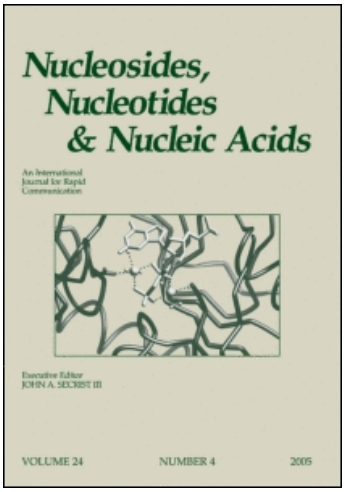

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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R. N. Warrener[a]; D. N. Butler[a]; M. Golic[a]
[a] Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland, Australia

To cite this Article Warrener, R. N. , Butler, D. N. and Golic, M.(1999) 'The Synthesis of Geometric Variants of Rigidly-Linked Uracil-{Spacer}-Uracil and Uracil-{Spacer}-Effector Molecules Using Block Assembly Methods', Nucleosides, Nucleotides and Nucleic Acids, 18: 11, 2631 — 2660
To link to this Article: DOI: 10.1080/07328319908044631
URL: http://dx.doi.org/10.1080/07328319908044631

NUCLEOSIDES & NUCLEOTIDES, 18(11&12), 2631–2660 (1999)

THE SYNTHESIS OF GEOMETRIC VARIANTS OF RIGIDLY-LINKED URACIL-{SPACER}-URACIL AND URACIL-{SPACER}-EFFECTOR MOLECULES USING BLOCK ASSEMBLY METHODS

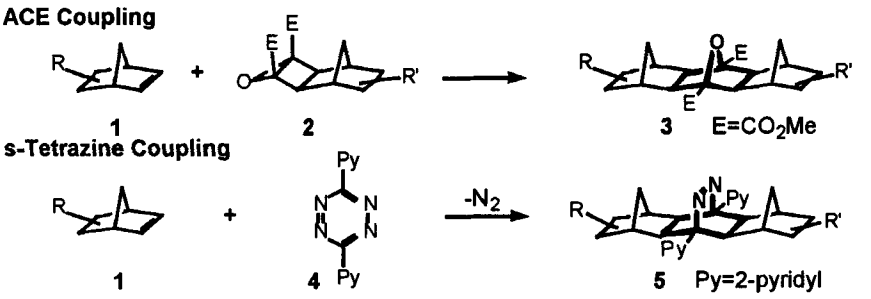
R.N. Warrener*, D.N. Butler and M. Golic

Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland, 4702, Australia

ABSTRACT: Pyrimidine-containing building BLOCKs, formed from the thermal reaction of norbornadiene with 2,4-dimethoxy-1,3-diazaanthracene, are linked together using LEGO-like assembly methods and chemically modified (hydrolysis) to form rigidly linked *bis*-uracils in which the pyrimidine rings can be aligned in northern or southern geometries and HH or HT variants. Similar methods are used to link pyrimidine BLOCKs to chromophore-containing BLOCKs to access rigid uracil-{spacer}-chromophore molecules which are available in a variety of different geometries.

Gene manipulation has become a recognised technique in modern biotechnology. The ability to cut sections from, or add sections to, nucleic acids is at the heart of this process. While enzymes are used to achieve the selective cleavages, the ability to incorporate natural and unnatural sequences of polynucleotides is available to the molecular geneticist. Another advance in this area has been the emergence of sequencing machines with which to build the polynucleotides. This methodology has impacted strongly owing, in part, to the opportunity to include unnatural nucleotides into the polynucleotides building program (modified NAs).

Our group has very recently devised a LEGO-like building BLOCK[1] approach to the synthesis of rigid molecules which contain specifically located chromophores or other groups.[2-5] These linking methods (ACE and s-tetrazine coupling, SCHEME 1) are stereoselective thereby allowing these molecules to be prepared in different molecular architectures, *eg* rods, spacers, cavities *etc,* depending only on the geometry of the individual BLOCKs employed. It seemed to us that having building BLOCKs



Scheme 1

incorporating nucleic acid bases such as uracil as the effector group could be of value for the preparation of rigidly linked *bis*-pyrimidines which could be elaborated to new unnatural nucleotides.

Reports on nucleic acid components being linked through their base component are not common. Initial work involved the preparation of *N,N*-linked thymines used in photodimerisation studies,[6-11] although a recent report describes a *bis*-guanosine **6** in which the nucleosides are linked by an anthracene spacer group (Fig 1).[12] This space-separated system has the guanosine and the spacer linked through an acetylene unit and this allows (restricted) rotation to occur, i.e. there is conformational mobility about the

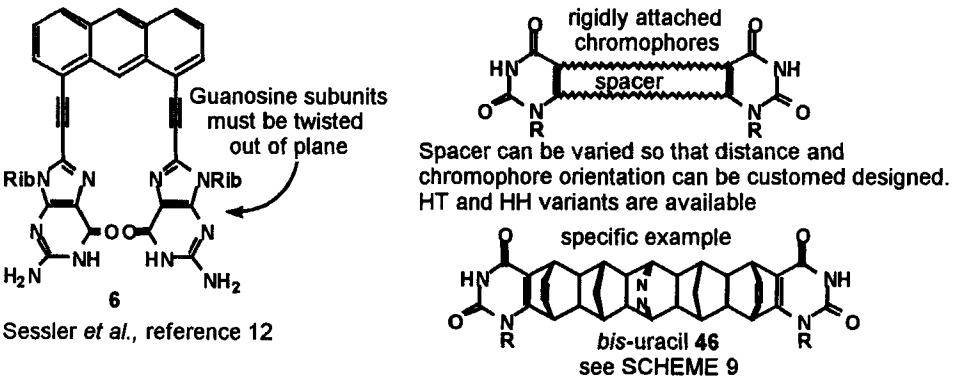


Figure 1

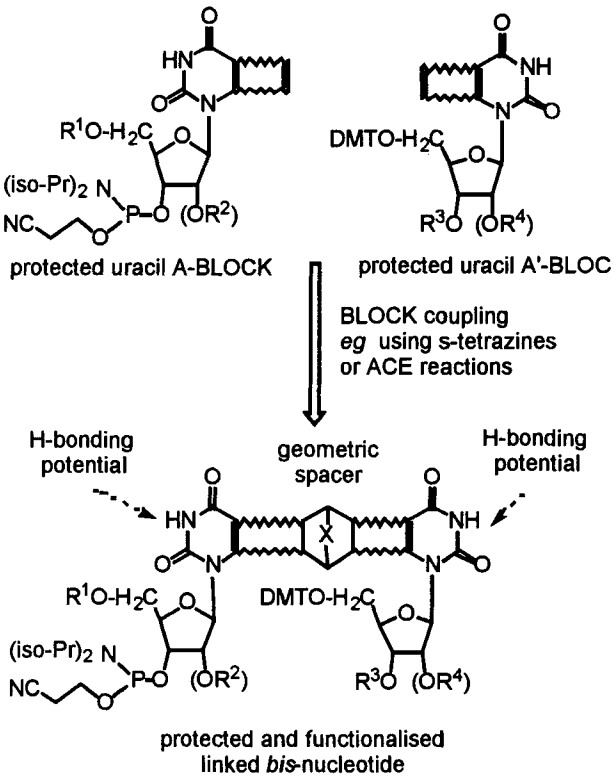


Figure 2. Schematic for BLOCK coupling to prepare a *bis*-nucleotide suitable for incorporation into a polynucleotide.

sigma bonds. The *bis*-uracil systems described herein, *eg* **46**, rigidly align the chromophore with the spacer unit since the linkage involves a pair of sigma-bonds.

Two like or unlike uracil BLOCKs can be linked together to produce a range of *bis*-uracils (HH and HT variants can be produced). All the compounds of this report have the uracil nitrogens unsubstituted, thereby allowing conversion to *bis*-nucleosides using standard ribo- or deoxyribosylation methods and ultimately to fully protected and functionalised *bis*-nucleotides. Compounds of this type have the two NA bases rigidly linked, so that their incorporation into DNA or RNA could serve as geometric turn-units. For solubility reasons, in recent work we have shown that the carbocyclic framework can be modified to produce hydrophilic or lipophilic variations; otherwise standard protecting groups can be introduced on the NA components to make them suitable for oligomerisation as 5th bottle components in automated NA synthesis (Fig 2).

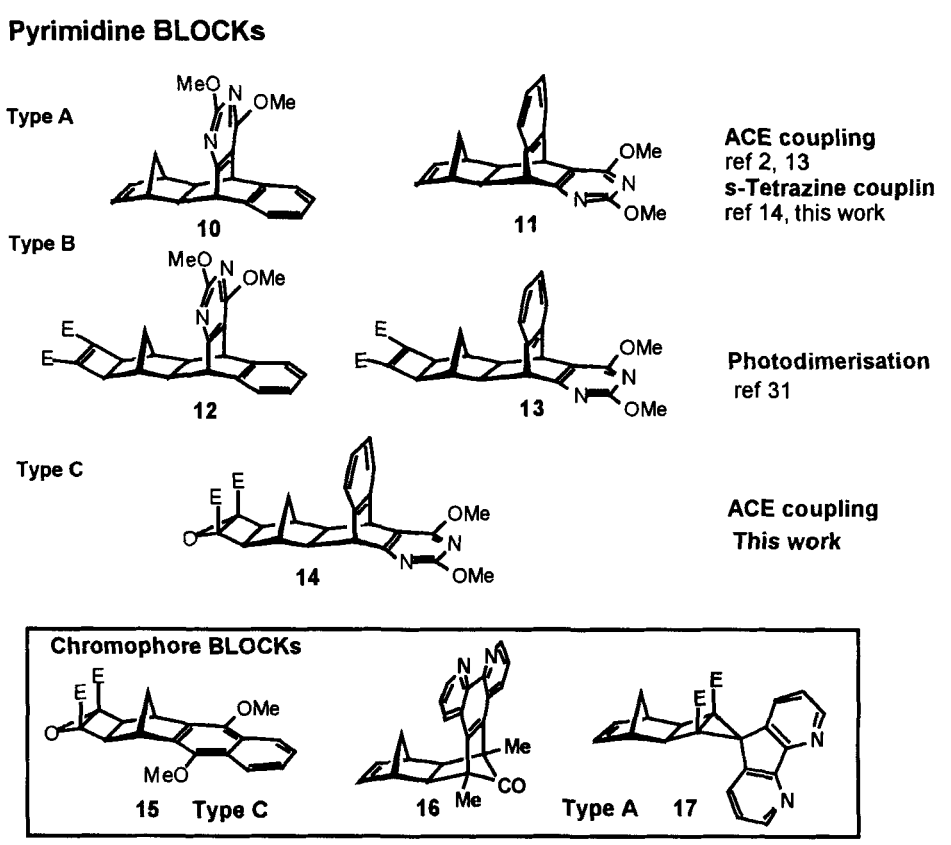
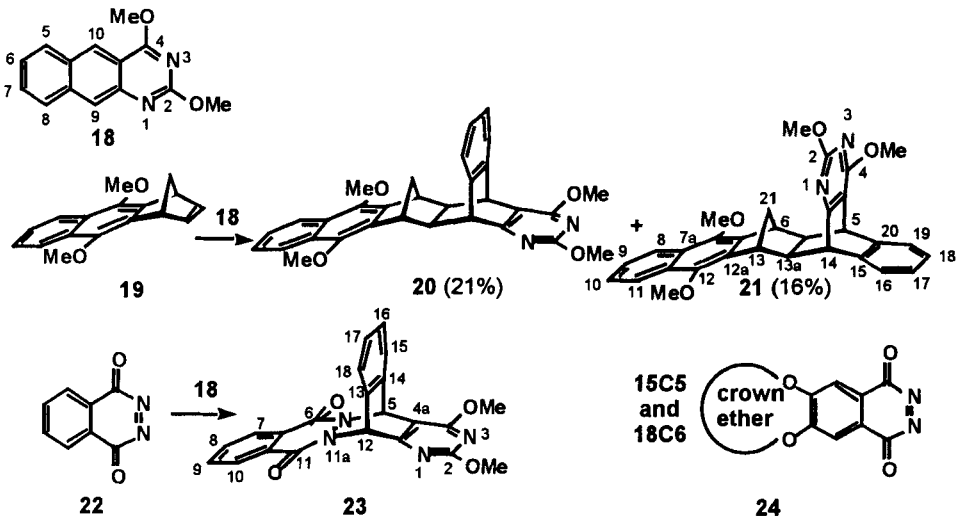


Figure 3

In this paper, we report on the use of activated s-tetrazines and ACE coupling techniques to form pyrimidine-{spacer}-chromophore and pyrimidine-{spacer}-pyrimidine systems from individual pyrimidine-containing BLOCKs. The BLOCKs employed in this work are shown in Fig 3 and their preparation has been reported elsewhere in preliminary form[13,14] or detailed in the experimental. Type A norbornene BLOCKs can participate in both ACE and s-tetrazine coupling, whereas Type C BLOCKs have been specifically designed for ACE coupling. The cyclobutene 1,2-diester Type B BLOCKs are formed as intermediates in the conversion of Type A to Type B BLOCKs (*vide infra*) and can participate in ACE reactions or serve as substrates for photodimerisation procedures.

