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## SYNTHESIS OF PYRROLIDINE 3,4-DIOL DERIVATIVES WITH ANTICANCER ACTIVITY ON PANCREATIC TUMOR CELLS

Frederic Steimer,<sup>a</sup> Ana T. Carmona,<sup>a</sup> Antonio J. Moreno-Vargas,<sup>a</sup> Irene Caffa,<sup>c</sup> Michele Cea,<sup>c</sup> Fabrizio Montecucco,<sup>c</sup> Alessio Nencioni,<sup>c</sup> Pierre Vogel,<sup>b</sup> and Inmaculada Robina<sup>a\*</sup>

<sup>a</sup> Department of Organic Chemistry, Faculty of Chemistry, University of Seville, Prof. García Gonzalez, 1, E-41012, Sevilla, Spain. Fax: +34954624960; Tel: +34 954556858; E-mail: robina@us.es

<sup>b</sup> Laboratory of glycochemistry and asymmetric synthesis, Swiss Institute of Technology (EPFL), Batochime, CH 1015 Lausanne, Switzerland

<sup>c</sup> Department of Internal Medicine, University of Genoa, 16132 Genoa, Italy

Dedicated to Professor Victor Snieckus, Queen's University, Ontario, Canada, on the occasion of his 77<sup>th</sup> birthday

**Abstract** – Novel pyrrolidine 3,4-diol derivatives of the type (2*R* and 2*S*,3*R*,4*S*)-{[(1*R*)-1-methoxycarbonyl and hydroxymethyl]-1-arylmethylamino}ethyl-pyrrolidine-3,4-diol have been prepared and evaluated as  $\alpha$ -mannosidase inhibitors and assayed for their anticancer activity in vitro. They all exhibit specific but moderate activity as inhibitors towards  $\alpha$ -mannosidase from Jack beans. Compounds **7** and **8b** bearing hydroxymethyl and trifluoromethylbiphenyl groups show the best antiproliferative effect in two pancreatic cancer cell lines.

## INTRODUCTION

Glycoproteins are expressed in all cell compartments and have a wide range of roles, including functions as receptors, transporters and structural proteins. In particular, glycoproteins are frequently involved in cell-cell communication, cell-cell recognition and cell adhesion. Iminosugars have previously been shown

to effectively interfere with glycoprotein quality control, maturation, transport and secretion, thereby altering cell-cell recognition processes. More than twenty glycoproteins have already been identified as regulators of cell division, differentiation and maturation, and to affect the development of macrophages.<sup>1</sup> Impaired cell adhesion and immune recognition are key features of oncogenesis and metastasis. Thus, targeting the metabolism and processing of glycoproteins with selective inhibitors seems to be a viable approach for treating cancer.

Several glycosidase inhibitors, some of which isolated from natural sources, have shown activity as anticancer agents. Castanospermine, an  $\alpha$ -glucosidase I inhibitor, has been shown to block platelet aggregation, angiogenesis, tumor colonization and growth.<sup>2</sup> The non-natural enantiomer of (+)-lentiginosine (a selective amyloglucosidase inhibitor), (-)-lentiginosine induces apoptosis in various types of cancer cells.<sup>3</sup> The  $\alpha$ -mannosidase I inhibitor 1-deoxymannojirimycin and swainsonine, an iminoalditol with potent inhibitory activity on lysosomal  $\alpha$ -mannosidase and Golgi  $\alpha$ -mannosidase II, both inhibit human melanoma cell invasion.<sup>4</sup> Unfortunately, phase 1B clinical trials have shown adverse secondary effects for swainsonine. In addition, a phase II study of oral swainsonine in patients gave no evidence of anti-tumor activity for this agent. Several derivatives of swainsonine with substituents at 3-, 5-, 6- and 7 positions were synthesized and their anti-cancer properties evaluated but none of them could reach the promising effects of the parent compound. Albeit less active than swainsonine, these compounds provided important information on the Golgi  $\alpha$ -mannosidase II active site allowing the subsequent design of swainsonine-like inhibitors.<sup>5</sup>

1,4-Dideoxy-1,4-imino-D-ribitol (**1**) (Figure 1) is a natural product with important biological activities. It was first isolated from the root bark of Mulberry tree (*Morus Alba* L.). This compound and other polyhydroxylated pyrrolidines have been studied in high details because of their ability to mimic their furanose analogues and, consequently, to interact with carbohydrate-processing enzymes. Iminoribitol **1** is a weak inhibitor<sup>6</sup> of several  $\alpha$ -D-glucosidases (bovine liver lysosomal, rat liver endoplasmatic reticulum II, rat liver lysosomal) and of  $\alpha$ -D-mannosidase from rat liver Golgi II apparatus as well. It also shows a moderate inhibitory activity toward  $\alpha$ -D-glucosidase from yeast ( $K_i = 23 \mu\text{M}$ ).<sup>7</sup> In addition to its glycosidase inhibitory activity, 1,4-dideoxy-1,4-imino-D-ribitol strongly inhibits eukaryotic DNA polymerases with almost no activity neither on prokaryotic DNA polymerases, nor on DNA metabolic enzymes.<sup>8</sup> These proprieties suggested a potential clinical application of **1** as anti-HIV agent.<sup>9</sup> This compound was proposed also to be a potential anti-neoplastic and anti-proliferative agent, but the *in vitro* studies on cancer cell lines did not evidence any cytotoxic activity, probably because of its high polarity which prevents it from crossing the cell membranes.

For the rapid discovery of  $\alpha$ -mannosidase inhibitors, we have developed a combinatorial method based on imines derived from (2*R*,3*R*,4*S*)-2-aminomethyl-3,4-dihydropyrrolidine scaffolds. These compounds can be considered as transition state or intermediate structure mimics of the hydrolytic process catalyzed by  $\alpha$ -mannosidases.<sup>10</sup>

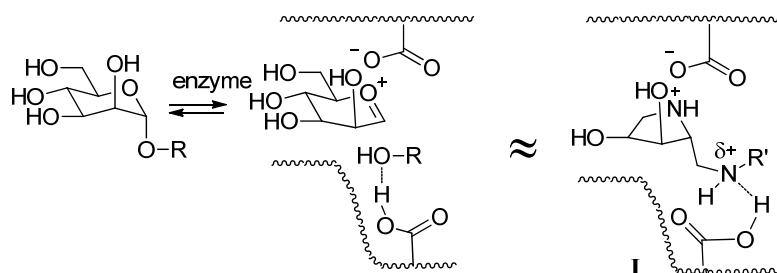


Figure 1. Model **I** of the active site of  $\alpha$ -mannosidase and its interaction with diamines derived from imino-D-ribitol **1**

This method led to the discovery of a lead compound bearing a 1,4-dideoxy-1,4-imino-D-ribitol moiety and to the corresponding (*R*)-2-amino-2-phenylethanol derivative **2**. Notably, although **2** exhibited a  $K_i$  of 135 nM towards Jack beans  $\alpha$ -mannosidase, it failed to inhibit cancer cell growth in culture.<sup>11</sup> This was ascribed to the hydrophilic nature of this compound that may prevent its cell internalization. This hypothesis is supported by the observation that the more lipophilic compound **3** is able to inhibit both glioblastoma and melanoma cell growth selectively.<sup>11</sup>

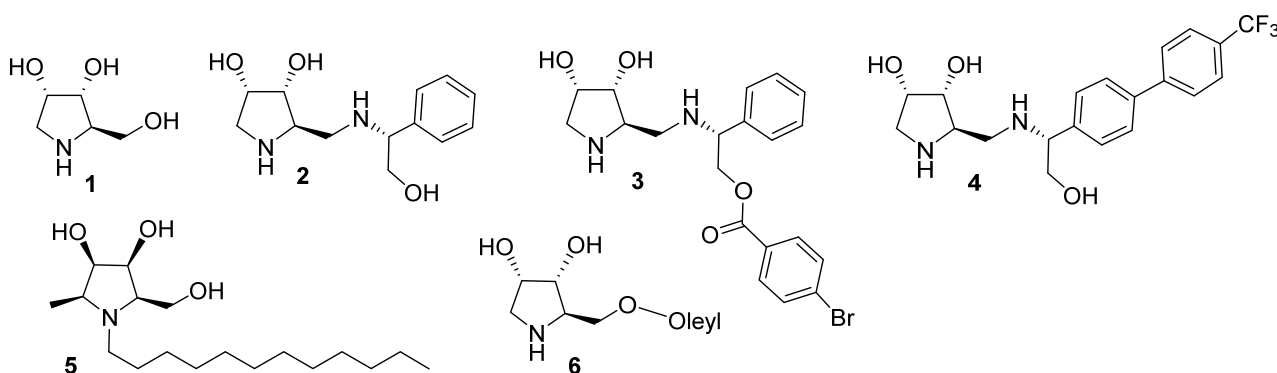


Figure 2. Examples of bioactive 1,4-dideoxy-1,4-imino-D-ribitol derivatives

Several 2-methyleneamino derivatives of **1** were synthesized in order to increase its lipophilicity and cell membrane permeability leading to new and selective  $\alpha$ -mannosidase inhibitors with promising anti-cancer activity.<sup>12</sup> Further studies allowed the identification of biaryl-containing dihydropyrrolidine analogues,

