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Enantiospecific Synthesis and Biological Evaluation of Seco Analogues of Antitumor Amaryllidaceae Alkaloids

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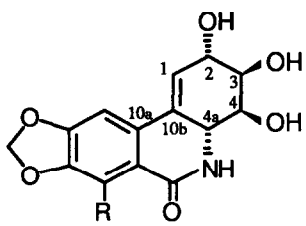
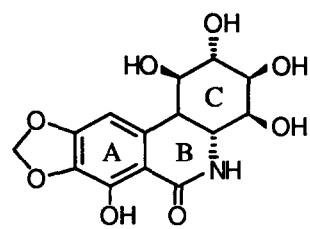
Abstract : *Some "seco" analogues of Amaryllidaceae alkaloids narciclasine and lycoricidine have been prepared in enantiomerically pure form from D-glucose using Ferrier carbocyclization as the key step. N-acylation of the resulting amines* ***21, 22, 25*** *and* ***26*** *with several aromatic acids led to amides* ***31-34*** *structurally related to narciclasine and lycoricidine. These seco analogues are devoided of biological activity.*

INTRODUCTION

Some plants from the genus Amaryllidaceae contain highly oxygenated alkaloids such as lycoricidine **1**, narciclasine **2**.[1] More recently, a new compound, pancratistatin **3** has been found in *Pancratium littorale*.[2] These compounds have interesting biological properties, particularly pancratistatin, which has shown promising antitumor activity *in vitro*.[3] The mode of action of narciclasine has been thoroughly studied, and it appeared that this alkaloid is an inhibitor of the ribosomal peptidyl transferase.[4] Pancratistatin seems to inhibit protein synthesis by the same mechanism.



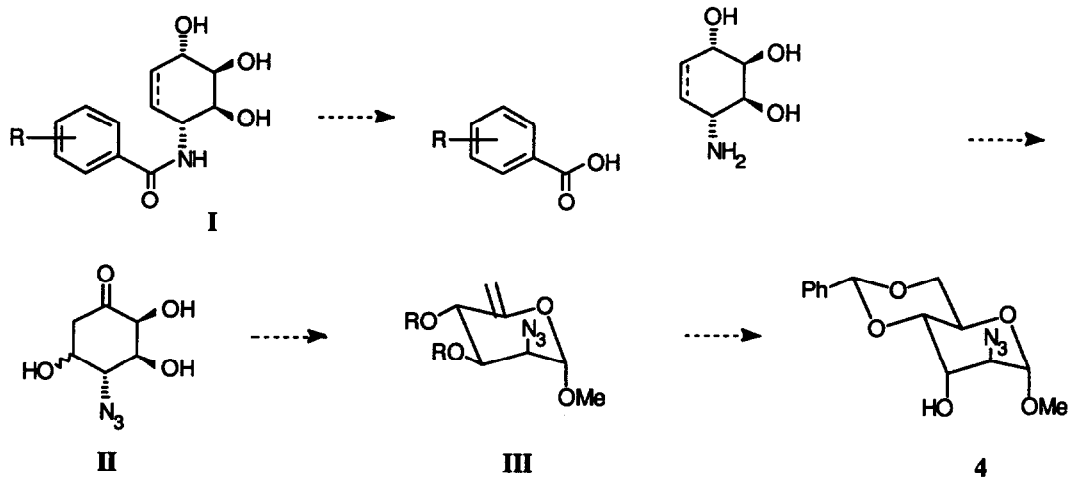
1 R = H Lycoricidine
2 R = OH Narciclasine



3 Pancratistatin

In the narciclasine series, an interesting structure-activity relationship study has been conducted by Krohn and Mondon in the seventies.[5] Some conclusions about the structural requirements needed for the biological activity were drawn, it was found *inter alia* that the highly oxygenated C-ring is necessary for the activity.[6] However, no data were available on the role of the aromatic ring and the absolute configuration of the different stereogenic centres. In view of their biological activities, these compounds may be regarded as

potential antitumor and/or antiviral agents. Thus, the search for synthetic routes to these compounds and analogues is crucial in order to have sufficient amount of material for more extended biological studies.[7, 8, 9] Some years ago, we embarked in a program of enantiospecific synthesis of narciclasine and analogues in order to test them as antitumor agents, and as antiviral since lycoricidine showed antiviral activity.[7e]



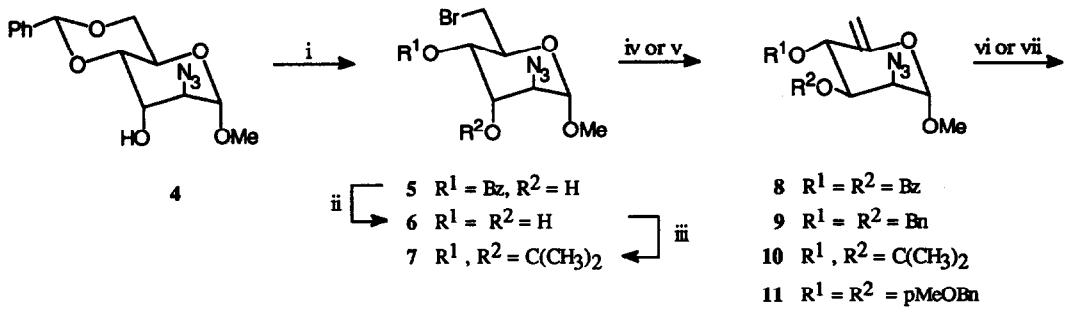
Scheme 1

We chosed to prepare some flexible seco derivatives **I**, in which the B-ring is not closed. Such derivatives which will incorporate the oxygenated C-ring anchored to differents aromatic rings by an amide bond, seemed to be good candidates for inhibition of protein synthesis. We report here the synthesis and biological evaluation of some of these derivatives.

RESULTS AND DISCUSSION

As seen from the retrosynthetic analysis depicted on Scheme 1, the most important feature of these syntheses would be the preparation of the highly oxygenated C-rings in enantiomerically pure form. This shoud be, in principle, carried out using carbohydrates **III** as starting material using the Ferrier carbocyclization of hexoses,[10] which will provide **II**. Thus, starting from the known derivative **4**[11] it should be possible to prepare the unsaturated carbohydrate derivative **III** which embodied some of the required functionalities of the future C-ring of the alkaloids. However, suitable protecting groups installed in **III**, should survive the carbocyclization reaction conditions and should be removed smoothly at the end of the synthesis. Initially, dibenzoate **8**, resulting from the benzylidene ring opening of **4** to provide **5** followed by subsequent benzoylation and elimination, was treated according to the method of Ferrier (see Table, entry 1).

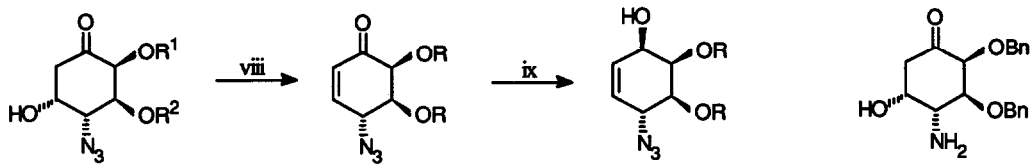
Although the expected cyclohexanone **12** was present in the reaction mixture, it was difficult to purify on silica gel without decomposition probably via β-elimination of benzoic acid. We decided to explore the use of benzyl ethers as protecting group. The 6-bromo derivative **5** was debenzoylated and the resulting diol **6** was submitted to standard benzylation conditions (NaH, BnBr, DMF, 0°C). We were pleased to find that using an excess of sodium hydride, it was possible to carry out *protection and dehydrobromination in one step*. This methodology proved to be efficient on several substrates.[12] Several 5,6 unsaturated derivatives were thus prepared and submitted to Ferrier carbocyclisation under different conditions.



4

5 R^1 = Bz, R^2 = H
6 R^1 = R^2 = H
7 R^1 , R^2 = $C(CH_3)_2$

8 R^1 = R^2 = Bz
9 R^1 = R^2 = Bn
10 R^1 , R^2 = $C(CH_3)_2$
11 R^1 = R^2 = pMeOBn



12 R^1 = R^2 = Bz
13 R^1 = R^2 = Bn
14 R^1 , R^2 = $C(CH_3)_2$
15 R^1 = R^2 = pMeOBn

16 R = Bn
17 R = pMeOBn

18 R = Bn
19 R = pMeOBn

20

Reagents: i) NBS, $CaCO_3$, CCl_4, 80°C; ii) MeONa, MeOH; iii) Me_2CO, H_2SO_4; iv) NaH, DMF; v) NaH, RBr, DMF; vi) $(CF_3CO_2)_2Hg$, Me_2CO-H_2O; vii) $HgSO_4$, H_2SO_4, dioxane, 60°C; viii) MsCl, pyridine; ix) $NaBH_4$, $CeCl_3$,7 H_2O, EtOH.