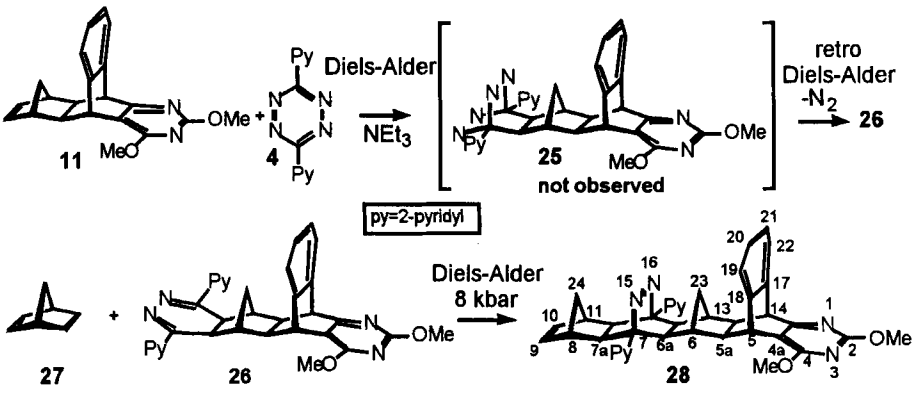


Scheme 3

We have reported a range of effector BLOCKs which could be used as chromophores units in this project *eg* those containing light absorbing chromophores,[2] porphyrins,[5,15,16] crown ethers,[17,18] bidentate ligands[4,5] and their metal complexes,[19] β-lactams,[20] anthraquinones,[21] and heterocycles.[22] Each of these pharmacophores or reporter groups (collectively referred to as effector groups) are good BLOCK substrates and can be attached to uracil subunits.

Part 1 Pyrimidine-{spacer}-Chromophore Systems

a) Direct Diels-Alder Cycloaddition. Pyrimidine-{spacer}-chromophore systems can be produced by Diels-Alder addition of the chromophore-carrying dienophile to an appropriately substituted diazaanthracene. Thus, cycloaddition (toluene, sealed tube, 200°, overnight) of 2,4-dimethoxy-1,3-diazaanthracene **18** with dimethoxynaphtho-norbornadiene **19** yields a mixture of stereoisomeric 1:1-adducts **20** and **21** (Scheme 3). An alternative Diels-Alder coupling reaction uses the addition of dimethoxy-diazaanthracene 18 with phthalazine dione 22, formed *in situ* by $Pb(OAc)_4$ oxidation of phthalhydrazide,[23] to access pyrimidine-chromophore systems. This reaction proceeds at room temperature to form the adduct **23**, albeit in low yield (14%, not optimised). The



Scheme 4

potential to deliver chromophore groups using this reaction is good, since we have recently described the efficient delivery of crown ether functionality to other spacer systems using the crown ethers **24**.[17,18]

b) The s-Tetrazine Coupling Route. 3,6-Di(2-pyridyl) s-tetrazine **4** is an active inverse electron-demand diene and readily reacts with norbornene partners. The coupling process involves three cycloaddition steps (Scheme 4), however, as the retro-Diels-Alder step (**25** to **26**) occurs spontaneously, the protocol thereby simplifies to a two step procedure. Where coupling of the same BLOCK is concerned, this simplifies even further, and can be achieved as a one-pot process by employing a 2:1 molar ratio of alkene to s-tetrazine.

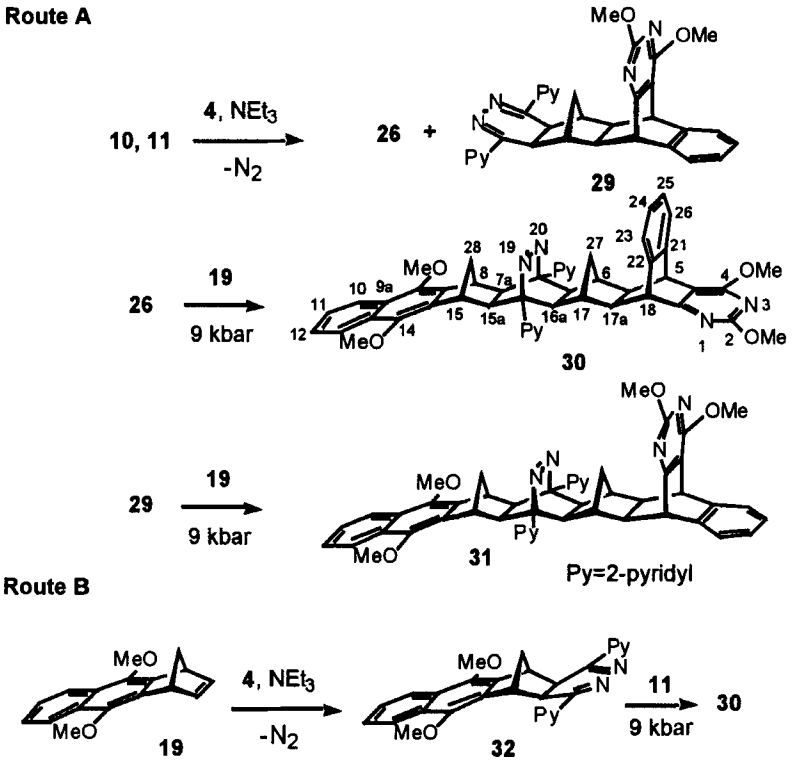
The ability to link two *different* norbornene partners using the s-tetrazine coupling protocol makes it an extremely versatile method. This is illustrated by the coupling of norbornadiene with pyrimidine BLOCK **11** which is achieved by reaction of BLOCK **11** with 3,6-di(2-pyridyl)-s-tetrazine **4** to form dihydropyridazine **26**, as the first step (Scheme 4). This reaction occurs at room temperature by stirring a suspension of the reagents together in a small volume of methylene chloride containing a drop of triethylamine. The s-tetrazine **4** serves as a monitor for the reaction, as the loss of nitrogen indicates the reaction is occurring and the change from the bright purple colour of the s-tetrazine to the yellow colour of the dihydropyridazine **26**, indicates when the first step is complete. When the colour has changed, the second reagent is added, in this

case norbornadiene **27** (in excess), and the mixture added to a variable-volume teflon cell and subjected to ultra high-pressure (8 kbar, 15 hours). The reaction product **28** was separated by column chromatography on silica and isolated as a colourless powder, mp 279 °C, in 68% yield. Another feature of this particular coupling reaction is that it can be used to lengthen a norbornene BLOCK by 4σ-bonds.

Some of the features of the ^{1}H NMR of adduct **28** can be used as a model for use with other structural assignments in this series. The methylene bridge protons are very diagnostic since they are shifted upfield by the aromatic rings (benzene>pyrimidine) and by the azo-bridge, a factor which can be used as a diagnostic for the *exo, exo*-fusion occurring in the coupling process. Thus, the doubly shielded methylene protons resonate at δ 0.30 (azo plus long-range aromatic shielding) and δ -1.04 (aromatic plus long-range azo-bridge shielding), while the other methylene pair originating from the norbornadiene reagent occur at δ 0.63 (azo-shifted) and δ 1.21 (small long-range azo-bridge coupling). The underface protons (H5a, H13a; H6a, H12a; H7a, H11a) occur as cross-frame pairs and each member of the pair might be expected to occur at different chemical shifts owing to the anisotropic shielding of the unsymmetrical pyrimidine ring. In practice, this effect falls off to zero after 3σ-bonds separate the proton from the pyrimidine ring.

The difference in ^{13}C-chemical shift between cross-frame carbons also falls off with distance, but extends further from the pyrimidine ring than for the proton shift, i.e. it is still apparent after 6σ bonds: Δδ 1.3 (2σ-bonds C5a, C13a), 0.3 (4σ-bonds C6a, C12a), 0.1 (6σ-bonds C7a, C11a). In contrast, the ^{13}C-chemical shifts of the bridgehead carbons drops off dramatically, *eg* the carbons directly attached to the pyrimidine (1σ-bond separation) are quite different, C5 (δ 49.8) and C14 (δ 39.7), but the difference is negligible at the adjacent bridgehead positions (3σ-bonds), C6 = C13 (δ 42.2). It should also be noted that the pyridyl groups are different and exhibit eight separate carbon resonances (two of which overlap). This is an important consideration when distinguishing between isomeric C_2 and σ_v *bis*-pyrimidines *(vide infra.)*

The coupling of the dimethoxynaphthalene and pyrimidine chromophores was achieved in both coupling modes (Scheme 5). In Route A, the dihydropyridazines **26** and **29** carried the pyrimidine functionality and were coupled with naphthonorbornadiene **19** to attach the naphthalene chromophore. Two geometric isomers **30** and **31** were

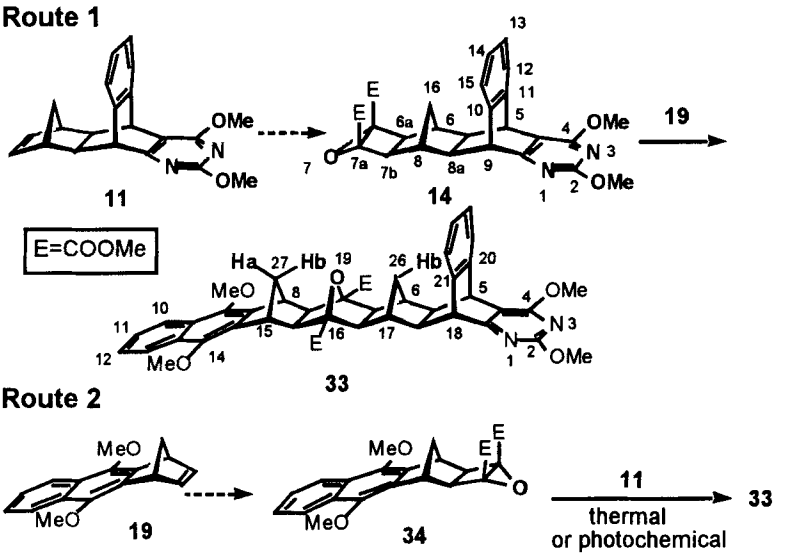


Scheme 5

produced, in which the relative orientation of the pyrimidine component to the naphthalene ring is quite different in the two products.

The alternative coupling (Route B) proceeds via the dihydropyridazine **32**, which is coupled with the dienophile **11** as the pyrimidine provider. These reactions demonstrate the ability of the s-tetrazine coupling protocol to introduce desired functionality into the pyrimidine-{spacer}-dimethoxynaphthalene compound in a geometrically precise fashion.

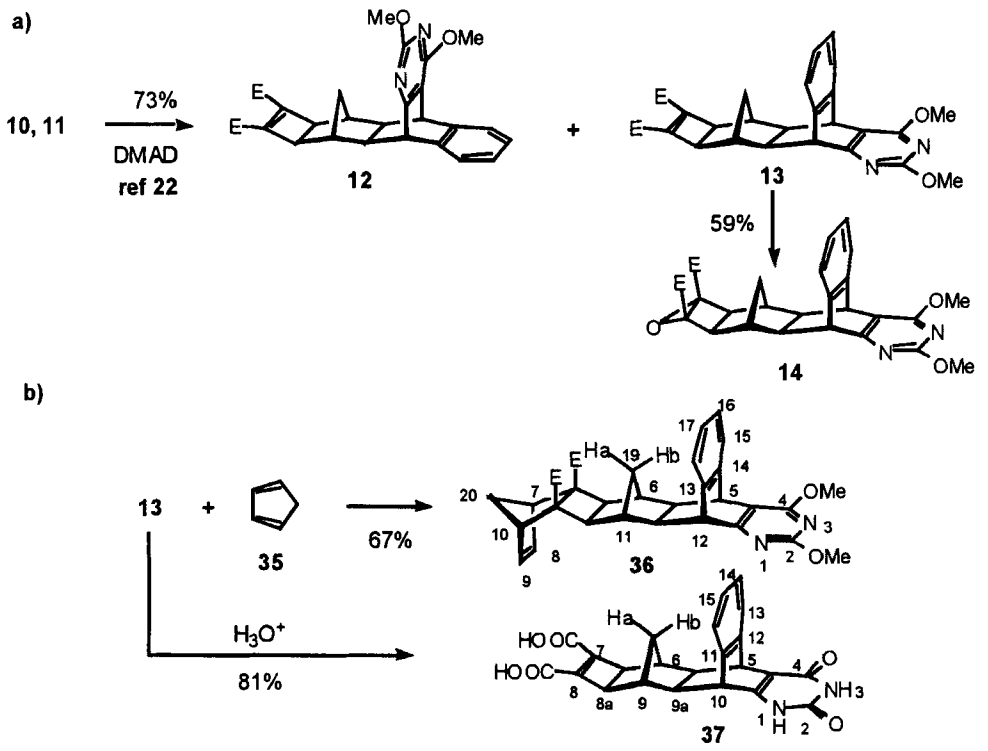
The products **30** and **31** failed to be separated by column chromatography on silica. Isomer **30** was isolated by fractional crystallisation (EtOAc/petrol) of a fraction in which it was enriched, while isomer **31** was obtained in pure form by reverse-phase HPLC chromatography. These compounds were characterised by EI mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy and their purity assessed by microanalysis (C, H, N) and high resolution EI and electrospray mass spectrometry.