such as **4**, which showed to be potent and selective jack beans  $\alpha$ -mannosidase inhibitor ( $K_i = 2.7 \mu\text{M}$ ).<sup>13</sup> It also displayed potent anticancer activity in cell lines of different histology and in primary leukemic cells (Figure 2). Derivatization of iminosugars with aliphatic side chains has been extensively studied in order to improve their biological activity, lipophilicity and bioavailability.<sup>14</sup> For instance, *N*-butyl-1-deoxynojirimycin (Zavesca) is a drug for the treatment of Gaucher's disease,<sup>15</sup> *N*-nonyl-1-deoxynojirimycin inhibits hepatitis B virus in cell based assays,<sup>16</sup> and  $\alpha$ -1-*C*-alkyl-1-deoxynojirimycin derivatives have shown inhibitory activity toward intestinal isomaltase.<sup>17</sup> *N*-Dodecyl-D-fagomine derivatives are  $\alpha$ -glucosidase inhibitors that exhibit anticancer activity against stomach, colon, pancreas, and breast cancer cell lines with  $\text{EC}_{50}$ 's ranging between 100 to 250  $\mu\text{M}$  for the dodecyl derivative.<sup>18</sup> The  $\alpha$ -L-fucosidase inhibitor *N*-dodecyl hydroxylated pyrrolidine **5** also demonstrated anti-proliferative activity in stomach, colon, pancreas, and breast cancer cell lines at 2  $\mu\text{M}$ .<sup>19</sup> 5-*O*-Oleyl 1,4-dideoxy-1,4-imino-D-ribitol (**6**) and the related 5-*O*-conjugates (linolenyl, linoleyl and octadecyl) derivatives were evaluated as enzyme inhibitors and for their toxicity on solid and haematological malignancies and indeed exhibited activities in the  $\mu\text{M}$  range (Figure 2).<sup>19</sup> Although these compounds are not  $\alpha$ -mannosidase inhibitors (data not shown), they demonstrated marked cytotoxicity on solid and haematological malignancies in the  $\mu\text{M}$  range, their activity essentially correlating with the length of their alkyl side chain. In particular, the oleyl-conjugate **6** showed to be the most effective at killing cancer cells in culture. With the hope to improve our understanding of the mode of action of diamines such as **4** both on  $\alpha$ -mannosidases and cancer cells, which we proposed to be modelled by the transition state mimic **I** (Figure I), we decided to explore what would be the effect in changing the distance between both amino moieties that interact with the two carboxylic groups at the  $\alpha$ -mannosidase active site. We thus embarked on the synthesis of **7**, the homologue of **4**, keeping the same absolute configuration (2'*R*,2*R*,3*R*,4*S*). As we found **7** to be a bad inhibitor of  $\alpha$ -mannosidase from Jack beans, we then explored what would be the effect of inverting configuration at C(2) of the pyrrolidine moiety. To our surprise, compound **8b**, the 2-epimer of **7** showed  $\alpha$ -mannosidase inhibitory activity, but not to the extent of that of **4** (**4** ( $K_i = 2.7 \mu\text{M}$ ) vs **8b** ( $K_i = 120 \mu\text{M}$ )). As both **7** and **8b** inhibited pancreas cell growth *in vitro*, we prepared more analogues of **7**, **8b** and **9** with the hope to find a potential drug against pancreas cancer (Figure 3) based on our models for transition state mimics of the hydrolytic process catalyzed by  $\alpha$ -mannosidases (Figures 1 and 7).<sup>10</sup> Our preliminary results are presented in this report and we shall show that the best tumor cell growth inhibitors are not necessarily the best  $\alpha$ -mannosidase inhibitors.

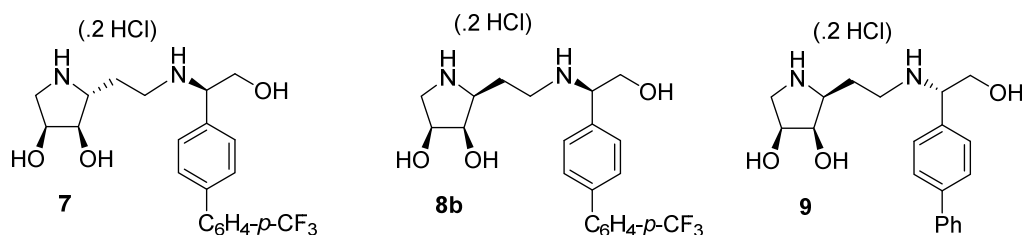


Figure 3. Structures of the main target pyrrolidines

## RESULTS AND DISCUSSION

Based on previous results,<sup>13</sup> we report herein the preparation and biological evaluation of new biphenyl-pyrrolidines. These were synthesized under the assumption that the biphenyl group would enhance their lipophilic character and thus facilitate compound internalization through the plasma membrane. The influence of the stereocenter at C-2 and other modifications (at the end of the aromatic moiety and at the side chain) on the ability of these compounds to inhibit  $\alpha$ -mannosidase, as well as on their anticancer activity were also studied (Figure 4).

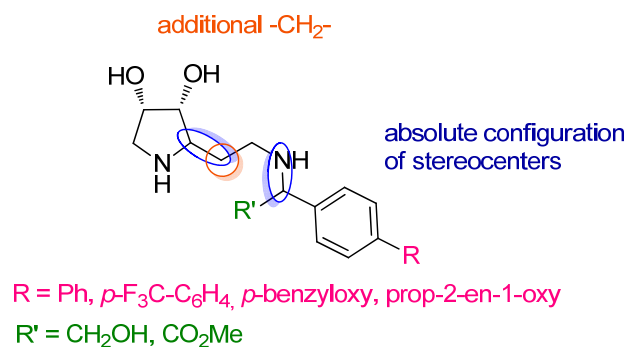


Figure 4. Modifications on lead structure

The new compounds were prepared from carbaldehydes **10** and **11** which were obtained from L-arabinose by applying a methodology developed in our group.<sup>20</sup>

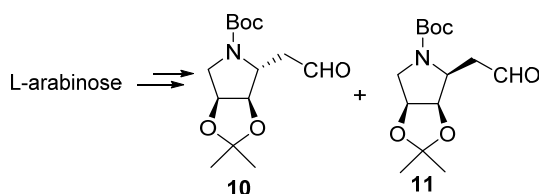
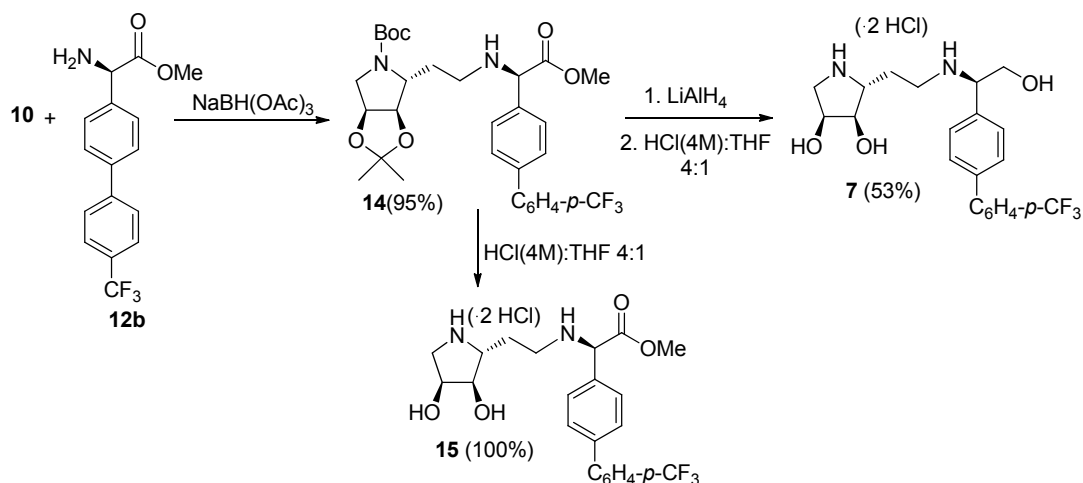
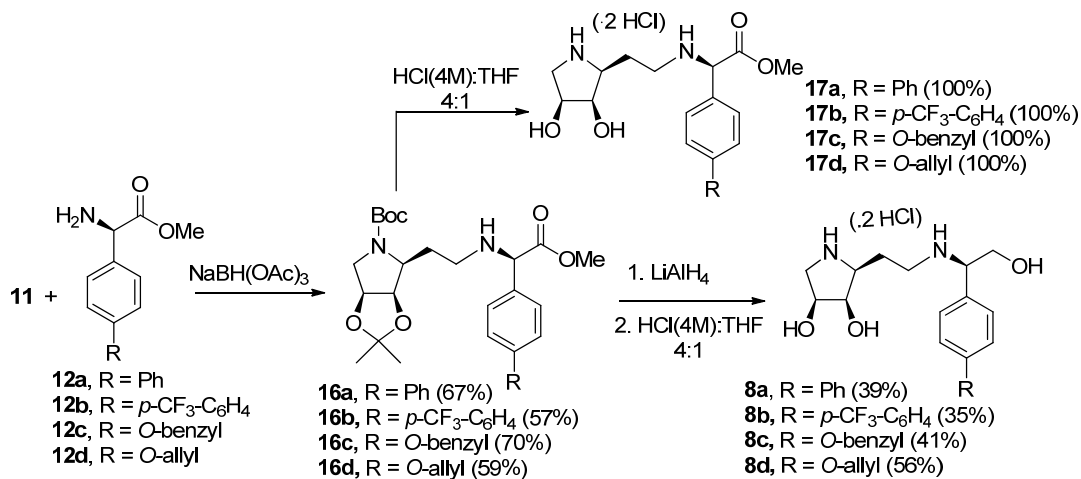
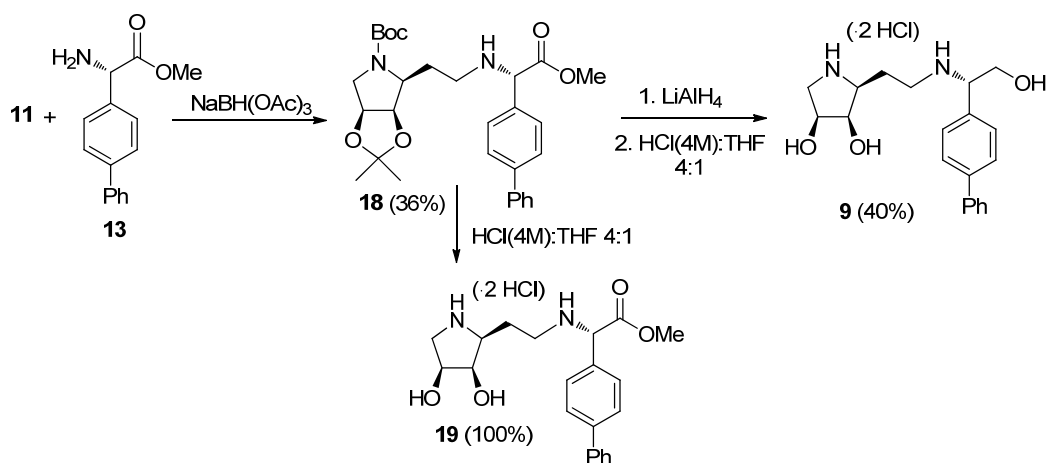


