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Synthesis of polyhydroxylated piperidines and evaluation as glycosidase inhibitors

Tony Tite,[a] Marie-Christine Lallemand,[a,*] Erwan Poupon,[a] Nicole Kunesch,[a] François Tillequin,[a] Christine Gravier-Pelletier,[b] Yves Le Merrer[b] and Henri-Philippe Husson[c,*]

[a]*Laboratoire de Pharmacognosie, Faculté des Sciences Pharmaceutiques et Biologiques, UMR 8638 associée au CNRS et à l'Université René Descartes, 4, Avenue de l'Observatoire, 75270 Paris Cedex 06, France*
[b]*Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 associée au CNRS et à l'Université René Descartes, 45, rue des Saints-Pères, 75270 Paris Cedex 06, France*
[c]*Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques, UMR 8638 associée au CNRS et à l'Université René Descartes, 4, Avenue de l'Observatoire, 75270 Paris Cedex 06, France*

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Abstract—A series of 16 new chiral nonracemic polyhydroxylated piperidines was synthesized utilizing several chiral β-amino-alcohols. They act as a nitrogen source, chirality inducer and iminium stabilizer, in the desymmetrization of *meso*-trihydroxylated glutaraldehyde. The biological activity of these compounds towards several glycosidases (α-D-glucosidase, α-D-mannosidase, α-L-fucosidase) has been evaluated.

1. Introduction

Glycosidases are involved in several metabolic pathways and the development of inhibitors is an important challenge towards the treatment of diseases,[1] such as diabetes, cancer and viral infections including AIDS. In recent years, polyhydroxylated piperidine alkaloids have attracted much attention due to the ability of some of them to act as selective glycosidase inhibitors.[2] The high therapeutic potential of these alkaloids has prompted considerable efforts towards their structural modifications, most notably for the natural azasugar 1-deoxynojirimycin **1** (Fig. 1). A first success is being recorded: *N*-butyl-1-deoxynojirimycin has recently been approved by the EMEA (European Agency for the Evaluation of Medicinal Products) for the treatment of type 1 Gaucher disease, a severe lysosomal disorder.[3] New exciting applications are being investigated. For example *N*-alkyliminosugar analogs have been found to reversibly induce infertility in male mice, opening the way to a nonhormonal approach to male contraception.[4] Considering the high potential of so called 'azasugars' for drug discovery, several approaches have been made for the modification of **1**, such as the introduction at specific positions on the piperidine ring system of fluoro,[5] alkyl[6] and acyl,[7] amino[8] and glucosyl substituents.[9] The synthesis of bicyclic diazasugars has also been reported.[10]

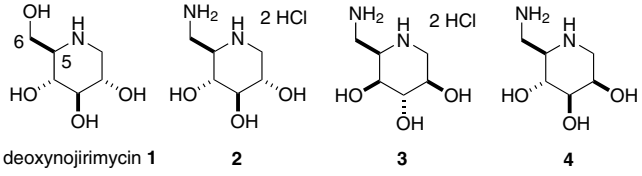

Figure 1.

In a preliminary note,[11] we disclosed the facile four steps synthesis of amino derivatives **2** and **3** (Fig. 1), in the 1-deoxynojirimycin series, from commercially available starting material. The strategy used for the synthesis of these compounds **2** and **3** involved the well established CN(*R*,*S*) method.[12]

Keywords: Chiral nonracemic polyhydroxylated piperidines; Biological activities; Glycosidases.
* Corresponding authors. Tel.: +33 153739811; fax: +33 140469658; e-mail: marie-christine.lallemand@univ-paris5.fr

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It is based upon the condensation of glutaraldehyde with a phenylglycinol in the presence of KCN, furnishing the N-cyanomethyloxazolidine system. The mainspring of the CN(*R*,*S*) method is a remarkable stereocontrol of the formation of a new chiral *R* or *S* centre by CN elimination. Furthermore in specific cases, the cyano group can be retained and used for its genius reactivity. The use of phenylglycinol allowed the hydrogenolysis of the chiral nitrogen protective group to obtain NH derivatives **2** and **3**.

Compounds **2** and **3** have been evaluated as glycosidase inhibitors: both derivatives were inactive on the α and β-glycosidase studied (K_i around 10^{-3} M). Recently, when screened against five common glycosidases (α-glucosidase, β-glucosidase, α-galactosidase, α-mannosidase, α-L-fucosidase)[13] the same results were observed for 6-amino-6-deoxy-1,5-imino-D-mannitol **4** (Fig. 1).