Scheme 6

c) The ACE Coupling Protocol. The ACE reaction is another of the suite of coupling procedures, developed by our group, for the coupling of alkene BLOCKs using LEGO-LIKE BLOCK construction methods to form the rigid space-separated systems (*vide supra*).

In demonstrating the coupling potential of this reaction, we again use the dimethoxynaphthalene chromophore as the chromophore group to link with the pyrimidine. Here also, the coupling can be achieved using complementary pairs of reagents to carry the chromophore groups (Scheme 6). The epoxide **14**, prepared by low temperature epoxidation of the **13** (Scheme 7), can be used to transport the pyrimidine ring to the spacer system **33** by reaction with the naphthonorbornadiene **19** (Route 1). In the complementary method (Route 2),[14] the known epoxide **34**[2] carries the naphthalene chromophore, which is coupled with pyrimidine BLOCK **11** to form pyrimidine-{spacer}-naphthalene **33**. The last step can be achieved either thermally (sealed tube, 140 °C, neat, yield 49%) or under photochemical conditions (300 nm, acetone) in 67% yield. The photochemical reaction is specific for the naphthalene-containing cyclobutene epoxide, since such reagents require light absorption to enter into this reaction.



Scheme 7

For ACE coupling protocols used to form pyrimidine-{spacer}-chromophore systems related to **17** (Fig 3), it was necessary to access cyclobutene epoxides carrying pyrimidine functionality. This is achieved by converting the norbornene BLOCK to the related cyclobutene-1,2-diester by Ru-catalysed addition of dimethyl acetylene dicarboxylate under conditions described by Mitsudo and his coworkers.[24,25] This is followed by epoxidation of the cyclobutene-1,2-diester using a nucleophilic epoxidising reagent (tBuOOH, MeLi, -78 °C) in 59% yield (Scheme 7a).

While hydrolysis of the 2,4-dimethoxy-pyrimidine ring in adduct **13** to the corresponding uracil can be achieved under acid conditions, concomitant hydrolysis of the ester groups also occurred to form the uracil-diacid **37** in 81% yield (Scheme 7b). The dienophilicity of the cyclobutene-1,2-diester in **13** was established by reaction with cyclopentadiene **35** to produce the *anti*-Alder adduct **36** (67% yield, >95% stereoselectivity). Good precedent exists for this stereoselective outcome.[26,27]

Part 2 Coupling to Form Pyrimidine-{spacer}-Pyrimidines

The coupling reactions we employ in this work all use cycloaddition chemistry involving at least one norbornene substrate. More importantly, BLOCK reagents incorporating a single nucleic acid base linked to a norbornene must be chiral (or a racemate) owing to the lack of symmetry of the base component. Two reaction scenarios arise when a racemic norbornene BLOCK is coupled with itself or a second BLOCK. If the second BLOCK is achiral, then a single racemate is produced (*vide supra*). However, when the second BLOCK is also a racemate, the coupling leads to a mixture of diastereomers being produced. This occurs because each enantiomeric form of the racemic substrate can react with either a partner with the same handedness or with a partner of the opposite hand.

Using the racemic uracil-fused norbornene (R,S)-**38** having the skeletal structure common to many of the compounds discussed herein, reference to the schematic in FIG 4 indicates that there are four products (**39-42**) available from the self-coupling process. The (RS)-product **39** and the (SR)-product **41** are mirror images of each other and superimosable, *ie* they are identical meso-isomers. The (SS)-product **40** and the (RR)-product **42** are mirror images and not superimposable, *ie* they are separate enantiomers. This analysis correctly predicts that all such self-dimerisations should lead to two diasteromers, one a meso product and the other a racemate. While the racemic pair can, in principle, be separated further into separate enantiomers using, for example, chromatography on a chiral column, this has not been conducted in the present study.

The "southern hemisphere" pyrimidine-{spacer}-pyrimidine system has the pyrimidine rings positioned othogonally to, and on the bottom face of, the carbocyclic frame (see molecular modelling,[28] Fig 5). Owing to the downward curvature of the frame, these rings are now orientated at an angle of 54° one with the other and form a distinct cavity shape. This orientation of the pyrimidine rings in **43** and **45** (Scheme 8) is quite similar to that which exists in the *anti* HH-photodimer **44** of 2,4-dimethoxy-1,3-diazaanthracene **18**,[30] where the angular relationship is 51°. The separation of the pyrimidine rings differs markedly between the two systems, with the centre to centre distance of the pyrimidine rings being 3.70 Å in the photodimer **44** and 12.36 Å in the coupled product **43** (Fig 5).

In this case, the s-tetrazine coupling of racemic norborneno-pyrimidine 11 was used in the production of **45** (mp 328-329 °C; 27% yield) and **43** (mp 317-319 °C; 33%

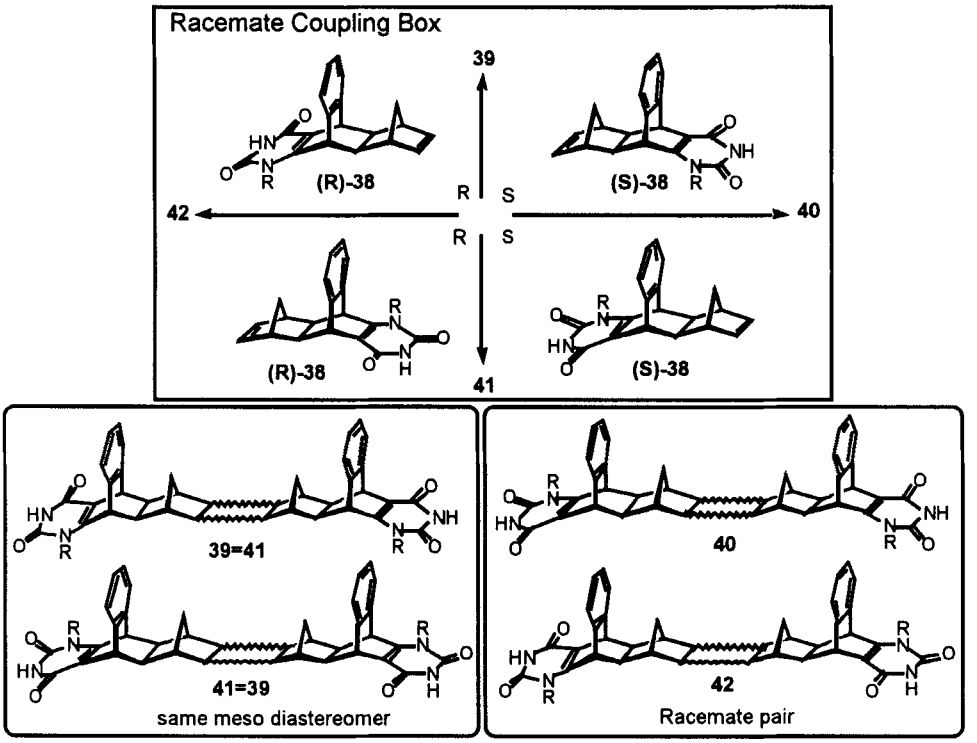
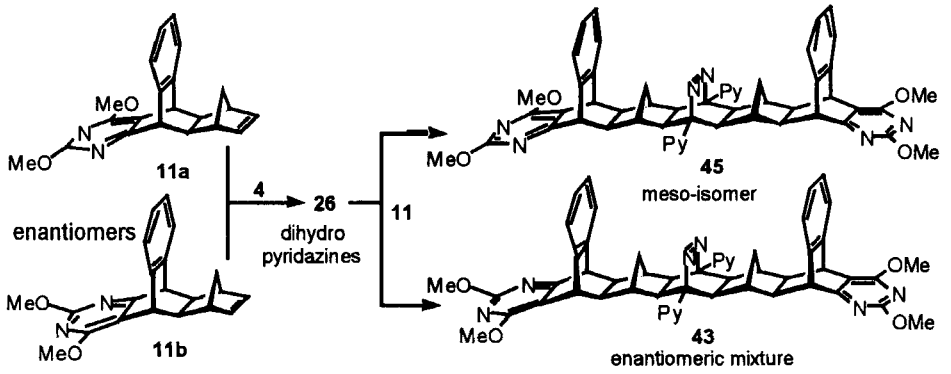


Figure 4



Scheme 8

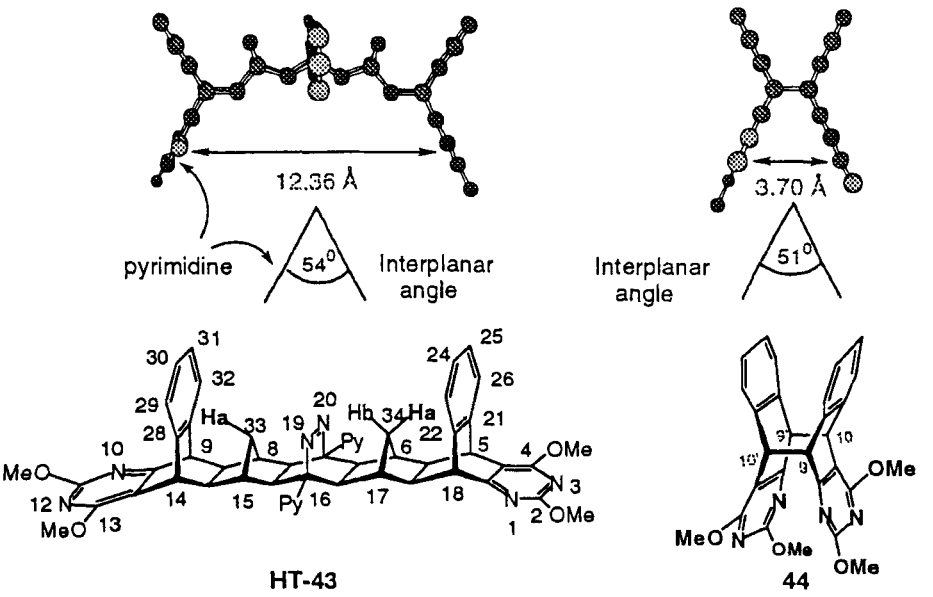
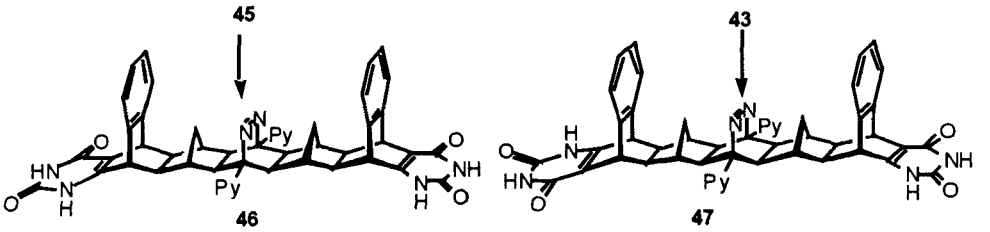


Figure 5



Scheme 9

yield): these isomers were separated by radial chromatography. Hydrolysis of the space-separated pyrimidines **45** and **43** was employed to produce the related 'southern hemisphere' HH *bis*-uracil **46** and HT *bis*-uracil **47** respectively (Scheme 9).