Figure 5. Starting aldehydes

Derivatives of phenyl glycine **12** and **13** were prepared by Suzuki coupling as was previously described by Bello, Vogel and co-workers.<sup>13</sup> The final compounds were synthesized from aldehydes **10** and **11** through reductive amination with the corresponding substituted phenylglycines followed by hydrolysis or reduction and hydrolysis (Schemes 1 - 3). All the compounds were obtained in moderate-to-good overall yields.

Scheme 1. Synthesis of **7** and **15**Scheme 2. Synthesis of derivatives **8** and **17**Scheme 3. Synthesis of **9** and **19**

## BIOLOGICAL EVALUATION

The new compounds were tested for their inhibitory activity against 11 glycosidases<sup>21</sup> from different sources, and as inhibitors of the growth of cancer cells in two pancreatic cell lines MiaPaCa2 and PK9. All the tested compounds were found to be selective and moderate-to-good Jack beans  $\alpha$ -mannosidase inhibitors (see Figure 6 for % of inhibition and  $IC_{50}$ ).<sup>22</sup> Compounds bearing an ester function at the side chain of the pyrrolidine framework (**17a-d**, **19** and **15**) showed a poor inhibitory activity (less than 50% at 1 mM) when compared to the corresponding hydroxy derivatives (**8a-d**, **9**), suggesting the requirement of the hydroxyl group for compound binding to the enzymatic active site.

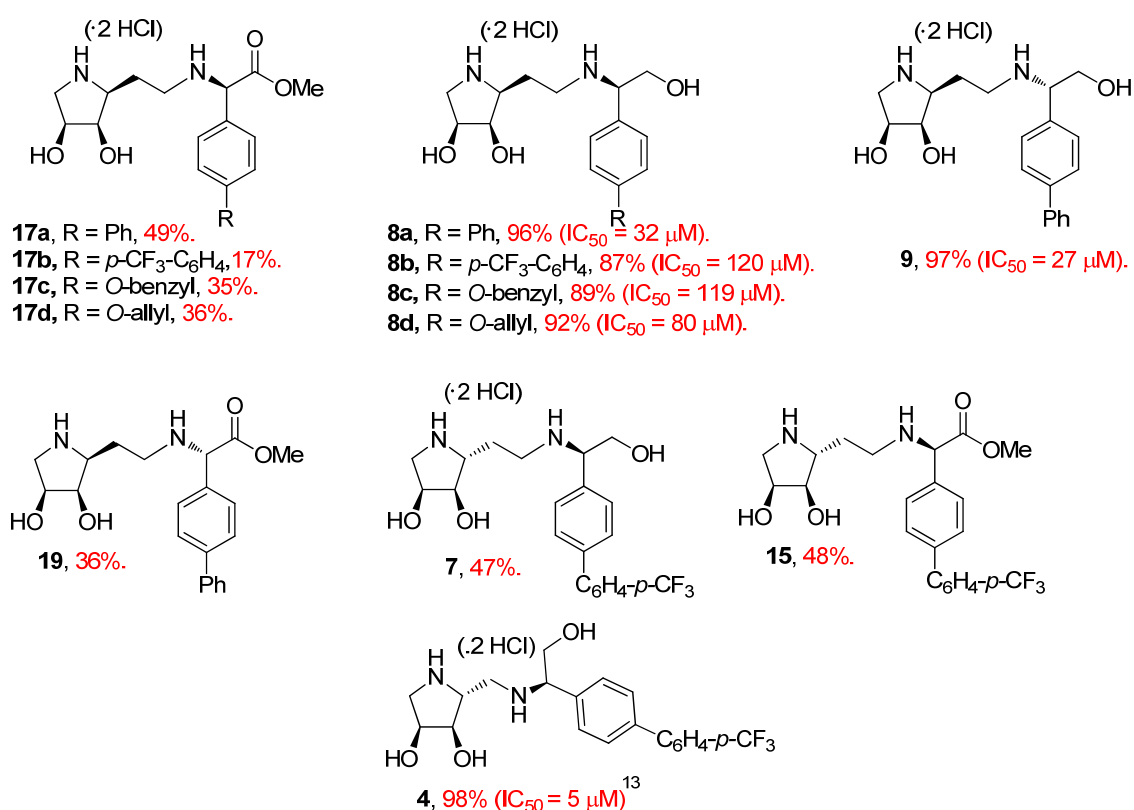


Figure 6. Percentage of inhibition at 1 mM ( $IC_{50}$ ) towards  $\alpha$ -mannosidase from Jack beans

We attribute the lower  $\alpha$ -mannosidase inhibitory activity of **7** compared to that of **4** to the too long distance separating the two amino groups. Its simultaneous interaction with the two carboxylic moieties of the enzyme becomes too costly as shown in transition state model **II** (Figure 7). On the contrary, in the case of **8b**, the 2-epimer of **7**, the separation between the two amino groups becomes shorter than that in **II** and thus **8b** can imitate **4** more than **7** as shown with **III**.

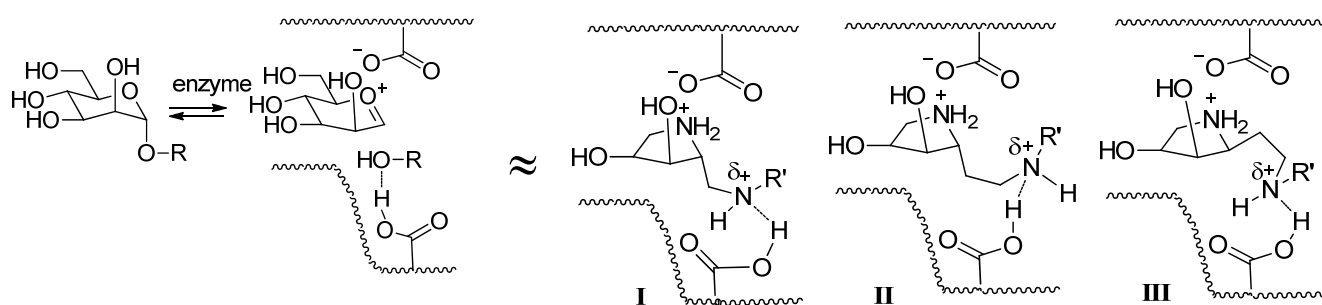


Figure 7. Models of the active site of  $\alpha$ -mannosidase and its interaction with diamines<sup>10</sup>

Analogues of **4** in which the *p*-trifluoromethylbiphenyl group is substituted by other biphenyl or *p*-substituted phenyl systems were less active than **4** both toward  $\alpha$ -mannosidase and cancer cells. However, it is a surprise also to find that compound **8a** with a biphenyl group is more active toward  $\alpha$ -mannosidase than **7** and **8b**. As another surprise, **7** and **8b** ( $EC_{50} = 12\text{-}13\ \mu\text{M}$ ) are found to be the most potent pancreas cancer cell growth inhibitors of this study (Table 1). Finally we decided to test the effect of inverting C(2') of the arylethanol group of **8a**. This led to the preparation of **9**, a compound which appears to inhibit  $\alpha$ -mannosidase and the growth of pancreas cancer cells as well as **8a**. However this is not the case for **7** and **8b** that present the best antiproliferative effect and are weak and moderate  $\alpha$ -mannosidase inhibitors.