In order to design more active and more specific enzyme inhibitors, we took advantage in Vasella's studies, reporting recent insights into inhibition, structure and mechanism of configuration-retaining glycosidases.[14] More recently, the authors showed[15] that C-2-substituted tetrahydroimidazopyridines **5** (Fig. 2) presented a very strong inhibition of glucosidases. The introduction of a hydrophobic and flexible substituent such as phenylethyl, led to a very strong inhibition against

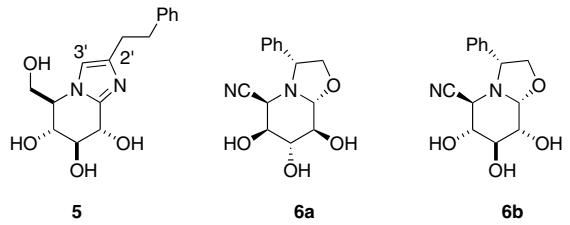


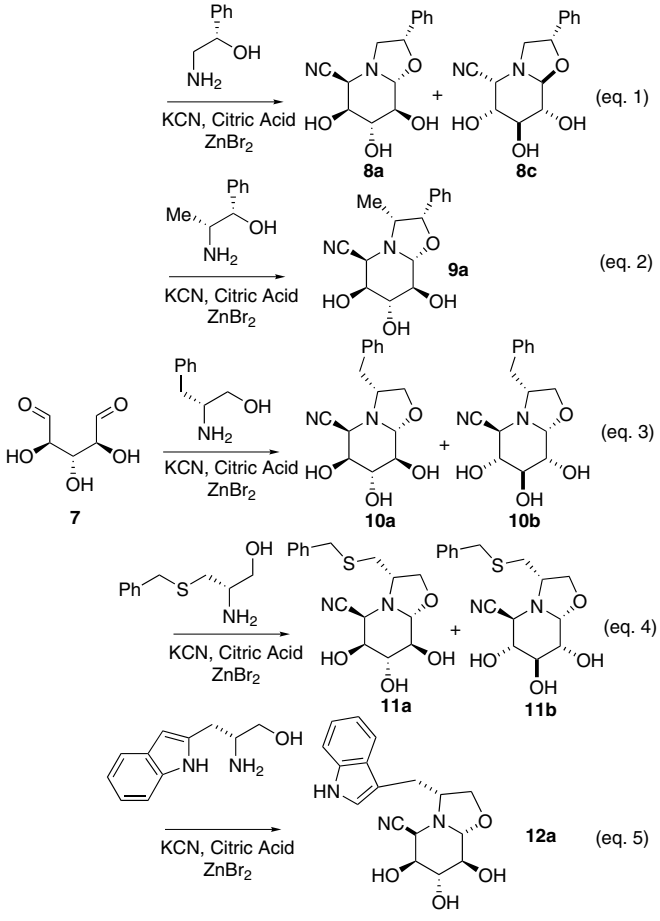
Figure 2.

β-glucosidases from almonds and *Caldocellum saccharolyticum*, with K_i values of 1.2 and 0.11 nM, respectively.

2. Results and discussion

Then we decided to synthesize *N*-substituted derivatives using other amino-alcohols allowing the introduction of hydrophobic or/and flexible substituents at different positions of the oxazolidine ring.

Our project was based on the utilization of β-amino-alcohols derived from commercially available L and D amino-acids.[16] They act as a nitrogen source, chirality inducer and iminium stabilizer in the desymmetrization of *meso*-trihydroxylated glutaraldehyde **7** (Scheme 1). The CN group will not be hydrolyzed or reduced in this



Scheme 1.

new series albeit it will be envisioned in the future since modulation of the p*K* of the piperidine nitrogen atom is an important parameter for the structure–activity relationship studies.

The condensations in the L-series when performed in an aqueous citric acid buffer containing potassium cyanide, afforded a crude material, which was then equilibrated in the presence of zinc bromide to the more thermodynamically stable derivatives **8a**–**12a** as the major products (10–35%). Compounds **8a**–**11a** possess an axial cyano group, a stable *trans*-oxazolidine and three hydroxyl groups in equatorial position. In some cases (Eqs. 3 and 4) the thermodynamically less-stable compounds (**10b** and **11b**), which displaying axial protons for all hydroxyl groups, were isolated in minute amounts. In the first note,[11] it was described that only two (**6a** and **6b**, Fig. 2) of the eight possible stereomers of the cyclization products were isolated. We have more closely examinated this reaction and have found that another stereomer **6c** was also formed. A benzylation reaction was necessary to separate compounds **6** and to fully characterize **6c** (Fig. 3). A careful analysis by 1D or 2D ^{1}H NMR analysis established the structure and stereochemistry of **13c**. In particular, the coupling constants *J*H-6/H-7, *J*H-7/H-8 = 9 Hz and *J*H-8/H-9 = 8 Hz were characteristic of an axial relationship between H-6, H-7, H-8 and H-9, while *J*H-5/H-6 = 5.5 Hz showed an equatorial/axial relationship between H-5 and H-6. For the other condensations, we isolated the stereomer c only in the case of L-phenylethanolamine (Eq. 1). It should be noticed that for each reaction, we were not able to isolate all diastereomers a, b and c.