Scheme 2

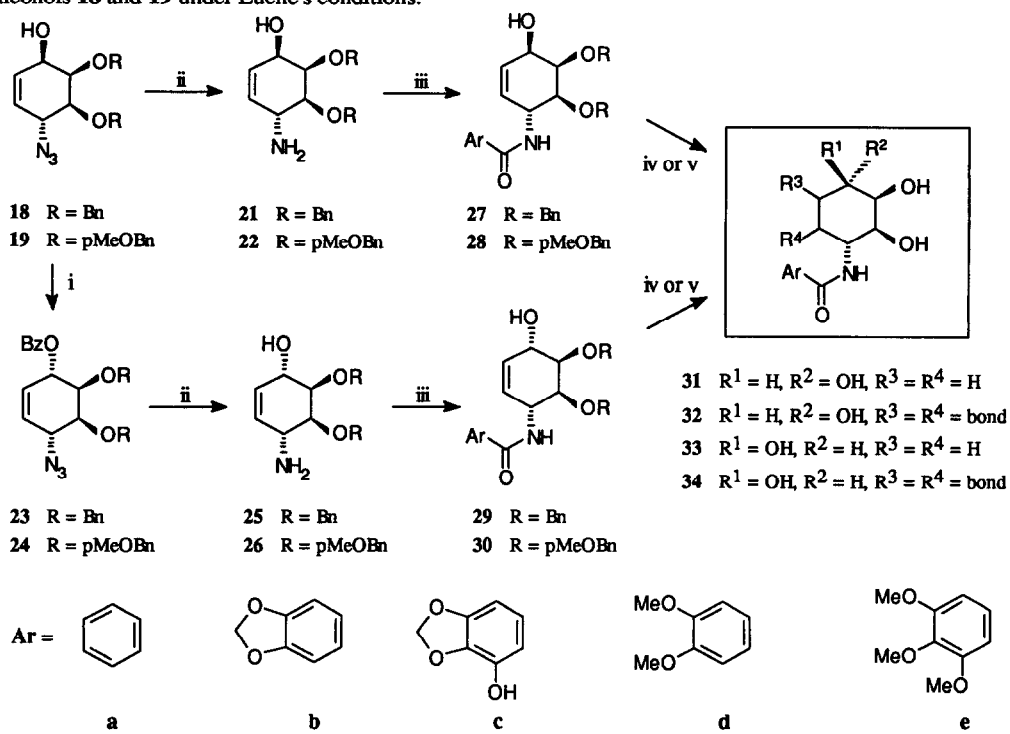
As seen from the results summarized in Table, mercuric trifluoroacetate seemed to be efficient in the case of benzylated derivative **9**[13] (entry 4) and paramethoxybenzylated compound **11** (entry 7). The use of other conditions recently proposed by Lukacs[15] (entries 5 and 8) gave good results. However in the case of

Table: Carbocyclisation reactions.

Entry	Starting compound	Mercury salt	Solvent	T °C	Carbocycle	Yield %
1	**8**	$HgCl_2$	Acetone/water	60	**12**	30
2	**9**	$HgCl_2$	Acetone/water	20	**13**	55
3	**9**	$Hg(OAc)_2$	Acetone/water	20	a	0
4	**9**	$Hg(CF_3CO_2)_2$	Acetone/water	20	**13**	75
5	**9**	$HgSO_4$	Dioxane/H_2SO_4	60	**13**	68
6	**10**	$Hg(CF_3CO_2)_2$	Acetone/water	20	**14**	17
7	**11**	$Hg(CF_3CO_2)_2$	Acetone/water	20	**15**	74
8	**11**	$HgSO_4$	Dioxane/H_2SO_4	60	**15**	60

a) No starting material recovered.

acetal **10** (entry 6) poor results were obtained, likely due to the concomitant hydrolysis of the isopropylidene group under acidic conditions. Similar observations have been reported by Ferrier et al[17-18]. It is worthy of note that, in the Ferrier carbocyclisation, a single isomer was formed, in which the substituent at C-3 and C-5 (cyclohexanone numbering) were *trans*.[19] This is in agreement with recent findings on the stereo-chemical course of the Ferrier carbocyclization which seems to depend on several factors, including the conformation of the starting compound.[20] In our case, the conformation was found to be $^1C_4$ by ^1H nmr.[15]Our plan was to prepare several amide analogues of narciclasine and congeners in which the 10a-10b bond (alkaloid numbering) would be missing. Two strategies were subsequently explored to anchor an aromatic ring to our cyclohexanone key intermediates by amide bond formation. In the first approach, the amino group was unravelled first by catalytic reduction of the azido group to provide **20**. Selective N-acylation with aromatic acids was immediately carried out using activated by benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent)[21] to provide the expected amides. Although this route was the most appropriate to furnish a wide range of analogues taking advantage of the early introduction of the aromatic ring, the intermediate amino ketone **20** was rather unstable. A second route was explored by simple change of the order of the reactions. Dehydration of the cyclohexanones **13** and **15** using methanesulfonyl chloride in pyridine gave the cyclohexenones **16** and **17** respectively which were reduced to the corresponding allylic alcohols **18** and **19** under Luche's conditions.[22]



Reagents: i) PPh_3, DEAD, PhCOOH, THF; ii) $LiAlH_4$, Et_2O; iii) ArCOOH, BOP, NEt_3, THF; iv) Pd/C 10 %, H_2, THF-EtOH; v) DDQ, CH_2Cl_2-H_2O,

Scheme 3

It should be noted that the stereochemistry at C-2 (alkaloid numbering) was opposite to that of the natural products. Mitsunobu inversion with benzoic acid proceeded cleanly providing the azido benzoates **23** and **24** with the correct configuration at C-2.[23] Reduction of the azido group of **18** and **19** with lithium aluminium hydride in ether gave the corresponding amines **21** and **22**. Alternatively, reduction of both the azido and ester functions of **23** and **24** gave the key amino alcohols **25** and **26**.[24] Selective N-acylation with different aromatic acids using "Le BOP" as activating agent gave the expected amides **27, 28, 29** and **30** in 65 to 90 % yield except for compound **27c** (31 %) Removal of the benzyl protecting groups of **27a, 27c, 27d, 27e 29a, 29c** and **29e** by hydrogenolysis gave the free saturated amides **33a, 33c, 33d, 33e, 31a** and **31c** respectively, whereas the unsaturated ones **34a, 34b** and **32b**were obtained by oxidative removal of p-methoxy benzyl protecting groups of amides **28a, 28b** and **30b**. It should be noted that the phenoxy amides **32c** and **34c** were not obtained by this method probably because of overoxidation of the product. Removal of the benzyl protective groups using iodotrimethylsilane was successfully accomplished on amide **27d** to provide **34d**. These compounds having different substitution patterns on the aromatic ring have been tested as antitumor but none of them showed significant biological activities against leukemia strain L1210. Even compound **32b** which possessed all the structural features of lycoricidine, except the C-10a-C-10b bond, and **33c** which possessed the substitution pattern of narciclasine were inactive. It is likely that these molecules adopt an extented conformation, more or less stabilized, that cannot assume a correct binding to ribosome.[25] One may also conclude that the aromatic ring is likely involved in this binding. No antiviral activity particularly against HIV has been detected for these amides.

In summary, syntheses of enantiomerically pure seco-analogues of narciclasine and lycoricidine have been performed starting from D-glucose using a stereospecific Ferrier carbocyclization . If cyclic acetals proved to be unusable protecting groups, benzyl and p-methoxybenzyl groups are well suited for the preparation of different bicyclic amides. These compounds are devoided of biological activity, providing evidences that the presence of a tricyclic structure is essential for the inhibition of ribosomal peptidyl transferase. However, these compounds might be regarded as precursors of tricyclic alkaloids provided that a reliable, general method for the formation of the C10a-C10b bond could be found.[26] We are currently exploring the synthesis of differently substituted tricyclic analogues.

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EXPERIMENTAL SECTION

Unless otherwise stated, ^1H nmr spectra were recorded at 400 MHz in $CDCl_3$ solution with tetramethylsilane as internal standard using a Bruker Aspect 3000 spectrometer. Optical rotations were measured at 20°C on a Perkin Elmer 141 polarimeter. Melting points were measured in capillary tubes and were uncorrected. Elementary analyses were performed at the "Service Central de Microanalyse du CNRS" at Vernaison. Thin layer chromatography was performed with a glass plate coated Kieselgel 60 F 256 (Merck). Crude reaction mixtures or extractive materials were chromatographed on silica gel (Merck 60, 70-230 mesh).

Methyl 2-Azido-4-*O*-benzoyl-6-Bromo-2,6-dideoxy-α-D-altropyranoside 5. Compound **4**[11] (25 g, 81 mmol) was treated according to reference 27 to provide **5** (27.35 g, 87 %).

Methyl 2-azido-6-bromo-2,6-dideoxy-3,4-*O*-methylethylidene-α-D-altropyranoside 7. Diol **6** (6.5 g, 23.3 mmol) was dissolved in dry acetone (80 ml) and concentrated sulfuric acid (1 ml) was added. The mixture was stirred 2 h at room temperature and neutralized with Na_2CO_3. The solution was filtered and concentrated. The residue was extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated and purified by column chromatography to give **7** (6.02 g, 80 %). R_f 0.6 (hexane/EtOAc 4:1); mp 57°C; $[\alpha]_D$ +23.4 (c, 0.67, $CHCl_3$); ir ν_{max} 2120, 1380, 1390 cm^{-1}; ^1H nmr δ 1.36 (s, 3H, C*H*$_3$), 1.50 (s, 3H, C*H*$_3$), 3.45 (dd, 1H, $J_{2,3}$ 8.5, $J_{3,4}$ 11.5 Hz, *H*-3), 3.51 (s, 3H, OC*H*$_3$), 3.56 (dd, 1H, $J_{1,2}$ 6 Hz, *H*-2), 3.68 (dd, 1H, $J_{4,5}$ 2.5 Hz, *H*-4), 3.92 (ddd, $J_{5,6}$ 7, $J_{5,6'}$ 6.5 Hz, 1H, *H*-5), 4.10 (dd, $J_{6,6'}$ 12 Hz, 1H, *H*-6), 4.17 (dd, 1H, *H*-6'), 4.52 (d, 1H, *H*-1). Anal. Calcd for $C_{10}H_{16}O_4N_3Br$: C, 37.28; H, 5.01; Br, 24.80; N, 13.04. Found: C, 37.27; H, 4.87; Br, 24.72 ; N, 12.99 %.

Methyl 2-azido-3,4-di-*O*-benzoyl-α-D-*arabino*-hex-5-enopyranoside 8 and **methyl 2-azido-3,4-di-*O*-phenylmethyl-α-D-*arabino*-hex-5-enopyranoside 9** were prepared according to ref. 12 .