Table 1. Inhibitory activity towards  $\alpha$ -mannosidase from Jack beans and the growth of pancreas cell lines<sup>(#)</sup>

Compounds	% of inhibition at 1 mM ( $IC_{50}$ ) towards $\alpha$ -mannosidase	Cell lines	
		MiaPaCa2 ( $EC_{50}$ ) <sup>(*)</sup>	PK-9 ( $EC_{50}$ )
<b>7</b>	47%	12.8 $\mu\text{M}$	12.4 $\mu\text{M}$
<b>8a</b>	96% (32 $\mu\text{M}$ )	59.4 $\mu\text{M}$	67.2 $\mu\text{M}$
<b>8b</b>	87% (120 $\mu\text{M}$ )	13.1 $\mu\text{M}$	13.3 $\mu\text{M}$
<b>8c</b>	89% (119 $\mu\text{M}$ )	89.1 $\mu\text{M}$	107.0 $\mu\text{M}$
<b>8d</b>	92% (80 $\mu\text{M}$ )	218.9 $\mu\text{M}$	282.9 $\mu\text{M}$
<b>9</b>	97% (27 $\mu\text{M}$ )	39.1 $\mu\text{M}$	42.6 $\mu\text{M}$
<b>15</b>	48%	31.2 $\mu\text{M}$	16.0 $\mu\text{M}$
<b>17a</b>	49%	172.7 $\mu\text{M}$	120.4 $\mu\text{M}$
<b>17b</b>	17%	37.2 $\mu\text{M}$	17.5 $\mu\text{M}$
<b>17c</b>	35%	234.0 $\mu\text{M}$	135.9 $\mu\text{M}$
<b>17d</b>	36%	504.9 $\mu\text{M}$	inactive
<b>19</b>	36%	114.0 $\mu\text{M}$	99.1 $\mu\text{M}$

<sup>(#)</sup>As a positive control 5-FU was used ( $EC_{50}=8.36\ \mu\text{M}$  for MiaPaCa2;  $EC_{50}=3.73\ \mu\text{M}$  for PK-9)

<sup>(\*)</sup>EC: effective concentration 50.



## CONCLUSIONS

A small library of new 3,4-dihydropyrrolidine analogues has been prepared starting from commercially available L-arabinose and 4-hydroxyphenylglycine methyl ester. The synthetic steps were straightforward and allowed their synthesis in moderate-to-good overall yields. The new compounds were assessed for their ability to inhibit glycosidases from different sources and for their antiproliferative effect on two pancreatic cancer cell lines. The enzyme inhibition measurements showed good selectivity towards  $\alpha$ -mannosidase from Jack beans with respect to other glycosidases. Nevertheless, homologation of the imino-D-ribitol side chain diminished the inhibitory activity which can be assigned to the longer distance separating the two amino groups. This prevents the simultaneous interaction of the amino groups with the two carboxylic moieties of the enzyme according to transition state model **II** (Figure 7). However, we found better inhibitory activity for the all-*cis* compounds such as **8** and **9**. As interpreted with model **III** (Figure 7), the distance between the two amino moieties is shortened, thus imitating **4** better and, as a consequence, improving the inhibitory activity.

The best biologically active compounds in this series possess a hydroxymethyl moiety. Compounds **7** and **8b** bearing an additionally trifluoromethylbiphenyl group exert the best antiproliferative effect on the tested cancer cell lines. The hydroxymethyl moiety is important for the  $\alpha$ -mannosidase inhibition while the trifluoromethylbiphenyl group is important (as other biphenyl groups) for the cancer cell growth inhibition. This is expected as the biphenyl moieties help the inhibitor to penetrate cell membranes. The absence of correlation of  $\alpha$ -mannosidase inhibitory and cell growth inhibitory action might be the result of differences in cell penetration of our compounds. From the data presented in this paper, it is possible that the cell growth inhibitory activity of our compounds is not due to  $\alpha$ -mannosidase inhibition. These preliminary studies will be followed by the synthesis of a large library of analogues with the hope to find a chemotherapeutic agent to fight pancreas cancer and other cancers, and to find the mechanism of action of these compounds.

## EXPERIMENTAL

### General methods.

Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Perkin–Elmer 241MC spectropolarimeter.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained for solutions in  $\text{CDCl}_3$ ,  $[\text{d}_6]\text{DMSO}$  and  $\text{CD}_3\text{OD}$ ;  $J$  values are given in Hz and  $\delta$  in ppm. All the assignments were confirmed by two-dimensional NMR experiments (COSY and HSQC). NMR and Mass spectra were registered in CITIUS (University of Seville). TLC was performed on silica gel HF<sub>254</sub> (Merck), with detection by UV light charring with ninhydrine or with Pancaldi reagent  $[(\text{NH}_4)_6\text{MoO}_4, \text{Ce}(\text{SO}_4)_2, \text{H}_2\text{SO}_4, \text{H}_2\text{O}]$ . Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography. Glycosidases and the corresponding *p*-nitrophenyl-*O*-

glycoside substrates for inhibition assays were purchased in Sigma-Aldrich.

### General procedure for reductive amination of $\alpha$ -aminoesters **12** and **13** with aldehydes **10** and **11**.

To a solution of aldehyde **10** (0.285 g, 1.0 mmol) in anhydrous 1,2-dichloroethane (5.5 mL),  $\alpha$ -amino ester derivative **12** (1.1 mmol) in 1,2-dichloroethane (4 mL) and NaBH(OAc)<sub>3</sub> (0.297 g, 1.4 mmol) were added under Ar. The reaction was stirred overnight at rt. Then, aq. sat. sol. of NaHCO<sub>3</sub> was added and the mixture extracted with AcOEt, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, evaporated in vacuo followed by flash column chromatography on silica gel (AcOEt:cyclohexane 1:2).

The following compounds were obtained:

#### (2*S*,3*R*,4*S*) *N*-*tert*-Butoxycarbonyl-2-{{{(1*R*)-1-methoxycarbonyl-1-[[1,1'-biphenyl]-4-yl]methyl}-amino}ethyl}-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (**16a**)

Reductive amination of **11** and **12a** following the general procedure gave pure **16a** as a colourless oil (0.343 g, 67% yield).  $[\alpha]_{\text{D}}^{25} +17.5$  (*c* 0.74, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3330, 2978, 1737, 1687, 1110, 1083, 867, 698 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.59-7.53 (m, 4H, Ar-H),  $\delta$  7.48-7.39 (m, 4H, Ar-H), 7.34 (m, 1H, Ar-H), 4.73-4.62 (m, 2H, H-3, H-4), 4.44 (m, 1H, CHCOOCH<sub>3</sub>), 4.05-3.93 (m, 1H, H-2), 3.92-3.77 (m, 1H, H-5a) 3.71 (s, 3H, CHCOOCH<sub>3</sub>), 3.29-3.18 (m, 1H, H-5b), 2.76-2.56 (m, 2H, H-2'a, H-2'b), 2.01-1.88 (m, 3H, H-1'a, H-1'b, NH), 1.49 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.42 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.31 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  173.5, 154.3, 141.0, 140.7, 137.3, 128.8, 127.9, 127.4, 127.4, 127.1, 112.9, 80.0, 79.8, 77.8, 65.3, 57.3, 52.2, 50.1, 44.9, 29.7, 28.4, 26.6, 25.2. CIHRMS *m/z* found 511.2824, calcd. for C<sub>29</sub>H<sub>39</sub>N<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup>: 511.2808.

#### (2*S*,3*R*,4*S*) *N*-*tert*-Butoxycarbonyl-2-{{{(1*R*)-1-methoxycarbonyl-1-[(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl}amino}ethyl}-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (**16b**)

Reductive amination of **11** and **12b** following the general procedure gave pure **16b** as a colourless oil (0.338 g, 58% yield).  $[\alpha]_{\text{D}}^{25} +12.3$  (*c* 1.05, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3345, 2981, 1736, 1684, 1119, 1086, 861, 734 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.72-7.63 (m, 4H, Ar-H),  $\delta$  7.56 (d, 2H, *J* = 8.3, Ar-H), 7.49 (d, 2H, *J* = 8.3, Ar-H), 4.80-4.63 (m, 2H, H-4, H-3), 4.44 (m, 1H, CHCOOCH<sub>3</sub>), 4.00 (m, 1H, H-2), 3.86 (m, 1H, H-5a) 3.71 (s, 3H, CHCOOCH<sub>3</sub>), 3.28-3.19 (m, 1H, H-5b), 2.77-2.56 (m, 2H, H-2'a, H-2'b), 2.04-1.85 (m, 3H, H-1'a, H-1'b, NH), 1.53-1.47 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.40 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.36-1.28 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  173.3, 154.3, 144.2, 144.2, 139.5, 128.1, 127.5, 127.3, 125.7, 112.9, 80.0, 79.8, 77.8, 65.1, 57.7, 52.3, 49.5, 44.9, 29.7, 28.3, 26.6, 25.2. CIHRMS *m/z* found 579.2688, calcd. for C<sub>30</sub>H<sub>38</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup>: 579.2682.