In the case of L-tryptophanol (Eq. 5) we observed the formation of product **12a** as a unique diastereomer in 20% yield. Nevertheless, formation of a by-product **14** resulting from the Pictet–Spengler condensation and the addition of cyanide, was also obtained (Fig. 4). Treatment of *meso*-trihydroxylated glutaraldehyde **7** and *S*-benzyl-cysteinol under acidic conditions (Scheme 1, Eq. 4), afforded as well a by-product **15**

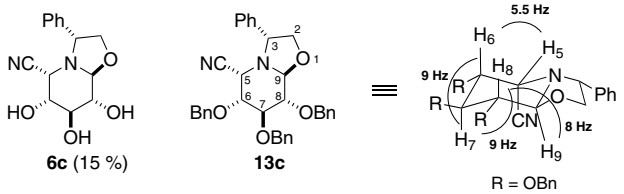


Figure 3.

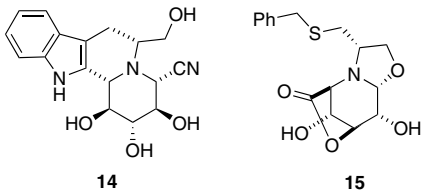
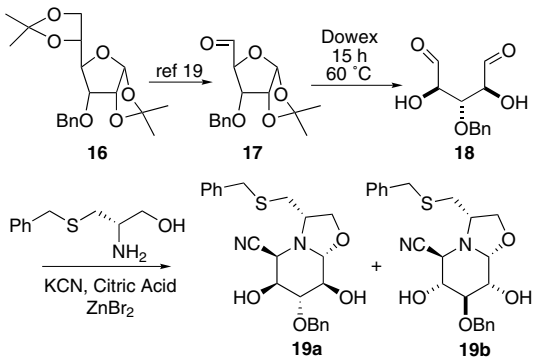


Figure 4.



Scheme 2.

(Fig. 4), in addition to the two expected stereomers **11a** and **11b**.

Characteristic features of the ^{13}C NMR spectrum of **15** included a carbonyl resonance at 174 ppm and a deshielded signal at 62.9 ppm corresponding to C-1. The IR spectrum showed a signal at 1747 cm^{-1}, characteristic of a carbonyl function. The obtention of 6-oxa-2-aza-bicyclo[3.2.1]octan-7-one derivative **15** was surprising because we had never observed such a cyclization with all other amino-alcohols. This difference in behaviour could be attributed to the presence of the sulfur atom and to a concerted mechanism. The sulfur atom may activate, via a potential six member ring, the attack of the OH at the position 4 onto the nitrile group, and allows further hydrolysis of the resulting imine.

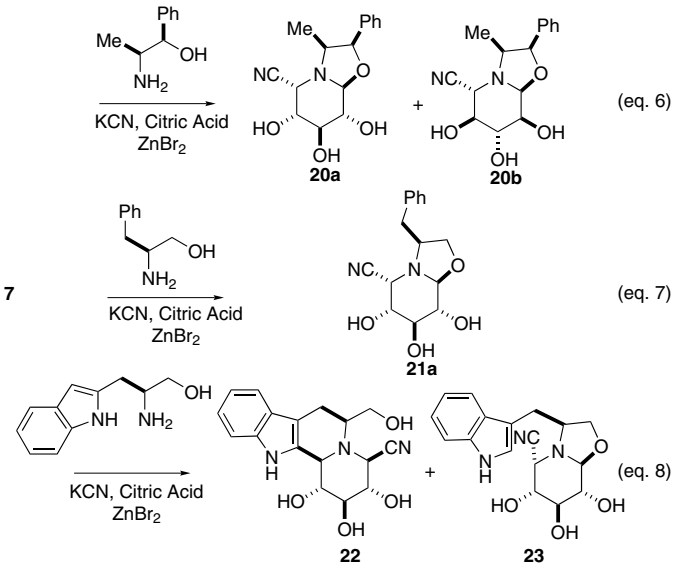
In good agreement with the proposal intramolecular process, when the 2,4-dihydroxy-3-*O*-benzyl-pentandial **18** (Scheme 2), synthesized via a slightly modified literature procedure,[17] was used instead of **7**, only the expected nitrile derivatives **19a** and **19b** were obtained.

The same condensation reaction with a D-amino-alcohol as the starting material, such as D-norephedrine (Eq. 6), D-phenylalaninol (Eq. 7) or D-tryptophanol (Eq. 8) was also performed (Scheme 3).

3. Inhibition studies

The new polyhydroxylated piperidines were screened against three common glycosidases (α-D-glucosidase from *Bacillus stearothermophilus*, α-D-mannosidase from Jack beans and α-L-fucosidase from bovine kidney) and biological evaluations were carried out as reported in the literature,[18] excepted for the α-L-fucosidase assays, which were run at 31 °C. The observed results are gathered in Table 1 and compared with the reported activity of the 1-deoxynojirimycin **1**.

The compounds in this study were found to be more effective against α-glucosidase than against the other tested enzymes. The selectivity can be attributed to the fact that they have a similar configuration of the hydroxyl groups. However, even if compounds **6** revealed



Scheme 3.

