^+-$OC(CH_3)_3$); 322 (M^+-$COOC(CH_3)_3$); 266 (M^+-($COOC(CH_3)_3$ + $C(CH_3)_3$)).

2,6-diamino-9-[3-(4,8-diaza-4,8-di-tert-butoxycarbonyl-octanamino)propyl]-9H-purine 25

Compound **17** (0.7 g, 1.4 mmol) was added to a suspension of 2,6-diaminopurine (0.22 g, 1.42 mmol) and potassium carbonate (1.17 g, 8.4 mmol) in DMF (10 mL) containing a catalytic amount of tetrabutylammonium iodide. The mixture was stirred 48 h at 80°C under nitrogen. After filtration, the solvent was removed under reduced pressure. The oily residue was diluted with water and extracted with dichloromethane. Evaporation of the organic layer gave an oil that crystallized in diethylether. Compound **25** was obtained as a brown powder (0.4 g, 50 % yield). mp: 75-80°C. ir: (KBr): 3320, 3200, 2980, 1660, 1640, 1600, 1530, 1470, 1410, 1360, 1280, 1220, 1160, 1120, 790 cm^{-1}. nmr: (80 MHz, $CDCl_3$); δ ppm = 7.50 (1H, s, DAP-C_8H); 5.50 (1H, s, NH CO); 5.30-4.60 (5H, m, NH CO and $2NH_2$); 4.10 (2H, t, DAP-CH_2); 3.60-2.85 (10H, m, $5CH_2$); 2.35 (2H, quint, $CH_2CH_2CH_2$); 1.70 (2H, quint, $CH_2CH_2CH_2$); 1.35 (18H, s, $2C(CH_3)_3$). ms: (CI, ammoniac, isobutane); M = 535; m/z: 536 (M^++H); 404 (M^+-$CH_2NHCOC(CH_3)_3$); 386 (M^+-DAP); 362 (M^+-DAP $(CH_2)_2$); 304 (M^+-DAP $(CH_2)_3$ $NHCOCH_2$).

9-[4-aza-6-((3-(tert-butoxycarbonylamino)propylamino)carbonyl)-4-tert-butoxycarbonylhexyl] 2,6-diamino-9H-purine 26

Title compound **26** was prepared as compound **25** with 40 % yield. mp: 79-82°C. ir: (KBr): 3330, 2960, 1670, 1590, 1520, 1470, 1410, 1360, 1270, 1250, 1160, 1090, 860, 790 cm^{-1}. nmr: (200 MHz, $CDCl_3$); δ ppm = 7.45 (1H, s, DAP-C_8H); 5.60 (2H, s, NH_2); 5.40 (3H, s, NH_2 and NH); 4.65 (1H, s, NH); 4.05 (2H, t, DAP-CH_2); 3.45 (2H, m, CH_2); 3.20 (2H, m, CH_2); 3.05 (4H, m, $2CH_2$); 2.50 (2H, m, CH_2CO); 2.00-1.45 (4H, m, $2CH_2CH_2CH_2$); 1.35 (18H, s, $2C(CH_3)_3$). ms: (FAB(+), glycerol); M = 535; m/z: 536 (M^++H); 436 (M^+-$COC(CH_3)_3$); 336 (M^+-2($COOC(CH_3)_3$); 277 (DAP-$(CH_2)_3$-N-$(CH_2)_2$-$CONH^+$).

2,6-diamino-9-[3-(4,8-diazaoctanamido)propyl]-9H-purine hydrochloride 31

Compound **25** (0.49 g, 0.9 mmol) was stirred 1 h in a 1N solution of hydrochloric acid in acetic acid (15 mL). After evaporation of the solvent under reduced pressure, compound **31** was precipitated in ethanol (15 mL). It was obtained as a white powder (0.38 g, 90 % yield). mp: 195-198°C. ir: (KBr): 3480, 1710, 1660, 1570, 1530, 1470, 1450, 1420, 1400, 1330, 1220, 1170, 1090, 1000, 910, 860 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 7.85 (1H, s, DAP-C_8H); 4.15 (2H, t, DAP-CH_2); 3.30-3.05 (8H, m, $4CH_2$); 2.55 (2H, t, CH_2 CO); 2.10 (4H, m, 2($CH_2CH_2CH_2$)). ms: (FAB(+), glycerol); M = 335; m/z: 336 (M^++H). uv: (H_2O): λ_{max} (ε): 281.5 (6250); 253.5 (5044) nm.