**(2S,3R,4S) *N*-tert-Butoxycarbonyl-2-{{{(1R)-1-methoxycarbonyl-1-{4-[(phenylmethoxy)phenyl]}-methyl}amino}ethyl}-3,4-*O*-isopropylidene pyrrolidine-3,4-diol (16c)**

Reductive amination of **11** and **12c** following the general procedure gave pure **16c** (0.30 g, 70% yield).  $[\alpha]_D^{25} +0.3$  (*c* 0.93, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\max}$  3326, 2977, 1737, 1689, 1107, 1082, 863, 697 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz)  $\delta$  7.39-7.18 (m, 7H, Ar-H),  $\delta$  6.90- 6.83 (m, 2H, Ar-H), 4.97 (s, 2H, O-CH<sub>2</sub>-C-arom.), 4.66-4.54 (m, 2H, H-3, H-4), 4.27 (s, 1H, CHCOOCH<sub>3</sub>), 3.90 (m, 1H, H-2), 3.76 (m, 1H, H-5a), 3.61 (s, 3H, CHCOOCH<sub>3</sub>), 3.15 (m, 1H, H-5b), 2.63-2.47 (m, 2H, H-2'a, H-2'b), 2.03-1.77 (m, 3H, H-1'a, H-1'b, N-H), 1.42 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.35 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.24 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  173.7, 158.6, 154.3, 136.9, 130.6, 128.6, 128.0, 127.4, 115.0, 112.8, 80.0, 79.8, 77.8, 70.0, 64.8, 57.7, 52.1, 50.1, 44.8, 29.6, 28.4, 26.6, 25.2. CIHRMS *m/z* found 541.2906, calcd. for C<sub>30</sub>H<sub>41</sub>N<sub>2</sub>O<sub>7</sub> (M+H)<sup>+</sup>: 541.2914.

**(2S,3R,4S) *N*-tert-Butoxycarbonyl-2-{{{(1R)-1-methoxycarbonyl-1-{4-[(prop-2-enyloxy)phenyl]}-methyl}amino}ethyl}-3,4-*O*-isopropylidene pyrrolidine-3,4-diol (16d)**

Reductive amination of **11** and **12d** following the general procedure gave pure **16d** (0.269 g, 59% yield).  $[\alpha]_D^{25} +0.3$  (*c* 1.14, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\max}$  3330, 2980, 1737, 1690, 1109, 1083, 862 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.28 (d, 2H, *J* = 8.8, Ar-H), 6.86 (d, 2H, *J* = 8.8, Ar-H), 6.04 (m, 1H, CH<sub>2</sub>=CHCH<sub>2</sub>O), 5.39 (dq, 1H, *J* = 17.4, *J* = 1.6, CH<sub>2</sub>=CHCH<sub>2</sub>O), 5.27 (dq, 1H, *J* = 10.5, *J* = 1.5, CH<sub>2</sub>=CHCH<sub>2</sub>O), 4.80-4.62 (m, 2H, H-3, H-4), 4.53-4.49 (m, 2H, CH<sub>2</sub>=CHCH<sub>2</sub>O), 4.35 (m, 1H, CHCOOCH<sub>3</sub>), 4.01-3.78 (m, 2H, H-2, H-5a), 3.67 (s, 3H, COOCH<sub>3</sub>), 3.22 (m, 1H, H-5b), 2.71- 2.51 (m, 2H, H-2'a, H-2'b), 2.01-1.83 (m, 3H, H-1'a, H-1'b, N-H), 1.50 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.41 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.33 (2m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  173.7, 158.4, 154.3, 133.2, 128.6, 128.6, 117.7, 114.8, 112.8, 80.0, 79.8, 77.8, 68.8, 64.8, 57.7, 52.1, 49.5, 44.8, 29.6, 28.4, 26.6, 25.2. CIHRMS *m/z* found 491.2755, calcd. for C<sub>26</sub>H<sub>39</sub>N<sub>2</sub>O<sub>7</sub> (M+H)<sup>+</sup>: 491.2757.

**(2R,3R,4S) 2-{{{(1R)-2-Hydroxy-1-[(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)]ethyl}amino}ethyl}-pyrrolidine-3,4-diol (7)**

Reductive amination of aldehyde **10** and amine **12b** afforded **14** (0.48 g, 95% yield).  $[\alpha]_D^{25} + -16.4$  (*c* 0.79, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz)  $\delta$  7.64-7.56 (m, 4H, Ar-H), 7.54-7.46 (m, 2H, Ar-H), 7.46-7.36 (m, 2H, Ar-H), 4.60 (m, 1H, H-4), 4.38-4.30 (m, 2H, CHCOOCH<sub>3</sub>, H-3), 4.08 (m, 1H, H-2), 3.82 (m, 1H, H-5a) 3.64 (s, 3H, CHCOOCH<sub>3</sub>), 3.17 (m, 1H, H-5b), 2.70-2.40 (m, 2H, H-2'a, H-2'b), 1.90 (m, 1H, N-H), 1.64-1.47 (m, 2H, H-1'a, H-1'b), 1.36 (2s, 9H, C(CH<sub>3</sub>)<sub>2</sub>, C(CH<sub>3</sub>)<sub>3</sub>), 1.21 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>). CIHRMS *m/z* found 579.2690, calcd. for C<sub>30</sub>H<sub>38</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup>: 579.2682.

Reduction of **14** afforded protected alcohol (2R,3R,4S) *N*-tert-butoxycarbonyl-2-{{{(1R)-2-hydroxy-1-

[(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethyl]amino}ethyl}-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (0.079 g, 53% yield).  $[\alpha]_{\text{D}}^{25}$  -9.1 (*c* 0.86, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3437, 2977, 1686, 1070, 823, 732 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.72-7.62 (m, 4H, Ar-H), 7.69-7.50 (m, 2H, Ar-H), 7.47-7.35 (m, 2H, Ar-H), 4.66 (m, 1H, H-4), 4.38 (m, 1H, H-3), 4.30 (m, 1H, H-2), 4.13-3.52 (m, 4H, H-5a, CHCH<sub>2</sub>OH, CH<sub>2</sub>OH), 3.23 (m, 1H, H-5b), 2.77-2.15 (m, 4H, H-2'a, H-2'b, N-H, O-H), 1.71-1.53 (m, 2H, H-1'a, H-1'b), 1.44 (m, 12H, C(CH<sub>3</sub>)<sub>2</sub>, C(CH<sub>3</sub>)<sub>3</sub>), 1.28 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>). CIHRMS *m/z* found 551.2739, calcd. for C<sub>29</sub>H<sub>38</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup>: 551.2733.

Subsequent deprotection of the above protected alcohol (0.1 mmol) afforded **7** in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  +4.7 (*c* 0.65, MeOH). IR  $\nu_{\text{max}}$  3341, 2934, 1127, 1068, 823 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, MeOD,  $\delta$  ppm, *J* Hz)  $\delta$  7.90-7.81 (m, 4H, Ar-H),  $\delta$  7.81-7.75 (m, 2H, Ar-H), 7.53-7.68 (m, 2H, Ar-H), 4.52 (m, 1H, H-4), 4.24 (m, 1H, H-3), 4.09-3.97 (m, 3H, CHCH<sub>2</sub>OH, CH<sub>2</sub>OH), 3.58-3.42 (m, 2H, H-2, H-5a), 3.30-3.05 (m, 3H, H-2'a, H-2'b, H-5b), 2.46-2.23 (m, 2H, H-1'a, H-1'b). <sup>13</sup>C NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  133.9, 130.4, 129.3, 128.7, 126.9, 77.0, 70.5, 65.2, 63.3, 59.0, 49.9-48.2, 44.2, 28.1. CIHRMS *m/z* found 411.1908, calcd. for C<sub>21</sub>H<sub>26</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 411.1896.

**(2*S*,3*R*,4*S*) N-tert-Butoxycarbonyl-2-{{{(1*S*)-1-methoxycarbonyl-1-[[1,1'-biphenyl]-4-yl]methyl}-amino}ethyl}-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (**18**)**

Reductive amination of aldehyde **11** and amine **13** afforded **18** (0.186 g, 36% yield).  $[\alpha]_{\text{D}}^{25}$  +37.0 (*c* 1.19, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  2979, 1737, 1691, 1160, 1078, 866, 699 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.60-7.53 (m, 4H, Ar-H),  $\delta$  7.48-7.39 (m, 4H, Ar-H), 7.34 (m, 1H, Ar-H), 4.72-4.62 (m, 2H, H-3, H-4), 4.44 (m, 1H, CHCOOCH<sub>3</sub>), 3.99 (m, 1H, H-2), 3.84 (m, 1H, H-5a) 3.71 (s, 3H, CHCOOCH<sub>3</sub>), 3.24 (m, 1H, H-5b), 2.77-2.56 (m, 2H, H-2'a, H-2'b), 2.09-1.88 (m, 3H, H-1'a, H-1'b, NH), 1.49 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.42 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.31 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  173.5, 154.3, 141.0, 140.7, 137.3, 128.8, 128.5, 127.9, 127.4, 127.1, 112.8, 80.1, 80.0, 77.7, 65.3, 57.7, 52.2, 50.2, 50.0, 29.7, 28.4, 26.6, 25.2. CIHRMS *m/z* found 511.2800, calcd. for C<sub>29</sub>H<sub>39</sub>N<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup>: 511.2808.

**General procedure for acidic deprotection of compounds 14, 16 and 18**

Pyrrolidines **14**, **16** or **18** (0.1 mmol) were dissolved in a mixture of HCl(4M):THF 2:1 (4.5 mL) and stirred at rt overnight. Evaporation of the solvent quantitatively afforded compounds **15**, **17** or **19**.