Table 1. Comparison of inhibitory activities for deoxynojirimycin **1** and polyhydroxylated piperidines

Compounds No.	α-D-Glucosidase	α-D-Mannosidase	α-L-Fucosidase
1	**0.44 μM**	—	—
2	**140 μM**	30	10
3	45	33	34
6a	50	16	22
6b	70	21	NI[a]
8a	5	10	NI
8c	NI	NI	NI
9a	NI	NI	NI
10a	NI	8	NI
10b	13	24	NI
11a	**77 μM**	12	23
11b	No soluble	No soluble	No soluble
12a	**700 μM**	NI	NI
14	**200 μM**	17	NI
20a	NI	6	NI
20b	NI	21	NI
21a	NI	19	NI
22	**730 μM**	NI	20
23 (%)	**290 μM**	NI	10

Percentage of inhibitions at 1 mM and K_i in μM (in bold) when measured.
[a] NI = no inhibition detected.

slight inhibition of α-D-glucosidase (50% and 70% for **6a** and **6b**, respectively), the absence of inhibition observed for derivatives **8**, **9a** and **10** shows that introducing the phenyl substitute at different positions on the oxazolidine ring did not increase the inhibition. More encouraging results were obtained with compounds **11a**, **14** and **23**. The better values observed, justifies the development of more hydrosoluble products in order to generate more potent inhibitors. It must be notified that the best result was obtained with compound **11a**, possessing the more hydrophobic flexible group, as suggested by Vasella. We now envision the reduction of the cyano group to an amine function. This synthetic work is in progress, and the results will be reported in due course.

4. Conclusion

Short and efficient synthesis of diversely functionalized piperidines has been carried out from commercially available starting materials. Sixteen new products have been obtained and some tested for their inhibition activities towards three glycosidases. This work demonstrates that inhibition activity of glucosidases of 1-deoxynojirimycin amino analogues **2** and **3**, which are weak inhibitors, can be increased to potent and selective inhibitors by simply linking a substituted oxazolidine ring to a hydrophobic and flexible group such as compounds **11a**. Our chemical modifications are currently being extended to transformations of the cyano functional group.

5. Experimental

5.1. General methods

IR spectra (max in cm^{-1}) were obtained on a Nicole et FT-IR instrument. ^1H NMR (δ [ppm], J [Hz]) and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using a Bruker Avance 400 spectrometer. When necessary, the signals were unambiguously assigned by 2D NMR techniques: COSY, NOESY, HMQC and HMBC. These experiments were performed using standard Bruker microprograms. Mass spectra were recorded with a Nermag *R*-10-10C spectrometer using chemical ionization technique (reagent gas: NH_3) (CI/MS) and with a ZQ 2000 Waters using a Zspray (ESI-MS). Optical rotations were measured on a Perkin–Elmer 141C polarimeter with sodium lamp (589 nm) at 20 °C. Column chromatographies were conducted using silica gel 60 Merck (35–70 m) with an overpressure of 200 mbar.

5.2. General procedure for the coupling reaction between amino-alcohol and *meso*-trihydroxylated glutaraldehyde

The *meso*-trihydroxylated glutaraldehyde **7** (20 mmole) was added to an aqueous citric acid (4%) solution of the amino-alcohol (10 mmole). The potassium cyanide (15 mmole) was added and the resulting mixture was stirred at rt for 15 h. The mixture was then carefully neutralized with $NaHCO_3$ and concentrated in vacuum. The residue was triturated in boiling methanol (3×150 mL) affording precipitation of brown solids, which were filtered on silica gel. The resulting solutions were collected and concentrated. The obtained oil was rediluted in methanol and $ZnBr_2$ (2.21 mmole, 500 mg) was added. After 4 h, the mixture was concentrated and the residue was purified by flash chromatography.

5.3. Hexahydro-2-phenyl-6,7,8-trihydroxy-2*R*-[2α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (8a)

Oil, R_f 0.30 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ −17.5 (*c* 1, MeOH). IR (KBr) cm^{-1}, 3405 (OH), 2229 (CN). ^1H NMR (MeOD): δ 3.06 (dd, 1H, J = 2.5, 8.5 Hz, H-3), 3.23 (t, 1H, J = 8.5 Hz, H-3), 3.5–3.6 (m, 2H, H-7 and H-8), 3.80 (dd, 1H, J = 6, 9 Hz, H-6), 4.03 (d, 1H, J = 7.5 Hz, H-9), 4.41 (d, 1H, J = 6 Hz, H-5), 5.20 (dd, 1H, J = 2.5, 8.5 Hz, H-2), 7.2–7.5 (m, 5H arom); ^{13}C NMR (MeOD): δ 54.2 (C-5), 56.5 (C-3), 71.5 (C-6), 75.0 (C-8), 76.1 (C-7), 80.2 (C-2), 93.5 (C-9), 115.4 (CN), 127.2, 128.7, 129.3 (CH arom), 143.6 (Cq arom). MS (CI), NH_3: m/z 277 $(M+1)^+$.