9-[6-((3-aminopropylamino)carbonyl)-4-azahexyl]-2,6-diamino-9H-purine hydrochloride 32

Compound **32** was prepared as compound **31** with 90 % yield. It was cristallized in acidic methanol (CH_3OH-12N HCl). mp: 210°C (dec.). ir: (KBr): 3330, 3060, 1690, 1660, 1580, 1540, 1460, 1420, 1390, 1230, 1150, 1080, 1060, 1000, 860, 770 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 7.85 (1H, s, DAP-C_8H); 4.15 (2H, t, DAP-CH_2); 3.25 (2H, t, CH_2 NH); 3.00 (4H, m, $2CH_2$); 2.80 (2H, t, CH_2 CO); 2.10 (2H, quint, $CH_2CH_2CH_2$); 1.85 (2H, quint, $CH_2CH_2CH_2$). ms: (CI,NH_3, isobutane); M = 335; m/z: 336 (M^++H). uv: (H_2O): λ_{max} (ε): 282 (7791); 254 (6808) nm. Anal. Calcd for $C_{14}H_{25}N_9O$, 4HCl, .5 CH_3OH: C, 35.05; H, 6.28; N, 25.35. Found: C, 35.25; H, 6.56; N, 25.21.

9-[3-(8-(6-chloro-2-methoxyacridin-9-yl)-4,8-diazaoctanamido)propyl]-2,6-diamino-9H-purine hydrochloride 6

Compound **31** (0.28 g, 0.58 mmol) and 6-chloro-2-methoxy-9-phenoxyacridine **33** (0.2 g, 0.6 mmol) were stirred in phenol heated at 100°C for 4 h under nitrogen. The solution was then pourred in a large volume of acetone (300 mL). The yellow solid was filtrated, washed three times with acetone. Compound **6** was purified on column chromatography (silica gel, Methanol-ethylacetate-triethylamine 50/50/1 v/v/v) It was further crystallized as the hydrochloride in acidic methanol (0.215 g, 50 % yield). mp: 185-190°C. ir: (KBr): 3260, 3060, 1700, 1680, 1640, 1590, 1560, 1500, 1470, 1440, 1380, 1250, 1230, 1180, 1090, 1060, 1030, 930, 840, 800, 760 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 8.10 (1H, d, Acr-C_8H); 7.55-7.30 (6H, m, DAP-C_8H and Acr-H); 4.10 (2H, t, DAP-CH_2); 3.95 (3H, s, OCH_3); 3.75 (2H, t, CH_2); 3.45 (2H, m, CH_2); 3.35 (2H, m, CH_2); 3.20 (2H, m, CH_2); 2.75 (2H, m, CH_2); 2.40 (2H, quint, $CH_2CH_2CH_2$); 1.65 (2H, quint, $CH_2CH_2CH_2$). hrms (FAB+): m/z $(M+H)^+$ Calcd for $C_{28}H_{34}N_{10}O_2Cl$ 577.2554; Found 577.2571.

9-[6-((3-((6-chloro-2-methoxyacridin-9-yl)amino)propyl-amino)carbonyl)-4-aza-hexyl-2,6-di-amino-9H-purine hydrochloride 7

Compound **7** was prepared as compound **6** with 55 % yield. mp: > 195°C (dec.). ir: (KBr): 3300, 3090, 2940, 2800, 1690, 1640, 1590, 1560, 1530, 1500, 1420, 1390, 1360, 1275, 1245, 1170, 1120, 1090, 1030, 930, 850, 800 cm^{-1}. nmr: (200 MHz, D_2O); δ ppm = 7.90 (1H, d, Acr-C_8H); 7.50-7.10 (6H, m, DAP-C_8H and Acr-H); 3.90 (5H, m, DAP-CH_2 and OCH_3); 3.65 (2H, m, CH_2); 3.45 (2H, m, CH_2); 3.00 (2H, m, CH_2); 2.70 (2H, m, CH_2); 2.55 (2H, m, CH_2); 2.10 (2H, quint, $CH_2CH_2CH_2$); 1.90 (2H, quint, $CH_2CH_2CH_2$). hrms (FAB+): m/z $(M+H)^+$ Calcd for $C_{28}H_{34}N_{10}O_2Cl$ 577.2554; Found 577.2576.

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