The following compounds were obtained:

**(2S,3R,4S) 2-{{{(1R)-1-Methoxycarbonyl-1-[[1,1'-biphenyl]-4-yl]methyl}amino}ethyl}pyrrolidine-3,4-diol (17a)**

Compound **17a** ( $\cdot\text{HCl}$ ) was obtained in quantitative yield as a white solid.  $[\alpha]_{\text{D}}^{25}$  -2.8 ( $c$  0.78, MeOH). IR  $\nu_{\text{max}}$  3367, 2949, 1736, 1234, 1134, 756, 697  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz, MeOD,  $\delta$  ppm,  $J$  Hz)  $\delta$  7.84-7.76 (m, 2H, Ar-H),  $\delta$  7.70- 7.60 (m, 4H, Ar-H), 7.53-7.44 (m, 2H, Ar-H), 7.40 (m, 1H, Ar- H), 5.41 (s, 1H,  $\text{CHCOOCH}_3$ ), 4.42 (m, 1H, H-4), 4.16 (m, 1H, H-3), 3.86 (s, 3H,  $\text{CHCOOCH}_3$ ), 3.69 (m, 1H, H-2), 3.45 (m, 1H, H-5a), 3.25 (m, 1H, H-2'a), 3.19-3.04 (m, 2H, H-2'b, H-5b), 2.56-2.14 (m, 2H, H-1'a, H-1'b).  $^{13}\text{C}$  NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  169.6, 145.0, 140.9, 130.6, 130.1, 129.9, 129.4, 129.3, 128.1, 71.9, 71.3, 64.2, 60.4, 54.4, 49.9-48.2, 44.3, 25.0. CIHRMS  $m/z$  found 371.1967, calcd. for  $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$ : 371.1971.

**(2S,3R,4S) 2-{{{(1R)-1-Methoxycarbonyl-1-[(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl}amino)ethyl}pyrrolidine-3,4-diol (17b).**

Compound **17b** ( $\cdot\text{HCl}$ ) was obtained in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  -9.9 ( $c$  0.67, MeOH). IR  $\nu_{\text{max}}$  3359, 2951, 1745, 1325, 1111, 1070, 825  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz, MeOD,  $\delta$  ppm,  $J$  Hz)  $\delta$  7.88 (d, 4H,  $J$  = 8.2, Ar-H),  $\delta$  7.79 (d, 2H,  $J$  = 8.2, Ar-H), 7.70 (d, 2H,  $J$  = 8.2, Ar-H), 5.42 (s, 1H,  $\text{CHCOOCH}_3$ ), 4.42 (m, 1H, H-4), 4.15 (m, 1H, H-3), 3.86 (s, 3H,  $\text{CHCOOCH}_3$ ), 3.74 (m, 1H, H-2), 3.40 (m, 1H, H-5a), 3.30-3.04 (m, 3H, H-2'a, H-2'b, H-5b), 2.55-2.18 (m, 2H, H-1'a, H-1'b).  $^{13}\text{C}$  NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  169.4, 144.7, 143.2, 131.2, 130.8, 129.7, 128.8, 127.0, 71.9, 71.3, 64.1, 60.3, 54.4, 49.9-48.2, 44.3, 25.0. CIHRMS  $m/z$  found 439.1850, calcd. for  $\text{C}_{22}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$ : 439.1845.

**(2S,3R,4S) 2-{{{(1R)-1-Methoxycarbonyl-1-{4-[(phenylmethoxy)phenyl]}methyl}amino}ethyl}pyrrolidine-3,4-diol (17c)**

Compound **17c** ( $\cdot\text{HCl}$ ) was obtained in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  -29.8 ( $c$  0.67, MeOH). IR  $\nu_{\text{max}}$  3353, 2930, 1736, 1231, 1181, 738, 696  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz, MeOD,  $\delta$  ppm,  $J$  Hz)  $\delta$  7.53-7.28 (m, 6H, Ar-H),  $\delta$  7.19-7.09 (m, 2H, Ar-H), 6.90 (m, 1H, Ar-H), 5.23 (s, 1H,  $\text{CHCOOCH}_3$ ), 5.15 (s, 2H, O- $\text{CH}_2$ -Ph), 4.41 (m, 1H, H-4), 4.14 (m, 1H, H-3), 3.83 (s, 3H,  $\text{CHCOOCH}_3$ ), 3.64 (m, 1H, H-2), 3.46 (m, 1H, H-5a), 3.28-2.94 (m, 3H, H-2'a, H-2'b, H-5b), 2.52-2.10 (m, 2H, H-1'a, H-1'b).  $^{13}\text{C}$  NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  169.6, 162.0, 138.1, 131.6, 129.6, 129.1, 128.6, 117.2, 71.9, 71.3, 71.2, 64.2, 60.4, 49.9-48.2, 25.0. CIHRMS  $m/z$  found 401.2068, calcd. for  $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_5$  ( $\text{M}+\text{H}$ ) $^+$ : 401.2076.

**(2S,3R,4S) 2-{{{(1R)-1-Methoxycarbonyl-1-{4-[(prop-2-enyloxy)phenyl]}methyl}amino}ethyl}pyrrolidine-3,4-diol (17d)**

Compound **17d** ( $\cdot\text{HCl}$ ) was obtained in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  -36.9 ( $c$  1.05, MeOH). IR  $\nu_{\text{max}}$  3357, 2948, 1742, 1610, 1229, 1182, 1130, 1134, 836, 792  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz, MeOD,  $\delta$  ppm,  $J$  Hz)  $\delta$  7.53-7.35 (m, 2H, Ar-H),  $\delta$  7.11- 6.96 (m, 2H, Ar-H), 6.04 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 5.38 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 5.30-5.12 (m, 2H,  $\text{CH}=\text{CH}_2$ ,  $\text{CHCOOCH}_3$ ), 4.64-4.50 (m, 2H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.38 (m, 1H, H-4), 4.11 (m, 1H, H-3), 3.79 (s, 3H,  $\text{CHCOOCH}_3$ ), 3.64 (m, 1H, H-2), 3.41 (m, 1H, H-5a), 3.23-2.89 (m, 3H, H-2'a, H-2'b, H-5b), 2.48-2.09 (m, 2H, H-1'a, H-1'b).  $^{13}\text{C}$  NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  169.7, 161.9, 134.4, 131.6, 123.0, 118.0, 117.0, 71.9, 71.4, 64.2, 60.6, 54.4, 49.9-48.2, 44.4, 25.0. CIHRMS  $m/z$  found 351.1932, calcd. for  $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_5$  ( $\text{M}+\text{H}$ ) $^+$ : 351.1920.

**(2S,3R,4S) 2-{{{(1S)-1-Methoxycarbonyl-1-[[1,1'-biphenyl]-4-yl]methyl}amino}ethyl}pyrrolidine-3,4-diol (19)**

Compound **19** was obtained in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  +15.3 ( $c$  1.40, MeOH). IR  $\nu_{\text{max}}$  3388, 2953, 1738, 1236, 1136, 759, 697  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz, MeOD,  $\delta$  ppm,  $J$  Hz)  $\delta$  7.84-7.76 (m, 2H, Ar-H), 7.70-7.60 (m, 4H, Ar-H), 7.53-7.44 (m, 2H, Ar-H), 7.40 (m, 1H, Ar-H), 5.38 (s, 1H,  $\text{CHCOOCH}_3$ ), 4.42 (m, 1H, H-4), 4.16 (m, 1H, H-3), 3.86 (s, 3H,  $\text{CHCOOCH}_3$ ), 3.69 (m, 1H, H-2), 3.46 (m, 1H, H-5a), 3.25 (m, 1H, H-2'a), 3.19-3.03 (m, 2H, H-2'b, H-5b), 2.57-2.14 (m, 2H, H-1'a, H-1'b).  $^{13}\text{C}$  NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  169.5, 144.9, 140.9, 130.6, 130.1, 130.0, 129.9, 129.3, 128.1, 71.8, 71.3, 64.0, 60.3, 54.3, 49.9-48.2, 44.2, 24.8. CIHRMS  $m/z$  found 371.1966, calcd. for  $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$ : 371.1971.

**(2S,3R,4S) 2-{{{(1S)-1-Methoxycarbonyl-1-[(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl}amino}ethyl}pyrrolidine-3,4-diol (15)**

Compound **15** was obtained in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  +0.9 ( $c$  0.87, MeOH). IR  $\nu_{\text{max}}$  3387, 2925, 1743, 1325, 1166, 1110, 824  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz, MeOD,  $\delta$  ppm,  $J$  Hz)  $\delta$  7.95-7.49 (m, 8H, Ar-H), 5.41 (s, 1H,  $\text{CHCOOCH}_3$ ), 4.20 (m, 1H, H-4), 4.00 (m, 1H, H-3), 3.84 (s, 3H,  $\text{CHCOOCH}_3$ ), 3.61-3.40 (m, 2H, H-2, H-5a), 3.28-3.05 (m, 3H, H-2'a, H-2'b, H-5b), 2.45-2.20 (m, 2H, H-1'a, H-1'b).  $^{13}\text{C}$  NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  169.4, 143.2, 131.1, 130.9, 129.7, 128.9, 127.0, 77.1, 70.5, 64.2, 58.9, 51.5, 49.9-48.2, 44.7, 28.1. CIHRMS  $m/z$  found 439.1857, calcd. for  $\text{C}_{22}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$ : 439.1845.