Methyl 2-azido-2,6-dideoxy-3,4-*O*-methylethylidene-α-D-*arabino*-hex-5-enopyranoside 10. Sodium hydride, 50% dispersion in mineral oil (1.3 g, 25 mmol) placed in a flask under argon, was washed with dry THF then suspended in dry DMF (150 ml). The reaction mixture was stirred at 0°C and compound **7** (3.52 g, 11 mmol) dissolved in dry DMF (15 ml) was slowly added. The reaction was completed within 2 h. DMF was evaporated, the residue was diluted with CH_2Cl_2, washed with water, diluted HCl and water until neutral. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Compound **10** (2.58 g, 98 %) was obtained after column chromatography using hexane/EtOAc (3:2) as the eluent. R_f 0.78 (ether/toluene 3:7); $[\alpha]_D$ +72.7 (c, 0.78, $CHCl_3$); ir ν_{max} 2100, 1380, 1390 cm^{-1}; ^1H nmr δ 1.38 (s, 3H, C*H*$_3$), 1.56 (s 3H, C*H*$_3$), 3.52 (dd, 1H, $J_{2,3}$ 9, $J_{3,4}$ 7.5 Hz, *H*-3), 3.59 (s, 3H, OC*H*$_3$), 4.04 (dd, 1H, $J_{1,2}$ 7 Hz, *H*-2), 4.45 (d, 1H, *H*-4), 4.62 (d, 1H, *H*-1), 4.78 (d, 1H, $J_{6,6'}$ 1 Hz, *H*-6), 4.88 (d, 1H, *H*-6'). Anal. Calcd for $C_{10}H_{15}O_4N_3$: C, 49.80; H, 6.27; N, 17.42. Found: C, 50.20; H, 6,22; N. 17.64 %.

Methyl 2-azido-2,6-dideoxy-3,4-di-*O*-[(4-methoxyphenyl)methyl]-α-D-*arabino*-hex-5-enopyranoside 11. Compound **6** (5.640g,20 mmol) was treated according to ref. 12 to provide **11** (5.94 g, 70 %)

General procedure for the carbocyclization*: *Method A : To a solution of mercury trifluoroacetate (1 mmol) in an acetone-water mixture (v/v, 1:1, 8 ml) was added the 6-deoxy-hex-5-enopyranoside (1 mmol) in acetone (4 ml) The mixture was stirred at room temperature until no more starting material was detected by tlc. At the end of the reaction, water (5 ml) was added and the solvent was evaporated under reduced pressure. The resulting water solution was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated. *Method B* : catalytic method according to reference 20 using mercuric sulfate, diluted sulfuric acid in 1-4 dioxane at 60°C was used.

2S-(2β, 3β, 4α, 5α) 4-azido-5-hydroxy-2,3-bis(phenylmethoxy) cyclohexanone 13 .[13] Obtained from **9** (2.62 g, 6.8 mmol) using method A. Purification by column chromatography using ether/hexane (3:2) as the eluent gave compound **13** (1.84 g; 75 %).

2S-(2β, 3β, 4α, 5α) 4-azido-5-hydroxy-2,3-methylethylidenoxy-cyclohexanone 14. Obtained from **10** (185 mg, 0.77 mmol) using method B. Purification by column chromatography using hexane/EtOAc (3:2) as the eluent gave compound **14**. (30 mg, 17 %). R_f 0.53 (hexane/EtOAc 3:2); $ir_{\nu\ max}$ 3500, 2100, 1730, 1380 cm^{-1}; ^1H nmr δ 1.40 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.28 (br s, 1H, O*H*), 2.72 (d, 1H, $J_{5,6}$ 2 Hz, *H*-6), 2.74 (d, 1H, $J_{5,6'}$ 4 Hz, *H*-6'), 3.97 (dd, 1H, $J_{3,4}$ 5, $J_{4,5}$ 2.5 Hz, *H*-4), 4.36 (m, 1H, *H*-5), 4.48 (d, 1H, $J_{2,3}$ 3 Hz, *H*-2), 4.58 (dd, 1H, *H*-3).

2S-(2β, 3β, 4α, 5α) 4-azido-5-hydroxy-2,3-bis[(4-methoxyphenyl)methoxy]-cyclohexanone 15. Obtained from **11** (6.17 g, 14 mmol) using method A. Purification by column chromatography using ether/hexane (3:2) as the eluent gave compound **15** (4.41g, 74 %). R_f 0.46 (hexane/EtOAc 3:2); $[\alpha]_D$ -22.2 (c, 0.63, $CHCl_3$); ir ν_{max} 2100, 1700 cm^{-1}; ^1H nmr δ 2.50 (ddd, 1H, $J_{6,6'}$ 13.5, $J_{5,6}$ 6, $J_{2,6}$ 1 Hz, *H*-6), 2.27 (br s. 1H, O*H*), 2.85 (dd, 1H, $J_{5,6'}$ 4 Hz, *H*-6'), 3.80 (s, 3H, Ph-OCH_3), 3.81 (s, 3H, Ph-OCH_3), 3.91 (dd, 1H, $J_{2,3}$ 3, $J_{3,4}$ 7.5 Hz, *H*-3), 4.04 (dd, 1H, *H*-2), 4.10 (dd, 1H, $J_{4,5}$ 3.5 Hz, *H*-4), 4.24 (ddd, 1H, *H*-5), 4.36 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.45 (d, 1H, PhCH_2), 4.55 (d, 1H, PhCH_2), 4.64 (d, 1H, PhCH_2), 6.74 (m, 4H, *Ph*), 7.24 (m, 4H, *Ph*). Anal. Calcd for $C_{22}H_{24}O_6N_3$: C, 61.96; H, 5.67; N, 9.86. Found: C, 62.23; H, 5.41; N, 9.65 %.

4R-(4α, 5β, 6β) 4-azido-5,6-bis(phenylmethoxy)-2-cyclohexen-1-one 16.[13] Compound **13** (3.67 g, 10 mmol) was dissolved in CH_2Cl_2 (70 ml), and pyridine (10 ml) was added. The reaction mixture was cooled to 0°C and mesyl chloride (2 ml) was added. The reaction mixture was stirred 10 h at room temperature. The solvent was evaporated and the residue was extracted with CH_2Cl_2. The organic layer was washed with NaOH (3N), HCl (3N), water, dried ($MgSO_4$) and concentrated. Compound **16** (2.51 g , 72 %) was obtained after column chromatography using hexane/EtOAc (4:1) as the eluent. $[\alpha]_D$ -230 (c, 0.47, $CHCl_3$).

4R-(4α, 5β, 6β) 4-azido-5,6-bis[(4-methoxyphenyl)methoxy]-2-cyclohexen-1-one 17. Compound **17** (2.13 g 60%) was obtained from compound **15** (3.72 g, 8.73 mmol). R_f 0.6 (hexane/EtOAc 3:2); mp 56°C; [$\alpha]_D$ -159.9 (c, 0.66 $CHCl_3$); ir ν_{max} 2100, 1700 cm^{-1}; ^1H nmr. δ 3.74 (dd, 1H, $J_{4,5}$ 7.5, $J_{5,6}$ 2.5 Hz, *H*-5), 3.81 (s, 3H, Ph-OCH_3), 3.82 (s, 3H, Ph-OCH_3), 4.02 (dd, 1H, $J_{2,6}$ 1 Hz, *H*-6), 4.62 (ddd, 1H, $J_{3,4}$ 2,5, $J_{2,4}$ 2 Hz, *H*-4), 4.42 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.44 (d, 1H, PhCH_2), 4.50 (d, 1H, PhCH_2), 4.65, (d, 1H, PhCH_2), 6.01 (ddd, 1H, $J_{2,3}$ 10 Hz, *H*-2), 6.66 (dd, 1H, *H*-3), 6.84 (m, 4H, *Ph*), 7.24 (m, 4H, *Ph*); Anal. Calcd for $C_{22}H_{23}O_5N_3$:C, 64.54; H, 5.66; N, 10.26. Found: C, 64.36; H, 5.57; N, 9.97 %.

1R-(1β, 4α, 5β, 6β) 4-azido-5,6-bis(phenylmethoxy)-2-cyclohexen-1-ol 18. . To a solution of **16** (1.22 g, 3.5 mmol) in methanol (8ml) was added a methanolic solution (18ml) of cerium (III) chloride, 7 H_2O (1.24 g, 3.5 mmol) and sodium borohydride (137 mg, 3.5 mmol). The reaction was completed within 45 minutes. The solvent was evaporated and the residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Purification by column chromatography using hexane/EtOAc (7:3) as the eluent afforded **18** (960 mg, 78%) as a gum. R_f 0.65 (hexane/EtOAc 3:2); $[\alpha]_D$ -174 (c, 0.97 $CHCl_3$) ir ν_{max} 3480, 2100 cm^{-1}; ^1H nmr. δ 3.57 (dd, 1H, $J_{5,6}$ 2, $J_{4,5}$ 8 Hz, *H*-5), 4.09 (dd, 1H, $J_{1,6}$ 4 Hz, *H*-6), 4.22 (ddd, 1H, $J_{1,2}$ 2, $J_{1,3}$ 2 Hz, *H*-1), 4.36

(ddd, 1H, $J_{3,4}$ 2, $J_{2,4}$ 1 Hz, *H*-4), 4.66 (dd, 1H, J_{gem} 11 Hz, PhCH_2), 4.77 (AB, 2H, PhCH_2), 5.00 (d, 1H, PhCH_2), 5.60 (ddd, 1H, $J_{2,3}$ 10 Hz, *H*-3), 5.72 (ddd, 1H, *H*-2), 7.34 (m, 10H, *Ph*)

1R-(1β, 4α, 5β, 6β) 4-azido-5,6-bis[(4-methoxyphenyl)methoxy]-2-cyclohexen-1-ol 19. Compound **19** (2.5 g, 76 %) was obtained from compound **17** (3.27g, 8 mmol) by the above procedure. R_f 0.48 (hexane/EtOAc 3:2); mp 68°C; $[\alpha]_D$ +145 (c, 0.69, $CHCl_3$); ir ν_{max} 3500, 2100 cm^{-1}; ^1H nmr δ 2.64 (d, 1H, $J_{1,OH}$ 12 Hz, O*H*), 3.55 (dd, 1H, $J_{4,5}$ 8, $J_{5,6}$ 2 Hz, *H*-5), 3.80 (s, 3H, Ph-OCH_3), 3.81 (s, 3H, Ph-OCH_3), 4.02 (dd, 1H, $J_{1,6}$ 4 Hz, *H*-6), 4.16 (dddd, 1H, $J_{1,2} = J_{1,3}$ 2 Hz, *H*-1), 4.32 (ddd, 1H, $J_{3,4}$ 2, $J_{2,4}$ 1 Hz, *H*-4), 4.75 (m, 4H, PhCH_2), 5.55 (ddd, 1H, $J_{2,3}$ 10 Hz, *H*-3), 5.68 (ddd, 1H, *H*-2), 7.02 (m, 8H, *Ph*). Anal. Calcd for $C_{22}H_{25}O_5N_3$: C, 64.22; H, 6.12; N, 10.21. Found : C, 64.46; H, 6.16; N, 10.05 %.