The "northern hemisphere" pyrimidine-{spacer}-pyrimidine systems have the pyrimidine rings positioned othogonally to, and on the top face of, the downward-curved carbocyclic frame (see molecular modelling, Fig 6). Such compounds come in two variants: one has the two pyrimidine rings in a head to head HH-orientation, *eg* meso-isomer **48**; the other has the pyrimidine rings opposed in a head to tail HT-orientation, *eg*

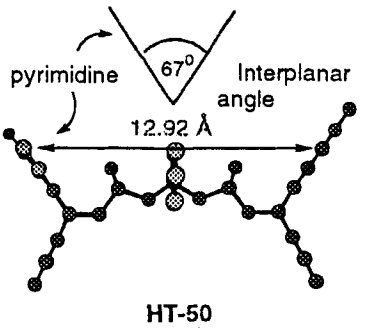
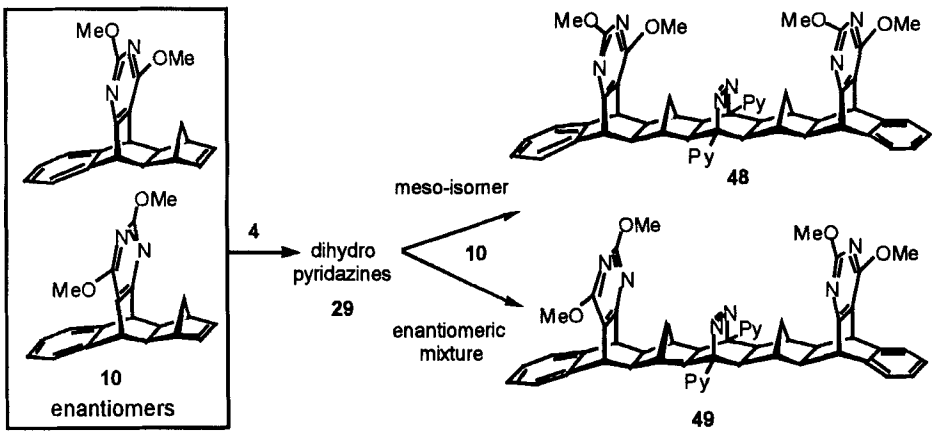


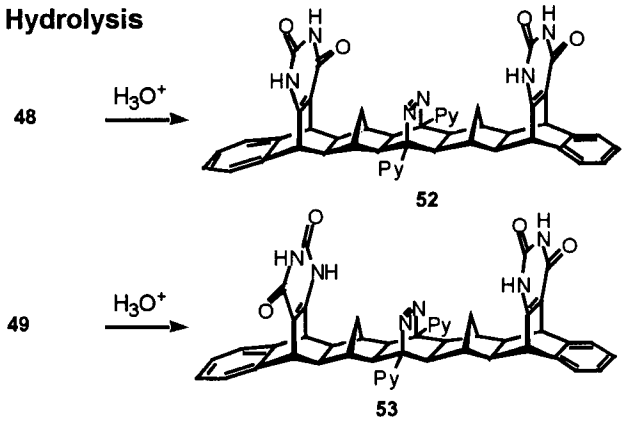
Figure 6

racemic pair **49**. Owing to the curvature of the frame, these rings are rigidly orientated at an angle of 67° one with the other.

For reasons discussed above, these products are formed side by side in the s-tetrazine coupling reaction of racemic norborneno-pyrimidine **10**, and individual isomers **48** (mp 327-328 °C; 23% yield) and **49** (mp 331-332 °C; 23% yield) were separated by radial chromatography.



Scheme 10



Scheme 11

Separate hydrolysis of the meso-compound **48** was used to access the uracil **52**, while similar hydrolysis of diastereomers **49** afforded the *bis*-uracils **53** (SCHEME 11).

Structural assignments for the pyrimidine-{spacer}-pyrimidine products.

Assignments of structures to the meso and racemic diastereomers in both southern and northern systems are not trivial as their ^{1}H NMR spectra are almost superimposable. Additionally, the ^{13}C NMR spectra are also very similar, except that symmetry considerations dictate that the HH-meso products, eg **45** and **48**, having a plane of symmetry passing through the azo-bridge, the pyridyl groups and the central pair of carbon atoms of the molecule, will have one more carbon signal in that section of the frame than the H,T-racemic isomers **43** and **49**, which have a C2 rotational axis making all carbon atoms the same as their inverted counterpart, *ie* the two carbon positions (C7, C16) that are different in the meso-isomer are identical in the racemate. While the relevant carbon resonances overlap in some cases, the pyridyl substituents attached to these central carbons are different in the racemates and the same in the meso-isomer for the same symmetry reasons, and can be used to assign structure. Indeed, we find that

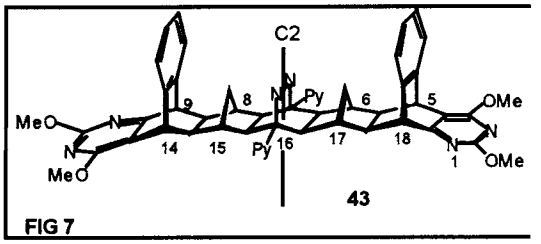


FIG 7

TABLE 1. The significant ^{13}C and ^{1}H NMR data for the *bis*-pyrimidines **43, 45, 48, 49**.

Atoms	Compound			
	45 (HH)	**43 (HT)**	**48 (HH)**	**49 (HT)**
C_7, C_{16}	78.6 (overlap)	78.6	78.5, 78.6	78.6
$2C_{2'}$	161.0, 161.2	161.2	160.9, 161.3	161.1
$2C_{3'}$	122.8, 123.1	122.9	123.0, 123.2	123.1
$2C_{4'}$	136.2, 136.9	136.5	136.2, 136.4	136.3
$2C_{5'}$	121.9, 122.0	122.0	122.0 (overlap)	122.0
$2C_{6'}$	149.98, 150.04	150.1	149.9, 150.0	150.0
$2H_{6'}$	8.79 (1H), 8.82 (1H)	8.80 (2H)	8.77 (1H), 8.83 (1H)	8.80 (2H)

isomer **48** alone shows two separate ^{13}C signals for C7, C16, which allows distinction between **48** and **49**, but not the other pair, since the racemic isomer must have coincident resonances (Table 1).

Consistent with isomers **45** and **48** being the meso-isomers and **43** and **49** having the racemate structure, the ^{13}C resonances for the pyridyl substituents appear as two partly overlapping sets of resonances in the former isomers and as a single set in the other two. A doubling of one of the pyridyl proton resonances (H6) is also apparent in the ^{1}H NMR spectrum for the meso-isomers, but not in the racemate isomers.

Conclusion

In this paper we have described new ways to access space-separated *bis*-uracils. By using the BLOCK coupling techniques (s-tetrazine, ACE), it is possible to separately prepare either head to head (HH) or head to tail (HT) products in different geometric arrangements. The same building protocols can be used to construct pyrimidine-{spacer}-chromophore structures by linking pyrimidine BLOCKs with different chromophore BLOCKs and such products are available in size and shape variants. The opportunity to apply the BLOCK coupling protocol to space-separate other nucleic basesis an area which is just opening up. Preliminary results on the coupling of cytosines

using BLOCK reagents formed from the photoadduct of cyclopentadiene with 2,4-dichlorodiazaanthracene **9** has been reported recently from our laboratory.[14]

The next advance in this work will be to make nucleoside and nucleotide BLOCKs and this target is much more achievable given that the uracil BLOCKs **50** and **51** are now available. Further, there are good synthetic protocols for converting nucleic acid bases to their nucleoside and nucleotide counterparts.[32]

Experimental

General Procedures. NMR spectra were recorded on a Bruker AMX-300 NMR spectrometer fitted with a dual or gradient probe, or a Bruker Avance DPX 400 NMR spectrometer fitted with a gradient quattro nucleus probe. Chemical shifts are quoted in δ relative to internal tetramethylsilane (TMS, δ=0). Low resolution mass spectra were recorded on a Shimadzu QP200 mass spectrometer. High resolution mass spectra were obtained on a Micromass Autospec (magnetic sector) instrument, with either electron impact (EI) or electrospray (ES) ionisation (negative or positive ion). Microanalysis was performed using a Fisons GSE EA 1108 microanalyser calibrated using acetanilide standards and performed at the CQUAIL microanalytical service, CQU.

All column chromatography separations were carried out on Merck silica gel 60 (180-230 mesh). Radial chromatography was performed on the Chromatotron model 7924T with Merck silica gel 60 PF_{254} as absorbent. Analytical thin layer chromatography was conducted with Merck silica gel 60 F_{254} aluminium-backed TLC plates using UV visualisation. HPLC was performed on Waters system comprising a 600 E controller, a 600 Multisolvent Delivery system and 486 Tunable Absorbance Detector. Column selection is specified in the individual experiments.

High pressure reactions (ambient temperature) were performed using a Hofer 14 kbar high pressure facility or Teczka high pressure apparatus (15 kbar, RT-100 °C). Melting point determinations were taken on a Gallenkamp Melting Point Apparatus and are uncorrected. Molecular modelling was conducted using the SPARTAN Version 5.0.2 molecular modelling package, operating on Silicon Graphics R4000 workstations.

(5α,5aα,6β,9β,9aα,10α)-2,4-dimethoxy-5,5a,6,9,9a,10-hexahydro-5,10-[1',2']benzeno-6,9-methanobenzo[*g*]quinazoline (10) and (5α,5aβ,6α,9α, 9aβ,10α)-2,4-dimethoxy-5,5a,6,9,9a,10-hexahydro-5,10[1',2']benzeno-6,9-methanobenzo-[*g*]quin-azoline (11). 2,4-Dimethoxy-1,3-diazaanthracene (**18**, 1 g, 4.16 mmol) was heated with norbornadiene (20 ml, 185 mmol) in a high pressure vessel (sealed tube) at 180 °C for two days. The resulting mixture was separated by column chromatography on silica. The column was first washed with petroleum ether to elute all excess

norbornadiene, and then with ethyl acetate/petrol 1:6 solvent mixture. A colourless, oily mixture of two isomers (**10** and **11**; 1.039 g, 75 %) was obtained and this was further separated by HPLC, using a C18 Nova-Pak reverse phase column (10 x 2.5 cm) and a methanol/water gradient elution system (from 70/30 to 95/5 ratio over a period of 20 minutes, flow rate 10 ml/min). **10** (175 mg, m.p. 142-144.5 °C) was eluted before isomer **11** (307 mg, m.p. 130-132 °C). **10**: ^{1}H NMR,^{13}C NMR and low resolution mass spectrum, see reference 13; Anal. calc. for $C_{21}H_{20}N_2O_2$ requires: C, 75.88; H, 6.06; N, 8.43, found: C, 75.72; H, 6.06; N, 8.21%.

11: ^{1}H NMR,^{13}C NMR and low resolutiom mass spectrum, see reference 13 ; Anal. calc. for $C_{21}H_{20}N_2O_2$ requires: C, 75.88; H, 6.06; N, 8.43, found: C, 75.73; H, 6.10; N, 8.39%.

(5α,5aα,6β,6aβ,8aβ,9β,9aα,10α)-6a,8a[3',4']Cyclobuta-7,8-carbomethoxy-2,4-dimethoxy-5,5a,6,6a,8a,9,9a,10-octahydro-5,10[1",2"]-benzeno-6,9-methano-benzo[*g*]-quinazoline (12) and (5α,5aβ,6α,6aβ,8aβ,9α,9aβ,10α)-6a,8a[3',4']cyclo-buta-7,8-carbomethoxy-2,4-dimethoxy-5,5a,6,6a,8a,9,9a,10-octahydro-5,10[1",2"]-benzeno-6,9-methanobenzo[*g*] quinazoline (13). A mixture of adducts **10** and **11** (200 mg, 0.60 mmol) was refluxed in benzene with DMAD (75 µl, 0.60 mmol) and $RuH_2CO(PPh_3)_3$ catalyst (30 mg, 0.03 mmol) for 3 days. After radial chromatographic separation of the reaction mixture, products **12** and **13** (210 mg of crude product, 73%) and some starting material were recovered. Isomer **19** was isolated in a pure form (m.p. 224-225 °C) by fraction crystallisation from petroleum ether, then ethyl acetate/petroleum ether. The isomer **12** remained in the mixture as an oil and was isolated (m.p. 124-126 °C) by preparative HPLC techniques. A C18 Nova-Pak reverse phase column (10 x 2.5 cm); methanol/water gradient elution system (from 70/20 to 90/10 ratio over a period of 25 minutes, flow rate 10 ml/min) was employed for this separation.

12: ^{1}H NMR, ^{13}C NMR , MS, see reference 13 ; HRMS (EI) for $C_{27}H_{26}N_2O_6$ requires for M^+ (*m/z*) 474.1791, found (*m/z*) 474.1784.

13: ^{1}H NMR ,^{13}C NMR , MS, see reference 13 ; Anal. Calc. for $C_{27}H_{26}N_2O_6$ requires: C, 68.34; H, 5.52; N, 5.90, found: C, 68.37; H, 5.46; N, 5.82.