5.4. Hexahydro-2-phenyl-6,7,8-trihydroxy-2*R*-[2α,5α,6α,7β,8α,8aα]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (8c)

Oil, R_f 0.27 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ −18.0 (*c* 1, MeOH). ^1H NMR (MeOD): δ 2.72 (t, 1H, J = 9 Hz, H-3), 3.40 (dd, 1H, J = 7.5, 9 Hz, H-8), 3.49 (t, 1H, J = 9 Hz, H-7), 3.62 (dd, 1H, J = 6, 9 Hz, H-3), 3.79 (dd, 1H, J = 6, 9 Hz, H-6), 4.20 (d, 1H, J = 7.5 Hz, H-9), 4.50 (d, 1H, J = 6 Hz, H-5), 5.20 (dd, 1H, J = 6, 9 Hz, H-2), 7.2–7.4 (m, 5H arom); ^{13}C NMR (MeOD): δ 52.4 (C-5), 57.8 (C-3), 71.5 (C-6), 75.3 (C-8), 76.2 (C-7), 80.8 (C-2), 93.7 (C-9), 115.4 (CN), 127.7, 128.4, 129.5 (CH arom), 142.1 (Cq arom). MS (CI), NH_3: m/z 277 $(M+1)^+$.

5.5. Hexahydro-2-phenyl-3-methyl-6,7,8-trihydroxy-2*R*-3*R*-[2α,3α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (9a)

Oil, R_f 0.33 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ −3.5 (*c* 1, MeOH). ^1H NMR ($CDCl_3$): δ 0.63 (d, 3H, J = 6.5 Hz, Me), 3.26 (dd, 1H, J = 6.5, 8 Hz, H-3), 3.5–3.6 (m, 2H, H-7 and H-8), 3.80 (dd, 1H, J = 6, 9 Hz, H-6), 4.06 (d, 1H, J = 7.5 Hz, H-9), 4.33 (d, 1H, J = 6 Hz, H-5), 5.20 (d, 1H, J = 8 Hz, H-2), 7.1–7.6 (m, 5H arom); ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 52.5 (C-5), 59.0 (C-3), 71.7 (C-6), 74.9 (C-8), 76.2 (C-7), 84.4 (C-2), 93.O (C-9), 115.0 (CN), 127.3, 128.3, 128.8 (CH arom), 140.2 (Cq arom). MS (CI), NH_3: m/z 291 $(M+1)^+$.

5.6. Hexahydro-3-benzyl-6,7,8-trihydroxy-3*R*-[3α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (10a)

Oil, R_f 0.32 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ +23.5 (*c* 1, MeOH). IR (KBr) cm^{-1}, 3366 (OH), 2229 (CN). ^1H NMR ($CDCl_3$/DMSO-d_6: 2:1): δ 2.04 (dd, 1H, J = 7.5, 13.5 Hz, H-10), 2.29 (dd, 1H, J = 5.5, 13.5 Hz, H-10), 2.5–2.8 (m, 3H, H-3, H-7 and H-8), 2.9–3.0 (m, 1H, H-6), 3.06 (t, 1H, J = 8 Hz, H-2), 3.27 (d, 1H, J = 8 Hz, H-9), 3.31 (t, 1H, J = 8 Hz, H-2), 3.47 (d, 1H, J = 5.5 Hz, H-5), 4.4–4.5 (b s, OH-7), 4.56 (d, 1H, J = 4 Hz, OH-8), 5.0–5.2 (b s, OH-6), 6.5–6.8 (m, 5H arom); ^{13}C NMR ($CDCl_3$/DMSO-d_6: 2:1): δ 37.2 (C-10), 51.2 (C-5), 58.4 (C-3), 69.9 (C-6), 70.9 (C-2), 72.8 (C-8), 74.5 (C-7), 91.9 (C-9), 114.3 (CN), 126.1, 128.1, 128.3 (CH arom), 136.9 (Cq arom). MS (CI), NH_3: m/z 291 $(M+1)^+$.

5.7. Hexahydro-3-benzyl-6,7,8-trihydroxy-3*R*-[3α,5β,6α,7β,8α,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (10b)

Oil, R_f 0.39 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (MeOD): δ 2.81 (dd, 1H, J = 7.5, 13.5 Hz, H-10), 3.09 (dd, 1H, J = 7.5, 13.5 Hz, H-10), 3.33 (m, 1H, H-3), 3.77 (t, 1H, J = 7.5 Hz, H-2), 3.9–4.0 (m, 3H, H-2, H-6 and H-8), 4.09 (t, 1H, J = 3.5 Hz, H-7), 4.28 (d, 1H, J = 2 Hz, H-5), 4.40 (d, 1H, J = 1.5 Hz, H-9), 7.1–7.5 (m, 5H arom); ^{13}C NMR ($CDCl_3$): δ 38.0 (C-10), 52.8 (C-5), 60.8 (C-3), 70.3 (C-6), 71.8 (C-8), 72.0 (C-7), 72.1 (C-2), 89.7 (C-9), 115.9 (CN), 127.7, 129.6, 130.2 (CH arom), 139.1 (Cq arom). MS (CI), NH_3: m/z 291 $(M+1)^+$.