1R-(1β, 4α, 5β, 6β) 4-amino-5,6-bis(phenylmethoxy)-2-cyclohexen-1-ol. 21. To a solution of compound **18** (3.51 g,10 mmol) in anhydrous Et_2O (250 ml) was added $LiAlH_4$ (1 g, 26 mmol). The reaction mixture was refluxed for 45 minutes and then cooled to 0°C. Water (1 ml), then 30% NaOH solution (3 ml) and finally water (3 ml) were slowly added. The reaction mixture was filtered through a pad of celite. The filtrate was evaporated to dryness to give compound **21** (3.1g, 95%). $[\alpha]_D$ -98.3 (c, 0.12, $CHCl_3$); ir ν_{max} 3500, 2200 cm^{-1}; ^1H nmr δ 2.00 (br s, 3H, O*H* + NH_2), 3.33 (dd, 1H, $J_{5,6}$ 1, $J_{5,4}$ 8 Hz, *H*-5), 3.78 (dd, 1H, $J_{3,4}$ 2 Hz, *H*-4), 4.13 (dd, 1H, $J_{1,6}$ 3.5 Hz, *H*-6), 4.22 (ddd, 1H, $H_{1,3} = J_{1,2}$ 1 Hz, *H*-1), 4.57 (d, 1H, J_{gem} 9 Hz, PhCH_2), 4.68 (d, 1H, J_{gem} 11 Hz ,PhCH_2), 4.78, (d, 1H, PhCH_2), 5.00 (d, 1H, PhCH_2), 5.58 (dd, 1H, $J_{2,3}$ 10 Hz, *H*-2), 5.64 (dd, 1H, *H*-3), 7.34 (m, 10H, *Ph*). Anal. Calcd for $C_{20}H_{23}O_3N$: C, 73.82; H. 7.12; N, 4.30. Found: C, 73.75; H, 6.98; N, 4.19 %.

1R-(1β, 4α, 5β, 6β) 4-amino-5,6-bis[(4-methoxyphenyl)methoxy]-2-cyclohexen-1-ol 22. Compound **22** (3.07 g, 80 %) was obtained from compound **19** (4.01 g, 10 mmol) by the above procedure. R_f 0.3 ($MeOH/CH_2Cl_2$ 1:9); mp 139°C; $[\alpha]_D$ -123,5 (c, 0.40, $CHCl_3$); ir ν_{max} 3500, 3200 cm^{-1}; ^1H nmr δ 1.82 (br s , 3H, O*H* + NH_2), 3.27 (dd, 1*H*, $J_{4,5}$ 8, $J_{5,6}$ 1.5 Hz, H-5), 3.72 (ddd, 1H, $J_{2,4} = J_{3,4}$ 2, $J_{1,4}$ 3.5 Hz, *H*-4), 3.79 (s, 3H, Ph-OCH_3), 3.82 (s, 3H, Ph-OCH_3), 4.09, (dd, 1H, $J_{1,6}$ 4, $J_{2,6}$ 1 Hz, *H*-6), 4.19 (ddd, 1H, $J_{1,2} = J_{1,3}$ 2 Hz, *H*-1), 4.46 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.58 (d, 1H, PhCH_2), 4.70 (d, 1H, PhCH_2), 4.92 (d, 1H, PhCH_2), 5.56 (ddd , 1H, $J_{2,3}$ 10 Hz, *H*-2), 5.62 (ddd, 1H, *H*-3), 6.88 (m, 4H, *Ph*), 7.26, m, 4H, *Ph*). Anal. Calcd for $C_{22}H_{27}O_5N$: C, 68.55; H. 7.06; N, 3.63. Found: C, 68.37; H, 7.15, N, 3.58 %.

1S-(1α, 4α, 5β, 6β)-4-amino-5,6-bis(phenylmethoxy)-1-benzoyl-2-cyclohexene 23. To a THF solution (60 ml) of **18** (2.05 g, 5.8 mmol), PPh_3 (3.04 g, 11.6 mmol) and PhCOOH (1.41 g, 11.6 mmol) was added dropwise a THF solution (5ml) of DEAD (2.01 g, 11.6 mmol).The reaction mixture was stirred at room temperature for 2h and then concentrated. The residue was purified by column chromatography using hexane/ Et_2O (4:1) as the eluent to afford **23** (1.85 g, 70 %) as a gum. $[\alpha]_D$ -24 (c, 0.51, $CHCl_3$); ir ν_{max} 2100, 1720 cm^{-1}; ^1H nmr δ 3.77 (dd, 1H, $J_{4,5}$ 8, $J_{5,6}$ 2 Hz, *H*-5), 3.91 (dd, 1H, $J_{1,6}$ 3.5 Hz, *H*-6), 4.42 (d, 1H, *H*-4), 4.60 (s, 2H, PhCH_2), 4.76 (s, 2H, PhCH_2), 5.62 (m, 1H, *H*-1), 5.87(m, 2H, *H*-3 + *H*-2), 7.26 (m, 10H, *Ph*), 7.42 (m, 2H, *Ar*), 7.58 (m, 1H, *Ar*), 7.93 (m, 2H, *Ar*).

1S-(1α, 4α, 5β, 6β) 4-azido-5,6-bis[(4-methoxyphenyl)methoxy]-1-benzoyl-2-cyclohexene 24 . Compound **24** (1.55 g, 83 %) was obtained from compound **19** (1.5 g, 3.7 mmol) by the above procedure. R_f 0.33 (hexane/EtOAc, 6:1); $[\alpha]_D$ +76.2 (c, 0.86, $CHCl_3$); ir ν_{max} 2100, 1720 cm^{-1}; ^1H nmr δ 3.73 (s, 3H, Ph-OC*H*$_3$), 3.80 (s, 3H, Ph-OC*H*$_3$), 3.73 (m, 1H, *H*-5),3.87 (dd, 1H, $J_{1,6}$ 3.5, $J_{5,6}$ 2,5 Hz, *H*-6), 4.36 (dd, 1H, $J_{3,4}$ 1, $J_{4,5}$ 8 Hz, *H*-4), 4.48 (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.53 (d, 1H, PhC*H*$_2$), 4.66 (s, 2H, PhC*H*$_2$),5.59 (m, 1H, *H*-3), 5.84 (m, 2*H*, *H*-1 + *H*-2), 6.77 (d, 2H, *Ar*), 6.87 (d, 2H, *Ar*), 7.20 (d, 2H, *Ar*), 7.28 (d, 2H, *Ar*), 7.47 (m, 2H, *Ar*), 7.59 (m, 1H, *Ar*), 7.99 (d, 2H, *Ar*). Anal. Calcd for $C_{29}H_{29}O_6N_3$: C, 67.56; H, 5.67; N, 8.15. Found: C, 67.44; H, 5.61; N, 7.98 %.

1S-(1α, 4α, 5β, 6β) 4-amino-5,6-bis(phenylmethoxy)-2-cyclohexen-1-ol 25. Prepared by $LiAlH_4$ reduction of compound **23** (610 mg, 1.34 mmol). Purification by column chromatography using first hexane/EtOAc (3:2) then CH_2Cl_2/EtOH (9:1) as the eluent afforded **27** (305 mg, 70 %). $[\alpha]_D$ -24 (c, 0.51, $CHCl_3$); ir ν_{max} 3460, 3355 cm^{-1}; ^1H nmr δ 2.23 (br s, 3H, N*H*$_2$ + O*H*), 3.62 (dd, 1H, $J_{4,5}$ 6.5, $J_{5,6}$ 1.5 Hz, *H*-5), 3.69 (d, 1H, *H*-4), 3.80 (dd, 1H, $J_{1,6}$ 5 Hz, *H*-6), 4.38 (m, 1H, *H*-1), 4.53 (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.65 (m, 3H, PhC*H*$_2$), 5.69 (m, 2H, *H*-3 + *H*-2), 7.30 (m, 10H, *Ar*). Anal. Calcd for $C_{20}H_{23}O_3N$: C, 73.82; H. 7.12; N, 4.30. Found: C, 73.97; H, 7.01; N, 4.39 %.

1S-(1α, 4α, 5β, 6β)4-amino-5,6-bis[(4-methoxyphenyl)methoxy]-2-cyclohexen-1-ol 26 Prepared by $LiAlH_4$ reduction of compound **24** (1.5 g, 2.9 mmol). Recrystallisation from EtOH gave **28** (872 mg, 78 %). R_f 0.28 (CH_2Cl_2/EtOH, 9:1); mp 122°C; $[\alpha]_D$ -13.02 (c, 0.19, $CHCl_3$); ir ν_{max} 3460, 3360 cm^{-1}; ^1H nmr δ 1.62 (br s, 3H, N*H*$_2$ + O*H*), 3.54 (dd, 1H, $J_{4,5}$ 6.5, $J_{5,6}$ 2 Hz, *H*-5), 3.62 (d, 1H, *H*-4), 3.74 (dd, 1H, $J_{1,6}$ 5 Hz, *H*-6), 3.79 (s, 6H, Ph-OC*H*$_3$), 4.36 (dd, 1H, $J_{1,2}$ 1.5 Hz, *H*-1), 4.46, (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.53 (d, 1H, PhC*H*$_2$), 4.60 (d, 1H, PhC*H*$_2$), 4.63 (d, 1H, PhC*H*$_2$)), 5.72 (m, 2H, *H*-3 + *H*-2), 6.88 (m, 4H, *Ar*), 7.27 (m, 4H, *Ar*). Anal. Calcd for $C_{22}H_{27}O_5N$: C, 68.55; H. 7.06; N, 3.63. Found: C, 68.42; H, 6.87; N, 3.68 %.