(5α,5aβ,6α,6aβ,6bβ,7aβ,7bβ,8α,8aβ,9α)-5,9[1',2']-benzeno-5,5a,6,6a,6b,-7a,7b,8,8a,9-decahydro-6b,7a-dicarbomethoxy-2,4-dimethoxy-6a,7b[3",4"]-(1",2'-epoxycyclobuta)-6,8-methanobenzo[*g*]quinazoline (14). To pyrimidine diester **13** (126 mg, 0.27 mmol) in dry tetrahydrofuran (15 ml) under nitrogen atmosphere at -78 °C (acetone/dry ice bath) *tert*-butyl peroxide (0.105 ml of 3M solution in toluene, 0.32 mmol) was added by syringe. The reaction mixture was stirred at the same temperature for ten minutes and then methyl lithium solution (0.285 ml of 1.4M solution in diethyl

ether, 0.40 mmol) was added dropwise. The mixture was allowed to warm to room temperature over a period of one hour, and stirred for an additional 2.5 hours. Dichloromethane was added (5 ml), followed by Na_2SO_3 solution (10%, 0.5 ml). The dichloromethane extract was rinsed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvents and recrystallisation from methanol yielded 78 mg (59%) of the product **14** (m.p. 282.5-284.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) see reference 14 ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8 (C16), 39.5 (C9), 39.8 (overlap, C6, C8), 46.1 (C5a), 47.7 (C8a), 49.8 (C5), 51.3 (C6a), 51.4 (C7b), 52.6 (overlap, 2COOMe), 53.6 (OMe), 54.6 (OMe), 64.0 (overlap, C6b, C7a), 114.8 (C4a), 124.3 (C15), 125.3 (C12), 126.6 (C14), 126.8 (C13), 139.7 (C10), 141.3 (C11), 163.1 (C4), 164.2 (C2), 164.5 (overlap, 2x carbonyl carbons), 175.4 (C9a); MS, *m/z* (%) 240 (2,4-dimethoxy-1,3-diazanthracene, 100), 225 (240-CH_3, 5), 211 (225-CH_2, 10), 169 (211-NCO, 8); HRMS (+ve ES) for $C_{27}H_{26}N_2O_7$ requires for M^++H (*m/z*) 491.1818, found (*m/z*) 491.1811.

2,4-Dimethoxy-1,3-diazaanthracene (18). 2,4-Dichloro-1,3-diazaanthracene[13] (3.7 g, 14.9 mmol) was added to a sodium methoxide solution that has been previously prepared by dissolving sodium (800 mg, 35 mmol) in *super-dry* methanol (400 ml). The reaction mixture was refluxed overnight, then cooled to room temperature and the methanol evaporated *in vacuo* leaving a yellow solid that was dissolved in diethyl ether (200 ml) and this solution washed with brine. Evaporation of the diethyl ether gave 3.9 g of crude 2,4-dimethoxy-1,3-diazaanthracene (**10**) which was purified by sublimation (0.4 mbar, 90 °C) to give 3.28 g (92%, m.p. 157 °C) of pure compound; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15, (s, 3H, C_4-OMe), 4.25, (s, 3H, C_2-OMe), 7.47 (m, 1H, H_6), 7.56 (m, 1H, H_7), 7.95 (d, *J*=8.4 Hz, 1H, H_5), 8.00 (d, *J*=8.6 Hz, 1H, H_8), 8.21 (s, 1H, H_{10}), 8.67 (s, 1H, H_9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.72 (overlap, 2xOMe), 113.6 (C4a), 122.7 (C10), 124.7 (C9), 125.2 (C6), 127.7 (C5), 128.0 (C7), 129.2 (C8), 130.2 (C10a), 136.9 (C8a), 146.8 (C9a), 161.5 (C4), 170.1 (C2); MS, *m/z*: (%) 240 (M^+, 100), 225 (M^+-CH_3, 20), 210 (225-CH_3, 11); Anal. calc. for $C_{14}H_{12}N_2O_2$ requires: C, 69.99; H, 5.03; N, 11.66, found: C, 70.20; H, 5.00; N, 11.46%.

(5α,5aβ,6α,13α,13aβ,14α)-5,14[1',2']-Benzeno-5,5a,6,13,13a,14-hexahydro-6,18-methano-2,4,7,12-tetramethoxy-1,3-diazapentacene (20) and (5β,5aα,6β,13β,-13aα,14β)-5,14[1',2']-benzeno-5,5a,6,13,13a,14-hexahydro-6,18-methano-2,4,7,12-tetramethoxy-1,3-diazapentacene (21). 2,4-Dimethoxy-1,3-diazaanthracene (**18**, 120 mg, 0.5 mmol) in toluene and 1,4-dimethoxynaphtho[*b*]norbornadiene (**19**, 300 mg, 1.2 mmol) were head together in a sealed tube at 200 °C overnight. The solvent was evaporated off under high vacuum and the product mixture purified by column chromatography on silica (ethyl acetate/petroleum ether 1:2) to give the isomeric mixture of **20** and **21** (150 mg as mixture). This was separated by HPLC, using a prep LC

module containing two Prep Nova-Pak, C18 reverse phase columns in series (each 10 x 2.5 cm). A methanol/water gradient elution system was employed (from 80/20 to 85/15 ratio over a period of 40 minutes, flow rate 12 ml/min). Compound **21** (24 mg, 16%, m.p. 189-192 °C) was eluted after 37 minutes, just before its isomer **20** (32 mg, 21%, m.p. 205-207 °C). ^{1}H NMR, ^{13}C NMR and MS, see reference 13 ; HRMS (EI) for $C_{31}H_{28}N_2O_4$ requires for M^+ (*m/z*) 492.2049, found (*m/z*) 492.2048. **21**: ^{1}H NMR, ^{13}C NMR and MS, see reference 13 ; HRMS (EI) for $C_{31}H_{28}N_2O_4$ requires for M^+ (*m/z*) 492.2049, found (*m/z*) 492.2048.

(5α,12α)-5,12[1',2']-Benzeno-2,4-dimethoxy-5,5a,11a,12-tetraahydro-1,3,5a,-11a-tetraazatetracen-6,11-dione (23). 2,3-Dihydro phthalazine-1,4-dione (54 mg, 0.3 mmol) was suspended in dichloromethane and mixed together with a threefold excess of **18** (240 mg, 1 mmol) in a conical flask. To the stirred reaction solution, lead tetraacetate (148 mg, 0.3 mmol) was added in small portions over the period of 40 min and stirred at room temperature for an additional 30 min. A milky white precipitate developed and was filtered off. The filtrate was passed onto a short alumina column, washed with dichloromethane to recover **18** (134 mg), followed by methanol to yield the product **23** (17 mg, 14 %, m.p. 249-252 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 3H, OMe), 4.04 (s, 3H, OMe), 7.31 (s, 1H, H_5), 7.33 (m, 2H, H_{16}, H_{17}), 7.55 (m, 1H, H_{15}), 7.57 (s, 1H, H_{12}), 7.61 (m, 1H, H_{18}), 7.76 (m, 2H, H_8, H_9), 8.30 (m, 2H, H_7, H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1 (C5), 54.3 (OMe), 55.3 (OMe), 58.3 (C12), 110.9 (C4a), 123.7 (C13), 125.3 (C15), 127.6 (2 signals, C8, C9), 128.2 (C7), 128.5 (C10), 128.6 (C17), 128.8 (C16), 133.3 (2 signals, C6a, C10a), 136.2 (C13), 138.4 (C14), 154.4 (C6), 154.9 (C11), 164.5 (C4), 164.6 (C2), 170.4 (C12a); MS *m/z* (%) 400 (M^+, 100), 254 (M^+-$C_8H_4O_2$-CH_2, 86), 240 (2,4-dimethoxy-1,3-diazaanthracene, 53), 225 (2,4-dimethoxy-1,3-diazaanthracene-Me, 16), 211 (225-CH_2, 30); HRMS (EI) for $C_{22}H_{16}N_4O_4$ requires for M^+ (*m/z*) 400.1172, found (*m/z*) 400.1173.

(5α,5aβ,6α,6aβ,7α,7aβ,8α,11α,11aβ,12α,12aβ,13α,13aβ,14α)-5,14[1',2']-Benzeno-7,12-diazo-6,13:8,11-dimethano-2,4-dimethoxy-7,12-di(2'-pyridyl)-(5,5a,-6,6a,7,7a,8,11,11a,12,12a,13,13a,14)-tetradecahydro-1,3-diazapentacene (28). To compound **11** (40 mg, 0.12 mmol) in dichloromethane (2ml) and triethylamine (0.5 ml) 3,6-di(2'-pyridyl)-*s*-tetrazine (**4**, 30 mg, 0.12 mmol) was added and the mixture stirred at room temperature for 3 hours (i.e. until the purple colour of **4** had disappeared). The reaction solution was transferred into a high pressure vessel and norbornadiene (0.5 ml, 4.6 mmol) added and left under 8 kbar pressure overnight to complete the second addition step. The product was isolated from the crude reaction mixture by column chromatography using a gradient elution technique (pure petroleum ether at start and gradual addition of ethyl acetate until 1:2 solvent ratio was achieved). The colourless

powder, **28** (52 mg, 68%, mp. 279 °C) was obtained by evaporation of solvents under vacuum. ^{1}H NMR (300 MHz, $CDCl_3$) see reference 14; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C23), 39.7 (C14), 42.2 (overlap, C6, C13), 42.4 (C24), 44.2 (overlap, C8, C11), 49.0 (C5a), 49.8 (C5), 50.3 (C13a), 50.4 (C7a), 50.5 (C11a), 53.6 (OMe), 54.6 (OMe), 54.7 (C6a), 55.0 (C12a), 78.4 (overlap, C7, C16), 115.0 (C4a), 121.89 (C5'), 121.93 (C5'), 122.9 (C3'), 123.1 (C3'), 123.8 (C22), 124.9 (C19), 126.2 (C21), 126.4 (C20), 136.2 (overlap, 2C4'), 139.1 (overlap, C9, C10), 139.7 (C18), 141.3 (C17), 150.0 (overlap, 2C6'), 161.3 (C2'), 161.4 (C2'), 163.0 (C4), 164.1 (C2), 175.7 (C14a); MS *m/z* (%) 539 (M^+-norbornadiene, -H^+, 5), 460 (539-pyridine, 15), 298 (539-2,4-dimethoxy-1,3-diazaanthracene, -H^+, 24), 241 (2,4-dimethoxy-1,3-diazaanthracene +H^+, 100), 232 (3,6-di(2-pyridyl)-1,2pyridazine, 36), 91 (tropylium cation, 3), 66 (cyclopentadiene, 10); HRMS (+ve ES) for $C_{40}H_{36}N_6O_2$ requires for M^++H (*m/z*) 633.2978, found (*m/z*) 633.2966; Anal. calc. for $C_{40}H_{36}N_6O_2 \cdot H_2O$ requires: C, 73.83; H, 5.89; N, 12.91, found: C, 74.07; H, 6.0.; N, 12.64.

(5α,5aβ,6α,6aβ,7α,7aβ,8α,15α,15aβ,16α,16aβ,17α,17aβ,18α)-5,18[1',2']-Benzeno-7,16-diazo-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(5,5a,6,6a,7,7a,8,15,-15a,16,16a,17,17a,18)-tetradecahydro-2,4,9,14-tetramethoxy-1,3-diazaheptacene (30) and (5β,5aβ,6α,6aβ,7α,7aβ,8α,15α,15aβ,16α,16aβ,17α,17aβ,18β)-5,18[1',2']-Benzeno-7,16-diazo-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(5,5a,6,6a,7,7a,8,-15,15a,16,16a,17,17a,18)-tetradecahydro-2,4,9,14-tetramethoxy-1,3-diazaheptacene (31). A mixture of the pyrimidine adducts **10** and **11** (500 mg, 1.5 mmol), was dissolved in dichloromethane (4 ml) containing triethylamine (1.5 ml). 3,6-Di(2'-pyridyl)-*s*-tetrazine (**4**, 355 mg, 1.5 mmol) was then added and the reaction mixture left in an open dish at room temperature until nitrogen evolution had ceased (about two hours). 1,4-Dimethoxynaphtho [*b*]-norbornadiene (**19**, 380 mg, 1.5 mmol) was then added and the reaction put under high pressure (8 kbar) overnight. The product mixture was purified by column chromatography on silica employing ethyl acetate petroleum ether = 1:4 solvent mixture for elution. A mixture of products **30** and **31** was obtained in 56% yield. The isomer **30** (m.p. 254-257 °C) was isolated from the mixture by fractional crystallisation from ethyl acetate/petroleum ether, whilst **31** (m.p. 264-266 °C (dec.)) was obtained by HPLC separation using a C18 Nova-Pak reverse phase column (10 cm), isocratic methanol/water 90:10 elution system over a period of 15 minutes, flow rate 10 ml/min.