5.8. Hexahydro-3-benzylsulfanylmethyl-6,7,8-trihydroxy-3*R*-[3α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (11a)

Oil, R_f 0.33 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ +32.0 (*c* 1, MeOH). IR (KBr) cm^{-1}, 3382 (OH), 2229 (CN). ^1H NMR (MeOD): δ 2.51 (dd, 1H, J = 7, 13.5 Hz, H-10), 2.64 (dd, 1H, J = 5, 13.5 Hz, H-10), 3.0–3.1 (m, 1H,

H-3), 3.26 (dd, 1H, $J = 8$, 9 Hz, H-8), 3.40 (t, 1H, $J = 9$ Hz, H-7), 3.65 (dd, 1H, $J = 6$, 9 Hz, H-6), 3.71 (dd, 1H, $J = 7$, 8 Hz, H-2), 3.76 (d, 1H, $J = 13.5$ Hz, H-11), 3.81 (d, 1H, $J = 13.5$ Hz, H-11), 3.92 (d, 1H, $J = 8$ Hz, H-9), 4.07 (t, 1H, $J = 8$ Hz, H-2), 4.48 (d, 1H, $J = 6$ Hz, H-5), 7.2–7.4 (m, 5H arom); ^{13}C NMR (MeOD): δ 33.5 (C-10), 37.2 (C-11), 53.2 (C-5), 58.3 (C-3), 71.6 (C-6), 72.8 (C-2), 74.9 (C-8), 76.1 (C-7), 93.8 (C-9), 115.7 (CN), 128.2, 129.6, 130.1 (CH arom), 139.6 (Cq arom). MS (CI), NH_3: m/z 337 $(M+1)^+$. HMRS calcd for $C_{16}H_{20}N_2O_4S$ 337.1222, found 337.1210.

5.9. Hexahydro-3-benzylsulfanylmethyl-6,7,8-trihydroxy-3*R*-[3α,5β,6α,7β,8α,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (11b)

R_f 0.38 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ +73.0 (c 1, MeOH). IR (KBr) cm^{-1}, 3426 (OH), 2230 (CN). ^{1}H NMR (MeOD): δ 2.55 (dd, 1H, $J = 7$, 13.5 Hz, H-10), 2.72 (dd, 1H, $J = 5$, 13.5 Hz, H-10), 3.2–3.3 (m, 1H, H-3), 3.71 (dd, 1H, $J = 7.5$, 8 Hz, H-2), 3.78 (d, 1H, $J = 13.5$ Hz, H-11), 3.84 (d, 1H, $J = 13.5$ Hz, H-11), 3.8–3.9 (m, 2H, H-6 and H-8), 4.02 (t, 1H, $J = 3$ Hz, H-7), 4.08 (t, 1H, $J = 8$ Hz, H-2), 4.42 (d, 1H, $J = 1$ Hz, H-9), 4.45 (d, 1H, $J = 2$ Hz, H-5), 7.2–7.4 (m, 5H arom); ^{13}C NMR (MeOD): δ 33.0 (C-10), 37.3 (C-11), 53.0 (C4-5), 58.4 (C-3), 70.3 (C-6), 71.9 (C-2), 72.0 (C-7 and C-8), 89.7 (C-9), 116.1 (CN), 128.1, 129.5, 130.1 (CH arom), 139.6 (Cq arom). MS (CI), NH_3: m/z 337 $(M+1)^+$.

5.10. Hexahydro-6,7,8-trihydroxy-3-(1*H*-indol-3-methyl)-3*R*-[3α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (12a)

Oil, R_f 0.23 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ −12.5 (c 0.92, MeOH). ^{1}H NMR (MeOD): δ 2.84 (dd, 1H, $J = 7$, 14.5 Hz, H-10), 3.10 (dd, 1H, $J = 6$, 14.5 Hz, H-10), 3.3–3.4 (m, 1H, H-8), 3.4–3.5 (m, 2H, H-3 and H-7), 3.66 (dd, 1H, $J = 6$, 9 Hz, H-6), 3.78 (t, 1H, $J = 8$ Hz, H-2), 3.94 (d, 1H, $J = 8$ Hz, H-9), 4.02 (t, 1H, $J = 8$ Hz, H-2), 4.25 (d, 1H, $J = 6$ Hz, H-5), 7.03 (t, 1H, $J = 7.5$ Hz, H arom), 7.11 (s, 1H, H arom), 7.12 (t, 1H, $J = 7.5$ Hz, H arom), 7.35 (d, 1H, $J = 8$ Hz, H arom), 7.57 (d, 1H, $J = 8$ Hz, H arom); ^{13}C NMR (MeOD): δ 28.6 (C-10), 53.3 (C-5), 59.9 (C-3), 71.7 (C-6), 73.6 (C-2), 75.0 (C-8), 76.3 (C-7), 93.9 (C-9), 112.4, 119.2, 119.9, 122.6, 123.7 (CH arom), 111.6, 115.7, 128.4, 138.2 (Cq arom). MS (CI), NH_3: m/z 330 $(M+1)^+$.