General procedure for amides formation. To a solution of amino alcohol (1 mmol) in THF (15 ml) was added BOP (486 mg, 1.1 mmol), aromatic acid (1.1 mmol) and triethylamine (111 mg, 1.1 mmol). The reaction mixture was stirred at room temperature during 4h and diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, water until neutral. The organic layer was dried ($MgSO_4$) and concentrated. The pure amide was obtained by recrystallisation from ethanol or by column chromatography.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-benzamide 27a: Compound **27a** (734 mg, 80%) was obtained from compound **21** (650 mg, 2 mmol); R_f 0.38 (hexane/EtOAc 2:3); mp 222°C (EtOH); $[\alpha]_D$ -172 (c, 0.33, $CHCl_3$); ir ν_{max} 3500, 3300,1635 cm^{-1}; ^1H nmr δ 3.87 (d, 1H, $J_{1,6}$ 6 Hz, *H*-6), 3.96 (br s, 1H, *H*-5), 4.25 (br s, 1H, *H*-4), 4.68 (m, 2H, PhC*H*$_2$), 4.79 (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.90 (d, 1H, PhC*H*$_2$), 4.98 (m, 1H, *H*-1), 5.70 (ddd, 1H, $J_{2,4}$ 1.5, $J_{1,2}$ 3, $J_{2,3}$ 10, *H*-2), 5.86 (d, 1H, *H*-3), 5.90 (d, 1H, N*H*), 7.2-7.65 (m, 15H, *Ar*). Anal. Calcd for $C_{27}H_{27}O_4N$: C, 75.50; H. 6.34; N, 3.26. Found: C, 75.67; H, 6.28; N, 3.12 %.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-5-carboxamide 27b. Compound **27b** (391 mg, 83 %) was obtained from compound **21** (325 mg, 1 mmol); $[\alpha]_D$ -1130 (c, 0.23, $CHCl_3$); ir ν_{max} 3500, 3300, 1650 cm^{-1}; ^1H nmr δ 3.02 (br s, 1H, O*H*), 3.36 (br s, 1H, *H*-6), 3.45 (br s, 1H, *H*-5), 4.24 (m, 1H, *H*-4), 4.67 (m, 2H, PhCH_2), 4.78 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.89 (d, 1H, PhCH_2), 4.94 (m, 1H, *H*-1), 5.69 (ddd, 1H, $J_{1,2}$ 3, $J_{2,3}$ 10, $J_{2,4}$ 1.5 Hz, *H*-2), 5.74 (d, 1H, N*H*), 5.86 (m, 1H, *H*-3), 6.05 (s, 2H, O-CH_2-O), 6.81 (d, 1H, *Ar*), 7.15 (m, 2H, *Ar*), 7.50 (m, 10H, *Ar*). Anal. Calcd for $C_{28}H_{27}O_6N$: C, 71.02; H. 5.75; N, 2.96. Found: C, 70.94; H, 5.82; N, 3.09 %.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-4-hydroxy-5-carboxamide 27c. After purification by column chromatography using EtOAc as the eluent compound **27c** (190 mg, 31 %) was obtained from compound **21** (400 mg, 1.23 mmol); R_f 0.37 (hexane/EtOAc 1:2); mp 141°C; $[\alpha]_D$ -150 (c, 0.17, $CHCl_3$); ir ν_{max} 3500, 3320,1660 cm^{-1}; ^1H nmr δ 1.6 (br s, 1H, O*H*), 3.74 (d, 1H, $J_{1,6}$ 7 Hz, *H*-3), 4.03 (br s, 1H, *H*-5), 4.24 (br s, 1H, *H*-4), 4.24 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.69 (d, 1H, PhCH_2), 4.78 (d, 1H, PhCH_2), 4.95 (d, 1H, PhCH_2), 4.95 (m, 1H, $J_{1,2}$ 3 Hz, *H*-1), 5.65 (ddd,1H, $J_{2,3}$ 10, $J_{3,4}$ =1.5 Hz, *H*-2), 5.80 (d, 1H, $J_{1,3}$ 1 Hz, *H*-3), 5.86 (d, 1H, J_{NH-1} 7.5 Hz, N*H*), 6.06 (s, 1H, O-CH_2-O), 6.07 (s, 1H, O-CH_2-O), 6.41 (d, 1H, *Ar*), 6.68 (d, 1H, *Ar*), 7.27 (m, 10H, *Ar*), 12.22 (br s, 1H, Ar-O*H*). Anal. Calcd for $C_{28}H_{27}O_7N$: C, 68.70; H. 5.56; N, 2.86. Found: C, 68.59, H, 5.72; N, 3.02 %.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-3,4-bis-(methoxy)-benzamide 27d. Compound **27d** (1.32 g, 68 %) was obtained from compound **21** (1.3 g, 4 mmol); R_f 0.67 (EtOAc); mp 207°C; $[\alpha]_D$ -15.8 (c, 0.5, $CHCl_3$); ir ν_{max} 3400,1640 cm^{-1}; ^1H nmr δ 3.04 (br s, 1H, O*H*), 3.90 (br d, 1H, $J_{1,6}$ 6 Hz, *H*-6), 3.93 (s, 1H, Ph-OCH_3), 3.94 (s, 3H, Ph-OCH_3), 3.97 (m, 1H, *H*-5), 4.26 (m, 1H, *H*-4), 4.67 (d, 1H, J_{gem} 11.5 Hz, PhCH_2), 4.69 (d, 1H, PhCH_2), 4.80 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.91 (d, 1H, PhCH_2), 4.96 (m, 1H, *H*-1), 5.71 (ddd, 1H, $J_{1,2}$ 3, $J_{2,3}$ 10, $J_{2,4}$ 15 Hz, *H*-2), 5.84 (m, 2H, N*H* + *H*-3), 6.84 (d, 1H, J 8.5 Hz, *Ar*), 7.12 (dd, 1H, J 8.5, J 2 Hz, *Ar*), 7.3 (m, 10H, *Ar*), 7.4 (d, 1H, J 2 Hz, *Ar*).

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-2,3,4-tris-(methoxy)-benzamide 27e. Compound **27e** (611 mg, 86 %) was obtained from compound **21** (444 mg, 1.36 mmol); mp 150°C (CH_2Cl_2/EtOH); R_f 0.32 (hexane/EtOAc, 2:3); $[\alpha]_D$ -160 (c, 0.40, $CHCl_3$); ^1H nmr δ 3.16 (m, 1H, *H*-5); 3.71 (s, 3H, Ph-OCH_3), 3.86, (s, 3H, Ph-OCH_3), 3.92, (s, 3H, Ph-OCH_3), 4.00 (d, 1H, $J_{1,6}$ 4 Hz, *H*-6), 4.30 (m, 1H, *H*-4), 4.69 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.80 (m, 3H, PhCH_2), 5.00 (m, 1H, *H*-1), 5.10 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, *H*-2), 5.96 (m, 1H, *H*-3), 6.80 (d, 1H, *Ar*), 7.30 (m, 10H, *Ar*), 7.83 (d, 1H, N*H*), 7.94 (d, 1H, *Ar*). Anal. calcd for $C_{30}H_{33}O_7N$: C. 69,35; H, 6.40; N, 2.70. Found: C, 69.67; H, 6.34; N, 2.90 %.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-[(4-methoxyphenyl)methyl]-4-hydroxy-2-cyclohexen-1-yl]-benzamide 28a. Compound **28a** (422 mg, 80 %) was obtained from compound **22** (412 mg, 1.07 mmol). R_f 0.4 (hexane/EtOAc 1:3); mp 222°C; $[\alpha]_D$ -140 (c, 0.24, $CHCl_3$), ir ν_{max} 3500, 3300,1630 cm^{-1}; ^1H nmr δ 1.06 (br s, 1H, O*H*), 3.76 (s, 6H, Ph-OCH_3), 3.82 (m, 1H, *H*-6), 3.92 (s, 1H, *H*-5), 4.21 (s, 1H, *H*-4), 4.55 (d,

1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.58 (d, 1H, PhC*H*$_2$), 4.70 (d, 1H, PhC*H*$_2$), 4.83 (d, 1H, PhC*H*$_2$), 4.44 (m, 1H, *H*-1), 5.69 (m, 1H, *H*-2), 5.81 (m, N*H* + *H*-3), 6.8-7.65, (m, 13H, *Ar*). Anal.calcd for $C_{29}H_{31}O_6N$: C, 71. 16; H. 6.33; N, 2.86. Found: C, 71. 21; H, 6.24; N, 2.73 %.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-[(4-methoxyphenyl)methoxy]-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-5-carboxamide 28b. Compound **28b** (348 mg, 65 %) was obtained from compound **22** (384 mg, 1 mmol). mp 208°C (EtOH); $[\alpha]_D$ -237.5 (c, 0.49, DMF); ir ν_{max} 3500, 3300, 1650 cm^{-1}; ^{1}H nmr (DMSO) δ 3.68 (s, 3H, Ph-OC*H*$_3$), 3.71 (dd, 1H, $J_{1,6}$ 9, $J_{6,5}$ 2 Hz, *H*-6), 3.74 (s, 3H, Ph-OC*H*$_3$), 4.05 (m, 1H, *H*-5), 4.22 (m, 1H, *H*-4), 4.38 (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.41 (d, 1H, PhC*H*$_2$), 4.71 (AB, 2H, PhC*H*$_2$), 4.78 (m, 1H, *H*-1), 4.85 (d, 1H, $J_{OH,4}$ 7.5 Hz, O*H*), 5.38 (ddd, 1H, $J_{1,3}$ 2, $J_{2,3}$ 10, $J_{3,4}$ 2 Hz, *H*-3), 5.50 (ddd, 1H, $J_{1,2}$ 2, $J_{2,4}$ 1.5 Hz, *H*-2), 6.10 (s, 2H, O-C*H*$_2$-O), 6.78 (d, 2H, *Ar*), 6.86 (d, 2H, *Ar*), 7.0 (d, 1H, *Ar*) 7.16 (d, 2H, *Ar*) 7.32 (d, 2H, *Ar*), 7.39 (d, 2H, *Ar*) 7.45 (d, 1H, *Ar*), 8.30 (d, 1H, N*H*). Anal. Calcd for $C_{30}H_{31}O_8N$: C, 67.53; H, 5.86; N, 2.63. Found: C, 67.27; H, 5.91; N, 2.63 %.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-[(4-methoxyphenyl)methoxy]-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-4-hydroxy-5-carboxamide 28c. After purification by column chromatography using hexane/EtOAc (1:2) as the eluent compound **28c** (600 mg, 67 %) was obtained from compound **22** (620 mg, 1.6 mmol). R_f 0.37 (hexane/EtOAc 1:2); mp 61°C; $[\alpha]_D$ -127.4 (c, 0.31, $CHCl_3$); ir ν_{max} 3520, 3380,1660 cm^{-1}; ^{1}H nmr δ 3.78 (s, 3H, Ph-OC*H*$_3$), 3.79 (s, 3H, Ph-OC*H*$_3$), 3.80 (s, 2H,PhC*H*$_2$), 4.00 (br s, 1H, O*H*), 4.21 (d, 1H, $J_{5,6}$ 1Hz, *H*-5), 4.47 (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.70 (d, 1H, PhC*H*$_2$), 4.60 (d, 1H, $J_{1,6}$ 10 Hz, *H*-6), 4.88 (m, 2H, *H*-4 + *H*-1), 5.64 (dd, 1H, $J_{1,2}$ 1.5, $J_{2,3}$ 10 Hz, *H*-2), 5.76 (d, 1H, *H*-3), 5.90 (d, 1H, $J_{NH,1}$ 7.5 Hz, N*H*), 6.05 (s, 1H, O-C*H*$_2$-O), 6.08 (s, 1H, O-C*H*$_2$-O), 6.3 (d, 1H, *Ar*),6.57 (d, 1H, *Ar*), 6.8-7.21 (m, 8 H, *Ar*), 12.21 (s, 1H, Ph-O*H*). Anal. Calcd for $C_{30}H_{31}O_9N$: C, 65.56; H, 5.69; N, 2.55. Found: C, 65.41; H, 5.99; N, 2.53 %.