**General procedure for the preparation of compounds 8 (or 9) from compounds 16 (or 18).**

Ester **16** (0.30 mmol) was added portionwise to a cooled suspension (-15 °C) of  $\text{LiAlH}_4$  (25 mg, 0.74 mmol) in anhydrous THF (8.0 mL). The solution was stirred at rt for 15 min, then  $\text{H}_2\text{O}$  was added dropwise (10 mL) and the mixture was extracted with AcOEt (3x30 mL). After solvent evaporation *in vacuo* and flash column chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$ :MeOH 20:1), Boc-protected alcohol was

obtained, that was subsequently deprotected. The above protected alcohol (0.1 mmol) was then dissolved in a mixture of HCl(4M):THF 2:1 (4.7 mL) and stirred at rt overnight. Evaporation of the solvent quantitatively afforded **8** ( $\cdot$ HCl).

The following compounds were obtained:

**(2*S*,3*R*,4*S*) 2-{{{(1*R*)-2-Hydroxy-1-[[1,1'-biphenyl]-4-yl]ethyl}amino}ethyl}pyrrolidine-3,4-diol (**8a**)**

Reduction of **16a** afforded protected alcohol (2*S*,3*R*,4*S*) *N*-*tert*-butoxycarbonyl-2-{{{(1*R*)-2-hydroxy-1-[[1,1'-biphenyl]-4-yl]ethyl}amino}ethyl}-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol as a colourless oil (56.5 mg, 39% yield).  $[\alpha]_{\text{D}}^{25} +25.8$  (*c* 0.74, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3329, 2971, 1689, 1081, 840, 699 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.60-7.53 (m, 4H, Ar-H), 7.47-7.30 (m, 5H, Ar-H), 4.74-4.62 (m, 2H, H-3, H-4), 4.05 (m, 1H, H-2), 3.90-3.72 (m, 3H, H-5a, CH<sub>2</sub>OH), 3.63 (m, 1H, CHCH<sub>2</sub>OH), 3.24 (m, 1H, H-5b), 2.89-2.45 (m, 4H, H-2'a, H-2'b, N-H, O-H), 2.01-1.83 (m, 2H, H-1'a, H-1'b), 1.48 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.41 (m, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.31 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  154.5, 140.8, 140.6, 137.3, 128.8, 127.8, 127.4, 127.3, 127.1, 112.9, 80.1, 80.0, 77.9, 66.4, 64.4, 57.4, 50.1, 44.3, 29.7, 28.4, 26.5, 25.1. CIHRMS *m/z* found 483.2863, calcd. for C<sub>28</sub>H<sub>39</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup>: 483.2859.

Subsequent deprotection of the above protected alcohol afforded **8a** ( $\cdot$ HCl) in quantitative yield as a white solid.  $[\alpha]_{\text{D}}^{25} +1.1$  (*c* 0.79, MeOH). IR  $\nu_{\text{max}}$  3342, 2926, 1132, 1061, 1038, 839, 767, 694 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, MeOD,  $\delta$  ppm, *J* Hz)  $\delta$  7.81-7.74 (m, 2H, Ar-H),  $\delta$  7.71-7.63 (m, 4H, Ar-H), 7.53-7.46 (m, 2H, Ar-H), 7.40 (m, 1H, Ar-H), 4.49 (t, 1H, *J* = 6.0, CHCH<sub>2</sub>OH), 4.40 (m, 1H, H-4), 4.12 (m, 1H, H-3), 4.09-3.98 (m, 2H, CH<sub>2</sub>OH), 3.67 (m, 1H, H-2), 3.48 (m, 1H, H-5a), 3.29-2.99 (m, 3H, H-2'a, H-2'b, H-5b), 2.54-2.13 (m, 2H, H-1'a, H-1'b). <sup>13</sup>C NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  144.0, 141.2, 132.8, 130.2, 129.0, 128.0, 71.8, 71.3, 65.2, 63.3, 60.5, 49.9-48.2, 43.8, 24.9. CIHRMS *m/z* found 343.2021, calcd. for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 343.2022.

**(2*S*,3*R*,4*S*) 2-{{{(1*R*)-2-Hydroxy-1-[(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]ethyl}amino}ethyl}-pyrrolidine-3,4-diol (**8b**)**

Reduction of **16b** afforded protected alcohol (2*S*,3*R*,4*S*) *N*-*tert*-butoxycarbonyl-2-{{{(1*R*)-2-hydroxy-1-[(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]ethyl}amino}ethyl}-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (0.057 g, 35% yield).  $[\alpha]_{\text{D}}^{25} +7.1$  (*c* 1.18, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3441, 2987, 1671, 1070, 824, 730 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.72-7.63 (m, 4H, Ar-H), 7.60-7.53 (m, 2H, Ar-H), 7.46-7.38 (m, 2H, Ar-H), 4.74-4.65 (m, 2H, H-3, H-4), 4.05 (m, 1H, H-2), 3.90-3.71 (m, 3H, H-5a, CH<sub>2</sub>OH), 3.60 (m, 1H, CHCH<sub>2</sub>OH), 3.23 (m, 1H, H-5b), 2.80-2.52 (m, 4H, H-2'a, H-2'b, N-H, O-H),

1.99-1.82 (m, 2H, H-1'a, H-1'b), 1.48 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.41 (m, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.31 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>, δ ppm) δ 154.5, 144.3, 140.8, 140.6, 139.0, 128.0, 127.5, 126.0, 125.7, 113.0, 80.0, 79.8, 78.0, 66.3, 64.5, 57.2, 49.9, 44.3, 29.9, 28.4, 26.5, 25.2. CIHRMS *m/z* found 551.2715, calcd. for C<sub>29</sub>H<sub>38</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup>: 551.2733.

Subsequent deprotection of the above protected alcohol afforded **8b** (·HCl) in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  -2.2 (*c* 0.82, MeOH). IR  $\nu_{\text{max}}$  3328, 2936, 1326, 1122, 1070, 823 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, MeOD, δ ppm, *J* Hz) δ 7.92-7.62 (m, 8H, Ar-H), 4.59-4.26 (m, 2H, CHCH<sub>2</sub>OH, H-4), 4.18-3.92 (m, 3H, H-3, CH<sub>2</sub>OH), 3.66 (m, 1H, H-2), 3.42 (m, 1H, H-5a), 3.25-2.89 (m, 3H, H-2'a, H-2'b, H-5b), 2.52-2.10 (m, 2H, H-1'a, H-1'b). <sup>13</sup>C NMR (75.4 MHz, MeOD, δ ppm) δ 145.1, 142.3, 130.7, 129.4, 128.8, 127.0, 72.1, 71.6, 65.2, 63.4, 60.8, 49.9-48.2, 44.6, 25.1. CIHRMS *m/z* found 411.1891, calcd. for C<sub>21</sub>H<sub>26</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 411.1896.

**(2*S*,3*R*,4*S*) 2-(((1*R*)-2-Hydroxy-1-{4-[(phenylmethoxy)phenyl]}ethyl)amino)ethyl}pyrrolidine-3,4-diol (**8c**)**

Reduction of **16c** afforded protected alcohol (2*S*,3*R*,4*S*)-*N*-*tert*-butoxycarbonyl-2-(((1*R*)-2-hydroxy-1-{4-[(phenylmethoxy)phenyl]}ethyl)amino)ethyl}-3,4-*O*-isopropylidene-pyrrolidine-3,4-diol (0.06 g, 41% yield).  $[\alpha]_{\text{D}}^{25}$  +4.3 (*c* 0.79, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3345, 2972, 1689, 1082, 829, 696 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ ppm, *J* Hz, mixture of rotamers) δ 7.48-7.31 (m, 5H, Ar-H), 7.28 (d, 2H, *J* = 8.1, Ar-H), 6.96 (d, 2H, *J* = 8.1, Ar-H), 5.05 (s, 2H, O-CH<sub>2</sub>-Ph), 4.75-4.63 (m, 2H, H-3, H-4), 4.13-3.62 (m, 7H, H-5a, H-2, CHCH<sub>2</sub>OH, N-H, CH<sub>2</sub>OH, O-H), 3.33 (m, 1H, H-5b), 2.81-2.55 (m, 2H, H-2'a, H-2'b), 2.08-1.83 (m, 2H, H-1'a, H-1'b), 1.47 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.41 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.31 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>, δ ppm) δ 158.6, 154.6, 136.9, 130.8, 128.7, 128.6, 128.0, 127.5, 115.1, 113.1, 80.2, 79.8, 78.0, 70.1, 65.7, 64.3, 57.1, 50.0, 44.0, 29.7, 28.4, 26.5, 25.1. CIHRMS *m/z* found 513.2954, calcd. for C<sub>29</sub>H<sub>41</sub>N<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup>: 513.2965.

Subsequent deprotection of the above protected alcohol afforded **8c** (·HCl) in quantitative yield.  $[\alpha]_{\text{D}}^{25}$  -4.8 (*c* 0.72, MeOH). IR  $\nu_{\text{max}}$  3339, 2931, 1611, 1515, 1454, 1248, 1132, 1024, 834, 737, 696 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, MeOD, δ ppm, *J* Hz) δ 7.48-7.27 (m, 5H, Ar-H), 7.28 (d, 2H, *J* = 8.1, Ar-H), 6.96 (d, 2H, *J* = 8.1, Ar-H), 5.12 (s, 2H, O-CH<sub>2</sub>-Ph), 4.43-4.24 (m, 2H, H-3, H-4), 4.08 (br s, 1H, CHCH<sub>2</sub>OH), 3.95 (br s, 2H, CH<sub>2</sub>OH), 3.60 (br s, 1H, H-2), 3.41 (br s, 1H, H-5a), 3.21-2.89 (m, 3H, H-5b, H-2'a, H-2'b), 2.45-2.08 (m, 2H, H-1'a, H-1'b). <sup>13</sup>C NMR (75.4 MHz, MeOD, δ ppm) δ 161.4, 138.3, 131.1, 129.6, 129.0, 128.6, 116.8, 71.8, 71.3, 71.1, 65.1, 63.3, 60.6, 49.8-48.1 (under MeOD), 43.7, 24.9. CIHRMS *m/z* found 373.2112, calcd. for C<sub>21</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub> (M+H)<sup>+</sup>: 373.2127.