5.11. Hexahydro-6,7,8-tribenzyloxy-3-phenyl-3*R*-[3α,5α,6α,7β,8α,8aα]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (13c)

The benzylation reaction was effected by procedure described in the literature.[19] Oil, R_f 0.31 (cyclohexane/ether, 8:3). $[\alpha]_D$ −24.0 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.49 (dd, 1H, $J = 8$, 9 Hz, H-8), 3.72 (dd, 1H, $J = 5.5$, 9 Hz, H-6), 3.82 (t, 1H, $J = 9$ Hz, H-7), 3.87 (d, 1H, $J = 5.5$ Hz, H-5), 4.08 (dd, 1H, $J = 5.5$, 8 Hz, H-2), 4.16 (t, 1H, $J = 6$ Hz, H-3), 4.38 (dd, 1H, $J = 6.5$, 8 Hz, H-2), 4.71 (2dAB, 2H, $J = 12$ Hz, O–CH_2–Ph), 4.88 (s, 2H, O–CH_2–Ph), 4.91 (d, 2H, $J = 11.5$ Hz, O–CH_2–Ph), 4.92 (d, 2H, $J = 7.5$ Hz, H-9), 7.1–7.6 (m, 20H arom); ^{13}C NMR ($CDCl_3$): δ 47.8 (C-5), 63.1 (C-3), 73.4 (O–CH_2–Ph), 73.7 (C-2), 74.0 (O–CH_2–Ph), 75.9 (C-6), 76.1 (O–CH_2–Ph), 81.3 (C-7), 81.6 (C-8), 90.8 (C-9), 115.2 (CN), 126–130 (CH arom), 136–139 (Cq arom). MS (CI), NH_3: m/z 547 $(M+1)^+$.

5.12. 1,2,3-Trihydroxy-6-hydroxymethyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine-4-carbonitrile (14)

Oil, R_f 0.18 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ +1.5 (c 0.74, MeOH). ^{1}H NMR (MeOD): δ 2.84 (dd, 1H, $J = 7$, 14.5 Hz, H-7), 3.10 (dd, 1H, $J = 6$, 14.5 Hz, H-7), 3.3–3.4 (m, 1H, H-3), 3.4–3.5 (m, 2H, H-2 and H-6), 3.66 (dd, 1H, $J = 6$, 9 Hz, H-1), 3.78 (t, 1H, $J = 8$ Hz, CH_2–OH), 3.94 (d, 1H, $J = 8$ Hz, H-3), 4.02 (t, 1H, $J = 8$ Hz, CH_2–OH), 4.25 (d, 1H, $J = 6$ Hz, H-12), 6.9–7.7 (m, 4H, H arom); ^{13}C NMR (MeOD): δ 18.5 (C-7), 53.6 (C-11), 56.1 (C-3), 59.2 (C-6), 63.1 (CH$_2$–OH), 73.1 (C-1), 73.5 (C-3), 74.9 (C-2), 112.2, 118.6, 119.9, 122.5 (CH arom), 106.5, 119.6, 128.1, 130.0, 146.6 (CN and Cq arom). MS (CI), m/z 352 $(M+Na)^+$.

5.13. 3-Benzylsulfanylmethyl-7,11-dihydroxy-5,9-dioxa-2-aza-tricyclo[6.2.1]undecan-10-one (15)

Oil, R_f 0.36 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D$ −5.0 (c 1, MeOH). IR (KBr) cm^{-1}, 3414 (OH), 1747 (CO). ^{1}H NMR ($CDCl_3$): δ 2.47 (dd, 1H, $J = 6.5$, 13.5 Hz, H-10), 2.56 (dd, 1H, $J = 6.5$, 13.5 Hz, H-10), 3.2–3.3 (m, 1H, H-3), 3.44 (dd, 1H, $J = 7.5$, 9 Hz, H-2), 3.55 (d, 1H, $J = 3.0$ Hz, H-5), 3.76 (dd, 2H, $J = 13.5$ Hz, H-11), 3.8–3.9 (m, 2H, H-6 and H-7), 4.03 (dd, 1H, $J = 6.54$, 9 Hz, H-2), 4.61 (d, 1H, $J = 4$ Hz, H-8), 4.95 (s, 1H, H-9), 7.2–7.4 (m, 5H arom); ^{13}C NMR ($CDCl_3$): δ 34.9 (C-10), 37.1 (C-11), 64.2 (C-3), 64.9 (C-5), 70.9 (C-2), 73.5 (C-7), 76.1 (C-6), 77.9 (C-8), 88.0 (C-9), 126–130 (CH arom), 136–139 (Cq arom), 171.9 (CO). MS (CI), NH_3: m/z 338 $(M+1)^+$.