[1R-(1α, 4β, 5β, 6β)] N-[5,6-bis-[(4-methoxyphenyl)methoxy]-4-hydroxy-2-cyclohexen-1-yl]-2,3,4-tris-(methoxy)-benzamide 28e. Compound **28e** (397 mg, 72 %) was obtained from compound **22** (363 mg, 0.95 mmol). R_f 0.71 (MeOH/CH_2Cl_2 1:9); mp 114°C (EtOH); $[\alpha]_D$ -191,7 (c, 0.6, DMF); ir ν_{max} 3500, 3280, 1630 cm^{-1}; ^{1}H nmr δ 1.68 (br s., 1H, O*H*), 3.74 (s, 3H, Ph-OC*H*$_3$), 3.78 (s, 3H, Ph-OC*H*$_3$), 3.79 (s, 3H, Ph-OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 3.81 (m, 1H, *H*-6), 3.92 (m, 1H, *H*-5), 4.23 (m, 1H, *H*-4), 4.59 (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.70 (m, 3H, PhC*H*$_2$), 5.00 (m, 1H, *H*-1), 5.73 (m, 1H, *H*-3), 5.89 (d, 1H, $J_{2,3}$ 10 Hz, *H*-2), 6.78 (m, 4H, *Ar*), 7.28 (m, 6H, *Ar*), 7.91 (d, 1H, N*H*).

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-benzamide 29a. After purification by column chromatography using hexane/EtOAc (2:3) as the eluent compound **29a** (450 mg, 80%) was obtained from compound **27** (400 mg, 1.23 mmol). $[\alpha]_D$ -34.67 (c, 0.62, $CHCl_3$); ir ν_{max} 3350, 1640 cm-^{1}; ^{1}H nmr. δ 3.50 (dd, 1H, $J_{4,5}$ 8, $J_{5,6}$ 2 Hz, *H*-5), 4.05 (dd, 1H, $J_{1,6}$ 3 Hz, *H*-6), 4.33 (d, 1H, J_{gem} 12 Hz, PhC*H*$_2$), 4.53 (d, 1H, PhC*H*$_2$), 4.57 (m, 1H, *H*-4), 4.79 (s, 1H, PhC*H*$_2$), 4.80 (s, 1H, PhC*H*$_2$), 4.87 (m, 1H, *H*-1), 5.69 (m, 1H, *H*-2), 5.96 (m, 1H, *H*-3), 6.02 (d, $J_{NH,1}$ 7 Hz, N*H*), 7.10 -7.75 (m, 15H, *Ar*). Anal. Calcd for $C_{27}H_{27}O_4N$: C, 75.50; H. 6.34; N, 3.26. Found: C, 75.43; H, 6.41; N, 3.22 %.

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-5-carboxamide 29b. After purification by column chromatography using hexane/EtOAc (2:3) as the eluent compound **29b** (765 mg, 70 %) was obtained from compound **27** (747 mg, 2.3 mmol); $[\alpha]_D$ -49.4 (c, 0.47, $CHCl_3$); ir ν_{max} 3400, 1650 cm^{-1}; ^1H nmr δ 2.61 (br s, 1H, O*H*), 3.50 (dd, 1H, $J_{4,5}$ 7.5, $J_{5,6}$ 2 Hz, *H*-5), 4.03 (m, 1H, *H*-6), 4.34 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.53 (d, 1H, PhCH_2), 4.56 (d, 1H, *H*-4), 4.78 (AB, 2H, PhCH_2), 4.82 (m, 1H, *H*-1), 5.62 (m, 1H, *H*-2), 5.90 (d, 1H, $J_{NH,1}$ 7 Hz, N*H*), 5.94 (m, 1H, *H*-3), 6.29 (s, 2H, O-CH_2-O), 6.82 (d, 2H, *Ar*), 7.25 (m, 10H, *Ar*), 7.41 (m, 2H, *Ar*). Anal. Calcd for $C_{28}H_{27}O_6N$: C, 71.02; H. 5.75; N, 2.96. Found: C, 71.17; H, 5.61; N, 2.82 %.

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-4-hydroxy-5-carboxamide 29c. After purification by column chromatography using hexane/EtOAc (1:2) as the eluent compound **29c** (110 mg, 74 %) was obtained from compound **27** (100 mg, 0.3 mmol). R_f 0.33 (hexane/EtOAc 1:2); $[\alpha]_D$ -54,4 (c, 0.2 $CHCl_3$); ir ν_{max} 3400. 1660 cm^{-1}; ^1H nmr δ 2.60 (br s, 1H, O*H*), 3.52 (dd, 1H, $J_{4,5}$ 7, $J_{5,6}$ 2 Hz, *H*-5), 3.93 (dd, 1H, $J_{1,6}$ 3 Hz, *H*-6), 4.36 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.51 (d, 1H, PhCH_2), 4.54 (m, 1H, *H*-4), 4.74 (s, 2H, PhCH_2), 4.80 (m, 1H, *H*-1), 5.67 (dd, 1H, $J_{1,2}$ 4, $J_{2,3}$ 10 Hz, *H*-2), 5.94 (ddd, 1H, $J_{1,3}$ 1.5, $J_{3,4}$ 2 Hz, *H*-3), 6.06 (d, 2H, -O-CH_2-O), 6.40 (d, 1H, *Ar*) 6.80 (d, 1H, *Ar*), 7.20 (m, 10H, *Ar*), 12.63 (br s, 1H, Ph-O*H*). Anal. Calcd for $C_{28}H_{27}O_7N$: C, 68.71; H. 5.56; N, 2.86. Found: C, 68.42; H, 5.67; N, 2.85 %.

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-3,4-bis-(methoxy)-benzamide 29d. After purification by column chromatography using hexane/EtOAc (1:2) as the eluent compound **29d** (398 mg, 81 %) was obtained from compound **27** (351 mg, 1 mmol); mp 149°C; R_f 0.64 (EtOAc); ir ν_{max} 3400, 1650 cm^{-1}, ^1H nmr δ 3.51 (dd, 1H, $J_{4,5}$ 7.5, $J_{5,6}$ 2 Hz, *H*-5), 3.95 (s, 6H, Ph-OCH_3), 4.09 (m, 1H, *H*-6), 4.34 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.53 (d, 1H, PhCH_2), 4.59 (dd, 1H, $J_{3,4}$ 1 Hz, *H*-4), 4.81 (m, 2H, PhCH_2), 4.85 (m, 1H, *H*-1), 5.71 (m, 1H, *H*-2), 5.95 (m, 2H, *H*-3 + N*H*), 6.86 (d, 1H, *Ar*), 7.29 (m, 12H, *Ar*).

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-(phenylmethoxy)-4-hydroxy-2-cyclohexen-1-yl]-2,3,4-tris-(methoxy)-benzamide 29e. After purification by column chromatography using hexane/EtOAc (1:2) as the eluent compound **29e** (965 mg, 82 %) was obtained as a gum from compound **27** (400 mg, 1.23 mmol); $[\alpha]_D$ -68.7 (c, 0.64, $CHCl_3$); ir ν_{max} 3370, 1650, 1640 cm^{-1}; ^1H nmr δ 2.49 (br s, 1H, O*H*), 3.49 (dd, 1H, $J_{4,5}$ 8, $J_{5,6}$ 2 Hz, *H*-5), 3.79 (s, 3H, Ph-OCH_3), 3.86 (s, 3H, Ph-OCH_3), 3.92 (s, 3H, Ph-OCH_3), 4.11 (m; 1H, *H*-6), 4.34 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.52 (d, 1H, PhCH_2), 4.62 (m, 1H, *H*-4), 4.85 (AB, 2H, PhCH_2), 4.90 (m, 1H, *H*-1), 5.70 (ddd, 1H, $J_{1,2}$ 4, $J_{2,3}$ 10, $J_{2,4}$ 2 Hz, *H*-2), 5.97 (ddd, 1H, $J_{1,3} = J_{3,4}$ 1.5 Hz, *H*-3), 6.82 (d, 1H, *Ar*), 7.25 (m, 10H, *Ar*), 7.44 (d, 1H, *Ar*), 7.92 (d, J 7 Hz, N*H*). Anal. Calcd for $C_{30}H_{33}O_7N$: C, 69.35; H. 6.40; N, 2.70. Found: C, 69.47; H, 6.42; N, 2.59 %.