30: ^{1}H NMR (300 MHz, $CDCl_3$) see reference 14; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7 (C27), 39.3 (C18), 42.4 (C28), 42.5 (C6), 42.7 (C17), 43.5 (ovelap, C8, C15), 49.7 (C5a), 50.2 (C5), 50.9 (C17a), 51.9 (C7a), 52.2 (C15a), 53.6 (OMe), 54.4 (C6a), 54.5 (C16a), 55.0 (OMe), 61.0 (ovelap, 2 OMe), 78.8 (overlap, C7, C16), 112.7

(C4a), 122.1 (overlap, 2C5'), 122.3 (overlap, C11, C12), 122.8 (C26), 123.1 (C3'), 123.2 (C3'), 123.9 (overlap, C9a, C13a), 125.2 (overlap, C10, C13), 125.7 (C23), 126.0 (overlap, C24, C25), 127.9 (overlap, C8a, C14a), 135.2 (overlap, C9, C14), 136.5 (C4'), 136.6 (C4'), 142.2 (C22), 143.1 (C21), 149.8 (C6'), 149.9 (C6'), 160.8 (C2'), 161.0 (C2'), 164.2 (C4), 166.5 (C2), 173.4 (C18a); MS *m/z* (%) 539 (M^+-1,4-dimethoxynaphtho[*b*]norbornadiene, -H^+, 12), 460 (539-pyridine, 10), 297 (539-2,4-dimethoxy-1,3-diazaanthracene, -$2H^+$, 11), 240 (2,4-dimethoxy-1,3-diazaanthracene, 100), 253 (1,4-dimethoxynaphtho[*b*] norbornadiene +H^+, 13), 226 (240-CH_2, 55), 211 (226-CH_3, 78), 78 (pyridine, 17), 66 (cyclopentadiene, 10); HRMS (EI) for $C_{50}H_{44}N_6O_4$ requires for M^+ (*m/z*) 792.3424, found (*m/z*) 792.3414. Anal. Calc. for $C_{50}H_{44}N_6O_4 \cdot H_2O$ requires: C, 74.06; H, 5.72; N, 10.36., found: C, 74.43; H, 5.63; N, 10.09.

31: ^1H NMR (300 MHz, $CDCl_3$) see reference 14; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7 (C27), 39.6 (C18), 42.3 (overlap, C6, C17), 42.5 (C28), 43.4 (ovelap, C8, C15), 48.8 (C5a), 49.7 (C5), 50.3 (C17a), 51.9 (C7a), 52.1 (C15a), 53.6 (OMe), 54.5 (overlap, C6a, C16a), 54.9 (OMe), 60.96 (OMe), 61.00 (OMe), 78.8 (overlap, C7, C16), 114.9 (C4a), 122.07 (C5'), 122.12 (C5'), 122.3 (overlap, C11, C12), 123.0 (C3'), 123.2 (C3'), 123.8 (overlap, C9a, C13a), 124.9 (C26), 125.2 (overlap, C10, C13), 126.2 (C23), 126.4 (C25), 127.9 (C24), 135.1 (C8a), 135.2 (C14a), 136.4 (C4'), 136.5 (C4'), 139.6 (C22), 141.2 (C21), 143.1 (overlap, C9, C14), 149.8 (C6'), 149.9 (C6'), 160.9 (C2'), 161.0 (C2'), 162.9 (C4), 164.0 (C2), 175.5 (C18a); MS *m/z* (%) 539 (M^+-1,4-dimethoxynaphtho[*b*]norbornadiene-H^+, 18), 460 (539-pyridine,2), 297(539-**18**-$2H^+$,11), 240 (**18**, 100), 253 (1,4-dimethoxynaphtho[*b*] norbornadiene +H^+, 10), 226 (240-CH_2, 61), 211 (226-CH_3, 94), 78 (pyridine, 17), 66 (cyclopentadiene, 11); HRMS (EI) for $C_{50}H_{44}N_6O_4$ requires (*m/z*) 792.3424. Found (*m/z*) 792.3418; Anal. calc. for $C_{50}H_{44}N_6O_4 \cdot H_2O$ requires: C, 74.06; H, 5.72; N, 10.36, found: C, 74.42; H, 5.78; N, 9.98%.

(5α,5aβ,6α,6aβ,7α,7aβ,8α,15α,15aβ,16α,16aβ,17α,17aβ,18α)-5,18 [1',2'] -benzeno-7,16-dicarbomethoxy-7,16-epoxy-6,17:8,15-dimethano-2,4,9,14-tetramethoxy-5,5a,6,6a,7,7a,8,15,15a,16,16a,17,17a,18-tetradecahydro-1,3-diazaheptacene (33).

Photochemical procedure: 2,4-Dimethoxy pyrimidine B-BLOCK **11** (100 mg, 0.3 mmol) was placed in a nitrogen-flushed quartz NMR tube (diameter=10 mm) and dissolved in acetone (4 ml). The epoxide **34** (CE-BLOCK; 122 mg, 0.3 mmol) was added and the reaction mixture irradiated with 300 nm light for 3 hours. The crude product was isolated by radial chromatography employing ethyl acetate/petroleum spirit solvent mixtures and gradient elution (from ethyl acetate/petroleum spirit=1:6 to pure

ethyl acetate). The isolated adduct was recrystallised from nitromethane to yield **33** as a white powder (142 mg, 64 %, m.p. 256-260 °C).

Thermal procedure A: 2,4-Dimethoxy pyrimidine B-BLOCK **11** (50 mg, 0.15 mmol) and the epoxide **34** (78 mg, 0.19 mmol) were heated together at 140 °C in a sealed tube for six hours. The crude product mixture was purified as above. Product **33** was recrystallised from nitromethane/2-methoxyethanol to yield a white powder (55 mg, 49 %).

Thermal procedure B: The 2,4-Dimethoxypyrimidine epoxide **14** (20 mg, 0.04 mmol) and the alkene **19** (10 mg, 0.04 mmol) were dissolved in dichloromethane (1.5 ml) and heated together at 140 °C in a sealed tube for four hours. The crude product was purified by radial chromatography as described above and recrystallised from nitromethane to yield **33** (15 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) see reference 14; ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0 (C26), 39.7 (C18), 41.8 (C5a), 41.9 (C27), 42.0 (C17a), 42.8 (overlap, C8, C15), 47.2 (C6), 48.9 (C17), 49.7 (C5), 52.2 (triple overlap, OMe, 2COOMe), 54.6 (OMe), 55.6 (C5a), 55.7 (C17a), 57.4 (C6a), 57.5 (C16a), 61.3 (overlap, 2OMe), 89.5 (overlap, C7, C16), 115.0 (C4a), 122.096 (C11), 122.138 (C12), 124.1 (C22), 125.2 (C25), 125.5 (overlap, C10, C13), 126.5 (C23), 126.7 (C24), 128.0 (overlap, C9a, C13a), 134.262 (C8a), 134.313 (C14a), 139.6 (C21), 141.2 (C20), 144.067 (C9), 144.101 (C14), 163.1 (C4), 164.1 (C2), 169.3 (carbonyl carbon), 169.4 (carbonyl carbon), 175.6 (C18a); MS *m/z* (%) 742 (38, M^+), 502 (M^+-2,4-dimethoxy-1,3-diazaanthracene, 61), 240 (2,4-dimethoxy-1,3-diazaanthracene, 100), 225 (240-CH_3, 45), 211 (225-CH_2, 94), 169 (211-NCO, 13); HRMS (EI) for $C_{44}H_{42}N_2O_9$ requires for M^+ (*m/z*) 742.2890, found 742.2891.

(5α,5aβ,6α,6aβ,6bα,7α,10α,10aα,10bβ,11α,11aβ,12α)-6b,10a-carbomethoxy-2,4-dimethoxy-5,5a,6,6a,6b,7,10,10a,10b,11,11a,12-dodecahydro-5,12[1',2']-benzeno-5,12:6,11-dimethano[2",3"]-biphenyleno[*g*]quinazoline (36). Diester **13** (10 mg, 0.021 mmol) was dissolved in chloroform and freshly distilled cyclopentadiene (1 ml) added. The reaction mixture was heated in a sealed tube at 70 °C for 10 hours. Solvent was removed under reduced pressure and the product separated from the dicyclopenadiene byproduct by preparative TLC using ethyl acetate/petroleum spirit 1:2 solvent mixture. Recrystallisation from methanol/dichloromethane gave 7.6 mg (67 %) of pure **36** (m.p. 135-137 °C). The formation of a linear isomer was not observed by ^{1}H NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.35 (d, *J*=12.2 Hz, 1H, H_{19b}), 1.09 (d, *J*=12.2 Hz, 1H, H_{19a}), 1.30 (brs, 2H, H_{6a}, H_{10b}), 1.53 (d, *J*=8.8 Hz, 1H, H_{20b}), 1.56 (m, 2H, H_{5a}, H_{11a}), 2.02 (d, *J*=8.8 Hz, 1H, H_{20a}), 2.31 (s, 1H, H_{11}), 2.34 (s, 1H, H_6), 3.07 (brs, 2H, H_7, H_{10}), 3.626 (s, 3H, MeE), 3.629 (s, 3H, COOMe), 3.93 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.22 (d, *J*=2.4 Hz, 1H, H_5), 4.44 (d, *J*=2.7 Hz, 1H, H_{12}),

6.39 (narrow m, 2H, H_8, H_9), 7.13 (m, 2H, H_{16}, H_{17}), 7.24 (m, 2H, H_{15}, H_{18}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7 (C19), 31.4 (C20), 40.0 (C12), 40.9 (C6), 41.2 (C11), 46.4 (C5a), 48.0 (C11a), 49.3 (C6a), 49.4 (C10b), 50.1 (C5), 51.1 (OMe), 51.5 (OMe), 53.4 (overlap, 2x COOMe), 53.5 (C7), 54.5 (C10), 59.7 (C6b), 59.8 (C10a), 115.1 (C4a), 124.2 (C18), 125.2 (C15), 126.3 (C17), 126.6 (C16), 137.6 (overlap, C8, C9), 139.8 (C13), 141.4 (C14), 161.8 (C4), 164.1 (C2), 172.9 (overlap, 2x carbonyl carbons), 175.7 (C12a); MS, *m/z*: 279 (6%), 244 (22%), 240 (11%), 167 (27%), 149 (100%); HRMS (EI) for $C_{32}H_{32}N_2O_6$ requires for M^+ (*m/z*) 540.2260, found (*m/z*) 540.2251.

6a,8a[3',4']Cyclobuta-7,8-carboxy-1,3,5,5a,6,6a,8a,9,9a,10-decahydro-5,10[1",2"]benzeno-6,9-methanobenzo[*g*]quinazoline-2,4-dione (37). A mixture of pyrimidine diester **13** (22 mg, 0.046 mmol), water (0.5 ml) and conc. HCl acid was heated to 100 °C for 3 days. After cooling to room temperature, water and excess of hydrochloric acid were evaporated off under high vacuum to give a white solid residue of **37** (15.5 mg, 81%, m.p. >370 °C) which was insoluble in chloroform. ^1H NMR* ($CDCl_3$/DMSO-d_6) δ -0.90 (d, *J*=12.6 Hz, 1H, H_{17b}), 0.15 (d, *J*=12.6 Hz, 1H, H_{17a}), 1.75 (brs, 1H, H_{9a}), 1.80 (brs, 1H, H_{5a}), 2.42 (s, 2H, H_6, H_9), 3.77 (s, 1H, H_{8a}), 3.80 (s, 1H, H_{6a}), 3.90 (s, 1H, H_5), 4.21 (s, 1H, H_{10}), 6.95 (m, 4H, H_{13}-H_{16}), 9.64 (s, 1H, NH), 11.06 (s, 1H, NH); MS, *m/z*: 212 (2,4-dioxo-1,3-diazaanthracene, 100%), 169 (212-HNCO, 68 %), 142 (169-NHC, 52%), 114 (acetylenedicarboxylic acid, 30 %), 71 (114-CO_2, 39%), 44 (CO_2, 47%); HRMS (EI) for $C_{23}H_{18}N_2O_6$ requires for M^+ (*m/z*) 418.1165, found (*m/z*) 418.1190.