5.14. Hexahydro-7-benzyloxy-3-benzylsulfanylmethyl-6,8-dihydroxy-3*R*-[3α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (19a)

White powder, R_f 0.25 (CH_2Cl_2/MeOH, 18:1). $[\alpha]_D$ +28.5 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.44 (dd, 1H, $J = 6.5$, 13.5 Hz, H-10), 2.48 (d, 1H, $J = 2.5$ Hz, OH-8), 2.51 (dd, 1H, $J = 5.5$, 13.5 Hz, H-10), 2.55 (d, 1H, $J = 2.5$ Hz, OH-6), 3.1–3.2 (m, 1H, H-3), 3.52 (t, 1H, $J = 9$ Hz, H-7), 3.60 (t, 1H, $J = 8.5$ Hz, H-8), 3.7–3.8 (m, 2H, H-2 and H-11), 3.83 (t, 1H, $J = 7$ Hz, H-6), 4.08 (d, 1H, $J = 8$ Hz, H-9), 4.13 (t, 1H, $J = 8$ Hz, H-2), 4.40 (d, 1H, $J = 6$ Hz, H-5), 4.91 (dd, 2H, $J = 11.5$ Hz, HO–CH_2–Ph), 7.2–7.5 (m, 10H arom); ^{13}C NMR ($CDCl_3$): δ 32.3 (C-10), 36.4 (C-11), 50.9 (C-5), 56.5 (C-3), 70.2 (C-6), 72.0 (C-2), 74.3 (C-8), 75.6 (O–CH_2–Ph), 82.7 (C-7), 92.3 (C-9), 114.0 (CN), 127–129 (CH arom), 137.4, 138.1 (Cq arom). MS (CI), m/z 427 $(M+H)^+$.

5.15. Hexahydro-7-benzyloxy-3-benzylsulfanylmethyl-6,8-dihydroxy-3*R*-[3α,5β,6α,7β,8α,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (19b)

Oil, R_f 0.47 (CH_2Cl_2/MeOH, 18:1). $[\alpha]_D$ +103.0 (*c* 2, $CHCl_3$). ^1H NMR (MeOD): δ 2.53 (dd, 1H, $J = 7.0$, 13.5 Hz, H-10), 2.68 (dd, 1H, $J = 5$, 13.5 Hz, H-10), 3.1–3.2 (m, 1H, H-3), 3.70 (t, 1H, $J = 8$ Hz, H-2), 3.76 (dd, 2H, $J = 13.5$ Hz, H-11), 3.85 (s, 1H, H-7), 4.01 (d, 1H, $J = 1.5$ Hz, H-8), 4.05 (t, 1H, $J = 8$ Hz, H-2), 4.14 (s, 1H, H-6), 4.40 (s, 1H, H-9), 4.49 (s, 1H, H-5), 4.60 (dd, 2H, $J = 12$ Hz, O–CH_2–Ph), 7.2–7.5 (m, 10H arom); ^{13}C NMR (MeOD): δ 31.7 (C-10), 36.0 (C-11), 52.0 (C-5), 57.0 (C-3), 67.2 (C-8), 67.7 (C-6), 70.7 (C-2), 71.9 (O–CH_2–Ph), 77.3 (C-7), 88.6 (C-9), 114.7 (CN), 127–129 (CH arom), 137.8, 138.3 (Cq arom). MS (CI), *m*/*z* 427 $(M + H)^+$.

5.16. Hexahydro-2-phenyl-3-methyl-6,7,8-trihydroxy-2*S*-3*S*-[2β,3β,5α,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (20b)

R_f 0.42 (CH_2Cl_2/MeOH, 9:1). ^1H NMR ($CDCl_3$): δ 0.76 (d, 3H, $J = 6.5$ Hz, Me), 3.40 (dd, 1H, $J = 6.5$, 8 Hz, H-3), 4.12 (m, 1H, H-7), 4.18 (m, 1H, H-8), 4.25 (t, 1H, $J = 3.5$ Hz, H-6), 4.37 (d, 1H, $J = 2.5$ Hz, H-5), 4.57 (d, 1H, $J = 1.5$ Hz, H-9), 5.23 (d, 1H, $J = 8$ Hz, H-2), 7.2–7.6 (m, 5H arom); ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 52.4 (C-5), 59.1 (C-3), 70.4 (C-8), 71.9 (C-7), 72.3 (C-6), 82.8 (C-2), 88.9 (C-9), 115.4 (CN), 128.7 128.8, 129.3 (CH arom), 140.7 (Cq arom). MS (CI), CH_4: *m*/*z* 291 $(M+1)^+$.

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