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-[(4-methoxyphenyl)methyl]-4-hydroxy-2-cyclohexen-1-yl]-benzamide 30a. After purification by column chromatography using hexane/EtOAc (2:3) as the eluent compound **30a** (403 mg, 88 %) was obtained from compound **28** (360 mg, 0.93 mmol); R_f 0,35 (hexane/EtOAc 2:3); $[\alpha]_D$ -

8.8 (c, 0.7 $CHCl_3$); ir ν_{max} 3400, 1640 cm^{-1}; ^1H nmr δ 2.44 (br s, 1H, O*H*), 3.45 (dd, 1H, $J_{4,5}$ 7.5, $J_{5,6}$ 1.5 Hz, *H*-5), 3.73 (s, 3H, Ph-OCH_3), 3.80 (s, 3H, Ph-OCH_3), 4.04 (s, 1H, *H*-6), 4.21 (d, 1H, J_{gem} 12 Hz, PhCH_2), 4.44 (d, 1H, PhCH_2), 4.73 (s, 2H, PhCH_2), 4.54 (m, 1H, *H*-4), 4.84 (m, 1H, $J_{1,2}$ 4 Hz, *H*-1), 5.70 (m, 1H, $J_{2,3}$ 10 Hz, *H*-2), 5.95, (d, 2H, N*H* + *H*-3), 6.72 (d, 2H, *Ar*), 6.84 (d, 2H, *Ar*), 7.10 (d, 2H, *Ar*), 7.36 (d, 2H, *Ar*), 7.44 (m, 2H, *Ar*), 7.54 (t, 1H, *Ar*), 7.70 (d, 2H, *Ar*). Anal. Calcd for $C_{29}H_{31}O_6N$: C, 71.15; H, 6.38; N, 2.86. Found: C, 70.96, H, 6.59, N, 2.75 %.

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-[(4-methoxyphenyl)methoxy]-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-5-carboxamide 30b. After purification by column chromatography using hexane/EtOAc (1:2) as the eluent compound **30b** (630 mg, 90 %) was obtained from compound **28** (505 mg, 1.31 mmol). R_f 0.54, (hexane/EtOAc 3:1); mp 52°C; $[\alpha]_D$ -29.3 (c, 0.33 $CHCl_3$); ir ν_{max} 3500, 1630 cm^{-1}; ^1H nmr δ 2.41 (d, 1H, O*H*), 3.43 (dd, 1H, $J_{4,5}$ 7.5, $J_{5,6}$ 2Hz, *H*-5), 3.72 (s, 3H, Ph-OCH_3), 3.82 (s, 3H, Ph-OCH_3), 4.01 (m, 1H, *H*-6), 4.50 (d, 1H, $J_{3,4}$ 2.5 Hz, *H*-4), 4.22 (d, 1H, PhCH_2), 4.44 (d, 1H, PhCH_2), 4.72 (s, 2H, PhCH_2), 4.79 (ddd, 1H, $J_{1,3}$ 1, $J_{1,2} = J_{1,6}$ 4.5 Hz, *H*-1), 5.67 (m, 1H, *H*-2), 5.81 (d, 1H, $J_{NH,1}$ 7.5 Hz, N*H*), 5.94 (ddd, 1H, $J_{2,3}$ 10 Hz, *H*-3), 6,04 (s, 2H, O-CH_2-O), 6.71-7.32 (m, 11H, *Ar*). Anal. Calcd for $C_{30}H_{31}O_8N$: C, 67.53; H, 5.83; N, 2.63. Found: C, 67.73; H, 6.16; N, 2.40 %.

[1R-(1α, 4α, 5β, 6β)] N-[5,6-bis-[(4-methoxyphenyl)methoxy]-4-hydroxy-2-cyclohexen-1-yl]-1,3 benzodioxole-4-hydroxy-5-carboxamide 30c. After purification by column chromatography using hexane/EtOAc (1:3) as the eluent compound **30c** (313 mg, 58 %) was obtained from compound **28** (384 mg, 1 mmol); R_f 0.49 (hexane/EtOAc 1:3); $[\alpha]_D$ -11.3(c, 0.75 $CHCl_3$); ir ν_{max} 3420,1660 cm^{-1}; ^1H nmr δ 2.51 (br s, 1H, O*H*), 3.45 (dd, 1H, $J_{4,5}$ 7 Hz, $J_{5,6}$ 2 Hz, *H*-5), 3.74 (s, 3H, Ph-OCH_3), 3.79 (s, 3H, Ph-OCH_3), 3.92 (m, 1H, $J_{1,6}$ 4 Hz, *H*-6), 4.25 (d, 1H, PhCH_2), 4.44 (d, 1H, PhCH_2), 4.49 (d, 1H, *H*-4), 4.66 (d, 2H, PhCH_2), 4.77 (ddd, 1H, $J_{1,2}$ 3,5, $J_{1,3}$ 1 Hz, *H*-1), 5.67 (m, 1H, *H*-2), 5.94, (ddd,1H, $J_{2,3}$ 10, $J_{3,4}$ 2.5,*H*-3), 6.01 (d, 1H, $J_{NH,1}$ 7.5 Hz, N*H*), 6.06 (d, 1H, O-CH_2-O), 6.07 (d, 1H, O-CH_2-O), 6.40 - 7.29 (m, 10H, *Ar*), 12.25 (br s, 1H, O*H*). Anal. Calcd for $C_{30}H_{31}O_9N$: C, 65.56; H, 5.69; N, 2.55. Found: C, 65.32; H, 5.89; N, 2.53 %.

General procedure for cleavage of the protecting groups: *Method A*. The protected amide (1 mmol) was dissolved in a mixture of THF-EtOH (v/v, 8:2, 10 ml) and palladium on activated carbon (10 %, 200 mg) was added. The mixture was stirred under hydrogen atmosphere for 2h. The mixture was filtered through a pad of celite. The filtrate was evaporated and the crude crystalline product was recrystallized from EtOH. *Method B*. The protected amide (0.5 mmol) was dissolved in a mixture of CH_2Cl_2-H_2O (v/v, 18:2, 5 ml) and DDQ (440 mg, 1.5 mmol), was added. The mixture was stirred overnight and then diluted with CH_2Cl_2 (20 ml) and H_2O (2 ml). The aqueous layer was separated, and evaporated to dryness. The residue was purified by column chromatography using CH_2Cl_2/MeOH (8:2) as the eluent. The pure product was recrystallized from EtOH.

[1R-(1α, 4α, 5β, 6β)] N-[2,3,4-tris-(hydroxy)-cyclohexanyl]-benzamide 31a. Catalytic hydrogenation (method A) of **29a** (350 mg, 0.75 mmol) gave **31a** (180 mg, 86 %) as an amorphous powder; $[\alpha]_D$ -38.16 (c,

0.49, DMF); ir ν_{max} 3300, 1630 cm^{-1}; ^1H nmr (DMSO) δ 1.44 (m, 1H, *H*-5), 1.56 (m, 2H, *H*-6 + *H*-6'), 1.71 (m, 1H, *H*-5'), 3.70 (m, 3H, *H*-4 + *H*-3 + *H*-2), 4.03 (m, 1H, *H*-1), 4.21 (d, 1H, J 7 Hz, O*H*), 4.56 (d, 1H, J 3 Hz, O*H*), 4.67 (d, 1H, J 3 Hz, O*H*), 7.47 (m, 3H, *Ar*), 7,88 (m, 2H, *Ar*), 8.09 (d, 1H, $J_{NH,1}$ 7 Hz, N*H*). Anal. Calcd for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.06; H, 6.90; N, 5.41 %.

[1R-(1α, 4α, 5β, 6β)] N-[2,3,4-tris-(hydroxy)-cyclohexanyl]-1,3 benzodioxole-4-hydroxy-5-carboxamide 31c . Catalytic hydrogenation (method A) of **29c** (366 mg, 0.75 mmol) gave **31c** (171 mg, 73 %) as a white foam : mp 71°C; R_f 0.36 (CH_2Cl_2/MeOH 9:1); ^1H nmr (DMSO) δ 1.44 (m, 1H) 1.52 (m, 1H), 1.62 (m, 1H), 1.70 (m, 1H), 3.62 (m, 3H, *H*-4 + *H*-3 + *H*-2), 4.05 (m, 1H, *H*-1), 4.36 (d, 1H, J 6.5 Hz), 4.68 (d, 1H, J 3 Hz), 4.75 (d, 1H, J 2.5 Hz, O*H*), 6.11 (s, 2H, O-CH_2-O), 6.59 (d, 1H, J 8 Hz, *Ar*), 7.61 (d, 1H, *Ar*) 8.43 (d, 1H, $J_{NH,1}$ 8 Hz, N*H*), 12.80 (s, 1H, Ar-O*H*).

[[1R-(1α, 4α, 5β, 6β)] N-[2,3,4-tris-(hydroxy)-cyclohexanyl]-2,3,4-tris-(methoxy)-benzamide 31e. Catalytic hydrogenation (method A) of **29e** (441 mg, 0.85 mmol) gave **31e** (246 mg, 86 %). mp 158°C; R_f 0.29 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ -26.9 (c, 0.26, DMF); ir ν_{max} 3250, 1640 cm^{-1}; ^1H nmr (DMSO) δ 1.39 (m, 1H, *H*-5), 1.48 (m, 1H, *H*-6), 1.75 (m, 2H, *H*-6' + *H*-5'), 3.62 (m, 2H, *H*-4 + *H*-2), 3.69 (m, 1H, *H*-3), 3.76 (s, 3H, Ph-OCH_3), 3.83 (s, 3H, Ph-OCH_3), 3.86 (s, 3H, Ph-OCH_3), 3.96 (m, 1H, *H*-1), 4.19 (d, 1H, J 7 Hz, O*H*), 4.39 (d, 1H, J 3 Hz, O*H*), 6.93 (d, 1H, *Ar*), 7.51 (d, 1H, *Ar*), 8.01 (d, 1H, $J_{NH,1}$ 7 Hz, N*H*). Anal. Calcd for $C_{16}H_{23}O_7N$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.15; H, 6.67; N, 4.03 %.