***Bis*-Pyrimidines 43, 45, 48 and 49.** Pyrimidine A-BLOCK **11** (42 mg, 0.12 mmol) was dissolved in dichloromethane (2 ml), triethyl amine (0.1 ml) added, and the mixture treated with the *s*-tetrazine **4** (14 mg, 0.6 mmol). After the evolution of nitrogen had ceased, the reaction mixture was pressurised to 8 kbar overnight. The volatiles were removed *in vacuo*, and the isomeric mixture of products **43** and **45** was separated by radial chromatography (gradient elution technique using petroleum ether and ethyl acetate). *Bis*-pyrimidine **45** (m.p. 328-329 °C) was isolated in 27%, and **43** (m.p. 317-319 °C) in 33% yields, respectively.The same synthetic method was used in the preparation of the "northern" *bis*-pyrimidines **48** (m.p. 327-328 °C, 23%) and the **49** (m.p. 331-332 °C, 23%) from two equivalents of pyrimidine A-BLOCK **10** (64 mg, 0.19) and the *s*-tetrazine **4** (23 mg, 0.09 mmol) in the presence of Et_3N (0.7 ml).

(5α,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9α,14α,14aβ,15α,15aβ,16α,16aβ,17α,17aβ,18α)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(5,5a,6,6a,7,7a,8,8a,9,14,14a,15,15a,16,16a,17,17a,18)-octadecahydro-2,4,-11,13-tetramethoxy-1,3,10,12-tetraazaheptacene (43). ^1H NMR (300 MHz, $CDCl_3$) δ –1.13 (d, *J*=12.2 Hz, 2H, H_{33a}, H_{34a}), 0.16 (d, *J*=12.2 Hz, 2H, H_{33b}, H_{34b}), 1.44 (s,

2H, H_8, H_{17}), 1.46 (s, 2H, H_6, H_{15}), 1.72 (m, 4H, H_{5a}, H_{8a}, H_{14a}, H_{17a}), 2.46 (brs, 4H, H_{6a}, H_{7a}, H_{15a}, H_{16a}), 3.90 (s, 12H, 4 OMe), 3.98 (d, J=1.9 Hz, 2H, H_5, H_{14}), 4.21 (d, J=2.2 Hz, 2H, H_9, H_{18}), 6.94 (narrow m, 8H, H_{23}-H_{26}, H_{29}-H_{32}), 7.35 (m, 2H, 2$H_{5'}$), 7.86 (m, 2H, 2$H_{4'}$), 8.41 (m, 2H, 2$H_{3'}$), 8.80 (m, 2H, 2$H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 28.6 (C33, C34), 39.6 (C9, C18), 42.3 (C6, C15), 42.5 (C8, C17), 48.9 (C5a, C14a), 49.7 (C5, C14), 50.1 (C8a, C17a), 53.6 (2 OMe), 54.5 (C6a, C15a), 54.6 (C7a, C16a), 54.9 (2 OMe), 78.6 (C7, C16), 114.9 (C4a, C13a), 121.9 (2C5'), 122.9 (2C3'), 123.8(C23, C32), 124.9 (C26, C29), 126.1 (C24, C31), 126.4 (C25, C30), 136.5 (2C4'), 139.6 (C22, C27), 141.2 (C21, C28), 150.1 (2C6'), 161.2 (2C2'), 163.0 (C4, C13), 164.1 (C2, C11), 175.6 (C9a, C18a); HRMS (+ve ES) for $C_{54}H_{48}N_8O_4$ requires for M+H (*m/z*) 873.3877, found (*m/z*) 873.3879.

(5α,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9α,14α,14aβ,15α,15aβ,16α,16aβ,17α,17aβ, 18α)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(5,5a,6,6a,7,7a,8,8a,9,14,14a,15,15a,16,16a,17,17a,18)-octadecahydro-2,4,10,12-tetramethoxy-1,3,11,13-tetraazaheptacene (45). ^{1}H NMR (300 MHz, $CDCl_3$) δ -1.13 (d, J=12.1 Hz, 2H, H_{33a}, H_{34a}), 0.16 (d, J=12.1 Hz, 2H, H_{33b}, H_{34b}), 1.44 (s, 2H, H_{15}, H_{17}), 1.46 (s, 2H, H_6, H_8), 1.72 (m, 4H, H_{5a}, H_{8a}, H_{14a}, H_{17a}), 2.46 (brs, 4H, H_{6a}, H_{7a}, H_{15a}, H_{16a}), 3.90 (s, 6H, 2 OMe), 3.91 (s, 6H, 2 OMe), 3.98 (brs, 2H, H_5, H_9), 4.22 (brs, 2H, H_{14}, H_{18}), 6.95 (narrow m, 8H, H_{23}-H_{26}, H_{29}-H_{32}), 7.37 (m, 2H, 2$H_{5'}$), 7.86 (m, 2H, 2$H_{4'}$), 8.42 (m, 2H, 2$H_{3'}$), 8.79 (m, 1H, $H_{6'}$), 8.83 (1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 28.6 (C33, C34), 39.7 (C14, C18), 42.3 (C6, C8), 42.5 (C15, C17), 48.7 (C5a, C8a), 49.7 (C5, C9), 50.2 (C14a, C17a), 53.6 (2 OMe), 54.5 (C6a, C7a, C15a, C16a), 55.0 (2 OMe), 78.6 (C7, C16), 114.9 (C4a, C13a), 121.9 (C5'), 122.0 (C5'), 122.8 (C3'), 123.1 (C3'), 123.8 (C23, C29), 124.9 (C26, C32), 126.1 (C24, C30), 126.4 (C25, C31), 136.2 (C4'), 136.9 (C4'), 139.6 (C22, C28), 141.2 (C21, C27), 149.98 (C6'), 150.04 (C6'), 161.0 (C2'), 161.2 (C2'), 162.9 (C4, C10), 164.0 (C2, C12), 175.6 (C13a, C18a); HRMS (+ve ES) for $C_{54}H_{48}N_8O_4$ requires for M+H (*m/z*) 873.3877, found (*m/z*) 873.3879.

(5β,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9β,14β,14aβ,15α,15aβ,16α,16aβ,17α,17aβ,18β)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(5,5a,6,6a,7,7a,8,8a,9,14,14a,15,15a,16,16a,17,17a, 18)-octadecahydro-2,4,10,12-tetramethoxy-1,3,11,13-tetraazaheptacene (48). ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.56 (d, J=12.3 Hz, 2H, H_{33a}, H_{34a}), 0.40 (d, J=12.3 Hz, 2H, H_{33b}, H_{34b}), 1.70 (s, 2H, H_{15}, H_{17}), 1.72 (s, 2H, H_6, H_8), 1.82 (m, 4H, H_{5a}, H_{8a}, H_{14a}, H_{17a}), 2.44 (brs, 4H, H_{6a}, H_{7a}, H_{15a}, H_{16a}), 3.81 (s, 6H, 2 OMe), 3.83 (s, 6H, 2 OMe), 3.98 (brs, 2H, H_5, H_9), 4.25 (brs, 2H, H_{14}, H_{18}), 7.02 (m, 4H, H_{24}, H_{25}, H_{30}, H_{31}), 7.12 (m, 4H, H_{23}, H_{26}, H_{29}, H_{32}), 7.37 (m, 2H, 2$H_{5'}$), 7.90 (m, 2H, 2$H_{4'}$), 8.48 (m, 2H, 2$H_{3'}$), 8.77 (m, 1H, $H_{6'}$), 8.83 (1H, $H_{6'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5 (C33, C34), 39.3 (C14,

C18), 42.4 (C6, C8), 42.6 (C15, C17), 49.7 (C5, C9), 50.1 (C5a, C8a), 50.8 (C14a, C17a), 53.5 (2 OMe), 54.5 (2 OMe), 54.6 (C6a, C7a), 54.8 (C15a, C16a), 78.5 (C7 or C16), 78.6 (C7 or C16), 112.7 (C4a, C9a), 122.0 (overlap, 2C5'), 122.9 (C23, C29), 123.0 (C3'), 123.2 (C3'), 124.0 (C26, C32), 125.7 (C24, C30), 126.0 (C25, C31), 136.2 (C4'), 136.4 (C4'), 142.3 (C22, C28), 143.8 (C21, C27), 149.9 (C6'), 150.0 (C6'), 160.9 (C2'), 161.3 (C2'), 163.2 (C4, C10), 164.1 (C2, C12), 173.4 (C13a, C18a); HRMS (+ve ES) for $C_{54}H_{48}N_8O_4$ requires for M+H (*m/z*) 873.3877, found (*m/z*) 873.3907.

(5β,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9β,14β,14aβ,15α,15aβ,16α,16aβ,17α,17aβ,-18β)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(5,5a,6,6a,7,7a,8,8a,9,14,14a,15,15a,16,16a,17,17a,18)-octadecahydro-2,4,11,13-tetramethoxy-1,3,10,12-tetraazaheptacene (49). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.55 (d, *J*=12.1 Hz, 2H, H_{33a}, H_{34a}), 0.39 (d, *J*=12.1 Hz, 2H, H_{33b}, H_{34b}), 1.61 (s, 2H, H_6, H_{15}), 1.65 (s, 2H, H_8, H_{17}), 1.74 (brs, 4H, H_{5a}, H_{8a}, H_{14a}, H_{17a}), 2.38 (d, *J*=8.6 Hz, 2H, H_{7a}, H_{16a}), 2.51 (d, *J*=8.6 Hz, 2H, H_{6a}, H_{15a}), 3.81 (s, 6H, 2 OMe), 3.83 (s, 6H, 2 OMe), 3.94 (brs, 2H, H_5, H_{14}), 4.26 (brs, 2H, H_9, H_{18}), 7.01 (m, 4H, H_{24}, H_{25}, H_{30}, H_{31}), 7.12 (m, 4H, H_{23}, H_{26}, H_{29}, H_{32}), 7.37 (m, 2H, $2H_{5'}$), 7.91 (m, 2H, $2H_{4'}$), 8.50 (m, 2H, $2H_{3'}$), 8.80 (m, 2H, $2H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 29.5 (C33, C34), 39.3 (C9, C18), 42.4 (C6, C15), 42.6 (C8, C17), 49.7 (C5a, C14a), 50.1 (C8a, C17a), 50.8 (C5, C14), 53.5 (2 OMe), 54.3 (C6a, C15a), 54.5 (C7a, C16a), 55.1 (2 OMe), 78.6 (C7, C16), 112.7 (C4a, C13a), 122.0 (2C5'), 122.9 (C23, C32), 123.1 (2C3'), 124.0 (C26, C29), 125.7 (C24, C31), 126.0 (C25, C30), 136.3 (2C4'), 142.3 (C22, C27), 143.8 (C21, C28), 150.0 (2C6'), 161.1 (2C2'), 163.2 (C4, C13), 164.1 (C2, C11), 173.3 (C9a, C18a); HRMS (+ve ES) for $C_{54}H_{48}N_8O_4$ requires for M+H (*m/z*) 873.3877, found (*m/z*) 873.3857.

***Bis*-uracils 46, 47, 52 and 53.** Tetramethoxy *bis*-pyrimidines **43, 45, 48 and 49** were individually hydrolysed to the *bis*-uracils **46, 47, 52 and 53**. Typically, reactions were performed with 15-20 mg of *bis*-pyrimidines and 2 ml of 5M HCl (16%) by heating under reflux for 6-8 hours. The reaction mixture was evaporated under reduced pressure to yield solid material which was treated with water (0.5 ml) and adjusted to pH 7 with sodium hydroxide solution (2 M). Excess water was evaporated off *in vacuo* and the individual *bis*-uracils (**46-49**) were recrystallised from methanol.

(5α,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9α,14α,14aβ,15α,15aβ,16α,16aβ,17α,17aβ,18α)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(1,3,5,5a,6,6a,7,7a,8,8a,9,11,13,14,14a,15,15a,16,16a,17,17a,18)-docosahydro-1,3,11,13-tetraazaheptacen-2,4,10,12-tetraone (46). Yield 89%, m.p.>380 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ −1.37 (d, *J*=11.1 Hz, 2H, H_{33a}, H_{34a}), 0.03 (d, *J*=11.1 Hz, 2H, H_{33b}, H_{34b}), 1.34 (s, 2H, H_{15}, H_{17}), 1.36 (s, 2H, H_6, H_8), 1.77 (m, 4H, H_{5a}, H_{8a}, H_{14a}, H_{17a}), signal for 4H, H_{6a}, H_{7a}, H_{15a}, H_{16a} underneath the signal for DMSO,

3.92 (brs, 2H, H_5, H_9), 4.09 (brs, 2H, H_{14}, H_{18}), 7.07 (narrow m, 8H, H_{23}-H_{26}, H_{29}-H_{32}), 7.58 (m, 2H, $2H_{5'}$), 8.10 (m, 2H, $2H_{4'}$), 8.40 (m, 2H, $2H_{3'}$), 8.93 (m, 2H, $2H_{6'}$), 10.82 (2H, 2NH), 11.24 (2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.7 (C_{33}, C_{34}), 39.1 (C_{14}, C_{18}), 42.2 (C_6, C_8), 42.5 (C_{15}, C_{17}), 45.1 (C_5, C_9), 48.7 (C_{5a}, C_{8a}), 51.3 (C_{14a}, C_{17a}), 54.7 (overlap, C_{6a}, C_{7a}, C_{15a}, C_{16a}), 79.8 (C_7 or C_{16}), 80.1 (C_7 or C_{16}), 113.3 (C_{4a}, C_{13a}), 123.2 ($2C_{5'}$), 123.3 ($2C_{3'}$), 124.4 (C_{23}, C_{29}), 125.2 (C_{26}, C_{32}), 126.8 (C_{24}, C_{30}), 127.4 (C_{25}, C_{31}), 136.9 ($C_{4'}$), 137.1 ($C_{4'}$), 138.8 (C_{22}, C_{28}), 143.1 (C_{21}, C_{27}), 149.8 ($C_{6'}$), 150.1 ($C_{6'}$), 151.6 (C_4, C_{10}), 159.4 (C_{13a}, C_{18a}), 160.3 ($C_{2'}$), 160.5 ($C_{2'}$), 161.5 (C_2, C_{12}); HRMS (-ve ES) for $C_{50}H_{40}N_8O_4$ requires for M^+-H (*m/z*) 815.3095, found for M^+-H (*m/z*) 815.3145.