**(2*S*,3*R*,4*S*) 2-{{{(1*R*)-2-Hydroxy-1-[4-[(prop-2-enyloxy)phenyl]]ethyl}amino}ethyl}pyrrolidine-3,4-diol (8d)**

Reduction of **16d** afforded protected alcohol (2*S*,3*R*,4*S*) *N*-*tert*-butoxycarbonyl-2-{{{(1*R*)-2-hydroxy-1-[4-[(prop-2-enyloxy)phenyl]]ethyl}amino}ethyl}-3,4-*O*-isopropylidenepyrrolidine-3,4-diol (0.08 g, 56% yield).  $[\alpha]_{\text{D}}^{25} +2.4$  (*c* 1.05, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3442, 2979, 2931, 1688, 1610, 1083, 830, 731 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz)  $\delta$  7.20 (d, 2H, *J* = 8.8, Ar-H), 6.87 (d, 2H, *J* = 8.8, Ar-H), 6.04 (m, 1H, CH<sub>2</sub>=CHCH<sub>2</sub>O), 5.40 (dq, 1H, *J* = 17.3, *J* = 1.6, CH<sub>2</sub>=CHCH<sub>2</sub>O), 5.27 (dq, 1H, *J* = 10.5, *J* = 1.5, CH<sub>2</sub>=CHCH<sub>2</sub>O), 4.72-4.62 (m, 2H, H-3, H-4), 4.45 (dt, 2H, *J* = 5.4, *J* = 1.5, CH<sub>2</sub>=CHCH<sub>2</sub>O), 4.02 (m, 1H, H-2), 3.83 (m, 1H, H-5a), 3.77-3.63 (m, 2H, CH<sub>2</sub>OH, CHCH<sub>2</sub>OH), 3.54 (m, 1H, CH<sub>2</sub>OH), 3.22 (m, 1H, H-5b), 2.77-2.46 (m, 4H, H-2'a, H-2'b, N-H, O-H), 1.97-1.80 (m, 2H, H-1'a, H-1'b), 1.47 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.41 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.30 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  158.1, 154.4, 133.3, 132.5, 128.3, 117.7, 114.8, 113.0, 80.0, 79.8, 77.9, 68.9, 66.3, 64.2, 57.3, 49.9, 44.2, 29.6, 28.4, 26.5, 25.1. CIHRMS *m/z* found 463.2797, calcd. for C<sub>25</sub>H<sub>39</sub>N<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup>: 463.2808.

Subsequent deprotection of the above protected alcohol (0.1 mmol) afforded **8d** (·HCl) in quantitative yield.  $[\alpha]_{\text{D}}^{25} -13.2$  (*c* 0.98, MeOH). IR  $\nu_{\text{max}}$  3343, 2940, 1610, 1132, 1054, 1018, 833 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, MeOD,  $\delta$  ppm, *J* Hz)  $\delta$  7.49 (m, 2H, *J* = 8.6, Ar-H), 7.04 (m, 2H, *J* = 8.6, Ar-H), 6.08 (m, 1H, CH=CH<sub>2</sub>), 5.41 (dd, 1H, *J* = 17.4, *J* = 1.7, CH=CH<sub>2</sub>), 5.27 (dd, 1H, *J* = 10.5, *J* = 1.6, CH=CH<sub>2</sub>), 4.59 (dt, 2H, *J* = 5.2, *J* = 1.5, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.44-4.30 (m, 2H, H-4, CHCH<sub>2</sub>OH), 4.09 (m, 1H, H-3), 3.97 (d, 2H, *J* = 6.0, CH<sub>2</sub>OH), 3.62 (m, 1H, H-2), 3.43 (m, 1H, H-5a), 3.20-2.92 (m, 3H, H-2'a, H-2'b, H-5b), 2.46-2.14 (m, 2H, H-1'a, H-1'b). <sup>13</sup>C NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  161.2, 134.6, 131.0, 125.8, 117.8, 116.6, 71.8, 71.3, 69.9, 65.0, 63.3, 60.5, 49.9-48.2, 43.5, 24.9. CIHRMS *m/z* found 323.1965, calcd. for C<sub>17</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub> (M+H)<sup>+</sup>: 323.1971.

**(2*S*,3*R*,4*S*) 2-{{{(1*S*)-2-Hydroxy-1-[[1,1'-biphenyl]-4-yl]ethyl}amino}ethyl}pyrrolidine-3,4-diol (9)**

Reduction of **18** afforded protected alcohol (2*S*,3*R*,4*S*) *N*-*tert*-butoxycarbonyl-2-{{{(1*S*)-2-hydroxy-1-[[1,1'-biphenyl]-4-yl]ethyl}amino}ethyl}-3,4-*O*-isopropylidenepyrrolidine-3,4-diol (0.060 g, 40% yield).  $[\alpha]_{\text{D}}^{25} +34.2$  (*c* 0.84, CH<sub>2</sub>Cl<sub>2</sub>). IR  $\nu_{\text{max}}$  3408, 2979, 1684, 1083, 839, 698 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$  ppm, *J* Hz, mixture of rotamers)  $\delta$  7.60-7.52 (m, 4H, Ar-H), 7.48-7.30 (m, 5H, Ar-H), 4.74-4.62 (m, 2H, H-3, H-4), 4.04 (m, 1H, H-2), 3.90-3.72 (m, 3H, H-5a, CH<sub>2</sub>OH), 3.62 (m, 1H, CHCH<sub>2</sub>OH), 3.24 (m, 1H, H-5b), 2.82-2.53 (m, 4H, H-2'a, H-2'b, N-H, O-H), 2.01-1.83 (m, 2H, H-1'a, H-1'b), 1.48 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.41 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.31 (m, 3H, C(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>,  $\delta$  ppm)  $\delta$  154.5, 140.8, 140.6, 139.5, 128.8, 127.7, 127.7, 127.4, 127.3, 113.0, 80.1, 80.1, 80.0, 66.4, 64.4, 57.4, 50.1, 44.4, 29.7, 28.4, 26.5, 25.2. CIHRMS *m/z* found 483.2858, calcd. for C<sub>28</sub>H<sub>39</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup>: 483.2859.

Subsequent deprotection of the above protected alcohol (0.1 mmol) afforded **9** ( $\cdot\text{HCl}$ ) in quantitative yield.  $[\alpha]_{\text{D}}^{25} +11.1$  ( $c$  0.70, MeOH). IR  $\nu_{\text{max}}$  3337, 2933, 1132, 1045, 1039, 838, 766, 694  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz, MeOD,  $\delta$  ppm,  $J$  Hz)  $\delta$  7.76-7.51 (m, 6H, Ar-H),  $\delta$  7.51-7.25 (m, 3H, Ar-H), 4.51-4.26 (m, 2H,  $\text{CHCH}_2\text{OH}$ , H-4), 4.08 (m, 1H, H-3), 4.03-3.90 (m, 2H,  $\text{CH}_2\text{OH}$ ), 3.60 (m, 1H, H-2), 3.40 (m, 1H, H-5a), 3.23-2.86 (m, 3H, H-2'a, H-2'b, H-5b), 2.53-2.06 (m, 2H, H-1'a, H-1'b).  $^{13}\text{C}$  NMR (75.4 MHz, MeOD,  $\delta$  ppm)  $\delta$  144.0, 141.2, 132.7, 130.4, 130.1, 129.0, 128.1, 71.9, 71.5, 65.3, 63.5, 60.7, 49.9-48.2, 44.2, 25.0. CIHRMS  $m/z$  found 343.2020, calcd. for  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$ : 343.2022.

### Viability assays

MiaPaCa2 or PK-9 cells were cultured in RPMI-1640 medium containing 10% FBS and antibiotics at 37 °C in 5%  $\text{CO}_2$ .  $3 \times 10^5$  cells/well were plated in 96-well plates and allowed to adhere overnight. Thereafter, the compounds were added at concentrations ranging from 1  $\mu\text{M}$  to 1 mM in triplicate wells and viability was detected 72h later with Celltiter96 Aqueous1 (Promega). Compound EC50 was estimated using GraphPad (GraphPad Software, Inc, Lajolla, CA, USA).

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21.  $\alpha$ -L-fucosidase from bovine kidney,  $\alpha$ -galactosidases from coffee beans,  $\beta$ -galactosidases from *Escherichia coli* and *Aspergillus oryzae*,  $\alpha$ -glucosidases from yeast and from rice, amyloglucosidases from *Aspergillus niger*,  $\beta$ -glucosidases from almonds,  $\alpha$ -mannosidases from Jack beans,  $\beta$ -mannosidases from snail, and  $\beta$ -N-acetylglucosaminidases from Jack beans.
22. IC<sub>50</sub> of inhibitors showing good activity (higher than 80% inhibition at 1 mM) were determined.