[1R-(1α, 4α, 5β, 6β)] N-[4,5,6-tris-(hydroxy)-2-cyclohexen-1-yl]-1,3 benzodioxole-5-carboxamide 32b. Compound **30b** (630 mg, 1.18 mmol) was treated with DDQ (method B) to give **32b** (210 mg, 61 %). R_f 0.17 (CH_2Cl_2/MeOH, 9:1); mp 208°C (EtOH); $[\alpha]_D$ -173.1 (c, 0.26, DMF); ir ν_{max} 3400, 3300, 1650 cm^{-1}; ^1H nmr (DMSO) δ 3.66 (m, 1H, $J_{5,6}$ 3 Hz, *H*-5), 3.76 (m, 1H, $J_{1,6}$ 7 Hz, *H*-6), 3.96 (m, 1H, $J_{3,4}$ 3.5, $J_{4,5}$ 5 Hz, *H*-4), 4.54 (m, 1H, *H*-1), 4.66 (d, 1H, $J_{OH,6}$ 5.5 Hz, O*H*), 4.72 (d, 1H, $J_{OH,5}$ 4 Hz, O*H*), 4.95 (d, 1H, $J_{OH,4}$ 4.5 Hz, O*H*), 5.45 (dd, 1H, $J_{1,2}$ 2.5 Hz, *H*-2),5.61 (ddd, 1H, $J_{1,3}$ 2 Hz, $J_{2,3}$ 10 Hz, *H*-3), 6.07 (s, 2H, O-CH_2-O), 6.97- 7.5 (m, 3H, *Ar*), 8.23 (d, 1H, $J_{NH,1}$ 10.5 Hz, N*H*). Anal.Calcd. for $C_{14}H_{15}O_6N$: C, 57.34; H, 5.16; N, 4.78. Found: C,57.69; H, 5.04; N, 4.66 %.

[1R-(1α, 4β, 5β, 6β)] N-[2,3,4-tris-(hydroxy)-cyclohexanyl]-benzamide 33a. Catalytic hydrogenation (method A) of **27a** (310 mg, 0.67 mmol) gave **33a** (131 mg, 70 %) R_f 0.18 (CH_2Cl_2/MeOH, 9:1); mp 254°C (EtOH); $[\alpha]_D$ -35.9 (c, 0.17, DMF); ir ν_{max} 3570, 3400, 3320,1630 cm^{-1}; ^1H nmr (DMSO) δ 1.17 (m, 1H, *H*-6), 1.46 (m, 1H, *H*-5), 1.67 (m, 2H, *H*-6' + *H*-5'), 3.38 (m, 2H, *H*-4 + *H*-2), 3.80 (m, 1H, *H*-3), 4.0 (m, 1H, *H*-1), 4.36 (d, 1H, J 7 Hz, O*H*), 4.45 (d, 1H, J 7 Hz, O*H*), 4.52 (d, 1H, J 3 Hz, O*H*), 7.47 (m, 3H, *Ar*), 7.84 (d, 2H, J 8 Hz, *Ar*), 8.06 (d, 1H, $J_{NH,1}$ 7 Hz, N*H*). Anal. Calcd for $C_{13}H_{17}O_4N$: C, 62.14; H. 6.82; N, 5.57. Found: C, 61.93; H, 6.90; N, 5.41 %.

[1R-(1α, 4β, 5β, 6β)] N-[2,3,4-tris-(hydroxy)-cyclohexanyl]-1,3 benzodioxole-4-hydroxy-5-carboxamide 33c. Catalytic hydrogenation (method A) of **27c** (170 mg, 0.35 mmol) gave **33c** (65 mg, 60 %). R_f 0.47 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D$ -18 (c, 0.23, DMF); ^1H nmr (DMSO) δ 1.18 (m, 1H,), 1.49 (m,

1H,), 1.63 (m, 1H,), 1.71 (m, 1H), 3.40 (m, 2H,), 3.76 (br s, 1H, OH), 3.98 (m, 1H, *H*-1), 4.14 (m, 1H), 4.48 (br s, 1H, O*H*), 4.53 (br s, 1H, O*H*), 5.92 (s, 2H, O-CH_2-O), 6.26 (d, 1H, J 8 Hz, *Ar*), 7.43 (d, 1H, *Ar*).

[1R-(1α, 4β, 5β, 6β)] N-[2,3,4-tris-(hydroxy)-cyclohexanyl]-3,4-bis-(methoxy)-benzamide 33d. Catalytic hydrogenation (method A) of **27d** (320 mg, 0.65 mmol) gave **33d** (193 mg, 95 %). mp 215°C (EtOH); $[\alpha]_D$ -30 (c, 0.78, DMF); ^{1}H nmr (DMSO) δ 1.17 (m, 1H), 1.47 (m, 1H), 1.67 (m, 2H), 2.95 (m, 2H, *H*-4 + *H*-2), 3.81 (s, 7H, 2 Ph-OCH_3 + *H*-3), 3.99 (m, 1H, *H*-1), 4.35 (m, 1H, O*H*), 4.45 (m, 1H, O*H*), 4.52 (m, 1H, O*H*), 7.00 (d, 1H, J 8 Hz, *Ar*), 7.43 (s, 1H, J 8 Hz, *Ar*), 7.47 (d, 1H, *Ar*), 7.90 (d, 1H, $J_{NH,1}$ 7 Hz, N*H*).

[1R-(1α, 4β, 5β, 6β)] N-[2,3,4-tris-(hydroxy)-cyclohexanyl]-2, 3 ,4-tris-(methoxy)-benzamide 33e. Catalytic hydrogenation (method A) of **27e** (300 mg, 0.58 mmol) gave **33e** (125 mg, 63 %). R_f 0.32 (CH_2Cl_2/MeOH 9:1); mp 129-130°C; $[\alpha]_D$ +16.8 (c, 0.25, $CHCl_3$); ir ν_{max} 3400, 3260, 1630 cm^{-1}; ^{1}H nmr δ 1.31 (m, 1H, *H*-6), 1.88 (m, 1H, *H*-5), 1.92 (m, 1H, *H*-5'), 2.00 (m, 1H, *H*-6'), 3.13 (br s, 1H, O*H*), 3.50 (dd, 1H, $J_{1,2}$ 9.5, $J_{2,3}$ 2 Hz, *H*-2), 3.68 (m, 1H, *H*-4), 3.77 (br s, 1H, O*H*), 3.86 (s, 3H, Ph-OCH_3), 3.90 (s, 3H, Ph-OCH_3), 3.96 (s, 3H, Ph-OCH_3), 4.15 (dd, 1H, $J_{3,4}$ 2 Hz, *H*-3), 4.25 (m, 1H, $J_{NH,1}$ 7 Hz, *H*-1), 5.14 (br s, 1H, O*H*), 6.75 (d, 1H, *Ar*), 7.83 (d, 1H, *Ar*), 8.14 (d, 1H, N*H*). Anal. Calcd for $C_{16}H_{23}O_7N$: C, 56.30; H, 6.79; N, 4.10. Found: C, 55.99; H, 6.94; N, 4.30 %.

[1R-(1α, 4α, 5β, 6β)] N-[4,5,6-tris-(hydroxy)-2-cyclohexen-1-yl]-benzamide 34a. From compound **28a** (method B) (1.176 g, 2.2 mmol) was obtained **34a** (439 mg, 68 %). R_f 0.27 (CH_2Cl_2/MeOH, 8:2); mp 230°C (EtOH); $[\alpha]_D$ -238 (c, 0.25, DMF); ir ν_{max} 3420, 3300, 1630 cm^{-1}; ^{1}H nmr (DMSO) δ 3.69 (m, 1H, *H*-6), 3.76 (dd, 1H, $J_{4,5} = J_{5,6}$ 2 Hz, *H*-5), 4.1 (m, 1H, *H*-4), 4.55 (m, 1H, *H*-1), 4.63 (d, 1H, $J_{OH,4}$ 8 Hz, O*H*), 4.66 (d, 1H, $J_{OH,5}$ 4 Hz, O*H*), 4.78 (d, 1H, $J_{OH,6}$ 6 Hz, O*H*), 5.40 (dd, 1H, $J_{1,2}$ 1.5, $J_{2,3}$ 9.5 Hz, *H*-2), 5.46 (dd, 1H, $J_{3,4}$ 1 Hz, *H*-3), 7.5-7.89 (m, 5H, *Ar*), 8.34 (d, 1H, $J_{NH,1}$ 8 Hz, N*H*). Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.37; H, 6.10; N, 5.70 %.

[1R-(1α, 4α, 5β, 6β)] N-[4,5,6-tris-(hydroxy)-2-cyclohexen-1-yl]-1,3 benzodioxole-5-carboxamide 34b. From compound **28b** (method B) (180 mg, 0.33 mmol).was obtained **34b** (70 mg, 71%); mp 206°C (EtOH); $[\alpha]_D$ -265.9 (c, 0.43, DMF); ir ν_{max} 3480, 3260, 1640 cm^{-1};.^{1}H nmr (DMSO) δ 3.66 (d, 1H, *H*-6), 3.88 (s, 1H, *H*-5), 4.10 (s 1H, *H*-4), 4.61 (m, 1H, *H*-1), 4.78 (m, 3H, 3 O*H*), 6.07 (s, 2H, O-CH_2-O), 7.21 (m, 3H, *Ar*), 8.15 (d, 1H, N*H*)

[1R-(1α, 4α, 5β, 6β)] N-[4,5,6-tris-(hydroxy)-2-cyclohexen-1-yl]-3,4-bis-(methoxy)-benzamide 34d. Compound **27d** (110 mg, 0,22 mmol) was dissolved in $CHCl_3$ (10 ml) and Me_3SiI (0,15 ml, 1 mmol) was added. The reaction mixture was stirred for 5 hours at room temperature. The solvent was evaporated and the residue was dissolved in H_2O (2ml) and washed with Et_2O. The aqueous layer was evaporated to dryness to give **34d** (50 mg, 75 %). R_f 0.59 (EtOAc/MeOH 1:1). 3.70 (m, 1H, *H*-6), 3.79 (s, 3H, Ph-OCH_3), 3.79 (s, 3H, Ph-OCH_3), 3.90 (m, 1H, *H*-5), 4.11 (m, 1H, *H*-4), 4.61 (m, 1H, *H*-1), 4.72 (m, 2H, O*H*), 4.91 (m, 1H, O*H*), 5.42 (m, 2H, *H*-2 + *H*-3), 6.99 (d, 1H, J 8Hz, *Ar*), 7.51 (s, 1H, *Ar*), 7.53 (d, 1H, *Ar*), 8.28 (br s, 1H, N*H*).

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