(5α,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9α,14α,14aβ,15α,15aβ,16α,16aβ,17α,17aβ,18α)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(1,3,5,5a,6,6a,7,7a,8,8a,9,10,12,14,14a,15,15a,16,16a,17,17a,18)-docosahydro-1,3,10,12-tetraazaheptacen-2,4,11,13-tetraone (47). Yield 94%, m.p.>380 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ −1.37 (d, *J*=12.2 Hz, 2H, H_{33a}, H_{34a}), 0.03 (d, *J*=12.2 Hz, 2H, H_{33b}, H_{34b}), 1.34 (s, 2H, H_8, H_{17}), 1.38 (s, 2H, H_6, H_{15}), 1.72 (d, *J*=5.3 Hz, 2H, H_{8a}, H_{17a}), 1.82 (d, *J*=5.3 Hz, 2H, H_{5a}, H_{14a}), signal for 4H, H_{6a}, H_{7a}, H_{15a}, H_{16a} underneath the signal for DMSO, 3.93 (brs, 2H, H_5, H_{14}), 4.09 (d, *J*=1.8 Hz, 2H, H_9, H_{18}), 7.07 (narrow m, 8H, H_{23}-H_{26}, H_{29}-H_{32}), 7.35 (m, 2H, $2H_{5'}$), 7.86 (m, 2H, $2H_{4'}$), 8.42 (d, *J*=5.9 Hz, 2H, $2H_{3'}$), 8.94 (d, *J*=3.3 Hz, 2H, $2H_{6'}$), 10.82 (brs, 2H, 2NH), 11.25 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.8 (C_{33}, C_{34}), 38.2 (C_9, C_{18}), 41.2 (C_6, C_{15}), 41.5 (C_8, C_{17}), 44.1 (C_5, C_{14}), 47.7 (C_{5a}, C_{14a}), 50.5 (C_{8a}, C_{17a}), 53.7 (C_{6a}, C_{15a}), 53.8 (C_{7a}, C_{16a}), 79.6 (C_7, C_{16}), 112.4 (C_{4a}, C_{13a}), 122.3 ($2C_{5'}$), 122.4 ($2C_{3'}$), 123.4 (C_{23}, C_{32}), 124.3 (C_{26}, C_{29}), 125.8 (C_{24}, C_{31}), 126.4 (C_{25}, C_{30}), 136.9 ($2C_{4'}$), 137.9 (C_{22}, C_{27}), 142.1 (C_{21}, C_{28}), 150.6 ($2C_{6'}$), 150.7 (C_4, C_{13}), 158.5 (C_{9a}, C_{18a}), 160.5 ($2C_{2'}$), 160.6 (C_2, C_{11}); HRMS (-ve ES) for $C_{50}H_{40}N_8O_4$ requires for M^+-H (*m/z*) 815.3095, found for M^+-H (*m/z*) 815.3087.

(5α,5aα,6β,9β,9aα,10α)-1,3,5,5a,6,9,9a,10-Octahydro-5,10[1',2']benzeno-6,9-methanobenzo[*g*]quinazolin-2,4-dione (50) and (5α,5aβ,6α,9α,9aβ,10α)-1,3,5,-5a,6,9,9a,10-Octahydro-5,10[1',2']-benzeno-6,9-methanobenzo[*g*]quinazolin-2,4-dione (51). Dry, powdered NaOH (3 g, 75 mmol) was placed in a test tube, previously heated and flushed with nitrogen, together with a mixture of **10** and **11** (500 mg, 1.5 mmol). The test tube was closed with a septum and the reactants fused by cautiously heating with a Bunsen burner for approximately 5 minutes (until all NaOH was melted) under nitrogen. To the cooled reaction mixture, water was added and the resulting milky solution filtered through celite. The filtrate was acidified to pH 2 with 10 % ag. HCl and the white precipitate filtered off to give 287 mg (yield 62 %) of crude products **50** and

51. The uracil **50** (3 mg, m.p. 316-318 °C) was obtained by sublimation of the isomeric mixture (48 mg), whilst the isomer **51** (8 mg, m.p. 325 °C, 90 %) was obtained by its separate synthesis (as above) from pure isomer **11** (10 mg, 0.03 mmol). **Compound 50**: ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 1.20 (d, J=9.4 Hz, 1H, H_{17b}), 1.50 (d, J=9.4 Hz, 1H, H_{17a}), 2.21 (m, 2H, H_{5a}, H_{9a}), 2.64 (s, 1H, H_9), 2.69 (s, 1H, H_6), 3.98 (s, 1H, H_5), 4.40 (s, 1H, H_{10}), 6.15 (m, 2H, H_7, H_8), 7.18 (m, 4H, H_{13}-H_{16}), 9.41 (brs, 1H, NH), 11.20 (brs, 1H, NH); MS, *m/z*: 304 (M^+, 7%), 212 (100%); HRMS (EI) for $C_{19}H_{16}N_2O_2$ requires for M^+ (*m/z*) 304.1212. Found (*m/z*) 304.1202. **Compound 51**: ^{1}H NMR (400 MHz, DMSO-d_6) δ −0.40 (d, J=9.1 Hz, 1H, H_{17b}), 0.67 (d, J=9.1 Hz, 1H, H_{17a}), 2.11 (narrow m, 1H, H_{9a}), 2.17 (narrow m, 1H, H_{5a}), 2.43 (s, 1H, H_9), 2.47 (s, 1H, H_6), 4.11 (d, J=2.8 Hz, 1H, H_5), 4.26 (d, J=2.8 Hz, 1H, H_{10}), 6.26 (m, 2H, H_7, H_8), 7.26 (m, 2H, H_{14}, H_{15}), 7.33 (m, 2H, H_{13}, H_{16}), 10.84 (brs, 1H, NH), 11.54 (brs, 1H, NH); ^{13}C NMR see reference 13 ; HRMS (EI) for $C_{19}H_{16}N_2O_2$ requires for M^+ (*m/z*) 304.1212, found (*m/z*) 304.1214.

(5β,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9β,14β,14aβ,15α,15aβ,16α,16aβ,17α,17aβ,-18β)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(1,3,5,5a,6,6a,7,7a,8,8a,9,11,13,14,14a,15,15a,16,16a,17,17a,18)-docosahydro-1,3,11,13-tetraazaheptacen-2,4,10,12-tetraone (52). Yield 93%, m.p.>380 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.39 (d, J=12.0 Hz, 2H, H_{33a}, H_{34a}), 0.64 (d, J=12.0 Hz, 2H, H_{33b}, H_{34b}), 1.57 (narrow m, 4H, H_6, H_8, H_{15}, H_{17}), 1.67 (brs, 4H, H_{5a}, H_{8a}, H_{14a}, H_{17a}), underneath the signal for DMSO (4H, H_{6a}, H_{7a}, H_{15a}, H_{16a}), 3.94 (brs, 2H, H_5, H_9), 4.17 (brs, 2H, H_{14}, H_{18}), 7.13 (m, 4H, H_{24}, H_{25}, H_{30}, H_{31}), 7.28 (m, 4H, H_{23}, H_{26}, H_{29}, H_{32}), 7.63 (m, 2H, 2H5'), 8.19 (m, 2H, 2H4'), 8.59 (m, 2H, 2H3'), 8.96 (m, 2H, 2H6'), 10.87 (s. 2H, 2NH), 11.23 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.2 (C_{33}, C_{34}), 36.7 (C_{14}, C_{18}), 42.0 (C_6, C_8), 42.3 (C_{15}, C_{17}), 44.2 (C_5, C_9), 49.8 (C_{5a}, C_{8a}), 50.3 (C_{14a}, C_{17a}), 53.9 (overlap, C_{6a}, C_{7a}, C_{15a}, C_{16a}), 78.47 (C_7 or C_{16}), 78.51 (C_7 or C_{16}), 110.0 (C_{4a}, C_{13a}), 122.6 (2C5'), 122.9 (C_{23}, C_{29}), 123.2 (C3'), 123.3 (C3'), 123.7 (C_{26}, C_{32}), 125.8 (C_{24}, C_{30}), 126.4 (C_{25}, C_{31}), 137.28 (C4'), 137.30 (C4'), 140.7 (C_{22}, C_{28}), 144.5 (C_{21}, C_{27}), 150.8 (C6'), 150.88 (C6'), 150.90 (C_4, C_{10}), 156.0 (C_{13a}, C_{18a}), 160.5 (C2'), 160.7 (C2'), 161.1 (C_2, C_{12}); HRMS (-ve ES) for $C_{50}H_{40}N_8O_4$ requires for M^+-H (*m/z*) 815.3095, found for M^+-H (*m/z*) 815.3082.

(5β,5aβ,6α,6aβ,7α,7aβ,8α,8aβ,9β,14β,14aβ,15α,15aβ,16α,16aβ,17α,17aβ,-18β)-7,16-Diazo-5,18:9,14-di[1',2']benzeno-6,17:8,15-dimethano-7,16-di(2'-pyridyl)-(1,3,5,5a,6,6a,7,7a,8,8a,9,10,12,14,14a,15,15a,16,16a,17,17a,18)-docosahydro-1,3,10,12-tetraazaheptacen-2,4,11,13-tetraone (53). Yield 96%, m.p.>380 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.45 (d, J=8.6 Hz, 2H, H_{33a}, H_{34a}), 0.64 (d, J=8.6 Hz, 2H, H_{33b}, H_{34b}), 1.61 (brs, 4H, H_6, H_8, H_{15}, H_{17}), 1.69 (narrow m, 4H, H_{5a}, H_{8a},

H_{14a}, H_{17a}), signal for 4H, H_{6a}, H_{7a}, H_{15a}, H_{16a} underneath the signal for DMSO, 3.97 (brs, 2H, H_5, H_{14}), 4.19 (brs, 2H, H_9, H_{18}), 7.13 (narrow m, 4H, H_{24}, H_{25}, H_{30}, H_{31}), 7.27 (narrow m, 4H, H_{23}, H_{26}, H_{29}, H_{32}), 7.69 (m, 2H, $2H_{5'}$), 8.25 (m, 2H, $2H_{4'}$), 8.62 (m, 2H, $2H_{3'}$), 9.00 (m, 2H, $2H_{6'}$), 10.86 (2H, 2NH), 11.22 (2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.0 (C_{33}, C_{34}), 38.0 (C_9, C_{18}), 42.0 (C_6, C_{15}), 42.2 (C_8, C_{17}), 43.8 (C_5, C_{14}), 49.4 (C_{5a}, C_{14a}), 49.8 (C_{8a}, C_{17a}), 53.5 (C_{6a}, C_{15a}), 53.7 (C_{7a}, C_{16a}), 80.6 (C_7, C_{16}), 109.5 (C_{4a}, C_{13a}), 122.5 ($2C_{5'}$), 122.6 (C_{23}, C_{32}), 123.4 (C_{26}, C_{29}), 125.4 ($2C_{3'}$), 125.5 (C_{24}, C_{31}), 126.0 (C_{25}, C_{30}), 137.3 ($2C_{4'}$), 140.5 (C_{22}, C_{27}), 144.3 (C_{21}, C_{28}), 150.4 ($2C_{6'}$), 150.5 (C_4, C_{13}), 155.4 (C_{9a}, C_{18a}), 160.4 ($2C_{2'}$), 160.5 (C_2, C_{11}); HRMS (-ve ES) for $C_{50}H_{40}N_8O_4$ requires for M^+-H (*m/z*) 815.3095, found for M^+-H (*m/z*) 815.3132.

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Received : 4 / 1 / 99

Accepted : 8 / 21 / 99